

Molecular Origin of the Chiral Interaction in Biomimetic Systems: Dipalmitoylphosphatidylcholine Langmuir Monolayer

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In the present study, we correlated for the first time, the molecular chiral structure of a phospholipid (dipalmitoylphosphatidylcholine; DPPC) and the handedness of the mesoscopic domain composed of DPPC using an effective pair potential (EPP) theory. The study uses a coarse-grained description of the molecule and calculates the pair potential between a pair of molecules without using any adjustable parameter. The agreement between the theoretical results and the experimental observations is excellent. In addition to the molecular explanation of the handedness, the study also explains why the distribution of the headgroup orientation in the aqueous subphase does not destroy the chirality of the domain shape. This study explains the influence of chirality at the lower level of structural hierarchy on the chirality at a higher level in biomimetic systems.

Introduction

The study of the chirality driven morphological features in biomimetic monolayer and bilayer systems remains unabated over years.^{1–15} This is mainly due to the importance of the structure–function relationship in related biological systems. Many of the biological structures such as protein and DNA are chiral at the secondary, tertiary, or quaternary level. The possible functional role of such chiral structures and the role of chirality of their basic building blocks in making such structures are yet to be explored. This is related to the famous question of why we have only L-amino acids in nature (*the origin of homochiral evolution*).¹⁶ It may be noted that enantiomeric drug design is a billion-dollar industry.¹⁷ Consequently, understanding the macro–micro relation of chirality in biological structures has fundamental as well as technological importance.

The existence of mesoscopic domains is well-known in condensed phase monolayers.^{1–11} When the constituent molecules are chiral, the domains give rise to fascinating curved chiral shapes (spirals, filigrees, triskelions),^{5,6,14,15} as observed by optical microscopic techniques.¹⁸ The domain curvature is specific for enantiomers, and no curvature is observed for racemic (Figure 1). Though it is now accepted that such curvature is due to the chirality of the constituent molecules, how molecular chirality plays a role in this phenomena is yet to be investigated in detail. McConnell and co-workers first indicated that the chiral shape of the domain could be due to chirality of the constituent molecules, which gives rise to an intrinsic twisting tendency or spontaneous curvature.¹¹ Analogous spontaneous curvature leading to three-dimensional chiral aggregates (helices) was observed in bilayers for which an effective pair potential (EPP) based theory was proposed.^{12,13} The concept of EPP was subsequently applied to monolay-

ers.^{10,14,15} However, it remained inconclusive that the assumed presence of chiral EPP in the total free energy is due to lipid (DPPC) or the added chiral substance (cholesterol).¹⁰ In other words, the origin of the spontaneous curvature was not quantitatively related to the molecular structure in the monolayers. Consequently, the origin of the handedness of the domain curvature specific for a particular enantiomer could not be explained.

In this work we attempted to calculate the EPP of a pair of DPPC molecules on the basis of a coarse-grained description of the molecular structure (Figures 2 and 3). This description is more realistic and an improvement over the equivalent sphere description of the groups used in previous theoretical studies^{12–15} and in simulation studies where the molecular structure was not considered.¹⁰ As a result, the EPP profile obtained from the present coarse-grained description is depicting the molecular interaction in much more detail than any such previous studies. From the minima of the pair potential, the preferred orientation of a pair of aggregating molecules can be obtained. The mutual orientation between the pair of molecules indicates the handedness of the aggregate in the condensed state where the molecules are aligned in next-to-next order. It is important to note that in the liquid condensed (LC) phase, where the domains are observed, the molecules are in a close separation and chiral interactions are dominant. We also investigated the effect of orientational distribution of the headgroup in the aqueous subphase on the chiral shape of the aggregate.

