

Calculation of Intermolecular Interaction Strengths in the $P_{\beta'}$ Phase in Lipid Bilayers

Implications for theoretical models

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ABSTRACT The existence of the $P_{\beta'}$ phase in certain lipid bilayers is evidence that molecular interactions between lipids are capable of producing unusual large-scale structures at or near biological conditions. The problem of identifying the specific intermolecular interactions responsible for the structures requires construction of theoretical models capable of clear predictions of the observable consequences of postulated intermolecular interactions. To this end we have carried out a twofold modeling effort aimed at understanding the ripple phase. First, we have performed

detailed numerical calculations of potential energies of interaction between pairs and triplets of lipid molecules having different chain tilt angles and relative vertical alignments. The calculations support the notion that chain tilting in the gel phase is a result of successive 3–5-Å displacements of neighboring molecules perpendicular to the bilayer plane rather than long-range cooperative chain tilting. Secondly, we have used these results as a guide to formulate a new lattice model for lipid bilayer condensed phases. The new model is less complex than our earlier model and it includes interac-

tions which are, based on the energy calculations, more likely to be responsible for the ripple phase. In a certain limit the model maps onto the chiral clock model, a model of much interest in condensed matter theory. In this limit the model exhibits a chain-tilted ordered phase followed by (as temperature increases) a modulated phase followed by a disordered phase. Within this limit we discuss the properties of the model and compare structures of the modulated phase exhibited by the model with experimental data for the $P_{\beta'}$ phase in lipid bilayers.

INTRODUCTION

Recent experimental studies of the $P_{\beta'}$ phase in phosphatidylcholine bilayers using scanning tunneling microscopy (Zasadzinski et al., 1988) have revealed new and unsuspected details of the periodic structure of this phase. In addition to striking high-resolution pictures of the ripples, Zasadzinski et al. find a basic wavelength of $\sim 130\text{\AA}$, an amplitude of $\sim 45\text{\AA}$, and an asymmetric profile to the waves. There are also defects and substructures with smaller wavelengths which appear in the micrographs. In order to clarify the molecular mechanism responsible for the appearance of the $P_{\beta'}$ phase, it is necessary to construct theoretical models which can clearly predict phase properties and structures as functions of the basic intermolecular interactions built into the model. This is a difficult problem in statistical mechanics because models tend to be either: (1) very simple so that rigorous calculation of phase diagrams is possible, but for which the phase diagrams do not apply well to complex systems; or (2) so complex that many mathematical approximations must be used to calculate the properties, clouding the predictive power of the model. In an attempt to adhere to the "simple model with rigorous analysis" approach, a theoretical model for $P_{\beta'}$ phase in lipid bilayers was previously presented by the authors (Pearce and Scott, 1982; Scott, 1984). In this model each lipid molecule in

each monolayer of a bilayer was represented by a rigid block in the shape of an "L," with the long part of the L denoting the hydrocarbon region and the short appendage of the L denoting the portion of the head group which protrudes over the chain volume. In the absence of significant hydrocarbon chain isomerization this is a reasonable portrait of a lipid molecule, and the number of state variables required to characterize the intermolecular interactions are reduced to two; an orientation variable, $\sigma = \pm 1$, describing the orientation of the L along a preferred axis, and a perpendicular displacement variable, $\tau = 0, \pm 1, \pm 2, \dots$. The molecules are confined to sites on a two-dimensional lattice and the L shape may point along only one of the axes of the lattice. The Hamiltonian for this model (to be referred to as the PS1 model) contains interactions which assign energies to a set of possible packing configurations of Ls in adjacent sites in the lattice. In the direction of the head group orientation the anisotropy leads to more complex interactions than in the other lattice direction, and in the former direction next-nearest neighbor interactions were included in the Hamiltonian. In a certain limit the model maps onto the axial next-nearest neighbor using model (ANNNI) and so in this limit the phase diagram could be obtained from that of the ANNNI model. However in the ANNNI model limit the modulated (ripple) phase only appears if the next-nearest neighbor (nnn) interaction

strength is nearly as strong as, and of the opposite sign as the nearest neighbor interaction. This seems unlikely for molecules interacting via 6–12 potentials which have very short range. Monte Carlo studies of the PS1 model suggest that a modulated phase exists at all temperatures above an ordered phase for a wide range of nnn strengths, but the data are difficult to interpret because of finite size effects and slow convergence characteristic of two-dimensional systems. Although there have been a number of theoretical studies of the ripple phase using thermodynamic Landau-Ginzburg approaches (Doniach, 1978; Marder et al., 1984; Carlson and Sethna, 1987), there have been no further statistical mechanical models proposed for the P_{β} phase.

