Intramolecular Displacement of Alkoxide Ions by the Ionised Carboxy-group: Hydrolysis of Alkyl Hydrogen Dialkylmaleates

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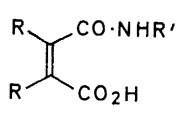
The pH-independent hydrolysis reactions of the title ester acids and their anions, and the acid catalysed hydrolysis of the ester acids, are all subject to highly efficient intramolecular nucleophilic catalysis. The carboxylate group of the ester anions can displace leaving groups as poor as isopropoxide, 10^{13} times more basic, in an unassisted reaction which shows the highest sensitivity to leaving group ever measured for ester hydrolysis. Intramolecular catalysis by the carboxy-group is more efficient for esters derived from alcohols with $pK_a > 13{\cdot}6$, and is itself subject to external general base catalysis.

OUR interest in the mechanisms involved in enzymic catalysis has led us to develop and study simple systems which show extreme reactivity under mild conditions of temperature and pH. The amide group of a dialkylmaleamic acid (1), for example, is hydrolysed with participation by the neighbouring carboxy-group with a half-life of about 1 s at 39°.[1] This is a consequence of a powerful driving force for cyclisation in these compounds: the equilibrium constants for formation of the dialkylmaleic anhydride from the diacid, for example are 5 and 25 for the dimethyl [2] and di-isopropyl [3] compounds, respectively, and that for the di-t-butyl compound is higher still (this work).

The efficiency of intramolecular catalysis by the carboxy-group should therefore be enhanced for other reactions involving cyclisation. A preliminary study [4] using methyl hydrogen di-isopropylmaleate (2) showed the expected fast hydrolysis at low pH, evidently catalysed by the carboxy-group. But the ester is also readily hydrolysed in a pH-independent reaction between pH 8 and 14, which must involve catalysis by the carboxylate group. It is well known that the carboxylate group can displace aryloxide anions from aryl esters,[5] but the displacement of simple alkoxide ions has not been observed previously. We report a moderately detailed investigation of the mechanism of the carboxylate catalysed reaction, which is kinetically uncomplicated, and of the carboxylic acid reaction, which is subject to external general base catalysis. We have used derivatives of three dialkylmaleic acids (3; R = Me, Pr^i, or Bu^t) and seven alcohols (R'OH).



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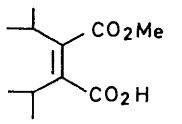

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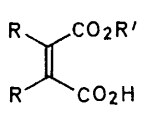


(3)

EXPERIMENTAL

The materials were obtained commercially or as previously described.[1] Di-isopropylmaleic anhydride was prepared by the method of Eberson and Welinder [3] and di-t-butylmaleic anhydride was a gift from Professor H. G. Viehe.

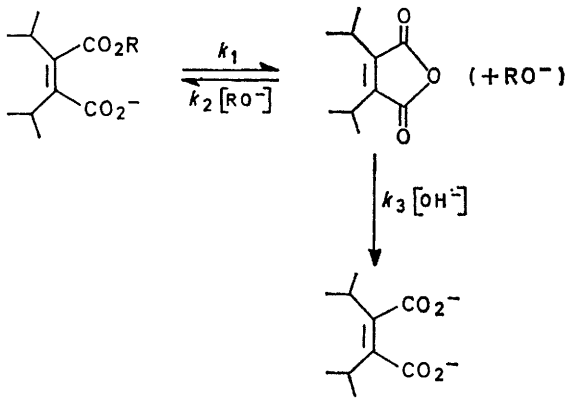
Alkyl Hydrogen Dialkylmaleates.—These were prepared by dissolving a small weighed amount of sodium in the alcohol concerned, then adding to the resulting solution of alkoxide an equivalent amount of the maleic anhydride. The anhydride dissolved on swirling, and this solution was generally used directly for kinetic work. This procedure proved satisfactory for all the esters studied, except those derived from prop-2-yn-1-ol. For these derivatives the excess of alcohol was evaporated off, and the white solid obtained dried carefully before dissolving in dry dimethyl sulphoxide. The solid showed the i.r. bands expected for a sodium alkyl dialkylmaleate (ester C=O at 1705, CO_2^- at 1570 and 1410 cm^{-1} for sodium prop-2-ynyl di-isopropylmaleate; 1695, 1580, and 1400 cm^{-1} for sodium methyl dimethylmaleate), but correct elemental analyses could not be obtained for these reactive esters. We have prepared 15—20 sodium alkylmaleates by the technique described: in every case tried we could isolate a solid with the expected i.r. bands,

[1] A. J. Kirby and P. W. Lancaster, *J.C.S. Perkin II*, 1972, 1206.
[2] L. Eberson, *Acta Chem. Scand.*, 1964, **18**, 1276.
[3] L. Eberson and H. Welinder, *J. Amer. Chem. Soc.*, 1971, **93**, 5821.
[4] M. F. Aldersley, A. J. Kirby, and P. W. Lancaster, *J.C.S. Chem. Comm.*, 1972, 834.
[5] T. C. Bruice and S. J. Benkovic, in 'Bioorganic Mechanisms,' Benjamin, New York, vol. 1, 1966, p. 176.

but we could obtain correct analyses only for less reactive esters. These latter included sodium methyl maleate itself, and the corresponding half-ester salts from cyclohexene and cyclopentene-1,2-dicarboxylic acids, but not derivatives of dimethyl-, di-isopropyl-, or di-t-butyl-maleic acids. Since the method of preparation does not leave the structures of the starting materials in doubt we have used the readily prepared solutions of the ester salts for the kinetic studies described below.