Theoretical Calculation

In the present study, the tails and the heads of the molecule are represented by an array of collinear spherical groups (CH₂, CH₃, CH, COO groups, etc.). Thus, although we neglect the atomistic details, the average orientations of the groups with

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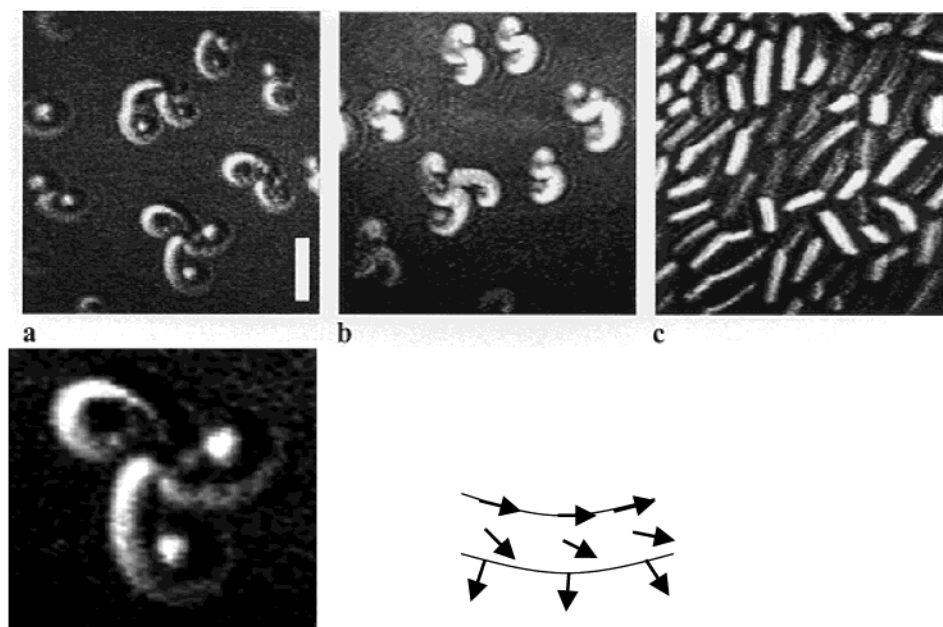


Figure 1. BAM images of (a) D, (b) L, and (c) racemic DPPC condensed phase domains. An enlarged view of a single domain is shown in (d) and the changes in molecular director within an arm of the triskelion are schematically shown in (e).

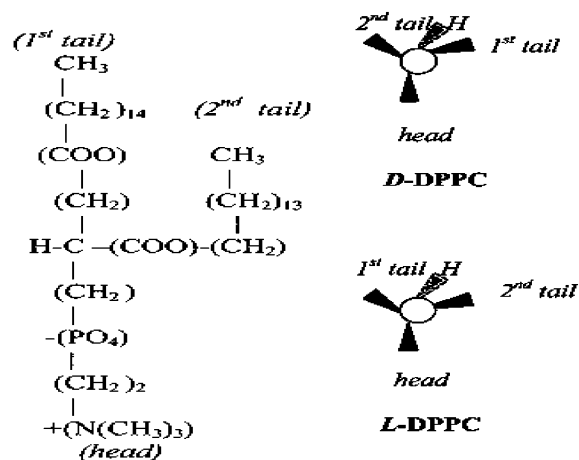


Figure 2. Molecular formula of DPPC and the configuration of mirror image isomers of the same.

respect to the chiral center are considered accurately over a reasonably small length scale. These tails and heads are denoted by the subscripts t and h, respectively. Such a coarse-grained description of the amphiphilic molecules is found to be useful in theoretical studies and simulation.¹⁹ The molecular segments are placed at the lattice positions and the two tails are designated as first and second tails, as shown in Figure 3. In the present study we used the first tail of the first molecule as a reference, and the relative orientation and distance of all other tails and heads are measured with respect to it. Note that the choice of reference is completely arbitrary and results of calculation are independent of the choice. The orientation of the first tail of the reference molecule with respect to the normal (μ) and the angle between the azimuthal tilt direction of the tail (projected on the perpendicular plane to the normal) and the X axis (denoted by α_t) are obtained from the grazing incidence X-ray diffraction (GIXD) data.⁹ The orientations and distances of groups necessary for calculation are shown in Figure 4.

