Phase Transitions between Vesicles and Micelles Driven by Competing Curvatures.

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Abstract. – We present a model explaining the phase transition between cylindrical micelles and vesicles (bilayers) in a mixed dilute solution of phospholipids and surfactants. The model predicts a first-order transition between micelles and vesicles, which depends on the relative concentration of the two components. The phase transition boundaries are calculated as a function of the specific areas of the two components, their spontaneous curvatures and elastic moduli. The transition is driven by a very large difference in spontaneous curvatures between lipid and surfactant. The free energy takes into account the entropy of mixing as well as the curvature energy. Our predictions are in qualitative agreement with experiments. For mixtures of octyl glucoside (surfactant) and phosphatidylcholine (phospholipid), we obtain good agreement with experimental data.

Phospholipid molecules (such as phosphatidylcholine) are the main building blocks of biological membranes. Being practically insoluble in water, they will self-assemble into bilayers forming a lamellar phase or vesicles [1, 2]. Surfactant molecules, on the other hand, are amphiphiles with different self-assembly properties. They are solubilized as monomers in water up to a critical concentration (called the *cmc*). Above this concentration, monomers in the solution coexist with aggregates of surfactant molecules (micelles) having different sizes and shapes, depending on the particular system [1, 2].

The use of mixed surfactant-lipid[1] systems is of prime importance in *membrane reconstitution*, a process widely used to study in a controlled fashion membrane proteins [3, 4]. It is quite desirable, therefore, to understand, on a more fundamental level, the parameters controlling the equilibrium properties of lipid-surfactant mixtures. This is

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[1] Throughout this paper we call the amphiphilic phospholipid molecules simply lipid.

also an interesting physical problem connected to the interplay of composition, curvature and shape transformations in vesicles and membranes, a subject that has received considerable attention in recent years [5-13].

Several experimental studies addressed the issue of micellar-to-vesicular transition using a variety of experimental techniques: quasi-elastic light scattering, turbidity and viscosity measurements, and cryo-transmission electron microscopy [14-21]. Experimentally, it is quite clear that the mixed system undergoes a phase transition from a vesicular to a micellar phase, as the ratio of surfactant to lipid increases. The experimental results describing this transition are summarized in the phase diagram, fig. 1, for the particular system of octyl glucoside (OG) and phosphatidylcholine (PC) [14-18]. Other commonly used «mild» surfactants, yielding similar phase diagrams, are bile salts such as sodium cholate [19-22].

For a fixed temperature, the dilute PC/OG solution can be in a *purely* vesicular or *purely* micellar phase (fig. 1). The equilibrium state of the system is defined by the number concentrations (per unit volume) ρ_S and ρ_L of the surfactant (OG) and lipid (PC), respectively. Sufficiently low surfactant concentration (the region bounded from above by the line with slope R_e^b) yields a vesicle phase , while at high ρ_S (the region bounded from below by the line with slope R_e^m) the system is in a micellar phase. Between those two lines, the system is in a two-phase region consisting of coexisting bilayer vesicles and micelles. The ratio of surfactant to lipid is $R_e^b = \rho_S^b/\rho_L^b$ in bilayer vesicles and $R_e^m = \rho_S^m/\rho_L^m$ in micelles [2]. While the distribution of material between the two phases varies, it was experimentally observed that the two ratios R_e^b and R_e^m remain constant *throughout* the two-phase region and coincide with the phase boundary values. For the PC/OG system, the values of R_e^b and R_e^m were measured to be about 1.4 and 3.2, respectively [18][3].
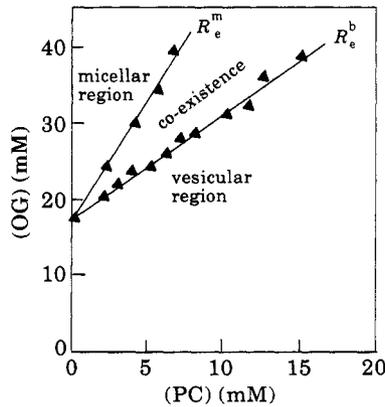
Fig. 1 – Experimental phase diagram adapted from ref. [18] for PC/OG mixtures. The vesicular-to-micellar phase transition is shown as a function of the total surfactant (OG) concentration, and total lipid (PC) concentration. The two lines of constant slope, $R_e^b \simeq 1.4$ and $R_e^m \simeq 3.2$, are the boundaries of the two-phase region. Their extrapolated value to zero lipid concentration defines the surfactant *cmc* value (of about 16.6 mM) for the PC/OG system.

In this letter we use a simple thermodynamic model to evaluate, on general grounds, the phase transition between vesicular and micellar phases in such mixed systems. Our findings are in good qualitative agreement with experimental data on the specific PC/OG system (fig. 1). Before introducing the model, we would like to discuss several simplifying assumptions which are motivated by the experiments. The first is that we assume the vesicles (close to the two-phase coexistence region) to have a large enough radius of curvature to make them indistinguishable from a flat bilayer. Accordingly, it does not matter whether the vesicles obtained in experiments are equilibrium structures or long-lived metastable ones evolving towards a lamellar phase of flat bilayers.

