Molecular Origin of the Intrinsic Bending Force for Helical Morphology Observed in Chiral Amphiphilic Assemblies: Concentration and Size Dependence

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Received October 3, 1995. Revised Manuscript Received May 22, 1996⊗

Abstract: The formation of the helical morphology in monolayers and bilayers of chiral amphiphilic assemblies is believed to be driven at least partly by the interactions at the chiral centers of the amphiphiles. However, a detailed microscopic understanding of these interactions and their relation with the helix formation is still not clear. In this article a study of the molecular origin of the chirality-driven helix formation is presented by calculating, for the first time, the effective pair potential between a pair of chiral molecules. This effective potential depends on the relative sizes of the groups attached to the two chiral centers, on the orientation of the amphiphile molecules, and also on the distance between them. We find that for the mirror-image isomers (in the racemic modification) the minimum energy conformation is a nearly parallel alignment of the molecules. On the other hand, the same for a pair of molecules of one kind of enantiomer favors a tilt angle between them, thus leading to the formation of a helical morphology of the aggregate. The tilt angle is determined by the size of the groups attached to the chiral centers of the pair of molecules considered and in many cases predicted it to be close to 45°. The present study, therefore, provides a molecular origin of the intrinsic bending force, suggested by Helfrich (*J. Chem. Phys.* **1986**, *85*, 1085−1087), to be responsible for the formation of helical structure. This effective potential may explain many of the existing experimental results, such as the size and the concentration dependence of the formation of helical morphology. It is further found that the elastic forces can significantly modify the pitch predicted by the chiral interactions alone and that the modified real pitch is close to the experimentally observed value. The present study is expected to provide a starting point for future microscopic studies.

I. Introduction

Amphiphilic molecules like lipids, fatty acids, etc. are involved in almost all cellular activities. An understanding of the physical principle that controls the structure of the molecular assemblies composed of such molecules is essential for an understanding of their physiological roles, since *structure* and *function* are much interrelated in this case.[1] It is well-known that monolayers and bilayers formed by chiral amphiphiles can exist in states of various morphologies, like helical ribbons, tubules, fibers, superhelical strands, flat crystals, etc. It has been observed that the morphology of the assembly composed of such amphiphiles is strongly dependent on the chirality[2] of the molecules concerned. The most simple source of chirality in an organic molecule is the presence of at least one carbon atom to which four other different atoms or groups are attached.[2] It has been observed that, if the amphiphilic monomer has at least one chiral center and the aggregate contains one kind of enantiomer (either D- or L-) in excess, helical fibers and gels may be formed from the compressed monolayers and bilayers in the gel state. The helical structure formed from a particular kind of enantiomer has unique handedness. The corresponding racemic modification, on the other hand, does not produce helical fibers but only flat platelets or ribbons without twist. A large number of experimental and theoretical studies have confirmed the above phenomenon.[3−17] As the helix is itself a chiral structure, it seems that the molecular chirality is reflected in the chirality of the aggregate. The objective of the present study is to understand and to provide a molecular explanation of this phenomenon.

A number of continuum theories have been proposed to explain the helical structure and the tubule formation made up of chiral molecules.[18−25] The initial theories of de Gennes[19]

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⊗ Abstract published in *Advance ACS Abstracts,* October 15, 1996.

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and of Lubensky and Prost[20] apparently disagreed with several experimental results. More recent theories start with the assumption that an intrinsic bending force exists due to the chirality.[21−26] The tendency of the chiral amphiphilic molecules to aggregate in the form of helical fibers has also been attempted to explain in terms of the positive effect of the chirality on the lifetime of the aggregate.[3] The dispersion and the induction interaction terms, which discriminate the interaction between the D−D pair and that between the D−L pair, have also been studied.[27]

However, one lacunae of all these treatments is a large gap between the macroscopic picture and the molecularity, as already discussed eloquently by Schnur.[6a] For example, even the elegant treatment by Helfrich[22] leaves the microscopic origin of the intrinsic bending force, especially the relation of the latter with the molecular dissymmetry unclear. The same applies for the other more abstract theories also. On the other hand, it is reasonable to draw the inference that the subtle stereogenicity at the chiral center of a chiral molecule is responsible for driving the aggregate shape to a particular morphology. Thus, it might be possible to predict and understand the structure formation from an *effective* intermolecular pair potential between the chiral centers of the monomers of the aggregate. Such a potential will necessarily be a reduced one, derived after summing over many other detailed interactions between the groups attached to the chiral centers of a pair of chiral molecules. Minimally, this potential should depend only on the distance and the orientation between the two participating chiral amphiphilic molecules. This effective pair potential can then be used to find out the relative arrangement of a pair of molecules. The minimal energy conformation of the aggregate can be studied by changing the orientation of the groups and by reducing the distance between the chiral centers. It is to be noted that, in the helical morphologies, the amphiphilic molecules have an erect conformation[4] and approximately have an area per molecule close to the cross-sectional area of a CH_2 group of an alkyl chain.[28] The molecules are, therefore, in a closed packed structure with a small separation between them. Thus, one expects short-range, both repulsive and attractive, interactions to play an important role in these systems. Note that the situation in amphiphiles, like lipids and fatty acids, is strikingly different from that in polypeptides and in DNA; in the latter cases, it is the *intramolecular* interaction that determines the helicity of the molecules. For lipids, on the other hand, it is the *intermolecular* interaction in the assembly that seems to determine the morphology of the aggregate.

In this work we shall calculate the effective interaction potential between the two adjacent chiral molecules by assuming that the molecular pair potential between the individual groups, that comprise the chiral centers, has the Lennard-Jones (6−12) form. Fortunately, the Lennard-Jones interaction parameters for the alkyl or other groups have recently been provided by Ben-Amotz and Herschbach.[29] The relative arrangements of the groups attached to the chiral centers of a pair of D−D and D−L molecules are different. If this difference in the interaction is controlling the relative arrangement of the D−D and D−L pairs, then very useful information about the aggregate structure can be obtained by studying the minimal energy conformation of the molecules.

