The Role of Intramolecular Bifunctional Catalysis of Ester Hydrolysis in Water

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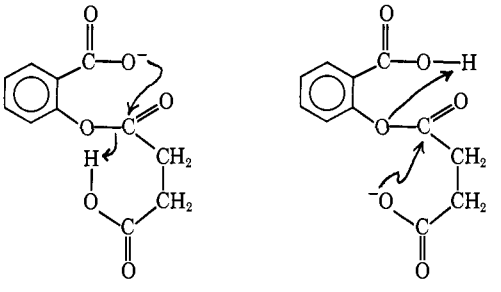
Abstract: In a search for intramolecular concerted general acid, general base and general acid, nucleophilic catalysis, the hydrolyses of four systems of esters were examined: (1) 6- and 8-quinolyl hydrogen glutarates and succinates; (2) *o*- and *p*-carboxyphenyl succinates; (3) methyl γ- and β-resorcylates; and (4) phenyl esters of 4- and 6-substituted salicylates. Bell-shaped pH-k_{obsd} profiles interpretable as resulting from bifunctional catalysis were obtained for compounds in each series. In all cases, however, only one functional group was found to participate directly in the hydrolytic reaction; the descending leg of the bell (at high pH) in all cases was shown to result from electrostatic and electronic inhibition resulting from the ionization of the nonparticipating functional group. There is, thus, no existing evidence for concerted intramolecular general acid, general base or general acid, nucleophilic catalysis for hydrolysis of esters in water.

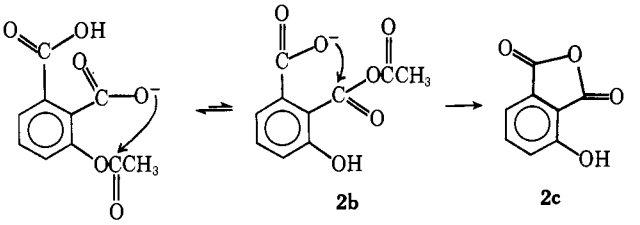
In the enzymatic catalysis of the conversion of substrate into product, the first step involves the reversible formation of an enzyme–substrate complex; the reaction then proceeds *via* intracomplex participation of (generally) two or more functional groups of the enzyme, collectively known as the active site.[3] The similarity between reactions within the active site and intramolecular reactions is obvious, and has prompted a great many studies in which both a reactive (ester, amide) and a catalytic (amine, carboxyl, etc.) species are combined in the same molecule.[4] There are, however, only a very limited number of "models" in which two catalytic species are incorporated in the same molecule as the reactive groups. The present study was initiated in order to ascertain the validity of proposals of bifunctional (nucleophilic, general acid, or general base, general acid) catalysis of ester hydrolysis in water.

Perhaps the first system in which intramolecular bifunctional catalysis was implicated was reported by Morawetz and Oreskes,[5] who observed a bell-shaped pH–log k_{obsd} profile for the hydrolysis of *o*-carboxyphenyl hydrogen succinate (**1**). At pH 4, the observed hydrolytic rate constant for **1** was found to be about 10^4-fold greater than that for the hydrolysis of acetyl salicylate. Two kinetically indistinguishable pathways of nucleophilic, general acid catalysis were considered (*i.e.*, **1a** and **1b**). The authors pointed out that if the reaction proceeds *via* **1a**, the rate of solvolysis would be 24,000 times as great as that for ionized aspirin, but if *via* **1b**, only 66 times as fast as that of *o*-carbomethoxyphenyl hydrogen succinate. The authors thus favored the path through **1b**.



1a **1b**

Fersht and Kirby[6] have obtained a similar bell-shaped profile for the hydrolysis of 3-acetoxyphthalate (**2**), for which there is no possibility of general catalysis of the initial nucleophilic attack. The presence of the second carboxyl group causes the observed hydrolytic rate constant for **2** at pH 3.8 to be 6.3×10^3-fold greater than that for ionized aspirin. Moreover, the authors were able to demonstrate the intermediacy of 3-hydroxyphthalic anhydride (**2c**) in the reaction pathway, indicating that the reaction proceeds by what they have aptly termed "series nucleophilic catalysis."



2a **2b** **2c**

Bender and Killian[7] obtained a bell-shaped pH–log rate profile for the hydrolysis of methyl γ-resorcylate (**3**), indicating that the rate of hydrolysis is dependent upon the state of ionization of both *o*-hydroxyl groups. Two kinetically indistinguishable mechanisms involving participation by both hydroxyl groups may be written for this reaction also (**3a** and **3b**). For case **3b**, the derived rate constants indicate that the reaction is 5.4-fold faster than a similar mechanism for methyl salicylate (**4b**); for **3a**, the calculated rate constant is 1.6 times *slower* than that for **4a**. The near equivalence of the rate constants for hydrolysis of **3** and **4** was deemed important by the authors because of the general extreme

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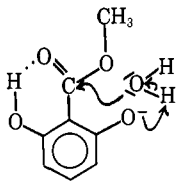
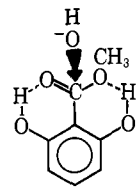
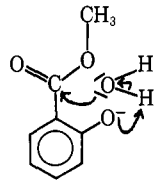
(2) To whom inquiries should be addressed.
(3) See, for example, E. L. Smith in "The Enzymes," P. D. Boyer, H. Lardy, and K. Myrback, Ed., Vol. IV, Academic Press, New York, N. Y., 1960, Chapter 1.
(4) For example, see T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, Chapter 1.
(5) H. Morawetz and I. Oreskes, *J. Amer. Chem. Soc.*, 80, 2591 (1958).
(6) A. R. Fersht and A. J. Kirby, *ibid.*, 90, 5833 (1968).
(7) F. L. Killian and M. L. Bender, *Tetrahedron Lett.*, 1255 (1969).



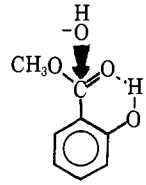
3a



3b



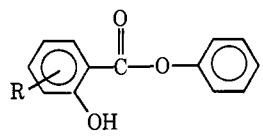
4a



4b

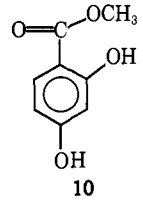
lack of reactivity of ortho-disubstituted benzoate esters in comparison to mono- or unsubstituted esters.[8,9]

The quinoline nitrogen has previously been shown to participate as a general base in the hydrolysis (and aminolysis) of 8-acetoxyquinoline[10] (**6**), giving a 500-fold rate increase over the electronically similar 6-acetoxyquinoline (**5**), and in the hydrolysis of 8-quinolyl phosphate,[11] which presumably also proceeds *via* intramolecular general base catalysis. The hydrolyses of the 8-quinolyl half esters of glutaric (**7**) and succinic (**8**) acids exhibit "bell-shaped" pH–k_{obsd} profiles which, on the basis of the work cited above, could be interpreted as bifunctional catalysis of hydrolysis. In order to evaluate the role, if any, of bifunctional catalysis in the hydrolysis of **1**, **3**, **7**, and **8** the kinetics of hydrolysis of esters **5–18** have been determined.

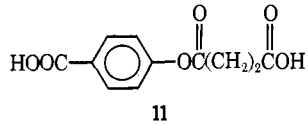


5, R = 6-OOCCH$_3$
6, R = 8-OOCCH$_3$
7, R = 8-OOC(CH$_2$)$_3$COOH
8, R = 8-OOC(CH$_2$)$_2$COOH
9, R = 6-OOC(CH$_2$)$_3$COOH

12, R = 6-OH
13, R = 4-OH
14, R = 6-OCH$_3$
15, R = 4-OCH$_3$
16, R = 6-CH$_3$
17, R = 4-CH$_3$
18, R = -H



10



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Experimental Section

Apparatus. All spectrophotometric kinetic measurements were made on either a Gilford Model 2000 spectrometer equipped with four thermospacers through which water at 30 ± 0.1° was circulated, a Zeiss PMQ II spectrophotometer equipped with a brass cuvette holder through which water at 30 ± 0.1° was circulated, a Durrum-Gibson Model 13001 stopped-flow spectrophotometer equipped with a Kel-F cell and valve block through which water was circulated at 30 ± 0.2°, or a spectrophotometric titration apparatus designed around the Cary 15 spectrophotometer and Radiometer autotitrator (described elsewhere by Bruice and Maley[12]) through which water was circulated at 30 ± 0.1°. Spectrophotometric titrations and titrimetric rates were carried out with the latter apparatus. Ultraviolet spectra were recorded on the Cary 15 at 30° or on a Perkin-Elmer 350 recording spectrophotometer at ambient temperature. pH measurements at 30 ± 0.1° were taken with a Radiometer Model 22 pH meter equipped with a Model 630 scale expander and a Radiometer GK2021C combined glass calomel electrode.

The hydrolysis of **10** was followed using a Radiometer TTT-1b autotitrator equipped with a PHA-630Ta scale expander and a water-jacketed 100-ml cell equipped with $\overline{\$}$ openings to accommodate a salt bridge leading to a calomel electrode, an EA-115 Metrohm glass electrode, an inlet capillary for titrant base addition, and a thermometer. A port in the side of the cell sealed with a serum cap allowed withdrawal of aliquots by means of a hypodermic syringe and needle. Water at 60 ± 0.2° was circulated through the cell jacket with a Haake bath. The same electrodes and the Haake bath were used with the Cary 15 for spectrophotometric titrations at 60 ± 0.2°.

Infrared spectra were recorded in potassium bromide disks using a Perkin-Elmer 137 sodium chloride spectrophotometer. Pmr spectra were recorded on a Varian A-60 spectrometer, using TMS or DSS (in water) as an internal standard. Melting points were measured on a Nalge hot stage and are uncorrected.

