

# Molecular Interactions in Amphiphilic Assemblies: Theoretical Perspective

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## ABSTRACT

In recent experimental studies, a number of morphological features have been revealed on amphiphilic assemblies that need consideration of the molecular chiral structure and the molecular polarity. Molecular chirality and polarity influence the intermolecular energy profile as a function of the distance and orientation between neighboring molecules in the condensed-phase aggregates of mono- and bilayers. After the experimental information is summarized, related microscopic theoretical works are presented. The molecular theory shows that the mesoscopic chiral shape of the condensed phase can be predicted from the molecular chiral structure studying the intermolecular energy profile. The theoretical insights have implications for related biological systems.

## Introduction

Amphiphilic assemblies range from simple structures, such as micelles, vesicles, microemulsions, and mono- and bilayers, to highly complex biological architectures as membranes. The shape of the aggregates is dependent upon the attractive and repulsive components of the free energy of their formation.<sup>1–3</sup> Recent experimental studies revealed several interesting observations that could not be explained by the macroscopic theories and needed new information about the detailed orientation and distance dependence of the intermolecular interaction between molecules within the aggregates. These studies indicate that both chirality and polarity of a particular amphiphile are controlling the features of the aggregates, such as shape, shape transition, and their temperature dependence. For example, the mirror-image isomers of a given molecule can lead to the development of two different handednesses of aggregates in both mono- and bilayers.<sup>4–15</sup>

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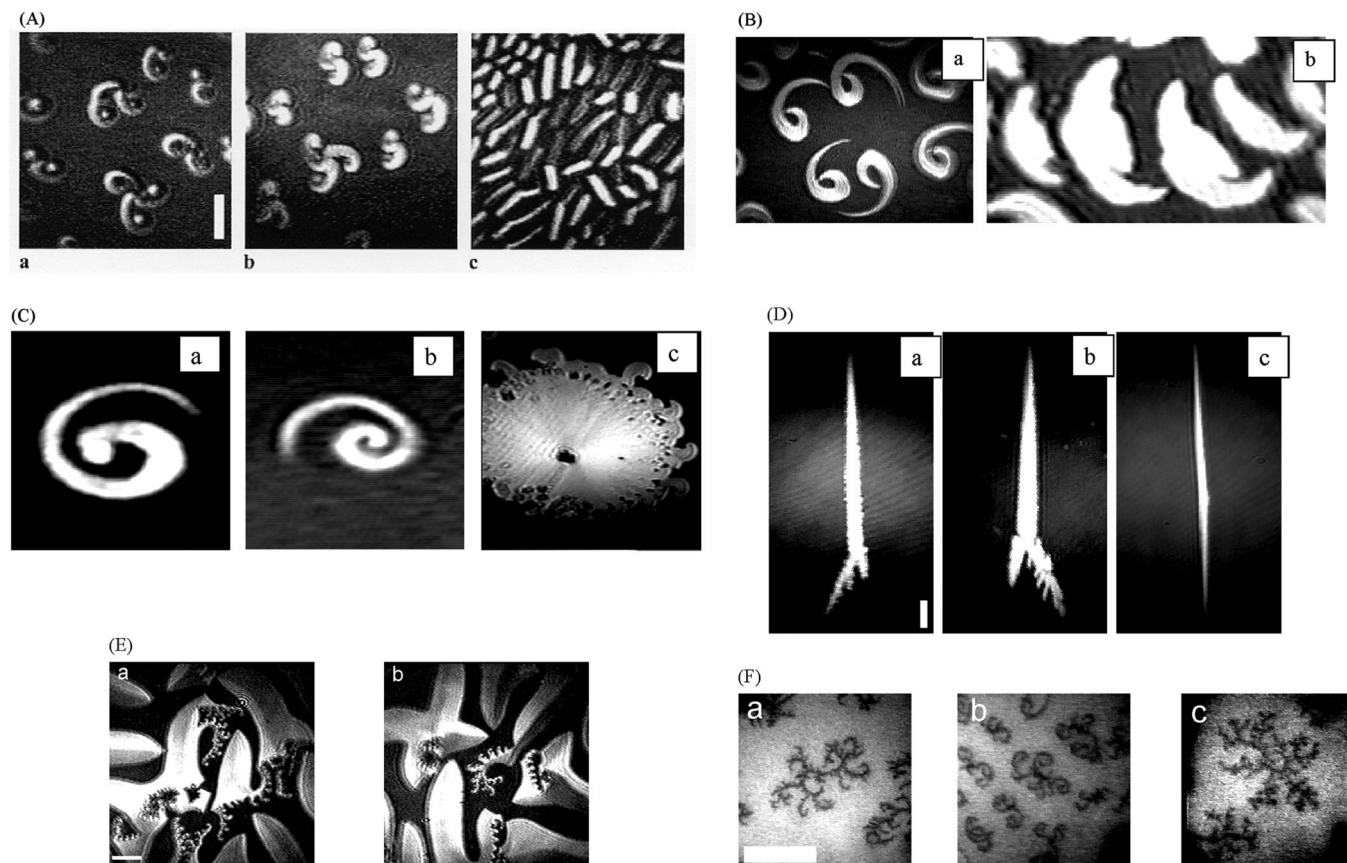
Typical examples for handedness in opposite directions are demonstrated for monolayers of various chiral amphiphiles in Figure 1. The condensed-phase domains show a mirror-image relation between the two enantiomeric forms. In all cases of the various chiral amphiphiles, one enantiomeric form gives a typical handedness of the domains, whereas the other enantiomeric form has the handedness of the domains in the opposite direction. Despite large differences in the domain shape of the various chiral amphiphiles, this feature can be clearly seen from opposite orientation or curvature of domains composed of the two different enantiomeric forms (parts A, C, and F of Figure 1). Similar observations are also made in bilayers, where the handedness of the helical aggregate is dependent upon the enantiomeric forms of the amphiphile. Subtle variation in the dipolar head-group structure of the amphiphile and the related change in the dipolar interaction can also influence the aggregate shape. This is shown in Figure 2, where small changes in the head-group structure drastically affect the domain shape. The influence of molecular chirality and polarity has been observed in Langmuir mono- and bilayers, fibrillar aggregates, or tubules formed from bilayers.<sup>5–10</sup> The consideration of attractive and repulsive components of free aggregation energy<sup>1–3</sup> does not suffice to explain these experimental observations because these theories in their existing form do not differentiate between the contribution of different enantiomeric forms and the free energies.

