with continuous stirring. The solution was allowed to stand at room temperature for 1 hr. The ether and excess diazomethane were removed by evaporation on a steam bath. To the resultant red oil was added 2 l. of 0.5 *N* sulfuric acid and the mixture was heated on a steam bath for 2 hr. After cooling, the acid solution was extracted with several portions of ether. The ether solution was dried over sodium sulfate and evaporated to give the crude ketol. The ketols were purified by sublimation, recrystallization from *n*-hexane (five times), and resublimation. In this way were prepared α-hydroxyacetophenone-C^{14}, m.p. 85.5–86.5°; *p*-methoxy-α-hydroxyacetophenone, m.p. 105.0–105.5° (49%) (*Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.1; H, 6.1. Found: C, 65.0; H, 5.8); *p*-methyl-α-hydroxyacetophenone, m.p. 93.0–93.5° (44%) (*Anal.* Calcd. for $C_9H_{10}O_2$: C, 72.0; H, 6.7. Found: C, 72.3; H, 6.6); *p*-bromo-α-hydroxyacetophenone, m.p. 134–135° (39%) (*Anal.* Calcd. for $C_8H_7BrO_2$: C, 44.7; H, 3.3; Br, 37.2. Found: C, 44.8; H, 3.2; Br, 37.0); and *m*-bromo-α-hydroxyacetophenone, m.p. 101–102° (20%) (*Anal.* Calcd. for $C_8H_7BrO_2$: C, 44.7; H, 3.3; Br, 37.2. Found: C, 44.7; H, 3.1; Br, 37.1).

α-Hydroxyacetophenone-α,α-d_2. α-Hydroxyacetophenone (50 g., 0.37 mole) was heated to reflux with 99.7% deuterium oxide (200 ml.) containing deuteriosulfuric acid (2.0 g., 0.02 mole) for 16 hr. with rapid stirring. Upon cooling, the ketol crystallized from solution. The air-dried solid was equilibrated with another equal portion of deuterium oxide–deuteriosulfuric acid for 18 hr. The ketol was filtered, dried over phosphorus pentoxide under vacuum, recrystallized from *n*-heptane, and sublimed twice at 85° (0.1 mm.). Before use, the ketol was recrystallized five times from *n*-heptane and resublimed, m.p. 86.0 and 86.5°.

Kinetic Method. The solution of copper(II) in pyridine–water was placed in one arm of a U-tube attached at its center to a spectrometer cell, and the solution of the ketol in pyridine–water was placed in the other arm. The solutions were degassed under a good vacuum by successive freezing and melting. The solutions were thermostated at the reaction temperature, and then mixed by inverting the tube. The absorbance of the solution was determined as a function of time at a wave length in the range 650–850 mμ. From two to eight runs were made for each set of experimental conditions and the average values are reported.

Rate of Enolization. Acetic acid-*d* was prepared by heating an equimolar mixture of freshly distilled acetic anhydride and deuterium oxide. It was distilled through a Vigreux column at atmospheric pressure, b.p. 115.5–116°. To a weighed amount of this acid was added an equimolar amount of pyridine. The preparation of the buffer was completed by the addition of 50 mole % pyridine–deuterium oxide.

An aliquot of a freshly prepared solution of the enolizable compound in the deuterated solvent was placed in an n.m.r. sample tube, degassed by the freeze–melt process, and sealed under vacuum. The n.m.r. spectrum was taken periodically to determine the rate at which the methylene peak disappeared. The samples were kept in a 25° thermostat between measurements and at 25 ± 2° while in the n.m.r. spectrometer.

Kinetic Demonstration of a Tetrahedral Intermediate in the Hydrolysis of Diethyl Acetylmalonate and Diethyl Acetylethylmalonate[1]

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The rates of hydrolysis of diethyl acetylmalonate and diethyl acetylethylmalonate to acetic acid and diethyl malonate or diethyl ethylmalonate, respectively, have been measured at pH values between 0 and 14. The pH–rate profile of each shows two regions in which the rate of hydrolysis is independent of pH and two regions in which it is proportional to the concentration of hydroxide ion. This dependence on pH has been interpreted in terms of a change from rate-determining cleavage of the carbon–carbon bond in a hydrated ketone intermediate at low pH to rate-determining formation of the intermediate at higher pH values. This interpretation is supported by the observations that the reaction is catalyzed by carboxylic acid buffers at pH 5 (slow hydration), whereas it shows no such catalysis at pH 3 (slow carbon–carbon bond cleavage), and that the catalytic constants for the buffers decrease with increasing buffer concentration at pH values in the range 4.25–4.98, which is caused by the (uncatalyzed) cleavage step becoming partially rate determining at high buffer concentrations.

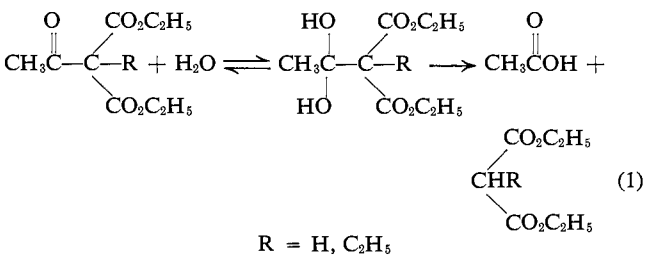
Introduction

Kinetic studies on the reaction of a number of nucleophilic reagents with carbonyl groups have provided evidence for the initial formation of an adduct between the carbonyl group and the nucleophile (a

(1) Supported by National Institutes of Health Grant No. HD-01247, National Science Foundation Grant No. GB-1648, National Institutes of Health, Division of General Medical Sciences Training Grant No. 5 T1-GM-212-04, and a Public Health Service Fellowship (G. E. L.) from the National Institutes of General Medical Sciences (1-F2-GM-18,818-01).

tetrahedral intermediate), although this adduct is not the final product of the reaction.[2] The kinetic evidence for the existence of such an intermediate has been the variation of the rate of the reaction with the concentrations of catalysts in a way that can be explained only by assuming that at some concentrations of catalysts the rate of reaction is determined by the rate of formation of the tetrahedral intermediate, whereas at others the rate of reaction is determined by the steady-state concentration of the intermediate and its rate of breakdown; this situation demands that an intermediate is formed in the reaction.

