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Demonstration of maximum solubilization in a polyoxyethylene alkyl ether series of non-ionic surfactants

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The solubilization of azobenzene, menaphthone, cortisone acetate, and griseofulvin was measured in a series of non-ionic surfactants of structure $CH_3[CH_2]_{(m-1)}[OCH_2CH_2]_{1.25m}OH$, where m varied from 8 to 18. Maximum solubilization occurs when m = 16 (the hexadecyl alkyl ether). This is explained in terms of changes in the oxyethylene mantle close to the micelle core/mantle interface, which appears to be the main locus of solubilization. Micellar properties of $CH_3[CH_2]_{17}[OCH_2CH_2]_{22}OH$ are also reported and discussed.

For ionic surfactants it has been well established that increasing the hydrocarbon chain length leads to bigger micelles and an increased solubilizing capacity (Klevens 1950). A more mature reflection on the literature supporting this conclusion suggests that the solubilizates used were largely hydrocarbon in nature (Elworthy et al 1968), and that there might be some doubts in applying it to drug molecules which are in general more polar. The solubility studies of Patel et al (1981) on a range of drug molecules in hexadecane and dimethoxytetraoxyethylene glycol (DMTG), indicated that the hydrocarbon was a very poor solvent for most of the drugs, and that the observed solubilizing capacity of non-ionic surfactants could not be accounted for on the basis of these hydrocarbon solubilities. DMTG was a much better solvent for most of the drugs studied.

The idea that increasing the hydrocarbon chain length gave increased solubilization of non-ionic surfactants was tested by Arnarson & Elworthy (1980, 1981). Using polyoxyethylene alkyl ethers such as $CH_3[CH_2]_{21}[OCH_2CH_2]_{21}OH$ (abbreviated to $C_{22}E_{21}$, where E is an ethylene oxide unit) and $CH_3[CH_2]_{31}[OCH_2CH_2]_{41}OH[C_{32}E_{41}]$, no such increase was observed and the solubilizing capacities of these surfactants were worse than that of $C_{16}E_{20}$. There is thus a complete contrast between solubilizing behaviour with increased hydrocarbon chain length between ionic and non-ionic surfactants. The purpose of this paper is to clarify the situation for the non-ionic series, by studying solubilization in a range of surfactants, commencing with C_8E_{10}, and keeping the ratio (no. ethylene oxide units, E)/(no. carbon atoms in the alkyl chain m) as close as possible to E/m = 1·25. In addition, micellar data on $C_{18}E_{22}$ is reported.

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MATERIALS AND METHODS

The methods used for measuring light scattering and viscosity (at 298K) were described by Arnarson & Elworthy (1980). The solubilization technique described by these authors was validated firstly, by showing that clarification of saturated solution by filtration through 0·22 μm Millipore filters gave the same results as for clarification by centrifugation; secondly, that approach to equilibrium solubility from over and under saturation gave the same result. 5 repeat determinations for the solubility of naphthalene in a 2% aqueous solution of $C_{18}E_{22}$ gave a coefficient of variation of 1%.

Densities of aqueous solutions of $C_{18}E_{22}$ were measured using a digital densimeter (Anton Paar, Model DMA 02C).

The partial specific volume $\bar{v}$ (cm^3g^{-1}) was calculated from

$$\rho_s = \rho_w + (1 - \bar{v}\rho_w)c_s,$$

where ρ_w and ρ_s are densities of solvent and solution, respectively (g cm^{-1}), and c_s is the solute concentration (% w/v).

The solubilizates used were as described by Arnarson & Elworthy (1980) except that betamethasone was recrystallized to increase its particle size, making clarification of its saturated solutions less time consuming.

The surfactants were prepared by the modified Williamson ether synthesis of Cooper & Booth (1977). Finely divided KOH (4 mol) was suspended in dry chlorobenzene (44 mol) containing the relevant glycol (4 mol) (from BDH or Fluka). The

redistilled alkyl bromide (1 mol) (Fluka), dissolved in dry chlorobenzene (22 mol), was added slowly with stirring to this suspension. After stirring overnight at room temperature (20 °C), inorganic salts were filtered off, the chlorobenzene evaporated, and excess polyoxyethylene glycol removed by the method of Arnarson & Elworthy (1980). After recrystallization from a 60–80 °C light petroleum containing variable amounts of chloroform, the compounds were chromatographed on activated basic alumina (Merck) using toluene–acetone–methanol (24:25:1, parts by volume) as eluent, or on silica gel (60–120 mesh, Fisons) using increasing concentrations of acetone in chloroform as eluent. The absence of glycols and alkyl bromides was checked by thin layer chromatography on silica, using acetone–methanol–toluene (25:25:50 parts by volume) as solvent, and Draggendorf's reagent for visualizing the spots.

The surfactants were analysed by n.m.r. spectroscopy (Crooks et al 1974).

