Towards the Atomic-level Simulation of Water-in-Crude Oil Membranes

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I. INTRODUCTION

Water-in-crude oil (W/O) emulsions form a ubiquitous part of reality for the majority of oil-production sites. The water component of W/O emulsions comes from either formation water or reinjected water mixed up with the crude oil produced, with the rate of water injection increasing as the deposits are worked out. When this mixture progresses through pipes, valves, and chokes, and the energy required to produce a colloidal system is dissipated, formation of emulsion will follow almost inevitably (though the latter could break down in a matter of seconds if certain demulsifiers are present or the content of natural stabilizers is insufficient) (1-4). Indeed, as a massive molecular-dynamics simulation (5) has proved, when placed in a two-phase water/oil environment even a system composed by very crudely denned hydrophilic headgroups and lipophilic tails will undergo self-assembly into a surfactant layer and micelles.

The stability of the resulting emulsion is known to depend heavily on surfactant stabilizers, both naturally occurring in crude oil and artificial ones (usually commercial). Natural surfactant stabilizers of W/O include asphaltenes and resins. Asphaltenes are often defined as pentane-insoluble and benzene-soluble portions of crude oil (6); on the other hand, the authors of Ref. 4 argue that the distinction between asphaltenes and resins is not so well defined and given the closeness in molecular weights, asphaltenes could be called heavy resins, an argument supported by showing the similarities in the infrared diffuse-reflec tance spectra of asphaltenes and resins (7). According to Table 1 of Ref. 4, the molecular weight of the two surfactant components found in the North Sea crude ranges from 1400-1300 (asphaltenes) to 1200-900 (resins).

Commercial stabilizers include among others, ionic sodium nonylphenol polyoxyethylene-25 sulfate (SNP-25S) (8), as well as nonionic Tween 20^{TM} [sorbitan mono-9-octadecenoate poly(oxy-l, l-ethanediyl)] and Tween 80 (8), tetraoxylene nonylphenolether (C₉PhE₄, NP-4), octaoxyethylene nonylphenolether (C₉Ph₈, NP-8), sorbitan monolaureate (Span 20), and sorbitan mono-oleate (Span 80) (4).

A. W/O Emulsion: Macroscopic Factors Affecting Stability

Colloidal systems containing both natural and com mercial surfactants display a wide range of behavior, for instance, 90% of the continuous phase decants after 12 h when NP-4 is added, while the figure is only 5% for Span 80 (4). Under the same mixing con ditions, Span 80 produces small, monodisperse droplets, while span 20 and NP-4 give

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substantially larger and more polydisperse droplets. The addition of NP-8 (a compound with eight ethoxy units as opposed to four units in NP-4) causes the system to invert from a W/O to an O/W emulsion as a result of interfacial conditions changing with the hydrophilic-lipophilic balance.

The composition of the oil phase can also influence the stability of W/O emulsions insofar as it affects the interfacially active components. It was found (2) that emulsion stability underwent dramatic alterations as the oil phase changed from aliphatic to aromatic; an initial increase in stability, peaking at a 4:1 decane-to-toluene ratio, was followed by monotonic decline towards total instability (separation within seconds of emulsification). Reference 4 explains this decline by monomerization and dissolution of the asphaltenes in toluene and their resulting removal from the interface.

Understanding the factors deciding either stability or instability of W/O emulsions means deciphering the stabilization mechanism. This last hinges on insights into the chemistry, physics, and dynamics of their interfacially active constituents. Experimental data show that interfacial activity alone could not be considered a measure of stabilizing capacity. Resins, though good surfactants, fail as stabilizers, whereas asphaltenes are able to stabilize emulsions by themselves if their fraction is high enough (2%), but not 1%). On the other hand, when the 1% aslphaltene fraction is combined with 1% of resin the resulting emulsion proves to be much more stable than one with only 1 % of asphaltenes.

While biological-scale permeation by water and ions apparently does not destroy lipid bilayers, we believe that evidence of any heavy mutual incursion of water and hydrocarbon components will indicate an imminent breakdown of the surfactant-stabilized interface and open the way to flocculation in the given W/O system. Consider Ref. 1, which states that the ability of alcohols to dissolve into the different regions of the emulsified system is an important parameter of their efficiency as destabilizers. Mediumchain alcohols readily dissolve into all three pseudo-phases (interface, and aqueous and oil phases). Kravczyk (9) concluded that the interfacial region becomes less rigid and structured as a result of considerable interfacial fluctuations occurring in the presence of medium-chain alcohols.

There is a considerable negative surface charge present on the interface between pure oil and water phases and even on water-oil interfaces containing nonionic surfactants (8). This relatively high surface potential (-50 to -70 mV) was found to contribute to an appreciably longer lifetime of emulsion drops. Conversely, a surfactant offsetting the surface potential either by displacing the surface charges or by creating a surface potential with opposite charge to that of the bare water-oil interface will undoubtedly destabilize the W/O emulsion.

