1180. *Potentiometric Studies on Solubilisation in Non-ionic Micellar Solutions. Part I. Interpretation of* pH *Changes and Mechanism of Solubilisation of Benzoic Acid.*

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The effect of a polyethylene glycol monoalkyl ether upon the pH values of mixtures of benzoic acid and sodium benzoate has been examined for potentiometrically method over a wide range of acid: benzoate ratios and surfactant concentrations at constant ionic strength and the results have been compared with other solubilisation data for benzoic acid. The pH differences can be correlated with the distribution of the benzoic acid between the water and the surfactant. Binding of benzoic acid by the surfactant is shown to be governed by the Langmuir isotherm. Since the benzoic acid is not dimerised in the micelles, it is probably located at the junction of the palisade layer and the hydrocarbon nucleus.

Solubilisation of a variety of solutes by aqueous solutions of ionic and non-ionic surface-active agents has been extensively studied by the solubility method.[1] Though universally applicable, this method is limited to measurements at saturation, below which, though the solute concentration is freely variable, the distribution between the continuous and micellar phases is normally not determinable. Attempts have been made to interpret solubilisation mechanisms qualitatively from changes in ultraviolet spectra,[2,3] oxidative rates of catalysed reactions,[4,5] and by gas chromatography.[6] Little use has been made of potentiometry, either in direct studies of solubilisation or in the investigation of its mechanism. Ekwall[7] and Lawrence[8] have used potentiometry to investigate the properties of cationic and anionic

[1] J. L. Moilliet, B. Collie, and W. Black, "Surface Activity," Spon, 1961.
[2] S. Riegelman, N. A. Allawa, M. K. Hrenoff, and L. A. Strait, *J. Colloid Sci.*, 1958, **13**, 208.
[3] S. Riegelman, *J. Amer. Pharmaceut. Assoc. (Sci. Edn.)*, 1960, **49**, 339.
[4] J. E. Carless and A. G. Mitchell, *J. Pharm. Pharmacol.*, 1962, **14**, 46.
[5] J. E. Carless and J. Swarbrick, *J. Pharm. Pharmacol.*, 1962, **14**, 97.
[6] S. Kaufman, *J. Colloid. Sci.*, 1962, **17**, 231.
[7] P. Ekwall, Nord. Kemistmötet, Berattelse Foredrag, 6th Meeting, Lund, 1947, p **179**.
[8] A. S. C. Lawrence and M. P. McDonald, Proceedings 2nd Internat. Congr. Surface Activity, London 1957, vol. I, p. 385.

surfactants and Christensen[9] has used a potentiometric method to follow the uptake of organic acids by the organic phase of an emulsion.

The present authors have described the effect of a polyethylene glycol monoalkyl ether upon the pH of buffer solutions and the potentiometric titration curves of organic acids.[10] At moderate concentrations of the non-ionic agent there was no appreciable change in the pH response of a glass electrode in hydrochloric acid or sodium hydroxide solutions. This indicated that pH values could be interpreted similarly to those in purely aqueous systems. In the present paper the Henderson equation is applied to yield information on the mechanism of solubilisation of benzoic acid. This method is shown to be a useful means of establishing the quantitative relationship between the micellar and non-micellar solute in a non-saturated surfactant system.

Theoretical Basis.—One would expect the distribution of a weak organic acid or base between the continuous and pseudo-phase of an aqueous solution containing micelles of a surface-active agent to be governed by the following equilibria:

$$\begin{array}{ccccc} HA_{solid} & \rightleftharpoons & HA_{water} & \rightleftharpoons & H^+A^-{}_{water} \\ & & \Downarrow\Uparrow & & \Downarrow\Uparrow NaOH \\ & & HA_{micelles} & & Na^+A^- + H_2O \end{array} \qquad (1)$$