In this paper we report a kinetic study of the hydrolysis of diethyl acetylmalonate and diethyl acetylethylmalonate to acetic acid and diethyl malonate or diethyl ethylmalonate (eq. 1). The results show that in this reaction there is a change from rate-determining



(1)

breakdown of a hydrated ketone intermediate at low pH to rate-determining addition of water and hydroxide ion to the carbonyl group at higher pH.

Experimental

Materials. Diethyl acetylmalonate (acetylmalonic acid diethyl ester), purchased from K & K Laboratories, Inc., was fractionally distilled; b.p. 94–96° (2.1 mm.), $n^{23}D$ 1.4463; reported[3a] b.p. 65–70° (0.5 mm.), $n^{25}D$ 1.4435, and[3b] 110–117° (13 mm.), $n^{20}D$ 1.4464–1.4477. Diethyl acetylethylmalonate, b.p. 109–111° (1.5 mm.), reported 137° (20 mm.), was prepared according to the method of Michael.[4] Methoxyacetic acid was fractionally distilled before use. Other chemicals were reagent grade and were used directly. Glass-distilled water was used throughout.

Rate Measurements. The pK_a' of diethyl acetylmalonate in 1 *M* potassium chloride at 25° was found by half-neutralization to be 6.65. The ultraviolet spectrum of the diethyl acetylmalonate anion has a maximum at 270 mμ with an extinction coefficient of 17,000 M^{-1} cm.$^{-1}$; the spectrum of the acid itself exhibits a maximum at 252 mμ with an extinction coefficient of 1700 M^{-1} cm.$^{-1}$, which may be attributed to the existence of the acid approximately 15% in the enol form.[5] Consequently, the rate of hydrolysis of diethyl acetylmalonate was followed spectrophotometrically by the disappearance of its absorption at 252 or 270 mμ, depending upon the pH of the reaction solution. A Zeiss PMQ II spectrophotometer equipped with a thermostated brass block cuvette holder was used. Reaction mixtures which contained everything but the diethyl acetylmalonate were prepared in 4-ml., 1-cm. quartz cuvettes and were temperature equilibrated in a water bath. The reaction was initiated by the addition of a small volume of a solution of diethyl acetylmalonate. In general, a solution identical with the reaction solution except for the absence of diethyl acetylmalonate was used as the blank in the spectrophotometer. In all cases the hydrolysis of diethyl acetylmalonate was studied at 25° and 1 *M* ionic strength, adjusted with potassium chloride. All reaction mixtures contained 10^{-4} *M* ethylenediaminetetraacetic acid.

Diethyl acetylethylmalonate is soluble in water only to the extent of about 0.003 *M*. Reaction mixtures that contained this compound were prepared by temperature equilibrating 50 ml. of the reaction buffer, which included 10^{-4} *M* ethylenediaminetetraacetic acid and sufficient potassium chloride to give the desired ionic strength, and then adding enough diethyl acetylethylmalonate (0.012–0.025 ml.) with vigorous mixing to give a 0.001–0.002 *M* solution. The rate of its hydrolysis was followed by measuring its disappearance with a hydroxylamine–ferric chloride test.[6] Generally, a 1- or 2-ml. aliquot of the reaction mixture was added to 1 ml. of a hydroxylamine reagent consisting of 2 parts of 4 *M* hydroxylamine hydrochloride, 2 parts of 4 *M* sodium hydroxide, and 1 part of 3 *M* tris(hydroxymethyl)aminomethane buffer, 40% free base (final pH about 8.0). After 10 min. at room temperature 2.0 ml. of 1 $FeCl_3 \cdot 6H_2O$ in 1.25 *M* HCl was added. The absorption of the resulting solution was measured at 540 mμ against a reagent blank after 2–4 min. with a Zeiss PMQ II spectrophotometer. Under these conditions 1 μmole of diethyl acetylethylmalonate yields the same absorbance as 1 μmole of acetohydroxamic acid, whereas 2 μmoles of diethyl ethylmalonate gives no absorbance above that of the reagent blank. When the rate of hydrolysis of diethyl acetylethylmalonate was followed in fairly concentrated acetate and methoxyacetate buffers, the amount of buffer in the aliquots for analysis was large enough to alter markedly the pH in the hydroxylamine–ferric chloride test, so that the following modifications were required. The sample aliquot (1–2 ml.) was added to 1 ml. of the hydroxylamine reagent, and this was immediately followed by the addition with vigorous mixing of an amount of sodium hydroxide, in 1 ml. or less, equivalent to the amount of acid in the buffer. After 10 min. 2 ml. of 10% $FeCl_3 \cdot 6H_2O$ in hydrochloric acid, of sufficient strength so that the final acid concentration would be approximately 0.1 *M*, was added.

The hydrolysis of both compounds was always measured in buffered solutions that maintained the pH at a constant value. With this condition, the kinetics are pseudo first order. Rate constants were obtained by plotting the extent of reaction, A_t, against time on semilogarithmic graph paper and calculating the pseudo-first-order constants from the equation $k = 0.693/t_{1/2}$. All such plots were linear for at least two half-times.

At the conclusion of the kinetic run measurements of the pH of the reaction solution were made with a

(2) (a) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **86**, 5616 (1964), and references therein. See also (b) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 4319 (1962); (c) R. B. Martin, A. Parcell, and R. I. Hedrick, *ibid.*, **86**, 2406 (1964); (d) R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 3197 (1964); (e) T. C. Bruice and L. R. Fedor, *J. Am. Chem. Soc.*, **86**, 4886, 5697 (1964).

(3) (a) H. M. Barnes, D. Kundiger, and S. M. McElvain, *ibid.*, **62**, 1281 (1940); (b) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).

(4) A. Michael, *Am. Chem. J.*, **14**, 503 (1892).

(5) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," 2nd Ed., Edward Arnold Ltd., London, 1957, p. 257.

