

Electrostatic Catalysis. II.¹ A Comparison of Spontaneous and Alkaline Hydrolytic Rate Constants for α -Substituted *o*-Nitrophenyl Esters

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Abstract: The pH-log k_{hydr} profiles for the hydrolysis of a series of α -substituted *o*-nitrophenyl acetate esters [XCOO-*o*-NP where X = CH₂CH₂, CH₃, PhCH₂, CH₃CH₂SCH₂, (CH₃)₃N⁺CH₂, PhOCH₂, BrCH₂, ClCH₂, C₅H₅-N⁺CH₂, and Cl₂CH] have been determined in water at 30°, ionic strength = 1.0, between pH 1 and 12.53. The values of k_{hydr} at all pH values are quantitatively provided by summation of rates for spontaneous general base catalyzed hydrolysis ($k_{\text{H}_2\text{O}}$) and hydroxide ion catalyzed hydrolysis ($k_{\text{OH}}[\text{HO}^-]$). For the esters in which the α -substituent group equals CH₃, CH₂CH₂, and PhCH₂ a specific acid catalyzed term ($k_{\text{H}^+\text{A}}$) must be included to provide k_{hydr} at low values of pH. A plot of log $k_{\text{H}_2\text{O}}$ vs. log k_{OH} for all esters, including the positive charged species, was found to be linear and to follow the equation log $k_{\text{OH}} = 0.84 \log k_{\text{H}_2\text{O}} + 8.0$. The fact that esters containing formal positive charges do not show positive deviations from the plot of log k_{OH} vs. log $k_{\text{H}_2\text{O}}$ is indicative that electrostatic facilitation for the nucleophilic displacement of *o*-nitrophenoxide by hydroxide ion is unimportant.

Although it is likely that the mechanisms available for enzymic catalysis are those established by physical organic studies (general base, general acid, nucleophilic), the efficiency of enzymic reactions is presumably the result of lowering of ΔF^\ddagger by orientation of catalytic groups and/or by directly lowering of ground- and increasing transition-state stabilities *via* distortion of substrate. The forces available for orientation which have been used to explain the efficiency of enzymatic processes include charge-transfer interactions,⁴ hydrophobic^{5,6} and hydrogen bonding,⁷ van der Waals forces,^{6,8} and electrostatic interactions. Examples of orientation by electrostatic effects of small molecules at the surface of enzymes include the acetylcholinesterase-catalyzed hydrolysis of acetylcholine in which the substrate acetylcholine is apparently electrostatically attracted to an anionic center on the enzyme⁹ and the reaction of α -halo acetates^{9,10} and *o*-nitrophenyl oxalate¹¹ with ribonuclease A in which a protonated histidine imidazolium ion in the active site reportedly facilitates these reactions. Also in attempts to mimic the surface or active sites of enzymes, studies of reactions in micelles¹² and on the surface of

polymers containing large numbers of charged residues¹³ have resulted in the observation of large rate accelerations and retardations presumably due in part to electrostatic effects.

The role of electrostatic effects in determining the rate constants for reactions between small molecules in aqueous solution remains in question. Formal attraction between unlike charges may account for the abnormal reactivity of anionic nucleophiles with acetyl-imidazolium ion¹⁴ and cations with *p*-nitrophenyl phosphate dianions¹⁵ and isopropyl methylphosphonofluoridate;¹⁶ however, in other cases where similar effects might be expected as in the reaction of formally negative, neutral, and positively charged nucleophiles with *o*-nitrophenyl oxalate anion¹ or the reactions of anions with 1-(*N,N*-dimethylcarbamoyl)pyridinium chloride,¹⁷ no facilitation or retardation was noted. By comparing the rates of alkaline hydrolysis of esters of the type XCH₂C(=O)OEt to the corresponding rates for ethyl acetate, Bell, *et al.*,¹⁸ have concluded that substantial facilitation is found when X is a charged substituent (trimethylammonium and dimethylsulfonium). However, on a plot of σ_1 ¹⁹ vs. log k_{OH} of all charged and neutral esters studied by Bell, *et al.*, we find that log k_{OH} for all esters fits well to a line of slope 3.89.

In this and the following paper, nucleophilic attack upon neutral and charged α -substituted *o*-nitrophenyl esters is studied to try to further clarify the importance of electrostatic effects on collision frequency or stability

(1) For the previous paper in this series see T. C. Bruice and B. Holmquist, *J. Amer. Chem. Soc.*, **89**, 4028 (1967).

