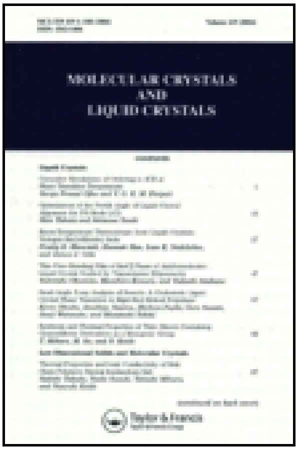

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Landau Phenomenological Theory of One and Two Component Phospholipid Bilayers

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A simple phenomenological model for the excess water phospholipid bilayer main phase transition is developed. The dependence of transition temperature and latent heat on chain length is calculated. Phase diagrams for binary mixtures with components differing in chain length by 2, 4 and 6 carbons are determined. It is found that there is phase separation in the gel state for a chain length difference of 6 carbons. Comparison of theory and experiment is discussed.

I INTRODUCTION

Starting with an article by Nagle,[1] a fairly large number of papers dealing with the theory of the phospholipid bilayer main phase transitions have appeared.[1–21] These works include a great diversity of approaches to the problem. A review of all these theoretical developments is beyond the scope of this paper. However, a few general observations are relevant. First, all of the authors view the main phase transition as a chain melting phenomena similar, to a degree, to the melting of a hydrocarbon crystal. Second, the data considered for model verification are those measured for the phosphatidylcholine (PC) series. This is not surprising in that the best and most complete data set is for this series. Third, none of the theories dealing with two component systems is free of adjustable parameters. Fourth, all of the theories have a degree of success in describing the thermodynamic properties of the PC main phase transition. This last point is interesting in view of the number of different effects that are included in some models and ignored in others.

In light of the degeneracy in successful theoretical approaches it seems worthwhile to inquire as to what is the simplest theory that can correctly describe the PC main phase transition. In this paper a simple phenomenological model is developed. In the spirit of a Landau phenomenology,[22] reasonable analytical forms of the various contributions to the free energy are chosen without reference to detailed model mechanisms. The magnitudes of these contributions are left as free parameters to be ultimately fit from data. The quantities calculated are those for the excess water multilamellar dispersion case. The transition temperatures and latent heats as a function of chain length, L, and the binary mixture phase diagrams are determined.

The fitting procedure necessarily reduces the predictive power of the phenomenology. However the model does correctly predict a variety of features which are independent of the fitting process. For the single component systems, the model yields the correct curvature of the $T_c(L)$ curve where T_c is the main transition temperature. The model also correctly predicts the slope of the $\Delta H(L)$ curve, where ΔH is the latent heat of the main transition. A single value of the parameter controlling the width of the binary mixture phase diagrams produces reasonably accurate phase diagrams for three different mixtures: DMPC/DPPC, DMPC/DSPC and DLPC/DSPC. Here DLPC is dilauroyl-PC, DMPC is dimyristoyl-PC, DPPC is dipalmitoyl-PC and DSPC is distearoyl-PC. It also correctly predicts that the gel phase in the DMPC/DSPC mixture is a single phase but that the gel phase in the DLPC/DSPC mixture is actually two distinct coexisting phases over a wide range of concentrations.

II PHENOMENOLOGICAL MODEL

The first step in the development of a phenomenology is the identification of the relevant degrees of freedom. The most important degrees of freedom, and the only ones that have been treated in a truly microscopic fashion, are the chain conformational degrees of freedom. The translational degrees of freedom have been taken into account in past work by consideration of two extensive thermodynamic variables, the density and the area per polar head group. Most of the change in entropy at the main phase transition is associated with the conformational degrees of freedom. On the other hand most of the change in energy at the phase transition is due to the small change in density. The 500 cal/mole energy associated with gauche bonds does not account for even one half the latent heat of the transition.[20] The area per polar head group undergoes a large discontinuity at the phase transition. However, it is not clear that this variable has an essential role. In the gel state the chains are nearly fully extended while in the fluid state they are appreciably shortened by the gauche bonds. Therefore, at the transition the bilayer will necessarily thin. Obviously, to avoid a drastic change in density the area per head group must change. In contrast to the conformational degrees of freedom and the density, the area per head group can be considred to give only a minor contribution to the thermodynamic properties of the phase transition. This is the point of view adopted in this paper. A contrasting point of view is developed in Ref. (19).

Since the conformational degrees of freedom and the density give the main contributions to the thermodynamic properties of the system we consider them in more detail. We choose as the order parameter, S, the fraction of bonds in the chain tails which are gauche. At first sight it would appear necessary to consider such an order parameter as a function of distance from the polar head group or position along the chain. However there are theoretical[3] and experimental[23] considerations which support the neglect of this possibility. The theoretical argument that the gauche bond density is spatially uniform except in the region of the bilayer midplane was originally given by DeGennes.[3] It is outlined in the appendix.

According to a wealth of experimental data S is small and only weakly temperature dependent in the gel phase. We follow other authors and ignore the small pretransition. We take the point of view that S is non-zero in the gel phase because of a constraint imposed by the organization of the polar head group in the plane. This constraint is also viewed as affecting the density in the gel phase—a point which will be discussed further below. The constraint prevents S from becoming less than some S_g where $S_g \ll 1$. We assume that the free energy F, is analytic for $S > S_g$ and that $F \to \infty$ for $S < S_g$. Under conditions that will be outlined below, there is a minimum in F at $S = S_g$ corresponding to the gel state. For the sake of simplicity we do not consider any dependence of S_g on chain length.