The intermolecular interaction energy between the groups composing tails and heads of the two molecules is given by a Lennard-Jones potential and represents the short-range repulsion

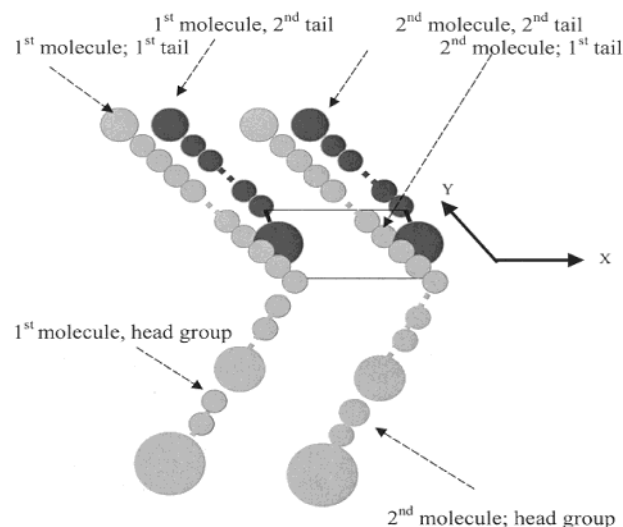


Figure 3. Coarse-grained picture of the pair of molecules placed on a lattice.

and long-range attraction over all nonbonded pairs of groups (g) of the i th and j th molecules.

$$U/k_B T = \sum_{\substack{g(i) \\ g(j)}} (4/T) (\epsilon^{g(i)g(j)}/k_B) [(s^{g(i)g(j)}/\sigma^{g(i)g(j)})^{-12} - (s^{g(i)g(j)}/\sigma^{g(i)g(j)})^{-6}] \quad (1)$$

Here, $s^{g(i)g(j)}$ is the orientation dependent distance between the $g(i)$ and $g(j)$ groups,^{14,15} $\sigma^{g(i)g(j)}$ is the average Lennard-Jones diameter of the corresponding groups, and the energy parameter $\epsilon^{g(i)g(j)}$ is given by the Berthelot rule,

$$\epsilon^{g(i)g(j)} = (\epsilon^{g(i)} \epsilon^{g(j)})^{1/2} \quad (2)$$

The α_t value for the pairs of tails or the α_h values of the pairs of head and tails along the lattice diagonal are calculated from lattice geometry (Figure 3 and Figure 4). The effective diameters of the groups are calculated from the group increment data tabulated by Bondi^{20,21} and using the empirical relations

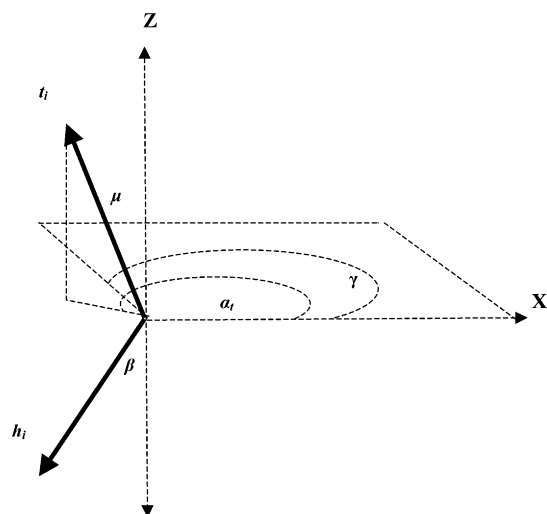


Figure 4. Orientations and distances of groups of an amphiphilic molecule. Only one tail group (t_i) and one headgroup (h_i) placed at a lattice corner are shown. Their tilt from normal (μ), azimuthal projection of the tail (α_t), the lattice angle (γ), and the orientation of the headgroup (β) are also shown.

TABLE 1: Parameters Used in the Calculation at Temperature 293.15 K^a

group	diameter (Å)	ϵ/k (I) (K)	ϵ/k (II) (K)
CH ₃	2.99	81.27	81.27
CH ₂	2.45	59.94	59.94
CH	1.40	40.64	40.64
COO	3.20	320	320
PO ₄	4.06	406	121.8
N(CH ₃) ₃	5.15	515	154.5

^a The average tilt direction with respect to the normal (μ) is 24.91°, orientation of the azimuthal projection of the first tail of the first molecule, α_t (see Figures 3 and 4 for notation), is 143°, and the lattice angle (γ) is 113°. The μ , α_t , and γ values refer to a temperature of 293.15 K and surface pressure of 41 mN/m.⁹ The choice of parameters is explained in the text, the Appendix, and in refs 20–26.