For this reason, we have reexamined the basic intermolecular interactions involved in lipid molecular packing at temperatures below the main chain melting phase transition. The goal is to accurately numerically estimate the strengths of these interactions and to construct a model similar to the PS1 model, but which is easier to analyze accurately using tools of statistical mechanics. In the following section the method used to calculate intermolecular interactions is described, and the results are presented. In the third section the numerical results will be used to construct a new lattice model for lipid bilayers below the chain melting phase transition. In the final section we study the phase properties of the new model in a limiting case in which it maps onto another model for which the phase properties are fairly well known. The properties of the model in this limit may be compared qualitatively to lipid bilayers in the region near the $L_{\beta} \rightarrow P_{\beta}$ phase transition.

Calculation of intermolecular interactions

The procedure used to calculate intermolecular interaction strengths between lipid molecules is very straightforward. Coordinates for the positions of all nonhydrogen atoms in two or more lipid molecules were generated for a number of different intermolecular distances, relative positions perpendicular to the bilayer plane, head group orientation, and chain tilt. Interaction energies were then calculated between all pairs of atoms on all different molecules. We first describe the generation of the molecular co-ordinates, and then the energy calculation.

The lipid molecular coordinates were produced by the same procedure used in earlier Monte Carlo simulations of lipid chains (Scott, 1977, 1986) and of the lipid–water interface (Hussin and Scott, 1987). The coordinates of the chain carbons were derived by a bond-by-bond series of steps using successive rotation matrices. Although the procedure can generate chains in any isomeric state only all-*trans* chains were considered. Coordinates of the non-

hydrogen atoms in the head group were simply entered directly using a configuration in which the head group dipolar alignment points about 17° above the interface plane (Hauser et al., 1981). The rotation matrix approach for chain coordinates allows for easy variation of such quantities as the inter chain distances, the chain tilt angles, and the relative vertical displacements of the chains. In this way it was possible to examine a variety of different intermolecular packing arrangements. *Gauche* rotations were not considered in the calculations, although data suggest an average of ~1–2 rotations per molecule in the P_{β} phase (Levin and Bush, 1981). This is because we believe that the primary driving force behind the phase transitions between ordered phases in lipid bilayers is packing competition between relatively rigid molecules. *Gauche* rotations will indeed appear where there are voids in the system large enough to accommodate them (such as near chain termini where the different depths of the 1 and 2 chains leave free volume), but they only drive the main lipid chain melting transition.

Once a configuration of two or more lipids is generated the intermolecular energies between all pairs of molecules are calculated. This is done by summing 1-6-12 pair potentials over all pairs of atoms in the hydrocarbon region, and between all pairs of head group atoms. The pair potential has the form:

$$V(r) = \epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right] + \frac{qq'}{r}, \quad (1)$$

where ϵ is the strength of the interaction, σ is the relative van der Waals radius for the interacting pair, and q, q' are the atomic charges, if any. In Table 1 we list the values of $q, \epsilon,$ and σ used for the calculations. When calculating interactions between two different molecules effective ϵ and σ parameters are: $\epsilon = \sqrt{\epsilon_1 \epsilon_2}, \sigma = (\sigma_1 + \sigma_2)/2$. It is important to point out that the 6–12 parameters in Table 1 are, whenever possible, obtained from optimized potential functions in which the parameters ϵ and σ have been carefully chosen to fit experimental densities and heats of vaporization for *N*-alkanes, based upon Monte Carlo simulations (Jorgensen, 1982). These are not adjusted

TABLE 1 6–12 parameters used in energy calculations

Molecule	σ	ϵ
	Å	cal/m
Methylene	3.98	457*
Terminal methyl	3.86	725*
Oxygen (all)	4.00	230 [†]
Amine nitrogen	2.77	160 [†]
Phosphate phosphorus	3.80	200 (est)
Glycerol carbon	3.80	50*
Carbonyl carbon	3.80	100*

*Jorgensen (1982). [†]Rosky et al. (1979).

