Papers

Microscopic origin of the chirality driven morphologies of the amphiphilic monolayers and bilayers

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It is widely known that the compressed monolayers and bilayers of chiral lipids or fatty acids form helical morphologies, while the corresponding racemic modification gives only flat platelets without twist. No molecular explanation of this phenomenon is yet available, although subtle interactions at the chiral centers have often been proposed as the driving force behind the morphology of the aggregate to form a particular shape. In the present study, the morphologies of the chiral amphiphilic assemblies have been predicted on the basis of an effective pair potential between the molecules, which depends on the relative sizes of the groups attached to the chiral centers, the orientation of the amphiphilic molecules and also on the distance between them. It is shown that for a pair of same kind of enantiomers, the minimum energy conformation favours a twist angle between them. This twist between the neighbouring molecules gives rise to the helicity of the aggregate. The present theory also shows from the molecular considerations that for a pair of mirror-image isomers (i.e. the racemic modification) the minimum energy conformation corresponds to the zero angle between the molecules, thus giving rise to flat platelets as observed in experiments. Another fascinating aspect of such chirality driven helical structures is that the sense (or the handedness) of the helix is highly specific about the chirality of the monomer concerned. The molecular theory shows, for the first time, that the sense of the helical structures in many cases is determined by the sizes of the groups attached to the chiral centers and the effective potential between them. The predicted senses of the helical structures are in complete agreement with the experimental results.

I. Introduction

It is widely known that the compressed monolayers and bilayers of lipids or fatty acids having at least one chiral carbon atom form many interesting supramolecular morphologies like helical ribbons, tubules, fibers, strands and flat crystals. In the gel state, the monolayers and bilayers form helical structures, provided one kind of enantiomer (either D- or L-) is present in excess within the aggregate. The corresponding racemic modification, on the other hand, gives only flat platelets without twist. The driving force for the formation of such helical morphologies from the chiral amphiphilic molecules is known to come partly from the interactions at the chiral centers of the amphiphiles. Another fascinating aspect of such chirality driven helicity is that the sense (or the handedness) of the helix is highly specific about the chirality of the monomer concerned. More explicitly, if right handed helix has been observed to be formed from the aggregate of the D-enantiomers of a particular chiral amphiphile, the corresponding aggregate of the L-enantiomers should gives rise to the helix of left handedness and vice-versa, in the compressed gel state.

Customarily, in studying the aggregate of the chiral amphiphilic molecules, the individual molecules are represented by a pseudovector (usually termed as a director) whose direction gives the orientation of the long hydrophobic tail of the amphiphile and it lacks the symmetry of reflection (i.e. not superimposable with its mirror image). Many of such continuum theories start with an assumption of the presence of an intrinsic bending force due to chirality. It is believed that within the assembly of one kind of enantiomers, any two neighbouring directors are tilted relative to each other and this tilt from neighbour to neighbour gives rise to the helicity of the aggregate. In theoretical formulation one usually employs a Ginzburg-Landau type free energy functional which is common in the study of the liquid crystals. This free energy provides only a coarse grained description where long wavelength properties are explicitly considered. Consequently, in
the above description, the detailed microscopic features of the molecules are completely averaged out and one cannot expect to understand the microscopic length scale interactions driving the assembly to a particular morphology, such as the sense of helix.

However, a fully microscopic description of the Hamiltonian of such a system is enormously difficult due to the complexities of the interactions between the molecules. One can, of course, describe the system in a mesoscopic scale in which the essential microscopic features of the effective chiral interaction are explicitly retained but other interactions like the hydrophobic effect or the electrical head group interaction, which are not different for the optical isomers, are averaged out.

It has been pointed out recently that it might be possible to predict and understand the structure formation from an effective intermolecular pair potential between the chiral centers of the aggregate, because, in these structures the subtle stereogenicity at the chiral centers is surely responsible for driving the aggregate to a particular morphology. Such reduced effective potentials may be derived after summing up many other detailed interactions between the groups attached to the chiral centers of a pair of chiral molecules and minimally this potential should depend only on the distance and orientation between a pair of chiral molecules. These minimal energy conformations can be studied by changing the orientation between the groups and the distance between the chiral centers. In this approach it has been assumed that the pair potential between the adjacent groups of the chiral centers has a Lennard-Jones (6-12) form. Thus, in principle, such microscopic theories are expected to be able to predict the tilt between the two neighbouring amphiphiles from the effective potential by studying the minimum energy configuration between a pair of the same kind of enantiomers. Thus, by knowing the sizes and the orientations of the groups attached to the two chiral centers, one can know the relative tilt of a pair of amphiphilic molecules. Consequently, the arrangement of an array of molecules in space can be predicted from the present molecular considerations. The sense of the array is thus predetermined from the relative sizes of the neighbouring groups of the chiral centers.

