Control of Modes of Intramolecular Imidazole Catalysis of Ester Hydrolysis by Steric and Electronic Effects

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Abstract: The various mechanisms by which a neighboring imidazolyl nitrogen base (both neutral and anionic) or the conjugate acid imidazolium cation may participate in the hydrolysis of an acetyl ester of a weakly basic or strongly basic phenol have been evaluated (pH 0–13). For this purpose *O*-acetyl esters of 2-(2′- and 4′-hydroxyphenyl)imidazoles were prepared (Ia, b, II, IIIa, b, and IV). Lyate species access to the ester carbonyl carbon is quite similar for Ia, b, II, and IV as shown by their nearly identical specific acid rate constants (k_1, Table III). For II the imidazole is para to the ester bond and therefore anchimeric assistance of hydrolysis is not possible. For esters IIIa and IIIb which possess bulky *tert*-butyl groups ortho to the ester bond, access by lyate species to the ester carbonyl group is greatly restricted as shown by the fact that the specific acid rate constant is $\sim 10^3$ less than that determined for the other esters. At low pH (2–4) intramolecular participation by the *o*-imidazole function of esters Ia and Ib is evidenced by a plateau in the pH–log k_{obsd} profiles. Arguments presented favor general acid assistance to H_2O attack by the neighboring imidazolium cation representing rate enhancements of 25- and 150-fold for esters Ia and Ib, respectively. At neutrality a second plateau is observed for esters Ia, b, IIIa, and IV and is attributed to general base catalyzed H_2O attack at the ester bond by neutral imidazole. The discussion correlates this mechanism with the like mechanism proposed elsewhere for the isomeric imidazolyl compound V and also for aspirin. Thus, a nearly 10^4-fold rate enhancement is seen over the uncatalyzed hydrolysis of Ia and similarly for Ib, IIIb, and IV. At alkaline pH (9–11) additional plateaus in the pH–log k_{obsd} profiles for esters Ib and IIIb are observed and present evidence for intramolecular acetyl group transfer to the imidazole anion with subsequent hydrolysis of the acetylimidazole intermediate. In the case of IIIb this intermediate is directly observable. Therefore the alkaline plateau regions and the ascending limbs of the pH–log k_{obsd} profiles in the most alkaline region represent rate-limiting specific base hydrolysis of acetylimidazole intermediates (AH and A, respectively of Scheme II) derived from Ib and IIIb. The only pathway operable in the hydrolysis of IIIa in the pH range studied (8–11.5) is *via* specific base attack on the corresponding acetylimidazole intermediate AH (Scheme II). For esters Ia, II, and IV (where IV cannot form an imidazole anion), specific base catalyzed hydrolysis of the ester bond is the preferred mechanism. Thus, depending upon the substituent groups on the phenyl acetate ring, three modes of intramolecular imidazole catalysis of ester hydrolysis can occur: (1) general acid assisted H_2O attack, (2) general base assisted H_2O attack, and (3) O→N acetyl transfer to imidazole anion with subsequent hydrolysis of the intermediate acetylimidazole. All three modes of catalysis attain in the single ester Ib. The electronic and steric factors which mediate these different modes are discussed in detail.

The implication of an imidazolyl group in the mechanism of catalysis by the serine esterases[2] has led to extensive investigations of imidazole catalysis of ester hydrolysis.[3] In intermolecular reactions involving phenyl acetates as substrates, bimolecular nucleophilic displacement of phenoxide (eq 1) is the exclusive pathway until the pK_a of the conjugate acid of the leaving group exceeds that of imidazolium ion by $(\Delta pK_a) \cong 3.0$. When $\Delta pK_a > 3$ (with phenyl esters) general base assistance of the attack of imidazole by imidazole (eq 2) becomes of importance. When $\Delta pK_a \gg 3$ (aliphatic esters), general base assistance of the attack of water by imidazole (eq 3) is the sole mechanism for catalysis of hydrolysis. In eq 1–3 the arrows are for bookkeeping purposes. The actual timing of proton transfer and covalent bond making and breaking processes is of much present concern.[4] The changes of mechanism from eq 1 to 2 to 3 on increase in ΔpK_a may be viewed as arising through the necessity of generating a nucleophilic species which is, in basicity, comparable to the leaving group.[5]

The dependence of mechanism upon ΔpK_a for intramolecular displacement reactions is amended by steric considerations. Thus, although acetate ion is incapable of displacing phenolate ion directly if $\Delta pK_a > 2.6$,[6] in intramolecular reactions the COO^- group may directly displace alkoxide ions ($\Delta pK_a \cong 10$) if a cyclic anhydride is formed and the alkoxide leaving group departs from the acyl product.[7,8] On the other hand, if the leaving group and COO^- moiety are part of a single molecule, as in acetyl salicylate, direct nucleophilic displacement gives way to COO^- general base catalyzed attack of H_2O when $\Delta pK_a > 0$.[9] Though intramolecular imidazole catalysis of ester hydrolysis[2] has received less attention than carboxylate intramolecular catalysis, the mechanistic requirements would seem to be similar. Thus, for phenyl esters of γ-(4-imidazolyl) butyrate, direct nucleophilic displacement is a very facile process yielding the bicyclic lactam intermediate.[10,11] For the acetyl ester,[12] and presumably sub-

(1) A portion of the material submitted by G. A. Rogers in partial fulfillment of the requirements for the Ph.D. in Chemistry, University of Califorina at Santa Barbara.

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

(3) (a) M. L. Bender and T. W. Turnquist, *J. Amer. Chem. Soc.*, **79**, 1956 (1957); (b) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957); (c) see Chapter 1 of ref 2 for a review.

(4) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).

(5) A tenet of the anthropomorphic rule: W. P. Jencks and J. E. Reimann, *J. Amer. Chem. Soc.*, 88, 3973 (1966).

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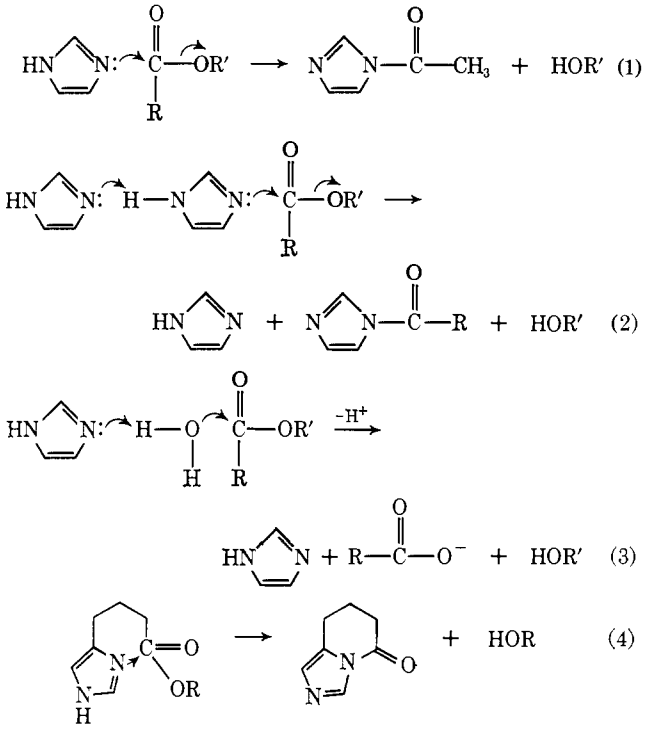
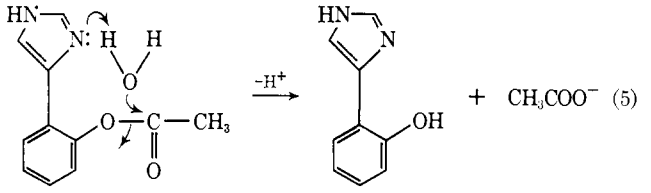
(8) If steric compression in the ground state is great, displacement may occur when $\Delta pK_a \cong 12$: A. J. Kirby, *J. Chem. Soc., Chem. Commun.*, 834 (1972).