Kinetic Methods and Results.—Methods and equipment were generally as described previously for the work on the corresponding amides,[1] save that reactions were initiated by injecting a few μl of a stock solution of ester, in the alcohol from which it was derived, into 2 ml of aqueous buffer pre-incubated at the temperature of the experiment in the cuvette. At pH > 6 the disappearance of the ester was followed, by using a wavelength close to 240 nm. Below pH 6 the appearance of the anhydride (the stable form of the diacid) was followed at its absorption maximum (near 265 nm in each case). Between pH 3 and 6 the anhydride first formed was hydrolysed in a relatively slow second reaction, so that the initial rapid increase in optical density was followed by a much slower decrease. The difference in rate between the two steps was large enough for the optical density maximum to be taken as the end-point of the first reaction, and all rate constants quoted are based on excellent first-order plots. Application of the simpler technique of finding the isosbestic point for the anhydride hydrolysis reaction was not possible because this reaction is itself complex, being subject to nucleophilic catalysis by the buffers used.

This deviation from simple pseudo-first-order kinetics provides evidence that the first product of the reaction is the anhydride, and thus that intramolecular nucleophilic catalysis is involved in the reaction catalysed by the carboxy-group (the predominant reaction up to about pH 7 for the methyl esters). Another deviation provides similar evidence for the carboxylate-catalysed hydrolysis.



The observed rates of hydrolysis at high pH of our most reactive esters, the prop-2-ynyl derivatives, were found to depend on the size of the sample injected, and thus apparently on the initial concentration of the substrate. The observed rate constants (between pH 9 and 14) decreased with increasing substrate concentration. The source of this deviation turns out to be the reverse of the initial anhydride formation: the prop-2-yn-1-ol in which the substrate was dissolved is sufficiently acidic to be significantly dissociated at pH 9—14, and the prop-2-ynyloxide in the reaction solution competes favourably with the hydroxide for the anhydride intermediate.

The simple steady state treatment gives (at constant pH) equations (i) and (ii). Thus a reciprocal plot of k_{obs} against

$$k_{obs} = k_1k_3/(k_3 + k_2[RO^-]) \quad (i)$$

$$1/k_{obs} = 1/k_1 + k_2[RO^-]/k_1k_3 \quad (ii)$$

$[RO^-]$ should be linear, with the intercept giving (the reciprocal of) the derived rate constant k_1, and slope $= k_2/k_1k_3$. We varied $[RO^-]$ by injecting 2, 4, 6, and 8 μl samples of stock solution of alkoxide in prop-2-yn-1-ol, and using the final optical density as a measure of $[RO^-]$ obtained the expected linear reciprocal plots at several different pH values. The treatment was confirmed by using 20% free base alkoxide as the buffer over a much wider concentration range (0·1—0·3M total buffer). This gave a value of k_1 consistent with other measurements, and allowed a calculation of $k_2/k_3 = 33$ at pH 12·8. This shows that the second order rate constant for attack of prop-2-ynyl oxide on di-isopropylmaleic anhydride is greater by about one order of magnitude then the rate constant for attack by hydroxide (pK_w *ca.* 13·3 under these conditions). This is in agreement with expectation: Gilchrist and Jencks have found a similar ratio for attack of hydroxide and several alkoxides on reactive carbonyl compounds.[6]

This is excellent evidence that the anhydride is an intermediate in the anion reaction. A less laborious way of obtaining the desired rate constant (k_1) was to evaporate the excess of prop-2-yn-1-ol from the alkoxide, which was then taken up in dimethyl sulphoxide. The problem then disappeared. The rate constants obtained by the two methods were identical within experimental error, but only data obtained by the direct method, using stock solutions in dimethyl sulphoxide, are employed in this paper. No interference from the back reaction was observed with the less reactive esters.

The kinetic evidence for the anhydride intermediate is supported by product studies. At low pH the anhydride precipitates out if higher than spectroscopic concentrations of alkyl di-isopropylmaleates are hydrolysed. At higher pH, where the hydrolysis taking place is that of the maleate anion, the anhydride is hydrolysed faster than it is formed, but it can be isolated by repeated extraction of the hydrolysing mixture of the most reactive esters with ether. For example, sodium prop-2-ynyl di-isopropylmaleate prepared from 15 mg of anhydride gave a 50% recovery of di-isopropylmaleic anhydride when dissolved in 10 ml of 0·1M-carbonate buffer, pH 8·95, and shaken with ether.

The full set of kinetic data for the hydrolysis of methyl hydrogen di-isopropylmaleate is given in Tables 1 and 2.* Table 1 gives data obtained in HCl and NaOH at high and low pH; Table 2 gives the results of experiments in which the buffer concentration was varied. The k_0 values of Table 2,* obtained by extrapolation of the linear second-order buffer catalysis plots to zero buffer concentration, complete the pH–rate profile (Figure 2). The buffer catalysis data show that there is no detectable catalysis of the hydrolysis of the ester anion, but strong catalysis of the hydrolysis of the ester acid. The rate constants given are calculated for buffer catalysis of the hydrolysis of the ester

* Tables 2 and 3 are available as Supplementary Publication No. SUP 21074 (3 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1973, Index Issue.