The free energy should properly be considered a function of the density, ρ, as well as of S. An experimental study of the density as a function of temperature[20] has revealed nearly universal behavior for $L = 14$, 16 and 18 in the fluid state. This suggests that in the fluid phase the density adjusts to accommodate the conformational state of the system as specified by S. This contrasts with the situation in the gel state. In the gel state the density depends markedly on chain length. We view this as being the other effect of the constraint imposed by the organization of the surface plane of polar head groups. Consequently the density of the gel phase will approach that of extended chain polyethylene in the limit of large L. The free energy will be a minimum with respect to ρ at a value $\rho(S, L)$ depending on conformational order and chain length.

We can make some general observations on the form that the free energy will take with the density replaced by $\rho(S, L)$. At fixed L the free energy as a function of S will, in general, have two minima: one at $S = S_g$ the other at a value of S typical of the fluid state—about 0.2–0.4. The minima at S_g is insured as long as $\partial F/\partial S|_{S=S_g} > 0$ since $F \to \infty$ for $S < S_g$. This gel minimum is of the cusp type. It serves as a convenient model for the actual behavior which is smoother. The cusp gel minimum is similar to that encountered in Nagle's exactly solvable model.[1]

The simplest phenomenological form of F having the properties mentioned above is:

$$\begin{aligned} F(S)/RT &= AS - \tfrac{1}{2}BS^2 + \tfrac{1}{3}CS^3 \quad && S > S_g \\ &= \infty && S < S_g \end{aligned} \tag{1}$$

Here, R is the gas constant and T is the temperature. We consider F to be the free energy per mole of chains. The parameters A, B and C are greater than zero. They are functions of T and L. In the discussion below we have in mind eventually letting S_g tend to zero. This has little effect since S_g is small and the cubic polynomial is analytic at $S = 0$. The cusp like minimum at $S = S_g$ insures that the value of S in the gel phase is only weakly temperature dependent. It should be noted that the phenomenological model defined by Eq. (1) is different in form from that of Ref. (19).

In order for the model to have some predictive power reasonable choices for $A(T, L)$, $B(T, L)$ and $C(T, L)$ must be made. We consider energetic and entropic contributions to these coefficients separately.

Entropic contribution

Temperature independent contributions to Eq. (1) are entropic in nature. It is customary to estimate the amount of entropy change which is due to a volume change by using the formula derived from a Maxwell relation:

$$\Delta S = \frac{\alpha}{\beta}\Delta V \tag{2}$$

Here α is the thermal expansivity and β is the compressibility of the fluid phase and ΔV is the volume change at the phase transition. For the PC series the change in entropy estimated from this formula is less than 25% of that observed. This supports the accepted point of view that most of the entropy change at the main phase transition is due to the conformational disordering of the chain tails of the lipid molecules. The problem is to calculate the number of conformations available to the chains having specified a set number of gauche bonds. We can estimate the number of configurations by considering the result appropriate to a dense isotropic system of chains. This result may be derived by following Flory.[24] Let the energy difference between the trans and gauche states be ε. Assume that the energy associated with a left-handed gauche bond follow by a right-handed gauche bond is infinite (the pentane exclusion). Then the free energy, F, per CH_2 group of a long chain is easily found by the transfer matrix method to be

$$-\beta F = \ln \tfrac{1}{2} + \ln\left(1 + a + \sqrt{(1 + a)^2 + 4a}\right) \tag{3}$$

where $a = e^{-\beta\varepsilon}$ and β is the reciprocal of the product of Boltzmann's constant and the temperature. The corresponding internal energy E may be calculated as $\beta E = \beta\partial(\beta F)\partial\beta$:

$$\beta E = \frac{\beta\varepsilon}{2}\left(1 + \frac{a - 1}{\sqrt{(1 + a)^2 + 4a}}\right) \tag{4}$$

The entropy per monomer, $\mathcal{S}$, is therefore

$$\begin{aligned}\mathcal{S} = \ln \tfrac{1}{2} &+ \ln\left(1 + a + \sqrt{(1 + a)^2 + 4a}\right) \\ &+ (-\ln a)\tfrac{1}{2}\left(1 + \frac{a - 1}{\sqrt{(1 + a)^2 + 4a}}\right)\end{aligned} \tag{5}$$

The internal energy E may also be written as $E = \varepsilon S$, where S is the fraction of bonds which are gauche. We use Eq. (4) to get a as a function of S and then eliminate a from Eq. (5) in favor of S to obtain

$$\begin{aligned}\mathcal{S} &= (1 + x)\ln\left(\frac{1 - x + \sqrt{2x^2 + 2}}{1 + x}\right) \\ &\quad + \tfrac{1}{2}(1 - x)\ln\left(\frac{1 + x + \sqrt{2x^2 + 2}}{1 - x}\right)\end{aligned} \tag{6}$$

where $x = 1 - 2S$. The number of configurations available to the chain corresponding to a given value of S is just $\exp(\mathcal{S})$. As can readily be seen from Eq. (6) the chief effect of the pentane exclusion is that the largest number of configurations corresponds to $S = \frac{1}{2}$ rather than $S = \frac{2}{3}$ as is the case when it is not taken into account.

We expect that Eq. (6) provides a reasonable guide to the number of configurations available in lipid bilayers. Unfortunately it is not in the form of Eq. (1). Furthermore it is not analytic at $S = 0$. This does not present a fundamental obstacle since the physically interesting region is $S_g < S < 0.5$.