(6) S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

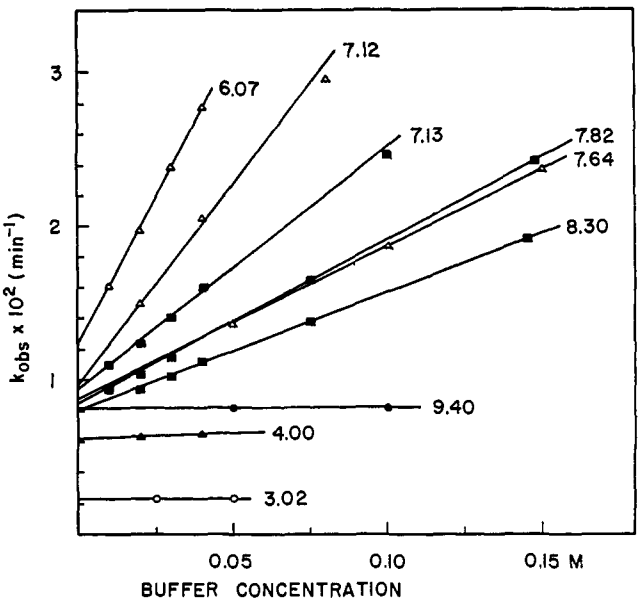


Figure 1. Dependence of the rate constants for the hydrolysis of diethyl acetylmalonate, at 25° and 1 *M* ionic strength, upon buffer concentration. The pH values of the buffers are shown. The buffers are: ○, potassium methoxyacetate; ▲, potassium acetate; △, potassium phosphate; ■, imidazole hydrochloride; ●, potassium carbonate.

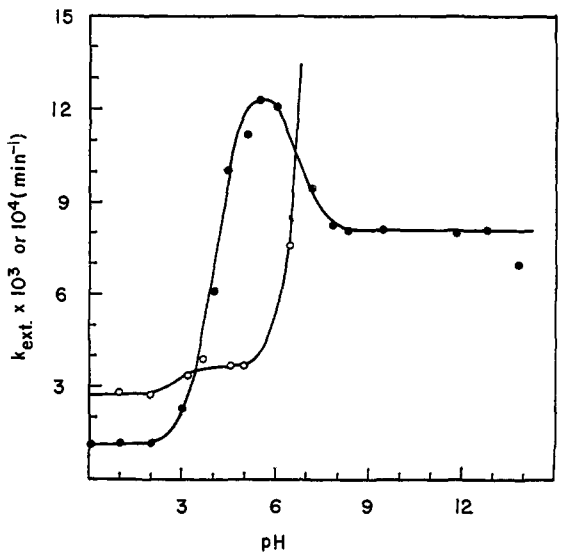


Figure 2. Dependence on pH of the hydrolysis of diethyl acetylmalonate at 25° and 1 *M* ionic strength (closed circles, $k_{ext} \times 10^3$) and the hydrolysis of diethyl acetylethylmalonate at 39° and 0.2 *M* ionic strength (open circles, $k_{ext} \times 10^4$). The rate constants are extrapolated to zero buffer concentration. The buffers used at the different pH ranges were hydrochloric acid (0–2.1), potassium methoxyacetate (3.0), potassium formate (3.1–3.7), potassium acetate (4.0–5.4), potassium phosphate (6.1–6.4), imidazole hydrochloride (7.1–8.3), tris(hydroxymethyl)aminomethane (8.3), potassium carbonate (9.4), and potassium hydroxide (11.8–13.8). The lines were calculated from the steady-state rate equation (3).

Radiometer Model 4 pH meter at the temperature of the kinetic run.

Product Analysis. A 0.01 *M* solution of diethyl acetylmalonate in 0.01 *M* HCl (pH *ca.* 2) was allowed to undergo complete hydrolysis at 25°. Titration of the reaction mixture with sodium hydroxide showed the formation of 1 equiv. of an acid with a p*K* the same as that of acetic acid. The infrared spectrum of a carbon tetrachloride extract of the neutralized reaction mixture was identical with that of diethyl malonate and indicated a yield of approximately 85% diethyl malonate. In another experiment, a mixture of 1 ml. of diethyl acetylmalonate and 9 ml. of water was maintained at pH 8 by the addition of sodium hydroxide with an automatic titrator. The infrared spectrum of a carbon tetrachloride extract of the reaction mixture after complete hydrolysis was identical with that of diethyl malonate and showed approximately an 80% yield of the compound. In a similar way the products of hydrolysis of diethyl acetylethylmalonate in aqueous solution at 25° and at pH 2 and 11 were identified as acetic acid and diethyl ethylmalonate.

Results and Discussion

pH–Rate Profiles of Hydrolysis. The hydrolysis of diethyl acetylmalonate and diethyl acetylethylmalonate is catalyzed by the buffers at some pH values. Consequently, in order to determine the rate constant for hydrolysis at a certain pH in the absence of buffer the rate constants for hydrolysis were measured in a buffer of that pH at several buffer concentrations in the range 0.010–0.150 *M* and were then extrapolated to zero buffer concentration. Such extrapolations for several buffers are shown for diethyl acetylmalonate in Figure 1.

The extrapolated rate constants (k_{ext}) for the hydrolysis of diethyl acetylmalonate are constant between pH 0 and 2, increase to a maximum at approximately pH 5.5, decrease from pH 5.5 to 8, and then remain constant from pH 8 to 13 (Figure 2).

The k_{ext} values for the hydrolysis of diethyl acetylethylmalonate are independent of pH between pH 1 and 2 and then increase approximately 36% between pH 2 and 3.5 (Figure 2). Although this increase is small, it is definitely real: the rate constants observed for hydrolysis are reproducible to within 3% of the average; there was no extrapolation at pH 1 and 2 (hydrochloric acid buffer); there was no extrapolation at pH 3.15 and 3.65 because the rate constants are independent of buffer concentration at the low concentrations (below 0.1 *M*) of formate buffer used; and the extrapolations at pH 4.55 and 4.95 (acetate buffers) amounted to only about 10% of the values of the lowest measured rate constants. Between pH 3.5 and 5 the rate of hydrolysis of diethyl acetylethylmalonate remains constant, and then above pH 5 it increases with pH (Figure 2).

