The Carbanion Mechanism of Ester Hydrolysis. II. *o*-Nitrophenyl α-Cyano- and α-Dimethylsulfonioacetate 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.
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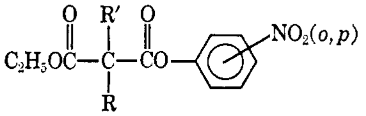
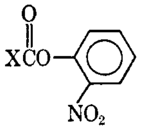
Abstract: The pH–log rate profiles for the hydrolysis of the *o*-nitrophenyl esters $\mathrm{CNCH_2COO}$-*o*-NP (III), $\mathrm{CNC(CH_3)_2COO}$-*o*-NP (IV), and $\mathrm{(CH_3)_2S^+CH_2COO}$-*o*-NP (V) have been determined at 30° in water at ionic strength = 1.0. The profile for IV is quantitatively expressed by spontaneous general-base catalysis by water- and hydroxide ion catalyzed hydrolysis. For III and V the term for spontaneous hydrolysis is obtained but at high pH the rates of alkaline hydrolysis become independent of pH. The plateau at high pH is attributed to specific base catalyzed α-proton abstraction with formation of a resonantly stabilized carbanion for III and a ylide for V. Accelerated rates of hydrolysis for III and V over those expected on the basis of linear free-energy relationships gives evidence that spontaneous collapse of carbanion to reactive ketenes occurs with III and possibly with V. Second-order rate constants for reaction of ten nucleophiles with the esters III, IV, and V have been determined and found to be independent of nucleophile concentration. This result supports carbanion formation as being specific base catalyzed. Reaction of nucleophiles other than hydroxide ion is most reasonably at the ester carbonyl carbon. Evidence is presented that *p*-nitrophenyl acetate does not form an unreactive carbanion in the alkaline pH range, as previously reported. The second-order rate constant for alkaline hydrolysis of *p*-nitrophenyl acetate is, within experimental error, invariant between pH 7 and 0.5 *M* KOH.

In the preceding paper[3] there are described kinetic studies of the hydrolysis of and reaction of nucleophiles with malonate esters of type I. The kinetics of reactions of ester types Ia and Ib with both lyate species



Ia, R = R′ = H
b, R = H; R′ = CH_3
c, R = R′ = CH_3

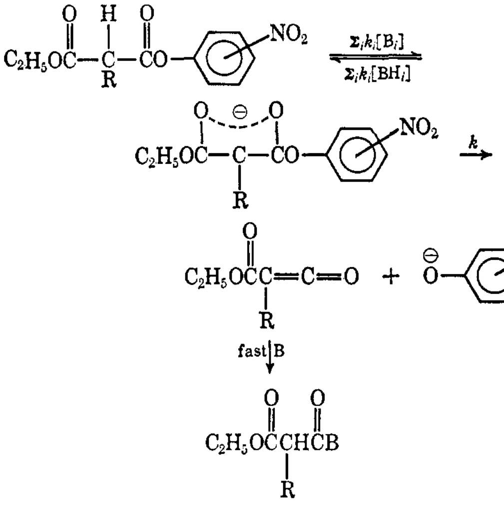
and buffer bases were found to be abnormal by comparison to the reactions of ten esters of type II, for which σ_I of X varies from −0.07 to +0.85.[4] The unique features of the reactions of Ia and Ib included



II

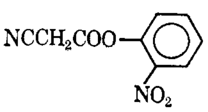
X = CH_3, CH_3CH_2, CH_3CH_2S, $PhCH_2$, $PhOCH_2$, $BrCH_2$, $ClCH_2$, Cl_2CH, $C_5H_5N^+CH_2$, $(CH_3)_3N^+CH_2$

large rate enhancements (to 10^3) of alkaline hydrolysis, log rate *vs.* pH profiles and buffer dilution plots which require the assumption of the formation of kinetically detectable intermediates. In contrast to Ia and Ib, the ester Ic, which has no enolizable protons, exhibited normal and predictable patterns of reaction with both lyate species and buffer bases. The reactions of Ia and Ib find explanation through a mechanism involving base attack at the ester α-hydrogen. The unique structural feature of Ia and Ib, as compared to the series of esters II, is the ability of the carbethoxy group to resonantly stabilize the proposed carbanion intermediate.

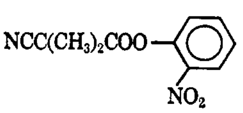


(1)

A logical extension of our initial investigation is to determine the ability of other substituents to stabilize the anionic intermediate through resonance delocalization or ylide formation. Herein we report kinetic studies involving esters III, IV, and V.



III



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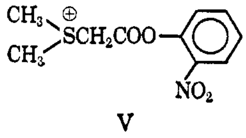

V

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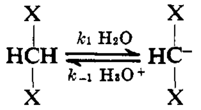
[1] Predoctoral Fellow of the National Institutes of Health. A portion of the material to be submitted by B. H. in fulfillment of the requirement for the Ph.D. in Chemistry, University of California at Santa Barbara.

[2] To whom inquiries should be addressed.

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

[4] (a) B. Holmquist and T. C. Bruice, *ibid.*, **91**, 2982 (1969); (b) B. Holmquist and T. C. Bruice, *ibid.*, **91**, 2985 (1969).

Stabilization of carbanions by the cyano group *via* decrease in the pK_a of the conjugate acid is well documented.[5] In comparing the rates of C–H bond ionization, and recombination of anions with H_3O^+ for compounds of VI, the order of ionization rate

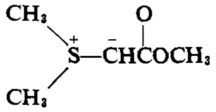


$$\mathrm{HC(X)_2H} \underset{k_{-1}\ \mathrm{H_3O^+}}{\overset{k_1\ \mathrm{H_2O}}{\rightleftharpoons}} \mathrm{HC(X)_2^-} \qquad (2)$$

VIa, X = $COOC_2H_5$
b, X = CN
c, X = NO_2

constants and recombination constants are found to be c > b > a and b > a > c, respectively.[5,6] This suggests that the cyano carbon anion possesses greater relative electron pair localization on carbon than in the case of the carbethoxy-stabilized anion for which case greater delocalization to oxygen is to be expected. Therefore, in reaction 1 it is anticipated that preequilibrium formation of carbanion intermediate should occur with III at a pH lower than noted in the hydrolysis of the corresponding malonate ester.[3] Our objectives in investigating III have been: first, to determine if the carbanion mechanism of (1) occurs and, second, to determine if the kinetics indicate the anticipated preequilibrium formation of a carbanion intermediate.