Our results lead to the interesting conclusion that the minimal energy conformation of a D−L pair is entirely different from that of a D−D or L−L pair. In the former, a single minimum occurs at zero twist angle, thus favoring a parallel alignment, which in turn suggests the absence of helicity in the racemic modification and a flat surface. On the other hand, in the case of a L−L or D−D pair, the effective potential shows a double-minimum structure, with one minimum at nearly zero degree but at large separation, while the second, *the deeper minimum*, is at a ~45° twist and is at a short distance. At close packing, the latter will be effective, thereby leading to the formation of the helical structure. The present work suggests that this may be the molecular origin of the helix formation, when one of the enantiomers is present in excess in the aggregate. We believe that this is the first such calculation of the role of effective interaction potential in driving the structure of the two chiral molecules.

The organization of the rest of the paper is as follows. In section II, we describe the calculation of the effective interaction potential between the pair of chiral molecules with one chiral center. In section III, we present the numerical results, and in the section IV, we discuss the molecular chirality and helical structure formation and also the prediction of the real pitch from molecular parameters, which is followed by a brief conclusion.

II. Theoretical Formulation

In this section we want to develop a 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). In order to understand the interaction between any two chiral molecules, each with only one chiral carbon atom, let us first designate the four different groups attached to the

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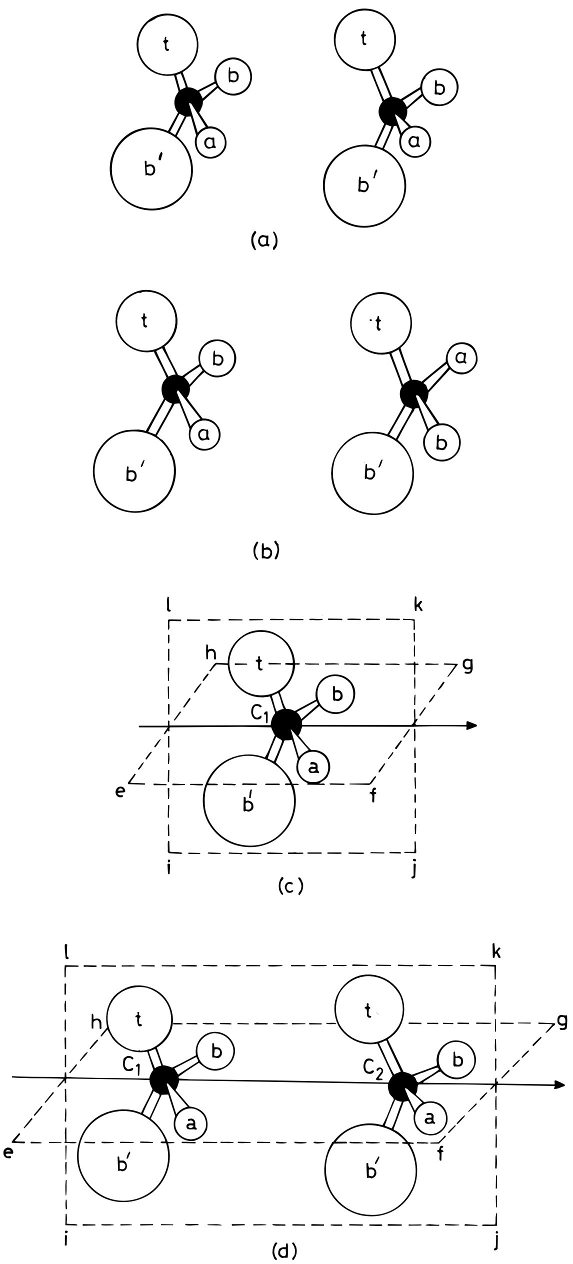

Figure 1. Three-dimensional model for (a) a pair of the same kind of enantiomers (D−D) and (b) a pair of mirror-image isomers (D−L). In both the figures, t is the group which includes the largest part of the hydrocarbon chain and b′ includes the hydrophilic head group. a and b are the two other groups attached to the chiral center, and their relative arrangement is different in the D−D (Figure a) and D−L pairs (Figure b). The b group is larger than the a group. Note that t may be either larger or smaller than b′. (c) Depiction of the two planes, containing the a, b and the t, b′ groups of a chiral molecule. (d) Initial configuration of a pair of chiral molecules, from which the search of minimal energy configuration has started.

chiral center of the amphiphile (see Figure 1a,b). We label the groups which form the backbone of the amphiphile as t and b′, respectively. The t group is the group which includes the largest part of the hydrophobic tail. In the case of double-chain amphiphiles, it is the chain with the largest hydrophobic chain. The b′ group includes the head group. In an amphiphilic molecule, the t and b′ groups lie in a plane and their average orientation represents the orientation of the *molecular director*. Thus, in the molecular assembly, the t group of one amphiphile molecule is next to the t group of another molecule. The b′ groups are also arranged in an analogous way. Now, if one looks at the arrangement of the other two groups attached to the chiral center (we shall designate them by a and b, respectively, the a group having smaller size than the b group), then one finds that the relative arrangements of the a and the b groups of a pair of chiral molecules are not identical for the D−D and D−L pairs (see Figure 1, parts a and b, respectively). When we attempt to closely pack a pair of the same kind of enantiomers (both D or both L), the a group of one molecule comes in contact with the a group of the other molecule, while the same happens for the b groups. But, when we attempt to pack a pair of mirror-image isomers, then a group of one molecule is in contact with the b group of the second molecule. It is thus obvious that the interactions at the sites of a and b groups are not alike for the molecules of one kind of enantiomer (say, D−D) and racemic modification (D−L pair). If this difference in the interaction is controlling the relative arrangement of the D−D and D−L pairs, then very useful information about the aggregate structure can be obtained by studying the minimal energy conformation of the molecules.

(a) Scheme of Calculation of the Effective Pair Potential. Our aim is to calculate the effective pair potential between the adjacent groups of a pair of chiral molecules (as shown in the Figure 1, parts a and b, respectively) and then to minimize it. It is, however, nontrivial to derive an expression for the pair potential of a pair of three-dimensional objects like chiral molecules. However, if we remember that a twist between a pair of molecules is a combination of two tilt angles in the two perpendicular planes passing through their chiral centers, then the present problem of describing three-dimensional objects can be reduced to two dimensions. In Figure 1c, we have considered two perpendicular planes through the C_1 chiral carbon atom. We designate the planes as *efgh* and *ijkl*, respectively. 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. It will be conceived soon that such a consideration will considerably simplify our calculation of the effective pair potential.

