Solubilization of Benzoic Acid Derivatives by Nonionic Surfactants: Location of Solubilizates in Hydrocarbon Core of Micelles and Polyoxyethylene Mantle

PASUPATI MUKERJEE

Abstract □ The micelles that nonionic surfactants containing polyoxyethylene head groups form in aqueous solution have a hydrocarbon core surrounded by a mantle, which can be described as a dense solution of polyoxyethylenes. Solubilization, or the uptake of organic molecules in such micelles, may involve two broadly defined loci: (*a*) the hydrocarbon core along with its interface, and (*b*) the polyoxyethylene mantle. It is shown that the solubilization of many benzoic acid derivatives and phenolic preservatives in such micelles can be described in terms of the two loci of solubilization. The relative importance of the two loci can be derived in an approximate fashion from solubilization data in systems where the polyoxyethylene chain length is varied on the basis of two simplifying assumptions. The distribution of the solubilized species between the two loci is related to the chemical structure of the solubilizate, and it is important in understanding the physical and chemical reactivities of the solubilized species.

Keyphrases □ Benzoic acid derivatives—solubilization in nonionic surfactant micelles, distribution □ Solubilization, benzoic acid derivatives—distribution in nonionic micelles □ Surfactant distribution loci—benzoic acid solubilizates

The solubilization of many benzoic acid derivatives and other solubilizates by the micelles of nonionic surfactants of the polyoxyethylene type has been the subject of a considerable amount of research in recent years (1, 2). One main interest has been the preservative action of some solubilizates in the presence of the nonionic surfactants. It is likely that only the free solubilizate molecules in the intermicellar fluid are primarily active as preservatives, whereas the molecules associated with the surfactant micelles are inactive. Therefore, the overall distribution coefficient of the solubilizate between the micelles and the intermicellar fluid is the quantity of primary interest in this connection.

For a better understanding of the interesting phenomenon of solubilization itself, there are two questions of some importance. The first concerns the variation of the overall distribution coefficient with solubilizate concentration in the micelle and the nature of the nonideality effects displayed by the distribution coefficients. This problem is discussed in another paper (3).

The second problem, the subject of the present paper, concerns the locus of solubilization and the relative importance of the hydrophobic core of the micelle and the hydrophilic exterior (mantle) as the seat of solubilizing action. Solubilization in the hydrocarbon core of the micelle is, of course, well established as a general phenomenon (4). For amphipathic, polar–nonpolar-type solubilizates, this solubilization in the micelle core may involve specific orientations. The hydrophilic part of the solubilizate molecule may be exposed to energetically favorable aqueous environments at the surface of the hydrocarbon core of the micelle, whereas the hydrophobic part may be buried inside the hydrocarbon core. Such statements can only be made for the average position and orientation of the solubilizate molecule in the micelle, because individual solubilizate molecules may be capable of assuming a variety of positions and orientations (5). Recent work (6, 7) suggested that even benzene and some of its nonpolar derivatives, which are only slightly hydrophilic when compared to saturated hydrocarbons, are located primarily at or near the hydrocarbon–water interface of the micelles.

For the purposes of the present discussion, we shall not distinguish between the location of the solubilized species strictly inside the hydrocarbon core of the micelle or partly at the interface of the hydrocarbon core and the surrounding aqueous media, since both types of location are made possible by the presence of the hydrocarbon core. Except for possible electrostatic effects at the micelle surface, solubilization of this type need not be qualitatively different for micelles composed of ionic or zwitterionic monomers and those containing polyoxyethylene-type head groups. For the latter, however, a different kind of solubilization is possible. Considerable evidence exists of weak interactions between long-chain nonmicellar polyoxyethylenes (polyethylene glycols) and many organic molecules as well as electrolytes in aqueous solution (8, 9). Thus, unlike most ionic and zwitterionic micelles, the polyoxyethylene-type nonionic micelles can, in principle, solubilize (bind, "complex," interact with) many organic substances in their outer layers or mantles, which can be looked upon as concentrated solutions of oxyethylene groups. These mantles, in many micelles, are comparable in dimension to the hydrocarbon core and often occupy much bigger volumes than the hydrocarbon core does.

