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Prediction of the Senses of Helical Amphiphilic Assemblies from Effective Intermolecular Pair Potential: Studies on Chiral Monolayers and Bilayers

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It is well-known that the senses (or the handedness) of the helical assemblies formed from compressed monolayers and bilayers of chiral amphiphiles are highly specific about the chirality of the monomers concerned. We present here a molecular approach that can successfully predict the senses of such helical morphologies. The present approach is based on a reduced tractable description in terms of an effective pair potential (*EPP*) which depends on the distance of separation and the relative orientations of the two amphiphiles. This approach explicitly considers the pairwise intermolecular interactions between the groups attached to the chiral centers of the two neighboring amphiphiles. It is found that for a pair of the same kind of enantiomers the minimum energy configuration favors a twist angle between molecules and that this twist from neighbor to neighbor gives rise to the helicity of the aggregate. From the known twist angles at the minimum energy configuration the successive arrangement of an array of molecules can be predicted. Therefore, the sense of the helicity can be predicted from the molecular interactions. The predicted senses of the helical structures are in complete agreement with all known experimental results.

I. Introduction

Amphiphilic monolayers and bilayers are often studied as simple model systems for the biological membranes. Much attention has been focused in recent years[1−14] to study and understand the diverse phases and morphologies formed by the amphiphilic monolayers and bilayers. It has been observed that the compressed monolayers and bilayers of amphiphiles having at least one chiral carbon atom form helical structures, provided one kind of enantiomer (either D or L) is present in excess.[12−46] The driving force for the formation of helical morphologies from the chiral amphiphilic molecules seems to come at least partly from the interactions at the chiral centers of the amphiphiles.[47−53] Another fascinating aspect of such chirality-driven helix formation is that the sense (or the handedness) of the helical structure is highly specific about the chirality of the monomer concerned. Explicitly, if a righ-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 give rise to a left-handed helix and vice versa, in the compressed gel state.[15,16]

There have been a number of continuum model theories,[47−58] which are devoted to the problem of structure or pattern formation in amphiphilic monolayers and bilayers. Most of the theories start with the assumption of the presence of an intrinsic bending force due to the chirality.[47−53] These theories usually employ a coarse-grained free energy functional, usually known in general as the Ginzburg−Landau free energy functional. In this coarse-grained description the individual molecules are replaced by a position and orientation dependent director and only the long-wavelength properties are explicitly considered. Consequently, the detailed microscopic features of the molecular assemblies are completely averaged out. One cannot expect to understand the features arising out of the microscopic length scale interactions in the above description such as the interactions at the chiral centers giving rise to the sense of the helix. As a result, though several aspects of the helix formation can be successfully predicted,[47−53] the prediction of the handedness of the helical aggregate seems to be impossible from these theories. Clearly a molecular approach is required to predict the sense.

However, a fully microscopic description of the observed handedness of the aggregate is enormously difficult due to the highly complex nature of the interactions involved in the present case. However, to study the sense, one can of course describe the system at an intermediate level in which the essential microscopic features of the effective chiral interaction are explicitly retained, but other nonchiral interactions are averaged out. In such a theoretical scheme we simplify the complicated interaction at the center of a tetrahedral molecule and specialize from the beginning. Such an *effective pair potential* (*EPP*) description may be able to predict the chirality-driven structure formation, because in these structures the subtle stereogenicity at the chiral centers may be primarily responsible for driving the aggregate to a particular morphology. Such a study based on an EPP description was carried out recently.[59] It was found that it can indeed predict the formation of helicity originating solely from the chiral interactions. In the present article, we show that even the sense of the helix can be predicted from the EPP description. The study is based on the assumption that the sense of a bilayer composed of chiral amphiphiles is determined by the interaction at the chiral centers.

The organization of the rest of the paper is as follows. In section II we have described the systematic formulation of the problem of calculating the minimal EPP configuration for a pair of the same kind of enantiomers and calculated the tilts. In section III we have predicted the senses of amphiphilic assemblies from the calculated tilts, and section IV includes the concluding remarks.

II. Formulation of the Problem

(a) The Importance of the Local Pairwise Interaction in Controlling the Sense of a Three-Dimensional Aggregate Morphology. Our objective is to find out only the sense or

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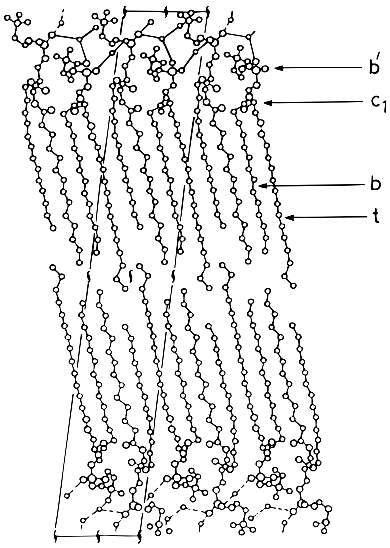


Figure 1. Schematic cross section through a crystalline planar bilayer formed from chiral amphiphiles. The symbols *t*, *b*, and *b*′ indicate different groups attached to the chiral carbon atom designated by C_1. See Figure 4 for details.

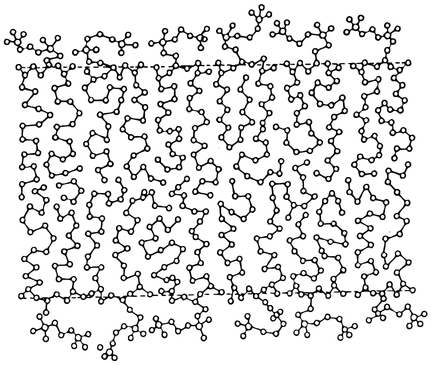


Figure 2. Schematic cross section through a fluid planar bilayer.

the handedness of the aggregate. The sense of the aggregate is controlled by the twist between the neighboring molecules. There are two equally possible modes of twist between any two neighboring molecules. Consequently, there are two possible handedness, and in dense bilayers one is favored over the other. It is sufficient for us to identify the more energetically favorable mode of twist from molecular considerations.

