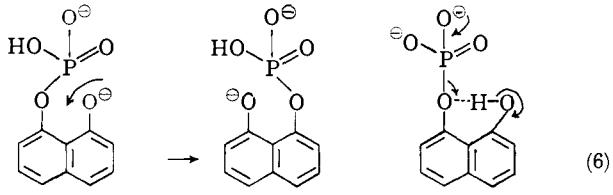
In summary it may be stated that there is considerable similarity between the deuterium oxide solvent isotope effect in the hydrolysis of salicyl phosphate and the isotope effects in a number of other reactions involving possible internal proton transfer, and that all these reactions may be explained most readily by mechanisms analogous to eq. 5.

(3) The dianion of 8-hydroxy-1-naphthyl dihydrogen phosphate hydrolyzes approximately ten times faster than the dianion of the 8-methoxy ester. The 8-hydroxy ester cannot hydrolyze through an intermediate of the salicyloyl phosphate type (*i.e.*, by nucleophilic phenoxide ion attack at the phosphorus atom) since this reaction would only regenerate the starting material (eq. 6). Although the direction of the difference in the hydrolytic rates is that predicted by the proton-transfer mechanism, the magnitude of the difference may not be large enough to be attributed with certainty to a particular mechanism.

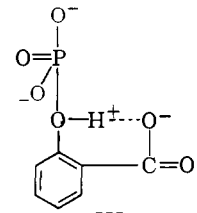


(6)

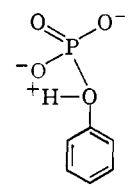
Nucleophilic attack mechanism Proton-transfer mechanism

No rate constants for the hydrolyses of aryl phosphate dianions have been reported, but it is probable that, unlike the monoanion hydrolyses, the order of reactivity is sensitive to the basicity of the phenoxide ion product. For example, the *p*-nitrophenyl phosphate dianion should hydrolyze much faster than the phenyl phosphate dianion. At 100° the dianion of *p*-nitrophenyl dihydrogen phosphate hydrolyzes faster than the dianion of 8-methoxy-1-naphthyl dihydrogen phosphate, but three times slower than the dianion of the 8-hydroxy ester. If it were not for strong intramolecular hydrogen bonding the 8-hydroxynaphthoxide ion should not differ greatly in basicity from the 8-methoxynaphthoxide ion—certainly it should be considerably more basic than *p*-nitrophenoxide. The observed order of reactivity must therefore be caused by the operation of the proton-transfer mechanism in the hydrolysis of the dianion of the 8-hydroxy ester.

The sum total of all the above arguments indicates that the best suggestion for the mechanism of the hydrolysis of salicyl phosphate is the proton transfer mechanism represented by eq. 5. Although no definitive experiment requires this conclusion, no other mechanism will satisfy the experimental criteria and, further, a large body of consistent evidence favors eq. 5. It may then be asked why proton transfer from an internal carboxylic acid group leads to a more facile reaction than proton transfer from the phosphoric acid group itself. In terms of eq. 9 it would appear that the stability of the zwitterion III is superior to that of zwitterion IV. This stability may be discussed on steric or electronic grounds. Electronically one may say that the carboxylic acid is a stronger acid than the second ionization of a phosphoric acid, and therefore the transfer of the proton to produce zwitterion III is more complete than to the zwitterion IV, or alternatively that the electrostatic stabilization of III is greater than that of IV.



III



IV

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

Intramolecular Catalysis in the Hydrolysis of *p*-Nitrophenyl Salicylates[1]

BY MYRON L. BENDER,[2] FERENC J. KÉZDY, AND BURT ZERNER

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The kinetics of hydrolysis and of nucleophilic reactions of *p*-nitrophenyl salicylate, benzoate, *o*-methoxybenzoate, 5-nitrosalicylate, 3-nitrobenzoate, and 2-methoxy-5-nitrobenzoate were determined in 34.4% dioxane–water at 25°. The pH–rate profile of the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate exhibits two pH-independent reactions, one in the acid region and one in the alkaline region. The pH-independent reaction in the alkaline region may be described either as a water reaction of the ionized ester or as a hydroxide ion reaction of the un-ionized ester. Deuterium oxide solvent isotope effects do not distinguish between these possibilities. If the pH-independent reaction in the alkaline region is interpreted as the reaction of hydroxide ion with the un-ionized salicylate ester, it is calculated that hydrolysis of the salicylate esters is 213 to 458 times as fast as that of the corresponding benzoate esters. However, nucleophilic reactions of imidazole, azide ion, and sulfite ion with salicylate esters proceed essentially at the same rate as with benzoate esters. Therefore, the pH-independent hydrolysis of the salicylate esters in the alkaline region cannot be interpreted as the reaction of hydroxide ion with the un-ionized ester but rather as the reaction of water with the ionized ester, leading to a description of this facile reaction as an intramolecular general basic catalysis.

Introduction

Neighboring hydroxyl groups can catalyze the hydrolysis of carboxylic acid derivatives by direct participation in the reaction, usually by formation of an intermediate lactone (*i.e.*, nucleophilic catalysis).[3] Recently neighboring hydroxyl groups which presumably do not form lactones have been shown to accelerate the hydrolysis of carboxylic acid derivatives significantly.[3b,4–9] This rate acceleration by a neighboring

(1) This research was supported by the National Science Foundation and the U. S. Atomic Energy Commission.

(2) Alfred P. Sloan Foundation Research Fellow.

(3) (a) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (b) M. L. Bender, G. R. Schonbaum, and G. A. Hamilton, *J. Polymer Sci.*, **49**, 82 (1961).

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(5) S. M. Kupchan and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 3864 (1956); S. M. Kupchan and C. R. Narayanan, *ibid.*, **81**, 1913 (1959); S. M. Kupchan, W. S. Johnson, and S. Rajagopalan, *Tetrahedron*, **7**, 47 (1959); S. M. Kupchan, P. Slade, and R. J. Young, *Tetrahedron Letters*, **24**, 22 (1960); S. M. Kupchan, P. Slade, R. J. Young, and G. W. A. Milne, *Tetrahedron*, **18**, 499 (1962); S. M. Kupchan, S. P. Eriksen, and M. Friedman, *J. Am. Chem. Soc.*, **84**, 4159 (1962); S. M. Kupchan, S. P. Eriksen, and Y.-T. Shen, *ibid.*, **85**, 350 (1963).

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hydroxyl group has been discussed principally in terms which can be described as intramolecular general acid catalysis. Specifically, the rate acceleration has been attributed to facilitation of the hydroxide ion attack on the ester by hydrogen bonding of the neighboring hydroxyl group to the leaving group or the carbonyl group in the ground state or transition state of the reaction, or internal solvation of the transition state. However, intramolecular hydrogen bonding or solvation does not explain the observed rate enhancement in semicarbazone formation from substituted benzaldehydes[10]; a lack of stabilization by resonance of the *o*-substituted aldehyde has been proposed to explain the increased reactivity observed in this reaction. An alternative explanation in the hydrolysis of carboxylic acid derivatives would be a general basic catalysis of the water reaction of the ionized neighboring hydroxyl group, which is kinetically indistinguishable from the hydroxide ion-catalyzed hydrolysis of the un-ionized hydroxy-substituted carboxylic acid derivative. This possibility never has been definitively ruled out[11]; it would be a more straightforward explanation of neighboring hydroxyl group catalysis, at least in cases where it has been shown that such catalysis occurs in spite of the absence of any measurable hydrogen bonding.