In the next step, we put another chiral molecule (having C_2 chiral center) in such a way that C_2 is lying on the line of intersection of the *efgh* and *ijkl* planes, a and b groups attached to C_2 lie on *efgh* plane, and t and b′ groups lie on the *ijkl* plane. This is shown in the Figure 1d. We shall divide the total interaction between the pair of chiral molecules into two parts. One is the interaction between a pair of adjacent t and b′ molecules in the *ijkl* plane, and the other is the interaction between adjacent a and b molecules in the *efgh* plane. By starting from this configuration of a pair of chiral molecules as shown in the Figure 1d, where the adjacent groups are parallel to each other, we shall search the whole configurational space to find the minimum energy configuration of the pair of molecules under consideration. This is to be done both by changing the distance between the chiral centers and by orienting the adjacent groups. We, therefore, separate the net twist of a molecule as a combination of two simultaneous *in-plane* tilts in the *efgh* and *ijkl* planes. *The net twist of a molecule is the resultant of the tilt angles in these two almost perpendicular planes*. Such a separation is possible because it can be easily shown that the interaction between the t group attached to the C_1 carbon and the a or the b groups attached to C_2 contributes only insignificantly to the effective pair potential. It is only the interaction between the nearest neighbors, which contributes effectively to the pair potential. Similarly, the interaction between the b′ group attached to C_1 and the a or the b groups attached to C_2 does not contribute significantly to the effective pair potential.

Strictly speaking, the choice of the initial configuration as shown in the Figure 1d 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. We can start with any other configuration. It is also completely unnecessary to restrict the position of the C_2 chiral center on the intersecting line of the *efgh* and *ijkl* planes. We can also start the search for the minimal energy configuration from a position, where the C_2 center is away from the line of intersection. Results of such calculations have been provided in the Supporting Information, where the line joining the C_1 and C_2 are oriented through an angle with the line of intersection of the *efgh* and *ijkl* planes. The results of the calculation remain the same as those from the calculation where the C_2 chiral center is on the line of intersection of the *efgh* and *ijkl* planes. Again note that the division of the total interaction as a sum of interactions in the *efgh* and *ijkl* planes is also completely arbitrary. We could have divided the total interaction as a sum of interactions into the plane containing t and a groups and the plane containing b and b′ groups.

Now, we calculate the effective pair potential between a 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 a pair of adjacent t and b′ groups attached to the C_1 and C_2 chiral centers in the *ijkl* plane. These two calculations have been done for both for both the D−D and D−L pairs. We have already indicated that the arrangements of the adjacent a and b groups are different for the D−D and the D−L pairs and that the expression for the pair potential in the *efgh* plane should be different for the two cases. On the other hand, the arrangement of the t and b′ groups are the same for the D−D and D−L pairs and the same expression is valid for both of the D−D and D−L pairs in the *ijkl* plane. We shall discuss this point further in the following subsections.

(b) Definition of the Angles Describing the Twist. For a pair of mirror-image isomers (racemic modification), the alignments of the molecules are parallel. It is thus expected that, if we calculate the effective pair potentials in the *efgh* and the *ijkl* planes, at the minimum of the pair potential, the molecules prefer to have a parallel alignment without any twist. Consequently, the minimum of the pair potential is expected to be obtained at a 0° relative orientation between the neighboring groups in both the planes (just the same as the initial configuration as shown in the Figure 1d).

However, for a pair of the same kind of enantiomers, the adjacent molecules have a twist between them. We have indicated earlier that this twist is a combination of two tilts in two perpendicular planes. At the minimum energy conformation, the adjacent a and b groups do not remain parallel as in the Figure 1d and these groups have to orient through an angle in the *efgh* plane. We designate this angle as ϕ_M. The exact value of the 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 the b′ groups are not parallel and they tilt through an angle in the *ijkl* plane (designated by θ_M). The twist of the second chiral molecule is a combination of these two tilts, designated by the angles ϕ_M and θ_M.

The main chiral interaction is expressed through the angle ϕ_M (in the plane of a and b groups). The reason is that the forces responsible for aggregation of the amphiphile act along the hydrophobic chain and the tilts of the t and b′ groups are unfavored. The splay of these larger groups is expected to be much small. Our calculation of the θ_M also supports this. These groups, being the major components of the hydrophobic tail and hydrophilic head group, respectively, have large sizes, and any tilt in their plane is expected to be unfavored compared to the tilt between the a and b groups. We will discuss this point further in section IV. It may be easily noted that it is completely unnecessary to develop the expression for the effective interaction for θ_M and ϕ_M, separately. It is sufficient to develop a general expression for the effective interaction potential for a pair of groups lying in a plane. This functional is then used to study the minimum energy configuration in the *efgh* and *ijkl* planes, using the explicit values of the parameters of the relevant groups under consideration.

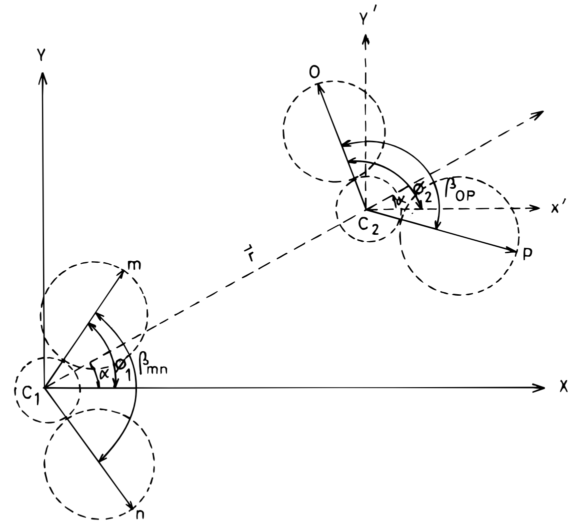

Figure 2. Graphical representation of the relative arrangement of the two pairs of groups attached to the two chiral centers C_1 and C_2. m and n are attached to the C_1, and o and p are attached to the C_2. C_1 is situated at the center of the arbitrary frame of reference *XY*. *X*′ and *Y*′ are parallel to the *X* and *Y*, respectively. *r* is the line joining C_1 and C_2, and α is the orientation of *r*. ϕ_1 and ϕ_2 give the orientations of m and o groups, respectively. B_{mn} and β_{op} are the angles between m and n and that between o and p, respectively. For details see the text.