The easiest way to circumvent these problems that is in the spirit of the phenomenological approach is to expand the RHS of Eq. (6) about its maximum point, $S = \frac{1}{2}$ in a Taylor series. In order to avoid any terms higher in S than 3rd order, in accordance with Eq. (1), we discard all terms in $(S - \frac{1}{2})$ of fourth order and higher. The result is

$$\mathscr{S}(S) = -\frac{\sqrt{2}}{2}(1 - 2S)^2 + \ln(1 + \sqrt{2}) \tag{7}$$

This form allows the relaxation: $S_g \to 0$. To completely specify the conformational entropy it is only necessary to multiply by the number of dihedral angles per chain. In the case of a chain free at both ends there are $L - 3$ dihedral angles. In the phospholipid case the chain is attached to the polar head group. The number of dihedral angles contributing to the entropy is $L - 2$. The conformational entropy in units of R is therefore

$$S = (L - 2)2\sqrt{2}(S - S^2) \tag{8}$$

We have omitted the constant term because it does not affect any of the calculations below.

Energetic contributions

Energetic contributions to the coefficients A, B and C are inversely proportional to RT. As mentioned in the introduction, there are two contributions to the energy. The first is simply the energy associated with the trans-gauche energy difference:

$$E_1 = E_0(L - 3)S \tag{9}$$

where E_0 is 500 cal/mole. The second contribution is the larger of the two. It is due to the assumed change in the optimal value of the density with changes in S. We expect that there will be a rapid change in this density as the first few gauche bonds are introduced and a negligible change once a sufficient number are present. To faithfully model this type of situation the associated energy E_2 would have to become independent of S for $S \geq 0.3$ (liquid densities). Obviously a cubic polynomial does not have this behavior. The closest approximation to this type of behavior that can be achieved with a cubic polynomial is an expression of the form:

$$E_2 \propto W(S - S_0)^2 - Z(S - S_0)^3 - WS_0^2 - ZS_0^3 \tag{10}$$

This form has the desired leveling off behavior for $S \lesssim S_0$. In order to keep the number of parameters in the model at an absolute minimum we choose a specific value for S_0, $S_0 = 0.39$. This is the value predicted for S at the melting point of Extended Chain Conformation (ECC) polyethylene, approximately 141°C.[25] This value is derived if only the contributions of Eq. (8) and Eq. (9) to the free energy in the limit of large L are considered.

Because there is no linear term in Eq. (10) for $S \sim S_0$ the result is not modified if the contribution of Eq. (10) is also included in the free energy. Therefore, in the limit of large L, the model will produce the correct value of S at the melting point of polyethylene. This feature enables us to consider the melting of ECC polyethylene to be the $L \to \infty$ limit of the model. This point will be developed further below.

It remains to specify the L dependence of E_2. The most important consideration in developing the model specification is the observation that the density of the gel phase is not a universal function of the temperature. The gel phase density for $L = 12$ is less than that for $L = 14$ which is in turn less than that for $L = 16$.[20] This data is consistent with the view that the organization of the polar head group plane tends to prevent the gel phase from attaining its optimal configuration.

If it were not for this effect E_2 could be taken proportional to L since we calculate quantities per mole of chains. However the energy E_2 has its origins in the changes in density. To reflect the dependence of the gel phase density on L we must let E_2/L be an increasing function of L which approaches a constant for large L. In the spirit of the phenomenological approach we choose E_2 to be a linear function of L.

$$E_2 = (L - L^*)[W(S - 0.39)^2 - Z(S - 0.39)^3 - W(0.39)^2 - Z(0.39)^3] \tag{11}$$

This form has the desired functional dependence on L. Eq. (11) introduces three parameters: L^*, W and Z to the model. As will be seen below one of them can be eliminated by appeal to the melting of polyethylene as the $L \to \infty$ limit of the model.

III SOLUTION OF MODEL AND PARAMETER FITTING

The full model free energy is obtained by combining Eqs. (8), (9) and (11). The free energy per mole of chains is given by:

$$\frac{F}{RT} = \frac{E_0}{RT}(L - 3)S + (L - L^*)\left[\frac{W(S - 0.39)^2}{RT} - \frac{Z(S - 0.39)^3}{RT} - \frac{W}{RT}(0.39)^2 - \frac{Z}{RT}(0.39)^3\right] - (L - 2)2\sqrt{2}(S - S^2). \tag{12}$$

At this point we let S_g tend to zero. It should be remembered that the cusp minimum at $S = 0$ should actually be a smooth minimum at S_g as discussed above. Another remark can be made at this point. We have not considered surface energy terms explicitly. However the term in Eq. (12) proportional to L^* is in the form of a surface contribution to the free energy. Since L^* will be fit from the data some influence of a surface energy is actually included in the model.

The expression of Eq. (12) is in the form of Eq. (1). The two minima are at $S = 0$ and $S = (B + \sqrt{B^2 - 4AC})/2A = S_c$. The two minima correspond to the same value of F when the conditions

$$\text{a) } A = (\tfrac{3}{16})B^2/C \text{ and}$$

$$\text{b) } S = S_c = (\tfrac{3}{4})B/C \tag{13}$$

are satisfied. Equation (13a) may be solved for $T(L)$. Since $F(0) = F(S_c) = 0$, the latent heat as a function of chain length may be given as:

$$\Delta H(L) = (L - 2)RT_c(L)2\sqrt{2}(S_c - S_c^2) \tag{14}$$

In order to use these results it is necessary to obtain values for W, Z and L^*. One relationship between these parameters can be obtained by considering the limit $L \rightarrow \infty$. In this case the surface constraint is ineffective so the interior of the bilayer differs very little from polyethylene liquid. The free energy of Eq. (12) is strictly valid only for $S > S_g$. Certainly the expressions for the entropy and energy are not valid for $S < S_g$. However we assume that the implied analytic continuation of F to $S = 0$ is reasonably accurate in the limit.