Specific base–general acid catalysis and general base catalysis are in general not kinetically distinguishable since the reactive species involved in these two mechanisms are related by a single equilibrium constant, and hence their concentrations cannot be independently changed. The specific reaction considered can be written

$$\begin{matrix}\text{COX}\\ |\\ \text{R—OH}\end{matrix} + \text{OH}^- \rightleftharpoons \begin{matrix}\text{COX}\\ |\\ \text{R—O}^-\end{matrix} + \text{H}_2\text{O} \qquad (1)$$

The ambiguity imposed by this equilibrium can, however, be removed by studying the effect of the neighboring hydroxyl group on reactions of the carboxylic acid derivative involving nucleophiles other than hydroxide ion. In that case, the ratio COX–R–OH/COX–R–O$^-$ can be changed independently of the concentration of the nucleophile and hence one can readily determine whether the carboxylic acid derivative involved in the reaction bears a protonated or unprotonated hydroxyl group. If the species involved in the hydrolytic reaction are the protonated ester and hydroxide ion, then the species involved in the nucleophilic reaction should be the protonated ester and the nucleophile, for the protonated hydroxyl group should exert the same special effect in both reactions. This parallelism requires that the rate acceleration due to a neighboring hydroxyl group in the hydrolytic reaction be also observed in the nucleophilic reaction. If, however, the species involved in the hydrolytic reaction are the ionized ester and water (a general basic catalysis), the special effect of the neighboring hydroxyl group may not be observed in the reaction of the ionized ester with a nucleophile, for presumably the reaction of the added nucleophile, unlike water, needs no general basic catalysis.

Since many nucleophilic reactions of *p*-nitrophenyl esters are known[12] and since these reactions can be easily followed spectrophotometically, *p*-nitrophenyl salicylate and *p*-nitrophenyl 5-nitrosalicylate were chosen as substrates to investigate the mechanism of intramolecular hydroxyl group catalysis in ester hydrolysis. These substances also have the advantage of holding the hydroxyl group in a relatively rigid position preventing lactone formation. The nucleophiles used were hydroxide ion, imidazole, azide ion, and sulfite ion.

Experimental

Materials.—*m*-Nitrobenzoic acid (Eastman Kodak Co.) was recrystallized three times from ethanol, the first time in the presence of charcoal; m.p. 143–143.5°. 5-Nitrosalicylic acid (Eastman Kodak Co.) was recrystallized three times from acetone, the first time in the presence of charcoal; m.p. 233°. The synthesis of 2-methoxy 5-nitrobenzoic acid is not straightforward. Earlier attempts to synthesize this acid by the methylation of 5-nitrosalicylic acid failed[13] and it was synthesized by nitration of 2-methoxybenzoic acid followed by a tedious separation of the isomers formed.[13] However, methylation of 5-nitrosalicylic acid was found to proceed in good yield by the following procedure. 5-Nitrosalicylic acid (10 g.) and potassium hydroxide (6.2 g.) were dissolved in absolute ethanol and mixed. The solution was evaporated together with the precipitate; the dipotassium salt obtained was dried under vacuum at 90° for 2 hr. and then heated with 80 ml. of dry xylene and 12 ml. of dimethyl sulfate for 3 hr. at 145° in an oil bath. The reaction mixture was then evaporated *in vacuo* and extracted with absolute alcohol; the alcoholic solution was then treated with charcoal and evaporated to dryness. The unreacted acid was separated by dissolving the crystals in a minimum amount of absolute alcohol and adding an alcoholic solution of potassium hydroxide until no more precipitation occurred. After filtration, the methyl ester of 2-methoxy-5-nitrobenzoic acid crystallized from the filtrate; m.p. 99–100° (lit.[13] m.p. 99–100°). The methyl ester was hydrolyzed by the stoichiometric amount of potassium hydroxide in absolute alcohol by heating on a water bath. The precipitated potassium salt was filtered after 3 hr., acidified in water, and the acid recrystallized from water; m.p. 161–162° (lit.[14] m.p. 161–162°).

The *p*-nitrophenyl esters were prepared by three methods. *p*-Nitrophenyl benzoate and *p*-nitrophenyl *o*-methoxybenzoate were synthesized from the corresponding acid chlorides and *p*-nitrophenol (Eastman Kodak Co., indicator grade) in pyridine solution. The crude material was isolated in water, washed with 10% sodium carbonate solution, and recrystallized from ethanol *p*-Nitrophenyl salicylate was synthesized by refluxing salicylic acid with a threefold excess of thionyl chloride for 3 hr., removing the excess thionyl chloride *in vacuo*, and treating the wine-red liquid containing the salicyloyl chloride with *p*-nitrophenol. The ester was recrystallized from ethanol or chloroform–hexane. *p*-Nitrophenyl 3-nitrobenzoate, *p*-nitrophenyl 5-nitrosalicylate, and *p*-nitrophenyl 2-methoxy-5-nitrobenzoate were prepared from the corresponding acids, *p*-nitrophenol, and phosphorus pentachloride according to the method of Tozer and Smiles.[15] The first ester was recrystallized from absolute ethanol, the second from Eastman Kodak Co. spectral grade acetone, and the third from ethanol–acetone and absolute ethanol. A summary of the physical constants of the ester substrates is given in Table I.

TABLE I

PHYSICAL CONSTANTS OF *p*-NITROPHENYL ESTERS

p-Nitrophenyl ester	M.p., °C.	Lit. m.p., °C.	Ref.
Benzoate	144–145	142, 142.5	16, 17
o-Methoxybenzoate[a]	87–88.5		
Salicylate	152–153.5	148, 150	18, 15
3-Nitrobenzoate	145–145.5	135.5	17
5-Nitrosalicylate	204–205	200, 204–205	15, 19
2-Methoxy-5-nitrobenzoate[b]	178–178.5		

[a] *Anal.* Calcd. for $C_{14}H_{11}O_5N$: C, 61.53; H, 4.06; N, 5.13. Found: C, 61.18; H, 4.03; N, 5.46.[20] [b] *Anal.* Calcd. for $C_{14}H_{10}N_2O_7$: C, 52.84; H, 3.17; N, 8.80. Found: C, 53.06; H, 3.39; N, 8.60.

The purity of all *p*-nitrophenyl esters was further determined by hydrolyzing a known amount of ester in 0.1 *N* sodium hydroxide solution and spectrophotometrically measuring the amount of *p*-nitrophenol released at 400 mμ (ϵ 18,320).[21] The

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(11) This possibility was considered by Bruice[6] but was ruled out on the basis of deuterium oxide solvent isotope effects (see later).
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TABLE II

SPECTRAL DATA OF REACTANTS AND PRODUCTS[a]

Substance	λ_{max}, mμ	ϵ_{max}	λ_{min}, mμ	ϵ_{min}	$\lambda_{iso\ point}$, mμ	
p-Nitrophenol	318	10167				
p-Nitrophenolate ion[c]	406	20840	307	724	350.5	4685
					270.2	2391
p-Nitrophenyl 5-nitrosalicylate	288.5	16840				
p-Nitrophenyl 5-nitrosalicylate anion[d]	393	18403	354	11424	323	9480
	342	11966	308.5	7660		
	274	12388				
5-Nitrosalicylic acid	307	10310	264	3020		
5-Nitrosalicylate monoanion[e]	322	9550	271	2940		
5-Nitrosalicylate dianion[b]	414	20250				

[a] 25°; 34.4% dioxane–water; buffers and concentration of substrates the same as in kinetic experiments. [b] pK_{a2} 11.50. [c] pK_a 7.62. [d] pK_a 6.023 (pK_a in D_2O = 6.49$_8$). [e] pK_a 2.55.

difference between the experimental and calculated absorbances was less than 1% with each ester.

