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On the Ripening of Vesicle Dispersions

Ulf Olsson* and Håkan Wennerström

Center for Chemistry and Chemical Engineering, Lund University, P.O. Box 124, SE-221 00 LUND, Sweden

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We analyze the ripening process where, in a dispersion of vesicles, amphiphile monomers diffuse between vesicles of different sizes, leading to a change in the size distribution. Since, typically, vesicles are not under tension, the driving force for the process comes from the curvature energy. With the conventional expansion of the curvature energy density, g_c, to harmonic order we find that the free energy change on adding a monomer is independent of vesicle radius. The monomer exchange is then a purely random process. By introducing corrections to the harmonic curvature energy, either by expanding g_c to fourth order in the curvatures, or by a term logarithmic in the vesicle size, one obtains a driving force for ripening. Depending on the correction, different scenarios are predicted. The fourth-order correction and a negative logarithmic correction term result in a ripening toward unimodal vesicle distribution around the mean vesicle size of the initial distribution. For a positive logarithmic correction term, on the other hand, the ripening by itself should result in the formation of many small vesicles and a few very big ones. The rate of the monomer redistribution is primarily determined by the magnitude of the thermodynamic driving force and by the monomer solubility. For vesicles formed by single chain surfactants we estimate that the size redistribution should occur at a measurable rate, providing an opportunity to experimentally study which correction to the leading curvature energy is most significant.

A range of surfactants and lipids self-assemble into bilayer sheets that are composed of two oppositely oriented monolayers. These bilayers usually stack in a lamellar liquid crystalline arrangement, but under certain conditions sponge phases and vesicular dispersions can also form. In the vesicle system the bilayers form a closed, usually spherical, aggregate present in excess solvent. Vesicles can be formed by mechanical disruption of the planar bilayer films of a lamellar phase by, e.g., extrusion, ultrasound, or in shear flow. Such vesicles dispersions are usually metastable only, although there are cases where there appears to be thermodynamically stable vesicles.[1,2] Once metastable vesicles are formed, the relaxation back to the equilibrium lamellar phase is often a very slow process.

In analogy with emulsion systems one can consider two basic mechanisms driving the vesicle dispersion toward the equilibrium state. One is vesicle fusion, corresponding to coalescence for emulsions, and one is ripening due to monomer exchange between different aggregates. Fusion can occur either between two vesicles in solution or, more likely, within a flock of adhering vesicles. The fusion rate is determined by the vesicle−vesicle interaction and by the inherent stability of the bilayer film. In this Letter we focus on the second mechanism involving changes in vesicle size due to the diffusion of monomeric amphiphiles between vesicles. This process, called Ostwald ripening, has been extensively studied for emulsion systems,[3−6] where it often is the major relaxation mechanism for emulsion droplets of small size (<1 μm).

For vesicular systems with a net repulsive interaction between the aggregates, it is generally found that equilibration is a very slow process and that the initially prepared size distrubution remains constant over the accessible time range.[7−10] However,

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there are also cases where such a ripening has been reported for vesicle systems.[9]

For emulsions it is the surface tension of the droplets that provides the basic driving force for the Ostwald ripening.[3] The chemical potential of a molecule in the droplet has a small positive contribution from the surface free energy term and as a consequence the monomer solubility is slightly enhanced relative to an equilibrium between two bulk phases. This enhancement of the solubility is larger the smaller the droplet. The concentration gradient in the system then drives a diffusion from small to large drops. However, for a vesicle, the bilayer is not under tension and one cannot apply the conventional surface free energy concept in the analysis of ripening in vesicular systems.