The present study is devoted to achieve such a goal. Here, we have calculated the tilts of the groups attached to the two chiral centers and have attempted to predict the sense of the aggregate from the tilts. Other parameters characterizing the helical structure like pitch, pitch angle, etc., are also expected to be predicted from the molecular theory. As indicated earlier, the flat morphology of the racemic modification is another problem left to be solved from molecular theory. We have also tried to understand the morphology of the racemic modification from the effective interaction between a pair of mirror image isomers.

The organization of the rest of the paper is as follows. In Section II we have described the calculation of the effective interaction potential between a pair of chiral amphiphiles. In Section III we have described the calculation of the tilt between a pair of same kind of enantiomers from the effective potential as calculated in Section II. In Section IV, we have described the systematic study of the sense of the helicity from the tilt angles calculated from the theory. In Section V, we have described the parameters characterizing the helicity like the pitch, pitch to diameter ratio, etc. In Section VI we have calculated the minimum energy configuration for a pair of mirror image isomers. Section VII includes discussions which is followed by brief concluding remarks.

II. Theoretical formulation for the effective interaction potential

In this section we briefly recapitulate the theoretical formulation for calculating the effective interaction between the two chiral molecules, each having one chiral center (designated by $C_1$ and $C_2$, respectively). Now, consider the plane of $a$ and $b$ groups as shown in Fig. 1. For a pair of molecules this plane contains four groups, two from each chiral center. The relative arrangements of these four groups depend on whether the molecules belong to D-D or D-L pair. Generally, we can represent these groups by four groups in a plane, $m$, $n$, $o$ and $p$, respectively (see Fig. 2). The $m$ and $n$ groups are attached with the $C_1$ chiral center and $o$ and $p$ groups are attached with the $C_2$ chiral center, respectively. We assume that the $C_1$ carbon atom is situated at the center of an arbitrary frame of reference (designated by a set of axes, X and Y). $\alpha$ is the orientation of the line joining the two chiral centers and $r$ is the distance between them. $X'$ and $Y'$ are the set of axes situated at $C_2$ and are parallel to X and Y respectively. $\phi_1$ and $\phi_2$ are the orientations of $m$ and $o$ groups with respect to the X and X' respectively. $\beta_{mn}$ and $\beta_{op}$ are the angle between $m$ and $n$ and that between the $o$ and $p$ groups, respectively.

We represent the effective sizes of the groups attached to the chiral centers by $\sigma_m$, $\sigma_n$, $\sigma_o$ and $\sigma_p$, respectively. These $\sigma$ values correspond to the
The effective diameters of the corresponding groups added with the effective radius of the chiral carbon atom. It is well known that the effective sizes of the alkyl groups increase linearly with the increase in the length of the corresponding carbon chain. We have calculated the effective diameters of the groups using the empirical correlations provided by Ben-Amotz and Herschbach and the group increments tabulated by Bondi. The empirical relations are as follows,

\[ V_{hs} = 1.086 \left( V_s - 9.94 \right), \]  
\[ \sigma = 1.244 \left( V_{hs} \right)^{1/3}, \]  

where \( V_s \) is the “space-filling” volume, which can be computed by summing the increments for the various atoms and the functional groups tabulated by Bondi. These values are expected to be remarkably accurate, as indicated in the literature. Also, these values are insensitive to substantial deviation in the shape of the group from sphericity. In order to facilitate connection with real experimental situation, we have given the sizes of the groups attached to the chiral centers of common amphiphiles forming helical morphology. The groups are designated as \( t', b, a \) and \( b' \), respectively. The tilt angles (in degrees) in the plane of \( t, b \) (represented by \( \theta_M \)) and that in the plane of \( a \) and \( b' \) (represented by \( \phi_M \)) in the minimal energy configuration are also shown.

As already discussed, the interaction between the chiral centers has been calculated by assuming a Lennard-Jones (6-12) form of the potential between the adjacent groups. If we assume that the adjacent groups belonging to the neighbouring chiral centers interact through pair potentials \( U_1 \) and \( U_2 \), respectively, then the total interaction potential between the two chiral centers is given by

\[ \epsilon_{ij} = \frac{k_B T}{u} \]  

where \( k_B \) is the Boltzmann constant. The Lennard-Jones (6-12) potential is given by

\[ V_{ij} = 4 \epsilon \left[ \left( \frac{r_{ij}}{\sigma} \right)^{12} - \left( \frac{r_{ij}}{\sigma} \right)^6 \right] \]

The Lennard-Jones energy parameters of the groups, \( m, n, a \) and \( p \), have been represented by \( \epsilon_M, \epsilon_N, \epsilon_A \) and \( \epsilon_P \), respectively. From the values of the \( \epsilon_{ij} \) of several classes of compounds like alkanes, alcohols, haloalkanes, etc., tabulated by Ben-Amotz and Herschbach, a linear dependence of the \( \epsilon_{ij} \) on the sizes of the groups is observed. For 1 \( \AA \) increment in the effective diameter of a group, the \( \epsilon_{ij}/k_B \) values of the group (\( k_B \) is the Boltzmann constant) increases by \( \sim 100 \) K. In the present study we have taken the \( \epsilon_{ij} \) values of the groups as proportional to their effective diameters.