(c) Choice of Coordinates and Other Parameters. Our problem is now to calculate the effective pair potential of a pair of groups attached to two chiral centers which lie on a plane and then to minimize it to get the tilt angle related to that plane. This plane may be of either the *efgh* or *ijkl* plane. The tilt angle obtained by minimizing should be either θ_M or ϕ_M according to the plane under consideration. As shown in the Figure 1d, in the initial configuration, this plane contains four groups, two from each chiral center. The relative arrangements of these four groups depend on whether the molecules belong to the D−D or D−L pair. We designate the pair of groups as m, n, o, and p, respectively (see Figure 2). It is repeated that these groups may be either the representatives of a pair of a and b groups in the *efgh* plane or the representatives of t and b′ groups in the *ijkl* plane. 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. Now we designate a frame of reference on the plane under consideration. 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*). 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 the *X* and *Y*, respectively. ϕ_1 and ϕ_2 are the orientations of m and o groups with respect to the *X* and *X*′, respectively. β_{mn} and β_{op} are the angles between m and n and that between o and p groups, respectively.

We represent the effective sizes of the groups attached to the chiral centers by σ_m, σ_n, σ_o, and σ_p, respectively. These σ

Table 1. Effective Diameters of the Groups (Å) attached to the Chiral Center of the Amphiphiles (A−E)$^{1-5}$ Forming a Helical Morphology[a]

amphiphile	t	b′	θ_M	a	b	ϕ_M
A[b]	8.19	6.51	11	1.4	7.81	45
B[c]	7.81	8.00	1	1.4	8.24	45
C[d]	7.81	8.81	6	1.4	2.99	31
D[e]	8.18	8.00	0.1	1.4	7.29	44
E[f]	5.53	7.35	14	1.4	1.92	15

[a] The groups are designated as t, b′, a, and b, respectively.[6] The tilt angles (deg) in the plane of t and b′ (represented by θ_M) and that in the plane of a and b (represented by ϕ_M) in the minimal energy configuration are also shown. [b] Amphiphile "A" is the double-chain ammonium amphiphile cited in the ref 7c with $n = 12$ and $m = 2$, where $n - 1$ and $m - 1$ are the number of the methylene groups attached to the carboxylic group in the hydrophobic tails and the N$^+$ atom of the head group, respectively. The molecular projection formula is shown in the Figure 6a. [c] Amphiphile "B" is the double-chain ammonium amphiphile cited in the ref 7c with $n = 12$ and $m = 11$, where $n - 1$ and $m - 1$ are the number of the methylene groups attached to the carboxylic group in the hydrophobic tails and the N$^+$ atom of the head group, respectively. The molecular projection formula is shown in the Figure 6b. [d] Amphiphile "C" is the single-chain ammonium amphiphile cited in the ref 7a. The molecular projection formula is shown in the Figure 6c. [e] Amphiphile "D" is the double-chain phospholipid with a nucleotide head group as cited in the ref 3a. The molecular projection formula is shown in the Figure 6d. [f] Amphiphile "E" is 12-hydroxystearic acid, cited in ref 4a. The molecular projection formula is shown in the Figure 6e.

values correspond to 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 an increase in the length of the corresponding carbon chain.[29,30] We have calculated the effective diameters of the groups using the empirical correlations provided by Ben-Amotz and Herschbach[29] and the group increments tabulated by Bondi.[30] The empirical relations are as follows:[29]

$$V_{\mathrm{hs}} = 1.086(V_{\mathrm{s}} - 9.94) \tag{1}$$

$$\sigma = 1.244(V_{\mathrm{hs}})^{1/3} \tag{2}$$

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.[30] These values are expected to be remarkably accurate, as indicated in the literature.[29] Also, these values are insensitive to substantial deviation of the shape of the group from sphericity. In order to facilitate connection with a real experimental situation, we have given the sizes of the groups attached to the chiral centers of common apmphiphiles (forming helical morphologies) in Table 1.

The Lennard-Jones energy parameters of the groups, m, n, o, and p, are represented by ϵ_m, ϵ_n, ϵ_o, and ϵ_p, respectively. From the values of the ϵ_{LJ} of several classes of compounds like alkanes, alcohols, haloalkanes, etc., tabulated by Ben-Amotz and Herschbach,[29] 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 value 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.

As already discussed, the interaction between the chiral centers has been calculated by assuming a Lennard-Jones (6−12) form of the potential[31] between the adjacent groups. If we assume that the adjacent groups belonging to the neighboring 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

$$\frac{U}{k_B T} = \frac{U_1}{k_B T} + \frac{U_2}{k_B T} \tag{3}$$

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:

$$\frac{U_1}{k_B T} = \frac{4}{T}\left(\frac{\epsilon_1}{k_B}\right)\left[\left(\frac{g_1}{\sigma_1}\right)^{-12} - \left(\frac{g_1}{\sigma_1}\right)^{-6}\right] \tag{4}$$

$$\frac{U_2}{k_B T} = \frac{4}{T}\left(\frac{\epsilon_2}{k_B}\right)\left[\left(\frac{g_2}{\sigma_2}\right)^{-12} - \left(\frac{g_2}{\sigma_2}\right)^{-6}\right] \tag{5}$$

where g_1 is the median distance between m and o and g_2 is the median distance between n and p groups, respectively. σ_1 and σ_2 are given by

$$\sigma_1 = \frac{\sigma_m + \sigma_o}{2} \tag{6}$$

$$\sigma_2 = \frac{\sigma_n + \sigma_p}{2} \tag{7}$$

and ϵ_1 and ϵ_2 are given by the Berthelot rule[33]

$$\epsilon_1 = \sqrt{(\epsilon_m)(\epsilon_o)} \tag{8}$$

$$\epsilon_2 = \sqrt{(\epsilon_n)(\epsilon_p)} \tag{9}$$

From the Figure 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 cases 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, using eqs 4 and 5 for both the *efgh* and *ijkl* planes.

(d) Interaction Potential in the Plane of a and b Groups in the *efgh* Plane. In the present subsections we shall develop the explicit expression for the pair potential in the *efgh* plane (see Figure 1d). It is again to be pointed out that the arrangements of the a and b groups are not identical for the D−L and D−D pairs (see Figure 1, parts a and b, respectively). Consequently, the expressions for the pair potentials for these two cases are different. In the following we derive the explicit expressions for the respective cases.

