The *E*1cb Mechanism for Ester Hydrolysis. Evidence for a Dianion Intermediate in the Hydrolysis of Aryl Malonate Anions[†]

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The hydrolysis of monoesters of malonic acid, but not of dialkylmalonic acids, with good (nitrophenolate) leaving groups, is catalysed by low concentrations of general acids and bases several hundred times more efficiently than expected. This catalysis disappears at high concentrations of catalyst. The same buffers catalyse the exchange of deuterium from solvent D_2O into the methylene group of monoethyl malonate. The results are explained in terms of the *E*1cb mechanism for ester hydrolysis. Oxyanion bases react only with the undissociated aryl hydrogen malonate, but basic tertiary amines remove a proton from the ester anion, generating an intermediate with a carbanionic centre next to, and significantly stabilised by, a carboxylate group.

The hydrolysis reactions of aryl hydrogen malonates, described in the preceding paper,[1,2] are buffer-catalysed. In most cases the reaction shows the usual first-order dependence on buffer concentration, but *m*- and *p*-nitrophenyl hydrogen malonates show complex behaviour. Catalysis by moderately basic buffers (*e.g.* phosphate, Tris), is several hundred times more efficient than expected at low concentrations of buffer. At higher buffer concentrations this catalysis gradually disappears, so that saturation kinetics are observed (see Figures 1 and 2).

The very similar behaviour of ethyl *o*-nitrophenyl malonate was convincingly explained by Bruice and his co-workers[3] in terms of a carbanion (*E*1cb) mechanism for ester hydrolysis. Such a mechanism is entirely reasonable for esters with doubly activated methylene groups, and has been observed[4] for nitrophenyl acetates with α-CN and $\text{-S}^+\text{Me}_2$ groups, as well as $\alpha\text{-CO}_2\text{Et}$[3] and $\alpha\text{-COCH}_3$.[5] It is not observed, however, with *p*-nitrophenyl acetate,[4] or with nitrophenyl acetates with a wide range of α-substituents, with σ_I values up to 0.85.[4,6] Since the CO_2^- group has a *negative* σ^I value[7] it seemed at first unlikely that our reaction was another example of the *E*1cb mechanism. This paper describes evidence that the base-catalysed hydrolysis of aryl malonate anions does indeed involve a carbanion intermediate, which must derive significant stabilisation from the adjacent CO_2^- group.

EXPERIMENTAL METHODS AND RESULTS

Materials and methods were largely as described in the preceding paper.[1]

Deuterium Exchange Experiments.—The exchange of deuterium into monoethyl malonate monoanion was followed in 70 : 30 v/v D_2O–acetone by n.m.r. [Varian HA 100 instrument; probe temperature 29.5 °C (from a standard correlation with temperature of the difference in chemical shift between the OH and CH_3 protons of neat MeOH)]. For each run the buffered solvent (2 ml) containing KCl to give a final ionic strength of 1.0M, was added to solid potassium ethyl malonate[8] (120 mg) (both in tubes incubated in a water-bath at probe temperature) to start the reaction, and the solution was used to fill the n.m.r. tube. The spectrometer was locked on the acetone singlet and the phase, tuning, and gain controls were optimised at once, then left untouched for the remainder of the run. The spectrum was scanned at intervals from 2.1 to 0.9 p.p.m. downfield from the lock signal, giving a record of the exchanging central malonate CH_2 group (0.98 p.p.m. downfield) and the unchanging quartet of the ester ethyl group (1.87 p.p.m. downfield). The latter signal was a convenient internal reference, but integration showed that it did not vary significantly during a run. The exchanging CH_2 group peaks could not be integrated reproducibly (too close to the lock signal), so the appropriate areas of the chart paper were cut out and weighed. Ten to fifteen scans for each run (taken over 2—2.5 half-lives) and an assumed end point of zero (the peak had always disappeared when the spectrum was checked after 10 half-lives) gave good first-order plots. Buffer catalysis constants were determined from least-squares fits of observed exchange rates *vs.* buffer concentration. These results are given in Table 1: the second-order rate constants

TABLE 1

Buffer catalysis of the exchange reaction, $\text{EtO}_2\text{C·CH}_2\text{·CO}_2^- \longrightarrow \text{EtO}_2\text{·C·CD}_2\text{·CO}_2^-$, in 70 : 30 D_2O–acetone at 29.5 °C and ionic strength 1.0

