

The effects of polyoxyethylene compounds on the hydrolysis of chlorbutol

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The rates of hydrolysis of chlorbutol are reduced by surface-active agents, but not by polyethylene glycols. The ratio of the rate-constant in simple aqueous systems to that in systems containing surface-active agents can be predicted if the distribution coefficient for chlorbutol between the micellar pseudo-phase and the aqueous phase is known and is independent of concentration.

THE hydrolysis of chlorbutol has been shown to be first-order with respect to both chlorbutol and hydroxyl ion, the overall reaction being second-order (Nair & Lach, 1959). The rate of reaction was stated to be independent of both the ionic strength and buffer species and it was concluded that the reaction was a specific hydroxyl ion catalysed reaction.

It is recognised that the presence of surface-active agents may affect the reaction rates of solutes which have been solubilised and the present experiments were made to investigate the effect of some polyoxyethylene compounds on the hydrolysis of chlorbutol.

Experimental

MATERIALS

Chlorbutol (May and Baker), polyoxyethylene lauryl ether (lauromacrogol, Brij 35 - Atlas Powder Company), polyethylene sorbitan mono-laurate (polysorbate 20, Tween 20, Atlas Powder Company) and polyethylene glycol (hard macrogol, Carbowax 4000 - Union Carbide) were used as received. A single batch of each was used throughout. All other chemicals were reagent grade. Water was distilled from a Sorrah all-glass still.

METHODS

Determination of chloride ion. The sample was adjusted to pH 7 by addition of acetate buffer, 1 ml 5% potassium chromate solution was added, and the solution was titrated with 0.02N silver nitrate. The end-point was taken as the first appearance of a red colour when viewed under blue light. Blank titrations were made as appropriate.

Determination of chlorbutol. The sample was allowed to stand for at least 15 min after addition of excess of a concentrated sodium hydroxide solution, and then the mixture was boiled to ensure complete hydrolysis. On cooling, the solution was neutralised to phenolphthalein with acetic acid, and the liberated chloride ion titrated with silver nitrate as described above (one molecule of chlorbutol yields three chloride ions). The surface-active agents and macrogol have no effect on the assay.

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Solubility of chlorbutol. The solution in which the solubility was to be determined was placed in a glass-stoppered jar and excess chlorbutol was added. The jar was maintained at $25^{\circ} \pm 0.05^{\circ}$ and the contents agitated with a magnetic stirrer. Duplicate samples were withdrawn at 2 hrly intervals and assayed as described above, until no increase in concentration was found in three consecutive determinations. In buffer solutions where chlorbutol underwent hydrolysis, two pairs of samples were taken. One pair was immediately neutralised with acetic acid and assayed for free chloride ion, and the other pair assayed for chlorbutol as described above. The difference in titres was used to calculate the chlorbutol solubility.

Dialysis. The distribution of chlorbutol between water and the micellar pseudophase was determined by the method of Patel & Kostenbauder (1958). Cells similar to those described by Patel & Foss (1964) were used with membranes of rubber latex which had been soaked in water with frequent changes until clear washings were obtained. The solution of surface-active agent was placed on one side of the membrane together with a weighed quantity of chlorbutol, and water on the other. The cells were tumbled at 25.0° for about three days when duplicate samples were taken from each side and assayed. Additional samples were taken after a further one or two days to confirm that equilibrium had been attained. (Identical results were obtained when the chlorbutol was added to the half-cell containing water.)

Determination of first-order rates. The required amount of chlorbutol was dissolved in water or aqueous surfactant solution and the solution allowed to equilibrate at 25.0° ; then sufficient sodium borate and boric acid were added to give the desired buffer composition, the solution made to volume with water at 25.0° , and the zero-time sample taken.

At selected intervals, samples were withdrawn and added to sufficient acetic acid to reduce the pH to 7, and then assayed for chloride ion. Finally, duplicate samples of the solution were taken and assayed to give the original chlorbutol concentration.

Each run was duplicated and the pH was checked frequently to ensure that the pH had not fallen significantly.

Determination of second-order rates. Equal volumes of chlorbutol solution and previously standardised sodium hydroxide solution were equilibrated at 25.0° in separate wide-mouthed flasks. At zero time the two solutions were mixed by pouring the solutions quickly to one flask, then to the other and back. Samples were taken at 15 sec intervals by pouring some of the solution into previously tared beakers containing excess nitric acid. The beakers with added sample were then reweighed; the differences in weight may be used to calculate the volume of sample taken, the sample solution being found to weigh 1.00 g per ml. The contents and washings of each beaker were transferred to flasks, neutralised to pH 7, and assayed for chloride ion. Finally, duplicate samples of the solution were taken and assayed to give the original chlorbutol solution. Two experiments were made for each concentration of lauromacrogol.