[6] M. Gilchrist and W. P. Jencks, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.

acid, since this is the form present at low pH, and is also the more reactive ionic form. The catalytic constants increase with increasing fraction of the free base form of the buffer and are consistent with only this form being active (Figure 1). The corrections for substrate ionisation are simply made: below pH 5 hydrolysis is due entirely to the ester acid; the fraction of ester acid at a given pH is thus given by dividing k_0 at the pH concerned by the limiting value of k_0

TABLE 1

Kinetic data for the hydrolysis of methyl hydrogen di-isopropylmaleate at 39° and ionic strength 1·0

Conditions	No of runs	k_{obs}/min^{-1}
1M-HCl	6	1·50
0·5M-HCl	6	1·32
0·2M-HCl	6	1·20
0·1M-HCl	6	1·21
0·04M-HCl	6	1·20
0·02M-HCl	6	1·17
0·01M-HCl	8	1·16
0·01—0·1M-DCl in D_2O	3	0·468
0·01—0·1M-HCl at 15·8°	3	0·174
0·01—0·1M-HCl at 28·6°	3	0·542
0·01—0·1M-HCl at 49·5°	3	2·43
0·01M-NaOH	3	$5·60 \times 10^{-3}$
0·1M-NaOH	3	$5·77 \times 10^{-3}$
0·1M-NaOD in D_2O	1	$3·54 \times 10^{-3}$
1M-NaOH	3	$6·05 \times 10^{-3}$
pH 9·67—14 at 15·5°	3	$2·73 \times 10^{-4}$
pH 9·67—14 at 28·8°	3	$1·64 \times 10^{-4}$
pH 9·67—14 at 49·5°	3	$2·25 \times 10^{-2}$

For acid (0·01—0·1M-HCl) $\Delta H^{\ddagger} = 13·9 \pm 0·2$ kcal mol^{-1}, $\Delta S^{\ddagger} = 21·9$ cal deg^{-1} mol^{-1}, $k_H/k_D = 2·51$. For anion (pH 9·67—14) $\Delta H^{\ddagger} = 23·3 \pm 0·4$ kcal mol^{-1}, $\Delta S^{\ddagger} = -2·2$ cal deg^{-1} mol^{-1}, $k_H/k_D = 1·64$.

at pH 1—2, *i.e.* 1·20. The variation of this fraction with the pH gives an apparent pK_a of 3·72, in the expected region for an acid of this type.

We have collected a similar though less extensive set of data on methyl hydrogen di-t-butylmaleate. The rate constants concerned are similar, and in most cases nearly identical with those in Tables 1 and 2, so these data are not tabulated. (For example $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the ester acid are $14·2 \pm 0·2$ kcal mol^{-1} and $-20·8$ cal deg^{-1} mol^{-1}, respectively. We also measured these parameters for methyl hydrogen dimethylmaleate, and found values of 14·0 kcal mol^{-1} and $-21·7$ cal deg^{-1} mol^{-1} for the hydrolysis of this ester acid.) Evidently it is sufficient for high reactivity in this system to have two unconnected alkyl groups on the double bond: the rate of hydrolysis does not depend significantly on their size.

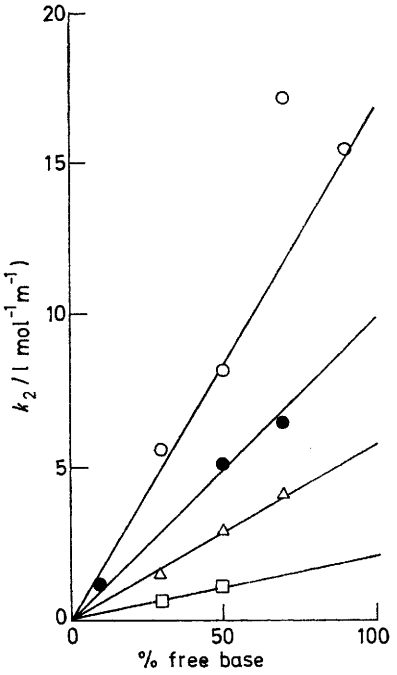


FIGURE 1 Buffer catalysis data for the hydrolysis of methyl hydrogen di-isopropylmaleate. The data are from Table 2, for (increasing order of reactivity) chloroacetate, methoxyacetate, formate, and acetate catalysis. The points are the k_2 values of Table 2, corrected for substrate ionisation by the factor of $1·20/k_0$ (see text)

Finally, we have varied the one structural parameter remaining, the nature of the leaving group. This does lead to large changes in the reactivity of the ester anion. Rates of hydrolysis were measured for seven alkyl di-isopropylmaleates and four alkyl di-t-butylmaleates at three different pH values in the pH-independent region, from pH 9·65 to 14. A more extensive set of data was collected for prop-2-ynyl hydrogen di-isopropylmaleate, which is of interest because the rates of hydrolysis of the ester anion and acid are equal. As a result the rate of hydrolysis is independent of pH over the whole range from pH 1 to 14. The remarkable pH–rate

TABLE 4

Hydrolysis data for sodium alkyl dialkylmaleates (3) at 39° and ionic strength 1·0

