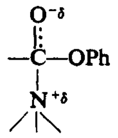
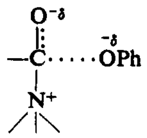
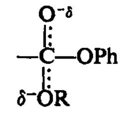


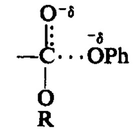
8a



8b



9a



9b

transition states for attack of nucleophile (**8a, 9a**) and departure of leaving group (**8b, 9b**). Alternatively the greater sensitivity of oxyanion nucleophilic attack to the nature of the α substituent has been suggested[9] to be due to the fact that the transition states for oxyanion attack (**7a, 7b**) is negatively charged and therefore more stabilized by electron withdrawal than that for amine attack which has no net charge. This conclusion is in complete accord with the results of this study as is the suggestion that the critical transition state for amine attack has no net charge (amine nitrogen is positively charged). The separation of oxyanion and amine rate constants (Figure 4) when the α substituents are polar is a manifestation of this proposal.

Acknowledgment. This work was supported by a grant from the National Institutes of Health.

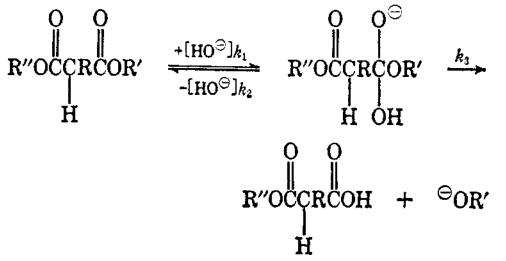
The Carbanion (E1cB) Mechanism of Ester Hydrolysis. I. Hydrolysis of Malonate Esters

Barton Holmquist[1] and Thomas C. Bruice[2]

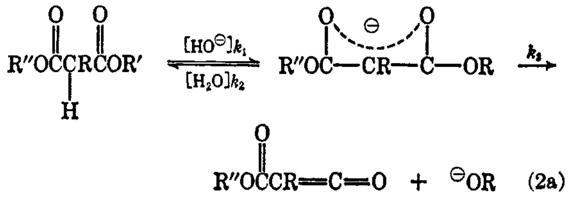
Contribution from the Department of Chemistry,
University of California at Santa Barbara, Santa Barbara, California 93106.
Received October 9, 1968

Abstract: The pH-log rate profiles for the hydrolysis of ethyl *o*-nitrophenyl malonate (I), ethyl *o*-nitrophenyl methylmalonate (III), ethyl *p*-nitrophenyl methylmalonate (IV), and ethyl *o*-nitrophenyl dimethylmalonate (V) have been determined in water at 30°, ionic strength = 1.0. Ester V hydrolyzes *via* the expected spontaneous general-base water-catalyzed and hydroxide-catalyzed mechanisms. Esters I, III, and IV, which contain α-protons, have rates of water-catalyzed hydrolysis of the expected magnitude; however, the profiles for these esters in the alkaline region are unusual and are characterized by accelerated rates and one or more plateaus. The reactions of 14 nucleophiles with the various esters were quantitatively studied and in certain cases the reactions were found to become independent of nucleophile at high nucleophile concentrations. Rate accelerations (up to 10^4) are observed only in the hydrolysis of esters containing α-hydrogens. The improbability that kinetically detectable tetrahedral intermediate formation accounts for the results is discussed. Neighboring-nitro-group participation is dismissed since ester IV and the *p*-nitrophenyl analog of I both show kinetic behavior of the same form as the *o*-nitrophenyl derivatives. A mechanism consistent with the kinetic data is proposed and discussed. Salient features of this mechanism include general base catalyzed α-proton abstraction to form resonantly stabilized carbanion intermediates and the spontaneous collapse of the formed carbanion to reactive ketenes.

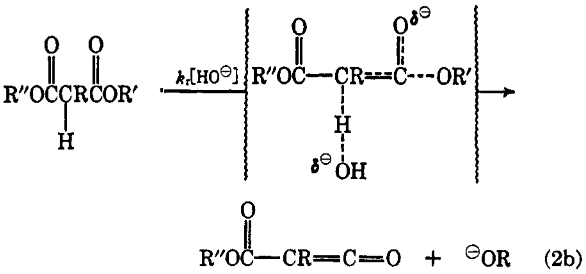
Three modes of HO^- attack on malonate esters are conceivable *a priori* (1 and 2a and 2b). In eq 1 the mechanism is that for normal alkaline hydrolysis of esters, in eq 2a it is preequilibrium formation of a carbanion with subsequent elimination of $R'O^-$, and in eq 2b it is a concerted reaction involving both proton abstraction and elimination in the single transition state. Since proton abstraction from an electron-deficient carbon may be general base catalyzed,[3] the

BAc2 

$$\mathrm{R''O\overset{O}{\overset{\|}{C}}\underset{H}{\underset{|}{C}}R\overset{O}{\overset{\|}{C}}OR'} \underset{-[HO^{\ominus}]k_2}{\overset{+[HO^{\ominus}]k_1}{\rightleftharpoons}} \mathrm{R''O\overset{O}{\overset{\|}{C}}\underset{H}{\underset{|}{C}}R\underset{OH}{\underset{|}{\overset{O^{\ominus}}{\overset{|}{C}}}}OR'} \xrightarrow{k_3} \mathrm{R''O\overset{O}{\overset{\|}{C}}\underset{H}{\underset{|}{C}}R\overset{O}{\overset{\|}{C}}OH} + {}^{\ominus}\mathrm{OR'} \quad (1)$$

E1cB 

$$\mathrm{R''O\overset{O}{\overset{\|}{C}}\underset{H}{\underset{|}{C}}R\overset{O}{\overset{\|}{C}}OR'} \underset{[H_2O]k_2}{\overset{[HO^{\ominus}]k_1}{\rightleftharpoons}} \mathrm{R''O\overset{O}{\overset{|}{C}}\text{—}\overset{\ominus}{C}R\text{—}\overset{O}{\overset{|}{C}}\text{—}OR} \xrightarrow{k_3} \mathrm{R''O\overset{O}{\overset{\|}{C}}CR{=}C{=}O} + {}^{\ominus}\mathrm{OR} \quad (2a)$$

E2 

$$\mathrm{R''O\overset{O}{\overset{\|}{C}}\underset{H}{\underset{|}{C}}R\overset{O}{\overset{\|}{C}}OR'} \xrightarrow{k_1[HO^{\ominus}]} \left[\mathrm{R''O\overset{O}{\overset{\|}{C}}\text{—}\underset{\underset{\delta^{\ominus}OH}{\vdots}}{\underset{H}{\underset{\vdots}{C}}}R{=\!=}\overset{O^{\delta\ominus}}{\overset{\|}{C}}\text{---}OR'}\right] \longrightarrow \mathrm{R''O\overset{O}{\overset{\|}{C}}\text{—}CR{=}C{=}O} + {}^{\ominus}\mathrm{OR} \quad (2b)$$

---

[1] Predoctoral Fellow of the National Institutes of Health. A portion of the material to be submitted by B. H. in fulfillment of the requirement for the Ph.D. in Chemistry, University of California at Santa Barbara.

[2] To whom inquiries should be addressed.

hydrolysis of malonate esters may occur through mechanisms analogous to eq 2a and 2b in which HO⁻ is replaced by general base.[4] In the E1cB mechanism of 2a the metastable product is a reactive ketene. The production of high-energy unsaturated products (benzynes, carbenes, and possibly fluorinated olefins)[5] has been suggested[6] to be a general characteristic of E1cB elimination reactions. Perusal of the literature reveals that no compelling cases of the E1cB or E2 mechanisms of ester hydrolysis have been described. The present study provides compelling evidence for the E1cB mechanism as a mode of hydrolysis of *o*- and *p*-nitrophenyl esters of α-carbethoxyacetic acid.

Experimental Section

Apparatus. All kinetic measurements were made either on a Gilford Model 2000 spectrometer equipped with four thermospacers through which water at 30 ± 0.1° was circulated or a Durrum-Gibson Model 13001 stopped-flow spectrophotometer equipped with a Kel-F cell and valve block through which water was circulated at 30 ± 0.2°. Ultraviolet and visible spectra were measured on a Perkin-Elmer 350 recording spectrophotometer at ambient temperature and infrared spectra were measured using a Perkin-Elmer 137 sodium chloride spectrophotometer. All pH measurements were taken at 30 ± 0.1° with a Radiometer Model 22 pH meter equipped with a Model 630 scale expander and combined glass calomel electrode (Radiometer GK 2021C).