during any of the calculations reported. As shown in Table 1 the head group zwitterions are treated as point charges of magnitude $\sim 0.5 e$ located at the P and N atomic sites. Monte Carlo studies of the lipid-water interface suggest that the effect of smearing the charges out over more of the head group atoms is very small (Hussin and Scott, 1987). The interaction strengths were calculated between chains and between head groups, but not between chains and head groups. Except in cases where one lipid is displaced by 6\AA or more along the CH_2 chains, head group-chain interactions are small and nearly constant, so they do not affect the comparative intent of the calculations. We also neglect interactions with water molecules, and any indirect water-mediated interactions between head groups. This should not affect the comparative conclusions either, since we are interested only in fully hydrated systems in which each head group has its full complement of bound water in all the configurations under examination. Further numerical evidence that water-related interactions need not be included in the present calculations is found in numerical simulations of the lipid-water interface mentioned above (Hussin and Scott, 1987). These Monte Carlo calculations suggest that the distribution and orientation of the water molecules near phosphatidylcholine head groups does not change appreciably when the lipid head group orientations and positions are altered by small amounts. Therefore interactions involving and mediated by water, although critical to the stability of the basic bilayer structure, are unaltered during the pretransition in these systems, and do not contribute to the mechanism which drives the pretransition.

To illustrate the configurations for which the energy calculations were carried out we show in Figs. 1 and 2 pairs of full dipalmitoylphosphatidylcholine (DPPC) molecules in all-*trans* configurations and in different juxtapositions: Fig. 1 shows two molecules with untilted chains, interchain separation of 4.85\AA , and a relative vertical displacement of 3\AA , and Fig. 2 shows two molecules with a 5.60\AA separation, but with chains tilted by 30° ($5.60 \cos 30^\circ = 4.85$). Results of the energy computations are shown in Fig. 3 and in Tables 2 and 3. Fig. 3 plots the interaction energies against relative vertical molecular displacement for all-*trans* chains with interchain separation of 4.85\AA , showing total energy as well as the chain and head group contributions. When there is no relative displacement steric contacts in the head group region produce strong repulsive forces which drive the energy up, and the minimum energy of this set of configurations occurs for a relative displacement of 3\AA . For comparison the energy calculated for two molecules with head group separation 5.60\AA and 30° chain tilt (Fig. 2) is shown in Table 2. This value, -12.12 kcal/m , is slightly lower than the minimum energy in Fig. 3. However, the

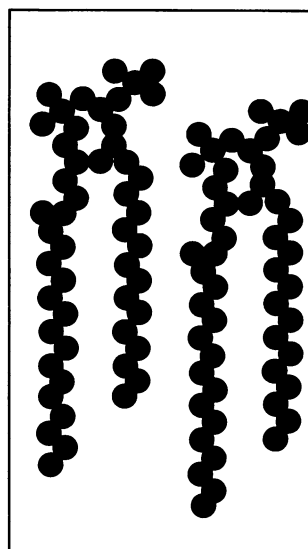


FIGURE 1 Two DPPC molecules as generated by the computer program described in the text. The interchain separation is 4.85\AA and there is a 3\AA relative vertical displacement between the molecules.

calculations in Fig. 3 only considered one monolayer so that as chains are displaced there is a loss of energy due to loss of near-neighbor methylenes. This energy is likely to be compensated in bilayers by methylenes from chains in the other monolayer. Therefore there should be little or no change in chain van der Waals energy for relatively small displacements. In Table 3 we give van der Waals energies for various vertical displacements using chain energies

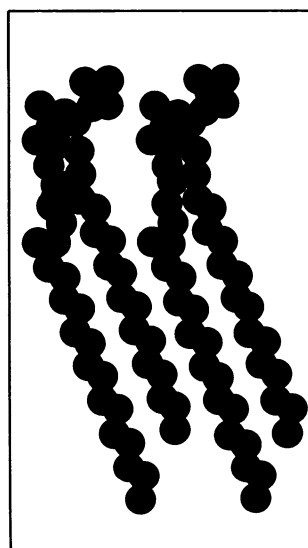


FIGURE 2 Same as Fig. 1, except the interchain separation is 5.60\AA and the chains are tilted by 30° .