R′	pK_a of R′OH [a]	k_{hyd}/min^{-1} under standard conditions			k_{hyd} for anion
		[b]	[c]	[d]	[e]
A Di-isopropylmaleates, R = Pr^i					
HC≡C·CH$_2$	13·55	2·26	2·26	2·17	2·22
ClCH$_2$·CH$_2$	14·31	0·173	0·161	0·203	0·183
MeO·CH$_2$·CH$_2$	14·82	$1·87 \times 10^{-2}$	$1·89 \times 10^{-2}$	$1·83 \times 10^{-2}$	$1·87 \times 10^{-2}$
EtO·CH$_2$·CH$_2$	15·12	$1·66 \times 10^{-2}$	$1·61 \times 10^{-2}$	$1·63 \times 10^{-2}$	$1·63 \times 10^{-2}$
Me	15·49	$6·07 \times 20^{-3}$	$5·77 \times 10^{-3}$	$6·05 \times 10^{-3}$	$5·96 \times 10^{-3}$
Et	15·90	$1·39 \times 10^{-3}$	$1·36 \times 10^{-3}$	$1·39 \times 10^{-3}$	$1·38 \times 10^{-3}$
Pr^i	16·57 [f]	$2·13 \times 10^{-4}$	$2·10 \times 10^{-4}$	$2·02 \times 10^{-4}$	$2·08 \times 10^{-4}$
B Di-t-butylmaleates, R = Bu^t					
HC≡C·CH$_2$	13·55	2·24	1·64	2·06	2·0
MeO·CH$_2$·CH$_2$	14·82	$1·88 \times 10^{-2}$	$1·89 \times 10^{-2}$	$1·81 \times 10^{-2}$	$1·86 \times 10^{-2}$
Me	15·49	$7·72 \times 10^{-3}$	$7·83 \times 10^{-3}$	$7·68 \times 10^{-3}$	$7·74 \times 10^{-3}$
Et	15·90	$1·49 \times 10^{-3}$	$1·46 \times 10^{-3}$	$1·39 \times 10^{-3}$	$1·45 \times 10^{-3}$

[a] pK_a Values measured by P. Ballinger and F. A. Long (*J. Amer. Chem. Soc.*, 1959, **81**, 1050) except for propan-2-ol. [b] 0·005M-Carbonate buffer, pH 9·65. [c] 0·01M-NaOH. [d] 1M-NaOH. [e] Mean of previous three values. [f] Value calculated by Takahashi and Cohen;[7] see text.

profile for the hydrolysis of this ester is shown in Figure 2: the data are given in Table 3: * the rate constant for hydrolysis is 2·2 ± 0·1 min^{-1} (39°; ionic strength 1·0), and for the anion $\Delta H^{\ddagger} = 19{\cdot}1$ kcal mol^{-1}, $\Delta S^{\ddagger} = -4{\cdot}1$ cal deg^{-1} mol^{-1}, and $k_H/k_D = 1{\cdot}41$.

The full set of data for the eleven ester acids referred to above appears in Table 4. In each case the rate of hydrolysis is independent of pH from pH 9·65 to 14. (The pK_a given for propan-2-ol is that calculated by Takahashi and Cohen [7] from σ^* values and their accurate value of ρ.)

DISCUSSION

The results described in this paper confirm and extend the conclusions reached by Thanassi and Bruice [8] in their study of the hydrolysis of alkyl and aryl hydrogen phthalates. Those authors also observed buffer catalysis of the hydrolysis of the ester acids, and found that the ester anion is hydrolysed more readily than the acid for compounds with good leaving groups. Our system is much more reactive: methyl hydrogen di-isopropylmaleate is hydrolysed some 40,000 times faster than methyl hydrogen phthalate at 39°, and the factor is close to 10^5 for the anions. Thanassi and Bruice did not measure the anion reaction for leaving groups poorer than prop-2-ynyloxide because the reactions concerned are too slow: we have not measured this reaction for leaving groups *better* than prop-2-ynyloxide because the reaction becomes too fast. In our system the neighbouring carboxylate group is a more powerful catalyst than 1M-NaOH, and can displace groups (*e.g.* isopropoxide) which are more than 10^{13} times more basic. And in every case we have measured the carboxy-group is more effective still: the half-life of methyl hydrogen di-isopropylmaleate between pH 1 and 2 is 35 s. Nevertheless, the pattern of reactivity which emerges is similar to that found [8] for the corresponding phthalate half-esters, and our mechanistic discussion can be applied to this, and other similar systems, also.

We have strong evidence, described in the Experimental section, that the dialkylmaleic anhydride is the initial product of hydrolysis of both acid and anion forms of the ester. The anhydride is the thermodynamically stable form of the diacid, and so is the final product at low pH. At high pH it is rapidly hydrolysed and thus a transient intermediate. Our evidence that it is formed on hydrolysis of the ester anion is described in the Experimental section. Data for the hydrolysis of dialkylmaleic anhydrides are available,[1,9] and we will discuss the mechanism of hydrolysis only as far as the formation of the anhydride.