Dyer[11] has shown such a scheme to be applicable in systems containing anionic and cationic surface-active agents. The activity of the micellar acid, $HA_{micelles}$, should hence be a function of the activity of the aqueous acid, HA_{water}. When excess of solid acid is present, both activities should reach their limiting values, the micellar acid then constituting the entire solubilised acid. The saturation activities should be pH-independent, changes of pH causing only changes in the quantities of anion formed. Provided the anion A^- is not bound by the micelles and the surface-active agent is inert to protons and hydroxyl ions, the activity ratio $(A^-)/(HA_{water})$ should be the same in the surfactant solutions as in surfactant-free blanks of identical pH. Consequently the concentrations of A^- and HA_{water} should be the same at equivalent ionic strength. This argument presupposes that the pH scale is equally applicable in both media, which is borne out by the authors' previous work,[10] and that the pK_a of the unbound acid is unaffected by the presence of the surfactant, which is reasonable for a non-ionic agent of very low critical micellar concentration. The validity should be demonstrable by a comparative study of the effect of pH on the solubilisation of benzoic acid in water and in a non-ionic surfactant solution, and such a study is reported below.

The equilibria in scheme (1) also govern distribution of the acid below saturation level. In the pH range of partial salt formation and between pH 4 and 10, the Henderson equation can be applied subject to the assumptions made previously.

Denoting pH values, salt and acid concentrations, and salt activity coefficients (γ) in the water by means of subscript 1 and the values in the surfactant by subscript 2, then we have:

$$pH_1 = pK_a - \log\frac{[HA_{water}]_1}{[A^-]_1} + \log\gamma_1, \text{ in the water} \qquad (2a)$$

$$pH_2 = pK_a - \log\frac{[HA_{water}]_2}{[A^-]_2} + \log\gamma_2, \text{ in the surfactant} \qquad (2b)$$

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[9] J. A. Christensen, *Acta Chem. Scand.*, 1962, **16**, 2363.
[10] M. Donbrow and C. T. Rhodes, *J. Pharm. Pharmacol.*, 1963, **15**, 233; Proceedings 23rd Internat. Congr. Pharmaceut. Sci,, Munster. 1963, Govi-Verlag GMBH, Pharmazeut. Verlag, Frankfurt, 1964.
[11] D. Dyer, *J. Colloid Sci.*, 1959, **14**, 640.

From the differences, $pH_2 - pH_1$, ($= \Delta pH$) between surfactant and water solutions containing identical ratios of total free acid (aqueous and micellar) to salt at similar ionic strengths, the apparent loss of free acid in the surfactant, representing the bound acid, can be calculated:

$$\Delta pH = \log \frac{[HA_{water}]_1}{[A^-]_1} + \log \frac{[HA_{water}]_2}{[A^-]_2} + \log \gamma_2/\gamma_1 \quad (3)$$

Further simplification results if it can be shown that the salt remains in the aqueous phase and the activity coefficients are identical.

Alternatively, for acids which cannot be titrated in water alone because of their low solubility, calculation of the bound acid can be made directly from equation (2b). A potentiometric titration technique has been used here to enable a wide range of acid:salt ratios to be studied.

Experimental

Materials.—Polyethylene glycol monocetyl ether (Cetomacrogol 1000 B.P.C., supplied by Evans Medical Ltd.) was de-ionised as previously[10] [Found: C, 58·4; H, 9·15, 10·01%. n_D^{25} for 20% solution, 1·358. Mean chain lengths: alkyl C_{16}, ethylene oxide groups 24 (by p.m.r.)].

AnalaR benzoic acid and sodium chloride and laboratory-grade sodium benzoate (all from B.D.H.) were used.

Effect of pH *on the Solubilisation of Benzoic Acid.*—A series of solutions containing 20 ml. of double-strength McIlvaine citrate–phosphate buffer solution, and either 20 ml. of water or 20 ml. of 20 per cent w/v de-ionised Cetomacrogol solutions was prepared. Sodium chloride (2 g.) was added to all solutions as a swamping electrolyte to minimise differences in solubilisation caused by variations in electrolyte concentration. The solutions were shaken with excess of benzoic acid at 25° for 8 days, and then set aside for 2 hr. to settle before samples of the supernatant liquid were collected through No. 4 filter sticks. The benzoic acid was determined spectrophotometrically at 273 mμ after suitable dilution of the samples and addition of excess of 0·5N-hydrochloric acid. A preliminary check showed that Beer's law was observed by benzoic acid in the presence of the buffer constituents, swamping electrolyte, and Cetomacrogol.

