Fine Chemicals Manufacture:

Technology and Engineering

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Preface

The sector of fine chemicals, including pharmaceuticals, agrochemicals, dyes and pigments, fragrances and flavours, intermediates, and performance chemicals is growing fast. For obvious reasons chemistry is a key to the success in developing new processes for fine chemicals. However, as a rule, chemists formulate results of their work as recipes, which usually lack important information for process development. This book is intended to show what is needed to make the recipe more useful for process development purposes and to transform the recipe into an industrial process that will be safe, environmentally friendly, and profitable. The goal of the book is to form a bridge between chemists and specialists of all other branches involved in the scale-up of new processes or modification of existing processes with both a minimum effort and risk and maximum profit when commercializing the process. New techniques for scale-up and optimization of existing processes and improvements in the utilization of process equipment that have been developed in recent years are presented in the book. We believe that even experienced process and developmental engineers will find these interesting and useful in their every day practice.

The book starts with general information on fine chemicals and characteristic features of their manufacture. Tools that are used in working out new industrial processes and optimization of existing plants and processes are presented in subsequent chapters. Finally, the target of all laboratory, pilot and design activities, namely a modern production plant, is described.

Fine chemicals have been produced for tens of years based upon conventional organic chemistry techniques that generate many wastes, are often insufficiently selective (so less profitable than they could be), use many hazardous species, and produce problems in scale-up, especially with respect to safe and economic operation of full-scale reactors. Improving process selectivity is a key factor in attempts to reduce the consumption of raw materials and minimize the amount of wastes. Therefore, much attention has been paid to selectivity engineering and catalysis. The use of suitable catalysts for new processes requires a deep knowledge of catalysis principles. Therefore, in Chapter 3 an extended course on all kinds of catalysis is given with particular attention to heterogeneous catalysis. Many important catalytic processes for fine chemicals manufacture are described in Chapter 2 and many existing and developmental catalytic processes are also summarized in Chapter 3. Engineering tricks for selectivity manipulation (heterogenization of homogeneous catalysis, manipulation of the 'micro-environment' and 'macro-environment', the use of an additional liquid phase, and some other unconventional techniques) are presented extensively in Chapter 4.

In the past, chemical processes for the manufacture of fine chemicals were scaled up gradually, using many steps between the laboratory and the full-scale plant. This evolutionary way of process scale-up is still in common use because of a number of requirements imposed by GMP and FDA regulations. However, this method of process development is not very effective in the elimination of all risks at a full scale. Therefore, in this book much space is dedicated to process development (Chapter 5). A variety of tools for safe scale-up of chemical processes are presented, beginning with evaluation using process profile analysis (see Chapter 2). Scale-up strategies and techniques including economic evaluations at any stage of process development are described in Chapter 5. Chemical reactors, being the heart of chemical plants, are discussed in more detail in this chapter. Classification of reactors, the most common industrial reactors, and reactor design, scale-up, and operation problems are presented in brief. Basic thermodynamics and kinetics and mathematical modelling of chemical reactions and reactors are the rational basis for reactor scale-up and as such they are extensively discussed. The use of empirical mathematical models (tendency modelling) for design, analysis, and optimization of chemical reactors has been found to be a very useful tool for solving problems associated with fine chemicals manufacture. As such they are presented in more detail. Examples illustrating what sort of laboratory data are needed for these modern scale-up techniques are given. A number of reactions in fine chemicals manufacture are carried out in a semibatch mode by adding one of the reactants to the other components of the reaction mixture. Mixing then is often crucial for yield and, especially, selectivity. Both a theoretical approach to that problem and practical guidelines for laboratory chemists are given in Chapter 5 to help in the identification and solution of problems associated with mixing and chemical reactions. In the past, safety was a problem that was not tackled carefully enough, as illustrated by the disastrous Seveso incident and many other accidents in industry. Useful information on methods and data needed for safe scale-up of chemical reactors are also given in Chapter 5. Selection of the most appropriate type of chemical reactor concludes Chapter 5 on process development.

Separations for removing undesirable by-products and impurities, and making suprapure fine chemicals constitute a major fraction of the production costs. There is an enormous variety of methods for product separation and purification and many books on the subject have been published. Here, we deal with the problem in a very general way and we refer the reader to advanced books for details. Conventional techniques for product isolation and purification, such as fractional distillation, extraction, and crystallization, still predominate. Some guidelines for scale-up of these techniques and producing experimental data for scale-up are given in Chapter 5. More information on specific separation and purification techniques applied to particular problems of fine chemicals manufacture the reader can find in Chapter 6.

Chapter 7 on production plants starts with the description of plant types with particular attention given to multiproduct and multipurpose plants, which dominate in fine chemicals manufacture. This is intended to bring to life before mind's eyes of laboratory chemists what kind of constraints exists that must be taken into account when thinking about a new (still laboratory) process to be commercialized in such plants. Equipment in plants for the manufacture of fine chemicals is very much diversified and includes all types of chemical apparatuses and machinery. Such equipment is presented in many books on chemical, mechanical, and process engineering. In a brief presentation of the equipment we intend to draw the reader's attention to some very typical pieces of equipment and some special equipment that is particularly useful in fine chemicals manufacture only. Some economic data on chemical equipment are also given to extend economical thinking of laboratory chemists. In sections on plant design and production planning and scheduling we have described typical design and planning procedures that exemplify what kind of information from the laboratory is needed to specify appropriate equipment for a process under development or to compose optimal production plans and schedules. We believe that even experienced process engineers are not well acquainted with techniques used in design and planning/scheduling. Therefore, these are described in more detail in this chapter.

A book like the present one, which is not intended as a textbook for students, cannot be written by a single author. In fact, it is a multidisciplinary subject and the authors have not tried to omit all jargon and the flavour of the various disciplines involved. The consequence, of course, is that parts are not easy to understand for chemists, while others are difficult for chemical reaction engineers. It is hoped that this book will strongly contribute to bridging the gap between chemists and chemical engineers in the field. The authors will be grateful for comments from the readers.

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1. Introduction

1.1. CHARACTERISTIC FEATURES OF FINE CHEMICALS MANUFACTURE

Fine chemicals are products of high and well-defined purity, which are manufactured in relatively small amounts and sold at relatively high price. Although a question of taste, reasonable limits would be 10kton/year and $ 10/kg (Stinson, 1998, Section 2.1 of this book). Fine chemicals can be divided in two basic groups; those that are used as *intermediates* for other products, and those that by their nature have a specific activity and are used based on their *performance characteristics*. Performance chemicals are used as active ingredients or additives in formulations, and as aids in processing.

Fine chemicals form a group of products of large variety: their number exceeds 10,000. The size of the global fine chemicals market in 1993 was estimated at $ 42,000 million. The average annual growth in the period 1989-95 was about 4.5 % (Polastro *et al.*, 1990). Figure 1.1. shows the division of fine chemicals production by outlet.

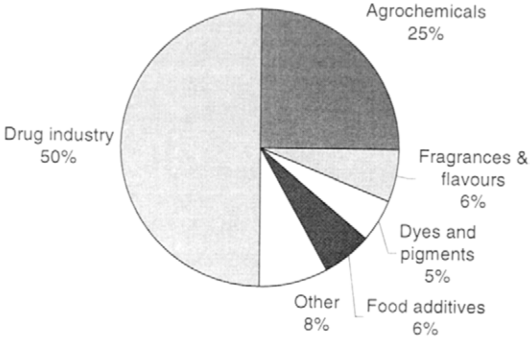

Figure 1.1. Outlets for fine chemicals.

Only 10 firms account for 75% of agrochemicals sales, while the 15 largest drug companies have a market share of only 33% (Stinson, 1995). About 85% of fine chemicals are manufactured by companies of the 'triad': the United States (28%), Western Europe (39%), and Japan (17%). Italy, with 4.0 million litres reactor capacity and 71 manufacturers, topped the European fine chemicals industry (Layman, 1993). Recently India, China, and Eastern-Central European countries have gained a significant proportion of the market, as a result of the lower direct labour costs and the more relaxed environmental and safety standards. It is fair to state that the high quality of chemists in these countries has also contributed to this development. In 1993, the cost of producing fine chemicals in India was 12% below that in Europe (Layman, 1993).

Production of pharmaceuticals is heavily concentrated in four countries, namely the USA, UK, Switzerland, and Germany (Pollak, 1998). Many companies active in fine chemicals business are rather small. Of course, there is no general rule for an optimal size. According to Stinson (1995) sales of companies producing fine chemicals should be at least $ 50 million per year to be able to afford the costs of quality control, environmental efforts and to run the plant profitably. This translates as follows: The minimum long-term economic size of a European fine chemicals producer would be about 85 to 90 people total, who would support a reactor capacity of about 120,000 litres (Layman, 1993). However, when these firms expand to, say, more than 500 people and annual sales of over $ 100 million, they might become too inflexible to respond to changes in customer and market needs, so it is not surprising that most compounds have sales below $ 10 million per year and form a network with several competing companies.

In recent years two trends have become visible in the manufacture of fine chemicals: (1) *custom synthesis*, and (2) specialization in groups of processes or products that are derived from specific raw materials (*chemical trees*).

Custom synthesis can be defined as the dedicated production for a single client, often using technology provided by the customers themselves. Custom chemicals world-wide are a $ 6000 million-per-year-business (Stinson, 1997). According to Illman's estimate about 40% of the world fine chemicals market is produced through contract manufacturing (Illman, 1995), half of which goes to the drugs industry. Custom manufacturing develops, among others, due to inflexibility of the bigger companies. However, experts are divided in their opinions about contract manufacturing: many of them see large companies with years of experience to be winners in contract manufacturing, while others insist that room for small specialists, particularly in the life sciences market, still exists. Mullin (1999) indicates that some of the fastest-growing contract manufacturers are large firms. For example, fine chemicals at DSM grew from 2% in 1987 to 25% of the company business in 1998. As is the trend in the Chemical Industry, this growth was achieved mainly through acquisitions: Andeno, Gist-Brocades, and businesses from Bristol Meyers Squibb and Chemie Linz.

Many companies specialize in the production of chemicals grouped in 'chemical trees' characterized by the same chemical roots (compounds) or the same/similar method of manufacturing. Examples are the Lonza trees based upon: (1) hydrogen cyanide, (2) ketene ($H_2C=C=O$) and diketene (4-methyleneoxetan-2-one), and (3) nitrogen heterocycles. A different type of tree is that of DSM Chemie Linz, which branches out from ozonolysis as the core technology (Stinson, 1996). Wacker Chemie has developed its chemical tree leading to acetoacetates, other acylacetates, and 2-ketones (Stinson, 1997). Table 1.1 shows examples of fine chemicals.

Processes in fine chemicals manufacture differ from processes for the manufacture of commodity chemicals in many respects (see also Chapter 2).

(1) A significant proportion of the fine chemicals are *complex, multifunctional large molecules*. These molecules are labile, unstable at elevated temperature, and sensitive towards (occasionally even minor) changes in their environment (e.g. pH). Therefore, processes are needed with inherent protective measures (e.g. chemical or physical quenching) or a precise control system to operate exactly within the allowable range. Otherwise the yield of the desired product can drop to nearly zero.

Table 1.1 Examples of fine chemicals

No.	Product	Nature of Industries	Catalytic (C) / Non-Catalytic (NC)[a]	Scale of Operation (tpa)	Type of Reactor[b]
1	Trimethylhydroquinone; Isophytol; Vitamin E	Vitamin	C (Homo; Het)	500 - 1000	STR
2	Methyl heptenone	Pharma; Aroma	NC & C (Het)	1000 - 2000	CR (nozzle)
3	Vitamin A (Wittig reaction)	Vitamin	NC	1000	CR (nozzle)
4	Isobutylbenzene Ibuprofen	Pharma Nonsteroidal analgestic	C (Homo; Het)	1000 - 3000	STR
5	Fenvalerate *p*-Hydroxy benzaldehyde	Agrochemical	C (PTC)	300 - 500	STR
6	*p*-Anisic aldehyde	Pharma; Aroma and Flavour; Agrochemical	C (Homo; Het)	1000 - 3000	STR; EC
7	Catechol; Hydroquinone	Agrochemical; Aroma and Flavour; Photography; Additives (antioxidants)	C (Homo) & NC	1000 - 5000	STR; BCR
8	p-Amino phenol	Pharma	C (Het) & NC	1000 - 5000	STR; EC
9	Isocyanates[c]	Pharma; Agrochemical; Rubber	NC	300 - 2000	STR
10	Citral	Aroma; Pharma	C (Het)	1000 - 3000	CR (short bed)
11	2,6-di-*tert*-butylphenol	Additives (antioxidants)	C (Homo)	1000 - 2000	STR
12	Phenylglycine/ p-hydroxy-phenyl glycine	Pharma	NC & C (Bio)	1500 - 2000	STR; CR
13	*p*-*tert*-butylbenzaldehyde; Benzaldehyde / Benzyl alcohol	Aroma; Pharma	C (Homo; Het)	1000 - 5000	STR
14	1,4 –dihydroxymethylcyclohexane	Polyester	C (Het)	5000	CR
15	Phenylethylalcohol	Aroma; Pharma	C (Homo; Het)	1000 - 3000	STR
16	Anthraquinone (AQ) and 2-alkyl AQ's	Dyes; H_2O_2; Paper	C (Het)	500 - 3000	STR
17	Indigo	Dyes	C (Het)	300 - 1000	STR
18	Diphenyl ether; *m*-phenoxy toluene	Aroma; Heat Transfer Fluids; Agrochemical	C (Het)	1000 - 10000	CR
19	Benzyl toluenes	Heat Transfer Fluids	C (Het)	500 - 2000	STR
20	*o*-, *m*-, and *p*-Phenylene-diamines	Dyes; Agrochemical; Aromatic Polyamide Fibres	C (Het)	1000 - 3000	STR
21	2,2,6,6-tetramethylpiperidinol	Additive (Light stabiliser)	NC & C (Het)	1000 - 2000	CR
22	Glyoxalic acid	Pharma	NC	500 - 2000	STR; BCR

[a] Homogenous (Homo); Heterogeneous (Het); Biocatalytic (Bio); Phase Transfer Catalysis (PTC).

[b] Stirred Tank Reactor (STR); Bubble Column Reactor (BCR); Continuous Reactor (CR); Electrochemical (EC).

[c] *e.g.*, *n*-propyl/*n*-butyl; cyclohexyl; p-isopropylphenyl isocyanate; isophorone diisocyanate; 1,5-naphthalene diisocyanate.

(2) Fine chemicals are high-added-value products. In general, expensive raw materials are processed to obtain fine chemicals, and therefore, the degree of their utilization is very important. With complex reaction pathways, *selectivity* is the key problem to make the process profitable. Selectivity is significant also because of difficulties in isolation and purification of the desired product from many side products, especially those with physico-chemical properties similar to those of the desired product (close boiling points, optical isomers, etc.). Furthermore, a low selectivity results in large streams of pollutants to be treated before they can be disposed of. Selectivity is even more an issue because in contrast with bulk chemicals production, where a limited single-pass conversion coupled with separation and recycling of unreacted raw materials is often applied, usually complete conversion is aimed at. Selectivity can be controlled by chemical factors such as chemical route, solvent, catalyst and operating conditions, but it is also strongly dependent on engineering solutions. *Catalysis* is the key to increasing the selectivity.

(3) In the manufacture of fine chemicals many hazardous chemicals are used, such as highly flammable solvents, cyanides, phosgene, halogens, volatile amines, isocyanates and phosphorous compounds. The use of hazardous and toxic chemicals produces severe problems associated with safety and effluent disposal. Moreover, fine chemistry reactions are predominantly carried out in batch stirred-tank reactors characterized by (i) a large inventory of dangerous chemicals, and (ii) a limited possibility to transfer the generated heat to the surroundings. Therefore, the risk of thermal runaways, explosions, and emissions of pollutants to the surroundings is greater than in bulk (usually continuous) production. That is why much attention must be paid to *safety, health hazards*, and *waste disposal* during development, scale-up, and operation of the process.

Fine chemicals are often manufactured in multistep conventional syntheses, which results in a high consumption of raw materials and, consequently, large amounts of by-products and wastes. On average, the consumption of raw materials in the bulk chemicals business is about 1 kg/kg of product. This figure in fine chemistry is much greater, and can reach up to 100 kg/kg for pharmaceuticals (Sheldon, 1994; Section 2.1). The high raw materials-to-product ratio in fine chemistry justifies extensive search for selective catalysts. Use of effective catalysts would result in a decrease of reactant consumption and waste production, and the simultaneous reduction of the number of steps in the synthesis.

(4) One of the most important features of fine chemicals manufacture is the great variety of products, with new products permanently emerging. Therefore, significant fluctuations in the demand exist for a variety of chemicals. If each product would be manufactured using a plant dedicated to the particular process, the investment and labour costs would be enormous. In combination with the ever changing demand and given the fact that plants are usually run below their design capacity, this would make the manufacturing costs very high. Therefore, only larger volume fine chemicals or compounds obtained in a specific way or of extremely high purity are produced in dedicated plants. Most of the fine chemicals, however, are manufactured in *multipurpose* or *multiproduct plants* (*MPP*s). They consist of versatile equipment for reaction, separation and purification, storage, effluent treatment, solvent recovery, and equipment for utilities. By changing the connections between the units and careful cleaning of the equipment to be used in the next campaign, one can adapt the plant to the intended process. The investment and labour costs are significantly lower for MPPs than for dedicated plants, while the flexibility necessary to meet changing demands is provided. The need for versatility of equipment originates from the great number of products in rather limited quantities to be manufactured in the plant every year. Such versatile equipment is suitable for all the processes, although it is

certainly not optimal. The most versatile reactors are *stirred-tank reactors* operated in batch or semibatch mode, so such reactors are mainly used in multiproduct plants. Continuous plants with reactors of small volume are sometimes used despite the small capacity required. This is the case when the residence time of reactants in the reaction zone must be short or when too much hazardous compounds could accumulate in the reaction zone.

From the foregoing it will be clear that in *fine chemicals process development* the strategy differs profoundly from that in the bulk chemical industry. The major steps are (i) adaptation of procedures to constraints imposed by the existing facilities with some necessary equipment additions, or (ii) choice of appropriate equipment and determination of procedures for a newly built plant, in such a way that procedures in both cases guarantee the profitable, competitive, and safe operation of a plant.

(5) The accuracy of analytical methods has increased enormously in the past decades and this has enabled detection of even almost negligible traces of impurities. The consequence is that both regulations and specifications for intermediates and final fine chemicals have become stricter. Therefore, very *pure compounds* must often be produced with impurities at ppm or ppb level. The production of complex molecules in many cases results in mixtures containing isomers, including optical isomers. The demand for enantiomeric materials is growing at the expense of their racemic counterparts, driven primarily by the pharmaceutical industry. Therefore, both *stereoselective synthesis* and effective, often non-conventional methods of *purification* (e.g. High Performance Liquid Chromatography (HPLC) and treatment under supercritical conditions) are in a wider use to meet the stricter requirements. The increasing need for optical purity, with complex and often not very effective methods of racemate resolution, stimulates the development of new stereoselective catalysts, including biocatalysts. In this respect, biotechnology is becoming a competitor to classical chemical technology.

All specialists involved in the business of fine chemistry should be aware of the characteristic features of fine chemicals and their manufacture. Obviously, the most important for the development of *new products* is chemistry, i.e. the choice of the most appropriate route to the desired product. The role of molecular modelling is growing, particularly in the field of performance chemicals. Chemistry is also crucial in developing or improving *processes* for the manufacture of fine chemicals. The chemistry of fine chemicals has been dealt with in many books and review papers. Therefore, only those chemical problems arising during process development will be emphasized that can contribute to solving problems of selectivity, environmental protection, safety, and optimization when commercializing the process, especially in existing multi-product plants.

The implications of the features of fine chemicals manufacture mentioned above, are, however, not that obvious to all parties taking part in process development. On the one hand, chemical and process engineers are dedicated mainly to the engineering part in process development, often neglecting process chemistry, as this might be erroneously considered less important for a full-scale plant. On the other hand, synthetic chemists often finish their work with laboratory recipes neglecting needs of procedures for process development. The reasons for this approach have been listed by Laird (1989):'

(1) research chemists are interested in the properties of the product, and how it is made on a small scale is of less importance,
(2) the synthetic route may be long (and therefore expensive),
(3) the raw materials and reagents may not be available in bulk quantities,
(4) the routes may not be stereospecific - in research the required isomer will often be isolated

by using a chromatographic step at the end,

(5) the reaction conditions may involve processes which are difficult to operate in standard plants - e.g. high pressure, very low temperatures,

(6) toxic reagents and intermediates, which are easy to handle on a gram scale, may prohibit working on a kilogram scale,

(7) exothermic reactions, which can be handled safely in the laboratory, are more difficult to control in a full-scale plant,

(8) effluents - easy to dispose of in the laboratory - are a serious consideration in process development. Heavy metal reagents, chlorinated solvents, toxic intermediates, etc. may have to be eliminated from the process before effluents can be safely treated. This subject is becoming very sensitive in Europe.'

This book deals with the problems neglected by laboratory chemists, having in mind needs of the process to be performed on a full scale. It is intended to form a bridge between specialists of various branches in the scale-up or modification of existing processes in fine chemistry, with both a minimum effort and risk and maximum profit when commercializing the process. The objective is to establish a good basis for the mutual understanding between chemists and engineers involved in R&D, design, and production planning in the fine chemistry business. To reach this objective, the following key ideas and technical issues associated with profitable, environmentally friendly, and intrinsically safe processes for the manufacture of fine chemicals will be discussed, i.e.

- catalysis and selectivity engineering as a means to increase selectivity and reduce production and/or emission of pollutants to the environment,
- process development with emphasis put on safe scale-up of chemical reactors with as high selectivity as possible,
- techniques for product isolation and purification yielding a product that will meet high quality requirements characteristic for fine chemicals, including combi-processes: reactor-separator systems (e.g. the reactor-distillation column) that have lower capital costs and lower separation costs, and
- implementation of new chemical processes and improvement of existing processes that will be realized in multipurpose plants typical for the fine chemicals manufacture.

1.2. CATALYSIS IN FINE CHEMISTRY

General aspects of catalysis are discussed in Chapter 3. Catalysis has been proven to be very effective in making processes faster, with a reduced number of synthetic steps, more selective, and characterized by simpler waste disposal and improved safety. Apart from increasing selectivity, the use of catalysts results in easier isolation and purification. Catalysts can be divided in homogeneous and heterogeneous catalysts or, depending on taste, in chemo- and biocatalysts. In terms of chemical performance, homogeneous catalysts are often quite satisfactory but they must be removed from process streams before disposing them to the surroundings. Heterogeneous catalysts can be separated from the product more easily, or even require no separation at all (fixed-bed reactors are very convenient reactors). When aged, the heterogeneous catalyst should be withdrawn from the reaction zone and replaced with a fresh or regenerated catalyst. Moreover, heterogeneous catalysts perform bifunctional functions better, which is advantageous in many applications. Therefore, heterogeneous catalysis simplifies processing downstream the reactor and can be used to make a process environmentally friendly. However, only 3% of all heterogeneous catalysts are used for the synthesis of fine chemicals, while 97% are used for the manufacture of bulk chemicals. Nevertheless, in terms of economics catalysis is already important: the 3% used accounts for approximately 20% of the profit in the fine chemicals sector. A book dedicated to heterogeneous catalysis in the production of fine chemicals has been published (Sheldon and van Bekkum, 2001).

Biocatalysts are distinguished from conventional catalysis due to their specificity originating from living organisms. Problems of chemo-, regio-, and stereoselectivity, and shape selectivity in both homo- and heterogeneous catalysis are presented. Zeolitic catalysts, cyclodextrins, and biocatalysts are extremely selective. Ion-exchange resins can also be advantageously used to catalyse a variety of reactions catalysed by acidic or basic functions. Clays as catalysts offer several advantages. Generally, catalytic activity of biocatalysts is not very high but some are very active allowing performing reactions under mild operating conditions.

Zeolites are receiving more attention also because of their integrated multifunctionality, i.e. the combination of the intrinsic zeolite properties of acidity and shape-selectivity with the additional function as support for active components. The well-defined micropore system of zeolites favours shape selectivity phenomena by allowing reactants to enter the zeolitic cage and product molecules of a given diameter to get out. The easy preparation of multifunctional zeolite catalysts provides a unique opportunity to combine individual reactions into a single synthetic step. Zeolitic catalysts can be accurately tailored to a highly selective process. Many useful and promising examples of zeolite catalysts in fine chemicals preparation already exist. Zeolites can be successfully applied for isomerizations, hydrogenations/dehydrogenations, aromatic substitutions, oxidations, cyclisations, skeletal rearrangements, and heterocyclic ring formation. For instance, when replacing conventional alkylation using Friedel-Crafts synthesis with zeolite-catalysed alkylation, much less wastes that are difficult to treat will be produced.

Effluents from conventional oxidations with classical stoichiometric inorganic oxidants, such as potassium dichromate and potassium permanganate, are very difficult to process and represent out-of-date chemistry. Replacement of conventional oxidations with catalytic oxidation using inexpensive and environmentally acceptable air as the oxidant is crucial. The same applies to hydrogenations using hydrides or the Wolf-Kizhner method with hydrazine. These methods of hydrogenation involve amounts of deleterious effluents and should be avoided.

Phase-transfer catalysis is a special type of catalysis. It is based on the addition of an ionic (sometimes non-ionic like PEG400) catalyst to a two-phase system consisting of a combination of aqueous and organic phases. The ionic species bind with the reactant in one phase, forcing transfer of this reactant to the second (reactive) phase in which the reactant is only sparingly soluble without the phase-transfer catalyst (PTC). Its concentration increases because of the transfer, which results in an increased reaction rate. Quaternary amines are effective PTCs. Specialists involved in process development should pay special attention to the problem of removal of phase-transfer catalysts from effluents and the recovery of the catalysts. Solid PTCs could diminish environmental problems. The problem of using solid supported PTCs seems not to have been successfully solved so far, due to relatively small activity and/or due to poor stability.

To rationally govern the selectivity of a catalytic process, the elementary reaction steps on real catalyst surfaces must be identified. The use of well-defined organometallic compounds (possible intermediates in surface reactions) can be very useful in the determination of these steps. The use of kinetic modelling techniques combined with statistical analysis of kinetic experiments is recommended to verify hypotheses postulated based on the general knowledge of chemistry considered or on experiments of all kinds performed.

1.3. SELECTIVITY ENGINEERING

Intelligent engineering can drastically improve process selectivity (see Sharma, 1988, 1990) as illustrated in Chapter 4 of this book. A combination of reaction with an appropriate separation operation is the first option if the reaction is limited by chemical equilibrium. In such combinations one product is removed from the reaction zone continuously, allowing for a higher conversion of raw materials. Extractive reactions involve the addition of a second liquid phase, in which the product is better soluble than the reactants, to the reaction zone. Thus, the product is withdrawn from the reactive phase shifting the reaction mixture to product(s). The same principle can be realized if an additive is introduced into the reaction zone that causes precipitation of the desired product. A combination of reaction with distillation in a single column allows the removal of volatile products from the reaction zone that is then realized in the (fractional) distillation zone. Finally, reaction can be combined with filtration. A typical example of the latter system is the application of catalytic membranes. In all these cases, withdrawal of the product shifts the equilibrium mixture to the product.

The rates of multiphase reactions are often controlled by mass transfer across the interface. An enlargement of the interfacial surface area can then speed up reactions and also affect selectivity. Formation of micelles (these are aggregates of surfactants, typically 400-800 nm in size, which can solubilize large quantities of hydrophobic substance) can lead to an enormous increase of the interfacial area, even at low concentrations. A qualitatively similar effect can be reached if microemulsions or hydrotropes are created. Microemulsions are colloidal dispersions that consist of monodisperse droplets of water-in-oil or oil-in-water, which are thermodynamically stable. Typically, droplets are 10 to 100 μm in diameter. Hydrotropes are substances like toluene/xylene/cumene sulphonic acids or their Na/K salts, glycols, urea, etc. These substances are highly soluble in water and enormously increase the solubility of sparingly soluble solutes.

The proper use of solvents is crucial for selectivity in fine chemical processes, both homo- and heterogeneous ones. It has been claimed that phenols can be chlorinated in aprotic solvents to give the *ortho* product selectively in the presence of a small amount of an amine. *Para* chlorination of phenol is favoured by the presence of diphenylsulphide.

As another example, hydrogen solubility can play an important role in catalytic hydrogenations. Dielectric constants can be important when polar groups are present in the reaction mixture. The stereoselectivity of the hydrogenation on a cyclic molecule containing a polar group can be controlled by the hydrophyllic-hydrophobic interactions between solvent, substrate and catalyst support. Polar solvents such as DMF (N,N-dimethylformamide), DMSO (dimethylsulphoxide) or NMP (N-methylpyrrolidone) can interact strongly with polar groups in the compound to be hydrogenated. Hydrogenation will then take place in a position different from that when a non-polar hydrophobic solvent (e.g. hexane) is used. The polar group will then tend to chemisorb on the catalyst, provided that it is more polar than the solvent.

Solvent acido-basicity can also play a role. For instance, acidity of the solvent favours hydrogenolysis, while basicity of the solvent limits hydrogenolysis when hydrogenation competes with hydrogenolysis. A solvent can modify chemisorption, thus influencing selectivity.

1.4. PROCESS DEVELOPMENT

Process development with particular attention to process profitability and safety and minimization of the environmental impact is presented in Chapter 5. A brief description of the present practice in scale-up, development, and production planning is given and the most promising trends and achievements are presented. Recommendations are given how to achieve success in the scale-up of a process: a successful scale-up can be defined as the procedure that allows the same yields and product distribution in a full-scale plant as on a small scale.

Before detailed engineering studies are started the chemical route chosen should be verified taking two aspects into account:

- often impurities in the raw materials can influence the process selected, and
- by-products recycled to the process can act as impurities, with the same consequences.

Accordingly, after laboratory experiments using chemically pure reagents have been completed, technical grade raw materials from different sources should be tested to find out whether their contaminants affect yields, selectivities and isolation/purification procedures. If recycling is suggested, the effect of recycled streams on yields, selectivities and isolation/purification procedures should be identified. The testing for recycled streams of increasing quality should be continued until no influence is found. Recycling of solvents and unconverted raw materials can greatly influence technology and cost of separation.

Ideal procedures require a detailed knowledge of process mechanisms to minimize the risk of the scale-up to a profitable and environmentally friendly process. However, this would need a long time within which competitors may have started production using non-optimal and risky but already profitable methods. This is the reason why so many products appear on the market relatively quickly, while the procedures are optimized later. This is not specific for fine chemistry. The Haber-Bosch high-pressure ammonia synthesis was put on stream at the beginning of this century. The mechanism of catalytic conversion of hydrogen and nitrogen into ammonia is still subject of debate! Subsequent steps on the route to deeper understanding of all the chemical and physical phenomena and quantification of experimental observations have led to significant improvements of the process. The evolution of ammonia synthesis to the present highly safe and efficient process took several decades.

Both the changing demand for fine chemicals and the need for competitiveness force companies to develop new products and processes within a very limited amount of time and with the least possible cost. Moreover, the great complexity of chemical reactions and the great variety of options in the choice of chemical and process routes make the ideal process impossible to achieve even if time and money available would not be restrictive. When studying a process for the production of fine chemicals, we have to stop the research at a certain level of process understanding to get a profitable process on stream. The aim of further research will be to improve the existing process to approach the process optimum. This approach is very common in all kinds of industries. If Ford had waited till his car had been optimized he would have gone bankrupt and his competitors would have earned all profits he has now gained. The design and manufacturing methods of cars have been improved step by step over decades with deepening knowledge about the processes of fuel burning, aerodynamics, etc. More science has been involved to improve the empirical (from our present viewpoint) Ford T-4. Modern car engines have been designed based upon detailed knowledge about mechanisms and kinetics of fuel oxidation. A new chassis is designed using a computer program to minimize drag forces and consequently decreases fuel consumption. New space vehicles have been developed using much more science from the very beginning. Quantitative models for all significant phenomena occurring in the vehicle have been developed. An empirical, evolutionary way of developing space vehicles would be more costly and more risky.

Progress in numerical methods and computer science has made user-friendly mathematical/computer tools available. Because of this, search for better chemical processes can be speeded up. Obviously, we have to stop at the degree of detail in process/equipment modelling that is allowed by time and money restrictions. Nevertheless, due to the progress in optimization techniques this degree has now shifted much to a better quantitative description (mathematical model) of chemical processes. This is one of the most important ways to develop more efficient processes for fine chemicals. Probably, the most important in this field will always be the detailed knowledge of process chemistry and this will certainly be the basis of all fine chemistry processes. Some present processes for the manufacture of performance fine chemicals (e.g. pheromones) even seem to be based on alchemy: specifications for raw materials include a source of the raw material instead of a full description of physico-chemical characteristics. Mathematical modelling has proven to be very effective in many cases in the chemical industry. Therefore, it is strongly advised that specialists involved in R&D for fine chemicals get acquainted with these methods, at least to become aware of how to advantageously modify their activities in this field.

The volume scale-up is straightforward if:

- the ratio of external surface of the reaction zone to its volume does not limit heat transfer or vapour-liquid characteristics, i.e. the desired temperature profile is achievable and gas/vapour dissolution or evolution does not pose any process constraint,
- reactor performance is not affected by mixing, and
- time of feeding reactant(s) does not influence yields and selectivity.

Establishing the process sensitivity with respect to the above-mentioned factors is crucial for further scale-up considerations. If the sensitivity is low, a direct volume scale-up is allowed and the use of standard batch reactor configurations is permitted. However, many reactions are characterized by a large thermal effect and many molecules are very sensitive to process conditions on molecular scale (pH, temperature, concentrations, etc.). Such processes are much more difficult to scale up. Mixing can then become a very important factor influencing reactor performance; for reactions where mixing times and reaction times are comparable, micromixing also becomes important.

For complex reaction systems the establishment of a reliable kinetic network and accompanying parameters is often difficult or even impossible. Paul (1988, 1990) has categorized complex systems of fine chemistry reactions in the following way:'

> (1) reactions that require resolution of kinetic problems to be run successfully in the laboratory,
> (2) reactions that can be run successfully in the laboratory but require special plant design considerations and equipment, and
> (3) reactions that pose both special laboratory and scale-up problems.'

It might be difficult to classify a reaction in any of these categories in the laboratory stage if no preliminary experience in scale-up has been gained. Reactions of the first type can only be run with satisfactory selectivity if a kinetic model has been established which does correspond at least to the gross process mechanism. When searching for the best operating conditions for the second class, a kinetic model is useful but not always necessary. Experimental techniques in kinetic studies and methods of processing kinetic data are presented in Chapter 5. Bearing the complexity of reaction systems in fine chemistry in mind, methods for obtaining simplified kinetic models such as tendency models are discussed.

Most accidents in the chemical and related industries occur in batch processing. Therefore, in Chapter 5 much attention is paid to theoretical analysis and experimental techniques for assessing hazards when scaling up a process. Reaction calorimetry, which has become a routine technique to scale up chemical reactors safely, is discussed in much detail. This technique has been proven to be very successful also in the identification of kinetic models suitable for reactor optimization and scale-up.

What is very important in process development is the personnel overlap when changing the scale of the process. The head of the team that is to continue the development of a process should be involved in the research on smaller scale. Also, an important member or head of the team in the smaller scale research should participate in the further step(s) of process development. Often, a parallel operation of teams is required instead of operation in series. A pilot plant, mostly composed of existing equipment items in a company, is often required as the final step in process development. A verification of procedures and models is usually not necessarily the main objective of pilot studies. The most common reason for manufacture at pilot scale is the production of kilograms of the product for market purposes and toxicity tests. A close interaction between chemists and chemical engineers is necessary at all stages of process development.

1.5. SEPARATION METHODS

A major fraction of the costs of production of a desired chemical is constituted by separations for removing undesirable by-products and impurities. Certainly we should aim at making reactions more selective and obtaining higher conversions, provided there are no thermodynamic or kinetic constraints. Many strategies to improve selectivity are discussed in Chapters 3 and 4, and to preserve the maximum laboratory selectivity when scaling up the process - in Chapter 5. Side reactions, especially those leading to stereo-isomers and introducing impurities into the reaction zone are, however, almost unavoidable. Therefore, isolation and purification techniques constitute a substantial part of the technology for the manufacture of fine chemicals. Conventional techniques for product isolation and purification, such as fractional distillation, extraction and crystallisation, still predominate. This particularly applies to multipurpose plants that are not equipped with non-standard equipment.

Recently unconventional methods in purification have been gaining recognition for full-scale purification, especially when a very high purity is required. Sorption techniques have been used in the laboratory for years. HPLC using conventional solid sorbents, possibly modified using the latest achievements of supramolecular chemistry, e.g. cyclodextrins, calixarenes, and ion-exchange resins have been implemented on a full scale for years. The same applies to reverse osmosis, sophisticated filtration techniques (micro-, ultra-, and nanofiltration), extractions using highly selective but expensive solvents such as crown ethers or supercritical liquids, other adsorptive and membrane separations, etc. Information on separation techniques is spread over this book. Guidelines for scale-up of basic separation and purification techniques with a brief presentation of their physical principles are presented in Chapter 5, while Chapter 6 mainly deals with arbitrarily chosen unconventional techniques.

1.6. PRODUCTION PLANTS

Plants for the manufacture of fine chemicals are discussed in Chapter 7 with emphasis put on multiproduct plants. Types of production plants and typical equipment for multiproduct plants with cost considerations are presented in more detail. Problems of designing and scheduling multiproduct and multipurpose plants with particular emphasis given on process data needed to realise this task are discussed.

Multipurpose/multiproduct plants are in very common use, due to their flexibility. Also safety considerations are important in deciding on the use of multipurpose equipment in which hazardous materials are confined for all processing steps such as reaction, crystallization, filtration, etc. Unsophisticated products, which dominate in the field of intermediates, can be successfully manufactured in such plants for a very long time. More sophisticated products, especially those of high purity may need abandoning of the multipurpose versatility in favour of apparently more expensive dedicated plants. 'Apparently' because costs of running the process for the sophisticated product in an existing multipurpose plant might be higher than in a new but much smaller plant that is well adjusted to the process requirements. Driving away from the principle of batch production might be stopped in the case of product families that are manufactured in a similar way and for which quality requirements are similar.

Batch production is predominant in fine chemicals manufacture. Continuous production is preferred, however, if:

- the batch size becomes too large demanding huge reactors and/or other equipment items to complete manufacturing in a reasonable time,
- there are kinetic restrictions, e.g. reaction is fast and might occur to a significant extent under unfavourable conditions when charging/adding reactants into a reactor or heating them up to the pre-set temperature,
- safety requirements impose minimizing in-process inventory of potentially hazardous reagents and this inventory is smaller in continuous reactors, and
- the rate of heat generation very much exceeds that of the heat removal to the surroundings.

Mixed plants combining batch and continuous units are gaining popularity. Reactions in these plants are run in a batch mode while unit operations such as distillation are run continuously.

Regulations issued by state agencies such as FDA of the USA force manufacturers of fine chemicals to design and organize production of fine chemicals following requirements of the agencies. Basic requirements for the GMP (Good Manufacturing Practice) are also described in brief in Chapter 7.

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2. Fine Chemicals and their Synthesis; a Chemical Point of View

2.1. WHAT ARE FINE CHEMICALS?

There are no universally accepted definitions of bulk, fine, and specialty chemicals, nor are these classifications based on any intrinsic properties. For example, a substance that is currently viewed as a bulk chemical may well have been classified as a fine chemical at an earlier stage in its development.

A useful way of classifying chemicals is shown in Fig. 2.1. Chemicals are divided on the basis of volume and character. Bulk chemicals, or commodities, are produced in large quantities and sold on the basis of an industry specification. There is essentially no difference in the product from different suppliers. Typical examples would be acetone, ethylene oxide, and phenol. Pseudo commodities are also made in large quantities but are sold on the basis of their performance. In many cases the product is formulated and properties can differ from one supplier to another. Examples include large volume polymers, surfactants, paints, etc.

Similarly, low volume chemicals are classified according to whether they are sold primarily on the basis of specification or performance. Specialties are generally formulations that are sold on the basis of their performance and their prices reflect their value rather than cost of production. Producers of specialty chemicals often provide extensive technical service to their customers. Examples of specialty chemicals include pharmaceuticals, pesticides, flavours and fragrances, specialty polymers, etc. Fine chemicals, on the other hand, are produced to customer specifications and are often intermediates or active ingredients for specialty chemicals, e.g. pharmaceutical and agrochemical intermediates and bulk actives.

⇑ VOLUME	COMMODITIES BULK-SPECIFICATION	PSEUDO-COMMODITIES BULK-PERFORMANCE
	FINE-CHEMICALS NONBULK-SPECIFICATION	SPECIALTIES NONBULK-PERFORMANCE
	CHARACTER ⇒	

Figure 2.1. Classification of chemicals.

Where is the dividing line between bulk and fine chemicals? Here again there is no universally accepted definition. Nonetheless, *a useful definition of a fine chemical is one with a price of more than 10 US dollars/kg and a volume of less than 10,000 tons per annum.* The latter is rather a large volume for most fine chemicals, e.g. most pharmaceutical intermediates are produced in quantities of less than 100 tons per annum. In practice, the type of technology used is probably more dictated by volume than by product application.

Fig. 2.2 illustrates the three types of chemicals by reference to the production of the semi-synthetic penicillin antibiotic, ampicillin.

From a chemical viewpoint, fine chemicals are generally complex, multifunctional molecules, and, consequently, often have low volatility and limited thermal stability. This implies that processes are generally performed in the liquid phase.

BULK CHEMICALS	⇒	FINE CHEMICALS	⇒ SPECIALTIES
Toluene	⇒	*D*-Phenylglycine	⇒ Formulated ampicillin
Glucose		6-Aminopenicillanic acid (6-APA)	
		Bulk ampicillin	
		Price > USD 10/kg Volume < 10,000 tpa	

Figure 2.2. Fine chemicals in ampicillin production.

2.2. HISTORICAL DEVELOPMENT OF ORGANIC SYNTHESIS

The term ‘organic chemistry’ was first used by the Swedish chemist Berzelius in 1807 (Larsson, 1981). He coined the name to describe the chemistry of substances derived from living matter. Berzelius was a staunch believer in the *vis vitalis* theory, which held that such substances were endowed with a mystical ‘vital force’ that precluded their synthesis in the laboratory from materials of mineral origin. Ironically, it was a student of Berzelius, Wöhler, who heralded the demise of vitalism with his synthesis of urea from ammonium cyanate (Wöhler, 1928). In a letter to Berzelius in 1828, Wöhler wrote: “I must tell you that I can make urea without requiring kidneys, or even an animal, whether a human being or a dog”.

Nevertheless, the vitalists were not easily convinced, and it took a few decades before the *vis vitalis* theory was finally laid to rest. The final nail in its coffin may have been provided by Kolbe’s synthesis of acetic acid from its constituent elements in 1845 (Kolbe, 1845).

The synthesis (Fig. 2.3) is a perfect example of what is wrong with many organic syntheses: it is circuitous, energy and raw materials intensive, generates copious amounts of waste, and involves intermediates that are smelly, hazardous and/or carcinogenic.

Nonetheless, Kolbe achieved his goal of proving that vitalism was untenable by designing and executing a logical synthesis of a natural organic substance from the elements.

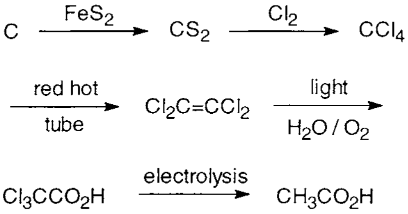
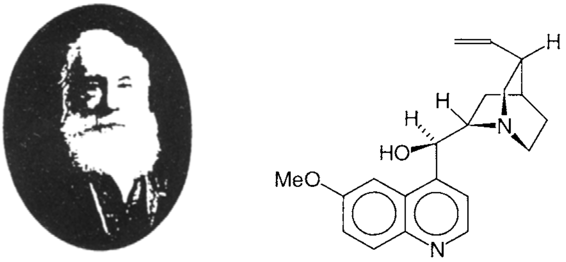


Figure 2.3. Kolbe's synthesis of acetic acid.

The next milestone in the development of organic synthesis was the preparation of the first synthetic dye, mauveine (aniline purple) by Perkin in 1856 Perkin, 1856, 1862). This is generally regarded as the first industrial organic synthesis. It is also a remarkable example of serendipity. Perkin's goal was the synthesis of the antimalarial drug quinine by oxidation of N-allyl toluidine (Fig. 2.4).



W.H. Perkin
Quinine synthesis (1856)

Quinine

Concept:

$$2\,C_{10}H_{13}N + 3\,\text{"O"} \xrightarrow{K_2Cr_2O_7} C_{20}H_{24}N_2O_2 + H_2O$$

Allyl toluidine — Quinine

Figure 2.4. Perkin's attempted synthesis of quinine.

This noble but naive attempt – bearing in mind that only the molecular formula of $C_{20}H_{24}N_2O_2$ was known at the time – was doomed to fail. In subsequent experiments with aniline, which was fortunately contaminated with toluidines, Perkin obtained a purple product in low yield. Perkin was quick to recognize the commercial potential of his findings: the natural dye, Tyrian purple, which was extracted from a species of Mediterranean snail, cost more per kilogram than gold in 1856. Within a few years the first commercial plant for the production of mauveine was in operation.

This serendipitous discovery marked the beginning of the synthetic dyestuffs industry, based on coal tar as its main raw material, which is, incidentally, a waste product from another industry, steel manufacture. The development of mauveine was followed by efficient syntheses of natural dyes such as alizarin in 1869 (Graebe and Liebermann, 1869), and indigo in 1878 (Bayer, 1878; Heumann, 1890). The synthetic production of these dyes marked the demise of the agricultural production of these materials and the advent of a science-based, predominantly German chemical industry. The present-day fine chemicals and specialties, e.g. pharmaceuticals, industries developed largely as spin-offs of this coal tar-based dyestuffs industry.

In the first half of the twentieth century, further advancements in organic synthesis led to many elegant total syntheses of natural products, noteworthy examples being Robinson's synthesis of tropinone (Robinson, 1917) and, almost a century after Perkin's unsuccessful attempt, the total synthesis of quinine by Woodward and Doerring in 1944 (Corey and Cheng, 1989). In the 1950s and 1960s, classical organic synthesis evolved almost into an art form. The total synthesis of vitamin B12 by the groups of Woodward and Eschenmoser (Corey and Cheng, 1989) is generally regarded as the intellectual pinnacle of this period. More recently, organic synthesis has risen to even higher levels of sophistication and organic chemists have undertaken syntheses of natural compounds of ever increasing complexity. A prime example is the anticancer drug, Taxol (Borman, 1992), which is derived from the bark of the Pacific yew tree, *Taxus brevifolia*. Taxol (see Fig. 2.5), and is composed of 12 asymmetric carbon atoms, which means that organic chemists must devise a synthesis that produces the correct isomer of the 2^{12} or 4096 possible stereoisomers, a formidable task.

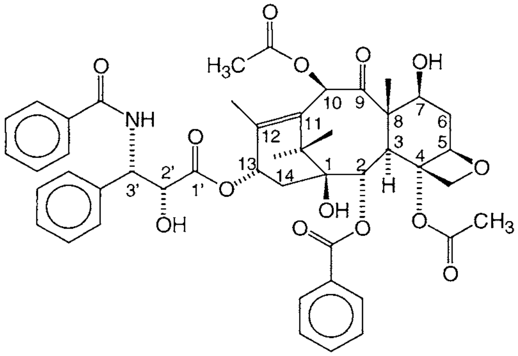


Figure 2.5. Structure of Taxol.

2.3. FINE CHEMICALS VS. BULK CHEMICALS MANUFACTURE

Characteristic features of bulk versus fine chemicals manufacture are shown in Table 2.1. Fine chemicals manufacture often involves multi-step syntheses and is generally performed batch-wise in multi-purpose equipment. This contrasts with bulk chemicals manufacture, which generally involves continuous processing in dedicated plants.

Table 2.1
Characteristics of bulk versus fine chemicals manufacture

	Bulk	Fine
Volume (tpa)	> 10,000	< 10,000
Price ($/kg)	< 10	> 10
Added value	low	high
Lifecycle	long	relatively short
Processing	continuous	batch-wise
Plants	dedicated	multi-purpose
Raw materials quote	relatively high	relatively low
Labour costs/kg product	low	high
Capital investment/kg product	high	even higher
Flexibility	low	high
Waste per kg product	relatively low	high

The cost price of a bulk chemical is determined primarily by the cost of raw materials, which could represent > 80% of the total costs. Process development/improvement in bulk chemicals is, hence, focused on decreasing these variable costs, e.g. for a product with a volume of 100,000 tpa and a raw materials quote of $ 2/kg, 1% increase in yield corresponds to savings of $ 2 million per annum. In fine chemicals, in contrast, emphasis is placed on the reduction of fixed costs, which are relatively high, by process simplification. For example, for a product with a volume of 100 tpa and fixed costs of $ 40/kg, if the volume yield (amount produced per unit reactor volume) is doubled, this corresponds to savings of $ 2 million per annum.

2.4. PROCESS SELECTION: PROCESS PROFILE ANALYSIS

Alternative processes to a particular product can be compared using the method of *process profile analysis* introduced by Berkoff and co-workers at SK&F in the 1980s (Berkoff *et al.*, 1986). They noted that the cost of goods supplied (CGS), which reflects the cost of raw materials, energy, and labour charges, is woefully inadequate in assessing the total impact of a new chemical process. Process profile analysis also addresses other issues, such as capital investment, patent and licensing considerations, and environmental and occupational risks and hazards. It is not uncommon that a process having an acceptable CGS proves to be unacceptable for some other reasons.

In process profile analysis, points are awarded to processes in the following categories:

- Operating costs
- Capital investment
- Process control
- Risks to personnel and plant
- External factors

The critical issue is how much weight to assign to the various parameters. This is obviously debatable and, to a certain extent, a moving target. The method was developed in the 1980s, and probably less emphasis is placed on environmental issues than if it were developed today. The score awarded for particular parameters is also influenced by the so-called volume value factor (VVF) which relates to the size of the business and is given by:

$$\mathrm{VVF} = \frac{(\mathrm{kg/yr})^{*} \times \$/\mathrm{kg}}{10^3} \qquad (1)$$

High:	VVF	> 70
Medium:	VVF	10-69
Low:	VVF	< 10

[*] In the 5th year of production.

The category operating costs is divided into various sub-categories that can be awarded a maximum number of points, which depends on the VVF (see Table 2.2).

Table 2.2
Operating costs analysis

Parameter	Maximum score by VVF class		
	High	Medium	Low
Raw materials costs/kg product	16	13	10
Yield efficiency 'average yield' of all steps	15	13	10
Throughput time Time for 1 cycle through all steps	10	9	8
Throughput volume Reactor space/kg product	9	8	7
Subtotal	50	43	35

For example, the score for raw materials costs varied from 16 for < $ 30/kg to 0 for > $ 2,000/kg for a high VVF product. The yield efficiency score represented a combination of points for overall yield ranging from 7 for > 86% to 0 for < 1 and average yield per step, ranging from 8 for > 92% to 0 for < 49% (for high VVF).

Similarly, tables can be constructed to award points based on throughput time and throughput volume (Berkoff *et al.*, 1986).

Two parameters determine the points awarded in the capital investment category: total number of steps and whether or not special equipment is needed (Table 2.3).

Table 2.3
Capital investment analysis

Parameter	Maximum score by VVF class		
	High	Medium	Low
Total number of steps	4	6	8
Special equipment/technology	2	7	12
Subtotal	6	13	20

For example, for a high VVF product the score varied from 4 for < 4 steps to 0 for > 10 steps. The special equipment score was obtained by subtracting points, from a basis score, for each item of specialised equipment not adaptable to other processes.

The process control score was determined by three parameters: reproducibility, tolerance to abuse and linearity of the reaction sequence (Table 2.4).

Table 2.4
Process control analysis

Parameter	Maximum score by VVF class		
	High	Medium	Low
Reproducibility Reproducible yields in each step	6	4	3
Tolerance to abuse Minimal need for critical control	6	4	3
Linearity of reaction sequence	2	2	3
Subtotal	14	10	9

To obtain the reproducibility score, for a high VVF product, two points were subtracted from the basic score of six for each step that exhibited more than 5% variation in yield per batch. Convergent or branched syntheses, in contrast with a linear sequence, allow for simultaneous processing of the branches, which improves scheduling flexibility and reduces risk of batch loss.

The category risks to personnel and plant consists of two parts: environmental abuse potential and occupational health/safety hazards and, here again, points are subtracted from a basic score for environmental/safety hazards.

Finally, the category external factors consists of three parts – raw material availability, susceptibility to regulatory changes and patent protection – for which points are awarded, up to a maximum of 14 for a high VVF product.

The maximum scores for the five categories are summarised in Table 2.5.

Table 2.5
Process profile analysis: process parameter categories

Parameter	Maximum score by VVF class		
	High	Medium	Low
Operating costs	50	43	35
Capital investment	6	13	20
Process control	14	10	9
Risk to plant and people	16	21	24
External factors	14	13	12
Subtotal	100	100	100

An example of the application of process profile analysis was provided by Berkoff and co-workers (Berkoff *et al.*, 1986). It concerned the synthesis of 7,8-dichloro-1,2,3,4-tetrahydro*iso*quinoline (**1**) according to the two step sequence shown in Fig. 2.6.

The estimated volume was 20,000 kg per annum with a cost estimate of $ 170/kg, which translates to a VVF of 3.4, i.e. a low VVF category product. An evaluation of the process shown in Fig. 2.6 led to a score of 72 points, the distribution of which is shown in Table 2.6.

The process profile is presented as a bar chart, with a separate bar for each parameter. The width of each bar reflects the relative importance of a parameter's maximum impact. The bar chart highlights process strengths and weaknesses. This is illustrated in Fig. 2.7, which shows the process profile for **1**. It is immediately apparent that the weakness of the process is its environmental abuse potential.

The first step uses 59 kg of ingredients (including solvents, acids and bases, etc.) per kg of final product. The second step uses 115 kg of ingredients and generates large volumes of aluminium-containing waste. This results in a score of 0 for this parameter. As noted above, in today's climate of increasingly stringent environmental regulation this point alone may be enough to prohibit the use of the process for large-scale production. This highlights the importance of how much weight is assigned to the various parameters in process profile analysis.

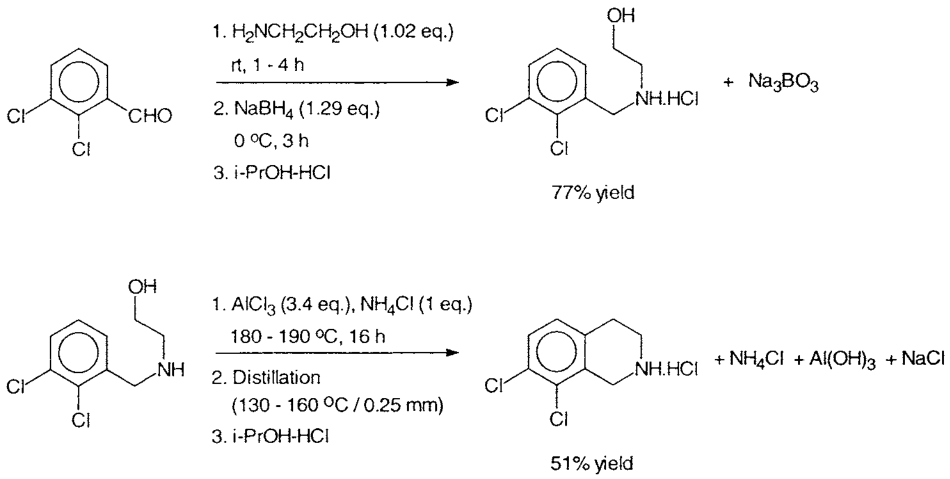


Figure 2.6. Synthesis of 7,8-dichloro-1,2,3,4-tetrahydroquinoline.

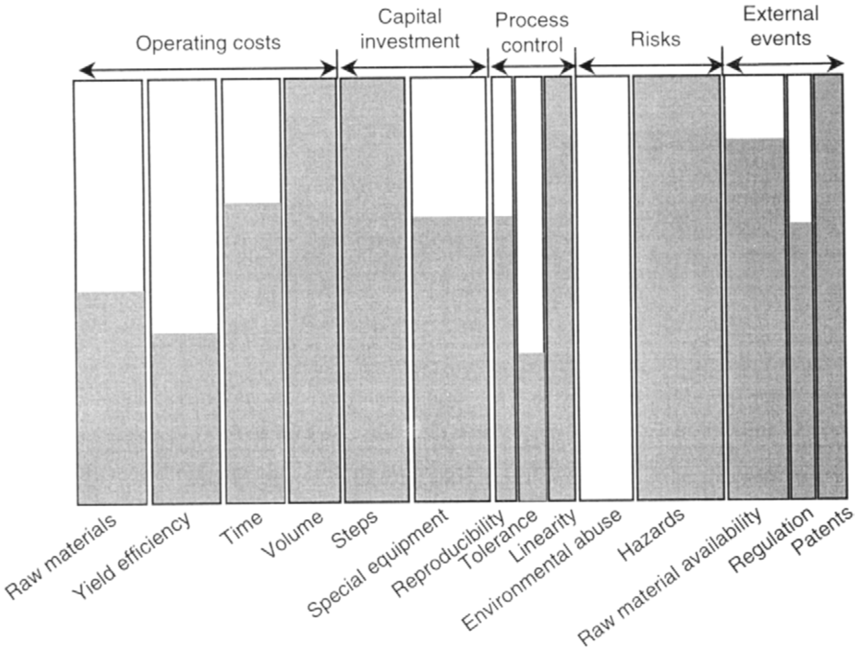


Figure 2.7. Process profile.

Table 2.6
Process profile analysis of **1** manufacture

Parameter	Score
• Raw materials quote ($ 143/kg)	5
• Yield efficiency (overall yield = 39%; average = 64%)	4
• Throughput time (14 h)	6
• Throughput volume (34 L/kg)	7
• Number of steps (2)	8
• Special equipment (temp. > 180 • C)	8
• Reproducibility	2
• Tolerance to abuse	1
• Linearity	3
• Environmental abuse potential	0
• Health/safety hazards	17
• Raw material availability (multiple suppliers)	7
• Susceptibility to regulatory changes (chlorinated compounds, -1)	2
• Patent protection (full patent coverage available)	2
Total score	72

2.5. FACTORS INFLUENCING PROCESS CHOICE: CLEANER AND SAFER TECHNOLOGIES

Organic synthesis is currently faced with a dichotomy. Laboratory-scale organic synthesis, on the one hand, has evolved to a level of sophistication that allows for the synthesis of extremely complex natural products such as Taxol (see earlier). On the other hand, these 'elegant' synthetic methodologies are largely unsuitable for large-scale production: they are circuitous, generate too much waste, and employ too many toxic and/or hazardous materials. Increasingly stringent environmental and safety legislation is stimulating chemical manufacturers to develop alternative technologies that produce a minimum amount (preferably zero) of waste and avoid, as much as possible, the use of toxic and/or hazardous reagents and solvents (Sheldon, 1992, 1992a, 1993, 1994, 1996, 1997, 1997a).

Zero emission plants, environmentally benign or green chemistry, and sustainable development have become the catch phrases of the 1990s (Anastas and Farris, 1994; Anastas and Warner, 1998; Anastas and Williamson, 1998; Clark, 1995). Consequently, traditional concepts of process efficiency are changing from an exclusive focus on chemical yields to one that assigns economic value to eliminating waste and avoiding the use of toxic and/or hazardous chemicals. Emphasis is clearly on the reduction of waste at the source – primary pollution prevention – rather than incremental end-of-pipe solutions. As we approach a new millennium, enviro-economics have become a major driving force in technological innovation.

2.6. E FACTORS AND ATOM UTILIZATION

The urgency of the need for waste reduction is readily appreciated by considering the amount of waste generated per kg product, designated as the E factor solvents (Sheldon, 1992, 1992a, 1993, 1994, 1996, 1997, 1997a) in various segments of the chemical industry (Table 2.7).

Table 2.7
The E factor

Industry segment	Product tonnage[a]	kg waste[b]/kg product
Oil refining	10^6-10^8	<0.1
Bulk chemicals	10^4-10^6	$<1-5$
Fine chemicals	10^2-10^4	$5->50$
Pharmaceuticals	$10-10^3$	$25->100$

[a] Typically represents annual production volume of a product at one site (lower end of range) or world-wide (upper end of range).

[b] Defined as everything produced except the desired product (including all inorganic salts, solvent losses, etc.).

We define waste as everything that is produced during operation of the process, except the desired product. The waste is predominantly comprised of inorganic salts, e.g. sodium chloride, sodium sulphate and ammonium sulphate, formed in the reaction or subsequent neutralization steps, or derived from stoichiometric inorganic oxidants, reducing agents, etc. An illustrative example from the bulk chemicals arena is caprolactam: for every kg of caprolactam produced (see later) roughly 4.5 kg of ammonium sulphate are generated.

The substantial increase in E factors on going downstream from bulk chemicals to fine chemicals and specialties is a reflection of the more widespread use of stoichiometric reagents and multi-step syntheses in the latter sectors. Fine chemicals manufacture is the domain of the synthetic organic chemist who traditionally used the time-honoured classical reactions of organic synthesis. Such reactions were originally developed primarily with emphasis on optimisation of product yield with little regard for the production of inorganic waste or the hazardous nature of reagents and solvents. Many of these reactions originate from the first half of this century, or even the last century, and are totally inadequate for today's environmentally conscious climate.

Put in another way, the E factor represents the ratio of 'kilos in to kilos out'; *i.e.* it is the mass balance or the weight ratio of all the raw materials, including solvent losses, to the amount of desired product. It can be readily calculated for a particular product line, production site, or even a whole company. It is quite amazing, therefore, that so few companies are aware of what their E factor is. Indeed, the concept of process efficiency is usually applied to the utilization of the key organic raw material. Optimisation of this parameter may unwittingly result in a deterioration of the E factor of the process.

The key to minimizing waste is, as in other industries, to design more precision into organic synthesis. Chemists use the concept of selectivity as a measure of how efficiently a synthesis is performed. The standard definition of selectivity is the yield of product divided by the amount of substrate converted, expressed as a percentage. Organic chemists also distinguish among other forms of selectivity:

- chemoselectivity (competition between different functional groups in a molecule),
- regioselectivity (e.g. ortho versus para substitution in aromatic rings),
- stereoselectivity (enantioselectivity and diastereoselectivity).

However, one category of selectivity is largely ignored by organic chemists: the ‘atom selectivity’, or what is variously called atom economy (Trost, 1991, 1995), atom efficiency, or atom utilization solvents (Sheldon, 1992, 1992a, 1993, 1994, 1996, 1997, 1997a). The complete disregard of this parameter is the root cause of the waste problem in fine chemicals manufacture.

The atom utilization or atom efficiency concept is a useful tool for rapid evaluation of the amount of waste that will be generated by alternative routes to a particular product. It is calculated by dividing the molecular weight of the desired product by the sum total of the molecular weights of *all* the substances produced in the stoichiometric equation of the reaction(s) in question. The comparison is made on a theoretical (i.e. 100% chemical yield) basis. Fig. 2.8 shows a simple illustration of the concept for ethylene oxide manufacture.

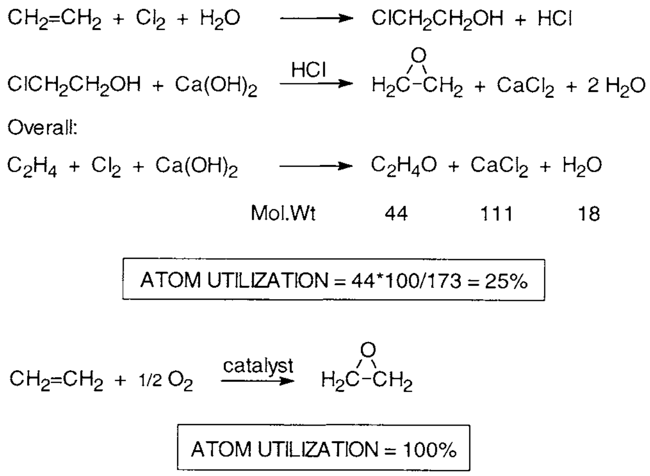


Figure 2.8. Atom efficiencies of routes to ethylene oxide.

The classical chlorohydrin route has an atom efficiency of 25% and is better described as a calcium chloride process, with ethylene oxide as the major by-product. In other words, even if the chemical yield were 100%, this process would produce 3 kg of waste per kg of ethylene oxide, corresponding to an E factor of 3. In practice, the E factor is higher because the yield is not 100% and excess amounts of reagents are used. In contrast, the petrochemical process used by most manufacturers is a one-step, catalytic process with an atom efficiency of 100%.

The reciprocal of the atom efficiency is the theoretical E factor, *i.e.* assuming 100% chemical yield, using only equivalent amounts of reagents, no subsequent neutralization steps, and no solvent losses. In practice, E factors are, of course, substantially higher. The gravity of the E factor situation in organic synthesis is perfectly illustrated by a recent report in which synthetic pathways to conditurol C (see Fig. 2.9) were compared (Hudlicky *et al.*, 1999). The preferred synthesis, based on a combination of an enzymatic oxidation and an electrochemical reduction, had an E factor of 391, replacing one having an E factor of 1125.

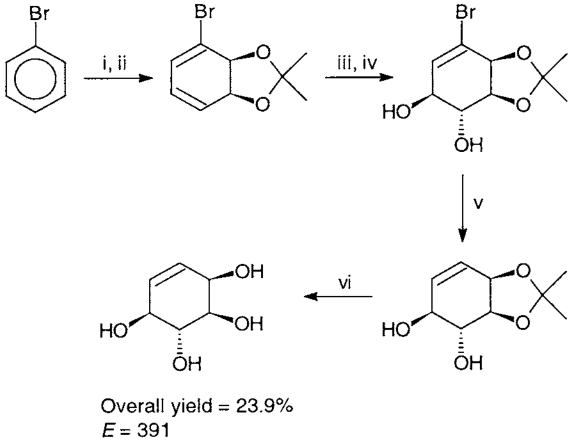


Figure 2.9. Synthesis of conditurol C; *Reagents and conditions*: i, *E. coli* JM109 (pDTG601A); ii, 2,2-dimethoxypropane, acetone, *p*-TsOH; iii, 1,3-dibromo-5,5-dimethylhydantoin, H_2O-acetone; iv, NaOH, H_2O-dimethoxyethane, heat; v, e^-, MeCN, Et_4NBr; vi, NaOBz, H_2O.

Evaluation of the *environmental impact* of alternative routes must also take the *nature of the waste* into account. After all, one kg of sodium chloride or one kg of a chromium salt has a very different environmental impact. To this end, we have introduced the environmental quotient EQ solvents (Sheldon, 1992, 1992a, 1993, 1994, 1996, 1997, 1997a), which is the product of the E factor and an arbitrarily assigned multiplier, the unfriendliness quotient, Q. For example, NaCl could be assigned a Q value of 1, and heavy metal salts, say 100-1,000, depending on their toxicity, ease of recycling, etc. Thus, 1 g of chromium salt waste would be equivalent to, say, 1 kg of sodium chloride. The assigned values of Q are obviously debatable and, to a certain extent, a moving target owing to changing environmental regulations. Nonetheless, it is possible to quantitatively evaluate the environmental impact of processes on this basis.

A further refinement should also take the energy consumption of alternative routes into consideration, as this also results in waste generation (primarily as CO_2). Extrapolating further leads to the concept of *environmental profile analysis*, in which processes are assessed on the basis of a weighted analysis of various parameters: raw materials and energy consumption, waste generation and its environmental impact, and safety aspects. Such an approach is completely analogous to the process profile analysis discussed earlier (Section 2.4) but with emphasis now clearly on environmental impact and safety issues.

2.7. THE ROLE OF CATALYSIS IN WASTE MINIMIZATION

As noted above, a prime cause of waste generation is the use of stoichiometric inorganic reagents. Fine chemicals and specialties manufacture is rampant with classical 'stoichiometric' technologies, many of which date from the 19th century. Examples that readily come to mind are stoichiometric reductions with metals (Na, Mg, Zn, Fe) or metal hydrides ($LiAlH_4$, $NaBH_4$, etc.), and stoichiometric oxidations with permanganate or dichromate. Hence, the solution is simple: replacement of antiquated stoichiometric methodologies with cleaner catalytic alternatives, e.g. catalytic hydrogenations, catalytic oxidations with O_2 or H_2O_2 and catalytic carbonylations (see Fig. 2.10).

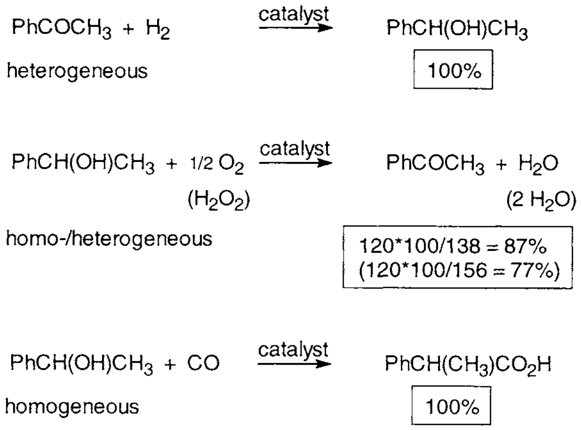


Figure 2.10. Atom efficiencies of catalytic processes.

Another major cause of waste is the use of mineral acids (H_2SO_4, H_3PO_4, etc.) and Lewis acids ($AlCl_3$, $ZnCl_2$), often in stoichiometric amounts, which cannot be recovered and recycled. A typical example is the HNO_3/H_2SO_4 mixture used in aromatic nitrations. Consequently, there is a discernible trend towards the use of solid, recyclable Brønsted and Lewis acids, e.g. zeolites, acidic clays, etc. (see later) as alternatives to conventional mineral and Lewis acids.

Hence, catalysis will play a pivotal role in the development of clean, environmentally benign processes that generate minimum amounts of wastes. But if the solution is so simple why are catalytic processes used so sporadically in fine and specialty chemicals manufacture? One reason for this is the more or less separate evolution (see Fig. 2.11) of organic synthesis and catalysis since the time of Berzelius, who not only coined the term organic chemistry (see Section 2.2) but also the term 'catalysis' in 1835. Subsequently, catalysis developed largely as a sub-discipline of physical chemistry. Following the advent of the petrochemical industry in the 1930s, catalysis was widely applied in oil refining and, later, in bulk chemicals manufacture. However, the scientists responsible for these developments were, generally speaking, not synthetic chemists. In contrast, organic synthesis followed a largely 'stoichiometric' line of evolution that can be traced back to Perkin's use of stoichiometric amounts of CrO_3 in his attempted synthesis of quinine (see Section 2.2).

A second reason is that there was no apparent necessity for minimizing waste in fine chemicals manufacture. Up until fairly recently, waste generation was not considered to be a problem in the fine chemicals industry. In the last decade, however, this situation has dramatically changed and the current emphasis on waste minimization has stimulated the development of clean, catalytic processes. The longer term trend in fine chemicals manufacture is towards the use of the simplest raw materials – H_2, O_2, H_2O, H_2O_2, NH_3, CO, O_2 – in low-salt, atom efficient processes employing homogeneous, heterogeneous, or biocatalysts.

Examples of replacement of classical stoichiometric technologies with cleaner catalytic alternatives will be delineated in the following sections.

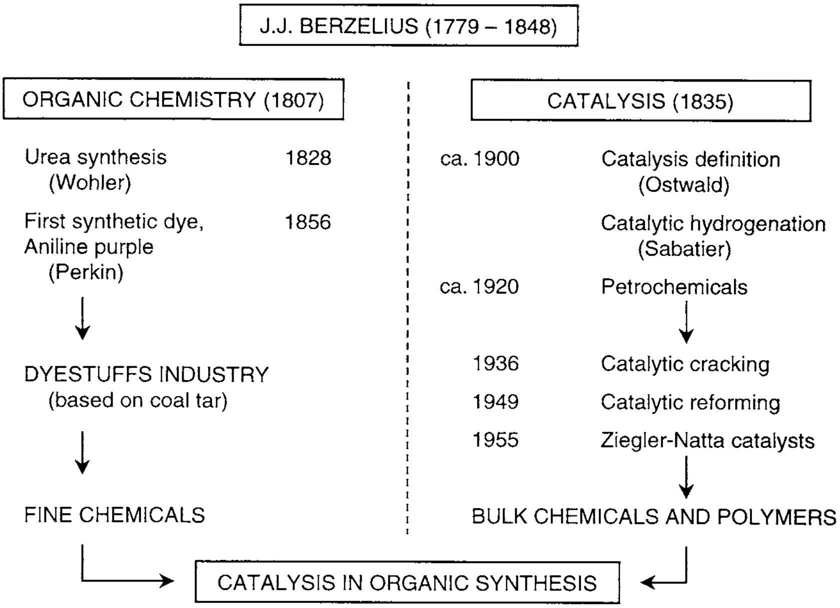


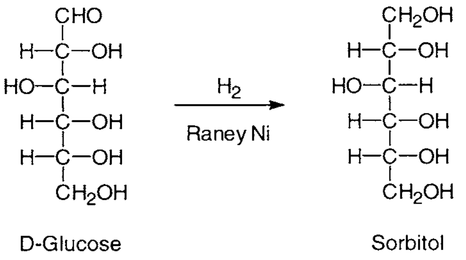
Figure 2.11. The origins of catalysis and organic synthesis.

2.8. FINE CHEMICALS AND CATALYSIS: EXAMPLES

Catalytic transformations can be divided on the basis of the catalyst-type – homogeneous, heterogeneous or enzymatic – or the type of conversion. We have opted for a compromise: a division based partly on type of conversion (reduction, oxidation and C-C bond formation, and partly on catalyst type (solid acids and bases, and biocatalysts). Finally, enantioselective catalysis is a recurring theme in fine chemicals manufacture, e.g. in the production of pharmaceutical intermediates, and a separate section is devoted to this topic.

2.8.1. Catalytic reduction

Catalytic hydrogenation (and dehydrogenation) is undoubtedly the workhorse of catalytic organic synthesis with a long tradition dating back to the days of Sabatier (Sabatier and Mailhe, 1904; Sabatier, 1923). It is widely used in fine chemicals manufacture. For example, 10 – 20% of all the reaction steps in the synthesis of vitamins (even 30% for vitamin E) at Hoffmann-La Roche are catalytic hydrogenations (Roessler, 1996). Selective catalytic hydrogenation of glucose to sorbitol (Eqn. (2)) forms the first step in the commercial synthesis of vitamin C.



(2)

It is worth noting, however, that up until fairly recently the reduction of aromatic nitro-compounds to the corresponding amines was commonly performed on an industrial scale, e.g. in the synthesis of azo dyes, with a mixture of iron and hydrochloric acid. This so-called Bechamp reduction has an E factor of ca. 15 compared to << 1 for catalytic hydrogenation.

The catalysts most frequently used are based on noble metals (mainly palladium and platinum) on various supports, or on nickel catalysts (mainly Raney type). Hydrogenations are generally performed in the liquid phase, under relatively mild conditions of temperature and pressure (1 – 40 bar). Most processes are performed batch-wise using powder catalysts in stirred tank or loop-type reactors with sizes up to 10 m^3.

Catalytic hydrogenations are generally highly selective with almost quantitative yield (Rylander, 1979; Augustine, 1976). As the metals are recovered from spent catalysts, essentially no non-combustible waste is generated.

The trend in fine chemicals and specialties is towards increasingly complex molecules, which translates into a need for hydrogenation catalysts that display a high degree of chemo-, regio-, and stereoselectivity. An illustrative example is provided by the synthesis (Roessler, 1996) of an intermediate for the Roche HIV protease inhibitor Saquinavir (Fig. 2.12). It involves performing a chemo- and diastereoselective hydrogenation of an aromatic ring without causing racemisation at the stereogenic centre in the substrate.

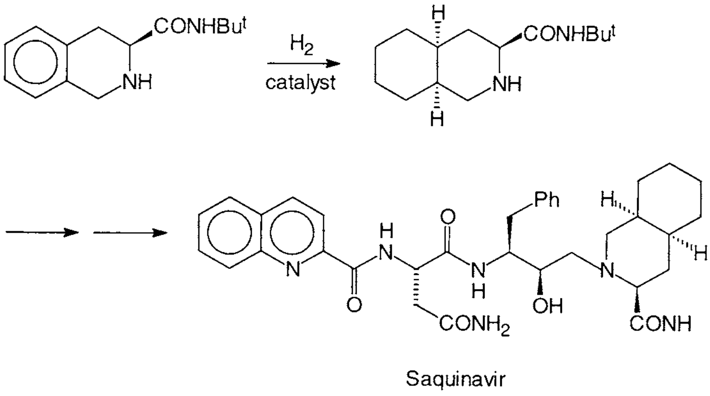
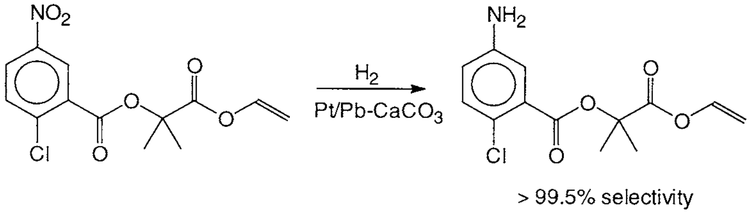


Figure 2.12. Synthesis of a Saquinavir intermediate.

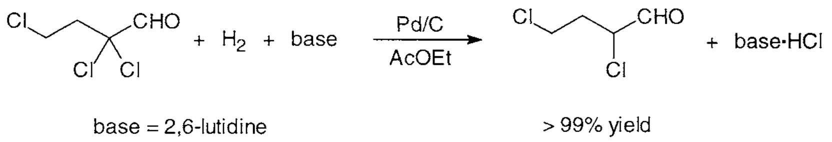
The selective hydrogenation of a nitro group in the presence of other reactive functionalities is a frequently encountered problem in fine chemicals manufacture. Ciba-Geigy (Novartis) scientists developed, in collaboration with a catalyst manufacturer, a new Pt/Pb on $CaCO_3$ catalyst that allows the chemoselective hydrogenation of an aromatic nitro group in the presence of C=C, C=O, C≡N as well as Cl or Br substituents in selectivities > 95% (even C≡C groups react very slowly) (Bader *et al.*, 1996). Eqn. (3) shows an example (Bader *et al.*, 1996).



(3)

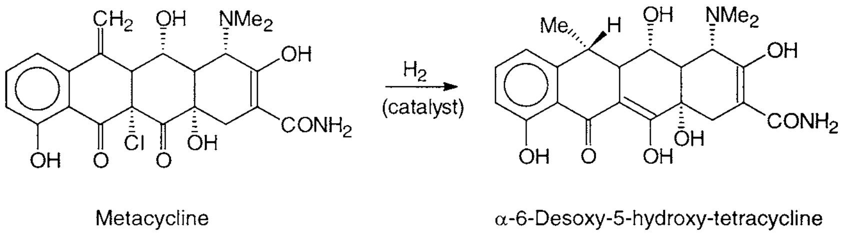
The same group showed (Baumeister *et al.*, 1997) that addition of vanadyl compounds as cocatalysts solved a recurring problem in hydrogenations: the build-up of arylhydroxylamine intermediates, which can lead to runaway reaction conditions. Vanadyl complexes catalyse the disproportionation of arylhydroxylamines and, hence, prevent their build-up during reaction.

Another example from the Ciba-Geigy group concerns the chemoselective reductive dehalogenation of 2,2,4-trichlorobutanal to 2,4-dichlorobutanol (Eqn. (4)), a herbicide intermediate (Bader *et al.*, 1996).



(4)

Sometimes the required high degree of chemo-, regio-, and stereoselectivity is achieved using a homogeneous hydrogenation catalyst. A pertinent example is the industrial synthesis of the tetracycline antibiotic shown in Fig. 2.13. (Villax and Page, 1985). The homogeneous rhodium catalyst is chemo- and regiospecific and displays 99% selectivity to the required α-stereoisomer.



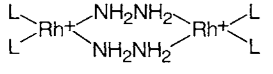
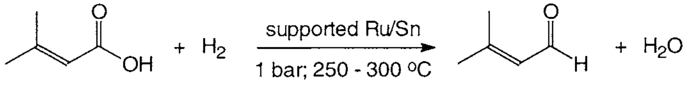
Catalyst	Ratio α/β
Pd/C	1
Pd + S/C	11
	99

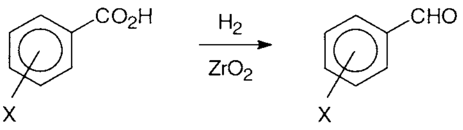
Figure 2.13. Synthesis of a tetracycline antibiotic.

Although hydrogenation is a well-established catalytic methodology, new advances continue to appear. For example, Rhône-Poulenc scientists reported (Ratton, 1998) the direct hydrogenation of carboxylic acids to the corresponding aldehydes, a notoriously difficult (most textbooks consider it impossible) transformation. The reaction is performed in the vapour phase using a supported Ru/Sn alloy catalyst. For example, 1-dodecanoic acid and trifluoroacetic acid afford 1-dodecanol and fluoral, respectively, and an α,β-unsaturated acid gives the corresponding aldehyde in 91% yield (Eqn. (5)).



(5)

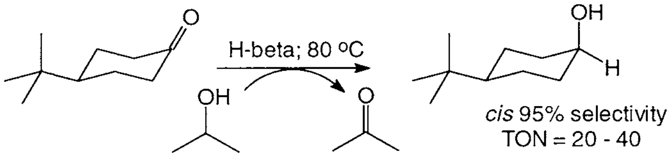
Similarly, Mitsubishi scientists developed commercial processes for the manufacture of aldehydes such as the agrochemical intermediate, *m*-phenoxybenzaldehyde, and the fragrance intermediate, *p-tert*-butylbenzaldehyde, by vapour-phase hydrogenation of the corresponding carboxylic acids over zirconia or chromia catalysts (Eqn. (6)) (Yokoyama *et al.*, 1992).



(6)

X = *m*-PhO, *p*-Bu^t

The Meerwein-Ponndorf-Verley (MPV) reduction of aldehydes and ketones is a well-established methodology in organic synthesis. It involves the reaction of a carbonyl substrate with a hydrogen donor, usually *iso*propanol, in the presence of an aluminium alkoxide, e.g. $Al(OPr^i)_3$. Although the latter is, in principle, a catalyst, MPV reductions often employ stoichiometric amounts of $Al(OPr^i)_3$ owing to the low rate of exchange of the alkoxy groups. Recently, a zeolite beta-catalysed MPV reduction of cyclohexanones was reported (Creyghton *et al.*, 1997). The method is truly catalytic and the catalyst can be readily separated, by simple filtration, and recycled. An additional benefit is that the reduction of 4-*tert*-butylcyclohexanone (Eqn. (7)) gives the thermodynamically less stable *cis*-alcohol, an important fragrance intermediate, in high (> 95%) selectivity. In contrast, conventional MPV reduction of this ketone mainly gives the *trans*-isomer. Preferential formation of the *cis*-isomer was attributed to transition-state selectivity imposed by confinement of the substrate in the zeolite pores.



(7)

2.8.2. Catalytic oxidation

Catalytic oxidation with O_2 is widely used in the manufacture of petrochemicals (Sheldon and Kochi, 1981). In some cases such technologies have been directly applied to the synthesis of fine chemicals. An elegant example is the BASF process (Chauvel *et al.*, 1994) for the manufacture of citral (Fig. 2.14), a key intermediate for fragrances and vitamins A and E. The key step is a catalytic vapour-phase oxidation, and the supported silver catalyst is essentially the same as that used in the manufacture of formaldehyde from methanol. This atom efficient, low-salt process has displaced a traditional route, starting from β-pinene, which involved, *inter alia*, a stoichiometric oxidation with MnO_2 (see Fig. 2.14). Analogous vapour-phase oxidation technology is used for the commercial production of long-chain aldehydes, e.g. 1-octanal, by oxidation of the corresponding linear alcohols.

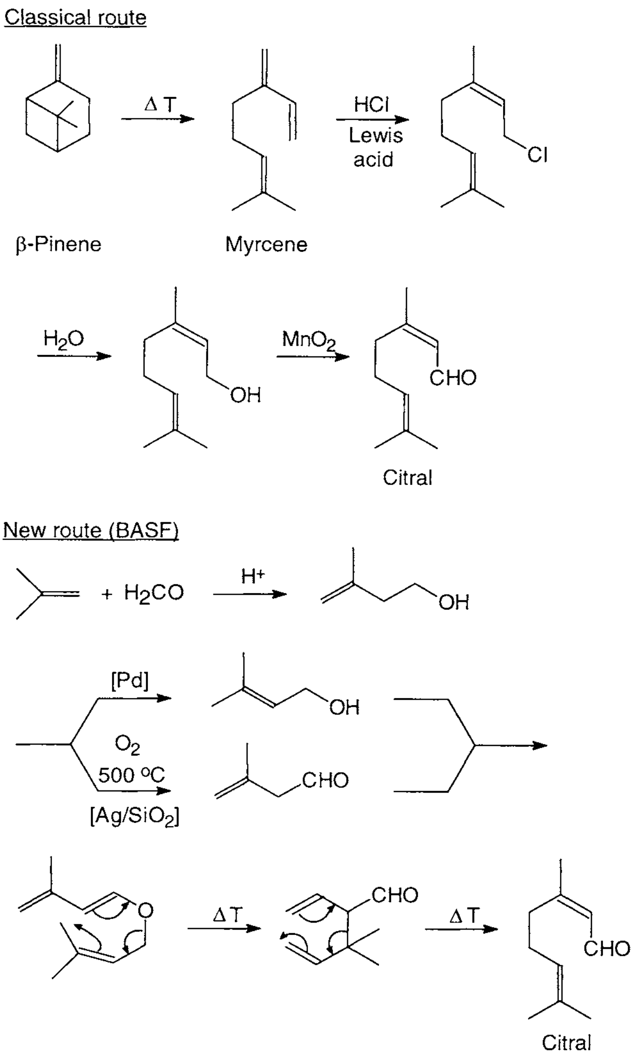


Figure 2.14. Two routes to citral.

Similarly, a catalytic route to indigo was developed by Mitsui Toatsu Chemicals (Inoue *et al.*, 1994) to replace the traditional process, which dates back to the nineteenth century (see earlier), and has a low atom efficiency/high E factor (Fig. 2.15). Indole is prepared by vapour-phase reaction of ethylene glycol with aniline in the presence of a supported silver catalyst. The indole is selectively oxidised to indigo with an alkyl hydroperoxide in the presence of a homogeneous molybdenum catalyst.

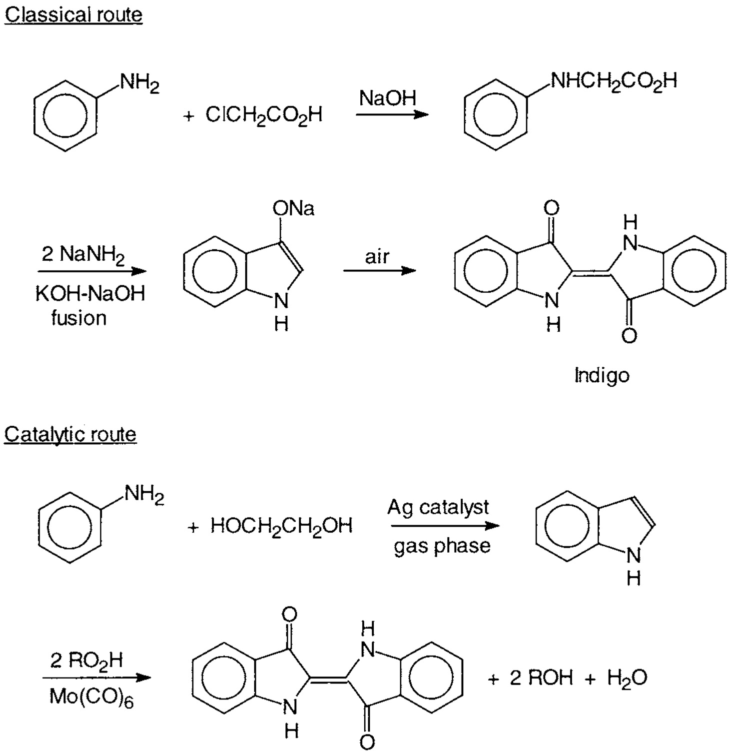


Figure 2.15. Two routes to indigo.

Whereas in bulk chemicals manufacture the choice of oxidant is largely restricted to molecular oxygen, the economics of fine chemicals production allow a broader choice of oxidants (see Table 2.8).

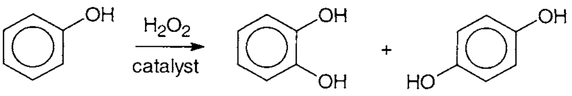
Even though it is more expensive per kilo than oxygen, hydrogen peroxide is often the oxidant of choice for fine chemicals, since it can be used in existing batch-equipment. Next to price and ease of handling, the two important factors that influence the choice of oxidant are the nature of the co-product and the percentage of available oxygen. The former is important from an environmental viewpoint, and the latter has direct bearing on the productivity (space time yield).

An extremely versatile catalyst for a variety of synthetically useful oxidations with aqueous hydrogen peroxide is obtained by isomorphous substitution of Si by Ti in molecular sieve materials such as silicalite (the all-silica analogue of zeolite ZSM-5) and zeolite beta. Titanium(IV) silicalite (TS-1), developed by Enichem (Notari, 1988), was the progenitor of this class of materials, which have become known as redox molecular sieves (Arends *et al.*, 1997).

Table 2.8
Oxygen donors

Donor	% Active oxygen	Co-product
H_2O_2	47.0	H_2O
O_3	33.3	O_2
CH_3CO_3H	26.6	CH_3CO_2H
t-BuO_2H	17.8	*t*-BuOH
NaClO	21.6	NaCl
NaBrO	13.4	NaBr
HNO_3	25.4	NO_x
$KHSO_5$	10.5	$KHSO_4$
$NaIO_4$	7.0	$NaIO_3$
PhIO	7.3	PhI

The TS-1 catalysed hydroxylation of phenol to a 1:1 mixture of catechol and hydroquinone (Fig. 2.16) was commercialized by Enichem (Romano *et al.*, 1990). This process offers definite advantages, such as higher selectivities at higher phenol conversions, compared to other catalytic systems. It also illustrates another interesting development: the use of solid, recyclable catalysts for liquid phase (oxidation) processes to minimize waste production even further.



Process/ (Catalyst)	Rhône-Poulenc ($HClO_4$, H_3PO_4)	Brichima (Fe^{II}/Co^{II})	Enichem (TS-1)
Phenol conversion, %	5	10	25
Selectivity on phenol, %	90	80	90
Selectivity on H_2O_2, %	70	50	70
Catechol/hydroquinone	1.4	2.3	1.0

Figure 2.16. Catechol via phenol hydroxylation.

The TS-1 catalysed ammoximation of cyclohexanone with NH_3/H_2O_2 is a new process (Romano *et al.*, 1990) for the production of cyclohexanone oxime, the precursor of caprolactam. In the existing process, the oxime is produced by reaction of cyclohexanone with hydroxylamine. The latter is produced as a salt by air oxidation of ammonia, followed by catalytic hydrogenation in an acidic medium. Substantial amounts of ammonium sulphate (ca. 4.5 kg/kg caprolactam) are produced in both the formation and subsequent rearrangement of the oxime to caprolactam (Fig. 2.17). The new ammoximation route uses the more expensive H_2O_2 instead of O_2 but circumvents the salt generation in the manufacture of the oxime. We note, however, that this does not solve the salt problem, since about two-thirds of the ammonium sulphate is derived from the Beckmann rearrangement of the oxime. However, Sumitomo has developed a solid catalyst (high-silica ZSM-5; Si/Al ≥ 1,000) for the vapour-phase rearrangement of cyclohexanone oxime, giving caprolactam in 95% selectivity at 100% conversion (Sato *et al.*, 1989).

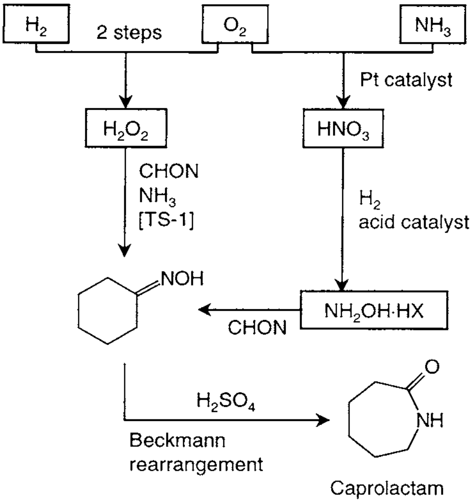


Figure 2.17. Two routes to cyclohexanone oxime.

The ammoximation reaction involves the *in situ* formation of hydroxylamine via TS-1 catalysed oxidation of NH_3 with H_2O_2. Hence, there are no size restrictions with regard to the ketone substrate, because the reaction of NH_2OH with the latter occurs in the bulk solution. For example, TS-1 catalyses the ammoximation of *p*-hydroxyacetophenone (Le Bars *et al.*, 1996). Beckmann rearrangement of the oxime product (see Fig. 2.18) affords the analgesic paracetamol (4-acetaminophenol).

An interesting example in the context of waste minimization is the manufacture of the vitamin K intermediate, menadione. Traditionally it was produced by stoichiometric oxidation of 2-methylnaphthalene with chromium trioxide (Eqn. (8)), which generates 18 kg of solid, chromium containing waste per kg of menadione. Catalytic alternatives have been reported, but selectivities tend to be rather low owing to competing oxidation of the second aromatic ring (the selectivity in the classical process is only 50-60%). The best results were obtained with a heteropolyanion as catalyst and O_2 as the oxidant (Kozhevnikov, 1993).

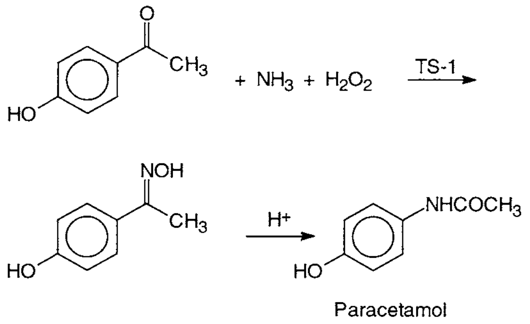
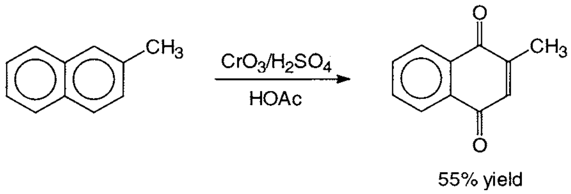


Figure 2.18. Paracetamol synthesis from *p*-hydroxyacetophenone.



(8)

An alternative approach (Matveev *et al.*, 1995), which avoids the selectivity problem mentioned above, is shown in Fig. 2.19. In this route, 1-naphthol is selectively methylated at the 2-position using methanol over a solid catalyst in the vapour phase. The product undergoes selective oxidation to menadione with O_2 and a heteropolyanion catalyst.

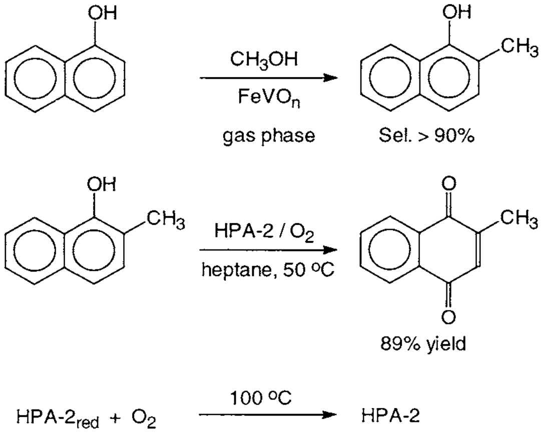
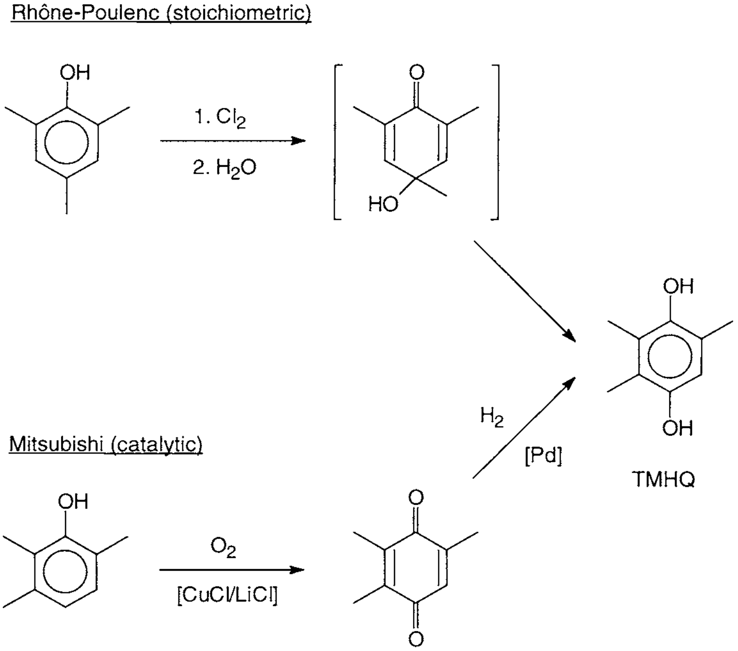


Figure 2.19. Menadione synthesis from 1-naphthol.

Similarly, 2,3,5-trimethyl-1,4-hydroquinone (TMHQ), a key intermediate in the synthesis of vitamin E, is produced via oxidation of 2,3,6-trimethylphenol to the corresponding benzoquinone. Originally this was performed by reaction with chlorine followed by hydrolysis, but this process has now been superseded by oxidation with O_2 in the presence of a $Cu_2Cl_2/LiCl$ catalyst (see Fig. 2.20) (Mercier and Chabardes, 1994). Alternatively, this oxidation can also be catalysed by a heteropolyanion (Kozhevnikov, 1995).



Higher raw materials costs and extra step, but no effluent problem

Figure 2.20. Synthesis of a vitamin E intermediate.

2.8.3. Catalytic C-C bond formation

The formation of C-C bonds is of key importance in organic synthesis. An important catalytic methodology for generating C-C bonds is provided by carbonylation. In the bulk chemicals arena this is used for the production of acetic acid by methanol carbonylation (Eqn. (9)) in the presence of rhodium- or, more recently, iridium-based catalysts (Maitlis *et al.*, 1998).

$$CH_3OH + CO \xrightarrow[I^-]{Rh^I \text{ or } Ir^I} CH_3CO_2H \tag{9}$$

This process accounts for more than half of the five million tons of acetic acid produced annually on a world-wide basis. The process is 100% atom efficient, highly selective (> 99%) and proceeds in one step from inexpensive feedstocks. Extrapolation of this methodology to more complex molecules can afford atom efficient routes to fine chemicals. An elegant example of this is the Hoechst-Celanese process (Fig. 2.21) for the manufacture of the over-the-counter analgesic, ibuprofen (Elango *et al.*, 1991), with an annual production in excess of 8,000 tons. In this process ibuprofen is produced in two catalytic steps (hydrogenation and carbonylation), with 100% atom efficiency, from *p-iso*butylacetophenone. This process replaced a more classical route, which involved more steps and a much higher E factor.

The starting material, *p-iso*butylacetophenone, is produced by Friedel-Crafts acylation of *iso*butylbenzene in liquid hydrogen fluoride. The latter acts as both a reagent and a solvent and is completely recycled, thus circumventing the generation of large amounts of aluminium chloride waste, which is associated with classical Friedel-Crafts acylations. However, because of the hazardous nature of liquid HF, there is still a definite need for solid acid catalysts for Friedel-Crafts acylations (see later).

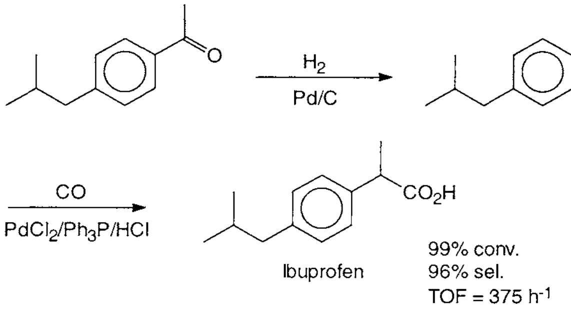
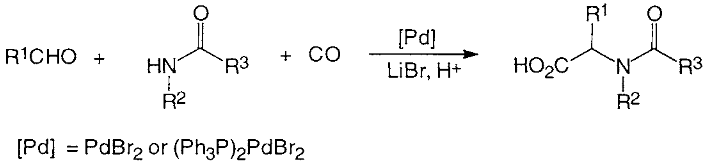


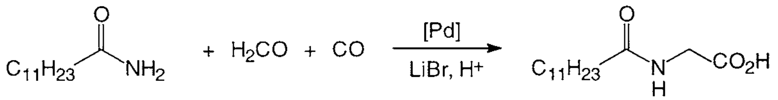
Figure 2.21. Ibuprofen synthesis.

Another elegant example of a highly atom efficient process is the use of palladium-catalysed amidocarbonylation for the one-step synthesis of amino acid derivatives from an aldehyde, CO, and an amide (Eqn. (10)) (Beller *et al.*, 1997, 1999).



(10)

The reaction is used, for example, to produce N-lauroylsarcosine (N-methylglycine), a surfactant, from formaldehyde, CO and N-methyllauramide (Eqn. (11)), replacing a classical route that generated considerable amounts of salts.


(11)

In a process developed by Hoffmann La Roche (Roessler, 1996) for the anti-Parkinsonian drug, lazabemide, palladium-catalysed amidocarbonylation of 2,5-dichloropyridine replaced an original synthesis that involved eight steps, starting from 2-methyl-5-ethylpyridine, and had an overall yield of 8%. The amidocarbonylation route affords lazabemide hydrochloride in 65% yield in one step, with 100% atom efficiency (Fig. 2.22).

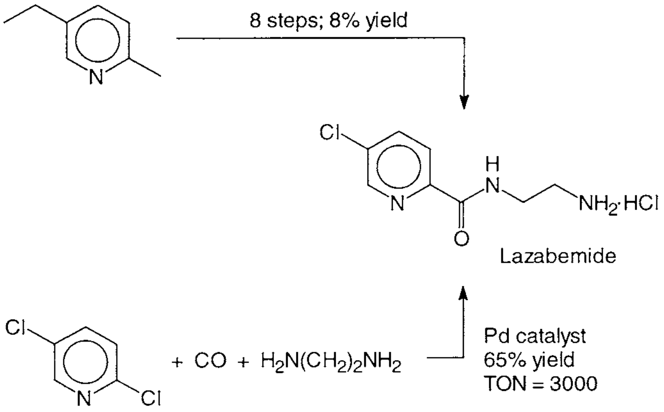
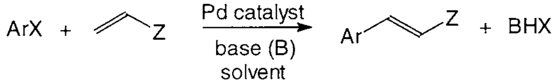


Figure 2.22. Two routes to lazabemide.

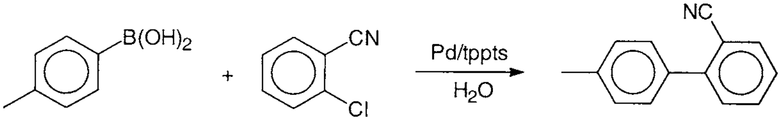
Another methodology that is widely used for C-C bond formation is the Heck coupling (Heck, 1985; Tsuji, 1995). The Heck reaction involves the palladium-catalysed arylation of olefinic double bonds (Eqn. (12)) and provides an alternative to Friedel-Crafts reactions for attaching carbon fragments to aromatic rings.


(12)

X = Br, I, OTf, COCl, SO_2Cl
Z = H, alkyl, Ar, CN, CO_2R, etc.

The reaction has a broad scope and is currently being widely applied in fine chemicals manufacture. One limitation is that the arylating agent is largely limited to relatively expensive aryl bromides and iodides (see, however, Reetz *et al.*, 1998), while the process generates one equivalent of halide ion. Of interest in this context, therefore, is the recent report of a halide-free Heck reaction that employs an aromatic carboxylic anhydride as the arylating agent (Stephan *et al.*, 1998). No base or phosphine ligands are required, and fast reactions were observed at substrate-catalyst ratios of 1,000. The carboxylic acid co-product can be recycled to its anhydride.

A closely related reaction that is currently receiving much attention is the palladium-catalysed Suzuki coupling of arylboronic acids with aryl halides (Fu and Littke, 1998). For example, this technology has recently been applied by Clariant workers for the production of *o*-tolyl-benzonitrile (Eqn. (13)), an intermediate to a series of so-called angiotensin-II antagonists, a new class of antihypertensive drugs (Bernhagen, 1998).



(13)

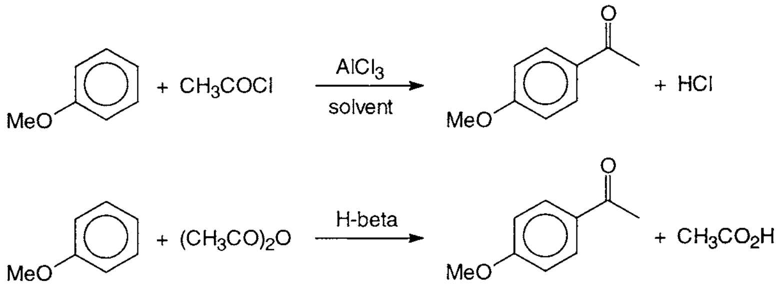
The reaction is performed in a biphasic aqueous-organic medium using a water-soluble palladium catalyst (see later).

2.8.4. Catalysis by solid acids

Many standard reactions that are widely applied in the production of fine chemicals employ strong mineral or Lewis acids, such as sulphuric acid and aluminium chloride, often in stoichiometric quantities. This generates waste streams containing large amounts of spent acid, which cannot easily be recovered and recycled. Replacement of these soluble mineral and Lewis acids by recyclable solid acids, such as zeolites, acid clays, and related materials, would represent a major breakthrough, especially if they functioned in truly catalytic quantities. Consequently, the application of solid acids in fine chemicals synthesis is currently the focus of much attention (Downing *et al.*, 1997).

A prominent example is Friedel-Crafts acylation, one of the most widely used reactions in the fine chemicals industry. In contrast with Friedel-Crafts alkylations, which are truly catalytic processes, acylations require more than one equivalent of, for example, $AlCl_3$ or BF_3. This is owing to the strong complexation of the Lewis acid by the ketone product. Although zeolites have successfully replaced mineral and Lewis acids in aromatic alkylations, the corresponding acylations have proven to be recalcitrant. Nevertheless, Rhône-Poulenc has recently announced the first commercial example of a zeolite-catalysed Friedel-Crafts acylation (Spagnol *et al.*, 1996). Zeolite beta is employed as a catalyst, in fixed-bed operation, for the acetylation of anisole with acetic anydride, to give *p*-methoxyacetophenone (Fig. 2.23). The original process used acetyl chloride in combination with 1.1 equivalent of $AlCl_3$, in a chlorinated hydrocarbon solvent, and generated 4.5 kg of aqueous effluent, containing $AlCl_3$, HCl, solvent residues, and acetic acid, per kg of product. The catalytic alternative generates 0.035 kg of aqueous effluent, i.e. more than 100 times less, consisting of 99% H_2O, 0.8% acetic acid, and < 0.2% other organics, and requires no solvent. Moreover, a higher product yield (> 95% vs. 85-95%) is achieved, the catalyst is recyclable, and the number of unit operations is reduced from twelve to two.

The above process involves the acylation of a relatively reactive aromatic substrate. In order to be widely applicable, catalytic methodologies must be effective with less reactive aromatics. In this case, however, there is a basic problem of adsorption imbalance (Downing *et al.*, 1997), *i.e.* the more polar acylating agent is preferentially adsorbed, preventing the aromatic substrate from reaching the active site. It has been reported, however, that benzene can be successfully acetylated even with acetic acid over H-ZSM-5 in the vapour phase at 250 °C (Singh and Pandey, 1997), suggesting that the adsorption ratio of the reactants, with their widely different polarities, is much more favourable in the vapour phase. The heteroaromatics furan, pyrrole, and thiophene also undergo selective acetylation over zeolites in the vapour phase (Lermer *et al.*, 1992), although in this case these polar substrates can compete favourably with the acylating agent for adsorption on the catalyst.



Homogeneous	**Heterogeneous**
$AlCl_3$ > 1 equivalent	H-beta, catalytic & regenerable
Solvent	No solvent
Hydrolysis of products	No water necessary
Phase separation	-
Distillation organic phase	Distillation organic phase
Solvent recycle	-
85-95% yield	> 95% yield, higher purity
4.5 kg aqueous effluent per kg	0.035 kg aqueous effluent per kg

Figure 2.23. Zeolite-catalysed versus classical Friedel-Crafts acylation.

Zeolites have been shown to catalyse a variety of related reactions (Downing *et al.*, 1997), *e.g.* zeolite beta catalyses the synthesis of coumarins via the Pechmann condensation. For example, condensation of resorcinol with ethyl acetoacetate over zeolite beta in refluxing toluene gave methylumbelliferone, a perfumery ingredient, in 70-80% yield (Fig. 2.24) (Gunnewegh *et al.*, 1996).

Acid-catalysed rearrangement of epoxides is another widely used reaction in the fine chemicals industry. Here again the use of solid acid catalysts such as zeolites is proving advantageous. Two examples are shown in Fig. 2.25: the isomerization of *iso*phorone oxide (Elings *et al.*, 1997) and the conversion of α-pinene oxide to campholenic aldehyde (Hölderich *et al.*, 1997; Kunkeler *et al.*, 1998). Both products are fragrance intermediates.

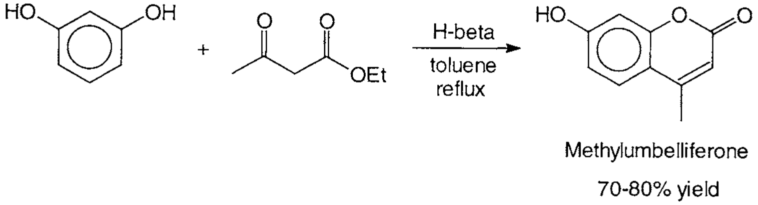


Figure 2.24. Zeolite-catalysed Pechmann condensation.

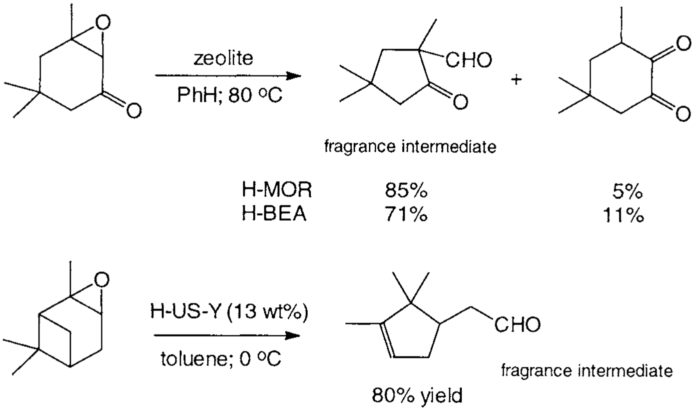


Figure 2.25. Zeolite-catalysed epoxide rearrangements.

These examples represent the proverbial tip of the iceberg. In the future, zeolites and related solid acids will be widely applied as catalysts in the fine chemicals industry. One final example, worthy of mention, is a widely used reaction of long standing: aromatic nitration.

Traditionally, aromatic nitrations have been performed with mixtures of concentrated nitric and sulphuric acids leading to considerable effluent problems associated with the spent acid. A heterogeneous alternative for sulphuric acid has been reported (Bertea *et al.*, 1995), namely dealuminated Mordenite, which is sufficiently robust to be able to catalyse the vapour-phase nitration of benzene with 65% aqueous nitric acid.

2.8.5. Catalysis by solid bases

Examples of commercially applied solid base catalysts are much fewer than for solid acids. Nevertheless, much attention is currently focused on the development of novel solid base catalysts for classical organic reactions such as aldol condensations, Michael additions, and Knoevenagel condensations, to name but a few.

Hydrotalcite clays, for example, are built up of positively charged brucite layers, for reviews see Cavani *et al.* (1991). Upon calcination they become active as solid bases in e.g. aldol and Knoevenagel condensations (see Fig. 2.26) (Fgueras *et al.*, 1998; Corma and Martin-Aranda, 1993; Climent *et al.*, 1995).

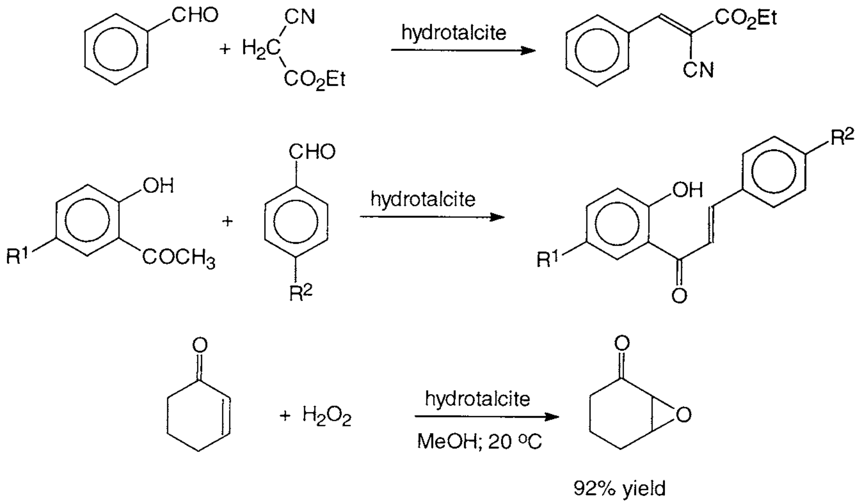


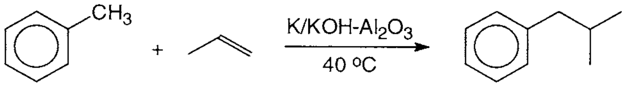
Figure 2.26. Hydrotalcite-catalysed condensations.

Another approach to designing solid base catalysts that is currently in vogue, is to immobilize an organic base by covalent attachment (tethering) to a solid surface (Brunel, 1999). For example, aminopropyl-silica, prepared by reaction of a silica surface with 3-aminopropyl (trimethoxy) silane, was an effective catalyst for Knoevenagel condensations (Macquarrie *et al.*, 1998). More strongly basic solid catalysts are obtained by tethering guanidine derivatives. For example, functionalization of the mesoporous silica, MCM-41, with 1,5,7-triazabicyclo[4,4,0]dec-5-ene (TBD) (see Fig. 2.27) yielded an active, recyclable catalyst for, *inter alia*, Michael addition (Subba Rao *et al.*, 1997).

Another approach involved encapsulation of a bulky guanidine, N,N,N-tricyclohexylguanidine, in the super-cages of hydrophobic zeolite Y (Sercheli *et al.*, 1997). The resulting 'ship-in-a-bottle' guanidine catalysed the aldol reaction of benzaldehyde with acetone to give 4-phenyl-4-hydroxybutan-2-one.

Solid super bases, prepared by successive treatment of γ-alumina with alkali metal hydroxide and alkali metal, are highly active catalysts for reactions involving reactive carbanions, and have been commercialised by Sumitomo (Suzukamo *et al.*, 1997). For example, *iso*butylbenzene, the starting material for ibuprofen (see earlier) is produced by side-chain alkylation of toluene with propylene over a $K/KOH/Al_2O_3$ catalyst (Eqn. (14)).

Obviously such super bases are suitable only for reactions of aprotic substrates such as hydrocarbons since the reactive alkali metals will be leached from the surface by reaction with protic molecules.



(14)

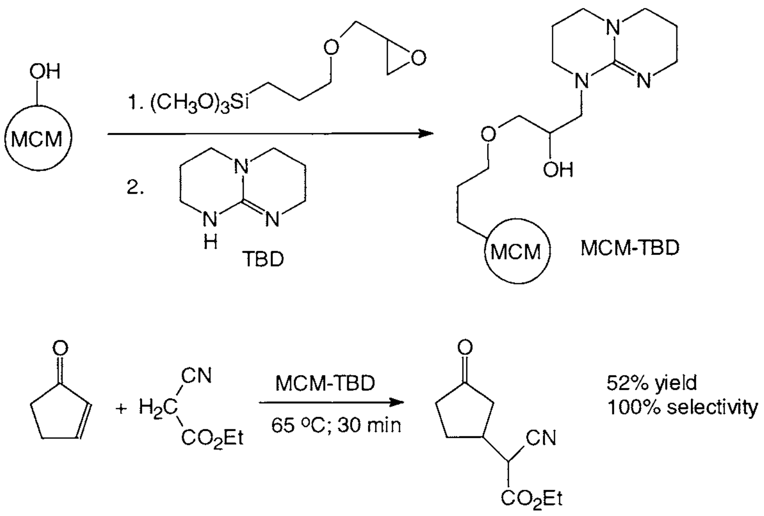


Figure 2.27. Tethered organic bases as solid catalysts.

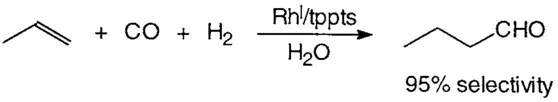
2.8.6. The question of solvents: catalytic conversions in water

A characteristic feature of homogeneous (metal) catalysts is their superior activity and/or selectivity compared to their heterogeneous counterparts. A serious shortcoming of homogeneous catalysts is the often cumbersome recovery and recycling of the catalyst. Hence, the ideal catalyst should combine the high activity and selectivity of a homogeneous catalyst with the ease of recovery and recycling of its heterogeneous equivalent. A novel approach to achieve this ideal is to perform the reaction in a liquid/liquid biphasic system, whereby the catalyst resides in one phase (e.g. water) and the product is dissolved in the other (organic) phase (Papadogianakis and Sheldon, 1996, 1997; Cornils and Herrmann, 1998). The catalyst is separated from the product (and reactants) by simple phase separation.

This concept meshes with another important environmental issue: solvents for organic reactions. The use of chlorinated hydrocarbon solvents, traditionally the solvent of choice for a wide variety of organic reactions, has been severely curtailed. In fact, so many of the solvents favoured by organic chemists have been blacklisted that the whole question of solvents requires rethinking. The best solvent is no solvent and if a solvent (diluent) is needed then water is preferred. Water is non-toxic, non-inflammable, abundantly available, and inexpensive. Moreover, owing to its highly polar character, one can expect novel reactivities and selectivities for organometallic catalysis in water.

An example of a large scale application of the aqueous biphasic concept is the Ruhrchemie/Rhône-Poulenc process for the hydroformylation of propylene to *n*-butanal (Eqn. (15)), which employs a water-soluble rhodium(I) complex of trisulphonated triphenylphosphine (tppts) as the catalyst (Cornils and Wiebus, 1996).

The same complex functions as the catalyst in the Rhône-Poulenc process (Mercier and Chabardes, 1994) for the manufacture of the vitamin A intermediate geranylacetone, via reaction of myrcene with methylacetoacetate in a biphasic system (Fig. 2.28).



(15)

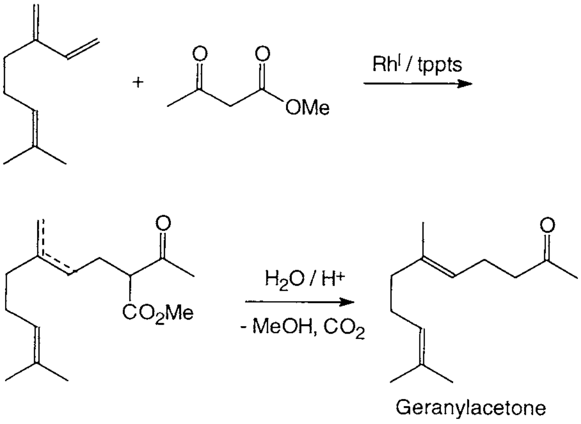
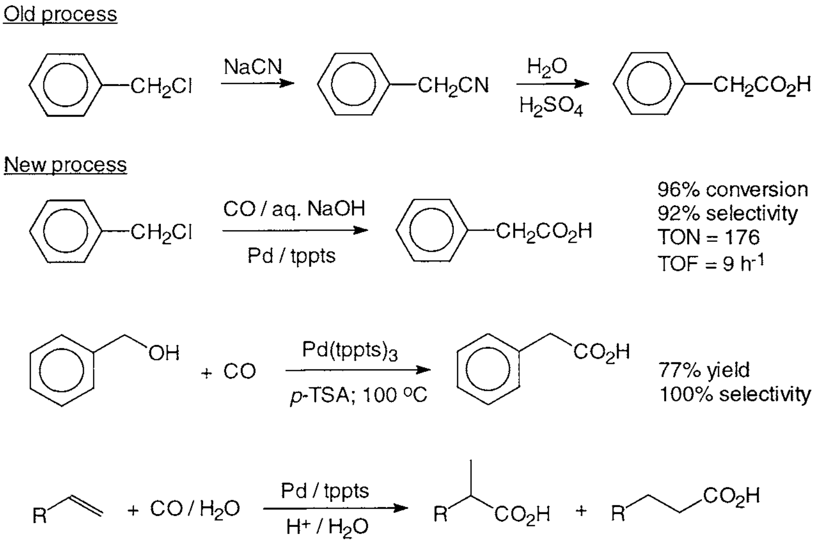


Figure 2.28. Rhône-Poulenc process for geranylacetone.

Similarly, Pd/tppts was used by Hoechst (Kohlpainter and Beller, 1997) as the catalyst in the synthesis of phenylacetic acid by biphasic carbonylation of benzyl chloride (Fig. 2.29). The new process replaces a classical synthesis by reaction of benzyl chloride with sodium cyanide, followed by hydrolysis of the resulting benzyl cyanide. Although the new process produces one equivalent of sodium chloride, this is substantially less salt production than in the original process. Moreover, sodium cyanide is about seven times as expensive per kg as carbon monoxide.

Pd/tppts also catalyses the selective biphasic carbonylation of benzyl alcohol, to phenylacetic acid, in an acidic aqueous medium (Papadogianakis *et al.*, 1997). In this case there is, in principle, no salt generation, but whether this reaction or the aforementioned carbonylation of benzyl chloride is more attractive depends on which starting material is the most readily available. This methodology was also applied to the synthesis of ibuprofen (see earlier) by biphasic carbonylation of 1-(4-*iso*butyl-phenyl) ethanol (Papadogianakis *et al.*, 1997a) and to the biphasic hydrocarboxylation of olefins (Papadogianakis *et al.*, 1997b; Tilloy *et al.*, 1997). In the latter case exceptionally high turnover frequencies (> 2,500 h^{-1}), higher than for the same reaction in organic media, were observed with propylene hydrocarboxylation at 110 – 120 $^{\circ}$C and 50 bar (Papadogianakis *et al.*, 1997b; Tilloy *et al.*, 1997).

Other non-conventional reaction media are also beginning to attract attention as a result of the tightening of environmental legislation regarding conventional organic solvents. These are discussed in more detail in Chapter 4.



R	Selectivity (%)	
	iso-	*n-*
CH_3	43	57
C_6H_5	56	33
4-*i*-BuC_6H_4	82	18

Figure 2.29. Pd/tppts-catalysed carbonylations in aqueous biphasic media.

2.8.7. Biocatalysis

Enzymes are the catalyst *per excellence* for reactions in water, which is their natural habitat. Moreover, the use of enzymes often circumvents the need for functional group protection and deprotection steps. For example, enzymatic hydrolysis of penicillin G to 6-APA (Fig. 2.30) proceeds in one step at ambient temperature while chemical deacylation requires three steps, a temperature of - 40 °C and various stoichiometric reagents, leading to a high E factor.

However, the main stimulus for switching from chemical to enzymatic deacylation was to avoid the use of dichloromethane as solvent (Brugging *et al.*, 1998). The enzymatic process acounts for most of the several thousands of tons of 6-APA produced annually on a world-wide basis.

Another advantage of biocatalysis is that chemo-, regio-, and stereoselectivities are attainable that are difficult or impossible to achieve by chemical means. A pertinent example is the production of the artificial sweetener, aspartame, which has become somewhat of an industrial commodity. The enzymatic process (Fig. 2.31), operated by the Holland Sweetener Company (a joint venture of DSM and Tosoh), is completely regio- and enantiospecific (Oyama, 1992).

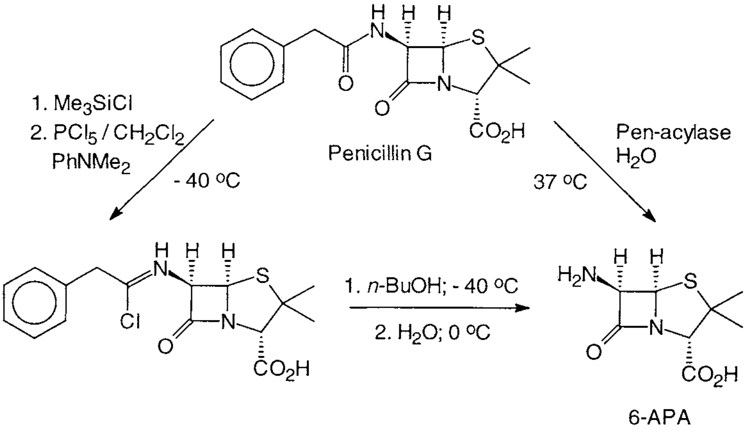


Figure 2.30. Enzymatic versus chemical deacylation of pencillin G.

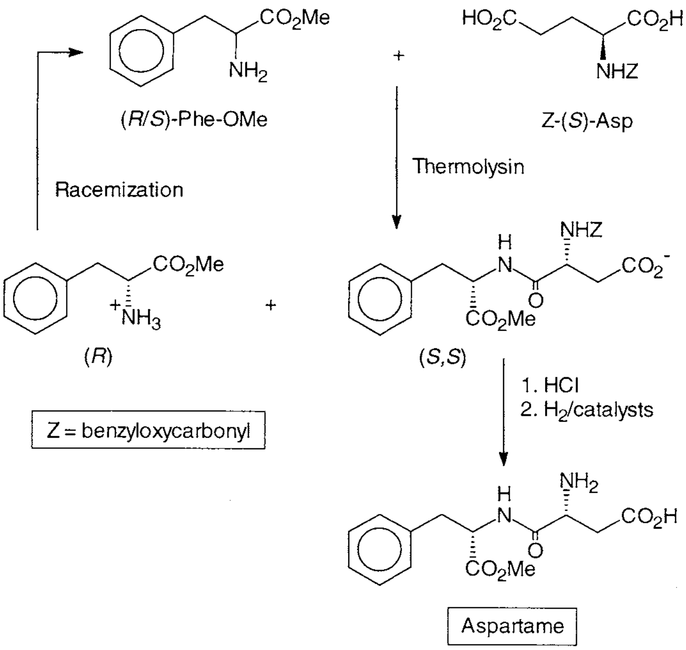


Figure 2.31. Aspartame via enzymatic coupling.

The above two processes employ isolated enzymes – penicillin G acylase and thermolysin, respectively – and the key to their success was an efficient production of the enzyme. In the past this was often an insurmountable obstacle to commercialization, but the advent of recombinant DNA technology has changed this situation dramatically. Using this workhorse of modern biotechnology most enzymes can be expressed in a suitable microbial host, which enables their efficient production. As with chemical catalysts another key to success often is the development of a suitable immobilization method, which allows for efficient recovery and recycling of the biocatalyst.

In some cases it is more attractive to use whole microbial cells, rather than isolated enzymes, as biocatalysts. This is the case in many oxidative biotransformations where cofactor regeneration is required and/or the enzyme has low stability outside the cell. By performing the reaction as a fermentation, *i.e.* with growing microbial cells, the cofactor is continuously regenerated from the energy source, e.g. glucose.

Lonza, for example, has commercialized processes for highly chemo- and regioselective microbial ring hydroxylation and side-chain oxidation of heteroaromatics (see Fig. 2.32 for examples) (Kiener, 1995, 1999). The pharmaceutical intermediate 5-methylpyrazine-2-carboxylic acid, for example, is manufactured by microbial oxidation of 2,5-dimethylpyrazine. Many conversions of the type shown in Fig. 2.32 would not be possible by conventional chemical means.

DuPont has developed a process for the manufacture of glyoxylic acid by aerobic oxidation of glycolic acid (Fig. 2.33) mediated by whole cells of a recombinant methylotrophic yeast (Gavagnan *et al.*, 1995). The glycolic acid raw material is readily available from the acid-catalysed carbonylation of formaldehyde. Traditionally, glyoxylic acid was produced by nitric acid oxidation of acetaldehyde or glyoxal, processes with high E factors, and more recently by ozonolysis of maleic anhydride.

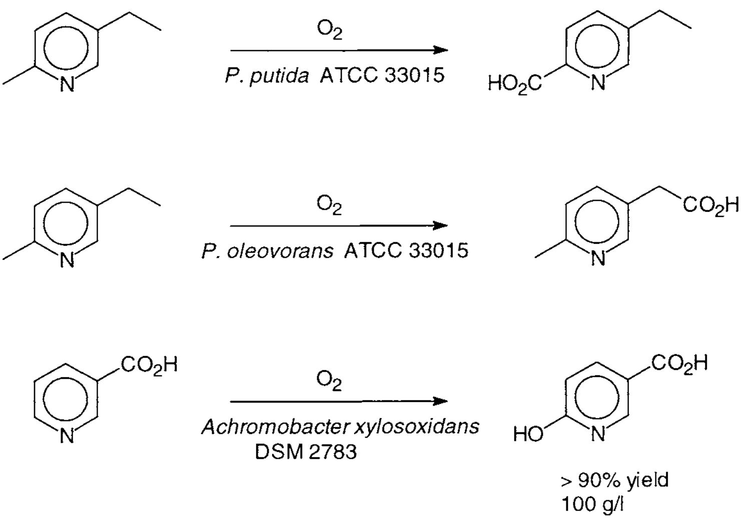


Figure 2.32. Microbial oxidations of heteroaromatics.

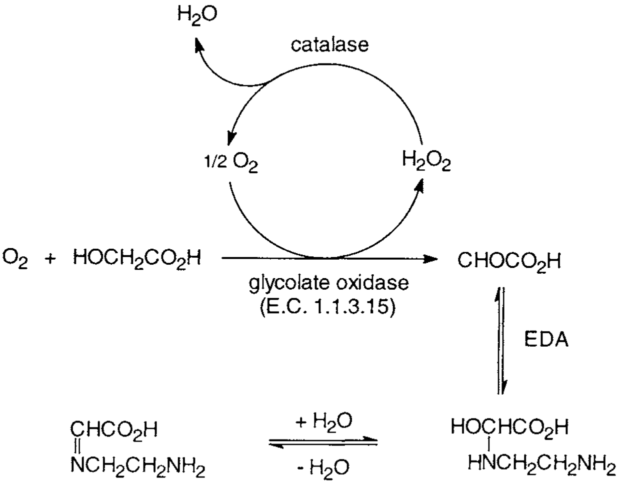


Fig. 2.33. DuPont process for glyoxylic acid.

Another example of a biocatalytic transformation ousting a chemical one, in a rather simple reaction, is provided by the Lonza nitotinamide process (Fig. 2.34) (Heveling, 1996). In the final step a nitrile hydratase, produced by whole cells of *Rh. rhodoccrous*, catalyses the hydrolysis of 3-cyano-pyridine to give nitotinamide in very high purity. In contrast, the conventional chemical hydrolysis afforded a product contaminated with nicotinic acid.

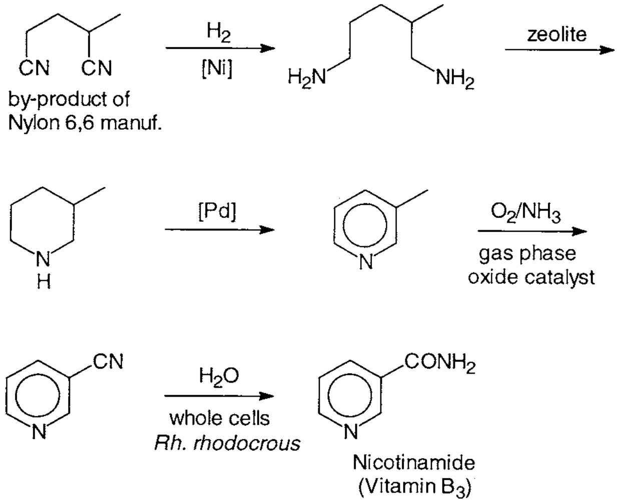


Figure 2.34. Lonza nicotinamide process.

The above processes are a mere fraction of the plethora of biotransformations that have been or are currently being commercialised. We expect biocatalysis to make further inroads into fine chemicals production in the future. Biotransformations have many advantages compared to conventional chemical processes: they are performed in water under mild conditions and with a high degrees of selectivity, thus avoiding emissions of organic solvents and reducing waste formation.

2.8.8. Enantioselective catalysis

Another major trend in performance chemicals is towards the development of products, e.g. drugs, pesticides, food additives, etc., that are more targeted in their action, with less undesirable side-effects.

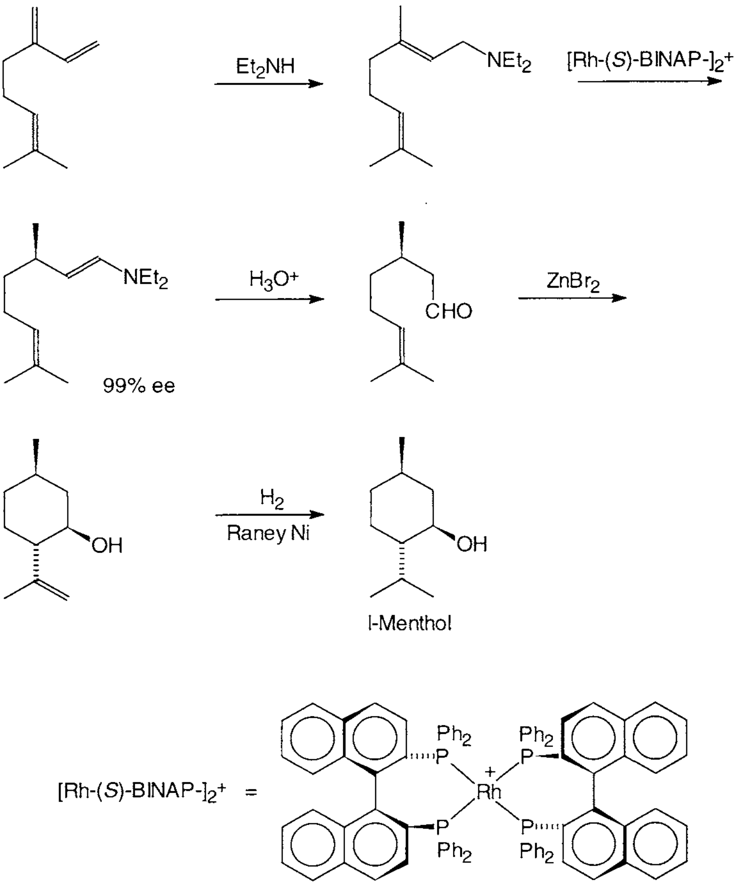


Figure 2.35. Takasago l-menthol process.

In the case of chiral molecules that are biologically active the desired activity almost always resides in only one of the enantiomers. The other enantiomer constitutes isomeric ballast that does not contribute towards the desired activity and may even exhibit unwanted side effects. Hence, there is a marked trend in pharmaceuticals, agrochemicals and flavours and fragrances towards the marketing of products as enantiomerically pure compounds. This, in turn, has generated a demand for economical methods for the synthesis of pure enantiomers (Sheldon, 1993a).

The same reasoning applies to the synthesis of pure enantiomers as to organic synthesis in general: processes should be atom efficient and have low E factors, *i.e.* involve catalytic methodologies. This is reflected in the increasing attention being focused on enantioselective catalysis, using either enzymes or chiral metal complexes.

An elegant example of a highly efficient catalytic asymmetric synthesis is the Takasago process (Akutagawa, 1992; Kumobayashi, 1996) for the manufacture of l-menthol, an important product in the flavours and fragrances industry. The key step is a Rh-Binap catalysed isomerization of a prochiral enamine to a chiral amine (Fig. 2.35). The product is obtained in 99% ee using a substrate/catalyst ratio of 8,000, and recycling of the catalyst affords total turnover numbers of up to 400,000. The Takasago process currently accounts for about half of the world production (ca. 4,500 tons) of l-menthol.

An even more impressive example of catalytic efficiency has recently been disclosed by Novartis (Bader and Blaser, 1997). The key step in a process for the synthesis of the optically active herbicide, (S)-metolachlor involves asymmetric hydrogenation of a prochiral imine catalysed by an iridium-ferrocenyldiphosphine complex (see Fig. 2.36).

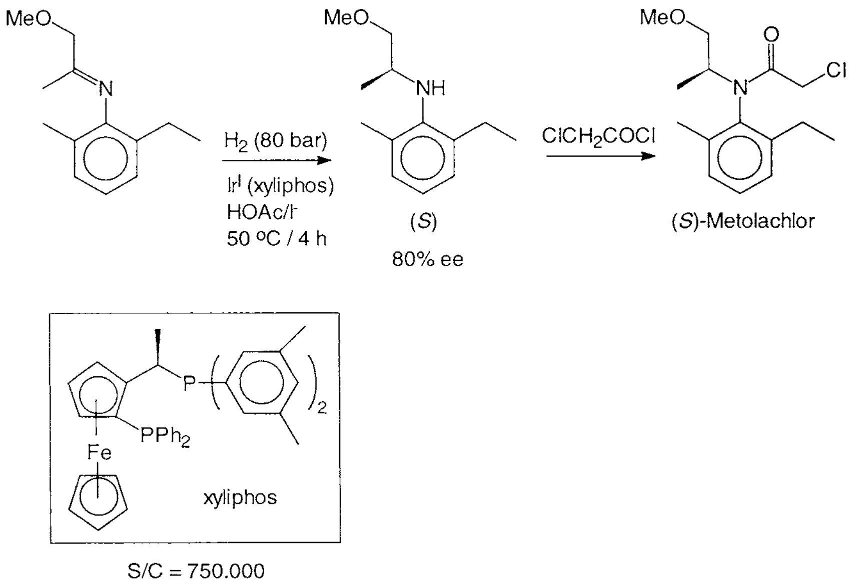


Figure 2.36. Synthesis of (S)-metolachlor.

The substrate/catalyst ratio is 75,000, and one million turnovers are achieved in six hours, giving a product with an ee of 80%. A higher ee can be obtained, at lower substrate/catalyst ratios, but are not actually necessary for this product. This process will be used to produce several thousands tons per annum of (S)-metolachlor, to replace the previously marketed racemic metolaclor.

2.8.9. Putting it all together: process integration

As mentioned earlier, a major cause of high costs in fine chemicals manufacturing is the complexity of the processes. Hence, the key to more economical processes is reduction of the number of unit operations by judicious process integration. This pertains to the successful integration of, for example, chemical and biocatalytic steps, or of reaction steps with (catalyst) separations. A recurring problem in the batch-wise production of fine chemicals is the (perceived) necessity for solvent switches from one reaction step to another or from the reaction to the product separation. Process simplification, e.g. by integration of reaction and separation steps into a single unit operation, will provide obvious economic and environmental benefits. Examples include catalytic distillation, and the use of (catalytic) membranes to facilitate separation of products from catalysts.

Some companies are successfully integrating chemo- and biocatalytic transformations in multi-step syntheses. An elegant example is the Lonza nicotinamide process mentioned earlier (see Fig. 2.34). The raw material, 2-methylpentane-1,5-diamine, is produced by hydrogenation of 2-methylglutaronitrile, a byproduct of the manufacture of nylon-6,6 intermediates by hydrocyanation of butadiene. The process involves a zeolite-catalysed cyclization in the vapour phase, followed by palladium-catalysed dehydrogenation, vapour-phase ammoxidation with NH_3/O_2 over an oxide catalyst, and, finally, enzymatic hydrolysis of a nitrile to an amide.

Another illustration of the enormous potential of catalytic methodologies in fine chemicals manufacture is the new Rhône-Poulenc process for the flavour ingredient, vanillin (Ratton, 1998). The process involves four steps, all performed with a heterogeneous catalyst, starting from phenol (Fig. 2.37).

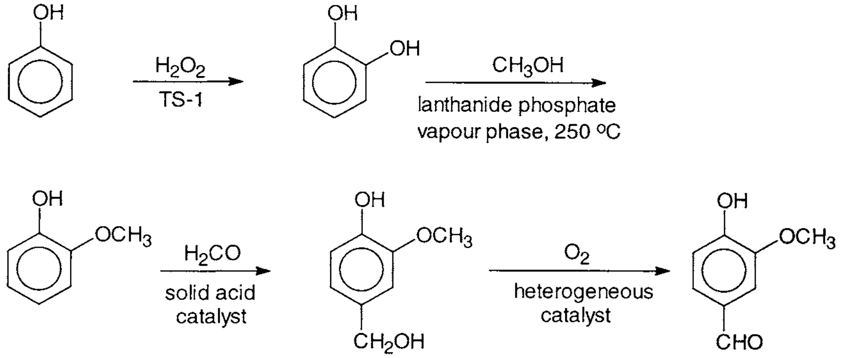


Figure 2.37. Rhône-Poulenc process for vanillin.

Finally, it is appropriate to close this chapter with an example from the roots of fine chemicals: the dyestuff, indigo. Manufacture of indigo involves chemistry (see Fig. 2.15) which has hardly changed from the time of the first commercial synthesis more than a hundred years ago (see earlier). Mitsui Toatsu has developed a two-step process in which indole is produced by vapour-phase reaction of ethylene glycol with aniline over a supported silver catalyst (Inoue *et al.*, 1994). Subsequent liquid-phase oxidation of the indole, with an alkyl hydroperoxide in the presence of a soluble molybdenum catalyst, affords indigo.

However, this environmentally attractive route in the future may have to compete with an even greener route: the fermentation of glucose. Genencor recently disclosed a method for the conversion of L-tryptophan to indigo (Figure 2.38) using a recombinant strain of *E. coli* (Murdock *et al.*, 1993). Since tryptophan can be produced by the fermentation of glucose, the direct conversion of the latter to indigo is, in principle, feasible.

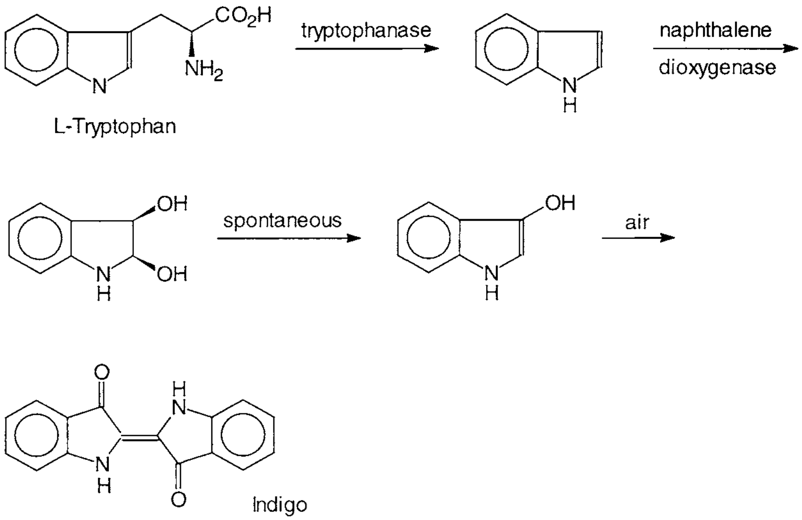


Figure 2.38. Genencor process for indigo.

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3. Catalysis in Fine Chemicals

3.1. INTRODUCTION

Catalysis opens reaction pathways that are not accessible to uncatalysed reactions. It should be self-evident that thermodynamics predict whether a reaction can occur. So, catalysis influences reaction rates (and as a consequence selectivities), but the thermodynamic equilibrium still is the boundary. Catalysis plays a key role in chemical conversions, although it is fair to state that it is not applied to the same degree in all sectors of the chemical industry. While in bulk chemicals production catalytic processes constitute over 80 % of the industrially applied processes, in fine chemicals and specialty chemicals production catalysis plays a relatively modest role. In the pharmaceutical industry its role is even smaller. It is the opinion of the authors that catalysis has a large potential in these areas and that its role will increase drastically in the coming years. However, catalysis is a multidisciplinary subject that has a lot of aspects unfamiliar to synthetic chemists. Therefore, it was decided to treat catalysis in a separate chapter.

Catalysis can be treated from various points of view. One might structure the discussion by starting from the organic reactions, e.g. selective hydrogenation, dehydrogenation, selective oxidation, and so on. Subsequently, for every class of reactions the potential of catalysis could be outlined. Section 2.8 is structured in roughly such a way. Here we have chosen to treat the subject in a more discipline-oriented way. First, the principle of catalysis is explained. Subsequently, the key properties of catalysts are discussed: *activity, selectivity*, and *stability*. For a good understanding it is crucial to have a good idea of the structure (both chemical and physical) of a catalyst. Chemists will immediately appreciate that the chemical structure should be understood, but it is equally important to have insight in the physical structure because it has direct consequences for the success or failure of the catalytic process. The way catalysis is described quantitatively is by kinetic equations. Catalysis is a kinetic phenomenon (see Berger *et al.*, 2001 and Chapter 5).

This chapter[1] focuses on heterogeneous catalysis, which is most important in fine chemicals production. Table 3.1 presents a number of examples of catalysis in fine chemistry. These examples are divided in heterogeneously catalysed processes and homogeneously catalysed processes. A detailed treatment of heterogeneously catalysed processes for the production of fine chemicals is also given in the book edited by Sheldon and van Bekkum (2001).

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[1] A large part of this chapter has been taken from the course notes 'Catalysis and Catalysts' by J.A. Moulijn, Xu Xiaoding, F. Kapteijn, and G. Mul, TU Delft, The Netherlands, 2001.

Table 3.1
Examples of gas-liquid catalytic reactions in fine chemistry, based on information compiled by Mills and Choudhari (1997) and Mills *et al.* (1992).

Reaction	Catalyst	Product	Application
Heterogeneous catalyst			
Hydrogenation of glucose	Raney Ni	Sorbitol	Pharma
Isomerization of lactose	Alkaline ion-exchangers	Lactulose	Pharma
Hydrogenation of cinnamaldehyde	Pt-Co/C or Pt-Ru/C	Cinnamyl alcohol	Fine chemicals, perfumery
Selective hydrogenation of citral	Rh/SiO_2	Geraniol, nerol	Fragrances
Hydrogenation of benzaldehyde	Ni	Benzyl alcohol	Fine chemicals
Hydrogenation of maleic anhydride	Cu/Cr (copper chromite)	γ-butyrol-acetone, THF	Solvents
Hydrogenation of 2,4-dinitrotoluene	Pd/alumina or Raney Ni	Toluene diamine	Fine chemicals
Hydrogenation of *o*-nitroanisole	Pd/C	*o*-Anisidine	Dyes, fine chemicals
Hydrogenation of 1,5,9-Cyclododecatriene	Pd/Al_2O_3	Cyclododecene	Intermediate for 12-laurolactam (pharma)
Hydrogenation of α,β-unsaturated esters	Raney Ni	Saturated esters	Fine chemicals, fragrances
Stereoselective hydrogenation of 11-hexadecynyl acetate	Pd Lindlar catalyst	Insect sex pheromones	Agrochemicals
Enantioselective hydrogenation of α-ketoesters	Pt/C, Pt/Al_2O_3	α-hydroxyesters	Chiral intermediates
Asymmetric hydrogenation of 4-phenyl-2-oxoethylbutyrate	Modified Raney Ni	Enalapoil	Pharma
Oxidation of glucose	Pd-Bi/C	Glutonic acid	Food, detergents, pharma
Oxidative dehydrogenation of 3-hydroxy-4-methyl-4-penten-2-one	CuO-based catalyst	4-methyl-4-penten-2,3-dione	Fine chemicals
Dehydration of carboxamides	Sulphated Zr catalyst	Nitriles	Fine chemicals
Pinacol rearrangement of 1,2-diols	Zeolites NaX, NaY, NaHX, NaHY	Carbonyl compounds	Fine chemicals
Acylation of benzofuran	Zeolite Y	Acetylbenzofuran	Fine chemicals
Homogeneous catalyst			
Selective hydrogenation of C-22/C-23 double bond in synthesis of ivermectin	$Rh(I)Cl(PPh_3)_3$	Ivermectin	Pharma
Oxidation of indole	Cumyl hydroperoxide	Indigo	Dye stuff
Oxidation of *p-tert*-butyltoluene	Br-promoted Co complex	*p-tert*-Butyl-benzaldehyde	Fine chemicals, perfumery
Hydroformylation of acrylonitrile	Co-carbonyl complex	$NC(CH_2)_2CHO$	Food products
Hydroformylation of 1-decene	$HRh(CO)\ (PPh_3)_3$	Undecanal	Perfumery
Carbonylation of 1,4-dacetoxy butane	Rh-carbonyl iodide complex	Adipic acid	Specialty chemicals
Asymmetric hydrogenation of 2-naphthyl-4-methoxyacrylic acid	Ru-BINAP-chiral complex	*S*-Naproxen	Pharma

3.2. MECHANISM OF CATALYSIS

In catalysis active sites are operative that allow for an alternative reaction path. For a satisfactory catalyst this alternative pathway leads to higher rates and higher selectivity. In heterogeneous catalysis reactant molecules adsorb at active sites on the catalyst surface; at the surface sites reactions occur and products are desorbed subsequently. After desorption, active sites are again available for reactant molecules and the cycle is closed. In homogeneous catalysis the situation is essentially identical. Here complexation and decomplexation occur. A complication in heterogeneous catalysis is the need for mass transfer into and out of the catalyst particle, which is usually porous with the major part of the active sites at the interior surface.

3.2.1. Heterogeneous catalysis

Fig. 3.1 (Kapteijn *et al.*, 1999) shows the model commonly used to present a reversible reaction ($A \leftrightarrow B$) taking place on the surface of a solid catalyst. Three elementary steps are distinguished, *i.e.* adsorption of A on an active site *, reaction of this adsorbed complex to adsorbed complex B^*, and desorption of B from the active site.

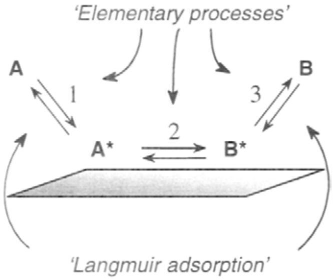


Figure 3.1. Chemical and physical steps in catalysis (Kapteijn *et al.*, 1999).

For a catalytic reaction of a reactant from a single fluid phase (either gas or liquid) to take place on a solid catalyst, diffusion processes also play a role, so in the complete process the following steps can be distinguished:

- diffusion from the bulk to the catalyst particle (1)
- diffusion to the active sites in the interior of the particle (2)
- adsorption at the active sites (3)
- reaction at the surface (4)
- desorption of products (5)
- diffusion out of the particle (6)
- diffusion from the particle to the bulk (7)

These steps apply to a system of a solid catalyst and a single fluid. When more than one fluid is present, additional steps occur. This situation is treated in Section 5.4. When we deal with homogeneous catalysis the picture does not change fundamentally. In this case the diffusion steps within the particle do not occur, but apart from that the picture is correct.

It is most convenient to explain catalysis using an example. We have chosen a hydrogenation catalysed by nickel in the metallic state. According to the schematic of Fig. 3.1 the first step in the actual catalysis is 'adsorption'. It is useful to distinguish 'physisorption' and 'chemisorption'. In the former case weak, physical forces and in the latter case relatively strong, chemical forces play a role. When the molecules adsorb at an active site physisorption or chemisorption can occur. In catalysis often physisorption followed by chemisorption is the start of the catalytic cycle. This can be understood from Fig. 3.2, which illustrates the adsorption of hydrogen on a nickel surface.

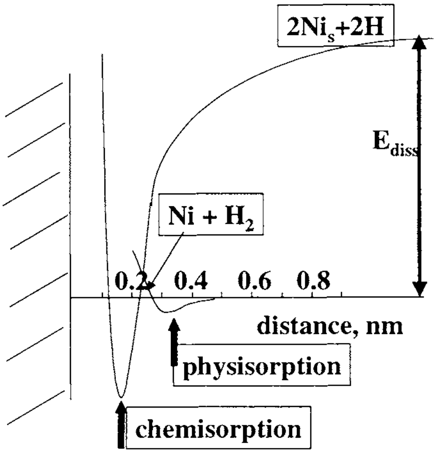


Figure 3.2. Potential energy diagram of chemisorption for the adsorption of hydrogen on nickel (after Le Page, 1987).

First H_2 is physically adsorbed on the surface. The forces are weak and the adsorption enthalpy is only slightly negative. Subsequently, chemical bonding between Ni atoms and the hydrogen atoms of H_2 molecule takes place while simultaneous dissociation of the H_2 molecule takes place. The chemisorption enthalpy is strongly negative (exothermic reaction).

Fig. 3.3 gives a model for the adsorption states. In physical adsorption the molecule is adsorbed as such (without dissociation): the forces are of the van der Waals type. In chemisorption chemical bonds have been formed; for H_2 this is only possible at the cost of dissociation. In the transition state the H-atoms are bonded both to each other and to Ni-atoms in the surface of the metal crystal.

The influence of the Ni atoms becomes clear from a comparison of the actual reaction path, which consists of physical adsorption and subsequent dissociative chemisorption, with the theoretical alternative reaction path, consisting of dissociation of H_2 followed by the formation of two Ni-H bonds. H_2 is a very stable molecule and, as a consequence, the potential energy of the dissociated H-atoms is very high. In moving to the adsorbed state, Ni-

H bonds are formed and the result is a strong decrease in potential energy. The path of the latter process is represented in Fig. 3.2 by the curve labelled '$2Ni_s$+2H', while the former process is represented in this figure by the curve labelled with 'Ni + H_2' and the left part of curve '$2Ni_s$ + 2H'. The fundamental point is that the Ni atoms facilitate the dissociation of H_2 by providing increasingly strong Ni-H bonding along the reaction co-ordinate. In this way the energetically unfavourable dissociation of the hydrogen molecules is compensated by the simultaneous formation of Ni-H bonds. In both cases the same products are formed, but the activation energy differs profoundly.

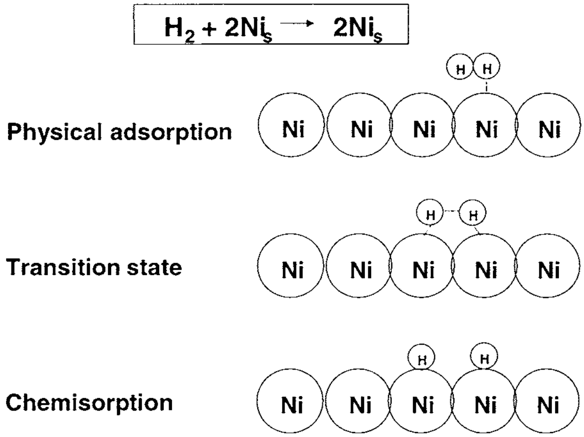


Figure 3.3. Adsorption of hydrogen on nickel (after Le Page, 1987).

It is of tremendous practical importance that at many metal surfaces chemisorption of a large variety of molecules can occur. This can easily be explained from a discussion on a molecular level as follows. At the surface of a crystal the co-ordination number of the metal atoms is lower than in the bulk of the crystal. Fig. 3.4 illustrates this for Ni. In the bulk the co-ordination number of all Ni atoms is 12, whereas on the three faces in Fig. 3.4 these numbers are only 8, 7 and 9 for the (100), (110) and (111) surfaces, respectively. So-called 'free valences' exist at the surface. The numbers between brackets are the Miller indices of the surfaces.

As the crystal surface exposed to the atmosphere is usually not ideal, specific sites exist with even much lower co-ordination numbers. This is shown schematically in Fig. 3.5, which gives a model comprising so-called step, kink and terrace sites (Morrison, 1982). This analysis suggests that even pure metal surfaces contain a wide variety of active sites, which indeed has been confirmed by surface science studies. Nevertheless, catalytic surfaces often behave rather homogeneously. Later it will be discussed why this is the case. In short, the most active sites deactivate easiest and the poorest active sites do not contribute much to the catalytic activity, leaving the average activity sites to play the major role.

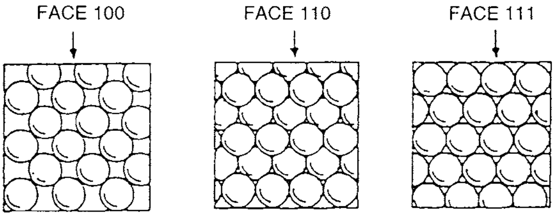


Figure 3.4. The influence of the crystallographic plane on the number of surface atoms and the structure of the metallic surface, as illustrated for nickel; The co-ordination numbers of the atoms in the three crystal surfaces are 8, 7 and 9 for the (100), (110) and (111) plane, respectively. Because bulk Ni has 12 neighbours, the surface atoms are unsaturated (after Le Page, 1987).

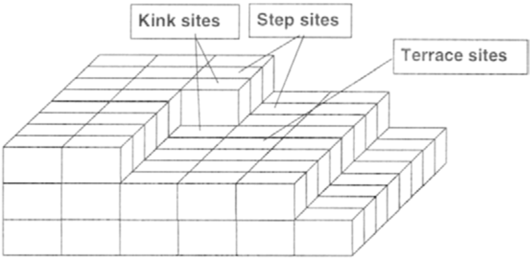


Figure 3.5. Simplified model of a metal surface.

In the foregoing it has been discussed how a metal can dissociate H_2. Fig. 3.6 explains the principle of catalysis with an example of the hydrogenation of ethylene, for which dissociative chemisorption of hydrogen is an elementary step in the catalytic cycle. The adsorption of alkenes, on the other hand, is non-dissociative.

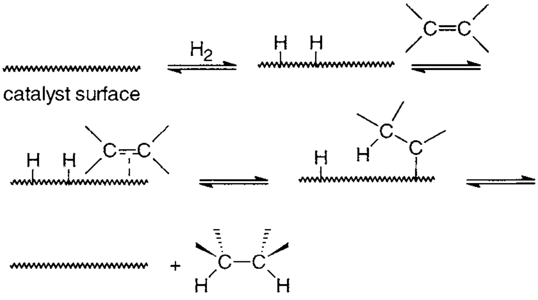


Figure 3.6. Mechanism of ethylene hydrogenation.

3.2.2. Homogeneous catalysis

The mechanism of homogeneous catalysis involves complexation and decomplexation steps, analogously to adsorption and desorption in heterogeneous catalysis. In homogeneous catalysis using transition metals the catalytic centre comprises a metal atom surrounded by ligands. Transition metals are very versatile catalysts, mainly as a result of their variability of oxidation state and co-ordination number. Of great importance is their ability to readily interchange between oxidation states and to rapidly change between co-ordination numbers. Figure 3.7 illustrates some principles of homogeneous transition-metal catalysis using the hydrogenation of ethylene on $RhCl(PPh_3)_3$ as an example.

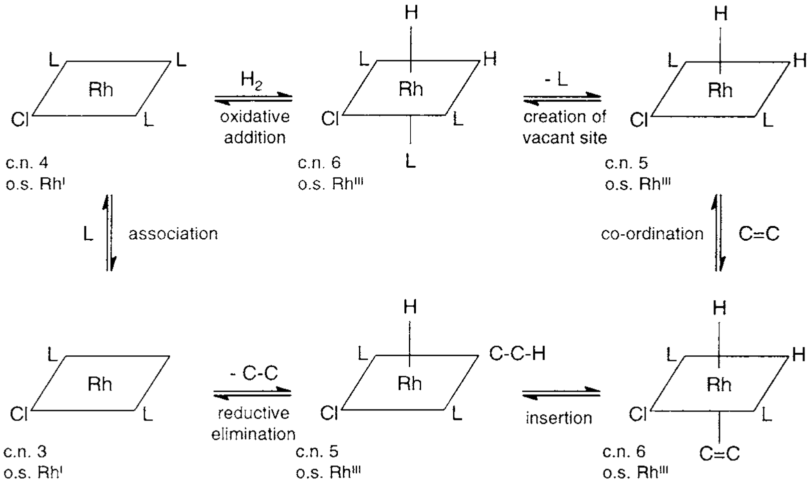


Figure 3.7. Some principles of homogeneous transition-metal catalysis; L = PPh_3 c.n. = co-ordination number; o.s. = oxidation state.

The catalytic cycle starts with the so-called oxidative addition (analogue in heterogeneous catalysis: dissociative adsorption) of hydrogen to the Rh complex. After the creation of vacant site by loosing a PPh_3 ligand, ethylene interacts with Rh by co-ordination, corresponding to non-dissociative adsorption in heterogeneous catalysis. Then insertion of the ethylene takes place to form an ethyl group. The hydride ion then combines with the ethyl to form ethane, which leaves the co-ordination sphere of the metal, corresponding to desorption in heterogeneous catalysis. This process is called reductive elimination. Reductive elimination is essentially the reverse of oxidative addition. The cycle is completed by addition of a PPh_3 ligand.

3.3. HETEROGENEOUS CATALYSTS - TYPES AND PREPARATION

Catalysts can be divided in classes in several ways. Based on their appearance catalysts can be subdivided into:

- soluble catalysts (homogeneous),
- bio-catalysts (enzymatic),
- solid catalysts (heterogeneous).

The third category is the major subject of this section.

3.3.1. Chemical composition of solid catalysts

Figure 3.8 shows a classification of solid catalysts according to their chemical composition.

Metals, alloys
- Raney Ni, Co, Ru, Fe
- Pt/Al_2O_3, Ni/Al_2O_3
- Ni/SiO_2
- Pt/C, Pd/C

Oxides
- Silica, alumina, zeolites, clays
- TS-1
- Fe_2O_3

Sulfides
- $CoS\text{-}MoS_2/Al_2O_3$

Chlorides
- $CuCl_2/Al_2O_3$

Ion-exchange resins

Figure 3.8. Types of solid catalysts – chemical composition.

Figure 3.8 shows a variety of materials. This, of course, is not surprising. In principle, the composition of a solid material will depend on several factors, including the reaction conditions. For example, when an oxidation is carried out a metal like Co will be in the metallic state or the oxidized state depending on the reaction conditions. When used in chlorination many systems will be present as chlorides.

Metals are widely used in catalysis. In some specific cases they are applied in the form of gauzes, but usually a higher 'dispersion' (even up to 90%) is aimed for. A major reason for this is the price of the metals (very often noble metals are used), in combination with an optimized use of the reactor volume. The ratio of number of surface atoms (n_S) to the total number of atoms (n_T) is called the 'dispersion', also known as '*D*':

$$D = \frac{n_S}{n_T} \qquad (1)$$

Usually, catalyst preparation is aimed at maximizing *D*.

Oxides are widely used as supports. The major examples are silica (porous SiO_2), alumina (porous Al_2O_3), and zeolites. Oxides are also used as catalysts. In bulk chemistry they are generally used in oxidation reactions. Examples are V_2O_5, CuO, and Fe_2O_3. Often the reactions are carried out in the gas phase. In fine chemicals production gas-phase reactions are much less common. An example in fine chemicals production is epoxidation. Many examples exist of homogeneous catalysis by Mo-complexes. A rather recent development is the epoxidation with hydrogen peroxide catalysed by titanium silicalites. In heterogeneous catalysis in the liquid phase leaching of the active phase is always a point of concern. The Mo-complexes cannot be substituted for a heterogeneous catalyst, although many research groups have attempted this. It has not been possible to find a Mo-based system inert towards leaching. Titanium silicates were a breakthrough. They can be used as a stable heterogeneous catalyst in liquid-phase epoxidations.

3.3.2. Shape and size of solid catalysts

Solid catalysts can be subdivided further according to the reactor chosen. Dependent on the type of reactor the optimal dimensions and shapes of the catalyst particles differ. Catalysts applied in fixed beds are relatively large particles (typically several mm in diameter) in order to avoid excessive pressure drops. Extrudates, tablets, and rings are the common shapes. Figure 3.9 shows some commonly encountered particle shapes.

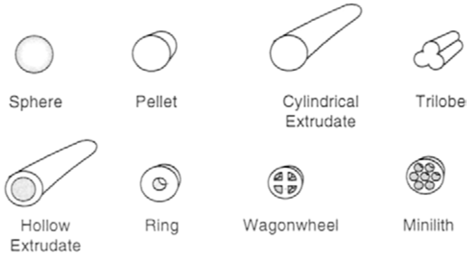


Figure 3.9. Various shapes of commercial catalysts.

The particle size and shape to a large extent determine mass- and heat-transfer characteristics, and also properties like catalyst wetting. Mechanical strength should be sufficiently high in order to avoid the formation of fines, which causes increased pressure drop and eventually plugging of the reactor. Slurry reactor catalysts are powders with a diameter of typically 25-50 μm. Here also mechanical strength is important because attrition occurs and, as a consequence, filterability decreases. In loop reactors the mechanical stresses the particles have to endure are considerable, and as a consequence, mechanical strength is an issue. In many applications, in particular in fine chemicals production, the catalyst is separated form the reaction mixture by settling. In that case, a high density is favourable.

The optimum size and shape of catalyst particles is a compromise between contrasting demands:

- minimum pressure drop,
- minimum pore diffusion resistance,
- maximum mechanical strength,
- minimum cost.

The main shaping processes used in catalyst manufacture are pelletization, extrusion, and granulation.

When hydrogenation is carried out in a continuous process often so-called trickle-flow reactors are used. Mass-transfer limitations often occur. An elegant improvement is the application of extrudates with a noncircular cross section, which increases the external surface without increasing the pressure drop. *'Trilobe'* and *'Quadrilobe'* shapes are generally used in oil-refinery processes and they might also be useful in fine chemicals production.

A modern development is the application of structured reactors, often of the monolith type. Structured reactors are not new. A catalyst particle can be considered as a (small) reactor. In the case of monoliths the difference between reactor and catalyst particle vanishes (see Fig. 3.10). Monoliths are applied at a very large scale in the cleaning of exhaust gases. Major advantages are their low pressure drop, high resistance against fouling by dust, and easy handling. Recently, the use of monolithic reactors in multiphase applications has also received attention (Cybulski and Moulijn, 1994; Kapteijn *et al.*, 1999a). Probably these multiphase applications will play a role in the fine chemicals industry as a result of several advantages (see Section 5.4.7).

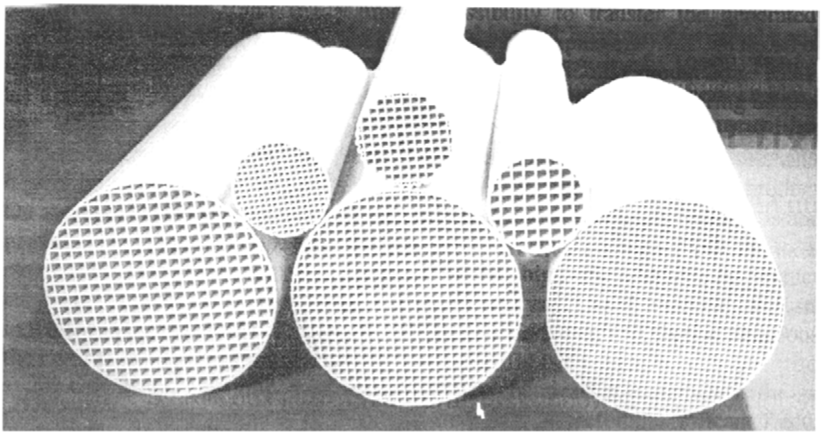


Figure 3.10. Examples of monolithic catalysts.

In heterogeneous catalysis reactions take place at the surface of the catalyst. In order to maximize the production rates, catalysts are, in general, porous materials. In practice, the surface area of catalysts ranges from a few up to 1500 square metres per gram of catalyst. It is instructive to calculate the specific surface area as a function of the particle size.

Suppose the catalyst material (density, ρ in kg/m^3) consists of uniform spherical particles. The specific surface area (in m^2/kg) can be calculated as follows:

volume of one particle, $V = 1/6\ \pi\ d^3$	(m^3)
weight of one particle, $W = 1/6\ \rho\ \pi\ d^3$	(kg)
surface area of one particle, $S_p = \pi\ d^2$	(m^2)
specific surface area, $S_A = S_p/W = \pi\ d^2/(\rho\ 1/6\ \pi\ d^3) = 6/\rho\ d$	(m^2/kg)

Figure 3.11 shows a plot of this latter equation. As an example nickel has been chosen. It is obvious that only at unrealistically low values of the particle sizes (1-10 nm) reasonable surface areas are obtained. It is impossible to apply such small particles in reactors: in slurry reactors filtering would be impossible and in fixed-bed reactors the pressure drop would be so high that flow rates would be too low to be practical. In practice, in nearly all applications of heterogeneous catalysis porous materials are used, of which the largest part of the surface area is that of the interior pore surface. So, the catalyst particles can be sufficiently large to exhibit acceptable pressure drop, while they possess the large surface area corresponding to extremely small particle sizes.

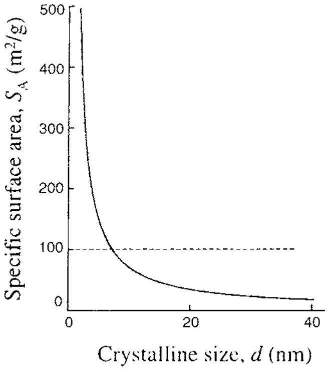


Figure 3.11. Specific surface area as a function of crystallite size of Ni (ρ = 8900 kg/m^3); d = particle diameter (nm).

3.3.3. Catalyst production

For a good understanding of the utilization of catalysts it is very helpful to know how catalysts are manufactured. Catalyst manufacture is even more important in catalytic process development, which often involves the preparation of catalysts in the laboratory in order to satisfy custom needs. Therefore, this section treats catalyst manufacture in some detail.

