Hydrolysis of 2,2,2-Trifluoroethyl Hydrogen 3,6-Dimethylphthalate

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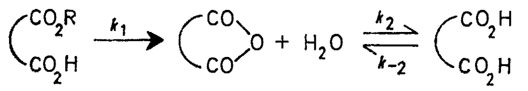
The hydrolysis of 2,2,2-trifluoroethyl hydrogen 3,6-dimethylphthalate in acid solution is found to proceed with neighbouring carboxylate anion participation *via* the anhydride intermediate. The hydrolysis follows the equation: rate = k[ionised ester], and $k_{obs} = k/(1 + [H^+]/K_a)$. The 3,6-dimethyl substitution results in a 150-fold increase in hydrolysis rate.

ENORMOUS increases in the hydrolysis rates of monoesters of dicarboxylic acids due to intramolecular catalysis have been reported.[1] Thanassi and Bruice [2] have shown that the mechanism of participation by the neighbouring carboxy-group in the hydrolysis of phthalic acid monoesters is a function of the pK_a' value of the leaving group. The change in mechanism occurs when the pK_a' of the alcohol forming the ester is *ca.* 13·5: esters of alcohols with pK_a' values greater than 13·5 (*e.g.* methanol,[3] pK_a' 15·54) are hydrolysed *via* neighbouring undissociated carboxy-group participation, whereas those with better leaving groups react by carboxylate anion participation. Some examples of rate enhancement by the presence of substituents in the 3- and 6-positions have been reported. For example, Bunnett and Hauser [4] found a 315-fold rate increase in the lactonisation of 2-(hydroxymethyl)-benzoic acids brought about by methyl groups in these positions.

The hydrolysis of 2,2,2-trifluoroethyl hydrogen 3,6-dimethylphthalate was investigated: (*a*) to find the effect of 3,6-dimethyl substitution on rate; (*b*) to determine the mechanism of intramolecular catalysis, as 2,2,2-trifluoroethanol has a pK_a' value (12·36) [5] lower than the value at which the mode of neighbouring group participation changes from carboxylate anion to undissociated carboxy-group in the unsubstituted phthalic acid derivatives; and (*c*), as 3,6-dimethylphthalic anhydride is moderately resistant to hydrolysis, to find out if k_1 is sufficiently greater than k_2 in the Scheme shown for the anhydride intermediate to be detected.



EXPERIMENTAL

Materials.—3,6-Dimethylphthalic anhydride was prepared as described in the previous paper.

2,2,2-*Trifluoroethyl hydrogen* 3,6-*dimethylphthalate.* Sodium (0·35 g, 0·015 mol) was dissolved in 2,2,2-trifluoroethanol (6 ml) and the solution was added to 3,6-dimethylphthalic anhydride (1·76 g, 0·01 mol) dissolved in 2,2,2-trifluoroethanol (12 ml). After 30 min at room temperature the mixture was evaporated to dryness at 25° under reduced pressure. The residue was dissolved in water and the filtered solution was acidified with 2M-hydrochloric acid at 0°. The precipitated white solid was quickly filtered off (Buchner funnel), washed with iced water until the washings were free of chloride ion, and then air-dried. The product was recrystallised twice from chloroform below 40°; overall yield 85%; $\nu_{max.}$ (Nujol) 2950, 2850vs, 2665, 2580m, 2330, 1920m, 1737vs, 1690, 1683vs, 1600m, 1572m, 1456vs, 1420s, 1384vs, 1310, 1300, 1275vs, 1270, 1250, 1200vs, 1162vs, 1122, 1110s, 1048ms, 1006m, 970, 962, 939, 918, 868ms, 831s, 800, 768, 723ms, 698, and 648s cm^{-1}; m.p. 105° (decomp.). If the ester is maintained at its m.p. the liquid slowly crystallises during 10 min to yield 3,6-dimethylphthalic anhydride, m.p. 142°, identified by its m.p. and i.r. spectrum.

Kinetics.—The hydrolysis of 2,2,2-trifluoroethyl hydrogen 3,6-dimethylphthalate and 3,6-dimethylphthalic anhydride was followed spectrophotometrically at 322 nm by using a Beckman DU spectrophotometer. The sodium acetate–hydrochloric acid buffer solutions for this work were prepared with double-distilled or ion-exchange-purified water from analytical grade reagents. A constant ionic strength was maintained by addition of sodium chloride. An E.I.L. pH meter, calibrated by using 0·05M-potassium hydrogen phthalate [6] was used for pH measurements. First-order rate constants for the 3,6-dimethylphthalic anhydride hydrolysis were calculated from the integrated first-order rate equation. During the hydrolysis of 2,2,2-trifluoroethyl hydrogen 3,6-dimethylphthalate the optical density at 322 nm first increased to a maximum and then underwent a first-order decay. This indicated that an intermediate was formed during the reaction (i). The pseudo first-order

$$\text{ester} \xrightarrow{k_1} \text{anhydride} \xrightarrow{k_2} \text{diacid} \qquad \text{(i)}$$

rate constant for the ester hydrolysis, k_1, was calculated from the equation (ii),[7] where $t_{max.}$ is the time required for the

$$k_1 t_{max.} = 2\cdot3(K - 1)^{-1} \log K \qquad \text{(ii)}$$

absorbance to reach a maximum and $K = k_2/k_1$, in which k_2 is the apparent first-order rate constant ($k_1' + k_{-1}'$) for the 3,6-dimethylphthalic anhydride hydrolysis at this temperature.