In recent years, a large number of stable sulfonium ylides have been prepared.[7] Of particular interest is the finding by Casanova and Rutolo[8] that the ester ylide VII can be isolated as a crystalline solid. The



VII

possibility of forming an ylide of type VII in the course of a hydrolytic reaction as an intermediate along the reaction path of hydrolysis has led us to investigate the kinetics of reaction of V with lyate species and nucleophiles..

Experimental Section

Materials and Apparatus. The apparatus used and the purification procedures for the buffers employed in this study are described in the preceding paper.[3] *p*-Nitrophenyl acetate was from an earlier study.[9] All crystalline solids were dried and stored over P_2O_5 prior to use. Freshly deionized and double-glass-distilled water was employed to prepare all solutions. Dioxane (Matheson Coleman and Bell) was spectroquality. Since our interests were not of a preparative nature, and our requirements for kinetic studies were minimal, our interest was to obtain pure esters and, therefore, yields were generally not recorded.

***o*-Nitrophenyl cyanoacetate (III)** was prepared by mixing phosphorus oxychloride (2 g, 0.013 mol), *o*-nitrophenol (6 g, 0.043 mol), and cyanoacetic acid (5 g, 0.059 mol), and heating the mixture at 60° for 3 hr. The solid which formed on cooling was crushed and extracted four times with diethyl ether. Concentration of the ether extracts gave the desired ester. Recrystallization from diethyl ether gave the pure ester as white crystals (mp 71–71.5°; $\nu_{\max}^{\mathrm{KBr}}$ 1787, 1612, 1530, 1355, and 1150 cm^{-1} (broad), weak C≡N absorbtion at 2280 cm^{-1}).

Anal. Calcd for $C_9H_6N_2O_4$: C, 52.43; H, 2.93; N, 13.58. Found: C, 52.35; H, 3.16; N, 13.41.

***o*-Nitrophenyl dimethylcyanoacetate (IV).** Dimethylcyanoacetyl chloride was prepared from cyanoacetic acid by the method of Biechler and Taft.[10] The acid chloride exhibited bp 41–42° (5 mm) (lit.[10] 75° (15 mm)). To excess sodium *o*-nitrophenolate (5 g, 0.025 mol) suspended in 20 ml of diethyl ether maintained at 0° was slowly added dimethylcyanoacetyl chloride (1 g, 0.0097 mol). After complete addition the mixture was brought to room temperature and allowed to stand for 1 hr. Solids were then removed by filtration, and the diethyl ether was flash evaporated from the filtrate to yield a yellow oil. Addition of methanol to this oil and subsequent cooling gave white crystals of the desired product. Recrystallization from absolute ethanol gave the pure material (mp 50–51°, $\nu_{\max}^{\mathrm{KBr}}$ 1780, 1540, 1350, and 1160 cm^{-1}).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.53; H, 4.39; N, 11.79.

***o*-Nitrophenyl α-Dimethylsulfonioacetate Bromide (V).** To 0.5 g, (0.002 mol) of *o*-nitrophenyl bromoacetate[3] was added, under anhydrous conditions, excess methyl sulfide (20 g, 0.32 mol). After 3 hr at room temperature the excess methyl sulfide was removed by flash evaporation and the residue taken up in hot methanol. Crystallization was initiated by the addition of diethyl ether, and, on cooling, white crystals of the product were obtained. Three recrystallizations from methanol–ether gave the pure material (mp 101–102°; strong $\nu_{\max}^{\mathrm{KBr}}$ 1175, 1530, 1342, and 1160 cm^{-1}).

Anal. Calcd for $C_{10}H_{12}BrNO_4S$: C, 37.28; H, 3.75; Br, 24.80; N, 4.34; S, 9.95. Found: C, 37.11; H, 3.89; Br, 24.66; N, 4.17; S, 9.76.

Kinetics. All kinetic measurements were carried out in water at μ = 1.0 (with KCl) and at 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. The release of *p*-nitrophenol was measured at 397.3 mμ, the isosbestic point for *p*-nitrophenol and its anion. Methods of determining and calculating rate constants were identical with those described in the preceding paper.[3]

Results

The pseudo-first-order rate constants (k_{obsd}) for disappearance of esters III, IV, and V were determined at constant pH values as a function of buffer concentration. Plots of k_{obsd} *vs.* buffer concentration were linear in all cases (with the exception of methoxyamine) providing as slope the apparent second-order rate constants for buffer reaction (k_2') and as intercept the rate of lyate species catalysis of hydrolysis (k_{hydr}). At each pH value eq 3 pertains. Values of k_{obsd} below pH 3 and above pH 11.8 were found in standardized solu-

$$k_{\mathrm{obsd}} = k_{\mathrm{hydr}} + k_2'[\mathrm{buffer_T}] \qquad (3)$$

tions of hydrochloric acid and carbonate-free potassium hydroxide, respectively. The log k_{hydr} *vs.* pH profiles for III, IV, and V are provided in Figure 1. The points of Figure 1 are experimental, and the curves theoretical, being derived from eq 4 for ester IV and eq 5 for esters III and V employing the constants of Table I. True

Table I. Hydrolytic Constants Used for Calculation of Theoretical pH *vs.* Log k_{hydr} Profiles for Esters III, IV, and V

