Effects of Substituents on the Hydrolysis of 4-Nitrophenyl Acetate catalysed by 2-Substituted Imidazoles

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The hydrolysis of 4-nitrophenyl acetate catalysed by a series of 2-substituted imidazoles has been studied in water at 30°. The substituents used are the alkyl groups Me, Et, Pr^i, and Bu^t, and a few hydroxyalkyl groups. Activation parameters and the deuterium oxide solvent isotope effect have been determined for some of these imidazoles. Increased bulkiness of the 2-substituents results in decreased rates for the nucleophilic catalysis observed for most of the imidazoles studied. The results are analysed in terms of the Brönsted catalysis law assuming a common slope of 0.80 and an equal pK_a of 7.80, giving an extrapolated rate value to each imidazole. Based on the analysis, a measure of the steric effect of the individual imidazole relative to the parent compound is estimated. The mechanism by which 2-(1,1-dimethyl-2-hydroxyethyl)imidazole acts for the hydrolysis is judged as a partial general base catalysis.

THERE are two types of mechanisms, nucleophilic and general base, in the imidazole-catalysed hydrolysis of carboxylic acid esters. The nucleophilic mechanism is predominant for esters with good leaving groups such as phenyl acetates, and a general base mechanism is observed for esters with poor leaving groups such as alkoxides.[1-4] Enzyme catalysed hydrolyses of these esters, however, are believed to proceed through the formation and breakdown of acyl serine intermediates with assistance of the histidine imidazole group as a general base.[5] A rigid array of the enzyme active site is supposed to confine the imidazole group to acting as the sole function of general catalysis. Imidazole is an excellent nucleophile and has a simple structure, when compared with a multi-regulating enzyme system. Therefore, it becomes necessary to change the steric environment of the molecule, in order to provide systems where even good leaving esters can be subjected to imidazole general base catalysis. It is generally accepted that in a series of bases, nucleophilic reactivity is more affected by steric bulk than is general-base reactivity.[2] Thus there is a possibility of change in mechanism from nucleophilic to general base catalysis when the steric bulk is increased. This study has been undertaken to examine the steric effects of substituents for imidazole base as catalyst.

Fife and Milstien studied the effect of substituents in the acyl portion of 4-nitrophenyl esters upon imidazole catalysis, but no mechanistic change was observed in that series.[6] In the hydrolysis of 4-nitrophenyl acetate, Bruice and Schmir noted a large rate retardation upon introduction of a methyl group in the 2-position of imidazole.[7] However, further work is yet to be done. Recently, for the pyridine-catalysed hydrolysis of 2,4-dinitrophenyl acetate, Butler and Robertson have observed a change in mechanism from nucleophilic to general base catalysis by methyl substitution at the 2-position.[8] In a related study, Williams and Naylor found that the imidazole-catalysed hydrolysis of aryl diphenylphosphinates proceeds by a general base mechanism which avoids the formation of a sterically crowded nucleophilic intermediate.[9]

In this paper, catalysis by a series of 2-substituted imidazoles of the hydrolysis of 4-nitrophenyl acetate is reported; this substrate is well known for its susceptibility to imidazole nucleophilic catalysis.[1-4] Our attention is given particularly to the following points. First, by how much can the nucleophilic reactivity of imidazole bases be diminished by the presence of steric bulk in the 2-position? Secondly, does the mechanism of imidazole catalysis change from nucleophilic to general base as the steric bulk increases? Thirdly, does a hydroxy-group proximate to the imidazole function facilitate general base catalysis, when the nucleophilic reactivity of the imidazole is effectively reduced?

[1] T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' Benjamin, New York, 1966, vol. 1.
[2] S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.
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[6] T. H. Fife, *J. Amer. Chem. Soc.*, 1965, **87**, 4597; J. B. Milstien and T. H. Fife, *ibid.*, 1968, **90**, 2164.
[7] T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, 1958, **80**, 148.
[8] A. R. Butler and I. H. Robertson, *J.C.S. Perkin II*, 1975, 660.
[9] A. Williams and R. A. Naylor, *J. Chem. Soc.* (*B*), 1971, 1967.