Dioxane was purified by treatment with hydrochloric acid and potassium hydroxide and distilled from sodium.[22] Ethanol ("95%") was distilled twice through a Vigreux column; density determination showed 93.94% by weight of ethanol[23]; deuterium oxide, batch XX, General Dynamics Corp., Liquid Carbonic Division, 99.5% D_2O, was used. Buffers were prepared from Mallinckrodt A. R. materials following the procedures of Kolthoff and Rosenblum.[24]

Spectral Data.—Spectral characteristics of the reactants and products were determined in 34.4% (v./v.) dioxane at 25° under the conditions of the kinetic experiments, using a Cary 14 PM recording spectrophotometer. The results of these determinations are listed in Table II.

The spectral changes which occur in the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate make this system particularly suitable for the detection of possible intermediates in its hydrolytic reactions by spectroscopic means. Let us consider the spectral observations made at 400 mμ on a reaction at pH 7. At pH 7 in 34.4% dioxane–water, the reactant will exist mainly in the anionic form (pK_a 6.02) while the product, 5-nitrosalicylate, will exist mainly in the monoanionic form (pK_2 11.5). The extinction coefficients of these two species at 400 mμ are 18,000 and 521, respectively, since the former compound exists in the nitrophenoxide ion form while the latter compound exists in the nitrophenol form. It is possible for a reaction of a nucleophile with *p*-nitrophenyl 5-nitrosalicylate to produce an unstable compound which spontaneously reacts with water, giving an over-all nucleophilic catalysis of hydrolysis. The intermediate compound in such a reaction should have an ionization constant, and therefore an ϵ_{400}, similar to that of the reactant. Of course, whether the reaction proceeds through an intermediate or not, *p*-nitrophenoxide ion, which was a pK_a of 7.62 in this solvent, will be formed.

On the basis of these considerations, nucleophilic catalysis of the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate may be observed in several different spectral patterns. (1) Nucleophilic catalysis of hydrolysis with the formation of a stable intermediate: In the initial state there is essentially one absorber at 400 mμ, the *p*-nitrophenyl 5-nitrosalicylate; in the intermediate there are two absorbers, the compound formed from reaction of the nucleophile and 5-nitrosalicylate, and *p*-nitrophenoxide ion; in the product there is only one absorber, *p*-nitrophenoxide ion (since 5-nitrosalicylate monoanion essentially does not absorb). Therefore, the over-all spectral behavior will be an increase in absorption with time, followed by a decrease. (2) Nucleophilic catalysis of hydrolysis with the formation of an unstable intermediate: In the initial state there is one absorber at 400 mμ, the reactant; in the product, there is one absorber, *p*-nitrophenoxide ion (as above). Since the pK_a of the nitrophenol groups in the reactants is less than that of the product, the extinction coefficient of the reactant will be greater than that of the product at a given pH around neutrality and therefore there will be an observable first-order decrease in absorption.

A nucleophilic reaction which does not result in hydrolysis will be characterized by an increase in absorption (the intermediate stage).

Experimentally, spectral behavior has been found only for nucleophilic catalysis of hydrolysis. Both possibilities corresponding to nucleophilic catalysis of hydrolysis have been observed, as well as an intermediate case (see Fig. 1). With the azide ion as nucleophile, a stable intermediate is formed, followed by a slow decay to products. With the sulfite ion as nucleophile, no observable intermediate is formed, only hydrolytic products. With imidazole as nucleophile, a small inhibition period is observed at the beginning of the reaction, indicating the formation of a steady-state concentration of 5-nitrosalicyloylimidazole. This is confirmed by using a smaller concentration of imidazole: the inhibition disappears and the first-order rate constant calculated from the decay curve is proportional to the imidazole concentration.

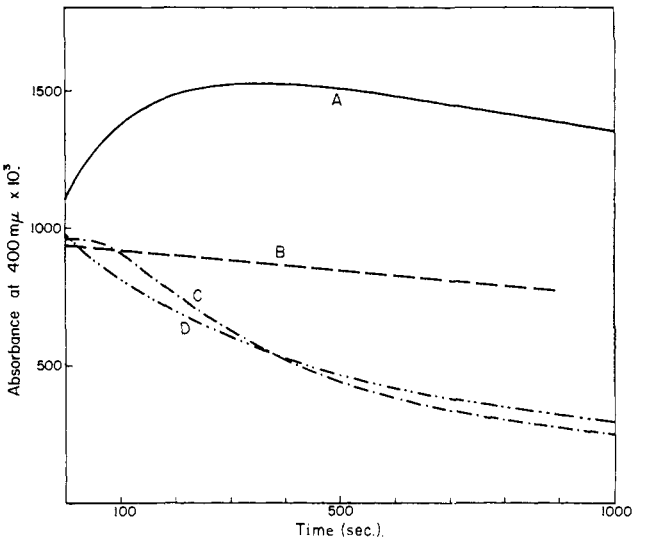

Fig. 1.—Nucleophilic reactions of *p*-nitrophenyl 5-nitrosalicylate in 34.4% dioxane–water at 25°; [ester] = 6.48 × 10^{-5} *M*: A, 0.656 *M* azide ion, pH 7.605; B, 0.0328 *M* imidazole, pH 6.71; C, 0.328 *M* imidazole, pH 6.71; D, 7.3 × 10^{-3} *M* sulfite ion, pH 6.69.

Kinetic Measurements.—The rate of liberation of *p*-nitrophenol was measured spectrophotometrically at 400 mμ on a Cary 14PM recording spectrophotometer with a thermostated cell compartment. The rate of appearance of salicylic acid and *p*-nitrophenol was measured at 270 mμ. The reaction was initiated by the addition of a small amount of the ester dissolved in an organic solvent (25 to 50 μl. of ethanol or dioxane) to the thermally equilibrated mixture of the buffer and the organic solvent. In slow reactions, aliquots were removed and measured, while in fast reactions, the reaction was carried out directly in the spectrophotometer and the absorbance of the solution recorded as a function of the time. Infinity readings were taken after at least seven times the estimated half-life, and conventional first-order kinetics were calculated, using a graphical method to determine the apparent rate constant. The logarithmic plots usually show linearity up to 90% of reaction (Fig. 2).

pH Measurement.—The pH or (pD − 0.4)[25] was measured immediately after the conclusion of a kinetic run, using a Radiometer 4c pH meter with G220B glass electrodes. The pH remained constant, within the experimental error, during even the longest runs. The pH meter was standardized with aqueous solutions, as recommended by Bates.[26]

For dioxane–water mixtures of the concentration used, the glass electrode gives the correct pH reading.[27] On the other hand, reaction mixtures containing 32.8% (w./w.) ethanol give only an apparent pH using the glass electrode. However, since the proportion of ethanol was constant throughout, changes in pH were proportional to changes in base concentration.[24,28]

Results

Solvolysis.—The kinetics of hydrolysis of *p*-nitrophenyl benzoate, *p*-nitrophenyl *o*-methoxybenzoate, and *p*-nitrophenyl salicylate in 32.8% (w./w.) ethanol are listed in Table III. The pseudo-first-order rate constants indicate that the salicylate ester (which has a pK_a 10.5)[9] is apparently hydrolyzed at a considerably faster rate than either the benzoate or *o*-methoxyben-