Ester	$k_{\mathrm{H_2O}}$, M^{-1} sec^{-1}	k_{OH}, M^{-1} sec^{-1}	k_a, sec^{-1}	pK_{app}, M
III	1.21×10^{-5}		1.74	8.57
IV	5.15×10^{-6}	1.7×10^2		
V	1.7×10^{-5}		1.20	9.08

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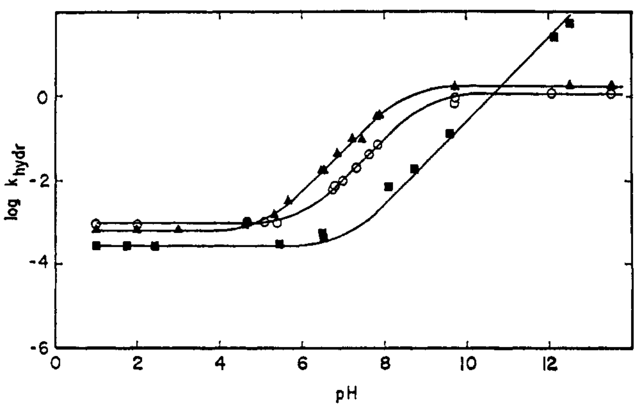

Figure 1. pH-log k_{hydr} profiles for the lyate species catalyzed hydrolysis of esters III (▲), IV (■), and V (○). Unitsof k_{hydr} are sec^{-1}. The points are experimental and the lines theoretical being derived from eq 5 for esters III and V and eq 4 for ester IV.

$$k_{\mathrm{hydr}} = k_{\mathrm{H_2O}} + k_{\mathrm{OH}}[\mathrm{HO^-}] \qquad (4)$$

$$k_{\mathrm{hydr}} = k_{\mathrm{H_2O}} + k_{\mathrm{a}}[K_{\mathrm{app}}/(K_{\mathrm{app}} + a_{\mathrm{H}})] \qquad (5)$$

second-order rate constants (k_2) for buffer base reacting with esters were obtained from

$$k_2 = k_2'[(K_{\mathrm{b}} + a_{\mathrm{H}})/K_{\mathrm{b}}] \qquad (6)$$

where K_{b} is the dissociation constant of the conjugate acid species of the buffer and a_{H} the hydrogen ion activity as determined with the glass electrode. In Tables II, III, and IV there are listed the bases employed and the conditions of the kinetic experiments, and in Table V the calculated values of k_2 are recorded. For trifluoroethoxide, an additional buffer was necessary to maintain constant pH since the rates were run at ≈5.4 pH units lower than the pK_{a} of trifluoroethanol. For these reactions 0.02 M phosphate buffer pH 7.10 was used. In the pH range investigated $a_{\mathrm{H}} \gg K_{\mathrm{b}}$ so eq 3 and 6 combine to give 7.

$$k_{\mathrm{obsd}} - k_{\mathrm{hydr}} - k_2[\mathrm{phosphate}] = k_2[\mathrm{F_3CCH_2O^-}] \qquad (7)$$

Plots of k_{obsd} *vs.* [methoxyamine$_{\mathrm{T}}$] according to eq 3 were found not to be linear but to exhibit upward curvature for all three esters (Figure 2). When ($k_{\mathrm{obsd}} - k_{\mathrm{hydr}}$)/[$\mathrm{NH_2OCH_3}$] was plotted against [$\mathrm{NH_2OCH_3}$] a linear relationship was obtained with slope k_{gb} and intercept k_2 (eq 8). For III, $k_{\mathrm{gb}} = 2.4 \times 10^{-1}\ M^{-2}$ sec^{-1} and $k_2 = 7.6 \times 10^{-2}\ M^{-1}$ sec^{-1}; for IV, $k_{\mathrm{gb}} = 5.65$

Table II. The Reaction of Nucleophiles with Ester III

Nucleophile	Concn range, M	pH range	No. of pH values	No. of k_{obsd}
Phosphate[a]	0.02–0.1	6.55–7.15	2	6
Acetate	0.05–1.0	4.63–5.33	3	18
Tris	0.015–1.0	7.83–7.90	2	14
Imidazole	0.02–0.1	6.04–6.33	2	7
Hydroxylamine	0.002–0.006	5.37	1	2
2-Aminopyridine	0.1–1.0	6.52	1	6
Carbonate[a]	0.04–0.15	9.73	1	3
Methoxyamine	0.04–1.0	4.66–5.58	3	17
2,2,2-Trifluoroethoxide	0.16–1.1	7.10	1	6
Water	53.4[b]	1–3	3	3
Hydroxide	0.05–0.5		2	4[c]

[a] As the dianion. [b] Approximate molarity of water at 30°, μ = 1.0 with KCl. [c] Duplicates at two pH values.

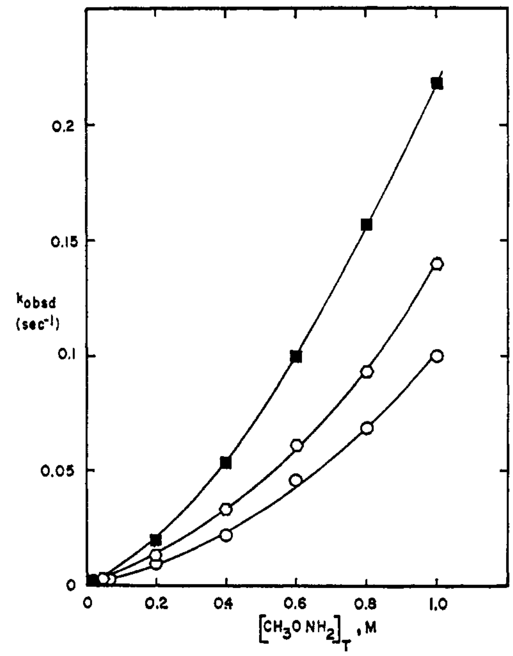

Figure 2. Plots of the pseudo-first-order rate constant for the hydrolysis of esters III (■, pH 5.26) and IV (○, pH 4.84; ○, pH 4.67) *vs.* total methoxyamine concentration.