Materials. Anhydrous potassium carbonate, potassium chloride, tris(hydroxymethyl)aminomethane (trizma base), boric acid, potassium phosphate monobasic, and hydroxylamine hydrochloride were reagent grade and used without further purification. Glacial acetic acid of reagent grade was redistilled. Morpholine (bp 128°) and N-ethylmorpholine (bp 138°) were distilled from barium oxide on a 1-ft Vigreux column prior to use. Ethylenediamine dihydrochloride, triethanolamine, hydrazine dihydrochloride, and glycine ethyl ester hydrochloride were recrystallized from aqueous ethanol. Methoxyamine was twice recrystallized from absolute ethanol (mp 148–150°). Imidazole was recrystallized from acetone–petroleum ether (bp 30–60°) and exhibited mp 88–89°. 2-Aminopyridine was recrystallized from chloroform–petroleum ether (mp 59–60°). All crystalline solids were dried and stored over P_2O_5 prior to use. Deionized freshly double-glass-distilled water was employed to prepare all solutions. Dioxane (Matheson Coleman and Bell) was of spectroquality. Since our interests were not of a preparative nature and our requirements for the kinetic studies were minimal our interest was to obtain pure ester. Therefore, yields were not recorded and no attempt was made to maximize them. Analyses were performed by Alfred Bernhardt, Max Plank Institute, Mülheim, Germany.

Ethyl *o*-Nitrophenyl Malonate (I). Ethyl hydrogen malonate was prepared from diethyl malonate by the method of Breslow, *et al.*[7] The crude acid was refluxed in excess thionyl chloride for 1 hr after which excess thionyl chloride was removed by flash evaporation and the resulting liquid distilled *in vacuo* to yield ethyl malonyl chloride (bp 60°, 5 mm). The *o*-nitrophenyl ester was prepared by slow addition of the acid chloride (3 g, 0.02 mol) to a hot solution of *o*-nitrophenyl (0.06 g, 0.022 mol) dissolved in dimethylaniline (2.66 g, 0.022 mol). After 1 hr at 50° the precipitate that formed was filtered off and excess dimethylaniline removed under vacuum. The resulting oil was zone sublimed[8] to yield ethyl *o*-nitrophenyl malonate as a light yellow oil. The infrared spectrum (neat) showed two sharp strong peaks at 1771 and 1733 cm^{-1} for C=O stretch as well as strong maxima at 1540 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.38; N, 5.33. Found: C, 51.92; H, 4.54; N, 5.53.

Ethyl *p*-Nitrophenyl Malonate (II). Anhydrous sodium *p*-nitrophenolate was prepared by addition of methanolic sodium methoxide to excess *p*-nitrophenol dissolved in methanol. Methanol was removed by evaporation and the resulting red solid washed with diethyl ether. To an ether suspension of excess sodium *p*-nitrophenolate (3 g, 0.0185 mol) was added 1 g (0.0067 mol) of ethylmalonyl chloride. After several hours the solution was filtered and the ether removed from the filtrate by evaporation to yield a yellow solid. Recrystallization of the solid from hexane gave the pure ester as white needles: mp 60–60.5°; strong ν_{max}^{neat} (KBr) 1769, 1734, 1590, and 1150 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO_6$: C, 52.27; H, 4.38; N, 5.53. Found: C, 52.37; H, 4.48; N, 5.71.

Ethyl *o*-Nitrophenyl Methylmalonate (III). To 300 ml of absolute ethanol containing 6 g (0.09 mol) of potassium hydroxide was added 20 g (0.115 mol) of diethyl methylmalonate (Aldrich). After 24 hr at 5°, ethanol was removed under vacuum and the monopotassium salt precipitated. The salt was washed with ether, taken up in 40 ml of water, and neutralized with concentrated hydrochloric acid. Extraction with ether, drying over magnesium sulfate, and evaporation of residual ether gave the half-ester as an oil. The crude half-ester was refluxed for 1 hr in a large excess of thionyl chloride, the excess thionyl chloride was removed by flash evaporation, and the ester acid chloride distilled from the residue *in vacuo* (bp 30–32° (1 mm)). Preparation of the *o*-nitrophenyl ester was identical with that of II with the exception that purification was by the zone sublimation technique;[8] light yellow oil: n^{25}D 1.5021; strong ν_{max}^{neat} 1785, 1741, 1540, and 1090 cm^{-1} (broad).

Anal. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.62; H, 5.20; N, 5.33.

Ethyl *p*-Nitrophenyl Methylmalonate (IV). This ester was prepared by the same procedure as for II using ethylmethylmalonyl chloride and anhydrous sodium *p*-nitrophenolate. Purification was by zone sublimation to yield a light yellow oil: strong ν_{max}^{neat} 1770, 1739, 1590, 1519, and 1336 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.91; H, 4.82; N, 5.37.

Ethyl *o*-nitrophenyl dimethylmalonate (V) was prepared by methylation of diethyl malonate, hydrolysis to the half-ester, conversion to the acid chloride, then reaction with *o*-nitrophenol to give the final product. Thus, to a solution of 300 ml of ethanolic sodium ethoxide (9.2 g, 0.4 g-atom, of Na dissolved in 300 ml of absolute ethanol) containing diethyl malonate (32 g, 0.2 mol) was slowly added methyl iodide (72 g, 0.5 mol). After 1 hr of reflux, excess methyl iodide and ethanol were removed by flash evaporation, and the resulting paste was poured into water. The ester was decanted from the two-phase system and the aqueous layer extracted with ether. The ester and ether extracts were combined and dried over anhydrous magnesium sulfate, and the ether was evaporated to give the diester as an oil. To the crude diester (22 g, 0.117 mol) was added potassium hydroxide (1.9 g, 0.105 mol) dissolved in 100 ml of absolute ethanol. Refluxing for 2 hr followed by evaporation of excess ethanol under vacuum gave a white solid which was washed with ether, then dissolved in 40 ml of water. Neutralization with concentrated hydrochloric acid and extraction with diethyl ether followed by drying over magnesium sulfate and evaporation of the ether afforded the half-ester. Refluxing of the crude half-ester in a large excess of thionyl chloride gave dimethylmalonyl chloride ethyl ester on distillation *in vacuo*, bp 42° (3.25 mm). Preparation and purification of the *o*-nitrophenyl ester were accomplished by the same method as for compound I, except that pyridine was used as a solvent in the esterification. The product was a light yellow oil: n^{25}D 1.4995; strong ν_{max}^{neat} 1783, 1751, 1612, 1536, and 1100 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.37; N, 4.98. Found: C, 55.41; H, 5.45; N, 5.17.

Ethylmalonylhydroxamic Acid. To 0.54 g (0.01 mol) of sodium methoxide and 2.1 g (0.03 mol) of hydroxylamine hydrochloride in 20 ml of methanol at 0° was added 1.5 g (0.01 mol) of ethylmalonyl chloride. After 1 min at 0°, 100 ml of diethyl ether was added and the solution filtered to remove the hydrochlorides. Evaporation of the ether and methanol from the filtrate gave a yellow oil which was zone sublimed in the usual manner. The product, a clear oil, was the last liquid band. Ir spectra showed carbonyl peaks at 1712 and 1785 cm^{-1}.

Anal. Calcd for $C_5H_9NO_4$: C, 40.81; H, 6.17; N, 9.52. Found: C, 40.32; H, 6.77; N, 9.41.

---

[3] (a) R. G. Pearson and F. V. Williams, *J. Amer. Chem. Soc.*, **76**, 258 (1954); (b) M. J. Gregory and T. C. Bruice, *ibid.*, **89**, 2327 (1967).

[4] For the E1cB mechanism, the discrete carbanion intermediate may be at steady state or formed *via* a facile preequilibrium. The limiting cases are, therefore, general and specific base catalysis [D. J. McLennan, *Quart. Rev.* (London), **21**, 490 (1967)].

[5] J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 187.

[6] H. M. R. Hoffman, *Tetrahedral Letters*, 4393 (1967).

[7] D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1286 (1944).

[8] T. C. Bruice and B. Holmquist, *ibid.*, **89**, 4028 (1967).

Table I. Derived Hydrolytic Rate Constants for Esters I, III, IV, and V Used to Calculate Theoretical Profiles

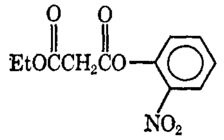
Ester	k_{H_2O},[a] M^{-1} sec^{-1}	k_{OH}, M^{-1} sec^{-1}	k_a, M^{-1} sec^{-1}	k_b, sec^{-1}	k_c, M^{-1} sec^{-1}	K_{a_1}, M	K_{a_2}, M
I	2.24×10^{-7}		3.16×10^{-1}	$\approx 1 \times 10^{2}$		1×10^{-7}	6.6×10^{-12}
III	8.12×10^{-8}		2.29×10^{-3}		4.93×10^{2}	1.75×10^{-7}	
IV	6.48×10^{-8}		6.02×10^{-4}		4.93×10^{2}	3.18×10^{-7}	
V	5.62×10^{-9}	2.82					

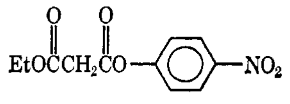
[a] The molarity of water 1.0 M in KCl, density 1.04 is *ca.* 53.4.