(d.1.) Interaction Potential for the Racemic Modification (D-L Pair) in the *efgh* Plane. The median distance between the groups can be easily obtained from the median of the tallest isosceles trapezoid that can be drawn between the C_1m and C_2o and that between the C_1n and C_2p (Figure 2), respectively. 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 a b group, n is equivalent to a b group, and p is equivalent to an a group, respectively. β_{mn} and β_{op} are equal. Both of them are represented by β. The other parameters have been explained earlier. The explicit expression for the distance- and

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(29) Ben-Amotz, D.; Herschbach, D. R. *J. Phys. Chem.* **1990**, *94*, 1038−1047.

(30) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441−451.

(31) Maitland, G. C.; Rigby, M. E.; Smith, B.; Wakeham, W. A. *Intermolecular forces: Their origin and determination*, Clarendon Press: Oxford, U.K., 1981.

orientation-dependent effective pair potential is then given by

$$\frac{U}{k_BT} = \left(\frac{4}{T}\right)\sqrt{\frac{\epsilon_a\epsilon_b}{k_Bk_B}}\Bigg[\left(\frac{2r}{\sigma_a+\sigma_b} - \frac{\sigma_a}{\sigma_a+\sigma_b}\sin(\phi_2-\alpha)\times \cot(\phi_1-\alpha) + \frac{\sigma_a}{\sigma_a+\sigma_b}\cos(\phi_2-\alpha)\right)^{-12} - \left(\frac{2r}{\sigma_a+\sigma_b} - \frac{\sigma_a}{\sigma_a+\sigma_b}\sin(\phi_2-\alpha)\cot(\phi_1-\alpha) + \frac{\sigma_a}{\sigma_a+\sigma_b}\cos(\phi_2-\alpha)\right)^{-6}\Bigg] + \left(\frac{4}{T}\right)\sqrt{\frac{\epsilon_a\epsilon_b}{k_Bk_B}}\Bigg[\left(\frac{2r}{\sigma_a+\sigma_b} - \frac{\sigma_a}{\sigma_a+\sigma_b}\cos(\beta-\phi_1+\alpha) + \frac{\sigma_a}{\sigma_a+\sigma_b}\sin(\beta-\phi_1+\alpha)\cot(\beta-\phi_2)\right)^{-12} - \left(\frac{2r}{\sigma_a+\sigma_b} - \frac{\sigma_a}{\sigma_a+\sigma_b}\cos(\beta-\phi_1+\alpha) + \frac{\sigma_a}{\sigma_a+\sigma_b}\sin(\beta-\phi_1+\alpha)\cot(\beta-\phi_2)\right)^{-6}\Bigg] \quad (10)$$

The parameters used in the equation have been explained in the Figure 2. We shall get ϕ_M for a pair of D–L molecules from the minima of the above pair potential.

(d.2) Interaction Potential between the Same Kind of Enantiomers (D–D or L–L Pair) in the *efgh* Plane. 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 an a group, n is equivalent to a b group, and p is equivalent to a b group, respectively. The explicit expression for the effective pair potential in this case is then given by

$$\frac{U}{k_BT} = \left(\frac{4}{T}\right)\sqrt{\frac{\epsilon_a\epsilon_a}{k_Bk_B}}\Bigg[\left(\frac{r}{\sigma_a} + \frac{1}{2}\cos(\phi_2-\alpha) - \frac{1}{2}\sin(\phi_2-\alpha)\times \cot(\phi_1-\alpha)\right)^{-12} - \left(\frac{r}{\sigma_a} + \frac{1}{2}\cos(\phi_2-\alpha) - \frac{1}{2}\sin(\phi_2-\alpha)\times \cot(\phi_1-\alpha)\right)^{-6}\Bigg] + \left(\frac{4}{T}\right)\sqrt{\frac{\epsilon_b\epsilon_b}{k_Bk_B}}\Bigg[\left(\frac{r}{\sigma_b} - \frac{1}{2}\cos(\beta-\phi_1+\alpha) + \frac{1}{2}\sin(\beta-\phi_1+\alpha)\cot(\beta-\phi_2)\right)^{-12} - \left(\frac{r}{\sigma_b} - \frac{1}{2}\cos(\beta-\phi_1+\alpha) + \frac{1}{2}\sin(\beta-\phi_1+\alpha)\cot(\beta-\phi_2)\right)^{-6}\Bigg] \quad (11)$$

The symbols have the same meaning as in eq 10. We shall get ϕ_M for a pair of D–D molecules from the minima of the above pair potential. Values for ϕ_M for five amphiphiles forming helical morphology are shown in Table 1.

(e) Interaction Potential in the Plane of t and b′ Groups for Both D–D and D–L Pairs. The arrangements of the t and b′ groups in both D–D and D–L pairs are such that the t group of the C_1 is adjacent to the t group of the C_2 and the b′ group of the C_1 is adjacent to the b′ group of the C_2 (see Figure 1a,b). Consequently, the same expression is valid for both D–D and D–L pairs. In this case, the same groups are adjacent to each other. Here, m is equivalent to the t group, o is equivalent to the t group, n is equivalent to the b′ group, and p is equivalent to the b′ group, respectively. We have already developed an expression for the pair potential for such kind as in the section d.2 for the interaction in the plane of a and b groups for a D–D pair. The explicit expression for the pair potential is, thus, identically given by

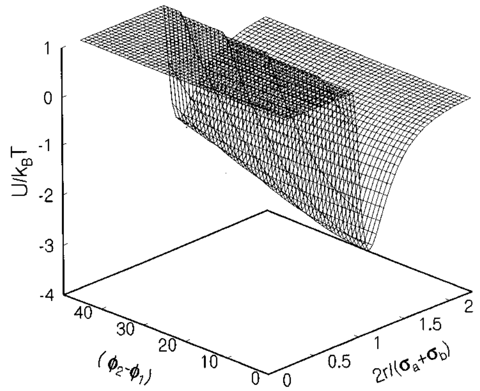

Figure 3. Calculated (from eq 10) effective pair potential profile for a pair of mirror-image isomers. Here, the pair potential is plotted against the difference in orientation, $\phi_2 - \phi_1$, as well as the separation between the chiral centers. The a and b groups have diameters of 1.4 and 8.24 Å, respectively. $\epsilon_a/k_B = 140$ K, and $\epsilon_b/k_B = 824$ K. $\beta = 110°$, and $\alpha = 0°$.