Under hydrate-formation conditions, the destruction of the colloidal system will bring available water into contact with hydrocarbon hydrate formers, allowing thermodyanmically favored growth of the solid phase (hydrate crystals); these crystals can plug a pipe in a matter of minutes.

II. LIPID BILAYERS: CELLULAR VERSIONS OF SURFACTANT-STABILIZED INTERFACES

Cellular membranes are complex multicomponent structures assembled from various lipids and proteins. It could be said that the majority of processes essential for the functioning of living cells involve the interface between water and those biomembranes. These include unassisted and mediated transport ions and nutrients, transmission of neural signals, mediation of immune response, and membrane fusion (10). The structural features of membranes are mainly determined by a bilayer arrangement of their basic amphiphilic components, lipids, with the polar head-groups facing the aqueous exterior, and the hydrocarbon tails extended towards the membrane interior. Lipid membrane formers include dipalmitoylphospha-tidylcholine (DPPC), dilauroylphosphatidylcholine, palmitoyloleoylphosphatidylcholine, and phosphati-dylserine.

As one can see from Figs 1 and 2, membranes in lipid bilayers and W/O emulsions have in common the general sequence of water/aqueous solution -polar/ionic heads hydrocarbon tail regions. The only bilayer section that does not find a direct parallel in W/O membranes is the region of low tail (and overall) density; its W/O counterpart does exist but its overall density will not be all that low due to the hydrocarbon phase filling the free volume. However, since the time scale available to state-of-the-art simulations does not allow for spontaneous penetration of this area (as opposed to deliberate placing of molecules for calculation purposes), the bulk of the insights gained from bilayer simulations could probably be transferred to a basic understanding of the factors determining stability/instability in W/O emulsions. Another structural difference between the membranes involves the fact that asphal-tenes must be polymeric to be able to act as stabilizers. This implies headgroups connected by hydrocarbon chains lying near the interface surface and imposing certain restrictions on the



Figure 1 Schematic representation of W/O membrane: water; headgroups, shown as spheres, are connected by chains; hydrocarbons tails protrude into the oil phase.

headgroup positions and movements. Yet another difference is the lipid bilayers' lack of "backwash" of apolar hydrocarbon components, occurring to a certain extent in real-life W/O membranes. On the other hand, water solubility in hydrocarbons is surprisingly high, much higher than hydrocarbon solubility in water, so the excursions of hydrocarbons into the water section could be treated as additive disturbances of the main process: penetration of the surfactant membrane by water molecules.

A. State of the Art in Molecular Modeling of Lipid Bilayers

Once the computer resources advanced far enough to allow their atomic-level simulation, few interfacial phenomena have attracted more attention from researches in the field of molecular modeling as the transport of small molecules in lipid bilayers. Simulation of unassisted transport of water (11) and ions (12); study of energetic and structural effects



Figure 2 Schematic representation of the bilayer membrane: water; two lipid membranes with headgroups, shown as spheres; and hydrocarbon tails protruding into membrane interior.

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that a net charge (13), an inclusion of cholesterol (14), or an amphiphilic pep-tide (15) has on the membrane; and general behavior of anesthetics and their interaction with the water-bilayer interface (16-18), to name only a tiny fraction of papers in this steadily growing field.

Existing models for permeation of small molecules through lipid membranes apply, for the most part, basic ideas developed for diffusion across polymer membranes, therefore treating lipid bilayers as soft polymer membranes with sharp boundaries. This approach emphasizes the significance of free volume and its fluctuations (11, 16). Small diffusing molecules are thought to spend most of the time confined to a cavity formed from the immediate neighboring mole cules. These cavities exist in all amorphous polymers whether pénétrants are present or not and they typically have the size to hold a gas molecule or a small solvent molecule. They fluctuate in size and shape, but do not migrate or disappear on the nanosecond time scale. Displacement of a molecule contained in such a "cage" is enabled by transient channels of free volume which are constantly being opened and closed owing to thermal fluctuations. Thus, solute diffusion across membranes should be facilitated by the dynamics of free volume pockets in the membrane, a process which could be studied by means of molecular simula tions. However, as we shall see, free volume is only one (and often not the deciding) factor governing transport across the membrane.

