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## Molecular simulations of mesoscopic bilayer phases

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Dissipative particle dynamics simulations are used to study the self-assembly of lipids into bilayers. With a simple mesoscopic lipid-water model, we observe the formation of the liquid crystalline phase  $L_\alpha$  and gel phases in which the tails are interdigitated  $L_{\beta I}$  or noninterdigitated  $L_\beta$ . For double-tail lipids experiments show all three phases, while for single-tail lipids only  $L_\beta$  and  $L_\alpha$  are observed. We show that at sufficiently high head-head repulsion the  $L_{\beta I}$  is stable for single-tail lipids. This suggests that it might be possible to induce an  $L_\beta \rightarrow L_{\beta I}$  transition by adding chaotropic salts.

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Since lipids are an important component of biological membranes, knowledge on the behavior of these systems is relevant for our understanding of biological membranes. In addition, the ability of lipids to form various liquid crystalline and mesophases has implications for various processes in membrane biology such as membrane function or membrane protein crystallization [1]. Lipids can self-assemble in water to form bilayer structures, in which the hydrophilic part of the lipid is oriented towards the water phase. Common phases that can form in a bilayer are the gel phase and the liquid crystalline phase. In the liquid crystalline, or  $L_\alpha$  phase, the lipids in the bilayer do not show a specific order. If the temperature is decreased the system forms a gel phase in which the hydrophobic tails show a nematic order (see Fig. 1). This gel phase can be either interdigitated  $L_{\beta I}$  or noninterdigitated  $L_\beta$ . Interestingly, for most double-tail lipids one can induce a transition from the  $L_\beta$  to the  $L_{\beta I}$  phase by adding salt or alcohol [2], whereas in single-tail lipids only the noninterdigitated structure has been observed [3,4]. Here, we use dissipative particle dynamics to study the  $L_{\beta I} \rightarrow L_\alpha$  and the  $L_\beta \rightarrow L_\alpha$  transition for a mesoscopic model. Our simulations correctly describe the hydrophobic tail length dependence of this transition and the effect of adding salt. In addition, the simulations predict that both the interdigitated and noninterdigitated phases can be formed in systems with single-tail lipids.

Phase transitions in lipid bilayers have been studied theoretically using phenomenological models [5–7]. Whereas these models give important information on the general aspects of the phase diagram, they are less convenient to study effects of changes in the chemical structure of the lipids. For this type of question molecular simulations are more convenient. At present, it is possible to study the formation of lipid mesophases using all atom molecular simulations [8], but these simulations are too time consuming to study the phase behavior. An alternative approach is to use a mesoscopic model, in which general aspects of changes in the chemical structure and interactions between the lipids can be studied [9–12]. Here, we present a mesoscopic model that allows us to study transitions between the various mesoscopic bilayer phases.

We use dissipative particle dynamics (DPD) [13] to simulate our system. In a DPD simulation one uses, in addition to the conservative forces between the particles, a dissipative

and a random force. The dissipative and random forces are chosen such that a proper Boltzmann distribution of configurations is sampled corresponding to the intermolecular interactions from which the conservative interactions are derived [14]. In analogy with previous simulations using the DPD technique, we use soft-repulsive interactions to mimic the coarse-grained interactions between the lipids and water molecules. Groot and Rabone [10] have shown that compared to a molecular dynamics (MD) simulation on an all-atom system, DPD on a coarse-grained model can be four to five orders of magnitude more efficient. Since these MD simulations are very demanding, they are often limited to a single temperature and type of lipid. The efficiency gained by DPD allows us to compute complete phase diagrams.

In our model, we distinguish three types of particles  $w$ ,  $h$ , and  $t$  to mimic the water and the head and tail atoms of a lipid, respectively. The conservative forces between these particles are given by

$$\mathbf{F}_{ij}^C = \begin{cases} a_{ij}(1 - |\mathbf{r}_{ij}|/R_c)\hat{\mathbf{r}}_{ij} & \text{if } |\mathbf{r}_{ij}| < R_c \\ 0 & \text{if } |\mathbf{r}_{ij}| \geq R_c, \end{cases} \quad (1)$$

where  $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$ ,  $\mathbf{r}_i$  is the position of particle  $i$ , and  $R_c$  is the cutoff radius. The values of the parameter  $a$  for the vari-

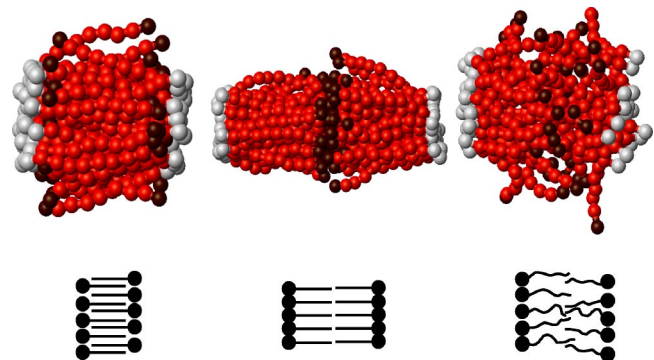


FIG. 1. (Color online) Schematic structure of the  $L_{\beta I}$  (left),  $L_\beta$  (middle), and  $L_\alpha$  (right) phases. The gray spheres are the hydrophilic heads and the red spheres the hydrophobic tails, the end of the hydrophobic tail is given a darker red color. In the  $L_\alpha$  phase, or liquid crystalline phase, the tails are disordered. In the  $L_\beta$  phases, the tails are ordered and in the  $L_{\beta I}$  phase the tails are interdigitated as well. In none of the phases the tails show a preferred tilt.

