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Client Number:	TN178583
Title:	**PROGRESS IN COLLOID & POLYMER SCIENCE.**
DB Ref. No.:	IRN10067279
ISSN:	0340255
Vol./Issue:	103
Date:	1997
Pages:	87–94
Article Title:	SELF–ASSEMBLY OF VOLATILE AMPHIPHILES
Article Author:	VANDERLICK
Report Number:	IRN10067279
Publisher:	D. STEINKOPFF,
Information Source:	INNOPAC

Estimated cost for this 8 page document: $11.4 document supply fee + $8 copyright = $19.4

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Progr Colloid Polym Sci (1997) 103:87–94
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Self-assembly of volatile amphiphiles

Received: 29 December 1996
Accepted: 3 January 1997

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Abstract Computer simulations are used to study the aggregation phenomena of volatile amphiphiles in a system displaying liquid/vapor coexistence. These molecular dynamics simulations are based on a simple, yet versatile, model used previously to study oil/water/amphiphile systems: amphiphiles are nothing more than water and oil particles connected together by stiff springs. We observe a highly regulated self-assembly process wherein amphiphiles form bilayers within the liquid phase. The density of amphiphiles in a bilayer varies from a well-defined lower to upper limit as the overall concentration of amphiphiles in the system is changed; we examine how these limits vary for amphiphiles having different hydrophobic chain lengths. The vapor phase plays an important role in this self-assembly process, serving as a reservoir for amphiphiles not included in the bilayers. Finally, we show that bilayer formation can be completely suppressed if the geometry of the amphiphiles is altered, as is predicted by simple packing arguments.

Key words Computer simulations – amphiphiles – bilayers – packing parameter

Introduction

Many molecules are composed of segments that if not bonded would phase separate. Amphiphiles made up of hydrophilic and hydrophobic moieties, and block copolymers formed of immiscible monomers are important examples. The interface that forms between oil and water is a natural habitat for amphiphiles; similarly, block copolymers are preferentially adsorbed at the interface between phase separated monomers.

As with the water/oil interface, amphiphiles can specifically adsorb to the interface between water and air. One limiting case is complete adsorption resulting in the so-called insoluble monolayer. Experimental studies of insoluble monolayers at the water/air interface are routinely carried out using a film balance developed by Langmuir [1] over 70 years ago; with this, the average area per molecule can be varied and the resulting change in surface tension can be measured. Amphiphiles which exhibit significant solubility in water form Gibbs monolayers; here, partitioning of amphiphiles between the interface and the bulk phase establishes the surface pressure, which is a function of the overall concentration of amphiphiles.

The interfacial activity of amphiphiles is but one manifestation of their discordant intramolecular makeup. These molecules can also self-assemble in solution to form a variety of microstructures, such as micelles and vesicles to name a few. Of course structures based on a bilayer motif, such as vesicles, have direct biological relevance as they serve as models for cell membranes.

Insight into the fundamental behavior of amphiphiles can be provided through computer simulations; however, the number of degrees of freedom is inherently large. Hence, in practice, various restrictions or approximations are often made, such as using external potentials (as opposed to explicit molecular models) to represent bulk fluid phases [2, 3]. Furthermore, different schemes have been

developed to deliberately maintain, or at least coax, the amphiphiles into specified microstructures. Simulations of phospholipid membranes, for example, often start with amphiphiles placed in the bilayer configuration [4]. Consequently, the initial set points of molecular area and bilayer thickness may influence simulation results [5].