Qualitative suggestions that solubilization of partially polar solubilizates in polyoxyethylene-type micelles may involve either the polyoxyethylene layer or the micelle core, including its interface, have been made by various investigators, and there has been some controversy in the literature as to the importance of either type of solubilization (1, 2, 10–12). The purpose of this paper is to show how, on the basis of two simplifying assumptions, the relative effectiveness of the two loci of solubilization may be evaluated in an approximate fashion from solubilization data obtained with surfactants of different polyoxyethylene chain lengths attached to the same hydrocarbon chain, and how the distribution of the solubilized molecules between the two loci of solubilization, the core and the mantle, is correlated with the chemical structure of the solu-

Table I—Distribution of Solubilizate between Core and Mantle of Polyoxyethylene Stearate Micelles

Solubilizate	r^a	a^b, eq./eq.	b^c, eq./eq.	Y^d	a'^e
Benzoic acid	0.996	0.016_9	0.98_2	0.69	—
p-Hydroxybenzoic acid	0.838	0.050_8	0.37_7	5.4	0.029
o-Hydroxybenzoic acid	0.986	0.015_1	0.98_5	0.61	0.0070
p-Aminobenzoic acid	0.870	0.025_9	0.47_4	2.2	—
Ethyl *p*-aminobenzoate	0.934	0.011_9	0.56_5	0.84	—
Butyl *p*-aminobenzoate	0.999	0.004_2	1.01_9	0.16	—
Methyl *p*-hydroxybenzoate	0.974	0.014_6	0.72_4	0.81	0.0073
Propyl *p*-hydroxybenzoate	0.991	0.006_9	0.76_3	0.36	0.0013_5

[a] Correlation coefficient using Eq. 2. [b] Amount solubilized in the mantle per equivalent of ethylene oxide. [c] Amount solubilized in the core per equivalent of stearyl group. [d] Ratio of the amount in the mantle and the amount in the core calculated for stearyl $(EO)_{40}$ micelles. [e] Binding in polyethylene glycol 4000 in equivalents per equivalent of oxyethylene group.

bilizate. Some applications of the findings in understanding chemical reactivities of solubilized molecules will also be indicated.

DISTRIBUTION OF SOLUBILIZATE BETWEEN CORE AND MANTLE

If micellar solubilization data are available from solubility studies (13) for a series of surfactants of the general formula $R(EO)_nOH$, where R is the alkyl chain moiety, EO stands for oxyethylene ($—OCH_2CH_2—$), and n, the number of EO groups, is varied, the distribution of the solubilizate between the micelle core composed of R groups and the mantle composed of the EO groups can be derived on the basis of two simplifying assumptions: (*a*) the amount solubilized in the core is proportional to the number of equivalents of R present in the micellar form, and (*b*) the amount solubilized (bound) to the mantle is proportional to the number of equivalents of EO group present. Suitable experimental data are available from the study of Goodhart and Martin (13). These authors measured the solubilities of eight benzoic acid derivatives at 25° in polyoxyethylene stearates[1] (so that R represents the stearyl group, $C_{17}H_{35}CO—$). The ionization of the solubilizate was suppressed by using 0.005 *N* hydrochloric acid. Goodhart and Martin (13) used five surfactants in which n varied from 20 to 100[2]. They expressed their micellar solubilities, *i.e.*, the solubility in excess of the saturation solubility in the absence of micelles, as equivalent of solubilizate per equivalent of EO group. According to the assumptions already stated, the amount solubilized, in equivalents per liter of solution, S', will be given by the simple equation:

$$S' = aC_{EO} + bC_R \qquad \text{(Eq. 1)}$$

where C_{EO} and C_R are the concentrations, in equivalents per liter, of EO groups and R, respectively; and a and b are proportionality constants. On dividing by C_{EO}, one obtains:

$$\frac{S'}{C_{EO}} = a + b\frac{C_R}{C_{EO}} \qquad \text{(Eq. 2)}$$

so that if S'/C_{EO}, in equivalents per equivalent, is plotted against the inverse of the EO/R mole ratio of the surfactant, a linear curve should be obtained, with the intercept a representing the solubilization in the mantle (equivalents of solubilizate/equivalent of EO group) and the slope b representing the solubilization in the core (equivalents of solubilizate/equivalent of R group).

