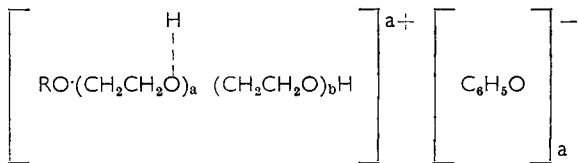# The solubilisation and inactivation of preservatives by non-ionic detergents*

W. P. EVANS

A novel potentiometric method, which depends on the pH changes which occur when an acidic material is solubilised, has been used to determine the solubilisation of the weakly acidic preservative, *p*-hydroxybenzoic acid, in a non-ionic detergent. From the pH changes observed, the partition coefficient, K_m, for the distribution of the un-ionised acid between the micellar and the aqueous phase has been calculated and found to be $2 \cdot 8 \times 10^3$. Specific interaction between the acid and the detergent. to form a complex is shown not to be important. It is suggested that the arguments against specific interaction apply generally to other preservatives and non-ionic detergents.

NON-IONIC detergents are used to an increasing extent as solubilising and emulsifying agents in cosmetic and pharmaceutical systems. They have some disadvantages, the main one being the inactivation of preservatives such as *p*-hydroxybenzoic acid and benzoic acid or their esters, which are commonly employed in such systems (de Navarre, 1953, 1956).

The cause of the inactivation has not been established, although complex formation between the preservative and the non-ionic detergent is often postulated. Higuchi & Lach (1954) state that Carbowax, a polyethylene glycol, forms complexes with benzoic, salicylic and *p*-hydroxybenzoic acid by reaction of the phenolic or carboxylic hydrogen with the ether oxygen of the glycol. Several authors have suggested that similar interactions also occur with non-ionic surface-active agents. The following formula has been proposed, but no quantitative data have been given, for a complex between phenol and a non-ionic detergent.

$$\left[\begin{array}{c} \overset{\displaystyle H}{\underset{\displaystyle |}{|}} \\ RO \cdot (CH_2CH_2O)_a \ (CH_2CH_2O)_bH \end{array} \right]^{a+} \left[\begin{array}{c} C_6H_5O \end{array} \right]_a^{-}$$

Protonation of the ether oxygen is, however, extremely improbable at the non-ionic detergent concentration and pH values of most cosmetic preparations; this is proved by the results described in this paper. Furthermore, it is unlikely that such interaction is the whole or even part of the inactivation, since inactivation may occur with preservatives of widely different types (Wedderburn, 1958). A more probable explanation is solubilisation of the preservative in the non-ionic micelles. Solubilisation of phenolic bactericides by micellar soap solutions is well known and it has been shown by many investigators that solubilisation results in a decrease of bactericidal activity (Alexander, 1946, 1949).

The normal method of estimating the amount solubilised by anionic and cationic detergents is to add increasing amounts of the solubilisate to the detergent solution and to equilibrate. When excess solubilisate is present the solutions are turbid and the amount solubilised can then readily be determined. Unfortunately, it is impossible in many cases to determine solubilisation by non-ionic detergents by this method because their cloud points are depressed by many solubilisates; the observed turbidity in such cases is not due to excess solubilisate but to "salted out" detergent or coacervate.

Apart from being inapplicable to many non-ionic detergents the equilibration solubilisation method is generally unsatisfactory even with anionic and cationic detergents since the results are difficult to interpret because measurements, apart from one or two exceptions (McBain, 1940), have always been made in saturated systems. The present paper describes a simple titration method which overcomes this difficulty, and which allows determination of solubilisation in unsaturated systems; it can be used with solubilisates containing a weak acidic group and depends on pH changes which result from preferential solubilisation of the un-ionised acid. It has been used in the present study to determine the solubilisation of *p*-hydroxybenzoic acid (a common cosmetic preservative) by the non-ionic detergent octyl phenol condensed with 8·5 moles of ethylene oxide.

