hexadecane in 60% yield based on GC comparison with standard mixtures of eicosane and hexadecane. The same procedure using 2 gave 47% hexadecane. Neither heating at 50 °C nor use of 3 equiv of octyllithium significantly changed the amount of hexadecane produced in these experiments.

Treatment of a stirred solution of 1 (231.2 mg, 0.797 mmol) and eicosane (73.8 mg, 0.262 mmol) in 3.0 mL of THF in a septum-protected, 3-necked flask under argon with butyllithium (0.25 mL of 1.6 M solution in hexane, 0.40 mmol) and octyllithium (0.48 mL of 0.83 M solution in diethyl ether, 0.40 mmol), added simultaneously from opposite necks of the reaction flask over 20 min and workup after 30 min, gave hexadecane in 40% yield. Dodecane was essentially absent (<0.5%). No attempt was made to separate octane from the solvent. When a similar experiment was carried out using identical amounts of ocytllithium and butyllithium solutions which were premixed then added to the solution of 1, 0.11 mmol of hexadecane and 0.13 mmol of dodecane were produced.

Phenyllithium (0.2 mL of 1.0 M solution in hexane, 0.2 mmol) was added to 1 (57.8 mg, 0.199 mmol) in 1.0 mL of THF and the mixture sealed in an evacuated ampule and heated at 50 °C for 48 h. The usual workup returned 53.3 mg of 1 with no GC- or NMR-detectable impurities (<2% biphenyl). Parallel results were obtained using 2.

Effect of the Leaving Group in the Hydrolysis of *N*-Acylimidazoles. The Hydroxide Ion, Water, and General Base Catalyzed Hydrolysis of *N*-Acyl-4(5)-nitroimidazoles

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The second-order rate constants k_{OH} for hydroxide ion catalyzed hydrolysis of *N*-acylimidazoles substituted in the imidazole group show only a moderate dependence on the pK_a of the leaving group ($\beta_{lg} = -0.28$), which indicates that there is little C–N bond breaking in the transition state. In this reaction the transition state must resemble the reactants. A plot of log k_{OH} vs. σ_p, the Hammett substituent constant ($\sigma_p = 0.778$ with NO_2), for hydrolysis of a series of *N*-(3,3-dimethylbutyryl)-4(5)-substituted-imidazoles, is linear ($r = 0.99$) with a slope of 1.9. The pK_a of the conjugate acid of *N*-acylbenzimidazoles is ~2 in contrast with a value of ~4 with corresponding *N*-acylimidazoles. The apparent hydronium ion catalyzed hydrolysis reactions of *N*-acylbenzimidazoles are accordingly ~100-fold slower than the corresponding reactions of analogous *N*-acylimidazoles, and the pH-independent reactions of the *N*-acylbenzimidazoles are 5–10-fold slower. The most likely mechanism for the pH-independent hydrolysis of the *N*-acylbenzimidazoles is concerted nucleophilic attack and protonation of the leaving group by water. The rates of hydrolysis of *N*-acyl-4(5)-nitroimidazoles are pH-independent from pH 6 to at least pH 1, and the reactions are considerably faster than those of the corresponding unsubstituted *N*-acylimidazoles. Thus, the reactions of the nitro derivatives are water reactions in which the ease of nucleophilic attack is of greater importance than protonation of the leaving group. General base catalysis by buffer bases occurs in the hydrolysis of *N*-(3,3-dimethylbutyryl)-4(5)-nitroimidazole, and the Brønsted β coefficient is 0.5 for the reactions of oxygen anions. The strict general base catalysis by acetate ion is in contrast with the apparent general acid catalysis in acetate buffers in the hydrolysis of *N*-acetylimidazole. The second-order rate constant for imidazole-catalyzed release of 4-nitroimidazole shows a large positive deviation from the Brønsted plot. That imidazole acts as a nucleophile was demonstrated by kinetically and spectrally identifying an intermediate, *N*-(3,3-dimethylbutyryl)imidazole, which hydrolyzes slowly.

The hydrolysis reactions of *N*-acylimidazoles have been actively studied[2-13] in view of the likely role of histidine in biological acyl group transfer reactions. Hydroxide ion and hydronium ion catalysis has been observed in these reactions, and a pH-independent reaction occurs near pH 6–7. The hydrolysis reactions are subject to general acid–general base catalysis. In addition, neighboring carboxyl[14] and acetamido[15] group participation occurs in suitable derivatives. Thus, most of the important pathways encountered in hydrolytic reactions[2] are exemplified in the reactions of *N*-acylimidazoles.