An alternative simulation strategy is to relinquish exacting molecular models in exchange for a simple particulate representation of all components in the system. In one of the simplest scenarios, all particles in the simulation interact with Lennard–Jones-type potentials; each is identified as one of two species, "oil" or "water"; and amphiphiles are nothing more than oil and water particles bonded together by way of stiff harmonic potentials. Simple simulations of this sort have been recently used to investigate the behavior of amphiphiles at the oil/water interface. In particular, Smit and co-workers [6–10] have employed this methodology to study the behavior of linear and branched chained amphiphiles. We extended this analysis further and showed how the observed tension reducing properties of various amphiphiles can be predicted with simple equations of state [11]. Moreover, simulations of this type are now being used to study membrane dynamics [12] and self-assembly in amphiphilic systems [13–15]. Beyond the specific results of all these studies, it is clear that this simple model of amphiphiles is sufficient to capture many basic elements of their behavior. Hence simulations of this nature can be quite useful, especially for exploratory work where more realistic molecular models become prohibitive.

In this study, we use the same simulation scheme to study the behavior of these model amphiphiles in the presence of a liquid/vapor interface. This is quite feasible since Lennard–Jones particles are known to exhibit liquid/vapor coexistence [16]. In short, we observe a highly regulated self-assembly process leading to the formation of one or more well-formed bilayers in the liquid phase; amphiphiles not included in the bilayers are dispersed in the vapor phase. In this paper, we report on this phenomenon, and examine how the size and overall concentration of amphiphiles govern the development and characteristics of the bilayers formed. We also show that bilayer formation can be suppressed if the geometry of the amphiphiles is altered, as is predicted by simple packing arguments.

Model and computational details

The model used was inspired by the free energy density functional theory developed by Telo da Gama and Gubbins [17] and put into practice by Smit and co-workers [6]. Each particle in the simulation can be identified as one of two species: oil or water. Amphiphiles are nothing more than water and oil particles connected via Hookean springs; this construction captures, at a basic level, the dual hydrophilic/hydrophobic character of these molecules. By connecting different amounts of particles in different configurations, this simple approach can be used to create molecules with varying architectures.

The two species of particles in the simulation interact with truncated Lennard–Jones potentials with energy parameter ε_{ij}, distance parameter σ_{ij}, and cutoff radius R_{ij}^{cut}.

$$\phi_{ij} = \begin{cases} \phi_{ij}(r) - \phi_{ij}(R_{ij}^{\mathrm{cut}}), & r \le R_{ij}^{\mathrm{cut}}, \\ 0, & r \ge R_{ij}^{\mathrm{cut}}, \end{cases}$$

$$\phi_{ij}(r) = 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r}\right)^{12} - \left(\frac{\sigma_{ij}}{r}\right)^{6}\right].$$

We have assumed that all interactions are governed by the same ε. Therefore, the only difference between oil–oil, water–water, and oil–water interactions is determined by the choice of R_{ij}^{cut}. Intra-species interactions have $R_{ij}^{\mathrm{cut}} = 2.5\sigma_{ij}$, and so attractive forces are present. On the other hand, the inter-species interactions have $R_{ij}^{\mathrm{cut}} = 2^{1/6}\sigma_{ij}$, restricting the interactions to be repulsive.

Amphiphiles are constructed by adding to the potential above (which continues to apply to all particles) harmonic potentials between designated pairs of their constituent particles. For this we use

$$\phi_{ij} = \tfrac{1}{2}k(r_{ij} - \sigma_{ij})^2 ,$$

where k is the spring constant, and σ_{ij} is the separation at zero force. The value of k employed in the simulations should not affect thermodynamic properties; evidence of this is given in a previous publication [11]. To avoid confusion with other particles in the system, we shall at times refer to water and oil particles which make up amphiphiles as head and tail particles, respectively.

Unless otherwise noted, we used a system of 512 particles in a rectangular box of size $6.84\sigma \times 6.84\sigma \times 27.36\sigma$. Periodic boundary conditions were kept in all three directions. A constant temperature of $T = 1\varepsilon/k_b$ was maintained by incorporating a constraint method into our leap-frog verlet algorithm as described in Allen and Tildesley [18]. We employed a time step of 0.005τ, where $\tau = \sigma(m/\varepsilon)^{1/2}$ (m is defined as particle mass).