Second, the shape and size of micelles are considered in the simplest way possible. Most of previous works tried to model the micelles as disklike objects (oblated ellipsoids)[21] in order to accommodate both surfactant with a strong tendency of forming spherical micelles and lipid preferring the flat bilayer. However, in recent electron microscopy[17,22] and small-angle neutron scattering[23] studies, it was shown that the micelles in large portion of the two-phase region can be regarded as elongated cylinders. We used this experimental evidence to model the micelles as long cylinders without taking into account the cylinder «end cap» energy[4]. Finally, in accord with the experimental findings[4], we take the concentration of surfactant in water (monomers) to be constant everywhere above the R_e^b transition line of the two-phase region (fig. 1). The concentration of lipid monomers, on the other hand, is always negligible. We note that this assumption is valid as long as we are not interested in studying the phase diagram at *extremely* low lipid concentrations[24].

In order to treat thermodynamically the phase transition between vesicles and micelles, we calculated the free energy in each of the phases as a function of concentrations and a few other parameters. The phase transition is determined by use of a common tangent construction. The surfactant-to-lipid ratios, R_e^m and R_e^b, are obtained for the two coexisting phases and compared with experimental values.

The free energy per unit volume is $f = u - Ts$, where u is the internal energy and s is the entropy. Designating the area per lipid molecule on the surface of bilayers and micelles as a_L, and that of the surfactant as a_S, we introduce the following dimensionless ratios:

$$\begin{cases} r = a_S/a_L\,, \\ \psi = (a_S\rho_S + a_L\rho_L)/a_L = r\rho_S + \rho_L\,, \\ \phi = a_S\rho_S/(a_S\rho_S + a_L\rho_L) = r\rho_S/(\rho_L + r\rho_S)\,. \end{cases} \tag{1}$$

With these definitions we get that the experimentally measured ratio

$$R_e = \rho_S/\rho_L = \phi/(r(1 - \phi)) \tag{2}$$

depends only on ϕ and not on ψ.

The entropy s is taken to be the mixing entropy of lipids and surfactants. It should be distinguished from the *translational* entropy of the (cylindrical) micelles and vesicles themselves. The latter entropy can be ignored because of the large size of those objects. Using a lattice model for the entropy of ideal mixing, we obtain

$$s = -k_B\psi[\phi \log \phi + (1 - \phi) \log(1 - \phi)]\,, \tag{3}$$

where k_B is the Boltzmann constant. Note that this expression accounts (but only approx-

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[4] As the issue of the micellar size distribution is not addressed here, we can ignore the «end cap» energy for long cylindrical micelles.

imately) for the different specific areas of the two components. The same expression for s, eq. (3), is applied indiscriminately to bilayers and (long) cylindrical micelles. This entropy merely expresses the tendency of the system to favour mixing of lipids and surfactants within bilayers and micelles.

The other term in the free energy f is the internal energy u. This term has to reflect the different tendency of the lipid and surfactant molecules to self-assemble. A convenient and simple model is the curvature model used extensively to study membranes[1,2]. The curvature energy per unit area of membrane is

$$\kappa(c_1 + c_2 - c_0)^2/2 + \kappa_G c_1 c_2 , \tag{4}$$

where κ and κ_G are the bending rigidity and the modulus of Gaussian curvature, respectively, and c_0 is the spontaneous curvature. The geometry of the surface is characterized by the principal curvatures c_1 and c_2. We consider only flat bilayers with $c_1 = c_2 = 0$, and cylinders with $c_1 = 1/R$ and $c_2 = 0$, where R is the radius of the cylinder. In both cases the second term in eq. (4) can be disregarded.

To express the internal energy (4) through ψ and ϕ, we have to calculate the spontaneous curvature c_0 of each of the monolayers in the bilayer membrane and in the micelles. A reasonable choice is to average it with respect to the specific areas of the two species, yielding

$$c_0 = (a_S \rho_S c_S + a_L \rho_L c_L)/(a_S \rho_S + a_L \rho_L) = \phi c_S + (1 - \phi)c_L , \tag{5}$$

where $c_S \simeq 1/R$ is the surfactant spontaneous curvature and $c_L \simeq 0$ is the lipid one. The bending rigidity κ is taken, hereafter, to be independent of composition.

It is convenient to introduce the following three dimensionless parameters, which together with the areas ratio r will specify our model:

$$t = (\kappa/2k_B T) a_S c_S^2 , \qquad \beta = 1/(Rc_S), \qquad \gamma = c_L/c_S . \tag{6}$$

The curvature energy for the bilayer is then

$$u^b/k_B T = \psi t(\phi + \gamma(1 - \phi))^2/r , \tag{7}$$

and for the micelles

$$u^m/k_B T = \psi t(\phi + \gamma(1 - \phi) - \beta)^2/r . \tag{8}$$

While the entropy of mixing, eq. (3), has the same form for bilayers and micelles, the difference in the free energies $f^b = u^b - Ts$ and $f^m = u^m - Ts$ arises from the different expressions for the curvature energies, eqs. (7), (8). Each one of the free energies, f^m and f^b, is a convex function of the relative composition ϕ. This reflects the tendency of the system to mix for entropical reasons and to reduce the overall curvature energy which depends in a quadratic way on ϕ.