Materials. Potassium chloride, tris(hydroxymethyl)aminomethane (Sigma 7-9), potassium phosphate monobasic, sodium borate, potassium acetate, acetic acid, and formic acid were reagent grade and were used without further purification. Deionized, freshly double-glass-distilled water was employed to prepare all solutions. Standard buffers at 30° were purchased from Fisher Scientific (7 and 10) and Beckmann (12.3). Those used at 60° were prepared by the method of Bates.[13]

8-Quinolyl Hydrogen Glutarate (7). In a dry apparatus fitted with a silica gel drying tube were combined 10 g (0.069 mol) of 8-hydroxyquinoline (Matheson) and 7.86 g (0.069 mol) of glutaric anhydride (Matheson). The reactants were dissolved in about 50 ml of sodium-dried ether and refluxed overnight, yielding a white precipitate. The solution was cooled and filtered, and the filtrate was crystallized several times from 100% ethanol, yielding 3.5 g (20%) of fine, cottony, white needles: mp 115–117°; strong ν_{max} 1750 (ester), 1700 (acid), 1280, 1120, 830, 800, 760 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found:[14] C, 64.82; H, 5.04; N, 5.78.

8-Quinolyl Sodium Succinate (8). 8-Hydroxyquinoline was recrystallized three times from 100% ethanol and thoroughly dried under vacuum over P_2O_5. Succinic anhydride (Matheson) was refluxed for 3 hr in acetic anhydride, crystallized, and recrystallized twice more from the same solvent.[15] The material was then dried at 80°, under a vacuum over P_2O_5. Dioxane (Baker) was scrupulously dried by the method of Fieser,[16] and was distilled directly into the reaction vessel as needed. 8-Hydroxyquinoline (1 g, 0.0069 mol) was placed in a dry flask equipped with a drying tube containing silica gel and Ascarite, and dissolved in about 25 ml of dioxane; 0.15 g (0.0069 mol) of sodium shot was added with stirring, and the flask was warmed to keep the sodium salt in solution. In a separate, similarly equipped flask, 0.69 g (0.0069 mol) of succinic anhydride was dissolved in a minimal volume of dioxane. After all of the sodium had reacted (about 3 hr), the succinic anhydride solution was added with a dry pipet. Heating was discontinued, and the solution was stirred at room temperature overnight. The golden precipitate was collected by filtration, thoroughly washed with sodium-dried ether, and stored under vacuum over P_2O_5. The powder showed strong ν_{max} at 3450, 1750 (ester), 1660 (sodium salt of acid), 1530, and 1380 cm^{-1}; no anhydride bands were present. Assay by pmr showed the presence of both the quinolyl group (multiplets at τ 1–3) and the succinate methylenes (multiplets

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(9) H. L. Goering, T. Rubin, and M. S. Newman, *J. Amer. Chem. Soc.*, 76, 787 (1954).
(10) S. M. Felton and T. C. Bruice, *ibid.*, 91, 6721 (1969).
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(12) T. C. Bruice and J. R. Maley, *Anal. Biochem.*, 34, 275 (1970).
(13) R. G. Bates, "Electrometric pH Determinations," Wiley, New York, N. Y., 1954, pp 118–121.
(14) Analyses performed either by Dr. E. E. Sutcliffe, Santa Barbara, Calif., or by Elek Laboratories, Torrance, Calif.
(15) R. L. Shriner and H. C. Struck, *Org. Syn.*, 12, 66 (1932).
(16) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath, Boston, Mass., 1955, p 284.

at τ 6.5–8.0). The material was initially water soluble at higher concentrations, but a precipitate rapidly formed as the ester hydrolyzed. By hydrolyzing the material in acetate buffer at pH 4.6, the material was shown to contain about 76% ester sodium salt (by the presence of 8-hydroxyquinoline, as compared to a Beer's law plot at 250 nm). Addition of the material to water at pH 4 produced a large, near instantaneous uptake of protons, followed by a slower release of protons, with a titrimetric rate constant k_{obsd} = 0.137 min^{-1}; under identical conditions, succinic anhydride was shown to hydrolyze with a rate constant k_{obsd} = 0.150 min^{-1}, indicating that the material was, indeed, the ester, which hydrolyzes by forming succinic anhydride as an intermediate. Also, repetitive scan spectrophotometry of the material in the ultraviolet yielded spectra, which, with the exception of the rates of change, were identical with those produced by **6** and **7**. The material was stable under vacuum, but on exposure to air turned red and lost its water solubility. All attempts either to purify the sodium salt or to convert it to the free acid or hydrochloride proved fruitless.

6-Quinolyl Glutarate (9). 6-Hydroxyquinoline (K & K Chemicals) was sublimed before use. 6-Hydroxyquinoline (2.5 g, 0.0175 mol) and glutaric anhydride (2 g, 0.0175 mol) were dissolved in a minimum volume of pyridine and refluxed overnight. The pyridine was then removed on a rotary evaporator and under a vacuum. The residue was decolorized with Norit and crystallized several times from 95% ethanol, yielding a white powder (1.5 g, 33%): mp 140–149°; strong ν_{max} 1750, 1700, 1275, 1205, 1145, 1130 cm^{-1}. Additional crystallizations did not improve the melting range.

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.78. Found: C, 65.08; H, 5.04; N, 5.48.

Methyl β-Resorcylate (10). Methyl β-resorcylate was prepared from β-resorcylic acid and diazomethane. The resulting oil was zone sublimed,[17] yielding white rhomboid crystals; mp 119–121° (lit.[18] 115–117°). The material had a broad carbonyl absorption in the ir at 1640 cm^{-1}; the pmr (DMSO-d_6) spectrum showed a sharp singlet at τ 6.03, indicating the methyl ester.

Phenyl γ-Resorcylate (12). γ-Resorcylic acid (2 g, 0.013 mol, Aldrich) and phenol (1.3 g, 0.013 mol, Mallinckrodt) were combined with trifluoroacetic anhydride (4 g, 0.0165 mol, Matheson) in 10 ml of dry ether and heated at 60° for 2 hr. The solution was then diluted with ether to about 200 ml, washed with saturated bicarbonate and saturated potassium chloride solutions, and dried over magnesium sulfate, and the ether was removed on a rotary evaporator. The residue was then zone sublimed, yielding white rhomboids: mp 96–98°; strong ν_{max} 3390, 1680, 1630, 1565, 1460, 800 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.86; H, 4.48.

Phenyl β-Resorcylate (13). The ester was synthesized from β-resorcylic acid in the same fashion as the β-resorcylate, but was found not to sublime. Treatment with Norit in toluene and precipitation with hexane gave a white powder free of phenol. A 1-g sample of this material dissolved in about 10 ml of toluene was applied to a 2-ft column containing about 175 ml of silica gel (Baker) in hexane. The column was eluted with hexane and hexane–ethyl acetate, the concentration of ethyl acetate being increased by 2% every 600 ml. Fractions (100 ml) were collected; the ester was found in fractions 24–30, as indicated by tlc on silica gel (ethyl acetate–hexane 1:1). The fractions were combined and the solvent was removed on a rotary evaporator. The residue was recrystallized from toluene–hexane, yielding white prisms: mp 147–149° (lit.[19] 145–146°); strong ν_{max} 3380, 1650, 1480, 1270, 1250, 900 cm^{-1}.

Phenyl 4-Methoxysalicylate (15). 4-Methoxysalicyclic acid, mp 156–161° (lit.[20] 157°) was prepared from β-resorcylic acid and dimethyl sulfate by the method of Gomberg and Johnson.[20] The phenyl ester was prepared from the acid, phenol, and $POCl_3$ by the method of Gaylord and Kamath,[21] and recrystallized from ethanol, yielding white needles: mp 61–63°; strong ν_{max} 1665, 1610, 1580, 1020, 960, 770, 686 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.85; H, 5.00.

Phenyl 6-Methoxysalicylate (14). 6-Methoxysalicylic acid, mp 136–139° (lit.[22] 136–138°) was prepared from γ-resorcylic acid by the method of Gomberg and Johnson,[20] but using only one-third the quantity of dimethyl sulfate. The ester was prepared from the acid and phenol by the same method as for **12**. The resulting oil was zone sublimed to yield a waxy solid: mp 66–72°; strong ν_{max} 1650, 1610, 1580, 1230, 1080, 805, 695 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.30; H, 5.19.

Phenyl 6-Methylsalicylate (16). 4-Carbethoxy-3-methyl-5-oxohexanal, bp 104° (3.75 mm), was prepared from ethyl acetoacetate and crotonaldehyde by the method of Bohlmann and Prezewowsky.[23] Ethyl 6-methylsalicylate was then prepared from this material by the method of Mousseron, *et al.*;[24] this material was not isolated, but was hydrolyzed in 2 *N* NaOH to give 6-methylsalicyclic acid as white needles, mp 172–174° (lit.[25] mp 169°).

The phenyl ester was prepared from the acid and phenol by the method of Gaylord and Kamath,[21] and recrystallized several times from 75% ethanol to yield white needles: mp 50–51°; strong ν_{max} 1650, 1280, 795, 735, 685 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.84; H, 5.33.

Phenyl 4-Methylsalicylate (17). 4-Methylsalicyclic acid, mp 170–176° (lit.[26] mp 176°), was prepared from acetone, ethyl formate, and ethyl acetoacetate by the method of Prelog, *et al.*[26] The ester was prepared by the method of Gaylord and Kamath,[21] and zone sublimed to yield a waxy solid: mp 44–46°; strong ν_{max} 1675, 1180, 1060, 770, 690 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.77; H, 5.32.

***p*-Carboxyphenyl Succinate (11).** In a variation of the method of Bischoff, *et al.*,[27] *p*-hydroxybenzoic acid (5 g, 0.0362 mol, Matheson) and potassium hydroxide (4.78 g, 0.0724 mol) were combined in 75 ml of water and cooled to 0° in an ice bath. Succinic anhydride (3.8 g, 0.0362 mol) was added and the solution stirred at 0° for 15 min. The solution was filtered to remove undissolved anhydride, and acidified with concentrated HCl, yielding a white precipitate which was collected and dried. The material had strong ν_{max} at 1750 and 1700 cm^{-1}, corresponding to the ester and the acid, respectively, and no bands corresponding to anhydride. No further purification could be obtained. Analysis of the material by the same procedure as used for **8** indicated purities of from 50 to 90% for several preparations. Rate constants obtained using materials of different purities yielded the same pH profile, indicating that the presence of impurities did not observably affect the rate of hydrolysis.