RESULTS AND DISCUSSION

Micellar structure of $C_{18}E_{22}$

Light scattering results are given in Fig. 1 as a plot of c/S_{90} vs.c, where S_{90} is the scatter at 90 ° to the incident beam from a solution of concentration, c. The value of dn/dc was 0·165 kg mol^{-1}, and using the Rayleigh equation the micellar mass was 138 000, and the aggregation number (n), 111. Viscosity results (Fig. 1) give an intrinsic viscosity [η] at 8·00 kg mol^{-1}, and using the surfactant partial specific volume of 0·9176 cm^{3}g^{-1}, a micellar hydration of 115 mol water mol^{-1} surfactant is obtained on the assumption that the micelle is spherical.

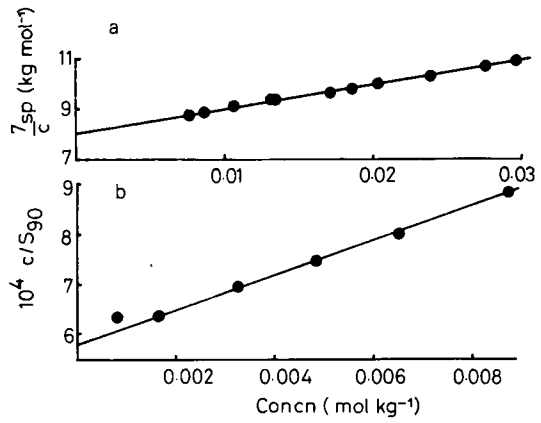

FIG. 1. (a) reduced viscosity against concentration for $C_{18}E_{22}$. (b) concentration/scattering ratio against concentration for $C_{18}E_{22}$.

The aggregation number of $C_{18}E_{22}$ lies between that of $C_{16}E_{20}$ (n = 83) and $C_{22}E_{21}$ (n = 203) (Arnarson & Elworthy 1980), and the observed value of 111 is close to that obtained (113) from a linear regression fit of n vs m (Arnarson & Elworthy 1981) for surfactants with an E/m ratio of 1·0–1·5. Macfarlane (1970) showed that cetomacrogol micelles ($C_{16}E_{22}$) were spherical. From the viscosity data on $C_{18}E_{22}$, the Huggins constant is 1·5 ± 0·15, a value closer to the figure for spheres (2·0) than to any other model. While the micellar shape and magnitude of the aggregation number are consistent with data for other members of the series, there are two inconsistencies. [η] for $C_{22}E_{27.5}$ (interpolated from the results of Arnarson & Elworthy (1980, 1982) is 10·48 kg mol^{-1}, i.e. an increase of 2·48 kg mol^{-1} over the value for $C_{18}E_{22}$; similarly the hydration of $C_{22}E_{27.5}$ micelles is 42 mol water mol^{-1} surfactant greater than that of $C_{18}E_{22}$. The inconsistencies are that [η] for $C_{16}E_{20}$ and $C_{18}E_{22}$ are almost the same, 7·88 and 8·00 kg mol^{-1}, and the hydrations are 116 and 115 mol mol^{-1}, respectively.

Calculation of the hydrodynamic volume, V_h, from: $[\eta] = 2{\cdot}5\ N\ V_h/M$ (Tanford 1961) gives V_h = 593 nm^3 for $C_{18}E_{22}$ and 503 nm^3 for $C_{16}E_{20}$. Increasing the hydrocarbon chain length from 16 to 18 carbon atoms causes the expected increase in aggregation number and hydrodynamic volume, but causes no significant increase in [η] or in the micellar hydration. This result will be discussed after the solubilization data.

Solubilization

In general $C_{18}E_{22}$ is not such a good solubilizer as $C_{16}E_{20}$. Azobenzene (A), menaphthone (M), griseofulvin (G), and cortisone acetate (C) (results in Fig. 2) are solubilized less than in $C_{16}E_{20}$. Tolbutamide 0·0220 g, betamethasone 0·0211 g, and naphthalene 0·0366 g were solubilized individually g^{-1} of $C_{18}E_{22}$; the amount of tolbutamide was less, while the amount of betamethasone was more, than the amounts solubilized in $C_{16}E_{20}$.

No corrections for the presence of a cmc have been made to the data in Fig. 2. The only compound having a cmc high enough to significantly affect the results is C_8E_{10}, where cmc has not been measured. Balmbra et al (1963) gave a value of 0·39% for the cmc of C_8E_6. Allowing for the cmc of C_8E_{10} to be slightly higher due to the longer polyoxyethylene chain, micellar solubilization may be ca 25% higher than those recorded in Fig. 2. This does not affect the trend of the discussion.