Experimental

TITRATIONS

p-Hydroxybenzoic acid solutions (100 ml, either 0·01 or 0·03 M) containing varying concentrations of the non-ionic detergent (from 0·03 to 0·20 M) were titrated potentiometrically with 0·1 N sodium hydroxide using calomel and glass electrodes. Preliminary titrations with acetic and hydrochloric acids showed that the titration curves of the two acids were unaffected by the detergent, proving that it did not affect the potentials of the electrodes.

CLOUD POINTS

Cloud points were determined by the usual method of heating a 1% solution of the detergent alone or with additive until a faint turbidity appeared. The temperatures at which turbidity first appeared were taken as the cloud point of the detergent. These were reproducible to ±0·2°.

Results and discussion

Fig. 1 shows a plot of the apparent "solubility" at 25° of *p*-hydroxybenzoic acid in varying concentrations of the detergent determined by the conventional turbidity method.

Up to a detergent concentration of about 3·5% (w/v), the apparent solubility of the acid in the detergent solution is less than its solubility in pure water. That the turbidity is due, not to excess solubilisate, but to a salted-out mixture of detergent plus solubilisate was confirmed by
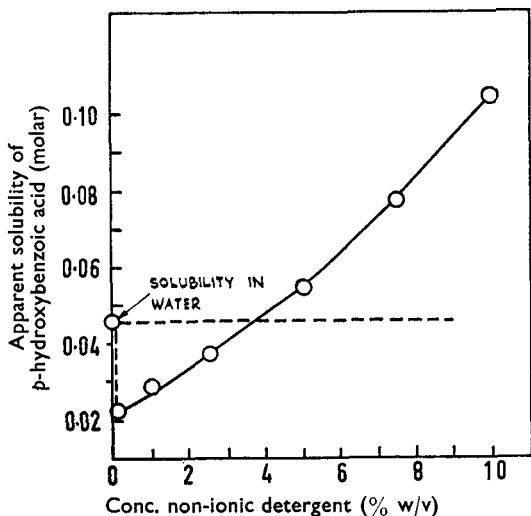
FIG. 1. Apparent solubility of p-hydroxybenzoic acid (molar) at 25° in varying concentrations of octyl phenol/8·5 moles ethylene oxide.

allowing the solutions to stand for some time, when two layers separate out, one layer being detergent rich, the other being water rich, but both layers containing the solubilisate. The separation of non-ionic detergents in this way is related to the cloud point phenomenon; a solution of the
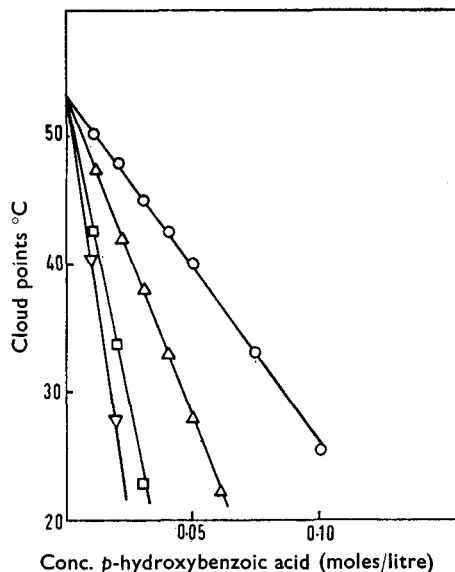

FIG. 2. Cloud points of various concentrations of octyl phenol/8·5 moles ethylene oxide in presence of p-hydroxybenzoic acid. ○ 10% (w/v) octyl phenol/8·5 moles ethylene oxide. △ 5% (w/v) octyl phenol/8·5 moles ethylene oxide. □ 1% (w/v) octyl phenol/8·5 moles ethylene oxide. ▽ 0·1% (w/v) octyl phenol/8·5 moles ethylene oxide.

detergent becomes cloudy when heated above a certain temperature—"the cloud point". The effect of *p*-hydroxybenzoic acid on the cloud point of different concentrations of the detergent is shown in Fig. 2.

