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Analysis of Distribution Model for Micellar Solubilization Using Thermodynamics of Small Systems: Nonideality of Solubilization of Benzoic Acid Derivatives in Nonionic Surfactants

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Abstract □ The distribution model for solubilization in micellar systems is investigated from the point of view of the thermodynamics of small systems. The description of solubilization in terms of distribution between two phases, the nonmicellar and micellar, provides a good approximation in many cases. Some consequences of treating the micellar phase as ideal and nonideal solutions are examined. It is shown that the solubilization of benzoic acid derivatives in polyoxyethylene-type nonionic surfactants shows serious deviations from ideality, which, however, can be incorporated quantitatively in the theory of regular solutions. The usual application of a Langmuir-type model, assuming binding to fixed sites in describing such nonidealities, is unwarranted.

Keyphrases □ Benzoic acid derivatives—solubilization in nonionic surfactants, thermodynamic nonideality □ Thermodynamics, nonideal solubilization—benzoic acid derivatives in nonionic surfactants □ Solubilization, benzoic acid derivatives—in nonionic surfactants □ Micelles—effect of solubilizates on monomer–micelle equilibrium

Several early investigators (1–3), exploring the nature of the monomer–micelle equilibrium in micelle-forming surfactant solutions, made it clear that although micelles may form as a result of the association of many monomers, the laws of chemical equilibria governing association–dissociation reactions could still be applied to monomer–micelle equilibria. Indeed, the existence of a narrow range of concentrations, called the CMC, below which micelles are undetectable and above which nearly all additional surfactant solute forms additional micelles, and also the sharpness of the changes observed at the CMC could be related to the values of the equilibrium constants associated with the monomer–micelle equilibrium and the number of the monomers and counterions involved. More recently, many investigators have preferred a phase-separation model for micelle formation (see *Reference 4* for a survey of the literature). This model leads to a considerable simplification of the thermodynamic treatment of monomer–micelle equilibria. However, a substantial body of observations, summarized recently (4, 5), does not agree with this model; it has been stressed that the older mass-action model is to be preferred (4). Thus, a surfactant solution, below and above the CMC, can be looked upon as a two-component one-phase system.

When a solubilizate is now added to the system, it must, acting as a third component, affect the monomer–micelle equilibrium (6–8). Many experimental and theoretical studies indicate that the solubilizate does indeed affect the CMC and the molecular weights of micelles (7–11). Nevertheless, the analysis of many mixed surfactant systems, particularly mixtures of homologs involving only variations in hydrocarbon chain lengths, has suggested that the mixed micelle can be considered an ideal solution of its constituents (10). In other words, the mixed micelle can be treated in terms of a separate phase. Similarly, the solubilization of nonmicelle-forming species frequently has been treated in terms of a distribution of the solubilizate between the micelles and the nonmicellar fluid, treating the micelles as a separate phase (12). Thus, although the two-phase model seems to be inappropriate in describing monomer–micelle equilibria, it appears to be useful for solubilizing systems.

The purposes of the present paper are to provide a simple rationale for this apparent contradiction and to

show why the distribution model based on the two-phase description of the system is frequently adequate. Based on this analysis, some nonidealities of solubilized systems are explored. It is shown, in particular, that the solubilization of preservatives in nonionic surfactants of the polyoxyethylene types can be described in terms of nonideality of mixing in the micelle phase and that the site-binding approximation of the Langmuir type, involving partial saturation of sites (13, 14), is probably unjustified.

DISTRIBUTION MODEL FOR SOLUBILIZATION

The recent elegant formulation of the thermodynamics of small systems by Hill (15) and its application to micellar systems by Hall and Pethica (16) greatly clarified the nature of the equilibria in micellar systems. The approach of thermodynamics of small systems seems to be particularly useful for describing solubilization (15, 16). The following discussion is based on this approach.

