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Size Distribution of Reversibly Formed Bilayer Vesicles

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Our previous model calculations [*cf.*: Bergström, M.; Eriksson, J. C. *Langmuir* **1996**, *12*, 624] together with a multiple chemical equilibrium approach indicate that the spontaneous formation of geometrically closed bilayer vesicles is geared primarily by the bilayer tension which in turn is largely determined by the work of bending the bilayer into a spherical vesicle and a statistical–mechanical factor that accounts for the fluctuations in composition, chain packing density, and shape. On this basis, we obtain vesicle size distributions with maxima located at radii several orders of magnitude larger than where the local free energy minimum of a single equilibrated vesicle actually occurs. Moreover, according to our analysis, the relative width of a vesicle size distribution, σ_R/R_{\max} , is generally equal to 0.283 for equilibrated vesicle dispersions, independently of the energetic vesicle parameters. An explicit relation between the bilayer bending constant and the most probable vesicle radius R_{\max} is also derived, showing a dramatic increase in size with the work of bending a planar bilayer into a vesicle. Employing our previous calculations of the bending work of mixed sodium dodecyl sulfate/dodecanol bilayers, we predict vesicles with R_{\max} in the range 0.1–10 μm , in qualitative agreement with experiments.

Introduction

For entropic reasons surfactant aggregates are generally more or less polydisperse; *i.e.*, there is a distribution of sizes about the mean aggregation number. Moreover, the shape and composition of an aggregate fluctuate substantially in the course of time. In the early sixties, Hill¹ developed a theoretical framework, called small systems thermodynamics, for dealing with systems of this kind, where the effects of fluctuations are invoked explicitly and where the fluctuation entropy concept is of central importance. He also showed that when it comes to micellar aggregates, the quasi-statistical–mechanical multiple chemical equilibrium approach is largely equivalent to the treatment derived from small systems thermodynamics.

Using the multiple chemical equilibrium approach, Israelachvili *et al.*,^{2,3} and later on, among others, Eriksson and Ljunggren,^{4–7} presented theoretical calculations as to size distributions of spherical, rod-shaped, and disk-shaped surfactant micelles. More recently (but on the same basis), Eriksson and Ljunggren derived the size distribution of microemulsion droplets, taking into account also the shape and surfactant film density fluctuations.⁸ They could show that the relative width of a microemulsion

droplet size distribution is typically about 0.15, *i.e.*, considerably less than had frequently been inferred earlier, but in agreement with the more recent experimental findings.⁹ Conceptually related theoretical works on microemulsions have been published by Borkovec *et al.*^{10–12}

Previously, the present authors have also applied the multiple equilibrium scheme when considering composition fluctuations for mixed rod-shaped micelles.¹³ The purpose of this paper was to derive size distributions of spontaneously formed vesicles composed of soluble surfactants employing, in essence, the same concepts and ideas.

About 20 years ago, Israelachvili *et al.*,^{2,3} considered vesicle size distributions using the multiple equilibrium framework. However, they took into account merely the fluctuations in size and, hence, ignored the composition, chain packing density, and shape fluctuations. In order to obtain a maximum of an exponential size distribution, $\exp[-\text{constant} \times R^2]$, a packing-constraint-related cutoff function was invoked for small radii.¹⁴ Later on, Helfrich¹⁵ derived a well-known vesicle size distribution function of the form $\propto R^3 \exp[-\text{constant} \times R^2]$ by considering shape as well as size fluctuations.

More recently, additional attempts to calculate vesicle size distributions have been presented. Hervé *et al.*¹⁶ derived a size distribution along lines similar to those of Israelachvili *et al.* and Helfrich. They included a (size-dependent) renormalization of the bending rigidity of the bilayer and found a relative peak width of about 0.3, in good agreement with their experimental results.

For the zero spontaneous curvature case, and assuming mobile surfactant charges, Kumaran¹⁷ obtained a preex-

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ponential factor $\propto R^4$ for the volume fraction distribution and a relative standard deviation in radius equal to $[(4-\pi)/\pi]^{1/2} = 0.523$, whereas, for the mixed amphiphile case, Safran *et al.*¹⁸ predicted a relative width of the size distribution that varies inversely with the square root of the bending modulus and falls in the range 0.1–0.4.

In two recent papers, Morse and Milner^{19,20} derived a vesicle size distribution with a preexponential factor proportional to $R^{-4/3}$ by considering the various shape states for an undulating closed membrane. However, their final result concerning the preexponential factor is quite absurd as they cannot account for vesicles much larger than the bilayer thickness.

Evidently, there is a lack of consensus in this research area with regard to both the proper theoretical approach to use and the more quantitative aspects. In particular, this holds true also for the fundamental issue of how to evaluate the entropy of a dispersion of relatively large particles in a solvent which in the end affects the mathematical form of the size distribution function considerably. In this context it is worth noting that, generally, the width of the size distribution is only weakly dependent on the exponent of R in the preexponential factor, whereas R_{\max} increases with the R exponent. Thus, as a rule, the relative width σ_R/R_{\max} decreases with the magnitude of the R exponent.

The present paper is in a continuation of a recent paper²¹ where we calculated the free energy of forming one single vesicle (local free energy). Below we will show how, on the basis of our previously obtained values of the local vesicle free energy together with a treatment based on the multiple equilibrium approach, we can account for the existence of reversibly formed bilayer vesicles of reasonable sizes without invoking any local free energy minimum.

Basic Notions

Earlier we have shown²¹ that the free energy of forming a large ($R > 10$ times half the bilayer thickness) equilibrated spherical bilayer vesicle out of surfactant monomers in the surrounding solution equals

$$\epsilon(R) = 4\pi(k_{bi} + 2\gamma_{\infty}R^2) \quad (1)$$

where R is the vesicle (midplane) radius, k_{bi} the (size-independent) bending work divided by 4π , and $2\gamma_{\infty}$ the residual tension of the planar bilayer. In other words, $8\pi R^2\gamma_{\infty}$ is the work of forming two planar monolayers with an overall area of $8\pi R^2$, and $4\pi k_{bi}$, the work of bending these monolayers into a spherical bilayer vesicle. Furthermore, there is no need to include R^{-2} or terms of higher order in $1/R$ for vesicles with radii larger than about five times the bilayer thickness.

By employing the free energy expression given by eq 1, we have restricted the treatment to reversibly formed bilayers which are *symmetrical* and have a spontaneous curvature H_0 equal to zero. It is well-known that a chemically pure bilayer, as a rule, is symmetrical in this sense. However, the same holds true also for the mixed case, where we generally have different compositions in the inner and outer vesicle monolayers. This is so because the monolayer composition adjusts upon changing the curvature so as to maintain constant chemical potentials

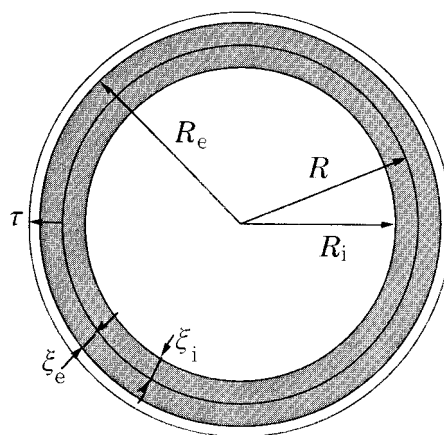


Figure 1. Model of a spherical, geometrically closed unilamellar bilayer vesicle. The two monolayers formally adhere at the radial distance R . τ is set equal to the length of the fully extended hydrocarbon chain. For a C_{12} chain τ equals 16.7 Å.

of the aggregated components and, consequently, the composition and the monolayer tension become monotonously varying functions of curvature about $H = 0$.²¹

Referring to the conventional Helfrich nomenclature, k_{bi} is determined by the two bending constants of the constituent monolayers, k_c^{bi} and \bar{k}_c^{bi} , and, in addition, by their spontaneous curvature and their combined thickness.²² In molecular terms, however, the bending work $4\pi k_{bi}$ is largely due to expulsion of aggregated monomers because of volume reasons, *i.e.*, to a chain packing constraint [*cf.* ref 21].

As the aggregation number is proportional to R^2 , the above free energy expression for a vesicle has the same mathematical form as that for a rod-shaped micelle,¹⁴ *i.e.* $\epsilon = \alpha + N\beta$, for which the length fluctuations are known to be of crucial importance,^{5,13} and, by analogy, there are reasons to anticipate that vesicles are likewise stabilized to a large extent by size fluctuations. However, an energy expression of the above kind merely yields an exponential distribution, and there is the problem of how to generate a peaked, approximately Gaussian, distribution function.

Below we argue that, in addition to the bilayer properties *per se*, a statistical–mechanical factor proportional to R^6 which is related to the various fluctuations plays a major role for the genesis and size distribution of large bilayer vesicles. Otherwise expressed, the circumstance that these aggregates can occupy a large multitude of states with slightly different stoichiometry yields a fluctuation entropy contribution to the free energy of formation which greatly promotes the aggregation process.

Through our previous model calculations,²¹ we have been able to compute the bending constant k_{bi} for pure sodium dodecyl sulfate (SDS) bilayers, as well as for SDS bilayers mixed with dodecanol (DOH). Furthermore, the different contributions to k_{bi} for these two cases have been examined, one important conclusion being that mixing can promote vesicle formation considerably by bringing down the magnitude of k_{bi} .

A spherical vesicle made up solely of, *e.g.*, SDS monomers can be considered geometrically as being composed of three separate parts (*cf.* Figure 1): an inner (i) and an outer (e) monolayer with a total number of $N_s = N_s^i + N_s^e$ aggregated surfactant molecules and an internal water core containing N_w^i water molecules. In addition, we have to take into account that N_w^e water molecules are mixed at the external monolayer surface within a zone

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confined by an external shell located at the fixed radial distance τ from the dividing surface at R where the inner and outer monolayers adhere. We may typically imagine τ to correspond to the length of an extended hydrocarbon chain, for a C_{12} chain $\approx 16.7 \text{ \AA}$. Beyond this external shell at $R + \tau$, the water solution is virtually unaffected by the presence of the vesicle.