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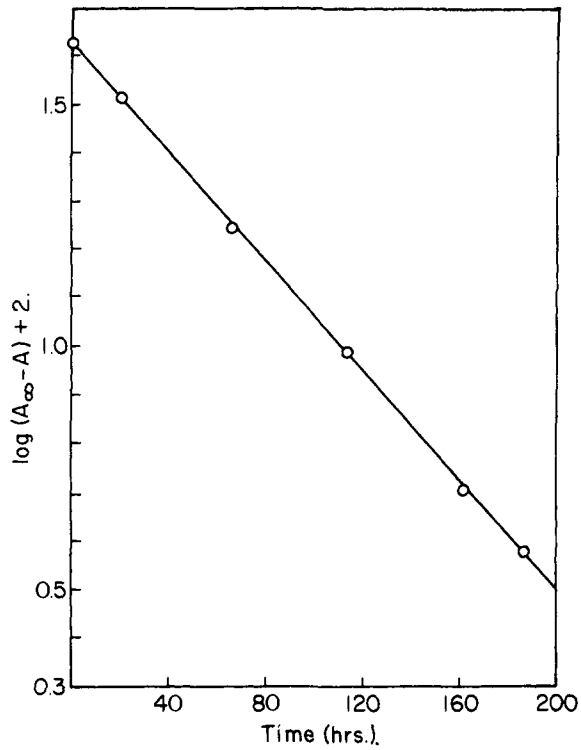


Fig. 2.—The hydrolysis of *p*-nitrophenyl 5-nitrosalicylate in 34.4% dioxane–water at 25° and pH 2.18.

zoate esters. Further, from runs at apparent pH's of 6.98 and 8.00, the salicylate ester hydrolysis appears to be dependent on the hydroxide ion concentration.

However, since the glass electrode pH readings are not related in a known way to the real pH in ethanol–water solution, it was decided to carry out the kinetics in dioxane–water solution where the glass electrode does yield the true pH of the solution. In dioxane–water solution, however, the situation is complicated by the fact that at higher pH's *p*-nitrophenyl salicylate undergoes the "Smiles rearrangement,"[15,29] which is negligible in ethanolic solution even in the presence of 0.1 *N* sodium hydroxide. For this reason, *p*-nitrophenyl 5-nitrosalicylate, which is known not to undergo the Smiles rearrangement in aqueous solution,[15] was chosen as the system to investigate. This finding has been confirmed by our experiments: at all pH's the stoichiometric amount of nitrophenol is liberated.[29]

TABLE III

KINETICS OF HYDROLYSIS OF *p*-NITROPHENYL ESTERS IN 32.8% ETHANOL[a]

Ester, *p*-nitrophenyl	[Ester]$_0$ × 10^5, *M*	Apparent pH	λ, mμ	k_{obsd} × 10^5,[b] sec.$^{-1}$
Benzoate	1.0	8.00	400	12.6
o-Methoxybenzoate	1.0	8.00	400	2.46
Salicylate	1.6	6.98	270	256
		6.98	400	250
		8.00	270	2670
		8.00	400	2710

[a] 25.0°; 0.012 *M* phosphate buffer. [b] Average of two runs.

Since *p*-nitrophenyl esters are known to react with the usual buffers,[12] all kinetic measurements were extrapolated to zero buffer concentration, and extrapolated rate constants were used throughout. A summary of the kinetics of hydrolysis of several *p*-nitrophenyl esters in 34.4% dioxane–water and dioxane–D_2O solution is given in Table IV.

(29) In the Smiles rearrangement of *p*-nitrophenyl salicylates the *o*-phenoxide ion carries out an intramolecular aromatic nucleophilic substitution leading to a *p*-nitrophenyl ether, which of course does not have an appreciable absorption at 400 mμ as *p*-nitrophenoxide does.

TABLE IV

HYDROLYSIS OF *p*-NITROPHENYL ESTERS IN 34.4% DIOXANE–WATER[a]

Ester, *p*-nitrophenyl	Solvent	Buffer	pH (pD)	k_{obsd} × 10^6,[b] sec.$^{-1}$	k_2K_w (H_2O) × 10^{14}[c]
5-Nitrosalicylate	H_2O	HCl	0.183	2.66	
		HCl	0.706	2.94	
		HCl	2.18	3.47	
		HCl[c]	2.18	3.52	
		Citrate	4.03	4.30	
		Acetate	5.90	41.5	9160
		Tris–HCl	8.20[f]	102	9700
		Tris–HCl	8.90	105	10000
		Carbonate	10.9	97	9200
		NaOH	12.85 + x[d]	536	0.0076
		NaOH	13.42 + x	2210	0.0083
	D_2O	DCl	1.104	1.61	
		Tris-DCl	8.68	61.8	
3-Nitrobenzoate	H_2O	Carbonate	10.36	4800	21.2
		Carbonate	10.64	9250	
	D_2O	Carbonate	10.90	5030	6.03
2-Methoxy-5-nitrobenzoate	H_2O	Carbonate	10.32	820	3.96
		Carbonate	10.92	3280	
	D_2O	Carbonate	10.94	900	1.03

[a] 25.0°. [b] Extrapolated to zero buffer concentration when necessary. [c] μ = 0.5 KCl. [d] x depends on the ion product of water in this medium which is unknown. [e] Calculated from k_{obsd}(H) when the reaction is hydroxide ion dependent and from $k_{obsd}(H + K_a)$ when the reaction is independent of hydroxide ion. [f] Although impurities in dioxane can catalyze the hydrolysis of some carboxylic acid derivatives,[30] this does not occur here. In 1% acetonitrile–water, pH 8.3, the rate constant is 134 × 10^{-6} sec.$^{-1}$, the expected value considering the increased concentration of water.

Nucleophilic Reactions.—Table V records the results of the nucleophilic reactions of the six *p*-nitrophenyl esters under investigation. The first-order rate constants are pH independent, within experimental error, for the reactions of those five esters not exhibiting protolysis under the experimental conditions. The reactions of *p*-nitrophenyl 5-nitrosalicylate, however, showed a marked pH dependence. In the reaction of this ester with azide ion, this pH dependence was successfully analyzed by assuming that both the un-ionized ester A and the ionized ester I react with the azide ion (at different rates). With this assumption

$$v = k_{obsd}[C] = k_A[N_3^-][A] + k_I[N_3^-][I]$$

where C = A + I

Hence

$$k_{obsd} = [N_3^-]\left\{\frac{k_A}{(K_a/H) + 1} + \frac{k_I}{(H/K_a) + 1}\right\}$$

and

$$k_{obsd}(K_a + H)/[N_3^-] = k_A(H) + k_IK_a \qquad (2)$$

The expected linear relationship was obtained when $k_{obsd}(K_a + H)/(N_3^-)$ was plotted *vs.* H (Fig. 3). A similar treatment fails to explain the complete pH dependence of the reaction of *p*-nitrophenyl 5-nitrosalicylate with imidazole. One can fit the experimental points with the above equation with less than 10% deviation between pH 5.85 and 6.90, but above pH 6.90 this relationship breaks down; the discrepancy at higher pH is probably due to the slow hydrolysis of the intermediate 5-nitrosalicyloylimidazole formed in this reaction. The results below pH 6.90 are, however, sufficient to determine the rate constant of the un-ionized ester.