<table>
<thead>
<tr>
<th>Amphiphile</th>
<th>( t' )</th>
<th>( b' )</th>
<th>( \theta_M )</th>
<th>( a )</th>
<th>( b )</th>
<th>( \phi_M )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A^1 )</td>
<td>8.19</td>
<td>6.51</td>
<td>11</td>
<td>1.4</td>
<td>7.81</td>
<td>45</td>
</tr>
<tr>
<td>( B^2 )</td>
<td>7.81</td>
<td>8.00</td>
<td>1</td>
<td>1.4</td>
<td>8.24</td>
<td>45</td>
</tr>
<tr>
<td>( C^3 )</td>
<td>7.81</td>
<td>8.81</td>
<td>6</td>
<td>1.4</td>
<td>2.99</td>
<td>31</td>
</tr>
<tr>
<td>( D^4 )</td>
<td>8.18</td>
<td>8.00</td>
<td>0.1</td>
<td>1.4</td>
<td>7.29</td>
<td>44</td>
</tr>
<tr>
<td>( E^5 )</td>
<td>5.53</td>
<td>7.35</td>
<td>14</td>
<td>1.4</td>
<td>1.92</td>
<td>15</td>
</tr>
</tbody>
</table>

\[ 1^1 \text{Amphiphile } A \text{ is the double chain ammonium amphiphile cited in the ref. 5 with } n = 12 \text{ and } m = 2, \text{ where } n - 1 \text{ and } m - 1 \text{ are the number of the methylene groups attached to the carboxylic group in the hydrophobic tails and the N\textsuperscript{+} atom of the head group, respectively. Here, } t = -(\text{CH}_2)_m\text{COO}(-\text{CH}_2)_n\text{COO}(-\text{CH}_2)_i\text{CH}_3 \text{ and } b' = \text{NH}_2\text{COO}(-\text{CH}_2)_i\text{COO}(-\text{CH}_2)_i\text{CH}_3. \text{ The } a \text{ and } b \text{ groups are } -\text{H} \text{ and } -\text{COO}(-\text{CH}_2)_i\text{COO}(-\text{CH}_2)_i\text{CH}_3, \text{ respectively.} \]

\[ 2^1 \text{Amphiphile } B \text{ is the double chain ammonium amphiphile cited in the ref. 5 with } n = 12 \text{ and } m = 11, \text{ where } n - 1 \text{ and } m - 1 \text{ are the number of the methylene groups attached to the carboxylic group in the hydrophobic tails and the N\textsuperscript{+} atom of the head group, respectively. Here, } t = -(\text{CH}_2)_m\text{COO}(-\text{CH}_2)_n\text{COO}(-\text{CH}_2)_i\text{CH}_3 \text{ and } b' = \text{COO}(-\text{CH}_2)_i\text{CH}_3. \text{ The } a \text{ and } b \text{ groups are } -\text{H} \text{ and } -\text{NHCO}(-\text{CH}_2)_i\text{CH}_3, \text{ respectively.} \]

\[ 3^1 \text{Amphiphile } C \text{ is the single chain ammonium amphiphile cited in: Kunitake T; Yamada N, J chem Soc Chem Commun, 1986, 655-656. Here, } t = \text{COO}(-\text{CH}_2)_i\text{CH}_3 \text{ and } b' = \text{COO}(-\text{CH}_2)_i\text{CH}_3. \text{ The } a \text{ and } b \text{ groups are } -\text{H} \text{ and } -\text{CH}_3, \text{ respectively.} \]

\[ 4^1 \text{Amphiphile } D \text{ is the double chain phospholipid with a nucleotide head group as cited in the ref. 1. Here, } t = \text{COO}(-\text{CH}_2)_i\text{COO}(-\text{CH}_2)_i\text{CH}_3 \text{ and } b' = \text{COO}(-\text{CH}_2)_i\text{CH}_3. \text{ The } a \text{ and } b \text{ groups are } -\text{H} \text{ and } -\text{PH}_3, \text{ respectively.} \]

\[ 5^1 \text{Amphiphile } E \text{ is 12-hydroxystearic acid, cited in ref. 4. The molecular projection formula is shown in Fig. 4. Here, } t = \text{COO}(-\text{CH}_2)_i\text{CH}_3 \text{ and } b' = \text{CH}_3\text{CH}_2\text{CH}_3. \text{ The } a \text{ and } b \text{ groups are } -\text{H} \text{ and } -\text{OH} \text{ respectively.} \]
\[
\frac{U}{kT} = \frac{U_1}{kT} + \frac{U_2}{kT},
\]