Depending on the process requirements catalysts are produced in a variety of ways. Fig. 3.12 shows some typical processes used in catalyst manufacture. In all cases the process starts from a solution. The various process steps used are explained in subsequent sections. Solid catalysts can be subdivided in bulk catalysts and supports and catalysts prepared by impregnation of shaped supports.

3.3.3.1. Bulk (Raney-metal) catalysts

The most important example of this category is Raney nickel, which is extensively used in hydrogenation reactions in fine chemistry. The catalyst has been named after Murray Raney who invented this catalyst in 1924. It is prepared by the reaction of a powdered nickel-aluminium alloy with aqueous sodium hydroxide to selectively remove a large fraction of the aluminium component (see Figure 3.12). The product consists of porous nickel with a high surface area. The remaining aluminium probably has an essential function in stabilizing the small nickel particles.

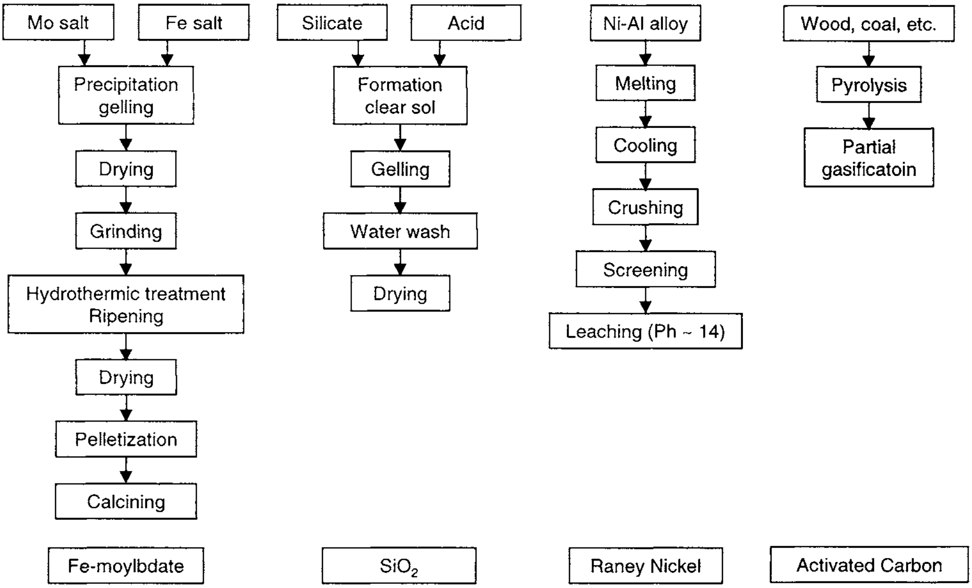


Figure 3.12. Typical examples of catalyst manufacture (after Le Page 1987).

Raney nickel is a useful catalyst for hydrogenations at mild conditions. It is, however, sensitive to poisoning and not very stable at high temperatures. Another disadvantage is that regeneration is not always possible; in many cases the catalyst must be melted with aluminium until the right Al-Ni alloy is formed. Then the preparation procedure has to be repeated again. Moreover, the preparation procedure is not very reproducible.

This type of catalyst is not limited to nickel; other examples are Raney-cobalt, Raney-copper and Raney-ruthenium. When dry, these catalysts are pyrophoric upon contact with air. Usually they are stored under water, which enables their use without risk. The pyrophoric character is due to the fact that the metal is highly dispersed, so in contact with oxygen fast oxidation takes place. Moreover, the metal contains hydrogen atoms and this adds to the pyrophoric nature. Besides the combustion of the metal also ignition of organic vapours present in the atmosphere can occur. Before start of the reaction it is a standard procedure to replace the water by organic solvents but care should be taken to exclude oxygen. Often alcohol is used. The water is decanted and the wet catalyst is washed repeatedly with alcohol. After several washes with absolute alcohol the last traces of water are removed.

During water storage slow oxidation takes place. In particular the most active Raney catalysts show severe deactivation (they should not be stored more than a few weeks). Other types of catalysts though less active are much more stable. In fine chemistry activity is often not the most important catalytic property. This certainly holds for Raney nickel. On a nickel basis, in general, they are much less active than supported nickel catalysts, but they are cheap, so the use of a large amount of catalyst does not result in very unfavourable economics. The catalyst can be removed from the reaction mixture by filtration. In general, Raney catalysts are not regenerated but treated as chemical waste or, preferably, sent to a company for recycling.

3.3.3.2. Catalyst supports

Support materials are commonly used in heterogeneous catalysis. Their major function is to maximize the dispersion of the active phase by providing a large surface area over which the active phase can be distributed. In this way the catalyst material is shaped into a form suitable for use in technical reactors. Supports are not always chemically inert: they can also show certain catalytic activity and often they act as a stabilizer for the actual active phase. A number of materials are used as catalyst supports. Table 3.2 gives an overview.

Table 3.2
Overview of catalyst carrier materials and their applications

Support	Application
Alumina	Hydrogenation Dehydrogenation Selective oxidation Metathesis
Silica	Polymerization Hydrogenation Oxidation
Zeolites	Organic synthesis
Diatomaceous earth	Hydrogenation
Clays	Hydrogenation Condensation
Cordierite monoliths	Automotive exhaust gas cleaning
Activated carbons	Hydrogenation in fine chemical industry
Silica-alumina	Ammoxidation Dehydrogenation
Titania	Selective oxidation (V_2O_5/TiO_2)

Most of these supports have large surface areas in the range of 100-700 m^2/g. They are porous solids composed of small micrograins. From Fig. 3.11 it should be clear that the size of these micrograins usually is in the nm range.

The choice of the carrier depends on several factors. The *texture* (size and shape of the pores, the way the pores are connected, etc.) of the support determines, to a large extent, mass- and heat-transfer characteristics. For instance, in selective oxidation and hydrogenation, pores that are too narrow or too long will reduce the selectivity because the sequential reactions towards complete oxidation are favoured.

Regenerability often is also a requirement. In the life cycle of a catalyst the most severe conditions are not always the reaction conditions; regeneration conditions may well be more severe that the regular reaction conditions. Examples are hydrogenation catalysts that are regenerated by oxidative treatment in diluted oxygen. These catalysts must be resistant to oxidative treatment at high temperatures. This makes alumina a suitable carrier for these processes.

Silicagel. Silicagel is usually prepared from sodium silicates, which are produced as glasses with a stoichiometry of SiO_2/Na_2O = 0.6-0.25. At the right pH they are soluble in water and the solution contains mixtures of silicate anions: monomeric, dimeric, trimeric species, etc. (Fig. 3.13).

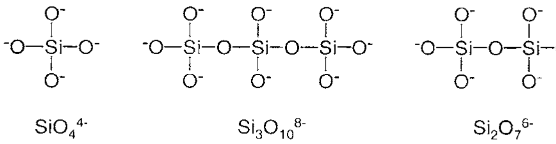


Figure 3.13. Examples of silicalite anions.

The composition of the solution depends on concentrations and pH value. In highly diluted solutions, mainly monomeric and dimeric species are present (Doesburg *et al.*, 1999).

When a sodium silicate solution is acidified condensation reactions occur. Firstly, silanol groups are formed:

$$\text{-O-Si-O}^- + H^+ \rightarrow \text{-O-Si-OH} \tag{2}$$

and subsequently Si-O-Si bonds are generated:

$$\text{-O-Si-OH} + \text{-O-Si-O}^- \rightarrow \text{-O-Si-O-Si-O-} + OH^- \tag{3}$$

These reactions initially lead to ring structures, see for example Figure 3.14.

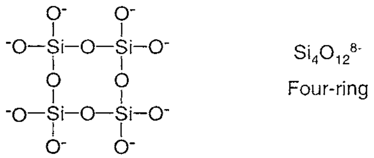


Figure 3.14. Ring structure.

The ring structures undergo further (poly)condensation reactions. These polymerization reactions proceed rapidly until particles with diameters of typically 1-2 nm are formed. Schematically, the process can be summarized as shown in Figure 3.15.

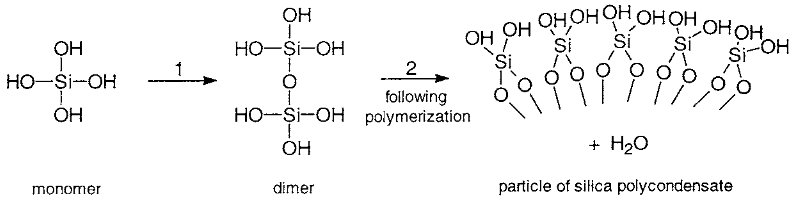


Figure 3.15. Formation of silica particle by polycondensation of silicic acid molecules (after Le Page, 1987).

The particles or micelles tend to ionize in the solution. From these micelles a three-dimensional network can be formed by interparticular condensation reactions of the silanol groups. The rate of these reactions will be a function of pH value, SiO_2 concentration, electrolyte concentration, and reaction temperature. The resulting solid is called '*hydrogel*'. Conditions are chosen such that a porous solid is formed. The charge of the micelles determines whether particle growth or particle aggregation and gelation occur. For instance, by lowering the pH sufficiently in acidifying a sodium silicate solution, the charge of the micelles is reduced and a gel will be formed (see Fig. 3.16).

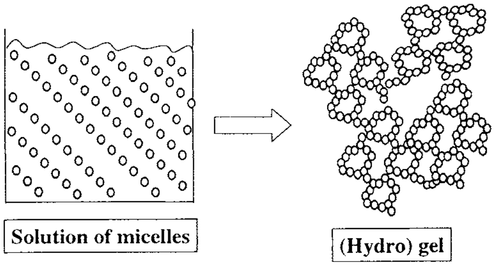
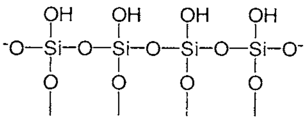


Figure 3.16. Formation of gels (after Le Page, 1987).

After washing in order to remove electrolytes, the hydrogel is dried. The dried gel is called '*xerogel*'. Often the xerogel is referred to as '*silicagel*' or simply '*silica*'. The detailed texture of the xerogel depends on the process conditions. The drying step is also critical. Upon drying dramatic phenomena can occur, e.g., cracks can be formed, similar to cracks formed during drying of a layer of clay. The reason is that the capillary forces cause a compression of the structure, thus upon drying collapse of the macro- and mesopore can take place, resulting in shrinking and cracking phenomena.

Drying has a profound influence on the structure of the xerogel. Sophisticated drying procedures have been developed. When the water is replaced by an alcohol the capillary force is reduced; an '*alcogel*' is formed. After drying, a more open pore structure is formed. The influence of the strong capillary forces during drying can be further minimized by drying at temperatures above the critical temperature of the solvent used. After drying the silica has a fully hydroxylated surface terminated by silanol groups (see Fig. 3.17). This surface is hydrophilic. The hydroxyl groups are almost neutral and pure silicas show hardly any catalytic activity.



$$^{-}\mathrm{O{-}\overset{OH}{\underset{O}{Si}}{-}O{-}\overset{OH}{\underset{O}{Si}}{-}O{-}\overset{OH}{\underset{O}{Si}}{-}O{-}\overset{OH}{\underset{O}{Si}}{-}O^{-}}$$

Figure 3.17. Fully hydroxylated silica surface.

Aluminas. Aluminas, porous Al_2O_3, are available in many forms. They constitute the most important carrier material in heterogeneous catalysis. Alumina is amphoteric and, as a consequence, soluble in both acidic and basic media. Precipitation can be performed from an acid solution by adding a base or from a basic solution by adding an acid, as schematically represented in Fig. 3.18. If, for example, at a pH of less than about 3 a base is added to an aqueous solution of aluminium sulphate, a precipitate is formed. If this material is filtered, dried and calcined, an amorphous porous Al_2O_3 is obtained. At other pH values different porous aluminas can be synthesized.

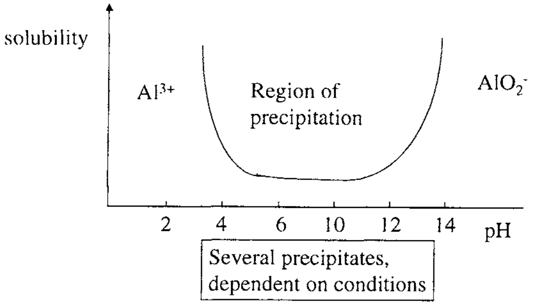


Figure 3.18. Precipitation regions of aluminum compounds (after Le Page, 1987).

Each form of crystalline alumina is only stable in a limited temperature range. Fig. 3.19 shows synthesis conditions and phase transformations of the most important aluminas.

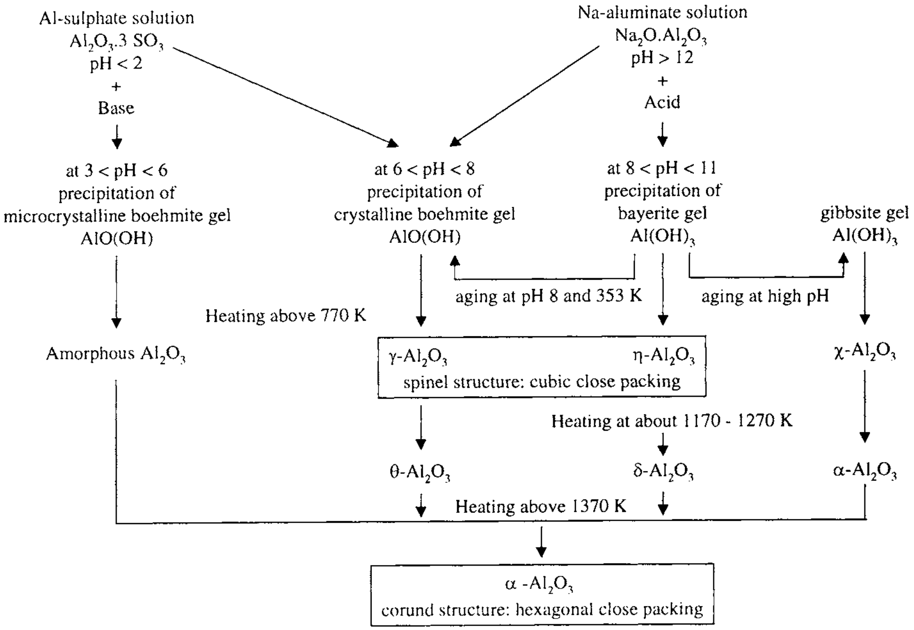


Figure 3.19. Formation of different aluminas (Doesburg *et al.*, 1999).

It is easiest to get a picture of the chemical structure of the surface of aluminas by starting from a fully hydroxylated surface (Fig. 3.20).

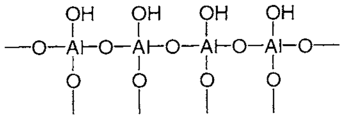


Figure 3.20. Fully hydroxylated alumina surface.

This surface is hydrophilic and will strongly adsorb water. During heating the following phenomena will be observed (see Fig. 3.21):

- desorption of physisorbed water,
- desorption of chemisorbed water,
- formation of water molecules from neighbouring surface hydroxyl groups.

Pairs of Lewis acid and Lewis base sites are formed. The Lewis acid site is an Al^{3+} ion that is co-ordinatively unsaturated. A water molecule will transform a Lewis site into a Brönsted site (Fig. 3.22).

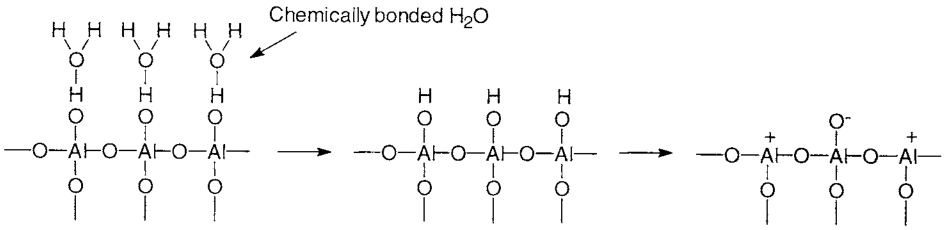


Figure 3.21. Dehydration of alumina upon heating.

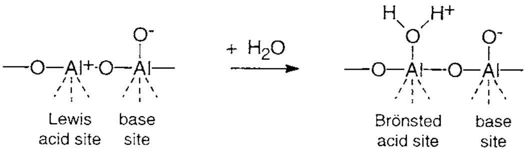


Figure 3.22. Transformation of Lewis site into Brönsted site.

Of all the aluminas, γ-alumina is the most used alumina, due to its high surface area and the high concentration of surface hydroxyl groups. η-alumina is used in isomerization because it has a higher density of acid sites at the surface.

Zeolites. In heterogeneous catalysis porosity is nearly always of essential importance. In most cases porous materials are synthesized using the above described sol-gel techniques resulting in so-called amorphous catalysts. Porosity is introduced in the agglomeration process in which the sol is transformed into a gel. From X-ray Diffraction patterns it is clear that the material shows only weak broad lines, characteristic of non-crystalline materials. Silica and alumina are typical examples. Zeolites are an exception: they are crystalline materials but nevertheless exhibit high (micro) porosity. Zeolites belong to the class of molecular sieves, which are porous solids with pores of molecular dimensions, *i.e.*, typically the pore diameter ranges from 0.3 to 10 nm. Examples of molecular sieves are carbons, oxides and zeolites.

Fig. 3.23 shows pore volume distributions of some commercially important porous materials. Note that zeolites and activated carbon consist predominantly of micropores, whereas alumina and silica have pores mainly in the mesopore range. Zeolites and active carbons have a sharp peak in pore size distribution, but in the case of the activated carbon also larger pores are present. The wide-pore silica is prepared specially to facilitate internal mass-transfer.

In the late 1940s zeolites were synthesized according to the procedure shown in Fig. 3.24. First an amorphous alumino-silicate gel is formed. This process is completely analogous to the production of alumina and silica gels described before. Subsequently this gel is crystallized into zeolite. The preparation of zeolites has drawn tremendous attention of the scientific and industrial community. A wide variety of zeolites have been synthesized, and reproducible synthesis procedures have been reported (often in the patent literature). Natural zeolites also exist; massive deposits have been discovered in many places in the world.

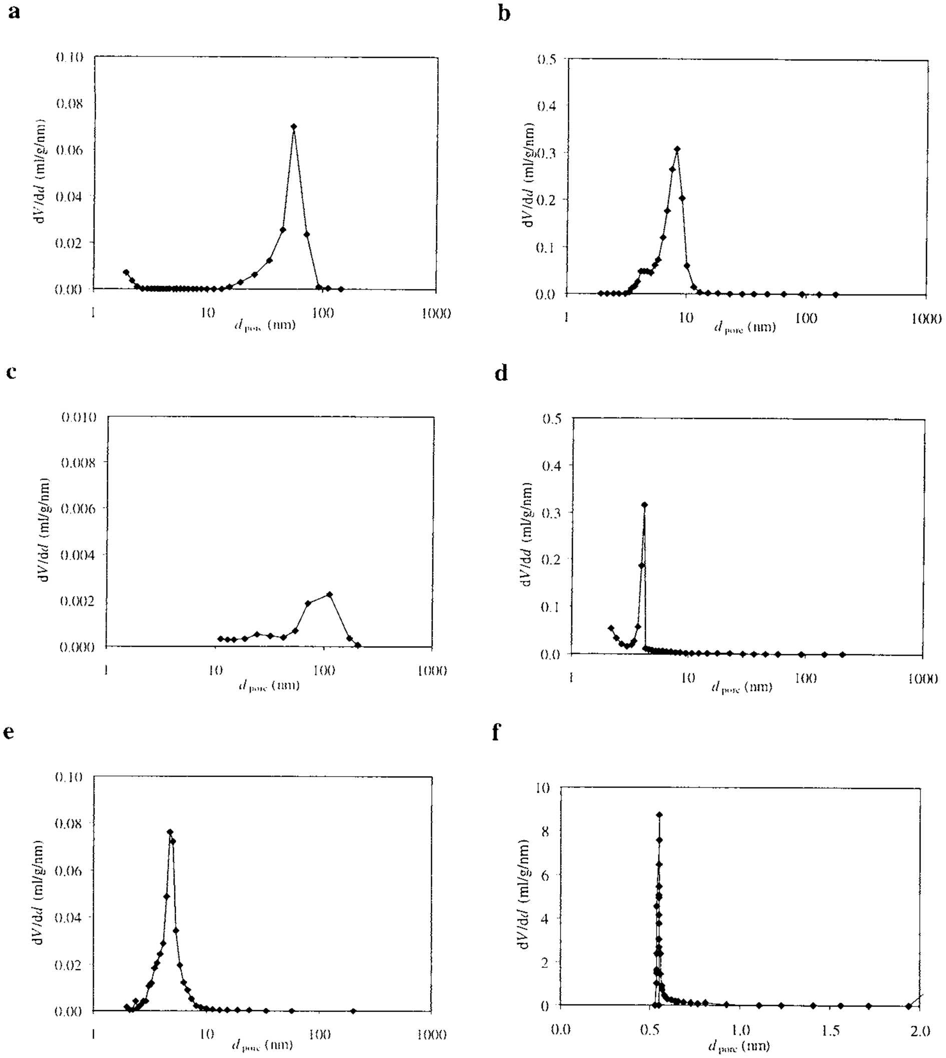


Figure 3.23. Pore volume distributions (N_2 physisorption) of: a. wide-pore silica, b. γ-alumina, c. α-alumina, d. activated carbon, e. Raney Nickel and f. ZSM-5.

Zeolites are applied in many fields (Fig. 3.25). It is clear that applications in catalysis are relatively modest. Nevertheless, in the absolute sense the contribution of catalysis to total usage is far from negligible.

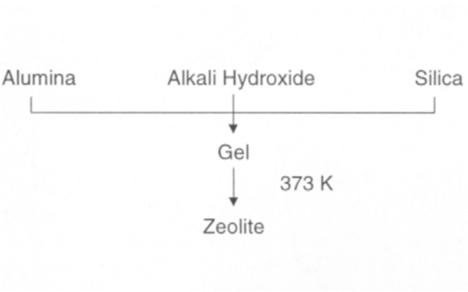


Figure 3.24. Schematic representation of early synthesis method for zeolites (Van Bekkum *et al.*, 1991).

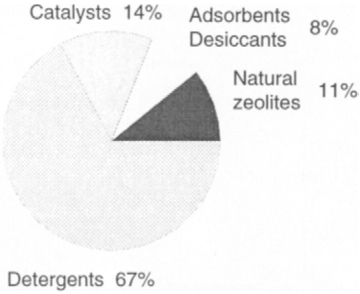


Figure 3.25. Use of zeolites in different areas in 1988; total volume 550.000 tpa.

A trend in industry is to benefit from the shape selectivity of zeolites. Figure 3.26 surveys the 'kinetic diameter' of some common industrially important organic molecules in relation to the dimension of some important zeolites (Van de Graaf *et al.*, 1998). This figure clearly indicates that subtle processes can be developed. Recently, researchers at Mobil have discovered a new class of zeolitic materials with pores in the mesorange (uniform arrays of pores in the range of 1.5 to 10 nm). Catalysis using zeolites is a booming area and it can be expected that many new materials will be discovered and that breakthroughs in practical processes will be the result.

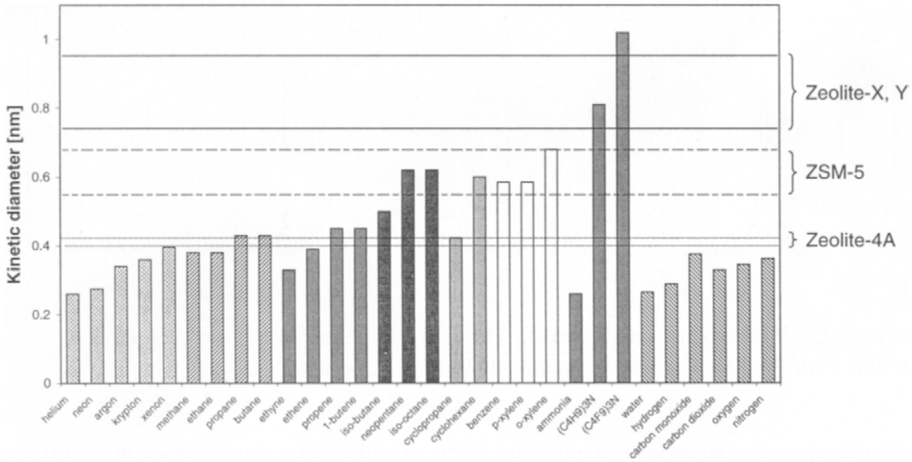


Figure 3.26. Kinetic diameters of some important organic molecules. For reference the pore dimensions of some common zeolites are shown (Van de Graaf *et al.*, 1998).

At present, the major applications of zeolites in catalysis are in the oil refinery. They find increasing application in petrochemical processes. When considering the enormous success of the application of zeolites in bulk chemistry, it is to be expected that the same trend will be seen in fine chemicals production. For this sector, it is fortunate that in bulk chemistry so much development work is being done in catalysis and in particular in zeolite synthesis and application.

Zeolites can be classified by their Si/Al ratios (see Table 3.3). The ion exchange capacity of zeolites is proportional to the number of Al^{3+}ions and, as a consequence, the number of active sites will be higher at a lower Si/Al ratio. The acid strength of the acidic sites is highest, however, for zeolites containing the least amount of Al ions. Zeolites with low Al contents are prepared by so-called 'dealumination', which consists of extracting Al^{3+} ions by a reactant such as $SiCl_4$ or by steaming at high temperatures. In the latter case Al is made mobile by transforming it into volatile hydrates.

Zeolites form a class with tremendous variety. Besides the microporous solids described in the above, mesoporous materials have been synthesized. A breakthrough were the MCM-41 mesoporous zeolites with pores of typically 3 nm. Later, many related materials have been reported allowing fine-tuning of pore sizes. A recent example is the synthesis of materials with pores in the 10nm range with satisfactory uniformity and stability (Sun *et al.*, 2001).

Table 3.3
Zeolites classified by their Si/Al ratios (Rollmann *et al.*, 1984).

Si/Al Ratio	Zeolite	Properties
Low (1-1.5)	A, X	Relatively low stability of framework. Low stability in acids. High stability in bases. High concentration of acid groups with moderate acid strength. Hydrophilic.
Intermediate (2-5)	Erionite Chabazite Clinoptilolite Mordenite Y	
High (~10 to ∞)	ZSM-5[a] Erionite[a] Mordenite[a] Y[a]	Relatively high stability of framework. High stability in acids. Low stability in bases. Low concentration of acid groups with high acid strength. Hydrophobic.

[a] By dealumination.

Activated carbons. Activated carbons are high-surface-area carbons. They are extensively used in industry, mainly as adsorbent. They are also used as a carrier material in catalysis because of their rather unique properties:

- stability in acid and basic solutions,
- high adsorption capacity for organic molecules,

- flexibility with respect to texture properties,
- resistance to high temperatures,
- suitability for pump around set-ups,
- intrinsic activity of active phase often not reduced.

Disadvantages of activated carbons are their reactivity in oxidising environments, their sometimes weak mechanical properties, and the formation of fines, which leads to limited filterability. Besides its use as support material, activated carbon also exhibits catalytic activity in reactions that require activation of oxygen and chlorine in selective oxidation, chlorination and dechlorination reactions. Activated carbons can be prepared from a wide variety of carbonaceous materials such as wood, coal, lignite, and sugar. Usually, the manufacturing process consists of pyrolysis followed by 'activation' (partial gasification). The specific surface area of activated carbon can be quite high, up to 1500 - 2000 m^2/g, and the surface can be highly functionalized. Figure 3.27 shows the types of groups it may contain. The surface composition depends on the pre-treatment. An activated carbon in oxidized state will exhibit acidic properties due to the presence of carboxylic, lactonic and phenolic groups. When subjected to temperature treatment in an inert atmosphere, functional groups will decompose and the acidic properties will disappear. As the acid groups are less stable than the basic groups the activated carbon becomes basic.

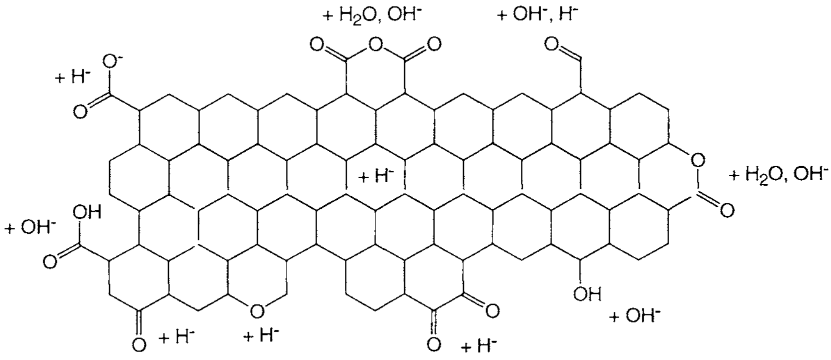


Figure 3.27. Functional groups on activated carbon surfaces (Vinke, 1991).

3.3.3.3. *Catalysts prepared by impregnation of shaped supports*

Preparation of catalysts starting from (commercially available) pre-shaped or structured supports is attractive, because a support with optimal properties can be selected. This facilitates catalyst development very much because a choice can be made from a wide variety of commercially available supports.

Impregnation. Two methods are used in adding the active phase: 'dry' and 'wet' impregnation. 'Dry' impregnation is also referred to as 'pore volume impregnation', because in this method the amount of liquid (solution of the precursors) used is just enough to fill the pore volume of the support. In 'wet' impregnation the support is dipped into an excess quantity of solution containing the precursor(s) of the active phase.

In dry impregnation the solubility of the catalyst precursors (usually soluble salts) and the pore volume of the support determine the maximum loading available each time of impregnation. If a high loading is needed, successive impregnations (and heat treatments) may be necessary. When several precursors are present in the impregnating solution simultaneously the impregnation is called 'co-impregnation'.

Depending on the process conditions, different profiles of the active phase over the particle will be obtained. A completely uniform distribution of the active material over the particle is not always the optimum profile for impregnated catalysts. It is possible to purposely generate profiles in order to improve the catalyst performance. Fig. 3.28 shows four major types of active phase distribution in catalyst spheres.

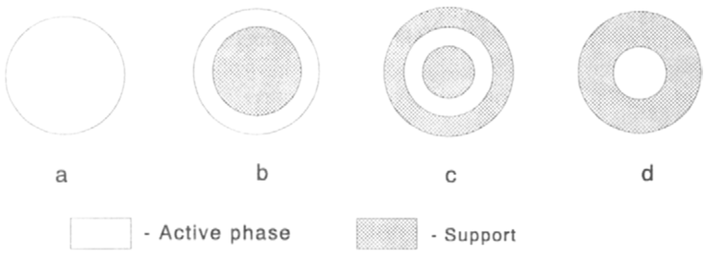


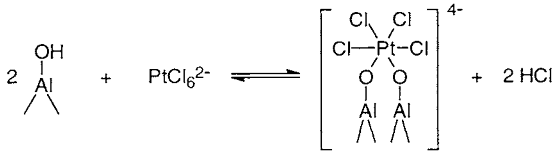
Figure 3.28. Four types of active phase distribution. a: uniform, b: egg-shell, c: egg-white, and d: egg-yolk.

The light-grey regions represent the areas impregnated with the active phases. Type (a) is a uniform catalyst, while the others have a non-uniform active phase distribution. They are sometimes referred to as 'egg-shell', 'egg-white' and 'egg-yolk' catalysts. The optimal profile is determined, among others, by the diffusion rates in the particle compared with the chemical reaction rate, the reaction kinetics, and the mode of poisoning. For example, an egg-shell catalyst is favourable in case of a reaction with a positive order, whereas an egg-yolk catalyst is the best choice for reactions with negative orders. When pore-mouth poisoning is dominant it might be attractive to locate the active sites in the interior of the catalyst particles. Another factor is attrition. If attrition is important and if the active phase is expensive (e.g. precious metals), it might be preferable to place the active phase in the interior of the catalyst particles (Lee and Aris, 1985). The preparation of catalysts with non-uniform active phase distribution over the particle will be illustrated for a Pt catalyst.

Drying. The drying step, which follows the impregnation step, also affects the distribution of the active phase. In drying, the solution in the pores will become supersaturated, so precipitation takes place. Because of the large surface area, and associated herewith the large number of nuclei, a high dispersion can be obtained. In principle, rapid evaporation is favourable because it causes rapid supersaturation, and associated with that, a high concentration of nuclei and, as a consequence, a high dispersion. However, as the support usually contains a range of pore sizes, the largest pores will first empty themselves and the solution leaving the large pores might be accumulated in the smaller pores. A loss of dispersion is the result.

Example 3.1. Pt on γ-alumina

We start the discussion by an analysis of the processes occurring in wet impregnation of alumina using a solution of H_2PtCl_6. The alumina surface interacts with H_2PtCl_6 by adsorption of $PtCl_6^{2-}$:



Naturally, the number of surface sites limits the amount of Pt complexes that can be adsorbed. Typically, these catalysts contain up to 1 wt% Pt. Adsorption is a fast process and in general an egg-shell catalyst will be formed. Figure 3.29 shows the processes that occur.

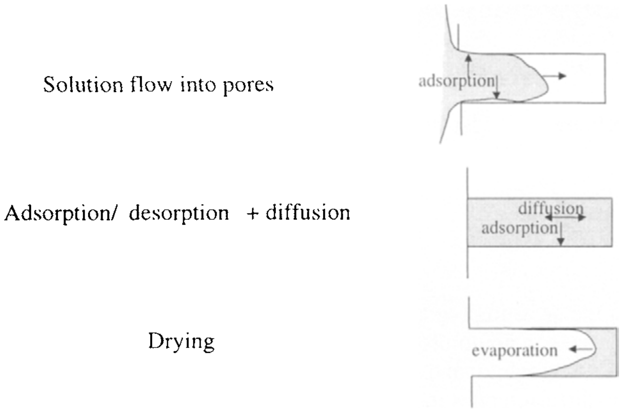


Figure 3.29. Processes occurring during impregnation with fast adsorption.

In the first step the solution enters the pores. The driving forces for the flow are capillary forces. During the flow, adsorption by ion exchange occurs. Due to the high rate of adsorption an uneven distribution of Pt ions results. Subsequently, a situation exists in which the diffusion through the pore mouth becomes rate determining. The active phase is present as a shell, which moves towards the interior of the particle as shown in Fig. 3.30.

During drying an outward flow of Pt can exist, leading to loss of dispersion. The resulting system will depend on many factors, including impregnation time and pH value, viscosity, concentration of the impregnating solution, and the presence of other ions or solute in the solution.

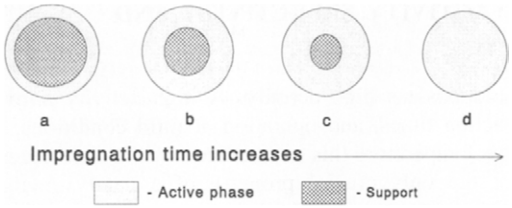


Figure 3.30. Change of Pt front with increasing impregnation time.

When compared to the capacity of the alumina used, a deficiency in $PtCl_6^{2-}$ ions is common. The reason is obvious: Pt is very expensive and, as a consequence, the dispersion should be very high. The profile becomes less sharp upon equilibrating of the system. When the pellets are kept in a wet state for a sufficiently long period before drying a uniform profile will emerge (see Fig 3.30). If the time needed for obtaining a uniform profile is unpractically long, competitive adsorbents can be added. An example is the following. When adsorption of H_2PtCl_6 is carried out in the presence of HCl, platinum is distributed more uniformly, because HCl adsorbs on the same sites:

$$\text{Al–OH} + HCl \rightleftharpoons \text{Al–Cl} + H_2O$$

The higher the HCl concentration the thicker the impregnated layer of Pt becomes.

The addition of a second component to the impregnating solution allows fine-tuning of the catalyst. Fig. 3.31 illustrates this.

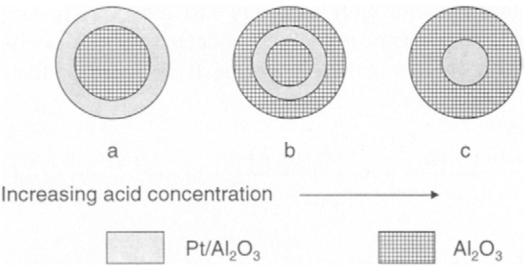


Figure 3.31. The influence of coadsorbing ions (citrate) on the Pt concentration profile (adsorption of chloroplatinic acid, H_2PtCl_6): a.-c. increasing amount of citric acid (Geus and Van Veen, 1999).

Impregnation of H_2PtCl_6 was carried out in the presence of citric acid, which adsorbs more strongly than H_2PtCl_6 (and HCl). Without the presence of citric acid an egg-shell type of profile for Pt is obtained (Fig. 3.31.a). When some citric acid is present, this will be adsorbed in an egg-white and the Pt ions will adsorb in a ring at the inside of the citric acid ring (Fig 3.31.b). This example demonstrates how catalysts with different active phase profiles can be prepared by choosing the right conditions.

3.4. CATALYST PERFORMANCE: ACTIVITY, SELECTIVITY, AND STABILITY

It is obvious that a good catalyst should possess high activity. A high activity allows relatively small reactor volumes, short reaction times, and operation at mild conditions. If thermodynamics is more favourable at a low temperature this can be decisive for the success of the process. Activity is, however, not the only crucial property of a catalyst. High selectivity is often even more important than high activity. Furthermore, a catalyst should maintain its activity and selectivity over a period of time, *i.e.* it should have sufficient stability. In particular with respect to selectivity and stability heterogeneous catalysis (and biocatalysis) differs fundamentally from homogeneous catalysis. Therefore, unless otherwise stated, in the next paragraphs the discussion is limited to heterogeneous catalysis, while homogeneous catalysis is treated in a separate section.

3.4.1. Activity

In any catalyst selection procedure the first step will be the search for an active phase, be it a solid or complexes in a solution. For heterogeneous catalysis the second step is also decisive for the success of process development: the choice of the optimal particle morphology. The choice of catalyst morphology (size, shape, porous texture, activity distribution, etc.) depends on intrinsic reaction kinetics as well as on diffusion rates of reactants and products. The catalyst cannot be chosen independently of the reactor type, because different reactor types place different demands on the catalyst. For instance, fixed-bed reactors require relatively large particles to minimize the pressure drop, while in fluidized-bed reactors relatively small particles must be used. However, an optimal choice is possible within the limits set by the reactor type.

The size of the catalyst particle influences the observed rate of reaction: the smaller the particle, the less time required for the reactants to move to the active catalyst sites and for the products to diffuse out of the particle. Furthermore, with relatively fast reactions in large particles the reactants may never reach the interior of the particle, thus decreasing the catalyst utilization. Catalyst utilization is expressed as the internal effectiveness factor η_i. This factor is defined as follows:

$$\eta_i = \frac{\text{observed reaction rate}}{\text{rate without internal gradients}} = \frac{r_{obs}(c,T)}{r_{v,chem}(c_s,T_s)} \tag{4}$$

where: $r_{obs}(c, T)$ = observed reaction rate, an average of the rates inside the particle at different concentrations c and temperatures T (mol s^{-1} $m^3_{particle}$)
$r_{v,chem}(c_s, T_s)$ = reaction rate at surface concentration c_s and temperature T_s (mol s^{-1} $m^3_{particle}$)

The internal effectiveness factor is a function of the generalized Thiele modulus (see for instance Krishna and Sie (1994), Trambouze *et al.* (1988), and Fogler (1986). For a first-order reaction:

$$\phi_{gen} = \frac{V}{SA}\sqrt{\frac{k_v}{D_{eff}}} \tag{5}$$

in which V/SA is the volume/external surface area ratio of the catalyst (for a sphere: $r_p / 3$, in which r_p is the particle radius), k_v the intrinsic reaction rate constant (per unit volume), and D_{eff} the effective diffusion rate of the molecule.

In order for diffusional limitations to be negligible, the effectiveness factor must be close to 1, *i.e.* nearly complete catalyst utilization, which requires that the Thiele modulus is sufficiently small (< ca. 0.5), see Figure 3.32. Therefore, the surface-over-volume ratio must be as large as possible (particle size as small as possible) from a diffusion (and heat-transfer) point of view. There are many different catalyst shapes that have different *SA / V* ratios for a given size.

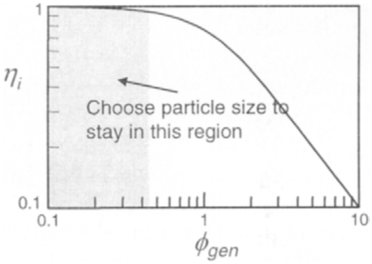


Figure 3.32. Internal effectiveness factor as a function of the generalized Thiele modulus for a first order reaction.

Of course, the relative surface area is not the only factor influencing the performance of the catalyst. Smaller particles result in larger pressure drop over the reactor, and in fixed-bed systems this is the main limiting factor. The catalyst shape also has effect on the pressure drop. In fixed-bed and moving-bed reactors the catalyst strength is also an important factor. The particles must be able to withstand the forces exerted by the bed above and by the pressure drop. In general, compact particles have a higher crushing strength than hollow ones, and the crushing strength increases with particle size. For the process economics it is also important that the manufacturing costs are within acceptable limits. The more exotic the catalyst shape, the more expensive its production will be.

With increasing particle size, the *SA / V* ratio and hence the reaction rate decreases, which is unfavourable, while the pressure drop, the crushing strength, and the manufacturing costs also decrease, which is favourable. At the same overall particle diameter the diffusion length decreases in the order:

Sphere> pellet > trilobe > hollow extrudate > wagon wheel/ minilith

The definitive catalyst size selection will be a compromise between high reaction rate (small particle, exotic shape), low pressure drop (large particle, exotic shape), large crushing strength (large particle), and low manufacturing cost (large particle), within the limits set by the reactor type.

3.4.2. Selectivity

In practice, high selectivity for the desired products often is even more important than high activity. For instance, in hydrogenation and oxidation reactions very often a good selectivity rather than a high activity is the objective of process development. Because of their tremendous practical impact examples of hydrogenation and oxidation reactions have been well documented. The most important application of catalysis in fine chemicals production probably is in the selective hydrogenation of functional groups. An example is the hydrogenation of benzaldehyde into benzyl alcohol. This reaction occurs through series kinetics (Fig. 3.33).

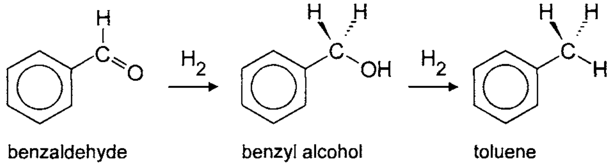


Figure 3.33. Reaction scheme for the hydrogenation of benzaldehyde.

The catalyst should catalyse the first step but not the second step. How can selectivity be maximized? In principle, a dilemma exists: both the desired reaction and the undesired consecutive reaction are hydrogenation reactions and, as a consequence, it has to be expected that a catalyst exhibiting activity for one of them is also active for the other. Of course, for a high selectivity the nature of the active sites of the catalyst should be right, but also other factors play a decisive role. Reactor, process lay-out and process conditions are crucial. Reactor and process aspects are treated in Chapter 5. Here we confine ourselves to the catalyst itself. A priori, it might not be expected that often selectivity is also dependent on the texture (pore structure, pore dimensions), and the morphology (shape, dimension) of the catalyst. The reason is that diffusion limitations influence the selectivity. In particular, when undesirable consecutive reactions occur, diffusion limitations should be minimized and, as a consequence, it is desired that the catalyst particles have an open structure and a short diffusion length. So, for selective hydrogenation for equal overall particle size and at the same conditions the same catalyst in the shape of spheres will be less selective than the one with more exotic shapes. It is probably needless to say that the smaller the size the higher the selectivity. When one realizes that the reactor type sets boundaries on the particle size, it will be clear that a fixed-bed reactor in general gives lower selectivities in selective hydrogenation than slurry reactors. When in a fixed bed an egg-shell catalyst is applied the difference will be smaller.

In summary, the important aspects for a high selectivity are:

1. active sites with a high intrinsic selectivity,
2. optimal particle texture,
3. optimal particle dimensions,
4. optimal conditions: concentrations, temperature, pressure,

5. optimal reaction configuration: solvent, reactor, process,
6. adequate start-up of the reactor.

In this chapter we confine ourselves to points 1-3. Points 4-6 are dealt with in Chapters 4 through 6.

3.4.3. Stability and deactivation

According to the classical definition of catalysis a catalyst does not change during reaction. In practice this is not true: during operation the catalyst loses activity, and often also selectivity and mechanical strength. Catalyst deactivation is a common phenomenon rather than exception.

3.4.3.1. Time scale of deactivation

The time scale of deactivation has profound consequences for process design. This is easiest illustrated for continuous processes by plotting the catalytic activity as a function of the time-on-stream. Qualitatively, often the type of behaviour shown in Fig. 3.34 is observed.

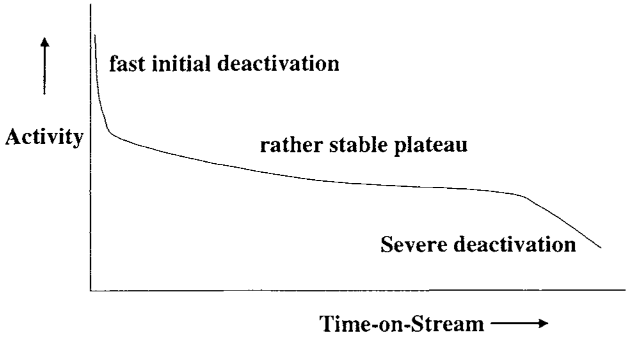


Figure 3.34. Typical activity versus time-on-stream plot.

Initially, deactivation is most pronounced, while in a second phase a more stable activity level is reached. In practice, the conditions will be adapted such that satisfactory conversions are achieved. In a batch reactor one might not be aware of such an activity profile. Nevertheless it can be important. For example, after the start-up initially a hot spot might occur due to very high initial activity. Often this will lead to damage of the catalyst. In continuous processes, which are gaining importance in fine chemicals production, the impact of such behaviour on the operation of the process is evident. In fact, it is common practice to add extra catalyst, but this means larger reactors (and higher investment), and perhaps a reduced selectivity. Often deactivation is compensated for by increasing the temperature, often at the expense of selectivity and accelerated further deactivation. For continuous processes catalyst deactivation behaviour is a dominant aspect in process design and in operation. The time scale of deactivation largely determines the type of reactor and process design; when a catalyst has a low stability, in general it is not wise to use a continuous fixed-bed reactor.

3.4.3.2. *Mechanisms of deactivation*

Deactivation processes can be subdivided into three groups, usually referred to as (see also Moulijn *et al.*, 2001a; and Bartholomew, 2001):

- mechanical deactivation (crushing, attrition),
- thermal deactivation (sintering, evaporation), and
- chemical deactivation (poisoning, fouling).

Mechanical deactivation. Mechanical strength is important in giving the catalyst resistance against crushing, e.g., during transport and loading of the catalyst into the reactor. In a fluidized-bed reactor for gas-phase processes attrition will always occur and the fines formed will be carried away with the product flow. In a fixed-bed reactor attrition will be less, but the consequences of even limited formation of fines are important: increased pressure drop and eventually blocking of the bed. So, loading of the reactor should be done carefully. In stirred-tank reactors and loop reactors attrition will reduce filterability. Mechanical strength is also related to porosity; for instance, the presence of macropores will lead to reduced strength.

Thermal deactivation. Thermal and chemical deactivation are often related. At high temperatures structural changes occur, often leading to deactivation. This is referred to as thermal deactivation. Although thermal deactivation in fine chemistry is of minor importance during the actual reaction (usually mild conditions are applied), it may be important due to the possible need for activation or regeneration at high-temperature. Examples are pre-reduction in H_2 and regeneration in air. Both reactions are highly exothermic, and, when not done carefully, can lead to high temperatures of the catalyst particles. An amorphous catalyst may crystallize, active components can form an alloy, active species may evaporate, the active phase can react with the catalyst support, etc. The loss of surface area by particle-size growth is called 'sintering'. This process is usually irreversible. As catalysts are usually porous solids, a driving-force for sintering exists ('Ostwald ripening'), because upon sintering the surface energy is minimized. Fig. 3.35 presents an example of sintering of porous alumina.

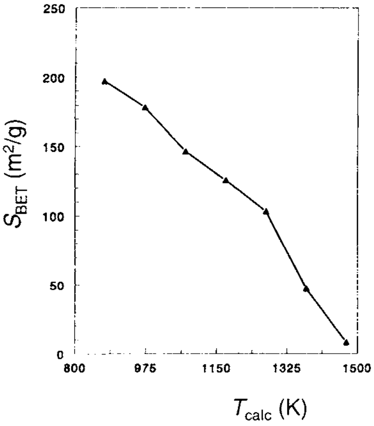


Figure 3.35. Change of BET surface area of an Al_2O_3 as a function of calcination temperature.

Fig. 3.35 shows the decrease of the specific surface area of a certain alumina as a function of calcination temperature. Apparently, the alumina is rather stable: at 1000 K still over 50 % of the original surface area is retained. For most applications in catalysis the reaction temperature is far below 1000 K, and, as a consequence, the thermal stability of alumina is often sufficient. Activated carbon, which is also often used, is even more stable.

Metal catalysts often consist of small metal crystallites deposited on a porous carrier. An important deactivation phenomenon is sintering of these small metal crystallites into larger ones. Of course, this leads to deactivation. Figure 3.36 shows a schematic representation of the phenomena occurring.

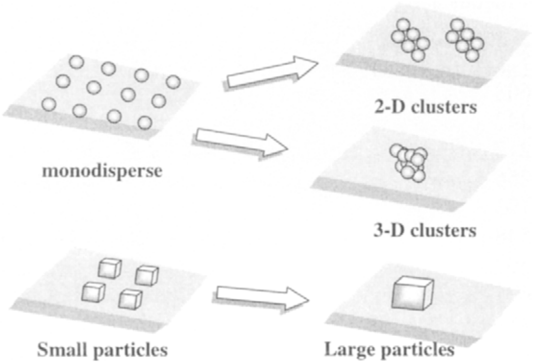


Figure. 3.36. Schematic of the various stages in the formation and the growth of particles from a monomer dispersion during sintering (after Satterfield, 1991).

Initially, the atoms are supposed to be present as clusters of atoms (or small metal particles). One can speak of a monomer dispersion. Surface diffusion of the atoms will lead to two-dimensional clusters, and upon further diffusion three-dimensional particles will be formed. These particles can grow into larger ones according to several mechanisms. Particles might move and coalesce, or atoms move from one particle to the other. The most important mechanism for sintering of small particles often is movement of atoms rather than particles; depending on the conditions (temperature, type of surface) atoms will move through a hopping mechanism or through surface diffusion.

Sintering is related to melting. It is to be expected that the rate of sintering increases when the temperature nears the melting point. The so-called Tamman and Hüttig temperatures, indicative for the temperature at which sintering may occur, are directly related to the melting temperature (in K). Upon temperature increase the mobility of atoms increases. First, when the Hüttig temperature is reached, atoms at defects will become mobile. Later, when the Tamman temperature is reached, atoms from the bulk will exhibit mobility and at the melting temperature the mobility will be so high that liquid-phase behaviour is observed. The following semi-empirical relations for the Hüttig and Tamman temperatures are recommended:

$$T_{\text{Hüttig}} = 0.3\ T_{\text{melt}} \quad (6)$$

$$T_{\text{Tamman}} = 0.5\ T_{\text{melt}} \quad (7)$$

Actually, the temperature at which the solid becomes mobile also depends on the shape and size of the metal crystallites. For small particles this temperature may become much lower than that indicated by the Tamman or Hüttig temperature. Table 3.4 presents T_{Tamman} and $T_{\text{Hüttig}}$ for some metals and their compounds.

Table 3.4

T_{melt}, T_{Tamman} and $T_{\text{Hüttig}}$ values (in K) of metals and their compounds, relevant for heterogeneous catalysis

	T_{melt}	T_{Tamman}	$T_{\text{Hüttig}}$
Pt	2028	1014	608
PtO	823	412	247
PtO_2	723	362	217
$PtCl_2$	854[c]	427	256
$PtCl_4$	643[c]	322	193
Pd	1828	914	548
PdO	1023[c]	512	307
Rh	2258	1129	677
Rh_2O_3	1373[c]	687	412
Ru	2723	1362	817
Fe	1808	904	542
Co	1753	877	526
Ni	1725	863	518
NiO	2228	1114	669
$NiCl_2$	1281	641	384
$Ni(CO)_4$	254	127	76
NiS	1249	625	375
Ag	1233	617	370
Au	1336	668	401
Cu	1356	678	407
CuO	1599	800	480
Cu_2O	1508	754	452
$CuCl_2$	893	447	268
Cu_2Cl_2	703	352	211
Mo	2883	1442	865
MoO_3	1068	534	320
MoS_2	1458	729	437
Zn	693	347	208
ZnO	2248	1124	675
Al_2O_3	2318	1159	695
SiO_2[a]	1986	993	596
SiO_2[b]	1883	942	565

[a] crystobalite. [b] quartz. [c] Decomposes at this temperature.

The melting point is not always well defined, for instance some oxides already begin to decompose before T_{Tamman} or $T_{\mathrm{Hüttig}}$ is reached.

Usually, metals are dispersed on a porous material, which has a very high melting temperature. They are called supports or carriers. Widely applied are porous Al_2O_3 and SiO_2. Table 3.4 shows that these have high Tamman and Hüttig temperatures. The small metal clusters are anchored to a so-called thermostable support, thus avoiding sintering. The anchoring between the support and the metal clusters is based on the formation of chemical bonds.

Table 3.4 illustrates that the composition of the gas phase easily can lead to sintering. For example, in air regeneration Pt metal crystallites will be transformed in to the oxides, and the Tamman temperature decreases to below 420 K.

Chemical deactivation. In chemical deactivation the active surface area changes by strong chemisorption of impurities in the feed, by blocking of active sites by heavy products formed in parallel or sequential reactions, etc. The most important chemical causes of deactivation are poisoning by impurities in the feed and deposition of carbonaceous material, usually referred to as 'coke'.

When impurities interact more strongly with the active sites than feed molecules do, the activity is decreased and poisoning is taking place. Poisoning can be either temporary, also referred to as reversible, or permanent, also referred to as irreversible. In the former case the poisons can be removed, whereas this is not the case in the latter situation. The distinction is not always this clear; poisons which are strongly adsorbed on the active sites at a low temperature can sometimes be removed at a higher temperature and could then be referred to as temporary poisons. An example of irreversible poisoning is the poisoning of Ni catalysts by arsenic, which cannot be removed easily. The relationship between amount of poison and catalytic activity is not always a simple linear function. In Fig. 3.37 typical curves are plotted representing the relationship between relative activity and the surface fraction poisoned.

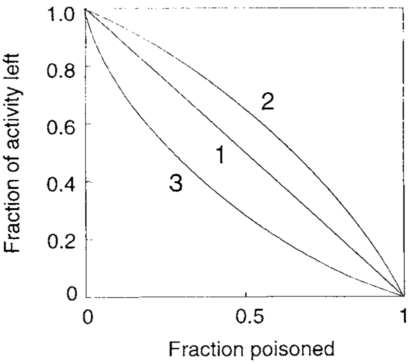


Figure 3.37. Relative reaction rates as a function of the fraction of sites poisoned.

The simplest case is represented by curve 1. The activity depends linearly on the number of unpoisoned active sites. The interpretation of curves 2 and 3 is less obvious. In the former case the interpretation might be that the least active sites are poisoned first, whereas in the latter case the most active sites are poisoned preferentially. Mass-transfer limitations also play a role in poisoning behaviour. If, for example, the poison is deposited in the outer shell of the catalyst particles, a decrease in catalytic activity can be expected as qualitatively described by curve 3 in Fig. 3.37.

Often poisoning described by curve 1 in Fig. 3.37 is referred to as 'nonselective' poisoning, whereas the deactivation according to curve 3, which implies disproportionately large deactivation, is called 'selective' poisoning. Explanations of selective poisoning are:

- heterogeneity of the active sites,
- interaction between poisoning molecules,
- poisoning of more than one site by one poisoning molecule at low coverage,
- pore mouth poisoning, *i.e.* entrances of pores are blocked by deposits.

In practice, it is very important to know the cause of poisoning in order to enable efficient operation.

Deposition of carbonaceous material is commonly encountered. These deposits can be formed by complex chemical reactions or they are simply formed by deposition of heavy compounds from the feed. It is rule rather than exception that the true character of a carbonaceous material is not known. Often, it is referred to as 'coke'.

3.4.3.3. Summary

Deactivation of catalysts is an important and complex phenomenon, which can have many causes. It can be kept to a minimum by carefully purifying the feed and by keeping process conditions optimal, which often implies a temperature as low as possible.

3.5. CATALYST SELECTION

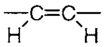
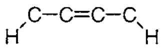
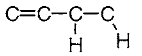
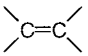
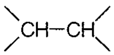
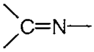
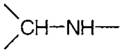
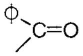
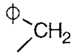
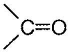
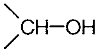
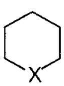
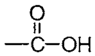
In process development the search for an active and selective catalyst often dominates the research efforts. It is very important to find leads and rules allowing efficient exploratory studies. It is not possible to give a generally valid approach. Usually, common sense and a thorough literature search (including patents) will lead to a logical selection of catalysts with potential. For instance, Augustine (1996) reports the following listing of catalysts (and conditions) useful in hydrogenation of the most common functional groups (Table 3.5). The table has been organized according to the ease of reaction. From top to bottom the reactions become more difficult. When a feed contains a mixture of two compounds with different functional groups, one at the top and one in the bottom of Table 3.5, in many cases the selective hydrogenation of the first will be easily achieved without hydrogenation of the second. Not surprisingly, many exceptions are found, depending on the specific chemistry of the molecules to be converted and the catalyst used. This is certainly the case when the different functional groups are present in one molecule, close to each other. An example is the hydrogenation of an unsaturated aldehyde (see Fig. 3.38), which over a platinum catalyst normally results in the formation of either the saturated aldehyde, or, on further hydrogenation, the saturated alcohol. However, modification of the platinum catalyst with Fe^{2+} ions to facilitate hydrogenation of the carbonyl group and with Zn^{2+} ions to inhibit hydrogenation of the carbon-carbon double bond, results in the selective formation of the unsaturated alcohol (Augustine, 1996).

If the aim of development is not a novel process but a process improvement, the type of catalyst to be used might be obvious.

Also, legal aspects can be important. For instance, it might be attractive to circumvent a patent by developing an own catalyst.

In the near future probably computer modelling, allowing the analysis of adsorption and elementary reactions at surfaces, will become increasingly helpful in catalyst selection. On the experimental side the field is changing drastically. Parallel testing equipment is now the state of the art. This field is often referred to as 'Combinatorial Chemistry'. It is expected to have a large impact already in the near future. In fact, at present already companies have been formed in this field.

Table 3.5
Hydrogenation of common functional groups (Augustine, 1996)

Group	Product	Catalyst	Reaction conditions[a]
$-C\equiv C-$	 $\underset{H}{-C}=\underset{H}{C-}$	Pd	low catalyst concentration partially poisoned catalyst
$C=C-C=C$	 $\underset{H}{C}-C=C-\underset{H}{C}$	Pd	
$C=C-C=C$	 $C=C-\underset{H}{C}-\underset{H}{C}$	Pd	low catalyst concentration partially poisoned catalyst
$-NO_2$	$-NH_2$	Pt, Pd, Rh	
		Pd, Ni	
$-C\equiv N$	$-CH_2NH_2$	Raney Ni Raney Co	1 – 4 atm, NH_3 1 – 4 atm
		Pt, Pd	1 – 4 atm
		Pd	1 – 4 atm
		Pt, Rh Ru	2 – 4 atm 1 – 3 atm, H_2O
Heterocyclic and carbocyclic aromatics	 X = C, N, O	Rh Raney Ni Ru	2 – 4 atm 373 – 393 K, 100 atm 423 K, 100 atm
 $-\overset{O}{\overset{\parallel}{C}}-OH$	$-CH_2OH$	Ru, CuCrO	High temperature and pressure

[a] Room temperature, 1 atm, unless stated otherwise.

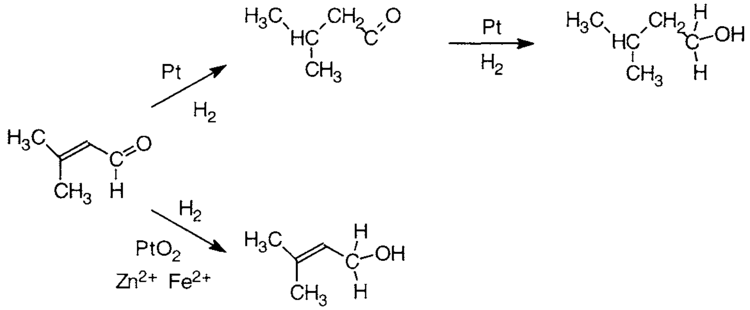


Figure 3.38. Hydrogenation of unsaturated aldehyde (Augustine, 1996).

3.6. CATALYST CHARACTERIZATION

3.6.1. Introduction

In heterogeneous catalysis catalyst characterization plays an important role. It is fair to state that improved characterization techniques have been the major drive towards the development of heterogeneous catalysis as a mature technology.

A wide variety of solid materials are used in catalytic processes. Generally, the (surface) structure of metal and supported metal catalysts is relatively simple. For that reason, we will first focus on metal catalysts. Supported metal catalysts are produced in many forms. Often, their preparation involves impregnation or ion exchange, followed by calcination and reduction. Depending on the conditions quite different catalyst systems are produced. When crystalline sizes are not very small, typically > 5 nm, the metal crystals behave like bulk crystals with similar crystal faces. However, in catalysis smaller particles are often used. They are referred to as 'crystallites', 'aggregates', or 'clusters'. When the dimensions are not known we will refer to them as 'particles'. In principle, the structure of oxidic catalysts is more complex than that of metal catalysts. The surface often contains different types of active sites: a combination of acid and basic sites on one catalyst is quite common.

Characterization is essential in catalysis research and development. Catalysts are complex entities, and therefore, it is not surprising that catalyst characterization is a broad subject. The crucial information that is needed can be summarized as:

- chemical composition (including speciation, concentration profiles),
- morphology (particle shape),
- texture (surface area, pore volume, pore dimension, structure pore network),
- thermal characteristics (specific heat, heat conductivity),
- reproducibility in synthesis,
- specific surface area of the active phases present,
- type(s) of active sites,
- number of active sites,
- reactivity of active sites, and
- stability of active sites.

The techniques used for catalyst characterization are partly the familiar ones used by chemists, while some are typical for heterogeneous catalysis. Elemental analysis, X-Ray Diffraction (XRD), and spectroscopy (mainly infrared) belong to the former category. More specific for heterogeneous catalysis are physisorption, mercury porosimetry, chemisorption, and Temperature Programmed Reduction (TPR). Surface techniques are also routinely applied, in particular X-ray Photoelectronspectroscopy (XPS), and Electron microscopy (EM). A good introduction is given by van Santen *et al.* (1999).

Two characterization techniques will be discussed in this chapter, *viz.* physisorption and chemisorption. Physisorption mainly yields information on catalyst texture and morphology, whereas chemisorption studies potentially give information regarding the active catalyst sites.

3.6.2. Physisorption

3.6.2.1. Catalyst texture and morphology

Solid catalysts and catalyst carriers are usually porous; their texture and morphology are important properties (Lercher, 1999 and Gregg and Sing, 1982). For the selection of a catalyst several questions regarding the porous structure have to be answered. What are the optimal sizes and the shapes of the pores? What is the desired pore size distribution (should the pores all have the same size or be of various sizes)? What should be the specific surface area of the catalysts? What should be the pore volume? All these questions are related to the texture and the morphology of the catalyst, which play an essential role in determining the diffusion rate of reactants and products, in influencing the mechanism of poisoning, and in affecting the actual reaction rate and selectivity.

The pore size has a strong influence on the diffusion rate and the activation energy for diffusion, as illustrated by Fig. 3.39. In a simple view three types of diffusion can be distinguished:

- molecular diffusion,
- Knudsen diffusion, and
- surface diffusion, sometimes called configurational diffusion.

Whether molecular or Knudsen diffusion takes place depends on the so-called Knudsen number, K_n:

$$K_n = \frac{\lambda}{l} \qquad (8)$$

λ is the molecular free path length and l is a representative channel length, which may be taken as the pore diameter. For $K_n < 1$ mass transfer in the pores is completely different from bulk diffusion: instead of molecule-molecule collisions, molecule-wall collisions prevail. For $K_n >> 1$, 'normal' bulk diffusion occurs. When the pore size and molecule size are of the same order of magnitude, the adsorbing molecule is permanently in the force field of the solid and a complex transport mechanism occurs, which is often called surface migration or configurational diffusion. In this region the diffusion process is activated. Fig. 3.39 shows typical values of Fick diffusion coefficients for gas-phase systems. In large pores diffusion takes place without the influence of the solid material: the Fick diffusion coefficient equals that of the gas phase. In smaller pores (1-100 μm) Knudsen diffusion prevails, with the Fick diffusion coefficient typically in the range of 10^{-8} - 10^{-4} m^2/s.

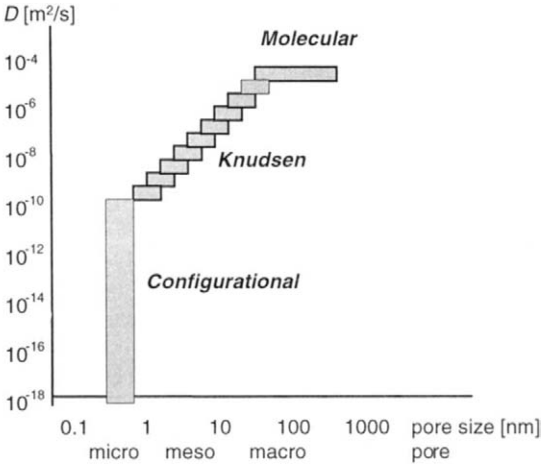


Figure 3.39. Typical values for the diffusion coefficient as a function of pore size.

Knudsen diffusion is generally encountered in heterogeneous catalysis. In the smallest pores configurational diffusion takes place with diffusion coefficient ranging from 10^{-18} to 10^{-8} m^2/s.

According to IUPAC (International Union of Pure and Applied Chemistry), pores are divided into three groups according to their pore diameters:

- micropores (diameter < 2 nm),
- mesopores (diameter between 2 and 50 nm), and
- macropores (diameter > 50 nm).

For most catalysts, mesopores are dominant, whereas for materials derived from zeolites or active carbons, micropores are the most important. Determination of the pore size distribution is indispensable in catalysis research.

When a microporous material, e.g. a zeolite, is used as a catalyst, only those molecules whose diameters are small enough to enter or pass through the pores can react and leave the catalyst. This is the basis for so-called shape-selectivity (Fig. 3.40). Reactant selectivity is encountered when a fraction of the feed molecules can enter the zeolite, whereas the other fraction cannot. For the molecules produced in the interior the same reasoning applies. The favoured products are the less bulky ones, *i.e.* those with diameters smaller than the pores of the zeolites. For instance, in the zeolite represented in Fig. 3.40 the production of *p*-xylene is favoured over the production of *o*- and *m*-xylenes. Also the bulkiness of the transition state can lead to a different selectivity, as shown in the last example in Fig 3.40.

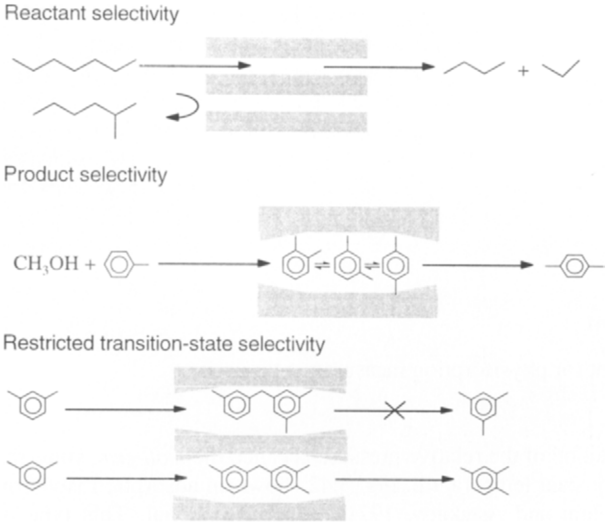


Figure 3.40. Different types of shape selectivity (after Van Bekkum *et al.*, 1991).

3.6.2.2. Physical adsorption isotherms

The surface area and the dimensions and volume of the pores can be determined in many ways. A convenient method is based on measurement of the capacity for adsorption. The experimental techniques do not differ from those used for chemisorption (see Section 3.6.3). The fundamental difference between physisorption and chemisorption is that in chemisorption chemical bonds are formed, and, as a consequence, the number of specific sites is measured, whereas in physisorption the bonds are weak so that non-chemical properties, in particular the surface area, are determined.

Usually, physisorption is carried out using nitrogen as an *adsorbate* at 77.3 K, the boiling point of liquid nitrogen. The solid material is called the *adsorbent.* Adsorption can be measured in many different ways. So-called volumetric adsorption, in which volumes of gas are introduced sequentially while simultaneously measuring the pressure, is a commonly used technique. Fig. 3.41 shows a schematic of the equipment used (referred to as 'barometric equipment').

After the solid sample has been weighed and degassed, a known amount of the adsorbate is admitted to the vessel containing the evacuated sample. When equilibrium has been reached, the amount of gas adsorbed can be calculated from the pressure change. Thus, a correlation between the equilibrium pressure, p, and the amount of gas adsorbed, n_{ad}, can be established. Usually, the pressure is expressed as the relative pressure, p/p^0, where p^0 represents the saturation pressure of the adsorbate at the temperature of measurement.

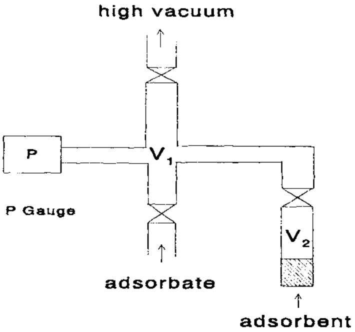


Figure 3.41. Barometric equipment for physisorption measurements.

The curve showing n_{ad} as a function of the relative pressure is called the *isotherm*, since the measurement is conducted at a constant temperature. Fig. 3.42 shows an adsorption isotherm of a so-called type IV (see Dubinin and Astakhov, 1971) isotherm material. This type of isotherm is very common.

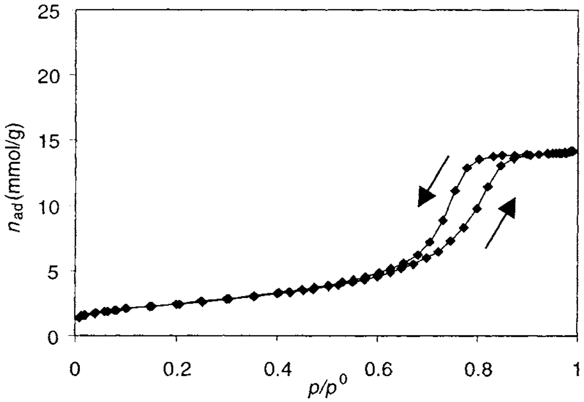


Figure 3.42. Nitrogen adsorption/desorption isotherm for a commercial γ-alumina. The arrows denote the mode of changing the pressure, *viz*. increasing or decreasing pressure.

With increasing pressure the amount adsorbed increases. It is striking that after a sharp increase (up to a p/p^0 of about 0.01) a relatively flat continuously increasing plateau is observed with a sudden large increase (starting at p/p^0 = 0.5-0.6), followed by a constant level (from p/p^0 = 0.9). When the pressure is gradually reduced, the same curve is not followed: the values measured are higher than those in the increasing pressure mode. This is often observed: so-called *hysteresis* occurs. The arrows in Figure 3.42 denote the direction of measurement. The interpretation of this isotherm is as follows. At the lowest pressure micropores are filled because of the high attraction forces; subsequently, molecules adsorb everywhere and a mono-multilayer adsorption equilibrium is established. At still higher pressures, capillary condensation takes place in the meso- and macropores. In this region hysteresis is often observed for porous materials.

Langmuir isotherm. Figure 3.43 shows a Langmuir-type isotherm. This isotherm is described with the following equation:

$$n_{\text{ad}} = n_{\text{m}} \cdot \frac{K \cdot p}{1 + K \cdot p} \tag{9}$$

in which n_{ad} is the amount of gas adsorbed, n_{m} is the amount of gas adsorbed at monolayer coverage, K is the adsorption constant, and p is the equilibrium partial pressure of the adsorbate.

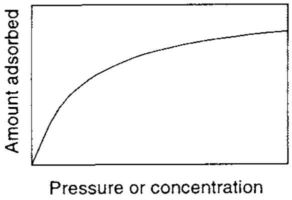


Figure 3.43. Langmuir isotherm.

The theoretical base for the assumption of Langmuir adsorption in physisorption can be questioned, since it is based on several assumptions:

- homogeneous surface (*viz.* all adsorption sites energetically identical),
- monolayer adsorption (no multilayer adsorption occurs),
- no interaction between the adsorbed molecules.

In fact, at the boiling point of an adsorbate physical adsorption on a solid is rarely restricted to a monolayer. When an isotherm is measured and the experimental results show a Langmuir-type shape, is this always a Langmuir-type adsorption? An interesting example is adsorption of N_2 on the walls of zeolite pores. Fig. 3.44 shows the isotherm for the adsorption of nitrogen in zeolite 13X. It is no surprise that this system does not obey the Langmuir theory. Although the shape resembles a Langmuir isotherm, the reason for this shape is quite different. Whereas for Langmuir adsorption the curvature originates from saturation of the active sites, for this example a strong adsorption is observed at low pressures due to condensation in the micropores of the zeolites. At higher pressures saturation is observed due to the finite (micro) pore volume of the zeolite: the micropores are already filled completely at low pressures. So, although the isotherm looks like a Langmuir isotherm, the adsorption mechanism is totally different from Langmuir adsorption. Nevertheless, for porous materials the Langmuir equation, due to its simplicity, is often used to describe adsorption behaviour. However, it is not useful in the calculation of surface areas.

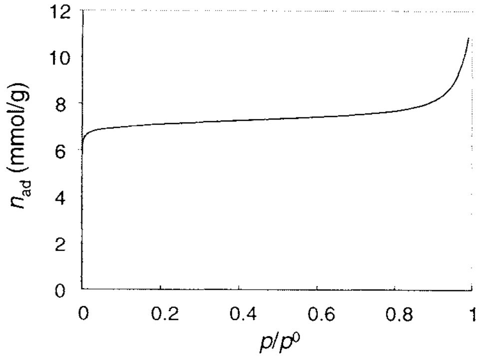


Figure 3.44. Nitrogen adsorption isotherm on zeolite 13X.

BET method. The most commonly used method for determining the specific surface area is the so-called BET method, which obtained its name from three Nobel prize winners: Brunauer, Emmett and Teller (1938). It is a modification of the Langmuir theory, which, besides monolayer adsorption, also considers multilayer adsorption. The equation allows easy calculation of the surface area, commonly referred to as the BET surface area (S_{BET}). From the isotherms also pore-radii and pore-volumes can be calculated (from classical equation for condensation in the pores).

Table 3.6 gives data on the mean pore radius and surface area of some commercial supports and catalysts. The BET surface areas of most commercial catalysts range from several up to about 1000 m^2/g.

Table 3.6
Texture data of some commercial catalysts

Material	Mean d_p (nm)	S_{BET} (m^2/g)
Catalyst supports		
Silica gel	10	200
	6	400
	4	800
γ-Al_2O_3	10	150
	5	500
Zeolites	0.6 – 2	400 – 800
Activated carbon	2	700 – 1200
Aerosil SiO_2	-	50 – 200
Catalyst		
Ra-Ru	11.6	58

These data show that, indeed, mesopores dominate except in zeolites and active carbons. Surface areas can be very high (*viz.*, up to a few football fields per kg!).

For microporous materials the S_{BET} values obtained are usually much higher than the real surface area, because in the region where the BET equation is applied (this equation assumes multilayer adsorption but not condensation) condensation already takes place.

Pore size and surface area distribution. Pore sizes and pore volume distributions may be calculated from the relative pressures at which pores are filled (in the adsorption mode) or emptied (in the desorption mode). Fig. 3.45 shows the pore size distribution of a commercial γ-alumina. The distribution is very broad: both meso- and macropores are present. In practice this is usually a desired situation: a texture consisting of a network of large pores (main roads) and small pores (side roads) is ideal.

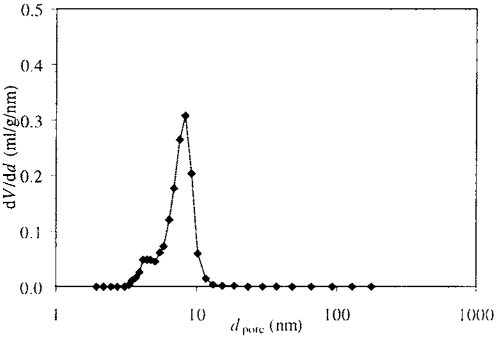


Fig. 3.45. Pore size distribution of a commercial γ-alumina calculated using the Kelvin equation.

3.6.3. Chemisorption

Active catalyst sites can consist of a wide variety of species. Major examples are co-ordination complexes of transition metals, proton acceptors or donors in a solution, and defects at the surface of a metallic, oxidic, or sulphidic catalyst. Chemisorption is one of the most important techniques in catalyst characterization (Overbury *et al.*, 1975; Bartley *et al.*, 1988; Scholten *et al.*, 1985; Van Delft *et al.*, 1985; Weast, 1973; and Bastein *et al.*, 1987), and, as a consequence, it plays an essential role in catalyst design, production and process development.

Fundamental is that the atoms in the surface phase are not fully co-ordinated. These sites are often called 'Co-ordinatively Unsaturated Sites (CUS)'. These sites chemisorb molecules because upon formation of bonds with the adsorbing molecules the Gibbs free energy is lowered.

3.6.3.1. *Metal dispersion*

In practice there is a need for characterization of the dispersion, if it were only to estimate the efficiency of the catalytically active component. This can be done by chemisorption of a gas that adsorbs at the surface of the metal particles. H_2, CO, O_2, and N_2O are applied most often. For the calculation of the dispersion it is of paramount importance that the stoichiometry of the adsorption reaction is known and that the reaction is limited to the surface.

3.6.3.2. *Stoichiometry of adsorption*

In calculating the metallic surface area, one has to take proper care of the reaction stoichiometry. In the ideal case, a molecule occupies one site, as shown for terminal adsorbed CO in Fig. 3.46.a. Alternatively, a molecule may chemisorb on more than one metal atom, as shown in Fig. 3.46.b and c for bridged-site adsorbed CO and in Fig. 3.46.d for valley-site adsorbed CO, respectively. In some specific cases of really big molecules, one can imagine that a molecule adsorbs on only one site, while simultaneously blocking adjacent sites for geometric reasons. In case an adsorbate molecule adsorbs dissociatively, it will occupy more than one site as shown in Fig. 3.46.e.

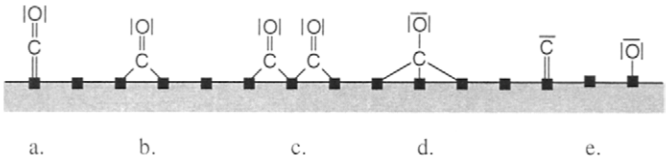


Figure 3.46. Representation of various modes of chemisorbed CO on a metallic surface; a. linear or terminal, b. bridged, c. bridged, d. valley or triple and e. dissociative adsorption.

In some specific cases one would like to convert the chemisorption data into an averaged particle size. In that case, the number of surface atoms per unit surface area (density of surface atoms) is an essential parameter. Since this number depends on the type of the crystallographic plane, (see Table 3.7), one also needs information on the types of crystallographic planes exposed to the gas phase. This is also important for another reason; the adsorption stoichiometry may depend on the crystallographic plane.

Table 3.7
Adsorption stoichiometry of some gases on some metals

Metal	N_2O/Me	H/Me	CO/Me
Pt		1	1
Cu	0.5	poor H_2 dissociation catalyst	1
Ni	0.67	1	carbonyl formation!
Rh d > 2 nm		1	1
Rh d < 2 nm		2	

Some data on the adsorption stoichiometry of various gases on relevant transition metals have been collected in Table 3.7, which illustrates the usefulness of certain molecules for catalyst characterization by chemisorption. Note that Cu as active phase can be measured well with N_2O and CO, but not with H_2. It is not wise to determine Ni dispersion with CO, due to the possibility of carbonyl formation; Ni carbonyls are volatile and poisonous. Note that in Table 3.7, for Rh the H/Me ratio is size dependent. This phenomenon is not restricted to Rh; it is common in the chemisorption of metals.

3.6.3.3. Dispersion and particle size of the catalyst

From the dispersion an estimate can be made of the mean particle size. Under the assumption that the particles are spherical or hemispherical, the following relation can be derived:

$$d_{vs} = 6\frac{V_A}{S_A}\frac{1}{D} \tag{10}$$

in which d_{VS} is the volume-surface mean diameter of the particle, V_A the effective volume per metal atom in the bulk (which can be derived from the molar volume of the solid), and S_A the effective average surface area per atom. The latter has to be estimated, since it depends (slightly) on the crystallographic planes present at the surface of the particle (see Table 3.8).

Table 3.8
The number of surface atoms per unit area for some transition metals for small and large particles (Scholten *et al.*, 1985)

Metal	part. size ca 5 nm 33% (111) plane 33% (100) plane 33% (110) plane (atoms.nm^{-2})	part. size ca 15 nm 70% (111) plane 25% (100) plane 5% (110) plane (atoms.nm^{-2})
Co	15.1	-
Ni	15.4	17.5
Pt	12.5	14.2
Pd	12.7	14.5
Ru	16.3	-
Rh	13.3	15.5
Cu	14.7	16.7

Using the number of Pt and Ni atoms per nm^2 for small particles (12.5 and 15.4, respectively, see Table 3.8), and their molar volumes of 9.09 and 6.59 cm^3/mol, respectively (Weast, 1973), as well as Avogadro's number ($6 \cdot 10^{23}$), one can easily calculate the curves shown in Fig. 3.47.

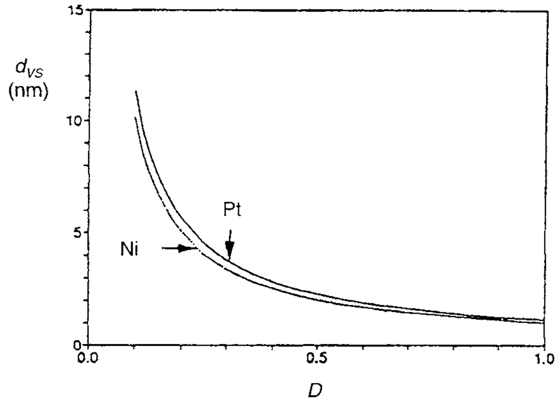


Figure 3.47. Volume-surface mean diameters for (hemi)spherical particles of Pt and Ni as a function of their dispersion, *D*.

As can be seen from Fig. 3.47, for particle sizes of a few nm the dispersion should be over 90 %. Of course, this relationship is based on a simplification; the particles are assumed to be spheres of which all the surface sites are accessible for the probe molecules. The data have a general validity, notwithstanding the fact that in reality these assumptions are not always fulfilled. Also, the numbers and types of the various crystallographic planes present in the surface, and hence the average surface area per atom, depends on the particle size. This effect has not been accounted for in the data shown since it leads to small corrections only. The concentration of surface atoms differs for the various crystallographic planes and also depends on the metal under consideration. Notice that for particles larger than about 15 nm, the surface mainly consists of the so-called 'low Miller index' planes with a high atomic density, whereas small particles of about 5 nm have a relatively large contribution of the crystallographic planes with high Miller index numbers.

Figures 3.48 shows an artist impression of some typical particle shapes of the active phase.

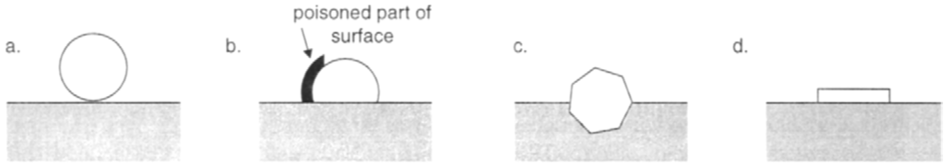


Figure 3.48. An artist impression of possible shapes of catalyst particles present on a support; a. spherical particle with only one point contact to support, b. hemispherical particle, strongly bonded to support and partially poisoned, c. metal crystallite, strongly bonded to and partially encapsulated in support, d. complete wetting of the support by the active phase. After Scholten *et al.*, 1985 and Bastein *et al.*, 1987.

Note that the particle shape is affected by the interaction between the active phase and the support and by the surface free energy. The former tends to lead to spreading of a particle, whereas the latter tends to form spherical particles (Scholten *et al.*, 1985). When particles are partially poisoned (Fig. 3.48.b), chemisorption data can be interpreted wrongly: the average particle size is overestimated. The same applies to particles encapsulated in the support.

3.6.3.4. Experimental techniques

For illustration we will present some commonly used techniques for chemisorption measurements. Chemisorption can be measured gravimetrically, volumetrically, or spectroscopically. Also, pulse techniques, and Temperature Programmed Desorption (TPD) can be used.

Gravimetry. The sample is located in a chamber that can be heated or exposed to vacuum or probe gases. Gravimetry is a convenient method although not always applicable. For instance, it is impossible to measure hydrogen chemisorption using gravimetry. An example of chemisorption measured by gravimetry is shown in Fig. 3.49.

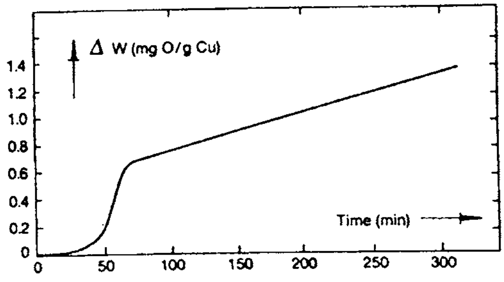


Figure 3.49. Gravimetric measurement of chemisorption of N_2O on a supported Cu catalyst (Luys *et al.*, 1989). Surface and bulk oxidation can be easily discriminated.

The curve consists or two parts, a fast initial weight increase followed by a slow weight increase. The interpretation is as follows. First a fast surface oxidation takes place. From these data the dispersion should be calculated. As the rate becomes lower, oxidation of the atoms below the surface occurs. This does not give direct information on the dispersion but rather on the kinetics of the bulk oxidation of the Cu particles.

Barometric chemisorption. Chemisorption on catalysts is measured routinely by the barometric method. The equipment is very similar to that commonly used in texture determination by physical adsorption (see Section 3.6.2), except that for chemisorption measurements facilities for pretreatment of the samples should be present. In particular for metal catalysts often the catalyst is received in a partly or fully oxidized form and, as a consequence, reduction is required when one wants to measure the amount of active sites. Moreover, during storage adsorption of various molecules might occur and evacuation is required before a useful measurement can be performed. After reduction and evacuation of the reactor, a known amount of gas is expanded from the reference volume into the reactor section. After establishment of equilibrium, the pressure is recorded. From this pressure and the volume of the system (which should be known, of course), the amount of adsorbed gas can be calculated.

To improve accuracy, usually data are collected at various pressures, followed by the extrapolation of the adsorbed amount of gas to zero pressure. In commercial equipment this is often done in the so-called 'increasing pressure mode' by the stepwise injection of small amounts of gas. Note that these methods can only be used easily for 'non-activated' adsorption (Reuel and Bartholomew, 1984), e.g. for CO chemisorption.

Alternatively, data points can be collected in the 'decreasing pressure mode'. This procedure is usually applied for the quantification of activated adsorption processes (Reuel and Bartholomew, 1984), such as the adsorption of H_2. After the pretreatment of the sample (usually after reduction or reaction, and evacuation for a certain period to remove all the adsorbed surface species) the temperature is lowered to the temperature of measurement. First, a known amount of adsorbate gas is added to the reactor. Subsequently, the pressure in the catalyst compartment is lowered stepwise by expansion of the gas into the repeatedly evacuated reference volume. The adsorbed amount of gas can be calculated for each step. From this procedure, the monolayer capacity of the catalyst can be evaluated.

Fig. 3.50 shows an example of the barometric method for a Ni/Al_2O_3 catalyst (Xu Xiaoding, 1998). After reduction and evacuation at high temperature the adsorption of H_2 on the catalyst sample was measured at 323 K: the upper isotherm (due to a combination of weak and strong chemisorption) in Fig. 3.50 was obtained. After evacuation at 323 K a second isotherm (lower curve) was determined. It might be surprising that in this latter measurement again adsorption takes place. The reason is that in the intermediate evacuation step the weakly bound molecules desorb form the surface. The amount of these molecules is directly calculated from the second adsorption isotherm (weak chemisorption). The difference between the two isotherms represents the strong chemisorption data. Generally, the adsorbed amount of gas is extrapolated to zero pressure, leading to the so-called 'monolayer capacity at zero pressure'.

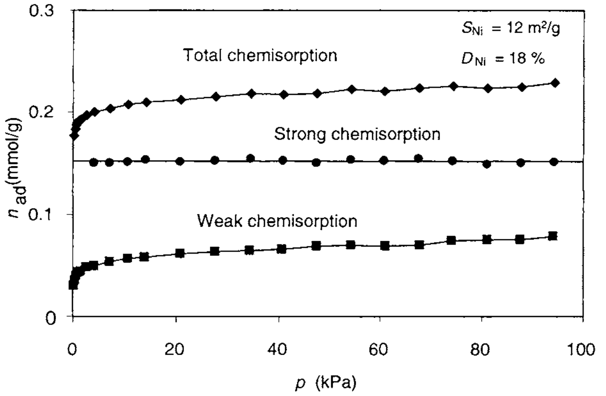


Figure 3.50. Reversible (weak chemisorption) and irreversible (strong chemisorption) H_2 adsorption on Al_2O_3 supported Ni catalyst at T= 323 K (Xu Xiaoding, 1998).

Table 3.9 shows the results of barometric hydrogen chemisorption on Cu/Al_2O_3, Ni/Al_2O_3, Pt/Al_2O_3 and a Ni on alumina-washcoated monolith.

Table 3.9
Metallic surface area and metal dispersions of some samples measured by barometric H_2 chemisorption

Sample	S_{metal} m^2/g	Metal Dispersion %
6 wt% Ni/Al_2O_3[a]	0.76	1.8
10 wt% Cu/Al_2O_3	0.6	0.8
10 wt% Ni/Al_2O_3	12	18
1 wt% Pt/Al_2O_3	1.54	55

[a] Monolithic catalyst.

Table 3.9 shows that the Pt catalyst has the highest dispersion, *i.e.* 55%. That is not unusual: Pt is extremely expensive and, as a consequence, high dispersion is a rule rather than an exception. In practice the dispersion is often over 50%. The value given for the Cu catalyst should be interpreted with some caution. Copper is a very poor hydrogen dissociation catalyst (see also Table 3.7), and, as a consequence, chemisorption (which requires dissociation) is not possible on most Cu sites. For the Ni and Pt catalysts, however, the method works well. This is not surprising because both metals are good hydrogenation catalysts. When comparing the numeric data for the Ni catalysts in Table 3.9, it is clear that the amount of Ni atoms exposed per gram of catalyst (dispersion) differs by a factor of 10. This illustrates the potential of chemisorption: a direct measurement of the number of active sites is obtained.

Step- and impulse-response methods. Chemisorption can conveniently be measured under flow conditions using transient techniques, in particular, step-response and impulse-response measurements. After pretreatment, pulses of probe gas are injected into a carrier gas stream passing through the reactor that contains the pre-treated sample. The response is detected at the reactor exit.

As always in chemisorption measurements, pretreatment of the samples should be done with care. For metal catalysts prepared from oxides in particular this is experimentally troublesome because a reduction step is always needed in the preparation of the metal catalyst. Hydrogen or hydrogen diluted with an inert gas is usually used for the reduction but it is difficult to remove adsorbed H_2 from the surface completely. So, after reduction the metal surfaces contains (unknown) amounts of H atoms, which are strongly retained by the surface and, as a consequence, it is not easy to find reliable values for the dispersion from H_2 chemisorption data.

The so-called CO intrusion method was invented using CO doses to a hydrogen-reduced sample instead of evacuation and using hydrogen doses. This method avoids the time-consuming procedure of evacuation after the reduction step. Since CO chemisorbs more strongly on the metals than hydrogen, CO pulses can be dosed to a reduced sample without prior removal of chemisorbed hydrogen. The CO molecules replace adsorbed hydrogen atoms.

Fig. 3.51 shows CO chemisorption data using the pulse method for a reduced Pt/Al_2O_3 sample. It is clear that the peak height gradually increases as more pulses are given. From the third pulse on, the peak height becomes constant (Fig. 3.51.a), *viz.* the surface is saturated with CO and no additional CO is chemisorbed. Fig. 3.51.b represents the cumulative values.

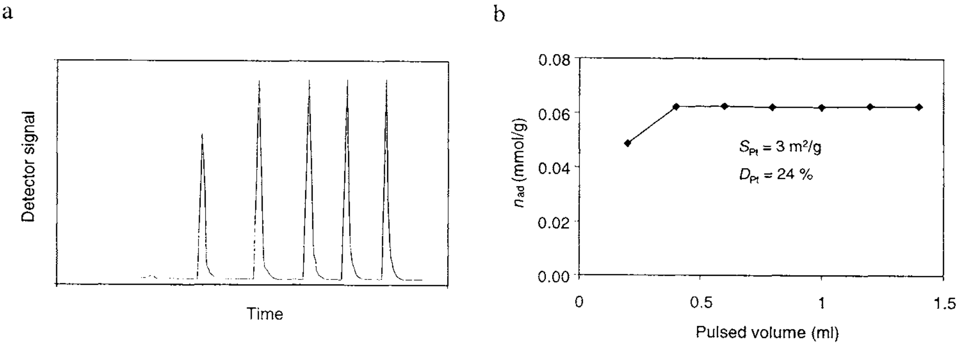


Figure 3.51. CO chemisorption by pulse response of a reduced 5 wt% Pt/Al_2O_3: a. Thermal Conductivity Detector (TCD) signals after the CO pulses, b. Cumulative amount of CO chemisorbed. The monolayer capacity is 0.06 mmol/g Pt, corresponding with a dispersion of 24%.

Besides CO, hydrogen, oxygen, and other gases can also be used in chemisorption, provided suitable conditions are applied for sample pretreatment and chemisorption measurements (Overbury *et al.*, 1975; Bartley *et al.*, 1988; Scholten *et al.*, 1985; and Van Delft *et al.*, 1985).

Temperature Programmed Desorption (TPD). Chemisorbed molecules are bonded to the surface by forces dependent on the nature of the sites. For instance, ammonia will be strongly adsorbed on acid sites, whereas it is only weakly adsorbed on basic sites. Consequently, the adsorbate complex formed with the basic sites will decompose at lower temperatures than that formed with the acid sites. The following example regarding the NH_3-zeolite H-ZSM-5 system will illustrate this.

First, after heat treatment (to desorb any adsorbed species), the zeolite is saturated with ammonia vapour at ambient temperature. Then the temperature is raised, usually according to a linear program while purging the reactor with an inert gas, e.g. He or Ar. As a result, desorption of ammonia in the effluent will be detected continuously, either by mass spectrometry or with a thermal conductivity detector (TCD). Figure 3.52 shows the resulting TPD pattern. The desorption spectrum consists of two broad overlapping peaks. The interpretation is as follows. The first (low-temperature) peak is assigned to NH_3 desorbing from weak acid sites. This desorption peak also emanates from silicalite which contains no Al so that the adsorption sites are essentially non-acidic. The high-temperature peak is due to ammonia desorbed from strong acid sites. Clearly, this method gives useful information since it is quantitative and the peak temperatures can be correlated to the acid strength of the adsorption sites.

Of course, diffusion limitations may affect the TPD pattern especially for microporous materials such as zeolites. Furthermore, no information is acquired on the nature of the acid sites. For instance, the technique does not discriminate between Lewis and Brönsted sites.

In summary, TPD is extensively applied. Commonly used molecules are NH_3, H_2, CO and CO_2. The desorption patterns can be modelled and in doing so much more information is obtained.

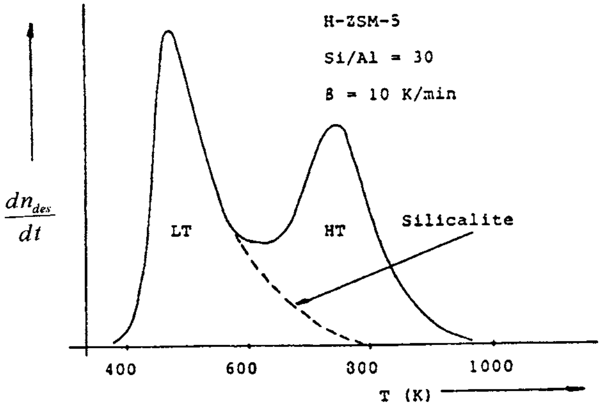


Figure 3.52. TPD spectrum of ammonia desorbing from H-ZSM-5 (Van Bekkum *et al.*, 1991).

Spectroscopy. In the methods discussed so far, the information obtained is essentially limited to the analysis of mass balances. In that respect they are 'blind' methods, since they only yield macroscopic 'averaged' information. It is also possible to study the spectrum of a suitable probe molecule adsorbed on a catalyst surface and to derive information on the type and nature of the surface sites from it. A good illustration is that of pyridine adsorbed on a zeolite containing both Lewis (L) and Brönsted (B) acid sites. Figure 3.53 shows a typical IR absorption spectrum of adsorbed pyridine. The spectrum exhibits four bands that can be assigned to adsorbed pyridine and pyridinium ions. Pyridine adsorbed on a Brönsted site forms a (protonated) pyridium ion whereas adsorption on a Lewis site only leads to the formation of a co-ordination complex.

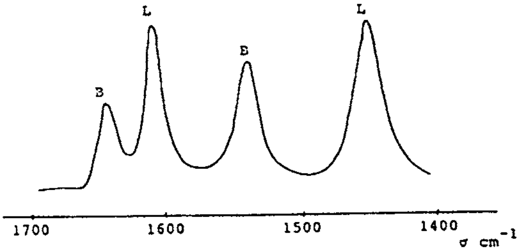


Figure 3.53. IR transmission absorption spectrum of pyridine adsorbed on partly dehydroxylated HY zeolite (Van Bekkum *et al.*, 1991); B = Brönsted acid sites; L = Lewis acid sites.

3.7. HOMOGENEOUS CATALYSIS

3.7.1. Introduction

In homogeneous catalysis soluble catalysts are applied, usually in the liquid phase, in contrast to heterogeneous catalysis, where solid catalysts are used. Homogeneous catalysis is applied in many processes in both bulk and fine chemicals production.

Inexpensive mineral acids, e.g. HF, HCl and H_2SO_4, and bases, e.g. KOH, are commonly used as catalysts, e.g. for alkylations, esterifications, and hydrolysis reactions. Although applied in large quantities in bulk chemicals production, this technology is not up to modern standards. In fact, a trend is to replace these systems by solid catalysts (see Chapter 4). Here, we will confine ourselves to homogeneous catalysts based on transition metals. These catalysts are becoming increasingly important and have already found a large number of industrial applications. Homogeneous transition-metal catalysis is applied in polymerization, in the synthesis of bulk chemicals (solvents, detergents, plasticizers), and in fine chemistry and pharmaceuticals production.

It is useful to compare homogeneous and heterogeneous catalysis (Moulijn *et al.*, 2001). In homogeneous catalysis the reaction mixture contains the catalyst complex in solution. This means that all of the metal is exposed to the reaction mixture. In heterogeneous catalysis, on the other hand, only the surface atoms are active. Thus, in terms of activity per metal centre, homogeneous catalysts are often more active (at lower temperature), *i.e.* metal utilization and productivity are higher for homogeneous catalysts. The high dispersion of homogeneous catalysts also minimizes the effect of catalyst poisons; in homogeneous catalysis one poison molecule only deactivates one metal complex, whereas in heterogeneous catalysts a poison molecule can block a pore containing many active sites (pore plugging).

Homogeneous catalysts are also capable of being much more selective; while with homogeneous catalysts there is usually only one type of active site, heterogeneous catalysts contain many different types of active sites, some of which could catalyse undesired reactions. The discrete metal complexes in homogeneous systems provide a well-defined catalyst system, which is highly specific and is easy to study by conventional techniques (infrared spectroscopy, NMR). From this another advantage of homogeneous catalysis arises, namely the possibility to follow the effect of changes in ligands and/or reaction conditions accurately. Hence, the selectivity for a specific product can be controlled by modification of the ligands. The behaviour of heterogeneous catalysts with their complex surfaces, is much more difficult to understand, and therefore, effective modification is not so easy.

Because homogeneous catalysis is usually carried out in the liquid phase, temperature control is relatively easy. However, the temperature must not be too high to prevent degradation of the catalyst complexes.

Of course, homogeneous catalysis of course also has disadvantages. The main problem is the separation of catalyst and product. This is often only feasible for low molecular weight products. The use of solvents requires an additional separation step.

In homogeneous catalysis often precious metals are used, while the ligands are also expensive. Therefore, the catalyst productivity indeed should be high, and catalyst losses should be minimized, requiring nearly complete recovery of the metal, and the ligands.

Fouling of the reactor and other equipment is another problem specific for homogeneous catalysis.

Most homogeneously catalysed reactions operate under mild conditions (which is possible as a result of the high catalytic activity), because the temperature should not exceed 100 to

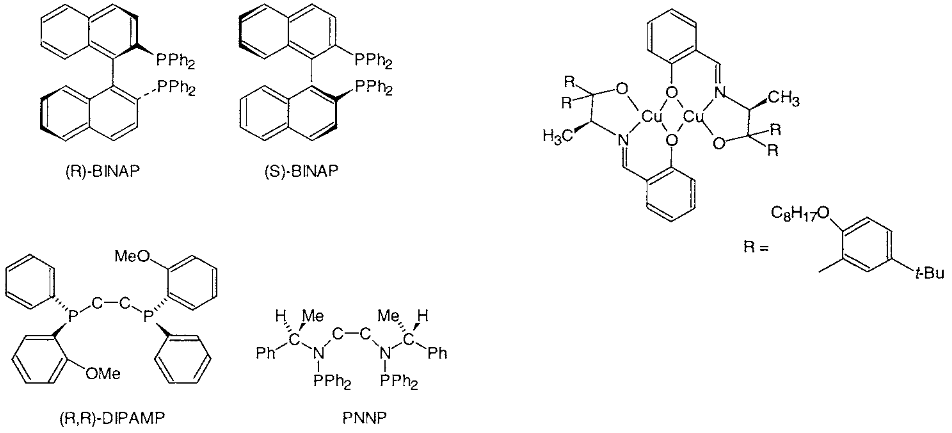
200 °C to prevent degradation of the catalyst complexes. Therefore, strongly endothermic reactions cannot be carried out with homogeneous catalysts.

3.7.2. Transition-metal catalysts

The value of transition metals for catalytic reactions can be attributed to their bonding ability with a great variety of ligands, the possibility of changing ligands at will to create a different catalyst, and on the variability of the oxidation state and co-ordination number of the metal. Organometallic catalysts consist of a central metal surrounded by organic and inorganic ligands in a regular pattern that depends on the co-ordination number and electronic properties of the metal and on the size and charge of the ligands. The properties of the catalyst are determined by both the metal and the large variety of ligands.

The key to the successful development of homogeneous catalysts has been the exploitation of the effects that ligands exert on the properties of metal complexes: by tailoring the electronic and steric properties of a catalytically active metal complex, activities and selectivities can be altered considerably. This especially holds for phosphorus based ligands, which are the most commonly encountered ligands associated with organometallic compounds.

A particular advantage of using metal complex catalysts in enantioselective syntheses is that the reaction can be tuned by ligand variation, e.g. chiral ligands can be applied. In heterogeneous catalysis the possibilities to produce chiral molecules are much more limited. The advantage of transition-metal complexes with chiral ligands over enzymes, which are important biological catalysts, is that both optical isomers of the ligand can be produced, while enzymes are only of one kind. Figure 3.54 shows the structures of some chiral ligands and a chiral copper catalyst.



(R)-BINAP (S)-BINAP

(R,R)-DIPAMP PNNP

Figure 3.54. Structures of some chiral phosphine ligands (left) and a chiral copper catalyst (right).

3.7.3. Catalyst performance

3.7.3.1. Activity

The activity of transition metal catalysts depends on both the metal and the ligands. In addition, solvent effects, etc. can play a role. Table 3.10 shows examples of transition- metal catalysts with the reactions for which they are active (Farkas, 1986).

Table 3.10
Examples of metal complexes with their activities (Farkas, 1986); L = ligand, R = alkene)

Catalyst	Activity	Catalyst	Activity
$Fe(CO)_5$	Hydrogenation	$RhClL_3$	Hydrogenation
$FeH(CO)_4^-$	Isomerization	$RhCl_3COL_2$	Hydroformylation
$Co(CN)_6^{3-}$	Hydrogenation	$RhCl_3R^{2-}$	Isomerization
$Co(CO)_4^-$	Hydrogenation, hydroformylation, isomerization	$RhCl_2R_2^-$ $Rh(CO)_2I_2^-$ $PdCl_4^{2-}$	Dimerization Carbonylation Isomerizaton, oxidation
$RuCl_6^{4-}$	Hydrogenation	$Pt(SnCl_3)_5^{3-}$	Hygrogenation, isomerization
$RuCl_2L_4$	Hydroformylation	$IrICOL_2$	Hydrogenation

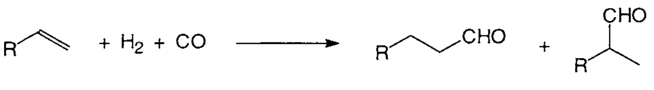
3.7.3.2. Selectivity

Homogeneous transition-metal catalysts are usually chosen because of their high selectivity. A distinction is made between chemoselectivity, regioselectivity, and stereoselectivity, of which a special form is enantioselectivity. The latter is especially important in the production of pharmaceuticals.

Selectivity is determined by a number of factors, such as intrinsic properties of the catalyst complex (metal and ligands), reaction conditions (concentration, temperature, pressure), and reactor configuration (solvent, reactor, process). Here, we will focus on the catalyst properties.

The so-called Wilkinson catalyst, $RhCl(PPh_3)_3$, *chemoselectively* hydrogenates carbon-carbon double bonds, while leaving other functional groups untouched. On the other hand, hydrogenation of other groups in the presence of carbon-carbon double bonds can be effected by using pentacyanocobalt(II) ($Co(CN)_5^{3-}$). This catalyst selectively hydrogenates R in C=C-R with R = $-CH=CH_2$, CO_2H, CO_2^-, CN, $C(O)NH_2$, C(O)R', aryl, α-C_5H_4N.

Regioselective reactions belong to the most important applications of homogeneous catalysis. An example is the hydroformylation of alkenes, which is a very important industrial reaction:



(11)

The linear aldehyde usually is the desired product. Often, this aldehyde is converted to the corresponding alcohol. Both Co and Rh complexes are used in hydroformylation. In general, Rh catalysts are more active and produce a higher *n*/*iso*-ratio. Co catalysts have higher aldehyde hydrogenation activity. Table 3.11 compares some Co catalysts with different ligands for the hydroformylation of 1-hexene.

The percentage of linear product increases greatly by replacing CO with the much bulkier phosphine ligands. Due to the increased steric hindrance the catalyst shows a distinct preference for the *n*- over the *iso*-isomer. Tkatchenko (1991) has reported a detailed analysis of this system in terms of the correlation between catalyst performance (activity and selectivity) and detailed structure.

A variety of other addition reactions occurring regioselectively are also known. These include hydrocyanation, hydroalumination, hydrosilylation, and hydrozirconation.

Table 3.11
Hydroformylation of 1-hexene using $Co(CO)_3L$ as the active catalyst
(T = 160 °C, p = 70 bar, H_2/CO = 1.2/1); Adapted from (Tkatchenko, 1991)

L	$10^3 k$ (min^{-1})	% n	Aldehyde-to-alcohol ratio
PEt_3	2.7	89.6	0.9
PEt_2Ph	5.5	84.6	2.2
$PEtPh_2$	8.8	71.7	4.3
PPh_3	14.1	62.4	11.7

Homogeneous catalysis has an important role to play in *enantioselective* reactions. To improve product safety, the pharmaceutical industry is producing an increasing number of products in enantiomerically pure form. Other important (future) markets include agrochemicals, polymers and fine chemicals. Although the number of practised processes is quite small the potential is high.

Table 3.12 surveys current industrial applications of enantioselective homogeneous catalysis in fine chemicals production. Most chiral catalyst in Table 3.12 have chiral phosphine ligands (see Fig. 3.54). The DIPAMP ligand, which is used in the production of L-Dopa, one of the first chiral syntheses, possesses phosphorus chirality. (see also Section 4.5.8.1) A number of commercial processes use the BINAP ligand, which has axial chirality. The PNNP ligand, on the other hand, has its chirality centred on the α-phenethyl groups two atoms removed from the phosphorus atoms, which bind to the rhodium ion. Nevertheless, good enantioselectivity is obtained with this catalyst in the synthesis of L-phenylalanine.

A breakthrough in asymmetric catalysis research was the development of titatinium complexes containing a chiral tartrate, for the so-called 'Sharpless epoxidation' of allylic alchohols (Sharpless, 1987). The Sharpless epoxidation catalyst is interesting because it shows high enantioselectivity with various reactants, provided they have an allylic alcohol directing group; thus the catalyst is less reactant specific than most other chiral catalysts, which makes it very versatile. Not surprisingly, the Sharpless epoxidation catalyst has been applied for the preparation of a wide range of molecules, including intermediates for pharmaceuticals such as glycidol (Shum and Cannarsa, 1997; Section 4.5.8.3 in this book).

The chiral copper catalyst (see Fig. 3.54) has been used to synthesize the drug Cilastatin. The desired biological activity is found in the stereoisomer derived from (+) 1*S*-2,2-

dimethylcyclopropanecarboxylic acid. A key step is the stereoselective assembly of the necessary cyclopropane ring. This is done by reaction of ethyldiazoacetate with *iso*butene in the presence of the chiral copper catalyst with a 92% enantiomeric excess (Parshall and Ittel, 1992).

Table 3.12
Examples of industrially applied enantioselective homogeneous catalysis in fine chemicals (Parshall and Ittel, 1992; Cornils and Herrmann, 1996)

Metal/Chiral ligand	Reaction	Product	Use	% *ee*
Rh/(*S*)-BINAP[a]	Isomerization of allylic amine	*L*-Menthol	Aroma and flavour chemical	96 - 98
Rh/DIPAMP[a] Rh/PNNP[a]	Hydrogenation of enamides	*L*-Dopa L-Phenylalanine	Pharmaceutical Food additive	95
Ru/(*S*)-BINAP[a]	Hydrogenation of substituted acrylic acid	*S*-Naproxen	Pharmaceutical	97
Ti/ *D*-diethyl tartrate Ti/ *D*- or *L*-diethyl tartrate	Epoxidation of allylic alcohol	(+)-Disparlure Glycidol	Insect attractant Intermediate	90-95 90
Chiral copper catalyst	Cyclopropanation	Cilastatin	Pharmaceutical	92

[a] See Fig. 3.54 for ligand structure.

3.7.3.3. Deactivation

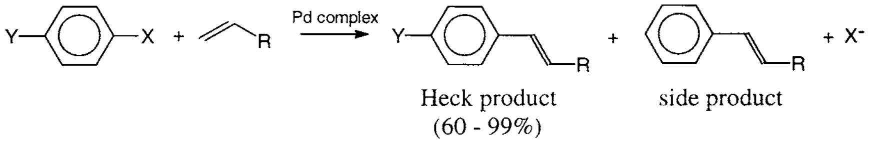
Most low-valence metal complexes are generally deactivated by air and sometimes also by water. Carbon monoxide, hydrogen cyanide, and PH_3 frequently act as poisons for these catalysts. Poisoning by strongly co-ordinating molecules occurs by formation of catalytically inert complexes. An example is the poisoning of Wilkinson's catalyst for alkene hydrogenation:

$$RhCl(PPh_3)_3 \xrightarrow{CO} RhCl(CO)(Ph_3)_2 \qquad (12)$$

$$RhCl(PPh_3)_3 \xrightarrow{PH_3} RhCl(PH_3)_n(Ph_3)_{3-n} \qquad (13)$$

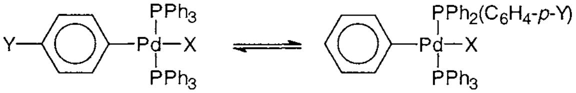
Ligands may decompose, especially at higher temperatures. Furthermore, most organic ligands are unstable in strongly oxidizing media. As one can imagine, the latter is particularly problematic for homogeneous catalytic oxidations.

An example of ligand decomposition is in the Heck C-C coupling using $Pd(PPh_3)_4$ (Cornils and Herrmann, 1996), Eqn. (14).



(14)

The phosphine ligands suffer from P–C-bond cleavage, which result in the corporation of the phosphine aryl groups into an unwanted side product. This is due to the facile exchange of Ph and PhY between the Pd^{II} centres and co-ordinated phosphines on an intermediates of type *trans*-$Pd(PPh_3)_2(aryl)X$:



(15)

Hence, P-C bond-cleavage followed by isomerization is responsible for the formation of side products. Furthermore, due to destabilization of the catalyst complex, deactivation occurs and palladium black is formed, which is a notorious disadvantage of Pd-phosphine catalysts in general. Catalyst decomposition and the formation of side products causes additional separation and catalyst recovery problems. These problems have been solved by the discovery of novel catalyst complexes, which are active and stable at temperatures of over 250 °C (Cornils and Herrmann, 1996).

See Van Leeuwen (2001) for more examples of deactivation of homogeneous catalysts.

3.7.4. Catalyst/product separation methods

The problem of separation of the catalyst from the product in homogeneous catalysis is the main disadvantage of this type of catalysis. In this section, we will summarize how this problem has been tackled in various homogeneously catalysed processes.

Complete catalyst recovery is important for several reasons:

- catalyst metal is expensive (especially rhodium),
- ligands are expensive (e.g. phosphines),
- catalyst metal or co-catalyst is hazardous to the environment (e.g. cobalt),
- metals act as oxidation catalysts,
- catalyst components are usually not allowed in the product.

Reactivation of the catalyst is also often required.

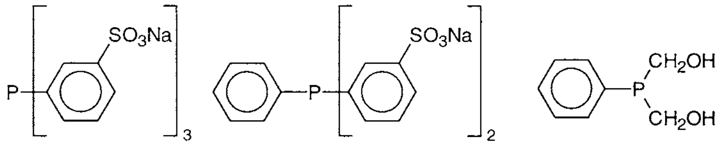
Product purification not only includes recovery of the catalyst. It also consists of removal of co-catalysts, decomposition products of the ligands, unconverted reactants, and by-products. The latter two, of course, are not specific for homogeneous catalysis.

Very active, not too expensive, catalysts may be left in the product if they are used in such small quantities that they are not detrimental to the properties of the product. An example is the gas-phase polypropylene process. When the desired product is formed as a solid, *i.e.* crystallizes from the homogeneous reaction mixture, the product can be removed in relatively simple way.

In the hydroformylation of lower alkenes using a modified cobalt catalyst complex separation is achieved by distillation. The ligands are high-boiling so that they remain with the heavy ends when these are removed from the alcohol product. Distillation is not possible when higher alcohols or aldehydes are produced, because of decomposition of the catalyst ligands at the higher temperatures required. Rhodium complexes can usually also be removed by distillation, since these complexes are relatively stable.

Thermal operations such as distillation, decomposition, transformation, and rectification often cause thermal degradation. Furthermore, with these processes quantitative catalyst recovery is generally not possible, which results in loss of productivity.

Application of biphasic catalysis, usually using an organic phase containing the reactants and an aqueous phase in which the catalyst is dissolved, greatly facilitates separation. By simple phase separation (decanting) the catalyst can be separated from the products and excess reactants just after reaction and at approximately the same temperature (Cornils and Hermann, 1996). The solubility of the catalyst in water is usually achieved by introduction of highly polar substituents such as $-SO_3H$, $-COOH$, $-OH$, or $-NH_2$, or their salts. Figure 3.55 shows water-soluble ligands for hydroformylation reactions.

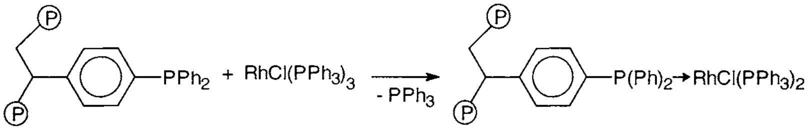


TPPTS TPPDS

Figure 3.55. Examples of water-soluble phosphine ligands.

Biphasic catalysis heterogenizes the homogeneous catalyst without anchoring (immobilizing) it. A different method to heterogenize the catalyst is immobilization of the catalyst on a support, which combines the advantages of homogeneous catalysis (high selectivity and specificity) with the advantage of heterogeneous catalysis (easy separation).

The most frequently used organic supports are polystyrene and styrene-divinylbenzene copolymer beads with functional groups such as diphenylphosphine covalently bonded. The polymer-anchored catalyst complex can then be obtained, for example, by displacement of a ligand already co-ordinated to a soluble metal complex (Cornils and Herrmann, 1996):



(16)

Ⓟ— = polymeric network

Another way of immobilizing catalyst complexes might be to trap them in the pores of solid particles, for instance by synthesizing the complex inside the pores of a zeolite ('ship in a bottle'). Another method could be to trap catalyst complexes in porous materials and deposit a membrane at the outer surface. These methods of immobilizing a homogeneous catalyst do not involve chemical linkage between the catalyst and the carrier. The fixation is the result of steric hindrance.

Smart chemical reaction engineering can also solve the separation problem. Multifunctional reactors based on distillation or membrane separation wil gain importance in the future (see also Chapter 6).

3.8. PHASE-TRANSFER CATALYSIS

3.8.1. Introduction

In the mid-1960s a series of papers by Makosza and Serafinowa (1965, 1966) appeared under the common title "Reactions of Organic Anions", in which the catalytic alkylation of phenylacetonitrile and its derivatives carried out in the presence of concentrated NaOH and the catalyst triethylbenzylammonium chloride (TEBA) was described. This was the beginning of phase-transfer catalysis (PTC), and since then thousands of papers haven been published on the subject.

Phase-transfer (PT) catalysts accelerate reactions of two immiscible reactants. Without a PT catalyst reactions between substances located in different phases are often slow or do not occur at all. The PT catalyst usually has the function of transferring anions, in the form of an ion pair, from the aqueous phase to the organic phase, in which the reaction with the water-insoluble reactant takes place (see schematic representation in Fig. 3.56).

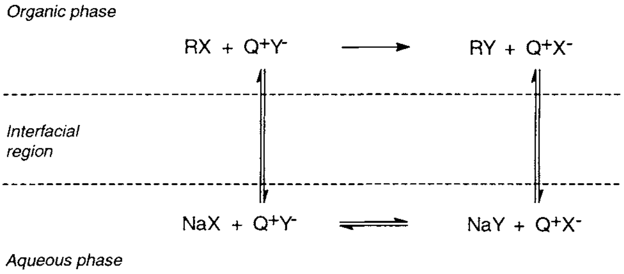


Figure 3.56. Schematic representation of phase-transfer catalysis for the reaction $RX + Y^- \rightarrow RY + X^-$; Q^+ is the phase-transfer agent.

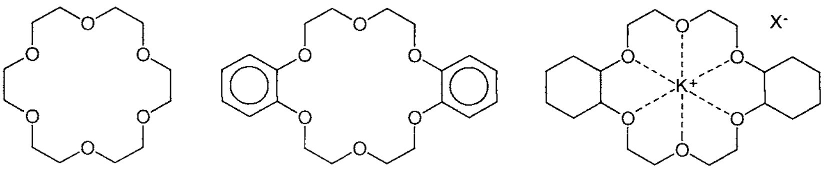
Typically, one or more reactants are organic liquids or solids dissolved in a nonpolar organic solvent (RX in Fig. 3.56), while the other reactants are salts or alkali metal hydroxides in aqueous solution (NaY in Fig. 3.56).

For reactions that are traditionally performed in hydroxylic solvents or in polar aprotic solvents, PTC has the following advantages: no need for expensive aprotic solvents, shorter reaction time and/or lower reaction temperature, use of aqueous alkali hydroxides instead of other expensive bases. Several examples are given in Section 4.2.2.

3.8.2. Catalysts for PTC

Suitable catalysts for PTC are those which have a highly lipophilic cation (*i.e.* have strong affinity for an organic solvent). Catalysts used most extensively are quaternary ammonium or phosphonium salts (quats). Examples are tetra-*n*-butylammonium bromide (TBAB), triethylbenzylammonium chloride (TEBA) and methyltrioctylammonium chloride (Aliquat 336 or Adogen 464). Neutral complexants for organic cations, e.g. crown ethers, poly(ethylene glycol)s (PEGs), cryptands, etc., are also suitable catalysts. Open chain PEGs (e.g. PEG 400) are the least expensive catalysts and may be preferable to quats in some processes (Sharma, 1997).

Crown ethers (Fig. 3.57) and cryptands (Fig. 3.58) can solubilize organic and inorganic alkali metal salts even in nonpolar organic solvents; they form a complex with the cation (see Fig. 3.57c), and thus act as an 'organic mask' (Gates, 1992).



a b c

Figure 3.57. Crown ethers; a) hexaoxaoctadecane (18-crown-6); b) dibenzo-18-crown-6; c) complex of dicyclohexyl-18-crown-6 with potassium salt.

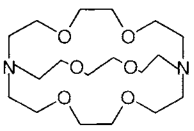


Figure 3.58. 2.2.2.-cryptate (Kryptofix 222).

Although crown ethers were often found to be as effective as the best onium salts in PTC, they have only found limited commercial application because of their high cost (10 to 100 times that of quats) and perceived toxicity. Cryptands are even more expensive than crown ethers.

3.8.3. Catalyst performance

3.8.3.1. Activity

The rate of reaction not only depends on the actual chemical reaction with the halide (I^-, Br^- or Cl^-), but also on the competitive extraction of Y^- versus X^- (see Fig. 3.56), which can be expressed as the extraction constant (E_{QX}) of the salt QX:

$$E_{QX} = \frac{[QX]_{org}}{[Q^+]_{aq} \cdot [X^-]_{aq}} \qquad (17)$$

in which the bracketed expressions stand for activities, or concentrations in the organic and aqueous phase. The catalyst structure strongly affects the reaction rate.

It is not surprising that for most solvent-water combinations and for many anions, the rate of extraction increases with the number of C atoms of the catalyst cation. To a first approximation, an average increase in log E_{QX} of about 0.54 per C atom has been reported (Esikova, 1997). It is important to note, however, that the extraction rate of ammonium salts with phenyl and benzyl groups is much lower than the number of C atoms would suggest, namely between that of *n*-propyl and *n*-butyl. The extraction constants (E_{QX}) with tetra-*n*-butylammonium salts are about 140 times larger than those with tetra-*n*-propylammonium salts of the same anion in the same solvent-water system (Dehmlow, 1993).

The catalyst anion has also been shown to have a large influence on the reaction rate. The extraction constant of tetra-*n*-butylammonium salts between water and chloroform decreases with different anions as follows: picrate >> ClO_4^- > I^- > toluene sulphonate > NO_3^- > Br^- > benzoate > Cl^- > acetate > OH^- (Esikova, 1997; Dehmlow, 1993).

Solvents for PTC should be nonhydroxylic and immiscible with water. $CHCl_3$, CH_2Cl_2, chlorobenzene, toluene, and acetonitrile are commonly employed. If the reactant is liquid, extra solvent is not required. Although chloroform and methylene chloride are favourable from a chemistry point of view, engineering considerations often lead to the choice of chlorobenzene (and toluene) because of their lower solubility in water and higher boiling point.

3.8.3.2. Selectivity

The selectivity in PTC can be steered by the choice of cation in quats. Examples are O- versus C-alkylation (Halpern *et al.*, 1982; Dehmlow and Schrader, 1990), substitution versus dihalocarbene addition (Dehmlow and Wilkenloh, 1990), and enantioselective alkylations (Dolling *et al.*, 1984, 1987; Bhattacharya *et al.*, 1986; Hughes *et al.*, 1987; Lee and Wong, 1991; O'Donnell *et al.*, 1989).

O- versus *C*-alkylation product ratios in the methylation of desoxybenzoin by dimethyl sulphate can be varied between 0.75 and 63 by the choice of catalyst. The reaction can be steered towards enol-ether formation by large, sterically shielded ammonium ions, while C-alkylation is favoured by small ammonium ions (e.g. RMe_3N^+) and by crown ethers (Dehmlow and Schrader, 1990).

Similarly, the ratio of dibromocarbene addition to CBr_3^- substitution in the reaction of propyl bromide with tribromomethyl can be varied between 92:1 and 1:91, depending on whether a small and accessible quat or a bulky anion-activating quat is used (Dehmlow and Wilkenloh, 1990).

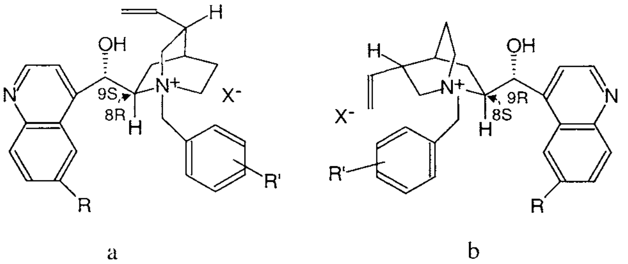


Figure 3.59. Chiral quats derived from cinchona alkaloids; R = H, derived from cinchonine, or MeO, derived from quinidine; a and b are diastereomers; aminoalcohol parts are enantiomeric.

For enantioselectivity to be possible multipoint interaction between the catalyst and the reactant in the transition state is necessary. The most effective chiral onium salts are derivatives of cinchona alkaloids (see Fig. 3.59).

3.8.3.3. Stability (deactivation/decomposition)

In general, the stability of a PT catalyst is a function of cation structure, presence of anions, type of solvent, concentration, and temperature. Degradation of catalysts under PTC conditions may occur. For instance, ammonium and phosphonium salts may be subject to decomposition by internal displacement (usually at temperatures of 100 – 200 °C):

$$R_4N^+ X^- \rightarrow RX + R_3N \qquad (18)$$

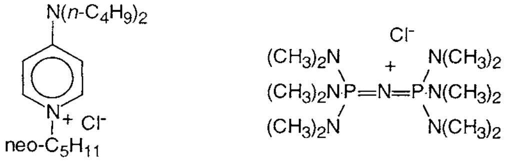
and, in the presence of strong bases, decomposition by Hoffman degradation:

$$R'CH_2CH_2NR_3^+ OH^- \rightarrow R_3N + R'CH{=}CH_2 + H_2O \qquad (19)$$

$$2\,R'CH_2CH_2NR_3^+ F^- \rightarrow R_3N + R'CH{=}CH_2 + R'CH_2CH_2NR_3^+HF_2^- \qquad (20)$$

Loss of catalytic activity resulting from internal displacements is not usually a serious problem below temperatures of about 100 °C. However, highly active R-groups, such as benzyl, methyl and allyl, undergo internal displacement more readily, particularly in the presence of strong nucleopfiles. For instance, the presence phenolates and thiolates may lead to the formation of benzyl alcohol, ethers, or sulphides from benzyl-substituted quaternary ammonium salts.

Obviously, higher temperatures can lead to faster decomposition. The use of quats above temperatures of 100 to 120 °C usually results in partial or total decomposition. Recently, quats that are stable up to about 200 °C have been prepared (Sharma, 1997; Dehmlow, 1993). Figure 3.60 shows two examples. Only the iminium chloride catalyst is also very stable in the presence of hot concentrated NaOH (Dehmlow and Knufinke, 1989).



a b

Figure 3.60. Quats with high temperature stability; a) 4-dialkylaminopyridinium chloride; b) bis [tris(dimethylamino)phosphine]iminium chloride.

If decomposition of quats in the presence of strong bases becomes too severe, one can switch to other PT catalysts such as PEGs or crown ethers. These are not very sensitive to bases but are sensitive to acids.

3.8.4. Catalyst separation and recovery

PT catalysts are often difficult to separate from the product, while it is also desirable that the catalyst should be reusable or recyclable. Distillation and extraction are the most common separation processes. The main disadvantage of lipophilic quats is their tendency to remain in the organic phase and consequently contaminate the product. Therefore, extraction in water often is not satisfactory. Furthermore, products in the fine chemicals industry often have high boiling points and/or are heat sensitive, which makes separation of the catalyst by distillation impossible. Often the only means to remove the catalyst in these cases is to adsorb it using a high surface area sorbent such as silica, Florisil or active carbon (Sasson, 1997). After filtration, the catalyst can then be recovered by elution.

The more hydrophilic quats (e.g. tetrabutyl- or tributylmethylammonium salts) can be separated from the product by extraction with water. PEGs are easily extractable into water.

In analogy with homogeneous catalysis the problem of separation could be solved by binding the catalyst to an insoluble support (triphase catalysis). Promising catalysts of this type are quats bound to microporous polystyrene resins or organophilic clays, while polymer-bound PEGs and crown ethers have also been developed. These supported PT catalysts can be easily separated by centrifugation and are reusable. Again, analogously to homogeneous catlaysis, a disadvantage of heterogenization is that the activity of the catalyst is generally lower than for homogeneous PT catalysts due to diffusional limitations. Furthermore, decomposition can be a serious problem for triphase quats catalysts. See Starks *et al.* (1994) and Tomoi (1997) for a more detailed description of triphase phase-transfer catalysis.

3.8.5. Applications of PTC

PTC has been applied in the synthesis or organic compounds since the late 1960s, and its applications have expanded rapidly, especially during the 1980s and 1990s. Some process characteristics which could render the replacement of a non-PTC process with a PTC process attractive are (Starks *et al.*, 1994):

- use of an alkoxide, amide, or hydride as a base in nucleophilic substitutions (esterification, etherification, *C*-, *N*-, *O*-, or *S*-alkylation),
- use of DMSO, DMF, or acetonitrile, etc., as solvent,
- oxidations using oxygen, hypochlorite, permanganate, or dichromate,
- erratic process behaviour (exothermicity, yield, purity),
- environmental, emission, or separation problems.

Section 4.2.2 gives specific examples of PTC. It is expected that the combination of PTC with a transition-metal cocatalyst and hydrogen peroxide or molecular oxygen will probably gain importance in fine chemicals applications.

3.9. BIOCATALYSIS

Biocatalysis is a very rich area and a separate book can easily be devoted to it. In this book it was decided to treat biocatalysis from a more practical point of view. Section 2.8.7 gives an introduction. In Section 4.5.2 several examples will convince the reader of the large potential of biocatalysis.

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4. Selectivity Engineering

4.1. HETEROGENIZATION OF HOMOGENEOUS CATALYSIS

4.1.1. Introduction

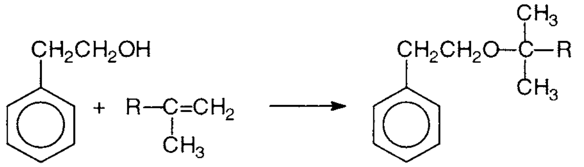
The manufacture of fine chemicals, which cater for a very wide variety of industries, such as pharmaceuticals, agrochemicals, fragrances and flavours, dyestuffs, photography and textiles, depends heavily on catalysts and process engineering. It is of utmost importance to have clean and safe processes that provide quality products with very stringent specifications, as many conventional processes produce 20–50 kg, and sometimes even 100 kg of unwanted products per kg of the desired product, while operating conditions are far from safe. For the synthesis of fine chemicals, reactions have to be very selective in various respects (chemo-, diastereo-, enantio-, regio-, stereo-). Thus, often multiple complex steps are involved. The need to adopt a plant for different types of chemicals, requiring stringent specifications, imposes further problems. Batch plants are commonly used, but in some cases, notably the production of peroxides, the Wittig process, processing of substances that can explode/ detonate, etc., it becomes necessary to adopt a continuous rather than a batch/semi-batch mode of operation. It also becomes necessary to adopt computer control of batch plants to ensure quality and safety. Catalysts play a very important role in processes with integrated environmental protection. Both heterogeneous and homogeneous catalysts are important. 'Catalyst engineering' and process engineering are important in realizing high selectivity and productivity for the reaction.

There are many instances where homogeneous acid catalysts can be replaced by heterogeneous catalysts (see also Chapter 2). Alkylation, esterification, etherification, etc. stand out as nice examples. Sometimes heterogeneous catalysts offer higher selectivity than homogeneous catalysts. In some instances homogeneous catalysts offer distinct advantages over the heterogeneous catalysts.

Tanabe and Hölderich (1999) have given an extensive statistical survey of industrial processes using solid acids/bases as catalysts. Over 300 solids and bases have been covered. A variety of reactions like alkylation, isomerization, amination, cracking, and etherification with catalysts like zeolites, oxides, complex oxides, phosphates and ion-exchange resins have been covered. Over 120 industrial processes are referred with 180 different catalysts.

4.1.2. Ion-exchange resins as catalysts

An ion-exchange material may be broadly defined as an insoluble matrix containing labile ions capable of exchange with ions in the surrounding medium without major physical change taking place in its structure. Although ion-exchange catalysis involves the use of ion-exchange resins to promote reactions that are normally catalysed by mineral acids, there are many instances where the use of ion-exchange resin (IER) catalysts has led to improved activity and/or yield over the homogeneous catalysts. For the reactions of linear ketones and alcohols to give ketals, the rates were impracticably low with soluble acids, but the use of acid ion-exchange resins provided higher reaction rates at lower temperatures (Lorette *et al.*, 1959). In the case of etherification of phenols with *iso*butylene, the yields of the corresponding *tert*-butyl ethers were remarkably high compared to those with *p*-toluene sulphonic acid (PTSA) (Ghosh and Sharma, 1991/92). Ion-exchange resins play an important role in the manufacture of fine chemicals. Some outstanding examples are in the area of alkylation of phenols, esterification, and acetalization. An example of a clean process is that of etherification of phenyl ethyl alcohol with *iso*butylene to give phenyl ethyl *tert*-butyl ether (Eqn. (1)), which has very good perfumery value (Gokulchandra and Sharma, 1994).



(1)

Some of the advantages of using IERs as catalysts are ease of separation of the catalyst from the reaction mixture, milder reaction conditions, catalyst reusability, ability of catalyst to work in both polar and nonpolar media, and higher catalytic activity, yield, and selectivity in some reactions. The major disadvantage of IERs in catalysis is their relatively low thermal stability. They cannot withstand temperature of over 125 °C for a long period of time. Perfluorosulphonic acid resins and Nafion (a polymer of tetrafluoroethelene and perfluoro-2-(fluoro-sulphonyl ethoxy) propyl vinyl ether) can withstand temperatures up to 200° C, but unfortunately such materials are expensive. A recent development is that of supported Nafions, which are superacidic, and these catalysts are available at much lower cost but with comparable activity and selectivity. Nafion-H/Silica nanocomposite variety (Harmer *et al.*, 1996) is superior to silica supported Nafion due to the large surface area and the increased accessibility of surface active sites to reactant. The characterization of acid sites was done through pyridine adsorption, using the surface FT-IR technique (Torok *et al.*, 2000).

Methods of controlling and understanding the microstructure of solid Brønsted acids have been outlined by Harmer *et al.* (1998). In such acids the acidic functionalities are present within discrete domains included within the framework of a high surface area. Surface areas of 300 m^2/g have been realized with Nafion on silica. Fujiwara *et al.* (2000) have prepared composites of Nafion with MCM-41 (for MCM see Section 4.4.1). Thus advantages of cationic ion-exchange resins can be exploited along with those of large pore zeolite like MCM-41. Table 4.1 gives some examples of industrially important applications.

Table 4.1
Some industrial processes based on cationic ion exchange resins (Partly adopted from Chakrabarti and Sharma, 1993)

Product	Reactants
Methyl *tert*-butyl ether (MTBE)	Methanol + *Iso*butylene
Ethyl *tert*-butyl ether (ETBE)	Ethanol + *Iso*butylene
tert-Amyl methyl ether (TAME)	Methanol + Iso-amylene
*Iso*butylene	*tert*-Butanol
tert-Butanol	*Iso*butylene + Water
*Iso*propanol	Propylene + Water
sec-Butanol	*n*-Butenes + Water
*Iso*propyl esters	Propylene + Carboxylic acids up to C_{20}
sec-Butyl acetate	*n*-Butenes + Acetic acid
sec-Butyl acrylate	*n*-Butenes + Acrylic acid
Acrylates and Methacrylates	Acrylic acid or Methacrylic acid + Alcohols (C_3 or C_4 olefins)
Alkylphenols / Arylphenols	Phenols + Olefins (propylene, *n*-butenes, *iso*butylene, nonenes, dodecenes etc.); styrene, alphamethyl styrene
Bisphenol A	Phenol + Acetone
Methyl glucoside	Dextrose + Methanol
Methyl *iso*propenyl ketone	Methyl ethyl ketone + Formalin
Methyl *iso*butyl ketone	Acetone + H_2
Di-*iso*butylene	*Iso*butylene
Alphamethyl styrene dimers	Alphamethyl styrene

The resins can be divided into two groups having major structural differences: gel and 'macroreticular'. In the case of gel type resins if the beads are totally dry, then the polymeric matrix collapses and the polystyrene chains will be as close as atomic forces allow. Therefore, swelling ability of the reactants is a prerequisite for catalysis by gel resins. Gel resins are characterized by a divinyl benzene content that is generally below 12%.

The limitation of gel resins has been largely overcome with the advent of 'macroporous' ion-exchange resins (Corte *et al.*, 1957, 1962; Rohm and Hass Co., 1963). They consist of agglomerates of very small micro spheres interspersed with micropores. Reactants may move easily into the interior through these micropores. The significant consequence is that these macroreticular resins can also function in nonswelling solvents, thereby greatly expanding the possibilities of resin catalysis (Bortnick, 1962; Litteral, 1972; Reinicker and Gates, 1974; Wesley and Gates, 1974). We now have macroporous resins in 'monodisperse' form, which implies uniform particle distribution.

Principal differences between catalysis by dissolved electrolytes and by resins are that with resins as catalysts catalysis overlaps with diffusion, adsorption, and desorption processes, while this is not the case with electrolytes (Naumann, 1959). Also, the matrix of the resin with fixed ionic group may have some influence on the course of reaction.

In homogeneous catalysis, the catalytically active species is dissolved in the reaction medium and is present uniformly throughout the system. However, with resin catalysis, the catalytically active groups are anchored to the matrix and in the solvent-resin system are located at the surface of and within the body of the resin bead only. Ion exchangers are, in fact, particulate active species and when used as catalysts combine with the physical and mechanical benefits of heterogeneous catalysts (Pitochelli, 1980).

4.1.2.1. Selectivity of ion-exchange resin catalysts

The selectivity of ion-exchange catalysts often leads to yields that are considerably higher than those obtained with catalysis by dissolved electrolytes (Helfferich, 1962). The heterogenized acidity can far exceed the value of 100 % H_2SO_4. Table 4.2 gives Hammet acidity function (H_0) for various acids used as catalysts, that are perhaps halfway the non selective dissolved electrolytes and extremely selective enzymes. Ion-exchange resin can be tailor-made to use as a means for selective catalysis of small molecules in the presence of large molecules. A cross-linked density may be chosen to inhibit matrix expansion sufficiently for the exclusion of large molecules from the interior of the bead by sieve action, while small molecules may enter the matrix thus favouring the reaction of small molecules only (Pitochelli, 1980). The preferential sorption of one of the reactants in the resin may favour the reaction that is insignificant in catalysis by dissolved electrolytes.

Table 4.2
Values of Hammet acidity function (H_0)

Acid	H_0
p-Toluene sulphonic acid	0.55
Montmorillonite	
Natural	1.5 to –3.0
Cation exchanged	–5.6 to –8.0
Amberlyst-15	–2.2
Sulphuric acid	
40%	–2.4
100%	–12.3
Nafions	–11 to –13
HY zeolites	–12.7 to –13.6
$H_3PW_{12}O_{40}$ and $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ (HPA)	–13.6
Lanthanum and Cerium exchanged HY Zeolites	< –14.5
Fluorosulphonic acid	–15.07
Sulphated zirconia	–16
HSO_3F-SbF_5	–20

A number of examples have been cited by Chakrabarti and Sharma (1993) and Sharma (1995). The example of etherification of phenols, substituted phenols, cresols, naphthols, etc., with *iso*butylene and *iso*amylene may be empahsized where homogeneous catalysts lead to essentially *C*-alkylated products. An example reported by Takeshi *et al.* (1994) refers to mono acylation of diols from 1, 2-ethanediol to 1,16-hexadecanediol; transesterification in ester/octane solvent mixtures with strongly acidic resin catalysts gives higher selectivity for the mono versus diacylated product compared to the use of homogeneous catalyst like methane sulphonic acid.

An example of regioselectivity in the alkylation of methyl salicylate with *iso*butylene and *iso*amylene may be cited. Here, during alkylation with *iso*butylene, in the presence of Indion 130 (a macroporous sulphonated styrene-divinyl benzene resin with an acidity of 4.7 meq. H^+/g and cross-linking of 14%) 100% regio-selectivity with respect to methyl [5-tert-butyl] salicylate was realized at 403 K and methyl [3-tert-butyl]salicylate was not obtained. It is striking that in this case of alkylation with 3 % (w/w) PTSA as a homogeneous catalyst, no alkylation was realized (Chopade and Sharma, 1995).

Fischer and Holderich (1999) have shown that Bayer-Villiger reaction of cyclopentanone with aqueous 30 % H_2O_2, to give delta-valerolactone, is amenable to catalysis with cationic ion-exchange resin (CIER), Amberlyst-15; without catalysts the conversion and the yield of the product are poor. Nafion on silica also works but was found to be poor compared to Amberlyst-15. Beta zeolite also works but was found to be inferior to Amberlyst-15.

Yamato (1995) has given an extensive coverage of a variety of reactions such as alkylation of benzene, condensation of benzene/toluene with benzyl alcohol, and condensation of benzoyl chloride with benzene/toluene using Nafion resin.

An interesting example of etherification of close boiling *cis* and *trans* 2-tert-butyl-cyclohexanol with *iso*amylene may be cited. At 353 K, and Indian 130 as catalyst at 10 % loading, about 94% selectivity for the *cis* isomer was realized with a feed consisting of about 68.5 % *cis* and 31.5% *trans* isomer (Matkar and Sharma, 1995).

Olah *et al.* (1999) have been able to realize selective cyclisation of *o*-benzoyl benzoic acid to anthraquinone using dichlorobenzene as a solvent and Nafion-H as a catalyst. This may lead to avoidance of the Friedel-Crafts reaction using a stoichiometric amount of aluminium chloride and resulting in a lot of waste. Many other examples of similar reactions have been reported.

The availability of Nafion on silica has not only lowered the cost of the resin but also has made it versatile (Sun *et al.*, 1997; Harmer *et al.*, 1998). A number of industrially important reactions have been attempted, with considerable success, with these catalysts. Consider the Fries rearrangement of phenyl acetate to *p*-acetyl phenol (*p*-hydroxy acetophenone). This has been accomplished by Hoelderich and co-workers (Heidekum, 1998). In the case of alkylation of benzene with benzyl alcohol, Amberlyst-15 and *p*-toluene sulphonic acid are ineffective and Nafion on silica works well at 80 °C.

The change of selectivity in the nitration of 1-nitro naphthalene, in the presence of Nafion H, has been claimed by Bayer. The ratio of the wanted isomer 1,5 to the undesired 1,8 has been claimed to change from 0.62 to 0.9 when using Nafion H. Furthermore, when sulpholane was used as a solvent, along with Nafion, at 100 °C, the ratio of 1,5 to 1,8 was raised to 1.65 (Bayer Patent ref, 1999).

4.1.2.2. Distillation column reactor

In a distillation column reactor (DCR), reaction and distillation occur simultaneously. This technology is also referred to as reactive distillation, or, if a catalyst is involved, as catalytic distillation. DCRs offer distinct advantages of exploiting the exothermicity of reactions, such as in alkylations, etherifications, etc., for supplying the heat required for distillation, lower mole ratio of reactants and yet get over the thermodynamic limitations encountered in simple reactors and lower resin inventory compared to common single-stage reactors. DCRs are now commercially exploited for the production of MTBE, ETBE, etc. with ion-exchange resins as catalysts. Independently, with zeolites as catalysts, DCRs are used for producing ethyl benzene from benzene and ethylene and cumene from benzene and propylene. DCRs have been used with homogeneous acid catalysts for the manufacture of esters like *n*-butyl acetate, dibutyl phthalate, etc. As an example, the recent very successful Eastman Kodak process for the production of methyl acetate may be cited, where not only the utilities consumption was brought down substantially but also the capital cost and the number of distillation columns.

Catalysts can be confined in porous cloth bags tied in the form of bundles, along with corrugated wire screens to provide the passage for vapour flow, as reported by Yuxiang and Xien (1992) for MTBE production. Resin catalyst packings have also been moulded from resin particles and thermoplastic powder in a furnace, as reported by Fuchigami (1990) for the hydrolysis of methyl acetate, which is obtained as a by-product in the manufacture of polyvinyl alcohol from polyvinyl acetate, and where recycle of acetic acid to produce vinyl acetate is desirable. It is also possible to mould the active polymeric components in the required shape (e.g. structured packings) after which the surface is suitably activated. For styrene-divinyl benzene type resins further improvement in the acidity of the catalysts can be realized through fluorination. Fibre composites as packings can also be considered.

4.1.2.3. Acetalization using ion-exchange resins

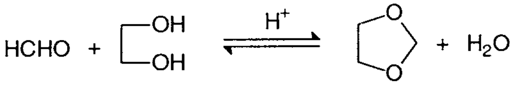
Various acetals and ketals from the reaction of alcohols and diols with aldehydes and ketones can be advantageously obtained using ion-exchange resin catalysts. Batch reactive distillation or DCR can be employed to obtain these acetals at high selectivity at very high conversion levels.

Masamuto and Matsuzaki (1993) have given a description of the commercial production of methylal by reactive distillation. Methylal can also be produced by reactive distillation using a cation-exchange resin made from supported sulphonated styrene-divinyl benzene or divinyl benzene on silica of size 2-4 mm (Kolah *et al.*, 1994). A single reactive distillation column was used. Up to 95% conversion of formaldehyde could be obtained by using 1.5 times the stoichiometric requirements of methanol; 80-90% methylal was obtained as distillate (Kolah and Sharma, 1995). Similarly, ethylal was obtained from 95% aqueous ethanol and aqueous formaldehyde in a DCR employing the cationic exchange resin packed in the form of wire mesh bags. Up to 97% conversion of formaldehyde could be obtained by using 1.5 times stoichiometric quantity of ethanol, with the distillate practically free of formaldehyde (Chopade and Sharma, 1995).

$$\mathrm{HCHO} + 2\,\mathrm{ROH} \xrightarrow{\mathrm{H^+}} \mathrm{CH_2(OR)_2} + \mathrm{H_2O} \qquad (2)$$

Also, 1,3-dioxolane was obtained from the reaction of ethylene glycol (EG) and aqueous formaldehyde in high yield using an ion-exchange resin catalyst. In a batch mode of operation, with 50% excess EG, the conversion of formaldehyde is limited to 50% due to equilibrium limitation, whereas in batch reactive distillation, formaldehyde conversion greater than 99%

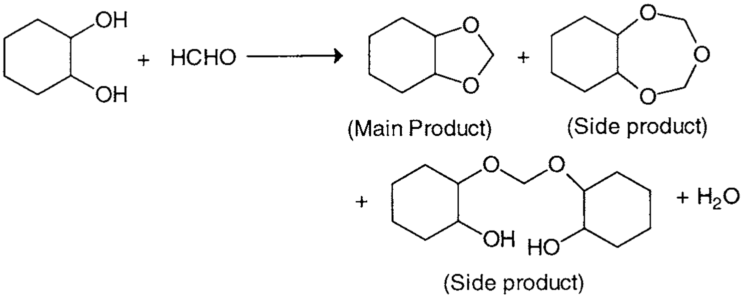
could be achieved (Chopade and Sharma, 1995). 97% Conversion of formaldehyde was obtained by reactive distillation when three times the stoichiometric quantity of ethylene glycol was used compared to 8% conversion obtained in a closed system (Chopade and Sharma, 1995).



(3)

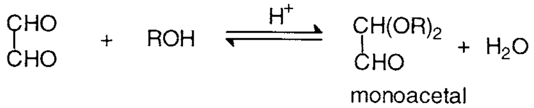
Removal of formaldehyde from aqueous 2-butyne-1,4-diol, or a similar solution, which is relevant in the subsequent manufacture of *cis*-2-butene-1,4-diol, by batch reactive distillation with methanol or ethylene glycol in the presence of Indion 130 as catalyst has also been reported; 98% conversion of formaldehyde was obtained by reactive distillation with 7 times the stoichiometric quantity of methanol, compared to 15% conversion obtained in a closed system (Kolah and Sharma, 1995).

Reaction of *trans*-1,2-cyclohexanediol with *para*-formaldehyde in the presence of Indion 130 as catalyst to yield the corresponding cyclic formal has been successfully carried out (Matkar and Sharma, 1995). A conversion of 52% was realized with 70% selectivity towards cyclohexanediol formal; the other side products are *trans*-hexahydrobenzo-1,3,5-trioxypin, di(*trans*-2-hydroxycyclo-hexyloxy) methane.

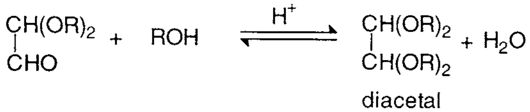


(4)

Acetilization of glyoxal with different alcohols to selectively produce the monoacetal, i.e. 2,2-dialkoxy ethanal, which has numerous applications in different organic syntheses, has been subject of investigation. Hoechst has developed a process for the manufacture of 2,2-dimethoxy ethenal (DME) in aqueous solution by mono-acetalization of glyoxal. As this molecule possesses the functional groups of both aldehyde and acetyl, it creates many options in organic syntheses (Blanc *et al.*, 1994). DME can be used as a substitute for formaldehyde for cross-linking cellulosic materials. Blanc and co-workers have reported some results on the mono-acetalization of glyoxal with different alcohols in the presence of homogeneous as well as heterogeneous catalysts (e.g. PTSA, $ZrSO_4.4H_2O$, sulphonic resin, etc.) and have recommended that a great excess of alcohols should be used for better selectivity (Blanc *et al.*, 1987; Stambouli *et al.*, 1988). Some work has been reported on the mono-acetalization of glyoxal with different alcohols, such as methanol, *n*-butanol and *iso*-amylalcohol, and it was found that macroporous resins like Indion 130 and Amberlyst 15 with sufficient loading (10% w/w) can be used successfully for this reaction. Lower temperatures and high mole ratios (>8:1) of alcohols to glyoxal offer high selectivity towards the monoacetal. In the case of less reactive alcohols such as *n*-butanol and *iso*-amylalcohol, simultaneous removal of water during the course of reaction is necessary as it enhances the equilibrium conversion and the rate of reaction. However, the removal of water should be done in a controlled manner as high rates of water removal result in an increase in the conversion to diacetal, thereby adversely affecting the selectivity with respect to the monoacetal. The use of volatile solvents like *n*-hexane brings down the boiling temperature of the reaction mixture, which has been proven to offer better selectivity at sufficiently high rates (Mahajani and Sharma, 1997).



$$\begin{array}{c}\mathrm{CHO}\\|\\\mathrm{CHO}\end{array} + \mathrm{ROH} \overset{H^+}{\rightleftharpoons} \underset{\text{monoacetal}}{\begin{array}{c}\mathrm{CH(OR)_2}\\|\\\mathrm{CHO}\end{array}} + H_2O \qquad (5)$$

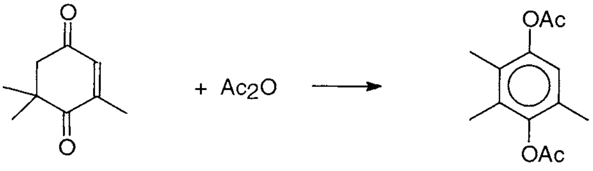


$$\begin{array}{c}\mathrm{CH(OR)_2}\\|\\\mathrm{CHO}\end{array} + \mathrm{ROH} \overset{H^+}{\rightleftharpoons} \underset{\text{diacetal}}{\begin{array}{c}\mathrm{CH(OR)_2}\\|\\\mathrm{CH(OR)_2}\end{array}} + H_2O \qquad (6)$$

Choi and Won (1999) have reported a very useful strategy of recovering relatively non-volatile lactic acid (e.g. from fermentation of carbohydrates) as volatile methyl lactate using a cationic ion-exchange resin as the catalyst. In another column reactor the methyl lactate is hydrolysed, using a cationic ion-exchange resin as the catalyst, to lactic acid and methanol, and the latter is recycled.

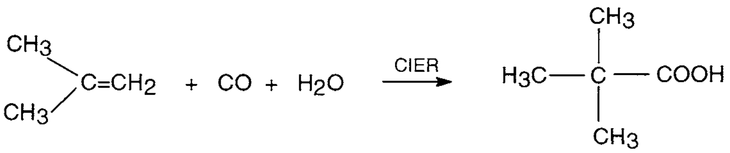
4.1.2.4. Other reactions catalysed by ion-exchange resins

Apart from examples given by Chakrabarti and Sharma (1993) and Sharma (1995), a number of additional examples can be cited. A reference will be made to the reaction of ketoisophorone with Ac_2O to give trimethyl hydroquinone diacetate where a cationic ion-exchange resin (CIER) works in an elegant and functional way (Eqn. (7)).



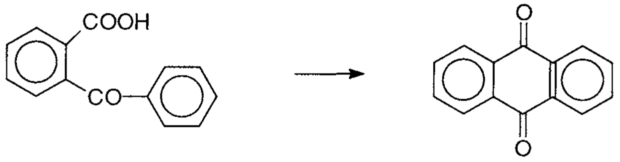
(7)

Shell has claimed that the Koch reaction to make Koch neo-acids can be carried out with a CIER, instead of concentrated sulphuric acid (Eqn. (8)).



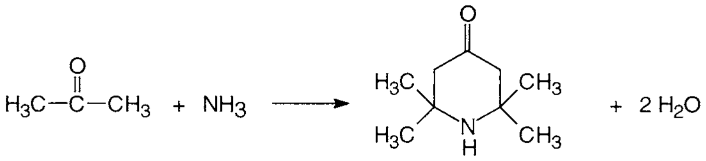
(8)

Olah and co-workers have used supported Nafion as a catalyst for cyclisation of benzoyl benzoic acid to anthraquinones, which otherwise requires concentrated sulphuric acid (Eqn. (9)).



(9)

There are several claims in literature for the reaction of acetone and ammonia, at temperatures like 50°C, to give triacetoneamine (2,2,6,6-tetramethyl 4-piperidone), using Nafion and other CIERs (Eqn. (10)). This product is the starting material for the renowned hindered amine light stabilizers.



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4.1.3. Tetrabutyl titanates as eco-friendly esterification and trans-esterification catalysts

The use of PTSA and related acids for alkylation reactions has been discussed and advantages of using cationic ion-exchange resin have been brought out in a convincing way. A similar situation exists in esterification/trans-esterification reactions. However, when the required temperatures are higher than 120 °C, as stated earlier, the established resins cannot be used. A neat solution is realized through the use of tetrabutyl (or propyl or *iso*-propyl) titanates. This is very relevant, for instance, in esterification of phthalic anhydride with alcohols like *n*-butanol, 2-ethyl hexanol, nonanols, etc., where PTSA can be advantageously replaced by tetrabutyl titanates. Here a temperature higher than 210 °C is preferred. Titanates give higher yields and the amount of unconverted monoester, which requires an alkali wash, is negligible. The catalyst is split to give benign TiO_2 after the reaction is over.

4.1.4. Clays as catalysts

Clays are widely used as catalysts in synthetic organic chemistry. Some of the clay catalysed reactions include alkylation and acylation of aromatics, esterification, etherification, dimerization, oligomerization, Diels-Alder reactions, cracking, elimination, and condensation. One of the major advantages of clay catalysts is their higher thermal stability compared to ion-exchange resins; the use of ion-exchange resins is generally not recommended beyond 120 °C, whereas clays can be safely used up to 200 °C. Also, clays are inexpensive compared to ion-exchange resins.

Chitnis and Sharma (1997) have given an exhaustive account of industrial applications of acid-treated clays. Table 4.3 gives some examples of industrial importance.

Table 4.3
Some examples of industrial applications of acid-treated clays (Adopted in part from Chitnis and Sharma, 1997)

Product	Reactants
Purification of vegetable oils	Vegetable oils containing phospholipids, gums, etc.
Purification of industrial oils, kerosene/jet fuel, lubricating oils	Industrial oils, kerosene, lubricating oils
Mono- & dicumyldiphenylamine	Diphenylamine + α-Methyl styrene
Mono- & dioctyldiphenylamine	Diphenylamine + Diisobutylene
Dimer fatty acids	Unsaturated fatty acids
Purification of xylenes	Xylenes containing impurities
Improvement of bromine number of recycle cumene in phenol plants	Cumene containing unsaturated compounds like alphamethyl styrene
Improvement of bromine number of recycle ethylbenzene in styrene plants based on liquid phase oxidation	Ethyl benzene containing styrene
Alkylation of xylenes with diisobutylenes to mono-*tert*-butyl derivatives	Xylenes + Diisobutylenes
Phenylxylyl ethane	*o*-Xylene + Styrene

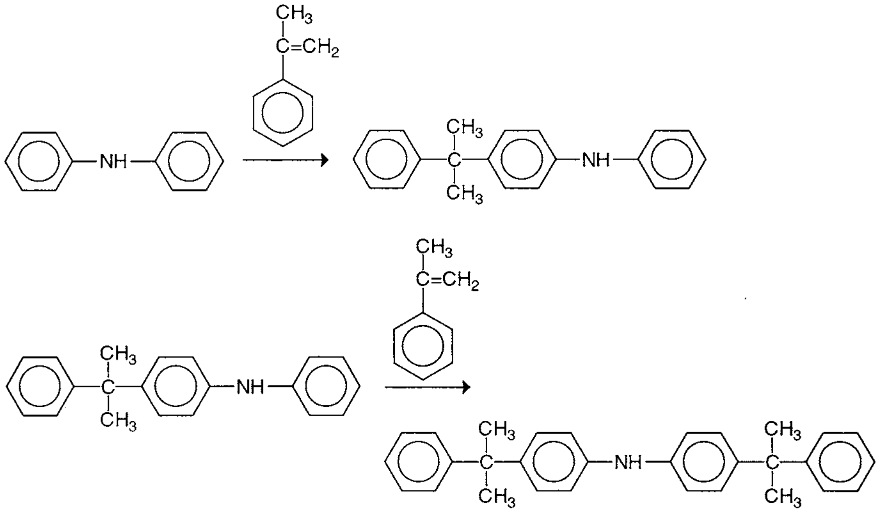
Vaccari (1983,1999) has given a state-of-the-art account of the preparation and catalytic properties of cationic and anionic clays. Some examples of industrial importance have also been reported. Clays exhibit many desirable features, such as low cost, wide range of preparation variables, ease of set-up and work-up, high selectivity, and environmental friendliness. Cationic clays are widespread in nature, whereas anionic clays are rarely found in nature, but they can be synthesized cheaply. Cationic clays are prepared from the minerals but industrial anionic clays are generally synthetic. Smectite clays exhibit both Brønsted and Lewis acid sites on the edges of the crystals. Hammet's acidity function values are as follows: Na^+-montmorillonite (M), -3 to + 1.5; NH_4^+-M -3 to 1.5; H^+-M -8.2 to -5.6; acid activated clay less than -8.2. Laporte also has a synthetic version of cationic clays, Laponite. The acid treatment conditions corresponding to maximum catalytic activity depend on the precise reaction being catalysed. Supported clay catalysts such as 'Clayfen', 'Claycop', 'Clayzic', etc. have acquired importance; even Friedel-Crafts acylations can be effectively catalysed.

Anionic clays, such as hydrotalchite, manasseite, stichtite, etc. are layered double hydroxides (Mg/Al; Mg/Fe; Mg/Cr_2; Ni/Al; Ni/Fe, etc.). Anionic clays exhibit poor acidic properties. The thermal decomposition of anionic clays gives rise to mixed oxides of industrial importance as catalysts.

Pillared clays (MELS) are also covered in this review. MELS have three-dimensional network structure like zeolites, and, unlike clays, which have two-dimensional layered structures, pillared cationic and anionic clays have been studied. Phthalocyanins intercalated in anionic clays have given interesting results for wastewater purification (Vaccari, 1998).

4.1.4.1. Alkylation of diphenylamine

Acid-treated clay catalyst Engelhard F-24 was found to be very effective for the alkylation of diphenylamine (DPA) with an olefin such as α-methyl styrene (AMS) to obtain a mixture of mono and dialkylated diphenylamines (Chitnis and Sharma, 1995). For example, alkylation of DPA with AMS produced a mixture of 4-(α,α-dimethyl benzyl) diphenylamine, i.e. monocumyl-diphenylamine (MCDPA) and 4,4'-bis(α,α-dimethylbenzyl) diphenylamine, i.e. dicumyldiphenylamine (DCDPA) (Eqn.(11)). The dialkylated diphenylamine, i.e. DCDPA, is industrially important as an antioxidant and heat stabilizer. DCDPA is reported to be an ideal antioxidant for many materials like polyethylene, polypropylene, polyether polyol, polyacetals, nylon 6, synthetic lubricants, hot melt adhesives, etc.



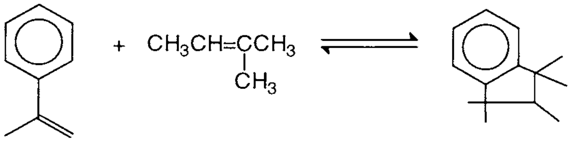
(11)

The various other grades of acid-treated clay catalysts like Engelhard F-25, F-34, F-44,F-54, F-124, F-224, G-62, Tonsil K 306, etc. were also found to be useful catalysts for the alkylation of DPA with AMS. This alkylation reaction was unsuccessful with macroporous ion-exchange resin catalyst Amberlyst-15 up to 120 °C, even in the presence of a solvent. Deactivation of the acid-treated clay catalyst occurred during the course of these reactions. Basic reasons for the deactivation of the catalyst were investigated by characterization of the fresh and used catalysts by determining the surface area and the pore size distribution, by temperature programmed desorption (TPD) of ammonia for measurement of the surface acidity, and by techniques such as X-ray defraction (XRD), UV-visible solid state reflectance spectroscopy, nuclear magnetic resonance spectroscopy (MAS-NMR), X-ray photoelectron spectroscopy (XPS), etc. The characterization of the catalysts indicated that the fresh catalyst had a microporous structure with a high surface area. Deactivation of the catalyst was due to adsorption of DPA and/or alkylated product(s) on the surface of the catalyst, which led to a decrease in the surface area of the catalyst. The deactivation of the catalyst was also due to loss of microporous structure and decrease in the number of Brønsted acid sites.

4.1.4.2. Cross-dimerization reaction

The cross-dimerization reaction is very commonly employed for the manufacture of intermediates for synthetic musks, which have become an important class of perfumery chemicals. Synthetic musks have been the target of extensive research over the years due to a conservation order placed on the musk deer. Nitro musks are being steadily replaced by non-nitro polycyclic musks because of technical drawbacks and health aspects of the former, which are explosive, sensitive, and virtually nonbiodegradable. Non-nitro musks, on the other hand exhibit better stability to light and alkali, and more nearly duplicate the odour of the macrocyclic musks occurring in nature. Indian musk odorants are easily soluble in alcohol and perfume compositions. They have the added advantage of non-discoloration in soap and domestic products. In view of the low price, their future in the perfume industry appears very promising.

Shah *et al.* (1994) have studied the preparation of a class of compounds called Indans, by cross-dimerization of AMS with amylenes, using an ion-exchange resin and acid-treated clay catalysts (Eqns. (12) and (13)). Indans can be subsequently converted, e.g. by acetylation, into perfumric compounds having musk odour. For example, 1,1,2,3,3-pentamethylindan, the product obtained by cross-dimerization of AMS and *iso*-amylene (Eqn. (12)), can be reacted with propylene oxide and *para*-formaldehyde to give an indan type isochroman musk compound, 6-oxa-1,1,2,3,3,8-hexamethyl-2,3,5,6,7,8-hexahydro-1H-benz(f)-indene, sold as Galaxolide commercially.



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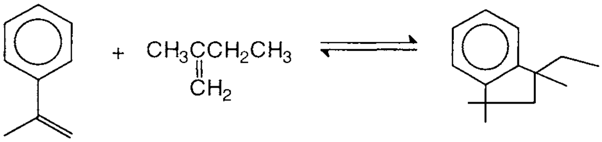


(13)

The selectivity for cross-dimerization relative to the dimerization of AMS, was found to be better with the acid-treated clay catalyst Engelhard F-24 than with the ion-exchange resin catalyst Amberlyst-15. Also, the formation of undesired side products, i.e. diisoamylenes, was lower in the case of Engelhard F-24 than for Amberlyst-15.

4.1.4.3. Dimerization of oleic acid

Dimerization of unsaturated fatty acids, to so-called dimer acids, is widely practised in industry, where acid-treated clays are invariably used as a catalyst. In the case of oleic acid the major products are dimers, trimers, and isosteric acid. Koster *et al.* (1998) have investigated the relative importance of the various acid sites as well as structural and textural parameters of montmorrilonite. The interlamellar space dominates the oleic acid dimerization and the active site is the tetrahedrol substitution site.

4.1.4.4. Other reactions

Tateiwa and Uemura (1997) have reviewed selective organic synthesis over metal cation-exchanged clay catalysts (M^{n+}-TSM). The following reactions were studied by these authors: Friedel-Crafts alkylation of phenol with 4-hydroxybutan-2-one to produce 4-(4-hydroxy phenyl) butan-2-one (Raspberry ketone); rearrangement of alkyl phenyl ethers to corresponding alkyl phenols; aromatic alkylation of phenol with aldehydes and ketones to produce corresponding *gem*-bis (hydroxy phenyl) alkanes (bisphenols) and alkyl phenols, respectively; a facile and an almost quantitative substrate selective acetalization; alkane oxidation with aqueous *tert*-butylhydroperoxide; Prins reaction of styrenes with aldehydes using clays as a Brønsted acid; inter- and intra-molecular carbonyl-ene reaction using clays as a Lewis acid at conditions similar to those of the Prins reaction. In most cases, the clay catalysts can be regenerated and reused several times, after filtration, washing and drying.

4.1.5. Sulphated zirconia as a catalyst

Sulphated zirconia catalysts can be acidic or superacidic depending on the method of treatment. A variety of acid-catalysed reactions, referred to earlier in this section, can be carried out with sulphated zirconia. Yadav and Nair (1999) have given a state-of-the art review on this subject. Examples of benzylation of benzene with benzyl chloride / benzyl alcohol, alkylation of *o*-xylene with styrene, alkylation of diphenyl oxide with 1-dodecene, isomerization of epoxides to aldehydes, acylation of benzene / chlorobenzene with *p*-chloro benzoylchloride, etc. are covered in the review.

4.1.6. Heteropoly acids as catalysts

Heteropoly compounds possess acidic and redox properties which can be controlled by choosing the constituent elements of the anionic and counter cations. The heteropoly compounds provide unique reaction environments such as pseudo-liquid phase, possess the ability of complex formation to stabilize reaction intermediates, and the structures can be much better defined at the molecular level of polyanions than for conventional oxide catalysts. Heteropoly acids (HPA) such as $H_3PW_{12}O_{40}$, $H_3Mo_{12}O_{40}$, $H_4SiW_{12}O_{40}$, $H_6P_2W_{18}O_{62}$ are strong acids and also good multi-electron oxidizing agents due to the presence of Mo^{6+}, W^{6+} and V^{5+} (Mizuno and Misono, 1994). Several papers have appeared on the examples of acid and oxidation catalysis by heteropoly compounds in both homogeneous and heterogeneous systems. Some of the industrial examples include hydrations of propene, *n*-butene and *iso*-

butene, glucoside synthesis, polymerization of tetrahydrofuran and oxidation of methacrolein. HPAs are also useful as catalysts for dehydration of 1,4-butanediol, alcoholysis of epoxides, conversion of methanol, oxygenation of alkenes or alkanes, and oxidative cleavage of vic-diols using H_2O_2 or *tert*-butyl hydroperoxides, etc (Misono, 1987; Ono, 1992).

Heteropoly acids can be synergistically combined with phase-transfer catalysis in the so-called Ishii-Venturello chemistry for oxidation reactions such as oxidation of alcohols, allyl alcohols, alkenes, alkynes, β-unsaturated acids, vic-diols, phenol, and amines with hydrogen peroxide (Mizuno *et al.*, 1994). Recent examples include the epoxidations of alkyl undecylenates (Yadav and Satoskar, 1997) and styrene (Yadav and Pujari, 2000).

The water-insoluble salts such as $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ efficiently catalyse dehydration of 2-propanol in the gas phase and alkylation of *m*-xylene and trimethyl benzene with cyclohexene; this catalyst is much more active than Nafion-H, HY-zeolite, H-ZSM-5, and sulphated zirconia (Okuhara *et al.*, 1992).

Clay-supported heteropoly acids such as $H_3PW_{12}O_{40}$ are more active and selective heterogeneous catalysts for the synthesis of MTBE from methanol and *tert*-butanol, etherification of phenethyl alcohols with alkanols, and alkylation of hydroquinone with MTBE and *tert*-butanol (Yadav and Kirthivasan, 1995; Yadav and Bokade, 1996; Yadav and Doshi, 2000), and synthesis of bisphenol-A (Yadav and Kirthivasan, 1997).