The calculated second-order constants are shown in the last column of Table V. The reaction of azide ion with *p*-nitrophenyl 5-nitrosalicylate anion is about one-sixteenth that of the reaction of azide ion with *p*-nitrophenyl 3-nitrobenzoate. This difference can be attributed to electrostatic repulsion in the former reaction; the anionic charge of the azide ion is distrib-

(30) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652 (1957).

TABLE V

NUCLEOPHILIC REACTIONS OF SOME *p*-NITROPHENYL ESTERS[h]

p-Nitrophenyl ester[g]	pH	[Nucleophile], *M*	$k_{obsd} \times 10^4$, sec.$^{-1}$	$k_2 \times 10^3$,[i] M^{-1} sec.$^{-1}$
		Sulfite ion		
5-Nitrosalicylate	6.69	7.3×10^{-3}	2.21	1710[e]
3-Nitrobenzoate	6.69		3.84	527
		Imidazole		
5-Nitrosalicylate	6.71	0.328	3.24	
	6.71	.0985	0.968	
	6.71	.0328	0.3	
	7.70	.059	0.18	
	7.69	.295[a]	0.81	
	7.42	.262[a]	1.31	
	7.17	.230[a]	1.57	
	6.90	.197[a]	1.66	
	6.78	.164[a]	1.61	
	6.58	.131[a]	1.51	
	6.45	.098[a]	1.27	
	6.20	.066[a]	0.96	
	5.85	.033[a]	0.62	32[f] (un-ionized) 5.4[f] (ionized)
3-Nitrobenzoate	6.71	.328	5.90	17.6
	6.71	.328	5.71	
	6.71	.328	5.73[d]	
2-Methoxy-5-nitrobenzoate	6.71	.328	8.79	26.8
Salicylate	6.71	.328	1.85	5.63
Benzoate	6.71	.328	0.865	2.94
o-Methoxybenzoate	6.71	.328	1.04	3.17
		Azide ion		
5-Nitrosalicylate	6.87[b]	0.656	20.8	237[f] (un-ionized)
	7.61[b]	.656	5.38	
	8.32[c]	.656	2.48	2.53[f] (ionized)
3-Nitrobenzoate	6.87	.656	27.0	
	7.61	.656	26.5	40.7
	8.32	.656	26.6	
5-Nitro-2-methoxybenzoate	6.87	.656	15.4	23.4
Salicylate	8.32	.656	15.3	
	6.87	.656	6.02	9.53
	8.32	.656	6.5	
Benzoate	6.87	.656	1.30	1.98
o-Methoxybenzoate	6.87	.656	0.70	1.01
	8.32	.656	0.62	

[a] Total imidazole concentration = 0.328 *M*; ionic strength = 0.5 *M*. In these conditions, pK_a of *p*-nitrophenyl 5-nitrosalicylate = 5.96 and pK_a of the imidazolium ion = 6.78. [b] 0.06 *M* phosphate buffer. [c] 0.06 *M* Tris–HCl buffer. [d] Different sample of dioxane. [e] $k_2 = (k_{obs}/[SO_3^{-2}])[K_a/H + 1]$. [f] Graphical solution according to eq. 2. [g] Ester concentration varied from 0.3 to 6×10^{-5} *M*. [h] 34.4% dioxane–water; 25.0 ± 0.5°. [i] $k_2 = k_{obs}/$[catalyst].

uted between the two terminal nitrogen atoms resulting in a repulsive electrostatic interaction between the anion of the salicylate and an effective half-anionic charge of the azide ion. At pH 6.69, the un-ionized ester is essentially the only species reacting with azide ion even though the ester is essentially all ionized; in the reaction of this ester with the dinegative species, sulfite ion, it was assumed that only the un-ionized species reacted.

Discussion

Hydrolysis of *p*-Nitrophenyl 5-Nitrosalicylate.—The pH–rate profile of the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate shown in Fig. 4 is an extraordinary profile for an ester hydrolysis. The log *k* *vs.* pH profile for a simple ester such as ethyl acetate is a V-shaped curve, the left-hand side corresponding to a hydronium ion-catalyzed hydrolysis and the right-hand side corresponding to a hydroxide ion-catalyzed hydrolysis. The profile of the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate, on the other hand, shows two pH-independent regions, one below and one above the ionization constant of the phenolic group of the ester.

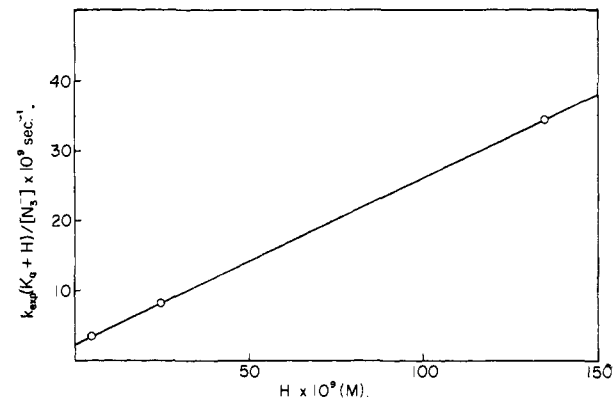


Fig. 3.—pH dependence of the reaction of azide ion with *p*-nitrophenyl 5-nitrosalicylate in 34.4% dioxane at 25°; $[N_3^-] = 0.656$ *M*, $[\text{ester}]_0 = 6.48 \times 10^{-5}$ *M*.

The hydrolysis of salicylate esters is of course complicated by the ionization of the hydroxyl group. Since we are dealing with two species of ester (un-ionized, A; and ionized, I; A + I = C, total ester) and three catalytic species, water, hydronium ion, and hydroxide ion, the rate equation for the hydrolytic system is composed theoretically of six terms[31]

$$-dC/dt = v = A[k_{AH}(H) + k_{AW}(H_2O) + k_{AOH}(OH)] + I[k_{IH}(H) + k_{IW}(H_2O) + k_{IOH}(OH)] \quad (3)$$

Using the relationships between the un-ionized ester and the total ester, and between the ionized ester and the total ester, eq. 3 can be transformed into

$$v = C/(H + K_a)[k_{AH}(H)^2 + k_{AW}(H_2O)(H) + k_{AOH}K_W(H_2O) + k_{IH}K_a(H) + k_{IW}K_a(H_2O) + k_{IOH}\cdot K_aK_W(H_2O)/(H)] \quad (4)$$

In the acid region, where $(H) \gg K_a$, and neglecting the term $k_{IOH}K_aK_W(H_2O)/(H)^2$

$$v = Ck_{exp} = C[k_{AH}(H) + \{k_{AW}(H_2O) + k_{IH}K_a\} + \frac{1}{H}\{k_{AOH}K_W(H_2O) + k_{IW}(H_2O)K_a\}]$$

where k_{exp} is the first-order apparent rate constant measured at constant pH. In the alkaline region where $K_a \gg (H)$ and neglecting the term $k_{AH}(H)^2/K_a$

$$v = Ck_{exp} = C\left\{(H)\left[\frac{k_{AW}}{K_a}(H_2O) + k_{IH}\right] + [k_{AOH}K_W(H_2O)/K_a + k_{IW}(H_2O)] + k_{IOH}K_W(H_2O)/(H)\right\}$$

Plotting a theoretical log k_{exp} *vs.* pH profile of eq. 4 would therefore lead to: (1) a straight line portion of slope −1 at low pH; (2) a straight line portion of slope 0 at higher pH (pH < pK_a); (3) a straight line of slope −1 or +1 at pH ≅ pK_a; (4) a straight line of slope 0 at pH > pK_a; (5) a straight line of slope 1 at very high pH. Of these five portions of the theoretical curve, four are observed experimentally. Only the first is not seen. This is presumably due to the fact that reactions at sufficiently low pH were not observed. The alkaline hydrolysis of the *p*-nitrophenyl 5-nitrosalicylate anion is considerably slower than the alkaline hydrolysis of *p*-nitrophenyl 3-nitrobenzoate, also shown

(31) *Cf.* A. Agren, U. Hedsten, and B. Jonsson, *Acta Chem. Scand.*, **15**, 1532 (1961).