Table III. The Reaction of Nucleophiles with Ester IV

Nucleophile	Concn range, M	pH range	No. of pH values	No. of k_{obsd}
Phosphate[a]	0.01–0.1	6.49	1	6
Acetate	0.1–0.5	5.46	1	6
Tris	0.01–0.2	8.12–8.77	2	11
Imidazole	0.02–0.5	6.04–6.33	2	12
Hydroxylamine	0.002–0.01	5.37	3	4
2-Aminopyridine	0.1–1.0	6.52	1	6
Carbonate[a]	0.02–0.2	9.60	1	6
Methoxyamine	0.2–1.0	5.26	1	6
Water	53.4[b]	1.0–3.0	3	3
Hydroxide	0.02–0.05		2	2
2,2,2-Trifluoroethoxide	0.08–1.1	7.10	1	6

[a] As the dianion. [b] Approximate molarity of water at 30°, μ = 1.0 with KCl.

Table IV. The Reaction of Nucleophiles with Ester V

Nucleophile	Concn range, M	pH range	No. of pH values	No. of k_{obsd}
Phosphate[a]	0.03–0.3	6.53–6.92	2	15
Acetate	0.08–1.0	5.13	1	6
Imidazole	0.05–0.25	7.14	1	3
Ethylenediamine[b,c]	0.1–0.01	7.35	1	6
Carbonate[a]	0.3–0.06	9.75	1	3
2-Aminopyridine	1.0–0.1	6.83	1	6
Methoxyamine	0.01–1.0	4.67–4.84	2	14
2,2,2-Trifluoroethoxide	0.08–0.48	7.10	1	4
Water	53.4[d]	1–3	2	2
Hydroxide	0.02–0.5		3	3

[a] As the dianion. [b] Corrected for contribution of neutral molecule. [c] Calculated on basis of monocation. [d] Approximate molarity of water at 30°, μ = 1.0 with KCl.

Table V. Second-Order Rate Constants for the Reaction of Esters III, IV, and V with Various Nucleophiles

Nucleophile	pK_a	l. M^{-1} sec^{-1}		
		Ester III	Ester IV	Ester V
Phosphate[a]	7.10	1.86	7.18×10^{-2}	1.85
Acetate	4.61	4.70×10^{-3}	1.37×10^{-3}	1.06×10^{-2}
Tris	8.10	*b*	8.50×10^{-2}	
Imidazole	7.15[c]	65.0	3.40	54.2
Hydroxylamine	5.98	280	1.50×10^{2}	
2-Aminopyridine	6.86[c]	3.88×10^{-2}	4.71×10^{-3}	3.05×10^{-2}
Carbonate[a]	10.33	*b*	1.89	121.0
Methoxyamine	4.68[c]	*d*	*d*	*d*
Ethylenediamine[e]	7.53			1.38[f]
Water	−1.74	1.21×10^{-5}	4.92×10^{-6}	1.72×10^{-5}
Hydroxide	15.7		1.70×10^{3}	
Trifluoroethoxide	12.36[g]	$2.0 \pm 0.5 \times 10^{4}$	3.04×10^{4}	6.7×10^{4}

[a] As dianion. [b] No apparent buffer catalysis over concentrations used. [c] See reference 11. [d] See Results section. [e] As monocation. [f] Corrected for contribution of neutral species. [g] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **81**, 1050 (1959).

$$k_{\text{obsd}} - k_{\text{hydr}} = k_2[\text{CH}_3\text{ONH}_2] + k_{\text{gb}}[\text{CH}_3\text{ONH}_2]^2 \quad (8)$$

$\times\ 10^{-3}\ M^{-2}$ sec^{-1} and $k_2 = 6.5 \times 10^{-2}\ M^{-1}$ sec^{-1}; and for V, $k_{\text{gb}} = 2.86 \times 10^{-1}\ M^{-2}$ sec^{-1} and $k_2 = 6.4 \times 10^{-2}\ M^{-1}$ sec^{-1}.

Spectrophotometric analysis was employed in order to detect possible intermediate formation. Repetitive scanning of the reactions in progress between 400 and 220 mμ gave spectra with tight isosbestic points for the reaction of all three esters with all the buffers investigated except imidazole. With the exception of imidazole, therefore, no intermediate formation could be noted. Because of the rapid rate of ester disappearance at high pH repetitive scanning studies were limited to pH values less than 7.50. In the case of the reaction of imidazole with III and V, intermediates were observed which by difference spectra showed $\lambda_{\max}$ at 270 and 266 mμ, respectively. The rates of intermediate disappearance were found to be at least tenfold slower than the release of *o*-nitrophenol from the parent ester. The second ionization constant of phosphoric acid is comparable to that for imidazolium ion but no intermediate could be detected on solvolysis of III, IV, and V in phosphate buffer at the same pH as employed for the imidazole experiments. The similarity of $\lambda_{\max}$ for the intermediates to those of other N-acylimidazoles,[3,9,11–13] the fact that the conditions are identical with those for generation of acetylimidazole from *p*-nitrophenyl acetate,[13] oxalylimidazole[11] and ethylmalonylimidazole[3] from the corresponding *o*-nitrophenyl esters, and the similar rates of decay of the intermediates to those of other N-acylimidazoles provides assurance that the intermediates observed with III and V are the corresponding acylimidazoles. No intermediate could be detected in the reaction of imidazole with ester IV indicating that either no intermediate is formed, or that, more likely, the rate of hydrolysis of dimethylcyanoacetylimidazole is faster than the attack of imidazole upon the parent ester under the conditions tested (0.1–0.008 *M*, imidazole, pH 7.14). It has been found that trimethylacetylimidazole hydrolyzes faster than acetylimidazole[14] and in a like manner dimethylcyanoacetylimidazole might be expected to hydrolyze faster than cyanoacetylimidazole. Thus, since the rate of disappearance of cyanoacetylimidazole, the most reactive of the two acetylimidazoles, is much faster than the rate of hydrolysis of ester IV a buildup of dimethylcyanoimidazole would not be expected.