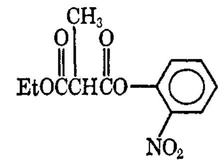
Kinetics. All kinetic measurements were carried out in water at $\mu = 1.0$ (with KCl) and at a temperature of 30 ± 0.1°. The appearance of *o*-nitrophenol with time was followed spectrophotometrically by recording the increase in optical density at 372.5 mμ, the isosbestic point of *o*-nitrophenol and *o*-nitrophenolate ion. For the *p*-nitrophenyl esters the appearance of *p*-nitrophenol was monitored at 347.3 mμ, an isosbestic point for *p*-nitrophenol and *p*-nitrophenolate ion. The disappearance of ester IV was monitored at 268.3 mμ, a λ_{max} of the ester and also an isosbestic point for the *p*-nitrophenol system. In a typical run, one drop of a peroxide-free dioxane solution of the ester was added to a 2-ml glass-stoppered cuvette containing a solution of nucleophile previously equilibrated at 30°.[9] The cuvette was quickly shaken and returned to the spectrophotometer for recording of absorbance. The concentration of ester was such that the absorbance of the solution at completion of reaction did not exceed 0.4, corresponding to a concentration of *o*-nitrophenol less than $\approx 2 \times 10^{-4}$ M or *p*-nitrophenol less than $\approx 8 \times 10^{-5}$ M. In all kinetic experiments the concentration of nucleophile and its conjugate acid were in large excess over that of the ester so that pseudo-first-order kinetics were obtained. The pH of the reaction solutions were checked before and periodically after reaction to ensure constancy. Reaction rates were followed for at least three half-lives and the values of the pseudo-first-order rate constants (k_{obsd}) were calculated from least-squares analysis of plots of ln $(OD_\infty - OD_0)/(OD_\infty - OD_t)$ *vs.* t, or by the method of Guggenheim.[10] All actual computations were carried out on an Olivetti-Underwood Programma 101 employing weighted least-squares programs written in this laboratory. The nucleophile and its conjugate acid served as buffer except where noted. Determination of rate constants for reactions whose half-lives were less than 2.5 sec were carried out on the stopped-flow spectrophotometer. For these experiments a 1 M KCl solution containing the appropriate amount of ester was mixed with the solution of nucleophile previously adjusted to $\mu = 1.0$ (with KCl) at the desired pH. In the case of I and II which were too unstable in 1 M KCl at neutral pH for stopped-flow measurement, the 1 M KCl solution of ester was brought to pH 3 (where hydrolysis is very slow) by addition of hydrochloric acid. Buffer capacity was such that the addition the pH 3 solution of ester in 1 M KCl did not effectively change the pH. The autoprotolysis constant used for water was 1.47×10^{-14}.[11]

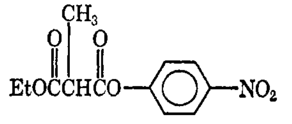
Product Analysis. In the case of the reaction of ethyl-*o*-nitrophenyl malonate (I) with hydroxylamine the concentration of the hydroxamic acid product, measured as the ferric complex, was determined by a modification of Lipmann's and Tuttle's[12] procedure. To eliminate solubility problems the ester–hydroxylamine reaction was run in 12.8% ethanol. The Beer's curve for ethyl malonyl hydroxamic acid was determined in the appropriate concentration of ethanol. In a typical analysis, to a cuvette containing 0.5 ml of ethanol was added 1 ml of 0.04 M hydroxylamine (pH 5.3) and 0.2 ml of ester dissolved in ethanol. The cuvette was then shaken and placed in the spectrophotometer for recording the release of *o*-nitrophenol. When liberation of *o*-nitrophenol was complete (ten half-lives) 1 ml of 3 M hydrochloric acid and 1 ml of 5% ferric chloride solution were added in that order. Absorbance of the hydroximate complex was measured at 540 mμ. In this way reaction at the ethyl ester carbonyl is kept at a minimum.

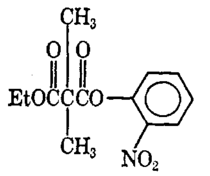
Results


I


II


III


IV


V

pH–Log k_{obsd} Profiles. The hydrolysis of esters I–V has been investigated. At constant pH, and in the presence of a great excess of buffer over ester, all hydrolytic rate constants (k_{obsd}) were found to be pseudo first order. Extrapolation of plots of k_{obsd} *vs.* buffer concentration to zero buffer provide as intercepts the values of the pseudo-first-order rate constants for lyate species (k_{hydr}). In certain cases, to be discussed later, curved buffer dilution plots were obtained and only approximate values of k_{hydr} could be obtained. For pH values of 3 or less, and 11.8 or greater, no external buffer was necessary to maintain constant pH. In Figure 1 there is plotted the log k_{hydr} *vs.* the constant pH at which the rate constants were determined for the malonate esters I, III, IV, and V. The points of Figure 1 are experimental and the lines are theoretical having been derived from eq 3 for I, eq 4 for III and IV, and eq 5 for V. In (5) k_{OH} is the second-order rate

$$k_{hydr} = k_{H_2O}[H_2O] + k_a \frac{K_{a_1}}{K_{a_1} + a_H} + k_b \frac{K_{a_2}}{K_{a_2} + a_H} \tag{3}$$

$$k_{hydr} = k_{H_2O}[H_2O] + k_a \frac{K_{a_1}}{K_{a_1} + a_H} + k_c \frac{K_{a_1}}{K_{a_1} + a_H}[HO^-] \tag{4}$$

$$k_{hydr} = k_{H_2O}[H_2O] + k_{OH}[HO^-] \tag{5}$$

constant for hydroxide ion catalysis and k_{H_2O} is the rate constant for spontaneous hydrolysis (*i.e.*, water attack). The rate constants k_a and k_b as well as the apparent dissociation constants K_{a_1} and K_{a_2} (Table I) will be

---

[9] Dioxane solutions of the esters were kept frozen when not in use. It has been reported (E. Sacher and K. J. Laidler, *Can. J. Chem.*, **42**, 2404 (1964)) that peroxides in dioxane can catalyze ester hydrolysis. For this reason esters were periodically made up in methanol and the rates compared to the dioxane solutions In no case did the rates differ by more than inherent experimental error.

[10] E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

[11] R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," Butterworth & Co. (Publishers), Ltd., London, 1959, p 544.

[12] F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).

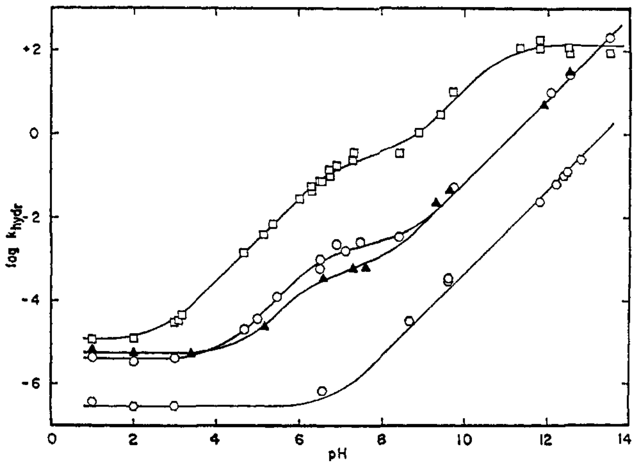


Figure 1. Plots of log k_{hydr} (k_{hydr} in units of sec^{-1}) *vs.* pH for the hydrolysis of esters: I (□), III (○), IV (▲), and V (○). The points are experimental and the lines calculated from eq 3 for I, eq 4 for III and IV, and eq 5 for V. Between steady-state and preequilibrium conditions reaction 9 predicts an $A \rightleftarrows B \rightarrow C$ process for which a lag phase should exist in the production of C. Due to the magnitude of the rate constant for *o*-nitrophenolate release at this pH differentiation of a lag phase from mixing time on the stopped-flow spectrophotometer could not be made. With the exception of the small pH range around 11, (9) predicts pseudo-first-order kinetics. In Figure 1 the values of log k_{obsd} pertain to these pseudo-first-order rate constants.

