

THE MECHANISM OF REACTIONS IN THE UREA SERIES

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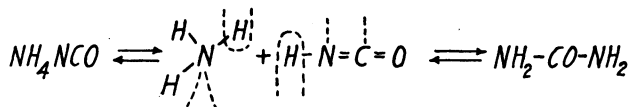
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Except for known reactions between ions and the corresponding dissociation of molecules into ions, chemical reactions in general—without prejudice to the electrical nature of chemical affinity—appear to take place between molecules. Of the reactions between molecules two sorts appear to be distinguishable, one in which metathesis occurs or the interchange of parts between two or more molecules, and the other in which the spontaneous combination or un-combination of molecules occurs directly. Reactions of the second sort may be reversible, like the combination of ammonia with hydrogen chloride, or irreversible, like the addition of bromine to ethylene, or the molecule first formed by the combination of the original molecules may break down again to yield molecules different from those from which it was first formed, as in the case of ammonium nitrate which is formed by the combination of ammonia with nitric acid and which yields nitrous oxide and water when it is heated.

At present there is a growing tendency among organic chemists in favor of the belief that there are no real metathetical reactions strictly so-called, that reactions consist of the spontaneous addition and separation of molecules, and that the appearance of metathesis which exists in many cases is due to the readiness of the molecule first formed from the reagents to break down again in a new sense to yield the products of the reaction. Such mechanisms have been proved in particular cases, such as in certain halogenations; they have been shown to be highly probable in others, such as in ester formation; but in many other cases, probably the large majority, they are hypothetical and unconvincing.

In the urea series we have been able to show that the mechanism of a large number of reactions is either the reversible combination of molecules or the direct combination of molecules to form new molecules which themselves break down in a predictable manner. By applying the end products as reagents it has been found possible to simplify a number of syntheses.

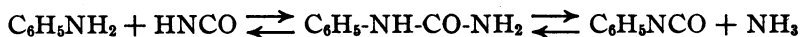


Ammonia and cyanic (or isocyanic) acid enter into reversible combination with one another in two ways which correspond to the two-fold chemical characters of these substances. If the ammonia functions in its basic

nature, the nitrogen increasing its valence to five, and if the ionizable cyanic acid acts as acid hydrogen and electronegative cyanate radicle, then the product is ammonium cyanate. If the ammonia acts in its other capacity of H and NH₂, and if the cyanic acid functions through the unsaturated character of its nitrogen-carbon linkage, then urea is the result.

The conversions of the cyanates of ammonium and of primary and secondary amines to urea and substituted ureas by the evaporation of their aqueous solutions have long been cited as examples of the "urea rearrangement." It seems proper and convenient to denominate the reverse of such changes the *urea dearrangement* and to say that a urea derivative *dearranges* when its molecule breaks down in an orderly fashion analogous to that in which urea breaks down into ammonia and cyanic acid. Just as the possibility of urea formation is determined by the presence of one unsubstituted hydrogen in the ammonia residue, so the possibility of the dearrangement is determined by one unsubstituted hydrogen in the urea molecule. The mechanism of the reactions is not affected by the substitution of the oxygen of the cyanic acid. Unsymmetrical urea derivatives, if they have hydrogen atoms on each of the nitrogens, dearrange in two modes which correspond to the movement of one or of the other of the hydrogen atoms.

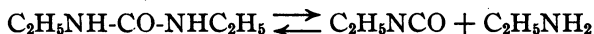
When urea is heated alone¹ or in aqueous solution² it dearranges into ammonia and cyanic acid. The ammonia escapes, and if aniline is present the cyanic acid combines with it to form phenylurea. Phenylurea dearranges in two modes which correspond to two methods for its formation.



