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

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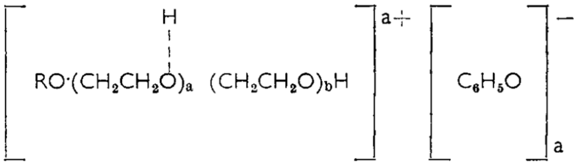
A novel potentiometric method, which depends on the pH changes which occur when an acidic material is solubilised, has been used to determine the solubilisation of the weakly acidic preservative, *p*-hydroxybenzoic acid, in a non-ionic detergent. From the pH changes observed, the partition coefficient, 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.



$$\left[\mathrm{RO{\cdot}(CH_2CH_2\overset{\overset{H}{\vdots}}{O})_a\ (CH_2CH_2O)_bH}\right]^{a+}\left[\mathrm{C_6H_5O}\right]^{-}_{a}$$

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).

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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

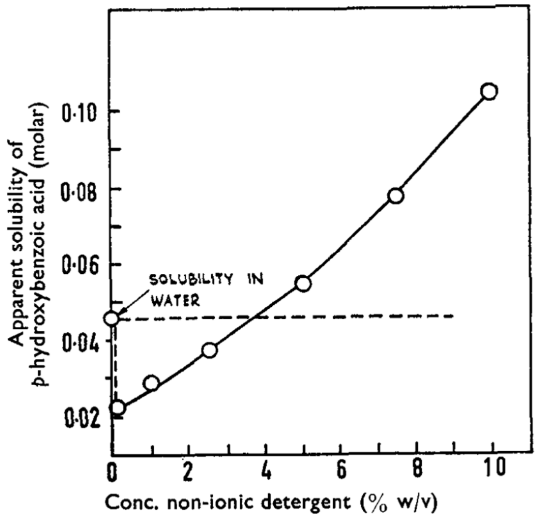

FIG. 1. Apparent solubility of p-hydroxybenzoic acid (molar) at 25° in varying concentrations of octyl phenol/8·5 moles ethylene oxide.

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

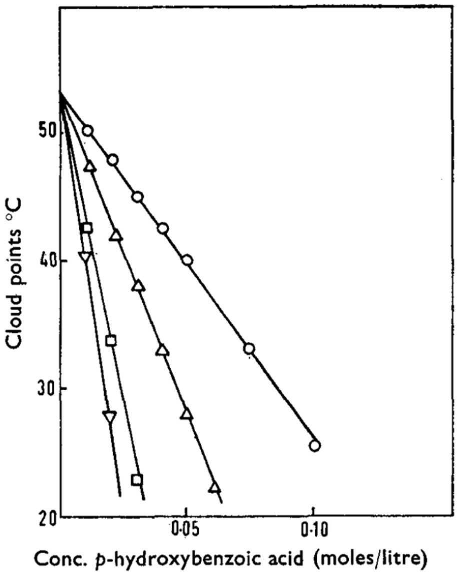

FIG. 2. Cloud points of various concentrations of octyl phenol/8·5 moles ethylene oxide in presence of *p*-hydroxybenzoic acid. ○ 10% (w/v) octyl phenol/8·5 moles ethylene oxide. △ 5% (w/v) octyl phenol/8·5 moles ethylene oxide. □ 1% (w/v) octyl phenol/8·5 moles ethylene oxide. ▽ 0·1% (w/v) octyl phenol/8·5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

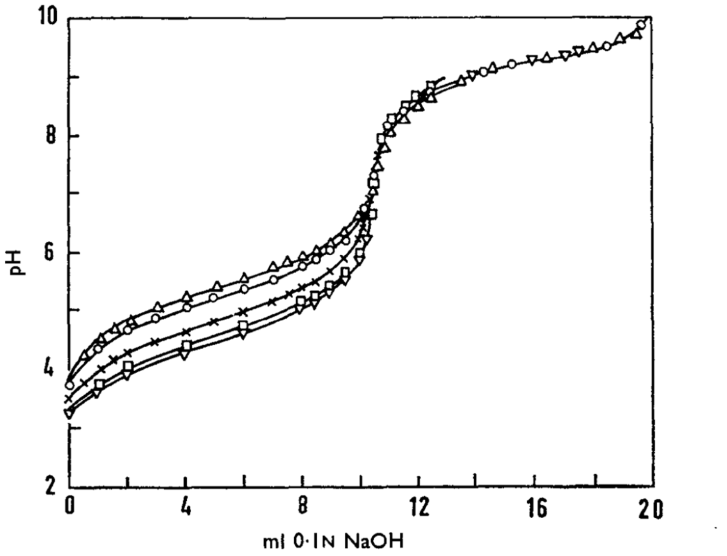

FIG. 3. Titration of 100 ml of 0·01 M *p*-hydroxybenzoic acid containing varying concentrations of octyl phenol/8·5 moles ethylene oxide with 0·1N NaOH. ▽ Acid alone. □ Acid containing 5% (w/v) ethanol. × Acid containing 0·03M octyl phenol/8·5 moles ethylene oxide. ○ Acid containing 0·10M octyl phenol/8·5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

$$\begin{tikzcd} HA_{\text{water}} \arrow[r, phantom, "\rightleftharpoons"] \arrow[d, shift left] & H^+ + A^- \\ HA_{\text{micelles}} \arrow[u, shift left] & \end{tikzcd}$$

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

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

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