Phenomenological Model and Phase Behavior of Saturated and Unsaturated Lipids and Cholesterol

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Abstract

We present a phenomenological theory for the phase behavior of ternary mixtures of cholesterol and saturated and unsaturated lipids, one which describes both liquid and gel phases, and illuminates the mechanism of the behavior. In a binary system of the lipids, the two phase separate when the saturated chains are well ordered, as in the gel phase, simply due to packing effects. In the liquid phase the saturated ones are not sufficiently well ordered for separation to occur. The addition of cholesterol, however, increases the saturated lipid order to the point that phase separation is once again favorable. For the system above the main chain transition of the saturated lipid, we can obtain phase diagrams in which there is liquid-liquid phase separation in the ternary system but not in any of the binary ones, while below that temperature we obtain the more common phase diagram in which a gel phase, rich in saturated lipid, appears in addition to the two liquid phases.
1 Introduction

The hypothesis that the plasma membrane is not uniform but consists of “rafts” rich in saturated lipids and cholesterol which float in a sea of unsaturated lipids remains an extremely exciting and controversial one (1, 2, 3). The extent to which one can define such entities in a biological membrane and the driving forces tending towards their formation is unclear. Much more certain are the results of studies on non-biological bilayer membranes with compositions designed to mimic those of biological ones. They consist of a high-melting point lipid, usually saturated, a low-melting point lipid, usually unsaturated, and cholesterol (4). These systems readily display co-existing liquid phases. One, the liquid ordered (lo) phase (5), is rich in cholesterol and saturated lipids whose chains are relatively well-ordered; the other, the liquid disordered (ld) phase, is rich in unsaturated lipids whose chains are not so well-ordered (4, 6, 7). In addition, at the temperatures of interest, there is usually a gel phase rich in saturated lipids with chains which are very well ordered. This phase behavior leads to the possibility that rafts in biological membranes are simply regions of one liquid phase in coexistence with, and surrounded by, the other liquid. A second scenario, engendered by the occurrence of a line of critical points in the system at which the two liquid phases become one, is that rafts are transient aggregates, manifestations of fluctuations which are particularly large near the critical line of a system which is effectively two-dimensional (8). A third interpretation is that such aggregates are the results of a line-active agent, perhaps cholesterol, which lowers the free energy of such aggregates and results in a liquid with much structure, as in a microemulsion of oil and water which is brought together by a surface-active agent.

It should be noted that not all ternary systems of lipids and cholesterol exhibit a gel and two liquid phases. Of particular interest is the system of diphytanoylphosphatidylcholine (diPhyPC), dipalmitoylphosphatidylcholine (DPPC), and cholesterol (9) which, at a temperature above the main-chain transition of the DPPC, exhibits a region of liquid-liquid coexistence in the middle of the Gibbs triangle; that is, at these temperatures none of the three binary systems undergo phase separation, whereas the ternary system does. This is unusual behavior in a liquid system, although other examples are cited in ref. (10). It is to be contrasted with that of most ternary liquid systems in which the existence of any phase separation is directly tied to the existence of such separation in one of the binary systems. As a consequence only two of the components are actually necessary to bring about the separation. A simple example is the ternary system of oil, water, and surfactant.
which, for modest concentrations of surfactant, displays two liquid phases, one oil-rich, the other water-rich with the surfactant partitioning between the two. Clearly these phases evolve from the ones resulting from separation of oil and water in the binary system. It is conceivable that the existence of two liquid phases in the ternary cholesterol, saturated and unsaturated lipid system could be similarly directly tied to the existence of liquid-liquid phase separation in the cholesterol, saturated lipid system, a separation which had been reported earlier (11). However there is now abundant experimental evidence (12) that such separation does not occur in this binary system. The significance of the phase diagram of the diPhyPC, DPPC, cholesterol system is that the existence of liquid-liquid phase separation in such ternary systems cannot be tied to phase separation in any of the binary systems, and must therefore be a consequence of the presence of all of the three components. This conclusion begs for theoretical understanding.