It is often stated that addition of organic additives such as phenol or hydroxybenzoic acid, results in precipitation of a complex of the non-ionic detergent and its additive. This is unlikely, however, since precipitation also occurs with additives such as benzene or sodium sulphate, with which it is difficult to visualise the formation of such a complex. The precipitate which separates in these instances is not a detergent-additive complex, but the separation of a detergent-rich layer containing the dissolved additive, i.e., a coacervate. For example, a 20% (w/v) solution of octyl phenol/8·5 mole ethylene oxide saturated with *p*-hydroxybenzoic acid separates into two layers at 25°. The analysis of the two layers is as follows:

	Cloud point °C	Surface tension dynes/cm at 25°	Acid in each layer %
Aqueous layer	>98	36·0	0·68
Non-ionic layer	—	—	19·0

The aqueous phase contains virtually no detergent as shown by the high "cloud point" and only 0·68% (w/v) of acid, while the detergent phase contains 19·0% (w/v) of the acid. [The solubility of the acid in pure water is 0·63% (w/v) and in the anhydrous detergent 26% (w/v]).
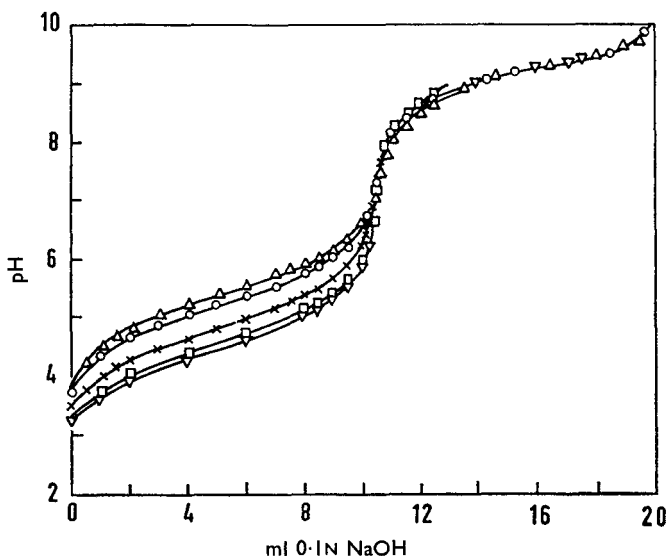

FIG. 3. Titration of 100 ml of 0·01 M *p*-hydroxybenzoic acid containing varying concentrations of octyl phenol/8·5 moles ethylene oxide with 0·1N NaOH. ▽ Acid alone. □ Acid containing 5% (w/v) ethanol. × Acid containing 0·03M octyl phenol/8·5 moles ethylene oxide. ○ Acid containing 0·10M octyl phenol/8·5 moles ethylene oxide. △ Acid containing 0·20M octyl phenol/8·5 moles ethylene oxide.

With sodium sulphate as the additive, separation into two phases again occurs, with the sodium sulphate dissolved in both phases, but, unlike the *p*-hydroxybenzoic acid, it is preferentially soluble in the aqueous phase. Further unpublished results confirm that with most additives the detergent-additive precipitate is not a definite chemical complex but a coacervate of varying stoichiometry.

Typical titration curves of *p*-hydroxybenzoic acid in the presence of a non-ionic detergent (below the cloud point) are given in Fig. 3.

The titration curves given in Fig. 3 show a pH shift to higher values in the presence of the detergent, therefore either the free concentration of the un-ionised acid has decreased as a result of some interaction with the detergent, or the detergent has changed the dielectric constant of the solution or the electrode potentials because it has been adsorbed on the glass electrode.* The titration curves of acetic acid and hydrochloric acid, however, were not affected by the presence of the detergent, so that the pH changes observed are not due to dielectric changes or to changes in the electrode potentials, but must be due to a decrease in the concentration of un-ionised acid. Furthermore, the normal titration results observed with acetic and hydrochloric acids show that protonation of the ether oxygen of the detergent as suggested by various authors does not take place, or, at least, the extent of protonation is too small to be detected by pH changes.

The titration results of *p*-hydroxybenzoic acid can be interpreted by assuming a decrease in the concentration of the un-ionised acid due either to complex formation of the type suggested by Higuchi & Lach (1954) or to solubilisation of the un-ionised acid; the results have therefore been used to calculate constants (K_c and K_m), assuming:

(1) Formation of a 1:1 complex between non-micellar detergent (i.e., single molecules) and the un-ionised acid (K_c).