4.1.7. Solid bases as catalyst

As in the case of homogeneous acids as catalyst, we would also benefit from using solid bases instead of dissolved bases as catalyst. A number of industrially important reactions are carried out with bases as catalyst. A well know example is the aldol condensation of acetone to diacetone alcohol, where dissolved NaOH in ethyl alcohol is used as a catalyst at about 200 to 300 ppm level. However, heterogeneous pelleted sodamide can be used as a catalyst for this reaction and it obviates the problem of alkali removal from the product, which would otherwise lead to reversion of diacetone alcohol to acetone during distillation of the product mixture.

The conversion of acetone to isophorone with dissolved NaOH as a catalyst is industrially practised. In the recent past, however, attempts have been made to use heterogeneous basic catalyst in the form of hydrotalcites.

A number of papers have appeared on the use of layered double hydroxides (e.g. Mg and Al containing oxides). A meixnerite-like catalyst has been reported to give 100% selectivity for diacetone alcohol from acetone at 0 °C at close to thermodynamic equilibrium conversion of 23% (Tichit and Fajula, 1999). The side-chain alkylation of toluene with propylene to give isobutylbenzene (for ibuprofen) is a well-known example where Na/K alloy on Na_2CO_3/K_2CO_3 is used as the catalyst.

4.2. ADDITIONAL LIQUID PHASE

4.2.1. Extractive reactions

4.2.1.1. Use of a biphasic system

The deliberate imposition of a second liquid phase should allow higher conversions from a thermodynamic standpoint compared to those which can be realized in either of the two phases alone (Semenov *et al.*, 1987). It can be shown, by a simple analysis, that for certain values of distribution coefficients, the two-phase system gives higher values of the equilibrium constant.

Consider the following thermodynamic analysis for a reaction of the type A + B ↔ C + D conducted in a two-phase system (aqueous/organic). The equilibrium constants in the separate phases are:

$$K_{eq,w} = \frac{[C]_w [D]_w}{[A]_w [B]_w} \tag{14a}$$

$$K_{eq,org} = \frac{[C]_{org} [D]_{org}}{[A]_{org} [B]_{org}} \tag{14b}$$

The equilibrium constant of the two-phase system is derived as follows (with $n_{i,tot}$ the total number of moles i in the system):

$$K_{eq,twophase} = \frac{[C]_{tot} [D]_{tot}}{[A]_{tot} [B]_{tot}} = \frac{\dfrac{n_{C,tot}}{V_{tot}} \cdot \dfrac{n_{D,tot}}{V_{tot}}}{\dfrac{n_{A,tot}}{V_{tot}} \cdot \dfrac{n_{B,tot}}{V_{tot}}} = \frac{\dfrac{n_{C,w}+n_{C,org}}{V_w+V_{org}} \cdot \dfrac{n_{D,w}+n_{D,org}}{V_w+V_{org}}}{\dfrac{n_{A,w}+n_{A,org}}{V_w+V_{org}} \cdot \dfrac{n_{B,w}+n_{B,org}}{V_w+V_{org}}} \tag{15a}$$

$$K_{eq,twophase} = \frac{\dfrac{n_{C,w}}{V_w}\left(\dfrac{1+n_{C,org}/n_{C,w}}{1+V_{org}/V_w}\right) \cdot \dfrac{n_{D,w}}{V_w}\left(\dfrac{1+n_{D,org}/n_{D,w}}{1+V_{org}/V_w}\right)}{\dfrac{n_{A,w}}{V_w}\left(\dfrac{1+n_{A,org}/n_{A,w}}{1+V_{org}/V_w}\right) \cdot \dfrac{n_{B,w}}{V_w}\left(\dfrac{1+n_{B,org}/n_{B,w}}{1+V_{org}/V_w}\right)} \tag{15b}$$

$$K_{eq,twophase} = \frac{\dfrac{n_{C,w}}{V_w} \cdot \dfrac{n_{D,w}}{V_w}\left(1+\dfrac{n_{C,org}/V_{org}}{n_{C,w}/V_w} \cdot \dfrac{V_{org}}{V_w}\right) \cdot \left(1+\dfrac{n_{D,org}/V_{org}}{n_{D,w}/V_w} \cdot \dfrac{V_{org}}{V_w}\right)}{\dfrac{n_{A,w}}{V_w} \cdot \dfrac{n_{B,w}}{V_w}\left(1+\dfrac{n_{A,org}/V_{org}}{n_{A,w}/V_w} \cdot \dfrac{V_{org}}{V_w}\right) \cdot \left(1+\dfrac{n_{B,org}/V_{org}}{n_{B,w}/V_w} \cdot \dfrac{V_{org}}{V_w}\right)} \tag{15c}$$

$$K_{eq,twophase} = K_{eq,w} \cdot \frac{(1+P_C r)(1+P_D r)}{(1+P_A r)(1+P_B r)} \tag{15d}$$

with distribution coefficients: P_A, P_B, P_C, P_D (organic/aqueous, e.g. $P_A = [A]_{org}/[A]_w$) and $r = V_{org}/V_w$. When C and D are confined to different phases, $K_{eq,\ twophase} > K_{org}$ and $K_{eq,\ w}$. For instance, when $P_A = P_B = 1$ and $P_C = 10^4$, $P_D = 10^{-4}$, we get $K_{eq,\ twophase} \approx 10^4$.

Similarly, a kinetic analysis for a system of the type A → (k_{11}) B → (k_{12}) C, in a batch mode gives:

Single Phase :
$$\frac{[B]_w}{[A]_w} = \frac{k_{11}}{(k_{12} - k_{11})}\{\exp(-k_{11}t) - \exp(-k_{12}t)\} \tag{14}$$

Two Phase :
$$\frac{[B]_{tot}}{[A]_{tot}} = \frac{k_{11}}{(k_{12} - k_{11})} \cdot \frac{(1 + P_B)}{(1 + P_A)}\{\exp(-k_{11}t) - \exp(-k_{12}t)\} \tag{15}$$

Thus an improvement by a factor of $(1+P_B)/(1+P_A)$ may be obtained.

The benefit of a carefully selected second liquid phase is particularly great when the desired intermediate product is capable of undergoing further facile, undesirable reactions. In the conversion of $HO(CH_2)_6OH$ to $HO(CH_2)_6Br$ with aqueous HBr, by using a hydrocarbon solvent the desired product is obtained in high yields and the dibromoproduct formation is reduced or even eliminated.

Consider the example of producing *iso*cyanates from the corresponding amides (e.g. 2-ethyl hexanoic acid amide to the corresponding *iso*cyanate). The Hofmann reaction, which converts $RCONH_2$ to RNH_2 with aqueous sodium hypochlorite, is well known. This process involves a haloamide as an intermediate, while rearrangement of the group R from C=O to N gives the *iso*cyanate RNCO as an intermediate which, in turn, adds water to give carbamic acid, after which alkaline conditions lead to its decarboxylation to RNH_2. However, by using a second liquid phase, the intermediate *iso*cyanate RNCO, which shows a high distribution coefficient into the selected second liquid phase, can be obtained in high yields (Rane and Sharma, 1994).

The epoxidation of olefinic compounds with metachloroperbenzoic acid, which is highly soluble in organic solvents, is capable of undergoing undesirable reactions with the epoxy compound thereby lowering the yield and making separation difficult in some cases. Here, by using an aqueous buffered medium at pH 7 and dichloromethane as a solvent, more than 99% of the metachlorobenzoic acid can be taken out in the aqueous phase (Brandstrom, 1983). In this case, the large difference in the pKa of the metachlorobenzoic acid and the peroxy acid (3.82 and 7.3, respectively) has been exploited like in dissociation extraction (Gaikar and Sharma, 1987). The distribution coefficient of the peroxy acid with respect to the organic phase is also more favourable. Anderson and Veysoglu (1973) have shown that epoxidation of 6-methyl-hept-5-en-2-one to the desired epoxide, which undergoes an acid-catalysed rearrangement to an undesired compound in a facile way, can be very substantially improved by using dichloromethane water two-phase system with buffering with $NaHCO_3$.

The superiority of extractive hydrolysis over acid hydrolysis with respect to its productivity, yield, raw materials, and waste streams, for the transformation of drug intermediates (e.g. for Primaxin) in formate ester form to the corresponding alcohol, has been effectively demonstrated by King *et al.* (1985). They carried out the hydrolysis of the relevant formate ester with simultaneous extraction of the desired product from the undesired impurities by two-phase reaction/extraction with a base.

The role of a second liquid phase in photochemical sulphoxidation of paraffins with SO_2 and O_2 mixtures may also be cited, where water is used to extract sulphonic acid to prevent formation of di- and poly-sulphonic acids (Fischer, 1978).

The adoption of a second liquid phase has also proved useful in the hydroformylation reaction of propylene for which Ruhrchemie and Rhône-Poulenc have used Rh based water soluble catalysts based on tri(*m*-sulphophenyl)phosphine. This complex is water soluble and extractable at $-1 < pH < 0$; the sodium salt is *not* extractable (Kuntz, 1987).

The hydroformylation reaction strategy has recently been extended, in a novel way, to the manufacture of primary amines by hydroaminomethylation of olefins with ammonia in a two-phase system. Thus, 1-pentene was reacted with ammonia; here hydroformylation to an aldehyde, with CO and H_2, with subsequent reductive amination occurs in a domino reaction. The catalyst was Rh/Ir/TPPS (Zimmermann *et al.*, 1999).

4.2.1.2. Hydrogenation of benzonitrile

The strategy of introducing water as second phase has been used by Greenfield for obtaining higher yields of dibenzylamine (>97%) by hydrogenation of benzonitrile. In this case, water seems to prevent poisoning of the catalyst (Doraiswamy and Sharma, 1984).

4.2.1.3. Biphasic oxo- and other reactions

Cornlis (1998, 1999) and Joo and Kaltio (1997) have discussed the status and directions of industrial aqueous biphase catalysis. This technique should allow the use of sensitive reactants and/or obtain sensitive reaction products through the novel method of 'heterogenizing' homogeneous catalysts. The most outstanding example, conducted on a large scale, is the biphasic oxo reaction of propylene to butyraldehyde. Shell's alpha olefins from ethylene using a biphasic system of hydrocarbons and butanediol, was an earlier successful example practised on a large scale. Here the product olefins are insoluble in the diol.

The hydrodimerization of butadiene and water (Eqn. (16)), a variant of telomerization, is carried out industrially in Japan.

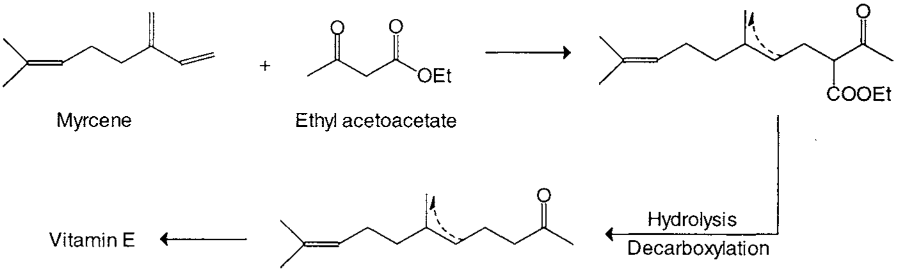
$$2\,CH_2{=}CH{-}CH{=}CH_2 + H_2O \longrightarrow CH_2{=}CH(CH_2)_3CH{=}CHCH_2OH \qquad (16)$$

The product is 2,7-octadien-1-ol which can be dehydrogenated/hydrogenated internally to give 7-octenal, which can be hydroformylated to the dialdehyde, nonadialdehyde, and then hydrogenated to nonadiol. The initial product can be hydrogenated to 1-octanol; the dialdehyde can be oxidized to the diacid. The catalyst used is Pd modified with the Li salt of monosulphonated triphenylphosphine.

In an analoguous case, two-phase telomerization of butadiene with ammonia to give octadienylamine has been reported where higher selectivity is realized in a two-phase system of water-toluene. Here, octadienylamine is more reactive than ammonia and consecutive reaction leads to *sec* and *tert* amines. By adopting a two-phase strategy, a primary amine selectivity as high as 91% has been realized (Drieben-Hoscher and Keim, 1998).

The C-C coupling through aqueous two-phase catalysis, is exemplified by reaction (17), which is carried out industrially in France. Here Ru with triphenylphosphine trisulphonate (TPPT) is used.

Ten Brink *et al.* (2000) have shown how biphasic systems, sometimes with the sparingly soluble alcohols as one phase and an aqueous phase as the other phase, benefit from the strategy for air oxidation to aldehydes/ketones by using water soluble Pd complex of bathophenanthroline disulphonate. This is a nice example of green technology.



(17)

A variety of new water-soluble ligands are being developed and the role of additives, particularly for enhancing solubility of sparingly soluble solutes in water, has been assessed; even the use of β-cyclodextrin to increase solubility has been studied.

The strategy of using two phases, one of which is an aqueous phase, has now been extended to 'fluorous' systems where perfluorinated solvents are used which are immiscible with many organic reactants; nonaqueous ionic liquids have also been considered. Thus, toluene and fluorosolvents form two phases at room temperature but are soluble at 64 °C, and therefore, solvent separation becomes easy (Klement *et al.*, 1997). For hydrogenation and oxo reactions, however, these systems are unlikely to compete with two-phase systems involving an aqueous phase. Recent work of Richier *et al.* (2000) refers to high rates of hydrogenation of alkenes with fluoro versions of Wilkinson's catalyst. De Wolf *et al.* (1999) have discussed the application and potential of fluorous phase separation techniques for soluble catalysts.

It is possible to synthesize cobalt complexes which are soluble in polyethylene glycols and not in solvents like hexane, hexene, heptenal etc. Ritter *et al.* (1996) have reported the oxo reaction of 1-hexene in such a system.

An interesting and potentially useful variant is deployment of thermoreversibility, a situation where the reaction occurs at relatively high temperature in a homogeneous phase, which becomes a two-phase system at lower temperatures, facilitating catalyst recovery. Here, tailored ligands have to be used. Ethoxylated phosphines have been suggested by Jin, Fell, and co-workers (1996, 1997).

An unusual enhancement of catalytic activity in a two-phase system has been reported by Fremy *et al.* (1998) for the hydroformylation of acrylic esters using Rh complex of TPTS as catalyst. Even though acrylic esters have reasonable solubility in water, rate enhancements in two-phase systems by a factor of 2 to 14 have been reported. It seems that water is not an inert solvent but also acts as a reactant or a co-ordinating solvent which can modify elementary steps of the catalytic cycle (Cornilis, 1997).

The concept of a 'promoter' ligand to improve rates in biphase systems via binding an organometallic catalyst and increasing its concentration near the interface of the aqueous phase has been suggested by Chaudhari *et al.* (1995). In this way the rate of oxo reaction of 1-octene using Rh catalyst was increased by 10 – 50 times when the promoter ligand was PPh_3.

Bayer (1997) has claimed that in a water-CH_2Cl_2 system, using water soluble $Pd(OAc)_2$ – triphenylphosphine trisulphonic acid catalyst, octa-2,7-dienyl-1-amine and octa 1,7-dienyl -3-amine can be obtained by telomerization of butadiene with ammonia.

Buhling *et al.* (1995) have used amphiphilic ligands in oxo-reactions, where with a pH swing the catalyst is made organic or water soluble (ligand $Ph_2Ar(P)$ with Ar = 3-hydroxy phenyl or 4- caroxy phenyl).

Gulyas *et al.* (1997) have suggested new amphiphillic or water-soluble ligands.

Monflier *et al.* (1995) have intensified the rate of the oxo reaction of sparingly soluble olefins like 1-decene using dimethyl β-cyclodextrine, which seems to form inclusion complexes with the olefin and deliver it in the aqueous phase.

Monflier *et al.* (1997) have suggested Pd catalysed hydrocarboxylation of higher alpha olefins in which chemically modified β-cyclodextrin (especially dimethyl β-cyclodextrin) is used in water in preference to a co-solvent like methanol, acetone, acetic acid, acetonitrile, etc. Here, quantitative recycling of the aqueous phase is possible due to easy phase separation without emulsions. A similar strategy has been adopted by Monflier *et al.* (1998) for biphasic hydrogenations for water-insoluble aldehydes like undecenal using a water-soluble Ru/triphenylphosphine trisulphonate complex with a suitably modified β-cyclodextrin.

Bortoletto *et al.* (1997) have used neutral and cationic triphenylphosphine trisulphonate or triphenylphosphine mono-sulphate Rh complexes. Monosulphonate is less readily oxidized and can replace trisulphonate in industrial processes. The presence of a quaternary ammonium counter ion associated with the trisulphonate confers phase-transfer properties to the catalytic species, which makes use of co-solvents unnecessary.

In some cases the use of a two-phase system may allow a change in the selectivity. Thus, Joo *et al.* (1998) have shown that water-soluble Ru hydrides (sulphanatophenylphosphine Ru complexes) give different products in the hydrogenation of cinnamaldehyde with variation in the pH of the aqueous media. At a pH greater than 7.2, cinnamyl alcohol is formed and at a pH less than 5 saturated aldehyde is formed.

In yet another version of adopting a biphase system, oxidation of alkanes with *tert*-butyl hydroperoxide has been conducted with an aqueous phase. Launay *et al.* (1998) have developed an efficient and highly selective conversion of cyclo-octane to cyclo-octanone using Ru colloïdial particles formed *in situ* from $RuCl_3$ $.5H_2O$. The aqueous phase can be recycled.

Betzemeier *et al.* (1998) have used *t*-BuOOH, in the presence of a Pd(II) catalyst bearing perfluorinated ligands using a biphasic system of benzene and bromo perfluoro octane to convert a variety of olefins, such as styrene, *p*-substituted styrenes, vinyl naphthalene, 1-decene etc. to the corresponding ketone via a Wacker type process. Xia and Fell (1997) have used the Li salt of triphenylphosphine monosulphonic acid, which can be solubilized with methanol. A hydroformylation reaction is conducted and catalyst recovery is facilitated by removal of methanol when filtration or extraction with water can be practised. The aqueous solution can be evaporated and the solid salt can be dissolved in methanol and recycled.

4.2.1.4. Selective hydrogenation of benzene to cyclohexene

The selective hydrogenation of benzene is a classical example of the combination of catalytic chemistry, chemical engineering ingenuity, and process design. In a single liquid phase over a noble metal catalyst, complete saturation of the benzene ring to cyclohexane takes place. Scientists at Asahi Chemical Industry in Japan successfully commercialized a process for partial hydrogenation of benzene to cyclohexene (Fukkoka and Nagahara, 1991). This was made possible by inventing a very selective hydrogenation catalyst system. They introduced water as the second immiscible phase, used $ZnSO_4$ as an additive and supported Ru as catalyst of choice to obtain cyclohexene yields greater than 50%. Although cyclohexene may come under the category of bulk chemicals, it is also used for fine chemicals production, e.g., cyclohexene epoxide.

A more detailed study of this system using benzene and toluene has been reported by Soede *et al.* (1993) from The Netherlands. They have shown that the role of $ZnSO_4$ is to make the Ru hydrophlilic so that the catalyst particles are surrounded by a stagnant water layer. This aids in the rapid removal of the cyclohexene from the catalyst surface to the organic phase. The reaction is operated in mass transfer controlled conditions.

4.2.1.5. Liquid-liquid-solid system versus liquid-solid system

An uncommon example of liquid-liquid-solid triphase system has been reported by Bhaumik *et al.* (1998). This concerns the hydroxylation of benzene with aqueous H_2O_2 using TS-1 zeolite (titanium silicate) as the catalyst. The liquid-liquid-solid system gives 15 to 25 times higher rate than a liquid-solid system in which a common solvent was used to homogenize the organic and aqueous layer. Competitive adsorption experiments indicated that under liquid-liquid-solid conditions benzene competes favourably with water for diffusion inside the TS-1 channels; under liquid-solid conditions benzene faces strong competition with organic solvents for diffusion inside hydrophobic TS-1 channels resulting in low conversion.

In earlier work, Bhaumik and Kumar (1995) have reported that the use of two liquid phases in the oxidation of hydrophobic organic substances with aqueous H_2O_2 using titanium silicate as the catalyst not only enhances the rate of oxidation but also improves selectivity for species like toluene, anisole, and benzyl alcohol. For a single liquid phase acetonitrile was used a solvent. The solid-liquid system gives high *ortho* selectivity. Thus, in the case of anisole the ratios of *o* to *p* for solid-liquid and solid-liquid-liquid system were 2.22:1 and 0.35:1, respectively.

De Vos *et al.* (2000) have given a survey of engineered solid catalysts for synthesis of fine chemicals in such systems. The activity and selectivity can be manipulated through matching of polarity between the catalyst and the biphasic system. Two major approaches reported are: modification of silica or siliceous materials like MCM-41 by covalent linking of functional groups; use of inorganic ion exchangers as host for catalytic species. A number of examples have been given by De Vos *et al.*

4.2.1.6. Catalytic reaction with extraction of intermediate product

The concept of extractive reaction, which was conceived over 40 years ago, has connections with acid hydrolysis of pentosans in an aqueous medium to give furfural, which readily polymerizes in the presence of an acid. The use of a water-immiscible solvent, such as tetralin allows the 'labile' furfural to be extracted and thus prevents polymerization, increases the yield, and improves the recovery procedures. In the recent past an interesting and useful method has been suggested by Rivalier *et al.* (1995) for acid-catalysed dehydration of hexoses to 5-hydroxy methyl furfural. Here, a new solid-liquid-liquid extractor reactor has been suggested with zeolites in protonic form like H-Y-faujasite, H-mordenite, H-beta, and H-ZSM-5, in suspension in the aqueous phase and with simultaneous extraction of the intermediate product with a solvent, like methyl *iso*butyl ketone, circulating countercurrently.

4.2.1.7. Use of a second liquid phase in catalytic hydrogenation

An interesting example of the use of a second liquid phase is to facilitate catalyst recycle when the reactor is operated as a slurry reactor.

4.2.1.8. Hydration of cyclohexene: two-phase system

The liquid-phase hydration of cyclohexene is carried out by a Japanese company with a slurry of zeolite ZSM-5 as the catalyst. Here, the product separates into two layers and cyclohexanol leaves in the organic cyclohexene phase and the catalyst stays in the aqueous phase, which is recycled. The two-phase strategy, therefore, has special significance in this case. A recent publication by Ogawa *et al.* (1998a) gives some details of this system.

4.2.2. Phase-transfer catalysis

There are a number of industrially important reactions where two liquid phases are involved and the aqueous phase contains ionic species. Here the rate may be severely limited due to low solubiblity of the reactant, located in the organic phase, in water. We would benefit from using a phase-transfer (PT) catalyst, which ferries the ionic species into the organic phase thus overcoming a severe limitation. Such PT catalysts are typically quaternary ammonium compounds like tetrabutylammonium halides, trioctylmethylammonium chloride, etc. (see also Section 3.8).

Higher selectivity, easier processing, use of inexpensive solvents, use of cheaper chemicals, and ease of heat removal have been realized through phase-transfer catalysis (PTC). It appears that no catalytic method has made such an impact as PTC on the manufacture of fine chemicals (Sharma, 1996). Many times we benefit by deliberately converting a single-phase reaction to a two-phase reaction. Consider catalysis by sodium methoxide in a dry organic solvent. This can invariably be made cheaper and safer by using a two-phase system with a PT catalyst.

Figure 3.56 in Section 3.8 illustrates the mechanism of phase-transfer catalysis. Tables 4.4 and 4.5 give examples of industrial importance in agrochemicals, pharmaceuticals, fine chemicals, oleochemicals, etc.

Table 4.4

Some examples of industrial applications of PTC in agrochemicals and pharmaceuticals (Adopted in part from Sharma, 1997)

Product	Reactants
Benzyl cyanide; *p*-chlorobenzyl cyanide	Benzyl chloride, sodium cyanide; *p*-chlorobenzyl chloride, sodium cyanide
C-Methylation of side chain of *p*-chlorobenzyl cyanide	*p*-chlorobenzyl cyanide, isopropyl halide
Trichloropyr	Trichloropyridinol, methyl chloroacetate
Butachlor (herbicide)	N-Chloroacetyl-2,6-diethylaniline
Picolylpyrrolidinone	Pyrrolidinone, 4-chloromethylpyridine
C-Alkylations in pharmaceuticals	Various reactants
Codeine	Morphine, methylating agent

Table 4.5
Some examples of industrial applications of PTC in fine chemicals, oleo chemicals and polymers (Adopted in part from Sharma, 1997)

Product	Reactants
Benzyl alcohol, benzyl esters (acetate, benzoate etc.)	Benzyl chloride, sodium carbonate/sodium hydroxide; sodium salt of acids
4-Nitroso diphenyl amine	Aniline, nitrobenzene, O_2
O-Alkylation of phenols	Phenol/cresols/catechols, alkyl halides/dimethyl sulphate/diethyl sulphate
Triphenyl/Tricresyl phosphate	Phenol/cresols, $POCl_3$
Methylene dioxybenzene	Catechol, methylene chloride
C-Alkylation of malonic acid esters	Malonic acid esters, alkyl halides
1,4-diamino anthraquinone-2,3-disulphonic acid	1,4-diamino-2,3-dichloro anthraquinone
Polycarbonates	Bisphenols, $COCl_2$

Most of the applications are for relatively slow reactions. However, Sharma and co-workers have shown that for a number of reactions, such as alkaline hydrolysis of sparingly soluble esters and reaction of $POCl_3$/RCOCl with substituted phenols, where mass transfer is accompanied by a fast reaction in the diffusion film, PTC can be advantageously employed (Krishnakumar and Sharma, 1983). In the case of triarylphosphates, an elegant, room temperature process has been developed using cheap solvents like toluene; it is desirable to use the organic phase as the continuous phase as it becomes very viscous. Talley and Berman (1987) have utilized the above strategy of Krishnakumar and Sharma (1983) to make the corresponding phosphorothionates based on the reaction of $PSCl_3$. Here, the conventional process based on the reaction of $PSCl_3$ with the corresponding phenolic substance at higher temperature does not work. The kinetics of reaction between $POCl_3$ and sodium salts of phenolic substances to make triarylphosphates show some interesting features of mass transfer with chemical reaction (Krishnakumar and Sharma, 1985), giving yields exceeding 90%. This high selectivity is realized in a two-phase system with the use of PTC.

Sato *et al.* (1997) have shown that 2-octanol can be converted to 2-octanone, with 95% selectivity, with 3-30% aqueous H_2O_2 in the presence of a tungsten catalyst and a PTC like trioctylmethylhydrogen sulphate. A similar strategy works for converting 4-*tert* butylcyclohexanol to 4-*tert* butylcyclohexanone.

In pursuit of green chemistry, Mr. Clean aqueous H_2O_2 leaves only water. Thus readily available aqueous 30% H_2O_2 has been used for oxidation of cyclohexene to adipic acid using a PTC and a noble metal catalyst (Sato, 1998).

The use of a PTC, tetramethylammonium hydroxide, to carry out the coupling under aeration of nitrobenzene and aniline to give nitroso diphenylamine (which on catalytic reduction with H_2 gives 4-aminodiphenylamine, required in the rubber industry) may be cited as a green chemistry route compared to the established process based on *p*-nitrochlorobenzene and aniline where Cl is wasted (Bashkin *et al.* 1999).

New interesting applications have been in the epoxidation of difficult olefin compounds (including hexafluoropropene) with NaOCl, side-chain chlorination of substituted toluenes, diazotization of pentafluoroaniline, polymerization with free radicals, etc.

A useful application in the manufacture of ion-exchange resins may well be possible which avoids the use of carcinogenic chloromethyl ether. Here, a polymer of *p*-methyl styrene is chlorinated on the side chain with aqueous NaOCl and a phase-transfer catalyst. Sasson *et al.* (1986) have shown how 'stubborn' substituted aromatics like nitro/chlorotoluenes can be oxidized to the corresponding acids by using aqueous NaOCl containing Ru based catalyst.

Lindblom and Elander (1980) have given a number of examples of relevance in the pharmaceutical industry. These include *C*-alkylations, *O*-alkylations, and *N*-alkylations. The *C*-alkylation of phenylacetonitrile, (mono- and di-) alkylation of benzylpenicillin with a-chlorodiethyl carbonate (where the acid part and the halide part in the esterification would have degraded quickly under normal conditions adopted for the reaction), *N*-alkylation of purines and adenine, etc. are discussed at some length and the supremacy of PTC is clearly shown.

For the delicate transesterification of a β–Lactam intermediate (for carbacephalosphorin skeleton), where originally hydrolysis of methyl ester was done homogeneously and then formation of the benzyl (or substituted benzyl) ester was done separately, Doecke *et al.* (1991) have devised a mild and efficient methodology using PTC. A dual use of a PT catalyst, Bu_4NBr, in one pot was made in a $CH_2Cl_2 - H_2O$ system. In the first step 5N NaOH was used, then the pH was adjusted to 7.2 to 7.8 and subsequently benzyl (or substituted benzyl) bromide was added.

PTC may well provide a way of recovering valuable chemicals from the waste streams of fine chemicals plants. Krishnakumar and Sharma (1984) have shown how phenolic substances from aqueous alkaline streams can be recovered as useful, saleable substances and their content brought down to below 5 ppm in the waste streams. Even penicillin from waste liquors discharged from fermentation plants can be recovered (Lindblom and Elander, 1980).

4.2.2.1. Steering of reactions

Dehmlow and Klauck (1994) have shown how *O*- vs *C*-alkylations of 2-naphtholate, with benzyl bromide in toluene, in solid-liquid mode can be influenced by the PT catalyst (benzyltriethylammonium chloride) concentration. The ratio of *O*- to *C*-alkylated product could be varied from 0.02 to 7.5 depending on the catalyst concentration, temperature, etc.

Chiral PTC has been used effectively for making intermediates for drugs. Dolling and co-workers have used 8-R, 9-5, N-(*p*-trifluoromethylbenzyl) cinchonium bromide to carry out an important asymmetric alkylation, giving 95% ee (Starks, 1987). Nucleophilic epoxidations of enones, Darzens reaction, Michael additions, etc. are some examples of reactions rendered asymmetric through chiral PTCs (Nelson, 1999).

One of the limiting factors has been the lack of stability of phase-transfer catalysts at higher temperatures, particularly under highly basic conditions. For this purpose, relatively cheap polyethylene glycols (of molecular weights 400 and 600) have proved very useful in some cases. These are stable at much higher temperatures up to about 200 °C. A new catalyst, trident, TDA-N $(CH_2CH_2O\text{-}CH_2CH_2OCH_3)_3$ has been commercially introduced which is effective for aromatic substitutions up to 130°C and also gives a synergetic effect in the Ullmann reaction of haloaromatics with phenols in the presence of copper catalysts. The dimethyl-aminopyridinium quaternaries have also been introduced, which are useful for aromatic nucleophilic displacements and are 100 times more effective than, say, tetrabutylammonium bromide and can function up to 200 °C (Starks, 1987). The utility of this type of catalyst has been tested for speciality engineering plastics like polysulphones. PTC is already used in making polycarbonates; even sterically hindered bisphenol-2, 2-bis (4-hydroxy-3,5-dimethylphenyl) propane has been successfully converted to polycarbonates (Vernaleken, 1977).

4.2.2.2. Recovery of PTC

The problem of recovering catalysts merits further attention. The strategy of using solid-supported PTC, on which a number of papers have appeared, does not, so far, seem to be commercially successful, either due to reduced activity and/or due to poor life. It would be useful to examine solubility of catalysts in different solvents for recovering them through extraction. In the case of catalysts like polyethylene glycol (PEG) and reactions involving 40-50% NaOH, three liquid phases may be encountered and this should facilitate the recovery of catalysts; kinetics of such reaction systems deserve to be studied (Neumann and Sasson, 1984).

4.2.3. Use of ionic liquids

Ionic liquid solvents are non-volatile and non-toxic and are liquids at ambient temperature. Originally, work was concerned with battery electrolytes. These ionic liquids (IL) show excellent extraction capabilities and allow catalysts to be used in a biphasic system for convenient recycling (Holbrey and Seddon, 1999). IFP France has commercialized a dimerization process for butenes using ($LNiCH_2R^1$) ($AlCl_4$) (where L is PR_3) as an IL and here the products of the reaction are not soluble in IL and hence separate out. The catalyst is very active and gives high selectivity for the dimers.

A variety of other reactions such as acylation of toluene, anisole, and chlorobenzene to give selectively *p*-isomer, alkylations, etc. have been conducted with IL.

Room temperature ionic liquids (RTILs), such as those based on *N,N*-dialkylimidazolium ions, are gaining importance (Bradley, 1999). The ionic liquids do not evaporate easily and thus there are no noxious fumes. They are also non-inflammable. Ionic liquids dissolve catalysts that are insoluble in conventional organic chemicals. IFP France has developed these solvents for dimerization, hydrogenation, isomerization, and hydroformylation reactions without conventional solvents. For butene dimerization a commercial process exists. RTILs form biphasic systems with the catalyst in the RTIL phase, which is immiscible with the reactants and products. This system is capable of being extended to a list of organometallic catalysts. Industrial Friedel-Crafts reactions, such as acylations, have been conducted and a fragrance molecule traseolide has been produced in 99% yield (Bradley, 1999).

4.3. RATE AND SELECTIVITY IMPROVEMENT VIA MANIPULATION OF 'MICRO-ENVIRONMENT'

4.3.1. Micelles

Micelles are aggregates of surfactants and are capable of solubilizing large quantities of hydrophobic substances; ionic reagents are also taken up due to electro-static interactions.

Micelles are typically 40-80 Å in diameter and thus provide an enormous area at low concentrations. Micelle catalysis provides a methodology for synthesizing novel and conventional products in aqueous media, resulting in improved rates and possibly eliminating the need of organic solvents. This strategy can be used in a single phase as well as in multiphase systems. Langevin (1992) has discussed important aspects of the physics of micelles and of microemulsion formation. There is a close relationship between the surfactant film properties, the bulk, structures, and the interfacial tension. Sharma and co-workers have shown how multiphase reactions can benefit from the use of micelles even when the reaction is mass-transfer limited with or without chemical reactions in the film (Janakiraman and Sharma, 1985; Mehra *et al.*, 1988). Intensification in specific rates by a factor of 70 has been realized. The theoretical aspects have been brought out by Janakiraman and Sharma (1982) and Mehra (1988). The ability of micelles, by manipulation of charge to repel ionic species, can be exploited to inhibit undesired reactions and thereby improve selectivity (Bunton, 1979).

Onyiriuica & Suckling (1982) have used functionalized micelles to realize *ortho*chlorination of phenol; *tert* butylhypochlorite in methanolic and aqueous solutions gives high yield of the *ortho* product when a *tert* alcohol is included in a detergent chain to the ionic head group.

Reversed micelles have also shown to be useful not only in bioconversions, but also in organic synthesis. Shield *et al.* (1986) have reviewed this subject and brought out its advantages in peptide synthesis, oxidation or reduction of steroids, selective oxidation of isomeric mixtures of aromatics, etc. In the oxidation of aromatic aldehydes to carboxylic acids with enzymes hosted in reverse micelles, the *ortho* substituted substrates react much more slowly than other isomers.

Nanometer size Pd colloids in block copolymer micelles of polystyrene polyvinylpyridine as catalysts have been used is a novel way by Klingelhofer for Heck reaction of C-C coupling of aryl halides with olefins.

A fascinating area is micellar autocatalysis; reactions in which surfactant micelles catalyse the reaction by which the surfactant itself is synthesized. Thus synthesis of dimethyldoceylamino oxide (reaction between dimethyl dodecyl amine and H_2O_2) benefits from this strategy. Here an aqueous phase can be used and an organic solvent can be avoided. Synthesis of mesoporous molecular sieves benefit through micellar catalysis and silicate polymerization rates have been increased by a factor 2000 in the presence of cetyltrimethyl ammonium chloride (Rathman, 1996).

An effect similar to that of cetyltrimethylammonium bromide micelles can be realized through the use of microgels with trimethylamino side-chain function and this may then allow solid supported microgels to be used in a continuous reaction. Evans *et al.* (1995) have utilized microgels incorporating 2-tetradecyl dimethyl amino/ethyl methacrylate bromide, which solubilizes aryl laurate esters in an aquous solution and catalyses the alkaline hydrolysis.

Micellar effects can play an important part in aqueous organometallic reactions. Surface active diphosphines have been synthesized and sparingly soluble solutes like decene may well benefit through miceller effects.

4.3.2. Microemulsions

Microemulsions (MEs) are colloidal dispersions consisting of monodisperse droplets of water-in-oil and are thermodynamically stable. Microemulsions are made with detergents as well as without detergents. The latter are especially useful as reaction media, because separation steps after reaction can be very simple and constituents of the media can be recycled. In principle, certain types of surfactants that are referred to as destructible detergents can also be conveniently used. Moulik and Paul (1998) have given an exhaustive account of structure, dynamics, and transport properties of microemulsions. Typically, droplets are 100-300 Å in diameter and the organic phase fraction can be as high as 0.3 providing very large interfacial area. Thus, microemulsion reaction media can enhance rates of multiphase reactions enormously. Sharma and co-workers have shown for oximation of cyclododecanone and other reactions, including gas-liquid reactions, that intensification factors can be very high; for oximation of cyclododecanone, an intensification factor of over 600 has been realized (Bhagwat and Sharma, 1988). The mechanism of solubilization throws some light on the possibilities of exploiting these media to realize selectivity or making some reactions possible that are otherwise difficult to conduct. Consider the reduction of *iso*phorone with $NaBH_4$ where two types of reduction, 1,2 (to 3,5,5-trimethyl-2-cyclohexenol) or 1,4 (to 3,3,5-trimethylhexanone and 3,3,5-trimethyl cyclohexanol), can occur. In the presence of anionic micelles and microemulsions, the ratio of 1,2 to 1,4 products was 90:10 as opposed to 58:42 in a simple aqueous medium. Cationic micelles will not be so favourable and the ratio of 1,2 to 1,4 was found to be 78:22 (Fargues-Sakellariou *et al.*, 1985).

Gonzalez and Holt (1981) have shown how macrocyclic lactones can be made conveniently in microemulsion media. Thus, intramolecular esterification of ω–hydroxy alkanoic acids can be carried out with a very small amount of acid catalysts like *p*-toluene sulphonic acid, and rates are markedly higher as compared to simple media.

Gutfelt *et al.* (1997) have evaluated various ME formulations as reaction media for synthesis of decyl sulphonate from decylbromide and sodium sulphite. The reaction rate was fast both in water-in-oil and in bicontinuous ME based on non-ionic surfactants. A comparison was made with this reaction being conducted in a two-phase system with quats as phase-transfer catalyst but was found to be much less efficient. However, when two other nucleophiles, NaCN and $NaNO_3$, were used the PTC method was almost as efficient as the ME media. It seems that in the case of decyl sulphonate there is a strong ion pair formation between the product and the PTC. The rate in the ME media could be further increased by addition of a small amount of a cationic surfactant.

Menger (1993) has brought out an unusual application of ME, through what is called 'chemical collectivism' for destruction of toxic mustard $Cl\text{-}CH_2\text{-}CH_2\text{-}S\text{-}CH_2\text{-}CH_2\text{-}Cl$ with bleach liquor.

Theoretical aspects of intensification have been, to some extent, covered by Bhagwat and Sharma (1988) but much more work is required. Our predictive capabilities for realizing higher selectivity need to be improved greatly.

Microemulsion media seem to be very useful in getting monodisperse $CaCO_3$ particles of 30 Å via carbonation of calcium phenates (Marsh, 1987); this process is relevant in making lube additives. The mechanism of reaction crystallization in such systems has hardly received attention.

A general analysis for 'microphase' catalysis, where microphase includes micelles, swollen micelles, microemulsions and macroemulsions, can be rigorously constructed by writing the relevant partial differential equations, for a species A diffusing across the interface into the liquid (which contains the microphase) where it undergoes a pseudo first-order reaction (also within the microphase), as has been shown by Mehra (1988). It may be possible to realize selectivity for a desired solute, in a multisolute system, through oil-in-water or water-in-oil emulsions and microemulsions and the latter type are expected to show relatively higher selectivity. The improvement in oil-in-water systems is given by:

$$\phi_s = \left[\frac{m_{A1}}{m_{A2}} \cdot \frac{k_{12}}{k_{11}}\right]^{1/2} \tag{18}$$

whereas in inverse systems such as water-in-oil we get:

$$\phi_s = \left[m_{A1} m_{A2} \cdot \frac{k_{12}}{k_{11}}\right]^{1/2} \tag{19}$$

where m_A denotes distribution coefficients (organic/water) and k_1 represents the rate constants; subscripts 1 and 2 refer to solutes 1 and 2, respectively (Mehra and Sharma, 1988; Mehra, 1989).

Chhatre *et al.* (1993) have reported that highly selective *ortho*-nitration of phenol with dilute nitric acid can be realized by using a microemulsion medium. It seems that in the microemulsion medium, phenol orients in such a way that the phenyl group remains extended towards the side of the organic phase, whereas the hydroxyl group protrudes in the aqueous phase where nitric acid exists.

Tjandra *et al.* (1998) have proposed an interfacial reaction model for the kinetics of the reaction between 1-bromo octane and sodium phenoxide to give 1-phenoxyoctane in a non-ionic microemulsion. In this model the microemulsion is assumed to consist of the aqueous phase and the interface is covered by a monolayer of surfactant molecules. It is thus possible to assess the interfacial area from the concentration of the surfactant in the microemulsion medium.

4.3.3. Hydrotropes

Hydrotropes are a class of substances like toluene/xylene/cumene sulphonic acids or their Na/K salt, glycols, urea, sodium butyl monoglycol sulphate, etc., which are highly soluble in water, and which enormously increase the solubility of sparingly soluble solutes. Subramaniam and Friberg (1993) have referred to hydrotopes as cousins of surfactant molecules whose tails have been partly chopped off. The structure of such solutions and the mechanism of solubilization have received very little attention. However, Subramaniam and co-workers (1987) have shown through a study of surface tension, NMR spectra, FTIR spectra, etc., that 'structured aggregates' are formed. There is a minimum hydrotrope concentration, referred to as the critical hydrotrope concentration, akin to CMC, above which solubilization occurs. Subramaniam and Friberg (1993) have reviewed this subject. Thus, apart from intensifying multiphase reactions, selectivity may also change. The alkaline hydrolysis of substituted phenyl benzoates has been intensified by a factor approaching 1000 (Pandit and Sharma, 1987). Laxman and Sharma (1990) have found that the ratio of 1,2:1,4 reduction product of *iso*phorone, obtained through sodium borohydride, changes substantially with the use of hydrotropes and depends on the type of hydrotrope and its concentration. There is a need for further studies in this area to arrive at a predictive method for the extent of solubilization and rates and selectivity that can be realized.

The Reimer-Tiemann reaction of phenol with chloroform, in the presence of 50% NaOH, gives a much higher ratio of *para* to *ortho* hydroxy benzaldehyde when polyethylene glycol is used as compared to the established procedure without any addition of a hydrotope. A *para* to *ortho* ratio of 1:1 has been realized (Neumann and Sasson, 1986).

Sadvilkar *et al.* (1995) have studied condensation of benzaldehydes with acetophenones (Claisen-Schmidt reaction) in an aqueous medium, containing sodium butylmonoglycol sulphate and sodium salts of aromaticsulphonic acids as hydrotropes. A substantial improvement in the rate of reaction was realized, while product recovery was facilitated.

4.3.4. Micromixing

When the half-life time of reaction and the half-life time of micromixing in the absence of chemical reaction are of the same order or the former is less than the latter, the role of micromixing may become crucial. For instance, nitration or bromination of resorcinol, even when the ratio of moles of resorcinol to moles of bromine is high, can lead to predominantly disubstituted product contrary to the general belief. In such cases, in many respects, the theory of coupling between reaction and micromixing has parallels with the formalism of theory of mass transfer with chemical reaction (Bourne, 1983).

Rys (1992) has discussed aspects of the mixing-sensitive product distribution of chemical reactions, with many examples involving azo coupling, nitration, bromination, etc. These are cases where isomer distribution is determined by mixing-sensitive positional selectivity. This positional (regio-) selectivity is amenable to alteration by mixing effects only if the competing reactions have a difference in kinetic order with respect to at least one of the reagents. In electrophilic aromatic substitutions, if one of the competing reactions is sterically hindered and exhibits a general base catalysis, their positional selectivity may change with mixing. In brominations of 1-(*tert* butyl)-3-methoxy benzene with molecular bromine, base catalysis is important and an increase in stirring rate decreases the concentration of added bases within the reaction zone, and hence the selectivity changes.

The role of micromixing in affecting selectivity in gas-liquid, liquid-liquid and gas-liquid-solid (including reaction crystallization) systems needs to be studied intensively. In particular, the formation of undesirable products, even though these might be present at levels below 3%, needs to be studied as these may affect the purity adversely, increase the cost of separation and may also lead to complicated liquid effluent disposal problems. There is considerable scope in improving selectivity via manipulation of micromixing (Baldyga and Bourne, 1990). Micromixing and its influence on reactor performance are discussed in more detail in Section 5.4.5.

4.4. RATE AND SELECTIVITY IMPROVEMENT VIA MANIPULATION OF 'MACRO-ENVIRONMENT'

4.4.1. Zeolites

In the recent past the potential of zeolites in the manufacture of fine chemicals has received considerable attention. High-Si zeolites can have Hammet's acidity function H_0 of -12.8 which is close to those for superacids. MCM (Mobil Catalytic Materials) have opened up new vistas due to larger pore sizes.

With L-type zeolites, chlorination of benzene has been claimed to give *para*dichlorobenzene with 95% selectivity and this is remarkably high compared to the common chlorination with homogeneous iron chloride catalyst (Saeki and Taniguchi, 1986). Similarly, chlorination of anisole at 70 °C in the presence of a zeolite has been claimed to give 73 % of the *para* derivative compared to the usual value of around 40 %. Halogenations with K-L zeolites to give high % of *para* isomers like *para* dichlorobenzene (90%), *para* chlorotoluene (75%), 4-chloro-*ortho*-xylene (90%) have been reported by Ratnasamy *et al.* (1996). Isomerization of *p*-dichloro benzene to an equilibrium mixture containing the desired *m*-dichloro product with zeolites has also been carried out. Nitration of toluene with acetyl nitrate ($AcOH/Ac_2O + HNO_3$) in the presence of *beta* zeolite gives 79% selectivity for the *para* derivative (Clark and Macquarrie, 1997). Smith *et al.* (1996) have nitrated alkyl benzenes and halobenzenes in quantitative yields and with high *para* selectivity, by using stoichiometric quantities of nitric acid and Ac_2O, at 0–20 °C, in the presence of zeolite-beta as a catalyst. Zeolites can be recycled and acetic acid is by-product.

It has been claimed that phenol can be selectively converted to hydroquinone with aqueous H_2O_2 using a zeolite like HZSM-5; selectivity as high as 99% has been claimed (Chang and Hellring, 1986). In the conventional process, the *para* derivative may not exceed 40 to 50% and the remaining is usually the *ortho* derivative. Ti-silicalites have opened new vistas in the area of hydroxylations with aqueous H_2O_2 and *tert*-butylhdroperoxide (TBHPO). Even titania-silica aerosols have been used for epoxidation of *iso*phorone with bulky cumene hydroperoxide.

Large pore zeolites have been used for selective alkylation of diphenyl with propylene to 4,4'-di*iso*propyl diphenyl with good selectivity. Similarly, naphthalene gives to 2,6 derivative.

Sheldon and co-workers (Elings *et al.*, 1995) have used H-Mordenite to rearrange allyl phenyl ether to 2-allyl phenol and subsequent cyclysation to 2-methyl dihydrobenzofuran.

O-methylation/ethylation of phenol, *o*-cresol, *p*-cresol, catechol (mono), hydroquinone (mono), etc. can be neatly conducted with zeolites rather than with hazardous processes using dimethyl/diethyl sulphate.

The use of zeolites like ZSM-5 for hydration of cyclohexene has seen successful in industry. Van der Waal *et al.* (1996) have hydrated α-pinene to α-terpeniol with β–zeolite; bycyclic terpenes are obtained as by-products.

Isomerization of α-pinene epoxide to campholenic aldehyde, an intermediate for perfumery chemicals, has been carried out elegantly with ultra stable Y-zeolite.

Aldol condensation reactions have also been conducted. A good example is provided by Climent *et al.* (1998) for making α-*n*-amyl cinnamaldehyde (Jasmin aldehyde) by condensing benzaldehyde with *n*-heptaldehyde, in the presence of mesoporous MCM-41 aluminosilicates. Mesoporous silica-aluminas with a narrow range of pore diameter such as MCM-41 also work. The self aldol condensation of *n*-heptaldehyde and Cannizzaro reaction of benzaldehyde to benzoic acid and benzyl alcohol are restricted and high selectivity with respect to benzaldehyde and *n*-heptaldehyde condensation is promoted.

The synthesis of Coumarin derivatives can be made cleaner using zeolite H-BEA and even cationic ion-exchange resin like Amberlyst-15 works. Reactions of resorcinol with acrylic/methacrylic acid, maleic anhydride and esters have been studied (Gunnewegh *et al.*, 1996).

Downing *et al.* (1997) have reported a number of examples, including isomerization of 2,3-dimethyl-2,3-epoxide to methyl-*tert*-butyl ketone, which is required for the production of photographic and crop-protection chemicals.

The use of zeolites can also be very helpful in removing a reaction product that unfavourably influences the yield of the desired product. Thus, in the manufacture of antibiotic cefoxitin, the amide acylation results in the generation of HCl, which can be removed by the addition of molecular sieve 3 Å or 4 Å, which has a large capacity for HCl (Weinstock, 1986). Other examples are reactions in which products like methanol or water retard the rate and prevent the reaction to reach the desired degree of completion. Molecular sieves capture methanol or water very well.

Sharpless and co-workers have shown how, with a catalyst developed by Sharpless, the rate and selectivity in asymmetric epoxidation of allylic alcohols can be improved substantially by using molecular sieve 3 Å / 4 Å (Gao *et al.*, 1987). In some cases, the use of molecular sieves has allowed asymmetric epoxidation, which was not possible with the original catalyst.

Smith *et al.* (1998) have reported selective *para* acetylation of anisole, phenetole, and diphenyl ether with carboxylic anhydrides at 100 °C, in the presence of catalytic quantities of zeolites H-beta. The zeolite can be recovered and recycled to give essentially the same yield as that given by fresh zeolite.

Recently mesoporous alumina molecular sieves have been reported which can have pore diameters exceeding even 100 Å (Pinnavia, 1998).

4.4.2. Molecular engineered layered structures

Bakke *et al.* (1982) have shown how montmorillonite catalyses chlorination and nitration of toluene; nitration leads to 56 % *para* and 41 % *ortho* derivative compared to approximately 40 % *para* and 60 % *ortho* derivatives in the absence of the catalyst. Montmorillonite clays have an acidity comparable to nitric acid / sulphuric acid mixtures and the use of iron-exchanged material (Clayfen) gives a remarkable improvement in the *para*: *ortho* ratio in the nitration of phenols. The nitration of estrones, which is relevant in making various estrogenic drugs, can be improved in a remarkable way by using molecular engineered layer structures (MELS), while a reduction in the cost by a factor of six has been indicated. With a Clayfen type catalyst, it seems possible to manipulate the *para*: *ortho* ratio drastically for a variety of substrates and this should be useful in the manufacture of fine chemicals. In principle, such catalysts may approach biomimetic chemistry; our ability to predict selectivity is very limited.

Kagan (1976) has brought the efficacy of using reagents trapped between carbon layers of graphite. Thus, the bromine-graphite combination leads to relatively high selectivity for monobromination of binaphthyl compared to the use of chloroform only as a solvent. In another example the use of $SbCl_5$ leads to ring chlorination. Even chiral reagents have been used with graphite with some specific advantages. The problems of diffusion in such catalysts require further studies.

4.4.2.1. Modified clays as catalysts

Pillared clays. Clay catalysts can be safely used up to 200 °C, but at temperatures beyond 200 °C the interlayer solvent species (or water) tends to be expelled, followed by collapse of the inter layer region. Such physical collapse can be overcome by inserting thermally stable robust cations which act as molecular props or pillars in keeping the silicate layers separated, in the absence of a swelling solvent. Initially tetra-alkylammonium cations were used for pillaring, but these were stable only up to 280 °C. Then, in 1978, polyoxy cations (of Si, Al, Zr, Cr, Fe, Mg) were used which result in structures that are stable above 600 °C. Various pillaring species have been tried till date, in addition to the most common Al_{13} and Zr_4. Other novel species in pillaring were chromium oxide and nickel oxide. Properties such as interlayer distance, surface area, thermal stability and acidity of these pillared clays can be exactly tuned by selecting proper experimental conditions. These *pillared clays* have a three-dimensional network structure like zeolites, unlike normal clays, which have a two-dimensional structure. Understanding of the pillaring process enables the preparation of a catalyst that can effectively perform specific duties.

Zinc chloride exchanged clay catalysts have been reported to be highly active for the Friedel-Crafts alkylation and acylation reactions; these are commercially sold by Contract Catalysts under the name Envirocats. These are montmorillonite catalysts modified by $ZnCl_2$ and $FeCl_3$. Some of the reported examples of Friedel-Crafts reactions are given below; there are claims that some of the processes are commercially practised.

Acylation reactions. Methoxyacetophenones and methoxypropiophenones can be obtained from acylation of methyl phenyl ether with the corresponding acid anhydrides and acid chlorides at 70 °C over Envirocat EPZG in 35 to 72 % yield. Other important reactions catalysed by this catalyst include acylation of $PhNHCOCH_3$ to acetamidoacetophenones and 1,3,5-trimethylbenzene to 1,3,5- trimethylacetophenone.

Alkylation reactions. In a laboratory procedure for the alkylation of benzene with benzyl chloride using the catalyst EPZ10 at room temperature 100% conversion of the alkylating agent in less than 15 minutes was obtained (Envirocats, 1990). EPZE was efficiently used in the sulphonation of *o*-xylene with benzenesulphonyl chloride to give 3,4-dimethyldiphenylsulphone, which is an intermediate to a polyimide monomer (Envirovcats, 1990).

4.4.3. Cyclodextrins

The use of cyclodextrins can allow stereo-, regio-, and optical selectivity, and thus molecular traffic control may be realized (Syamala *et al.* 1986). It has been claimed that the reaction of phenol with aqueous formaldehyde in the presence of cyclodextrins gives a 3:1 mixture of *para* to *ortho* at 38 % conversion; in the absence of cyclodextrins, the ratio of *para* to *ortho* is around 2:3.

The well-known reaction between phenol and chloroform in the presence of concentrated sodium hydroxide is amenable to dramatic changes with cyclodextrins. β-cyclodextrin, immobilized with epichlorohydrin, seems to give 100 % selectivity for *para* hydroxybenzadehyde. In the chlorination of anisole with HOCl, α-cyclodextrin gives a *para* to *ortho* chloro derivative ratio as high as 21.

Tabushi *et al.* (1979) have shown that β-cyclodextrin in aqueous alkaline solution allows highly selective one-step synthesis of vitamin K_1 (or K_2) analogues; here the key step is alkylation of 2-methyl hydronaphthoquinone with allyl, crotyl, methallyl, or prenyl bromide.

Harada *et al.* (1986) have shown how in the Wacker process for the conversion of alpha olefins to the corresponding carbonyl compounds, the use of alphacyclodextrin can make a remarkable change. Thus, C_8-C_{10} olefins give the corresponding methyl ketones but higher alpha olefins (C_{12}-C_{14}) do not react; it is even more remarkable to find that oct-2-ene gives poor results. Shiraishi *et al.* (1998) have made 4,4'-biphenyldicarboxylic acid by a one-step reaction of biphenyl, carbon tetrachloride, and copper powder in aqueous alkali containing β-cyclodextrins as catalysts at 70 °C and under N_2 atmosphere; 61 mole % yield with 85% selectivity was realized. In all the cases cited above, the fundamental aspects pertaining to the prediction of rate and selectivity remain to be studied in depth.

The covalent connection of a catalytically active transition metal center with a water-soluble receptor (host molecule) generates a new type of supramolecular catalyst in which the features of molecular recognition, phase-transfer catalysis and transition-metal catalysis are combined in a single system (Reetz, 1998). β–Cyclodextrin is a relatively cheap supramolecule, which can be the receptor, while Rh complexes of diphosphanes can be the catalytically active centre, being covalently connected to one another through a spacer. The competitive hydrogenation of certain olefins presents an example of molecular recognition, where unusual degrees of substrate selectivity based on molecular recognition are observed, which cannot be realized through conventional transition-metal catalysts. Thus, $PhCH_2CH_2CH{=}CH_2$ and n-$C_6H_{13}CH_2CH{=}CH_2$ show remarkable differences. Even the two-phase hydrogenation of *p*-chloronitrobenzene is smoothly carried out with 98% selectivity. Only about 0.5% of the corresponding dehalogenated products is found. Hydroformylation of 1-octene, in the above biphasic system has shown remarkable results with respect to rate and selectivity.

4.5. UNCONVENTIONAL TECHNIQUES

4.5.1. Photochemical reactions

For the manufacture of fine chemicals, photochemical reactions may prove to be very useful (Fischer, 1978). The most important application is in the area of radical chain reactions. The key advantages is specificity; the best-known examples, *viz.* side-chain chlorination of toluene and addition of chlorine to benzene may be cited (sulphochlorination and sulphoxidation are additional examples). The photochemical initiation permits operation at low temperatures. It is particularly useful when the radical chains are very short resulting in the requirement of very many initiating radicals. We do not suffer from the disadvantages inherent to large-scale processes where multiple photochemical reactors are required (e.g. in Nylon production, for the oximation of cyclohexane with NOCl). In the synthesis of vitamin D_3 and the hydroxy-derivative of vitamin A, photochemical processes have been employed. Photo-isomerization of *cis-* to *trans-* vitamin A acetate has been successfully practised. Photo-oxygenation is an important step in the manufacture of the perfumery chemical Rose oxide, starting from citronellol. Reactions based on ozone are also amenable to intensification /

improvement through photoactivation. It is possible to scale up photochemical reactions from bench scale work to industrial units employing 40-60 kW lamps. Photochemical reactions can be further improved by manipulation of the microenvironment through the use of micelles, microemulsions, etc. and through macroenvironment by using cyclodextrins (Kalyansundaram, 1987). In gas-liquid reaction where mass-transfer resistance is important, we need to analzse the problem more intensively, although some preliminary work has been done by Mahajani and Sharma (1981).

4.5.2. Biocatalysis

A biocatalyst is an enzyme or cell that should have the required activity to make it cost effective (see also Section 2.8.7). Biological catalysts allow many important transformations to be conducted under mild conditions, and very high regio-, and stereo-specificity can be realized (Semenov *et al.*, 1987). Immobilized catalysts offer additional opportunities (Rich *et al.*,1996). Success in bioprocess development depends on several pillars, i.e. knowledge about the involved microorganism, characterization of microorganisms, control of fermenters, and downstream processing. Table 4.6 shows some enzyme-catalysed reactions that have been applied on a larger scale in the pharmaceutical industry.

In some cases enzymes can increase the rate of reaction by up to 10^{12} times. Carnell and Roberts (1997) have briefly discussed the scope of biotransformations that are used to make pharmaceuticals like penicillins, cephalosporines, erythromycin, lovastatin, cyclosporin, etc., and for food additives like citric acid, *L*-glutamate, and *L*-lysine. A very successful transformation by Zeneca has been that of benzene reduction, with *Pseudomonase Putida*, to dihydrocatechol and catechol; the dihydro derivative is used to produce (+/-) pinitol. Fluorobenzene has been converted to fluorodihydrocatechol, an intermediate for pharmaceuticals. The highly stereo selective Bayer–Villeger reaction has been carried out with genetically engineered *S-cerevisvae*. Hydrolases have allowed enantioselective, and in some cases regioselective, hydrolysis of racemic esters.

Cheetham (1998) has given an account of what makes a good biocatalyst. The major source of new biocatalysts continues to be from nature, microbial as well as plant, notwithstanding the promise of newer techniques such as site directed mutagenesis and catalytic antibodies. Selective screening methods and/or high throughput screening provide convenient and useful methods. Once a strain has been found modern techniques, including gene coding, can be employed to obtain higher activity. It is essential to discover new biocatalysts as the present range is limited in numbers as well as in the range of reactions that can be carried out.

For biotransformations, hydrolytic enzymes such as lipases and esterases are used due to their commercial availability. These enzymes have broad substrate spectra, are usually simple, robust, have no cofactor requirements, and are therefore easy to use. Meyer *et al.* (1997) have opined that the future use of other enzyme types, e.g. lyases and reductases will be influenced by commercial factors and will depend on advances in cofactor recycling and protein engineering. Table 4.7 gives a list of commercial biotransformations developed at Lonza. Petersen and Kiener of Lonza (1999) have given some details of the conversion of beta nicotinic acid to the 6-hydroxy derivative. An interesting example is the conversion of 3-substituted pyridine to obtain a building block for Imidaccoprid (a major breakthrough of Bayer in insecticides).

Table 4.6
Some biotransformations of industrial importance

Biotransformation	Reference
Antibiotics: Penicillins, Streptomycin, Rifampicin, Erythromycin, etc.	Carnell and Roberts (1997), Bruginnic (1996)
Cefalexin from penicillin G	Van Loon *et al.* (1996)
6-APA from penicillin G, 7-ACA from cephalosporin C, 7-ADCA from desaacetoxy cephalosporin G	De Vroom (1998), Rasor and Tischer (1998)
Biotransformation in steroids, e.g. cortexolone to hydrocortisone and prednisolone	Giorno and Drioli (2000)
Food additives: Lactic Acid (now a bulk chemical for making polylactate), Citric acid, *L*-Glutamate, *L*-Lysine, etc.	Carnell and Roberts (1997)
Vitamines C, B_2, B_{12}	Van Loon *et al.* (1996)
Acarbose (antidiabetic drug)	Bodekar (1999)
Conversion of benzene to dihydrocatechol and catechol; Fluorobenzene to fluorodihydrocatechol and fluorocatechol	
Conversion of 2,5-dimethyl pyrazine to 5-metyl pyrazine-2-carboxylic acid, conversion of 5-ethyl-2-methyl pyridine to 2-methyl pyridine-5-carboxylic acid	Glockler and Roduit (1996)
Beta nicotinic acid to 6-hydroxy nicotinic acid; 3-substituted pyridine to a building block for imidacloprid (an insecticide)	Petersen and Kiener (1999)
R-Cyanohydrins from benzaldehydes and HCN;	DSM Chemie Linz (1996)
S (2)-hydroxy-3-butenenitrile from acrolein and HCN; *trans*	Effenberger (1999)
hydrocyanation using, for instance, acetone cyanohydrin	Griengl *et al.* (2000)
Hydrolysis of nitriles to amides, e.g. acrylonitrile to acrylamide	Cheetham (1998)
Isomerization of glucose to fructose	Cheetham (1998)
Esterifications and transesterifications	Yeo *et al.* (1998)
Interesterify positions 1 and 3 of natural glycerides	Schmid and Verger (1998)
Oxidation of glucose to gluconic acid, glycolic acid to glyoxalic acid	Seip *et al.* (1993)
Epoxidation of olefins (e.g. 1-octene) to optically active epoxides	De Bont *et al.* (1983)
Oxidation of *n*-paraffins to C_{13} brassylic acid (dicarboxylic acid)	Mitsutani (1997)
S-chloropropionic acid from ester of racemic chloropropionic acid esters	Taylor (1998)
Enzymatic resolutions of racemic amines or aminoalcohols via enantioselective acylation	Carrea and Riva (2000)
Fumaric acid to *L*-aspartic acid, *L*-aspartic acid to *L*-alanine	Giorno and Drioli (2000)
Enzymatic resolution of methyl ester of (+/-) *trans* 4- methoxy-3-phenyl glycidic acid (intermediate for the drug diltiazem)	Lopez and Matson (1997)

Table 4.7

Some industrially important electrochemical processes (Adopted in part from Sharma, 1990)

Glucose to gluconic acid
Adiponitrile from acrylonitrile
p-tert-Butyl toluene to *p-tert*-butyl benzaldehyde; *p*-methoxy toluene to *p*-anisic aldeyde; *p*-xylene to *p*-tolualdehyde (direct electrochemical as well as indirect process, e.g. manganous salt, obtained from the use of stoichiometric reagent $MnO_2 + H_2SO_4$, is recycled via electrochemical oxidation of manganous to manganic) (see also Walsh and Robinson, 1998)
Naphthalene to naphthaquinone
Vitamin C
Electrochemical fluorinations (Vreeke et al., 1998)
Hexafluoropropylene oxide from hexafluoropropylene
Fenoprofen, Mg is used as a sacrificial electrode and additionally a phase transfer catalyst is used (Anderson, 2000)
Paired electrosynthesis of phthalide and *p-tert*-butyl benzaldehyde (Putter and Hannebaum, 2000) and 2,5 Dimethoxy-2,5-dihydrofuran from furan (Steckhan *et al.*, 2000)

Esterification of tertiary alcohols poses several problems and expensive catalysts, like dimethylamino pyridine, are recommended. While esterification/transesterification/hydrolysis involving primary and secondary alcohols has been reported both with chemocatalysts and biocatalysts, *tert*-alcohol based esters have not found success. Recent work of Yeo *et al.* (1998) reports successful results for *tert*-butyl octonoate using a new strain of lipase. This is a significant finding as the production of esters based on *tert*-alcohols (and reciprocally with hindered acids) may well be possible with biocatalysts, avoiding expensive catalysts and allowing easier separation.

DSM Chemie Linz (1996) has developed (*S*)-hydroxynitrile lipase, (-)-methyl and other glyoxalates (as enantiomeric synthons) and succinimidyl esters of amino acids for peptide coupling. Thus, (*R*)-cyanohydrins can be made from aldehydes and HCN with an (*R*)-hydroxy lipase. DSM Chemie Linz as also developed an (*S*)-enzyme for making substances like (*S*)-mandelnitrile in 98% ee from benzaldehyde, and (*S*)-(2)-hydroxy-3-butenenitrile from acrolein in 95% ee. Effenberger (1999) has given examples of optically active cyanohydrin, and stressed the role of solvents and biphasic conditions. The most important point brought out is that in organic solvents or biphasic systems, the chemical addition of HCN to the carbonyl compounds can be suppressed, resulting in high optical yields. Several (*R*)- and (*S*)-cyanohydrins have been made with yields sometimes approaching 99%; the best results are realized in organic solvents or two-phase systems. It is also possible to carry out transhydrocyanation to avoid hazards of handling HCN (Griengl *et al.*, 2000).

The enzyme catalysed epoxidation of alpha-olefins like 1-octene with oxygen to the optically active epoxide provides an interesting example of a four-phase system (de Bont *et al.*, 1983). The hold-up of the organic phase may be 2-4 % and the presence of biosurface active agents leads to the creation of a large liquid-liquid interfacial area; the liquid droplet size becomes smaller than the gas-liquid diffusion film thickness.

Bruggink (1996) has given an account of how the production of cefalexin, which is the largest cephalosporin in the market, can be converted from a ten-step process based on benzaldehyde and penicillin into a six-step process where biocatalysis is involved in three steps. The wastewater stream, containing 30-40 kg of unwanted materials in the conventional process, has been substantially reduced. Similarly, Van Loon *et al.* (1996) have given details of fermentation processes for cleaner and cheaper compared to the process practised so far.

Rasor and Tischer (1998) have brought out the advantages of enzyme immobilization. Examples of penicillin-G to 6-APA`, hydrolysis of cephalosporin C into 7-ACA`, hydrolysis of isosorbide diacetate and hydrolysis of 5-(4-hydroxy phenyl) hydantom are cited. De Vroom (1998) has reported covalent attachment of penicillin acylase (EC 3.51.11) from E.Coli in a gelatine-based carrier to give a water insoluble catalyst 'assemblase' which can be recycled many times, and is suitable for the production of semi-synthetic antibiotics in an aqueous environment. The enzyme can be applied both in a hydrolytic fashion and a synthetic fashion. 6-APA was produced from penicillin-G; similarly, 7-ADCA was produced from desa acetoxycephalosporin G, a ring expansion product of penicillin G.

The role of reversed micelles in the manufacture of fine chemicals with enzymes also needs to be assessed and analysed. An outstanding example is lipase catalysed interesterification to produce cocoa butter substitute from readily available cheap materials (Luisi, 1985). This example of reversed micelles is sometimes referred to as a colloidal solution of water in organic systems. A number of water insoluble alkaloids, prostanoids, and steroids have been subjected to useful transformations (Martinek *et al.*, 1987). Peptide synthesis has also been conducted. The advantages of two liquid phases are retained to a very great extent; the amount of water can be manipulated to gain advantages from an equilibrium viewpoint.

Regioselective introduction of oxygen into alkanes has been realized giving alkanols, alkanediols, and alkanoic acids. Even toluene, xylene, etc. can be converted to the corresponding benzyl alcohols in liquid-liquid systems. Seip *et al.* (1993) have shown how glycolic acid can be biocatalytically oxidized to glyoxalic acid using the soluble enzymes glycolate oxidase and catalase as catalyst. The well-known example of oxidation of glucose, with glucose oxidase and catalase, to gluconic acid, can be cited as an industrial process.

4-Oxo *iso*phorone has been reduced stereospecifically at the C=C bond by Bakers' yeast, after which this product is chemically reduced at the sterically less hindered 4-oxo group to give (4*R*, 6*R*)-4-hydroxy-2,2,6-trimethylcyclohexanone, a useful building block for the synthesis of (3*R*, 3'*R*)-zexanthis.

Crocq *et al.* (1997) have synthesized trimegestone through Bakers' yeast mediated reduction of a ketone (this material is a new progestomimetic molecule for the treatment of postmenopausal diseases). The key step of the multistep synthesis is the chemo-, regio- and almost stereospecific bioreduction of a triketone to the desired alcohol.

Archelas and Furstoss (1998) have given details of how epoxide hydrolases can be used to hydrolyse an epoxide to its corresponding vicinal diol. These hydrolases have been shown often to be highly enantio- and regio-selective, thus allowing both the epoxide and the diol to be prepared at high enantiomeric purity. Thus, styrene epoxide with *Aspergillus niger* can give pure (96% ee) (*S*)-epoxide and (*R*)-diol (51% ee); *Bacillus sulfurescens* gives (*R*)-epoxide (98% ee) and (*R*)-diol (83% ee).

Many lipases exhibit Sn-1,3 specificity in triglycerides and can therefore be used to regioselectively interesterify positions 1 and 3 of a natural glyceride. Fats with improved spreadability, cocoa-butter equivalents, highly digestive triglycerides, etc. have been made (Schmid and Verger, 1998).

(*S*)-chloropropionic acid (CPA), an intermediate required for optically active herbicides (e.g. dichloroprop., mecoprop.) of considerable industrial importance, which replaces the racemic material, can be made by using esterase and lipase enzymes for selective hydrolysis of CPA esters, e.g. *iso*butyl ester. Zeneca has commercialized a process on a relatively large scale (approaching 2000 tpa) through a different approach, involving an enzymatic dehalogenation process that produces (*S*)-CPA and lactic acid, which are easy to separate. *Pseudomones putida*, NCIMA 12018, was found to be a robust organism that is able to grow in the presence of a relatively high concentration (>100 mmol) of CPA in minimal growth media; the substrate can be cheap glucose. A whole cell approach was adopted as being most cost-effective; a proprietary cell-drying process was also developed (Taylor, 1998).

The cross-linked enzyme crystal (CLEC) technique of Altus Biologics, Massachusets, USA, is getting increasing recognition as an economical process. Here enzymes are purified as protein crystals and then cross-linked with agents such as glutaraldehyde. CLECs have the same catalytic activity as the purified enzyme, but are also stable at relatively high temperatures, extremes of pH, and in organic solvents. α-Phenylethyl alcohol has been resolved using a CLEC based on lipase from *Pseudomonas capacia* (Davies, 1998).

In the recent past extremozymes, e.g. bacterium *Pyrococcas furiosus* the 'flaming fireball,' which can work at temperatures even above 100 °C, have opened up new vistas (Rice, 1998).

The manufacture of fine chemicals and speciality polymers by biocatalytic routes invariably involves the use of organic solvents as the reaction media due to increased solubility of non-polar substances. Nonaqueous enzymology has gained a lot of importance and is particularly suitable for the modification of precursors of pharmaceutical compounds and fine chemicals, which are invariably poorly soluble in water. Enzymes are often more stable in organic solvents and can catalyse reactions that are impossible or difficult in water. Enzyme selectivity may also differ from that in water and can change or even reverse, from one solvent to another. Thus, 'medium engineering' can play a vital role (Carrea and Riva, 2000). The presence of water may hydrolyse acetic anhydride and sensitive esters like halosubstituted acetic acid esters. Carrea and Riva (2000) have given many examples of practical importance. Chemoselective acylation of 6-amino-1-hexanol, at the OH group, rather than the NH_2 group by the chemical method, with hydrolases has been cited. Enantioselectivity of subtilisin in the transesterification of racemic 1-phenylethanol (phenyl methyl carbinol) varied from 3% in methyl acetamide to 61% in dioxane. Use of lipases for the regioselective esterification of primary and secondary hydoxyl groups of monosaccharides has been exploited. Carrea and Riva (2000) have given a reasonably good account of large-scale applications, drawn from patents and allied literature. Enzymatic resolution of racemic amines or aminoalcohols, by BASF, seems to be an example practised on the largest scale. Here enantioselective acylation is carried out in the presence of a hydrolase with an ester, where the acid component bears a fluorine, nitrogen, oxygen, or sulphur atom in the proximity of the carbonyl group. Thus, ethyl methoxyacetate has been used.

The role of biocatalysis in two-phase systems has many parallels with the subject we have covered under extractive reactions. It appears that a two-phase system was originally considered for transformations of water insoluble substances like steroids. Now, a series of treatises are available which teach us that the maximum value of the apparent equilibrium constant for a second-order reaction in a two-phase system can exceed the equilibrium constant for the pure phases taken separately by a factor of over 10^4. This strategy of using two phases enables us to prevent enzyme denaturation, while pH conditions favourable to enzyme stability and optimality can be maintained without adversely affecting the reaction thermodynamics. Unlike immobilized enzymes on a solid matrix, no activity is lost. The two-phase strategy can be seen in the example of the α-chymotrypsin catalysed synthesis of *N*-benzoyl-L-phenylalanine ethyl ester from ethanol and the corresponding acid, where in water the yield of ester is negligible, but in a two-phase system the yield approaches 100 %. Rich *et al.* (1996) have reported α-chymotrypsin catalysed peptide synthesis. Klibanov (1986) has indicated that many enzymes can be used advantageously for a variety of reactions (e.g. phenol to dihydroxybenzenes).

An important problem in emulsified organic-aqueous systems is that of scale-up, which is concerned with the realization of stable emulsions and the separation of phases after the reaction. The use of biphasic membrane systems that contain the enzyme and keep the two phases separated is likely to solve this problem. In the case of *S*-naproxen an ee of 92% has been demonstrated without any decay in activity over a period of two weeks of continuous operation. A number of examples of biocatalytic membrane reactors have been provided by Giorno and Drioli (2000) and include the conversion of fumaric acid to L-aspartic acid, L-aspartic acid to L-alanine, and cortexolone to hydrocortisone and prednisolone.

Lopez and Matson (1997) have demonstrated how enzyme membrane reactors can be used to enhance the productivity and practicality of some biotransformations. This is achieved by improving the substrate/enzyme contact, by enzyme 'immobilization' in a simple and reversible way, and overcomes the inhibitory role of reaction products. This concept has been applied to an enzyme mediated resolution of a racemic mixture used in the production of a drug, diltizem. There is a fairly comprehensive coverage of activities from bench scale to a production scale of 75 tpa of the intermediate for diltizem. The intermediate is the racemic mixture of the two (±)-*trans* enantiomers of the methyl ester of 4-methoxy-3-phenylglycidic acid (MMPG). MMPG has two chiral centres, at the 2- and 3-position of the oxirane ring. Hence, four stereoisomers, *viz.* the (2*R*, 3*S*)-*trans*, (2*S*, 3*R*)-*trans*, (2*R*, 3*R*)-*cis* and (2*S*, 3*S*)-*cis* diastereomers exists. Sepracor Company of USA have succeeded in the enzymatic resolution of the (±)-*trans* MMPG racemic mixture, instead of via an expensive chemical method. It is necessary to begin the synthesis of diltizem with optically pure (2*R*, 3*S*)-*trans* MMPG. In the Sepracor process this pure isomer is prepared by a biphasic substractive resolution process wherein an enzyme in aqueous solution stereoselectively hydrolyses the poorly water soluble (2*S*, 3*R*) ester of the corresponding water soluble acid, preferentially leaving the major part of the desired (2*R*, 3*S*) ester in the organic phase. An ingeneous method of inhibition by a product, *p*-methoxyphenylacetaldehyde due to decarboxylation of the free acid in the aqueous phase, was overcome through a bisulphite adduct. The engineering of this reaction system was done through a multiphase extractive membrane reactor. Toluene was used as a solvent.

Chemo-enzymatic epoxidation of unsaturated fatty acids with aqueous H_2O_2 has been conducted with considerable success and here we have a remarkable situation that undesirable ring opening of the epoxide does not occur. Excellent activity and stability has been realized with Novozym 435, a *Candida antartica* lipase B immobilized on polyacryl. This enzyme is readily separable, can be used several times without loss of activity, and has a turnover of more than 2,00,000 moles of products per mole of catalyst (Bierman *et al.*, 2000).

There is a need for rigorous analysis of such systems. The thickness of the water film may be less than or comparable to the diffusional film thickness and this has particular relevance to reactions that have mass-transfer limitations. The effect of local pH has to be assessed properly. The mechanism of uptake of the substrate also needs elucidation.

If one of the species is anionic and we need to transport it to the organic phase, then a phase-transfer catalyst may be employed. Consider the example of benzyl penicillin where the reaction between phenyl acetic acid and the penicillin carboxylate ion, with penicillin amidase as a catalyst, is relevant, and which at pH 4.5 – 5.0 is shifted in the desired direction. Here a catalyst like tetrabutylammonium halide works, and with chloroform as a solvent 60% yield can be realized in contrast to a yield of only 5 – 10 % in water.

Woodly and Lye (1998) have reviewed recent advances in improving biocatalytic processes via *in situ* product removal (ISPR). Through ISPR it should be possible to overcome problems associated with end-product inhibition, toxicity, thermodynamic limitations, etc. As an example, the condensation of glycoaldehyde with beta-hydroxypyruvate to give L-erythrulose was considered for different options of ISPR like ion exchange, heterocomplex formation, carbonaceous adsorbent, and phenylboronate reaction. Immobilization on Affigel 60 of boronates prevented the toxicity found with soluble boronates. In another example, a 30-fold improvement in the synthesis of the valuable pharmaceutical precursor fluorocatechol from fluorobenzene by *Pseudomonas pudita* HLZ was realized by adsorption of the toxic product on activated carbon in an external column, together with restricted feeding of the toxic raw materials to prevent co-adsorption.

The strategy of manipulation of the 'macro-environment' can be utilized for biotransformations. Thus, Zelinski and Kula (1997) have enzymatically reduced lipophillic ketones like 2-acetylnaphthalene using dimethylether of β-cyclodextrin in the organic phase. The use of cyclodextrin increases the solubility of the ketone by a factor of 147 resulting in high yields with excellent enantioselectivity.

Microemulsion media can be adopted for biotransformations; lipases have been used and large difference in rates of esterification, e.g. 1-pentanol vs 2-pentanol with oleic acid, have been observed (Stamatis *et al.*, 1993).

Enzymatic reactions have also been conducted in supercritical media.

While many virtues of enzyme catalysis need to be recognized, it should be realized that industrial enzymes can cost from US $ 10,000 to $ 11,000 per kg. Therefore, the enzyme catalysed production of chemicals that sell at US $ 1 to 5 per kg may not be economical even if the yield is 100 % and downstream cost is not excessive. Enzymes are easier to justify for pharmaceutical that sell at US$ 30 to $ 50,000 per kg. Even noble metal catalysts like 5% Pd on carbon cost about US$ 720 per kg.

Some of the industrial biocatalysts are nitrile hydralase (Nitto Chemicals), which has a productivity of 50 g acrylamide per litre per hour; penicillin G amidase (Smith Kline Beechem and others), which has a productivity of 1 – 2 tonnes 6-APA per kg of the immobilized enzyme; glucose isomerase (Novo Nordisk, etc.), which has a productivity of 20 tonnes of high fructose syrup per kg of immobilized enzyme (Cheetham, 1998). Wandrey *et al.* (2000) have given an account of industrial biocatalysis: past, present, and future. It appears that more than 100 different biotransformations are carried out in industry. In the case of isolated enzymes the cost of enzyme is expected to drop due to an efficient production with genetically engineered microorganisms or higher cells. Rozzell (1999) has discussed myths and realities of commercial scale biocatalysis. Myths like enzymes are too expensive, enzymes are too unstable, productivity is too low, redox co-factors cannot be recycled efficiently and enzymes do not catalyse industrially interesting reactions have been discussed with suitable examples.

Direct molecular evolution (DME) may well revolutionize the way we do chemistry (Affholter and Arnold, 1999). The ubiquitous perturbation-response algorithm of 'rational selection' has helped organisms (and their individual protein catalysts) to adapt to an incredible range of environments, from boiling acid from volcanoes to Antarctic ice fields. DME has resulted in the following improved properties: increased thermostability, increased activity in organic solvents, altered substrate specificity, increased enantioselectivity, increased activity, and increased gene expression. DME uses mutation and selection to identify and accumulate beneficial changes in protein function. It is very likely that DME will be used to improve already widely used hydrolases and many other industrial enzymes. The Maxygen group has developed a dual enzyme cellular pathway capable of converting atrazine and other triazines to a variety of commercially interesting intermediates.

Metabolic and enzyme engineering have received a lot of attention in academic institutions and are now being applied for the optimization of biocatalysts used in the production of a diverse range of products. Engineered microorganisms, even with non-native enzyme activities, are being used for novel products and process improvements for the production of precursors, intermediates and complete compounds, required in the pharmaceutical industry (Chartrain *et al.*, 2000).

4.5.3. Ultrasonochemistry

Sonic wavelengths in liquids are typically 0.1 to 100 nm, well beyond molecular dimensions. The sound acts as a source of vibrational energy, causing the molecules in the liquid to vibrate, which in turn compresses/stretches the liquids molecular structure. This type of movement 'tears' holes within the liquid structure to produce bubbles. Subsequently, due to the stresses within the liquid that are generated by the sound waves, the bubbles collapse. Chemical effects are due to the collapse phase of this cavitation cycle (i.e. the successive formation, growth, and implosive collapse of bubbles). Pestman *et al.* (1994), Mason (1998) and Cains *et al.* (1998) have reviewed this subject. The use of ultrasonics can even cause the course of reaction to change. For example, in the reaction between benzyl bromide and KCN in toluene in the presence of Al_2O_3, with mechanical agitation diarylmethane products are obtained by Friedel-Crafts attack on the solvent, whereas with ultrasonication benzylcyanide is obtained (Suslick, 1986).

Ultrasonics (u/s) can have one or more of the following effects:

- mechanical and dispersive effects on powdered solids,
- generation of free radicals,
- promotion of electron transfer, and
- removal of chemical and biological contamination from surfaces and liquids.

The reaction between 60% HNO_3, octanol, and 3-bromo-2,3-dimethyl propanol proceeds slowly under mechanical stirring at room temperature and gives quantitative yields of the nitrate only after 12 hours. By contrast ultra-sonochemistry (u/s) gives quantitative yields of carboxylic acids in just 20 minutes at room temperature (Pestman *et al.*, 1994).

Ultrasonics can activate inactive catalysts, as illustrated by the activation of extremely inactive Ni powder for hydrogenation purposes. Surface studies of the metal after sonication have indicated dramatic changes in surface morphology. The standard Raney Ni catalyst is substantially activated by sonication. Ultrasonics can also help in preparing impregnated catalysts, and can favourably influence enzyme catalysed reactions.

The use of sonochemistry to make a purer product is illustrated by the example of the Strecker synthesis based on the reaction of benzaldehyde with KCN and NH_4Cl in an acetonitrile medium at 50 °C. In this reaction, the desired 2-aminonitrile is $PhCH(NH_2)CN$, while PhCH(OH)CN and PhCH(OH)COPh are produced as by-products. By using Al_2O_3 and ultrasonics, a 90% yield of the desired product is realized compared to 64% with only stirring in the presence of alumina; only stirring, without Al_2O_3 gives a 6% yield and only ultrasonication gives a 23% yield (Mason and Phull, 1995).

The application of ultrasonics not only leads to the intensification of rates but also to the possible improvement of yields, and thus can make the process cleaner. Solid-liquid reactions hopefully stand to benefit most from the application of ultrasonics due to 'clean' surfaces, arising from the disruption of passivating layers on the metal surface. This may even enable the use of technical rather than pure-grade materials. Thus, Grignard reactions (which may, for instance, suffer from lattice defects), reductions with $LiAlH_4$, etc. are likely to be very favourably influenced (Gaskin, 1987). The Barbier reaction involving reactions between a ketone and an organic halide in the presence of Mg or Li, has been shown to benefit immensely through ultrasonification (Luche and Damiario, 1980). The Ullmann reaction, between a sodium salt of a phenolic substance and an alkyl/aryl halide, in the presence of copper, also stands to benefit from the application of u/s. Wan *et al.* (1992) have shown that hydrogenation of refined and bleach soya bean oil at 170 °C with 0.02% Ni catalyst and u/s gave much higher rates. The cost of applying ultasonics is expected to be low. The analysis of multiphase reactions (gas-liquid, solid-liquid and gas-liquid-solid (reactant or catalyst)) subjected to ultrasonification requires attention (Lorimar and Mason, 1987); the existence of the sonochemical hot spot has been reformed (Suslick *et al.*, 1986) near a collapsing vapour cavity. The possible use of this hot-spot as micro-reactor can be explored. Pandit and Joshi (1993) have successfully carried out the hydrolysis of fatty oils at ambient conditions, which otherwise require temperatures of the order of 240-250 °C and pressure of 8-10 atm, using sonification.

Similarly, reactions which are substantially enhanced by the use of PTC can be carried out even with reduced use of PTC with substantial enhanced rates of reaction as has been demonstrated by Sivakumar and Pandit (2000) in the case of conversion of benzamide to benzonitrile. In the case of *N*-alkylation of diphenylamine with benzyl bromide, in the presence of KOH as the anion source and PEG methyl ether as the PTC, some improvement in the rate has been observed. (Cains *et al.*, 1998). Metal catalysed hydrogenations, such as those based on Ni, Pd/C, and Ru/C also benefit from ultra-sound.

Electroorganic synthesis will be covered in section 4.5.4. It is appropriate, however, to make a reference here to the role of u/s in electroorganic processes. Atobe *et al.* (2000) have reported the effect of u/s in the reduction of acrylonitrile and mixtures of acrylonitrile and methyl acrylate. The selectivity for adiponitrile in the reduction of acrylonitrile was significantly increased under u/s irradiation with a power intensity over the u/s cavitation threshold (~ 600 cm^{-2}). This favourable influence of u/s can be attributed to the improved mass transfer of acrylonitrile to the electrode interface by the cavitational high-speed jet-stream.

The presence of a hot spot is known to generate free radicals. Thus, reactions that are initiated by the presence of free radicals can be carried out with less or no catalyst, as has been discovered in the case of isomerization of maleic acid to fumaric acid with an 3 to 16 fold increase in the isomerization rates at reduced catalyst (thiourea) concentrations (Muzumdar, 1988).

Pandit and co-workers have shown that scale-up may be possible on a more rational basis if cavitation is employed, and some data have been reported by Pandit and Mohalkar (1996), Mohalkar *et al.* (1999), Senthil *et al.* (1999), and Cains *et al.* (1998). A variety of reactors can be used, *viz.* the liquid whistle reactor, the Branson sonochemical reactor, the Pote reactor, etc. The principal factors affecting the efficiency of a hydrodynamic cavitation reactor are irreversible loss in pressure head and turbulence and friction losses in the reaction rates.

Gogate and Pandit (2000a,b) have successfully demonstrated that hydrodynamically generated cavitation is the most attractive and energy efficient for both physical and chemical transformations, while it is also amenable to scale-up using conventional chemical engineering scale-up criteria. They have analysed cavitating conditions through bubble/cavity behaviour. Their experimental results have been scaled up to 200 litres capacity vessels, for instance, for microbial cell disruption, where only 10% of the energy is used in comparison with conventional methods. The chemical reactions they studied under hydrodynamic cavitation conditions have been scaled up to 50 litres capacity and include KI decomposition, which is two to three times more energy efficient than using ultra-sound; sulphur digestion to produce $Na_2S_2O_3$ from Na_2SO_3 along with a surface active agent where synergism results; benzamide conversion to benzonitrile where the rates are intensified five- to six-fold; and hydrolysis of methyl benzoate to benzoic acid with a ten-fold rate increase.

4.5.4. Electrochemical processes

Electrochemical processes are particularly well suited for the manufacture of fine chemicals in view of their high specificity (almost comparable to that offered by enzymes), the smaller number of steps required, adoption of milder conditions, lack of scale-up problems, avoidance of effluents, etc. The ease with which oxidation and/or reduction can be carried out with the practically mass-free 'clean' electrons makes electrochemical processes well suited for such jobs, including paired synthesis; in effect, we use electricity as a 'reagent'. Consider a standard chemical oxidant like manganic or chromic sulphate. Here, a stoichiometric amount of the reduced salt will be formed the disposal of which can be a serious problem. If we adopt an electrochemical process, then the reduced salt is converted into the desired oxidized salt.

Plate and frame and capillary gap cells are widely used (Goodridge, 1987). A recent development, which has provided dimensionally stable anodes (e.g. Ru coated Ti anode for caustic soda/chlorine cells), coupled with the availability of outstanding membranes based on perfluoro-compounds and the availability of small gap electrolytic cells, have further brightened the prospects of adopting electrochemical routes. The utilization of solid polyelectrolytes is yet to be exploited (oxidation reactions may be a good starting point). In addition, the corrosive conditions that are sometimes encountered in electrochemical processes can be overcome by using engineering plastics like polyphenylene sulphide as a material of construction. Such materials can be injection moulded to make cell parts, pump heads, etc. and enable replacement of expensive materials of construction based on Zr, Ti, etc. Proper seals and separators are also available. The earlier promise of electrosynthesis was to some extent thwarted by economical and technological hurdles but now most of the hurdles have been overcome as economical, well engineered, commercial electrolysers have become available on the market (Vreeke *et al*, 1998).

Many expensive reductions such as the Birch reduction of naphthalene to isotetralin, benzene to cyclohexene, with metallic sodium and liquid ammonia, or reduction with $LiAlH_4$, can generally be carried out electrochemically at much lower cost and under safe conditions. Electrochemical processes allow fluorinations to be carried out without using fluorine gas. Conducting polymers have been made by electrochemical processes which operate under ambient conditions, and the polymer can be synthesized, doped and shaped in film form in a single step.

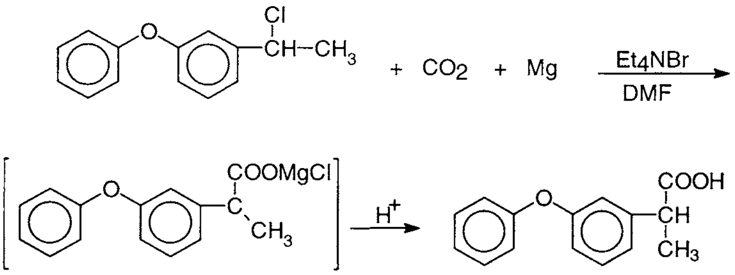
When organic substances are sparingly soluble in aqueous solutions several methods can be adopted, based on strategies covered earlier in this chapter. For example, hydrotopes can be used and miceller and microemulsion media can also be adopted. Many advantages that we have cited earlier may well be relevant in electrochemical processes. Thus, in the outstanding example of the electrohydrodimerization of acrylonitrile to adiponitrile, quaternary ammonium salts increase the solubility of acrylonitrile and, in addition, produce a relatively aprotic layer adjacent to the electrode, which inhibits the reduction of acrylonitrile to propionitrile. Adiponitrile gets extracted into the acrylonitrile phase. Anodic cyanation of naphthalene, which involves aqueous cyanide solutions, has been carried out using phase-transfer catalysts like tetrabutylammonium hydrogen sulphate (organic phase: methylene chloride). Emulsifiers have been used for hypochlorination of allyl chloride. Anodic cyanations of dimethoxybenzenes and anisoles have been conducted using miceller solutions; cationic micelles are beneficial, whereas anionic and non-ionic micelles inhibit the reaction (Laurent *et al.*, 1982).

A second liquid phase may be deliberately employed in an emulsified form to gain advantages similar to those cited earlier for organic processes. Such two-phase systems, and even two-phase enzymatic reactions, allow both the electrochemistry and organic chemistry to take place in their optimum medium. Further, the aqueous phase allows acidity to be controlled in the organic medium and the organic phase allows the desired intermediate product to be extracted to improve yields.

A number of useful reviews have appeared in the course of the last few years, and a number of chemicals, such as vitamin C, β-tetralone, hexafluoropropylene oxide, piperidine, glyoxalic acid, pinacol, *p*-hydroxypropiophenone, sebacic acid, *p*-anisaldehyde, maltol/ethyl maltol, Rose oxide, linalool, perfluorooctanoic acid, hydroquinone, etc., that are commercially made (or can be made) electrochemically have been catalogued.

Electrochemical hydrogenations have also been reported. Partial hydrogenation of unsaturated oils, in a solid polymer electrolyte reactor operating at 50-80 °C and ambient pressure, gives much lower amounts of the unwanted *trans*-isanes as compared to the conventional catalytic process. 3M company, USA, practises the Simons electrochemical fluorination process, and mathematical models of 3M's new, undivided, flow-through, bipolar reactor design suggest that industrial scale units having as many as 25 unit cells, with each unit cell having an area of up to 4 m^2, may be feasible (Vreeke *et al.*, 1998). Conversion of *p*-cresol to *p*-hydroxy benzaldehyde by using *tert*-butyl ether and subsequent facile cleavage and recycle of *iso*butylene has been reported (Genders and Pletcher, 1996). Givaudan-Roure, Switzerland, has a commercial unit for converting toluene derivatives, notably *p-tert*-butyl toluene, to the corresponding benzaldehydes in the liquid phase using pyrolusite. Regeneration of the carrier, a slurry of $MnSO_4$ and $Mn_2(SO_4)_3$ in 55% H_2SO_4, takes place in an undivided electrochemical reactor that consists of a bipolar stack of 5 – 40 plate electrodes with surface areas that can vary from 1 to 40 m^2. Givaudan-Roure has 18 elements with a 20 m^2 anode surface area. This route is commercially attractive, as the vapour-phase catalytic process, particularly for *p-tert*-butyl toluene, does not give high yields. The side-chain chlorination to give benzal chloride derivatives and subsequent hydrolysis leaves chlorine residue, which is not acceptable in pharmaceutical and cosmetic applications (Vreeke *et al.*, 1998). Electrochemical oxidation of naphthalene to naphthaquinone is industrially used. The potential of adopting an electrochemical process appears to be great and even *iso*cyanates and their derivatives can be made through this strategy (Jansson, 1984). Anderson (2000, p286) has cited an example of a commercial flow-cell technology for making fenoprofen where magnesium is used as a sacrificial electrode and a phase-transfer catalyst is employed (see Eqn.(20)).

Walsh *et al.* (2000) have reported the reduction of *L*-cystine hydrochloride to *L*-cysteine hydrochloride and have covered laboratory kinetics to process modelling for several m^2 cells.



(20)

Paired synthesis (combination of a cathodic and an anodic electrosynthesis in one electrochemical cell) has attracted a lot of attention, but a persistent caveat has emphasized the difficulties in separation when undivided cells are used. Recently BASF, Germany, has announced the commercial production of two important products, phthalide and *p-tert*-butyl benzaldehyde, as a paired synthesis (Putter and Hannebaum, 2000). The cell is a unique design, the capillary-gap-cell or disk-stack-cell using bipolar graphite plates as electrodes. Both chemicals have been produced separately. The electrochemical production of *p-tert*-butyl benzaldehyde from *p-tert*-butyl toluene leads to hydrogen as (cathodic) by-product. By using dimethyl phthalate, an ingeneous combination is realized as hydrogen reduces the phthalate to phthalide and two moles of methanol released fix *p-tert*-butyl benzaldehyde as an acetal. The economic advantages of this paired synthesis are obvious in terms of reduction in capital cost and energy cost.

Steckhan *et al.* (2000) have brought out an elegant example of the same product being formed on the anode and the cathode (200% cell). This principle has been accomplished by generating an oxidant, e.g. hydrogen peroxide or an oxidized tungstate, at the cathode, which then oxidizes the substrate to the same product as formed at the anode. A multi-mediated system was used. Hydrogen peroxide formation was catalysed by using either a water soluble cobalt porphyrine or a tris (1,10-phenanthrolin-5,6-dione) Ru(II) perchlorate complex as mediator, which is cathodically reduced to the corresponding hydroquinone (HQ). The HQ generates the H_2O_2 by reaction with O_2 from the air. The H_2O_2 is then used to oxidize bromide to bromine. Thus, bromine is formed at both electrodes. This oxidant is used to form 2,5-dimethoxy-2,5-dihydrofuran from furan regenerating the bromide. In this way, two electrons generate two molecules of a two-electron oxidation product, tantamount to a 200% process. The authors have realized current yields up to 190%.

Electrochemical oxidation and reduction can sometimes be manipulated to be stereoselective. Koop *et al.* (2000), in connection with the synthesis of one of the most potent coronary active compounds, nifedipine, where the configuration at the stereogeneric C_4-atom is important, have shown that anodic oxidation of a pertinent analogue in this category (4-phenyldihydropyridine) could give *R*-2 or *S*-2 with up to 90% ee and 98% ee, respectively. This ee depends on the supporting electrolyte, anode material, added base, and temperature, and appears to be partially due to a neighbouring group effect in the intermediate radical cation and/or adsorption of the intermediate at the anode.

Various designs of electrochemical reactors are available: traditional plate-in-tank designs; rotating electrode cells; static, porous, three dimensional electrode cells; and moving, three-dimensional reactors such as fluidized-bed electrodes. Filter-press cells have been used in organic synthesis, and electroregeneration of redox reagents is practised (Walsh and Robinson, 1998). Modular designs are also available, some examples being the Dished Electrode Membrane Cell; The Filter-Press Monopolar; FM; and Filter-Press Bipolar, FB. The reactors have a maximum current density of 5 Amp/m^2. Some typical examples of electrochemical processes in filter-press cells are the manufacture of monomethyl adipate, dimethyl sebacate, and 4-hydroxy mandelic acid; conversion of *p*-xylene to *p*-methyl benzaldehyde; and conversion of naphthalene to naphthaquinone with Ce (IV). In the latter case conversion of Ce (III) to Ce (IV) is done in Filter-Press Cells.

The chemical reaction engineering aspects have received some attention (see, for instance, Wendt, 1986, Goodridge, 1987), but much more needs to be done. Mass-transfer factors are usually quite important, as is evident from, for instance, the work of Wendt and Schneider (1986) on mediated oxidation of toluene with a Mn^{3+} based oxidant. We should make a systematic study of how mass-transfer coefficients can be improved through changes in the design of cells including turbulence promoters and circulation of electrolytes, how the second phase (liquid or gas) influences mass-transfer coefficients, etc. (Feess and Wendt, 1982; Alkire, 1985). The evolution of gas at the electrode can lead to a substantial increase in the mass-transfer coefficient as the bubble motion occurs within the mass-transfer boundary or just outside this layer. In addition, convective currents are set up due to bubble swarms. Dees and Tobias (1987) have adopted the limited current density technique of measuring mass-transfer coefficients at electrodes that are sectioned on the microscopic scale; the micro-mosaic electrode simulates a continuous surface, but contains a large number of electrically isolated electrode elements. This should allow a more complete study of the effect of evolution of gas at the electrodes so that a still better design of electrodes and the cell can be conceived. Problems of mass transfer in composite membranes also need investigation. New techniques are being developed for the above problems. Thus, a laser beam and photodioxide array combination has been used to obtain concentration versus distance profiles.

So far, uncatalysed electrochemical processes have had to compete with catalytic organic processes. There is considerable scope for a specific catalyst to be developed for specific organic electrochemical reactions. This implies reduced overpotential and acceleration of slow chemical rather than relatively fast charge-transfer steps (Jansson, 1984). Electrocatalysis depends on the chemical nature of the catalyst, which determines its adsorptive and fundamental catalytic properties, and on the morphology of the catalyst, which mainly determines its utilization. Long-term stability is a necessity (Wendt *et al.*, 1994).

4.5.5. Solid-supported reagents

There is a merit in considering the use of polymeric or non-polymeric (alumina, silica, zeolites, etc.) supports for reagents which are normally used in dissolved form. Problems with the removal of desired product from the reaction mixture may be overcome if the chemical reagent is to be covalently linked to an insoluble support, because then the product of the reaction will remain attached to the insoluble support and can simply be filtered from the reaction mixture. The use of a highly porous support also provides a large effective area for the reaction, and the presence of pores may constrain both substrate and reactant, and thus lower the entropy of activation. Several examples have been reported in the literature indicating that many reactions that are not possible in a homogeneous medium or give poor yields can be conveniently carried out with solid-supported reagents under mild conditions and with high selectivity. For rapid reactions a continuous column reactor can be considered to facilitate synthesis. Thus, insoluble supports may provide powerful 'handles' to facilitate synthesis. Leznoff (1974), McKillop and Young (1979), and Hodge and Sherrington (1980) have given exhaustive accounts of this subject.

Consider the case of protecting one of the groups in a polyfunctional compound like terephthaldehyde, which can form a cyclic ether with a supported reagent like (P)-C_6H_5-CH_2-O-CH_2-CH(OH)CH_2OH: only one -CHO group is converted into the ether, while the other -CHO group is available for other reactions. Subsequently, the cyclic ether can be cleaved with an acid catalyst. Similarly, consider the monoesterification of a dicarboxylic acid. Here, the use of an alumina or silica support may allow monoesterification. The reaction of a mixture of *cis*- and *trans*-1,2-cyclohexanediol provides yet another interesting example. By using supported phenylboronic acid, only the *cis*-isomer will react and form a chelate, whereas the *trans*- isomer will be free.

We have cited the case of epoxidation with peracids earlier in this book. A cross-linked polymethacrylic acid can, in principle, be treated with a sulphonic acid catalyst and H_2O_2 to give the peracid, which will allow epoxidation to be carried out in a convenient way, while the polymer can be reused. The key advantage is that the product stream does not contain an acid, which may be harmful in several ways.

Sukh Dev and co-workers (Singh *et al.*, 1979; 1981) have utilized this strategy for the oxidation of alcohols (e.g. steroidal secondary alcohols) containing acid labile groups (e.g. a cyclopropane ring or a ketal function) with pyridinium chromate on silica gel (Singh *et al.*, 1979). Reagents supported by silica gel have also been used to recover valuable compounds. Thus, semicarbazide-on-silica gel has been used to recover aldehydes and ketones from other neutral organic compounds (Singh *et al.*, 1981).

Metallic nitrates, supported on clays, have been used for nitrations and oxidations. Recent interesting studies involve nitration of 4-hydroxybenzaldehyde with Fe nitrate and K10 montmorillonite, in which nuclear nitration was preferentially realized and practically no oxidation of the aldehyde occurred. Even more interesting, simple addition of Fe nitrate to dealuminated or natural clay gave comparable or even better results. A 100% yield was realized at 60 ^{o}C with toluene as the solvent (Bekassy *et al.*, 1998).

Ogawa *et al.* (1998b) have shown how 1,4-butanediol to 1,16-hexadecanediol and 1,4-cyclohexanediol, adsorbed on silica gel, can be reacted with acetyl chloride to give nearly 100% selectivity for the mono-acyl derivative. The above examples give an indication of the versatility of this strategy in the manufacture of fine chemicals. There are, however, many aspects associated with the role of mass transfer, which have yet to be studied thoroughly.

4.5.6. Membrane reactors

It is useful to combine reaction and separation for equilibrium-limited reactions and also for consecutive reactions, particularly when the desired intermediate products undergo faster undesirable reactions. The concept of extractive reactions for equilibrium-limited and consecutive reactions has been covered in Section 4.2.1. Distillation column reactors provide yet another strategy.

Consider an equilibrium-limited esterification reaction. One way to drive the reaction to completion is to remove the water formed by the reaction selectively through a membrane. This can be an attractive strategy when higher temperatures are undesirable due to factors like colouration of the materials and formation of undesirable products even though these may be present at a low level. As another example, consider the air oxidation of cyclohexane or cyclododecane to cyclohexanone/-ol or cyclododecanone/-ol, where the product can undergo more facile oxidation to unwanted or much lower value products. Consequently, industrial processes operate at a level of less than 5% conversion. If a membrane can selectively remove cyclohexanone as it is formed, the problems mentioned above can be thwarted. However, selective polymeric membranes, which can work at oxidation temperature, have not yet been proved.

In many bioconversions, product inhibition is critical and this forces the transformations to relatively low concentrations, so if a membrane that selectively permeates the desired product could work in a 'dirty' environment, this would be very useful.

Kragl and Dreisbach (1996) have carried out the enantioselective addition of diethyl zinc to benzaldehyde in a continuous asymmetric membrane reactor using a homogeneous soluble catalyst, described in their paper. Here α,α-diphenyl-*L*-proline was used as a chiral ligand, coupled to a copolymer made from 2-hydroxy ethyl methacrylate and octadecyl methacrylate, which had a sufficiently high molecular weight to allow separation by ultra-filtration (U/F). The solvent-stable polyaramide U/F Hoechst Nadir UF PA20 retained more than 99.8% of the catalyst. The ee was 80 %, compared to 98 % for a noncoupled catalyst.

Hydrogenations involving consecutive reactions are common in the organic process industry and even in the hydrogenation of fats. In the fine chemicals industry we have examples of acetylenic (triple) bonds to be selectively converted to olefinic (double) bonds. Lange *et al.* (1998) have shown, for the comversion of the model substance 2-hexyne into *cis*-2-hexene, how catalytically active microporous thin-film membranes can accomplish 100% selectivity. This unusual selectivity is attributed to avoidance of backmixing.

Most solid-catalysed vapour-phase reactions operate in the temperature range of 200 – 600 °C. Many dehydrogenation reactions like propane to propylene, ethylbenzene to styrene, etc., which are part of this class of reactions, are equilibrium limited. Polymeric membranes cannot withstand the high operating temperatures, so inorganic membranes become a necessity. Saraco *et al.* (1994) have discussed this subject at length and have pointed out the hurdles. High costs, low permeability, synthesis of defect–free permselective layers, instability of membranes and catalysts, and sealing of membranes into modules are some key problems affecting commercial exploitation. There is a large disparity between typical rates of reaction and permeation. Space-times for commercial gas-phase catalytic and non-catalytic reactions are of the order of 0.1 to 50 seconds but no known or projected membrane has permeation rates that can match these rates of product formation (Keller and Bryan, 2000).

Tilgner *et al.* (1998) have reported three-phase hydrogenations with new microporous catalytic membranes. Here hydrogen is supplied directly to the active centres, avoiding the liquid phase, by having a spatial separation of the gas and liquid phase realized through a membrane catalyst. Improved activity, and, most likely, selectivity control can be realized through this strategy. It needs to be emphasized that this methodology is significantly different from the hydrogenation conditions where hydrogen is added on the same side of the membrane as the substrate.

The use of a second phase to derive several advantages, in the form of a second liquid phase, was illustrated in Section 4.3. In the case of the cationic ion-exchange resin catalysed reaction of phenol with methyl-*tert*-butyl ether to give *o*- and *p*-*tert*-butyl phenols, methanol is a product of reaction that reduces the rate of reaction, and also the extent of reaction, due to adsorption on the resin. Gokul Chandra and Sharma (1993) have shown that a stronger adsorbent for methanol, such as zeolite 3A and 4A, can increase the rate and the extent of the reaction. Subsequently, resin and adsorbent can be separated and the adsorbent can be regenerated and recycled. In the section on zeolites (Section 4.4.1) it was shown, for a specific reaction, how the presence of generated HCl affects the reaction and adding a zeolite makes a substantial difference.

In the recent past Adsorptive Chemical Reactors (ACRs), in a more rigorous way, have attracted attention. In these reactors the chemical reaction, with gaseous or liquid reactants, is carried out in presence of a solid adsorbent capable of selectively adsorbing the components of the reaction mixture. The reaction could be homogeneous or catalysed by the adsorbent or a deliberately added catalyst. This strategy may lead to higher selectivity for the desired product and higher conversions in an equilibrium-limited reaction. The adsorbent provides an extra degree of freedom for selectivity, by manipulating the concentration profile, and may have distinct advantages over reactive distillation and extraction with reaction. A fixed packed bed containing a mixture of a catalyst and an adsorbent may be used; the latter is periodically regenerated, say, by principles of pressure swing adsorption. This presumes that compatability exists and that protocols for regeneration of the catalyst, if required, do not clash with regeneration of the adsorbent. The regeneration of the adsorbent may be done by a desorbent or even a purge stream. A simulated moving-bed reactor configuration (see Section 6.4.4.3) can also be employed.

4.5.7. Adoption of supercritical conditions

The 'tuning' of solubility with a relatively small jump or fall in pressure can possibly bestow many benefits with respect to rates, yields, and selectivity. Reaction parameters can be changed over a wide range. Replacement of solvents with high boiling points by supercritical (SC) fluids offers distinct advantages with respect to removal of the solvent. SC fluids like CO_2 are cheap and environmentally friendly; the critical temperature of CO_2 is 31 °C and the critical pressure 73.8 atm (Poliakoff and Howdle, 1995). Eckert and Chandler (1998) have given many examples of the use of SC fluids. Alkylation of phenol with *tert*-butanol in near critical water at 275 °C allows 2-*tert*-butyl phenol to be formed (a major product when the reaction is kinetically controlled; 4-*tert*-butyl phenol is the major product, when the reaction is thermodynamically controlled). Cyclisation of *o*-benzoyl benzoic acid to anthraquinone, at 275 °C, with mineral acids as catalyst has been reported. Brennecke (1997) has brought out the advantages of SC CO_2 for 'green' chemistry. Two-phase reactions can be made single phase to avoid mass-transfer resistance. Downstream processing can be made easy for small molecules as well as large molecules. A small amount of a co-solvent may be added to the CO_2, typically intermediate in size and polarity between CO_2 and the target solute. The solubility of heavy organic solutes may increase by an order of magnitude. CO_2-loving perfluoropolyether surfactants, which form micelles in CO_2, are also known, and thus miceller catalysis can be realized.

Hydrogenation reactions have been studied in SC CO_2 as H_2 has very high solubility in SC CO_2. From an engineering standpoint batch hydrogenators can be replaced by continuous hydrogenators. For example, Roche carries out an industrial hydrogenation in a process for the manufacture of a vitamin, in which a 10,000 litre batch reactor has been replaced by a 40 litre SC flow reactor with a product output of about 800 tpa. Hydrogenation of *iso*phorone under SC conditions has been found to be advantageous over conventional methods.

Koch and Leitner (1998) have recently conducted the oxoreaction of 1-octene with CO and H_2, using a Rh-based catalyst, in SC CO_2. Fischer *et al.* (1999) have reported enhancements in selectivity by a factor of 4 to 18 with near critical ammonia, during Co- and Ni-catalysed synthesis of 1,3-diaminopropane. This is attributed to a higher concentration of ammonia at the catalyst surface.

An interesting example is photodimerization of *iso*phorone where the use of SC CO_2 increases the yield of the *anti*–dimer relative to the *syn*-dimer. Special polymers can be made by using SC fluids. Apart from SC CO_2, SC propane can be very useful and act as a convenient medium. Roche has also reported replacement of an expensive Rh catalyst with a cheaper Ru catalyst using a high-pressure application of hydrogen.

A variety of reactions have been conducted. Catalysts based on noble metals on Deloxan amino poly siloxane supports have been used. Hitzler *et al.* (1998) have reported alkylation of mesitylene with propylene or *iso*propanol in SC propylene or CO_2 using a solid acid Deloxan catalyst. Pesiri *et al.* (1998) have carried out selective epoxidation in SC CO_2 with transition metal catalysts (V, Ti, Mo) and *tert*-BHPO; high conversion and selectivity have been reported.

Scott Oakes *et al.* (1999a, b) have shown how adoption of SC conditions can lead to a dramatic pressure-dependent enhancement of diastereoselectivity. In the case of sulphoxidation of cysteine derivatives with *tert*-butyl hydroperoxide, with cationic ion-exchange resin Amberlyst-15 as a catalyst, 95% de was realized at 40 °C and with SC CO_2. By contrast, with conventional solvents no distereoselectivity was observed. Another example is the Diels-Alder reaction of acrylates with cyclopentadiene in SC CO_2 at 50 °C, with scandium *tris* (trifluoromethanesulphonate) as a Lewis acid catalyst. The *endo*:*exo* ratio of the product was as high as 24:1, while in a solvent like toluene it was only 10:1.

In a series of publications, Eckert and co-workers have shown the efficacy of carrying out a reaction in SC water and SC polar solvents, which might even dispense with the use of acid and base catalysts. Reference may also be made to a recent publication, which describes the acylation of resorcinol with acetic acid in a near SC acetic acid medium (T_c = 319 °C) without any catalyst; at 290 °C nearly 50 mol % yield was realized, which is close to the equilibrium value (Brown *et al.*, 2000).

Scott Oakes *et al.* (1999a) have reported a dramatic pressure-dependent enhancement of diastereoselectivity for sulphoxidation of cysteine and methionine derivatives by using SC CO_2 rather than conventional solvents. In the case of a derivative of cysteine, toluene/ methylene chloride gave a 50-50 mixture of stereoisomeric forms. With SC CO_2 and *tert*-butyl hydroperoxide, however, 95% selectivity for just one stereoisomer was realized.

4.5.8. Asymmetric synthesis

Optically active drugs now occupy 'centre' stage status and some agrochemicals like (*S*)-metolachlor, have also been introduced as optically pure isomers, so that the ballast of the unwanted isomer is avoided. Asymmetric synthesis is a topic of great interest in current research, and there is a steady flow of articles, reviews and books on almost every aspect of this subject. Table 4.8 lists examples of industrially important asymmetric synthesis.

Synthesis of optically pure compounds via transition metal mediated chiral catalysis is very useful from an industrial point of view. We can produce large amounts of chiral compounds with the use of very small quantities of a chiral source. The advantage of transition metal catalysed asymmetric transformation is that there is a possibility of improving the catalyst by modification of the ligands. Recently, olefinic compounds have been transformed into the corresponding optically active alcohols (ee 94–97%) by a catalytic hydroxylation-oxidation procedure.

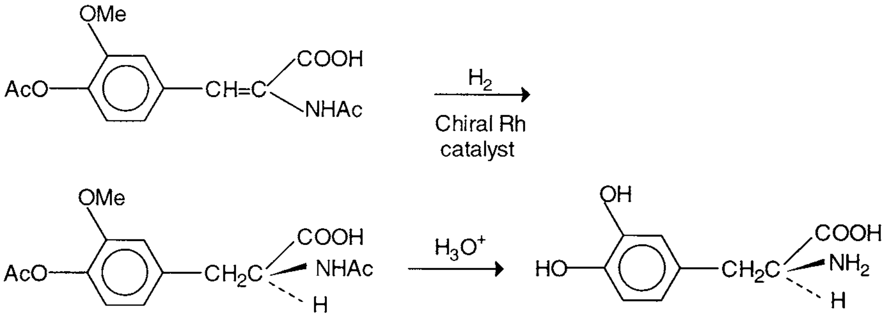
Table 4.8
Some examples of industrially important asymmetric synthesis

Synthesis	Reference
L-Dopa using chiral Rh based catalyst for hydrogenation	
Asymmetric hydrogenation in making dextromethorphan	
Asymmetric hydrogenation in making *L*-menthol	
Asymmetric hydrogenation of geraniol and nerol to citronellol	
Asymmetric reduction of α-ketoesters such as methyl and ethyl pyruvate	
Asymmetric hydrogenation of β-ketoester for a pancreatic lipase inhibitor using a modified Ni, *L*-tartaric acid and NaBr	Blaser et al. (1988)
Asymmetric hydrogenation in making a new calcium antagonist, Mibefradil (POSICOR)	Crameri et al. (1997)
Asymmetric hydrogenation of α-acylaminoacrylic acids with Dupont's DuPhOS catalyst	Stinson (1996)
Asymmetric hydrogenation for making S-metolachlor (Dual Magnum)	Blaser and Spindler (1997)
Asymmetric hydrogenation of diketene with Ru-(*S*)-BINAP to β-(*S*)-hydrolactone	Maxwell (1997)
Sharpless asymmetric epoxidation for glycidol, *S*-propanolol	Gao *et al.* (1987)
Asymmetric epoxidation of indene as a step in making the HIV protease inhibitor Crixivan (Indinavir)	Davies and Reider (1996)

4.5.8.1. *Enantioselective hydrogenation*

Catalytic asymmetric hydrogenation is a relatively developed process compared to other asymmetric processes practised today. Efforts in this direction have already been made. The first report in this respect is the use of Pd on natural silk for hydrogenating oximes and oxazolones with optical yields of about 36%. Izumi and Sachtler have shown that a Ni catalyst modified with (*R,R*)-tartaric acid can be used for the hydrogenation of methylacetoacetate to methyl-3-hydroxybutyrate. The group of Orito in Japan (1979) and Blaser and co-workers at Ciba-Geigy (1988) have reported the use of a cinchona alkaloid modified Pt/Al_2O_3 catalyst for the enantioselective hydrogenation of α–keto-esters such as methylpyruvate and ethylpyruvate to optically active (*R*)-methylacetate and (*R*)-ethylacetate.

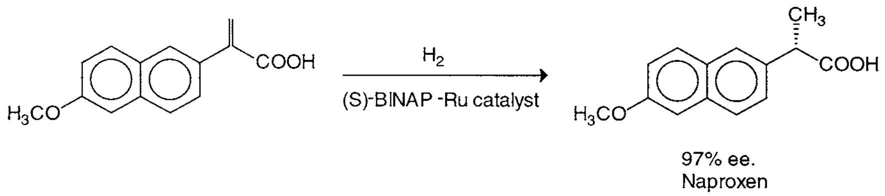
The modifier in these cases seems to generate enantioselective sites at the metal surface and helps the molecule to adsorb in a preferred fashion so that the formation of only one stereo- product is possible. There are several milestones that have contributed to this state-of-the-art technology. Discovery of Wilkinson's catalyst led to the feasibility of asymmetric hydrogen transfer with the aid of an optically active Wilkinson-type catalyst for L-DOPA (Monsanto's anti-Parkinson disease drug) synthesis (Eqn. (21)).



(21)

Some important aspects of L-DOPA synthesis are the high costs of making the DPAMP ligands, the high catalyst:substrate ratio (1: 20.000), and the robustness of the ligand/catalysts, which makes the usual poisoning problems rare. However, low oxygen levels (down to ppm level) during hydrogenation are crucial for maintenance of catalyst activity.

A potentially attractive route for the production of *S*-naproxen is based on the following reaction:

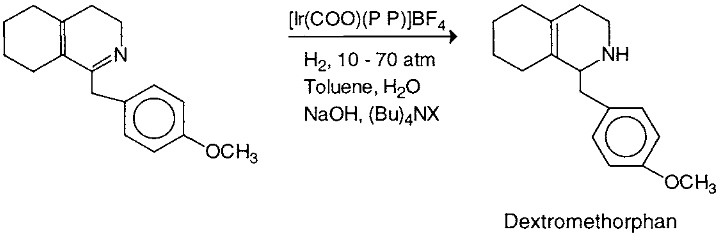


(22)

Asymmetric hydrogenation of geraniol and nerol in methanol at room temperature and an initial hydrogen pressure of 90-100 atm gives citronellol in 96–99% ee and in quantitative yields. The allylic and non allylic double bonds in the substrate can be clearly differentiated to obtain the product contaminated with less than 0.5% dihydrocitronellol (Mookherjee, 1997).

Roche carries out asymmetric hydrogenation of a β–keto-ester for a pancreatic lipase inhibitor using their Ru (II) BIHEHP catalyst. For scaling up, Roche decided to use a heterogeneous catalyst, modified Ni /L-tartaric acid with NaBr, since this was economically more attractive.

The asymmetric hydrogenation of C=N (Eqn. (23)), in contrast with C=O and C=C bonds, is much less developed. Hexahydro*iso*quinoline was used as its phosphoric acid salt. Iridium-ferrocenyl complexes were found to be satisfactory. After optimisiation, Meyer et al. (1997) were able to realize an enantioselectivity of 89% ee.



(23)

Crameri *et al.* (1997) have reported an asymmetric hydrogenation constituting an important step in the production of a new calcium antagonist, Mibefradil (POSICOR) (of Hoffmann-LaRoche). Pilot-scale synthesis of (*S*)-2-(4-flurophenyl)-3-methylbutanoic acid by the asymmetric hydrogenation of 2-(4-fluorophenyl)-3-methyl but-2-enoic acid with a [Ru (*R*)-MeOBIPHEP)$(OAc)_2$]-catalyst has been described. The hydrogenation was performed in a continuous mode in a cascade stirred-tank reactor system at a pressure of 270 bar. A large reduction in total reactor volume compared to the batch mode was realized.

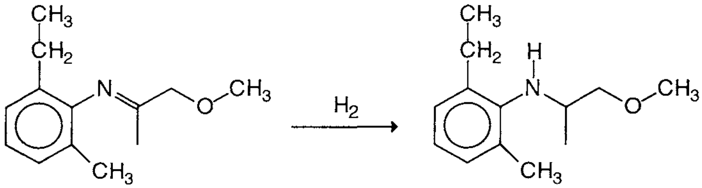
Eastman Chem. Co. has utilized a Ru(I) (*R,R*)-dimethyl-DuPhOS catalyst, based on single-isomer 2,5-dialkylphospholane ligands, to hydrogenate an enol ester such as 4-phenyl-1,3-butadien-2-yl acetate, to give 4-phenyl-3-buten-(2*R*)-yl acetate in 94% ee (Stinson, 1999).

Jacobsen (1999) has carried out carbomethoxylation of asymmetric epoxides. Thus, the carbomethoxylation of (*R*)-propylene oxide with CO and methanol yields 92% of (3*R*)-hydroxybutanoic acid in greater than 99% ee. Similarly, the reaction of (*R*)-epichlorohydrin gives 96% of 4-chloro-(3*R*)-hydroxybutanoic acid in greater than 99% ee. The catalyst consists of dicobalt octacarbonyl and 3-hydroxy pyridine. A continuous process for making enantiomeric 1-chloro-2-propanol has been suggested. With a suitable catalyst propylene reacts with O_2, water, cupric and lithium chloride to give 78% of (*S*)-1-chloro-2-propanol in 94% ee.

4.5.8.2. Enantioselective catalysis for agrochemicals: (S)-metolachlor

A fascinating example of enantioselective catalysis for agrochemicals is the production of a well-known herbicide of Novartis (formerly Ciba Geigy), metolachlor (Trade name: Dual

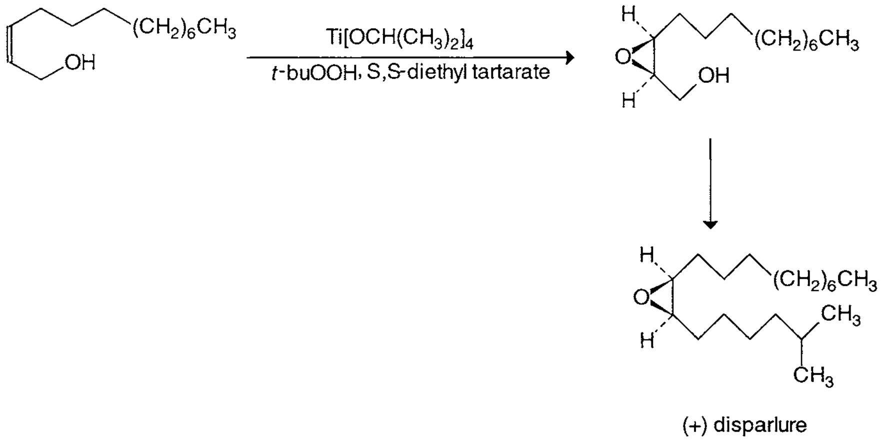
Magnum), which has been marketed for nearly 20 years. In 1997 the optically active form, (*S*)-metolachlor, has been introduced, also on a large scale, with a capacity exceeding 10000 tpa. Blaser and Spindler (1997) have given a fairly detailed account of enantioselective catalysis for this case and two other agrochemicals, (*R*)-metaloxyl and Clozylacon. Metolachlor is an *N*-chloroacetated, *N*-alkoxy alkylated *ortho*-substituted aniline. It has four stereoisomers, of which the two (1*S*)-enantiomers are biologically active. Ir based ferrocenyldiphosphines were used as catalysts for the hydrogenation of a key intermediate (Eqn. (24)). When optimized, one molecule of the Ir catalyst could produce more than 500,000 molecules of (S)-*N*-(2-ethyl-6-methyl-phen-1-yl)-1-(methoxymethyl) ethylamine within 2 to 3 hours. Catalyst performance was found to be good. A 50 ml autoclave, stirred with a magnetic stirrer bar; a 300 ml and 6.3 litre autoclave using a turbine impeller; and a loop reactor were used. The loop reactor showed the best results.



(24)

4.5.8.3. Asymmetric epoxidation

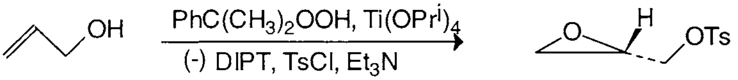
The enantioselective epoxidation method developed by Sharpless and co-workers is an important asymmetric transformation known today. This method involves the epoxidation of allylic alcohols with *tert*-butyl hydroperoxide and titanium *iso*propoxide in the presence of optically active pure tartarate esters, see Eqn. (25).



(25)

This is the first example of a reaction for which the presence of a chelating ligand was observed to facilitate rather than retard metal-catalysed epoxidation (Gao *et al.*, 1987). It was found that the use of molecular sieves greatly improves this process by removing minute amounts of water present in the reaction medium. Water was found to deactivate the catalyst. All these developments led to an improved catalytic version that allows a five-fold increased substrate concentration relative to the stoichiometric method. Sensitive water-soluble, optically active glycidols can be prepared in an efficient manner by an *in situ* derivatisation. This epoxidation method appears to be competitive with enzyme-catalysed processes and was applied in 1981 for the commercial production of the gypsy moth pheromone, (+) disparlure, used for insect control (Eqn. (25)).

Sharpless used asymmetric epoxidation as the crucial method in the preparation of the β-Adrenergic blocker, (*S*)- propanolol (Eqn. (26)).



(26)

ARCO chemical company has used this epoxidation method to produce (*S*)- and (*R*)-glycidol in 90% ee. Glycidols are useful building blocks for highly functionalized chiral targets.

Davies and Reider (1996) have given some details of the HIV protease inhibitor CRIXIVAN (INDINAVIR) for which (1S,2*R*)-*cis*-amino indanol is required. Indene is epoxidized enantioselectively, using the Jacobsen strategy (SS-salen Mn catalyst, aqueous NaOH and P_3NO), to (1*S*,2*R*)-indene oxide in a two-phase system, in which the OH^- concentration is controlled. Indene oxide was subjected to the Ritter reaction with MeCN, in the presence of oleum, and subsequent hydrolysis and crystallization in the presence of tartaric acid gives the desired amino indanol.

4.5.9. Microwave-assisted reactions

For fine chemicals there is a considerable scope in exploiting microwaves for what are referred to as 'kitchen' reactors. It is possible to conduct many reactions in an expeditious way through this strategy. Even reactions based on phase-transfer catalysts have been further assisted with microwaves. Sometimes even commercial microwave ovens, so common in kitchens, have been used. Domestic microwave ovens use a magnetron to generate microwaves with wavelengths of around 12.2 cm. Microwaves heat the liquid by inducing rotation of polar molecules to align and relax, at a given frequency. The energy dissipated during collisions leads to heating effects and non-nucleated super heating of the medium occurs, without boiling, leading to higher rates. A variety of reactions, such as polycondensation reactions, eco-friendly synthesis of dioxolanes, dithiolanes, and oxathiolanes, and synthesis of perfluorooctanoyl derivatives of fatty alcohols have been studied in microwave ovens. So far batch units, like the domestic versions, have been used, but progress is now being made in assembling on-line continuous-flow systems (Mingos, 1999; Cresswell and Haswell, 1999). For small-scale manufacture, involving fine chemicals produced in quantities of a few kg per day, there may be a merit in adopting this strategy.

4.5.10. Aprotic solvents

There are many instances where the use of aprotic solvents like dimethyl sulphoxide (DMSO), *N*-methylpyrrolidone (NMP), dimethylformamide (DMF), etc. may prove to be useful. These solvents are nontoxic, high boiling and have high polarity (e.g. the dielectric constant of DMSO is 48). DMSO has a high solvating ability towards cations, which increases the basicity and nucleophilicity of reagents in this medium. Thus, sodium methoxide is a much stronger base in DMSO than in methanol, since DMSO effectively traps Na^+ as $(CH_3)_2$-S^+-O^--Na^+, thus releasing the methoxide ion almost as a powerful naked ion. Many displacement reactions can be carried out in a facile way, which may not be easily possible otherwise or may give lower yields. For example, *para*-nitrochlorobenzene in a DMSO medium reacts with KF to give the corresponding fluorocompound; even *para*-chlorophenol reacts with CuCN in DMSO to give *para*-cyanophenol. Sankar and Sharma (1987) have shown that higher alkyl bromides can be converted to the corresponding chlorides in a DMSO/DMF/NMP medium. Conversion of benzyl chloride and *para*-chlorobenzyl chloride to the corresponding diarylsulphide with Na_2S in DMF has also been studied. Here, mass-transfer resistance has been found to be important. If the nitration mixture from *ortho*-dichlorobenzene, consisting of 2,3-dichloronitrobenzene and 3,4-dichloronitrobenzene, is reacted with NaCN/CuCN in DMSO only the 2,3-isomer reacts.

Harusava *et al.* (1987) have shown that in a tetrahydrofuran medium, halides like *n*-$C_8H_{17}Br$, $C_6H_5CH_2Cl$ (or Br), etc. can be converted in high yields to the corresponding nitriles with LiCN.

Gohring *et al.* (1996) have given a very useful account of the conversion of 2-chloropyrimidine to 2-cyanopyrimidine using different strategies. For example, the reaction in a DMF medium containing NaCN, at 80–90 °C yielded a considerable amount of tarry side products, resulting in a costly and troublesome work-up procedure; the yield was 66–70%. The use of a quaternized derivative of 2-chloro pyrimidine with trimethyl amine along with KCN in a CH_2Cl_2-water two-phase system, using tetramethylammonium chloride as the phase-transfer catalyst, at 25 °C gives an overall yield of 92%. However, a two-step procedure is involved. The disposal of the aqueous phase containing the quat is also a problem; it is not biodegradable. Gohring *et al.* (1996) finally recommended the use of dimethyl sulfoxide (DMSO) as a solvent (solubility of NaCN 1.8% w/w at 25 °C; in DMF it is only 0.11% w/w at 25 °C and hence DMF is not a good solvent), and DABCO (1,4-diazabicyclo [2.2.2.] octane) as the catalyst (it quickly forms the quat with the 2-chloropyrimidine).

Aprotic solvents may also dissolve a phase-transfer catalyst to realize higher rates/selectivities. Thus, in a claim, dichloronitrobenzene was reacted with KF in an aprotic solvent like 2-chlorotoluene, in the presence of hexadecyltributyl phoshonium bromide /crown ether/ PEG-dimethyl ether, to give chlorofluoronitrobenzene.

The selection of the solvent can affect a reaction drastically. In the Halex process for the conversion of 2,4-dichloronitrobenzene with KF to 2,4-difluoronitrobenzene, no reaction occurs in toluene as a solvent, presumably because KF has negligible solubility in toluene. In water, in which KF is highly soluble, no reaction occurs either, due to poor solubility of 2,4-dichloronitrobenzene in water and heavy solvation of fluoride rendering it ineffective. Dimethylformamide is suitable as the solvent; KF has some solubility, while the product KCl precipitates (Atherton and Jones, 1995).

The solvent can also affect regioselectivity. Consider *O*- vs *C*-alkylation of phenoxide ion with allyl chloride or bromide. In water, with allyl chloride the *O*- to *C*-alkylation ratio is 49:41; with phenol as a solvent it is 22:78; with methanol, dimethylformamide, and dioxane 100% *O*-alkylation is achieved. The selective solvation of the more electronegative *O* by the more protic solvents perhaps leads to some *C*-alkylations.

A reference to the role of solvents in biocatalysis was made in Section 4.5.2.

4.5.11. Additional strategies

Doraiswamy and Sharma (1984) have discussed many practical aspects of conducting multiphase reactions to derive some benefits.

Many substitution brominations are carried out with bromine. However, it may be advisable to resort to a cheaper material, BrCl, which can be easily made by reacting one mole of Br_2 with one mole of Cl_2. An additional advantage is that the outgoing product will be HCl and not HBr. Alternatively, in two-phase (liquid-liquid) reactions, we can additionally incorporate H_2O_2 so that HBr is converted *in situ* to Br_2 which then gets transferred to the organic phase. An analysis of such new systems is required.

Air Products, USA., has developed bis-(2-methoxy ethyl) aminosulphur trifluoride as a cost effective, safe, stable fluorinating agent, made by reaction of di-2-methylethylamine with sulphur tetrafluoride and trade named Deoxo-Fluor, which replaces the more temperamental diethylaminesulphur trifluoride. Thus, β-phenylethyl alcohol was converted to β-phenylethyl fluoride in 85% yield (Stinson, 1999).

We can recycle some by-products in a simple way. For example, when chlorosulphonic acid is used for sulphonation/sulphation, HCl gas leaves as a product the disposal of which may be a problem. Here, the dry gas can be reacted with SO_3 to give chlorosulphonic acid, which can be recycled. We are, through this methodology, also able to take care of organic materials leaving with the HCl gas. Likewise, when SO_2Cl_2 is used for chlorination, SO_2 can be recycled via reaction with Cl_2.

Many solid-liquid reactions are likely to benefit from the careful selection of the reactant (particle size, method of manufacture, etc.). Many reaction-crystallization systems may benefit from the use of seed crystals (see Section 5.4).

Gnaim and Sheldon (1995) have shown that an amine like di*sec*butylamine (0.8 mol% relative to phenol) at 70 °C gives a 90% yield of *o*-chlorophenol when phenol is chlorinated with sulphuryl chloride. Chlorination with tetraethylammonium chloride has been suggested to realize higher yields of the desired product. Thus, anisole gives 80% *p*-chloroanisole, lauraldehyde gives a 83% yield of α,α-dichlorolauraldehyde.

Sometimes it is possible to combine the manufacturing method with separation by a chemical method. Gaikar and Sharma (1987) have given a concise account of separations through reactions. Consider the case of making dixylylethane from *m*-xylene. Here, we can take a mixture of *m*- and *p*-xylene, which is much cheaper than pure *m*-xylene, and react it with acetaldehyde in the presence of $99^+\%$ H_2SO_4 as the catalyst. The selectivity for *m*-xylene is exceptionally high (Vasudevan and Sharma, 1983). In the manufacture of flurbiprofen, the separation of the unwanted product (dimeracid) from the wanted product can be organized by dissociation extraction using a stoichiometric deficiency of a base (Robinson and Cha, 1985).

Multistep batch processes are amenable to microprocessor-based control systems. Porte *et al.* (1982) have shown that the seven-step process for making (1-ethyl-2-pyrrolidinyl) (2-

methoxy-5-sulphamoyl)acetanilide can be subjected to the above control strategy resulting in further optimization. The key steps in the synthesis can themselves be assisted through new, computer assisted strategies, e.g. REKEST (Research for the Key Step of a Synthesis; Barone and Chanon, 1986). Wilson (1987) has shown how modelling can be helpful and has illustrated this through an example of the conversion of *A* into *B* which in turn gives an undesired, less volatile *C*. In normal practice, the reactor is followed by a distillation system. However, an integrally mounted distillation column on the reactor is desirable, as the desired, more volatile product *B* is removed while it is formed.

The strategy of intrinsic continuous process safeguarding merits further attention. Consider the example of Grignard's synthesis using highly flammable ether as a solvent. The use of a safer solvent mixed with a minimum amount of ether to reduce its vapour-phase concentration, along with a more predictable initiation, would be very helpful. We should ensure that in the vapour phase, explosive mixtures are not encountered.

4.6. CONTINUOUS PROCESSES

Continuous reactors are generally associated with large volume products. However, such reactors are also of special interest in the manufacture of fine chemicals if reactions are relatively fast and hazardous conditions are involved, requiring low inventory of reactants and/or products (e.g. Wittig reaction, manufacture of triphenylphosphine, nitration). Problems of heat transfer can sometimes be tackled by precooling the reactants (e.g. in the Wittig reaction where a small volume nozzle reactor is used). It is possible to select equipment that allows excellent micromixing. In loop reactors excellent mass transfer between gaseous and liquid phases and liquid-liquid phases can be ensured, while heat-transfer problems can be completely circumvented by incorporating an external heat exchanger in the loop. A number of sensitive hydrogenations involving chloronitroaromatics have been conducted in loop reactors with high selectivity with respect to the nitro group and negligible dehydrohalogenation. Loop reactors have also been considered for making *tert*-butyl hydrazine hydrochloride from *iso*butylene, hydrazine and HCl (Eichinger and Fiege, 1996; Anderson, 2000, p. 277).

Anderson (2000, p.278) has quoted the example of alendronate (of Merck) where the process involves phosphonation of H_2N-$CH_2CH_2CH_2COOH$ with H_3PO_3 and PCl_3 at 90 °C. In batch operations PCl_3 (boiling point: 76 °C) was difficult to charge and contain, while with the loss of PCl_3 by-products were also formed; the reaction is also very exothermic and posed safety problems. By using a small volume continuous reactor, both the stoichiometry and reaction temperature could be controlled. Anderson (2000, p. 282) has also quoted the example of cyclopropylamine manufacture (by Hüls) involving a Hofmann degradation reaction in a tubular reactor, fed with a suspension of cylclopropyl carboxamide, aqueous NaOH, and aqueous NaOCl, maintained at less than 15 °C for 20 minutes, and maintained at 80 °C for about 1 to 5 minutes. In order to allow good micromixing and prevent undesired by-products formation, a continuous pipeline reactor with static mixer can prove to be advantageous. Exothermicity can be controlled, as the heat-transfer coefficient for external cooling through a jacket is efficient. The Kowalski reaction has been conducted in a static-mixer reactor (Anderson, 2000, p. 282). Static mixers are also suitable for immediate quench or pH adjustment.

Strongly exothermic reactions can be conducted in reactors with a small tube diameter, operated continuously.

The advantages of continuous plants are associated with technology, safety, lower labour costs, and environmental and volume/cost requirements. Continuous plants are also of value to pharmaceutical customers as they give rise to inherently stable processes that can provide a product of consistent quality that is easier to validate. Furthermore, chances of contamination are much less than in batch plants (Higgins, 1998). Despite significant advances in batch plants, associated with better mixing, better heat and mass transfer, superior materials of construction, etc., there are many significant disadvantages. Batch plants are often constrained by heat- and mass-transfer capability. Cooling and heating can be very inefficient, particularly in glass-lined vessels. There is significant downtime due to filling, emptying, etc. It appears that quite commonly the actual reaction time in a reactor occupancy cycle is only about 30%, which results in under-utilization of the capacity of expensive equipment.

With respect to safety, the classical example of nitration of glycerine can be cited, for which, instead of a 1000 kg batch reactor, a small continuous plant, containing only 1 kg of material at any time, can be used.

Eastman Chemicals produces cyclopropylaldehyde from epoxy butene via 2,5-dihydrofuran and 2,3-dihydrofuran in a continuous plant for safety reasons. Another example cited by Eastman chemicals is that of the production of diketene from ketene, for which process technology dictates a continuous plant (Higgins, 1998).

In the production of 4,4'-bipyridyl from pyridine, the reaction between pyridine and metallic sodium in liquid ammonia is involved, followed by oxidation. By adopting a continuous reactor, the process has been made safer and yields have probably improved. For a hazardous chemical like diazomethane, even at a capacity of 60 tpa a continous plant has been adopted.

Consider the case of the production of peroxy esters (e.g. *tert*-butyl peroxy 2-ethyl hexanoate), based on the reaction between the corresponding acid chloride and the hydroperoxide in the presence of NaOH or KOH. These are highly temperature sensitive and violently unstable, and solvent impurities are detrimental in their applications for polymerization. Batch operations to produce even 1000 tpa will be unsafe. A continuous reactor can overcome most of the problems and claims have been made for producing purer chemicals at lower capital and operation cost; the use of solvent can be avoided. Continuous reactors can produce seven to ten times more material per unit volume than batch processes. Since the amount of hazardous product present in the unit at any given time is small, protective barrier walls may be unneccessary (Kohn, 1978).

Marynowski (1987) has given an example of nitration in a narrow tubular reactor that can withstand very high pressure, while heat transfer is greatly facilitated. If, during a nitration, large volumes of NO_x are produced, then the volume of the reactor can be reduced by having two consecutive zones, separated by a disengaging vessel. If a large amount of heat is evolved (e.g. when oleum is used and water of reaction, on dilution, causes large heat evolution) continuous reactors are also helpful.

A continuously operated multistage reactor may offer advantages due to overcoming problems associated with thermodynamic equilibrium. Thus, in making imides by the reaction of ammonia with molten anhydride (e.g. phthalimide from ammonia and molten phthalic anhydride), a multistage sparged reactor gives a product of high purity, containing a negligible amount of unreacted anhydride, and with a very much lower water content (Bartholome *et al.*, 1978).

In the Grignard reaction, which is very important in the manufacture of a variety of fine chemicals, the continuous reactor for production of the reagent consists of a column of magnesium particles through which a solution of the organohalogen compound in an ether-class solvent is passed. The continuous mode of operation reduces side reactions, particularly Wurtz-type coupling, which make many reactions impractical.

For transesterification/esterfication, continuous reactors may be more attractive than batch reactors. This is particularly true if a distillation-column reactor can be adopted, as it tends to use a much lower ratio of reactants to drive the reaction to the desired degree of conversion, entailing lower energy lost. Even when metal alcoholates are used these can be recycled, eliminating problems faced in batch plants. Relative process costs may well approach 50% of those in batch plants. Higher purity, less plant down time, better process control, and improved yield are other attractive features of continuous plants (Braithwate, 1995).

Continuous reactors have limited flexibility compared to batch reactors, which have the versatility to accommodate changes of products – an important feature of fine chemical manufacture.

In some cases we may benefit from adopting a semi-continuous mode of operation, e.g. to a batch of one reactant we continuously feed the other reactant, while removing a volatile product continuously. An example where this is advantageous is the production of ethyl-4-pentenoate, $CH_2{=}(CH_2)_3(CO)OEt$ from allyl alcohol and triethyl orthoacetate, $CH_3\text{-}C(OEt)_3$. Continuous addition of allyl alcohol to a batch of triethyl orthoacetate and continuous removal of the produced ethylalcohol (and some allyl alcohol) by distillation resulted in high yields of the dersired ester ethyl-4-pentenoate. By contrast, if allyl alcohol and triethyl orthoacetate were reacted in a batch-wise manner the product consisted of a 1:1 mixture of the desired ester and the undesired ester (Anderson, 2000, p 279; Bollyn and Wright, 1998).

There are instances where the reflux temperature decreases with conversion of the reagents, and exothermic reactions may even lead to hazardous runaway conditions. In such cases it may become necessary to optimize an addition sequence of reagents to avoid unwanted exotherms. Anderson *et al.* (1997) have given a practical example for an important intermediate in making the drug monopril.

In some pharmaceutical operations we may benefit from operating a specified part in a continuous mode and collect the material in a holding vessel for subsequent isolation and drying as a discrete batch.

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5. Process Development

5.1. INTRODUCTION

Process development is a set of research, design, and engineering activities, accompanied by economic studies, which transforms a recipe for carrying out a synthesis in the laboratory into an industrial process that is environmentally friendly, fulfilling safety and good manufacturing practice (GMP) regulations, and profitable, in sum 'the best' process. When seeking 'the best' engineers mean 'the cheapest over the lifetime of the plant' from both an investment and operational viewpoint, whereby reliability of operation at a satisfactory risk level must be warranted. The original recipe is usually modified during process development.

Selection of the most advantageous methods of product isolation and purification and effluent treatment, the most suitable sequence of operations, and the best full-scale equipment are the essence of process development. Basic parts of process development are *process design*, *process engineering*, and *scale-up* procedures. Process design involves determination of all items necessary to construct a plant and/or to run the process, including piping, instrumentation for process control, auxiliary operations, and equipment. Process engineering is a set of activities that leads to the specification of process equipment that is most suitable for processing mixtures with a predetermined composition. Scale-up involves undertakings aimed at finding how to carry out reactions/operations at a large scale, while preserving performance indices (yield, selectivity, product quality, etc.) achieved at small scale. Therefore, the desired output of a scale-up effort is the data needed to reach this aim rather than search for a better production process at the scale investigated. The most significant part of process development is scale-up of reactors or those equipment items of which the performance at full scale is difficult to predict sufficiently accurate, *i.e.* the risk associated with these predictions is considered large.

Process development for fine chemicals differs from that for commodities, mainly because:

- batch processing is predominant,
- usually it is required to adjust the process to the existing equipment of the MPP, possibly slightly modified, and
- often there is a need to produce increasingly large batches of high purity products (for testing biological activity of pharmaceuticals and agrochemicals) during process development.

Batch processing often results in irreproducible procedures (e.g. in batch crystallization), which are difficult to describe in terms of mathematical equations used in the design of full-scale plants. Moreover, batch processing requires large inventories of, often hazardous, materials. In combination with the limited heat-transfer capabilities of batch reactors, this makes the manufacture of fine chemicals less safe than the production of commodities.

Procedures often must be limited to the existing equipment in spite of recommendations drawn from unrestricted optimization considerations. Moreover, introducing a new product into the market quickly and ahead of competitors can sometimes be more important and profitable than realizing the lowest manufacturing costs. The best process must be selected from a subset of all process options and thus can be quite far from the global process optimum.

The need for high quality products from the early stages of process development forces scale-up of the process under conditions of incomplete process knowledge: Unexpected 'mysterious' scale-up effects, which result from this (at least partial) ignorance rather than from the nature of the process, are often encountered. Moreover, procedures applied for the preparation of products for biological (especially clinical) tests cannot easily be modified during process development due to regulatory reasons (GMP procedures), despite the fact that these changes could improve the process. Therefore, process development must be planned well to anticipate changes, and one must consider the need for increasing batch sizes of the product as an important objective of scale-up efforts. We agree with Basu (1998) on his statement:

> "People involved in process development should focus on the long-term vision of developing a cost-effective approach, and less on the short-term issues with making chemicals. It is easy for the process development team to lose the focus and get immersed in such short-term issues."

Until about the second World War chemical processes were developed in an evolutionary way by building plants of increasing size and capacity. The capacity of the next plant in the series was determined by a scale-up factor that depended mainly upon experience gained from scale-ups of similar plants. Due to a lack of predictive models for chemical processes and operations, processes had to be scaled up in many small steps. This procedure was very expensive and the results unreliable. Therefore, large safety margins were incorporated in scale-up procedures, which often resulted in a significant unintended overcapacity of the designed plant.

The progress in formulation of predictive models enhanced the scale-up factors, enabling extrapolation directly from miniplants to full-scale plants with an acceptable risk. This is particularly important since delays in entering the market can cost millions of dollars. Therefore, in the fine chemicals business profits that can be achieved by earlier implementation of the process must be balanced against losses arising from incomplete knowledge of process details during the whole period of process development. Despite the progress in predictive modelling there are still steps that require testing on an intermediate scale (e.g. batch crystallization and extraction), although the room for direct extrapolation has increased considerably. Returns to smaller scale experiments are also often needed.

Section 5.2 gives an overview of the stages involved in process development. The very basic data for process development are those on the chemistry of all process steps and the market prognosis. Both are essentially beyond the scope of this book, although Chapter 2 contains some information on the proper choice of the chemical route. Scale-up procedures are crucial for the reliability of industrial plant operation and minimization of the technical risk in process development. A general approach to scale-up problems is presented in Section 5.3. Some guidelines on scale-up of basic separation/purification operations are also given in Section 5.3. Although the cost of reactors does not constitute the major proportion of the total investment, the reactor is usually the most unreliable piece of equipment, and its operation can influence the operation of the whole plant heavily. Therefore, procedures for scale-up of reactors using modern techniques are discussed in more detail separately (see Section 5.4). Elements of reactor design and operation, which are the essence of modern scale-up of chemical reactors, are presented in Section 5.4 with the emphasis on kinetics (the basis of predictive models for chemical reactors), mixing, and safety. Criteria for the selection of the reactor type and mode of operation are also presented also in Section 5.4.

5.2. STEPS IN PROCESS DEVELOPMENT

Figure 5.2-1 illustrates the iterative and interactive nature of process development for fine chemicals. As shown, a process is evaluated at any stage to decide whether to continue or to stop process development and abandon it. In the development of fine chemistry processes, the sequence of steps is often laboratory-miniplant-commercial production. It must be emphasized that in process development for fine chemicals efforts in various sectors, including process design, are often made in parallel and not necessarily in sequence.

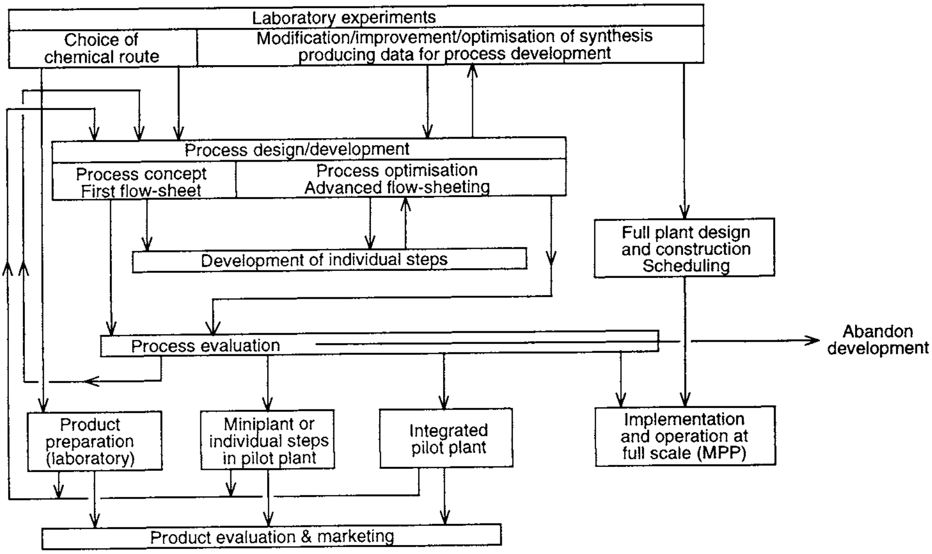

Figure 5.2-1. Steps in process development.

5.2.1. Laboratory studies

The starting point for any chemical process is the choice of the chemical route based upon literature studies and preliminary laboratory experiments. The 'most' promising route is the one characterized by the following:

- the possibility to manufacture a product characterized by strictly specified purity and impurity profile must be provided,
- raw materials must be available, and stability of their supply should be provided,
- toxicity and hazards of materials to be handled in the process should be as small as possible,
- waste streams and their toxicity should be minimized, degradability of these streams should be as high as possible,
- the process must not be blocked by valid patents or legal constraints (e.g. environmental regulations),
- reactions to be carried out must be controllable and selective in various respects (chemo-,

diastereo-, enantio-, regio-, stereoselectivity),

- separation and purification of the product must be as easy as possible.

For pharmaceutical products, the synthesis route is usually established very early on because of drug registration procedures carried out with governmental agencies, e.g. the Food and Drug Administration (FDA).

The product must be specified as early as possible although the final specification often differs from the preliminary one. For pharmaceuticals specification might be delayed because of the need to perform biological studies. Those studies are necessary to complete the evaluation of the product quality. In search of raw materials one has to evaluate their quality (and impurities profile), potential price (planning to obtain raw materials in excess of the project requirements is often useful since price can decrease by orders of magnitude if larger quantities are ordered), and hazards associated with handling them. Co-operation with potential suppliers to develop means for shipping, handling, and storing of raw materials is recommended.

At the laboratory stage, data on substances involved and their mixtures must be gathered: material properties, physicochemical data, ecological and toxicological data, costs of raw materials and intermediates, an estimate of product price, energy and equipment costs, etc. These data are needed in simulation programs and to determine toxicity, safety, and impact on the environment. The data on toxicity, degradability, and safety are required by the authorities to execute an approval procedure for the plant.

In the early stages of development, laboratory experiments are usually carried out using pure raw materials and glass equipment. The very first target of the laboratory investigations is the choice of the chemical route. Laboratory studies are carried out continuously throughout the whole period of process development. In later stages they are aimed at elimination of unacceptable or critical reagents[1] (because of safety, ecology, or technical reasons), search for better solvents (e.g. carcinogenic benzene and environmentally unfriendly halogenated solvents should be avoided), better reaction conditions, more active and selective catalysts, less troublesome separations, more efficient purification, etc. Solvent selection is of particular significance: by using solvents one can increase yields, 'liquefy' many solid reactants for easy contact with each other, facilitate transport of reaction mixtures between equipment items, and enable easy absorption of reaction heat (especially when carrying out the reaction under reflux). Laboratory studies should also be driven at the determination of the kinetics of the main reactions and the dependence of conversions and selectivities on operating conditions. Modern design-of-experiments (factorial design) procedures have been proven to help in minimizing the number of experiments with simultaneous uniform covering of the whole range of process conditions. These methods of experiment planning tend to replace traditional investigations that rely on studying the influence of one process variable only while keeping the others constant.

Synthetic chemists often focus on products of high quality, no matter how these are

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[1] Unacceptable reagents, e.g. (1) solvents and reagents with flame point < 200 °C (diethyl ether, carbon disulphide, acetaldehyde) - dangerous due to inflammable and explosive potential; (2) ethanedithiol - stenching odour, environmentally unfriendly; (3) peracids (e.g. *m*-chloroperbenzoic acid) - shock sensitive and highly explosive material; (4) HN_3 - toxic and explosive. Critical reagents, e.g. (1) sodium cyanoborohydride -produces HCN and H_2 when contacted with acids, requires special handling; (2) chromium(VI) compounds for oxidations - disposal problems, heavy-metal contamination likely; (3) *tert*-amines (e.g. tri-ethylamine) - non-biodegradable (see Ching-Pong Mak *et al.*, 1997).

obtained and at what cost. Therefore, despite their deep knowledge and extended experience the usefulness of information gained is very much limited as far as process development and scale-up is concerned. We agree with Agam (1994) who wrote:

> 'Often, the chemist tends to report: "Here is the process. These are the starting materials and reaction conditions. The product is obtained (analytically determined) with a good yield. Let the engineers deal with the rest of it from now on". This attitude may cause serious damages and losses. Until the chemist himself is confident that all the chemical, technological and economic aspects of the developed process meet the required criteria, his work is not finished.'

Below, a list is given of (dis)recommendations and pitfalls for laboratory experiments:

- a round reaction flask with bath cooling/heating is unsuitable for scale-up; use a cylindrical reactor equipped with a properly selected agitator (e.g. a marine propeller for suspensions, a turbine stirrer for additions in case of fast reactions, an anchor stirrer for better heating and cooling, etc.) of controlled and measured speed of rotation; breakers (sheets for sensors also act as breakers) must be present in the reactor to prevent vortex formation (considered vigorous agitation by chemists),
- dosing of reactants on the liquid surface should be avoided, especially in case of fast reactions (add reactants below the liquid level, preferably near the stirrer),
- measuring concentrations only at the end of experiments produces results that are often almost useless for process development and scale-up; concentrations versus time profiles for key components of the reaction mixture should be measured and a temperature-time profile recorded; the rate of gas evolution, if any, should be measured over the reaction period; analyse the reaction mixture before it is left overnight, before the reaction is started the next day, and after the pre-set temperature in the reactor has been reached; this will prevent misleading conclusions concerning the time needed for completing the reaction,
- density and viscosity of the reaction mixture (both needed for evaluation of heat removal from a full-scale reactor) versus time should be observed; dramatic changes in viscosity are of particular informative importance,
- observe any uncommon behaviour in the course of the reaction: unexpected gas evolution, uncontrolled change in the speed of rotation, solid precipitation (when), temperature runaways, change of colour, deposition on surfaces, etc.,
- check whether the course of the reaction, the final yield, and the product quality depend on the speed of rotation, concentrations in a dosed stream, and rate and location of additions; the rate (feeding time) should not be adjusted to the heat-removal capability in the laboratory only; the speed of rotation usually affects heterogeneous processes such as gas-liquid, liquid-liquid, liquid-solid and gas-liquid-solid reactions,
- measure heats of reaction and other caloric properties of the reaction mixture or estimate them; in this respect the value of reaction calorimetry can hardly be overestimated,
- determine the influence of conditions on crystallization or precipitation that accompanies the reaction (solvent, concentrations, rate of cooling, seeding of the liquor, speed of rotation, and rate of feeding) on crystal quality (impurities content, crystal shape and size, agglomeration of crystals, and filterability); solids should be easy to filter off,
- after the precipitation/crystallization procedure has been fixed, measure filtration rates at various pressures; observe changes in filter cake during drying and washing; measure an approximate cake thickness and area of the filtration device; observe cracks, colour, and stickiness of the filter cake, determine dry mass content before drying, determine brittleness

of crystals during centrifugation, determine the impurity content versus the method (piston washing or reslurrying) and number of washings, trials of dewatering; be aware of the fact that all the information above can become useless if conditions of solid formation change,

- observe the heat sensitivity of mixtures and products, especially during batch evaporation, batch distillation, and batch drying; determine the Hickman and Embree (1948) index[2] describing the thermal stability; find out whether mixtures/products are sensitive to air, pH, etc.

Mostly, these data are not recorded since the laboratory chemist does not know that the information is needed. This information is, however, of great importance for people involved in process development. Collecting these data during laboratory experiments will save engineers repeating time-consuming procedures. Furthermore, the laboratory operating procedure is not aimed at the best laboratory process but at the collection of basic data for the extrapolation of the process, *i.e.* its scale-up. A chemical engineer should be part of the laboratory team to identify difficult operational issues and the need for new equipment, and to develop preliminary models, prepare a preliminary cost estimate for the process, etc.

Complementary to the recommendations above concerning studies on chemical reactions are guidelines regarding the choice of separation processes (Agam, 1994):

- first separate the most plentiful component: try to carry as little material as possible through the process; in a complex system, first separate the basic essential product,
- minimize, as much as possible, the number of stages of the separation (to minimize unavoidable losses of the material in any stage, to shorten the production cycle, and to decrease investment),
- in choosing between investment in energy (heating or cooling) and addition of ingredients (e.g. solvent for extraction) it is preferable to opt for the former (otherwise more additional equipment and more effort to recover the solvent will be required, and up to 10 – 15 % of the solvent can be lost to the surroundings),
- wherever possible, avoid high pressures or extreme temperatures (expensive equipment); if there is no choice, high temperature and pressure are preferable to extremely low temperature and high vacuum (except when dealing with poisonous substances that can escape outside equipment),
- separate and isolate poisonous and corrosive materials as early as possible,
- difficult separations (more expensive than others) should be carried out at the end of the work-up (less voluminous steps are done at the end),
- minimize addition of a solvent if needed (cost, losses, equipment volume, time and costs of recovery should be taken into consideration),
- when screening alternative routes for chemical reactions do not only consider yields and selectivities but also other issues (separations, environmental aspects, etc.).

There is a great number of separation and purification processes to choose from in process development, but classical separations such as crystallization, filtration, drying, liquid-liquid extraction and distillation are still predominantly used. For solid products crystallization, filtration, and drying are the first options although vacuum distillation and extraction combined with the other techniques are also possible. For liquid products, liquid-liquid

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[2] $D = t{\cdot}k/k_{\mathrm{ref}}$ (decomposition rates at temperature T and T_{ref}); $0.02 < D < 10^{12}$; Hickman and Embree index $Dh = \ln D$; Dh = 12-14 for hydrocarbons C_4-C_8.

extraction and distillation are mainly utilized. One of the first steps in the selection of the separation technique is the examination of equilibrium data (Cusack, 1998a,b).

Figure 5.2-2 presents typical equilibrium curves. The first system (Fig. 5.2-2a) follows Henry's law. Absorption and stripping (for solvent regeneration) are separations that can be successfully carried out for such systems. The smooth curve of the type in Fig. 5.2-2b suggests that distillation and stripping (e.g. for removal of organic components from wastewater) would be efficient separations in this case. Equilibrium curves of the type shown in Fig. 5.2-2c are characteristic of close-boiling components of the mixture. Distillation can be used for separation of such mixtures, but would require large distillation columns and/or high reflux ratios. Therefore, extractive distillation and liquid-liquid extraction are the most commonly used techniques in this case. Azeotropes as shown in Fig. 5.2-2d make separation by simple fractionating distillation impossible. Extractive distillation, azeotropic distillation (with the addition of an auxiliary component), pressure-swing distillation, liquid-liquid extraction, and reactive distillation are techniques that can be effective for separation of such systems.

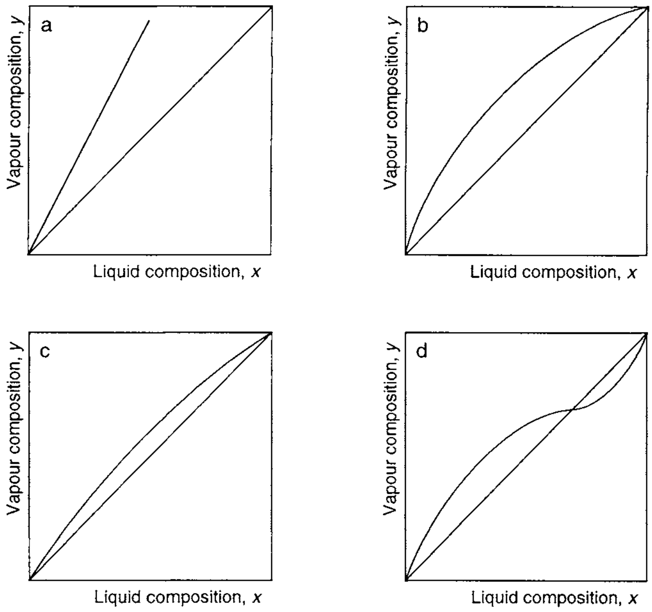

Figure 5.2-2. Typical vapour-liquid equilibrium curves; a) system obeying Henry's law; b) regular system; c) system of close-boiling components; d) azeotrope.

Freedom in process design is greatest at this stage of development, while the cost of error elimination is smallest (see Fig 5.2-3). Therefore, downscaling and extension of laboratory investigations in later phases of development is common practice. Compared to large-scale studies, laboratory work is less expensive by orders of magnitude and less sensitive to mistakes.

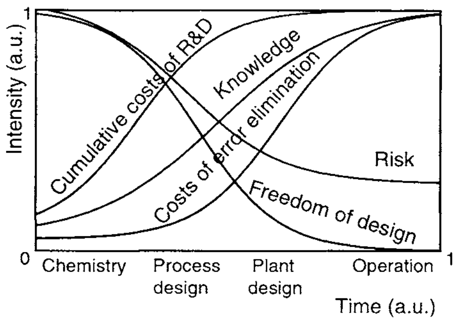

Figure 5.2-3. Characteristic features of process development.

5.2.2. Conceptual design

Based on the data collected in the first laboratory stage, a process concept is developed and the first economic analysis is performed. Conceptual process designs are prepared to identify promising options and areas to be covered with experimental work in both the laboratory and semi-technical plant scales to decrease the risk of scale-up. Particularly the necessity of investigations on the influence of recycle streams and their purification is determined based on conceptual designs. This allows accounting for the effect of accumulation of impurities in process streams on process performance. Preliminary plant flow-sheets are prepared using commercially available programs. Many flow-sheets will be eliminated for regulatory, technical, or economic reasons. After comparison of various process options, the best ones will be selected for further studies. Making conceptual designs is the first step in process optimization. If possible, the 'best'[3] version of the process for further development should be chosen as a basis of this design. Extended investigation of several variants at larger scales should be avoided. Of course, research can lead to modification, but this should not happen when the process is studied at a larger scale. Any process correction at the large-scale stage is more costly by orders of magnitude (see Fig. 5.2-3).

When seeking the best version of the process it is advisable to consider the technological principles that have been formulated by Bretsznajder *et al.* (1973):

- maximize gradients of potentials for reaction or separation (the largest possible temperature, pressure, and concentrations of reactants, the largest concentration gradients in multiphase systems),
- utilize raw materials as much as possible (the cheaper reactant should be used in excess, carry out operations countercurrently wherever possible, beat equilibria by withdrawal of product or use of reactant in large excess, adopt reaction conditions that are unfavourable for undesired side reactions, quench a process in the most wanted state, regenerate reagents),

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[3] The 'best' process means the optimal one. It is difficult to optimize the process under conditions of incomplete knowledge. Finding the optimum not only requires the necessary data but also creativity to compose the most promising version of an almost infinite number of processes leading to the desired product(s).

- maximize the degree of energy utilization (regenerate heat, countercurrent operation),
- utilize equipment as much as possible (recirculation, minimization of pressure drop, reduction of resistances of the process),
- in case of contradiction between any of the above principles try to find a solution of 'technological reserve'.

The waste-disposal situation must be recognized in more detail at the conceptual stage. Based upon preliminary estimates one should propose waste-disposal facilities (incineration for flammable materials, sewage treatment plant, and solid waste disposal site). Regulations might have impact on changes in synthetic or separation/purification routes. Processes that produce large amounts of salts or aqueous solutions containing materials that are difficult to degrade biologically should preferably be replaced by cleaner processes.

Outsourcing should be considered at this stage to replace one or more process steps with purchasing or custom synthesis. This might be particularly advantageous for technologies the company is not familiar with (e.g. membrane processes or operations under supercritical conditions). Criticality of the intermediate, certainty of deliveries, cost, secrecy, etc. should be taken into consideration when contemplating outsourcing.

Physicochemical and material data necessary for making the conceptual design should be provided by the laboratory. The missing data should be estimated using methods that are described in many books, see e.g. Reid *et al.* (1989). There are also many data banks commercially available. Some of them are listed in Tables 5.2-1 and 5.2-2, others are incorporated in computer programs for process simulations (see exemplary programs in Table 5.2-3). The reader can find more information about such computer programs in supplements (SOFTWARE DIRECTORY) to *Chemical Engineering Progress* that are published every year.

5.2.3. Development of individual steps of the process

Individual process steps identified in a conceptual design (reactors or separation/purification units) are studied experimentally in the laboratory and/or by computer simulation (see simulation programs as given in SOFTWARE DIRECTORY or Computational Fluid Dynamics (CFD) programs for studying fluid dynamics, such as PHOENIX, FLUENT, and FIDAP).

Table 5.2-1
Data banks; physical and thermodynamic data; compiled by Berger (2001)

Data bank	Supplier
DETHERM	Dechema, Germany
DIPPR	Brighton Young University / AIChE, USA
PPDS2	Technical Database Services, USA
ChemSage	GTT Technologies, Germany
DDB (Dortmund Data Bank)	DDBST GmbH, Germany
HSC Chemistry (thermodynamics only)	Outokumpu Research DY, Finland
Multiflash	Infochem Computer Services Ltd., UK
NIST	NIST (National Institute of Standards and Technology Laboratory), USA
TAPP	ESM Software, USA

Table 5.2-2
Data banks; related to safety; compiled by Berger (2001)

Data bank	Supplier
MSDS (Material Safety Data Sheets)	Several
RTECS (Registry of Toxic Effects of Chemicals)	NIOSH (National Institute for Occupational Safety and Health, USA
ECDIN (Environmental Chemicals Data & Information Network)	Environmental Research Programme (EC)
The Accident Database (concerns incidents and accidents that really happened	IChemE, UK

Table 5.2-3
Simulation programs; compiled by Berger (2001)

Program	Supplier
ASPEN PLUS	Aspen Technology, USA
CHEMCAD	Chemstations Inc. USA
PRO/II, PROVISION & PROTIS	Simulation Science Inc., USA
ProSim	ProSim, France
HYSIM & HYSYS	Hyprotech Ltd., Canada
BATCHES	Batch Process Technologies, UK
SuperPro Designer	Intelligen, USA
BatchMaster	BatchMaster Software Corporation, USA
BatchDesignKit	Hyprotech, AEA Technology Engineering Software, UK
Batch CAD	GSE Systems, USA
Design II	WinSim Inc., USA
GPROMS	Process Systems Enterprise Ltd., UK
GPS-X	Hydromantic Inc., Canada
Chemical Workbench	Kinetic Technologies Ltd., Russia

Some operations usually only require a small amount of experimental work. For instance, for distillation columns the required scale-up information is either available from literature or can be easily determined in the laboratory unless complicating phenomena (e.g. foaming, deposition of unidentified species on cooled surfaces, etc.) have been observed. Batch distillation must be studied in more detail if heat-sensitive materials are processed. In contrast, reactors usually require pilot plant testing, especially if a satisfactory mathematical model is not available. The objective of experimental work at this stage is to minimize uncertainties originating from insufficient knowledge of the process step in order to make the scale-up risk of the operation acceptable. Table 5.2-4 gives some rules of thumb for deciding which unit operations need to be investigated at the pilot-plant scale. The use of technical grade raw materials, incorporation of recycle streams, and testing the influence of construction materials on process performance are of particular importance at this stage of process development. If problems with the individual separation/purification step remain severe despite extended studies on the operation, this might be indicative that reaction conditions should be altered or the catalyst modified.