For a *mixed* vesicle composed of SDS and DOH monomers we denote the number of aggregated alcohol molecules in the inner and outer monolayers by N_{OH}^i and N_{OH}^e , respectively. The mole fractions of aggregated dodecanol in the two monolayers are then $x_{\text{OH}}^i = N_{\text{OH}}^i/N$ and $x_{\text{OH}}^e = N_{\text{OH}}^e/N^e$, where N stands for $N_s^i + N_{\text{OH}}^i$ and N^e for $N_s^e + N_{\text{OH}}^e$.

The radii of the spherical hydrocarbon/water interfaces at the inner and outer monolayers, $R_i = R - \xi_i$ and $R_e = R + \xi_e$, are related to the midplane radius R through the geometrical relations $4\pi(R^3 - R_i^3)/3 = N v_s$ and $4\pi(R_e^3 - R^3)/3 = N^e v_s$, or, putting $N^i = 4\pi R_i^2/a_i$ and $N^e = 4\pi R_e^2/a_e$

$$R_i^3 + \frac{3v_s}{a_i} R_i^2 - R^3 = 0 \quad (2)$$

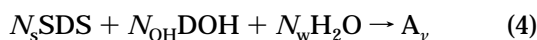
$$R_e^3 - \frac{3v_s}{a_e} R_e^2 - R^3 = 0 \quad (3)$$

where ξ_i and ξ_e are the thicknesses of the hydrocarbon cores of the two monolayers (Figure 1) and a_i and a_e denote the surface areas per chain at the hydrocarbon/water interface in the two monolayers, respectively. The volume of a C_{12} hydrocarbon chain v_s is equal to 351 \AA^3 .

Note that eqs 2 and 3 merely imply that we assume an incompressible hydrocarbon core of the vesicle bilayer and that these equations do not exclude mixing of the chains ascribed to the inner and outer monolayers across the R surface, where the monolayers formally adhere to each other. Moreover, for a fixed hydrocarbon chain volume v_s , eqs 2 and 3 determine R_i and R_e as functions of R and a_i , and of R and a_e , respectively.

Aggregation Equilibrium

Within the framework of the multiple equilibrium approach we are dealing with chemical complexes, and any compositional vesicle state becomes fully defined upon assigning certain values to the independent variables N_s^i , N_s^e , N_w^i , N_w^e , N_{OH}^i , and N_{OH}^e , which determine the stoichiometry of a single vesicle. An arbitrary vesicle state, here denoted by ν , can in principle be reached by means of the aggregation process



which epitomizes that DS^- and DOH monomers (and the proper setup of counterions) aggregate into a vesicular complex in the solution. The free energy of mixing vesicles in state ν with solvent molecules result in a whole set of equilibrium conditions, one for each complex, of the kind [cf. ref 4]

$$\epsilon_\nu + kT \ln \phi_\nu = 0 \quad (5)$$

where ϕ_ν represents the volume fraction of vesicles in state ν , and ϵ_ν is, strictly speaking, the *partial* free energy required to form an additional vesicle in state ν in a solution where equilibrium is already established between aggregates and monomers.

We note that by invoking eq 5 to account for the free energy of mixing large, compact aggregates with small solvent molecules, we follow Guggenheim²³ and Andelman *et al.*²⁴ in using the volume fraction of vesicles rather than the mole fraction as has frequently been done in the past. Recently, we have scrutinized this rather evasive issue in full once more and convinced ourselves that for the sake of consistency it is actually necessary to employ volume fraction as the particle concentration measure.²⁵

The total volume fraction of vesicles is then obtained by means of evaluating the vesicular "partition function"

$$\phi_{\text{tot.}} = \sum_\nu e^{-\epsilon_\nu/kT} \quad (6)$$

where the sum runs over all accessible states. The corresponding integral approximation becomes

$$\phi_{\text{tot.}} = \int_\nu e^{-\epsilon(\nu)/kT} d\nu = \int_R S(R) e^{-\epsilon(R)/kT} dR \quad (7)$$

where we have introduced the size distribution function $\phi(R) \equiv S(R) e^{-\epsilon(R)/kT}$ and where the preexponential factor $S(R)$ accounts for the number and accessibility of fluctuational states in the vicinity of the (spherical) microscopic equilibrium state with free energy equal to $\epsilon(R)$.

Model Calculations of the Free Energy of a Bilayer Vesicle

In our model calculations we have evaluated the free energy ϵ needed to bring $N^i + N^e$ monomers from the surrounding solution to a vesicle as a sum of several separate contributions:²¹ (i) the free energy of transferring $N^i + N^e C_{12}$ hydrocarbon chains from the water phase into a *n*-dodecane bulk phase as quantified by Tanford,²⁶ (ii) the electrostatic free energy related to the charged surfaces and counterions of an ionic surfactant vesicle as calculated by Mitchell and Ninham²⁷ using nonlinearized Poisson–Boltzmann theory, (iii) the chain conformational free energy caused by packing restrictions arising in the hydrocarbon part of a (planar) bilayer as evaluated by Gruen and Lacey,²⁸ (iv) the hydrocarbon/water contact free energy as estimated by employing the (macroscopic) value, 50.7 mJ/m^2 , together with a curvature-dependent term equal to $-2/r$ (spherical case) or $-1/r$ (cylindrical case), where r is the radius of curvature at the hydrocarbon surface, (v) the free energy of mixing different C_{12} monomers in the monolayers, and, finally, (vi) a residual constant free energy term related to the head groups.

It turns out to be convenient to write down the resulting vesicle (excess) free energy expression in the form

$$\epsilon = \epsilon^* + kT \ln [2\pi N^i (1 - x_{\text{OH}}^i) x_{\text{OH}}^i]^{1/2} + kT \ln [2\pi N^e (1 - x_{\text{OH}}^e) x_{\text{OH}}^e]^{1/2} \quad (8)$$

where, in the case of a mixed vesicle, the free energy ϵ^* becomes proportional to the aggregation number earlier than the free energy denoted by ϵ when the bilayer curvature tends to zero.

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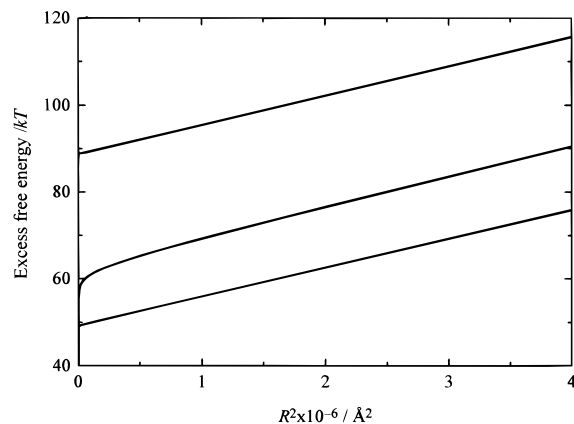


Figure 2. Excess free energy ϵ of a pure SDS (upper curve) and a mixed SDS/DOH vesicle (middle curve) plotted against the square of the radius R . The free energy function ϵ^* for the mixed vesicle is plotted as well (lower curve). The bending bilayer constant for the pure SDS vesicle is $k_{bi} = 16.6$ kT , and the solution state is given by $c_{salt} = 2.0$ M and $c_{surf} = 0.216$ mM. For the mixed vesicle, the bilayer bending constant is $k_{bi} = 3.94$ kT and the solution state is $c_{surf} = 8.78$ mM and $x_{alc} = 5 \times 10^{-8}$ giving a mole fraction of dodecanol for the planar bilayer $x_{OH}^p = 0.52$.

The last two terms in eq 8 arise because we have used $M \approx [2\pi N]^{1/2} (N/e)^N$ in the combinatorial expression for the ideal free energy of mixing in each of the monolayers instead of the conventional Stirling approximation $M \approx (N/e)^N$, and, hence, the mixing contribution (v) for each monolayer is given by the expression

$$\frac{\epsilon_{mix}}{kT} = -\ln\left(\frac{N}{N_s}\right) = M(1 - x_{OH}) \ln(1 - x_{OH}) + x_{OH} \ln x_{OH} + \ln[2\pi N(1 - x_{OH})x_{OH}]^{1/2} \quad (9)$$

where x_{OH} is the mole fraction of aggregated alcohol. Thus, ϵ^* merely includes the first two standard (macroscopically important) terms of ϵ_{mix} .

As will appear below, a vanishingly small *planar* bilayer tension ($2\gamma_\infty = \lim_{R \rightarrow \infty} \epsilon^*(R)/4\pi R^2 < 10^{-3}$ mJ/m²) is a prerequisite for large vesicles to form. This is the main reason why the last term of eq 9 becomes important even for comparatively large N . Employing this more accurate expression in place of the usual Stirling approximation (without the $[2\pi N]^{1/2}$ factor) has in fact rather far-reaching consequences as to the resulting size distribution.

In Figure 2 we have plotted the free energy $\epsilon(R)$ for a pure SDS vesicle and $\epsilon(R)$ and $\epsilon^*(R)$ for a mixed SDS/DOH vesicle. It appears that, for the mixed case, $\epsilon^*(R) = 4\pi(k_{bi} + 2\gamma_\infty R^2)$ is actually a somewhat better approximation than the original eq 1 in the sense that k_{bi} can be regarded as a constant.

General Discussion About the Fluctuations

As was mentioned above, within the multiple chemical equilibrium approach the primary compositional state variables for a mixed surfactant vesicle are $N_s^i, N_s^e, N_w^i, N_w^e, N_{OH}^i, N_{OH}^e$, or, alternatively, $N, N^e, N_w^i, N_w^e, N_{OH}^i, N_{OH}^e$, where N and N^e are the number of hydrocarbon chains in the two monolayers. In the end, however, it turns out to be convenient to switch to another set of independent variables, *viz.*, the midplane radius, R ; the vesicle shape factor, $\chi \equiv$ the midplane surface area A_{mid} divided by $4\pi R^2$; the surface areas per chain, a_i and a_e ; and the monolayer mole fractions, x_{OH}^i and x_{OH}^e . From a mathematical point of view, a central problem is then to

evaluate the Jacobian, here denoted by J_6 , of the variable transformation

$$J_6 = \left| \frac{\partial(N^i, N^e, N_w^i, N_w^e, N_{OH}^i, N_{OH}^e)}{\partial(R, \chi, a_i, a_e, x_{OH}^i, x_{OH}^e)} \right| \quad (10)$$

in order to solve the integral of eq 7. Nevertheless, to achieve a more lucid account, we will make an equivalent, though stepwise, approach. We first discuss the nature of the main type of fluctuations taking place under the ordinary regime of macroscopic equilibrium.

Depending upon the vesicle size and shape, and the chain packing densities in the two monolayers, the number of hydrocarbon chains, N and N^e , in the inner and outer monolayers, respectively, will fluctuate in accordance with the relations

$$N^i = 4\pi R_i^2 \chi / a_i \quad (11)$$

$$N^e = 4\pi R_e^2 \chi / a_e \quad (12)$$

which relations define the (instantaneous) average surface areas per hydrocarbon chain, a_i and a_e , respectively. Here, we have invoked the rather reasonable approximations

$$\chi \equiv A_{mid}/4\pi R^2 \approx A_i/4\pi R_i^2 \approx A_e/4\pi R_e^2 \quad (13)$$

Moreover, as to the number of water molecules taking part, we have the following approximate expressions,

$$N_w^i v_w + N^i v_s = \frac{4}{3} \pi R^3 \quad (14)$$

$$N_w^e v_w + N^e v_s = 4\pi R_e^3 \chi \tau \quad (15)$$

where, in eq 15, we have also assumed the vesicles to be large enough for a planar approximation to be valid for the outer layer of monomers and adjacent water molecules. Finally, the number of dodecanol molecules aggregated in the vesicle is obtained simply by multiplying eqs 11 and 12 with x_{OH}^i and x_{OH}^e , respectively.

Now, it is rather evident that for any fixed size and shape and for any monolayer chain packing density, the mole fractions x_{OH}^i and x_{OH}^e can fluctuate freely about the average compositions, keeping N, N^e, N_w^i , and N_w^e unaffected. In other words, the integrals over N_{OH}^i and N_{OH}^e can be separated out from the multiple integral in eq 7 and we can treat the composition fluctuations separately. Likewise, by considering the outer layer, composed of N^e monomers and N_w^e water molecules, as a planar layer (which is very reasonable for the comparatively large vesicles we consider), we can treat the integral over N_w^e in eq 7 separately as will become evident below. However, due to computational reasons, we cannot separate the corresponding integral of the inner monolayer. This is so because in our definition of the vesicle we have included the entire water part enclosed by the bilayer. Hence, employing the geometrical expressions given above makes it most convenient to treat the chain packing density fluctuations in the two monolayers *mathematically* differently. We emphasize that our choice to include the whole water core in the definition of the vesicle aggregate is arbitrary and does not influence the final result.

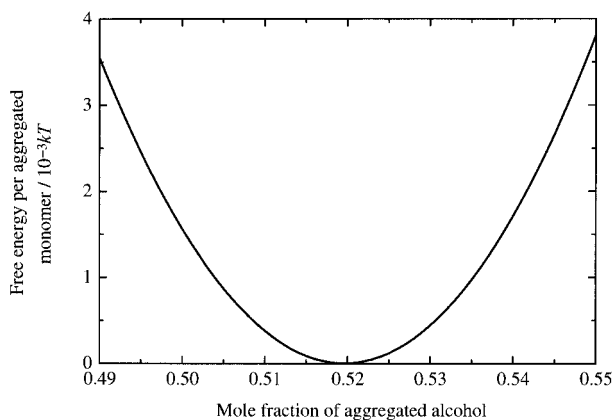


Figure 3. Excess free energy per aggregated monomer, ϵ/NkT , for a planar bilayer of SDS mixed with dodecanol, as a function of the mole fraction of aggregated alcohol monomers, x_{OH} . To a very good approximation, it can be written as $\epsilon(x_{OH})/NkT = \kappa_x(x_{OH} - \bar{x}_{OH})^2 + \epsilon_{eq}/NkT$, where κ_x is found to be equal to 4.13 in accordance with our previous model calculations presented in ref 21. The solution state is identical to that in Figure 2.

Composition Fluctuations

In order to account for the composition dependence of the excess free energy function for a single *monolayer* at a fixed solution state we make a truncated Taylor expansion about the equilibrium composition, \bar{x}_{OH} . In Figure 3 we have plotted the excess free energy per chain $\epsilon_{N_{OH}}/N$, against the mole fraction of aggregated DOH for a planar monolayer with a fixed chain packing density as obtained from model calculations. Thus, for given N and N_w , we have a set of equations corresponding to each compositional state of the monolayer of the kind

$$\frac{\epsilon_{N_{OH}}(N, N_w)}{NkT} = \kappa_x(x_{OH} - \bar{x}_{OH})^2 + \frac{\epsilon_{eq}(N, N_w)}{NkT} \quad (16)$$

where N , N_{OH} , and N_w now denote the respective number of chains and dodecanol and water molecules in the inner or outer parts of the vesicle and κ_x is determined by the curvature at the minimum

$$\kappa_x \equiv \frac{1}{2} \frac{\partial^2(\epsilon_{N_{OH}}/NkT)}{\partial x_{OH}^2} [x_{OH} = \bar{x}_{OH}] \quad (17)$$

The free energy at the minimum is, of course, $\epsilon_{eq} = \epsilon_{N_{OH}}(\bar{x}_{OH})$. Furthermore, according to our model calculations, κ_x is practically independent of the geometrical shape (and, within limits, also of the chain packing density and \bar{x}_{OH}), and, hence, considering that the fluctuation states in the vicinity of the equilibrium state will anyhow be the most important, we may always insert the same value of the constant κ_x . Multiplying eq 16 with N yields

$$\frac{\epsilon_{N_{OH}}(N, N_w)}{kT} = \frac{\kappa_x}{N}(N_{OH} - \bar{N}_{OH})^2 + \frac{\epsilon_{eq}(N, N_w)}{kT} \quad (18)$$

or

$$\frac{\Delta \epsilon_{N_{OH}}(N)}{kT} = \frac{\kappa_x}{N}(\Delta N_{OH})^2 = \frac{(\Delta N_{OH})^2}{2\sigma_{N_{OH}}^2} \quad (18)$$

implying that, approximately, we have a Gaussian distribution of vesicles about the equilibrium number of dodecanol molecules, \bar{N}_{OH} , as an immediate consequence

of the quadratic N_{OH} dependence. It follows that, the standard deviation with respect to N_{OH} in a monolayer, $\sigma_{N_{OH}}$, is given by the simple expression

$$\sigma_{N_{OH}} = [N/2\kappa_x]^{1/2} \quad (20)$$

and that it increases with the square root of the chain aggregation number N . Accordingly, a growing number of compositional states become involved as the system size increases. On the other hand, the *relative* standard deviation,

$$\frac{\sigma_{N_{OH}}}{N} = \frac{1}{[2N\kappa_x]^{1/2}} \quad (21)$$

decreases with the size of the system, as must necessarily be the case.

The corresponding factor contributing to the vesicular partition function in eq 6 becomes

$$\sum_{N_{OH}} e^{-\Delta \epsilon_{N_{OH}}/kT} = \int_{-\infty}^{+\infty} \exp\left[-\frac{\kappa_x(\Delta N_{OH})^2}{N}\right] d(\Delta N_{OH}) = \left[\frac{\pi N}{\kappa_x}\right]^{1/2} \quad (22)$$

and implies integrating over all amphiphile compositions in the monolayer. This compositional partition function is thus proportional to $N^{1/2}$. By comparison of eqs 20 and 22, it is seen that the compositional partition function equals $[2\pi]^{1/2}\sigma_{N_{OH}}$.

Chain Packing Density Fluctuations in the External Monolayer

The number of water molecules adjacent to the hydrocarbon core of the outer monolayer which are located between $R + \xi_e$ and $R + \tau$ (Figure 1) determine indirectly the chain packing density at the hydrocarbon/water contact surface, $\Gamma_e = N^e/A_e = 1/a_e$. For a given composition and overall number of chains in the monolayer we set, similarly to that above,

$$\frac{\Delta \epsilon_{N_w^e}}{N^e kT} \equiv \frac{\epsilon_{N_w^e}(N^e, N_{OH}^e) - \epsilon_{eq}(N^e, N_{OH}^e)}{N^e kT} = \kappa_a(a_e - \bar{a}_e)^2 \quad (23)$$

where $\epsilon_{eq} = \epsilon_{N_w^e}(\bar{a}_e)$ is the equilibrium value for $a_e = \bar{a}_e$ in the monolayer, and the constant κ_a is defined by

$$\kappa_a \equiv \frac{1}{2} \frac{\partial^2(\epsilon_{N_w^e} N^e kT)}{\partial a_e^2} [a_e = \bar{a}_e] \quad (24)$$

In practice κ_a is independent of curvature, and, hence, we can put κ_a equal for the inner and outer monolayers. $\epsilon_{N_w^e}/N^e kT$ as obtained from model calculations for a planar monolayer is plotted against a_e in Figure 4 and is seen to fulfill the quadratic expression 23 within a fairly wide range.

From eq 23 we can now derive a partition function similar to the expression for composition fluctuations, eq 22. Approximately, the volume of the hydrocarbon core of the external monolayer plus a layer of adjacent water

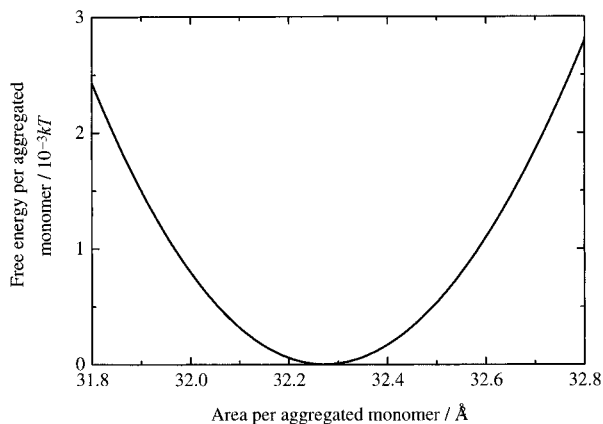


Figure 4. Excess free energy per aggregated monomer, ϵ/NkT , for a planar bilayer of SDS mixed with dodecanol, as a function of the area per headgroup, a . To a very good approximation it can be written as $\epsilon(a)/NkT = \kappa_a(a - \bar{a})^2 + \epsilon_{eq}/NkT$, where κ_a is found to be equal to 108 nm^{-4} in accordance with our previous model calculations given in ref 21. The solution state is identical to that for the mixed case in Figure 2.

molecules within the thickness τ equals $N^e a_e \tau = N_w^e v_w + N^e v_s$ (cf. Figure 1), and we can rewrite eq 23 as follows

$$\frac{\Delta \epsilon N_w^e}{kT} = \frac{\kappa_a v_w^2}{N^e \tau^2} (\Delta N_w^e)^2 \quad (25)$$

where $\Delta N_w^e = N_w^e - \bar{N}_w^e$. The standard deviation becomes

$$\sigma_{N_w^e} = \frac{\tau}{v_w} \left[\frac{N^e}{2\kappa_a} \right]^{1/2} \quad (26)$$

By summing the Boltzmann factors over all chain packing density states, we obtain the following expression for the partition function

$$\sum_{N_w^e} e^{-\Delta \epsilon N_w^e/kT} = \int_{-\infty}^{+\infty} \exp \left[-\frac{\kappa_a v_w^2}{N^e \tau^2} (\Delta N_w^e)^2 \right] d(\Delta N_w^e) = \frac{\tau}{v_w} \left[\frac{\pi N^e}{\kappa_a} \right]^{1/2} \quad (27)$$

which is also equal to $[2\pi]^{1/2} \sigma_{N_w^e}$. By setting τ equal to the fully extended hydrocarbon chain length, the minimum accessible value of a_e will correspond to $N_w^e = 0$. However, in order to solve the integral, we have replaced its lower limit, $\Delta N_w^e = -\bar{N}_w^e$, with $-\infty$. We can safely do so since the free energy term given in eq 25 of a monolayer with a thickness equal to the length of a fully extended hydrocarbon chain is about $6000kT$ using typical values of κ_a from our model calculations. The result can be rationalized considering the enormous loss in chain conformational entropy of forming such a monolayer.²⁸ The final result as to the chain packing density partition function is not influenced by this approximation as the contribution to the integral in the interval $[-\infty, -\bar{N}_w^e]$ for all practical purposes equals zero.

General Form of the Size Distribution

Since the deviations in monolayer compositions and chain packing densities are comparatively small for the most frequently occurring vesicles, we can, to a good approximation, assume constant values of κ_x and κ_a . This means that the compositions and chain packing densities

in the two monolayers are assumed to fluctuate independently. Accordingly, we may now write eq 7 as follows

$$\begin{aligned} \phi_{\text{tot.}} &= \int_0^{+\infty} \int_0^{+\infty} \int_0^{+\infty} \left[\int_0^{+\infty} e^{-\Delta \epsilon N_{\text{OH}}^i/kT} dN_{\text{OH}}^i \int_0^{+\infty} e^{-\Delta \epsilon N_{\text{OH}}^e/kT} \times \right. \\ &\quad \left. dN_{\text{OH}}^e \int_0^{+\infty} e^{-\Delta \epsilon N_w^i/kT} dN_w^i \right] e^{-\epsilon_{\text{eq}}(N^e, N^i, N_w^i)/kT} dN^e dN^i dN_w^i \\ &= \int_0^{+\infty} \int_0^{+\infty} \int_0^{+\infty} \left[\frac{\pi N^e}{\kappa_x} \right]^{1/2} \left[\frac{\pi N^i}{\kappa_x} \right]^{1/2} \frac{\tau}{v_w} \times \\ &\quad \left[\frac{\pi N^e}{\kappa_a} \right]^{1/2} e^{-\epsilon_{\text{eq}}(N^e, N^i, N_w^i)/kT} dN^e dN^i dN_w^i \quad (28) \end{aligned}$$

where $\epsilon_{\text{eq}}(N^e, N^i, N_w^e)$ denotes the excess free energy associated with any setup of size, shape, and chain packing density in the inner monolayer but with the monolayer compositions as well as the chain packing density in the outer monolayer fixed at the proper equilibrium values. Making use of eq 8, we derive

$$\phi_{\text{tot.}} = \frac{C}{2\kappa_x} \int_0^{+\infty} \int_0^{+\infty} \int_0^{+\infty} \frac{\tau}{v_w} \times \left[\frac{\pi N^e}{\kappa_a} \right]^{1/2} e^{-\epsilon_{\text{eq}}(N^e, N^i, N_w^i)/kT} dN^e dN^i dN_w^i \quad (29)$$

where the (mixed case) factor C is defined by

$$C = [\bar{x}_{\text{OH}}^i (1 - \bar{x}_{\text{OH}}^i) \bar{x}_{\text{OH}}^e (1 - \bar{x}_{\text{OH}}^e)]^{-1/2} \quad (30)$$

In spite of the circumstance that \bar{x}_{OH}^i and \bar{x}_{OH}^e both depend on curvature, one can verify that to a good approximation C is given by the relation

$$C = [\bar{x}_{\text{OH}}^p (1 - \bar{x}_{\text{OH}}^p)]^{-1/2} \quad (31)$$

where \bar{x}_{OH}^p denotes the alcohol mole fraction in the equilibrated planar monolayer. This is why the factor C can be placed in front of the integration signs in eq 29. Note that eq 29 holds for pure aggregates as well, provided the factor $C/2\kappa_x$ is omitted. We also point out that, for identical monomers, the factor $C/2\kappa_x$ becomes equal to 1, as should obviously be the case.

It is noteworthy and even somewhat surprising that $\pi[N^e N^i]^{1/2}$ in eq 28 cancels owing to the inclusion of the nonconventional mixing terms in eq 8. In the end this means that the preexponential factor on the right hand side of the second equality in eq 7 depends less strongly on R than one might first have anticipated. In order to solve the triple integral in eq 29, it is convenient to switch to using R , χ , and a_i as independent variables instead of N^e , N^i , and N_w^i . Hence, we have to evaluate the Jacobian

$$J_3 = \left| \frac{\partial(N^i, N^e, N_w^i)}{\partial(R, \chi, a_i)} \right| \quad (32)$$

This, however, is easily done by means of employing eqs 11–14 above. One finds the following expression

$$J_3 = \frac{64\pi^3 \chi}{\bar{a}_e a_i^2 v_w} R_i^2 R_e^2 R^2 \left[1 - \frac{2a_i}{R_i} \left(\frac{\partial R_i}{\partial a_i} \right)_{R, \chi} \right] \quad (33)$$

For small deviations from spherical shape we can use eq 2 to obtain

$$\left(\frac{\partial R_i}{\partial a_i}\right)_{a_i, x} = \frac{R_i v_s}{a_i(R_i a_i + 2v_s)} \quad (34)$$

and, consequently, the Jacobian is

$$J_3 = \frac{64\pi^3 \chi}{\bar{a}_e a_i^2 v_w} R_i^3 R_e^2 \quad (35)$$

where we have set $\xi_i + \xi_e \approx 2v_s/a_i$. Thus, eq 29 is transformed into the largely equivalent integral

$$\phi_{\text{tot.}} = \frac{64C\tau\pi^4}{\kappa_x \kappa_a^{1/2} \bar{a}_e^{3/2} v_w^2} \times \int_0^{+\infty} \int_{+1}^{+\infty} \int_{a_{\min}^i}^{+\infty} \frac{R_i^3 R_e^2 R^2 \chi^{3/2}}{a_i^2} e^{-\epsilon_{\text{eq}}^*(R, \chi, a_i)/kT} da_i d\chi dR \quad (36)$$

where a_{\min}^i corresponds to the fully extended hydrocarbon chain. Next we wish to evaluate the contributions due to the fluctuations occurring for the surface area of the hydrocarbon chains in the inner monolayer a_i , *i.e.*, the chain packing density in the inner monolayer. With this purpose in mind we should first find an appropriate form of the free energy expression $\epsilon_{\text{eq}}^*(R, \chi, a_i)$.