The melting transition temperature of ECC polyethylene is approximately 141°C.[25] The value of S_0 was chosen so that the fluid minima of F $(L \rightarrow \infty)$ at this temperature is the correct value for liquid polyethylene. It remains to place one condition on the set W, Z, L^* to insure that F evaluated at $S = 0$ is the same as F evaluated at $S = S_0$. That is we set $T_c(L = \infty) = 141°\text{C}$. This yields the condition

$$\frac{A}{R} + S_0\frac{B}{R} = 1192°\text{K} \tag{15}$$

Imposing the condition $T_c(L = \infty) = 141°\text{C}$ can be viewed as a short cut method of considering heats of sublimation, magnitude of Van der Waals forces, etc.

With Eq. (15) taken into account there are only two free parameters in the model. These two parameters must be fit from the data. Two conspicuous features of the $\Delta H(L)$ and $T_c(L)$ data may be used to fix the parameters. The first is the zero of $\Delta H(L)$. The experimental data indicate that $\Delta H = 0$ at approximately $L = 11$.[26] According to the model, this requires that the phase transition be second order for $L = 11$. In terms of the parameters of Eq. (1) at $L = 11$ and $T = T_c(L = 11)$

$$\begin{aligned} A &= 0 \\ B &= 0 \end{aligned} \tag{16}$$

By combination of these equations $T_c(11)$ may be eliminated and a new relation between A, B and L^* obtained. Equations (15) and (16) can be cast in the form

$$\begin{aligned} \frac{A}{R} &= \frac{[851(11\text{-}L^*) - 97.5(11\text{-}3)]^\circ\mathrm{K}}{0.628} \\ \frac{B}{R} &= \frac{[250(11\text{-}3) - 262.0(11\text{-}L^*)]^\circ\mathrm{K}}{0.628} \end{aligned} \tag{17}$$

The form of Eq. (17) makes it obvious that there remains only a single parameter, L^* to be fit from the data. A numerical investigation shows that

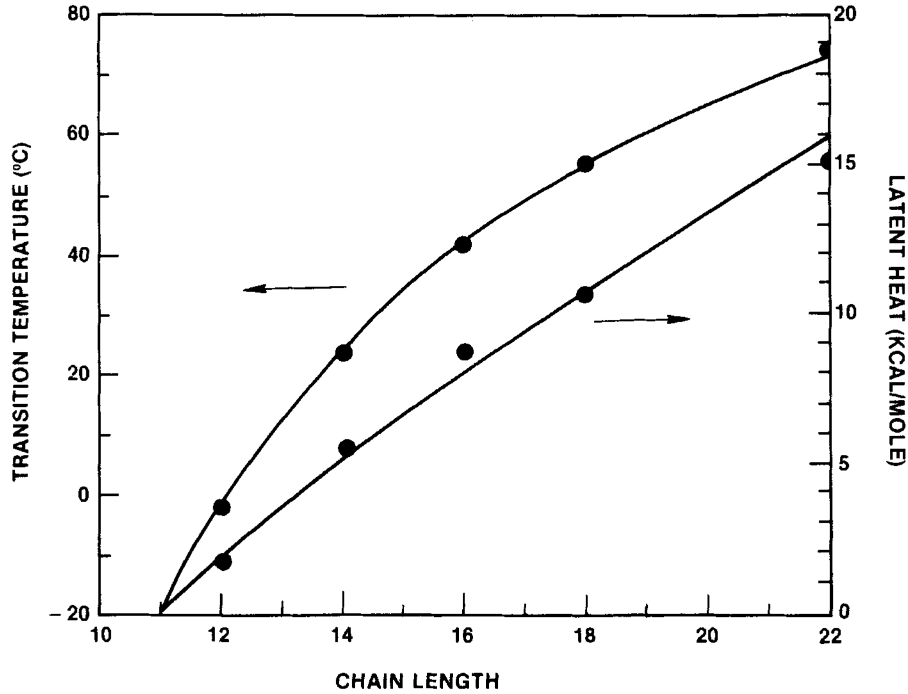

FIGURE 1 Right hand scale: Latent heat as a function of chain length. Left hand scale: transition temperature as a function of chain length. Solid curves are model results. Data except for $L = 22$ from Ref. 26., Data for $L = 22$ from Ref. 27.

this parameter sets the overall scale of temperature. The value of L^* may be viewed as setting $T_c(11)$. Since $T_c(11)$ is not accessible experimentally we choose L^* to obtain the best fit of the $T_c(L)$ data for $L = 12, 14, 16, 18$ and 22. This value is $L^* = 6.4$. The model results for $T_c(L)$ and $\Delta H(L)$ are shown in Figure 1 together with the experimental results of Mabrey and Sturtevant[26] and Ladbrooke and Chapman.[27]

As can be seen from Figure 1 the model does have predictive power for the single component system. The curvature and slope of the $T_c(L)$ curve are predicted correctly. Aside from the asymptotic approach to 141 °C neither the slope nor the curvature entered into the determination of the parameters. The slope of the $\Delta H(L)$ curve is predicted nearly correctly. The value of this slope did not enter into the determination of the parameters. The latent heat in the limit $L \to \infty$ is less than that of the melting of polyethylene for the reasons discussed in the introduction. With the choice $L^* = 6.4$ the curve $T_c(L)$ continues to the point $T_c(6.4) = 0°K$. This is in agreement with the extrapolation obtained from volumetric data by Nagle and Wilkinson.[20]

