shown. The points of Figure 3 are experimental and the line drawn from eq 3. Included in Figure 3 are the points found for *o*-nitrophenyl oxalate anion,[1] ethyl-*o*-nitrophenyl oxalate[1] and *o*-nitrophenyl dimethylcyanoacetate.[20] Examination of Figure 3 reveals that a good correlation between log k_{OH} and log k_{H_2O} exists and no significant deviations occur for the reactions of hydroxide with the negatively or positively charged esters. Although the trimethylammonium ester shows a slight positive deviation this is not significant since the neutral esters VI and VII also show deviations of the same order. The pyridinium ester IV also falls very close to the line. Thus, electrostatic effects, on rates arising from either unit charge repulsion or attraction or from ion–dipole or dipole–dipole[28] interactions, are no more important in the case of HO^- than with H_2O reacting with α-substituted *o*-nitrophenyl acetates. From eq 3 it follows that (ρ_{OH^-}/ρ_{H_2O}) = 0.84 and, therefore, even though $k_{OH} \gg k_{H_2O}$ for all esters investigated the relative sensitivity of k_{H_2O} to substituent effects is not greatly larger than for k_{OH}. In the following paper we examine the reaction of other nucleophiles with esters I–X in a further attempt to determine in what cases electrostatic effects can be important in the reactions between small molecules in aqueous solution.

$$\log k_{OH} = 0.84 \log k_{H_2O} + 8.00 \qquad (3)$$

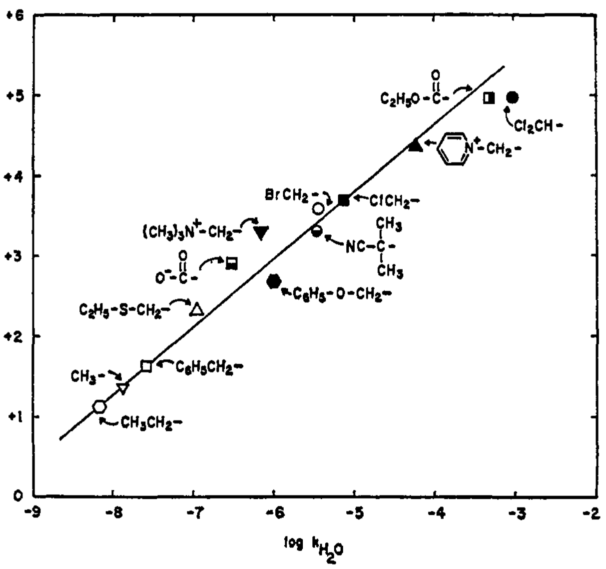

Figure 3. Plot of the log of the second-order rate constants for the hydroxide-catalyzed hydrolysis *vs.* the log of the second-order rate constant for the hydrolysis catalyzed by water for esters of type $XCO_2(o\text{-}NO_2C_6H_4)$. The substituent groups X are indicated for each point.

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

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[28] K. Koehler, R. Skora, and E. H. Cordes, *J. Amer. Chem. Soc.*, **88**, 3577 (1966).

Electrostatic Catalysis. III.[1] Comparison of the Reactivity of α-Substituted *o*-Nitrophenyl Esters with Anionic and Amine Nucleophiles

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Abstract: Second-order rate constants for reaction of a variety of charged and uncharged nucleophilic reagents with a series of neutral and charged *o*-nitrophenyl acetates of the type XCOO-*o*-NP where X = CH_3, CH_3CH_2, $PhCH_2$, $PhOCH_2$, $CH_3CH_2SCH_2$, $BrCH_2$, $ClCH_2$, Cl_2CHCH_2, $C_5H_5N^+CH_2$, $(CH_3)_3N^+CH_2$ have been measured in aqueous solution at 30°, ionic strength = 1.0. The importance of electrostatic effects was adjudged for each nucleophile from plots of the log of the second-order rate constants for water-catalyzed hydrolysis *vs.* the log of the second-order rate constants for the individual nucleophile It is established that the positive charged esters exhibit abnormally rapid reactions with the anionic nucleophiles, acetate, phosphate, and carbonate, but not with hydroxide nor trifluoroethoxide, and abnormally slow reactions with the amines, ethylenediamine, methoxyamine, and glycine ethyl ester. Since the deviations are observed with neutral amines and certain anionic nucleophiles and not others, electrostatic effects on collision frequency are adjudged to be insignificant. These results find explanation through electrostatic stabilization or destabilization of transition states.

In the preceeding publication[1b] the catalytic efficiency of water and hydroxide ion in the hydrolysis of a series of neutral and positively charged α-substituted *o*-nitrophenyl esters were compared in an attempt to assess the importance of electrostatic attraction of the negatively charged hydroxide ion by positively charged α substituents. It was found that, under the conditions used (30 ± 0.1°, μ = 1.0), the reactivity of hydroxide

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(1) For previous papers in this series, (a) T. C. Bruice and B. Holmquist, *J. Am. Chem. Soc.*, **89**, 4028 (1967): (b) B. Holmquist and T. C. Bruice, *ibid.*, **91**, 2982 (1969).

(2) 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.

(3) To whom inquiries should be addressed.

ion closely paralleled that of water for all esters. These results led us to conclude that electrostatic attraction of hydroxide ion by positively charged α substituents was not important. In a related study[1a] the reactivity of ethyl *o*-nitrophenyl oxalate and *o*-nitrophenyl oxalate anion with a series of neutral, negative, and positively charged nucleophiles, including water and hydroxide ion, were studied and again it was found that no significant rate alterations due to electrostatic effects could be established.

In continuing the study of the role of electrostatic attraction of formal charges in the determination of rate constants for nucleophilic displacement the rate constants for the reaction of a series of α-substituted *o*-nitrophenyl acetates with a number of nucleophiles bearing formal charges have been determined.

Experimental Section

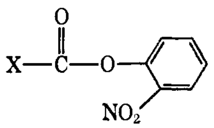
Materials. The preparation and purification procedures for the esters used in this study have previously been described.[1b] Acetic acid and 2,2,2-trifluoroethanol (bp 74°) were redistilled prior to use. Potassium phosphate (dibasic) and potassium carbonate were of reagent grade and used without further purification. Imidazole (mp 88–89°) was recrystallized from acetone-petroleum ether (bp 30–60°). Ethylenediamine dihydrochloride was recrystallized from ethanol-water. Methoxyamine (mp 149–150°) and glycine ethyl ester were recrystallized from absolute ethanol. 2-Aminopyridine (mp 59–60°) was recrystallized from chloroform-petroleum ether. All solids were dried and stored over P_2O_5. Deionized freshly glass-distilled water was used to prepare solutions.

Apparatus. Ultraviolet spectra were recorded on a Perkin-Elmer 350 recording spectrophotometer or a Cary 15 spectrophotometer at ambient temperature. Kinetic measurements were made on a Gilford Model 2000 spectrophotometer equipped with four thermospacers through which water at 30 ± 0.1° was circulated or on a Durrum-Gibson Model 13001 stopped-flow spectrophotometer equipped with an all Kel-F cuvette and valve assembly through which water was circulated at 30 ± 0.2°. All pH measurements were taken at 30 ± 0.2° with a Radiometer Model 22 pH meter equipped with a Model PHA 630 scale expander and combined glass calomel electrode (Radiometer GK 2021C).