Buffer[a] (pK_a[b])	k_0/min^{-1}	k_{BH^+}/dm^3 mol min^{-1}	k_B
(H_2O)	*2×10^{-2}*		
Phosphate (7.08)		*0.11* ± 0.01	
50% free base	2×10^{-2}	0.11	0.11
100% free base[c]			*d*
N-Methylmorpholine (7.86)		*0.43* ± 0.03	0.06 ± 0.30
50% free base	1.6×10^{-2}	0.49	0.49
75% free base		0.62	0.21
100% free base[e]			*d*
Carbonate (10.44)	2.4×10^{-2}	*d*	*d*
Triethylamine		*d*	*1.5* ± 0.3
50% free base	2×10^{-2}	1.2	1.2
75% free base	2×10^{-2}	4.8	1.7

[a] Concentrations up to 0.25, 0.375, 0.125, and 0.075M (free base) for phosphate, *N*-methylmorpholine, carbonate, and triethylamine, respectively. [b] Measured pD (glass electrode) for 50% free base buffer solution in 70 : 30 D_2O–acetone at 21 °C. [c] 0.125M-HPO_4^{2-} in 0.125M-carbonate, 50% free base. [d] No catalysis detectable. [e] 0.5M-*N*-Methylmorpholine in 0.125M-carbonate, 50% free base, pD 10.44.

[†] No reprints available.

[1] A. J. Kirby and G. J. Lloyd, preceding paper.

[2] A. J. Kirby and G. J. Lloyd, *Chem. Comm.*, 1971, 1538.

[3] B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969, **91**, 2993.

[4] B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969, **91**, 3003.

[5] R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5956.

[6] B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969, **91**, 2985.

[7] M. Charton, *J. Org. Chem.*, 1964, **29**, 1222.

[8] R. E. Strube, *Org. Synth.*, Coll. Vol. IV, 1963, 417.

are calculated for both ionic forms of the buffer at each buffer ratio, to show how the pattern changes from apparent general acid catalysis, by phosphate and *N*-methylmorpholine, to general base catalysis by triethylamine. Extrapolation to zero buffer concentration reveals a significant pH-independent exchange reaction of the ethyl malonate anion, but no catalysis by up to 0.125M-carbonate.

Catalysis by phosphate can be accounted for in terms of a reaction between the phosphate free base (dianion) and ethyl hydrogen malonate. If we take the enolisation of diethyl malonate [9] as a suitable model, we can estimate a rate constant of the order of 10^2 dm^3 mol^{-1} min^{-1} for the reaction of phosphate with ethyl hydrogen malonate (based on the figure of 80 dm^3 mol^{-1} min^{-1} given by Bell *et al.*[9] for the reaction with diethyl malonate in water at 25 °C; we make no allowance for the change in ionic strength or solvent). The ratio of the rate constants for the kinetically equivalent reactions of buffer (B) and ethyl hydrogen malonate (HA) [equation (i)] is given by the ratio of the dissociation constants of HA

$$\text{rate} = k_a[\text{BH}^+][\text{A}^-] = k_b[\text{B}][\text{HA}] \qquad \text{(i)}$$

and BH$^+$ ($k_a/k_b = K_{\text{BH}^+}/K_{\text{HA}}$). The p$K_a$ value of the ester acid at ionic strength 1.0 will be close to 3.15 (the value found for most of our aryl hydrogen malonates), 3.33 pK units lower than that of phosphate (comparison in water). So the rate constant for the removal of a C–H proton by phosphate from ethyl hydrogen malonate is expected to be about 5×10^{-2}, about half the measured value of 11×10^{-2} dm^3 mol^{-1} min^{-1}.

This reasonable agreement suggests that the CO_2H group of ethyl hydrogen malonate does not greatly assist the enolisation reaction, in contrast to the results of Cox and Hutchinson [10] with 2-oxocyclohexanecarboxylic acid. If this is correct, then a similar calculation shows that the pH-independent deuterium exchange reaction of ethyl malonate anion cannot be accounted for as a reaction of hydroxide with the protonated ester acid. The rate constant for the hydroxide-catalysed enolisation of diethyl malonate in water is less than 10^6 dm^3 mol^{-1} min^{-1} at 25 °C, according to Bell *et al.*[9] Since pK_w − pK_a for ethyl hydrogen malonate in water will be about 10.3, the rate of deuterium exchange into ethyl hydrogen malonate catalysed by hydroxide is not likely to be more than 6×10^{-5} min^{-1} at 30 °C, to be compared with an observed rate of 2×10^{-2} min^{-1}. We therefore take the observed pH-independent deuterium exchange to be a spontaneous reaction, involving ethyl malonate anion and water only.

The data for catalysis by triethylamine can only reasonably be interpreted in terms of a reaction of the free base with ethyl malonate anion. At the pH of these measurements the proportion of undissociated ethyl hydrogen malonate is less than 10^{-7}, and catalysis by *N*-methylmorpholine and phosphate, which involves reactions with the acid ester at lower pH, is not observed when the bases are dissolved in carbonate buffer.

Rate constants representing what we consider the significant reactions are printed in italics in Table 1.