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(3) To whom inquiries should be addressed.

(4) E. M. Kosower, "Molecular Biochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(5) G. Nemethy, *Angew. Chem. Intern. Ed. Engl.*, **6**, 195 (1967).

(6) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," John Wiley & Sons, Inc., New York, N. Y., 1967.

(7) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960.

(8) I. B. Wilson in "The Enzymes" Vol. 4, P. Boyer, H. Lardy, and K. Myrbäck, Ed., Academic Press, New York, N. Y., 1960, p 501.

(9) A. M. Crestfield, W. H. Stein, and S. Moore, *J. Biol. Chem.*, **238**, 2421 (1963).

(10) R. L. Heinrikson, W. H. Stein, A. M. Crestfield, and S. Moore, *ibid.*, **240**, 2921 (1965).

(11) T. C. Bruice, B. Holmquist, and T. P. Stein, *J. Amer. Chem. Soc.*, **89**, 4221 (1967).

(12) T. C. Bruice, J. Katzhendler, and L. R. Fedor, *ibid.*, **90**, 1333 (1968), and references therein.

(13) (a) H. Morawetz and J. A. Shafer, *J. Phys. Chem.*, **67**, 1293 (1963); (b) H. Morawetz, C. G. Overberger, J. C. Salamone, and S. Yaroslavsky, *J. Amer. Chem. Soc.*, **90**, 651 (1968).

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

(15) A. J. Kirby and W. P. Jencks, *ibid.*, **87**, 3209 (1965).

(16) J. Epstein, H. O. Michel, D. H. Rosenblatt, R. E. Plapinger, R. A. Stephani, and E. Cook, *ibid.*, **86**, 4959 (1964).

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

(18) (a) R. P. Bell and B. A. W. Collier, *Trans. Faraday Soc.*, **61**, 1445 (1965); (b) R. P. Bell and F. J. Lindars, *J. Chem. Soc.*, 4601 (1954).

(19) σ_1 values derived from the pK_a values of XCH₂COOH [M. Charton, *J. Org. Chem.*, **29**, 1222 (1964)]. The σ_1 value of the S⁺(CH₃)₂ group determined from the pK_a of (CH₃)₂S⁺CH₂COOH is +0.86 [B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 3003 (1969)].

of the transition states for nucleophilic attack. Comparison of the rates of attack of water, hydroxide, and other bases are used as a means of measuring the significance of these effects. In this paper a comparison is made of the rates of hydrolysis of α -substituted *o*-nitrophenyl acetate by neutral water and charged hydroxide ion.

Experimental Section

Apparatus. Kinetic measurements were determined on a Gilford Model 2000 spectrophotometer equipped with four thermostats through which water at $30 \pm 0.1^\circ$ was circulated or a Durrum-Gibson Model 13001 stopped-flow spectrophotometer equipped with an all Kel-F valve and cuvette assembly through which water at $30 \pm 0.2^\circ$ was circulated. pH measurements were made with a Radiometer Model 22 pH meter equipped with a Model PHA 630 Pa scale expander. The combined glass electrode (Radiometer G. K. 2021C) was thermostated at $30 \pm 0.1^\circ$. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer and ultraviolet spectra on a Perkin-Elmer Model 350 recording spectrophotometer. Melting points were measured on a Mel-Temp melting point apparatus and have not been corrected. Analyses were performed by Alfred Bernhardt, Max Plank Institute, Germany.

Materials. Potassium phosphate monobasic, potassium bicarbonate, potassium chloride, potassium hydroxide, and tris-(hydroxymethyl)aminomethane (trizma base) were of reagent quality and used without further purification. Acetic acid was freshly distilled. Methoxyamine was recrystallized from ethanol-diethyl ether (mp $149\text{--}150^\circ$). 2-Aminopyridine was recrystallized from chloroform-petroleum ether (bp $30\text{--}60^\circ$), mp $59\text{--}60^\circ$. Imidazole was recrystallized from acetone-petroleum ether, mp $88\text{--}89^\circ$. The bromide salt of *o*-nitrophenyl α -dimethylsulfonioacetate was from another study.²⁰ All crystalline solids were stored over P_2O_5 prior to use. Deionized freshly double-glass-distilled water was used to prepare all solutions. Dioxane (Matheson Coleman and Bell) was of spectral quality. Since only very small amounts of pure material were necessary for the kinetic studies, yields in the preparation of the esters were not considered and are not reported.