Table 5.2-4
Rules of thumb to decide which operations require pilot-plant testing

Operation	Pilot plant required?	Comments
Reactors	Often yes	Direct scale-up from the laboratory to the full scale often possible for homogeneous systems.
Distillation	Usually not	Foaming or thermally unstable materials may become a problem. Solvent recovery must often be examined in the laboratory.
Evaporation, Heat exchange, condensing vapours	Usually not	May become necessary when processing thermally sensitive materials or if fouling of heat-transfer surfaces is possible.
Crystallization, filtration, drying	Almost always	Pilot studies are usually done using vendor equipment. Caution: batch crystallization may not be reproducible with respect to contamination and size distribution of the solid. Filtration and crystallization problems should often be studied simultaneously.
Extraction	Almost always	Large uncertainty with respect to the operation time will remain unless pilot studies are performed. Impurities in raw materials of technical grade and in recycle streams can heavily influence mass transport through interfaces and separability of phases.

5.2.4. Pilot- and miniplants

A pilot plant is built and operated in series or in parallel with studies of individual process steps if needed. There are several reasons for pilot-plant studies:

- manufacture of the product in quantities needed for biological (clinical) and formulation studies, and for market development if the product can not be manufactured at laboratory or miniplant scale in a reasonable time,
- confirmation of process feasibility, checking experimental results obtained in smaller scale equipment,
- generation of additional data for the design of the commercial plant, especially when the scale-up risk seems to be too large to proceed directly from the miniplant to the full-scale

plant (e.g. handling of solids, novel or difficult technology); solving scale-up problems, debottlenecking of equipment, and checking procedures for cleaning (joints, gaskets, dead spaces),
- examination of critical process steps and long term effects (e.g. safety procedures, catalyst aging, impurities build-up),
- determination of quantities and compositions of process effluents and testing methods for their degradation, validation of the measures to treat wastes,
- collection of corrosion data and testing/determination of construction materials,
- gaining operational process know-how (e.g. start-up and shut-down procedures, dynamic behaviour of the plant), working out procedures for handling (charging) highly hazardous materials, training of staff which is to be involved in industrial manufacture, evaluation of maintenance requirements for the final plant, testing control systems,
- validation of analytical procedures,
- demonstration of a new process.

If the product is to be used for pharmaceuticals the GMP rules must be obeyed during plant operation. All chemicals to be tested in clinical studies with humans must be prepared according to GMP. This leads to very detailed documentation since 'if you haven't documented it, you haven't done it'. All procedures for manufacturing and changes in procedures are subject to approval by quality control departments. This decreases the flexibility in process development. Products that are contaminated too much must be reprocessed according to the GMP guidelines. All equipment to be used in the pilot plant must be validated before use.

The construction and operation of complete pilot plants is very costly. For commodity chemicals the investment for a pilot plant is about 10% of the investment for the full-scale plant. Companies active in the fine chemicals business usually possess a number of equipment items of pilot-plant size on standby. This equipment can be easily assembled into the pilot plant according to the process flow-sheet under consideration. Hence, the construction of a pilot plant for fine chemicals is much cheaper than for commodities. However, costs are still significant, and therefore, there is a large incentive to use miniplants, often in combination with computer simulation of the process. The miniplant includes all recycle paths. It contains items that are often the same as those used in laboratory experiments. The equipment is usually standardized and can be reused in other miniplants, resulting in reduced investment costs and high flexibility. The miniplant is to be operated for a prolonged period and as such it is automated to a large extent. As it will serve to verify the mathematical model of the process the miniplant must be provided with appropriate control equipment including data-logging facilities. Usually the miniplant is located in a separate chamber so that explosion-proof operation is possible and safety requirements can be met easily.

5.2.5. Environmental and safety aspects of process development

Based upon laboratory and mini- or pilot-plant experiments process flow-sheets are prepared that also take environmental and safety aspects into consideration. Studies on these aspects are carried out in parallel with chemistry and engineering research in the form of so-called Integrated Process Development (see Heinzle and Hungerbühler, 1997).

Environmental aspects are very important in the development of a process concept. The formation of pollutants (everything that is not product is waste) should be prevented and efficient strategies for treatment of effluents should be developed. Sources of wastes are impurities in raw materials, unreacted raw materials, solvents and catalysts that have not been recovered, scrubbing solutions, by-products, purges caused by work-up of solvents, aqueous washing solutions, utilities (flue gas and ash from burners, boiler blow-down water and feed water treatment, cooling towers, etc.).

The following measures should be considered to decrease air pollution:

- use solvents of low volatility,
- do not use very toxic substances,
- attach vents to a liquid scrubber or absorber, an activated carbon adsorber, possibly a catalytic incinerator; for the former two methods regeneration of ab- and adsorbents is necessary.

In case of possible water pollution one should:

- limit the use of non-biodegradable materials,
- remove or destroy poisons (cyanides, heavy metals) first,
- then remove suspended solids (filtration, sedimentation, or flotation for coarse particles; coagulation and flocculation for fine particles), dissolved salts, dissolved or suspended organic materials,
- consider biological oxidation (destruction of organic materials), reverse osmosis (removal of both organic and inorganic pollutants), use of active carbon (organic contaminants).

Handling solid wastes can be done using incineration (ca. 1000 °C, formation of toxic dioxins and polychlorinated biphenyls possible at low temperature) or composting under anaerobic conditions after removal of glass and metals, and use compost as landfill or fertilizer.

The following areas must be covered when considering safety in process development at this stage:

Toxicity, *i.e.* the ability to injure living creatures:

- LD_{50}, the average lethal dose, which, when administered in a specified way to identified laboratory animals will kill 50% of them,
- LC_{50}, the average lethal concentration in the air that will kill 50% of the laboratory animals provided they are exposed to the vapours sufficiently long (specify),
- TLV, the threshold limit value, a safe, average concentration of the toxic material which can be withstood daily for eight hours a day,
- TDL, the toxic dose low, the smallest possible dose of the material causing poisonous effects, carcinogenicity, mutagenicity, or teratogenicity).

Hazard, i.e. the potential of the material to cause injury under certain conditions (flammability, explosion limits in air, ignition and autoignition temperatures, static electricity (explosions have occurred during drying due to static electricity), dust explosion, boiling point, fire protection (specification of extinguishers, compounds formed when firing), R&S (nature of special risk and safety precautions). Table 5.2-5 lists hazards associated with typical chemical reactions.

Storage and transportation, regulations concerning amounts allowed, packing, DOT (European AID/ADR), IATA and IMDG regulations (class, hazard, maximum quantity), safety codes, incompatibility of materials.

Risk, *i.e.* the probability that injury of a certain severity will occur under certain conditions, *safety*, *i.e.* the measures, procedures and conditions which will minimize the risk, and *loss prevention*, *i.e.* the systematic approach to preventing accidents and their consequences to people, equipment and environment.

Table 5.2-5
Hazards associated with typical chemical reactions

Reaction	Hazards
Oxidation	highly exothermic so temperature excursions possible, poisonous permanganates and bichromates sometimes used as oxidation agents (ecological problems)
Reduction and hydrogenation	exothermic reactions, hazard associated with use of hydrogen (high flammability, explosion possible)
Nitration	Combination with oxidation possible, both highly exothermic, compounds explosive when having more than one nitro-substituent
Chlorination	highly exothermic reactions, temperature runaways possible, high toxicity, corrosion problems, mixtures with oils and grease very hazardous because of explosivity of such mixtures
Fluorination	Extremely reactive element, difficult to control, problems the same as those with chlorine but strongly enhanced
Bromination	See chlorination but milder
Sulphonation	Use of concentrated sulphuric acid or oleum, high corrosivity
Neutralization	Exothermic but easy to control, corrosivity sometimes a problem
Esterification	Hazardous if flammable solvents are used
Amination and ammonolysis	Exothermic, ammonia is flammable and toxic gas, special attention required due to high pressures and temperatures at which these processes occur
Methylation	Toxic methylating agents (dimethyl sulphate, methyl iodide, methyl bromide), disposal problems
Polymerization	High viscosity may cause problems with heat removal from the reaction zone, reaction often uncontrollable

5.2.6. Process evaluation

After each development stage the status of the process should be evaluated. The important questions to be answered are:

- Is the production technically feasible?
- Is the process safe and clean? Does the process meet requirements of safety and ecology?
- Is it economically attractive?
- How big is the risk in economic and technological terms?

5.2.6.1. Technical evaluation

The technical evaluation of a process includes the determination of the technical risk during design, start-up, and operation of the process. Factors increasing the technical risk are:

- unfamiliarity of the company with the particular technology (e.g. use of toxic or explosive materials, high-pressure operations, gas-phase oxidation, phosgenation technology, etc.),

- use of new materials of construction for equipment for processing highly corrosive media or materials sensitive to contamination,
- use of units which are difficult to scale-up (e.g. processing of solids or non-Newtonian liquids),
- exceeding size limits (e.g. if the dimensions of the largest equipment previously operated by a company are considerably exceeded),
- use of technically non-established equipment (e.g. equipment of a new type which has not been produced yet).

The technical risk can be reduced in either of two ways: (1) increasing the expenditure on research and development of the weak point (e.g. extension of pilot-plant testing of the unit questioned, search for well-established alternative equipment, use of assistance of a company advanced in the field or use of another already proven way to perform the operation), or (2) developing failure scenarios, *i.e.* determining what can be done if problems occur and what to do to prevent the occurrence and to minimize the effects of failure. The decision which option to choose is basically an economic question: The costs of increased R&D expenditure must be weighed against the cost of eliminating the risk when the plant is started up or on stream. The technical risk is evaluated by engineers from the process development group in a company.

5.2.6.2. Safety and environmental friendliness

Sources of wastes must be identified and reduced as much as possible. In addition, processing of unavoidable wastes must be incorporated in the design (see Section 5.2.5).

The worst hazard scenarios (excessive temperature and pressure rise accompanied by emission of toxic substances) must be worked out based upon calorimetric measurements (e.g. means to reduce hazards by using the inherent safety concept or Differential Scanning Calorimetry, DSC) and protection measures must be considered. If handling hazardous materials is considered too risky, procedures for generation of the hazardous reactants *in situ* in the reactor might be developed. Micro-reactor technology could also be an option. Completeness of the data on flammability, explosivity, (auto)ignition, static electricity, safe levels of exposure, environmental protection, transportation, etc. must be checked. Incompatibility of materials to be treated in a plant must be determined.

It should be checked whether the process fulfils the state and local regulations concerning environmental protection, safety, and occupational health hazards. These criteria are not directly applicable in the early development stages.

5.2.6.3. Economic evaluation

An economic evaluation can be based on several common criteria.

The pay-out time (*POT*) is the time (in years) to recover the initial capital investment from cash flows:

$$POT = \frac{\text{total capital investment}}{CF} \qquad \textbf{(5.2-1)}$$

where CF is the total annual cash flow which equals the total income minus operating costs minus tax. The criterion is typically used for evaluation of projects with a short life and can be considered particularly useful for evaluation of projects for fine chemicals whose lifetime is often relatively short. An investment with a *POT* of three to five years is generally considered profitable in the CPI (Chemical Process Industries). For fine chemicals the *POT* should be shorter, e.g. from one to two years. The total capital investment for fine chemicals that are to be manufactured in an MPP is usually small as far as equipment is considered. However, the cost of R&D, which is rather high[4], should be considered as a part of the investment.

Return on investment (*ROI*) is the ratio of profit to capital investment:

$$ROI = \frac{net\ profit}{total\ capital\ investment} \cdot 100\% \qquad \textbf{(5.2-2)}$$

The net profit is the total income minus operating costs minus depreciation minus tax. The *ROI* is often calculated for the anticipated best year of the project; the year in which the profit is greatest. This criterion is also used for small investments. In general, acceptable *ROI*'s are about 20 %, but typical values are difficult to give. Both *POT* and *ROI* provide a one-moment-in-time view and do not take into account future cash flows, which may not be constant in the lifetime of the venture.

The net present value (*NPV*) method is based on discounting of cash flows (*DCF*) to be realized in the future:

$$DCF_j = \frac{CF_j}{(1+i)^j} \qquad \textbf{(5.2-3)}$$

where CF_j is a cash flow to be received at the end of year j discounted to the end of year 0 by dividing through $(1+i)^j$, in which i is the yearly interest. The net present value (NPV) at a given interest i of a series cash flows CF_j at the end of years 1 to n, as generated by an investment I_0 at the end of year 0, is the sum of the discounted cash flows over the time of the project:

$$NPV = \sum_{j=0}^{n} \frac{CF_j}{(1+i)^j} \qquad \textbf{(5.2-4)}$$

with $CF_0 = -I_0$, *i.e.*

$$NPV = -I_0 + \sum_{j=1}^{n} \frac{CF_j}{(1+i)^j} \qquad \textbf{(5.2-5)}$$

A negative *NPV* value means that the project does not meet the required interest rate while a positive sign indicates that the investment meets the required interest rate and generates an amount of extra cash. The yearly interest i can be reliably estimated in stable economies. If i can change significantly over a period for which a project is evaluated an interest for each year j, *i.e.* i_j should be anticipated. This is always a slightly unreliable procedure.

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[4] Pollak (1998) has estimated the cost of R&D for the pharmaceutical industry to be about 16 % of the expenditure for new drugs. For intermediates this percentage is certainly lower but still significant.

The discounted cash flow rate of return (*DCFRR*) or internal rate of return (*IRR*) is the percentage interest *i* at which the *NPV* becomes equal to zero. Fig. 5.2-4 illustrates the relationship between *NPV* and *DCFRR* (*IRR*); the intersection of the *NPV* curve with the axis of percentage interest *i* corresponds to the *DCFRR* (*IRR*) for *NPV* = 0. The investment is considered advantageous if *DCFRR* > 15 - 20 % (depending on the risk).

Economic evaluations are usually carried out by a specialists group within a company, although in a small fine chemicals company the economic analysis often is the task of the chemical engineer.

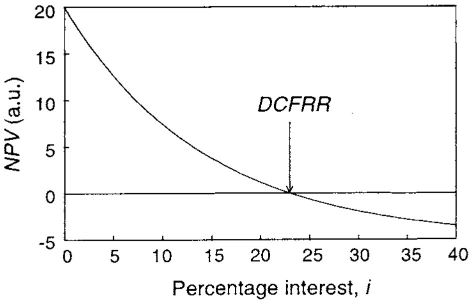


Figure 5.2-4. Discounted cash flow rate of return (DCFRR).

5.2.6.4. Sensitivity analysis

Calculations of economic profitability can only be predictive in the phase of process development, before a plant is on stream for a long time. Therefore, individual components of costs and market evaluations will bear some uncertainty. This uncertainty is relatively high for pharmaceuticals and agrochemicals. The impact of these uncertainties on the profitability of a process may be quantified by a sensitivity analysis. This analysis provides information about the sensitivity of the process economics to changes in parameters relevant for the profitability (investment costs, price and consumption of raw materials, utility unit costs, product value and demand, etc.), and therefore on the reliability of the result of the economic evaluation. In the early stages of process development, a high sensitivity indicates the areas requiring attention for continued R&D work.

A sensitivity analysis is performed by varying each parameter over a range with the base case as a starting point. Each parameter is changed by an increment of, for example, 10%, while keeping the other parameters constant. Then the resulting change of profit or *DCFRR* is calculated. The greater the change of profit or *DCFRR* due to the same change in the parameter, the more sensitive the project is to this parameter. Fig. 5.2-5 illustrates trends in fine chemicals manufacture. It is not surprising that the profit is most sensitive to the product price. The sensitivity to the price of raw materials is also relatively high. Changes in sales, which are related to the degree of utilization of the plant, have a moderate effect: the plant can often still be run profitably at 60 to 70% of its design capacity. Sensitivity to investment is rather low.

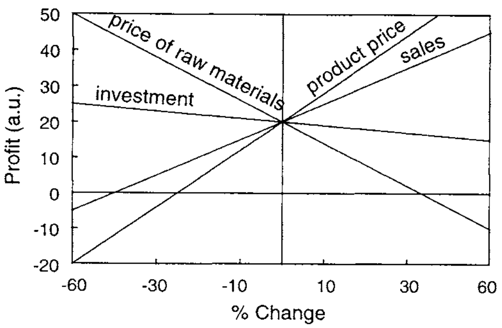


Figure 5.2-5. Sensitivity analysis.

5.2.6.5. *Study report*

Process evaluation is composed in a study report (feasibility study). It usually includes the following chapters:

- a summary and introduction which defines the objective of the project: product definition and production capacity, market and trend analysis, examination of the state of knowledge, patent/license situation and legal aspects, chemistry of the process with conversions and selectivities, and major risks,
- physicochemical, hazard, and toxicity data for raw materials, intermediates, products, and their mixtures, impurity profiles needed for pharmaceutical and agrochemical products (see restrictions imposed by pharmacopeas, food chemicals codex (FCC), etc.); a typical data sheet for individual substances, also called material safety data sheet (MSDS), includes several sections: material identification and name, specifications, or typical properties, applications, toxicity, handling and storage, environmental constraints and other legal reservations, and analytical methods for raw materials, intermediates, and products,
- a basic flow diagram and a process flow-sheet with a process description: all equipment items, machines, pipelines, valves and fittings, as well as all streams should be shown in the flow-sheet, detailed process data for materials recovery and recycling should be described, specifications of utilities given (characteristics of cooling water, compressed air, de-ionized water, refrigerants, and electricity, types of steam, and heating gas), materials of construction discussed, instrumentation for process control proposed, adaptation for processing in existing plant suggested,
- a waste-disposal flow diagram: information on toxicity (towards human beings, bacteria and fishes), degradability (COD, BOD, and TOD), fire properties (ignition and auto-ignition point, explosion limits), amounts and/or mass flows of effluents, state and approximate composition of streams should be given and methods for disposal proposed (sewage treatment plant, incineration, waste-disposal site),
- an estimate of the investments needed (see Chapter 7), an estimation of manufacturing costs: costs of raw and auxiliary materials, utilities, waste-disposal, staff, maintenance, and overheads; profitability considerations,
- a technology evaluation with an assessment of the level to which the experimental details

have been worked out, weak points or unavailable data arranged in order of technical risk, and steps which should be taken to reduce the risks (extension of R&D on the weak point, development of failure scenarios, process rearrangement with the intention of increasing the percentage of process steps that can be safely scaled-up), risk analysis, process behaviour under extreme conditions and quenching methods to be used, review of scale-up methods and equipment selection procedures, plans to collect data during plant operation, and laboratory experiments still to be performed with costs of these activities assigned.

5.3. SCALE-UP PROCEDURES

The performance of a chemical plant depends upon an enormously high number of design and operating variables. This great number of process variables makes it impossible to find optimal conditions within the region of safe operation if no quantitative relationships (defined in terms of mathematics) between performance indices and process variables are known. In general, optima are complex functions of process variables, and therefore quantification of experimental results is needed. The methods for scale-up that were conventionally used at the time of 'Perkin chemistry' resulted in successful commercialization of many laboratory recipes. This evolutionary, step-by-step method of scale-up is illustrated in Fig. 5.3-1 (after Moulijn *et al.* 2001).

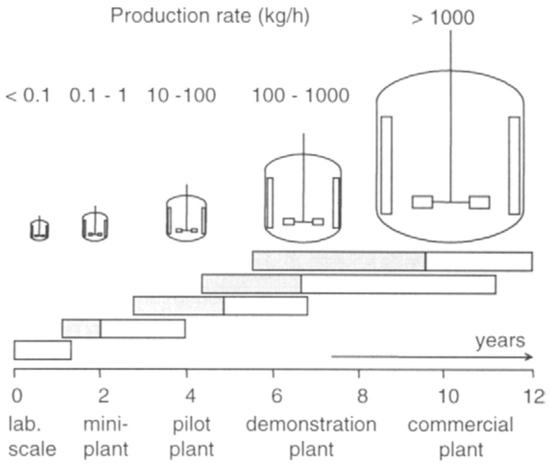


Figure 5.3-1. Typical conventional scale-up procedure.

Evolutionary methods cannot guarantee the development of an optimal process. In the past, process optimization in fine chemicals manufacture was not that important because the vast majority of products were **H**(igh)-**A**(dded)-**V**(alue) products, and even non-optimal manufacture provided a sufficiently large profit. Today, the number of competitors in this field is growing fast, and this competition forces companies to optimize processes via better understanding of the process. This is also a prerequisite for safety and environmental protection.

To illustrate the complexity of process optimization, suppose that we are to scale-up a semibatch stirred-tank reactor for carrying out the following consecutive reactions:

$$A + B \rightarrow P \rightarrow S \qquad \textbf{(5.3-6)}$$

where P is the desired product and S is an unwanted product. A procedure starts with loading of the reactor with (a mixture containing) the reactant A, dosing (a mixture containing) the reactant B, and maintaining the resulting mixture at elevated temperature during a certain period of time. Suppose that both reactions are exothermic, but with different heat effects and with different temperature sensitivity. Obviously, the rate of any reaction at any instant will depend on both the current composition of the reaction mixture and the temperature. The current composition in turn depends on the history of both dosing and temperature up to the moment considered. A constraint imposed with respect to temperature: The maximum amount of heat which can be removed from the stirred-tank reactor (per unit volume of reactor) decreases significantly with increasing reactor size and can depend on the reactor shape, stirrer shape, and speed of the stirrer rotation. Consequently, in the case of exothermic reactions we might not be able to control the temperature as we wished, and the temperature history will depend on the scale of the reactor. Therefore, instantaneous conversions to both products will depend on the time-trajectories of both dosing and temperature, with the constraint set by the reactor size (and shape). There are an infinite number of strategies for dosing reactant B; a commonly applied way is to dose at a steady rate. This is the simplest option, which, however, is not necessarily the best and safest one. The same applies to the temperature of the reaction mixture, which can be varied in time. It would be only a dream to be able to conclude upon the best trajectory and to accurately determine the best region of reactor operation, if relationships describing the dependence of rates of individual reactions on both temperature and concentrations remained unknown; the rate of heat removal from the reaction zone must also be known as a function of reactor size.

Due to the complexity of the problem, it is generally accepted that we will not reach the optimal reactor design and operating variables, but still we would like to design and operate the reactor safely and near the optimum. Further in this section, we will give a general discussion of scale-up methods for chemical processes, in particular with respect to chemical reactors suitable for the manufacture of fine chemicals. Next, we will discuss how to obtain reasonable quantitative relationships necessary for optimal and safe scale-up according to the art. The reader can find an extensive treatment of scale-up problems in the book of Bisio and Kabel (1985).

5.3.1. Scale-up effects

In spite of decades of experience gained with scale-up of chemical processes, there still appear unexpected, sometimes 'mysterious' scale-up effects. In terms of chemical reaction characteristics, these effects are mainly lower yields (selectivities) and products less pure than on the laboratory scale. Chemists involved in fine chemistry usually do not study the nature of scale-up effects. They expect these effects to appear if engineers do not take 'appropriate steps'. The extent of scale-up effects depends very much upon the sensitivity of a process to mixing conditions, to heat- and mass-transfer conditions, and the presence of unexpected species at large scale. The scale-up uncertainty can be significantly reduced if these sensitivities are studied in more detail during laboratory research.

Factors responsible for the occurrence of scale-up effects can be either material factors or size/shape factors. In addition, differences in the mode of operation (batch or semibatch reactor in the laboratory and continuous reactor on the full scale), or the type of equipment (e.g. stirred-tank reactor in the laboratory and packed- or plate- column reactor in commercial unit) can be causes of unexpected scale-up effects. A simple misuse of available tools and information also can lead to wrong effects.

5.3.1.1. Material factors

Raw materials and auxiliary products used in a process as well as materials of construction for equipment items can be the cause of 'scale-up effects'. Pure raw and auxiliary materials must be used in laboratory studies to eliminate the influence of impurities on the choice of the process route, catalyst selection, and search for satisfactory process conditions. However, pure chemicals are usually too expensive to use for manufacture on a commercial scale. It is common practice to use raw materials of technical grade in a full-scale plant. These materials contain impurities, which can act as catalysts or inhibitors. They can react with reactants or intermediates, thereby decreasing yields and selectivities of desired products. Therefore, raw materials of technical grade, even from different suppliers must first be tested on laboratory scale.

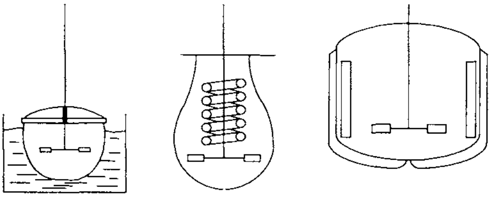
Glass or quartz equipment is utilized in the laboratory to exclude effects of construction materials. For large-scale production glass-lined (enamelled) reactors or metal-surface reactors (made from stainless steel or other alloys) are used. Sealings in these reactors as well as the metal (alloy) itself can be a source of product impurities. Especially product contamination with heavy metals is a significant drawback for products that are to be administered directly or indirectly to human beings or animals. Glass-lined equipment is generally more resistant to chemical attack, and, consequently, products are less contaminated. However, glass-lined reactors and other glass equipment items are more expensive than typical stainless steel apparatuses. Moreover, there are some limitations on the use of enamelled equipment concerning operating temperature range, rates of heating/cooling, etc.

Finally, in multipurpose plants compounds, which can be deposited in various places (e.g. corners, zones near sealings) in equipment, can contaminate products of the subsequent batch. Therefore, all equipment must be thoroughly cleaned before the next production campaign starts. Contaminants can be formed in the process, sometimes at ppm level, and be recycled with streams of solvents and/or reactants. Hence, the influence of recycling on process performance indices must be included in the program of laboratory studies, at least in their final stage.

5.3.1.2. Size/shape factors

In scale-up of equipment both shape and size are changed. For instance, a one-litre round-bottom laboratory flask reactor is scaled up to a 50-litres pilot reactor and further to a 4 m^3 cylindrical reactor with an ellipsoidal or torispherical bottom (see Fig 5.3-2).

Shapes are different, so mixing conditions differ, the more so because different types of stirrers are used in these reactors. The ratio of heat-exchange surface area per unit volume of the reaction zone exceeds 20 m^2/m^3 in laboratory round-flask reactors, while it decreases to about 2 - 3 m^2/m^3 for typical full-scale stirred-tank reactors. Even if all reactors were of a similar shape (e.g. cylindrical), proportions between dimensions of reactor parts (e.g. the ratio of reactor height to reactor diameter) would be different. An industrial reactor is usually equipped with an impeller of a shape different from that in a laboratory reactor, while the rotation speed of the stirrer also differs. Inlets for feeding reactants, stream distributors, and outlets of the reactors are arranged in different ways on both scales. Therefore, the flow characteristics of laboratory and industrial reactors are different. As a consequence, the mixing time of components added gradually to the reaction mixture in a semibatch reactor, or the residence time of the reaction mixture in a continuous reactor varies with scale. Sometimes zones of different intensity of mixing, even stagnant ('dead') zones, are formed. The above listed differences give rise to a change of mixing conditions and heat/mass transfer conditions with scale. So in the case of processes sensitive to temperature and/or mixing conditions evolutionary scale-up procedures can produce unreliable data.



laboratory
1 l flask
reactor

pilot
50 l
reactor

commercial
4000 l
reactor

Figure 5.3-2. Typical shapes of laboratory, pilot, and full-scale stirred reactors.

Influence of reactor size/shape on process performance via mixing conditions. Mixing is usually very intensive in well-designed small laboratory equipment. The mixing time in laboratory reactors is usually shorter than 1 s (for definition and measurements of mixing time, see Section 5.4.5), provided they are equipped with baffles. Thus, the concentration of any component added gradually to the reaction mixture is almost instantaneously equalized all over the reaction zone, especially if the component is added near the stirrer. Very good mixing can be provided in large reactors also, but at a high cost of energy consumed by the stirrer. To keep manufacture profitable, stirrers in large reactors are rotated slower than in the laboratory, because otherwise the cost of energy for mixing would be too high. As a consequence, mixing conditions in full-scale reactors are usually worse than in laboratory reactors. The mixing time in large reactors can be of the order of tens seconds, especially in the case of highly viscous liquids. With poor mixing, the concentration of the component added to the reaction mixture will be higher than the average concentration near the inlet of the reactor. This can influence the course of a process in a system where some reactions proceed much faster than others (e.g. neutralizations, iodinations, brominations, diazotizations, etc.). The faster reactions will be favoured by the greater concentration of the component being added. Therefore, in large reactors the faster reactions will be favoured in zones nearby reactants inlet, while good mixing in a laboratory scale reactor will disfavour these faster reactions. In general, a difference in mixing conditions can change proportions between rates of individual reactions, and, consequently, yields of various products. This might be one of the sources of 'mysteries' upon scale-up. Examples of influence of mixing conditions on process selectivities are given below.

Example 5.3.1.1. Iodination of L-tyrosine (after Paul and Treybal, 1971)

Paul and Treybal studied iodination of *L*-tyrosine. The overall scheme of iodination is shown in Fig. 5.3-3. The reactions can be summarized as:

$$\begin{gathered} A + B \rightarrow R \\ R + B \rightarrow S \end{gathered} \tag{5.3-7}$$

The reactions are parallel with respect to iodine (*B*) and consecutive with respect to iodine-substituted derivatives of *L*-tyrosine (*R*).

A solution of iodine in aqueous potassium iodide was added to a solution of *L*-tyrosine in aqueous base. Phosphate buffers were added to minimize the change in pH due to the formation of hydrogen iodide. Two reactors of different size (5 and 36 litres) were studied. The reactor parameters and operating conditions are given in Table 5.3-1. The mixing conditions were changed by varying the speed of stirrer rotation, use of baffles, and the position of the feed line opening in the tank. Two positions were used for the majority of investigations, while a third position, directly below the centre line of the impeller, was used for a limited number of experiments (see Fig. 5.3-4). The effect of feed distribution was studied by introducing the feed through a nine-hole distributor placed well above the turbine in the smaller vessel. The distributor was circular with holes of diameters by about four times smaller than that of the distributor. The 5-litre tank contained a coil of stainless steel tubing.

Yields of the desired derivative of *L*-tyrosine (*R*) versus turbine speed for different reactor configurations are shown in Figs 5.3-5 and 5.3-6, together with the expected yield, which is defined as the yield that would be reached if mixing was ideal. This yield was calculated based on rate constants determined by the authors in separate experiments. As shown in the figures, the yields of iodo-*L*-tyrosine are always lower than the expected yield, and strongly depend on impeller speed, turbine diameter, and feed-line position. The higher the speed of rotation and the greater the diameter of the stirrer, the higher the yield. The reactor performed best when feeding it near the tip of the impeller. This position is clearly superior to that commonly used, directly below the turbine centre line.

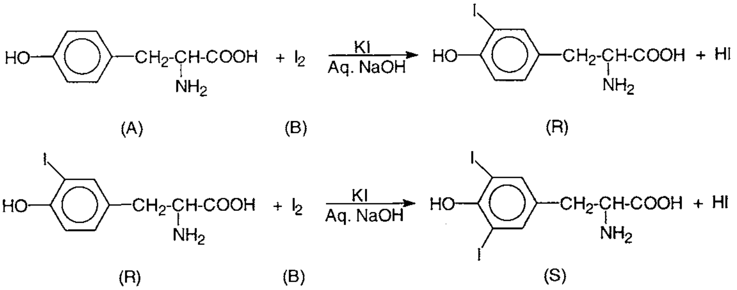


Figure 5.3-3. Scheme of iodination of *L*-tyrosine (adapted from Paul and Treybal, 1971).

Table 5.3-1
Reactor parameters and process conditions for iodination of *L*-tyrosine

Variable	Reactor 1	Reactor 2
Design parameters		
Reactor volume [L]	5	36
Reactor diameter [cm]	14.9	28.7
Turbine diameter [cm]	5.8	11.6
Turbine speed [rpm]	200 to 1600	95 to 788
Feed location, number of positions	3	2
Operating variables		
Temperature [^{o}C]	25	11; 43
Initial concentration of A [mol L^{-1}]	0.2	0.1; 0.4
Feed concentration of B [mol L^{-1}]	2.0	-
Dosing time for B [s]	1080	15; 60

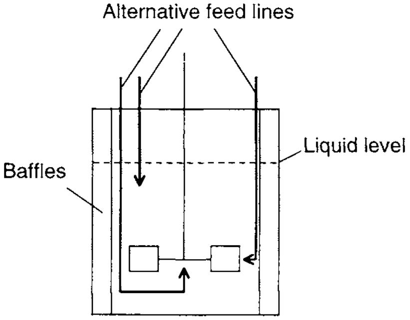


Figure 5.3-4. Semibatch stirred-tank reactor with alternative feed lines; homogeneous reaction.

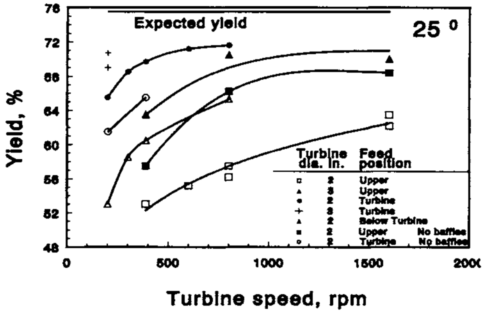


Figure 5.3-5. Yield of *R* in the 5-litre reactor (adapted from Paul and Treybal, 1971).

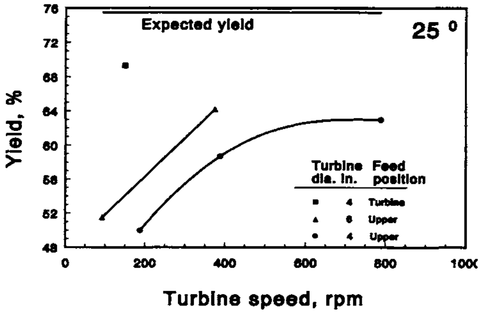


Figure 5.3-6. Yield of *R* in the 36-litre reactor (adapted from Paul and Treybal, 1971).

Example 5.3.1.2. Preparation 1-naphthol based dye (after Bourne and Hilber, 1990)

Bourne and Hilber (1990) studied the reaction between diazotized sulphanilic acid (*B*) and 1-naphthol (*A*) with the formation of two products, mono- and bis-azo dyes (*R* and *S*), mono-compound (*R*) being the product desired (see Fig. 5.3-7). The process proceeds according to the reaction scheme given by Eqn. (5.3-2). A solution of diazotized sulphanilic acid was added to a 1-naphthol solution. The reaction was buffered using a solution of sodium carbonate and bicarbonate. The feed lines were located just below the liquid level and near the stirrer tip. In addition to a single feed, a feed distributor consisting of 4 nozzles spaced at 90° in a ring was employed at the two positions. Reactors of 2.5 litres and 20 litres were investigated.

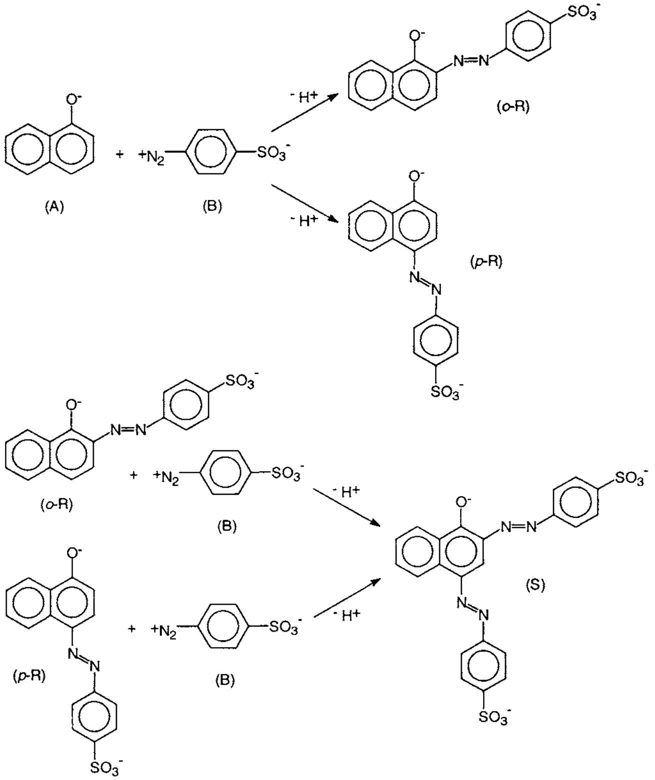


Figure 5.3-7. Scheme of reaction between diazotized sulphanilic acid (*B*) and 1-naphthol (*A*).

Fig. 5.3-8 shows a plot of the yield of the undesired bis-azo dye (*S*) versus the modified time of dosing for different rotation speeds for the 20-litre reactor fed at the tip of turbine. The yield X_S is defined as:

$$X_S = \frac{2c_S}{c_R + 2c_S} \tag{5.3-8}$$

where c_R and c_S are the concentrations of R and S, respectively, while the modified time of dosing is defined as the product of the time of real dosing, t, and the number of nozzles at the tip of the stirrer, n_z (one or four). The strong influence of rotation speed is seen in this case as well. The speed, however, can be reduced significantly if more than one nozzle is installed near to the turbine tip at its stream discharge. A higher yield of the dye (S) was achieved if reactant (B) was introduced into the reaction zone near the liquid surface. This is because mixing conditions at the liquid surface are poorer. The maximum yield of S would be reached (and no R at all) if there was no mixing at all.

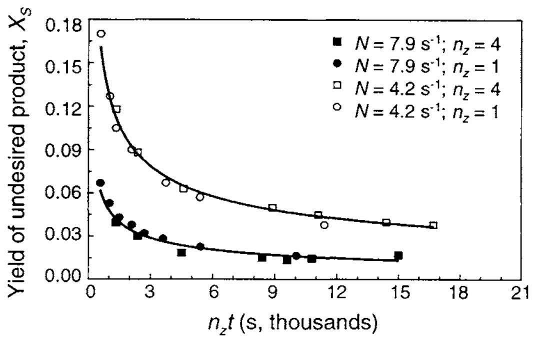


Figure 5.3-8. Yield of S versus modified time of dosing; N = rotation speed; n_z = number of nozzles (adapted from Bourne and Hilber, 1990).

Example 5.3.1.3. Acid-base neutralization (after Paul et al., 1992)

A system of parallel reactions as shown in Fig. 5.3-9 was studied by Paul *et al.* (1992). The reactions are an acid-base neutralization and a base-catalysed hydrolysis of product (C). The labile compound (C) is in solution in an organic solvent, and aqueous NaOH is added to raise the pH from 2 to 7. Enolization occurs under basic conditions and is accompanied by irreversible decomposition (ring opening), which is not shown in the figure. The system was studied in the laboratory using the 6-litre reactor shown in Fig. 5.3-10.

A local high concentration of base was considered to be the reason of significant amounts of by-product Q formed at low speed of rotation. At higher speed, faster dispersion of the base throughout the reaction mixture would occur and local base concentrations would be decreased. This is likely to be the reason of the decrease of by-product formation with increasing rotation speed (see Fig 5.3-11).

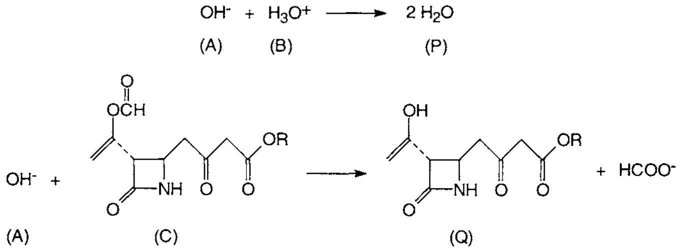


Figure 5.3-9. Scheme of neutralization (adapted from Paul *et al.*, 1992).

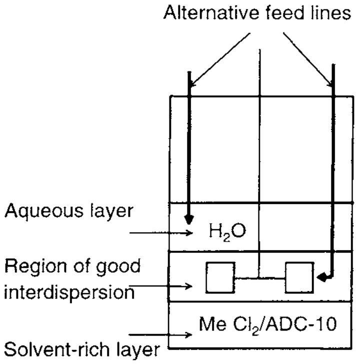


Figure 5.3-10. Semibatch stirred-tank reactor with alternative feed lines; heterogeneous reaction (adapted from Paul *et al.*, 1992).

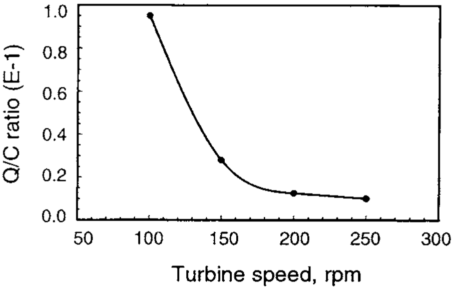


Figure 5.3-11. The ratio of by-product Q to desired product C versus rotation speed; 7 N NaOH addition (adapted from Paul *et al.*, 1992).

In general, addition of the base to the solvent-rich part of the reaction zone, near the tip of the impeller, resulted in higher levels of Q formation due to higher local concentration of the base. Addition of the base to the upper part of the reactor, where the mixture is water-rich, resulted in local dilution before reaction with C, and in a lower amount of by-product Q. So, the concentration of base is the solvent-rich layer should be low, and the optimal procedure is a high turbine speed and base introduction in the top layer.

Influence of reactor size/shape on process performance via heat transfer. Heat transfer between a reaction mixture and its surroundings strongly depends on the size of the reactor. The amount of heat evolved during an exothermic reaction is proportional to the volume of the reaction mixture ($Q_{\text{generated}} \sim V$), *i.e.* the effective volume of the reactor, whereas the amount of heat removed from the mixture is proportional to the heat-transfer surface area ($Q_{\text{removed}} \sim A_r$). More precisely, the amount of heat transferred is given by:

$$Q = U \cdot A_r \cdot \Delta T \tag{5.3-9}$$

in which Q is the amount of heat transferred (J/s or W), U the overall heat-transfer coefficient (W m^{-2} K^{-1}), A_r the heat-transfer surface area (m^2), and ΔT the temperature difference between the reaction mixture and the coolant. The overall heat-transfer coefficient depends on the size and shape of both reactor and stirrer, but this influence on the amount of heat transferred to the coolant is much less than that of the ratio of the heat-transfer surface area to the reactor volume. The A_r/V-ratio strongly decreases with increasing reactor size (see Fig. 5.3-12).

The A_r/V-ratio for a glass-lined reactor with a nominal volume of 63 litres is about 9.5 m^2/m^3, while that for a 6,300 litres reactor amounts to approximately 2.6 m^2/m^3 (both reactors of DIN-series). Hence, the heat flux in a large reactor will be about three times smaller per unit exchange surface area.

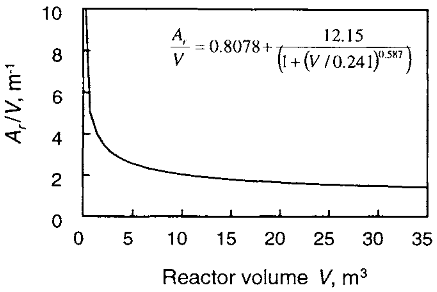


Figure 5.3-12. A_r/V-ratio as a function of reactor volume.

This agrees with industrial data reported by Rogers (1989); the amount of heat exchanged in a 50 litres reactor was estimated to be 0.2 W kg^{-1} K^{-1} while that for a 22.5 m^3 reactor is only 0.04-0.08 W kg^{-1} K^{-1}. The significance of the influence of the reactor size on heat transfer, and in turn on the yield and selectivity, is illustrated by *Example 5.3.1.4.*

Example 5.3.1.4. Selectivity versus heat transfer in batch reactors

Cybulski (1990) simulated the behaviour of a batch (BSTR) and semibatch (SBSTR) reactor in which consecutive reactions take place:

$$A \xrightarrow{k_1} P \xrightarrow{k_2} S \qquad \textbf{(5.3-10)}$$

The desired product is P, while S is an unwanted by-product. The reaction is carried out in a solution for which the physical properties are independent of temperature and composition. Both reactions are of first-order kinetics with the parameters given in Table 5.3-2; the specific heat of the reaction mixture, c_p, is 4 kJ kg^{-1} K^{-1}, and the density, ρ, is 1000 kg m^{-3}. The initial concentration of A is c_{A0} = 1 mol litre $^{-1}$ and the initial temperature is T_0 = 295 K. The coolant temperature is 345 K for the first period of 1 h, and then it is decreased to 295 K for the subsequent period of 0.5 h. Figs. 5.3-13 and 5.3-14 show temperature and conversion curves for the 63 and 6,300 litres batch reactors, which are typical sizes of pilot and full-scale plants. The overall heat-transfer coefficient was assumed to be 500 W m^{-2} K^{-1}. The two reactors behaved very different. The yield of P in a large-scale reactor is significantly lower than that in a pilot scale: 1.2 mol % and 38.5 mol %, respectively. Because conversions were commensurate in both reactors, the selectivity of the process in the large reactor was also much lower.

Table 5.3-2
Reaction parameters ($r_i = k_{0,i} \cdot \exp(-E_i/RT) \cdot c_i$)

Reaction number i	Pre-exponential factor, $k_{0,i}$ (s^{-1})	Activation energy, E_i (kJ mol^{-1}K^{-1})	Heat of reaction, ΔH_i (kJ mol^{-1})
1	0.5	20	-300
2	$1.0 \cdot 10^{11}$	100	-250

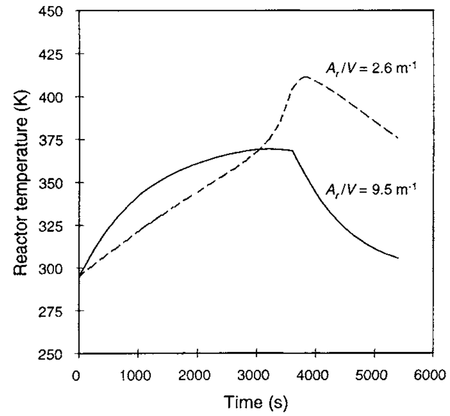


Figure 5.3-13. Temperature versus time in a batch reactor.

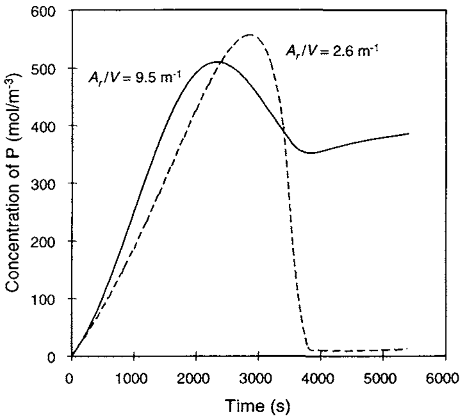


Figure 5.3-14. Concentration versus time in a batch reactor.

The reason is that the A_r/V- ratio in a full-scale reactor is much smaller that than in a small one. This resulted in a more dramatic temperature rise in the large reactor. This increased the rate of the second reaction with the higher activation energy, and, consequently, decreased the selectivity.

Influence of the mode of operation on process performance. The mode of operation of stirred-tank reactors can also significantly affect reactor performance. The history of concentrations will be changed by the time policy of reactant(s) addition to the reaction mixture. In view of our very limited possibility of controlling of temperature in stirred-tank reactors, the temperature-time dependencies for different policies of dosing will also be different. For example, the result of nitration depends upon the method of addition of nitric acid to aromatics, and the choice which phase is dispersed and which is continuous. Consequently, if the reaction is concentration- or temperature-sensitive the result will be dependent on the mode of operation (see Example 5.3.1.5).

Example 5.3.1.5. Selectivity versus mode of operation in semibatch reactors

In order to illustrate how the mode of operation can positively modify selectivity for a large reactor of poor heat-transfer characteristics, simulations of the reactions specified in Example 5.3.1.4 carried out in a semibatch reactor were performed. The reaction data and process conditions are essentially the same as those for the batch reactor, except that the initial concentration of A was decreased to c_{A0} = 0.46 mol litre^{-1}, and the remaining amount of A is dosed: (1) either for the whole reaction time of 1.5 h with a rate of 0.1 mol m^{-3} s^{-1}, or (2) starting after 0.5 h with a rate of 0.15 mol m^{-3} s^{-1}. It is assumed that the volume of the reaction mixture and its physical properties do not change during dosing. The results of these simulations are shown in Fig. 5.3-15. The results of calculation for reactors of both types are summarized in Table 5.3-3.

It is clear from the presented data that the yield and selectivity in a large semibatch reactor can be improved compared to those in a small batch reactor that has much better heat-transfer capability. This has been achieved by decreasing the rate of heat evolution, which has been obtained by lowering the instantaneous concentration of reactant A. The results also indicate that the dosing policy can have a very significant influence on reactor performance.

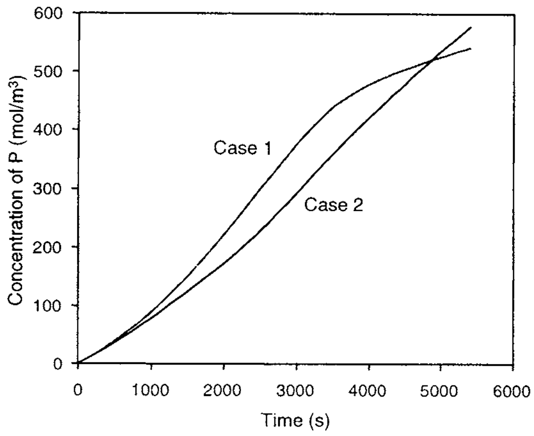


Figure 5.3-15. Concentration versus time in a semibatch reactor.

Table 5.3-3
Results of simulations of batch stirred-tank reactors (BSTR) and semibatch stirred-tank reactor (SBSTR).

Reactor	*A*/*V* (m^2/m^3)	Conversion of *A* (% mol)	Yield of *P* (% mol)	Selectivity (% mol)
BSTR	9.5	92.5	38.5	41.6
BSTR	2.6	97.4	1.2	1.2
SBSTR (case 1)	2.6	77.4	54.1	69.9
SBSTR (case 2)	2.6	68.4	57.8	84.5

As illustrated by the examples above, the possibility of removing the generated heat from the reaction zone decreases with an increase in reactor size. As proven above, it can happen that the temperature of the reaction mixture in a full-scale reactor becomes higher than in the laboratory flask reactor. If multiple chemical reactions of distinctly different temperature sensitivities take place, differences in yields and selectivities between small and large reactors will be observed. This has a large influence on safety also. The laboratory reactor might still show satisfactory performance, while the industrial reactor might even explode.

Summarizing, the output of the reactor is an integral over time and over the entire reaction space with all interconnections between different zones of the reactor. Mixing and heat- and mass-transfer conditions are usually different in various zones and the pattern of these differences as well as proportions between size of zones vary with scale. Obviously, the histories of concentrations and temperatures in the zones differ. Whether the integral outputs of laboratory and full-scale reactors differ from each other, depends on the sensitivity of the process to mixing and heat- and mass-transfer conditions. If the sensitivity is low only minor scale-up effects might be expected to occur. In case of high sensitivity, the extent of scale-up effects might be surprising if the influence of these factors was not taken into consideration.

5.3.2. Scale-up strategies

The ideal of the process engineer is to develop a full-scale plant based on results of small-scale experiments and experience gained up to date. The way to do it would be to set up a mathematical model which describes the behaviour of the plant in all microscopic details. Computer simulations using such a model would fully correspond to plant operation as far as 'performance' of the plant was regarded. The better the model reflects the true mechanism, the better the plant design and operation. In terms of fine chemistry processes this translates to optimum yields and selectivities in a full-scale reactor. This, in turn, would make downstream isolation and purification of the end products easier. In practice, due to restrictions in knowledge, time, and money available, a full description of all mechanisms cannot be obtained and approximations must be made. Accordingly, we are always dealing with quasi-mechanistic models. Scale-up using empirical models or no modelling at all is still also practised. In general, scale-up is always a blend of theory and experimentation. The strategy of scale-up must be adjusted to the time, money, and tools available, experience gained, and the scale of the final production.

There are several scale-up strategies as illustrated in Fig. 5.3-16. The shortest way is to scale up a process directly from the laboratory data to a commercial plant, possibly via an empirical (correlative) model. This can be done only if much information on similar processes is available. In practice, it is nearly always impossible to follow a straight path from laboratory to commercial unit. As shown in the Figure 5.3-16, information from different sources is utilized for scale-up: basic (laboratory) research, mathematical modelling, engineering studies (studies on hydrodynamics, evaluation of mass- and heat-transfer coefficients), engineering design studies, pilot (sometimes also demonstration) plant studies, and finally experience gained from commercial units operation (mainly for similar processes and operations).

5.3.2.1. Incremental, sequential scale-up; scale-up ratio

At present, the most common approach to scale-up in fine chemicals technology is incremental scale-up, via sequential scales. This strategy involves studies in equipment of sequentially increasing sizes, each increment built using experience from the previous increment. Basically, the objective of incremental scale-up is to determine the significance of scale-up effects. If yields, selectivities, etc. at pilot-plant conditions are similar to laboratory data, the process is ready for full-scale implementation. More detailed studies are necessary if scale-up effects are significant. In R&D for fine chemicals usually a two-step scale-up procedure is applied that includes an intermediate plant (bench-to-pilot scale and pilot-to-commercial scale). The pilot-plant park that a company active in the field of fine chemicals possesses sometimes is a decisive factor when selecting the strategy of scale-up. This is even more so because sequential scale-up has frequently been applied successfully in fine chemicals business in terms of satisfactory and profitable full-scale manufacture, although certainly non-optimum. The pilot-plant parks contain versatile items that are usually on stand-by. A new process can be easily tested using these items after some rearrangements. A larger amount of a new product can be manufactured for marketing reasons, for the development of formulations comprising the product, and for extensive tests, also as formulations.

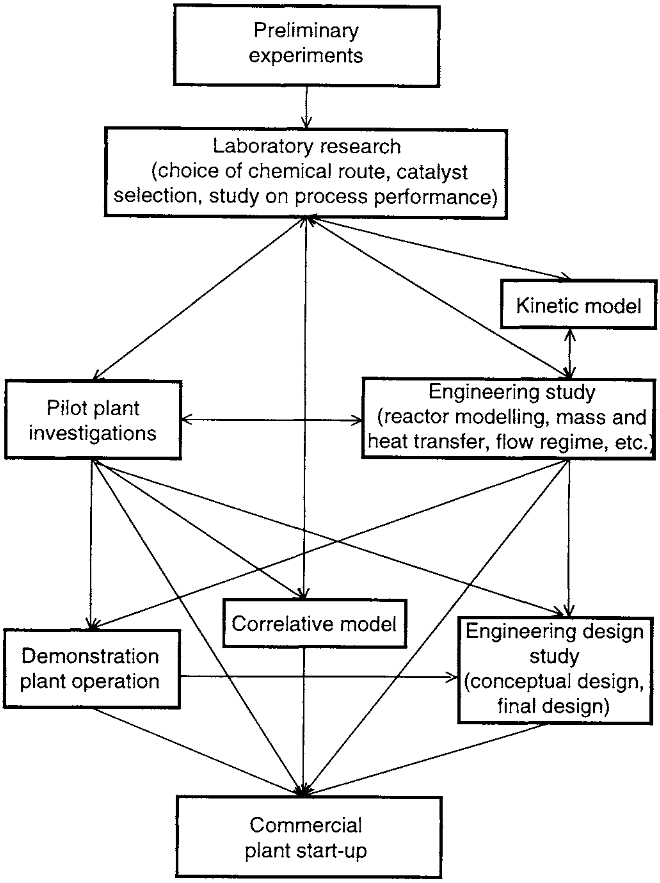


Figure 5.3-16. Scale-up routes.

In the past, in fine chemicals technology sequential scale-up was preferred over the more fundamental approach as the development of a good predictive model was costly and time-consuming. Specialists in fine chemicals manufacturing preferred to scale up processes without attempting to search for the best process conditions by means of modelling. The goal was to get a new process on stream, with non-optimum design and operation, rather than to delay the implementation of the process for determination of a sufficiently accurate kinetics-based process model. This should no longer be the case. Good versatile laboratory equipment and computer programs to process laboratory data for scale-up purposes are now available. Kinetic models of reasonable precision can be easily attained. There is no longer a significant limit on the use of mathematical modelling for scale-up of fine chemistry processes. At present, psychological barriers have to be broken among the people who are bound to a traditional approach to the problem of process design in the fine chemistry area. However, the sequential, empirical approach might still be successfully used for processes whose sensitivity to mixing, and mass- and heat-transfer conditions is negligible. Scale-up of such processes is straightforward.

The *scale-up ratio* is defined as the relationship between productivities of large-scale and small-scale equipment items, *i.e.*

$$\textit{Scale-up ratio} = \frac{\textit{large- scale production rate or equipment size}}{\textit{small-scale production rate or equipment size}} \qquad \mathbf{(5.3\text{-}11)}$$

Typical scale-up ratios for the incremental approach are shown in Table 5.3-4. It is not surprising that single-phase systems are easier to scale up than multi-phase systems. The reason is that the contact between phases changes with scale. In particular, the presence of solids complicates scale-up.

Table 5.3-4
Typical scale-up ratios

System	Reactor volume (L)		Maximum scale-up ratio	
	Laboratory	Pilot plant	Laboratory to pilot plant	Pilot plant to Commercial plant
Single liquid-phase reactions (some esterifications)[a]	0.5-2	50	1000	1000
Liquid-liquid reactions (nitrations, oxidations or hydroxylations using H_2O_2, brominations, iodinations)	1-5	50-250	250	500
Gas-liquid reactions (chlorinations, carbonylations, oxidations)	1-5	50-100	500	1000
Gas-liquid-solid reactions (catalytic hydrogenations and oxidations)	1-5	50-250	250	500
Liquid-solid reactions (Friedel-Crafts acylations and alkylations, Grignard reactions)	1-5	50-250	250	250

[a] Direct scale-up from laboratory to commercial size often possible.

The interfacial surface often depends on a minor amount of impurities in liquids and these impurities are sometimes difficult to detect. So conditions of mass and heat transfer between solids and fluids change as well. Local differences can be even greater due to an uneven distribution of reactants in the reaction zone. The results of non-uniform distribution at the inlet of the reaction zone can be easily propagated throughout the zone. Accordingly, processes and operations involving single-phase flow, distillation, heat exchangers, homogeneous and fixed-bed reactors, etc. are relatively easy to scale-up with large scale-up ratios, or can even be designed without small-scale experiments, provided that mixing phenomena are not critical and enough data are available. 'Homogeneous' fine and specialty chemicals manufacture might pose some problems in case of complex reaction networks combined with large thermal effects of the reactions. Operations and processes that include multi-phase flow, surface phenomena, non-Newtonian liquids, problems with heat transfer, and the presence of solids in the reaction mixture, are more difficult to scale-up.

A low scale-up ratio is characteristic of the incremental approach, and, as a consequence, this is a slow procedure. Moreover, material and labour costs of pilot experimentation are quite significant. These costs might be greater than costs of fundamental studies at laboratory scale, while the scope of information useful for scale-up might be narrower. Very simple mathematical models, *i.e.* purely empirical models (black models, correlative models), are sometimes developed during sequential scale-up. Although these models are convenient, extrapolation outside the range of experiments using such models is risky. Some equipment suppliers offer pilot tests for mixtures delivered by teams dealing with scale-up of the process. Based on results of these tests, the supplier selects the most suitable type and size of apparatuses from the equipment he produces.

5.3.2.2. Fundamental approach

Another extreme in scale-up is the fundamental approach. It is based upon phenomenological relationships (theoretical models or white models) that are theoretically well justified. As this method allows for extrapolation outside the range investigated, it is characterized by reliable high scale-up ratios. Operation of larger-size equipment plays a different role in scale-up of this kind. The essence is to determine whether predictions made using the model that was worked out at the earlier stage of process development agree with results of large-scale experiments, and to improve the model if necessary. The development of fully theoretical models is still too costly and time-consuming. This is, however, the most promising trend in scale-up, especially in view of the fast development of powerful computers and new generations of computer languages. Also, it should be stated that the chemical engineering discipline has been developed further, enabling more sophisticated process development.

What is commonly understood by a fundamental approach is applying theoretically based mathematical models of necessary equipment items. Intrinsic (not falsified by processes other than a chemical transformation) kinetics of all processes are investigated, transport phenomena are studied, flow patterns are identified, and relevant microscopic phenomena are studied. It is intended to separately study as many intrinsic stages as possible and to combine results of these investigations into a mathematical model. Such a model contains only a limited amount of theory (grey models, gross models, or tendency models). Obviously, the extrapolation power of these models strongly depends on the content of theory. The model coefficients are at least partially 'effective', *i.e.* the coefficients are estimated by fitting. As a rule, processes for the manufacture of fine chemicals are multi-reaction systems. Therefore, the development of the true mechanistic kinetic model might not be practical within the time available. Grey models of limited content of the theory might then be a good solution, as such models can be developed rather fast. Grey models allow for limited scale-up only. They can, however, play an important role in the identification of areas of uncertainty in scale-up in subsequent process or product development.

Modelling can at least facilitate the determination of the most effective scale-up program. Information from three fields is needed for modelling: (1) chemical kinetics, (2) mass transfer, and (3) heat transfer. The importance of information for different processes has been qualitatively evaluated (see Table 5.3-5). Obviously, sufficiently accurate information on heat transfer is needed for batch reactors, which are of great interest for fine chemicals manufacture. Kinetic studies and modelling requires much time and effort. Therefore, the kinetics often is not known. Presently, this approach is winning in the scale-up of processes for bulk chemicals. The tools developed for scale-up of processes for bulk chemicals have been proven to be very useful. Therefore, the basics of this approach will be discussed in more detail in subsequent sections.

5.3.2.3. Scale-up based on similarity principles; scale-up correlations

Systems (e.g. laboratory installations and full-scale plants) behave similarly, i.e. are similar, if geometric similarity, kinematic similarity, dynamic similarity, thermal similarity, and chemical similarity are preserved.

Geometric similarity between two systems exists if the ratio of corresponding dimensions in one system are the same as those in the other, *i.e.* both systems have the same shape.

Kinematic similarity exists if the systems are geometrically similar, the ratios of velocities at corresponding points are equal, and the direction of flow at corresponding points is the same in both systems (similar field of velocities).

Dynamic similarity exists if the systems are similar geometrically and kinematically, and moreover, the ratios of forces between corresponding points are equal in both systems (similar field of forces).

Thermal similarity exists if, in addition to geometric, kinematic, and dynamic similarity, temperature differences between corresponding points in both systems have a constant ratio.

Chemical similarity exists between systems that show geometric, kinematic, dynamic, and thermal similarity, if concentration differences between corresponding points in the two systems have a constant ratio to one another.

Similar systems in which temperature and concentration profiles are identical will perform the same, *i.e.* yields and selectivities will be the same in both systems over the whole equipment volume. However, it is impossible to reach all similarities simultaneously. This does not mean that the same overall yields and selectivities cannot be reached. This is possible for systems that are only partially similar (or even not similar at all).

Dimensionless numbers (**Re**ynolds number = $ud_t\rho/\mu$, **Nu**sselt number = hd_t/λ, **Sc**hmidt number = $c_p\,\mu/\lambda$, etc.) are the measures of similarity. Many correlations between them (known also as scale-up correlations) have been established. The correlations are used for calculations of effective (mass- and heat-) transport coefficients, interfacial areas, power consumption, etc.

Table 5.3-5

Relative importance of different information in scale-up;

Key: 1. Critical/very important; 2. Necessary/important; 3. Desirable/some importance; 4. Little value/irrelevant

	Single phase		Gas-liquid or liquid-liquid (semibatch reactors)			Catalytic (three-phase) (semibatch or continuous)	
	(Semi)batch reactor	Continuous stirred-tank reactor	Kinetics rate controlling	Mass transfer rate controlling	Mixed, mass transfer and kinetic regime	Kinetics rate controlling	Mass transfer rate controlling
Phenomena studied							
Chemical kinetics	1	1	1	3	1	1	3 or 4
Mixing	2	2	4	2	2	2	2 or 3
Mass transfer	4	4	4	1	1	4	1
Heat transfer	2 or 3	4	3	3	3	3	3
Scale-up methods							
Laboratory studies	1	1	1	2	1	1	2
Modelling	1	1	1	2	1	1 or 2	1
Pilot plants	3 or 4	3 or 4	4	3	3	3 or 4	2 or 3

The data obtained from industrial plants are scarce and usually are not published for proprietary reasons; they are used exclusively within the company where the correlations have been obtained. The literature correlations scatter for not always obvious reasons. A usual recommendation is to use the correlation within the range of process variables for which the correlation was developed. Generally, scale-up is limited if literature correlations are used. Impurities often change properties of products and mixtures of known compounds, with the consequence that the use of these correlations leads to unacceptable errors. In practice, only heat exchangers can be designed with high precision based on literature correlations. All other equipment can at best be designed with an accuracy of about 20%.

5.3.2.4. Uncertainties at scale-up

Regardless measures taken at scale-up and the content of theory in models, there will always be some uncertainty in a commercial unit. Performance of equipment in which surface phenomena take place or surfaces can be fouled (this particularly concerns deposition of some components already introduced to or formed in the equipment), will certainly differ from predictions. Legislation and market conditions (changes in legislation and changing demand for product) increase the margin of uncertainty. Risks arising from deficiency in technical and natural sciences can be approximately assessed and preventive actions taken, although there is no general method for evaluation of uncertainty at scale-up. The usual remedies are: (1) overcapacity of equipment items, (2) more versatile equipment, and (3) more resistant (durable) equipment. However, one has to be very cautious with increasing the size above the requirements. The use of larger equipment can lead to operation within an undesired flow regime or to maldistribution inherent to the regime. The general rule is to operate equipment reasonably far from unwanted (especially dangerous) conditions even if this gives rise to increased investment. Fortunately, this usually does not lead to excessively higher costs, because the region around the minimum of costs is usually rather flat. The costs of installation of equipment, costs of auxiliary equipment, etc. remain constant for larger equipment and the unitary costs of purchase or manufacture of larger units only increase slightly (see Section 7.3).

5.3.3. Modelling techniques

Models are widely used in the design of equipment and the analysis of existing equipment or equipment under design. There are three main classes of models:

- graphical models,
- physical models, and
- mathematical models.

5.3.3.1. Graphical models

Graphical models are all sorts of drawings that represent existing objects or objects to be constructed. Preparation of technical drawings of various degrees of details belongs to the standard procedures in the design and analysis of chemical plants. Chemical engineering drawings of equipment comprise dimensions of basic parts of equipment, specifications of materials to be used, etc. Such a drawing is the basis for detailed mechanical design.

Flow-sheeting is a very useful tool at any stage of process development, regardless the strategy taken. A flow-sheet is a graphical representation of the equipment in the commercial plant. It can be considered to be a graphical model of the plant. A flow-sheet contains: (1) all processes and operations (possibly with pictures of equipment) for transformation of raw materials into products of desired characteristics; all interconnections should be shown to follow all possible process sequences, (2) means for transportation and storage of raw and auxiliary materials, (3) means for conversion and transfer of energy, (4) units for treating waste and by-products, (5) pipes, lines, and valves, and (6) control equipment. The extent of details in pictures of the equipment depends on the stage of process development. They can be drawn more schematic or not at all at early stages and much more detailed at the stage of process design. An exemplary flow-sheet is shown in Fig. 5.3-17. Pictures of equipment on this flow-sheet correspond to the type of equipment items and are scaled to the equipment size. Operating conditions, mass and heat flows, batch sizes and compositions of streams can be also shown in the flow-sheet.

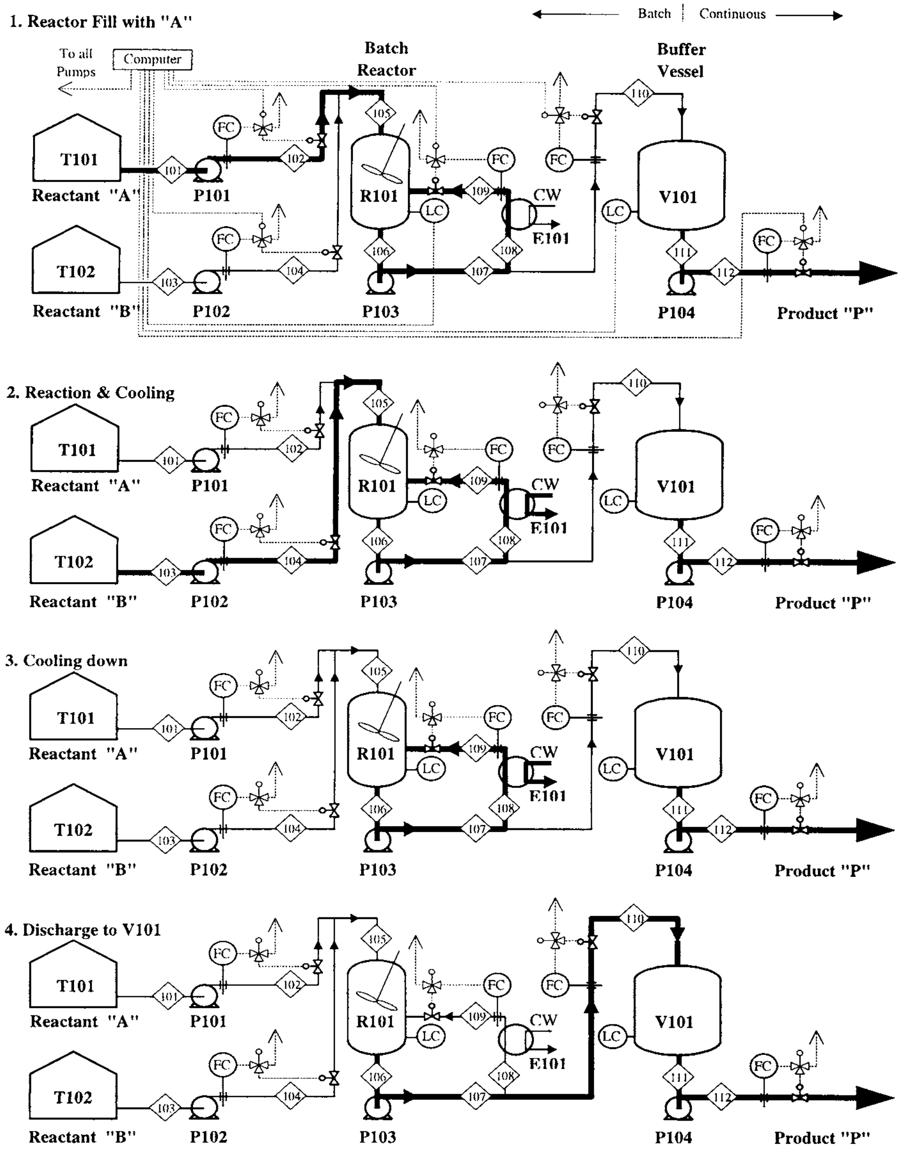
A flow-sheet should be prepared even at the exploratory stage of the process development. It will be based on literature data, preliminary process data, and data on similar processes. At any stage of scale-up, a flow-sheet will help in identification of critical phenomena to be studied in more detail with an indication regarding the scale at which these phenomena should be investigated. The final objective of process flow-sheeting is a cost evaluation for the whole plant, including investment and operating costs. This is achieved via an evaluation of all the streams and sizes of equipment items. The sizes are determined using more sophisticated modelling techniques for unitary equipment and using typical design techniques for conventional equipment.

5.3.3.2. Physical models

Physical models are representations of full-scale objects, mainly miniaturized ones. The models are usually made from easily processable materials such as wood, plastic, etc. Such models have been used for years in architectural designing. Physical models have also been applied in the design of chemical plants to visualize spatial disposition of equipment and all connecting lines. One-to-one scale models (mock-ups) are still often used in scale-up of chemical equipment to study hydrodynamics, if this significantly affects the performance of the equipment. Usually, segments of a full-scale apparatus are built of transparent material to enable easy studies on flow behaviour. Various aspects of hydrodynamic behaviour can be studied such as flow segregation, recirculation of solid particles suspended in a fluid, interface phenomena, etc. Mock-ups are operated at ambient temperature and pressure. As such, mock-up studies are less expensive (in both investment and operation) than pilot-plant studies. Of course, they are rarely used for single-phase processes. Exceptions are processes where non-Newtonian or very viscous liquids are processed. Mock-up studies can be more informative with respect to flow behaviour than pilot plant operation. The final output of mock-up studies consists of correlations in the form of dimensionless groups. Mock-ups are in common use for studying the performance of large equipment items such as those used in petrochemical plants and plants for bulk chemicals. They have proven to be extremely valuable. The use of mock-ups in development of technologies for fine chemicals is rare.

5.3.3.3. Mathematical models

Mathematical models are relationships in the form of mathematical expressions which describe the dependence of a process output (yield, product properties etc.) upon process variables, which include:



5. Idle : Only P104 running.

Figure 5.3-17. Flow-sheet of a batch process; unit symbols: E = heat exchanger, P = pump, R = reactor, T = storage tank, V = vessel; controllers: FC = flow controller, LC = level controller; ◇ stream number.

(1) design parameters (size and shape of equipment and of individual parts of equipment), (2) operating (process) conditions (temperature, pressure, flow rates, compositions), and (3) physicochemical properties (thermodynamic data, transport properties, kinetic constants). There are models of different complexity, ranging from simple algebraic equations to complex systems of partial differential equations. The increasing availability of powerful computers and efficient user-friendly computer programs makes modelling easy also for chemists who usually are not skilled in mathematics. Mathematical models are a very powerful tool in the design and analysis of chemical equipment and chemical plants.

There are two basic classes of mathematical models (see Fig. 5.3-18): (1) purely empirical models, and (2) models based on physicochemical principles.

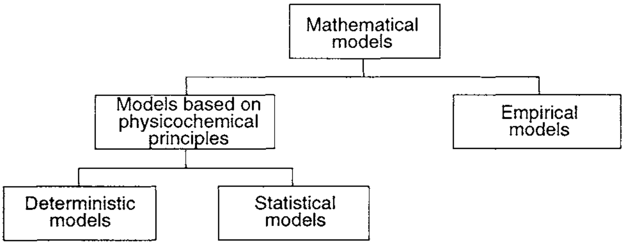


Figure 5.3-18. Mathematical models according to their physical principles.

(1) Empirical models are the ones whose form has nothing in common with the process mechanism, e.g. a rate expression such as $r = k \cdot c^{1/3}$. The usefulness of such models is very limited since they cannot be used for extrapolation, and, as a consequence, for scale-up. (2) Physically based models consist of conservation law equations for mass, energy, and momentum. These models are most commonly used in chemical engineering for scale-up and design. They can be subdivided into deterministic models and statistical models. The former are characterized by a determined set of dependent values for any given set of independent variables and model parameters. In statistical models, the variables and parameters are statistical quantities. The outputs of statistical models are quantities given with a certain probability. Deterministic models based upon physicochemical principles can be further divided according to their complexity (see Fig. 5.3-19).

Ideally, a mathematical model would link yields and/or product properties with process variables in terms of fundamental process phenomena only. All model parameters would be taken from existing theories and there would be no need for adjusting parameters. Such models would be the most powerful at extrapolating results from small scale to a full process scale. The models with which we deal in practice do never reflect all the microscopic details of all phenomena composing the process. Therefore, experimental correlations for model parameters are used and/or parameters are evaluated by fitting the calculated process performance to that observed.

In the construction of a model only those phenomena are accounted for which are thought to significantly lead to a better understanding of the process behaviour.

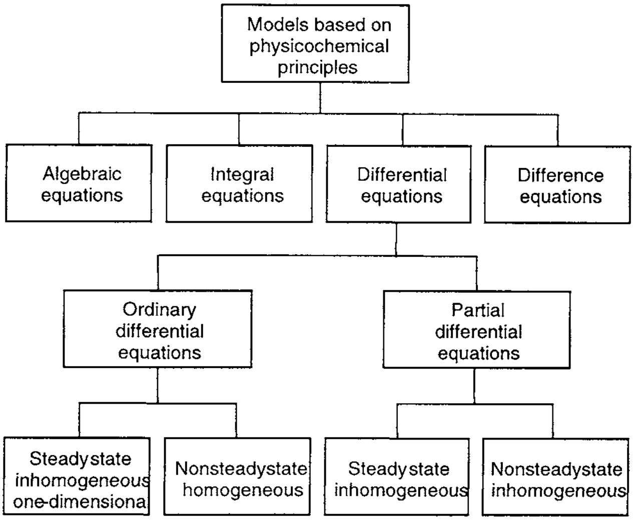


Figure 5.3-19. Deterministic models based on physicochemical models according to the type of equations.

The consequence of all these (conscious and unconscious) simplifications and eliminations might be that some information not present in the process will be included in the model. Conversely, some phenomena occurring in reality are not accounted for in the model. The adjustable parameters in such simplified models will compensate for inadequacy of the model and will not be the 'true' physical coefficients. Accordingly, the usefulness of the model will be limited and risk at scale-up will not be completely eliminated. In general, in mathematical modelling of chemical processes two principles should always be kept in mind. The first was formulated by G.E.P. Box of Wisconsin: 'All models are wrong, some of them are useful'. As far as the choice of the best of 'wrong' models is concerned, words of S.M. Wheeler of New York are worthwhile to keep in mind: 'The best model is the simplest one that works'. This is usually the model that fits the experimental data well in the statistical sense and contains the smallest number of parameters. The problem at scale-up, however, is that we do not know which of the models works in a full-scale unit until a plant is on stream.

In spite of all doubts, mathematical modelling in fine chemicals process development is strongly recommended. The following steps in mathematical modelling of chemical reactors can be distinguished:

- Problem definition,
- Model formulation,
- Estimation of parameters,
- Process optimization,
- Model verification,
- Choice of reactor type, process stability, optimization.

Problem definition. To successfully develop a model, the problem must be precisely defined. Chemists, engineers, and managers together have to determine the purpose of the model. When the model is to be applied for improving an existing process/product, the extrapolative properties of the model are not very important. Then the model is mainly used for interpolation within the range of operating variables investigated. Even if the content of theory in the model is insufficient from a scientific viewpoint, the model can be successfully applied to determine operating conditions close to the optimum. Areas of process performance in the vicinity of optimum are often nearly flat. Therefore, there is not always a need to search for the rigid optimum conditions. In contrast, a model for scale-up should contain much more theory since it will be used for extrapolation outside the range studied. An extensive treatment of the problem definition can be found in books of Himmmelblau and Bischoff (1968) and Luyben (1990).

Model formulation. After the objective of modelling has been defined, a preliminary model is derived. At first, independent variables influencing the process performance (temperature, pressure, catalyst physical properties and activity, concentrations, impurities, type of solvent, etc.) must be identified based on the chemists' knowledge about reactions involved and theories concerning organic and physical chemistry, mainly kinetics. Dependent variables (yields, selectivities, product properties) are defined. Although statistical models might be better from a physical point of view, in practice, deterministic models describe the vast majority of chemical processes sufficiently well. In principle model equations are derived based on the conservation law:

$$\left\{\begin{matrix} \textit{accumulation} \\ \textit{within} \\ \textit{the system} \end{matrix}\right\} = \left\{\begin{matrix} \textit{inflow to} \\ \textit{the system} \end{matrix}\right\} - \left\{\begin{matrix} \textit{outflow from} \\ \textit{the system} \end{matrix}\right\} + \left\{\begin{matrix} \textit{net generation} \\ \textit{within} \\ \textit{the system} \end{matrix}\right\} \qquad \textbf{(5.3-12)}$$

A variety of models of chemical reactors is discussed in more detail in Section 5.4. Readers who are interested in modelling of chemical reactors are also referred to books of Carberry and Varma (1987), Fogler (1986), Froment and Bischoff (1990), Levenspiel (1999), Smith (1981), Trambouze *et al.* (1988), Walas (1959), and Westerterp et al. (1990). With respect to heterogeneous reactions athe book of Doraiswamy and Sharma (1984) is also recommended.

Estimation of parameters. Model parameters in the selected model are then estimated. If available, some model parameters (e.g. thermodynamic properties, heat- and mass-transfer coefficient, etc.) are taken from literature. This is usually not possible for kinetic parameters. These should be estimated based on data obtained from laboratory experiments, if possible carried out isothermally and not falsified by heat- and mass-transport phenomena. The methods for parameter estimation, also the kinetic parameters in complex organic systems, and for discrimination between models are discussed in more detail in Section 5.4.4. More information on parameter estimation the reader will find in review papers by Kittrell (1970), or Froment and Hosten (1981) or in the book by Froment and Bischoff (1990).

Model verification. A very important, crucial step in modelling is model verification. This is a cyclic, iterative process which must be repeated with respect to all models at all stages of modelling until the desired agreement between calculated and observed performances is reached (or no more money and/or time for research is available). At every step simplifying assumptions are validated and compared with new observations. If any observation contradicts assumption(s), the latter have to be modified, new models derived based on modified assumptions, and model parameters re-estimated. The calculated performance should be in the desired agreement with observations. Other data than those used for fitting procedures should be used to assess whether the model is physically meaningful: the model should be in agreement with commonly accepted theories. For instance, estimated rate constants and activation energies must be positive. Thus, if any of these coefficients is significantly negative in terms of statistical analysis, the model must be rejected and search for a better one continued. The data must, however, be critically assessed before the model is rejected. It might happen that the model is adequate but the data are charged with an unacceptable, perhaps systematic error. One should keep in mind that the conclusion that a model should not be rejected does not necessarily imply that the model reflects reality. There might exist models based on different assumptions regarding mechanisms, but with very similar predictive power.

Choice of the reactor type, process stability, optimization. Based upon the accepted model, the process can be optimized without reference to any particular spatial configuration of the reaction zone. The objective of such an optimization is to determine the best time trajectories of operating variables such as temperature and concentrations, the most appropriate catalyst structure, etc. The optimum trajectories are then used for selection of the reactor type. If the optimum temperature profile is one increasing along the time co-ordinate, an adiabatic reactor might be a good option for exothermic reactions. When the best policy is to keep the concentrations of reactants as high as possible, batch or plug-flow reactors should be considered. If the concentration of one of the reactants should be low, this component should be added gradually (continuously or portion-wise) in time. The time-changes policy will thus determine the choice of the reactor type.

In fine chemicals manufacture, the reactor type is often given a priori. This is due to the need of fitting the process under development to existing multiproduct and multipurpose plants (see Chapter 7). The reactor can be simulated and/or optimized. Optimization of a reactor as an individual equipment item is rarely practised. Usually a system comprising the reactor and separation-purification units is optimized. It might well be that the optimum for the reactor itself lies outside the most advantageous region for the whole system. Simulations for studying the process sensitivity to operating conditions will indicate in which areas the process can easily run out of control. Perturbations like temperature, flow rate, or composition fluctuations can be imposed on the model and responses to these perturbations studied. After areas of high parameter sensitivity of the model and unstable process operation have been identified, it should be experimentally verified whether this is a characteristic feature of the model itself or a property of the real system. The range of the highest performance indices should be found within the constraints of stable, safe reactor operation. When safe operation is only possible at low performance, it is nearly always better to lower the process efficiency and operate safely, than to maximize performance when operating within an unstable region.

Full process models of commercial importance are not published for obvious commercial reasons.

5.3.4. Guidelines for scale-up of basic separation and purification techniques

Below, physical principles of basic separation and purification techniques are given and guidelines concerning collection of data that are needed or useful for scale-up of these unit operations.

5.3.4.1. Crystallization

A significant proportion of fine chemicals are solids. Therefore, crystallization is a major processing technique for separation and purification of these products. Crystallization is performed by bringing a solution into the state in which the solute concentration exceeds its equilibrium saturation (solubility). This is usually done: (1) by evaporation of the solvent and subsequent cooling of the solution, or (2) adding a substance which reduces the solubility of a solute in the solvent. The latter technique is called salting-out crystallization. Crystallization proceeds in two stages: (1) nucleation and (2) crystal growth. Both processes are strongly dependent on heat- and mass-transfer rates on a molecular scale and these, in turn, depend very much on the hydrodynamics, *i.e.* the pattern of fluid and particle movement. Hydrodynamics in the system is, however, a function of the solid content and particles shape and size distribution, and these usually vary with time. The rate of both stages can be very sensitive to impurities in the solution down to parts per million. Moreover, the system is thermodynamically unstable because of the existence of zones of supersaturation and unsaturation in the crystallizer. All these factors make crystallization very difficult to scale up and highly irreproducible in batch processing.

As mentioned above, crystallization is possible when the concentration of the solute is larger than the equilibrium saturation, *i.e.* when the solution is supersaturated with the solute. The state of supersaturation can be easily achieved if the solution is cooled very slowly without agitation. Above a certain supersaturation (this state is also called supersolubility) spontaneous formation of crystals often, but not always, occurs. Spontaneous nucleation is less probable in the state between equilibrium saturation and supersolubility, although the presence of fine solid impurities, rough surfaces, or ultrashort radiation can cause this phenomenon to occur. The three regions: (1) unsaturation (stable zone), where crystallization is impossible and only dissolution occurs, (2) metastable zone, extending between equilibrium saturation and supersolubility, and (3) labile zone, are shown in Fig. 5.3-20.

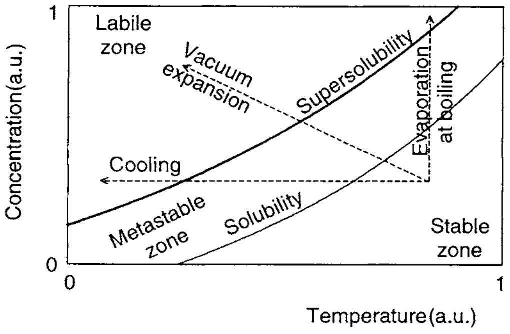


Figure 5.3-20. Saturation regions.

The location of the supersaturation boundary depends, among others, on the intensity of agitation and the content of impurities. The latter factor is of particular importance: Even very small amounts of impurities can significantly change the position of the supersolubility line. There are three ways to reach the labile zone starting from the stable zone: (1) by cooling, (2) by vacuum expansion, and (3) by solvent evaporation. When the temperature decreases the solution becomes more viscous. This can inhibit nucleation, and a glassy mixture or oily phase is then formed instead. Penetration of the labile zone by evaporation or expansion is less probable. The solution is heavily supersaturated in the vicinity of a heating surface. In this situation bulky nucleation occurs and crystals formed there move to the bulk of the solution inducing nucleation before the bulk concentration reaches the zone of lability.

Supersaturation can be expressed as the concentration driving force Δc, the supersaturation ratio, S, or the relative supersaturation, σ:

$$\begin{gathered}\Delta c = c - c_{sat} \\ S = \frac{c}{c_{sat}} \\ \sigma = \frac{\Delta c}{c_{sat}} = S - 1\end{gathered} \tag{5.3-8}$$

where c_{sat} is the saturation concentration at a given temperature. Supersolubility can be evaluated by measuring the concentration of the solute at a given temperature and comparing this with the equilibrium saturation. The concentration can be determined by measuring a property of the solution that is sensitive to the concentration, most commonly the density and the refractive index. The width of the metastable supersaturation zone can be determined as follows (see e.g. Mullin, 1972; Nyvlt, 1971; Rojkowski and Synowiec, 1991). The undersaturated solution of initial temperature T_0 is quickly cooled to temperature T_f in the stirred vessel, and the time at which a number of small crystals appear (visual or photometric evaluation) t is recorded. The experiment is repeated for various values of ΔT (= T_0-T_f). The plot $1/t$ versus ΔT is constructed (see Fig. 5.3-21).

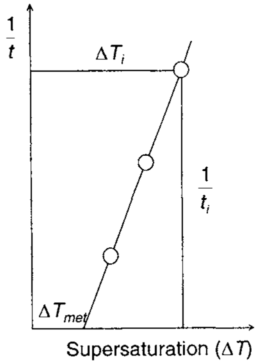


Figure 5.3-21. Determination of supersolubility line.

The extrapolated value of $\Delta T_{1/t \to 0}$ on this plot corresponds to the width of the metastable zone as expressed in terms of temperature, ΔT_{met}. The width of the metastable zone expressed in concentrations Δc_{met} can be read from the saturation line for the measured ΔT_{met}.

Supersaturation is a necessary but insufficient condition for crystallization. Before crystal growth starts, crystal nuclei must appear in the system by spontaneous or induced nucleation, or by adding crystals (seeding) to the solution. According to theory nucleation (birth of crystals) starts explosively above a certain level of supersaturation. This process of primary homogeneous nucleation is superimposed with heterogeneous nucleation at industrial conditions. Heterogeneous nucleation occurs starting with particles of impurities present in the system or on surfaces of equipment elements. The size of the generated nuclei are submicron to one micron and their number is enormous. Nuclei below 1 micron are likely to re-dissolve in the solution zones, which are away from the highest Δc.

For mixed homogeneous/heterogeneous primary nucleation, the following empirical expression can be used to describe its rate (*Kirk-Othmer Encyclopedia of Technology*, 1978-1984):

$$r_{nucl} = k_{nucl} (\Delta c)^b \tag{5.3-9}$$

where k_{nucl} and b are empirical coefficients (rate constant and order of nucleation). The order of nucleation typically ranges from 2 to 5. Nuclei are also formed by secondary nucleation. This proceeds when existing crystals contact other crystals or elements of the equipment (especially the agitator) with the resulting disintegration of primary crystals into very small ones. The rate of secondary nucleation is difficult to predict and can vary depending on mixing conditions in the crystallizer.

In general, excessive production of nuclei is detrimental since crystals produced under these conditions are fine, difficult to filter, and may contain a large fraction of impurities. Therefore, the solution should be kept in the metastable zone and be prevented to enter the labile zone. This can be achieved by seeding crystals into the solution to obtain a sufficient number of nuclei in the solution when penetrating the metastable zone. The mass of seeds m_{seed} of size L_{seed} that is required to produce crystals of size L_{cr} with the desired yield Y_{cr} is given by:

$$m_{seed} = Y_{cr} \left(\frac{L_{seed}^3}{L_{cr}^3 - L_{seed}^3} \right) \tag{5.3-10}$$

The difference between the course of seeded and unseeded crystallization is shown in Figs. 5.3-22 and 5.3-23. In case of unseeded crystallization the labile zone is entered and spontaneous crystallization starts. This results in decreasing concentration, temporary movement into the metastable zone accompanied by a temperature increase due to the exothermic crystallization, further cooling, and entering the labile zone again, etc. Finally, the crystal growth starts to dominate with a significant decrease of solute concentration until the equilibrium saturation line has been reached. Slow cooling of a seeded solution leads to a metastable zone in which the solution remains throughout cooling. Temperature control is much easier and penetration of the labile zone is avoided.

The growth of crystals proceeds in two subsequent-parallel stages: (1) diffusion and (2) integration.

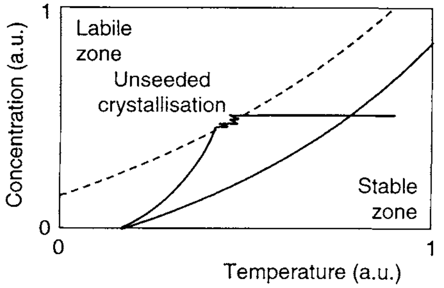


Figure 5.3-22. Unseeded crystallization by cooling.

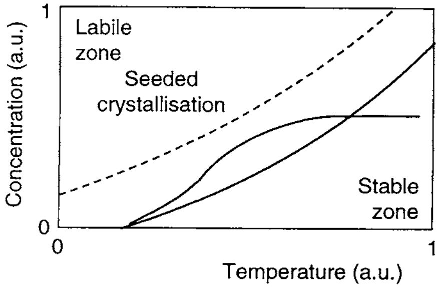


Figure 5.3-23. Seeded crystallization by cooling.

In the former, the solute diffuses from the bulk of the solution to the external surface of crystals. Molecules of the solute already adsorbed on the surface are then integrated into the crystal lattice. The rate of both steps can be expressed by the equation:

$$\frac{dm}{dt} = k_{diff}\, A_{cr}\left(c_b - c_s\right) = k_{int}\, A_{cr}\left(c_s - c_{sat}\right)^{\alpha_{int}} \qquad \textbf{(5.3-11)}$$

where m is the mass deposited in time t; c_b, c_{sat}, and c_s are the bulk solute concentration, the saturation concentration, and the concentration at the crystals surface, respectively; A_{cr} is the surface area of the crystals; k_{diff} and k_{int} are the mass-transfer coefficients for external diffusion and integration, respectively; and α_{int} is the order of integration. The concentration of the solute at the crystals surface, c_s, is difficult to determine. Therefore, for practical applications an empirical equation is used instead:

$$\frac{dm}{dt} = k_{gr}\, A_{cr}\left(c_b - c_{sat}\right)^{\alpha_{gr}} \qquad \textbf{(5.3-12)}$$

where k_{gr} is the rate constant for crystal growth. The value of the overall order of crystal growth, α_{gr}, varies widely. For aqueous solutions of inorganic salts it ranges from 1 to 2. The rate of crystal growth for organic compounds ranges from 10^{-8} to $8\cdot10^{-8}$ m/s.

The crystal size can be controlled by the cooling rate. If the rate is too high, supersaturation increases excessively (e.g. during 'natural' cooling, *i.e.* cooling which occurs when 'leaving the solution overnight' as specified in many laboratory recipes). This favours the formation of more nuclei instead of the growth of crystals. This is illustrated in Figs. 5.3-24 and 5.3-25. During natural cooling, a peak of supersaturation appears while in crystallization controlled by temperature, a constant supersaturation can be maintained. The following equation approximately describes the best temperature policy for crystallization:

$$T = T_0 - \left(T_0 - T_f\right)\left(\frac{t}{t_{total}}\right)^3 \qquad \textbf{(5.3-13)}$$

where T_0, T_f, and T are the initial and final temperature, and temperature at time t, respectively. An alternative method for evaluation of the best temperature-time policy was published by Ramanarayanan (1990).

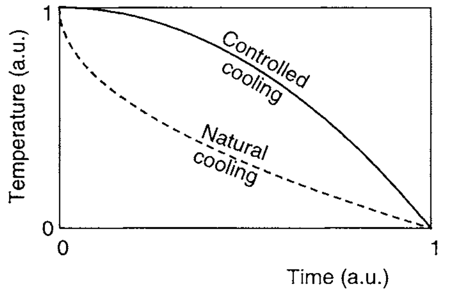


Figure 5.3-24. Temperature versus time for two cooling policies.

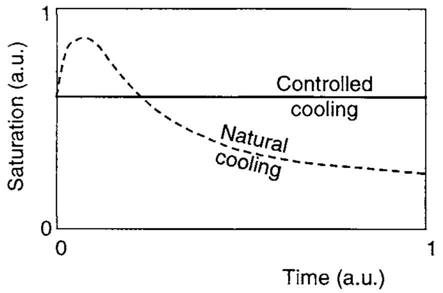


Figure 5.3-25. Saturation versus time for two cooling policies.

Supersaturation can also be achieved by adding a liquid that is miscible with the solvent and decreases the solubility of the solute in the mixed solvent. This is called precipitation. In fine chemicals manufacture, the solid is usually dissolved in an organic solvent and water is used as the desalting agent. Precipitation also occurs when a solid product, which is insoluble in the reaction mixture, is formed by chemical reaction. For instance, a phenolic product can be purified by three possible routes:

- classical crystallization by heating a mixture of the compound and the solvent until the compound is dissolved, and subsequent cooling of the solution,
- dissolution of the compound in an alkaline solution and subsequent addition of acid to the solution, and
- dissolution of the compound in methanol or acetone and subsequent addition of water to the solution.

The latter two methods are purifications by precipitation (salting-out crystallization). Precipitation is usually effected at ambient temperature. By proper selection of both the solvent and the desalting agent, a high concentration of the solution (and accordingly, a low volume of the crystallizer) and a high purity of crystals can be reached. Solvent recovery may be more difficult than for classical crystallization. The acidification-alkalination-neutralization method gives products with nearly 100 % yield. However, the purity is often questionable because of the presence of inorganic salts formed during dissolution-precipitation. The disadvantage of purification by precipitation is that small crystals with rather poor filterability are produced.

The crystal quality depends on: (1) inclusions that determine the content of impurities, and (2) shape and size distribution to which filterability of crystals is related. Formation of detrimental inclusions is caused by incorporation of 'strange' bodies (gas, liquid, or solid) into the crystal. Any dirt, rust, or other fines in the solution can result in incorporation of these materials into the crystals. The mother liquor can also adhere to the crystal surface or can be entrapped between agglomerated crystals. Formation of inclusions can be prevented by avoiding vigorous agitation (resulting in suction of the gas into the solution/slurry) and boiling during crystallization. This requirement contradicts with the need for agitation to improve nucleation and crystal growth. In general, very fast crystal growth favours the formation of inclusions. Therefore, conditions at which crystal growth is moderate or slow (e.g. low supersaturation) are recommended to avoid formation of inclusions. In case of difficulties in obtaining sufficiently pure crystals, the solution must be appropriately purified prior to crystallization. Boiling with active carbon is the commonly used method of purification. Knowledge of size distributions is rarely necessary in fine chemicals manufacture. Specification of crystals is mainly expressed in terms of a certain percentage of crystals that should be contained within a predetermined range. This range origins from requirements that are imposed either by applications of the crystals or determined by filtration. Larger crystals can be produced by adding a surfactant at ppm level, as proved by Wintermantel (1999) for a carboxylic acid.

There is almost no degree of freedom in the choice of the crystallizer type: Crystallization in fine chemicals manufacture is usually carried out in jacketed stirred tanks. Coils can also be used to enhance cooling, but crystals are often formed on their surface. This encrustation results in a large increase of the thermal resistance, and, consequently, a decrease of the cooling capability of the tank. Any roughness of inner surfaces of the tank can be a germ for crystals, particularly the cooled surfaces. Therefore, crystallizers are often made with polished cooled surfaces.

It can be concluded from the above that the following experiments on crystallization should be performed to produce data for decreasing the risk at scale-up of crystallizers:

- specify the desired characteristics of the product: the purity and the average size with the size range for 80-90% of crystals,
- select a solvent from which the crystals will grow without extreme geometries: dissolve pure product by heating in a solvent, add small amounts of the product till it remains undissolved, cool with agitation; find out whether crystal quality (size, shape, purity) is satisfactory,
- determine the solubility curve using the liquor from which the solid will be crystallized; do not use literature data concerning the solubility in pure solvents ⇒ other components of the liquor, even minor impurities, can change the solubility very much; check whether density and refractive index can be used as measures of the concentration,
- determine the location of the supersaturation boundary for the intensity of mixing that is expected to occur in a full-scale crystallizer; the metastable zone width provides the first measurable and predictable constraint for controlling supersaturation during cooling crystallization,
- identify and eliminate or reduce impurities that impede crystal growth; determine the location of the supersaturation boundary for different impurities; the larger the metastable zone width, the more detrimental the impurity is to the crystallization process,
- determine an approximate crystal size distribution (e.g. by using sieves) and crystal purity as a function of the rate of cooling for natural cooling and a for temperature versus time profile as calculated from Eqn. (5.3-13); if crystals are too small reduce the rate of nucleation by: (1) reducing the rotation speed of the mixer (consequently, energy dissipated per unit volume of the slurry), (2) slowing down the rate of cooling ⇒ in general, modifying the temperature versus time profile, (3) temporarily increasing the temperature at the end of crystallization (to dissolve small crystals), (4) seeding the slurry when approaching the solubility line ⇒ determine the influence of seeding crystal size on product size; check whether impurities affect the crystal size; determine the crystal size distribution versus time; in general, the

longer the batch crystallization time, the better the result,

- observe whether encrustation of cooled surfaces occurs during crystallization; determine the temperature at which encrustation starts; try different cooling profiles; temporarily heat heat-exchange surfaces to determine conditions at which encrustation is removed,
- if crystal growth is too slow and/or crystal purity is poor, consider the removal of impurities from the solution prior to crystallization or the increase of mixing intensity,
- when seeding, add the seed between the feed saturation temperature and the saturation temperature plus 40% of the metastable zone width, avoid seeding solutions with a very narrow metastable zone,
- limit supersaturation everywhere in the crystallizer to avoid primary nucleation and growth rates that would entrap impurities in occlusions.

The guidelines listed above are helpful in the scale-up of crystallization processes, but they will certainly not guarantee complete success. Flow characteristics of both liquid and solid can differ in small and large tanks to an extent that significant differences in rates of nucleation and crystal growth can be observed. Turbulence at baffles in an industrial apparatus enhance differences in hydrodynamics between both scales. Moreover, the energy dissipation distribution in industrial tanks is very wide and this will result in zones of more and less vigorous mixing. In the latter zones, transfer of the solute to the external surface of crystals will be slower, resulting in slower crystal growth. In general, one can expect a wider size distribution for the product obtained in large crystallizers. For all the mentioned and other reasons, the scale-up of crystallizers is highly uncertain. However, if the information listed above is available the risk of scale-up will be much reduced. To further decrease the risk, scale-up coefficients should not exceed, say 20 to 50.

5.3.4.2. Filtration

Filtration is the separation of a solid from the liquid in which it is suspended. This is done using a filter medium (tissue) which is permeable to the liquid and impermeable to the solid particles. The flow of the liquid is caused by the pressure difference between the slurry and the zone behind the filter medium. The pressure difference is due to: (1) pressurization of the slurry (pressure filtration), formation of a vacuum behind the filter medium (vacuum filtration), or centrifugal forces (centrifugation). Vacuum filtration of slurries containing highly volatile solvents should be avoided. There are two basic modes of filtration: with and without formation of a filter cake on the filter medium. In the former case the thickness of the cake increases during the process. In the latter case the slurry flows in parallel to the filter medium with a sufficiently large velocity to avoid cake formation. Here, we will deal with filtration involving the formation of a filter cake. The liquid in the cake must be washed out to an extent that depends on requirements with respect to solid and liquid quality. The liquid present in the raw or washed filter cake must be removed by deliquoring (passing a gas through the cake, compressing the cake, etc.) to make the process of drying the cake less expensive.

In fine chemicals manufacture, batch filtration prevails. This operation is the subject of R&D in various steps of process development. The aim of R&D on filtration is: (1) to establish an effective procedure of filtration and washing providing a filter cake and/or filtrate of desired quality, and (2) to select the most appropriate filter or centrifuge for full-scale operation and determine its productivity. The productivity is defined as:

$$P_{filter} = \frac{V_f}{t_{cycle}} \tag{5.3-14}$$

where V_f is the total volume of filtrate to be obtained and t_{cycle} is the overall time of the filtration cycle. The time t_{cycle} consists of the following components:

$$t_{cycle} = t_{ch} + t_{filtr} + t_{wash} + t_{disch} + t_{cl} \tag{5.3-15}$$

The time of charging the suspension to the filter, t_{ch}, is easy to determine if the density and viscosity of the liquid are known. The time of discharging, t_{disch}, can be evaluated as the time of removal of the filter cake and depends on whether the filter is equipped with an automatic discharge. If so, the discharge time is provided by the filter supplier. The time of filter cleaning, t_{cl}, is evaluated based on experience from using filters of the same type. The filtration time, t_{filtr}, washing time, t_{wash}, and time of deliquoring the cake, t_{deliq}, must be determined based on experimental studies at laboratory or pilot scale.

Filtration time. The filtration rate depends on the pressure difference, the solids content in the slurry, the particle shape and size distribution, the resistance of the filter medium to flow, and properties of the liquor. Observations show that the volume of the permeated liquor increases parabolically with time (see Fig. 5.3-26).

In order to make the liquor flow, the resistance of the formed cake and the resistance of the filter medium must be overcome. The flow through the cake can be assumed to be laminar, and can thus be described by:

$$\frac{1}{A}\frac{dV}{dt} = \frac{K\Delta P_c}{L\mu} \tag{5.3-16}$$

where dV/dt is the volumetric rate of filtration, A is the surface area of the filter medium, L is the instantaneous thickness of the filter cake, ΔP_c is the pressure difference over the filter cake, μ is the viscosity of the liquor, and K is the permeability of the filter cake. The permeability is related to the bed porosity and the particle shape and size distribution. For fibrous media K is of the order of magnitude of tens, while for sand $K = 5$.

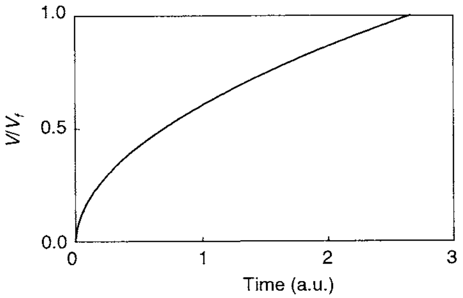


Figure 5.3-26. Volume of filtrate versus time.

The thickness of the filter cake is a function of the filtrate volume already permeated. This relationship can be expressed by the material balance of the solid:

$$(1-\varepsilon)LA\rho_s = Vw \tag{5.3-17}$$

where w is the effective solid concentration defined as the mass of dry solid deposited per unit volume of filtrate ($w = m_s/V$), ε is the porosity of the filter cake, $(1\text{-}\varepsilon)LA$ is the volume of the solid in the cake, and ρ_s is the density of the solid. Instead of permeability a 'specific cake resistance', α, is often used:

$$\alpha = \frac{1}{K\rho_s(1-\varepsilon)} \tag{5.3-18}$$

Combining Eqns. (5.3-16) to (5.3-18) and rearranging leads to the following equation for the flow rate through the filter cake:

$$V\frac{\alpha w\mu}{A^2}\frac{dV}{dt} = \Delta P_c \tag{5.3-19}$$

Both permeability, K, and specific cake resistance, α, depend on the particle shape and size distribution. However, this relationship has not been recognized conclusively. Therefore, information on the crystal shape and size distribution, which can be obtained from experiments on crystallization, cannot be easily translated into the language of filtration characteristics.

The resistance of the filter medium to flow, R_{fm}[5], is defined as:

$$\frac{R_{fm}\mu}{A}\frac{dV}{dt} = \Delta P_{fm} \tag{5.3-20}$$

where dV/dt is constant if the structure of the filter medium does not change during the flow of liquid. The total pressure difference over both the filter cake and the filter medium ΔP_t is given by:

$$\Delta P_t = \Delta P_c + \Delta P_{fm} = \left(\frac{\alpha w\mu}{A^2}V + \frac{R_{fm}\mu}{A}\right)\frac{dV}{dt} \tag{5.3-21}$$

Rearranging and integrating the above equation yields:

$$\frac{t}{V} = \frac{\alpha w\mu}{2A^2\Delta P_t}V + \frac{R_{fm}\mu}{A\Delta P_t} \tag{5.3-22}$$

The values of the specific cake resistance, α, and the resistance of the filter medium, R_{fm}, can be determined from the slope and the intercept of the plot t/V versus V for a given ΔP (see Fig.

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[5] Specific cake resistance α ranges from 10^8 m/kg for easily filtered large particles to 10^{13} m/kg for gelatinous cakes. The membrane resistance R_{fm} typically equals 10^8 to 10^{14} m^{-1}. Both α and R_{fm} depend on the filtering pressure.

5.3-27). If R_{fm} rises when repeating experiments several times N_f (Fig. 5.3-28) at constant ΔP, the filter medium should be considered unsuitable (apparently, the cloth is deteriorated by the medium or fine particles retained in the filter medium thereby clogging it). If the filtration rate is too low 'filter-aids' (silicagel, diatomaceous earth, active carbon, etc.) can be added to the suspension to improve the filterability of the cake. Alternatively, the slurry can be appropriately treated (e.g. by coagulation or flocculation). An improvement of the slope in the t/V versus V plot will show the effectiveness of the means applied. Filter aids are usually effective adsorbents and this property must be taken into account when balancing advantages and disadvantages of using a filter aid, especially when the desired product is the solute.

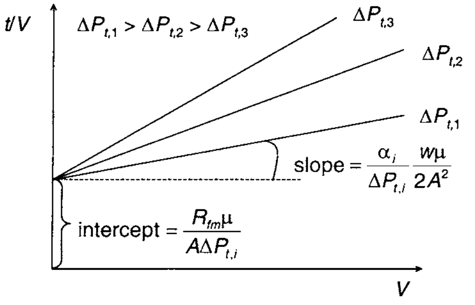

Figure 5.3-27. Linearization of filtration equation.

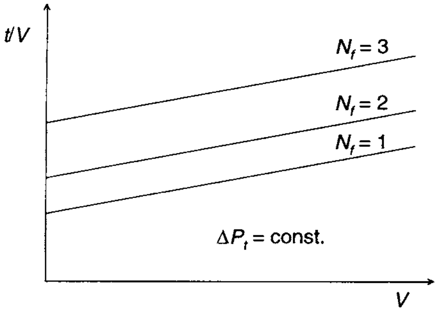

Figure 5.3-28. Linearized filtration equation for a clogging filter medium; N_f is the experiment number.

Measurements of filtration rates should be repeated at different pressures or different vacuum levels. This gives information on the influence of pressure on the specific cake resistance. The specific resistance of cakes that are difficult to filter is often pressure-dependent. Thus, use of excessive pressure can result in blocking of the cake, causing filtration to stop. In the case of compressible cakes, information is needed over the whole range of pressures being considered for industrial filters since extrapolation of compressibility beyond the experimentally covered region is always risky. The larger the scale of an experimental filter, the less risky predictions based on the experimental data.

The pressure dependence of the specific resistance is given by:

$$\alpha = \alpha_0 \Delta P_c^n \qquad \textbf{(5.3-23)}$$

where n is the cake compressibility[6]. If n is close to zero, the cake is incompressible and the influence of the pressure difference on the filtration rate is large. When n approaches one, the effect of pressure on the filtration rate is significantly diminished. Hence, highly compressible cakes should not be filtered under high pressures or be centrifuged. Filtration of highly

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[6] For compressible cokes of inorganic hydroxides like aluminium or ferric (III) hydroxide $n \approx 0.56 - 0.90$, for non-compressible cakes of calcium or magnesium carbonates $n \approx 0.10 - 0.15$, and for diatomaceous earth or silica $n \approx 0.01 - 0.02$.

compressible cakes under high ΔP can result in non-linearities on plots of t/V versus V. Another reason for such non-linearities is that the filter medium is getting clogged during operation.

The filtration equation (5.3-21) must be adopted if a centrifuge is used for separation. During centrifugation, the surface of the filter cake accessible for flow decreases since the cake builds up toward the axis of the centrifuge. Therefore, A^2 must be substituted by the product $A_a A_{lm}$ where A_a is the average flow area and A_{lm} is the logarithmic mean area through the cake. This yields:

$$\Delta P_t = \left(\frac{\alpha w \mu}{A_a A_{lm}} V + \frac{R_{fm} \mu}{A} \right) \frac{dV}{dt} \tag{5.3-24}$$

where A is the centrifuge bowl surface area for filtration, which remains unchanged because this term concerns the resistance of the filter medium. The pressure difference in centrifuges is given by:

$$\Delta P_t = \frac{\rho \omega^2}{2} \left(r_i^2 - r_e^2 \right) \tag{5.3-25}$$

where ω is the rotational speed and r_i and r_e are the bowl radius and the liquid pool radius, respectively. Compression of filter cakes during spinning should be expected because the pressure difference ΔP for centrifugation is much higher than that for pressure filtrations. Even a small compressibility n will result in a change in the packing density of the particles, and, consequently, in an increase of the specific cake resistance with pressure (spinning rate) and time.

Washing time. Washing of the filter cake is done to replace the liquor retained in the cake with the washing liquid to the desired extent. Washing can be performed by (1) a series of reslurryings of the filter cake with the washing liquid and subsequent filtrations of the slurry, or (2) displacement of the liquor retained in the cake after filtration by the washing liquid. In the former case, the degree of washing (DW) can be determined using the following equation derived for non-adsorptive solids and filter cakes of porosity that does not change by washings:

$$DW = 1 - \frac{c_f}{c_0} = 1 - \frac{1}{\left(1 + \frac{V_{wl}}{N_r V_l} \right)^{N_r}} \tag{5.3-26}$$

where c_0 and c_f are the concentrations of the mother liquor in the liquid remaining in the filter cake for the unwashed cake and the washed cake, respectively, V_l and V_{wl} are the volumes of the liquid retained in the cake after deliquoring and the volume of the washing liquid, respectively, and N_r is the number of reslurryings. Eqn. (5.3-26) is valid for a constant ratio of V_l/V_{wl} in all reslurryings. The total volume of the washing liquid that is needed to reach the desired degree of washing is minimum when preserving this condition. Cybulski and Choliński (1990) have estimated that the degree of washing can easily reach the value of 0.999 for moderate amounts of washing liquids. Modern filters and filter-dryers are equipped with appropriately designed agitators (see Chapter 7). These agitators enable reslurrying of the cake after filtration is finished. The filtration time for the slurry obtained by reslurrying can be evaluated using the filtration equation (5.3-21), in which the viscosity of the washing liquid, μ, and the effective solid concentration in the reslurried suspension, w, replace these properties of the initial slurry.

Washing by displacement of the mother liquor with the washing liquid consists in that: (1) filtration is stopped before the blanketing gas enters the cake, (2) the filter is depressurized and the washing liquid is poured on the cake so that no craters are formed in it, and (3) a pressure differential is established again and filtration is continued. The washing liquid moves like a piston (plug flow) pushing the mother liquor and displacing it in the cake. Therefore, washing of this type in theory requires less washing liquid than reslurryings at the same degree of washing. In practice, a proportion of the mother liquid remains in stagnant zones between the particles. This liquor can be removed by diffusional mass transfer which is slower than that by pushing. This is illustrated in Fig. 5.3-29.

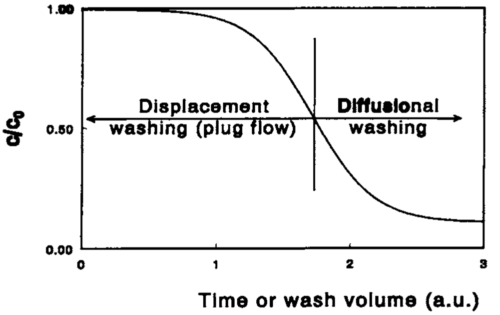

Figure 5.3-29. Washing of the filter cake by displacement.

For scale-up of filtration-washing the following information is necessary: (1) the amount of washing liquid for reaching the desired level of solid purity and/or solute concentration in the filtrate, and (2) the time t_{wash} to reach a desired DW. Washing is filtration at constant filter cake thickness. Accordingly, its rate is nearly constant and only varies because of the difference in the viscosity of the mother liquor and the washing liquid. There are many theories on displacement washing of filter cakes in the second phase. However, evaluation of the time required for washing is hampered by (1) changes in the cake structure when replacement is done, resulting in ruptures of the filter cake, (2) difficult and expensive determination of the level of the slurry inside the filter, and (3) problems with the uniform distribution of the washing liquid over the whole filter (nozzles are often plugged), and with cake deterioration (jets of the liquid hollow up craters in the cake). Therefore, the washing time must be determined experimentally and usually it is not very reproducible.

Time of deliquoring. Deliquoring of the filter cake must be done in case of reslurrying of the filter cake with the washing liquid and after washing has been completed. The cake can be deliquored by: (1) blowing with compressed gas, (2) application of a vacuum, (3) compression of the filter cake, and (4) centrifugation if a centrifuge was used for filtration. Removal of the liquid by compression is obviously limited to the smallest possible porosity of the cake. Using the other methods, deliquoring can be effected to a greater degree. The degree of deliquoring depends on the pressure difference and temperature. A time profile of the cake saturation (the ratio of volume of the liquid still present in the cake to the cake porosity that is equivalent to the maximum amount of the liquid in the cake) is shown in Fig. 5.3-30.

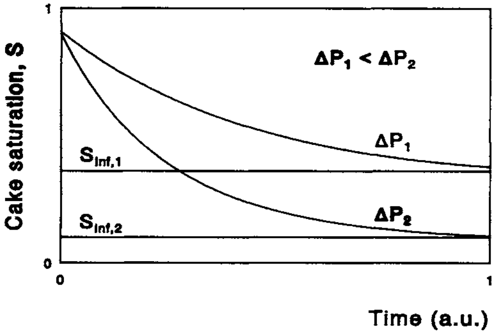

Figure 5.3-30. Deliquoring-time dependence.

Depending on the deliquoring conditions the cake saturation goes to an asymptote whose location is determined by the cake properties (porosity, internal pore size distribution, etc.), the viscosity and surface tension of the liquid, the pressure difference, and the temperature. Deliquoring has been studied extensively, but with no conclusive generalizations. Therefore, the most practical is to determine curves like those shown in Fig. 5.3-30 for cakes under consideration. Even the simplest deliquoring (with compressed gas or vacuum) usually results in cracks in the filter cake, which no longer sticks to the filter walls where clearances are formed. Any fluid (compressed gas or washing liquid) will preferentially flow through the cracks and clearances. Accordingly, neither washing nor deliquoring by passing the gas through the filter cake can be effective if the cracked filter cake has been treated in this way. Cracks can be removed by compression of the cake or cracks can be filled by using a mixer that is sliding on the upper surface of the cake (see filters in Chapter 7).

In conclusion, the following experiments on filtration-washing-deliquoring should be performed to produce data (viscosity of liquids, effective solid concentration, specific cake resistance, cake compressibility, etc.) that are necessary to evaluate times of individual steps of filtration at an industrial scale, *i.e.* to obtain the proper basis for scale-up of filtration processes:

- measure the filtrate volume versus time; make marks on your vacuum flask and take down the time when the filtrate level reaches the mark ⇒ no more experiments are needed for preliminary evaluations of filtration properties of slurries; initially fines pass the filter medium ⇒ recirculate them to the slurry,
- measure the viscosity of the mother liquor at process temperatures,
- determine the effective solid concentration, *i.e.* the ratio of the dry solid to the total volume of filtrate collected prior to deliquoring,
- repeat experiments with the same slurry at the same temperature and pressure difference at least three times to find out whether the filter medium preserves its permeability; if clogging occurs, check whether slowing down filtration at the initial stage prevents plugging of the filter medium; consider replacement of an unsuitable filter medium,

- repeat measurements at different pressure differences (different vacuum levels, different speeds of centrifugation); determine compressibility of the filter cake,
- if filtration is too slow also after 'filter-aids' have been added, use flocculation and coagulation media, modify the crystallization procedure, or change the viscosity of the solution by diluting or heating the slurry; repeat studies on the effect of ΔP on filtration rate,
- for centrifugation measure volume versus time profiles for different spinning rates; if the rate of filtration does not increase much with the speed of rotation lower the centrifugal acceleration, because otherwise the cake may be compressed and produce too high a resistance to flow; measure the rate of the cake drainage; if it is too low, lower the viscosity of the liquid or add a surfactant to decrease the surface tension of the liquid (particularly water),
- if washing by displacement is to be studied, complete filtration just after 'dry' particles appear on the upper surface of the slurry (do not continue filtration, because otherwise cracks and clearances at the filter walls will appear and these will make washing nonsensical), equalize pressures on both sides of the cake and pour a predetermined volume of the washing liquid uniformly and thoroughly over the cake to avoid formation of caves on its surface, measure concentration versus time curves for washing ⇒ take samples of filtrate and analyse concentrations; observe whether the cake ruptures during washing,
- wash the filter cake by reslurrying at least three times with the same volume of washing liquid, weigh the wet cake before reslurrying, determine the mass of the dry solid after washing has been completed; these experiments will let you know whether the solid has strong sorption properties towards process liquids,
- measure the weight change of the filter cake with time for different pressures and temperatures when deliquoring the filter cake, alternatively measure the time profile of the mass fraction of the solid in the filter cake by sampling and analysing the samples.

5.3.4.3. Drying of solids

The quality of solid products depends, among others, on the moisture content. Removal of the liquid that covers the outer surface of particles and is present inside pores is done by heating the material, possibly in contact with a gas or under vacuum, *i.e.* by drying. The aim of scale-up of driers is to find operation conditions in which the material will be dried in the shortest possible time while preserving its properties. The rate of drying depends on both mass and heat transfer. Fig. 5.3-31 shows typical moisture-versus-time profiles, while Fig. 5.3-32 shows corresponding drying rates-versus-moisture content curves. From these graphs it appears that drying proceeds in two stages after the material has been heated up to a pre-set temperature: (1) a step at constant rate, and (2) a step at a falling rate of drying. The two regions occur no matter how the material will be dried.

During the first period of drying, the liquid that covers the particle external surface and is present in the macropores evaporates. The material structure does not affect the rate of evaporation. The liquid evaporates with the rate at which heat is supplied to the surface. The rate of drying is thus limited by heat transfer between the particles and their surroundings. The temperature at the particle surface remains constant. If heat is delivered by convection this temperature is the wet-bulb gas temperature. In case of radiation (e.g. microwave driers) or conduction (e.g. indirect contact driers) the surface temperature ranges between the wet-bulb gas temperature and the boiling point of the liquid. The moisture content at the end of the constant rate of drying period is called the critical moisture content.

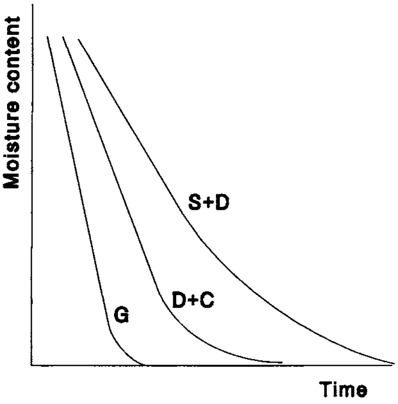

Figure 5.3-31. Drying-time dependence; *G*: materials of low porosity and large granule; *D* + *C*: fine and porous materials; *S* + *D*: material contains liquid in form of solution

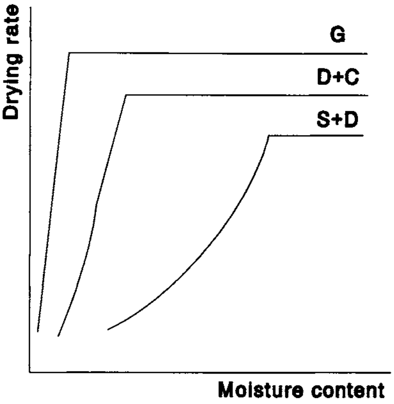

Figure 5.3-32. Steps in drying; see Fig. 5.3-32 for meaning of letters.

The critical moisture content is a complex function of material properties, particle size (the critical moisture content is higher for large granules), and rate of drying during the constant rate period (the lower the rate, the less the critical moisture content). Therefore, the critical moisture content is difficult to predict and should be determined experimentally for the selected drier and conditions of drying.

During the second period, the liquid in the pores moves to the external particle surface and then is removed to the particle surroundings. The rate of drying in this period is a complex function of the moisture content in the material. In general, the rate in this period is controlled by diffusion inside pores and by capillary forces whereby diffusion takes place in both the liquid and the gas phase. Materials of low porosity and large granule (*G*) are dried fast. Drying of fine and porous materials (*D*+*C*) proceeds following a more complex mechanism. During liquid evaporation in the constant rate period, liquid menisci are formed at the pore entrances and capillary forces draw the liquid from the interior to the outer surface. The situation changes at the critical moisture content. Some of the menisci begin to retreat into the pores and this causes a decrease in the wetted surface area inside the pores. The gas replaces the liquid that still forms the continuous phase. At a certain instant the liquid breaks into separate spots and evaporates at the cost of heat conducted inside the particles. Then the gas becomes the continuous phase inside the pores. Hence, capillary forces cause a drop of the drying rate during the second period of drying. Drying during this period can be speeded up by modification of the surface tension of the liquid (very high for water) inside pores. This can be achieved by replacing water with a volatile organic solvent of lower surface tension (three to four times lower). If the material contains the liquid in a form of solution (*S*+*D*) the falling rate period and time of drying is the longest.

The final moisture content depends on a type of solid. For non-hygroscopic materials the content may go down to nearly zero provided that the relative moisture of the drying air is less than one. If the material is hygroscopic the final moisture content depends on the balance of forces driving the moisture out of the pores and those preventing the removal.

The rate of drying during the constant rate period can be expressed by the following equation:

$$-\frac{dw}{dt_c}=\frac{h_t}{\rho_s \delta_L L_v}\Delta T_m \qquad \textbf{(5.3-27)}$$

where w is the moisture mass per unit mass of dry material, h_t is the overall heat-transfer coefficient between a heating surface and the particle surface, ρ_s is the dry material bulk density, δ_L is the thickness of the liquid layer, L_v is the latent heat of vaporisation, and ΔT_m is the difference between the mean temperature of the heat sources and that of the dried material. The heat-transfer coefficient, h_t, must be measured in the prototype of the commercial drier to be used in the full-scale plant. Use of h_t values that have been obtained for a drier of a different type is risky and may cause a considerable error in the evaluation of the drying time in the selected drier type.

When diffusion becomes the rate-limiting step, the time required for falling-rate drying can be estimated using an approximate equation:

$$t_{fd}=\frac{4d_p^2}{\pi^2 D}\ln\left[\frac{8(w_c-w_e)}{\pi^2(w_t-w_e)}\right] \qquad \textbf{(5.3-28)}$$

where d_p is the particle size, D the diffusivity, w_t, w_c, and w_e the moisture content at any time, the critical moisture content, and the moisture content in equilibrium with the environment, respectively. Drying of particulate solids by capillarity and diffusion can be approximately described using the following equation:

$$-\frac{dw}{dt_{fd}}=k_{dr}(w_t-w_e) \qquad \textbf{(5.3-29)}$$

where k_{dr} is the rate coefficient for the constant rate period at the critical moisture content, *i.e.*

$$-\frac{dw}{dt_c}=k_{dr}(w_c-w_e) \qquad \textbf{(5.3-30)}$$

Combining Eqns. (5.3-27) and (5.3-30), the following expression is obtained:

$$k_{dr}=\frac{h_t}{\rho_s \delta_L L_v}\frac{\Delta T_m}{(w_c-w_e)} \qquad \textbf{(5.3-31)}$$

Substitution of this expression into Eqn. (5.3-29) and integrating yields:

$$t_{fd}=\frac{\rho_s \delta_L L_v (w_c-w_e)}{h_t \Delta T_m}\ln\left(\frac{w_c-w_e}{w_t-w_e}\right) \qquad \textbf{(5.3-32)}$$

This equation can be used to relate the drying time of the material to the moisture content w_t in the falling rate region.

Laboratory and, mainly, pilot experiments should provide data that can be processed into parameters in equations for the calculation of the drying time in both regions. To collect these and other data useful in the scale-up of driers the following experiments should be performed:

- determine the initial and the final moisture content in the material to be dried, its chemical composition, consistence, heat sensitivity, ability to agglomerate, and toxic data (including products of decomposition if any can occur),
- dry the material using a tray drier in circulating air: weigh the sample over time at various temperatures, observe whether particles agglomerate, stick to each other or to the tray; find out whether the colour of the material changes or the material decomposes,
- in case of any detrimental influence of air repeat experiments under vacuum, determine the maximum allowable temperature of drying at which no observable change in the material properties will occur,
- based upon the preliminary experiments mentioned above select a type of drier to be used in the full-scale plant (possibly from driers present in the plant in which the process is to be implemented; among batch driers the following are of primary interest: fluid-bed drier and rotary drier for non-paste materials, and tray drier, microwave drier, and agitator drier for any material to be dried),
- repeat the experiments listed above using a pilot drier of the selected type, estimate the time of drying for the constant drying rate and parameters in expressions for the calculation for the falling drying rate regions; optionally, the experiments are performed in vendor test equipment with the material delivered by the process development team.

5.3.4.4. Liquid-liquid extraction

Liquid-liquid extraction (also called solvent extraction) is the transfer of a substance (a consolute) dissolved in one liquid to a second liquid (the solvent) that is immiscible with the first liquid or miscible to a very limited degree. This operation is commonly used in fine chemicals manufacture: (1) to wash out impurities from a contaminated solution to a solvent in order to obtain a pure solution (raffinate) from which the pure substance will be isolated, and (2) to pull out a desired substance from a contaminated liquid into the solvent leaving impurities in the first liquid. The former operation is typically employed when an organic phase is to be depleted from impurities which are soluble in acidic, alkaline, or neutral aqueous solutions: Water or a diluted aqueous solution is then used as the solvent. The pure raffinate is then appropriately processed (e.g. by distillation) to isolate the desired consolute. In the latter version of extraction impurities remain in the first phase. The extract that has become rich in the desired consolute is then appropriately processed to isolate the consolute. Extraction can also be used to fractionate multiple consolutes.

Distribution of the consolute C between the phases A and B in equilibrium can be described using the distribution coefficient, K_{extr}:

$$K_{extr} = \frac{c_B}{c_A}\left(\text{or } \frac{x_B}{x_A} \text{ or } \frac{a_B}{a_A}\right) \qquad \textbf{(5.3-33)}$$

where c_A and c_B are the concentration of C in phase A and B, respectively, x_A and x_B are mole or mass fractions of C in phase A and B, respectively, and a_A and a_B are activities of C in phase A and B, respectively. For immiscible liquids A and B, the distribution coefficient, K_{extr}, is constant over the entire range of concentrations of C in both phases if activities are used. The ratio of quantities C in both phases is related to distribution coefficient as follows:

$$\frac{quantity\ of\ C\ in\ phase\ B}{quantity\ of\ C\ in\ phase\ A} = K_{extr}\ \frac{quantity\ of\ B}{quantity\ of\ A} \tag{5.3-34}$$

The situation becomes more complex if liquids A and B and/or any of the two liquids and the consolute C are partially miscible. This is illustrated on a typical equilateral triangle for two different mixtures of A, B, and C (see Figs. 5.3-33 and 5.3-34).

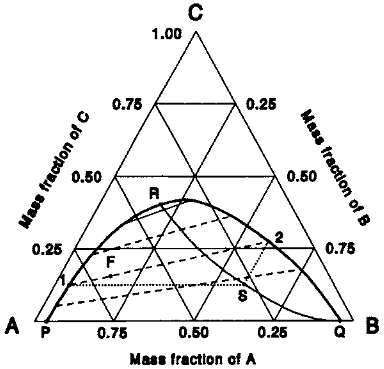

Figure 5.3-33. Extraction equilibrium triangle; system A.

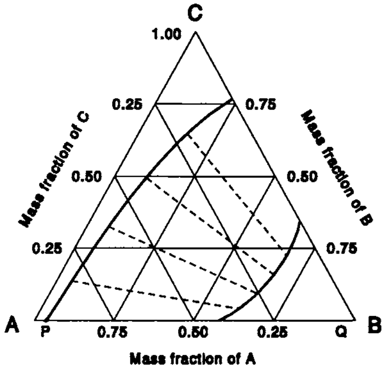

Figure 5.3-34. Extraction equilibrium triangle; system B.

Fractions of all components in the overall mixture (regardless whether separated in two phases or as a homogeneous system) are equal to distances between the point and the triangle side opposite the appropriate cusp of the triangle measured along axes inclined at an angle of 60°: The composition of the mixture represented by point F in Fig. 5.3-33 is $x_A^F = 0.69$, $x_B^F = 0.16$, and $x_C^F = 0.15$. The envelope represents an equilibrium line above which the homogeneous three-components phase exists while under the line the system separates into two phases. The composition of two phases being in equilibrium is given by points of intersection of tie lines with the equilibrium line. The tie lines are usually inclined to the axes and their inclination changes within the envelope. All the tie lines can be represented by a conjugate line RSQ from which any tie line can be constructed as shown in Fig. 5.3-33 for the tie line (1,2). The point R on the envelope is called the plait point. It defines the maximum concentration of the consolute that may be present while still maintaining two liquid phases, and also the point where the two phases become one. Points P and Q represent limits of the homogeneous mixture of the liquids A and B. For the case considered, the consolute and any of the two liquids A and B are miscible infinitely. A mixture of composition F separates into two phases whose compositions are given by points *1* and *2*. Relative amounts of both phases at the point F can be evaluated by the inverse lever rule:

$$\frac{quantity\ of\ phase\ 1}{quantity\ of\ phase\ 2} = \frac{distance\,(F,2)}{distance\,(F,1)} \qquad \textbf{(5.3-35)}$$

Equilibrium data are thus necessary to estimate compositions of both extract and raffinate when the time of extraction is sufficiently long. Phase equilibria have been studied for many ternary systems and the data can be found in the open literature. However, the position of the envelope can be strongly affected by other components of the feed. Furthermore, the envelope line and the tie lines are a function of temperature. Therefore, they should be determined experimentally. The other shapes of the equilibrium line can be found in literature. Equilibria in multi-component mixtures cannot be presented in planar graphs. To deal with such systems lumping of consolutes has been done to describe the system as pseudo-ternary. This can, however, lead to considerable errors in the estimation of the composition of the phases. A more rigorous thermodynamic approach is needed to regress the experimental data on equilibria in these systems.

The equilibrium determines the extraction limit and is a component of a driving force for the process: the greater the distance from equilibrium, the faster extraction will be. The rate of transfer of a component C between two phases A and B can be given by the following equation:

$$N_A = k_A(c_A - c_{Ai}) = k_B(c_{Bi} - c_B) \qquad \textbf{(5.3-36)}$$

where N_A is the mass-transfer rate per unit interfacial area, k_A and k_B are mass-transfer coefficients[7], and c_A, c_B, c_{Ai}, and c_{Bi} are the concentrations of the consolute in the bulk of phases A and B, and in both phases at the interface, respectively. The flux may be expressed in terms of bulk concentrations only, if it can be assumed that $c_{Ai} = c_B/K_{extr}$. Then:

$$N_A = K_B(c_A K_{extr} - c_B) \qquad \textbf{(5.3-38)}$$

or

$$N_A = K_A\left(c_A - \frac{c_B}{K_{extr}}\right) \qquad \textbf{(5.4-37)}$$

where

$$\frac{1}{K_A} = \frac{1}{k_A} + \frac{1}{K_{extr}k_B} \qquad \textbf{(5.3-39)}$$

and

$$\frac{1}{K_B} = \frac{K_{extr}}{k_B} + \frac{1}{k_B} \qquad \textbf{(5.3-40)}$$

The mass-transfer rate per unit volume of the extractor is given by:

$$N_A \cdot a = K_A a\left(c_A - \frac{c_B}{K_{extr}}\right) \qquad \textbf{(5.3-41)}$$

where a is the interfacial surface area per unit volume. For spherical droplets of the dispersed phase of an average size d_m, the interfacial surface area amounts to:

$$a = \frac{6\,\varepsilon_{disp}}{d_m} \tag{5.3-42}$$

where ε_{disp} is the volume fraction of the dispersed phase (hold-up). The mean droplet diameter is defined as:

$$d_m = \frac{\sum_{i=0}^{N_p} d_i^3}{\sum_{i=0}^{N_p} d_i^2} \tag{5.3-43}$$

where N_p is the number of droplets. For turbulent agitation, the mean droplet diameter is given by:

$$d_m = K' \frac{\sigma^{0.6}}{\rho_c^{0.6}\,\psi^{0.4}} \tag{5.3-44}$$

where σ is the interfacial surface tension, ρ_c is the density of the continuous phase, ψ is the rate of energy dissipation per unit mass of fluid, and K' is a dimensionless coefficient[8]. The product K_Aa[9] strongly depends on the properties of the liquids and the geometric characteristics of the system. In particular, it can be influenced by the presence of even traces of surface-active contaminants or other products accumulating at the interface and inhibiting interfacial mass transfer. Therefore, the value of the product K_Aa should be estimated using experimental data produced in a set-up similar to that predicted for the full-scale equipment for a full range of process conditions (type of stirrer, speed of rotation/pulsation, temperature, flow rate of inlet streams, etc.). One should keep in mind, however, that both the rate and the distribution of energy dissipation in the large apparatus will differ from that in the laboratory extractor even when both apparatuses are of the same type. These factors may cause differences between the performance of pilot and full-scale extractors.

Separation of phases is sometimes a problem, especially in the case of mixtures of alkaline aqueous solutions and organic liquids. Addition of materials that decrease the surface tension, filtration of the emulsion to remove interfacial contamination, and the use of sedimentation centrifuges should be considered if the separation time is too long.

In conclusion, the following experiments on extraction should be performed to produce data which will be helpful in the scale-up of extractors:

- investigate liquid-liquid equilibrium data: analyse and mix (using an agitator that guarantees vigorous mixing) a known quantity of the feed material with a known amount

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[7] Mass-transfer coefficients range from 10^{-5} to 10^{-2} m/s.

[8] For stirred tanks with hold-ups up to 0.35 the constant $K' = 0.024\cdot(1+\varepsilon_{disp})$. For reciprocating-plate extraction columns $K' = 0.18$, while for pulsed perforated-plate columns $K' = 0.18$ (*Kirk-Othmer Encyclopedia of Technology*, 1978-1984).

[9] A typical value for the product K_Aa is $0.1\,s^{-1}$.

of the fresh solvent for a predetermined period of time, separate phases and analyse samples of both; check whether the time of mixing was sufficient to reach equilibrium ⇒ if so, compositions of both phases will not change despite continuation of mixing; repeat experiments with a new portion of the solvent and the raffinate obtained; this process should be repeated until the entire range of consolute concentrations of interest has been covered; the experiments specified above in principle are sufficient to scale-up batch tank extractors equipped with stirrers,

- observe the behaviour of both phases during mixing (perform experiments in an apparatus made of glass using the actual process feed material for tests) in a continuous column extractor to determine: (1) whether stable emulsions form, (2) how droplet dispersion is distributed along the extractor, (3) whether coalescence of the dispersed phase occurs followed by flooding of the column, (4) whether droplets coalesce (increase energy input to beat coalescence or reverse the phases), (5) whether the light phase is entrained at the bottom or the heavy phase is entrained at the top of the column (increase the volume of the settling compartment or add a coalescing agent to the compartment),
- measure flow rates and compositions of inlet (feed and solvent) and outlet (extract and raffinate) streams at a set temperature and mixing conditions (type of mixing, energy input); repeat measurements for other sets of operating conditions ⇒ 3-5 displacements of the column volume are usually sufficient to reach new steady-state conditions,
- determine the best operation conditions (within the operating range constrained by undesired phenomena) for which the sensitivity to changes of process conditions is acceptable.

5.3.4.5. Distillation

Distillation is commonly used in fine chemicals manufacture for: (1) separation of volatile components in solutions obtained from chemical reactions or extractions, and (2) purification of liquid products. Distillation is based on diffusion-thermal separation utilizing the well-know fact that the composition of a vapour differs from the composition of the boiling liquid being in equilibrium with the vapour. Fig. 5.2-2 shows typical relationships between the vapour composition (mole fraction of the more volatile component, y) and the liquid composition (mole fraction in the liquid, x), which illustrates a vapour enrichment in the low-boiling component. The distance between the equilibrium line and the diagonal is large and this mixture can be easily fractionated. Fractionation is also possible for a smaller distance between the two lines although the column for this case would have to be much higher and/or recycle much larger. If the equilibrium line and the diagonal intersect, separation by normal distillation is not possible. The intersection point represents an azeotrope and this is the limiting composition that can be achieved by distillation.

Distillation is a well-known process and scale-up methods have been well established. Many computer programs for the simulation of continuous distillation columns that are operated at steady state are available. In fine chemicals manufacture, this concerns separations of products in the production of 'bulk' fine chemicals and for solvent recovery/purification. In the past decade, software for modelling of distillation columns operated at non-steady state, including batch distillation, has been developed. In the fine chemicals business, usually batch distillation is applied.

In general, the only problem in the scale-up of distillation is to obtain reliable vapour-liquid equilibrium (VLE) data. Computer programs cover the vast majority of physical systems and data banks for VLE are included in these programs. However, VLE data are not available for new products and often not for known products. In these cases, experiments on VLE are necessary to provide the basic data for distillation scale-up and design:

- determine vapour compositions for various liquid compositions using a typical ebulioscope for VLE studies (see Krell, 1963),
- set up an experimental installation consisting of: (1) a heated still with a temperature indicator and a sampling device, (2) an adiabatic packed column with efficient packing ⇒ the ratio of the column diameter to the size of packing elements should not be less than 10:1, (3) an overhead condenser (enabling separation of phases, if two form) with temperature sensor located before cooling, and (4) a reflux splitter (see Cusack, 1998a),
- determine the efficiency of the packing (the number of theoretical plates) using test mixtures such as, e.g. *n*-heptane-methylcyclohexane, benzene-ethylene dichloride or benzene-carbon tetrachloride for atmospheric pressure distillations or *n*-decane-*trans*-decaline for reduced pressure distillations (see Krell, 1963),
- charge the material into the pot and distill it under different reflux ratios; comparison of modelling results based upon VLE data and efficiency of the packing with experiments will provide data for modification of design equations for the distillation column,
- in case of azeotropes evaluate methods to break azeotropes: repeat measurements under vacuum or under elevated pressure (location of azeotropes moves when pressure is swung), evaluate solvents for extractive distillation (see Chapter 6), or evaluate solvents for azeotropic distillation; observe the overhead decanter to get the data to allow sizing of this decanter,
- observe the material in the distillation system to detect changes during prolonged heating (heat sensitivity of the material) and other possible problems such as fouling of the equipment (e.g. foaming); compare results of calculations based on VLE data and literature design procedures with experiments to assess whether fouling of any sort should be taken into consideration in scale-up,
- if distillation is to be carried out batch-wise determine the degree to which distillation may be carried out (considering safety aspects and possibility of emptying the still), find a solvent that can be used to clean the still, determine the atomic composition and flash point of the residue dissolved in the solvent.

5.4. CHEMICAL REACTOR SCALE-UP, DESIGN, AND OPERATION

5.4.1. Introduction; reactor classification

A chemical reactor is an apparatus of any geometric configuration in which a chemical reaction takes place. Depending on the mode of operation, process conditions, and properties of the reaction mixture, reactors can differ from each other significantly. An apparatus for the continuous catalytic synthesis of ammonia from hydrogen and nitrogen, operated at 720 K and 300 bar is completely different from a batch fermenter for the manufacture of ethanol from starch operated at 300 K and 1 bar. The mode of operation, process conditions, and physico-chemical properties of the reaction mixture will be decisive in the selection of the shape and size of the reactor.

There are several criteria based on which chemical reactors are classified: (1) mode of operation, (2) number and type of phases participating, (3) thermal conditions, and (4) design features.

5.4.1.1. Mode of operation

Figure 5.4-1 illustrates the various modes of operation.

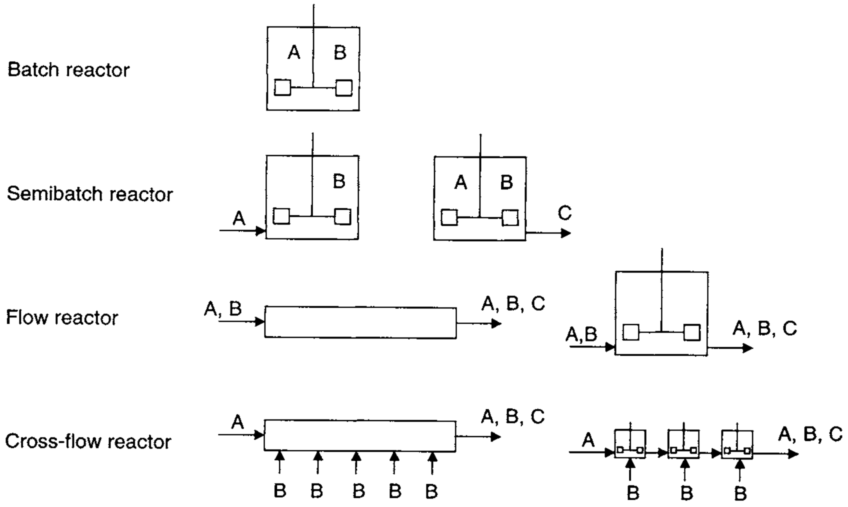

Figure 5.4-1. Modes of reactor operation.

In *batch reactors* all components of the reaction mixture are charged into a reactor. Then operating conditions (temperature, pressure) are brought to and maintained at a pre-set level or changed in time to be as close as possible to profiles determined as optimum ones. After the required state of the reaction mixture has been reached, the reactor content is brought to operating conditions which allow for emptying of the reactor (sometimes a physical or chemical quench is necessary) and the reaction mixture is removed from the reactor. After the reactor has been cleaned, a new batch of reactants is charged. Batch reactors are non-stationary: concentrations and, usually, temperature are functions of time:

$$c_i, T = f(\text{time}) \tag{5.4-1}$$

Fortunately, often they are practically the same everywhere in the reaction zone. If mixing in the batch reactor is not ideal, temperature and concentrations might become a function of position in the reactor. In extreme cases dead zones might appear with no mixing at all. Inhomogeneities arise in viscous mixtures (especially in the case of non-Newtonian liquids) and multiphase reaction mixtures. Tank reactors equipped with stirrers and heating/cooling jackets (*stirred-tank reactors*) are typically operated as batch reactors. Gas inducing impellers are in common use for dead-end hydrogenations.

Semibatch reactors are operated in two different modes: (1) Some components of the reaction mixture are loaded into the reactor. After the operating conditions have reached the required level, the other components are dosed continuously or portion-wise, whereby temperature and pressure are kept as close as possible to profiles determined as optimum ones. This mode of operation allows easy control of the concentration of the reactant added. When addition is completed the reaction mixture is usually kept in the reactor for some time. (2) All reactants are charged into the reactor and operating conditions are brought to and maintained at the pre-set level or changed appropriately with time. During the reaction some components of the reaction mixture are withdrawn continuously, usually at a flow rate varying with time. This can be realized, e.g., by evaporation or filtration. Semibatch reactors can be also operated in a combined (1)+(2) mode. In semibatch reactors the reaction is carried out under non-stationary conditions:

$$c_i, T = f(\text{time}) \qquad \textbf{(5.4-2)}$$

The semibatch mode of operation is very practical when the reaction rate(s) must be carefully controlled, e.g. to balance the rate of heat removal (limited by the reactor design and properties of the reaction mixture) and the rate of heat evolution. A feed stream must be well mixed with the reaction mixture inside the reactor. Mixing is provided either by mechanical agitation (stirred-tank reactors) or by the kinetic energy of the injected stream (e.g. vertical *column reactors* with a gaseous reactant introduced through a sparger). Semibatch reactors are also used when a high ratio of reactants is necessary to reach a high selectivity (e.g. nitrations carried out by periodical addition of fuming nitric acid to a mixture of aromatics and concentrated sulphuric acid). Batch and semibatch reactors are most often used in the manufacture of fine chemicals.

Flow reactors are fed continuously at one location with streams of reactants already at the required temperature and pressure. The reaction mixture flows out continuously from the end of the reaction zone. Flow reactors are operated under steady-state conditions, i.e. concentrations, temperature, and pressure at a point of the reaction zone are constant. To be precise, they fluctuate with the quality of raw materials and the accuracy of controllers maintaining flows, temperatures, and pressure.

There are two main kinds of flow reactors: *tubular reactors* and *tank reactors*. Tubular reactors are characterized by a high length-to-diameter ratio. Generally no mixing device is installed in the tubular reactor. However, this is not a judicious practice. In recent designs static mixers are used to enhance mixing inside the tube and heat transfer between a stream flowing through the tube and a cooling medium outside the tube. An ideal case of the tubular reactor is the *plug-flow reactor (PFR)*. The reaction mixture flows through the PFR as if a piston were moving forward. There is ideal fast radial mixing of the reaction mixture so no radial difference in concentrations exists. The residence time of each microscopic part of the reaction mixture is identical. Concentrations, temperature, and pressure depend on the position in the reactor zone:

$$c_i, T, p = f\ (\text{position}) \qquad \textbf{(5.4-3)}$$

The concentration of reactants is highest at the inlet of the reactor. Real reactors behave as if they were ideal if: (1) the thermal effect of the reaction is negligible or heat generation/consumption is far slower than heat exchange with the surroundings, (2) radial mixing is intense (this is nearly fulfilled for turbulent flow, e.g. through tubes filled with solid particles), and (3) axial transport of molecules in the direction opposite to the flow is negligible.

The length (height) and the diameter of tank reactor are close to each other or at least of the same order of magnitude. Tank reactors are usually equipped with a stirrer. In an ideal *continuous stirred-tank reactor (CSTR)*, a feed stream is instantaneously mixed with the reaction mixture before molecules of the stream start to react. In reality, small reactors with vigorous stirring where relatively slow reactions occur behave as if they were ideal CSTRs. The concentration of the feed components is immediately decreased to a level which depends on the ratio between the feed flow rate and the volume of the reactor. The larger the reactor the lower the concentration becomes. Thus the concentration in a CSTR is lower than that at the inlet of a PFR. As a consequence, for 'normal' kinetics, the reaction rate is also lower in the CSTR. The residence time is not the same for every microscopic part of the feed. Concentrations, temperature, and pressure are constant, *i.e.* independent of the position in the ideal CSTR:

$$c_i, T, p = \text{position independent} \qquad \textbf{(5.4-4)}$$

When a CSTR is replaced by a series of many CSTRs with a total volume that is equal to the volume of the single CSTR, plug-flow behaviour is approached. This configuration is called a *cascade of CSTRs*. The concentration in the first reactor is higher than in one large CSTR and the reaction will proceed faster. The overall reaction rate expressed per total reactor volume is higher in a cascade of CSTRs than in a single CSTR of the same volume. A cascade consisting of more than five reactors nearly always behaves similarly to an ideal PFR.

In a certain range of process conditions, column reactors for multiphase processes behave as a tubular reactor with respect to gaseous reactants and as an ideally mixed tank reactor with respect to condensed phases.

The continuous mode of operation makes reactors less versatile. Therefore, flow reactors, especially tubular reactors, are dedicated to a particular reaction system.

Cross-flow reactors are fed continuously with streams of components of the reaction mixture whereby some components are introduced at the inlet, while others are introduced at other locations. The reaction mixture flows out continuously from the end of the reaction zone. A cascade of CSTRs with additional feeds to individual reactors represents a cross-flow reactor system. Cross-flow reactors are also operated at steady-state conditions:

$$c_i, T, p = f\,(\text{position}) \qquad \textbf{(5.4-5)}$$

whereby position should be read as the distance from the inlet of the tubular reactor or the number of the reactor in a cascade. Cross-flow reactors with plug flow are equivalent to ideally mixed semibatch reactors that are fed portion-wise with time intervals corresponding to distances between dosing locations (mathematical models of both reactor types are *isomorphic*).

5.4.1.2. Number and type of phases participating in a process

Depending on the number and type of phases, we can distinguish the following reaction systems:

- reactors for homogeneous processes,
- multiphase reactors (in fine chemicals manufacture mainly gas-liquid, liquid-liquid, gas-liquid-solid, liquid-solid, and gas-solid),
- multiphase catalytic reactors as a specific case of multiphase reactors.

In *homogeneous process* the components of the reaction mixture are mutually soluble including a homogeneous catalysts if used. Mixing of reactants is necessary if the process to be carried out either (1) consists of a series of reactions of which the rates differ significantly and at least one of the important reactions is very fast, or (2) is exothermic and fast enough to produce problems with removal of heat from the reaction zone to the surroundings.

Mixing by mechanical agitation is almost always necessary in *multiphase reactors* (exceptions are those with an immobile solid), in order to increase the overall rate of the process by developing interfacial surface area and/or intensifying mass transfer between phases. Catalytic processes are distinguished because of the specific nature of one of the components of the reaction mixture: the heterogeneous solid catalyst. The catalyst is usually present in the form of particles of different shape and size, usually uniformly distributed over the reaction zone. Particles are either fixed or moving in the reaction zone.

In the case of *gas-liquid* reactions, the reaction takes place between liquid components of the reaction mixture and those dissolving in the liquid from the gas. Reactions are often accelerated by using a soluble catalyst, e.g. organo-metallic complexes. A volatile component of the liquid phase can also react with some components of the gas phase. Among this type of reactions widely used in fine chemicals manufacture are: oxidations with homogeneous catalysts (Mn and/or Co salts) dissolved in the liquid phase; carbonylations typically carried out in the presence of a dissolved catalyst (complexes of Co, Rh, Pd, Pt, and Ni); hydroformylations of olefins with H_2 and CO using soluble catalytic organo-metallic complexes (e.g. rhodium complexes); ozonolysis; homogeneous catalytic hydrogenations; chlorinations; ammoniations, e.g. for the production of amides and nitriles; and phosgenations for isocyanates.

In *liquid-solid* processes reaction takes place between a liquid reactant and an insoluble or sparingly soluble solid which must be finely divided to speed up the process. Another measure to accelerate the process is to use an aqueous solution of a phase-transfer agent (typically a quaternary ammonium salt). The solid can also be a catalyst for reactions between liquid components, e.g. in acylations, carried out both conventionally in the presence of metal chlorides (mostly $AlCl_3$) or catalysed by zeolites; and Grignard reactions.

Probably the largest number of processes in commercial use for the manufacture of fine chemicals are *gas-liquid-solid* reactions. Such processes can be realized in various manners but slurry reactors are most commonly used. Powdered catalyst particles are suspended in the liquid phase through which the gas phase flows. The liquid reactant and the dissolved gaseous component react at the catalytic surface. Among the three-phase reactions utilized in fine chemicals manufacture hydrogenations are most common. Other processes important in fine chemicals are: partial oxidations; catalytic aminations of long chain aldehydes, alcohols, and ketones with ammonia, or short-chain amines with hydrogen as reducing agent (so-called ammonolysis); and alkylations using $Na/K_2CO_3/Al_2O_3$ as the catalyst (e.g. toluene to *iso*-butylbenzene).

Liquid-liquid reactions occur between two or more liquid phases whereby a system consisting of an organic and an aqueous phase is applied most frequently. Usually reaction takes place in one phase only. Phase-transfer catalysts are sometimes used to make transfer of a reactant to the reacting phase easier. Among typical liquid-liquid reactions utilized in fine chemicals manufacture are: nitrations with mixtures of nitric and sulphuric acid, conventional hydroxylations performed with hydrogen peroxide, esterifications, alkylations, brominations, and iodinations.

In the vast majority of *gas-solid* reactions, gaseous or evaporated compounds react at the surface of a solid catalyst. These catalytic processes are very frequently used in the manufacture of bulk chemicals. They are much less popular in processing of the large molecules typical of fine chemistry. These molecules are usually thermally sensitive and as such they will at least partially decompose upon evaporation. Only thermally stable compounds can be dealt with in gas-solid catalytic processes. Examples in fine chemicals manufacture are gas-phase catalytic aminations of volatile aldehydes, alcohols, and ketones with ammonia, with hydrogen as reducing agent; and gas-phase hydrogenations of volatile organic compounds. For instance, citral is produced using a short-bed catalytic reactor in which the residence time is of the order 10^{-3} s (Sharma, 1998).

Above, typical examples of processes have been given, but they are not intended to form a complete list of processes used in the manufacture of fine chemicals. Chapters 2 and 4 provide more examples.

5.4.1.3. Thermal conditions

Based on thermal conditions a distinction can be made between:

- isothermal reactors,
- adiabatic reactors, and
- non-isothermal and non-adiabatic reactors.

To run a reactor *isothermally* a balance must be made between the rate of heat removal or supply and the rate of heat generation or consumption at constant temperature. In practice, only reactions can be carried out isothermally for which the thermal effect is negligible, or the rate of heat removal is the same as the rate of heat generation. The latter occurs in case of relatively slow reactions or in case of high potential of heat removal (high surface area for heat transfer and high heat-transfer coefficients). Accordingly, isothermal operation is easier to achieve when using reactors with a high aspect ratio (length-to-diameter ratio).

The easiest introduction to a discussion on the thermal characterization of a reaction is a plot of heat generation/removal rate versus temperature for a single exothermic reaction as shown in Fig. 5.4-2. The rate of heat generation, q_P, is represented by an exponential curve, since the rate of reaction and, as a consequence, the rate of heat generation depends exponentially on temperature (This is strictly only the case for a zero order reaction: $r = k$). The rate of heat removal, q_R, is represented by a straight line as it is proportional to the temperature difference between that inside the reactor, T_r, and that of cooling medium in the jacket, T_c. The reactor can be operated isothermally at the points of intersection of both lines where rates of heat generation and heat removal are equal. For sufficiently low temperature of the cooling medium, $T_{c,1}$, there are two such points, $T_{r,1}$ and $T_{r,2}$. The point at $T_{r,1}$ is characteristic for low rates of both reaction and heat generation. The point at $T_{r,2}$ is characteristic for high rates of reaction and heat generation.

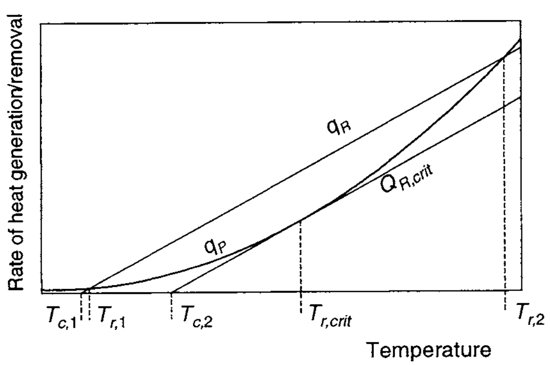

Figure 5.4-2. Rate of heat generation/removal as a function of temperature.

Regardless the starting temperature, the system will drive to any of these two points of thermal equilibrium. The desired temperature T_r can be reached by manipulating the temperature of the cooling medium. When increasing the temperature T_c the rate of heat removal will decrease. This means that the straight line of the rate of heat removal will shift down. For any cooling temperature two new intersection points of thermal equilibrium will appear. Accordingly, one can find a cooling temperature with which the desired temperature T_r will be achieved. In this way isothermal operation is enabled. Not all cooling temperatures can be chosen. Temperature $T_{c,2}$ is the highest cooling temperature at which isothermal operation is possible, and only at the point $T_{r,crit}$. If the cooling temperature is higher than $T_{c,2}$, *i.e.* the straight line moves below the lower line on the plot, the rate of heat generation (the exponential curve) will always be larger than the rate of heat removal. Consequently, the reaction temperature will run away uncontrollably. The slope of the straight line for heat removal is determined by the heat-exchange surface area and the heat-transfer coefficient, which are both characteristics of reactor geometry and hydrodynamics of the system. Accordingly, there is not much freedom for manipulation of this slope for an existing reactor.

If there is no possibility to maintain a constant temperature by manipulating the temperature of the cooling medium the reaction can be slowed down by diluting the reaction mixture and/or the catalyst. After some components of the reaction mixture have been consumed to a sufficient extent and the reaction becomes too slow, more catalyst or reactants can be added to complete the reaction with the rate of heat generation not yet exceeding that of heat removal. This is the normally used semibatch operation.

A reactor is run *adiabatically* when no heat is exchanged between the reaction zone and the surroundings. The reaction temperature can then only be controlled by quenching with a cold stream of the reaction mixture or by inter-stage heat exchangers. For highly thermally sensitive large molecules treated in the fine chemicals sector this is a very impractical mode of operation. Therefore, adiabatic reactors will not be discussed here.

In practice, nearly all reactors used for the manufacture of fine chemicals are neither isothermal nor adiabatic. The temperature-versus-time (location) profile is determined by the kinetic and physical characteristics of the reaction mixture as well as by the reactor geometry and hydrodynamics. The relationships governing this profile will be discussed in Section 5.4.2.

5.4.1.4. Design features

A particular shape of reactor, its specific internals, arrangements made because of special properties and/or behaviour of the reaction mixture, etc. are used as criteria to qualify a reactor. In fine chemicals manufacture two main groups of cylindrical reactors are in common use, *viz.* stirred-tank reactors with a small aspect ratio, and column reactors with a relatively large aspect ratio. Both types can be equipped with specific internals depending on process requirements. Researchers and designers are well acquainted with these reactors. A tendency to duplicate known equipment usually wins when considering the choice of reactor for a particular process. As a consequence, more and more stirred-tank reactors and column reactors are in use.

A typical *stirred-tank reactor* is shown in Fig. 5.4-3. It is a cylindrical vessel with elliptical or torospherical bottom and cover. It is equipped with an axially mounted stirrer rotating with a speed from 25 rpm (large scale) to 2000 rpm (laboratory). Fig. 5.4-4 shows the stirrers that are mostly used in fine chemicals manufacture, *viz.* the marine propeller, turbine, flat- or pitched-blade agitator, and anchor. Agitators move the fluid into axial and radial direction. Marine propellers and pitched-blade stirrers predominantly impose axial motion.

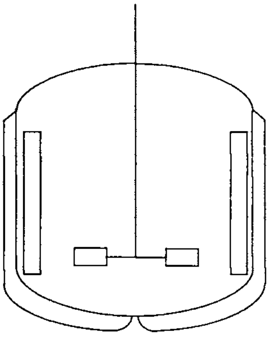

Figure 5.4-3. Stirred-tank jacketed reactor.

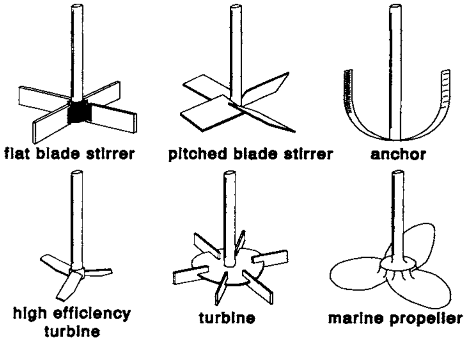

Figure 5.4-4. Typical agitators.

In contrast, flat-blade stirrers and turbines mainly cause radial movement (see Figs. 5.4-5 and 5.4-6). An anchor is used to enhance heat transfer between the reaction mixture and the cooling medium.

The tank reactor is usually jacketed to heat up and cool down the reaction mixture. The reactor is often equipped with 2-4 baffles located at a small distance from the wall. The baffles are designed to prevent vortex formation and rotation of the reaction mixture with the stirrer. The latter takes place when the viscosity of the reaction mixture is high and an anchor is used as a stirrer. Sheets protecting thermal sensors from the reaction mixture also function as baffles. Tank reactors are typically made of stainless steel or glass-lined standard steel. Standard glass-lined tank reactors can withstand pressures up to 10 bar and temperatures ranging from -30 to 200 °C. These limits are much broader for stainless steel reactors. When a tank reactor is used for carrying out a gas-liquid-solid (catalytic) reaction, the particles size ranges from 15 to 450 μm. Stirred-tank reactors are flexible reactors which may be used to carry out a variety of reactions in which *at least one liquid phase* participates. A disadvantage is the large power consumption for mixing. Stirred-tank reactors can be operated as (semi)batch or continuous reactors. They are the most commonly used reactors in the manufacture of fine chemicals.

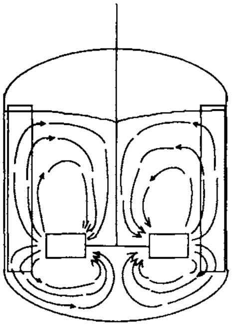

Figure 5.4-5. Streamlines for a radial-flow stirrer (turbine).

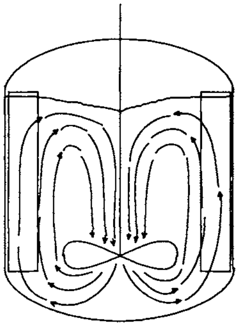

Figure 5.4-6. Streamlines for an axial-flow stirrer (propeller).

Column reactors are continuously operated vertical cylinders which can contain a stagnant or moving solid. Empty bubble-column reactors (see Fig. 5.4-7) are typically used for *gas-liquid* reactions with both phases flowing upward. Mass transfer between the gas and the liquid can be intensified by filling the column with inert particles. The flow of both phases can be arranged cocurrently or countercurrently whereby each phase can flow up- or downward (see Fig. 5.4-8). When both phases flow cocurrently upward, the reactor is called a packed bubble-column reactor. In case of countercurrent flow with the gas flowing upward, the reactor is often referred to as a packed column reactor. In the reactors mentioned above, the gas is the dispersed phase while the liquid is the continuous phase. In the case of cocurrent downflow of both phases, which of the phases is dispersed depends on the flow regime. A reactor operating in the regime where the gas is the continuous phase is called a trickle-bed reactor (see Fig. 5.4-8).

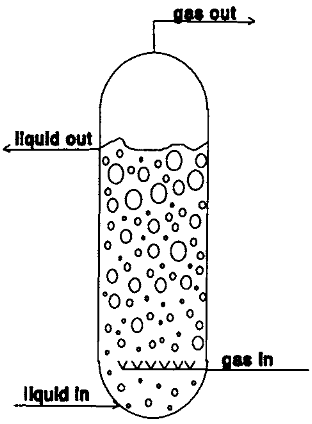

Figure 5.4-7. Empty bubble column.

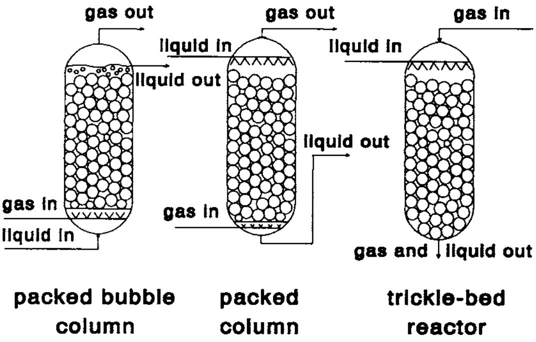

Figure 5.4-8. Packed-bed column reactors.

Column reactors can contain a draft tube – possibly filled with a packing characterized by low pressure drop – or be coupled with a loop tube, to make the gas recirculating within the reaction zone (see Fig. 5.4-9). In recent years, the Buss loop reactor has found many applications in two- and three-phase processes: About 200 Buss loop systems are now in operation worldwide, also in fine chemicals plants. This is due to the high mass-transfer rate between the gas and the liquid phase. The Buss loop reactor can be operated semibatch-wise or continuously. As a semibach reactor it is mostly used for catalytic hydrogenations.

Column reactors for *gas-liquid-solid* reactions are essentially the same as those for gas-liquid reactions. The solid catalyst can be fixed or moving within the reaction zone. A reactor with both the gas and the liquid flowing upward and the solid circulating inside the reaction zone is called a slurry column reactor (Fig. 5.4-10). The catalyst is suspended by the momentum of the flowing gas. If the motion of the liquid is the driving force for solid movement, the reactor is called an ebullated- or fluidized-bed column reactor (Fig. 5.4-10). When a catalyst is deactivating relatively fast, part of it can be periodically withdrawn and a fresh portion introduced.

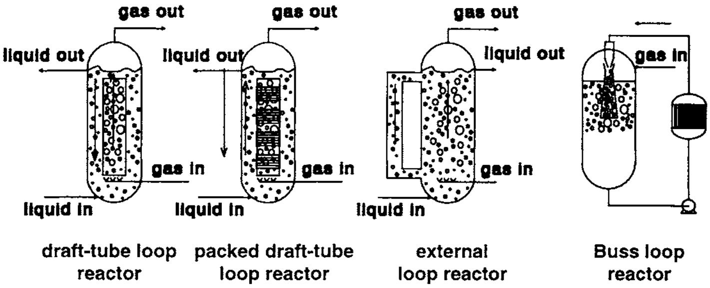

Figure 5.4-9. Loop reactors.

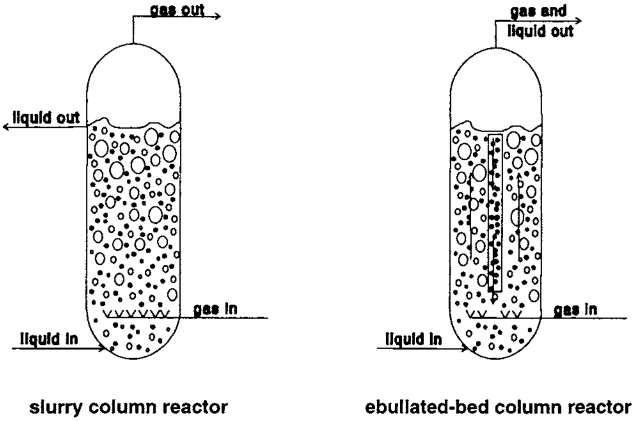

Figure 5.4-10. Column reactors with moving catalyst.

Reactors with a packed bed of catalyst are identical to those for gas-liquid reactions filled with inert packing. Trickle-bed reactors are probably the most commonly used reactors with a fixed bed of catalyst. A draft-tube reactor (loop reactor) can contain a catalytic packing (see Fig. 5.4-9) inside the central tube. Structured catalysts similar to structural packings in distillation and absorption columns or in static mixers, which are characterized by a low pressure drop, can also be inserted into the draft tube. Recently, a monolithic reactor (Fig. 5.4-11) has been developed, which is an alternative to the trickle-bed reactor. The monolith catalyst has the shape of a block with straight narrow channels on the walls of which catalytic species are deposited. The already extremely low pressure drop by friction is compensated by gravity forces. Consequently, the pressure in the gas phase is constant over the whole height of the reactor. If needed, the gas can be recirculated internally without the necessity of using an external pump.

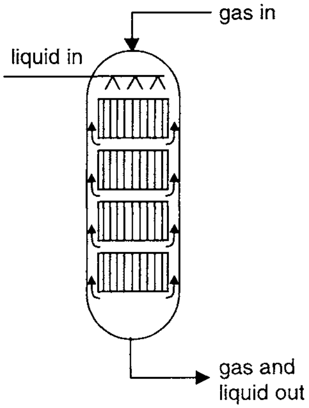

Figure 5.4-11. Monolithic reactor.

Column reactors are the second most popular reactors in the fine chemistry sector. They are mainly dedicated reactors adjusted for a particular process although in many cases column reactors can easily be adapted for another process. Cocurrently operated bubble (possibly packed) columns with upflow of both phases and trickle-bed reactors with downflow are widely used. The diameter of column reactors varies from tens of centimetres to metres, while their height ranges from two metres up to twenty metres. Larger column reactors also have been designed and operated in bulk chemicals plants. The typical catalyst particle size ranges from 1.5 mm (in trickle-bed reactors) to 10 mm (in countercurrent columns) depending on the particular application. The temperature and pressure are limited only by the material of construction and corrosivity of the reaction mixture.

Slurry reactors are often preferred for carrying out *three-phase catalytic processes* because of reactor flexibility and ease of operation. Drawbacks of these reactors are that a finely powdered catalyst is difficult to separate from the liquid, finely powdered metallic catalysts are often pyrophoric, and, consequently, difficult and dangerous to handle, and erosion of equipment can occur due to the motion of particles. Moreover, in mechanically agitated slurry reactors, catalyst particles are subject to attrition. Problems of handling fine catalyst particles can be overcome by using a packed-bed reactor. However, the diffusion path in large catalyst particles is much longer than in fine particles. If diffusion inside catalyst particles influences the rate or the selectivity to the desired product, the fixed-bed reactor loses its advantage. The diffusion path can be shortened by using an *egg-shell* catalyst (see Chapter 3) but then the majority of the catalyst volume is inert and as such is lost for reaction. Monolithic reactors with their thin catalyst layer fixed to a monolithic structure seem to be better than conventional packed-bed reactors.