TABLE 2 Close packing energy: 30° chain tilt

No relative molecular displacement	
Interhead group separation	5.6 Å
(5.6 * cos(30) 4.85)	
Chain energy	-11,636 cal/m
Head group energy	-479 cal/m
Total energy	-12,115 cal/m

calculated for the zero displacement case. In this case the lowest energy occurs for the 3 Å displacement, and now it is lower than the tilted chain energy (-12.46 kcal/m). An additional significant point which emerged from energy calculations for groups of three or more lipid molecules is that in all cases considered next nearest neighbor interactions are at least two orders of magnitude smaller than the nearest neighbor energies. The calculations we present do not represent a thorough search of all possible lipid pair configurations. However, for a system of rigid chains in a periodic lattice we have thoroughly sampled the energy states for perpendicular molecular displacement, chain tilt, and head group orientation along one lattice axis. In a bilayer at low temperature the only other intermolecular configurations which may frequently occur involve molecular long axis rotation (which preserves the crystal structure) or phonon-like in-plane lattice vibrational energies. Neither of these mechanisms appear to play a significant role in the perpendicular displacements required in the ripple phase. The data presented in the tables are indicative of the relative strengths of the interactions which are presumed to be important in the establishment of the ripple phase.

The next step is to construct theoretical models based upon the data, and to compare the model properties with experiment. We take up this problem in the following section. First, we summarize the numerical results. The salient points are firstly, the optimal configuration of a pair of all-*trans* DPPC molecules is that of Fig. 1: chains separated by 4.85 Å and head groups displaced vertically

TABLE 3 Close packing energy: chain energies fixed

Relative molecular displacement	Energy per molecule (cal/m)	
	Chains only	Chains plus head group
Å		cal/m
0	-12,038	-8,669
1	-12,038	-11,081
2	-12,038	-12,356
3	-12,038	-12,458
4	-12,038	-12,347
5	-12,038	-12,259
6	-12,038	-12,197
12	-12,038	-12,062

Chain energies set at zero displacement value.

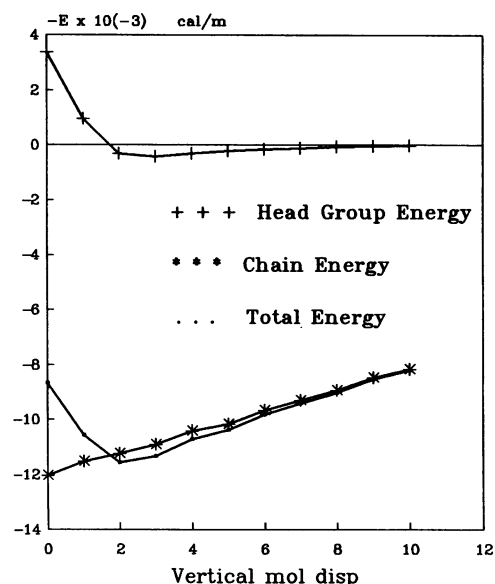


FIGURE 3 Calculated van der Waals energies between pairs of molecules as a function of the molecular displacement (*mol disp*) to the bilayer plane. Head group and chain contributions as well as the total energy are shown.

by 3–5 Å (the upper limit of 5 Å reflects the fact that bound water molecules should effectively increase the sizes of the head groups so that greater vertical displacements may be necessary). The observed chain tilt in the gel phase is reproduced by this configuration (the tilt angle θ can be calculated from $\tan \theta = \text{vertical displacement} / (2 \times \text{chain separation})$, and is 17° for a 3 Å displacement and 27° for a 5 Å displacement). This mechanism for producing chain tilt is much more natural than a long-range cooperative rearrangement suggested by Fig. 2 and is consistent with an earlier calculation of Hawton and Keeler (1986) using an approximate free energy minimization scheme. Secondly, the interchain interaction is effectively confined to nearest neighbors.

A theoretical model

The numerical calculations described above may be used to critically examine existing theoretical models for lipid bilayer condensed phases which are based upon microscopic interactions. Any microscopic model for these phases should be consistent with the above numerical calculations and should contain interactions that depict the packing competition which arises from anisotropic molecules in a low-temperature condensed phase. The PS1 model is only partially consistent with the numerical results in that the chain-tilted ordered state is produced in the PS1 model by molecular packing like that shown in

Fig. 1. However the PS1 model relied upon significant next-nearest neighbor interactions to produce a modulated (ripple) phase, and these interactions were shown above to be extremely weak. An additional difficulty associated with the PS1 model is that its complex Hamiltonian which couples head group orientation and vertical displacements has made definitive analysis of the model by analytic means very difficult.