Chiral discrimination is a subtle phenomenon where only atom(s) or group(s) exchange the position in space (molecular dissymmetry) and induces as well as controls the chirality of the helix and domains at the mesoscopic length scale. Furthermore, differences between L–L (or equivalently D–D) and D–L interactions are observed in the cases where chiral segregation takes place. This phenomenon raises the questions of (i) how such a slight/subtle molecular feature controls higher length-scale structural features; (ii) why a particular chemical structure (of different amphiphiles) of molecular chirality (D or L form) gives rise to its typical mesoscopic chirality (right- or left-handed domain); (iii) how in some cases the chiral segregation takes place (despite the same energies of D or L); and (iv) how to treat the intermolecular interaction in a situation where the customary assumption of isotropicity or symmetry over the length scale of the system (as commonly used in liquid-state theories) does not work. These questions cannot be explained by theories, which do not consider the orientation dependence of intermolecular interactions. The traditional Landau–Ginzburg-type continuum theories “include terms that generate distinct physical effects”.<sup>6</sup> The energy contributions in such expressions being fitted to describe a system are not promising in explaining the experimental facts that emerged by the experimental results.

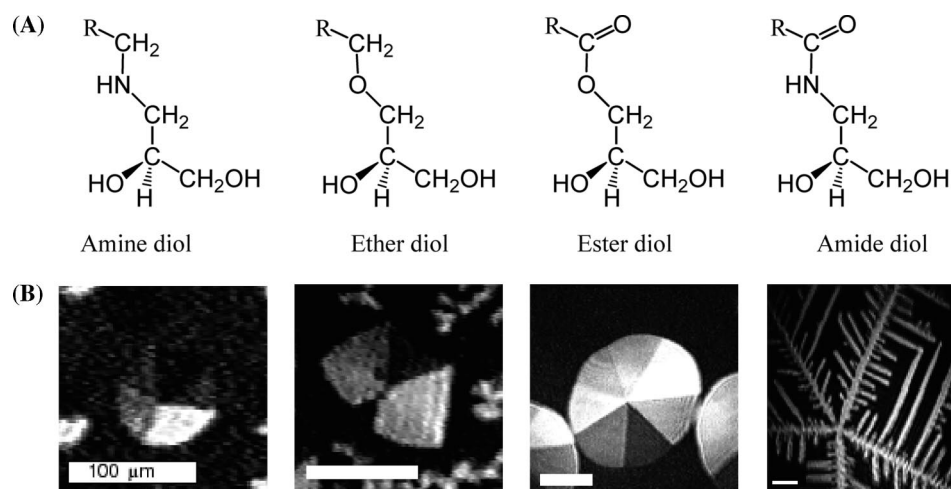
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**FIGURE 1.** (A) Brewster angle microscopy (BAM) images of (a) D, (b) L, and (c) racemic dipalmitoyl phosphatidylcholine (DPPC) condensed-phase domains. Bar length = 100  $\mu\text{m}$ . (B) Chiral discrimination in the domain texture of palmitoyl aspartic acid (PAA) monolayers. (a) D enantiomer and (b) D,L racemate. Image size = 350  $\times$  350  $\mu\text{m}$ . (C) Chiral discrimination of the condensed-phase domains of stearoyl serine methyl ester (SSME) monolayers spread on pH 3 water. (a) D enantiomer, (b) L enantiomer, and (c) D,L racemate. Image size = 80  $\times$  80  $\mu\text{m}$ . (D) Chiral discrimination of the condensed-phase textures of *N*-tetradecyl- $\gamma,\delta$ -dihydroxypentanoic acid amide (TDHPAA) monolayers. (a) *S* enantiomer, (b) *R* enantiomer, and (c) *R,S* racemate. Bar length = 50  $\mu\text{m}$ . (E) Chiral discrimination in 1-*O*-hexadecyl glycerol (HDG) domains. (a) Racemic mixture with spirals curved in two opposite directions and (b) *S* enantiomer with spirals curved in only the clockwise direction. (F) Chiral discrimination in 1-stearylamine glycerol (SAG) monolayers. (a) *S* enantiomer, (b) *R* enantiomer, and (c) racemate. Bar length = 100  $\mu\text{m}$ .