provided by Ben Amotz and Herschbach.^{22,23} The Lennard-Jones energy parameter of CH₂, CH₃ and CH are taken from the OPLS set of Jorgensen and Tirado-Rives.^{24,25} It is known that for alkanes the energy parameter is also linearly dependent on the size of the group.²² For a 1 Å increase in the effective size of the group, the ϵ/k_B increases by ~100 K.²² We take the ϵ/k_B values of the groups for which the parameters are unavailable from the OPLS set as proportional to their diameters.^{22,24,25} The calculation uses no adjustable parameter. Parameters used in the present calculation are shown in Table 1. To test the sensitivity of the results, we made variations of parameters. These variants are shown in Table 1 and are discussed in the Appendix. In set II, the changed values of ϵ/k of PO₄ and N(CH₃)₃ are obtained by taking an increment per 1 Å as 30 K (less than 100 K and consistent with the OPLS set). Results are presented for a pair of D-enantiomers.

It is unreasonable to assume that two tails of a DPPC molecules have same azimuthal tilt direction, α_t (measured with respect to the X axis). As pointed out earlier, only orientation of the first tail is taken from GIXD data. We calculated the EPP of the first and second tails of a molecule. It is observed that the mutual orientation between them (measured anticlockwise; $\delta\alpha_t^{\min}$) lies in the range 330–350° with respect to the first tail at the minimum of the EPP. Consequently, the second tail is oriented in a right-handed way with respect to the reference tail. No information about the orientation of the headgroup is available from the GIXD studies. The angle

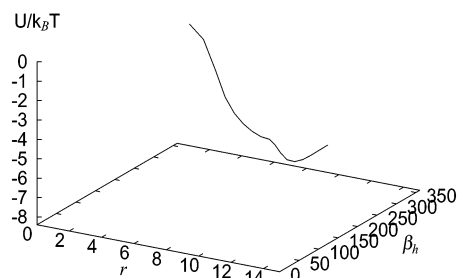


Figure 5. EPP plot expressed in $k_B T$ ($T = 293.15$ K) for the headgroups with variation in orientation of the headgroups with respect to the direction opposite to the normal to the interfacial plane (β_h) and the intermolecular separation (r).

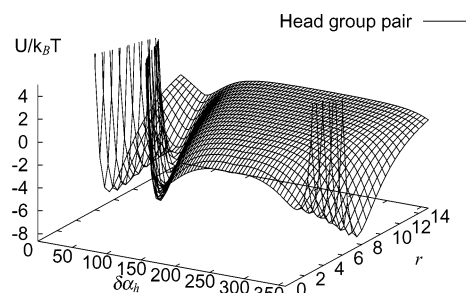


Figure 6. EPP plot expressed in $k_B T$ ($T = 293.15$ K) for the headgroups with variation in mutual azimuthal orientation of the headgroups ($\delta\alpha_h$) and intermolecular separation (r) using the parameter set indicated by (I) and given in the third column of Table 1.

between the azimuthal tilt direction of the headgroup projected on the plane perpendicular to $-Z$ direction and measured with respect to X axis (α_h) is taken as same as α_t of the first tail (i.e., they lie in the same plane parallel to Z direction). This assumption about the α_h value of the reference molecule is supported by the fact that if α_h differs from α_t by π , then the molecular configuration changes to its enantiomeric state. However, no assumption is made about the orientation of the headgroup with respect to the surface normal (β_h) or the α_h of the adjacent (second) molecule. These parameters are calculated as follows.

The pair potential of a pair of headgroups of neighboring amphiphiles is calculated as a function of three variables: (i) the distance between the headgroups in terms of intermolecular separation (r), (ii) the β_h values of both headgroups (varied by π), and (iii) the mutual orientation, $\delta\alpha_h$, between the first and second headgroups (varied by 2π). Thus, for each value of r , a range of β_h is investigated, and for each orientation within that range of β_h a range of $\delta\alpha_h$ is investigated. The minimum pair potential is found for each value of r and β_h , and these values are plotted in Figure 5. Thus, the plot in Figure 5 corresponds to the energy minima of several energy surfaces generated by calculating β_h and $\delta\alpha_h$ for a particular value of intermolecular separation. The lowest value of all such minima is, thus, the most probable orientation of the headgroups in the aqueous subphase with respect to the interface. It is observed that the pair potential is stable over a broad range of orientations but most stable (β_h^{\min}) when they are oriented at an angle 30° with respect to the air/water interface (Figure 5).