Kinetics. Reactions were run at 30 ± 0.1° in all cases. Ionic strength was held at 1.0, unless otherwise noted, by the addition of calculated amounts of KCl. Rates were measured by monitoring the appearance of the product, *o*-nitrophenol, spectrophotometrically by recording the increase in optical density at 372.5 mμ, an isosbestic point for the *o*-nitrophenol-*o*-nitrophenolate equilibria. In all kinetic experiments the concentration of the nucleophile (0.01–1.0 *M*) was in great excess over substrate (7.4×10^{-4} *M*) and thus pseudo-first-order kinetics were obtained. Methods of addition of substrate[1a] and calculation of rate constants[1b] have been previously discussed. The nucleophile and its conjugate acid served as buffer except in the case of 2,2,2-trifluoroethanol where 0.02 *M* phosphate was used as an external buffer.

Results

The second-order rate constants for the reactions of various nucleophiles with esters I–X have been determined. Under conditions of nucleophile in large excess over ester and constant pH, all rates were pseudo first order to at least three half-lives. With the exception of methoxyamine reacting with esters V and IX (discussed below) the hydrolysis of all esters is kinetically described by eq 1 where k_{hydr} is the term for lyate species



I, X = CH_3CH_2
II, X = CH_3
III, X = $PhCH_2$
IV, X = $CH_3CH_2SCH_2$
V, X = $(CH_3)_3N^+CH_2$
VI, X = $PhOCH_2$
VII, X = $BrCH_2$
VIII, X = $ClCH_2$
IX, X = $C_5H_5N^+CH_2$
X, X = Cl_2CH

$$k_{\text{obsd}} = k_{\text{hydr}} + k_2'[N_T] \qquad (1)$$

catalysis at any given pH, the values of which have previously been determined,[1b] and $[N_T]$ is the total nucleophile concentration. Plots of k_{obsd} *vs.* total nucleophile concentration were linear, with slope k_2', the pH-dependent apparent second-order rate constant. The true second-order rate constants k_2 for attack by nucleophile in its free base form were calculated from eq 2, where a_H is the hydrogen ion activity as determined

$$k_2 = k_2'[(K_a + a_H)/K_a] \qquad (2)$$

by the glass electrode and K_a is the acid dissociation constant for the conjugate acid of the nucleophile. The values obtained for k_2 and conditions under which they were obtained are listed in Tables I–IX.

Table I. The Reaction of Acetate Anion (pK_a = 4.61) with the Various Esters

Ester	pH range	No. of k_{obsd}	No. of pH values	k_2, M^{-1} sec^{-1}
II	5.45	3	1	9.86×10^{-6} [a]
IV	5.15–5.43	12	2	$4.53 \pm 0.4 \times 10^{-5}$
V	4.65–5.43	12	2	$6.90 \pm 0.4 \times 10^{-4}$
VI	4.65–5.43	18	2	$3.65 \pm 0.2 \times 10^{-4}$
VII	4.65–5.43	12	2	$1.50 \pm 0.15 \times 10^{-3}$
VIII	4.65–5.43	12	2	$1.95 \pm 0.15 \times 10^{-3}$
IX	4.63–5.55	6	2	$2.80 \pm 0.2 \times 10^{-2}$
X	5.25	12	1	4.9×10^{-2}

[a] The corresponding value found by V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc.*, 515 (1968), at 25° is 4.13×10^{-6} M^{-1} sec^{-1}.

Table II. The Reaction of Phosphate Dianion (pK_a = 7.10) with the Various Esters

Ester	pH range	No. of k_{obsd}	No. of pH values	k_2, M^{-1} sec^{-1}
I	7.87	6	1	1.42×10^{-4}
II	7.51	6	1	2.56×10^{-4}
III	7.51	6	1	3.9×10^{-4}
IV	7.51	6	1	1.1×10^{-3}
V	6.53–6.92	6	2	$7.86 \pm 0.7 \times 10^{-2}$
VI	7.51	6	1	9.40×10^{-3}
VII	6.50–7.51	6	3	$7.20 \pm 1.4 \times 10^{-2}$
VIII	6.50–7.51	18	3	$9.15 \pm 0.12 \times 10^{-2}$
IX	6.53–7.03	12	2	5.7 ± 1.0
X	7.10–7.84	12	2	6.0 ± 0.5

Table III. The Reaction of Carbonate Dianion (pK_a = 10.33) with the Various Esters

Ester	pH range	No. of k_{obsd}	No. of pH values	k_2, M^{-1} sec^{-1}
I	9.69–10.23	18	3	$1.85 \pm 0.15 \times 10^{-2}$
II	8.76–10.23	6	3	$2.26 \pm 0.02 \times 10^{-2}$
III	9.69–10.23	12	2	$6.00 \pm 0.2 \times 10^{-2}$
IV	8.78–10.23	18	3	$2.30 \pm 0.8 \times 10^{-1}$
V	9.73	3	1	2.56×10^{1}
VI	8.78–10.23	17	3	1.00 ± 0.09
VII	8.78–9.69	11	3	1.85×10^{1}
VIII	8.78–9.69	13	2	$1.61 \pm 0.07 \times 10^{1}$
IX	9.69	3	1	7.74×10^{2}

Table IV. The Reaction of Trifluoroethoxide[a] (pK_a = 12.36) with the Various Esters

Ester	pH	No. of k_{obsd}	k_2, M^{-1} sec^{-1}
II	7.10	6	64.4
V	7.10	6	6.83×10^3
VII	7.10	6	1.38×10^4
IX	7.10	5	7.3×10^4

[a] Reactions were run in 0.01 *M* phosphate buffer to maintain constant pH.

Table V. The Reaction of Imidazole (pK_a = 7.15) with the Various Esters

Ester	pH range	No. of k_{obsd}	No. of pH values	k_2, M^{-1} sec^{-1}
I	7.10	4	1	1.16
II	7.10–7.15	12	2	1.07 ± 0.03
III	7.14	3	1	1.90
IV	7.10	6	1	4.57
V	7.15	6	1	7.06
VI	7.10	4	1	2.91×10^1
VII	7.13	3	1	3.66×10^1
VIII	7.13	3	1	5.1×10^1
IX	7.13	3	1	1.01×10^2

Table VI. The Reaction of 2-Aminopyridine (pK_a = 6.86)[a] with the Various Esters

Ester	pH range	No. of k_{obsd}	No. of pH values	k_2, M^{-1} sec^{-1}
I	7.40	5	1	4.27×10^{-4}
II	6.91–7.40	10	2	$4.25 \pm 0.3 \times 10^{-4}$
IV	6.91–7.40	10	2	$3.54 \pm 0.3 \times 10^{-3}$
V	6.83	6	1	5.41×10^{-3}
VI	6.91–7.40	10	2	$4.67 \pm 0.16 \times 10^{-3}$
VII	6.91–7.40	10	2	$2.4 \pm 0.4 \times 10^{-2}$
VIII	6.91–7.40	10	2	$2.46 \pm 0.18 \times 10^{-2}$
IX	6.91–7.40	5	1	5.43×10^{-2}

[a] The first proton to add to 2-aminopyridine resides on the ring nitrogen [H. H. Jaffé and G. O. Doak, *J. Amer. Chem. Soc.*, 77, 4441 (1955)].

