Aggregation of Amphiphiles as Micelles or Vesicles in Aqueous Media

R. NAGARAJAN AND E. RUCKENSTEIN

State University of New York at Buffalo, Faculty of Engineering and Applied Sciences, Buffalo, New York, 14214

Received August 22, 1977; accepted February 16, 1979

The physical factors responsible for the aggregation of amphiphiles in aqueous media are examined and expressions for their contribution to the attractive or repulsive components of the free energy change of aggregation are established. Whereas in previous treatments, an arbitrary repulsive force was necessary to explain the behavior of nonionic systems, no such ad hoc assumption is made here. Rather the free energy changes due to interfacial tension at the hydrocarbon core (of the aggregates)–water interface and to the loss of a part of translational and rotational degrees of freedom of the amphiphiles when they aggregate are the two main repulsive contributions. On the other hand, the factors favoring aggregation are: (i) the van der Waals interactions between the hydrocarbon tails of the amphiphiles, and (ii) the structural changes in water and the changes in the interactions between amphiphiles and water resulting from aggregation. For ionic and zwitterionic amphiphilar systems additional free energy contributions are included to account for the repulsive electrostatic interactions between the head groups. For vesicles, the repulsion caused by the overlapping electrical double layers inside the vesicles is also considered. The expressions established for the various free energy changes associated with aggregation are used to examine the formation of micelles and vesicles, from single and double chain amphiphiles with nonionic, ionic, or zwitterionic head groups. In general, single chain amphiphiles aggregate as micelles, rather than as vesicles, for all types of polar head groups. Depending upon the nature of the head groups small and/or large micelles can form. Nonionic amphiphiles which have head groups of small cross-sectional areas form large micelles, whereas those with large cross-section aggregate as small micelles. This happens because the repulsion caused by the loss of translational degrees of freedom is larger in the latter of the two cases. Ionic or zwitterionic amphiphiles form small micelles even though they have small head groups because of the electrostatic repulsion between the head groups. At large ionic strengths, large micelles can form because the repulsive interactions between the head groups are small. Nonionic double chain amphiphiles aggregate predominantly as vesicles. Ionic or zwitterionic double chain amphiphiles aggregate as micelles when the electrostatic repulsion between the head groups is large and as vesicles when this repulsion is small. However for intermediate values of these interactions both micelles and vesicles form depending upon the length of the hydrocarbon tail. Most biologically significant double chain amphiphiles have long, complex polar head groups and they aggregate as micelles when the hydrocarbon tail length is short, even if the electrostatic repulsion between the head groups is weak; but they aggregate as vesicles when the hydrocarbon tail length is long. The size distributions calculated for different types of amphiphiles can be unimodal, representing a single population of aggregates, bimodal, or trimodal representing the coexistence of two or three distinct populations of aggregates. The three possible populations are small micelles, large micelles, and vesicles.

I. INTRODUCTION

Amphiphilar molecules in aqueous media aggregate as micelles and/or as vesicles. Thermodynamic attempts to predict aggregation make use of empirical expressions for the various free energy changes. The total free energy change due to aggregation is decomposed either into attractive and repulsive components, or into bulk and surface contributions. The most representative of these approaches is that developed by Tanford (1) for micelles, an approach which has also been extended to vesicles

0021-9797/79/120580-25$02.00/0
Copyright © 1979 by Academic Press, Inc.
All rights of reproduction in any form reserved.

(2, 7). In Tanford's treatment the total free energy change is decomposed into an attractive part of a hydrophobic nature, and a repulsive part due to the head group interactions.

The attractive component seeks to minimize the hydrocarbon–water contact and is assumed to be independent of the nature of the head group. It has been estimated from the experimental free energy change for the transfer of an alkyl chain from water to a liquid hydrocarbon.To this attractive part, positive free energy corrections have been added, (i) to account for the partial contact of hydrocarbon chains with water, and (ii) to allow for the greater constraint of the hydrocarbon chains in a micelle than in the hydrocarbon liquid phase. The attractive component of the free energy change was further adjusted (1) to improve agreement with the experimental dependence of the critical micelle concentration (CMC) on the length of the amphiphilar tail.

To explain the finite size of the aggregates a repulsive component of the free energy change is required. For ionic amphiphiles one of the contributions to this repulsive component is provided by the electrostatic repulsion between the head groups. However, the other repulsive contributions, present in both ionic and nonionic amphiphiles have not yet been identified. Consequently the repulsive component has been estimated empirically (1), using either the experimental values of the CMC, or monolayer compression data. This component was assumed to depend on the nature of the polar head group and on the separation distance between them and to be independent of the length of the hydrocarbon tail.

The empirical expressions proposed by Tanford are simple and yield a satisfactory qualitative and quantitative picture for the behavior of the amphiphilar systems. In spite of the success of Tanford's approach, its physical basis is not entirely clear. In particular the question of the origin of the repulsive component of the free energy in nonionic systems has not yet been addressed. The main purpose of the present paper is to try to answer this question and to clarify further the physical factors which give rise to the attractive component of the free energy.

In an earlier paper (3), partition functions for aggregates, single amphiphiles, and solvent molecules have been derived from a synthesis of the theories of Hoeve and Benson (4) and of Poland and Scheraga (5). In the present paper these results are used to calculate the attractive and repulsive components of the free energy. In this manner the simplicity of Tanford's approach is retained, while the corresponding expressions for the components of the free energy change are provided with a clearer physical picture.

Using the expressions obtained for the attractive and repulsive components of the free energy, the formation of micelles and/or vesicles from single or double chain amphiphiles with nonionic, ionic, or zwitterionic head groups is examined. From this analysis follow the conditions under which these amphiphiles aggregate as (a) small micelles, (b) large micelles, and (c) vesicles. The effect of the size and of the molecular conformation of the head groups on the formation of small or large micelles from nonionic single chain amphiphiles is examined. The formation of small micelles at low ionic strengths and of large micelles at high ionic strengths from ionic single chain amphiphiles is then discussed. It is explained why some double chain amphiphiles aggregate as micelles while most aggregate as vesicles. In addition, the existence of unimodal, bimodal, or trimodal size distributions for the aggregates is established. The conclusions are found to be consistent with available experimental data.

In Section II the size distribution of aggregates is derived. In Section III, expressions are developed for the attractive and repulsive components of the standard free energy change. Illustrative examples

for the formation of micelles and/or vesicles from single chain or double chain amphiphiles are presented in Section IV. The last section summarizes the main results.

II. SIZE DISTRIBUTION OF AGGREGATES

At equilibrium the aqueous medium contains aggregates of all sizes, in the form of micelles, vesicles, and single amphiphiles. The system is composed of N_S solvent molecules, N_A single amphiphiles, and N_{gi} aggregates of size g and type i ($i = 1$ for micelles, $i = 2$ for vesicles). The system is assumed to be very dilute.

Aggregates of different sizes and types are considered as distinct chemical species each characterized by its own standard chemical potential. The standard chemical potential of an aggregate of size g and type i is denoted by μ^0_{gi}. The standard chemical potentials of the solvent molecule and of the single amphiphile are denoted by μ^0_S and μ^0_A, respectively.

The standard states for the single amphiphiles and the aggregates are defined here as the infinitely dilute solutions, whereas the standard state for the solvent is the pure liquid. Since the system is dilute, the mutual interactions between different species are neglected. Consequently the total thermodynamic potential of the system is given by

$$\Phi = N_S\mu^0_S + N_A\mu^0_A + \sum_{i=1}^{2}\sum_{g=g_{\min}}^{\infty} N_{gi}\mu^0_{gi} + kT\left[N_S \ln\frac{N_S}{F} + N_A \ln\frac{N_A}{F} + \sum_{i=1}^{2}\sum_{g=g_{\min}}^{\infty} N_{gi}\ln\frac{N_{gi}}{F}\right], \quad [1]$$

where k is the Boltzmann constant, T is the absolute temperature, and F is the total number of particles:

$$F = N_S + N_A + \sum_{i=1}^{2}\sum_{g=g_{\min}}^{\infty} N_{gi}. \quad [2]$$

The lower limit of the summation over g, $g_{\min}$ is 2 for micelles. For vesicles, $g_{\min}$ is the smallest size (defined below) allowed by the geometry.

The equilibrium state of the system corresponds to the minimum of the total thermodynamic potential Φ. This condition gives the following expression for the equilibrium size distribution of the aggregate of type i:

$$(N_{gi}/F) = (N_A/F)^g \exp - [g\Delta G^0_{gi}/kT]. \quad [3a]$$

Here

$$\Delta G^0_{gi} = (\mu^0_{gi}/g) - \mu^0_A, \quad [3b]$$

is the difference in the standard free energy between an amphiphile within an aggregate of size g and type i and an amphiphile in the aqueous medium.

From the size distribution function [3a] one can compute any average quantity, such as the number average, weight average aggregation numbers, and the size dispersion index $\sum$ (defined as the ratio of the weight average to the number average) (6).

Geometrical Characteristics of Aggregates

It is generally assumed that micelles are spherical for small aggregation numbers and cylindrical with hemispherical ends for sufficiently large aggregation numbers; for aggregates of intermediate sizes, shapes such as discs, prolate and oblate ellipsoids, toroids, etc., have been suggested (1, 7, 8). Concerning the shape of the micelles and their area per amphiphile we assume: (a) The small micelles are spherical up to an aggregation number $g = g_s$ at which the radius r_{og} of the hydrocarbon core equals the extended length l_o of the hydrocarbon tail; their area per amphiphile is uniform. (b) The very large micelles are cylinders of length L and radius l_o with hemispherical ends; the area per amphiphile is that for spheres for the hemispherical ends and that for infinite cylinders for the cylindrical part. (c) The micelles in the transition region probably have several of the shapes that have been suggested; for this reason the area per amphiphile is considered quasi-uniform and

is evaluated as the average area of a cylinder with hemispherical ends. The largest aggregation number g^* for this transition region is taken as the value for which $L/2l_0 \approx 3$.

Spherical geometries have been observed for vesicles in dilute systems (1, 9) and hence are assumed here. For a spherical vesicle with the hydrophobic shell of outside radius R_0 and inside radius R_i, the thickness of the shell is assumed twice the length l_0 of the extended hydrocarbon tail of the amphiphile although in reality it is somewhat smaller (1). It is also assumed that the amphiphiles distribute themselves such as to result in equal surface areas per amphiphile at both the outer and the inner surfaces (1, 2, 7).

In order to accommodate the polar head groups of the inner layer of amphiphiles, the inner radius R_i of the hydrophobic shell should at least equal the length l_p of the polar head group. In addition the volume $4\pi R_i^3/3$ should be equal to or greater than the volume $g_i v_p$ of the polar head groups of the g_i amphiphiles constituting the inner layer of the vesicles. This defines the minimum aggregation number of vesicles.

The notation convention used and expressions for some useful quantities are given in Table I. The geometric characteristics of different types of aggregates are described in Table II.