(9) A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, **90**, 5818, 5826 (1968).



stituted benzoyl esters[13] of 4-(2′-hydroxyphenyl)imidazole (V), catalysis involves imidazolyl general base assisted water attack at the ester bond (eq 5).[14]



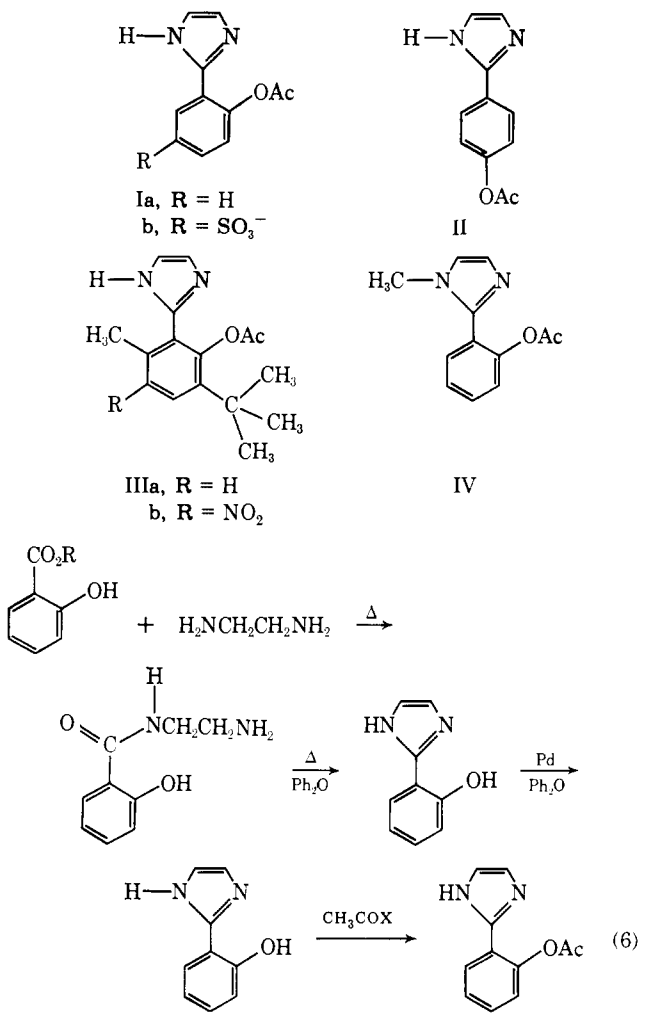
In order to better comprehend the influence of electronic and steric factors on the means of intramolecular imidazole catalysis, a detailed investigation of the hydrolysis of the acetyl esters I–IV has been carried out. (The phenols derived on hydrolysis will be referred to as PIa, PIb, PII, PIIIa, PIIIb, and PIV.) The results of this study are reported herein.

Experimental Section

Materials. Sodium formate, acetic acid, potassium phosphate (mono- and dibasic), potassium carbonate and bicarbonate, Tris, and potassium chloride were reagent grade and used without further purification. All water used in kinetic runs was deionized and double glass distilled.

All of the following phenyl esters were prepared by a similar synthetic procedure outlined for Ia below (eq 6).

2-(2′-Acetoxyphenyl)imidazole (Ia). Methyl salicylate (City Chemical Corp.) (distilled) (10 g, 66 mmol) was added to freshly distilled ethylenediamine (Mallinckrodt) (12 g, three times excess) in a round-bottomed flask and refluxed overnight. Excess ethylenediamine was removed by distillation. The resulting amide could then either be heated at atmospheric pressure to cyclize to the imidazoline (followed by crystallization from a large volume of $CHCl_3$), or directly sublimed under reduced pressure to the pure



imidazoline in 59% yield. Powder from the sublimation sublimes without melting at *ca.* 150°; nmr (D_2O) δ 3.82 (s, 4) and *ca.* 7 ppm (m, 4).

The imidazoline (1.8 g, 11 mmol) was dissolved in 12 ml of diphenyl ether to which was added *ca.* 150 mg of Pd/C (10%). The mixture was refluxed for 5 hr (progress monitored by tlc). The charcoal was removed by filtration while the solution was hot and the cooled filtrate was chromatographed on a silica gel column. 2-(2′-Hydroxyphenyl)imidazole was eluted from the column with benzene and crystallized from H_2O to yield 1.25 g (78%) of white compound: mp 133–134°; nmr (DMSO-d_6) δ 7.20 (s, 2), 7–8 (m, 4), and 12.86 ppm (broad s, 2); pK_a = 6.5 (ImH^+) and 9.25 (PhOH).

Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.58; H, 5.31; N, 17.29.

Acetylation of 2-(2′-hydroxyphenyl)imidazole to give Ia was carried out under Schotten–Baumann conditions. The crude product was dried under vacuum over P_2O_5 and crystallized from benzene to give white needles: mp 162–163°; ir (KBr) 1760 cm^{-1} (C=O); nmr ($CDCl_3$–DMSO-d_6) δ 2.30 (s, 3), 6.25 (broad peak, 1), 7.02 (s, 2), and 7–7.9 ppm (m, 4).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.46; H, 5.12; N, 13.48.

2-(4′-Acetoxyphenyl)imidazole (II). Methyl 4-hydroxybenzoate (City Chemical Corp.) (20 g) was added to freshly distilled ethylenediamine (24 g) and refluxed overnight. Excess ethylenediamine was removed under reduced pressure yielding a viscous oil which was brought to a boil for *ca.* 15 min. The structure of the resulting glass was verified as the imidazoline by nmr (H_2O–HCl) δ 3.93 (s, 4), 7.11 (AA′BB′ quartet, 4), and 9.05 ppm (s, 1.5).

Ca. 150 mg of Pd/C (10%) was added to the molten glass and the mixture was heated with a flame for 30 min while being evacuated at a water aspirator. After dehydrogenation the reaction mixture was dissolved in 1 *M* KOH, filtered, and cooled to 0° by addition of ice. Excess acetic anhydride was added followed by vigorous shaking. The voluminous precipitate was collected by filtration and dried under vacuum over P_2O_5. The dry solid was dissolved in a small amount of $CHCl_3$ and chromatographed on

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(11) T. C. Bruice, *J. Amer. Chem. Soc.*, 81, 5444 (1959).
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(13) U. K. Pandit and T. C. Bruice, *J. Amer. Chem. Soc.*, 82, 3386 (1960).
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silica gel. The second fraction (eluted with $CHCl_3$) was 4–5 g of II. Further purification was achieved by zonal sublimation: mp 194–195°; ir (KBr) 1745 cm^{-1} (C=O); nmr ($CDCl_3$–DMSO-d_6) δ 2.27 (s, 3), 6.98 (s, 2), 7.45 (AA'BB' quartet, 4), and 9.05 ppm (broad s, 1); pK_a = 7.0 (ImH^+) and 9.25 (PhOH).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.45; H, 5.11; N, 14.23.

2-(2'-Acetoxy-3'-*tert*-butyl-6'-methylphenyl)imidazole (IIIa). 3-*tert*-Butyl-6-methylsalicyclic acid (Aldrich) was recrystallized from MeOH–H_2O, dried under vacuum, and converted to the methyl ester *via* treatment with diazomethane:[15] white crystals (91%); mp 68–70° (lit.[16] mp 65°); ir (KBr) 1650 cm^{-1} (C=O). The ester (27.56 g, 124 mmol) was refluxed in 80 ml of ethylenediamine overnight and the excess ethylenediamine was removed under vacuum. The resulting oil was heated to 170° for 30 min in an oil bath in an attempt to cyclize the intermediate amide to the imidazoline. However, upon crystallization from $CHCl_3$–petroleum ether (65–110°) 13.82 g of amide was recovered as white fluffy crystals: mp 146–146.5°; ir (KBr) 1625 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.37 (s, 9), 2.36 (s, 3), 2.84 (t, 2), 3.44 (m, 2), 4.20 (s, 2), 6.55 (d, 1, J = 8 Hz, ArH), *ca.* 6.55 (broad s, 1), and 7.14 ppm (d, 1, J = 8 Hz, ArH); mass spectrum (70 eV) *m/e* 250 (parent peak). The mother liquor from the crystallization was evaporated to dryness *in vacuo* and the resulting residue was sublimed in a canon sublimator under reduced pressure. Dehydration occurred and 5 g of yellow imidazoline was obtained: mp 106–106.5°; ir (KBr) 1580 cm^{-1} (C=N); nmr ($CDCl_3$) δ 1.40 (s, 9), 2.42 (s, 3), 3.67 (s, 4), 6.45 (d, 1, J = 8 Hz, ArH), 7.12 (d, 1, J = 8 Hz, ArH), and 9.65 ppm (broad s, 2); mass spectrum (70 eV) *m/e* 232 (parent peak).

The imidazoline (5 g, 2.26 mmol) was refluxed for 30 min in diphenyl ether with 400 mg of Pd/C (10%). An nmr of the reaction mixture showed the disappearance of the four-proton singlet at δ 3.67 ppm due to the imidazoline. The cooled reaction mixture was chromatographed on silica gel and eluted with 30% benzene–petroleum ether (30–60°). The second fraction contained *ca.* 4 g of colorless oil which was identified as the corresponding imidazole: ir (liquid film) 1610 cm^{-1} (C–N); nmr ($CDCl_3$) δ 1.44 (s, 9), 2.32 (s, 3), 6.50 (d, 1, J = 8 Hz, ArH), 6.85 (s, 2), 7.10 (d, 1, J = 8 Hz, ArH), and 11.20 ppm (broad s, 2); pK_a = 6.7 (ImH^+) and 11.1 (PhOH).

