

# THE HYDROLYSIS OF ETHYL BENZOATE, DIETHYL PHTHALATE AND BENZOCAINE IN CETRIMIDE SOLUTIONS

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Received September 25, 1961

The effect of cetrimide on the alkaline hydrolysis of emulsions and solutions of ethyl benzoate and diethyl phthalate and solutions of benzocaine has been investigated. In the initial stages of the reaction, the hydrolysis rate of emulsions increases with cetrimide concentration while that of solutions decreases. In the later stages the rate of hydrolysis decreases with increasing cetrimide concentration.

RECENT studies have shown that surface-active materials are capable of stabilising insoluble organic liquids against attack by atmospheric oxygen, and that solutions are less readily oxidised than emulsions (Carless and Nixon, 1957, 1960).

Complexing (Higuchi, 1955, 1956, 1957) and the addition of organic solvents (Ikeda, 1960) have been shown to confer protection against hydrolysis but little work has been reported on the influence of surface-active agents. McBain and Bolam (1918) showed that soap solutions could protect dissolved material against hydrolysis. More recently Riegelman (1960) and Nogami, Awazu, Watanabe and Sato (1960) have studied the effect of surface-active agents on the hydrolysis of drugs in solution. These results and those presented here indicate that stabilisation is effected when dissolved material is transferred from the aqueous phase to the micellar "phase" of the dispersion.

The literature on the alkaline hydrolysis of fats and oils is extensive (Clayton, 1954). It is believed that the reaction takes place at the oil-water interface. To avoid complications arising from the surface-active nature of the saponification products, King and Mukerjee (1938) studied the alkaline hydrolysis of amyl acetate emulsified in various surface-active materials. However the solubilising action of soap on the dispersed oil does not appear to have been considered. The alkaline hydrolysis of solutions and emulsions of esters in cetrimide is now reported.

## EXPERIMENTAL

### *Materials*

Cetrimide B.P. containing 96.8 per cent alkyltrimethylammonium bromides calculated as  $C_{14}H_{29}(CH_3)_3N, Br$ . Benzocaine B.P. recrystallised from 80 per cent ethanol m.p.  $91^\circ$ , ethyl benzoate b.p.  $212^\circ$ ,  $n_{22}^{20}$  1.504<sub>6</sub>, diethyl phthalate b.p.  $292^\circ$ ,  $n_{22}^{20}$  1.500<sub>4</sub>.

### *Determination of Solubility*

Varying concentrations of cetrimide solution were added to the required amount of ester in glass-stoppered cylinders. The cylinders were immersed in a water bath at  $35^\circ$  and rotated until equilibrium was reached. This

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took 6–8 hr. for liquid esters but several days for benzocaine. The solubility point was estimated visually.

### *Determination of Hydrolysis*

Ester and cetrimide solution were equilibrated at 35° in a controlled temperature bath. A turbine stirrer was used to maintain uniform dispersion. Sodium hydroxide solution sufficient to provide 100 per cent in excess of that needed for complete hydrolysis was added, and the zero time noted. Samples were withdrawn at definite time intervals and the remaining alkali titrated with hydrochloric acid using phenolphthalein as indicator. Cetrimide does not interfere with the indicator. Preliminary work showed that hydrolysis was independent of stirring at the rates used and reproducible within  $\pm 5$  per cent. The amount of cetrimide did not affect the size of the emulsion droplets with the concentrations of esters used.

TABLE I  
SOLUBILITIES OF ESTERS IN CETRIMIDE SOLUTIONS AT 35°

Ester	moles/litre	Cetrimide moles/litre
Ethyl benzoate ..	0.05	0.038
Diethyl phthalate ..	0.05	0.096
Diethyl phthalate ..	0.1	0.187
Benzocaine .. ..	0.05	0.068