**FIGURE 2.** (A) Chemical structure of the four monoglycerols. (B) Representative BAM images of the four monoglycerols.

An elegant theoretical framework has been developed by McConnell and coworkers,<sup>11</sup> followed by others, to bridge the gap between the continuum theories and the available experimental results on domain shapes in monolayers. Their works have revealed that the shape of the

condensed-phase domains and their transitions is governed by an intricate interplay between molecular interactions between dipoles present, the difference in non-bonded interactions across the fluid/condensed-phase boundary (that means the line tension at the domain

boundary), and the interactions influenced by the chirality of molecules.

Unfortunately, a similar theoretical basis has not been developed for bilayers beyond the approach taken by Helfrich et al.,<sup>9,10</sup> until recently. Earlier theories by de Gennes<sup>7</sup> and Lubensky and Prost<sup>8</sup> encountered discrepancies with the experimental results. Improved theories by Helfrich et al. proposed that an intrinsic bending force exists because of the chirality.<sup>9,10</sup> However, the microscopic origin of the intrinsic bending force driving such an aggregate structure, especially the relation of the latter with the molecular dissymmetry, remained unclear until recently.<sup>5</sup> Therefore, a molecular or microscopic approach has been attempted in recent years and is the subject of this Account.

The understanding of these phenomena is useful in many respects. Knowledge of the influence of molecular chirality to the dissymmetry of the aggregate (of meso- or macroscopic length scales) can help to gain insights into the role of chirality in biological systems, such as proteins, nucleic acids, and membranes. This is related to the *origin of homochiral evolution*. Besides, the biomimetic amphiphilic assemblies are known to have diverse practical applications.<sup>2</sup> An understanding of the interactions in aggregates is also useful in gaining control over designing new structures. Such a “bottom-up” approach facilitates the construction of complex molecular devices with better functionality using step by step subunit association, and it could lead to rational nanofabrication.<sup>4</sup> A further motivation of studying biomimetic systems comes from the necessity to understand the molecular interactions in the heterogeneous and interfacial structures. With this end in view, the recent theoretical work on the molecular interaction in chiral and polar amphiphilic molecules and the interpretation of experimental results are discussed in this Account.

## Chirality- and Polarity-Dependent Intermolecular Interactions in Amphiphiles: Related Experimental Observations

An early study of chirality effects in amphiphilic aggregates goes back to more than 50 years. Hotten and Birdsall reported that salts of 12-hydroxystearic acid produce twisted structures in bilayer gels depending upon the chirality of the amphiphile.<sup>16</sup> Later, definitive correlations between handedness and the chiral helical structures formed in bilayer gels have been reported.<sup>5,16–24</sup> Langmuir monolayers are successful model systems to correlate the molecular chirality with the mesoscopic structure.<sup>4,12–15</sup> The experimental results on the morphology of the condensed-phase domains and the two-dimensional lattice structure, obtained from Brewster angle microscopy (BAM) and grazing incidence X-ray diffraction (GIXD), provide an excellent resource for molecular interpretations.<sup>14</sup> When the monolayer of a chiral amphiphile is composed of a pure enantiomer, the molecules within the corresponding domains develop mutual intermolecular azimuthal orientation. Whereas the molecular tilt from the

normal remains unchanged, the continuous or sudden variation of the azimuthal orientation is a feature of the enantiomerically pure domains. The intermolecular orientation varies along the length and width of the domain. This mutual orientation is propagated over the mesoscopic length scale, and the domains or fragments of domains become curved [see parts A, C, and F (a and b) and B (a) of Figure 1].

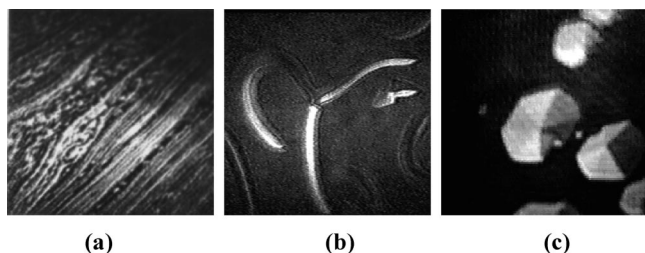
In general, the racemic domains do not show anisotropic shape development (see parts A and D of Figure 1). This indicates that either the mutual intermolecular azimuthal orientation is absent or cancelled over the mesoscopic length scale in the case of heterochiral racemic systems. However, chiral separation occurs in the cases where the racemic domains develop curved arms with opposite handedness (parts B, C, and F of Figure 1). This happens when the interaction between the same enantiomers (D–D or L–L) is favored over the two different enantiomers (D–L) and is designated as homochirality, whereas the opposite case where the interaction of the two different enantiomers (D–L) is more favored than the interaction between the same type of enantiomers (D–D or L–L) is called heterochirality.

Representative examples of condensed-phase domains, where chiral discrimination have been observed, are shown for dipalmitoyl phosphatidylcholine (DPPC), palmitoyl aspartic acid (PAA), stearoyl serine methyl ester (SSME), *N*-tetradecyl- $\gamma,\delta$ -dihydroxypentanoic acid amide (TDHPAA),<sup>25</sup> 1-*O*-hexadecyl glycerol (HDG), and 1-stearylamine glycerol (SAG)<sup>26</sup> in Figure 1.

The HDG monolayers revealed subtle features of chiral discrimination not observed previously (Figure 1E).<sup>27,28</sup> In this system, the surface pressure of the main-phase transition of the pure enantiomers is above that of the racemic mixture, indicating a heterochiral preference. On the other hand, the appearance of spirals with opposite curvatures at the same domain in racemic monolayers suggests chiral segregation, which means a homochiral preference. The simultaneous observation of surface-pressure-dependent hetero- as well as heterochirality based on the domain morphology is of special interest.