$$\text{anhydride} + H_2O \underset{k_{-1}'}{\overset{k_1'}{\rightleftharpoons}} \text{diacid} \qquad \text{(iii)}$$

RESULTS AND DISCUSSION

The experimental values of the first-order rate constant k_1 for hydrolysis of the ester at 39·5° are plotted in the Figure. The pH–rate profile indicates participation

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[1] B. Capon, *Quart. Rev.*, 1964, **18**, 45; W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969; E. K. Euranto, 'The Chemistry of Functional Groups: Carboxylic Acids and Esters,' eds. S. Patai, Interscience, New York, 1969, ch. 11; T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' Benjamin, New York, 1966, vol. I; 'Organic Reaction Mechanisms,' eds. B. Capon and C. W. Rees, Interscience, London, annually from 1965; S. L. Johnson, *Adv. Phys. Org. Chem.*, ed. V. Gold, Academic Press, New York, 1967, vol. 5, p. 237.

[2] J. W. Thanassi and T. C. Bruice, *J. Amer. Chem. Soc.*, 1966, **88**, 747.

[3] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1960, **82**, 795.

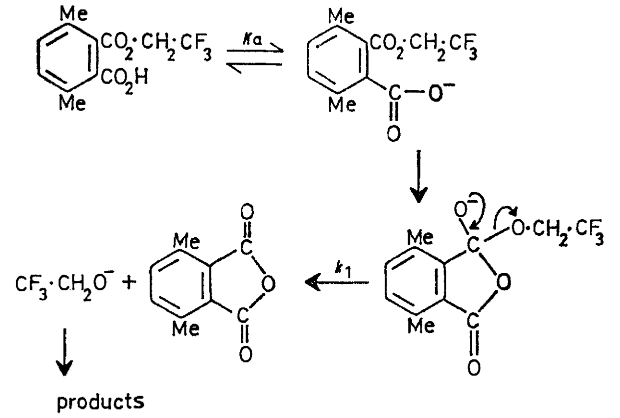
[4] J. F. Bunnett and C. F. Hauser, *J. Amer. Chem. Soc.*, 1965, **87**, 2214.

[5] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1959, **81**, 1050.

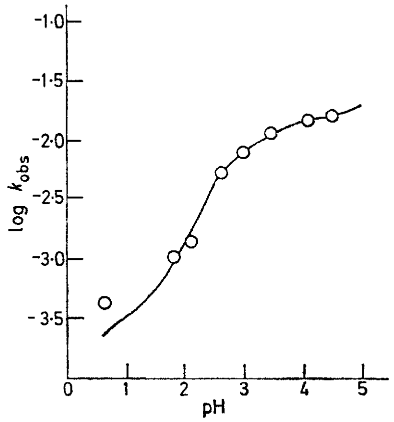
[6] British Standards Institute, B.S. 1647/1961.

[7] A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism,' Wiley, New York, 1961, 2nd edn., pp. 166—169.

by the carboxylate anion and the mechanism is presumably that shown in the Scheme. The change of optical density with time during the reaction, taken in conjunction with the values of the molar extinction coefficients at 322 nm of the ester (ε negligible), 3,6-dimethylphthalic anhydride (ε 3·37 × 10^3),[8] and the 3,6-dimethylphthalic anhydride–diacid equilibrium mixture (ε 480 at 39·5°) [8] confirm that the anhydride and not the acid is the intermediate, as this latter reaction sequence (iv) would not involve the initial increase followed by the decrease in absorbance observed during the hydrolysis of this ester.



SCHEME



Hydrolysis of 2,2,2-trifluoroethyl hydrogen 3,6-dimethylphthalate at 39·5°

$$\text{ester} \xrightarrow{k_1} \text{diacid} \longrightarrow \text{anhydride} \qquad \text{(iv)}$$

The rate equation for the hydrolysis is equation (v),

$$\text{rate} = k[\text{ionised ester}] = k_{obs}[\text{total ester}] \qquad \text{(v)}$$

from which equation (vi) follows. This equation was

$$k_{obs} = k/(1 + [H^+]/K_a) \qquad \text{(vi)}$$

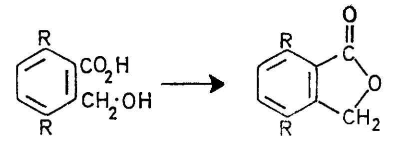
analysed by computer to yield the following values from the experimental rate constants: $k = 1{\cdot}63 \times 10^{-2}$ s^{-1}; $K_a = 9{\cdot}6 \times 10^{-4}$ mol l^{-1}. These figures give a theoretical rate profile which agrees well with the experimental results (Figure). The experimental rate constant at pH 0·63 does not fit the calculated curve, presumably because of hydrogen ion catalysis at these low pH values, and was omitted from this analysis of the rate equation.