B. Simulation of Water Transport Across a Lipid Membrane

Work was undertaken on an atomic-level study of water transport through a phospholipid/water bilayer system (11). The simulation cell contained a bilayer composed of 64-DPPC molecules as well as 736 water molecules modeled as SPC (simple point charge). Periodic bound ary conditions in all three dimensions have been applied and a GRO-MOS (19, 20) force field was used. The sys tem was weakly coupled with constant-temperature and constantpressure baths (21) (at 350 K and 1 atm, respectively). Molecular-dynamics simulation showed that four drastically different regions could clearly be discerned in the system, namely, (1) a low headgroup density zone with comparable density of water and headgroups; (2) a zone of high headgroup density with water density under 1%; (3) a region of high tail density; and (4) a low-density membrane interior. All of the regions except for the interior have their counter parts in W/O membranes. The W/O system's counter part of zone 4 would be a region of low tail velocity blending into the bulk hydrocarbon fluid. Judging by the tempera-

ture-dependent data (11), neither of the sub-regions will present any great resistance to water trans port [diffusion coefficient of water in hexadecane is estimated as 12×10^5 cm²/s at 350 K; self-diffusion in bulk SPC is 7.5×10^{-5} cm^2/s (11)]. The relative wdith of zone 1 indicates that the interface between the dipolar groups and water is significantly diffused, with distributions of water and headgroups demon strating a wide overlap. These findings are confirmed by experimental data (11). No evidence for singledis persed molecules of water has been found in the course of simulations. It appears that water molecules pene trate the membrane "in a school crocodile," trying to keep at least one hydrogen bond to a neighboring water molecule. Radial distribution functions exhibited well-defined first and second hydration shells for choline-methyl groups, but phosphate-oxygen and carbonyl-oxygen groups were found to have only the first shell.

The free-energy profiles were roughly trapezoidal, with a maximum reached in the high tail density region. This is in contrast to the step function assumed in soft-polymer models with sharp boundaries. As expected, the four different membrane regions have widely varying diffusion coefficients. The highest diffu sion rate corresponds to the membrane interior, the lowest one to the start of the high tail density region. Diffusion on the local scale appears essentially aniso-tropic everywhere except for the high tail density zone where the alignment of tails appears to favor the diffu sion along the membrane normal in comparison with the lateral one. On the other hand, this difference might be something of an artifact resulting from the particular estimation technique. The low diffusion rate in zone 2 does not necessarily mean high resistance to permeation, since this is mostly determined by the free-energy barrier, which is almost non-existent there.

C. Charged Biological Membrane

The importance of net charge on the lipid membrane has been highlighted in the molecular-dynamics study of dipalmitoylphosphatidylserine (DPPS) lipid mem brane (13). Experimental data suggest that at neutral pH aqueous dispersions of DPPS assemble into lamel-las with a net negative charge. The membrane model consisted of 64 DPPS⁻, 64 Na⁺ and 732 H²O mole cules. Weak coupling (21) with the constant-tempera ture bath (350 K) and reference pressure bath (1 atm) was used to maintain temperature and pressure. The simulated system of Ref. 13 has been able to reproduce seemingly illogical experimental findings that the per-lipid surface area in charged DPPS is smaller than in the case of neutral phospholipid DPPC. It appears that

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the ammonium group displays a strong intermolecular coordination, preferring to be bound to serine carbo-nyl oxygen rather than to phospatidyl or carbonyl tail oxygen, which could lead to an increase in the per-phospholipid surface area. Thus, the charge interactions between phospholipids are able to offset the elec trostatic repulsion.

The model system has also showed much lesser hydration of phosphate groups, a feature probably contributing to easier penetration by water, since the water molecules do not have to remain bound within the hydration shells. The atom charge distribution across the membrane showed that phospholipid head-groups provide an electrostatic environment conductive to penetration of the headgroup zone by water molecules and sodium ions. This conclusion was also borne out by the fact that water diffused faster in the interface region of the DPPS membrane than in the DPPC membrane.

D. A Cholesterol-containing Bilayer

It is a well-known experimental fact that incorporation of cholesterol in lipid bilayers affects the mechanical and transport properties of membranes. This includes their increased bending elasticity (22) and reduced passive permeability to small molecules (23, 24). Despite a great deal of theoretical and experimental research, no definitive microscopic understanding of phospholipid-cholesterol interactions has been proposed yet.

Incidentially, this modification of bilayers by cholesterol could be considered a rough parallel to increased rigidity and stability of heterogeneous W/O membranes resulting from addition of resins to asphal-tene-containing crude.

Constant-temperature and constant-pressure moleculardynamics simulations of a cholesterol-containing DPPC bilayer were reported in Ref. 14 where eight well-separated DPPC molecules were replaced in a configuration representing a fully hydrated liquid crystal phase bilayer at 50°C. The analysis of changes brought about by addition of cholesterol proves that the impact plays itself on the microscopic scale so far attainable only through atomistic molecular simulations. For example, though cholesterol is known to have a "condensing" effect on the bilayer (a definite macroscopic-scale event), the examination of the freevolume fractions suggests that cholesterol-induced reduction of bilayer passive permeabilities (by a factor of 3.5 for acetic acid upon addition of 20% cholesterol in DPPC at 50% does not result exclusively from a "condensation" or repacking of chains.