Table VII. The Reaction of Glycine Ethyl Ester (pK_a = 7.75) with the Various Esters

Ester	pH	No. of k_{obsd}	No. of pH values	k_2, M^{-1} sec^{-1}
II	7.63	4	1	1.82×10^{-1}
IV	7.63	4	1	3.76×10^{-1}
V	7.63	4	1	6.34×10^{-2}
VI	7.63	4	1	1.72
VIII	7.63	4	1	4.08
IX	7.63	4	1	2.34

Table VIII. The Reaction of Ethylenediamine (pK_a = 7.53) with the Various Esters

Ester	pH range	No. of k_{obsd}	No. of pH values	k_2,[a] M^{-1} sec^{-1}
I	6.62–7.43	12	2	$1.29 \pm 0.01 \times 10^{-1}$
II	6.73–7.62	17	3	$2.34 \pm 0.13 \times 10^{-1}$
III	6.73–7.34	11	2	$1.34 \pm 0.05 \times 10^{-1}$
IV	6.75–7.34	10	2	$5.09 \pm 0.05 \times 10^{-1}$
V	6.75–7.93	24	4	5.1×10^{-1}
VI	6.59–7.43	12	2	3.25 ± 0.02
VII	6.75–7.34	12	2	6.00 ± 0.08
VIII	6.75–7.34	12	2	6.48
IX	6.87–7.29	12	2	1.54

[a] Calculated on the basis of the monocation.

Table IX. The Reaction of Methoxyamine (pK_a = 4.68) with the Various Esters

Ester	pH range	No. of k_{obsd}	No. of pH values	k_2, M^{-1} sec^{-1}
I	4.68	5	1	6.85×10^{-3}
II	4.25–4.68	12	2	$1.19 \pm 0.05 \times 10^{-2}$
III	4.68	5	1	7.05×10^{-3}
IV	4.25–4.68	10	2	$1.59 \pm 0.07 \times 10^{-2}$
V	4.67–4.84	12	2	2.45×10^{-3} [a]
VI	4.68	6	1	3.8×10^{-2}
VII	4.68	6	1	1.05×10^{-1}
VIII	4.25–4.68	12	2	$9.58 \pm 0.22 \times 10^{-2}$
IX	4.25–4.77	18	3	$1.03 \pm 0.08 \times 10^{-1}$ [a]

[a] General-base terms for esters V and IX were also obtained and were determined to be $3.54 \pm 0.04 \times 10^{-3}$ l.^{2} mol^{-2} sec^{-1} and 4.0×10^{-1} l.^{2} mol^{-2} sec^{-1}, respectively.

The reaction of methoxyamine with esters V and IX gave a general-base term in free methoxyamine as indicated by upward curvature of plots $k_{obsd} - k_{hydr}$ *vs.* total methoxyamine. Plots of $(k_{obsd} - k_{hydr})/[N_f]$ *vs.* $[N_f]$ were linear and thus eq 3 holds for these reactions. The

$$k_{obsd} = k_{hydr} + k_2[N_f] + k_{gb}[N_f] \qquad (3)$$

values for k_2 and k_{gb} are given in Table IX.

In Figures 1 and 2 are shown the plots of log k_{H_2O} *vs.* log k_2 for the reactions of the oxyanion and nitrogen nucleophiles with esters I–X. Also included in Figures 1 and 2 are the corresponding points found for the positively charged *o*-nitrophenyl dimethylsulfonioacetate.[4] The lines of Figures 1 and 2 are drawn using a least-squares analysis of the points for the neutral esters. The values for k_{H_2O} are from an earlier study.[1b] Examination of Figure 1 reveals that the primary amines, methoxyamine, glycine ethyl ester, and ethylenediamine monocation, show negative deviations when in reaction with the positively charged esters with the maximum deviation being *ca.* 100-fold in the reaction of glycine ethyl ester and ethylenediamine monocation with ester V. With the anionic nucleophiles, AcO^-, HPO_4^{2-}, and CO_3^{2-} (Figure 2), it is observed that significant positive deviations are obtained with the positive charged esters (HPO_4^{2-} and CO_3^{2-} giving the largest positive deviations). As in the case of hydroxide ion, 2,2,2-trifluoroethoxide shows only little or no acceleration with the positive esters.

In general, product analyses were not carried out; however, spectral scanning of the reaction of imidazole with selected esters gave evidence for nucleophile attack by the spectral identifications of acylimidazole intermediates. The reaction of imidazole (pH 7.14, 0.1 *M*) with esters II, III, IV, V, VII, and VIII produced rapid liberation of *o*-nitrophenol as measured at 372.5 mμ followed by a much slower decrease in absorbance in the region around 250 mμ. By measuring the difference between the spectra immediately after release of *o*-nitrophenol and the spectra after complete reaction of the intermediate the λ_{max} values for the intermediates were determined. The λ_{max} values are: II, 245 mμ; III, 250 mμ; IV, 250 mμ; V, 254 mμ; VII, 250 mμ; VIII, 250 mμ. The similarity of the λ_{max} values for these intermediates to acetylimidazole[5] and oxalylimid-

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(4) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 3003 (1969).

(5) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272, 1280 (1959).

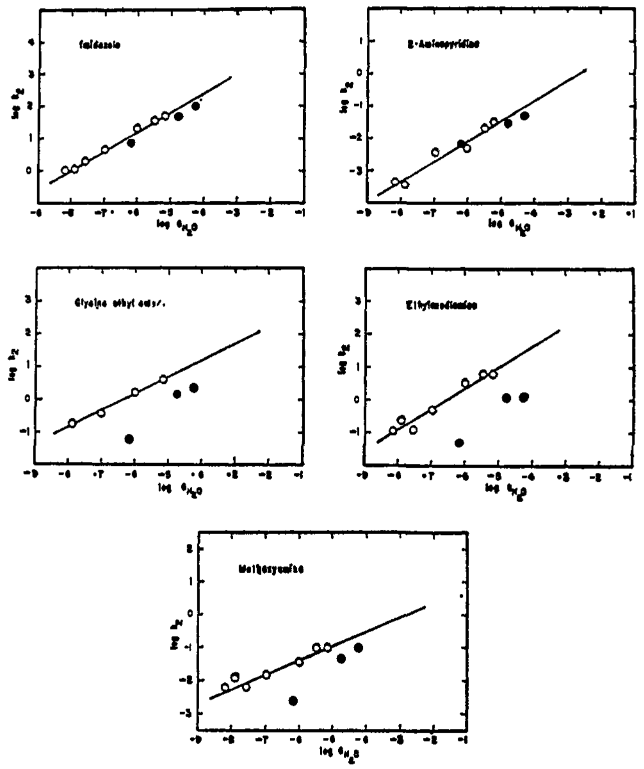

Figure 1. Plots of the log of the second-order rate constants for nitrogen nucleophiles *vs.* the log of the second-order rate constants for water for the hydrolysis of the *o*-nitrophenyl esters (units for k_2 and k_{H_2O} are M^{-1} sec^{-1}): (○) neutral esters, (●) charged esters V, IV, and α-dimethyl sulfonioacetate.

azole[1a] and other acylimidazoles generated from *o*-nitrophenyl esters[6] support the contention that the intermediates are indeed the acylated imidazoles.