The simplest approach would be to employ regular solution theory which can, in fact, give rise to the kind of phase diagram described above (11) (13) (14), but to do so requires an attractive interaction between at least two of the components which is extremely large, and for the system of interest, inexplicably so. Further, regular solution theory considers only the concentration of each component. To employ it, therefore, would be to ignore the many degrees of freedom of the lipid tails which are certainly involved in the transition from the liquid to the gel phase, and might be involved in the liquid-liquid transition. Thus one must consider explicitly that some of the components are lipids.

There is surprisingly little theoretical work on the phase behavior of cholesterol and lipids, however, and most of that concerns binary systems (5) (15) (16) (17) which, as emphasized above, cannot explain the origin of liquid-liquid separation in the ternary systems of interest. Of the few papers on the phase behavior of ternary systems of saturated and unsaturated lipids and cholesterol (16) (18) (19), only that of Radhakrishnan and McConnell (18) has produced a phase diagram exhibiting liquid-liquid coexistence in the ternary system without phase separation in any of the three binary ones. Their theory posits that the cholesterol and saturated lipids form complexes which then interact repulsively with the unsaturated lipids. The origin of this repulsion is not specified. In the explicit realization of this idea (18), the complexes are treated as a distinct, fourth component in the system, and the free energy is assumed to be well approximated by regular solution theory. The authors note that such complexes have never been isolated in bilayers, but stress that they should be considered as rapidly fluctuating entities. The evidence from simulation for such transitory complexation with
a specific stoichiometry is mixed \( [20, 21, 22] \). Nevertheless, they emphasize the utility of the concept, as clearly demonstrated by its ability to reproduce the unusual phase diagram of the diPhyPC, DPPC, cholesterol system. The theory does not describe the more usual ternary mixtures of lipids and cholesterol which, in addition to two liquid phases, also display a gel phase. This is probably due to the choice of order parameter of the saturated lipid, one which they define as the fraction of saturated lipid found in complexes. In the pure saturated-lipid system there can be no complexes, so this order parameter always vanishes and cannot distinguish between the system’s gel and liquid phases.

Given the transitory nature of the posited complexes, it would be advantageous to formulate a theory which describes the system only in terms of the original three components, and which would provide further insight into the physics governing the system. In addition, one would also like it to describe systems exhibiting a gel phase. Lastly, it should be able to describe the evolution of the normal phase behavior into the more unusual one displayed by the diPhyPC, DPPC, cholesterol system.

It is the purpose of this paper to present such a theory, one which highlights what we believe to be the basic physics of these ternary systems. This is easily stated. Saturated and unsaturated lipids undergo phase separation when the former are sufficiently ordered, as they are in the gel phase. The reason for this is a simple packing effect: the presence of one or more kinks in an unsaturated chain prevents the efficient packing, and free energy reduction, of the ordered, saturated, chains. Hence the system lowers its free energy by separating into a gel phase rich in saturated lipids, and a liquid phase rich in unsaturated lipids. When the saturated and unsaturated lipids are in a liquid phase, the former are not sufficiently ordered to bring about a phase separation. The addition of cholesterol to the liquid phase, however, tends to increase the order of the saturated lipids, as is well known \( [23, 24, 25, 26] \). With the addition of enough cholesterol, the saturated chains become sufficiently ordered that phase separation from the unsaturated chains becomes free energetically favorable once again. The theory produces phase diagrams which display two liquid phases and a gel, as well as those like that of the diPhyPC system in which there is only liquid-liquid coexistence, and that in the middle of the Gibbs triangle.
2 The Model

We consider a system of cholesterol, whose concentration is denoted $c$, a high melting-temperature lipid, henceforth referred to as “saturated”, whose concentration is $s$, and a low melting-temperature lipid, henceforth referred to as “unsaturated”, with concentration $u = 1 - s - c$. By describing the system in terms of two independent concentrations, rather than three independent areal densities, we are making the implicit simplifying assumption that the actual areal density of the system is not a crucial parameter in the description of its phase behavior. We define an order parameter, $\delta$, of the saturated lipid which is related to the order of its chains (15). It will be largest in the gel phase, and is non-zero in the liquid phases.