The quasi-crystalline state of the bilayer has a three-dimensional structure. In Figure 1 and Figure 2, we have shown the schematic side views of the crystalline state and the fluid state of a planar bilayer, respectively.[1,12] In Figure 3, we have shown the schematic representation of the bilayer viewed from the top. The molecules have an erect conformation[25,66] and a side-by-side arrangement, where a particular molecule is surrounded by many molecules. Now, let us designate a few neighboring molecules within a bilayer as follows.

$$\begin{gathered}...(m-1, n-1), \quad (m-1, n), \quad (m-1, n+1), ...\\ ...(m, n-1), \quad (m, n), \quad (m, n+1), ...\\ ...(m+1, n-1), \quad (m+1, n), \quad (m+1, n+1), ... \qquad (1)\end{gathered}$$

Here, the change in the *m* designates the molecular arrangement along the width of the bilayer, and the change in the *n* designates the molecular arrangement along its length. It is important to note that the tilt angles describing the twist between the (*m*,*n* − 1)th and (*m*,*n*)th molecule is the same as that between the tilt angles between the (*m*,*n*)th and (*m*,*n* + 1)th molecule.

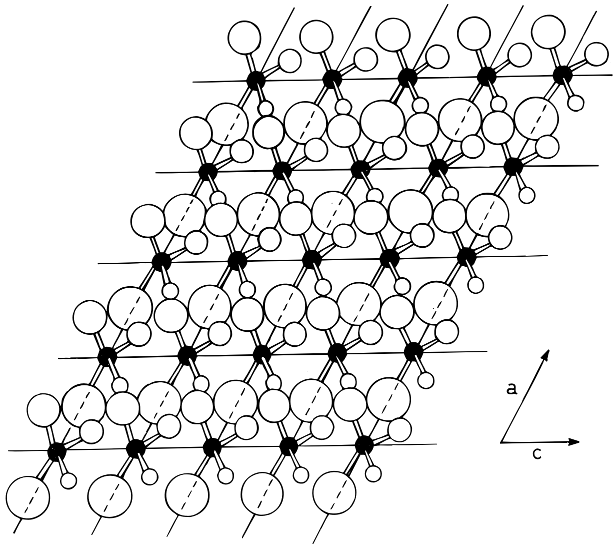


Figure 3. Schematic cross section through the chiral centers of a planar bilayer formed from chiral amphiphiles. Here we have shown a schematic cross section parallel to the *a*,*c* planes of the crystalline bilayer, as shown in Figure 2 of ref 36.

It is also important to note the length and width ratio of a bilayer. The length of the ribbon formed from helical structures is ∼1000 times longer than the width of the ribbon.[12] For *N*-octyl aldonamides[12] the length to diameter ratios are often higher than 1000. Double-chain ammonium amphiphiles of 2-C_{12}-L-Glu-$C_{11}N^+$ have helical structures[30] having length 10 μm and diameter 500 Å. We also refer to the micrographs of the helical structures formed from chiral amphiphiles, as shown in the micrograph of Figure 1 of ref 15, Figures 4,5a,6,9a,10,-11, and 13, and several other micrographs of ref 12 of the present paper. It is clearly observed in all the micrographs that the width is much smaller than the length of the aggregate in all cases. In such an arrangement, the interaction between the two adjacent molecules can trigger the arrangement within the aggregate due to the periodicity along the longer axis of the ribbon. Thus, it is expected that if the sense of the aggregate is determined by the effective interaction at the chiral center at the close packing density, then the favored twist will be determined by the interaction along the longer axis of the chain. Note that the final pattern is three-dimensional. It is the twist between the two neighbors that gives rise to the three-dimensional arrangement.

It is further important to note the difference in the separation distance between the adjacent chiral centers along the length and along the width of the bilayer. Crystal structures of *N*-(*n*-alkyl)-D-gluconamides (the alkyl chain length varies from heptyl to dodecyl) have been analyzed by X-ray diffraction methods. The cell constants of *N*-(*n*-alkyl)-D-gluconamides are as follows. The *a* dimensions range from ∼5.183 to 5.31 Å for the alkyl chain length varying from heptyl to dodecyl. The corresponding *b* dimensions vary from 16.183 to 39.85 Å, and *c* dimensions vary from 4.803 to 4.82 Å. The variations in the *b* dimensions reflect the variations in the alkyl chain lengths.[36] This shows that the *a* and *c* dimensions of the unit cells of the crystals of the amphiphilic aggregates differ by at least ∼0.5 Å for alkyl gluconamides. We shall show later in this paper that even such a small difference in the distance between the chiral centers along the *a* and *c* axes can have a great effect on the interaction energy of the aggregate in the compressed state (for example, as shown in Figure 6 of this paper, where we have shown the pair potential profile for a pair of the same kind of enantiomers with the variation of the separation between the chiral centers within an aggregate, it is clearly shown that a small separation between the chiral centers can have a large effect on the pair interaction potential; see discussions later). The molecules are packed in sheets extending parallel to the crystallographic *a*,*c* planes. We have shown the arrangement of the chiral centers parallel to the *a*,*c* plane within a sheet of a planar bilayer in Figure 3. In such a structure, where short-range interactions are important and where the chiral centers are unequally spaced along the length and width of the ribbon, the effect of the chiral interactions are expected to be different along the length and the width of the same. Experimental studies using the atomic force microscope have shown that the molecular packing in the polymerizable two-chain lipids[60] is such that the intermolecular separations along the two perpendicular directions in the plane of the bilayer are unequal, as described earlier for glycolipids. We can thus argue that the effect of the chiral interaction along the dimension in which the chiral centers are more closely spaced is more dominant in determining the morphology compared to the other perpendicular dimension, along which the chiral centers are spaced at larger separation.

Now, the idea of the present work is that if one can find the favorable twist by summing over the effective interaction between the adjacent groups of two neighboring chiral molecules, then one can find the three-dimensional structure of the aggregate.

(b) Calculation of the Pairwise Interaction within a Bilayer. As discussed above, the favorable interaction along the longer axis of the ribbon (along the length) is expected to guide the favorable arrangement of the molecular assembly. As our objective is to get only the sense of the helical arrangement of the molecular assembly, we can write the relevant partition function of the aggregate using a reduced description where only the favorable arrangement of the molecules along the longer axis of the ribbon is considered. In the following, we describe the calculation of the orientation dependent partition function of the aggregate of one particular enantiomer of a chiral compound.