Phase stability in amphiphile systems has been successfully analyzed in terms of the curvature elasticity of the surfactant films.[11−13] The starting point is the expansion of the curvature free energy density, g_c, in the principal curvatures,[14] where a truncation at harmonic order is generally found to be sufficient for a quantitative description of the systems. The films are two-dimensional, but if we restrict ourselves to spherical vesicles, there is only one curvature variable, the inverse radius, $1/R$, or mean curvature. Expanding g_c in $1/R$ around a planar reference state thus gives to second order

$$g_c = \frac{2\kappa'}{R^2} \tag{1}$$

where κ' is the spherical bending modulus.[15] Integrating over the vesicle bilayer gives the vesicle energy

$$G_c = 8\pi\kappa' \tag{2}$$

With a curvature energy density truncated at harmonic order (eq 1), the curvature energy, eq 2, of a vesicle is independent of its size. This means that the transfer of a surfactant molecule from one vesicle to another leaves the total curvature energy unchanged, irrespective of the sizes of the two vesicles, in contrast to a fusion of two vesicles which lowers the curvature energy by the amount given by eq 2. We conclude that a harmonic curvature energy cannot provide a driving force for ripening.

To see this more explicitly, let us analyze the process

$$A_1 + A_n \rightleftarrows A_{n+1} \tag{3}$$

where A_1, the amphiphile monomer, is added to a vesicle, A_n, of aggregation number n, to form a vesicle, A_{n+1}, of aggregation number $n + 1$. At equilibrium, the free energy change is zero and

$$\Delta G_n - \mu_1 = 0 \tag{4}$$

where $\Delta G_n = G_{n+1} - G_n$. G_n, is the free energy of a vesicle of aggregation number n, that can be written as

$$G_n = n\mu^0 + 8\pi\kappa' - TS_n \tag{5}$$

Here, μ^0 is the standard surfactant chemical potential with the reference aggregate state being a free planar bilayer and S_n is the partial entropy of mixing of vesicles with aggregation number n. μ_1 is the chemical potential of the monomer state that we can write as

$$\mu_1 = \mu_1^* + k_B T \ln c \tag{6}$$

where μ_1^* is the standard chemical potential of the amphiphile in solution and c is the free monomer concentration. From eqs 4−6 we then obtain the equilibrium condition

$$\mu_1 = \mu^0 - T(S_{n+1} - S_n) \tag{7}$$

In other words, it is only the small contribution from the entropy of mixing of vesicles that affect the equilibrium with monomers. Thus, with a curvature energy as in eq 2 we find, in contrast to ref 9, that the monomer exchange between vesicles is a purely random process.

The fact that the leading term in the expression for the curvature energy does not affect the ripening process indicates that higher order correction terms should qualitatively influence the process. For vesicles there has been several suggestions as to the nature of such correction terms. Several authors argue[16−18] that thermal undulations of the bilayer membrane leads to a logarithmic correction term

$$G_{corr} = \alpha k_B T \ln \{n\} \tag{8}$$

Here, α is a universal numerical coefficient; hence eq 8 has the property of being independent of the physical characteristics of the vesicles. Both positive[17,18] and negative[16] signs of α have been suggested in the literature, although with an absolute value near unity. Clearly, the effect of the correction term depends on the sign of α. For negative α large vesicles are favored over small ones while the opposite holds when the sign is positive.

Another approach is to assume that the curvature free energy is an analytical function of $1/R$ (or $1/n$) and then the next higher order term relative to eq 2 yields

$$G_{corr} = 4\pi \frac{\kappa_4'}{R^2} = \frac{32\pi^2}{a_S} \frac{\kappa_4'}{n} \tag{9}$$

since terms odd in R are zero by symmetry. Here κ_4' is the fourth-order spherical bending modulus and a_S is the area per amphiphile in the bilayer film, assuming $4\pi R^2 = na_S/2$. For $\kappa_4' > 0$ eq 9 corresponds to an energetic penalty for small vesicle sizes. Clearly, both types of terms could be operating in one and the same system. We then expect the fourth-order curvature correction to dominate for small n while the logarithmic term dominates for large n. However, below we will consider how these different correction terms separately would influence the ripening process.