The phase behaviour of the mixed system can now be investigated as a function of ϕ. Whereas for systems rich in surfactant the micellar phase is more stable, it is the opposite for systems rich in lipid, where the vesicular phase is more stable. As the two curves of the free energy cross each other, we can obtain the location of the two coexisting phases by performing a common tangent construction.

In fig. 2 we show the ratios of surfactant to lipid R_e^b and R_e^m for the coexisting vesicular and lamellar phases, as determined from a common tangent construction. The results are presented as functions of the three dimensionless parameters of our model: t, r and β. In all
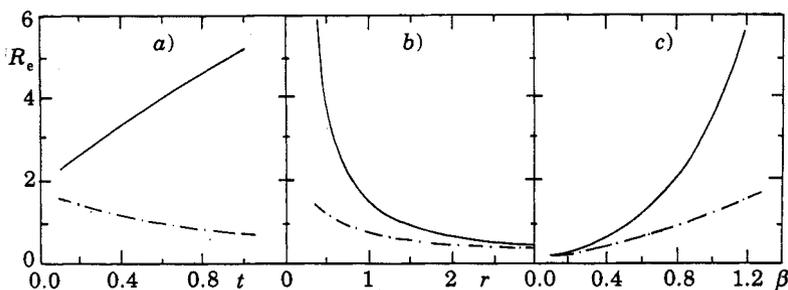
Fig. 2 – The surfactant-to-lipid ratios in the micellar phase R_e^m (solid upper line), and in the vesicles R_e^b (dot-dashed lower line) are plotted as a function of *a)* t, *b)* r, and *c)* β. The parameter γ is set to zero in all cases. In *a)* $r = 0.53$, $\beta = 1$; in *b)* $t = 0.4$ and $\beta = 1$, while in *c)* $r = 0.53$ and $t = 0.4$. Two (out of the three) different parameters are chosen in parts *a)*-*c)* to fit best the PC/OG experimental data, while the third parameter shows the variation around the best fitted point.

cases, γ, which is proportional to the lipid spontaneous curvature c_L, is taken as zero. We take R_e as a variable in fig. 2 in order to compare our results with the experimental ones. Recall the R_e is related to ϕ (our thermodynamic variable) via eq. (2). The difference in specific areas between lipid and surfactant ($r = a_S/a_L \neq 1$) is taken into account and changes the location of the coexisting phases. The upper and lower lines in each of the figure parts describe the dependence of R_e^m and R_e^b, respectively. The range of the parameters t, r and β is chosen in fig. 2 in accord with known (or estimated) values for lipids and surfactants. We find that $R_e^m > R_e^b$ for this entire physical range.

For the PC/OG systems, it is known [14-18] that the specific areas are $a_{PC} = 68 \text{ Å}^2$ and $a_{OG} = 38 \text{ Å}^2$, giving a ratio of $r = 0.53$. This value of r is chosen in fig. 2*a)* and *c)*. For this value of r, the best fit to experimental PC/OG values is for $t \simeq 0.4$ and $\beta \simeq 1$. Those are reasonable values corresponding to a surfactant spontaneous curvature c_S which is about equal to $1/R$, $R \simeq 20 \text{ Å}$ being the radius of the cylindrical micelle. The value of t chosen means that the bending modulus κ is of order $8 k_B T$, again a reasonable estimate.

Our thermodynamic model predicts a phase transition between vesicles and micelles driven by the difference in the bending energy of the two modes of self-assembly of surfactant and lipids. The calculated phase diagram is in accord with the experimental one, fig. 1. Assuming that the monomeric surfactant concentration in the aqueous solution remains constant, the two calculated values R_e^m and R_e^b for the coexisting micelles and vesicles, respectively, give exactly the *constant* slopes of the two boundary lines in fig. 1.

We investigated the trends of the phase behaviour with three parameters r, t, and β, which are functions of the specific areas, temperature, bending rigidity, the micelle size and the spontaneous curvature of the two species. Since not all those parameters are known experimentally, we could only verify, at present, that there is a qualitative agreement between our theory and the experimental phase behaviour, assuming reasonable values. It may be noted that an increase in t (or the bending modulus κ) tends to increase R_e^m and decrease R_e^b. An increase in β (decrease of the surfactant spontaneous curvature) leads to the larger surfactant-to-lipid ratio in both coexisting phases, although the increase is faster in R_e^m than in R_e^b. Those trends can be compared to experiments on several other systems, provided more accurate values of the physical parameters will be measured in the future.

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