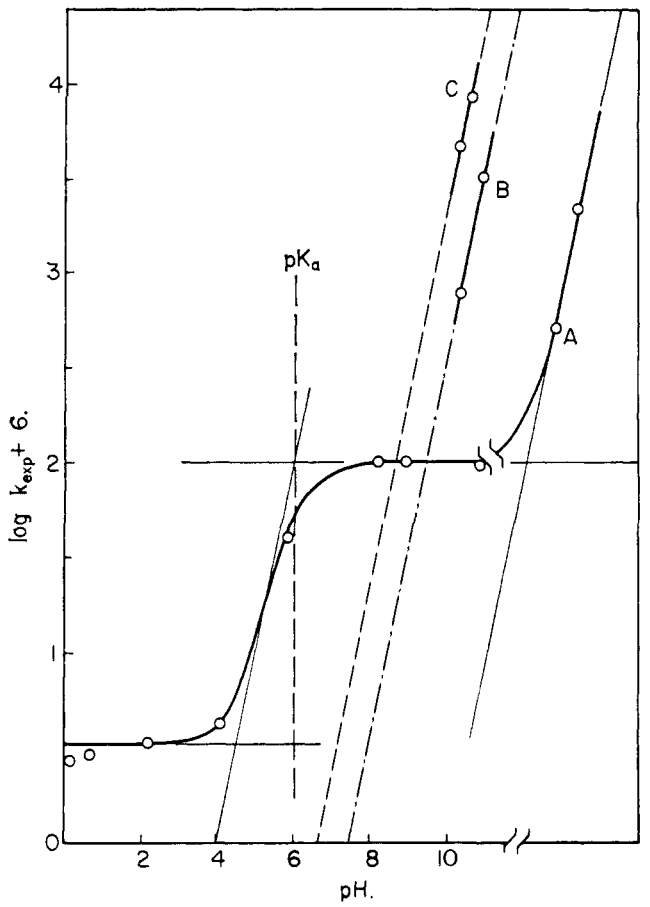


Fig. 4.—The hydrolysis of *p*-nitrophenyl 5-nitrosalicylate (A), *p*-nitrophenyl 2-methoxy-5-nitrobenzoate (B), and *p*-nitrophenyl 3-nitrobenzoate (C) in 34.4% dioxane-water at 25°.

in Fig. 4, because of the expected electrostatic repulsion between the ester anion and the negatively-charged hydroxide ion. The ratio of these hydrolytic rate constants is 2700, much larger than the effect observed with azide ion because with hydroxide ion one observes the effect of a complete electric charge. The pH-independent reaction at low pH decreases slightly with decreasing pH; no obvious explanation is available for this phenomenon.

Each of the two pH-independent regions in the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate can be ascribed to at least two different mechanisms. The pH-independent reactions in the acid and alkaline regions could simply be the water reactions of the un-ionized and ionized ester, respectively, or, alternatively, the hydroxide ion reactions of the protonated and un-ionized ester, respectively. Furthermore, the pH-independent region at acid pH could be the hydronium ion-catalyzed hydrolysis of the ionized ester.

Previous authors have favored a mechanism for the alkaline region involving the hydroxide ion-catalyzed hydrolysis of the un-ionized ester.[3-9] Assuming this mechanism is the proper description of the pH-independent reaction at high pH, the relative rates in Table VI can be calculated.

The hydrolysis of the esters containing an *o*-hydroxyl group is apparently a facile reaction, as judged by comparison with either the corresponding *o*-methoxy compound or the corresponding unsubstituted compound in the *p*-nitrophenyl ester families. However, in the ethyl ester family, this large rate enhancement of the *o*-hydroxyl group is not seen. It is difficult to explain why the nitrophenyl esters should be much more sensitive to intramolecular hydroxyl group catalysis.

TABLE VI

RELATIVE RATES OF HYDROLYSIS OF SOME *p*-NITROPHENYL ESTERS[a]

Parent compound	Solvent	$\frac{k_{o\text{-hydroxy}}}{k_{o\text{-methoxy}}}$	$\frac{k_{o\text{-hydroxy}}}{k_{\text{unsubstd}}}$	$\frac{k_{\text{unsubstd}}}{k_{o\text{-methoxy-benzoate}}}$
p-Nitrophenyl benzoate	32.8% ethanol	1093	213.4	5.12
Ethyl benzoate[9]	50% ethanol		7.5[b]	
p-Nitrophenyl 3-nitrobenzoate	34.4% dioxane	2450	458	5.34

[a] Calculated assuming the reaction of hydroxide ion with the un-ionized ester. [b] Corrected for pK_S = 14.88 (B. Gutbezahl and E. Grunwald, *J. Am. Chem. Soc.*, **75**, 565 (1953)).

However, by assuming the reaction of water with the ionized ester is the proper description of the pH-independent reaction at high pH, the acceleration due to the presence of the *o*-hydroxy group is much less. *p*-Nitrophenyl acetate is hydrolyzed by water (in water) with a second-order rate constant $k_W = 1 \times 10^{-8}\ M^{-1}$ sec.$^{-1}$,[12] and the un-ionized *p*-nitrophenyl 5-nitrosalicylate would have a rate constant $k_W = 9.6 \times 10^{-8}\ M^{-1}$ sec.$^{-1}$ with this mechanism, which implies that the salicylate ester is not exceptionally reactive. Furthermore, if one compares the two pH-independent regions in this context, it is calculated that the reaction of the ionized salicylate ester with water (in the alkaline region) is 30 times faster than the reaction of the un-ionized salicylate ester with water (in the acid region); this comparison indicates that the reaction of the ionized salicylate ester is exhibiting some exceptional reactivity (presumably by intramolecular general basic catalysis), but this accelerating effect is not large.

It might be hoped that the effect of deuterium oxide on these reactions could serve as a criterion for the differentiation between the two mechanisms discussed above for the pH-independent region at alkaline pH. Unfortunately this is not the case; the deuterium oxide kinetic isotope effects are compatible with both sets of mechanisms.