Hydrolysis reactions that are independent of pH have also been detected in the hydrolysis of acyl activated esters[16-18] and esters having a leaving group of low pK_a.[2,19,20] There is kinetic ambiguity in these reactions and in the similar reactions of *N*-acylimidazoles in that they could involve water catalysis, attack of OH^- on a protonated species, or other mechanistic possibilities. Likewise, there can be kinetically equivalent possibilities in general acid–base catalysis. For example, the apparent general acid catalysis by acetic acid in the hydrolysis of *N*-acetylimidazole[4] could reflect a reaction of acetic acid and neutral

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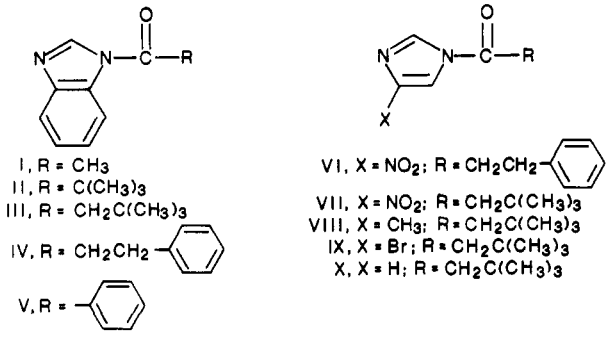
N-acetylimidazole or a reaction of acetate ion and N-acetylimidazolium ion. The pK_a values of the conjugate acids of N-acylimidazoles are approximately 4,[4,15] i.e., in an experimentally accessible pH range, unlike those of usual esters and amides. Therefore, variation of the leaving group of N-acylimidazoles by appropriate substitutions that will affect the pK_a of the conjugate acid should give information on the mechanisms of these important reactions. There have been no previous detailed kinetic studies of the hydrolysis of such substituted N-acylimidazoles. We have therefore studied the reactions of a series of N-acylbenzimidazoles and N-acyl-4(5)-substituted-imidazoles.



The unambiguous demonstration of a water-catalyzed reaction in the hydrolysis of an amide would allow an assessment of the structural requirements for such a reaction.[21] That has now been possible with the nitro-substituted compound VII for which the leaving group, 4-nitroimidazole, has a pK_a of 9.1.[22]

Experimental Section

Materials. Benzimidazole, 4-methylimidazole, and 4-nitroimidazole were from Aldrich. 4-Bromoimidazole was prepared by methods previously described.[23] The imidazole employed was from Aldrich and was purified by sublimation before use. Acid chlorides were prepared from the commercially obtained carboxylic acids by reaction with thionyl chloride. After removal of the excess thionyl chloride the acid chlorides were purified by distillation.

The N-acylbenzimidazoles I–V were prepared by dissolving 2 equiv of benzimidazole in dry THF with heating and slowly adding 1 equiv of the appropriate acid chloride dissolved in dry THF. The mixture was generally refluxed overnight with stirring. The precipitated benzimidazole hydrochloride was removed by filtration. The filtrate was then rotary evaporated, and the residue was recrystallized from an appropriate solvent; N-acetylbenzimidazole (I) melted at 110–111 °C after recrystallization from hexane (lit.[3b] mp 113 °C). N-(Trimethylacetyl)benzimidazole (II) melted at 71 °C after recrystallization from hexane. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.28; H, 6.93; N, 13.86. Found: C, 71.25; H, 6.95; N, 13.88. N-(3,3-Dimethylbutyryl)benzimidazole (III) melted at 54–55 °C after recrystallization from hexane. Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.22; H, 7.40; N, 12.96. Found: C, 72.02; H, 7.42; N, 12.90. N-(β-Phenylpropionyl)benzimidazole (IV) melted at 126–127 °C after recrystallization from cyclohexane. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.71; H, 5.68; N, 11.19. N-Benzoylbenzimidazole (V) melted at 91–92 °C after recrystallization from a chloroform–hexane mixture (lit.[24] mp 93–94 °C). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.61; H, 4.76; N, 12.66.