III. CONTRIBUTIONS TO THE FREE ENERGY CHANGE OF AGGREGATION

The physicochemical phenomena associated with the aggregation of amphiphilar systems are: (a) the freezing of some translational and rotational degrees of freedom by the transfer of amphiphiles from the solution into the aggregates; (b) intermolecular and intramolecular interactions of the hydrocarbon chains of amphiphilar molecules within the aggregates and intramolecular interactions within single amphiphiles in solution; (c) interactions between amphiphiles and water and structural modifications of water resulting from the transfer of the amphiphiles from the aqueous medium into aggregates; (d) generation of the interface between the hydrocarbon core of the aggregate and the surrounding aqueous medium; (e) electrostatic interactions between the head groups (when applicable). These latter interactions account either for the ion–ion interactions in the case of ionic amphiphiles or the dipole–dipole interactions in the case of zwitterionic amphiphiles. Because the dipole moments of the nonionic head groups are rather small and the dielectric constant of the aqueous medium is large, the dipole–dipole interactions in aggregates of nonionic amphiphiles is of the order of only 0.5 erg/cm^2 (10) and thus it is negligible compared to the other contributions listed above. Further, for vesicles, the repulsive interactions due to the overlapping of the inner electrical double layers constitute an important contribution; the interaction energy between the two layers of polar head groups is only about 0.25 erg/cm^2 (11) and thus can be neglected.

The difference ΔG^0_{gi} between the standard free energy of an amphiphile within an aggregate of size g and type i and an amphiphile in the aqueous medium can consequently be written as follows:

$$\Delta G^0_{gi} = [(\mu^0_{gi}/g) - \mu^0_A] = \Delta G^0_{\text{loss of trans-rot. degrees of freedom}} + \Delta G^0_{\text{hydrocarbon interactions}} + \Delta G^0_{\text{solvent effects}} + \Delta G^0_{\text{interfacial tension}} + \Delta G^0_{\text{electrostatic interactions}} \text{ (only for ionic and zwitterionic amphiphiles)} + \Delta G^0_{\text{overlapping of inner double layers}} \text{ (only for vesicles formed of ionic amphiphiles)} \cdot \quad [4]$$

TABLE I

Notation and Expressions Used in the Calculation of the Free Energy Change

a_o	= area per amphiphile shielded from contact with the aqueous medium by the head group
a_c	= area per amphiphile of the cylindrical part of the micelle = $2v_o/l_o$
a_p	= effective area of the polar head group
a_s	= area per amphiphile of the largest spherical micelle = $3v_o/l_o$
C_A	= molar concentration of single amphiphiles, moles/liter
C_{add}	= molar concentration of added salt, moles/liter
C_h	= free energy due to changes in the structure of water = 2.25×10^{-14} erg/CH_2 group
C_{total}	= total concentration of amphiphiles, moles/liter
d	= distance between the charges of a dipole
D	= dielectric constant of the interfacial region = 80
f_1	= ratio between the free volume per mole and the molar volume of solvent = 0.01457
f_2	= ratio between the free volume per mole and the molar volume of the pure amphiphilar phase = $[14/(16.2\,nz)]^3$
F^{vW}	= van der Waals energy per CH_2 group in the pure hydrocarbon phase = 6.30×10^{-14} erg/CH_2 group
F^{vWs}	= intramolecular van der Waals energy per CH_2 group = $0.5\,F^{vW}$
g_i	= number of amphiphiles in the inner layer of the vesicle = $gR_i^2/(R_o^2 + R_i^2)$
g_o	= number of amphiphiles in the outer layer of the vesicle = $gR_o^2/(R_o^2 + R_i^2)$
$\bar{g}_n$	= number average aggregate number = $\sum_{g=g_{min}}^{\infty} gN_g \Big/ \sum_{g=g_{min}}^{\infty} N_g$
$\bar{g}_w$	= weight average aggregation number = $\sum_{g=g_{min}}^{\infty} g^2N_g \Big/ \sum_{g=g_{min}}^{\infty} gN_g$
g_s	= aggregation number of the largest spherical micelle = $(4\pi l_o^3/3v_o)$
h	= Planck's constant = 6.625×10^{-27} erg sec.
$\bar{I}_1$	= average moment of inertia of a single amphiphile treated as a sphere = $\frac{2}{5}m\left(\frac{3v}{4\pi}\right)^{2/3}$
I_{1z}	= moment of inertia of a single amphiphile treated as a cylinder about its long axis = $mv/2\pi l$
$\bar{I}_g$	= average moment of inertia of the aggregate
k	= Boltzmann constant = 1.380×10^{-16} erg/degree K
l_o	= extended length of the amphiphilar tail = $[1.50 + 1.269n] \times 10^{-8}$ cm
l_p	= effective length of the polar head group
l	= length of a single amphiphile = $l_o + l_p$
M	= molecular weight of the polar head group
m	= mass of a single amphiphile = $[M + z(14n + 1)] \times 1.66 \times 10^{-24}$ g
n	= number of CH_2 and CH_3 groups per hydrocarbon tail
T	= absolute temperature = 298°K
v_o	= volume of the amphiphilar tail = $z[27.4 + 26.9n] \times 10^{-24}$ cm^3
v_p	= volume of the polar head group
v	= volume of a single amphiphile = $v_o + v_p$
v_e	= volume of a solvent molecule = 30×10^{-24} cm^3
z	= number of alkyl chains per amphiphile
β	= degree of dissociation of the ionic headgroups
β^*	= degree of dissociation of the ionic headgroups at zero ionic strength
ΔS^{config}	= configurational entropy change due to internal rotation, $=[0.3\,k(n - 4)z]$ erg/molecule
δ	= separation distance between the hydrophobic surface and the location of charge on the head group
ϵ	= proton charge = 4.8×10^{-10} esu
κ	= reciprocal Debye length at 25°C = $(C_A + C_{add})^{1/2}/(3.04 \times 10^{-8})$ cm^{-1}
σ	= hydrocarbon–water interfacial tension = 50 erg/cm^2
Σ	= size dispersion index = $\left(\sum_{g=g_{min}}^{\infty} g^2N_g \Big/ \sum_{g=g_{min}}^{\infty} gN_g\right) \Big/ \left(\sum_{g=g_{min}}^{\infty} gN_g \Big/ \sum_{g=g_{min}}^{\infty} N_g\right) = \bar{g}_w/\bar{g}_n$

TABLE II

Geometrical Properties of Amphiphilar Aggregates of Size g

	Spherical micelle	Cylindrical micelle with hemispherical ends	Spherical vesicle
Radius of the hydrocarbon core	$r_{og} = (3gv_o/4\pi)^{1/3}$	$r_{og} = l_o$	$R_o = [(gv_o/8\pi l_o) - (l_o^2/3)]^{1/2} + l_o$ $R_i = [(gv_o/8\pi l_o) - (l_o^2/3)]^{1/2} - l_o$
Length of the cylindrical part of the micelle	—	$L = \left[gv_o - \frac{4\pi r_{og}^3}{3}\right] \Big/ \pi r_{og}^2$	—
Surface area of the hydrophobic surface	$A_{og} = 4\pi r_{og}^2$	$A_{og} = 4\pi r_{og}^2 + 2\pi L r_{og}$	$A_{og} = 4\pi(R_o^2 + R_i^2)$
Radius of the aggregate at a distance δ from the hydrophobic core	$r_g = r_{og} + \delta$	$r_g = r_{og} + \delta$	$R_{outer} = R_o + \delta$ $R_{inner} = R_i - \delta$
Surface area of the aggregate at a distance δ from the hydrophobic core	$A_g = 4\pi r_g^2$	$A_g = 4\pi r_g^2 + 2\pi r_g L$	$A_g = 4\pi[(R_o + \delta)^2 + (R_i - \delta)^2]$
Surface area per amphiphile at a distance δ from the hydrophobic core	$\frac{A_g}{g} = \frac{4\pi}{g}\left[\left(\frac{3gv_o}{4\pi}\right)^{1/3} + \delta\right]^2$	$\frac{A_g}{g} = \frac{2v_o}{l_o}\left(\frac{l_o + \delta}{l_o}\right) + \left[\frac{4\pi(l_o + \delta)^2 - \frac{8\pi}{3} l_o(l_o + \delta)}{g}\right]$	$\frac{A_g}{g} = \left(\frac{v_o}{l_o}\right) + \frac{8\pi}{g}\left[(l_o + \delta)^2 - \frac{l_o^2}{3}\right]$
Average moment of inertia of the aggregate	$\bar{I}_g = \frac{2}{5} mg(r_{og} + l_p)^2$	$\bar{I}_g = mg\left[\left(\frac{\{r_{og} + l_p\}^2}{2}\right)\left(\frac{\{r_{og} + l_p\}^2}{4} + \frac{\{L + r_{og} + l_p\}^2}{12}\right)^2\right]^{1/3}$ [a]	$\bar{I}_g = \frac{2}{5} mg\left[\frac{(R_o + l_p)^5 - (R_i - l_p)^5}{(R_o + l_p)^3 - (R_i - l_p)^3}\right]$

[a] For the purpose of calculating $\bar{I}_g$ the cylinder with the two hemispherical ends is approximated by a cylinder of the same radius and equal volume.

The free energy changes due to the hydrocarbon–hydrocarbon interactions and solvent effects are negative. Therefore they provide the attractive component of aggregation. The electrostatic interactions between the zwitterionic head groups can be either repulsive or attractive. As will be shown below, they are repulsive in aqueous systems. All the remaining free energy changes are positive and hence contribute to the repulsive component of the free energy of aggregation.

Reduction of Translational and Rotational Degrees of Freedom

The single amphiphiles and the aggregate as a whole have full translational freedom in all three directions in the free volume of the aqueous medium. However, the internal translation of an amphiphile within an aggregate is severely restricted since the polar head group is constrained to remain at the interface between the aggregate and the aqueous medium. The extent of this restriction depends on the size and conformation of the head groups at the interface. The free energy change due to the reduction of the translational degrees of freedom is given by:

$$\Delta G^{\circ}_{\substack{\text{loss of trans.}\\ \text{degrees of freedom}}} = \frac{1}{g} kT\left\{-\left[\ln\left\{\left(\frac{2\pi mgkT}{h^2}\right)^{3/2} f_1 v_e\right\}\right]\right.$$

$$\left. - \left[(g-1)\ln\left\{\left(\frac{2\pi mkT}{h^2}\right)^{3/2} g v f_2\left(\frac{A_{og} - g a_p}{A_{og}}\right)\right\} - g\ln(g) + g\right]\right.$$

$$\left. + \left[g\ln\left\{\left(\frac{2\pi mkT}{h^2}\right)^{3/2} f_1 v_e\right\}\right]\right\} . \quad [5]$$

Here, the first and the last term represent the translation of the aggregate as a whole and the translation of the single amphiphiles, respectively, both within the free volume of the aqueous medium. The remaining terms describe the internal translation of the amphiphiles within the aggregate. In Eq. [5] m is the mass of an amphiphile, h is Planck's constant, v_e is the volume of one molecule of solvent, f_1 and f_2 are the ratios free volume per mole/molar volume for the aqueous medium, and for the hydrocarbon core, respectively, and a_p is the area of the polar head group at the interface. The area a_p depends on the size of the head group and on its conformation.