Other reactor types are also used for *gas-liquid* reactions, but they are not very common in fine chemicals manufacture. Spray towers and jet reactors are used when the liquid phase is to be dispersed. In spray towers the liquid is sprayed at the top of the reactor while the gas is flowing upward. The spray reactor is useful when a solid product, possibly suspended in the liquid, is formed, or if the gas-phase pressure drop must be minimized. In a jet reactor, the liquid is introduced to the reaction zone through a nozzle. The gas flows in, being sucked by the liquid, through a concentric tube surrounding the nozzle. Very high mass-transfer rates can be achieved in jet reactors.

Packed columns, sieve and tray columns, and spray towers are also used for *liquid-liquid* reactions. Equipment typical for extraction, such as mixer-settlers, pulsed columns, rotating-disc columns, centrifugal contactors, and multistage agitated columns also can be applied for liquid-liquid reactions. The principle of *multisegment equipment* is widely utilized in chemical reactor engineering. Multisegment reactors consist of a number of reactors in one vessel. Such reactors are designed to operate as a cascade of CSTRs, but with savings in construction material for vessels. Individual compartments of a multisegment reactor are interconnected in series.

A rational choice between a variety of reactor types requires knowledge of reaction kinetics, thermodynamics, and properties of the reaction mixture throughout the reaction. Based on this information, a mathematical model of the reactor can be developed and used for simulation of various reactor types, reactor selection, and finally reactor optimization. Table 5.4-1 summarizes properties of the reactors discussed above which can be used as guidelines for a preliminary reactor selection. The liquid hold-up (volume fraction of the liquid in the gas-liquid mixture) gives an idea about the fraction of the reaction zone that is effectively utilized. The volume fraction of the solid is related to the catalyst load in the reaction zone. The more catalyst per unit volume the faster the reaction may become. Hence, if the reaction is slow, *i.e.* it proceeds in the kinetic regime, a reactor with as high a catalyst load as possible (packed columns) will probably be the best choice. Mass transfer coefficients, k_L and k_G, and interfacial surface area per unit volume, a, give information concerning the rate of mass transfer through the interface. These quantities are related to the mass flux:

$$N_V = k_L a (c_i - c_b) \qquad \textbf{(5.4-6)}$$

$$N_V = k_G a (p_b - p_i) \qquad \textbf{(5.4-7)}$$

for processes controlled by mass transfer in the liquid phase or in the gas phase, respectively. Accordingly, the greater the product of k_La or k_Ga, the faster mass transfer is. So if gas-liquid mass transfer resistance is the rate controlling step, the use of mechanically agitated tank reactors with a maximal volumetric mass-transfer coefficient k_La of value 1 s^{-1} or a loop reactor with a k_La ranging from 0.5 to 2 s^{-1} is likely to be a better choice than a bubble column, for which the maximal k_La is 0.24 s^{-1}. The latter reactor would be preferred, however, if poor mass transfer enhanced selectivity.

5.4.2. Basic thermodynamics and kinetics

5.4.2.1. Thermodynamics - heat of reaction and chemical equilibria

Thermodynamics provides information, among others, about the feasibility of a reaction. In assessing the feasibility of a reaction the following aspects are important:

- the composition of the reaction mixture at chemical equilibrium; this composition determines the maximum achievable conversion and selectivity, and
- the distance of the initial composition of the reaction mixture from that at chemical equilibrium; the greater the distance, the faster the reaction.

Table 5.4-1 Characteristics of typical multiphase reactors

	Stirred-tank reactor	Column reactors					
		Bubble column	Loop reactor	Packed column		Plate column	Monolithic reactor
				Bubble flow	Non-bubble flow		
Dispersed phase	gas (and solid, if used)				depends on flow regime	gas	
Continuous phase	liquid					liquid	
Solid (if used)	mobile small particles, 15-450 μm, follow the motion of the liquid			spheres, cylinders, extrudates, etc., 1-6 mm; fixed		none	blocks with channels covered with catalyst
Mixing force	mechanical agitation+ movement of the gas	momentum transfer between gas and liquid					gravity, convection and concentration gradients
Mode of operation	(Semi)batch or continuous; concurrent; upward motion of phases	Continuous; concurrent; upward motion of phases	Continuous: concurrent; upward or downward in different parts of the reaction zone	Continuous: concurrent: upward motion of phases	Continuous: concurrent (1) or countercurrent (2): upward (a) or downward (b); trickle-bed (1+b)	Continuous: countercurrent: gas upward liquid downward	Continuous: concurrent downward
Height-to-diameter ratio	1:1 to 3:1	>>1:1					
Liquid hold-up [%]	20÷95	60÷98		60÷98	countercurrent: 2÷24 cocurrent: 2÷45	10÷95	10÷50
Volume fraction of the solid [%] (if used)	0.5÷1	<40, usually 1÷20		50÷60		-	7÷15
$k_G \cdot 10^4$ [mol/(cm^{2}s bar)]	-	0.5÷2		0.5÷2	countercurrent: 0.03÷2 cocurrent: 0.01÷3	bubble caps: 0.5÷2 sieve plates: 0.5÷6	-
$k_L \cdot 10^2$ [cm/s]	0.3÷4	1÷4		1÷4	countercurrent: 0.4÷2 cocurrent: 0.4÷6	bubble caps: 1.5 sieve plates: 1÷20	-
a [m^2/m^3]	100÷2000	500-2000	1000-3000	50÷300	countercurrent: 10÷350 cocurrent: 10-170	bubble caps: 100÷400 sieve plates: 100÷200	1000-2500
k_La [s^{-1}]	0.003÷1	0.005÷0.24	0.5-2	0.005÷0.12	countercurrent: 0.0004÷0.07 cocurent: 0.0004÷1.02	bubble caps: 0.01÷0.2 sieve plates: 0.01÷0.4	0.05÷0.1
Remarks	Dead-end reactor with a hollow shaft or a multistirrer system possible	Internals like disc-donuts or perforated plates can be inserted					Internal gas circulation without pumping device possible

The change in total *Gibbs energy*, *G*, determines whether a reaction can proceed and how far it can proceed. A reaction can occur only in the direction in which the Gibbs energy decreases; the larger the decrease, the more a reaction is favoured. The system is in equilibrium if the total Gibbs energy is at a minimum with respect to all possible changes. At equilibrium:

$$K_a \equiv \exp\left(\frac{-\Sigma \nu_j G^0_{j,T}}{R_g T}\right) = \exp\left(\frac{-\Delta G^0_T}{R_g T}\right) = \prod_j a^{\nu_j}_{j,eq} \tag{5.4-8}$$

where $G^0_{j,T}$ is the standard Gibbs free energy of pure species *j* at fixed pressure (usually 1 atm), a_j is the activity of species *j* in the solution, and ΔG^0_T is the *standard Gibbs energy change of reaction*. ΔG^0_T and $G^0_{j,T}$ only depend on temperature, and so does K_a, the ***equilibrium constant***. The stoichiometric coefficient ν_j is negative for reactants and positive for products. The activity of species *j* is given by:

$$a_j = \begin{Bmatrix} x_j \gamma_j & \text{for liquids} \\ y_j \phi_j p & \text{for gases} \end{Bmatrix} \tag{5.4-9}$$

where x_j and y_j are mole fractions in the liquid and the gas, respectively, γ_j is the activity coefficient in the liquid solution, ϕ_j is the fugacity coefficient in the gas phase, and *p* is the total pressure. The methods for estimation of activity coefficients and fugacity coefficients are discussed in many books on thermodynamics or properties of gases and liquids (see, e.g., Smith and van Ness, 1988; or Reid *et al.*, 1989).

The temperature dependence of ΔG^0_T is given by:

$$-\frac{d\left(\Delta G^0_T / R_g T\right)}{dT} = \frac{d \ln K_a}{dT} = \frac{\Delta H^0_T}{R_g T^2} \tag{5.4-10}$$

where ΔH^0_T is the *standard enthalpy change of reaction*. The rigid solution of Eqn. (5.4-10) requires integration accounting for the temperature dependence of ΔH^0_T. If it may be assumed that ΔH^0_T is temperature-independent, integration of Eqn. (5.4-10) leads to the simple expression:

$$\ln \frac{K_{a,T}}{K_{a,T_{ref}}} = -\left(\frac{\Delta H_{T_{ref}}}{R_g}\right) \cdot \left(\frac{1}{T} - \frac{1}{T_{ref}}\right) \tag{5.4-11}$$

where T_{ref} is the reference temperature. This has been proven to often be a good approximation.

An evaluation of the equilibrium constant requires the value of ΔG^0_T. This value can be calculated from the equation:

$$\Delta G^0_T = \Delta H^0_T - T \Delta S^0_T \tag{5.4-12}$$

where the temperature dependence of ΔH^0_T and the *standard entropy change of reaction*, ΔS^0_T, are given by:

$$\Delta H_T^0 = \Delta H_{T_0}^0 + \int_{T_0}^{T} \left(\sum_{j=1}^{N_c} \nu_j c_{p,j} \right) dT \tag{5.4-13}$$

$$\Delta S_T^0 = \Delta S_{T_0}^0 + \int_{T_0}^{T} \frac{1}{T} \left(\sum_{j=1}^{N_c} \nu_j c_{p,j} \right) dT \tag{5.4-14}$$

with

$$\Delta H_{T_0}^0 = \sum_{j=1}^{N_c} \nu_j \left(\Delta H_{f,j}^0 \right)_T \tag{5.4-15}$$

$$\Delta S_{T_0}^0 = \sum_{j=1}^{N_c} \nu_j \left(\Delta S_{f,j}^0 \right)_T \tag{5.4-16}$$

and $c_{p,j}$ is the heat capacity whose temperature dependence for gases is given by:

$$C_{p,j} = a_j + b_j T + c_j T^2 + \frac{d_j}{T^2} \tag{5.4-17}$$

Standard enthalpies of formation, $\Delta H^0_{f,j}$, and standard entropies of formation, $\Delta S^0_{f,j}$, at temperature $T_0 = 298$ K, as well as the coefficients in expression (5.4-17) have been tabulated or can be calculated from group contributions (see Reid *et al.* (1989), Bretsznajder (1962), Perry and Chilton (1984), Smith and van Ness (1988), or Weast (1990)).

Equilibrium for a single reaction in the liquid-phase. A significant proportion of fine chemistry processes occur in the liquid phase. The equilibrium constant is expressed by Eqn. (5.4-8), which can be rewritten as:

$$K_a = \prod_{j=1}^{N_c} \left(x_j \gamma_j \right)_{eq}^{\nu_j} = \prod_{j=1}^{N_c} x_{j,eq}^{\nu_j} \cdot \prod_{j=1}^{N_c} \gamma_{j,eq}^{\nu_j} = K_x K_\gamma \tag{5.4-18}$$

The relation between mole fractions in the liquid and concentrations is:

$$x_j = c_j V_m \tag{5.4-19}$$

where V_m is the molar volume in the liquid phase. Combining Eqns. (5.4-18) and (5.4-19) yields the following expression:

$$K_a = V_m^{\Delta\nu} \prod_{j=1}^{N_c} \left(c_j \gamma_j \right)_{eq}^{\nu_j} = V_m^{\Delta\nu} K_c K_\gamma \tag{5.4-20}$$

where

$$\Delta\nu = \sum_{j=1}^{N_c} \nu_j \tag{5.4-21}$$

If the reaction mixture can be considered to be an ideal solution, the activity coefficients are unity and Eqn. (5.4-18) becomes:

$$K_a = \prod_{j=1}^{N_c} x_{j,eq}^{\nu_j} = K_x \tag{5.4-22}$$

Example 5.4.2.1. Equilibrium in esterification of acetic acid with ethanol (after Smith and van Ness, 1988)

Esterification of acetic acid with ethanol proceeds according to the reaction:

$$CH_3COOH(l) + CH_3CH_2OH\,(l) \leftrightarrow CH_3COOCH_2CH_3(l) + H_2O(l) \tag{5.4-23}$$

Estimate the composition of the reaction mixture at chemical equilibrium at 25 °C and 100 °C for an initial mole ratio of $CH_3COOH/CH_3CH_2OH = 1$.

SOLUTION. Data for $\Delta H^0_{f,298}$ and $\Delta G^0_{f,298}$ for all components of the reaction mixture can be found in handbooks of chemistry and physics. The data set for the above reaction, shown in Table 5.4-2, was taken from *Lange's Handbook of Chemistry* (Dean, 1992).

Table 5.4-2

Values of $\Delta H^0_{f,298}$ and $\Delta G^0_{f,298}$ for components of the reaction mixture in the liquid state

Component	$\Delta H^0_{f,298}$ (kJ/mol)	$\Delta G^0_{f,298}$ (kJ/mol)
Acetic acid	-484.4	-390.2
Ethanol	-277.0	-174.2
Ethyl acetate	-473.3	-332.7
Water	-285.8	-237.1

$\Delta H^0_{298} = -473.3 + (-282.8) - [-484.4 + (-277.0)] = 1.3$ kJ/mol
$\Delta G^0_{298} = -332.7 + (-273.1) - [-390.2 + (-174.2)] = -5.4$ kJ/mol

From Eqn. (5.4-8):

$$K_{a,298} = \exp\left(-\frac{\Delta G^0_{298}}{R_g T}\right) = -\frac{-5{,}400}{8.3144 \cdot 298.15} = 8.829 \tag{5.4-24}$$

For esterification with an equimolar initial mixture of reactants, the mole fractions of the components in the reaction mixture are the following functions of conversion:

$$\begin{aligned} x_{AcH} = x_{EtOH} &= \frac{1-X}{2} \\ x_{EtAc} = x_{H_2O} &= \frac{X}{2} \end{aligned} \tag{5.4-25}$$

Assuming that the reaction mixture is an ideal solution, Eqn. (5.4-22) can be used to calculate the equilibrium conversion and composition of the reaction mixture:

$$K_a \approx K_x = \frac{x_{EtAc}\, x_{H_2O}}{x_{AcH}\, x_{EtOH}} = \left(\frac{X}{1-X}\right)^2 = 8.829 \tag{5.4-26}$$

from which follows:

$X = 0.748;\quad x_{AcH} = x_{EtOH} = 0.126;\quad x_{H2O} = x_{EtAc} = 0.374$

The literature data on the equilibrium constant K_x and equilibrium composition for an equimolar initial reaction mixture show that $x_{H2O,exp} = x_{EtAc,exp} \approx 0.33$ (Gerasimov, 1974 and Jencks and Gilchrist, 1964). The reason for the discrepancy between calculated and experimental compositions might be non-ideal behaviour of the reaction mixture. To take the non-ideality into account, Eqn. (5.4-18) is applied to calculate the equilibrium constant K_x. The values of the activity coefficients, γ_j, are estimated using UNIFAC data (see e.g., Smith and van Ness (1988) or Reid *et al.* (1989) for the procedure, and Reid *et al.* (1989) or Sørensen and Arlt (1980) for data for the calculations). The activity coefficients are a function of temperature, pressure, and composition of the solution. Therefore, to determine these, an assumption must be made concerning the composition. Assume that the composition is given by the mole fractions obtained from calculations for the ideal solution. Based on these mole fractions, the following values of the activity coefficients are estimated:

$\gamma_{AcH} = 0.707; \gamma_{EtOH} = 0.772;\quad \gamma_{AcEt} = 0.978;\quad \gamma_{H2O} = 0.956$

So

$$K_\gamma = \frac{\gamma_{EtAc}\,\gamma_{H_2O}}{\gamma_{AcH}\,\gamma_{EtOH}} = \frac{0.978 \cdot 0.956}{0.707 \cdot 0.772} = 1.713 \tag{5.4-27}$$

and

$$K_x = \frac{K_a}{K_\gamma} = \frac{8.829}{1.713} = 5.154 \tag{5.4-28}$$

from which follows:

$X = 0.694;\quad x_{AcH} = x_{EtOH} = 0.153;\quad x_{H2O} = x_{EtAc} = 0.347$

For the new composition of the reaction mixture, the activity coefficients are recalculated:

$\gamma_{AcH} = 0.722; \gamma_{EtOH} = 0.787;\quad \gamma_{AcEt} = 0.980; \gamma_{H2O} = 0.939$

The corrected values of K_x and K_γ are as follows:

$K_\gamma = 1.620;\quad K_x = 5.450$

and the corresponding values are:

$X = 0.700;\quad x_{AcH} = x_{EtOH} = 0.150;\quad x_{H2O} = x_{EtAc} = 0.350$

No significant changes in conversion and in mole fractions are observed if iterations are continued. The mole fractions of water and ethyl acetate are now very close to the experimental data.

For the relatively small temperature change from 25 to 100 °C ΔH^0_T for this reaction may be assumed to be independent on temperature and Eqn. (5.4-11) can be used to predict the equilibrium constant at 100 °C. Thus:

$$\ln\frac{K_{373}}{K_{298}} = -\frac{\Delta H_{298}^{0}}{R_g}\left(\frac{1}{373.15}-\frac{1}{298.15}\right) = \frac{-1{,}300}{8.3144}\left(\frac{1}{373.15}-\frac{1}{298.15}\right) = 0.1067 \qquad \textbf{(5.4-29)}$$

or

$$K_{373} = 8.829\exp(0.1057) = 9.813 \qquad \textbf{(5.4-30)}$$

When the procedure described above is repeated, the following values are obtained:

$K_\gamma = 1.629$; $K_x = 6.023$
$X = 0.710$; $x_{AcH} = x_{EtOH} = 0.147$; $x_{H2O} = x_{EtAc} = 0.353$

Thus, the influence of temperature on equilibrium composition of the given reaction mixture is small, as indicated by the low value of ΔH^0_{298}.

Equilibrium in multiphase and/or multireaction systems. If more than one phase is present in the system, a criterion of phase equilibria has to be satisfied together with the chemical equilibrium criterion. For instance, in a gas-liquid system components are in chemical equilibrium in the phase where the reaction occurs, but vapour-liquid equilibria between the gas and the liquid phases must also be taken into account. To determine the equilibrium composition of a reacting mixture in both phases, chemical equilibrium constants as well as data concerning vapour-liquid equilibria for all components of the reaction mixture should be known. In the equilibrium state:

$$y_{j,eq} = k_j\, x_{j,eq} \qquad \textbf{(5.4-31)}$$

where k_j is the *vapour-liquid equilibrium coefficient* of component j. For solutions which are close to ideal, the values of k_j can be estimated from Raoult's law for high concentrations in the liquid, while for low concentrations k_j has the meaning of Henry's constant. In general, the coefficient k_j depends on temperature, pressure, and composition.

For gas-phase reactions, when combining Eqns. (5.4-8) and (5.4-9), the equilibrium constant is expressed as:

$$K_a = p^{\Delta\nu}\prod_{j=1}^{N_c}\left(y_j\phi_j\right)_{eq}^{\nu_j} = \prod_{j=1}^{N_c} y_{j,eq}^{\nu_j}\cdot\prod_{j=1}^{N_c}\phi_{j,eq}^{\nu_j} = p^{\Delta\nu}K_y K_\phi \qquad \textbf{(5.4-32)}$$

For relatively low pressures and relatively high temperatures, the reaction mixture approximately behaves as an ideal gas. Hence, each $\phi_j = 1$ and Eqn. (5.4-32) reduces to:

$$K_a = K_p = p^{\Delta\nu}\prod_{j=1}^{n_c} y_{j,eq}^{\nu_j} = p^{\Delta\nu}K_y \qquad \textbf{(5.4-33)}$$

When combining Eqns. (5.4-31) and (5.4-33), the following expression is obtained:

$$K_a = p^{\Delta\nu}\prod_{j=1}^{N_c}\left(\phi_j k_j x_j\right)^{\nu_j} = p^{\Delta\nu}K_\phi K_k K_x \qquad \textbf{(5.4-34)}$$

Problems with the determination of chemical equilibria in multiphase systems are solved in practice by assuming that the reaction takes place in any phase and all components are also equilibrated between phases. Accordingly, for a single reaction any of Eqns. (5.4-32) and (5.4-33) must be solved, while the relationships of Eqn. (5.4-31) must also be fulfilled. Since vapour-liquid equilibrium coefficients are functions of the compositions of both phases, the search for the solution is an iterative procedure. Equilibrium compositions are assumed, vapour-liquid equilibrium coefficients are then estimated, and new equilibrium compositions are evaluated. If the new equilibrium compositions are close to those assumed initially one may consider the assumed values to be the solution of the problem. Otherwise the evaluated compositions are taken as the start for repetition of the procedure until a reasonable agreement between assumed and evaluated compositions has been reached.

Methods discussed for a one-reaction system can easily be extended to multireaction systems. For all independent reactions, a separate equilibrium constant is defined as:

$$K_{a,i} = \prod_{j=1}^{N_c} a_{j,eq}^{\nu_{i,j}} \qquad \textbf{(5.4-35)}$$

where i is the reaction index. For N_r independent reactions there are N_r independent equations (5.4-35), combined with expressions connecting the initial composition with extents (conversions) of all reactions. This set of non-linear equations is then solved simultaneously. An alternative to the above mentioned procedure consists in minimizing the total free Gibbs energy for the system:

$$G^t_{T,p} = G(\text{compositions of all phases}) \qquad \textbf{(5.4-36)}$$

with a constraint on the number of atoms present in all components of the reaction mixture. Computations are time-consuming and are performed using computers. Computer programs for the estimation of equilibrium compositions are usually included in software for simulation of chemical processes (see Section 5.1). Readers who are interested in the estimation of equilibria in multiphase and multireaction systems are referred to books by Smith and van Ness (1988) and Reid *et al.* (1989).

The methods discussed above for the estimation of equilibrium constants and equilibrium compositions are very sensitive to the accuracy of data concerning thermodynamic properties of individual components of the reaction mixture. The exponential relationship between equilibrium constant and the free Gibbs energy implies that even a minor error in the estimation of $\Delta G^0{}_T$ can result in a significant difference in the K values. The smaller $\Delta G^0{}_T$, the stronger the influence of the absolute error in $\Delta G^0{}_T$ on the value of K. Smith and van Ness (1988) calculated the equilibrium constant and equilibrium composition of the reaction mixture for esterification of acetic acid with ethanol (see *Example 5.4.2.1*). By using slightly different values of the free Gibbs energies of formation, much lower values of the equilibrium constant were obtained, and, consequently, lower than observed equilibrium conversions were calculated. The use of estimates of $\Delta G^0{}_T$ is, therefore, risky and experimental data on equilibria should be used instead. Only when such data are missing the methods presented above might be applied, but one has to be very cautious with drawing conclusions from results of estimations and must compare these results with known literature data for similar systems. Evaluation of equilibria in processes for fine chemicals manufacture is often very difficult or even impossible. This is because the product palette is often unknown, while this palette must be defined at the very beginning of the calculations. Despite this difficulty, any attempt to evaluate what is possible is worth the effort.

5.4.2.2. Kinetics - basics

Reaction rate. The rate of reaction is defined as the number of moles of reactant disappearing (or the number of moles of product formed) due to reaction per unit time and per unit volume of reaction mixture (or per unit mass of catalyst). Let us denote r_S as the rate of disappearance of reactant S for the simple reaction:

$$\nu_S S \rightarrow \nu_P P \tag{5.4-37}$$

and r_P as the rate of formation of P. The relationship between the rate of consumption of the reactant and the rate of formation of the product is:

$$r_S = -\frac{\nu_P}{\nu_S} r_P \tag{5.4-38}$$

Note that the stoichiometric coefficients for reactants are negative and those for products positive. As a consequence, r_S and r_P are both positive.

In closed systems (batch reactors), the instantaneous overall rate of accumulation of the reactant S is related to the reaction rate by the following expression:

$$\left(\frac{dn_S}{dt}\right) = \nu_S (r_S V_r) \tag{5.4-39}$$

where V_r is the volume of the reaction mixture. Note that the accumulation of reactants is negative (disappearing) since ν_S is negative. For a constant volume of the reaction mixture (this is often a good approximation for liquid reaction mixtures):

$$r_S = \frac{1}{\nu_S V_r}\frac{dn_S}{dt} = \frac{1}{\nu_S}\frac{d(n_S/V_r)}{dt} = \frac{1}{\nu_S}\frac{dc_S}{dt} \tag{5.4-40}$$

where c_S is the concentration of the reactant S. This is the equation most chemists are familiar with. Often it is erroneously thought that it is actually the definition of the reaction rate. It should, however, be realized that the equation represents a mass balance. For a continuous reactor (open system), $dc_S/dt = 0$, but, nevertheless, reaction can take place!

Obviously, the more molecules occupy the reactor volume, the more opportunities the molecules will get to collide with other molecules or with energetically rich sites in the reaction zone, and the larger the probability of a chemical reaction occurring will be. Therefore, the reaction rate must be dependent on the concentration of reactants in general and on the pressure for reactions in the gas phase in particular. In general, the rate will increase with concentration and pressure. Only those molecules having reached the appropriate energetical state, which depends on the temperature in the reaction zone, can be subject to transformations. Consequently, the reaction rate depends on temperature. For reversible reactions, the rate also depends on the distance from chemical equilibrium. The greater the distance from equilibrium, the faster the reaction will be, and the rate will go to zero when approaching the equilibrium. In the case of heterogeneous catalytic processes, reactants adsorb on active sites on the surface of the catalyst where the reaction occurs. The larger the number of active sites per unit volume (mass) of catalyst, the larger the probability of the occurrence of a reaction will be. Some of the active sites may be blocked by components of the reaction mixture that do not participate in the reaction considered. This will decrease the number of sites available for reactants, hindering the reaction itself. Accordingly, the reaction rate will also depend on the adsorption capability of components of the reaction mixture with respect to the particular catalyst. A stronger adsorption and a larger concentration of even non-reactive components of the reaction mixture will result in a smaller chance for the reactants to adsorb and, accordingly, the reaction will be slower.

The kinetic equation describing the relationship between reaction rate and temperature, pressure, and concentrations is a function of the type:

$$r_A = k(T) \cdot \varphi(T, p, c_A, c_B, \ldots) \qquad \textbf{(5.4-41)}$$

where $k(T)$ is the *rate constant*, which only depends on temperature only, and φ is a function of concentrations, pressure, and temperature. Taking all the factors influencing the reaction rate into account, another general form of this dependence can be expressed as:

$$\text{rate} = \frac{\text{(kinetic factor)(driving - force group)}}{\text{(hindering group)}} \qquad \textbf{(5.4-42)}$$

The *kinetic factor* is proportional to the energetic state of the system and (for heterogeneous catalytic systems) the number of active sites per unit volume (mass) of catalyst. The *driving-force group* includes the influence of concentration and distance from chemical equilibrium on the reaction rate, and the *hindering group* describes the hindering effect of components of the reaction mixture on the reaction rate. The kinetic factor is expressed as the rate constant, possibly multiplied by an equilibrium constant(s) as will be shown later.

Reaction order. One of the most widely used (particularly for homogeneous reactions) kinetic expressions is the *power law kinetic equation*:

$$r = k\, c_A^{\alpha_A} c_B^{\alpha_B} \ldots \qquad \textbf{(5.4-43)}$$

where α_j is the *reaction order* with respect to reactant j (*partial reaction order*). Partial reaction orders for homogeneous reactions are usually around one or two. For heterogeneous catalytic processes, partial reaction orders can also be close to zero or even negative. The values of reaction orders determined by fitting experimental data are often physically meaningless. They often depend on the range of concentrations of the reactants and as such they can vary with the extent of reaction. Therefore, these orders only indicate what might be the true mechanism of the chemical transformation (this will be discussed in more detail later).

The overall reaction order α is the sum of the partial reaction orders:

$$\alpha = \alpha_A + \alpha_B + \ldots = \sum_j \alpha_j \qquad \textbf{(5.4-44)}$$

Steady-state approximation. Fractional reaction orders may be obtained from kinetic data for complex reactions consisting of elementary steps, although none of these steps are of fractional order. The same applies to reactions taking place on a solid catalyst. The steady-state approximation is very useful for the analysis of the kinetics of such reactions and is illustrated by *Example 5.4.2.2a* for a solid-catalysed reaction.

Example 5.4.2.2a. Steady-state approximation in heterogeneous liquid-phase reaction

Consider the reversible reaction $A \rightleftharpoons B$ which proceeds via three elemental steps, *viz.* adsorption of A on an active site *, reaction of adsorbed A, and desorption of product B:

$$A + * \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A^* \qquad \textbf{(5.4-45a)}$$

$$A^* \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} B^* \qquad \textbf{(5.4-45b)}$$

$$B^* \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} B + * \qquad \textbf{(5.4-45c)}$$

Since the three steps are considered to be elementary processes, their rates can be directly derived from their reaction rate expressions:

$$r_1 = r_{+1} - r_{-1} = k_1 c_A N_T \theta_* - k_{-1} N_T \theta_A \qquad \textbf{(5.4-46a)}$$

$$r_2 = r_{+2} - r_{-2} = k_2 N_T \theta_A - k_{-2} N_T \theta_B \qquad \textbf{(5.4-46b)}$$

$$r_3 = r_{+3} - r_{-3} = k_3 N_T \theta_B - k_{-3} c_B N_T \theta_* \qquad \textbf{(5.4-46c)}$$

Note that under steady-state conditions the rate of each reaction step equals the overall net rate, r_A. θ_*, θ_A, and θ_B represent the fractions of the total number of sites that are vacant, or occupied by A and B, respectively. N_T represents the total concentration of active sites. Conservation of the total number of active sites leads to the site balance expression:

$$1 = \theta_* + \theta_A + \theta_B \qquad \textbf{(5.4-47)}$$

Under steady-state conditions, the concentrations of the vacant sites, sites occupied by A, and sites occupied by B do not change with time:

$$\frac{d\theta_A}{dt} = 0 = k_1 c_A \theta_* - k_{-1}\theta_A - k_2\theta_A + k_{-2}\theta_B \qquad \textbf{(5.4-48a)}$$

$$\frac{d\theta_B}{dt} = 0 = k_{-3} c_B \theta_* - k_3\theta_B - k_{-2}\theta_B + k_2\theta_A \qquad \textbf{(5.4-48b)}$$

Using Eqns. 5.4-47 and 5.4-48, the unknowns θ_*, θ_A, and θ_B can be expressed as functions of the rate constants and concentrations and then substituted in the overall net rate equation ($r_A = r_1 = r_2 = r_3$) which finally yields the following reaction rate expression:

$$r_A = \frac{k(c_A - c_B / K)}{(k_1k_3 + k_1k_{-2} + k_1k_2)c_A + (k_{-1}k_{-3} + k_2k_{-3} + k_{-2}k_{-3})c_B + (k_{-1}k_{-2} + k_{-1}k_3 + k_2k_3)} \qquad \textbf{(5.4-49)}$$

where $k = N_T\, k_1\, k_2\, k_3$ and $K = K_1\, K_2\, K_3$ ($K_i = k_i / k_{-i}$) being the overall equilibrium constant for the reaction. The rate expression can be simplified by using the rate-determining step method.

Rate-determining step. Fortunately even in the case of complex reactions a simplified kinetic expression often describes the course of reaction sufficiently accurately. The reason might be that one of the steps constituting the overall mechanism is relatively slow so that the other steps are essentially in equilibrium. This step is called the *rate-determining step.* An application of the principle of the rate-determining step (or *rate-limiting step*) is given in *Example 5.4.2.b.*

Example 5.4.2.2b. Rate-determining step in reaction of Example 5.5.2.2a

The aforementioned reaction $A \rightleftharpoons B$ proceeds through three elementary processes in series. Consequently, the net rates of the individual steps are equal to the overall rate. It can be imagined that the forward and backward rates of two of these steps are large compared to the third one. They might be so large that these steps can be considered to be in *quasi*-equilibrium. The third step is then called the *rate-determining step* (r.d.s.). Now let the surface reaction be the r.d.s. The rate expression is then obtained as follows. Starting with the rate-determining step:

$$r_A = r_{+2} - r_{-2} = k_2 N_T \theta_A - k_{-2} N_T \theta_B \tag{5.4-50}$$

and using the *quasi*-equilibrium conditions:

$$K_A = \frac{k_1}{k_{-1}} = \frac{\theta_A}{\theta_* c_A} \quad \Leftrightarrow \quad \theta_A = K_A c_A \theta_* \tag{5.4-51a}$$

$$K_B = \frac{k_3}{k_{-3}} = \frac{\theta_* c_B}{\theta_B} \quad \Leftrightarrow \quad \theta_B = \frac{c_B \theta_*}{K_B} \tag{5.4-51b}$$

enables the elimination of the unknown quantities θ_A and θ_B from Eqn. (5.4-50). The remaining θ_* can be eliminated by use of the site balance (5.4-47):

$$\theta_* = \frac{1}{1 + K_A c_A + c_B / K_B} \tag{5.4-52}$$

The resulting rate expression for the case that the surface reaction is rate determining is given by:

$$r_A = \frac{k K_A (c_A - c_B / K)}{1 + K_A c_A + c_B / K_B} \tag{5.4-53}$$

Similar equations can be derived in case adsorption or desorption is the rate-determining step.

Using the concept of the rate-determining step significantly simplifies the overall rate expression. Therefore, it is widely used in the analysis of kinetic data, especially in the field of heterogeneous catalysis.

Influence of temperature on the reaction rate. It is usually assumed that the rate constant is a function of temperature only, expressed by the *Arrhenius equation*:

$$k(T) = k_0 e^{-E/R_g T} \tag{5.4-54}$$

where k_0 is the frequency factor, E the activation energy, R_g the universal gas constant, and T the absolute temperature. The activation energy ranges from 40 to 300 kJ $\mathrm{mol}^{-1}\ \mathrm{K}^{-1}$. The larger the activation energy, the more temperature-sensitive[10] the reaction becomes; the reaction rate is entirely independent on temperature if the activation energy is equal to zero. The temperature-sensitivity of the rate constant decreases with increasing temperature, although the absolute value of the rate constant increases.

There might be various reasons that lead to finding an 'apparent' instead of the true activation energy. The use of power-law kinetic expressions can be one of the reasons. An apparent fractional reaction order can vary with the concentration, *i.e.* with conversion, in one experimental run. Depending upon the range of concentrations or, equivalently, conversions, different reaction orders may be observed. As an example, consider the a simple reaction:

$$S \rightarrow \text{Products} \qquad \textbf{(5.4-55)}$$

which is carried out batch-wise. The volume of the reaction mixture does not change during the reaction. Using the power law kinetics one obtains:

$$r_S = -\frac{dc_S}{dt} = k\, c_S^{\alpha_S} \qquad \textbf{(5.4-56)}$$

It is no exception that α_S depends on the experimental conditions. On integration and rearrangement of Eqn. (5.4-56), the following expression is obtained:

$$k = \frac{c_{S,0}^{1-\alpha_S}\left\{(1-X)^{1-\alpha_S} - 1\right\}}{(1-\alpha_S)t} \qquad \textbf{(5.4-57)}$$

Thus, depending on the estimated α_S, different k's and possibly E_{obs}'s will be obtained. So, the values found will depend on the experimental conditions, i.e. temperature, concentrations, conversions. Experimentally determined E-values may have nothing in common with the true activation energy.

For catalytic reactions carried out in the presence of a heterogeneous catalyst, the observed reaction rate could be determined by the rate of mass transfer from the bulk of the reaction mixture and the outer surface of the catalyst particles or the rate of diffusion of reactants within the catalyst pores. Consider a simple first order reaction; its rate must be related to the concentration of species S at the outer surface of the catalyst as follows:

$$r_S = k\, c_{S,s} \qquad \textbf{(5.4-58)}$$

where $c_{S,s}$ is concentration in the fluid at the fluid-solid interface. The rate of mass transfer of S from the bulk of the fluid to the interface (so-called *external mass transfer*) is given by:

$$N_{A,S} = k_s\left(c_S - c_{S,s}\right) \qquad \textbf{(5.4-59)}$$

where k_s is the mass-transfer coefficient and c_S concentration of S in the bulk of the fluid phase. The rate of disappearance of S at the catalyst surface must be equal to the rate of its transfer from

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[10] The 'temperature-sensitivity' shows how much the rate constant changes upon a temperature change. If the rate constant varies much with a small temperature change, we say that it is highly sensitive to temperature.

the bulk of the fluid to the interface, so:

$$k\,c_{S,s} = k_s\left(c_S - c_{S,s}\right) \qquad \textbf{(5.4-60)}$$

and

$$c_{S,s} = \frac{k_s}{k + k_s}\,c_S \qquad \textbf{(5.4-61)}$$

Consequently, the observed disappearance rate of S will be given by:

$$r_S = \left(\frac{1}{k} + \frac{1}{k_s}\right)^{-1} c_S = k_{obs}\,c_S \qquad \textbf{(5.4-62)}$$

in which the observed 'overall' rate constants is defined as

$$\frac{1}{k_{obs}} = \frac{1}{k} + \frac{1}{k_s} \qquad \textbf{(5.5-63)}$$

If the mass-transfer coefficient is much smaller than the chemical reaction rate constant, i.e. $k >> k_s$, Eqn. (5.4-63) gives $k_{obs} \approx k_s$. We then say that the overall process is controlled by external mass transfer, or that external mass transfer is the rate-limiting step, or that the reaction proceeds in the external-mass-transfer regime. The mass-transfer coefficient is only very slightly dependent on temperature. This corresponds to a very low observed activation energy. Hence, if $E_{obs} \approx 0$ it is nearly certain that the overall catalytic process is strongly influenced by external mass transfer and that the activation energy found from experiments is probably far from the true activation energy. If k and k_s are similar the apparent activation energy will be between 0 and the true activation energy E.

Analogously to external mass transfer, internal mass transfer can be the rate-limiting step. In that case, it appears that the observed activation energy is related to the true activation energy as follows:

$$E_{obs} \approx \frac{E}{2} \qquad \textbf{(5.4-64)}$$

i.e. the apparent activation energy observed is half the true activation energy. Hence, if unusually low activation energies are found, say from 20 to 40 kJ mol^{-1}, the true activation energy is likely to be about two times higher.

Fig. 5.4-12 presents an Arrhenius plot for a catalytic heterogeneous process for data that are partly falsified by mass-transfer phenomena. The slope of the curve is proportional to the activation energy. Clearly, depending on the temperature, E_{obs} has a different value. In the range a, with the steepest slope, the reaction is likely to proceed in the kinetic regime, *i.e.* without mass-transfer effects. The activation energy determined from this part of the graph is close to that for the chemical reaction. In range b, the slope ($\tan\gamma$) is approximately two times lower than that ($\tan\eta$) in range a. This is characteristic of internal-mass transfer limitations. There might be no distinct straight line in this range such as shown in the figure; a more or less distinct curvature of the plot is usually seen in this region. Finally, in range c, the rate constant becomes almost independent on temperature. Here, external mass transfer probably is the rate-limiting step. There are intermediate regions between those distinguished, where the slope is determined by a combination of the different steps of the overall mechanism.

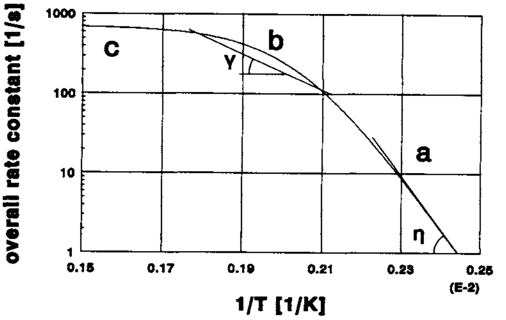

Figure 5.4-12. Arrhenius plot for a catalytic heterogeneous reaction.

In practice, the parameters in the Arrhenius equation are evaluated by fitting calculated values to experimental data. If an inadequate kinetic expression is applied to regress the experimental data, estimates of these parameters will only have the meaning of adjustable coefficients correlating the rate constant with temperature. The same applies to kinetic equations that have been determined based on data falsified by mass-transfer phenomena. This leads to *falsified* or *disguised* kinetics. The only adequate expression(s) is that which fully corresponds to the true reaction mechanism with its coefficients estimated based on unfalsified data. Determination of the true mechanism is a very difficult and time-consuming task. In the research in the field of fine chemicals, this will be difficult to be repaid. Therefore, inadequate but nevertheless useful kinetic models usually are accepted, in which Arrhenius parameters are only correlating coefficients. This is the reason why the frequency factor is termed pre-exponential coefficient to avoid confusion with the strict scientific term; the traditional term ‘activation energy’ is still in common use.

The reader is recommended to read a very practical paper on kinetics by Berger *et al.* (2001) for more information on kinetics in practice.

5.4.3. Mathematical models of chemical reactors

Deterministic mathematical models (usually starting from mass and energy balance equations[11]) are most commonly used in modelling of chemical reactors (see Eqn. 5.3-7). Tables 5.4-3 to 5.4-5 and Tables 5.4.7 and 5.4.8 list models for several reactor types. Four groups of independent variables that influence the course of the process can be distinguished: (1) design parameters (size and shape of the reactor and agitator, speed of rotation, etc.), (2) operating variables (flow rates, concentrations, temperature, pressure), (3) physical properties of the reaction mixture and its components, and (4) model parameters (coefficients of mass, heat, and momentum transfer, rate constants). The variables of groups (2) and (3) appear in the equations *explicitly*. Model parameters are functions of design variables, operating conditions, and physicochemical properties of the system: Transfer coefficients can be evaluated using literature correlations, while coefficients in rate equations must be determined experimentally.

The list of models has been composed to show which data are necessary to predict reactor

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[11] Full mathematical models also include momentum balance equations, which have been omitted here.

behaviour. Only the simplest models have been included, *i.e.* those derived based upon, among others, the assumption that the physical properties of the reaction mixture are independent of temperature and composition. An extension to more sophisticated models is quite easy. Such models have been presented in many books and review papers on chemical reactor engineering (see Carberry and Varma (1987), Carrà and Morbidelli (1987), Chaudhari *et al.*, (1986), Danckwerts (1970), Doraiswamy and Sharma (1984), Froment and Bischoff (1990), Hofmann (1983), Kapteijn and Moulijn (1997), Mills *et al.* (1992), Mills and Chaudhari (1997), Perry and Chilton (1984), Ramachandran and Chaudhari (1983), Satterfield (1970), Shah (1979, 1991), Shah and Sharma (1987), Smith (1981), Szarawara *et al.* (1991), Trambouze *et al.* (1988), Walas (1959), Westerterp *et al.* (1990), and Whitaker and Cassano (1986)).

Table 5.4-3 summarizes the design equations and analytical relations between concentration, c_A, and batch time, t, or residence time, τ, for a homogeneous reaction $A \rightarrow$ products with simple reaction kinetics (Van Santen *et al.*, 1999). Balance equations for multicomponent homogeneous systems for any reaction network and for gas-liquid and gas-liquid-solid systems are presented in Tables 5.4-7 and 5.4.8 at the end of Section 5.4.3.

Table 5.4-3
Design equations and relations between, c_A, and t or τ for homogeneous zero-, first-, and second order reactions (constant density); $\tau = V_r/F_V$.

Design equation	Order	r_A (mol m^{-3} s^{-1})	c_A (mol m^{-3})
BR:	0	k	$c_{A0} - kt$
$\frac{dc_A}{dt} = -r_A$	1	kc_A	$c_{A0}e^{-kt}$
	2	kc_A^2	$\frac{kc_{A0}t}{1 + kc_{A0}t}$
CSTR:	0	k	$c_{A0} - k\tau$
$\frac{1}{\tau}(c_A - c_{A0}) = -r_A$	1	kc_A	$\frac{c_{A0}}{1 + k\tau}$
	2	kc_A^2	$\frac{-1 + \sqrt{1 + 4kc_{A0}\tau}}{2k\tau}$
PFR:	0	k	$c_{A0} - k\tau$
$u\left(\frac{dc_A}{dz}\right) = -r_A$	1	kc_A	$c_{A0}e^{-k\tau}$
	2	kc_A^2	$\frac{kc_{A0}\tau}{1 + kc_{A0}\tau}$

5.4.3.1. Gas-liquid systems

Models for gas-liquid and gas-liquid-solid systems, listed in Table 5.4-8 at the end of Section 5.4.3, are limited illustratively to a simple irreversible reaction between a pure gaseous reactant A and a non-volatile liquid reactant B:

$$A(g) + \nu_B B(l) = \text{products} \tag{5.4-65}$$

with intrinsic kinetics given by:

$$r_{intr} = k\, c_{L,A}^{\alpha_A} c_{L,B}^{\alpha_B} \tag{5.4-66}$$

Usually, mass transfer in gas-liquid models is based on a film model (see Fig. 5.4-13). The rate of transfer of A from the gas bubble to the liquid, *i.e.* absorption of A in the liquid phase, equals:

$$r_{abs} = k_{L,A}\, a \left(c_{i,A} - c_{L,A}\right) \tag{5.4-67}$$

in which $c_{i,A}$ and $c_{L,A}$ are the concentration of A in the liquid phase at the gas-liquid interface and in the bulk, respectively. $c_{i,A}$ can be calculated using Henry's law:

$$c_{i,A} = \frac{p_A}{H_A} \tag{5.4-68}$$

The reaction (Eqn. 5.4-65) takes place in the liquid phase. The molecules are transferred away from the interface to the bulk of the liquid, while reaction takes place simultaneously. Two limiting cases can be envisaged: (1) reaction is very fast compared to mass transfer, which means that reaction only takes place in the film, and (2) reaction is very slow compared to mass transfer, and reaction only takes place in the liquid bulk. A convenient dimensionless group, the **Ha**tta number, has been defined, which characterizes the situation compared to the limiting cases. For a reaction that is first order in the gaseous reactant and zero order in the liquid reactant ($\alpha_A = 1$, $\alpha_B = 0$), Hatta is:

$$Ha = \delta \sqrt{\frac{k}{D_A}} \tag{5.4-69}$$

in which D_A is the diffusion coefficient of A and δ is given by:

$$\delta = \frac{D_A}{k_{L,A}} \tag{5.4-70}$$

The meaning of Ha is best illustrated with the concentration profiles (see Fig. 5.4-13).

It has been observed that under reaction conditions mass transfer is often significantly faster than would be expected based on the film model. This is modelled by introducing an 'enhancement' factor, E. In case the concentration in the bulk liquid, c_A, is zero, the rate of mass transfer of A now becomes:

$$r_{abs} = k_{L,A}\, a c_{L,A}\, E \tag{5.4-71}$$

The interpretation is straightforward. At reaction conditions the concentration in the film is lowered by reaction, and, as a consequence, the driving force for mass transfer increases. In a homogeneous system this results in high values of Ha. In a slurry reactor this enhancement can occur if the catalyst particles are so small that they accumulate in the film layer. Table 5.4-4 summarizes expressions for the reaction rate or enhancement factor for various regimes.

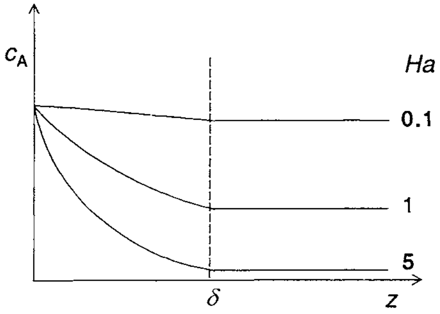

Figure 5.4-13. Film model.

Table 5.4-4
Rate equations for heterogeneous reactions at steady state under various conditions[a]

Regime	Conditions	Expression for absorption rate or enhancement coefficient
Very slow reaction, kinetically controlled	$(k_{L,A}a)\frac{p_A}{H_A} >> r_{\text{int}\,r}$ and $Ha << 1\ (< 0.1)$	$r_{abs} = r_{\text{int}\,r}$
Slow reaction, mass transfer controlled	$(k_{L,A}a)\frac{p_A}{H_A} << r_{\text{int}\,r}$ and $Ha << 1$	$E = 1$
Fast reaction, pseudo-first order	$1 < Ha < 1$	$E = \frac{Ha}{\tanh Ha}$
Fast reaction	$Ha \sim Z$	Numerical solution of diffusion-reaction equations in the film needed
Instantaneous reaction	$Ha >> Z\ (Ha \sim 10^3 \Rightarrow E \sim 10^3)$	$E = Z + 1$

[a] diffusion-concentration number $Z = \frac{1}{\nu_B}\frac{c_{L,B}}{c_{i,A}}\frac{D_B}{D_A}$

5.4.3.2. Gas-liquid-solid catalyst systems

In catalytic gas-liquid-solid systems mass transfer is more complex. The catalyst particles are present in the liquid phase. The expression for the rate of mass transfer from the gas to the liquid is identical to that for systems without a solid catalyst (Eqn. 5.4-67). However, now also mass transfer from the liquid to the solid surface (external mass transfer) and inside the particle (internal mass transfer) have to be considered.

For external mass transfer again a film model is usually applied:

$$r_{ext} = k_{s,A} a_p \left(c_{L,A} - c_{s,A}\right) \qquad \textbf{(5.4-72)}$$

in which in which $c_{s,A}$ is the concentration of A at the external surface of the catalyst particle and a_p is the external surface area per unit volume of catalyst particle.

If diffusion of reactants to the active sites in pores is slower than the chemical reaction, internal mass transfer is at least partly limiting and the reactant concentration decreases along the pores. This reduces the reaction rate compared to the rate at external surface conditions. A measure of the reaction rate decrease is the *effectiveness factor*, η, which has been defined as:

$$\eta = \frac{\textit{reaction rate with internal diffusion limitation}}{\textit{reaction rate at external surface conditions}} \qquad \textbf{(5.4-73)}$$

or

$$\eta = \frac{\frac{1}{V_p} \int\limits_{V_p} r_{v,p}\left(c_A\right) dV}{r_{v,p}\left(c_{s,A}\right)} \qquad \textbf{(5.4-74)}$$

where V_p is the volume of the particle and c_A the concentration of A in the particle interior. The effectiveness factor can be evaluated experimentally or calculated if the intrinsic rate equation and the diffusion coefficients are known, by using the reaction-diffusion equation for particles:

$$D_{eff,A}\left(\frac{d^2 c_A}{dx^2} + \frac{s}{x}\frac{dc_A}{dx}\right) = r_{intr,v,A} \qquad \textbf{(5.4-75)}$$

where s is a shape constant (0 for an infinite slab, 1 for a cylinder, and 2 for a sphere), with appropriate boundary conditions. For an irreversible first-order reaction the following expressions for the effectiveness factor are obtained for a catalyst in the shape of a slab (e.g. at the walls of a monolithic catalyst) and a sphere, respectively:

$$\eta = \frac{\tanh \phi_L}{\phi_L} \qquad \textbf{(5.4-76)}$$

$$\eta = \frac{3}{\phi_s}\left(\frac{1}{\tanh \phi_s} - \frac{1}{\phi_s}\right) \qquad \textbf{(5.4-77)}$$

where ϕ is the *Thiele modulus* defined for this reaction as:

$$\phi = \frac{V_p}{A_{ex}}\sqrt{\frac{k_{v,p}}{D_{eff,A}}} = \frac{1}{a_p}\sqrt{\frac{k_{v,p}}{D_{eff,A}}} \qquad \textbf{(5.4-78)}$$

where A_{ex} is the external surface area of the catalyst particle. The asymptotic effectiveness factor equals:

$$\eta_{\phi\to\infty}=\frac{1}{\phi_L}=\frac{3}{\phi_s} \qquad \textbf{(5.4-79)}$$

regardless the form of the rate equation and the diffusivity relationship (see Fig. 5.4-14). The higher the Thiele modulus the lower the effectiveness factor, and, consequently, the lower is the observed reaction rate. An analytical solution of the reaction-diffusion equations is generally not possible. Therefore, they must be integrated numerically to obtain the internal concentration profiles and the value of the effectiveness factor. Table 5.4-5 lists analytically obtained equations for the Thiele moduli for simple reactions of various orders.

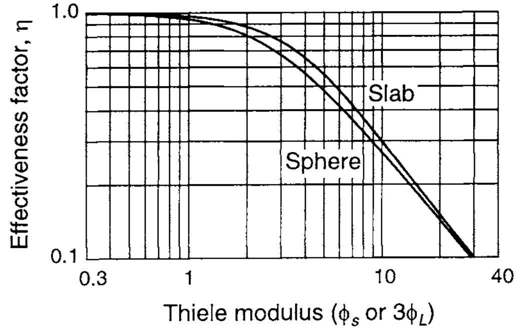

Fig. 5.4-14. Effectiveness factor versus Thiele modulus for first-order reaction.

Table 5.4-5
Thiele moduli for simple reactions

Reaction	Thiele modulus
Irreversible $\alpha_A=1,\ \alpha_B=0$	$\phi=\frac{1}{a_p}\sqrt{\frac{\alpha_A+1}{1}\frac{k_{v,p}c_{i,A}^{\alpha_A-1}}{D_{eff,A}}}$
Reversible $\alpha_A=1,\ \alpha_B=0$	$\phi=\frac{1}{a_p}\sqrt{\frac{K+1}{K}\frac{k_{v,p}}{D_{eff,A}}}$
Irreversible $(\alpha_A\text{-}\alpha_B)$th order	$\phi=\frac{1}{a_p}\sqrt{\frac{\alpha_A+1}{2}\frac{k_{v,p}c_{s,A}^{\alpha_A-1}c_{L,B}^{\alpha_B}}{D_{eff,A}}}$

For linear kinetics ($\alpha_A = 1$, $\alpha_B = 0$), the overall rate of absorption is expressed by:

$$r_{abs}=\frac{p_A}{H_A}\left(\frac{1}{k_{L,A}a}+\frac{1}{k_{s,A}a_p}+\frac{1}{\eta k}\right)^{-1} \qquad \textbf{(5.4-80)}$$

A survey of the mathematical models for typical chemical reactors and reactions shows that several hydrodynamic and transfer coefficients (model parameters) must be known to simulate reactor behaviour. These model parameters are listed in Table 5.4-6 (see also Table 5.4-1 in Section 5.4.1). Regions of interfacial surface area for various gas-liquid reactors are shown in Fig. 5.4-15. Many correlations for transfer coefficients have been published in the literature (see the list of books and review papers at the beginning of this section). The coefficients can be evaluated from those correlations within an average accuracy of about 25%. This is usually sufficient for modelling of chemical reactors. Mathematical models of reactors are often more sensitive to kinetic parameters. Experimental methods and procedures for parameters estimation are discussed in the subsequent section.

Table 5.4-6

Hydrodynamic and mass/heat-transfer coefficients in industrial reactors

Symbol	Definition	Unit	Typical range
ε_G	gas hold-up (volumetric fraction of gas in reaction mixture)	dimensionless	0.02-0.4
ε_L	liquid hold-up	dimensionless	0.02-0.95
a	interface surface area between fluids	$m^2\ m^{-3}$	10-3000
a_p	external surface area of solid particles	$m^2\ m^{-3}$	500-2500
k_G	mass-transfer coefficient from gas to liquid on gas side	$mol\ cm^{-2}\ s^{-1}\ bar^{-1}$	0.000001-0.001
k_L	mass-transfer coefficient from gas to liquid on liquid side	$m\ s^{-1}$	0.4-30
k_La	volumetric mass-transfer coefficient on the liquid side	s^{-1}	0.0003-1
k_S	mass-transfer coefficient from liquid to solid particles	$m\ s^{-1}$	
D	diffusion coefficient (liquid)	$m^2\ s^{-1}$	10^{-10}-10^{-8}
D_{eff}	effective diffusion coefficient (diffusivity)	$m^2\ s^{-1}$	$5\cdot10^{-12}$-$2\cdot10^{-9}$
H	Henry's constant	$bar\ m^3\ mol^{-1}$	
U	overall coefficient of heat transfer between reaction mixture and coolant	$W\ m^{-2}\ K^{-1}$	500-1500

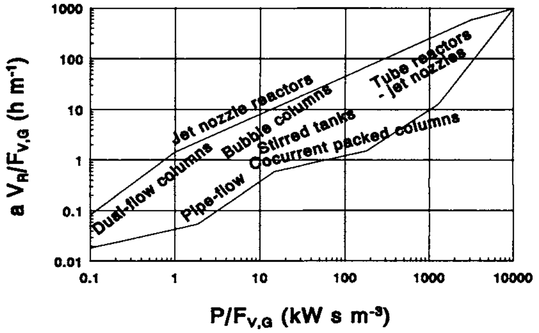

Fig. 5.4-15. Interfacial area versus power dissipation density for various reactor types; P = power; $F_{V,G}$ = gas flow rate (adapted from Carra and Morbidelli, 1987).

Table 5.4-7
Mass and heat balance equations for typical reactors, homogeneous systems

Reactor type	Balance equations[a]	Remarks
Stirred-tank (semi)batch reactor	$\frac{dn_i}{dt} = \left(V_{r,0} + F_{V,in} t - F_{V,out} t\right) \sum_j \nu_{ji} r_j + F_{V,in} c_{i,in} - F_{V,out} c_i$ $\left[V_{r,0} + \left(F_{V,in} t - F_{V,out} t\right)\right] \rho c_p \frac{dT}{dt} = \left(V_{r,0} + F_{V,in} t - F_{V,out} t\right) \sum_j \left(-\Delta H_j\right) r_j$ $+ F_{V,in} \rho c_p \left(T_{in} - T_0\right) - F_{V,out} \rho c_p \left(T - T_0\right) - A_r U \left(T - T_c\right)$	Ideal mixing assumed BR: $F_{V,in} = F_{v,out} = 0$ SBR, dosing of reactants: $F_{v,out} = 0$ SBR, removal of components: $F_{V,in} = 0$
CSTR steady-state	$V_r \sum_j \nu_{ji} r_j = F_{V,out} c_i - F_{V,in} c_{i,in}$ $\left(F_{V,in} t - F_{V,out} t\right) \sum_j \left(-\Delta H_j\right) r_j + F_{V,in} \rho_{in} c_{p,in} \left(T_{in} - T_0\right)$ $- F_{V,out} \rho_m c_{p,m} \left(T - T_0\right) - A_r U \left(T - T_c\right) = 0$	Ideal mixing assumed
Tubular reactor	$u \frac{dc_i}{dz} = \rho_{cat} \sum_j \nu_{ji} r_j$ $u \rho c_p \frac{dT}{dz} = \sum_j \left(-\Delta H_j\right) r_j - \frac{A_r}{V_r} U \left(T - T_c\right)$	Plug flow assumed

[a] The reaction rate, r_j, depends on temperatures and concentrations: $r_j\left(T, c_{i=1,\ldots,N_c}\right)$. All reactions mentioned in this table are operated adiabatically if $U = 0$. Note that stoichiometric coefficients ν_{ji} are negative for reactants and positive for products.

Table 5.4-8
Mass and heat balance equations for typical gas-liquid reactors in heterogeneous systems at steady state

Reactor type	Balance equations	Remarks
SBR (mechanically agitated)	$\varepsilon_L \frac{dc_{L,B}}{dt} = \nu_B r_{abs}$ $(\varepsilon_G \rho_G c_{p,G} + \varepsilon_L \rho_L c_{p,L}) \frac{dT}{dt} + \frac{1}{V_R} F_{V,G} \rho_G c_{p,G} (T - T_{G,in}) = (-\Delta H) r_{abs} - \frac{A_r}{V_r} U (T - T_c)$	Ideal mixing; nonisothermal operation; gas is dosed
Continuous reactor: both phases mixed ideally (CSTR with mechanical agitation)	$F_{V,G}(c_{G,A,in} - c_{G,A,out}) = r_{abs} V_r$ $F_{V,G}(c_{G,A,in} - c_{G,A,out}) + F_{V,L}(c_{L,A,in} - c_{L,A,out}) = \frac{1}{\nu_B} F_{V,L}(c_{L,B,in} - c_{L,B,out})$	Isothermal operation; r_{abs} calculated using concentrations of both gas and liquid at the outlet
Continuous reactor: liquid mixed ideally, plug flow of gas (bubble gas column, tall reactors with multistirrer system)	$-u_G \frac{dc_{G,A}}{dz} = r_{abs}$ $F_{V,G}(c_{G,A,in} - c_{G,A,out}) + F_{V,L}(c_{L,A,in} - c_{L,A,out}) = \frac{1}{\nu_B} F_{V,L}(c_{L,B,in} - c_{L,B,out})$	Isothermal operation; r_{abs} calculated for the assumed liquid concentration at the outlet and current gas concentration; concentration of liquid updated and calculations repeated; iterative procedure
Continuous reactor: plug flow of gas and liquid (bubble packed column)	$-u_G \frac{dc_{G,A}}{dz} = r_{abs}$ $-u_L \frac{dc_{L,B}}{dz} = \nu_B r_{abs}$	Isothermal operation; r_{abs} calculated for current gas and liquid concentrations

5.4.4. Kinetics - experimentation and rate analysis

5.4.4.1. Experimentation objectives

The specific application of a laboratory reactor determines its shape and size, and the degree of sophistication in design. However, no matter which application is under consideration, the final goal in process development is always the highest product yield and the lowest yields of side products, the highest activity of the reaction system (reactants + solvent + catalyst), the lowest cost, and stable and safe operation.

Several objectives of experimentation on a small scale can be distinguished:

- search for acceptable operating conditions (coarse screening), including preliminary choice of solvent, catalyst, etc.,
- optimization of selected reaction systems/operating conditions,
- identification of reaction mechanism,
- kinetic analysis of reaction system,
- study of the role of mixing conditions and mass- and heat-transfer processes on overall reactor performance,
- tests for stability of catalyst,
- quality control tests or improvement of existing processes.

Screening of operating conditions/catalysts/solvents. Tests of commercial catalysts and solvents prevail in this field. Tests are carried out at standard process conditions and results are evaluated based on a single reaction parameter. Usually one of the following measures is used as the reaction parameter: (1) the reactant conversion or yield of the desired product at given operating conditions (temperature, pressure, composition, and reaction time), (2) the reaction rate at given operating conditions, (3) the temperature required to achieve a given reactant conversion or a given product yield, (4) the time necessary to attain a given conversion or yield at given operating conditions, or (5) rate constants.

Screening is usually performed using a relatively simple, non-optimum reactor and pure reactants. Since a number of potentially good catalysts/solvents must be evaluated, the use of identical reactors in parallel with one analytical instrument is recommended. Conventional (semi)batch-operated, mechanically stirred reactors are predominantly used for this purpose in the field of fine chemicals and pharmaceuticals. One of the main reasons for this is the limited supply of raw materials tested and their high price. Continuous flow systems would require much larger amounts of reactants. The use of such reactors is necessary, however, in the case of gas-phase and/or fast reactions, e.g. partial catalytic oxidations in the gas phase and partial oxidations in the liquid phase using strong oxidants. It is fair to state that the development of fast screening methods (high-throughput testing) in combination with miniaturization has changed the field. These developments also enable continuous testing for fine chemicals.

Optimization of selected reaction systems/operating conditions. The most promising reaction systems selected based on screening tests are subjected to a more detailed comparison. The optimum operating conditions are established for each reaction system and optima are compared. Optimization of the catalyst composition and of preparation and activation techniques is performed in this stage. The influence of impurities from raw materials of technical grade and from recycled streams on process performance is tested. Again a relatively simple reactor is used, although the analytical tools are more sophisticated than those for screening purposes.

Conventional (semi)batch-operated, mechanically stirred reactors equipped with a multinozzle system for feeding components of the reaction mixture predominate at this stage.

Identification of reaction mechanism (reaction networks). The reaction mechanism (networks) for the optimum reaction system is identified. Suggestions concerning kinetic models for the selected reaction system, routes for process/catalyst improvements, and guidelines for scale-up of the process are the practical outcome of studies on the reaction mechanism. A reactor providing a well-defined concentration profile and isothermal operation is often used. Transient techniques (e.g. a pulse reactor) and flow reactors are beneficial in mechanistic studies. Highly sophisticated analytical equipment is usually needed and labelled compounds are often necessary to detect reaction intermediates at low concentrations. However, obtaining a reliable reaction mechanism requires rather time-consuming investigations. Therefore, experiments of this kind are usually omitted in the case of fine chemistry processes that must be developed and implemented on a full scale in a limited amount of time.

Kinetic analysis of reaction system. In this stage kinetic expressions not disguised by mass- and heat-transport influences (so-called *intrinsic kinetics*) for the selected reaction system are established and kinetic parameters in these equations are estimated. Main reactions, reactions leading to the formation of by-products, and reactions in which impurities (present in technical-grade raw materials or in recycled streams) participate as reactants or catalysts, must be taken into account. In general, for fine chemicals production not all by-products can be identified and usually they are lumped as pseudo-components consisting of species of similar physicochemical behaviour. Experiments for catalytic processes must be carried out in the absence of inter- and intraparticle temperature and concentration gradients. The kinetics of catalyst deactivation (and possibly regeneration) should be identified. Kinetic expressions are the core of design models for scale-up. Isothermally operated reactors, possibly gradientless with respect to concentrations, are preferred in kinetic investigations. (Semi)batch-operated mechanically stirred reactors equipped with a multinozzle system for feeding components of the reaction mixture are predominantly used for homogeneous liquid-phase and gas-liquid-solid (catalyst) processes, although in the latter case fixed-bed reactors can also be used. In case of gas-solid catalytic processes, continuous fixed-bed reactors predominate. For fluid-fluid (possibly homogeneously catalysed) processes, the use of reactors with a well-defined interfacial surface area per unit volume and known fluid dynamics is recommended.

Study of the role of mixing conditions and mass- and heat-transfer processes on overall reactor performance. The objective of these investigations is to find transport-kinetic interactions that might be important in a full-scale reactor. Mass-transfer coefficients, interfacial areas, effective diffusivities, effectiveness factors for catalyst particles, etc. are determined. This is particularly important for the scale-up of systems where existing literature data are not applicable due to a limited reliability. Reactors providing the possibility of varying the mixing conditions (e.g. varying the rotation speed of the agitator, use of replaceable stirrers, different feeding locations, etc.) should be used in these studies. Catalyst particles of different size should be tested, and the influence of the flow rate of the reaction mixture on reactor performance in continuous reactors should be studied. The scale-up of many multiphase reactors is mainly determined by the hydrodynamics. This is usually very complex in fluidized-bed reactors, trickle-bed reactors, bubble column reactors, and loop reactors. The hydrodynamics of stirred-tank reactors is the best known as a result of the frequent use of these reactors. This is likely to be one of the reasons why these reactors are the most widely used in scale-up of procedures for the manufacture of fine chemicals.

Stability tests of catalyst. All catalysts deactivate during their life by various causes (see Chapter 3). The aim of stability tests is to examine the cause and rate of deactivation. These experiments are usually performed at conditions similar to those planned for the commercial unit. In some cases, accelerated tests are carried out using a feedstock with an elevated level of impurities or at a temperature significantly higher than that anticipated for the full-scale reactor. A laboratory reactor used for such tests is usually a down-scaled reactor or a part of the full-scale-reactor. Standard analytical equipment is used.

Quality control tests or improvement of existing processes. Raw materials from various sources can be used in the manufacture of fine chemicals and pharmaceuticals. The raw materials can contain different impurities at various concentrations. Therefore, before the raw material is purchased and used in a full-scale batch its quality should be tested in a small-scale reactor. Existing full-scale procedures are subject to continuous modifications for troubleshooting and for improving process performance. Laboratory reactors used for tests of these two kinds are usually down-scaled reactors or reactors being a part of the full scale-reactor.

5.4.4.2. Types of laboratory reactors

A classification of laboratory reactors is shown in Fig. 5.4-16 (after Mills *et al.* (1992)).

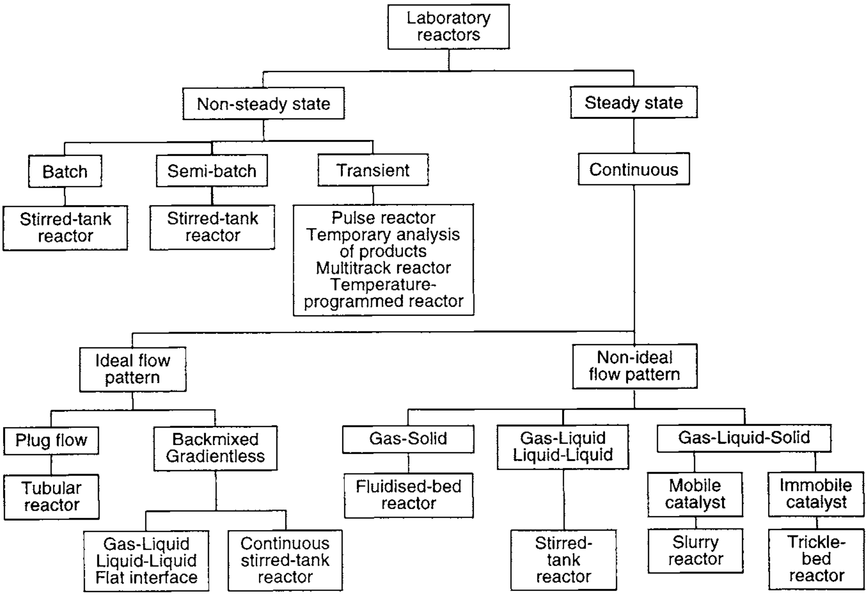

Figure 5.4-16. Classification of laboratory reactors (adapted from Mills *et al.*, 1992).

Non-steady-state reactors. Batch reactors are the most widely used versatile reactors in studying processes for the manufacture of fine chemicals and pharmaceuticals. They can be, and usually are, equipped with efficient agitators providing an essentially uniform concentration of reactants and catalyst throughout the reaction zone, and they can be run isothermally in the vast majority of reactions. Typically, reactors of 100-500 cm^3 equipped with a standard six-blade turbine agitator or marine propeller (the agitator-to-reactor diameter ratio ranges from 1/3 to 1/2) with a rotation speed controlled between 500 to 2000 min^{-1} are used. Propeller agitators are strongly recommended for stirring of suspensions, in order to keep them as uniform as possible. (Stirrers used most often in full-scale reactors are shown in Fig. 5.4-3 in Section 5.4.1) At least two breakers like thermometer sheets should be inserted into the reaction zone to avoid vortex formation, which impairs mixing (contrary to common opinion among synthetic chemists). Glass, stainless steel, and ordinary steel enamelled or lined with inert chemically resistant material (e.g. Teflon^R) are typical materials of construction of these reactors. For heterogeneous catalytic processes, commercial powdered or laboratory-made catalysts with a particle diameter ranging from 10 to 150 μm are used. By withdrawing samples during the course of the experiment kinetic curves of the type *concentration* = *f*(*time*) are produced. One family of curves obtained from one isothermal run is usually sufficient to estimate kinetic parameters of the assumed kinetic expression. However, processing the experimental data can be complex and troublesome. It requires numerical integration of balance equations in combination with non-linear regression techniques, and as such it requires the use of computers. Simple calculations made graphically or using the pocket calculator are seldom applicable. However, software necessary for these computations is readily available.

For higher pressures, autoclaves are in common use by organic chemists. As tools for reactor scale-up, most commercial autoclaves show significant deficiencies:

- Built to withstand high pressures, autoclaves have a large thermal capacity. In combination with constraints imposed on heating and cooling rates, this makes temperature control difficult in spite of the use of sophisticated temperature controllers. The performance indices must be referred to the particular temperature-time dependence in which periods for heating and cooling may be comparable or even longer than the time needed for the reaction itself. The temperature-time relationship $T = f(time)$ in large-scale reactors will be entirely different from that in the laboratory autoclave. Accordingly, conclusions drawn regarding the best operating conditions or potentially best catalyst cannot be directly applied to the full-scale equipment.
- Temperature and composition of the gas phase cannot be controlled independently; the partial pressures are determined by the temperature and the physical properties of the reaction mixture, and thus they vary with time.
- Mixing in the vast majority of autoclaves of older design can be poor. Easily sedimenting catalysts (e.g. Raney nickel) will tend to settle down, and their distribution over the reaction zone will be non-uniform. Reactants added during autoclave operation may not be uniformly distributed throughout the reaction zone and may not be mixed with the reaction mixture sufficiently fast. Some autoclave designs have magnetically coupled stirrers, which avoid problems with sealing the stirrer shaft. The stirrer speed of rotation must be regulated so that the influence of rotation on process performance can be tested. Kinetic and scale-up experiments should be carried out at the rotation speed above which no further influence of this variable is observed, because otherwise yields and selectivities can be significantly affected by mass- and heat-transfer processes.

- Obtaining representative samples can be difficult due to a change in composition of the reaction mixture during depressurization. Sampling during the experiment with finely ground catalyst is difficult and requires thorough filtering of the catalyst in the sampling line. In general, complete product recovery is difficult and this makes balancing of the experiment difficult.

Despite the aforementioned shortcomings the experimental data obtained using commercial autoclaves can be kinetically interpreted in spite of non-isothermal operation, as shown further on in this chapter. Kinetic expressions obtained in this manner will rather be interpolation equations than equations reflecting real reaction mechanisms.

Shaker tube reactors are commonly used for the evaluation of catalysts at elevated pressure. The liquid reactant and powdered catalyst are introduced into a metal or glass ampoule, which is sealed and pressurized to a predetermined level with the gaseous reactant. The ampoule is immersed into a thermostatted liquid and maintained at this temperature for a certain period of time while shaking. Then the reactor is opened and the reaction mixture analysed. Ampoules of ca. 10-100 cm^3 are typically used. The usefulness of data obtained using such reactors for process scale-up is nearly zero due to poor agitation and unknown hydrodynamics in the ampoule. These reactors are, however, very useful for fast screening of catalysts.

Semibatch reactors are often used to run highly exothermic reactions isothermally, to run gas-liquid(-solid) processes isobarically, and to prevent dangerous accumulation of some reactants in the reaction mixture. Contrary to batch operation, temperature and pressure in semibatch reactors can be varied independently. The liquid reaction mixture can be considered as ideally mixed, while it is assumed that the introduced gas flows up like a piston (certainly this is not entirely true). Kinetic modelling of semibatch experiments is as difficult as that of batch, non-isothermal experiments.

Transient reactors, such as pulse (chromatographic) reactors, temporary analysis of products (TAP) reactors, multitrack reactors, and temperature-programmed reactors have been developed mainly to study gas-solid (catalyst) reactions. These are rather sophisticated techniques used to study mechanisms of catalytic processes at the molecular level in great detail. Since this is rarely done in the development of processes for the manufacture of fine chemicals and pharmaceuticals, these reactors are not discussed further. The interested reader is referred to works by Anderson and Pratt (1985) and Kapteijn and Moulijn (1997).

Steady-state reactors with ideal flow pattern. In an ideal isothermal tubular *plug-flow reactor* (*PFR*) there is no axial mixing and there are no radial concentration or velocity gradients (see also Section 5.4.3). The tubular PFR can be operated as an *integral reactor* or as a *differential reactor*. The terms 'integral' and 'differential' concern the observed conversions and yields. The differential mode of reactor operation can be achieved by using a shallow bed of catalyst particles. The mass-balance equation (see Table 5.4-3) can then be replaced with finite differences:

$$u\left(\frac{\Delta c_A}{\Delta z}\right) = \nu_A r_A \qquad \textbf{(5.4-81)}$$

In integral reactors conversions and yields are quantities obtained by integration over the whole length of the reactor.

Tubular reactors are widely used in studying single-phase processes and gas-solid catalytic processes. Catalyst particles are placed in a tube, which is either jacketed with a thermostatted heat carrier (liquid or fluidized sand particles) or put into an electric oven, whereby the particles are placed far from the inlet and outlet of the tube, between layers of chemically inert material, e.g. quartz wool (see Fig. 5.4-17). The reason for this is that significant heat losses to the surroundings occur at the inlet and the outlet, which can cause operation to be far from the desired isothermicity. The reaction mixture flowing through the layer of inert material is expected to heat up to the desired temperature before entering the catalyst bed. In case of narrow tubes, the temperature in the oven or in the jacket is measured and this is assumed to be the temperature of the reactor. These measures do not necessarily guarantee isothermal operation of a catalyst bed in case of fast reactions with a large heat effect. For such reactions isothermal operation can be realized by (1) using reactors of small diameter (<10 mm, typically 4-7 mm ID), (2) diluting the catalyst bed with inert material, or (3) by using shallow beds (differential reactors) in which conversions are low, and, consequently, the amount of heat to be exchanged with the surroundings is small. However, in general the assumption that the temperature measured outside the bed is equal to that inside the bed reflects wishful thinking rather than reality. The temperatures at the inlet and outlet of the bed should at least be measured for shallow beds, and axial temperature profiles should be measured for longer beds. Tubular reactors are simple and cheap.

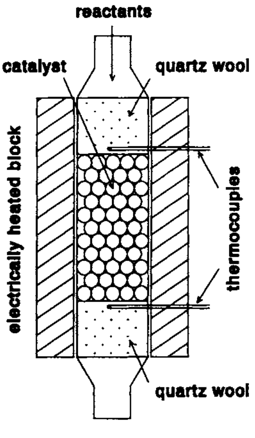

Figure 5.4-17. A laboratory tubular reactor.

The flow pattern of fluids in gas-liquid-solid (catalyst) reactors is often far from ideal. Special care must be taken to avoid by-passing of the catalyst particles near the reactor walls, where the packing density of the catalyst pellets is lower than in the centre of the bed. By-passing becomes negligible if the ratio of reactor to particles diameter is larger than 10; a ratio of 20 is recommended. Flow maldistributions might be serious in the case of shallow beds. Special devices must be used to equalize the velocity over the cross-section of the reactor before reactants are introduced onto the catalyst bed.

Chemical analysis of the reaction mixture is easy in integral reactors because of the high conversions. However, these high conversions can make an assumption concerning the absence of axial mixing unrealistic due to large longitudinal concentration gradients. In contrast, conversions in differential reactors are low (< 5 %), which makes an accurate analysis of the reaction mixture more difficult; the error of the analytical methods should be much lower than the difference in concentrations between the inlet and the outlet. If higher conversions are to be simulated using a differential reactor, products must be added to the inlet stream or an integral pre-reactor installed upstream the differential reactor to raise the conversion to a predetermined level.

Kinetic analysis of the data obtained in differential reactors is straightforward. One may assume that rates are directly measured for average concentrations between the inlet and the outlet composition. Kinetic analysis of the data produced in integral reactors is more difficult, as balance equations can rarely be solved analytically. The kinetic analysis requires numerical integration of balance equations in combination with non-linear regression techniques and thus it requires the use of computers.

When balancing advantages and drawbacks of differential and integral tubular reactors one may conclude that single-pass differential reactors are impracticable. We do not recommend their use at any stage in the development of processes for manufacture of fine chemicals and pharmaceuticals. *Differential reactors with recycle* can solve problems encountered in single-pass differential reactors. Due to a very small conversion per pass, temperature and concentration gradients inside the catalyst bed are essentially eliminated and, therefore, differential reactors with recycle are said *gradientless*.

The principle of the differential reactor with recycle is illustrated in Fig. 5.4-18.

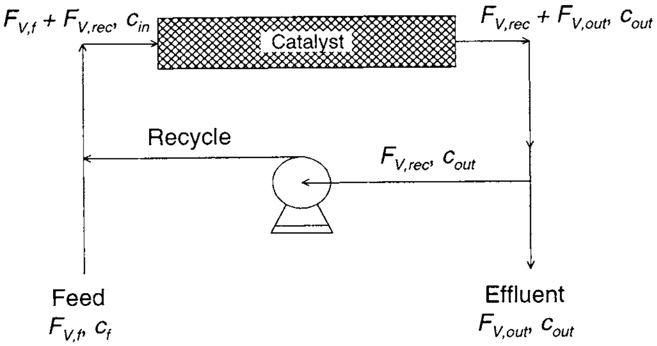

Figure 5.4-18. Differential reactor with recycle of the reaction mixture.

The average reaction rate over the catalyst bed, r_{ave}, must be the same as the overall rate r_{ov}. Thus:

$$r_{ave} = \left(F_{V,f} + F_{V,rec}\right)\frac{c_{in} - c_{out}}{V_r} = r_{ov} = F_{V,f}\,\frac{c_f - c_{out}}{V_r} \qquad \textbf{(5.4-82)}$$

where $F_{V,f}$, $F_{V,out}$, and $F_{V,rec}$ are volumetric flow rates for feed, effluent, and recycle, respectively;

c_f, c_{in}, and c_{out} are reactant concentrations in the feed, and at the inlet and outlet of the catalyst bed, respectively; and V_r is the reactor volume. The mass balance equation for mixing feed with recycle is as follows:

$$F_{V,rec}c_{out} + F_{V,f}\,c_f = \left(F_{V,rec} + F_{V,f}\right)c_{in} \qquad \textbf{(5.4-83)}$$

or, after rearranging:

$$c_{in} = \frac{c_{out} + c_f\left(F_{V,f} / F_{V,rec}\right)}{1 + \left(F_{V,f} / F_{V,rec}\right)} \qquad \textbf{(5.4-84)}$$

It follows from the equation above that $c_{in} \approx c_{out}$ if $F_{V,rec} >> F_{V,f}$. This means that for a recycle stream much larger than the feed stream, the catalyst bed operates as a differential reactor, while the whole system gives an outlet concentration differing significantly from that of the feed. This significantly simplifies problems of chemical analysis. In practice, the recycle reactor operates differentially if the recycle ratio $F_{V,rec}/F_{V,f}$ is larger than 25. The rate is then given by the overall rate:

$$r_{ov} = F_{V,f}\frac{c_f - c_{out}}{V_r} \qquad \textbf{(5.4-85)}$$

As will be shown later the equation above is identical to the mass balance equation for a continuous stirred-tank reactor. The recycle can be provided either by an external pump as shown in Fig. 5.4-18 or by an impeller installed within the reaction chamber. The latter design was proposed by Weychert and Trela (1968). A commercial and advantageously modified version of such a reactor has been developed by Berty (1974, 1979), see Fig. 5.4-19. In these reactors, the relative velocity between the catalyst particles and the fluid phases is increased without increasing the overall feed and outlet flow rates.

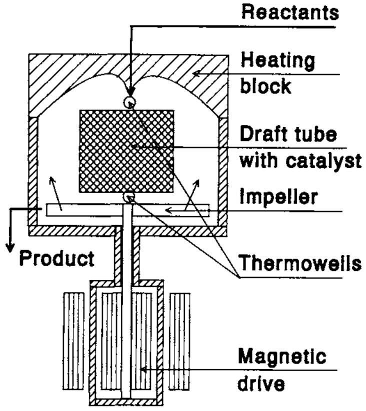

Figure 5.4-19. Internally recycled reactor (Berty reactor).

The catalyst can, alternatively, be present in a basket located in the annular space at the wall. A reactor of this type is particularly useful for gas-liquid-solid reactions.

Gradientless recycle reactors are also commonly used for studying multiphase catalytic processes. They can be operated in continuous-flow or semibatch mode. Recycle reactors can also be very attractive for studying reactions in batch mode. In contrast with integral reactors, in each experiment in a differential reactor with recycle the rate is obtained directly by measuring the concentration in the effluent stream. Kinetic analysis of such experimental data is simple and numerical integration or error-producing differentiation is avoided. Internally recycled reactors are characterized by isothermal operation at steady state, a well-defined residence time, high transport rates, ease of sampling, and the possibility to examine phenomena occurring at a specific point in the commercial fixed-bed reactor. Reactors of this type combine the advantages of differential and integral reactors and eliminate the disadvantages.

In *Continuous stirred-tank reactors* (*CSTR*) the concentration inside the reactor is the same as the concentration in the stream leaving the reactor. In each experiment the reaction rate is obtained directly from the measured effluent concentration c_{out}. A CSTR was used for studying gas-solid catalytic processes by several researchers, starting with Carberry (1964). This kind of CSTR contains a rotating basket with catalyst particles (see Fig. 5.4-20). A rectangular-paddle basket, a cylindrical basket(s), and a circular basket have been used. Basket-type reactors are very useful for studying fluid-solid catalytic processes. However, heat- and mass-transfer resistances in the catalyst basket could be significant. Therefore, results of kinetic investigations may be falsified by transport processes.

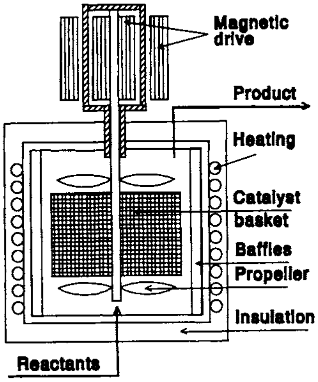

Figure 5.4-20. Basket-type reactor (Carberry reactor).

Steady-state reactors with non-ideal flow pattern. In fact, all reactors presented as reactors with ideal flow patterns show some non-idealities as already mentioned above. The deviation from the ideal state for multiphase reactors arises from the presence of phases with very different physical properties.

The most widely used reactors for *gas-solid reactions* in fine chemistry are fixed-bed tubular reactors. There are several other types of reactors for carrying out gas-solid reactions, e.g. fluidized-bed reactors, riser reactors, and moving-bed reactors. These reactors will not be discussed owing to their limited applications in the field of fine chemicals.

Laboratory reactors for studying *gas-liquid processes* can be classified as (1) reactors for which the hydrodynamics is well known or can easily be determined, *i.e.* reactors for which the interfacial area, a, and mass-transfer coefficients, k_L and k_G, are known (e.g. the laminar jet reactor, wetted wall-column, and rotating drum, see Fig. 5.4-21), and (2) those with a well-defined interfacial area and ill-determined hydrodynamics (e.g. the stirred-cell reactor, see Fig. 5.4-22). Reactors of these two types can be successfully used for studying intrinsic kinetics of gas-liquid processes. They can also be used for studying liquid-liquid and liquid-solid processes.

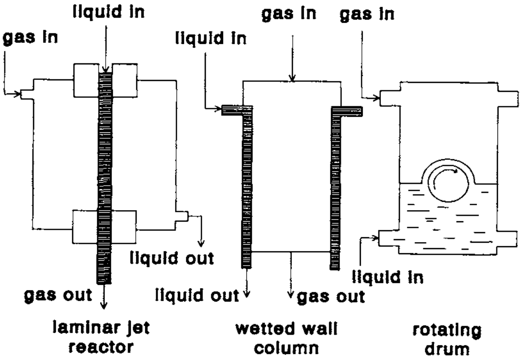

Figure 5.4-21. G-L, L-L, and L-S reactors; hydrodynamics known.

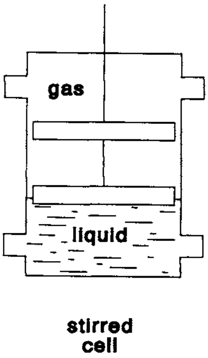

Figure 5.4-22. G-L and L-L reactor; hydrodynamics not known well.

Bubble-column reactors are also widely used in laboratory investigations. The liquid in bubble-column reactors (see Fig. 5.4-7 in section 5.4.1) is fed near the bottom of the column and withdrawn at the top. The gas is introduced through a sparger to disintegrate the gas into small bubbles. The bubbles tend to coalesce when flowing upward. The diameter of a laboratory bubble-column reactor should not be too small, because otherwise the reactor walls will stimulate coalescence of gas bubbles and this will significantly worsen the performance of the reactor. A minimum diameter of 0.1 m is recommended. The operation of the bubble-column reactor is unstable when the gas flow rate is too low. The liquid then trickles through orifices inside the sparger and blocks the gas flow. The pressure in the sparger builds up to the level where the liquid is blown out and the gas restarts flowing. However, then the pressure drops again, the liquid penetrates through orifices, etc.

In a properly operated bubble-column reactor, the liquid phase can be considered to be perfectly mixed, *i.e.* concentrations in the liquid are the same everywhere and correspond to those in the effluent. The gas is supposed to flow like a piston, *i.e.* the reactor is a plug-flow reactor with respect to the gas. These two assumptions are not entirely true, but within a certain flow regime they are not far from the reality.

A continuous, mechanically stirred tank reactor with a sparger located below the agitator or near the agitator's tip shows similar behaviour as a continuous bubble-column reactor. The gas dispersion is usually better, and, consequently, the interfacial area per unit volume is higher than in bubble-column reactors. Therefore, in upscaling studies CSTRs are usually preferred over bubble-column reactors.

Laboratory reactor for studying *three-phase processes* can be divided in reactors with mobile and immobile catalyst particles. Bubble (suspension) column reactors, mechanically stirred tank reactors, ebullated-bed reactors and gas-lift reactors belong the class of reactors with mobile catalyst particles. Fixed-bed reactors with cocurrent (trickle-bed reactor and bubble columns, see Figs. 5.4-7 and 5.4-8 in Section 5.4.1) or countercurrent (packed column, see Fig. 5.4-8) flow of phases are reactors with immobile catalyst particles. A mobile catalyst is usually of the form of finely powdered particles, while coarser catalysts are studied when placing them in a fixed place (possibly moving as in mechanically agitated basket-type reactors).

Mechanically agitated tank reactors (see Fig. 5.4-3 in Section 5.4.1) are most often used for collection of kinetic and scale-up data for three-phase processes. The reactor is fed with the liquid reactant and the catalyst at any position in the reaction zone while the gaseous reactant is introduced below the agitator or near the tip of the agitator. The suspension is collected at the overflow while the unreacted gas leaves the reactor via the gas-liquid separator and recycle condenser. The reactor, agitator, and catalyst characteristics are the same as for mechanically agitated reactors operated in batch-mode. The liquid is considered to be ideally mixed with a uniform concentration of reactant over the reaction zone. Accordingly, overall process rates are directly measured in reactors of this type. Kinetic analysis is rather simple provided that the influence of external and internal diffusion is eliminated by the proper choice of operating conditions.

Fixed-bed reactors are used for testing commercial catalysts of larger particle sizes and to collect data for scale-up (validation of mathematical models, studying the influence of transport processes on overall reactor performance, etc.). Catalyst particles with a size ranging from 1 to 10 mm are tested using reactors of 20 to 100 mm ID. The reactor diameter can be decreased if the catalyst is diluted by fine inert particles; the ratio of the reactor diameter to the size of catalyst particles then can be decreased to 3:1 (instead of the 10 to 20 recommended for fixed-bed catalytic reactors). This leads to a lower consumption of reactants. Very important for proper operation of fixed-bed reactors, both in cocurrent and countercurrent mode, is a uniform distribution of both phases over the entire cross-section of the reactor. If this is not the case, reactor performance will be significantly falsified by flow maldistribution.

Requirements regarding laboratory *liquid-liquid reactors* are very similar to those for gas-liquid reactors. To interpret laboratory data properly, knowledge of the interfacial area, mass-transfer coefficients, effect of contaminants on mass-transport processes, ionic characteristics of the system, etc. is needed. Commonly used liquid-liquid reactors have been discussed by Doraiswamy and Sharma (1984).

5.4.4.3. ***Reaction calorimetry***

Reaction calorimetry is a technique which uses data on the rate of heat evolution or consumption to evaluate the thermokinetic reaction characteristics needed for reactor scale-up and/or optimization and safety. Since the late seventies, the application of this technique has been steadily growing and reaction calorimeters are now commercially available. Probably the first commercial reactor calorimeter was developed by CIBA-GEIGY (Bench Scale Calorimeter: BSC) (see Beyrich *et al.*, 1980; and Regenass *et al.*, 1978, 1980, 1983, 1984, 1985, 1997)) which has been commercialized by Mettler under the registered names RK1 and RC1. Now several tens such calorimeters are in every day use for process development and safety analysis in CIBA-GEIGY laboratories (Regenass, 1997). Every year a Reaction Calorimeter Forum is organized (see e.g. Amery *et al.*, Bachhuber, Buser and Urwyler, Fahrni *et al.*, Nebuloni and Cardillo and O'Rourke (6th *RC User Forum*, 1993) and Gilbert, Giusto, Godard, Gortsema, Landau *et al.*, Leach *et al.*, Machado, Mani and Cuony, and Stefanick (7th *RC User Forum*, 1994)) where tens of papers, mostly by companies, on the practical uses of RCs are presented. A significant proportion of the papers presented at the 1st International Conference on *The Scale-Up of Chemical Processes* (Brighton, 1994) also treated problems that have been solved using RCs, see Amery, Bourne, Knoechel, Sink, and Wright (1994).

Fig. 5.4-23 shows a sketch drawing of a BSC (Brogli *et al.*, 1981). The stirred-tank reactor made of glass (a metal version is also available) is surrounded by a jacket through which a heat-transfer fluid flows at a very high rate; the jacket is not insulated. The temperature of the circulation loop is regulated by a cascaded controller so that the heat evolution in the reactor is equilibrated by heat transfer through the reactor wall. The temperature in the loop is adjusted by injection of thermostatted hot or cold fluid.

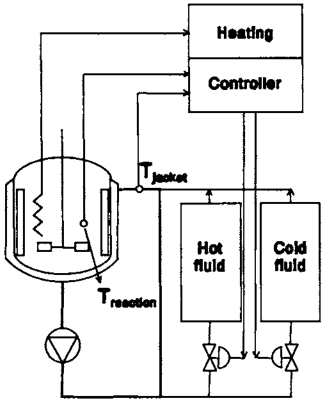

Figure 5.4-23. Bench scale reaction calorimeter (adapted from Brogli *et al.*,1981) .

The amount of heat transferred through the reactor wall is proportional to the temperature difference:

$$q = U \cdot A_r \cdot (T_r - T_j) = f_c \cdot \Delta T \tag{5.4-86}$$

where U is the overall heat-transfer coefficient, A_r is the heat exchange surface area, T_r and T_j are the temperature in the reactor and in the jacket, respectively, and f_c is the calibration factor. So, the rate of heat transfer is known once the calibration factor, f_c, which is the product of the overall U and A_r, has been determined. Both U and A_r can vary during the course of reaction because of variations in physical properties and volume of the reaction mixture. Therefore, frequent calibration is needed, which is somewhat inconvenient. This disadvantage is compensated by the use of uninsulated glass equipment allowing for very valuable visual observation of the reaction mixture during the reaction. Calibration is performed by producing a known heat input rate to the reaction mixture by means of an electric heater. Calibration must be done under isothermal conditions, because otherwise a part of the heat input could be used for heating up the reaction mixture as given by the heat balance at any moment in time:

$$q_P = U \cdot A_r \cdot (T_r - T_j) + m \cdot c_p \cdot \frac{dT_r}{dt} \tag{5.4-87}$$

where q_P is the amount of heat generated by the reaction, m is the mass of the reaction mixture, and c_p is the specific heat of the reaction mixture. Thus, under isothermal conditions realized by manipulation of the jacket temperature (see calibration period in Fig. 5.4-24), the derivative dT_r/dt is zero and Eqn. (5.4-87) becomes identical to Eqn. (5.4-86). Hence, knowing q_P (power rating of the probe), T_r, T_j, and A_r, the overall heat-transfer coefficient can be determined. If the temperature of the reaction mixture is raised by increasing the jacket temperature, e.g. in the form of a short temperature ramp (see Fig. 5.4-24) in the absence of a heat source ($q_P = 0$) and with $\Delta T = const$, then Eqn. (5.4-87) can be rearranged to give the following expression:

$$c_p = -\frac{U \cdot A_r \cdot (T_r - T_j)}{m \cdot \Delta T_r / \Delta t} \tag{5.4-88}$$

Hence, both c_p and U can be evaluated for the physical and geometrical system under consideration instead of using literature correlations with an accuracy of ± 30 %. For a single reaction the rate of heat generation q_P is the product of the reaction rate, the volume of the reaction mixture, and the heat of reaction, which for a batch apparatus can be written as:

$$q_P = \left(-\frac{dc}{dt}\right) \cdot V_r \cdot (-\Delta H) \tag{5.4-89}$$

The amount of heat evolved per mole of reactant until the reaction is completed ($t = t_r$) is the heat of the reaction:

$$(-\Delta H) = \frac{1}{c_0 V_r} \int_0^{t_r} q_P \, dt \tag{5.4-90}$$

while the amount of heat evolved up to any time t:

$$Q_P = \frac{1}{c_0 V_r} \int_0^{t} q_P \, dt \tag{5.4-91}$$

is proportional to the conversion over this period of time:

$$X = \frac{Q_r}{(-\Delta H)} \tag{5.4-92}$$

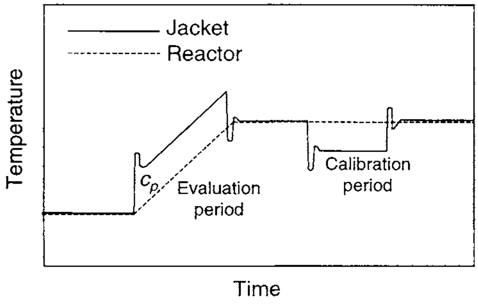

Figure 5.4-24. Temperature profiles during calibration (adapted from Landau and Willimas, 1991).

Heat flux data are directly related to the rate of reaction if only a single reaction takes place in the system considered. Otherwise, the generated heat provides rather unspecific information. Then these data may not be reprocessed into the kinetic equation. However, in a large number of fine chemistry processes, the main reaction predominates to such a degree that the thermal information is sufficient to develop a gross kinetic model suitable for reactor modelling. This makes reaction calorimetry a very useful tool for reactor scale-up and safety analysis. Obviously, calorimetry will never give the detailed information necessary for the elucidation of the kinetic mechanisms. In this respect, detailed chemical and physical analysis of the reaction mixture is required. What can be investigated using a calorimeter is macrokinetics without obtaining a deeper insight into microscopic phenomena. Thermal methods themselves are also not appropriate for selectivity studies. However, in combination with a chemical analysis of samples taken from the reaction mixture during the course of reaction, these methods can provide valuable information on complex reaction systems. Reaction calorimetry is an extremely useful supplement to the data obtained by means of classical methods.

At present, several companies offer reaction calorimeters. Below, the specifications of the most commonly used commercial calorimeter (RK1 of Mettler) are given:

reactor temperature : -20 to 200 °C
temperature program : ± 1 to 200 °C/hour
pressure (glass reactor) : vacuum to 300 kPa
reactor volume : 0.5/2.5 litres
sensitivity : 0.5 Watts for low viscosity reaction mixtures
heat removal capacity : 500 Watts (for temperature > 30 °C).

Table 5.4-9 gives examples of the use of reaction calorimetry in process development and optimization.

5.4.4.4. Guidelines for reactor choice

General guidelines concerning the choice of the most proper reactor type for the particular system to study, modified after Mills *et al.* (1992) are given in Table 5.4-10. The types, applications, advantages, and disadvantages of several laboratory reactors for kinetic measurements are given in Table 5.4-11.

Table 5.4-9
Examples of the use of reaction calorimeter for process development and optimization

Process	Industrial partner	Reference
Ammonolysis (1.5 bar, 25 °C)	The R.W. Johnson Pharm. Res. Inst.	Stefanick (1994)
Productivity in a pharmaceutical reaction vs catalyst characterisation (hydrogenation of *N*- ethyl pyrolidone, step in Primaxin^{TM} manufacture)	Merck & Co.	Gortsema *et al.* (1994)
Optimization of WIN 8883 particles size (pharmaceutical product)	Sterling Winthrop	Gilbert (1994)
Silylation reaction	Merck & Co.	Landau *et al.* (1994)
Synthesis of phenylbenzoate from benzoyl chloride and phenol	Eastman Chemical Company	Leach *et al.* (1994)
Catalytic autoxidation	Russel Uclaf	Godard (1994)
Evaluation of quality of diallyl dimethyl ammonium chloride solution (for polymerizations)	Fraunhofer Inst. Appl. Polym. Res.	Hahn (1993)
Improvement of process distillation	Societe Chimique Roche S.A	Dlubala (1993)
VLE: THF-water, acetone-water	Ciba-Geigy	Mani and Cuony (1994)
Thermal conductivity for viscous systems	Unilever	Smith and Edwards (1993)
VLE: MeOH-EtOH, $CHCl_3$-EtOH, NH_3-water	Ciba-Geigy	Mani and Cuony (1994)
Determination of heat capacity and heat of reaction vs temperature	Eli Lilly & Co.	Peck (1994)
Increase of semibatch reactor productivity for the addition of acrylonitrile to an amine	Ciba-Geigy	Stoessel (1994)
Chlorination of aniline hydrochloride; oxidation of 1,4-aminonaphthol; oxidation of alkylsulphides; synthesis of ether from phenol and chlorobenzene	Eastman Chemical Company	Leach *et al.* (1990)

5.4.4.5. Kinetic modelling for scale-up - introduction

Progress in chemical reaction engineering, knowledge on physical processes (fluid dynamics and mass- and heat-transport processes) in equipment of various configurations and sizes, methods of chemical analysis, and mathematical methods for interpretation of experimental data, especially in computational techniques, enables more reliable predictions of reactor behaviour, which makes scale-up sufficiently accurate. In general, good predictions can be achieved only if kinetic expressions used in scale-up procedures reflect the true mechanism or are close to the true mechanism. The kinetic coefficients in the true kinetic equations are termed *true* or *intrinsic* coefficients. Such kinetic models are versatile: they can be used for optimal scale-up as well as for the analysis of operation and optimization of existing reactors. However, in scale-up operating conditions might be chosen which lie far outside the range of variables used during kinetic experimentation.

Table 5.4-10
General guidelines for reactor selection for laboratory use

Application	Homogeneous reactions	Liquid-Solid reactions	Gas-Liquid-Solid reactions	Gas-Liquid reactions	Liquid-Liquid reactions
Screening	(S)BSTR	(S)BSTR	(S)BSTR, TBR	(S)BSTR	BSTR
Optimization	(S)BSTR, CSTR	PFR, CSTR	CSTR, TBR	CSTR	CSTR
Reaction Mechanism	BSTR	CSTR	CSTR, TBR	CSTR	CSTR
Kinetic analysis	(S)BSTR	CSTR	CSTR	SBSTR	BSTR
Physical phenomena	(S)BSTR	Slurry	Slurry, TBR	Bubble column	CSTR
Stability tests	n.a.	Slurry	Slurry, TBR	n.a.	CSTR
Quality control & process improvement	(S)BSTR	Slurry	Slurry, TBR	BSTR, CSTR	CSTR

Key: PFR = Plug Flow Reactor, BSTR = Batch Stirred-Tank Reactor, (S)BSTR = (Semi)Batch Stirred -Tank Reactor, SBSTR = Semibatch Stirred-Tank Reactor, CSTR = Continuous Stirred-Tank Reactor, TBR = Trickle-Bed Reactor.

It is well known that mechanisms can vary with temperature, pressure, etc. Accordingly, there always will be a risk that even true kinetic expressions developed at laboratory conditions are not valid for conditions used at a large scale. This is the well-known extrapolation risk. In practice, the situation is worse. Identification of the true mechanism often is troublesome and time-consuming. Therefore, we often deal with kinetic expressions that are empirical to a high degree rather than physically sound.

In general, the problem of kinetic modelling comprises three intermingled parts: (1) *model selection*, which starts with a preliminary choice of models to be considered for further processing and ends with the discrimination between rival models using parameters estimated based on experimental data, (2) *estimation of kinetic parameters*, and (3) *statistical analysis*, aimed at testing of models with the estimated parameters. The aim of step (1) is the development of a kinetic model reflecting process mechanisms as well as possible. The model must at least describe experimental data well. In step (2) unknown parameters of a selected model are estimated by fitting dependent variables calculated from the model to experimentally determined variables. For some cases model parameters can be estimated roughly using graphical methods. Usually, the method of least squares is used. It consists in the search for a set of model parameters for which the sum of squared deviations of calculated dependent variables from observed variables (residuals)

$$SS_{res} = \sum_{i=1}^{N_e} \left(y_{i,calc} - y_{i,exp}\right)^2 \qquad \textbf{(5.4-93)}$$

is minimized.

Table 5.4-11
Laboratory reactors used for kinetic measurements

Type	Major applications	Major advantages	Major disadvantages
Agitated reactor (possibly with catalyst particles)	Catalytic and noncatalytic Reactions, polymerizations (special agitator required)	High transport rates, convenient to operate, easy variation of parameters, most versatile	Catalyst erosion
Basket-type reactor (CSTR) for gas-phase reactions)	High temperature, high pressure catalytic processes	High transport rates, easy variation of parameters	Limited particle size, high equipment cost, difficult to operate under a wide range of conditions without creating flow maldistribution
Microreactors	Low conversion, catalytic reactions	Simple design, transport rates can be increased by external recycling	Limited ease of variation of parameters, maldistribution of flow can be prohibitive
Internally recycled reactor (Berty)	High temperature, high pressure catalytic processes	High transport rates, intense mixing	Limited ease of variation of parameters
External recycle reactor	Polymerizations, catalytic reactions	Very useful for viscous mixtures	Equipment cost can be high (for viscous systems and for high pressure operations)
Reaction calorimeter	Wide variety of operations	Useful for thermal parameters	Heat is non-specific source of information for multi-reaction systems

The adequacy of a chosen model must be tested to reject wrong models and to compare between rival models describing observations accurately within the accuracy of measurements. Measurements are charged with experimental errors. Accordingly, even if an ideal model were found, the chance of determining true values of model parameters would be small. In fact, only regions where true values are located (so-called *confidence regions* or *confidence limits*) can be evaluated with a certain probability. Evaluation of these confidence regions is the next step. Below, all three stages will be discussed in brief. For simplicity of explanation only single reactions studied under isothermal conditions, preferred for kinetic analysis, will be discussed. A more detailed discussion of procedures for parameter estimation and statistical analysis, the reader can find in Appendix B or in review papers by Kittrell (1970) and Froment and Hosten (1981) or in books by Draper and Smith (1966), Bates and Watts (1993), Himmelblau (1970), and Froment and Bischoff (1990).

5.4.4.6. Differential and integral analysis

Depending on whether instantaneous dependent variables such as reaction rates, or variables integrated over reaction time (concentrations, yields, reaction extents, etc.) are processed to estimate kinetic parameters two basic methods of interpretation of kinetic data are distinguished: *integral* and *differential analysis.* Reaction rates used in differential analysis are available from experiments using differential reactors or can be calculated by graphical or numerical differentiation of concentration-time experimental data obtained from integral reactors. The latter method for the determination of rates is recommended for rough evaluations only. This is because the non-analytical differentiation is an error-magnifying procedure. Moreover, the distribution characteristics of the error of the variable that is transformed by derivation becomes unknown, which makes statistical analysis of the results of parameter estimation impossible. Concentrations-versus-time points are measured using batch reactors or integral flow reactors.

Thus, in *differential analysis* rates are known for sets of operating conditions. Based on literature data, knowledge of the reaction mechanism, or preliminary experiments the form of the kinetic expression must be assumed:

$$r = f\,(\underline{\mathbf{k}}, \underline{\mathbf{c}}, T, p) \qquad \textbf{(5.4-94)}$$

where $\underline{\boldsymbol{k}}$ is a vector of kinetic parameters to be estimated and $\underline{\boldsymbol{c}}$ is a vector of concentrations. The vector $\underline{\boldsymbol{k}}$ is evaluated in such a way that the rates calculated from the above equation are as close as possible to the measured rates.

In *integral analysis* concentration-versus-time (or equivalently concentration-versus-distance from the inlet of the integral flow reactor) data are known. Kinetic expressions to be determined are incorporated into the differential material balance equations:

$$\frac{d\,c_i}{dt} = f_i(\underline{\mathbf{k}}, \underline{\mathbf{c}}, T, p) \qquad \textbf{(5.4-95)}$$

which can be integrated analytically or numerically. In the former case an algebraic equation is obtained:

$$c_i = g_i(\underline{\mathbf{k}}, \underline{\mathbf{c}}, T, p) \qquad \textbf{(5.4-96)}$$

If this is an explicit equation with respect to c_i the estimation of the vector $\underline{\boldsymbol{k}}$ is mathematically identical to a differential analysis. The only difference is that values of k_i are searched, for which the concentrations calculated from the above equation are as close as possible to the measured concentrations. Below, a simple example illustrating both techniques is given.

Example 5.4.4.2a. Differential analysis of integral data for synthesis of dioctyl phthalate

The reaction between mono-octyl phthalate and *iso*-octanol (see Fig. 5.4-25) in the presence of a homogeneous catalyst (*tert*-butyl titanate) was studied in a batch reactor (Szarawara *et al.*, 1991). This is the second step of the reaction between phthalic anhydride and *iso*-octanol. First the ring is opened and mono-octyl phthalate is formed. Water is removed by evaporation as it is formed. The reaction was carried out at 174 °C. The initial concentration of mono-octyl phthalate was $c_{Ph,0}$ = 1.85 mol/L and the ratio of initial concentrations of *iso*-octanol to mono-ooctyl phthalate $c_{Oc,0}/c_{Ph,0}$ = 1.4. The reaction was monitored by analysis of the concentration of mono-octyl phthalate in the reaction mixture. Based on results of chemical analysis conversions were determined (see Table 5.4-12). The non-zero initial conversion $X = 0.05$ resulted from a non-isothermal initial period of heating the reaction mixture up to the desired temperature.

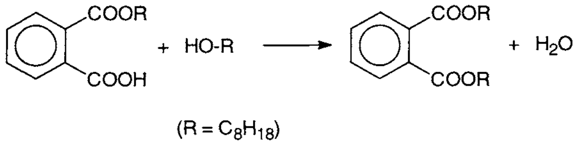

Figure 5.4-25. Reaction scheme.

Table 5.4-12
Kinetic data for esterification of mono-octyl phthalate with *iso*-octanol

Time, min	0	5	20	35	50	65	80	95	110	125	140
Conversion	0.05	0.23	0.56	0.71	0.82	0.86	0.91	0.93	0.95	0.96	0.97

Determine whether the kinetics of esterification can be described by the second-order rate equation:

$$r_{Ph} = k\, c_{Ph}\, c_{Oc} \tag{5.4-97}$$

If so, estimate the rate constant.

SOLUTION. *Differential analysis.* The change in the volume of the reaction mixture due to removal of water is small compared to the total volume and can be neglected. Hence, the reactant concentrations are the following functions of conversion:

$$\begin{aligned} c_{Ph} &= c_{Ph,0}(1-X) \\ c_{Oc} &= c_{Oc,0} - c_{Ph,0}X = c_{Ph,0}(b-X) \end{aligned} \tag{5.4-98}$$

where $b = c_{Oc,0}/c_{Ph,0}$. Combining these equations with the rate equation one gets:

$$r_{Ph} = k\, c_{Ph,0}^2(1-X)(b-X) \tag{5.4-99}$$

From the mass balance follows:

$$r_{Ph} = -\frac{dc_{Ph}}{dt} = c_{Ph,0}\frac{dX}{dt} \tag{5.4-100}$$

Upon combining these two equations and rearranging the following balance expression is obtained:

$$c_{Ph,0}\frac{dX}{dt} = k\, c_{Ph,0}^2(1-X)(b-X) \tag{5.4-101}$$

Consequently, the plot $c_{Ph,0}(dX/dt)$ versus $c^2_{Ph,0}(1-X)(b-X)$ should yield a straight line with slope k if the chosen rate equation is appropriate. Derivatives $(dX/dt)_i$ at times t_i are calculated numerically using the two-point equation:

$$\left(\frac{dX}{dt}\right)_i \approx \frac{X_{i+1} - X_{i-1}}{2\Delta t} \tag{5.4-102}$$

for conversions equidistant in time, for the time range from 20 to 125 minutes. The derivative for the reaction time of 5 minutes was determined graphically. The results of differentiation have been plotted in Fig. 5.4-26.

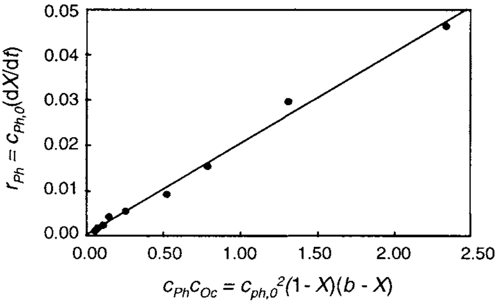

Figure 5.4-26. Reaction rate versus concentrations' product.

The experimental points scatter uniformly on both sides of the line. Accordingly, it can be concluded that the tested rate equation should not be rejected. The slope, k, is 0.02 min^{-1}. This is only a rough estimate of the rate constant because numerical and graphical differentiations are very inaccurate procedures. The slope was also calculated by the least squares technique minimizing the sum of squares of residuals:

$$SS_{res} = \sum_i \left[\left(\frac{dX}{dt}\right)_{i,calc} - \left(\frac{dX}{dt}\right)_{i,exp}\right]^2 \tag{5.4-103}$$

The k-value is very similar to that found from graphical calculations: $k = 0.021\ \text{min}^{-1}$. Differential kinetic analysis would be much more accurate if experiments were performed in a CSTR. The rates would then be measured directly with greater accuracy and no differentiation error would be made. Moreover, the concentration of the reactant and products could then be varied independently.

Integral analysis. Equation 5.4-101 can be solved analytically by integration:

$$k\, c_{Ph,0} t = \frac{1}{b-1} \ln \frac{b-X}{1-X} + C \tag{5.4-104}$$

where C is an integration constant. Applying the initial condition $X_{t=0} = 0.05$ to this one gets:

$$kt = 1.35 \ln \frac{1.4 - X}{1 - X} - 0.48 = \Phi(X) \qquad \textbf{(5.4-105)}$$

For any experimental point $[X,t]$, the value of the rate constant k can be calculated directly. The arithmetic mean of these values can be considered to be the best estimate of k. The graph $\Phi(X)$ versus t can also be plotted (see Fig. 5.4-27) and the slope, k, evaluated. The values of $\Phi(X)$ scatter uniformly around the straight line, which indicates the proper choice of the kinetic expression.

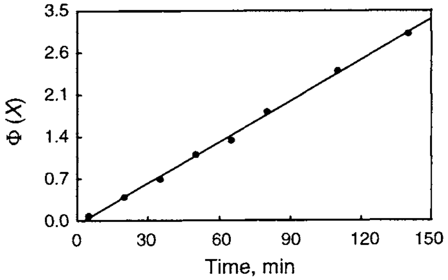

Figure 5.4-27. The $\Phi(X)$-function versus time.

The k-value can be estimated by minimization of the sum of squares of residuals (the least squares technique):

$$SS_{res} = \sum_i \left(X_{i,calc} - X_{i,exp}\right)^2 \qquad \textbf{(5.4-106)}$$

where $X_{i,calc}$ is the conversion calculated by solving the implicit equation (5.4-105) or by numerically solving the balance equation (5.4-101) for any time t_i. The results of calculations of the second order rate constant with their confidence limits at 95 %-probability level using different methods are given in Table 5.4-13. Fig. 5.4-28 shows a parity diagram of X_{calc} versus X_{exp} (conversions calculated using the last method). In view of lack of directly produced differential data, the integral method is a more appropriate method of kinetic analysis in the case considered.

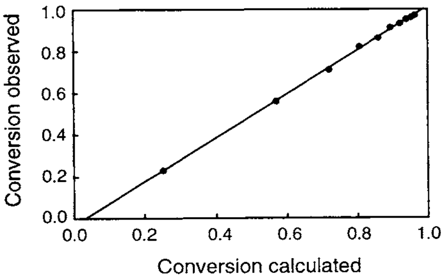

Figure 5.4-28. Parity diagram: X_{calc} versus X_{exp}.

Table 5.4-13
The results of calculations of the rate constant k

Method of kinetic analysis	Method of calculation of k	k-value, min^{-1}
Differential	Eqn. (5.4-101), graphical calculations	0.02
	Eqn. (5.4-101), least squares	0.0210±0.009
	Eqn. (5.4-101), arithmetic mean of k_i's	0.0218
Integral	Eqn. (5.5-105), graphical calculations	0.02
	Eqn. (5.5-105), arithmetic mean of k_i's	0.0207
	Eqn. (5.5-105), least squares	0.0221±0.006
	Eqn. (5.5-101) solved numerically by Runge-Kutta method, least squares	0.0207±0.01

Numerical methods increase the inaccuracy of parameter estimation because of errors introduced by numerical approximations. Therefore, we recommend parameter estimation by using equations of explicit algebraic form if such expressions can be derived. Certainly differential reactors directly produce data that can be processed in this way. However, experimentation using such reactors is the most time-consuming and as such cannot be considered to be the best experimental tool for fine chemistry kinetic studies. The data from integral reactors can be processed in the way recommended if kinetic equations are simple enough for integration of the differential balance equation analytically. In most cases, however, we will have to estimate kinetic parameters by least squares technique with numerical solution of differential balance equations containing kinetic expressions.

5.4.4.7. Preliminary model selection

Preliminary screening of kinetic models can be done relatively fast by starting with power-law models. The values of apparent reaction orders will indicate what kind of kinetic equation to choose: fractional and negative reaction orders are characteristic of expressions in the form of fractions such as the Langmuir-Hinshelwood equation. The steady-state assumption and rate-determining-step concept are very useful in the derivation of kinetic expressions. The form of the mathematical expression implies its graphical representation. From this representation we can deduce information about the form of the kinetic equation which might be appropriate to describe the experimental results. From such a representation we can at least conclude about rejection of our assumption if the shape of kinetic curves does not fit our experimental data. Two methods are very useful in graphical screening of kinetic models to be processed: (1) method of initial rates and (2) linearization.

Initial rates. Consider the reversible solid-catalysed reaction:

$$\mathrm{A} \rightleftharpoons \mathrm{R} + \mathrm{S} \tag{5.4-107}$$

Applying the concept of the rate-determining step (see Section 5.4.2) one can derive the following kinetic equations for adsorption of A, surface reaction, and desorption of R or S, respectively, as rate-limiting processes:

$$r_A = \frac{k\left(c_A - \frac{c_R c_S}{K}\right)}{1 + \frac{K_A c_R c_S}{K} + K_R c_R + K_S c_S} \tag{5.4-108}$$

$$r_A = \frac{k K_A\left(c_A - \frac{c_R c_S}{K}\right)}{\left(1 + K_A c_A + K_R c_R + K_S c_S\right)^2} \tag{5.4-109}$$

$$r_A = \frac{kK K_A\left(c_A - \frac{c_R c_S}{K}\right)}{c_S + K_A c_A c_S + K K_R c_R + K_S c_S^2} \tag{5.4-110}$$

At the start of the reaction negligible amounts of products are present in the reaction mixture. Consequently, the expressions above with respect to initial rates $r_{A,0}$ may be simplified to the following equations:

$$r_{A,0} = k c_{A,0} \tag{5.4-111}$$

$$r_{A,0} = \frac{k K_A c_{A,0}}{\left(1 + K_A c_{A,0}\right)^2} \tag{5.4-112}$$

$$r_{A,0} = k \tag{5.4-113}$$

Plotting these relationships yields the graphs shown in Fig. 5.4-29. If plots for experimental data show similarity to any of these curves, the kinetic models based on rate-limiting steps corresponding to the other curves can be rejected and the model corresponding to the similar plots will be processed.

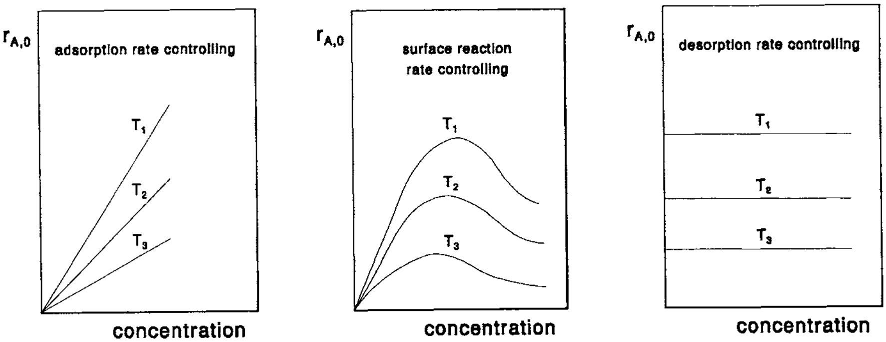

Figure 5.4-29. Initial rate versus concentration for different processes controlling.

Linearization. In preliminary screening of reaction mechanisms, it is very useful to construct plots of experimental data transformed in such a way that the plot of the dependent (transformed) variable versus the independent (transformed) variable is a straight line if the rate equation being the basis of transformation has been chosen properly. This is illustrated with the rate expression for α-th order kinetics:

$$r_A = k\, c_A^{\alpha_A} \tag{5.4-114}$$

The equation can be transformed to

$$\ln r_A = \ln k + \alpha_A \ln c_A \tag{5.4-115}$$

to obtain a linear relationship between transformed dependent and independent variables. If the assumption concerning the α-th order kinetic equation is appropriate, a plot of ln r_A versus ln c_A should yield a straight line with experimental points scattered uniformly on both sides of the line (see Fig. 5.4-30a). If experimental points deviate significantly from the straight line and distinct curvature is seen (see Fig. 5.4-30b), the hypothesis about α-th order kinetics must be rejected and search for the more appropriate kinetic equation continued.

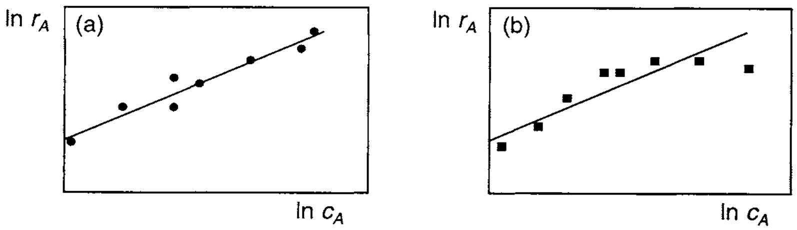

Figure 5.4-30. Data fitted to α-th order kinetics; a: satisfactory fit; b: unsatisfactory fit.

Quantitative information can be drawn from such plots. For the α-th order kinetics the slope is the reaction order α and the intercept is ln k. For the catalytic reaction considered above with the surface reaction as the rate-limiting process, linearization of the rate equation (5.4-112) leads to:

$$\sqrt{\frac{c_{A,0}}{r_{A,0}}} = \frac{1}{\sqrt{k K_A}} + \sqrt{\frac{K_A}{k}}\, c_{A,0} \tag{5.4-116}$$

Values of $1/\sqrt{(kK_A)}$ and $\sqrt{(K_A/k)}$ can be determined from the intercept and the slope, respectively, of the straight line obtained by plotting $\sqrt{(c_{A,0}/r_{A,0})}$ versus $c_{A,0}$. From these values k and K_A can be easily calculated.

A straight line on a plot of transformed variables should not be considered as proof that the kinetic model corresponds to the true reaction mechanism. It only shows that the particular kinetic model can be successfully used to describe the relationship between the reaction rate and process conditions. However, a significant deviation from the straight line *is* sufficient to reject the rate equation tested. In fact, the procedure described has resulted in model selection, or rather model rejection. Graphical calculations can only be used for a rough, preliminary estimation of kinetic parameters. This is due to the low accuracy of graphical calculations and difficulties with rigorous statistical analysis of the results, which is necessary to assess the adequacy of the kinetic model and the significance of the estimated kinetic parameters. Moreover, kinetic parameters estimated from transformed equations and corresponding plots can differ from those evaluated using the original equation. While it may be assumed that the error of the original data has a normal distribution, the transformation changes the error distribution and this affects the values of the model parameters.

In fine chemistry reaction mixtures are often very complex. The ideal of including all the species into the analysis is rarely achievable because of limits on time and resources, problems in chemical analysis of reaction mixtures, etc. A problem often encountered is catalyst stability. When a catalyst is not stable, kinetic analysis is much more difficult. Moreover, the search for a large number of parameters simultaneously causes convergence problems resulting in time-consuming computations and difficulties in finding the global minimum of the criterion for estimation. Therefore, *lumping* of components of the reaction mixture into groups, so-called *pseudocomponents*, is the only way to go. Of course, this must be done carefully. The physical and chemical behaviour of lumped components should be similar. A lot of effort has been put into the formulation of rigorous lumping of mixtures processed in refineries and the petrochemical industry. A good collection of papers on this subject can be found in the book edited by Astarita and Sandler (1991). Obviously, when chemical analysis is not sufficiently precise, lumping must be done by necessity without preserving rigid rules. Lumping should be done at the stage of preliminary screening of the model.

Essentially, there are no general guidelines for preliminary model selection for complex reactions. Mechanistic studies are the best basis for model formulation. Literature data and indications clear to experienced organic chemists will certainly be the most helpful. Studies on individual reactions are always recommended, but for the complex reactions involved in fine chemistry such an opportunity is rather a rare case.

5.4.4.8. Parameter estimation

Below, some useful simple methods for the estimation of kinetic parameters by linearization are presented. The problem is treated in more detail in Appendix B.

Rate constant. It is easiest to estimate the value of the rate constant if it is the only unknown in the kinetic expression. Typically these expressions are the power law equations:

$$r = k\, c_A^{\alpha_A} c_B^{\alpha_B} \ldots. \qquad \textbf{(5.4-117)}$$

When differential data (r's for known c's) are available, the above equation can directly be used to calculate k-values if reaction orders α_j are known or assumed. For data from integral reactors the balance equation:

$$-\frac{dc_j}{dt} = k\, c_A^{\alpha_A} c_B^{\alpha_B} \ldots \qquad \textbf{(5.4-118)}$$

can be integrated analytically or numerically, after which k-values calculated.

Reaction order. Partial reaction order can be estimated by studying the reaction rate at surplus of all reactants but the one for which the order is to be evaluated. The concentrations of the reactants present in excess will not change significantly during the course of reaction and may be assumed to be constant. A rate equation of the form (5.4-117) then changes into:

$$r = k' c_A^{\alpha_A} \tag{5.4-119}$$

where

$$k' = k\, c_B^{\alpha_B} \ldots \tag{5.4-120}$$

Eqn. (5.4-119) can be linearized as described earlier (see Eqn. (5.4-115) with $k = k'$) and plotted. If the model is adequate, this will yield a straight line with slope α_A and intercept ln k'.

Activation energy and frequency factor (pre-exponential coefficient). The Arrhenius equation can be rewritten in logarithmic form:

$$\ln k = \ln k_0 - \frac{E}{R_g} T \tag{5.4-121}$$

Thus, a plot of ln k versus the reciprocal temperature should yield a straight line with slope $-E/R_g$ and ln k_0. These two kinetic parameters are strongly interconnected; even a minor change in slope evaluation will result in a major change of the intercept. Theoretically, values of rate constants at two temperatures are sufficient to estimate the activation energy:

$$E = -R_g \frac{\ln k_2 - \ln k_1}{1/T_2 - 1/T_1} \tag{5.4-122}$$

Rates observed at different temperatures but at the same initial and current compositions can also be used for evaluation of the activation energy. For a single irreversible reaction

$$r = kf(X) = k_0 \mathrm{e}^{-\frac{E}{R_g T}} f(X) \tag{5.4-123}$$

the dependence of r and k on temperature is the same. If c_0 and $f(X)$ are constant

$$\ln r = \ln k + const \tag{5.4-124}$$

and

$$E = R_g T^2 \frac{d \ln r}{dT} = -R_g \frac{d \ln r}{d(1/T)} = -R_g \frac{\ln r_2 - \ln r_1}{1/T_2 - 1/T_1} \tag{5.4-125}$$

Similar procedures can be used to estimate coefficients in the van 't Hoff equation. The least squares method for estimation of pre-exponential factor and activation energy is illustrated in *Example 5.4.4.2b.*

Example 5.4.4.2b. Estimation of kinetic parameters in Bisphenol A synthesis

Miller *et al.* (1981) studied the kinetics of the reaction of phenol and acetone to bisphenol A in the presence of hydrogen chloride[12] (see Fig. 5.4-31) in an isothermal batch reactor.

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[12] Bisphenol A is produced commercially using ion-exchange resins as the catalyst. Many special bisphenols, notably those obtained in reactions based on phenol and acetophenone/cyclohexanone/3,3,5-trimethylcyclohexanone, are made using HCl as the catalyst.

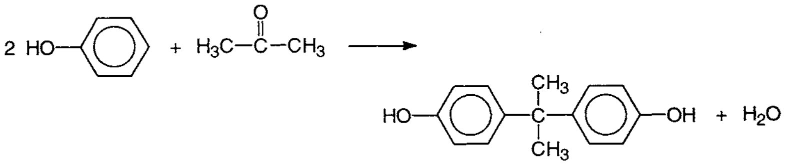


Figure 5.4-31. Reaction scheme.

We used the experimental data of Miller *et al.* (1981) to evaluate rate constants in the power law kinetic expression:

$$r = k\, c_{HCl}\, c_{Ph}\, c_{Ace} \tag{5.4-126}$$

The results of calculations are given in Table 5.4-14.

Table 5.4-14
Rate constants for Bisphenol A synthesis

Temperature, °C	35	50	70	80
Rate constant k, $m^6\ mol^{-1}\ s^{-1}$	0.000516	0.001034	0.001916	0.002611

Estimate the pre-exponential factor and activation energy in the Arrhenius equation.

SOLUTION. Kinetic parameters are estimated by using the least squares technique, by minimizing the function defined as squared residuals between calculated and experimental rate constants:

$$SS_{res,k} = \sum_{i=1}^{4} \left(k_{i,calc} - k_{i,exp}\right)^2 \tag{5.4-127}$$

and by minimizing the function defined as squared residuals between logarithms of calculated and experimental rate constants:

$$SS_{res,\ln k} = \sum_{i=1}^{4} \left(\ln k_{i,calc} - \ln k_{i,exp}\right)^2 \tag{5.4-128}$$

where $k_{i,calc}$ are rate constants calculated from the Arrhenius equation and $k_{i,exp}$ are rate constants evaluated from experimental data tabulated above. A commercially available computation package was used to find numerical values of kinetic parameters using both target functions. The results are given in Table 5.4-15. The rate constants calculated from both sets of kinetic parameters are also given in the table together with the averaged relative difference between the calculated and experimental rate constants and $SS_{res,\ln k}$. The calculated rate constants are very close to the experimental ones for both sets of kinetic parameters: the average error is 5.08 % for estimates obtained by minimization of $SS_{res,k}$ and 4.90 % for estimates obtained by minimization of $SS_{res,\ln k}$. However, $SS_{res,\ln k}$, which is a better measure of differences between calculated and experimental variables, amounts to $2.0426 \cdot 10^{-8}$ for estimates obtained by minimization of $SS_{res,k}$, while it is about two times larger ($3.5604 \cdot 10^{-8}$) for estimates obtained by minimization of $SS_{res,\ln k}$.

Table 5.4-15

Results of estimation of kinetic parameters

		Values for $SS_{res,\,k}$	Values for $SS_{res,\,\ln k}$
k_0 [$m^6\ mol^{-1}\ s^{-1}$]		111	216
E [$kJ\ mol^{-1}$]		31175	33060
k_{calc} [$m^6\ mol^{-1}\ s^{-1}$] at T [°C]	35	0.000576	0.000534
	50	0.001013	0.000973
	70	0.001992	0.001995
	80	0.002714	0.002770
Average abs(Δk)/k_{exp} [%]		5.08	4.90
$SS_{res,\,k}$		$2.0426{\cdot}10^{-8}$	$3.5604{\cdot}10^{-8}$

The Arrhenius plots for both sets of kinetic parameters together with experimental points are shown in Fig. 5.4-32. Experimental points scatter uniformly on both sides of the straight lines indicating that the power-law model with the evaluated rate constant can be satisfactorily used to describe the kinetic experiments under consideration.

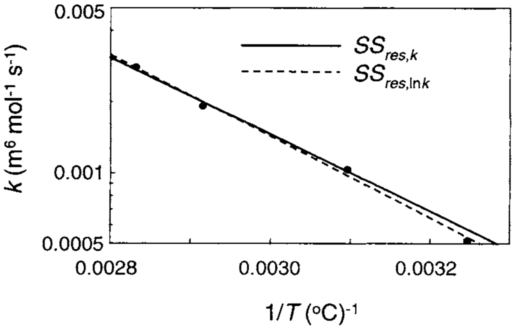


Figure 5.4-32. Arrhenius plot for Bisphenol A synthesis.

5.4.4.9. *Kinetic modelling for optimization*

Kinetic models developed for reactor scale-up are also suitable for reactor optimization. The development of detailed kinetic models accounting for all factors influencing process rates is a time-consuming task. Therefore, more empirical simplified models are often used for simulation and optimization of existing reactors.

An extreme case of these empirical models are *black box* models, predominantly polynomials, the application of which is strictly restricted to the range of operating conditions and design variables for which the models were developed. Even in this range, optimization using black box models can lead to operating conditions far from the real optimum. This is due to non-linearities of the real systems, which cannot be modelled by polynomials. Black box models can slightly be improved if properly transformed dependent and independent variables are applied. These improvements have been extensively discussed by Kittrell (1970).

An alternative to purely black box models are *grey* models (*gross* kinetics), the structure of which better fits the real mechanisms although no attempt is made to produce evidence for this. These models are based on sound judgement and experience of scientists engaged in modelling. Experiments leading to grey models are often carried out with gradients present but at flow conditions quite close to those in the existing full-scale reactor. This limits extrapolation outside the reactor configuration and operating conditions at which experiments have been carried out. Fitted parameters in such models inherently include effects of different mechanisms, thereby compensating for physical inadequacies of the model.

Empirical grey models based on non-isothermal experiments and tendency modelling will be discussed in more detail below. Identification of gross kinetics from non-isothermal data started in the 1940-ties and was mainly applied to fast gas-phase catalytic reactions with large heat effects. Reactor models for such reactions are mathematically isomorphical with those for batch reactors commonly used in fine chemicals manufacture. Hopefully, this technique can be successfully applied for fine chemistry processes. Tendency modelling is a modern technique developed at the end of 1980-ties. It has been designed for processing the data from (semi)batch reactors, also those run under non-isothermal conditions.

Non-isothermal experiments. Non-isothermal data offer distinct advantages in the estimation of model parameters, especially for fast and highly exothermic reactions. Many reactions catalysed by particulate catalysts were studied based on non-isothermal data. Wilson (1946) was presumably the first who identified the gross kinetic expression (for nitrobenzene hydrogenation) and estimated kinetic parameters from non-isothermal data. Hydrogenations were also studied by Pászthory *et al.* (1959) and Pašek *et al.* (1967, 1968). More complex reactions such as partial oxidations (Emig *et al.* (1972), Skrzypek *et al.* (1975), Krajewski *et al.* (1975, 1976, 1977), Cybulski *et al.* (1980), and Adamska-Rutkowska (1992)) also were the subject of kinetic studies under non-isothermal conditions. Löwe and Stock (1983, 1985) developed a technique for processing non-isothermal data from monolithic reactors for a single reaction. Kunst *et al.* (1995) used a similar technique to interpret experimental data from a monolithic reactor.

Generally, the temperature changes with time or, equivalently, with distance from the reactor inlet (for flow reactors). This change is usually controlled well in reaction calorimeters but can become uncontrolled in other conventional laboratory flow or (semi)batch reactors. The balance equations of a batch reactor for a single reaction of α-th order kinetics are given by:

$$-\frac{dc}{dt} = k_0 \cdot \exp\left(-\frac{E}{R_g T}\right) \cdot c^{\alpha} \qquad \textbf{(5.4-129)}$$

$$\rho c_p \frac{dT}{dt} = k_0 \cdot \exp\left(-\frac{E}{R_g T}\right) \cdot c^{\alpha} \cdot (-\Delta H) + U \cdot \frac{A_r}{V_r} \cdot (T_c - T) \qquad \textbf{(5.4-130)}$$

with k_0, E, and α to be determined. There are essentially two methods for the evaluation of these model parameters:

1) Correlate temperature-versus-time (distance) data with an appropriate function $T = T(t)$, replace T with $T(t)$ in heat balance equation (5.4-130) and minimize SS_{res} defined as

$$SS_{res} = \sum_i \left(c_{i,calc} - c_{i,exp}\right)^2 \qquad \textbf{(5.4-131)}$$

where $c_{i,calc}$ is calculated by numerical solution of Eqn. (5.4.129) with $T = T(t)$.

The function $T(t)$ can be chosen for the whole reaction time interval, or two or three subsequent temperature-time data points $T(t_{i-1})$, $T(t_i)$, and $T(t_{i+1})$ can be approximated by polynomials of second or third order $T_i(t)$, respectively. These polynomials will then be used in a procedure for numerical integration in each integration step i. This method has been successfully applied in a kinetic study of the partial oxidation of hydrocarbons (Skrzypek *et al.*, 1975, Krajewski *et al.*, 1975, 1976, 1977).

2) Minimize a modified target function:

$$SS_{res} = \frac{1}{\sigma_c^2} \sum_i \left(c_{i,calc} - c_{i,exp}\right)^2 + \frac{1}{\sigma_T^2} \sum_j \left(T_{j,calc} - T_{j,exp}\right)^2 \qquad \textbf{(5.4-132)}$$

where σ_c^2 and σ_T^2 are error variances for concentration and temperature, respectively. These variances can be evaluated by sound judgement based on known accuracy of chemical analysis and temperature measurements or determined by repetition of the analysis and measurements. The concentration and temperature are calculated by numerical solution of the mass and heat balance equations (5.4-129) and (5.4-130) whereby the heat-transfer coefficient U can be obtained from literature correlations or considered a model parameter and estimated simultaneously with the kinetic parameters.

Thermal methods in kinetic modelling. Methods for the estimation of thermokinetic parameters based on experiments in a reaction calorimeter will be discussed below. As mentioned in section 5.4.4.3, instantaneous heat evolved due to a single reaction is directly proportional to the reaction rate. Assume that the reaction is of first order. Then for isothermal operation:

$$q_P = -k \cdot c \cdot V_r \cdot \Delta H \qquad \textbf{(5.4-133)}$$

and

$$q_{P,0} = -k \cdot c_0 \cdot V_r \cdot \Delta H \qquad \textbf{(5.4-134)}$$

Hence

$$\frac{q_P}{q_{P,0}} = \frac{c}{c_0} \qquad \textbf{(5.4-135)}$$

Finally

$$\frac{dc}{dt} = -kc \Rightarrow \ln\left(\frac{c}{c_0}\right) = -kt \Rightarrow \ln\left(\frac{q_P}{q_{P,0}}\right) = -kt \qquad \textbf{(5.4-136)}$$

This relationship can be used to calculate rate constant k at any time t of the isothermal run. This is illustrated by the following example.

Example 5.4.4.3a. Kinetics of R-hydroxynitrile formation by using a reaction calorimeter.

Landau *et al.* (1994) studied the reaction between a cyclic sulphite and sodium cyanide (Fig. 5.4-33) using an RC1 calorimeter. All components were loaded into the reactor at ambient temperature. Then the temperature was raised to 90 °C at 1.5 °C/min. After 15 min at 90 °C the temperature was ramped to 100 °C at 1.5 °C/min. The same procedure was repeated to raise the temperature to 110 °C. The reactor was maintained at that temperature until heat evolution had ceased. Calibrations were performed prior to reaction and after reaction was completed.

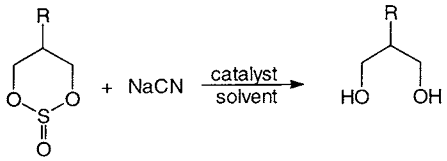


Figure 5.4-33. Reaction scheme.

The results of the calibrations and the evaluation of the total heat evolved are given in Table 5.4-16. The product A_rU and the heat capacity of the reaction mixture increased by about 20 % during the reaction period. The total amount of heat released per unit mass of reaction mixture is 190 kJ/kg indicating a moderate heat effect. However, the adiabatic temperature rise ($\Delta T_{ad} = \Delta H/(m{\cdot}c_p)$) is quite significant (109 °C). This is due to the relatively low heat capacity of the reaction mixture.

Table 5.4-16
Results of calibrations and measurements

Quantity	Value
$UA_{r,t=0}$	2.17 W K^{-1}
$UA_{r,t=tf}$	2.72 W K^{-1}
$c_{p,t=0}$	1400 J kg^{-1} K^{-1}
$c_{p,t=tf}$	1700 J kg^{-1} K^{-1}
Mass of the reaction mixture	0.120 kg
Total amount of heat released	22.8 kJ

Figs 5.4-34 to 5.4-37 show results of the measurements and calculations. In Figs 5.4-34 and 5.4-35 the results of temperature and heat flow measurements are shown. Isothermal operation was quite easy to reach due to the relatively low heat of reaction and the high value of the product of the heat-transfer coefficient and the heat-exchange surface area A_rU in relation to the volume of the reaction mixture.
Peaks in the heat flow-versus-time diagram correspond to the times at which isothermal operation at the next temperature level started. After each peaks the heat flow decreased because of the decrease in the concentrations of the reactants.

Pseudo-first order kinetics was assumed to interpret the experimental data. Fig. 5.4-36 shows that the fit of the experimental data using first order-kinetics is acceptable. However, a systematic deviation is observed in the curve obtained at 110 °C. This indicates inadequacy of the first-order kinetics, which is inappropriate from the view of theory. On the other hand, the kinetic equation seems to describe the results sufficiently accurately to use it for scale-up and safety evaluations. Rate constants calculated from the data are plotted (see Fig. 5.4-37). The Arrhenius equation fits the data fairly well although the standard error of Arrhenius parameters is relatively high ($E = 132 \pm 21$ kJ mol^{-1}; $k_0 = (6 \pm 2) \cdot 10^{16}$ min^{-1}) and a curvature can be observed. Certainly more experiments are needed to produce more reliable data. However, it is fair to emphasize that all the data on thermal and approximate kinetic characteristics of the reaction system have been obtained from one run only.

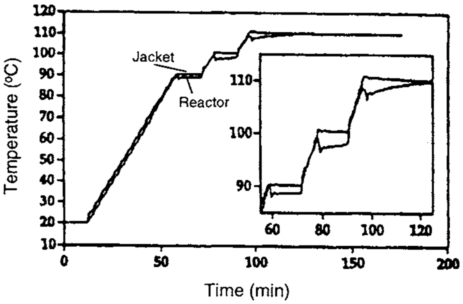


Figure 5.4-34. Temperature profiles measured during heating and isothermal periods (reprinted with permission from Landau *et al.* (1994). Copyright (1994) American Chemical Society).

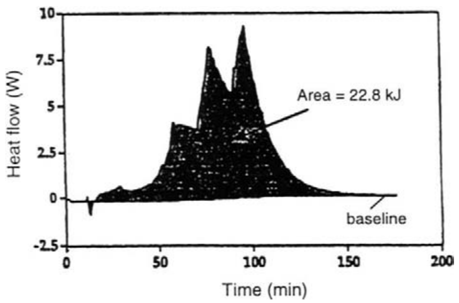


Figure 5.4-35. Baseline and reaction heat flows calculated during heating and isothermal periods (reprinted with permission from Landau *et al.* (1994). Copyright (1994) American Chemical Society).

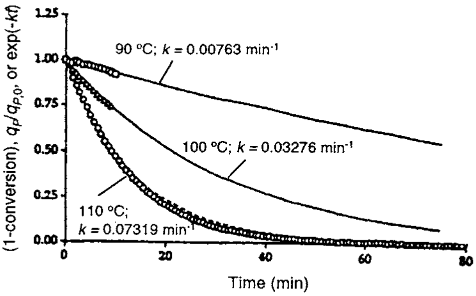


Figure 5.4-36. Fit of first-order kinetics for three isothermal reaction periods (reprinted with permission from Landau *et al.* (1994). Copyright (1994) American Chemical Society).

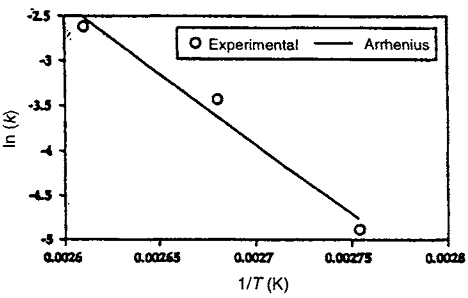


Figure 5.4-37. Arrhenius plot for rate constants obtained from the isothermal reaction periods (reprinted with permission from Landau *et al.* (1994). Copyright (1994) American Chemical Society).

More complex kinetic expressions can be analysed, either in a manner similar to that shown in the above example or using methods discussed in the previous section. More complex reaction systems can also be studied if the reaction mixture is analysed during the course of reaction; Tufano (1993) presented a theoretical analysis of such a case. Several examples of the use of a reaction calorimeter for kinetic studies were presented at *RC User Forum* (see, e.g., meetings in Zermatt, 1993, and in St.Petersburg Beach, Florida, 1994) and also at *The 1st International Conference of The Scale-Up of Chemical Processes* (Brighton, 1994). The kinetics of homogeneous and heterogeneous processes was studied: ammonolysis (Stefanick, 1994), hydrogenation of substituted pyrazines (Landau *et al.*, 1994), emulsion polymerization (de la Rosa *et al.*, 1994), hydrogenation of nitrobenzene to aniline (Machado, 1994), isomerization of trimethylphosphite (Regenass, 1978), hydrolysis of acetic anhydride, and oxidation of 4-chlorotoluene (Regenass, 1983). The BatchCAD computer program (Wright and Bramfitt, 1994) is a convenient tool for parameter estimation and process simulation based on reaction calorimeter studies.

Tendency modelling. Groups of scientists from the Laboratoire des Sciences du Genie Chimique, CNRS-ENSIC, Nancy, France and Chemical Process Modelling and Control Research Center, Lehigh University, Bethlehem, USA have proposed the use of approximate kinetic models to optimize processes for the manufacture of fine chemicals. They called these models *tendency models*. An evolutionary approach to optimization and modelling has been suggested. An initial model, developed based on initial data and process knowledge, is applied in optimization. Results of the optimized run are used for improvement of the model (change of its structure and/or re-estimation of kinetic parameters) and subsequent optimization. An updated model will lead to better accuracy of the model, and, consequently, to a closer approach of the real process optimum.

Tendency models have been developed based on a minimum of experimental data. A realistic collection of data includes the following:

- initial concentrations in the reactor are known,
- concentrations of reactants, intermediates, and products versus time are not available,
- final concentrations of main components of the reaction mixture can be measured, while the others can be evaluated,
- the reaction mechanism and the kinetics are known only approximately,
- the flow of reactants added into the reaction mixture is known,
- the reaction temperature is known during the entire run,
- heat-transfer coefficients are known.

Based on the experimental data kinetic parameters (reaction orders, activation energies, and pre-exponential factors) as well as heats of reaction can be estimated. As the kinetic models might not be strictly related to the true reaction mechanism, an optimum found will probably not be the same as the real optimum. Therefore, an iterative procedure, *i.e.* optimization-model updating-optimization, is used, which lets us approach the real process optimum reasonably well. To provide the initial set of data, two-level factorial design can be used.

The very basis of the kinetic model is the reaction network, *i.e.* the stoichiometry of the system. Identification of the reaction network for complex systems may require extensive laboratory investigation. Although complex stoichiometric models, describing elementary steps in detail, are the most appropriate for kinetic modelling, the development of such models is time-consuming and may prove uneconomical. Moreover, in fine chemicals manufacture, very often some components cannot be analysed or not with sufficient accuracy. In most cases, only data for key reactants, major products and some by-products are available. Some components of the reaction mixture must be lumped into pseudocomponents, sometimes with an ill-defined chemical formula. Obviously, methods are needed that allow the development of simple stoichiometric models for such complex systems. These models should incorporate *a priori* information on process chemistry, especially on main reactions, and be consistent with experimental data. The methods should also enable the determination of the validity of stoichiometrics proposed by chemists based on their experimental studies or general knowledge.

Several methods have been developed for the evaluation of the minimum amount of significant independent reactions to give a sufficiently accurate stoichiometry of complex processes. For a systematic treatment of this problem see the paper by Aris and Mah (1963). In the past decades, a number of researchers have dealt with biological systems such as fermentations, see Cooney *et al.* (1977), San and Stephanopoulos (1984), and Hamer (1989). In recent years, several papers were published regarding identification of the stoichiometry in organic chemical synthesis, see Filippi *et al.* (1986), Filippi-Bossy *et al.* (1989), Marchal-Brassely *et al.* (1992), Rastogi *et al.* (1990, 1991, 1992), Fotopoulos *et al.* (1994), and Bonvin and Rippin (1990). Two methods are presented in Appendix A: (1) a mathematically rigorous method based on factor analysis, and (2) the more arbitrary 'Nancy algorithm', which is simpler in use.

Example 5.4.4.3b. Optimization of partial oxidation reaction by tendency modelling (after Filippi-Bossy et al. (1989))

A partial oxidation reaction of commercial interest to Rhône-Poulenc was studied. Reactant A was oxidized with an oxidizing agent B to produce two main products, C and D, of different commercial value. Heavy by-products E were formed as well. The objective of the study was to maximize the production of $C+D$ over E and to increase the amount of C at the cost of D. The process is exothermic, with a heat of reaction of the order of 250 kJ per mole of reactant converted. The reaction was carried out isothermally in a 2-litre semibatch reactor equipped with a cooling coil and a six-blade helix stirrer. Reactant A, used in large excess, was first loaded into the reactor. The reactor was then heated to the pre-set temperature, dosing of the oxidizing agent B started, and control of the reaction temperature initiated. The feed B was injected near the stirrer to provide excellent mixing of reactant B with the reaction mixture. At the end of the run a sample of the reaction mixture was withdrawn and analysed. The amount of by-product E, which was difficult to analyse, was estimated from the balance between the number of moles of B consumed and the number of moles of C and D produced. It was found that the feed rate of B and the temperature strongly influenced the formation of by-products and the selectivity of C versus D.

The overall cost optimization criterion (5.4-137) to be minimized is composed of two terms. The first, which is called proportional, is related to the yield of both C and E: one needs to maximize the yield of C, Y_C, while minimising the ratio of yields, Y_E/Y_C. Y_C and Y_E are $n_{C,f}/n_{B,0}$ and $n_{E,f}/n_{B,0}$, respectively, n is number of moles, and γ is a factor expressing the relative weight of the two terms (γ was assumed to be one). The second term, called the non-proportional or fixed cost of operation, is the reciprocal of the ratio of yield of C per batch time, t_B, and as such it should be minimized. β is the weighing factor (equal to 174 in the process under consideration) in this term.

$$J = \frac{1+\gamma Y_E}{Y_C} + \frac{\beta t_B}{Y_C} = \frac{1+\gamma Y_E + \beta t_B}{Y_C} \qquad \textbf{(5.4-137)}$$

Six initial experiments were carried out at the same batch time (355.6 dimensionless undisclosed units) varying the temperature, the ratio of reactants $(n_B/n_A)_0$, and the feed time. The results of these experiments are given in Table 5.4-17.

Table 5.4-17
Results of six initial experiments used for the estimation of model parameters

Run	Temp. [a]	$(n_B/n_A)_0$	Feed time	$n_{B,f}/n_{A,0}$ $*10^4$	Y_C	Y_D	Y_E	J
E1	1.2465	0.05645	222.2	6.1554	0.093938	0.026366	0.020072	20.16
E2	1.2326	0.05504	222.2	18.077	0.012237	0.027764	0.013232	14.57
E3	1.2674	0.05833	222.2	1.3458	0.010141	0.026841	0.021216	19.31
E4	1.2151	0.05887	222.2	21.460	0.015217	0.027931	0.013589	12.48
E5	1.1855	0.05824	202.6	58.366	0.013149	0.025968	0.013287	14.30
E6	1.1890	0.05399	200.7	49.076	0.012975	0.022354	0.013755	13.54

[a] Dimensionless temperature normalized to a reference temperature T_r (close to ambient temperature).

The stoichiometric model developed using the method described in Appendix A is as follows:

$$\begin{aligned} 2B &\rightarrow C + D \\ C &\rightarrow E \end{aligned} \qquad \textbf{(5.4-138)}$$

In this stoichiometric model it was assumed that the first reaction is of second order while the second reaction is of first order. Using these assumptions and the data given in Table 5.4-17 kinetic parameters were estimated for both reactions, see Table 5.4-18.

For a fixed molar ratio $(n_B/n_A)_0$ equal to 0.05887, the temperature as applied in experiment E4, and a batch time of 347.8 dimensionless units, the feed rate of B (and thus the feed time) was optimized by computation to find t_f = 323.19 dimensionless units. A run was carried out at these conditions. The data collected from this experiment were then used for re-estimation of the kinetic parameters. The new kinetic model was used to evaluate the new optimum feed rate for the same total amount of B. The optimum batch time reduced to 275.36 and the feed time to 242.75 units. Table 5.4-19 summarizes the results for three successive optimizations and re-estimations. Evidently, even a very simplified kinetic model can be successfully used in search for an optimum provided that kinetic parameters are updated based on every subsequent run carried out at the optimum conditions evaluated from the preceding set of kinetic parameters.

Table 5.4-18
Kinetic parameters

Dimensionless kinetic parameters	Value
E_1/R_gT_r	7.81
k_1·ref time	826.90
E_2/R_gT_r	30.41
k_2·ref time	$1.39 \cdot 10^8$

Table 5.4-19
Experimental data of the optimized runs

Run	Feed time		Batch time	Yield		Selectivity	J	Improvement
	Optimal	Obtained	t_B	Y_C	Y_E	Y_C/Y_D		in J [%]
E4	217.39		347.83	0.2585	0.2308	0.5448	12.48	
O1	323.19	313.04	347.83	0.2800	0.1531	0.5951	11.26	9.78
O2	242.75	251.74	275.36	0.2623	0.1670	0.5829	10.48	6.93
O3	229.71	228.48	253.62	0.2891	0.2154	0.6560	9.23	11.93

Marchal-Brassely *et al.* (1992) proposed the use of tendency modelling to optimize the batch time, the amount of initial reactants, the feed time of reactants, the temperature profile, and the feed-rate profile. The method proposed is an iterative one. Its principle is as follows:

- Optimization is performed for constant values of the parameters optimized.
- Initial and final temperature and feed rate are taken as parameters to be optimized, whereby the other variables are optimized in the same run. Temperature and feed rate between these two points are assumed to be straight lines connecting the initial and final values. The optimal values of variables obtained in the first step are taken as initial guesses for optimization.
- The interval of the batch time is split in two equal intervals. Temperature and feed rate at the boundaries of sub-intervals are subjected to optimization together with the other variables. Temperature and feed rate between the boundaries of sub-intervals are assumed to be straight lines connecting the initial and final values. The optimum values of variables obtained in step two are taken as initial guesses for optimization. The new profiles consist of two ramps joining optimized points.
- The iteration is continued for more intervals of the same time. It is stopped when the gain in terms of the technical-economical criterion becomes too small. It has been found that in many cases a very limited number of intervals was sufficient to decrease the value of a criterion drastically, presumably close to the optimum.

At each step of the optimization, experiments can be performed to update the kinetic model both with respect to structure and values of the kinetic parameters. The method is illustrated with the following example.

Example 5.4.4.3b. Optimization of time-profiles for a multireaction and multiphase reaction system (after Marchal-Brassely et al. (1992))

The following reaction system of industrial importance was studied: a liquid reactant A simultaneously reacts with a liquid B and a gas G to give products R and S and by-products lumped as L. For proprietary reasons, the names of the species are not specified. The reaction is carried out in semibatch mode. The amounts of A, B, G, R, and S at the end of experiments leading to identification of the kinetic model were determined analytically while the amount of L was evaluated from the material balance.

The objective of optimization was to maximize the amount of product R within as short a time as possible by manipulating the following variables:

- initial amount of A and G (amount of B fixed),
- time-dependent temperature profile,

- feed time and feed-rate profile of G,
- feed time of B (constant rate),
- total batch time, t_B.

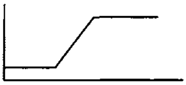
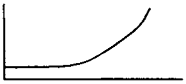
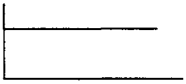
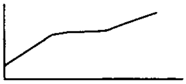
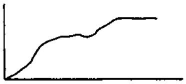
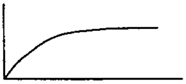
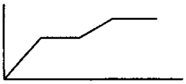
The technical-economical criterion to be minimized was formulated as follows:

$$J = \frac{1+\beta t_B}{n_{R,f} / n_{B,0}} \tag{5.4-139}$$

where $n_{R,f}$ is the moles of R at the end of the run, $n_{B,0}$ is the of moles B at the beginning of the run, and β is a weighing factor.

Table 5.4-20

Optimization sequence (experimental data, arbitrary units); Runs 1 and 2 are initial experiments. From run 3 to run 6 the amounts of A, B, G, and feed rate of G are fixed. These constraints are relaxed for runs 7 and 8. (Reprinted from Marchal-Brassely *et al.* (1992), 'Optimal operation of a semi-batch reactor by self-adaptive models for temperature and feed profiles', Copyright (1992), with permission from Elsevier Science).

Run	Amount of reactants		Feed time		Batch time	Temperature profile	Feed-rate profile
	A	*G*	*B*	*G*			
1	a	g	1	1.5	2.5		—
2	a	g	1	1	3.5		—
3	a	g	1	0.66	1.02		—
4	a	g	1	0.8	1.05		—
5	a	g	1	1.23	1.28		—
6	a	g	1	1.1	1.32		—
7	a	1.33 g	1	1.05	1.1		
8	1.25 a	1.53 g	1	1.04	1.04		

At the start of optimization only the temperature profile, the batch time, and the feed time of G were optimized, while the other variables were kept constant. At the end all the variables specified above were relaxed and optimized. The optimization sequence is shown in Table 5.4-20. The changes in criterion J are shown in Fig. 5.4-38.

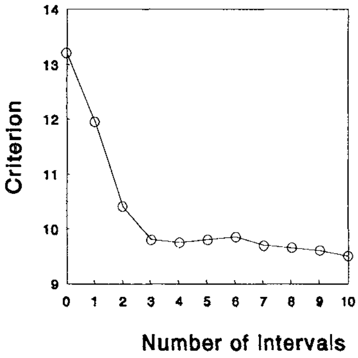


Figure 5.4-38. Criterion for optimization as a function of run number (reprinted from Marchal-Brassely *et al.* (1992), 'Optimal operation of a semi-batch reactor by self-adaptive models for temperature and feed profiles', Copyright (1992), with permission from Elsevier Science).

The predictive power of tendency models is obviously limited. However, the models can be useful in evaluation of the effect of changing heat-transfer conditions upon scale-up of reactors. Tendency models can be extremely useful for improvement and optimization of existing industrial reactors/reactions, especially for the improvement of the time-temperature policy and the policy of addition of component(s) to the reaction mixture.

Recently, Wang and Hofmann (1999) have proved that for the investigation of chemical reaction kinetics one not necessarily requires the mechanism of the reactions, but must develop a mathematical function which, based on experimental results, can present or interpret the experimental data best in the range of experiments. With this function the design and analysis of a chemical reactor operating at steady state can be carried out. Errors in the simulation should be the same as with mechanistic kinetics requiring knowledge of a detailed process mechanism. This strongly supports the idea of using approximate kinetic models and the methods presented above for kinetic modelling in the fine chemistry business.

5.4.5. Influence of mixing on reactor performance

5.4.5.1. Introduction

The role of mixing in heterogeneous reactions is obvious. In multiphase processes mixing imposed by a stirrer or an external pump is necessary to increase the interface through which reactants pass to meet their partner in the other phase and/or to intensify mass transfer between phases. Mixing can also play a significant role in the case of homogeneous reactions. Chemical reactions occur at the molecular level. Reactant molecules introduced into a reactor encounter the environment in the vicinity of the inlet. The composition of the mixture there is obviously different from the average composition in the reactor that would be reached if the molecules were instantaneously distributed uniformly all over the reaction zone. Hence, if reaction is much faster than mixing, local conditions will differ from those averaged over the reaction zone. The overall conversion and yields, which are integrals over time and reaction space, might be surprisingly different from expectations based on the average concentrations.

This can be illustrated by results of Bourne and Hilber (1990) and Bourne and Thoma (1991) who studied the competitive, consecutive reactions:

$$A + B \xrightarrow{k_1} R \tag{5.4-140}$$

$$R + B \xrightarrow{k_2} S \tag{5.4-141}$$

with rates differing significantly from each other. The process was carried out in a semibatch reactor. The selectivity of the undesired product S, S_S, defined as

$$S_S = \frac{2c_S}{c_R + 2c_S} \tag{5.4-142}$$

was found to depend on the feed time as illustrated in Fig. 5.4-39.

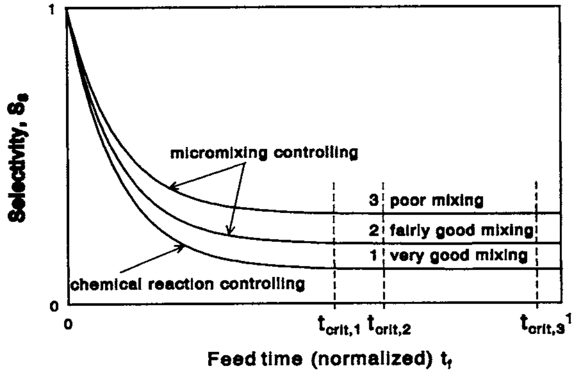


Figure 5.4-39. Selectivity versus feed time.

For sufficiently slow addition ($t_f > t_{crit}$) the selectivity becomes independent on the feed time. The position of the asymptote depends on whether the reaction is controlled by mixing on the molecular scale or by chemical reaction: it is higher for the former case.

Bourne (1994) modelled the reactions (with $k_1 = 20\ k_2$) carried out in a semibatch reactor, whereby 1 mole of B is added at a constant rate for every 1.1 mole of A in the reactor. When mixing is perfect, the conversion of A is 85.7 % at 100 % conversion of B, and the yield of R, Y_R, is 80.5 %, based on the amount of A initially charged into the reactor. The selectivity S_S of 0.115 corresponds to this yield. When mixing fully controls the process, the primary product R does not survive and only A and S are found in the final reaction mixture, *i.e.* $Y_R = 0$ and $S_S = 1$. Studying this phenomenon by a visualization technique it was found that the reaction zone can be highly localized. The bulk of the reaction can proceed in the vicinity of the outlet of the feeding pipe. The real reaction zone is a kind of plume restricted sometimes to a few centimetres from the inlet of the reactor.

The critical feed time t_{crit} depends on the location and number of feed pipes, stirrer type, and mixing intensity, and increases with increasing reactor volume. When a constant power-to-volume ratio is preserved, t_{crit} is proportional to $D_s^{8/3}$ and $V_r^{8/9}$, where D_s is the stirrer diameter and V_r the reactor volume (Bourne and Hilber, 1990; Bourne and Thoma, 1991). The productivity of the reactor expressed as the amount of product formed per unit time becomes almost independent of reactor volume. The reason is that the reaction goes to completion in the zone nearby the stirrer tip. The size of this zone increases independently of the tank size: it only depends on the velocity of the liquid being injected, the location of the nozzle, and the stirrer geometry and speed of rotation. Accordingly, for rapid reactions, the feed time will also be the reaction time.

By applying a multipipe feed system, t_{crit} can be significantly reduced: the critical time will be inversely proportional to the number of pipes. However, too many nozzles could result in intermingling of the local reaction zones, thus affecting the selectivity. The critical time is roughly two orders of magnitude longer than the blend time τ_{99}, which is defined later in this section.

Mixing can also influence selectivity of parallel competing reactions

$$A + B \xrightarrow{k_1} R \qquad \textbf{(5.4-143)}$$

$$C + B \xrightarrow{k_2} S \qquad \textbf{(5.4-144)}$$

as proven by investigations of Bałdyga and Bourne (1990a), Tipnis *et al.* (1994), Villermaux *et al.* (1994), and Wang and Mann (1992). This phenomenon can be observed if at least one of the reactions is instantaneous or fast. If the reactions proceed in the kinetic regime the selectivity ratio S/R is equal to the ratio of rate constants k_2/k_1 in case of reactions with the same reaction order. An experimental study by Tolgyesi (1965) on the nitration of toluene-benzene mixtures revealed that the selectivity ratio at constant temperature ranged from 1.37 to 27 when varying initial concentration, stirring speed, and stirrer type, while the ratio of rate constants was 27. With decreasing mixing rate, the selectivity ratio becomes independent of the kinetics and will approach 1.

The following stages of mixing between two fluids occurring in sequence and in parallel can be distinguished:

- division of a stream introduced to a reactor into lumps not yet mixed with the surroundings,
- distribution of the lumps throughout the mixing zone,
- reduction of the lump size, and
- diffusion of components of both fluids in the deformed and reduced lumps.

Lumps can be observed when introducing a stream with a colour and viscosity significantly different from the fluid in the reactor. These blobs can behave as if a separate liquid phase was dispersed in the reactor. If no mass transfer between the blobs and the surroundings occurs, the system stays inhomogeneous; we say that the system is completely segregated. For a stirred-tank reactor (STR) the inhomogeneity is macroscopic on the whole tank scale when the mean residence time τ_{rt} in the CSTR or the feed time t_f to the SBSTR are of the order of the circulation time in the reaction zone, t_C, or shorter.

Before the blobs are dispersed in the surroundings, at a molecular level reaction rates will be low in spite of the apparently good mixing. If the segregation of blobs from the surroundings is sufficiently stable in a continuously operated reactor, the overall conversion will be practically nil! A significant conversion in batch reactors will only be observed when the batch time is sufficiently long. The reaction will speed up only when these blobs are 'dissolved' in their environment sufficiently fast. 'Dissolving' includes the formation of aggregates consisting of both fluids, deformation and breakage of these aggregates, and diffusion of reactants within the aggregates. If the rate of mixing is infinitely high, *i.e.* mass transfer between the blobs and the surroundings is instantaneous, a state of ideal dispersion on a molecular scale is achieved.

The time required to reach uniform dispersion of added reactants over the reaction zone at the molecular level depends on the intensity of mixing, the distribution of the intensity, and the history of mixing in all points of the reaction zone. The reactor size and shape, the geometric characteristics of the stirrer, the speed of rotation, and the properties of both liquids as a function of time will define the distribution and history of mixing in a reactor. In semibatch operated tanks the distribution is rather uniform. In large full-scale reactors, the distribution is rarely known. For a rough assessment of the mixing intensity the concept of blend time is commonly accepted for non-reactive systems. This concept was introduced by Khang and Levenspiel (1976) and is illustrated in Fig. 5.4-40.

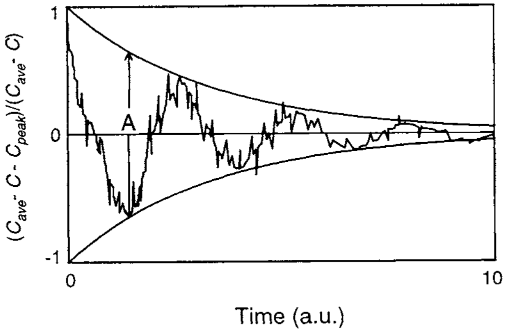


Figure 5.4-40. Oscillations of tracer concentration in time.

A tracer is injected into the reactor and its concentration is measured at a certain location. The observed tracer concentration will oscillate whereby the amplitude of the oscillations, A, decreases with time, finally approaching the asymptote determined by the averaged concentration over the mixing zone. This relationship can be presented as:

$$\frac{A}{2} = e^{-kt} \qquad \textbf{(5.4-145)}$$

where k is the mixing rate constant. As $A/2$ can be considered as the fraction of non-uniformity, the fractional degree of uniformity U can be then defined as

$$U = 1 - \frac{A}{2} = 1 - e^{-kt} \qquad \textbf{(5.4-146)}$$

So U depends on the time, called the blend time, and on k. The longer the blend time, the higher the uniformity. The blend time to achieve U = 99 %, which is considered sufficient for many cases, τ_{99}, ranges from seconds in small reactors to minutes in large reactors of tens of cubic metres volume. A uniformity of 90 % is achieved at only half the mixing time required to reach U = 99 % while mixing to a uniformity of 99.9999 % requires three times as much mixing time τ_{99}.

The reactor performance for instantaneous or fast reactions will depend on the mixing conditions and the mechanism and kinetics of the reactions occurring. For single fast reactions the reaction time, reactor volume, or conversion at a given time will be different than expected based on the average concentration in the reactor (except for first-order, irreversible reactions). In fast, complex reactions, selectivity can also be influenced by micromixing. Slow reactions are controlled by kinetics only. Their rate is a function of the average concentration and is fully independent of mixing conditions. So-called *time scales* (or *time constants*) are parameters for comparison of the rates of the individual steps of mixing and chemical reaction, and can be used to determine which step is controlling the overall reactor performance. For an n-th order reaction the characteristic time constant, τ_R, is defined as:

$$\tau_R = \frac{1}{k \cdot c_{A,0}^{n-1}} \qquad \textbf{(5.4-147)}$$

Characteristic time constants for various stages of mixing will be defined in the next section.

The vast majority of chemical reactions are sufficiently slow not to observe a dramatic influence of mixing on yields and selectivities. Exceptions are polymerizations, interfacial polycondensations, precipitations, and some fast reactions - usually performed in semibatch mode - such as autocatalytic reactions, neutralizations, nitrations, diazo couplings, brominations, iodinations, and alkaline hydrolysis, which are often encountered in the manufacture of fine chemicals.

5.4.5.2. Macro-, meso- and micromixing mechanisms

The interpretation of mixing phenomena as discussed below is based on the concept of Pohorecki and Bałdyga (1983a,b,c), developed further by Bałdyga and Bourne (1984, 1984a,b,c, 1986) and Bałdyga (1989). According to this concept, mixing proceed as shown in Figs. 5.4-41, 5.4-42, and 5.4-47 to 5.4-49.

At the inlet of the reaction zone a plume is formed which elongates and becomes wider as illustrated in Fig. 5.4-41. This plume is then broken up into large blobs, which are deformed and reduced by an inertial-convective mechanisms (see Fig. 5.4-42).

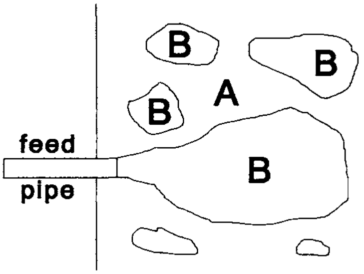


Figure 5.4-41. Feed distribution in the vicinity of inlet of the reactor.

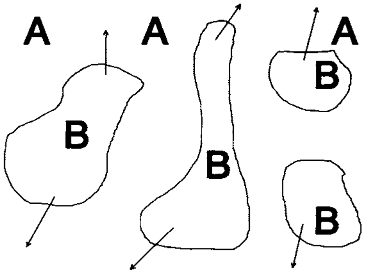


Figure 5.4-42. Breakage of blobs by an inertial-convective process.

Macromixing. Macromixing refers to the distribution of large blobs over the reaction zone. The blend time as defined earlier can be considered to be the characteristic time constant for macromixing. It has been commonly accepted that in a stirred tank without chemical reaction, uniform distribution over the mixing zone to a degree of 99 % is achieved when the liquid has circulated in the mixing zone 4-5 times; this state is reached within the blend time τ_{99}. The dependence of blend time on mixing conditions is as shown in Fig. 5.4-43.