N-(β-Phenylpropionyl)-4(5)-nitroimidazole (VI) was prepared by adding 1 equiv of 4-nitroimidazole and 1 equiv of triethylamine in dry acetonitrile to 1 equiv of the appropriate acid chloride in acetonitrile and stirring the mixture for 48 h. The mixture was then filtered, and the filtrate was rotary evaporated. Dry chloroform was added to the residue, and the mixture was filtered. Crystallization occurred upon addition of hexane. After recrystallization from a chloroform–hexane mixture the compound melted at 150–151 °C. Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.48; N, 17.14. Found: C, 58.41; H, 4.54; N, 16.93.

N-(3,3-Dimethylbutyryl)-4(5)-nitroimidazole (VII) was prepared by adding 2 equiv of 4-nitroimidazole to a freshly dried and distilled sample of acetonitrile. This mixture was refluxed until the 4-nitroimidazole was completely dissolved. One equivalent of 3,3-dimethylbutyryl chloride in acetonitrile was then added dropwise. The mixture was refluxed for 3 days. The mixture was then cooled and filtered, and the acetonitrile was removed by rotary evaporation. The residue was dissolved in dry THF, and the solution was heated and then cooled and filtered. The THF was removed by rotary evaporation. The residual solid after several recrystallizations from hexane melted sharply at 105 °C. Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.16; N, 19.90. Found: C, 51.04; H, 6.13; N, 19.99.

N-(3,3-Dimethylbutyryl)-4(5)-methylimidazole (VIII) and N-(3,3-dimethylbutyryl)-4(5)-bromoimidazole (IX) were prepared by the same general method outlined for the N-acylbenzimidazoles. The methyl derivative (VIII) was an oil which would not crystallize. The hydrochloride salt was therefore prepared by dissolving the material in ether and passing in dry HCl gas. After recrystallization from chloroform–hexane the compound melted at 115–116 °C. Anal. Calcd for $C_{10}H_{17}ClN_2O$: N, 12.93. Found: N, 1293. The bromo-substituted compound (IX) melted at 66–68 °C after recrystallization from hexane. Anal. Calcd for $C_9H_{13}BrN_2O$: C, 44.08; H, 5.31; N, 11.43. Found: C, 43.79; H, 5.27; N, 11.41. The unsubstituted derivative N-(3,3-dimethylbutyryl)imidazole (X) was the same as previously reported.[6] Two isomers could result from the method of preparation of VI–IX (the 4- and 5-substituted isomers).

All other chemicals were reagent grade. Amine buffer components were freshly distilled or recrystallized before use.

Kinetic Methods. The rates of hydrolysis of the N-acylbenzimidazoles and the N-acyl-4(5)-substituted-imidazoles were measured spectrophotometrically in H_2O at 30 °C by following the large absorbance decrease due to disappearance of the substrate at wavelengths between 240 and 260 nm, with the exception of the nitro-substituted compounds VI and VII with which the absorbance increase at 320 nm was followed. The rate measurements were carried out on a Beckman 25 or Pye Unicam SP8-100 recording spectrophotometer. In these determinations 17–25 μL of an acetonitrile stock solution of substrate was added to 2–3 mL of buffer in the reaction cuvette maintained at 30 °C. The reactions were pseudo-first-order for at least 4 half-lives. Reactions that were too rapid to be monitored with a conventional spectrophotometer were followed using a Durrum–Gibson stopped-flow spectrophotometer Model D-110. In the study of these reactions the substrate was dissolved at the desired concentration in distilled water containing 0.1 M KCl. This solution was introduced into one of two identical drive syringes. The other syringe contained the appropriate buffer. Optical density changes after mixing were recorded on a Hewlett-Packard storage oscilloscope (Model 1207B). Reaction mixture pH values were obtained at 30 °C with a Radiometer Model 22 or Beckman 3500 pH meter.

Results

In Figure 1 is presented a plot of log k_{obsd} vs. pH for hydrolysis of N-acetylbenzimidazole (I) in H_2O at 30 °C and μ = 0.1 M. The values of k_{obsd} follow eq 1, where k_1

$$k_{obsd} = k_1\left[\frac{a_H}{K_a + a_H}\right] + (k_0 + k_{OH}(OH^-))\left[\frac{K_a}{K_a + a_H}\right] \quad (1)$$

is the rate constant for hydrolysis of the protonated species, k_{OH} is the second-order rate constant for hydroxide ion catalysis, k_0 is the rate constant of the pH-independent reaction, and K_a is the dissociation constant of the con-