Results and discussion

The solubility of chlorbutol in solutions of macrogol and lauromacrogol is shown in Figs 1 and 2. The solubility of chlorbutol in water is affected by the amount of salt present; this does not seem to affect the interaction of chlorbutol with the polyoxyethylene compounds because the solubility plots show pairs of parallel lines (changes of pH did not appear to affect solubility).

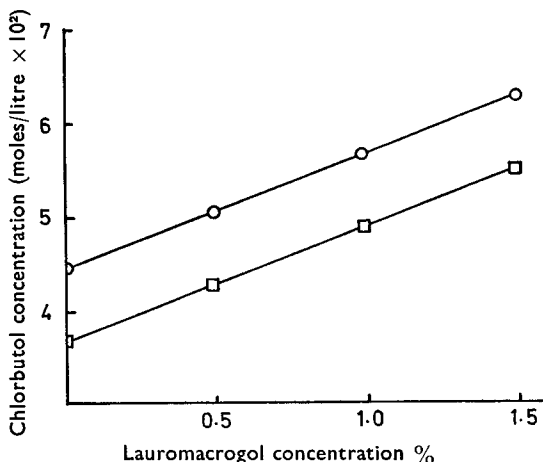


FIG. 1. Solubility of chlorbutol in lauromacrogol solutions at 25°. ○—○ Salt-free solution. □—□ 0.4 M Borate solution.

From such solubility plots, it is possible to calculate, *for saturated systems*, the ratio of free chlorbutol to that bound by the surface-active agent. The equilibrium dialysis studies showed that these ratios are independent of the degree of saturation of the system by chlorbutol and that apparent distribution coefficients may be calculated as suggested by Evans (1964).

The cloud point of polysorbate 20 is below 25.0° in systems saturated with chlorbutol and solubilities could not be determined. The dialysis data from unsaturated systems are plotted in Fig. 3 in the manner suggested by Patel & Kostenbauder (1958). The amounts of chlorbutol bound by macrogol are much less than those bound by equivalent amounts of the surface-active agents. The relatively small increases in solubility effected by polyethylene glycols have been reported for many solutes.

TABLE 1. APPARENT DISTRIBUTION COEFFICIENTS OF CHLORBUTOL IN AQUEOUS SOLUTIONS OF SURFACE-ACTIVE AGENTS

Surface-active agent	Apparent distribution coefficient	
	in absence of 0.4M borate	in presence of 0.4M borate
Lauromacrogol	27	32
Polysorbate 20	24	29

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The concept of a distribution coefficient between the true aqueous phase and the micellar phase does not depend on any particular site of solubilisation, and can be applied provided the value is (essentially) independent of the concentrations of solute and surface-active agent. These conditions are met by the systems studied here, and the apparent distribution coefficients listed in Table 1 are calculated from the relationship,

$$q = \frac{(C_t - C_a)(1 - s)}{C_a \cdot s} \quad \dots \quad (1)$$

where C_t = total chlorbutol concentration in the system expressed as moles/litre of total system; C_a = chlorbutol concentration in the true aqueous phase expressed as moles/litre of total system, and s = the weight fraction of micellar phase. The value of s has been approximated by using the w/v percentage of surface-active agent divided by 100.

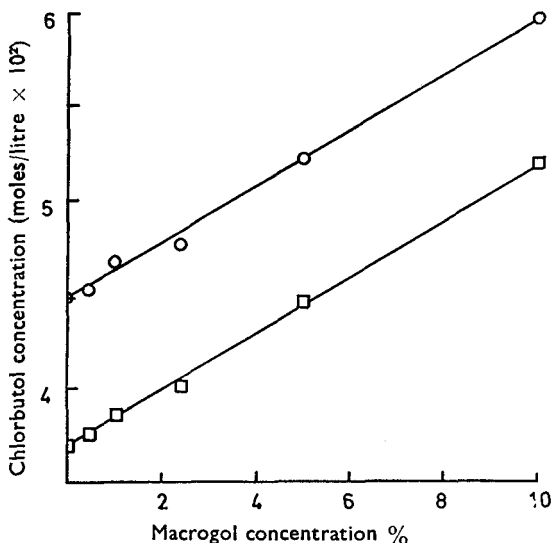


FIG. 2. Solubility of chlorbutol in macroglol solutions at 25°. ○—○ Salt-free solutions. □—□ 0.4 M Borate solution.