The fact that the kinetically apparent acid dissociation constant for the trifluoroethyl monoester of 3,6-dimethylphthalic acid is lower than that of the corresponding phthalic acid derivative (9·60 × 10^{-4} and 1·32 × 10^{-3}, *i.e.* pK_{app} values of 3·02 and 2·88,[2] respectively) is consistent with the expected decrease in acid strength due to the inductive effect of the two methyl groups.

At 39·5° and pH 2·0, 2,2,2-trifluoroethyl hydrogen 3,6-dimethylphthalate ($k_{obs} = 1{\cdot}35 \times 10^{-3}$ s^{-1}) is hydrolysed *ca.* 1·7 × 10^3 times faster than methyl hydrogen phthalate (rate constant calculated from the data published by Thanassi and Bruice,[2] 7·95 × 10^{-7} s^{-1}). The rate constants for 2,2,2-trifluoroethyl hydrogen phthalate and methyl hydrogen phthalate at this pH value and at 64·6° are *ca.* 1·33 × 10^{-4} and 1·17 × 10^{-5} s^{-1}, respectively,[2] *i.e.* the trifluoroethyl monoester is hydrolysed 11—12 times faster than methyl hydrogen phthalate. Thus the two methyl groups in the monotrifluoroethyl ester produce a *ca.* 150-fold rate increase. This is almost double the 80-fold rate enhancement calculated from Eberson's results for the hydrolysis of the corresponding methyl ester: methyl hydrogen 3,6-dimethylphthalate,[9] $k = 7{\cdot}1 \times 10^{-4}$ s^{-1} at pH 2·0 and 61·5°; *cf.*[2] methyl hydrogen phthalate at the same temperature and pH, $k = 8{\cdot}7 \times 10^{-6}$ s^{-1}.

The activation parameters determined for hydrolysis at pH 4·48 ($\Delta H^\ddagger = 90{\cdot}8$ kJ mol^{-1}; $\Delta F^\ddagger = 87{\cdot}9$ kJ mol^{-1}; $\Delta S^\ddagger = +8{\cdot}4$ J mol^{-1} K^{-1}) are consistent with the mechanism proposed [1] and permit a direct comparison with the published rate profile for 2,2,2-trifluoroethyl hydrogen phthalate [2] which confirms the rate enhancement factor of *ca.* 150 calculated above.

The 150-fold rate increase resulting from dimethyl substitution in this phthalic acid monoester may be compared with the 80-fold increase in the rate of acidic hydrolysis of methyl hydrogen phthalate [9] and the similar increase found in the case of the 3,6-dimethylphthalanilic acids [10] (as compared with the corresponding unsubstituted derivatives). These rate enhancements must be due to the steric rather than the electronic effects of 3,6-dimethyl substitution as the change in rate calculated from σ values for the Hammett equation assuming a ρ value of *ca.* 1 would not even account for a doubling in the raction rate. This is confirmed by the work of Bunnett and Hauser,[4] who found that, while 3,6-disubstitution has a pronounced rate-enhancement effect on the reaction (vii), all substituents (except fluorine) in these positions, irrespective of their electronic effects, increase the reaction rate. The largest effect was observed



(vii)

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[8] M. D. Hawkins, preceding paper.

[9] L. Eberson, *Acta Chem. Scand.*, 1964, **18**, 2015.

[10] M. D. Hawkins, unpublished results.

when both substituents were methyl groups: this gave a 315-fold rate enhancement. These rate increases are clearly due to the effect of the methyl groups in constraining the carboxylic acid and ester or hydroxymethyl group to a conformation favourable to ring closure. The *ca.* 1000-fold increase in the rate of hydrolysis of tetramethylsuccinanilic acid at pH 5 as compared with succinanilic acid similarly illustrates the way in which the methyl groups assist in bringing the reacting and catalysing groups together and favour the formation of a cyclic intermediate.[11] An extreme example of this effect is the very rapid cyclisation of the corresponding *o*-hydroxycinnamic acid to form 3,4-dihydro-4,4,5,7,8-pentamethylcoumarin.[12] Here the methyl groups appear to interlock, producing a severe conformational restriction of the side chain and a ground state geometry which is highly favourable to the formation of the transition state. This conformational effect is thought to operate primarily by increasing the steady-state concentration of the tetrahedral intermediate and the phenomenon, which can produce rate enhancement factors as high as 5×10^{10}, has been proposed as a model for the conformational restraint imposed by an enzyme on its substrate and the resulting largely accelerated reaction.

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[4/1464 *Received, 17th July,* 1974]

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