***o*-Nitrophenyl Propionate (I).** To 1.4 g (0.01 mol) of *o*-nitrophenol and 7 g (0.095 mol) of propionic acid dissolved in 25 ml of chloroform at 0° was slowly added 2 g (0.01 mol) of dicyclohexylcarbodiimide (DCC) dissolved in 20 ml of chloroform. After complete addition the mixture was allowed to remain at 5° for 8 hr after which the solid dicyclohexylurea was filtered off and the chloroform removed by flash evaporation. The resulting yellow oil was taken up in 10 ml of absolute ethanol and cooled to 0° to allow crystallization. The crystalline material thus obtained was recrystallized from absolute ethanol to give the pure material as light yellow crystals: mp 26° ; ν_{\max}^{KBr} 1780, 1620, 1540, and 1130 cm^{-1} .

Anal. Calcd for $C_9H_9NO_4$: C, 55.38; H, 4.64; N, 7.17. Found: C, 55.22; H, 4.77; N, 7.33.

***o*-Nitrophenyl acetate (II)** was prepared by the method of Bender and Chow²¹ and was recrystallized from ether-petroleum ether, mp $40\text{--}41^\circ$ (lit.²¹ $40.5\text{--}41^\circ$).

***o*-Nitrophenyl phenylacetate (III)** was prepared in the same manner as for I using phenylacetic acid and ethylene dichloride as solvent. The yellow oil obtained by flash evaporation of the ethylene dichloride was zone sublimed.¹ Pure ester was obtained as a light yellow oil: n_D^{20} 1.5747; ν_{\max}^{KBr} 1790, 1630, 1460, and 1120 cm^{-1} .

Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.44. Found: C, 65.26; H, 4.46; N, 5.57.

***o*-Nitrophenyl ethylthiolacetate (IV)** was prepared by the DCC method as for I. The yellow oil obtained on removal of chloroform from the reaction mixture was zone sublimed to give the product ester as the last liquid band: n_D^{20} 1.5535; ν_{\max}^{KBr} 1780, 1620, 1540, 1350, and 1100 cm^{-1} .

Anal. Calcd for $C_{10}H_{12}NO_3S$: C, 49.78; H, 4.60; N, 5.80; S, 13.29. Found: C, 49.72; H, 4.88; N, 5.95; S, 13.36.

1-(Carboxymethyl)trimethylammonium chloride *o*-nitrophenyl ester (V) was prepared by the addition of excess anhydrous tri-

methylamine (1.8 g, 0.03 mol) at 0° to 2.94 g (0.014 mol) *o*-nitrophenyl chloroacetate dissolved in 20 ml of benzene at 0° . The reaction mixture was maintained at 0° for 3 hr after which the precipitated ester was removed by filtration, washed with diethyl ether, and recrystallized three times from methanol-ether to give the pure material: mp $165\text{--}170^\circ$ dec; ν_{\max}^{KBr} 1790, 1620, 1530, 1340, and 1160 cm^{-1} .

Anal. Calcd for $C_{11}H_{13}ClN_2O_4$: C, 48.09; H, 5.46; N, 10.19; Cl, 12.94. Found: C, 47.93; H, 5.73; N, 9.81; Cl, 12.39.

***o*-Nitrophenyl phenoxyacetate (VI)** was prepared from phenylacetic acid by the DCC method as for I using instead tetrahydrofuran as solvent. The product was recrystallized from anhydrous ethanol to give white crystals: mp $51\text{--}53^\circ$; ν_{\max}^{KBr} 1780, 1590, 1530, 1330, and 1440 cm^{-1} .

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.54; H, 4.06; N, 5.12. Found: C, 61.59; H, 4.28; N, 5.23.

***o*-Nitrophenyl bromoacetate (VII)** was prepared using DCC as for I but with ethylene dichloride as solvent. The crude ester crystallized directly on removal of the ethylene dichloride from the filtered product, and was further purified by sublimation which afforded white crystals, mp $53\text{--}54^\circ$ (lit.²² $55.5\text{--}56^\circ$).

***o*-Nitrophenyl chloroacetate (VIII)** was prepared by the DCC method as used for I using ethylene dichloride as solvent. The yellow oil remaining on evaporation of solvent was taken up in a minimum volume of hot petroleum ether. Cooling of the solution afforded the product which on further recrystallization gave the pure product as white crystals, mp $62\text{--}62.5^\circ$ (lit.²² 63°).

