Solubilization by amphiphilar aggregates

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Solubilization of organic molecules in aqueous surfactant solutions has been actively investigated. Correlations for micelle–water partition coefficients have been developed using linear solvation free energy relationships. The solubilization of vesicles by surfactants and the accompanying structural transitions have been explored. The solubilization behavior of aggregates adsorbed on solid surfaces has been compared to that of micelles in solution. The factors that influence the solubilization of proteins into and their release from reverse micelles in nonpolar solvents have been investigated. The solubilization of hydrophobic molecules has been shown to induce shape transitions in block copolymer aggregates. The solubilization of metal salts by micelles has been made possible via novel lipophilic/metalophilic block copolymers.

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Abbreviations

AOT	aerosol OT
CPC	cethylpyridium chloride
CTAB	hexadecyl trimethylammonium bromide
CTN	α-chymotrypsinogen
DAPA	dodecylammonium trifluoroacetate
DCP	dicetyl phosphate
DEAPFN	diethylammonium perfluorononanoate
DEATS	diethylammonium tetradecyl sulfate
DSA	1-dodecane sulfonic acid
DTAB	dodecyl trimethylammonium bromide
EO	ethyleneoxide
LiFOS	lithium perfluorooctane sulfonate
LiPFN	lithium perfluorononanoate
LiTS	lithium tetradecyl sulfate
LSER	linear solvation free energy relationships
OG	octyl glucoside
SDeS	sodium decyl sulfate
SDS	sodium dodecyl sulfate
STS	sodium tetradecyl sulfate
TTAB	tetradecyl trimethylammonium bromide

Introduction

Solubilization refers to the phenomenon of an increase in the solubility of solvophobic substances in a solvent medium caused by the presence of amphiphilar aggregates. The aggregates provide a microenvironment conducive to the solubilizate molecules, which are otherwise only sparingly soluble in the bulk solvent. In aqueous solutions containing surfactant micelles, vesicles or block copolymer micelles, the solubility of hydrophobic solutes is increased by many orders of magnitude. In nonpolar solvents, the presence of reverse micelles promotes the solubility of polar solutes such as water, amino acids, and proteins. As a consequence, solubilization serves as the basis of a wide variety of industrial, pharmaceutical and biological applications of surfactants.

This review is a continuation of the one which appeared in this journal last year [1], and concentrates on the literature published in 1996. A few papers published in 1995 but not included in last years' review are also discussed. Solubilization in aggregates of both low molecular weight surfactants and higher molecular weight block copolymers is considered. In addition to the topics reviewed last year, we consider also the solubilization of vesicles by surfactants, the solubilization of organic molecules by surfactant aggregates adsorbed on solid surfaces (phenomenon referred to as adsolubilization), and the solubilization of proteins by reverse micelles present in nonpolar solvents.

Understanding the solubilization phenomenon implies discovering how the extent of solubilization is controlled by the molecular properties of the solubilizate and the surfactant, the concentration of the surfactant and other solution conditions such as temperature, pH, ionic strength, presence of other additive molecules, and so on. In addition, one is interested in knowing how the cmc of the surfactant is influenced by the presence of the solubilizate and how the size and shape of the aggregate are affected by solubilization. Further, one would like to identify the microenvironment of the solubilizate within the aggregate. We discuss below how these questions have been addressed in the literature published in 1996.

Solubilization by micelles

Many applications of solubilization, especially in the field of analytical chemistry and chemical separations, require knowledge of the micelle–water partition equilibrium constant K defined as the ratio between the concentration of the solubilizate in the micelle and that in the aqueous phase. Various concentration variables, such as mole fractions, molar concentrations and so on, have been used in the literature. As K is not a constant but depends on the amount of solubilizate in the micelles, most recent experiments have concentrated on obtaining K in the limit of infinite dilution of the solubilizate in the aqueous medium. A free energy of solubilization can be calculated from K as $\Delta G = -RT\ln K$, and from the temperature dependence of K, the enthalpy and the entropy of solubilization are estimated.

Headspace gas chromatography has been used to measure the water-to-sodium dodecyl sulfate (SDS) micellar partition coefficients for 20 solutes [2•] belonging to the homologous series of *n*-alkylbenzenes (benzene to *n*-amylbenzene), 1-nitroalkanes (nitrobutane to nitrohexane), 1-alkanols (methanol to 1-hexanol), and 2-ketones (butanone to *n*-nonanone). The mole fractions of the solutes in the micelles were small and the measured partition coefficients thus corresponded to very dilute solution conditions. For *n*-alkylbenzenes, the transfer free energy per methylene group was estimated to be $-2230\ J\ mol^{-1}$ whereas for the other three families of polar solutes, it was $-2560\ J\ mol^{-1}$. The water–SDS partition coefficients for the methylene groups and for the whole solutes were compared to the corresponding water–organic solvent partition coefficients. The latter partition coefficients were calculated using thermodynamic data available in the literature. The water–hexadecane transfer was found to be more favorable than the water–SDS transfer by $1050\ J\ mol^{-1}$ suggesting that the solutes do not partition into the hydrocarbon liquid-like interior of the micelle, but rather are located in the more polar outer region of the micelle. The water–SDS transfer free energies were comparable to the transfer free energies to nitromethane, acetonitrile and hexafluoro-2-propanol, which are all small polar molecules with no long alkyl chains. Indeed, in place of the conventional use of 1-octanol, bulk methanol was suggested as a better model for the micellar environment experienced by the methylene unit and the whole solute. The comparison of the partition coefficients was extended to mixed aqueous–organic solvents. The water–SDS partition coefficients were found to be comparable to the calculated partition coefficients for mixed aqueous–organic solvents containing any one of 90–100% methanol, 70–80% acetonitrile, 80–100% 2-propanol, or 50–60% tetrahydrofuran. These are all very polar solvent mixtures and support the conclusion that the sites of solubilization at very dilute conditions are very polar, hydrated environments, such as the surface region of the micelle.

The solubilization of aliphatic 2-ketones (butanone, 2-hexanone, 2-octanone, and 2-decanone) at high dilution in anionic SDS, cationic dodecyl trimethylammonium bromide (DTAB), and nonionic Triton X-100 micelles were studied by head space chromatography and IR spectroscopy [3•]. Infra-red spectroscopy was used to ascertain by direct means the location of the solubilizates, rather than obtaining this information indirectly from thermodynamic data. The 2-ketones were selected for the study because the stretching vibrational frequency of their carbonyl group is highly sensitive to the nature of the solvent. It was found that there is hydrogen bonding between the ketone carbonyl group and water. With increasing length of the aliphatic chain, however, the relative amount of the ketone whose carbonyl groups occur in the alkane microenvironment completely free of water increases. It was concluded that both hydrophobic interactions and hydrogen bonding interactions were the driving forces behind solubilization. It may be noted that for 2-ketones (from butanone to 2-nonanone), the measurements in [2•] suggest a very polar microenvironment resembling methanol. Also, the partition coefficients listed in [3•] are substantially different from those reported in [2•], when compared after conversion to a common concentration unit (mole fraction or molarity).