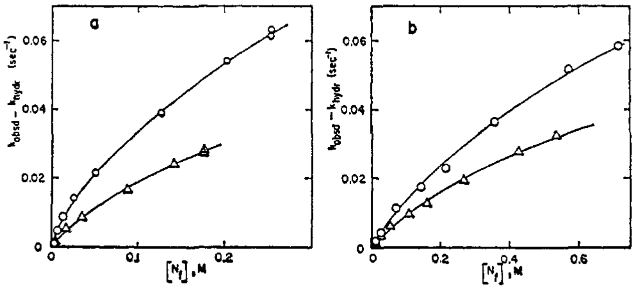


Figure 2. Plots of $k_{\mathrm{obsd}} - k_{\mathrm{hydr}}$ *vs.* [N_f], where [N_f] is the concentration for the free base form of the nucleophile, for the reactions of ester III with ethylenediamine (a) (○, pH 7.77; △, pH 7.38) and triethanolamine (b) (○, pH 8.37, △, pH 8.00).

shown to be complex combinations of rate constants. The K_{a_2} term could only be determined for ester I due to the magnitude of k_{hydr} at high pH.

Nucleophiles. In the case of ester V where no α-hydrogens are present, the rate of disappearance of ester was found to be dependent on the first power of the concentration of the basic form of the nucleophile, *viz.*

$$k_{\mathrm{obsd}} - k_{\mathrm{hydr}} = k_2'[N_T][K_n/(K_n + a_H)] = k_2[N_f] \quad (6)$$

where k_{obsd} is the first-order rate constant for appearance of *o*-nitrophenol plus *o*-nitrophenolate, k_{hydr} is the first-order hydrolytic constant provided by (5), k_2 the second-order rate constant for reaction of nucleophile with ester and [N_T] = [N_f] + [NH], where [N_f] represents the concentration of nucleophile and [NH] that of its conjugate acid. K_n is the acid dissociation constant of NH. All nucleophiles studied in the reaction with ester V gave linear plots of k_{obsd} *vs.* [N_f] from whose slopes was calculated k_2 (Table II).

Table II. Reaction of Nucleophiles with Ester V

Nucleophile	Concn range, M	No. of pH values	No. of k_{obsd}	k_2, M^{-1} sec^{-1}
Hydroxylamine	0.01–1.0	2	12	6.60×10^{-1}
Imidazole	0.04–0.5	2	12	1.26×10^{-2}
Carbonate	0.02–0.2	2	12	3.02×10^{-2} [a]
Methoxyamine	0.1–1.0	1	5	5.16×10^{-3}
Morpholine	0.05–1.0	2	10	3.36×10^{-4}
Hydroxide[b,c]	0.01–0.1	5	5	2.88
H_2O[d]	53.4	3	3	5.65×10^{-9}

[a] Only a slight slope is obtained in the plots of [CO_3^{2-}] *vs.* k_{obsd} and, therefore, k_2 here is given as a maximum value which may be in error by as much as 100%. [b] Determined in standardized solutions of KOH. [c] Calculated on the basis of $K_W = 1.47 \times 10^{-14}$. [d] Determined in HCl solutions.

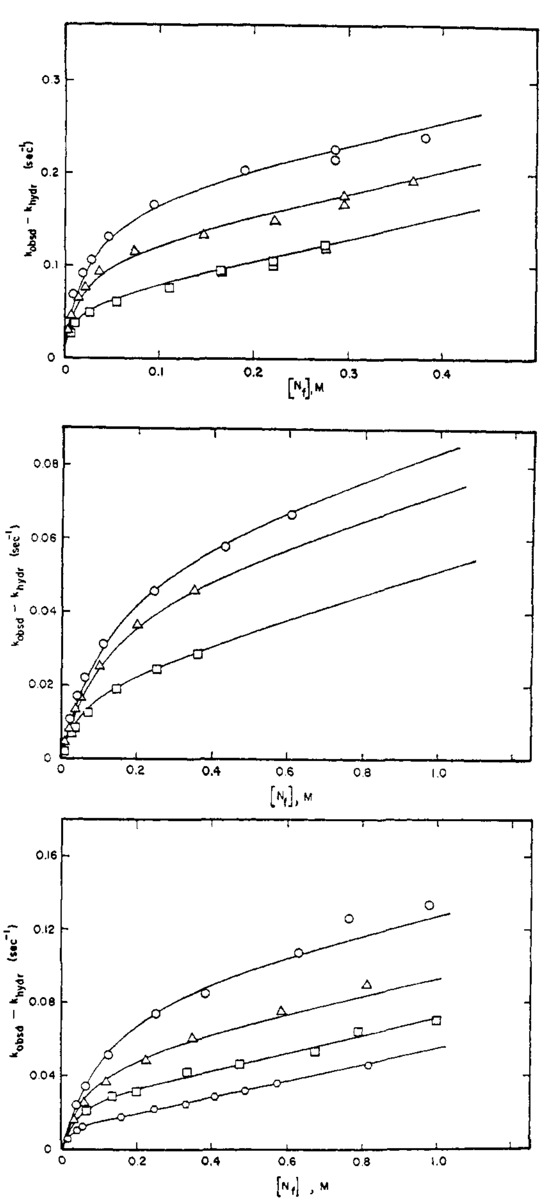


Figure 3. Plots of $k_{\mathrm{obsd}} - k_{\mathrm{hydr}}$ *vs.* the concentration of nucleophile in its free base form for the hydrolysis of ester III: top, morpholine (○, pH 8.66; △, pH 8.47; □, pH 8.28); middle, Tris (○, pH 8.30; △, pH 8.13; □, pH 7.85); bottom, N-ethylmorpholine (○, pH 8.43; △, pH 8.23; □, pH 8.02; ○, pH 7.78). The points are experimental and the lines theoretical having been derived from eq 20 using the constants of Table V.

The kinetics of the reactions of nucleophiles with the malonate esters containing either one or two enolizable

Table III. The Reaction of Nucleophiles with Esters I and III (Solvent H_2O; 30 ± 1°; $\mu = 1.0$ with KCl)

Nucleophile	pK_a	Concn range, M	No. of pH values[a]	No. of k_{obsd}	k_2,[b] M^{-1} sec^{-1}
		Ester I			
Acetate	4.61	0.1–1.0	3	10	[c]
Hydroxylamine	5.98	0.01–0.1	2	9	1.91×10^{1}
2-Aminopyridine	6.86	0.1–1.0	1	6	2.77×10^{-1}
Imidazole	7.15	0.02–0.5	2	12	7.77
Carbonate	10.33	0.04–0.15	1	3	7.34×10^{2} [d]
Methoxyamine	4.68	0.1–1.0	1	6	3.76×10^{-2}
Phosphate	7.10	0.04–0.15	3	11	5.1×10^{-1} [d,e]
Hydrazine	8.10	0.04–0.15	1	8	3.83×10^{1}
Borate		0.02–0.15	2	12	4.3×10^{1} [e]
Tris	8.10	0.02–1.0	4	34	[f]
Glycine ethyl ester	7.75	0.01–0.25	2	18	[f]
Morpholine	8.70	0.02–1.0	1	8	[f]
		Ester III			
Acetate	4.61	0.02–0.5	2	12	$>6 \times 10^{-5}$
Hydroxylamine	5.98	0.01–0.4	2	12	6.79
2-Aminopyridine	6.86	0.1–1.0	1	6	4.23×10^{-3}
Imidazole	7.15	0.02–0.5	2	12	3.47
Carbonate	10.33	0.06–0.3	2	6	4.6[d]
Methoxyamine	4.68	0.1–1.0	1	5	5.16×10^{-3}
Phosphate	7.10	0.012–1.0	3	18	[e]
Hydrazine	8.10	0.01–0.1	2	11	1.28×10^{-1}
Borate		0.04–0.2	3	16	[f]
Tris	8.10	0.01–1.0	3	25	[f]
Glycine ethyl ester	7.75	0.01–1.0	4	33	[f]
Morpholine	8.70	0.01–1.0	3	36	
N-Ethylmorpholine	7.98	0.01–1.0	4	41	[f]
Triethanolamine	7.95	0.01–1.0	2	18	[f]

[a] The pH values used are generally within ±0.5 pH unit of the pK_a of the buffer. [b] k_2 is the second-order rate constant calculated from the slope of k_{obsd} *vs.* concentration of the conjugate base of the buffer. [c] Term not detectable. [d] Calculated on the basis of the dianion. [e] Slight curvature noted. [f] Definite curvature was evident with these nucleophiles.

hydrogens (I, II, III, and IV) were found to be more complex than first- or second-order terms in nucleophile would predict. When the rates of hydrolysis of III were followed in the presence of increasing concentration of buffer at constant pH, the slopes of plots of k_{obsd} *vs.* $[N_T]$ decreased with increasing $[N_T]$ until at sufficiently high $[N_T]$ the lines appear to approach linearity. The following nucleophiles show this characteristic: phosphate, borate, Tris, glycine ethyl ester, N-ethylmorpholine, morpholine, ethylenediamine, and triethanolamine. A sampling of the curves obtained by plotting $k_{obsd} - k_{hydr}$ *vs.* $[N_f]$ is shown in Figure 2. With Tris, morpholine, and N-ethylmorpholine the linear portion at high $[N_f]$ is easily discernable and, therefore, a more detailed analysis of the dependence of $k_{obsd} - k_{hydr}$ on nucleophile concentration and pH was made (Figure 3). An analysis of the results of Figure 3 is given in the Discussion.