Here, \( U_1 \) gives the interaction between the groups \( m \) and \( o \) and the \( U_2 \) gives the interaction between the groups \( n \) and \( p \) respectively. These interactions themselves are given by the following expressions

\[
\frac{U_1}{kT} = \frac{4}{T} \left( \frac{\varepsilon_1}{k} \right) \left[ \left( \frac{g_1}{\sigma_1} \right)^{-12} - \left( \frac{g_1}{\sigma_1} \right)^{-6} \right],
\]

\[
\frac{U_2}{kT} = \frac{4}{T} \left( \frac{\varepsilon_2}{k} \right) \left[ \left( \frac{g_2}{\sigma_2} \right)^{-12} - \left( \frac{g_2}{\sigma_2} \right)^{-6} \right],
\]

where, \( g_1 \) is the median distance between \( m \) and \( o \) and \( g_2 \) is the median distance between \( n \) and \( p \) groups, respectively. \( \sigma_1 \) and \( \sigma_2 \) are given by

\[
\sigma_1 = \frac{\sigma_m + \sigma_o}{2},
\]

\[
\sigma_2 = \frac{\sigma_n + \sigma_p}{2},
\]

and \( \varepsilon_1 \) and \( \varepsilon_2 \) are given by the Berthelot rule

\[
\varepsilon_1 = \sqrt{\varepsilon_m(\varepsilon_o)},
\]

\[
\varepsilon_2 = \sqrt{\varepsilon_n(\varepsilon_p)}.
\]

From Fig. 2 it is clear that the orientations of the groups attached to one chiral center (say \( C_1 \)) relative to those attached to the other chiral center (\( C_2 \)) and also the separation between the two chiral centers \( r \) influence the median distance between the groups. Consequently, the effective pair potential depends on the orientation and the separation of the groups. In order to calculate the effective interaction potential between the chiral centers, we need to consider explicitly the orientation and the distance between the chiral centers in the case of D-D and D-L pairs. In the following two subsections we describe the explicit expressions of the pair potential of the D-D and D-L pairs.

In the foregoing formulation the interaction potential in the plane of the \( a \) and \( b \) groups has been explicitly considered. The minimal energy configuration of the \( t \) and \( b' \) groups attached to the \( C_1 \) and \( C_2 \) chiral centers (Fig. 1) can also be understood in an analogous way.

Fig. 2—Relative arrangement of the two pairs of groups attached to the two chiral centers \( C_1 \) and \( C_2 \). \( m \) and \( n \) are attached to the \( C_1 \) and \( o \) and \( p \) are attached to the \( C_2 \). \( C_1 \) is situated at the center of the arbitrary frame of reference \( XY \). \( X' \) and \( Y' \) are parallel to the \( X \) and \( Y \) respectively. \( r \) is the line joining \( C_1 \) and \( C_2 \) and \( a \) is the orientation of \( r \). \( \theta_1 \) and \( \theta_2 \) are the orientations of the \( m \) and \( o \) groups, respectively. \( \beta_{mn} \) and \( \beta_{op} \) are the angle between the \( m \) and \( n \) and that between the \( o \) and \( p \) respectively. These groups are the representatives of the \( a, b, t, b' \) groups (see Fig. 1) in the two dimension.

III. Calculation of the tilt between a pair of same kind of enantiomers (e.g. \( o-b \)) from the effective pair potential

It is again to be noted that when we are considering the interaction in the plane of \( a \) and \( b \) groups of the two chiral centers of a D-D pair (or a L-L pair), \( m \) is equivalent to \( a \), \( o \) is equivalent to \( a \) group, \( n \) is equivalent to \( b \) group and \( p \) is equivalent to \( b \) group, respectively. The explicit expression for the effective pair potential in this case is then given by

\[
\frac{U}{kT} = \frac{4}{T} \left[ \frac{\varepsilon_m\varepsilon_a}{k} \left[ \left( \frac{r}{\sigma_a} + \frac{1}{2} \cos(\phi_2 - \alpha) \right)^{-12} - \frac{1}{2} \sin(\phi_2 - \alpha) \cot(\phi_1 - \alpha) \right]^{-12} \right.
\]

\[
- \frac{1}{2} \sin(\phi_2 - \alpha) \cot(\phi_1 - \alpha)
\]

\[
+ \frac{4}{T} \sqrt{\frac{k}{k}} \left[ \left( \frac{r}{\sigma_a} + \frac{1}{2} \cos(\phi_2 - \alpha) - \frac{1}{2} \sin(\phi_2 - \alpha) \right) \right]
\]

\[
\times \cot(\phi_1 - \alpha)^{-6} \right] + \frac{4}{T} \sqrt{\frac{k}{k}} \left[ \left( \frac{r}{\sigma_b} - \frac{1}{2} \cos(\beta - \phi_1 + \alpha) \right)^{-12} \right.
\]

\[
- \frac{1}{2} \sin(\beta - \phi_1 + \alpha) \cot(\beta - \phi_2)
\]

\[
\times \cot(\beta - \phi_2)^{-12} - \left( \frac{r}{\sigma_b} - \frac{1}{2} \cos(\beta - \phi_1 + \alpha) \right)
\]