The solubilization of alcohols (1-butanol to 1-heptanol) by dodecyl-, tetradecyl-, and hexadecyl trimethylammonium bromide (DTAB, TTAB, CTAB) and SDS micelles was measured by piezoelectric gas sensors [4]. The partition coefficients at infinite dilution were estimated and these values were used to calculate the transfer free energies to different micelles. These were compared to the transfer free energies to *n*-dodecane and to pure 1-alkanols available in the literature. The transfer free energies to the micelle were more negative than that to *n*-dodecane, suggesting that the solubilization occurs mainly in the palisade layer near the micelle/water interface. The solubilized alkanol molecules can be oriented with their polar hydroxyl groups exposed to the water and their alkyl groups in the micelle interior, whereas alcohol partitioned into bulk *n*-dodecane must undergo an energetically unfavorable dehydration. The transfer free energy decreased linearly with increasing chain length of the alkanol, indicating the importance of hydrophobic interactions. The incremental methylene group transfer free energy to micelles is smaller than those to *n*-dodecane and *n*-alkanols, signifying that the solubilization sites are less lipophilic compared to the two bulk solvents. Further, the transfer of an alcohol to SDS was found to be more favorable compared to DTAB, implying the possibility of hydrogen bonding between the sulfate group of SDS and the hydroxyl group of alkanols. It may be noted that the partition constants for alkanols, derived from this work [4], are in reasonable agreement with the measurements in [2•].

The maximum additive concentrations of benzene, naphthalene, anthracene and pyrene and of *n*-alkylbenzenes (benzene to *n*-pentylbenzene) in dodecylammonium trifluoroacetate (DAPA) and 1-dodecane sulfonic acid (DSA) micelles were measured at various temperatures [5]. DAPA is a hydrocarbon surfactant with a fluorocarbon counterion and micelles formed from such surfactants are generally larger in size when compared to those with similar hydrocarbon counterions. Using an association model, the partition equilibrium constant at infinite dilution was deduced. It increases with the number of rings and the length of the alkyl chain of the solubilizate, indicating the importance of hydrophobic interactions to solubilization. Further, from the dependence of the transfer energy on the chain length, it was concluded that there is a difference in the solubilization site between benzene and other arene molecules. The location of solubilizates was also examined

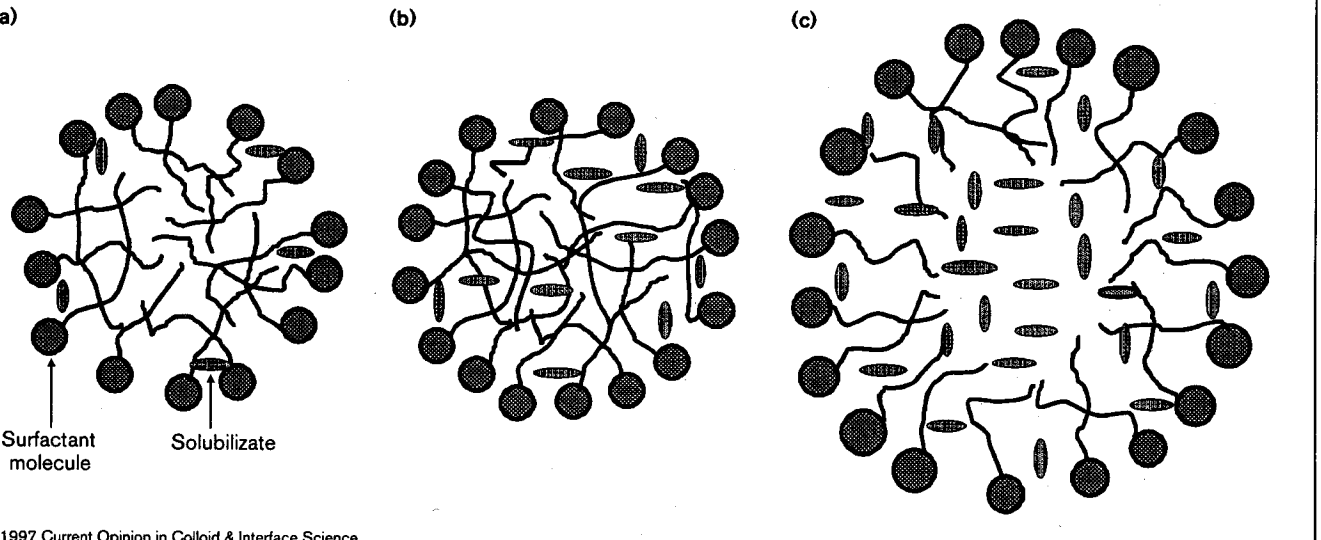
by absorption spectroscopy using different reference solvents. For benzene as the solute, the estimated dielectric constant of its microenvironment is 63.9, very similar to water. It has been determined in previous studies that the micellar surface is almost neutralized by the fluorinated counterions, resulting in large aggregation numbers. Therefore, the micellar surface is covered by a fluorocarbon/water interface where benzene also sits. Other arenes have a less polar microenvironment (estimated dielectric constants are about 40), but are certainly not in the hydrophobic micelle core. They are probably more stabilized by crossing the fluorocarbon layer and becoming located near the hydrocarbon/surfactant head group interface. For the arenes, the incremental transfer free energy per methylene group is $-1500\,J\,mol^{-1}$ in DAPA micelles and $-1770\,J\,mol^{-1}$ in DSA micelles. The lower magnitude in DAPA micelles is attributed to the less hydrophobic solubilization site formed by the concentration of fluorocarbon counterions on the cationic head groups.

In discussing the microenvironment of the solubilizates, it is necessary to realize that all of the above experimental interpretations pertain to very dilute concentrations of the solubilizate in the micelles. Indeed, the same solubilizate molecule can occupy a variety of sites depending upon the amount present in the micelles, as shown in Figure 1. The very first solubilizate molecules can be located near the micellar surface, as observed by the experimental studies discussed above. As the amount of solubilizate increases, however, the molecules begin to appear in the region of the surfactant tails. At saturation conditions, they even occupy the interior core region of the micelle. Indeed, for benzene solubilized in SDS micelles, the scheme shown in Figure 1 has been suggested by experimental studies on saturation solubilization [6] and molecular thermodynamic modeling of solubilization [7].