Using the minimum value of β_h (β_h^{\min}) obtained from Figure 5, we calculate the pair potential profile of a pair of headgroups as a function of r and $\delta\alpha_h$. This is shown in Figure 6. We note that the energy parameters used for PO₄ and N(CH₃)₃ in calculation of the headgroup pair potential (and indicated by the “I” within parentheses of the third column of Table 1) are rather large compared to parameters used from the OPLS set

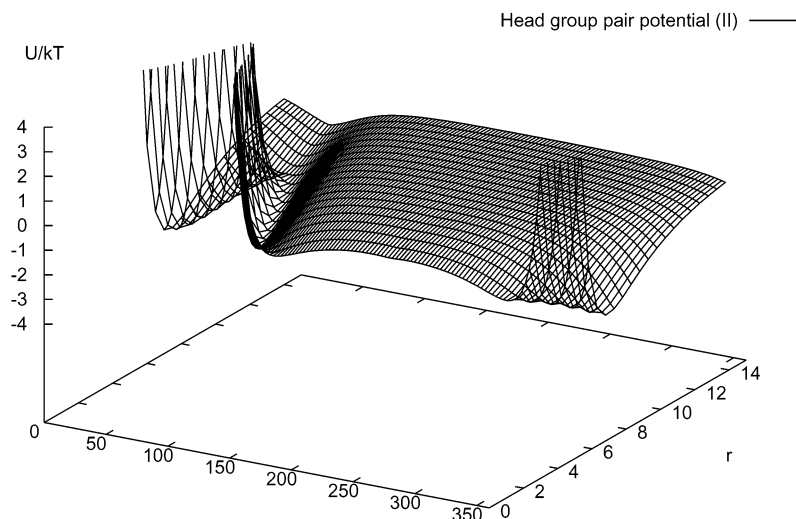


Figure 7. EPP plot expressed in $k_B T$ ($T = 293.15$ K) for the headgroups with variation in mutual azimuthal orientation of the headgroups ($\delta\alpha_h$) and intermolecular separation (r) using the parameter set indicated by (II) and given in the third column of Table 1.

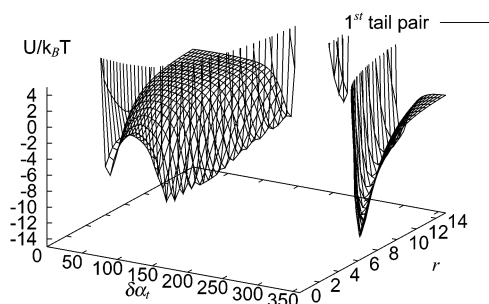


Figure 8. EPP plots expressed in $k_B T$ ($T = 293.15$ K) for the first tails of neighboring DPPC molecules with variation in mutual azimuthal orientation of the tails ($\delta\alpha_t$) and intermolecular separation (r).

for CH_3 , CH_2 , and CH_3 . To test the sensitivity of the results on these parameters, we vary the mentioned energy parameters substantially. Detailed discussion about the variation of parameters and sensitivity of results is in the next section and in Appendix I. The varied parameters are shown in Table 1 and indicated by “II” within parentheses of the fourth column of Table 1. As mentioned before, the changed values of ϵ/k in set II are consistent with the OPLS set. The corresponding result is shown in Figure 7. Further variations are also made, which we discuss in Appendix. The $\delta\alpha_h$ values at minimum pair potential energies for different values of r are in the range of $217\text{--}355^\circ$ for the range $r = 5.0\text{--}7.7$ Å. Upon a further increase in separation, the $\delta\alpha_h^{\text{min}}$ gradually moves to the parallel arrangements between the headgroups ($\delta\alpha_h = 0^\circ = 360^\circ$). In the following we discuss the features of the pair potential profile of different molecular segments such as tails and headgroups and discuss the result.