Suppose within an aggregate of chiral enantiomers of the same kind there are a total of N amphiphiles and each amphiphile has M monomeric units. We designate the number of chiral enantiomeric molecules by the index $i = 1,2,...,l,...,j$ and the number of constituent groups for each monomer by the index $n = 1,2,...,k,...,m$. Then we can write the partition function for any array of compressed molecules (at high packing) as follows.

$$Q_{N,M} = \frac{1}{N!}\int\prod_{i=1}^{N}\prod_{n=1}^{M} \mathrm{d}\mathbf{r}_{i,n}\,\exp[-\beta U] \tag{2}$$

where U is the distance and orientation dependent total potential energy and is given by the following expression:

$$U = \sum_{l,k\neq j,m} u(\mathbf{r}_{l,k} - \mathbf{r}_{j,m}) \tag{3}$$

where $u(\mathbf{r}_{l,k} - \mathbf{r}_{j,m})$ represents the two-particle interaction between the adjacent molecules. Within the compressed aggregate, the molecules are aligned in a side-by-side form. The distance between the head groups are almost fixed in such a state. We also assume that no bending is allowed within the molecular structure (rigid bond assumption). This assumption is expected to be valid for the amphiphiles in the compressed gel state. Then $|\mathbf{r}_{l,k} - \mathbf{r}_{j,m}|$ is determined by the orientations only. The partition function is thus reduced to the following form:

$$Q_N^R = \frac{1}{N!}\int \mathrm{d}\boldsymbol{\chi}_i\,\mathrm{d}\boldsymbol{\Omega}_i\,\exp[-\beta U] \tag{4}$$

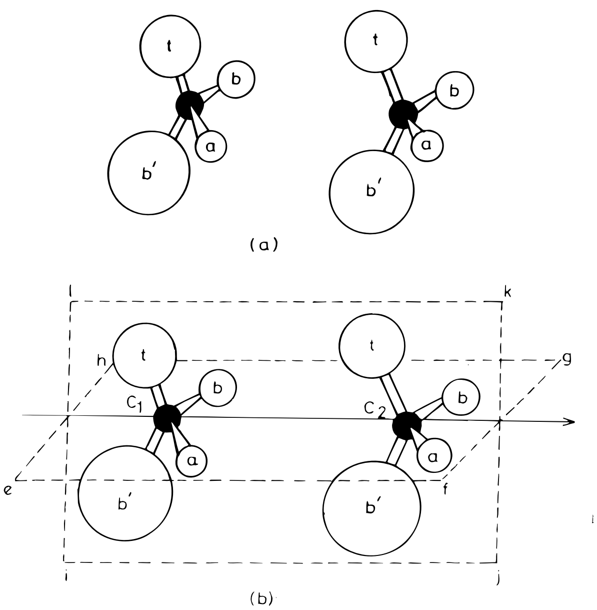


Figure 4. (a) Three-dimensional model for a pair of the same kind of enantiomers (D−D). Here, *t* is the group that includes the largest part of the hydrocarbon chain; *b*′ includes the hydrophilic head group. The *a* and *b* are the two other groups attached to the chiral center. The *b* group is larger than the *a* group. Note that *t* may be either larger or smaller than *b*′. (b) Initial configuration for a pair of chiral molecules from which the search for the minimum energy configuration has been started. The figure also shows the two perpendicular planes passing through the chiral centers of the molecules.

At high packing density of the aggregate (compressed gel state) composed of the same kind of enantiomers (all D or all L), the arrangement of the molecules is such that the smaller of the two side groups comes closer and the larger side group goes next to the larger side group of the adjacent molecule. In this case the arrangement of the adjacent molecules is determined by the *relative orientations of the neighboring amphiphiles. Now, if the sense is determined by the molecular chirality, then it is also determined by the short-range interaction between the neighboring groups attached to the adjacent chiral centers.* Since we are interested just in the sense of the twist, then it is sufficient to determine that the relative orientation between a pair of molecules can be a minimum energy arrangement, as this twist will be propagated along the longer axis of the monolayer/bilayer.

The above considerations motivate us to introduce an effective interaction potential defined below. Let us consider two perpendicular planes, designated by *efgh* and *ijkl*, respectively, through the C_1 chiral carbon atom (see Figure 4a,b). The reason for such a division is as follows. If we remember that a twist between a pair of molecules is a combination of two tilt angles in two perpendicular planes, then the present problem of describing three-dimensional objects can be reduced into two dimensions. The *a* and *b* groups of the C_1 chiral center are in the *efgh* plane and the *t* and *b*′ are in the *ijkl* plane, respectively. In the next step, we place another chiral molecule in such a way that its chiral center (C_2) is lying on the line of intersection of the *efgh* and *ijkl* planes, the *a* and *b* groups attached to C_2 lie on the *efgh* plane, and the *t* and *b*′ groups lie on the *ijkl* plane, as shown in Figure 4b. Starting from this configuration of a pair of chiral molecules, we shall search the whole configurational space to find out the minimum energy configuration of the pair of molecules. This is to be done both by changing the distance between the chiral centers and by orienting the adjacent groups. At the minimum energy configuration, the adjacent *a* and *b* groups do not remain parallel, as in Figure 4b, and they have to orient through an angle in the *efgh* plane. We designate this angle as ϕ_M. The exact value of ϕ_M will depend on the sizes and depth of the potential well of the adjacent *a* and *b* groups. Similarly, in the minimum energy configuration, the adjacent *t* and *b′* groups tilt through an angle in the *ijkl* plane (designated by θ_M). *The net twist of a molecule is the result of the two tilts in the two almost perpendicular planes*. We, therefore, separate the net twist of a molecule as a combination of two simultaneous tilts in the *efgh* and *ijkl* planes. It is also to be noted that the choice of the initial configuration as shown in Figure 4b is only to comprehend easily the search for the minimal energy configuration of a pair of molecules. Such a choice of initial configuration of the pair of molecules never restricts the generality of the present calculation.[59] Thus we write the total effective interaction potential as a sum of interactions into two perpendicular planes as follows:

$$\frac{U_{\text{eff}}}{k_B T} = \left[\frac{u_{a,a}}{k_B T} + \frac{u_{b,b}}{k_B T}\right]_{\text{efgh}} + \left[\frac{u_{t,t}}{k_B T} + \frac{u_{b',b'}}{k_B T}\right]_{ijkl} \tag{5}$$

Here, $u_{a,a}$ gives the pairwise interaction between the adjacent *a* groups and $u_{b,b}$ gives the same between the adjacent *b* groups attached to the two chiral centers in the *efgh* plane, respectively. Similarly, $u_{t,t}$ gives the pairwise interaction between the adjacent *t* groups and $u_{b',b'}$ gives the same between the adjacent *b′* groups in the *efgh* plane, respectively. Note that we have not considered the cross interaction terms like $u_{a,b}$, etc., because their contribution to the EPP is negligible due to the large separation between the *a* (attached to C_1) and *b* (attached to C_2) groups. The interactions between the adjacent groups give the effective contribution to the pair potential. These two particle interaction terms are determined by the relative orientations only.