We first assume the system to be at a temperature, $T$, sufficiently high that there are only liquid phases. We write the free energy per particle of the system, in units of $kT$, in the form

$$\tilde{f}_{\text{liq}}(T, c, s, \delta) = \tilde{f}_{\text{mix}} + \tilde{f}_{\text{chain,liq}} + \tilde{f}_{\text{int,liq}},$$

where

$$\tilde{f}_{\text{mix}} = c \ln c + s \ln s + u \ln u,$$

is the usual entropy of mixing. The second term describes the interactions between the saturated lipids, and is therefore proportional to $s^2$,

$$\tilde{f}_{\text{chain,liq}} = Jss s^2 \left[ k_1 (\delta - 1)^2 + (\delta - 1)^4 \right].$$

Note that the strength of the interaction between saturated lipids depends upon their configuration, as is to be expected. The information about the configurations is encapsulated in the order parameter. Because of this interaction between saturated lipids, the free energy in the liquid phase has a single minimum as a function of $\delta$. Taking advantage of the freedom to set the scale of the temperature and of the order parameter, we have used one of these degrees of freedom to assign $\delta$ the value unity in the pure saturated-lipid system. The constants $Jss$ and $k_1$ are positive. The last term in eq. (1) is that due to the interaction between the saturated lipid and the other two components,

$$\tilde{f}_{\text{int,liq}} = Jus us \delta - Jcs cs(\delta - k_2 \delta^2),$$

with $Jus$, $Jcs$ and $k_2$ all positive. The first term represents the repulsive interaction between saturated and unsaturated lipids due to the inability of the latter to pack well with the former. The strength of this repulsion depends, again, on the degree of order of the chains of the saturated lipids,
a concept expressed in the earliest modeling of these systems \(^5\). It is this
term which will drive the separation of saturated and unsaturated chains if
its strength is sufficiently great. In the absence of cholesterol, it is not. The
second and third terms in the above express the tendency of cholesterol to
increase the order of the saturated chains, provided that order is not too
large; i.e. cholesterol increases the order in the liquid phase but decreases
it in the gel phase \(^11\). The attractive term, proportional to \(cs\delta\), is crucial
as it causes the addition of cholesterol to increase the chain order which
thereby increases the repulsion between saturated and unsaturated lipids so
that they separate. Collecting the separate terms of eq. \(^1\) we have

\[
\tilde{f}_{liq}(T, c, s, \delta) = c \ln c + s \ln s + u \ln u + J_{ss}s^2[k_1(\delta - 1)^2 + (\delta - 1)^4] + J_{us}us\delta - J_{cs}cs(\delta - k_2\delta^2).
\]

(5)

Because the order parameter is not controlled externally, its value as a func-
tion of composition, \(\delta_{liq}(T, c, s)\), is determined from the condition that it
minimize the free energy. Then the Helmholtz free energy per particle of
the liquid phase, \(f_{liq}(T, c, s)\) is obtained from \(\tilde{f}_{liq}(T, c, s, \delta)\) according to

\[
f_{liq}(T, c, s) \equiv \tilde{f}_{liq}(T, c, s, \delta_{liq}(T, c, s)).
\]

(6)

Two-phase coexistence is found in the usual way. Of the four unknowns, the
two independent compositions in the two coexisting phases, three are deter-
mmed by the conditions of equality of two independent chemical potentials
and of the Gibbs free energy per particle, \(g\), which is essentially the surface
tension:

\[
\mu_c(T, c_1, s_1) = \mu_c(T, c_2, s_2),
\]

(7)

\[
\mu_s(T, c_1, s_1) = \mu_s(T, c_2, s_2),
\]

(8)

\[
g(T, c_1, s_1) = g(T, c_2, s_2), \text{ where}
\]

(9)

\[
\mu_c = \frac{\partial f_{liq}}{\partial c},
\]

(10)

\[
\mu_s = \frac{\partial f_{liq}}{\partial s},
\]

(11)

\[
g = f_{liq} - \mu_c c - \mu_s s.
\]

(12)

Because one composition is undetermined, there can be a region of concen-
trations over which two-phase coexistence occurs.