(2) Solubilisation of the un-ionised acid in the detergent micelles (K_m). The equilibria considered here are:

$$HA_{water} \rightleftharpoons H^+ + A^-$$
$$\Updownarrow$$
$$HA_{micelles}$$
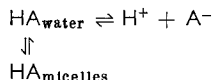
The constants obtained are given in Table 1, from which it is evident that the "constant", K_c, for a 1:1 complex shows considerable drift; interaction of the acid with monomeric detergent molecules is therefore unlikely.

Furthermore, any such interaction should, at constant acid concentration, result in pH shifts which are independent of total detergent concentration provided this is above the critical micelle concentration (about $1 \cdot 7 \times 10^{-4}$ M for the detergent used here) since the concentration of the monomeric detergent molecules is constant above the CMC. Further evidence against complex formation was obtained by titrating aqueous

* Since this work was completed (Paris, 1959), Donbrow & Rhodes (1963) have published titration curves showing similar pH shifts, but no quantitative treatment was given.

solutions of p-hydroxybenzoic acid containing polyethylene glycol 400, a polymer of 9 ethylene oxide units, identical with the hydrophilic part of the non-ionic detergent, but, unlike the latter, not aggregating to form micelles; no pH shifts were observed.

TABLE 1. THE pH, CONCENTRATION OF THE VARIOUS SPECIES, AND SOLUBILISATION AND COMPLEXING CONSTANTS $(K_m K_c)$ FOR VARIOUS CONCENTRATIONS OF p-HYDROXYBENZOIC ACID AND OCTYL PHENOL/8·5 MOLES ETHYLENE OXIDE

$[HA]_t$	[Detergent]	pH	$[A^-]$	$[HA]_{aq}$	$[HA]_m$	$K_c \times 10^{4*}$	$K_m \times 10^{-3}$
0·009902	0·02970	3·97	0·001056	0·003557	0·005289	1·2	2·8
0·009710	0·02913	4·48	0·002824	0·002803	0·004083	1·2	2·8
0·009346	0·1869	5·73	0·006269	0·000330	0·002747	0·21	2·5
0·02670	0·02678	4·59	0·01030	0·007101	0·009300	1·3	2·7
0·02577	0·1724	5·44	0·01322	0·001248	0·01130	0·19	2·9
0·009524	0·09524	5·20	0·004568	0·000836	0·004120	0·35	2·9
0·02770	0·1852	4·96	0·007109	0·002175	0·01842	0·20	2·6
0·009616	0·09616	5·05	0·003695	0·000970	0·004951	0·3	2·9
0·009854	0·02957	4·14	0·001488	0·003342	0·005024	1·1	2·8
0·02670	0·1786	5·22	0·01028	0·001666	0·01475	0·19	2·8
0·02718	0·1818	5·12	0·008718	0·001807	0·01666	0·19	2·8

$[A^-]$ = Concentration acid anion HO · ⬡ · COO^- (moles/litre).

$[HA]_t$ = Total concentration of acid in system (moles/litre).

$[HA]_{aq}$ = Concentration un-ionised acid HO · ⬡ · COOH in water phase (moles/litre).

$[HA]_m$ = Concentration un-ionised acid HO · ⬡ · COOH in micelle (moles/litre).

[Detergent] = Concentration of detergent (moles/litre).

* Calculations assuming 1:2 or 1:3 complexes also gave unsatisfactory constants, K_c.