Cholesterol impact translates into a roughly one-third decrease in diffusion motion of both DPPC and cholesterol

molecules, with different sections of lipid bilayer being affected to a very different degree: the bilaver interior shows only a slight influence, manifesting as a small decrease in empty free volume. It is the water/bilayer interface that undergoes significant changes. The bilayer/water interface is more pronounced, with the DPPC and water densities decreasing more abruptly at the edge of the membrane, in the cholesterol-containing bilayer. The peaks of constituent electron densities have been shifted slightly towards the bilayer center, consistent with the decreased bilayer thickness. The choline density, roughly symmetrical in the pure DPPC bilayer, has been skewed significantly towards the center and its peak is now coincident with the phosphate peak. Thus, the presence of the cholesterol causes the choline group to move inward and lie nearly flat to the bilayer plane (P-N vector's average inclination is 6° compared to 17^o for pure DPPC). The authors of Ref. 14 suggest that this effect is caused by cholesterol lying low and leaving holes in the bilayer surface that are generally filled by choline ammonium groups from neighboring DPPC molecules. Cholesterol hydroxyl groups were found to lack strong preferences for interacting with specific DPPC moieties; statistical analysis revealed that the hydroxyls interact exclusively with water about half of the time, with the other half equally split between the phosphate and carbonyl groups. As shown by both electrostatic measurements and molecular-dynamics simulations, water molecules in the DPPC/cholesterol bilayer vicinity are "orientationally polarized" to a greater extent than in pure DPPC bilayer. The high percentage of time spent in hydrogen bonding with water could explain the lower permeability of the cholesterol-containing DPPC bilayer.

Another factor contributing to a higher free-energy barrier for a passively penetrating solute is the cholesterol-induced narrowing of the interface. A significant influence of cholesterol on the subnanosecond lipid dynamics, namely, freezing of the center of mass and large-amplitude chain motions, could translate into increased microscopic viscosity for the unassisted transport of solute.

III. POSSIBLE SIMULATION STRATEGY FOR MOLECULAR DYNAMICS INVESTIGATION OF WATER/OIL LIQUID MEMBRANE SYSTEMS

A. Grand Canonical Ensemble: Fixing the Chemical Potential

While able to simulate constant temperature and pressure/temperature ensembles in atomistic detail, all the

membrane simulations reviewed so far have one feature in common - the number of molecules remains a constant. If surfactants under study fail to stabilize W/O membrane and it is breached by water and oil molecules at an appreciable rate, an essentially none-quilibrium process (flux) would develop, leaving open the possibility of water density deviating from its bulk value event at positions furthest from the water-surfactant interface. With this in mind we believe it would be instructive to review approaches and set-ups used to model systems at constant temperature, constant pressure/volume, and, most important, constant chemical potential gradient, even though the membrane modeled were fixed.

B. Dual-control Volume Approach for Gradient-driven Diffusion: Monte Carlo versus Molecular Dynamics

Earlier simulations of flux in slit pores and diffusion of gas through micro- and nano-pore membranes (25-28) essentially simulated particle flow between a source and sink regions with a pore or a fixed membrane in the middle. Particles were removed once they reached the sink area. The source region density has been kept constant by means of particle insertion. However, since it is the chemical potential gradient that is the driving force of diffusion, simulation in the grand canonical ensemble (uVT) would be the one most true to real-life diffusion situations. The authors of Refs 28 and 29 proposed using the recipes of grand canonical Monte Carlo (GCMC) to control the chemical potential in two control volumes placed at a distance of a half-cell length from each other. Periodic boundary conditions could then be applied in all three dimensions. The hybrid GCMC-molecular dynamics (GCMC/MD) scheme employed two types of moves, stochastic MC moves which aimed at adjusting the density in control volumes to match the driving chemical potential, and dynamic ones providing mass transport across the system. This dual-control volume approach has been implemented by means of a massively parallel algorithm LADERA (30) and has yielded correct values of transport properties for a simple Lennard-Jones system undergoing color diffusion (31), "uphill diffusion" in a bulk ternary Weeks-Chamber-Andersen potential (WCA) Lennard-Jones system (32), and gradient-driven diffusion through polymers (33).