$$\frac{U}{k_BT} = \left(\frac{4}{T}\right)\sqrt{\frac{\epsilon_t\epsilon_t}{k_Bk_B}}\Bigg[\left(\frac{r}{\sigma_t} + \frac{1}{2}\cos(\theta_2-\alpha) - \frac{1}{2}\sin(\theta_2-\alpha)\times \cot(\theta_1-\alpha)\right)^{-12} - \left(\frac{r}{\sigma_t} + \frac{1}{2}\cos(\theta_2-\alpha) - \frac{1}{2}\sin(\theta_2-\alpha)\times \cot(\theta_1-\alpha)\right)^{-6}\Bigg] + \left(\frac{4}{T}\right)\sqrt{\frac{\epsilon_{b'}\epsilon_{b'}}{k_Bk_B}}\Bigg[\left(\frac{r}{\sigma_{b'}} - \frac{1}{2}\cos(\beta-\theta_1+\alpha) + \frac{1}{2}\sin(\beta-\theta_1+\alpha)\cot(\beta-\theta_2)\right)^{-12} - \left(\frac{r}{\sigma_{b'}} - \frac{1}{2}\cos(\beta-\theta_1+\alpha) + \frac{1}{2}\sin(\beta-\theta_1+\alpha)\times \cot(\beta-\theta_2)\right)^{-6}\Bigg] \quad (12)$$

Parameters have the same meaning as explained in Figure 2, but the respective parameters for the plane of t and b′ groups need to be considered here. The minimum of the above pair potential gives the value of θ_M. It may be reiterated again that the above expression is valid for both D–D and D–L pair cases, as explained earlier. Values for θ_M for five amphiphiles forming a helical morphology are shown in Table 1. These values of θ_M arises from bare chirality only.

III. Numerical Results

The pair potential profiles of the racemic modification (D–L pair) and the pure (L–L or D–D) enantiomers are depicted in Figures 3 and 4, respectively. We have presented here the plots for the pair potential in the plane of a and b groups (*efgh* plane). We indicated earlier that the main chiral interaction is expressed by the tilt (designated by ϕ_M) in this plane. However, the plots of the pair potential in the plane of t and b′ groups (*ijkl* plane) have the same features, except the magnitudes of θ_M ($\theta_M < \phi_M$). Here we present the plots with $\alpha = 0°$ only (plots with $\alpha = 20°$ have been provided in the Supporting Information.

As we increase the angle ($\phi_2 - \phi_1$), the o group (equivalent to the a group attached to C_2 in the *efgh* plane) is tilted toward the m group (equivalent to the a group attached to C_1) and the p group (equivalent to the b group attached to C_2) goes away from the n group (equivalent to the b group attached to C_1) (see Figure 2). As discussed in the Introduction, the molecules being in a compressed or gel state, should try to pack as efficiently as possible. This can be achieved by minimizing

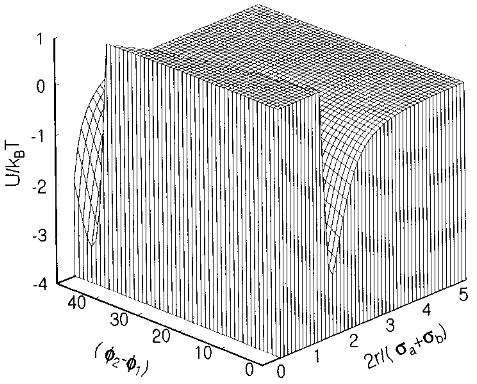

Figure 4. Calculated (from eq 11) effective pair potential profile for a pair of the same kind of enantiomers (D−D pair). Here, the pair potential is plotted against the difference in orientation $\phi_2 - \phi_1$ as well as the separation between the chiral centers from eq 11. The a and b groups have diameters 1.4 and 8.24 Å, respectively. $\epsilon_a/k_B = 140$ K, and $\epsilon_b/k_B = 824$ K, $\beta = 110°$, and $\alpha = 0°$.

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.

When we look into the molecular arrangement between the D−L pair (racemic modification), we see that, as the a group attached to the C_2 chiral center orients more toward 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 Figure 2). So, the orientation of the groups toward each other does not lead the packing arrangement to a more favorable state, and parallel arrangement is thereby favored. From Figure 3 it is seen that, as the value of $(\phi_2 - \phi_1)$ increases, the pair potential becomes increasingly unfavorable.

It is clear from Figures 3 and 4 that the effective pair potential profile of the D−D pair (Figure 4) is strikingly different from that of the D−L pair. Unlike the single minimum observed in the case of the D−L pair, there are two minima in the case of the D−D pair. One minimum is at $(\phi_2 - \phi_1) = 0°$ and at a small separation, while the other minimum is at $(\phi_2 - \phi_1) \simeq 45°$. But 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 closed packed state.

It has been pointed out earlier that the plane of the a and b groups and that of the t and b′ groups are nearly perpendicular. Consequently, one chiral molecule experiences two tilts in the two perpendicular planes and undergoes a twist relative to the adjacent chiral molecule. This favored twist propagates from molecule to molecule in the closed packed state, and the chiral centers follow a twisted path.

Thus, the present molecular study explains the experimental observation that the relative arrangement between a pair of mirror-image isomers (D−L pair) favors parallel alignment and generates a flat surface, while a pair of molecules of one kind of enantiomer (D−D or L−L) favors a twist between them, giving rise to helicity of the aggregate. The twist of the molecules is found to depend strongly on the relative sizes of the groups and the concentration of the amphiphiles. We have also shown that the major chiral interaction is expressed through the tilt angle ϕ_M, which is close to ∼45° in many cases.

IV. Relation between the Molecular Chirality and the Helical Morphology

It is clear from the above results that enantiomers of the same kind prefer a non-zero twist angle between them, while a pair of D and L molecules do not prefer to have any twist relative to each other in the closed packed state. It has been suggested earlier[6] that a favored twist from neighbor to neighbor may lead the whole aggregate to a twisted form. In order to correlate the preceeding observation with the molecular origin of the helical morphology, it is necessary to calculate the characteristic parameters of the helix that would be predicted by the molecular theory. If the adjacent chiral centers (of D−D or L−L pair) follow a circular helical path due to the twist between each molecule, then we can develop the exact geometric equation for the pitch as follows.