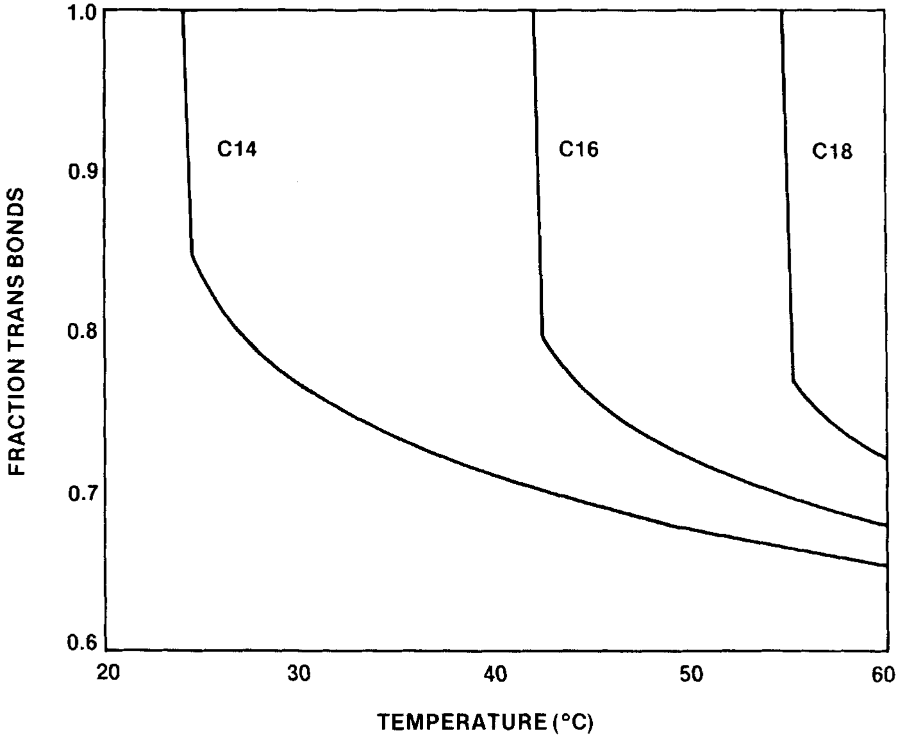

FIGURE 2 Calculated fraction of bonds which are trans for C14 (DMPC), C16 (DPPC) and C18 (DSCP) as a function of temperature.

In addition to calculating $T_c(L)$ and $\Delta H(L)$ it is possible to calculate the order parameter S as a function of temperature for given L. This result comes directly from the expression proceeding Eq. (13). In Figure 2 we have presented the results for $L = 14$, 16 and 18. In this figure the value of S in the gel phase is given as zero. The correct value is S_g as discussed above. The fluid phase values are the actual predictions of the model.

IV BINARY MIXTURE PHASE DIAGRAMS

In order to further test the model we consider the calculation of the phase diagram for binary mixtures of PC differing in chain length by 2, 4 and 6 carbons. The most conspicuous feature of the experimentally determined phase diagrams is that they are highly non-ideal. This is especially true for chain length differences of more than two carbons. The phenomenological model developed above on the other hand, leads to nearly ideal phase diagrams if augmented only by an entropy of mixing term.

The shape of the experimentally determined phase diagrams indicate that lipids of differing chain lengths do not mix as well in the gel state as they do in the fluid state. There are various model mechanisms which can lead to this situation. Since we have adopted the phenomenological approach in this paper the details of the mechanisms are not important except to motivate the choice of analytic form of a contribution to the free energy.

In a random mixture of equal numbers of long and short chain molecules, half of the neighbors of long chains are short chains. In the absence of interdigitation between the bilayers, the final few CH_2 groups of the long chains will be lacking neighbor CH_2 groups on the adjacent short chains. This insures that in such mixtures there will be unsatisfied Van der Waals bonds in the region of the bilayer midplane. In the gel phase the terminal methyl groups are located in a narrower zone in the bilayer than is the case in the more disordered fluid phase. Consequently the chains in the binary mixture gel phase are less able to avoid unsatisfied Van der Waals bonds than is the case in the fluid phase. Another way of viewing this is to note that defects are more easily accommodated in an amorphous state than in a crystalline state.

With these observations we write for the free energy of a binary mixture of PC differing in chain length the free energy $G(S, X)$

$$\frac{G(S, X)}{RT} = \frac{F(S)}{RT} + \tfrac{1}{2}X \ln X + \tfrac{1}{2}(1 - X)\ln(1 - X) + \Delta U X + \Delta L\left(\frac{\sigma}{RT}\right)(\tfrac{1}{2} - S)X(1 - X) \qquad (18)$$

Here $F(S)$ is given by Eq. (12) with $L = L_S + X\Delta L$ where L_S is the chain length of the short species, ΔL is the chain length mismatch and X is the mole fraction of long chains. The second and third terms in Eq. (18) are the entropy of mixing. The factor $\frac{1}{2}$ comes about from the fact that there are two chains per head group. The difference in chemical potential between the long and short chains is denoted by ΔU. The difference in chemical potential is an intensive thermodynamic variable conjugate to X. By adjustment of ΔU, the minimum of G with respect to X can be caused to fall at the value of X set in an experiment.

The last term in Eq. (18) represents the non-ideal effects. It vanishes in a maximally disordered system ($S = \frac{1}{2}$) and is a maximum for the gel state ($S = 0$). The form $X(1 - X)$ is the simplest expression that vanishes in both pure component limits. The magnitude of the non-ideal term, σ, is a free parameter. Following the approach of Ref. (14), we hope to find a single value of σ which can produce accurate phase diagrams for three different mixtures: DMPC/DPPC, DMPC/DSPC and DLPC/DSPC. That is for chain length differences of 2, 4 and 6 carbons.