Kinetics. All kinetic measurements were performed in water at a calculated ionic strength of 1.0 (KCl) and at a temperature of 30°, except for compound **10**, which was hydrolyzed at 60° in water containing 1.5% acetonitrile. For those esters whose disappearances were followed by monitoring loss of absorbance, the wavelengths (nm) used were: **7**, 288; **12**, 330 or 355; **13**, 320; **14**, 335; **15**, 355; **16**, 335; **17**, 350. The disappearances of **9** and **11** were followed by monitoring increase in absorbance at 246 and 250 nm, respectively; that of **8** was followed by monitoring loss of absorbance at 227 nm or increase in absorbance at 239 nm (stopped flow). Stock solutions of **7**, **9**, and **10** were prepared in acetonitrile; those of **12**–**17** were prepared in acetone. All were stable for several days at −5°. Stock solutions of **11** were prepared in methanol, and those of **8** in 0.01 *M* borate buffer at pH 9; these were stable about 15–30 min at 0°. Reactions performed using the borate stock solutions had rate constants identical with reactions performed using stock solutions prepared in water; the latter were far less stable, however. Reactions were initiated by the addition of 5–20 μl of a stock solution with an Eppendorf pipet to the preequilibrated buffer solution. The pH of the solutions was checked both before and—except for the stopped-flow

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(18) H. N. Knastgir, P. C. Duttagupta, and P. Sengupta, *Tetrahedron*, **14**, 275 (1961).
(19) U. N. Hirwe and G. V. Jadhau, *J. Univ. Bombay*, **22**, 11 (1954).
(20) M. Gomberg and L. C. Johnson, *J. Amer. Chem. Soc.*, **39**, 1687 (1917).
(21) N. G. Gaylord and P. M. Kamath, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 178.
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(24) M. Mousseron, R. Jacquier, A. Fontaine, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 1246 (1954).
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(26) V. Prelog, O. Metzler, and O. Jeger, *Helv. Chim. Acta*, **30**, 675 (1947).
(27) C. A. Bischoff and A. Von Hedenstrom, *Ber.*, **35**, 4076 (1902).

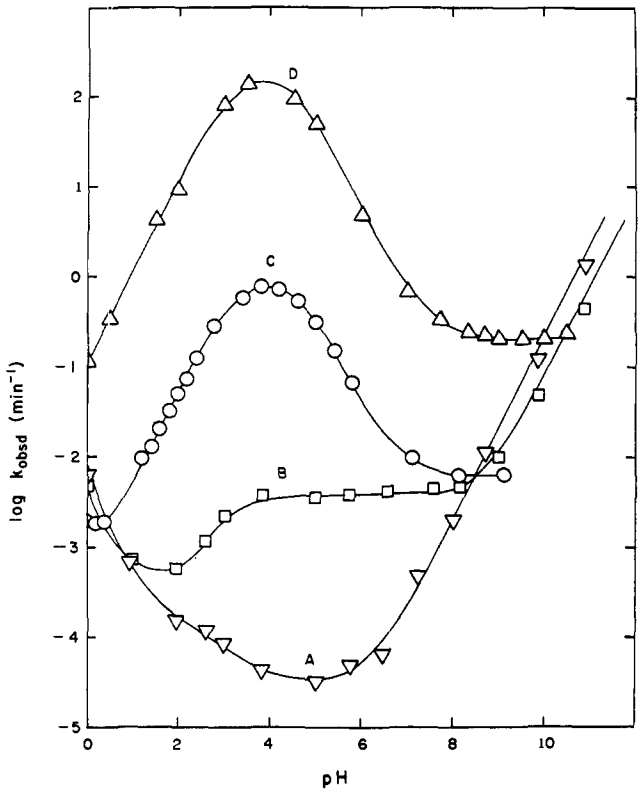


Figure 1. pH–log k_{obsd} profiles for the hydrolysis of esters **5** (A), **6** (B), **7** (C), and **8** (D).

measurements—after every reaction. Determinations of rate constants for reactions whose half-lives were less than 5 sec (ester **8**) were carried out on a stopped-flow spectrometer. For these experiments, a solution of 0.005 *M* borate, pH 9, μ = 1.0 (KCl), was equilibrated separately at 32°, while the buffer solution (at a pH which gave the desired pH on mixing) was equilibrated in the spectrometer at 30°. To initiate the reaction, the borate solution was placed in the storage syringe of the spectrometer, 1 drop of stock solution of ester was added, and the rate constant was measured. The rapid hydrolysis of the ester at all pH's made this the only practicable method.

The hydrolysis of **10** required a different technique. The above-mentioned pH–stat apparatus was used to maintain constant pH (60°). Reaction was initiated by dissolving the ester in sufficient acetonitrile to give a final concentration of 1.5% acetonitrile and injecting the solution with a syringe. Appearance of free acid was followed by withdrawing 1-ml aliquots from the pH–stat cell with a syringe and mixing with 4 ml of a 20% solution of ferric chloride in 0.3 *N* HCl (0.6 *N* HCl at the most alkaline pH's) equilibrated at 30°. The absorbance of this solution was then measured (against a blank of the ferric chloride solution) at 540 nm exactly 2 min after the mixing. Job plots for the ester and the free acid prepared in the same manner were found to be linear, so that the observed absorbance could be plotted directly against time and the rate constant calculated.

All rates were followed for at least four half-lives and the values of the pseudo-first-order rate constants (k_{obsd}) were calculated by least-squares analysis of plots of ln $(OD_\infty - OD_0)/(OD_\infty - OD_t)$ *vs.* *t* for the stopped-flow measurements, or by the method of Guggenheim.[28] Experimental K_a values for the bell-shaped profiles were calculated by the method of Alberty and Massey.[29] All actual computations were carried out on an Olivetti-Underwood Programma 101 employing least-squares programs written in this laboratory.

Deuterium Solvent Isotope Effects. Deuterium solvent isotope effects were determined for **7** at 30° in 99.8% deuterium oxide (Stohler Isotope Chemicals), using acetate and formate buffers to maintain pH. The pD values were taken as the pH meter readings plus the proper correction at 30°.[30]

pK_a Determinations. Spectrophotometric titration of the resorcylates indicated that in each case, removal of the first proton was associated with one set of isosbestics, and removal of the second proton with a different set of isosbestics. Thus, in each case, pK_{a_1} could be determined *via* spectrophotometric titration at an isosbestic wavelength associated with pK_{a_2}, and *vice versa*. The wavelengths used were: **10**, pK_{a_1} at 315 nm, pK_{a_2} at 243 nm; **12** pK_{a_1} at 281 nm, pK_{a_2} at 265 nm; **13**, pK_{a_1} at 290 nm, pK_{a_2} at 245 nm.

The phenyl salicylates were titrated spectrophotometrically in the normal manner. The wavelengths used were: **14**, 230 nm; **15**, 330 nm; **16**, 345 nm; and **17**, 335 nm. All titrations were performed at the same temperature, ionic strength, and concentration of ester as the rate determinations.

Results

At constant pH, and in the presence of a great excess of buffer over ester, all spectrophotometrically determined rate constants (k_{obsd}) were found to be pseudo first order. Extrapolation of plots of k_{obsd} *vs.* buffer concentration to zero buffer provides as intercepts the values of the pseudo-first-order rate constants for the nonbuffer-catalyzed reactions. With the exception of Tris buffers, there was only a small buffer effect. For the stopped-flow buffer dilutions, an average value for each dilution was obtained, since the slopes of the dilutions were small, and there was a larger amount of scatter. For pH values below 2, above 11.5, or when the Cary 15 pH–stat cell apparatus was used, no external buffer was necessary.

Quinolyl Esters. In Figure 1 is plotted log k_{obsd} *vs.* the constant pH at which the rate constants were determined for the quinolyl esters **5, 6, 7,** and **8.** In Figure 2 is plotted log k_{obsd} *vs.* pH (pD) for esters **7** and **9** in water and ester **7** in deuterium oxide. The plots for **5** and **6** are from a previous work[10] at 55°, and have been extrapolated to 30° by determining k_{obsd} at 30° for several pH's. The points of Figures 1 and 2 are experimental and the lines are theoretical; the lines for **5** and **6** are derived from eq 1 and those for **7** (in H_2O and D_2O), **8**, and **9** from eq 2. K_{a_1} and K_{a_2}

$$k_{obsd} = \left[\frac{1}{K_{a_1} + a_H}\right][(k_{OH}[OH^-] + k_1 + k_H a_H)K_{a_1} + k_H' a_H^2] \quad (1)$$

$$k_{obsd} = \frac{k_H' a_H^2}{K_{a_1} + a_H} + \frac{(k_1 a_H + k_2 K_{a_2} + k_{OH}'[OH^-]K_{a_2})K_{a_1}}{K_{a_1}(K_{a_2} + a_H) + a_H^2} \quad (2)$$

are the first and (when applicable) second dissociation constants for the ester, a_H is the activity of the hydrogen ion as measured at the glass electrode, k_H' represents acid-catalyzed hydrolysis of the nondissociated ester, k_H, k_1, and k_{OH} represent, respectively, the acid, spontaneous (water-catalyzed), and hydroxide-catalyzed hydrolysis of the mono-ionized ester, and k_2 and k_{OH}' represent the spontaneous and hydroxide catalyzed hydrolysis of the di-ionized ester. Not all constants were obtained for all esters. The values of the various rate and equilibrium constants are given in Table I. Repetitive scan spectra of the 8-quinolyl esters show sharp isosbestic points at 233, 267, and 307 nm, and those of the 6-quinolyl esters at 235, 260, and 313 nm, indicating

(28) E. A. Guggenheim, *Phil. Mag.*, 2, 538 (1926).
(29) R. A. Alberty and V. Massey, *Biochim. Biophys. Acta*, **13**, 347 (1954).
(30) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

Table I. Hydrolytic Rate Constants for Quinolyl Esters

Ester	5[a]	6[a]	7	7[b]	8	9
$k_{OH}(30°)$, M^{-1} min^{-1}	304	90.2				
$k_{OH}'(30°)$, M^{-1} min^{-1}						373
$k_1(55°)$, min^{-1}	0.00022	0.0262				
$k_1(30°)$, min^{-1}			1.16	1.11	223	0.320
$k_2(30°)$, min^{-1}			0.0058		0.201	0.0126
$k_H(55°)$, M^{-1} min^{-1}	0.83	2.36				
$k_H'(55°)$, M^{-1} min^{-1}	0.04	0.028				
$k_H'(30°)$, M^{-1} min^{-1}			0.00145			0.00265
$pK_{a_1}(30°)$[c]	4.44[d]	3.64[d]	3.32	3.75	3.24	4.16
$pK_{a_2}(30°)$[c]			4.57	5.05	4.43	4.54

[a] Reference 10. [b] In deuterium oxide. [c] Kinetically determined. [d] Determined by spectrophotometric titration.

that absorbing intermediates do not accumulate in the course of the hydrolytic reactions.

