

## Solubilisation of preservatives: interaction of benzoic acid with short-chain glycol ethers in water and in aqueous polysorbate 80 solution

M. DONBROW AND JOHN JACOBS\*

Using a potentiometric titration technique, ethylene glycol mono-ethers (Me, Et, n-Bu, Ph) and diglycol mono-ethers (Me, Et) have been shown to cause elevation of pH in benzoic acid-sodium benzoate solutions. The butyl glycol ether is shown to form micelles; critical micelle concentration values are given and the "loss" of benzoic acid from aqueous solution is considered. In mixtures with polysorbate 80, the glycol ethers increase the uptake of benzoic acid by the micelles.

IN the course of work to study the effect of additives on the distribution of benzoic acid between the aqueous and the micellar phase of a surfactant, the potentiometric method (Donbrow & Rhodes, 1963a,b, 1964, 1965) was applied in the presence of several glycol ethers. These compounds are good solvents as they contain alkyl, ether and alcohol groups in a single molecule; they are somewhat hydrophilic in character, and it was thought that they would have an effect on the hydrophilic lipophilic balance of the surfactant when added to its solution. Members of two series were used which were of the following general formulae: (a)  $R \cdot O \cdot CH_2 \cdot CH_2 \cdot OH$  and (b)  $R \cdot O \cdot CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OH$  where R is a short-chain alkyl or an aryl group. Initial work showed that there was a distinct elevation of pH in mixtures of the glycol ethers with polysorbate 80 containing benzoic acid. This paper reports on the phenomenon.

### Experimental

#### EQUIPMENT AND METHODS

*Potentiometric titrations.* An E.I.L. Vibron Electrometer with a C 33 B-2 unit was used for pH measurement, with GHS 33 glass electrode and calomel electrode (Electronic Instruments Ltd.). The meter was set up in an earthed aluminium box to reduce drift and external electrostatic influences. Linearity of electrode response was checked using three standard buffer solutions covering the pH range studied. The meter was overset 1.0 pH unit during standardisation to enable readings to be made down to pH 2.0. For each titration 5 ml of 0.1M sodium benzoate was used with the appropriate quantity of additives in a total initial volume of 40 ml, and this was titrated with standard 0.1N hydrochloric acid. Titrations were made under nitrogen to exclude carbon dioxide, and the titration cell was thermostatically controlled at 25° ( $\pm 0.1^\circ$ ).

From the Department of Pharmacy, School of Pharmacy, P.O.B. 517, The Hebrew University, Jerusalem, Israel.

\* Present address: Department of Pharmacy Services, Hadassah Medical Organisation, P.O.B. 499, Jerusalem, Israel.

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*Surface tension measurements* were made using a Cenco DuNouy tensiometer: solutions were prepared using triple-distilled water.

*Refractive index measurements* were obtained at 25° using an Abbé Refractometer (Bausch and Lomb Model 3L).

*Chemicals.* Sodium benzoate, reagent quality; potassium hydrogen phthalate of pH-standard grade (National Chemical Laboratory, certified for use as pH primary standard); 2-ethoxyethanol (BDH); butyl cellosolve (Union Carbide Chemicals); phenoxetol, B.P.C. (Nipa Laboratories); diethylene glycol monoethyl ether (Union Carbide Chemicals) and diethylene glycol monomethyl ether (BDH). All these solvents were purified thus: after standing over calcium carbonate, they were decanted and distilled under reduced pressure, middle cuts of constant b.p. being collected. The boiling points were correct and the free acid contents negligible. Polysorbate 80 (Tween 80, Atlas Chemical Company) was deionised according to Donbrow & Rhodes (1963a).

Solutions were prepared on a v/v basis, using carbon dioxide-free water; they were stored under nitrogen.