Buffer Catalysis of Ester Hydrolysis.—Measurement of the pH–rate profiles of the ten substituted-aryl malonate half esters described in the preceding paper [1] involved at least a cursory investigation of catalysis by several buffer systems in each case. All the esters derived from dialkylmalonic esters, whatever the leaving group, show normal behaviour; catalysis, where it is observed, is a simple reaction first order in the free base form of the buffer. This is true also for half esters of malonic acid itself with all but the best leaving groups. But *m*-nitrophenyl and particularly *p*-nitrophenyl malonate anions show the unusual behaviour referred to in the introduction. We discuss the reaction on the basis of data for *p*-nitrophenyl malonate, *p*-$O_2N{\cdot}C_6H_4{\cdot}O_2C_2CH_2{\cdot}CO_2^-$.

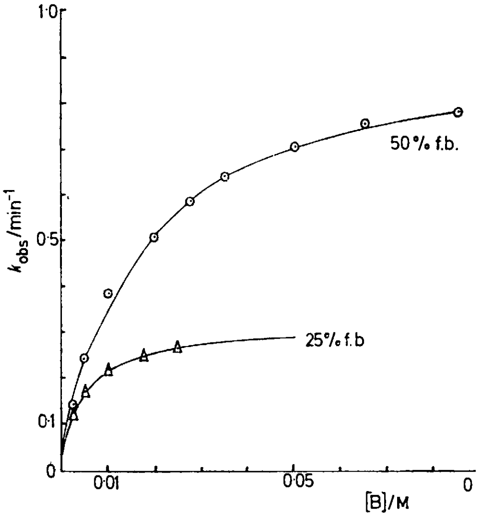

FIGURE 1 Catalysis by *N*-methylmorpholine buffers (25 and 50% free base) of the hydrolysis of *p*-nitrophenyl malonate, at 39.6 °C and ionic strength 1.0

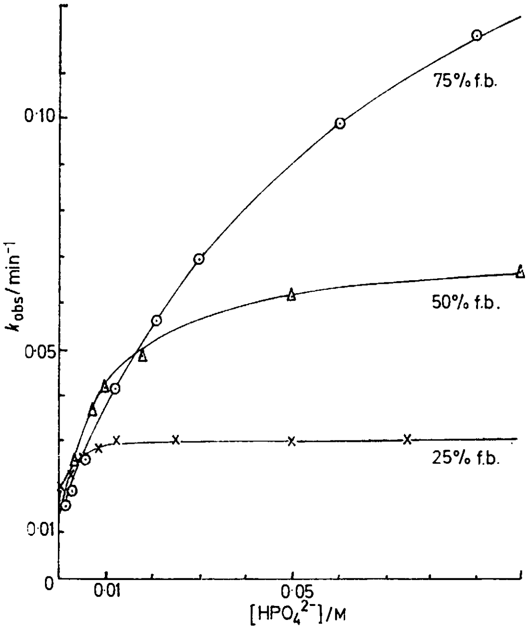

FIGURE 2 Catalysis of the hydrolysis of *p*-nitrophenyl malonate by phosphate buffers

Typically (Figures 1 and 2) plots of the observed first-order rate constants for the release of *p*-nitrophenolate against buffer concentration show sharp curvature. A high

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[9] R. P. Bell and J. E. Crooks, *Proc. Roy. Soc.*, 1965, *A*, **286**, 285; R. P. Bell, D. H. Everett, and H. C. Longuet-Higgins, *Proc. Roy. Soc.*, 1946, *A*, **186**, 443.

[10] B. G. Cox and R. E. J. Hutchinson, *J.C.S. Perkin II*, 1974, 613.

initial slope at lower buffer concentrations, corresponding to a second-order rate constant for catalysis many hundreds of times greater than expected for a *p*-nitrophenyl ester, falls off sharply as the concentration of the buffer is increased at constant pH, until the rate is effectively independent of buffer concentration when this is high enough (in most cases well below 1M).

This kinetic behaviour is common for complex reactions which have at least one step subject to buffer catalysis, and at least one step which is not. The curvature then represents a change in rate-determining step, from the former to the latter, and if other reasonable explanations are ruled out, as they can be in the present case, is evidence that the reaction involves at least two steps, and thus at least one intermediate. The parameters of interest are the initial slope of the curve, which depends on the transition state of the catalysed step, and the rate constant, k_∞, for the buffer-independent reaction reached at higher buffer concentrations which relates to the transition state for the second step. These can readily be extracted in the present case by plotting $1/(k_{obs} - k_0)$ *vs.* $1/[B]$ (k_0 is the rate constant obtained by extrapolation to zero buffer concentration). This procedure gave good straight line plots in almost every case. Evidently the intercept of this plot (at $1/[B] = 0$) will be $1/k_\infty$, and the slope is $1/k_B$, the initial slope of the original plot.