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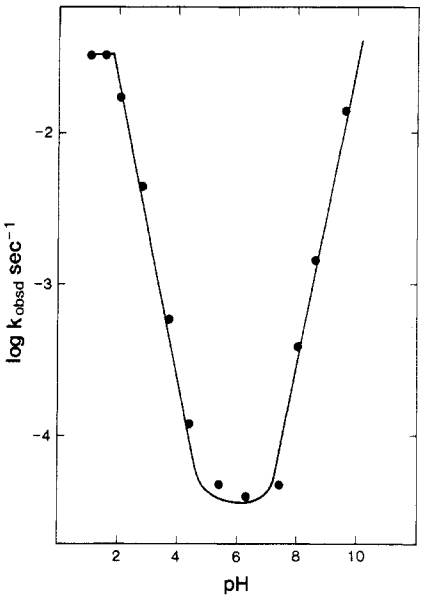

Figure 1. Plot of log k_{obsd} vs. pH for hydrolysis of *N*-acetylbenzimidazole (I) at 30 °C in water with μ = 0.1 M (KCl). The values of k_{obsd} were obtained in HCl solutions or by extrapolation to zero buffer concentration.

Table I. Rate Constants for Hydrolysis of *N*-Acylbenzimidazoles in H_2O at 30 °C and μ = 0.1 M

compd	k_H,[a] M^{-1} s^{-1}	k_1, s^{-1}	k_0, s^{-1}	k_{OH}, M^{-1} s^{-1}	pK_a
I	2.5	0.033	3.0×10^{-5}	204	1.8
II	30	0.30	1.7×10^{-4}	612	2.0
III	0.10		2×10^{-5}	68	
IV	10		4.9×10^{-5}	340	
V	1.35	0.02	4.1×10^{-5}	143	1.8

[a] $k_H = k_1/K_a$.

jugate acid. The values of k_{obsd} were obtained in HCl solutions or by extrapolation to zero buffer concentration. The plot is similar to that for hydrolysis of imidazole[4] except that the hydronium ion catalyzed and pH-independent reactions are slower and the apparent pK_a of the conjugate acid is 1.8 rather than 3.6. The rate constants are given in Table I for hydrolysis of the *N*-acylbenzimidazoles I–V.

The values of k_{obsd} for the hydrolysis reactions of *N*-acylimidazoles are also given by eq 1. The rate constants for hydrolysis of a series of *N*-(3,3-dimethylbutyryl)-4-(5)-substituted-imidazoles with the substituent groups NO_2, Br, H, and CH_3 are given in Table II. It can be seen that there is an appreciable effect of the leaving group in the OH^--catalyzed reaction and in the pH-independent reaction governed by k_0. A plot of log k_{OH} vs. σ_p, the Hammett substituent constant,[25] in Figure 2 is linear with a slope (ρ) of 1.9 (r = 0.99).

In Figure 3 the plot is shown of log k_{obsd} at zero buffer concentration vs. pH for hydrolysis of *N*-(β-phenylpropionyl)-4(5)-nitroimidazole (VI) and *N*-(3,3-dimethylbutyryl)-4(5)-nitroimidazole (VII). In both cases k_{obsd} is pH-independent from pH 1–6. The D_2O solvent isotope effect ($k_0^{H_2O}/k_0^{D_2O}$) in the hydrolysis of VI and VII is 3.5. The rate constants for the hydrolysis of VI and VII are given in Table II along with those of other *N*-acylimidazoles for purposes of comparison.

The hydrolysis of these compounds is subject to buffer catalysis. Figure 4 presents a plot of k_{obsd} for the hydrolysis of VII vs. the total concentration of acetate buffer (HAc + OAc^-) at three constant pH values. The slope increases as the pH increases, which shows that the base component of the buffer (acetate ion) is catalytically active. A plot of k_{total} (the slope of the plot of k_{obsd} vs. total acetate buffer concentration) vs. the percentage of CH_3COO^- in the buffer solution (Figure 5) is linear and extrapolates to zero at zero CH_3COO^- concentration, thereby showing that no general acid catalysis is occurring. The second-order rate constants for general base catalysis of the hydrolysis of VII are given in Table III. The Brønsted plot of log k_B vs. the pK_a of