### Results and discussion

Titration of the sodium benzoate with hydrochloric acid in the presence of 10% polysorbate 80 showed that the addition of 10% of various glycol monoethers produced a significant elevation of pH throughout the titration (Fig. 1 and Table 2). The pH displacements were not caused

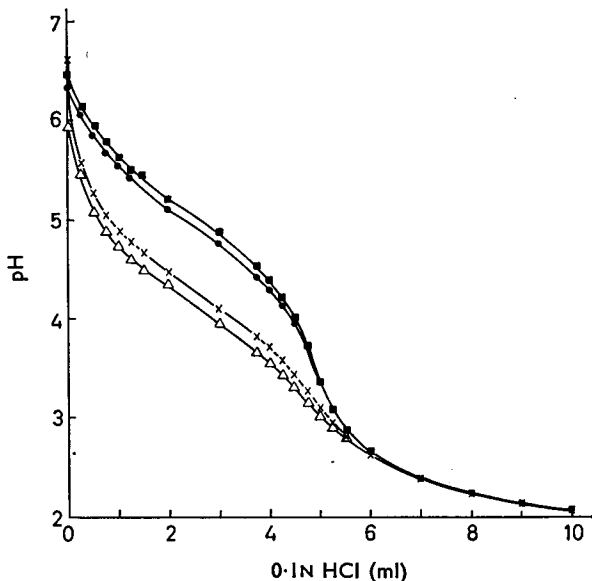


FIG. 1. Titration of sodium benzoate with 0.1N hydrochloric acid in the presence of diethylene glycol monoethyl ether and polysorbate 80. ■, Sodium benzoate + 10% polysorbate + 10% diethylene glycol monoethyl ether. ●, Sodium benzoate + 10% polysorbate 80. ×, Sodium benzoate + 10% diethylene glycol monoethyl ether. △, Sodium benzoate solution.

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by basic impurities, as purified materials were used and blanks were run (see Fig. 2), the end-points being identical in all instances.

In the absence of polysorbate, all the monoglycol and diglycol ether-sodium benzoate titration curves were also elevated above the sodium benzoate blank. Up to the level of 10% glycol ether elevations were small but at 20% they were disproportionately large in most instances,

TABLE 1. PH ELEVATIONS OF SODIUM BENZOATE\* IN THE PRESENCE OF GLYCOL MONO ETHERS AT 50% NEUTRALISATION. (Simple aqueous solutions—no polysorbate 80.)

% Solvent	Diglycol ethers		Monoglycol ethers		
	Methyl	Ethyl	Ethyl	Butyl	Phenyl
2	0.025	0.025	0.005	0.012	0.052
5	0.075	0.112	0.075	0.125	—
10	0.150	0.162	0.137	0.300	—
20	0.350	0.345	0.375	0.940	—

\* pH = 4.125 at half neutralisation point of blank.

$\Delta$ pH = pH in glycol ether - pH in blank.

Total benzoate, as salt and free acid, 0.01177M.

the butyl monoether showing the greatest effects (see Fig. 2). Because of solubility limitations, only 2% of the phenyl glycol ether could be titrated. The pH displacements increase in the order—ethyl, butyl, phenyl, though the pH elevations are relatively small at 2% (Table 1). Where no surfactant is present the ethers thus appear to have the general properties of elevating the pH in a similar manner to the surfactant.

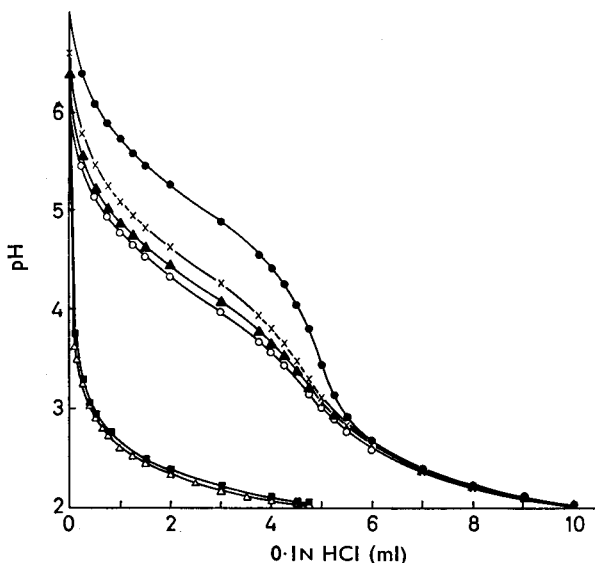


FIG. 2. Titration of sodium benzoate with 0.1N hydrochloric acid in the presence of ethylene glycol monobutyl ether. ●, Sodium benzoate + 20% ethylene glycol ether. X, Sodium benzoate + 10% ethylene glycol ether. ▲, Sodium benzoate + 5% ethylene glycol ether. ○, Sodium benzoate + 2% ethylene glycol ether. ■, Ethylene glycol ether 10% in water. △, Water blank.