An attempt to acetylate the phenol was made using the previously employed procedure. When carried out on this compound, however, no precipitate was obtained. After standing overnight at ambient temperature, the solution was titrated with aqueous KOH until no further precipitation was observed. The precipitate was collected and dried *in vacuo*. Two-dimensional rosette crystals were obtained upon purification by zonal sublimation: mp (sealed tube) 212–213°; ir (KBr) 1755 cm^{-1} (C=O); nmr ($CDCl_3$–DMSO-d_6) δ 1.33 (s, 9), 1.93 (s, 3), 2.17 (s, 3), 7.03 (s, 2), and 7.22 ppm (AB quartet, J = 8 Hz, ArH).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40. Found: C, 70.48; H, 7.30.

2-(2'-Hydroxy-3'-*tert*-butyl-5'-nitro-6'-methylphenyl)imidazole (PIIIb) was prepared from PIII by nitration in benzene–acetic acid. PIII (1.3 g, 6.65 mmol) was dissolved in 15 ml of benzene and 1 ml of acetic acid. The solution was cooled to 0° and a solution of concentrated (aqueous) HNO_3 in acetic acid was added dropwise. After 1 equiv had been added a yellow solid precipitated. After an additional equiv of HNO_3 had been added *via* 2 ml of acetic acid, the solution was allowed to warm to ambient temperature. The product was collected by filtration and dissolved in 50 ml of boiling EtOH, and the resulting solution was filtered free of *ca.* 100 mg of yellow solid. Crystallization commenced upon dilution to *ca.* 30% H_2O and proceeded at ambient temperature. Beautiful golden platelets (300 mg) were obtained upon filtration; mp 223°; ir (KBr) 1615 (ImH^+) and 1570 cm^{-1} ($ArNO_2$); nmr (D_2O–KOD) 1.33 (s, 9), 2.15 (s, 3), 7.21 (s, 2), and 8.03 (s, 1); pK_a = 4.8 (ImH^+), 8.2 (PhOH), and 10.84 (Im).

Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.23; N, 15.26. Found: C, 61.27; H, 6.08; N, 15.34.

Acetylation of the nitrophenol was carried out by dissolving 90 mg (0.327 mmol) of PIII phenol in 6 ml of dry $CHCl_3$ by warming, cooling to ambient temperature, and adding 80 mg of acetyl chloride with stirring. After 3 min 53 mg of white compound could be collected by filtration and identified (uv and ir) as the hydrochloride of the nitrophenol. This was returned to the reaction solution and an additional 80 mg of acetyl chloride and *ca.* 40 mg of pyridine (dried over KOH) were added. After 30 min another white compound began to precipitate. After 5 hr, 88 mg of IIIb as fine, white crystals was collected by filtration and washed with $CHCl_3$ and Et_2O: mp >180°, turns yellow and melts at 206–222°; ir (KBr) 1760 (CO) and 1530 cm^{-1} ($ArNO_2$); mass spectrum (70 eV) *m/e* 317 (parent peak − HCl).

Anal. Calcd for $C_{16}H_{20}ClN_3O_4$: C, 54.31; H, 5.70; Cl, 10.02. Found: C, 54.43; H, 5.69; Cl, 9.83.

2-(2'-Acetoxy-5'-sulfophenyl)imidazole (Ib). PIa (1 g, 6.2 mmol) was dissolved in 8 ml of concentrated H_2SO_4 and heated at 100° for 4 hr. The solution was cooled to 0° and ice–water was added slowly with stirring until precipitation was complete. The white solid was collected by filtration and redissolved in hot aqueous KOH. After the solution was acidified and cooled, small white needles of the sulfonic acid (PIb) were obtained as the zwitterion in 98% yield: mp 344–345° dec; ir (KBr) 3280 (OH), 1630 (ImH^+), 1190, and 1035 cm^{-1} (SO_3^-); nmr (D_2O–NaOD) δ 7.03 (d, 1, J = 9 Hz), 7.25 (s, 2), 7.82 (q, 1, J = 9 Hz, J = 2.5 Hz), and 8.26 ppm (d, 1, J = 2.5 Hz); pK_a = 5.70 (ImH^+) and 8.32 (PhOH).

Anal. Calcd for $C_9H_8N_2O_4S \cdot H_2O$: C, 41.85; H, 3.90; S, 12.4. Found: C, 41.96; H, 3.78; S, 12.12.

Acetylation of 1.12 g (4.7 mmol) of PIb was accomplished in 25 ml of dry $CHCl_3$ with 300 mg of acetyl chloride and 400 mg of pyridine. The solution was stirred overnight and the resulting white solid was collected by filtration and washed with $CHCl_3$. Purification was achieved by dissolving a sample of the ester in DMSO and adding an equal volume of Et_2O. The solution was placed in the freezer until the DMSO froze. After sufficiently warming the solution to melt the DMSO, Ib was collected by filtration. The purified ester (Ib) still contained a small amount (<10%) of the free phenol *via* ir (small peak at 3280 cm^{-1}) and nmr (free acetate peak at 2.12 ppm when sample dissolved in D_2O); mp 327–329°; ir (KBr) 1780 (CO_2R), 1630 (ImH^+), 1180, and 1030 cm^{-1} (SO_3^-); nmr (D_2O) δ 2.38 (s, 2.5 decreasing with time), 7.70 (s, 2), and 7.6–8.3 (m, 3).

1-Methyl-2-(2'-acetoxyphenyl)imidazole (IV). PIV was prepared by the general procedure used to synthesize PIa using *N*-methylethylenediamine (Aldrich) and methyl salicylate which were refluxed for 24 hr. Excess *N*-methylethylenediamine was removed and cyclization to the imidazoline was accomplished by distillation and finally by the addition of diphenyl ether and distillation until distillate temperature reached 140° (1 hr). Pd/C (10%) was added to the diphenyl ether solution which was refluxed for 4 hr, cooled, filtered, and extracted with aqueous HCl. The aqueous HCl was neutralized with $NaHCO_3$ and KOH and extracted with $CHCl_3$ which was then dried ($CaCl_2$), filtered through $MgSO_4$, and evaporated to a dark, viscous oil on a rotary evaporator. Chromatography on silica gel (CCl_4) and recrystallization from Et_2O provide white crystals (52%); mp 106–106.5°; ir (KBr) *ca.* 2500 and 1800 (broad, OH bonded) and 1615 cm^{-1} (Im); nmr ($CDCl_3$) δ 3.68 (s, 3), 6.6–7.6 (m, 6), and 12.40 ppm (s, 1); pK_a = 7.20 (ImH^+) and 9.40 (PhOH). An analytical sample was prepared by sublimation; mp 106.5–107°.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.79; N, 16.08. Found: C, 69.05; H, 5.65; N, 15.94.

Acetylation using either acetyl chloride or bromide in benzene (Na dried) gave an immediate, quantitative precipitate of IV as the hydrochloride or bromide both of which were extremely hygroscopic. Uv shows O-acetylation.

Apparatus. All spectrophotometric kinetic measurements were made on either a Gilford Model 2000 spectrophotometer 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 value block through which water was circulated at 30 ± 0.2°, or a spectrophotometric titration apparatus designed around a Cary 15 spectrophotometer and Radiometer autotitrator (described elsewhere by Bruice and Maley[17]) through which water was circulated at 30 ± 0.1°. Ultraviolet spectra were recorded on the Cary 15 at 30° or on a Perkin-Elmer 350 recording spectrophotometer at ambient temperature. pH was determined (30 ± 0.1°) with a Radiometer Model 26 pH meter equipped with a Metrohm EA 125 combined glass–calomel electrode.

Infrared spectra were recorded using a Perkin-Elmer 137 sodium

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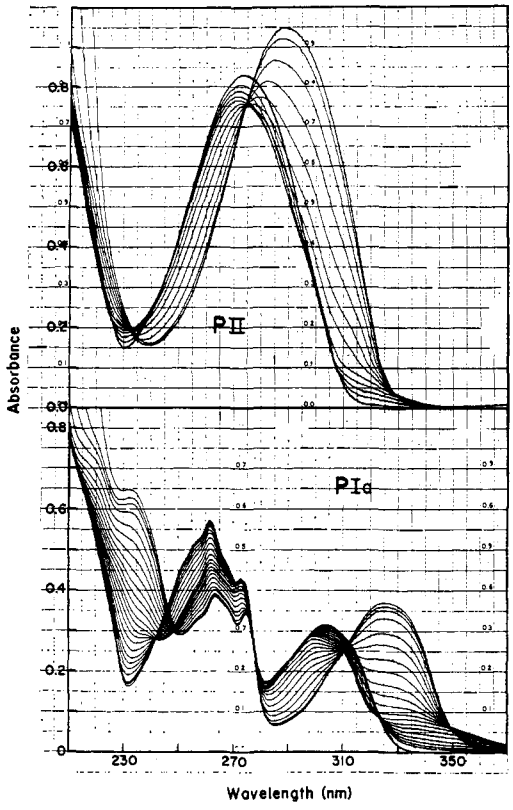


Figure 1. Absorbance *vs.* wavelength (nm) recorded from pH 4.33 to 11.96 for PII (1.58×10^{-5} *M*) and pH 3.30 to 11.95 for PIa (1.02×10^{-5} *M*). Reference to the λ_{max} values of Table II provides the assignment of spectra to the various ionic species in solution at different pH's. The cell path length is 3.3 cm which gives the following molar absorptivities for the major peaks: PII, 273 (15.9) and 288 (18.2); PIa, 262 (ImH^+) (17.0), 303 (9.4), and 325 (11.0).

chloride spectrophotometer. Pmr spectra were recorded on a Varian T-60 spectrophotometer, using TMS or DSS (in water) as an internal standard. Melting points were measured on a Mel-temp and are uncorrected. Mass spectra were run on an AEI MS 902.