Although the spectrophotometrically determined rates were rigorously first order, those determined titrimetrically indicated the presence of a slowly hydrolyzable intermediate. The identity of this intermediate is easily established in the case of **8**, at pH 4,

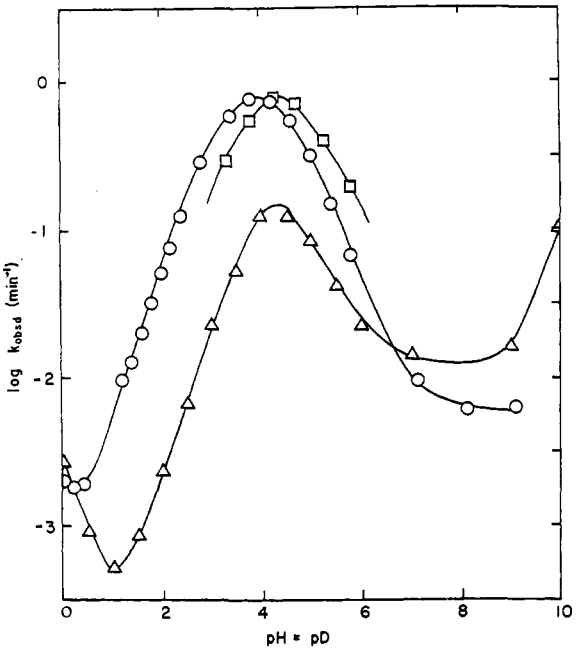


Figure 2. pH (pD)-log k_{obsd} profiles for the hydrolysis of esters **7** (○) and **9** (△) in water and **7** (□) in deuterium oxide.

since the spectrometrically observable reaction is over in seconds. A second, titrimetric rate constant is then obtained; as discussed in the Experimental Section, this rate constant is, within experimental error, identical with that obtained for the hydrolysis of succinic anhydride under the same conditions. Since succinic acid does not form the anhydride under these conditions,[31] any mechanism written for the hydrolysis of the esters must include the intermediacy of succinic anhydride (and, therefore, presumably glutaric anhydride).

Carboxyphenyl Succinates. In Figure 3 is plotted k_{obsd} *vs.* the constant pH at which the hydrolytic rate constants were determined for succinate esters **1** and **11**. The data for **1** are taken from ref 5, while the points

(31) T. C. Bruice and U. K. Pandit, *J. Amer. Chem. Soc.*, **82**, 5858 (1960).

Table II. Hydrolytic Rate Constants for Carboxyphenyl Succinates[a]

Ester	1[b]	11
pK_{a_1}[c]	3.62	3.6
pK_{a_2}[c]	4.5	4.2
k_1, min^{-1}	5.95	1.8
k_2, min^{-1}	0.0043	1.12

[a] T = 30°, μ = 1.0 (KCl). [b] Data derived from ref 5. [c] Kinetically determined.

for **11** are from this study; the lines for both are theoretical, being derived from eq 3. The constants in

$$k_{obsd} = \frac{K_{a_1}(k_1 a_H + k_2 K_{a_2})}{K_{a_1}(K_{a_2} + a_H) + a_H^2} \quad (3)$$

this equation are as previously defined. The values of the various rate and equilibrium constants are given in Table II. Both K_{a_1} and K_{a_2} are required to fit

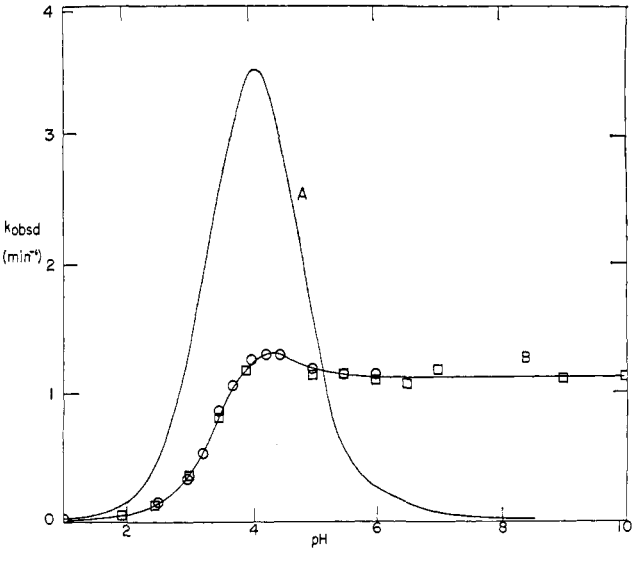


Figure 3. pH-k_{obsd} profiles for the hydrolysis of esters **1** (A) and **11** (B). The different symbols for **11** indicate rates run with esters of different purities.

the data to a theoretical curve, even if one ignores the small "hump" in the pH-k_{obsd} profile.

Salicylate Esters. The methyl esters **3, 4,** and **10** were hydrolyzed at 60° in water containing 1.5% acetonitrile. In Figure 4 is plotted log k_{obsd} *vs.* the constant pH at which the rate constants were determined. The data for **3** and **4** are taken from ref 7; the points for **10**

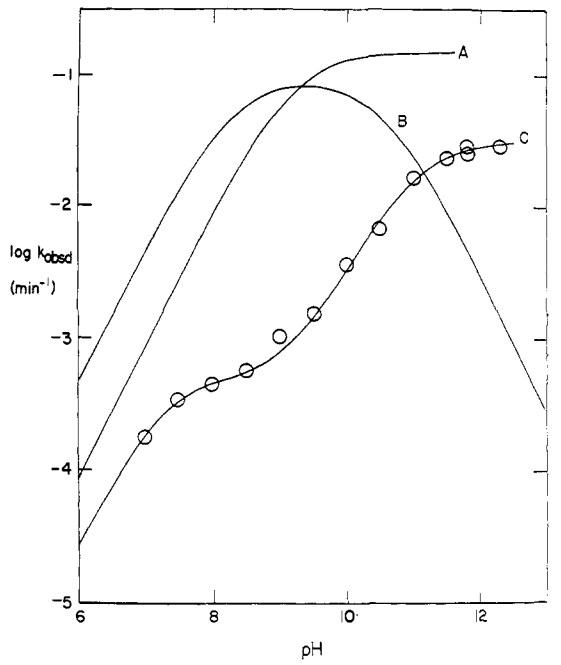


Figure 4. pH-log k_{obsd} profiles for the hydrolysis of esters **4** (A), **3** (B), and **10** (C).

are from this study. The lines of Figure 4 were generated from eq 4 for **4**, eq 5 for **3**, and eq 3 (k_{gb} = k_1, $k_{gb}' = k_2$) for **10**. The values of the various rate and equilibrium constants are given in Table III.

$$k_{obsd} = \frac{k_{gb}K_{a_1}}{K_{a_1} + a_H} \quad (4)$$

$$k_{obsd} = \frac{k_{gb}K_{a_1}a_H}{K_{a_1}(K_{a_2} + a_H) + a_H^2} \quad (5)$$

Table III. Hydrolytic Rate Constants for Methyl Resorcylates and Methyl Salicylate[a]

Ester	**4**[b]	**3**[b]	**10**
pK_{a_1}[c]	9.22	8.3	7.24
pK_{a_2}[c]		10.5	11.0
pK_{a_1}[d]			7.6
pK_{a_2}[d]			10.6
k_{gb}, min^{-1}	0.149	0.095	0.0005
k_{gb}', min^{-1}			0.0315
k_{ga}, M^{-1} min^{-1} [e]	894	4800	298
k_{ga}', M^{-1} min^{-1} [e]			3.3

[a] T = 60°, μ = 1.0 (KCl), 1.5% acetonitrile in water. [b] Data from ref 7. [c] Kinetically determined. [d] Determined by spectrophotometric titration. [e] See Discussion for explanation.

The phenyl esters **12–17** were hydrolyzed at 30°. In Figure 5 is plotted k_{obsd} *vs.* the constant pH at which the rate constants were determined for these esters. Complete profiles were obtained only for esters **12** and **17**. The points of Figure 5 are experimental and the lines are generated from eq 5 for **12**, eq 3 for **13**, and eq 6 for **14–17**. The values for the various rate and equilibrium constants are provided in Table IV.

$$k_{obsd} = \frac{K_{a_1}(k_{gb} + k_{OH}K_w/a_H)}{K_{a_1} + a_H} \quad (6)$$

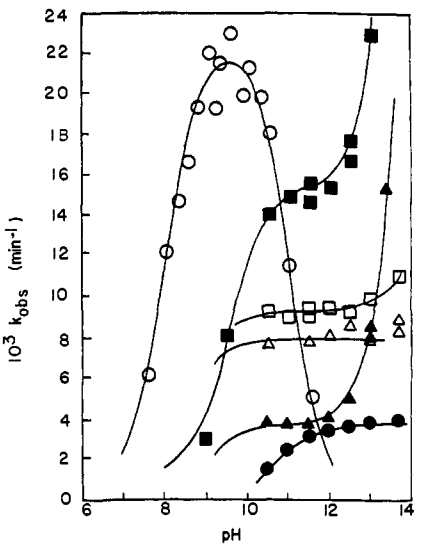
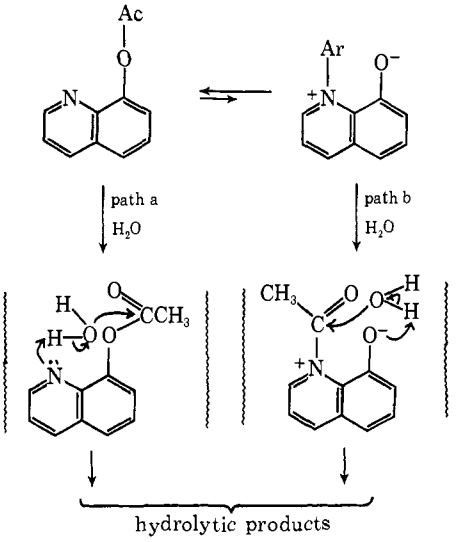


Figure 5. pH-k_{obsd} profiles for the hydrolysis of esters **12** (○), **13** (●), **14** (△), **15** (▲), **16** (□), and **17** (■).