\[
+ \frac{1}{2} \sin(\beta - \phi_1 + \alpha) \cot(\beta - \phi_2)^{-6} \right] \]
As indicated earlier, it is expected that a pair of same kind of enantiomers should prefer to be oriented with respect to each other at the minimum energy conformation. This orientations can be studied by minimizing equation 10. It is to be noted that there should be a tilt in the plane of the \(a\) and \(b\) groups (let us designate this angle by \(\theta_M\)) arising out of the interaction between the \(a\) and \(b\) groups of the neighbouring molecules. Simultaneously, there should be another tilt in the plane of the \(t\) and \(b'\) groups due to the interaction between the \(t\) and \(b'\) groups (designated by \(\phi_M\)). The helical structure formed from these tilts is schematically shown in the Fig. 3.

IV. Prediction of the sense using the tilts calculated from the effective intermolecular potential

From the foregoing molecular considerations, it is seen that there are two tilts in the plane of \(t\) and \(b'\) and in the plane of \(a\) and \(b\) groups. These two synchronous tilts in the two almost perpendicular planes give rise to a twist between a pair of chiral amphiphilic molecules in the compressed state. Thus, when same kind of chiral enantiomers (only D- or only L-) are stacked together, due to the twist between each pair of molecules, the chiral centers of all the molecules cannot lie on a straight line. Instead, they should follow a helical path. It is well known that twist between the two successive neighbours can lead to helicity, but it is for the first time that the handedness of the helicity can be predicted from the sizes and the effective potentials of the groups attached to the chiral centers. To predict the sense, we shall follow the following stepwise systematic approach.

1. First, consider a chiral amphiphilic molecule having only one chiral center. The Fisher projection formula has been drawn for the molecule [see Fig. 4(a)]. The longest carbon chain should be vertical and the most highly oxidized end of the molecule should be at the top.

2. The tetrahedral structure of the amphiphile is drawn from the projection formula. According to the standard conventions\(^{14}\), all the vertical bonds in the projection formula point backwards in the corresponding tetrahedral configuration [see Fig. 4(b)].

3. To construct an array of amphiphilic molecules, we shall place the successive molecules in such a way that the second molecule is placed behind the first, third behind the second and so on. Note that it is customary to observe the handedness of the helix by placing it in such a way that the helix propagates away from the eye. From the consideration of the tilt (see Section III) we can see how the array of the molecules propagates in the space. It is clearly seen that depending on the effective interaction potential of the groups, the helical assembly would turn either in a left-handed way or in a right-handed way [see Fig. 4(c) and 4(d) for a left-handed helix formed by D-12 hydroxystearic acid].

Thus, it is clearly seen that once we know the absolute configuration of the chiral molecule and the effective interaction potential of the groups attached to the chiral center, we can easily predict the sense of the helical aggregate formed from the chiral monomers.

Next, we have attempted to predict the senses of the helical structures of some amphiphilic assemblies and compared the theoretical prediction with the experimentally determined senses.

(i) Prediction of the sense of d-12 hydroxystearic acid:

From the Fisher projection formula, the absolute configuration is drawn as shown in Fig. 4(a, b). In the figures, the dotted bonds point backwards to the plain of the paper and the filled in bonds point towards the top of the plain of the paper. The sizes of the different groups are given in Table 1. Among the four groups, the size decreases as follows: \((\text{CH}_2)_11 - \text{COOH} > (\text{CH}_2)_4 - \text{CH}_3 > - \text{OH} > - \text{H}\.}
Thus, as shown in Fig. 4(c), when we place the chiral center of the second amphiphile (designated by \( C_2 \)) behind the chiral center of the first amphiphile (designated by \( C_1 \)), the second molecule is tilted with respect to the first and the magnitudes of the tilts in the top and bottom planes and the left and right planes (see Fig. 1) are given in Table 1 as predicted from the theory outlined in section III of the present paper. In constructing a helix from an array of amphiphiles we have to place molecules one behind another in succession because the sense of helix is observed as the turn of the helix goes away from the eye. It is clearly seen from Fig. 4(c) that in the plane drawn by dotted lines, the two \(-\text{OH}\) groups are away and the two \(-\text{H}\) atoms attached to the \( C_1 \) and \( C_2 \) chiral centers are closer. Similarly, in the perpendicular plane, the two \((\text{CH}_2)_n - \text{COOH}\) groups are away relative to each other and the two \((\text{CH}_2)_n - \text{CH}_3\) groups are closer compared to them. If we construct an array of molecules then it is easily seen from Figs 4(c) and 4(d) that the assembly should have a left-handed twist.

(ii) Prediction of the sense of \(\text{L}-\text{12-hydroxystearic acid}\)

The second helical aggregate we have considered is the \(\text{L}\)-hydroxystearic acid. From the Fisher projection formula, the absolute configuration is drawn as shown in Fig. 5(a). The sizes of the different groups are given in Table 1. Then, following the steps outlined earlier to determine the sense of \(\text{D}\)-isomer, we can easily find that the sense of the assembly should be right handed. We have not depicted the assembly of \(\text{i}\)-isomers because it can be easily visualized from the corresponding \(\text{D}\)-isomers.