Figure 2 shows pH–rate profiles for the hydrolysis of three alkyl hydrogen dialkylmaleates. For prop-2-ynyl hydrogen di-isopropylmaleate this consists of a straight line of zero slope: the rate of hydrolysis is the same for both ionic forms of the ester, and is not increased in 0·1M-HCl or M-NaOH. A similar pH–rate profile was found for prop-2-ynyl hydrogen phthalate between pH 2 and 4·5 by Thanassi and Bruice: [8] evidently the factors inducing the very high reactivity in our system affect the carboxylic acid and carboxylate catalysed mechanisms equally.

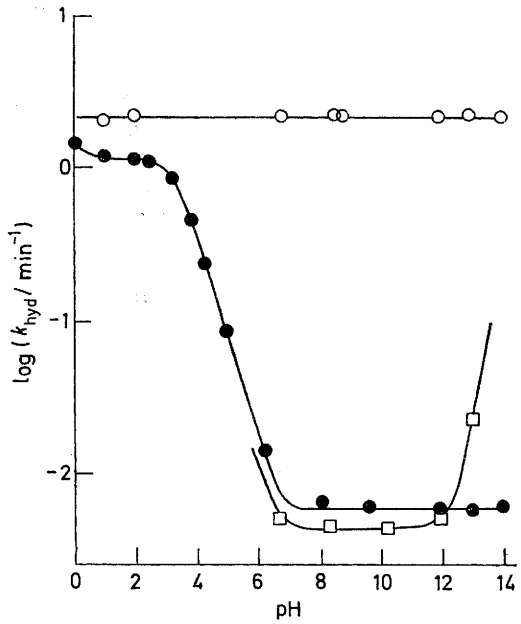
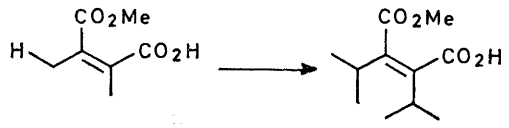


FIGURE 2 pH–Rate profiles for the hydrolysis of methyl hydrogen dimethylmaleate (□), methyl hydrogen di-isopropylmaleate (●) and prop-2-ynyl hydrogen di-isopropylmaleate (○), at 39° and ionic strength 1·0

The pH–rate profiles for the hydrolysis of methyl hydrogen dimethylmaleate and di-isopropylmaleate are closely similar up to pH 11. Each shows a narrow pH-independent region between pH 1 and 2, representing the hydrolysis of the ester acid, and a broader pH-independent region, due to the hydrolysis of the ester anion, above pH 7. In 1M-HCl significant external acid catalysis of hydrolysis is observed for both esters, and at high pH methyl dimethylmaleate shows a significant reaction with hydroxide ($k_{OH} = 0{\cdot}18$ l mol^{-1} min^{-1}, which is the expected region for an ester of this type [10]). But the hydrolysis of methyl di-isopropylmaleate is no faster in 1M-NaOH than at pH 8. Since steric effects are at least approximately equal for acid- and for base-catalysed ester hydrolysis [10] this observation is at first sight surprising. The simplest explanation of the result at high pH is that the change from methyl to isopropyl groups causes a sharp increase in steric hindrance of attack by hydroxide: the change is comparable with the introduction of a second *ortho*-substituent in a benzoate, as shown in (4), and could account for a large drop in reactivity.



(4)

* See footnote on p. 1505.

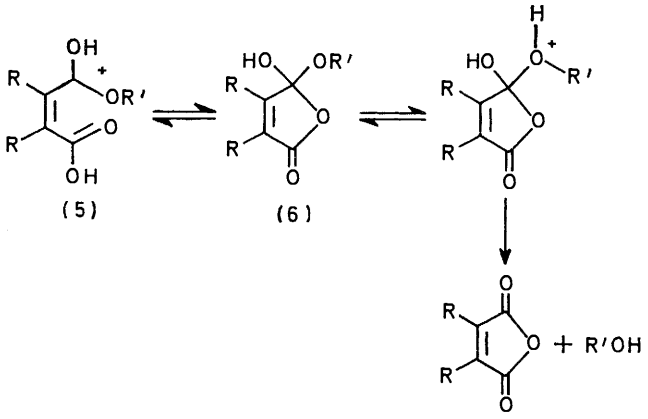
[7] S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, 1971, **36**, 1205.

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

[9] J. Koskikallio, *Acta Chem. Scand.*, 1956, **10**, 822.

[10] A. J. Kirby in 'Comprehensive Chemical Kinetics,' eds. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, vol. 10, 1972, p. 57.

But no comparable effect is observed on the acid-catalysed hydrolysis. On the contrary, k_H is higher for methyl hydrogen di-isopropylmaleate (0·37 l mol^{-1} min^{-1}) than for methyl hydrogen maleate (3 × 10^{-3} l mol^{-1} min^{-1}),[11] and is higher still for methyl hydrogen di-t-butylmaleate (k_H = 1·0 l mol^{-1} min^{-1}). This last rate constant is also several orders of magnitude higher than expected for acid catalysis of ester hydrolysis, and indicates that external acid catalysis of the hydrolysis of the alkyl hydrogen dialkylmaleates is not a simple $A_{AC}2$ reaction. The clear implication of these data is that this process also involves intramolecular catalysis by the carboxy-group. A mechanism which accounts satisfactorily for the observed catalysis is shown in Scheme 1. (This mechanism differs only in detail from one suggested by Hurst and Bender[12] to account for the corresponding reaction of methyl 2,6-dicarboxybenzoate.) In the dialkylmaleate systems steric hindrance affects the approach of an external nucleophile [of water to (5)] but not intramolecular attack. It is not an invariable rule that steric hindrance should be selective in this way, but