The values of k_{ext} for diethyl acetylmalonate may be corrected to give the rate constants for reaction of the non-ionized species by dividing k_{ext} by the fraction of non-ionized diethyl acetylmalonate, $(H^+)/K_a' + (H^+) = \alpha$. A plot of log k_{ext}/α against pH shows two regions (pH 0–2 and pH 4.5–5.5) in which the rate constants for hydrolysis of the non-ionized form of diethyl acetylmalonate are pH independent, and two regions (pH 2–4.5 and above 5.5) in which the rate constants increase with pH (Figure 3). Thus, after correction for ionization, the pH–rate profile for the hydrolysis of diethyl acetylmalonate is of the same form as that for diethyl acetylethylmalonate. Since diethyl acetylethylmalonate cannot undergo ionization or enolization, this similarity indicates that the non-ionized form of diethyl acetylmalonate is the reactive

Table I. Kinetic Constants for the Hydrolysis of Diethyl Acetylmalonate and Diethyl Acetylethylmalonate[a]

Compd.	Assumption	Rate-determining step: At low pH	Rate-determining step: At high pH	k_1, min.$^{-1}$	k_2,[b] M^{-1} min.$^{-1}$	k_1k_3/k_{-1},[b] min.$^{-1}$	k_1k_4/k_{-1}, M^{-1} min.$^{-1}$	k_2/k_1, M^{-1}
Diethyl acetylmalonate[c]	A	C–C cleavage	Hydration	1.3×10^{-2}	1.8×10^{5}	1.25×10^{-3}	1.3×10^{8}	1.4×10^{7}
	B	Hydration	C–C cleavage	1.25×10^{-3}	1.3×10^{8}	1.3×10^{-2}	1.8×10^{5}	10^{11}
Diethyl acetylethylmalonate[d]	A	C–C cleavage	Hydration	3.7×10^{-4}	4.7×10^{3}	1.1×10^{-3}	$\sim 7 \times 10^{7}$[e]	1.3×10^{7}
	B	Hydration	C–C cleavage	1.1×10^{-3}	$\sim 7 \times 10^{7}$[e]	3.7×10^{-4}	4.7×10^{3}	$\sim 6 \times 10^{10}$[e]
Acetaldehyde[f]		Hydration		0.24	2.4×10^{6}			10^{7}

[a] The constants are defined by the kinetic scheme (2) presented in the text. [b] These second-order constants for reaction with hydroxide ion are in terms of the activity of the hydroxide ion and were calculated by taking $K_w = 10^{-14}$ at 25° and $K_w = 10^{-13.5}$ at 39°. [c] At 25° and 1 M ionic strength. [d] At 39° and 0.2 M ionic strength. [e] Estimated value. [f] At 25°, from R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956).

species and that ionization or enolization of this compound is not the explanation of the unusual pH–rate profile for its hydrolysis.

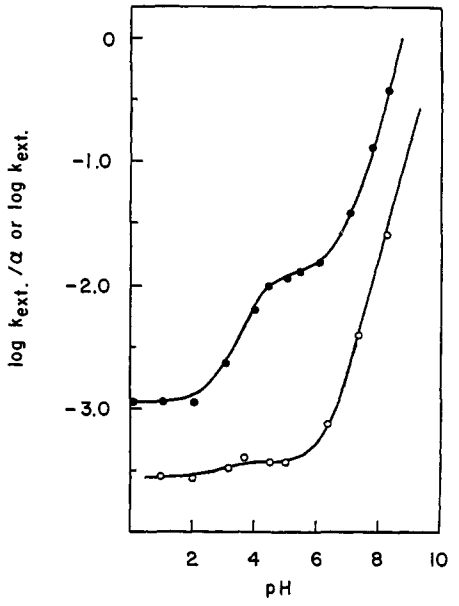
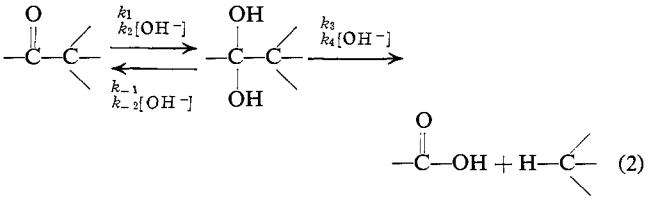


Figure 3. Logarithmic plot of the variation with pH of the extrapolated rate constants for the hydrolysis of diethyl acetylmalonate, corrected to the non-ionized species (k_{ext}/α), at 25° and 1 M ionic strength (closed circles) and of diethyl acetylethylmalonate (k_{ext}) at 39° and 0.2 M ionic strength (open circles). The lines were calculated from eq. 3.

The cessation at around pH 4 of the hydroxide ion catalyzed hydrolysis which is observed between approximately pH 2 and 4 cannot be explained by a one-step reaction mechanism or rate law and is evidence for a change in the rate-determining step of the reaction with increasing hydroxide ion concentration. A change in rate-determining step demands that there be an intermediate in the reaction, the formation of which is rate determining under some conditions and the steady-state concentration and rate of breakdown of which determine the rate under other conditions.[2]

A kinetic scheme which will explain the data for both compounds is one in which there is a hydrated carbonyl intermediate, the formation and breakdown of which occur by pH-independent and hydroxide ion dependent pathways (eq. 2). This scheme leads to two limiting cases. In the first case (assumption A), carbon–carbon cleavage is slow at low pH ($k_{-1} > k_3$) and formation of the *gem*-diol is slow at high pH ($k_4[OH^-] > k_{-2}[OH^-]$). At the lowest pH values k_{ext}/α (k_{ext} for diethyl acetylethylmalonate) is equal to the equilibrium constant for hydrate formation (k_1/k_{-1}) times the rate constant for cleavage of the hydrate (k_3) and is independent of



(2)

pH. As $k_4[OH^-]$ becomes significant with increasing pH the rate will increase. However, at higher pH the term $k_4[OH^-]$ becomes greater than k_{-1}, so that pH-independent hydration, k_1, becomes rate determining. Finally, in the highest pH region, base-catalyzed hydration becomes significant and k_{ext}/α becomes equal to $k_2[OH^-]$, which accounts for base catalysis of the reaction in this region.

In the second case (assumption B), addition of water or hydroxide ion is rate determining at low pH ($k_3 > k_{-1}$) and carbon–carbon cleavage is rate determining at high pH ($k_{-2}[OH^-] > k_4[OH^-]$). This assumption is the inverse of assumption A and leads to an identical dependence of rate upon pH.

The steady-state rate equation for k_{ext}/α (diethyl acetylmalonate) or k_{ext} (diethyl acetylethylmalonate) for the scheme of eq. 2 is given in eq. 3, where c is the

$$\frac{k_{ext}}{\alpha} \text{ or } k_{ext} = \frac{1}{c}\frac{dP}{dt} = \frac{(k_1 + k_2[OH^-])(k_3 + k_4[OH^-])}{k_{-1} + k_{-2}[OH^-] + k_3 + k_4[OH^-]} \quad (3)$$

concentration of non-ionized diethyl acetylmalonate or of diethyl acetylethylmalonate.