In contrast to the buffers enumerated above, linear plots of k_{obsd} *vs.* $[\text{buffer}_T]$ for the hydrolysis of III were obtained with acetate, hydroxylamine, methoxyamine, imidazole, 2-aminopyridine, and carbonate, Apparent second-order rate constants k_2 were calculated for these buffers *via* eq 6 (Table III).

Although esters I and II were somewhat difficult to work with, due to their rapid hydrolysis rates, qualitatively similar results were obtained to that of ester III. Thus, with Tris, glycine ethyl ester, borate, and morpholine, plots of k_{obsd} *vs.* $[\text{buffer}_T]$ were similarly curved and with imidazole, hydroxylamine, acetate, 2-aminopyridine, hydrazine, methoxyamine, and carbonate, they were apparently straight. For morpholine, buffer dilutions at two pH values are shown in Figure 4. Conditions employed for reaction of I and III with nucleophiles as well as derived rate constants for reactions clearly first order in $[N_f]$ [calculated from (6)] are given in Table III.

The values of k_{obsd} for the *p*-nitrophenyl analog of ester III (*i.e.*, ester IV) also exhibited nonlinear dependence on [buffer] with carbonate, phosphate, Tris, and morpholine, while that for acetate was linear. No other buffers were studied with this ester. In addition, it was found that k_{obsd} values for the disappearance of the *p*-nitrophenyl analog of ester I (*i.e.*, ester II) was not linearly dependent on morpholine concentration at the constant pH of 8.69. Additional assurance that the curved plots of k_{obsd} *vs.* [buffer] obtained with the malonate esters with enolizable hydrogens are characteristic of the ester and nucleophile comes from the linear dependence of k_{obsd} on [buffer] for the reaction of many α-substituted *o*-nitrophenyl acetates with N-ethylmorpholine, morpholine, and other buffers.[13]

Attempts to detect the accumulation of intermediates by means of spectral-time studies were unsuccessful. In Figure 5 are shown actual recordings of absorbance *vs.* time curves obtained on the Perkin-Emer 350 spectrophotometer for the reaction of Tris (0.1 M; pH 7.60, ambient temperature) with esters III and IV. With Tris as high as 1.0 M, tight isosbestic points were observed at 276 and 248 mμ for ester III, and at 305 and 242 mμ for IV. In general, time-spectral studies could not be made with other nucleophiles because of the rapid rates of hydrolysis. However, the rates of disappearance of ester IV measured at 268.7 mμ, a λ_{max} for the ester, were compared to the rates of appear-

---

(13) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 2985 (1969).

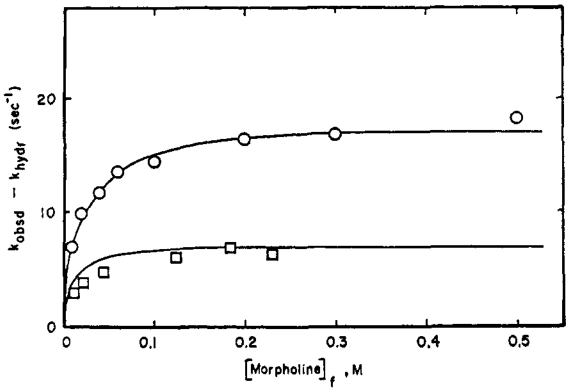


Figure 4. Plots of the pseudo-first-order rate constant corrected for lyate species catalysis *vs.* total morpholine concentration for the hydrolysis of ester I at two pH values: pH 8.69 (○), pH 8.29 (□).

ance of the *p*-nitrophenol measured at 347.3 mμ on the stopped-flow apparatus. The rates of ester disappearance and product appearance were found to be the same within experimental error in every experiment when morpholine (pH 8.66, 1.0–0.015 *M*), phosphate (pH 7.30, 0.3–0.03 *M*), and carbonate (pH 9.33, 0.3–0.03 *M*) were used as buffers.

Products. The hydroxamate test for the reaction of I with hydroxylamine (0.04 *M*, pH 5.3, 28.5% ethanol–H_2O (v/v)) indicated that a 57 ± 10% yield of ethylmalonylhydroxamic acid was formed. With no other esters or conditions was this analysis attempted.

Evidence that acylated imidazoles are formed when imidazole is used as a buffer with esters I and III comes from spectral analysis of these reactions. Imidazole (pH 7.14, 0.1 *M*) reacts with ester III with a rapid liberation of *o*-nitrophenol followed by a much slower (less than ten times) first-order decrease of optical density in the region around 250 mμ. By measuring the difference between the spectra immediately after complete liberation of *o*-nitrophenol and after complete reaction of the intermediate as measured at 250 mμ, the λ_{max} of the intermediate product was determined. The λ_{max} for the intermediate formed with ester III is 250 mμ. No intermediate was directly observable in the spectra generated from the reaction of imidazole (0.008 *M*, pH 7.14) with I. However, by comparing the rate of appearance of *o*-nitrophenol at 372.5 mμ to the rate of decrease in optical density at 250 mμ, the intermediate formed from I was shown to exist since the rate constant for release of *o*-nitrophenol was three times greater than the rate constant calculated from the absorbance decrease at 250 mμ. Likewise, intermediates exhibiting characteristics of those found with the malonate esters have been obtained from the reaction of imidazole with the *o*-nitrophenyl esters of α-bromo-, chloro-, and phenylacetic acids as well as others.[13] The similarity of the spectra of these intermediates to acetylimidazole (λ_{max} 245 mμ) and oxalylimidazole (λ_{max} 257 mμ),[8] the fact that conditions are identical with those for generation of oxalylimidazole from *o*-nitrophenyl hydrogen oxalate,[8] and the similar rates of absorbance decrease at 250 mμ to the rates of hydrolysis of oxalylimidazole all support the contention that the intermediates are the acylated imidazoles.

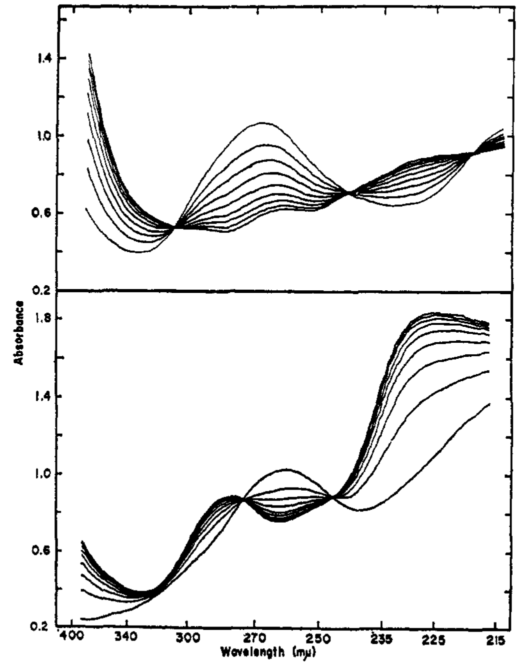


Figure 5. Time-spectral studies of the reaction of Tris with esters IV (top) and III (bottom) as recorded on the Perkin-Elmer 350 spectrophotometer at ambient temperature. For both reactions the concentration of Tris is 0.04 *M* at pH 7.60. The time between scans is ~4 min.