Hydroxide Ion Catalysis of *p*-Nitrophenyl Acetate (*p*-NPA) Hydrolysis. Table VI summarizes the results obtained for the spectrophotometrically determined rate constants for the hydrolysis of *p*-NPA determined in potassium hydroxide solutions with no added buffer. The concentration of hydroxide ion was in large excess of ester in order to maintain a constant pH. Also included in Table VI are the corresponding values of k_{OH} determined by Bruice and Mayahi[15] autotitrimetrically. It is evident that over the pH range of 7.94 to 0.5 *M* KOH the second-order rate constant for hydroxide attack remains constant within experimental error.

Table VI. Dependence of Calculated Second-Order Rate Constants for Hydroxide Ion Catalyzed Hydrolysis of *p*-Nitrophenyl Acetate on the Concentration of Hydroxide Ion

[HO$^-$], *M*	k_{obsd}, sec^{-1}	k_{OH},[a] M^{-1} sec^{-1}
5.00×10^{-1}	7.85	15.7[b]
5.00×10^{-2}	6.39×10^{-1}	12.8[b]
2.00×10^{-2}	2.89×10^{-1}	14.4[b]
1.00×10^{-2}	1.29×10^{-1}	12.9[b]
5.00×10^{-3}	6.70×10^{-2}	13.4[b]
7.75×10^{-5}	1.21×10^{-3}[c]	15.6[d]
1.48×10^{-5}	2.30×10^{-4}[c]	15.6[d]
5.88×10^{-6}	9.15×10^{-5}[c]	15.6[d]
1.29×10^{-6}	2.10×10^{-5}[c]	16.3[d]

[a] The value of k_{OH} determined by Jencks and Carriuolo [*J. Amer. Chem. Soc.*, **82**, 1778 (1960)] at 25°, $\mu = 0.3$, is 14.8 M^{-1} sec^{-1}. [b] In this study *via* stopped-flow spectrophotometry, no buffer used. [c] Autotitrimetric rates of Bruice and Mayahi.[15] [d] Recalculated on basis of pK_w = 13.83 for 30° [R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," Butterworth & Co. (Publishers), Ltd., London, 1959, p 544] rather than 14 as employed by Bruice and Mayahi.[15]

Discussion

The pH *vs.* log k_{hydr} profiles for the hydrolysis of esters III, IV, and V are provided in Figure 1. The

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(14) T. H. Fife, *ibid.*, **87**, 4597 (1965).

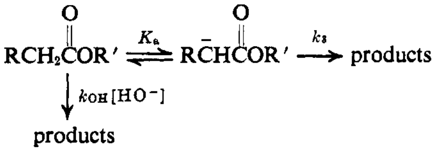
(15) T. C. Bruice and M. F. Mayahi, *ibid.*, **82**, 3067 (1960).

profile for ester IV, which contains no enolizable hydrogens, is normal when compared to the pH *vs.* log k_{hydr} profiles for other α-substituted *o*-nitrophenyl acetates.[4a] The plateau rate at low pH is due to spontaneous water hydrolysis ($k_{\mathrm{H_2O}}$) and the region of slope +1 to hydroxide ion catalyzed hydrolysis (k_{OH}). We have previously found that eq 9 pertains for the hydrolysis of α-substituted *o*-nitrophenyl acetates.[4a] When the value of $k_{\mathrm{H_2O}}$ for IV is substituted in eq 9 it is

$$\log k_{\mathrm{OH}} = 0.84 \log k_{\mathrm{H_2O}} + 8.0 \tag{9}$$

found that the calculated value of k_{OH} is close to that obtained experimentally. Therefore, it is concluded that the hydrolysis of IV is quite normal involving attack of H_2O and HO^- at the ester carbonyl.

In contrast to the pH *vs.* log k_{obsd} profile for IV those for esters III and V are found to be unusual when compared to the profiles for numerous other α-substituted *o*-nitrophenyl acetate esters.[4a] For III and V the unusual feature is the plateau region in the alkaline pH range. The rate expression (eq 5) for hydrolysis of both III and V suggests a normal mode of spontaneous hydrolysis (*i.e.*, water-assisted general base attack of water at the carbonyl group[3,4a,11]). In the alkaline pH range the change from first-order to zero-order dependence on hydroxide ion establishes the formation of a species which may, or may not be, intermediate along the reaction path. Since it is most unlikely that these species could be kinetically detectable tetrahedral intermediates formed by addition of HO^- to the ester carbonyl[16] and since the structural dissimilarity between III and IV is the lack of enolizable hydrogens in IV, it appears likely that the intermediates are kinetically distinguishable carbanions. Carbanion formation may be specific base catalyzed (10) or general base catalyzed (14). For eq 10, if equilibrium



$$\mathrm{RCH_2\overset{\overset{O}{\|}}{C}OR'} \overset{K_a}{\rightleftharpoons} \mathrm{R\bar{C}H\overset{\overset{O}{\|}}{C}OR'} \xrightarrow{k_3} \text{products} \qquad \downarrow k_{\mathrm{OH}}[\mathrm{HO^-}] \text{ products} \tag{10}$$

conditions exist between ester and carbanion then eq 11

$$k_{\mathrm{hydr}} = \frac{k_{\mathrm{OH}}K_{\mathrm{w}} + k_3K_{\mathrm{a}}}{K_{\mathrm{a}} + a_{\mathrm{H}}} \tag{11}$$

pertains. If k_3 is large and constitutes the major path to products, eq 12 results; however, if k_3 is insignificant,

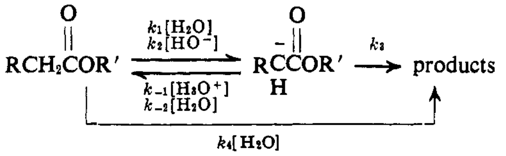
$$k_{\mathrm{hydr}} = \frac{k_3K_{\mathrm{a}}}{K_{\mathrm{a}} + a_{\mathrm{H}}} \tag{12}$$

eq 13 is obtained. Equations 11, 12, and 13 are kinetically equivalent and the inclusion of the spontaneous

$$k_{\mathrm{hydr}} = \frac{k_{\mathrm{OH}}K_{\mathrm{w}}}{K_{\mathrm{a}} + a_{\mathrm{H}}} \tag{13}$$

water rate in 11, 12, and 13 results in equations which are of the same form as 5 and thus produce the expected pH *vs.* log rate profiles.