We launched our simulations in the following way. We first started with a single component system of water particles in a homogeneous liquid phase. From this a vapor phase was formed using the method described by Harris [19], after which the system was equilibrated for approximately 1×10^5 time steps. At this point, sets of particles were randomly chosen to make up the amphiphiles; the requisite number were changed from water to oil species; and harmonic potentials were added to

connect head and tail particles in the desired fashion. Since the particles which make up an amphiphile were not necessarily in close proximity to one another, the spring constant was initially set at a small value (ca. $1.0\varepsilon/\sigma^{-2}$) and then slowly ramped to its final value (ca. $1 \times 10^5 \varepsilon/\sigma^{-2}$) over 5×10^3 time steps. We note that creation of amphiphiles frequently disturbed the liquid/vapor phase coexistence, often causing cavitation in the liquid phase. This disruption subsided, and thermodynamic quantities were usually stabilized after 5×10^4 time steps; we allowed, however, an additional 2×10^4 steps to pass before equilibrium was assumed.

On average, data were collected for 1.2×10^5 time steps after equilibration. However, some simulations were run for an additional 4×10^5 time steps with no appreciable changes in thermodynamic quantities. The accuracy of our simulations was estimated by dividing the data collection steps into sub-runs of 1×10^4 time steps; determining the average quantities within each sub-run; and calculating standard deviations from sub-run averages. Density profiles were calculated at every time step within a sub-run. Density profiles shown herein represent a sub-run averaged profile.

Results and discussion

We first consider amphiphiles which have a cylindrical geometry, composed of one water particle and numerous oil particles – all of the same size–linked together in series as shown in Fig. 1. Furthermore, the size of the particles which comprise the amphiphiles is also equal to that of the free water particles which make up the liquid and vapor coexisting phases. The general behavior of these amphiphiles as seen in our simulations can be described as follows. At low overall concentrations, the amphiphiles are present exclusively in the vapor phase, showing only slight preferential adsorption to the vapor/liquid interface. At higher concentrations, the molecules form a distinct bilayer (or more than one) solubilized within the liquid water phase. Under conditions where bilayers do form, the vapor phase plays an important role, serving as a sink for excess amphiphiles so that the bilayers can exist with a preferred density (i.e. number of amphiphiles per unit area). Figure 2 shows the density profile of amphiphiles in a system displaying bilayer formation. In this particular simulation (consisting of 1300 total particles), the amphiphile was composed of four-tail particles attached to one head particle; henceforth denoted (4:1).

Before describing this self-assembly process in more detail, it is worth comparing this overall behavior to that which we observed for the same amphiphiles in the presence of a water/oil interface. In that case, we found [11]

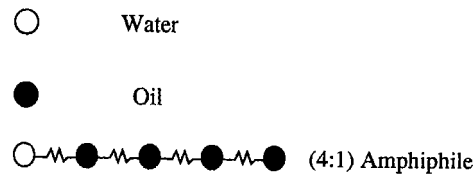

Fig. 1 Schematic drawing of water/oil/amphiphile model

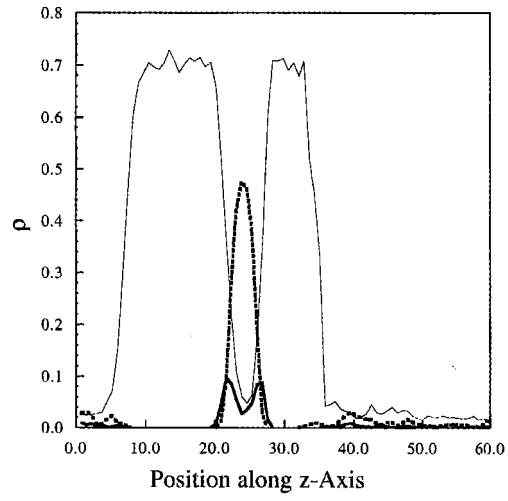

Fig. 2 Density (σ^{-3}) vs. position along z-axis (σ) for: (·····) free water particles; (▬) head particles; ▬▬▬ (tail particles)