The results can, however, be interpreted satisfactorily by assuming solubilisation of the p-hydroxybenzoic acid in the detergent micelles, without postulating any specific interaction. McBain & Hutchinson (1955) point out that many instances of solubilisation can be quantitatively described as a partition of solute between two immiscible phases. When the solubilisate carries a polar group, as in the present study, it may orient itself on the surface of the micelle instead of passing into the hydrocarbon interior, but even in this case the solubilisation may be approximately characterised by a simple distribution coefficient. In the present work the solubilisation is also treated as a distribution phenomena of the un-ionised acid between the aqueous phase and the micellar phase and a distribution constant, K_m, calculated. The distribution constant is defined as:

$$K_m = \frac{[HA]_{micelle}}{[HA]_{water}} \quad \frac{\text{mole acid/mole detergent}}{\text{mole acid/mole water}}$$

That solubilisation and not complex formation is the correct interpretation of the pH shifts is further supported by the fact that pH shifts are also observed when long-chain fatty acids are titrated in the presence of anionic detergents (e.g., lauric acid in the presence of sodium dodecyl sulphate). Again there is no evidence of specific interaction to form complexes but from the results (to be published) similar partition coefficients for solubilisation can be calculated. (From the data on page 326

a partition coefficient was also calculated and found to be $2\cdot3 \times 10^3$, in good agreement with that calculated from the potentiometric data).

The anions of the acid would not be expected to be solubilised to the same extent, and this is proved by the fact that there are no pH shifts when the phenolic group of the p-hydroxybenzoic acid is titrated. A number of authors (e.g., Maclay, 1956) have stated that solubilisation results in a decrease in the hydrophilic character of the non-ionic micelles, and any solubilised material would therefore decrease the cloud point whereas the mono-sodium salt, which is not solubilised, increases the cloud point (Fig. 4).
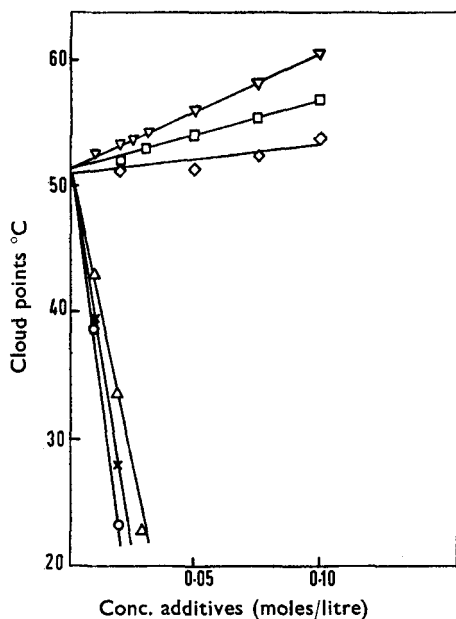

FIG. 4. Cloud points of 1% (w/v) octyl phenol/8·5 moles ethylene oxide in presence of various additives. △ p-hydroxybenzoic acid, ☐ mono sodium salt of p-hydroxybenzoic acid, ⊙ benzoic acid, ▽ sodium benzoate, × phenol, ◇ sodium phenate.

The value of the distribution constant, K_m, obtained in this work ($K_m = 2\cdot8 \times 10^3$) is constant over the whole concentration range examined, and is of the same order as those values reported in the literature for solubilisation by anionic and cationic detergents (McBain & Hutchinson, 1955). Few data are available for solubilisation by non-ionic detergents; Moore & Bell's results (1957) on the solubilities of phenyl ethyl alcohol and benzaldehyde in hexadecyl/14 moles ethylene oxide and in hexadecyl/24 moles ethylene oxide respectively as determined by the conventional turbidity method are given in Table 2 (in Moore and Bell's study, saturation of the solution by the solubilisate was apparently reached before the cloud point was reduced sufficiently to precipitate the detergents).

Moore and Bell's results have been used to calculate the relevant distribution constants, K_m, which are of the same order as those obtained in the present study.