If it is heated alone at 160°, ammonia comes off rapidly, the aniline and phenylisocyanate may be detected by their odor but they combine in large part to form *sym.*-diphenylurea which crystallizes out from the hot liquid, and cyanic acid may be detected by means of silver nitrate in the water with which the apparatus is washed out after the experiment. When an aqueous solution² of phenylurea is distilled, aniline may be detected in the distillate and *sym.*-diphenylurea crystallizes from the boiling liquid. By heating urea with the amine or with its hydrochloride² at 160°, or by refluxing urea in aqueous solution³ with the amine or its hydrochloride, we have prepared *sym.*-di-*o*- and *p*-tolyl, di- α - and β -naphthyl, dimethyl, di-*n*-butyl, di-*n*- and *iso*-amyl and dibenzylureas in satisfactory yield.

The dearrangement of phenylthiourea may be demonstrated very simply by heating a small quantity of the material in a test-tube. It undergoes a violent decomposition slightly above its melting-point, the odors of ammonia, of aniline, and of phenyl mustard oil may be detected, and the residue which consists largely of *sym.*-diphenylthiourea gives with ferric chloride the red color characteristic of thiocyanic acid.

Symmetrical disubstituted ureas in which the two subsequent groups are alike can dearrange in only one manner.



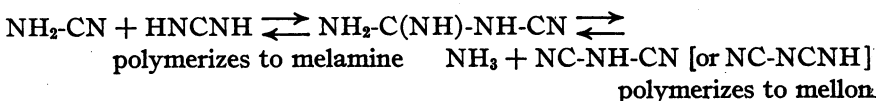
If *sym.*-diethylurea is heated with aniline, the gaseous ethylamine which results from the dearrangement escapes and the ethyl isocyanate combines with the less volatile aniline to form *sym.*-ethylphenylurea. This substance can now dearrange into two modes.



When *sym.*-ethylphenylurea is heated alone at 160°, ethylamine escapes and the phenylisocyanate and aniline combine to form *sym.*-diphenylurea. The urea dearrangement then provides the true explanation of the apparently metathetical reaction in which the ethyl groups of *sym.*-diethylurea are successively replaced by phenyl.²

Unsymmetrical disubstituted ureas are obtained in poor yield by refluxing an aqueous solution of urea with the hydrochlorides of secondary amines,² and in much better yield by the interaction of secondary amines with nitrourea in aqueous solution at ordinary temperature.³ They can dearrange in only one manner, namely, to produce cyanic acid and the secondary amine: and their tendency toward dearrangement is so great that they have the odor of the amine even after recrystallization to the highest purity. If *unsym.*-ethylphenylurea is heated for a short time at 150°, the cyanic acid polymerizes to a cyanuric acid which separates from the melt in crystals and the ethylaniline remains in the tube and is readily identified as such.³ A study of the rate and extent of the dearrangement of a number of *unsym.*-disubstituted ureas is now under way in this laboratory with the expectation that the results will show us the effect of various substituents on the reactivity of molecules in these reversible addition reactions.

The tautomeric substance, cyanamide, is at once a derivative of ammonia and a derivative of cyanic acid; it is ammonia with a cyan group in place of one hydrogen, and it is cyanic acid with NH in place of the oxygen. The formation of dicyandiamide or cyanoguanidine when an aqueous solution of cyanamide is evaporated appears then to be a clear case of urea formation. Dicyandiamide can dearrange in two senses, and when heated above its melting point does indeed yield the expected products, ammonia, cyanamide, and melamine and mellon, the trimers respectively of cyanamide and of dicyanamide.



aqueous solution of nitrourea, crystals of phenylurea are deposited³ after two days standing at ordinary temperature. By the use of other primary and secondary amines, many mono-substituted and unsym.-disubstituted ureas may be obtained in excellent yield.³ If nitrourea is refluxed with alcohols, carbamic and allophanic esters are produced.³ A solution of nitrourea in concentrated sulfuric acid is a convenient reagent³ for the nitration of organic substances which are not injured by contact with sulfuric acid.