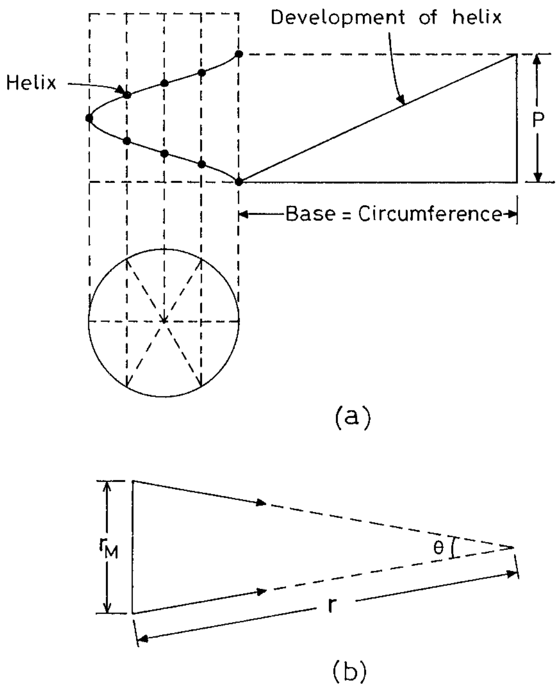

Figure 5. (a) Schematic diagram of a circular helix and a geometrical description of the pitch. The dotted lines indicate the projections of different points of the helix on a circle. (b) Schematic diagram showing the minimum separation between the adjacent chiral centers (r_M) and the tilt angle between the corresponding molecular directors (θ angle).

Note that the helix is a curve traced out by a point when it moves around a cylindrical surface and at the same time advances in the direction of its axis. The distance the point moves in the direction of its axis per revolution is called the pitch of the helix (*P*). From the present molecular consideration it is observed that the azimuthal angle of the molecular director (ϕ_M) is ≃45°. It is also confirmed from earlier studies that the edge line of the helical bilayer is parallel to the azimuthal direction of the molecular director.[22,24b] Consequently, the gradient angle of the helix is 45°. Using this value of the gradient angle of the helix, we can derive the following simple but general expression (see Figure 5a) for the pitch *P*.

$$\frac{P}{2\pi r} = \tan(45°) \tag{13}$$

so

$$P = 2\pi r \tag{14}$$

where *r* is the radius of the helix. Now, the tilt angle between the two adjacent directors is given by θ_M. The radius of the helix is thus related to the minimum separation between the adjacent molecules (r_M) by the following relation (see Figure 5b),

$$r_M = r \times \theta_M \tag{15}$$

Note that the above equation is valid because θ_M is small. We shall show later that the value of the tilt angle should be even smaller due to the elastic properties of the bilayer. Thus, the pitch, P, is given by the following expression:

$$P = \frac{2\pi r_M}{\theta_M} \tag{16}$$

Note that the angle θ_M here arises from the chiral interaction only. Consequently, if we give θ_M as the input in eq 16, it gives us the bare pitch. However, it should be pointed out that, if we assume that the chiral interaction as the only driving force for a helical structure, the situation is entirely unrealistic as there is no elastic force to resist the twist of the monolayer or bilayer. Neglect of this elastic force will certainly lead to a prediction of the twist which will be much higher than what is expected in a real situation. In fact, 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.[22] In bilayers, due to the elastic properties of the system, the constituent molecules try to minimize the θ_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 ϕ_M. In fact, de Gennes has pointed out long ago that the *natural twist* or the *microscopic twist* is always small and is on the molecular scale.[18]

The angle θ_M is in the plane containing the t and b′ groups. These groups constitute 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 favor the tilts of the t and the b′ groups. Thus, the *splay* of these groups is expected to be very small. Note that the main chiral interaction is expressed by the twist through the angle ϕ_M (in the plane of the a and b groups).

The elasticity of the bilayer tries to prevent the splay of the large t and b′ groups. Thus, the angle θ_M is expected to be further reduced. The equation for pitch indicates that the inclusion of this reduced value of θ_M (which we shall designate as the real θ or θ_{RM}) results in an increase of the pitch (a small change in θ can largely increase the pitch). Thus, the real pitch is expected to be larger than the bare pitch. We shall now attempt to calculate the real pitch by including the elastic free energy as well as the chiral free energy into the free energy functional of the bilayer. When the morphology of the helical aggregate is driven by the elastic as well as the chiral interactions, then we can write the total free energy of a helical aggregate as follows:

$$\frac{U_{\text{total}}}{k_B T} = \frac{U_{\text{chiral}}}{k_B T} + \frac{U_{\text{elastic}}}{k_B T} \tag{17}$$

The chiral interaction is expressed by the ϕ_M angle, and it has already been shown that at $\phi_M \simeq 45°$ the chiral interaction energy is minimized. At this minimal value of ϕ, we can write the θ dependence of the total free energy based on a harmonic approximation (neglecting the ϕ dependence of the elastic free energy term) as follows:

$$\frac{U_{\text{total}}}{k_B T} = \frac{1}{2}{\omega_{\text{chiral}}}^2(\theta - \theta_M)^2 + \frac{1}{2}{\omega_{\text{elastic}}}^2\theta^2 \tag{18}$$

Here, the ω terms are the corresponding force constants of the elastic and chiral interaction energies. It is again to be pointed out that all the U values are at the minimum of the chiral interaction energy (expressed by the tilt via the $\phi_M \simeq 45°$ angle).

By minimizing the free energy ($\partial U_{\text{total}}/\partial\theta = 0$) and designating the θ value at the minimum as θ_{RM}, we get

$$\theta_{RM} = \frac{{\omega_{\text{chiral}}}^2}{{\omega_{\text{chiral}}}^2 + {\omega_{\text{elastic}}}^2}\theta_M \tag{19}$$

Note that this θ_{RM} is the real θ angle, which we can use to estimate the real pitch using our geometrical expression for pitch derived earlier. We have estimated the ${\omega_{\text{chiral}}}^2$ from the dependence of the chiral interaction energy on the θ angle (see section II(e)) by Newton's forward difference method. The estimated value of ${\omega_{\text{chiral}}}^2$ is $\sim 3.83 \times 10^{-12}$ erg/rad^2. The ${\omega_{\text{elastic}}}^2$ is on the order of $\sim 2.0 \times 10^{-12}$ erg/rad^2. For the double-chain ammonium amphiphile we have $\theta_M = 1.0°$ (compound B in Table 1).[7c] This gives a value for $\theta_{RM} \simeq 0.0114$ rad. Using the real θ_{RM} angle in eq 16 and the value for r_M as 6.266 Å, we get the value of pitch as ~3470 Å. This value is near the value of the experimental pitch of ~5000 Å.[7c]

The ratio of the pitch and the diameter (d) of the helixes is predicted from Helfrich's theory as $P/d = \pi$. Our present consideration also gives the pitch to diameter ratio as π from eq 14.