that the amphiphiles behaved as an insoluble monolayer when present at low enough concentrations. At higher concentrations, amphiphiles exhibited solubility in the oil phase but showed no tendency to self-organize therein. In our small-scale simulations we also saw no evidence of micelle formation in the water phase; however, this was seen in the larger-scale simulations of Smit et al. [8, 13]. Interestingly, over large simulation times, these investigators noted that micelles tended to cluster until a single bilayer structure was formed [10]. The simulations reported in this paper demonstrate that these mock amphiphiles are in fact quite volatile, and that the presence of a vapor phase plays an important role in the self-assembly process which occurs in the denser liquid phase. This same self-assembly process is not observed when the vapor phase is exchanged for an oil phase.

Returning the to self-assembly process that occurs in our liquid/vapor system, we now describe in general terms the evolution of bilayers as the concentration of amphiphiles in the system is increased. At some point a concentration is reached where amphiphiles become soluble in the liquid phase. When this first happens the amphiphiles aggregate into featureless clusters. However, soon thereafter, as the concentration continues to increase, the

amphiphiles in the liquid all come together to form a bilayer, displaying a characteristic width given by the distance between the exposed head groups. As more amphiphiles are added to the system, these molecules are directly incorporated into the bilayer making it more dense (in amphiphiles) and also decreasing the degree of chain interdigitation. Concomitantly, water trapped within the bilayer is gradually squeezed out, as the bilayer width increases to some asymptotic value. Thereafter, any further increase in overall amphiphile concentration does not change the properties of the first bilayer, but rather leads ultimately to the formation of a second bilayer. The new bilayer evolves in structure and form in the same way as the first. As stated before, the vapor phase serves as a reservoir for amphiphiles when not enough are present to form the first, or the second, bilayer. In contrast to the oil/water interface, adsorption at the liquid/vapor interface is not significant; this is not surprising given that the tension [20] is an order or magnitude lower than that of the liquid/liquid interface.

We studied in detail the specific conditions for bilayer formation and their resultant characteristics for a variety of amphiphiles of different sizes (differing in the number of oil particles). We note here that to maximize the number of different simulations which could be performed, most were conducted with 512 total particles. A few larger simulations (such as the one reported in Fig. 2) were conducted to confirm that the properties of the bilayers, as reported below, were not affected by system size. We did notice, however, that simulations containing only 512 total particles did not usually contain enough free water particles to display bulk liquid behavior on both sides of the bilayer; instead one side of the bilayer was usually contacted by a thin water film.

As discussed qualitatively above, the properties of the bilayered microstructures depend on the number of amphiphiles present in the system; it is, in fact, the nature of this dependence that we wish to report. The overall number density of amphiphiles in this two-phase system is not, however, a useful independent variable; in particular, differently shaped simulation boxes of the same volume (containing the same total number of particles) would not exhibit the same behavior. A better choice, which allows us to compare directly simulations of different sizes, is a two-dimensional number density, χ, defined to be the total number of amphiphiles in the system divided by the area of the simulation box which lies parallel to the liquid–vapor interface. It is also convenient to define a similar number density χ^B, associated with the number of amphiphiles in the simulation that are incorporated in one or more (if they exist) bilayers. Thus, $\chi^B \leq \chi$, with the equality holding only when all the amphiphiles in the system are assimilated in bilayers.

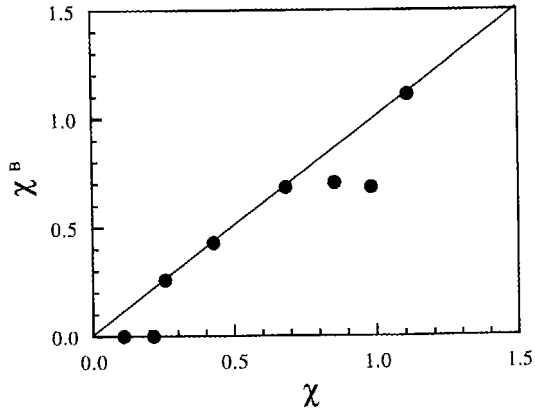

Fig. 3 χ^B (σ^{-2}) vs. χ (σ^{-2}). The 45° line corresponds to the situation where all amphiphiles are incorporated in bilayer(s)