The pH values of samples of the filtrate were measured by using an E.I.L. Vibron electrometer with unit 33B attached. Electrodes: indicator E.I.L. GH 533; reference. Cambridge saturated calomel.

Potentiometric Titrations.—The apparatus used and method of calibration of the glass electrode were as described previously.[10]

Quantities (25 ml.) of 100mM(approx.)-sodium benzoate solutions were titrated, in the absence of surfactant and in solutions containing 20, 12, 8, and 4% of Cetomacrogol, with hydrochloric acid.

Solubility of Benzoic Acid in Water and Cetomacrogol Solutions.—Excess of solid benzoic acid (AnalaR; B.D.H.) was shaken with 0·005N-hydrochloric acid in the presence of 0·1N-sodium chloride. Similar solutions containing 4, 8, 12, and 20% of Cetomacrogol were also prepared. The solutions were shaken for 8 days and then assayed as described above.

Results and Discussion

Effect of pH *on the Solubilisation of Benzoic Acid.*—The change in the solubility of benzoic acid is shown as a function of pH for the aqueous (blank) and 10% Cetomacrogol buffer solutions in Fig. 1. The curves are similar in form, the solubility rising with increase in pH owing to the increase in ionisation of the acid. The relative increase in solubility is greater in the blank than in the surfactant as would be expected of a system containing a reserve of un-ionized benzoic acid in a pseudo-phase.

From the data, it is possible to calculate the acid solubilised, $HA_{micelles}$; Table 1 shows a series of such calculations. The constancy of the calculated values of $HA_{micelles}$ indicates that the salt form of this organic acid is not solubilised by Cetomacrogol nor does the presence of the surfactant affect the pK_a of the acid. These results are in agreement with those reported by Dyer[11] for anionic and cationic agents.

TABLE 1.

Effect of pH upon the solubilisation of benzoic acid.

pH	*A* Total benzoic acid in blank A^- (millimole)	*B* Total benzoic acid in surfactant solution $HA_w + A^- + HA_m$ (millimole)	*C* $(B-A)\ HA_m$ (millimole)
3·1	0·85	6·15	5·30
3·3	0·90	6·15	5·25
3·5	0·95	6·30	5·35
3·7	1·15	6·45	5·30
3·9	1·50	6·75	5·25
4·1	2·00	7·20	5·20
4·3	2·70	7·80	5·10
4·5	3·65	8·75	5·20

Potentiometric Titrations.—The potentiometric-titration curves of sodium benzoate were displaced in comparison with a blank, the displacement increasing with concentration of surfactant added. All the curves were similar to those previously reported.[10] From equations (2) and (3) the following were derived for the calculation of the amounts of bound and free acid at any stage of the titration.

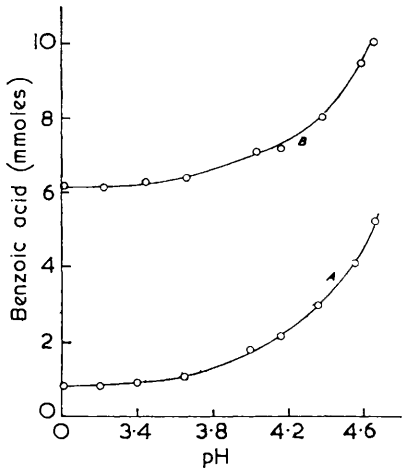

FIG. 1. Effect of pH on the solubilisation of benzoic acid, *A*, blank; *B*, 10% Cetomacrogol.

