Intramolecular Catalysis. Part II.[1] Hydrolysis of Diphenylmethyl Hydrogen Phthalate: Neighbouring Group Participation and Alkyl–Oxygen Fission

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Diphenylmethyl hydrogen phthalate is hydrolysed in acid solution *via* alkyl–oxygen fission and intramolecular catalysis involving participation of the neighbouring undissociated carboxy-group. The hydrolysis rate is 1.8 × 10^3 and *ca.* 10^3 times faster respectively than the terephthalate isomer and methyl hydrogen phthalate. 4-Methoxy-substitution of the diphenylmethyl group results in a *ca.* 25-fold rate enhancement owing to increased resonance stabilisation of the carbonium ion.

THE results of a number of studies of the hydrolysis of dicarboxylic acid monoesters have been reported in recent years.[2] Intramolecular catalysis by the carboxy-group is possible in these esters and, as the polypeptide chains of many enzymes are known to contain free carboxy-groups in the form of glutamate or aspartate *etc.*, such compounds have frequently been used as models for the study of enzyme action.

The hydrolysis of diphenylmethyl hydrogen phthalate was studied as, in addition to intramolecular catalysis by the neighbouring carboxy-group, there was a possibility that with an ester containing aromatic groups in the alcohol part of the molecule sufficient resonance stabilisation of a carbonium ion could occur for the reaction to proceed *via* alkyl–oxygen rather than the more usual acyl–oxygen fission. The 4-methoxydiphenylmethyl ester was examined to determine the effect of the increased resonance stabilisation of the carbonium ion (if formed) by methoxy-substitution. Finally the rate constant for the hydrolysis of diphenylmethyl hydrogen terephthalate was determined for comparison with that of the phthalate isomer as a test for neighbouring group

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[1] Part I, M. D. Hawkins, *J.C.S. Perkin II*, 1975, 285.

[2] T. C. Bruice and S. J. Benkovic, 'Bio-organic Mechanisms,' Benjamin, New York, 1966, vol. I; 'Organic Reaction Mechanisms,' eds. B. Capon and C. W. Rees, Interscience, London, 1965; E. R. Euranto, 'The Chemistry of Functional Groups: Carboxylic Acids and Esters,' ed. S. Patai, Interscience, New York, 1969; W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969.

participation[3] and to give an indication of the rate enhancement produced by the *o*-carboxy-group. This was part of a study of the influence of substituents in the ring and in the side-chain on the hydrolysis rates of monoesters[1] and *N*-phenylamides with neighbouring carboxy-groups.[4,5]

EXPERIMENTAL

Materials.—Diphenylmethyl hydrogen phthalate was prepared by the method of Balfe *et al.*[6] for the preparation of (±)-4-methoxybenzhydryl hydrogen phthalate. The viscous oil, obtained by the reaction of equimolecular amounts of diphenylmethanol and phthalic anhydride in pyridine, was decomposed by a slight excess of 2M-hydrochloric acid to yield a crystalline solid which was filtered off, washed with distilled water, and dried. The crude ester (91%) was crystallised once from carbon disulphide and then three times from benzene. The pure product, m.p. 154.5—155° [Found: M (= equiv. wt.), 330. Calc. for $C_{21}H_{16}O_4$: M, 332], was stored in a vacuum desiccator for several days before carrying out kinetic studies in order to remove the last traces of benzene, $\nu_{\text{max.}}$ (Nujol) 2 950, 2 850vs, 2 680, 2 560ms, 1 723vs, 1 690vs, 1 593, 1 582ms, 1 498, 1 457, 1 422s, 1 380ms, 1 300—1 290vs, 1 273, 1 260vs, 1 182, 1 147m, 1 122s, 1 073vs, 1 032m, 1 002w, 979ms, 804, 788ms, 759s 742, 737vs, 701vs, and 650m.

4-Methoxydiphenylmethyl hydrogen phthalate, m.p. 100—103° (lit., 102—103,[6] 98—99[7]) (Found: M, 359. Calc. for $C_{22}H_{18}O_5$: M, 362), was prepared by the reaction between 4-methoxydiphenylmethanol and phthalic anhydride using the published method[6] and was recrystallised twice from benzene. 4-*Methoxydiphenylmethanol*, m.p. 67° (lit.,[7] 68°) was prepared in 62% yield from the reaction of anisaldehyde with phenylmagnesium bromide.[8] It was recrystallised from carbon tetrachloride–light petroleum (b.p. 40—60°). Diphenylmethyl hydrogen terephthalate was obtained by the 'half-hydrolysis' method[9] of the diester formed by reacting diphenylmethanol with terephthaloyl chloride.