Correlations of micelle–water partition coefficients

As experimental data on the partition coefficient for solutes in micelles continue to be accumulated, there has been a parallel interest in correlating these partition coefficients to the molecular properties of the solute and the surfactant. Recent efforts have focused on developing such correlations based on linear solvation free energy relationships (LSER). This approach has been employed before for correlating octanol–water partition coefficients. Abraham *et al.* [8••] have presented such LSER correlations for SDS micelles using data on 132 solutes, and for cetylpyridinium chloride (CPC) micelles based on 46 solutes [9•]. They have also applied this approach to microemulsions employed in microemulsion electrokinetic chromatography [10•]. A similar approach has been discussed by Quina *et al.* [11•], who have developed correlations based on LSER for SDS micelles using 66 solutes, for CTAB micelles using 42 solutes, for DTAB micelles using 39 solutes and nonionic Brij-35 micelles using 19 solutes. The general solvation equation has the form

Figure 1



The location of the solubilizate in a micelle is shown at various concentrations. In **(a)**, the first solubilizate molecules are located near the micelle surface, for which the microenvironment similar to methanol has been suggested. In **(b)**, the solubilizate molecules have penetrated the surfactant tail region in addition to being at the surface. In **(c)**, the solubilizate molecules are also present in the interior core of the micelle, forming a region of the pure solubilizate phase.

$$\log K = c + r R_2 + s \pi_2^H + a\Sigma\alpha_2^H + b \Sigma \beta_2 + vV_x \quad (1)$$

Here, K is the partition equilibrium constant defined using mole fractions as concentration units, R_2 is an excess molar refraction that is determined from knowledge of the solute refractive index, π_2^H is the solute dipolarity/polarizability, $\Sigma\alpha_2^H$ is the solute overall or effective hydrogen bond acidity, $\Sigma\beta_2$ is the solute overall or effective hydrogen bond basicity, and V_x is the McGowan characteristic volume of the solute. The values for these parameters describing the solute are listed in [8••,9•–11•]. The constants c, r, s, a, b, r appearing in Equation 1 relate to the differences in the particular properties between water and the phase of interest, in this case the micellar pseudo-phase. The constant r gives the relative ability of the phase to interact with π and n electron pairs, s is a measure of the difference in dipolarity/polarizability of the phase and water, a and b measure the difference in hydrogen bond basicity and hydrogen bond acidity, respectively, v is a measure of phase hydrophobicity. The constant c is the value of log K when all the solute descriptors are zero. Table 1 summarizes the correlation results from [8••,9•–11•], including the number of solutes n, the correlation coefficient ρ, and the standard deviation sd.

The magnitude and the sign of the coefficients provide information on the important solubilizate–micelle interactions that control the solubilization. For SDS, the correlations show that log K increases weakly with the solute excess molar refraction (positive, small r) and decreases weakly with the solute dipolarity/polarizability (negative, small s) and hydrogen bond acidity (negative, small a). On the other hand, log K has a strong dependence on the solute volume with which it increases (positive, large v) and the solute hydrogen bond basicity with which it decreases (negative, large b). Even the alkanes fit the correlation equation well. When the correlation for water–SDS partition coefficient is compared to those for water–alcohols (saturated with water), the hydrophobicity of the SDS pseudophase (denoted by v) is found to be similar to that of water-saturated isobutanol which contains nearly 17 wt% water. One can identify a similar microenvironment for DTAB, whereas for CPC the v coefficient is equal to that of water-saturated *n*-pentanol, and for CTAB it is close to that of water-saturated hexanol. Thus in all cases, the correlations suggest polar microenvironments for all solutes and also that the solute volume and its hydrogen bond basicity control the partitioning into micelles.

The LSER correlations also show that the micelle–water partition coefficient does not correlate very well with the octanol–water partition coefficient, but the correlation can be improved by the use of solute volume as a second descriptor [8••]. One has to keep in mind that these correlations are valid only in the limit of low saturations of micelles with the solutes. Further, this approach does not address other features of solubilization such as the maximum capacity of the micelle for the solutes, the changes in cmc, micelle size and shape due to solubilization, and so on. One has to depend on more fundamental molecular theories for obtaining such detailed microscopic information.

Kinetics of solubilization in micelles

Practical applications of solubilization depend also upon the rate at which the solute is taken into the micelles and the rate at which it can exit the micelles. It was shown by molecular dynamics simulation [12] that there are at least three mechanisms by which oil molecules are transferred from the oil phase to micelles: first, the dissolution of oil molecules in the solvent phase before they are captured by the micelles, second, the exchange of oil molecules between the oil droplets and the micelles during a soft collision, and third, the collective desorption of surfactants and oil molecules from the surface of the oil droplet to form a micelle. For longer chain solutes, the first two mechanisms tend to dominate, whereas for shorter chain solutes the third mechanism is dominant [12]. An experimental investigation of the solubilization mechanism was recently undertaken using the light scattering technique [13•]. Emulsion droplets of controlled sizes were prepared with hexadecane as the oil and the time dependence of droplet concentration and size distribution was followed by light scattering and turbidity measurements. The experiments showed that the concentration of the droplets decreased with time

Table 1

LSER coefficients for micelle–water partition equilibrium constants.

Micelle	r	s	a	b	v	n	ρ	sd	Ref.
SDS	0.54	− 0.40	−0.13	−1.58	2.79	132	0.9849	0.171	[8••]
SDS	0.32	− 0.57	−0.08	−1.84	3.25	66	0.9895	0.13	[11•]
CPC	0.97	− 0.74	0.77	−2.84	3.39	46	0.9737	0.147	[9•]
DTAB	0.57	− 0.40	0.28	−1.82	2.98	39	0.975	0.16	[11•]
CTAB	0.76	− 0.32	1.02	−3.78	3.57	42	0.986	0.19	[11•]
Brij-35	1.63	− 0.37	1.62	−3.83	3.65	19	0.99	0.09	[11•]
Octanol	0.56	− 1.05	0.03	−3.46	3.81	613	0.9974	0.116	[10•]

Where n denotes the number of solutes; ρ denotes the correlation coefficient; and sd denotes the standard deviation.

and the mean droplet size increased in the course of solubilization, despite their being a net movement of oil molecules from the emulsion droplets into the micelles. Also, the kinetics of the solubilization process was found to be strongly dependent on the initial droplet size and concentration. These observations have been explained in terms of the competition between two mechanisms: solubilization by micelles which tends to decrease the mean droplet size, and Ostwald ripening which tends to increase the mean droplet size. Solubilization occurs more rapidly in the emulsions with the smaller droplet size. The importance of the first mechanism, suggested by molecular dynamics simulations, was confirmed by this kinetic study whereas the other two mechanisms could not be tested by these experiments.