A phase diagram which results from this theory is shown in Fig. \(\text{1}\). It
reproduces the kind of phase diagram found in the diPhyPC, DPPC,
cholesterol system. We have indicated values of the order parameter at several concentrations. As expected, it is large in the regions in which the concentration of the saturated lipid is large, and tends to increase with the concentration of cholesterol due to its ordering effect.

We now consider the system to be at a temperature at which it could exhibit a gel phase in addition to liquid phases. For the free energy of the gel phase we write

\[ \tilde{f}_{gel}(T, c, s, \delta) = \tilde{f}_{mix} + \tilde{f}_{chain,gel} + \tilde{f}_{int,gel}, \]

\[ \tilde{f}_{mix} = c \ln c + s \ln s + u \ln u, \]

\[ \tilde{f}_{chain,gel} = J_{ss}s^2[k_1(\delta - 2)^2 + (\delta - 2)^4 + k_3], \]

\[ \tilde{f}_{int,gel} = J'_{us}us\delta + J'_{cs}cs\delta. \] (13)

We note the following. The single minimum of the free energy in the gel phase has been set to occur at \( \delta = 2 \) when the system consists only of the saturated lipid. In such a system the free energy of the gel phase exceeds that of the liquid phase by \( k_3J_{ss} \), hence \( k_3 \) is proportional to \( T - T^* \), with \( T^* \) the liquid-gel transition temperature in the pure system. By changing \( k_3 \) from positive to negative values, we induce a liquid to gel transition in our system. The interaction strengths \( J'_{us} \) and \( J'_{cs} \) are positive so that the addition of cholesterol, as well as unsaturated lipid, reduces the order of the saturated lipid in the gel phase (11). The value of the order parameter, \( \delta_{gel}(T, c, s) \), is determined by minimization of the above free energy, and the Helmholtz free energy in this phase is

\[ f_{gel}(T, c, s) = \tilde{f}_{gel}(T, c, s, \delta_{gel}(T, c, s)). \] (14)

The free energy of the entire system is now

\[ f(T, c, s) = \min[f_{liq}(T, c, s), f_{gel}(T, c, s)], \] (15)

and phase coexistence is again found by the conditions of the equality of two chemical potentials and of the Gibbs potential as in eqs. (7) to (12) but with \( f_{liq}(T, c, s) \) replaced by \( f(T, c, s) \) above. A phase diagram which results when the temperature is below that of the gel transition of the saturated lipid is shown in Fig. 2. Values of the order parameter at various concentrations are shown. The phase diagram shows all the features of most of those observed experimentally. In particular, there are two liquid phases and a gel. Tie lines between the liquid phases indicate a greater presence of cholesterol in one liquid than the other. The values of the order parameter in the coexisting phases justify the designation of “liquid ordered” for the one and “liquid disordered” for the other. The order is greatest in the gel phase of course. Little cholesterol is needed to destabilize this phase.
3 Discussion