In an additive manner we can write $\epsilon_{\text{eq}}^*(R, \chi, a_i)$ as a sum of the work of forming a vesicle, fully equilibrated with respect to compositions and chain packing densities in the two monolayers, $\epsilon^*(R, \chi)$, and the work of changing the chain packing density in the inner monolayer from its equilibrium value \bar{a}_i , *i.e.*,

$$\frac{\epsilon_{\text{eq}}^*(R, \chi, a_i)}{kT} = \frac{\epsilon^*(R, \chi)}{kT} + \frac{4\pi R_i^2 \chi}{a_i} \kappa_a (a_i - \bar{a}_i)^2 \quad (37)$$

where the asterisks denote that we have subtracted the logarithmic free energy of mixing terms according to eq 8 from both sides of the equality sign. Note that, for simplicity, we have omitted the subscript (*eq*) in the ϵ^* -(R, χ) function. Inserting eq 37 in eq 36 gives

$$\phi_{\text{tot.}} = \frac{64\pi^4 C\tau}{\kappa_x \kappa_a^{1/2} \bar{a}_e^{3/2} v_w^2} \int_0^{+\infty} \int_{+1}^{+\infty} R_e^2 R^2 \chi^{3/2} e^{-\epsilon^*(R, \chi)/kT} \times \left[\int_{a_{\min}^i}^{+\infty} \frac{R_i^3}{a_i^2} \exp\left[-\frac{4\pi R_i^2 \chi}{a_i} \kappa_a (a_i - \bar{a}_i)^2\right] da_i \right] d\chi dR \quad (38)$$

We can solve the chain packing density integral by writing

$$\int_{a_{\min}^i}^{+\infty} \frac{R_i^3}{a_i^2} \exp\left[-\frac{4\pi R_i^2 \chi}{a_i} \kappa_a (a_i - \bar{a}_i)^2\right] da_i = \int_{-\infty}^{+\infty} R_i^3 \frac{\exp[-4\pi R_i^2 \chi \kappa_a t_i^2/a_i]}{(t_i + \bar{a}_i)^2} dt_i \approx \frac{R_i^3}{a_i^2} \left[\frac{\pi \bar{a}_i}{4\pi R_i^2 \chi \kappa_a} \right]^{1/2} \quad (39)$$

where we have set $t_i = a_i - \bar{a}_i \ll \bar{a}_i$, $t_e = a_e - \bar{a}_e \ll \bar{a}_e$, $a_i \approx \bar{a}_i$, and $a_e \approx \bar{a}_e$ and assumed R_i to be constant within the interval of integration. Since the integral equals zero in the interval $[-\infty, t_{\min}]$, where t_{\min} corresponds to the

fully extended hydrocarbon chain length, we have set the lower limit of the integral equal to $-\infty$. This yields

$$\phi_{\text{tot.}} = \frac{32\pi^4 C\tau}{\kappa_x \kappa_a v_w^2} \int_0^{+\infty} \int_{+1}^{+\infty} \frac{(R_i R_e)^2}{(\bar{a}_e \bar{a}_i)^{3/2}} \chi e^{-\epsilon^*(R, \chi)/kT} d\chi dR \quad (40)$$

For small deviations from spherical shape we can set $(\bar{a}_i \bar{a}_e)^{3/2} \approx \bar{a}_p^3$ and move this factor outside the integration signs. We also have $R^4 \approx R_i^2 R_e^2$, and eq 40 can be simplified into

$$\phi_{\text{tot.}} = \frac{32\pi^4 C\tau}{\kappa_x \kappa_a v_w^2 \bar{a}_p^3} \int_0^{+\infty} \int_{+1}^{+\infty} \chi R^6 e^{-\epsilon^*(R, \chi)/kT} d\chi dR \quad (41)$$

In order to integrate eq 41 over all the various shape states, we need an expression of the free energy $\epsilon^*(R, \chi)$ as a function of χ . This can be achieved if we consider the process of increasing the midplane surface by deforming the shape of the vesicle while keeping the volume inside R fixed; *i.e.*, χ is changed at constant R . Since we are dealing with small deviations from spherical shape, we can expand the free energy it takes to deform a spherical shaped vesicle to first order in the surface area of the midplane. Writing the total free energy of the vesicle as a sum of the work of forming a perfectly spherical vesicle $\epsilon^*(R) = 4\pi(k_{bi} + 2\gamma_\infty R^2)$, and the deformation work results in

$$\epsilon^*(R, \chi) = \epsilon^*(R) + \gamma'(R) \Delta A_{\text{mid}} = \epsilon^*(R) + 4\pi R^2 \gamma'(R) (\chi - 1) \quad (42)$$

which holds for small values of the relative deviation of the midplane radius $\Delta A_{\text{mid}}/A_{\text{mid}}$.

The bilayer tension related to the work of deforming the vesicle is defined by

$$\gamma'(R) \equiv \left(\frac{\partial \epsilon^*(R, \chi=1)}{\partial A_{\text{mid}}} \right)_R \quad (43)$$

Inserting eq 42 in eq 41 gives

$$\phi_{\text{tot.}} = \frac{32\pi^4 C\tau}{\kappa_x \kappa_a v_w^2 \bar{a}_p^3} \int_0^{+\infty} R^6 e^{-\epsilon^*(R)/kT} \times \left[\int_1^{+\infty} \chi e^{-4\pi R^2 \gamma'(R) (\chi-1)/kT} d\chi \right] dR \quad (44)$$

and after integrating over all the shape states,

$$\phi_{\text{tot.}} = \frac{2\pi^2 C\tau (kT)^2}{\kappa_x \kappa_a v_w^2 \bar{a}_p^3} \int_0^{+\infty} \frac{R^2}{\gamma'(R)^2} \times \left(\frac{4\pi R^2 \gamma'(R)}{kT} + 1 \right) e^{-\epsilon^*(R)/kT} dR \quad (45)$$

This means that at the present stage, before considering the influence of the shape fluctuations in detail, we can write the size distribution function as follows

$$\phi(R) = \frac{2\pi^2 C\tau (kT)^2}{\kappa_x \kappa_a v_w^2 \bar{a}_p^3} \frac{R^2}{\gamma'(R)^2} \times \left(\frac{4\pi R^2 \gamma'(R)}{kT} + 1 \right) e^{-4\pi(k_{bi} + 2\gamma_\infty R^2)/kT} \quad (46)$$

where we have inserted the excess free energy expression for a perfectly spherical vesicle $\epsilon^*(R) = 4\pi(k_{bi} + 2\gamma_\infty R^2)$.

Influence of Shape Fluctuations

In order to proceed with the Taylor expansion eq 42 in terms of the shape parameter χ , it is necessary to specify the shape-related bilayer tension $\gamma'(R)$. We shall do so by referring to the well-known Helfrich curvature free energy expression, which is given by

$$\gamma_{bi}(H, K) = \gamma_{bi}^p + 2k_c^{bi}(H - H_0)^2 + \bar{k}_c^{bi}K \quad (47)$$

and which approximately accounts for the effects of curvature on the bilayer tension at constant chemical potentials. Here, $H \equiv (c_1 + c_2)/2$ is the mean curvature and $K \equiv c_1 c_2$ the Gaussian curvature of the midplane surface. The spontaneous curvature H_0 equals zero for a symmetrical bilayer. Hence, γ_{bi}^0 equals $\gamma_{bi}^0(H=0, K=0)$, i.e., for a planar bilayer, and is the same as twice the planar monolayer tension γ_∞ . The overall free energy of a vesicle becomes

$$\begin{aligned} \epsilon^*(R, \chi) &= \int_{A_{mid}} \gamma_{bi}(H, K) dA = 2\gamma_\infty A_{mid} + \\ &2k_c^{bi} \int_{A_{mid}} H^2 dA + \bar{k}_c^{bi} \int_{A_{mid}} K dA \\ &\approx 8\pi R^2 \gamma_\infty + 2k_c^{bi} \int_{A_{mid}} H^2 dA + 4\pi \bar{k}_c^{bi} \end{aligned} \quad (48)$$

where γ_{bi}^0 has been replaced by $2\gamma_\infty$ and we have taken due account of the Gauss–Bonnet theorem according to which the integral over the Gaussian curvature, i.e., the last term of eq 48, is a constant equal to $4\pi \bar{k}_c^{bi}$ for any geometrically closed surface.

The change in surface area and free energy upon deforming a spherical vesicle at a fixed radius R , i.e., for a given interior volume, has been calculated by Milner and Safran²⁹ to second order in the relative radial deformation $u(\theta, \varphi) \equiv 1 - r(\theta, \varphi)/R$ by means of an expansion into spherical harmonics $r(\theta, \varphi) = R(1 + \sum u_{lm} Y_{lm}(\theta, \varphi))$. For a given shape fluctuation mode l they obtained the following expressions (assuming $\gamma_{bi}^0 = 0$)

$$\Delta\epsilon_l(R, \chi) = \frac{k_c^{bi}}{2} |u_{lm}|^2 l(l+1)(l-1)(l+2) \quad l \geq 2 \quad (49)$$

$$\Delta A_{mid, l}(R, \chi) = \frac{R^2}{2} |u_{lm}|^2 l(l-1)(l+1) \quad l \geq 2 \quad (50)$$

where the $l=0$ and $l=1$ modes have been excluded because they represent radial and translational oscillations of the vesicles, respectively. For the small deviations from spherical shape that we consider here, we can combine eqs 49 and 50 to give the shape-related bilayer tension

$$\gamma'_l(R) \approx \frac{\Delta\epsilon_l(R, \chi) + 2\gamma_\infty \Delta A_{mid, l}(R, \chi)}{\Delta A_{mid, l}(R, \chi)} = l(l+1) \frac{k_c}{R^2} + 2\gamma_\infty \quad (51)$$

where we have also included the stretching free energy $2\gamma_\infty A_{mid}$. Thus, in accordance with eq 42,

$$\epsilon^*(R, \chi) = 4\pi(k_{bi} + 2\gamma_\infty R^2) + 4\pi(\chi - 1)[2\gamma_\infty R^2 + l(l+1)k_c^{bi}] \quad (52)$$

where the first term refers to the undistorted spherical

vesicle and the second term accounts for the free energy needed for small spherical–harmonic shape changes. This result implies that there is a substantial resistance with respect to deviations from spherical shape because, by and large, we can expect $4\pi l(l+1)k_c^{bi}$ to be of the order $\geq 10^2 kT$, and, thus, shape fluctuations with $\chi \geq 1.05$ are for the most part excluded. Moreover, anticipating $2\gamma_\infty R^2$ to be of the order of kT , we reckon that $l(l+1)k_c^{bi}$ is usually the predominant term in the last parentheses.