ous interactions are chosen such to mimic the hydrophobic and hydrophilic interactions. Our parameters are  $a_{ww}=a_{tt}=25$ ,  $a_{wh}=15$ , and  $a_{wt}=80$ , which are based on those optimized by Groot [15]. The value of  $a_{ww}=25$  reproduces the compressibility of water and the interactions of the lipid segments are based on the Flory-Huggins solubility parameters. To avoid an unrealistic high density in the bilayer hydrophobic core, we have reduced the tail-tail interaction. In addition, we vary the head-head interaction parameter  $a_{hh}$  to study the effect of changing the interactions between the hydrophilic segments of a lipid. In a real system, the head-head interactions can be changed by adding salt to the system. The lipid particles are connected via harmonic springs, with spring constant  $k_r=100$  and equilibrium distance  $r_0=0.7$ . In addition, the flexibility of the tail is controlled with a harmonic bond-bending potential between two consecutive bonds, with bending constant  $k_\theta=10$  and equilibrium angle  $\theta_0=180^\circ$ . We have used a system with 3500 particles with a total of 200 lipids. We performed several tests in which we increased or decreased the total number of lipids (up to 1800) but could not detect significant size effects. All results are expressed in the usual reduced units, i.e., using  $R_c$  as the unit of length and repulsion parameter  $a=1$  as the unit of energy.

A biological membrane is not subject to external constraints and therefore adopts a configuration that is tensionless. In a molecular simulation in which the total area and number of lipid molecules are fixed, the resulting membrane has a nonzero surface tension. Lipowski and co-workers [11,16] emphasize the importance of locating (iteratively) the exact area for which the surface tension is zero. In this work, we use a different approach to ensure that our simulations are performed in a tensionless state, we use an ensemble in which we can impose the surface tension. After a randomly selected number of DPD steps, we perform a Monte Carlo move in which we change the area of the bilayer in such a way that the total volume of the system remains constant. This move is accepted with a probability given by [12]

$$P_{\text{acc}}(o \rightarrow n) = \min \left( 1, \frac{e^{-\beta[U(n) - \gamma A_n]}}{e^{-\beta[U(o) - \gamma A_o]}} \right), \quad (2)$$

where  $U(n)$  denotes the energy associated with the conservative part of the interactions of the new configuration  $n$  and  $U(o)$  is the energy of the old configuration  $o$ ,  $\beta=1/(k_B T)$  is the reciprocal temperature, and  $A_o$  and  $A_n$  are the areas of the old and new configuration of the bilayer, respectively. The state of zero surface tension is obtained by setting  $\gamma=0$ . We initialize our system by distributing lipids randomly in water and we observe the self-assembly of a bilayer using DPD simulations only. After the bilayer is formed, we perform, in addition to the DPD moves, Monte Carlo moves in which we change the area as well. The equilibration is finished when the area of the bilayer fluctuates around the equilibrium value. Explicit calculation of the surface tension confirmed that indeed a state of zero surface tension was simulated. The importance of this method is that it allows us to observe directly transitions in which the area per lipid

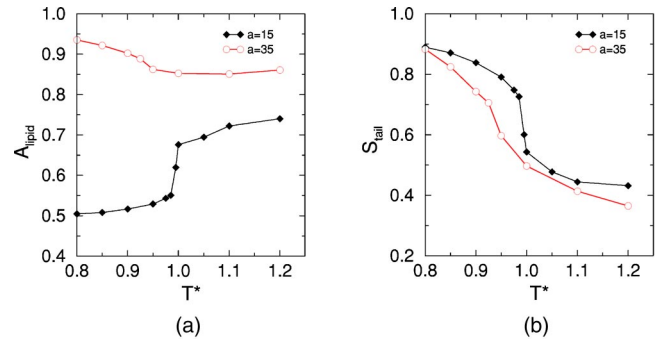


FIG. 2. (Color online) Area per lipid (left) and chain order parameter (right) as a function of the temperature for two types of lipids that differ in their head-head interaction. Upon cooling for high head-head repulsion (circles, red curve) a  $L_\alpha$  to  $L_{\beta I}$  transition is observed, while for low head-head repulsion the  $L_\alpha$  to  $L_\beta$  transition occurs. The units of  $A_{\text{lipid}}$  and  $T^*$  are reduced units as was explained in the text.

changes. To ensure that our simulations were sufficiently long to observe the stable phase, we repeated some simulations starting from a random distribution of lipids. These simulations reproduced both the gel and the liquid crystalline phases.