To determine the phase diagrams Eq. (18) is minimized with respect to X and S. The cases of $\Delta L = 2$ and 4 are similar and will be discussed first.

There are two local minima of G. One is at $S = 0$ and a large value of X. This is the long chain rich gel minimum. The other minimum is at a fluid value of S and a small value of X. This is the short chain rich fluid minimum. The global minimum of G is the free energy of the system for given ΔU and T. As a function of ΔU and T, the equilibrium values of X and S correspond to the global minimum of G. For fixed T the fluid minimum is the global minimum for large values of ΔU. As ΔU is reduced past a certain value, $\Delta U = \Delta U_c(T)$, the fluid minimum ceases being the global minimum and the gel minimum becomes the global minimum. At the value $\Delta U_c(T)$ both local minima are global minima of G. The value of X at the gel minimum may be thought of as a function of T and ΔU: $X_g(\Delta U, T)$. The same is true for the fluid minimum: $X_f(\Delta U, T)$. For a given value of T values of X satisfying $X < X_f(\Delta U = \Delta U_c(T), T)$ are characteristic of pure fluid phases. That is there exists a value of ΔU for which the fluid minima is at the particular value X and is the global minimum of G. Likewise, values of X satisfying $X > X_g(\Delta U = \Delta U_c(T), T)$ are characteristic of pure gel phases. The region $X_f(\Delta U = \Delta U_c(T), T) < X < X_g(\Delta U = \Delta U_c(T), T)$ is the mixed phase region. For these values of X a short chain rich fluids coexists in equilibrium with a long chain rich gel. In the mixed phase region each of the separate phases has $\Delta U = \Delta U_c(T)$ and the gel phase has $X = X_g(\Delta U = \Delta U_c(T), T)$ while the fluid phase has $X = X_f(\Delta U = \Delta U_c(T), T)$. The calculation of the phase diagram therefore consists in numerically de-

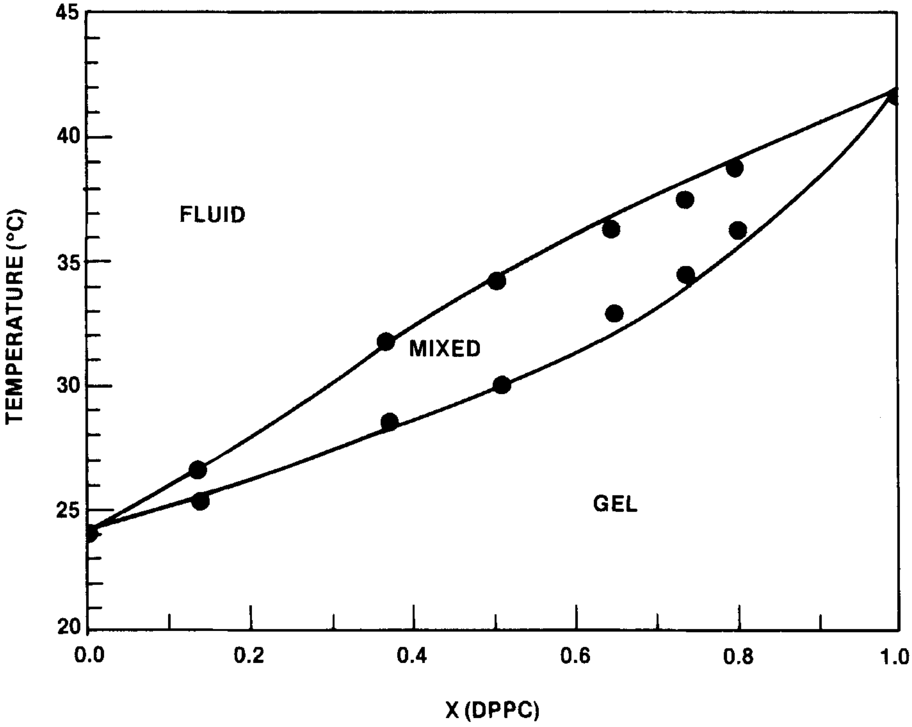

FIGURE 3 Phase diagram for DMPC/DPPC mixture in the temperature-mole fraction of DPPC plane. Solid curves are the model results. Points indicate data from Ref. 26.

termining the relation $\Delta U_c(T)$ and then calculating X_f and X_g. The results of this calculation are presented in Figures 3 and 4. These calculations were done for the case $\sigma/R = 125°\text{K}$. This value gives the best fit for the phase diagrams of DMPC/DPPC and DMPC/DSPC as well as that for DLPC/DSPC to be discussed below. Also included in Figures 3 and 4 are calorimetric data of Mabrey and Sturtevant.[26] In the figures no attempt is made to indicate the experimental uncertainty. The agreement of the calculated curves and the data is good. The largest discrepancy is for the $\Delta L = 4$ boundary between the gel and mixed regions for $X > 0.6$. As reported in Ref. 26, this boundary is subject to the greatest experimental uncertainty. Phase diagrams have also been measured by ESR[28] and Raman methods.[17] These results are in qualitative agreement with the calormetric data.