If a three-component system is considered where Component 1 is the solvent, Component 2 is the micelle-forming surfactant, and Component 3 is the solubilizate, the following equations can be written for the chemical potentials of the unmicellized Component 2, assumed to be monomeric, and Component 3 in free solution (16):

$$\mu_2^s = \mu_2^{os}(T,P) + kT \ln x_2^s\gamma_2^s \quad \text{(Eq. 1)}$$

$$\mu_3^s = \mu_3^{os}(T,P) + kT \ln x_3^s\gamma_3^s \quad \text{(Eq. 2)}$$

where μ = chemical potential, superscript s = free solution state, o = standard value, k = Boltzmann constant, T = absolute temperature, P = pressure, x = mole fraction, and γ = activity coefficient. For the same components in the micelle, one has:

$$\mu_2^m = \mu_2^{om}(T,P,\epsilon_m) + kT \ln x_2^m\gamma_2^m \quad \text{(Eq. 3)}$$

$$\mu_3^m = \mu_3^{om}(T,P,\epsilon_m) + kT \ln x_3^m\gamma_3^m \quad \text{(Eq. 4)}$$

where x_2^m and x_3^m = mole fractions in the micelle, and γ_2^m and γ_3^m = corresponding activity coefficients. Unlike the usual thermodynamics of large systems, in small system thermodynamics the standard μ^{om} values must be defined for constant$T$, P and also the so-called "subdivision potential" of the small system, ϵ_m (15, 16); ϵ_m is defined as:

$$\epsilon_m = -kT \ln x_m \quad \text{(Eq. 5)}$$

where x_m is the mole fraction of the micelle.

The monomer–micelle equilibrium and, therefore, the CMC in the presence of the solubilizate will, of course, be determined by the equation:

$$\mu_2^s = \mu_2^m \quad \text{(Eq. 6)}$$

Because of the dependence of μ_2^{om} on ϵ_m, Eq. 6, in the absence of a solubilizate (*i.e.*, in solutions of a pure surfactant) does not lead to the prediction of an infinitely sharp CMC or a constancy of the monomer activity above the CMC (16). These predictions, which are contrary to experience (4), have been the major objections against the earlier two-phase models for micelle formation based on macroscopic thermodynamics (4).

The usual operational definition of the CMC (4), where a small fraction of the order of 2% of the surfactant is micellized, corresponds effectively to a constant value of ϵ_m or x_m at a constant temperature in solubilizing systems. Equations 6 and 3 clearly show that any substance being solubilized by the micelle will affect the CMC through x_2^m and γ_2^m.

If Component 3, the solubilized component, is considered, one has at equilibrium:

$$\mu_3^s = \mu_3^m \quad \text{(Eq. 7)}$$

From Eqs. 2 and 4, one has:

$$(\mu_3^{om} - \mu_3^{os}) = -kT \ln (x_3^m\gamma_3^m/x_3^s\gamma_3^s) = -kT \ln K_3 \quad \text{(Eq. 8)}$$

where K_3 is the distribution coefficient of Component 3 between micelles and the free solution:

$$K_3 = \frac{x_3^m\gamma_3^m}{x_3^s\gamma_3^s} \quad \text{(Eq. 9)}$$

Unlike the distribution coefficients between bulk phases, K_3 is not only a function of T,P but also ϵ_m, and, therefore, the micellar concentration x_m. This dependence was derived by Hall and Pethica (6) to be:

$$-\left(\frac{\partial \ln K_3}{\partial \ln x_m}\right)_{T,P} = \frac{1}{\bar{N}_3^o} \quad \text{(Eq. 10)}$$

where $\bar{N}_3^o$ is the average value of the number of "micellized" solubilizate molecules of Component 3 in its standard state. If the interactions between the monomers and the solubilized component *in the micelles* can be considered to be ideal over the whole composition range $0 < x_3^m < 1$, then the standard state for Component 3 is a small system of pure 3 at the same T, P and ϵ_m as those of the mixed micellar system composed of monomers and the solubilized species. For nonmicelle-forming solubilized species, this "ideal" value for $\bar{N}_3^o$ when Component 3 forms its own "micelles" should be infinity; therefore, K_3 should be independent of x_m, and the distribution model should hold. When the solubilizate is a solid, the whole composition range may not be experimentally accessible, even though the mixing is ideal. Most solubilized systems are expected to be nonideal. It is unlikely, however, that the nonideality effects would alter the distribution model itself drastically. If the experimentally obtained ratio, x_3^m/x_3^s, can be shown to be independent of x_m, it would provide good evidence that K_3 is independent of x_m and can be handled as a bulk-phase distribution constant.

In the application of the distribution equation to practical situations, the equivalent concentration of micellized surfactant is needed for the calculation of x_3^m. This is usually calculated on the assumption that the surfactant monomer concentration remains constant above the CMC, its value being that of the CMC. This assumption is usually satisfactory when micellar degrees of association are high (16, 17). However, the CMC itself is affected by the presence of the solubilizate to a variable degree, depending upon $x_2^m\gamma_2^m$ (Eq. 3). In solubilizing systems where x_3^s is allowed to vary, x_3^m is substantial, and the total surfactant concentration is such that changes in the CMC are significant; this factor may be important in calculating x_m. However, in many solubilization experiments, particularly when long-chain nonionic surfactants are used, the CMC itself may be low enough to be negligible. In many solubilization experiments performed at saturation concentrations of the solubilizate, *i.e.*, an effectively constant value of $x_3^s\gamma_3^s$, the amount solubilized increases linearly with the total concentration of the surfactant above the CMC of the mixed system as determined from the solubilization experiment itself, even though the CMC of the mixed system may be substantially different from the CMC in the absence of the solubilizate (18). Such systems are consistent, therefore, with the distribution equilibrium with a constant x_3^m and γ_3^m and with a constant value of the CMC of the mixed system. However, systems are known [for example, the solubilization of some slightly soluble dyes in dodecylamine hydrochloride (19–21)] where the linear behavior is not maintained at high concentrations of micelles, suggesting changes in γ_3^m.

When x_3^s is very small, as in the systems to be discussed here, γ_3^s may be considered to be unity. The distribution coefficients of the solubilizate between the micelles and the nonmicellar solutions may, therefore, be redefined as:

$$K_D' = \frac{xf}{c} \quad \text{(Eq. 11)}$$

and:

$$K_D = \frac{x\gamma}{c} \quad \text{(Eq. 12)}$$

where, after dropping all the subscripts and superscripts, x = mole fraction of the solubilized component *in the micelle; c*, the molar concentration of the solubilizate in the solution, is proportional to x_3^s; γ = activity coefficient of the solubilized component in the micelle, defined for the infinite dilution standard state, so that $\gamma \to 1$ as

$x \rightarrow 0$; and f = activity coefficient defined with respect to the pure component as the standard state. For ideal mixtures, f is unity.

HENRY'S LAW BEHAVIOR

As is well known for bulk solutions (22), irrespective of the nature of the nonideality, in dilute solutions (*i.e.*, when $x \rightarrow 0$) $\gamma \rightarrow 1$ and $f \rightarrow$ constant. Therefore, x should be proportional to c. Such behavior, akin to Henry's law for gas solubilities, was reported for the solubility of propylene in potassium oleate solutions (12).

A corollary of this result is that for two solubilizates of similar structures, a and b, and similar kinds of interactions with micelles, the solubilities in different micelles may be related, particularly if the solubility is low. In other words, for different micelles the changes in f for a and b may be similar so that the saturation solubilities, x_a and x_b, may be proportional to each other. Such proportionalities were observed for the solubilities of several solubilizates in potassium myristate and potassium laurate (12). Figure 1 shows an example of the correlation of the solubilizing power of various micellar systems (expressed as the mole fraction of the solubilizate in the micellized surfactant at saturation) over a wide range for two solubilizate dyes, dimethylaminoazobenzene and Orange OT, the data being taken from the extensive work of Kolthoff and his coworkers (19–21). Such correlations may have some predictive value. The rough linearity of this correlation is presumably due to the facts that the solubilizing powers of micellar systems and liquid hydrocarbons of similar chain lengths are similar for these two dyes (19–21) and the value of x is low, so that the variation in f with x is small. For *trans*-azobenzene and naphthalene, for which x is considerably higher, the correlation is no longer linear (Fig. 1), suggesting that changes in f are no longer parallel, and changes in γ are significant because x is not small.

NONIDEALITY OF SOLUBILIZATION OF PRESERVATIVES IN NONIONIC SURFACTANTS

The solubilization of benzoic acid and various phenolic preservatives in polyoxyethylene-type surfactant micelles was investigated by a variety of techniques in unsaturated solutions (13, 14). The apparent distribution coefficient, *i.e.*, the amount solubilized per equivalent of surfactant at a particular equilibrium concentration of the free solubilizate, is usually found to be independent of the surfactant concentration (*i.e.*, x_m), providing experimental evidence that K_3 in Eq. 9 is a true constant independent of x_m. However, when the data are plotted as x *versus* c, pronounced deviations from Henry's law behavior are observed. Patel and Kostenbauder (13), who studied the solubilization of methyl *p*-hydroxybenzoate in polysorbate 80[1], assumed that solubilization occurs in the polyoxyethylene layer and used a Langmuir-type site binding picture for solubilization to explain their data. Donbrow *et al.* (14) arrived at different conclusions about the locus of solubilization but also used the Langmuir-type analysis. In another paper (23), it was shown that solubilized preservatives are associated in part with the hydrocarbon core of the nonionic micelles and in part with their polyoxyethylene mantle, the distribution between these two loci depending to a great extent on the molecular structure of the preservatives. These considerations suggest that the major part, about 70%, of the solubilized methyl *p*-hydroxybenzoate should be associated with the core of the polysorbate 80 micelles.

Although some evidence was recently obtained about *some* solid-like character of the micelle core (24), a variety of other evidence suggests that the micelle core is essentially fluid in nature. The description of the solubilization in terms of binding to fixed sites, an essential ingredient of the Langmuir model, does not, therefore, seem to be physically plausible. On the other hand, the concentrations of the preservatives in the micelles are often high, with a mole fraction as high as 0.5, so that substantial nonidealities are expected, particularly in view of the asymmetric nature of methyl *p*-hydroxybenzoate. It seems reasonable, therefore, to attempt to explore if the solubilization behavior can be interpreted in terms of nonideality of mixing in the micelle phase.

[1] Tween 80.

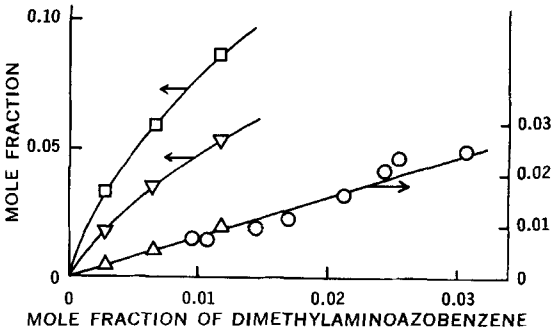

Figure 1—*Correlation of solubilizing powers of different surfactants for different solubilizates. Key:* ○, *Orange OT, in potassium laurate and dodecylamine hydrochloride solutions, at various concentrations of electrolyte and surfactant, 50°;* △, ▽, *and* □ *are all in potassium caprate, potassium laurate, and potassium myristate solutions (in order of increasing mole fraction) at 30°,* △, *Orange OT;* ▽, *trans-azobenzene; and* □, *naphthalene.*

Since the numerical data were not available, the distribution data for a typical system (methyl *p*-hydroxybenzoate in polysorbate 80) were obtained from the Langmuir-type equation:

$$\frac{\text{grams of polysorbate 80}}{\text{moles of methyl } p\text{-hydroxybenzoate}} = 2.5 \times 10^2 + \frac{11.6}{c} \quad \text{(Eq. 13)}$$

and were found to fit the data by Patel and Kostenbauder (13), where c = molar concentration of free methyl *p*-hydroxybenzoate. The numerical constants were derived from the straight-line plot of the authors, and "synthetic" distribution data were generated from the equation in the range of 0.0025–0.01 mole/l. for c, the range covered by the authors. The "synthetic" data are thus in exact agreement with the Langmuir-type equation. These data were then converted to mole fractions of methyl *p*-hydroxybenzoate in the micelle by using the estimated molecular weight of 1400 for the surfactant. No attempt was made to treat the fraction solubilized in the mantle separately; that is, the nonidealities were assumed to be similar for the solubilizate molecules in the two loci. Since roughly 70% of the solubilization is expected to be in the micelle core, reasonable corrections for the fraction in the mantle do not change the qualitative conclusions.

REGULAR SOLUTION APPROACH

The simplest type of nonideality of mixing is displayed by the so-called regular solutions (22) for which the activity coefficient f of the solubilized component in the micelle can be expressed as:

$$\ln f = (1 - x)^2 \omega / RT \quad \text{(Eq. 14)}$$

where ω = an interaction energy parameter, R = molar gas con-

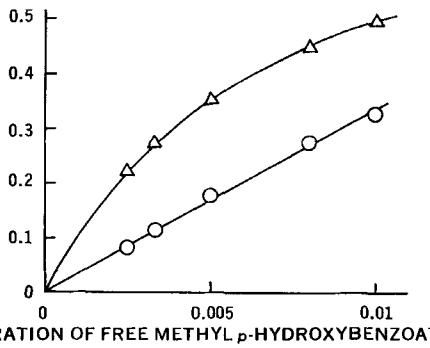

Figure 2—*Distribution behavior of methyl* p*-hydroxybenzoate in polysorbate 80 micelles. Key:* △, *mole fraction* x *of methyl* p*-hydroxybenzoate in micelles; and* ○, xf, *the activity coefficient* f *calculated by using regular solution theory.*

stant, and T = absolute temperature. For such solutions, as $x \rightarrow 0$, $\rightarrow \exp(\omega/RT)$. For the surfactant component, the activity coefficient f' is given by:

$$\ln f' = x^2\omega/RT \qquad \text{(Eq. 15)}$$

so that $f' \rightarrow 1$ as $x \rightarrow 0$.

In Fig. 2, a plot of x *versus* c shows the pronounced deviation from Henry's law at high x values. By using the activity coefficient from the regular solution theory, with $\omega/RT = -1.64$, the product xf, however, varies linearly with c within an average variation of about 2.5%, which is of the order of the experimental error. The distribution law (Eq. 11) is thus obeyed. The solubilization data are thus in good accord with a simple picture of nonideality. It should be stressed that the regular solution theory uses two parameters to relate the x *versus* c data, namely, K_D' and ω/RT, just as the Langmuir-type analysis does.

The success of the regular solution approach suggests that even fairly severe nonidealities in solubilized systems may be amenable to analysis in terms of the distribution law.

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Bis-Quaternary Ammonium Compounds: Derivatives and Congeners of Bicyclo[2.2.2]octane

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Abstract □ A series of rigid congeners of hexamethonium was prepared, based upon bicyclo[2.2.2]octane, in which the interquaternary distance is varied and in which this distance is known with some degree of certainty. Data on hypotensive activities, taken as an index of ganglionic blocking potency, are consistent with earlier proposals that an interquaternary distance of 6.5–7.5 Å is optimum for polyalkylene bis-quaternary ganglionic blocking agents.

Keyphrases □ Hexamethonium congeners—bicyclo[2.2.2]octane, hypotensive activity □ Bicyclo[2.2.2]octane derivatives—interquaternary distances correlated with hypotensive effects □ Hypotensive activity—bis-quaternary ammonium compounds of bicyclo[2.2.2]octane □ Bis-quaternary ammonium compounds—interquaternary distance correlated with hypotensive effects

There has been controversy in the literature for many years concerning the validity of the "two-point attachment" hypothesis of Barlow and Ing (1) for explaining the ganglionic blocking mechanism of bis-quaternary ammonium salts, typified by hexamethonium. The attractive theory that the length of the most active bis-quaternary polyalkylene molecule corresponds to, or even is a measure of, an interreceptor distance is complicated by the fact that these flexible compounds can assume an infinite number of conformations and, consequently, their "molecular length" cannot be defined precisely. Gill (2) concluded that ganglionic blocking molecules must possess a "range" of interquaternary distances between the limits of 6 and 7.8 Å. Biel and DiPierro (3) introduced a triple bond into a series of C_5 and C_6 bis-quaternary compounds and found that these derivatives (in which the rigid carbon–carbon triple bond limits somewhat the flexibility of the carbon chain and forces it into a more extended form) were more potent than their saturated parent compounds in producing hypotension, which was considered to be at least in part due to an action at autonomic ganglia. This effect of the acetylenic link on blood pressure was verified in somewhat similar C_5 and C_6 bis-quaternary polyalkylene systems by Neumeyer *et al.* (4). They reported that when the triple bond was reduced to a *cis*-olefinic group, hypotensive activity diminished, but that reduction to a *trans*-olefin increased activity above that observed for the parent saturated molecule. It was concluded that the