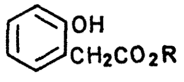
A Comparison of Neighbouring Group Participation by Phenolic and Alcoholic Hydroxy-groups in Ester Hydrolysis

By B. Capon,* S. T. McDowell, and W. V. Raftery
(*Chemistry Department, Glasgow University, Glasgow W.2*)

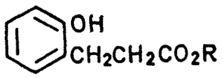
Summary Aryl esters of 2-hydroxyphenylacetic acid, 3-(2-hydroxyphenyl)propionic acid, 4-hydroxybutyric acid, and 5-hydroxyvaleric acid react with neighbouring group participation in aqueous solution.

Neighbouring group participation by hydroxy-groups in ester hydrolysis where the hydroxy-group acts as a nucleophile appears to have been little studied if at all.[1] We now report an investigation of the lactonisation of esters (I)—(IV) which occurs with substantial anchimeric assistance. In the pH range 3·39—4·48 the rates of lactonisation of esters (Ib), (Ic), and (Id) are proportional to $a(\text{OH}^-)$ with second-order constants 6·96, 5·07, and 39·7 × 10^7 l mol^{-1} s^{-1}, respectively, at 25°. Phenyl phenylacetate is stable under these conditions. The ρ-value for the lactonisation reaction is 2·01. No buffer catalysis could be detected in the lactonisation of phenyl 2-hydroxyphenylacetate in acetate buffer. The second-order constant for the analogous intermolecular reaction, the phenolysis of phenyl acetate is 2·79 × 10^{-2} l mol^{-1} s^{-1} at 25°.[2] If the lactonisations involve the form with the phenolate group ionised, the first-order constant for the reaction of the ion of phenyl 2-hydroxyphenylacetate would be 6·96 × 10^3 s^{-1} at 25°,



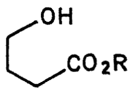
(I)

R
a; 2-naphthyl
b; Ph
c; *m*-tolyl
d; *m*-chlorophenyl



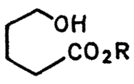
(II)

a; R = 2-naphthyl



(III)

R
a; 2-naphthyl
b; Ph
c; *m*-tolyl
d; *m*-chlorophenyl
e; *m*-fluorophenyl



(IV)

R
a; 2-naphthyl
b; Ph
c; *m*-tolyl
d; *m*-chlorophenyl

assuming a pK_a of 10·0. Hence the ratio of the rate constant for the intramolecular reaction to that for the intermolecular reaction is *ca.* 2·5 × 10^{5} mol l^{-1}.

In the pH$_{app}$ range 3·70—5·56 in 20% aqueous dioxan (v/v) (Ia) lactonises about 5 times faster than (IIa) showing that with these compounds, reaction *via* a five-membered ring occurs faster than *via* a six-membered one.

In the pH range 6·49—8·65 the rate of lactonisation of phenyl 4-hydroxybutyrate (IIb) is proportional to a(OH$^-$) and the second-order constant is 5·42 × 10^{3} l mol^{-1} s^{-1} at 30° which is about 300 times greater than that for the hydrolysis of phenyl acetate [k(OH$^-$) = 1·37 l mol^{-1} s^{-1} at 25°].[3] At pH 7·47 the hydrolyses of (IIIb)—(IIIe) yield a ρ-value of 1·1 and those of (IVb)—(IVd) yield a ρ-value of 1·2. The hydroxybutyrate esters (III) react 10—20 times faster than the analogous hydroxyvalerate esters (IV) and so in this case also reaction proceeds faster *via* a five-membered ring than *via* a six-membered one.

In acetate buffers of pH 5·17 the hydrolysis of phenyl 4-hydroxybutyrate shows buffer catalysis with k_{OAc} = 1·8 × 10^{-4} l mol^{-1} s^{-1} at 49·97°. This is 50—100 times greater than the catalytic constant for the hydrolysis of phenyl acetate (k_{OAc} = 3·84 × 10^{-7} at 25°)[4] which suggests that the catalysis is associated with participation by the hydroxy-group. The hydrolysis of phenyl 4-hydroxybutyrate is also catalysed by imidazole but k_{Im} is similar to that for the hydrolysis of phenyl acetate.

In acid solution the hydrolyses of (III) and (IV) are approximately 20 and 40 times faster than those of the corresponding butyrates. This rate enhancement is similar to that found in the hydrolyses of 4-hydroxybutyramide and 5-hydroxyvaleramide[5] and presumably arises from a similar cause, intramolecular nucleophilic assistance. Thus, under these conditions reaction proceeds faster *via* a six-membered ring than *via* a five-membered one. The ρ-values are −0·2 and −0·15, respectively, which are similar to the values of −0·198 for the acid-catalysed hydrolysis of aryl acetate.[6] Phenyl 2-hydroxyphenylacetate and phenyl phenylacetate are hydrolysed at similar rates in aqueous perchloric acid and so the neighbouring phenolic group does not provide appreciable anchimeric assistance for the hydrolysis of the former compound.

The rate of hydrolysis of phenyl 4-hydroxybutyrate increases more rapidly with acid concentration than that of phenyl butyrate does. Thus the rate for phenyl 4-hydroxybutyrate is increased 17·5 times on going from 1M- to 5M-perchloric acid, whereas that for phenyl butyrate is increased 5·2 times. Presumably the effect of decreasing water activity with increasing acid concentration is much less significant with the former reaction since it is the internal hydroxy-group which acts as the nucleophile. Plots of logk_{obs} *versus* H_0,[7] logk_{obs} *versus* log C(H$_3$O$^+$),[7] log k_{obs} + H_0 *versus* log a(H$_2$O),[8] and log k_{obs} − log C(H$_3$O$^+$) *versus* log a(H$_2$O),[8] are curves but the plot of log k_{obs} + H_0 *versus* H_0 + log C(H$_3$O$^+$)[9] is a straight line with ψ = 0·6. For the hydrolysis of phenyl butyrate ψ = 1·0 and the smaller ψ-value for the intramolecular reaction is in accord with the change in hydration on going to the transition state being smaller.

We thank the S.R.C. for support.

(*Received, January 8th,* 1971; *Com.* 035.)

---

[1] *Cf.* B. Capon, *Quart. Rev.*, 1964, **18**, 45; T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Benjamin, New York, 1966, vol. 1, p. 146.

[2] M. L. Bender and W. A. Glasson, *J. Amer. Chem. Soc.*, 1959, **81**, 1590.

[3] *Cf.* E. K. Euranto in The Chemistry of Carboxylic Acids and Esters, ed. S. Patai, Interscience, London, 1969, p. 518.

[4] V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc.* (*B*), 1968, 515.

[5] L. Zürn, *Annalen*, 1960, **631**, 911.

[6] E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1938, 1801; see H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 204.

[7] *Cf.* F. A. Long and M. A. Paul, *Chem. Rev.*, 1957, **57**, 935.

[8] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956.

[9] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1917.