Kinetics. All kinetic measurements were in aqueous solutions at 30° with $\mu = 1.0$ by addition of a calculated amount of KCl. Stock solutions of esters Ia, II, and IIIa were made up in dioxane (freshly distilled from Na) and were kept frozen and protected from light between runs. IIIb was dissolved in dry DMF (distilled from CaH) prior to addition to kinetic solutions while the solubility of Ib and IV in water allowed their addition as solids. Concentrations of added organic solvents were always <1%. It was necessary to carry out rate studies with IIIa in 2.5×10^{-4} *M* EDTA to avoid the effects of metal ions. Concentrations of esters were between 4×10^{-5} and 10^{-4} *M*. All reactions were checked by repetitive scanning in the uv and, unless otherwise indicated, were found to hold tight isosbestic points (disappearance of ester corresponds to appearance of phenol or phenoxide). Therefore all reactions were monitored by following the appearance of product at 300–305 nm of Ia, II, and IIIa, 408–440 nm for IIIB, 310–335 nm of Ib, and 290–305 nm for IV. All reaction solutions were either pH-stated or the pH's of the buffers were checked before the reaction and that of the buffer of lowest concentration was routinely checked after the reaction to ensure constancy. Reactions were usually followed to completion and the pseudo-first-order rate constants (k_{obsd}) were obtained from least-squares analysis of plots of ln $(OD_\infty - OD_0)/(OD_\infty - OD_i)$ *vs.* time. Some of the slower rates were followed to only 4–5 half-lives, in which case k_{obsd} was calculated by the method of Guggenheim.[18] The reaction of IIIb in 1 *M* HCl was followed to only 1.5% completion. All actual computations were carried out using an Olivetti-Underwood Programma 101, a Hewlett-Packard 9820A, or an IBM 360 Model 75 computer employing programs written in this laboratory.

Deuterium solvent isotope effects were determined for the hydrolysis of Ia and II at 30° in 99.8% deuterium oxide (Stohler Isotope Chemicals), using either phosphate buffers to maintain pH or the previously described pH-Stat assembly.[17] The pD values were taken as the pH meter readings plus the proper correction (0.39) at 30°[19] which was verified for this electrode.

Uv Spectral Characteristics of Esters and Phenolic Products. The uv spectra of all esters exhibited only one transition (above 220 nm) for each ionic species in solution. In Table I are indicated the ionization state of the ester and the wavelength of maximum absorbance. The uv and visible transitions for the phenolic products were much more complex than the esters and are tabulated in Table II. Spectra of PIa and PII are shown in Figure 1.

Table I. λ_{max} (nm) for Esters[a]

Ester	ImH^+	Im
Ia	254	262
Ib	256	268
II	263	271
IIIa	238	242
IIIb		(256)[b]
IV	240	247

[a] ImH^+ and Im refer to the ionic state of the imidazolyl substituent group (*i.e.*, $[ester]_T = [ImH^+] + [Im]$). [b] Shoulder only.

Table II. λ_{max} (nm) for Phenolic Products[a,b]

Phenol	ImH^+, PhOH	Im, PhOH	Im, PhO^-	Im^-, PhO^-
PIa	303 (9.4)	300	325 (11.0)	
	273 (12.8)	272	274 (10.2)	
	262 (17.0)	262	263 (11.4)	
			232 (19.2)	
PIb	306 (6.09)	338	327 (7.98)	
	274 (7.89)	313	269 (7.35)	
	263 (10.5)	[274]	247 (20.1)	
	228 (18.6)	265		
		[246]		
		238		
PII	273 (15.9)	271	288 (18.2)	
PIIIa	281 (2.34)	[297]	303 (3.98)	
	[240] (4.69)	[277]	279 (2.55)	
	216 (15)	264	[235] (10)	
PIIIb	308 (5.67)	413	426 (19.2)	429 (21.6)
	[235] (12.4)	275	275 (6.61)	276 (5.97)
PIV	286 (4.31)	[281]	301 (5.39)	
	242 (8.66)	272	[225] (17.3)	
	213 (16)			

[a] Wavelengths in brackets are shoulders. Extinction coefficients are provided in parentheses and should be multiplied by 10^3. [b] Where $[product]_T = [ImH^+, PhOH] + [Im, PhOH] + [Im, PhO^-] + [Im^-, PhO^-] = \Sigma$[ionic species obtained from a 2-[2′-(or 4′-)hydroxyphenyl]imidazole].

pK_a Determinations. Spectrophotometric titration of PIa–PIV indicated that in each case removal of the first proton was associated with one set of isosbestic points, and removal of the second proton with a different set of isosbestic points. Thus, in each case, pK_{a1} could be determined *via* spectrophotometric titration at an isosbestic wavelength associated with pK_{a_2}, and *vice versa*. The wavelengths used were: PIa, pK_{a_1} at 248.5 nm, pK_{a_2} at 323.5 nm; PIb, pK_{a_1} at 309 nm, pK_{a_2} at 319.5 nm; PII, pK_{a_1} at 274 nm, pK_{a_2} at 307 nm; PIIIa, pK_{a_1} at 254.5 nm, pK_{a_2} at 345 nm; PIIIb, pK_{a_1} at 408 nm, pK_{a_2} at 352.5 nm, pK_{a_3} at 408 nm; and PIV, pK_{a_1} at 287 nm, pK_{a_2} at 301 nm. The apparent pK_a of a transient intermediate formed during the alkaline hydrolysis of IIIb was determined by the addition of 20 μl (*via* eppendorf automatic pipet) of a DMF solution (1.08×10^{-2} *M* in IIIb) to 25.0 ml of aqueous solution (1 *M* KCl) in the Cary 15 pH-Stat cell.[17] The pH was recorded after the initial drop (substrate was added as the hydrochloride) and was correlated to an OD (extrapolated to zero reaction time where necessary) at the top of the mixing curve. A plot of the sigmoidal

(18) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

(19) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

Table III. Hydrolytic Rate Constants Employed to Fit Theoretical Curves Generated by Eq 7–10 to Experimental Points of Figures 3 and 4

	Ester					
	Ia	Ib	II	IIIa	IIIb	IV
k_1, M^{-1} min^{-1}	4.16×10^{-3}	4.10×10^{-3}	4.86×10^{-3}	$\sim 10^{-6}$	$\sim 5 \times 10^{-6}$	6.50×10^{-3}
k_2, min^{-1}	6.00×10^{-5}	3.60×10^{-4}				
k_3, min^{-1}	1.00×10^{-2}	1.20×10^{-2}			1.15×10^{-2}	4.50×10^{-3}
k_4, M^{-1} min^{-1}	8.00×10^{2}	1.20×10^{4}	2.30×10^{2}	1.80×10^{2}	2.00×10^{5}	1.50×10^{2}
k_5, M^{-1} min^{-1}		9.00×10^{2}			2.50×10^{3}	
pK_{app_1}[a]	6.19	5.65			5.30	7.85
pK_{app_2}[a]		10.25			8.75	

[a] Kinetically apparent pK_a's from Figures 3 and 4.

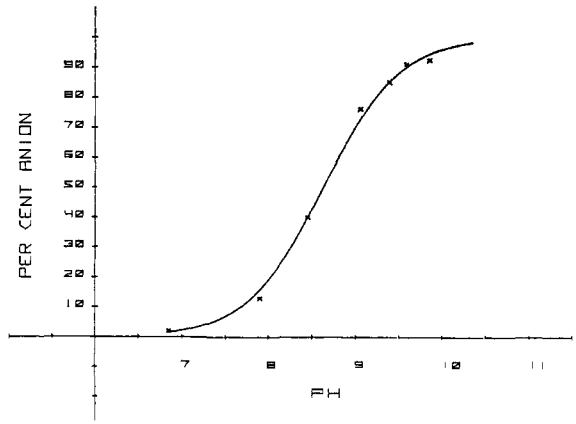


Figure 2. Acid dissociation curve for the transient intermediate formed during hydrolysis of ester IIIb. The points are experimental and the line computer generated to give a theoretical sigmoidal curve with inflection at pH 8.6.