Solubilization in mixed micelles

The solubilization of hexanol and hexane in anionic–cationic mixed micelles has been investigated [14] using mixtures of anionic sodium dodecyl heptaoxyethylene sulfate ($C_{12}E_7S$) and cationic dodecyl trihydroxyethyl ammonium chloride ($C_{12}NEt_3$), and mixtures of anionic sodium octylphenyl decaoxyethylene sulfate ($C_8\Phi E_{10}S$) and cationic $C_{12}NEt_3$. The addition of oxyethylene units to the surfactant head groups ensures that mixtures of the anionic and cationic surfactants remain homogeneous at any mixing ratio and concentration. The aggregation number of the mixed micelles has been found to increase as the mixing molar ratio approaches 1 : 1, at which the two mixed surfactant systems are shown to form rod-like micelles. As the molar mixing ratio of the surfactant increases, the extent of hexanol solubilized decreases and reaches a minimum at the equimolar surfactant mixture. In contrast, the extent of solubilization of hexane shows a positive deviation from the simple composition-averaged behavior of the two surfactants, and exhibits a maximum when the molar mixing ratio of the surfactants is near 1 : 1. The increase in the amount of hexane solubilized and the decrease in the amount of hexanol solubilized as the surfactant molar ratio tends to 1 : 1 can both be explained by the changes in the aggregate size as the surfactant composition is modified. In the case of hexane, which can be located in the micelle core, the increase in the aggregate size caused by the mutual charge neutralization of the anionic and the cationic surfactants leads to an increase in solubilization. In contrast, when hexanol is solubilized in the micelles, the hydroxyl group has to retain its contact with water and be a part of the micelle surface. In the case of pure anionic or cationic micelles, such incorporation of hexanol is favored because it causes the ionic head groups to be farther apart on the micellar surface lowering the free energy. When the two kinds of surfactants are present together, however, they can mutually neutralize their charges more effectively and thus the solubilization of hexanol in the mixed micelles is less favorable compared to the pure surfactant micelles.

The solubilization of pyrene and octafluoronaphthalene (a fluorocarbon solute) by mixed micelles of anionic hydrocarbon and anionic fluorocarbon has been investigated [15]. Mole ratios of the solubilizates to the surfactant in the mixed micelles have been measured for mixtures of lithium perfluorononanoate (LiPFN) and anionic lithium tetradecyl sulfate (LiTS), diethylammonium tertradecyl sulfate (DEATS) and diethylammonium perfluorononanoate (DEAPFN), and lithium dodecyl sulfate (LiDS) and lithium perfluorooctane sulfonate (LiFOS). A large, positive deviation from the composition-averaged behavior was seen in DEAPFN–DEATS mixtures and LiFOS–LiDS mixtures for the fluorocarbon solubilizate, whereas there was a small, negative deviation in the case of pyrene. In the case of LiPFN–LiTS mixtures, the solubilization of octafluoronaphthalene was small and closer to the composition-averaged value, whereas there was a weak negative deviation for pyrene. The positive and negative deviations have been explained in terms of the aggregate growth as the micelle composition changes and the phobicity between the hydrocarbon and fluorocarbon molecules in the mixed aggregate.

Solubilization in vesicles

Very few studies on this topic are available in the literature. The solubilization behavior of paclitaxel (taxol, an anti-cancer drug) in small unilamellar lipid vesicles composed of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine has been studied using titration calorimetry and fluorescence spectroscopy [16]. The partition equilibrium constant was measured and the partition was found to be enthalpy driven. This is attributed to the van der Waals interactions between the hydrophobic drug and the hydrophobic region of the lipid bilayer. A strong temperature dependence of the partition is found, with the paclitaxel solubility in the lipid phase decreasing by a factor of four for an increase of 10°C in the temperature. These solubilization studies are important for developing ways of delivering the hydrophobic drug and improving its bioavailability.

Solubilization of vesicles and bilayers

The solubilization of vesicles and bilayers by surfactants refers to the disintegration of the bilayer structure and the eventual formation of closed micellar aggregates as the surfactant-to-lipid ratio is increased. Although this topic can be viewed as one of aggregate formation in mixed surfactant systems, the phenomenon is commonly referred to as solubilization in the literature and hence is included in this review. This is a problem of importance to biomembranes research and liposome technology because many metabolites and therapeutics are amphiphilic and are capable of partitioning between water and natural or synthetic bilayers.

It is generally agreed that at low concentrations, the surfactant simply distributes between the water and

bilayer phases without causing any major alterations in the bilayer structure. Surfactants, however, have been found to induce vesicle growth or aggregation even at these low surfactant-to-lipid ratios. Further, the presence of the surfactant can cause changes in the permeability properties of the bilayer system. The surfactant-induced leakage of the liposome or membrane contents can be initiated as well as probably completed within this regime of surfactant-to-lipid ratio. Then, at a critical surfactant-to-lipid ratio, the bilayer becomes saturated with the surfactant and a breakdown of the bilayer structure is initiated. As the surfactant-to-lipid ratio is further increased, a final stage is reached when complete solubilization of the bilayer structure and the formation of surfactant-rich and lipid-poor mixed micelles form.

The solubilization of egg yolk lecithin vesicles by SDS, sodium decyl sulfate and tetradecyl sulfate (SDeS, STS) was investigated by light scattering and transmission electron microscopy [17•]. All three surfactants were found to cause vesicle growth at low concentrations and lead to small globular mixed micelles at high surfactant-to-lipid ratios. The types of structures formed during the vesicle-to-micelle transition and the amount of surfactant necessary to solubilize the vesicles were both dependent on the chain length of the alkyl sulfates. At 0.15M NaCl, a coexistence between vesicles and thread-like micelles was observed with SDeS, whereas an intermediate holey lamellar phase appeared in the case of the other two surfactants with longer chains. At lower salt concentration, disk-like micelles were seen with SDS which, upon increasing the surfactant concentration, transformed into thread-like micelles having many interconnections with one another in the three dimensions.

The amount of surfactant needed for the solubilization increased with increasing chain length of the alkyl sulfates. This has been explained on the basis of molecular packing considerations which show that cylindrical micelles can form at lower surfactant-to-lipid ratios as the chain length is decreased. The intermediate structures formed when nonionic octyl glucoside (OG) was used to solubilize vesicles based on 47.5% diglycerol hexadecyl ether ($C_{16}G_2$), 47.5% cholesterol and 5% dicetyl phosphate (DCP) have also been investigated [18]. Nonspherical, peanut-like shapes for vesicles, their fusion retaining the cylindrical shape (with the extremities serving as the nodes of fusion), the formation of single-walled vesicles and small vesicles followed by their aggregation, and finally the formation of closed micelles were seen as the proportion of the surfactant OG is increased. The small mixed micelles were found to be not cylindrical or discoidal but globular in shape.