RESULTS

The imidazole base catalysed hydrolysis of 4-nitrophenyl acetate was carried out in water by utilizing a series of 2-substituted imidazoles as buffer under pseudo-first-order reaction conditions. The imidazole base catalysis may be expressed by equation (1) where k_0 is a catalytic constant

$$k_{obs} = k_{im}[Im]_f + k_0 \quad (1)$$

due to the solvent species. Equation (1) is valid for imidazole,[10] and was also confirmed for 2-methyl-, 2-isopropyl-, and 2-(1,1-dimethyl-2-hydroxyethyl)-imidazole in preliminary experiments. The values of k_{im} in water at 30° and at two additional temperatures for some of the imidazoles are given in Table 1 together with the pK_a values at 30°. The k_{im} values for imidazole at 20 and 30° are similar to those determined under comparable conditions.* The value for 2-methylimidazole at 30° was larger than that reported,† probably due to a difference in the solvent compositions used. The k_{im} value for 2-t-butylimidazole is an approximate value and shows an upper limit, since the buffer concentration range was limited by the low solubility and rate differences among different buffer concentrations were very small. But no such difficulties were experienced with the other imidazoles, and the plots of k_{obs} *versus* $[Im]_f$ gave good linear relations. In order to obtain mechanistic information on the catalysis, the deuterium oxide solvent isotope effect was determined for some of the imidazoles. Activation parameters were calculated from the data in Table 1. Each data set gave a good straight line in the plot of log k_{im} *versus* $1/T$. These results are collected in Table 2. The parameters for imidazole here agree with the reported values [6] of $\Delta S^{\ddagger}$ −34 cal mol^{-1} K^{-1} and $\Delta H^{\ddagger}$ 7.4 kcal mol^{-1}, since both the calculations partly utilized similar values of k_{im} as mentioned above. For additional confirmation of the mechanism, repeat scanning of the spectrum during hydrolysis was made. For 2-(1,1-dimethyl-2-hydroxyethyl)imidazole no evidence of the formation of an acylimidazole intermediate [10] was obtained. Absorptions at *ca.* 255 nm were merely decreased with progress of the reaction, but an isosbestic wavelength [9] at 250 nm was obscured by cut-off.

TABLE 1

Substituted imidazole catalysed hydrolysis of 4-nitrophenyl acetate in water [a]

Imidazole substituent	pK_a [b]	Second-order rate constant 10^3k_{im}/l mol^{-1} s^{-1} 20°	30°	41°	10^3R_X [c] l mol^{-1} s^{-1}	$-\log(R_X/R_H)$
1. 2-H [d]	7.19	470	800		2 500	0
2. 2-$HOCH_2$	6.90	15	25	48	130	1.3
3. 2-Me	8.10	98	160	280	94	1.4
4. 2-Et	8.07		60		37	1.8
5. 2-HOCH(Me)CH_2	7.68		23		29	1.9
6. 2-Pr^i	8.01	2.1	13	26	9.1	2.4
7. 2,4,5-Me_3	9.03	3.4	7.3	13	0.76	3.5
8. 2-$HOCH_2C(Me)_2$	7.54	0.025	0.049	0.085	0.079	4.5
9. 2-Bu^t	7.93		0.03		0.023	5

[a] Acetonitrile (0.8% v/v) and ionic strength 1.0 (KCl); 4-nitrophenyl acetate 1.0×10^{-4}M. [b] At 30° and ionic strength 1.0. [c] Extrapolated rate value, see Figure 1. [d] At 10° $10^3k_{im} = 260$.

TABLE 2

Second-order rate constants in D_2O, solvent isotope effects, and activation parameters for hydrolysis of 4-nitrophenyl acetate catalysed by substituted imidazoles at 30° [a]

Imidazole substituent	$10^3k_{im}^D$/ l mol^{-1} s^{-1}	k_{im}^H/k_{im}^D	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$-\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
1. 2-H			8.7	30
2. 2-$HOCH_2$	21	1.2	9.7	34
3. 2-Me			8.6	34
6. 2-Pr^i	13	1.0	10.6	32
7. 2,4,5-Me_3	4.7	1.6	11.0	29
8. 2-$HOCH_2C(Me)_2$	0.029	1.7	10.3	44

[a] Acetonitrile (0.8% v/v) and ionic strength 1.0 (KCl).

No useful information was obtained with 2,4,5-trimethyl- and 2-t-butyl-imidazole, because the former has cut-off at 290 nm and the latter participated little in the catalysed reaction. Most of the latter reaction was due to hydroxide ion catalysis, showing two clear isosbestic wavelengths [9] at 251 and 317 nm.