Chirality influences the features of both mono- and bilayers via the intermolecular interaction. The result is the induction of a curvature in three dimension giving rise to a helix with typical handedness in the three-dimensional assembly (bilayer) and the induction of two-dimensional curved domain shapes in monolayers at the air/water interface. The most fascinating aspect of the domains composed of chiral molecules is that the sense of their curvature (or their handedness) is completely specific for the concerned chirality. Explicitly, if the condensed-phase domains of the D-enantiomeric monolayers show right handedness, the L-enantiomeric monolayers give left handedness and vice versa [see parts A, C, and F (a and b) of Figure 1]. The monolayers of heterochiral racemic mixtures cannot show any curvature or chiral segregation. The significance of the corresponding





**FIGURE 3.** Domain shapes of *rac*-HDG monolayers at (a) 278.15 K,  $\pi = 0.1$  mN/m, (b) 288.15 K,  $\pi = 2.2$  mN/m, and (c) 308.15 K,  $\pi = 18$  mN/m.

experimental results and their theoretical interpretations are discussed in the context of microscopic theoretical studies.

Striking variations in monolayer domain shapes and features are observed when chirality effects are absent in heterochiral racemic systems. This suggests studying the role of dipolar interactions for the specificity of the domain shape. Although the chemical structures of the amide, ether, ester, and amine monoglycerol amphiphiles are quite similar, their domain shapes are dramatically different (Figure 2).<sup>29</sup> The crystalline nature of the monolayer domains increases from the amine to the amide monoglycerols. The amide domains are thin and brittle, with the highest orientational correlation. On the other hand, the monoglycerol amine domains are of fractal nature with certain fluidity, with far less orientational correlation. The crystallinity and orientational correlation of the monoglycerol ester and ether domains fall between the monoglycerol amide and amine. These observations indicate that the molecular dipolar properties should be responsible for the drastic change over longer length scales.

An interesting anomaly has been observed in racemic HDG monolayers, which points out a subtle interplay of the dipolar interaction at the interface. The domain shape of numerous amphiphilic monolayers studied thus far follows the tendency to be more compact at low temperatures and to increase the contact line or elongate the shape at higher temperatures. This is expected from the temperature dependence of two competing factors in determining the shape, namely, the line tension and dipolar repulsion. The line tension decreases with increasing temperature. In contrast, compact domain shapes are formed at higher temperatures of racemic HDG monolayers, whereas elongated arms or even long stripes are developed, as the temperature is lowered.<sup>30</sup> This is shown in Figure 3. Such a behavior suggests a dominating role of the dipolar interaction for the shape change. That is substantiated by a detailed analysis of dipolar components at the air–water interface.

Considerable differences in the equilibrium domain shape also exist between enantiomeric phospholipids of similar chemical structure, such as palmitoyl phosphatidylcholine (DPPC) and dipalmitoyl phosphatidylethanolamine (DPPE). Whereas the DPPC has  $N(\text{CH}_3)_3^+$  present in the head group, the DPPE headgroup has  $\text{NH}_3^+$  in the corresponding molecular segment. The observed differences in the domain shape, explicitly, the elongated arms

of DPPC and the nearly round shape of DPPE, are obviously due to the difference in the polarity of the head groups. A comparison of the dipolar interaction can provide insight into the role of dipolar repulsion in determining the domain shape variation.<sup>31</sup>

A theoretical framework starting from the molecular structure should be the basis in understanding the experimental findings.

### Chirality-Dependent Intermolecular Interactions: Microscopic Theoretical Results

Andelman and coworkers used a model in which the chiral molecule is assumed to be composed of a chiral carbon to which four groups are attached.<sup>32</sup> This model is limited by modeling a three-dimensional molecule as a planar tripod and consideration of only near-neighbor distance-dependent interactions. A more realistic theory of the helical structure in bilayers was developed<sup>8</sup> in which the effective pair potential between a pair of chiral molecules is calculated to find the mutual orientation at minimum energy. It is reasonable to infer that the subtle stereogenicity at the chiral center of a chiral molecule is responsible for driving the aggregate shape to a particular morphology.

It is possible to predict and understand the structure formation from an effective intermolecular pair potential between the chiral centers of the monomers of the aggregate. Minimally, this potential should depend only upon the distance and the orientation between the two participating chiral amphiphilic molecules. This effective pair potential can then be used to find the relative arrangement of a pair of molecules. The minimal energy conformation of the aggregate can be studied by changing the orientation of the groups and reducing the distance between the chiral centers. The molecules are in a closed packed structure with a small separation between them. Thus, one expects short-range, both repulsive and attractive, interactions to play an important role in these systems. It is found that, for mirror-image isomers in the racemic modification, the minimum energy conformation is a nearly parallel alignment of the molecules. On the other hand, the same for a pair of molecules of one kind of enantiomer favors a tilt angle between them, thus leading to the formation of a helical morphology of the aggregate. It is also shown that the sense of the helix can be predicted from the effective pair potential description. In all considered cases, a complete agreement between the theoretical prediction and the experimental results<sup>33</sup> was observed. This surprising success of the simple and straightforward early molecular approach strongly indicates that the formation of meso- or macroscopic chiral structures, such as a helix, can be predicted from the intermolecular energy profile when the molecular chiral structure is considered explicitly. However, these early studies made several approximations that needed modification.