The solubilization of liposomes, formed from egg yolk phosphatidylcholine, by a series of nonionic surfactants having head groups of differing oxyethylene (EO) units (from 7.5–30 EO units) has been investigated [19•] to identify the influence of the polar head group size. Triton X-102 with 12.5 EO units was found to be most effective because it required the smallest amount of surfactant to completely solubilize the bilayer. As surfactants are used in membrane reconstitution processes from which they eventually have to be removed, the identification of most effective solubilizers for biomembranes is important. The measurements of the surfactant-to-lipid ratios at which the membrane leakage begins and ends, as well as the ratios at which the membrane solubilization begins and ends, show that the permeabilization process and the solubilization process are independent of one another.

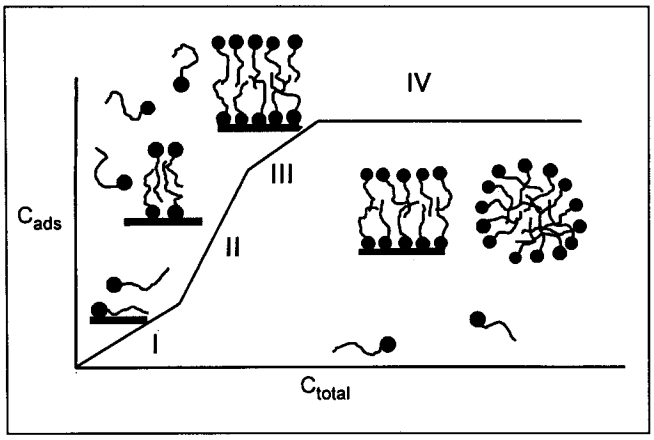
Although the transformation of vesicle or bilayer structure to closed globular micellar structure can be easily understood in the framework of current theories of self-assembly, the formation of intermediate structures and the initial growth of vesicles remain to be explored from a fundamental point of view.

Solubilization in adsorbed surfactant aggregates

The formation of aggregates by surfactants adsorbed on solid surfaces has been known for quite some time. Recent studies have focused on evaluating the ability of these adsorbed aggregates to solubilize water-insoluble organic compounds, the phenomenon being termed adsolubilization. This topic was not included in last years review and hence some papers published in 1995 are also discussed here.

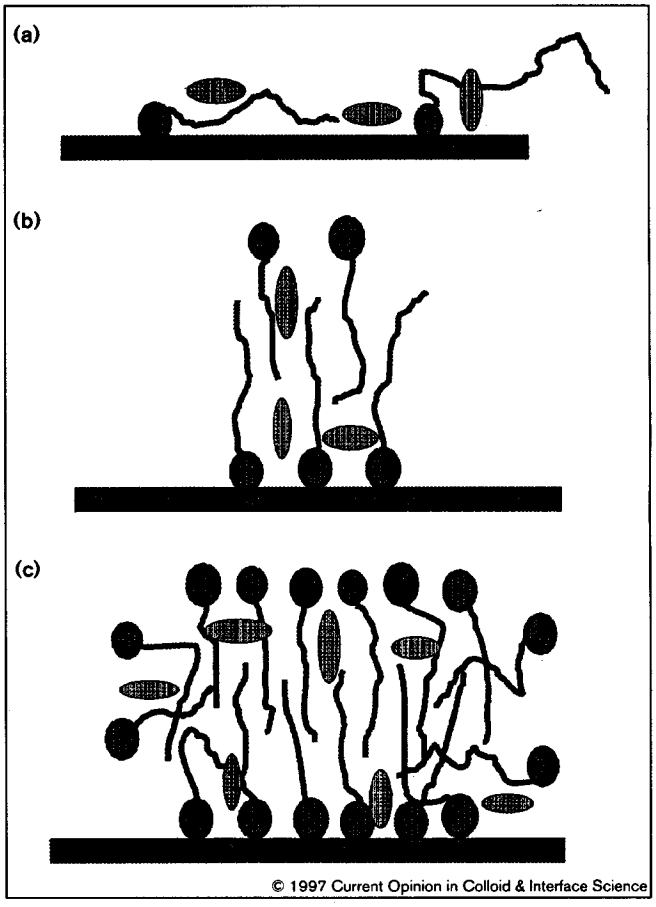
A qualitative view [20•] of the formation of surface aggregates of surfactants is shown in Figure 2. In region I, the surfactants adsorb as individual molecules. In region II, the formation of the surfactant aggregates leads to a sharp increase in the amount of surfactant adsorbed. Local monolayers or bilayers are formed in this region. The micelle-like nature of these aggregates and their occurrence even at adsorption densities that are only 1% of monolayer coverage have been demonstrated. The change in slope observed in region III has been attributed to many possible factors, such as a more complete transition from monolayer to bilayer or surface heterogeneities, *et cetera*. In region IV, the free micelles begin to appear in solution coexisting with the admicelles at the surface. The solubilization of solutes by adsorbed surfactant aggregates can be visualized, as shown in Figure 3. It is conceivable for the solutes to be present on the solid surface due to their direct adsorption in the absence of any surfactant and their coadsorption with surfactants even in the infinitely dilute range of surfactant concentrations (Fig. 3a), their coadsorption and solubilization into small surfactant clusters (Fig. 3b), and their solubilization in fully formed admicelles with preferential location in the core, the surface or the edge of the admicelle (Fig. 3c).

Figure 2



Schematic of an adsorption isotherm for surfactants at solid surfaces. Region I corresponds to the Henry's law domain of adsorption at dilute conditions. Both surfactant head and tail groups may interact with the surface. In region II, surfactant aggregates form and the amount adsorbed increases dramatically as the total concentration of surfactant is increased. Region III has been attributed to rearrangements of the adsorbed micelles and the possible formation of complete bilayer structures. In region IV, the solid surfaces are saturated with admicelles and excess surfactant appears as free micelles in solution. Adapted with permission from [20•].

Figure 3



Schematic of solubilization of organic molecules at solid surfaces with adsorbed surfactants. In **(a)**, the solute molecule is shown to directly adsorb on the solid and also interact with the individually adsorbed surfactant molecules. In **(b)**, the solute molecules are solubilized in small aggregates of adsorbed surfactants. In **(c)**, the admicelles are more fully formed and the solute molecules are solubilized both near the surface region and also the interior of the aggregate.