If A_T = initial moles of benzoate and N = fraction titrated (burette reading/equivalence reading), then the total free acid, HA_T, is given by equation (4).

$$HA_T = N.A_T \tag{4}$$

The amount of free acid, HA_w, is given by equation (5).

$$\log HA_w = pK_a - pH + \log(1-N)A_T + \log \gamma_{\pm} \tag{5}$$

Substituting the apparent dissociation constant, pK_a', for $pK_a + \log\gamma_{\pm}$ and rearranging, equation (6) is obtained.

$$HA_w = \text{antilog}\,[pK_a' - pH + \log(1-N)A_T] \tag{6}$$

Now

$$HA_T = HA_m + HA_w \tag{7}$$

hence the value of HA_m may be determined by difference.

The apparent dissociation constant used must be that determined from a blank titration performed at identical ionic strength for no activity correction to be necessary. In the case

of benzoic acid, since precipitation occurred in the blank, the pK_a' was calculated by means of the Henderson equation from pre-precipitation pH values.

The results obtained by use of equations 6 and 7 are shown in Fig. 2. For comparison purposes the saturation values obtained from the solubility study are included.

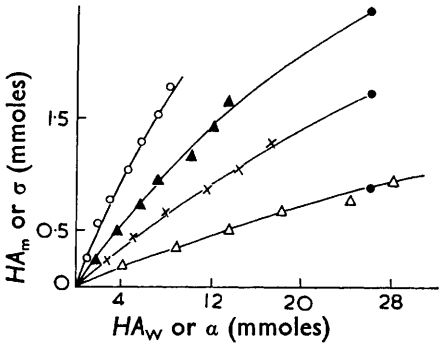

FIG. 2. Solubilisation isotherms for benzoic acid: $C_{16}E_{24}$ solutions ○, 20%; ▲, 12%; X, 8%; △, 4%; ● Solubility points.

Solubilisation Mechanism.—The solubilisation isotherms shown in Fig. 2 are of considerable use in elucidating solubilisation mechanism.

Solubilisation has been interpreted by a number of workers in terms of complex formation.[12–14] By using the data reported in this paper, constant values could not be obtained for stability constants calculated on the basis of a range of possible molar ratios. However, as complexes of differing molar ratios could be formed simultaneously, the possibility of complex formation cannot be ruled out.

If the solubilised benzoic acid were incorporated into the hydrocarbon centre of the micelle, the acid would be expected to dimerise. The solubilisation curves would then be governed by equation 8:

$$K_d = [(2HA)_{micelles}]/[HA_{water}]^2 \quad (8)$$

However, the curvature in Fig. 2 is contrary to that predicted from equation 8.

Were the benzoic acid distributed as a monomer between micellar and non-micellar forms in accordance with the partition law, the curves shown in Fig. 2 would approximate to straight lines of slope equal to the distribution constant. It can, however, be seen from Fig. 2 that the relative amount of acid solubilised decreases with increase in free acid concentration. This type of relationship is frequently indicative of adsorption.[15,16] Fig. 3

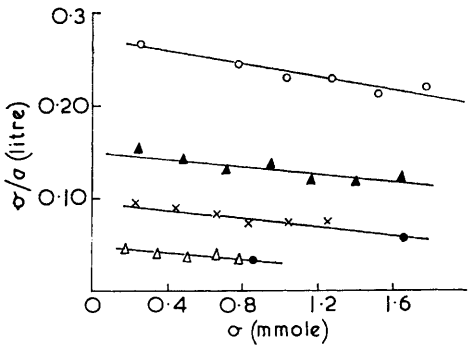

FIG. 3. Adsorption isotherms for benzoic acid: $C_{16}E_{24}$ solutions ○, 20% w/v; ▲, 12%; X, 8%; △, 4% surfactant. ● Solubility points.