We have, therefore, replaced eq 4 by the following equation:

$$Q_N^R \simeq \frac{1}{N!} \int \prod_{i,j=1(i<j)}^{N} \mathrm{d}\theta_j \sin\theta_{i,j}\, \mathrm{d}\phi_{ij} \exp[-\beta U_{\text{eff}}] \tag{6}$$

where θ_{ij} and ϕ_{ij} give the relative orientations of the two amphiphiles. Thus, at low temperatures, the minimum of this pair potential corresponds to the minimum of free energy of the system. Note that the elasticity of the bilayer prevents the splay of the molecules, and it tries to minimize the tilt angles generated by the chiral force along the molecular director (along the large tail part and the head group). Note that although the elastic force modifies the tilt angles generated by the chiral force, it does not determine the handedness, which is solely controlled by the chiral force. As our objective is to find the sense, it is sufficient to consider the pairwise interactions between the adjacent chiral molecules only. Moreover, the elastic interaction does not discriminate between the D−D and L−L pair.

Since we assume that in the determination of the sense of the aggregate the interaction at the chiral center plays an important role, we also assume that the interaction is simply controlled by the relative sizes of the groups and the interaction among them. Both the above factors can be included if we introduce a reduced description when all four groups at the chiral centers are replaced by their equivalent spheres and the size is described by the well-defined prescription of Ben-Amotz and Herschbach. It is this potential that we refer to as the effective pair potential (EPP). Note that sizes alone may not always give a unique sense, as two senses can be found with the same size groups that have different L-J potentials.

The following comments about the above scheme are in order. first, eq 6 would make sense only at very high density. Second, the minimum of energy would correspond to a minimum of free energy only at low temperatures. A measure of the relevance of the U_{eff} can be checked from βU_{eff} itself. This must be significantly greater than unity in order for this procedure to make sense. The minimal energy configuration in the present study is nearly a zero-energy configuration, in which the molecules get locked and give rise to the twisted structures. Note that at an elevated temperature the constituent molecules may be trapped into the second minimum, which is observed at nearly zero twist angle at relatively large intermolecular separation. Indeed, it has been shown that at high temperatures, where the ordered state of the lipid bilayer is unstable, the system cannot express its chirality even when it is present at the molecular level, and consequently the helicity is not observed.[14,55] The observed helicity is thus dependent on the temperature and the concentration of the amphiphile. It has been indicated in the experimental studies on the tubule formation that the morphology of the amphiphilic assembly is indeed dependent on the lipid concentration.[28]

Even with all the above assumptions, the finding of the minimum is highly nontrivial. However, if the selection of sense is governed by the *local* interactions, then we may approximate the various groups involved by equivalent spheres of appropriate sizes and try to evaluate the integral in eq 6.

In the following we calculate the effective pair potential between the pair of adjacent *a* and *b* groups, which belong to the two chiral centers, attached to the C_1 and C_2 chiral centers in the *efgh* plane. Similarly, we calculate the effective pair potential between the pair of adjacent *t* and *b′* groups attached to the C_1 and C_2 chiral centers in the *ijkl* plane. We have shown the detailed geometrical description of the position and the orientation of the groups in the *efgh* plane in Figure 5. The relative arrangement of the groups in the *ijkl* plane can be easily understood in an analogous way. 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*). α 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. ϕ_1 and ϕ_2 are the orientations of adjacent *a* groups with respect to *X* and *X′*, respectively. β_{ab} is the angle between the *a* and *b* groups.

We represent the effective sizes of the groups attached to the chiral centers by σ_a and σ_b, respectively. These σ values correspond to the effective diameters of the corresponding groups added to 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.[61,62] We have calculated the effective diameters of the groups using the empirical correlations provided by Ben-Amotz and Herschbach[61] and the group increments tabulated by Bondi.[62] The empirical relations are as follows:[61]

$$V_{\text{hs}} = 1.086(V_{\text{s}} - 9.94) \tag{7}$$

$$\sigma = 1.244(V_{\text{hs}})^{1/3} \tag{8}$$

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.[62] These values are expected to be remarkably accurate, as indicated in the

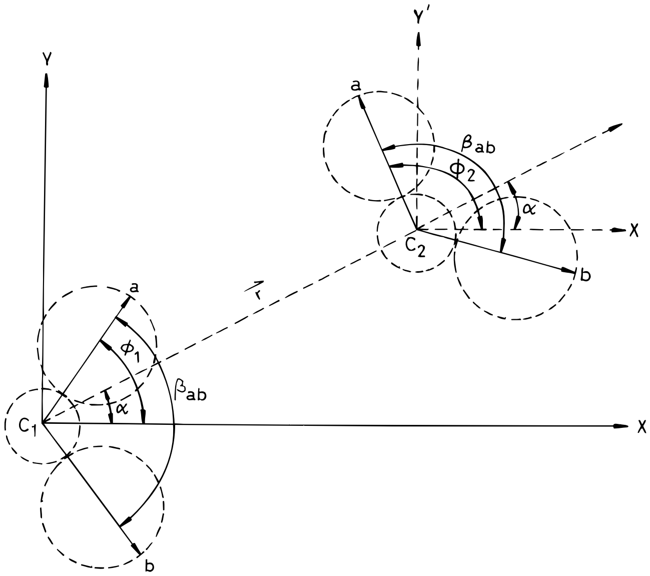


Figure 5. Relative arrangement of the groups that belong to the *efgh* plane and are attached to the two chiral centers C_1 and C_2. C_1 is situated at the center of the arbitrary frame of reference *XY*. *X'* and *Y'* are parallel to *X* and *Y*, respectively. *r* is the line joining C_1 and C_2, and α is the orientation of *r*. ϕ_1 and ϕ_2 are the orientations of the *a* groups attached to the two chiral centers, respectively. β_{ab} is the angle between the *a* and *b* groups. The arrangement of the adjacent *t* and *b'* in the *ijkl* plane attached to the C_1 and C_2 chiral centers is not shown here. Their arrangement can also be understood in an analogous way.