If solubilization was solely in the hydrocarbon

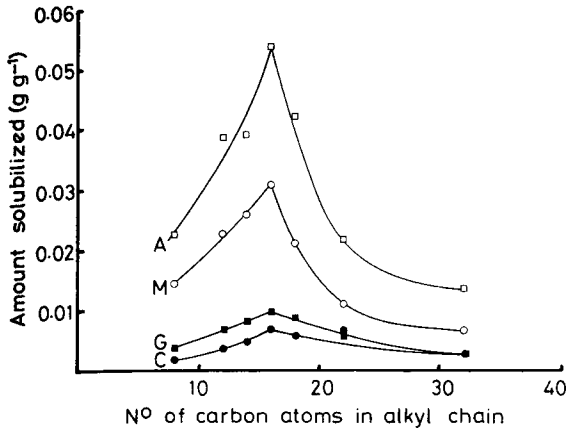

FIG. 2. g solubilized g^{-1} surfactant against number of carbon atoms in the alkyl chain for $C_mE_{1.25m}$. For key to abbreviation of solubilizates see text. Data for $C_{16}E_{20}$ from Arnarson & Elworthy (1980) for $C_{32}E_{41}$ from Arnarson & Elworthy (1981), and interpolated data for $C_{22}E_{27.5}$ from Arnarson & Elworthy (1982).

region of the micelles, then lines in Fig. 2 would run parallel to the abcissa as all the surfactants contain the same amount of hydrocarbon. Taking into account the data of Patel et al (1981) which showed that only azobenzene had a significant hydrocarbon solubility, while all four compounds had good solubilities in DMTG, then solubilization must be expected in the polyoxyethylene rich layer close to the hydrocarbon core. This is in accordance with previous findings, for griseofulvin, (Elworthy & Lipscomb 1968), and for steroids (Barry & El Eini 1976; Tomida et al 1978) in various polyoxyethylene alkyl ethers. The solubilization increases with hydrocarbon chain length, and is maximum at C_{16}. This increase is in accordance with that found for ionic surfactants, but the factors causing it are quite different.

Two major factors can affect solubilization in the polyoxyethylene region close to the micellar core (PRCM): concentration of polyoxyethylene in this region, and geometrical factors. Based on the aggregation numbers (Arnarson & Elworthy 1981) and values for the hydrocarbon densities (Weast 1976) the radius of the micellar core can be calculated, and also the surface area per monomer at the core interface. This varies from 0·64 nm^2 per monomer for C_8E_{10} to 0·65 nm^2 per monomer for $C_{16}E_{20}$. The exact concentration of polyoxyethylene in this region is unknown. While the cross sectional area of this chain is about 0·18–0·20 nm^2 from Catalin models, leaving an area of about 0·45 nm^2 which could be occupied by water molecules, the configuration of the polyoxyethylene chain is that of an expanding spiral (Elworthy & Macfarlane 1962). This means that the actual concentration at the core boundary could be higher than that defined by one polyoxyethylene chain emerging at right angles to the core, as above. It may be that as the micellar size increases in going from C_8E_{10} to $C_{16}E_{20}$, the concentrated region around the core increases in thickness, and this gives increased solubilization.

The principle geometrical factor is how well the solubilizate molecule fits into the concentrated polyoxyethylene region. The larger the micelle becomes, the more planar is the region, and large rigid molecules can be more completely immersed in it. This may be an important factor in the solubilization of steroids.

While both concentration effects and geometrical factors could increase solubilization with increased hydrocarbon chain length, the end result is a balance of both factors, and cannot be explored in more detail at the present time. The decline in solubilization above C_{16}, must also be attributable to effects in the PRCM. As the series is ascended, $C_{18}E_{22}$ is the first surfactant to contain a hydrocarbon chain melting above 298K, i.e. n-octadecane melts at 301K (Weast 1976). A discussion of chain liquidity and micellization was given by Arnarson & Elworthy (1980). Possible intrusion of polyoxyethylene chains into the core has been suggested by these authors (1980, 1982) and by Robson & Dennis (1977). The net effect would be to depress the core melting point, and maintain the normal liquid nature of micelle interiors. If we follow this hypothesis, then the longer the alkyl chain, the higher its melting point, and the more intrusion is required to maintain liquidity. This causes an increase in the size of the micellar core, and hence a dilution of the PRCM, as it is essentially moved outwards in the micelle. Crude calculations of the % area occupied by the polyoxyethylene chain at the core boundary, show that it drops off very rapidly as the core is expanded. Hence the decreased solubilization above C_{16} is attributed to the intrusion effect causing a decrease in solubilization at the PRCM, and this effect predominates over any geometrical ones. The anomalous closeness of the values of [η] and micellar hydration of $C_{16}E_{20}$ and $C_{18}E_{22}$ may be some evidence for the intrusion effect.

There are now two major questions to be answered: (1) Can the intrusion effect be substantiated experimentally? (2) Can the relatively useless hydrocarbon core of non-ionic surfactants be replaced with something useful, in terms of solubilization?

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