Typical hybrid MC/MD approaches suffer from two major drawbacks. First, they call for insertion of a fullyfledged molecule, and the acceptance probability of such a

step will be quite low for dense fluids (as witnessed by the poor sampling of Widom particle insertion, which makes it fail in the case of water) and/or systems containing molecules widely differing in size. Indeed, according to Ref. 34, "because the accompanying change in energy of the insertion or deletion of large molecules is so great as to make the probability of accepting such a move prohibitively small, the range of applicability of the DCV-GCMD method as well as all other grand canonical simulation methods is limited." This limitation forced the authors of Ref. 34 to abandon constant-chemical potential treatment for the larger species in favor of the constant number of particle technique. However, the above statement is strictly true only for Monte Carlo-based grand canonical simulations. Pure GC/MD pioneered by Pettitt and coworkers (35-38) entails insertion/deletion of virtually ghost-like particles, whose interaction with all the other particles, both full and fractional, is attenuated by a factor of 0.01-0.02. This feature has permitted successful introduction of water molecules at real-life densities in two different integration schemes (36, 39) and should, in principle, be perfectly feasible for a constant-)! (constant-chemical potential) simulation involving large molecules.

Lynch and Pettitt (36) employed a pure Nose thermostat and RATTLE-like algorithm for bond constraint, as well as a single fraction particle. Our approach (40) used quaternions (41) to allow separate Nose-Hoover thermostats for translational and rotational modes. We found that the system's tendency to freeze in metastable states could be overcome by introduction of multiple fractional particles (four were used). Curve (b) of Fig. 3 is an extreme example of runaway insertions at high chemical potential as compared to curve (a) where the actual chemical potential of water resulted in a stable density virtually undistin-guishable from the experimental one.

The second, and no less important disadvantage of hybrid MC/MD approaches lies in the fact that if the insertion step is accepted, the newly created particle is assigned a velocity drawn from Maxwell's distribution. In one study (27) the particle was also assigned a streaming velocity calculated from the averaged previous flux, which raises the problem of self-consistency. Given the relatively small size of control volumes and the possibility of several particles being created or deleted within just a few time steps, there are no guarantees against the GCMC/MD procedure completely destroying the dynamics of the system and thus defeating the purpose of the exercise - simulating mass transport driven by the gradient in chemical potential. In the case of the pure GC/MD the newly created almost-zero particle is assigned zero velocity, the system is undisturbed, and the fledgling particle is free to probe its surrounding



Figure 3 Time evolution of TIP4P water system density in a grand canonical ensemble driven by two different chemical potentials; solid horizontal line corresponds to experimental water density at 298 K (0.9982 g/cm³.

and gain appropriate velocity. Playing the devil's advocate, we must point out that the advantage of the MC scheme lies in the fact that, while any straightforward application of GC/MD relies on the ensemble's intrinsic responses to correct for the possible density deviation in the control volumes, the hybrid GCMC/MD technique allows one to tailor the ratio between stochastic and dynamic steps to match the system's dynamics.

Application of the relationship between density and chemical potential allows one to use both GCMC/MD and GC/MD to calculate chemical potential in model singlecomponent systems of interest (e.g., 35, 36). The application of the schemes to interface systems could follow the general set-up suggested in Refs 26 and 31. One possible way to overcome the problem of slow response to pure GC/MD mentioned earlier will be to take a leaf out of the hybrid technique book and periodically freeze the entire system outside the control volumes (the distance between them insures that they do not affect each other). While the GC/MD steps are executed in two control volumes, the rest of the system is treated as static background. Full and fractional particles alike are confined to control volumes. In between the grand canonical steps it is the number dynamics that will be put on hold, with the fractional particles bouncing off the control volume walls in a direction normal to the interface.

C. Nose-Hoover Thermostat, Parameter Optimization, and the Issue of Ergodicity

Ever since its introduction, the Nose-Hoover thermo-state (42, 43) became a technique of choice for implementation of molecular-dynamics simulations in various constanttemperature ensembles, especially the canonical one (NVT). Since the use of molecular dynamics is mainly prompted by a desire to obtain the systems' dynamic characteristics, any method used to control the temperature must yield canonical distribution not only in coordinate space but also in velocity space. This in its turn raises the problem of the ergodic property of the system behavior. While it is universally accepted that even the most straightforward of constant-temperature schemes such as velocity scaling, will yield canonical distribution in configurational space (and yield, for instance, very good estimates of potential energy), canonical distribution of dynamic properties is a much more difficult problem. Curve (a) of Fig. 4 demonstrates the typical behavior of trans-lational modes in the NVE ensemble. We should draw attention to the highly irregular shape of the waveform, indicating a substantial coupling between trans-lational and rotational modes reported previously by DiCola and Deriu (44) and contributing to the ensemble's ergodicity. Curve (b) of Fig. 4



Figure 4 Variations of translational kinetic energy: (a) microcanonical ensemble; (b) tight thermostating (frequency about four times higher than the natural one); (c) optimum thermostating (response time about half again of the resonance value).

corresponds to a case of short thermostat response times; it shows clearly that chaoticity of motion, ergodicity's prerequisite, is clearly violated because of too tight restrictions imposed on the individual degrees of freedom. It is also obvious from the curve that low thermostat masses will severely inhibit mode mixing as well, since the modes will be driven by their own thermostats suppressing any possible interactions. We should also note that temperature fluctuations in this case are much smaller than those corresponding to intermediate and large thermostat response times.