The rate constants of this scheme which may be derived from the experimental data are summarized in Table I and were obtained as follows, based on assumption A. The values of k_1 and $k_2[OH^-]$ were obtained directly from k_{ext}/α in the pH-independent region between pH 4.5 and 5.5 and the pH-dependent region at alkaline pH, respectively. At very low pH, eq. 3 reduces to eq. 4 and, knowing k_1, it was possible to cal-

$$\frac{k_{ext}}{\alpha} \text{ or } k_{ext} = \frac{k_1k_3}{k_{-1} + k_3} \quad (4)$$

culate k_3k_1/k_{-1}. In the pH-dependent region between pH 2 and 4, eq. 3 reduces to eq. 5, and k_4k_1/k_{-1}

$$\frac{k_{ext}}{\alpha} \text{ or } k_{ext} = \frac{k_1(k_3 + k_4[OH^-])}{k_{-1} + k_3 + k_4[OH^-]} \quad (5)$$

may be calculated from the known values of k_{ext}/α, k_1, and k_3k_1/k_{-1}. The values of these rate constants for assumption B were calculated in an analogous manner and are also given in Table I. Both sets of values were used with the complete steady-state rate eq. 3 to calculate the entire pH–rate profiles. These calculated profiles are shown as the solid lines in Figures 2 and 3 and provide a satisfactory fit to the experimental data.

In the case of diethyl acetylmalonate the values of k_1 and k_3k_1/k_{-1} differ by tenfold so that, according to assumption A, hydration of the ketone and cleavage of the *gem*-diol are almost completely rate determining in the plateau regions at high and low pH, respectively. In the case of diethyl acetylethylmalonate, the values of k_{ext} differ by only 36% in the plateau region, so that both k_1 and k_3k_1/k_{-1} are partly rate determining in the lower pH region. Consequently, the relatively small contribution of k_4k_1/k_{-1} in the region between 2 and 4 is difficult to evaluate accurately, and the value of this rate constant in Table I is not of high precision.[7]

From the known characteristics of the hydration of aldehydes and ketones, the decision can be made that in fact the rate-determining step below pH 3 is carbon–carbon bond cleavage and above pH 5 is hydration (assumption A). The reasons are:

(1) If one assumes that hydration is the rate-determining step above pH 5, the rate constant for the hydroxide ion dependent hydration of acetaldehyde is about 10 times faster than that for diethyl acetylmalonate and about 500 times faster than that for diethyl acetylethylmalonate. Such decreases can reasonably be explained by the steric effects of the diethyl malonate and diethyl ethylmalonate groups. On the other hand, the assumption (B) that hydration is rate limiting below pH 3 would give rate constants for the hydroxide ion dependent hydration that are about 40 times larger than that for acetadehyde in the face of values for pH-independent hydration which are smaller than those for acetaldehyde (Table I).

(2) The ratios of the second-order rate constant for hydroxide ion dependent hydration (k_2) to the pseudo-first-order constant for the pH-independent hydration (k_1) are given for the alternate assumptions in Table I. For assumption A, these ratios are about the same as that for acetaldehyde (10^7 M^{-1}); for assumption B, these ratios are 10^4 greater (10^{11} M^{-1}) than that for acetaldehyde. Moreover, Kirsch and Jencks[8] have recently compiled such ratios for the hydrolysis of a number of esters, and the values vary between $10^{5.6}$ for acetic anhydride and $10^{8.8}$ for ethyl acetate. There is good evidence from O^{18} exchange studies that the rate of ester saponification is largely or entirely dependent upon the rate of attack by hydroxide ion on the carbonyl group.[9]

(7) It is possible that the change in rate-determining step (based on assumption A) is more complete than is implied by this discussion. If, as is the case with many carbonyl compounds, acid-catalyzed reaction paths contribute to the observed rate of hydration at pH values as high as 4, hydration would be faster than is accounted for by the rate constant for pH-independent hydration, k_1, and cleavage of the *gem*-diol would become fully rate-determining at low pH values. This would not have a significant effect on the value of k_3k_1/k_{-1} for diethyl acetylmalonate, which is ten times smaller than k_1 for this compound. However, the value of k_3k_1/k_{-1} for diethyl acetylethylmalonate would be 2.7×10^{-4} min.$^{-1}$ rather than the value of 1.1×10^{-3} obtained from the steady-state rate equation, if such acid catalysis led to this term becoming fully rate-determining for this compound below pH 4.

(8) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, **86**, 837 (1964).

(3) The hydration of both aldehydes[10,11] and ketones[12] is known to be subject to hydronium ion catalysis. For acetaldehyde[10] and propionaldehyde,[11] the rate constant for such acid-catalyzed hydration is about 10^5 times greater than the pseudo-first-order rate constant for the pH-independent hydration, so that the hydronium ion catalyzed hydration is significant at pH 5 and dominant below pH 4. Consequently, if the hydration of the acetylmalonate esters were rate limiting at low pH, acid catalysis of the reaction should be observed. However, the rate of hydrolysis of diethyl acetylmalonate is independent of pH between pH 2 and 0. Acid catalysis of the hydration step, which surely occurs, is not observed because the rate-limiting step at low pH is cleavage of the carbon–carbon bond.

(4) The hydration of aldehydes and ketones is strongly catalyzed by general acids and general bases, such as carboxylic acids and carboxylate ions.[10-13] The data presented below show that, at pH values above approximately pH 4, carboxylic acid buffers catalyze the hydrolysis of the diethyl acetylmalonates, whereas below pH 4 they do not.

Buffer Catalysis of Hydrolysis. The dependence of the buffer catalysis of the hydrolysis of diethyl acetylmalonate and diethyl acetylethylmalonate upon pH and upon buffer concentration provides further evidence for a change in the rate-determining step between pH 3 and 5. Plots of the observed rate constants for hydrolysis against carboxylate ion concentration show that catalysis occurs at pH 5 with diethyl acetylmalonate in potassium formate buffers and with diethyl acetylethylmalonate in potassium methoxyacetate buffers, whereas no such catalysis occurs at pH 3 (Figures 4 and 5). It is evident that, even if carboxylate ion were the only species responsible for the buffer catalysis, the absence of catalysis at pH 3 could not be accounted for by the decreased fraction of carboxylate ion in the buffers at the lower pH value.