TABLE 2

Buffer catalysis constants for the hydrolysis of *p*-nitrophenyl hydrogen malonate, at 39.6 °C and ionic strength 1.0

Buffer [a] (% free base form)	pH	k_0/min^{-1}	k_∞/min^{-1} [b]	k_B/dm^3 mol^{-1} min^{-1} [c]
Formate (25, 50, 75%)			*d*	*d*
Acetate (50, 75%)			*d*	*d*
Acetate (90%)	5.58	1.4×10^{-2}	7.8×10^{-3}	0.26
Pyridine (90%)	6.12	1.4×10^{-2}	0.26	0.60
Phosphate (25%)	6.01	1.4×10^{-2}	1.7×10^{-2}	8.5
Phosphate (50%)	6.48	1.4×10^{-2}	6.0×10^{-2}	5.3
Phosphate (75%)	7.01	1.4×10^{-2}	0.18	2.7
2,6-Lutidine (75%)	7.27	1.4×10^{-2}	0.38	1.15
N-Methylmorpholine (25%)	7.25	1.7×10^{-2}	0.29	65
N-Methylmorpholine (50%)	7.68	2.0×10^{-2}	0.90	60
Tris (25%)	7.48	1.5×10^{-2}	0.95	6.7
Tris (50%)	8.05	3.1×10^{-2}	2.2	5.8
Tris (50%)	8.48	6.1×10^{-2}	5	6.3
Carbonate (15%)	8.94	0.15	*e*	2.27
Carbonate (50%)	9.66	0.71	*e*	2.35
Triethylamine [f] (25%)	10.4		*e*	385 [f]

[a] Concentration range generally 5×10^{-3}—0.5M-free base. [b] Obtained by extrapolation to zero buffer concentration. [c] Obtained by analysis based on equation (ii), as described in text, unless noted otherwise. [d] No detectable catalysis. [e] Simple first-order dependence on buffer concentration. [f] At 20.4 °C (too fast to measure at 39 °C).

The success of this treatment shows that buffer catalysis can be described by the relationship (ii). This is of the

$$k_{obs} = k_0 + k_B[B]/(1 + k_B[B]/k_\infty) \qquad \text{(ii)}$$

form expected for a reaction of the type (iii), since applic-

$$HA \underset{k_2[BH^+]}{\overset{k_1[B]}{\rightleftharpoons}} A^- \xrightarrow{k_3} \text{products} \qquad \text{(iii)}$$

ation of the steady state assumption gives (iv). In fact it

$$k_{obs} = k_1[B]/(1 + k_2[BH^+]/k_3) \qquad \text{(iv)}$$

is not possible to rationalise all our results in terms of a simple two-step reaction, so the data are presented (Table 2) in terms of the empirical parameters of equation (iii). This equation gives an accurate description of the observed behaviour (the curves of Figures 1 and 2 are calculated from the values of k_0, k_B, and k_∞ given in Table 2; the points are experimental), and the constants obtained serve as a basis for the discussion of kinetics and mechanism below.

Buffer Catalysis in D_2O.—Buffer catalysis by *N*-methylmorpholine, which appears to involve a change of rate-determining step in the region 0.01—0.1M-buffer, was studied in this concentration range using 50% free base buffer in D_2O. Some of the results are shown in Figure 3. At most concentrations of buffer the first-order plots obtained were curved. Curvature was small at very low buffer concentrations, was most pronounced at about 0.04M-total buffer, and then gradually disappeared, until above about 0.5M-buffer linear first-order plots were obtained. We have not attempted a quantitative analysis of these data, but the ratio of initial to final slopes of the curved plots obtained rises to about 3 for the most highly curved plots. The rates observed at high buffer concentrations where good linear first-order plots were obtained, were identical, within experimental error, with rates found for the corresponding reactions in H_2O.

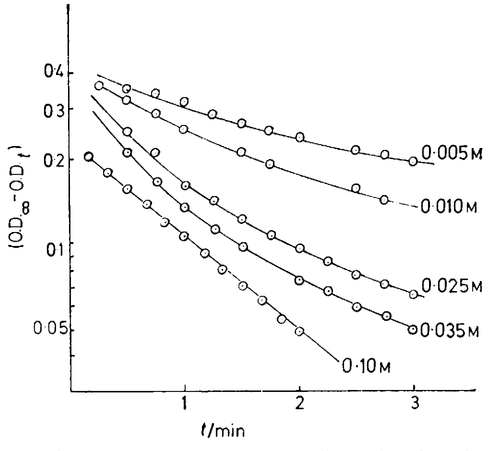


FIGURE 3 First-order plots for the hydrolysis of *p*-nitrophenyl malonate in D_2O, catalysed by various concentrations of *N*-methylmorpholine buffer (50% free base; concentration given is that of free amine), at 39.6 °C and ionic strength 1.0

Trapping Experiment.—We suggest below that the general base catalysed hydrolysis of *p*-nitrophenyl hydrogen malonate involves a keten intermediate. This should be a highly reactive acylating agent, and might be trapped by a suitable nucleophile which does not react directly with the ester. We carried out a series of experiments to this end using aniline.