In recent years, a more detailed molecular approach has been attempted for monolayers.<sup>3,17,29–31,33–41</sup> The

theory assumes that the intermolecular pair potential determines the mesoscopic chiral structure of the condensed-phase domain. It investigates the orientation and distance dependencies of the pair potential between neighboring chiral amphiphilic molecules. The objective is to find the most favorable mutual azimuthal angle at various separations when a pair of molecules is in their minimal energy state with individual molecules in their most likely conformational state.

While entropic factors contribute to the aggregation of amphiphiles, the study of the intermolecular energy profile suffices to explain the chirality-dependent structural features of amphiphilic aggregates for the following reason. Entropy changes during the aggregation of pure enantiomers or racemic mixtures into respective domains are not significantly different because the changes in rotational, translational, and vibrational degrees of freedom of the molecules as a result of the transfer from a free state to an aggregated state should be similar for L-L (or D-D) and L-D pairs. Consequently, the entropy difference hardly contributes to the observed difference in the aggregate shape, such as the mirror-image relation of the opposite curvatures [see parts A, C, and F (a and b) of Figure 1] or the intersection angle of main growth directions [see Figure 1D (a and b)]. Thus, the energy profile is important to determine chirality-related effects.

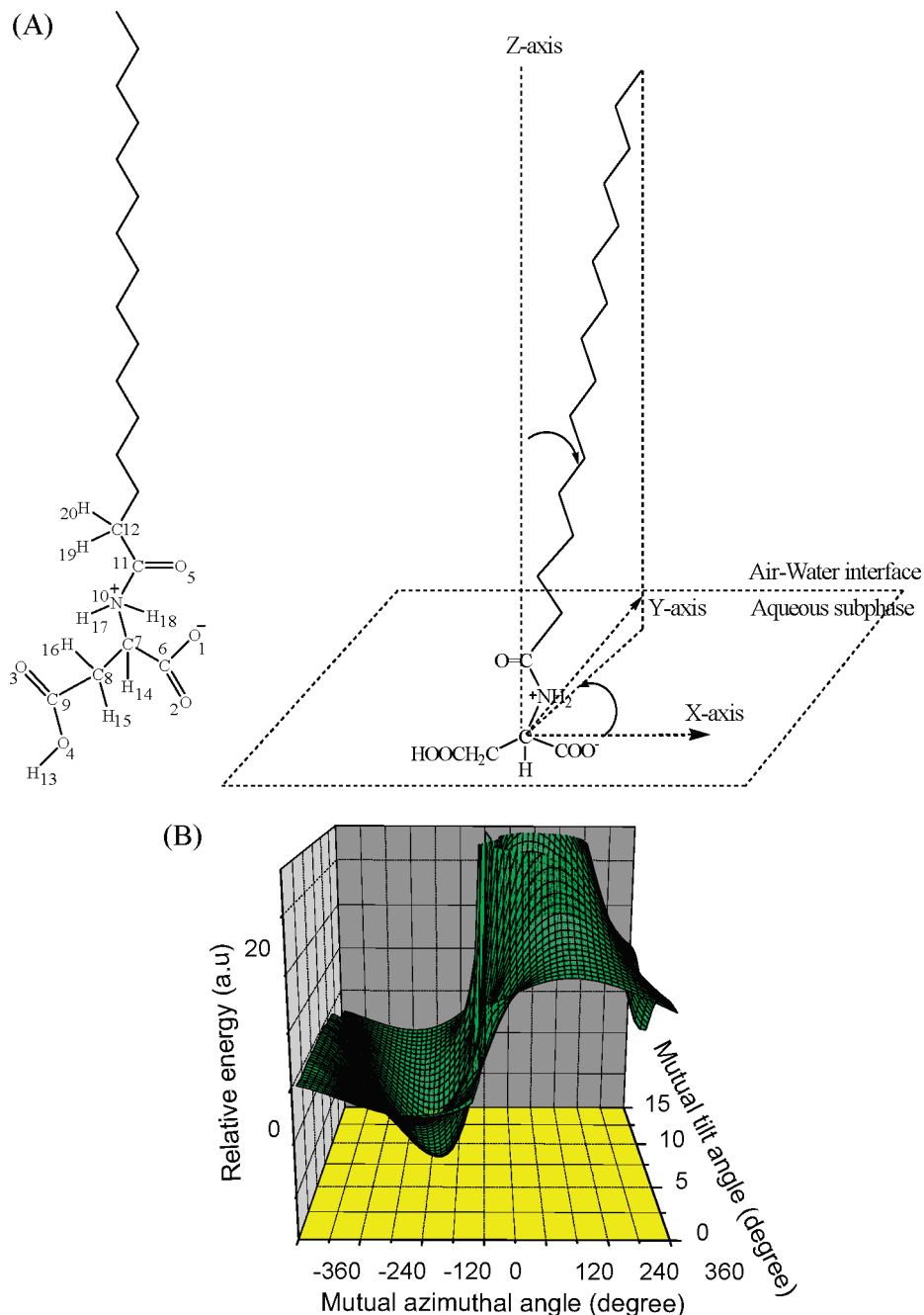
For molecules as large as amphiphiles, the potential energy profile is a function of a large number of degrees of freedom. In principle, the intermolecular energy profile should be calculated as a function of all intra- as well as intermolecular degrees of freedom, which are relevant to the interface. However, the intermolecular energy variation against many of them is redundant when chirality-induced effects are of interest. Systematic approximations have been made in numerical calculations to handle large molecular systems.