The data presented above may now be used to derive a new lattice model for the ripple phase. The new model, which is defined in Table 4, retains the state variables σ (head group orientation) and τ (vertical displacement—renamed n in Table 4). The new model also preserves the chain tilted low energy state of the PS1 model. The major differences are that the new model contains only nearest neighbor interactions, and that the new model has a simpler mathematical form than the PS1 model. Table 4 shows the Hamiltonian for the model and relates energies of the Hamiltonian to lipid molecule pair-packing configurations. There is an anisotropy in the interactions along rows (by definition the direction of head group orientation) defined by the parameter Δ and the field term h . The interactions between rows (the J_2 term) depends only upon relative vertical displacements of neighboring mole-

cules in adjacent rows. There are four parameters in the new model: J_1 ($=J_2$), h , Δ , and q . We have used these parameters to order the energy states of the model Hamiltonian (Table 4) to fit as closely as possible to the calculated energies described in the previous section. The most important energies which the model must reproduce are the ground state and the low-level excited states. Fitting these values requires that Δ is close to 1 and q is between 5 and 10, but for this range of Δ and q it is possible to pick J_1 and h to fit the lowest two energies precisely, and some of the other energies with less accuracy. In Table 4 we show energies calculated from the model Hamiltonian for pairs of lipids with $q = 8$ and $\Delta = 0.95$, which fixes $J_1 = -12.45$ kcal/m and $h = -85$ cal/m. The numerical calculation of pair energies of the higher energy configurations is very ambiguous because in these arrangements there is likely to be some chain folding or other rearrangement which reduces the packing energy. The calculated energy for the third state differs from that of the model by a factor of ~ 12 . This state involves large-amplitude vertical intermolecular displacements. It is possible that neglected effects such as hydrophobicity makes this state less likely. In any case this state is *not* important very near the boundary between the ordered phase and the modulated phase. Farther from this boundary it may be more significant.

The next step in the modeling process is to determine the properties predicted by the new model and to compare these with current experimental data. In the next section we show that it is possible to obtain an approximate phase diagram for the model by considering a limiting case for which the model maps onto another model which has been studied by condensed matter theorists. We then discuss the relation of the model to experimental data in this limit.

TABLE 4 Chiral spin-Potts model for the ripple phase

State variables: Head group orientation: $\sigma = +1 \rightarrow \uparrow$ $\sigma = -1 \rightarrow \downarrow$	
Displacement \perp to bilayer: $n = 0, \pm 1, \pm 2, \dots \pm q - 1$	
Hamiltonian (two-dimensional square lattice; index i labels axis of head group orientation)	
$H = \sum_{ij} J_1 \cos \left[\frac{2\pi}{q} \left(n_{i+1,j} - n_{i,j} + \frac{\Delta}{2} (\sigma_{i+1,j} + \sigma_{i,j}) \right) \right]$ $+ \sum_{ij} J_2 \cos \left[\frac{2\pi}{q} (n_{i,j+1} - n_{i,j}) \right] + \sum_{ij} h \sigma_{i+1,j} \sigma_{i,j}$	
$J_1 = J_2 = -12.46$ kcal/m $h = -85$ cal/m $\Delta = 0.95$ $q = 8$	

State	Model energy	Computed energy
		<i>kcal/m</i>
$n_{i+1,j} - n_{i,j} = \pm 1$ $\sigma_{i+1,j} = \sigma_{i,j} = \mp 1$	$\uparrow \uparrow$ or $\uparrow \downarrow$	-12.46
$n_{i+1,j} - n_{i,j} = 0$ $\sigma_{i+1,j} = -\sigma_{i,j}$	$\uparrow \downarrow$ or $\downarrow \downarrow$	-12.28
$n_{i+1,j} - n_{i,j} = \pm 2$ $\sigma_{i+1,j} = \sigma_{i,j} = \mp 2$	$\uparrow \uparrow$ or $\uparrow \downarrow$	-0.85
$n_{i+1,j} = n_{i,j}$ $\sigma_{i+1,j} = \sigma_{i,j}$	$\uparrow \uparrow$ or $\uparrow \downarrow$	-0.92
$n_{i+1,j} - n_{i,j} = \pm 1$ $\sigma_{i+1,j} = -\sigma_{i,j}$	$\uparrow \downarrow$ or $\downarrow \downarrow$	-0.87
		$>0^*$

*Numerical calculations ambiguous due to possible chain folding or reorientation.