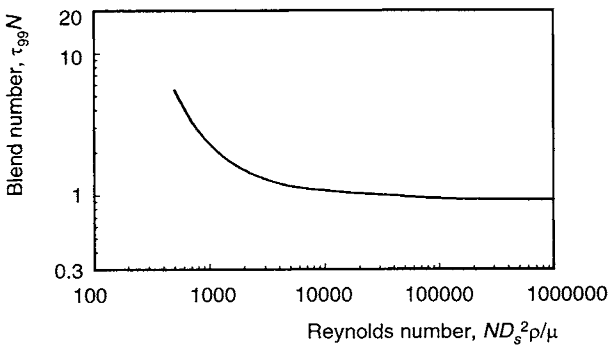


Figure 5.4-43. Blend number versus Reynolds number.

For Reynolds numbers higher than 5,000 (usually the case in practice), the blend number ($\tau_{99}N$) is only slightly dependent on the Reynolds number. In this region the blend time becomes inversely proportional to the speed of rotation. It is also dependent on the geometric characteristics of both the tank and the stirrer as shown below:

$$\tau_{99}N = C\cdot\left(\frac{D_r}{D_s}\right)^a\cdot\left(\frac{H_r}{D_r}\right)^b \tag{5.4-148}$$

where N is the speed of rotation, D_s and D_r are the diameter of stirrer and reactor, respectively, and H_r is the fluid height; C, a, and b are coefficients that are experimentally determined for various geometric characteristics of the system. The coefficient b for baffled tanks is approximately 0.5 while the coefficients a and C strongly depend on the type of stirrer. These coefficients for typical stirrers are given in Table 5.4-21 (after Fasano and Penney, 1991a).

Table 5.4-21
Coefficients in Eqn. 5.4-148

Stirrer type	C	*a*
Six-bladed disk turbine	1.06	2.17
Four-bladed flat turbine	1.01	2.30
Four-bladed pitched turbine	0.641	2.19
Chemineer HE-3 turbine	0.272	1.67
Marine propeller	0.274	1.73

The following convenient expression may be used to approximately evaluate the mixing times in baffled tanks:

$$N \cdot \tau_{99} N_P = \begin{matrix} 40 \text{ for a propeller} \\ 300 \text{ for a turbine} \end{matrix} \qquad \textbf{(5.4-149)}$$

where N_P is the power number defined as: $N_P = P/(\rho N^3 D_s^5)$. Correlations for the relationship between power number and mixing conditions can be found in literature, e.g. in Chemical Engineers' Handbook (Perry and Chilton, 1984). Some typical curves of N_P versus Reynolds number are shown in Fig. 5.4-44.

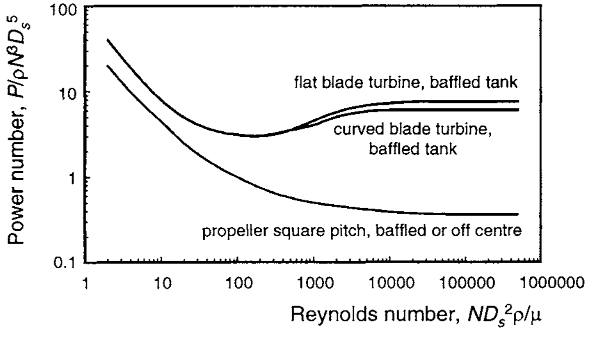


Figure 5.4-44. Power number versus Reynolds number.

The power number becomes independent on mixing at turbulent conditions, which are achieved at Reynolds numbers greater than 20,000. Typical power numbers at high Reynolds number for some common stirrer types are shown in Table 5.4.22.

Table 5.4.22
Typical power numbers at Re > 20,000

Stirrer type	N_P
High-efficiency turbine	0.2 – 0.5
Pitched-blade turbine	1.2 – 1.5
Straight-blade turbine	3.8 – 5.6
Disk turbine	5.8 – 6.2

Mesomixing. Blobs of B-rich fluid are surrounded by A-rich fluid. If turbulent flow dominates, the movement results in breakage of the blobs due to inertial forces. The partitioned blobs then move independently. The above mechanism is referred to as mesomixing. The primary blobs of initial size equal to the integral scale of concentration fluctuations, L_c (ranging from $0.3D_s$ to D_s) are reduced by the fluid motion to blobs with a size of the order of the Kolmogoroff microscale η_K [13]. Reaction only occurs at the outer surface of the blobs. The rate of mass transfer between the liquids via molecular diffusion is negligible compared to the rate of blobs deformation and breakage.

The characteristic time constant for mesomixing caused by turbulence is given by Bałdyga and Bourne (1992):

$$\tau_D = \frac{F_{V,j}}{u_{in,ave}\, D_{turb}} \qquad \textbf{(5.4-150)}$$

where $F_{V,j}$ is the volume flow rate of component j, $u_{in,ave}$ is the superficial velocity of component j in the inlet pipe, and D_{turb} is the turbulent diffusivity.

The characteristic time constant for mesomixing by the inertial-convective process (Corrsin, 1964) is given by

$$\tau_{ms} = \frac{3}{2}\left(\frac{5}{\pi}\right)^{2/3} L_c^{3/3}\,\varepsilon^{-1/3} \qquad \textbf{(5.4-151)}$$

in which ε is the specific energy dissipation and L_c is the integral scale of concentration

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[13] The Kolmogoroff microscale, η_K, has the physically meaning of the size of the region within which energy is dissipated by viscous forces. It can be estimated by:

$$\eta_K = \left(\frac{\nu^3}{\psi}\right)^{0.25}$$

in which ψ is the rate of energy dissipation and ν is the kinematic viscosity.

fluctuations in the vicinity of the feed pipe, which according to Bałdyga *et al.* (1995a) is initially proportional to:

$$L_c \sim \sqrt{\frac{F_{V,f}}{u_f}} \tag{5.4-152}$$

where $F_{V,f}$ is volume flow rate of the feed and u_f is the velocity of the feed in the injection nozzle. Deformation and breakage of the plume can be significantly enhanced by accelerating radial (with respect to the axis of the feed pipe) mixing using in-line mixers.

Micromixing. Forces leading to deformation and breakage of blobs (mesomixing mechanism) originate from velocity differences. A typical velocity profile produced by radial flow turbines is shown in Fig. 5.5-45. In particular in the vicinity of the stirrer the forces are large, leading to a relatively high degree of mixing. Mixing is much less far from the stirrer, so deformation and breakage of blobs is less intense there.

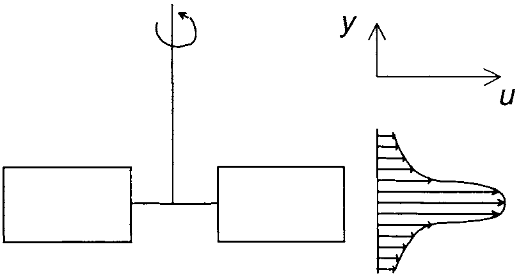

Figure 5.4-45. Typical velocity pattern for turbine.

At any point in the fluid the velocity fluctuates. If the flow is fully turbulent, the time-dependence of the velocity at a point in the tank is schematically represented in Fig. 5.4-46.

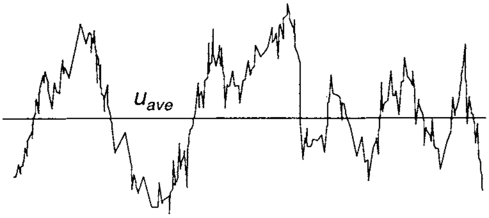

Figure 5.5-46. Velocity fluctuations at one point in the tank.

The shear rate between liquid layers moving at the average velocity is an important factor in macroscale processes involving large blobs. The velocity fluctuations are responsible for microscale processes of homogenization at the molecular level. The data for turbine agitators show that the mean velocity fluctuation, defined as

$$u' = \sqrt{\frac{1}{t-t_0}\int_0^t \left(u - u_{avg}\right)^2 dt} \qquad \textbf{(5.4-153)}$$

is about 50 percent of the mean velocity in the agitator zone. For a comparison, velocity fluctuations range from 5 to 15 % in other parts of the tank (Oldshue, 1986). Velocity fluctuations result from local vortices of rather short lifetime. They result in structures as shown in Fig. 5.4-47. The size of these structures increases during the lifetime of the vortex. The vortex gradually deforms and decays, and finally loses its hydrodynamic identity returning to the state of isotropy. During the vortex lifetime the size of the laminated structure l increases up to 12 times the Kolmomogoroff microscale.

This mechanism is shown in more detail in Figs. 5.4-48 and 5.4-49. Fluid elements are deformed in such a way that intense elongation occurs in one direction, rapid shrinking in the second direction, and a moderate elongation in the third direction.

Long, thin slabs, separate or in the form of tongues, are formed as a result of this process. The decreasing thickness of the slabs becomes stable when it reaches the Batchelor microscale[14]

$$\eta_B = \eta_K\, Sc^{-1/3} \qquad \textbf{(5.4-154)}$$

where Sc is the Schmidt number $(c_p\mu/\lambda)$. Diffusion does not plays a part yet when the blob size is in the order of the Kolmogoroff microscale, while this mechanism becomes important if the blob size is in the order of the Batchelor microscale.

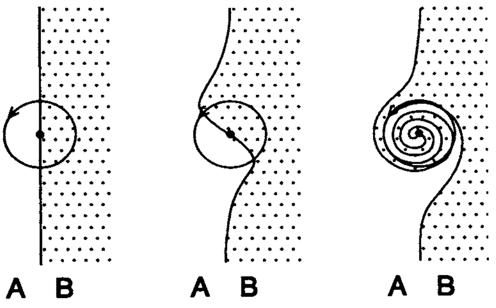

Figure 5.4-47. Formation of lamellar structure through action of vorticity (adapted from Bałdyga and Bourne, 1986).

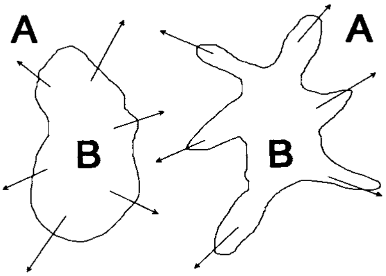

Figure 5.4-48. Deformation of blobs by stretching(convective-viscous process).

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[14] The Batchelor microscale physically means a size of the region within which a compound moves due to diffusional forces. This does not occur outside these regions, where compounds move because of turbulences.

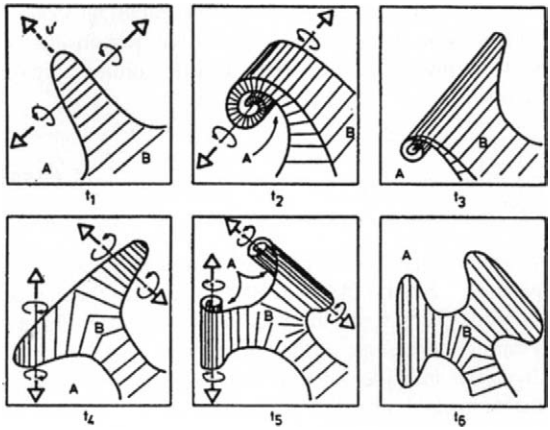

Figure 5.5-49. Engulfment of elongated blobs (reproduced from Bałdyga and Bourne, 1986 with permission of Gulf Publ. Corp.).

According to Pohorecki and Bałdyga (1995) the characteristic time constant for diffusion is given by

$$\tau_{Ds} \approx \left(\frac{\nu}{\psi}\right)^{1/2} \ln Sc \tag{5.4-155}$$

Bałdyga and Bourne (1984) gave a more precise definition, according to which

$$\tau_{Ds} \cong 2\left(\frac{\nu}{\psi}\right)^{1/2} \operatorname{arc\,sinh}(0.05 \cdot Sc) \tag{5.4-156}$$

The elongated thin slabs are subject to twisting and convolution by the action of local vorticity as illustrated in Fig. 5.4-49 (after Bałdyga and Bourne, 1984b). At time t_1, the tongue (slab) starts rotating by a local burst of vorticity as shown in Fig. 5.4-47. At time t_2, a laminated structure is formed comprising layers of A and B: A is engulfed by B. The layers turn and are simultaneously stretched along the vortex axis (see time t_3). All lamellae are of approximately equal volume and thickness. Diffusional mixing and chemical reaction proceed within the lamellar structure that ultimately results in fusion of fluids A and B. After vorticity decays a sheet of liquid with two tongues is formed (time t_4). When the next burst of vorticity occurs, two laminated structures are formed (time t_5) and the process continues till four tongues have been formed. Hence, the number of vortices follows a geometric progression with ratio 2. The characteristic time constant for engulfment is given (Bałdyga and Bourne, 1984) by

$$\tau_{\omega} = 12\left(\frac{\nu}{\psi}\right)^{1/2} \tag{5.4-157}$$

Micromixing comprises the mechanisms of stretching and shrinking of slabs discussed above, accompanied by molecular diffusion, which finally lead to homogenization at the molecular level. Contrary to turbulent macromixing it depends on viscosity. This has been proven experimentally by Bourne *et al.* (1989).

The micromixing mechanism presented above, **Engulfment-Deformation-Diffusion**, is the basis of the *EDD* model proposed by Bałdyga and Bourne (1984c). This model was the result of a series of studies performed in the Technisch-chemisches Laboratorium ETH (Zürich, Switzerland) and the Institute of Chemical and Process Engineering, Technical University of Warsaw (Poland) (see Angst *et al.*, 1982a,b, 1984; Bałdyga and Bourne, 1984; Belevi *et al.*, 1981; Bolzern and Bourne, 1983; Bourne and Rohani, 1983a,b; Bourne *et al.* 1981a,b; Pohorecki and Bałdyga, 1983a,b). The vast majority of experimental work was performed by studying the reaction between 1-naphthol and diazotized sulphanilic acid with kinetics investigated extensively by Bourne *et al.* (1981a, 1985, 1990, 1992). A full reaction network is shown in Fig. 5.3-7 in *Example 5.3.1.2*. As formation of the primary *ortho-* and *para*-azo dyes is much faster than that of the secondary bisazo dye, both intermediates were lumped into one pseudocomponent and the overall reaction scheme was represented by the system of reactions (5.4-140) and (5.4-141).

The first approach in modelling is to assume a uniform distribution of the rate of energy dissipation ψ over the reaction zone. Bałdyga and Bourne (1988a,b) extended the model taking non-uniformity of the rate of energy dissipation over the reaction zone into account. This seems to be important as the local rate of energy dissipation in a stirred tank varies with position over two to three orders of magnitude. The local rate of energy dissipation can be related to the average energy dissipation by:

$$\psi = \phi \cdot \psi_{ave} = \frac{\phi N_P N^3 D_s^5}{V_r} \qquad \textbf{(5.4-158)}$$

where ϕ is a proportionality factor dependent on position (e.g. Nagata, 1975). The location of the feed pipe will obviously affect the reactor performance if the time scale for diffusion, τ_{Ds}, and reaction is much shorter than the circulation time. Bałdyga and Bourne (1984c) found that ϕ equals 8 if the feed pipe is located on the suction side of the stirrer (Rushton turbine or marine propeller), while it drops to about 1/6 if the feed is added far from the impeller. A location of the feed pipe half way between the stirrer and the wall in the plane of the stirrer resulted in a ϕ of 1. According to Rice and Baud (1991) ϕ is about 0.1 at the liquid surface, 1 between the surface and the stirrer, and 3.3 nearby the stirrer (slightly higher, close to the tip). For a larger impeller ϕ increases to of 4.3. Like Angst *et al.* (1984), these authors also found that the selectivity S_S is dependent on the average rate of energy dissipation, decreasing with an increase of this rate and approaching an asymptote at sufficiently high rate of energy dissipation. Villermaux *et al.* (1994) found a ϕ of 1.6 if the feed pipe is located outside the projection of and above the stirrer (at a distance of 0.7 of the distance between the stirrer and the bottom), a ϕ of 4 at a radial position of the stirrer and of 2.5 if the feed pipe was positioned below the stirrer. Bourne and dell'Ava (1987) also studied the influence of feed location on reactor performance. A ϕ of about 0.2 was found to correlate the results of measurements best for a feed pipe located between the stirrer and the liquid surface. For a feed pipe positioned slightly below the stirrer outside the impeller projection ϕ is 4, whereby an almost equally satisfactory fit was achieved using a $\phi = 3$. Values of ϕ ranging from 1.5 to 6 for this location were obtained by laser doppler velocimetry.

Based on literature data from two sources only, Bałdyga and Bourne (1988b) prepared a map of the distribution of the rate of energy dissipation (see Fig. 5.4-50). The map is not intended to be a quantitative guide for calculations of agitated reactors of all types, but only has illustrative value. It is, however, consistent with the aforementioned values for energy dissipation rates. Some apparent inconsistencies in literature data on inhomogeneity of the rate of energy dissipation over the reaction zone can be caused by differences in energy of jets of injected liquids. Tatterson (1994) proved that at high liquid velocities this energy can be of the same order of magnitude as that transferred by the stirrer.

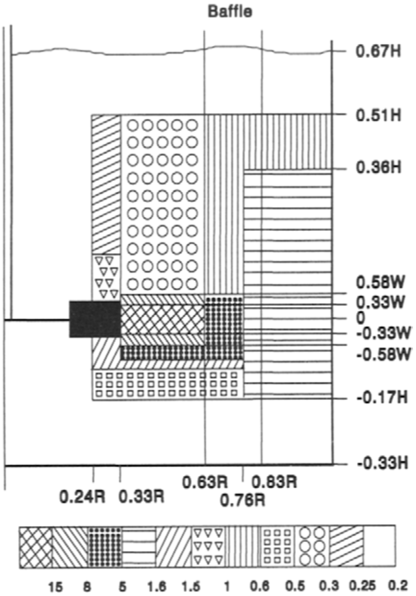

Figure 5.4-50. Distribution of rate of energy dissipation (adapted from Bałdyga and Bourne, 1988b).

Bałdyga *et al.* (1994, 1995a,b) studied the performance of jet reactors without mechanical stirring. The effect of diffusion on the overall mixing rate was found to be small (Bałdyga and Rohani, 1987; Rohani and Bałdyga, 1987). The *EDD*-model was simplified (Bałdyga and Bourne, 1989a) to the E(ngulfment)-model, which approximates the *EDD*-model very well if low-viscous liquids ($Sc \ll 4000$) with $c_{A0}/c_{B0} \gg 1$ are processed. Engulfment then is the rate determining step. The model of mixing by engulfment is formulated for the growth of the volume of a single feed eddy having a volume V_e. Eddies start their growth at different times and averaging over all these families gives a continuous growth law. Eddies of component i grow according to:

$$\frac{dV_e}{dt} = E \cdot V_e \tag{5.4-159}$$

with

$$E = 0.05776\left(\frac{\psi}{\nu}\right)^{1/2} \tag{5.4-160}$$

where E is the engulfment rate constant. A high value of E relates to a high rate of mixing.

For a semibatch reaction between A already present in the reactor and B being fed into the reactor, each portion of B introduced is a source of vortices that grow by engulfement of the A-rich environment. The mass balance of component i in this growing zone is:

$$\frac{d(V_{ei}c_i)}{dt} = E \cdot V_{ei} < c_i > + r_i V_{ei} \tag{5.4-161}$$

where $<c_i>$ is the concentration of species i in the local environment of the growing eddy, and c_i is the uniform concentration of i within the growing reaction zone. The first term on the right-hand side of this equation is the rate of addition of i by the engulfment. Combination of Eqns. (5.4-159) and (5.4-161) and rearrangement yields the following expression:

$$\frac{dc_i}{dt} = E \cdot (< c_i > - c_i) + r_i \tag{5.4-162}$$

This equation can be solved provided that $<c_i>$, which changes with time, is known. Example 5.4.5.1 illustrates the potential of this method.

Example 5.4.5.1. Application of the E-model for simulation of the coupling of 1-naphthol with diazotized sulphanilic acid in a semibatch reactor (after Bałdyga and Bourne, 1989b).

The complete reaction scheme is shown in Fig. 5.3-7, while Fig. 5.4-51 gives a simplified representation. 1-naphthol (A) is primarily coupled with diazotized sulphanilic acid (B) to form monoazo dyes coupled in *para* and *ortho* positions (p-R and o-R, respectively). This reaction is first order in both A and B. Each of the primary products can react with diazotized sulphanilic acid to form bisazo dye (S). Rate constants at 298 K and pH 10 are: k_{11} = 10600 $m^3mol^{-1}s^{-1}$; k_{21} = 8.0 $m^3mol^{-1}s^{-1}$; k_{12} = 700 $m^3mol^{-1}s^{-1}$; k_{22} = 1.7 $m^3mol^{-1}s^{-1}$ (see Fig. 5-4-51).

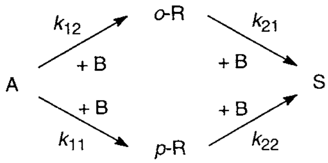

Figure 5.4-51. Reaction network.

The E-model in dimensionless form is

$$\frac{dC_i}{dT} = < C_i > - C_i + Da\sum_j \beta_{ij} C_i C_j \tag{5.4-163}$$

where dimensionless concentrations C_i, time T, the Damköhler number Da, and dimensionless rate constants β_{ij} are defined as:

$$C_i = \frac{c_i}{c_{B0}} \tag{5.4-164}$$

$$T = tE \tag{5.4-165}$$

$$Da = \frac{k_{22} c_{B0}}{E} \tag{5.4-166}$$

$$\beta_{ij} = \frac{k_{ij}}{k_{22}} \tag{5.4-167}$$

and k_{ij} are second-order rate constants of the jth reaction.

The sum of k_{11} and k_{12} is so high relative to the rate of micromixing that A and B will not coexist. Thus the number of ordinary mass balance differential equations requiring integration can be reduced from five to four by defining the following composite variables:

$$U = C_B - C_A \tag{5.4-168}$$

$$Z = \beta_1 C_A + C_{p-R} \tag{5.4-169}$$

$$W = \beta_2 C_A + C_{o-R} \tag{5.4-170}$$

$$\beta_1 = \frac{k_{11}}{k_{12} + k_{11}} \tag{5.4-171}$$

$$\beta_2 = \frac{k_{12}}{k_{12} + k_{11}} \tag{5.4-172}$$

When A and B do not coexist then:

$$C_A = \frac{|U| - U}{2} \tag{5.4-173}$$

$$C_B = \frac{|U| + U}{2} \tag{5.4-174}$$

$$C_{p-R} = Z - \beta_1\left(\frac{|U| - U}{2}\right) \tag{5.4-175}$$

$$C_{o-R} = W - \beta_2\left(\frac{|U| - U}{2}\right) \tag{5.4-176}$$

The balance equations (excluding the balance for formation of S) then are:

$$\frac{dU}{dT} = \langle U \rangle - U - Da(Z + \beta_3 W)\left(\frac{|U| + U}{2}\right) \tag{5.4-177}$$

$$\frac{dZ}{dT} = \langle Z \rangle - Z - Da \cdot Z\left(\frac{|U| + U}{2}\right) \tag{5.4-178}$$

$$\frac{dW}{dT} = \langle W \rangle - W - \beta_3 Da \cdot W\left(\frac{|U| + U}{2}\right) \tag{5.4-179}$$

where

$$\beta_3 = \frac{k_{21}}{k_{22}} \tag{5.4-180}$$

The initial conditions for the growing reaction zone are:

$$U_0 = 1;\ Z_0 = W_0 = 0 \tag{5.4-181}$$

while for the A-rich surroundings:

$$\langle U \rangle_0 = -F;\ \langle Z \rangle_0 = \beta_1 F;\ \langle W \rangle_0 = \beta_2 F \tag{5.4-182}$$

where F is concentration ratio:

$$F = \frac{c_{A0}}{c_{B0}} \tag{5.4-183}$$

On integration of the above system of differential equations until B has been completely consumed U, W, and Z values are obtained. Monoazo dyes concentrations are then calculated using Eqns. (5.4-175) and (5.4-176). The concentration of 1-naphthol is calculated knowing its surplus for the reaction and the concentration of bisazo dye S can be determined from any of the mass balances:

$$C_{A0} = C_A + C_{p-R} + C_{o-R} + C_S \tag{5.4-184}$$

$$C_{B0} = C_B + C_{p-R} + C_{o-R} + 2C_S \tag{5.4-185}$$

whereby $C_B = 0$ at the end of each integration. The selectivity is defined by two indices, which measure the formation of the bisazo product and the fraction of the ortho monoazo product, respectively:

$$X_S = \frac{2C_S}{C_{p-R} + C_{o-R} + 2C_S} \tag{5.4-186}$$

$$S_{o-R} = \frac{C_{o-R}}{C_{p-R} + C_{o-R}} \tag{5.4-187}$$

Results of calculations for $Sc = 1000$ are given in Table 5.4-23. The total stream of B added was divided into 20 portions ($N = 20$). Each CPU time was less than 5 s at an integration step size of 10^{-4}. The formation of the bisazo product is promoted by poor mixing (low values of E, and, consequently, high values of Da) and high volume ratio of reagent solutions V_A/V_B..

Table 5.4-23
Results of simulation

V_A/V_B[a]	$\overline{Da}$[a]	F	S_S	$S_{o\text{-}R}$
10	0.026	0.105	0.084	0.056
10	0.260	0.105	0.389	0.043
50	0.260	0.021	0.452	0.043

[a] $\overline{Da} = Da/(1 + V_A/V_B)$

The E-model was also applied to a system of parallel reactions (Bałdyga and Bourne, 1990a). It was found that selectivity depends on compositions of both the initial reactor content and the stream added for chemically equivalent mixtures of three reactants (see reaction system given by Eqns. (5.4-143) and (5.4-144)). For an instantaneous reaction, the yield of S varies from 0 to 100 % depending on the mode of composing the feeding stream.

Pohorecki and Bałdyga (1983a) developed a micromixing model to simulate a chemical reaction with accompanying precipitation (important for the manufacture of pigments). They also presented experimental results (Bałdyga and Pohorecki, 1986). Bałdyga *et al.* (1995) extended the engulfment model to such systems. The model involves interactions between macro-, meso-, and micromixing coupled with the population balance of crystallization and kinetics of precipitation. It enables the prediction of the supersaturation history, which governs the crystal size distribution. A model for precipitation was also subject of studies by Aoun *et al.* (1999).

A model for calculation of processes limited by mesomixing was proposed by Bałdyga and Bourne (1992). Results of calculations using the model were in reasonable agreement with observations.

Apart from the *EDD*-model discussed above, other multizone models have also been developed. Multizone mixing models which include interactions with the mean environment mechanism (MZM-IEM) have been developed in the Laboratoire des Sciences du Genie Chimique (CRNS-ENSIC/INPL, Nancy, France) (see papers of Villermaux and Devillon, 1972; Villermaux and David, 1983; David *et al.*, 1992; David, 1991; David and Villermaux, 1987, 1989; and Zoulalian and Villermaux, 1974). The model consists in that fractions of injected liquid are considered to be associated with a volume of surrounding fluid to form a reacting cloud which starts growing. The reacting cloud is transferred with the recirculation streams according to the trajectories determined by the average velocities. All microscopic volumes (eddies) within the cloud exchange material with each other. Such an exchange has been represented by the IEM model where it is assumed that exchange occurs between one particular eddy and a fictitious concentration averaged over the cloud population. Mathematically, the model is very simple, but it is physically less realistic than the *EDD* model, as indicated in the paper of Bałdyga and Bourne (1990b).

Scientists of the Institute of Science and Technology of UMIST (Manchester, UK) and collaborating laboratories have developed a network-of-zones model (Mann *et al.*, 1981; Mann and Knysh, 1984; Mann and El-Hamouz, 1992, 1995; Mann *et al.*, 1995; Nienow *et al.*, 1992; Togatorop *et al.*, 1994; and Wang and Mann, 1990, 1992). According to this model a reaction volume is represented by an assembly of backmixed zones, each of equal volume. The liquid circulates through zones whereby the total flow generated is apportioned into nested circulation flow loops with an equal flow through a series of zones. The configuration of network-of-zones is based on observations of streamlines in a stirred tank. Separate loops are set below and above the impeller. Zones experience an equal and opposite exchange flow with adjacent zones in adjacent loops of liquid recirculated over the reaction volume. This model requires significant computational effort (hundreds or even thousands of differential equations to be solved) and does not reflect all phenomena occurring at the micro level.

Extensive reviews on micromixing can be found in papers of Bałdyga and Bourne (1986) and Pohorecki and Bałdyga (1993, 1995).

5.4.5.3. Criteria for competition between reaction and mixing

Table 5.4-24 summarises the various characteristic time constants for reaction and mixing. Instantaneous (very rapid), fast (rapid) and slow (very slow) reactions have been classified based on characteristic time constants (time scales) for mixing and reaction. Denoting the mixing time scale by τ_M (τ_{99}, τ_D, τ_{ms}, τ_{Ds}, or τ_ω) reactions can be classified as follows from the viewpoint of competition with individual stages of mixing:

$\tau_M >> \tau_R \Rightarrow$ instantaneous
$\tau_M \sim \tau_R \Rightarrow$ fast
$\tau_M << \tau_R \Rightarrow$ slow

The reaction can be slow compared to micromixing but fast or instantaneous compared to meso- or macromixing.

Combining the characteristic rate constant for engulfment and the characteristic time for mesomixing for the *i*-th species into the ratio

$$Q = \frac{E_i F_{V,i}}{u_{in,ave} D_t} \tag{5.4-188}$$

a comparison between effects of meso- and micromixing by engulfment can be easily made. If $Q >> 1$, mesomixing is the controlling factor, if $Q << 1$, micromixing dominates, and if $Q \approx 1$, both mechanisms are of similar importance and have to be taken into account in scale-up. Similarly, the relative importance of inertial-convective mesomixing and micromixing by engulfment can be evaluated using the parameter M introduced by Bałdyga and Rohani (1987):

$$M = E \cdot \tau_{ms} \tag{5.4-189}$$

Inertial-convective mesomixing controls the process if $M >> 1$, micromixing limitations prevail if $M << 1$, and both are of similar significance if $M \approx 1$.

An important criterion allows for the evaluation of the importance of the energy dissipation field in the reaction zone. This characteristic time constant has been formulated by Pohorecki and Bałdyga (1993, 1995):

$$\tau_\psi = \frac{|\Delta\psi|}{\left|\left(\frac{\partial\psi}{\partial x}\right)_{\max}\right| u_{ave}} \tag{5.4-190}$$

Table 5.4-24
Characteristic times for reaction and mixing

Characteristic time constant for	Equation	Authors
n-th order reaction	$\tau_R = \dfrac{1}{k \cdot c_{A,0}^{n-1}}$	
Blending	$\tau_{99} = C \cdot \dfrac{1}{N} \cdot \left(\dfrac{D_r}{D_s}\right)^a \cdot \left(\dfrac{H_r}{D_r}\right)^b$	
Mesomixing by turbulence	$\tau_D = \dfrac{F_{V,j}}{u_{in,ave}\, D_{turb}}$	Bałdyga and Bourne (1992)
Inertial-convective mesomixing	$\tau_{ms} = \dfrac{3}{2}\left(\dfrac{5}{\pi}\right)^{2/3} L_c^{3/3} \varepsilon^{-1/3}$	Corrsin (1964)
Diffusion	$\tau_{Ds} \approx \left(\dfrac{\nu}{\psi}\right)^{1/2} \ln Sc$	Pohorecki and Bałdyga (1995)
	$\tau_{Ds} \cong 2\left(\dfrac{\nu}{\psi}\right)^{1/2} \operatorname{arc\,sinh}(0.05 \cdot Sc)$	Bałdyga and Bourne (1984)
Engulfment	$\tau_\omega = 12\left(\dfrac{\nu}{\psi}\right)^{1/2}$	Bałdyga and Bourne (1984)

If $\tau_\omega >> \tau_\psi$ the energy dissipation averaged over the reaction zone can be applied in the engulfment equations, while for $\tau_\omega << \tau_\psi$ the local values of ψ should be used. Experimental data on the distribution of energy dissipation are rather scarce. *C*omputational *F*luid *D*ynamics (*CFD*) can provide such data via modelling (see e.g. Bakker and Fasano, 1994; Kresta and Wood, 1991; Middleton *et al.*, 1986; Ranade and Joshi, 1990; Ranade *et al.*, 1991; and Togatorop *et al.*, 1994). An example of CFD computations by using the commercial FLUENT package is presented by Kresta and Wood (1991). They distinguished the following three zones in a stirred-tank reactor: (1) intensely agitated *impeller control volume* (*ICV*), (2) *impeller discharge stream* (*IDS*), and (3) *circulation zone* (*CZ*). For a turbulently mixed reactor of standard geometry with a six-bladed disk turbine ($D_r = H_r = 0.456$ m; $D_s/D_r = 1/3$; $b = D_r/10$; D_s:L_s:W_s = 20:5:4) the relative volumes of these zones approximately are: ICV:IDS:CZ = 1:10:89. Kresta and Wood found that proportions between energies dissipated per unit volume in these zones are as follows: ICV:IDS:CZ = 54:35:11. This is equivalent to ratio ϕ_{ICV}:ϕ_{IDS}:ϕ_{CS} = 54:3.5:0.12 (see Fig. 5.4-50).

5.4.5.4. Guidelines for scale-up of semibatch reactors for fast homogeneous reactions in the absence of data on chemical kinetics and on the distribution of energy dissipation in the reaction zone

Evaluation of the influence of micromixing on reactor performance requires knowledge of the reaction scheme, and data on the kinetics and physical properties (k_i, ν, and D_i) as well on the distribution of E over the reaction zone (ψ ,or, equivalently, ϕ). As mentioned before, for most industrial reactions in the field of fine chemistry the kinetics is unknown at the stage of scale-up of the reactor. Data on the distribution of energy dissipated per unit volume in stirred tank vessels are also very scarce. Therefore, approximate methods for scale-up of semibatch-operated stirred-tank reactors with fast reactions and labile reactants/products must usually be used. Determination (identification) of design and operating variables or composites containing these variables to be held constant or changed in a prescribed manner to preserve constant yields is the essence of approximate scale-up procedures.

There are many parameters influencing the size-related performance of a reactor where feed mixing is important: concentrations of reactants, feed flow rate, feed pipe velocity, geometry and size of both reactor and stirrer, and stirrer rotational speed. The following remarks should be kept in mind when composing an experimental program for engineering studies:

- Concentration of reactants should be maintained as high as possible and kept constant upon scale-up;
- The feed flow rate must be changed in the experimental program; maintaining the flow rate of the smallest scale would lead to enormously long feed addition, and, consequently, low productivity, large size, and high cost of the reactor; moreover, some reaction systems need quenching to avoid or decrease undesired side reactions;
- Stirrer(s) of the type anticipated for the full-scale reactor should be used in engineering studies;
- The feed should be introduced into zones of the highest turbulence, *i.e.* near the tip of the stirrer at the plane of the agitator or slightly above this plane; the velocity of injected reactants should prevent backmixing of the reaction mixture into the feed pipe; if the addition time will be too long, consider a multi-injection system with nozzles located at different angular positions.

Three basic criteria have been widely used for the scale-up of stirred-tank reactors, *viz.* maintain: (1) equal speed at the impeller tip (tip speed, u_T), (2) equal blend time, and (3) equal power-to-volume ratio in the small reactor and the large reactor. The last criterion is highly impractical because it would lead to an enormous consumption of energy for large reactors. The first criterion implies that the rate of energy dissipated per unit volume decreases (P/V is proportional to $V^{1/3}$) while the second criterion involves an increase of this rate with increasing reactor size (P/V is proportional to $V^{2/3}$), but not as dramatically as in the third case. None of these criteria should be used *a priori* without investigations aiming at the determination of which factor controls reactor performance (τ_{99}, u_t, P/V, or others). To illustrate how rotational speed, tip speed, and blend time vary with tank size at constant power-to-volume ratio, consider geometrically similar stirred tanks as specified in Table 5.4-25.

The blend time increases significantly with reactor size. To keep the average energy dissipation constant one has to decrease the speed of rotation. However, as the stirrer diameter increases, the tip speed becomes greater despite the lower rotation speed. In this situation energy dissipated in the vicinity of the stirrer increases with reactor size.

Table 5.4-25

Scale-up comparison at constant P/V (four-bladed pitch turbine; $D_s/D_r = 0.5$; $H_r/D_r = 1.0$; $\rho = 1.0$ g/mL; $P/V = 2$ kW/m^3) (Fasano and Penney, 1991b).

Batch size, L	3.8	38	380	3800
D_r [m]	0.17	0.365	0.78	1.70
D_s [m]	0.085	0.183	0.39	0.85
N [rpm]	661	396	237	142
u_T [m/s]	0.94	1.21	1.54	2.01
Blend time [s]	3.0	5.0	8.3	13.8

Accordingly, the proportion between the maximum shear rate in the reactor and the minimum shear rate is greater in large reactors than in small reactors. Therefore, the location of the feed pipe in the region of the highest turbulence is more important in full-scale reactors than in small laboratory reactors. However, the high turbulence can cause backmixing of the reaction mixture from the reactor into the feeding pipe if no protective measures are taken (see Bourne *et al.*, 1981b). When backmixing occurs, reactions can proceed in the pipe under undesired process conditions (no mixing at all). Bourne *et al.* (1981b) suggested that backmixing occurs down to a u_f/u_T (ratio of the feed to the tip velocity) of about 0.14. Fasano *et al.* (1992) found that no backmixing occurs for a feed pipe located at the impeller discharge if u_f/u_T is greater than 0.2. Fasano and Penney (1991b) gave a more conservative rule according to which the velocity of the stream introduced in the vicinity of the impeller should be larger than half the tip speed to prevent backmixing and less than 12 m/s to prevent penetration of the feed jet through the impeller high-shear zone. Tipnis *et al.* (1994) recommended an even more conservative value of u_f/u_T equal to 0.6 or 1.2 for positions above the stirrer feed and radial feed, respectively. For other locations u_f/u_T may be smaller: for the feed located in the upper zone of the tank, the lower and the upper limits for the velocity ratio are 0.09 and 0.12, respectively. Detailed recommendations (after Jo *et al.*, 1994) concerning the ratio of u_f/u_T are given in Table 5.4-26 (see Fig. 5.4-52 for the meaning of symbols used in Table 5.4-26). A multi-injection system can have the form of a ring sparger (with four to six bottom orifices) located above the stirrer at the same distance as one nozzle.

The type of stirrer to be selected for an industrial reactor depends on the relationship between the rate of mixing and chemical reaction. A slow reaction can be carried out using any stirrer because mixing does not affect the overall rate of the process. Stirrers characterized by small energy consumption such as a propeller agitator or a high-efficiency turbine are recommended. If the process is controlled by mixing in the whole reaction zone, *i.e.* by the blend time, axial-flow agitators such as a propeller or pitched-blade turbine are preferred. For processes requiring high shear stresses and high velocity fluctuations, *i.e.* processes controlled by micromixing, a turbine is likely to be the best agitator. Paul (1988, 1990) recommended the use of a combined system of radial- and axial flow impellers.

Table 5.4-26

Recommended u_f/u_T for selected geometries for turbulent feed pipe flow conditions (after Jo *et al.*, 1994).

Impeller	Feed position	D_s/D_r	G/D_s	u_f/u_T
Six-blade pitched turbine	radial	0.53	0.1	1.9
	above turbine	0.53	0.55	0.25
Chemineer HE-3 turbine	radial	0.53	0.1	0.1
	above turbine	0.53	0.55	0.15

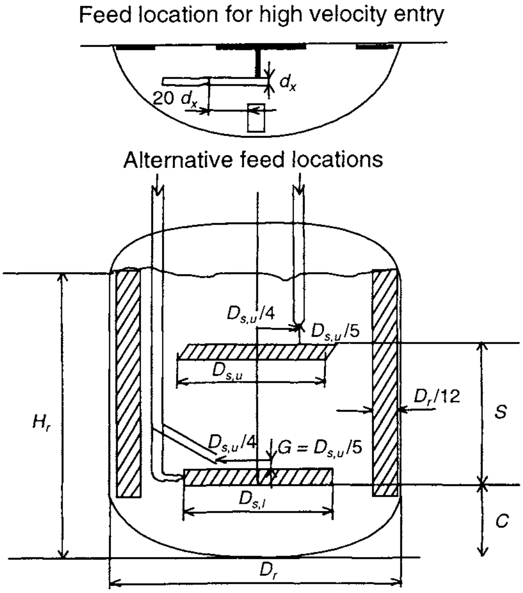

Figure 5.4-52. A system with an axial-flow turbine (upper stirrer) and a four-bladed flat turbine (lower stirrer) (adapted from Fasano and Penney, 1991b).

The recommended ranges for impeller dimensions are given in Table 5.4-27. A high-efficiency turbine or four-bladed flat turbine with D_s/D_r as advised in Table 5.4-27 and C/D_s equal to 0.75 seem to be the most versatile agitators in reactors for multiproduct plant.

If the feed time of a concentrated fluid is short the reaction will often be completed within the circulation zone, outside the impeller zone. Macromixing can then be important and the blend time will be an important scale-up parameter. For long feeding times and low concentrations in the feed all the important mixing processes could be completed almost immediately in the vicinity of the outlet of the feed pipe.

Table 5.4-27
Recommended geometry of dual impeller agitation system

	H_r/D_r	$D_{s,l}/D_r$	$D_{s,u}/D_r$	$S/D_{s,l}$	$S/D_{s,l}$	W_b/D_r	G/D_s
Small D_s/D_r	1	0.25	0.33	1.75	0.75	0.08	0.3
Large D_s/D_r	1	0.36	0.48	1.25	0.75	0.08	0.3

The intensity of mixing can be roughly considered to be proportional to the tip speed, which might then be successfully used as the scale-up parameter. Experimental procedures to determine the controlling scale factor for consecutive-competing reactions were proposed by Fasano and Penney (1991b) and modified later by Tipnis *et al.* (1994) to include parallel reactions. A test program for the reactor shown in Fig. 5.4-52 is given in Table 5.4-28. The blend times for a liquid with a density of 1000 kg/m^3 and a viscosity of 1 cP are also given in this table for illustrative purposes. The program should be completed with variation of the feed time if the reaction is to be carried out in a semibatch reactor.

Table 5.4-28
Test program for 4-litre laboratory reactor

N (rpm)	$D_{s,l}$ (cm)	$D_{s,l}/D_r$	$D_{s,u}$ (cm)	$D_{s,u}/D_r$	τ_{99}[a] (s)
100	4.3	0.25	5.7	0.33	22.6
200		0.25		0.33	11.3
300		0.25		0.33	7.5
400		0.25		0.33	5.66
600		0.25		0.33	3.77
800		0.25		0.33	2.83
100	7.7	0.45	10.3	0.60	5.86
200		0.45		0.60	2.93
300		0.45		0.60	1.95
400		0.45		0.60	1.47
600		0.45		0.60	0.948
800		0.45		0.60	0.73

[a] Blend time for two impellers evaluated as $1/(1/\tau_{99,l} + 1/\tau_{99,u})$.

The following conclusions can be drawn:

- If the feed time seems to be important, yields and selectivities for t_f = 1, 2, 4, 8, and 16 minutes at rotational speeds ranging from 200 to 800 rpm should be determined. A flat section on a plot of S_S versus t_f (which is different for low and high t_f's) indicates that scale-up at constant feed time is acceptable. For subsequent studies a t_f from the flat portion of the graph should be selected.
- The selectivity for various rotational speeds should be determined with stirrers of small and large D_s/D_r, while maintaining the other design and operating variables constant (see Table 5.4-26). Plots of yields of unwanted products S versus N, τ_{99}, and P/V_r should then be made for both stirrers to determine the independent parameter which best correlates the data for both stirrer systems.
- If yields/selectivities correlate reasonably with blend time, the blend time should be chosen as the scale-up criterion, *i.e.* the blend time corresponding to the smallest S_S should be preserved at scale-up. The blend time can be calculated using any of the literature correlations mentioned above. If an unreasonable or impractical stirrer size (2-4 kW/m^3 is a practical range for industrial reactors) is required to reach the desired blend time, a pump-around loop through a static mixer should be used to enhance mixing. Fasano and Penney (1991b) advised to determine the recirculation rate assuming that in-line mixing will give a 6-to-1 dilution at $(L/D)_{Static\ Mixer}$ equal to about 20. After calculation of the blend time for any geometric characteristics of the reactor using literature correlations, the yield of undesirable products can be evaluated from the aforementioned plot.
- If yields/selectivities for large agitators are significantly lower than those for small agitators, then S_S versus P/V_r or S_S versus tip speed u_T should be plotted. If the former plot correlates all data well, a criterion of constant power per unit volume might be appropriate for scale-up. If the latter graph is OK, the tip speed should be chosen as a scale-up criterion. Fasano and Penney (1991b) recommended that the tip speed should not be less than 12 m/s.

The design methods described above rely on correlations of the overall reactor average quantities obtained from experimental tanks of different scales. The most important deficiency of these methods is that local effects are not taken into consideration, while these might be responsible for the overall reactor performance. Accordingly, if none of the above scale-up criteria is found satisfactory (see e.g. data of Middleton *et al.*, 1986) a more fundamental approach must be applied, although not necessarily as complex as the one presented in Section 5.4.5.2. Such an approach was presented by Paul *et al.* (1971) who found that the yield of the desired intermediate in a system of consecutive reactions (iodination of *L*-tyrosine) correlates reasonably with fluctuations of the velocity, *u'*. So, these fluctuations could be chosen as a criterion for scale-up of the reactor. The average value for *u'* in the upper part of the tank was evaluated from:

$$u' = 0.581 \frac{N D_s^2}{(D_r^2 H_r)^{1/3}} \qquad \textbf{(5.4-191)}$$

while for the position of the feed line near the stirrer tip:

$$u' = 0.45 \pi N D_s \qquad \textbf{(5.4-192)}$$

When scaling up the reactor by maintaining *u'* constant, the yields of the intermediate were identical for the small and large scale. The use of this type of correlation requires, however, even approximate knowledge of the distribution of velocity fluctuations to which the distribution of energy dissipation over the reaction zone is related. This relation is given by Brodkey (1975):

$$\varepsilon = 3.68\frac{(u')^3}{L} \qquad \textbf{(5.4-193)}$$

One might then expect that the yield of the desired product would correlate well with the local rate of energy dissipation. Villermaux *et al.* (1994) studied a system of the following parallel competing reactions:

$$\mathrm{H_2BO_3^-} + \mathrm{H^+} \rightleftharpoons \mathrm{H_3BO_3} \qquad \textbf{(5.4-194)}$$

$$5\,\mathrm{I^-} + \mathrm{IO_3^-} + 6\,\mathrm{H^+} \rightleftharpoons 3\,\mathrm{I_2} + 3\,\mathrm{H_2O} \qquad \textbf{(5.4-195)}$$

$$\mathrm{I_2} + \mathrm{I^-} \rightleftharpoons \mathrm{I_3^-} \qquad \textbf{(5.4-196)}$$

in reactors of three different sizes. They found that the micromixedness ratio defined as:

$$\alpha = \frac{1 - X_S}{X_S} \qquad \textbf{(5.4-197)}$$

where S_S stands for I_3^- reasonably correlates with the local rate of energy dissipation.

Readers who are interested in problems of mixing in stirred tanks are referred to books and review papers of Dickey (1991, 1992), Dickey and Fenic (1976), Hicks *et al.* (1976), Nagata (1975), Oldshue (1983, 1985, 1986, 1992), Tatterson (1991, 1992), and Villermaux (1982, 1988).

5.4.5.5. Mixing in heterogeneous systems

Reviews on mechanically agitated reactors have been presented recently by Shah (1991) and Carpenter (1997). The latter discussed the construction of such reactors and the influence of design and operational parameters on the behaviour of the phases and possible interaction between them in detail.

Gas-liquid reactors. Carrà and Morbidelli (1987) compared a number of design parameters for various agitators in multiphase systems (see Table 5.4-29). Clearly, paddle mixers, anchor impellers, and helical mixers are not advisable in heterogeneous processes, which predominate in fine chemicals manufacture. The most commonly used stirrer for gas-liquid operations is the six-blade flat turbine. A stirrer of diameter given by the ratio $D_s/D_r = 0.4\text{-}0.5$ and installed at the distance given by the ratio $H_{i,s}/D_r$ is recommended. Four 90° baffles of $D_r/12$ in width should be installed to improve gas-liquid dispersion. Agitation causes rotational motion of the liquid and vortex formation. At a higher critical speed the vortex can reach the stirrer and cause the gas above the liquid to be entrapped by the liquid. Vortex formation is highly undesirable since it results in very high mechanical stresses on the stirrer shaft, bearings, and seal. In two-phase systems it results in inefficient mixing.

Table 5.4-29
Qualitative comparison of a number of design parameters for various agitators in multiphase systems; $u_{G,max}$ and $\mu_{G,max}$ are the maximum allowable agitator tip velocity and liquid viscosity, respectively

Stirrer design	D_s/D_r	$u_{G,max}$ (m/s)	$\mu_{G,max}$ (Pa s)	Baffled	Heat transfer		Gas-liquid dispersion	Liquid-solid dispersion
					Wall	Coil		
Propeller	0.15-0.4	15	5	yes	gg	g	gg	gg
Disk flat-blade Turbine	0.2-0.45	15	10	yes	gg	g	gg	g
Pitched-blade turbine	0.2-0.45	12	20	yes	gg	gg	gg	gg
Impeller	0.5-0.7	12	20	yes	gg	-	g	g
Paddle mixer	0.4-0.5	5	50	yes	gg	gg	g	bg
Anchor impeller	0.9-0.98	5	50	no	gg	-	g	bg
Helical mixer	0.9-0.98	1	1000	no	gg	-	-	-

Key: gg: highly suitable; g: suitable; bg: conditionally suitable

The intensity of mixing in gas-liquid systems, given by the product of rotational speed and mixing time $N\tau_M$, is mainly dependent on the geometrical characteristics of the stirrer and the reactor and can be expressed as:

$$N\tau_M \sim \left(\frac{D_r}{D_s}\right)^{\beta} \qquad \textbf{(5.4-198)}$$

where the coefficient β varies from 2 to 2.57 for flat-blade turbines and equals 2 for propellers. The other geometric parameters such as a baffle size and location, distance between the stirrer and the reactor bottom, height of the liquid, etc, and the rotational speed influence the intensity of mixing too. These design/operational parameters also affect the hydrodynamics, gas hold-up, mass-transfer coefficients, etc. Many correlations can be found in the literature (see e.g. Shah, 1992). Those correlations are, however, not valid for highly viscous liquids, particularly viscoelastic and non-Newtonian liquids.

For dead-end operations, complete consumption of the solute gas is necessary (e.g. hydrogenations using pure hydrogen). Entrapping of the gas is then advantageous. In these cases, reactors with a high aspect ratio (height/diameter ratio) are used that are equipped with a multistirrer system with the highest agitator entrapping the gas.

A gas-inducing agitator system is an alternative to a multistirrer system. It contains a hollow shaft with orifices above the liquid level and a hollow impeller. A typical hollow impeller consists of a tube that is, at the centre, connected to the hollow shaft. Both ends of the impeller are cut at 45° so that, at rotation, the open portions of the tube are at the near side of the stirrer. There are several modifications of this design. Obviously, there is a minimum impeller speed at which the onset of gas induction occurs. Loop reactors are also successfully used.

Slurry reactors. For three-phase systems the definition of conditions at which (catalyst) particles are in motion is important. Two limiting states with respect to particle behaviour can be distinguished: (1) 'complete' suspension, *i.e.* all particles just move, and (2) uniform suspension, *i.e.* the particles are evenly distributed over the whole reaction zone. The power required to reach the second state is much higher, while uniform suspension is not often necessary. Circulation of the liquid with the dissolved gas is usually sufficiently fast to provide reactants to the surface of catalyst particles if they are suspended at all.

The presence of a gas in the suspension results in an increase of the stirrer speed required to establish the state of 'complete' suspension. The propeller usually requires a higher speed than the turbine. Furthermore, a critical volume gas flow exists above which drastic sedimentation of particles occurs. Hence, homogenisation of the suspension requires an increase of the rotational speed and/or a decrease of the gas flow rate. The hydrodynamics of suspensions with a solid fraction exceeding 0.25-0.3 becomes very complex because such suspensions behave like non-Newtonian liquids. This produces problems in the scale-up of operations. Hydrodynamics, gas hold-up, mass-transfer coefficients, etc. have been widely studied and many correlations can be found in literature (see e.g. Shah, 1991).

Multistirrer systems operate better than single mixers whereby efficiency of cross-beam stirrers (beam angle $\alpha < 45^{\circ}$) is particularly high. Multi-sparger systems enhance the effectiveness of a reactor. Perforated rings are usually used as gas spargers. Gas-inducing impellers have been proposed also for use in slurry reactors. However, they proved to be effective only in small installations. They operate much worse in case of a large height of the liquid above the stirrer, which is the case in large reactors.

Liquid-liquid reactors. A system consisting of immiscible liquids will only be considered here. Systems with an interfacial surface governed by the presence of surfactants (emulsification) are out of the scope of the present considerations. There is a minimum speed of rotation at which droplets of one liquid are formed in the second liquid. The droplets continuously coalesce into larger ones. A steady state can be established when the rates of both processes become equal. In chemical reactors, the situation changes continuously since physical properties of the reaction mixture vary with the progress of reaction. Therefore, dispersion processes in reaction systems are difficult to scale-up. It can be safely assumed that the interfacial area remains unaltered at turbulent mixing if the power per unit volume in a small-scale and a large-scale reactor is the same. In fact, the power consumption per unit volume needed for complete dispersion can be achieved at lower cost. It depends upon the geometry of the system:

$$\frac{P}{V} \sim \left(\frac{D_r}{D_s}\right)^{\alpha} D_r^{-1.3} \qquad \textbf{(5.4-199)}$$

where the value of α varies from -0.85 to 3.17, depending on the stirrer type and its position in the tank. Interfacial mass transport not only strongly depends on the interfacial area but also on the interfacial tension, and the viscosity and density of both liquids. The interfacial tension often changes unexpectedly throughout the reaction and this makes scale-up difficult. Predictions are also difficult if one liquid is viscoelastic or Non-Newtonian.

5.4.6. Safety in design and analysis of chemical reactors

5.4.6.1. Introduction

The underestimation of hazards in batch processing as well as lack of kinetic and thermal characteristics of processes has caused many incidents. According to Rasmussen (1987, 1988) 57% of all incidents in the chemical process industries originated from batch processes and 24% from storage, which can be considered batch or semibatch operation as well. 34% of those incidents were classified as resulting from insufficient information about the process, 32% from design errors and 24% from a poor or deficient process concept. Barton and Nolan (1984, 1987, 1991) have analysed industrial incidents in batch processing that occurred in the UK during the period 1962-87 and were brought to the attention of the Health and Safety Executive. Principal unit operations were involved but the largest proportion was attributed to polymerizations (particularly phenol-formaldehyde polycondensations), nitrations, and sulphonations. Other reactions featuring were Grignard reagent preparation, alkylation using Friedel-Crafts synthesis, amination, diazotisation, halogenation (chlorination and bromination), hydrolysis, oxidation, and neutralization. A significant proportion of accidents was due to uncontrolled temperature excursions. In fact, the primary reason of these accidents was the lack of knowledge of reaction chemistry, thermokinetics of main and potential side reactions, and physical properties of reactants, intermediates, and products. A study by Brogli (1982) shows that within the Ciba-Geigy group, during the period 1971-1980, 56% of the incidents leading to temperature excursions or near excursion situations were directly related to the actual, intended plant reactions. Also in these cases, there were significant deficiencies in knowledge of those processes.

5.4.6.2. Hazards from chemical structure and reactivity of compounds

The hazards associated with the operation of chemical reactors can originate from the following main areas:

- uncontrolled chemical reactions (chemical reaction hazards),
- ignition of flammable atmospheres (operational hazards),
- emissions of materials that are dangerous to people and the surroundings (health hazards).

Only the first group will be considered in this section. Operational hazards are discussed in much detail by Rogers (1997). Hazards associated with emissions and handling of harmful (toxic) materials can be assessed based upon information about toxicity. This can be found in many books and handbooks, see e.g. *The Sigma-Aldrich Library of Regulatory and Safety Data* (Lengma and Votoupal, 1993). The following essential stages in hazard assessment can be distinguished:

- characterization of materials,
- identification of hazard sources,
- assessment of the risk in the process under consideration,
- determination of safety measures that are most appropriate for the process.

Chemical structure and reactivity. A wide variety of chemicals exist that are thermodynamically unstable. These chemicals easily react, usually with a large heat effect. Most of these chemicals can undergo violent self-reaction or decomposition initialized by mechanical shock, friction, or heat. An incomplete list of dangerously reactive groups is given below:

- $-NO_2$ (nitro), -O-NO (nitrite), -NO (nitroso), and $-O-NO_2$ (nitrate ester) connected to organic or inorganic radicals, e.g. HNO_3, $-C(NO_2)$, $-C_6H_3(NO_2)_2$;
- -N=N- (diazo), $-N=N^+=N^-$- (azide) and -N≡N- connected to inorganic or organic radicals, e.g. PbN_6, CH_3N_3;
- =N-Cl (N-chloroamine), $-NX_2$, e.g. NCl_3, $R-NCl_2$;
- -O-N=C (fulminate), =C=N-, e.g. HONC, $Hg(ONC)_2$;
- -O-Cl (hypohalite), $-ClO_3$ (chlorate), $-ClO_4$ (perchlorate), $-OClO_2$ and $-OClO_4$ connected to inorganic or organic radicals;
- -O-O-H (hydroperoxide), ozonides, -C(O)-O-O-H peracids, -O-O- (peroxide), and -O-O-O- connected to inorganic or organic radicals;
- -C≡C- (acetylide), e.g. acetylene, acetylenic compounds, and metallic derivates;
- metal atom connected by an unstable bond to carbon or to certain organic radicals, e.g. organic compounds of mercury, thallium and lead.

Thermodynamic instability is related to a positive heat of formation. Compounds with a positive heat of formation are termed endothermic. This group of materials has an inherent tendency to spontaneous decomposition. Some common structural features of endothermic compounds are: (1) relatively high degree of unsaturation, (2) high proportion or high local concentration of nitrogen in the molecular structure, and (3) nitrogen to halogen bonds. Bretherick (1990) reported examples of hazardous endothermic compounds, see Table 5.4-30.

The internal energy is generally close to enthalpy of formation. As such it can also be a measure of the instability of compounds. The range of values of the change in internal energy by decomposition of some characteristically unstable types of compounds are given in Table 5.4-31 (Grewer and Klais, 1988). More data on decomposition energies can be found in books of Bretherick (1990) and Grewer (1994).

Hazards associated with chemical reactions depend on the energy that can evolve in the course of reaction. The chemical reaction energy is categorized in Table 5.4-32 (based on data of Hoffman, 1985, and Rogers, 1997).

Table 5.4-30
Structure and enthalpies of formation of endothermic compounds

Compound	Structure	ΔH^0_f [kJ/mol]	[kJ/g]
Cyanogen	N≡C-C≡N	308	5.9
Benzotriazole	$C_6H_4NHN=N$	250	2.1
Acetylene	HC≡CH	227	8.7
Allene	$H_2C=C=CH_2$	192	4.8
Diazomethane	H_2CN_2	192	4.6
Hydrogen cyanide	HC≡N	130	4.8
Butadiene	$H_2C=CH-CH=CH_2$	112	21.1
Nitrogen trichloride	NCl_3	230	1.9

Table 5.4-31
Unstable group decomposition energies

Compounds	Molecular grouping	Range of $-\Delta U$ values [kJ/mol]
Aromatic nitro	$-C-NO_2$	220 - 410
Aromatic nitroso	-C-N=O	90 - 290
Oxime	-C=N-OH	110 - 170
Isocyanate	-C-N=C=O	50 - 55
Aromatic azo	-C-N=N-C	100 - 180
Hydrazo	-C-NH-NH-C	65 - 80
Aromatic diazonium	$-C-N_2^+$	130 - 165
Peroxide	-C-O-O-	200 - 340
Epoxide	$-CH-CH_2-O$	65 - 100
Olefin	-C=C-	40 - 90

Explosibility screening. In the literature an extensive collection of explosion properties of chemical compounds can be found. However, if literature is unavailable or properties have not been examined yet, a number of initial screening techniques exist. If the checks for explosibility of the starting materials, intermediates, or products reveal a great hazard from deflagration or detonation, it is advisable to abandon the process.

The *oxygen balance* of an organic compound is a guide to its propensity to decompose, deflagrate, or detonate using only the oxygen contained in the molecule. The oxygen balance is a useful concept for compounds containing oxidizing groups. If a molecule $C_xH_yO_z$ reacts completely with oxygen according to the stochiometric equation:

$$C_xH_yO_z + (x+y/4-z/2)\,O_2 \rightarrow xCO_2 + y/2\,H_2O \qquad \textbf{(5.4-200)}$$

the oxygen balance is

$$-3200\,(x+y/4-z/2)/(\text{molecular weight}) \qquad \textbf{(5.4-201)}$$

Nearly all recognized detonating explosives have oxygen balances between -100 and +40. Any substance with an oxygen balance higher than -200 should be treated as potentially dangerous and explosibility testing for these compounds should be carried out.

Average bond energy summation. The approximate heat of reaction (decomposition) can be predicted from the difference between the sums of bond energies of the reactants and the assumed products. The approximate heat of reaction can also be predicted from the difference in heats of formation of the products and the reactants. The energy produced per mole of reactant is the sum of energies of the products minus the sum of energies of the reactants. The bond energies and heats of formation of many compounds can be found in literature, e.g. *Handbook of chemistry and physics* (Weast, 1990) and *Lange's Handbook of Chemistry* (Dean, 1992), or estimated using methods described by Reid *et al.* (1989).

Table 5.4-32
Chemical reaction energy categorization

Process	Energy		Chemical hazard potential
	High, medium, or low	Typical ΔH_r [kJ/mol]	
Oxidation	Highly exothermic Equilibrium favoured	-1000 (combustion)	High
Nitration	Exothermic Potential oxidation	-150	High
Reduction	Low	-80	Low
Halogenation	Higly exothermic chain reaction for chlorine and fluorine		High
Sulphonation	Moderately exothermic	-100	Low
Hydrolysis	Mildly exothermic		Low
Polymerization	Can be highly exothermic	-70	Moderate to high
Condensation	Moderately exothermic		Low to moderate
Hydrogenation	Moderately to highly exothermic	-300	Moderate to low
Alkylation	Mildly exothermic, side reactions generally a problem		Low
Organo-metallic	Highly exothermic		High
Amination	Moderately exothermic		Low
Diazotization	Moderately exothermic	-65	Low
Epoxidation	Moderately exothermic	-95	Low
Amination	Moderately exothermic	-120	Moderate
Neutralization	Moderately exothermic	-50 (per H^+)	Low
Diazo decomposition	Exothermic	-140	Moderate to high
Nitro decomposition	Exothermic	-400	High

Example 5.4.6.1. Heat of hydrazine oxidation.
Calculate the heat of oxidation of hydrazine in the gas phase:

$$H_2NNH_2 + 3\ O_2 \rightarrow 2\ H_2O + 2\ NO_2 \tag{5.4-202}$$

Use the data on bond energies. The bond energies for the compounds taking part in the reaction are given in Table 5.4-33.

The heat of this reaction is $4 \cdot 498 + 4 \cdot 305 - 3 \cdot 498.36 - 4 \cdot 366.1 - 275.3$, i.e. 7.22 kJ/mol. The heat of reaction is positive, *i.e.* the reaction enthalpy is negative, so the reaction is slightly exothermic.

Table 5.4-33
Bond energies

Bond	Bond energy at 298K [kJ/mol]
$H\text{-}HNNH_2$	366.1
$H_2N\text{-}NH_2$	275.3
H-OH	498±4
O-NO	305
O-O	498.36±0.17

Example 5.4.6.2. Heat of benzene oxidation.
Calculate heat of oxidation of benzene in the gas phase:

$$C_6H_6 + 15/2\ O_2 \rightarrow 3\ H_2O + 6\ CO_2 \qquad \textbf{(5.4-203)}$$

Use the data on standard enthalpies of formation (see Table 5.4-34).

The sum of the enthalpies of the gaseous products minus the sum for the reactants at room temperature is 6·(-393.5) + 3·(-241.8) -82.6, is -3169 kJ/mol. The complete oxidation of benzene is strongly exothermic.

Table 5.4-34
Standard enthalpies of formation; all compounds are in the gas phase at 298 K

Compound	Molecular formula	ΔH^0_f (298K) [kJ/mol]
Benzene	C_6H_6	82.6
Carbon dioxide	CO_2	-393.5
Water	H_2O	-241.8
Oxygen	O_2	0

Computer methods. There are many computer programs that are able to estimate hazard potential by calculating the equilibrium products and the theoretical heat release of decomposition and combustion reactions. The most often used program is the Chemical Thermodynamic and Energy Release Evaluation program, usually referred to as CHETAH (Davies *et al.*, 1984, Cardillo, 1991). CHETAH has been developed by the American Society for Testing and Materials (ASTM). It is a useful tool for preliminary screening of the reactivity of organic compounds and some inorganic compounds.

Potentially hazardous reactions. Bretherick (1990) used a few general types of potentially hazardous reactions to classify the majority of exothermic reactions involving two or more components. By far the most common type is that involving an oxidant and an oxidizable material. The most common oxidant is air. Some materials will react so rapidly with air that ignition occurs spontaneously. Finely divided metals or metal hydrides, or fully alkylated metals and non-metals are examples of such pyrophoric compounds. Also, very slow oxidation reactions may lead to insidious hazards if susceptible materials become converted into peroxides, which may decompose violently a long time after exposure to air. Typical structures susceptible to auto-oxidation (slow formation of a peroxide) are the following: -O-C-H (in ethers, cyclic ethers, and acetals), -CMe_2-H (*iso*propyl derivatives), -C=C-C-H (allyl compounds), -C=C-H (vinyl compounds, dienes), $PhMe_2$-H (cumene), and PhCH=C-H_2 (styrene). The initially formed hydroperoxide subsequently undergoes further reactions under formation of explosively unstable peroxidic products. Besides air, the most common oxidant is nitric acid, exceptional in that it will oxidize materials even as a cold and dilute aqueous solution. It almost invariable evolves gaseous oxidation products that may lead to pressure development. Other common industrial oxidants include ozone, hot sulphuric acid, hydrogen peroxide, nitrates, nitrites, permanganates, and chlorine. Incompatibility of some compounds must also be considered in the choice of manufacturing procedures.

Reduction reactions are perhaps the second most common type of potentially hazardous reactions. Materials such as metallic sodium, aluminium, and magnesium; hydrazine; diborane; sodium hydride; and hydrogen have all been involved in a wide variety of chemical accidents.

Reactions or compounds of exceptional hazard are those involving combinations of powerful oxidants and reducing agents, in the so-called redox reactions or redox compounds. Such systems are capable of very large energy release rates, the best known examples being the propellant pairs used in rocket technology.

A final group of reactions are those involving water. A wide variety of materials such as the alkali metals; light metals and their hydrides; strong acids, such as sulphuric acid; anhydrous metal oxides; anhydrous metal halides; and non-metal oxides all react vigorously or violently with water under various circumstances.

All the data on health and fire/explosion hazards for compounds and (if possible) mixtures to be dealt with in a process should be collected in the form of an *MSDS* (Material Safety Data Sheet). It is common practice for users to require that suppliers attach an *MSDS* to all batches of materials delivered.

5.4.6.3. Analysis of chemical reaction hazards

As mentioned before, the vast majority of accidents in batch processing arise when the control of the temperature of the reaction mixture is lost. This situation often leads to a *temperature* (*thermal*) *runaway*, *i.e.* a temperature overshoot that can result in undesired reactions (decompositions), evaporation, or gas formation. As a consequence, pressure is built up inside a reactor and this can cause an explosion. The explosion is usually accompanied by damage to the equipment and release of hazardous (toxic, explosive, or flammable) species to the surroundings.

Risk analysis. The risk of accidents can be assessed in terms of two factors: *severity* and *probability* of the accident. Severity is high if consequences of the accident to employees, the public, the environment, and the plant are significant. Severity is related to the amount and properties of hazardous (toxic, flammable, explosive) substances that can escape to the surroundings during the accident, and to the energy that is released during the accident. Probability is associated with the likelihood of the occurrence of unwanted chains of events and the time of development of undesired events starting from the disturbance. If the time required to undertake corrective actions is short compared to the time of developing an unwanted event, the probability is small. Stoessel (1993) has proposed simple ciriteria to assess the severity and probability of an accident (see Table 5.4-35).

Table 5.4-35
Criteria for severity and probability

Criterion	Severity	Probability
High	$\Delta T_{ad} > 200$ K or T_b surpassed	$TMR_{ad}{}^{a} < 8$ h $8 < TMR_{ad} < 24$ h
Medium	$50\text{ K} < \Delta T_{ad} < 200$ K	
Low	$\Delta T_{ad} < 50$ K	$TMR_{ad} > 24$ h

[a] TMR_{ad}: time to reach maximum reaction rate under adiabatic conditions.

Regions of high and low risk are shown in Fig. 5.4-53. If both probability and severity are high, the risk is always high. A combination of even very low probability with high severity is usually considered to be a high risk. Consequently, it is more important to search for a design that decreases the severity than the probability of an accident. Measures should always be taken to move from the high-risk region to the low-risk region.

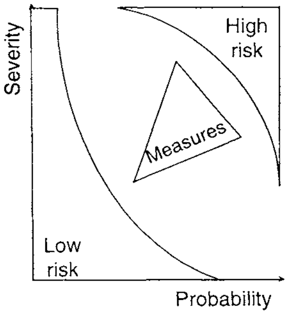

Figure 5.4-53. Risk regions.

Runaway scenario. Regenass (1984 b) presented perhaps the most complete scheme of possible runaway scenarios (see Fig. 5.4-54, after Regenass, 1984b). There can also be other reasons for accidents that, in fact, are related to those specified by Regenass: (1) other mechanical problems (leaking valves in the cooling system, failure of auxiliary equipment, breakthrough of reactive heat-transfer fluid), (2) problems with temperature (failure of control system, incorrect temperature setting, wrong position of sensors, too much delayed sensor's response by, e.g. deposits on sensors, sensor failure, too rapid heating upon reaction initiation), (3) inadequate cooling (maldesign, intentional stoppage of the agitator for sampling and analysis, too late switch onto cooling, faulty condenser, pump failure), (4) incorrect charging (too much, too little, or omission of a component of the reaction mixture, contamination of the feed, charging at wrong temperature, wrong sequence of addition), and (5) inadequate agitation (wrong choice of stirrer, too low rate of stirring, shut off due to power failure). The danger of a thermal runaway will always exist if: (1) the capacity of heat removal facilities is much lower than the potential heat generation rates, and (2) accumulation of exothermically reacting species takes place in a reactor. Chemical reaction hazards and causes of accidents have been discussed by Barton and Nolan (1984, 1987, 1991), Hofmann (1985), van Roekel (1985), Marrs *et al.* (1989), and Nolan (1991).

Usually, experience of the past is used as the basis of failure scenarios, whereas one should look at a process each time again as if all unexpected events could occur. One has to keep in mind that accidents are often due to the highly unlikely coincidence or complex casual chains that seem improbable. It is necessary to examine all failure modes for all possible design alternatives in order to decrease the probability of an incident.

A '*100 Degree Rule*' was often used in the past throughout the chemical industry to assess whether an accident would occur. According to this rule, if the operating temperature of a process is 100 °C away from the nearest detectable exotherm observed in a *DSC* (*D*ifferential *S*canning *C*alorimetry) experiment the operation will not experience this thermal event. In such a case no more detailed information on hazards need be searched for. The 100 °C degree rule is, however, often far from the safety margin: The use of this rule was the reason of many accidents.

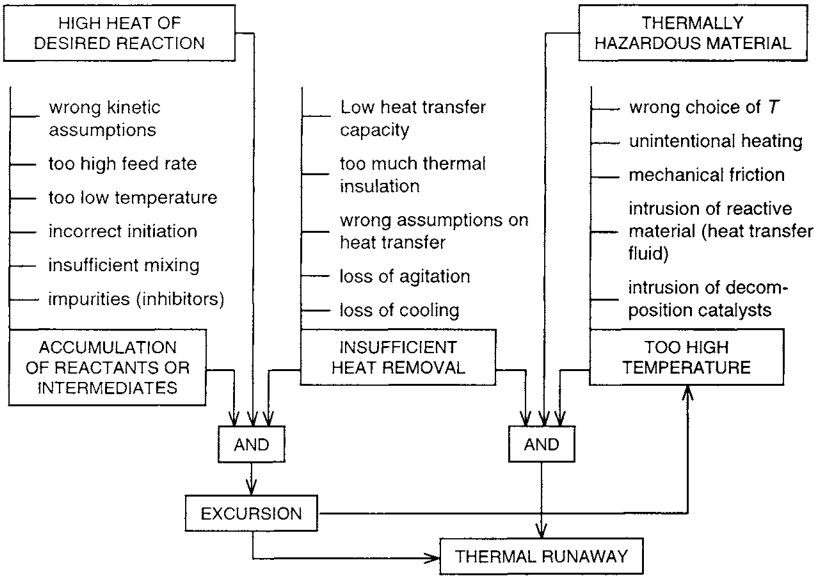

Figure 5.4-54. Causes of thermal runaways (adapted from Regenass, 1984b).

In order to develop the safest process the worst runaway scenario must be worked out. This scenario is a sequence of events that can cause the temperature runaway with the worst possible consequences. Typically, the runaway starts with failure that results in an adiabatic course of exothermic reaction, inducing secondary reactions that proceed with a high thermal effect. Such a sequence of typical events is shown in Fig. 5.4-55 (after Gygax, 1988-1990; Stoessel, 1993). It starts with, for instance, a cooling failure at time t_x when the temperature is at the set level, T_{set}. Then the temperature rises up to the Maximum Temperature for Synthetic Reaction (*MTSR*) within the time Δt_R. Assuming adiabatic conditions: $MTSR = T_{set} + \Delta T_{ad,R}$ where $\Delta T_{ad,R}$ is the adiabatic temperature rise due to the desired reaction for the amount of reactants that have been accumulated in the reactor by the time t_x. If the *MTSR* exceeds the onset temperature of the undesired secondary reaction, additional heat is generated due to this reaction. Within the time Δt_{Dec} the temperature rises to $T_{max} = MTSR + \Delta T_{ad,Dec}$. If T_{max} is greater than the permitted temperature, an accident will occur. Among undesired reactions the following groups of reactions can be distinguished: (1) decomposition reactions, (2) polymerization reactions, (3) undesired reactions caused by catalytic effects, (4) secondary reactions caused by contamination with heating or cooling media or air, and (5) side reactions that are within a network of reactions leading to the desired product.

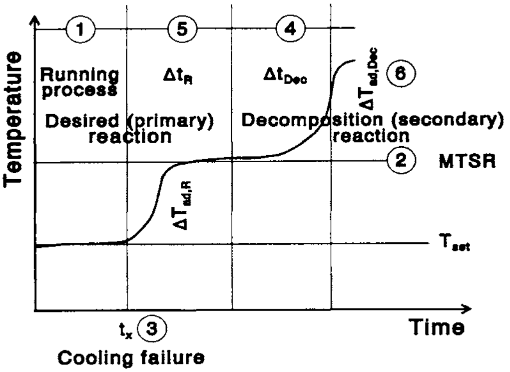

Figure 5.4-55. A typical runaway scenario (adapted from Gygax, 1988-1990).

Grewer *et al.* (1989) formulated a set of criteria for risk assessment (see Fig. 5.4-56) that are related to scenarios like that described above:

1. Case 1: if $T_S > T_{max}$ $(= T_R + \Delta T_{ad})$ the process is safe.
2. Case 2: the process is safe if the heat of the secondary reaction is small (< 100-200 kJ/kg).
3. Case 2: if $T_R < T_S < T_{max}$ a considerable hazard can appear. The temperature should be maintained below T_S.
4. Case 3: if $T_S < T_R$ and $\Delta T_{ad} < 50$ K the process can be run safely.
5. Case 3: if $T_S < T_R$ and $\Delta T_{ad} >> 50$ K the process can be dangerous even at laboratory conditions.

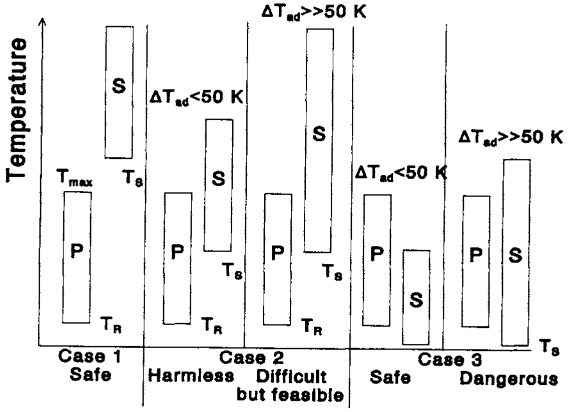

Figure 5.4-56. Approximate criteria for risk assessment (P: primary reaction; S: secondary reaction) (adapted from Grewer *et al.*, 1989).

Another list of approximate criteria for criticality in runaway scenarios was formulated by Stoessel (1993), see Table 5.4-36.

5.4.6.4. Experimental techniques for acquisition of data needed for runaway evaluation

The typical runaway scenario as illustrated in Fig. 5.4-55 shows that the following data are needed to determine what would happen if this scenario materialized (reference is made by numbers in circles in the figure):

- the rate of heat generation as a function of time [$Q_R(t)$] at operating conditions; this is necessary to assess whether cooling facilities can cope with it during a standard,
- the temperature that will be reached in result of a runaway of the desired process (*MTSR*) assuming adiabatic conditions,
- the most critical instant t_x for a cooling failure for which *MTSR* is maximal,
- the time to develop a runaway due to a secondary reaction starting with the initial temperature T_0 set equal to *MTSR*, $\Delta t_{Dec}(T_0)$,
- the time to reach *MTSR*, $\Delta t_R(T_{set}, t_x)$,
- the adiabatic temperature rise for the secondary reaction, $\Delta T_{ad,Dec}$.

All these necessary data can be obtained from the primary physicochemical data listed below:

- heat of primary and secondary reactions,
- heat capacity and other heat-transfer properties of the reaction mixture,
- adiabatic temperature rise for all reactions ΔT_{ad},
- mixture formed at runaway conditions and released to the surroundings upon a runaway,
- onset temperatures of all reactions occurring in the system,
- reaction kinetics (at least macro-kinetics, kinetic equations, time to develop adiabatic runaway, autocatalysis) of all reactions,
- effect of mixing conditions on the course of the process,
- factors affecting accumulation: degree of accumulation at operating conditions, sensitivity of accumulation to variations in process conditions and scale,

Table 5.4-36
Approximate criteria for criticality in runaway scenarios; T_b = boiling point

Situation when temperature control is lost	Countermeasures
Neither T_b is reached nor decomposition can be triggered. The process is thermally safe.	No special measures are required but the reaction mixture should not be held under heat accumulation conditions for longer time.
Neither T_b is reached nor decomposition can be triggered. If the reaction mass is maintained under heat accumulation conditions T_b can be reached or decomposition can start. Hazard if T_b is high. At normal process conditions the process is thermally safe.	No special measures are required but the reaction mixture should not be held under heat accumulation conditions for longer time. Evaporative cooling should be considered.
T_b is reached but decomposition cannot be triggered. Process safety depends on the rate $Q_{R,bp}$.	Evaporative cooling to maintain the reaction mass under control. Dumping (dump-tanks as safe discharging areas) of the reaction mass or quenching (thermal inhibitors) can be used.
T_b is reached and decomposition can be triggered. Process safety depends on both rates, $Q_{R,bp}$ and $Q_{Dec,bp}$.	Similar to the above class but the additional heat release rate due to the secondary reaction has to be taken into account.
Decomposition will be triggered and T_b reached during a runaway of the decomposition reaction. The rate $Q_{Dec,bp}$ determines the thermal safety of the process.	Evaporative cooling is very unlikely to be a safety barrier. Only dumping or quenching can be used. Reduce concentrations, optimize operating conditions in order to minimize accumulation, change to continuous operation, etc.

- rates of heat evolution (rate of reaction multiplied by its thermal effect) and heat removal (heat-transfer coefficients, heat-dissipation capacity),
- rate of gas evolution (rate of pressure build-up), total quantity of the gas evolved, and vapour-pressure data,
- boiling points,
- mass, toxicity, and flammability/explosivity of materials present in the reaction mixture,
- effects of impurities, materials of construction, ageing, mischarging, and other errors.

If a reliable kinetic model and data on cooling capacity are at hand, runaway scenarios can be examined by computer simulations and only final findings have to be tested experimentally. Such an approach has been presented, e.g. by Zaldivar *et al.* (1992). However, the detailed reaction mechanism and reaction kinetics are rarely known. Therefore, thermokinetic methods with gross (macro-)kinetics dominate among methods for data acquisition. The most useful thermal methods include Differential Thermal Analysis (*DTA*), Differential Scanning Calorimetry (*DSC*), Adiabatic Calorimetry (*Dewar* Calorimeter), Accelerating Rate Calorimetry (*ARC*), and Reaction Calorimetry (*RC*). Differential Thermal Analysis and Differential Scanning Calorimetry belong to the temperature-programmed techniques. Both methods can also be used for isothermal measurements. An extensive treatment of experimental techniques can be found in the review papers and books by Grewer (1987), Hoeflich (1989), Benuzzi and Zaldivar (1991), Barton and Rogers (1993), Grewer (1994), and Cardillo (1991).

Temperature-programmed techniques. DTA and *DSC* consist in that a sample of the material and a reference sample are placed in an oven in which the temperature is constant or programmable (linearly increasing). Small samples (about 5-10 milligrams) are studied. Therefore, even the most energetic material can be examined in the laboratory without any danger of explosion. Depending on the aim of the investigation and nature of the sample studied, the measurements are performed in an open system (in air or under an inert gas), or in a closed system under pressure produced by the sample alone or exerted from outside. Metal closed cups are often used for experiments under elevated pressure. A reusable closed cup is equipped with a Teflon 'rupture disk' seal that can usually withstand a pressure of approximately 30 bar. The heating rate typically ranges from 0.2 to 20 K/min whereby the final temperature typically is 300 ^{o}C. Tests are usually done within a short time, typically one hour. These techniques provide information about the temperature range in which the thermal effects are located and about the temperatures where pronounced exothermicity is revealed.

Differential Thermal Analysis. A sample and inert reference sample are heated in an oven and the temperature difference between them is recorded. Typical results of a *DTA* analysis are shown in Fig. 5.4-57 (Grewer, 1994). This experiment can be used to determine the onset temperature for a decomposition reaction $T_{onset,Dec}$. Isothermal *DTA* diagrams (see Fig. 5.4-58, (Grewer, 1994)) can be used as a source of kinetic information. Temperature peaks characteristic for exothermic reactions appear earlier and are higher when increasing the temperature of the oven. This is due to the faster reaction, and, accordingly, the higher rate of heat production at higher temperatures. An isothermal *DTA* run can provide very important information, namely the Time to the Maximum Rate (*i.e.* the one at the peak temperature) or isothermal induction time, $TMR_{isotherm}$ (or t_{ind}).

Differential Scanning Calorimetry. A sample and an inert reference sample are heated separately so that they are thermally balanced, and the difference in energy input to the samples to keep them at the same temperature is recorded. Similarly to *DTA* analysis, *DSC* experiments can also be carried out isothermally. Data on heat generation rates within a short period of time are obtained. Experimental curves from *DSC* runs are similar in shape to *DTA* curves. The results are more accurate than those from *DTA* as far as the $TMR_{isotherm}$ is concerned.

The heat of reaction is estimated by integrating the area below the rate of heat generation curve:

$$(-\Delta H)=\frac{1}{m}\int_{t_{onset}}^{t_{final}} q_P(t)dt \qquad \textbf{(5.4-204)}$$

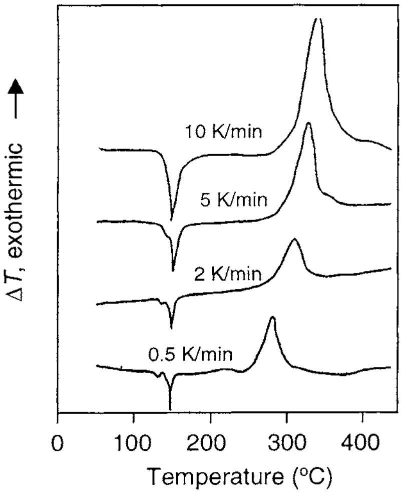

Figure 5.4-57. Programmable *DTA* plots for various heating rates: 4-nitrobenzoic acid (reprinted from Grewer (1994), 'Thermal hazards of chemical reactions', Copyright (1994) with permission from Elsevier Science).

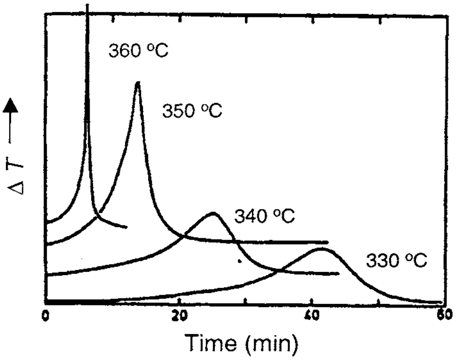

Figure 5.4-58. Isothermal DTA runs for 4-nitrobenzoic acid ((reprinted from Grewer (1994), 'Thermal hazards of chemical reactions', Copyright (1994) with permission from Elsevier Science).

where m is the mass of the sample. Data on the rate of heat evolution are determined for different reaction extensions and different temperatures of the samples. When it is desired to determine the rates of heat generation at high accuracy, lower heating rates must be applied than in screening runs. The data on the rates of heat generation may not be directly applied for the scale-up of reactors. The rates observed at non-adiabatic conditions are lower than those at a large scale, where near adiabatic conditions can be expected in case of failure of the cooling system. The results should be examined to determine whether the observations are affected by the material of the analytical instrument or of the reactor considered for industrial application.

'Arrhenius graphs' can be produced from thermal data obtained for constant heating rates (see Fig. 5.4-59, after Grewer and Klais, 1988). Plotting the heating rate, ln(w), versus the reciprocal of the peak temperature, T_{max}, a straight line should be obtained. The observed (or apparent) activation energy of decomposition can be estimated from the line:

$$E_{obs} = -R_g \frac{d\ln(w)}{d(1/T_{\max})} \qquad \textbf{(5.5-205)}$$

The slope of the straight lines is E_{obs}/R_g.

If no exothermic peak appears up to 500 K in *DTA/DSC* curves for heating rates of 5-10 K min^{-1} and no other signs of vigorous reaction are observed, then the material can usually be considered safe. In case of the occurrence of a temperature peak, measurements should be repeated at lower heating rate.

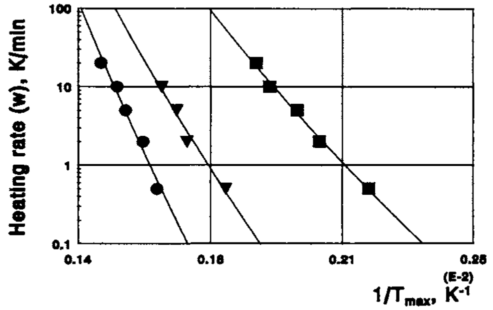

Figure 5.4-59. Heating rates versus $1/T_{max}$; ●: 4-nitrobenzaldehyde, ▼: 2-nitrobenzoic acid, ■: 4-nitrobenzoic acid (plots drawn based on data from Grwer and Klais, 1988).

The maximum operating temperature may be evaluated from *DTA/DSC* curves if the shift of the peak due to reduction of the heating rate to 0.5-1 K min^{-1} does not exceed 40 K. This corresponds to moderate activation energies of the secondary reactions, *i.e.* less than 50 kJ/mol for values obtained from the 'Arrhenius plots'.

According to Grewer (1994), the effect of the secondary unwanted reaction may be regarded as non-critical if the decomposition energy, as determined by integration of the appropriate sections of the *DTA/DSC*-curves, is less than 100-200 J g^{-1}. Higher values of the decomposition energy require a further detailed analysis. For instance, if the energy is distributed over several *DTA* peaks that are relatively far from each other, or if the exothermic peak is followed by endothermic effects, a high energy of secondary reactions may not be critical. The boundary of 100-200 kJ kg^{-1} is characteristic of organic substances of rather low specific heat (~ 2 kJ kg^{-1} K^{-1}). For aqueous media, higher values of the decomposition energies may be considered non-critical because of the high specific heat of water (approximately twice that of organic liquids).

Adiabatic heat storage or accumulation tests are performed to obtain data on temperature- and pressure-time behaviour of a substance at quasi-adiabatic conditions. Where heat dissipation by evaporation is anticipated, the measurements have to be performed in a closed system. If this is not the case the experiment may be carried out in an open system.

Adiabatic calorimetry. Dewar tests are carried out at atmospheric and elevated pressure. Sealed ampoules, Dewars with mixing, isothermal calorimeters, etc. can be used. Temperature and pressure are measured as a function of time. From these data rates of temperature and pressure rises as well as the adiabatic temperature rise may be determined. If the log p versus $1/T$ graph is a straight line, this is likely to be the vapour pressure. If the graph is curved, decomposition reactions should be considered. Typical temperature-time curves obtained from Dewar flask experiments are shown in Fig. 5.4-60. The adiabatic induction time can be evaluated as a function of the initial temperature and as a function of the temperature at which the induction time, t_{ad}, exceeds a specified value.

Adiabatic induction times are always shorter than induction times from isothermal experiments, see Fig. 5.4-61 (Grewer *et al.*, 1989).

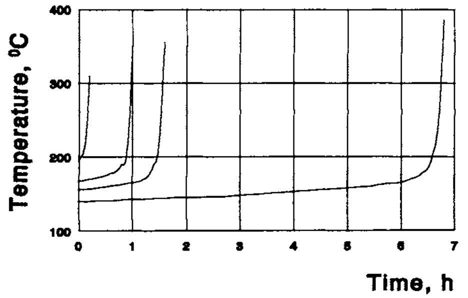

Figure 5.4-60. Temperature verus time in Dewar flask; 2-nitrobenzaldehyde (adapted from Grewer, 1994).

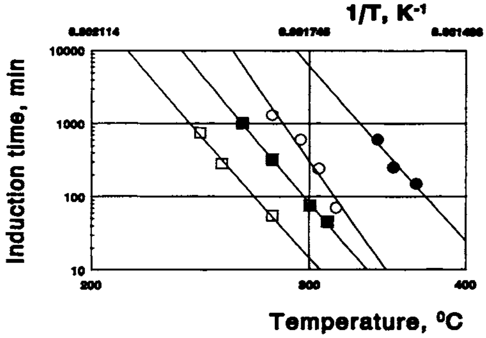

Figure 5.4-61. Induction times; 4-nitrotoluene, □: iso, ■ ad; nitrobenzene, ○: iso, ●: ad (adapted from Grewer, 1994).

In general, adiabatic calorimeters are more sensitive than *TPA* techniques. The induction time can be used for direct evaluation of boundaries for safe operation. Obviously, the time of a corrective action must be less than t_{ad}. The fully safe operational temperature is that corresponding to t_{ad} = 24 h and is denoted as ADT_{24} (Adiabatic Decomposition Temperature for 24 hours).

Accelerating Rate Calorimetry. This is a 'heat-wait-search' technique (see Fig. 5.4-62). A sample is heated by a pre-selected temperature step of, typically, 5 °C, and then the temperature of the sample is recorded for some time. If the self-heating rate is less than the calorimeter detectability (typically 0.02 °C) the *ARC* will proceed automatically to the next step. If the change of the sample temperature is greater than 0.02 °C, the sample is no longer heated from outside and an adiabatic process starts. The adiabatic run is continued until the process has been completed. *ARC* is usually carried out at elevated pressure.

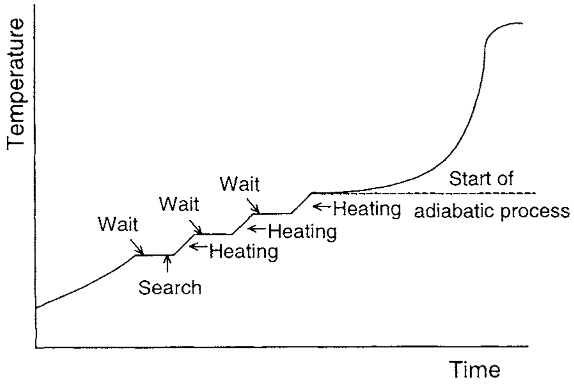

Figure 5.4-62. Heat-wait-search operation mode of ARC.

Many kinetic data can be collected from *ARC* experiments: the exothermic onset temperature, the rate of temperature rise, the rate of pressure rise, and the apparent activation energy. The basic data obtained are, however, thermodynamic properties: the adiabatic temperature rise, the maximum pressure potential, the quantity of gaseous products generated, and the heat of reaction can be obtained in one run. The heat of reaction is estimated from:

$$(-\Delta H) = \phi \Delta T_{ad} c_p \tag{5.5-206}$$

where

$$\phi = \frac{(mc_p)_{sample} + (mc_p)_{calorimeter}}{(mc_p)_{sample}} \tag{5.5-207}$$

Reaction calorimetry (Regenass, 1978; Brogli *et al.*, 1981; Hoppe and Grob, 1990; Hoppe, 1989). A number of methods have been developed for measuring thermal effects of chemical processes (see reviews by Becher, 1968; and Regenass, 1997). The principle of the operation of a reaction calorimeter is shown in Section 5.4.4.3. A representative sample (typically 1-4 L) of reactants (or post-reaction mixture) is heated following a pre-set program and the heat flux is measured. The heat flux is indicative of chemical and physical transformations. This quantity is equal to the overall rate of heat generated or consumed by the reaction mixture. Instantaneous, gradual, or continuous addition of reactants is possible. At atmospheric pressure a glass reactor is used, which allows visual observation. Pressures up to 60 bar are possible if a metal reactor is used (*Mettler-Toledo* Bulletin, 1995). Four temperature control modes can be realized in the reaction calorimeter, which correspond to four industrial processes: (1) control of the jacket temperature, (2) control of the temperature of the reaction mass, (3) adiabatic mode – compensation of the heat losses, and (4) distillation mode – distillation and refluxing. Thermal effects, specific heat, heat of phase transitions (evaporation, crystallization, etc.), heat of mixing, heat due to stirring, and heat-transfer coefficients (as a function of time and/or properties of the reaction mixture) can be measured by using reaction calorimetry (see, e.g.. Chaudhary *et al.*, 1990).

The reaction calorimeter is a very useful tool for scale-up, for kinetic work, and for hazard assessment. In some respects it suits those tasks in fine chemistry even better than the classical chemical reaction engineering tools. Investigation of the process under various batch and semibatch temperature-time conditions is possible. One can experimentally determine the rate of heat evolution as a function of temperature and time for a given composition of the reaction mixture. Based on these data and on the evaluation of the rate of heat removal from the full-scale reactor, the temperature-versus-time relationships in an industrial reactor can be evaluated. Then, the reaction calorimeter can be programmed for these conditions and experiments carried out for the anticipated industrial conditions, heating and cooling periods included. The thermal sensitivity of the process to various process conditions can also be easily determined in this way. This considerably helps in the search for a safe and stable area for full-scale reactor operation. Moreover, when conducting research with technical-grade raw materials, the reaction calorimeter can act as an ideal miniplant reactor. It is good to emphasize that thermal effects, other than those from heats of reactions, can be easily detected. Accordingly, the use of the reaction calorimeter can accelerate development of the optimal procedure suitable for the plant. The reaction calorimeter is very useful for the verification of the safe operation concept (concentrations, rate of dosing, temperature of the jacket as a function of time) for testing safe procedures that have been developed as inherently safe ones based on other thermo-kinetic experiments. All these features of the reaction calorimeter have led to the more and more common use of this equipment for hazard evaluation and process modifications. Exemplary applications of reaction calorimeters for hazard evaluation are shown in Table 5.4-37.

The various thermal techniques give different results. Snee (1991) determined the heat of the esterification reaction between *sec*-butanol and propionic aldehyde using different thermal techniques.

Table 5.4-37
Examples of the use of reaction calorimeters for chemical reaction hazards evaluation

Evaluation of chemical reaction hazards	Industrial partner	Reference
Isocyanic acid from sodium cyanate	Schering Plough Res. Inst.	Giusto (1994)
Complex heterogeneous process (two immiscible liquids and decomposing solid)	Air Products & Chemicals	Latshaw (1994)
Grignard reagent formation; amidation of a peptide compound	Lepetit Research Center	Nebuloni and Cardillo (1993)
Hydrogenations of substituted 2-nitrophenols and nitrobenzenesulphonic acid; double bond hydrogenation;	Ciba-Geigy	Buser and Urwyler (1993)
Nitration of 2-chloro-5-nitrobenzenesulphonic acid	Ciba-Geigy	Fahrni *et al.* (1993)
Ether formation from alcohol and alkanoyl chloride	Wacker-Chemie	Bachhuber (1993)
Reduction of substituted 2-nitrobenzoic acid to 2-nitrobenzyl alcohol	Sterling Organics	Amery *et al.* (1993)
Benzyl chloride + sodium methoxide, and esterification of acetic acid with methanol	SmithKline Beecham	O'Rourke (1993)
Sulphonation of nitro-aromatic compound	Ciba-Geigy	Stoessel (1994)
Complex amine formation from cyclic anhydride and aromatic amine; formation of triaryl phosphine	Sterling Organics	Amery *et al.* (1994)
Hydroxynitrile formation from a cyclic sulphite and sodium cyanide	Merck & Co.	Landau *et al.* (1994)
Catalytic partial oxidation of a substituted alcohol to an aldehyde using sodium hypochlorite; oxidation of a water-soluble organic with hydrogen peroxide using a sodium tungstate catalyst		Knoechel (1994)
Formation of Grignard reagent; formation of cyclopropanenitrile from aliphatic chloronitrile	Ciba-Geigy	Brogli *et al.* (1981)
Toluene mononitration		Cronin *et al.* (1989)
Methanol-acetic anhydride reaction	Fire Research Station Site	Singh (1993)
sec-Butyl propionate from *sec*-butyl alcohol and propionic anhydride	Health & Safety Executive	Snee (1991)

He obtained the following results: *DSC*: -261 kJ/kg; *ARC*: -281 kJ/kg; *RC*: -306 kJ/kg. Reaction calorimetry is considered to be the most accurate technique. Accordingly, the values obtained from *DSC* and *ARC* are underestimated by about 10 %. Cronin *et al.* (1989) investigated hazards associated with *tert*-butyl peroxybenzoate. Results of their experiments are shown in Table 5.4-38. *DSC* is generally less sensitive to the onset temperature. This, however, can be significantly improved if the heating rate is reduced to 1 K/min. On the other hand, this technique yields a heat of reaction closest to the thermochemically determined heat of reaction based on an analysis of decomposition products. Lower reaction heats obtained using the other techniques can be attributed to the eventual expulsion of hot decomposition products from the sample containment. This demonstrates limits on 'adiabatic' determination of thermal effects for violent decomposition reactions. Table 5.4-39 compares calorimeters of the various groups.

Table 5.4-38
Thermal data for *tert*-butyl peroxybenzoate

Test method	Experimental conditions	Sample mass	Initial exotherm detected, K	Adiabatic temperature increase, K	Heat of reaction, J/g
DSC	10 K/min	3.42 mg	395		
	1 K/min	6.48 mg	366		1441
ARC	Heat step: 10 °C Wait: 15 min	3.57 g	354.8	394.4	721.8
DTA	0.5 K/min	3.0 g	353	446.3	816.6
Adiabatic		5.0 g	345	373.1	682.8

Example 5.4.6.3. Safety in a new process for nitration of a substituted aromatic compound (after Hoppe and Grob, 1990).

In a Ciba-Geigy plant a conventional process was used to produce a nitro compound. Nitration was performed in a semibatch reactor. The reactor was charged with a substituted aromatic compound and an organic solvent. Then nitric acid was fed. The acid/aromatic ratio was 1.3:1, the process temperature 27 °C. The product demand had increased significantly and expansion of the production capacity was considered. However, the solvent process was out of consideration because of safety reasons: A reactor already present in the plant that could be used to manufacture the compound was not adapted for handling flammable organic solvents. A new process, in which the organic solvent was replaced by water, was developed in the laboratory. Nitration was to be carried out by feeding the aromatic compound to a mixture of water and nitric acid in the semibatch reactor. The acid/aromatic ratio would be 3:1, the process temperature 50 °C. The new procedure was to be evaluated from a safety viewpoint before steps were taken to implement the process at the full scale.

The existing process and the new procedure were examined using a reaction calorimeter: (1) at design process parameters (isothermal runs) and (2) using a 25% larger amount (concentration) of nitric acid. The latter had a negligible thermal effect on the solvent process and a significant effect on the water process (formation of dinitro compound). Heat generation curves for both cases are shown in Figs. 5.4-63 and 5.4-64. On integration of the heat generation curves process heats of 138 kJ/kg and 167 kJ/kg were obtained for the solvent process and the water process, respectively. The adiabatic temperature rises are 92 °C and 45 °C for the solvent and the water process, respectively.

Table 5.4-39
Comparison of calorimeters

DTA/DSC	*Adiabatic calorimeters*	*Heat flow calorimeters*
sample size: 1-20 mg; open cups, sealed ampoules, in metal crucibles catalytic action possible, the small sample may be unrepresentative	sample size: 10g (*ARC*) to 5 L (typically less than 1 L), mixing possible	sample size: 0.3 to 4 L, typically 2 L; glass reactor standard, metal reactors exist
temperature < 500 °C, typically atmospheric pressure, open cup or ruptured glass ampoule, gas or vapour formed at boiling may be corrosive to the equipment	adiabatic operation with a maximum temperature determined by construction materials; pressure operation typical, determination of pressure-time curves possible	-70 to 230 °C, operation under pressure up to 10 bar in glass reactor and 400 bar in metal reactors possible
low thermal sensitivity, uncertainties in determination of ΔH and onset temperatures (strong dependence on heating rate, true onset temperature is lower than that found using *DTA/DSC*); accuracy to within 5-20 %; *DSC* more accurate than *DTA*	thermal sensitivity higher than that of *DSC*, more precise determination of onset temperatures	high calorimetric sensitivity: 0.2 W/kg
no mixing, no additions	additions and mixing possible	mixing and dosing as a standard
kinetics - for one reaction or well-separated peaks in a temperature sequence of reactions, assumptions concerning a form of kinetic equations necessary, t_{ad} underestimated	kinetics - as for *DTA/DSC* techniques (heat is never a specific source of kinetic information for more than one reaction proceeding in a system)	kinetics, sampling possible, more detailed kinetic study possible
advantageous for first examination of even the most explosive unknown products and reaction mixtures, quick screening providing a rough, overall picture of potential hazards, simple and efficient	the best simulation of adiabatic process developing upon cooling failure (induction times and safe/onset temperatures); representative pressure-time curves obtainable	allows simulation of plant conditions (including dosing of reactants) and simultaneous determination of heat generation data accurately
DTA should be used for reaction mixtures that can be well mixed at room temperature, and that start reacting at higher temperatures		

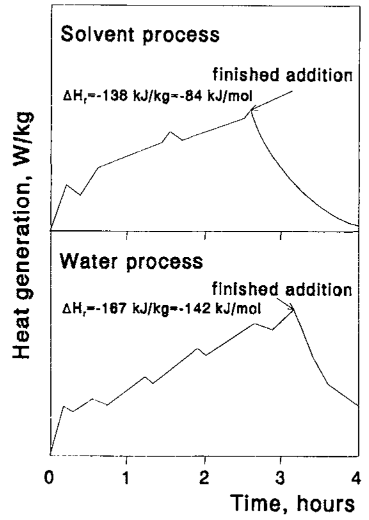

Figure 5.4-63. Nitration; isothermal runs in reaction calorimeter (adapted from Hoppe and Grob, 1990).

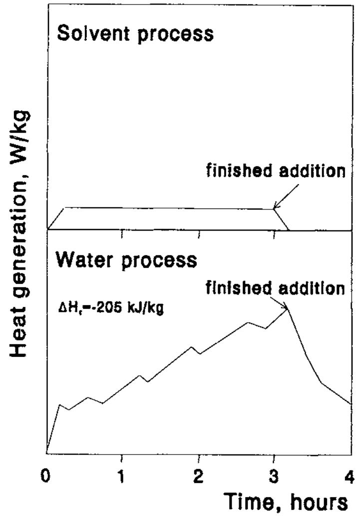

Figure 5.4-64. Nitration: isothermal runs in reaction calorimeter; 25 % more HNO_3 (adapted from Hoppe and Grob, 1990).

This difference originates from the different heat capacities of the reaction mixtures. The large difference between the process heats could not be attributed to dilution of the aromatic compound in the nitric acid/water mixture. The difference increased by adding a larger amount of nitric acid.The heat of the solvent process, that was run in such a way that the heat flux was kept constant, only increased slightly due to the aromatic dilution by the acid added to the reaction mixture. In contrast, extra acid addition resulted in a significant rise of the thermal effect of the water process (to 209 kJ/kg), indicating that formation of a di-nitro compound proceeds.

A *DSC* instrument was used to assess the possible consequences of a potential thermal runaway using post-nitration mixtures for evaluations (see Fig. 5.4-65). For the solvent process two minor peaks between 150 and 220 °C appeared, which correspond to thermal effects of -15 kJ/kg and -9 kJ/kg. In contrast, a large thermal effect (-730 kJ/kg) was observed for the reaction mixture from the water process, located between 90 and 160 °C. Based on these data the risk of a thermal runaway for both processes was assessed.

Fig. 5.4-66 outlines the probability and consequences of a thermal runaway in case of a plant incident. For the solvent process, failure results in a temperature rise from 27 °C to 119 °C. This is far from the onset temperature of secondary processes, which only start at 150 °C or higher. Consequently, the solvent process can be considered safe. A failure of the water process can cause a temperature rise from 50 to 95 °C, *i.e.* higher than the onset temperature (90 °C) of the secondary decomposition of the di-nitro compound. The decomposition would start before the reaction mixture started boiling. Hence, the water process cannot be considered inherently safe.

5.4.6.5. Theories on thermal explosion, runaway criteria

There are many theories that enable the prediction of when a thermal runaway will occur and how it will proceed (Semenov, 1928; Frank-Kamenetski, 1969; Thomas, 1961).

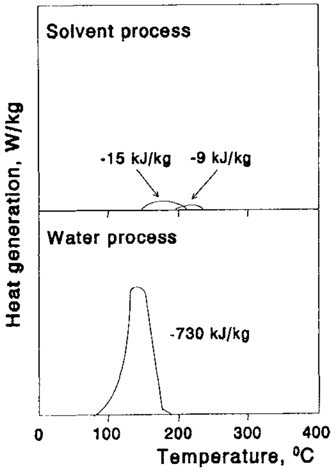

Figure 5.4-65. *DSC* curves for nitration of reaction mixtures; 1 mg sample, sealed crucible, 10 °C/min (adapted from Hoppe and Grob, 1990).

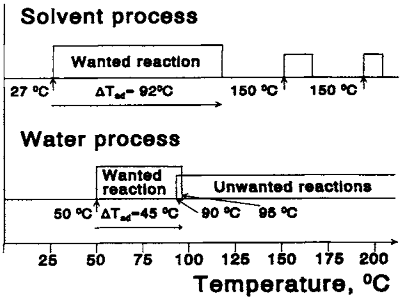

Figure 5.4-66. Comparison of the solvent and the water process (adapted from Hoppe and Grob, 1990).

Comprehensive discussions on reactor stability theories and safe engineering problems were presented by Eigenberger and Schuler (1986, 1989), Zaldivar (1991), Barton and Rogers (1993), and Grewer (1994). The very basic theory developed by Semenov (1928) for zero-order reactions is very illustrative for a physical explanation of explosion phenomena. The theory enables evaluation of conditions at which thermal explosion will occur.

The mass and energy balance equations for ideally mixed components where zero-order reaction proceeds are:

$$-\frac{dc}{dt} = \delta k_0 \exp\left(-\frac{E}{R_g T_r}\right) \tag{5.4-208}$$

$$\delta \Delta H k_0 \exp\left(-\frac{E}{R_g T_r}\right) + \rho c_p \frac{dT_r}{dt} = \frac{UA_r}{V}\left(T_c - T_r\right) \tag{5.4-209}$$

The Kronecker delta, δ, means that the reaction term is non-zero only when reactant is present, i.e.

$$\begin{aligned} \delta &= 1 \quad \text{for}\, c > 0 \\ \delta &= 0 \quad \text{for}\, c = 0 \end{aligned} \tag{5.4-210}$$

Typical results of calculations using this model are shown in Fig. 5.4-67. The discontinuity of the *dT/dt*-curves corresponds to the complete consumption of the reactant (δ = 0). This is followed by cooling to temperature T_c. If the initial temperature is sufficiently high, the reaction proceeds rapidly. Consequently, the rate of heat evolution is so high that the rate of heat transfer to the coolant can be considered negligible.

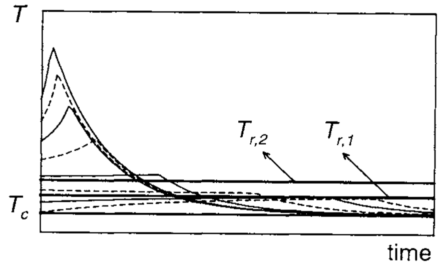

Figure 5.4-67. Temperature versus time for various initial temperatures of the reaction mixture; zero-order kinetics.

The temperature rise due to this exothermic reaction then approaches the adiabatic temperature rise. The final steady state is always characterized by conditions $T = T_c$ and $c = 0$. A batch reactor, in which a zero order reaction is carried out, always has a unique and stable mode of operation. This is also true for any batch and semibatch reactor with any order or combination of reactions.

The plots in Fig. 5.4-67 are characterised by the existence of two initial temperatures, $T_{r,1}$ and $T_{r,2}$,delimiting the regions in which the temperature initially rises or falls. If $T_r = T_{r,1}$ or $T_r = T_{r,2}$, the temperature remains constant as long as any reactant remains unconsumed. This corresponds to the balance of rates of heat generation and heat removal as given by:

$$q_R = UA_r(T_r - T_c) = V(-\Delta H)k_0 \exp\left(-\frac{E}{R_g T_r}\right) = q_P \qquad \textbf{(5.4-211)}$$

heat removed heat produced

The equilibrium temperatures $T_{r,1}$ and $T_{r,2}$ are equivalent to points of intersection of heat generation and heat removal lines (see Fig. 5.4-2 in Section 5.4.1). The lower temperature is a stable operating point while the higher one is unstable. It is clear from the plot that a temporary state of equilibrium in the meaningful temperature range may not exist above a critical cooling temperature $T_{c,crit}$, with accompanying temperature of the reaction mixture, $T_{r,crit}$. The rate of heat evolution then is always greater than that of heat removal, and the temperature increases until all the reactants have been consumed. The conditions for $T_{c,crit}$ are given by Eqn. (5.4-211) and the following expression:

$$\frac{dq_R(T_{r,crit})}{dT_r} = \frac{dq_P(T_{r,crit})}{dT_r} \qquad \textbf{(5.4-212)}$$

Combining Eqns. (5.4-211) and (5.4-212) and rearranging leads to:

$$\ln\left\{\frac{E}{R_g T_{r,crit}^2}\frac{V}{UA_r}(-\Delta H)k_0 \exp\left(-\frac{E}{R_g T_{r,crit}}\right)\right\} = 0 \qquad \textbf{(5.4.213)}$$

This equation is commonly used for evaluation of the thermal stability of a substance in safety engineering. This corresponds to the assumption that reactions under assessment are considered to be of pseudo zero order. This is reasonable in the early stage of reaction (fractional conversion less than 0.05). For any ratio of A_r/V, the self-ignition temperature T_{ign} ($= T_{r,crit}$) is determined from a graph like that in Fig. 5.4-68. For experimental values of $V/(A_r T_{ign}^2)$ in the region above the plotted line, the temperature increases regardless of the coolant temperature. This is the region in which there exists no point of intersection between q_R and q_P and a runaway occurs.

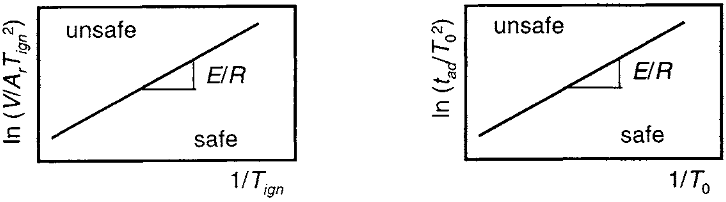

Figure 5.4-68. Regions of safe and unsafe operation.

The safety engineering data can also be determined from the adiabatic induction times t_{ad} (or TMR_{ad}) for various initial temperatures at adiabatic conditions ($U = 0$). The following analytical solution of Eqn. (5.4-209) for $\delta = 1$, *i.e.* for unlimited supply of reactants, then is obtained:

$$t_{ad} = \frac{R_g T_0^2}{E \Delta T_{ad}} \frac{1}{k_0 \exp\left(-\frac{E}{R_g T_0}\right)} \tag{5.4-214}$$

The adiabatic induction time can be approximately evaluated from graphs in Fig. 5.4-68. They are plotted for the condition $q_R >> q_P$, which is nearly equivalent to adiabatic operation if the initial temperature is greater than $T_{r,2}$. Eqn. (5.4-214) is the basis of the graph in Fig. 5.4-68. From both graphs in Fig. 5.4-68 the apparent activation energies (E/R_g) for pseudo-zero order reactions can be determined.

There are many studies in the literature on the derivation of runaway criteria. Theoretically derived criteria are described briefly in Table 5.4-40, while those based on experiments are listed in Table 5.4-41.

Runaway criteria developed for plug-flow tubular reactors, which are mathematically isomorphic with batch reactors with a constant coolant temperature, are also included in the tables. They can be considered conservative criteria for batch reactors, which can be operated safer due to manipulation of the coolant temperature. Balakotaiah *et al.* (1995) showed that in practice safe and runaway regions overlap for the three types of reactors for homogeneous reactions: (1) batch reactor (BR), and, equivalently, plug-flow reactor (PFR), (2) CSTR, and (3) continuously operated bubble column reactor (BCR).

Table 5.4-40
Runaway theories and theoretical criteria

Model for derivation of safe operation criteria; criteria	Reference
Non-uniform temperature distribution in a reactor assumed; model based on the Fourier heat conduction in an isotropic medium; equality of temperatures of the medium and the surroundings assumed at the boundary; critical values of Frank-Kamenetskii number given.	Frank-Kamenetskii (1969)
As above except that the condition of the second kind assumed the Boundary; for $Bi \rightarrow 0$, the Thomas model becomes the Semenov Model; for $Bi \rightarrow \infty$, the Thomas model becomes the Frank-Kamanetskii Model; critical conditions for various geometries given.	Thomas (1961)
Runaway boundary determined by the existence of ignition (inflection) point in the reaction path; analytical equations and graphically presented boundaries in co-ordinates $<1/Se, B>$; in practice, safe operation if $1/Se > 3$ and/or $B < 4$.	Balakotaiah *et al.* (1995), Balakotaiah (1989)
Regions of stable and unstable operation determined by numerical simulation of mass and heat balances equations; first- and second-order, autocatalytic, and product-inhibited kinetics; graphically presented boundaries in co-ordinates $<1/Se, B>$; in practice safe operation if $1/Se>2$.	Barkelew (1959)
Equality of heat generation and heat removal rates; Semenov approach modified for first-order kinetics.	Schuler (1982)
Stability of adjacent trajectories criterion.	Schuler (1982)
Mathematical stability of maximum temperature criterion.	Kreyszi (1993)
Slope criterion for temperature time trajectory of runaway ($d^2T/dt^2 > 0$ and $dT/dt > 0$).	Dente and Collina (1964)
Positive second-order derivative in the temperature-conversion plane ($d^2T/dX^2 > 0$ and $dT/dX > 0$).	Adler and Enig (1964)
Maximum parametric sensitivity criterion.	Morbidelli and Varma (1982, 1985); Morbidelli *et al.* (1987); Vajda and Rabitz (1993)

5.4.6.6. Safety strategies

There are essentially three routes to safe reactors, with a clear hierarchy:

- Elimination or minimization of all causes of accidents by applying the inherent safety concept.
- Stopping excursions from normal operation conditions before they become hazardous, by correction of process control variables when dangerous situations are detected: on-line detection of process deviations associated with trip systems for corrective actions.
- Decreasing the amount of damage done by an accident by taking preventive protection measures against the potential consequences of dangerous situations: containment.

Clearly the elimination of hazards is the most effective safety measure and often the least costly. However, it requires a thorough understanding of the potential hazards. On-line detection systems combined with automatic actions to stop a runaway in most cases will prevent thermal explosions or at least reduce the extent of an incident. Trip systems have been well established and have become more sophisticated. They are becoming less expensive due to the enormous progress in electronics. Containment is usually an expensive means for reducing damage resulting from what has already happened.

Table 5.4-41
Semi-empirical criteria for runaways

Conditions for safe operation	Reference
Batch reactors	
$B(T_0) < 5$	Barton and Rogers (1993)
$T_{max}/T_c \leq 1.25$ if $St/Da > (\alpha\, Ar)^{1.18}$	Trambouze *et al.* (1988)
Regions of stable and unstable operation given in co-ordinates $<B(T_{max}), \gamma>$ (for kinetics $r = k(1-X)^n$)	Hugo (1981)
Semibatch reactors	
$Da/[\varepsilon(1+St)] > 1$	Barton and Rogers (1993)
$Da_0/[\varepsilon/(1+\varepsilon) + St] > 1$ for $T_0 = [\varepsilon \cdot T_{feed} + (1+\varepsilon) \cdot St \cdot T_c]/[\varepsilon(1+\varepsilon) \cdot St]$	Steinbach (1994)
$B \leq [\sqrt{(St + 2\varepsilon)} + 1.2 \sqrt{\varepsilon}]^2$ and $Da \geq St$	Hugo & Steinbach (1985-6)
Liquid-liquid reactions; safe operation regions given in co-ordinates *<reactivity, exothermicity>*	Steensma and Westerterp (1988, 1990)

$Ar = E/(R_g T)$ (Arrhenius number)
$B = Ar\, (\Delta T_{ad}/T)$ (Reaction thermal number)
$Da = [r(T, c_{i,0})\, t_D]/c_{i,0}^{\,n-1}$ (Damköhler number)
$St = [U\, A_r\, t_D]/(\rho\, V_r\, C_{p,m})$ (Stanton number)
$Se = Da \cdot B/St$ (Semenov number)
$\Delta T_{ad} = [(-\Delta H_r)\, c_{A,0}]/[\rho C_{p,m} t]$
$\alpha = \Delta T_{ad}/T_{c,min}$
$\gamma = (T_{max} - T_0)/\Delta T_{ad}$
$\varepsilon = V_D/V_{r,0}$

Inherent safety concept. This route requires the deepest understanding of the chemical process, and, accordingly, of the potential hazards. It is not easy, even at a high degree of understanding, to eliminate mistakes in assessment. However, this approach is strongly supported by many specialists in problems of safety in the chemical industry. According to Kletz (1983):

> "Almost all the papers and committees have overlooked the fact that there may be a better and cheaper solution to the problem. If we could design our plants so that they use safer raw materials and intermediates, or not so much of the hazardous ones, or use the hazardous ones at lower temperatures and pressures, then we would avoid rather than solve a lot of our problems. Such plants can be described as intrinsically or inherently safe, while the conventional plant, in which the hazards are kept under control, is extrinsically safe."

A process is inherently safe in a rigorous sense, when no fluctuation or disturbance can cause an accident. To search for synthetic routes that avoid hazardous reactants, intermediates, and reaction mixtures, is an impetus to be seriously considered by chemists and process designers. Nevertheless, there will always be a need to cope with potentially hazardous materials and reaction mixtures in future process design work, the more so because process streams are expected to become potentially more dangerous in the future. The process streams will be more concentrated to increase energy efficiency, to ease purification, and to decrease the load of wastewater and spent acids. More concentrated process streams have a higher specific content of latent energy and are hence less stable.

An inherently safe process is not easy to attain. However, if hazards have been identified and safety measures incorporated in the design phase, it is often possible to approach the ideal. This can be done, e.g., by an appropriate selection of the heating medium or reaction solvent to prevent reaching the minimum decomposition temperature, by specification of charge vessel sizes to limit the quantity that can be added at once, by the appropriate choice of the orifice plate that will limit the feeding rate, etc. Organization of manufacturing processes according to GMP requirements such as strict recording of all materials used, elimination of crossings of ways through which the materials are transported, etc. can also contribute to improvement of safety in industrial plants.

In the elaboration of a safe process it is necessary to look for those synthetic routes which do not incorporate hazardous raw materials, solvents, and additives. This is unfortunately rarely achievable. Therefore, the best way to insure higher intrinsic safety is:

- identification of all reactions that can result in the formation of dangerous materials, and to find process conditions which would disfavour these reactions,
- storage and handling of hazardous (toxic or unstable) materials in as small amounts as possible,
- keeping energy densities low by either avoiding accumulation of reactants that can react with a high thermal effect or by increasing the capacity for heat removal to the surroundings (maximize the heat-transfer capacity per unit reactor volume),
- avoiding the arrangement of materials in a dangerous way with regard to the process streams or contents of the equipment and avoiding external sources that could trigger runaways (e.g. by using utility fluids which do not dangerously react with reaction mixtures),
- keeping the process far within the region of stability, which is easier to attain if a low energy density is maintained, and the heat transfer-capacity per unit volume is maximized.

Inherent safety must be achieved during process development. The first principle does not require any comment. To attain the second and third goals one has to apply obvious technical measures during plant design (low concentrations, low rates of dosing at as high a temperature as possible, evaporative cooling, etc.). Implementation of the fourth point means the consideration of all possible runaway scenarios and their quantitative assessment on as small scale as possible (leakage of steam heating system is unavoidable, liquid circulation heating/cooling system is usually the most safe one). Inherent safety should be an objective in process design and the question whether a design alternative makes a process inherently safer or less safe should be an essential design criterion.

Inherent safety can rarely be attained in an established process by simple measures. In cases of process modification, one of the following must be involved to make the process safer (Sharkey *et al.*, 1992): (1) new chemistry, (2) new reaction solvent, (3) added recycle streams, and (4) major concentration changes (reactants, products, by-products, solvents).

Preventive and protective measures. Technical safety measures must always be developed no matter how inherently safe we think the process is. The scope of preventive and protection measures is large for the whole plant. Below, some preventive measures to be taken to prevent thermal runaways when a dangerous situation is recognized are listed:

- full cooling (effective only when the maximum cooling capacity exceeds the actual rate of heat generation),
- quenching (addition of an inhibitor or addition of a calculated amount of a suitable inert cold liquid which reduces the reaction rate by cooling and dilution of reactants),
- stopping the addition of reactants,
- transferring the reactor contents to a vessel that contains a cold diluent with or without inhibitors (this requires more time and is less reliable than quenching).

Protective measures become effective when a runaway can no longer be prevented. Examples of protective measures are:

- emergency relief venting,
- explosion suppression,
- design of reactors to withstand the maximum pressure in runaway situations,
- containment systems, installation of reactors in bunkers.

Emergency relief venting and containment systems are effective means to reduce the consequences of thermal runaways. The Design Institute of Emergency Relief Systems (*DIERS*) has developed a methodology for the design of relief systems. In fine chemicals manufacture the lack of a safe discharge area for existing plants, added to the cost of secondary treatment and explosion protection, often precludes venting as a viable safety measure. Therefore, in batch and semibatch reactors venting and containment systems are seldom used. The liquid present in these reactors can be transformed into an enormous amount of gas when experiencing a thermal runaway, which would require very large containment systems. Venting would result in spreading quite a lot of material into the environment. Nevertheless, in most batch and semibatch reactors venting provisions are made, to prevent damage to the reactor. A comprehensive review on safety measures has been presented by Maddison and Rogers (1994). Detailed information on the design of safe processes can be found in *Guidelines for Engineering Design for Process Safety* (1993).

5.4.7. Reactor selection

Based on a detailed mathematical model, one can make computer simulations of the behaviour of various reactor types. Optimization of operating conditions and design parameters can be done for each reactor type. Downstream equipment should also be taken into account since the cost of product isolation and purification can heavily influence the final choice of all equipment items. A proper combination of investment and operating costs is used as the optimization criterion. Optima for all reactor types studied are then compared and the best reactor or combination of reactor with separation equipment chosen.

In fine chemistry, mathematical models are scarce yet. However, even gross kinetics provides a lot of information on the influence of the mode of operation on selectivity. In general, semi-quantitative criteria are used in preliminary reactor selection. They are mainly based mainly on operational characteristics, experience, and a rough economic estimation. Factors affecting the choice of the reactor and mode of operation are listed in Table 5.4-42.

Table 5.4-42
Checklist for selection of reactor/operation mode

Factor
Scale of operation
Continuous versus (semi)batch, reaction time, flow rates
Materials of construction
Selectivity, backmixing or plug flow required
Mixing and micromixing, number and type of phases
Mechanical stirring versus agitation by energy of the feed
Countercurrent, cocurrent, or cross-flow operation
Rate of heat generation, heat removal/supply
Hazards
Solubility of product in reaction mixture
Solid particles presence in any of the feeds
Rheological behaviour
Foaming behaviour
Recycling of reactants
Size and shape of solid particles
Fouling of catalyst and/or heat exchange surface
Max/min pressure
Max/min temperature
Allowable pressure drop

5.4.7.1. Scale of operation, continuous versus batchwise

The fine chemicals business is characterized by a small volume of products manufactured. Therefore, batch production predominates and small-scale reactors are used. The need to implement fine chemistry processes into existing multiproduct plants often forces the choice of batch reactors. However, safety considerations may lead to the choice of continuous processing in spite of the small scale of operation. The inventory of hazardous materials must be kept low and this is achieved only in smaller continuous reactors. Thermal runaways are less probable in continuous equipment as proven by statistics of accidents in the chemical industries. For short reaction times, continuous or semicontinuous operation is preferred.

5.4.7.2. Materials of construction

Typical reactors are made of stainless steel (e.g. 316 L) or are glass-lined. Standard glass-lined reactors are limited in size and intensity of mixing; although 200 m^3 reactors for suspension polymerizations are available, mixing in such huge units might be insufficient for fast reactions that are encountered in fine chemicals processes. Reactors of any size and shape, operated in the desired mode, can be constructed of materials with a specific chemical resistance.

5.4.7.3. Selectivity

Many fine chemistry processes can be lumped into a system of two parallel or two consecutive reactions. Selectivity can roughly be assessed using the gross kinetics for such lumped schemes, and this can be used to derive approximate criteria for reactor selection.

Consider the following reaction schemes for parallel reactions:

$$\begin{aligned} A + B &\xrightarrow{k_1} P \\ A + B &\xrightarrow{k_2} S \end{aligned} \tag{5.4-215}$$

and for consecutive reactions:

$$A \xrightarrow{k_1} P \xrightarrow{k_2} S \tag{5.4-216}$$

with P being the desired product. Assume that the reaction kinetics can be described by power law expressions

$$\begin{aligned} r_1 &= k_1 c_A^{\alpha_{A1}} c_B^{\alpha_{B1}} = k_{10} \exp\left(- \frac{E_1}{R_g T} \right) c_A^{\alpha_{A1}} c_B^{\alpha_{B1}} \\ r_2 &= k_2 c_A^{\alpha_{A2}} c_B^{\alpha_{B2}} = k_{20} \exp\left(- \frac{E_2}{R_g T} \right) c_A^{\alpha_{A2}} c_B^{\alpha_{B2}} \end{aligned} \tag{5.4-217}$$

To maximize the production of the desired P the ratio r_1/r_2 must be maximized for parallel reactions

$$\frac{r_1}{r_2} = \frac{k_1}{k_2} c_A^{\alpha_{A1}-\alpha_{A2}} c_B^{\alpha_{B1}-\alpha_{B2}} \tag{5.4-218}$$

and the ratio $(r_1\text{-}r_2)/r_2$ for consecutive reactions:

$$\frac{(r_1 - r_2)}{r_2} = \frac{k_1}{k_2} c_A^{\alpha_{A1}-\alpha_{A2}} c_B^{\alpha_{B1}-\alpha_{B2}} - 1 \tag{5.4-219}$$

Below some typical kinetic situations for the system of parallel reactions will be considered.

(1) Parallel reactions, isothermal reactor, $\alpha_{A1} \neq \alpha_{A2}$, $\alpha_{B1} \neq \alpha_{B2}$, see Table 5.4-43.

(2) Parallel reactions, isothermal reactor, $\alpha_{A1} = \alpha_{A2}$, $\alpha_{B1} = \alpha_{B2}$ or nonisothermal reactor, $\alpha_{A1} = \alpha_{A2}$, $\alpha_{B1} = \alpha_{B2} = 0$, $E_1 = E_2$. In this case the ratio r_1/r_2 always equals k_1/k_2 and is independent on

Table 5.4-43
Advantageous modes of operation for different kinetic situations

Situation	Preferred mode of operation
$\alpha_{A2} > \alpha_{A1}$, $\alpha_{B2} > \alpha_{B1}$	Concentration of both reactants should be minimized. Dilute the initial reaction mixture or add both reactants continuously into the reactor. A CSTR is advantageous.
$\alpha_{A1} > \alpha_{A2}$, $\alpha_{B2} > \alpha_{B1}$	Concentration of A should be minimized. Dosing of *A* into the reaction mixture containing *B* is advantageous. A semibatch reactor or a cross-flow reactor is recommended.
$\alpha_{A2} > \alpha_{A1}$, $\alpha_{B1} > \alpha_{B2}$	Concentration of *B* should be minimized. Dosing of *B* into the reaction mixture containing *A* is advantageous. A semibatch reactor or a cross-flow reactor is recommended.
$\alpha_{A1} > \alpha_{A2}$, $\alpha_{B1} > \alpha_{B2}$	Concentration of both reactants should be maximized. A batch reactor or a tubular reactor is recommended.

the mode of reactor operation. Initial reactant concentrations and temperature do not influence the selectivity either. The highest allowable temperature and the highest reactant concentrations should be applied. A batch reactor, a tubular reactor, or a cascade of many CSTRs is the best choice.

(3) Parallel reactions, isothermal reactor $\alpha_{A1} < \alpha_{A2}$, $\alpha_{B1} = \alpha_{B2} = 0$. The course of reactions is shown in Fig. 5.4-69.

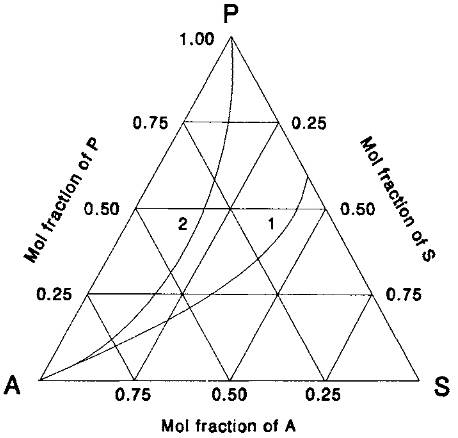

Figure 5.4-69. Parallel reactions of different reaction order; 1: SBR or PFR, 2: CSTR.

If the process is carried out in a stirred batch reactor (SBR) or in a plug-flow reactor (PFR) the final product will always be the mixture of both products, *i.e.* the selectivity will be less than one. Contrary to this, the selectivity in a continuous stirred-tank reactor (CSTR) can approach one. A selectivity equal to one, however, can only be achieved in an infinite time. In order to reach a high selectivity the mean residence time must be very long, and, consequently, the productivity of the reactor will be very low. A compromise must be made between selectivity and productivity. This is always a choice based upon economics.

(4) Parallel reactions, $\alpha_{A1} = \alpha_{A2}$, $\alpha_{B1} = \alpha_{B2} = 0$, $E_1 > E_2$. The selectivity to the desired product increases with temperature. The highest allowable temperature and the highest reactant concentrations should be applied. A batch reactor, a tubular reactor, or a cascade of CSTRs is the best choice.

(5) Parallel reactions, $\alpha_{A1} = \alpha_{A2}$, $\alpha_{B1} = \alpha_{B2} = 0$, $E_1 < E_2$. The selectivity of the desired product decreases with temperature. However, a low temperature disfavours the reaction rate. A nonuniform temperature-time profile should be applied to maximize the reactor productivity (see Fig. 5.4-70). Initially the temperature should be low to avoid the formation of too much unwanted product. The temperature is gradually raised with time to increase the reaction rate until the maximum allowable temperature is reached. At T_{max} the reaction is completed.

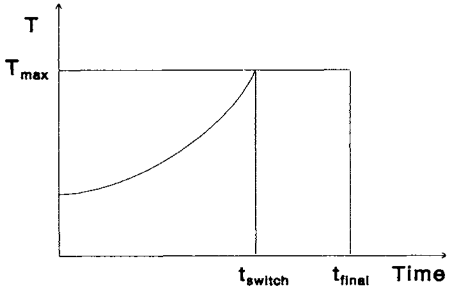

Figure 5.4-70. Optimal temperature profile for parallel reactions of the same order.

(6) Consecutive reactions, isothermal reactor $\alpha_{A1} < \alpha_{A2}$, $\alpha_{B1} = \alpha_{B2} = 0$. The course of reaction is shown in Fig. 5.4-71. Regardless the mode of operation, the final product after infinite time is always the undesired product *S*. Maximum yields of the desired product exist for non-complete conversion. A batch reactor or a plug-flow reactor performs better than a CSTR ($Y_{SBR,max} = 0.63$, $Y_{CSTR,max} = 0.445$ for $k_1/k_2 = 4$). If continuous operation and intense mixing are needed (e.g. because a large interfacial surface area or a high rate of heat transfer are required) a cascade of CSTRs is recommended.

(7) Consecutive reactions, $E_1 = E_2$. The selectivity is temperature-independent. The highest allowable temperature should be applied to maximize reactor productivity.

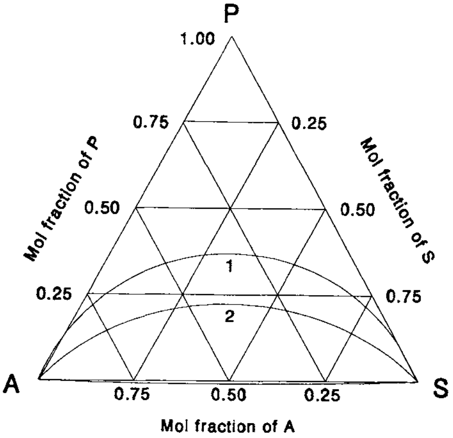

Figure 5.4-71. Consecutive reactions of equal reaction orders; 1: SBR or PFR, 2: CSTR.

(8) Consecutive reactions, $E_1 > E_2$. The selectivity increases with temperature. The highest allowable temperature should be applied to maximize reactor productivity.

(9) Consecutive reactions, $E_1 < E_2$. The selectivity of the desired product decreases with temperature. However, a low temperature disfavours the reaction rate. A nonuniform temperature-time profile should be applied to maximize reactor productivity (see Fig. 5.4-72). At the start, no desired product is present in the reaction mixture. The temperature should then be as high as possible to keep the rate of P formation high. During the course of reaction, the amount of P in the reaction mixture increases. Therefore, the temperature should be lowered to minimize the rate of formation of the unwanted product from the desired product.

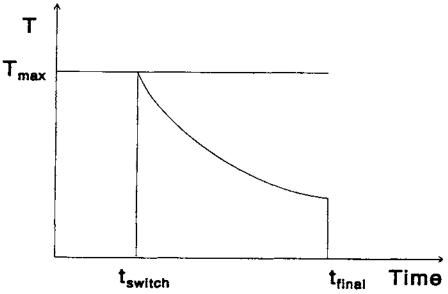

Figure 5.4-72. Optimal temperature profile for consecutive reactions of equal order.

5.4.7.4. Backmixing in gas-liquid(-solid) reactors

Column reactors (packed beds, bubble columns, packed bubble columns, plate bubble columns, spray columns, sieve plate columns), horizontal pipeline contactors, and Venturi scrubbers are operated close to the plug-flow pattern as far as the gas flow is concerned. Backmixing of the gas predominates in mechanically agitated reactors (including the Buss-loop reactor). The gas is also backmixed in column reactors with an internal loop (draft tube) and in spray columns under certain conditions. Plug flow of the liquid is approached in film-type gas-liquid reactors (packed columns and trickle-bed reactors), spray columns, Venturi scrubbers, and horizontal pipeline contactors. The liquid can be considered backmixed in the other types of the aforementioned reactors.

5.4.7.5. Mixing, mechanical agitation

Intense mechanical mixing is always required for competitive fast homogeneous reactions (see Section 5.4.5). Multiphase reactions often also require mechanical agitation for dispersion of the phases and for maintaining solid particles in suspension. Intense mechanical agitation is also required in case of fast, complex reactions. Mixing can be provided by a mechanical stirrer installed inside the reaction zone or by another device (e.g. a static mixer, ejector, or stator-rotor mixer) mounted on the recycle line of the reaction mixture. For low gas consumption (slow reactions), gas-sparged reactors can also be considered. However, mechanical agitation in the reaction zone may be required to keep the catalyst in suspension and to provide sufficiently high rates of mass and heat transfer. In large reactors, problems with sealing of the shaft, shaft stability, etc. may appear. High gas flow rates and recycling of unreacted gas can be used instead of mechanical agitation. Recycling of the reaction mixture associated with entrapping the gas on the recycle (Venturi scrubber) can also replace mechanical agitation in the reaction zone. This is particularly advantageous for highly exothermic reactions: External heat exchangers can be installed on the recycle line. Contrary to gas-sparged reactors, mechanically agitated reactors can be operated in the 'dead-end' mode (e.g. hydrogenations using pure hydrogen). Hollow shaft impellers and multistirrer systems are effective for this type of operation. Mechanical agitation is preferred in case of frequent changes in the feedstock or the process (mulitiproduct plants). Reactors with mechanical agitation are more versatile than gas-sparged reactors. Mechanical agitation (also by recycling of the reaction mixture through nozzles or a Venturi scrubber) is necessary when the interfacial area should be maximized and rapid mass transfer is required.

5.4.7.6. Multiphase reactor selection

Based on the Krishna and Sie (1994) concept three stages of reactor sub-sets or attributes can be distinguished:

- micro-level in the reactor: catalyst particles, bubbles, and droplets,
- additions to and withdrawals from the reaction zone, and
- hydrodynamic flow regimes.

Microlevel. The starting point in multiphase reactor selection is the determination of the best particle size (catalyst particles, bubbles, and droplets). The size of catalyst particles should be such that utilization of the catalyst is as high as possible. A measure of catalyst utilization is the effectiveness factor η (see Sections 3.4.1 and 5.4.3) that is inversely related to the Thiele modulus (Eqn. 5.4-78). Generally, the effectiveness factor for Thiele moduli less than 0.5 are sufficiently high, exceeding 0.9. For the reaction under consideration, the particles size should be so small that these limits are met.

The catalyst shape also plays a role in catalyst selection. There is a variety of extrudates that are mostly shaped as cylinders, which are appropriately modified (see Section 3.3.2). The more complex the shape of the catalyst particles, the larger the surface area per particle volume, and, consequently, the higher the Thiele modulus. Extrudates of complex shape can be produced at little extra cost at diameters below 1 mm. The pressure drop over the catalyst bed depends, among others, on void fraction (fraction of free volume for the fluids). Accordingly, the pressure drop over a bed of shaped extrudates is significantly lower than for spheres. The strength of complex particles is, however, much lower than the strength of compact shapes (spheres, discs, full cylinders). Therefore, thick layers of complex particles, which are subject to larger stresses, can be destroyed during operation. Moreover, more complex particles of lower mechanical strength are more susceptible to stresses during mechanical transport of catalyst particles. Moving particle reactors are then excluded from considerations.

The selectivity in a system of parallel reactions does not depend much on the catalyst size if effective diffusivities of reactants, intermediates, and products are similar. The same applies to consecutive reactions with the product desired being the final product in the series. In contrast with this, for consecutive reactions in which the intermediate is the desired product, the selectivity much depends on the catalyst size. This was proven by Edvinsson and Cybulski (1994, 1995) for selective hydrogenations and also by Colen *et al.* (1988) for the hydrogenation of unsaturated fats. Diffusion limitations can also affect catalyst deactivation. Poisoning by deposition of impurities in the feed is usually slower for larger particles. However, if carbonaceous depositions are formed on the catalyst internal surface, ageing might not depend very much on the catalyst size.

If, from transport-reaction considerations, a particle size smaller than 1 mm is chosen, slurry or monolith reactors will be considered. For larger particles, packed-bed reactors are more suitable.

Structured catalysts, including monoliths, are very promising as far as pressure drop and high performance for selective reactions are concerned. The perspectives for the use of monolithic catalysts in heterogeneous catalysis have been analysed by Cybulski and Moulijn (1994) and are further discussed in Section 5.4.7.7.

The parameter β ($= \varepsilon_l/(\delta \cdot a)$) in gas-liquid systems plays the same role as V_p/A_{ex} in catalytic reactions. This parameter amounts to 10-40 for a gas and liquid in film contact, and increases to 10^3-10^4 for gas bubbles dispersed in a liquid. If the Hatta number (see section 5.4.3) is low (below 1) this indicates a slow reaction, and high values of β (e.g. bubble columns) should be chosen. For instantaneous reactions ($Ha > 100$, enhancement factor $E = 10$-50) a low β should be selected with a high degree of gas-phase turbulence. The sulphonation of aromatics with gaseous SO_3 is an instantaneous reaction and is controlled by gas-phase mass transfer. In commercial thin-film sulphonators, the liquid reactant flows down as a thin film (low β) in contact with a highly turbulent gas stream (high k_G). A thin-film reactor was chosen instead of a liquid droplet system due to the desire to remove heat generated in the liquid phase as a result of the exothermic reaction. Similar considerations are valid for liquid-liquid systems. Sometimes, practical considerations prevail over the decisions dictated from a transport-reaction analysis. Corrosive liquids should always be in the dispersed phase to reduce contact with the reactor walls. Hazardous liquids are usually dispersed to reduce their hold-up, *i.e.* their inventory inside the reactor.

Additions to and withdrawals from the reaction zone. General indications concerning the choice between batch and continuous reactors have been discussed above. Pulsed injections might be advantageous when competitive reactions are of different reaction orders. The selectivity of the process can then be improved. A typical example of this policy is the hydrogenation of dinitriles to diamines, e.g. succinonitrile. This process proceeds via imines, which are extremely reactive. When the reaction mixture is depleted with hydrogen imines will react to unwanted by-products. When pulsing the inlet concentration of the dinitrile, a significant improvement of the yield and selectivity can be obtained. Staged injection of reactants (cross-flow reactors) can also influence the selectivity of complex reactions. An example is the chlorination of propene to allyl chloride. This reaction is accompanied by side reactions leading to 1,3-dichloropropane and 1,3-dichloropropene. The staged addition of chlorine increases the yield of the main product.

Removal of reaction products can shift the equilibrium, forcing the reaction to go to completion. This can be effected by evaporation of products from the reaction mixture (reactive distillations), extraction (including supercritical extraction) of products from the reaction mixture (reactive extractions), or membrane processes. Counter- and cocurrent operation also falls within this category. If the reaction is equilibrium-limited or inhibited by reaction products countercurrent operation outperforms cocurrent operation.

Hydrodynamics. For gas-liquid systems, the following flow regimes are possible: stagnant liquid bed, homogeneous bubbly flow, heterogeneous regime, slug (Taylor) flow, turbulent bed, and spray flow, with β decreasing in this series.

5.4.7.7. Monolith reactor vs. slurry and trickle-bed reactor

The trickle-bed reactor (TBR) and slurry reactor (SR) are the most commonly used for multiphase reactions in the chemical industries. A new reactor type, the monolithic reactor (MR), offers many advantages. Therefore, these three types of reactors are discussed below in more detail. Their general characteristics are given in Table 5.4-44. With respect to slurry reactors, the focus will be on mechanically agitated slurry reactors (MASR) because these are more widely used in fine chemicals manufacture than column slurry reactors.

For simple reactions occurring fully in the kinetic regime, the TBR will outperform the SR and the MR due to a higher load and lower cost of catalyst. In processes involving faster reactions, especially if there are selectivity concerns (like the intermediate product being the desired one), it is not obvious which reactor is best suited. In a fixed bed the reactor vessel is filled with catalyst particles with a size in the range of 1-3 mm. The catalyst particles may be spherical, cylindrical, or of more sophisticated shapes (e.g. multilobes) including egg-shell catalysts with active species concentrated near the outer surface of the particle. The gas and the liquid phase are passed through the bed. Several flow arrangements are possible, though cocurrent downflow is often preferred. An important flow regime is trickling flow, hence the term trickle-bed reactor (see Fig. 5.4.73).

Main advantages of TBRs are the high catalyst loading and the low investment cost. A drawback is the high pressure drop. Fines may also be formed and can then accumulate during operation, thereby increasing the pressure drop. A remedy is to use larger particles, which in the case of fast reactions can result in low catalyst utilization due to the relatively long diffusion distance. In addition, this can also have an adverse effect on the selectivity. The diffusion length in a particulate catalyst is longer than in a monolithic catalyst, so the effectiveness factor is typically lower for the TBR (Edvinsson and Cybulski, 1994). As a consequence, the conversion per unit volume of catalyst is lower in the TBR. Moreover, the diffusion length can influence the selectivity of the reaction if the rate is controlled by diffusion.

Table 5.4-44

Characteristics of trickle-bed reactor (TBR), slurry reactor (SR), and monolithic reactors (MR) for three-phase catalytic processes

Aspect	TBR	SR	MR
Catalyst			
Manufacture	well established	well established techniques	established for gas phase; techniques for liquid phase at developmental stage
cost	low to high, depending on size and shape	low to moderate	high
volumetric catalyst load (ε_s)	0.55-0.6 for conventional packings; <0.3 for shell catalysts	0.05-0.35	0.05-0.25
handling	replacement using well established procedures, continuous possible	continuous replacement possible, filtration can be difficult (except for metals), entrapping possible	monolithic blocks are assembled in frames that can be stacked on top of each other
size	pellets, 1-5 mm	1-200 μm	channels 1-4 mm, walls 0.1-0.3 mm, possibly washcoated, 20-150 μm
stability	high, no mechanical stresses	abrasion and erosion by impeller	
internal diffusion influence	can be significant	rather low	rather low
external catalyst surface area	1000-3000 m^2/m^3	> 3000 m^2/m^3	1500-2500 m^2/m^3
diffusion length	0.1(shell)-2.5 mm	0.5-100 μm	20-150 μm
Operation			
superficial velocities	liq. 0.005-0.05 m/s; gas 0.05-1.5 m/s	gas 0.001-0.05 m/s	liq. 0.03-0.15 m/s; gas 0.05-1.0 m/s; sum ~ 0.4 m/s
residence time	short for both phases possible	short for gas, long for liquid	short for both phases
pressure drop	high for small particles	moderate, low for short liquid layers	very low
mode of operation	pseudo steady-state, non-isothermal (nearly adiabatic); hot spots possible	pseudo steady-state, unsteady-state; usually isothermal	inherently unsteady; non-isothermal (nearly adiabatic)
scale of operation	large	small to large	experience scarce
mixing	nearly plug flow	liquid backmixed, gas plug flow	nearly plug flow
solid particles in the feed	catalyst bed plugged	can be handled	can be handled
high-pressure operation	suitable	problems with sealing may appear	suitable
Design			
experience	many units in operation	many units in operation	only one full-scale process in operation
gas recirculation	external, needs compression	both internal and external	internal, no pump needed
scale-up	gas/liquid maldistribution can appear	rather simple	simple
inlet distribution	good distribution required; liquid tends to flow towards the wall	good distribution needed if no mechanical device is used	very good distribution needed; problems with liquid redistribution between blocks

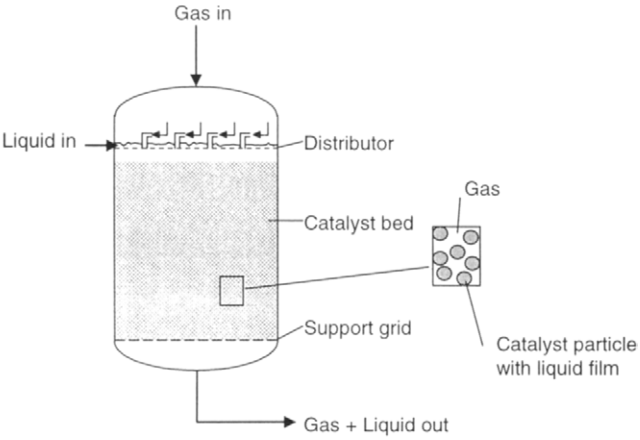

Figure 5.4.73. Schematic of trickle-bed reactor.

Two ways to reduce the diffusion length in TBRs are: 1) use of smaller catalyst particles, or 2) use of an egg-shell catalyst. The first remedy, however, will increase pressure drop until it becomes unacceptable, and the second reduces the catalyst load in the reaction zone, making the loads of the TBR and the MR comparable. For instance, the volumetric catalyst load for a bed of 1 mm spherical particles with a 0.1 mm thick layer of active material is 0.27. The corresponding load for a monolithic catalyst made from a commercial cordierite structure (square cells, 400 cpsi, wall thickness 0.15 mm), also with a 0.1 mm thick layer of active material, is 0.25.

In a slurry reactor (Fig 5.4.74), the catalyst is present as finely divided particles, typically in the range 1-200 μm. A mechanical stirrer, or the gas flow itself, provides the agitation power required to keep the catalytic particles in suspension. One advantage is the high catalyst utilization; not only is the diffusion distance short, it is also possible to obtain high mass-transfer rates by proper mixing.

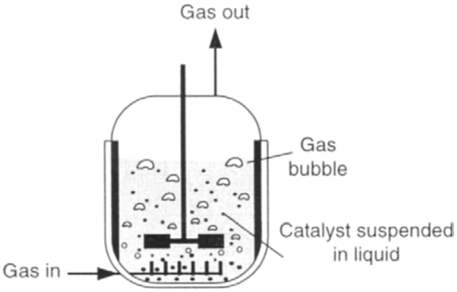

Figure 5.4.74. Schematic of slurry reactor.

Temperature control is also reasonably simple. An important advantage in the case of a rapidly deactivating catalyst is the possibility of continuous catalyst replacement. There are, however, a number of problems associated with handling fine catalyst particles. They have to be separated from the products, which is usually troublesome, plugging of lines and valves can occur, and pyrophoric catalysts may also require special procedures. This is less important if the product can be removed from the reaction mixture (e.g. products are volatile and are stripped during the operation). In case of excessive gas flow rates, however, small catalyst particles can be entrapped and deposited in downstream equipment. The catalyst load is limited to what can be kept in suspension with a reasonable power input.

An alternative for slurry and trickle-bed reactors, which in some aspects can be considered as a compromise between the two, is the monolithic reactor (MR). It is a fixed-bed reactor, although the use of a special, structured catalyst endows it with properties that are quite different from conventional packed beds. The support structure is a block with a large number of parallel channels with diameters in the order of 1 mm (see Fig. 5.4.75). Monoliths are widely used in exhaust gas cleaning, e.g. in car mufflers and in industrial installations. An important advantage is the very low pressure drop, up to two orders of magnitude lower than for a comparable packed bed. If a solid catalyst is to be used, it is typically necessary to create a large surface area to obtain acceptable reaction rates. There are two basic methods to achieve this: 1) use a support structure that is porous itself (e.g. γ-Al_2O_3) or, 2) deposit a thin layer of a porous material onto the channel walls. This layer is called a washcoat and is typically 20-100 μm thick. The use of a washcoat offers the possibility to combine a substrate with good thermal and mechanical properties with the desired catalyst support phase. This may justify the extra costs incurred by using a separate washcoat. For operation in the kinetic regime, monoliths can be more advantageous due to their easier operation. The catalyst does not disintegrate as a result of stirrer action and catalyst separation is avoided. Benefits of monolithic reactors can only be achieved with stable catalysts. For quickly deactivating catalysts, slurry reactors are easier to operate, since replacement of decayed catalysts is simpler.

Obviously, the least experience has been accumulated with monoliths, particularly in three-phase applications. They are also more expensive than the other reactors. Therefore, the use of monoliths can only be economically justified for three-phase processes in which it offers a distinct advantage, like higher yield, improved selectivity, increased throughput of a plant, or lower overall investment or operating costs. Of particular interest are situations in which a MR substantially simplifies the design or operation of a unit.

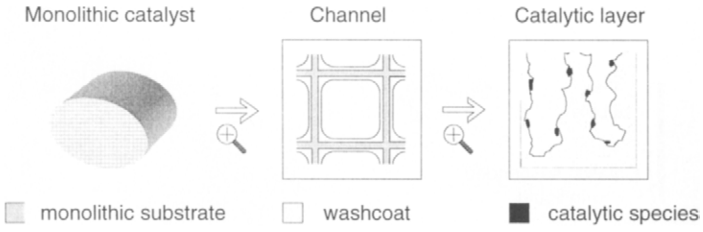

Figure 5.4.75. Example of a monolith with square channels.

It should be possible to reduce the cost of monoliths by making use of the experience of manufacturers of modern heat exchangers, which contain similar structures. It should also be noted that the high cost of monoliths is in part explained by the fact that they are mostly designed to meet demands of high-temperature operation.

A monolithic reactor can be an attractive alternative to a trickle-bed reactor for hydrogenations proceeding by a consecutive reaction scheme with an intermediate as the desired product. Reactants preferably flow down forming a train of gas and liquid plugs being driven by gravity force. The flow pattern is close to plug flow for both phases. Due to the very low pressure drop, pressure losses are balanced by the hydrostatic head and the pressure can be considered constant along the reactor. For a MR operating in downflow mode, it is possible to balance the pressure drop with the hydrostatic pressure of the liquid inside the channels. The essentially zero net pressure drop provides an opportunity to operate the MR with internal recirculation of hydrogen. Since the gas does not need to be recompressed, an open passway from the bottom of the reactor to the top is all that is needed. When operating in the Taylor flow regime (see Fig. 5.4.76) it is possible to obtain low axial dispersion and high mass-transfer rates (Irandoust and Andersson, 1989). In this flow regime the gas and the liquid form a sequence of distinct plugs flowing alternately. The gas plugs are separated from the wall by a thin layer of liquid. This has a number of advantages: 1) the gas bubbles disturb the laminar flow in the liquid plugs and force the liquid to recirculate within a plug (see Fig. 5.4.76), thus improving radial mass transfer, 2) since all exchange of liquid between plugs must take place through the thin liquid film surrounding the bubble, axial dispersion is reduced, 3) the thin liquid film provides a short diffusion barrier between the gas and the catalyst and, in addition, enlarges the gas/liquid contact area.

Major drawbacks of the MR are the higher cost (although steadily decreasing), the lower catalyst load compared to a TBR, and the relatively little experience with this type of reactor. Due to the higher cost of monolithic catalysts only processes in which the catalyst is reasonably stable and/or easy to regenerate are feasible.

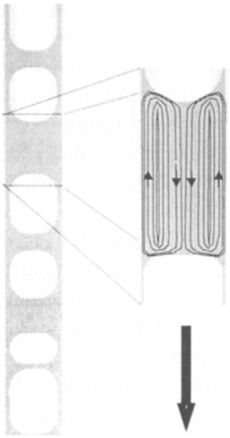

Figure 5.4.76. Taylor flow in monolith channels.

In principle, scale-up of monoliths can be expected to be straightforward since the conditions within the individual channels are scale-invariant. However, care must be taken to produce a uniform distribution of the flow at the reactor inlet. This is even more important for the MR than for the TBR since the monolithic structure does not permit radial flow, except at the passage between blocks stacked on top of each other. Non-uniform distribution will be propagated along the reactor but no maldistribution will be formed inside the reactor as opposed to the situation in packed-bed reactors. Maldistribution can cause incomplete wetting in some parts of the reactor. This could result in lower overall production rates and poorer selectivity. For strongly exothermic reactions the consequences may be more severe, *i.e.* the occurrence of hot spots and possibly even runaways. The relatively low radial heat-transfer rate in a large reactor implies that operation is essentially adiabatic.

Trickle-bed reactors are operated at comparable superficial liquid velocities as and much higher superficial gas velocities than monoliths. The gas velocities for the latter are restricted by the Taylor flow requirements; for higher velocities a transition into annular flow would occur. Hence, in this respect trickle-bed reactors are superior to monolithic reactors for processes characterized by a high consumption of gaseous reactants. However, this superiority is achieved at the cost of a much higher pressure drop in trickle-bed reactors. External mass transfer in monoliths is better than that in trickle beds. Thus for external mass transfer-limited processes, monoliths could be favoured. For internal diffusion-controlled processes a detailed comparison for each process has to be made. However, the short diffusion path in monoliths implies an easier manipulation of the selectivity than in trickle-beds. Therefore, changes in flow, temperature and/or concentrations can more easily influence the rate and selectivity in monolithic reactors; periodic operation (an alternate flow of gas and liquid plugs in the Taylor flow regime) is an inherent feature of monolithic pseudo steady-state processes.

Below some more detailed considerations are given with respect to hydrogenations that are typical catalytic reactions in fine chemicals manufacture.

Circulation pattern. The MR can be operated in either single-pass mode or with external liquid recycle (see Fig. 5.4.77) whereby in both cases the MR can be operated in (semi)batch or continuous mode. Unreacted gas can be recycled internally without a compressor since no pressure drop exists inside the reactor. The rate of mass transfer is rather high, which is particularly advantageous in case of hydrogenation processes, which can be carried out in the kinetic regime without the necessity of passing large volumes of gas to minimize tmass-transfer resistance. This also applies to the continuously operated MR. Since a liquid recycle introduces back-mixing that can influence the selectivity negatively, single-pass (plug flow) mode is preferred. A requirement is that the desired conversion can be reached in one pass and that the (adiabatic) temperature rise is acceptable.

The MASR can be operated either as a batch reactor or a CSTR, both working in the regime close to ideal mixing. Unreacted gas can be recycled internally using a hollow shaft or multistirrer systems with a rather limited rate of circulation. Internal liquid circulation is inherent to this reactor type. External liquid recirculation is considered impractical since it would require undesired pumping of the catalyst slurry with accompanying extra energy expenditure. The typical energy input for mixing/circulation of the liquid in a MASR in fine chemicals plants (4-5 m^3) ranges from 7.5 to 25 kW (1.5 to 5 kW/m^3), while that needed for the external liquid circulation in an MR of similar throughput is only about 5 kW.

Heat transfer. Rates of three-phase industrial processes range from 0.5 to 15 mol/m^{3}s. The corresponding rate of heat generation for typical concentrations and heats of reaction varies from about 0.25 to 7.5 MW/m^3. The heat-exchange surface area per unit volume in the MASR ranges from 2.5 to 3.5 m^2/m^3 for standard reactors with a volume of 3-6 m^3. The cooling duty of such reactors is about 0.25-0.35 MW/m^3. Reactors used for hydrogenations catalysed by slurry catalysts are of higher aspect ratio, which results in a larger cooling duty, amounting to 0.65-1 MW/m^3. This is, however, insufficient to remove the heat generated by fast and exothermic reactions, *i.e.* the MASRs used in fine chemicals manufacture (hydrogenations) are reactors which are limited by heat removal. The required rate of heat removal can be controlled, for example, by the amount of catalyst and its metal content, the temperature, or the hydrogen pressure and its flow rate.

There is no indirect heat transfer in the reaction zone in the MR. The reaction proceeds almost adiabatically: More than 90 % of heat evolved due to reaction is used for heating up the liquid flowing through the channels of the monolithic catalyst. The maximum adiabatic temperature rise, assumed to be 20 °C, can usually be preserved for single-pass operation with respect to the liquid. For more exothermic and/or faster reactions, circulation of the liquid is necessary. The heat of reaction can be removed outside the reaction zone by using a heat exchanger located in the external loop for the liquid circulation. In compact designs, the heat exchanger can be inside the reaction column, below the catalyst. In typical plants for hydrogenations that use jet reactors with external heat exchangers, the heat-exchange surface area per unit volume is about 27 m^2/m^3 (Concordia, 1990). The cooling capacity of MR plants with such heat exchangers would be about 2.5-3 MW/m^3 of the reaction zone and can be appropriately adjusted to the requirements.

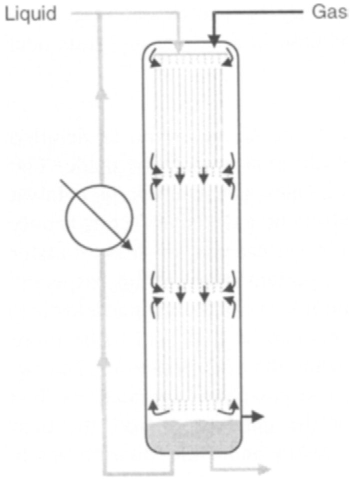

Figure 5.4.77. Monolith reactor with external liquid recycle.

Reactor throughput. For a comparison, let us consider a semibatch hydrogenation process run in a MASR with a volume of 1 m^3. The reaction mixture occupies about 75 % of the reaction zone. The gas hold-up is typically 30-35 % and this means that the reactor is filled with liquid for only 50 %. A typical catalyst content is ca. 3 %, *i.e.* 15 kg in the reactor under consideration. In an MR with such an amount of catalyst the reaction zone would be 0.5 m^3. For a compact reactor design with a heat exchanger below the reaction zone in the same column and a space for the circulating liquid the maximum total volume of such a MR would be 1.5 m^3. However, catalytic hydrogenations in MASRs are limited by heat removal, which is about 2.5 times more intense in MRs with an external heat exchanger. Moreover, the proportion of 'unproductive' time (charging, heating up reaction temperature, cooling, emptying, filtration of solids from the reaction mixture, etc.) in MASRs is larger by 30-150 % than that in the MR (filling and emptying of the bottom of the reactor only), depending on the size of the reactor, see, e.g., data for MASRs and jet reactors (Concordia, 1990). Summarising, the capacity of the MR per unit volume of reactor is ca. 2.5 times larger than that for the MASR. It is worth noting that standard MASRs have a maximum volume of 15 m^3 and that the maximum pressure for such reactors is 3.5 MPa (EKATO *Handbook of Mixing Technology*, 1991). There are no such limits for column reactors like the MR.

Safety. The MR is much safer than the MASR. (1) The reaction zone contains a much smaller amount of the reaction mixture (hazardous material), which always enhances process safety. (2) In case of pump failure, the reaction automatically stops since the liquid falls down from the reaction zone. (3) There is no need to filter the monolithic catalyst after the reaction has been completed. Filtration of the fine catalysts particles used in slurry reactors is a troublesome and time-consuming operation. Moreover, metallic catalysts used in fine chemicals manufacture are pyrophoric, which makes this operation risky. In a slurry reactor there is a risk of thermal runaways. (4) If the cooling capacity is insufficient (e.g. by a mechanical failure) a temperature increase can lead to an increase in reaction, and thus heat generation rate.

Process economics. An economical evaluation of the process alternatives requires detailed knowledge of price and cost factors. However, some general observations can be made. The cost of monoliths is higher than that of conventional catalyst shapes, and when large catalyst volumes are required for a relatively slow reaction this is likely to be a decisive factor. If only the outer portion of the catalyst can be utilized effectively (selectivity or mass-transfer constraints) the monolithic reactor becomes competitive. An important factor in this respect is the acceptable pressure drop, since this determines the minimum size of catalyst particles in a TBR but has little effect on the performance of the MR. This can be expected to be more important when only small pressure drops are accepted, e.g. when the system pressure is low. Most of the progress made in monolith technology is related to gas-phase applications. For gas-liquid processes in which only slight modifications of the catalyst suffice, the cost difference should be moderate. The design of the reactor vessel and fluid distributors is perhaps slightly more complex and more expensive for the MR than for the TBR. Much more experience is available in the design of TBRs compared to MRs, in which only one process is operated at full scale. TBRs are, however, liable to problems with fluid distribution throughout the bed. The scale-up of MRs in principle is more straightforward, though little help is available in the literature on the design of liquid distributors. A possibly unique feature of the MR operated at zero net pressure drop, hydrostatic pressure balancing the frictional one, is the simple way in which internal gas recirculation can be achieved. Since the gas does not need to be recompressed an open passway from the bottom of the reactor to the top is all that is needed. This can simplify the process and hence reduce operation and investment costs.

Summary. A monolithic reactor can be an attractive alternative to a trickle-bed reactor for hydrogenations proceeding by a consecutive reaction scheme with an intermediate as the desired product. For the model parameters and design/operating variables considered, a MR can perform better for fast reactions characterised by initial rates higher than 10 mol m^{-3} s^{-1}. For such fast reactions, performance indices are better than those for a TBR with particles of sizes larger than 2 mm. The selectivity is better for MRs over almost the whole range of design and operating variables studied. The selectivity of the TBR can be increased for this type of reaction if an egg-shell catalyst is used. The use of egg-shell catalysts leads to a reduction in catalyst load, which then becomes comparable to that of a MR. The higher productivity of the TBR is reached at the cost of a relatively high pressure drop, up to 5 bar per reactor unit, which limits the size of the reactor.

Mass transfer-limited processes favour slurry reactors over monoliths as far as the overall process rates are concerned. Moreover, slurry reactors are more versatile and less sensitive to gas flow rates. However, the productivity per unit volume is not necessarily higher for slurry reactors because of the low concentration of catalyst in such reactors. There also is no simple answer to the selectivity problem, and again, each process should be compared in detail for both reactors.