TABLE 2. SOLUBILITY (g/100 ml) OF PHENYLETHYL ALCOHOL AND BENZALDEHYDE IN HEXADECYL/24 MOLES ETHYLENE OXIDE AND HEXADECYL/14 MOLES ETHYLENE OXIDE RESPECTIVELY AT $25°$ (Moore & Bell, 1957)

| | Solubility of phenylethyl alcohol in hexadecyl/24 moles ethylene oxide | | | Solubility of benzaldehyde in hexadecyl/14 moles ethylene oxide | | |
| | Concentration of detergent % | | | | | |
	2·5	5·0	10·0	2·5	5·0	10·0
Total wt solubilised (g)	3·24	5·04	8·28	1·38	2·40	4·13
Wt in aqueous phase (g) ..	1·60	1·60	1·60	0·33	0·33	0·33
Wt in micellar phase (g) ..	1·64	3·44	6·68	1·05	2·07	3·8
$K_m \times 10^{-3}$	2·7	2·9	2·8	6·0	5·9	5·4

Apart from the exception noted (McBain, 1940), all previously reported solubilisation data have been obtained by examination of systems containing excess insoluble phases, where both the micellar phase and the aqueous phase are saturated with the solubilisate. By subtracting the solubility of the solubilisate in pure water from its solubility in the detergent solution, the amount of solubilisate dissolved in the micelles can be obtained. This type of calculation, however, assumes that the concentration of the solubilisate in the aqueous phase in a saturated detergent solution is the same as its solubility in pure water; this may not always be true, e.g., potassium laurate even below the CMC increases the water solubility of phenol five times. Furthermore, due to deviation from ideal behaviour, the distribution constant of a solute between two immiscible phases changes as the two phases become saturated. That the results obtained in the present paper are of the same order as those calculated from Moore and Bell's work must therefore be regarded as somewhat fortuitous. .

TABLE 3. MOLAR CONCENTRATION OF UN-IONISED p-HYDROXYBENZOIC ACID IN THE WATER PHASE IN THE PRESENCE AND ABSENCE OF $5·8\%$ (w/v) DETERGENT AT VARIOUS pH's USING $0·1\%$ (w/v) TOTAL CONCENTRATION OF p-HYDROXYBENZOIC ACID

pH	$[HA]_{water}$	$[HA]_{water}$ in presence of 5·8 % detergent	Total (%) (w/v) acid required in presence of 5·8 % (w/v) detergent to be equivalent to 0·1 % (w/v) acid in pure water
3·5	0·00662	0·00118	0.56
4·0	0·00559	0·00114	0·49
4·5	0·00376	0·00104	0·36
5·0	0·00220	0·000805	0·27

All the results obtained in this study can be adequately explained by solubilisation of the un-ionised p-hydroxybenzoic acid in the non-ionic micelles, without postulating specific interaction or formation of complexes as has been done by most authors. Since the un-ionised acid (Simon, 1952), is generally regarded as being the active preservative, and

since only the acid in the aqueous phase is effective, it is reasonable to assume, at least in the case of p-hydroxybenzoic acid and the detergent used, that solubilisation and not complex formation is the cause of the inactivation by non-ionic detergents. Knowing the total concentration of p-hydroxybenzoic acid, its dissociation constant, K_c, ($2 \cdot 95 \times 10^{-5}$), the concentration of the detergent, and the partitition coefficient, K_m, it is easy to calculate the amounts of the acid dissolved in the aqueous and the micellar phases at varying pH, detergent, and total acid concentration. The results of such a calculation, assuming a total concentration of $0 \cdot 1\%$ (w/v) p-hydroxybenzoic acid and $5 \cdot 8\%$ (w/v) detergent are given in Table 3.

Thus if $0 \cdot 1\%$ (w/v) is the optimum total concentration of acid needed to give the required preservative effect in water at pH $4 \cdot 0$, the concentration of the un-ionised acid (the 'active' species) is $0 \cdot 00559$ M. Addition of $5 \cdot 8\%$ of the detergent reduces this concentration of un-ionised acid to $0 \cdot 00114$ M (Column 3, Table 3), and Column 4 shows that at pH $4 \cdot 0$, $0 \cdot 49\%$ (w/v) of acid would be required in presence of $5 \cdot 8\%$ (w/v) of the detergent to give the optimum molar concentration of the un-ionised acid in the water phase—i.e., five times as much acid would be required to give the same concentration of the un-ionised acid in the aqueous phase in the presence of the detergent as in the absence of the non-ionic detergent.

Acknowledgements. The author wishes to acknowledge many valuable discussions with Dr. T. G. Jones of this Department.

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