Kinetics.—The ester hydrolyses were followed spectrophotometrically using a Beckman model DU spectrophotometer. For the slower reaction samples of a stock solution of the ester in solvent–buffer were sealed in small Pyrex ampoules and heated in a thermostatted bath. At suitable intervals the ampoules were removed, cooled to freeze the reaction, and opened. The optical density of the solution at a convenient u.v. wavelength was determined using a sample of the solvent–buffer heated under identical conditions as a blank. Faster reactions were followed by removing samples for spectrophotometric analysis at regular intervals from flasks (preferably fitted with serum caps) heated in a thermostatted bath.

Owing to the insolubility of the phthalate and terephthalate esters of diphenylmethanol in water, the hydrolysis of these compounds was studied using sodium acetate–acetic acid buffers in aqueous 20% v/v dioxan. The sodium acetate concentration was kept at 0.040M to maintain constant ionic strength and the pH, which was calculated from the Henderson equation using the published pK_a value[10] of acetic acid in 20% dioxan, was varied by changing the acetic acid concentration.

At first difficulties were experienced in getting satisfactory optical density–time plots for diphenylmethyl hydrogen phthalate hydrolysis. The absorbance would increase beyond the infinity reading expected from synthetic mixtures of the hydrolysis products and values obtained for the rate constant in duplicate runs would often differ considerably. This erratic behaviour was traced to oxidation by dissolved oxygen catalysed by traces of metal ions in solution. It was cured by degassing the solutions and sealing the ampoules under nitrogen or, more conveniently, by adding EDTA (*ca.* 10^{-5}M) to the buffer solutions to complex the small traces of catalysing ions. In either case the observed data gave satisfactory, reproducible linear Guggenheim[11] plots for at least three half-reaction times.

RESULTS AND DISCUSSION

The kinetic data are summarised in the Table. Although the use of sodium acetate–acetic acid buffers in 20% dioxan considerably limited the pH range available for examination in this study, the experimental rate–pH curve for diphenylmethyl hydrogen phthalate nevertheless indicated undissociated carboxy-group participation. Intramolecular catalysis was confirmed by the 1.8×10^3 fold rate enhancement compared with the corresponding 1,4-ester. The rate constant for the hydrolysis of the terephthalate ester is only approximate owing to the extreme slowness of the reaction, the low solubility of the substrate in 20% dioxan and the small difference between the u.v. spectra of the ester and of the hydrolysis products. However rate increases of this magnitude in the 1,2-monoester compared with the

Hydrolysis of phthalic acid monoesters in 20% dioxan at 89.6°

Sodium acetate–acetic buffers, [NaOAc] = 0.040M

Diphenylmethyl hydrogen phthalate

pH	4.29	4.42	4.64	4.89	5.29	5.59	5.89
$10^5 k_{\text{obs}}/\text{s}^{-1}$	42.8	39.5	28.9	24.7	12.8	2.87	1.38

4-Methoxydiphenylmethyl hydrogen phthalate

k_{obs} 9×10^{-4} s^{-1} at pH 5.59.

Diphenylmethyl hydrogen terephthalate

k_{obs} 7×10^{-8} s^{-1} at pH 5.59.

Diphenylmethyl hydrogen phthalate: activation parameters for hydrolysis in 0.1M-hydrochloric acid

$\Delta H^{\ddagger}$/kJ mol^{-1}	108
$\Delta F^{\ddagger}$/kJ mol^{-1}	116
$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	−20.9

Hydrolysis of diphenylmethyl hydrogen phthalate: effect of electrolytes

Sodium acetate–acetic acid buffer in 20% dioxan (pH 5.29)

[NaCl]/M	0	0.20	0.30
$10^4 k_{\text{obs}}/\text{s}^{-1}$	1.28	1.81	1.85

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[3] B. Capon, *Quart. Rev.*, 1964, **18**, 48.

[4] M. D. Hawkins, following paper.

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

[6] M. P. Balfe, M. A. Doughty, J. Kenyon, and R. Poplett, *J. Chem. Soc.*, 1942, 605.

[7] R. Adams, W. V. Wirth, and H. E. French, *J. Amer. Chem. Soc.*, 1918, **40**, 430.

[8] Adapted from triphenylmethanol preparation, A. I. Vogel, 'A Textbook of Practical Organic Chemistry,' Longmans, London, 1957, 3rd edn., p. 813.

[9] J. B. Cohen and H. S. de Pennington, *J. Chem. Soc.*, 1918, **113**, 57.