Discussion

Quinolyl Esters. The mechanism of the pH-independent hydrolysis of **6** has been discussed extensively in ref 10. Briefly, the deuterium solvent isotope effect (k^{H_2O}/k^{D_2O} = 2.35), the entropy of activation ($T\Delta S^{\pm}$ = −8.7 kcal mol^{-1}), and the different mode of reaction with H_2O, primary and secondary amines compared to HO^-, and tertiary amines dictates an intramolecular general base catalyzed attack of H_2O. Two kinetically indistinguishable mechanisms were considered (Scheme I). The mechanism proceeding through path a was

Scheme I



favored over that through path b primarily on the basis that (a) any reasonable value for the pK_a of the quinolyl hydroxyl group would require an exceptionally facile intramolecular catalyzed hydrolysis by the oxyanion species at the low pH end of the plateau; and (b) in analogy with the general base catalysis mechanisms for the hydrolysis of substituted aspirins,[32,33] path a should

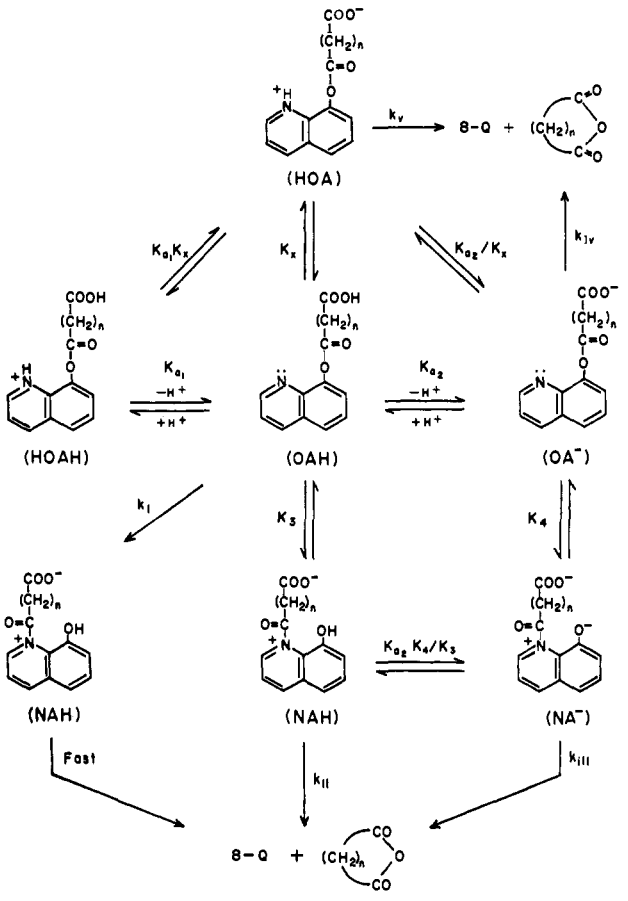
(32) A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, **89**, 4853 (1967).
(33) A. R. Fersht and A. J. Kirby, *ibid.*, **90**, 5818 (1968).

Table IV. Hydrolytic Rate Constants for Phenyl Salicylates[a]

Ester	12	13	14	15	16	17
pK_{a_1}[b]	7.95					
pK_{a_2}[b]	11.05					
pK_{a_1}[c]	8.08	7.55	8.46	9.1	8.63	9.44
pK_{a_2}[c]	10.58	10.76				
k_{gb}, min^{-1}	0.023		0.0080	0.0038	0.00935	0.0153
k_{gb}', min^{-1}		0.00372				
k_{ga}, M^{-1} min^{-1} [d]	17,700		1890	206	1490	37.8
k_{ga}', M^{-1} min^{-1} [d]		4.4				
k_{OH}, M^{-1} min^{-1}				0.0323	0.0025	0.058

[a] $T = 30°$, $\mu = 1.0$ (KCl). [b] Kinetically determined. [c] Determined by spectrophotometric titration. [d] See Discussion for explanation.

Scheme II



be favored over path b (Scheme I) due to the magnitude of the ΔpK_a difference between the conjugate acids of the quinolyl nitrogen and the 8-hydroxyl groups. The favoring of path a over that of path b was based, therefore, to a considerable extent on an anticipated analogy between systems involving a neighboring nitrogen base and a neighboring oxygen base. The reasonableness of this assumption is of course open to some criticism, and the choice between paths a and b (Scheme I) must be considered tentative, particularly in light of the fact that the types of differential experiments amenable to the acyl salicylate studies (^{18}O exchange and methanolysis) are not applicable to **4**.

The hydrolysis of **8** has been shown to yield, as the immediate products of hydrolysis, both 8-hydroxyquinoline and succinic anhydride (see Experimental Section). In the case of esters **7** and **9**, the intermediacy of the anhydride was not definitely established because of the similar magnitudes of the rate constants for ester disappearance and anhydride hydrolysis. In the light of the titrimetric results with **8**, however, it is reasonable to assume that the three esters hydrolyze by similar mechanisms, and that cyclic anhydrides are formed on hydrolysis of the ester. To obtain anhydride intermediates, it is necessary that the terminal carboxylates of **7**, **8**, and **9** participate as anionic nucleophiles in an intramolecular displacement reaction. The soundness of this mechanism is demonstrated by a considerable literature dealing with intramolecular nucleophilic displacement of substituted phenols from dicarboxylic acid monophenyl esters by the carboxyl anion.[34-38]

In Scheme II there are presented all reasonable reaction pathways that could yield anhydride on the hydrolysis of esters **7** and **8**. Paths iv and v are appropriate for the hydrolysis of ester **9** also. The relationships of the observed first-order rate constants to the hydrogen ion concentration for each pathway are given in eq 7-11.

$$k_{obsd_i} = \frac{k_i K_{a_1} a_H}{K_{a_1}(K_{a_2} + a_H) + a_H^2} \quad (7)$$

$$k_{obsd_{ii}} = \frac{k_{ii} k_{a_1} K_3 a_H}{K_{a_1}[K_{a_2}(K_4 + 1) + (K_3 + 1)a_H] + a_H^2} \quad (8)$$

$$k_{obsd_{iii}} = \frac{k_{iii} K_{a_1} K_4 K_{a_2}}{K_{a_1}[K_{a_2}(K_4 + 1) + (K_3 + 1)a_H] + a_H^2} \quad (9)$$

$$k_{obsd_{iv}} = \frac{k_{iv} K_{a_1} K_{a_2}}{K_{a_1}(K_{a_2} + a_H) + a_H^2} \quad (10)$$

$$k_{obsd_v} = \frac{k_v K_{a_1} K_x a_H}{K_{a_1}[K_{a_2} + (K_x + 1)a_H] + a_H^2} \quad (11)$$

Inspection of these equations shows that eq 7, 8, and 11 have the same mathematical form as the k_1 term (describing a bell-shaped profile) of eq 2; eq 9 and 10 have the same form as the k_2 term (describing a plateau region) of eq 2. The paths are thus kinetically equivalent to the appropriate terms of the experimentally derived rate law.

In the simplest case, the hydrolysis of ester **9** produces a profile which has a bell-shaped curve centered around pH 4 and a pH-independent region at alkaline pH's (Figure 1). Steric considerations prevent direct participation by the quinoline nitrogen as either a general acid or a general base. This profile is described by eq 10 and 11 for $k_{obsd_{iv}}$ and k_{obsd_v}. The unique shape of the profile, then, results simply from acid-base equi-

(34) E. Gaetjens and H. Morawetz, *J. Amer. Chem. Soc.*, **82**, 5328 (1960).
(35) T. C. Bruice and U. K. Pandit, *ibid.*, **82**, 5858 (1960).
(36) T. C. Bruice and W. C. Bradbury, *ibid.*, **87**, 4581, 4846 (1965).
(37) J. W. Thanassi and T. C. Bruice, *ibid.*, **88**, 747 (1966).
(38) T. C. Bruice and W. C. Bradbury, *ibid.*, **90**, 3808 (1968).