Equation [5] is used for small micelles ($g < g^*$) as well as for vesicles with the relevant area per amphiphile given in Table II.

As mentioned before, for $g_s < g < g^*$, the area per amphiphile is considered quasi-uniform and A_{og} is evaluated as for a cylindrical micelle with hemispherical ends. In large cylindrical micelles ($g > g^*$) the amphiphiles populating the end regions (there are $g_s/2$ molecules at either end) have a somewhat greater translational freedom than those in the cylindrical part because of the larger area per amphiphile available. This can be accounted for by replacing in Eq. [5] the term representing the internal translation by two terms, one of which is due to the translation in the end regions, while the other to the translation in the cylindrical part. One obtains

$$\Delta G^{\circ}_{\substack{\text{loss of trans.}\\ \text{degrees of freedom}}} = \frac{1}{g} kT\left\{-\left[\ln\left\{\left(\frac{2\pi mgkT}{h^2}\right)^{3/2} v_e f_1\right\}\right]\right.$$
$$-\left[g_s \ln\left\{\left(\frac{2\pi mkT}{h^2}\right)^{3/2} f_2 g v\left(\frac{a_s - a_p}{a_s}\right)\right\}\right.$$
$$\left.\left. + (g - g_s - 1)\ln\left\{\left(\frac{2\pi mkT}{h^2}\right)^{3/2} f_2 g v\left(\frac{a_c - a_p}{a_c}\right)\right\} - g\ln(g) + g\right]\right.$$
$$\left. + \left[g \ln\left\{\left(\frac{2\pi mkT}{h^2}\right)^{3/2} v_e f_1\right\}\right]\right., \quad [5']$$

where a_s is the surface area per amphiphile when $g = g_s$ and a_c is the surface area per amphiphile corresponding to an infinite cylinder.

Although the single amphiphile in the aqueous medium has a coiled configuration, it maintains extensive contacts with the medium. The water molecules in the proximity of the hydrocarbon part of the amphiphile arrange themselves in a more regular fashion. Consequently, the rotation of the single amphiphile in aqueous medium must be restricted since free rotation would involve the breaking up of this structure of neighboring water molecules. The restricted free energy change of rotation is taken to be a fraction f_3 of the full free energy change of free rotation. f_3 is estimated by comparing the experimental standard free energy change for the transfer of a hydrocarbon molecule from the hydrocarbon phase to water (1) with that computed from the partition functions. Bondi's correlation (12) is used to account for the restricted rotation in the hydrocarbon phase. From the available information on the structure of water (13) and Bondi's correlation it results that $f_3 \approx 0.45$ for the chain lengths considered in this paper.

For amphiphiles within the aggregate, the constraints on rotation are even more restrictive, because the head groups are anchored at the interface. Hence, rotation of the amphiphiles within an aggregate is possible only around their long axis, their rotation around the two short axes being completely frozen. Further, a larger number of configurations of internal rotation around the C–C bonds are possible in the coiled amphiphile in the aqueous medium than those possible in the rod-like amphiphile in a pure amphiphilar phase. The free energy change due to the reduction of the rotational degrees of freedom is given by:

$$\Delta G^{\circ}_{\substack{\text{loss of rot.}\\ \text{degrees of freedom}}} = \frac{1}{g} kT\left\{-\left[\ln\left\{\left(\frac{2\pi \bar{I}_g kT}{h^2}\right)^{3/2} 8\pi^2\right\}\right]\right.$$
$$\left. - \left[(g-1)\ln\left\{\left(\frac{2\pi I_{1z} kT}{h^2}\right)^{1/2} 2\pi\right\}\right] + \left[f_3 g \ln\left\{\left(\frac{2\pi \bar{I}_1 kT}{h^2}\right)^{3/2} 8\pi^2\right\}\right] + \left[g\frac{\Delta S^{\text{config}}}{k}\right]\right\}^{1}. \quad [6]$$

Here $\bar{I}_g$ is the average moment of inertia of the aggregate, $\bar{I}_1$ is the average moment of inertia of a single amphiphile treated as a sphere, I_{1z} is the moment of inertia of a single amphiphile treated as a cylinder about its long axis, f_3 accounts for the restricted rotation of the single amphiphile in the aqueous medium due to structuring of neighboring water, and ΔS^{config} is an entropic contribution due to the difference in the number of

[1] In Eq. [37] of Ref. (3) Q_1^{rot} has to be replaced by $[Q_1^{\text{rot}}]^{f_3}$. The numerical computations in Ref. (3) have been performed with $[Q_1^{\text{rot}}]^{f_3}$.

internal rotational configurations of the amphiphile in water and in the aggregate. In the above equation, the first term is due to the rotation of the aggregate as a whole in the aqueous medium and the second to the rotation around the long axis of the amphiphile within the aggregate. The third term corresponds to the restricted rotation of the single amphiphile in the aqueous medium, and the last term to changes in internal rotation around the C–C bonds of single amphiphiles when they are transferred from the aqueous medium to the aggregate.

Expressions for the parameters appearing in Eqs. [5], [5′], and [6] are given in Tables I and II. With these expressions, the free energy change due to the reduction of translational and rotational degrees of freedom becomes, for small micelles ($g < g^*$) and vesicles:

$$\Delta G^{\circ}_{\substack{\text{loss of trans-rot.}\\ \text{degrees of freedom}}} = kT\left[\{0.3nz + 0.3n - 0.4\} - \frac{1}{g}\left\{16 + 3\ln(g) + (g-1)\ln(v/v_e) + (g-1)\ln\left(\frac{A_{og} - ga_p}{A_{og}}\right)\right\}\right], \quad [7]$$

and for larger micelles ($g > g^*$):

$$\Delta G^{\circ}_{\substack{\text{loss of trans-rot.}\\ \text{degrees of freedom}}} = kT\left[\{0.3nz + 0.3n - 0.4\} - \frac{1}{g}\left\{16 + 3\ln(g) + g_s\ln\left(\frac{1 - a_p/a_s}{1 - a_p/a_c}\right) + (g-1)\ln(v/v_e) + (g-1)\ln\left(1 - \frac{a_p}{a_c}\right)\right\}\right]. \quad [7']$$

In Eqs. [7] and [7′], n is the number of CH_2 and CH_3 groups in the hydrocarbon tail and z is the number of hydrocarbon tails per amphiphile. Since this is a positive contribution to the free energy, it represents a part of the repulsive component of the free energy of aggregation.

Hydrocarbon–Hydrocarbon Interactions

The hydrocarbon chain of an amphiphile within an aggregate is also involved in attractive van der Waals interactions with the other amphiphilar tails in the same hydrophobic core. The CH_2 group adjacent to the polar head group lies in the hydration sphere of the head group and is not considered to interact with the other CH_2 groups.

In the aqueous medium some intramolecular van der Waals attractions exist between parts of the same hydrocarbon tail. However, these interactions are weaker than the corresponding interactions in the pure hydrocarbon phase (13).

The contribution to the free energy change due to both intermolecular and intramolecular hydrocarbon–hydrocarbon interactions is:

$$\Delta G^{\circ}_{\substack{\text{hydrocarbon}\\ \text{interactions}}} = [-F^{vW}(n-1) + F^{vWs}n^{vW}]z. \quad [8]$$

Here F^{vW} and F^{vWs} are the van der Waals interaction energies per CH_2 group between hydrocarbon molecules, in a bulk hydrocarbon medium and in the aqueous medium, respectively, n is the total number of CH_2 and CH_3 groups in the hydrocarbon tail of an amphiphile, and n^{vW} is the number of groups involved in the intramolecular interactions because of the coiling of the hydrocarbon chain in the aqueous medium.

It should be noted that the extent of intramolecular contacts is expected to be somewhat larger for double chain amphiphiles than for single chain amphiphiles. It has been assumed here that 25% of CH_2 groups are involved in intramolecular contacts in single chain amphiphiles (13) and about 60% in double chain amphiphiles (1). Based

on the expressions given in Table I, the free energy change due to hydrocarbon–hydrocarbon interactions becomes:

$$\Delta G^{\circ}_{\substack{\text{hydrocarbon}\\ \text{interactions}}} = z[-1.5(n-1) + 0.75n^{\text{vW}}]kT. \quad [9]$$

Solvent Effects

The degree of hydrogen bonding is enhanced in the proximity of the hydrocarbon tails of the amphiphiles. This results in the structuring of water and hence gives rise to a negative entropy change. The ordering of water molecules disrupts the attractive dipole–dipole interactions between water molecules while establishing attractive van der Waals interactions between hydrocarbon and water molecules. When the single amphiphile is transferred into an aggregate, the water structure can become more disorganized, giving rise to an increase in entropy. In addition, the attractive dipole–dipole interactions are reestablished between water molecules. The contributions to the free energy change arising from structural modifications of water and water–amphiphile interactions are given by:

$$\Delta G^{\circ}_{\substack{\text{solvent}\\ \text{effects}}} = -C_{\text{h}}nz, \quad [10]$$

where C_{h} is the magnitude of the free energy per CH_2 group. Estimating the value of C_{h} (3) on the basis of the model of Nemethy and Scheraga (13) for the structure of water, this free energy change is:

$$\Delta G^{\circ}_{\substack{\text{solvent}\\ \text{effects}}} = (-0.536nz)kT. \quad [11]$$

Interfacial Tension

As single amphiphiles aggregate, new interfaces are created. These interfaces consist of polar head groups protruding into the aqueous medium, shielding part of the surface of the hydrocarbon core, while the remaining surface of the core remains in contact with the aqueous medium. The interactions between the polar head groups and water remain essentially unchanged by aggregation. However, those between the hydrocarbon core and water differ from the interactions (already included under solvent effects) between single amphiphilar tails and water. The hydrocarbon core–water interactions are given by

$$\Delta G^{\circ}_{\text{interfacial tension}} = \sigma[(A_{\text{og}}/g) - a_{\text{o}}], \quad [12]$$

where σ is the interfacial tension of a hydrocarbon–water interface (50 erg/cm^2) and a_{o} is the area per amphiphile shielded by the head group from contact with water. The area a_{o} is equal to a_{p} as long as a_{p} is smaller than the cross-sectional area of the hydrocarbon tail; otherwise a_{o} has to be taken equal to that cross-sectional area. The cross-sectional area of the hydrocarbon tail is 21 Å^2 for single and 42 Å^2 for double chain amphiphiles. Although the interfacial tension of small aggregates depends on the curvature this effect is neglected here. $\Delta G^{\circ}_{\text{interfacial tension}}$ contributes to the repulsive component of the free energy of aggregation.