DISCUSSION

The 2-position of the imidazole ring is a suitable site for substitution, since the 2-substituent can affect both nitrogen atoms equally and effectively, irrespective of the imidazole prototropy. From Table 1, it is seen that the k_{im} value at 30° decreased gradually as the steric bulk of the 2-substituents increased. It is worthwhile to analyse the data in terms of the influence of the substituents upon catalysis. Since the pK_a values of the imidazoles are different, direct comparison of the k_{im} values is not useful. Therefore, an extrapolated rate value may be derived for each imidazole from its k_{im}. Two assumptions are made for this purpose: each substituent series obeys the Brönsted catalysis law and there is an imidazole with a hypothetical pK_a of 7.80 in the individual series. For the Brönsted correlation a universal slope of 0.80 was used, because the catalysis seen here for most imidazoles is considered to be nucleophilic (see later). Parallel plots of the log k_{im} *versus* pK_a are shown in Figure 1, and the extrapolated rate value (R_X) for each imidazole is obtained by taking the k_{im} value at pK_a 7.80 on the plot. In the nucleophilic reactions of 4-nitrophenyl acetate, Bruice and Lapinski

* Values of 0.47 (20°) and 0.83 (30°) 1 mol^{-1} s^{-1} in 1.64% dioxan–water at ionic strength 1.0 have been reported.[6]

† A value of 0.070 1 mol^{-1} s^{-1} is derived from data for 28.5% ethanol–water.[7]

[10] M. L. Bender and B. W. Turnquest, *J. Amer. Chem. Soc.*, 1957, **79**, 1652.

showed parallel Brönsted correlations with a common slope of 0.80 for different types of bases, and the correlations included a series of 2-unsubstituted imidazoles.[11] Jencks and Gilchrist also showed correlations with slope 0.80 for similar reaction series which comprised structurally related amine nucleophiles.[12] There are three points apart from the vertical line of pK_a 7.80 in Figure 1. These are for imidazole, 2-hydroxymethyl-, and 2,4,5-trimethyl-imidazole. The other points are situated near the line, so that if the slope is not exactly 0.80, deviations may be insignificant. Extrapolation for imidazole is valid, since the correlation has been demonstrated.[11] In all, a slope of 0.80 may be used in practice within a narrow range of pK_a (*ca.* 2 units). Figure 1 also shows that the hydroxy-group acted rather favourably in catalysis in spite of the larger steric requirement than that for hydrogen. The rate acceleration due to a neighbouring hydroxy-group was observed in several cases.[13-15] Some of these were explained in terms of a microscopic solvent effect.[13] The small accelerations here, if any, may be ascribed to the similar effect in nature. A measure of the steric

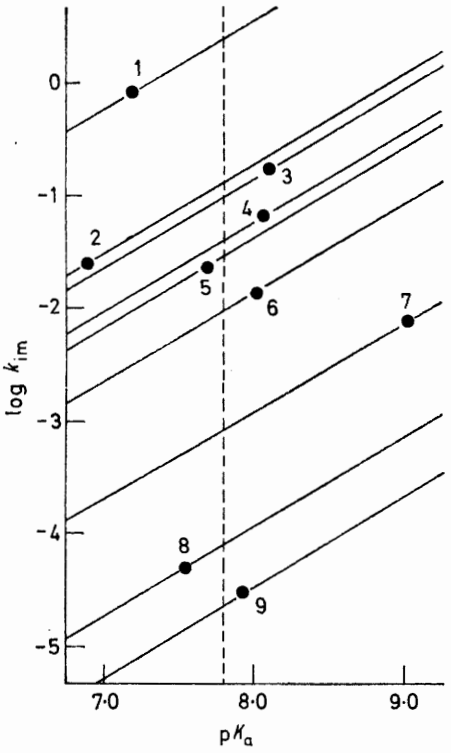

FIGURE 1 Parallel Brönsted plots to provide extrapolated rate values of substituted imidazoles having hypothetical pK_a of 7.80. A common slope of 0.80 is assumed. For key, see Table 1

effect of a substituent in the imidazole base is estimated by equation (2) where R_X and R_H represent the extrapolated rate value of a substituted and of the parent imidazole, respectively. Table 1 also contains values of

$$\text{measure of steric effect} = \log(R_X/R_H) \qquad (2)$$

R_X and of $\log(R_X/R_H)$. A plot of $\log(R_X/R_H)$ values *versus* the Taft steric constant parameters [16] is shown in