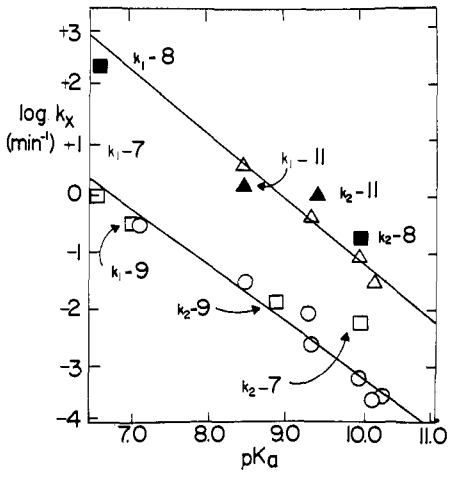


Figure 6. Plot of the log of the rate constants for intramolecular carboxylate catalyzed hydrolysis of meta- and para-substituted phenyl succinates (△) and glutarates (○), *vs.* the pK_a of the conjugate acid of the leaving phenolate groups. Calculated values for quinolyl glutarates (□) and succinates (■), and for *p*-carboxyphenyl succinate (▲) are also included.

libria and the inductive effect of protonation of the nitrogen. The profile for this ester may thus be interpreted in the following manner: the pH independent region at alkaline pH is due simply to nucleophilic attack by the carboxyl anion to form anhydride, the leaving group being the nonnitrogen-protonated quinoline (path iv). As the solution becomes acid, the nitrogen protonates, forming a better leaving group and providing the ascending limb of the bell (path v). And finally, as the solution becomes still more acid, the carboxyl protonates, reducing the amount of active nucleophile and producing the descending limb of the bell. This general hydrolytic behavior will be referred to as *intermolecular nucleophilic catalysis–electronic inhibition* (INCEI). The general characteristics of pH–k_{obsd} profiles associated with this phenomenon are as noted in this paragraph, and are found also for *intramolecular general catalysis–electronic inhibition* (IGCEI).

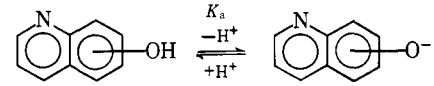
Ester **7** was examined in both water and deuterium oxide. No kinetic deuterium solvent isotope effect was found: k_1^H/k_1^D was 1.05, and the ratios $K_{a_1}^H/K_{a_1}^D$ and $K_{a_2}^H/K_{a_2}^D$ (where superscripts H and D refer to dissociation constants in H_2O and D_2O, respectively) were both found to fit on a Rule–LaMer plot[39] for oxygen acids. This finding makes unlikely any mechanism involving general catalysis in a rate-determining step: the remaining possibilities for the k_1 term then are path ii, which involves a preequilibrium O → N acyl shift, followed by rate-determining nucleophilic attack by the carboxylate, and path v. For the k_2 term, we must choose between path iii, which involves preequilibrium O → N acyl transfer, followed by rate-determining nucleophilic attack by the carboxyl anion, and path iv.

Ester **8** was not examined in deuterium oxide; it is, however, eminently reasonable that any conclusions drawn for **7** should be valid for **8** also.

A priori, because of the similarities of **7**, **8**, and **9**, one would expect their hydrolyses all to proceed by the same pathways, which must, therefore, be iv and v. This expectation is reinforced by the following evidence.

(39) C. K. Rule and V. K. LaMer, *J. Amer. Chem. Soc.*, 60, 1974 (1938).

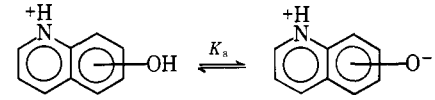
The hydrolysis of substituted phenyl glutarates and succinates proceeds through an anhydride intermediate resulting from intramolecular nucleophilic attack of carboxyl anion.[34-38] A plot of the rate constants[34] for intramolecular carboxyl attack in meta- and para-substituted phenyl succinates and glutarates *vs.* the pK_a of the phenolic leaving group[40] is provided in Figure 6. Inspection of Figure 6 reveals two straight lines, with slopes of −1.0 for the glutarate esters and −1.14 for the succinate esters. If we then plot log k_2 for esters **7**, **8**, and **9** *vs.* the pK_a of the "normal" hydroxyl group ionization (**19a**, pK_a = 9.88; **19b**, pK_a = 8.87),[41] the



19a, 8-OH
b, 6-OH

points fall very close to the appropriate lines. Thus, in all probability, the leaving group for the formation of cyclic anhydride is the phenolic oxygen (rather than the nitrogen), the quinolinols behave like phenols of similar pK_a, and path iv represents the mechanism for the pH independent hydrolysis of these esters.

The microscopic constants for hydroxyl ionization of the protonated quinolinols are also known (**20a**, pK_a = 6.6; **20b**, pK_a = 7.03);[41,42] if we then plot log k_1[43] for

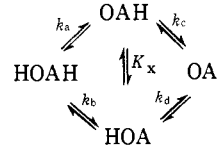


20a, 8-OH
b, 6-OH

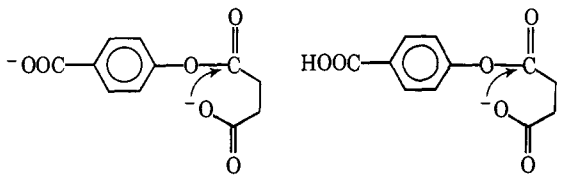
7, **8**, and **9** *vs.* these pK_a's, we see that these also fall nicely on the appropriate lines. The conclusion must be reached, therefore, that the pH–k_{obsd} profiles for the esters **7**, **8**, and **9** arise from the INCEI effect.

Carboxyphenyl Succinates. The interpretation of the pH–k_{obsd} profile for ester **11** (Figure 3) is straightforward. The pH independent rate (k_2) at alkaline pH occurs when the *p*-carboxyl group is ionized (**11a**); proceeding to a more acid pH, the "ascending limb"

(40) Phenol pK_a's from ref 30 and references cited therein.
(41) (a) S. F. Mason, *J. Chem. Soc.*, 674 (1958); (b) A. Albert and J. N. Phillips, *ibid.*, 1294 (1956).
(42) R. E. Ballard and J. W. Edwards, *ibid.*, 4868 (1964).
(43) The values of k_1 which are plotted are actually combinations of rate constants, i.e., $k_1 = k_V K_X$, so that actually we should be plotting k_V *vs.* pK_a. We must thus estimate the value of the prototropic equilibrium K_X. Consider the ionization scheme from Scheme II

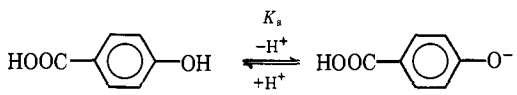


where the small k's represent microscopic ionization constants. K_{a_1} and K_{a_2} are the macroscopic ionization constants. We then have the relationships:[44] $K_{a_1}K_{a_2} = k_a k_c = k_b k_d$, $K_{a_1} = k_a + k_b$, $1/K_{a_2} = 1/k_c + 1/k_d$, and $K_X = k_b/k_a$. To find K_X, then, we must know k_a or k_b. Following well-established procedures,[44,45] we may assume that K_{a_1} for **6** is a good model for k_a for **7**, and that K_{a_1} for **5** is a good model for k_a for **9**. Using these values and solving, we find that K_X = 1.1 for **7** and 0.9 for **9**. Hence, on a log plot, no error is introduced by using k_1 rather than k_V.
(44) J. T. Edsall and J. T. Wyman, "Biophysical Chemistry," Vol. I, Academic Press, New York, N. Y., 1958.
(45) L. Ebert, *Z. Phys. Chem.*, **121**, 385 (1926).



11a 11b

of the bell (k_1) results from protonation of the *p*-carboxyl group, which increases the leaving tendency of the phenoxide (**11b**). The descending limb observed at the most acid pH's then results from protonation of the succinate carboxyl group, preventing nucleophilic attack. If we make the reasonable assumption[46] that the pK_a for the ionization represented by **21** is similar



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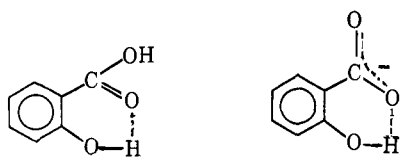
to that for *p*-carbomethoxyphenol (pK_a = 8.47[40]), we may plot (Figure 6) log k_1 and log k_2 *vs.* the pK_a of the leaving groups in **11b** and **11a**, respectively. These points are found to lie very close to the line for the substituted phenyl succinates: hence, the "hump" in the pH–rate profile not only is real, but also arises solely from the change in basicity of the phenoxide leaving group resulting from ionization of the *p*-carboxyl group. Inspection of structure **11** dictates that the two carboxyl groups could only participate *via* INCEI, as found.

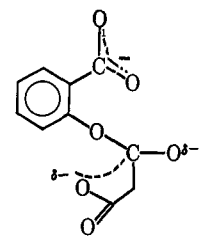
The situation is much less obvious in the case of ester **1**, since there are many complicating factors. In the first place, plots such as that of Figure 6 are not applicable, due to ortho-steric and intramolecular hydrogen bonding[47] effects. Consider the conjugate acids of the leaving groups associated with the k_1 (**22a**) and k_2 (**22b**) terms in the hydrolysis of **1**. Using *o*-



22a 22b

carbomethoxyphenol as a model for the hydroxyl ionization of **22a**, we obtain pK_a = 10.2;[45] the pK_a for the ionization of **22b**, however, is 13.1.[47] The high pK_a of **22b** is attributed to intramolecular hydrogen bonding.

The ratio of 10^3 obtained for the ionization constants of the conjugate acids of the leaving groups for the k_1 and k_2 terms is observed to be very similar to the ratio of the rate constants for intramolecular carboxylate attack on the esters containing these leaving groups. k_1/k_2 = 1380 for ester **1**. This is, however, probably just a fortuitous agreement since there is no possibility of intramolecular hydrogen bonding in the transition state (**1c**) associated with k_2 or in the leaving phenoxide. There will certainly be a difference in the basicity of the leaving phenoxide group in the reaction paths asso-



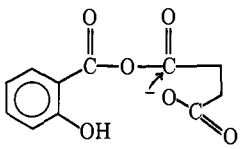
1c

ciated with k_1 and k_2, but the magnitude of this difference should be close to that observed for the similar ionization states of **11**.

A perhaps more enlightening approach is to compare the k_1 term for **1** with the rate constant for hydrolysis of *o*-carbomethoxyphenyl succinate (**23**).[49] The ratio of k_1 for **1** to k_1 for **23** is found to be 8.8, rather than the 66 quoted in the text of ref 5. This small difference in rates could easily result from the differing steric requirements of the carboxyl and carbomethoxy groups and from the small difference in the pK_a's of the leaving groups. Hence, the proton of the carboxyl need not be catalytic at all.