1-(Carboxymethyl)pyridinium bromide *o*-nitrophenyl ester (IX) was prepared by the addition of excess pyridine (3.2 g, 0.04 mol) to 50 ml of diethyl ether containing (5.2 g, 0.02 mol) *o*-nitrophenyl bromoacetate. After 12 hr the precipitated ester was removed by filtration and recrystallized three times from acetonitrile to give the pure ester as white needles: mp $156\text{--}158^\circ$; ν_{\max}^{KBr} 1770, 1640, 1530, and 1360 cm^{-1} .

Anal. Calcd for $C_{12}H_{11}N_2O_4Br$: C, 46.13; H, 3.49; N, 8.32; Br, 22.76. Found: C, 46.02; H, 3.27; N, 8.26; Br, 23.57.

***o*-Nitrophenyl dichloroacetate (X)** was prepared by stirring a mixture of 5 g (0.037 mol) of dichloroacetic anhydride, 2.9 g (0.021 mol) of *o*-nitrophenol, and three drops of pyridine in 25 ml of diethyl ether for 12 hr. Evaporation of the ether gave a yellow oil as product which was zone sublimed to give the pure ester as the last liquid band: ν_{\max}^{KBr} 1790, 1620, 1540, and 1350 cm^{-1} .

Anal. Calcd for $C_9H_7Cl_2NO_4$: C, 38.31; H, 2.18; N, 5.46; Cl, 28.13. Found: C, 38.43; H, 2.00; N, 5.60; Cl, 28.36.

Kinetics. All kinetic measurements were carried out in water at $\mu = 1.0$ with KCl unless otherwise noted. The appearance of the product *o*-nitrophenol was monitored spectrophotometrically by recording the rate of increase in optical density at $372.5\text{ m}\mu$, an isosbestic point for the *o*-nitrophenol-*o*-nitrophenolate equilibria. Kinetics were measured under pseudo-first-order conditions by maintaining constant pH through the use of buffers at concentrations greater than 0.01 M and substrate concentrations less than $2 \times 10^{-4}\text{ M}$. Kinetic runs were initiated by the addition of one drop of the appropriate ester dissolved in dioxane²⁴ to a thermostated cuvette containing a solution of buffer. In cursory experiments the substitution of ethanol or water for the dioxane and acetonitrile used to make the stock solutions of esters had no measurable effect on rate constants. The pH of the reaction solutions were measured before, and periodically after, to ensure constancy. The values of pseudo-first-order rate constants were calculated employing a Programma 101 computer using a weighted-least-square analysis in determining the slopes of plots of $\log(\text{OD}_\infty - \text{OD}_0)/(\text{OD}_\infty - \text{OD}_0)$ vs. time.

Results

The dependence on the pH for the hydrolysis of esters of the type between pH 1 and 14 are shown in Figure 1. The points of Figure 1 are experimental, being determined by extrapolation of plots of $[\text{buffer}]_T$ vs. the pseudo-first-order rate constants for hydrolysis (k_{obsd}) to zero buffer to provide values of k_{hydr} dependent on lyate species alone. Figure 2 shows a typical series of buffer

(22) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 469 (1915).

(23) C. Mannich and W. Dhauzberg, *Arch. Pharm.*, **250**, 532 (1912).

(24) Due to their insolubility in dioxane, stock solutions of esters V and IX were made up in reagent grade water and acetonitrile, respectively.

(20) See B. Holmquist and T. C. Bruice, ref 19.

(21) M. L. Bender and Y-L. Chow, *J. Amer. Chem. Soc.*, **81**, 3929 (1959).