Figures 1 and 2 show the plots of the data according to Eq. 2 for the eight systems investigated by Goodhart and Martin (13). Table I shows the values of a and b obtained by least-squaring procedures and the correlation coefficient, r, for linear regression. Considering the uncertainties in the composition of the commercial surfactants, the correlation coefficients are satisfactory, except for the strongly bipolar *p*-hydroxybenzoic acid and *p*-aminobenzoic acid, both of which show some curvature. This curvature is probably due to the breakdown of assumption (*b*). Although *p*-hydroxybenzoic acid appears to show the lowest correlation coefficient, the mean deviation of the experimental data from the best straight line is only about 5%.

STRUCTURAL CORRELATION

The satisfactory representation of the experimental data for all eight systems studied by Goodhart and Martin (13) suggests that the two assumptions used to derive Eq. 2 are reasonably valid for this system. The a and b values of Table I can now be used to calculate the distribution of the solubilized material between the core and the mantle of the micelles for any particular surfactant composition. Table I gives some examples of the calculated ratio, Y, of the amount in the mantle and the amount in the core for a typical surfactant $R(EO)_{40}OH$. The value of Y varies over a wide range, depending upon the structure of the solubilizate.

The values of a and b, and the values of Y calculated therefrom, show excellent qualitative correlations with the structure of the solubilizate as regards the distribution of the polar moiety in the molecule and the size of the nonpolar moiety. Thus, benzoic acid, which has a polar group at one end only and is amphipathic in the same sense as the surfactant molecules themselves, has a low value of a and high value of b. *o*-Hydroxybenzoic acid, which shows intramolecular hydrogen bonding (14), behaves very similarly to benzoic acid. *p*-Hydroxybenzoic and *p*-aminobenzoic acids, however, have polar groups at both ends of the molecule. As is to be expected, their solubility in the micelle core is lower than that of benzoic acid, while the binding to the polyoxyethylene mantle is more pronounced, presumably because this binding with the oxyethylene groups involves hydrogen bonding in part, and bipolar molecules of this kind have two hydrogen bond donor functions for attachment, unlike benzoic or *o*-hydroxybenzoic acid. As the acid group of either *p*-hydroxy or *p*-amino acid is esterified, however, it loses its hydrogen bond donor activity and becomes more hydrophobic. As a result, the binding to the polyoxyethylene mantle is reduced, whereas the solubility in the core becomes higher. Both the

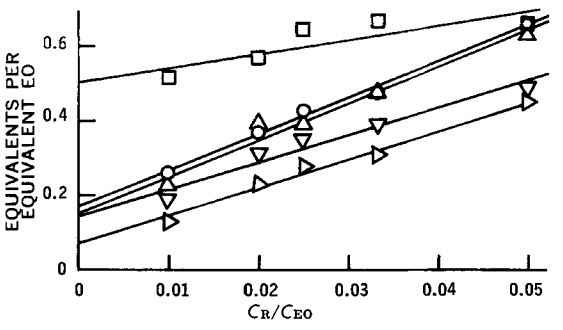

Figure 1—*Micellar solubilization in polyoxyethylene stearates. The number of equivalents solubilized per equivalent of oxyethylene group is plotted as the ordinate against the stearate–ethylene oxide mole ratio for the surfactants. Key:* □, p-*hydroxybenzoic acid;* ○, *benzoic acid;* △, o-*hydroxybenzoic acid;* ▽, *methyl* p-*hydroxybenzoate; and* ▷, *propyl* p-*hydroxybenzoate.*

[1] Commercially available as the Myrj class of surfactants.