We must then explain the 1000-fold difference in the k_1 and k_2 terms for ester **1**. If the undissociated carboxyl group is not acting as a catalyst, then the ratio of k_1 to k_2 may be best ascribed to a depression in rate brought about by ionization of the *o*-carboxyl group. As stated above, the inductive change in the pK_a of the leaving group due to electronic effects associated with the ionization of the carboxyl group should be comparable to that noted with **11**; this should result in at least a tenfold decrease in the rate. Moreover, the presence of the *o*-carboxyl anion should have a very large electrostatic effect: its presence should tend both to destabilize formation of the transition state (**1c**) and the incipient hydroxyl anion. This kind of destabilization by adjacent charged moieties has previously been shown to occur,[50] and should easily account for a 10- to 100-fold decrease in the rate. These effects, then, are probably sufficient to explain the observed differences in the rates for intramolecular carboxylate attack on the neutral and ionized esters. In any event, we must conclude from comparison of k_1 for **1** and **23** that there is no significant general acid catalysis occurring in this reaction, and that the bell-shaped profile for **1** results from a combination of intramolecular nucleophilic catalysis and electrostatic and electronic inhibition (*i.e.*, INCEI).

The possibility remains, of course, that the hydrolysis of **1** proceeds *via* series nucleophilic catalysis (**1a**) in a manner similar to that observed for **2**. The reactive intermediate would then be **1d**. The basicity of the



1d

(46) See, for example, D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 23, 420 (1958).

(47) G. E. Dunn and F.-L Kung, *Can. J. Chem.*, 44, 1261 (1966), and references therein.

(48) A. Agren, *Acta Chem. Scand.*, 9, 49 (1955).

(49) The data for ester **1** listed in Table II were obtained by enlarging the figure shown in ref 5 and, using the pK_a's given in the text, fitting the curve to eq 3. The pH–log k_{obsd} profile for **23** is described by eq 4, and the value of the rate constant for its hydrolysis may be obtained either in the same manner from the figure of ref 5 or from the data of ref 34.

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

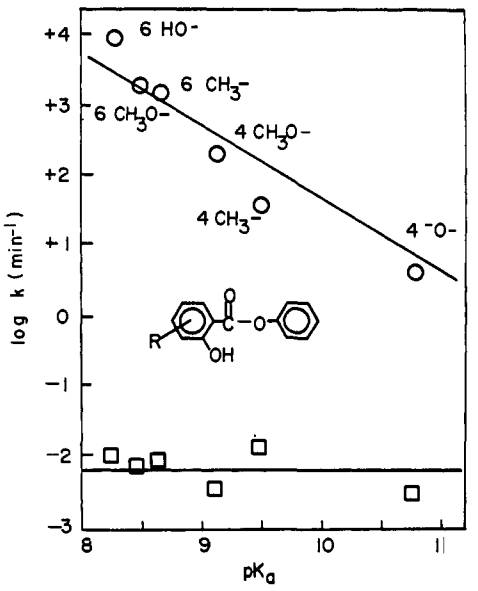


Figure 7. Brønsted plot of log k_i (○) or log k_1 (□) *vs.* the pK_a of the 2-hydroxyl group for phenyl salicylates.

leaving group for this species (p$K_a \cong 3$) is sufficient, however, to explain the high reactivity of ester **1** as compared to the acetate, so the *o*-hydroxyl would appear to have no function in this mechanism either.

Salicylate Esters. The *o*-hydroxyl group has previously been shown to participate in the hydrolysis of various salicylate esters and amides;[7,51-53] in all cases, the pH–log k_{obsd} profile obtained was similar to that shown for **4** in Figure 4. The profile is generally interpreted as indicating the participation of the hydroxyl group either as a general base catalyzing the attack of water (**4a**) or as a general acid catalyzing the attack of hydroxide (**4b**). The magnitudes of the observed rate constants for hydrolysis of the salicylates in this study compared to other mono- and di-ortho-substituted benzoate esters[8,9] indicate that in all cases at least one *o*-hydroxyl group must actively participate in the hydrolysis reaction.

Phenyl γ-resorcylate (**12**) was found to exhibit the same type of bell-shaped pH–log k_{obsd} profile as that previously observed for the methyl ester **3**. For convenience then, a more complete study of the resorcylate system was made with the hydrolytically more labile phenyl esters **12–17** (Figure 5), whose hydrolyses may be conveniently followed spectrophotometrically. A complete profile was obtained only for the hydrolytically most susceptible ester **17**. For compounds **14–16**, which by all logic should have the same type profile, only the kinetically important plateau rates (from which k_1 or k_i may be calculated) were obtained. Similarly, for ester **13**, which should have the same profile as **10**, only the upper plateau region for hydrolysis with the *o*-hydroxyl ionized was examined.

Two kinetically indistinguishable mechanisms may be written for esters **14–17** (and for **13** in the pH range 10–14); they are the general base catalyzed attack of water [k_{gb}(**4a**)] and the general acid catalyzed attack of hydroxide [k_{ga}(**4b**)], and are described by eq 4 and 12,

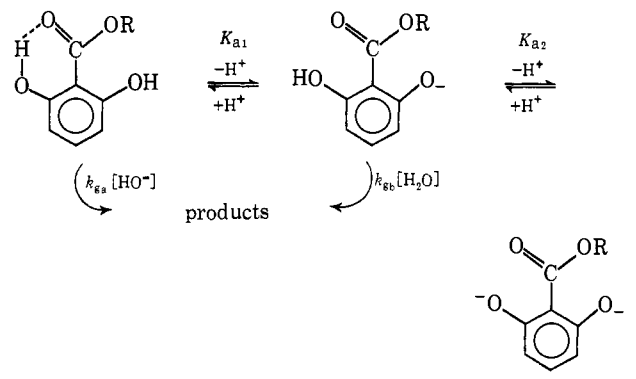
$$k_{obsd} = \frac{k_{gb}K_w}{K_{a1} + a_H} \quad (12)$$

respectively. The value of k_{gb} is obtained directly from the experimental plots, while k_{ga} is calculated from the relationship $k_{ga}K_w = k_{gb}K_{a1}$.

The most striking feature of Figure 5 or Table IV is the similarity of the observed plateau or of the calculated first-order rate constants (k_{ga}) for intramolecular general base catalyzed hydrolysis of the various phenyl 4- and 6-substituted salicylates: the largest and the smallest rate constants vary only by a factor of 6. The immediate conclusion is that there is no special increase or decrease of reactivity in the intramolecular general base catalyzed attack of water associated with 6-substitution of salicylate ester anions (although substituents larger than methoxyl were not examined). However, a pronounced steric decrease in the rate of uncatalyzed attack of hydroxide upon ionized salicylate esters accompanies 6-substitution (6-OCH_3, 6-CH_3). This effect is not seen with substituents in the 4 position (except for 4-O^-). For the 4-O^- and 6-O^- esters, it would appear that the two oxyanions deactivate the carbonyl electronically to the extent that it is inert to unassisted attack of hydroxide.

The hydrolysis of ester **12** produces a simple bell-shaped pH–k_{obsd} profile; the two kinetically equivalent mechanisms, corresponding to **3a** and **3b**, are illustrated in Scheme III. The observed rate constants are related

Scheme III



to the hydrogen ion concentration for the k_{gb} term by eq 5 and for the k_{ga} term by eq 13.

$$k_{obsd} = \frac{k_{ga}K_w a_H}{K_{a1}(K_{a2} + a_H) + a_H^2} \quad (13)$$

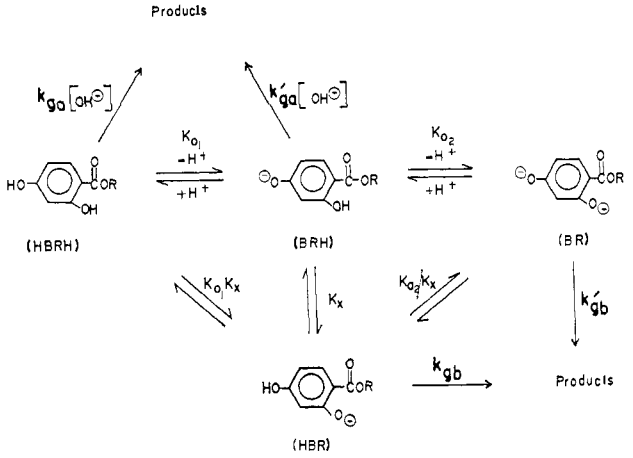
In Figure 7 are plotted the values of log k_{gb} and log k_{ga} for esters **12–17** *vs.* the pK_a for ionization of the 2-hydroxyl. The values of k_{gb}, k_{ga}, and K_{a1} for **12** have each been divided by two to correct for the fact that there are two *o*-hydroxyl groups which may participate.[54] Considering first the k_{gb} points for a general base mechanism we find that all the points lie very close to a line with slope $\beta = 0$. The k_{ga} points for a general acid mechanism are seen to lie very close to a line with slope $\alpha = -1$. In the transition state for either mechanism, then, the proton is almost completely transferred and the observed first-order rate constant is consequently insensitive to changes in the basicity of the intramolecular catalyzing acid or base. The most im-

(51) M. L. Bender, F. J. Kezdy, and B. Zerner, *J. Amer. Chem. Soc.*, **85**, 3017 (1963).
(52) T. C. Bruice and D. W. Tanner, *J. Org. Chem.*, **30**, 1668 (1965).
(53) B. Capon and B. C. Ghosh, *J. Chem. Soc. B*, 472 (1966).
(54) R. P. Bell, "The Proton in Chemistry," Methuen and Co., London, 1959, p 158.

portant feature of Figure 7 is that the points representing the hydrolysis of **12** fall on the same line as those for other 4- and 6-substituted salicylates: hence, the participation of only one hydroxyl group is sufficient to explain the observed maximum rate of hydrolysis. Again, then, we must explain the descending leg of the bell at alkaline pH's; the most obvious explanation is found in the IGCEI effect since the ortho oxyanion should strongly deactivate the ester carbonyl group to nucleophilic attack *via* inductive, resonance, and electrostatic interaction.