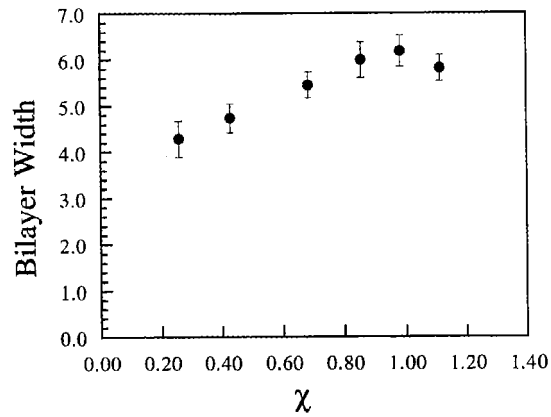

Fig. 4 Bilayer width (σ) vs. χ (σ^{-2})

As a basis for comparison, it is worthwhile to present first the results for the (4:1) amphiphiles; these, in fact, display the most sensitivity to concentration. The development of bilayers as a function of concentration is shown in Fig. 3 (χ^B versus χ). As can be seen therein, a bilayer is first formed when χ reaches 0.26 (e.g. 12 amphiphile molecules in a simulation with interfacial area $46.8\sigma^2$). At this point, the effective area per amphiphile, determined by dividing the area of the bilayer (equal to the areal size of the simulation box) by the number of amphiphiles in the bilayer, is $3.9\sigma^2$. As χ is increased up to 0.68, the added amphiphiles are incorporated directly into the bilayer (hence the associated points in Fig. 3 fall on the 45° line). The bilayer widens as it takes on more amphiphiles, as can be seen in Fig. 4 which plots the width of the bilayer, as measured by the distance between the centers of the exposed head particles, as a function of χ. At its maximum width, the effective area per amphiphile in the bilayer diminishes to $1.5\sigma^2$. Further increase in overall amphiphile

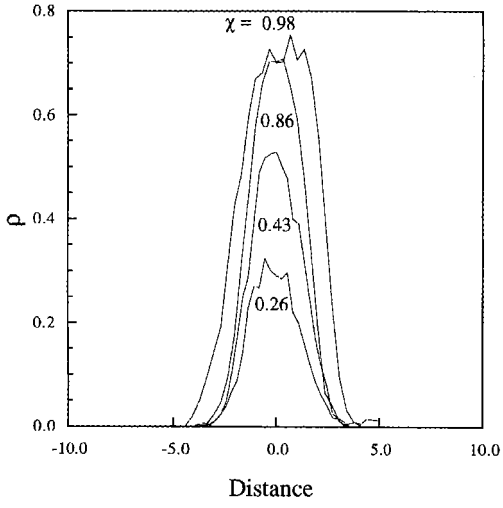

Fig. 5 The density profile of amphiphilic tail particles (σ^{-3}) vs. position along z-axis (σ) for various χ values

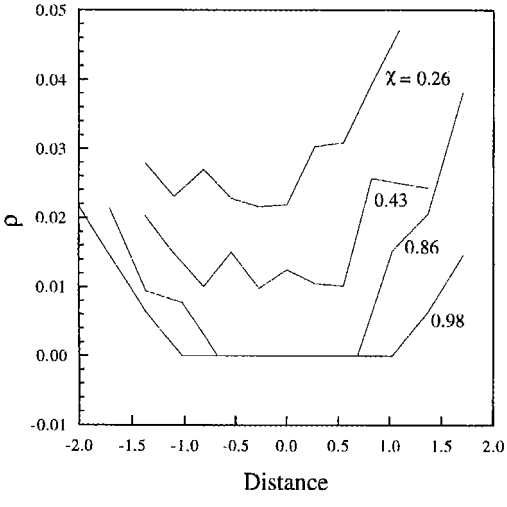

Fig. 6 The density profile of free water particles (σ^{-3}) vs. position along z-axis (σ) for various χ values

concentration beyond this point does not affect the properties of this bilayer; excess amphiphiles simply build up in the vapor phase until enough are present to form a second bilayer. As can be seen in Fig. 3, this occurs at $\chi = 1.1$ (as all the amphiphiles now make up two bilayers, this point then lies on the 45° line).