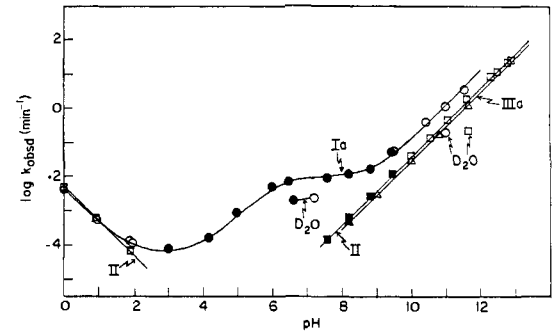


Figure 3. Plots of log k_{obsd} *vs.* pH for esters Ia(○), II(□), and IIIa(△) at 30°. The points are experimental and the lines theoretical employing eq 7a, 8, and 9a and the rate constants recorded in Table III. All rates are spectrophotometric. Open symbols denote either lyate species buffering or the use of the Cary 15 pH-Stat assembly. Filled symbols denote k_{obsd} values obtained by extrapolation of buffer dilution plots to zero buffer concentration.

dependence of the calculated percent anion *vs.* pH is shown in Figure 2. All spectrophotometric titrations were performed at the same temperature, ionic strength, and concentration range of ester as the rate determinations employing a specially designed repetitive scan spectrophotometric titration apparatus.[17]

Results

At constant pH, and in the presence of a great excess of buffer over ester or when the Cary pH-Stat was employed, all spectrophotometrically determined rate constants were found to be pseudo first order (k_{obsd}). For those few experiments employing buffers, extrapolation of plots of k_{obsd} *vs.* buffer concentration to zero buffer provided as intercepts the values of the pseudo-first-order rate constants for non-buffer-catalyzed hydrolysis. For pH values below 2, above 11.5, or when the Cary 15 pH-Stat cell apparatus was used, no external buffer was necessary to maintain constant pH.

Plotted in Figure 3 are the values of log k_{obsd} at zero buffer concentration *vs.* the constant pH (pD) at which k_{obsd} was measured for esters Ia, II, and IIIa in water and Ia and II in deuterium oxide. In Figure 4 are plotted the values of log k_{obsd} at zero buffer concentration *vs.* pH for esters Ib, IIIb, and IV. So that the plots of Figures 3 and 4 may be compared the line depicting the pH–log k_{obsd} profile for Ia (Figure 3) is included in Figure 4. For both figures the points are experimental and the curves were manually iterated and computer drawn to the experimental points using eq 7a for Ia, eq 7b for Ib, eq 8 for II, eq 9a for IIIa, eq 9b for IIIb, and eq 10 for IV, employing the derived constants in Table III. The kinetically apparent pK_a values (pK_{app}) used to fit eq 7–10 to experimental points

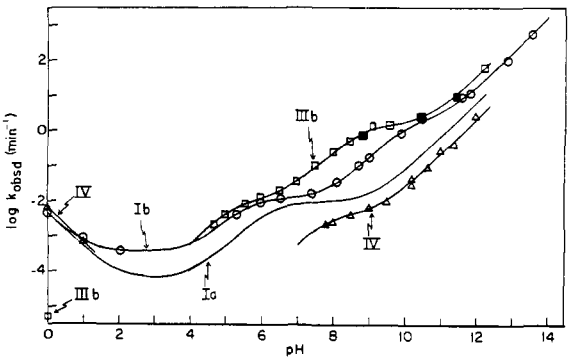


Figure 4. Plots of log k_{obsd} *vs.* pH for esters Ib (○), IIIb (□), and IV (△) at 30°. The points are experimental and the lines theoretical employing eq 7b, 9b, and 10. The line for ester Ia from Figure 3 is reproduced for comparison. All rates are spectrophotometric. Open symbols denote either lyate species buffering or the use of the Cary 15 pH-Stat assembly. Filled symbols denote k_{obsd} values obtained by extrapolation of buffer dilution plots to zero buffer concentration.

$$k_{obsd} = k_1 a_H + k_2 + \frac{k_3 K_{app_1}}{a_H + K_{app_1}} + k_4 a_{OH} \quad (7a)$$

$$k_{obsd} = k_1 a_H + k_2 + \frac{k_3 K_{app_1}}{a_H + K_{app_1}} + \frac{k_4 K_w}{a_H + K_{app_2}} + \frac{k_5 K_{app_2} a_{OH}}{a_H + K_{app_2}} \quad (7b)$$

$$k_{obsd} = k_1 a_H + k_4 a_{OH} \quad (8)$$

$$k_{obsd} = k_4 a_{OH} \quad (9a)$$

$$k_{obsd} = \frac{k_3 K_{app_1}}{a_H + K_{app_1}} + \frac{k_4 K_w}{a_H + K_{app_2}} + \frac{k_5 K_{app_2} a_{OH}}{a_H + K_{app_2}} \quad (9b)$$

$$k_{obsd} = k_1 a_H + \frac{k_3 K_{app_1}}{a_H + K_{app_1}} + k_4 a_{OH} \quad (10)$$

are also listed in Table III, while the spectrophotometrically measured pK_a values of the phenolic products are listed in Table IV.

Table IV. pK_a Values of Phenolic Products[a]

Phenol	pK_{ImH^+}	pK_{PhOH}	pK_{Im}
PIa	6.5	9.32	
PIb	5.7	8.32	
PII	7.0	9.25	
PIIIa	6.7	11.1	
PIIIb	4.8	8.2	10.84
PIV	7.20	9.40	

[a] Where

$$ImH^+, PhOH \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} Im, PhOH \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} Im, PhO^- \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} Im^-, PhO^-$$

Reaction rates in D_2O for ester Ia in the plateau region (k_O) between pH 6 and 9 and the most alkaline region (k_{OH}) and ester II in the alkaline region are included in Figure 3. From these values and values of k_{obsd} in H_2O interpolated from the appropriate pH–log k_{obsd} profile were calculated deuterium solvent kinetic isotope effects which are listed in Table V. The ratio of autoprotolysis constants of H_2O and D_2O [$K_M(H_2O)/K_M(D_2O)$] = 8.93[20] was employed to determine at what pH (pD) values $a_{OH} = a_{OD}$ so that $k_{obsd}^H/k_{obsd}^D = k_{OH}/k_{OD}$. The deuterium solvent kinetic isotope effect for *p*-nitrophenyl acetate was determined from values of k_{obsd} measured in H_2O and D_2O between pH 10 and 11.2.

Table V. Deuterium Solvent Isotope Effects[a]

	Ester		
	Ia	II	*p*-NPA[c]
k_O^H/k_O^D	3.91,[d] 3.82[b,e]		
k_{OH}^H/k_{OD}^D	0.62[f]	0.81[g]	0.52[h]

[a] All reactions were run in Cary 15/pH-Stat assembly unless specifically stated otherwise. [b] Phosphate buffered. [c] *p*-NPA = *p*-nitrophenyl acetate. [d] pH = pD = 6.67. [e] pH = pD = 7.21. [f] pH = pD = 10.99. [g] pH = pD = 11.64. [h] pH = 10.03–11.07, pD = 10.80–11.17.

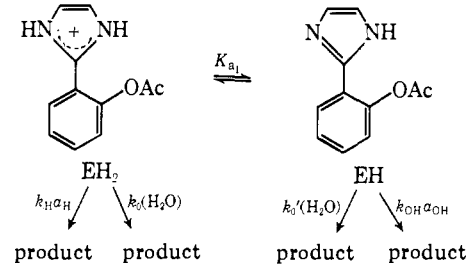
When the hydrolysis of Ib was followed *via* stopped-flow spectrometry at 335 nm (λ_{max} 327 nm for phenoxide) in 0.1–0.5 *M* KOH a decrease in absorbance with time was observed. This was unexpected since Ib has minimal absorbance at 335 nm. At completion of reaction a uv scan exhibited the spectrum of PIb. This result provides evidence that Ib is converted in an exceedingly rapid reaction to an intermediate which yields PIb. Similar results were obtained when the hydrolysis of IIIb was followed at pH >10 when all that is observed is a small decrease of a large absorbance (400–440 nm). In the pH region 7–10 an initial, very rapid increase in absorbance (408 nm) was observed followed by a slower increase which followed first-order kinetics to give the phenol as product. It is this rate which is plotted for IIIb in Figure 4. The magnitude of the absolute value of the absorbance after the initial reaction is pH dependent with an inflection at pH *ca.* 8.6 (Figure 2). The rapid increase in absorbance could not be followed *via* stopped-flow spectrophotometry (at pH 8.85 in 0.01 *M* Tris buffer) and therefore its associated rate constant exceeds 2×10^4 min^{-1}.

(20) A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Chem. Phys.*, 70, 3820 (1966).

Discussion

In Scheme I is depicted the minimum number of hydrolytic pathways required to fit the pH–log k_{obsd} profile for Ia (Figure 3). The mechanisms of hydrolysis of II and IV may also be discussed in terms of Scheme I. As will be shown a more complex scheme is required for Ib, IIIa, and IIIb. Equation 11 pertains to Scheme I and relates k_{obsd} to the hydrogen ion activity and is derived from a material balance in EH_2 + EH and assumed acid–base equilibria in these species. Equation 11 may be employed to generate the same pH–log k_{obsd} profile (Figure 3) for Ia as obtained with the empirical rate law of eq 7a. In discussing the mechanisms of hydrolysis we will begin with the specific acid catalyzed hydrolysis of species EH_2 and proceed to specific base catalysis at high pH.