The hydrolysis of chlorbutol in solutions held at constant pH proceeds at first-order rates both in the presence and absence of surface-active agents. Fig. 4 shows the influence of buffer concentration on the rate of hydrolysis; the fall in rate as the buffer concentration is reduced conflicts with the conclusions of Nair & Lach (1959) who reported that buffer concentration did not affect the rate of hydrolysis. All subsequent first-order rates were determined using 0.4M buffer.

Figs 5 and 6 show plots for systems containing surface-active agents and which are initially half-saturated and one-twentieth saturated with respect to chlorbutol. The rate constants calculated from these and other

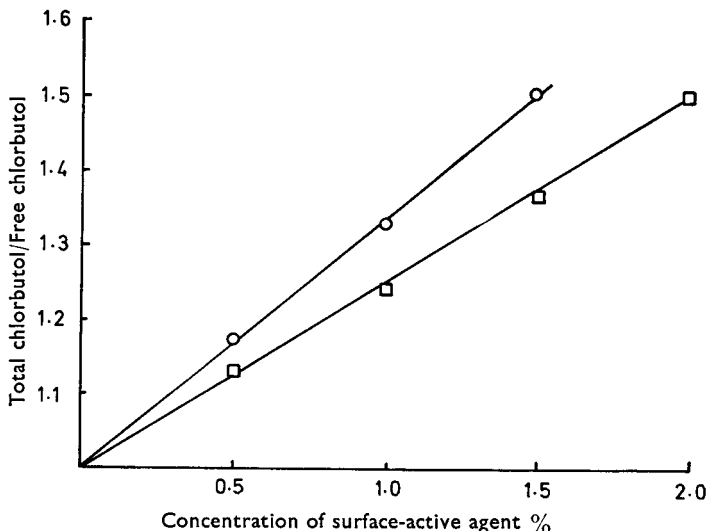


FIG. 3. Binding of chlorbutol by surface-active agents in aqueous solution at 25°. ○—○ Polysorbate 20. □—□ Lauromacrogol.

similar plots are listed in Table 2. The reaction between chlorbutol and sodium hydroxide follows second-order kinetics in the presence and absence of surface-active agents, and conventional plots (Moore, 1957) of the data are shown in Fig. 7; the second-order rate constants are listed in Table 3.

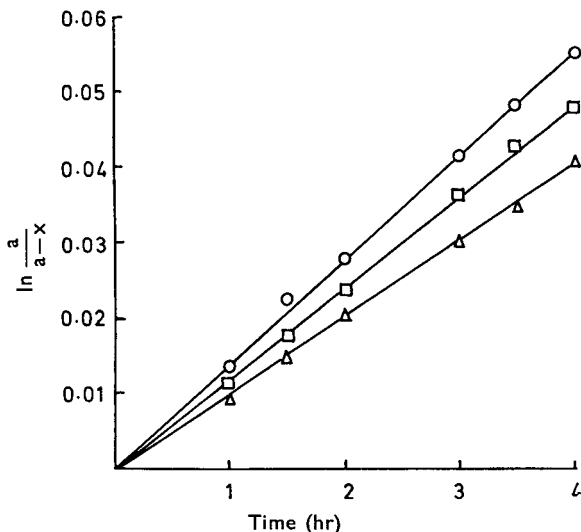


FIG. 4. Hydrolysis of chlorbutol in borate buffer systems, pH 9.2 at 25°, plotted as a first-order reaction. ○—○ 0.6 M Borate. □—□ 0.4 M Borate. △—△ 0.2 M Borate.

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The rate of hydrolysis is not affected by the presence of macrogol in concentrations up to 10%. Although the solubility of chlorbutol is increased by macrogol, presumably by bonding through the hydroxyl hydrogen to an ether oxygen on the polyethylene glycol chain, the trichloromethyl groups are not shielded by the interaction and can be attacked by hydroxyl ions as readily as in simple aqueous solution.