In addition to the phase diagram it is also of interest to calculate the order parameter S for the binary mixture case. This is straightforward for values of X and T corresponding to pure phases. For values in the mixed

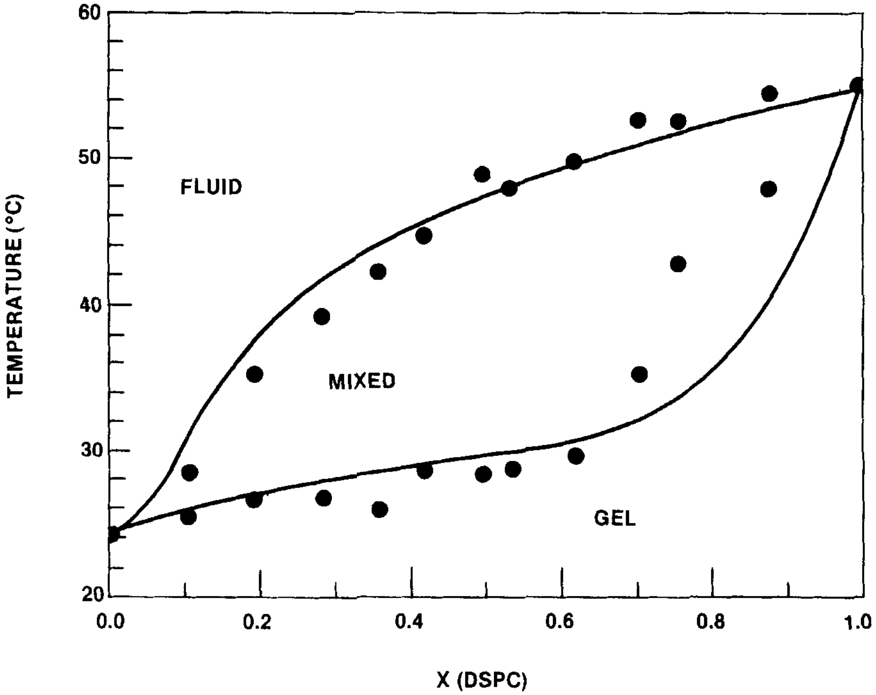

FIGURE 4 Phase diagram for DMPC/DSPC mixture in the temperature-mole fraction of DSPC plane. Solid curves are the model result. Points indicate data from Ref. 26. No experimental uncertainty is indicated.

phase region S can be calculated by finding the fraction of chains in the gel and fluid states from X, X_g and X_f. In Figure 5, S is plotted as a function of T for three different DMPC/DSPC mixtures. The interesting feature of this figure is the pronounced point of inflection of the $X = 0.5$ curve. This result is in qualitative agreement with Raman data obtained in this laboratory.

The situation for the DLPC/DSPC mixture is more complex. For $\Delta L = 6$ there are three local minima of G in the X, S plane. These can be classified as a fluid minimum, a short chain gel minimum and a long chain gel minimum. At a certain value of T and $\Delta U(T_t, \Delta U_t)$ all three of the local minima are global minima of G. For DLPC/DSPC $T_t \cong 2°\text{C}$. (The model value for $T_c(L = 12)$ is $-1°\text{C}$). At $T = T_t$ and for $X_f(T_t, \Delta U_t) < X < X_g(T_t, \Delta U_t)$ all three phases coexist in equilibrium. The phase diagram is shown in Figure 6. The horizontal line at $T = T_t = 2°\text{C}$ is the line of triple points

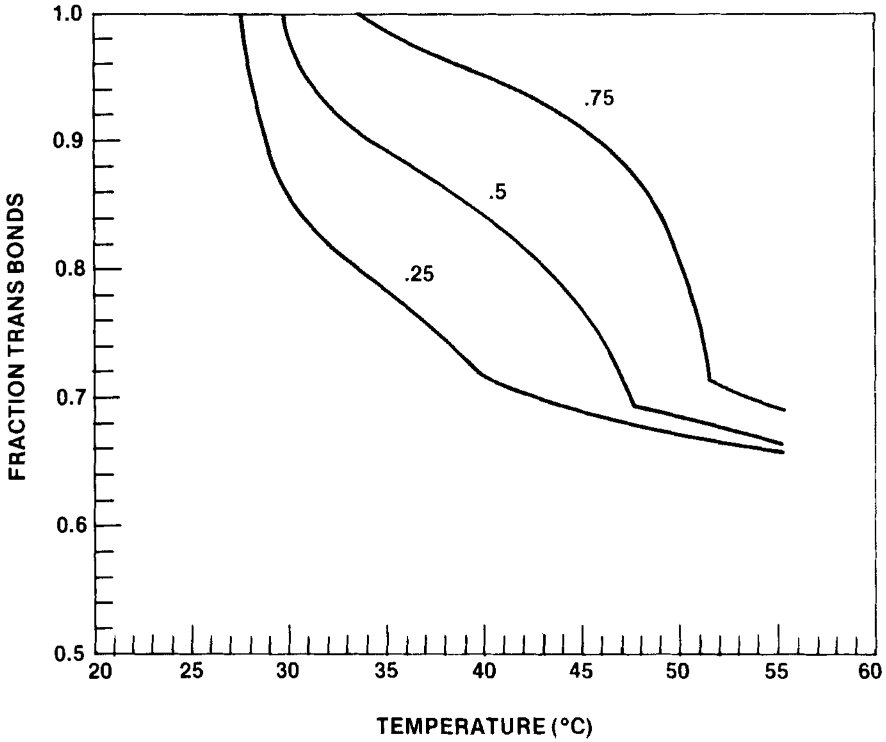

FIGURE 5 Calculated fraction of bonds which are trans for three DMPC/DSPC mixtures as a function of temperature. The mixtures indicated are 25%, 50% and 75% molar DSPC.

where all three phases coexist. In the region labeled mixed gel the two gel phases coexist in equilibrium. In the region labeled mixed I a short chain rich fluid coexists with a long chain rich gel. This is the usual mixed phase region. The region labeled mixed II is quite small and may be difficult to detect experimentally. In this region a gel state coexists with a fluid state. However the compositions of the fluid and gel states are quite different from those in the neighboring mixed I region. Also shown in Figure 6 is the calorimetric data.[26] The major theoretical-experimental discrepancy is that the theory predicts that T_t is about 3°C higher than $T_c(12)$ while the experimental result is that they are the same. Recent volumetric data indicate that T_t is about 0.5°C higher than $T_c(12)$.[29]

The most significant prediction of theory for this mixture is that the gel phase is separated into two coexisting phases over a wide range of concentrations. It may be possible to verify this prediction by study of a mixture of deuterated and protonated lipids.