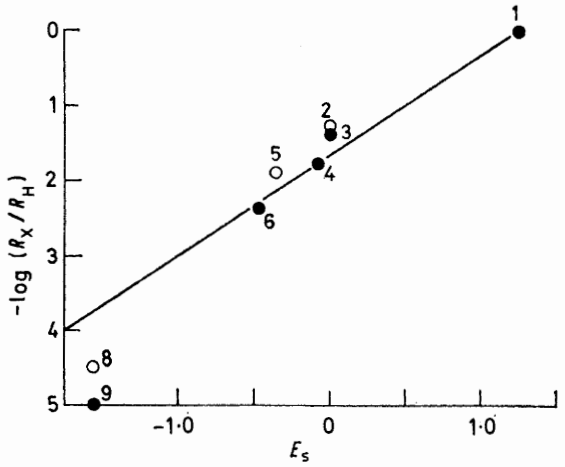

FIGURE 2 Plot of $\log(R_X/R_H)$ *versus* Taft E_s parameter: E_s values are given in ref. 16; hydroxyalkyl groups (○) are tentatively plotted at the same scale of the corresponding alkyl groups. For key, see Table 1

Figure 2. The correlation is rather good except for the t-butyl group. Hydroxylalkyl groups are tentatively plotted on the same scale as the corresponding alkyl groups. A similar result was obtained for a plot against the υ parameter defined by Charton.[17] E_s is a parameter for X derived from the acid hydrolysis of a series of esters XCO_2R.[16] The way in which the substituent X exerts its influence in the transition state is probably different from that of the 2-substituent for nucleophilic catalysis, since X is directly bonded to the electrophilic carbonyl centre whereas the 2-substituent is at the sp^2 carbon atom next to the nucleophilic centre. The sensitivity to the Taft constant of the present reaction is **1.33** from the slope of the plot in Figure 2, although the t-butyl derivatives deviate considerably. A value of 1.4 was reported for the imidazole catalysed hydrolysis of 4-nitrophenyl esters.[6] This coincidence may be ascribed to the similar nature of the transition states in these reactions.

For the mechanistic investigation, the solvent isotope effect alone is not a decisive criterion, since the effect is known to have several origins.[18,19] It is generally accepted, however, that an isotope effect (k_{im}^H/k_{im}^D) of near unity is taken as an indication of a nucleophilic

[11] T. C. Bruice and R. Lapinski, *J. Amer. Chem. Soc.*, 1958, **80**, 2265.
[12] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.
[13] T. C. Bruice and S. J. Benkovic, ref. 1, p. 146.
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[15] B. Capon, S. T. McDowell, and W. V. Raftery, *J.C.S. Perkin II*, 1973, 1118.
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[19] W. P. Jencks, ref. 3, p. 243.

mechanism while a value >2 is evidence for a general base mechanism.[2] The value of 1.0 for 2-isopropylimidazole indicates that no mechanistic changeover occurs in the substituent series from 2-H to 2-Pr^i, despite the considerable decrease in k_{im}. The negligible isotope effect (1.15) found for 4-nitrophenyl pivalate led to the conclusion that no mechanistic change occurred for a large variation of the steric bulk in the acyl portion.[6] From Table 2, the nucleophilic mechanism is similarly assigned to 2-hydroxymethylimidazole, but the slightly large isotope effects for 2,4,5-trimethyl- and 2-(1,1-dimethyl-2-hydroxyethyl)-imidazoles are considered as a borderline case for mechanistic discrimination. In a case where both general base and nucleophilic mechanisms operate concurrently, the isotope effect might become <2. Effects of 1.8 and 1.9 have been reported for the acetate-catalysed hydrolysis of 2,4-dinitrophenyl and 4-nitrophenyl acetates, and it was shown that the nucleophilic pathway involved was 71 and 70%, respectively, for the total catalysed reaction.[20]