Discussion

The rate expressions necessary to describe the kinetics for hydrolysis of esters I, III, and IV are unusual (eq 3 and 4) whereas the rate expression (eq 5) for the hydrolysis of V is that previously established for the hydrolysis of simple α-substituted *o*-nitrophenyl acetate esters.[14] The log k_{hydr}–pH profiles for α-substituted *o*-nitrophenyl acetates are characterized[14] by a plateau region at low pH (k_{H_2O}) and an ascending slope of +1.0 at alkaline pH (from which k_{OH} is calculated). Inspection of the log k_{hydr} *vs.* pH profiles for esters I, III, and IV (Figure 1) reveals not one plateau and one ascending leg of slope +1 but two or three plateaus and one or two ascending regions of slope +1. The plateau at lower pH undoubtedly results from simple spontaneous hydrolysis (k_{H_2O}) as found for α-substituted nitrophenyl acetates,[14] *o*-nitrophenyl ethyl oxalate, *o*-nitrophenyl hydrogen oxalate,[8] etc. Indeed the values of k_{H_2O} for I, III, and IV are those predicted on the basis of a plot of log k_{H_2O} *vs.* σ_I for other α-substituted *o*-nitrophenyl acetates.[14] Because at zero [buffer] only the lyate species and ester are present in solution, the two ascending regions and the plateaus at alkaline pH must be associated with an unusual mechanism for lyate species catalysis. The transitions in the log k_{hydr}–pH profiles above pH 6 establish the formation of at least one kinetically detectable intermediate, whose rate of formation and breakdown to products is pH dependent.

The *o*-nitro group has been shown to provide anchimeric assistance in a number of reactions.[15] To ensure that the *o*-nitro group is not directly partic-

---

(14) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **90**, 2982 (1968).

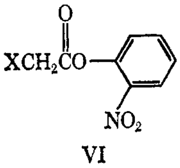
(15) A. D. Mease, M. J. Strause, I. Hornman, L. J. Andrews, and R. M. Keefer, *ibid.*, **90**, 1797 (1968), and references therein.

ipating in the solvolysis of the malonate esters the *p*-nitro isomer of III (*i.e.*, IV) was synthesized and its hydrolytic profile determined. This profile (Figure 1) can be seen to parallel closely that for ester III eliminating direct nitro-group participation as the cause of the unusual profiles. In addition, the reaction of IV with buffers exhibits the same type plots of [buffer$_T$] *vs.* k_{obsd} as noted for the reaction of the corresponding *o*-nitrophenyl ester with the same buffers.

The reaction of bases with esters I, II, III, and IV can yield one of two type intermediates. The first, and most likely, is a malonate carbanion; the second is a tetrahedral intermediate formed by addition of nucleophile to the ester carbonyl carbon. The following evidence indicates that the rationale for the tetrahedral intermediate is chemically unsound. First, through O^{18} exchange experiments it has been established that nucleophilic attack of HO^- on phenyl benzoate is rate determining (*i.e.*, partitioning of the tetrahedral intermediate, if formed, being completely to products).[16] Since *o*- or *p*-nitrophenolate ion are better leaving groups than phenolate ion the rate-determining step for HO^- attack at the carbonyl carbon of *o*- or *p*-nitrophenyl esters is most assuredly initial nucleophilic attack. Secondly, comparison of the second-order rate constants for nucleophilic attack by 14 nucleophiles on 2,2,2-trifluoroethyl thiolacetate (k_s) and *p*-nitrophenyl acetate (k_n) established the relationship of (7).[17] The lack of an element effect is reasonably

$$\log k_s = 1.0 \log k_n + 0.6 \qquad (7)$$

attributable to nucleophilic attack being rate determining for both substrates. Thirdly, formation of a detectable tetrahedral intermediate can not account for the fact that the malonate esters with enolizable hydrogens are more susceptible to hydrolysis in the alkaline pH range than anticipated. Thus, the lyate species catalyzed rate constants for hydrolysis of a large series of esters of type VI, where X represents substituents with σ_I[18] values ranging from -0.07 to $+0.85$, have been found[14] to follow the relationship of (8). For



VI

$$\log k_{\mathrm{OH}} = 0.84 \log k_{\mathrm{H_2O}} + 8.0 \qquad (8)$$

the *o*-nitrophenyl malonate esters possessing an α-hydrogen (I and III) the values of k_{OH}, calculated from (8), are approximately 2.6×10^2 l. mol^{-1} sec^{-1} and 1.1×10^2 l. mol^{-1} sec^{-1}, respectively. The experimental values of k_{OH} (calculated from the ascending leg of the log k_{obsd} *vs.* pH profile between pH 3 and 5) for I and III are *ca.* 8×10^3 and *ca.* 2×10^2 fold greater, respectively, than the calculated values. This same analysis may be made employing the ascending portion of the log k_{obsd}–pH profiles above pH 9 on the assumption that this catalysis might represent normal hydroxide attack on the carbonyl. Again, the experimental values for the rate constants are greater than predicted by eq 8. For I the ratio of $k_{\mathrm{OH}}^{\mathrm{expt}}/k_{\mathrm{OH}}^{\mathrm{calcd}}$ is 2.8×10^2. Lastly, the necessity for an enolizable hydrogen in order to observe the special features of this facile mechanism for hydrolysis finds no rationale through a supposition of the formation of a tetrahedral intermediate.

In contrast to mechanisms involving tetrahedral intermediates a mechanism involving a carbanion intermediate is readily supported. Thus, of the numerous α-substituted *o*-nitrophenyl esters of type VI examined by us,[14] the abnormal mechanism for lyate species hydrolysis is seen only when X = COOEt, and probably CN, and perhaps $(CH_3)_2S^+$ (see following paper). Though carbanion formation can be facilitated by strong inductive withdrawal of electrons,[19] carbon acids which possess pK_a values less than pK_w are invariably those characterized by resonance delocalization of the nonbonded electron pair on carbon to a more electronegative heteroatom.[20] Of the esters of general structure VI the abnormal mechanisms were found only when X could resonantly stabilize a carbanion intermediate or perhaps where an ylide structure could result.

All data obtained in this study suggest a reasonantly stabilized carbanion to be the necessary intermediate. For lyate species catalyzed hydrolysis of I, II, III, and IV the only basic species present to effect proton abstraction are H_2O and HO^-. By the principle of microscopic reversibility recombination of carbanion must be with H_3O^+ and H_2O, respectively. These considerations lead to (9). As stated previously the $k_{\mathrm{H_2O}}[H_2O]$ path of (9) is associated with the plateaus in the log k_{hydr}–pH profiles at lowest pH. This path represents the kinetically isolatable general base catalyzed (by H_2O) attack of H_2O at the ester carbonyl and will not be referred to again. If the $k_{\mathrm{H_2O}}[H_2O]$ path is ignored, a steady state assumption in S^- leads to (10). A comparison of (10) and (4) reveals both are

$$\begin{tikzcd} \mathrm{SH} \arrow[r, shift left, "\substack{k_1[\mathrm{H_2O}] \\ k_2[\mathrm{HO^-}]}"] \arrow[rr, bend left, "k_{\mathrm{H_2O}}[\mathrm{H_2O}]"] & \mathrm{S^-} \arrow[l, shift left, "\substack{k_{-1}[\mathrm{H_3O^+}] \\ k_{-2}[\mathrm{H_2O}]}"] \arrow[r, "k_3"] & \text{products} \end{tikzcd} \qquad (9)$$

$$k_{\mathrm{obsd}} = \left(\frac{k_1k_3}{k_{-2} + k_3}\right)\left\{\frac{(k_{-2} + k_3)/k_{-1}}{[(k_{-2} + k_3)/k_{-1}] + a_{\mathrm{H}}}\right\} + \frac{k_2k_3[\mathrm{HO^-}]}{k_{-2} + k_3}\left\{\frac{(k_{-2} + k_3)/k_{-1}}{[(k_{-2} + k_3)/k_{-1}] + a_{\mathrm{H}}}\right\} \qquad (10)$$

of the same mathematical form so that (10) provides the correct log k_{hydr}–pH profile for esters III and IV. From the comparison of (10) and (4) the relationships shown in (11) are obtained. Inspection of (9) reveals

$$\begin{aligned} K_{a_1} &= (k_{-2} + k_3)/k_{-1} \\ k_a &= k_1k_3/(k_{-2} + k_3) \\ k_c &= k_2k_3/(k_{-2} + k_3) \end{aligned} \qquad (11)$$

---

(16) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956).

(17) (a) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2121 (1967); (b) N. G. Kundu and T. C. Bruice, *J. Org. Chem.*, **33**, 422 (1968).

(18) M. Charton, *ibid.*, **29**, 1222 (1964).

(19) (a) A. Streitwieser, Jr., and D. Holtz, *J. Amer. Chem. Soc.*, **89**, 692 (1967); (b) A. Streitwieser, Jr., A. P. Marchard, and A. H. Pudjaatmaka, *ibid.*, **89**, 693 (1967).