A crucial quantity determining the driving force for changes in aggregate size is the difference in intrinsic free energy $\Delta G_n = G_{n+1} - G_n$. To leading order in $1/n$, we find

$$\Delta G_n = \mu^0 + \alpha \frac{k_B T}{n} \tag{10}$$

for the case of a logarithmic correction and

$$\Delta G_n = \mu^0 - \frac{32\pi^2}{a_S} \frac{\kappa_4'}{n^2} \tag{11}$$

for the case of a fourth-order correction of the bending free energy. Starting from a vesicle size distribution $f(n)$, the diffusional monomer exchange will lead to a time evolution of $f(n,t)$ under the constraint of constant number of vesicles, N

$$\sum f(n) = N \tag{12}$$

and constant total number of associated monomers

$$\sum n f(n) = n_0 N \tag{13}$$

where n_0 is the mean aggregation number.

The outcome of the ripening process is qualitatively different depending on the sign of $(\Delta G_n - \mu^0)$. For the case of the logarithmic correction (eq 10) it depends on the sign of α. With $\alpha > 0$ the size distribution that gives the lowest intrinsic vesicle free energy is when there is one big vesicle and $N_v - 1$ small ones. Hence, in this situation we expect an Ostwald-like ripening of the initial vesicle population. With $\alpha < 0$ or with the fourth-order correction term (eq 11) the optimum occurs for all vesicles having the same size. Thus, in this case the ripening process does not lead to the large ones growing at the cost of small ones, but rather the reverse.

To obtain the conditional equilibrium vesicle distribution under the constraints of eqs 12 and 13, we have to add the entropy of mixing of vesicles

$$G_{\mathrm{mix}} = k_B T \sum f(n)[\ln\{f(n)/N\} - 1] \tag{14}$$

For the cases of $(\Delta G_n - \mu^0) < 0$ a minimization of the free energy including G_{mix} results in

$$f_{\mathrm{eq}}(n) = A \exp\left\{-\frac{1}{k_B T}(G_{\mathrm{corr}}(n) + \lambda n)\right\} \tag{15}$$

where λ is a Lagrangian multiplier determined by the constraint of eq 13. Let us first, as a reference case, consider the situation where we have only a second-order curvature term so that $G_{\mathrm{corr}} = 0$. In that case eq 15 combined with the constraints, eqs 12 and 13, yields an exponentially decaying size distribution

$$f_{\mathrm{ceq}}(n) = \frac{N}{n_0} \exp\{-n/n_0\} \tag{16}$$

for the conditional equilibrium. This is unphysical for low values of n, and to obtain a realistic description, one is forced to impose additional features into the model. With a higher order term, G_{corr}, the distribution function has a maximum when

$$\lambda = -\frac{\partial G_{\mathrm{corr}}}{\partial n} \tag{17}$$

and in a Gaussian approximation

$$f(n) = A \exp\left\{-\frac{1}{2k_B T}\frac{\partial^2 G_{\mathrm{corr}}}{\partial n^2}\bigg|_{n=n_0}(n - n_0)^2\right\} \tag{18}$$

In the case of the logarithmic correction with $\alpha < 0$

$$\frac{\partial^2 G_{\mathrm{corr}}}{\partial n^2}\bigg|_{n=n_0} = -\alpha k_B T n_0^{-2} \tag{19}$$

and in the case of the higher order correction

$$\frac{\partial^2 G_{\mathrm{corr}}}{\partial n^2}\bigg|_{n=n_0} = \frac{64\pi^2\kappa_4'}{a_S n_0^3} = \frac{2G_{\mathrm{corr}}(n_0)}{n_0^2} \tag{20}$$

In both cases the distribution is wide. For the logarithmic correction the relative standard deviation $\sigma/n_0 = \sqrt{-\alpha} \approx 1$. For the fourth-order correction we obtain $\sigma/n_0 = (k_B T/2G_{\mathrm{corr}}(n_0))^{1/2}$, where it is possible that $G_{\mathrm{corr}}(n_0)$ is significantly lower than $k_B T$. Since for this case $G_{\mathrm{corr}} \sim n^{-1}$, the relative width increases with increasing average size.