Acronyms

ARC	Accelerating Rate Calorimetry
ASTM	American Society for Testing and Materials
BSC	Bench Scale Calorimeter
BOD	Biological Oxygen Demand
BSTR	Batch Stirred-Tank Reactor
CF	Cash Flow
CFD	Computational Fluid Dynamics
cGMP	current Good Manufacturing Practice
CHETAH	Chemical Thermodynamics and Energy Release Evaluation
COD	Chemical Oxygen Demand
CPI	Chemical Process Industries
CSTR	Continuous Stirred-Tank Reactor
CZ	Circulation Zone
DIERS	Design Institute of Emergency Relief Systems
DCF	Discounted Cash Flow
DCFRR	Discounted Cash Flow Rate of Return
DOT	US Department of Transportation
DSC	Differential Scanning Calorimetry
DTA	Differential Thermal Analysis
DW	Degree of Washing

FCC	Food Chemicals Codex
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
IATA	International Air Transport Association
ICV	Impeller Control Volume
IDS	Impeller Discharge Stream
IMDG	International Maritime Dangerous Goods code
IRR	Internal Rate of Return
MASR	Mechanically Agitated Slurry Reactor
MPP	MultiProduct or MultiPurpose Plant
MR	Monolithic Reactor
MSDS	Material Safety Data Sheet
MTSR	Maximum Temperature for Synthetic Reaction
NPV	Net Present Value
PFR	Plug-Flow Reactor
POT	Pay-Out Time
RC	Reaction Calorimetry
R&D	Research and Development
ROI	Return On Investment
SBSTR	SemiBatch Stirred-Tank Reactor
STR	Stirred-Tank Reactor
TBR	Trickle-Bed Reactor
TDL	Toxic Dose Low
TLV	Threshold Limit Value
TOD	Total Oxygen Demand
VLE	Vapour-Liquid Equilibrium

Symbols

a	- activity	mol m^{-3}
a	- unit interfacial surface area	m^{2} m^{-3}
a_p	- external surface area of particles	m^{2} m^{-3}
a_j	- coefficient in Eqn. (5.4-17)	kJ mol^{-1} K^{-1}
A	- heat-transfer surface area, surface area of filter medium	m^{2}
A	- amplitude of oscillations	
A_{ex}	- external surface area of the catalyst particle	m^{2}
A_r	- heat transfer surface area in the reactor	m^{2}
A_{cr}	- surface area of crystals	m^{2}
b	- order of nucleation	dimensionless
b_j	- coefficient in Eqn. (5.4-17)	kJ mol^{-1} K^{-2}
c	- concentration	mol m^{-3}
c_b	- concentration in bulk	mol m^{-3}
c_f	- final concentration	mol m^{-3}
c_i	- concentration at interface	mol m^{-3}
c_j	- coefficient in Eqn. (5.4-17)	kJ mol^{-1} K^{-3}

c_s	- concentration at solid surface	mol m^{-3}
c_0	- initial concentration	mol m^{-3}
c_p	- heat capacity	kJ kg^{-1} K^{-1}
C	- coefficient in Eqn. (5.4-148)	
CF	- total annual cash flow	\$/year
d_j	- coefficient in Eqn. (5.4-17)	kJ K mol^{-1}
d_m	- mean droplet diameter	m
d_p	- particle diameter	m
d_t	- tube diameter	m
D	- diffusivity	m^2 s^{-1}
D_{eff}	- effective diffusivity	m^2 s^{-1}
D_r	- reactor diameter	m
D_s	- stirrer diameter	m
D_{turb}	- turbulence diffusivity	m^2 s^{-1}
DCF	- discounted cash flow	\$/year
$DCFRR$	- discounted cash flow rate of return	dimensionless
DW	- degree of washing of the filter cake	dimensionless
E	- activation energy	kJ mol^{-1}
E	- enhancement factor (Eqn. 5.4-71)	dimensionless
E	- engulfment rate constant	s^{-1}
F_V	- volumetric flow rate	mol s^{-1}
G	- distance between the feed pipe and the stirrer	m
$G_{j,T}^0$	- standard Gibbs free energy for species j	kJ mol^{-1}
ΔG_T^0	- standard Gibbs energy change of reaction	kJ mol^{-1}
h_t	- overall heat-transfer coefficient	W m^{-2} K^{-1}
H	- Henry's constant	Ps m^3 mol^{-1}
H_r	- height of fluid in the reactor	m
ΔH	- heat of reaction	kJ mol^{-1}
ΔH_T^0	- standard enthalpy change of reaction	kJ mol^{-1}
$\Delta H_{f,j}^0$	- standard enthalpy of formation of species j	kJ mol^{-1}
IRR	- internal rate of return	dimensionless
k	- frequency factor, pre-exponential factor	s^{-1}
k_A	- mass-transfer coefficient for component A	m s^{-1}
k_{diff}	- mass-transfer coefficient for external diffusion	kg m mol^{-1} s^{-1}
k_{dr}	- rate constant for constant drying rate	s^{-1}
k_{gr}	- rate constant for crystal growth	s^{-1}
k_G	- mass-transfer coefficient from the gas to liquid on gas side	mol m^{-}1 Ps^{-1} s^{-1}
k_{int}	- mass-transfer coefficient for integration	kg m mol^{-1} s^{-1}
k_L	- mass-transfer coefficient from the gas to liquid on the liquid side	m s^{-1}
k_j	- vapour-liquid equilibrium coefficient of species j	dimensionless
k_{nucl}	- rate constant for nucleation	s^{-1}
k_s	- mass-transfer coefficient at the solid surface	m s^{-1}
K	- permeability of the filter cake	m^2
K	- chemical equilibrium constant	dimensionless
K	- adsorption equilibrium constant	m^3 mol^{-1}
K_{extr}	- distribution coefficient	dimensionless

L	- thickness of the filter cake	m
L_c	- integral scale of concentration fluctuations	m
L_{cr}	- size of crystals	m
L_{seed}	- size of seeding crystals	m
L_v	- latent heat of vaporisation	kJ kg^{-1}
m	- mass	kg
m_s	- mass of solid	kg
m_{seed}	- mass of seeds	kg
n	- number of moles	mol
n	- filter cake compressibility	dimensionless
N	- speed of rotation	s^{-1}
N_A	- mass-transfer rate per unit interfacial area	mol m^{-2} s^{-1}
N_c	- number of components of the mixture	dimensionless
N_e	- number of experiments	dimensionless
N_f	- number of filtration experiments	dimensionless
N_p	- number of particles	dimensionless
N_r	- number of reslurryings of the filter cake	dimensionless
N_T	- total concentration of active sites	mol m^{-2}
N_V	- mass-transfer rate per unit volume area	mol m^{-2} s^{-1}
NPV	- net present value	\$
p	- pressure	Pa
p_b	- pressure in bulk of the gas phase	Pa
p_b	- pressure at interface	Pa
P	- power	W
P_{filter}	- filter productivity	m^3 s^{-1}
ΔP_c	- pressure difference over the filter cake	Pa
ΔP_{fm}	- pressure difference over filter medium	Pa
ΔP_t	- total pressure difference	Pa
POT	- pay-out-time	year
q	- heat flux	W
q_P	- heat evolved due to reaction	W
Q	- heat evolved due to reaction	J/mol
Q	- ratio of time constant for engulfment to time constant for micromixing	dimensionless
r	- rate of chemical reaction	mol m^{-3} s^{-1}
r	- absorption rate	mol m^{-3} s^{-1}
r_{nucl}	- nucleation rate	nuclei s^{-1}
R_g	- universal gas constant	m Pa mol^{-1} K^{-1}
R_{fm}	- resistance of filter membrane	m^{-1}
ROI	- return on investment	year
S	- supersaturation ratio	dimensionless
S	- selectivity	dimensionless
SS_{res}	- sum of squares of residuals	
$\Delta S_{f,j}^{0}$	- standard entropy of formation of species j	kJ mol^{-1}
ΔS_T^{0}	- standard entropy change of reaction	kJ mol^{-1} K^{-1}
t	- time	s

t_c	- time at constant period of drying	s
t_{charge}	- time of charging	s
t_{cl}	- time of cleaning	s
t_{crit}	- critical time	s
t_{cycle}	- cycle time	s
t_D	- time of dosing	s
t_{disch}	- time of discharging	s
t_{filtr}	- time of filtration	s
t_{fd}	- time required for falling rate of drying	s
T	- temperature	K
T_0	- initial temperature	K
T_f	- final temperature	K
T_j	- jacket temperature	K
T_r	- temperature in the reactor	K
TMR_{ad}	- time to reach maximum reaction temperature under adiabatic conditions	s
ΔT_{ad}	- adiabatic temperature rise	K
u	- velocity	$m\ s^{-1}$
u_f	- liquid velocity at feed pipe	$m\ s^{-1}$
u_T	- agitator tip speed	$m\ s^{-1}$
u'	- mean velocity fluctuation	$m\ s^{-1}$
U	- overall heat-transfer coefficient	$W\ m^{-2}\ K^{-1}$
U	- degree of uniformity	dimensionless
V	- reactor volume, volume of filtrate	m^3
V_e	- volume of single eddy	m^3
V_f	- volume of filtrate	m^3
V_l	- volume of liquid retained in the filter cake	m^3
V_m	- molar volume in the liquid phase	$m^3\ mol^{-1}$
V_r	- volume of the reaction mixture	m^3
V_{wl}	- volume of washing liquid	m^3
w	- mass of dry solid per unit volume of filtrate	$kg\ m^{-3}$
w	- moisture mass per unit mass of dry material	dimensionless
w_c	- critical moisture content	wt. %
w_e	- moisture content at equilibrium	wt. %
w_t	- moisture content at any time	wt. %
x	- molar or mass fraction	dimensionless
x_j	- molar fraction of species j in the liquid	dimensionless
X	- conversion	dimensionless
y	- dependent variable	
y_j	- molar fraction of species j in the gas	dimensionless
Y	- yield	dimensionless
Y_{cr}	- yield of crystallisation	dimensionless

Dimensionless numbers

Ar	- Arrhenius number = $E/(R_gT)$
B	- reaction thermal number = $Ar\ (\Delta T_{ad}/T)$

Da	- Damköhler number for micromixing = $k\ c/E$
Da	- Damköhler number = $r\ t_D/c_0^{n-1}$
Ha	- Hatta number = $\sqrt{(k\ D_A/k_{L,A}^2)}$ for first order reaction in the gaseous reactant and zero order in the liquid reactant
N_p	- power number = $P/(\rho N^3 D_s^5)$
Nu	- Nusselt number = $h\ d_t/\lambda$
Re	- Reynolds number = $u\ d_t\ \rho/\mu$
Re	- Reynolds number = $N\ D_s\ \rho/\mu$
Sc	- Schmidt number = $c_p\ \mu/\lambda$
Se	- Semenov number = $Da\ B/St$
St	- Stanton number = $[U\ A_r\ t_D]/[\rho\ C_{p,m}\ t]$

Greek symbols

α	- specific cake resistance	m kg^{-1}
α	- reaction order	dimensionless
α_{int}	- order of integration	dimensionless
α_0	- coefficient in Eqn. (5.3-23)	m kg^{-1}
β	- coefficient in eqn (5.4-198)	dimensionless
γ_j	- activity coefficient for species j in the liquid phase	dimensionless
δ	- Kronecker delta	dimensionless
δ_L	- thickness of the liquid layer	m
ε	- porosity of the filter cake	dimensionless
ε	- specific energy dissipation	kJ m^{-3}
ε_{disp}	- volume fraction of the dispersed phase	dimensionless
ε_G	- gas hold-up	dimensionless
ε_L	- liquid hold-up	dimensionless
η	- effectiveness factor	dimensionless
η_B	- Batchelor microscale	m
η_K	- Kolmogoroff microscale	m
θ_j	- fraction of total active sites covered by species j (coverage)	dimensionless
λ	- thermal conductivity	W m^{-1} K^{-1}
μ	- coefficient of dynamic viscosity	Pa s
ν	- kinematic viscosity	m^2 s^{-1}
ν_j	- stoichiometric coefficient for species j	dimensionless
ρ_c	- density of continuous phase	kg m^{-3}
ρ_s	- density of solid	kg m^{-3}
σ	- relative supersaturation	dimensionless
σ	- surface tension	N m^{-1}
σ^2	- error variance	
τ	- residence time	s
τ_M	- mixing time	s
τ_D	- time scale (constant) for mesomixing by turbulence	s
τ_R	- time scale (constant) for reaction	s
τ_{ms}	- time scale (constant) for mesomixing by inertial convective process	s
τ_ω	- time scale (constant) for engulment	s

τ_{99}	- blend time for 99 % uniformity	s
ϕ_j	- fugacity coefficient for species *j*	dimensionless
ϕ	- Thiele modulus	dimensionless
ψ	- rate of energy dissipation per unit mass of fluid	W m^{-3} or W kg^{-1}
ω	- rotational speed	s^{-1}

Subscripts

a	- in respect to activity
abs	- for absorption
ave, avg	- average
c	- critical
c	- continuous phase
calc	- calculated
cr	- crystallisation
ch	- charging
cl	- cleaning
diff	- diffusion
disch	- discharging
disp	- dispersion
e	- equilibrium
eff	- effective
exp	- experimental
ex, ext	- external
extr	- extraction
f	- final
f	- feed
fd	- falling rate of drying
filtr	- filtration
fm	- filter membrane
i	- interface
in	- at the inlet
int	- integration
intr	- intrinsic
j	- species *j*
l	- lower
L	- liquid
m	- mean
max	- maximum
met	- metastable region
ms	- mesomixing
nucl	- nucleation
obs	- observed
out	- at the outlet
ov	- overall
p	- particle

peak - in peak
rec - recirculation
s - solid (surface)
seed - seeds
t - total
turb - turbulence
u - upper
V - volumetric
wl - washing liquid
0 - initial

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6. Separation Methods

This chapter will be concerned with some general aspects of separation methods with specific reference to fine chemicals. Several textbooks and authoritative state-of-the-art reviews are available for individual methods of separations.

6.1. DISTILLATION

Distillation is still the most widely used method of separation in the manufacture of fine chemicals and is often the first choice in view of low costs, wealth of experience, and proven performance.

6.1.1. Batch distillation

Batch columns are widely used in industrial practice for making fine chemicals. Very often these are packed columns and structured packings of different configurations are now widely used. These packings offer very low values of height equivalent to a theoretical stage; values of 0.15 to 0.20 m are common, and if desired even a value of 0.10 m can be realized. Structured packings also exhibit low pressure drop, which is a great advantage in distillation at reduced pressure commonly employed in the fine chemicals industry. Absolute pressures at the top of the column of 5 mm Hg are common and at times even have values as low as 1 mm Hg.

We may encounter problems in the purification of substances with a high normal boiling point. If purification only requires a small number of theoretical stages, Short Path Distillation (SPD), in which pressures can be as low as 0.001 bar, can prove useful. Many vitamins and pharmaceuticals can be processed without deterioration of quality. It is now common to use mechanical vacuum pumps with proper condensers preceding the pump.

Strategies for optimum reflux ratio are covered in standard texts on the subject. In the recent past the subject of batch distillation has attracted attention, and different column configurations and operating policies have been suggested. The column configuration is concerned with the arrangement of the column as to where the product is withdrawn. The operating policy is concerned with how to operate the column, e.g. at constant reflux ratio or constant distillate composition. Inverted, middle-vessel, and multi-vessel configurations have been suggested (Sorensen, 1997).

In the *inverted* configuration the feed is charged to the reflux drum and then continuously added to the top of the column. The *inverted column* seems to be better suited for cases in which the products are to be recovered at high purity from a feed low in light components, whereas the regular column appears to be best for cases in which the products are to be recovered at high purity from a feed rich in light components.

A *middle-vessel* batch column consists of two column sections and one middle vessel. The feed mixture is introduced in the middle vessel and the products are simultaneously withdrawn from the top and the bottom of the column, with the result that the material in the vessel is increasingly purified.

A *multi-vessel* configuration has a number of vessels equal to the number of components minus two. Each of the components is collected from the corresponding vessel, depending on their relative volatilities. The purity of the components is determined by the separation in the column sections above and below the vessel. This configuration offers some advantages over regular batch distillation. The operation is simple since no product changeovers are required during operation; the energy requirement may be much less due to the multi-effect nature of the operation, in which heat required for separation is supplied only to the reboiler and cooling is done only at the top.

Sorensen (1999) has suggested a cyclic operation policy for batch distillation with repeated filling and dumping of the reflux drum. This configuration achieves the maximum attainable separation and requires minimal control. Furthermore, such a column can be operated very safely.

Mixtures containing small amounts of both lights and heavies are common. Typically, such mixtures are separated in two columns by 'direct sequence' (Dimian and Kersten, 1997).

A single-column distillation configuration called Flash Compact System has been proposed which is capable of delivering an equivalent high purity product. The key advantage lies in the lower capital and operating costs. The feed is heated and pre-flashed and then sent to a distillation column as two separate vapour and liquid feeds.

For the distillation of a multi-component system in a batch column, the established practice leads to sequential removal of products from lower to higher boiling points. A strategy has been suggested, with a proper analysis, which involves the removal of all the products except the heavies, with subsequent fractionation of the mixture.

There are situations in practice where feeds containing suspended solids have to be distilled. In such cases liquid distributors have to be carefully designed; pipe-orifice distributors should never be used and the trough type is probably the best. Grid-structured packing and third generation random packings can probably handle most of the feeds containing solids (Sloley and Martin, 1995).

6.1.2. Azeotropic distillation

Azeotropes are frequently encountered in the distillation of industrial mixtures; these can be binary or ternary and homogenous or heterogeneous. Heterogeneous azeotropes offer many advantages, because the products separate into two layers upon cooling. When azeotropes are undesirable it should be ascertained whether these will vanish with a pressure swing; in some cases we may even encounter reversal of relative volatilities, to the advantage of obtaining pure product as an overhead material, in a two-column system or a single column operated sequentially at the selected pressure (Horwitz and Frank, 1997).

In some cases we may find it expeditious and convenient to remove an undesired impurity (or even the desired product) azeotropically and then deal with the streams. For example, in the separations of vanillin from close-boiling substances such as *p*-hydroxybenzaldehyde, azeotropic distillation with dibenzylether is claimed to be useful (Dimian and Kersten, 1997).

6.1.3. Extractive distillation

A trade-off between selectivity and solvability should be considered when selecting a solvent. Adding co-solvents can make tough separations technically and economically feasible. Lee and Gentry (1997) have tabulated dielectric constants of selected solvents. A new class of solvents is based on the use of an aqueous solution of hydrotropes. Gaikar and Sharma (1989) have reported the separation of close-boiling *p*-cresol and 2,6-xylenol with aqueous solutions of hydrotropes, such as the sodium salt of *p*-toluene sulphonic acid, as a novel solvent in extractive distillation.

6.1.4. Reactive distillation

A reference was made to distillation-column reactors (DCRs) with cationic ion-exchange resins as a catalyst, in different forms, in Section 4.1.2.2. Similarly, zeolites have been used as catalysts in distillation-column reactors. In the recent past this subject has received a lot of attention. The key advantages are related to combining reaction and separation and utilizing the heat of reaction in a meaningful way. An additional advantage can be enhanced selectivity to the desired product, particularly when consecutive/parallel reactions are involved. The ratio of the reactants can be much lower than in batch reactors and the capital and energy costs decrease substantially. In spite of the advantages mentioned above and some other benefits, this strategy is still confined to a limited number of reactions, e.g. esterification, etherification, and alkylation reactions. The success seems to depend much on the properties of the particular system. When a homogeneous catalyst is used, we can use packed or plate columns. However, if the reaction is slow and a long residence time is required, we use plate columns with higher weir heights so that submergence is high and hence liquid hold-up becomes high, which in turn allows a longer residence time.

The availability of ion-exchange resin catalysts in the shape of random and structured packings has further improved the prospects of this technology. Internally-finned monoliths as packings have also been proposed (Lebens *et al.* 1999). The removal of impurities like formaldehyde from aqueous solutions of butynediol can be accomplished in a DCR with a cationic ion-exchange resin as catalyst and methanol (sometimes already present in formaldehyde) as reactant via conversion to volatile methylal (Kolah and Sharma, 1995). Manufacture of special solvent reactants like dioxolan and ethylal can be carried out in a DCR with a cationic ion-exchange resin as the catalyst (see Section 4.1.2.3), in which for dioxolane ethylene glycol and formaldehyde are involved and for ethylal formaldehyde and ethanol.

The side-chain substitution of toluene, *p*-chlorotoluene, etc. is industrially practised. This reaction is carried out in a photochemical reactor. It is an exothermic reaction in which HCl is produced. The reaction is consecutive, and hence Cl_2 first reacts with toluene reacts to form the desired benzyl chloride, which is then converted to benzal chloride, and finally benzotrichloride. We may, however, well be interested in the selectivity to benzyl chloride. An additional complication arises due to nuclear chlorination, which is most undesirable. A distillation-column reactor can offer advantages (Xu and Dudukovic, 1999).

6.2. EXTRACTION

6.2.1. Solvent extraction

Whenever a product mixture cannot be separated by distillation or distillation is too expensive due to high capital and energy costs, as in the case of dilute aqueous solutions of acetic acid, dimethylformamide, etc., it may be prudent to consider separation through solvent extraction. The selected solvent should obviously not be a close-boiling substance with respect to the solute and should not be toxic while it should be relatively cheap. When aqueous solutions are handled it is important to recognize the solubility of the selected solvent in water, so that treatment of the raffinate will not become too important and solvent losses are kept to a minimum. Aqueous solutions of hydrotropes sometimes can be used to separate water-immiscible close-boiling mixtures.

Extractors with mechanical agitation, such as mixer-settlers, Kuhni columns, York-Schiebel columns, etc., should be avoided as much as possible. Up to seven theoretical stages packed extraction columns can be conveniently adopted. Sieve-plate extractors can be used up to 20 stages. When a very efficient extraction has to be carried out with expensive solutes, and for reasons of material stability and requirements of low expensive product inventory, we may have to use centrifugal extractors or hollow-fibre extractors.

Weatherley (1998) has discussed all the relevant aspects of the separation of low molecular weight biologically produced molecules by solvent extraction. A high degree of selectivity can be realized by careful selection of the solvent. Problems associated with the rheology of the broth, the presence of surfactants and solid materials needs to be recognized. There is a scope to consider intensified electrostatic contact for broth dispersion and separation. Examples covered in this treatise include penicillin G and *cis*-dihydrodiols.

6.2.2. Solvent extraction with aqueous hydrotropes

In Section 4.3.3 the use of hydrotropes for intensifying multiphase reactions and making them more selective was covered. The key advantage of an aqueous solution of a hydrotrope is that the solute can be recovered by diluting the aqueous solution, after extraction, to a hydrotope concentration below the critical hydrotrope concentration, when a major part of the product will separate out. The diluted solution can then be reconcentrated at reduced pressure to the original concentration for recycle. Thus a number of products of commercial value, such as phenyl ethyl alcohol, can be recovered (Friberg *et al* 1996; Gaikar and Phatak, 1999).

6.2.3. Extraction in aqueous-aqueous systems

Two immiscible liquid phases are formed when, for instance, dextran and polyethylene glycols (PEG) are used (Albertsson, 1986). Such an extraction system is suitable for the separation of proteins and enzymes, which generally cannot withstand an organic solvent in extraction. The interfacial tension between the two phases is extremely low and therefore a high interfacial area can be generated. Further improvements can be realized through the use of ligands, such as polymer derivatives of reactive triazine dyes. Rito-Palomares and Lyddiat (2000) have reported details pertaining to the practical implementation of this strategy for protein recovery from yeast, involving a PEG-phosphate aqueous-aqueous system. Recycling of PEG was established and it was found that debris particles did not significantly influence the partition behaviour of the intercellular products.

6.2.4. Reactive extraction

When the distribution coefficient for the desired solute from aqueous solutions into even the best of solvents is unfavourable it may become attractive to superimpose reaction. Consider the separation of citric acid from aqueous solutions, for which physical extraction is unattractive. Here we can use a bulky tertiary amine, e.g. tri-2-ethylhexylamine, which has a very low solubility in water, and dissolve it in a suitable, water-insoluble solvent; this will allow efficient extraction of citric acid even at relatively low concentrations. Citric acid can be recovered with a concentrated alkali, and the solvent can be recycled. This strategy was originally conceived for solvent extraction of metal ions like U, Cu, Ni, Co, Zn, etc. Even aqueous HF has been converted to anhydrous HF (obtained by heating the tertiary amine hydrofluoride dissolved in, for example, kerosene).

6.2.5. Dissociative extraction

The problem of close-boiling mixtures of isomeric and non-isomeric acids and bases is sometimes encountered in industrial practice. Consider the classical case of coal tar acids and bases which provided feedstocks for chemicals. *p*-Cresols, 2,6-xylenol and guaicol have very close normal boiling points. Many derivatives like 2,4- and 2,5-dichlorophenol, *o*-cresol, 6-chloro- *o*-cresol, etc. are also close boiling; in picolines there are also close-boiling mixtures. Sometimes mixtures such as those of nitrophenols occur, for which it is not advisable to separate them by distillation. Chlorobenzoic acids also provide an example. In such cases we can exploit the differences in the ionization constant, and by manipulating a suitable solvent, for which a rational criterion has been suggested (Gaikar and Sharma, 1989), a good separation can be realized.

6.2.6. Extraction with ionic liquids

A reference to the versatility of ionic liquids was made in Section 4.2.3. These liquids are a new class of solvents which do not have any problems associated with volatile organic liquids. Rogers *et al.* (1999) have used butylmethylimidazolium hexafluorophosphate to extract a benzene derivative from water.

6.2.7. Extraction with supercritical fluids

The advantages of adopting supercritical (SC) fluids in a reaction system were referred to in Section 4.5.7. For product recovery, SC fluid extraction can prove to be beneficial for a variety of situations.

Thus, synthetic vitamin E is purified by short-path distillation under high vacuum or by extraction with SC CO_2 (Baldenius *et al.*, 1996).

In the production of alkyl polyglucosides unreacted higher alcohols like C_{12}-C_{14} are left in the product. It is possible to remove these unreacted alcohols by solvent extraction with SC ethane (Sridhar and Mullar, 1995).

Adrian *et al.* (2000) have reported a novel high-pressure liquid-liquid extraction process with reference to processing in biotechnology; the example of cardiac glycosides (digitoxin and digoxin) is cited. A completely miscible, binary system of water and a hydrophobic organic solvent like ethanol can split into two liquid phases when a 'near-critical' gas (e.g. CO_2) is added. The 'near-critical' CO_2/water/1-propanol system is reported, for which possibilities for industrial exploitation exist.

6.3. CRYSTALLIZATION

6.3.1. Morphic states (Anderson, 2000; Bernstein *et al.*, 1999)

Solid compounds can have four morphic states: polymorphic, pseudo-polymorphic (solvates), amorphous, and desolvated solvates. Crystals usually exhibit narrow melting point ranges and defract light under an optical microscope. When a change in the arrangement of the unit cells occurs, without any change in composition, polymorphs are obtained. When crystals of the desired material contain a fixed mole ratio of solvents in the unit cell, these are referred to as *pseudo*polymorphs, or, more commonly, solvates. When solvation is by water, we call it a hydrate. When solvated solids undergo loss of solvents, through heating under vacuum or through exposure to air, desolvated solvates are obtained; these typically have lower bulk densities. In the case of amorphous solids, no discrete melting ranges exist and they have no significant order on a molecular scale.

The morphic state can affect the stability, solubility, crystal morphology, hydration, and calorimetric behaviour. Even the bio-availability of some drugs is affected by polymorphism. A change in crystal morphology can influence filtration and drying characteristics. A variety of techniques is used to distinguish morphic forms, i.e. X-ray powder diffraction, differential scanning calorimetry (DSC), melting point determination, thermogravimetrical analysis (TGA), microscopy, infra-red (IR) spectroscopy, solid-state nuclear magnetic resonance (NMR), solution NMR, gas chromatography (GC), elemental analysis, Karl Fischer titration, and powder density determination.

It is important to have an understanding of the competing thermodynamic and kinetic factors that govern crystallization. Situations exist where one polymorph formation is kinetically controlled, while another is thermodynamically controlled.

6.3.2. Crystallization from solution

Crystallization is an important unit operation in the manufacture of fine chemicals. It may be a manufacturing method, in part or full, such as for production of pure *p*-chloronitrobenzene from mixtures of *o*- and *p*-isomers, pure *p*-cresol from *m*-/*p*-cresol mixtures, etc. It may be used for purification, e.g. for naphthalene, *p*-cresol, etc. Crystallization from solutions as well as melts is important. In the manufacture of pharmaceuticals, crystallization plays a vital role. It is important to produce products of the right particle size distribution (including mean and spread) and bulk density. Even more important, when polymorphs can be formed a specific polymorph may be desired. Thus, composition, texture, size, morphology, etc. are relevant in making optically pure materials from racemic mixtures. Crystallization into a chosen optically active material occupies an important position. It may also be possible to crystallize optically active isomer from the racemic material by using a crystallizer (e.g. a conical fluidized bed) with seeds of the desired optically active material. Batch crystallizers are common in fine chemicals industry, although continuous crystallizers may also be used, depending on the situation and scale of production. It is important to emphasize that reproducibility is essential for industrial batch manufacture. Seeded crystallizers with an external recirculating system are often used. There is a complex interaction between the physical chemistry, associated with nucleation and growth rates, and aspects of chemical engineering, associated with agitation, residence time, hold up, etc., which controls the form and the stability of the crystal size distribution. Studies in the last two decades have enabled much better understanding of the crystallization process (Davey, 1994; Anderson, 2000). The concept of population balances has been very successful in predicting the particle size distribution. In some cases a monodisperse size distribution is demanded, such as in the case of human insulin, which is made by recombinant DNA techniques. Since all crystals are of the same size, the rates at which they dissolve and are taken up by the body are known, so the process should be reproducible (Ruthven, 1997). Clearly, crystallization as a separation process is far more demanding then other separations, for which product purity usually is the key demand. A good crystallization method invariably provides a high quality product with low levels of impurities.

In some cases we may benefit from using an external agent to carry out the desired separation through crystallization. Thus, in the case of isomeric and non-isomeric mixtures of close-boiling acidic or basic materials we may use a suitable base or acid to carry out dissociative extractive crystallization, akin to dissociative extraction referred to in Section 4.2.1. For instance, for a mixture of *p*- and *m*-cresol or *p*-cresol and 2,6-xylenol we may use a base like anhydrous piperazine to obtain a precipitate of relatively pure *p*-cresol salt of piperazine, which can then be filtered and subjected to recovery of piperazine for recycle. Similarly, we may add a substance which forms an adduct with the desired substance.

Crystallization may be carried out in several ways, depending on circumstances. Thus, if the solubility does not change significantly with temperature, evaporative crystallizers may be used. On the other hand, if the solubility changes substantially with temperature, a cooling crystallizer may be more suitable. In some cases an antisolvent may be added to carry out crystallization. This antisolvent should be added slowly. In some cases inverse addition may prove useful, in which a solution of the product is added to the antisolvent. There are many instances where reaction precipitation is carried out, a very simple example being acidification of aqueous sodium salicylate solution to obtain salicylic acid. Impurities get incorporated in the crystalline products through adsorption of impurities on the crystal surface, inclusion of pockets of liquid, and solvent entrapment in the cracks, crevices and agglomerates. Furthermore, an impurity having a structure close to that of the substance being crystallized may get incorporated through substitution or entrapment (Ruthven, 1997). For zwitterionic (internally neutralized) compounds such as amino acids the minimum solubility is found at the iso-electric point, and control of the pH provides the means for crystallization. In some very specific cases, crystallization may be done from supercritical fluids.

In batch processes, the crystal size is maximized through a combination of control of supersaturation and temperature. Supersaturation management is perhaps the most important aspect in crystallization, as this dominates the kinetic processes of nucleation and growth. The morphology, purity, structure, etc. of the product is ultimately controlled by the balance of the kinetics with the molecular interactions. Needles and plate-like crystals should be avoided, as they tend to lie in the filter coat surface and adversely affect washing and separation. The rate of development of supersaturation should be minimized to keep the nucleation rate low. We should crystallize near, but not at, the cloud point. During gradual cooling, very small crystals (fines) dissolve and crystallize as part of the existing larger crystals. This is referred to as 'Ostwald ripening'. A number of control strategies for cooling have been reported in literature. Subsequently the temperature is kept as high as possible to maximize growth rates. If a cooling crystallizer is used, the temperature profile must be suitably devised. If a chemical reactor is used for crystallization, the feed rate, the reactor configuration, the location of the feed addition, mixing levels, etc. will be important. It must be emphasized that nucleation is an 'on-off' phenomenon and its control can be exercised over a narrow range of conditions. This basic nature of the operation is not conducive for a robust process technology. For these reasons, seeding is often employed to catalyse nuclei formation at low supersaturation. Recently, attempts have been made to approach this problem from supramolecular transport, using the concept of molecular recognition and ion binding (Davey, 1994 and Ruthven, 1997). Funakoshi *et al.* (1999) have given details on the purity of *m*-chloronitrobenzene agglomerates from batch-seeded suspension crystallization; a eutectic of *m*- and *o*-isomers was used (*m*-chloronitrobenzene is used in the fine chemicals industry for, e.g., the production of *m*-chloroaniline).

Sometimes it may become necessary to change the solvent. An example of phosphinyl acetic acid may be cited where crystallization from the aqueous phase did not provide a rugged process, whereas the use of methyl *iso*-butyl ketone (MIBK) as a solvent did.

Some guidelines have been provided for defining the metastable region. If the seed crystals dissolve when added to the metastable solution, this implies that saturation conditions have not been reached. If the addition of the seed leads to the formation of an oil dispersion, it may be concluded that supersaturation has been realized (Anderson, 2000).

The crystallization process can have a profound effect on the subsequent steps of filtration and drying; in the pharmaceutical industry crystallization is often carried out under sterile conditions. The uneven particle size distribution, particle size and particle shape may render the filtration process, even through a centrifuge, difficult. The bulk density of the particles may be off specification. The crystals may even contain solvent (water and organic solvents) at a significant level, as a result from inclusions, quite apart from surface materials. This may pose a problem in drying regarding meeting the specifications with respect to 'loss on drying'. This is particularly important for organic solvents, which are not acceptable even at a few ppm, in, for instance, pharmaceutical products. There may be a need for recrystallization. The crystallized product may also show problems with respect to dust emissions, as fines pose a problem; dryers often use large flows of air. In the pharmaceuticals industry even tableting a product may be influenced by the process of crystallization.

It may become necessary to work up solid products with the same solvent as used for crystallization. Cakes should not be allowed to dry out before washing, as air or inert gases result in evaporation of the solvent, and this may result in the deposition of impurities, present in the dissolved state, on the crystals. Such impurities when deposited are difficult to wash. In some cases washing of wet cake is done by replacing the solvent with another one, typically having a lower boiling point, so that in the final material loss of drying is within limits and the new solvent is more acceptable than the earlier one.

Reslurrying can sometimes be advantageously employed for removal of impurities adsorbed on the surface. Anderson (2000) has given an example of the removal of excess *p*-nitrobenzyl bromide from a modified penicillin by reslurrying.

In recent years a lot of work has been done regarding the role of additives in changing the particle morphology, particle size distribution, etc., and predictive methods for crystal habit modifications have even been proposed. Blagden and Davey (1999) have referred to the example of *L*-glutamic acid which has two polymorphs, alpha and beta. Trimeric acid, which is a conformational and molecular mimic of the beta form, at 10 mol% loading allowed the alpha form to crystallize without conversion to the stable beta form. It is known that impurities can change the course, and pilot-scale and full-scale plants may well produce different polymorphs. This has been demonstrated through the example of sulphathiazole. Size enlargement, particularly in precipitation processes, can be carried out through ageing.

The crystallization step is generally studied quite exhaustively at the laboratory scale and often at the pilot scale. The reaction chemistry should be properly understood to access effects, if any, of the synthesis step on the impurity profile. In batch cooling crystallizers attempts have been made to create optimum conditions by on-line turbidity analysis (Moscosa-Santillán *et al.*, 2000). Physicochemical characterization of the products should be done rigorously (Tanguy and Marchal, 1996).

6.3.3. Crystal purity

Crystalline materials are commonly associated with purity, but recent demands lead to almost suprapure materials, and it is common to ask for an impurity profile. Crystallization epitomizes purification at the molecular level and the technology exploits the ability of a crystal surface to reject molecules that it does not recognize (Davey, 1994). This is essentially a supramolecular process. Two types of approaches are possible, *viz.* the use of eutectic and solid solutions. In the eutectic approach there is efficient rejection, whereas in solid solutions molecular level discrimination is difficult.

Sulzer, Switzerland, uses semi-batch falling-film technology, which has the advantage of not using any solvent. Separation takes place at the melting point, and hence the material must be stable at the temperature applied. In the Sulzer design, a multi-tube heat exchanger is used, which employs a cold surface on which the impure melt crystallizes from a falling liquid film. It is important to regulate the heat-transfer rate to moderate crystal growth, which in turn results in a uniform layer of high purity solids. With the thickening of the crystal layer, the melt becomes enriched in the unwanted impurities, and the crystallization is stopped at a suitable point, determined by the phase diagram. The impure melt is removed and subsequently the crystal layer is heated to a temperature just below its melting point (sweating) to allow any impure solid to remelt and drain away. Then the crystal layer is melted and this is the product. The impure melt and sweatings are recycled and the purified product is retreated until the desired purity has been realized.

In the Kobe process (Japan) the feed liquor is adiabatically compressed to a point just below the eutectic, where crystallization occurs. Then the mother liquor is removed and the pressure is gradually reduced to atmospheric pressure. It appears that for this process cycle times are short, in the order of 5 minutes.

Impinging jets, which consist of a cylindrical chamber with two spray nozzles that enter from opposite sides of the chamber, provide small particles with narrow size distribution. The solution of the material is fed through one nozzle and the crystallization agent through the second nozzle. Finasteride has been crystallized in this way; a solution of the material in acetic acid plus some water was fed from one nozzle and water from the other; the average crystal size was 10 to 15 μm.

Spray drying can be used to crystallize small particles. Due to the short residence time amorphous material may even be obtained.

6.3.4. Use of supercritical fluids

Precipitation of solids from supercritical solutions can be carried out by rapid expansion through an orifice or a nozzle. It may well be possible to obtain the desired solids morphology by manipulating the upstream and downstream temperatures and pressures. We can also consider a situation where a compressed fluid like CO_2 is rapidly added to a solution of a crystalline solid in an organic solvent. This works through the antisolvent effect. By manipulating the operating conditions it may be possible to obtain monodisperse particles. The recrystallization of β-carotene and acetaminophenol (paracetamol) have been reported. In the case of special explosives, where comminution is not possible, this procedure may work. Spraying an organic solution into a compressed fluid is also possible. Spray crystallization of protein powders to form uniform microspheres has been demonstrated.

6.3.5. Optically pure materials

The need for optically pure materials for pharmaceuticals, agrochemicals, aroma chemicals, etc. has been emphasized (see Sections 2.8.8 and 4.5.8). Diastereisomeric salt formation is commonly employed, but this method is expensive as it involves the use of chirally pure reagents. It is also inefficient, since the unwanted isomer cannot be readily recycled. (Davey, 1994).

The original approach of Pasteur merits consideration. In this approach, the molecule of interest must crystallize as a racemic mixture, and not as a racemic compound. Then a simple process is required to separate the crystals. We need a strategy to selectively discourage the crystallization of the unwanted isomer or effectively remove it by simultaneous crystallization and racemisation. For instance, in the case of *D*- and *L*-asparagin, in the presence of *D*-glutamic acid crystals of *L*-asparagin are formed and these can be separated with high chiral purity, leaving the opposite isomer uncrystallized in the solution. Chiral growth inhibitors have been reported. Racemates can also be resolved through clathrates (Ruthven, 1997).

The technique of purification based on seeded crystallization of the desired isomer and simultaneous racemisation of the undesired isomer, termed 'crystallization induced asymmetric transformation', has been covered by Davey (1994) with the example of a chiral pesticide, paclobutrazol (**P**).

Black *et al.* (1989) have reported a practical method for preparing the desired isomer of paclobutrazol, (2*RS*,3*RS*)-1-(4-Chlorophenyl)-4,dimethyl-2-(IH-1,2,4 trizol-1-yl) pentan-3-ol, which is a racemate, as the (2*S*,3*S*) enantiomer, which is a growth regulator. The separation of the racemate can be done via diastereoisomeric salt formation, but this is expensive and, in addition, the undesired isomer cannot be recycled. **P** is manufactured from the corresponding ketone by reduction with $NaBH_4$. The racemic ketone gives the (2*RS*, 3*RS*) diastereoisomer. It is expected that the enantiomers of the ketone will give the corresponding enantiomer of **P**. An understanding of the organic, solution and crystal chemistry led to an inexpensive method that has some general applicability. The success hinged on a viable separation method for the ketone enantiomers, recycling of the unwanted ketone enantiomer, and conversion of (*S*)-ketone into (2*S*,3*S*)-P stereospecifically. The above factors were successfully exploited. It is important to emphasize that upon crystallization a 'racemic mixture' or 'conglomerate' is obtained, and not a racemic (a 'racemic compound') or solid solution of the two enantiomers. Thus, in the first case, seeding by the desired optically active isomer will lead to the wanted result. It is clear that the crystal chemistry selects the appropriate separation method. It is important to properly control the supersaturation, which should be kept at low level. Black *et al.* (1989) were able to combine seeded crystallization and racemisation (base catalysed) steps into a single process, 'crystallization-induced asymmetric transformation' ((*R*)-ketone from solution is converted into solid (*S*)-ketone).

6.3.6. Adductive crystallization

An interesting example of adductive crystallization is the separation of a close boiling 1,3- and 1,4-dichlorobenzene mixture, as claimed by Standard Chlorine of Delaware, USA. *p*-Dichlorobenzene is easily manufactured by the chlorination of benzene. *m*-Dichlorobenzene is obtained by isomerization of *p*-dichlorobenzene to a nearly equilibrium mixture, either with a zeolite or an $AlCl_3$ catalyst, with zeolites being preferred as 'Green Technology'. Polyethylene glycol (PEG) of different molecular weight was used to form an adduct with the 1,4-isomer, which leaves as a solid and can be filtered and then flash distilled to 1,4-isomer and PEG, which can be recycled (George *et al.*, 1995).

6.4. ADSORPTION

6.4.1. Conventional methods

The differences in the adsorption potential of mixture constituents are exploited for separation by adsorption, which is essentially a surface phenomenon. The literature on adsorbent-adsorbate interaction in the liquid phase is largely restricted to patents and the selection of a suitable adsorbent for a specified duty depends on experience and prior art. The selected adsorbent should exhibit high selectivity, capacity, mass-transfer rate, and long-term stability. These objectives can be realized through the use of microporous materials with pore diameters ranging from a few tenths to a few tens of nanometres. The classic adsorbents are various grades of activated carbon, silica gel, and alumina. The introduction of zeolites (molecular sieves) with specified uniform pore sizes, e.g. 3 Å, 4Å, etc. have had a major impact, as these materials allowed 'sieving' (separation) at a molecular level. The selectivity is so articulate that *n*-alkanes can be separated from *iso*-alkanes and *p*-xylene from *o*- and *m*-xylenes (in fact, any *p*-isomer of benzene derivatives can be separated from the *o*- and *m*-isomers). Subsequently, molecular sieve carbons became available. Clays and activated clays have been used for a long time, particularly for treatment of edible oils. In the recent past, pillared clays have been made available (see Section 4.4.2). These two-dimensional layered structures can have the desired spacing of 10 Å, 20 Å, or even 100 Å. Besides the usefulness of ion-exchange resins as catalysts, covered in Section 4.1.2, polymeric resins are also attractive as adsorbents for aqueous phase separations and offer a range of useful properties. Polymeric resins are effective in partitioning by size and molecular weight. In many instances, desorption, with a suitable solvent, is easier from polymeric adsorbents than from activated carbon. However, polymeric resins may be affected by some chemicals. Polymeric adsorbents are relatively new entrants, but have wide applications.

Three types of adsorptive processes are practised: Temperature Swing Adsorption (TSA), Pressure Swing Adsorption (PSA), and Concentration Swing Adsorption (CSA). In TSA adsorption is carried out at close to ambient conditions and desorption is realized through direct or indirect heating of the adsorbent. The key area of the application of TSA is removal of impurities from gaseous or liquid streams. The separation of gaseous mixtures is done through PSA. PSA is mainly used for bulk gas separations, and therefore, will not receive further attention in the context of fine chemicals. Bulk liquid mixtures are separated through CSA at ambient temperatures; desorption is realized through the use of a less strongly adsorbed liquid over the adsorbent. TSA is suitable for strongly adsorbed species, as a small increase in temperature leads to considerable desorption and the desorbate can be recovered at high concentration. PSA is suitable in the case of more weakly adsorbed species and when high purity is required. This requires rapid cycling and the adsorbent is efficiently used.

6.4.2. Reactive adsorbents

Absorption with reversible chemical reaction is widely used for the recovery of acid gases like CO_2 and H_2S. We have already referred to the need and advantages of combining chemical reaction and extraction (Section 4.2.1). Similarly, if in physical adsorption the fluxes are low and removal and recovery to the desired extent is not realized, we may consider superimposing reversible reactions. A well-known example is that of CO to be adsorbed on a simple physical adsorbent versus a zeolite exchanged with cuprous ions. For the latter, high rates of adsorption and the desired degree of recovery from the feed gas can be achieved. Through a swing in pressure and/or temperature CO is desorbed and pure CO can be obtained.

It is important for oxygen to be absent in the feed to avoid oxidation of cuprous to cupric ions rendering adsorption with reaction unworkable. This strategy can be extended to the removal/recovery of olefinic compounds, for which cuprous-exchanged zeolites may also be useful.

In many instances we are not able to develop a process in which a reversible reaction takes place but instead an irreversible reaction occurs, so that the adsorbent, after exhaustion, has to be disposed. This strategy has relevance in removing impurities present at ppm level to vanishing levels, levels that may well approach a few ppm. Consider H_2S removal from natural gas, particularly in offshore locations, at a few ppm, where the established processes based on absorption with reaction and aqueous-phase reactions to convert H_2S to S, are very expensive and even unwieldy. As an alternative, special reactive adsorbents based on ZnO have been developed, which work at ambient conditions. Consider removal of COS from C_3 fractions when present at ppm levels. We could have easily used a gas-liquid or liquid-phase reaction with aqueous NaOH or aqueous alkanolamines. Special grades of basic alumina can accomplish this job and Chaudhari and Sharma (1992) have reported results on such an investigation. A similar strategy works for removal of arsine. These strategies have a general applicability for removal of impurities in the fine chemicals industry. Thus, we may use magnesia particles to remove phenolic impurities at a few ppm from perfumery or heat transfer grade diphenyloxide. Tien (1994) has given an analytical insight into such processes, particularly for removing toxic components from gases.

6.4.3. Regeneration of adsorbents

Regeneration of adsorbents is crucial in their repeated use. When solvents from, say, lean gases, are recovered through use of activated carbon, steam regeneration is invariably employed for water-insoluble solvents, such as CH_2Cl_2, $CHCl_3$, CCl_4, toluene, etc. Schweiger (1996) has presented an approximate solution to the material and energy balances for steaming a fixed-bed adsorber and has proposed a method for optimization.

Solvent regeneration is also adopted. Common regeneration solvents are methanol, acetone, isopropanol, and toluene. Water immiscible solvents have generally been less effective in solvent regeneration of aqueous phase activated carbon due to problems of ineffectively exchanging the water from inside the pores of the carbon at the start of the solvent regeneration process (McLaughlin, 1995). In the case of polymeric adsorbents, which can even recover aromatic sulphonic acids from aqueous streams and can be used for heterocyclic amines like morpholine, regeneration can be done with solvents like methanol and *iso*-propanol.

Supercritical gases, particularly CO_2, have been proposed for a number of difficult regenerations and recovery of some valuable substances.

In some cases it becomes necessary to use a chemical method of regeneration. Thus, phenolic substances, when adsorbed on activated carbons or polymeric adsorbents, are regenerated using aqueous solutions of sodium hydroxide of an appropriate concentration.

6.4.4. Examples of separation of mixtures in the fine chemicals industry

Both batch and continuous adsorption processes are used. In a batch process, the adsorbent bed is allowed to become saturated with adsorbed material and is subsequently regenerated in a cyclic manner. In a continuous process, usually the counter-current mode is adopted for adsorption and desorption, either in time form or in simulated mode. Continuous operation offers many advantages with respect to the efficiency of adsorbent utilization. Thus, for difficult separations it has been pointed out that batch operation may require 25 times more adsorbent inventory and twice the desorbent circulation rate than continuous operation. Furthermore, the height equivalent to a theoretical stage in batch operation may be three times larger than in continuous mode, as large sections of the bed do not perform in a functional way at a given time during batch operation (Ruthven, 1997).

6.4.4.1. Zeolites as adsorbents

p-Cymene, p- and m-cresol. Alkylation of toluene with propylene gives a mixture of cymenes. Even with the best of zeolite catalysts, unlike alkylation of benzene and toluene with ethylene, pure *p*-isomer is not obtained. Poisoning of pore mouths reduces the amount of the *m*-isomer (*o*-isomer is not formed to a significant extent due to steric hindrance) but still the mixture contains a substantial amount of the *m*-isomer. Pure *p*-cymene has uses in the perfumery industry, while it is also the starting material for the manufacture of pure *p*-cresol. Mixtures of *m*- and *p*- cymene are oxidized, in a cumene-to-phenol type route, to mixed *m*- and *p*-cresols, which can then be separated through crystallization for pure *p*-isomer and through adsorptive separation for pure *p*- and *m*-isomers. Adsorptive separation using zeolites, allows pure *p*- and *m*-cymenes to be obtained from their mixture.

m-Xylene. Pure *m*-xylene is an intermediate for perfumery chemicals as well as for specialty chemicals. *p*-Xylene is a bulk intermediate for purified terephthalic acid and is produced in large quantities, exceeding 10 million tpa. In the recent past even *m*-xylene has been acquiring the status of a bulk intermediate due to the large emerging market for isophthalic acid for modification of PET (poly-ethylene terephthalate) resin. Originally, pure *m*-xylene was obtained from a *p*-/*m*-mixture through reaction-based separation such as distillation with an organo-sodium compound or a HF complex, or alkylation with *iso*butylene, and separation by distillation and subsequent dealkylation. In the recent past zeolites have been developed to produce pure *m*-xylene; zeolites for pure *p*-xylene were developed over 20 years ago, while *p*-xylene can also be recovered by crystallization.

Drying of liquids. In many processes for the manufacture of fine chemicals, e.g. those involving Friedel-Crafts reactions, it is necessary to have organic raw materials free from moisture down to below 5 ppm. In the case of solvents/reactants like benzene and toluene azeotropic distillation with a large number of theoretical stages (typically more than 25) can accomplish this job, but adsorptive separation using zeolites 3Å or 4Å can be very attractive with respect to capital costs as well as operating costs. Adsorbents are now routinely used for drying of liquids, quite apart from drying of gases, down to a dew point below –30 °C. This method should, however, be compared with pervaporation and relative economics should be assessed.

6.4.4.2. Column chromatography

Column chromatography (CC) can be used at laboratory, pilot-plant, and commercial-plant scales. Preparative chromatography has been utilized for the purification of many fine and even bulk chemicals.

6.4.4.3. Simulated moving bed chromatography

The concept of simulated moving bed chromatography (SMBC) is based on the elution chromatography principle and is a continuous process. SMBC implies a simulated counter-current movement of the solid and the fluid phase, which is most efficient in terms of separation, performance, and eluent consumption. The elution profile can be held in place if the stationary phase 'moves' in one direction and the mobile phase moves in the other direction. However, if the feed can be continuously introduced at the midpoint of the column, the concentration profiles can be maintained, and the bands are spread out over the entire column. Although the profiles are only partially resolved, high purity products can be collected at either end. Rather than requiring an infinite column length, a circular column can be used. The stationary phase and the mobile phase 'move' in opposite directions, but the concentration profile can be maintained, and it is possible to withdraw two products continuously. Small particles with relatively narrow size distribution allow a higher loading and better resolution. Recent developments in hardware, software, and modelling have made SMBC even more attractive. SMBC has proved its versatility and ruggedness, and large-scale plants (~500,000 tpa) for *p*-xylene are operating successfully. UOP's Sorbex process for fructose and glucose has been operating from the 1960s. In the fine chemicals industry, the productivity and separation cost of SMBC can be superior to that of one-injection batch chromatography. SMBC has also been considered for recovery of lactic acid from glucose fermentation.

Citric acid (Ruthven, 1997). In the separation of citric acid from fermentation liquors the Sorbex process can be used. In the conventional process neutralization is carried out with lime followed by acidification with sulphuric acid to produce calcium sulphate as waste. The Sorbex technology avoids lime and sulphuric acid wastage and calcium sulphate disposal.

Separation of fatty acids (Ruthven, 1997). Tall oil from the pulp and paper industry is subjected to separation of rosin acid, linoleic acid, oleic acid, and neutral compounds. Distillation at reduced pressure is used, but this leads to degradation of products. A Sorbex process eliminates this problem.

Chiral separations. Chiral separations are now widely done by SMBC and may sometimes compete economically with chemical transformation process. Racemic fluoxetine (Prozac) is a solid to treat depression. Some reports have appeared on racemic mixtures having adverse toxic or psychological effects, a delayed onset of action, and a low response rate. A recent claim discloses that the *S* (+) enantiomer of fluoxetine does not cause these effects, while it has a rapid onset of action and a high response rate. Another claim states that the *R* (-) isomer has therapeutic activity to treat migraine headaches, pain (in particular chronic pain), psychoactive substance abuse disorders, and obsessive compulsive disorders. It is, therefore, desirable to produce each enantiomer in high enantiomeric purity. Chiral SMBC shows promise for this job. In a report in Chemical and Engineering News, a reference has been made to the world's largest pharmaceutical SMBC unit, capable of producing 50 tpa of an enantiomer (McCoy, 2000). Several units with a capacity of 2 to 20 tpa for pure enantiomer have been constructed at different locations. In Denmark, H. Lundeck has erected a unit to make pure *S*-enantiomer of the antidepressant drug citalopram.

Counter-current chromatography using two immiscible liquid phases rather than a conventional solid phase ligand support allows chromatographic quality separations to be scaled up to large scale; 500 to 1000 stages can be realized. Enantioselective hydrolysis of 2-cyano-cyclopropyl-1,1-dicarboxylic methyl ester has been carried out.

Strube *et al.* (1998) have compared batch elutions and continuous SMBC. For resins, zeolites, and similar low-priced adsorbents the influence of the stationary phase on the total separation costs can be neglected. For expensive adsorbents, a careful consideration is required of optimum solvent requirement and optimum productivity, and the costs of the stationary and mobile phases have to be taken into account. For enantioseparations, SMBC has major advantages over batch elution due to higher productivity, lower product dilution, and lower separation costs. It is necessary to adopt rigorous models, as real effects for peak tailing have to be considered to optimize chromatographic processes. It would be useful and instructive to carry out a few experiments on an analytical HPLC column to optimize the stationary and mobile phase for the production scale and to prepare the equilibrium phase isotherms. A detailed optimization by rigorous simulation studies can even lead to about double feed throughput and half the adsorbent requirements.

6.4.4.4. Recovery of valuable chemicals from aqueous streams, including waste streams

Whenever activated carbons can be used for the recovery of valuable chemicals from aqueous streams, these are preferred as they are cheap, can often be conveniently regenerated, and their final disposal, by combustion, is easy. The disposal of activated carbons is usually undertaken by vendors. Regeneration can be done, as pointed out in Section 6.4.3, with steam or another solvent, and sometimes chemically, e.g. using NaOH from phenolic substances.

Polymeric adsorbents have also been found to be very useful, and even highly water-loving undesired materials like *p*-toluene sulphonic acid from waste streams can be recovered via adsorption and regeneration with solvents like *iso*-propanol. In such instances, the regeneration of activated carbons is not satisfactory, even with aqueous sodium hydroxide. Solutes like phenols, substituted phenols, aromatic amines, heterocyclic amines (pyridine, picolines, etc.) can be recovered, in a rewarding way, from aqueous solutions.

6.4.4.5. Ion-exchange resins

Removal of dissolved alkalis and acids. There are a number of processes of industrial importance (e.g. diacetone alcohol from acetone), in which the reaction is catalysed by dissolved alkali, typically at 200 to 1000 ppm level. In the subsequent catalyst recovery step, sometimes the dissolved alkali is removed via crystallization of a suitable salt like disodium hydrogen phosphate, by addition of phosphoric acid. This is an environmentally unfriendly process due to deposition of solids, problems associated with the separation of solids and liquids, loss of organic material, washings of deposited solids from heat-transfer surfaces and the consequent effluent load, etc. Instead of this messy way, a clean process using a suitable cation-exchange resin will accomplish the job elegantly. This also applies to the removal of dissolved acids by use of a suitable anion-exchange resin. Robust polymeric matrices are commercially available for a variety of organic liquids to ensure a long life for the ion-exchange resins (IERs). Thus, formic acid can be removed by using a weak anion-exchange resin. Oxazole can be removed from acrylonitrile using a strong acid resin. When nanofiltration membranes are developed with a suitable life and cost, the removal of dissolved acids/bases from organic systems should be considered and relative economics of ion-exchange methods should be assessed.

IERs for recovery of antibiotics, chemicals, etc. Antibiotics produced by fermentation, such as streptomycin, neomycin, and cephalosporin C are processed through the use of ion-exchange or polymeric adsorbents. Anionic and cationic IERs can often be effectively used for the recovery of chemicals; the use of liquid anion exchangers is well known.

A very useful, but difficult, case has been reported by Smith and Barclay (1992) for the recovery of Monsanto's highly successful herbicide, glyphosphate (N-phosphonomethyl-glycine, tradename Roundup), from an aqueous waste stream. This stream contains a lot of unwanted products like HCHO, HCOOH, aminomethylphosphoric acid, and N-phosphonomethyl iminodiacetic acid (PMIDA). The removal of PMIDA and HCOOH from glyphosphate is essential as HCOOH can react to give the formyl derivative. Amberlite IRA-93 and Amberlite IRA-68 (anionic resins) were chosen to separate glyphosphate from PMIDA and HCOOH, respectively (HCHO does not get adsorbed). 1500 recovery cycles were tried, and the resin has two years plant life; scale-up with a factor of 90,000 was very successful.

Recovery of phenylalanine from aqueous solutions by cation-exchange resins has been reported by Carta and co-workers (Borst *et al.*, 1997). It might be possible to improve the efficiency of resin treatment by raising the operating temperature, to, say, 65 °C.

Continuous ion-exchange separation technology, which adopts counter-current processing in a rotating turntable, is currently making an impact and 70% of the world's lysine manufacture units use this technology.

6.5. MEMBRANE SEPARATIONS

There has been a remarkable progress in membrane technology (MT) in the last twenty years, and it has progressed in a fascinating way from the days of desalination. MT offers advantages in terms of essentially room temperature operation (except in pervaporation) so that heat-sensitive materials can be conveniently handled. The designs are modular and closed for sanitary purposes (a requirement in food and pharmaceutical industries). MT is benign on energy consumption. Process streams, aqueous or non-aqueous, and waste streams, aqueous or non-aqueous, can be handled through membrane technology, sometimes in a remarkably facile way.

Novel chiral separations using enzymes and chiral surfactants as carriers have been realized using facilitated transport membranes. Japanese workers have reported the synthesis of a novel norbornadiene polymeric membrane with optically active pendent groups that show enantioselectivity, which has shown promise in the separation of propronalol.

Metal nanotube membranes with electrochemically suitable ion-transport selectivity, which can be reversibly switched between cation-permeable and anion-permselective states, have been reported. These membranes can be viewed as universal ion-exchange membranes. Gold nanotube molecular filtration membranes have been made for the separation of small molecules (< 400 Da) on the basis of molecular size, eg. separation of pyridine from quinine (Jirage and Martin, 1999).

New membranes have been developed with significantly enhanced mass-transfer characteristics. These membranes include rotating membrane systems that use a torsional oscillation to produce shear rates as high as 150,000 s^{-1}. Coiled hollow fibres that exploit Dean vortices to increase solute transport and reduce fouling are receiving attention (Zydney, 2000).

An survey of recent developments in membrane processes, involving reverse osmosis (RO), ultrafiltration (UF), microfiltration (MF), electrodialysis (ED), dialysis (D), pervaporation (Pr), gas permeation (GP), and emulsion liquid membrane (ELM), has been provided by Sirkar (1997).

In the case of UF, progress is being made in different ways: novel/improved membranes, fouling control in tangential flow devices, new module designs for high solids, and improved permselectivity for viral retentions. Inorganic UF membranes have been introduced, e.g. ceramic honeycomb monoliths (multichannel units) of alumina with ZrO_2 layers having pore sizes between 4 and 50 nm.

In the case of MF, ceramic high temperature units, which can operate up to 900 °C, are available. Large-scale protein harvesting from mammalian cell cultures by tangential flow filtration over MF hollow fibres (0.2 μm AKZO Microlyn) is now a reality. A 'submerged' continuous micro-filtration unit has been developed, which can be directly submerged into on-site rectangular tanks, cutting capital costs by an additional 10-20%.

In the case of ED, the availability of bipolar membranes allows electrodialitic water dissociation, and NaX can be separated into NaOH and HX.

Nanofiltration (NF) has features intermediate between U/F and RO. Most commercially available NF membranes are only suitable for separation processes in aqueous solutions. A small number of composite membranes with a higher cross-linked selective layer show a technically interesting resistance towards organic solvents, such as ketones, esters, ethers, or alcohols. Some progress has been made in removing dissolved organic compounds, alkalis and acids from polar media like DMF, DMAC, etc. by NF (Schmidt *et al.*, 1999). Whu *et al.* (2000), have presented an experimental study of recovery of organic solutes with molecular weights ranging from 351 to 1351, dissolved in methanol, through NF. Attempts are being made to make ceramic NF membranes, which can be either positively or negatively charged, depending on pH, and thus become ion permselective.

6.5.1. Electrodialysis

Electrodialysis was developed for desalination of brackish water. Electrodialysis can be found to purify as well as recover valuable chemicals depending on circumstances. This is very convenient for removing dissolved electrolytes from aqueous solutions containing organic substances of lower molecular weight. Thus, when glyoxal is made by oxidation of acetaldehyde with nitric acid, the removal of nitrate ions can be conveniently carried out by using ED. Furthermore, it may be possible to valorize some waste streams. Thus, Grib *et al.* (2000) have given details of the recovery of phenylanine from an industrial waste stream containing ammonium and sodium sulphate using ED.

Novalic *et al.* (2000), have reported modifications in the ED process. When electrodialytic bipolar membranes are used in a three-compartment arrangement to recover organic acids having molecular weights of around 200, the mass-transfer rate is low and energy consumption is relatively high. It is suggested that the three-compartment arrangement be split into a conventional ED, and a two-compartment system with a bipolar and a cation-exchange membrane.

6.5.2. Nanofiltration

There is a considerable interest in using γ-alumina NF membranes. Grib *et al.* 2000 have reported amino acid retention in such membranes with four amino acids. The charge effects facilitate rejection of the amino acids by the alumina membrane. The performance of NF is strongly influenced by the solute environment and by hydrodynamic parameters.

NF membranes have been used to remove pesticides from aqueous streams, as their molecular weight invariably is more then 200. Kiso *et al.* (2000) have studied the rejection properties of a number of pesticides, and it appears that this method is very promising.

6.5.3. Membranes in the manufacture of dyes

In the manufacture of a variety of dyestuffs we encounter the problem of separation of dyes from aqueous electrolyte solutions, which may also contain a small amount of fine suspended particles. It is now possible to commercially adopt ultrafiltration membranes to take care of particles in the range of 0.05 to 0.15 μm; particles up to a few μm can be handled in a microfiltration system (Meindersma and Kuczynski, 1996). Membrane systems have been used in the manufacture of high quality reactive acid and direct dyes. Membranes have even been used for sulphur dyes. Since many dyes have molecular weights higher than 250, and typically 600 to 900, nanofiltration membranes can be used. This also allows the capacity of existing spray dryer systems to be enhanced as the feed concentration of the dyes can be raised form 7–10% to a convenient 25% or sometimes even higher. Liquid dyes also benefit, as desalting can easily be carried out. Tubular and spiral membranes are used. If desired, membrane systems can also be employed for recycling of water. It is important to document the lifetime of a membrane before commercialization (Crossley, 1998).

6.5.4. Pervaporation

Aroma compounds are often heat sensitive and their purification by membrane processes, which work at near ambient conditions, can be attractive. Alternatively, when pervaporation is used then temperatures can be kept low. A variety of aroma substances from aqueous solutions have been recovered. Baudot and Marin (1997) and Baudot *et al.* (1999) have made an extensive study of this subject. Hydrophobic low boilers to very hydrophobic high boilers have been studied.

Volkov (1994) has given a state-of-the-art review on pervaporation. A number of industrial plants exist for dehydration of ethanol-water and *iso*propanol-water azeotropes, dehydration of ethyl acetate, etc. There is considerable potential in removing dissolved water from benzene by pervaporation. The recovery of dissolved organics like CH_2Cl_2, $CHCl_3$, CCl_4, etc. from aqueous waste streams also lends itself for pervaporation and pilot plants already exist.

6.5.5. Hollow-fibre-membrane contactors

A hollow-fibre-membrane contactor (HFMC) (Abellman and Hwang, 1999) achieves gas-liquid and liquid-liquid mass transfer without dispersion of one phase into the other, by passing the fluids on opposite sides of a microporous membrane. By careful manipulation of the pressure difference between the fluids, one of the fluids is immobilized in the pores of the membrane so that the fluid-fluid interface is located at the mouth of each pore. This device offers a number of distinct advantages: emulsion formation is avoided; there is no flooding at high flow rates, while at the same time no unloading occurs at low flow rates; the density difference between the two phases is inconsequential; interfacial areas are very high compared to, say, packed and sieve plate extraction columns, and may well be 100 times as high on a per unit volume basis; modular design allows operation over a wide range of capacities and scale-up is straightforward; aseptic operation is possible, and hence during fermentation broth can be circulated through a HFMC; the conversion in equilibrium-limited reactions can be increased; solvent hold-up is low, which makes the HFMC attractive for sensitive and expensive substances; and there are no moving parts like in mixer-settlers, Kuhni columns, etc. However, HFMC may experience shell-side bypassing, which results in a loss in efficiency. Several design improvements have been made to overcome this problem. The number of equilibrium stages is limited in a HFMC. It should be realized that, unlike in most membrane operations, the membrane in HFMC does not impart any selectivity as it has no impact on the partition coefficients. Further, the driving force with HFMC is a concentration rather than a pressure gradient, as in MF, UF, and RO.

Due to bypassing in the shell-side fluid, a high degree of extraction is often difficult to realize with solute-containing fluid on the shell side. It is desirable that the pores are filled with the fluid in which the solute is most soluble.

In the pharmaceutical industry the HFMC offers advantages in extraction of substances like 4-methylthiazole, 4-cyanothiazole, mevinolinic acid, etc.; industrial streams have been treated. A variety of fermentation products can be handled. Even chiral separations have been considered; the example of recovery of *d*-leucine from the racemic mixture, with a 1-octanol solution of *N*-*n*-dodecyl-l-hydroxyproline, may be cited. Another example refers to the drug diltiazen, which is used to treat hypertension and angina. The precursors of interest are methylesters of (6)-*trans*-4-methoxy-3-phenyl-glycidic acid. The (2*R*,3*S*) form has a higher activity. A stereoselective lipase converts the undesirable (2*R*,3*S*)-*trans* enantiomer into (2*R*,3*S*)-methoxy-phenylglycidic acid and methanol, and the acid, which is unstable, rapidly decarboxylates to form *p*-methoxyphenylacetaldehyde. This aldehyde is a strong inhibitor of the enzyme but can be arrested by the reversible formation of an adduct with sodium bisulphite.

Prasad and Sirkar (1990) have worked with actual streams obtained from Merck. Their work includes the recovery of mevinolinic acid, obtained by fermentation, which is a precursor to the hypocholestermic agent Mevinolin.

Kawasaki *et al.* (1996) have used a supported membrane catalyst for extraction of erythromycin from its dilute, slightly alkaline aqueous solutions. 1-Decanol was used as an intermediate fluid membrane phase and a buffered acidic aqueous solution was used to strip the organic membrane.

Keurentjes *et al.* (1996) have also reported the separation of racemic mixtures. Two liquids are made oppositely chiral by the addition of *R*- or *S*-enantiomers of a chiral selector, respectively. These liquids are miscible, but are kept separated by a non-miscible liquid contained in a porous membrane. These authors have used different types of hollow-fibre modules and optimization of shell-side flow distribution was carried out. The liquid membrane should be permeable to the enantiomers to be separated but non-permeable to the chiral selector molecules. Separation of racemic mixtures like norephedrine, ephedrine, phenyl glycine, salbutanol, etc. was attempted and both enantiomers of 99.3 to 99.8% purity were realized.

6.5.6. Other examples

6.5.6.1. Recovery of enzymes

Meindersma and Kuczynski (1996) compared conventional filtration with a filter aid and membrane technology for the separation of enzymes. In cases in which the enzyme is sufficiently cheap for once-through use filtration is the process of choice, whereas for expensive enzymes, which have to be recycled, ultrafiltration is clearly advantageous, with enzyme retention of 99% versus 50% recyclability when using filtration with a filtration aid.

6.5.6.2. Membrane process for recovery of valuable organic chemicals from aqueous waste streams containing electrolytes

Monsanto has developed proprietary composite membranes, which have unique properties of recovering low molecular weight organics from aqueous solutions containing low to high concentrations of salts. These membranes operate in a dialytic mode, in which the driving force is the concentration and solubility difference rather than the pressure difference. Thus, *p*-nitrophenol at a level of about 1% was recovered from an aqueous solution containing 20% KCl, C_2-C_6 monobasic carboxylic acids at 3800 mg per litre, and 1% nitric acid. It is claimed that this route for *p*-nitrophenol recovery is much cheaper than via adsorption using activated carbon (Ho, 1995).

6.5.6.3. Separation of isomers

In the recent past separation of isomers has been attempted using aqueous liquid membranes based on β-cyclodextrin. Thus, separation of a mixture of *o*- and *p*-nitroaniline (in 80% *n*-octanol, 20% *n*-heptane) has been studied, with the *p*-isomer showing a selectivity of 5 at 0.7 molar β-cyclodextrin. Even stereoisomers of stilbene (*cis* and *trans*) were separated using a 0.02 to 0.2 M cyclodextrin solution, but the selectivity was less than 2 (Mandal *et al.*, 1998).

6.5.6.4. Bioseparation with smart polymers

Smart polymers respond to changes in their environment in a predictable and pronounced way. These water-soluble polymers show dramatic changes with pH, temperature, ionic strength, and specific chemicals. Smart polymers can be charged macromolecules, or show hydrogen bonding with water molecules. Smart polymers that have been widely used (with their lower critical solution temperature in parenthesis) are: poly(N-isopropylacrylamide) (NIPAM)(32–34 °C), poly(vinyl methyl ether) (34 °C), and poly(N-vinylcaprolactam) (34–40 °C). Smart polymers possess the potential to convert some of the existing processes to more elegant, efficient, and economical versions.

6.5.6.5. Protein isolation with affinity precipitation

Protein isolation with affinity precipitation has been discussed in detail by Mattiasson and co-workers (see, e.g. Galaev and Mattiassion, 1997) and they have provided an exhaustive tabulation. Polymers varied from alginates/chitosan to dextran to NIPAM. Examples of the used proteins are from trypsin, β-glucosidase, xylanase, alkaline protease, etc. It is remarkable that affinity precipitation can sometimes give results comparable to affinity chromatography.

6.5.6.6. Solvent recovery

The recovery of solvents during reaction, distillation, evaporation, drying, filtration, mixing, and other vacuum operations is very common in industry. A single stage liquid ring vacuum can be a good system which allows the recovery and reuse of clean solvent with minimum air emissions and zero liquid emissions. A typical example is that of low boiling methylene chloride. The use of membranes for recovery of solvents from gaseous streams and adsorptive methods have been covered in previous sections. In the recent past considerable attention has been given to adoption of cryogenic conditions through use of liquid nitrogen. (Perlmutter, 1997).

6.5.6.7. Recovery of volatile organic compounds using liquid nitrogen

Whenever liquid nitrogen (LN) is used in the chemical industry (boiling point −196 °C), it can prove useful for the recovery of volatile organic compounds (VOCs) from lean mixtures with inert gases, as LN-based condensation can be integrated with the gaseous uses, thus fully utilizing the refrigeration potential.

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7. Production Plants

7.1. TYPES OF PRODUCTION PLANTS

There are three basic types of plants for the manufacture of fine chemicals: dedicated plants, multiproduct and multipurpose plants, and mixed plants.

7.1.1. Dedicated plants

Dedicated plants predominate in the bulk chemicals industry. They suit the manufacture of well-defined products using a determined technology. Any change of the product or the production process usually produces problems, which illustrates the inflexibility of a dedicated plant. A batch plant may also be operated as a dedicated plant to produce a single chemical. Some fermentation plants (with reactors of up to 200 m^3 volume) are examples of dedicated batch plants for the production of a family of similar products. So-called bulk fine chemicals, *i.e.* compounds that are produced in larger quantities, are also manufactured in dedicated plants, e.g. vitamin C and aspirin (see Fig. 7.1-1). The vast majority of batch plants, however, produce several chemicals.

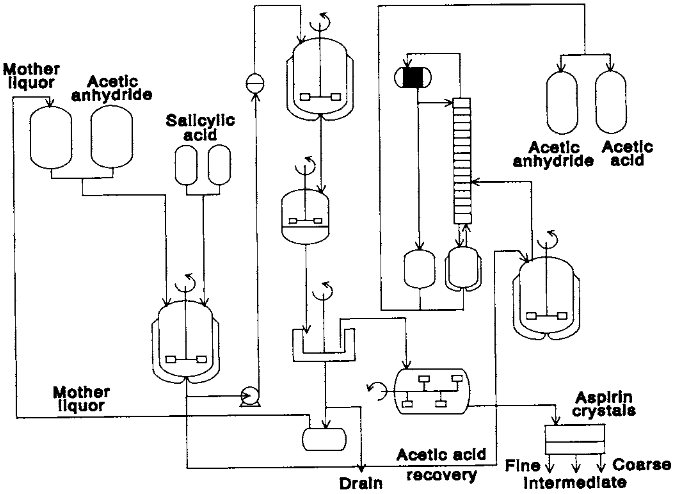


Figure 7.1-1. Flow-sheet of a dedicated plant for aspirin manufacture.

Dedicated batch plants for fine chemicals are constructed to manufacture products of larger volumes: up to some thousands tons per year. However, a large batch size results in a large reaction vessel (e.g. larger than 10 m^3), which may cause problems with heat transfer and proper agitation, especially for heterogeneous systems. Such large batch sizes increase the risks in terms of both safety and economics. Apparently, the larger the apparatus the lower the investment and labour costs per unit volume of product, and, accordingly, the cost of manufacturing. However, off-grade batches can be very expensive and this would worsen the economics significantly. Therefore, continuous processes are often developed in such cases. Continuous processes are also used for the manufacture of compounds of the same class and similar properties, especially of similar reactivities.

No matter whether the plant is operated continuously or batchwise, some chemical reactions require very specific equipment. The character of a chemical reaction can be the reason that the design and operation of an installation are dedicated to a particular reaction or reactions of the same type. An example is the manufacture of 11β,16α,17α,21-tetra-hydroxy-1,4-pregnadiene-3,20-dione acetate-21, which is an intermediate for the synthesis of an antiasthmatic drug with a production of a few kilograms per year. This intermediate is obtained by oxidation of 11β,21-dihydroxy-1,4,16-pregnatriene-3,20-dione acetate-21 as illustrated in Fig. 7.1-2. The reaction is carried out at low temperature within a few seconds, and any extension of the reaction time results in significant oxidation of the desired product. Accordingly, the best solution is to carry out the reaction continuously, with chemical 'quenching' of the reaction mixture at the reactor exit. The nature of this particular chemical reaction makes it necessary to use special equipment, which of course is strictly monopurpose.

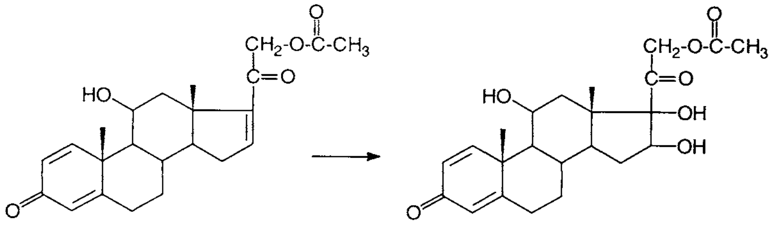


Figure 7.1-2. Oxidation of 11β,21-dihydroxy-1,4,16-pregnatriene-3,20-dione acetate-21.

Dangerous materials may require special equipment. Chlorination with gaseous chlorine requires quite expensive storage facilities. Chlorination with chlorine, thionyl chloride, sulphuryl chloride, phosphorus oxychloride, phosphorus trichloride, or phosphorus pentachloride, all of which are fairly hazardous, requires off-gas treatment. Some of these reactants can be recycled. Pyrophoric solids such as hydrogenation catalysts, anhydrous aluminium trichloride for Friedel-Crafts reactions, or hydrides used as reducing agents should usually be handled using special facilities. Therefore, all of the above processes are usually carried out in dedicated plants.

Safety is another reason for constructing dedicated installations, sometimes for a continuous process. The inventory of dangerous materials in continuous equipment is usually much smaller than that in batch equipment, which results in a safer process. Danger of explosions leads to performing reactions in isolated bunkers, the cost of which is comparable to that of the equipment contained within. Grignard reactions and nitrations are typical examples of such reactions. Nitrated products are often explosive; sodium azide is explosive itself. Grignard reactions are conducted in either ether or THF, both of which are quite dangerous, due to a low ignition and auto-ignition point and due to the formation of highly reactive peroxides. Another example of a hazardous reaction is the sulphonation of *p*-nitrotoluene (see also Section 5.4.6). *p*-Nitrotoluene sulphonic acid, one of the key intermediates for dyestuffs, is produced and used in quantities of thousands tons per year. Under certain conditions the compound becomes thermally unstable, which over the years has led to a number of serious explosions in plants processing the acid. To avoid this danger Ciba-Geigy developed a continuous sulphonation process. This enables the manufacture of the required quantities using a small reactor in which the amount of product is rather small (Gygax, 1988). The reaction between α,β-unsaturated ketone and acetylene in the presence of lithium in liquid ammonia was studied at Hoffmann-LaRoche (Wiederkehr, 1988). In spite of the long reaction time, the heterogeneous reaction medium, and the elevated pressure, a continuous reactor was chosen for the full-scale plant because of safety reasons. A non-conventional solution was proposed: a compartmental vertical column with a multistirrer system and sectional cooling.

Handling of highly toxic substances may require operation in confined areas. Cyanation, which produces dangerous by-products such as HCN and residual cyanides, and phosgenation are examples of dedicated processes designed for dealing with toxic materials. Handling of hazardous or toxic materials (e.g. dimethylsulphate, chlorosulphonic acid, bromine, and concentrated nitric acid) in drums is generally avoided. This trend has made it necessary to provide specialized storage and transfer facilities that are suited to particular hazardous compounds. This has resulted in the fact that companies once producing a very broad spectrum of compounds have either built new plants, or limited their range of activities. The drive toward specialization also affects the organization of manufacturing. Small companies nowadays cannot perform all the stages of multistep syntheses. Larger companies have been extending their production palette by acquiring smaller specialized manufacturers. Independent fine chemicals producers have started to work together on a given synthesis, each carrying out only those steps for which their plant is suited best. In this way, plants of the individual members of the group of small producers, although built as small and multiproduct ones, are now being operated as if they were dedicated.

Other factors can also make manufacturers of fine chemicals specializing in certain areas, which is more or less equivalent to constructing and/or running plants as dedicated ones. For example, experienced people make a company an expert in certain fields. Therefore, the company plant then becomes specialized/dedicated in these fields.

7.1.2. Multiproduct and multipurpose plants (MPP's)

The manufacture of several chemicals in one plant is typical for fine chemistry technology. Two types of such plants can be distinguished: *multiproduct plants* and *multipurpose plants*. In a multiproduct plant, all products require all stages and/or follow almost the same sequence of operations. This means that multiproduct plants are usually designed for a fixed set of products having similar characteristics, e.g. dyestuffs of similar chemical structure. Usually only one product is manufactured at any one time. The time required for the manufacture of the needed amount of this product is called a *production campaign*. A multipurpose plant is characterized by the fact that products are manufactured using different equipment items, while the sequence of operations might also be different for various products. A number of products are often manufactured at the same time using a set of equipment units in different arrangements.

The heart of the MPP is a set of stirred, jacketed, stainless-steel and/or glass-lined reactors that are equipped with reflux condensers (which can also be operated as distillation coolers), pits for gravity charging of solids, equipment for dosing liquid reactants, spargers for blanketing inert gases or feeding gaseous reactants, etc. In some plants, reactors are grouped to conduct special reactions such as oxidation, reduction, esterification, etc.

An MPP with a total reactor volume of 30-50 m^3 is considered to be small; medium-sized plants range from 50 to 100 m^3; and a plant equipped with over 100 m^3 is considered to be fairly large. The total reactor volume is comprised of many small, several medium-sized, and a few large reactors. The volume of the reactors ranges from 0.25 to 15 m^3, typically 4-5 m^3. The larger reactors increase the economic risk of costly off-grade batches. They also exhibit some technical drawbacks such as more difficult temperature control, less effective mixing leading to possible non-uniform concentrations in the reaction zone, etc. Large MPPs typically contain 20 to 25 production reactors. Downstream the reactors, there are usually the following installations/apparatuses:

- facilities for solid/liquid separation, *i.e.* filters and centrifuges,
- driers of various types such as contact (often vacuum) driers, fluidized-bed driers, tray driers, rotary driers, etc.; some of them also function as disintegrators, granulators, or blenders,
- grinding devices,
- fractionation units for separation and purification of liquid products,
- solvent recovery facilities,
- storage of liquids and solids,
- effluent-treatment installations (sewage treatment, liquids and solids incinerators, off-gas treatment),
- utilities (water supply unit, gas supply unit, refrigeration unit, steam generation station, electrical system, etc.).

Generally, in MPPs one centrifuge or pressure/vacuum filter, one drier, and one fractionation system of reasonable capacity are installed for every two or three reactors/crystallizers. On average, about 2 to 5 m^3 solvent storage capacity and the same amount for intermediates are needed per 1 m^3 of reactor capacity.

Utilities in an MPP must provide flexibility with respect to operating temperatures. The typical boiler maximum pressure is approximately 0.7 MPa. This corresponds to a temperature of 410 K. The maximum pressure in the jacket of a standard glass-lined jacketed reactor is usually 0.7 MPa and 1.1 MPa at the most. Accordingly, if temperatures over 410 K are required a heating medium other than steam is needed. Organic heat-transfer media such as Marlotherm or Mobiltherm are usually used. These organic heat liquids are used over a broad temperature range and as such they increase the versatility of the reactor. Most reactions involved in fine chemicals synthesis are exothermic and, therefore, cooling must also be provided. Water cooling systems work satisfactory for removal of reaction heat as well as for crystallizations down to 295 K. When a temperature of 250 K is required, a brine cooling system can be used. Some nitrations, acylations, alkylations, reductions with metal hydrides, etc. are carried out at even lower temperatures. Freon-like refrigeration stations allow operation at temperatures ranging from 125 to 175 K (Note that CFC's are being banned for environmental reasons; in modern installations they are being replaced by freons in which fluorine and hydrogen atoms have been substituted for chlorine atoms; a problem with these freons, however, is their higher explosiveness). Plants without such facilities, and requiring low temperatures only occasionally, can manage by using dry-ice or liquid nitrogen injection into the reaction mixture. The use of various cooling and heating media within the same equipment results in operational difficulties: any change of the heat carrier in the jacket causes the mutual contamination of both media. The contaminated media frequently have to be replaced with fresh ones, which increases the operating costs and results in an additional amount of waste to be handled. Therefore, heating/cooling systems containing a single organic heat medium, are becoming more and more common. The heat liquid is recirculated and heat exchangers for heating and cooling the organic liquid are installed together with control valves that direct hot and cold medium streams flowing to the required apparatus. This concept is illustrated by the Ciba-Geigy and Sandoz MPPs (see *Example 7.1.1*).

MPPs for fine chemicals are generally run at well below their maximum capacity. At present, 60-70% of the maximum capacity is a representative figure. The theoretical capacity is difficult to define for several reasons:

- the production program of the MPP is open even within a year period,
- yields vary greatly, typically from 60 to 80 % of the stoichiometric quantity; so overall yields of multistep syntheses also vary much,
- dilutions also vary enormously, e.g. from 1:500 (some steroid solutions) up to 30%; 5 to 25 % is a typical range,
- the number of operations per unit time per reactor varies much; for a simple one-step synthesis from advanced intermediates up to three batches per day for a given reactor can be run; in a multistep synthesis, this figure can be less than 100 operations per year at full capacity; a typical figure is around 200-250 operations per reactor per year.

Taking all this into consideration, the actual output of isolated and purified products ranges from 1 to 80 kg per litre of reactor volume per year.

Example 7.1.1. The Ciba-Geigy and Sandoz multipurpose plants

The MPP of Ciba-Geigy in Basel was presented to the participants of Xth International Symposium on Chemical Reaction Engineering (ISCRE) in 1988. The plant was commissioned in 1986 and put on stream in 1987. The production program projected the manufacture of about 2500 tons of fine chemicals per year.

The basic equipment comprises 15 reactors, over 50 % being glass-lined reactors. Six reactors have a volume of 6.3 m^3; six of 4 m^3, and three of 2.5 m^3. All the reactors are provided with vapour coolers, which can be operated as reflux condensers. Two pressure plane filters (nutches) and three centrifuges, each for a batch of about 200 to 300 kg of wet material, have been installed in the plant. Above the reactors, measuring vessels with volumes up to 1 m^3 are positioned on balances. The flow rate of liquids metered into the reactors is controlled automatically, and the dosages are fixed by weight. Three stainless steel crystallizers with volumes of 4 to 6.3 m^3 are on the same floor as the measuring vessels. At ground level there are three horizontal vacuum driers with a total volume of about 4 m^3, and one double-cone drier. The horizontal driers are provided with low-speed agitators. In the basement there are installations for water treatment, a boiler, refrigeration units, a system for circulation of an organic heat carrier, storage space, and the workshop. The principle of the cascade positioning of equipment has been applied in this plant.

Off-gases are combusted in a furnace that is followed by a heat regenerator and a scrubber. Organic components of the gases are burnt there at a temperature of about 1300 K. Liquid and solid combustible wastes are incinerated in three installations which differ from each other mostly by their lining: (1) for phosphorus containing wastes, (2) for halogen containing products, and (3) for other wastes. Downstream the incinerators, there are scrubbers to clean the combustion gases.

After the production campaign for one compound has been completed, all the equipment is thoroughly washed, including multiple boiling with different solvents. The connections between the equipment items are dismantled and re-connected according to the flow-sheet for the next product to be manufactured. All operations are controlled automatically except weighing and dosing of particulate materials.

A similar MPP of Sandoz was open to participants of the Xth ISCRE. It has been operated in Basel since 1981. More than 50 products per year have been manufactured there. A cascade principle has also been used in the Sandoz plant. On the top floor there are measuring vessels; liquids are dosed by volume, contrary to the Ciba-Geigy plant. At a lower level there are eleven reactors and crystallizers, which are mostly glass-lined. One level further down there are two vertical centrifuges for a batch of about 300 kg wet material and one pressure plane filter provided with a stirrer. At ground level there are three double-cone driers, each with a volume of about 3-4 m^3. The reconnection of equipment for a new production cycle is realized via a connection valve station. The outlets of all the measuring vessels, reactors, and crystallizers, provided with liquid counters and stop-valves are located in this station, as well as the inlets (also provided with stop-valves) of all process plant facilities. Outlets are connected with inlets using flexible hoses, according to the flow-sheet for the product to be manufactured.

7.1.2.1. Modular plants

In recent years, modular batch plants have gained popularity, especially in developing countries where materials in compliance with current good manufacturing practice (cGMP) standards are difficult to find or their quality poor. In these countries there is also a shortage of skilled personnel and local bureaucracies sometimes create problems in the construction and commission of plants. These difficulties result in excessive investment costs and delays in plant start-up. The Sweden based company Pharmadule A.B. in 1987 completed its first project of a modular batch plant that can be considered to be a remedy for the above problems (Rogers, 1999). The modules, which are made of robust steel, are heavy, durable, and designed to withstand extreme conditions. They house the equipment used in the manufacturing of pharmaceuticals, utility services, and laboratories. The size of the modules is restricted by the conditions and the cost of transportation. On completion, modules are assembled in Sweden, the production facilities are tested and validated, and the staff is trained. Then the plants are disassembled and shipped to the place of destination where they are reassembled and put into operation with the staff already trained in Sweden and supervised on site. Equipment for modules must be specified in detail and ordered much ahead of construction on site. The period of construction will be significantly reduced and start-up times will be much faster. Storage areas and administrative offices are either constructed locally or are located in the existing premises. Up to 1999, the company has completed 25 plants and has over 130 plants on the prospect list. The largest modular plant is a biotechnology facility in China for the North China Pharmaceutical Corp., China's largest pharmaceutical company. Astra, Baxter, Bristol-Myers Squibb, Eli Lilly, and Pharmacia & Upjohn have contracted modular production plants with Pharmadule.

7.1.2.2. Pipeless plants

In conventional MPPs thorough washing of basic equipment and connecting lines/valves is needed at the changeover to the next campaign. Accurate cleaning of pipelines and valves is always a problem. It takes quite a long time and requires large amounts of solvents, which must be recovered, while wastes obtained during cleaning must be treated. Stringent GMP regulations for pharmaceuticals and food additives increase the time required for washing and put high requirements on the specification of solvents. This has led to a new concept of MPPs in which the number of pipelines has been significantly reduced. The concept was developed and implemented by the Japanese companies Asahi Engineering, Toyo Engineering, Mitsui Toatsu Chemicals, etc. (Takahashi and Fuji, 1990; Hasebe and Hashimoto, 1991; Niwa, 1991, 1993; Zanetti, 1992; Shimatami and Okuda, 1992). Materials in these plants are placed in vessels that can either be used for transporting materials between plant facilities or serve as mixers/reactors. The vessels are moved between non-mobile specialized stations. Each station is equipped with leak-free connections between the moveable vessel/reactor and appropriate external fixed facilities in order to charge raw materials and discharge products; if necessary, the vessel can also be connected to appropriate heating or cooling systems. Charging the vessels with raw materials, agitation/heating/cooling of the mixture, discharging the products, and cleaning between different uses is performed at these specialized stations. Each vessel is provided with sensors for liquid level, pressure, and temperature. Processing in these vessels is computer-controlled based upon signals from the sensors. Mainly optical and radio signals are used to transmit data and to control the process. Dosing of materials is mass-metered by weighing the vessels. This ensures a high accuracy in composing the mixtures. Easy programming of weight measurements enables variations in processing and quick implementation of new recipes. The transport between the stations can be 'track' or 'non-track' depending on the type of plant. The track system uses a rail-guided transporter that is driven by an explosion-proof electric motor. This system is suitable for dealing with flammable materials. A push-pull device installed on the transporter is used for transferring the vessel to the station after it has been delivered there. The non-track system employs automated guided vehicles (AGV) that are powered by batteries. As such, this system is unsuitable for dealing with flammable materials.

As mentioned, cleaning is performed at independent cleaning stations without disturbing production. Accordingly, no changeover and cleaning time has to be considered in the evaluation of the time needed for manufacturing. This permits greater flexibility in scheduling and processing of multiple products. The highly flexible process readily accommodates product changeovers and can typically cut inventories of both raw materials and products by about 80%. In turn, the lowering of inventories pushes down production costs. Niwa (1993) evaluated that the amount of wastes in pipeless plants is reduced by a factor of over two compared to conventional batch processes.

Pipe-free transfer of materials makes the plants particularly suitable for processing solid, granular, or powdered materials, and slurries that are difficult to transport via pipelines. Pipeless plants are also very suitable for simultaneous production of a large number of products. They are less suitable for processing hazardous materials that require special arrangements. Nevertheless, special leak-free connections also allow for treating of some dangerous materials. Pantelides *et al.* (1995) considered the short-term scheduling of pipeless batch plants. The mathematical formulation of the problem using mixed-integer linear programming (MILP) allows recipes of arbitrary complexity to be accommodated, while fully exploiting the flexibility of the available plant equipment.

The experience gained with the design and operation of pipeless plants is only limited up to now. Therefore, capital investments of pipeless plants are probably higher than for traditional MPPs. Due to the high efficiency, the pipeless plant requires fewer reactors, less auxiliary equipment, pipes, and automatic valves. However, the need for sophisticated transporting equipment, stations, connectors, etc. may make the total investment for a pipeless plant higher that for conventional plants. For small MPPs with three to five reactors, the pipeless plant costs more. Of course, in pipeless plants pipes and automatic valves are also needed, but the number is less than 30% of that required for a conventional plant. According to Itsuo Aishima, president of Asahi Engineering (Zanetti, 1992): "It produces less waste, requires one operator for every four, and is 20% smaller." Changeover is faster, product quality is improved, and the possibility of cross-contamination is significantly reduced.

The first commercial-scale pipeless plant for adhesives was completed in 1991 for Mitsui Toatsu Chemicals Inc., at its Chiba (Japan) Works (Shimatami and Okuda, 1992). The plant is a two-story, 25-m-long and 15-m-wide facility, with two trains of three stations (preparation, mixing, and filling). An AGV with a capacity of 3.5 metric tons conveys one of the four tanks from one station to another following programmed instructions. Adhesives are produced by batch processing in each of the stations. Connecting, disconnecting, up-down lift of the agitator shaft in mixers, and coupling of product-filling pipes is controlled by a computer. Nearly 100 types of industrial adhesives are manufactured at the facility at a yearly rate of 5,000 metric tons. Compared to conventional production methods, labour savings of 50% and a 200% increase in productivity have been achieved in the plant.

7.1.3. Mixed plants

In mixed installations, reactions are often carried out batchwise, whereas the subsequent isolation and purification steps are performed continuously. Sometimes the character of the chemical reaction forces running the reaction in a continuous manner, while existing batch facilities for isolation and purification of the product are used to process the reaction mixture from the reactor. An example of this type of mixed plant is presented in *Example 7.1.2.*

Example 7.1.2. Plant for the manufacture of 1-(2,6-dimethyl)phenoxy-2-aminopropane hydrochloride (with permission of the Pharmaceutical Institute, Warsaw)

Drugs containing 1-(2,6-dimethyl)-phenoxy-2-aminopropane hydrochloride are commonly used as antiarrhythmic medicines, the demand of which is of the order of tons per year (on the basis of the active ingredient). A process for the manufacture of 1-(2,6-dimethyl)phenoxy-2-aminopropane hydrochloride has been developed by the Pharmaceutical Institute, Warsaw. Fig. 7.1-3 shows the main reactions.

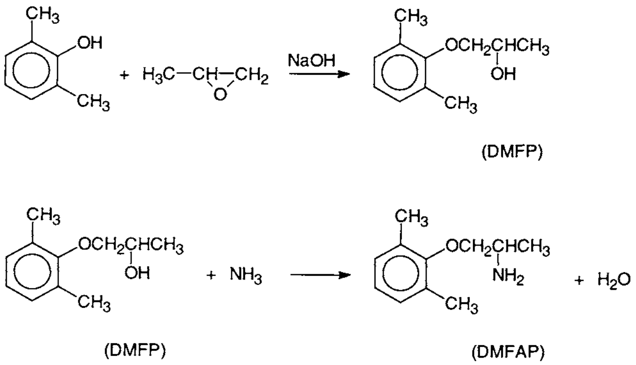


Figure 7.1-3. Reaction scheme.

In the first step 2,6-xylenol is condensed with propylene oxide in the presence of NaOH at elevated temperature and pressure yielding 1-(2,6-dimethyl)-phenoxy-propanol-2 (*DMFP*). In the second step, ammonia is reacted with *DMFP* in the gas phase in the presence of hydrogen and a solid catalyst at a temperature of 450-475 K under atmospheric pressure. The product, 1-(2,6-dimethyl)-phenoxy-2-aminopropane (*DMFAP*) is isolated from the condensed reaction mixture and purified as its hydrochloride.

Flow-sheets of the plant are shown in Figs. 7.1-4 to 7.1-6. The plant consists of three units: (1) *DMFP* synthesis and purification (Fig. 7.1-4), (2) synthesis of *DMFAP* (Fig. 7.1-5), and (3) separation and purification of *DMFAP* hydrochloride (Fig. 7.1-6). Steps (1) and (3) are performed in MPPs, while unit (2) is a dedicated plant, that would be difficult to adapt for other processes.

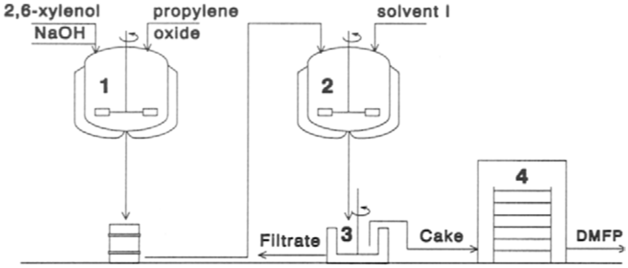


Figure 7.1-4. Flow-sheet of plant for the manufacture of *DMFP*.

(1) In reactor 1 2,6-xylenol is condensed with propylene oxide in the presence of NaOH at elevated temperature and pressure. The reaction is reasonably selective. However, some isomers are also formed in minor proportions. Therefore, the crude *DMFP* is dissolved in the organic solvent *I* and crystallized in tank 2, separated from the mother liquor in centrifuge 3, and dried in drier 4.

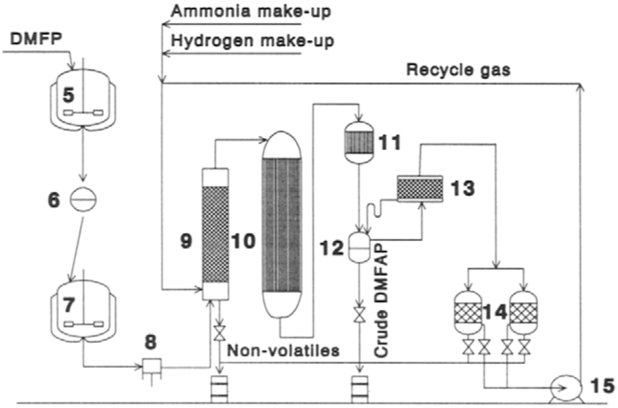


Figure 7.1-5. Flow-sheet of plant for the manufacture of crude *DMFA*P.

(2) *DMFP* is melted in tank 5 equipped with a stirrer and then passed batchwise, via filter 6, to measuring vessel 7. From this vessel, the liquid is dosed by a metering pump 8 to evaporator 9, to which a recycled gas containing mainly ammonia and hydrogen and a minor proportion of volatile reactants is also introduced. The mixture is heated to 450 K and passed to reactor 10 containing a pelleted catalyst. The outflowing reaction mixture is cooled in heat exchanger 11. The liquid is separated in separator 12 and demister 13, while the gas is recycled to the evaporator. A small amount of gas is purged via an absorption system not shown in Figure 7.1-5. Fresh ammonia and hydrogen are added to the recycled gas in such amounts that a predetermined concentration of ammonia is maintained in the gas. Other demisters 14 are located before to and after recycle compressor 15.

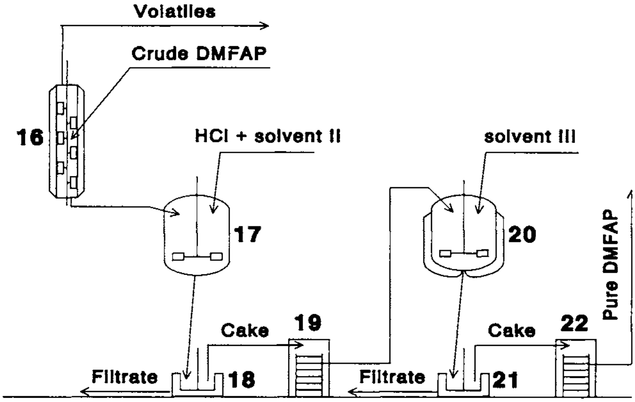


Figure 7.1-6. Flow-sheet of plant for *DMFAP* isolation and purification.

(3) The condensed reaction mixture is evaporated in film evaporator 16 under vacuum. The crude 1-(2,6-dimethyl)-phenoxy-2-aminopropane hydrochloride is precipitated in tank 17 using HCl dissolved in organic solvent *II*, separated in centrifuge 18, and dried in tray drier 19. The final purification by crystallization from solvent *III* occurs in crystallizer 20. Pure 1-(2,6-dimethyl)-phenoxy-2-aminopropane hydrochloride is separated in centrifuge 21 and dried in tray drier 22. The plant is equipped with typical solvent recovery and storage facilities not shown in the figures.

7.2. TYPICAL EQUIPMENT IN A MPP

In this section, a selection of process equipment that seems to be the most promising and most versatile in batchwise operated MPPs will be briefly presented.

7.2.1. Reactors

Jacketed tank reactors, mainly stainless steel reactors and glass-lined reactors equipped with a stirrer, predominate in plants for the manufacture of fine chemicals. Glass-lined reactors are in common use although they are by 30-50 % more expensive than stainless steel reactors. This is because of the high chemical resistance of enamels towards typical chemical media and the much lower possibility of contamination of products with heavy metals, which should not be present in most pharmaceuticals and food additives.

Enamels offered by all leading European manufacturers of glass-lined equipment (Pfaudler, DeDietrich, Technoglass, Tycon, Lampart) are characterized by very high chemical resistance to almost all organic materials and acids, except hydrofluoric acid, even at ambient temperatures. Typically, the rate of corrosion at 30% H_2SO_4 at 130 °C is about 0.1 mm per year. The chemical resistance of enamels to 20% hydrochloric acid is similar. This figures show that enamels are more resistant to acids than tantalum and Hastelloy B. The heat conductivity of these glasses is unexpectedly high: The overall heat-transfer coefficient between an organic liquid on one side of the wall to water on the other side is 185 $W\ m^{-2}\ K^{-1}$ for a reactor lined with the Pfaudler glass 9100, while for a stainless steel reactor this coefficient is 199 $W\ m^{-2}\ K^{-1}$, only about 6% higher (Pfaudler Bull. No. SB95-910-2). The corrosion rate increases significantly if alkaline solutions are in contact with enamel. The corrosion rate ranges from 0.24 to 0.38 mm/year for 4% NaOH at 80 °C. It is reduced by factor of about two for a special glass 4100 developed by Pfaudler. Usually enamels are not sufficiently resistant to phosphorus compounds, especially at elevated temperatures.

A standard AE (DIN) stirred-tank jacketed reactor is shown in Fig. 7.2-1. It is equipped with several nozzles for loading and discharging the materials, and measuring probes that can also act as baffles, a manhole with sight glass, and a stirrer with driving system.

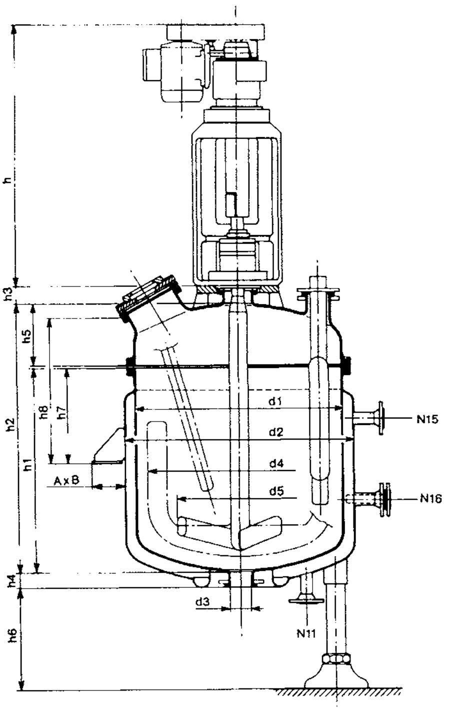


Figure 7.2-1. Glass-lined reactor (by courtesy of De Dietrich).

Very efficient enamelling techniques have been developed but usually they are restricted to items without sharp edges. This limits the types of stirrers in glass-lined reactors. Anchor agitators (for effective heating and cooling) and impellers (for more intense stirring) are mainly used in glass-lined tanks. De Dietrich has developed a stirrer (known under the trade name of GasLock) with individually removable and adjustable blades, see Fig. 7.2-2. The slope of the blades on this stirrer can be changed easily. This allows for adjustment of mixing efficiency depending on the purpose, e.g. particle suspension and crystallization (blades tilted at 30 °) or gas dispersion and dissolution (blades tilted at 60 to 90 °). For gas dispersion, a very good effect is obtained with blades tilted at 60 ° and introduction of gas by a dippipe (Fig. 7.2-2a). The gas can also be introduced from the bottom (Fig. 7.2-2b). In this case an angle of 90 ° is ideal. GlasLock agitators with two sets of blades (Figs. 7.2-2c and d) improve the agitation efficiency in large-size vessels. A cryogenic technique developed by Pfaudler allows for independent enamelling of a stirrer itself and subsequently mounting it on a shaft. More sophisticated and versatile stirrers are used in stainless steel reactors. Stirred-tank jacketed reactors are produced in a variety of sizes, from 50 cm^3 up to some tens of cubic meters.

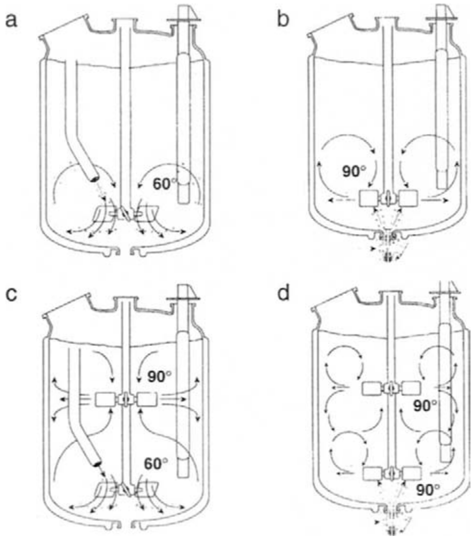


Figure 7.2-2. Glass-Lock agitator (by courtesy of De Dietrich).

7.2.2. Filters and centrifuges

A significant proportion of products are solids that are separated from a reaction mixture by filtration and centrifugation and purified by crystallization. Recently, more sophisticated techniques for purification (e.g. HPLC) have come in use but crystallization still remains the predominant method. In order to separate solid/liquid mixtures, centrifuges and plane filters (nutches) are used. Generally, filters and centrifuges are operated batchwise. No specific demands are put on centrifuges. Devices that guarantee operation according to GMP, *i.e.* are easy to clean, will be preferred in the pharmaceuticals business. A modern centrifuge that is adapted for GMP operations is shown in Fig. 7.2-3.

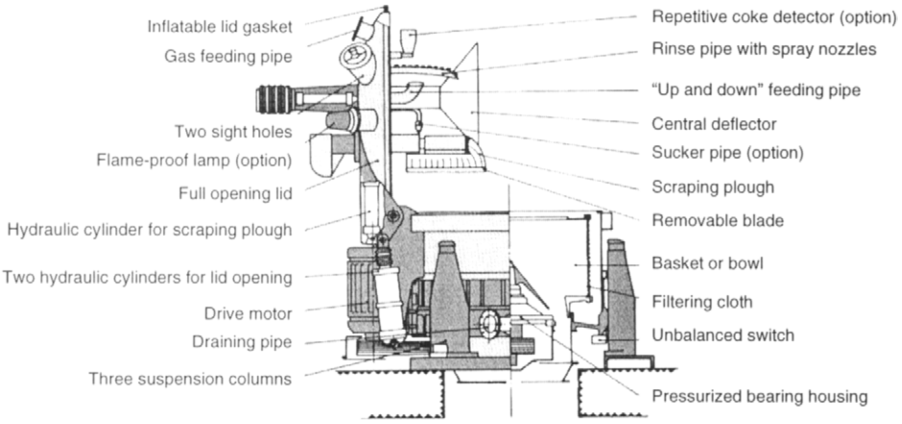


Figure 7.2-3. Vertical centrifuge SC-DEC (by courtesy of Rousselet Centrifugation).

A traditional enamelled nutch filter is shown in Fig. 7.2-4. Recently, nutches equipped with a stirrer with variable speed, position, and reverse rotation have become more common. These filters ensure thorough washing of a filter cake either by a sequence of re-slurryings and filtrations or by replacement. Typical nutches of this kind are shown in Figs 7.2-5 and 7.2-6.

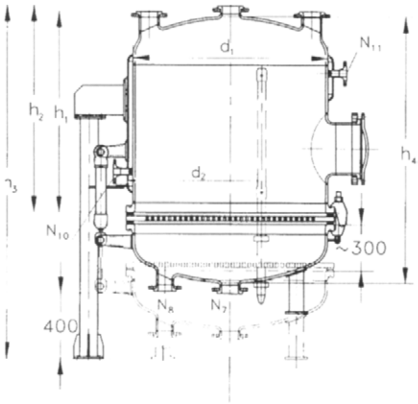


Figure 7.2-4. Nutch glass-lined filter (by courtesy of Lampart Co.).

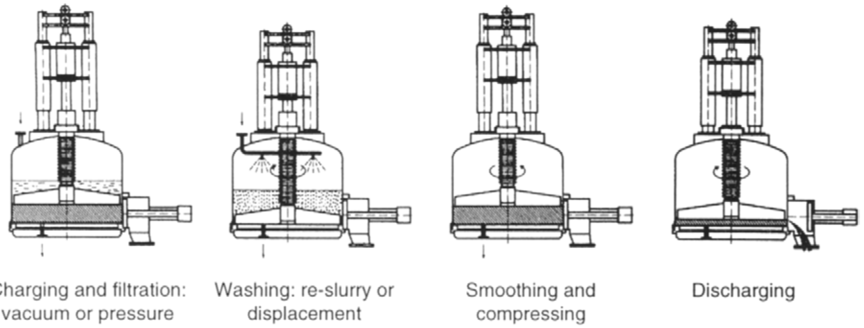


Figure 7.2-5. Nutch filter with side discharge, pharma performance (by courtesy of Rosenmund AG).

Side discharge (Fig. 7.2-5) permits pressure-tight shut-off after discharging of the product without cleaning of the sealing surfaces, which is a distinct advantage in automated processing and contamination-free production. Side-discharge filters are also produced in Pharma-performance with a total containment and polished finish to meet pharmaceutical standards for GMP production. Central-discharge paddle filters are equipped with paddle agitators, which are very effective in re-slurrying a filter cake. A central discharge filter has an improved product discharge system, particularly effective for pasty, sticky cakes. The filtering area of nutches ranges from 1 to 16 m^2. Filters of this kind are offered by many European Manufacturers (Rosenmund, Comber, Giovanola, Cogeim, etc.).

Combinations of nutches and driers, so called filter-driers, are becoming increasingly common. Particularly suitable are jacketed filter-driers having a heated bottom plate (below the filtration membrane) and a heated agitator, such as the Schenk filter-drier (see Fig. 7.2-7).

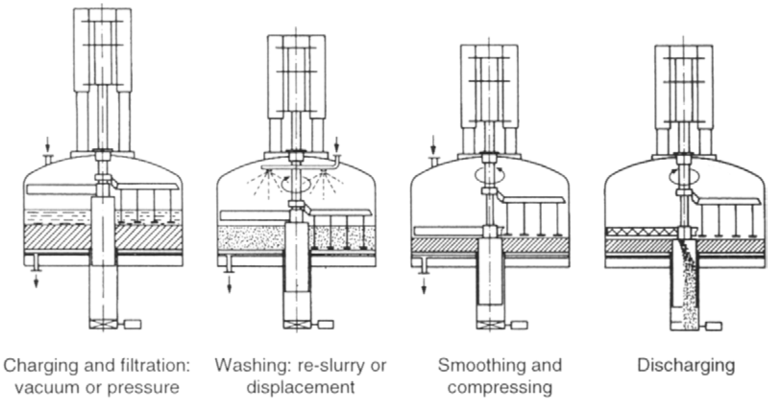


Figure 7.2-6. Central discharge-auger filter (by courtesy of Rosenmund AG).

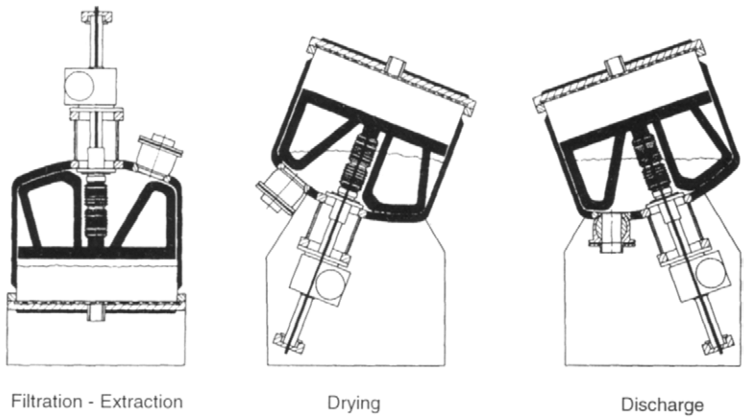


Figure 7.2-7. Filter-drier (by courtesy of Schenk Filterbau GmbH).

At the basic position the suspension is filtered. The filter cake can be brought into suspension with washing liquid that can be added in amounts exactly to the requirements. At the end of filtration, the agitator can be lowered onto the filter cake to compress it and smoothen the surface to avoid crack formation during deliquorisation. In the tilted position, the filter cake can be moved about the heating surfaces (the vessel wall and the heated agitator) by means of the agitator in the raised position. Drying is effected by a combination of movement, temperature, and vacuum. The solids do not come in contact with the filter medium. After drying has been completed, the solids can be discharged automatically through the discharge valve with the aid of the agitator. Special equipment for dustfree transfer even under sterile conditions is available. Filter-driers can be particularly useful for handling toxic, irritating, and other hazardous materials. The hermetic operation of filter-driers prevents contact with these hazardous materials during filtration, re-slurrying, and drying. Some companies offer filter-driers in combination with a system of a circulating inert gas that is preheated before entering the filter-drier. This enhances the heat and mass transfer inside the apparatus. The exiting gas is cooled (even frozen if the filter-drier is operated under vacuum). The condensate is separated and the gas is recycled to the filter-drier. Recently, a centrifuge-drier has appeared on the market (see Fig. 7.2-8).

An extension of the filter-driers are the reactor-filter-driers, as illustrated in Fig. 7.2-9 by an apparatus known under trademark name Nutrex^R and developed by Rosenmund. Equipment of this kind is still more versatile and operation safer. In one vertical position the device can act as a filter, a granulator, and an apparatus for all operations with filter cakes (*i.e.* re-slurrying, smoothing, and squeezing). In the reverse position, it can operate as a reactor, extractor, evaporator, crystallizer, drier, etc. There are many other companies offering reactor-filter-driers, e.g. SEN, Giovanola, Schenk, and Cogeim.

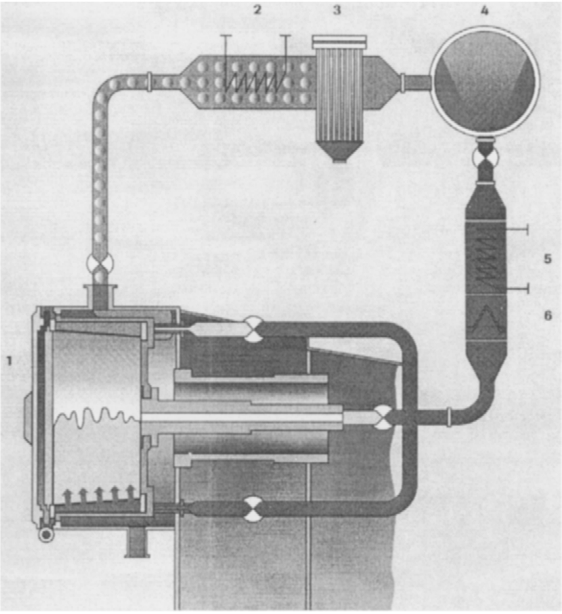
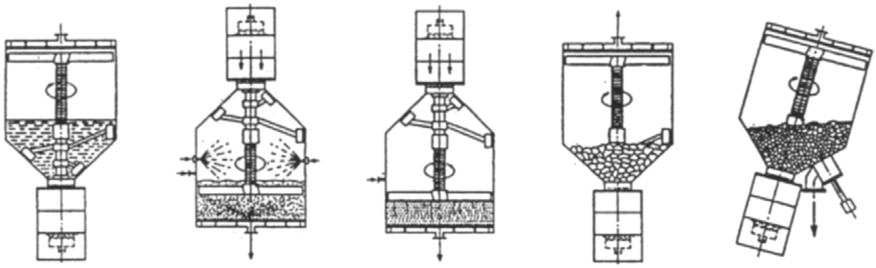


Figure 7.2-8. Centrifuge-drier system (by courtesy of FIMA, Fischachtaler Maschinenbau); 1 - centrifuge, 2 - condenser, 3 - demister, 4 - compressor, 5 - reheater, 6 - filter.



Reaction, crystallization

Filtration, washing, re-slurry

Smoothing

Drying

Discharge

Figure 7.2-9. Reactor-filter-drier, Nutrex (by courtesy of Rosenmund AG).

7.2.3. Driers

Versatile driers that are easy to clean are preferred in MPPs for fine chemicals. Therefore, shelf driers that can also be operated under vacuum are still in common use. They are easy to clean and may be used for a variety of products. Shelf driers, however, have poor heat- and mass- transfer characteristics.

Fluidized-bed driers are also widely used due to their large heat- and mass-transfer coefficients. However, materials of even moderate adherence and cohesiveness cannot be dried in a fluid bed. The same applies to materials that are sensitive to oxygen, especially at elevated temperatures. Vacuum drying is often necessary for oxygen sensitive materials and this is not easy to realize in fluid-bed driers, although there are systems to deal with this problem. Fluid-bed driers are not as easy to clean as shelf driers or rotary driers.

Rotary driers like tumble or double-cone driers are commonly used in the fine chemicals industry. These driers are also produced as glass-lined equipment, which is particularly suitable for drying of adhesive materials. Rotary driers are easy to load, discharge, and clean. Usually they are designed for vacuum operation. A spherical contact drier (Rosenmund AG) is very effective. It is equipped with a fast rotating agitator. This results in high heat-transfer coefficients and short drying times. The agitator is shaped in such a way that cleaning is easy. The drier wall is polished and also easy to clean. This makes the drier particularly suitable for GMP operation. Paddle driers or conical-screw driers (Fig. 7.2-10) are conventional contact driers. There are versions of paddle driers with stirrers and shafts that can be taken out of the vessel easily, which makes cleaning of the drier much easier. Both paddle driers and conical-screw driers have been adapted to handle pharmaceutical products, although screw-conical driers are relatively difficult to clean.

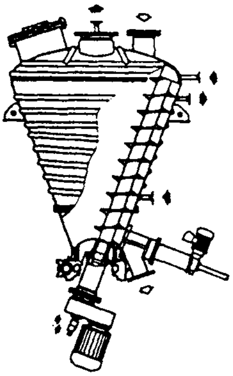


Figure 7.2-10. Vrieco-Nauta pharmavacuum drier (by courtesy of Hosokawa Micron BV).

All the driers discussed above are unsuitable for mixtures with a high liquid proportion (slurries). For such mixtures spray driers (see Fig. 7.2-11) or cyclone driers (see Fig. 7.2-12) are effective. In the former the slurry is injected into the drier by a nozzle that atomizes the suspension. Small droplets fall down countercurrently to the hot gas that rises in the conical drier zone. In cyclone driers the slurry and the hot gas flow cocurrently. Driers of both kinds are characterized by short residence times. Therefore, they are particularly suitable for temperature sensitive products. A significant proportion of driers of all kinds, appropriately modified, can also be operated as solids mixers and/or granulators.

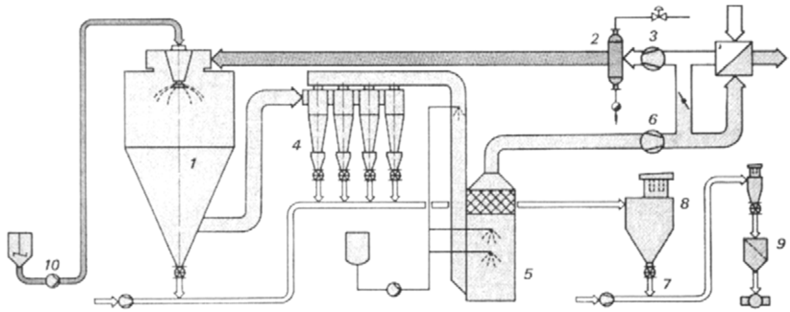


Figure 7.2-11. Spray drier with heat recovery system; 1. Spray tower and drying system; 2. Air heater; 3. Air fan; 4. Cyclone dust separator; 5. Wet dust separator and entrainment separator; 6. Exhaust air fan; 7. Pneumatic product conveyer; 8. Intermediate product storage; 9. Product sieving and packing; 10. Wet product pumping system (by courtesy of BMA, TAG-Division).

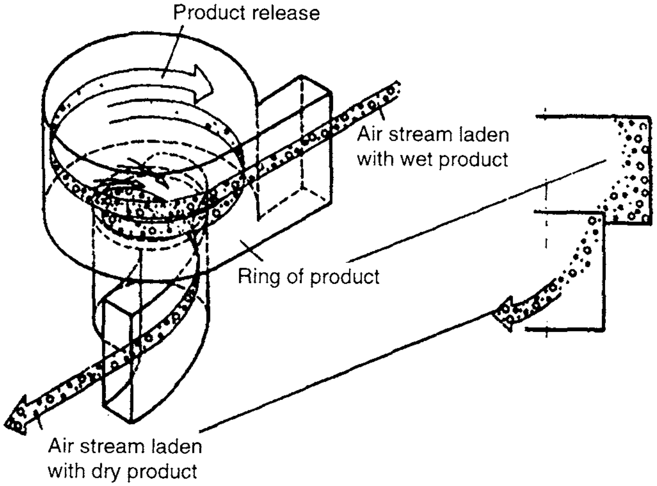


Figure 7.2-12. Operating principle of Convex® drier (by courtesy of Buss-SMS GmbH Verfahrenstechnik).

7.2.4. Extractors

Extraction can be performed in stirred tanks if the process proceeds fast and separation of phases is easy, but column extractors are most commonly used. The column can be filled with a particulate material. The liquids flow countercurrently whereby the flow can be uniform or pulsed. Reciprocated and rotary agitators are often used to enhance mass transfer. An example of the latter type is shown in Fig. 7.2-13 (asymmetric rotating disk (ARD) extractor).

7.2.5. Evaporators

Evaporation can be performed directly from reactors or kettles provided that substances are thermally stable. Such evaporation is time consuming because of the low heat-transfer surface area per unit volume. In the case of temperature sensitive materials, the residence time in the evaporator must be short and the temperature should be as low as possible. Consequently, continuous vacuum evaporators with a short residence time should be used to treat such materials. Falling-film (thin-film) evaporators are suitable to perform such operations. A typical falling-film evaporators is shown in Fig. 7.2-14. Centrifugal evaporators are also commonly used.

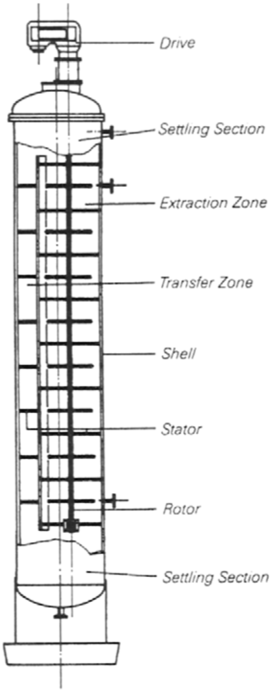


Figure 7.2-13. ARD-extractor (by courtesy of Buss-SMS GmbH Verfahrenstechnik).

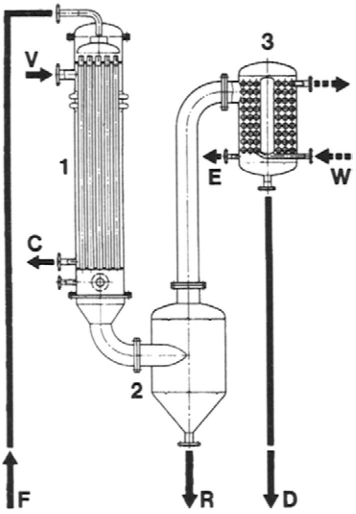


Figure 7.2-14. Falling-film evaporator with centrifugal separator and condenser (by courtesy of Kühni AG); 1. Falling-film evaporator; 2. Separator; 3. Condenser; F = feed; D = distillate; E = vent/vacuum; R = residue; V/C = heating medium; W = cooling medium.

7.3. PRODUCTION COSTS

Production costs include capital-dependent costs, e.g. depreciation, interest, insurance, and taxes; and operating costs such as costs of raw materials and auxiliaries, costs of utilities, waste-disposal costs, labour costs, maintenance costs, and overheads.

7.3.1. Capital investment costs

Capital investment costs can be divided into two categories: (1) costs that are independent of the location (Inside Battery Limits, *ISBL*), and (2) costs that are dependent on the location (Outside Battery Limits, *OSBL*).

The *ISBL* costs include process costs such as the cost of process equipment and the associated control rooms, laboratories, storage and loading/unloading facilities, insulation costs, protective painting, instrumentation and control, piping, engineering and supervision, contractor's fee, and start-up expenses. Although only 25-45 % of the equipment and machinery costs are related to the reactors, these are considered to be the most important part of MPPs. Process equipment typically constitutes 31% of the costs, auxiliaries (pipes, valves, fittings, tubing, insulation) 44%, construction expenses (tools, sheds, timber, all used for construction but not permanent parts of the plant) 15%, and engineering (tools, papers, pencils, reproduction costs) 10%. All the figures also include labour costs associated with the respective cost component (Perry and Chilton, 1984). The overall proportion of reactors in the annual operating costs ranges from 10 to 20 %, or even down to 3-5 % of total costs when considering the cost of raw materials as well. An estimation of the contribution of some groups of equipment pieces to the total equipment and machinery costs for batch plants is given in Table 7.3-1.

The reactor contribution depends on the reactor size and material of construction. Glass-lined reactors are about 40-50 % more costly than the stainless steel reactors. The total investment costs also depend upon the equipment size, as illustrated by Fig. 7.3-1.

The *OSBL* costs comprise land, site development, process buildings, auxiliary buildings, storage buildings, equipment and construction for utilities including cooling towers, construction expenses, waste-disposal facilities, etc. The *OSBL* costs may be assumed to be about 20-40% of the *ISBL* costs, with the upper limit applying better to small batch plants.

The *ISBL* costs can be roughly estimated by multiplying the sum of the purchased-equipment costs by a certain factor, the so-called *Lang factor*:

$$\textit{direct plant costs} = \textit{Lang factor} \cdot \sum(\textit{cost of machines and equipment items}) \qquad \mathbf{(7.3\text{-}1)}$$

Table 7.3-1
Fine chemicals capital investment

Component of costs	Contribution, %
Reactor system	25-45
Solids & liquids recovery	15-20
Filtration, drying, size reduction	10-25
Liquid storage	4-6
Analytical instruments	1-2
Control instrumentation	5-8
Utilities	5-8
Effluent treatment	10-20

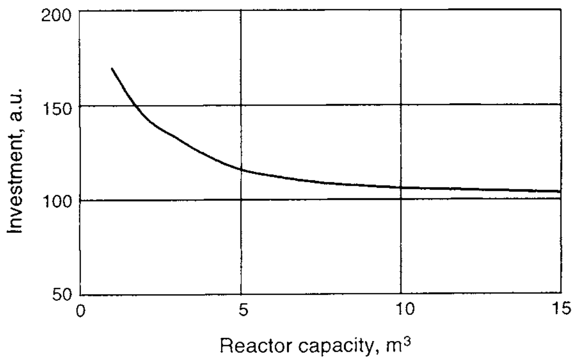


Figure 7.3-1. Total investment costs versus reactor capacity.

The Lang factor ranges from three to five. In 1984, the average value of for BASF investment projects (*Jahrbuch der Chemiewirtschaft*, 1991) was 3.9. The Lang factor includes all costs of equipment installation, transportation of the equipment to the site, foundations, supports, platforms, etc. The total installed cost of equipment depends on the type of equipment and varies from 25 to 90 % of the purchased-equipment costs. In general, the cost of the purchased equipment ranges from 65 to 80 % of the total installed costs. The installation costs for some types of equipment are given in Table 7.3-2 as a percentage of the purchased-equipment cost.

Table 7.3-2
Installation cost as a percentage of the purchased-equipment costs (after Peters and Timmermans, 1980)

Type of equipment	Installation cost, %
Centrifuges	20-60
Driers	30-60
Evaporators	25-90
Filters	65-80
Heat exchangers	30-60
Metal tanks	30-60
Mixers	20-40
Pumps	25-60
Towers	60-90
Vacuum crystallizers	40-70

Engineering companies have data at hand on equipment costs covered by orders and inquiries over the years. Based upon these data companies can estimate the relationship between the cost and the equipment size expressed in terms of mass, throughput, operating conditions (temperature, pressure), etc. However, the best source of cost data are manufacturers of chemical machinery and equipment whereby the economic situation of the manufacturer must be taken into account when critically assessing cost data. More detailed information on equipment sizing and costing can be found in books of Peters and Timmerhaus (1980), Ulrich (1984) and Biegler *et al.* (1994).

An analysis of equipment costs and capital investment for chemical plants (Wilson, 1947; Chilton, 1950; Vilbrandt and Dryden, 1959; Guthrie, 1970) showed that the 'six-tenths factor' can be applied for a rough evaluation of the influence of equipment size on its cost. The 'six-tenths rule' can be described as a power law expression:

$$\frac{C}{C_{ref}}=\left(\frac{V}{V_{ref}}\right)^{n} \qquad \textbf{(7.3-2)}$$

where C and C_{ref} are the capital cost of a new plant and of the base reference plant, respectively, V and V_{ref} are the capacities of the corresponding plants, and n is a factor that ranges from 0.6 to 0.7 for a large number of processes. Ostwald (1992) suggests that the following equation fits the actual cost data better:

$$C=C_V\cdot\left(\frac{V}{V_{ref}}\right)^{n}+C_F \qquad \textbf{(7.3-3)}$$

where C_V is the variable portion of the cost dependent on the plant size and C_F is the fixed portion of the cost (related to the *OSBL* costs). Eqn. (7.3-3) becomes equivalent to Eqn. (7.3-2) if C_F is negligible, which applies to large plant capacities. Haseltine (1996) points out that the power law exponent n depends on the plant size, more specifically on the contribution of auxiliary equipment (the cost of which also follows the power law with an exponent that can be anywhere between zero and one, typically 0.6 to 0.75) of the total investment costs. For small plants n ranges from 0.3 to 0.5 while for very large plants it approaches unity. In between the value of n is as was found by most analysts, i.e. 0.6-0.7.

Equation (7.3-3) with $C_F = 0$ also holds for individual equipment pieces and machines:

$$C_p=\alpha\, V^{\beta} \qquad \textbf{(7.3-4)}$$

where C_p is the purchased cost of equipment, and V is the size (which can be volume, e.g. for tanks, reactors, and driers, surface area, e.g. for filters and heat exchangers, etc.), and α and β are cost coefficients. The exponent β for chemical equipment varies significantly depending upon the equipment type. Some typical values of β for chemical equipment are given in Table 7.3-3 (based on data given by Perry and Chilton, 1984; Remer and Chai, 1990; Vatavuk, 1995; Ulrich, 1984; Peters and Timmerhaus, 1980; and the authors' estimations).

As shown by Garnett and Patience (1993), the exponent β is inversely proportional to the number of scaled dimensions of the production-rate-limiting activity. As such, it should vary from 1/3 to 1/1. Indeed, factors given in Table 7.3-3 do support this thesis. One would expect that towers of constant cross-sectional area should be scaled with an exponent of 1/1 since only one dimension is changed. Remer and Chai (1990) report $\beta = 1$ for such equipment. For storage tanks that are scaled volumetrically (three dimensions), the value of β should be around 0.33 and this agrees with findings of Remer and Chai (1990). Similarly, for vacuum crystallizers $\beta = 0.37$, for reactors $\beta = 0.32$-0.42, for some driers $\beta = 0.22$-0.4. Filter presses should have an exponent of 0.5. Guthrie (1976) found $\beta = 0.58$ for plates and press, and $\beta = 0.5$ for pressure leaf filters.

Corrective indexes are needed to adapt old prices to the current or future situation. The purchased equipment cost in year s, $C_{p,s}$ can be evaluated based on the purchased equipment cost in one of the former year r, $C_{p,r}$ using the following expression:

$$C_{p,s} = C_{p,r}\frac{I_s}{I_r} \tag{7.3-5}$$

where I_r and I_s are cost indexes for years r and s. In Germany in the decade 1980-1990 the average rise of the average index for chemical equipment was 5 to 5.5 per year. *Chemical Engineering* publishes data on the plant cost index (*CP* index) that can be considered a good measure for chemical plants cost, although there are some variations with respect to individual machines and equipment pieces.

Table 7.3-3

Typical exponents β for equipment costs versus capacity

Equipment[a]	Size range	Exponent β
Agitator, c.s.	power, 1-40 kW	0.50-0.54
Propeller		0.5
Turbine		0.3
Blender, double cone, c.s.	volume, 1.5-7.0 m^3	0.49
Centrifuge, automatic, batch, horizontal, c.s.	basket dia., 1-1.7 m	0.81
Centrifuge, vertical, c.s.		1.00
Drier, drum, atmospheric	heat surface area, 1-10 m^2	0.40
Drier, drum, vacuum	heat surface area, 1-10 m^2	0.55-0.80
Drier, shelf, vacuum	heat surface area, 1-100 m^2	0.53
Evaporator, agitated falling-film, s.s.	heat surface area, 3-6 m^2	0.55
Filter, plate and frame, c.i.	filtering surface area, 1-60 m^2	0.58
Filter, plate and frame, s.s	filtering surface area, 1-30 m^2	0.85
Heat exchanger, shell-and-tube	heat exchange area, 0.6-2.9 m^2	0.43
Reactor, 20 bars, s.s	volume, 0.5-4 m^3	0.56-0.7
Reactor, glass-lined	volume, 0.2-2.5 m^3	0.54
	volume, 0.5-10 m^3	0.32-0.42
Refrigeration unit	power, 25-14,000 kW	0.70-0.72
Tank, vertical, c.s.	volume, 0.75-40 m^3	0.52-0.82
Tank, horizontal, c.s.	volume, 5-20 m^3	0.60-0.67
Tank, glass lined	volume, 0.5-4 m^3	0.49
Tower, process, c.s.	volume, 10-60 m^3	0.60-0.71

[a] c.s. - carbon steel; c.i. - cast iron; s.s. - stainless steel.

The history of the *CP* index of the last fifty years is shown in Fig. 7.3-2. For the decade 1980-1990, the average rise of the *CP* index correlates well with the data for Germany given above.

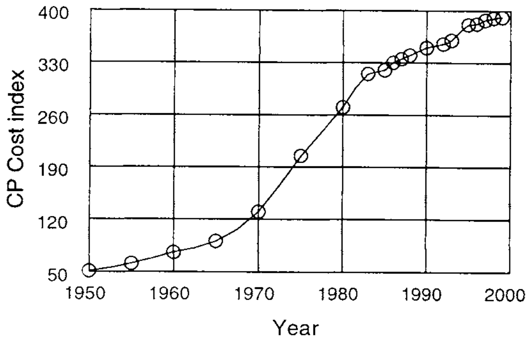


Figure 7.3-2. History of the CP plant cost index.

7.3.2. Operating costs

Operating costs can be estimated based on statistical analysis of operating costs in existing plants. Costs of waste disposal can be evaluated in the same way as costs for any chemical process since procedures for disposal include, in fact, unit chemical processes and operations. Costs of utilities and maintenance are best assessed based on the company data banks. Typical utility figures per m^3 capacity of reactors in MPPs are: 800-1100 kg steam/h, 60-80 kW power, and 7,000-8,000 kJ/h refrigeration capacity.

Labour costs in chemical plants vary over a broad range. They include direct labour costs (operators, supervision, maintenance staff, storage operators, and pay-roll burden on all labour charge), plant overhead (administration, laboratory staff, technical service, shops, purchasing, accounting, communication, plant protection), distribution costs (packaging, freight, operators of terminals and warehouses), and marketing. For small batch plants staff costs can be up to 25% of the other manufacturing costs. The proportion of labour in operating costs, raw materials excluded, ranges from 25 to 70 %. Labour requirements can be correlated with the overall capacity and are typically about 1.0-1.2 employee per m^3 of the total capacity. This figure applies to plants that are in the diversified fine organic synthesis business. If the production program is well defined and comparatively large reactors are used, 0.2-0.5 employees per m^3 capacity is sufficient. The staff costs can be readily evaluated based on the detailed process description and the demand from the actual state of the installation. However, almost regardless of the size of a well-automated plant, a single-product installation requires the following minimum direct staff: one shift foreman, two shift employees for the control room, one shift employee for outside operations, and one shift employee as a reserve.

7.4. DESIGN AND SCHEDULING OF BATCH PLANTS

7.4.1. Introduction

Industrial chemical processes are determined by *recipe* and *production route*. The recipe is the specification of a sequence of processing steps for the transformation of raw materials into the desired product(s). Specifications include quantity and quality of raw materials, composition of feeds, sequence of additions to the reaction zone, rate of dosing, temperature-time dependencies, pressures, etc. The production route also includes the specification of equipment in which processing steps are performed.

Most batch processes are realized in several *processing stages (tasks or jobs), i.e.* unit operations (crystallization, filtration, drying, etc.) and processes (chemical reactions) that must be performed to satisfy the recipe requirements. Each stage is characterized by the processing capacity of equipment and the time needed to complete the task. In the simplest case these requirements are fixed by the recipe. In most cases, however, they are dependent on the design and size of the equipment and operating conditions of the particular stage. Individual *steps* in multistep syntheses can be considered to be composite stages. Stages may be joined into *sequences* (*campaigns*) in which sufficiently stable intermediates are manufactured.

Each stage is carried out using one or more equipment items, e.g. reactors, tanks, filters, and driers. One or more identical equipment items may be operated in parallel to form a *batch stage*. The plants consist of *true batch equipment*, e.g. tanks, reactors, and tray driers, and of *semicontinuous equipment*, e.g. pumps, centrifuges, some filter types, and heat exchangers. The batch units are usually linked together by semicontinuous equipment. The vast majority of stirred-tank reactors work both as semicontinuous and batch apparatus. The true batch equipment is specified by *volume* or *surface area* while semicontinuous equipment is specified by *throughput* or *processing rate*. Semicontinuous equipment can be coupled in series, a so-called *semicontinuous subtrain*, e.g. a pump coupled to a centrifuge. All equipment in such a subtrain must operate simultaneously.

The equipment size and operating conditions must be specified at the design stage or the size is determined by the existing plant in which the process is to be implemented. The size of equipment items needed to manufacture the same amount of product is generally different for various products. It depends on many factors, first of all on concentrations. The size requirements may conveniently be represented by the *size factor*. For batch equipment, the size factor S_{ij} for product i and stage (equipment unit) j is defined as the size of equipment needed at stage j (V_j) to produce a unit mass of product i in the batch leaving the process, *i.e.* a batch at the final stage of the process:

$$S_{ij} = \frac{V_j}{B_i} \qquad \textbf{(7.4-1)}$$

where B_i is the *batch size*. The batch size must meet requirements with respect the degree of filling of the equipment. For instance, stirred batch reactors are filled typically to 0.7-0.8 of the total volume. The degree of filling should be reduced for foaming mixtures. The size factor is usually assumed to be independent of the equipment size. This may not be true if a process is scaled-up by orders of magnitude. Then, concentrations must sometimes be decreased to enable maintaining the temperature at the desired level.

B_i is defined as the amount of product i that is manufactured during the cycle time of product

i (cycle time is defined in Section 7.4.1.1, after Sparrow *et al.*, 1975) in a given set of either existing or designed equipment units. The batch size is limited by the equipment unit for which the ratio of the capacity V_j to the corresponding size factor S_{ij} is smallest[1]:

$$B_i = \min_{j=1,\dots,NS} \left(\frac{V_j}{S_{ij}} \right) \tag{7.4-2}$$

where NS is the number of stages. The relationship between the processing time in a batch unit t_{ij}, batch size B_i, production capacity Q_i, and time available for manufacturing a product i (*time horizon*) H_i is given by:

$$B_i = \frac{t_{ij} Q_i}{H_i} \tag{7.4-3}$$

The size requirements of a semicontinuous unit k for product i are characterized by *duty factors* D_{ik} whose physical meaning is similar to the size factors, and the *processing rates* R_k; the duty factor is related to the processing time for semicontinuous equipment as follows:

$$D_{ik} = \frac{\theta_{ik} R_k}{B_i} \tag{7.4-4}$$

where θ_{ik} is the processing time of a semicontinuous unit. Typical size factors and processing times for commonly used equipment are given in Table 7.4-1 (Sparrow *et al.* 1975).

7.4.1.1. Cycle times

The basic cycle of a batch equipment unit j is composed of the sum of the *operating time* (charging + chemical and/or physical processing of the batch + emptying), *changeover time* (cleaning if necessary), and *time of waiting* (*idle time*). The time to carry out the sequence of tasks in equipment unit j, excluding the waiting times, is called the *processing time* t_{ij} for product i and batch stage j. The processing time will generally be different for each equipment unit and depends on the size of equipment (Grossmann and Sargent, 1979), e.g. owing to changes in the ratio of heat-transfer area to reactor volume. This relationship may be formulated as follows:

$$t_{ij} = t_{ij}^{(0)} + \alpha_{ij} V_j^{\beta_{ij}} \tag{7.4-5}$$

where t_{ij} is the processing time for equipment unit j and product i, V_j is the size (volume or surface area) of equipment unit j, and $t_{ij}^{(0)}$, α_{ij}, and β_{ij} are coefficients which have to be determined either using data taken from an existing plant or by calculations based on thermokinetic characteristics of the system. The size-dependence of the cycle time is illustrated by *Example 7.4-1* for jacketed stirred-tank reactors. If the uncertainty in the evaluation of the

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[1] The operator $\min_j x_j$ is used to indicate that the lowest value of x from a range of values is chosen.

processing time is significant the processing time t_{ij} should be extended by a *time safety factor*, which is usually taken from industrial practice. The processing time for semicontinuous equipment θ_{ik} is inversely proportional to the processing rate R_k.

Table 7.4-1
Data for a number of equipment types

Type	Unit of size	Cost coefficients α, SFr (1975)	β	Probability of occurrence	S_{ij} range, unit of size/kg	t_{ij} range h/batch	Standard size range
Stirred tank	dm^3	400	0.6	0.55	0-10	0-10	63-40000
Filter press	m^2	2500	0.85	0.1	0-0.033	0-10	0.21-133
Filter nutch	m^2	60000	0.5	0.1	0-0.002	0-10	0.0126-8
Paddle drier	m^3	110000	0.5	0.1	0-0.001	0-10	0.0063-4
Tray drier	m^3	60000	0.5	0.1	0-0.001	0-10	0.0063-4
Centrifuge	m^3	230000	0.8	0.05	0-0.001	0-10	0.0063-4

Example 7.4-1. Cycle time versus size of stirred-tank reactor operated in batch or semicontinuous mode

Consider enamelled jacketed stirred-tank reactors of the AE series (DIN standards) for which Table 7.4-2 gives characteristics.

Table 7.4-2
Volume V_r and the ratio of heat-transfer surface area A_r to volume V_r for reactors of AE series

Reactor type	AE100	AE250	AE630	AE1600	AE4000	AE6300
V_r, m^3	0.10	0.25	0.63	1.6	4.0	6.3
A_r/V_r, m^{-1}	8.8	6.8	4.9	3.9	2.9	2.5

The recipe for a batch process includes: (1) heating of the reaction mixture from $T_0 = 20$ °C to $T_{set} = 100$ °C, (2) maintaining the mixture at this temperature for two hours whereby heat generated within this period is removed by effective cooling, and (3) cooling the mixture down to $T_f = 30$ °C. The first and the third step of a semicontinuous process are the same as those of the batch process but only 90% of the entire batch is charged into the reactor initially. In the second step of the semicontinuous process, the remaining 10% of the reactants is dosed at such a rate that the temperature of the batch is maintained at $T_{set} = 100$ °C while the exothermic reaction occurs. This step is completed by heating for 1.5 hours. The density of the reaction mixture is $\rho = 800$ kg m^{-3} and the heat capacity is $c_p = 2.5$ kJ kg^{-1} K^{-1}. The maximum temperature of the heating agent inside the jacket $T_{j,max} = 120$ °C, the minimum temperature of the coolant $T_{j,min} = 20$ °C. Assume that the time for switching from heating to cooling is negligible. The overall heat-transfer coefficient is $U = 350$ W m^{-2} and is assumed to be independent of the reactor size and the level of the reaction mixture in the reactor. The reaction is of zero order with respect to all reactants and the heat of reaction ($-\Delta H$) = 3,000 kJ m^{-3} reactant. Assume that the changes in the volume of the reaction mixture and the ratio A_r/V_r in the course of dosing are negligible. Calculate cycle times for both processes neglecting times for charging and emptying the reactors.

Heating and cooling of the reaction mixture are described by the following heat balance equation:

$$c_p \rho V_r \frac{dT}{dt} = UA_r \left(T_j - T\right) \tag{7.4-6}$$

which on integration and rearrangement yields:

$$t_{heating\ or\ cooling} = \frac{c_p \rho V_r}{UA_r} \ln\left(\frac{T_j - T_{in}}{T_j - T_{end}}\right) \tag{7.4-7}$$

where $T_j = T_{j,max}$, $T_{in} = T_0$ and $T_{end} = T_{set}$ for heating, and $T_j = T_{j,min}$, $T_{in} = T_{set}$ and $T_{end} = T_f$ for cooling of the reaction mixture. The heat balance for the period of dosing in a semicontinuous process is:

$$UA_r \left(T_{set} - T_{j,min}\right) = \frac{0.1 V_r}{t_{dosing}} \left(-\Delta H\right) \tag{7.4-8}$$

Rearranging leads to:

$$t_{dosing} = \frac{0.1\left(-\Delta H\right)}{\frac{A_r}{V_r} U \left(T_{set} - T_{j,min}\right)} \tag{7.4-9}$$

Results of calculations using expressions (7.4-7) and (7.4-9) are presented in Table 7.4-3, also including results for a laboratory glass reactor with a capacity of 1 dm^3. The overall cycle times have been regressed using Eqn. (7.4-5).

Table 7.4-3
Processing times for the batch and semicontinuous processes

Time, h		Lab	AE 100	AE 250	AE 630	AE 1600	AE 4000	AE 6300
	$t_{heating}$	0.10	0.29	0.38	0.52	0.66	0.88	1.02
	$t_{cooling}$	0.13	0.38	0.49	0.68	0.85	1.15	1.33
Batch	$t_{reaction}$	2	2	2	2	2	2	2
	$t_{processing}$	2.23	2.67	2.87	3.20	3.51	4.03	4.35
Semicontinuous	t_{dosing}	0.12	0.31	0.44	0.61	0.77	1.03	1.20
	$t_{completion}$	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	$t_{processing}$	1.85	2.48	2.81	3.31	3.78	4.53	5.05

Results of regression are given in Table 7.4-4. The cycle time is size-dependent whereby this dependency is stronger for the semicontinuous process at these particular process conditions. The exponent β is almost the same for both processes and is approximately 1/3. Clearly, the physical properties of the reaction mixture and thermokinetic data are needed to evaluate processing times and cycle times at a large scale.

Table 7.4-4
Regression results

	$t^{(0)}$, h	α, h	β, dimensionless
Batch	2.1	1.23	0.326
Semicontinuous	1.65	1.85	0.328

The time required for a batch of material to pass through the entire process is called the *residence time* or *flow time* t_{Ri} for product i. The residence time is defined by:

$$t_{Ri} = \sum_{j=1}^{MB} t_{ij} + \sum_{k=1}^{MS} \theta_{ik} \qquad \textbf{(7.4-10)}$$

where t_{ij} and θ_{ik} are processing times of a batch and semicontinuous unit j and k, respectively, in a process for product i, and MB and MS are numbers of batch and semicontinuous units. For non-overlapping operation (see Fig. 7.4-1a), the residence time is the same as the *cycle time* (the time interval between the start of two successive batches) $t_{c,i}$ for the product i.

The concepts of cycle time and residence time are illustrated by *Gantt charts* or *bar charts* (see Fig. 7.4-1). The length of rectangles (or bars) on Gantt charts is directly proportional to the processing time. The transfer of a task output to the next task is denoted by an arrow. Times for transfer of the material between two linked units are usually included in processing times to avoid a too complex graphical presentation of the process. Fig. 7.4.1 shows exemplary Gantt charts of a process for the manufacture of a product A consisting of three stages: 1 - reaction, 2 - separation of the product from the reaction mixture, and 3 - drying. The processing times for the stages are 2.5, 8.5, and 3.5 *time units* (t.u., e.g. hours). A batch process may be operated in *non-overlapping* mode (Fig. 7.4-1a) or in *overlapping* mode (Fig. 7.4-1b). In the former case, the whole product cycle must be completed at the third stage before a new batch is started at the first stage. No two batches are processed at the same time. The *cycle time* for non-overlapping operation is given by Eqn. (7.4-10), in this case $t_c = 2.5 + 8.5 + 3.5 = 13.5$ t.u. The total time t_P required for the production of all of the product (the so-called *makespan*) is then given by:

$$t_P = NB\, t_c \qquad \textbf{(7.4-11)}$$

where NB is the number of batches. The makespan for two batches in this case is $t_P = 2 \cdot 13.5$ t.u. = 27 t.u.

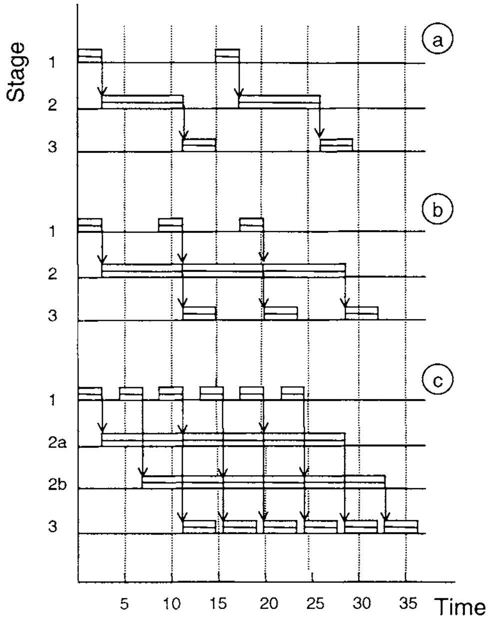

Figure 7.4-1. Gantt charts; (a) non-overlapping mode, (b) overlapping mode, (c) overlapping, parallel units out-of-phase.

With overlapping operation (Fig. 7.4-1b), a new batch starts with stage 1 before stage 2 of the preceding batch has been completed so that both stages 1 and 2 finish at the same instant. In the case considered, stage 1 is started when stage 2 has advanced over 70% [(8.5 t.u. - 2.5 t.u.)/8.5 t.u.·100%]. In this way idle times (slacks between rectangles in the figure) are greatly reduced. For stage 2 the idle time is zero and the stage is operated without interruption. This stage represents the *bottleneck* for the manufacture of the product. Idle times for all stages should be reduced as much as possible. This can be done by debottlenecking the stage with zero idle times. The cycle time for overlapping operation is given by the longest processing time of all stages and is called the *limiting cycle time* t_L.:

$$t_L = \max_{j=1...NS} t_j \tag{7.4-12}$$

For the case considered, $t_L = 8.5$ t.u. The makespan for overlapping operation is given by:

$$t_P = NB\, t_L + head_{first\ batch} + tail_{last\ batch} \tag{7.4-13}$$

where *head* is the interval between the start of manufacture and the instant when repetitive operation is reached and *tail* is the interval between the end of the repetitive operation and the end of product manufacture. For the case considered ($NB = 2$) the makespan is $t_P = 2.5 + 2 \cdot 8.5$

+ 3.5 t.u. = 23 t.u. Thus, overlapping operation is much more efficient than non-overlapping operation. If *NB* is sufficiently large, the makespan for overlapping operation may be well expressed by:

$$t_P = NB\, t_L \tag{7.4-13a}$$

The idle times for stages 1 and 3 in Fig. 7.4-1b remain large even for the overlapping operation and the utilization of the equipment in these stages is low. Adding a parallel unit in stage 2 with simultaneous size reduction of all equipment units by a factor of two can increase the equipment utilization. The Gantt chart for such a system is presented in Fig. 7.4-1c. The degree of equipment utilization is significantly increased: Idle times are much smaller than those in Fig. 7.4-1b. The limiting cycle time for overlapping operation with parallel units is defined by:

$$t_L = \max_{j=1\ldots NS}\left(\frac{t_j}{m_j}\right) \tag{7.4-14}$$

where m_j is the number of units j of the same size. For the case considered with two parallel units in stage 2, $t_L = 8.5/2 = 4.25$ t.u. If three parallel separators were used, co-operating with one reactor and one drier, then the cycle time would be limited by the processing time in the drier (stage 3):

$$t_L = \max\left(\begin{matrix} 2.5\,t.u \\ 8.5/3\,t.u. = 2.63\,t.u. \\ 3.5\,t.u. \end{matrix}\right) = 3.5\,t.u. \tag{7.4-15}$$

Note that times of transferring materials from one stage to another have been incorporated into the processing time, no cleaning times were taken into account, and no intermediate storage (tanks) was used in the case considered. Cleaning is often not needed if only one product is being manufactured. The cleaning time must be added to the processing time and as such extends the production time proportionally. Intermediate storage tanks are used in single-product plants only if the production can be divided into several campaigns in which successive sufficiently stable intermediates are produced with the last campaign dedicated to the final product. As a rule, storage of intermediates must be used if more than one product is manufactured simultaneously.

7.4.1.2. Production campaigns

If many products are manufactured in a plant, the same equipment units can be used for different stages of various processes. As mentioned in section 7.1, two types of plants producing more than one chemical can be distinguished: multiproduct plants and multipurpose plants. A multiproduct plant is characterized by the fact that all products A_i (see Fig. 7.4-2, weeks 1,...,i) are manufactured following essentially the same paths through the process and use essentially the same equipment. For some products certain stages can be omitted and then equipment units for these stages will remain unused. The whole range of products is covered by carrying out *production campaigns* for each product. The campaigns can be performed sequentially, one after another, or a number campaigns can be mixed. Fig. 7.4-2 (weeks 1,..., *i*) illustrates the operation of a multiproduct plant with all products following the same path. In week 1 product A_1 is manufactured in a given sequence of equipment units. After the equipment has been cleaned, the manufacture of product A_2 starts and is continued during week 2, etc.

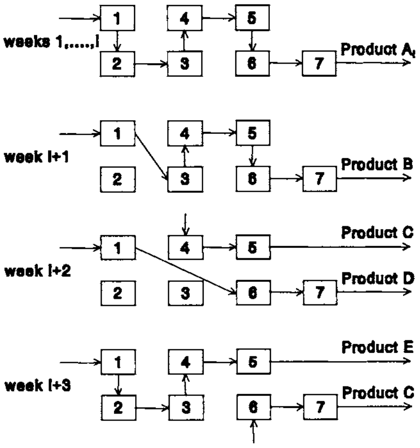

Figure 7.4-2. Multiproduct and multipurpose plants.

The characteristic of a multipurpose plant is that more than one product can be manufactured at one time using a set of equipment units in different arrangements. Jobs can start in equipment units as they become available on completion of earlier jobs. Successive batches of the same product may follow different routes through the process. This mode of operation is illustrated in Fig. 7.4-2 (weeks *i* to *i*+3) for the same arrangement of equipment units as in the multiproduct plant for the manufacture of the products A_i. In week *i* product A_i is manufactured. In week *i*+1 product *B* is manufactured using only six of the seven existing equipment units (unit 2 remains unused). After production of *B* has been completed in week *i*+1, another arrangement is made. In week *i*+2 products *C* and *D* are manufactured whereby two equipment units, 2 and 3, remain on stand-by. Product *C* is also manufactured in week *i*+3 together with product *E*. Thus, different routes (different equipment units) are used to produce product *C* in weeks *i*+2 and *i*+3. The sequence of chemical processes and physical operations for the manufacture of product *C* must remain unchanged (i.e. units 4 and 6 and units 5 and 7 represent the same type of operation). Production routes for *A*, *B*, *C*, *D*, and *E* differ from each other. The product palette of a batch plant may be subject to changes according to market demands, new products may be added, and old products may be withdrawn due to stopping the product or passing it to a new plant.

The makespan for multiproduct plants depends on the campaign arrangement. If the campaigns are carried out in series (product *A*,*A*,*A* ... product *B*,*B*,*B*), the makespan is the sum of times required for all campaigns if time for cleaning between campaigns is negligible.

When campaigns for products *A* and *B* are mixed, e.g. *A,B,A,B,A,B*, the makespan can be reduced compared to the sequential arrangement of campaigns. This is illustrated in Fig. 7.4-3 for two two-stage processes characterized in Table 7.4-5. The makespan for the successive campaign arrangement is 27 t.u. (Fig. 7.4-3a) while that for the mixed arrangement is only 25 t.u. (Fig. 7.4-3b). Accordingly, both the production time and the equipment utilization is superior for the latter arrangement. This might not necessarily be true if the cleaning times or changeovers are significant when switching from one product to another. Suppose that cleaning is necessary when a switch between products is made, and the time for cleaning is 1 t.u.. For the successive arrangement, the makespan increases by one hour only, i.e. to 28 t.u. For the mixed arrangement, the makespan becomes 30 t.u. since the equipment must be cleaned five times between batches of the products *A* and *B* (see Fig. 7.4-3c where hatched areas represent cleaning). Thus, the mixed arrangement is worse than the successive one when cleaning is taken into account. This is often the case, especially if thorough (and, consequently, solvent- and time-consuming) cleaning is necessary. For pharmaceutical products, cleaning down to *ppb* level is sometimes needed.

Table 7.4-5
Processing times for products *A* and *B* (t.u.)

Stage	Product *A*	Product *B*
1	4	2
2	3	4

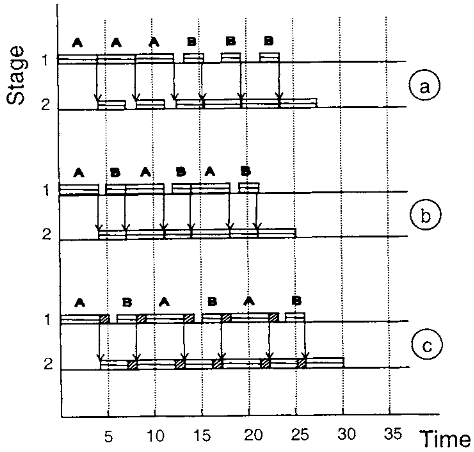

Figure 7.4-3. Single- and mixed-product campaigns.

For multipurpose plants, the variety of arrangements becomes even greater. Therefore, there is no simple way to determine the makespan. It is usually determined by an optimization procedure that takes into account processing sequences for different products and the possibility of splitting the production route into smaller steps. The number of processing sequences is generally very large. Time and costs of changeover are often significant when considering processing sequences. Note that the time of cleaning between A and B batches is not necessarily the same as the time of cleaning between B and A batches. For instance, cleaning of equipment for a switch from the production of black paint to the production of white paint will take longer than for the reverse sequence. In practice, many technological constraints are imposed on the production routes and this makes the number of options for the arrangements of stages limited. Generally, if cleaning, transfer, and/or changeover times are large compared to processing or campaign times single-product campaigns are favoured, especially for productions that must meet GMP requirements.

When demand rates differ from production rates an inventory problem arises. Products manufactured and not sold yet must be stored. The annual inventory cost is calculated by determining the average inventory and knowing the unit cost of storing the material. The average inventory of a product is evaluated as the difference between the production rate and the demand rate multiplied by the length of the manufacturing period and divided by the length of the production cycle for all products.

7.4.1.3. Policies for intermediate storage

Operation and scheduling of a batch plant can be affected significantly by *intermediate storage*, which is used between subsequent stages in a process to held an intermediate product until a unit becomes available to process it. It is practical to use a storage tank to link only one pair of subsequent equipment units when manufacturing a given product or intermediate. However, if the tank has been emptied and is waiting for the next batch of product i, in a multipurpose plant it can be used for simultaneous manufacture of another product $i+1$. The tank must then be cleaned before every changeover. The decision on storage of intermediates is usually dictated by the feasibility of keeping intermediate materials in storage. Unstable materials must be processed without any delay and cannot be stored. There are four different schemes for storage operations:

- unlimited intermediate storage (*UIS*),
- no intermediate storage (*NIS*),
- finite intermediate storage (*FIS*), and
- zero-wait or no-wait policy (*ZW* or *NW*).

Unlimited intermediate storage (UIS) means that any intermediate product i of a process can be transferred to storage immediately after processing in a certain equipment unit j has been completed. The unit then becomes available to perform another processing stage for any process. This is equivalent to no storage capacity limit both in number and volume of storage units. In contrast, in the case of *no intermediate storage (NIS)*, on completion of processing in unit j the intermediate material must be held in this unit until a unit for subsequent processing is ready to receive it. In practice, an intermediate situation occurs, *i.e. finite intermediate storage (FIS)*, in which the capacity and number of storage tanks is limited.

No matter whether intermediate storage is available or not, some intermediates must be processed immediately because otherwise the batch will be off-grade. For instance, if the reaction shown in Fig. 7.1-2 was not quenched chemically (a quench is considered to be the next stage), the desired product would be oxidized to a high extent. Consequently, the batch would be practically lost. The *zero-wait (ZW)* policy must then be adopted. This policy is the most restrictive. Despite their apparent similarity, *NIS* and *ZW* policies may have different scheduling consequences (see Fig. 7.4-4). Sometimes different intermediate storage policies can be used in different stages and/or processes. This is the so-called ***mixed intermediate storage*** policy.

Fig. 7.4-4 shows Gantt charts for a four-product, three-stage plant for which processing times are given in Table 7.4-6. At each stage (unit) the processes are arranged in the following order: *P1-P2-P3-P4*.

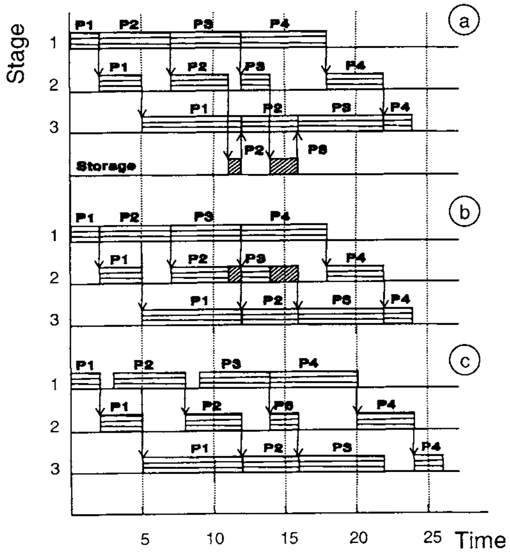

Figure 7.4-4. Various intermediate storage policies (a - *UIS*, b - *NIS*, c - *ZW*).

Table 7.4-6
Processing times for a four-product and three-stage plant (t.u.)

Stage	Product *P1*	Product *P2*	Product *P3*	Product *P4*
1	2	5	5	6
2	3	4	3	4
3	7	4	6	2

The *UIS* policy is illustrated in Fig. 7.4-4a. The blank slacks represent the idle times. Between stage 2 and stage 3 product 2 is stored for 1 t.u. and product 3 for 2 t.u. In the second schedule (Fig. 7.4-4b) a *NIS* policy is assumed. The hatched segments in stage 2 represent the time periods during which the equipment units are unproductively occupied, *i.e.* used for storing material but not for processing it was designed for. Finally, a *ZW* policy is shown in the last schedule (Fig. 7.4-4c). In this mode of operation the start time of each product is delayed until uninterrupted processing is assured. For each product the completion time of one stage is the same as the start time for the next stage. Note that for the same product sequence *P1-P2-P3-P4* the makespans are 24, 24, and 26 t.u., respectively. Here, the makespan is not reduced when replacing *NIS* with *UIS* policy. This is a rare case. The *ZW* policy results in an increase of the makespan.

The insertion of an intermediate storage tank at a point in a process de-couples the process into two subprocesses and decomposes the operations of the subprocesses upstream and downstream the tank. This in turn allows the cycle times t_{Li} for product i and batch sizes B_i on either side of the tank to be chosen independently provided that storage capacity is sufficiently large. The t_{Li} of a subprocess represents the time interval between successive emergence of product batches from the subprocesses. The installation of a tank increases the investment cost of the plant, but due to de-coupling of the process, subprocesses with smaller t_{Li}'s can have smaller equipment sizes. Simple storage tanks are much less expensive than other process equipment. Thus, installation of storage tanks at appropriate locations may result in a net reduction of the overall plant cost. Apart from this financial advantage, the insertion of storage tanks at suitable positions has a number of other positive effects. These include an increase in plant availability, dampening of the effects of process fluctuations, and flexibility in sequencing and scheduling. These benefits, however, do not come without a price. Apart from the cost of the tanks themselves, there is a number of difficult to identify additional costs. These include the inventory costs of the material held, maintenance and clean-out costs, plant space costs, and labour and supervision costs associated with transporting material, controlling tank contents, and monitoring and maintaining the pipe and valve networks in tank areas. Moreover, the use of intermediate storage could introduce possibilities for material contamination, safety hazards, operator errors, processing delays, loss of batch integrity, which is usually against GMP with respect to pharmaceuticals, or the requirement of expensive holding operations such as refrigeration or agitation. Clearly, not all of these factors can be quantified adequately.

7.4.1.4. Criteria and constraints in production planning, scheduling, and design of batch plants

Production planning deals with the allocation of production capacity and time, inventories of raw materials, intermediates, and final products, as well as labour and energy resources to meet the market demands over an extended period of time. This is a long-term strategy for selection of goals to achieve on a long time horizon. In production planning the following questions must be answered:

- What products will be manufactured?
- What quantities of products will be produced?
- How will the products be produced?
- What equipment is to be used for manufacturing?

A palette of products that are to be manufactured within the horizon and with the required time sequence is chosen at this stage. The palette depends on orders received, which determine the required quantities and the due dates for all products manufactured in the plant. However, to avoid frequent changeovers in the plant, smoothing-out the changing demand is one of the goals of production planning. Anticipation of bottlenecks is related to the above activities. Generally, production planning defines a target function to be reached and provides a number of constraints for scheduling in shorter periods.

Scheduling involves the best choice of time sequences of campaigns and stages to manufacture all products before the due dates defined in the planning stage. At this stage, it is decided in which equipment items the individual tasks of the production process should be carried out (task-to-unit allocation), in what amount (batch size) the product should be manufactured, and when tasks should be started and completed. A performance criterion for the optimization of scheduling must be defined. The recipes for all products, a matrix of processing and cleaning times, and rules covering de-coupling of processes and storage between stages and campaigns must be provided. The five most commonly used performance criteria in optimization are:

- minimization of the total time required to produce all products, *i.e.* the makespan (Kuriyan and Reklaitis, 1989),
- minimization of the average residence time of all products in the system (Reklaitis, 1982),
- minimization of the maximum or average *tardiness* of the schedule, tardiness being the absolute value of the difference between the completion time of a product and its due date (Ku and Karimi, 1988),
- minimization of the changeover costs, and
- maximization of equipment utilization (Jänicke, 1989).

For most applications the makespan criterion is applied. For a very heavy load of the plant, the tardiness might be the most appropriate criterion that will enable to keep delivery dates undue. No matter which criterion is used, scheduling is always a problem of combinatorial character: a large number of sequences must be simulated and the best combination chosen. Contrary to production planning, the problem of optimal scheduling is considered to be deterministic and static. This means that all problem parameters are known in advance and remain unchanged during the realization of the schedule.

In fact, no model can represent every aspect of an actual production process. Accordingly, the scheduler must have some flexibility to modify the schedule proposed by the optimization algorithm, based on experience that is gained also at the realization of the 'optimal' schedule. This leads to evolutionary improvement strategies starting from approximate optimization techniques. An interactive graphical presentation of the plant should enable quick intervention.

There are several constraints in scheduling. Applequist *et al.* (1997) categorized these constraints into five groups:

- *Organisational* constraints: goals based on information most frequently used by management. These include meeting due dates, minimizing costs, and meeting overall production targets.
- *Physical* constraints: the processing times and the compatibility of tasks with different types of equipment. Colour, viscosity, grade, or aroma can be important factors that can affect the sequence of operations or campaigns and often are not taken into account in

computer scheduling. There might also be energy constraints that must be taken into account in scheduling. Simultaneous operation of stages that consume much electrical energy may lead to line overloading and breaking the operation. If too much thermal energy is required as a result of simultaneous operation, processing times may increase due to longer heating times.

- *Casual* constraints: the precedence or required sequence of tasks and resource requirements. There are unexpected events, failures, and/or events that have not been included in the scheduling program. Off-specification batches occasionally disturb the schedule.
- *Availability* constraints: the macroscopic limits on material resources and the availability or up-time of equipment. Availability of raw materials is an obvious constraint at scheduling. Obviously, no catalytic hydrogenation can be done if the catalyst is unavailable. Simultaneous operation of certain tasks is restricted by the limited availability of common utilities such as steam, electricity, or labour. The priority sequence in a product chain needs to be respected by ensuring that intermediate products are manufactured in time to be available when required by a batch of the consecutive product.
- *Preference* constraints: preferred alternatives for equipment to use for certain tasks and for a processing sequence. Experienced operators may prefer some equipment or sequence of operations for reasons that are difficult to specify in a computer program.

Design has been treated most extensively in the literature. A formulation of the deterministic problem for optimal design is presumably the best defined and the solution of the problem is presumably the easiest, although not easy, especially for multipurpose plants. Generally, the criterion used for evaluation of a plant design is composed of a weighed sum of annualized capital costs of the plant, depreciation, production costs, and associated penalty costs. The most commonly used criteria are those discussed in section 5.2, e.g. rate of discounted cash flow return and internal rate of return. In the fine chemicals sector, operating conditions or specified conversions are usually fixed by recipe and will not change in an optimization procedure. Therefore, the major design variable is the capital cost of the plant. Purchased equipment costs constitute a fixed fraction of the capital investment costs. The cost of units for semibatch processing is approximately 20% of the total equipment for batch plants. Therefore, the sum of purchased costs of batch units is usually considered to be a sufficient criterion for the optimal design.

There are numerous constraints and factors that affect procedures for design of multiproduct and multipurpose plants:

- There are various uncertainties in all the data influencing the selection of a set of equipment: uncertainties in recipe parameters, product specifications, processing times and size factors, equipment availability, product requirements, and resource availability. Data needed for the evaluation of processing times and equipment sizes are never 100% reliable. The market situation when the plant is started up will certainly be different from the situation at the time of the definition of a production program for the plant. Unpredictable process disturbances may also occur.
- There is no continuity in sizing of chemical equipment. There are discrete changes in capacities of chemical equipment of all kinds, either due to state and international standards or due to internal standards of individual manufacturers of chemical equipment. For instance, according to DIN standards, the volumes of glass-lined reactors increase in

the ratio 1.6:1. Results of the optimization with real data may fall between the standard sizes. Rounding of these results may lead to a non-optimal solution. The proper solution can only be reached if a search for the optimum is performed on integers, *i.e.* over the available discrete sizes, e.g. in the vicinity of the continuous solution. Mixed integer nonlinear programming techniques enable the solution of this problem. In practice, however, the continuous solutions are first rounded up to the next larger standard sizes, and then for each equipment unit in decreasing order of equipment cost the next size down is tried; if product demands are still fulfilled, the size is fixed at the next smaller size and the next processing step is considered.

- Technology and equipment are continually changing. The recipes are permanently being improved. New or improved equipment is offered.
- There are specific GMP requirements, particularly for medicinal products and food additives. Both the European institutions and the *FDA* impose constraints and require the approval of any modification in manufacturing of the products concerned.

7.4.2. Design of batch plants

Several subproblems of design, production planning, and scheduling of batch plants have been treated in recent years. The development stage of these subproblems differs greatly. These differences were illustrated by assigning the following research trends to subproblems (Rippin, 1993):

multiproduct plant design:	"filling the holes"
production planning:	"still in search of a solution"
short-term scheduling:	"comparison of exact algorithms heuristics"
flexibility and uncertainty:	"understanding the problem"

Below, all subproblems will be dealt with in selected examples that we consider to be most illustrative; more advanced and more extended formulations have already been presented in literature.

7.4.2.1. Single-product batch plants

Optimal for single-batch operation. For the sake of simplicity suppose that: (1) the performance of an equipment unit is the fraction of the feed material converted to the material that is suitable for the next stage (e.g. the yield of the desired intermediate or final product), and (2) that the objective function is the amount of suitable material produced per unit time. Let us consider the situation shown in Fig. 7.4-5. On completion of cleaning at time t_{cl} processing of a batch begins. This processing is characterized by the performance curve $f(t)$, e.g. the yield or conversion versus time relationship. The objective function F is defined as:

$$F = \frac{f(t)}{t} \qquad \textbf{(7.4-16)}$$

The maximum of the criterion F is found by:

$$\frac{dF}{dt} = \frac{t\, f'(t) - f(t)}{t^2}\bigg|_{opt} = 0 \qquad \textbf{(7.4-17)}$$

which gives:

$$f'(t_{opt}) = \frac{f(t_{opt})}{t_{opt}} \qquad \textbf{(7.4-18)}$$

This corresponds to the tangency condition shown in Fig. 7.4-5. Note that both cleaning and processing times can be dependent on equipment size.

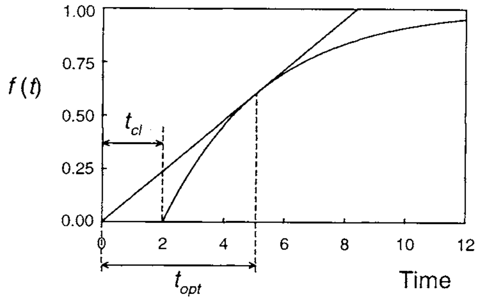

Figure 7.4-5. Optimal of the performance of an individual equipment unit.