(iii) Prediction of the sense of \(\text{2-C}_{12}\text{L-Glu-C}_{11}\text{N}^+\) amphiphile

The third helical aggregate we have considered is the above mentioned \(\text{L}\)-ammonium amphiphile. The molecular formula is given in Fig. 6. The Fisher projection formula and the absolute configuration are shown in the Fig. 6(a,b). The size of the group decreases as follows: \(\text{CH}_3(\text{CH}_2)_1\text{COO-}(\text{CH}_2)_2 > \text{COO}(\text{CH}_2)_3 - \text{CH}_3 > \text{NHCO}(\text{CH}_2)_{10^-N^+-(\text{CH}_3)_3 \geq -\text{H}}\).

The sizes of the different groups are given in Table 1. In the plane containing (indicated by the dashed lines in Fig. 6c) the \(\text{CH}_3(\text{CH}_2)_1\text{COO}(\text{CH}_2)_2\) and the \(\text{COO}(\text{CH}_2)_3 - \text{CH}_3\) groups, the former with greater effective interaction potential and larger effective size should be more apart than the
latter. In the plane containing NH·CO·(CH₂)₅N-(CH₃), and -H, the former being much larger than the latter, the two -H groups should be closer than the two NH·CO·(CH₂)₅N'(CH₃) groups. From Fig. 6(d) we can easily find that the sense of the assembly should be right-handed. The steps are outlined in the Fig. 6(c,d).

(iv) Prediction of the sense of 2-C₁₂-D-Glu-C₁₁⁻N⁺ amphiphile

The fourth and the last example we have considered is the D-isomer of the ammonium amphiphile considered just before. The molecular formula is given in Fig. 5(b). From the Fisher projection formula, the absolute configuration is drawn as shown in Fig. 5(b). The sizes of the different groups are given in Table 1. Then, following the steps outlined earlier to determine the sense, we can easily find that the sense of the assembly should be left-handed.

V. Prediction of the parameters characterizing the helicity from the calculated tilts

In order to facilitate comparison with experiments, it is necessary to calculate the characteristic parameters of the helix that would be predicted by the molecular theory. In the following, we calculate the pitch of the helix formed by the aggregate of one kind of enantiomer. If the adjacent chiral centers (of D-D or L-L pair) follow a circular helix due to the twist between each molecule, then the pitch of the helix, P, is given by the following expression

\[ P = \frac{2\pi}{\theta_M} \text{sin} \left[ \tan^{-1} \left( \frac{\tan \phi_M}{\sqrt{2(1 - \cos \theta_M)}} \right) \right] r_M, \quad \ldots (11) \]

Fig. 5—(a) Fisher projection formula of L-12-hydroxystearic acid and (b) Fisher projection formula of 2-C₁₂-D-Glu-C₁₁⁻N⁺.

Fig. 6—(a) Fisher projection formula of 2-C₁₂-L-Glu-C₁₁⁻N⁺; (b) three dimensional structure of the 2-C₁₂-L-Glu-C₁₁⁻N⁺ molecule derived from the projection formula. (c) A pair of 2-C₁₂-L-Glu-C₁₁⁻N⁺ molecules in the closed packed state and (d) a section of the helical aggregate formed by an array of 2-C₁₂-L-Glu-C₁₁⁻N⁺ molecules.
where the angles $\theta_M$ and $\phi_M$ are the angles corresponding to the minimum of the pair potential and $r_M$ is the corresponding straight line distance between the two chiral centers. From the expression 11 it is seen that $P$ increases rapidly as $\theta_M$ becomes smaller. For $\phi_M = 45^\circ$ and $r_M = 2.4\text{Å}$, the calculated value of the pitch corresponding to the $\theta_M = 0.75^\circ$ is 1105 Å and for $\theta_M = 0.165^\circ$, it is 5002 Å. Pitches of comparable order are observed in the superhelical strands (P = 1100 Å) and in the duplex (P = 5000 Å). The angle $\theta_M$ is in the plane containing the $t$ and $b'$ groups. These groups constitutes the major parts of the hydrophobic tail and the head group. The sizes of the groups attached to the chiral centers of common amphiphiles are given in Table 1.

The forces responsible for the aggregation of the amphiphile act in this plane along the hydrophobic chain and do not favour the tilts of the $t$ and the $b'$ groups. Thus, the splay of these groups is expected to be much small. Note that the main chiral interaction is expressed by the twist through the angle $\phi_M$ (in the plane of the $a$ and $b$ groups).