As indicated in the Introduction, the amphiphilic molecules have an erect conformation in the helical state[4c] and approximately have an area per molecule close to the cross-sectional area of a CH_2 group of an alkyl chain.[28] 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 (Figure 4), a second minimum is observed at nearly zero twist angle at a 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.[7b,32] 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.[6c]

From the present study, it is clear that the sense of helix should be predetermined by the effective pair potential. The reason 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 the complete knowledge about 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. Indeed, it is indicated from the experimental studies that the sense of the helix is unique for the enantiomers[3,4b] and is strongly guided by the chirality of the monomers concerned. We have attempted to predict the sense of the chiral amphiphilic assemblies, on the basis of the effective pair potential description as described here. The results indicate that the effective pair potential description can successfully predict the senses in all the cases.[33]

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[33] Nandi, N.; Bagchi, B. *J. Phys. Chem.*, submitted.

V. Conclusion

Let us first summarize the main results of the present study. We have formulated 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 mirror-image isomers (D−L pair) favors parallel alignment, while a pair of molecules of one kind of enantiomer (D−D or L−L) favors a twist between them. The theory explains the experimentally observed characteristics of the helical aggregate, such as the pitch and the sense, which are found to depend on the sizes of the groups attached to the chiral center and also upon the concentration of amphiphile molecules. The present study provides a molecular understanding of the origin of the intrinsic bending force in chiral monolayers and bilayers.

It is instructive to compare the relevance of the present work with the more abstract continuum model theories.[23] In the latter, one includes only a chirality-induced driving force in the free energy to obtain the helical morphology. No information regarding the minimum in the interaction energy is necessary or even assumed. This scenario is different from that envisaged by Helfrich,[21,22] where a minimum at a given bending conformation has been assumed to be present to stabilize the helix. The present work, although it justifies the Ginzburg−Landau-type free energy functional based theories, is more close to the work of Helfrich.[21,22] Another important contribution of the present work is the explicit treatment of the racemic modification for the first time.

It has also been shown in the present study that in the helical bilayers, due to the elastic properties of the system, the constituent molecules try to minimize the θ_M angle. Our calculation is that the pitch increases rapidly as θ_M becomes smaller. It has been indicated that the elastic forces can significantly enhance the pitch of the helix from the value predicted by consideration of the chiral forces alone. The predicted real pitches are in good agreement with the experimental results. To the best of our knowledge, this aspect of helical morphology has not been discussed in the past.

It should also be mentioned that a full statistical thermodynamic treatment of the present problem is yet to be carried out. This and further microscopic studies of the morphological transitions in lipid bilayers can hopefully now be carried out with the *effective* pair potential calculated here. These are certainly worthwhile problems for future studies.

Acknowledgment. It is a pleasure to thank Prof. Santanu Bhattacharya for pointing out important references, helpful discussions, and also a critical reading of the manuscript. The authors are thankful to Prof. P. Balaram for pointing out some important references and helpful discussions. Discussions with Prof. Manju Bansal are gratefully acknowledged. This work was supported by financial assistance from the Department of Science and Technology, India.

Supporting Information Available: Theoretical formulation for the configuration when two larger groups (e.g., the b group in the plane of a and b groups) are approaching each other for a pair of D−D or L−L molecules; Figure 6. Molecular projection formulae for amphiphiles A−E; Figure 7. Effective pair potential profile for a pair of mirro image isomers (D−L pair) (from eq 10) with the variation in $\phi_2 - \phi_1$ as well as the separation between the chiral centers from eq 10. a and b groups have diameters 1.5 and 4.5 Å, respectively. $\epsilon_a/k_B = 150$ K, and $\epsilon_b/k_B = 450$ K. $\beta = 110°$, and $\alpha = 0°$; Figure 8. Effective pair potential profile for a pair of mirror-image isomers (D−L pair) (from eq 10) with the variation in $\phi_2 - \phi_1$ as well as the separation between the chiral centers from eq 10. a and b groups have diameters 1.5 and 4.5 Å, respectively. $\epsilon_a/k_B = 150$ K, and $\epsilon_b/K_B = 450$ K. $\beta = 110°$, and $\alpha = 20°$ plot a is with transparent grids, and plot b is with block grids.; Figure 9. Effective pair potential profile for a pair of the same kind of enantiomers (D−D pair) (from eq 11) with the variation in $\phi_2 - \phi_1$ as well as the separation between the chiral centers. a and b groups have diameters 1.5 and 4.5 Å, respectively. $\epsilon_a/k_B = 150$ K, and $\epsilon_b/k_B = 450$ K. $\beta = 110°$, and $\alpha = 0°$; Figure 10. Effective pair potential profile for a pair of the same kind of enantiomers (D−D pair) (from eq 11) with the variation in $\phi_2 - \phi_1$ as well as the separation between the chiral centers. a and b groups have diameters 1.5 and 4.5 Å, respectively. $\epsilon_a/k_B = 150$ K, and $\epsilon_b/k_B = 450$ K. $\beta = 110°$, and $\alpha = 0°$. This plot is a transparent grid representation of Figure 9; Figure 11. Pair potential profile for a pair of the same kind of enantiomers (D−D pair) with the variation in $\phi_2 - \phi_1$ as well as the separation between the chiral centers from eq 11. a and b groups have diameters 1.5 and 4.5 Å, respectively. $\epsilon_a/k_B = 150$ K, and $\epsilon_b/k_B = 450$ K. $\beta = 110°$, and $\alpha = 20°$. Plot a is with transparent grids, and plot b is with block grids; Figure 12. Pair potential profile for a pair of the same kind of enantiomers (D−D pair) with the variation in $\phi_2 - \phi_1$ as well as the separation between the chiral centers when the larger groups are approaching each other (from eq 20). a and b groups have diameters 1.5 and 4.5 Å, respectively. $\epsilon_a/k_B = 150$ K, and $\epsilon_b/k_B = 450$ K. $\beta = 110°$, and $\alpha = 0°$ (13 pages total). See any current masthead page for ordering and Internet access instructions.

JA9533757