Intramolecular General Base Catalysis by the Ionised Carboxy-group of the Hydrolysis of Aryl Hydrogen Malonates

By A. J. KIRBY* and G. J. LLOYD
(*University Chemical Laboratory, Lensfield Road, Cambridge* CB2 1EW)

Summary The hydrolysis of aryl hydrogen malonates is subject to intramolecular general base catalysis by the ionised carboxyl group; general base catalysis of the hydrolysis of the *p*-nitrophenyl ester shows unexpectedly complex kinetics, and appears to involve a ketene mechanism.

AN important part of our study of simple reactions as models for enzymic processes is a detailed investigation of the effects of structural variation on the efficiency of intramolecular catalysis.[1] We[2] and other workers[3] have found that relatively small changes in structure can have very large effects on the rates of reactions involving nucleophilic catalysis. It would be of great interest to extend this approach to the enzymically more common general species catalysed reactions, particularly since known examples in simple systems are characteristically rather inefficient. A major problem is that the required structural variation will in many cases lead to a change of mechanism, to the more efficient nucleophilic catalysis. So we are investigating systems in which this mechanism is selectively inhibited, and

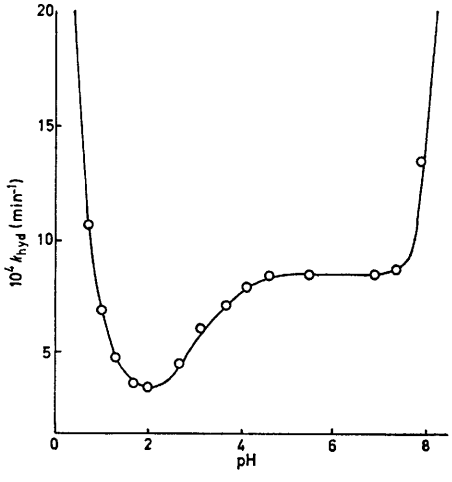
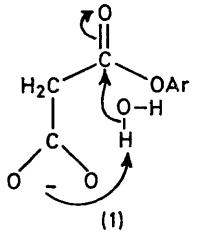


FIGURE 1. *pH–rate profile for the hydrolysis of phenyl hydrogen malonate, at* 39° *and ionic strength* 1·0. *The release of phenol was measured spectrophotometrically.*

report here results with one such system, the aryl hydrogen malonates.

The pH–rate profile shown in Figure 1 for the hydrolysis of phenyl hydrogen malonate is typical. The rate increases as the carboxyl group ionises, as expected if CO_2^- is the more effective catalytic form, to a pH-independent rate of $8{\cdot}45 \times 10^{-4}$ min^{-1} between pH 4·5 and 7. This represents a rate enhancement of over 150 times, compared with the hydrolysis of phenyl acetate under the same conditions, which we attribute to intramolecular general base catalysis (1) of the attack of water by the ionised carboxyl group.



(1)

All the kinetic evidence is consistent with this mechanism. $\Delta S^{\ddagger}$ is −23·7 e.u.; the solvent isotope effect, $k_H/k_D = 2{\cdot}21$; and Hammett's ρ, measured for six substituted-phenyl hydrogen malonates, is 0·93. Each of these parameters is identical, within experimental error, with the corresponding figure for the hydrolysis of the anion of aspirin,[4] a well-established example of intramolecular general base catalysis of this sort. As expected, nucleophilic catalysis is inhibited because it would require a highly strained 4-membered cyclic anhydride. We are now studying esters of substituted malonic acids, to establish whether the efficiency of intramolecular general base catalysis is significantly sensitive to the geometry of the system.

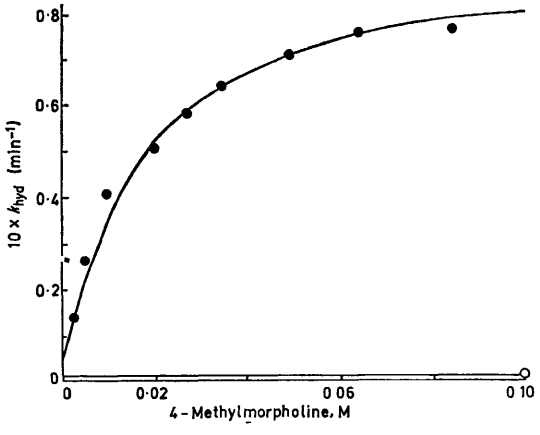
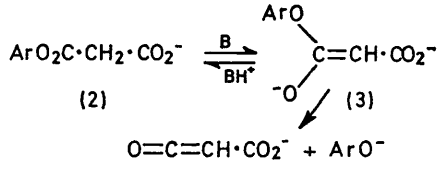


FIGURE 2. *Second-order plots for catalysts by 4-methylmorpholine of the hydrolysis of* p*-nitrophenyl hydrogen malonate anion (curve, closed circles) and* p*-nitrophenyl acetate (almost parallel to base line, open circle), at* 39° *and ionic strength* 1·0.