Inserting eq 51 in eq 46 and assuming that $4\pi l(l+1)k_c^{bi} \gg kT$ yield the size distribution for a given shape mode l

$$\phi_l(R) = \frac{8\pi^3 C \tau k T R^6}{l(l+1)k_c^{bi} \kappa_x \kappa_a V_w^2 \bar{a}_p^3} e^{-4\pi(k_{bi} + \gamma_\infty R^2)/kT} \quad (53)$$

The size distribution of the most favorable nonspherical vesicles, which are in (the 5-fold degenerate) $l=2$ state, is readily found to be

$$\phi(R) = \frac{4\pi^3 C \tau k T}{3k_c^{bi} \kappa_x \kappa_a V_w^2 \bar{a}_p^3} R^6 e^{-4\pi(k_{bi} + 2\gamma_\infty R^2)/kT} \quad (54)$$

These $l=2$ shapes include, of course, the oblate/prolate spheroids. Higher order shape modes can, in principle, be included in the $\epsilon^*(R)$ function and might give rise to an additional logarithmic contribution to the local free energy. However, it is reasonable to assume that the large free energy contributions due to higher order bending terms restrict the short-wavelength shape undulations to such an extent that highly rippled membranes give a negligible contribution to the vesicle size distribution and that eq 54 after all holds true to a sufficiently good approximation. Furthermore, only such fairly regular shapes which are compatible with a uniform pressure inside a vesicle are likely to be of any importance. This constraint is actually expressed by the Laplace equation for Helfrich surfaces³⁰

$$\begin{aligned} \Delta P &= 2H\gamma_{bi}^0 - 4k_c^{bi}(H - H_0)(H^2 + HH_0 - K) - \\ &2k_c^{bi} \nabla_s^2 H = \text{constant} \end{aligned} \quad (55)$$

where ∇_s^2 is the Laplace–Beltrami operator of the surface. Accordingly, we envisage that, for the most part, just (observable) spheroidal $l=2$ vesicle shapes should be invoked here which chiefly arise due to fusion/fission events and which persist for some length of time while slowly varying their contours and, hence, their stoichiometric compositions.

Examples of size distributions are presented in Figures 5 and 6. The deviations from Gaussian shape are rather minor. In the figures we have employed numerical values of the various thermodynamical parameters in eq 54 as calculated from our model presented in detail in ref 21.

Referring back to eq 7, we find that the statistical–mechanical factor is equal to

$$S^*(R) = \frac{4\pi^3 C \tau k T R^6}{3k_c^{bi} \kappa_x \kappa_a V_w^2 \bar{a}_p^3} \quad (56)$$

where the asterisk denotes that $\epsilon^*(R)$ has been inserted, not $\epsilon(R)$. Hence, $S(R)$ as it stands in eq 7 is proportional to R^8 since a $[N^l N^e]^{1/2}$ factor arises owing to the relation

(29) Milner, S. T.; Safran, S. A. *Phys. Rev. A* **1987**, *36*, 4371.

(30) Ljunggren, S.; Eriksson, J. C.; Kralchevsky, P. A. *J. Colloid Interface Sci.* **1997**, *191*, 424.

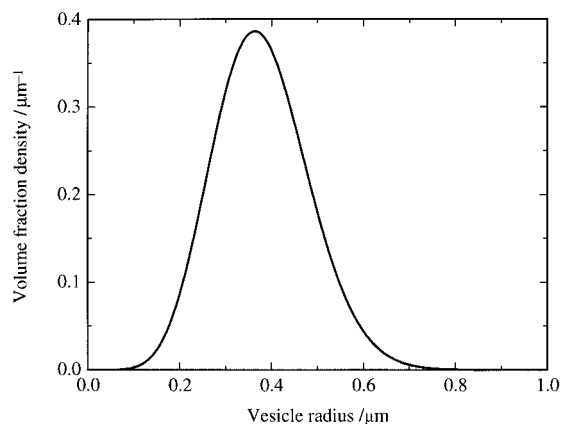


Figure 5. Vesicle size distribution for a mixed SDS/DOH case in agreement with eq 54 obtained for the same solution state as in Figure 2, giving a total mole fraction of aggregated dodecanol equal to 52 mol %. The position of the size distribution maximum is at $R_{\max} = 0.363 \mu\text{m}$. The planar bilayer tension is $2\gamma_{\infty} = 7.45 \times 10^{-6} \text{ mJ/m}^2$, giving a total volume fraction of vesicles $\phi_{\text{tot}} = 0.1$. The bilayer bending constant $k_{\text{bi}} = 3.90 \text{ kT}$ and $k_c^{\text{bi}} = 3.16 \text{ kT}$ were calculated in accordance with the model presented in detail in ref 21.

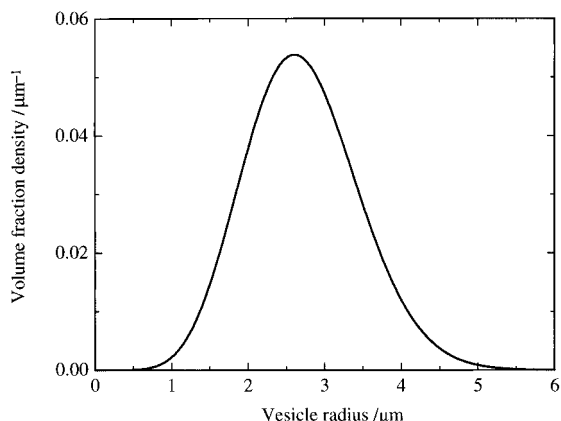


Figure 6. Vesicle size distribution for a mixed SDS/DOH case according to eq 54 obtained for the SDS monomer concentration $c_{\text{surf}} = 4.86 \text{ mM}$ and a mole fraction of dodecanol $x_{\text{alc}} = 1 \times 10^{-7}$, giving a total mole fraction of aggregated dodecanol equal to 72 mol %. The planar bilayer tension $2\gamma_{\infty}$ equals $1.45 \times 10^{-7} \text{ mJ/m}^2$, resulting in a total volume fraction of vesicles $\phi_{\text{tot}} = 0.1$. The bending parameters $k_{\text{bi}} = 5.02 \text{ kT}$ and $k_c^{\text{bi}} = 1.99 \text{ kT}$ were calculated in accordance with the model presented in detail in ref 21. The position of the maximum is at $R_{\max} = 2.61 \mu\text{m}$.

between $\epsilon^*(R)$ and $\epsilon(R)$. $S^*(R)$ is an extremely large factor, typically amounting to 10^{25} – 10^{30} m^{-1} .

It is worth noting that $S^*(R)$ is independent of the hydrocarbon chain volume, v_s , but depends linearly on the overall thickness, τ , of the external monolayer. Further, the size distribution is the product of two competing R -dependent factors, one of largely entropic origin, $S^*(R)$, and one of local energetic nature, $\exp(-\epsilon^*(R)/kT)$. The latter exponential factor represents a balance between the entropy of mixing surfactant aggregates with solvent molecules, favoring small aggregates, and a *positive* bending work, favoring large aggregates, resulting in vesicles of finite size but exhibiting no maximum in the size distribution as a function of the aggregation number.¹⁴ The prefactor $S^*(R)$ is favoring large vesicles, and together with the exponential factor it gives rise to a size distribution with a maximum corresponding to the most probable vesicle size.

Considering the origin of the factor $S^*(R)$, one finds that integration over all chain packing density states using

a quadratic free energy expression results in a preexponential factor proportional to $[N^{\text{w}}N^{\text{s}}]^{1/2}$; it contributes with a factor R^2 to $S^*(R)$. Moreover, changing the variable from the number of water molecules within the core of the vesicle, N^{w} , to R results in another R^2 factor. As was shown above, the composition fluctuations and the finite size-correction term to the free energy of mixing yield no resulting net contribution to the exponent of R in the preexponential factor.

Integration over all the shape states using the linear shape free energy $4\pi R^2 \gamma'(R)(\chi - 1)$ gives no R -dependent contribution to $S^*(R)$ *per se*. However, since $\gamma'(R)$ is proportional to $1/R^2$, an additional R^2 factor appears in the preexponential factor, finally resulting in $S^*(R) \propto R^6$.

Width of the Size Distribution

A comparatively large bending work necessitates a very low bilayer tension γ_{∞} in order to obtain an appreciable volume fraction of vesicles. Consequently, the factor $S^*(R) \exp(-4\pi k_{\text{bi}}/kT)$ in the size distribution expression becomes indirectly important in generating broad size distributions, the maximum of which is obtained by setting the derivative of eq 54 equal to zero,

$$R_{\max} = [3kT/8\pi\gamma_{\infty}]^{1/2} \quad (57)$$

and which is solely determined by the planar bilayer tension. However, in conjunction with a condition of given overall concentration, γ_{∞} becomes dependent on the bilayer bending constant, as will appear below. By integrating the size distribution, we obtain the overall volume fraction of vesicles

$$\phi_{\text{tot}} = \frac{5\sqrt{2}C\tau(kT)^{9/2}e^{-4\pi k_{\text{bi}}/kT}}{8192k_c^{\text{bi}}\kappa_x\kappa_a v_w^2 \bar{a}_p^3 \gamma_{\infty}^{7/2}} \quad (58)$$

The (volume-weighted) probability of finding a vesicle of radius R is independent of all of the system parameters τ , k_c^{bi} , k_{bi} , κ_x , κ_a , v_w , and \bar{a}_p and depends, besides on R and T , only on the planar monolayer tension γ_{∞} ,

$$P(R) = \frac{\phi(R)}{\phi_{\text{tot}}} = \frac{16384\sqrt{2}\pi^3\gamma_{\infty}^{7/2}}{15(kT)^{7/2}} R^6 e^{-8\pi\gamma_{\infty}R^2/kT} \quad (59)$$