The IGCEI effect also serves to explain the pH dependence of the pseudo-first-order rate constants for hydrolysis of the methyl esters **3** and **10**. The pH–log k_{obsd} profile for the hydrolysis of **10** (Figure 4) is observed to have two pH-independent plateaus and two regions of slope +1. In Scheme IV are presented all

Scheme IV



reasonable pathways which might produce this type of profile. In this scheme, the observed rate constants will result from a combination of either paths k_{ga} and k_{ga}' (general acid, 1) or paths k_{gb} and k_{gb}' (general base, 2). The relationships of the observed rate constants to the hydrogen ion concentration for these pathways are given by eq 14 and 15, respectively. Inspection reveals

$$k_{obsd} = \frac{k_{ga}K_w a_H + k_{ga}'K_w K_{a_1}}{K_{a_1}(K_{a_2} + a_H) + a_H{}^2} \quad (14)$$

$$k_{obsd_b} = \frac{k_{gb}K_x K_{a_1} a_H + k_{gb}'K_{a_1}K_{a_2}}{K_{a_1}(K_{a_2} + a_H) + a_H{}^2} \quad (15)$$

that both equations are identical in form with the empirical equation (3). Pathways k_{ga} and k_{ga}' are analogous to the mechanism of **3b**, while k_{gb} and k_{gb}' are analogous to that of **3a**.

There is little doubt that the first observed ionization constant for **10** is associated with the 4-hydroxyl group, because of both the shape of the curve and the fact that hydrogen-bonded hydroxyls invariably have a higher pK_a than nonhydrogen-bonded.[47] Considering either possible mechanism then, the initial line of slope +1 corresponds to intramolecular general base catalyzed hydrolysis with the nonparticipating (4-) hydroxyl group protonated. Ionization of this group creates a strong electron source which donates electrons to the ester carbonyl thereby deactivating it to nucleophilic attack. This inhibition is manifested in the first plateau area. The second line of slope +1 then represents catalyzed hydrolysis with the 4-hydroxyl group

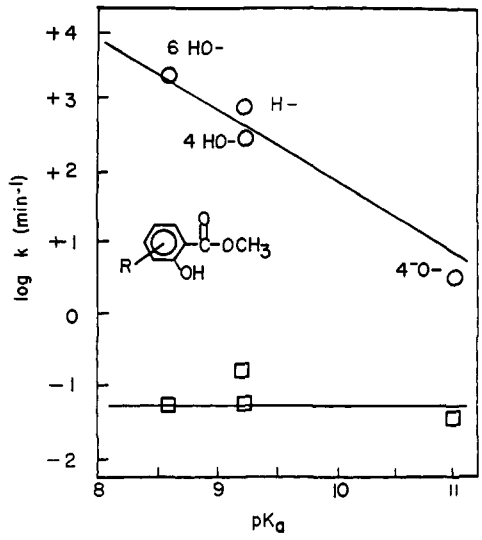
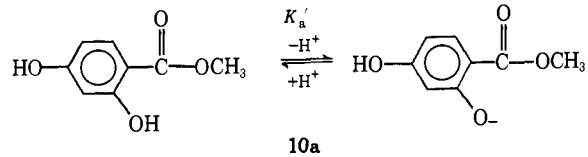


Figure 8. Brønsted plot of log k_1 (○) or log k_1 (□) *vs.* the pK_a of the 2-hydroxyl group for methyl salicylates.

ionized; the perpendicular distance between the two lines of slope +1 indicates the amount of inhibition resulting from ionization of the nonparticipating hydroxyl group. The final plateau is associated with ionization of the 2-hydroxyl group in the "normal" manner. The unique shape of the profile for **10**, then, as compared to that for **3**, results from the fact that the nonparticipating (inhibiting) hydroxyl group has a lower pK_a than does the participating hydroxyl group.

The hydrolysis of ester **3** produces a simple bell-shaped pH–log k_{obsd} profile; the two kinetically equivalent mechanisms are those of **3a** and **3b**, as in Scheme III. In Figure 8 are plotted the values of log k_{gb} and log k_{ga} for esters **3**, **4**, and **10** *vs.* the pK_a for ionization of the 2-hydroxyl group. Again, the values of k_{gb}, k_{ga}, and K_{a_1} for **3** have been divided by two[52] as a statistical correction. The value of K_a' for the ionization represented by **10a** was obtained from the relationship



10a

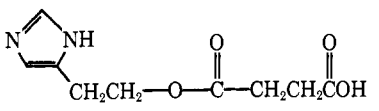
$K_a' = K_{a_1}K_x$ (Scheme IV). K_x was estimated in the same manner as before,[43] using pK_a = 9.80 (30°) for methyl 4-methoxysalicylate[55] as a model for pK_a, and pK_{a_1} = 7.8 at 30°.[56] The values thus obtained are $K_x = 10^{-2}$ and pK_a' = 9.24. The observed value of k_{gb} for **10** must also be divided by K_x for correct interpretation.

Inspection of Figure 8 shows it to be virtually identical with Figure 7, so that anything said about hydrolysis of the phenyl esters applies equally to the methyl esters. Again, the points for the 6-hydroxy compounds lie very close to the lines for the other compounds. There is thus absolutely no evidence for catalytic participation by the second hydroxyl group in either of the 2,6-dihydroxy esters.

We are thus forced to the conclusion that there are no evident examples in the literature for intramolecular

(55) J. Sunkel and H. Staude, *Ber. Bunsenges Phys. Chem.*, 72, 567 (1968).
(56) This work.

general acid, general base or nucleophilic, general acid catalysis of the hydrolysis of esters in water. (This statement applies to models employing two separate potential catalytic functional groups.) This result is in accord with previous searches for intramolecular bifunctional catalysis: thus, Koshland could find no evidence for concerted catalysis by imidazolyl and carboxyl groups in the hydrolysis of ester **24**,[57] and Coward and Bruice[58] could find no evidence for intramolecular concerted general acid, general base catalysis by



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tertiary amino groups in the enolization of ketones. Thus, the many postulated mechanisms for enzyme mediated reactions embodying a push–pull mechanism await experimental confirmation that such a mechanism is actually possible.

Acknowledgment. This work was supported by grants from the National Institutes of Health and the National Science Foundation.

(57) D. E. Koshland, Jr., *J. Cellular Comp. Physiol.*, **47** (1), 245 (1959); *J. Theoret. Biol.*, **2**, 75 (1962).
(58) J. K. Coward and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 5339 (1969).

α Effects. III. The Reaction of Malachite Green with Primary Amines, Methoxylamine, and Hydrazines

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Abstract: The rate and equilibrium constants associated with the addition of hydrazine, methylhydrazine, and methoxylamine (all possessing a pair of unshared α electrons) to malachite green are larger than are corresponding rate and equilibrium constants for primary amines of similar pK_a'. It may be concluded for this reaction that the α effect results in great part from a product of greater stability than predicted from the pK_a' for amines. For the "more stable product" to transmit its stability to the transition state (kinetic α effect) it is essential that a large amount of bond formation has occurred in the critical transition state. Therefore, reactions exhibiting large Brønsted β values exhibit the α effect, whereas those with small β values, where the transition state resembles reactants rather than products, generally do not. The Brønsted β values for the reaction of amines and hydrazines with malachite green are identical at 0.4. Plots of $\Delta F^{\pm}$ *vs.* ΔF^0 afford the linear free energy relationship, $\Delta\Delta F^{\pm}/\Delta\Delta F^0 = 1.0$. Thus all changes in ΔF^0 are reflected quantitatively in a concomitant change in $\Delta F^{\pm}$. However, since ΔF^0 values are close to zero and the Brønsted $\beta \approxeq 0.4$, so that the transition state must reside *ca.* midway between reactants and products, it would appear as though factors in addition to product stability account for a portion of the kinetic α effect. The possibility that solvent effects or intramolecular general base catalysis are the source of the α effect is ruled out by consideration of activation parameters. Polarizability seems to be of little or no importance in accounting for the hyperreactivity of hydrazines in nucleophilic substitution on dinitrohalobenzenes.

The term α effect[3] has been used to denote the high reactivity of nucleophiles possessing an unshared pair of electrons adjacent (α) to the nucleophilic atom. This phenomenon was probably first placed on a firm experimental footing by Epstein, Demek, and Rosenblatt in their investigations of nucleophilic attack upon phosphonates.[4] Nucleophiles exhibiting the α effect include hydrazines, hydroxylamine, hydroperoxide anions, oxime anions, hypochloride ion, etc. The mechanism by which the α electrons can influence the rate of reaction has been discussed, but it cannot be said that it is understood.[3] Substrates which are susceptible to the α effect include activated esters,[5] tetrahedral phosphorus,[6] etc.[7]

The majority of previous investigations deals solely with the determination of rate constants. In the present study we sought a system that did not involve metastable intermediates and would provide: (a) rate constants, (b) equilibrium constants, and (c) Brønsted β constants. Our objective has been to determine the relationship of the decreased $\Delta F^{\pm}$ associated with the α effect to ground state free energies and to the position of the transition state along the reaction coordinate. Such a system has been found in the reaction of malachite green (A) with a number of amines and hydrazines (*i.e.*, eq 1). The choice of amine addition to

(1) A portion of the material to be submitted by J. E. D. in fulfillment of the requirement for the Ph.D. in Chemistry, University of California at Santa Barbara.
(2) To whom inquiries should be addressed.
(3) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).
(4) J. Epstein, M. M. Demek, and D. H. Rosenblatt, *J. Org. Chem.*, **21**, 796 (1956).
(5) (a) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, **89**, 2106 (1967); (b) W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 1778 (1960).
(6) A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1583 (1958).
(7) D. L. Ball and J. O. Edwards, *J. Amer. Chem. Soc.*, **78**, 1125 (1956); K. B. Wiberg, *ibid.*, 77, 2519 (1955); C. A. Bunton and C. J. Minkoff, *J. Chem. Soc.*, 665 (1949); H. O. House and R. S. Ro, *J. Amer. Chem. Soc.*, **80**, 2428 (1958); R. P. Bell, *J. Phys. Chem.*, **55**, 885 (1951).