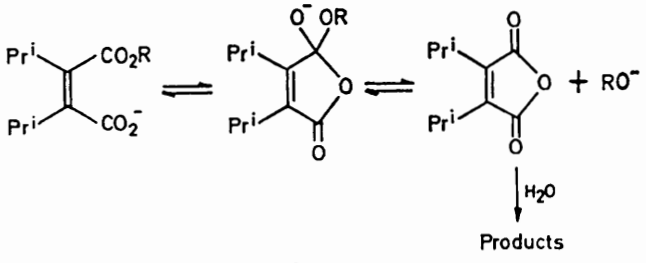
Intramolecular Displacement of Methoxide by the Ionised Carboxy-group

By M. F. ALDERSLEY, A. J. KIRBY,* and P. W. LANCASTER
(*University Chemical Laboratory, Cambridge* CB2 1EW)

Summary The anion of methyl hydrogen di-isopropylmaleate is rapidly hydrolysed under mild conditions in a reaction involving unassisted nucleophilic displacement of methoxide by the carboxylate group.

WE have found[1,2] that the hydrolysis of dialkylmaleamic acids is too fast to measure by conventional techniques, because of the powerful driving force for cyclisation in these compounds.[3] The efficiency of intramolecular nucleophilic catalysis should be enhanced for reactions of other groups also, and we report evidence that the ionised carboxy-group can displace simple alkoxide ions in this system.

Methyl hydrogen di-isopropylmaleate, made by dissolving di-isopropylmaleic anhydride[3] in methanolic sodium methoxide, is hydrolysed very rapidly in acid, with a half-life of 35 s in the narrow pH-independent region from pH 1—2



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(see Figure). This is the expected CO_2H-catalysed reaction: like the hydrolysis of the corresponding amides it is orders of magnitude faster than known[4] examples, and involves the dialkylmaleic anhydride as an intermediate. The unprecedented feature of the pH-rate profile is the pH-

independent region from pH 8—14. The ready hydrolysis in this region ($t_{\frac{1}{2}}$ = 112 min at 39°) must represent a reaction catalysed by the CO_2^- group, since it is over 10^5 times faster than expected[5] for the neutral hydrolysis of a methyl ester.

The only previous report of a reaction of this type is that of Hurst and Bender,[6] who found that the rate of hydrolysis of the dianion of methyl 2,6-dicarboxybenzoate at 100° was too fast to be accounted for by alkaline hydrolysis, or the faster reaction of the monoanion, at the minimum in the pH-rate profile near pH 9. The relative catalytic efficiencies of the CO_2H and CO_2^- groups are similar in their system and ours, suggesting that Hurst and Bender's assignment is correct. But since CO_2^- is a much more effective catalyst in our system—at least an order of magnitude more efficient than molar NaOH—we have been able to collect enough data to define the mechanism of the reaction.

Our evidence is consistent with the mechanism shown in the Scheme. Preliminary results with several different alkyl esters show that the rate of hydrolysis is very sensitive to the nature of the leaving group, suggesting that the rate-determining step must be the loss of methoxide from the tetrahedral intermediate; and since the reaction is not buffer-catalysed this step is apparently unassisted. This is consistent with the observed entropy of activation, which is close to zero, though there is a solvent deuterium isotope effect (k_H/k_D = 1·6). The anhydride intermediate cannot be observed directly in the reaction of the methyl ester, but can be isolated from the reaction mixture when the more reactive prop-2-ynyl ester is used.

The effect of strain in this system is to make the carboxylate group a more effective nucleophile, and thus to increase the concentration of the tetrahedral intermediate sufficiently for the relatively unfavourable elimination of methoxide to become significant. There is little doubt that this is an important feature of enzyme-catalysed displacement reactions on carbonyl compounds, and we hope soon to be able to identify the structural factors responsible for the special reactivity of this system.[1]

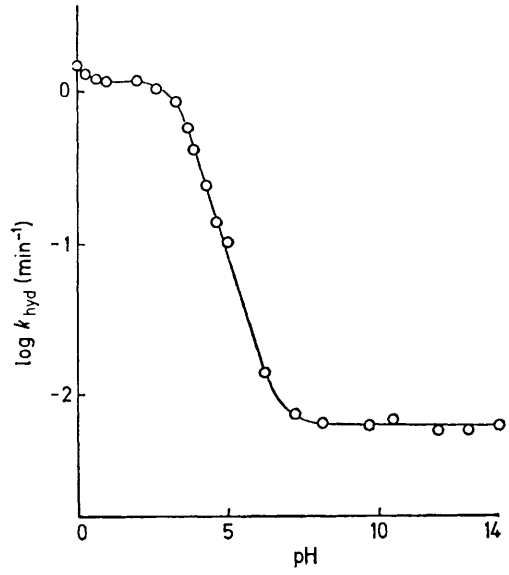

FIGURE. *pH-rate profile for the hydrolysis of methyl hydrogen di-isopropylmaleate at* 39° *and ionic strength* 1·0 (KCl). *Points between pH* 2—8 *represent extrapolations to zero buffer concentration* (*formate, acetate, trishydroxymethylaminomethane*). *Methods are described in ref.* 1.

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