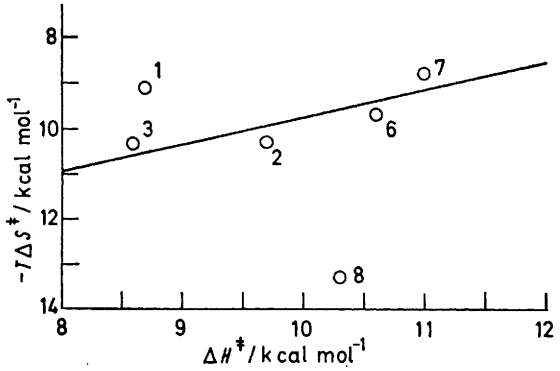

FIGURE 3 Plot of $-T\Delta S^{\ddagger}$ against $\Delta H^{\ddagger}$ at 30°. For key, see Table 2

Among activation parameters, $\Delta S^{\ddagger}$ for 2-(1,1-dimethyl-2-hydroxyethyl)imidazole is larger and more negative. The general base mechanism which entails a water molecule as well as the substrate and catalyst molecules at the transition state usually shows a large negative entropy of activation.[8,20] The data in Table 2 are further analysed in terms of the isokinetic relationship.[21] The plot of $-T\Delta S^{\ddagger}$ *versus* $\Delta H^{\ddagger}$ is shown in Figure 3. In order to correlate four points out of six a straight line was drawn, although it is difficult to be certain that any real correlation exists. The three points near the line represent 2-methyl-, 2-isopropyl-, and 2-hydroxymethyl-imidazoles, respectively, and all of them have been indicated to act as the nucleophilic catalyst. So that it seems likely that the fourth point, 2,4,5-trimethylimidazole, is also nucleophilic, despite its sizeable isotope effect. Imidazole itself deviates above the line, which might be interpreted to reflect an entropically more favourable case among the substituted imidazoles. The point for 2-(1,1-dimethyl-2-hydroxyethyl)imidazole is far below the line, suggesting a mechanism different from nucleophilic catalysis. Together with the significant isotope effect, it seems reasonable to conclude that the mechanism involves general base catalysis at least partially though not exclusively. In line with this, no intermediate formation was detected in the spectral scan during hydrolysis.*

From the present study, it can be said that a systematic change of the substituent in the 2-position of imidazole leads to a gradual decrease in the nucleophilic reactivity, approaching almost negligible activity for the t-butyl group. This is different from the weakly nucleophilic pyridine series where introduction of a 2-methyl group virtually inhibited catalytic activity toward the same substrate.[8] It might be expected that reduction of nucleophilic reactivity by 4—5 orders of 10 would result in a mechanistic changeover from nucleophilic to general base catalysis, the latter usually being overshadowed [8,20] by the former. However, it is also known that when steric bulk is present general base activity is also decreased, though moderately, as observed with pyridine bases.[22] The combined effects of the rate retardation by steric bulk and of the slight acceleration by a hydroxy-group may be a partial occurrence of the general base, as observed with 2-(1,1-dimethyl-2-hydroxyethyl)imidazole.

EXPERIMENTAL

4-Nitrophenyl acetate was recrystallized twice from ether, m.p. 76—77°. Deuterium oxide (Merck; Uvasol) was of minimum 99.75% purity. Water and deuterium oxide were glass distilled before use. Imidazole was twice recrystallized from benzene, m.p. 88—89°. The following three imidazoles were obtained from Shikoku Fine Chemicals Ind. Ltd., Tokyo, and purified by recrystallization from benzene or petroleum–benzene : 2-methylimidazole, m.p. 144—145° (lit.,[23] 144°); 2-ethylimidazole, m.p. 83—83.5° (lit.,[23] 79—80°); 2-isopropylimidazole, m.p. 131—132° (lit.,[23] 129°). 2,4,5-Trimethylimidazole, m.p. 131—132° (lit.,[24] 132—133°) and 2-(hydroxymethyl)imidazole, m.p. 112—113° (lit.,[25] 112°) were prepared according to the literature.

2-(1,1-*Dimethyl*-2-*hydroxyethyl*)*imidazole*.—To a solution of 2,2-dimethyl-3-hydroxypropionaldehyde (51 g, 0.50 mol) in ether–ethanol (50% v/v; 100 ml) was added an aqueous glyoxal solution (40%, 73 g). To this mixture was added ammonia (28%, 81 ml) slowly under stirring through a capillary dropping funnel over 3 h at −10°. The resulting mixture was kept at room temperature for 12 h, and then evaporated under reduced pressure below 50° to leave a

* This is weak evidence, since it is also possible that only an intermediate accumulation was not observed because of slowness of the reaction.