However, it should be pointed out that if we assume that the chiral interaction is the only driving force for a helical structure and that there is no force to resist the twist due to the chirality, the situation is unrealistic. This will certainly lead to a prediction of the twist which will be much higher than that observed in a real situation. The reason is, when the chirality is the only driving force for helical morphology, the surface is elastically relaxed and the net curvature becomes equal to the spontaneous curvature. In bilayers, due to the elastic properties of the system, the constituent molecules try to minimise the $\theta_M$ angle. The chiral interaction, on the other hand, helps the aggregate to shift the potential to a minimal state by developing a twist through the angle $\phi_M$. In fact, deGennes has pointed out long ago that the natural twist or the microscopic twist is always small in the molecular scale.

It has been observed in some recent experiments that the ratios of the pitch and the diameter (d) of the helices are higher than the value predicted by Helfrich’s theory ([$Pd = \pi$]). From the present molecular consideration, we find that the ratio of the pitch to the diameter is given by the following, somewhat modified, expression

$$\frac{P}{d} = \frac{\pi \tan \phi_M}{\theta_M} \quad \ldots (12)$$

The above expression indicates that, when $\theta_M$ is small, the ratio $Pd$ should be significantly higher than $\pi$. This ratio should also depend upon the value of $\phi_M$. In general, $\theta_M$ should be small and $\phi_M > \theta_M$. Thus, the present theory indicates that the ratio $Pd$ can be higher than the value of $\pi$ and should, in fact, depend upon the sizes of the groups attached to the chiral center of the specific amphiphile under consideration. Experimental evidences seem to support this conclusion.

VI. Minimum energy conformation for a pair of mirror-image isomers (racemic modification, D-L form) from the effective pair potential

In this Section we consider the effective interaction between a pair of mirror image isomers. It must be mentioned that when we are considering the interaction between the two chiral centers of a D-L pair, in the plane of the $a$ and the $b$ groups, then $m$ is equivalent to $a$, $o$ is equivalent to $b$ group, $n$ is equivalent to $b$ group and $p$ is equivalent to $a$ group, respectively. The median distance between the groups can be easily obtained from the median of the tallest isosceles trapezoid that can be drawn between $C_{1m}$, $C_{20}$ and that between $C_{1n}$ and $C_{2p}$ (Fig. 2), respectively. The other parameters have been explained earlier. The explicit expression for the distance and the orientation-dependent effective pair potential is then given by

$$\frac{U}{kT} = \left(\frac{4}{T}\right) \sqrt{\frac{\varepsilon_a \varepsilon_b}{k k}} \left[ \left( \frac{2r}{\sigma_a + \sigma_b} - \frac{\sigma_a}{\sigma_a + \sigma_b} \sin(\phi_2 - \alpha) \right) \times \cot(\phi_1 - \alpha) + \frac{\sigma_a}{\sigma_a + \sigma_b} \cos(\phi_2 - \alpha) \right]^{12}$$

$$\left[ - \left( \frac{2r}{\sigma_a + \sigma_b} - \frac{\sigma_a}{\sigma_a + \sigma_b} \sin(\phi_2 - \alpha) \right)^{6} + \left( \frac{4}{T} \right) \sqrt{\frac{\varepsilon_a \varepsilon_b}{k k}} \right] \times \left[ \left( \frac{2r}{\sigma_a + \sigma_b} - \frac{\sigma_a}{\sigma_a + \sigma_b} \cos(\beta - \phi_1 + \alpha) \right) \right. \right.$$

$$\left. + \frac{\sigma_a}{\sigma_a + \sigma_b} \sin(\beta - \phi_1 + \alpha) \right)^{12} \right.$$
The parameters used in the equation have been explained in Fig. 2.

VII. Discussion

The pair potential profiles of the pure (l-L or d-D) and racemic modifications (d-l pair) are depicted in Figs 7 and 8, respectively. We have presented here the plots with \( \alpha = 0^\circ \) only. However, plots with other \( \alpha \) values have the same features. It is clear from Figs 7 and 8 that the effective pair potential profile of the d-d pair (Fig. 7) is strikingly different from that of the d-l pair (Fig. 8). Unlike the single minimum observed in the case of d-l pair, there are two minima in the case of d-d pair. One minimum is at \( (\phi_2 - \phi_1) = 0^\circ \) and at a small separation, while the other minimum is at \( (\phi_2 - \phi_1) = -45^\circ \). The global minimum is the latter one in which the groups are oriented at a certain angle and the separation between the chiral centers is much less than that in the former, thus favouring a more closed packed state. The reason for the difference in behaviour of d-d and d-l pairs is that as we increase the angle \( (\phi_2 - \phi_1) \), the \( a \) group is tilted towards the \( m \) group and the \( p \) goes away from the \( n \) group (see Fig. 2). The molecules being in a compressed or gel state, should try to pack as efficiently as possible. This can be achieved by minimizing the separation between the chiral centers. The latter can, of course, be achieved without invoking the hindrance between the groups of the adjacent chiral centers. For a d-l pair (racemic modification), as the \( a \) group attached to the \( C_2 \) chiral center orients more towards the \( b \) group of the \( C_1 \) chiral center, the other two \( a \) and \( b \) groups (on the other side of the \( X \) and \( X' \) axes) move equally away from each other (see Fig. 2). So, the orientations of the groups towards each other do not lead the packing arrangement to a more favourable state and parallel arrangement is thereby favoured. From Fig. 7 it is seen that as the value of \( (\phi_2 - \phi_1) \) increases, the pair potential becomes increasingly unfavourable.