To reduce the variables in the numerical calculation of pair potential, the molecular structure of the amphiphile has been approximated at various levels of molecular detail while retaining the spatial chirality around the stereogenic center intact. Initially, a tetrahedral model with equivalent sphere representation of the groups has been used.<sup>8,17</sup> In the spirit of the condensed-state theories, the tetrahedral model assumes that equivalent spheres are effective representations of the groups or atoms of the molecular structure that are attached to the chiral center. Hence, the calculated effective pair potential provides essential information about the chirality-induced orientation dependence between molecules. This model has been successfully applied to mono-<sup>17,34,35</sup> and bilayers.<sup>8,33</sup> The theoretically predicted handedness agrees well with the experimental data. Subsequently, coarse-grained molecular models have been applied to DPPC and PAA monolayers.<sup>36–39</sup> In these studies, the alkyl chains are assumed to be composed of spherical groups, such as  $-\text{CH}_2-$ ,  $-\text{CH}_3$ , etc., and are in *all-trans* configuration, which is a reasonable approximation of the molecular state in condensed phases where chirality effects are relevant. However, different head-group conformations

are possible, and it is necessary to locate the most likely conformational state of the head group, as considered in theoretical studies.<sup>36</sup> The atomic coordinates of PAA in its energy-minimized state, obtained from semi-empirical quantum mechanical calculations, are used to calculate the intermolecular pair potential.<sup>40</sup> The effects of coarse graining on the theoretical predictions are also evaluated.<sup>38</sup>

Recently, the handedness of PAA has been studied using the three-layered hybrid quantum mechanical-molecular mechanical model.<sup>41</sup> Aspartic and palmitic acids are optimized separately at the level of the *ab initio* Hartree-Fock theory. The optimized structure of aspartic acid compares well with the experimental enantiomeric crystal structure and ensures that the most likely conformation is considered. Individual energy-minimized structures are used to generate the enantiomeric PAA and are further subjected to energy minimization with the hybrid method.<sup>42</sup> The three-layered hybrid with the combined molecular orbital and molecular mechanics method is used for the optimization. The *ab initio* theory is applied to the atoms of the head-group region involved in hydrogen bonding in the head-group region. The semi-empirical theory is used for atoms of the head-group region that are not directly involved in hydrogen bonding. The low-level molecular mechanical theory is applied for the alkyl chain part. Once the probable molecular conformational structure is assigned, the intermolecular pair potential is calculated with rigid geometry as a function of the distance and mutual orientation. The assumption of rigid geometry is supported by the fact that the individual molecules are in their most likely state. Because the tilt from the normal is unchanged on an average in the monolayers, the remaining variable to be investigated is the azimuthal orientation. Note that approximations made above are not necessary ingredients of the theory. When enhanced computational time is available, the molecular structure can be considered with the higher level electronic structure-based method for studying the intermolecular energy profile.

Optimized structures of a pair of molecules are used to calculate the azimuthal projection of the molecular pairs. The pair of molecules shows a distinct minimum at the mutual azimuthal orientation that corresponds to the handedness at the optimized separation (Figure 4). The other handedness is unfavorable. A mutual large tilt between the molecules is also unfavored in agreement with the concept that molecules should not have a large mutual tilt in the condensed phase. The energy surface is gradually flattened with increasing intermolecular separation. This is in agreement with the common wisdom that chirality-induced effects decrease at large intermolecular distances. The handedness defined in reference to the growth direction of an aggregate depends upon how one considers the growth of an aggregate. The theory indicates that it is possible to understand the structure of the condensed-phase domains from the intermolecular pair potential, which has been observed to be strongly orientation-dependent in the condensed phase of monolayers.



**FIGURE 4.** (A) Molecular orientation at the air/water interface. (B) Pair potential profile for PAA calculated using the hybrid quantum mechanical/molecular mechanical method.

The orientation dependence acts over a mesoscopic length scale in the condensed phase, where the “rotation in a cone” is restricted because of the dense packing, and it is smaller than that in the fluid monolayer phase.

The orientation dependence of chirality-dependent interactions is clearly evident from theoretical studies of chiral discrimination energies.<sup>38,39</sup> Calculations of the pair potential of SSME, PAA, and TDHPAA indicate homochiral preference obtained for both the packing of a molecule pair (separation at low energy states) and the intermolecular energy profile. The enantiomeric pairs of these amphiphiles are more closely packed and have a lower pair potential minimum than the racemic pairs. The pair potential shows that homochirality is preferred at shorter

intermolecular separations, whereas heterochirality is preferred at larger separations and is also a function of the intermolecular orientation. The predicted novel crossover of homo- and heterochirality and the orientation dependence is a new observation.

The distance- and orientation-dependent crossover of homo- and heterochiral discrimination is also confirmed by experimental and theoretical studies of HDG monolayers.<sup>39</sup> Also, in that case, the theoretical calculation of the pair potential for intermediate mutual separation indicates a heterochiral preference, whereas a homochiral preference is concluded to be gradually preferred for relatively shorter separations. This result explains the experimental finding of a heterochiral preference re-

sulting from the higher phase-transition pressure of the enantiomeric monolayer compared to that of the monolayer of the racemic mixture. On the other hand, the appearance of spirals with opposite curvatures within the same domains of racemic monolayers indicates chiral segregation of the two enantiomers, suggesting a homo-chiral preference above the transition pressure. Both homo- and heterochiral discriminations are not only dependent upon the interpair separation but also upon their mutual orientation. Chirality-dependent interactions are not dominant at relatively larger separations (corresponding to the fluid phase), and in all cases, the calculated discrimination approaches zero at large separations.