[10] H. S. Harned and G. L. Kazanjian, *J. Amer. Chem. Soc.*, 1936, **58**, 1912; R. A. Robinson and R. H. Stokes, 'Electrolyte Solutions,' Butterworths, London, 1965, p. 538.

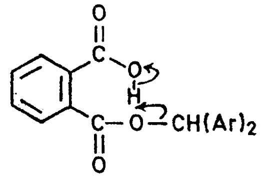
[11] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

1,4-isomer are sufficient evidence for intramolecular catalysis.[3]

Undissociated carboxy-group participation in diphenyl methyl hydrogen phthalate hydrolysis is consistent with the work of Thanassi and Bruice,[12] who found that phthalic acid monoesters containing good leaving groups, *i.e.* an alcohol having a low pK_a', hydrolyse *via* carboxylate anion participation, while those with poor leaving groups hydrolyse with participation of the undissociated carboxy-group. The change in mechanism occurs with alcohols of pK_a' *ca.* 13.5. As diphenylmethanol has $pK_a' > 13.5$ an undissociated carboxy-group participation mechanism is in accord with the findings of Thanassi and Bruice.

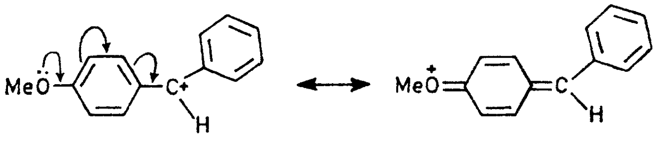
Comparison of the rate constant calculated for diphenylmethyl hydrogen phthalate at 100° in 20% dioxan (E_a 103.6 kJ mol^{-1}) with that published[12] for methyl hydrogen phthalate at the same temperature and pH in aqueous solution shows that diphenylmethyl hydrogen phthalate in 20% dioxan is hydrolysed 200 times faster than the corresponding methyl ester in aqueous solution. As reaction rates in 20% dioxan are usually between a half and a third of the rate in aqueous solution,[5] the hydrolysis of diphenylmethyl hydrogen phthalate would therefore be between 400 and 600 times faster than methyl hydrogen phthalate under the same conditions of temperature and pH. Rate increases of this order indicate alkyl–oxygen fission. Such reactions are even more susceptible to non-aqueous solvents than hydrolyses involving acyl–oxygen fission as the dioxan strongly reduces the (faster) Al contribution; for example the contribution of the $A_{Al}1$ mechanism in the hydrolysis of t-butyl acetate in 0.05M-hydrochloric acid at 30° decreases from 84.6% in aqueous solution to 57.7 and 5% in 50.06 and 90.29 wt. % of dioxan respectively.[13] The actual rate enhancement in the case of diphenylmethyl hydrogen phthalate is thus probably in excess of 10^3.

A possible mechanism for the reaction is shown in Scheme 1.



SCHEME 1 Intramolecular general-acid catalysis for monophthalate esters with alkyl–oxygen fission

The 20—25 fold rate increase in the 4-methoxydiphenylmethyl monoester compared with diphenylmethyl hydrogen phthalate may be accounted for in terms of the added resonance stabilisation of the carbonium ion, and hence an increased $A_{Al}1$ contribution and faster hydrolysis rate, by contribution of forms of the type known in Scheme 2.



SCHEME 2

The electronic effect of 4-methoxy-substitution calculated from the Hammett equation using the corresponding σ value (0.268 for 4-MeO),[14] even using a ρ value as high as 2 or 3, could not possibly account for a rate increase of this magnitude for a mechanism involving undissociated carboxy group participation and acyl–oxygen fission. The fact that added electrolytes (NaCl, $NaClO_4$, and KCl) *increase* the hydrolysis rate of diphenylmethyl hydrogen phthalate also agrees with a reaction scheme involving alkyl–oxygen fission and carbonium ion formation.[15]

The activation parameters for hydrolysis in 0.1M-hydrochloric acid (see Table) are of the same order of magnitude as those published for other esters which hydrolyse by this mechanism.[16] Alkyl–oxygen fission is in accordance with the results of Anantaraman and his co-workers,[16] who found that optically active monophthalates of 1-phenylethyl and 1-(*p*-t-butylphenyl)ethyl alcohols yielded racemic alcohols on hydrolysis. They also found that *p*-methoxy-substitution of the 1-phenylethyl alcohol group in the ester similarly resulted in an enormous rate increase owing to greater resonance stabilisation of the carbonium ion.

[5/1371 *Received*, 11*th July*, 1975]

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