From the present study it is clear that the sense of helix should be predetermined by the effective pair potential. The reason for this is that the potential and hence the relative tilt between the two chiral molecules depend on the sizes of the groups attached to the chiral center. Thus, it is expected that a complete knowledge of the absolute conformation of the monomer, sizes and the effective intermolecular pair potential, should enable one to predict the sense of the helical shaped aggregate formed from the chiral monomers in the closed packed state. The d-12-hydroxystearic acid gives left-handed helix and the l-12-hydroxystearic acid gives right-handed helix. The \( l \)-isomer of the ammonium amphiphile \( (2-C_{12}-l$-Glu-C_{11}N^+) \) gives right-handed helix, whereas the \( d \)-isomer of the ammonium amphiphile \( (2-C_{12}-d$-Glu-C_{11}N^+) \) gives the left-handed helix. We have calculated the tilt angles \( \theta \) and \( \phi \) for all the molecules from the effective pair potential between the molecules following the theoretical framework as given in Section III. The tilts have been listed in Table 1. In Fig. 4(a-d) and in Fig. 6(a-d) we have schematically outlined the steps followed to determine the senses of the helical aggregates of the d- and l-hydroxystearic acids and the d- and l-ammonium amphiphiles. The complete agreement between the theoretically predicted senses and those observed experimentally (Table 2) suggests that the effective intermolecular pair potential, at least partially, governs the chirality driven helix formation.
Table 2—The theoretically predicted senses of the amphiphilic aggregate forming helical morphology calculated from the effective intermolecular pair potential

<table>
<thead>
<tr>
<th>Amphiphile</th>
<th>Theoretically predicted sense</th>
<th>Experimentally observed sense</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-12-hydroxystearic acid</td>
<td>Left-handed</td>
<td>Left-handed (ref. 4)</td>
</tr>
<tr>
<td>l-12-hydroxystearic acid</td>
<td>Right-handed</td>
<td>Right-handed (ref. 4)</td>
</tr>
<tr>
<td>d-ammonium amphiphile</td>
<td>Left-handed</td>
<td>Left-handed (ref. 5)</td>
</tr>
<tr>
<td>l-ammonium amphiphile</td>
<td>Right-handed</td>
<td>Right-handed (ref. 5)</td>
</tr>
</tbody>
</table>

It has been shown earlier that the present microscopic approach can successfully predict and help in understanding the experimentally observed pitch and pitch to width ratio of several helical aggregates. The agreement between the theoretical and experimental senses observed in the present study further substantiates the view that the intermolecular pair potential between a pair of chiral molecules has a major role in dictating the morphology of the aggregate.

As indicated in the Introduction, that the amphiphilic molecules have an erect conformation in the helical state and approximately have an area per molecule, close to the cross-sectional area of a CH₂ group of an alkyl chain. In such a closed packed state the preferred minimum is the one which is at shorter separation and at a finite twist angle. However, in the pair potential profile of the D-D pair (Fig. 4) a second minimum is observed at nearly zero twist angle at relatively large intermolecular separation. At an elevated temperature, the constituent molecules may thus be trapped into this second minimum at nearly zero angle relative to each other. Consequently, the helicity would not be observed. Theoretical and experimental studies indicate that at high temperatures, where the ordered state of the lipid bilayer is unstable, the system cannot express the chirality even if it is present at the molecular level. The observed morphology is thus dependent on the temperature and the concentration of the amphiphile. Experimental studies on tubule formation also indicate that the aggregate morphology is indeed dependent on the lipid concentration.

VIII. Summary

In this work we have presented a scheme to calculate the effective pair potential between the two chiral amphiphile molecules in order to understand the relative orientation among them. We find that the relative arrangement between a pair of molecules of one kind of enantiomers (D-D or L-L) favours a twist between them. From the calculated tilts the sense of the helix has been predicted. Complete agreement between the theoretically predicted senses and the experimental result has been observed in all the cases. The theory also explains the experimentally observed characteristics of the helical aggregate, such as the pitch and the sense, and is found to be dependent on the sizes of the groups attached to the chiral center and also upon the concentration of amphiphile molecules. The theory also indicates that for a pair of mirror-image isomers (D-L pair), the minimized effective potential favours parallel alignment giving rise to a flat state. The surprising success of the molecular approach strongly indicates that the chirality driven helix formation is governed by the subtle stereochemical interactions at the chiral centers, which in turn are controlled by the effective pair potential between the groups attached to the chiral centers of the pair of amphiphiles.

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