(1) *p*-Nitrophenyl hydrogen malonate (13.2 mg) was dissolved in 0.4M-phosphate buffer (5 ml; 75% free base) containing aniline (0.07M). The solution was incubated at 39 °C for 1 h, then extracted with CH_2Cl_2 to remove aniline and *p*-nitrophenol, and a sample was acidified (HCl) and diluted with an equal volume of MeOH. T.l.c. on silica (developed with 4 : 1 $CHCl_3$–MeOH) showed a spot running with an authentic sample of the monoanilide of malonic acid (R_F 0.43; prepared by the method of Staudinger and Ott [11]).

(2) The u.v. spectrum of the products of reaction under the conditions described in (1) showed the absorption ($\lambda_{max.}$ at 242 nm) expected for the monoanilide.

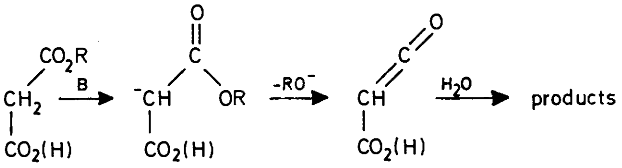
(3) When *p*-nitrophenyl hydrogen malonate (40 µl of a solution in dioxan containing 12.62 mg ml^{-1}) was injected into phosphate buffer (2 ml; 75% free base; various concentrations) containing aniline (0.07M), and hydrolysed for 3—4 h at 39 °C, the concentration of monoanilide produced could be estimated (after extraction with CH_2Cl_2), from the intensity of the absorption at 242 nm ($\varepsilon_{max.}$ 11 600). The rate of release of *p*-nitrophenolate was not changed by the addition of the aniline, but 73 ± 1% of anilide was produced in 0.04, 0.12, and 0.24M-buffer.

DISCUSSION

It is clear that the complex buffer-catalysed hydrolysis of *p*-nitrophenyl malonate anion described in this paper is quite different from familiar reactions involving nucleophilic attack on the ester carbonyl group. It is observed specifically for the most reactive esters: the hindered base 2,6-lutidine is a more effective catalyst than pyridine: and catalysis by tertiary amines is many hundreds of times more effective than it is in the hydrolysis of *p*-nitrophenyl acetate. [Under the conditions of our experiments *N*-methylmorpholine and triethylamine catalyse the hydrolysis of *p*-nitrophenyl acetate in a simple second-order reaction, with rate constants of 2.5×10^{-3} and 10 dm^3 mol^{-1} min^{-1}, respectively at 29 °C, some 2 000 times smaller than k_B for the reactions of these bases with *p*-nitrophenyl malonate (Table 2).]

There is also strong evidence that the reaction involves cleavage of a C–H bond of the malonate methylene group, and that this step is rate-determining under certain conditions. The reaction is not observed at all for derivatives of dialkylmalonic acids, which have no such C–H bond; the central CH_2 group of ethyl hydrogen malonate exchanges with deuterium from solvent D_2O, in a reaction which is catalysed by the same set of buffers; and when *p*-nitrophenyl malonate is hydrolysed in D_2O in the presence of concentrations of buffer chosen so that exchange and hydrolysis should proceed at comparable rates, hydrolysis is seen to slow down as the reaction proceeds, as the starting material is gradually converted into the less reactive CD_2 compound.

The simplest interpretation of these results is that the catalyst acts as a general base to remove a proton from the methylene group of the malonate ester, generating an intermediate carbanion, which can break down to give a keten if the leaving group is good enough (see Scheme 1). When *p*-nitrophenyl malonate was hydrolysed in the presence of a high concentration of phosphate buffer containing 0.07M-aniline, the major product was the monoanilide, $PhNH{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$, obtained in 73% yield. Under these conditions aniline does not react with the starting material, or catalyse its hydrolysis detectably, so it must be reacting after the rate-determining step with an acylating agent produced during the reaction. This evidence is consistent with a mechanism involving a keten intermediate. We therefore limit further discussion to the *E*1cb mechanism. It is convenient to start with the proton transfer, since this step can be observed independently with a suitable ester in D_2O.

