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Identification of the site of solubilization of various compounds by cetomacrogol

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Solubilization of some of the esters of *p*-hydroxybenzoic acid by cetomacrogol 1000 solutions has been investigated by ultraviolet spectrophotometry, nuclear magnetic resonance spectrometry and viscometry to provide evidence on the environment of each part of the solubilizate molecule as well as the detergent molecule. Hydration of the micelles calculated from the viscometry results, gave further evidence on the site of solubilization of the compounds. On the basis of these results and solubility results published previously it is suggested that the compounds are solubilized as follows: *p*-Hydroxybenzoic acid is wholly solubilized deep in the oxyethylene layer of the micelle. Ethyl *p*-hydroxybenzoate is solubilized mostly in the oxyethylene layer and is situated adjacent to the core: some solubilization occurs within the core. Butyl *p*-hydroxybenzoate is solubilized mainly at the oxyethylene-hydrocarbon junction, the phenyl ring in the oxyethylene layer and the butyl chain in the core: some solubilizate is wholly present in the core. Methyl *p*-methoxybenzoate: most of the compound is dissolved in the micellar core, but some is also present in the oxyethylene layer. Benzene is solubilized in a similar manner to methyl *p*-methoxybenzoate.

Physical methods provide invaluable tools in the study of solubilization. Ultraviolet spectrophotometry (Riegelman, Allawala & others, 1958; Donbrow & Rhodes, 1966; Tokiwa, 1968) and nuclear magnetic resonance spectroscopy (Donbrow & Rhodes, 1966; Eriksson & Gilberg, 1966) have both been used to identify the site of solubilization of many different compounds.

The size and shape of micelles can be inferred from measurements of the viscosity of systems and comparison of one system with another can yield evidence of the micellar structure. The hydration of the micelles can be calculated from the following:

$$\text{The volume of 1 micelle } V_h = \frac{1}{\mathcal{N}}[(n_2M_2v_2 + n_3M_3v_3) + w_1v_1(n_2M_2 + n_3M_3)] \quad (1)$$

where $\mathcal{N}$ = Avogadro's Number; n_1 = the number of water molecules bound in the micelle; n_2 = the number of detergent molecules bound in the micelle; n_3 = the number of solubilizate molecules bound in the micelle. (The subscripts always refer to the same three species.) M = molecular weight; v = specific volume of the bound compounds; w = weight of compound bound per g of detergent.

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The partial specific volume of the detergent in the solution is:

$$\left(\frac{dv}{dg_2}\right)_{T.P.\ g_1g_3} = w_2v_2 + w_1v_1 + w_3v_3 - w_1v_1^0 - w_3v_3^0 \quad .. \quad (2)$$
$$= \bar{v}_2$$

where v^0 = specific volume of the unbound compound, and where g = total weight of the compound in the solution. Substituting 2 into 1 and rearranging gives

$$v_h = \frac{1}{\mathcal{N}}[(n_2M_2 + n_3M_3)(\bar{v}_2 + w_3v_3^0 + w_1v_1^0)] \quad .. \quad .. \quad .. \quad (3)$$

If the total concentration of micellar substance is $c_2 + c_3$ g/ml the volume fraction, ϕ, of the micelles is:

$$\phi = (c_2 + c_3)(\bar{v}_2 + w_1v_1^0 + w_3v_3^0)$$

for spherical micelles: $\eta_{sp} = 2{\cdot}5\phi$

at infinite dilution $\left[\frac{\eta_{sp}}{(c_2 + c_3)}\right]_{c_2 + c_3 = 0} = [\eta]$

$$\therefore w_1 = \frac{[\eta] - \bar{v}_2 - w_3v_3^0}{2{\cdot}5v_1^0} \quad .. \quad .. \quad .. \quad .. \quad (4)$$

METHODS

Ultraviolet absorption spectra were recorded at a path length of 1 cm using a Unicam SP800 recording spectrophotometer. The sample in the reference beam was either the corresponding solvent or detergent solution.

Proton magnetic resonance spectra of the solubilizates in 20% w/v cetomacrogol solutions were recorded using a Perkin Elmer R10 60 MHz spectrometer.

Viscosity of solutions was determined using a suspended level dilution viscometer (flow time for water 206 s) at 20° ± 0·1°.

RESULTS

Ultraviolet spectrophotometry

As expected, spectra of the compounds show an increased degree of fine structure in n-hexane compared with more polar solvents. The fine structure is also more noticeable for the less polar solubilizates. In cetomacrogol solutions, the wavelength maximum for each compound shifts to longer wavelengths as the concentration of cetomacrogol increases; this is probably due to the relative increase in the micellar phase and consequently in the amount of the compound solubilized (Table 1). For benzene, the wavelength maximum shifts from the water value in 0·1% cetomacrogol solution to the hexane value in 8% cetomacrogol solution indicating that the benzene is predominantly in a hydrocarbon environment in 8% cetomacrogol solution.

In contrast to benzene the spectra for *p*-hydroxybenzoic acid and its butyl and ethyl esters suggest that in the more concentrated cetomacrogol solutions these compounds are in an oxyethylene environment.