Now, we can easily calculate the mean radius and the mean square radius:

$$\langle R \rangle = \int_0^{+\infty} R P(R) dR = \frac{4}{5\pi} \left[\frac{2kT}{\gamma_{\infty}} \right]^{1/2} \quad (60)$$

$$\langle R^2 \rangle = \int_0^{+\infty} R^2 P(R) dR = \frac{7kT}{16\pi\gamma_{\infty}} \quad (61)$$

The variance of the size distribution is hence given by

$$\sigma_R^2 = \langle R^2 \rangle - \langle R \rangle^2 = \frac{(175\pi - 512)kT}{400\pi^2\gamma_{\infty}} \quad (62)$$

By combining eqs 57 and 62, we get the relative standard deviation of the size distribution

$$\frac{\sigma_R}{R_{\max}} = \left[\frac{175\pi - 512}{150\pi} \right]^{1/2} \approx 0.283 \quad (63)$$

which is a *pure number*. Accordingly, we conclude that σ_R/R_{\max} should have one and the same value, 0.283, for all

fully equilibrated surfactant vesicle systems in the dilute regime, pure as well as mixed, and regardless of the magnitude of the bending work or the planar bilayer tension $2\gamma_\infty$. Otherwise expressed, according to our theory γ_∞ can be obtained independently from measurements of the location of the peak, R_{\max} , and of the width, σ_R , of the size distribution. The relative peak width $\sigma_R/R_{\max} = 0.283$ is approximately twice what we have derived previously for microemulsions which obey a size distribution function of the form $(R^3/\gamma) \exp(-4\pi R^2\gamma/kT)$.⁹ The large difference in polydispersity between vesicles and microemulsions can be understood if one considers that the latter fluctuate in size slightly above a distinct local free energy minimum at some particular radius, whereas this is by no means the case for symmetric bilayer vesicles which experience an extremely slowly rising excess free energy $2\gamma_\infty R^2$ and have a spontaneous curvature equal to zero.

Quite recently, and independently from the present authors, Kegel and Reiss³¹ have treated microemulsion and vesicle size distributions on a vaguely reminiscent basis. For vesicles they also find that the relative width of the size distribution, σ_R/R_{\max} , to be a pure number though ranging between 0.32 and 0.37, depending on the choice of a numerical parameter z ($3/4 < z < 3/2$).

Relation between k_{bi} and R_{\max}

Since the overall vesicle volume fraction as given by eq 58 is ultimately determined by the surfactant and alcohol monomer concentrations in the one-phase region where vesicles are dispersed in water, the total amphiphile concentration, the planar bilayer tension γ_∞ , and the bilayer bending constant k_{bi} are interrelated. According to eq 58, γ_∞ decreases with the bending work at a fixed overall vesicle concentration. By combining eqs 57 and 58 to eliminate γ_∞ , we obtain an explicit relation between the bilayer bending constant and the most probable vesicle radius

$$k_{bi} = \frac{7kT}{4\pi} \ln R_{\max} + C \quad (64)$$

where $C \equiv kT \ln 5\sqrt{3}C\tau^{7/2} \tau kT/324k_c^{bi} \kappa_x \kappa_a V_w^2 \bar{a}_p^3 \phi_{tot}/4\pi$ is a constant which depends only slightly on the solution state. In Figure 7 we have plotted the bilayer bending constant against the most probable radius R_{\max} according to eq 64, and it is seen that the magnitude of k_{bi} strongly influences where the size distribution is located. Setting a lower size limit of the vesicles to $R_{\max} = 100 \text{ \AA}$ and an upper limit to $R_{\max} = 100 \text{ \mu m}$ corresponds roughly to a bilayer bending constant in the range $2 < k_{bi}/kT < 7$ ($\phi_{tot} = 0.1$). k_{bi} is rather sensitive to the detailed solution state, and its magnitude is determined by a delicate balance of several contributions. Exactly how a change of the solution state, for example, the addition of electrolyte, influences the vesicle formation depends on whether k_{bi} will diminish within the above range or not. Addition of salt generally increases the bilayer bending constant, and, hence, it should tend to destabilize such vesicles which form without adding salt.

In our previous model calculations²¹ we have obtained bilayer bending constants k_{bi} ranging between 3.5 and 7 kT for mixed SDS/DOH vesicles ($c_{salt} = 0$). Much larger values resulted upon adding salt. According to eq 58, k_{bi} values between 3.5 and 7 kT would imply bilayer tensions in the range $\gamma_\infty = 5 \times 10^{-5}$ to $5 \times 10^{-11} \text{ mJ/m}^2$ and R_{\max} in the range 0.1–100 μm in order to obtain appreciable

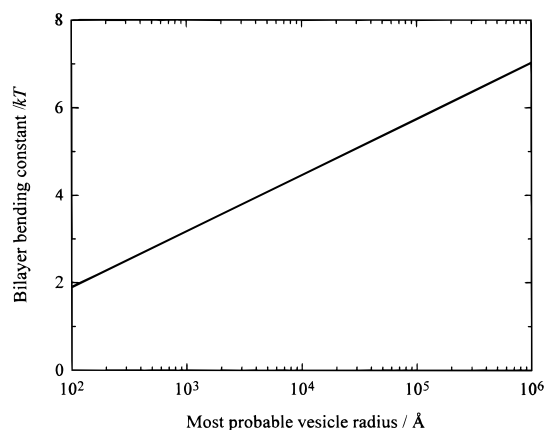


Figure 7. Bilayer bending constant plotted against the most probable vesicle radius R_{\max} according to eq 64 using the following values of the state-dependent parameters: $\bar{a}_p = 32.3 \text{ \AA}^2$, $\bar{x}_{OH}^p = 0.52$, $\kappa_a = 108 \text{ nm}^{-4}$, $\kappa_x = 4.13$, and $k_c^{bi} = 3.16 \text{ kT}$ in accordance with our previous model calculations given in ref 21. The overall vesicle volume fraction was set equal to $\phi_{tot} = 0.1$.

vesicle concentrations. Such extremely small γ_∞ values imply a very slowly diminishing exponential factor in the size distribution, and, hence, the preexponential, R -dependent factor becomes important, resulting in the formation of very large vesicles in spite of the fact that the free energy minimum is actually at some very small vesicle size. Thus, the size, shape, composition, and chain packing density fluctuations all influence the appearance of the vesicle size distribution to a large extent.

Comparison with Experiments

A wealth of experiments show that spherical micelles predominate in a pure SDS/water solution just above the critical micelle concentration (cmc). When salt is added, less curved geometries are favored. Eventually, rod-shaped micelles ($0.4 \text{ M} < c_{salt} < 0.6 \text{ M}$), small disk-micelles ($0.6 \text{ M} < c_{salt} < 2 \text{ M}$), and large bilayers ($c_{salt} > 2 \text{ M}$) become the predominant aggregate types.⁷ At $c_{salt} = 2.0 \text{ M}$ we have a bilayer bending constant $k_{bi} = 16.6 \text{ kT}$, which, according to eq 58, would require a planar bilayer tension of about 10^{-25} mJ/m^2 and a vesicle radius of 3 km ($\phi_{tot} = 0.1$) which is, of course, unreasonable.²¹ Hence, we predict that large lamellar structures rather than vesicles tend to form in a dilute SDS solution with added electrolyte.

While promotion of spontaneous vesicle formation by adding electrolyte has never been observed, several recent experiments support the occurrence of mixed equilibrated vesicles. According to our calculations, presented here and in ref 21, the addition of DOH, in contrast to the case of added salt, yields a lower k_{bi} , thereby facilitating the formation of mixed SDS/DOH vesicles. Figures 5 and 6 show size distributions for two mixed cases with 52 and 72 mol % aggregated dodecanol, respectively. The total vesicle volume fraction was chosen equal to $\phi_{tot} = 0.1$, for the two cases. The size distribution is peaked at $R_{\max} = 0.36 \text{ \mu m}$ for $\bar{x}_{OH}^p = 0.52$, and because the bending work increases with the DOH mole fraction, for $\bar{x}_{OH}^p > 0.5$ the vesicles progressively become large and reach $R_{\max} = 2.6 \text{ \mu m}$ for $\bar{x}_{OH}^p = 0.72$. The order of magnitude of the vesicle sizes and the trend toward increasing size when \bar{x}_{OH}^p is raised from about 0.5 to 0.7 is in agreement with experiments made by Hargreaves and Deamer³² on the formation of mixed SDS/DOH vesicles. These authors

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found, however, the aggregates to be oligolamellar and not unilamellar as we have assumed in our model. Their findings can be rationalized simply by considering the packing restrictions for the comparatively large vesicles in the solution.

At a fixed total amount of amphiphile in the solution, ϕ_{tot} increases with the size of the aggregates which in turn increases with the bending work, because a larger fraction of water molecules are located within the closed bilayer as the vesicle size increases, giving rise to an excluded volume interaction between the vesicles. For large vesicles ($R \gg \xi_p$) the volume fraction of vesicles is related to the volume fraction of bilayer as $\phi_{\text{tot}}/\phi_{\text{tot}}^{\text{surf}} \approx 4/3\pi\langle R \rangle^3/8\pi\xi_p\langle R \rangle^2$, where the total mole fraction of amphiphile is given by $x_{\text{tot}}^{\text{surf}} = v_w\phi_{\text{tot}}^{\text{surf}}/v_s$ for a dilute surfactant solution. Hence, we can write the overall volume fraction of vesicles as

$$\phi_{\text{tot}} = \frac{v_s\langle R \rangle}{6v_w\xi_p} x_{\text{tot}}^{\text{surf}} \quad (65)$$

where the average vesicle radius is related to R_{max} as $\langle R \rangle = 4/3[2/\pi]^{1/2}R_{\text{max}}$ [cf. eqs 57 and 60]. According to eq 65, vesicles with $\langle R \rangle$ larger than about $0.3 \mu\text{m}$ are overpacked ($\phi_{\text{tot}} > \pi/6$) at an overall amphiphile concentration of about 50 mM. Our estimates of k_{bi} to be $3.90 kT$ at $x_{\text{OH}}^{\text{P}} = 0.52$ gives a radius $R_{\text{max}} = 0.36 \mu\text{m}$ which increases with the DOH/SDS ratio. Hence, a solution of unilamellar vesicles, equimolar with respect to amphiphile, would be overpacked at surfactant concentrations of about 50 mM, which was the amphiphile concentration chosen by Hargreaves and Deamer. Although our expression for the free energy of mixing of the vesicles with water molecules (eq 5) is not strictly valid when the solution becomes overpacked, it is striking that our simple model, which neglects interactions between the aggregates, yields reasonable vesicle sizes and can predict in what regions multilamellar aggregates would start to form.