It has been argued (42) that since the thermsotat's purpose is to provide the transfer of energy between the system and the heat "bath" the most efficient coupling would be insured when the thermostat frequency is at resonance with the natural frequencies of the system. Our analysis shows that the resonance conditions might be far from ideal where the ergodicity considerations are concerned. Substantial coupling between the modes, present in the NVE ensemble, appears to be absent at resonance, with the complex shape of the translational NVE mode substituted by a regular sine wave though with almost identical frequency. Curve (c) corresponds to thermostat response times, which are about half again of the resonance values; it is obvious that the mode behavior shows a striking resemblance to the natural one. This seems to indicate that thermostat response frequencies should be set somewhat below the resonance values to allow for the proper coupling of translational and rotation modes.

D. Simulating Water Penetration into NAM Membrane: Combining Single Control Volume with Pure Molecular Dynamics in a Grand Canonical Ensemble

N-Acetylmorpholine (NAM, see Fig. 5) is a solvent used in a mixture with JV-formylmorpholine (NF) for the removal of acidic gas compoounds (CO², H²S) from subquality natural gases by Morphysorb[®] technology from Krupp Uhde GmbH, Germany. The key economic advantages of using the process in a hydrocarbon-transporting pipeline stems from the very low solubility of C₁-C₆ hydrocarbons in NAM/NFM mixtures and the high capacity for acidic gases. This is why we believed it would be highly instructive to study the processes of an NAM membrane being penetrated by polar and apolar compounds. To this end we have used the suitably modified methodology of gradientdriven diffusion (30, 32-34). One modification consisted of using just one control volume (for water only). Another one involved application of Pettitt's purely molecular dynami-



Figure 5 NAM molecule.

cal version of the grand canonical ensemble, instead of Monte Carlo, to insure a constant chemical potential (35-38).

We constructed our simulation system by adding two identical slabs of 512 TIP4P water molecules on both sides of a cubic pre-equilibrated section of 64 NAM molecules (subsequently kept fixed throughout the simulation run). Water was chosen as a quintessential example of a polar solute [with a proven ability to reproduce the correct density at an experimental chemical potential as well (36, 39). The resulting simulation cell measured $52.25 \times 22.8 \times 22.8$ å, with the four fractional particles confined to an 11 å-wide control volume located in the middle of the water region. Periodic boundary conditions were applied in all three directions. The cut-off radius was set at 10 å for all interactions. The electrostatic part of the inter-molecular forces was handled by means of Ewald summation (45). Separate Nose-Hoover thermostats with optimum parameters established in our previous research constrained the kinetic energy of translational and rotational modes.

E. Simulation Details, Results, and Discussion

Our simulation program was a modification of the MC-MOLDYN package (46); the alterations involved changing the integration scheme to allow for the fractional particle dynamics with a Nose-Hoover thermostat and parallelizing it by means of a shared-memory approach. The parallel version was run on the 128-processor Cray Origin 2000 at Par-

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allab (Høgteknologi Center in Bergen); the sequential one on a DEC Workstation 400.

Some results obtained over the 0.8 ns run are presented in Figs 6-11. The number of water molecules in the chemical potential-control system first fell to 505 and staved at this number for 0.3ns, then the system corrected its own density, with the number of water molecules growing to 512, and subsequently starting to rise in response to gradual penetration of water into the NAM membrane. The number of full particles grew to 516-520 and then to 533 molecules (current number corresponding to the configuration shown in Figs 8 and 11). Consider the patterns of water penetration obtained in two systems, starting from identical initial configurations, but one run with the constant chemical potential within the control volume, and another under constant particle conditions. As can be seen by comparing Figs 7 and 8, and 10 and 11, water penetration proceeded significantly more vigorously under the constant chemicalpotential regime, since the fractional particles that scan the control volume have been able to "feel" the decrease in density resulting from water molecules moving into the NAM membrane, and compensate for it. No such compensation mechanism is available in constant-number schemes, causing them to underestimate the permeability of a membrane by a given species.



Figure 6 Starting configuration of the composite system in *XY* projection. Atoms in NAM molecules are connected by dotted lines. Section shown includes one of two water-NAM interfaces.



Figure 7 Same projection and area after 0.8 ns. No chemical potential control has been imposed in the control volume.

F. Free Energy and Chemical Potential: the Stumbling Block of Conventional Canonical Ensemble Calculations

A number of important physical properties, such as internal energy, heat capacity, diffusion coefficient, and pressure, could be expressed as NVE and NVT ensemble averages over the phase-space trajectory. And as such they could be



Figure 8 Projection, area, and time elapsed are the same as in Fig. 7. Chemical potential control was switched on from the start.