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There are several factors operating in solution which might be responsible for an apparent change of pH being observed when a hydroxy ether is added to water or a surfactant solution. Dielectric constant changes in the medium may alter several properties. These are (a) the solubility of a solute and its distribution between two phases, (b) the ionic activity coefficients (so affecting the dissociation equilibrium of benzoic acid), (c) the dissociation constant and the activity of benzoic acid, and (d) the response of the electrode system to a given hydrogen ion activity. On the other hand, the glycol ethers may form micelle-like aggregations, capable of removing the benzoic acid from the aqueous environment or, alternatively, the addition of benzoic acid may assist in the formation and stabilisation of micelles.

TABLE 2. EFFECT OF GLYCOL ETHERS ON THE pH OF SODIUM BENZOATE-POLYSORBATE 80 TITRATION CURVES

	Polysorbate-glycol ether mixture		Glycol ether alone
	pH	$\Delta\text{pH}^*$	$\Delta\text{pH}^\dagger$
10% Ethylene glycol ethyl ether + polysorbate 80 .. .. .	4.804	0.049	0.140
10% Ethylene glycol butyl ether + polysorbate 80 .. .. .	4.914	0.159	0.314
10% Diethylene glycol ethyl ether + polysorbate 80 .. .. .	4.860	0.105	0.160
Polysorbate 80 .. .. .	4.755	—	

$\Delta\text{pH}^* = \text{pH in (glycol ether + polysorbate 80)} - \text{pH in polysorbate 80.}$

$\Delta\text{pH}^\dagger = \text{pH in glycol ether} - \text{pH in water.}$

pH and  $\Delta\text{pH}$  values measured at 60% neutralisation of the sodium benzoate solution (0.01163M total benzoate).

The titration curves in Fig. 2 offer some evidence as to which of these mechanisms might operate. Beyond the end point, the benzoic acid ionisation will be greatly suppressed by excess hydrochloric acid, the concentration of which is identical in each of the solutions. Were the activity coefficient of the hydrochloric acid or the response of the electrode altered, the pH values of the hydrochloric acid at any given burette reading would show a progressive shift with glycol ether concentration. Allowing for scatter, such shifts are not observed in any of the glycols. The results do not favour an explanation in terms of activity coefficient changes or electrode effects.

The disproportionate pH shift observed between 10 and 20% glycol ether is compatible with micelle formation between these concentrations. In contrast, surfactants of low critical micelle concentration (CMC) show a large pH shift at low concentrations, while further shifts decrease with increasing surfactant concentration (Donbrow & Rhodes, 1963a). Surface tension measurements of an aqueous solution of ethylene glycol monobutyl ether gave a curve typical of a surfactant, the sharp break characteristic of the CMC occurring at 11% v/v (Fig. 3). A refractive index plot, showing a break at 12% v/v (Fig. 4), confirmed that the butyl glycol ether forms a micelle-like aggregation (CMC 11–12% v/v, 0.88–0.98M). Elworthy & Florence (1964) obtained similar values (about 0.8M) for  $\text{C}_n\text{E}_6$  compounds ( $n = \text{number of oxyethylene groups}$ ). The

small difference is not surprising since Mulley & Metcalf (1962) observed that the CMC was little affected by an increase in  $n$  value from 3 to 6. However, no values have hitherto been reported for  $C_4$  compounds containing fewer than  $n_6$ , or for compounds containing less than  $n_2$  with a carbon chain below  $C_{(8)}$  (see Sirianni & Gingras, 1961; Mulley & Metcalf, 1962; Corkill, Goodman & Harrold, 1964). Of the other glycol ethers listed in Table 1, none gave sharp inflexions in the surface tension curves nor showed breaks of slope in the refractive index curves up to 40% v/v.