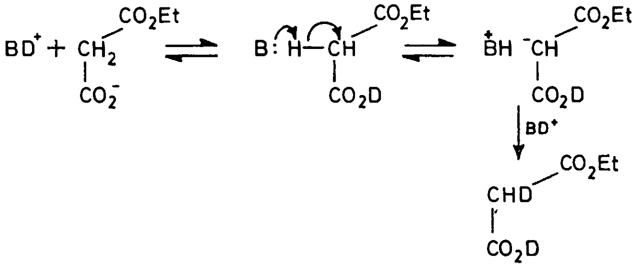


SCHEME 1

Deuterium Exchange Reaction.—We chose to study this reaction with ethyl hydrogen malonate, since this ester is stable under the conditions of our experiments, and complications associated with concurrent hydrolysis are avoided.

The reaction $EtO_2C{\cdot}CH_2{\cdot}CO_2^- \xrightarrow{D_2O} EtO_2C{\cdot}CD_2{\cdot}CO_2^-$ is catalysed by buffers (phosphate, *N*-methylmorpholine, triethylamine), and the results fall into a logical pattern. Three separate reactions can be distinguished.

(1) Catalysis by phosphate and *N*-methylmorpholine involves a reaction between ethyl hydrogen malonate and the conjugate base of the buffer. This reaction is apparent as general acid catalysis, since the ester is present, at the pD values employed, almost exclusively as the anion (Scheme 2). The rate constants observed can be accounted for quantitatively, as described in the Experimental Section, by using known rate constants for the removal of protons from malonate diesters.



SCHEME 2

(2) Catalysis by triethylamine is a reaction between the amine and the ester anion. The simplest mechanism

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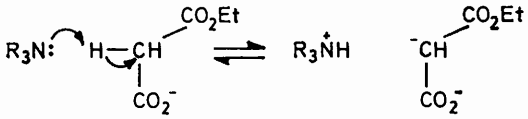
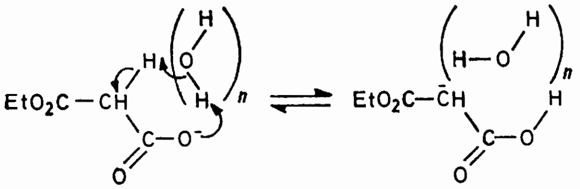
[11] H. Staudinger and E. Ott, *Ber.*, 1921, **41**, 2208.

for this process is that in Scheme 3. (A small contribution from a reaction of this type may be observed with *N*-methylmorpholine.) The reaction evidently requires a strong neutral base; carbonate is not a catalyst, presumably because it is anionic; and, since extrapolation to zero buffer concentration gives the same k_0 over the full pH range studied, it appears that hydroxide is ineffective also.

(3) Hydroxide will of course remove a proton from a neutral malonate ester. But from the known rates of such reactions[9] we calculate (see Results section) that the observed pH-independent exchange reaction of ethyl malonate anion (2×10^{-2} min^{-1} at 39.6 °C) is several hundred times too fast to be accounted for in terms of a reaction between HO^- and undissociated ethyl hydrogen malonate. It is also some three times faster than the H_2O-catalysed enolisation of diethyl malonate,[9] though on electronic grounds the reaction would be expected to be much slower for the ester anion. A reasonable explanation is that the C–H proton is not lost, but transferred to the carboxylate group, presumably *via* one or more molecules of water (Scheme 4).

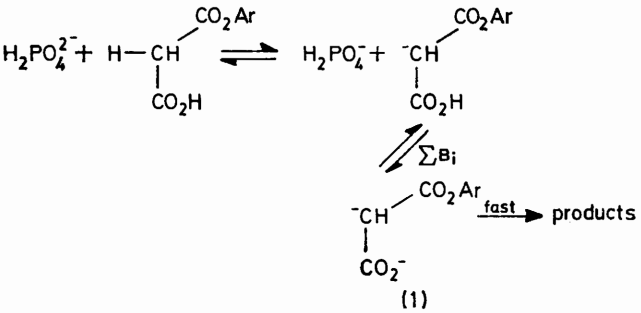


SCHEME 3



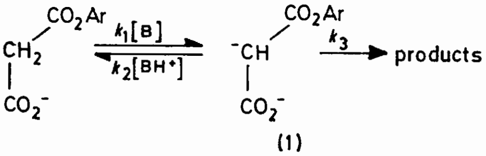
SCHEME 4

Hydrolysis; Catalysis by Oxyanions.—Catalysis of hydrolysis follows the same overall pattern as found for deuterium exchange. No hydroxide reaction is apparent up to pH 10, and catalysis by carbonate is a slow reaction, with k_B in the region expected for nucleophilic catalysis of a normal *p*-nitrophenyl ester. We therefore consider that there is no significant proton transfer reaction between *p*-nitrophenyl malonate anion and oxyanions. Catalysis by the weaker general bases acetate and phosphate must therefore involve reactions of the conjugate base of the buffer with undissociated *p*-nitrophenyl hydrogen malonate. The observed value of k_B for acetate can be accounted for on this basis, but phosphate shows complex behaviour: k_B decreases with increasing pH (Figure 2), but less than expected for a simple reaction between phosphate dianion and undissociated *p*-nitrophenyl hydrogen malonate. It is possible that the further ionisation of the carboxy-group of the first-formed carbanion is kinetically significant at pH 6—7, providing an indirect route to the highly reactive dianion (1), which is accessible directly with amine bases. The complex rate laws describing mechanisms of this sort, and the large amounts of accurate data required to test them, deterred us from further investigation of this point.