In summary, we see that a surprisingly limited number of amphiphiles is required to form a stable bilayer. And although more amphiphiles are readily accepted into the microstructure, an upper limit is eventually reached. The evolution of bilayer structure from one limit to the other can be further appreciated by examining the density profiles of tail particles and free water particles within the bilayer; these are shown in Figs. 5 and 6, respectively. As is readily seen, as the bilayer takes on more amphiphiles, the density of tail groups in the interior region rises and broadens, reaching an asymptotic limit. Correspondingly, water in the interior of the bilayer is reduced, until the region is completely void of water. It appears that the maximum number of amphiphiles included in the bilayers is that which yields a interior tail particle density of about 0.7, which corresponds to the density of bulk oil that could exist in equilibrium with bulk water at this temperature [16].

It is worthy to examine more fully the role of the vapor phase in the bilayer formation process. To do this, we examined the behavior of (4:1) amphiphiles in a one phase liquid system, composed of water particles. A constant volume simulation was carried out with the concentration of amphiphiles set to yield an effective χ equal to 0.86; at this same concentration, the two phase liquid–vapor system shows one bilayer at the asymptotic width and density, and excess amphiphiles are hosted in the vapor phase. In the single-phase system, we found that a bilayer did form, but all amphiphiles in the simulation were included in it. Although the width of this bilayer (5.6σ) was not significantly different from that formed in the two-phase system (6σ), the density of tail particles in the interior was considerably greater. We did find, however, that if the normal pressure was lowered (by increasing the length of the simulation box along the axis perpendicular to the bilayer) the bilayer stretched out (to 7.1σ) and the density in the interior relaxed to the same value found for bilayers in the two-phase system. The main point is, however, that the presence of the vapor reservoir allows self-regulation of the intrinsic properties of the bilayers formed.

In examining similar amphiphiles of different lengths, the general features of bilayer formation exhibited by the (4:1) amphiphiles were followed, as long as the chain of the amphiphile contained at least 3 oil particles. On the other hand, we found that (1:1) and (2:1) amphiphiles showed no tendency to self-assemble into layers. The (1:1) amphiphile was, in fact, soluble in both the vapor and liquid phases at all concentrations, and did not demonstrate any form of aggregation. The (2:1) was slightly soluble in the liquid phase at higher concentrations. Clearly, inter-chain interactions are very important in stabilizing the lamellar structures. In fact, for the longer chained amphiphiles, stable bilayers are formed sooner, i.e., with less amphiphiles, the longer the chain. Figure 7 shows this dependence (circular symbols) for amphiphiles containing 3-, 4- and 6-tail particles. Chain length also affects the asymptotic density of the bilayers: bilayers formed of longer chained molecules contain less molecules per unit area. This is also illustrated in Fig. 7 (square symbols). As expected, longer chains also form bilayers with larger asymptotic widths.

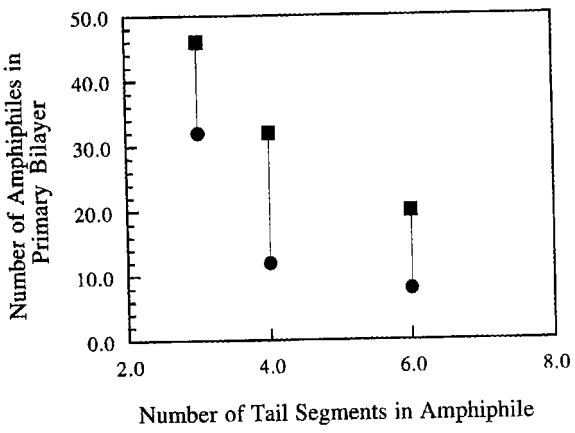

Fig. 7 The number of amphiphiles in primary bilayer vs. number of tail segments in amphiphile. (●) first appearance of stable bilayer; (■) packing limit of bilayer