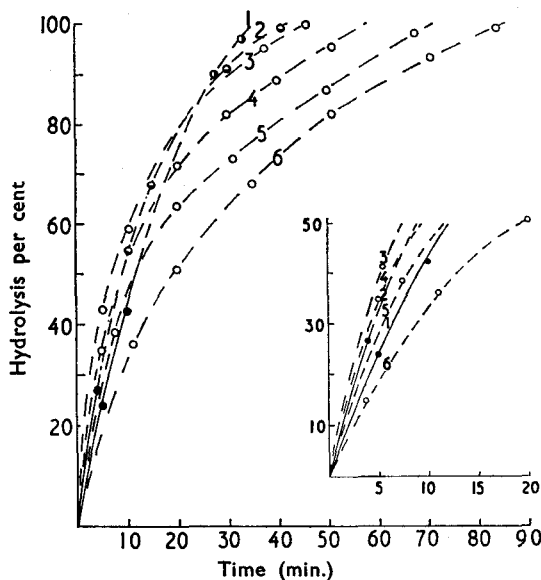


Fig. 1. Alkaline hydrolysis of ethyl benzoate (0.05 moles/litre) in cetrimide solutions, at 35°.

Cetrimide concentration (moles/litre)

1. 0.002. 2. 0.02. 3. 0.04. 4. 0.1. 5. 0.2. 6. 0.4.

—●— Emulsion      - - - - ○ - - - - Solution.

① ● are to distinguish curves 1 and 2.

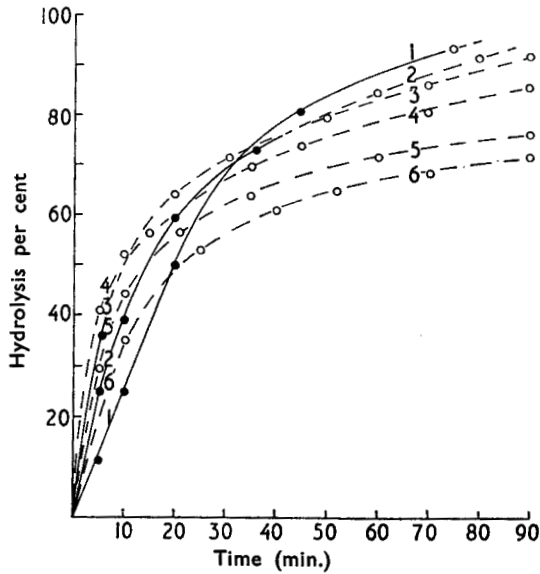


FIG. 2. Alkaline hydrolysis of diethyl phthalate (0.05 moles/litre) in cetrimide solutions at 35°.

Cetrimide concentration (moles/litre)

1. 0.002. 2. 0.02. 3. 0.05. 4. 0.096. 5. 0.14. 6. 0.35.

—●— Emulsion.      - - - ○ - - - Solution.

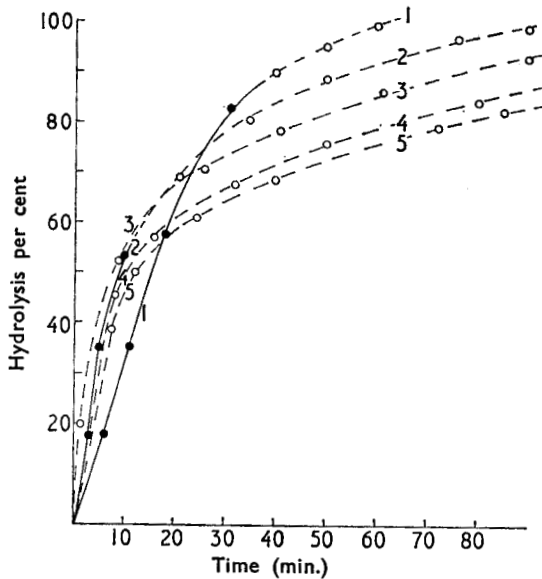


FIG. 3. Alkaline hydrolysis of diethyl phthalate (0.1 mole/litre) in cetrimide solutions at 35°.

Cetrimide concentration (moles/litre)

1. 0.02. 2. 0.08. 3. 0.187. 4. 0.35. 5. 0.43.

—●— Emulsion      - - - ○ - - - Solution.