In the case of the hydrolysis of nitrophenyl malonate esters it was concluded[3] that the mechanism was one of general base catalyzed proton abstraction to yield intermediate carbanions. For lyate species general-base catalysis eq 14 would pertain. Ignoring the step



$$\mathrm{RCH_2\overset{\overset{O}{\|}}{C}OR'} \underset{k_{-1}[\mathrm{H_3O^+}],\ k_{-2}[\mathrm{H_2O}]}{\overset{k_1[\mathrm{H_2O}],\ k_2[\mathrm{HO^-}]}{\rightleftharpoons}} \mathrm{R\underset{H}{\overset{-}{C}}\overset{\overset{O}{\|}}{C}OR'} \xrightarrow{k_3} \text{products};\quad \mathrm{RCH_2COR'} \xrightarrow{k_4[\mathrm{H_2O}]} \text{products} \tag{14}$$

$k_4[H_2O]$ for spontaneous solvolysis, a steady-state assumption in carbanion leads to eq 15. Inspection of

$$k_{\mathrm{hydr}} = \frac{(k_3k_2/k_{-1})[\mathrm{HO^-}] + (k_1k_3/k_{-1})}{(k_{-2} + k_3)/k_{-1} + a_{\mathrm{H}}} \tag{15}$$

eq 15 reveals that it is not kinetically identical with eq 11, 12, or 13 and unless the term $(k_3k_2/k_{-1})[\mathrm{HO^-}]$ is considered unimportant, it does not predict the correct pH *vs.* log k_{hydr} profile for III and V in the alkaline pH range. Since it is certain that $k_2 \gg k_1$ and since the plateau in the alkaline range of pH (Figure 1) pertains to as high as $[\mathrm{HO^-}] = 0.5$, we conclude that carbanion formation is specific base catalyzed by hydroxide ion.

The question remains: are the carbanions intermediates along the reaction path (k_3 of eq 10 is kinetically important) or are they formed in a nonproductive equilibrium? A means of answering this question is to ascertain if the value of k_{hydr} in the range of pH where k_{hydr} is dependent on the first power of $[\mathrm{HO^-}]$ is greater than anticipated. For this purpose we have employed the linear free-energy relationship of plotting log k_{OH} *vs.* log $k_{\mathrm{H_2O}}$.[17] If k_3 in eq 10 is assumed to be insignificant then the slope of +1 of the pH–log rate profiles represents hydroxide attack at the carbonyl carbon of the un-ionized ester. If this were so, then the values of k_{OH} calculated from the portion of the pH–log rate profiles of the slope +1 should fit the line obtained when log k_{HO} is plotted *vs.* log $k_{\mathrm{H_2O}}$, *i.e.*, eq 9, for other α-substituted *o*-nitrophenyl acetates. Substitution of values for log $k_{\mathrm{H_2O}}$ found for esters III and V into eq 9, one obtains values of k_{OH} for these esters which are approximately 100 and 10 times greater than

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[16] See ref 3 for a discussion of this point.

[17] This means of plotting is essentially equivalent to a $\rho\sigma_{\mathrm{I}}$ plotting procedure since log $k_{\mathrm{H_2O}}$ is a linear function of σ_{I}. The assignment of kinetic σ_{I} values to the substituent $-\mathrm{S^+(CH_3)_2}$ as well as to the substituent $-\mathrm{N^+(CH_3)_3}$ apparently cannot be made on the basis of the acid dissociation constants of the corresponding acids. Thus, the pK_{a} of $\mathrm{(CH_3)_2S^+CH_2COOH}$ determined in this laboratory is 1.15 ± 0.1 at 30°, $\mu = 0.2$ [compare to 1.3 by R. P. Bell and A. A. W. Coller, *Trans. Faraday Soc.*, **61**, 1445 (1965)] and when this value is employed along with the data of Charton [M. Charton, *J. Org. Chem.*, **29**, 1222 (1964)] one obtains the σ_{I} value of +0.86. Employing this value plus the σ_{I} constants provided by Charton, it is found that in a log $k_{\mathrm{H_2O}}$ *vs.* σ_{I} plot the points for $-\mathrm{S^+(CH_3)_2}$ and $-\mathrm{N^+(CH_3)_3}$ are quite low indicating either that the water rates for these esters are unusually low or that the thermodynamically based σ_{I} values are not kinetically applicable for these formally charged substituents. [That these large deviations are not a consequence, in some way, of the high ionic strength used (1.0) is shown by the relatively small changes in apparent second-order rate constants for attack by HO^- (calculated from eq 13) and 2-aminopyridine on ester V with decreasing ionic strength. At 0.1 μ, the value of $k_{\mathrm{OH_{app}}}$ was increased ≈20% while k_2 for 2-aminopyridine was approximately doubled as compared to rates at $\mu = 1.0$.] On similar plots with all other nucleophiles examined similar negative deviations occur suggesting the inapplicability of the σ_{I} values calculated from thermodynamic ionization constants to our kinetic data and that σ_{I} values should be assigned. Comparing the Hammett plots for water, imidazole, and 2-aminopyridine (nucleophiles previously shown to be insensitive to electrostatic effects) the adjusted σ_{I} values for the trimethylammonium and dimethylsulfonium esters are +0.34 and +0.58, respectively. These values bring the points for the charged esters to within 0.2 log unit of the best line of the Hammett plots for water, imidazole, and 2-aminopyridine nucleophiles. The difference in the σ_{I} values for the correlation of ionization of the parent acid and the hydrolysis of the esters can be ascribed to the different processes involved. Expulsion of the proton in the ionization process will involve, in addition to the inductive effect, a strong field effect due to the positive charge of the α substituent and proton and thus decrease the pK_{a} values.