Further evidence of the failure of the catalysis to obey a simple rate law for a one-step reaction is the decrease in the catalytic constant with increasing buffer concentration at a single pH value that is observed at pH 4.98 for diethyl acetylmalonate with potassium formate buffer (Figure 4) and at pH 4.25 for diethyl acetylethylmalonate with potassium acetate buffer (Figure 5). At the higher pH of 5.53, the observed rate constant for hydrolysis of diethyl acetylethylmalonate is linearly dependent upon the potassium acetate buffer concentration (Figure 5). The decrease in the catalytic constant with increasing buffer concentration at constant pH at the lower pH values occurs because the rate of carbon–carbon bond cleavage, which is not subject to buffer catalysis, becomes partially rate determining as the rate of the (catalyzed) hydration step increases. In kinetic terms (eq. 6), k_{-1} and $k_4(OH^-)$ are of the same magnitude in this pH region, so that an increase in $k_5[B]$ and $k_{-5}[B]$ causes an approach to a situation in which hydration occurs in a pre-equilibrium step and carbon–carbon bond cleavage becomes

(9) M. Bender, *Chem. Rev.*, **60**, 53 (1960).

(10) R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956).

(11) L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5224 (1963).

(12) M. Cohn and H. C. Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938); R. P. Bell and M. B. Jensen, *Proc. Roy. Soc.* (London), **A261**, 38 (1961).

(13) E. H. Cordes and M. Childers, *J. Org. Chem.*, **29**, 968 (1964).

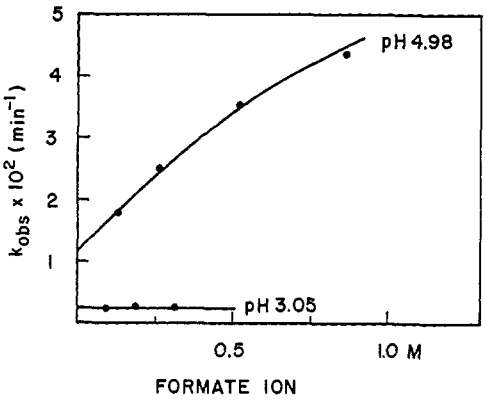


Figure 4. Dependence of the observed rate constants for the hydrolysis of diethyl acetylmalonate in potassium formate buffers upon formate ion concentration at 25° and 1 *M* ionic strength. Formate buffers of pH 4.98 contain 96% formate ion; those of pH 3.05, 21%. The line at pH 4.98 was calculated from the steady-state rate equation derived from the kinetic scheme (eq. 6) given in the text.

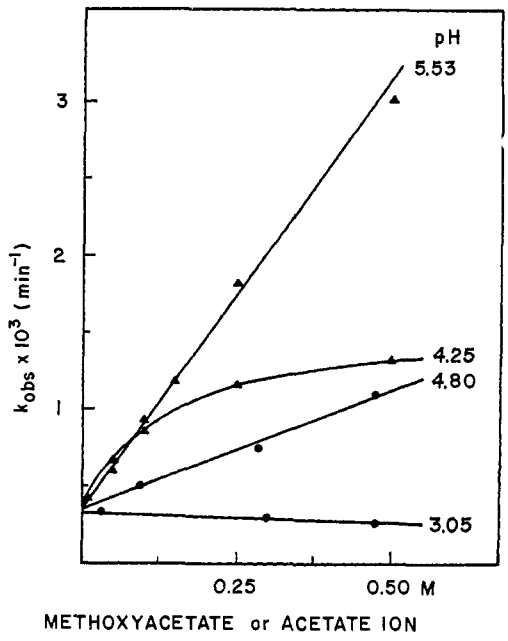
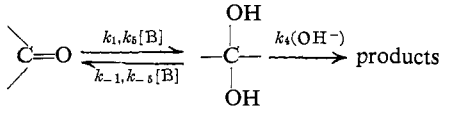


Figure 5. Dependence of the observed rate constants for the hydrolysis of diethyl acetylethylmalonate in potassium methoxyacetate (circles) and acetate (triangles) buffers upon methoxyacetate or acetate ion concentration, at 39° and 0.5 *M* ionic strength The fractions of carboxylate ion in the buffers are: methoxyacetate, pH 3.05, 31%, pH 4.80, 96%; acetate, pH 4.25, 33%, pH 5.53, 90%.

entirely rate determining. The system is analogous to that observed for general-acid catalysis of the addition of semicarbazide to aldehydes, which also shows a



(6)

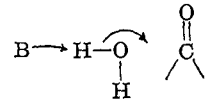
leveling off of the rate with respect to catalyst concentration in the pH region in which a change in rate-limiting step occurs[2b]; similar behavior has been observed in other reactions.[2a-d] The steady-state rate equation derived from scheme 6 has been used with the values of k_1 and $k_4(k_1/k_{-1})$ obtained from the pH–rate profile of diethyl acetylmalonate (Table I, assumption A) and a value of 0.065 M^{-1} min.$^{-1}$ for k_5[formate buffer] at pH 4.98 obtained by successive approximation, to calculate the line in Figure 4. The fit to the measured rate constants is good. Similar calculations were not made for diethyl acetylethylmalonate because of the uncertainty in the value for $k_4(k_1/k_{-1})$.

A detailed investigation of the buffer catalysis of hydrolysis was not carried out. However, an analysis of the rate constants for hydrolysis of diethyl acetylmalonate in imidazole buffers at three pH values (Figure 1) shows that the rate law for catalysis by imidazole buffers contains a term that is first order in respect to non-ionized diethyl acetylmalonate (CH) and first order in imidazole base (Im), and also a term containing these two species and the reciprocal of the hydrogen ion activity (a_{H^+}). This rate law, with the values of the constants at 25° and 1 *M* ionic strength, is

$$v = (1.3\ M^{-1}\ \text{min.}^{-1})[\text{CH}][\text{Im}] + (1.4 \times 10^{-8}\ M^{-2}\ \text{min.}^{-1})(1/a_{H^+})[\text{CH}][\text{Im}] \quad (7)$$

An analysis of the catalysis by phosphate buffers at three pH values (Figure 1) indicates only a single term in the rate law, which is first-order in respect to both non-ionized diethyl acetylmalonate and phosphate dianion and has a value of 1.3 M^{-1} min.$^{-1}$ for the second-order rate constant. The fact that the second-order rate constants for catalysis by imidazole base and by phosphate dianion are the same suggests that the second-order terms represent classical general-base catalysis of hydration, which is the rate-limiting step in this pH range in the absence of buffer; for nucleophilic catalysis the rate of imidazole attack on esters is 10^3 times the rate of phosphate attack, but for general-base catalysis the rates are similar.[14] The third-order term for imidazole catalysis may represent hydroxide ion catalysis of nucleophilic attack by imidazole, which occurs in the imidazole-catalyzed hydrolysis of certain esters,[15] or possibly hydroxide ion assistance to general-base catalysis by imidazole, a reaction path suggested by a recent study on imidazole catalysis of the hydration of *sym*-dichloroacetone.[13]

Mechanisms of Hydrolysis. Mechanisms for general-acid-catalyzed, general-base-catalyzed, hydroxide ion dependent, and pH-independent hydration of aldehydes have been discussed elsewhere[10,16,17] and will not be reviewed here. A reasonable mechanism for the hydration step in the hydrolysis of diethyl acetylmalonates is shown in eq. 8 in which B may be water, the basic component of a buffer, or hydroxide ion.