The wavelength maxima for methyl anisate in cetomacrogol solutions is shifted 1 nm towards longer wavelengths compared with the spectrum in aqueous solution,

Table 1. *The wavelengths of the absorption maxima for the solutions (nm).*

Compound	Solvent					
	Water	n-Hexane	PEG 1000 30% w/v	Cetomacrogol 0·1%	Cetomacrogol 2%	Cetomacrogol 8% w/v
Benzene	254·0	255·0	254·5	254·0	254·5	255·0
p-Hydroxybenzoic acid	255·5	—	257·0	255·5	257·0	257·5
Ethyl *p*-hydroxy benzoate	255·0	246·5	257·5	256·0	257·0	258·0
Butyl *p*-hydroxy benzoate	256·0	246·5	258·5	258·0	259·0	259·0
Methyl *p*-methoxy benzoate	257·0	253·0	258·5	257·0	257·5	258·0

with the concomitant small increase in the complexity of the spectrum in 8% cetomacrogol solution. This suggests that a large amount of the ester is solubilized in the hydrocarbon core. The nmr data also support this viewpoint.

Nmr spectroscopy

Fig. 1 shows the dependence of chemical shift of various protons (measured from the water reference line) on the mol ratio of solute to detergent. It has already been shown (Eriksson, 1963; Eriksson & Gilberg, 1966) that the water line moves only a very small amount, compared with an external reference, on solubilization of various compounds in aqueous cetyl trimethylammonium bromide and cetyl pyridinium chloride.

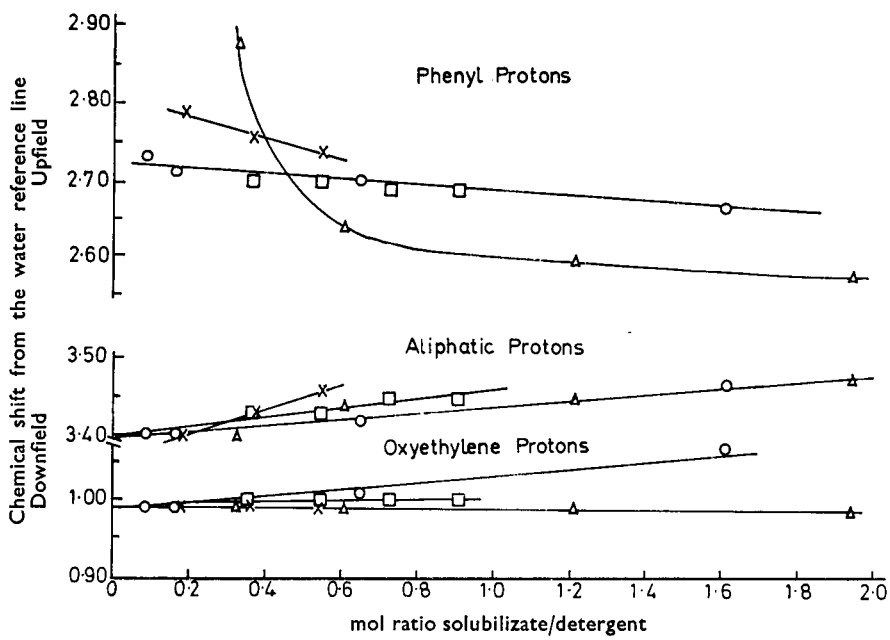

FIG. 1. The chemical shifts of the solubilized systems. ○ = *p*-Hydroxybenzoic acid. △ = Benzene. □ = Ethyl paraben. × = Methyl anisate.

The chemical shift of the oxyethylene protons is independent of the amount of solute solubilized by the surfactant except in the case of *p*-hydroxybenzoic acid where there is a concentration dependence. *p*-Hydroxybenzoic acid thus appears to be the

only compound to appreciably alter the structure of the oxyethylene water complex. The other compounds, may not be present in sufficient concentration in the oxyethylene complex to modify the environment of the protons and so alter the line position. The chemical shift of the aliphatic protons of the cetomacrogol is dependent on the mol ratio of solute to detergent whatever the solute involved. As the mol ratio increases, the environment of the aliphatic protons is continually changing. The slope of the curve in Fig. 1 for methyl anisate is greater than that for ethyl paraben and is probably due to the greater concentration of the former compound in the hydrocarbon core. Since *p*-hydroxybenzoic acid is insoluble in hydrocarbon solvents its effect on the chemical shift of cetomacrogol aliphatic protons is probably due to the solubilization of the acid molecules in the oxyethylene water complex, thus resulting in a changed configuration of the oxyethylene chains which modifies the structure of the hydrocarbon core.

Resonance lines for the phenyl protons of *p*-hydroxybenzoic acid and its ethyl ester both show the same shifts, probably indicating that both are in the oxyethylene layer. Since shifts for the phenyl protons of methyl anisate are different from those of the other two solids, this probably reflects the increased solubilization of the ester in the micellar core. The plot for benzene shows a large change in slope at about 0·5 mol/mol detergent suggesting that at very low concentrations of benzene the site of solubilization is different to that at higher benzene concentrations. It is suggested that benzene may be adsorbed on the micelle surface at less than 0·4 mol/mol detergent and only enters the core above 0·6 mol/mol. Eriksson & others (1966) have reported similar results for the solubilization of benzene by cetyl trimethylammonium bromide and cetyl pyridinium chloride.