The time of cleaning/changeover is usually evaluated based on industrial practice. It is assumed that the performance for any process conditions (temperature, pressure, amount and composition of the feed) is available as a function of time. The performance curve is usually monotonic and non-decreasing. If this curve was to decrease with a further extension of the time the process should be stopped at that point at the latest. An example of a curve with a maximum in time can be a sequence of consecutive reactions with the intermediate product being the desired one. Any further processing after the time corresponding to the maximum yield of the desired product will result in decreasing this yield. Another example is the critical point after which a temperature runaway and, possibly, an explosion could develop. In both cases, the time at which stopping action must be undertaken may vary with the size of equipment. For any particular piece of equipment, this time can be appropriately assessed if rates of chemical reaction, and mass and heat transfer are known as a function of the physical properties of all mixtures and the geometric characteristics of the equipment. In conclusion, in order to optimize the operation performance, curves $f(t)$ must be determined for various process conditions during laboratory studies and/or pilot plant experiments. Unfortunately, a typical laboratory recipe for organic processes usually does not provide sufficient data for evaluation of the optimal cycle time of the individual equipment unit.

The optimal cycle time t_{opt} evaluated as described above is not necessarily the best if more than one unit is considered. For instance, separation of a reaction mixture of relatively low conversion can be troublesome and expensive. Therefore, the usefulness of the above procedure must be critically assessed before it is applied. If equipment units are operated in a sequence according to a *NIS* policy, a common cycle time which accounts for the performance curves of the different units can be selected. Assume that the overall yield is the product of the yields of individual units. In this case the objective function is:

$$F = \frac{\prod_j f_j(t)}{t} \qquad \textbf{(7.4-19)}$$

where $f_j(t)$ is the performance of unit j. The condition for the maximum is:

$$\frac{dF}{dt} = \left\{ \frac{t \sum_j \left(f_j'(t) \prod_{k \neq j} f_k(t) \right) - \prod_j f_j(t)}{t^2} \right\}_{opt} = 0 \qquad \textbf{(7.4-20)}$$

which gives:

$$\sum_j \frac{f_j'(t_{opt})}{f_j(t_{opt})} = \frac{1}{t_{opt}} \qquad \textbf{(7.4-21)}$$

The solution can be found by constructing the tangent to the overall yield curve that begins at a distance of t_d from the origin, or by solving Eqn. (7.4-21). The best common time for a sequence of units will always be longer than the longest of the best individual cycle times with respect to individual performance curves. Hence, cycle times for individual units should not be optimized without considering the potential effects on the performance of other units that will operate in sequence.

Sizing of batch equipment for a single-product plant. The simplest arrangement in a batch plant is to compose a one-to-one assignment of each processing stage to a suitable equipment unit or several units in parallel. This is usually a satisfactory and justified policy if the required operation time in the selected equipment is roughly the same for all stages. The one-to-one assignment also applies if the equipment for various stages differs significantly with respect to design and mode of operation (e.g. an autoclave for high pressure hydrogenations in one stage, a glass-lined reactor for Friedel-Crafts alkylations in another stage, and a continuous, tubular reactor for fast oxidations in the last stage).

For a single-product plant the calculation of equipment sizes is straightforward. First the limiting cycle time t_L is determined using Eqn. (7.4-14) or Gantt charts. The batch size is then evaluated for an assumed production capacity Q and available production time H:

$$B = \frac{t_L Q}{H} \qquad \textbf{(7.4-22)}$$

Each equipment unit is chosen so that this batch size can be accommodated. Size factors are calculated based on the recipe. The following expression is used for sizing without minimization of the total equipment costs:

$$V_j = S_j B \tag{7.4-23}$$

Note that equipment is supplied in standard sizes that change discretely. Accordingly, the closest standard size larger than that calculated from Eqn. (7.4-23) must be selected. The procedure is illustrated by *Example 7.4-2*.

Example 7.4-2. Sizing of equipment units for a single-product plant

Consider a three-stage plant that is to produce 500,000 kg/y of product *C*. The on-stream time of the plant is 6000 h/y. The recipe for the manufacture of product *C* is as follows:

1. Mix 1 kg *A* and 1 kg *B*, and react for 5 hours to form *C*. The yield is 50% by weight and the density of the mixture ρ_m is 800 kg/m^3. The reaction vessel can be filled to 70% of the total volume.
2. Add 1 kg solvent and separate during 2 hours to recover 95% of product *C*. The density of the mixture ρ_m is 850 kg/m^3. The separation vessel can be filled to 70% of the total volume.
3. Dry the wet product *C* (75% dry mass, total weight 1.27 kg) for 3 hours. No material loss is assumed. The density of the wet material ρ_m is 1250 kg/m^3. The material occupies 20% by volume of the drier.

The amount of product *C* produced in the batch is 0.95 kg. Size factors for all equipment units are calculated using Eqn. (7.4-1). For this example the specific volume ($\nu = 1/\rho_m$) for stage 1 is $\nu_1 = 1/800$ $\mathrm{kg_{mix}\ m^{-3}} = 0.00125\ \mathrm{m^3/kg_{mix}}$. Hence:

$$S_1 = 0.00125\ (\mathrm{m^3/kg_{mix}}) \cdot 2\ \mathrm{kg_{mix}}/0.95\ \mathrm{kg_{prod}} \cdot (1/0.7) = 0.00376\ \mathrm{m^3/kg_{prod}}$$

Size factors for stages 2 and 3 are calculated similarly:

$$S_2 = 1/850\ (\mathrm{m^3/kg_{mix}}) \cdot 3\ \mathrm{kg_{mix}}/0.95\ \mathrm{kg_{prod}} \cdot (1/0.8) = 0.00531\ \mathrm{m^3/kg_{prod}}$$
$$S_3 = 1/1250\ (\mathrm{m^3/kg_{mix}}) \cdot 1.27\ \mathrm{kg_{mix}}/0.95\ \mathrm{kg_{prod}} \cdot (1/0.2) = 0.00114\ \mathrm{m^3/kg_{prod}}$$

If one unit is used per stage and the plant is operated with zero-wait transfer, the cycle time is:

$$t_L = \max\{5,1;\ 2,2;\ 3,3\} = 5\ \mathrm{h}$$

The number of batches to be processed in 6000 hours is:

$$N_B = 6000\ \mathrm{h} / 5\ (\mathrm{h/batch}) = 1200\ \mathrm{batches}$$

Since the production is 500,000 kg, the batch size of the final product *C* is:

$$B = 500{,}000\ \mathrm{kg}/1200 = 417\ \mathrm{kg}$$

The volumes of the equipment can be easily calculated:

$$V_1 = 0.00376\ \mathrm{m^3/kg_{prod}} \cdot 417\ \mathrm{kg_{prod}} = 1.57\ \mathrm{m^3}$$
$$V_2 = 0.00531\ \mathrm{m^3/kg_{prod}} \cdot 417\ \mathrm{kg_{prod}} = 2.21\ \mathrm{m^3}$$
$$V_3 = 0.00114\ \mathrm{m^3/kg_{prod}} \cdot 417\ \mathrm{kg_{prod}} = 0.48\ \mathrm{m^3}$$

The volume of the closest standard stirred tanks are 1.6 and 2.5 m^3 while a tray drier of 0.5 m^3 can be assumed standard. The total volume of the equipment is 4.6 m^3. Since the bottleneck is in stage 1 two units in parallel out-of-phase operation may be considered. The cycle time then becomes:

$$t_L = \max\{5/2,1;\ 2,2;\ 3,3\} = 3 \text{ h}$$

and the bottleneck is shifted to stage 3. The number of batches for the new configuration is 2000 per year with a batch size of 250 kg. The new volumes of the equipment units are:

two vessels V_1, each of 0.94 m^3
V_2 = 1.33 m^3
V_3 = 0.29 m^3

The volume of the closest standard stirred tanks are 1.0 and 1.6 m^3 while a tray drier of 0.3 m^3 can be assumed standard. The total volume of the equipment is now 3.9 m^3. Thus, adding one reactor for stage 1 the total volume decreases from 4.6 m^3 to 3.90 m^3. Depending on cost correlations for all units the economics of both arrangements can be assessed.

Loonkar and Robinson (1972) extended the design problem to the optimal selection of semi-continuous equipment for pre-selected batch equipment that was fixed by the recipe.

Example 7.4-3. Minimization of equipment costs for a single-product plant (after Loonkar and Robinson, 1970)

The batch plant shown in Fig. 7.4-6 is to be optimized. The required production capacity is 11070 m^3 per year. The cost coefficients (see Eqn. 7.3-4) are given in Table 7.4-7. The fixed processing times in the batch units, $t_{1\text{-}3}$, are given in Table 7.4-8 together with initial values of processing times in the semi-continuous units, $\theta_{4\text{-}6}$, and those found by optimization. The total batch times, volumes, and costs are also given in this table.

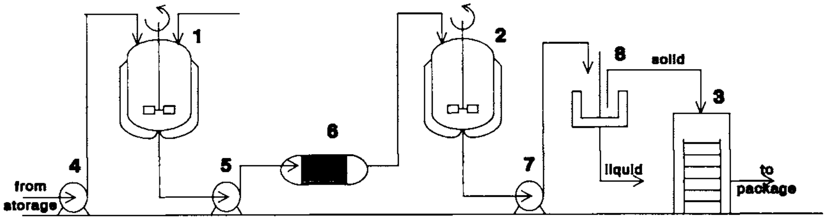

Figure 7.4-6. Batch plant to be optimized.

The minimal cost of equipment was used as the criterion in the design of the plant, which was to be operated in a non-overlapping mode. For a plant consisting of *MB* true batch units (*MB* = 3) and *MS* semi-continuous units (*MS* = 5) which are grouped in *MST* semi-continuous trains (*MST* = 3), the cycle time is given by Eqn. (7.4-10). Combining this expression with Eqn. (7.4-22) and rearranging yields:

$$B=\frac{Q}{H}\left(\sum_{j=1}^{MB} t_j+\sum_{k=1}^{MS} \theta_k+t_{cl}\right) \quad \textbf{(7.4-24)}$$

where H is the yearly operating time (or time horizon).

Table 7.4-7
Cost coefficients in Eqn. 7.3-4 ($C_p = \alpha V^{\beta}$)

Unit No. j	Equipment	α_j, USD	β_j	α_k, USD	β_k
1	Reactor A	592	0.65	-	-
2	Reactor B	582	0.39	-	-
3	Tray drier	1200	0.52	-	-
4	Pump 1	-	-	370	0.22
5	Pump 2	-	-	250	0.40
6	Heat exchanger	-	-	210	0.62
7	Pump 3	-	-	250	0.40
8	Centrifuge	-	-	200	0.85

Using Eqn. (7.3-4) to calculate the purchased cost of equipment, the following expression is obtained for the total equipment costs:

$$C_p=\sum_{j=1}^{MB}\alpha_j V_j^{\beta_j}+\sum_{k=1}^{MS}\alpha_k R_k^{\beta_k} \quad \textbf{(7.4-25)}$$

whereby relationships between capacities of equipment units V_j, processing rates R_k, and batch size B are given by Eqns. (7.4-4), (7.4-22), and (7.4-23). The processing times θ_j in the semi-continuous units are not all independent, because there are only three semi-continuous trains with five units: Processing times of pump <u>5</u> and heat exchanger <u>6</u> must be equal to each other ($\theta_5 = \theta_6$). The same applies, approximately, to pump <u>7</u> and centrifuge <u>8</u> ($\theta_7 = \theta_8$). Since t_i's are fixed by the recipe they cannot be adjusted in the design. The problem is then to minimize C_p by the choice of MS processing times θ_k with Eqn. (7.4-24) satisfied. The necessary conditions for a minimum in C_p are:

$$\frac{\partial C_p}{\partial \theta_k}=0, \qquad k=1,2,\ldots,MS \quad \textbf{(7.4-26)}$$

Combining equations (7.4-24)-(7.4-26) gives a system of non-linear equations that can be solved using iterative techniques. Savings in equipment costs as compared to initial guesses are approximately 30 %. The real savings will be lower because the 'optimal' choices for equipment units are usually not available on the chemical equipment market. The standard sizes greater but nearest to the optimal sizes will be selected. The total cost for the standard equipment is very close to the minimum found. Robinson and Loonkar (1972) extended their procedure for multiproduct batch plants.

Table 7.4-8
Results of minimization

	Initial guesses	Optimal values
t_1, h	3	3
t_2, h	3	3
t_3, h	3	3
θ_4, h	0.25	0.106
θ_5, h	0.50	1.40
θ_7, h	0.50	3.29
Total batch time, h	11.25	14.80
Volume of batch (B), m^3	15.4	20.2
Total equipment cost (C_p), USD	162,000	116,000

The essential problem in the design of a single-product plant is to determine the best cycle time. The one-to-one assignment results in the worst cycle time and is usually the most costly solution for multistage, single-product plants. Simultaneous running of a number of equipment units requires much labour, even if the plant is highly automated and computerized, while the capital costs for the many relatively small units are high. The size and/or number of equipment units can be reduced in one of the following ways:

- merging stages,
- adding parallel equipment units,
- interrupting the process, and
- breaking the process.

Merging of stages that are performed in similar (sets of) equipment units is useful when these stages are much shorter than the others. It consists in that the faster stages are performed in the same equipment unit or a set of units, thereby allowing for the reduction of the number of units. Carrying out preheating, reaction, cooling, and possibly extraction in the same vessel is an example of merging of stages. The rest of the stages are run in the other equipment units. Merging of stages makes processing times of individual and composite stages commensurate and this always improves equipment utilization. Merging is facilitated by recent achievements in the manufacture of chemical equipment. New multifunctional apparatuses, e.g. reactor-crystallizer-filter-driers (see Section 7.2), enable merging of many stages. These are, however, still expensive units and are mostly used when harmful or expensive materials must be confined to avoid release to the surroundings.

Addition of parallel equipment units reduces the size of equipment for faster stages (see section 7.4.1.1). This is done at the cost of a greater number of units for processing slower stages whereby the total volume of these units remains constant. An economic trade-off between the larger number of equipment items and their smaller size will decide whether installing parallel units will improve the process.

For both merging and installation of parallel equipment units the one-to-one (task-to-equipment unit) allocation remains unchanged. A process can also be improved by carrying it out to a certain stage using the whole equipment line, cleaning it, and continuing the process from the intermediate it was interrupted with. Further processing of the intermediate is then done using the same equipment line whereby not all units are necessarily used in both stages. Some of them can be on stand-by. This procedure usually increases the cycle time since: (1) the process is operated in non-overlapping mode, at least between the sequences of stages to and from the interruption, and (2) cleaning of the whole equipment line is necessary upon changeover from the intermediate to the final product or the next intermediate. Thus, the number of equipment items is reduced but their size must be larger due to the longer cycle time.

Finally, the process can be broken into several campaigns in which intermediates are manufactured and stored for the next campaign. The final product is manufactured in the last campaign. Essentially all the equipment units of the plants are used in each campaign. This mode of process operation is possible if batch integrity is not essential and/or intermediates are sufficiently stable and can be stored for a certain period of time.

For both interrupting and breaking the process sufficient intermediate storage capacity must be provided to buffer between two succeeding intermediates. Storing solid intermediates is usually easier and requires less expensive means. Therefore, splitting the process into campaigns is often done at stages in which a solid intermediate is produced. Both process modifications change the allocation of stages from one-to-one mode to multitask equipment operation. Larger and less equipment units will be used in both cases compared to one-to-one task allocation. This saves capital costs for the basic equipment but some additional costs must be incurred for intermediate storage. Labour costs are also less when splitting the process into campaigns. Inventory of raw materials might be increased due to longer processing cycles. In fact, partitioning the process into campaigns is equivalent to transformation of a single-product plant into a multiproduct or multipurpose plant where intermediates are considered to be the product of the preceding campaign. The question of where and into how many campaigns the process should be divided can be solved taking into account the equipment costs, the cost of intermediate storage, and costs of cleaning, including solvent recovery and waste treatment. The use of recovered solvent must be thoroughly considered also from the viewpoint of GMP requirements, which often impose constraints in this respect. Each of the campaigns can be optimized independently. Obviously, cycle times of individual equipment units can be chosen independently. The capacities of the units must then be such that each unit can handle the average amount of material per unit time coming from the preceding unit.

7.4.2.2. Sizing of intermediate storage

As mentioned, intermediate storage dampens the effects of process fluctuations, reduces process cycle times, and increases flexibility in process scheduling. It is intuitively clear that the size and location of intermediate storage will influence the plant performance. Below, a basic analysis will be given for single-product plants.

Intermediate storage de-couples the process into periodically operated subprocesses in the sense that each of the subprocesses can be operated with its own limiting cycle time and batch size. If the storage capacity is sufficiently large to accommodate the intermediate product of an entire production campaign, then the subprocesses can be operated completely independently. Alternatively, the storage capacity can be selected so that it de-couples the cycle time but not the batches. In this case, the ratio of the batch sizes to the limiting cycle times of both subprocesses must be the same:

$$\frac{B_U}{t_{LU}} = \frac{B_D}{t_{LD}} \tag{7.4-27}$$

where B_U and t_{LU} are upstream batch size and limiting cycle time, and B_D and t_{LD} are downstream batch size and limiting cycle time, respectively. The intermediate storage must accommodate at least an amount of material on the order of the sum of the upstream and downstream batch sizes. It is usually assumed that the capital cost of intermediate storage is negligible compared to the costs of processing units. This is generally true, although refrigerated and sterilized containers, which are also used in the manufacture of pharmaceuticals, are rather costly. Karimi and Reklaitis (1983b) assumed that Eqn. (7.4-27) is satisfied, i.e. the long-term supply and demand of the storage tank are in balance, and that there exist integers β_U and β_D such that:

$$\beta_U t_{LU} = \beta_D t_{LD} \tag{7.4-28}$$

The storage hold-up $H(t)$ is related to the input and output rates $F_U(t)$ and $F_D(t)$ by the mass conservation equation:

$$\frac{dH(t)}{dt} = F_U(t) - F_D(t-\omega) \tag{7.4-29}$$

where $F_U(t)$ and $F_D(t)$ are periodic and piecewise linear and ω is the time delay between the upstream and downstream batches. Exemplary data for the construction of hold-up plots are shown in Table 7.4-9 and Fig. 7.4-7. The diagram illustrates a situation in which the upstream flow $F_U(t)$ of 10,000 litres/h starts at zero time, continues for 0.5 hour, and is repeated every five hours, and the downstream flow $F_D(t)$ of 1333 litres/h starts after 45 minutes, continues for 3 hours, and is repeated every four hours. The time delay ω is 45 minutes.

From Fig. 7.4-8, which shows the variations in hold-up of the intermediate storage, it is clear from that the cycle is periodically repeated every 20 hours. At a time of 20 hours the storage tank is empty and the inflow to the tank starts again.

Each step in Fig. 7.4-7 may be represented by a Fourier series that can be integrated term by term. This leads to the determination of minimum and maximum values for the hold-up, H_{min} and H_{max}, respectively. The required storage capacity HR is given by the difference between these two:

$$HR = \max_{0 \le t \le \beta_U t_{LU}} H(t) = H_{max} - H_{min} \tag{7.4-30}$$

HR is a periodic function in ω/t_{LD} with period $1/\beta_U$.

Yeh and Reklaitis (1987) showed that the equipment cost of a production line decreases monotonically with the number of storage locations if the cost of intermediate storage and the time lost due to transfers to the storage vessels can be neglected. Of course, this is not true.

Table 7.4-9
In- and outflow characteristics of an intermediate storage tank

Time period, Δt h	$F_U(t)$-$F_D(t$-$\omega)$, litres/h	Hold-up in intermediate storage, $H(t)$, at boundaries of the period Δt, litres
0.0-0.5	10000	0-5000
0.5-0.75	0	5000-5000
0.75-3.75	-1333	5000-1000
3.75-4.75	0	1000-1000
4.75-5.0	-1333	1000-667
5.0-5.5	8667	667-5000
5.5-7.75	-1333	5000-2000
7.75-8.75	0	2000-2000
8.7510.0	-1333	2000-333
10.0-10.5	8667	333-4667
10.5-11.75	-1333	4667-3000
11.75-12.75	0	3000-3000
12.75-15.0	-1333	3000-0
15.0-15.5	8667	0-4333
15.5-15.75	-1333	4333-4000
15.75-16.75	0	4000-4000
16.75-19.75	-1333	4000-0
19.75-20.0	0	0-0

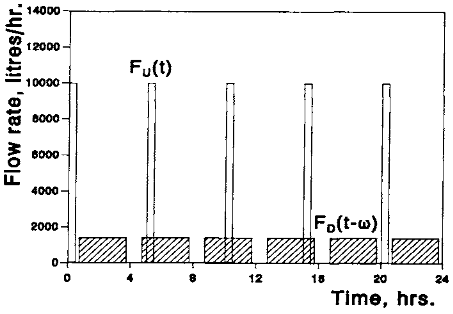

Figure 7.4-7. In- and output flow rates (adapted from Karimi and Reklaitis, 1989b).

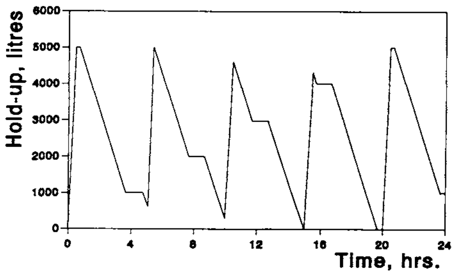

Figure 7.4-8. Hold-up in intermediate tank (adapted from Karimi and Reklaitis, 1989b).

The capital and operating costs of intermediate storage are significant, and, consequently, maximum use of storage is not economical. A trade-off between storage costs and equipment costs must be searched for. More information on this subject and an extension to multistorage problems with attention paid to storage locations, also in multiproduct plants, is presented in, among others, papers of Karimi and Reklaitis (1983a,b, 1985), Modi and Karimi (1989), Takamatsu *et al.* (1979, 1982, 1984) and in the recent paper of Ravemark and Rippin (1998).

7.4.2.3. Multiproduct plants

A major problem to be solved for multiproduct plants is the occurrence of disparities in the cycle times and size requirements for the different stages. In the following it will be assumed that the size factors as well as the cycle times of all units are independent on equipment size. This assumption is usually relaxed in further stages of the design. In case of batch heating and cooling, or reactors operated in semi-continuous mode, this is necessary in order to adopt the cycle times to the capacity of equipment, which is related to batch size.

Optimal design. As mentioned in section 7.4.1.4, the cost of batch equipment can be used as the objective function to be minimized:

$$C_p = \sum_{j=1}^{MB} m_j \, \alpha_j V_j^{\beta_j} = \min \tag{7.4-31}$$

The production of the desired amount of product(s) must be achieved within the available time. For continuous plants the on-stream time H is generally assumed to be 8000 h per year. In batch processing it is common practice not to operate the plant during weekends. This must be taken into account when considering the available time and limiting cycle times. Sizing and/or scheduling must be adopted using available weeks per year and batches per week of each product, instead of total production time per year and the limiting cycle time of each product. Fig. 7.4-9 shows the difference between uninterrupted batch plant operation and five-days-per-week operation.

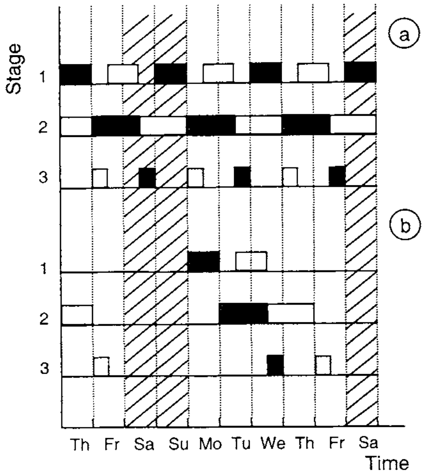

Figure 7.4-9. Batch production that is non-interrupted (a) and interrupted (b) for weekends.

If the plant is run in a seven-days-per-week overlapping mode with $t_L = 1.5$ days (Fig. 7.4-9a) the number of batches per week is $7/t_L = 7/1.5 = 4.666$. If the plant is not operated on weekends, only two batches per week are obtained. For this mode of operation, the number of batches per week of product i, NB_{wi}, is calculated by rounding down the numerical value of the ratio:

$$NB_{wi} = \text{INT}\left\{\frac{t_{wi}}{t_{Li}}\right\} \qquad \textbf{(7.4-32)}$$

where t_{wi} is the time available per week for product i (usually $t_w = 120$ h). The total number of batches per year, NB_i, is calculated as:

$$NB_i = NB_{wi}\, N_w \qquad \textbf{(7.4-33)}$$

where N_w is the number of weeks available per year (usually $N_w = 48$). Thus, the total time available for production in batch plants is evaluated to be at best 5800 h per year.

Single-product campaigns. When solving Eqn. 7.4-31 the following time constraint must be taken into account for overlapping operation:

$$\sum_{i=1}^{NP} \frac{Q_i t_{Li}}{B_i} \leq H \qquad \textbf{(7.4-34)}$$

with:

$$t_{Li} = \max_j \left(\frac{t_{ij}}{m_j} \right) \qquad \textbf{(7.4-35)}$$

The maximum batch size is:

$$B_i = \min_j \left(\frac{V_j}{S_{ij}} \right) \qquad \textbf{(7.4-36)}$$

Other, obvious constraints originate from material and heat balances on each batch stage (size factors can be calculated from these balance equations), i.e. $V_j \geq B_i S_{ij}$, and limits on the sizes of commercially available equipment units and on the maximum number of units in parallel. This leads to a formulation corresponding to an MINLP (Mixed Integer Non Linear Programming) problem where the variables m_j are restricted to take integer values. The calculated continuous optimal equipment sizes will be rounded up to the corresponding discrete sizes. This is an obvious oversimplification since the resulting solution might be suboptimal, especially if successive increases in the discrete sizes are relatively large.

A rigorous approach to the discretization of equipment sizes involves the use of standard equipment sizes already at the start of the cost minimization problem, i.e. Eqn. 7.4-31 is solved but with V_j chosen for each stage from a set of standard equipment units DSV_j of type j. The objective function then is formulated as:

$$C_p = \sum_{j=1}^{MB} \sum_{k=1}^{MEQS_j} z_{jk}\, \alpha_j\, DSV_j^{\beta_j} = \min \qquad \textbf{(7.4-37)}$$

where $MEQS_{jk}$ is the number of standard sizes k of equipment units of type j and z_{jk} is a binary variable which takes the value 1 if size k is selected for stage j and the value 0 otherwise (and only one size is selected for each stage). The time constraint is now formulated as:

$$S_{ij} Q_i t_{Li} \sum_{k=1}^{MEQS_j} \frac{Z_{jk}}{DSV_{jk}} \le t_{Pi} \qquad \text{for } i = 1, \ldots, NP; \quad j = 1, \ldots, NS \tag{7.4-38}$$

with:

$$\sum_{i=1}^{NP} t_{Pi} \le H \tag{7.4-39}$$

In this way the problem is reformulated as an MILP (Mixed Integer Linear Programming) problem. Readers who are interested in the problem of discrete sizing are referred to the paper of Voudoris and Grossmann (1992).

Mixed-product campaigns. Optimization procedures should be extended for the manufacture of products in parallel during some of the campaigns (*mixed-product campaigns*) whereby equipment units are assigned to all stages for all products. If product i is manufactured in more than one campaign, the time requirement imposed on a campaign by that product is no longer explicitly defined. Instead, it is necessary that the production capacity summed over the campaigns in which that product participates is at least sufficient to meet its requirement Q_i. If the times assigned to campaigns l and k in which product i participates are t_l and t_k, the production constraint has the form:

$$\frac{t_l B_{Li,l}}{t_{Li,l}} + \frac{t_k B_{Li,k}}{t_{Li,k}} \ge Q_i \tag{7.4-40}$$

In plants for mixed-product campaigns a possibility must be provided to connect appropriate equipment items to ensure processing of raw materials and intermediates in the best arrangement. Modern multiproduct plants are designed in such a way that most or all of the equipment items can be interconnected and arranged in any sequence to meet any requirement in this respect. However, mixed-product campaigns always result in more complex operation of the plant, and usually also in an increase of the costs for cleaning of equipment and solvent regeneration, which are not included in the objective function (7.4-31).

The criterion for optimal design is the same as that for single-product campaigns. The horizon constraint (7.4-34) is reformulated in that the cycle times are defined differently. Assuming *UIS* policy, this constraint for mixed-product campaigns is given by:

$$\max_j \left(\sum_{i=1}^{NP} \frac{Q_i t_{ij}}{B_i} \right) = \max_j \left(\sum_{i=1}^{NP} NB_i t_{ij} \right) \le H \tag{7.4-41}$$

The problem of an optimal multiproduct plant design may be solved by heuristic, branch and bound, and mathematical programming methods in versions adapted for operation on both real and integer numbers (linear programming, MILP, non-linear programming, MINLP, geometric programming). Often, non-linear programs (NLP) for real variables are used and results are further processed in the vicinity of the solution with real numbers by rounding up and the use of techniques such as the trial and error method. This, however, leads to suboptimal solutions. Below a heuristic method proposed by Sparrow *et al.* (1975) is presented in more detail.

The relative sizes of batch equipment are specified by means of size factors S_{Hj} for a *hypothetical product*. The production requirements and characteristics of each product are converted to the equivalent data for the hypothetical product and the equipment sized to achieve the required production of the hypothetical product. The method proceeds in three steps: (1) calculation of exact equipment sizes for a fixed number of units of the same size m_j, (2) conversion of exact equipment sizes to standard sizes, and (3) choice of m_j.

At the start it is assumed that values of S_{ij}, t_{Li}, Q_i, and H are available. It is practical to set all initial values of m_j to one. A good selection of initial values of the size factors S_{Hj} can be evaluated from:

$$S_{Hj} = \frac{\sum_{i=1}^{NP} Q_i S_{ij}}{\sum_{i=1}^{NP} Q_i} \qquad j = 1, \ldots, MB \tag{7.4-42}$$

Based on the size factors, batch size conversion factors F_i are calculated from:

$$F_i = \max_j \left\{ \frac{S_{ij}}{S_{Hj}} \right\} \qquad i = 1, \ldots, NP \tag{7.4-43}$$

F_i is the ratio of the amount of hypothetical product to the amount of product i that can be manufactured in one batch, i.e.

$$B_H = F_i \cdot B_i \tag{7.4-44}$$

If in any batch stage the size requirement of each of the actual product is, in fact, less than that of the hypothetical product, then the size factor postulated for the hypothetical product can be reduced to:

$$S_{Hj} = \max_j \left\{ \frac{S_{ij}}{F_i} \right\} \qquad j = 1, \ldots, MB \tag{7.4-45}$$

The number of batches required per year to produce an amount Q_i (kg) of i is:

$$NB_i = \frac{Q_i F_i}{B_H} \tag{7.4-46}$$

The time required per year for the manufacture of product i (neglecting changeovers) is:

$$t_{P,i} = \frac{t_{Li} Q_i F_i}{B_H} \tag{7.4-47}$$

The total time required for the manufacture all products is:

$$t_P = \sum_{i=1}^{NP} \frac{t_{Li} Q_i F_i}{B_H} \tag{7.4-48}$$

Accordingly, the batch size of the hypothetical product can be determined from:

$$B_H \geq \frac{\sum_{i=1}^{NP} t_{Li} Q_i F_i}{H} \tag{7.4-49}$$

The sizes of the batch equipment units are then calculated from:

$$V_j = B_H S_{Hj} \qquad j = 1, .., MB \tag{7.4-50}$$

If the t_{Li}'s and/or the S_{ij}'s are functions of V_j (this is often the case) then the basic procedure may be repeated until convergence is obtained on V_j.

The conversion of calculated V_j's to standard sizes is carried out in stages. First, the V_j's are rounded up to the next larger standard size. The equipment cost for each stage is then calculated. Working through the stages in decreasing order of equipment cost, the effect of using one standard size smaller is evaluated. If the constraint on production time ($\Sigma t_{Pi} \leq H$) is not violated then the smaller size is accepted. If the time constraint is violated then the larger standard size is assumed.

The following algorithm is used to minimize equipment costs by varying the number of equipment units m_j. Initially all the m_j's are set equal to one. A feasible set of standard equipment sizes is calculated. Then, m_j is temporarily increased by one for each stage in turn and the value of B_H calculated using the expressions given above. The value of m_j for the stage yielding the minimum value of B_H is increased permanently by one and standard sizes are calculated as before. The m_j's are increased until the total equipment cost does not improve further. This solution is considered optimal. *Example 7.4-4* illustrates the heuristic method.

The heuristic method is simple and effective, and has turned out to be faster than direct application of mathematical programming codes. It gives insight into the problem of equipment sizing and leads to a better understanding. The heuristic solution satisfies the constraints but does not guarantee the optimal situation. Therefore, the use of mathematical programming methods is increasing rapidly, which is stimulated also by the fast progress in computers. As mentioned in section 7.4.1.4, a rigorous design based on deterministic plant models has a very limited meaning. The procedures are, however, presented here in more detail since they are similar and illustrative for problems of scheduling.

Example 7.4-4. Equipment sizing by using the heuristic method (after Sparrow et al., 1975)

A plant for the manufacture of three products (NP = 3) using four stages (MB = 4) is to be sized. The amounts of the products to be manufactured are: Q_1 = 436,000 kg/y; Q_2 = 324,000 kg/; Q_3 = 258,000 kg/y. The time available for production is assumed to be 6000 hours per year. The standard sizes of vessels are: 2500, 4000, 6300, 10000, and 16000 L. Size factors, processing times, and cost coefficients are given in Table 7.4-10. Results of calculations are presented in Table 7.4-11.

Table 7.4-10
Data for equipment sizing

Quantity		$j = 1$	$j = 2$	$j = 3$	$j = 4$
S_{ij}	$i = 1$	8.28	3.70	2.95	6.56
	$i = 2$	5.57	4.09	3.27	6.16
	$i = 3$	2.34	0.80	5.69	5.98
t_{ij}	$i = 1$	1.15	9.86	5.27	5.30
	$i = 2$	5.95	7.01	6.99	1.08
	$i = 3$	3.95	6.00	5.13	0.65
α_j		400	400	400	400
β_j		0.6	0.6	0.6	0.6

Table 7.4-11
Results of calculations (batch size for hypothetical product $B_H = 1900$)

(i or j) → Quantity	1	2	3	4	Equipment cost, SFr	Production time, h
F_i	1.40	1.32	1.52			
t_{Li}	9.86	7.01	6.00			
S_{Hj}	5.91	3.09	3.75	6.29		
S_{Hj} (slack removed)[a]	5.91	3.09	3.75	4.69		
m_j	1	1	1	1		
V_j (exact)	11234	5874	7122	8911		
V_j (standard)	10000	6300	10000	10000	377 000	5972
m_j (final)	1	2	1	1		
V_j standard	10000	4000	6300	6300	369 000	5993

[a] i.e. no idle times.

Approximate equipment sizing. There are many combinations of equipment units that meet the requirements concerning the functions of all equipment units and the time horizons for all products. Based on the Flatz (1980) concept, a simple procedure is presented to determine feasible equipment sizes that meet all requirements for plants operated in a single-product campaign mode (no process overlapping). The procedure is illustrated in Fig. 7.4-10.

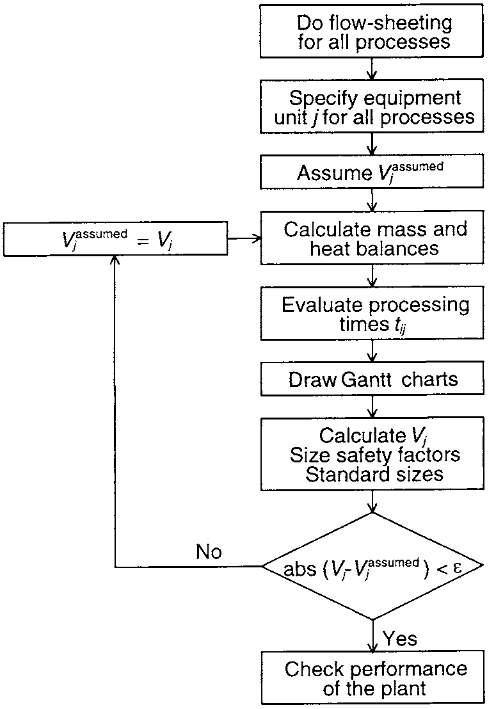

Figure 7.4-10. Equipment sizing (multiproduct plant, non-overlapping campaigns).

The starting point of the approximate sizing procedure is to compose blank flow-sheets for all products (processes) specifying types of all equipment units of yet unknown capacity for each process no matter whether units are common for a majority of stages or unique for one process only. Preliminary mass and heat balances for all items and processes must be made. The size factors S_{ij} are evaluated based on these balances. The balances can be corrected after equipment has been selected. Evaluation of size factors thus is an iterative procedure.

Capacities of all equipment units for all processes V_j^{assumed} are guessed. Notice that not all units are necessarily used in all processes. Further steps only concern the units that are used in more than one process.

Processing times t_{ij} for all equipment units of the assumed capacities V_j^{assumed} are calculated based on recipes and heat and mass balances. Time safety factors are used if necessary or desired. It is common practice to round off processing times t_{ij} so that a round number of batches will make up a full 24 h. Processing rates of semi-continuous items are chosen such that processing times in these items θ_{ik} are reasonable (e.g. commensurable with t_{ij}'s or significantly shorter than t_{ij}'s if a semi-continuous item k is to be connected with batch equipment unit j). Upper and lower limits on processing rates must be specified. These limits may result in the necessity to use more than one semi-continuous unit operating in parallel.

Gantt charts for all processes (products) are made. In case of significant disparities in processing times of individual units, it must be decided whether to use more than one unit operated in parallel and out-of-phase. This could be recommended for only a few equipment units for which processing times are longer than the processing times of associated units by about 100% or more. Notice that disparities may not occur in all processes but only in some of them. The limiting cycle times t_{Li} are determined from the Gantt charts.

Capacities of all equipment units V_j for all processes are calculated from the following equation:

$$V_j = \frac{1}{H} \sum_{i=1}^{NP} Q_i t_{Li} S_{ij} \qquad \textbf{(7.4-51)}$$

When calculating the capacity of equipment that remains unused in some processes, the time H should be reduced by subtracting the times to realize these production campaigns. It is recommended to increase the calculated capacities by multiplying by size safety factors. These factors depend on the type of equipment. For instance, for heat exchangers the capacity should be increased by a factor of 1.2 to 1.4 (due to unpredictable fouling of surfaces), while for vessels this factor is 1.05. If standard equipment is available the standard sizes V_j^{stand} larger but nearest to V_j are chosen. If V_j is larger than available standard equipment or larger than the allowed or preferred size (e.g. no larger units may be used because of the size of existing buildings or the production supervisor limits the maximum size because of his experience with a certain type of process), a number of units must be used in parallel and operated in-phase. If V_j's match V_j^{assumed}'s the next step in the procedure is executed. Otherwise new values of $V_j^{\text{assumed}} = V_j$ are set and the calculations are repeated until a reasonable agreement is reached.

The units of capacity V_j are expected to meet the size requirements and are likely to also meet the cycle time requirements for all processes. It must, however, be checked whether the chosen equipment item will perform the process function and whether it will do this within the processing time for all processes.

The sizes determined by means of this procedure are certainly non-optimal. However, the obvious advantage of the procedure is that all calculations can be performed using even a pocket calculator. Accordingly, a person who makes an analysis of a multiproduct plant can easily track how his decisions on the type and size of equipment units affect the performance of the plant. The rough dimensioning by means of this procedure gives a good background for the estimation of capital costs and preliminary product-cost evaluation, and raises questions for further process studies. The procedure does not require knowledge of sophisticated computer techniques, which are needed to search for the optimal set of equipment items. Sizes of equipment determined by means of this procedure can be used as initial guesses for a rigorous search for an optimal using computer optimization programs. The sizes are overestimated. In practice, overlapping of processes or partly parallel operation is possible. This will improve the utilization of equipment, and, consequently, reduce the total production time. The procedure described above for fixed processing times is illustrated with *Example 7.4-5.*

Example 7.4-5. Dimensioning of equipment for Stardust Chemical Co. plant (after Flatz, 1980)

Stardust Chemical Co. planned a new plant for two intermediates. The chemical production processes were not yet fully worked out because of lack of data on how large the production plant would have to be. The following information is not complete and partly misleading.

Process for Product *A*

The raw material, *R*, which is not pure, is transformed into A by reaction: $R \rightarrow A + S$. The content of *A* in crude *A* is 90.7 %. The laboratory recipe is as follows: (1) Dissolve raw material: 50 g of *R* is dissolved in 250 cm^3 (197 g) ethanol at room temperature, while stirring. The required time is approximately 1 h. (2) Reaction: In a 1 dm^3 flask, put 250 cm^3 (197 g) of ethanol, and heat to boiling. Over a period of 3 h, let the solution of *R* drop into the flask, while keeping the ethanol boiling. During the reaction, *S* is lost as a gas through a cooled trap. There is so much froth that the flask is completely filled. Information about the heat of reaction is not available. At the end of the reaction, cool down the solution of crude *A* to 40 °C. 25 g of crude *A* in solution is obtained. Usual precautions must be taken when working with ethanol. Waste-gas purification is required for ethanol.

Process for Product *B*

Materials *X* and *Y* are reacted according to the following scheme: $X + Y \rightarrow B$. The laboratory recipe is as follows: (1) Dissolve raw material *X*: In a pilot plant, 100 kg of *X* is added to 100 kg of water, and dissolved at room temperature, while stirring. The required time is approximately 1 h. (2) Reaction: put 100 kg of *Y* and 100 kg of water in a vessel and heat to 100 °C. Over a period of 0.5 h, add the solution of *X*, keeping the batch at 100 °C. Information about the heat of reaction is not available. After completion of the reaction, cool down to 30 °C (about 1.5 h in the pilot plant). 200 kg of *B* is obtained as a suspension in water. No safety and environmental problems are expected.

Plant design specifications

Production capacity:	*A* - 32,000 kg/year *B* - 180,000 kg/year
Production time:	5-day week; 24 h/day
Production changes:	16 times/year; 0.5 week/cleaning
Maintenance:	4 weeks/year
Heating:	Steam at 6 bar.
Cooling water:	20 °C.

Note: Data for frequency of production changes come from preliminary ideas concerning the storage policy; the time for cleaning comes from experience in similar plants.

Calculations

The size factors are evaluated from mass balances based on the recipe. 22.7 g of product *A* is obtained by processing, in vessel 1, 247 g of a mixture with a density of approximately 800 kg/m^3. Thus the value of S_{11} is:

$$S_{11} = 247/(22.7 \cdot 800) = 0.0136 \text{ m}^3\text{/kg of product } A$$

22.7 g of product *A* is obtained from 1 dm^3 vessel 2 of total volume 1.25 dm^3 with the whole volume filled with the reaction mixture and foam. Thus:

$$S_{12} = 1.25/22.7 = 0.055 \text{ m}^3\text{/kg of product } A$$

200 kg of product *B* is obtained by processing, in vessel 1, 200 kg of a mixture with a density of approximately 1000 kg/m^3. Thus:

$$S_{21} = 200/(200 \cdot 1000) = 0.001\ \text{m}^3/\text{kg of product } B$$

Finally, in vessel 2, 400 kg of a mixture with a density of 1000 kg/m^3 is processed into 200 kg of product B, *i.e.*

$$S_{22} = 400/(200 \cdot 1000) = 0.002\ \text{m}^3/\text{kg of product } B$$

The available yearly production time H = 52 weeks – 4 weeks for maintenance, holidays, etc. – 16 changeovers/year · 0.5 weeks/changeover = 40 weeks, i.e. 40 · 120 = 4800 h. For the calculation of processing times, assume that physical properties of the reaction mixtures are the same as those of the pure solvents. The capacities of both stirred tanks are: $V_1^{\text{assumed}} = 1$ m^3 and $V_2^{\text{assumed}} = 4$ m^3. The time programs for the two vessels for both processes are presented in Table 7.4-12.

Table 7.4-12
Time programs

Time program	Times, h Process A	Process B
Vessel 1		
Filling with liquid	0.25	0.25
Addition of raw material	0.25	0.25
Dissolve raw material	1	1
Emptying into Vessel 2	3	0.5
Rounding-off time	-	-
Processing time for vessel 1	4.5	2
Vessel 2		
Filling	0.25	0.25
Heating	0.5	1.25
Addition of solution from vessel 1	3	0.5
Cooling	3	9
Emptying	0.25	0.25
Rounding-off time	1	0.75
Processing time for vessel 2	8	12

Without making Gantts charts, it is obvious from these data that the limiting times are: t_{L1} = 8 h and t_{L2} = 12 h. Now, capacities of both vessels can be calculated using expression (7.4-52). For vessel 1:

V_1 = (32,000 kg of product A per year · 8 h/cycle for product A · 0.0136 m^3/kg + 180,000 kg of product B per year · 12 h/cycle for product B · 0.001 m^3/kg)/4800 h/year = 1.17 m^3.

Multiplying this value by a safety factor of 1.05 (the value for stirred tanks) we obtain $V_1 = 1.23\ \text{m}^3$. For the vessel 2,

V_2 = (32,000 kg of product A per year · 8 h/cycle for product A · 0.055 m^3/kg + 180,000 kg of product B per year · 12 h/cycle for product B ·0.002 m^3/kg)/4800 h/year = 3.83 m^3.

Multiplying this value by a safety factor of 1.05 we obtain $V_2 = 4.03\ \text{m}^3$. In both cases the calculated capacities are very close to the initial guesses and there is no need to continue iterations. The standard capacities of AE series (according to German DIN that is often used in Europe) glass-lined stirred tanks that can be chosen to carry out both stages of both processes are AE1000 and AE4000 with total capacities of 1.458 and 5.381 m^3, respectively. The coefficients of utilization of the standard vessels will be: $\varepsilon_1 = 1.17/1.458 = 0.80$ and $\varepsilon_2 = 3.83/5.381 = 0.71$. Both coefficients are within a reasonable range and the choice of the above standard sizes can be considered justified.

Conclusions concerning further process studies can be drawn from this simple analysis. (1) There is a need to try to reduce foaming at stage 2 of process A. If the requirement concerning the volume of vessel 2 in process A could be reduced by 40%, tank AE2500 with a capacity of 3.46 m^3 might be sufficient, which would significantly decrease the capital costs. (2) Physical properties of all mixtures should be determined and thermokinetic data for the second steps of both processes provided to make calculations of the schedule more reliable.

7.4.2.4. Multipurpose plants

Generally, equipment utilization in multiproduct plants is relatively low due to significant differences in the limiting cycle times t_{Li} of the products. In a perfect plant, the stage cycle times of each product for all stages (tasks) would be equal to its t_{Li} (no idle times at all). In real plants of different production routes, number of stages, and processing times, the utilization of equipment may be improved if different products share processing facilities at the same time. This results in simultaneous manufacturing of two or more products and lowering of production costs.

Optimal design. Let us start with a multipurpose plant with products that are manufactured by single production routes. This is presumably the most practical problem in the analysis of multipurpose plants. Only products using different equipment units may be manufactured simultaneously. Such products/processes are termed *compatible*. Products (processes) that would share facilities cannot be run at the same time. Such products (processes) are termed *incompatible*. Compatibility and incompatibility are conveniently presented on compatibility and incompatibility graphs (Fig. 7.4-11) where products are represented by circles. Lines connecting two circles on the compatibility graph indicate that the products may be manufactured simultaneously contrary to the incompatibility graph where the line excludes manufacturing of the products at the same time. A polygon with more products (*subgraphs*) shows that all products at edges of the polygon and interlinked with each other may be manufactured simultaneously. For instance, chemicals A, E, and F may be produced simultaneously while A and C may not be manufactured at the same time. The maximum sets of products that can be processed simultaneously (the graph *cardinality*) is delineated by maximum complete subgraphs.

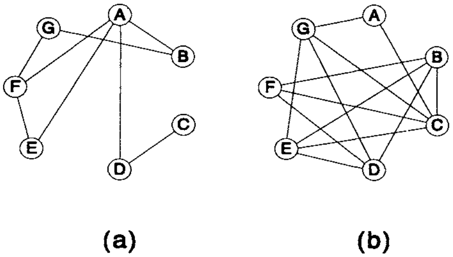

Figure 7.4-11. Compatibility (a) and incompatibility (b) graphs.

For the graph shown in Fig. 7.4-11, the cardinality is: <*A*,*B*>, <*A*,*E*,*F*>, <*A*,*D*>, <*B*,*G*>, <*C*,*D*>, and <*F*,*G*>. This means that only these six sets should be considered as possible sequences of campaigns in an analysis of the plant. The permitted campaigns matrix is formulated as follows:

$$X_{ik} = \left\{ \begin{array}{c} 1 \text{ if product } i \text{ can be produced in campaign } k \\ 0 \text{ otherwise} \end{array} \right\} \quad k = 1, \ldots, NC \qquad \textbf{(7.4-52)}$$

The production time for each product *i* is given by:

$$t_{P,i} = \sum_{k=1}^{NC} X_{ik} t_k \qquad \textbf{(7.4-53)}$$

where t_k denotes the campaign time.

In addition to the assumption that one production route exists for each product, the following simplifying assumptions are made (after Suhami and Mah, 1982):

- Long production campaigns are involved and limiting cycle times are used as reasonable approximations of reality.
- In any plant design each product will be manufactured using one batch size in all its campaigns. Obviously, the batch size can vary for different plant designs.
- One equipment type is assigned uniquely to each product task.
- For each stage the parallel units are identical and operated out-of-phase.
- Parallel units in a stage are deployed as a block. At any one instant, all parallel units of a given stage can be dedicated to only one product. Parallel processing of two or more products within one stage is excluded.
- Only batch stages are considered in the design.

The objective function, Eqn. 7.4-31, will be minimized subject to the horizon constraints of Eqn. (7.4-54) and other 'conventional' constraints, imposed by limits on equipment sizes, etc. *Example 7.4-6* illustrates the use of the above model for the minimization of equipment costs in the design of a batch plant.

$$\begin{gathered}\sum_{k=1}^{NC} t_k \le H \\ t_{Pi} \le \sum_{k=1}^{NC} X_{ik} t_k \\ \frac{Q_i}{B_i} t_{Li} \le t_{Pi}\end{gathered} \tag{7.4-54}$$

Example 7.4-6. Optimal design of a multipurpose plant (after Faquir and Karimi (1988)

A batch plant for 7 products and 10 batch stages (equipment units) is to be designed. Products must be manufactured within $H = 6200$ hours. Tables 7.4-13 to 7.4-15 show processing times t_{ij}, size factors S_{ij}, and yearly production requirements Q_i for all products and stages. Cost coefficients for all equipment items are the same: $\alpha = 250$ and $\beta = 0.6$.

Table 7.4-13
Processing times, t_{ij}, h/batch

j	1	2	3	4	5	6	7	8	9	10
A								7.456		
B			7.143	2.595			3.974		5.719	
C			4.360					2.554	7.318	2.297
D				2.404	9.987		6.758			
E	6.534				5.516				1.932	
F			1.269			2.005	5.469			7.725
G	6.855	7.326			5.062			6.650		

Table 7.4-14
Size factors, S_{ij}, L/kg$_{\text{prod}}$

j	1	2	3	4	5	6	7	8	9	10
A								5.404		
B			9.768	1.125			3.205		3.304	
C			8.065					4.620	4.529	8.163
D				1.922	9.415		4.833			
E	9.422				2.653				5.982	
F			3.174			2.895	5.731			3.587
G	3.757	5.640			9.381			6.418		

Table 7.4-15
Production requirements, Q_i, kg$_{\text{prod}}$ (in one year)

i	A	B	C	D	E	F	G
Q_i	300 000	150 000	200 000	190 000	140 000	172 000	106 000

Equipment sizes are subject to the constraint that $250 \leq V_j \leq 10\ 000$ L for all j, and the maximum number of parallel units $m_j = 3$. The compatibility and incompatibility graphs are shown in Fig. 7.4-11. As pointed out above, only simultaneous campaigns <*A*,*B*>, <*A*,*E*,*F*>, <*A*,*D*>, <*B*,*G*>, <*C*,*D*>, and <*F*,*G*> are allowed. Campaign numbers are assigned from 1 to 6 in the above order.

Optimization results are shown in Tables 7.4-16 to 7.4-18 (size of batches and production times, continuous and integer, with respect to m_j's, solutions for size of vessels, and times of campaigns duration) and the optimal production plan is shown in Fig. 7.4-12. For optimal conditions only three out of a total of six potential campaigns were used: campaign 3 <*A*,*E*,*F*>, campaign 4 <*B*,*G*> and campaign 5 <*C*,*D*>. The optimal plan corresponds to the situation that each product is manufactured over the full campaign length. The sequence of campaigns shown in the figure can be arbitrarily changed.

Table 7.4-16
Batch sizes and production times (integer solution)

Product	Batch size, B_i, kg	Production time, t_{Pi}, hours
A	1036	2159
B	744	1440
C	563	2600
D	730	2600
E	424	2159
F	615	2159
G	539	1440

Table 7.4-17
Vessel sizes, L (rounded to full litres)

Stage, j	Continuous solution		Integer solution	
	V_j	m_j	V_j	m_j
1	3787	1.000	3992	1
2	2976	1.000	3041	1
3	7112	1.000	7266	1
4	1331	1.000	1403	1
5	6521	1.116	6870	1
6	1691	1.000	1782	1
7	2247	1.000	3527	1
8	5314	1.000	5598	1
9	2406	1.123	2549	1
10	4336	1.000	4594	1
Objective function	354,778		355,516	

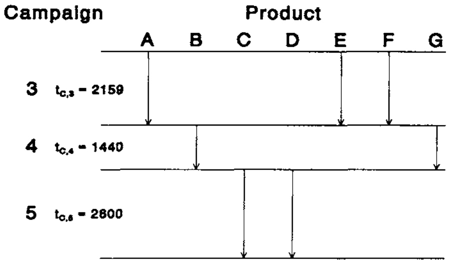

Figure 7.4-12. Optimal production plan.

Table 7.4-18
Campaign length, hours

Campaign number, k	Campaign length, hours
1: <*A*,*B*>	0
2: <*A*,*D*>	0
3: <*A*,*E*,*F*>	2159
4: <*B*,*G*>	1440
5: <*C*,*D*>	2600
6: <*F*,*G*>	0

Energy considerations. Objective functions for design usually comprise capital costs for batch operated equipment units. Some authors have also paid attention to energy consumption, which may affect the choice of equipment. This was the subject of studies by Knopf *et al.* (1982), Corominas *et al.* (1993), Kondili *et al.* (1993), and Goršek and Glavič (1997). The last authors compared continuous and batch plants consisting of four processing units and a number of storage tanks. Energy integration in both plants was assessed. It turned out that the batch plant is economically favoured below a capacity of 1300 tons/year. Energy integration was about 28% for hot and cold utilities for the batch plant while it was about 36% for the continuous plant.

7.4.2.5. Retrofitting of batch plants

Multiproduct batch plants are designed to meet requirements defined at the design stage, with some necessary flexibility to account for uncertainties. After a few years of operation, the initial plant configuration may sometimes become obsolete and insufficient to meet the changed demand. Such plants can be retrofitted, *i.e.* redesigned to accommodate necessary changes in products and/or production sequences and to improve the operability of the process by means of increasing the process flexibility and reducing the operating costs. Upon plant expansion, products and recipes remain unchanged. The most important then is the selection of the production tasks that will need more capacity and the introduction of nonidentical units operating in- and out-of-phase. When the palette of products is changed new types of equipment may become necessary and old units may go into retirement. The objective of plant retrofitting is to find (1) feasible types of equipment (including existing units) that will be used for the manufacture of all products in the new plant and (2) the sizes of new equipment units and intermediate storage vessels and the number of units of each equipment type (new and old), for optimization of the given performance criterion, usually expressed in terms of appropriately weighed costs. The problem of retrofit design of batch plants was treated, among others, by Knopf *et al.* (1982), Yeh and Reklaitis (1985), Espuña and Puigjaner (1989), and Papageorgaki and Reklaitis (1993).

Various criteria were proposed for the optimal selection of the equipment configuration and the number and sizes of units. In grass-root design, the capital cost of equipment is mostly used as the optimization criterion. In retrofit design a more appropriate objective function seems to be the net profit, which has to be maximized. Papageorgaki and Reklaitis (1993) formulated the criterion as follows:

$$\sum_{i=1}^{NP} C_i P_i - \sum_{e=1}^{MEQ} MU_e \alpha_e V_e^{\beta_e} - \sum_{i=1}^{NP} \sum_{m \in TA_i} \sum_{e \in EQ_{im}} COP_{ime} Q_{ime} = \max \tag{7.4-55}$$

where P_i is the production demand for product i, C_i its selling price, V_e and MU_e are the size and number of units of equipment type e, α_e and β_e are cost coefficients, TA_i is the set of tasks for product i, EQ_{im} is the set of feasible equipment types for task m of product i, Q_{ime} is the amount of product i manufactured in equipment type e during the execution of task m, and COP_{ime} is the associated operating costs per unit of product i that is manufactured in equipment type e and includes costs such as the cost of energy consumed, labour costs, and maintenance costs. This objective function is subject to several groups of constraints, as classified by Papageorgaki and Reklaitis (1990a), see below.

Constraint groups

1. Constraints for assignment of tasks to equipment units and for *connections* between units

$$Z_{imgk} \geq Z_{im(g+1)k} \quad \text{for all } i,k \quad m \in TA_i, \text{ and } \quad g = 1, \dots, MG_{imk}^{\max} - 1 \tag{7.4-56}$$

where Z_{imgk} is a continuous variable representing the assignment of equipment group g to task m of product i in campaign k. This variable is constrained to binary values with the following constraints:

$$\begin{aligned} &Z_{imgk} \geq X_{imegk} \quad \text{for all } i,k \quad m \in TA_i \quad g = 1, \dots, MG_{imk}^{\max} - 1 \quad \text{and} \quad e, g \in EQ_{im} \\ &Z_{imgk} \leq \sum_{e \in EQ_{im}} X_{imegk} \quad \text{for all } i,k \quad m \in TA_i \quad \text{and} \quad g = 1, \dots, MG_{imk}^{\max} \end{aligned} \tag{7.4-57}$$

where $MG_{imk}^{\max}$ is the number of equipment groups assigned to task m of product i in campaign k, and X_{imegk} is the following binary variable:

$$X_{imegk} = \left\{ \begin{array}{c} 1 \quad \text{if task } m \text{ of product } i \text{ is performed in unit type } e \\ \text{equipment group } g \text{ and campaign } k \\ 0 \quad \text{otherwise} \end{array} \right\} \tag{7.4-58}$$

2. Production demand constraints

$$\begin{aligned} &\sum_{e \in EQ_{im}} Q_{ime} \geq P_i \qquad \text{for all } i \text{ and } m \in TA_i \\ &\sum_{k=1}^{NC} Q_{ik} = P_i \qquad \text{for all } i,k \end{aligned} \tag{7.4-59}$$

where Q_{ik} denotes the amount of product i that is manufactured in campaign k, and NC is the number of campaigns. In addition, the constraints limiting batch sizes must be fulfilled:

$$\begin{aligned} &\sum_{k=1}^{NC} \sum_{g=1}^{MG_{imk}^{\max}} MU_{imegk} B_{imegk} NB_{imgk} \leq Q_{ime} \qquad \text{for all } i \quad m \in TA_i \text{ and } e \in EQ_{im} \\ &\sum_{g=1}^{MG_{imk}^{\max}} \sum_{e \in EQ_{im}} MU_{imegk} B_{imegk} NB_{imgk} \geq Q_{ik} \qquad \text{for all } i,k \quad m \in TA_i \end{aligned} \tag{7.4-60}$$

where B_{imegk} denotes the batch size of product i in campaign k which is manufactured in unit type e and in equipment group g during the execution of task m, MU_{imegk} denotes the number of units of type e that are contained in equipment group g which is assigned to task m of product i in campaign k, and NB_{imgk} is the number of batches of product i that are being processed by equipment group g with task m and in campaign k.

3. Cycle time and horizon constraints

$$t_{imgk} \geq t_{ime}^{0} + \alpha_{ime} B_{imegk}^{\beta_{ime}} \qquad \text{for all } i,k \quad m \in TA_i \quad e \in EQ_{im} \text{ and } g = 1, \dots MG_{imk}^{\max} \tag{7.4-61}$$

for processing times that are assumed to be dependent on the batch size, and:

$$t_{Lik} \geq \frac{t_{imgk}}{MG_{imk}} \qquad \text{for all } i,k \quad m \in TA_i \quad g = 1, \dots, MG_{imk}^{\max} \tag{7.4-62}$$

4. Equipment constraints

Conventional constraint for the equipment size:

$$V_e \geq S_{ime} B_{imegk} \qquad \text{for all } i,k \quad m \in TA_i \quad e \in EQ_{im} \text{ and } g = 1, \dots MG_{imk}^{\max} \tag{7.4-63}$$

where S_{ime} is the size factor of task m of product i in equipment type e. The total number of units of type e is determined by:

$$N_e = \sum_{(im)\in U_e} \sum_{g=1}^{MG_{ime}^{\max}} MU_{imegk} \quad \text{for all } i \quad m \in TA_i \text{ and } e \in EQ_{im} \qquad \textbf{(7.4-64)}$$

where U_e denotes a set of tasks that can be executed by equipment type e, while the number of equipment groups is constrained by:

$$MG_{imk} = \sum_{g=1}^{MG_{ime}^{\max}} g\, W_{imegk} \quad \text{for all } i \quad m \in TA_i \qquad \textbf{(7.4-65)}$$

where W_{imgk} is a continuous variable that takes the value of 1 if exactly g equipment groups are assigned to task m of product i in campaign k and the value of zero otherwise. This variable is restricted to binary values through the following constraints:

$$W_{imgk} = Z_{imgk} - Z_{im(g+1)k} \quad \text{for all } i,k \quad m \in TA_i \text{ and } g = 1,\dots MG_{imk}^{\max} - 1 \qquad \textbf{(7.4-66)}$$

and

$$W_{imgk} = Z_{imgk} \quad \textit{for} \text{ all } i,k \quad m \in TA_i \text{ and } g = MG_{imk}^{\max} \qquad \textbf{(7.4-67)}$$

5. Batch size and batch number constraints

The batch size manufactured in each equipment group assigned to each product task cannot exceed the maximum batch size:

$$\sum_{e\in EQ_{im}} MU_{imegk} B_{imegk} \le B_i^{\max} \quad \textit{for} \text{ all } i,k \quad m \in TA_i \text{ and } g = 1,\dots MG_{imk}^{\max} \qquad \textbf{(7.4-68)}$$

Additionally, the total number of batches of product i manufactured in campaign k, N_{ik} is determined by the following inequality:

$$NB_{ik} \ge \sum_{g=1}^{MG_{imk}^{\max}} NP_{imgk} \quad \textit{for all } i,k \quad m \in TA_i \qquad \textbf{(7.4-69)}$$

This is an MINLP problem for which Papageorgaki and Reklaitis (1993) proposed a solution. Espuña and Puigjaner (1989) showed that the problem of retrofitting formulated for single-product campaigns can be solved more effectively in the heuristic way. The problem of batch plants retrofitting was also the subject of considerations of Valsenak *et al.* (1987) and Póvoa and Macchietto (1993). The reader interested in these algorithms is referred to the original papers.

Papageorgaki and Reklaitis (1993) presented case studies for the procedure shown above. A profit increase was reached in all cases, while the percentage of the increase depended upon the case. The most pronounced was the case of a plant manufacturing three products. Withdrawal of one product and adding a new one together with the retirement of two old equipment units and the introduction of four new facilities resulted in an increase of the net yearly profit from $470,800 to $2,069,200.

7.4.2.6. Designing under uncertainty

In contrast with continuous plants, batch plants are intrinsically flexible. Designed properly, they meet changes in product demand and characteristics of processes in the plant. These changes originate from uncertainties in variables determining the performance of the batch plant. There are two different types of uncertainties in the design of batch plants: (1) short-term, and (2) long-term variations.

Short-term uncertainties include those in processing times and recipes of the individual products, which are expressed by size and duty factors. These variations can usually be accommodated by intermediate storage provided that the variations are not too large. These uncertainties appear already at the early design phase and include later scale-up effects. The deeper the knowledge of the processes the smaller the effect of these uncertainties on the performance of the plant. They can be absorbed to some extent by incorporating planned overcapacity and/or sufficient flexibility or by including the possibility of later modification or expansion of the plant, which is equivalent to planned overcapacity, at least with respect to utilities and space. An intuitive approach is used to tackle the problem of market uncertainties and flexible design.

Random disturbances also cause short-term uncertainties. They may result in changes of product quality, throughput of equipment items, or failure of equipment units. All of these can be dealt with to a limited degree by the provision of storage capacity at appropriate locations. If each of the units in a sequence is subject to independent random variations about the common mean, the provision of sufficient intermediate storage between the units will decouple these variations so that the average throughput will be equal to the common mean values. The capability of intermediate storage for accommodation of the fluctuations depends on the location of the storage tank, the volume of storage available, and the initial amount of material in storage.

Long-term uncertainties arise from both seasonal changes in demand and projections of product demand patterns. Significant changes in the level or nature of the demand or of the plant capability are a recurring feature in fine chemicals production and the capability of dealing with such changes is often quoted as one of the major reasons why batch plants are preferred to continuous ones for such products. Seasonal changes, e.g. for agriculture chemicals, can be accommodated in the production planning stage by producing more than necessary during low periods of demand, with, consequently, increased product inventories, to meet the product demand at the peak periods. Plant expansions may be the best method to accommodate long-term uncertainties in product demand. However, any expansion means investment and time to remodel the plant. This limits the plant flexibility, at least during restructuring of the plant. Therefore, it is useful to include uncertainties into design procedures to make the plant as flexible as possible already at the design stage.

Reinhart and Rippin (1986) proposed two methods for design under uncertainty: (1) introduction of a penalty function for the probability of exceeding the available production time, whereby the probability can be generated by standard error propagation techniques for technical or commercial uncertainties, and (2) the 'Here and Now' method.

(1) The total production time for single production campaigns is given by:

$$t_P = \sum_{i=1}^{NP} \frac{Q_i t_{Li}}{B_i} \tag{7.4-70}$$

with t_{Li} and the maximum batch size B_i given by Eqns. 7.4-35 and 7.4-36, respectively.

Uncertainties in amounts of products to be manufactured Q_i, processing times t_{ij}, and size factors S_{ij} will influence the production time t_P, whose uncertainty reflects the individual uncertainties that can be presented as probability distributions. The distributions for short-term uncertainties (processing times and size factors) can be evaluated based on knowledge of probability distributions for the uncertain parameters, *i.e.* kinetic parameters and other variables used for the design of equipment units. The probability of not being able to meet the total demand is the probability that the production time is larger than the available production time H. Hence, the objective function used for deterministic design takes the form:

$$C_{opt} = \sum_{j=1}^{MB} m_j \alpha_j V_j^{\beta_j} + \lambda \cdot P(t_P > H) = \min \tag{7.4-71}$$

where $P(t_P > H)$ is the probability of exceeding the available time (not meeting the demand) and λ is the weighing factor. The product is a stochastic penalty function. The increase in the weighing factor results in the increase of equipment sizes compared to the deterministic model, whereby substantial differences between the enlargement of individual units may appear.

(2) The method above does not account for differences in the profitability of various products. Reinhardt and Rippin formulated an objective function that takes these into account. They proposed to use the 'Here and Now' design including that objective function. The 'Here and Now' design comprise three steps: (1) optimization of the design and operating variables for the worst possible realization of the uncertain parameters:

$$C_{opt} = \underset{d}{optimize}\left(\underset{\theta}{worst\,value}\, \phi(d,\theta) \right) \tag{7.4-72}$$

where d is the vector of decision variables, θ is the vector of uncertain parameters, and ϕ is the deterministic objective function, (2) optimization of the expected value of the objective function:

$$C_{opt} = \underset{d}{optimize}\left(\underset{\theta}{E}(\phi(d,\theta)) \right) \tag{7.4-73}$$

where E is the expected value of the deterministic objective function, and (3) choice of design and operating variables to maximize the probability that the objective function value exceeds a certain specified level:

$$C_{opt} = \max_{d}\left(\underset{\theta}{P}(\phi(d,\theta) > \phi_0) \right) \tag{7.4-74}$$

Reinhart and Rippin used the expected value of the objective function part with a two stage formulation in which design variables d must be fixed before values of the uncertain parameters are known but operating variables x_0 may be chosen with knowledge of the values of the uncertain parameters:

$$C_{opt} = \underset{d}{optimise}\left\{ \underset{\theta}{E}\left[\underset{x_0}{optimise}\left(\phi(d,\theta)\right)\right]\right\} \tag{7.4-75}$$

The objective function of profitability with the possible expansion at some future date t_e takes the form:

$$\phi = \sum_t \frac{1}{(1+r)^t} \sum_i C_i Q_i - \sum_j m_j \alpha_j V_j^{\beta_j} - \frac{1}{(1+r)^{t_e}} \sum_j m_{ej} \alpha_j V_{e,}^{\beta_j} \tag{7.4-76}$$

where r is the interest rate, and t is the number of years. The expected value is evaluated by the Monte Carlo method.

The problems of uncertainties and flexibility of multiproduct plants were discussed, among others, by Bhatia and Biegler (1997), Fichtner *et al.* (1990), Pistikopoulos *et al.* (1990), Pistikopoulos (1990), Rippin (1983a,b; 1993), Shah and Pantelides (1992), Straub and Grossmann (1992), Lee and Reklaitis (1989), and Wellons and Reklaitis (1989a,b). Readers interested in details of the flexibility and uncertainties are referred to these papers.

Early works on equipment sizing (Loonkar & Robinson, 1970, 1972; Sparrow *et al.*, 1974, 1975; Flatz, 1980) provide a good basis for a near optimal design of batch plants with tools that are simple and enable the understanding of the plant and its operation. Later, several authors proposed extended formulations and methods for solving models (Espuna *et al.*, 1989; Papargeorgaki and Reklaitis, 1990a,b; Espuna *et al.*, 1989; Grossmann and Sargent, 1979; Kiraly *et al.*, 1989; Cerda *et al.*, 1989, 1990; Faquir and Karimi, 1989, 1990; Valsenak *et al.*, 1989; Birewar and Grossmann, 1989b; and many others). In the most recent work, Ravemark and Rippin (1998) accounted for both batch units (operated in- and/or out-of-phase) and semicontinuous units (operated in-phase). Their model enables the search for the optimal location and size of intermediate storage. The objective function consists of purchased costs of units of all three types. The method for solving of the MINLP problem requires less computational effort than in the past. Grossmann (1996, 1995) has reviewed methods for solving MINLP problems. Comprehensive descriptions of the design problem and discussions on the issues that characterize the batch process design problem have been presented in literature (Rippin, 1993 and Reklaitis, 1990).

Design for precisely specified duties of the plant is only rarely realistic in fine chemicals manufacturing. The set of equipment that was found to be optimal at the design stage will become non-optimal already at the start-up of the plant. It is also possible that a set of equipment designed using the procedure for 'non-optimal' sizing is closer to the current optimum than the 'optimum' at the design stage. Therefore, multiproduct plants are usually designed non-optimal, with some overcapacity towards 'the best' set of equipment. Moreover, due to the discrete sizing there will be inherent overcapacities of some equipment items. The marginal overcapacity of the entire plant is also usually planned at the design phase to deal with an unpredictable rise of the demand or to be able to start the manufacture of a new product quickly, possibly after some new equipment items have been installed. The overcapacity mostly concerns utilities and space. Accordingly, in the start-up period the problem of the search for the optimum is usually converted from the minimization of equipment costs into the best utilization of the existing plant.

In general, there is no frequent need to design new batch plants. For all the above listed factors deterministic models for plant design will be of limited significance. Plant retrofitting (replacement of equipment, installation of new equipment, and elimination of old equipment) is more often encountered in the field of batch plants. The uncertainty then is much lower than for the design of new plants.

The 'death' of old products, the 'birth' of new ones, changing demands, and the need to compose the optimal hierarchical production plan with an optimal use of the equipment and the shortest possible total production time make the timing of production more important than plant design. The use of rigorous optimization techniques can be most profitable at production planning and scheduling of existing batch plants, especially multipurpose plants.

7.4.3. Production planning and scheduling

7.4.3.1. Production planning

Production planning includes considerations on production objectives over a certain time horizon given marketing forecasts for prices and product demands, equipment availability, and inventories. This is a *macrolevel* problem of the allocation of production capacity, time, product inventories, and labour and energy resources, so as to determine the production goals that maximize the total profit over an extended period of time into the future (e.g. a few months to a few years).

Studies on production planning were started by Mauderli and Rippin (1979, 1980). Their procedure consists of two stages: (1) the generation of dominant (effective) single- or multi-product campaigns, and (2) the allocation of time to selected campaigns to produce any desired mix of products in the planning period. The procedure starts with an evolutionary enumeration of alternative production strategies. Campaigns are generated accounting for methods that allow the manufacture of batches of different products in the available equipment. Candidates are screened by identifying and rejecting non-dominant (*i.e.* inefficient) strategies to retain only those that produce products or their mixtures at the highest possible rates. Executing the selected dominant campaigns will result in more of any specified product mix than campaigns that do not belong to the dominant set. The second stage maximizes the profitability by allocating the time to the selected dominant campaigns. This procedure has been extended and modified by several authors, and rigorous methods for solving production planning problems have also been developed (Lázaro and Puigjaner, 1985; Musier and Evans, 1991; Papageorgiou and Pantelides, 1993; Wellons and Reklaitis 1991a,b; Shah and Pantelides, 1991; Ku and Karimi, 1988, 1990; Kuriyan and Reklaitis, 1989; and Barrera and Povoa, 1989).

Below, the procedure for the determination of dominant campaigns in a version that was proposed by Lázaro *et al.* (1989) is outlined. Their methodology includes enumeration of feasible production sequences, selection of dominant production lines, task sequencing, and search for an optimum with constraints. All possible production variants are generated by an enumeration procedure that takes into account the possibility of available equipment working in parallel, initial and final task overlapping, and instability of intermediate products. Non-feasible sequences are eliminated so that only favourable candidates are subjected to full evaluation. Dominant production lines are selected by maximizing the criterion:

$$\log P_4 = a_1 \log P_1 + a_2 \log P_2 + a_3 \log P_3 \tag{7.4-77a}$$

where P_1 is given by:

$$P_1 = \frac{\text{processing capacity}}{\text{total processing time}} \tag{7.4-77b}$$

P_2 is defined by:

$$P_2 = \frac{1}{NB_k} \sum_{j=1}^{NB_k} \sum_{n \in EQ_j} \left(R_{ijn} - B_{ijn}\right)^2 \tag{7.4-77c}$$

where NB_k is the number of batches in campaign k, R_{ijn} is the maximum production capacity of product i for a task j in the equipment unit n given by:

$$R_{ijn} = \frac{\text{size of equipment unit } n}{S_{ijn}} \tag{7.4-77d}$$

B_{ijn} is the batch size for product i in stage j and equipment unit n, and EQ_j is a set of feasible equipment units to perform task j. P_3 is expressed by:

$$P_3 = \frac{\text{overall production cost}}{\text{processing capacity}} \tag{7.4-77e}$$

The second parameter, P_2, represents the idleness of the equipment used in the production line to make product i. The values of a_i may be specified by the user according to specific problem characteristics and the objective function used for the determination of dominant lines. Lázaro *et al.* suggested the following default values: $a_1 = 1$, $a_2 = a_3 = -1$.

Birewar and Grossmann (1990a) proposed a model for the simultaneous determination of the best production goals and the best allocation of tasks to the equipment units. They incorporated inventory costs into the objective function. To keep commitments that have been made at the stage of production planning, a penalty (PN_{it}) was incurred in the objective function for not meeting the commitments for product i in interval t as a linear function in terms of the shortfalls (SF_{it}):

$$PN_{it} = SF_{it}\,\Omega_{it} \tag{7.4-77f}$$

where Ω_{it} is some cost with the meaning of penalty factor.

In recent works of Papageorgiou and Pantelides (1996a,b) the problem of scheduling has been treated most extensively. Many general features of batch processing such as material recycles, shared intermediates, mixed storage policies, limited resources, and flexibility of operation of parallel units have been taken into account. The possible campaign structure is determined by taking into account all relevant factors such as the availability of sufficient storage capacity to store large amounts of intermediates produced in one campaign for consumption in later ones, the cost of holding inventories, the product demand and raw materials availability patterns, and the relative durations and costs of cleaning equipment due to campaign and intercampaign plant reconfigurations. The problem was formulated as an MINPL.

7.4.3.2. Scheduling

Scheduling is a *microlevel* problem that is embedded in the problem of production planning. It is considered to be a short-term problem (e.g. a few weeks). In scheduling, the sequences in which various products should be processed in each piece of equipment to meet the production targets as defined at the production planning are decided upon. The most efficient utilization of the available equipment to manufacture the planned products is the main objective of scheduling. Scheduling is the last stage in the procedure for determination of the best production plan and allocation of tasks to existing equipment.

There are two main procedures for the best scheduling. (1) a batch sequence is scheduled to match as closely as possible cumulative demand curves expressing due dates for product requirements, while satisfying additional constraints such as operational preferences, product priorities, availability of raw materials and utilities, etc. (Egli and Rippin, 1986). (2) Another explicit use of the cumulative production curve is described by Yamasaki *et al.* (1988). Other procedures that are at least partly heuristic were applied for solving large-scale practical problems (e.g. Kudva *et al.*, 1991; Hasebe *et al.*, 1991; and Lazaro *et al.*, 1989). Heuristic methods can, however, lead to suboptimal solutions. Exact integer programming algorithms have been developed for more restricted problems, and the range of problems that can be solved in this way is increasing steadily. Ku and Karimi (1988, 1990), Birewar and Grossmann (1989b, 1990a), Kondili *et al.* (1988), Tsirukis *et al.* (1993), and Zentner *et al.* (1994) formulated and solved various problems of scheduling using methods of mathematical programming.

The scheduling problem is to determine the order in which tasks will use equipment and resources, and the detailed timing of the execution of all tasks so as to meet requirements. Below, scheduling methods for optimal plant performance for typical options (*UIS* and *ZW* policies for intermediate storage, zero and non-zero cleaning times) in mixed-product campaigns are presented. The case of single-product campaigns is trivial.

The sequencing is not known *a priori*. The Gantt charts in Fig. 7.4-13 illustrate the essence of sequencing.

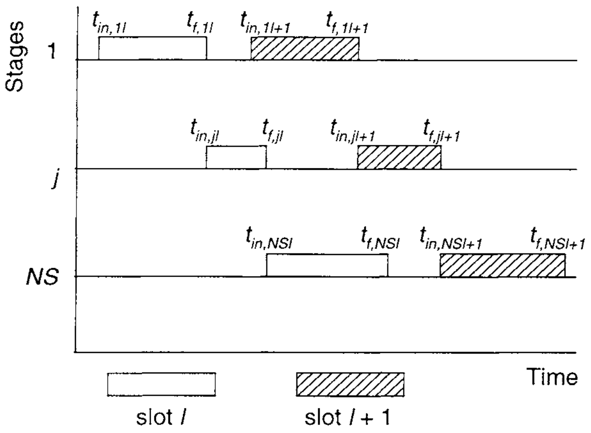

Figure 7.4-13. Start and completion times for production of slots l and l+1.

Before sequencing is started slots representing stages (equipment units) with no tasks assigned yet are empty. Production slots l and $l+1$ start at yet undefined times $t_{in,jl}$ and $t_{in,jl+1}$, and tasks in these slots finish at times $t_{f,jl}$ and $t_{f,jl+1}$, respectively. In sequencing, every slot must be assigned exactly to one batch i and *vice versa*. This is denoted by the binary variable Y_{il}, where a value of one implies that batch i is assigned to production slot l. Accordingly,

$$\sum_{i=1}^{NB_s} Y_{il} = 1 \qquad l = 1, \ldots, NB_s \tag{7.4-78}$$

$$\sum_{l=1}^{NB_s} Y_{il} = 1 \qquad i = 1, \ldots, NB_s \tag{7.4-79}$$

where NB_s is the number of batches in a sequence. For fixed processing times t_{ij} of batch i in stage j, the times of starting and finishing processing are related in terms of assignment variables Y_{ij} by the equation:

$$t_{f,jl} = t_{in,jl} + \sum_{i=1}^{NB_s} Y_{il}\, t_{ij} \tag{7.4-80}$$

where

$$t_{in,1l} = 0 \tag{7.4-81}$$

It is clear that the task in slot $l+1$ at every stage j may only be started after the task in slot l at this stage is finished, *i.e.*

$$t_{f,jl} \le t_{in,jl+1} \qquad for \quad l = 1, \ldots, NB_s - 1; \quad j = 1, \ldots, N_S \tag{7.4-82}$$

Clearly, slacks SL_j ($t_{f,jl} \le SL_j \le t_{in,jl+1}$) between slots should be minimized to decrease cycle times, and, consequently, to increase the plant throughput.

The *UIS* (unlimited intermediate storage) policy is characterized by the existence of at least one stage j that is permanently occupied (no idle times = *bottleneck*). This applies to both processing only (zero cleaning times) and processing followed by subsequent cleaning. For zero cleaning times, the cycle time for a sequence $t_{c,s}$ is the longest cycle time of all stages j and thus is given by:

$$t_{c,s,UIS} = \max_j t_{c,j,UIS} = \max_j \sum_{i=1}^{NB_s} t_{ij} \tag{7.4-83}$$

The cycle time for the sequence, $t_{c,s,UIS}$, should be minimized to find the optimal sequence of batches for the *UIS* policy. The form of the objective function implies that the optimization of a schedule for *UIS* with minimum cycle time simply reduces to selecting *any* sequence of batches with slack times of bottleneck stage(s) set to zero.

For the *ZW* (zero wait) policy idle times (slacks) between consecutively produced batches may appear in all stages including the one that defines the bottleneck. It should be noted that the slacks are only a function of consecutive pairs of batches. Therefore, the slacks for each pair of batches can easily be calculated *a priori* with the binary variable for any two consecutive batches:

$$YC_{ik} = \begin{Bmatrix} 1 \text{ if batch } i \text{ is followed by batch } k \\ 0 \text{ otherwise} \end{Bmatrix} \quad i \neq k \tag{7.4-84}$$

Since every batch is manufactured only once in each cycle, it will appear exactly once in the first position and exactly once in the second position in the pairs <*i*,*k*> of batches that are produced during a production cycle. Therefore, the following two assignment constraints must apply:

$$\sum_{i=1}^{NB_s} YC_{ik} = 1 \quad k = 1, \ldots, NB_s \tag{7.4-85}$$

$$\sum_{k=1}^{NB_s} YC_{ik} = 1 \quad i = 1, \ldots, NB_s \tag{7.4-86}$$

The cycle time of any stage j is composed of the batch processing times for all products manufactured in that stage and the slacks between consecutive batches:

$$t_{c,j,ZW} = \left(\sum_{i=1}^{NB_s} t_{ij} + \sum_{i=1}^{NB_s} \sum_{k=1}^{NB_s} YC_{ik} SL_{ikj} \right) \tag{7.4-87}$$

where SL_{ikj} is the slack in stage j between batches (slots) i and k that are produced successively in that order. The cycle time for the sequence, $t_{c,j,ZW}$ should be minimized to find the optimal sequence of batches for the *ZW* policy.

Cleaning times are easily accounted for in both policies. The method of search for the shortest cycle time does not change in the case of the *ZW* policy if non-zero cleaning times are considered. The slacks can also be easily calculated *a priori* with non-zero cleaning times. In case of the *UIS* policy, cleaning times must simply be added to the processing times:

$$t_{c,j,UIS} = \max_j t_{c,j,UIS} = \max_j \left\{ \sum_{i=1}^{NB_s} \left(t_{ij} + \sum_{k=1}^{NB_s} Y_{ik} CL_{ikj} \right) \right\} \tag{7.4-88}$$

where CL_{ikj} is the cleaning time in stage j between batches (slots) i and k that are produced successively in that order.

Below, a simple algorithm for determining the slacks between every pair of batches for product i and product k with cleaning times is presented.

1. Set start times for batch k (produced after batch i) with the assumption that the bottleneck is in stage 1 (the method can be easily adopted in case the bottleneck is in another stage):

$$\begin{gathered} t_1^0 = t_{i1} + SL_{ik1} \\ t_j^0 = t_{j-1}^0 + t_{kj-1} \quad j = 2, \ldots, NB_s \end{gathered} \tag{7.4-89}$$

2. Calculate slacks d_j corresponding to the assumption of step 1:

$$d_j = t_j^0 - \sum_{l=1} t_{il} - SL_{ikj} \quad j = 1, \ldots, NB_s \tag{7.4-90}$$

and the smallest corresponding value δ:

$$\delta = \min_j d_j \tag{7.4-91}$$

3. Calculate actual slacks SL_{ikj} from:

$$SL_{ikj} = d_j - \delta \tag{7.4-92}$$

Birewar and Grossmann (1990b) incorporated scheduling into the design of multiproduct batch plants. The first step of their procedure consists of systematic generation of candidates for merging processing stages. By considering the potential assignment of units to tasks, the problem is then formulated as an MINLP in which the following major options are considered: (1) scheduling with single-product campaigns (*ZW* policy) and possibility of parallel equipment, (2) scheduling with mixed-product campaigns (*ZW* policy) and one piece of equipment per unit, and (3) scheduling with mixed-product campaigns (*UIS* policy) and possibility of parallel equipment units. Significant economic savings can be reached using the proposed models in the design of multiproduct batch plants if the demand pattern does not change during plant construction. Combination of scheduling and design of batch plants, however, is of limited practical meaning. This is because the market situation at start-up is usually entirely different from that at the design stage.

Comprehensive descriptions of the problems of production planning and scheduling have been presented by Reklaitis (1982, 1992), Reklaitis *et al.* (1997), Ku *et al.* (1987), and Musier and Evans (1990). Readers who are interested in the subject of Sections 7.4.1-7.4.3 are referred to review papers and books of Applequist *et al.* (1997), Biegler *et al.* (1995), Mah (1992), Rippin (1983a,b, 1993), Reklaitis (1990, 1993), and Reklaitis *et al.* (1997). No single comprehensive program covering all structural alternatives for the design and scheduling of batch plants exists at present. A few industrial companies have reported the development of batch planning and scheduling tools, e.g. ICI's BatchMASTER for design, debottlenecking, and scheduling (Cherry *et al.*, 1985, Cherry, 1989), BPSM (Batch Production Scheduling Model) developed by Rohm and Haas (Musier and Evans, 1990), and Simscript II.5 by DuPont (White, 1987). Academic institutions have advanced methods for optimal design and scheduling of batch plants. Among these are the following process modelling systems, starting with MULTI-BATCH of historical significance, developed in ETH, Zürich (Sparrow *et al.*, 1974), gPROMS (Barton and Panteildes, 1991), SRSBP for short-term scheduling (Egli and Rippin, 1986) and its predecessor BATCHEM for scheduling (Mauderli and Rippin, 1980), UNIBATCH (Czulek, 1988), BOSS (Joglekar and Reklaitis, 1984), and BATCHES (Joglekar *et al.*, 1987). Mah (1992) in his book has included a computer program in FORTRAN for optimal permutation schedules. The RCSPec language has been proposed for expressing process scheduling problems and a scheme for parsing and translating the language to a mathematical programming formulation has been described (Zentner *et al.*, 1992, 1995). It should be noted that programs as well as long-term third-party support in computer-aided design and scheduling of batch plants may be prohibitively expensive for many firms.

Example 7.4-7. Scheduling of a six-product batch plant (after Birewar and Grossmann, 1989a)

Find the best schedule for the manufacture of six products *A*, *B*, *C*, *D*, *E*, and *F* ($N_P = 6$) that are to be produced in four stages ($NS = 4$) in five cycles ($NC = 5$) each involving two batches of *A*, *B*, *C*, and *D*, and one batch of *E* and *F*, *i.e.* ten batches ($NB_s = 10$). Processing times are given in Table 7.4-19. Consider cleaning times of zero, three, and five hours between subsequent products, and no cleaning if the same product is manufactured in the subsequent batch.

Table 7.4-19
Processing times (h)

	A	*B*	*C*	*D*	*E*	*F*
Stage 1	10	15	20	14	6	13
Stage 2	20	8	7	6	11	7
Stage 3	5	12	9	15	5	17
Stage 4	30	10	5	10	15	10

Optimal schedules are given in Table 7.4-20. Clearly, for cleaning times of five hours, single-product campaigns are the best solution of the scheduling problem, while for zero cleaning times (theoretical case) mixed-product campaigns would be best.

Table 7.4-20
Optimal schedules

Scheduling policy	Optimal schedule	Makespan, h
Zero cleaning time		
ZW policy	(*E-DD-BB-AA-F-CC*)-(*E-DD-BB-AA-F-CC*)-(*E-DD-BB-AA-F-CC*)-(*E-DD-BB-AA-F-CC*)(*E-DD-BB-AA-F-CC*)	485
UIS policy	(*E-AA-BB-F-DD-CC*)-(*E-AA-BB-F-DD-CC*)-(*E-AA-BB-F-DD-CC*)-(*E-AA-BB-F-DD-CC*)-(*E-AA-BB-F-DD-CC*)-	400
Cleaning time of 3 h		
ZW policy	(*F-CC-E*)-(*F-CC-E*)-(*F-CC-E*)-(*F-CC-E*)-(*F-CC-E*)-(*DD-DD-DD-DD-DD*)-(*BB-BB-BB-BB-BB*)-(*AA-AA-AA-AA-AA*)	551
UIS policy	(*E-E-E-E-E*)-(*AA-AA-AA-AA-AA*)-(*BB-BB-BB-BB-BB*)-(*F-F-F-F-F*)-(*DD-DD-DD-DD-DD*)-(*CC-CC-CC-CC-CC*)	418
Cleaning time of 5 h		
ZW policy	(*E-E-E-E-E*)-(*DD-DD-DD-DD-DD*)-(*BB-BB-BB-BB-BB*)-(*AA-AA-AA-AA-AA*)-(*F-F-F-F-F*)-(*CC-CC-CC-CC-CC*)	585 or more
UIS policy	(*E-E-E-E-E*)-(*AA-AA-AA-AA-AA*)-(*BB-BB-BB-BB-BB*)-(*F-F-F-F-F*)-(*DD-DD-DD-DD-DD*)-(*CC-CC-CC-CC-CC*)	430 or more

Pioneering academic institutions have contributed very much to the development of methods and programs on design and scheduling. It seems to be worthwhile to mention the teams that published a significant proportion of papers on this subject. Among them are teams of Imperial College (London), ETH (Zürich), Purdue University (West Lafayette, Indiana), Northwestern University (Evanston, Illinois), MIT (Cambridge, USA), and Carnegie-Mellon University, with pioneers and distinguishing scientists L.B. Evans, I. Grossman, S. Macchietto, R.S.H. Mah, D.W.T. Rippin, G.V. Reklaitis, and R.W.H Sargent.

7.5. PRINCIPLES OF GOOD MANUFACTURING PRACTICE[2]

In the manufacture of some dangerous, toxic, or potent materials, especially biologically active materials like pesticides, nutrients, and cosmetics or medicinal products for human and veterinary use, overall control is essential to ensure that the client always receives products of high quality. European Commission Directives (*The Rules Governing Medicinal Products in the European Union*, 1997) lay down the principles and guidelines of good manufacturing practices for medicinal products. The directives require that "the manufacturer shall establish and implement an effective pharmaceutical quality assurance system, involving the active participation of the management and personnel of the different services involved".

Supervising the quality of medicinal products relies on two main aspects (*Good Manufacturing Practice and certification of starting materials for the industrial manufacture of medicinal products*, 1995), *viz.* quality of design and quality of conformity with that design. Quality of design is assessed by the competent licensing authorities. Quality of conformity relies mainly on the quality of manufacture to ensure consistency of production and operate an effective quality assurance system. According to *The Rules Governing Medicinal Products in the European Union* (1997), good manufacturing practice "is that part of the quality assurance system, which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use ..." and "... is concerned with both production and quality control".

Medicinal products and bulk pharmaceutical chemicals are produced mainly in batch processes. Controlling these products and chemicals at the end of their manufacturing processes is not in line with the general principle of quality assurance, which is that quality should be built into the product. It is then necessary to ensure that appropriate good manufacturing practices are adhered to throughout the manufacture of both bulk pharmaceutical chemicals (active ingredients as well as excipients) and medicinal products.

Three types of batch control should be performed (*Instrument Society of America*, 1995), *viz.* basic, procedural, and co-ordination. Basic control includes interlocking, monitoring, exception handling, and repetitive discrete or sequential control. Procedural control assures the manufacturing equipment to carry out the process by defining the operating procedures to be followed. Co-ordination control includes assigning equipment, materials and personnel to a batch, and selecting procedural control elements to be executed.

Good Manufacturing Practice (GMP) is covered in several reports, such as The Rules Governing Medicinal Products in the European Union (1997), Current Good Manufacturing Practice for Finished Pharmaceuticals (1995), PIC Guide to Good Manufacturing Practice for Pharmaceutical Products (1992), Good Manufacturing Practice for Pharmaceutical Products (1992), Good Automated Manufacturing Practice 3 (1998), Good Manufacturing Practice for

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[2] This section was written by M. Woźniak.

Active Ingredient Manufacturers (1996), and Pharmaceutical Engineering Guides for New Facilities, Vol. 1 (1996). According to pharmaceutical good manufacturing practices, batch control should include control of personnel (training, health examination, hygienic practices, protective clothing); control of premises (lay-out, working space, interior finishing, lighting, heating, ventilation, sanitation, maintenance, qualification); control of utilities, such as process water, purified water, water for injection, process steam, pure steam, and compressed air systems (design and construction, installation, maintenance, sanitation, qualification and/or validation, monitoring); control of equipment (design and construction, exchangeable tooling, material of critical surfaces, location, maintenance, cleaning and disinfection, calibration, qualification); control of starting and packaging materials (auditing of suppliers, receiving control, sampling, labelling, storage in quarantine, testing, release from quarantine, issue for the manufacture in accordance with FI-FO (First-In-First-Out) principles, reconciliation, traceability); control of storage conditions of materials and products (temperature, humidity, light); control of environment in production areas (temperature, humidity, overpressure, air changes, air flow patterns, particular and microbiological contamination, noise level, ionizing radiation); control of manufacturing operations (supervision by competent people, standard operating procedures, monitoring of critical parameters, prevention of cross-contamination and mix-ups, practical yields, data records, traceability, assessment of deviations from specified requirements, change control); and quality control of intermediates and products (sampling, testing, assessment against approved specifications, release from quarantine or rejecting).

Sterile products, either finished dosage forms or bulk pharmaceutical chemicals, should be manufactured in clean areas of an appropriate airborne particulate cleanliness grade. The clean areas should be maintained to a required cleanliness standard and supplied with air that has passed filters of high efficiency. The requirements for these areas depend on the nature of the operations carried out. The highest cleanliness grade is required for aseptically conducted manufacturing operations. The utilization of isolator technology is recommended for these operations to minimize human interventions in processing areas, and thus decrease the risk of microbiological contamination.

One of the basic requirements of good manufacturing practice is that critical steps of manufacturing processes and significant changes to the processes are validated. In the European GMP guidelines (*The Rules Governing Medicinal Products in the European Union*, 1997) validation is defined as "the action of proving, in accordance with principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results". In practice, "to validate the process" means to establish documented evidence that a specific process will consistently produce a product meeting its predetermined specification, at any conditions within experimentally confirmed operating limits.

The manufacturer of medicinal products and bulk pharmaceutical chemicals is obliged to establish and follow the Validation Master Plan (Berg *et al.*, 1996) that comprises all aspects of validation activities. Process validation should at least include establishment of specifications and performance characteristics; qualification of analytical equipment and validation of analytical methods; testing of the final product to ensure that it meets specifications; qualification and validation of the processing facility and equipment, including validation of computerized systems; validation of cleaning procedures; validation of processing and packaging operations (at least three consecutive batches); auditing, monitoring, sampling, or challenging of the main steps in the process for conformity with intermediates and product specifications; and periodical revalidation and validation of any significant change in either the product or the manufacturing process.

Process validation can be done in different ways, *viz.* prospectively, by carrying out a planned program of experiments, before routine production is started; concurrently, during routine production; retrospectively, by statistical analysis of historical data; and during scale-up studies (developmental validation).

To achieve regulatory compliance during the design, construction, commissioning, and validation of new facilities one can use ISPE (formerly International Society of Pharmaceutical Engineers, now The Leading Global Society for Selfcare Technology) guides (*Pharmaceutical Engineering Guides for New Facilities*, Vol. 2, 1998; *Guide to Inspections of Bulk Pharmaceutical Chemicals*, 1991). These guides are prepared by pharmaceutical engineers and are intended to offer a consistent interpretation of GMP requirements. The successively issued guides will cover bulk active, bulk intermediate, and bulk excipient facilities, as well as different dosage form facilities. The key concepts used as a basis for guidance are to properly select and define critical process steps and critical process parameters, adequately evaluate product exposure and required level of protection, properly select and manage critical instruments and systems, apply good engineering practice, properly define the required extent of validation, prepare and maintain enhanced documentation. The latter includes specifications for starting and packaging materials, intermediates, bulk products, and finished products; manufacturing formulae, processing and packaging instructions; batch processing and packaging records; standard operating procedures and the associated records of actions taken; and validation plans, protocols, and reports.

Obviously, GMP requirements, especially extensive personnel training, calibration, qualification and validation, enhanced documentation, extensive cleaning and sanitation, and sharpened in-process control must considerably influence process organization and output. All these GMP-related activities are costly and time consuming, and will result in decreased productivity and increased production costs. On the other hand, a quality assurance system contributes to consistent production with a lower number of rejected batches and complaints.

In any case, one must consider the following limitations resulting from GMP requirements:

- time for personnel training (typically 2 - 8 hours per month),
- enhanced costs of investment (for cloakrooms, cleanrooms, testing and calibrating laboratories, HVAC (Heating, Ventilation, and Air Conditioning) systems, CIP (Cleaning-In-Place) systems, etc.),
- time for commissioning, qualification, and validation of a new facility with its equipment (typically several months),
- time for extensive cleaning and sanitation of equipment and premises,
- enhanced operational costs resulting from sharpened quality and in-process controls.

It must be pointed out that GMP guides are not intended to cover health security aspects for the personnel engaged in manufacturing. They may be very important in the manufacture of certain bulk pharmaceutical chemicals or medicinal products, such as cytostatics, antibiotics, or other highly active, biological and radioactive products, but they are governed by other provisions of law.

Acronyms

AGV	Automated Guided Vehicles
CP	Purchased equipment Cost
DIN	Deutsches Institut für Normierung
DSV	Standard size of equipment unit
ETH	Eindgenossische Technische Universität (Zürich)
FDA	US Food and Drug Administration
FI-FO	First-In-First-Out policy
FIS	Finite Intermediate Storage
cGMP	current Good Manufacturing Practice
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
HVAC	Heating, Ventillation, and Air Conditioning
CIP	Cleaning-In-Place
ISBL	Inside Battery Limits
ISPE	International Society of Pharmaceutical Engineers
MILP	Mixed Integer Linear Programming
MINLP	Mixed Integer Non Linear Programming
MPP	Multi Product Plant or Multi Purpose Plant
NLP	Non Linear Problem
NIS	No Intermediate Storage
NW	No-Wait policy for storage
OSBL	Outside Battery Limits
THF	tetrahydrofuran
UIS	Unlimited Intermediate Storage
ZW	Zero-Wait policy for storage

Symbols

A_r	- heat exchange surface area in a reactor	m^2
B_i	- batch size of product i	kg
B_D	- downstream batch size	kg
B_H	- batch size of hypothetical product	kg
B_U	- upstream batch size	kg
B_{imegk}	- batch size of product i in campaign k which is manufactured in unit type e and in equipment group g during the execution of task m	dimensionless
c_p	- specific heat	$kJ\ kg^{-1}\ K^{-1}$
C	- capital cost of plant	\$
C_F	- fixed portion of plant cost	\$
C_i	- selling price of product i	\$/kg
C_p	- purchased cost of equipment	\$
C_{opt}	- optimal production costs	\$
C_V	- variable portion of plant cost	\$
COP_{ime}	- operating costs per unit of product i that is manufactured	

	in equipment type *e* (includes costs such as cost of energy consumed, labour cost, and maintenance cost)	\$/kg
d	- vector of decision variables	
D_{ik}	- duty factor of equipment unit *k* for product *i*	$kg_{mixture,ik}/kg_{product,i}$
DSV_j	- standard size of equipment unit *j*	m^3
$E(\phi)$	- expected value of the deterministic objective function ϕ	
EQ_{im}	- set of feasible equipment types for task *m* of product *i*	dimensionless
EQ_j	- set of feasible equipment types for stage/task *j*	dimensionless
F	- function to be optimised, objective function	
F_i	- size conversion factor for product *i*	dimensionless
$F_D(t)$	- output rate of intermediate storage tank	$m^3 h^{-1}$
$F_U(t)$	- input rate of intermediate storage tank	$m^3 h^{-1}$
H	- time horizon (time available for manufacturing of all products)	h
$H(t)$	- hold-up	m^3
HR	- required storage capacity	m^3
H_i	- time available for manufacturing of product *i*	h
H_{max}	- maximum hold-up	m^3
H_{min}	- minimum hold-up	m^3
I	- cost index	dimensionless
m_j	- number of batch units *j* of the same size	dimensionless
m_k	- number of semi-continuous units *k* of the same size	dimensionless
MB	- number of batch units	dimensionless
MEQ	- number of equipment types	dimensionless
MEQ_e	- number of units of equipment type *e*	dimensionless
$MEQS_j$	- number of discrete sizes of equipment unit *j*	dimensionless
MG_{imk}	- number of equipment groups assigned to task *m* for product *i* in campaign *k*	dimensionless
MS	- number of semi-continuous units	dimensionless
MST	- number of subtrains that couple semi-continuous units	dimensionless
MU_{imegk}	- number of units of type *e* that are contained in equipment group *g* which is assigned to task *m* of product *i* in campaign *k*	dimensionless
n	- factor of increase of equipment/plant cost	dimensionless
NB	- number of batches	dimensionless
NB_{ik}	- total number of batches of product *i* manufactured in campaign *k*	dimensionless
NB_{imgk}	- number of batches of product *i* that are being processed by equipment group *g* in stage *m* and in campaign *k*	dimensionless
NB_{wi}	- number of batches of product *i* manufactured per week	dimensionless
NC	- number of campaigns	dimensionless
NP	- number of products	dimensionless
NS	- number of stages	dimensionless
N_c	- number of cycles	dimensionless
N_w	- number of weeks available for production per year	week/year
p_i	- penalty factors	

P_i	- production demand for product i	kg
$P(t_P>H)$	- probability of exceeding the available time (not meeting the demand)	dimensionless
PN	- penalty function	
Q	- production capacity	kg
Q_i	- production (capacity) of product i	kg
Q_{ij}	- production in process i in stage j per unit time	kg
Q_{ime}	- amount of product i manufactured in equipment type e during the execution of task m	kg
Q_{ik}	- amount of product i that is manufactured in campaign k	kg
r	- interest rate	
R_{ijn}	- maximum production capacity of product i for a task j in the equipment unit n	kg/h
R_k	- processing rate of semi-continuous equipment unit k	kg/h
S_{ij}	- size factor of equipment unit j for product i	$m^3/kg_{product}$
S_{ime}	- size factor of task m of product i in equipment type e	dimensionless
S_{Hj}	- size factor of equipment unit j for hypothetical product	$m^3/kg_{product}$
SL	- duration of slack	h
t	- time	h
$t^{(0)}$	- coefficient in Eqn. (7.4-5)	h
t_c	- cycle time	h
t_{ch}	- changeover time	h
t_{cl}	- cleaning time	h
t_{dosing}	- time of dosing	h
t_e	- time of plant expansion	h
t_{idle}	- idle time	h
t_{ij}	- processing time in stage j for product i	h
t_k	- time of campaign	weeks
t_L	- limiting cycle time	h
t_{LD}	- downstream limiting cycle time	h
t_{LU}	- upstream limiting cycle time	h
t_{opt}	- optimal time	h
t_P	- makespan, time for total production	h
t_{Ri}	- residence time of product i	h
t_{wi}	- time available for product i per week	h
T_0	- temperature at $t = 0$	K
T_{end}	- end temperature	K
T_f	- final temperature	K
T_{in}	- initial temperature	K
T_j	- temperature in jacket	K
T_{set}	- set (predetermined) temperature	K
TA_i	- set of tasks for product i	dimensionless
U	- overall heat-transfer coefficient	$W\ m^{-2}\ K^{-1}$
U_e	- set of tasks that can be executed by equipment type e	dimensionless
V	- volume	m^3

V_e	- size of units of equipment type *e*	m^3
V_j	- size/volume of equipment unit *j*	m^3 (or m^2)
V_r	- reactor volume	m^3
x_o	- vector of operating variables	
X_{ik}	- binary variable, product produced in campaign *k* yes or no	dimensionless
z_{jk}	- binary variable for selection of equipment size	dimensionless

Greek symbols

α	- coefficient in Eqn. (7.4-5)	h
α	- cost coefficient, Eqn. (7.3-4)	$\$/\mathrm{m}^3$
β	- coefficient in Eqn. (7.4-5)	dimensionless
β	- cost coefficient, Eqn. (7.3-4)	dimensionless
ε	- degree of filling	dimensionless
θ	- vector of uncertain parameters	
θ_{ik}	- processing time in semi-continuous unit *k* for product *i*	h
θ_T	- processing time in subtrain of semi-continuous units	h
λ	- weighing factor	
ν	- specific volume	$\mathrm{m}^3\ \mathrm{kg}^{-1}$
ρ	- density	$\mathrm{kg}\ \mathrm{m}^{-3}$
ϕ	- deterministic objective function	
ω	- time delay	h

Subscripts

B	- batch
e	- equipment type *e*
g	- equipment group *g*
i	- product *i*
j	- stage, equipment unit *j*
k	- campaign *k*
m	- task *m*
min	- minimum
opt	- optimal
ref	- reference
S	- semi-continuous
ST	- subtrain

Superscripts

max	- maximum
L	- lower value
U	- upper value

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Appendix A. Identification of stoichiometric expression

A1. 'Nancy algorithm' (the method of Filippi *et al.* (1986))

The basic expression used in the procedure for identification of stoichiometry is the one defining reaction extents, *i.e.*

$$D_{jk} = \sum_{i=1}^{N_r} \nu_{ij}\xi_{ik} \qquad \text{for } j = 1,2,\ldots,N_c \qquad \text{and } k = 1,2,\ldots,N_e \tag{A-1}$$

where N_r is the number of reactions, N_c the number of components, and N_e the number of experiments. Extents of reaction ξ_{ik} can be expressed in mole fractions, and D_{jk} is defined as:

$$D_{jk} = x_{jk} - x_{jk,0} \tag{A-2}$$

where x_{jk} and $x_{jk,0}$ are dimensionless mole fractions in the final and initial reaction mixture, respectively. Concentrations of major components *c* are measured in N_e experiments, so the mole fractions can be calculated for all the runs. The unknown variables in Eqn. (A-1) are:

a) the stoichiometric coefficients ν_{ij} of component *j* in reaction *i*, and
b) the extents of reaction, ξ_{ik} of reaction *i* in experiment *k*.

When starting the algorithm, it is assumed that there occurs only one reaction ($N_r = 1$). The corresponding stoichiometric coefficients are determined by minimizing the following error function:

$$E(1) = \sum_{k=1}^{N_e}\sum_{j=1}^{N_c}\left(D_{jk} - \nu_{1j}\xi_{1k}\right)^2 \tag{A-3}$$

Minimization is performed on real numbers and results in stoichiometric coefficients which may not be integers or their simple fractions. Hence the calculated coefficients are rounded and the error $E(1)$ recalculated. If the error is larger than a given desired value an additional reaction is introduced in the model and the stoichiometric coefficients for this reaction are estimated by minimization of the error function $E(2)$ similar to Eqn. (A-3). Estimations are iterated until the error functions for all reactions $E(i)$ satisfy a given condition. The estimates of the stoichiometric coefficients of the previous reaction(s) are not allowed to change when estimating coefficients for the next reaction. In the case of one reaction ($N_r = 1$) the sign of the average value of the variable D_{jk} over all experiments gives an indication of the overall behaviour of species *j*. If such average value is negative (positive), then this component is consumed (produced) and its stoichiometric coefficient is initialized in the first reaction as equal to -1 (+1). If more reactions are considered ($N_r > 1$), the following average value is calculated:

$$M_j = \frac{1}{N_e}\sum_{k=1}^{N_e}\left(D_{jk} - \sum_{i=1}^{N_r-1}\nu_{ij}\xi_{ik}\right) \tag{A-4}$$

The sign of M_j indicates whether component j should be considered as a reactant ($M_j < 0$) or as a product ($M_j > 0$) in the next reaction. If M_j is small for a given component, this indicates that the already established reactions in the network have accurately accounted for concentration changes of this component in the runs considered. Consequently, this component will be bared from being involved in any of the following reactions to be identified, forcing its stoichiometric coefficients to be equal to zero in the additional reactions. This species is called a masked one. The following indices are estimated to distinguish which component of the reaction mixture should be frozen for the next iteration:

$$E_1(j) = \frac{1}{N_e} \sum_{k=1}^{N_e} \left(D_{jk} - \sum_{i=1}^{N_r} \nu_{ij}^{pi} \xi_{ik}^{pi} \right)^2 \qquad \textbf{(A-5)}$$

$$E_2(j) = \frac{1}{N_e} \sum_{k=1}^{N_e} w(j) \left(D_{jk} - \sum_{i=1}^{N_r} \nu_{ij}^{pi} \xi_{ik}^{pi} \right)^2 \qquad \textbf{(A-6)}$$

$$E_3 = N_e \sum_{j=1}^{N_c} E_1(j) \qquad \textbf{(A-7)}$$

$$E_4 = \frac{\sum_{j=1}^{N_c} E_2(j)}{\sum_{j=1}^{N_c} w(j)} \qquad \textbf{(A-8)}$$

where ν_{ij}^{pi} and ξ_{ik}^{pi} are the values obtained from the previous iteration whereby the stoichiometric coefficients are rounded. If a component is masked, $w(j) = 1$, otherwise:

$$w(j) = abs\left(1 - \frac{\nu_{ij}^{pi}}{\nu_{ij}} \right) \cdot abs\left(\nu_{ij} - \nu_{ij}^{pi} \right) \qquad \textbf{(A-9)}$$

(a) If $E_2(j)$ is smaller than a given value of precision in the k-th iteration, then $\nu_{kj} = 0$ and the j-th component is masked. (b) If for all the unmasked components the stoichiometric coefficients are of the same positive (negative) sign, masking of the components with the largest possible value of $E_2(j)$ among those with negative (positive) values of $E_1(j)$ will be suppressed and $\nu_{ij} = -1$ (+1). (c) If the calculated stoichiometric coefficients have different signs but the largest among the negative is an order of magnitude larger or smaller than the largest among the positive, then masking of one component is suppressed as shown in (b). (d) If the number of all masked components is N_c - 1 then all masks are suppressed. The details of the algorithm can be found in the paper by Filippi *et al.* (1986).

Example A.1. Identification of the stoichiometry in a three-reaction network (after Filippi et al. (1989))
A process proceeds according to the following reaction scheme

$$\begin{aligned} A_1 + 2A_2 &\rightarrow A_3 + A_4 \\ A_1 + A_4 &\rightarrow A_5 \\ 2A_3 &\rightarrow A_6 \end{aligned} \qquad \textbf{(A-10)}$$

Based on the above scheme and data concerning rates of individual reactions, fictitious experimental results for a batch reactor were generated in the form of initial and final concentrations for all components of the reaction mixture (see Table A-1). Identify the stoichiometry based on these data. The desired precision for E_3 is 10^{-3}.

Table A-1
Temperature and initial and final concentrations of simulated data for seven different batch runs

		Concentrations (mol litre^{-1})							
		Initial		Final					
Run	T(K)	A_1	A_2	A_1	A_2	A_3	A_4	A_5	A_6
1	300	1.000	2.000	0.141	0.351	0.657	0.795	0.032	0.083
2	300	1.000	1.000	0.504	0.102	0.386	0.400	0.048	0.032
3	300	1.000	3.000	0.018	1.080	0.644	0.940	0.021	0.158
4	300	0.500	1.000	0.099	0.221	0.345	0.380	0.011	0.022
5	320	1.000	2.000	0.174	0.594	0.378	0.522	0.120	0.162
6	340	1.000	2.000	0.189	0.846	0.225	0.345	0.231	0.176
7	280	1.000	2.000	0.188	0.402	0.741	0.780	0.016	0.027

SOLUTION. Taking into account the limited number of experiments and the relatively large number of components of the reaction mixture, the maximum number of reactions is three ($N_r = 3$). Assuming one reaction occurring only, the following stoichiometric coefficients were computed using Eqn. (A-3):

$$(-0.987, -1.812, 0.685, 0.816, 0.080, 0.110)$$

for A_1, A_2, ... A_6. These coefficients were approximated making the stoichiometric coefficients simple integers as follows:

$$\nu_{1j} = (-1, -2, 1, 1, 0, 0)$$

The desired precision with respect to E_3 was not reached. On the other hand, $E_2(1)$, $E_2(2)$, $E_2(4)$, and $E_2(5)$ were less than E_4 and hence A_1, A_2, A_4, and A_5 were masked for the next iteration. The minimization for the second reaction resulted in the following fractional stoichiometric coefficients:

$$(0, 0, -0.764, 0, 0, 0.382)$$

and the following approximations of these results were made:

$$\nu_{2j} = (0, 0, -1, 0, 0, 0.5)$$

The stoichiometric model precision was not attained yet. For the next iteration A_2, A_3, and A_6 were masked because $E_2(2)$, $E_2(3)$, and $E_2(6)$ were less than E_4. In the third iteration the following stoichiometric coefficients were estimated:

$$(-0.557, 0, 0, -0.617, -0.550, 0)$$

which were approximated by:

$$\nu_{3j} = (-0.5, 0, 0, -0.5, 0.5, 0)$$

After this iteration the desired model precision was achieved. Using the estimates of stoichiometric coefficients in chemical reaction equations, the following system is obtained:

$$\begin{aligned} A_1 + 2A_2 &\rightarrow A_3 + A_4 \\ 0.5A_1 + 0.5A_4 &\rightarrow 0.5A_5 \\ A_3 &\rightarrow 0.5A_6 \end{aligned} \qquad \textbf{(A-11)}$$

which is fully equivalent to the true reaction scheme, see Eqn. (A-10). However, the scheme would be different if the stoichiometric coefficients were rounded in a different way.

The maximum allowable error $E(i)$ for all reactions and the maximum number of reactions should be defined by an experienced researcher who provides the data for analysis. For certain values of these two criteria, a solution might not be found. The solution depends on decisions concerning the rounding of estimates of the stoichiometric coefficients. Accordingly, two persons may arrive at two different solutions if their simplification of the stoichiometric coefficients is not identical. Freezing (masking) of the previously estimated stoichiometric coefficients when the new reactions are identified results in a large degree of correlation between the stoichiometric vectors and the corresponding reaction extents. This may give rise to large uncertainties in their values. Furthermore, *a priori* ideas of the researcher on the reaction network are difficult to incorporate in the reaction scheme. Masking of stoichiometric coefficients fixes a certain element of the reaction scheme to some extent although this is certainly not equivalent to the use of prior reaction schemes before identification of the network starts. Finally, the method cannot predict the total number of reactions required for an adequate description of stoichiometry before its identification begins. All these features of the method presented are not considered to be a significant limitation, since the goal is to obtain a satisfactory model, instead of determining the true reaction network. The satisfactory model is not necessarily that which fully corresponds to the true mechanism. The method of factor analysis, which is described below, has less constraints, although usually no true stoichiometry is determined by this method either.

A2. Factor analysis

Factor analysis is a statistical technique that has been used to interpret numerous types of data. Hamer (1989), Rastogi *et al.* (1990, 1991, 1992), Fotopoulos *et al.* (1994), and Bonvin and Rippin (1990) have used it successfully for the identification of stoichiometries of complex reactions. The technique is applied to Eqn. (A-1) which are rewritten in matrix form:

$$\underline{D}_m = \underline{X}\,\underline{N} \qquad \textbf{(A-12)}$$

where $\underline{D}_m$ is an $N_e \times N_c$ matrix of data, $\underline{X}$ is an $N_e \times N_r$ matrix of unknown reaction extents, and $\underline{N}$ is the unknown $N_r \times N_c$ matrix of stoichiometric coefficients. Note that the original data should be scaled due to different uncertainties associated with measurements of individual species. Before further processing, the data matrix $\underline{D}_m$ is usually scaled to account for measurement uncertainty that can be different for different components of the reaction mixture. The matrix is simply subjected to linear transformation:

$$\underline{D} = \underline{D}_m \underline{U}_m^{-1} \qquad \textbf{(A-13)}$$

where $\underline{U}_m$ is a diagonal matrix containing measurement uncertainties (e.g. standard deviations) for all components.

The scaled data matrix $\underline{D}$ is decomposed using singular value decomposition (see Bonvin and Rippin (1990), Hamer (1989), Golub and van Loan (1983)) into matrices with one containing stoichiometric information which can be processed into acceptable stoichiometry. The decomposition can be easily done by any available software packages (e.g. Dongarra *et al.* (1979), Press *et al.*, (1989)). Upon decomposing one obtains:

$$\underline{D} = \underline{U}_D \underline{S}_D \underline{V}_D^T = \underline{U}_{D1} \underline{S}_{D1} \underline{V}_{D1}^T \qquad \textbf{(A-14)}$$

where $\underline{U}_D$ is an $N_e \times N_e$ orthonormal matrix, $\underline{S}_D$ is an $N_e \times N_c$ matrix whose diagonal elements are the singular values of $\underline{D}$, and $\underline{V}_D$ is an $N_c \times N_c$ orthonormal matrix. $\underline{S}_{D1}$ is a submatrix of $\underline{S}_D$, which would contain N_r non-zero singular values on the diagonal if the data did not contain experimental errors. The matrix $\underline{S}_{D1}$ obtained from real experimental data always exhibits the full rank, *i.e.* N_c or N_e whichever is smaller. N_r of these singular values are usually much greater than the others and these are considered significant, the rest being associated with experimental noise only. N_r is the rank of matrices $\underline{D}$ and $\underline{N}$. $\underline{U}_{D1}$ and $\underline{V}_{D1}$ contain the corresponding N_r left and right singular vectors, respectively. The submatrix $\underline{V}_{D1}$ forms an orthonormal basis for the row space of $\underline{D}$ and as such it contains a linear combination of the smallest number of singular vectors N_r.

Equation (A-13) can be rewritten as

$$\underline{D} = \underline{X}_a \underline{N}_a \qquad \textbf{(A-15)}$$

where $\underline{X}_a$ and $\underline{N}_a$ are matrices of dimensions $N_e \times N_r$ and $N_r \times N_c$, respectively, given as follows:

$$\underline{X}_a = \underline{U}_{D1} \underline{S}_{D1} \qquad \textbf{(A-16)}$$

$$\underline{N}_a = \underline{V}_{D1}^T \qquad \textbf{(A-17)}$$

The columns of the orthonormal matrix $\underline{V}_{D1}$ are linear combinations of 'reaction invariants'. In fact, the only invariants for the batch reaction being analyzed can be stoichiometric coefficients. Hence the matrix $\underline{V}_{D1}$ may be interpreted as containing the stoichiometric information (Waller and Makila (1981)) and its rank N_r can be considered to be equal to the number of independent reactions. However, the columns may have no direct physical meaning of stoichiometric coefficients being only linear combinations of them. Therefore, the matrix $\underline{N}_a$ is named the abstract stoichiometric matrix. The columns of the matrix $\underline{V}_{D1}$ must be transformed according to some criteria and qualitative knowledge about the system under study to obtain a realistic stoichiometry. In general the transformation should provide a certain parsimony. For instance, the columns are best transformed so that at least some of the elements of the columns of the transformed matrix are zeros; this is equivalent to zero-stoichiometric coefficients for components that have non-zero elements in another reaction. Moreover, the transformation should lead to positive reaction extents, *i.e.* to non-negative columns in the transformed matrix $\underline{X}_t$ if possible.

As mentioned before, the physically meaningful stoichiometries are linear combinations of the N_r columns of $\underline{V}_{D1}$. To identify these stoichiometries one must find an $N_r \times N_r$ linear transformation matrix such that

$$\underline{\boldsymbol{D}} = \underline{\boldsymbol{U}}_{D1}\underline{\boldsymbol{S}}_{D1}\underline{\boldsymbol{V}}_{D1}^{T} = \underline{\boldsymbol{X}}_a\underline{\boldsymbol{N}}_a = \underline{\boldsymbol{X}}_a\underline{\boldsymbol{T}}^{-1}\cdot\underline{\boldsymbol{T}}\underline{\boldsymbol{N}}_a = \underline{\boldsymbol{X}}_t\underline{\boldsymbol{N}}_t \qquad \textbf{(A-18)}$$

where $\underline{X}_t$ and $\underline{N}_t$ are the transformed extent-of-reaction and stoichiometric matrices, respectively. A number of methods can be used to calculate the transformation matrix. A graphical method used by Hamer (1989) consists in the following. The linear combinations of the stoichiometry and resulting reaction extents are best selected by considering only two reactions at a time, *i.e.* operations in two-dimensional subspaces. In these sub-spaces, taking linear combinations is equivalent to performing oblique rotations. The transformations matrix for an oblique rotation, where one axis (ordinate) is rotated through α and the other axis (abscissa) is rotated through β, is given by:

$$\underline{\boldsymbol{T}} = \frac{1}{\cos(\beta-\alpha)}\begin{bmatrix}\cos\beta & -\sin\alpha\\ \sin\beta & \cos\alpha\end{bmatrix} \qquad \textbf{(A-19)}$$

whereby the inverse matrix transpose is given by:

$$\left(\underline{\boldsymbol{T}}^{T}\right)^{-1} = \begin{bmatrix}\cos\alpha & -\sin\beta\\ \sin\alpha & \cos\beta\end{bmatrix} \qquad \textbf{(A-20)}$$

The angles α and β are selected according to the criteria mentioned above. The method is described in more detail in *Example A.2.* This method is, however, practically limited to systems of two to three reactions. For dealing with more complex systems the reader is referred to papers of Rastogi (1991) or Bonvin and Rippin (1990).

Example A.2. Identification of stoichiometry in a three-reaction system using factor analysis (after Hamer (1989))

Consider the following reaction scheme:

$$\begin{aligned} A(l) + B(l) &\rightarrow C(l) + D(g)\\ A(l) + C(l) &\leftrightarrow E(l)\\ E(l) &\rightarrow F(l) + D(g) \end{aligned} \qquad \textbf{(A-21)}$$

where indices *(l)* and *(g)* denote the liquid and the gas phase, respectively. The process is carried out in semibatch mode with only *B* present initially in 2000 L of a solution with a concentration of 1 mol L^{-1}. A solution containing 4 mol L^{-1} of *A* is fed at a constant flow rate of 20 L min^{-1} for 60 min. Then the reaction is continued batchwise for 40 min. The molecular masses of the components *A, B, C, D, E*, and *F* are 150, 90, 200, 40, 350, and 310 g mol^{-1}, respectively. Only components of the liquid are analyzed, with associated standard deviations for *A, B, C*, and *F* of 0.1, 1.0, 5.0, and 0.5 mol L^{-1}; the concentration of *E* is lower by about one order of magnitude. The reaction mixture is analyzed every 5 min for the first 30 min, every 10 min for the next 50 min, and at the end of the reaction at 100 min. This gives 12 composition measurements in addition to the initial composition. The simulated data, charged with Gaussian noise, are shown in Table A-2.

Table A-2
Concentrations of *A, B, C* and *F* vs. time

Time (min)	A(g L^{-1})	B(g L^{-1})	C(g L^{-1})	F(g L^{-1})	Volume (L)
0	0.0000	90.0000	0.0000	0.0000	2000
5	6.2720	74.0568	34.0258	1.6069	2100
10	7.0219	57.1407	55.3665	7.4805	2200
15	7.9769	42.3879	77.4833	17.4908	2300
20	8.9174	31.4453	69.8651	32.7361	2400
25	9.8951	22.2794	81.8892	48.6482	2500
30	11.8180	13.3329	80.6627	68.9917	2600
40	17.0346	5.6954	55.9551	110.6896	2800
50	27.2758	1.3356	35.9551	149.1504	3000
60	45.4616	-1.6192	0.3887	175.0076	3200
70	39.6976	0.0060	2.9033	188.5924	3200
80	38.1572	0.0005	0.8743	192.2098	3200
100	37.5622	0.0000	0.0829	193.6044	3200

SOLUTION. The cumulative mass change of each measured species is calculated based on the data from Table A-2 and the information on flow rate and molecular masses. The results of the calculations are shown in the matrix $\underline{\mathbf{D}}_m$ (negative values for components consumed and positive values for components produced) in Eqn. (A-22).

$$\underline{\boldsymbol{D}}_m = \begin{bmatrix} -46.83 & -24.48 & 71.45 & 3.37 \\ -104.55 & -54.29 & 121.81 & 16.46 \\ -161.54 & -82.51 & 178.21 & 40.23 \\ -218.60 & -104.53 & 167.68 & 78.57 \\ -275.26 & -124.30 & 204.30 & 121.61 \\ -329.27 & -145.33 & 209.72 & 179.38 \\ -432.30 & -164.05 & 156.67 & 309.93 \\ -518.17 & -175.99 & 106.36 & 447.45 \\ -574.52 & -185.18 & 1.24 & 560.02 \\ -592.97 & -179.98 & 9.29 & 603.50 \\ -597.90 & -180.00 & 2.80 & 615.07 \\ -599.80 & -180.00 & 0.27 & 619.53 \end{bmatrix} \qquad \textbf{(A-22)}$$

The uncertainties in the measurements (standard deviations) are placed in the diagonal matrix $\underline{\boldsymbol{U}}_m$:

$$\underline{\boldsymbol{U}}_m = diag\begin{bmatrix}0.1 & 1.0 & 5.0 & 0.5\end{bmatrix} \qquad \textbf{(A-23)}$$

The data in each column of experimental matrix $\underline{\boldsymbol{D}}_m$ are scaled by dividing that column by the uncertainty associated with that measurement resulting in the matrix $\underline{\boldsymbol{D}}$:

$$\underline{\boldsymbol{D}} = \underline{\boldsymbol{D}}_m \underline{\boldsymbol{U}}_m^{-1} = \begin{bmatrix} -468.3 & -24.48 & 14.3 & 6.7 \\ -1045.5 & -54.29 & 24.4 & 32.9 \\ -1615.4 & -82.51 & 35.6 & 80.5 \\ -2186.0 & -104.53 & 33.5 & 157.1 \\ -2752.6 & -124.30 & 40.9 & 243.2 \\ -3292.7 & -145.33 & 41.9 & 358.8 \\ -4323.0 & -164.05 & 31.3 & 619.9 \\ -5181.7 & -175.99 & 21.3 & 894.9 \\ -5745.2 & -185.18 & 0.2 & 1120.0 \\ -5929.7 & -179.98 & 1.9 & 1207.0 \\ -5979.0 & -180.00 & 0.6 & 1230.1 \\ -5998.0 & -180.00 & 0.1 & 1239.1 \end{bmatrix} \qquad \textbf{(A-24)}$$

The four singular values of $\underline{\boldsymbol{D}}$ found via decomposition are:

$$\begin{bmatrix}14820 & 593.7 & 10.10 & 60.27\end{bmatrix} \qquad \textbf{(A-25)}$$

The last two singular values are of equal magnitude and much smaller than the others. This indicates that the data might be described by two independent reactions. The right singular vectors associated with the largest two singular values are:

$$\underline{N}_a = \underline{V}_{D1}^T = \begin{array}{c} \begin{array}{cc} Rxn1 & Rxn2 \end{array} \\ \begin{bmatrix} 0.9838 & 0.1685 \\ 0.0331 & 0.1368 \\ -0.0031 & -0.1291 \\ -0.1764 & 0.9676 \end{bmatrix} \end{array} \qquad \textbf{(A-26)}$$

The associated extents of reaction are calculated from Eqn. (A-12):

$$\underline{X}_a = \underline{N}_a^T \underline{D} = \begin{bmatrix} -462.7 & -77.6 \\ -1036.2 & -154.9 \\ -1607.3 & -210.4 \\ -2181.8 & -234.9 \\ -2755.0 & -250.8 \\ -3307.4 & -233.0 \\ -4367.6 & -155.2 \\ -5261.3 & -34.1 \\ -5855.6 & 90.3 \\ -6052.3 & 143.8 \\ -6104.8 & 158.1 \\ -6125.1 & 163.6 \end{bmatrix} \qquad \textbf{(A-27)}$$

In order to compare the agreement with the original data, the stoichiometry matrix $\underline{N}_a$ must be converted back:

$$\underline{N}_{am} = \underline{U}_{m}\underline{N}_a = \begin{bmatrix} 0.0984 & 0.0169 \\ 0.0331 & 0.1368 \\ -0.0155 & -0.6455 \\ -0.0882 & 0.4838 \end{bmatrix} \qquad \textbf{(A-28)}$$

The experimentally determined values of D_{jk} and those calculated from matrices $\underline{X}_a$ (Eqn. (A-27)) and $\underline{N}_{am}$ (Eqn. (A-28)) for the model with two reactions are given in Fig. A-1. The agreement is very good. If there were significant discrepancies between calculated and experimental data more singular vectors could be used to improve the agreement. Before any further processing of the data, each column of the reaction stoichiometries (Eqn. (A-28)) is scaled so that the largest elements are unity. This is performed using a diagonal matrix containing the maximum absolute value of each column:

$$\underline{T}_s = diag\left[0.0984 \quad 0.6455\right] \qquad \textbf{(A-29)}$$

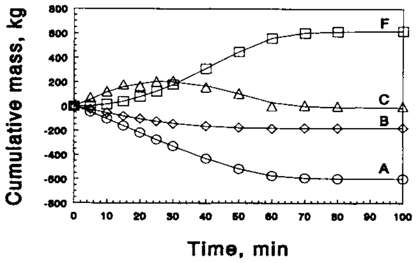

Figure A-1. Cumulative masses of species consumed and produced (markers are 'experimental' data, lines are matrix data (A-27)).

After scaling, the stoichiometry matrix $\underline{N}_{am,s1}$ is:

$$\underline{N}_{am,s1} = \underline{N}_{am}\left(\underline{T}_s^T\right)^{-1} = \begin{bmatrix} 1.0000 & 0.0261 \\ 0.3364 & 0.2120 \\ -0.1572 & -1.0000 \\ -0.8966 & 0.7495 \end{bmatrix} \tag{A-30}$$

and the reaction extent matrix $\underline{X}_{a,s}$ is:

$$\underline{X}_{a,s} = \underline{X}_a \underline{T}_s = \begin{bmatrix} -45.5218 & -50.0779 \\ -101.9362 & -99.9784 \\ -158.1164 & -135.8246 \\ -214.6382 & -151.6455 \\ -271.0277 & -161.8618 \\ -325.3708 & -150.3990 \\ -419.6695 & -100.1604 \\ -517.5812 & -21.9984 \\ -576.0460 & 58.2626 \\ -595.3942 & 92.8309 \\ -600.5666 & 102.0271 \\ -602.5600 & 105.5737 \end{bmatrix} \tag{A-31}$$

In order indicate the contribution of each reaction to the overall model more clearly, the matrix of reaction extents is differenced, giving the reaction extents in each interval:

$$\underline{X}_{a,dt1} = \begin{bmatrix} -45.5218 & -50.0779 \\ -56.4143 & -49.9005 \\ -56.1802 & -35.8462 \\ -56.5165 & -15.8209 \\ -56.3949 & -10.2163 \\ -54.3430 & 11.4628 \\ -104.2987 & 50.2386 \\ -87.9118 & 78.1620 \\ -58.4648 & 80.2610 \\ -19.3482 & 34.5683 \\ -5.1724 & 9.1962 \\ -1.9934 & 3.5466 \end{bmatrix} \tag{A-32}$$

Stoichiometry matrix $\underline{N}_{am,s1}$ is then plotted as shown in Fig. A-2. The matrix of reaction extents is scaled by dividing by the maximum value (104.3) and plotted as shown in Fig. A-3. The stoichiometric interpretation of the data given in $\underline{N}_{am,s1}$ is as follows:

$$\begin{aligned} &\text{Reaction 1:} \quad 0.157\,C + 0.897\,F \leftrightarrow 1.0\,A + 0.336\,B \\ &\text{Reaction 2:} \quad 0.026\,A + 0.212\,B + 0.795\,F \leftrightarrow 1.0\,C \end{aligned} \tag{A-33}$$

As shown in Fig. A-3 reaction 1 goes backwards while reaction 2 proceeds in two directions. This fits the data well but it seems very improbable that the starting material B reacts with final product F into intermediate C.

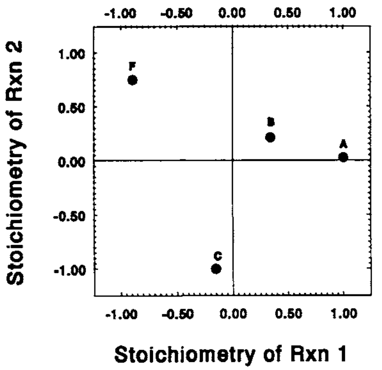

Figure A-2. Normalized stoichiometric coefficients for the two reactions associated with the singular vectors.

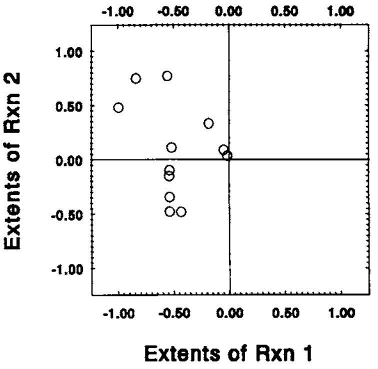

Figure A-3. Normalized extents of reaction for the two reactions associated with the singular vectors.

The task now is to select the linear combinations that will most probably correspond to independent parts of the reaction network with easily interpretable stoichiometry. A simplification of the data in the matrix $\underline{\boldsymbol{N}}_{am,s1}$ can be achieved by such a rotation that the axes go through the points in Fig. A-2 (this is equivalent to some zero-stoichiometric coefficients) and that the points of Fig. A-3 are in the first quadrant (this corresponds to positive reaction extents) if possible. Rotations of the abscissa through 220° and the ordinate through 240° lead to attaining both objectives. The associated rotation matrix is:

$$\underline{\boldsymbol{T}} = \begin{bmatrix} -0.8152 & -0.9216 \\ 0.6840 & -0.5321 \end{bmatrix} \tag{A-34}$$

After rotating and scaling to make the largest stoichiometric coefficients unity, the matrices of stoichiometry and reaction extents are:

$$\underline{\boldsymbol{N}}_{am,s2} = \underline{\boldsymbol{N}}_{am,s1}\left(\underline{\boldsymbol{T}}^{T}\right)^{-1}\left(\underline{\boldsymbol{T}}_{s}^{T}\right)^{-1} = \begin{bmatrix} -0.4350 & -0.7644 \\ 0.0140 & -0.4367 \\ -0.7175 & 1.0000 \\ 1.0000 & 0.0025 \end{bmatrix} \tag{A-35}$$

$$\underline{\boldsymbol{X}}_{a,dt2} = \underline{\boldsymbol{X}}_{a,dt1}\underline{\boldsymbol{T}}_{s}\underline{\boldsymbol{T}} = \begin{bmatrix} 3.1325 & 59.4794 \\ 13.0104 & 68.1016 \\ 23.3514 & 61.4305 \\ 38.6849 & 52.4605 \\ 42.7834 & 49.7777 \\ 57.2218 & 38.1364 \\ 131.0221 & 60.1659 \\ 137.3234 & 34.1888 \\ 112.5550 & 9.6898 \\ 43.2593 & -0.4873 \\ 11.5308 & -0.1095 \\ 4.4457 & -0.0433 \end{bmatrix} \tag{A-36}$$

where the scaling matrix is:

$$\underline{\boldsymbol{T}}_{s} = diag\begin{bmatrix} 1.097 & 0.867 \end{bmatrix} \tag{A-37}$$

The matrices above are plotted in Fig. A-4, whereby the extents of reaction have been divided by the maximum value (137.3). The matrix $\underline{\boldsymbol{N}}_{am,s2}$ (Eqn. (A-35)) can be interpreted (in mass units) as follows:

$$\begin{aligned} &\text{Reaction 1, product formation:} && 0.44\,A + 0.72\,C \rightarrow 1\,F \\ &\text{Reaction 2, intermediate formation:} && 0.76\,A + 0.44\,B \rightarrow 1\,C \end{aligned} \tag{A-38}$$

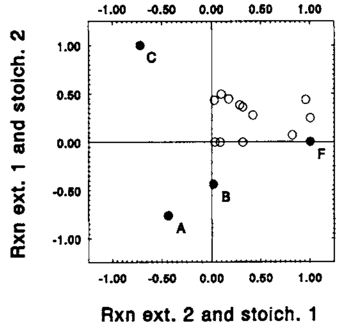

Figure A-4. Stoichiometric coefficients and extents of reaction after rotation.

The 'stoichiometric' coefficients in mass units can be recalculated to molar stoichiometric coefficients and then the reactions become:

$$\begin{aligned} &\text{Reaction 1, product formation:} && 0.90\,A + 1.11\,C \rightarrow 1\,F \\ &\text{Reaction 2, intermediate formation:} && 1.02\,A + 0.97\,B \rightarrow 1\,C \end{aligned} \qquad \textbf{(A-39)}$$

This example shows that the method discussed can deal with the difficulties frequently met in real situations. One of the products (*D*) was difficult to measure and another one (*E*) not accurately analyzed. So the balance could not close and conventional methods of determining stoichiometry via balancing could fail. The standard error in determination of species (*C*) was in the range of 6-14 % of the measured value in the first period of the 'experiment'. Despite these difficulties, two simple reactions were found with stoichiometry that can adequately represent the reactions. The final representation of the chemical system is not unique but the final stoichiometric coefficients are within 10 % of the original ones. This indicates that the proposed methodology can yield reasonable approximations.

References for Appendix A

See end of Chapter 5.

Appendix B. Parameter estimation and statistical analysis of regression

B1. Single reactions

B1.1. Parameter estimation

B1.1.1. Linear regression

Drawing straight lines through data points is a slightly arbitrary procedure. The slope of the straight line does not depend very much on this arbitrariness but the value of the intercept usually depends very much on it. Consequently, the value of the kinetic parameter related to the intercept will be estimated with the accuracy of the eyes capability of finding the best fit between experimental points and those lying on the line drawn. An objective method of parameter estimation consist in evaluation of the minimum of the function:

$$SS_{res} = \sum_{k} \left(y_{k,calc} - y_{k,exp} \right)^2 \qquad \textbf{(B-1)}$$

where $y_{k,calc}$ are dependent variables (rates, concentrations, etc.) calculated from the model, and $y_{k,exp}$ are observed dependent variables. The procedure of parameter estimation is commonly called *regression*.

For linear or linearized models:

$$y_{calc} = b_0 + b_1 x_1 + b_2 x_2 + \ldots + b_{N_p-1} x_{N_p-1} \qquad \textbf{(B-2)}$$

where N_p is the number of model parameters. If a set of N_e measurements of y_{exp} is made, the following set of equations can be written for the linear model:

$$\begin{aligned} y_{1,\exp} &= b_0 + b_1 x_{11} + b_2 x_{12} + \ldots + b_{N_p-1} x_{1,N_p-1} + \varepsilon_1 = y_{1,calc} + \varepsilon_1 \\ y_{2,\exp} &= b_0 + b_1 x_{21} + b_2 x_{22} + \ldots + b_{N_p-1} x_{2,N_p-1} + \varepsilon_2 = y_{2,calc} + \varepsilon_2 \\ &\vdots \\ y_{N_e,\exp} &= b_0 + b_1 x_{N_e 1} + b_2 x_{N_e 2} + \ldots + b_{N_p-1} x_{N_e,N_p-1} + \varepsilon_{N_e} = y_{N_e,calc} + \varepsilon_{N_e} \end{aligned} \qquad \textbf{(B-3)}$$

where ε_k are experimental errors in measuring $y_{k,exp}$. It is assumed that accurate values of independent variables (temperature, time, etc.) are known. Accordingly, minimization of SS_{res} defined by Eqn. (B-1) corresponds to minimization of the sum of squares of errors in y:

$$SS_{res} = \sum_{k=1}^{N_e} \left(y_{k,calc} - y_{k,exp} \right)^2 = \sum_{k=1}^{N_e} \varepsilon_i^2 \xrightarrow{b_0, b_1, b_2, \ldots, b_{N_p-1}} \min \qquad \textbf{(B-4)}$$

The function SS_{res} is minimum if:

$$\frac{\partial SS_{res}}{\partial b_i} = 0 \qquad \text{for } i = 0,1,2,\ldots,N_p - 1 \tag{B-5}$$

or, expanding:

$$\begin{aligned}
\frac{\partial SS_{res}}{\partial b_0} &= 2\sum_{k=1}^{N_e}\left(b_0 + b_1 x_{k1} + b_2 x_{k2} + \ldots + b_{N_p-1} x_{k,N_p-1} - y_{1,exp}\right) = 0 \\
\frac{\partial SS_{res}}{\partial b_1} &= 2\sum_{k=1}^{N_e} x_{k1}\left(b_0 + b_1 x_{k1} + b_2 x_{k2} + \ldots + b_{N_p-1} x_{k,N_p-1} - y_{k,exp}\right) = 0 \\
\frac{\partial SS_{res}}{\partial b_2} &= 2\sum_{k=1}^{N_e} x_{k2}\left(b_0 + b_1 x_{k1} + b_2 x_{k2} + \ldots + b_{N_p-1} x_{k,N_p-1} - y_{k,exp}\right) = 0 \\
&\vdots \\
\frac{\partial SS_{res}}{\partial b_{N_p-1}} &= 2\sum_{k=1}^{N_e} x_{k,N_p-1}\left(b_0 + b_1 x_{k1} + b_2 x_{k2} + \ldots + b_{N_p-1} x_{k,N_p-1} - y_{k,exp}\right) = 0
\end{aligned} \tag{B-6}$$

This system of linear algebraic equations is easy to solve to find the estimates of model parameters b_i. It can be rewritten in more general matrix notation:

$$\underline{b} = \left(\underline{X}^T \underline{X}\right)^{-1} \underline{X}^T \underline{Y} \tag{B-7}$$

where $\underline{b}$ is a $(N_p - 1)\times 1$ column vector of estimates of model parameters:

$$\underline{b} = \begin{bmatrix} b_0 \\ b_1 \\ \vdots \\ b_{N_p-1} \end{bmatrix} \tag{B-8}$$

$\underline{Y}$ is $N_e \times 1$ column of observed $y_{k,exp}$:

$$\underline{Y} = \begin{bmatrix} y_0 \\ y_1 \\ \vdots \\ y_{N_p-1} \end{bmatrix} \tag{B-9}$$

$\underline{X}$ is a matrix of N_v independent variables measured in N_e experiments:

$$\underline{X} = \begin{bmatrix} x_{11} & x_{12} & \cdots & x_{1N_v} \\ x_{21} & x_{22} & \cdots & x_{2N_v} \\ \vdots & & & \\ x_{N_e 1} & x_{N_e 2} & \cdots & x_{N_e N_v} \end{bmatrix} \tag{B-10}$$

and T stands for matrix transpose. The equations represented by Eqn, (B-7) are termed *normal equations*; they result in parameter estimates for which the distance between the data $\underline{Y}$ and the $y_{k,calc}$ from the model is minimum, thus representing a line that is perpendicular (*normal*) from the point y to the model surface.

It has been implicitly assumed in the procedure described above that all experimental points were independent on each other and were determined with the same error variance, *i.e.* they had the same uncertainty. Performing replications for each observation, the error variance for each point σ_k^2 can be calculated. The function SS_{res} to be minimized can be then modified as follows:

$$SS_{res} = \sum_k \frac{1}{\sigma_k^2}\left(y_{k,calc} - y_{k,exp}\right)^2 \qquad \textbf{(B-11)}$$

or in a matrix notation:

$$\underline{b} = \left(\underline{X}^T \underline{C}^{-1} \underline{X}\right)^{-1} \underline{X}^T \underline{C}^{-1} \underline{Y} \qquad \textbf{(B-12)}$$

where $\underline{C}$ is a diagonal matrix with error variances on the diagonal:

$$\underline{C} = \begin{bmatrix} \sigma_1^2 & 0 & \cdots & 0 \\ 0 & \sigma_2^2 & \cdots & 0 \\ \vdots & & & \\ 0 & 0 & \cdots & \sigma_{N_p}^2 \end{bmatrix} \qquad \textbf{(B-13)}$$

Weights will be unconsciously applied if operating conditions are non-uniformly distributed in the experimental space. Estimated model parameters will then better reproduce the experimental data from that part of the space where the density of experimentation is greater. Therefore, statistical methods of planning of kinetic experiments, possibly modified by appropriate transformation of variables, are strongly recommended.

B1.1.2. Non-linear regression

In many cases, the kinetic equation is non-linear:

$$y_{k,calc} = f(\underline{x};\underline{b}) \qquad \textbf{(B-14)}$$

and cannot be linearized. The least squares method is then based on minimization of the objective function:

$$SS_{res} = \sum_k \left(f(\underline{x};\underline{b}) - y_{k,exp}\right)^2 \qquad \textbf{(B-15)}$$

which cannot be solved directly. The objective function (B-15) is minimized *iteratively*. Several efficient methods have been developed to minimize non-linear functions based on the principle of *linearization*, the *steepest-descent* methods, and the like (see the method of Newton-Raphson, the method of Newton-Gauss with modifications by Marquardt and Levenberg, the method of Rosenbrock-Storey, the method of Powell-Fletcher (possibly modified by Davidon), the Simplex method Nelder and Mead, etc.). In some cases functions $f(\underline{x};\underline{b})$ are given as differential equations which cannot be solved analytically. Then numerical methods for solving the differential equations should be involved such as the Runge-Kutta modifications, the Fehlberg method, etc. During the search for a minimum, sets of model parameters can appear that will cause stiffness of the differential equations. Accordingly, an appropriate test for stiffness and an appropriate numerical method for solving stiff equations should be incorporated into computation procedures[1]. In general, parameter estimation for differential equations is a time-consuming task. Good initial guesses of parameters are required, because otherwise convergence can be poor.

The convergence of different methods to the global minimum depends on the shape of the objective function to be minimized and on the initial guesses of parameters to be estimated (starting values of model parameters). For instance, the method of Rosenbrock has been developed as a very effective method to search for extrema of functions located in long canyons. Such functions are usually less effectively solved using other methods. Reparametrization often helps in better convergence in the case of multidimensional canyons leading to the minimum. This is the redefinition of independent variables such that the centre of the new co-ordinate system is located in the vicinity of the experimental design. For instance, the Arrhenius equation can be rearranged to:

$$k = k_0^{'} \exp\left\{-\frac{E}{R_g}\left(\frac{1}{T}-\frac{1}{T_{ref}}\right)\right\} \qquad \textbf{(B-16)}$$

where

$$k_0^{'} = k_0 \exp\left(-\frac{E}{R_g T_{ref}}\right) \qquad \textbf{(B-17)}$$

where T_{ref} is the reference temperature chosen near the centre of the experimental temperature range. The elongated confidence region has been transformed into a more circular confidence region (see Figs. B-1 and B-2). (A confidence region is the region where parameters do not differ significantly from the optimal estimates found by regression.) Obviously the search for minimum will be easier after reparametrization.

Some methods are very sensitive to the initial guesses: in case of a starting point located very far from the minimum they converge slowly or even to a local minimum. Kinetic parameters estimated via graphical calculations are usually good initial values for iterative calculations. Based on the experience of the authors it can be recommended to start minimization using the Simplex method, which is relatively insensitive to initial guesses. After the minimum has been found, the search for the global minimum is continued using the method of Newton-Raphson with modifications by Marquardt and Levenberg, which can deal better with problems associated with

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[1] Computer programs or packages containing programs for minimization are commercially available. These programs can usually deal with linear and non-linear regressions and also with parameter estimation in differential equations. Readers interested in such programs can find names and addresses of companies offering programs in journals on computers, e.g. in *Personal Computers*. Exemplary packages are: *Simusolve* developed by Dow Chemical Co., Michigan. USA and *Scientist* developed by MicroMath Scientific Software, Salt Lake City, Utah, USA.

complicated shapes of the objective function in the vicinity of the minimum. Obviously, the above statement cannot be treated as a generalization for all cases.

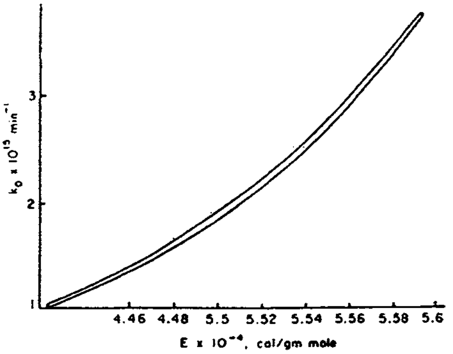

Figure B-1. Approximate 95% confidence region for first-order decomposition model. Reproduced from Kittrell (1970) with permission from Academic Press.

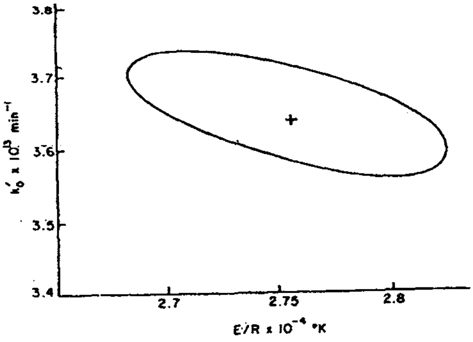

Figure B-2. Approximate 95% confidence region for reparametrized first-order decomposition model. Reproduced from Kittrell (1970) with permission from Academic Press.

Problems in finding the global minimum increase with the dimension of the target function: the more parameters have to be estimated the more difficult the search for minimum becomes. Therefore, it can be practical to fix some model parameters at least at the initial stages of the search for the minimum: reaction equilibrium coefficients or changes of the entropy due to adsorption on the catalyst surface, ΔS_{ads}, can often be evaluated from thermodynamics. The coefficients estimated from thermodynamics are not necessarily the true coefficients because of the approximate character of thermodynamic evaluations, and as such these coefficients can be released in further steps of the search for the minimum. For the same reason it is advantageous to start processing experimental data for different temperatures separately. Subsequently, rate constants and adsorption equilibrium constants will be correlated with the Arrhenius and van 't Hoff equations, respectively, and coefficients of these equations will be used as initial guesses for minimization of the objective function over all experimental data at different temperatures. Here, some useful techniques will be discussed for simple evaluations of model parameters, which can be used as initial guesses for non-linear regression. Note that final estimates of model parameters found via non-linear regression and linearization can differ very much from each other as shown in *Example B.1*.

The regression for integral kinetic analysis is generally non-linear. Differential equations may include unobservable variables, which may produce some additional problems. For instance, heterogeneous catalytic models include concentrations of species inside particles, while these are not measured. The concentration distributions, however, can affect the overall performance of the catalyst/reactor.

Example B.1. Parameter estimation for pentane isomerization (after Kittrell (1972))

Two equations have been proposed for correlation of experimental data on pentane isomerizaton: the single-site Langmuir-Hinshelwood expression:

$$r_1 = \frac{kK_2(p_2 - p_3/K)}{1 + K_1 p_1 + K_2 p_2 + K_3 p_3} \qquad \textbf{(B-18)}$$

and the dual-site expression:

$$r_2 = \frac{kK_2(p_2 - p_3/K)}{(1 + K_1 p_1 + K_2 p_2 + K_3 p_3)^2} \qquad \textbf{(B-19)}$$

where p_1, p_2, and p_3 are the partial pressures of hydrogen, normal pentane, and isopentane, respectively. Rearranging and redefining variables the following linearized kinetic equations are obtained:

$$y_1 = b_0 + b_1 p_1 + b_2 p_2 + b_3 p_3 \qquad \textbf{(B-20)}$$

$$y_2 = b_0 + b_1 p_1 + b_2 p_2 + b_3 p_3 \qquad \textbf{(B-21)}$$

where

$$y_1 = \left(\frac{p_2 - p_3/K}{r_1}\right); \quad y_2 = \left(\frac{p_2 - p_3/K}{r_2}\right)^{1/2} \qquad \textbf{(B-22)}$$

$$b_0 = \frac{1}{kK_2}; \quad b_1 = \frac{K_1}{kK_2}; \quad b_2 = \frac{1}{k}; \quad b_3 = \frac{K_3}{kK_2} \qquad \textbf{(B-23)}$$

Model parameters estimated by linear regression, weighted linear regression, and unweighted non-linear regression are shown in Table B-1.

Table B-1
Parameter estimates for pentane isomerization

Parameter		Unweighted linear regression	Weighted linear regression	Non-linear regression
Single site	k	189	30.5	36.2
	K_1	-0.4	2.0	0.9
	K_2	-0.03	1.3	0.5
	K_3	-1.08	4.1	2.1
Dual site	k	289	73.9	133
	K_1	0.03	0.03	0.03
	K_2	0.005	0.02	0.02
	K_3	0.09	0.07	0.07

Unweighted linear regression leads to physically meaningless estimates for the single-site model. These estimates are, however, not very far from those obtained using non-linear regression. As such they can probably be successfully used as initial guesses for non-linear regression. Parameters estimated via weighted linear regression are quite close to non-linear estimates. The latter ones are considered to be the best and are usually reference values for comparisons with estimates obtained from other techniques.

Non-linear regression is likely to give the most reliable estimates of model parameters, as the original, non-transformed variables are used for minimization. Numerical errors, problems in finding the global minimum using non-linear regression, and difficulties in rigorous statistical analysis of non-linear regression as well as easiness of data processing and statistical analysis using linear regression make linear regression still very popular.

Another problem which can appear in the search for the minimum is intercorrelation of some model parameters. For example, such a correlation usually exists between the frequency factor (pre-exponential factor) and the activation energy (argument in the exponent) in the Arrhenius equation or between rate constant (appears in the numerator) and adsorption equilibrium constants (appear in the denominator) in Langmuir-Hinshelwood kinetic expressions.

If a model is inadequate and/or experimental data are insufficiently accurate, the minimization methods might show up a tendency to simultaneously decrease or increase both coefficients outside the range of physical meaning. In this case fixation of ΔS_{ads} can be a sufficient remedy. For evaluation of the entropy change due to adsorption, books and papers of Adamson (1982), Barrow (1973), Černy (1983), Waugh (1994), and Zhdanov *et al.* (1988) are recommended.

B1.2. Statistical analysis

Statistical testing of model adequacy and significance of parameter estimates is a very important part of kinetic modelling. Only those models with a positive evaluation in statistical analysis should be applied in reactor scale-up. The statistical analysis presented below is restricted to linear regression and *normal or Gaussian distribution of experimental errors*. If the experimental error has a zero mean, constant variance σ^2, and is independently distributed, its variance can be evaluated by dividing SS_{res} by the number of degrees of freedom, *i.e.*

$$s^2 = \frac{SS_{res}}{N_e - N_p} \tag{B-24}$$

where N_p is the number of model parameters.

B1.2.1. Test for model adequacy

A number of replications under at least one set of operating conditions must be carried out to test the model adequacy (or *lack of fit of the model*). An estimate of the pure error variance is then calculated from:

$$s^2 = \frac{\text{pure error sum of squares}}{\text{number of degrees of freedom}} = \frac{\sum_{k=1}^{N_{re}} \left(y_{k,exp} - y_{k,exp,mean}\right)^2}{N_e - 1} \tag{B-25}$$

where N_{re} is the number of replications and $y_{exp,mean}$ is the arithmetic mean of replicates. Partitioning of sums of squares, which is the basis of the adequacy test, is shown in Fig. B-3 (after Draper and Smith (1966)).

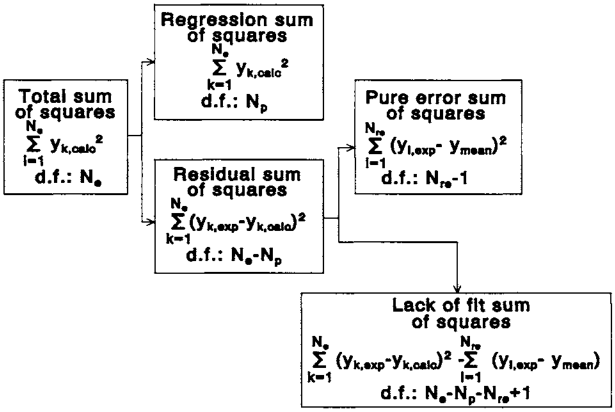

Figure B-3. Partitioning of sums of squares.

An F-test for lack of fit is based on the ratio of the lack of fit sum to the pure error sum of squares divided by their corresponding degrees of freedom:

$$F_{c1} = \frac{\dfrac{\text{lack of fit sum of squares}}{N_e - N_p - N_{re} + 1}}{\dfrac{\text{pure error sum of squares}}{N_{re} - 1}} \qquad \textbf{(B-26)}$$

If $F_{c1} > F(N_e - N_p - N_{re} + 1; N_{re} - 1; 1-\alpha)$ there is 1-α probability that the model is inadequate. Such a model should be rejected because the lack of fit. $F(N_e - N_p - N_{re} + 1; N_{re} - 1; 1-\alpha)$ is the α-percentage point of the F-distribution with $N_e - N_p - N_{re} + 1$ and $N_{re} - 1$ degrees of freedom. The model adequacy is usually tested for an α of 0.05 or 0.01. The distribution is tabulated and the F-values for these typical values of α can be found in books concerning statistics or engineering (e.g., in *Chemical Engineer's Handbook*). If $F_{c1} < F(N_e - N_p - N_{re} + 1; N_{re} - 1; 1-\alpha)$ the model does not exhibit the lack of fit and is considered meaningful.

If replicates are not available a test based on the ratio of the regression sum of squares to the residual sum of squares can be applied:

$$F_{c2} = \frac{\dfrac{\text{regression sum of squares}}{N_p}}{\dfrac{\text{residual sum of squares}}{N_e - N_p}} = \frac{\sum_k \dfrac{y_{k,calc}}{N_p}}{\sum_k \dfrac{\left(y_{k,calc} - y_{k,exp}\right)^2}{N_e - N_p}} \qquad \textbf{(B-27)}$$

If $F_{c2} > F(N_p; N_e - N_p; 1-\alpha)$ the regression is considered meaningful.

B1.2.2. Tests on estimates of model parameters

Parameter estimates are tested on whether they differ significantly from zero at a certain probability level. If not, the parameter should be skipped from the model and the model should be redefined even if the test for model adequacy was positive. When the errors have constant variance, the random variable

$$\frac{|b_j - \beta_j|}{\sigma(b_j)} \tag{B-28}$$

in which β_j is the true value of the model parameter, is distributed like the normal distribution. If the error variance $\sigma^2(b_j)$ is unknown, an unbiased estimate $s(b_j)$ is used instead. This is calculated from:

$$s(b_j) = \sqrt{[\underline{V}(\underline{b})]_{jj}} \tag{B-29}$$

where $\underline{V}(\underline{b})$ is the $(N_p \times N_p)$-variance-covariance matrix of the estimates $\underline{b}$ given by:

$$\underline{V}(\underline{b}) = (\underline{X}^T \underline{X})^{-1} s^2 \tag{B-30}$$

The random variable

$$\frac{|b_j - \beta_j|}{s(b_j)} \tag{B-31}$$

is distributed like $t(N_e - N_p)$. As mentioned before, the parameter estimate b_j is considered meaningless if it does not differ significantly from $\beta_j = 0$. If

$$t_c = \frac{|b_j - 0|}{s(b_j)} > t\left(N_e - N_p; 1 - \frac{\alpha}{2}\right) \tag{B-32}$$

the hypothesis that b_j would be zero can be rejected with only α percent chance that it would be equal to zero. The quantity $t(N_e - N_p; 1-\alpha/2)$ is the tabulated $\alpha/2$ percentage point of the t distribution with $N_e - N_p$ degrees of freedom. The t-values are tabulated, usually for an α of 0.05 and 0.01 (see e.g. *Chemical Engineers' Handbook*).

Reliability analysis of parameters estimated in differential equations should be performed rigorously via *sensitivity analysis*. The details of this analysis can be found in the paper by Froment and Hosten (1981).

B1.2.3. Confidence limits and regions

Confidence limits for the parameter estimates define the region where values of b_j are not significantly different from the optimal value $b_{j,opt}$ at a certain probability level $1-\alpha$ with all other parameters kept at their optimal values estimated. The confidence limits are a measure of uncertainty in the optimal estimates $b_{j,opt}$; the broader the confidence limits the more uncertain are the estimates. These intervals for linear models are given by

$$b_j - t\left(N_e - N_p; 1 - \frac{\alpha}{2}\right) \cdot s(b_j) \le \beta_j \le b_j + t\left(N_e - N_p; 1 - \frac{\alpha}{2}\right) \cdot s(b_j) \qquad \textbf{(B-33)}$$

The joint confidence region is the region of joint parameter uncertainty accounting for variation of all the parameters. It is defined as

$$\underline{S}(\hat{a}) \le \underline{S}(\underline{b}) \cdot s(b_j) \cdot \left[1 + N_p s^2 F(N_p; N_e - N_p; 1 - \alpha)\right] \qquad \textbf{(B-34)}$$

The boundary of the joint confidence region is defined by all combinations $\underline{\beta}$ that satisfy

$$(\underline{b} - \underline{\hat{a}})^T X^T X (\underline{b} - \underline{\hat{a}}) = N_p s^2 F(N_p; N_e - N_p; 1 - \alpha) \qquad \textbf{(B-35)}$$

For linear models the joint confidence region is an N_p-dimensional ellipsoid. All parameters encapsulated within this hyperellipsoid do not differ significantly from the optimal estimates $b_{j,opt}$ at the probability level of 1-α.

Determination of confidence limits for non-linear models is much more complex. Linearization of non-linear models by Taylor expansion and application of linear theory to the truncated series is usually utilized. The approximate measure of uncertainty in parameter estimates are the confidence limits as defined above for linear models. They are not rigorously valid but they provide some idea about reliability of estimates. The joint confidence region for non-linear models is exactly given by Eqn. (B-34). Contrary to ellipsoidal contours for linear models it is generally banana-shaped.

B2. Complex reactions

B2.1. Parameter estimation

For complex reactions more than one dependent variable is measured. The fitting procedure should take all the observed variables into account. When each of the variables has a normally distributed error, all data are equally precise, and there is no correlation between the variables measured, parameters can be estimated by minimizing the following function:

$$SS_{res} = \sum_j \sum_k \left(y_{kj,calc} - y_{kj,exp}\right)^2 \qquad \textbf{(B-36)}$$

where k is the number if experiment and j is the number of observed variables. Determination of these variances requires replication of experiments under at least one set of operating conditions. When replicates are not available, the weighing factors are chosen based on sound judgement. It should be noted that the least squares technique is a particular case of the maximum likelihood principle, which consists in maximization of the likelihood function:

$$L = \frac{1}{(2\pi)^{\frac{N_e N_v}{2}}} \exp\left\{-\frac{1}{2} \sum_{i=1}^{N_v} \sum_{j=1}^{N_v} \sigma^{ij} \sum_{k=1}^{N_e} \left(y_{ki,calc} - y_{ki,exp}\right)\left(y_{kj,calc} - y_{kj,exp}\right)\right\} \qquad \textbf{(B-37)}$$

where N_v in the number of dependent variables and σ^{ij} are the elements of the inverse of Σ:

$$\Sigma^{-1} = \{\sigma^{ij}\} \tag{B-38}$$

while Σ is the covariance matrix of statistically interdependent errors. Froment and Hosten (1981) summarized criteria of multiresponse maximum likelihood parameter estimation and conditions for their application; these are given in Table B-2.

Table B-2
Criteria of multiresponse maximum likelihood parameter estimation and conditions for their application.

Conditions for application	Criterion	
Experimental errors independent with equal variances.	$\sum_{j=1}^{N_v}\sum_{k=1}^{N_e}\left(y_{jk,exp} - y_{jk,calc}\right)^2$	**(B-39)**
Experimental errors independent with unequal variances.	$\sum_{j=1}^{N_v}\frac{1}{\sigma_k^2}\sum_{k=1}^{N_e}\left(y_{jk,exp} - y_{jk,calc}\right)^2$	**(B-40)**
Experimental errors interdependent with known covariance matrix Σ.	$\sum_{j=1}^{N_v}\sigma^{ij}\sum_{k=1}^{N_e}\left(y_{ki,exp} - y_{ki,calc}\right)\left(y_{kj,exp} - y_{kj,calc}\right)$	**(B-41)**
Experimental errors interdependent with known covariance matrix Σ: No missing observations.	det S where $S = \{s_{ij}\} = \left\{\sum_{k=1}^{N_e}\left(y_{ki,exp} - y_{ki,calc}\right)\left(y_{kj,exp} - y_{kj,calc}\right)\right\}$	**(B-42)**
Experimental errors interdependent with known covariance matrix Σ: Few observations, y^*, are missing.	$\det S \xrightarrow{b,y^*} Min$	**(B-43)**
Experimental errors interdependent with known covariance matrix Σ: Many, N_l say observations of l-response are missing.	$\sum_{j=1}^{N_v}\left[\sum_{k=1}^{N_e}\left(y_{kj,exp} - y_{kj,calc}\right)^2\right]^{\frac{N_l}{2}}$	**(B-44)**

The commonly encountered case mentioned in the forth row of the table can be rewritten in the extended, more commonly known form:

$$Det = \begin{bmatrix} \sum_i\left(y_{i1,exp} - y_{i1,calc}\right)^2 & \sum_i\left(y_{i2,exp} - y_{i2,calc}\right)\left(y_{i1,exp} - y_{i1,calc}\right) & \cdots & \sum_i\left(y_{ik,exp} - y_{ik,calc}\right)\left(y_{i1,exp} - y_{i1,calc}\right) \\ \sum_i\left(y_{i1,exp} - y_{i1,calc}\right)\left(y_{i2,exp} - y_{i2,calc}\right) & \sum_i\left(y_{i2,exp} - y_{i2,calc}\right)^2 & \cdots & \sum_i\left(y_{ik,exp} - y_{ik,calc}\right)\left(y_{i2,exp} - y_{i2,calc}\right) \\ \vdots & \vdots & & \\ \sum_i\left(y_{i1,exp} - y_{i1,calc}\right)\left(y_{ik,exp} - y_{ik,calc}\right) & \sum_i\left(y_{i2,exp} - y_{i2,calc}\right)\left(y_{ik,exp} - y_{ik,calc}\right) & \cdots & \sum_i\left(y_{ik,exp} - y_{ik,calc}\right)^2 \end{bmatrix} \tag{B-45}$$

What is striking in the minimization of this criterion is that the size of the confidence region of parameters is significantly reduced.

B2.2. Statistical analysis

The significance of the overall regression can be tested by means of the F-test. The quantity

$$F_c = \frac{\sum_{i=1}^{N_v}\sum_{j=1}^{N_v}\frac{\sigma^{ij}}{N_p}\sum_{k=1}^{N_e} y_{ki,calc}\, y_{kj,calc}}{\sum_{i=1}^{N_v}\sum_{j=1}^{N_v}\frac{\sigma^{ij}}{N_e N_v - N_p}\sum_{k=1}^{N_e}\left(y_{ki,calc} - y_{ki,exp}\right)\left(y_{kj,calc} - y_{kj,exp}\right)} \qquad \textbf{(B-46)}$$

is distributed like F with N_p and $N_e N_v$ - N_p degrees of freedom. If this ratio exceeds the value of F tabulated for percentage α and $<N_p, N_e N_v - N_p>$ degrees of freedom, the regression can be considered to be meaningful.

B3. Criteria for model rejection and selection of the best model

There are several methods for discrimination between rival models. Froment and Hosten (1981), Bischoff and Froment (1991), and Kittrell (1970) summarized them and discussed applications for kinetic models. Here only approximate methods will be presented.

1) Parameter estimates must have physical meaning, *i.e.* the activation energy and (adsorption) equilibrium constants must be positive, the adsorption enthalpy must be negative (warning: adsorption can be endothermic if some of the adsorbed molecules dissociate), the change of entropy due to adsorption must be negative. However, if physically meaningful values fall into the confidence limits, the apparently meaningless estimate should not be rejected but methods for improving the accuracy of experiments and search for model parameters should be found. The models with undoubtedly (in a statistical sense) physically meaningless estimates cannot be accepted.

2) Parameter estimates should not differ by orders of magnitude from those evaluated using well established methods of thermodynamics or known from the literature; several rules concerning adsorption phenomena have been worked out by Boudart *et al.* (1967); the optimal parameter estimates should not differ very much from the initial guesses if the latter were determined in well designed separate dedicated experiments.

3) The qualitative proportion between some model parameters should be as that known from existing knowledge; e.g. the relative adsorption strength of various species on different metals is quite well known and a totally different order of strength found by regression can be considered as an indication that the model should be rejected.

4) Parity diagrams: the quantity calculated y_{calc} vs. the quantity observed y_{exp} or plots of residual deviations (y_{calc} - y_{exp}) vs. predicted values y_{calc} should show uniform bands: the scatter of points should be uniform; any systematic deviations disqualify the model, which should then be rejected. The data points on plots of linearized equations should scatter uniformly.

5) The models characterized by small intercorrelation coefficients are preferred to the models of large intercorrelation coefficients; arbitrarily it can be assumed that intercorrelation coefficients of an absolute value over 0.8 should not be accepted.

6) The models with insignificant overall model regression as indicated by the F_c-value and with meaningless parameter estimates (with confidence limits) as indicated by t-values should be rejected. If rejection of the parameter does not lead to a physically nonsensical model structure, repeat parameter estimation and statistical analysis.

7) The model with the largest F_c can be considered to be the best of all adequate models.

8) The principle of parsimonious parametrization should be applied, according to which the model with as few parameters as possible should be selected; this is in accordance with the Wheeler recommendation: "the best model is the simplest one that works". This is also a guideline for making increasingly complex models: stop when the model is sufficiently complex to get an adequate fit of the data.

References for Appendix B

See end of Chapter 5.