Employing the σ_I values of Charton[7] (not including positively charged α substituents) and the data of Tables I–IX, values of ρ_I may be determined for the various nucleophiles. These values are provided in Table X.

Table X. Calculated ρ_I Values for Reaction of α-Substituted *o*-Nitrophenyl Acetates with Various Nucleophiles

Nucleophile	pK_a	ρ_I
Water	−1.74	5.7
Acetate	4.61	4.3
Methoxyamine	4.68	2.4
2-Aminopyridine	6.86	3.6
Phosphate	7.10	5.2
Imidazole	7.15	3.4
Ethylenediamine	7.53	3.6
Glycine ethyl ester	7.75	3.0
Carbonate	10.33	5.9
Trifluoroethoxide	12.83	5.1
Hydroxide	15.7	4.8

From Table X it is observed that no correlation exists between ρ_I and the pK_a of the nucleophile. The ρ values for the reactions of various nucleophiles with a series of *meta*- and *para*-substituted phenyl acetates have been compiled[8] and here also no correlation exists between ρ and the pK_a of the nucleophiles. However, it may be noted that the ρ_I values in Table X for oxygen bases are, in general, significantly greater (5.2 ± 0.4) than for nitrogen bases (3.2 ± 0.4).

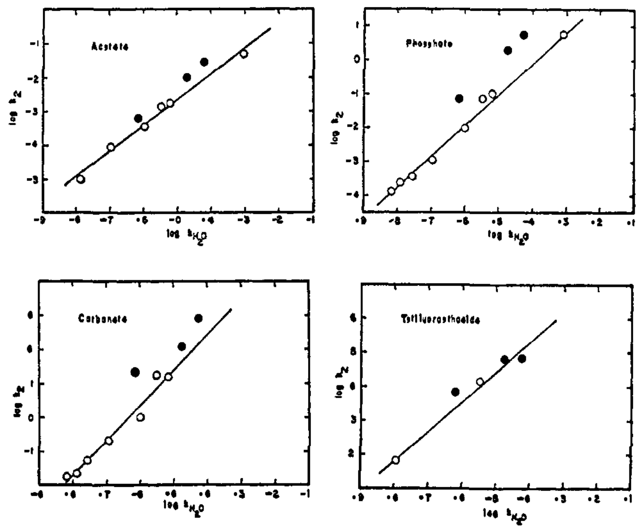

Figure 2. Plots of the log of the second-order rate constants for oxyanion nucleophiles *vs.* the log of the second-order rate constants for water for the hydrolysis of the *o*-nitrophenyl esters (units of k_2 and k_{H_2O} are M^{-1} sec^{-1}): (○) neutral esters, (●) charged esters V, IX, and α-dimethyl sulfonioacetate.

Discussion

In the previous paper in this series[1] the reactivity of hydroxide ion was compared to that of water in reaction with esters I–X. This was accomplished by a plot of log k_{H_2O} *vs.* log k_{HO^-}. Explicit in the method is the assumption that electronic effects on the electron density of the carbonyl carbon due to the α substituents will have a parallel influence on the reactivity of the esters toward both water and hydroxide ion. This assumption would appear most reasonable and is that tacitly assumed in employment of ρσ relationships. In addition, it is apparent that steric effects due to the α substituents will also tend to cancel out in this type plot. Any special effects, as those due to charge–charge interaction on collision frequency, which are not continuous throughout the ester series should be manifest in deviations in the log k_{H_2O} *vs.* log k_{OH} plot. It was found that with all esters, regardless of charge, a good correlation between log k_{H_2O} and log k_{OH} existed and it was, therefore, concluded that formal charge–charge attraction or repulsion was not significant for nucleophilic attack by hydroxide ion. In the present investigation the standard and neutral nucleophile H_2O has been retained in order to evaluate possible electrostatic interactions of other nucleophiles with the same series of esters *via* plots of log k_{H_2O} *vs.* log k_2. Some objection to the employment of k_{H_2O} as a standard might be raised since spontaneous hydrolysis may not involve rate-determining attack of H_2O upon the ester carbonyl carbon. However, since log k_{OH} = 0.84 log k_{H_2O} + 8.00,[1] the employment of k_{H_2O} as standard is tantamount to using k_{OH} as standard. For HO^- as nucleophile the rate-determining step is certainly attack at the ester carbonyl.

With the additional nucleophiles studied here significant deviations from log k_2 *vs.* log k_{H_2O} plots occur

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

(7) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).

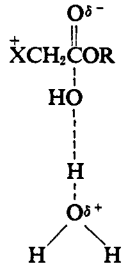
(8) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, p 20.

with certain nucleophiles. The decrease in reactivity of methoxyamine, glycine ethyl ester, and ethylenediamine toward the positively charged esters (Figure 1) cannot reasonably be attributed to electrostatic effects on collision frequency since these neutral nucleophiles would not be expected to be repulsed by the positive charge in the α position. Although ethylenediamine cation has a positive charge, which is removed from the nucleophilic nitrogen, the close resemblance of the reactivity of this nucleophile (pK_a = 7.53) to glycine ethyl ester (pK_a = 7.75)—Figure 1—shows that the positive charge is not responsible for the negative deviation. For the anionic nucleophiles (Figure 2), for which positive acceleration is obtained with AcO^-, HPO_4^{2-}, and Co_3^{2-} but not significantly with hydroxide or 2,2,2-trifluoroethoxide, it appears that electrostatic effects on collision frequency are also not responsible for the deviations observed. If acceleration were due to interaction of the positive α substituent with the oxyanions by increasing the collision frequency it would be expected that the hydroxide and trifluoroethoxide anions, in which the charge is highly localized on the nucleophilic oxygen, would also show electrostatic accelerations when compared to esters with neutral α substituents, as is found with the other oxyanions.

The occurrence of abnormal rates of reaction of the charged esters with certain anionic nucleophiles (AcO^-, HPO_4^{2-}, and CO_3^{2-}) and not others (hydroxide and trifluoroethoxide) and with neutral amines is indicative that electrostatic interactions are not affecting collision frequency and that these interactions are not responsible for the deviations observed. The deviant rate constants of Figures 1 and 2 can, however, be rationalized by examining the electrostatic interactions which will occur in the transition states for these reactions.