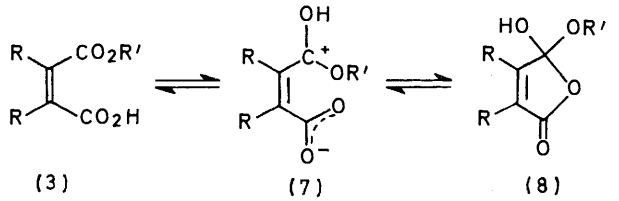


SCHEME 1

in the special case where the neighbouring functional group itself forms part of the steric hindrance of approach to an electrophilic centre this is to be expected. In fact the rate constants quoted above show that the intramolecular reaction of (5) is favoured by the factors which increase steric hindrance to external attack.

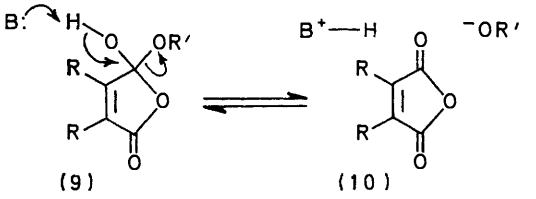
Hydrolysis of the Ester Acids.—For the three methyl hydrogen dialkylmaleates used in this work the activation parameters for hydrolysis in the pH-independent region between pH 1 and 2 are identical within experimental error, with $\Delta H^{\ddagger}$ = 14 kcal mol^{-1} and $\Delta S^{\ddagger}$ = 21—22 cal deg^{-1} mol^{-1}. There is a considerable solvent deuterium isotope effect: k_H/k_D = 2·51 for methyl hydrogen di-isopropylmaleate and 2·41 for the di-t-butyl derivative; and the reaction is general base catalysed. All this evidence is consistent with a mechanism which involves more than one molecule in the transition state, and is in contrast to the corresponding data for the hydrolysis of the ester anions, which are hydrolysed by a unimolecular mechanism. Kinetically the reaction is pH-independent, so the simplest mechanism will be one in which the transition state is composed of a molecule of ester acid and a molecule of solvent water.

We have considered various routes to the anhydride, including those suggested by Thanassi and Bruice,[8] and do not favour mechanisms which do not involve the tetrahedral addition compound (8) as an intermediate.

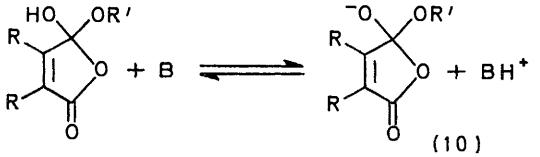


The fastest mode of breakdown of (8) will be the elimination of the carboxylate group to regenerate (7). To generate the anhydride, product (8) must lose R'OH, which will be a slower process under almost any conditions, so the rate-determining step of the overall reaction is expected to be the breakdown of (8) to products. The paths by which (8) is formed are not therefore amenable to kinetic study, but the route shown from the ester acid *via* the zwitterion (7), together with the acid-catalysed route *via* the conjugate acid (6) (Scheme 1) can readily account for the rapid formation of (8).

If the breakdown of (8) to anhydride is indeed the rate-determining step of the reaction, then we know that this step must be general base catalysed. Two different mechanisms could account for the observed kinetic properties of the reaction. The simplest is classical general base catalysis, with H–O and C–O bond cleavage concerted, as in (9). This mechanism has not found



favour with authors who have discussed reactions of this sort.[13] It implies an unlikely general acid catalysis of the attack of an alkoxide on an anhydride as the mechanism of the reverse reaction; and requires that the

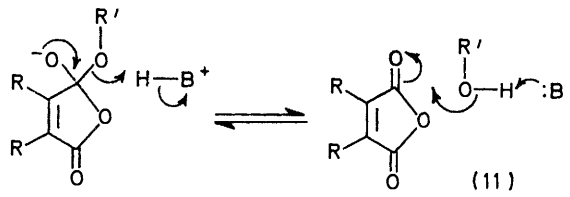


conjugate base (10) break down faster than its diffusion-controlled protonation by a general acid—otherwise (10) would be formed as an intermediate and only specific

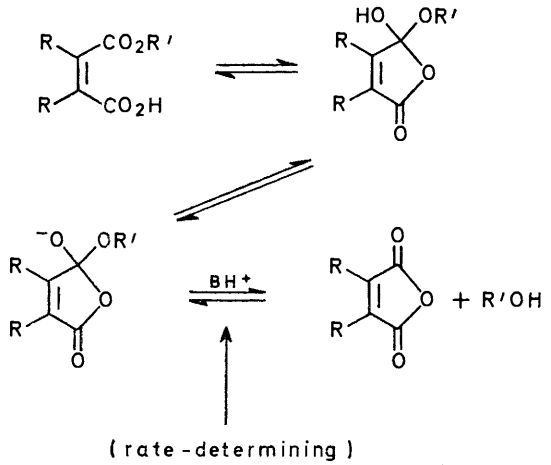
[11] P. W. Lancaster, Ph.D. Thesis, Cambridge, 1971.
[12] G. H. Hurst and M. L. Bender, *J. Amer. Chem. Soc.*, 1971, **93**, 704.
[13] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, p. 514.

base catalysis would be observed. The mechanism that we favour for the hydrolysis of the ester anion involves (10) as an intermediate, and we cannot account satisfactorily for the evidence without it.