Electrostatic Interactions between Head Groups

In ionic amphiphilar systems repulsive electrostatic interactions exist between the head groups. The theoretical computation of this repulsive interaction is complicated by a number of factors, such as the size, shape, and orientation of the charged head groups, the dielectric constant of the medium (which in this case is the interfacial region of the aggregate), the occurrence of Stern layers, discrete charge effects, etc. However, as a simple approximate expression, the Debye–Hückel approximation (1) for the work of charging the aggregate will be used here.

For small micelles ($g < g^*$), the contribution of electrostatic interactions is:

$$\Delta G^{\circ}_{\substack{\text{electrostatic}\\ \text{interactions}}} = \frac{\epsilon^2\beta^2 g}{2Dr_g}\left[\frac{1 + \kappa a_i}{1 + \kappa a_i + \kappa r_g}\right], \quad [13]$$

where ϵ is the proton charge, β is the degree of dissociation of the head groups at the surface of the aggregate, D is the dielectric constant of the medium, κ is the reciprocal Debye length, and a_i is the average radius of the counterions in the aqueous medium.

For $g < g_s$ the radius r_g is calculated using the expression given in Table II for spherical micelles. For $g_s < g < g^*$, the radius r_g is computed as that of an equivalent sphere having the same surface area as the rigid cylinder with hemispherical ends:

$$(r_g)_{\text{eqv.}} = \left\{\frac{1}{4\pi}[4\pi(l_o + \delta)^2 + 2\pi L(l_o + \delta)]\right\}^{1/2}. \quad [13']$$

For large micelles ($g > g^*$), the electrostatic interaction energy is calculated by combining the equations valid for spheres of aggregation number $g = g_s$ and for infinite cylinders of length L:

$$\Delta G^{\circ}_{\substack{\text{electrostatic}\\ \text{interactions}}} = \frac{1}{g}\left\{\frac{\epsilon^2\beta^2 g_s^2}{2D(l_o + \delta)}\left[\frac{1 + \kappa a_i}{1 + \kappa a_i + \kappa(l_o + \delta)}\right] + \frac{\epsilon^2\beta^2(g - g_s)^2}{DL}\left[\frac{K_o(x)}{xK_1(x)} + \ln\left\{\frac{l_o + \delta + a_i}{l_o + \delta}\right\}\right]\right\}. \quad [14]$$

Here $x = \kappa(l_o + \delta + a_i)$, and $K_o(x)$ and $K_1(x)$ are the modified Bessel functions of the second kind of order 0 and 1, respectively.

The degree of dissociation β depends on the ionic strength of the aqueous medium. When the ionic strength is large, a greater number of counterions bind thereby causing a decrease of the degree of dissociation β. This decrease of β is larger when the distance of closest approach between the coions and counterions is smaller (1). To calculate the dependence of β on ionic strength an expression of the type

$$\beta = \beta^*/(1 + K\{C_A + C_{add}\}), \quad [15]$$

is generally used (14), where β^* is the degree of dissociation at negligibly small ionic strengths, C_A is the concentration of single amphiphiles, C_{add} is the concentration of added salt, and K is the equilibrium constant for counterion binding at the aggregate surface. K depends among others on the distance of closest approach between coions and counterions.

For vesicles, there are repulsive electrostatic interactions between head groups at both the external and the internal surfaces. Considering both contributions, the free energy change is:

$$\Delta G^{\circ}_{\substack{\text{electrostatic}\\ \text{interactions}}} = \left\{\frac{\epsilon^2\beta_o^2 g_o^2}{2D(R_o + \delta)}\left[\frac{1 + \kappa a_i}{1 + \kappa a_i + \kappa(R_o + \delta)}\right] + \frac{\epsilon^2\beta_i^2 g_i^2}{2D(R_i - \delta)}\left[\frac{1 + \kappa a_i}{1 + \kappa a_i + \kappa(R_i - \delta)}\right]\right\}\frac{1}{g}, \quad [16]$$

where the subscripts o and i refer to the external and the internal surfaces of the vesicle. Assuming $\beta_o = \beta_i = \beta$ and replacing g_o and g_i by $g_o = gR_o^2/(R_i^2 + R_o^2)$ and $g_i = gR_i^2/(R_i^2 + R_o^2)$, the electrostatic interaction energy for spherical vesicles is given by:

$$\Delta G^{0}_{\substack{\text{electrostatic}\\ \text{interactions}}} = \frac{\epsilon^2\beta^2 g}{2D}\left\{\left[\frac{1+\kappa a_i}{1+\kappa a_i+\kappa(R_o+\delta)}\cdot\frac{1}{(R_o+\delta)}\cdot\frac{R_o^4}{(R_o^2+R_i^2)^2}\right] + \left[\frac{1+\kappa a_i}{1+\kappa a_i+\kappa(R_i-\delta)}\cdot\frac{1}{(R_i-\delta)}\cdot\frac{R_i^4}{(R_o^2+R_i^2)^2}\right]\right\}. \quad [16']$$

This positive contribution to the free energy has a restrictive effect on the size of the aggregate.

Dipole–Dipole Interactions between Head Groups

For zwitterionic amphiphilar systems, either attractive or repulsive interactions can exist, depending upon the orientation of the head groups (10). If the dipoles are oriented parallel to the interface then the mutual dipole–dipole interactions are attractive and the magnitude of the interaction energy is determined by the particular arrangement of the dipoles at the interface. If the dipoles are oriented normal to the interface and are stacked such that the poles are located on parallel planes, then the dipole–dipole interactions are repulsive. For intermediate orientations and stacking order, there are two components of the dipole moment, one parallel to the interface and the other normal to the interface, and hence the dipole–dipole interactions have both attractive and repulsive components. For the air–water interface it has been suggested that because of the polarization by the interfacial field, the dipole remains oriented normal to the interface (10). At the oil–water interface (corresponding to aqueous micellar systems) one can also expect that the dipoles are oriented normal rather than parallel to the interface and are stacked such as to give rise to repulsive dipole–dipole interactions. Indeed for several zwitterionic systems that have been studied (15), the CMCs and the aggregation numbers fall in between those of nonionic and ionic systems, demonstrating that repulsive dipole–dipole interactions between the head groups play a role.

The dipole–dipole interaction free energy is approximated by that of an electrostatic capacitor. The distance between the planes of the capacitor is equated to that between the charges of the zwitterionic head group. For small micelles ($g < g^*$), the dipole–dipole interaction free energy is therefore

$$\Delta G^{0}_{\substack{\text{dipole-dipole}\\ \text{interactions}}} = \frac{\epsilon^2 g}{2Dr_g}\left[\frac{d}{d+r_g}\right]. \quad [17]$$

For larger micelles ($g > g^*$), the dipole–dipole interaction free energy is calculated combining the expression valid for a spherical capacitor for the amphiphiles located at the ends with that valid for a cylindrical capacitor for the remaining amphiphiles

$$\Delta G^{0}_{\substack{\text{dipole-dipole}\\ \text{interaction}}} = \frac{1}{g}\left\{\frac{\epsilon^2 g_s^2}{2D(l_o+\delta)}\left[\frac{d}{d+l_o+\delta}\right] + \frac{\epsilon^2(g-g_s)^2}{DL}\left[\ln\left(\frac{l_o+\delta+d}{l_o+\delta}\right)\right]\right\}. \quad [17']$$

For vesicles, the dipole–dipole interactions between the head groups located on the same surface, either external or internal, should be considered. As already mentioned the dipole–dipole interactions between the two surfaces are negligibly small. Accounting for these contributions, the dipole–dipole interaction free energy is

$$\Delta G^{0}_{\substack{\text{dipole-dipole}\\ \text{interactions}}} = \frac{\epsilon^2 g}{2D}\left\{\left[\frac{d}{R_o+\delta+d}\cdot\frac{1}{(R_o+\delta)}\cdot\frac{R_o^4}{(R_o^2+R_i^2)^2}\right] + \left[\frac{d}{R_i-\delta-d}\cdot\frac{1}{(R_i-\delta)}\cdot\frac{R_i^4}{(R_o^2+R_i^2)^2}\right]\right\}. \quad [18]$$

Interaction of Overlapping Electrical Double Layers

In vesicles formed of ionic amphiphiles, there are electrical double layers both within and surrounding the vesicles. Because the amphiphilar system is dilute, the vesicles are widely separated and hence the electrical double layers surrounding the vesicles do not overlap. However, there is considerable overlap of the inside double layers, particularly in small vesicles. This gives rise to large repulsive free energies. Because no relation is available to estimate the repulsion for this particular geometry, the results available for the overlap of planar double layers is used for its evaluation. Of course, for the spherical geometry inside the vesicles, the overlap of the double layers is more extensive and the repulsion larger than for planar double layers. Hence, this estimation of the interaction energy provides a lower bound of the interaction energy of the overlapping double layers inside the vesicles. The free energy due to overlapping double layers, assuming a constant surface charge (16) is:

$$\Delta G^{0}_{\substack{\text{overlapping}\\ \text{double layers}}} = \frac{\lambda\beta^2\epsilon^2 g}{D\kappa(R_i - \delta)^2} \cdot \frac{R_i^4}{(R_0^2 + R_i^2)^2} \times [\coth\{\kappa(R_i - \delta)\} - 1]. \quad [19]$$

The above equation has been obtained by substituting the diameter $2(R_i - \delta)$ of the double layer inside the vesicles in the place of the distance between two planar double layers. In Eq. [19], λ is a factor larger than unity representing the ratio of the electrostatic free energy due to overlapping spherical double layers and that due to overlapping planar double layers. In the present computations λ is taken equal to 2.

IV. RESULTS AND DISCUSSION

A. Nonionic Amphiphiles

Aggregation of single chain amphiphiles. The behavior of alkyl glucosides [R_n–OCH–$(CHOH)_5$, R_n is the alkyl chain] in aqueous media, is examined as a typical example of the nonionic single chain amphiphile. The parameters characterizing the polar head groups of various amphiphiles investigated in the present paper are summarized in Table III. The polar part of alkyl glucoside has a compact conformation (17) with a ring structure with diameter of about 7 Å. The estimated volume v_p of the polar head group is 290 Å^3. Correspondingly, the area a_p occupied by the polar head group is 40 Å^2 and its length l_p is 7 Å. The calculations predict that alkyl glucosides aggregate as micelles rather than as vesicles.

The calculated values for CMC and the weight average aggregation number $\bar{g}_w$ are presented in Fig. 1 where they are also compared with experimental data (18). The CMC has been calculated from a plot of the single amphiphile concentration against the total amphiphilar concentration. It corresponds to the intersection of two straight lines, one in the region of almost negligible aggregate concentration and the other in the region of large aggregate concentration where the concentration of single amphiphiles is almost constant. The calculated average aggregation numbers of the micelles are larger than those corresponding to spherical micelles. However their sizes lie in the region of (what one usually considers as) small micelles and are characterized by a narrow size distribution.

Formation of large micelles. Experiments (1, 19) show that n-alkyl hexoxyethylene glycol monoethers, R_n–$(OCH_2CH_2)_6OH$ (denoted as R_nE_6, with E representing an oxyethylene unit), aggregate into very large micelles for $n > 12$, with average aggregation numbers in the range of thousands. Their size distribution is very broad similar to that of other amphiphilar systems where large micelles are formed (20).