The calculations necessary to obtain correct comparison of the rate constants in water and deuterium oxide are detailed below. With the definition $K_{D_2O} = (D)(OD)$, the following equations are obtained for the calculation of the deuterium oxide kinetic isotope effect for the pH-independent reaction at alkaline pH.[32]

In the pH-independent reaction at alkaline pH the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate may be described as a hydroxide ion-catalyzed hydrolysis of the un-ionized ester, mechanistically a general acid-specific hydroxide ion catalysis.

$$v = k_{AOH}(A)(OH) = k_{AOH}\frac{(C)}{1 + (K_a/(H))}\frac{K_W(H_2O)}{(H)} = k_{obs}(C)$$

Since $K_a \gg H$

$$(k_{AOH}/K_a)K_W(H_2O)(C) = k_{obs}(C)$$

Therefore

$$\frac{k_{AOH}}{k_{AOD}} = \frac{k_{obs}{}^{H}K_a{}^{H}K_{D_2O}(D_2O)}{k_{obs}{}^{D}K_a{}^{D}K_W(H_2O)} \qquad (5)$$

Using eq. 5 and the experimental quantities $k_{obsd}{}^{H}$ at pH 8.20, $k_{obsd}{}^{D}$ at pD 8.68 (from Table IV), $K_a{}^{H}$ and $K_a{}^{D}$ from Table II, K_W/K_{D_2O} and $(D_2O)/(H_2O)$ from footnote 32, one may derive $k_{AOH}/k_{AOD} = 0.85$. For

(32) In all calculations, two assumptions were made: (1) $(H_2O)/(D_2O) = 1$ and K_W/K_{D_2O} in 34.4% dioxane = 5.8. The latter assumption is based on a $K_W/K_{D_2O} = 6.5$ in water[32] and the finding that in 34.4% dioxane-water $K_a{}^{W}/K_a{}^{D_2O} = 2.96$ for *p*-nitrophenyl 5-nitrosalicylate, while in pure water this ratio is 3.32 for 2,5-dinitrophenol (R. P. Bell, "The Proton in Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1959, p. 188) which difference is interpreted to reflect a difference in K_W/K_{D_2O} between the two solvent systems.

other hydroxide ion-catalyzed hydrolyses this ratio has been found to vary from 0.71 to 0.83 in pure water.[33] For the hydroxide ion-catalyzed hydrolyses of *p*-nitrophenyl benzoate and *p*-nitrophenyl 2-methoxy-5-nitrobenzoate, this ratio was calculated to be 0.60 and 0.66, respectively.[34] Thus, there is reasonable consistency of the deuterium oxide solvent isotope effect with this mechanism. This is especially true since the unknown effect of deuterium oxide on the hypothetical interaction between the *o*-phenolic group and the ester carbonyl group, which has not been taken into account, would be expected to increase k_{AOH}/k_{AOD} over that for the hydrolysis of simple esters.

In the pH-independent reaction at alkaline pH's, the reaction can be alternatively described as the water reaction of the ionized ester, mechanistically an intramolecular general basic catalysis by phenoxide ion.

$$v = k_{IW}(I)(H_2O) = k_{IW}\frac{(C)}{1 + ((H)/K_a)}(H_2O) = k_{obs} \quad (C)$$

Since $K_a \gg H$

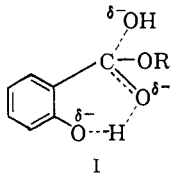
$$k_{IW}(C)(H_2O) = k_{obsd}(C)$$

Therefore

$$\frac{k_{IW}}{k_{ID2O}} = \frac{k_{obsd}{}^{H}(D_2O)}{k_{obsd}{}^{D}(H_2O)} \quad (6)$$

Using eq. 6, and the experimental quantities $k_{obsd}{}^{H}$ at pH 8.20; $k_{obsd}{}^{D}$ at pD 8.68 (from Table IV), one may derive $k_{IW}/k_{ID_2O} = 1.68$. General basic catalysis of ester hydrolysis usually leads to a rate ratio in water and deuterium oxide of 2–3, although there are some exceptions to this generalization.[35] Thus the deuterium oxide solvent isotope effect is reasonably consistent with this mechanism also.

It is reasonable that the two mechanisms of general acid catalysis–specific hydroxide ion catalysis and general basic catalysis should have the same deuterium oxide kinetic isotope effect.[36] Intuitively these two mechanisms should have the same deuterium oxide isotope effect, on the grounds that they are identical except that in one a pre-equilibrium step occurs while in the other it does not. The deuterium oxide isotope effect depends on the difference in the free energy differences between the ground state in water and D_2O and the transition state in water and D_2O. Therefore, if the general acid–specific hydroxide ion catalysis and the general basic catalysis do indeed have identical ground states and identical transition states, the deuterium oxide isotope effects for these two reactions must be identical. Certainly the ground states for the two mechanisms are identical, for one starts with the same species. The transition states for general acid–specific hydroxide ion catalysis and general basic catalysis are shown in I and II, respectively. The two transition states are not exactly identical but from the point of view of deuterium isotope effects they would appear to give similar results, for they contain identical numbers of protons, hydrogen bonds, charge distributions, etc.



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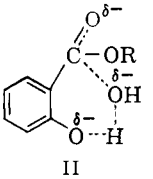


II

(33) F. A. Long and J. Bigeleisen, *Trans. Faraday Soc.*, **55**, 2077 (1959); F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).

(34) These values were calculated from the expression

$$k_{OH}/k_{OD} = k_{obsd}{}^{H}(H)K_{D_2O}(D_2O)/k_{obsd}{}^{D}(D)K_{H_2O}(H_2O)$$

and the experimental data from Table IV, Table II, and footnote 32.

(35) M. L. Bender, E. J. Pollock, and M. C. Neveu, *J. Am. Chem. Soc.*, **84**, 595 (1962).

(36) Similar conclusions have been reached by Professor T. C. Bruice, personal communication.

In a formal mathematical way, it can be shown that the experimental rate constant ratio for both mechanisms is

$$\frac{k_{exp}{}^{H}}{k_{exp}{}^{D}} = \frac{k_{OH}\text{-}K_a{}^{D_2O}K^{H_2O}}{k_{OD}\text{-}K_a{}^{H_2O}K^{D_2O}} \quad (7)$$

Equation 7 is eq. 5 written in rearranged form. Therefore eq. 7 is the kinetic isotope effect for the mechanism involving the un-ionized ester and hydroxide ion. Equation 7 is also the kinetic isotope effect for the reaction of the ionized ester and water using the following interpretation: (1) the first term represents the isotope effect in the attack of an hydroxide ion on the ester group (after removal of a proton from water); (2) the second term represents the isotope effect in the basicity of the phenoxide ion (for removal of a proton); (3) the third term represents the isotope effect in the acidity of the water as an acid (for donation of a proton).

The deuterium oxide kinetic isotope effects in the pH-independent reaction in the acid region can be treated in a similar, ambiguous way.

Nucleophilic Reactions of *p*-Nitrophenyl 5-Nitrosalicylate.—In Table V, the rate constants for the hydrolysis of this ester with three nucleophiles, imidazole, azide ion, and sulfite ion, are listed. It is of interest to inquire whether one can observe an exceptional effect of an *o*-hydroxyl group on these nucleophilic reactions, which are not subject to kinetic ambiguity as are the hydrolytic reactions. Table VII summarizes the effect of the *o*-hydroxyl group on various reactions by listing the ratios of rate constants of 2-substituted ester to unsubstituted ester.

TABLE VII

RATIOS OF RATE CONSTANTS OF 2-SUBSTITUTED BENZOATES: BENZOATES WITH VARIOUS NUCLEOPHILES

	Nucleophile			
p-Nitrophenyl ester	Sulfite ion[b]	Azide ion[b]	Imidazole[b]	Hydroxide ion[c]
5-Nitrosalicylate[a]:3-nitrobenzoate	3.25	5.82	1.82	...
2-Methoxy-5-nitrosalicylate:3-nitrobenzoate		0.58	1.52	0.195
Salicylate[a]:benzoate		4.81	1.92	...
o-Methoxybenzoate:benzoate		0.51	1.08	0.188

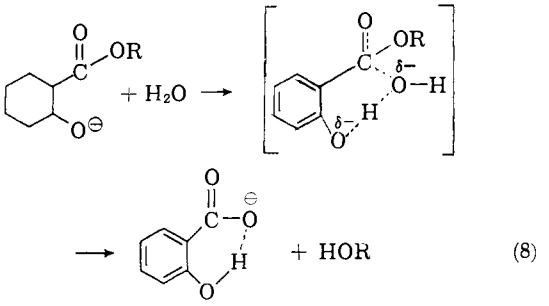
[a] Un-ionized ester. [b] Data from Table V. [c] Data from Table IV.