It is interesting to note that chiral discrimination and chiral segregation are experimentally found only in Langmuir monolayers, but they are not yet observed in more complicated amphiphilic systems, such as bilayers or three-dimensional liquid crystalline states. The reason may be differences in the nature of orientation-dependent intermolecular interactions in these systems.

### Polarity-Dependent Interaction: Theoretical Results

For monolayers at the air/water interface, little experimental information is available about the structure of head groups or their dipolar nature. However, as shown in the experimental section, the drastic change in the domain morphology caused by a subtle modification of the head-group structure suggests a dipolar origin. Because of the presence of the interface, the head-group dipole is restricted within the aqueous subphase (generally insignificant polarity exists in the alkyl chain region) and it is useful to consider the in-plane (plane of the interface) and out-of-plane components of the dipole moment. In the fluid phase of amphiphilic monolayers, the in-plane component cancels out on an average (because of the free rotation of the molecule at the interface), whereas it is not cancelled in the condensed monolayer phases because of the restricted molecular rotation. Because of the large conformational space available for the head-group region, a number of minimum energy conformations are studied using semi-empirical quantum mechanical methods and the corresponding dipole moments are calculated. Subsequently, from the theoretically calculated conformation and GIXD data, it is possible to calculate the populations of in-plane and out-of plane components of the dipole moment assuming that the geometry of the molecule is rigid and the molecule is oriented on average according to the X-ray diffraction data.

The theoretically calculated population of dipole moments for the amphiphilic monoglycerols follows the sequence amine < ether < ester < amide.<sup>29</sup> The calculated dipolar energies also follow the same trend for different possible mutual head-group orientations (Figure 5).<sup>29</sup> These results are in good agreement with the features of the domain shape of the monoglycerols observed experi-

mentally, as described in Figure 2. The variations in the head-group molecular structure drastically alter the domain shape, and the theoretical calculations conclusively reveal the important role of the electrostatic interactions for the mesoscopic domain architecture.

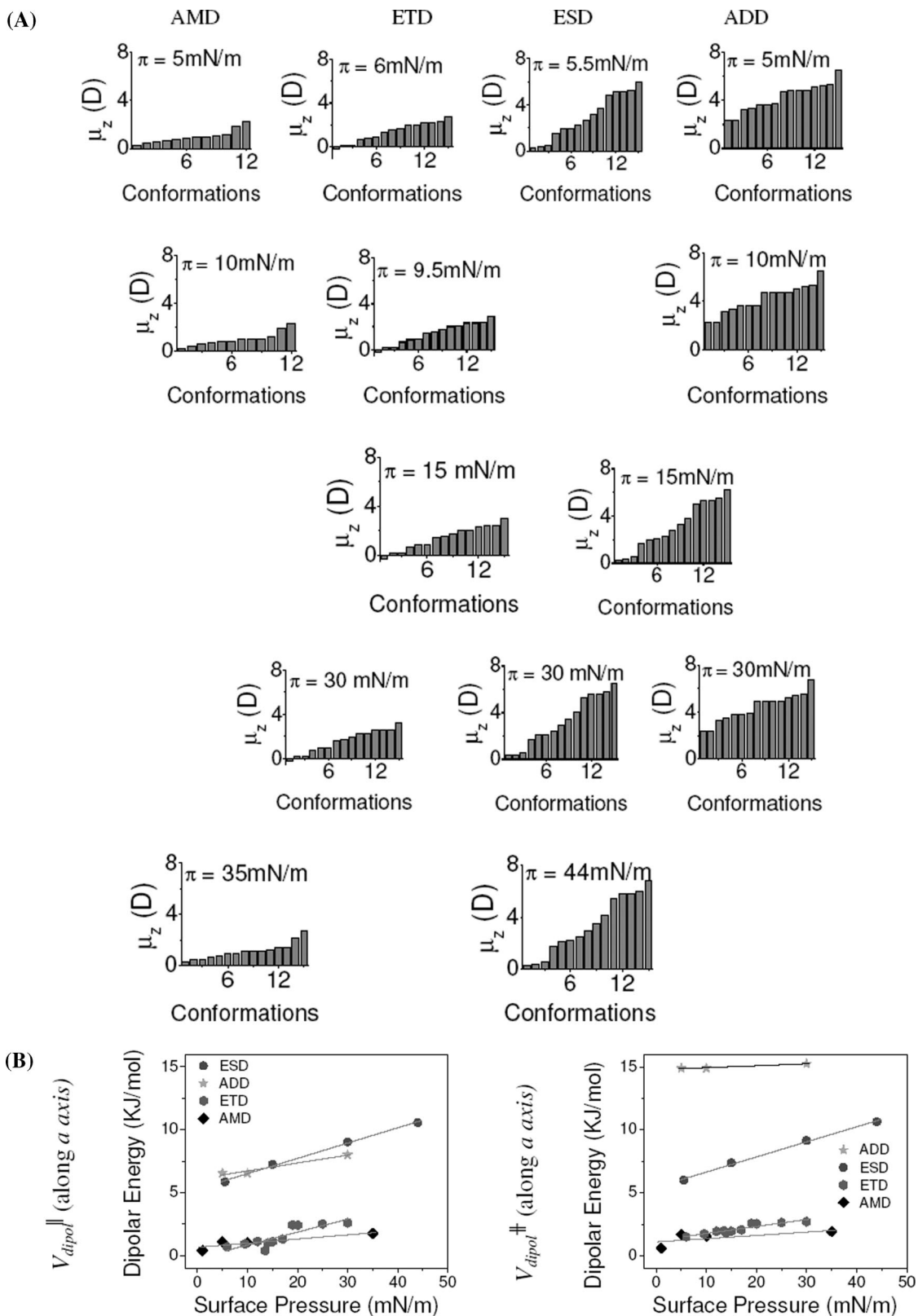
Quantum mechanical calculations of molecular dipole moments and the analysis based on X-ray data have been performed to gain insight into reasons for the interesting anomalous temperature-dependent variation of glycerol ether domains, as described in the experimental section (see Figure 3). The results reveal that the azimuthal orientation of the molecules enhances the in-plane dipole moment at lower temperatures, which dictates the anomalous shape transition.<sup>30</sup> For all conformers studied, the ratios of in-plane/out-of-plane dipole moments are higher at lower temperatures relative to those at higher temperatures. This demonstrates that the temperature dependence of the molecular tilt and azimuthal orientation can have a decisive influence on the contribution of in-plane dipole moments aligned to a particular direction to the electrostatic repulsive interaction. The higher in-plane dipole moments at lower temperatures favor the elongated shapes along the azimuthal tilt direction. The ordering of amphiphiles will be more at lower temperatures, which is also expected to favor the alignment of dipoles toward the azimuthal direction and, thereby, to increase the repulsive interaction in that direction.