Using for the density of polyoxyethylene chains the value 1.15 g/cm^3 (21), the volume v_p of the hexoxyethylene head group is evaluated to be about 270 Å^3. To calculate

TABLE III

Characteristics of the Head Groups of Different Surfactant Molecules Used in the Present Computations[a]

Head group	M	v_p (Å³)	a_p (Å²)	l_p (Å)	δ (Å)	a_i (Å)	β^*	K liter/mole	d (Å)
$-OCH(CHOH)_5$	179	290	40	7	—	—	—	—	—
$-(OCH_2CH_2)_6OH$	281	370	34	11	—	—	—	—	—
$-SO_4Na$	119	100	17	6	2.3	1.0	0.65	1.0	—
$-N(CH_3)_3Br$	139	180	17	6	1.5	2.2	0.71	0.5	—
$-NH_3Cl$	52.5	58	12	5	0.7	1.9	0.65	2.2	—
$-N(CH_3)_3Cl$	94.5	170	17	6	1.5	1.9	0.8	0.5	—
$>N(CH_3)_2Cl$	79.5	120	17	6	1.5	1.9	0.85	1	—
$-N(CH_3)_2CH_2COO$	102	180	30	6	1.5	—	—	—	3.6
>lecithin	310	420	35	11	6.5	—	—	—	4.5

[a] M, molecular weight of the head group; v_p, volume of the head group; a_p, cross-sectional area of the head group; l_p, length of the head group; δ, distance from the hydrophobic core where charges are located; a_i, radius of the counterion; β^*, degree of dissociation of the head group at zero ionic strength; K, equilibrium constant for counterion binding at aggregate surface; d, distance between charges in zwitterionic head group.

the length l_p and the area a_p, information about the conformation of the polyoxyethylene head group is needed. Polyoxyethylene chains with a large number of oxyethylene units have a random coil conformation, whereas short chain polyoxyethylenes may have extended, helical, or meander conformations (22). By extrapolating the curve end-to-end distance vs the number x of oxyethylene units, given in Ref. (22) for the range $8 \leq x \leq 63$, to $x = 6$ the value of $l_p = 11$ Å is obtained for the head group of R_nE_6. This corresponds to a meander conformation of the head group E_6 with $a_p = 34$ Å² (Fig. 2).

The calculated CMCs and the average aggregation numbers of R_nE_6 are compared with available experimental data (19) in Fig. 1. The results obtained earlier for alkyl glucosides which form small micelles are in sharp contrast with those obtained for R_nE_6, which form large micelles when $n > 12$. The essential difference rests with the different values of a_p which is 40 Å² for alkyl glucosides and 34 Å² for R_nE_6. This decrease in a_p implies that the repulsive contribution to the free energy due to the reduction of the translational degrees of freedom is smaller for R_nE_6 than for alkyl glucosides. Consequently the R_nE_6 amphiphiles form large micelles. This is consistent with the results obtained earlier (using the empirical expressions of Tanford for the attractive and the repulsive components of the free energy) where a reduction in the repulsive component resulted in the formation of very large aggregates (1, 2, 6) with broad size distribution (2). Even though the repulsive component of the free energy is small for both R_8E_6 and $R_{10}E_6$, they form only small micelles. This happens because the attractive component of the free energy is not sufficiently large when $n \leq 12$.

Effect of a_p on CMC and aggregation number. Experiments show that alkyl polyoxyethylene glycol monoethers (R_nE_x, E_x is the head group with x oxyethylene units) aggregate as large micelles when $x < 8$, as indicated by the case $x = 6$ considered earlier, and as small micelles when $x \geq 8$ (19, 23–25). Assuming a random coil conformation of the polyoxyethylene chains, Tanford *et al.* (22) have calculated the intrinsic viscosity of micellar solutions of $R_{16}E_x$ amphiphiles. Their results compare well with experiments. In the present paper, we will follow Ref. (22) and use for the length l_p of the polyoxyethylene head group E_x,

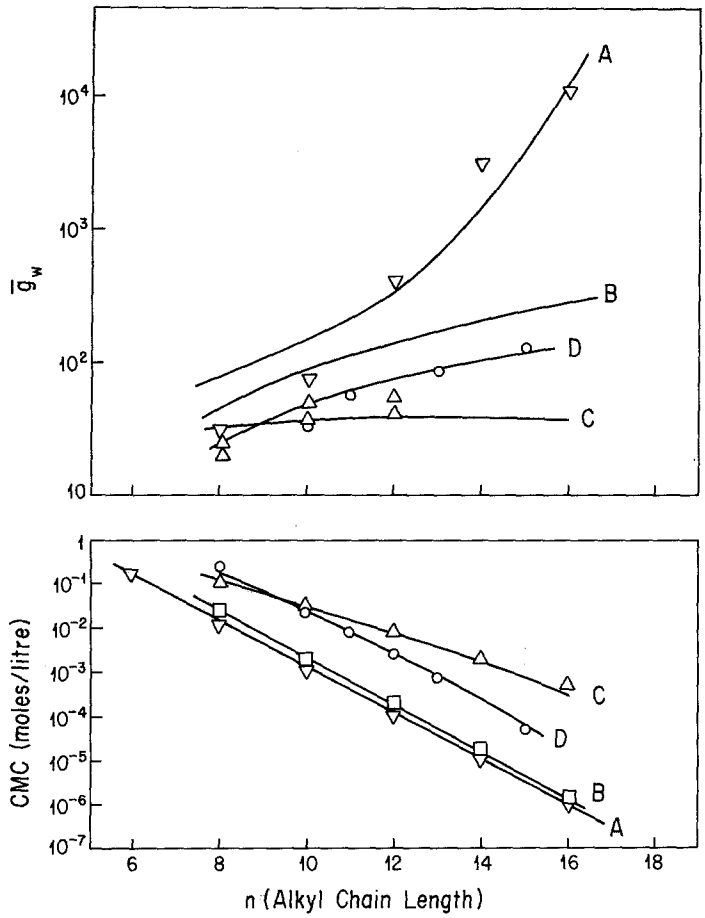


FIG. 1. The CMC and the average aggregation number $\bar{g}_w$ vs the hydrocarbon chain length at 25°C for single chain amphiphiles. The continuous lines represent the calculated values and the points represent the experimental data. Curve A is for alkyl hexoxyethylene glycol monoethers; curve B is for alkyl glucosides; curve C is for alkyl sodium sulfates; curve D is for *N*-alkyl betaines.

the end-to-end distance in a random coil conformation of polyoxyethylene chains. The volume v_p of the head group is calculated as before by taking the density of the oxyethylene chains as 1.15 g/cm^3 (21). Using the resulting values of v_p, a_p, and l_p (shown in Fig. 2), the CMCs and the average aggregation numbers are calculated for $R_{12}E_x$ ($8 \leq x \leq 23$) and for $R_{16}E_x$ ($9 \leq x \leq 63$). The results are compared with available experimental data (19, 22, 25) in Fig. 3. The increase of the CMC and the decrease in the average aggregation numbers as x increases is due to the corresponding increase of a_p and hence of the repulsion due to the reduction of the translational degrees of freedom of the amphiphiles.

Aggregation of double chain amphiphiles. For illustrative purposes the head group is assumed to be a glucoside, with the same size and orientation as in a single chain alkyl glucoside. The nonionic double chain amphiphiles aggregate predominantly as vesicles. The results for double chain glucosides are presented in Fig. 4. The critical vesicle concentration CVC (calculated as the analog of the CMC) is much lower than the CMC of the single chain amphiphiles with the same chain length. One can expect that the CVC of a double chain

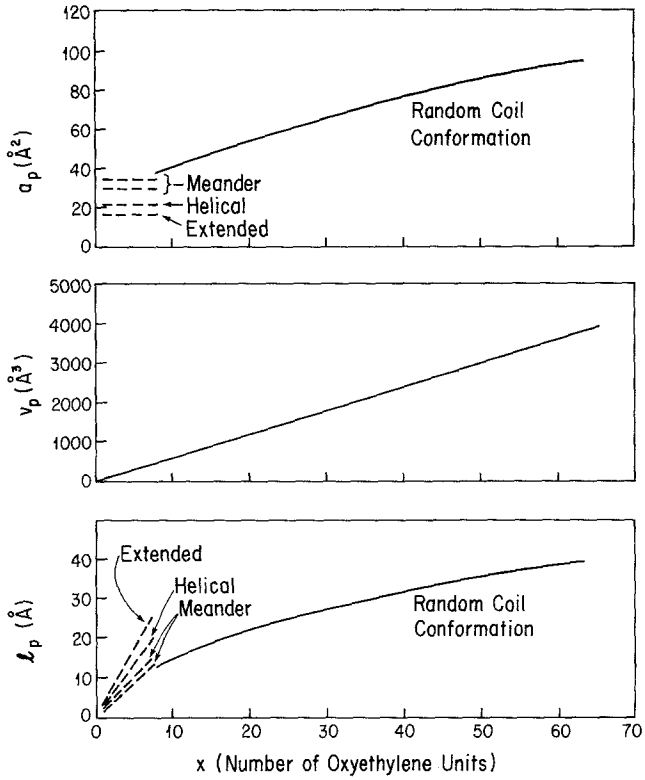


FIG. 2. The length l_p, the area a_p, and the volume v_p of polyoxyethylene head groups vs the number of oxyethylene units for different conformations.

amphiphile with, say, $n = 6$ is comparable to, though somewhat higher than, the CMC of a single chain amphiphile with twice that chain length, i.e., $n = 12$. The size dispersion index $\sum$ for vesicular aggregates is smaller than that of micellar aggregates, indicating that the vesicles have a comparatively narrow size range.

Effect of l_p on vesicle formation. Biologically important molecules have long, complex polar head groups. An increase in the length l_p of the head group results in an increase in the minimum aggregation number at which vesicles become geometrically allowed. The size distribution of aggregates of double chain amphiphiles are calculated retaining the value of $a_p = 40$ Å^2 as for glucosides but increasing the length l_p to 10 and 15 Å. Under these conditions for short double chain amphiphiles ($n < 8$), our computations show that micelles of low aggregation numbers are preferred thermodynamically to vesicles. This is because the area per amphiphile corresponding to even the smallest possible vesicle is quite small (not much larger than a_p), and thus the repulsion due to reduction of translational degrees of freedom is relatively large. However, amphiphiles with longer hydrocarbon tails aggregate predominantly as vesicles because the increase in attraction (due to large n) can offset the large repulsion due to loss of translational degrees of freedom.