Scheme I



$$k_{obsd} = \frac{a_H^2 k_H}{a_H + K_{a_1}} + \frac{k_0 a_H}{a_H + K_{a_1}} + \frac{k_0' K_{a_1}}{a_H + K_{a_1}} + \frac{k_{OH} K_{a_1} a_{OH}}{a_H + K_{a_1}} \quad (11)$$

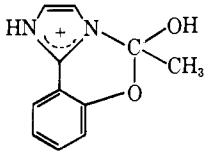
It is noteworthy that the values of k_H for Ia, Ib, II, and IV are nearly identical (k_1 of Table III) and very close to the value of 4.6×10^{-3} M^{-1} min^{-1} (25°) for *p*-carboxyphenyl acetate.[21] Since specific acid rate constants for ester hydrolysis are indifferent to electronic effects, one must conclude that the imidazolium group exhibits no more effective bulk than a hydrogen atom. This is in contrast to other "ortho–para" models[14,21] (where a twofold decrease in ester hydrolysis is observed) but is not unprecedented[22,23] and may be rationalized from viewing a CPK model of Ia. If the plane of the cisoid–ester bond is rotated 45° from a perpendicular with the plane of the benzene ring so that the phenolic oxygen faces the imidazolyl–NH then no hindrance to the approach to the carbonyl carbon by nucleophiles of moderate size is seen. That this conformation is reasonable is attested to by a 20-cm^{-1} shift in ir frequency for the ester carbonyl of Ia *vs.* II which establishes intramolecular H-bonding. Introduction of

(21) T. St. Pierre and W. P. Jencks, *J. Amer. Chem. Soc.*, 90, 3917 (1968).
(22) T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, 87, 4846 (1965).
(23) S. Sicsic and Z. Welvart, *Chem. Commun.*, 499 (1966).

the bulky *tert*-butyl group (IIIa,b) prevents the attainment of this conformation and there results *ca.* 10^3 decrease in rate due to the combined steric interactions (Table III).

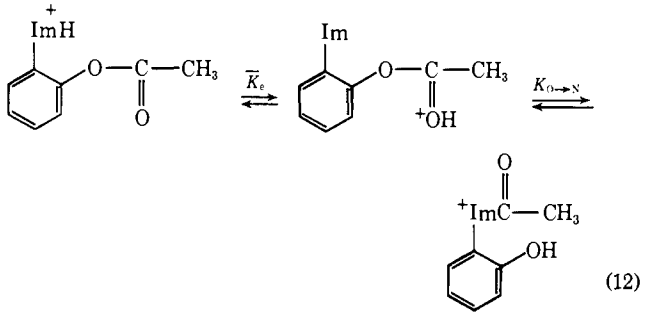
Except for the hydrolytic pathway involving specific acid catalysis of hydrolysis of EH_2 (*i.e.*, $k_H a_H$), each of the pathways of Scheme I has one or more kinetically equivalent terms. Thus, the pathway represented by k_2 for esters Ia and Ib (eq 7a and 7b) pertains to the plateau region of the pH–log k_{obsd} profiles between pH 2 and 4 and dictates that the transition state(s) composition must include $EH_2 + H_2O\ (H_2O)_n$ or $EH + H_3O^+\ (H_2O)_n$ (Scheme I). Intramolecular participation of the conjugate acid of a nucleophilic species has been seen in the hydrolysis of the amide of γ-(4′-imidazolyl)-butyric acid,[24a] phthalamic acid,[24b] monoesters of phthalic acid in which the alcohol leaving moiety is of $pK_a > 13.5$,[24c] and acetyl salicylate.[9,24d] That II does not exhibit the plateau rate at low pH indicates that an ortho imidazole function is required. Three possible mechanisms are in accord with the above requirements: (i) intramolecular nucleophilic attack by imidazole on the preequilibrium protonated ester group; (ii) intramolecular imidazolyl general base assistance to attack of H_2O upon the preequilibrium protonated ester group; (iii) imidazolium ion general acid catalyzed assistance to the attack of H_2O upon the ester carbonyl.

Specific acid assisted nucleophilic attack by the imidazolyl group (i) requires formation of the intermediate (or transition state like) structure VI, from which partitioning back to EH_2 would be overwhelmingly favored. Considering ground-state stabilities



VI

in the case of Ia and Ib, however, the equilibria $K_{O\rightarrow N}$ (eq 12) would be most favorable, suggesting the feasi-



(12)

bility of the mechanism of nucleophilic specific acid catalysis as suggested for aspirin.[24d] For i and ii $\bar{K}_e \cong K_{app_I}/K_{ester}$ (K_{ester} = dissociation constant of protonated ester oxygen). If k_{gb} and k_{ga} are the overall rate constants for the general base and general acid catalyzed mechanisms of hydrolysis and k_{na} the rate constant for nucleophilic specific acid catalysis then the relationships of k_{ga} to the empirical rate constant k_2 (eq 7a and 7b) and in turn k_{gb} and k_{na} to k_{ga} are provided by eq 13 and 14, respectively.[25] Values of k_2 for

$$k_{ga} = k_2/[H_2O] \quad (13)$$

$$k_{na} = k_{gb} = (k_2/[H_2O]\bar{K}_e) - (k_{ga}/\bar{K}_e) \quad (14)$$

Ia and Ib obtained from the best fit of the empirical rate equations (eq 1a and 1b, respectively) to the pH–log k_{obsd} profiles are recorded in Table III and the calculated constants k_{ga} and $k_{na} = k_{gb}$ in Table VI. It

Table VI. Rate Constants for Esters Ia and Ib Representing the Low pH Plateau Region of the pH–Log k_{obsd} Profiles

Ester	k_{ga}, M^{-1} min^{-1}	$k_{na} = k_{gb}$, M^{-1} min^{-1}
Ia	1.1×10^{-6}	$\sim 10^{8}$ [a]
Ib	6.7×10^{-8}	$\sim 10^{6}$ [a]

[a] Assuming pK_a for protonation of the ester (pK_{ester}) to be ≤ -8 for Ia and ≤ -9 for Ib. The pK_a of the conjugate acid of ethyl benzoate is −7.4: J. Hine and R. P. Bayer, *J. Amer. Chem. Soc.*, **84**, 1989 (1962).

should be noted that the calculated values of k_{gb} and k_{na} for Ib are of such magnitude to make the mechanisms of (i) and (ii) somewhat unlikely since they involve the making and breaking of bonds to heavy atoms. In addition it should be noted that the pH–log k_{obsd} profile for the sterically hindered ester IIIb does not exhibit a low pH plateau. However, its associated plateau at high pH can be shown to result from nucleophilic attack of the imidazole anion group (by spectral observation of the *N*-acetyl intermediate, *vide infra*). This establishes that, sterically, a nucleophilic attack of the imidazole group of IIIb upon the protonated ester moiety should be allowed. Further, the fact that the rate constants for the high plateau reactions of IIIb and Ib have near identities (Table III) suggests that if nucleophilic specific acid catalysis were operating for Ib, then IIIb should also exhibit a low pH plateau. This reasoning may be taken as further evidence against the mechanism of nucleophilic specific acid catalysis. The k_{ga} constant for Ia exceeds the second-order rate constant for attack of water on *p*-nitrophenyl acetate (25°)[26] and thus the *o*-(2′-imidazolium) group would appear to be an efficient general acid catalytic entity. In regard to a general acid assisted water attack (mechanism iii) it should be noted that intramolecular hydrogen bonding can occur in Ia and Ib between the imidazolium moiety and phenolic oxygen. This fact is apparent from the gross differences in uv spectral transitions (Figure 1 and Table II; bathochromic shift of *ca.* 30 nm for phenolic transition in the imidazolium species) for PIa (also compounds PIb, PIIIa, and PIIIb) as compared to PII where no intramolecular hydrogen bonding can occur. Hydrogen bonding of the imidazolyl NH to the phenolic oxygen in Ia,b is also evident from the position of the ester carbonyl bands in the ir (Table VII). Again using II as a nonbonding model, both Ia and Ib (as a zwitterion) exhibit shifts in the >C=O absorbance in the ir indicating polarization of the ester bond in the ground state by both imidazole

(24) (a) T. C. Bruice and J. M. Sturtevant, *J. Amer. Chem. Soc.*, 81, 2860 (1959); (b) M. L. Bender, Y. L. Chow, and F. Chloupek, *ibid.*, 80, 5380 (1958); (c) J. W. Thanassi and T. C. Bruice, *ibid.*, 88, 747 (1966); (d) A. R. Fersht and A. J. Kirby, *ibid.*, 89, 4853 (1967).