SCHEME 5

Amine-catalysed Hydrolysis.—The results shown in Table 2 are calculated on the basis of a rate equation (ii) of the form expected for a simple two-step reaction, with one of the steps buffer-catalysed. The deuterium exchange results, and much precedent, suggest that the buffer-catalysed step is the cleavage of the C–H bond. The simplest mechanism would then be that in Scheme 6. This requires the reaction of the ester anion to depend on the concentrations of the conjugate base of the buffer at low buffer concentrations, and this is the kinetic behaviour observed with amine buffers. For those amines measured at more than one pH, the second-order rate constant, k_B (Table 2), calculated for reaction with the free base, is constant within experimental error. Under these conditions of low buffer concentration the cleavage of the C–H bond should be securely rate-determining, so the observed rate constants might be expected to be similar to those for deuterium exchange. In fact the observed values of k_B are much larger than those for deuterium exchange into ethyl malonate. Where the data are comparable (with triethylamine, and perhaps *N*-methylmorpholine) k_B is several hundred times larger for hydrolysis of the *p*-nitrophenyl ester.



SCHEME 6

This might be a consequence of internal return[12] [(a) in Scheme 7] of the ion pair created by the removal of the proton, with elimination (b) several hundred times faster than the fastest process (c) leading to deuteriation of the carbanion (Scheme 7). But it is clear from the hydrolysis reactions run in D_2O that elimination and deuterium exchange occur at comparable rates for *p*-nitrophenyl malonate, under conditions where steps (a)

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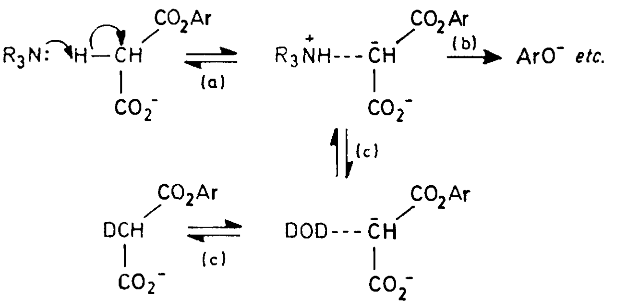
[12] D. J. Cram in 'Fundamentals of Carbanion Chemistry, Academic Press, New York, 1965, ch. 1.

and (b) also go at similar rates (see below). The true explanation of the difference in rates must therefore simply be that proton removal from *p*-nitrophenyl malonate is substantially faster than from ethyl malonate anion. This is at any rate qualitatively predictable, since delocalisation from the ester oxygen into the nitrophenyl ring must reduce π-donation into the carbonyl group, making it a better π-acceptor than the carbonyl of the ethoxycarbonyl group (*cf.* the greater kinetic acidity of thiolacetates in comparison with oxygen esters [13]). The effect can be seen with malonate diesters, where the removal of the C–H proton by water is about 100 times faster from ethyl 2- and 4-nitrophenyl malonates [5] than it is from diethyl malonate; [9] and would be expected to be greater for the less stable carbanion (1), which depends for delocalisation more heavily on its single ester group.



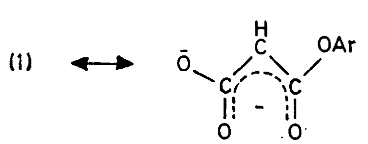
SCHEME 7

If we accept that amine-catalysed hydrolysis is a reaction of the type shown in Scheme 6, then the dependence of rate on catalyst concentration is as described in equation (iv). The empirical rate coefficients given in Table 2 can thus be identified, with $k_B = k_1$, and k_∞ equal to the composite constant $k_1k_3k_B/k_2a_H$, where K_B is the dissociation constant of the buffer. The data are not extensive enough for a detailed analysis, but it is clear that k_1 increases with increasing pK_B in the series of tertiary amines. And k_2/k_3 can be calculated for *N*-methylmorpholine, Tris, 2,6-lutidine, and pyridine as 67, 2.8, 8.9, and 21, respectively. Since k_2 represents the protonation of a strongly basic carbanion, which may be expected to be close to diffusion-controlled, k_3 is evidently very large, of the order of 10^8—10^9 min^{-1}. It is noteworthy that the values obtained for k_2/k_3 for the reaction of the carbanion (1) are of the same order of magnitude as those found by Holmquist and Bruice [3] for the similar reactions of the anion from ethyl *o*-nitrophenyl malonate. Evidently the stabilisation of the carbanion by the second ester group affects the transition states for protonation and elimination to much the same extent, which is reasonable, since the transition state must be very early in each case, and thus close in structure to the carbanion.