When nitroguanidine is dissolved in concentrated sulfuric acid, the solution contains two substances one of which gives off nitrous oxide rapidly on heating while the other gives off carbon dioxide later and more slowly.⁴ The first of these substances cannot be ammonium nitrate because ammonium nitrate is converted to nitric acid by the action of one equivalent of concentrated sulfuric acid and therefore would not sustain the action of a large excess of that reagent. It cannot be nitric acid for the solution does not yield nitric acid when it is heated: it yields laughing gas. It cannot be guanidine nitrate for then the carbon dioxide and nitrous oxide would come off simultaneously when the solution is heated. But the substance is convertible to nitric acid, for the solution gives up its NO_2 group quantitatively in the nitrometer and has been found to be a suitable reagent for the nitration⁴ of aniline, phenol, etc. The solution therefore contains nitroamide, capable of losing water to form nitrous oxide and capable of combining with water to produce nitric acid. The other substance which is present in a sulfuric acid solution of nitroguanidine, the substance from which the carbon dioxide is produced, might conceivably be guanidine, but, if guanidine were present, nitric acid would be present also. The other possibility is cyanamide. And the production of cyanamide by the dearrangement of nitroguanidine is demonstrated by the fact that an aqueous solution of nitroguanidine boiled with methylamine or aniline yields⁴ methylguanidine or phenylguanidine. Although we have not isolated the products, we have thus been able nevertheless to show that nitroguanidine dearranges into nitroamide and cyanamide and have been able to carry out certain syntheses based upon the dearrangement.

To summarize: the mechanism of many reactions in the urea series is the reversible combination of molecules, and all urea derivatives which we have studied dearrange or break down, often in more than one fashion, but always in a predictable manner analogous to that in which urea dearranges into ammonia and cyanic acid. The ease with which various substituted ureas undergo the dearrangement is determined by the nature and position of the substituent groups, and it is expected that a further study of the matter will throw light upon the effect of groups in determining the reactivity of molecules. The products arising from the predictable dearrangement of urea derivatives have been used in synthesis and in some cases have shown themselves to be more convenient for use than other reagents.

¹ Davis and Underwood, *J. Am. Chem. Soc.*, **44**, 2595 (1922).

² Davis and Blanchard, *Ibid.*, **45**, 1816 (1923).

³ Observations not yet published.

⁴ Davis and Abrams, not yet published.

AN EQUATION FOR THE HABER EQUILIBRIUM¹

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The equation:

$\log K_p = (2679.35 + 1.1184 p) 1/T - (5.8833 + 0.001232 p)$
represents within the experimental error the equilibrium constant values determined by the Fixed Nitrogen Research Laboratory over the temperature range about 325° to 500°C and from 100 atmospheres to the lowest pressures. The equation is serviceable for calculating " K_p ," exactly for an equilibrium mixture resulting from the use of a reacting mixture made from atmospheric nitrogen and having a hydrogen-nitrogen ratio equal to 3.24.

The equation:

$\log K_p = (2172.26 + 1.99082 p) 1/T - (5.2405 + 0.0021550 p)$
represents well the high pressure data of the same laboratory, but not so many decimal places are serviceable in this case, because the hydrogen-nitrogen ratio is less definitely known.

An attempt to construct one equation for both high and low pressure data fails because of a discontinuity, which is too small to be shown by plotting of isobars, but is strikingly exhibited when the pressure variations of the parameters of the isobars are examined. A similar discontinuity exists between the given data at 30 atmospheres and Haber's data at the same pressure. Both discontinuities are believed to be the result, not of experimental error, but of variation in the composition of the gas mixture.

Evidence is therefore found in the data for the Haber equilibrium that the function K_p is not strictly constant with respect to any variation whatsoever of the internal variables, the number of independent variables being given by the phase rule.

An important experimental task therefore remains; to determine at least around the stoichiometrical composition, the variation of K_p with the composition. At high pressures the maximal yield of ammonia may occur at a hydrogen-nitrogen ratio different from three.

Details of the calculations will shortly be published in the *Journal of*