[12] D. E. Guttman and T. Higuchi, *J. Amer. Pharmaceut. Assoc.* (*Sci. Edn.*), 1955, **44**, 669.
[13] T. Higuchi and D. A. Zuck, *J. Amer. Pharmaceut. Assoc.* (*Sci. Edn.*), 1952, **41**, 10.
[14] M. Barr and L. F. Tice, *J. Amer. Pharmaceut. Assoc.*, (*Sci. Edn.*), 1957, **46**, 445.
[15] M. E. L. McBain and E. Hutchinson, "Solubilisation and Related Phenomena," Academic Press 1955.
[16] J. W. McBain and J. McHan, *J. Amer. Chem. Soc.*, 1948, **70**, 3838.

shows a Langmuir plot from which it can be seen that the solubilisation of benzoic acid is apparently governed by the Langmuir isotherm. It is of interest that Patel and Kostenbauder[17] found, by using the equilibrium dialysis technique, that the binding of methyl *p*-hydroxybenzoate by a non-ionic surfactant was also governed by the Langmuir isotherm.

Using the notation of de Boer,[18] the values of K, the binding constant (the slope) and σ_s the amount of acid bound at monolayer saturation (the intercept) have been calculated from Fig. 3. The values obtained are shown in Table 3. It is noteworthy that the values

TABLE 2.

Data and calculated free and bound benzoic acid (amounts of acid measured in millimoles, concentrations in mM).

Burette reading (ml.)	0·50	1·00	1·50	2·00	2·50	3·00	3·50
20% Ceto. Soln.: pH	6·118	5·744	5·454	5·208	4·980	4·734	4·430
σ or HA_m	0·2640	0·5728	0·7828	1·035	1·291	1·533	1·792
a or $[HA_w]$	0·9917	1·988	3·211	4·522	5·687	7·250	8·175
12% Ceto. soln.: pH	5·906	5·506	5·210	4·986	4·744	4·506	4·212
σ or HA_m	0·2481	0·4891	0·7187	0·9530	1·172	1·401	1·640
a or $[HA_w]$	1·615	3·441	5·630	6·990	10·00	11·98	13·51
8% Ceto. soln.: pH	5·726	5·338	5·056	4·798	4·586	4·350	
σ or HA_m	0·2267	0·4469	0·6552	0·8430	1·052	1·256	
a or $[HA_w]$	2·445	5·065	8·026	11·63	14·34	17·15	
4% Ceto. soln.: pH	5·506	5·098	4·826	4·604	4·358	4·134	
σ or HA_m	0·1859	0·3497	0·5067	0·6660	0·7790	0·9460	
a or $[HA_w]$	4·055	8·804	13·63	18·18	24·30	28·21	

TABLE 3.

Absorption parameters of benzoic acid and $C_{16}E_{24}$.

Surfactant (%)	Surfactant (G)	σ_s(mmole)	σ_s/G(mmole)	K (mole^{-1})
4	1	2·4	2·4	20
8	2	4·6	2·3	20
12	3	7·2	2·4	20
20	5	10·5	2·1	26

of K and σ_s/G for the 4, 8, and 12% surfactant solutions are very similar whilst the values for the 20% solution show a considerable difference. Ekwall has also observed a change in solubilising power at high surfactant concentration.[19]

This mechanism of solubilisation may also be interpreted in terms of co-micellisation.[20] Solubilisation of benzoic acid not accompanied by dimerisation would require the monomer molecules to be solvated or hydrogen bonded to ether oxygen atoms of the palisade layer. It would thus seem probable that the solubilised acid is located at the junction of the hydrocarbon nucleus and the palisade layer of the micelle. For amphiphilic molecules of this kind, such an orientation would allow greater energy stabilisation of the system. However, Langmuir-isotherm observance indicates that such co-micellisation is a saturation process governed by "quasi-site" availability considerations. Further evidence on mechanism, together with extension of these studies to other acids, amines, and surfactants, will be reported shortly.

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[18] J. H. de Boer, "The Dynamical Character of Adsorption," O.U.P., 1953.
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[20] E. L. Valko and M. B. Epstein, ref. 8, p. 336.