From the value of k_2/k_3 (67) for catalysis by *N*-methylmorpholine it is apparent that the rate of protonation of the carbanion is equal to the rate of elimination of ArO$^-$ when the amine concentration is (1/67 =) 1.5×10^{-2}M. When *p*-nitrophenyl malonate anion was hydrolysed in D_2O containing various concentrations of *N*-methylmorpholine buffer the apparent first-order rate constant fell gradually during the reaction (Figure 3). Approximate initial and final rates can be obtained from the data, and their ratio is seen to pass through a maximum of about 3 near 4×10^{-2}M-amine. These facts are accommodated nicely by the proposed mechanism, because a substantial deuterium isotope effect is expected for the initial proton removal step. When $k_2[BH^+]$ is twice k_3, at 3×10^{-2}M-base, the rates of hydrolysis and of conversion into twice-deuteriated malonate are equal. The value of k'_2/k'_3 for the CD_2 compound will be greater than for the CH_2 compound by a factor almost equal to the primary isotope effect on k_2, so that under these conditions the first step is still rate-determining for the CD_2 compound. As reaction proceeds the stock of CH_2 compound is progressively depleted by hydrolysis and exchange, so that the observed hydrolysis in the later stages is almost entirely that of the slower CD_2 compound. At much lower concentrations of catalyst, $k_3 > k_2$, and the CH_2 compound is hydrolysed with little conversion into CD_2. At higher catalyst concentrations a pre-equilibrium is set up, and the observed hydrolysis is almost entirely that of the CD_2 compound; isotope effects on k_3 and the pre-equilibrium are small, and the observed rate is the same as in H_2O under the same conditions.

Conclusions.—In addition to the expected reactions of alkyl and aryl hydrogen malonates, we find that tertiary amines can remove a C–H proton from monoester anions, to generate the strongly basic carbanion (1). Concentrations of (1) must be very low, but are sufficient to lead to rapid hydrolysis by the *E*1cb route when the ester carries a good (nitrophenoxy) leaving group. This reaction is not observed at all with *p*-nitrophenyl acetate, so the stabilising effect of the CO_2^- group on the adjacent carbanion centre, modest though it must be, is evidently decisive.

This effect is familiar in the stabilisation of the carbonate ion, which is over 5 pK units less basic than hydroxide; and indeed the best representation of the dianion (1) is as a vinylogous carbonate (1a). Quantitatively



(1a)

the effect should be proportional to σ^-, which is 0.24 (based on the ionisation of substituted phenols [12]), about the same as that of Br. The combined carbanion-stabilising effects of the CO_2^- and CO_2Et groups should thus match those of one CN or sulphone group. And there is evidence, discussed above, that the combination of CO_2^- and *p*-nitrophenoxycarbonyl is more effective still.

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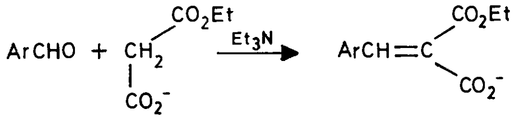
[13] G. E. Lienhard and T. C. Wang, *J. Amer. Chem. Soc.*, 1968, **90**, 378.

Finally, it is likely that the dianion (1) is an intermediate in certain Knoevenagel reactions. For example, Galat [14] condensed methyl and ethyl hydrogen malonates with aromatic aldehydes in refluxing pyridine containing a catalytic quantity of piperidine, to give cinnamate esters in good yield. These conditions are commonly used for condensations with malonic acid,[15] and the role of the piperidine is probably the activation of the carbonyl reagent by formation of the iminium compound. If the dianion [1] is an intermediate it should be advantageous to use more strongly basic conditions for reactions of malonate half esters; and we find that potassium ethyl malonate condenses with *p*-nitrobenzaldehyde in ethanol in the cold in the presence of triethylamine. The product is a single isomer of the half-ester of the benzylidenemalonic acid (Scheme 8).



SCHEME 8

We thank the Salters' Company for a Scholarship (to G. J. L.).

[6/593 *Received, 29th March,* 1976]

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[14] A. Galat, *J. Amer. Chem. Soc.*, 1946, **68**, 376.

[15] G. Jones, *Org. Reactions*, 1967, **15**, 204.