Viscometry

The intrinsic viscosities and line slopes for plots of $\frac{\eta_{sp}}{c}$ vs. c are presented in Table 2.* Addition of *p*-hydroxybenzoic acid (or its ethyl ester) to solutions of cetomacrogol result in a small decrease in micellar hydration. This is probably due to simple displacement of some of the bound water by the large number of solubilizate molecules in the micelle.

Table 2. *The intrinsic viscosity and hydration of the saturated systems at* 20°.

	[η]			Hydration g water/g detergent
	PEG 1000	Hexagol	Cetomacrogol	(w_1)*
No additive	5·9	3·0	7·6†	2·2 ± 0·2
p-Hydroxybenzoic acid	5·3	2·8	6·4	1·9 ± 0·2
Ethyl paraben ..	5·6	2·4	5·8	1·6 ± 0·1
Butyl paraben ..	5·9	3·2	6·7	2·2 ± 0·2
Methyl anisate ..	5·6	2·7	7·2	2·1 ± 0·2
Decane	—	—	5·3	1·2 ± 0·1

* Applies to cetomacrogol only.
† The error in intrinsic viscosity determinations is approximately ±5% (Macfarlane, 1963).

* A computer program for this calculation can be obtained from the authors on request.

The decrease for the ethyl ester is greater than for the acid and is ascribed to the larger size of the ester molecule displacing more water molecules. The hydrophobic ester chain may also cause the oxyethylene chains to coil more tightly and thus squeeze out some of the trapped water molecules.

The values of w_1 for the butyl paraben and methyl anisate systems are close to that of cetomacrogol in the absence of solubilizate and this may be due to a balance of two factors. Although these solubilizates displace water from the polyoxyethylene/water layer of the micelle, *decreasing* w_1, they may also affect the structure of the micelle, expanding the hydrocarbon core, and *increasing* w_1.

The decane system has a very low hydration. If most of the solubilized decane enters the micellar core, then expansion of the micellar core would result. Provided the structure of the palisade has not been modified, the overall size of the micelle may remain constant. This would result in a decreased volume of the palisade layer and therefore a low degree of hydration.

The site of solubilization

Decane is miscible with the hydrocarbon core of the micelles and the only restriction on the magnitude of the M.A.C. is that which limits the volume of the micelle. This is the ability of the oxyethylene chains to orientate themselves to effectively cover the expanded core. It follows that the M.A.C. of decane is higher in non-ionic detergents than in ionic detergents (McBain & Richards, 1946; Corby & Elworthy, 1971).

Benzene has an appreciable solubility in the oxyethylene layer of the micelle (Corby & Elworthy 1971). which would result in dehydration of this layer and this is probably the limiting factor in the M.A.C. Evidence presented above suggests that only a very small amount of benzene is dissolved in the oxyethylene layer, most being solubilized in the hydrocarbon core. The limit is reached when the core becomes so large that the partially dehydrated oxyethylene–water complex cannot any longer hold the micelle in solution.

p-*Hydroxybenzoic acid and its derivatives.* Whereas the free acid appears to be wholly solubilized in the oxyethylene layer of the micelles, its ethyl ester is solubilized partly in the micelle core and partly in the palisade layer, but with most near to the core-palisade junction. Orientation of ester molecules at this junction is likely so that the ethyl chain is just within the hydrocarbon core. The corresponding butyl ester is similarly solubilized but the proportions of the two esters present at each site are different because of the different polarity of each compound. To account for the greater M.A.C. of the butyl derivative in cetomacrogol solutions, it is suggested that this compound modifies the micellar structure to a much greater extent than ethyl paraben.

Methyl anisate. Some solubilization of methyl anisate takes place within the oxyethylene layer with most present in the micellar core.

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REFERENCES

DONBROW, M. & RHODES, C. T. (1966). *J. Pharm. Pharmac.*, **18**, 424–428.
ERIKSSON, J. C. (1963). *Acta chem. scand.*, **17**, 1478–1481.
ERIKSSON, J. C. & GILLBERG, G. (1966). *Ibid.*, **20**, 2019–2027.
CORBY, T. C. & ELWORTHY, P. H. (1971). *J. Pharm. Pharmac.*, **23**, *Suppl.*, 39S–48S.
MCBAIN, J. W. & RICHARDS, P. H. (1946). *Ind. Engng Chem.*, **38**, 642–646.
MACFARLANE, C. B. (1963). Ph.D. Thesis, University of Glasgow.
RIEGELMAN, S., ALLAWALA, N. A., HRENOFF, M. K. & STRAIT, L. A. (1958). *J. Colloid Sci.*, **13**, 208–217.
TOKIWA, F. (1968). *J. phys. Chem.*, **72**, 1214–1217.