The solubilization of alkanes in adsorbed SDS aggregates [20•] shows that adsolubilization increases with increasing alkane partial pressures. The amount of alkane solubilized decreases with increasing molecular size of the solute. The molar ratio of the adsorbed alkane to the adsorbed surfactant increases with increasing amount of adsorbed surfactant. All these features are qualitatively similar to the solubilization behavior exhibited by free micelles in solution.

Whereas the adsolubilization of alkanes was not found to cause any increase in the amount of adsorbed surfactant, the 1-alkanols showed markedly different behavior [20•]. The presence of high concentrations of alcohol in the system greatly increased the adsorption of surfactant at the solid surface; the slopes observed in region I (Fig. 2) were much larger even though the surfactant in solution is considered to be very dilute in this region. It has been proposed that coadsorption of alcohol and surfactant occur with the alcohol promoting increased adsorption of the surfactant. There was no adsorption of alcohol, however, in the absence of the surfactant and the amount of alcohol adsolubilized in region I was not measurable. The plateau adsorption of surfactant (region IV of Fig. 2) in the presence of alkanols was found to be somewhat smaller than in the presence of alkanes. Further, the partition equilibrium constant for adsolubilization was found to increase for alkanes and decrease for alkanols, as the surfactant concentration was increased. It has been proposed that alkanes adsorb in the interior of the admicelles whereas the alcohols adsorb in the interior as well as along the edges of the aggregates visualized as disk-like structures. As the aggregates increase in size with increasing amount of adsorbed surfactant, the impact of the edge diminishes compared to the bulk of the aggregate. Therefore, the molar ratio of adsolubilized alcohol to adsorbed surfactant shows a small decrease with increasing levels of surfactant adsorption. The total amount of adsolubilized alcohols, however, increases with increasing amount of adsorbed surfactant. In contrast, when the solute is hydrophobic and solubilized only in the interior of the aggregate, the molar ratio of adsolubilized alkane to adsorbed surfactant increases. Most interestingly, a significant difference between adsolubilization and solubilization by free micelles was found to be in the approximately three-fold increase observed in the solute uptake by admicelles.

The adsolubilization of 2-naphthol by CTAB adsorbed on porous and nonporous silicates has been studied [21•]. The amount adsolubilized was found to be dependent on the pH and the concentration of the adsorbed surfactant but not on the type of silica. The partition equilibrium constant for adsolubilization was found to be roughly three times larger than that for solubilization by free micelles. To explain this, various suggestions have been made including possible differences in aggregate microviscosities or in the aggregate shapes. The adsolubilization of 2 (2-naphthyl) ethanol and 1-naphthylamine into CTAB aggregates adsorbed on alumina, titanium dioxide and silica surfaces has been examined at pH values where all three surfaces are negatively charged [22]. The adsolubilization partition equilibrium constants were found to be independent of the nature of the mineral oxide surfaces. The solute adsolubilization was found to increase with surfactant coverage until the free micelles begin to form, after which the admicelles and the free micelles compete for the solutes. The partition coefficients for adsolubilization were similar to that for solubilization by free micelles in the case of the alcohol but larger by a factor of two in the case of the amine.

The adsolubilization of three steroids (hydrocortisone, testosterone, and progesterone) by the nonionic amphiphiles Triton X-100 and Poloxamer 188 adsorbed on polystyrene latex particles has been investigated [23•]. Poloxamer 188 is a triblock copolymer with two terminal poly(ethylene oxide) chains of 79 units and a middle poly(propylene oxide) chain of 28 units ($E_{79}P_{28}E_{79}$). The hydrophobicity range of the three steroids is given by their octanol–water partition coefficients of 98, 633 and 1330, respectively. In the absence of the surfactant, the most hydrophobic solute progesterone is adsorbed on the solid at all solute concentrations, whereas testosterone is adsorbed only at high solute concentrations and hydrocortisone is not adsorbed at all. The adsolubilization of hydrocortisone increases with increasing amount of adsorbed surfactant, but the partition equilibrium constant decreases with increasing solute concentration in the admicelles. The adsolubilization of the more hydrophobic testosterone was smaller compared to that of hydrocortisone. In the case of the most hydrophobic solute progesterone, both direct adsorption on the latex surface and the adsolubilization in the adsorbed surfactant aggregates occur. The partition equilibrium constants for adsolubilization were estimated to be much larger than that for solubilization by free micelles. The presence of small amounts of ethanol in the system (added to increase the aqueous solubility of the steroids) was found to cause an increase in the adsorption of surfactants on the latex and also an increase in the amount of adsolubilization. The effect of ethanol has been explained in terms of the swelling of the latex.

The solubilization of the hydrophobic dye, Orange OT has been studied in anionic LiTS aggregates on an alumina surface [24•]. As in the other studies discussed above, the admicelles were found to be better solubilizers than the free micelles. The mole fraction of Orange OT in the admicelles was about 2.7 times larger than that in the free micelles. The increase in the partition equilibrium constant for adsolubilization has been interpreted by invoking the concept of Laplace pressure in the micelles, proposed many years ago by Mukerjee (discussed also in last years review [1]). The Laplace pressure model assumes that the decreased solubility of the solute inside the micelles compared to that in bulk solvents (representing the hydrophobic part of the surfactants) is caused by the existence of a Laplace pressure differential across the micelle/water interface. One can write the relation

$$X_m = X_b\, e^{-\frac{\Delta P \bar{v}}{RT}}\left[1+\beta\frac{A}{RT}\left(-\frac{d\gamma}{dX}\right)\right] \qquad (2)$$

where X_m is the mole fraction of the solubilizate inside the micelle and X_b is that in a bulk solvent equivalent to the hydrophobic tail of the surfactant. ΔP is the Laplace pressure inside the micelle, $\bar{v}$ is the partial molar volume of the solubilizate inside the micelle, $(d\gamma/dX)$ is the rate of change of interfacial tension at the oil/water interface caused by the adsorption of the solute, A is the area per mole of the surfactant molecule at the micelle/water interface, T is the temperature and R is the gas constant. The first term in the above equation refers to the effect of Laplace pressure on solubilization whereas the second term accounts for the effect of adsorption of the solute at the exposed hydrocarbon/water interface of the micelle. The fact that only a part of the micellar surface is exposed to water and available for solute adsorption because of the presence of the surfactant head groups is accounted for by the variable β. Even though the area A is smaller for the admicelle compared to the free micelle (especially because one surface of the admicelle is in contact with the solid), the decrease in the partition coefficient for adsolubilization due to this effect is more than compensated by the abolition of the Laplace pressure effect for the adsorbed bilayer (compared to the large Laplace pressure attributed to spherical micelles in solution). The net effect is the increase in the partition equilibrium constant for adsolubilization compared to micellar solubilization.