Results and Discussion

The EPP profile of the tail of the reference molecule and the first tail of the neighboring molecule is shown in Figure 8. $\delta\alpha_t$ corresponding to the minima is in the range $330\text{--}350^\circ$ (considered in anticlockwise way) orientation. This deepest minimum is separated from other shallower minima (which are in the range $0\text{--}180^\circ$ orientation) by a high-energy barrier. Consequently, in the closed packed state, the first tail of the second molecule will be preferentially oriented in a right-handed way with respect to the first tail of the reference molecule (keeping the latter closest to the eye and second molecule away

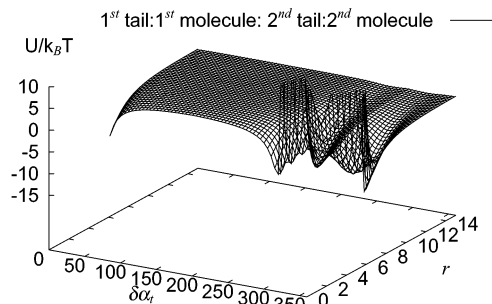


Figure 9. EPP plots expressed in $k_B T$ ($T = 293.15$ K) for the first tail of the first molecule and second tail of the second molecule (see Figure 3 for notation) with variation in mutual azimuthal orientation of the tails ($\delta\alpha_t$) and intermolecular separation (r).

from the eye). Due to the similarity in molecular structure, the EPP profile of the second tail pair of the pair of molecules is similar to the first tail pair, as expected (not shown). Thus, the second tail of the second molecule will be preferentially oriented in a right-handed way with respect to the second tail of the reference molecule.

The EPP profiles due to the interaction between the pairs of tails located along the diagonals of the lattice are necessary to investigate. According to Figure 3, the closest diagonal pair is the first tail of the reference molecule and the second tail of the second molecule. This pair potential is expected to give rise to substantial contribution to the energy minimum of the pair of molecules. The EPP of this pair has a minimum close to $\delta\alpha_t = 235^\circ$. However, it is important to note that this mutual orientation, $\delta\alpha_t$, is measured with respect to the line joining the center of the two tails, which is the diagonal axis of the lattice joining the first tail of the reference molecule and the second tail of the second molecule. This diagonal axis is oriented at an angle 56.1° with respect to the X axes.⁹ Thus, $\delta\alpha_t$ is 291.1° when measured with respect to the X axes. Consequently, the second tail of the second molecule prefers to be oriented in a right-handed way with respect to the first tail of the first molecule. The EPP profile is shown in Figure 9. As mentioned before, the line joining the tails is the diagonal axis of the lattice in this case.

The other diagonal pair is far separated and their pair potential is contributing less to the total energy of the pair of molecules. Similarly, the interactions between the headgroup and the tails give rise to negligible energy contributions. However, $\delta\alpha_t$ or

$\delta\alpha_h$ is in the range 275–360° for all minima of the corresponding EPP plots.

The results of the calculation of the EPP of the tails and heads of a pair of molecules described above can be summarized as follows. Taking the orientation of a tail of any molecule as the same as that obtained from GIXD data, the orientation of the other tail of the same molecule as well as the orientation of the tails of an adjacent molecule is oriented in a right-handed way. The first tail of the reference molecule is located closest to the observer and the second tail of the neighboring molecule is located farthest from the observer. The progress of such an arrangement represents the growth process of the domain where the molecules are aligned in next-to-next fashion. A simple way to define the handedness of the domain is to refer to the direction of the progress of the longer direction (always measured away from the observer) starting from a nucleus, which can be concluded from the kinetics of growth. Thus, the interaction between the pair of tails and pair of heads indicates that all pairs of molecular segments have large favorable pair potentials (measured pairwise with the reference) when the $\delta\alpha_{t/h}$ is $\sim 350^\circ$ to $\sim 235^\circ$. This indicates that the molecular segments have a large favorable energy when they all are oriented in a right-handed way with respect to the reference in an aggregate composed of a D enantiomer. This mutual orientation is cooperative in the sense that all segments favor the tendency to have a right-handed turn with respect to the reference at the minima of the pair potential. A high-energy barrier in all cases separates the minimum of the EPP, which favors the opposite handedness (left-handedness).

The favorable $\delta\alpha_{t/h}$ value gradually moves to 0° (parallel arrangement) with an increase in molecular separation, as can be seen from all EPP plots. Also, the EPP becomes increasingly shallow with an increase in temperature. These facts corroborate well the wisdom that an increase in molecular separation (by lowering pressure) or an increase in temperature destroys the effect of chirality.