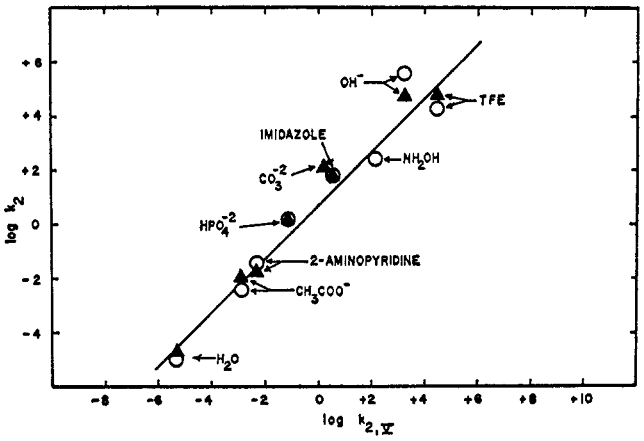
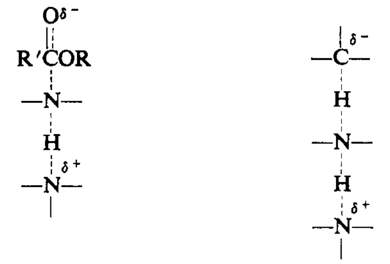


Figure 3. Plot of the logs of the second-order rate constants for esters III (○) and V (▲) *vs.* the log of the second-order rate constants for ester IV for nucleophile-catalyzed hydrolysis.

expected, respectively. Ester IV which contains no α-hydrogens shows no apparent deviation. These results suggest that the BAc2 mechanism does not account for the major path of hydrolysis and that an ElcB mechanism pertains for the hydrolysis of III and possibly V.

Nucleophiles

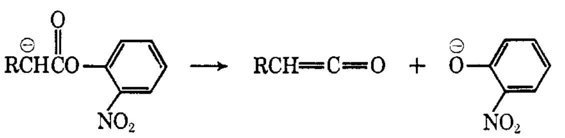
The second-order rate constants for reaction of all nucleophiles with III and IV are independent of nucleophile concentration. Because of the wide variety of nucleophiles used (oxyanions, primary and secondary amines, and carboxylic acids) Brønsted plots (not shown) for the esters have considerable scatter. However, normalization of the nature of the nucleophiles can be achieved by plotting log k_2 for III and V *vs.* log k_2 for IV as shown in Figure 3. The line of Figure 3 is drawn with a slope of +1. It is evident that the points for hydroxide show the expected positive deviations for both III and V. The mechanism for the hydroxide-catalyzed reaction appears to differ from that for other nucleophiles. This observation finds ready explanation from the conclusion previously drawn that the formation of carbanion is specific base catalyzed requiring that the second-order rate constants associated with other nucleophiles derive from nucleophilic attack at the ester carbonyl carbon. The independence of the calculated second-order rate constants for the reaction of nucleophiles with III and V upon nucleophile concentration over the large concentration ranges studied is not in accord with the expectations for an ElcB mechanism.[3] The parameter $k_{gb}[N_f]^2$ found for reaction of methoxyamine with esters III and V has precedence in the like term noted in the aminolysis and ammonolysis of substituted phenyl acetates.[18] In particular the reaction of methoxyamine with highly activated α-substituted o-nitrophenyl esters is dependent on the second order of the concentration of methoxyamine.[4b] The constant k_{gb} most certainly pertains to self-assisted general-base attack at the ester carbonyl groups (VIIIa). The authors are not aware of any such transition state as VIIIb.



VIIIa VIIIb

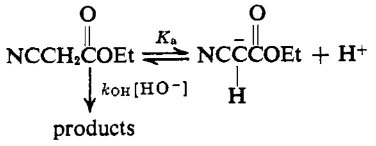
It is of interest to compare the results of the study on the hydrolysis of o- and p-nitrophenyl malonates to those obtained with esters III and V. In both studies kinetic evidence for the elimination reaction has been obtained, although with the cyano and dimethylsulfonium substituents the evidence is not nearly as definitive. The ability to detect general-base α-proton abstraction in the malonates but not with the cyano- or dimethylsulfonium-substituted o-nitrophenyl esters is apparently a result of the differences in pK_a and rates of ionization of the corresponding esters. The pK_a of ethyl cyanoacetate determined by Lienhard and Jencks[19] is 11.7 compared to the pK_a of diethyl malonate 13.3,[5] and a similar difference would be expected for the o-nitrophenyl esters. It has also been noted that cyano compounds in general ionize faster, and their carbanions are recaptured faster than their pK_a values predict.[5] Thus, with III, preequilibrium conditions exist and this determines the fact that general-base catalysis of α-proton removal is not observed. A similar condition apparently exists with ester V. The sulfonium group is known to be very effective in acidifying α-hydrogens and the dissociation constants of a number of compounds of the type $R_1R_2S^+CH_2C(=O)Ph$ have been determined[7b] [for the dimethylsulfonium compound the pK_a is 7.68]. Thus, it is expected that, as with the cyano substituent, the pK_a of ester V is such that preequilibrium ionization is determinant in its hydrolysis.

A probable mechanism for path k_3 of eq 10 is direct elimination of o-nitrophenol to afford the transient ketene (eq 16).[20] The reactive ketene thus produced will then react further with either lyate species to produce the carboxylic acid or with other bases in solution to produce acyl derivatives.