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Table II. Rate Constants for Hydrolysis of Substituted *N*-Acylimidazoles in H_2O at 30 °C and μ = 0.1 M

compd	k_H, M^{-1} s^{-1}	k_1, s^{-1}	k_0, s^{-1}	k_{OH}, M^{-1} s^{-1}	pK_a
N-acetylimidazole[a]	183	0.046	8.3×10^{-5}	316	3.6
N-(trimethylacetyl)-imidazole		0.53[b]	1.1×10^{-3}	533[c]	
N-(β-phenylpropionyl)-imidazole[d]	500		3.0×10^{-4}	860	3.5
N-benzoylimidazole			4.7×10^{-4}	350	
VI			1.0×10^{-2}	28000	
VII			1.25×10^{-4}	6800	
VIII	12.5	0.001	2×10^{-5}	88.4	4.0
IX	0.019			540	
X	11.0	0.002	2.0×10^{-5}	216	3.8

[a] Reference 4 (25 °C, μ = 0.2 M). [b] Reference 7. [c] Reference 6. [d] Reference 15.

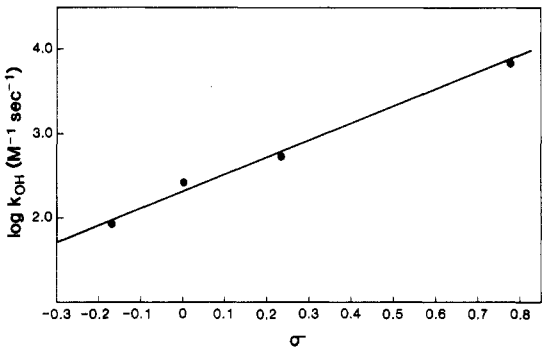


Figure 2. Plot of log k_{OH} for hydrolysis of *N*-(3,3-dimethylbutyryl)-4(5)-substituted-imidazoles in H_2O at 30 °C (μ = 0.1 M) vs. σ_p, the Hammett substituent constants.

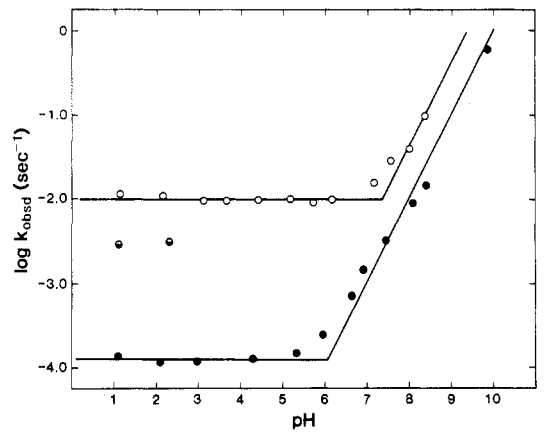


Figure 3. Plots of log k_{obsd} vs. pH for hydrolysis of *N*-(β-phenylpropionyl)-4(5)-nitroimidazole (VI) (○) and *N*-(3,3-dimethylbutyryl)-4(5)-nitroimidazole (VII) (●) at 30 °C in water with μ = 0.1 M (KCl) or in D_2O (◒). The values of k_{obsd} were obtained in HCl solutions or by extrapolation to zero buffer concentration.

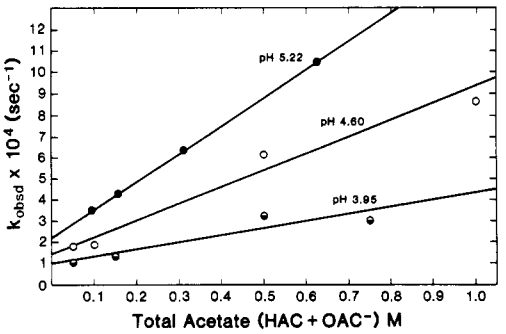


Figure 4. Plot of k_{obsd} for hydrolysis of N-(3,3-dimethylbutyryl)-4(5)-nitroimidazole vs. the total concentration of acetate buffer (HAC + OAC^-) at 30 °C in water with μ = 0.5 M.