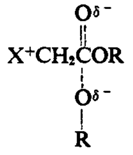
The rate-determining step in the reactions of amine nucleophiles with phenyl esters has been suggested to be attack of the nucleophile even if the pK_a of the amine is less than that of the phenol leaving group.[9] This is most assuredly the case with the *o*-nitrophenyl esters. For oxygen nucleophiles it has been reasoned that a transition from rate-limiting attack to departure of the leaving group occurs when the oxyanion is of lower basicity than the departing phenol. The water-catalyzed reaction undoubtedly is self-assisted general base with water acting to partially remove the proton from the water molecule which attacks the carbonyl carbon.[1,10] For this mechanism there is no means of ascertaining whether attack or departure of the leaving group is rate determining. It has been shown that the acetate-catalyzed hydrolysis of *o*-nitrophenyl acetate proceeds by both nucleophilic and general base mechanisms, each contributing approximately 50% of the total catalytic rate.[11] With nucleophiles of pK_a values greater than acetate the nucleophilic mechanism should predominate over that of general base. Such mechanism changes from general base to nucleophilic with increasing pK_a of the nucleophile have been observed with acetylimidazole[12] and *p*-nitrophenyl acetate.[11,13] Alkoxide ions are also known to function as nucleophiles toward *p*-nitrophenyl acetate and by analogy *o*-nitrophenyl acetate should react identically. The reaction of imidazole with the various *o*-nitrophenyl esters of both high and low reactivity in this study shows that nucleophilic attack is operational since spectral identification of the intermediate acylimidazoles was accomplished. In addition, as the electronegativity of the α substituent increases (thus causing increasing reactivity of the esters to attack by bases) within the *o*-nitrophenyl leaving group series, the esters will become more susceptible to direct nucleophilic attack.[9] Therefore, for the α-substituted *o*-nitrophenyl acetates it is likely that nucleophilic attack accounts for virtually 100% of the rate for all nucleophiles reacting with all esters in which σ_I of X is more positive than that for H (all esters in which the α substituent is positively charged). The squared term for methoxyamine—$k_{gb}[NH_2OH]^2[ester]$—found with esters V and IX is undoubtedly due to self-assisted general-base nucleophilic attack. However, the nucleophilic term is also present and has been separately evaluated (see Results).

The transition state for the general-base water-catalyzed hydrolysis reaction is depicted in **1**. According to

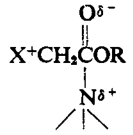


1

the Hammond postulate,[14] bond formation between the attacking water molecule and the carbonyl carbon is expected to be rather complete in the transition state with this weak base (pK_a = −1.74). Therefore, the partial positive charge on the attacking oxygen has been moved to the oxygen of the catalyst in the transition state and removed from interaction with the positive charge of the α substituent. Thus, it might be argued that water should show no unusual reactivity with the charged esters when compared to the neutral esters. However, in the transition states for nucleophiles of pK_a greater than water significantly less bond formation should occur. As depicted in **2a** and **2b**



2a



2b

the transition states for oxyanion and neutral amine nucleophiles (pK_a values between 4 and 10) can be conceived in such a way that a greater amount of bond formation occurs relative to water. With the oxyanions, acetate, HPO_4^{2-}, and CO_3^{2-}, the partial negative charge on the oxygen atom of the nucleophile in the transition state is situated such that electrostatic inter-

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[9] For a recent discussion of this point see W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 90, 2622 (1968).

[10] S. L. Johnson, *Advan. Phys. Org. Chem.*, 5, 237 (1967).

[11] (a) D. G. Oakenfull, J. Riley, and V. Gold, *Chem. Commun.*, 385 (1966); (b) V. Gold, D. G. Oakenfull, and J. Riley, *J. Chem. Soc.*, 515 (1968).

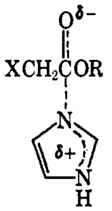
[12] (a) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **88**, 104 (1966); (b) J. Gerstein and W. P. Jencks, *ibid.*, **86**, 4655 (1964).

[13] W. P. Jencks and M. Gilchrist, *ibid.*, **84**, 2910 (1962).

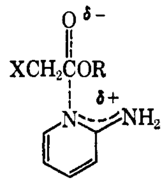
[14] G. S. Hammond, *ibid.*, 77, 334 (1955).

actions with the positive α substituent may occur and cause stabilization of the transition state. This interaction is offered to explain the enhanced reactivity toward the positively charged esters by oxyanions when compared to water. The greater deviations obtained with HPO_4^{2-} and CO_3^{2-} than with acetate may be seen from Figure 2. Since both HPO_4^{2-} and CO_3^{2-} are dianions, one might anticipate greater stabilization effects than for the acetate monoanion. Alternatively since bond formation should be of less importance than departure of the leaving group in the case of acetate ion little or no electrostatic effect should be anticipated.

With the nitrogen nucleophiles ($pK_a = 4.7$–7.8) the transition state can again be considered to involve significant bond formation. The deviations of the rate constants for reaction of the charged esters with methoxyamine, ethylenediamine monocation, and glycine ethyl ester (Figure 1) may then be attributed to electrostatic destabilization of the transition state by interaction of the positive α substituent with the partial positive charge developed on the nucleophilic nitrogen atom (**2b**). In the cases of imidazole and 2-aminopyridine, whose second-order rate constants correlate well with those for water for all esters (Figure 1), the positive charge developed in the transition state on the nucleophilic nitrogen may be delocalized as in **3a** and **3b**



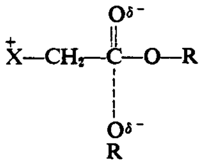
3a



3b

so that electrostatic interactions will no longer be of much significance.

With oxyanion nucleophiles of much higher basicity (hydroxide and trifluoroethoxide) the transition state will be reached when very little bond formation has occurred and charge on the entering nucleophile will be at a greater distance from X than in the case of nucleophiles of intermediate basicity (**4**). Thus, with the



$$\overset{+}{X}\text{—CH}_2\text{—}\overset{O^{\delta-}}{\overset{\|}{C}}\text{—O—R} \quad \cdots O^{\delta-}R$$

4

oxyanions of very strong basicity very little electrostatic stabilization of the transition state should occur.

The effects of ion–dipole and dipole–dipole interactions in determining transition-state stabilities have been referred to by Bunnett.[15] Koehler, *et al.*,[16] have found that anionic and neutral nucleophiles react differently with greater increase in reaction with anionic nucleophiles than with nitrogen nucleophiles upon the addition of strong electron-withdrawing α substituents in the ester. This was attributed to dipole–dipole interaction between the charged nucleophilic center and the dipole formed by the acyl substituent. It is concluded, therefore, that electrostatic effects, as determined in water at $\mu = 1.0$, may be observed in the hydrolysis of charged esters but that these effects are due to transition state interactions and not due to collision frequency alterations, etc.