The reactions described above are buffer catalysed, and hydrolysis rates were obtained by the usual method of extrapolation to zero buffer concentration. The hydrolysis of aryl esters normally shows a first-order dependence on buffer concentration, but with two of our compounds, the *m*- and especially the *p*-nitrophenyl esters, complex behaviour was observed. At low concentrations of moderately basic buffers (acetate, phosphate, TRIS, 2,6-lutidine and 4-methylmorpholine, but not carbonate or hydroxide) catalysis was several hundred times more efficient than expected, and at higher buffer concentrations saturation kinetics were observed (see Figure 2).

Intramolecular catalysis of the usual mechanisms for ester hydrolysis can be ruled out. A mechanism involving general base catalysis by acetate, for example, would not be expected to be faster than the neutral hydrolysis, which is catalysed by this mechanism by the neighbouring carboxylate group; and any mechanism involving nucleophilic catalysis is precluded by the observation that the sterically hindered base, 2,6-lutidine, shows undiminished reactivity. So the evidence is that the hydrolysis of the *m*- and *p*-nitrophenyl malonate anions catalysed by general bases of moderate basicity goes by a special mechanism, which shows a change of rate-determining step[5] with increasing buffer concentration. The reaction, which is clearly very sensitive to the basicity of the leaving group, thus involves an intermediate which is not the tetrahedral addition intermediate of the normal hydrolysis reaction.



Almost identical properties have been found by Bruice and his co-workers[6] for the buffer-catalysed hydrolysis of ethyl *p*-nitrophenyl malonate, and of similar esters with strongly activated methylene groups. Their explanation, that these esters are hydrolysed by the *E1cb* mechanism, is well substantiated, and entirely reasonable for β-keto-esters and related compounds. The esters (2) used in our work do not have strongly activated methylene groups, and the dianions (3) seem much less likely intermediates, particularly since *p*-nitrophenyl acetate shows no sign of similar behaviour.[6] But what evidence we have is consistent with a keten mechanism in this case also, with partitioning of an intermediate [possibly (3)] dependent on buffer concentration. For example, catalysis of the hydrolysis of *p*-nitrophenyl hydrogen dimethylmalonate, which has no enolisable hydrogens, is normal: and the methylene protons of the ethyl hydrogen malonate anion $EtO_2C{\cdot}CH_2CO_2^-$ are readily exchanged for deuterium in D_2O at room temperature. This reaction is catalysed by phosphate buffer, and becomes too fast to measure conveniently at sufficiently high buffer concentration (0·29M-buffer, pH 7·0). Thus an enolisation is a feasible first step in the hydrolysis reaction. But the mechanism shown almost certainly represents an over-

simplification, and a detailed interpretation is not possible without further results.

One of us (G. J. L.) wishes to thank the Salter's Company for the award of a Scholarship.

(*Received, September 20th,* 1971; *Com.* 1636.)

[1] A. J. Kirby and A. R. Fersht, *Progr. Bio-organic Chem.*, 1971, **1**, 1.
[2] A. J. Kirby and P. W. Lancaster, in 'Chemical Reactivity and Biological Role of Functional Groups in Enzymes', ed. R. M. S. Smellie, Biochemical Society Symposia No. 31, Academic Press, London and New York, 1970, p. 99.
[3] D. R. Storm and D. E. Koshland, *Proc. Nat. Acad. Sci. U.S.A.*, 1970, **66**, 445. S. Milstien and L. A. Cohen, *ibid.*, 1970, **67**, 1143
[4] A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 1967, **89**, 4857.
[5] W. P. Jencks, 'Catalysis in Chemistry and Enzymology', McGraw-Hill, New York, 1969, p. 572.
[6] B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969, **91**, 2993, 3003.