Although many studies have begun to appear regarding adsolubilization, much needs to be done to characterize the admicelles and also to understand the role of the solid surface with respect to both surfactant adsorption and adsolubilization. The influence of solutes on the adsorption of surfactant and on the size and structure

of the admicelles also need to be investigated. Further, a more fundamental theoretical modeling of admicelle formation and adsolubilization has to be developed as has been done for free micelles in solution.

Solubilization by reverse micelles in nonpolar media

Reverse micelles containing a polar interior and hydrophobic exterior, formed when surfactants are present in a nonpolar solvent, have been explored for a number of years. Studies, especially of the solubilization of water by reverse micelles, can also be viewed as studies of the formation of water-in-oil type microemulsions. A typical recent study is that concerning the dependence of the amount of water solubilized on the amount of *n*-decanol added to a nonionic water-in-oil microemulsion containing olive oil as the oil phase and nonylphenol ethoxylate as the surfactant [25]. Such studies are more conveniently included in reviews of microemulsion and phase behavior, and hence are not treated here.

We will limit this review to the problem of solubilization of proteins in reverse micelles. This has been an active area of research because of the potential applications of reverse micelles for enzymatic biocatalysis in nonaqueous media [26–29] and for large scale chemical separations of proteins [30–32]. It has been shown that the limit of solubilization of proteins in reverse micelles is a function of the pH, the water content and size of the micelle, temperature, the isoelectric point of the protein, its hydrophobicity, the nature and the concentration of the surfactant, and so on. Qualitatively, one can visualize (see Fig. 4) that very hydrophilic proteins may be located in the water-pool of the reverse micelles, the surface active proteins can be adsorbed near the water/surfactant head group interface, and the hydrophobic or membrane-integral proteins may be located in the surfactant tail region of the reverse micelles. Many earlier studies have dealt with hydrophilic proteins, and reasonable interpretation of their solubilization into reverse micelles has been presented in terms of their electrostatic interactions with the micelle and the relative sizes of the reverse micelles and the proteins. Even for these cases, however, it has been found that the factors that control the uptake of proteins into the micelles do not control protein release from the micelles, probably because of kinetic reasons [33]. As such release is very important for the applications of reverse micelles in protein separation technologies, the mechanisms of solubilization and of release should both be explored systematically.

The solubilization of two milk proteins, α-lactalbumin and β-lactoglobulin, into reverse micelles from the anionic surfactant Aerosol OT (AOT) has been investigated as a function of the pH and the ionic strength [34••]. For hydrophilic proteins where electrostatic interactions dominate the solubilization behavior, the maximum solubilization of proteins occurs at pH values below the isoelectric point where the protein and the anionic surfactant are oppositely charged. But in the case of the two milk proteins the maximum solubility occurred above their isoelectric points, indicating that electrostatic interactions cannot be the sole factor controlling the solubilization. Significant solubilization was observed even at high ionic strengths where the solubilization of other hydrophilic proteins is usually very much reduced. For analyzing the nature of solubilization, it has been suggested that a critical micelle radius, at which 50% or more of the transfer of proteins into the reverse micelles occurs, can be used as a criterion. This critical radius is found to be insensitive to pH and small in the case of the two milk proteins – unlike its pH sensitivity and larger values in the case of hydrophilic proteins. These results are interpreted as suggesting that primarily, hydrophobic interactions are

Figure 4

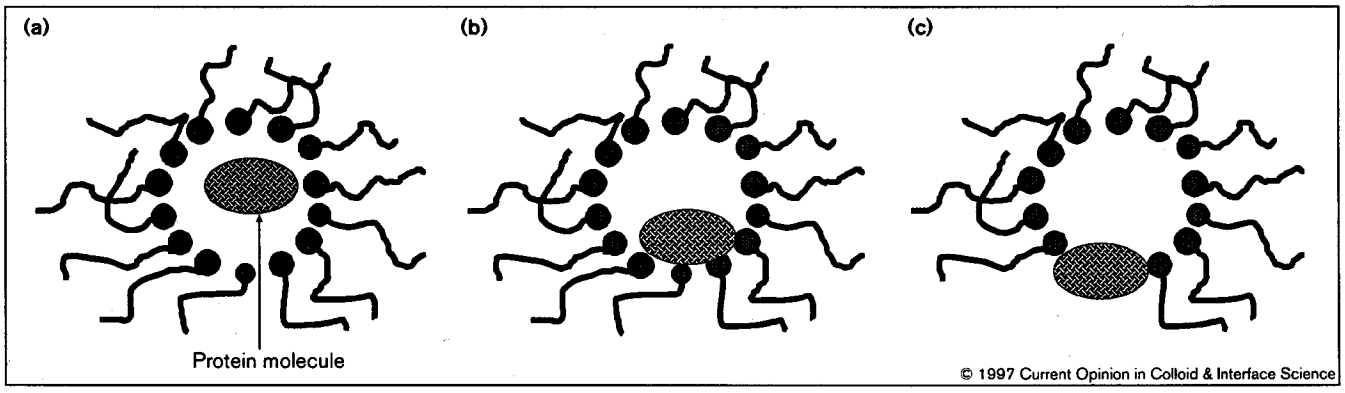


Illustration of possible locations of protein molecules in reverse micelles present in nonpolar solvents. In **(a)**, a hydrophilic protein molecule is shown to be present in the water-pool of the reverse micelle. In **(b)**, a more surface active protein molecule is seen located near the head group region of the micelle sampling the micelle/water interface. More hydrophobic proteins that are integral to membrane structure can be located in reverse micelles as shown in **(c)**, penetrating the surfactant tail region of the micelle.

responsible for the solubilization of these milk proteins in contrast to the primary role assumed by electrostatic interactions in the case of hydrophilic proteins. Further, the amount of water solubilized into the reverse micelles was found to have a linear dependence on the amount of α-lactalbumin solubilized. This has been attributed to the possible role of this protein as a cosurfactant and thereby its ability to expand the micelle/water interface.

The factors that control the solubilization of proteins into, and also their release from, the reverse micelles have been recently reviewed [35••]. In particular, two examples of recombinant proteins (cytochrome b_5 and a cutinase from *Fusarium solani pisi*) are discussed. For both these proteins, the solubilization behavior is found to be controlled not simply by electrostatic interactions but also very significantly by hydrophobic interactions. The review also highlights the difficulties in achieving the release or the back-transfer of the proteins from the reverse micelles into an aqueous medium. Generally, very low transfer efficiencies are achieved and most methods that have been developed result in the destruction of reverse micelles in order to release the solubilized proteins. In [33], a method based on the addition of an alcohol has been demonstrated to facilitate the uptake of proteins into, as well as their back-transfer from, reverse micelles without affecting the integrity of the reverse micelles, for the enzymes pepsin and chymosin. The applicability of this approach for other proteins and especially hydrophobic proteins of the kind mentioned in this review remains to be investigated.