The implication of electrostatic effects depends on the observation of deviations of points for charged species or separation of nucleophile according to charge type in linear free-energy plots. Three types of plotting techniques have been employed in the literature and conclusions derived from such plots may depend on the particular mode of plotting. The linear free-energy correlations employed are: (a) plots of log k_2 for a particular nucleophile *vs.* log k_2 for a chosen nucleophile as standard, employing a series of substrates differing in substitution at a particular position (the method chosen in the present study); (b) plots of log k_2 values for a series of nucleophiles reacting with a charged substrate *vs.* log k_2 for the same series of nucleophiles reacting with a neutral substrate; and (c) plots of log k_2 for a series of nucleophiles of varied charge *vs.* the pK_a of the nucleophile (Brønsted plot) or pK_a of the leaving group.

In a study of the rates of reaction of nucleophiles with a series of acetyl derivatives (leaving groups: phenoxide, *p*-nitrophenoxide, 2,4-dinitrophenoxide, and 4-methoxypyridine N-oxide), Jencks and Gilchrist[9] plotted the pK_a of the leaving group *vs.* log k_2. From the plots, the authors concluded that anionic nucleophiles exhibited enhanced rates toward the positively charged substrate 1-acetoxy-4-methoxypyridinium ion (AMPP). This enhanced nucleophilicity by anionic nucleophiles was interpreted as an electrostatic effect. However, a plot of log k_2 values for AMPP *vs.* log k_2 for the neutral ester *p*-nitrophenyl acetate (*p*-NPA) provides no clear cut separation of neutral and anionic nucleophiles. Johnson[10] has chosen this latter means of detecting electrostatic effects by plots of log k_2 for *p*-NPA *vs.* log k_2 for charged and uncharged acyl derivatives [which include 1-(N,N-dimethylcarbamoyl)-pyridinium ion (NNDC),[17] N-acetylimidazolium ion (AIM),[18] N-*trans*-cinnamoyl-N-methylimidazolium ion (CIMM),[10] N-acetyl-N-methylimidazolium ion (AIMM),[19] and acetyl phenylphosphate (APP)[20]]. For NNDC, all nucleophiles investigated, regardless of charge type fit a single plot indicating by this criteria no electrostatic effects. In the case of AIM a line drawn through the points for nucleophiles H_2O and HO^- is found to fit points for anionic nucleophiles (with the exception of acetate anion) whereas amines fall on a separate line of negative displacement. From this plot one might draw the conclusion that anionic nucleophiles are more reactive with the positively charged substrate than neutral amines. For AIM it is also possible that the separation of the plots for positively charged nucleophiles and amines is due, in part, to the buildup of positive charge on the amine nitrogen in the transition state **2b**. For CIMM the same type plot is obtained as for AIM and like deductions may be made. In the case of the phosphate ester anion, APP, nucleophiles associated with like values of k_2 toward *p*-NPA may be separated into the more reactive amines

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(15) J. F. Bunnett, *Ann. Rev. Phys. Chem.*, **14**, 271 (1963).

(16) K. Koehler, R. Skora, and E. H. Cordes, *J. Amer. Chem. Soc.*, **88**, 3577 (1966).

(17) S. L. Johnson and K. Rumon, *ibid.*, **87**, 4782 (1965).

(18) W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 1778 (1960).

(19) R. Wolfenden and W. P. Jencks, *ibid.*, **83**, 4390 (1961).

(20) G. Di Sabato and W. P. Jencks, *ibid.*, **83**, 4393 (1961).

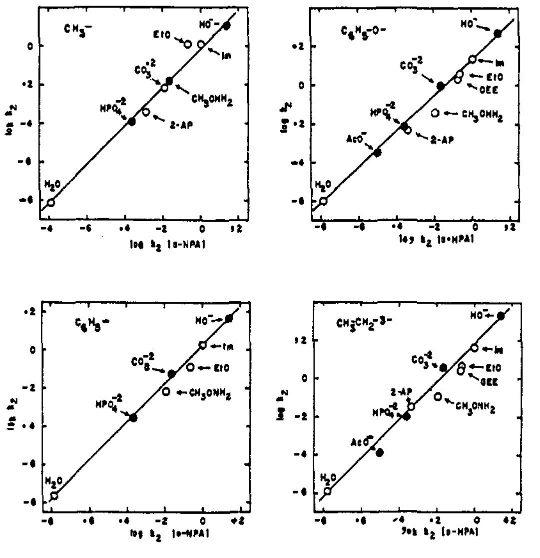


Figure 3. Plots of log k_2 for the reaction of nucleophiles (AcO^-, acetate; TFE, trifluoroethoxide; IM, imidazole; EtD, ethylenediamine monocation; GEE, glycine ethyl ester; 2-AP, 2-aminopyridine) with α-substituted *o*-nitrophenyl acetates (the α substituent is provided in each plot) *vs.* the log of the second-order rate constant for the same nucleophiles reacting with *o*-nitrophenyl acetate. The solid points are those for the anionic nucleophiles. Units of k_2 are $M^{-1}\,sec^{-1}$.

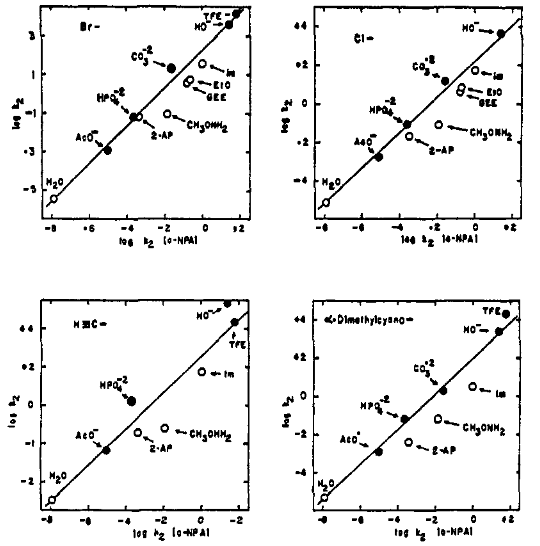
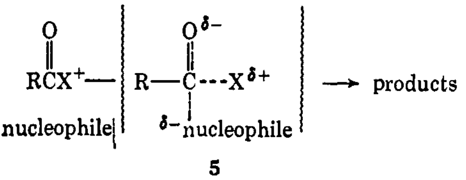


Figure 4. Plots of log k_2 for the reaction of nucleophiles (AcO^-, acetate; TFE, trifluoroethoxide; Im, imidazole; EtD, ethylenediamine monocation; GEE, glycine ethyl ester; 2-AP, 2-aminopyridine) with α-substituted *o*-nitrophenyl acetates (the α-substituent is provided in each plot) *vs.* the log of the second-order rate constant for the same nucleophiles reacting with *o*-nitrophenyl acetate. The solid points are those for the anionic nucleophiles. Units of k_2 are $M^{-1}\,sec^{-1}$.