(20) (a) R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953); (b) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965.

that as pH is increased, $k_1[\mathrm{H_2O}] + k_2[\mathrm{HO^-}]$ will increase and $k_{-1}[\mathrm{H_3O^+}] + k_{-2}[\mathrm{H_2O}]$ will decrease, while k_3 will not change. This leads directly to the conclusion that at some pH value, S^- will change from a steady-state concentration to one predictable on the basis of preequilibrium formation (12) and at still higher pH, k_3 will be rate determining (13). When k_3 becomes rate

$$\mathrm{SH} \underset{+\mathrm{H}^+}{\overset{\overset{K_{\mathrm{a}_1}}{-\mathrm{H}^+}}{\rightleftharpoons}} \mathrm{S}^- \xrightarrow{k_3} \text{products} \tag{12}$$

$$k_{\mathrm{obsd}} = \frac{k_3 K_{\mathrm{a}_1}}{K_{\mathrm{a}_1} + a_{\mathrm{H}}} \tag{13}$$

$$k_{\mathrm{obsd}} = k_3$$

determining it follows from eq 13 that a third plateau in the pH–log k_{obsd} profile should be observed. Inspection of the log k_{obsd}–pH profile for I (Figure 1) reveals a third plateau at pH values above 11. For esters III and IV this plateau is not reached at the technical limits of applicability of the stopped-flow spectrophotometer and one must assume that within the pH range available for study k_3 never becomes rate limiting for III and IV.

A test of the reasonableness of (9) is possible by employing the relationships of (11)—values of K_{a_1}, k_{a}, and k_{c} are found in Table I—and the limiting rate at high pH (*i.e.*, k_3). For ester I, eq 10 pertains in the range of pH 4 to 10 where carbanion is at steady state ($k_{\mathrm{c}} = 6.5 \times 10^4\ M^{-1}\ \mathrm{sec}^{-1}$). The calculated values for the various constants for ester I are: $k_1 = 0.32\ \mathrm{sec}^{-1}$; $k_2 = 6.5 \times 10^4\ M^{-1}\ \mathrm{sec}^{-1}$; $k_{-1} = 10^9\ M^{-1}\ \mathrm{sec}^{-1}$; and from the plateau at highest pH, $k_3 = 100$. A value of k_{-2} was obtained ($4.0\ \mathrm{sec}^{-1}$) by ascertaining that constant which must be employed with the determined values of k_1, k_2, k_{-1}, and k_3 to fit the experimental pH profile. The pH dependence of the calculable pseudo-first-order rate constants which determine the shape of the reaction coordinant picture associated with (9) are provided in Table IV. Inspection of Table IV leads to the conclusion that the species S^- is at steady state below pH 9 but approaches preequilibrium formation at higher pH values with the rate-determining step being k_3 at pH 12. At pH 7.0, the partitioning coefficient ($k_{\mathrm{r}_1}/k_{\mathrm{f}_2}$) of S^- to reactants and products is unity.

Table IV. Reaction Coordinant Parameters for the Mechanism of (9) with Ester I

$$\mathrm{SH} \underset{k_{\mathrm{r}1}}{\overset{k_{\mathrm{f}1}}{\rightleftharpoons}} \mathrm{S}^- \xrightarrow{k_{\mathrm{f}2}} \text{products}$$

pH	k_{f_1}, sec^{-1}	k_{r_1}, sec^{-1}	k_{f_2}, sec^{-1}
7	0.32	100	100
9	0.96	5.0	100
11	65	4.0	100
12	650	4.0	100

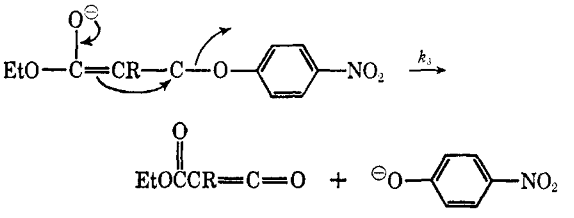
Values of the rate constants for recombination of carbanion with hydronium ion (k_{-1} of eq 10) for acetone, acetylacetone, and ethyl acetoacetate have been measured by Eigen[21] at 25° but recombination constants for malonate esters are not known. Comparing the value obtained for k_{-1} (10^9) in the case of I to those above, it is found that this value is *ca.* 100 times greater than for acetylacetone ($1.2 \times 10^7\ M^{-1}\ \mathrm{sec}^{-1}$), *ca.* 20 times greater than for ethyl acetoacetate but *ca.* 50 times less than that for acetone ($5 \times 10^{10}\ M^{-1}\ \mathrm{sec}^{-1}$). Thus, the calculated value of k_{-1} in the hydrolysis of I is of the magnitude expected. The value calculated for k_{-2} ($4.0\ \mathrm{sec}^{-1}$) is *ca.* 10 times greater than the corresponding value for acetylacetone. This value is most reasonable since the enol of I should be less internally hydrogen bonded than that of acetylacetone so that proton transfer from $\mathrm{H_2O}$ to S^- should be associated with a rate constant greater than that for the anion of acetylacetone (whose recombination rate with $\mathrm{H_2O}$ is $0.4\ \mathrm{sec}^{-1}$).[22]

As a further check of the reasonableness of the constants it may be noted that $(k_1/k_{-1})(k_{-2}/k_2) \cong 10^{-14}$ which is the approximate value of K_{w}. With the knowledge that $k_3 \gg k_{-2}$ in the case of I, inspection of (10) and (11) reveals that k_{a} of (4) equals k_1, k_{c} equals k_2, and also that K_{a_1} is k_3/k_{-1}—the actual partitioning coefficient of the steady-state carbanion between products and reactants.

If $k_3 \gg k_{-2}$ in the case of esters III and IV (which is assuredly the case since k_3 for these esters is greater than 10^2) then values of k_2 and k_1 may be calculated. Thus, for III $k_2 = 4.93 \times 10^2\ M^{-1}\ \mathrm{sec}^{-1}$ and $k_1 = 2.29 \times 10^{-3}\ \mathrm{sec}^{-1}$, for IV $k_2 = 4.93 \times 10^2\ M^{-1}\ \mathrm{sec}^{-1}$ and $k_1 = 6.02 \times 10^{-4}\ \mathrm{sec}^{-1}$. The value for k_3/k_{-1} for III and IV are 1.75×10^{-7} and 3.18×10^{-7}, respectively. The conclusions applied to I can then be applied to III and IV with the exception that the carbanion will be at steady state up to pH *ca.* 13, depending of course on the actual value of k_3.

The ratios of k_2/k_1 for I and III are $2.06 \times 10^5\ M^{-1}$ and $2.15 \times 10^5\ M^{-1}$, respectively, while for IV this ratio is *ca.* $8 \times 10^5\ M^{-1}$. The Brønsted β calculated from these values and the pK_{a} of $\mathrm{HO^-}$ (15.7) and $\mathrm{H_2O}$ (−1.74) is close to 0.3 for I, III, and IV. This rather low sensitivity of rate to base strength indicates that the proton is little transferred in the transition state for carbanion formation.

In mechanism (9) the step k_3 most reasonably involves an elimination of phenolate species and the transient formation of ketenes (14). The formation of the hydroxamate with hydroxylamine and acylimidazoles in imidazole buffer solutions (see Results) is in accord with the trapping of ketene intermediates.



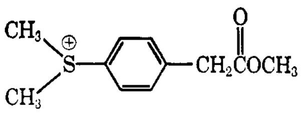
(14)

Little attention has previously been accorded the possibility of a carbanion mechanism for ester hydrolysis. In fact, perusal of the literature resulted in our finding but two studies in which this type mechanism has been postulated. To explain the small positive entropy of activation for the hydrolysis of 4-dimethylsulfoniophenylacetate (VII), Casanova, Werner, and

---

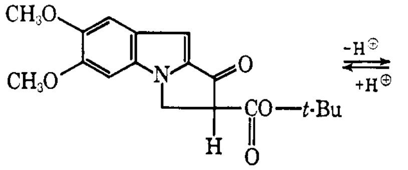
[21] M. Eigen, *Angew. Chem. Int. Ed. Engl.*, 3, 1 (1964).

[22] I. Amdur and G. G. Hammes, "Chemical Kinetics: Principles and Selected Topics," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 148.

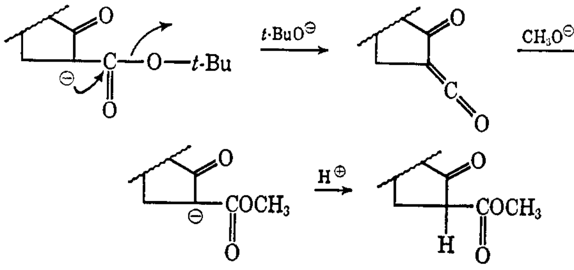


VII

Kiefer[23] have suggested a preequilibrium carbanion formation with slow decomposition to product alcohol and a ketene. In support of their suggestion was the finding that the α-hydrogen exchange rate exceeded that for hydrolysis by eightfold. Remers, Roth, and Weiss[24] have suggested carbanion formation with subsequent elimination to yield a ketene to explain the *t*-butoxide-catalyzed transesterification reaction of VIII (15). The similarity of VIII to I–IV is obvious.