The chiral clock model limit

The ultimate test of the model is comparison with experiment. In the present case this requires calculating the phase diagram of the model and the detailed structure of any ripplelike phase which may appear. Such calculations for models which are not spatially homogeneous are very laborious (for a review, see Selke [1988]). This effort is presently underway, and will be reported elsewhere. In this section we show that in a simple approximation the model of Table 4 may be mapped onto another statistical mechanical model for which the details of the phase diagram are fairly well known. To this end, consider the Hamiltonian of Table 4. Suppose that all the head group orientation variables σ_{ij} are all fixed at the same value, which we take without loss of generality to be $+1$ (this is

equivalent to perfect head group alignment). Then the Hamiltonian may be written as:

$$H = \sum_{i,j} J_1 \cos\left(\frac{2\pi}{q}(n_{i+1,j} - n_{i,j} + \Delta)\right) + \sum_{i,j} J_2 \cos\left(\frac{2\pi}{q}(n_{i,j+1} - n_{i,j})\right) + \text{constant terms.} \quad (2)$$

This is the Hamiltonian of the q state Chiral Clock (or Potts) model (Ostlund, 1981). The phase diagram for this model has been determined by Ostlund (1981) and is shown in Fig. 4. As can be seen in Figure 4 the model has two ground states. For $\Delta \leq 1/2$ the ground state occurs when all the n_{ij} are equal (corresponding to a flat bilayer with no chain tilt). For $\Delta \geq 1/2$ the ground state has "chiral order," favoring $n_{i+1,j} - n_{i,j} = -1$ and $n_{i,j+1} - n_{i,j} = 0$. This latter ground state corresponds precisely to a flat bilayer with tilted chains, so the part of Fig. 4 that applies to PC bilayers is that with $\Delta \geq 1/2$.

For all values of Δ the ground state undergoes a phase transition into a state with spatially modulated order at some temperature. The modulated phase structure has been analyzed using low temperature series expansion techniques for $q = 4$ and $q = 10$ (Yeomans, 1984). In this approximation the chiral ground state breaks up into a series of periodic structures consisting of chiral order followed by a pair of sites with the same n_{ij} followed by more chiral order. As the temperature increases these states break up into longer wavelength periodic structures until the upper limit of the modulated region is reached. In two-dimensional lattice models there is no true long-range order. The signal of two-dimensional "order" is correlations which decay algebraically rather than exponentially as in a disordered phase.

In the lipid interpretation the variables n_{ij} are vertical

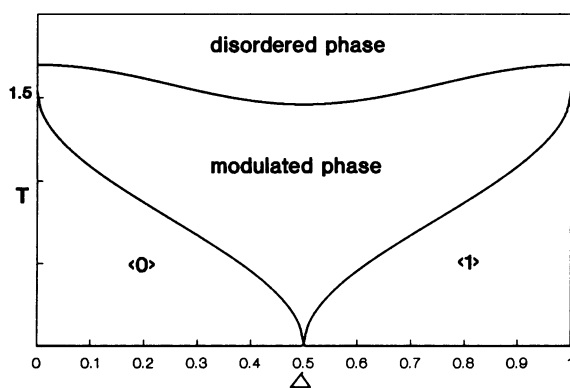


FIGURE 4 Schematic phase diagram of the q -state chiral clock model as calculated by Ostlund (1981) for $q \geq 5$. The symbols are: $\langle 1 \rangle$ labels the chiral, or tilted chain phase; $\langle 0 \rangle$ labels the flat nontilted chain phase (see text). The modulated phase is characterized by a complex series of periodic structures (Yeomans, 1985).

displacements, so the periodic structures resemble sequences of tilted chains interrupted by regions of zero tilt, where the n_{ij} for two adjacent sites take the same value. This structure resembles a periodic staircase with the flat portions narrower than the step height. It is noteworthy that in this picture, as in the micrographs of Zasadzinski et al. (1988) the structures are asymmetric rather than perfectly trigonometric in shape. In general, the larger q is, the longer is the wavelength of the structures (Yeomans, 1984). The major difference between the modulated structures of the chiral clock model and the P_B phase is that the ripples are able to turn back down like waves, rather than always go upward like a staircase. Of course, in our approximation, all the head groups are forced to remain perfectly parallel. Since the pair energy of two lipids at the same vertical position is greatly reduced when the head groups are antiparallel (Table 4, the second state vs. the fourth state) it is tempting to conjecture that inclusion of the orientation variables $\sigma_{i,j}$ will insert into the Hamiltonian a mechanism by which the staircase may reverse directions at the flat parts of the steps. Efforts to determine the validity of this conjecture, as well as other properties of the PS2 model, are in progress. The picture of the ripple phase which emerges from this preliminary analysis of the model is one of a chain-tilted low temperature phase followed by a phase characterized by periodic arrays of steplike structures. This is qualitatively similar to the experimental picture seen in the scanning tunnelling microscopy work of Zasadzinski et al. (1988).

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