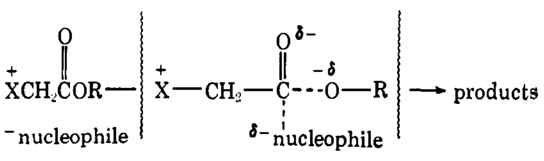
and less reactive anions. Thus, when log k_2 for *p*-NPA is employed as a standard, electrostatic effects are not evident with the pyridinium cations of AMPP and NNDC but are evident with the N-acylimidazolium cations of AIM, CIMM, and AIMM, and with the phosphate ester APP. It is still not evident why, in particular, acylimidazolium cations exhibit electrostatic effects while pyridinium ions may not (for AMPP?). These aforementioned cases of electrostatic influence on rates from the recent literature involve attack of a charged nucleophile upon substrates with charged leaving groups. In these cases bond formation between nucleophile and substrate is associated with diminution of charge on both leaving group and nucleophile (5). In the cases considered in this study the



$$\underset{^{-}\text{nucleophile}}{R\overset{\overset{O}{\|}}{C}X^{+}\text{—}}\ \left|\ R\text{—}\underset{\underset{^{\delta-}\text{nucleophile}}{|}}{\overset{\overset{O^{\delta-}}{\|}}{C}}\text{---}X^{\delta+}\ \right| \longrightarrow \text{products}$$

5

leaving group is constant and uncharged, while the charge on X remains constant across the reaction coordinant (6). Some differences are, therefore,



$$\underset{^{-}\text{nucleophile}}{\overset{+}{X}CH_2\overset{\overset{O}{\|}}{C}OR\text{—}}\ \left|\ \overset{+}{X}\text{—}CH_2\text{—}\underset{\underset{^{\delta-}\text{nucleophile}}{|}}{\overset{\overset{O^{\delta-}}{\|}}{C}}\text{---}\overset{-\delta}{O}\text{—}R\ \right| \longrightarrow \text{products}$$

6

expected in the interpretation of type reactions (5 and 6). When the data of this study is plotted in the manner of Johnson[10] (*i.e.*, log k_2 for *o*-nitrophenyl acetate *vs.* log k_2 for a charged, or uncharged ester, both with a series of nucleophiles) rather than as presented (*i.e.*, log k_{H_2O} *vs.* log k_2 for a single nucleophile reacting with a series of esters) the plots (Figures 3, 4, and 5) tend to support our previous conclusions. Thus, for *o*-nitrophenyl propionate, phenylacetate, phenoxyacetate, and ethylthiolacetate a single line accommodating all nucleophiles (Figure 3) is obtained—no electrostatic effect is evident with these nonpolar esters. With *o*-nitrophenyl chloro-, bromo-, dimethylcyano-, and cyanoacetate (Figure 4), a line accommodating the points for H_2O, $CF_3CH_2O^-$, and HO^- lies below points for CH_3COO^-, HPO_4^{2-}, and CO_3^{2-} but above the points for 2-aminopyridine, CH_3ONH_2, glycine ethyl ester, and imidazole. For the amines the greatest negative deviation is found for CH_3ONH_2, glycine ethyl ester, and ethylenediamine and these amines exhibit an intermediate value of k_2 toward the halo esters. The differences in the sensitivity of k_2 toward nitrogen and oxyanion nucleophiles for polar but not formally charged esters may be due to the electrostatic stabilization of the transition state due to ion–dipole or dipole–dipole interaction as suggested by Koehler, *et al.*[16] One should note that the separation does not conflict with our suggestion that k_{H_2O} and k_{HO^-}, as well as $k_{CF_3CH_2O^-}$, are not subject to electrostatic effects due to the extent or lack of extent, respectively, of bond formation in the transition state. Thus, those nucleophiles associated with medium rate constants exhibit the maximum deviation and the deviation is negative for amines which provide a positive charge in the transition state and positive for negative nucleophiles which impart this charge to the transition state. The sorting by charge type for the halo esters is not great compared to the case for the positively charged *o*-nitrophenyl esters in which a pyridinium, trimethylammonium, or dimethylsulfonium substituent is in the α position. For these esters a line drawn through the points for H_2O, HO^-, and $CF_3CH_2O^-$ (Figure 5) is again found to be below the points for negative nucle-

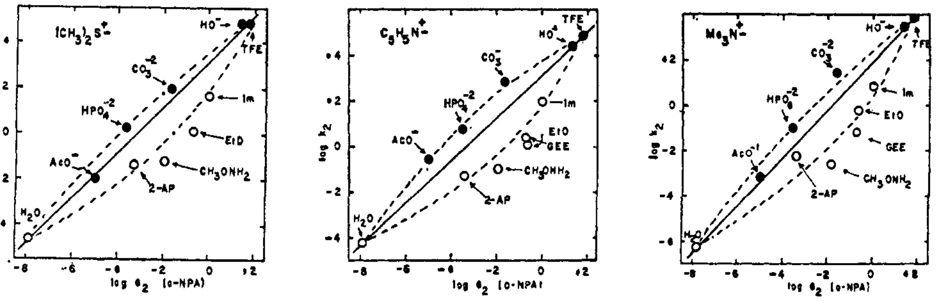
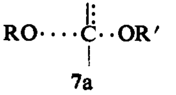


Figure 5. Plots of log k_2 for the reaction of nucleophiles (AcO^-, acetate; TFE trifluoroethoxide; Im, imidazole; EtD, ethylenediamine monocation; GEE, glycine ethyl ester; 2-AP, 2-aminopyridine) with α-substituted *o*-nitrophenyl acetates containing positive charges in the α position *vs.* the log of the second-order rate constant for the same nucleophiles reacting with *o*-nitrophenyl acetate. The solid points are for the anionic nucleophiles. Units of k_2 are M^{-1} sec^{-1}.

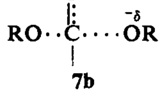
ophiles and above those for amines. However, the displacement of the points from the line are much greater than for the haloacetates. Comparing the thermodynamic σ_I values for the α substituents considered [Cl, +0.47; Br, +0.45; CN, +0.58; $C_5H_5N^+$, +0.66; $(CH_3)_3N^+$, +0.73] it is possible that the separation of nucleophiles into charge type and the magnitude of the separation by plots of this type is most dependent upon the polar nature of the substituent and does not concern or makes it difficult to detect formal charge attraction or repulsion. Of significance is the fact that the separation of nucleophiles into charge types in the plots of log k_2 for the haloacetates *vs.* log k_2 for *o*-NPA is comparable in magnitude to the like separation of nucleophiles in plots of log k_2 for AIM, CIMM, AIMM, and APP *vs.* log k_2 for *p*-NPA. Differentiation of induced dipole–dipole and formal electrostatic repulsion by this type plot may not be possible. We propose that plots involving log k_2 for a series of nucleophiles *vs.* log k_2 for the same series of nucleophiles with a standard ester should not be employed to detect formal charge–charge interactions. In their place the procedure of plotting log k_2 for a single nucleophile reacting with a series of esters *vs.* log k_2 for a standard nucleophile (H_2O or HO^-) reacting with the same series of esters should be used. In this means of plotting dipole–dipole, inductive, etc., interactions increase regularly from ester to ester and is reflected in both k_{H_2O} (or k_{HO^-}) and k_2. The difference in the importance of these effects for k_{H_2O} (or k_{HO^-}) and k_2 is reflected in the slope of the least-squares line through the points for esters not possessing formal charged substituents (*i.e.*, reflected in the ρ_2 and ρ_{H_2O} values). This study provides evidence that plots of this nature exhibit significant deviations for only charged substrates and that these deviations are reasonably explained through stabilization and destabilization of the transition state due to formal electrostatic attraction or repulsion.