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### RESULTS

The solubilities of esters in cetrimide are given in Table I. The influence of cetrimide concentration on the hydrolysis of emulsions and solutions of ethyl benzoate and diethyl phthalate is shown in Figs. 1-3. Fig. 4 shows the hydrolysis of benzocaine solubilised in various cetrimide solutions. With increase in cetrimide concentration the initial rate of hydrolysis of emulsions increased, while that of solutions decreased. In the final stages the rate of hydrolysis decreased progressively with increase in the amount of cetrimide.

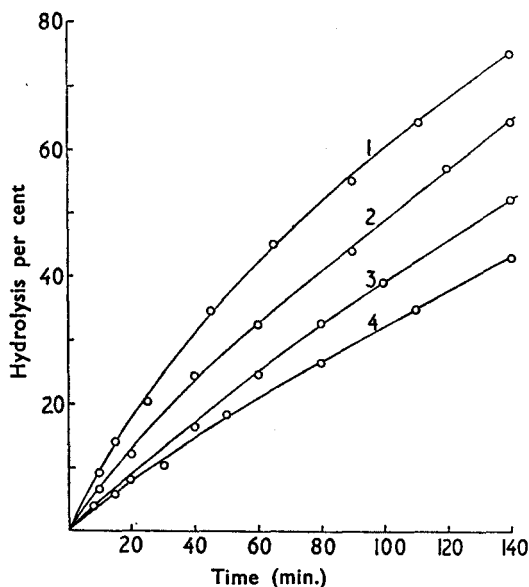


FIG. 4. Alkaline hydrolysis of benzocaine (0.05 moles/litre) in cetrimide solutions at 35°.

Cetrimide concentration (moles/litre)  
1. 0.07. 2. 0.1. 3. 0.2. 4. 0.4.

### DISCUSSION

The rate of hydrolysis both of the solid ester, benzocaine, and of the liquid esters, ethyl benzoate and diethyl phthalate, varies with the concentration of cetrimide.

Where the esters are in solution the rate of hydrolysis decreases as the concentration of surface-active material is increased. A property of solutions of surface-active materials is their ability to take insoluble materials into solution. It is accepted that this phenomenon is associated with the presence of colloidal aggregates of soap molecules or micelles. The solute distributes itself between the micelles and the aqueous "phase" and since it is preferentially soluble in the micellar pseudo-phase an increase in the concentration of surface-active material will increase the amount of solute in this phase relative to that in true solution. Hydrolysis

will occur most readily in the aqueous "phase" where the ester molecules are easily accessible to attack by hydroxyl ions. Hence increasing the concentration of cetrimide alters the distribution of ester in favour of the micelles and the rate of hydrolysis decreases. Besides the reduction in the amount of ester available in true solution it is possible that the charged atmosphere around the micelles may act as a partial barrier to the penetration of hydroxyl ions.

Using liquid esters it was possible to study the effect of cetrimide on the hydrolysis both of emulsified and solubilised esters. In emulsions the initial rate of hydrolysis increases with cetrimide concentration reaching a maximum when the amount of cetrimide present is sufficient to solubilise all the ester. The solubility of esters increases with cetrimide concentration and the change in rate of hydrolysis is due therefore to an increase in the proportion of ester in solution relative to that in the emulsion droplets. The more rapid hydrolysis of solubilised compared with emulsified ester is the result of the greatly enlarged "interface" available both for attack by hydroxyl ions and for diffusion of ester molecules from the micelles into the true aqueous "phase." Reaction at the emulsion droplet-water interface will contribute to the overall effect but is not responsible for the increase in hydrolysis rate with increasing cetrimide concentration. Addition of cetrimide in excess of that needed for complete solution causes a reduction in the initial rate of hydrolysis for the reasons discussed above.

As the hydrolysis proceeds and ester is removed, emulsions become solutions and solutions become progressively less saturated. In the final stages the rate of reaction decreases systematically with increase in cetrimide concentration causing the hydrolysis curves to cross over as shown in Figs. 1-3.

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