TABLE 2. FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF CHLORBUTOL IN 0.4M BORATE BUFFER AT 25°

Surface-active agent and concentration	Initial concentration of chlorbutol $M \times 10^3$	pH	Rate constant in hr^{-1}	
			Experimental	Predicted by Equation 2
Nil	3.70	8.7	0.0050	
	3.70	9.2	0.0117	
	1.85	"	0.0116	
	0.37	"	0.0117	
	0.18	"	0.0118	
			Av. 0.0117	
Lauromacrogol	4.30	8.7	0.0044	0.0043
0.5%	4.30	9.2	0.0096	
	2.15	"	0.0102	
	0.43	"	0.0092	
	0.21	"	0.0101	
				Av. 0.0098
Lauromacrogol	4.90	8.7	0.0040	0.0038
1.0%	4.90	9.2	0.0083	
	2.45	"	0.0085	
	0.49	"	0.0081	
	0.24	"	0.0081	
				Av. 0.0082
Lauromacrogol	5.50	8.7	0.0034	0.0034
1.5%	5.50	9.2	0.0074	
	2.75	"	0.0075	
	0.55	"	0.0065	
	0.27	"	0.0068	
				Av. 0.0070
Polysorbate 20	2.31	9.2	0.0101	0.0104
	2.41	"	0.0078	0.0073

However, the presence of surface-active agents has a marked effect on the rate of hydrolysis.

The data in Tables 2 and 3 and Figs 5 and 6 show that neither the degree of saturation of the system with respect to chlorbutol nor the

TABLE 3. SECOND-ORDER RATE CONSTANTS FOR REACTION OF CHLORBUTOL WITH SODIUM HYDROXIDE AT 25.0°

Concentration of lauromacrogol	Rate constant in $litre\ mole^{-1}\ min^{-1}$	
	Experimental	Predicted by Equation 2
Nil	8.0	
0.5%	6.8	7.1
1.0%	6.0	6.3

chlorbutol concentration affect the rate constant for the reaction. However the concentration of surface-active agent present does affect the rate constant.

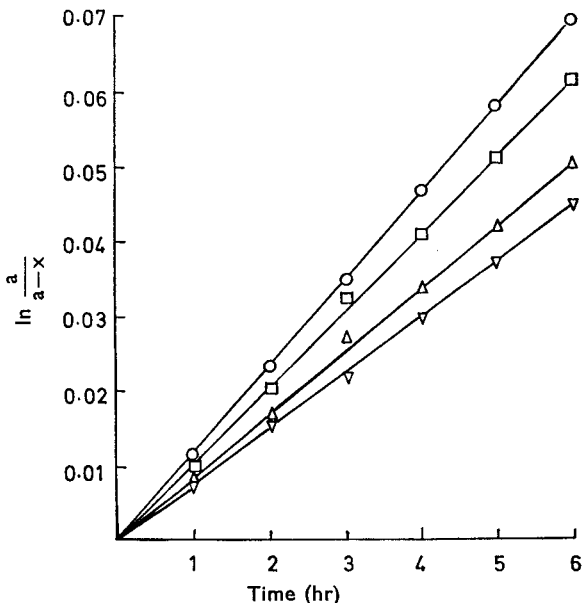


FIG. 5. Hydrolysis of chlorbutol (initially half saturated) in lauromacrogol solutions with 0.4 M borate, pH 9.2 at 25°, plotted as a first-order reaction. Initial concentrations of chlorbutol: ○—○ 1.85 × 10⁻²M (no lauromacrogol). □—□ 2.15 × 10⁻²M in 0.5 % lauromacrogol. △—△ 2.45 × 10⁻²M in 1.0 % lauromacrogol. ▽—▽ 2.75 × 10⁻²M in 1.5 % lauromacrogol.

If one makes the assumptions that: (a) only the chlorbutol free in the aqueous phase undergoes hydrolysis, and (b) the distribution ratio between the chlorbutol in the micellar and aqueous phases is instantaneously restored, it can be shown that

$$\frac{k}{k_s} = 1 + \frac{qs}{1 - s} \quad \dots \quad (2)$$

where k = the rate constant in the absence of surface-active agent; k_s = the rate constant in the presence of surface-active agent; q = the distribution coefficient defined in equation (1); s = the weight fraction of micellar phase approximated as in equation (1).

In addition to the terms previously defined, let a = original chlorbutol concentration in the total system (moles/litre of system); x = concentration decomposed after time t (moles/litre of system); A = original chlorbutol concentration in the aqueous phase (moles/litre of water). The ratio $a/A = 1 - s + qs$, because $a = A(1 - s) + qAs$.

After time t , the concentration of chlorbutol remaining in the system is $(a - x)$ moles/litre, and (since the distribution ratio remains constant) the concentration remaining in the aqueous phase is $(a - x)A/a$ moles/ litre of water.

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This equation has been applied to the prediction of rate constants for the chlorbutol hydrolysis in lauromacrogol and polysorbate 20 at pH 8.7 and 9.2 and the comparisons are shown in Table 2. The predicted values are within a few per cent of those found experimentally, and suggest that the assumptions and approximations made in deriving the equation are reasonable.