(16)

The hydrolysis of the ethyl ester of cyanoacetic acid[19] has been found to have a profile similar to V. The previously proposed mechanism (17), in which a preequilibrium formation of unreactive carbanion occurs, is undoubtedly correct. Support for this



$$\mathrm{NCCH_2\overset{\overset{O}{\|}}{C}OEt} \overset{K_a}{\rightleftharpoons} \mathrm{NC\underset{H}{\overset{-}{C}}\overset{\overset{O}{\|}}{C}OEt} + \mathrm{H^+} \qquad (17)$$
$$\downarrow k_{OH}[HO^-]$$
$$\text{products}$$

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[18] T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, p 75.

[19] G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, 87, 3863 (1965).

[20] An alternate mechanism involving participation of water can not be ruled out (see previous paper).

statement derives from our finding that the value obtained for k_{OH} (eq 17) falls on the plot of σ_I *vs.* log k_{OH} constructed from the data of Bell and Coller (references provided in footnote 17) for alkaline hydrolysis of α-substituted ethyl acetates. The difference in the mechanisms of hydrolysis of ethyl cyanoacetate and III is attributable to the large difference in leaving tendency of ethoxide and *o*-nitrophenoxide ions. One might argue that the evidence for an E1cB mechanism in the hydrolysis of V is not totally conclusive but we believe it to be quite compelling for III. It should be noted that the ylide of ethyl dimethylsulfonium acetate has been isolated[8] as a stable material. It may be concluded that the ρ values associated with the leaving group for the BAc2 mechanism is less positive than that for the E1cB mechanism.

Sacher and Laidler[21] have studied the hydrolysis of *p*-nitrophenyl acetate (*p*-NPA) at high pH (pH 8–10) and concluded that the mechanism is of the form of eq 13. In attempts to detect the plateauing of the rate with increasing hydroxide ion concentration we have restudied the hydrolysis of *p*-NPA measuring the spectrophotometric rate for *p*-nitrophenol release to as high as 0.5 *M* KOH. As Table V shows the second-order rate constant for hydroxide remains constant from pH ≈ 6 to ≈ 13.5 so that the kinetics are described by $k_{obsd} = k_{OH}[HO^-]$. This result is not surprising since the pK_a of *p*-NPA is at least greater than 14.0 and only kinetically insignificant quantities of the carbanion would be formed in the pH ranges investigated.

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

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[21] E. Sacher and K. J. Laidler, *Can. J. Chem.*, **42**, 2404 (1964).

Catalytic Reactions Involving Azomethines. XI.[1] The Kinetics of Condensation of Histamine with 3-Hydroxypyridine-4-aldehyde. An Intramolecular Mannich Reaction

Thomas C. Bruice and Anthony Lombardo

Contribution from the Department of Chemistry,
University of California at Santa Barbara, Santa Barbara, California 93106.
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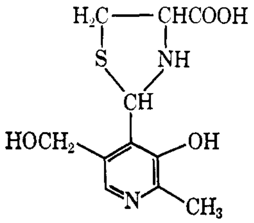
Abstract: The kinetics of the condensation of the pyridoxal analog 3-hydroxypyridine-4-aldehyde with histamine to yield VII have been investigated. It has been established that the reaction proceeds *via* rapid imine formation followed by a much slower ring-closure step. Under the conditions in which total histamine concentration far exceeds that of aldehyde, the rate-limiting step of imine formation changes from carbinolamine formation to carbinolamine dehydration. From the pH dependence of the observed first-order rate constants for conversion of imine species to final product, values of rate constants for ring closure of each imine species have been determined. Two favored mechanisms of product formation are provided. These are, nucleophilic attack of the 5 position of the neutral imidazolyl group on the unprotonated imine linkage and a like attack of the anionic imidazolyl group; both paths being assisted by proton donation from the phenolic hydroxyl group.

In aqueous solutions pyridoxal reacts with amino acids to provide pyridoxamine and the corresponding α-keto acids.[1,2] The transamination reaction has been clearly established to occur through imine formation followed by a general base catalyzed[1] prototropic shift and hydrolysis of the resultant ketimine. In the case of the amino acids histidine and cysteine, intramolecular condensation reactions successfully compete with prototropy to provide cyclic products (I and II) rather than ketimine.[3] Structure II resembles closely that of the condensation product of formaldehyde with histidine (III).[4] The reactions leading to the formation of II and III may be placed in the category of Mannich-type reactions.



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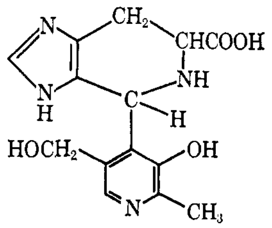
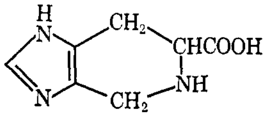


II



III

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[1] For previous papers in this series see (a) T. C. Bruice and R. M. Topping, *J. Amer. Chem. Soc.*, **85**, 1480 (1963); (b) *ibid.*, **85**, 1488 (1963); (c) *ibid.*, **85**, 1493 (1963); (d) T. C. Bruice, *Biochemistry*, **3**, 1589 (1964); (e) T. C. French, D. S. Auld, and T. C. Bruice, *ibid.*, **4**, 77 (1965); (f) J. W. Thanassi, A. R. Butler, and T. C. Bruice, *ibid.*, **4**, 1463 (1965); (g) D. S. Auld and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2083 (1967); (h) *ibid.*, **89**, 2090 (1967); (i) *ibid.*, **89**, 2098 (1967); (j) J. R. Maley and T. C. Bruice, *ibid.*, **90**, 2843 (1968).

[2] For a critical review see: T. C. Bruice and S. J. Benkovic "Bioorganic Mechanisms," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 8.

[3] D. Heyl, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, **70**, 3429 (1948).

[4] J. Wellisch, *Biochem. Z.*, **49**, 173 (1913).