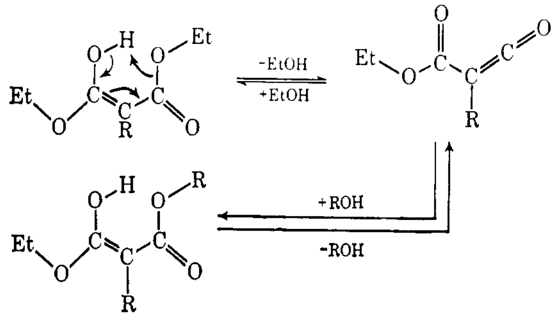


VIII



(15)

From equilibrium, kinetic and activation parameter measurements for the alcoholysis of diethyl malonate and a series of substituted malonates, it has been concluded that the uncatalyzed transesterification involves a cyclic enolate intermediate.[25] We believe it likely that the mechanism is that of (16).



(16)

Buffer Catalysis. The kinetics for the reaction of V with buffers is normal by comparison to the reaction of other acyl *o*- and *p*-nitrophenyl esters.[26] Thus, the pseudo-first-order rate constants for ester disappearance, when corrected for lyate species catalyzed hydrolysis (*i.e.*, $k_{obsd} - k_{hydr}$), are proportional to the first power of the concentration of the conjugate base species of the buffer. In contrast, for some buffers, the rates of hydrolysis of esters I, II, III, and IV exhibit a nonlinear dependence on buffer concentration (Figures 2, 3, and 4) with the apparent second-order rate constant calculated on the basis of the conjugate base species of buffer decreasing with increasing concentration of base species (see Results). From the previous discussion, these findings suggest (17). From (17) the kinetic expression of (18) may be derived

$$\mathrm{SH} \underset{k_{-2}[\mathrm{BH}]}{\overset{k_1[\mathrm{B}]}{\rightleftharpoons}} \mathrm{S}^- \xrightarrow{k_3} \text{products} \qquad (17)$$

$$k_{obsd} = \frac{k_1[\mathrm{B}]}{k_2 a_\mathrm{H}[\mathrm{B}]/K_\mathrm{B} k_3 + 1} \qquad (18)$$

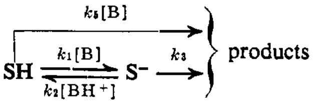
where [B] is the concentration of the base species of the buffer and K_B the acid dissociation constant of its conjugate acid. The experimental data for the reaction of I with morpholine (Figure 4) at two pH values were fit to (18) by manual regression analysis solving for the coefficients of B (*i.e.*, k_1 and k_2a_H/K_Bk_3). The points of Figure 4 are experimental and the lines calculated from (18) employing the coefficients tabulated in Table V. Equation 18 predicts that at constant pH k_{obsd} is a linear function of [B] at low values of [B], but independent of [B] and dependent on the pH at high concentrations of [B]. For ester III reacting with morpholine, N-ethylmorpholine, and Tris (Figure 3), k_{obsd} is found to be linearly dependent on [B] at low concentrations of [B] changing to a lessened linear dependence on [B] at its high concentrations. In order to fit these experimental data to theoretical plots eq 19 was employed. Equation 19 is derivable from a kinetic scheme assuming the base species to simultaneously attack at both the α-hydrogen (k_1) and ester carbonyl (k_5) group (20) and may be compared to (9).

Table V. Kinetic Parameters for the Reactions of Esters I and III with Selected Nucleophiles

Buffer	k_1, M^{-1} sec^{-1}	k_2/k_3, M^{-1}	k_5, M^{-1} sec^{-1}
	Ester I		
Morpholine	9.0×10^2	5.0×10^1	
	Ester III		
Tris[a]	0.45	1.85	0.032
Morpholine[a]	8	4.32×10^1	0.24
N-Ethylmorpholine[a,b]	1	3.6×10^1	0.044

[a] Results dependent upon 6 to 11 k_{obsd} values determined at each of 3 pH values. [b] N-Ethylmorpholine proved to be somewhat unstable at the pH values used for this nucleophile and solutions drifted a maximum of 0.07 unit during some of the slower reactions. Degassing solutions with N_2 had no effect. For this reason the values for k_1 and k_2/k_3 may have up to 50% error.

$$k_{obsd} = \frac{k_1[\mathrm{B}]}{k_2 a_\mathrm{H}[\mathrm{B}]/K_\mathrm{B} k_3 + 1} + k_5[\mathrm{B}] \qquad (19)$$



$$\mathrm{SH} \underset{k_2[\mathrm{BH}^+]}{\overset{k_1[\mathrm{B}]}{\rightleftharpoons}} \mathrm{S}^- \xrightarrow{k_3} \text{products}; \quad \mathrm{SH} \xrightarrow{k_5[\mathrm{B}]} \text{products} \qquad (20)$$

The points of Figure 3 are experimental and the lines theoretical having been derived from (19)—for constants employed see Table V.

---

(23) J. Casanova, Jr., N. D. Werner, and H. R. Kiefer, *J. Amer. Chem. Soc.*, **89**, 2411 (1967).

(24) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Org. Chem.*, **30**, 2910 (1965).

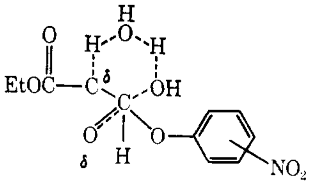
(25) S. P. Rowland, L. Z. Pearcy, C. H. Mack, and H. J. Janssen, *J. Chem. Soc.*, *B*, 404 (1968).

(26) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1.

The buffer rates which are linear functions of buffer concentration all derive from the reaction of weaker bases ($pK_a < \sim 7.5$) with the esters I, II, III, and IV. The linear dependence of k_{obsd} on [B] for these cases may be attributed to the value of $k_1[B]/k_2[BH^+]$ decreasing with decrease in pK_a of BH^+ so that for weaker bases product arises predominantly through the path associated with $k_5[B]$. The ratio of a_H/K_B for all buffer experiments was close to unity to assure maximum buffer capacity. Therefore, in the cases of linear plots of $k_{obsd} - k_{hydr}$ *vs.* [buffer], reactions were carried out at lower pH than for the cases in which these plots were curved. Since the values of $a_H[B]/K_B$ must vary in a like fashion for all buffers, the linearity of the plots for buffer bases of low K_B must be found in the ratio of k_2/k_3. The value of k_3 is constant, but as K_B decreases k_2 must increase, since BH becomes a better general acid catalyst. It follows, therefore, that as pK_B decreases, $k_2a_H[B]/K_Bk_3$ will become greater than 1.0 and the rate constant for reaction *via* proton abstraction will become independent of [B]. The linear dependence on [B] must then be attributed to the k_5 step of (20). In other words, sensitivity of the overall reaction of proton abstraction to pK_B in the acidity range of pH $\cong$ pK_B is greater than that for nucleophilic attack at the ester carbonyl group so that for bases characterized by conjugate acids of low pK_a simple nucleophilic attack at the ester carbonyl group predominates.

The best line (plot not shown) through the points obtained by plotting log k_1 for ester I *vs.* pK_a' for the bases water, hydroxide, tris(hydroxymethyl)aminomethane, morpholine, and N-ethylmorpholine is of slope ≈ 0.4. Though no great importance can be placed on Brønsted coefficients derived from studies employing bases of divergent structures[26] the value of 0.4 may be compared to that of 0.3 obtained for lyate species reacting with esters I, III, and IV.

In conclusion, we have shown that malonate esters possessing both enolizable hydrogens and good leaving groups (*o*- and *p*-nitrophenoxide) are converted *via* a general-base mechanism to intermediates which spontaneously decompose to products. We are unable to envision any reasonable mechanism which does not include a carbanion as the intermediate. The conversion of carbanion to products is spontaneous. Therefore, the direct product formed from carbanion depends upon the involvement or lack of involvement of solvent water in the transition state. If solvent is not involved the direct product must be a ketene. However, it is possible to conceive of a transition state (IX) in which solvent is involved. In IX hydrolytic products are formed directly from carbanion *via* an intramolecular general base catalyzed attack of water at the ester carbonyl carbon. At present we really have no evidence to differentiate between transition state IX and mechanisms involving ketene formation (as eq 9 and 20).



IX

Acknowledgment. This work was supported by a grant from the National Institutes of Health.