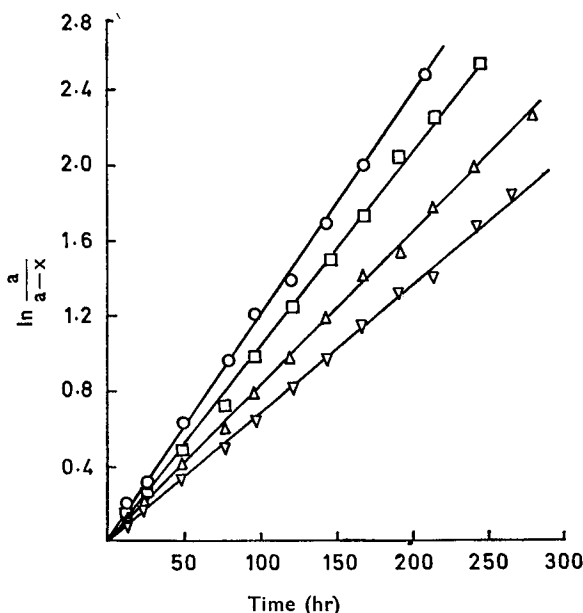


FIG. 6. Hydrolysis of chlorbutol (initially one twentieth saturated) in lauromacrogol solutions with 0.4M borate, pH 9.2 at 25°, plotted as a first-order reaction. Initial concentrations of chlorbutol: ○—○ $1.85 \times 10^{-3}M$ (no lauromacrogol). □—□ $2.15 \times 10^{-3}M$ in 0.5% lauromacrogol. △—△ $2.45 \times 10^{-3}M$ in 1.0% lauromacrogol. ▽—▽ $2.75 \times 10^{-3}M$ in 1.5% lauromacrogol.

Because the instantaneous rate of formation is first-order,

$$\frac{dx}{dt} = k \cdot \frac{(a-x)A}{a} (1-s),$$

the factor $(1-s)$ being introduced because dx is the concentration change with respect to total system.

Integration and rearrangement gives

$$k = \frac{a}{A(1-s)} \cdot \frac{1}{t} \ln \frac{a}{(a-x)}.$$

The experimentally determined rate constant in the presence of surface-active agent,

$$k_s = \frac{1}{t} \ln \frac{a}{(a-x)},$$

and so

$$\frac{k}{k_s} = \frac{a}{A(1-s)} = \frac{1-s+qs}{1-s} = 1 + \frac{qs}{1-s}$$

A similar procedure may be used to show the same relationship between the second-order rate constants.

The comparisons for the second-order reaction between chlorbutol and hydroxyl ions are shown in Table 3, and again the values are in reasonable agreement. These reactions are almost complete in a few minutes and might be expected to challenge the assumption that chlorbutol is released from the micelle to instantaneously restore equilibrium.

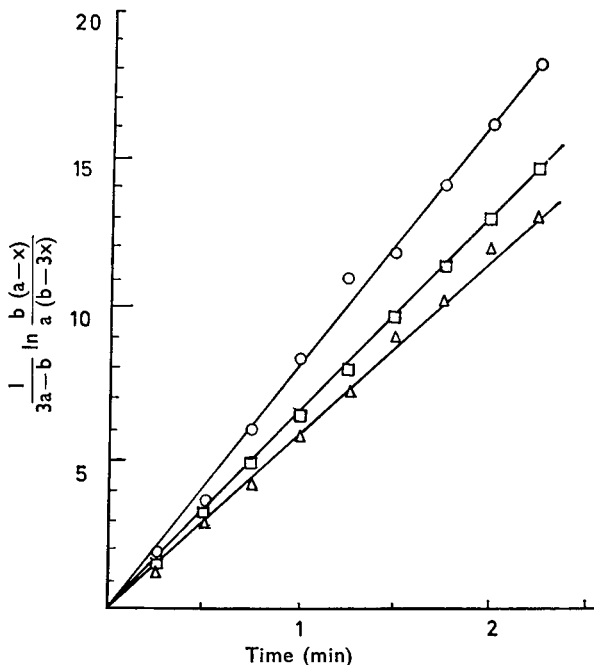


FIG. 7. Reaction between chlorbutol and hydroxyl ions in lauro-macroglol solutions at 25°. ○—○ No lauro-macroglol. □—□ Lauro-macroglol 0.5%. △—△ Lauro-macroglol 1.0%.

It seems likely that this relationship would be of general application to other solubilised systems.

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