The alternative mechanism, which would also be apparent as general base catalysis, is general acid



catalysis of the hydrolysis of (10). This is the reverse of the mechanism (11) commonly accepted for general base catalysis of the addition of hydroxy-compounds to carbonyl groups, and accounts satisfactorily for the low sensitivity of this reaction to the basicity of the leaving group (first noted by Thanassi and Bruice [8] and found in this work also). For a good (weakly basic) leaving group C–O cleavage will be easy but the transfer of the proton to the leaving group oxygen will be less favourable. We therefore propose the mechanism shown in Scheme 2 for



SCHEME 2

intramolecular catalysis of ester hydrolysis by the carboxy-group. The uncatalysed reaction of the ester acid, according to this mechanism, is the special case of Scheme 2 where $BH^+ = H_3O^+$. Figure 3 is a Brønsted plot of the buffer catalysis constants from Table 2, and includes a point calculated for catalysis of H_2O ($k_2 = 1{\cdot}20/55$ l mol^{-1} min^{-1}). There is a good linear correlation of all the points, as would be expected if the mechanism of Scheme 2 is correct. The Brønsted coefficient $\beta = 0{\cdot}46$ for general base catalysis is identical within experimental error with the β value of 0·47 found by Jencks and Carriuolo [14] for general base catalysis of the hydrolysis of the acyl-activated ester ethyl dichloroacetate, in which the breakdown of a similar tetrahedral intermediate is at least partially rate-determining. A β value of 0·46 for the forward reaction implies $\beta = 0{\cdot}54$ for the reverse reaction (11), addition of the hydroxy-compound to the carboxy-group. The hydration of aldehydes and ketones is a well known reaction of this type: it is general base catalysed, and measured values of β are generally close to 0·5.[15]

Hydrolysis of the Ester Anions.—The hydrolysis of the methyl di-isopropylmaleate anion is characterised by enthalpy and entropy of activation ($\Delta H^\ddagger = 23{\cdot}3$ kcal

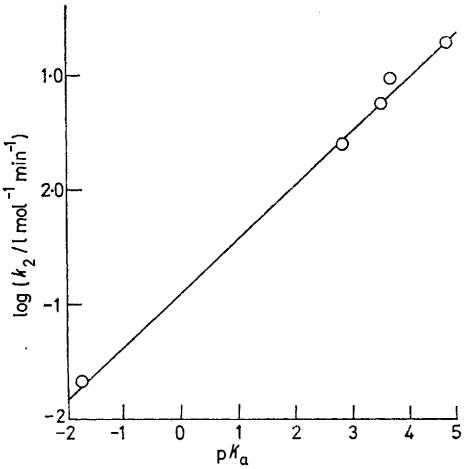
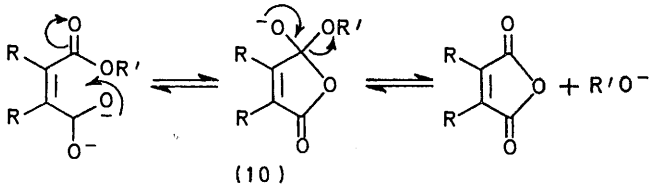


FIGURE 3 Brønsted plot for general base catalysis of the hydrolysis of methyl hydrogen di-isopropylmaleate by carboxylate anions (data from Table 2) and water (1·20/55 l mol^{-1} min^{-1}; see text). The slope of the line drawn is 0·46

mol^{-1}, $\Delta S^\ddagger = -2{\cdot}2$ cal deg^{-1} mol^{-1}) which are both substantially higher than for the acid ester. The prop-2-ynyl derivative is more reactive than the methyl ester because of a more favourable enthalpy term: for this compound (Table 3) $\Delta H^\ddagger = 19{\cdot}1$ kcal mol^{-1}, $\Delta S^\ddagger = -4{\cdot}1$ cal deg^{-1} mol^{-1}. The solvent deuterium isotope effect is low in both cases ($k_H/k_D = 1{\cdot}64$ and 1·41, respectively), and no buffer catalysis can be detected. These data are most closely consistent with a unimolecular mechanism for the hydrolysis reaction, and we propose Scheme 3 to account for the evidence.



SCHEME 3

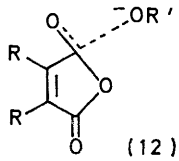
For reasons already discussed, the rate-determining step will be the breakdown of (10) to products. This step involves the elimination of an alkoxide anion * from an anhydride, and would be expected to be readily reversible. We find a kinetically significant reverse

* General acid catalysis of the breakdown of (10) by water (Scheme 2, with $BH^+ = H_3O$) presumably occurs, but is evidently a slower process than the uncatalysed breakdown shown in Scheme 3.

[14] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1961, **83**, 1743.

[15] R. P. Bell, *Adv. Phys. Org. Chem.*, 1965, **4**, 1.

reaction in the hydrolysis of prop-2-ynyl di-isopropylmaleate at high pH (9·65 and above) when as little as 1 μl per *ml of prop*-2-yn-1-ol is present in solution. This is the most acidic alcohol we have used in this work, and sufficient alkoxide is present in solution to compete favourably with hydroxide for the anhydride produced. We describe in the Experimental section how we can account quantitatively for the observed reverse reaction using the steady state approximation for the concentration of the anhydride.