For a sample of unilamellar vesicles where the vesicle−vesicle interaction is such that fusion occurs at a negligible rate, the rate of change of the size distribution is determined by the diffusional flux of monomers between vesicles. The rate of change depends on both the intrinsic driving force ΔG_n and distribution function $f(n,t)$. To obtain an estimate of the rate of change, we can analyze the case when a vesicle is placed in a solution containing a concentration c_∞ of monomers corresponding to the monomer solubility of an infinitely large vesicle (or a free bilayer). The diffusion-limited steady-state association rate leading to a change in vesicle radius is

$$\frac{\mathrm{d}R}{\mathrm{d}t} = -\frac{Da_S c_\infty(\Delta G_n - \mu^0)}{4k_B T} \tag{21}$$

where D is the diffusion coefficient of the monomer. With ΔG_n given by eq 10 we have

$$\frac{\mathrm{d}R}{\mathrm{d}t} = -\frac{Da_S^2 c_\infty \alpha}{32\pi R^2} \tag{22}$$

and for ΔG_n given by eq 11 we have

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{Da_S^2 c_\infty \kappa_4}{8k_B T R^4} \tag{23}$$

The rate due to the fourth-order correction (eq 23) decreases more rapidly with increasing R than for the logarithmic correction. It is interesting to also consider the sign of $\mathrm{d}R/\mathrm{d}t$. For the fourth-order correction and for a logarithmic correction with negative α, the prediction is that when a vesicle dispersion is placed in contact with an infinitely dilute lamellar phase (having a monomer solubility of c_∞), the vesicles grow in size. With a positive α, on the other hand, the effect of the logarithmic correction is the reverse. The vesicles will shrink in size and there is net flow of monomers to the lamellar phase.

It is also interesting to compare the rates with the corresponding rate for an emulsion drop in an analogous situation. If an emulsion drop is placed in a solution containing a monomer concentration c_∞ (corresponding to the bulk solubility), the drop will shrink with the rate[3]

$$\frac{\mathrm{d}R}{\mathrm{d}t} = -\frac{2Dv^2\gamma c_\infty}{k_B T R^2} \tag{24}$$

where γ is the interfacial tension. This has the same radius dependence as eq 22, and we can directly compare the coefficients. If D and c_∞ are the same, we could consider $a_S^2/3\pi \approx 0.2$ nm,[4] assuming $a_S \approx 0.5$ nm^2, and $2v^2\gamma/k_B T \approx 0.6$ nm,[4] if we assume $v = 0.3$ nm^3, $\gamma = 10$ mN/m and room temperature. Hence, the logarithmic correction should give a rate of change that is comparable to the Ostwald ripening rate of an emulsion with $\gamma = 10$ mN/m, when D and c_∞ are equivalent. If we consider vesicles of nonionic surfactants, c_∞ is of the order of 10^{-5} M. In other words, the logarithmic correction leads to an equilibration rate similar to the Ostwald ripening rate of hexane in water, which should be possible to observe experimentally.

For the fourth-order correction, the comparison with emulsions is less straightforward, partly because of the different radius dependence, but also because it is difficult to reliably estimate κ_4'. If we define a radius R^* at which G_{corr} equals the harmonic bending energy, $8\pi\kappa'$, we can write $\kappa_4' = 2\kappa' R^{*2}$,

where κ' for nonionic surfactants are typically a few times $k_B T$. For $R \approx R*$ the rate given by eq 23 will be significant and similar to that deduced for the case of a logarithmic correction. However, the rate decreases as R^{-4}. If for example, $R* = 10$ nm, the growth rate will be very small for radii >100 nm.