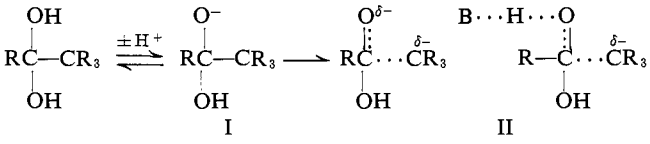
(8)

There is a question as to whether the hydration of diethyl acetylmalonate occurs by attack upon the enol or the keto form. The second-order rate constant for the hydroxide ion catalyzed hydration step in the

(14) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 83, 1743 (1961).
(15) J. F. Kirsch and W. P. Jencks, *ibid.*, 86, 833 (1964).
(16) W. P. Jencks, *Progr. Phys. Org. Chem.*, 2, 63 (1964).
(17) Y. Pocker, *Proc. Chem. Soc.*, 17 (1960).

hydrolysis of diethyl acetylethylmalonate was found to be $5.1 \times 10^3\ M^{-1}$ min.$^{-1}$ at 25° and 1 M ionic strength based upon the hydroxide ion activity, a value which is one-thirtieth that for diethyl acetylmalonate under identical conditions (Table I). This rate decrease can reasonably be explained by the inductive and steric effects of substitution of an ethyl group for hydrogen, without postulating a change from attack on the enol form of diethyl acetylmalonate to attack on the keto form of diethyl acetylethylmalonate. For example, the rate constant for the alkaline hydrolysis of ethyl trimethylacetate is one-tenth that of ethyl dimethylacetate,[18] and the slow step in the alkaline hydrolysis of esters is probably the attack of hydroxide ion upon the carbonyl group.[9]

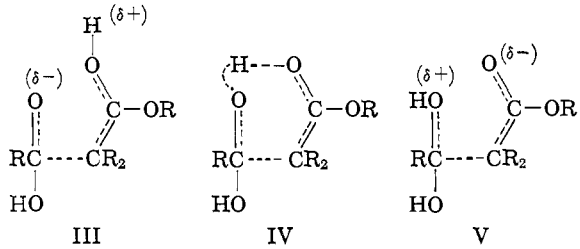
The catalysis of carbon–carbon cleavage by hydroxide ion which is observed at low pH may occur either by the pre-equilibrium formation of the hydrate anion, which subsequently cleaves in a slow step (I), or by general-base catalysis (II), in which proton transfer to hydroxide ion occurs simultaneously with carbon–carbon bond cleavage. In the first mechanism hydroxide ion catalysis would be observed because the



I II

hydrate can be inferred to have a pK_a' of about 13,[19] so that the concentration of the conjugate base of the hydrate would be directly proportional to hydroxide ion concentration at lower pH values. The absence of detectable general-base catalysis of the cleavage of the carbon–carbon bond in the presence of up to 0.45 M carboxylate ion (Figures 4 and 5) at those pH values where this cleavage is the rate-limiting step suggests that the hydroxide ion catalysis represents the pre-equilibrium formation of the ionized hydrate (I) rather than general-base catalysis (II).

Possible transition states for the uncatalyzed cleavage of the hydrate (kinetically dominant at very low pH) involve complete (III), partial (IV), or no (V) transfer of a hydrate hydroxyl proton to the carbonyl oxygen of one of the carboethoxy groups when the cleavage of the carbon–carbon bond occurs, or transfer of a hydroxyl proton to a water molecule during the cleavage (general-base catalysis by water, II, B = H_2O). As in



III IV V

the case of the hydroxide ion reaction, the absence of general-base catalysis by carboxylate ions argues against a mechanism which involves general-base catalysis by water.

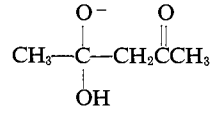
(18) K. Kindler, *Ber.*, **69**, 2792 (1936).
(19) The pK_a of acetaldehyde hydrate is 13.48: R. P. Bell and P. T McTigue, *J. Chem. Soc.*, 2983 (1960).

These conclusions are generally in agreement with the results of other studies of the hydrolysis of carbon–carbon bonds. The mechanism of the hydrolysis of 2-nitroacetophenone and nitroacetone (nitro-2-propanone) to nitromethane and carboxylic acid appears to be similar to that of the acetylmalonate esters. Pearson, *et al.*,[20] have shown that the pH–rate profiles for the hydrolysis of these compounds have a maximum somewhere between pH 5 and 8, the occurrence of which was explained qualitatively in terms of a change in the rate-determining step of the reactions, from rate-determining hydroxide ion dependent hydration at high pH to rate-determining hydroxide ion catalyzed cleavage of a hydrated ketone intermediate at low pH. The hydrate of thenoyltrifluoroacetone undergoes rapid cleavage in base, whereas the unhydrated ketone is relatively stable in base because of the slow rate of hydration of the enolate anion in alkaline solution.[21] Moreover, although there may be some question as to the detailed assignment of rate-determining steps, the over-all mechanism of the hydrolysis of 3,4-methylenedioxy-β-nitrostyrene to piperonal and nitromethane resembles that of the acetylmalonate esters.[22] The pH-independent formation and accumulation of an addition intermediate in this reaction has been demonstrated; above pH 6 the hydroxide ion catalyzed decomposition of the intermediate becomes rapid and its formation becomes rate determining. It has been shown that in the condensation of ketones with substituted benzaldehydes the condensation step is rate determining in acid solution, whereas dehydration of the hydroxy ketone intermediate becomes partially or entirely rate determining in alkaline solution.[23] In the reverse, hydrolytic reaction, this corresponds to rate-determining cleavage in acid solution and at least partially rate-determining hydration in alkaline solution.