TABLE 1: Effective Diameters (Å) of the Groups Attached to the Chiral Center of the Amphiphiles[a,b] (12-Hydroxystearic Acid and 2-C_{12}-D-Glu-C_{11}-N^+); The Groups Are Designated as *t, b', a,* and *b*, Respectively (See Figure 4); The Tilt Angles (deg) in the Plane of *t, b'* (Represented by θ_M) and That in the Plane of *a* and *b* (Represented by ϕ_M) at the Minimal Energy Configuration Are Also Shown

amphiphile	*t*	*b'*	θ_M	*a*	*b*	ϕ_M
12-hydroxy stearic acid[a]	5.53	7.35	14	1.4	1.92	15
glutamic ammonium amphiphile[b]	7.81	8.00	1	1.4	8.24	45

[a] Tachibana, T.; Kambara, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3422−3424. The molecular projection formula is shown in Figures 7a and 5a. Here, *t* is $-(CH_2)_{11}(COOH)$ and *b'* is $-(CH_2)_4(CH_3)$. The *a* and *b* groups are −H and −OH, respectively. [b] Nakashima, N.; Asakuma, S.; Kim, J. M.; Kunitake, T. *Chem. Lett.* **1984**, 1709−1712. Here, *t* is $-COO(CH_2)_{11}(CH_3)$ and *b'* is $-(CH_2)_2COO(CH_2)_{11}CH_3$. The *a* and *b* groups are −H and $-NHCO(CH_2)_{10}N^+(CH_3)_3$, respectively.

literature.[61] Also, these values are insensitive to substantial deviation of the shape of the group from sphericity. To facilitate connection with a real experimental situation, we have given the sizes of the groups attached to the chiral centers of common amphiphiles (forming helical morphologies) in Table 1.

The Lennard-Jones energy parameters[63] of the groups, *a* and *b*, have been represented by ϵ_a and ϵ_b, respectively. From the values of the ϵ_{LJ} of several classes of compounds such as alkanes, alcohols, and haloalkanes, tabulated by Ben-Amotz and Herschbach,[61] a linear dependence of the ϵ_{LJ} on the sizes of the groups is observed. For a 1 Å increment in the effective diameter of a group, the ϵ_{LJ}/k_B values of the group (k_B is the Boltzmann constant) increases by ~100 K. In the present study we have taken the ϵ_{LJ} values of the groups as proportional to their effective diameters.

The $u_{a,a}$, etc., interactions themselves are given by the following expressions:

$$\left[\frac{u_{a,a}}{k_BT}\right]_{efgh} = \frac{4}{T}\left(\frac{\epsilon_a}{k_B}\right)\left[\left(\frac{g_a}{\sigma_a}\right)^{-12} - \left(\frac{g_a}{\sigma_a}\right)^{-6}\right] \tag{9}$$

$$\left[\frac{u_{b,b}}{k_BT}\right]_{efgh} = \frac{4}{T}\left(\frac{\epsilon_b}{k_B}\right)\left[\left(\frac{g_b}{\sigma_b}\right)^{-12} - \left(\frac{g_b}{\sigma_b}\right)^{-6}\right] \tag{10}$$

$$\left[\frac{u_{t,t}}{k_BT}\right]_{ijkl} = \frac{4}{T}\left(\frac{\epsilon_t}{k_B}\right)\left[\left(\frac{g_t}{\sigma_t}\right)^{-12} - \left(\frac{g_t}{\sigma_t}\right)^{-6}\right] \tag{11}$$

$$\left[\frac{u_{b',b'}}{k_BT}\right]_{ijkl} = \frac{4}{T}\left(\frac{\epsilon_{b'}}{k_B}\right)\left[\left(\frac{g_{b'}}{\sigma_{b'}}\right)^{-12} - \left(\frac{g_{b'}}{\sigma_{b'}}\right)^{-6}\right] \tag{12}$$

where, g_a, etc., are the median distances between the corresponding adjacent *a* groups and so on. In the following we derive the explicit forms of the EPP for the two planes from eqs 9−12.

In the *efgh* plane the explicit expression for the effective pair potential in this case is given by

$$\begin{aligned}\left[\frac{u}{k_BT}\right]_{efgh} &= \left[\frac{u_{a,a}}{k_BT}\right]_{efgh} + \left[\frac{u_{b,b}}{k_BT}\right]_{efgh} \\ &= \left(\frac{4}{T}\right)\left(\frac{\epsilon_a}{k_B}\right)\left[\left(\frac{r}{\sigma_a} + \frac{1}{2}\cos(\phi_2 - \alpha) - \frac{1}{2}\sin(\phi_2 - \alpha)\cot(\phi_1 - \alpha)\right)^{-12} - \left(\frac{r}{\sigma_a} + \frac{1}{2}\cos(\phi_2 - \alpha) - \frac{1}{2}\sin(\phi_2 - \alpha)\cot(\phi_1 - \alpha)\right)^{-6}\right] \\ &\quad + \left(\frac{4}{T}\right)\left(\frac{\epsilon_b}{k_B}\right)\left[\left(\frac{r}{\sigma_b} - \frac{1}{2}\cos(\beta - \phi_1 + \alpha) + \frac{1}{2}\sin(\beta - \phi_1 + \alpha)\cot(\beta - \phi_2)\right)^{-12} - \left(\frac{r}{\sigma_b} - \frac{1}{2}\cos(\beta - \phi_1 + \alpha) + \frac{1}{2}\sin(\beta - \phi_1 + \alpha)\cot(\beta - \phi_2)\right)^{-6}\right]\end{aligned} \tag{13}$$

The symbols are explained in Figure 5. We shall get ϕ_M for a pair of D−D molecules from the minimum of the above pair potential. Values for ϕ_M for two amphiphiles forming a helical morphology are shown in Table 1.