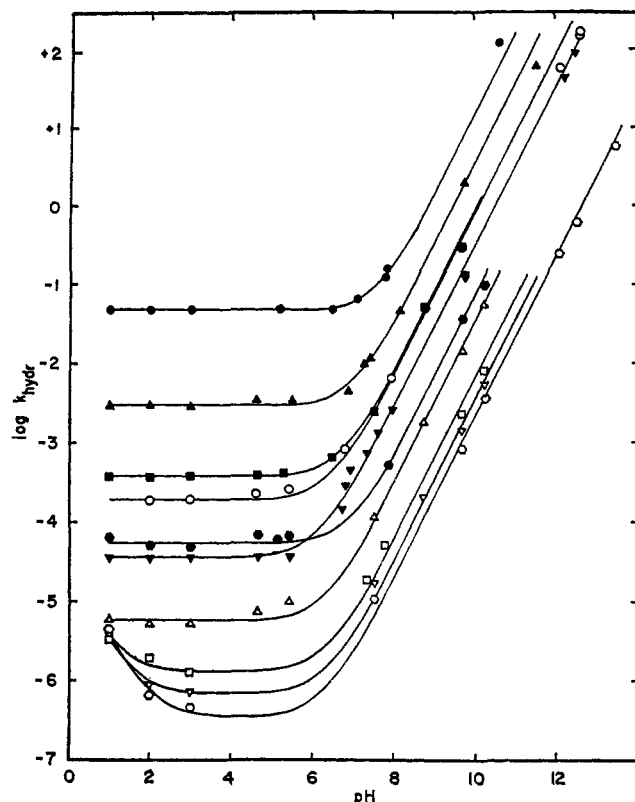
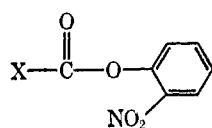



Figure 1. Hydrolytic profiles for the lyate species catalyzed hydrolysis of esters I (○), II (▽), III (□), IV (△), V (▼), VI (●), VII (○), VIII (■), IX (▲), and X (●).

dilutions at three pH values for the reaction of phosphate buffer with VII. The lines of Figure 1 are theoretical having been derived from eq 1 for esters I-III and



- I, X = CH₃CH₂ VI, X = PhOCH₂
 II, X = CH₃ VII, X = BrCH₂
 III, X = PhCH₂ VIII, X = ClCH₂
 IV, X = CH₃CH₂SCH₂
 V, X = (CH₃)₃N⁺CH₂ IX, X = 
 X, X = Cl₂CH

eq 2 for esters IV-X, where a_{H} is the hydrogen ion activity as determined by the glass electrode. Values used

$$k_{\text{hydr}} = k_{\text{H}_2\text{O}}[\text{H}_2\text{O}] + k_{\text{OH}}(K_w/a_{\text{H}}) + k_{\text{H}}a_{\text{H}} \quad (1)$$

$$k_{\text{hydr}} = k_{\text{H}_2\text{O}}[\text{H}_2\text{O}] + k_{\text{OH}}(K_w/a_{\text{H}}) \quad (2)$$

for construction of the theoretical profiles are given in Table I. The value for the autoprotolysis constant of water, K_w , at 30° is $1.47 \times 10^{-14} M$.²⁵ The buffers and pH ranges used for determining k_{hydr} are: HCl, pH 1-3; acetate, 4.63-5.67; phosphate, 6.50-8.14; methoxyamine, 4.25-4.86; imidazole, 7.10; Tris, 7.80-8.77; carbonate, 8.75-9.75; hydroxide, 11-13.5.

Discussion

The mechanisms expected for the hydrolysis of acyl- and aryl-activated esters²⁶ are those found in the hy-

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

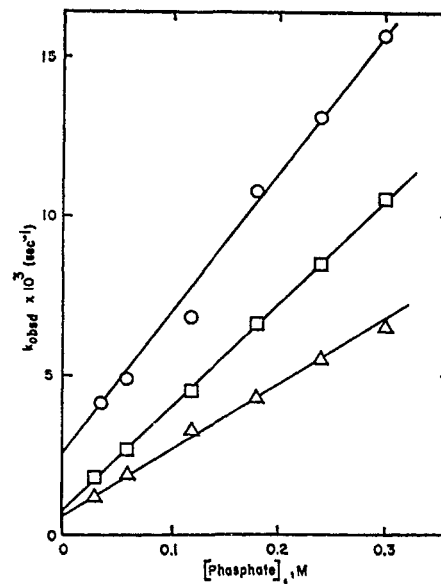


Figure 2. Plot of k_{obsd} (sec^{-1}) vs. concentration of total phosphate buffer for the hydrolysis of ester VII at pH 7.52 (○), pH 7.00 (□), and pH 6.53 (△).

drolysis of the α -substituted *o*-nitrophenyl acetates I-X of this study. The plateau regions between pH 2 and 5 as found for all esters is undoubtedly the result of water-catalyzed hydrolysis ($k_{\text{H}_2\text{O}}$). This is in agreement with the results found for other *o*- and *p*-nitrophenyl acetates.^{1, 20, 27} Above pH 6 the positive slope of +1

Table I. Experimental Values of Hydrolytic Rate Constants for Esters I-X

Ester	$k_{\text{H}_2\text{O}}$, l. mol ⁻¹ sec ⁻¹	k_{OH} , l. mol ⁻¹ sec ⁻¹	k_{H} , l. mol ⁻¹ sec ⁻¹
I	6.84×10^{-9}	1.37×10^1	4.26×10^{-5}
II	1.32×10^{-8}	2.50×10^1	3.16×10^{-5}
III	2.71×10^{-8}	4.36×10^1	1.90×10^{-5}
IV	1.08×10^{-7}	2.15×10^2	
V	6.64×10^{-7}	2.09×10^3	
VI	1.00×10^{-6}	4.81×10^3	
VII	3.48×10^{-6}	4.94×10^3	
VIII	7.10×10^{-6}	5.54×10^3	
IX	5.65×10^{-5}	2.29×10^4	
X	8.94×10^{-4}	9.10×10^4	

is indicative of normal base-catalyzed ester hydrolysis by nucleophilic attack of hydroxide ion (k_{OH}). Below pH 3 esters, I, II, and III exhibit an acid catalysis (k_{H})—slope -1 in Figure 1—which is characterized by an expected negative ρ^* (≈ -2.3).

Comparison of the reactivities of the neutral water molecule and the hydroxide anion with the various esters of neutral and positive charge can best be accomplished by a plot of $\log k_{\text{OH}}$ vs. $\log k_{\text{H}_2\text{O}}$ with inclusion of all esters. In Figure 3 the plot of $\log k_{\text{OH}}$ vs. $\log k_{\text{H}_2\text{O}}$ is

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

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

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 oxalate¹ and *o*-nitrophenyl dimethylcyano-

$$\log k_{\text{OH}} = 0.84 \log k_{\text{H}_2\text{O}} + 8.00 \quad (3)$$

acetate.²⁰ Examination of Figure 3 reveals that a good correlation between $\log k_{\text{OH}}$ and $\log k_{\text{H}_2\text{O}}$ 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-dipole²⁸ 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 $(\rho_{\text{OH}}/\rho_{\text{H}_2\text{O}}) = 0.84$ and, therefore, even though $k_{\text{OH}} \gg k_{\text{H}_2\text{O}}$ for all esters investigated the relative sensitivity of $k_{\text{H}_2\text{O}}$ 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.

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

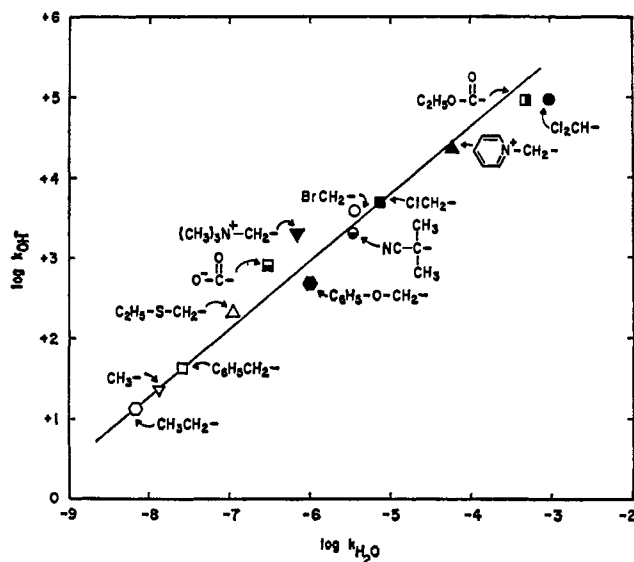


Figure 3. Plot of the log of the second-order rate constants for the hydroxide-catalyzed hydrolysis vs. the log of the second-order rate constant for the hydrolysis catalyzed by water for esters of type $\text{XCO}_2(o\text{-NO}_2\text{C}_6\text{H}_4)$. The substituent groups X are indicated for each point.

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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 $\text{XCOO-}o\text{-NP}$ where $\text{X} = \text{CH}_3, \text{CH}_3\text{CH}_2, \text{PhCH}_2, \text{PhOCH}_2, \text{CH}_3\text{CH}_2\text{SCH}_2, \text{BrCH}_2, \text{ClCH}_2, \text{Cl}_2\text{CHCH}_2, \text{C}_6\text{H}_5\text{N}^+\text{CH}_2, (\text{CH}_3)_3\text{N}^+\text{CH}_2$ 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 preceding 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 ($30 \pm 0.1^\circ, \mu = 1.0$), the reactivity of hydroxide

(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

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