Figure 2(a) shows the area per lipid as a function of the temperature for two types of head-group particles, one system with the conventional head-head repulsion ( $a_{hh}=35$ ) and a system in which we have decreased the head-head repulsion ( $a_{hh}=15$ ). These two systems show completely different temperature dependence. For  $a_{hh}=15$ , we observe a slight increase of the area if we increase the temperature until, for  $T^*=1$ , a jump in the area is observed. A further increase in the temperature increases the area further. For  $a_{hh}=35$ , we observe an initial decrease of the area if we increase the temperature. At  $T^*=0.95$ , we observe a transition above which the decrease of the area is less and at higher temperature the area increases similarly to what is observed for the system with the smaller head-head repulsion. The snapshots shown in Fig. 1 indicate that at high temperatures in both systems the bilayer is fluidlike ( $L_\alpha$  phase), while at low temperature a gel phase is observed; for the high repulsion parameters we find an interdigitated phase, while for the low repulsion parameters we find a non-interdigitated phase. In Fig. 2(b), we also plot the tail order parameter, characterizing the nematic order in the bilayer. The tail order parameter is defined as  $S_{\text{tail}} = \frac{1}{2} \langle 3 \cos^2(\theta) - 1 \rangle$ , where  $\theta$  is defined as the angle between the orientation of the vector along the first and the last bead in the tail and the bilayer normal. This figure shows that the order in the tail is lost if the system goes from the gel phases into the liquid crystalline phase. Further analysis of the structure and diffusion coefficients in the bilayer planes of these phases shows that the systems behave like two-dimensional liquids and no preferred tilt is observed in these phases. A solid phase is observed at much lower temperatures. From these figures, we have obtained the phase transition temperatures for various tail lengths and head-group repulsions.

Figure 3 shows the phase diagrams for the bilayer phases for various tail lengths and head-group repulsions. For high

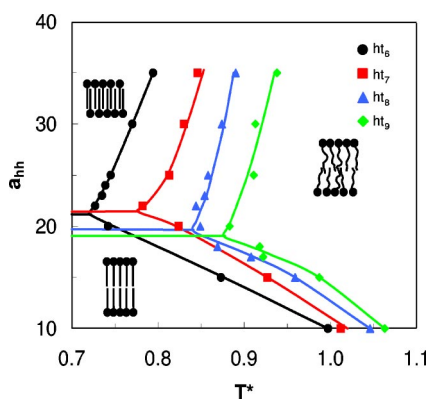


FIG. 3. (Color online) Phase diagrams for different tail lengths  $ht_6$  (black, circles),  $ht_7$  (red, squares),  $ht_8$  (blue, triangles), and  $ht_9$  (green, diamonds).

head-head repulsion, the system can gain energy by adding water particles in between the heads. As a result, the distance between the head groups increases and the interdigitated phase is stabilized. For low values of  $a_{hh}$ , the head groups expel water and the stable phase is the noninterdigitated phase. As we increase the tail length, the gel phases are stabilized and the transition shifts to higher temperatures. The effect of increasing the head-head repulsion on the gel to liquid crystalline transition temperature is much more pronounced for the  $L_\beta \rightarrow L_\alpha$  compared to  $L_{\beta I} \rightarrow L_\alpha$ . This can be understood from the fact that in the interdigitated phase the average distance between the heads is already much larger compared to the noninterdigitated phase, and a further increase in this distance does not have a dramatic effect on the stability of the gel phase. It is interesting to compare these results with the experimental data of Misquitta and Caffrey [17], who systematically investigate the phase diagrams of monoacylglycerols, a single-tail lipid, and show a similar tail length dependence for the  $L_\beta \rightarrow L_\alpha$  transition. Interestingly,

for a similar model of a double-tail lipid, we do not observe the formation of an interdigitated phase. This corresponds to the experimental observation that for the most common double-tail lipids the interdigitated phase does not form spontaneously, but should be induced by the addition of, for example, alcohol [2].

The effect of adding salt on the gel to liquid crystalline transition has been observed for double-tail lipids [18] and recently for single-tail lipids [19]. These studies show that adding so-called kosmotropic salts increases the  $L_\beta \rightarrow L_\alpha$  transition temperature, while chaotropic salts decrease this transition temperature. Similar effects have been observed for nonionic single-tail lipids [20]. Takahashi *et al.* [19] explain these observations by assuming that kosmotropes tend to be excluded from the interfacial region and hence reduce the amount of interfacial water, while chaotropic salts have the inverse effects, i.e., are adsorbed at the interfacial region and increase the amount of interfacial water. In our model, a similar effect can be achieved by changing the head-head interactions; increasing or decreasing  $a_{hh}$  corresponds to adding chaotropes or kosmotropes, respectively. Our simulations show that decreasing the head-head repulsion stabilizes the  $L_\beta$  phase, which corresponds to the case that water is excluded from the interface. Adding chaotropic salts has the reverse effect; it increases the head-head repulsion and stabilizes the  $L_\alpha$  phase. Our simulations show that at sufficiently high head-head repulsion the interdigitated phase  $L_{\beta I}$  is stable. This suggests that it might be possible to induce the  $L_\beta \rightarrow L_{\beta I}$  phase transition by adding chaotropic salts to the systems.

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