A favorable broad range of orientation of a molecular segment is also expected to diminish the effect of chirality due to effective sphericalization. The present calculation shows that the headgroup pair potential remained favorable over a broad range of β_h as well as a range of $\delta\alpha_h$. The headgroup of the second molecule is found to be oriented in a right-handed way, keeping the reference molecule closest to the observer. This indicates that the effect of chirality is not destroyed even if a distribution of orientation of headgroups (β_h and α_h) exists in the aqueous subphase.

It is worthwhile to comment on the sensitivity of the results on the choice of parameters. The objective of the present paper is to find the orientations of the segments of the second molecule (with respect to that of other segments of the first, reference molecule) by minimizing the potential. The effective diameters of the groups are calculated with sufficient accuracy, and the necessary orientations used as theoretical ingredients are from accurate experimental data. The effective diameter and orientations used in a given set determine the mutual separation and orientation at which the minimum of the corresponding potential well will be observed (eq 1). Only the *depth* of the well will be determined by the corresponding set of used ϵ/k_B parameters. Explicitly, for a particular (fixed) set of effective diameter and orientation, the variation of the ϵ/k_B parameter affects only the depth of the well, i.e., the minimum (for a smaller energy parameter, the well becomes shallow and vice versa) but not the mutual orientation and distance at which this minimum is observed. It suffices for our purpose to study the handedness if

the EPP is reasonably stable (negative) when compared to the $k_B T$ scale so that the mutual orientation observed at the minimum (favored by the chiral interaction) is not destroyed by thermal motion. The exact magnitude of the energy, which is determined by the ϵ/k_B , is not crucial for predicting the handedness. The ϵ/k_B parameters for a few groups are available from standard data sets and are used here. The approximation for the other groups, for which the OPLS or any other data set is unavailable, that the ϵ/k_B are proportional to the effective diameter does not affect the validity of the present approach to determine handedness.²⁶ Even a different set of energy parameters of these groups is used, which will affect only the depth of the well but the orientation and distance at which the minimum is observed will remain completely unaffected. Such calculation of the sensitivity of the result about handedness is carried out as shown in Figure 7 (as mentioned earlier) and in the Appendix. It is important to note that using the representative values of diameter and energy parameters for the model tetrahedral molecule, Andelman and Orland have taken a similar approach in the study of chiral discrimination.²⁷

In conclusion, we attempted to start from a coarse-grained description of a chiral lipid molecule to build up an effective pair potential description that can predict the features of the mesoscopic domain specific to the particular enantiomer such as the handedness. To the best of our knowledge no such quantitative approach was made before to calculate the EPP from detailed molecular chiral structure. The calculated pair potential indicates that chiral molecules can be arranged starting from a reference molecule in a successive way, leading into a stable aggregate only if the molecules mutually orient in a specific direction characteristic of the enantiomer. Orientation of molecules in the opposite direction is unfavorable. This explains the high specificity of the chiral interactions in determining the aggregate curvature at the molecular level. The present study also provides the molecular explanation for why the available orientational distribution of the headgroups in the subphase does not destroy the chiral features of the domains. It also indicates that the increase in molecular separation or increase in temperature could destroy the effect of chirality. This study explains the influence of chirality at the molecular level of structural hierarchy of a biomimetic system on the chirality of the aggregate composed of such molecules, which form a higher level mesoscopic structure.

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Appendix

It is indicated in the text that the LJ energy parameter for CH_2 , CH_3 , and CH groups are taken from OPLS parameter set and for other groups for which such data is unavailable are taken as proportional to their diameter. In the latter case (in the case of COO , PO_4 , and $\text{N}(\text{CH}_3)_3$ groups), ϵ/k_B is taken to be increased by $\sim 100 \text{ K}^{22}$ for a 1 Å increase in the effective size of the group. Now, an anonymous referee indicated that the increment per 1 Å in the OPLS set is less than 100 K and is roughly 30 K. Here we show that our results on handedness of the aggregate are insensitive to the choice of the ϵ/k_B parameter by varying the same. We calculated only head–head interactions to test the sensitivity. Here the groups involved (in the headgroup segment starting from the chiral center) are CH_2 , PO_4 , and