The ratios in Table VII indicate that the effect of an *o*-hydroxyl group on the reaction of three different nucleophiles of varying charge type is small, if not negligible. Since the ratios of $k_{salicylate}/k_{benzoate}$ are slightly greater than one, one could say that there is a hydroxyl group catalysis, but since it is impossible to evaluate correctly the relative influence of steric, inductive, and resonance effects of the *o*-hydroxyl group, it is not proposed to amplify this point.

The ratios in Table VII are much smaller than the ratios of 213 and 458 listed in Table VI for the hypothetical reactions of hydroxide ion with *p*-nitrophenyl salicylate and *p*-nitrophenyl 5-nitrosalicylate, compared to the corresponding benzoates. Therefore it appears that this hypothetical calculation was incorrect and that one cannot explain the pH-independent region at alkaline pH as the reaction of hydroxide ion with the un-ionized ester, but rather must interpret it as the kinetically equivalent reaction of water with the ionized ester. There is, of course, the possibility that the reaction of these esters with hydroxide ion will exhibit different kinetic characteristics from the corresponding reactions with other nucleophiles, but it would appear to a first approximation that if the special effect of an *o*-hydroxyl group appeared in the reaction of hy-

droxide ion with an ester, it would appear in the reaction of other nucleophiles with that ester. Since the special effect of the *o*-hydroxyl group does not appear in the latter reactions, it must be concluded that it also does not operate in the former reaction and further that the former reaction must be interpreted as the reaction of water with the ionized form of the ester.

If one interprets the pH-independent reaction in the alkaline region in terms of the reaction of water with the ionized form of the ester, the question may be raised as to the reason for the facile reaction of this species. The most straightforward explanation is that the phenoxide ion may act as an intramolecular general basic catalyst for the reaction of water with the ester group, as suggested above. The mechanism may be depicted as in eq. 8, or alternatively as the corresponding mechanism



(8)

in which the internal base removes a proton from the addition compound of water and the ionized ester, as discussed by Jencks and Carriuolo for general basic catalysis.[37] It appears, however, that in this instance one can rule out those mechanisms which are kinetically general basic catalysis, but which are mechanistically general acid–hydroxide ion reactions.[37]

Previous results in the literature concerning catalysis by neighboring hydroxyl groups can all be interpreted according to the above mechanism.[4-9] Bruice and Fife[6] considered eq. 8 as the mechanism for the effect of a neighboring hydroxyl group, but discarded this mechanism on the grounds of an argument involving deuterium oxide solvent isotope effects.[38] The deuterium oxide isotope effects in our hands are compatible with both possible mechanisms of general acid–specific hydroxide-catalyzed hydrolysis and general base-catalyzed hydrolysis (see above).

It is not mandatory, of course, that all examples of neighboring hydroxyl group catalysis occur by the same mechanism. Some may operate *via* eq. 8 involving general basic catalysis by the alkoxide ion while others may operate *via* general acidic catalysis by the un-ionized hydroxyl group. However, since the hydrolysis of salicylate esters, which when calculated as the hydroxide ion reaction of the un-ionized ester has the most significant neighboring hydroxyl group catalysis, appears to involve the phenoxide ion and not the phenolic group, it would appear that the other examples of neighboring hydroxyl group participation should be re-examined in this light.

(37) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83**, 1743 (1961).

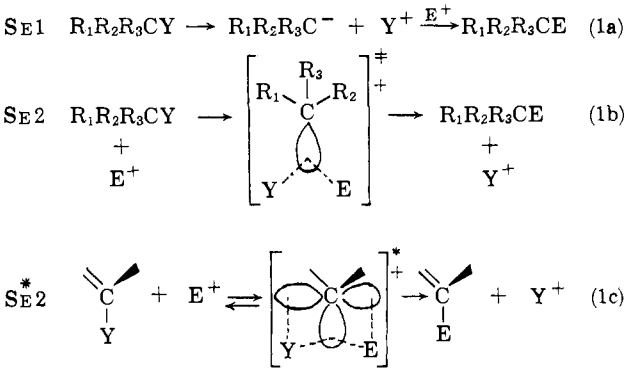
(38) The equation of Bruice and Fife[6] for calculating the isotope effect does not agree with eq. 5, but a revised equation from Professor T. C. Bruice (personal communication) does agree with eq. 5. When their isotopic data are calculated according to eq. 5, the resulting isotope effect does not support general base catalysis. Their isotopic data are, however, in accord with nucleophilic catalysis by hydroxide ion.

COMMUNICATIONS TO THE EDITOR

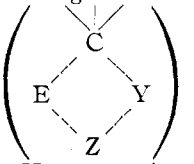
Electrophilic Substitution. Electronic Effects in SE2 Reactions

Sir:

There are many reactions in which a carbon–Y bond is broken by the attack of an electrophilic group or atom where the usual result is retention of configuration at the center of displacement. Examples are: base catalyzed H–D exchange in carbon acids,[1] electrophilic cleavage of organometal bonds,[2] oxidation of organoboron compounds with hydrogen peroxide,[3] and Beckmann, Lossen, and hydroperoxide rearrangements.[4] All these reactions can be represented[5] by mechanisms intermediate between the limiting cases 1a, 1b, and 1c.



These formulations represent rearrangement to an electron-deficient E if an E–Y bond is present in the reactant and typical electrophilic substitutions otherwise. When a ligand connects E with Y in the transition state



the mechanism is generally called SEi. However, since this process differs so little from SE2 we are including it in the designation SE2.

The electronic effects can be predicted for such formulations. Electron supply by R will accelerate

(1) D. J. Cram, D. A. Scott, and W. D. Nielsen, *J. Am. Chem. Soc.*, **83**, 3696 (1961).

(2) (a) S. Winstein, T. G. Traylor, and C. S. Garner, *ibid.*, **77**, 3741 (1955); (b) H. B. Charman, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2523 (1959); (c) F. R. Jensen and L. H. Gale, *J. Am. Chem. Soc.*, **81**, 1261 (1959).

(3) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, p. 67.

(4) See, *e.g.*, J. A. Berson and S. Suzuki, *J. Am. Chem. Soc.*, **81**, 4088 (1959) for references.

(5) The term[6] SE1 refers to dissociations into ions or ion pairs; SE2 is conceived to have a transition state in which two electrophiles are attached to the carbon orbital without appreciable rehybridization or development of charge on carbon. In this respect it is analogous to the SN2 mechanism. The term S*E2, representing what is usually called aromatic substitution, is introduced to specify an intermediate of the Pfeifer-Wizinger[7] type (*i.e.*, σ-complex) denoted by * instead of ‡ to differentiate an intermediate from a transition state. This terminology allows for SE1 and SE2 aromatic substitution, the latter demonstrated herein, and for the nonaromatic Pfeifer–Wizinger intermediates which are required to explain some accelerated electrophilic reactions at vinyl and cyclopropyl groups.[9d]

(6) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 244 (1935).

(7) P. Pfeifer and R. Wizinger, *Ann.*, **461**, 132 (1928).