Similarly, in the *ijkl* plane, the explicit expression for the effective pair potential in this case is thus identically given by

$$\begin{aligned}\left[\frac{u}{k_BT}\right]_{ijkl} &= \left[\frac{u_{t,t}}{k_BT}\right]_{ijkl} + \left[\frac{u_{b',b'}}{k_BT}\right]_{ijkl} \\ &= \left(\frac{4}{T}\right)\left(\frac{\epsilon_t}{k_B}\right)\left[\left(\frac{r}{\sigma_t} + \frac{1}{2}\cos(\theta_2 - \alpha) - \frac{1}{2}\sin(\theta_2 - \alpha)\cot(\theta_1 - \alpha)\right)^{-12} - \left(\frac{r}{\sigma_t} + \frac{1}{2}\cos(\theta_2 - \alpha) - \frac{1}{2}\sin(\theta_2 - \alpha)\cot(\theta_1 - \alpha)\right)^{-6}\right] \\ &\quad + \left(\frac{4}{T}\right)\left(\frac{\epsilon_{b'}}{k_B}\right)\left[\left(\frac{r}{\sigma_{b'}} - \frac{1}{2}\cos(\beta - \theta_1 + \alpha) + \frac{1}{2}\sin(\beta - \theta_1 + \alpha)\cot(\beta - \theta_2)\right)^{-12} - \left(\frac{r}{\sigma_{b'}} - \frac{1}{2}\cos(\beta - \theta_1 + \alpha) + \frac{1}{2}\sin(\beta - \theta_1 + \alpha)\cot(\beta - \theta_2)\right)^{-6}\right]\end{aligned} \tag{14}$$

The parameters have the same meaning as explained in Figure 5, but the respective parameters for the plane of *t* and *b'* groups needs to be considered here. The minimum of the above pair potential gives the value of θ_M. Values of θ_M for five amphiphiles forming a helical morphology are shown in Table 1. These values of θ_M arise from bare chirality only.

The EPP profiles of a pair of the same kind of enantiomers (L−L or D−D) in the plane of the ϕ angle are depicted in Figure

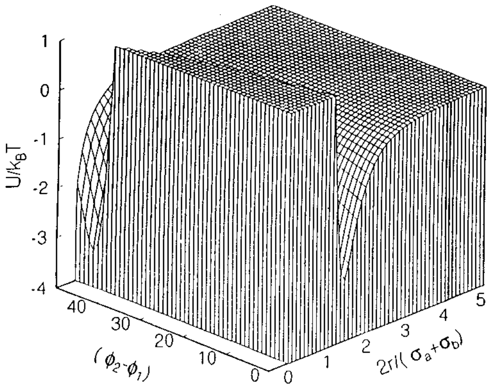


Figure 6. Pair potential profile for a pair of the same kind of enantiomers with the variation in $\phi_2 - \phi_1$ as well as the separation between the chiral centers from eq 11. The *a* and *b* groups have diameters 1.5 and 4.5 Å, respectively. $\epsilon_a/k = 150$ and $\epsilon_b/k = 450$, $\beta = 110°$ and $\alpha = 0°$.

6. We have presented here the plot with $\alpha = 0°$ only. However, plots with other α values have the same features[59] and are not shown here. The EPP profile in the plane of the θ angle has the same features except the magnitude of the θ angle, which is much less than the ϕ angle.

The plot of the pair potential profile of the D—D pair has a double-minima structure. One minimum is at $(\phi_2 - \phi_1) = 0°$ and at a larger separation, while the other minimum is at $(\phi_2 - \phi_1) \simeq 45°$. 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 favoring a more close packed state.

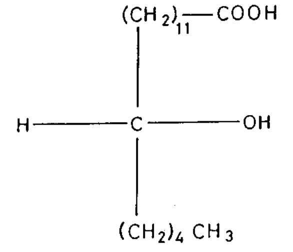
We have tabulated the sizes of the groups (*t*, *b*′, *a*, and *b*) and the corresponding tilt angles at the minimal EPP configuration (designated by θ_M and ϕ_M, respectively) in Table 1.

III. Prediction of the Sense

(a) Methodology. As shown above, a tilt between the two neighboring amphiphiles is characterized by two angles. One is in the plane of *t* and *b*′ (θ_M), and another is in the plane of the *a* and *b* groups (ϕ_M). These two angles are in two almost perpendicular planes. It is well-known that the twist between two successive neighbors can lead to helicity, but we show here for the first time that the sense or the handedness of the helicity can be predicted from the first principles. This has been possible because the present model allows correlation of the fundamental molecular parameters of the groups attached to the chiral centers with the twist angles between the two adjacent molecules. To predict the senses from the calculated tilt angles, we follow the following systematic steps.

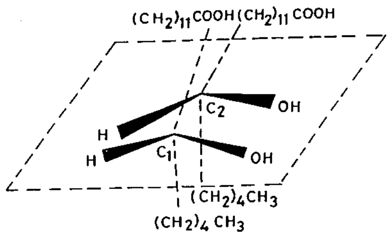
(1) Consider a chiral amphiphilic molecule having only one chiral center. The Fisher projection formula has been drawn for the molecule (see Figure 7a,b). The longest carbon chain should be vertical, and the most highly oxidized end of the molecule should be at the top. All the vertical bonds point backward. Then the absolute configuration of the amphiphile is retrieved from the projection formula. This gives us a visualization of how the different groups attach to the chiral centers are arranged in three-dimensional space (see Figure 4).

(3) Next we bring another chiral amphiphilic molecule from the rear side to a close separation from the first chiral center. As discussed earlier, in this state, the two molecules are tilted



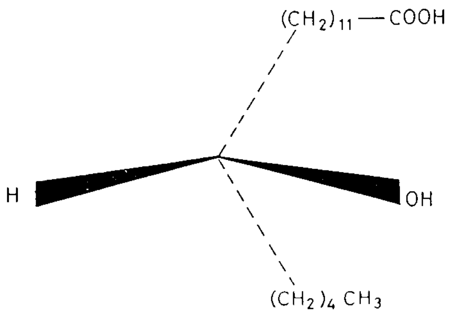
Projection formula of D-12-hydroxystearic acid molecule

(a)

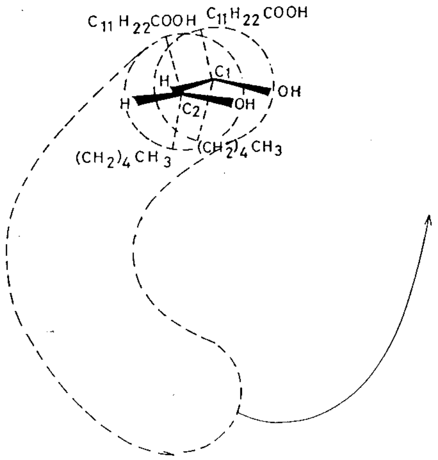


A pair of D-12-hydroxystearic acid

(c)



(b)



Left handed helix formed by an array of D-12-hydroxy-stearic acid molecules

Figure 7. (a) Fisher projection formula of D-12-hydroxystearic acid. (b) Three-dimensional structure of the D-12-hydroxystearic acid derived from the projection formula. (c) Pair of D-12-hydroxystearic acid molecules in the close packed state. (d) Section of the helical aggregate formed by an array of D-12-hydroxystearic acid molecules.

relative to each other and the tilt angles are known from the foregoing molecular considerations.