The mechanism of protein solubilization in the AOT reverse micellar system has been investigated — α-chymotrypsinogen (CTN) was selected as the model protein [36•]. It is suggested that the extraction of CTN by the reverse micelles involves two processes. In the first fast step, the adsorption of AOT onto the surface of CTN, through electrostatic interactions, between the AOT anions and the CTN cations converts CTN from a hydrophilic protein into a hydrophobic protein. This is responsible for the fast extraction of the protein into the oil phase. In the second slow step, the adsorption of AOT, due to hydrophobic interaction with CTN, makes the CTN surface hydrophilic and back extraction occurs. The weak interaction between the microemulsion droplet surface and the AOT tails adsorbed on CTN was considered to play an essential role in solubilization, through the size effect. When compared to this weak interaction, the energy of the droplet deformation necessary to accommodate the protein is very large hence the droplet is considered to have the ability to recognize the size of the AOT-coated protein molecule. Experiments using various salinities and organic solvents confirmed this size effect on solubilization.

Solubilization in block copolymer aggregates

Block copolymers are high molecular weight analogs of the conventional surfactants. In last years' review [1], both experimental and theoretical studies concerning the solubilization behavior of micelles formed from block copolymers in aqueous solutions were discussed. It is very well recognized that by changing the molecular weight of the block copolymer and the relative proportions of the hydrophobic and hydrophilic blocks, one can achieve various kinds of micelles differing in their core radius, corona thickness and aggregation numbers. Further, the aggregate shapes can also be modified. Such shape transformations are known to be possible also via changes in the nature of the solvent. The interesting possibility that a block copolymer of given molecular weight and composition present in a solvent can be made to form spherical, cylindrical and lamellar aggregates by controlling the amount of solubilization has been theoretically predicted recently based on a molecular thermodynamic analysis [37••]. The experimental verification of such solubilization-induced morphological transitions of aggregates has only recently been obtained (A Eisenberg, personal communication).

The solubilization of various hydrocarbons in diblock and symmetric triblock copolymers composed of hydrophilic poly(ethylene oxide) (E), and hydrophobic poly(propylene oxide) (P) have been compared [38] in the framework of the molecular thermodynamic theory mentioned above. The predictions show that for identical overall molecular weights and compositions, the diblock ($E_{200}P_{64}$) copolymer micelles have a much larger core radius, corona thickness, aggregation number and volume fraction of hydrocarbon solubilized in the core compared to the symmetric triblock copolymer ($E_{100}P_{64}E_{100}$) micelles. In contrast, the diblock copolymer $E_{100}P_{32}$ having half the molecular weight but the same composition as the symmetric triblock copolymer $E_{100}P_{64}E_{100}$, gives rise to micelles having identical core radius, corona thickness, and volume fraction of solubilizate in the core as the triblock copolymer micelle, but an aggregation number twice that of the triblock copolymer micelle.

The solubilization of naphthalene in three triblock copolymers based on E and P has been studied [39•], with special emphasis on the influence of temperature. It was found that the solubilization of naphthalene can be appreciably increased by moderate increases in the temperature. The solubilization process was found to be reversible such that the solubilizate which separates and crystallizes out at a lower temperature can be readily separated from the block copolymer micelles. This is very useful for the recovery of solubilizates from the micelles and for the recycling of the micelles in a process for treating environmental pollutants like polycyclic aromatics. A thermodynamic model for the solubilizate uptake was also developed [39•] that considered the enthalpy and the entropy of interactions between the solubilizates and the micellar core block, the two conformations proposed for the E and P chains [40], and the energy of creation of the interface. It was concluded that the enhancement of naphthalene solubility

was closely related to the growth of micelles and the polarity change of the micelle core is not important.

Novel block copolymers have been synthesized to allow the solubilization of metal salts in block copolymer micelles having a polar core and a nonpolar corona and formed in toluene [41••]. The diblock copolymers were synthesized starting from commercially available polystyrene–polybutadiene block copolymers. The polybutadiene block was subjected to epoxidation and the resulting polyepoxide block was subsequently modified by different types of ring-opening chemical reactions to create blocks with metal-complexing side groups. The lipophilic–metalophilic diblock copolymer was used to solubilize numerous metal salts of gold, silver, palladium, rhodium, copper and zinc. The possibility of preparing metal nanocolloids through such a solubilization route has been demonstrated, this opening an important application of solubilization by block copolymer micelles.

Conclusions

In the past year, many studies of solubilization by micelles, mixed micelles, vesicles, admicelles, reverse micelles and block copolymer micelles have appeared in the literature. The availability of extensive solute partition equilibrium data for some surfactants has made possible the development of useful correlations based on linear solvation free energy relationships. It is necessary to note, however, that these data and their correlations correspond to very dilute conditions of the solute. The inferences regarding the locus of solubilization of solutes is, obviously, pertinent only to these conditions and not applicable when the micelle is saturated with the solubilizate. Experimental studies on the solubilization of vesicles and bilayers by surfactants have revealed the structural transitions accompanying the solubilization process. Also, some surfactants have been identified as effective solubilizers. The understanding of structural transitions, especially the growth of vesicles following the addition of a small amount of surfactant, is presently incomplete. The solubilization of organic molecules by surfactant aggregates adsorbed on solid surfaces has received considerable attention. The studies show that adsolubilization leads to larger solute partition equilibrium constants compared to solubilization by micelles in solution. This result has been explained by invoking the concept of Laplace pressure in the micelles. A fundamental approach to the treatment of adsolubilization needs to be developed so that one can characterize the adsorbed surfactant aggregates and the extent of adsolubilization more quantitatively, similar to what has been done for free micelles in solution.

The study of solubilization of proteins by reverse micelles continues to be an active field. Understanding the factors that control the solubilization of proteins into and release from reverse micelles is of great importance to protein separation technologies. The solubilization behavior of block copolymer aggregates has been theoretically treated. It would be useful to conduct further experimental studies that will determine the changes in the aggregate size and shape accompanying solubilization, so that available theories can be evaluated and improved. Very interesting practical application of solubilization by block copolymer micelles has been demonstrated for the preparation of metal nanocolloids. It is clear that studies of solubilization will continue to be important in future years.

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