Figure 9 XZ projection of the configuration in Fig. 6.

evaluated in the course of a single simulation run with constant thermodynamic parameters. This is possible because these "mechanical" properties are related to the ratio of two high-iimensional integrals rather than integrals themselves. Entropy and entropy-related functions prove to be a very important exception. By its very définition sntropy depends on the volume of phase space available to the system,



Figure 10 XZ projection of the configuration in Fig. 7.



Figure 11 XY projection of the configuration in Fig. 10.

which makes it very difficult to determine within a canonical ensemble. On the other hand, knowledge of chemical potential and free energy of different phases and components is essential for determination of phase equilibria in chemical reactions and multicomponent systems, while it is the spatial distribution of free energy that determines the barriers to unassisted transport across various membranes, as discussed earlier. This is why considerable effort has been expended by numerous researchers to formulate techniques able to estimate these thermodynamic functions from computer simulations. Thermodynamic integration, the simplest and perhaps the most reliable of these techniques, requires a series of simulations. Straightforward application of Widom's particle insertion method (47, 48) is known to fail at high densities because of poor sampling. Various versions of the cavity-biased insertion technique were used by several authors to overcome the sampling problem for water and other dense liquids (17, 49).

Extending the system under investigation into a discrete set of balanced subensembles differing in such parameters as temperature, number of particles, or "ghostliness" of chains gives rise to the method of expanded ensembles (50, 51). All information necessary for determination of free energy or chemical potential could be extracted in the course of a single simulation run, since the system's evolution takes it from one subensemble to another through a Monte Carlo routine. This approach appears to work even for such an exotic system as the quantum Heisenberg model (52).

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Yet another line of attack could be implemented within the framework of the grand canonical ensemble (36—38) where chemical potential is treated as an input parameter and the number of particles as a dynamic variable. Following the determination of density for several input values, chemical potential at the density of interest could be estimated by interpolation.

G. Hybrid Method for Chemical Potential Estimation

"Hybrid," or modified real particle method was proposed by Kumar (53) as a method suitable for calculation of chemical potential at high densities. This technique combines Widom's test particle and the so-called real particle methods and calls for factious removal and subsequent reinsertion of particles already present in the y stem. The hybrid technique can be classified as a "nondestructive" one since it does not affect the proper time evolution of the system. It was suggested that this method would be particularly advantageous for simulation of macromolecules when a removal of a whole polymer chain is likely to create substantial free space and thus facilitate the reinsertion. This technique was tested in the original paper on Lennard-Jones particles and proven to yield good results at densities up to 1.1 and T^* down to 0.7.

The hybrid technique was applied by us (40) to the bulk TIP4P water system at 273 and 298 K. The "instant" chemical potentials provided by the method proved to be heavily dependent on the number of insertions, an expected feature shared with the test particle method, and on the particular molecule chosen for removal and reinsertion. The hybrid method also yielded chemical potentials lying below both experimental and model-specific values, and our simulations indicate that it may give rise to a "premature" convergence of results. We have come to the conclusion that this technique could be treated as a sort of convenient mathematical trick enabling one, once the "correct" density of reinsertion points has been determined for a bulk system at "reference" temperature, to estimate the chemical potential at different temperatures and system sizes. When applied to the grand canonical ensemble, Kumar's method (53) proved to be totally unsuitable, thus indicating the need for a reliable technique capable of calculating the spatial distribution of free energy and chemical potential for both solute and solvents.