The foregoing studies indicate that the analysis of the dipole moments for a population of probable head-group conformations is useful in correlating the features of the aggregate shape when a subtle change in the chemical structure influences the polarity. It should be useful to sample the head-group conformational space in detail and further analyze the population of the charge distribution in the head-group region. For future studies, the inclusion of the air/water interface into the microscopic consideration would be a complicated but desirable feature.

### Intermolecular Interaction: Overview of Theoretical Results

First, theoretical works have been presented to explain the highly substance-specific orientational order of condensed-phase domains observed in amphiphilic mono- and bilayers. The studies demonstrate that the intermolecular interaction profile is strongly orientation-dependent for dissymmetric molecules and gradually loses symmetry with increasing dissymmetry of the molecules concerned.<sup>43</sup> The increasing dissymmetry in the pair potential profile indicates preferential orientations between molecules rather than arbitrary mutual orientation. The preferred mutual orientation is the controlling factor of morphology in the condensed phase of aggregates. The concept of broken symmetry, as used in the continuum theory, naturally arises from the microscopic view point,<sup>43</sup> and there is no need to invoke artificially the existence of a preferred orientation in the free-energy expression. It is also shown that individual molecular structures at various levels of detail (tetrahedral model, coarse grained,





**FIGURE 5.** (A) Comparison of the population of the normal component of dipole moments of four monoglycerols, as referred to in Figure 2. (B) Comparison of the in-plane component of dipolar energies of four monoglycerols, as referred to in Figure 2.

atomistic, or electronic structure based) used to calculate the intermolecular energy profile are successful in describing the properties of the aggregate. The molecular chirality is dependent upon the configuration with a certain population of low-energy conformations. Hence,

once the essential spatial dissymmetry of a given configuration is incorporated into the theoretical consideration, the observed manifestations of chirality at the condensed phase can be correlated with the microscopic structure. When the conformational variation is large (i.e., at en-



hanced temperature), the effect of spatial dissymmetry can be drastically reduced because the intermolecular energy profile loses its orientation dependence (or preference).

## Concluding Remarks

Little molecular understanding has been available thus far of the chiral structure–function relationship in biological systems. The role of chirality at lower levels for the formation of higher level structures has not been clarified because of the structural hierarchy in biological systems. In most cases, the higher level structure is the functional form. The contribution of chirality of lower level blocks to a higher level structure and function is therefore necessary to understand. The study of biomimetic systems, as described in this Account, is a first step in this direction. Thus far, the objective of these studies was to correlate the molecular chiral structure and polarity with the properties of mesoscopic length scale aggregates and to gain insight into the role of the interactions involved. A few microscopic theoretical studies were initiated toward understanding chirality-dependent interactions in mimetic systems, such as compounds with nucleic acid mimetic head groups and amino acids.<sup>44,45</sup> More work is required regarding the subtle but decisive principle of chirality in nature.

Other bottom–up studies have been directed toward understanding the driving forces for the aggregation (condensation) processes of amphiphilic monolayers. Different types of interactions including hydrogen bonding have been successfully considered. Using semi-empirical quantum chemical methods, thermodynamic quantities (enthalpy, entropy, and Gibbs energy) of the dimerization and clusterization in finite and infinite clusters of fatty alcohols and long-chain alcohols have been calculated.<sup>46–49</sup> The results have been correlated to the main-phase transition of the amphiphiles at the air/water interface and allowed for a conclusion on the properties of cluster formation, the ordering at clusterization, and reorganization of clusters.

Despite the experimental and theoretical studies of biomimetic models, the complexity of large biological systems requires more detailed and systematic studies to understand the role of the molecular interaction influenced by chirality and polarity. Such work may contribute knowledge to the difficult, complex question, on which basis nature has developed diverse biological structures with highly specific functionality.

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