(25) Approximate molarity of H_2O in 1.0 *M* KCl at 30° = 53.4.

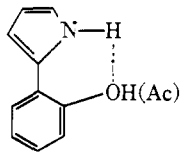
(26) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 90, 2622 (1968).

Table VII. Frequency (cm^{-1})[a] of Ester Carbonyl Bands

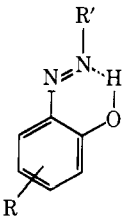
Ester	$\nu_{C=O}$
Ia	1765
Ib (ImH^+)	1775
II	1745
IIIa	1755
IIIb (ImH^+)	1755

[a] All spectra in KBr.

and imidazolium.[27] A smaller shift is seen for IIIa and IIIb and is consistent with CPK models which indicate steric hindrance to hydrogen bonding by the 6-methyl group (uv data of Tables I and II also show an alteration and diminution of bands most probably correlatable with the pseudo-five-membered ring, coplanar system of VIIa[28]) and buttrussing of the ester by the *tert*-butyl group, holding it in a position unfavorable for hydrogen bonding of either the ether or carbonyl oxygens to the imidazolyl-NH. The observation in a solid solution



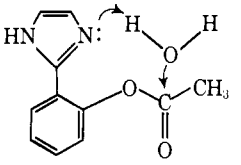
VIIa



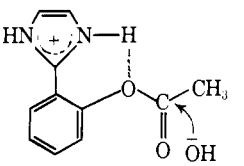
VIIb

does not of course relate necessarily to what might be the situation in H_2O. Whether hydrogen bonding does or does not occur in the ground state these results clearly support a supposition that it could be of importance in the transition state (*i.e.*, CPK models show that a good linear hydrogen bond can be formed between the imidazolyl NH and the oxygen of a tetrahedral-like transition state). Additional support for the proposed existence in solution of the hydrogen bond depicted in VIIa comes from T-jump experiments on a series of azo-phenols (VIIb, above) by Rose and Stuehr[29] which provide evidence for hydrogen bonding between the phenol and weakly basic azo group.

In the neutral pH region the hydrolyses of Ia (*ca.* pH 6.25–9), Ib (*ca.* pH 6–6.75), IIIb (*ca.* pH 5.75–6.25), and IV (*ca.* pH 8–9) proceed through a pathway associated with the rate term k_3 (Table III) of the empirical rate eq 7a, 7b, 9b, and 10. One again encounters the complexities of several possible, kinetically equivalent mechanisms. The possibilities are: (1) imidazole general base assisted attack of water (VIIIa), (2) imidazolium ion general acid assisted attack of hydroxide (VIIIb), (3) nucleophilic attack by the neutral imidazolyl group, and (4) specific acid assisted nucleophilic attack by the imidazolyl anion. The last possibility can be discarded since it would require a second-order rate constant of 10^{12} M^{-1} min^{-1} in violation of a limiting

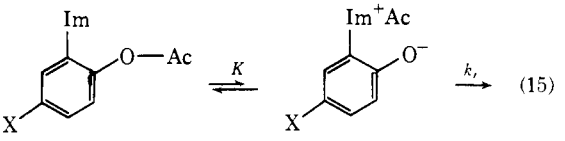


VIIIa



VIIIb

diffusion controlled process.[30] A deuterium solvent kinetic isotope effect of 3.9 is associated with k_3. This would be equally in accord with H_2O general base catalyzed hydrolysis of an *N*-acetylimidazolium ion intermediate (3) or the possibilities of (1) or (2) since these mechanisms differ only by the position of a proton in the transition state. Consonant with the evidence that intermolecular reactions of imidazole with esters show various modes of catalysis which are sensitive to electronic effects both in the acyl and alkyl portions of the ester,[2] Bruice and Felton suggested that V (eq 5) hydrolyzes through general base assisted water attack in the neutral pH region. For V as in the present study the various kinetically indistinguishable mechanisms cannot be differentiated as was accomplished in the case of aspirin hydrolysis through conversion of any mixed anhydride intermediate to ester and ^{18}O exchange.[9] For V it was suggested that the nucleophilic pathway would be expected to become predominant if the leaving tendency of the phenol were enhanced, thus shifting the unfavorable equilibrium of eq 18 to the right.[31] As will be seen (*vide infra*) this supposition is borne out in the hydrolysis of Ib and IIIb.



(15)

As required by the anthropomorphic rule[5] for catalysis, the pK_a of the imidazolium group falls between that of H_2O and the protonated tetrahedral intermediate formed on adding H_2O to the ester carbonyl group in VIIIa and is intermediate to the pK_a's of the protonated ester and the product phenol for VIIIb. In addition the specific rate constants for VIIIa and VIIIb (k'_{gb} and k'_{ga}, respectively) calculated from k_3 are 1.8×10^{-4} and 5×10^5 M^{-1} min^{-1}, respectively.[32] Numerically, both values would appear to be reasonable. The calculated rate constant based on VIIIa would represent a 10^3–10^4 rate enhancement over water general base catalyzed attack of water upon Ia.[33] The rate constant for intramolecular carboxyl anion general base catalyzed assistance of attack of H_2O in the hydrolysis of aspirin has been determined to be 2.8×10^{-6} M^{-1} min^{-1} (25°)[21] which is reasonably comparable to that calculated for VIIIa (30°) when one considers the greater basicity of imidazole as compared to carboxyl groups. Also, the general base catalyzed constant for Ia may be compared to that determined for the quite similar 4-(2′-

(27) Similar, although smaller, effects have been reported for hydrogen bonding of neighboring hydroxyl groups to esters: T. C. Bruice and T. H. Fife, *J. Amer. Chem. Soc.*, 84, 1973 (1962).

(28) (a) For the synthesis of variously alkyl-substituted 2- and 4-arylimidazoles and uv spectral evidence for coplanarity, see T. Hayashi and H. Middorikawa, *Sci. Pap. Inst. Phys. Chem. Res., Tokyo*, **58**, 139 (1964). (b) For uv evidence for coplanarity of 2-(2′-hydroxyphenyl)- and 2-(2′-methoxyphenyl)benzimidazole, see C. Wiegand and E. Merkel, *Justus Liebigs Ann. Chem.*, **557**, 242 (1947).

(29) M. C. Rose and J. E. Stuehr, *J. Amer. Chem. Soc.*, **94**, 5532 (1972).

(30) M. Eigen, *Discuss. Faraday Soc.*, No. **39**, 7 (1965).

(31) The value of the equilibrium constant for the reaction

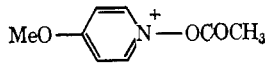
$$XPhOAc + Im \overset{K_e}{\rightleftharpoons} XPhO^- + AcImH^+$$

increases by a factor of 10^5 upon going from X = OMe to NO_2: J. Gerstein and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 4655 (1964).

(32) Where $k'_{gb} = k_3/[H_2O]$ and $k'_{ga} = k_3K_{appl}/K_w$.

(33) Based on an estimate for the uncatalyzed hydrolysis of V in ref 14 of 4.5×10^{-8} M^{-1} min^{-1}.

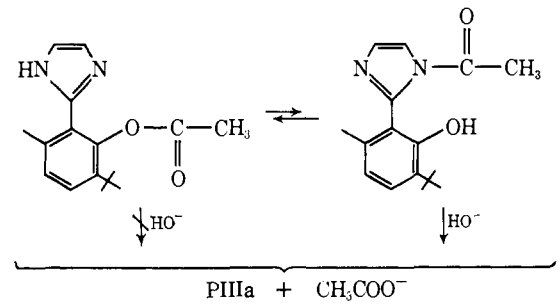
acetoxyphenyl)imidazole (eq 5).[14] The calculated rate constant for HO^- nucleophilic attack upon the EH_2 species of Ia (VIIIb) is quite comparable to the specific base catalyzed hydrolysis of IX ($5.7 \times 10^5\ M^{-1}\ min^{-1}$).[26] If the proton in VIIIb is considerably transferred to the ether oxygen of the ester group in the critical transition



IX

state, then HO^- attack upon IX might be a reasonable model for VIIIb. If neighboring imidazolium ion assistance in the spontaneous hydrolysis of Ia and Ib does occur, as the experimental data indicate, then like assistance of HO^- attack would be anticipated. However, a comparison of k'_{ga} for Ia ($5 \times 10^5\ M^{-1}\ min^{-1}$) with the rate constant for the uncatalyzed attack of OH^- on II (k_4 of Table III) reveals a 2×10^3-fold rate enhancement attributable to general acid catalysis. In contrast, the general acid catalyzed attack of H_2O upon Ia (k_{ga} of Table VI) represents a maximum rate enhancement of 25-fold over the estimated rate of spontaneous hydrolysis of II. With all other factors such as steric requirements and electronic effects identical for the two mechanisms the attack of OH^- ($pK_a = 15.74$) is facilitated 100 times more than is the attack of H_2O ($pK_a = -1.74$). This apparent result, of course, violates the axiom that "you get catalysis where you need it" and would tend to eliminate VIIIb in favor of the general base mechanism of VIIIa. Thus this study supports the choice of mechanism made for the isomeric ester V[14] in the neutral pH plateau region and is harmonious with the established mechanism for aspirin hydrolysis.[9]