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REFERENCES

- O Udahl, J Sjöblom. J Dispers Sci Technol 16: 557—574, 1995.
- J Sjöblom, H Førdedal, T Jakobsen, T Skovdin. In: KS Bird, ed. Handbook of Surface and Colloid Chemistry. Boca Raton: CRC Press, 217–237, 1997.
- H Førdedal, Y Schildberg, I Sjöblom, IL Volle. Colloids Surfaces A 106: 33–47, 1996.
- 4. J Sjöblom, T Skovdin, Ø Holt, FP Nilsen. Colloids Surfaces A 123/124: 593—607, 1997.
- 5. B Smit, PAI Hilbers, K Esselink, LAM Rupert, NM van Os, AG-Schlijper. Nature 348: 624—625, 1990.
- 6. AA Christy, B Dahl, OM Kvalheim. Fuel 68: 430–435, 1989.
- 7. DJ McClements. Adv Colloid Interface Sci 37: 33-72, 1991.
- B Ivanov, PA Kralchevsky. Colloids Surfaces A 128: 155– 175, 1997.
- 9. M Kravczyk. PhD thesis, Illinois Institute of Technology, Chicago, 1990.
- RB Gennis. Biomembranes: Molecular Structure and Function. New York: Springer-Verlag, 1989.
- 11. SJ Marrink, HJC Berendsen. I Phys Chem 98: 4155-4168, 1994.
- MA Wilson, A Pohorille. J Am Chem Soc 118: 6580— 6587, 1996.
- JJ Lòpez Cascales, J Garcia de la Torre, SJ Marrink, HJC Berendsen. J Phys Chem 105: 2713—2720, 1996.
- 14. K Tu, M Tarek, ML Klein, DJ Tobias. Biophys J 75: 2147-2156, 1998.
- K Belohorcová, JH Davis, TB Woolf, B Roux. Biophys I 73: 3039—3055, 1997.
- K Tu, M Tarek, ML Klein, D Scharf. Biophys J 75: 2123— 2134, 1998.
- 17. A Pohorille, MA Wilson. J Chem Phys 104: 3760—3773, 1996.
- JJ Lòpez Cascales, JG Hernandez Cifre, J Garcia de la Torre. I Phys Chem 102: 625–631, 1998.
- WF van Gundsteren, HIC Berendsen. GROningen Molecular Simulation is a Software Package. Groningen, The Netherlands: Biomos, 1997.
- WF van Gundsteren, HIC Berendsen. Angew Chem Int Ed Engl 29: 992—1023, 1990.
- HJC Berendsen, JPM Postma, WF van Gundsteren, A Di-Nola, JR Haak. J Chem Phys 8: 3684, 1984.

- PC Méléard, C Gerbeaud, T Pott, L Fernandez-Puente, I Bivias, MD Mitov, J Dufourcq, P Bothorel. Biophys J 72: 2616, 1997.
- 23. A Caruthers, DL Malchior. Biochemistry 22:5797—6010, 1983.
- 24. TX Xiang, BD Anderson. Biophys J 72: 223, 1997.
- 25. S Furukawa, T Shigeta, T Nitta. J Chem Eng Jpn 29: 725–728, 1996.
- PI Pohl, GS Heffelfinger, DM Smith. Molec Phys 89: 1725—1731, 1996.
- 27. RF Cracknell, D Nickolson, N Quirke. Phys Rev Lett 74: 2463—2466, 1995.
- GS Heffelfinger, F van Swol. J Chem Phys 100: 7548— 7552, 1994.
- 29. JMD MacElroy. J Chem Phys 101: 5274-5280, 1994.
- 30. DM Ford, GS Heffelfinger. Molec Phys 94: 659-671, 1998.
- GS Heffelfinger, F van Swol. J Chem Phys 100: 7548— 7552, 1994.
- AP Thompson, DM Ford, GS Heffelfinger. J Chem Phys 109: 6406—6414, 1998.
- 33. DM Ford, GS Heffelfinger. Molec Phys 94: 673-683, 1998.
- AP Thompson, GS Heffelfinger. J Chem Phys 110: 10693—10705, 1999.
- 35. S Weerasinghe, BM Pettitt. Molec Phys 82: 897—912, 1994.
- CG Lynch, BM Pettitt. J Chem Phys 107: 8594—8610, 1997.

- 37. T Çagin, BM Pettitt. Molec Simul 6: 5-26, 1991.
- J Ji, T Çagin, BM Pettitt. J Chem Phys 96: 1333—1342, 1992.
- T Kuznetsova, B Kvamme. Molec Phys 97: 423–431, 1999.
- 40. T Kuznetsova, B Kvamme. Molec Simul 21: 205–225, 1999.
- 41. D Fincham. Molec Simul 8: 165-178, 1992.
- 42. S Nosé. Progr Theor Phys 103: 1-46, 1991.
- 43. WG Hoover. Phys Rev A 31: 1695, 1985.
- 44. D Di Cola, A Deriu. J Chem Phys 104: 4223-4232, 1996.
- 45. MP Allen, DJ Tildesley. Computer Simulation of Liquids. Oxford: Clarendon Press, 1990.
- 46. A Laaksonen, MCMOLDYN. Daresbury Laboratory, UK, 1995.
- 47. B Widom. J Chem Phys 39: 2808–2812, 1963.
- 48. B Widom. J Chem Phys 86: 869-872, 1982.
- 49. Y Tamai, H Tanaka, K Nakahashi. Fluid Phase Equil 104: 363—374, 1995.
- AP Lyubartsev, AA Martsinovski, SV Shevkunov, PN Vorontsov-Velyaminov. J Chem Phys 96: 1776—1783, 1992.
- 51. FA Escobedo, JJ De Pablo. J Chem Phys 103: 2703—2710, 1995.
- TV Kuznetsova, PN Vorontsov-Velyaminov. J Phys: Cond Matt 5: 717–724, 1993.
- 53. S Kumar. J Chem Phys 97: 3550—3556, 1992.