One common trait shared by all bilayer forming systems we examined is that every bilayer experiences a large degree of interdigitation, having widths which are much smaller than the sum length of two extended amphiphiles. Notably this is not the characteristic of cell membranes, which display widths nearly twice the thickness of a well-packed monolayer; however, interdigitated bilayers are not entirely uncommon, particularly in systems of mixed phosphatidylcholines [21]. Within the gross limitations of the simple molecular model we are employing, we probed the influence of two factors that might seem intuitively to influence bilayer structure: the rigidity of amphiphiles; and the relative strength of inter- and intra-molecular interactions. These are now discussed in turn.

In the simulations reported above, the amphiphiles were composed of a train of particles, each linked by springs to its immediate neighbors. The resulting molecules are quite flexible, bearing no constraints other than a preferred separation between each successive pair of particles (as set by the length of interconnecting spring). It is easy, however, to create more rigid molecules by additionally connecting together, with a spring of appropriate length, the first and last particles of the train. We did this for simulations of (4:1) amphiphiles and found that the bilayer width increased by only about 10% (to achieve no inter-digitation would require an approximately 60% increase). We also noticed that in comparison to the flexible amphiphiles, larger overall concentrations of rigid amphiphiles were required to achieve the first stable bilayer: $\chi = 0.68$ as opposed to $\chi = 0.26$.

One seeming advantage of tightly packed, non-interdigitated, bilayer is the screening of interactions between chain particles and bulk water particles. However, in the simulations reported above, oil–water interactions are very short-ranged: the oil particles do not interact with water particles until they are within 1.12σ of one another, at which point they experience repulsive interactions given by the Lennard–Jones potential. We attempted, in an *ad hoc* fashion, to increase the range and strength of repulsive forces exerted between free water particles and amphiphile tail particles; in particular, we added to the repulsive inverse-12 potential a repulsive inverse-6 potential which acts out to a distance of 2σ. We found that this alteration had no effect on the bilayer width. However, because of the longer-ranged repulsive interactions between water and oil particles, no water was able to penetrate into any of the bilayers which formed.

In summary, we were not able to find conditions that lead to "bilayered" structures akin to the cell membrane; this is arguably a result of the overly simplified molecular model used in these simulations. On the other hand, the ease of the model facilitates investigations which examine the role of general molecular characteristics, such as size and shape. We take advantage of this possibility to study the role of molecular geometry, and compare our results with predictions using the simple packing arguments of Israelachvili [22, 23]. Like the simulation model itself, these arguments neglect the fine details of molecular structure.

According to this analysis, the so-called packing parameter dictates the type of microstructures that an amphiphile will form:

$$\text{Packing parameter} = \frac{v}{a_0 \cdot l_c}.$$

Here, v is the hydrocarbon chain volume, a_0 is the optimal head group surface area, and l_c is the critical chain length. For packing parameters between $\frac{1}{2}$ and 1, amphiphiles should form flexible bilayers (vesicles), or planar bilayers as the packing parameter approaches 1. On the contrary, a packing paramter less than $\frac{1}{2}$ should hinder the formation of bilayers; in particular, the theory predicts micelle formation.