B. Ionic Amphiphiles

Aggregation of single chain amphiphiles. The characteristics of the head group of sodium alkyl sulfates (R_n–SO_4Na) as given by Stigter (26) can be found in Table III. As in the case of nonionic systems, the single chain ionic amphiphiles aggregate

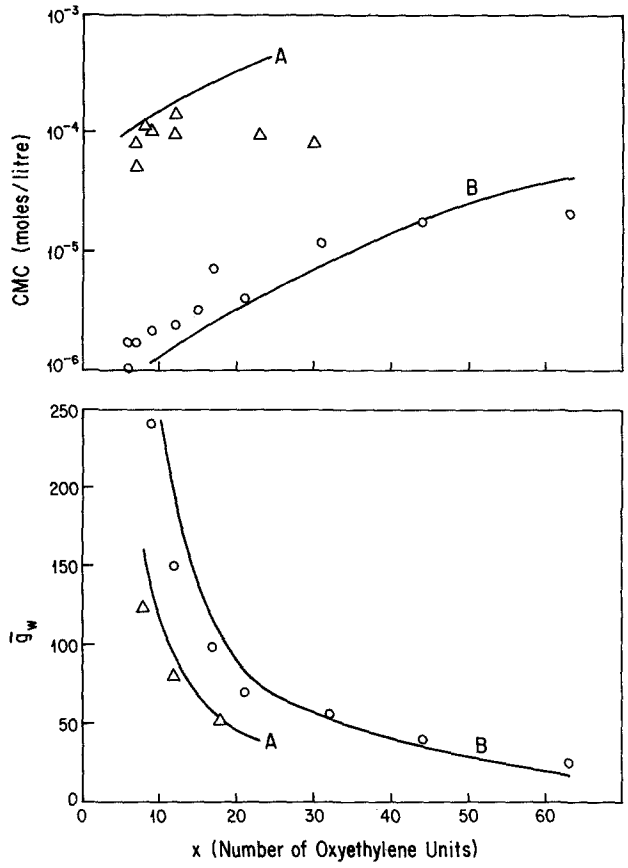


FIG. 3. The CMC and the average aggregation number $\bar{g}_w$ for $C_{12}E_x$ and $C_{16}E_x$ at 25°C. The continuous lines represent calculated values and the points the experimental data. Curve A is for $C_{12}E_x$; curve B is for $C_{16}E_x$.

as micelles rather than as vesicles. The values calculated for CMC and for the average aggregation numbers are presented in Fig. 1 where they are compared with available experimental data (27, 28). The average aggregation numbers are small and consequently the aggregates have a spherical or near-spherical shape. Even though a_p is in this case very small, and this decreases the repulsive contribution due to the reduction of translational degrees of freedom, the presence of the additional repulsive electrostatic interactions between head groups results in formation of small micelles.

Effect of ionic strength and formation of large micelles. The values of the CMC and of the average aggregation numbers for sodium dodecyl sulfate ($R_{12}SO_4Na$) calculated for various ionic strengths are compared with experimental data (29–31) in Fig. 5. Below an ionic strength of about 0.5 M, only small micelles form. However when the ionic strength is further increased, very large micelles begin to form in appreciable concentrations. As the total surfactant concentration is increased, the average aggregation number increases and, for very large amphiphilar concentrations, the computations predict that vesicles may also form. The latter result should not be taken as conclusive because at such high concentrations of amphiphiles, the mutual interactions between aggregates is no longer negligible as assumed above.

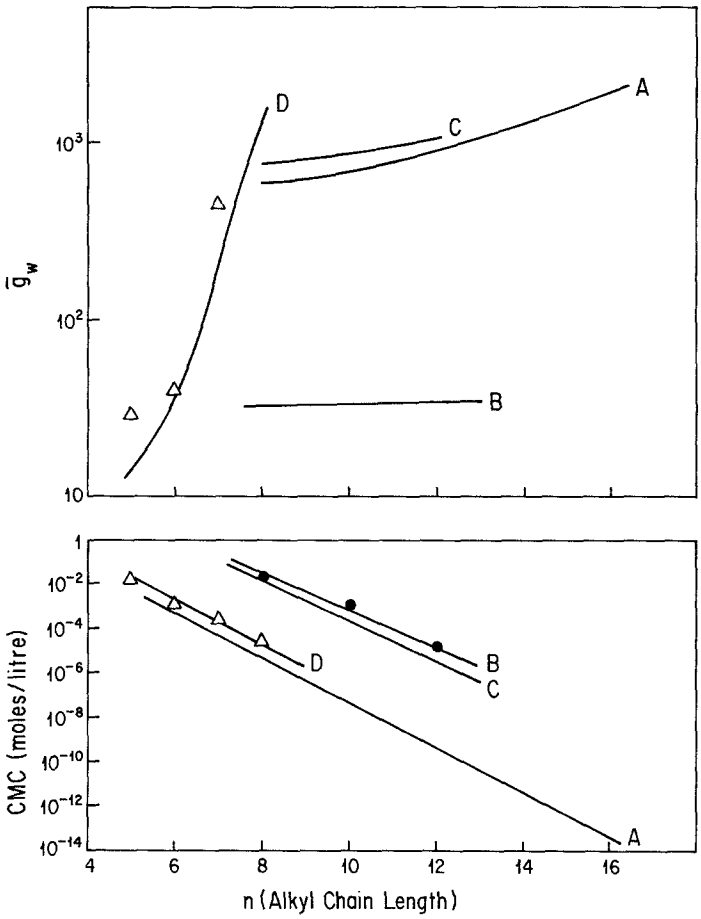


FIG. 4. The CMC or the CVC and the average aggregation number $\bar{g}_w$ vs the hydrocarbon chain lengths at 25°C for double chain amphiphiles. The points represent the experimental data and the curves the calculated values. Curve A is for dialkyl glucoside; curve B is for dialkyl dimethyl ammonium chloride at 0 added NaCl; curve C is for dialkyl dimethyl ammonium chloride at 0.05 *M* added NaCl; curve D is for dialkyl synthetic lecithins.

The calculated values of the CMC and of the average aggregation numbers for alkyl trimethyl ammonium bromide (R_n–N-$(CH_3)_3Br$) in solutions containing 0.5 *M* NaBr were compared with experimental data (1). The computations show that small micelles arise when $n < 14$ whereas when $n \geq 14$ very large aggregates form. The average aggregation number of the large aggregates increases with increasing total concentration of amphiphiles.

In the cases of alkyl sodium sulfates and alkyl trimethyl ammonium bromides, large aggregates form only when the electrostatic interactions become sufficiently small and the attractive component of the free energy (which increases when n increases) is sufficiently large. This result is similar to that obtained for nonionic amphiphiles R_nE_x. In that case, large micelles form when the repulsive free energy due to the reduction of translational degrees of freedom is sufficiently small (as for $x < 8$) and n is sufficiently large.

Effect of the nature of the head group. Even though more refined methods for calculating electrostatic interactions are needed to obtain reliable quantitative results, the

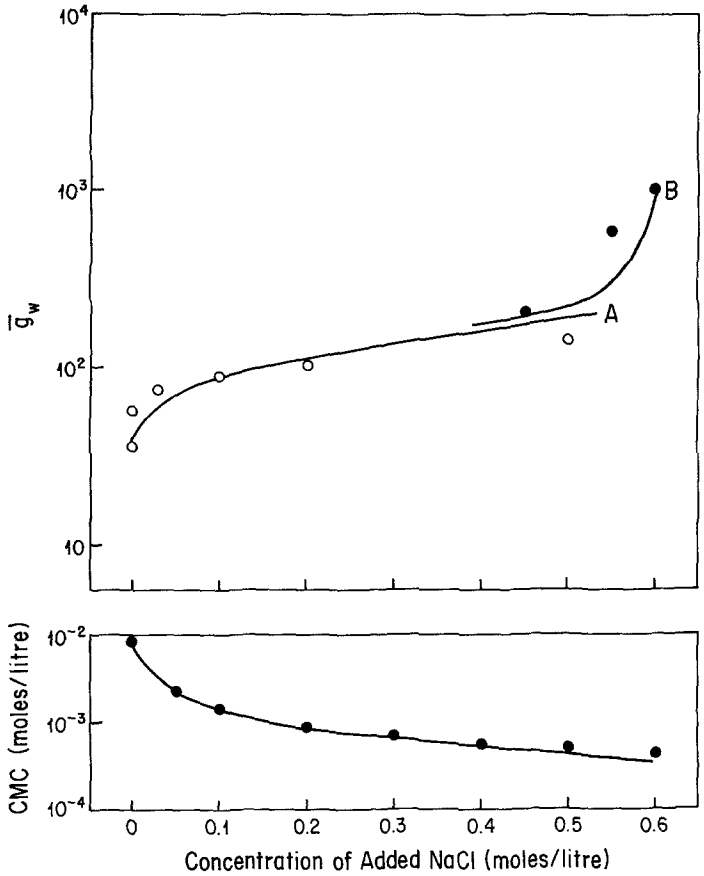


FIG. 5. Effect of added salt on the CMC and on the average aggregation numbers for sodium dodecyl sulfate at 25°C for different total amphiphilar concentrations. The experimental data are represented by points and the calculated values are represented as continuous lines. Curve A is for C_{total} = CMC; curve B is for $C_{total} = 6.9 \times 10^{-2}$ M.

equations given in this paper allow one to obtain at least semi-quantitative information concerning the effect of the nature of the head group. To illustrate this effect we compare the aggregation behaviors of R_nSO_4Na, R_nNH_3Cl, and of $R_nN(CH_3)_3Cl$.

R_nNH_3Cl has a smaller cross sectional area a_p of the head group than R_nSO_4Na. The distance of closest approach between the co- and counterions is smaller in R_nNH_3Cl than in R_nSO_4Na and thus the constant K (in Eq. [15]) is larger for R_nNH_3Cl than for R_nSO_4Na. Using the head group characteristics given in Table III, the computed values of the CMC and of the average aggregation number for $R_{12}NH_3Cl$ are compared with experimental data (1, 32) in Fig. 6, for different concentrations of added NaCl. One finds that $R_{12}NH_3Cl$ forms large micelles at ionic strengths as low as 0.15 ~ 0.20 M, whereas $R_{12}SO_4Na$ forms large micelles (Fig. 5) at ionic strengths of 0.5 to 0.6 M.