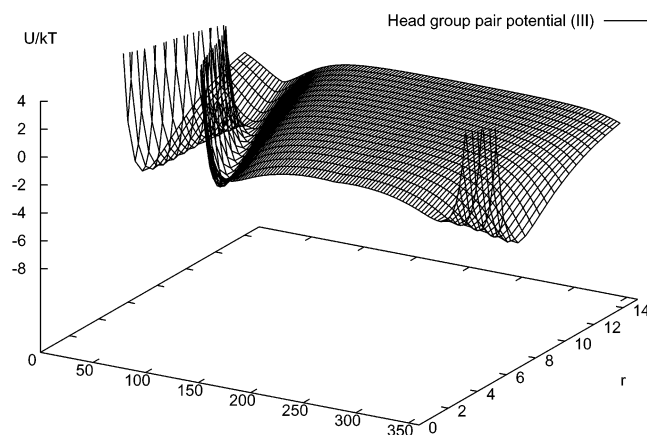


Figure 10. EPP plot expressed in $k_B T$ ($T = 293.15$ K) for the headgroups with variation in mutual azimuthal orientation of the headgroups ($\delta\alpha_h$) and intermolecular separation (r) using the parameter set indicated by (III) and given in third column of Table 2.

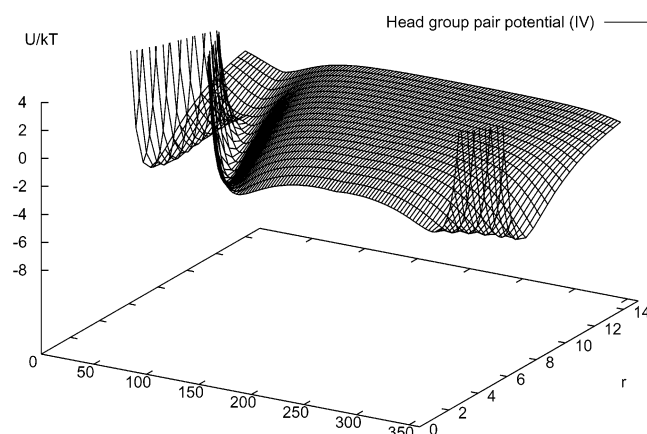


Figure 11. EPP plot expressed in $k_B T$ ($T = 293.15$ K) for the headgroups with variation in mutual azimuthal orientation of the headgroups ($\delta\alpha_h$) and intermolecular separation (r) using the parameter set indicated by (IV) and given in fourth column of Table 2.

TABLE 2: Parameters Used in the Calculation at Temperature 293.15 K for Sets III and IV

group	diameter (\AA)	ϵ/k (III) (K)	ϵ/k (IV) (K)
CH ₂	2.45	59.94	59.94
CH	1.40	40.64	40.64
PO ₄	4.06	121.8	406
N(CH ₃) ₃	5.15	515	154.5

N(CH₃)₃. We vary the corresponding energy parameters in addition to that shown in set II in Table 1 as follows in Table 2 in two other sets (sets III and IV, respectively).

In set IV, the changed value of ϵ/k of N(CH₃)₃ is obtained by taking the increment per 1 \AA as 30 K (less than 100 K and consistent with the OPLS set). Here we keep the parameter for PO₄ as same as in Table 1. The results are shown in Figure 11. It can immediately be noticed from Figures 6, 7, 10, and 11 that despite a variation of the ϵ/k parameter by 284.2 K for PO₄ and 360.5 K for N(CH₃)₃, respectively, the overall features of the profile are closely similar. Indeed, by lowering the values of ϵ/k of PO₄ and N(CH₃)₃, the complete profile of the head-head interaction energy (calculated by data given in Table 1 and shown in Figure 6) is scaled (lowered). The minimizations

of the energy profiles of these figures show that the intermolecular orientation at the energy minimum varies only by $\pm 1^\circ$ by the change in energy parameter. Thus, the conclusion about the handedness is unaffected by the change in the energy parameter. Despite the scaling of energy, the headgroup pair potential remains significantly stable and in the range of about $-3 k_B T$ to about $-8 k_B T$. This is also shown in Figures 6, 7, 10, and 11. This clearly shows that the results are insensitive to the choice of parameters.

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- (26) For a pair of molecular segments (e.g., head of first molecule—head of second molecule), the EPP being sum of groups contributions, the change in ϵ/k_B parameter for the COO, PO₄, and N(CH₃)₃ groups will either make the minimum of this EPP shallow or deep. However, the orientation and distance at which the minimum will be observed is determined only by the effective diameters and orientations of these collinear groups and will not be affected by a change in energy parameter.
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