[20] D. G. Oakenfull, T. Riley, and V. Gold, *Chem. Comm.*, 1966, 385; V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc.* (*B*), 1968, 515.

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dark syrup, which was extracted into acetone (300 ml). The extract was treated with charcoal and concentrated to give a crude solid product. The product was recrystallized from acetone and dissolved in the minimum volume of acetone. The acetone solution was passed through an alumina column (3 × 10 cm) to give a colourless solution. The *product* was obtained from the solution (23 g, 33%), m.p. 117—118°, δ($CDCl_3$) 1.20 (6 H, s), 3.57 (2 H, s), and 6.90 (2 H, s) (Found: C, 59.9; H, 8.6; N, 20.0. $C_7H_{12}N_2O$ requires C, 60.0; H, 8.6; N, 20.0%).

2-(2-*Hydroxypropyl*)*imidazole*.—To a solution of 3-hydroxybutyraldehyde (b.p. 58° at 7 mmHg; 86 g, 0.98 mol) and the glyoxal solution (142 g) in ethanol (400 ml) was added ammonia (200 ml) dropwise under stirring in 4 h at −10°. The mixture was kept at room temperature for 12 h, followed by reflux for 1 h. Evaporation of the solvents under reduced pressure left a dark oily substance. This was dried by azeotropic distillation from benzene–ethanol solution (5 : 6 v/v; 550 ml) and heated further (140° at 5 mmHg) to remove the unchanged aldehyde. A coloured viscous oil which remained was dissolved in hot acetone. Upon standing the acetone solution, a crude solid product was obtained (34 g). After similar work-up as described above, the pure product was obtained (26 g, 21%), m.p. 93—94°, δ($CDCl_3$) 1.23 (3 H, d), 2.80 (2 H, d), 4.16 (1 H, m), and 6.90 (2 H, s) (Found: C, 57.1; H, 8.0; N, 22.1. $C_6H_{10}N_2O$ requires C, 57.1; H, 8.0; N, 22.2%).

2-*t*-*Butylimidazole*.—To a magnetically stirred mixture of 2,2-dimethylpropionaldehyde in ether (30%; 50 g, 0.17 mol) and the glyoxal solution (30 g), ammonia (45 ml) was added slowly during 3 h at −5°, and the mixture was left overnight at room temperature. Crystals which separated were collected (18.2 g, 84%). The product was recrystallized from acetone, m.p. 226—227° (lit.,[26] 176—180°), δ($CDCl_3$) 1.40 (9 H, s) and 6.92 (2 H, s) (Found: C, 67.9; H, 9.7; N, 22.7. Calc. for $C_7H_{12}N_2$: C, 67.7; H, 9.7; N, 22.6%).

Imidazole Buffers.—These were prepared by partial neutralization of an appropriate imidazole free base with constant boiling hydrochloric acid. The ionic strength was kept constant (1.0) by addition of KCl. The D_2O buffer was obtained by dissolving in D_2O a deuterium-exchanged imidazole and its deuteriochloric acid salt.

The pK_a *of Imidazoles*.—This was determined by measuring the pH value at half neutralization at ionic strength of 1.0 and 30° with a Toadenpa HM 20B pH meter.

Kinetic Method.—The hydrolysis of 4-nitrophenyl acetate was followed by observing the liberation of 4-nitrophenolate anion at 400 nm with a Hitachi 124 spectrophotometer. A constant temperature (±0.1°) was maintained by circulation of water through the automatic exchange cell holder. To a buffer solution (3.0 ml) in a cuvette was added the ester in acetonitrile (0.025 ml) with vigorous stirring. The initial concentration of the ester was 1×10^{-4}M, and imidazole free base concentrations were >0.01M, so that pseudo-first-order reaction conditions with imidazole bases were maintained. Each rate was measured in triplicate. The first-order rate constant (k_{obs}) was obtained as the slope of the plot of $\ln[(OD_0 - OD_\infty)/(OD_t - OD_\infty)]$ *versus* time. Good first-order dependence was observed for more than two half-lives in every kinetic run. Errors were estimated at < ±5% for most k_{obs} values. To obtain the second-order rate constant (k_{im}), three different buffer concentrations were usually used in the ranges of the free base concentration (0.01—0.1M). The pH of the solutions was measured before and after each kinetic run and was found to remain constant (±0.01 pH unit).

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