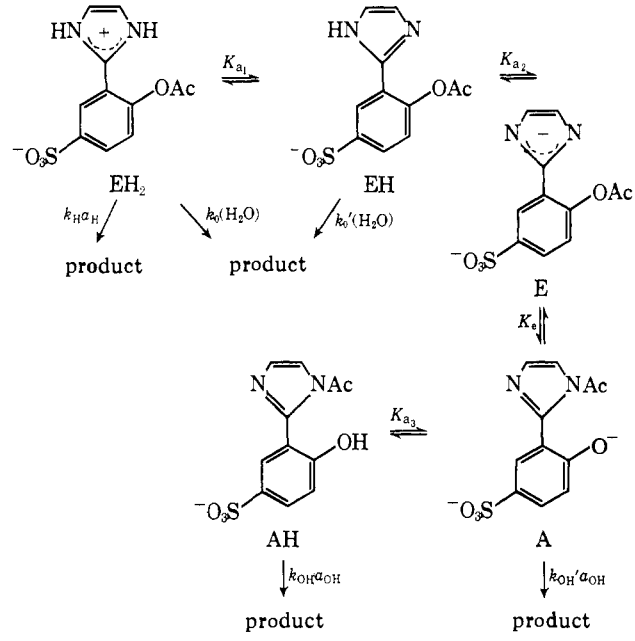
As noted previously, steric effects provide a *ca.* 10^3 decrease in rate for the specific acid catalyzed hydrolysis of IIIb when compared to Ia, Ib, and II. From the known similarity in sensitivity of specific acid and base catalyzed ester hydrolysis to steric hindrance[34] it would be anticipated that the specific base catalyzed hydrolysis of IIIa,b would also proceed with associated rate constants *ca.* 10^3 less than for the hydrolysis of Ia and II. In actuality the value of k_4 for IIIa is comparable to that for II. This similarity in k_4 values (less than 30% difference) is made more surprising by the fact that the pK_a of the phenolic product of IIIa (Table IV) is *ca.* 2 units greater than that for the product of II, so that the leaving group is poorer in the hydrolysis of IIIa. One may conclude that, on the basis of steric and electronic effects, the rate constant for the specific base catalyzed hydrolysis of IIIa is *ca.* 10^4 greater than anticipated for HO^- attack on the phenyl ester moiety. This suggests that steric inhibition is not in effect for specific base catalyzed hydrolysis. It is most reasonable, therefore, that intramolecular nucleophilic attack by imidazole on the carbonyl center stands as the only tenable mechanism by which the acetyl group of IIIa can be transferred to solvent or buffer species (eq 16). In eq 16 although the N→O acyl transfer is thermodynamically unfavorable the rate constant for the specific base catalyzed hydrolysis of an *N*-acetylimidazole should exceed that of a sterically hindered phenyl acetate. This case is very similar to that observed for the



PIIIa + CH_3COO^- (16)

structural change from aspirin to 2-carboxyphenyl mesitoate,[35] where the latter, hindered ester hydrolyzes only through nucleophilic attack by the neighboring carboxylate. Additional information is difficult to deduce from the profile of IIIa (straight line with slope +1). The nitro derivative of IIIa (*i.e.*, IIIb) possesses a much better phenoxide leaving group and its hydrolysis provides experimental evidence for the N→O acyl shift and subsequent HO^- attack. For IIIb (and Ib) the pH–log k_{obsd} profile (Figure 4) exhibits two kinetically apparent pK_a's associated with three reaction paths (rate constants). Scheme II (shown for

Scheme II



Ib) is proposed to account for these observations as well as the additional pathways of hydrolysis for Ib at low pH. The relationship between k_{obsd} and the hydrogen ion activity as derived from a material balance in EH_2 + EH + E + A + AH and assumed acid–base equilibria in these species is expressed in eq 20. The proposal of the necessity for an *N*-acetylimidazole intermediate in the hydrolysis of Ib, IIIa, and IIIb, based on kinetic arguments, is verified for IIIb by the direct observation of an intermediate. The first reaction (pH 8–12) is too rapid to follow even by stopped-flow spectrometry. The absorbance at completion of the first reaction when plotted *vs.* pH provides an acid dissociation curve for an acid of $pK_{app} = 8.6$ (Figure 2).

Comparison of the separate terms of the empirical rate equations employed to fit the pH–log k_{obsd} profiles for Ib, IIIa, and IIIb (*i.e.*, eq 7b, 9a, and 9b, re-

(34) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(35) H. D. Burrows and R. M. Topping, *Chem. Commun.*, 1389 (1970).

spectively) to the like terms of eq 17 provides the equivalent expressions of eq 18–22. The values of pK_{app_1} for Ib and IIIb are quite similar to the titrimetric pK_{ImH^+} values of Table IV. It is safe to assume, therefore, that $pK_{app_1} = pK_{a_1}$. It necessarily follows that in eq 21, $K_{a_3} > K_{a_2}K_e$. This being so then from eq 18, $k_3 = k_0'$; from eq 19, $k_4 = k_{OH}K_{a_2}K_e/K_{a_3}$; from eq 20, $k_5 = k_{OH}'$; and from eq 22, $K_{app_2} = K_{a_3}K_e$. Further, for IIIa and most certainly for IIIb, $K_{a_3} > K_{a_2}$ so that K_e probably cannot exceed *ca.* 10^2.

Both k_4 and k_5 for Ib and IIIb pertain to the specific base catalyzed hydrolysis of acetylimidazoles which are electronically and sterically similar. Therefore, it is reasonable to anticipate that k_5, which equals k_{OH}', for Ib would equal k_5 for IIIb. This is found to be the case (Table III). That k_4 for IIIb exceeds k_4 for Ib finds

$$k_{obsd} = \frac{a_H^2K_{a_3}[a_H(k_Ha_H + k_0) + k_0'K_{a_1}] + (k_{OH}a_H + k_{OH}'K_{a_3})K_{a_1}K_{a_2}K_eK_w}{a_H[K_{a_3}(a_H^2 + a_HK_{a_1} + K_{a_1}K_{a_2}) + K_{a_1}K_{a_2}K_e(a_H + K_{a_3})]} \quad (17)$$

$$k_3 = \frac{k_0'K_{a_3}}{K_{a_3} + K_{a_2}K_e} \quad (18)$$

$$k_4 = \frac{k_{OH}K_{a_2}K_e}{K_{a_2}K_e + K_{a_3}} \quad (19)$$

$$k_5 = k_{OH}' \quad (20)$$

$$K_{app_1} = (K_{a_1}/K_{a_3})(K_{a_3} + K_{a_2}K_e) \quad (21)$$

$$K_{app_2} = K_{a_2}K_{a_3}K_e/(K_{a_3} + K_{a_2}K_e) \quad (22)$$

explanation in the compound nature of the k_4 term (eq 19). The tenfold increase which is observed for the specific base catalyzed hydrolysis of AH (Scheme II) for IIIb compared to Ib must be the result of K_e or K_{a_2} or both being greater for IIIb as compared to Ib. The further depression of k_4 observed for IIIa is probably also a result of the dependence of this term upon K_{a_2} and K_e plus an actual decrease in k_{OH} due to the decreased leaving ability of the imidazolyl anion. Thus, pK_{ImH^+} (Table IV) is greater for PIIIa than for PIIIb and it has been established that the first and second pK_a values for imidazoles are linearly related[36] so that pK_{Im} for IIIa should be greater than for IIIb. Poorer leaving tendency of the imidazolyl group of A compared to AH (Scheme II) would also account for the 100-fold decrease in k_4 as compared to k_5 for IIIb (and *ca.* 20-fold for Ib) upon ionization of the phenol (K_{a_3}). Another explanation can be found in general acid catalysis by the phenolic hydroxyl group assisting the attack of hydroxide on the acetylimidazole. However, it has been shown for acetylimidazole itself that the mechanism of specific acid catalysis of hydrolysis probably involves protonation of the free ring nitrogen.[37] This mode of catalysis, while sterically possible for Ib, appears from both CPK or Lapine models for IIIa(b) to be very unlikely due to the unfavorable steric interaction between the acetyl of the acetylimidazole and the 6-methyl group. The same models also show that hydrogen bonding between the hydroxyl of the phenol and the carbonyl oxygen of the acetylimidazole is favorable and could lead to general acid catalysis. In the absence of more compelling arguments, however, the decrease in the observed rate of hydrolysis upon ionization of the phenol is most likely attributable to electronic inhibition of nucleophilic attack by hydroxide. This source of inhibition is well documented.[38]

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

(36) T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, **80**, 148 (1958).

(37) R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4390 (1961).

(38) T. Maugh II and T. C. Bruice, *J. Amer. Chem. Soc.*, **93**, 3237 (1971).