The head group of $R_nN(CH_3)_3Cl$ is larger than that of R_nNH_3Cl and has a higher a_p. The distance of closest approach between $[N(CH_3)_3]^+$ and Cl^- ions is larger than between NH_3^+ and Cl^-. Hence K in Eq. [15] is smaller for $R_nN(CH_3)_3Cl$ than for R_nNH_3Cl. The values of the CMC and the average aggregation numbers calculated for $R_{12}N(CH_3)_3Cl$ are presented in Fig. 6 where

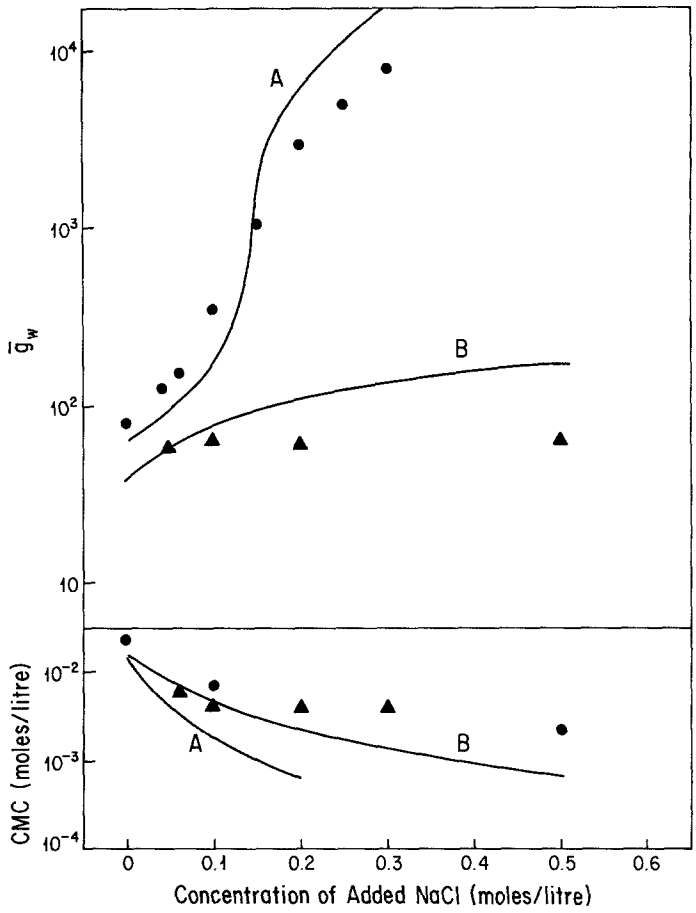


FIG. 6. Effect of head group specificity: the CMC and the average aggregation numbers vs concentration of added electrolyte. The calculated values at 25°C are presented by the continuous curve and the experimental data by points. Curve A is for $R_{12}NH_3Cl$, the experimental data are for 30°C; curve B is for $R_{12}N(CH_3)_3Cl$, the experimental data are for 23 to 25°C.

they are compared with experimental data (1, 32, 33). Only small micelles are formed because the decrease in the electrostatic repulsion energy is not sufficient to facilitate the formation of large micelles. One may recall that $R_{12}N(CH_3)_3Br$ at 0.5 M NaBr does not aggregate into large micelles. However both $R_nN(CH_3)_3Cl$ and $R_nN(CH_3)_3Br$ aggregate as large micelles for higher alkyl chain lengths (for example, $n = 16$) and high ionic strengths.

Aggregation of double chain amphiphiles. The characteristics of the head group of dialkyl dimethyl ammonium chloride $\begin{matrix} R_n \\ R_n \end{matrix} > N(CH_3)_2Cl$ fall in between those of R_nNH_3Cl and $R_nN(CH_3)_3Cl$. The calculated values of the CMC (or of the CVC) and of the average aggregation numbers are presented in Fig. 4. Ionic double chain amphiphiles form both micelles and vesicles. However for low ionic strengths only micelles arise in appreciable concentrations. This is in marked contrast to the case of nonionic double chain amphiphiles which form vesicles. This happens (a) because the electrostatic repulsion between the head groups is larger in vesicles than in micelles and (b) because an additional repulsive contribution, caused by the overlapping of the

inner electrical double layers, arises in vesicles. However, when the alkyl chain length becomes sufficiently large ($n \geq 8$) and for larger ionic strengths (0.1 M), vesicles are preferred thermodynamically to micelles, as confirmed by recent experiments on aggregation of dialkyl dimethyl ammonium chlorides (9).

C. Zwitterionic Amphiphiles

Aggregation of single chain amphiphiles. The calculated values of the CMC and of the average aggregation numbers for alkyl betaines (R_n–$N(CH_3)_2CH_2COO$) are compared with experimental data (15) in Fig. 1. The results show that only small micelles with narrow size distributions form.

Aggregation of double chain amphiphiles. Tausk *et al.* (34) found that synthetic analogs of lecithin molecules with short dialkyl chains form small micelles when $n = 5$ or 6, large micelles when $n = 7$, and vesicles when $n \geq 8$. The aggregation characteristics of these double chain lecithin molecules have been computed using the parameters listed in Table III for the lecithin head group. The results and their comparison with the experimental data of Tausk *et al.* (34) are given in Fig. 4.

In general, for double chain zwitterionic amphiphiles, micelles form in preference to vesicles when either a_p, l_p/l_o, or d is large. However, when a_p, l_p/l_o, and d are all small, vesicles are the predominant type of aggregates.

D. Multimodal Size Distributions

Single chain amphiphiles. The computations show that both unimodal and bimodal size distributions can arise. The peak in the unimodal size distributon lies either in the "small" or in the "large" micelle regions. The former case is illustrated by the alkyl glucosides while the latter by the hexoxyethylene glycol monoethers with $n > 12$ (Fig. 7). One can observe that the small micelles are narrowly dispersed, whereas the large micelles are very broadly dispersed (7, 20). In the case of bimodal size distributions small micelles coexist with large micelles as exemplified by the sodium dodecyl sulfate micelles at 0.6 M ionic strength (Fig. 7). Though the small micelles are present in appreciable concentrations, their contribution to the total aggregate concentration is small because of the presence of polydispersed large micelles. Therefore the average aggregation numbers determined from gross physical properties may not reveal the existence of these small micelles. In some cases trimodal size distribution may also exist, with the third peak corresponding to vesicles. For example, at high ionic strengths and for very large total amphiphilar concentrations, vesicles may form from single chain amphiphiles in addition to small and large micelles.

A qualitative phase diagram for different populations of aggregates is represented in Fig. 8. In general large micelles form when a_p and β (or d) are small and n sufficiently large. This happens because (a) for small a_p and β (or d) the repulsive free energy due to the reduction of translational degrees of freedom and due to the electrostatic interactions between the head groups is small, and (b) for large n, the attraction is also large. For larger a_p and β (or d) and small n, only small micelles form. Finally when a_p and β (or d) are very large and thus give rise to a very large repulsion, the amphiphiles remain singly dispersed.

Double chain amphiphiles. Double chain amphiphiles aggregate as small micelles, large micelles as well as vesicles with either unimodal, bimodal, or trimodal size distributions. Examples of unimodal size distributions are: (i) the small micelles of di–C_8 lecithin ($n = 7$) studied by Tausk *et al.* (34) at low total concentration of surfactant, (ii) the large micelles of di–C_8 lecithin ($n = 7$) at higher total concentrations, (iii) the vesicles of dialkyl glucosides (Fig. 9). Bimodal size distributions can be illustrated by the coexistence of either small

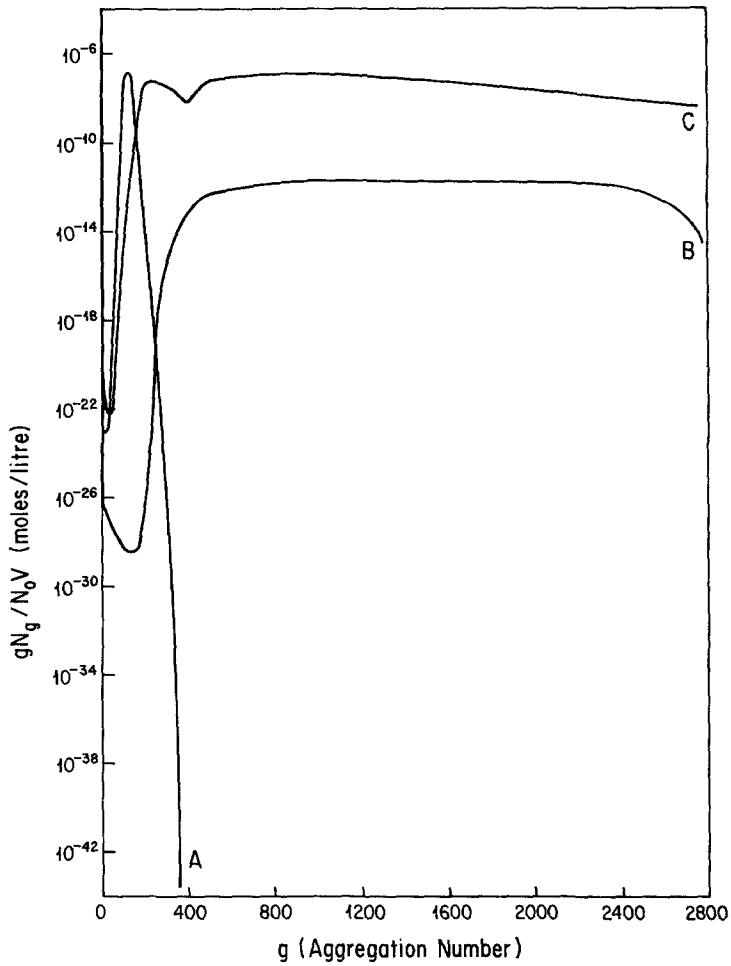
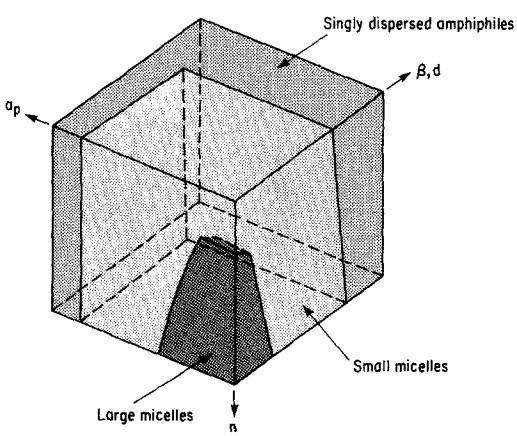


FIG. 7. The size distribution curves for single chain amphiphiles. Curve A is for alkyl glucosides (n = 12); curve B is for alkyl hexoxyethylene glycol monoether (n = 14); curve C is for sodium dodecyl sulfate at 0.6 M ionic strength. All the size distribution curves are for micelles.



or large micelles with vesicles as in the case of $\frac{R_n}{R_n} > N(CH_3)_2Cl$ for n = 8 and for 0.03 M ionic strength (Fig. 9). For a restricted set of conditions trimodal size distribution, due to simultaneous presence of small micelles, large micelles, and vesicles, may exist.

The regions where different types of aggregates form, and different size distributions may exist are qualitatively represented

FIG. 8. Qualitative phase diagram for single chain amphiphiles showing the ranges of a_p, β (or d), and n where different types of aggregates form.