[2] The ethylene oxide–stearate mole ratios used here for calculations are 20:1 for Myrj 49, 30:1 for Myrj 51, 40:1 for Myrj 52, 50:1 for Myrj 53, and 100:1 for Myrj 59. These composition figures were obtained from Dr. Paul Becher, Atlas Chemical Industries, Wilmington, Del. They differ slightly from the values used by Goodhart and Martin (13), whose solubility data were recalculated for the present compositions.

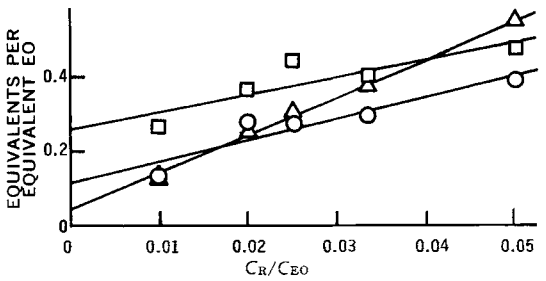

Figure 2—*Micellar solubilization in polyoxyethylene stearates. The number of equivalents solubilized per equivalent of oxyethylene group is plotted as the ordinate against the stearate–ethylene oxide mole ratio for the surfactants. Key:* □, p-*aminobenzoic acid;* ○, *ethyl* p-*aminobenzoate; and* △, *butyl* p-*aminobenzoate.*

increase in b and the decrease in a depend upon the size of the hydrophobic group used for esterification.

The structural correlations discussed here point out the great importance of the distribution of polar groups in a solubilizate molecule in micellar solubilization.

It is interesting to compare the values of a for the micellar systems with the corresponding values of the solubilities of the benzoic acid derivatives in polyethylene glycol itself. For this purpose, the latter quantity, termed a' and defined as equivalents bound per equivalent of EO group, was calculated from some data in the literature (15, 16) for four of the eight substances in Table I. These data are also given in Table I. The data were obtained from solubility studies in relatively dilute solutions of polyethylene glycol 4000 at 30°. This difference in temperature is not of great significance. The solubility of the two acids was determined in the presence of 0.003 N H_2SO_4 to suppress dissociation (15). The a and a' values are similar in order of magnitude, although the a' values are uniformly lower, by a factor of about 2 for three compounds and a factor of about 5 for propyl p-hydroxybenzoate. The a value derived for the latter is very low and, therefore, uncertain.

The comparison of a and a' values indicates that the ability of the polyoxyethylene mantle of the micelles to bind such molecules is substantially higher than that of polyoxyethylene glycol 4000 at low concentrations. Considering the structure of the micellar interface in detail, this effect does not seem unreasonable. The binding of p-hydroxybenzoic acid to polyethylene glycol was found to increase with the molecular weight of the glycol (17), presumably because multiple-site interactions are involved in these weak associations. Polyethylene glycol exists approximately as a random coil (18). In comparison, because of the geometrical restraints imposed by the micelle core, the oxyethylene groups near the micelle surface are forced to be in close proximity, a factor that leads to the head group self-interaction effect, previously analyzed, which reduces the stability of the micelles (19). The polyoxyethylene groups at the micelle surface are expected, therefore, to have much higher local concentrations of oxyethylene groups than polyethylene glycols, and the solubilization (binding) in the surface layer is likely to be facilitated by multiple interactions with neighboring chain elements.

The agreement of a and a' in their order of magnitude provides some additional support for this simple analysis and the relative importance of both loci of solubilization in polyoxyethylene-type micelles. For propyl p-hydroxybenzoate, for example, the experimental value of S'/C_{EO} is as high as 0.0448 for polyoxyethylene stearate 49. If the solubilization is ascribed entirely to the polyoxyethylene mantle, as is sometimes done, the value of a will exceed a' by a factor of more than 30. On the other hand, ascribing the micellar solubilization entirely to solubilization in the core, *i.e.*, assuming an a value of zero, is clearly inconsistent with the a' values in Table I.