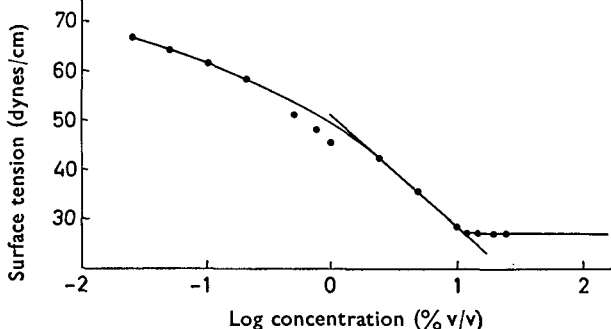


FIG. 3. Surface tension of aqueous solutions of ethylene glycol monobutyl ether at 25° C. Corrected by method of Zuidema & Waters (1941).

The pH shifts reported in Table 1 suggest that some molecular aggregation may also occur in other compounds, the tendency being greatest in the phenyl compound. It is difficult to distinguish between pH effects due to aggregation and to  $pK_a$  changes for compounds which do not give a sharp CMC. Parallels cannot be drawn with other solvents of equivalent dielectric constant because of the specific structural factors involved (e.g. see Gutbezahl & Grunwald, 1953). Since the aggregation numbers of these short-chain materials are probably quite small, it

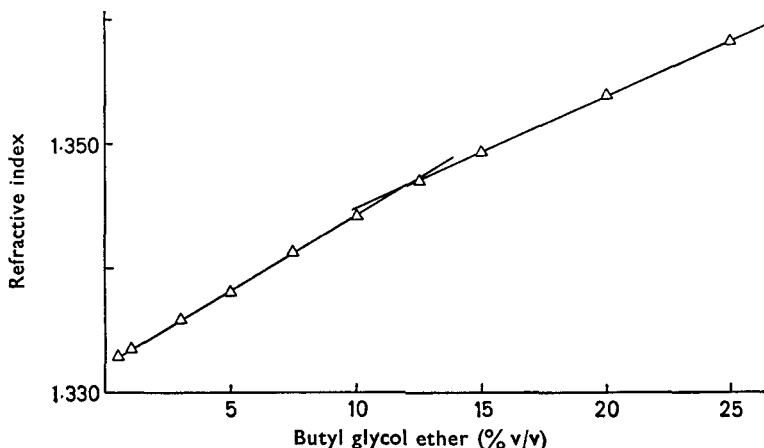


FIG. 4. Refractive index/concentration curve of ethylene glycol monobutyl ether at 25° C.

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would be expected from the mass action approach that the transition from monomer to aggregated state would be less sharp than with typical surfactants (Murray & Hartley, 1935); the monomer concentration would therefore continue to increase after micellisation had begun (Elworthy & Macfarlane, 1965). For such compounds, it would be difficult to designate a specific concentration as the CMC, and one would expect properties associated with micellisation, such as solubilisation, to be shown over a wide concentration range. The surface tension curves of the glycol monoethyl ether and the diglycol monomethyl and monoethyl ethers lend some support to this argument; after an initial sharp fall, they continue to decline up to high concentrations. The mechanism of benzoic acid interaction might range from mutual lipophile attraction with orientated solvent molecules, assisted by squeezing-out effects of the water, at one extreme, to complete co-micellisation (Valko & Epstein, 1957) at the other.

The apparent loss of (% free) benzoic acid from the aqueous phase equivalent to such pH shifts is as follows: 86.7, 48.1, 20.5, 12.9 for pH shifts of 0.940, 0.350, 0.162, 0.125 respectively (see Donbrow & Rhodes, 1963b, 1964). As with long-chain surfactants (Wedderburn, 1964), the loss is very large above the CMC of the butyl ether. If the pH changes at lower concentrations are at least partially due to a reduction in benzoic acid activity, it is evident that some care must be exercised in formulating it in preparations containing other amphiphilic substances.

In the polysorbate 80-glycol ether mixtures, the magnitude of the pH shift is similar to that in the polysorbate-free systems (Fig. 1 and Table 2). Most probably the glycol ethers are incorporated in the polysorbate micelles, thereby changing the solubilising power of the surfactant and hence the distribution of the benzoic acid.

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