(4) To construct an array of amphiphilic molecules, we shall place the successive molecules in such a way that the second molecule should be placed behind the first, the third should be placed behind the second, and so on. The justification of such a placement has been elaborately discussed in section II. Note that it is customary to observe the handedness of the helix by placing it in such a way so that the helix propagates away from the eye. From the consideration of the tilt angles described in section II, we can observe how the array of the molecules propagates in the space. It is clearly seen that depending on the EPP of the groups attached to the chiral centers, which in turn depends on the absolute configuration of the concerned molecules, the helical assembly would turn in either a left-handed way or a right-handed way (see Figure 7c,d).

From the present study it is clear that the sense of helix should be predetermined by the EPP. Thus, it is expected that the complete knowledge about the absolute conformation of the monomer, sizes, and the EPP should enable us to predict the sense. In the following subsection we shall attempt to predict the senses of some specific helical amphiphilic assemblies and compare the theoretical prediction with the experimentally determined senses.

(b) Specific Examples. *(i) Prediction of the Sense of* D*-12-Hydroxystearic Acid*. The first example considered is the D-12-hydroxystearic acid. From the Fisher projection formula, the absolute configuration is drawn as shown schematically in Figure 7a,b. In the figure, the dotted bonds point backward to the plain of the paper and the filled-in bonds point toward the top of the plane of the paper. The sizes of the different groups are given in Table 1. The decreasing order of the sizes of the four groups is as follows:

$$-(\mathrm{CH_2})_{11}\mathrm{COOH} > -(\mathrm{CH_2})_4\mathrm{CH_3} > -\mathrm{OH} > -\mathrm{H}$$

Thus, as shown in Figure 7c, 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. The tilt angles θ_M and ϕ_M are shown in Table 1. In the plane containing the $-(CH_2)_{11}COOH$ and $-(CH_2)_4CH_3$ groups, the adjacent $-(CH_2)_{11}$-COOH groups are farther away from each other compared to the corresponding $-(CH_2)_4CH_3$ groups. Similarly, in the place of the −H and −OH groups, the two −OH groups attached to C_1 and C_2 are farther away from each other compared to the −H groups. The tilted pair of amphiphiles are shown in Figure 7c. In constructing a helix from an array of amphiphiles, we have to place molecules one behind the other in succession because the sense of the helix is observed as the turn of the helix goes away from the eye. It is clearly seen from Figure 7c that in the plane drawn by dotted lines the two −OH groups are farther away and the two −H attached to the C_1 and C_2 chiral centers are closer. If we construct an array of molecules, then it is easily seen from Figure 7c,d that the assembly should have a left-handed twist.

*(ii) Prediction of the Sense of 2-C_{12}-*L*-Glu-C_{11}-N^+ Amphiphile*. The second helical aggregate we have considered is the 2-C_{12}-L-Glu-C_{11}-N^+ amphiphile. The Fisher projection formula and the absolute configuration are shown in Figure 8a,b. The sizes of the groups decrease as follows:

$$\mathrm{CH_3(CH_2)_{11}COO(CH_2)_2}- > -\mathrm{COO(CH_2)_{11}CH_3} > -\mathrm{NHCO(CH_2)_{10}N^+(CH_3)_3} > -\mathrm{H}$$

The sizes of the different groups are given in Table 1. In the plane containing the $CH_3(CH_2)_{11}COO(CH_2)_2-$ and the $-COO(CH_2)_{11}CH_3$ groups (indicated by the plane drawn by the dotted line in Figure 8c), the former, having larger EPP and larger effective size, should be farther apart than the latter. Similarly, in the plane containing the $-NHCO(CH_2)_{10}N^+(CH_3)_3$ and the −H, the former being much larger than the latter, the two −H groups are closer than the two $-NHCO(CH_2)_{10}N^+$-$(CH_3)_3$ groups. From Figure 8d we can easily find that the sense of the assembly should be right-handed. The steps to determine the sense are outlined schematically in Figure 8c,d.

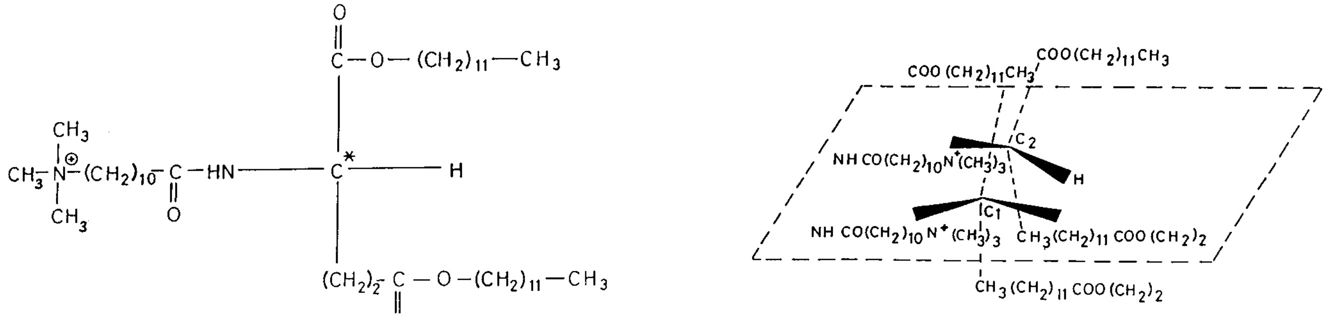
(iii) Prediction of the Sense of L*-12-Hydroxystearic Acid*. The third helical aggregate we have considered is the L-12-hydroxystearic acid. From the Fisher projection formula, the absolute configuration is drawn as shown in Figure 9a. The sizes of the different groups are given in Table 1. Their decreasing order is just the same as that in the D-acid, as shown before. In this case, although the positions of the $-(CH_2)_{11}$-COOH and the $-(CH_2)_4CH_3$ groups remained the same as that of the D-acid in space, the relative positions of the −H and −OH groups are just reversed. Then, following the steps outlined earlier to determine the sense of the D-isomer, we can easily find that the sense of the assembly should be just the reverse of that of the L-acid, i.e. right-handed. We have not presented the detailed schematic description of the assembly of the L-isomer because it can be easily followed from the corresponding D-isomer.

*(iv) Prediction of the Sense of 2-C_{12}-*D*-Glu-C_{11}-N^+ Amphiphile*. The fourth and last example we have considered is the D-isomer of the ammonium amphiphile. The molecular formula is given in Figure 9b. The sizes of the different groups are given in Table 1. Then, following the steps outlined earlier to determine the sense of the corresponding L-isomer, we can easily find that the sense of the assembly should be left-handed.