We have presented a phenomenological theory of ternary mixtures of cholesterol, a high-melting temperature (or saturated) lipid, and a low-melting temperature (or unsaturated) lipid. It is capable of producing the usual phase diagrams observed in this system in which there is a gel and two liquid phases, and also the unusual phase diagram of the DiPhyPC, DPPC, cholesterol system in which, for a range of temperatures, the ternary system exhibits phase separation even though none of the binary systems do. The model highlights the interesting physics of these systems; mixtures of high- and low-melting temperature lipids can phase separate when the chains of the former are sufficiently well ordered, as occurs in the gel phase. This is simply a result of packing constraints. In the liquid phase, the chains of the high-melting temperature lipid are not sufficiently ordered to induce phase separation from the more disordered low-melting temperature lipids. However the addition of cholesterol tends to order the chains of the former until, with sufficient cholesterol, the chains have sufficient order to bring about phase separation. This repulsion arising from packing constraints gives an explicit origin to the unknown repulsion between low-melting temperature lipids and the complexes of Radhakrishnan and McConnell (18). However we do not introduce complexes with a definite stoichiometry, but rather consider only the compositions of the components of the ternary system. We also note that, because our theory is able to describe the gel as well as the liquid phases, it is able to make clear that the existence of two liquid phases has little to do with that of the gel. The gel phase simply occupies regions of the phase diagram which might otherwise be occupied by liquid phases.

The theory is sufficiently flexible to describe various possible evolutions of the phase diagram with temperature, or equivalently, with the interaction strengths as they are generally inversely proportional to temperature. With the parameters we have chosen in Figs. 1 and 2, liquid-liquid phase separation remains even above the main chain temperature of the saturated lipid. This can be traced to the large repulsion, $J_{as}$, between saturated and unsaturated lipids which might be expected given the bulky tails of DiPhyPC. Were the magnitude of this repulsion to be reduced, liquid-liquid coexistence would only be observed below the main chain transition of the saturated lipid. As a second example, we note that the model is easily augmented to permit the liquid-liquid coexistence to extend to the binary cholesterol, unsaturated lipid system as is observed in some systems (27).

Because of the attractive interaction between cholesterol and saturated lipids in the liquid phase, the concentration of cholesterol is greater in one
of the liquid phases than the other. This agrees with some experiments (9, 28, 29), but not others (28, 30). Due to the preference of cholesterol for the saturated over the unsaturated lipids, it enhances their phase separation; i.e., it increases the temperature at which such separation occurs (13). This is clear from the phase diagram of Fig. 1. The binary lipid system is above its temperature of phase separation, but as cholesterol is added, that temperature increases until it exceeds the temperature for which the diagram is drawn. It follows from this that cholesterol is not expected to migrate to the interface between lo and ld phases and therefore is not expected to reduce the line tension between these phases. Thus, if one wants to think of the existence of “rafts” as indicating the formation of some sort of microemulsion, then one cannot attribute to cholesterol the role of a line active agent which brings it about. Rather one must assign such a role to a protein (31), like N-Ras, which has two anchors, one of which prefers the lo environment, and the other the ld environment (52).

Finally we note that, while we have referred to the non-lipid component in the ternary system as cholesterol, it could equally be another molecule, such as a protein. The crucial ingredient of our theory is that the non-lipid component interact with the saturated lipid in such a way as to increase its order parameter. If that be the case, then such a ternary system should exhibit a similar phase diagram to the one we have calculated here. Analogous conclusions also apply to a system consisting of such a protein and cholesterol and the unsaturated and saturated lipids.

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5 Figure Captions

Figure 1 Phase diagram of the ternary system at a temperature above the main chain transition of the saturated lipid. Values of the order parameter are shown at four composition marked by dots. The values of the parameters are as follows: $J_{ss} = 1.0, k_1 = 1.0, J_{us} = 1.8, J_{cs} = 2.4, k_2 = 0.21$.

Figure 2 Phase diagram of the ternary system as a temperature below the main chain transition of the saturated lipid. Values of the order parameter are shown at four compositions shown by dots. The values of the parameters are as follows: $J_{ss} = 1.0, k_1 = 1.0, J_{us} = 1.8, J_{cs} = 2.4, k_2 = 0.21, k_3 = -0.25, J'_{us} = 0.7, J'_{cs} = 0.0$. 
Figure 1:
Figure 2: