

## SOLUBILIZATION IN MICELLAR SYSTEMS

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**Abstract** - Solubilization in micellar systems is intimately related to the structure and properties of micelles as also the molecular structure of the solubilized species. The effects of solubilization on monomer-micelle equilibria and the micellar size-distribution, including the sphere-to-rod transition, are analysed. The location and distribution of solubilized species in the micelle are examined in terms of a recently proposed two-state model of solubilization which postulates an equilibrium distribution between a 'dissolved state', associated with the hydrocarbon core, and an 'adsorbed state' arising from the interfacial activity of the dissolved species. This interfacial activity and the influence of the Laplace pressure arising from the curvature of the micelle-water interface are shown to be of considerable importance in determining the solubilization capacities of micelles for solubilizes of different molecular structures. The implications of this two-state model for understanding chemical reactions of solubilized species and for assessing the significance of spectroscopic 'probes' are reviewed briefly.

### INTRODUCTION

The peculiar solvent properties of micellar systems in aqueous media and the related phenomenon of the distribution of dissolved species between micelles and the intermicellar solution pose many questions of considerable scientific interest. Solubilization in micelles is responsible for some of the most important technical applications of micellar systems (1-3). The understanding of the detailed nature of micellar solubilization is a prerequisite for the understanding and control of chemical and photochemical reactions of solubilized species (4,5). As model systems, micellar solubilization can provide considerable insight into the nature of the interactions of small molecules with other lipid assemblies such as bilayers or biological membranes which are responsible for the binding or uptake of the small molecules, their transport, and their chemical and metabolic reactivities. Such interactions are responsible in part for the activities of drugs, toxicants, carcinogens, and many endogenous substances in biological systems.

The literature on solubilization is extensive and has been covered in many monographs and review articles (1-4). This paper is confined to the discussion of some fundamental problems associated with micellar solubilization with emphasis on some recent developments.

### SOLUBILIZATION AND MONOMER-MICELLE EQUILIBRIA

The peculiar solvent property of micelle forming surfactants is closely related to the peculiar nature of the self-association responsible for the formation of the micelles themselves. In the case of the flexible chain surfactants, if the rate of change of the solubility of a hydrophobic solubilize with surfactant concentration is plotted against the concentration, the cooperative self-association that is responsible for the existence of the critical micellization concentration (c.m.c.) in such systems (6-9) is clearly reflected in the plot (10). Formation of micelles is a prerequisite for micellar solubilization in simple systems. Such diagrams clearly demonstrate the difference between the solubilizing patterns of flexible chain surfactants from the patterns exhibited by other surfactants such as the bile salt sodium cholate which shows a lower degree of cooperativity of self-association, good cosolvents such as ethanol, and hydrotropic agents (10,11).

The distribution of a solubilize between the micelles and the intermicellar fluid is a complex phenomenon in general. The presence of the solubilize affects monomer-micelle equilibria, the sizes of the micelles and their stability in various degrees. The mole ratio of the solubilize to the surfactant in the micelles and the changes in electrostatic interactions for ionic micelles or ionic solubilizes can affect the distribution equilibrium. A qualitative review of many other relevant factors has been presented recently (10). A Nernst-type distribution equilibrium formulation for uncharged solubilizes between the

micelles, treated as a separate phase, and the intermicellar fluid is frequently useful for solubilizates having low concentrations in micelles (1,12).

In the presence of a solubilizate, the c.m.c. may be affected only slightly if the mole fraction of the solubilizate in the micelles around the c.m.c. is small (10,13). However, even if the overall concentration of a solubilizing additive is small, if the first few micelles that form near the c.m.c. have a high concentration of the solubilizate, the c.m.c. may be affected in a pronounced manner (14). These considerations are of considerable importance in evaluating the use of solubilizing additives for the determination of the c.m.c. (15) and the interactions of highly hydrophobic solubilizates (10).

The effects of solubilizates on micellar sizes have been studied in several cases (2,16,17). A solubilizate usually increases the sizes of micelles not only by the incorporation of the solubilizate itself but also by causing an increase in the average number of surfactant molecules in the micelles. Viscosity and sedimentation studies indicate that in some micellar systems the formation of very large asymmetric micelles may be induced by some solubilizates but not others (17).

Some qualitative considerations (10), which will be presented later in more detail (18), provide a rationale for many of the observations. The basic arguments concern the effects of a solubilizate on micelles of different sizes and shapes. A generally applicable association model for surfactants (6,8) has indicated that in many systems only 'small' micelles are present, which are approximately similar in size to a spherical micelle with a radius equaling the length of a stretched-out monomer. For such systems the size distribution is controlled by a cooperativity in the self-association process in the early stages of the growth of the micelles followed by an anticooperativity for larger micelles arising out of a sphere-to-rod transition. In some cases, this anticooperative region of growth is not pronounced enough to prevent the formation of 'large' micelles, presumably rod-like but flexible (6,19,20), and the average aggregation numbers are large. As indicated by Mysels (21), a solubilizate is likely to confer greater stability on larger micelles than smaller ones because the former incorporate a relatively greater number of the solubilizate molecules. This effect will tend to increase the average aggregation number of the surfactant. When the micelles are 'small', they usually exhibit a narrow size distribution (6,19), and the increase in the aggregation number on the introduction of a solubilizate is expected to be relatively small (18). Some data obtained by Nakagawa *et al.* (22) for a nonionic system can be interpreted on this basis. For an ionic surfactant, an additional effect arises from the lowering of the c.m.c. and the counterion concentration upon solubilization. This factor will tend to decrease the average aggregation number, as in the case of ionic surfactants in the absence of solubilizates. This effect has also been observed (2).

With some long-chain cationic surfactants, for example, cetyl trimethylammonium bromide or cetyl pyridinium chloride containing a high concentration of sodium chloride, the interaction with aromatic solubilizates such as benzene or toluene leads to the formation of viscous systems containing highly asymmetric micelles (17). In these surfactant systems the sphere-to-rod transition is expected to be facile (6,23). The aromatic solubilizates, up to moderate concentrations in the micelles, are expected to be primarily at the micelle-water interface because of their interfacial activity (24). As a result, such solubilizates are likely to be particularly effective in increasing the surface-to-volume ratios of asymmetric micelles, for example, rod-like micelles (10). Since the sphere-to-rod transition is primarily opposed by the repulsive interactions of the head groups (6), aromatic solubilizates can facilitate the transition by reducing the surface group densities. This qualitative reasoning is supported by the observation that a non-aromatic solubilizate such as cyclohexane, which is not expected to be concentrated at the micelle-water interface (24), does not promote the formation of large asymmetric micelles (17). This approach is also useful for rationalizing a curious phenomenon observed with aromatic solubilizates. When their concentration in micelles becomes very high, the highly viscous system obtained at moderate concentrations of the solubilizate becomes progressively less viscous and swollen spheroidal micelles become predominant (17). At such high mole ratios of the solubilizate to the surfactant, the fraction of the solubilizate present at the surface is expected to be substantially lower than at lower mole ratios on the basis of the interfacial behavior of mixtures of aliphatic and aromatic hydrocarbons (24). Thus the major factor that stabilizes rod-like micelles becomes less important.

#### LOCATION AND DISTRIBUTION OF SOLUBILIZATES INSIDE MICELLES

The previous section has indicated the important role of the distribution of a solubilizate between different locations in micelles as regards the effect of the solubilizate on micellar size distributions. The location, distribution and orientation of solubilized species in micelles and other lipid assemblies such as biological membranes are of fundamental interest in the understanding of the role of the molecular structure of the solubilizate in solubilization processes, the physical, chemical and metabolic activities of the solubilized species, as also the solubilization capacities of micelles and micelle-water distribution coefficients.

Since the micelle is not homogeneous and its interior is fluid-like, in general a distribution and rapid exchange between many states of different location, orientation, and energy are to be expected (25). A complete description of solubilization based on the existence of many states is not available. In the earlier literature it was generally recognized that some locations and orientations were greatly preferred for some solubilizates (1,2). Thus, for example, a purely hydrophobic solubilizate such as heptane could be assumed to be dissolved and distributed in the hydrocarbon core of a micelle whereas an amphipathic solubilizate such as heptanol could be expected to be oriented at the micellar interface roughly in the same manner as the surfactants themselves.

Recent research on slightly polar solubilizates such as benzene, its derivatives containing various numbers of aliphatic substituent groups, and naphthalene has given rise to a two-state model of solubilization which appears to be generally useful (24). It involves a distribution between a 'dissolved state', associated with the hydrocarbon core, and an 'adsorbed state', associated with the micelle-water interface. According to this general model, the examples of heptane and heptanol are approximately at the extreme limits of the two-state model.

The two-state model of solubilization was proposed to explain some ultraviolet spectroscopic data on benzene derivatives which indicated that the microenvironment of benzene dissolved in micelles was quite polar but the effective average polarity sensed by the solubilized species decreased as benzene derivatives with progressively larger numbers of aliphatic groups were used (24,26). These results suggested that a large fraction of the benzene molecules, when present at trace concentrations in sodium dodecyl sulfate micelles, was located at the micelle-water interface, the fraction decreasing on progressive alkyl substitution. The results could be readily rationalized in terms of the observed interfacial activity of benzene in heptane-water systems (24), i.e., its tendency to adsorb at the interface, and the expected reduction in this surface activity on alkyl substitution. The effects of this mild surface activity are enormously magnified by the extremely high surface-to-volume ratios of micelles (24,25).

The distribution between the 'adsorbed state' and the 'dissolved state' is expected to differ for solubilizates of different structures because of variations in surface activity and also with micellar size and shape to some extent (10). Of particular interest is the effect of increasing concentration of the solubilizate. From the interfacial tension data of the benzene-heptane-water system (24), it is found that the surface excess of benzene, when plotted against its mole fraction in heptane, goes through a maximum and decreases at high mole fractions of benzene. With increasing mole fraction of benzene in micelles it is thus expected that the fraction of benzene located at the surface will decrease substantially. As mentioned earlier, this phenomenon is probably responsible for the unusual effects of benzene and similar substances on micellar shape changes.

#### Some Implications of the Two-State Model of Solubilization

The two-state model has some important implications for the understanding of chemical reactions in micellar systems (5). In general, solubilized molecules in the 'dissolved state' and in the 'adsorbed state' are likely to interact differently with other reactive species, particularly if the reactive species, for example, hydrogen ions, are primarily confined to the aqueous medium. The theoretical aspects of the catalysis of chemical reactions in ionic micelles have been investigated recently (5). A comparison of two reactions caused by the attack of hydrogen ions demonstrates that the micellar catalysis for the hydrolysis of sodium dodecyl sulfate in its own micelles and the catalysis in the case of the hydrolysis of a somewhat polar ester such as methyl o-benzoate when solubilized in sodium dodecyl sulfate micelles are very similar when appropriate corrections are made for changes in the electrostatic potential at the surface of micelles. In the former reaction, the hydrogen ion attack is on the sulfate head group which is completely exposed to water and, therefore, to the hydrogen ions. For the latter reaction to have similar catalysis, a major fraction of the solubilized molecules must be available for attack by hydrogen ions. This is consistent with the location of the major fraction of such solubilized molecules at the micelle-water interface as would be inferred from the previous analysis of benzene derivatives.

Another important implication of the two-state model of solubilization in micelles, membranes and other lipid assemblies concerns the use of spectroscopic 'probes'. In general, because of the high surface-to-volume ratios in these systems, any solubilized species which is even slightly surface active has an inhomogeneous distribution. If such species are used as 'probes' for investigating the lipid assemblies, any implied assumption of uniform distribution is highly suspect. For example, if the spectroscopic results on benzene derivatives (24) were interpreted in terms of the average microenvironments of the micelles themselves, the conclusions would have been highly misleading. An unpublished set of results on some currently popular nitroxide 'probes' in micellar systems (27) indicates that the average microenvironment experienced by such probes is highly polar. This observation is consistent with the observed interfacial activity of such systems at hydrocarbon-water interfaces (27).

## SOLUBILIZATION CAPACITIES OF MICELLES

A comprehensive theory of solubilization capacities of micelles would require a much more detailed knowledge about the intermolecular forces involved between the solubilizate and the micelle forming surfactants, the structure of the micelles themselves, and the effect of the solubilizate on this structure than is presently available (10). Even for a simple solubilizate such as an aliphatic hydrocarbon, the solubility in micelles containing a core composed of aliphatic hydrocarbons is considerably different from its solubility in bulk hydrocarbon liquids (1,10). A large number of factors must be responsible for this difference. For example, a part of the surfactant chain close to the polar head group may not contribute to the solvent power of the micelles (1). The interior of the micelle is likely to have a somewhat more solid-like character than bulk hydrocarbons (28). When a solubilizate is incorporated in a micelle, and there is a change in the size and, possibly, the shape of micelle, the corresponding changes in the hydrophobic interactions and the interactions between the head groups responsible for the formation of the micelle itself (6,29) affect the solubilization equilibrium. As the mole ratio of the solubilizate to the surfactant in the micelle increases, complex non-ideality effects must also be expected (12).

Two other factors that are likely to be of considerable general importance for understanding the solubilization capacities of micelles have been recognized relatively recently (10,24,25). The first one involves the effect of the curved interfacial region of the micelle (28). If it is assumed that this interface is at least approximately similar to the interface between a bulk hydrocarbon liquid and water containing the appropriate surface density of polar groups arising from the adsorption of a surfactant (10,24,28), the interfacial tension predicts a very substantial Laplace pressure inside the micelles (28) which must reduce the solubility of all solubilizates (10,24). Wishnia (30) showed some years ago that the solubilities of some hydrocarbon gases in sodium dodecyl sulfate micelles in presence of 0.1 mol/dm<sup>3</sup> sodium chloride were less than the solubilities in bulk hydrocarbon liquids, the difference increasing with the size of the gas molecules. These data can be described quantitatively by assuming a Laplace pressure of 296 atmospheres inside the micelles (10). If the micelle-water interfacial tension is estimated from the interfacial tension data in bulk hydrocarbon liquid systems containing adsorbed sodium dodecyl sulfate (10), the Laplace pressure is calculated to be 264 atmospheres assuming the micelles are spherical. This surprisingly good agreement indicates that some of the other factors mentioned earlier are either of minor consequence or cancel each other in part.

The influence of the Laplace pressure provides a ready explanation of the frequently observed phenomenon that the solubilities of bulk hydrocarbon liquids in micelles decrease with increasing molar volume of the hydrocarbons. The effect of the Laplace pressure is likely to be significant in more complex cases also, for example, when additives affect this pressure by changing the micelle-water tension. Klevens reported many years ago (31) that the solubility of heptane in potassium tetradecanoate solutions increases markedly when long-chain alcohols are added to the system. Since long-chain alcohols are known to reduce interfacial tensions of adsorbed surfactant films, they are likely to reduce the micelle-water interfacial tension very significantly, thus decreasing the effective Laplace pressure and increasing the solubility of heptane. An extension of this argument is likely to provide a basis for understanding the stability of microemulsions (18).

The second important factor comes from the recognition of the importance of the very high surface-to-volume ratio of micelles for solubilizates which are surface active when dissolved in micelles (10,24). The two-state model of solubilization is probably a much more appropriate model for such systems than a model which involves a uniform distribution of the solubilizate in the micelles. Thus, the total amount solubilized by a micelle includes both 'the dissolved state' and 'the adsorbed state' but only the former is to be described in terms of the usual solubility relations. This approach gives a ready explanation of the otherwise highly puzzling observation frequently made that slightly polar substances such as esters or ketones and aromatic hydrocarbons are much more soluble in micelles than aliphatic hydrocarbons although theories of mixing of bulk liquids predict the contrary (1,2,10). It can also be extended to amphipathic solubilizates such as octanol (18).

When solubilizates carry charges, their interactions with ionic micelles involve strong electrostatic forces. Even for nonionic micelles, however, the detailed nature of the microenvironment at the micelle-water interface is important for such ionic solubilizates. Some investigations on the dissociation constants of solubilized indicator dyes in micelles containing different kinds of head groups have been carried out (25). The observed changes in the apparent dissociation constants upon solubilization in micelles carrying no net charge can be attributed to a lower micelle-water distribution constant of the indicator dye species containing a greater amount of charge. This effect can be ascribed, in part, to the electrostatic image forces experienced by charged species at dielectric boundaries which are, however, modified to some extent by additional factors (25). Such image interactions may also be significant for solubilized species containing dipoles.

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