To summarize, the main conclusions from our analysis of the vesicle ripening process due to monomer diffusion between vesicles follow: (i) The leading term of vesicle curvature energy does not affect the ripening process. (ii) When higher order correction terms are included, the somewhat paradoxical finding is that if the correction term thermodynamically favors the formation of larger aggregates, as in eq 9 or in eq 8 with $\alpha <$ 0, the conditional equilibrium reached by a ripening process corresponds to a unimodal size distribution, with a most probable vesicle size approximately equal to the mean size of the initial distribution. If, on the other hand, the correction term gives a preference to small sizes (eq 8 with $\alpha > 0$) the ripening process should yield a bimodal size distribution with many small vesicles and a few very large ones. (iii) For amphiphiles with low monomer solubility ($c_\infty < 10^{-8}$ M) the ripening process is very slow, while for more soluble substances the ripening should have a rate that results in experimentally observable consequences. (iv) Observation of the ripening process could yield experimental data useful for discriminating between the different free energy expressions (eqs 8 and 9). Since these have relevance far beyond the vesicle problem, this is an issue of general interest.

References and Notes

(1) Kaler, E. W.; Murthy, A. K.; Rodriguez, B. E.; Zasadzinski, J. A. *Science* **1989**, *245*, 1371.

(2) Safran, S. A.; Pincus, P.; Andelman, D. *Science* **1990**, *248*, 354.

(3) Kabalnov, A.; Shchukin, E. D. *Adv. Colloid Interface Sci.* **1992**, *38*, 69.

(4) Taylor, P.; Ottewil, R. *Colloids Surf. A* **1994**, *88*, 303.

(5) Weers, J. G.; Arlauskas, R. A. *Langmuir* **1995**, *11*, 474.

(6) Egelhaaf, S.; Olsson, U.; Schurtenberger, P.; Morris, J.; Wennerström, H. *Phys. Rev. E* **1999**, *60*, 5681.

(7) Olsson, U.; Nakamura, K.; Kunieda, H.; Strey, R. *Langmuir* **1996**, *12*, 3045.

(8) Marques, E. F. *Langmuir* **2000**, *16*, 4798.

(9) Madani, H.; Kaler, E. W. *Langmuir* **1990**, *6*, 125.

(10) Cantù, L.; Corti, M.; Musolino, M.; Salina, P. *Europhys. Lett.* **1990**, *13*, 561.

(11) Wennerström, H.; Daicic, J.; Olsson, U.; Jerke, G.; Schurtenberger, P. *J. Mol. Liq.* **1997**, *72*, 15.

(12) Le, T. D.; Olsson, U.; Wennerström, H.; Schurtenberger, P. *Phys. Rev. E* **1999**, *60*, 4300.

(13) Safran, S. A. *Statistical Thermodynamics of Surfaces, Interfaces, and Membranes*; Addison-Wesley: Reading, MA, 1994.

(14) Helfrich, W. *Z. Naturforsch.* **1973**, *28c*, 693.

(15) A more general expression for the harmonic curvature energy density is $g_c = 2\kappa H^2 + \bar{\kappa}K$, where H and K are the mean and Gaussian curvatures, respectively, and κ and $\bar{\kappa}$ are the bending and saddle splay modulus, respectively.[14] The relation between the spherical bending modulus, as defined by eq 1, and κ and $\bar{\kappa}$ is $2\kappa' = 2\kappa + \bar{\kappa}$.[19]

(16) David, F. In *Statistical Mechanics of Membranes and Interfaces*; Nelson, D., Piran, T., Weinberg, S., Eds.; World Scientific: Singapore, 1989.

(17) Morse, D. C.; Milner, S. T. *Europhys. Lett.* **1994**, *26*, 565.

(18) Helfrich, W. *Eur. Phys. J. B* **1998**, *1*, 481.

(19) Wennerström, H.; Anderson, D. M. In *Statistical Mechanics and Differential Geometry of Micro-Structured Materials*; Friedman, A., Nitsche, J. C. C., Davis, H. T., Eds.; Springer-Verlag: Berlin, 1991.