Jencks and Gilchrist[9] have concluded that the transition states for reaction of oxygen nucleophiles with esters resemble **7a** when the attacking group is more basic than the leaving group and **7b** when less basic than



$$\mathrm{RO\cdots\overset{\overset{\displaystyle O^{-\delta}}{\vdots}}{\underset{|}{C}}\cdot\cdot OR'}$$

7a



$$\mathrm{RO\cdot\cdot\overset{\overset{\displaystyle O^{-\delta}}{\vdots}}{\underset{|}{C}}\cdots\overset{-\delta}{O}R}$$

7b

the leaving group. This deduction was based on the observation that the slopes, β, of logarithmic plots of reaction rate against the basicity of the nucleophile or the leaving group approach a value of *ca.* 0.3 for type **7a** reactions and 1.0 for type **7b** reactions. For amines a single transition state involving nucleophilic attack suffices.[9,21] In the normal case, values of β of 0.8 for the amine nucleophile and approximately 1.0 for the leaving group were interpreted in terms of a transition state involving a large amount of bond formation and bond breaking (*i.e.*, the transition state for amine attack is proposed to resemble products, in contrast to that for attack of oxyanion of equal basicity which is suggested to resemble starting materials). A similar conclusion concerning the extent of bond formation in the transition state for aminolysis has been reached in studies from this laboratory.[21,22] In addition, from the fact that tertiary amines exhibit a sensitivity to amine basicity similar to that for primary and secondary amines, it was proposed that a proton is not lost on formation of the transition states involving primary and secondary amines.

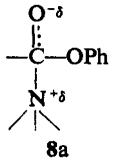
Examination of Table X reveals that the sensitivity to alterations in electron withdrawal of α substituents in α-substituted *o*-nitrophenyl acetates is much greater for oxyanion nucleophiles than for amines (average ρ values of 5.2 ± 0.4 and 3.2 ± 0.4, respectively). A similar finding has been reported by Koehler, Skora, and Cordes.[16] Also, from Table X it may be seen that within the oxyanion or amine series there is no systematic variation of ρ with the pK_a of the nucleophile. When the ρ values for nucleophilic attack upon *meta*- and *para*-substituted phenyl acetates are compared it is found that amine attack is much more sensitive than is oxyanion attack to the leaving tendency of the phenolate moiety.[8,22-24] The greater sensitivity of oxyanion attack to the nature of the acyl group and the greater sensitivity of amine attack to the nature of the leaving group may be rationalized through two alternative interpretations. Possibly the most conventional interpretation invokes the consideration of transition states involving less bond making and more bond breaking for amine nucleophiles than for oxyanion nucleophiles. This conclusion is tantamount to the probability of a tetrahedral intermediate and associated

[21] M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2121 (1967).

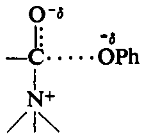
[22] T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967).

[23] T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964).

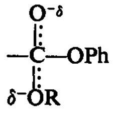
[24] L. do Amaral, K. Koehler, D. Bartenbach, T. Pletcher, and E. H. Cordes, *ibid.*, **89**, 3537 (1967)



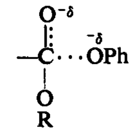
8a



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

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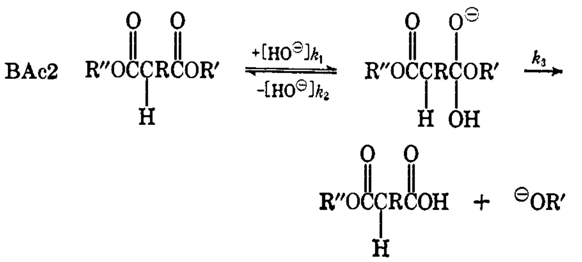
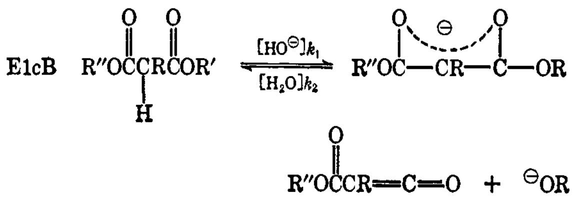
Received October 9, 1968

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.

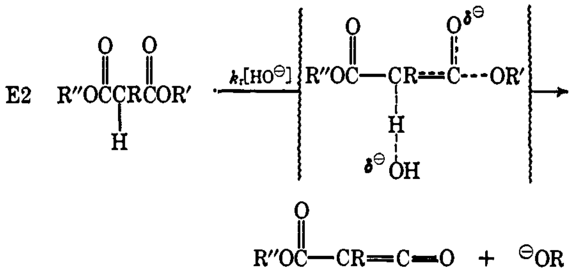
Three modes of HO⁻ attack on malonate esters are conceivable *a priori* (1 and 2a and 2b). In eq 1 the mechanism is that for normal alkaline hydrolysis of esters, in eq 2a it is preequilibrium formation of a carbanion with subsequent elimination of R′O⁻, and in eq 2b it is a concerted reaction involving 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



$$\text{BAc2}\quad \mathrm{R''OC(=O)CH(R)C(=O)OR'} \underset{-[\mathrm{HO}^{\ominus}]k_2}{\overset{+[\mathrm{HO}^{\ominus}]k_1}{\rightleftharpoons}} \mathrm{R''OC(=O)CH(R)C(O^{\ominus})(OH)OR'} \xrightarrow{k_3} \mathrm{R''OC(=O)CH(R)C(=O)OH} + {}^{\ominus}\mathrm{OR'} \qquad (1)$$



$$\text{E1cB}\quad \mathrm{R''OC(=O)CH(R)C(=O)OR'} \underset{[\mathrm{H_2O}]k_2}{\overset{[\mathrm{HO}^{\ominus}]k_1}{\rightleftharpoons}} \mathrm{R''OC(=O)\!-\!\overset{\ominus}{C}R\!-\!C(=O)\!-\!OR} \xrightarrow{k_3} \mathrm{R''OC(=O)CR{=}C{=}O} + {}^{\ominus}\mathrm{OR} \qquad (2a)$$



$$\text{E2}\quad \mathrm{R''OC(=O)CH(R)C(=O)OR'} \xrightarrow{k_1[\mathrm{HO}^{\ominus}]} \left[\mathrm{R''OC(=O)\!-\!C(R)(H\cdots\overset{\delta\ominus}{O}H)\!\cdots\!C(O^{\delta\ominus})\cdots OR'}\right] \longrightarrow \mathrm{R''OC(=O)\!-\!CR{=}C{=}O} + {}^{\ominus}\mathrm{OR} \qquad (2b)$$

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