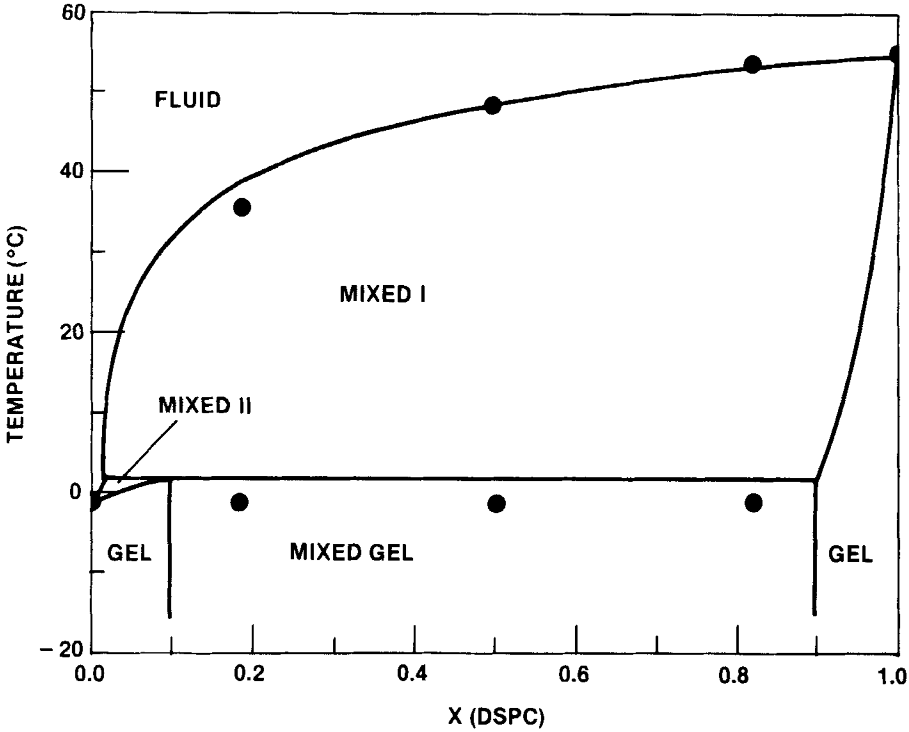

FIGURE 6 Phase diagram for DLPC/DSPC mixture in the temperature-mole fraction plane. Solid curves are model results. Points indicate data from Ref. 26. See text for explanation of labeling.

V CONCLUSIONS

A simple phenomenological model with structure based on considerations independent of detailed model mechanisms can adequately describe the main phase transition and related phenomena in PC bilayers. The model has 2 adjustable parameters which can be thought of as fixing the chain length and transition temperature for a second order gel-fluid phase transition. The number of parameters in the model compares favorably with the number in other published theories. The agreement with the data is also comparable with that obtained from far more detailed models. In order to study binary mixtures of PC the model is augmented by an additional term specifying the degree of non-ideality of mixing. This necessitates the inclusion of a 3rd parameter. However a single value of this parameter allows a reasonable fit of all the binary mixture phase diagrams.

Other phospholipid series such as the phosphatidylethanolamines could also be modeled along the lines of this paper. Different values of the parameters would apply to these systems. Another class of systems amenable to this type of analysis are binary mixtures of protonated and deuterated PC. This will be the subject of another article.

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Appendix

Consider a stretching vector field $\mathbf{J}(\mathbf{r})$ defined by:

$$\mathbf{J}(\mathbf{r}) = \rho(\mathbf{r})\langle \mathbf{R}_{m+1} - \mathbf{R}_m \rangle$$

Here ρ is the density of methylene groups and $\mathbf{R}_{m+1} - \mathbf{R}_m$ is a vector joining the m and $m + 1$ methylene groups on a chain. The average indicated by the angle brackets is a coarse grained average over all chains in the vicinity of the point **r** and over all values of m that occur in that vicinity. The dimension of J is $(\text{length})^{-2}$. The chains may be thought of as propagating away from the plane of polar head groups toward the bilayer midplane. The number of chains crossing the area element $\mathbf{d}S$ is $\mathbf{J}\cdot\mathbf{d}S$. If there are no chain ends, the number of chains propagating into a volume element is equal to the number propagating out. This implies the continuity condition on **J**:

$$\nabla\cdot\mathbf{J} = 0$$

For the planar bilayer geometry this implies $\mathbf{J} = \text{const.}\,\hat{Z}$, where $\hat{Z}$ is a unit vector normal to the bilayer surface. If $\rho(\mathbf{r})$ is constant, the order parameter S is a function of $|J|$. This implies that S is independent of **r**. This argument does not apply in the vicinity of the bilayer midplane because chain ends occur and $\rho(\mathbf{r})$ is not constant in that region.