(12)

If the breakdown of the tetrahedral intermediate is rate-determining then a high degree of bond-breaking is expected in the transition state (12). It is known from structure–reactivity correlations that bond formation has proceeded only to a very small extent for reactions involving the addition of strongly basic nucleophiles like

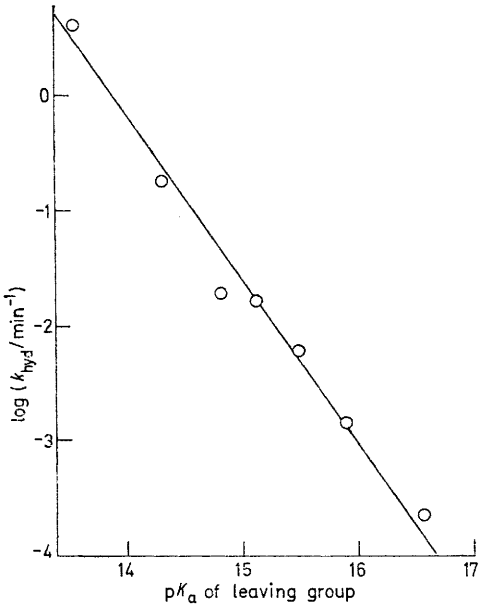


FIGURE 4 Linear free energy relationship between the rate constant for hydrolysis of the half-ester anion and the pK_a of the conjugate acid of the leaving group, for seven alkyl di-isopropylmaleates. Data, for 39° and ionic strength 1·0, are from Table 4. The slope of the line drawn is 1·43

alkoxide ions to reactive carbonyl groups: β_N (nucleophilic) values of 0·3 are typical.[6] We have measured the rates of hydrolysis of a series of alkyl dialkylmaleate anions, and find that the rate is indeed highly sensitive to the basicity of the leaving group. Figure 4 shows the good linear free energy relationship obtained for the hydrolysis of seven alkyl di-isopropylmaleate anions. A similar curve is defined by the data (Table 4) for four alkyl di-t-butylmaleates. The slope of the line drawn in Figure 4 is 1·43. The equilibrium for the transfer of an acyl group from a constant acyl donor to an alkoxide has a β-value of 1·7, so 'the reverse of the reaction with a β-value of 0·3 should exhibit β values of 1·7—0·3 = 1·4'.[6] For various reasons a value as high as 1·4 has not been observed previously,* and this result provides independent support for the analysis of Jencks and Gilchrist.[6] The intramolecular reaction *via* the transition state (12) thus shows the highest sensitivity to leaving group yet measured for ester hydrolysis, and if the analysis of Jencks and Gilchrist is correct, close to the highest sensitivity possible.[17] We have found an identical value of β (1·44 ± 0·18) for a similar intramolecular reaction of phosphate triesters.[18] The phosphate reaction also involves displacement of oxyanions (aryloxides) by the carboxylate group. Reactions of this sort, in which a weak nucleophile displaces a much more basic leaving group, are the least likely to involve concerted (S_N2-like) mechanisms. The addition intermediate [*e.g.* (10)] must be a high energy species because it cannot be detected even in systems where it would carry only poor leaving groups, whereas here the elimination of carboxylate will be very fast. Nevertheless it must be present in sufficient concentration for the much slower elimination of alkoxide to become significant in these systems.

Conclusions.—The alkyl hydrogen dialkylmaleates are extremely reactive esters, but their kinetic behaviour is otherwise normal for compounds of this type. The only significant abnormality is a low enthalpy of activation for all the intramolecular reactions measured. They are thus similar to the corresponding amides.[1] The pH-independent reactions of the ester acid and anion both involve as an intermediate the conjugate base (10) of the tetrahedral addition compound formed by cyclisation of the acid. The anion reaction represents its spontaneous breakdown, and the apparently uncatalysed hydrolysis of the acid ester represents (the kinetically equivalent) general acid catalysis by H_3O^+ of the elimination of the leaving group. Both mechanisms are efficient enough to be considered as possible mechanisms for enzyme-catalysed reactions. Catalysis by carboxylate is more effective than catalysis by the carboxy-group for leaving groups derived from alcohols with pK_a values below 13·68, which include the OH group of serine side chains (the pK_a of *N*-acetylserinamide [8] is 13·6). There is no reason to suppose that the rates of hydrolysis of the esters studied in this work cannot be exceeded in suitable systems, but we would expect the relative efficiencies of carboxylate *vs.* carboxylic acid as catalysts for a given leaving group, and of different alcohols as leaving groups, to remain the same.

[4/342 *Received*, 21*st February*, 1974]

* The data of Gaetjens and Morawetz [16] for the hydrolysis of the anions of aryl hydrogen glutarates, a close analogy of the reaction described here, give a value of −1·15 for β.

[16] E. Gaetjens and H. Morawetz, *J. Amer. Chem. Soc.*, 1960, **82**, 5328.
[17] A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, 1970, **92**, 5432.
[18] R. H. Bromilow, S. A. Khan, and A. J. Kirby, *J.C.S. Perkin II*, 1972, 911.