The alkaline hydrolysis of acetylacetone to acetone and acetate follows a different kinetic scheme from that of the acetylmalonate esters. The cleavage of acetylacetone shows two terms in the rate law, one of which is first order with respect to non-ionized acetylacetone (CH) and first order with respect to hydroxide ion, and another which is first order with respect to non-ionized acetylacetone and second-order with respect to hydroxide ion (eq. 9).[24] The term which is second-order

$$v = k_1[\mathrm{CH}][\mathrm{OH}^-] + k_2[\mathrm{CH}][\mathrm{OH}^-]^2 \qquad (9)$$

with respect to hydroxide ion has been interpreted as the hydroxide ion dependent removal of the second hydroxyl proton from a singly ionized hydrate intermediate



It is not known whether this proton transfer occurs before or simultaneously with the cleavage of the carbon–carbon bond. The rate laws for the hydrolysis of 2,6-dihalobenzaldehydes to formate and *m*-dihalo-

(20) R. G. Pearson, D. H. Anderson, and L. L. Alt, *J. Am. Chem. Soc.*, 77, 527 (1955).
(21) E. H. Cook and R. W. Taft, Jr., *ibid.*, **74**, 6103 (1952).
(22) T. I. Crowell and A. W. Francis, Jr., *ibid.*, **83**, 591 (1961).
(23) D. S. Noyce and W. L. Reed, *ibid.*, **81**, 624 (1959); M. Stiles, D. Wolf, and G. V. Hudson, *ibid.*, **81**, 628 (1959).
(24) R. G. Pearson and E. A. Mayerle, *ibid.*, **73**, 926 (1951).

benzenes[25] and for the hydrolysis of chloral hydrate to formate and chloroform[26] consist of a single term[27] which is first order with respect to the monoanion of the hydrated substrate and first order with respect to hydroxide ion. In the alkaline hydrolysis of the 2,6-dihalobenzaldehydes, the occurrence of a twofold increase in rate in deuterium oxide solution and a positive entropy of activation of +9 e.u. indicate that in this reaction the proton removal by hydroxide ion occurs in a pre-equilibrium step, with subsequent decomposition of the hydrate dianion. From the reported values[26] of the rate constants for the hydroxide ion catalyzed hydrolysis of the chloral hydrate anion at different temperatures, an entropy of activation at 25° of +11 e.u. can be calculated, a value which suggests that proton transfer also occurs in a pre-equilibrium step in this reaction.

Regardless of whether or not the term in the rate law for the alkaline hydrolysis of acetylacetone that is second order with respect to hydroxide ion represents general-base catalysis, its occurrence shows that the rate-determining step in this reaction involves the cleavage of the carbon–carbon bond. Thus, a change in the leaving group from diethyl malonate anion to acetone anion leads to a change in the rate-determining step of alkaline hydrolysis from attack by hydroxide ion upon the carbonyl carbon to cleavage of the carbon–carbon bond. This change can be correlated with the pK values of diethyl malonate[28] (15.2) and acetone[29] (*ca.* 20) relative to that of water (15.7). When the leaving group is a good one relative to hydroxide ion, such as a diethyl malonate anion, attack upon the carbonyl group by hydroxide ion yields a hydrated ketone anion that almost always decomposes to products, rather than to reactants. When the leaving group is a poor one with respect to hydroxide ion, such as the acetone anion, both the rate of attack of hydroxide ion upon the carbonyl group and the rate of breakdown to products of the intermediate hydrate anion are decreased compared to the rates in the reaction with a good leaving group. However, this change in structure will cause a larger decrease in the rate of the step in which the leaving group is expelled than of the addition step. As a consequence, there is a change in rate-determining step, so that in the case of the poor leaving group the intermediate hydrate anion returns to reactants many more times than it decomposes to products.

A similar change in rate-determining step has been postulated to occur in the nucleophilic reaction of imidazole with acetyl esters upon varying the leaving group of the acetyl esters.[8] A somewhat analogous change in rate-determining step occurs in semicarbazone formation from benzaldehydes in 25% ethanol at pH 3.9 with variation in the substituents on the benzaldehyde.[30] Such changes in rate-determining step from rate-determining addition to the carbonyl group to rate-determining breakdown of the tetrahedral addition intermediate appear to be the basis for a number of nonlinear structure–reactivity correlations in the reactions of carbonyl groups with nucleophiles.[8]

Although the pK of ethanol (16)[31] is about the same as that of diethyl malonate (15.2), the second-order rate constant for the reaction of hydroxide ion with ethyl acetate[8] at 25° is 6.8 M^{-1} min.$^{-1}$, a value which is about 10^4 smaller than that for the attack of hydroxide ion upon diethyl acetylmalonate. The oxygen ester contains a partial π-bond between the alcoholic oxygen and the carbonyl carbon, whereas there is no such bond in the ketone. The striking difference in rates, then, can in large measure be attributed to the increased activation energy required for partial cleavage of this partial π-bond.

The absence of detectable acid catalysis of the cleavage of diethyl acetylmalonates in 1 M hydrochloric acid (Figure 2) is in contrast to the acid catalysis which is observed for the cleavage of β-diketones.[32] This difference presumably reflects a difference in the stability of the leaving groups in the two reactions, *i.e.*, a smaller stability of the enol of diethyl malonate compared to the enol of a ketone.

(25) J. F. Bunnett, J. H. Miles, and K. V. Nahabedian, *J. Am. Chem. Soc.*, **83**, 2512 (1961).
(26) E. Pfeil, H. Stache, and F. Lömker, *Ann. Chem.*, **623**, 74 (1959).
(27) G. Gustafsson and M. Johanson [*Acta Chem. Scand.*, **2**, 42 (1948)] had explained small deviations from this single term rate law for the hydrolysis of chloral hydrate by assuming two other terms in the rate law, one simply first order with respect to the chloral hydrate anion and the other second order with respect to the chloral hydrate anion. However, these deviations were the result of a side reaction in which chloral hydrate is hydrolyzed to glyoxylate for which Gustafsson and Johanson had not corrected.
(28) C. Vermesse-Jacquinot, R. Schaal, and P. Rumpf, *Bull. soc. chim. France*, 2030 (1960).
(29) R. P. Bell, *Trans. Faraday Soc.*, **39**, 253 (1943).
(30) B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, **82**, 1773 (1960).
(31) P. Ballinger and F. A. Long, *ibid.*, **82**, 795 (1960).
(32) H. Adkins, W. Kutz, and D. D. Coffman, *ibid.*, **52**, 3212 (1930).