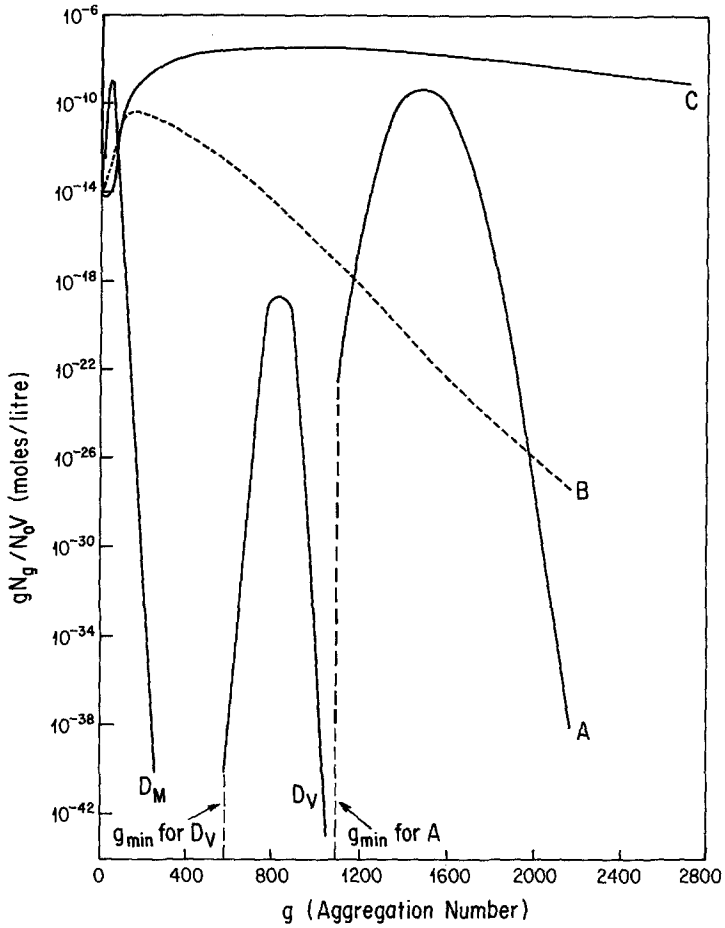


FIG. 9. The size distribution curves for double chain amphiphiles. Curve A is for dialkyl glucoside (n = 16) vesicles. The size distribution curve starts from $g = g_{min}$, which is the minimum aggregation number at which vesicles become geometrically possible. Curve B is for di-C_8 lecithin micelles at $C_{total} = 1 \times 10^{-5}\,M$; curve C is for di-$C_8$ lecithin micelles at $C_{total} = 5 \times 10^{-2}\,M$; curves D_M and D_V are the two branches of the size distribution curve for dialkyl dimethyl ammonium chloride (n = 8, 0.03 M NaCl) representing the coexistance of micelles and vesicles respectively.

in Fig. 10. In general, vesicles form for small values of a_p, l_p/l_o, and β (or d) and for large n. For higher values of a_p, l_p/l_o, and β (or d), either small or large micelles form depending upon the relative balance between the repulsive and attractive forces. And similar to the case of single chain amphiphiles, the molecules remain singly dispersed if a_p, l_p/l_o, and β (or d) are very large.

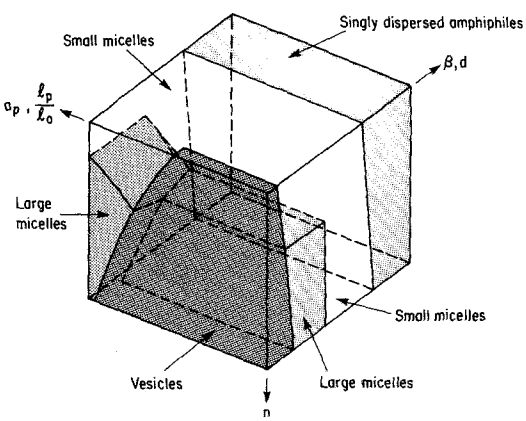


FIG. 10. Qualitative phase diagram for double chain amphiphiles showing the ranges of a_p, l_p/l_o, β (or d), and n where different types of aggregates form.

V. CONCLUSIONS

The purpose of this paper is twofold. First of all we attempt to identify the origin of the attractive and repulsive forces responsible for the aggregation of amphiphiles in aqueous media and to develop expressions representing their contribution to the free energy change associated with aggregation. Second, we use these expressions to provide a unified treatment of aggregation as micelles and/or as vesicles of single chain or double chain amphiphiles with nonionic, ionic, or zwitterionic head groups.

For nonionic systems the attractive van der Waals interactions between the hydrocarbon tails of the amphiphiles and the changes in the structure of water and in the interactions between the amphiphiles and water caused by the transfer of the amphiphiles to the aggregates generate the attractive component of the free energy. The interfacial tension arising from the contact of the hydrocarbon core with the aqueous medium and the reduction of the translational and rotational degrees of freedom are the major repulsive factors. For ionic and zwitterionic amphiphiles, electrostatic interaction between the head groups and the repulsion due to overlapping of electrical double layers inside the vesicles constitute additional repulsive contributions. In earlier treatment of nonionic surfactants (1, 2), it was necessary to introduce an empirical repulsive term without a clear physical significance to balance the attractive component of the free energy of aggregation. The present approach has clarified the nature of the repulsive term for nonionic amphiphiles.

Illustrative calculations have been carried out for single chain and double chain amphiphiles with a variety of head groups. In general single chain amphiphiles aggregate as micelles rather than as vesicles. For nonionic amphiphiles a reduction in the area of the head group a_p decreases the repulsion due to the reduction of translational degrees of freedom and facilitates the formation of large micelles. For ionic or zwitterionic systems although the head groups are small, the presence of electrostatic repulsion between the head groups is the cause of formation of small micelles. However, when repulsion is decreased by increasing the ionic strength large micelles form.

Double chain amphiphiles aggregate as micelles and/or as vesicles. When the electrostatic repulsion between the head groups is large or when the ratio between length of the polar head group and the length of the alkyl chain (i.e., l_p/l_0) is large, only micelles form. For small head groups and relatively small electrostatic repulsion between the head groups, vesicles are the preferred mode of aggregation.

The calculations revealed unimodal, bimodal, or trimodal size distributions which indicates the possibility of coexistence of three distinct populations of aggregates: small micelles with narrow size distribution, large micelles with broad size distribution, and vesicles with narrow size distribution. Related work concerning aggregation in nonaqueous media will be published elsewhere.

REFERENCES

1. Tanford, C., "The Hydrophobic Effect." Wiley, New York, 1973; Tanford, C., *J. Phys. Chem.* **78,** 2469 (1974).
2. Ruckenstein, E., and Nagarajan, R., *in* "Micellization, Solubilization and Microemulsions" (K. L. Mittal, Ed.), Plenum Press, New York, 1977.
3. Nagarajan, R., and Ruckenstein, E., *J. Colloid Interface Sci.* **60,** 221 (1977).
4. Hoeve, C. A. J., and Benson, G. C., *J. Phys. Chem.* **61,** 1149 (1957).
5. Poland, D. C., and Scheraga, H. A., *J. Phys. Chem.* **69,** 2431 (1965); *J. Colloid Interface Sci.* **21,** 273 (1966).
6. Ruckenstein, E., and Nagarajan, R., *J. Phys. Chem.* **79,** 2622 (1975); *J. Colloid Interface Sci.* **57,** 388 (1976).
7. Israelachvilli, J. N., Mitchell, D. J., and Ninham, B. W., *Trans. Faraday Soc.* **72,** 1525 (1976).
8. Tartar, H. V., *J. Phys. Chem.* **55,** 1195 (1955).

9. Kunitake, T., and Okahata, Y., *J. Amer. Chem. Soc.* **99**, 3860 (1977); *Chem. Lett.* **1977**, 1337.
10. Phillips, M. C., Cadenhead, D. A., Good, R. J., and King, H. F., *J. Colloid Interface Sci.* **37**, 437 (1971).
11. Ohki, S., *in* "Physical Principles of Biological Membranes" (F. M. Snell *et al.*, Eds.). Gordon and Breach, New York, 1970.
12. Bondi, A., *J. Phys. Chem.* **58**, 929 (1954).
13. Nemethy, G., and Scheraga, H. A., *J. Chem. Phys.* **36**, 3382, 3401 (1962).
14. McLaughlin, S. G. A., Szabo, G., and Eisenman, G., *J. Gen. Physiol.* **58**, 667 (1971).
15. Herrman, K. W., *J. Colloid Interface Sci.* **22**, 352 (1966); Molyneux, P., Rhodes, C. T., and Swarbrick, J., *Trans. Faraday Soc.* **61**, 1043 (1965); Swarbrick, J., and Daruwala, J., *J. Phys. Chem.* **74**, 1293 (1970).
16. Usui, S., *J. Colloid Interface Sci.* **44**, 107 (1973).
17. Mukerjee, P., *Adv. Colloid Interface Sci.* **1**, 241 (1967).
18. Shinoda, K., Yamanaka, T., and Kinoshita, K., *J. Phys. Chem.* **63**, 648 (1959); Shinoda, K., Yamaguchi, T., and Hori, R., *Bull. Chem. Soc. Japan* **34**, 237 (1961).
19. Becher, P., *in* "Non-Ionic Surfactants" (M. J. Schick, Ed.), Chap. 15 (Tables 15-3, 15-6). Marcel Dekker, New York, 1967.
20. Mukerjee, P., *J. Phys. Chem.* **76**, 565 (1972).
21. Mulley, B. A., *in* "Non-Ionic Surfactants" M. J. Schick, Ed.), Chap. 13 (Table 13.2). Marcel Dekker, New York, 1967.
22. Tanford, C., Nozaki, Y., and Rohde, M. F., *J. Phys. Chem.* **81**, 1555 (1977).
23. Balmbra, R. R., Clunie, J. S., Corkill, J. M., and Goodman, J. F., *Trans. Faraday Soc.* **60**, 979 (1964).
24. Elworthy, P. H., and Macfarlane, C. B., *J. Chem. Soc.* 907 (1963).
25. Barry, B. W., and El Eini, D. I. D., *J. Colloid Interface Sci.* **54**, 339 (1976).
26. Stigter, D., *J. Phys. Chem.* **78**, 2480 (1974).
27. Shinoda, K., *in* "Colloidal Surfactants" ed. (K. Shinoda, T. Nakagawa, B. Tamamushi, and T. Isemura, Eds.), (Tables 1.9 and 1.10). Academic Press, New York, 1963.
28. Leibner, J. F., and Jacobus, J., *J. Phys. Chem.* **81**, 130 (1977).
29. Williams, R. J., Philips, J. N., and Mysels, K. J., *Trans. Faraday Soc.* **51**, 728 (1955); Mysels, K. J., and Princen, L. H., *J. Phys. Chem.* **63**, 1696 (1959).
30. Stigter, D., *J. Colloid Interface Sci.* **47**, 473 (1974).
31. Mazer, N. A., Benedek, G. B., and Carey, M. C., *J. Phys. Chem.* **80**, 1075 (1976).
32. Kushner, L. M., Hubbard, W. D., and Parker, R. A., *J. Res. Natl. Bur. Std.* **59**, 113 (1957).
33. Emerson, M. F., and Holtzer, A., *J. Phys. Chem.* **71**, 1898 (1967).
34. Tausk, R. J. M., Karmiggelt, J., Oudshoorn, C., and Overbeek, J. Th. G., *Biophys. Chem.* **1**, 175 (1974); Tausk, R. J. M., and Overbeek, J. Th. G., *Biophys. Chem.* **2**, 175 (1974).