The numerical values of a and b in Table I are obviously dependent upon the applicability of the two simplifying assumptions mentioned previously. Although the correlation coefficients and the description of the data (Table I) are fairly satisfactory, possibilities of compensating effects cannot be ruled out. In particular, the crowding of oxyethylene groups at the micelle surface as compared to polyethylene glycol, the factor mentioned in explaining why a values are likely to be higher than a' values, is expected to be a function of the ethylene oxide chain length. Because of the radial nature of the distribution of the EO groups around a spherical micelle, as the EO number becomes higher, the volume available to the EO groups increases nonlinearly. This effect should reduce the effective value of a as the EO chain length is increased and may be responsible, in part, for the curvature exhibited in Figs. 1 and 2, particularly by p-hydroxybenzoic and p-aminobenzoic acids.

APPLICATION TO OTHER SYSTEMS

The two loci of solubilization in polyoxyethylene-type micelles, the core and the mantle, differ greatly in the nature of the interactions the solubilized molecules display and the nature of the local environment around the solubilized molecules. The physical and chemical properties of the solubilized species thus depend, to a great extent, on its distribution between the core and the mantle.

Thakkar and Hall (20) and Bjaastad and Hall (21) investigated the effective polarities of the environments of solubilized testosterone, 2-heptanone, and D-camphor in polyoxyethylene-type surfactant micelles, using changes in absorption spectra. In such studies, the molecules solubilized in the mantle, if any, are likely to behave differently from those solubilized in the core. Similarly, the chemical reactions of solubilized species depend to a great extent on where they are located. Riegelman (22), for example, studied the effect of solubilization in micelles of $C_{16}H_{33}(EO)_nOH$ on the hydrolysis of benzocaine in sodium hydroxide solutions. The measured half-lives can be interpreted in terms of pseudo-first-order rate constants for the hydrolysis of free benzocaine in the intermicellar fluid and that of the solubilized benzocaine in terms of a distribution model (23). The rate constant for benzocaine solubilized in $C_{16}H_{33}(EO)_{14}OH$ is estimated to be about 22% of that of the free benzocaine (23). The structure of benzocaine, which is the ethyl ester of p-aminobenzoic acid, makes it unlikely that the molecules solubilized in the core of the micelle will be very accessible to attack by OH^- ions on the ester linkage, which is likely to be largely buried in the hydrocarbon core, resulting in steric protection. Experimental evidence for this can be derived from the half-life data of benzocaine hydrolysis in sodium dodecyl sulfate and cetyl trimethylammonium bromide solutions (22), both of which show much better protection against hydrolysis than $C_{16}H_{33}(EO)_{14}OH$.

With sodium dodecyl sulfate, this protective action can, in part, be ascribed to the fact that the negatively charged micelles repel the OH^- ions. However, with cetyl trimethylammonium bromide, the positively charged micelle should increase the reaction rate because OH^- ions concentrate at the positively charged micelle surface (23). In fact, a pronounced reduction of the rate is observed for the cationic system, indicating excellent steric protection (23). For the nonionic micelles, however, the previous considerations of this paper suggest that a substantial fraction of the solubilized benzocaine will be located in the mantle, where it is accessible to OH^- attack. From the data in Table I, the calculated fraction of solubilized molecules that reside in the mantle for stearyl $(EO)_{14}OH$ is 23%. The hydrolytic reactions were conducted in unsaturated systems, whereas the values in Table I were obtained for saturated solutions; cetyl ether and stearate esters are likely to show small differences in a and b values. Nevertheless, the similarity in the order of magnitude of the calculated fraction of benzocaine in the mantle for stearyl $(EO)_{14}OH$ (0.23) and the fractional decrease in the rate constant of benzocaine solubilized in cetyl $(EO)_{14}OH$ (0.22) as compared to free benzocaine suggests that the two-state model of solubilization in polyoxyethylene-type micelles should be of use in understanding chemical reactions of solubilized species.

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ACKNOWLEDGMENTS AND ADDRESSES

Received February 16, 1971, from the *School of Pharmacy, University of Wisconsin, Madison, WI 53706*
Accepted for publication June 18, 1971.

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