Esselink and co-workers [10] showed that the shapes of micelles formed in amphiphile/oil/water systems were indeed consistent with packing parameter arguments; they changed the geometry of the amphiphiles by connecting together different numbers of particles in different arrangements. Interestingly, they found that packing parameters were not always predictable *a priori*. For example, a linear train of particles of equal size, composed of four tails and four heads, formed highly spherical micelles stabilized by the large area conformation taken on by the chain-like headgroup. In our study, we changed the packing parameter by simply increasing the size of the one water particle which forms the head group of the amphiphiles. We

used three values for the diameter of the head particle, 1.0σ, 1.25σ, and 1.5σ; these led to packing parameter values of 1.0, 0.64, and 0.44, respectively. Following the theoretical predictions, the first two cases should self-assemble into bilayers while the third geometry should not. Indeed, we found this to be the case. In the third case (where bilayers are not predicted to form), we saw significant but not well-defined aggregation of amphiphiles within the bulk liquid. The small system size employed in our simulations probably prohibits the formation of micelles [8, 11, 13]. Nevertheless, these simulations reveal that this simple molecular model used to construct amphiphiles is sufficient to capture many important elements of their behavior, and provide a valuable tool for studying the role of molecular architecture in self-assembling systems.

Granted, the simulations reported herein may have limited practical relevance. Most real surfactants demonstrate negligible volatility; the high surface tension of water induces strong adsorption to the interface; and applications based on closed liquid–vapor systems are not prevalent. We are, in fact, unaware of any systems that demonstrate the reported vapor-regulated self-assembly process. Of course there is always the possibility that some or all aspects of this phenomenon may be ultimately realized; short-chained alcohols, or mixed amphiphilic systems containing them, may be candidate systems. We do believe, however, that the lack of direct relevance does not totally diminish the utility of these simulations. In particular, these simulations might be ideal for fundamental investigations of the effects of perturbants on self-assembly. For example, one might be able to determine the size and/or shape of inclusions that serve to break apart a bilayer. The distinct formation of bilayers in the liquid phase, combined with their self-regulating properties associated with having the vapor reservoir, makes these simulations useful platforms for these investigations.

Conclusions

We have used a simple molecular model employed in simulations of oil/water/amphiphiles to investigate the self-assembly of amphiphiles in systems displaying liquid/vapor equilibrium. Studies of oil/water/amphiphile systems rarely concentrate on the role of the oil phase. Although it is rarely emphasized, many (if not most) amphiphiles in such systems are dissolved in the high-density oil phase. Exchanging the oil phase for one of water vapor significantly modifies the behavior of the amphiphiles. As we have shown herein, this creates a high driving force to self-assemble into well-formed bilayers within the dense water phase. Curiously, we are unaware of any oil/water/amphiphile simulations that exhibit similar well-formed layers. (The closest is perhaps the work Smit et al. [13], who report seeing "bilayer micelles".) The enhanced tendency of these amphiphiles to self-assemble in the water/vapor environment seems clearly related to the lack of any other oil particles in the system.

We probed the formation and structure of bilayers as a function of amphiphile chain length (i.e. number of oil particles). We found that amphiphiles must have at least three oil particles to form stable bilayers. For those that do, we found that the resulting bilayer had a characteristic width that increases with increasing amphiphile concentration until reaching an asymptotic value. At this point, amphiphiles added to the system are hosted in the vapor phase until enough are available to form a new bilayer. The minimum number of amphiphiles needed to form a bilayer, as well as the maximum number that one bilayer can have, depends on the chain length of the amphiphiles: both are less the longer the chain. We did not, however, find conditions leading to closed-packed bilayers with small or no chain interdigitation.

Finally, the architecture dependence of bilayer formation was also examined by altering the size of the amphiphiles' head particle and thus varying its packing parameter. Results of these simulations were in agreement with conditions for bilayer formation as predicted by simple geometric arguments. Thus there is increasing evidence that this simple model of amphiphiles – one that can be readily implemented on stand-alone workstations – is sufficient to capture many elements of their inherent behavior. In future work, we plan to take advantage of the building block nature of this model to study the behavior of amphiphiles with more complex architectures, such as those containing rings. In addition, we plan to use the simulations reported herein to study the effects of inclusions on bilayer formation.

Acknowledgments We gratefully acknowledge support for this work provided by the David and Lucile Packard Foundation and the National Science Foundation (CTS-89-57051).

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