IV. Conclusion

Let us first summarize the main results of the present study. We have formulated a microscopic scheme to predict the sense of a helical morphology formed by chiral amphiphiles based on a molecular approach. The theoretical scheme considers the minimal EPP between the two chiral amphiphile molecules. The EPP is dependent on the sizes of the groups attached to the chiral centers, their relative orientations and the distance between them. The predicted senses are compared with the experimentally determined senses for four systems. The results are given in Table 2. Complete agreement between the theoretical prediction and the experimental result has been observed in all the cases. This 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 is controlled by the EPP between the groups attached to the chiral centers of the pair of amphiphiles.

However, it has been observed that the senses of the helicity of the D- and L-12-hydroxystearic acids are just reverse of those of the corresponding optical isomers of the lithium salts. Although the reason for this reversal of the sense is not understood, it seems that the influence of the ionic atmosphere in the head group zone generated by the Li^+ counterions of the latter may be responsible for the reversal of the handedness. It has been indicated earlier[1] that in the bilayers and the membranes the cation-regulated hydration forces have a profound effect on the arrangement of the head groups. Consequently, the morphology of the bilayer is expected to be influenced by the hydration of the counterions. It may also be noted that the magnitudes of the electrical head group repulsion free energies

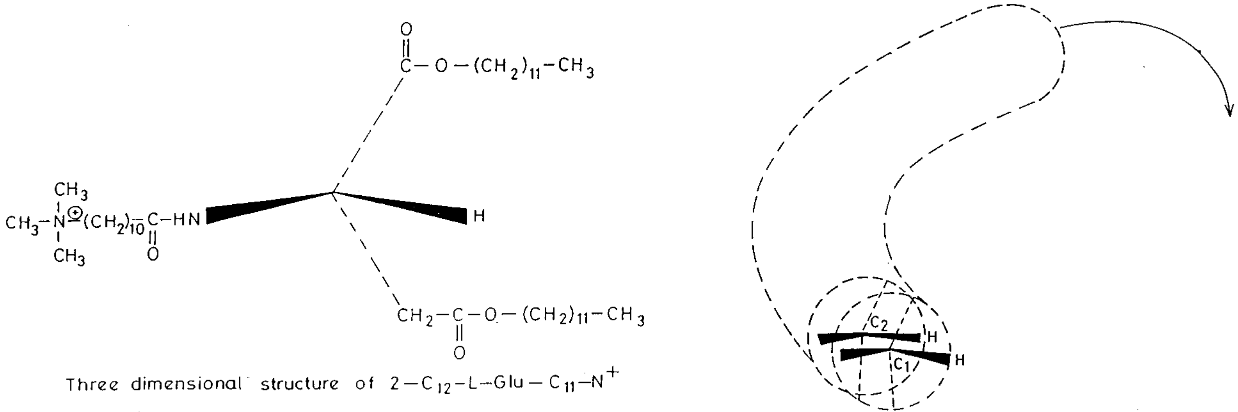


Projection formula of 2—C_{12}—L—Glu—C_{11}—N^+molecule

(a)

A pair of 2—C_{12}-L-Glu − C_{11} N^+ molecule

(c)



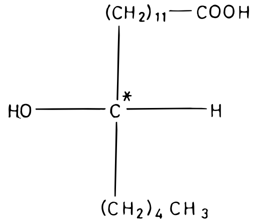
Three dimensional structure of 2—C_{12}-L-Glu — C_{11}—N^+ molecule

(b)

Right handed helix formed by an array of 2—C_{12} — L -Glu — C_{11}—N^+ molecule

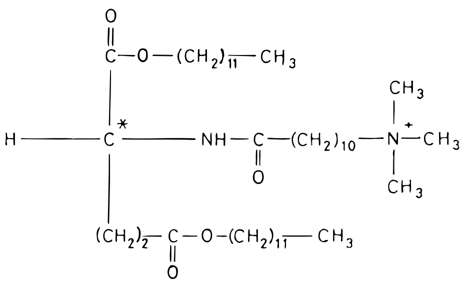
(d)

Figure 8. (a) Fisher projection formula of 2-C_{12}-L-Glu-$C_{11}N^+$. (b) Three-dimensional structure of the 2-C_{12}-L-Glu-$C_{11}N^+$ molecule derived from the projection formula. (c) Pair of 2-C_{12}-L-Glu-$C_{11}N^+$ molecules in the close packed state. (d) Section of the helical aggregate formed by an array of 2-C_{12}-L-Glu-$C_{11}N^+$ molecules.



Projection formula of L−12-hydroxystearic acid molecule

(a)



Projection formula of 2 — C_{12} — D— Glu — $C_{11}N^+$ molecule

(b)

Figure 9. (a) Fisher projection formula of L-12-hydroxystearic acid and (b) Fisher projection formula of 2-C_{12}-D-Glu-$C_{11}N^+$.

range from ~2 to 3 k_BT, depending on their aggregation number, ionic charge, etc., for the spherical micelles formed from sodium alkyl sulfate surfactants.[68] This suggests that the energy of the electrical head group repulsion interaction has magnitude comparable to the energy of the effective chiral interaction term. Consequently, a variation in the repulsive term may easily tune the shape of the aggregate morphology. Surely, more molecular studies should be initiated for a better understanding of this still poorly understood problem.

TABLE 2: Theoretically Predicted Senses of the Amphiphilic Aggregate Forming Helical Morphology Calculated from the EPP

amphiphile	theoretically predicted sense	experimentally observed sense
D-12-hydroxy stearic acid	left-handed	left-handed[a]
L-12-hydroxy stearic acid	right-handed	right-handed[a]
D-glutamic ammonium amphiphile	left-handed	left-handed[b]
L-glutamic ammonium amphiphile	right-handed	right-handed[b]

[a] Tachibana, T.; Kambara, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3422−3424. [b] Nakashima, N.; Asakuma, S. Kim, J. M.; Kunitake, T. *Chem. Lett.* **1984**, 1709−1712.

An important limitation of the present work is that it is based solely on an effective pair potential. This should be generalized to include many-body effects, as done elegantly by Rice and co-workers for Langmuir monolayers.[5−11] To begin with, one may assume that the two-body interaction potential is given by the effective pair potential derived here. We hope to address this problem in a future study.

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