There are several possibilities for the large vesicles to avoid overpacking. They can shrink in size at the expense of increased bending energy, or a phase of large planar membranes can form in order to reduce the interactions between the bilayers. However, owing to the fact that the vesicles are able to enclose each other, a phase of multilamellar liposomes or onions can form instead of a lamellar phase. A more detailed theoretical study of the transition unilamellar vesicles \rightarrow multilayered liposomes (onions) \rightarrow lamellar bilayers as the overall monomer concentration is increased has been presented by Simons and Cates.³³ Hervé *et al.*¹⁶ have reported observations of mixed unilamellar SDS/octanol and SDS/nonanol vesicles which form multilayered liposomes when $x_{\text{tot}}^{\text{surf}}$ is increased to the regime of close packing. The phase transitions described above would also occur as the bilayer bending constant and the average size increases at fixed $x_{\text{tot}}^{\text{surf}}$.

Hervé and co-workers¹⁶ investigated SDS/octanol vesicles in water with a fixed amount of added NaCl, and they observed vesicle radii of a few hundred angstroms. It is not surprising that a substantially shorter alcohol yields smaller vesicles than the SDS/dodecanol mixture as a thinner bilayer should result in a lower bending constant.

In a recent paper³⁴ we have shown that the bending constant of a bilayer composed of both an anionic and a cationic surfactant assumes a lower value than that of a

mixed SDS/DOH bilayer. This sets the stage for spontaneous formation of small unilamellar vesicles with $R_{\text{max}} < 500 \text{ \AA}$.

A large number of experimentally derived polydispersities can be found in the literature, mainly from CRYO-TEM, small-angle and light scattering measurements, ranging from σ_R/R_{max} equal to about 0.1–0.5.^{35–43} It should, however, be emphasized that our theoretically established value = 0.283 of the polydispersity paper is obtained for the case of reversibly formed aggregates in the absence of all intervesicular interactions. In order to make a rigorous test of our theory, it would be important to ascertain that the system studied actually has reached thermodynamical equilibrium and, furthermore, that the measurements are carried out at large dilution. We may also add that when the vesicles become comparatively small, *i.e.*, less than about $R = 10\xi$, higher order terms (proportional to $1/R^2$, $1/R^4$, etc.), which have been omitted in eq 1, begin to play a role and the relative width of the vesicle size distribution should become smaller than that anticipated from our derivation.

Evaluation of k_c^{bi} and \bar{k}_c^{bi}

For spherical geometry the mean and Gaussian curvatures are equal to $H = 1/R$ and $K = 1/R^2$, and for a spherically shaped bilayer with a spontaneous curvature $H_0 = 0$ from eq 47 we obtain a bilayer tension equal to $\gamma_{\text{sph}}^{\text{bi}} = 2\gamma_{\infty} + (2k_c^{\text{bi}} + \bar{k}_c^{\text{bi}})/R^2$, or written as free energy

$$\epsilon_{\text{sph}}^*(R) = 4\pi R^2 \gamma_{\text{sph}}^{\text{bi}} = 4\pi(2k_c^{\text{bi}} + \bar{k}_c^{\text{bi}} + 2\gamma_{\infty}R^2) \quad (66)$$

For cylindrical geometry, the mean curvature is $H = 1/2R$, whereas the Gaussian curvature equals zero. This means that for a cylindrically shaped bilayer, eq 47 becomes $\gamma_{\text{cyl}}^{\text{bi}} = 2\gamma_{\infty} + k_c^{\text{bi}}/2R^2$, or written as the free energy of a cylindrical bilayer of length L

$$\epsilon_{\text{cyl}}^*(R) = 2\pi LR \gamma_{\text{cyl}}^{\text{bi}} = 4\pi L \left(\frac{k_c^{\text{bi}}}{2R} + 2\gamma_{\infty}R \right) \quad (67)$$

From model calculations for the cylindrical case we can calculate k_c^{bi} , and hence we get indirectly $\bar{k}_c^{\text{bi}} = k_{\text{bi}} - 2k_c^{\text{bi}}$. Values of the two bending constants k_c^{bi} and \bar{k}_c^{bi} as well as of k_{bi} are included in Table 1 for some typical solution states. Note that k_c^{bi} and \bar{k}_c^{bi} are related to the monolayer bending constants k_c and \bar{k}_c according to the relationships²²

$$k_c^{\text{bi}} = 2k_c \quad (68)$$

$$\bar{k}_c^{\text{bi}} = 2(\bar{k}_c - 4k_c H_0 \xi_p) \quad (69)$$

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Table 1. Surface Areas per Aggregated Monomer at the Hydrocarbon/Water Interface and the "Elasticity" Constants Related to Composition and Chain Packing Density Fluctuations κ_x (Dimensionless) and κ_a As Defined by Equations 17 and 24 for Pure SDS and Mixed SDS/DOH Bilayers^a

	$\bar{x}_{OH}^P = 0$	$\bar{x}_{OH}^P = 0.52$	$\bar{x}_{OH}^P = 0.72$
$\bar{a}_p/\text{\AA}^2$	34.0	32.3	31.7
κ_x		4.13	6.05
κ_a/nm^{-4}	77	108	114
$R_{\max}/\mu\text{m}$		0.311	2.23
k_c^{bi}/kT	12.3	3.16	1.99
\bar{k}_c^{bi}/kT	-8.0	-2.42	1.04
k_{bi}/kT	7.06	3.90	5.02

^a The values for the two mixed cases are the same used to calculate the size distributions in Figures 5 and 6. The mole fraction of alcohol in a planar bilayer \bar{x}_{OH}^P unambiguously defines the solution state. All values were calculated for planar bilayers. We have also included the vesicle radius R_{\max} , where the maximum of the size distribution is located ($\phi_{\text{tot}} = 0.1$), and the bilayer bending constants k_c^{bi} , \bar{k}_c^{bi} and $k_{bi} = 2k_c^{bi} + \bar{k}_c^{bi}$ as defined by the Helfrich expression given in eq 47.

Discussion

In thermodynamic theories of water dispersed surfactant aggregates it is well-established how to derive size distributions by taking into account, in some way or the other, thermodynamic aggregate factors and the free energy of mixing the aggregates with solvent. However, the fluctuations in shape composition and chain packing density have only rather recently been brought into the picture. Israelachvili *et al.*² and most of their followers primarily obtain exponential vesicle size distribution functions. This is because they do not invoke any size-dependent statistical-mechanical preexponential factor which in a straightforward way results from the multiple equilibrium treatment of the aggregation process. Israelachvili stressed that, in general, entropy favors small aggregates. In order to account for a peaked distribution, a rising free energy branch with diminishing size had to be assumed for the vesicles. This course of the vesicle energy function was attributed to a packing constraint.

Safran *et al.*¹⁸ have attempted to account for the spontaneous formation of vesicles by invoking higher order terms in the curvature free energy expansion and using an exponential size distribution function. For the mixed case, the (second order) bending constant can be reduced below zero and a well-defined free energy minimum is obtained as higher order terms in the expression for $\epsilon(R)$,

proportional to $1/R^2$, $1/R^4$, *etc.*, grow in significance. However, if the vesicles were "energetically" stabilized by higher order terms, their size would be of the same order of magnitude as the thickness of the vesicle bilayer. The occurrence of such very small equilibrated vesicles is in disagreement with a large number of experimental observations.³⁸

By taking due account of the various fluctuations occurring, the emerging picture becomes entirely different. We can rationalize entropically stabilized vesicles with dimensions as large as several microns and with a size distribution maximum located at a vesicle radius far above the local free energy minimum of a fully equilibrated vesicle. In other words, there is a competition which actually matters a great deal, between the entropy of mixing and vesicle fluctuation entropies. Moreover, since we solely are dealing with symmetrical vesicle bilayers, we do not even need to consider the vesicle free energy minimum in detail as it is of no practical significance with regard to the resulting size distribution.

Conclusions

Considering surfactant vesicles as thermodynamically open systems where the two monolayers comprising the vesicle bilayer are able to exchange molecules with the surrounding solution in a dynamical equilibrium, we have found that the fluctuations in composition, chain packing density, and shape give rise to a statistical-mechanical factor which favors the formation of polydisperse solutions of fairly large vesicles as is in agreement with experiments. The position of the maximum of the size distribution can occur at a radius R_{\max} that is $10-10^4$ times the radius where the (average) local vesicle free energy minimum is found.

Somewhat surprisingly, we find a relative standard deviation $\sigma_R/R_{\max} \approx 0.283$ which is the same for all fully equilibrated vesicle dispersions and independent of any energetic parameters as far as the vesicle radius is much larger than the bilayer thickness and higher order bending terms are negligible.

An overall volume fraction of vesicles equal to $\phi_{\text{tot}} \approx 0.1$ is obtained for $k_{bi} = 2-7 kT$, and bilayer tensions in the range $\gamma_{\infty} = 5 \times 10^{-3}$ to 5×10^{-11} mJ/m². The corresponding R_{\max} values range between 100 Å and 100 μm. Our calculations of k_c^{bi} and \bar{k}_c^{bi} show that k_c^{bi} can vary between 2 and 4 *kT* in regimes where vesicles tend to form, whereas \bar{k}_c^{bi} can vary considerably between about $\pm 5 kT$.

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