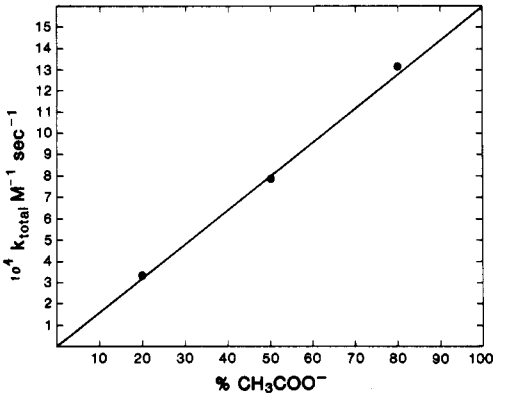


Figure 5. Plot of k_{total} (slope of a plot of k_{obsd} vs. total acetate buffer concentration) vs. the percentage of acetate ion in the buffer for the hydrolysis of N-(3,3-dimethylbutyryl)-4(5)-nitroimidazole in H_2O at 30 °C with μ = 0.5 M (KCl).

Table III. Second-Order Rate Constants for General Base Catalyzed Hydrolysis of N-(3,3-Dimethylbutyryl)-4(5)-nitroimidazole in H_2O at 30 °C (μ = 0.5 M)

base	pK_a	k_B, M^{-1} s^{-1}
H_2O	−1.74	2.25×10^{-6}
chloroacetate	2.72	1.81×10^{-4}
formate	3.60	8.99×10^{-4}
acetate	4.60	1.60×10^{-3}
pyridine	5.25	4.10×10^{-3}
MES[a]	6.10	1.10×10^{-3}
cacodylate	6.19	4.76×10^{-2}
2,6-lutidine	6.60	2.52×10^{-4}
HPO_4^{2-}	6.75	2.46×10^{-2}
imidazole	7.05	2.26
N-ethylmorpholine (NEM)	7.70	1.23×10^{-2}

[a] 2-morpholinoethanesulfonic acid.

the conjugate acid of the base catalyst is shown in Figure 6. Statistical corrections were not employed. The slope β for a least-squares line drawn through all the points is 0.51. A line through the points for the oxygen bases has a slope of 0.50 (r = 0.98). Imidazole acts as a nucleophile in the reaction in which 4-nitroimidazole is released with an absorbance increase at 320 nm. An intermediate N-acylimidazole is formed which hydrolyzes slowly with a decline in absorbance at 245 nm. The values of k_{obsd} for this reaction (30 °C) in imidazole buffers were similar to those expected for hydrolysis of N-(3,3-dimethylbutyryl)imidazole, k_{Im} = 0.0004 M^{-1} s^{-1}.[6]

Discussion

The log k_{obsd} vs. pH profiles for the hydrolysis of N-acylbenzimidazoles (e.g., Figure 1) are similar in shape to those for hydrolysis of corresponding N-acylimidazoles.[2,4,15]

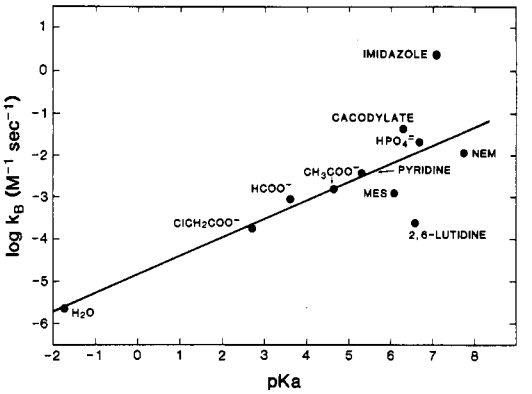
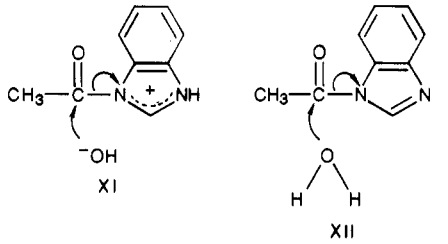


Figure 6. Plot of log k_B for general base catalyzed hydrolysis of N-(3,3-dimethylbutyryl)-4(5)-nitroimidazole vs. the pK_a of the conjugate acid of the catalyzing base at 30 °C.

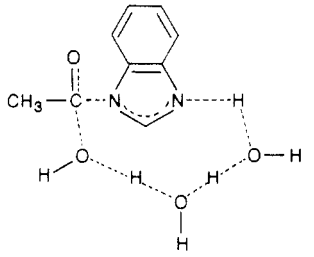
However, the rate constants k_H and k_0 for N-acylbenzimidazole hydrolysis are considerably less than those obtained for hydrolysis of the N-acylimidazoles having the same acyl groups. The k_H values for hydrolysis of the benzimidazole derivatives are 50–100-fold less and k_0 values are 5–10-fold less than those of the corresponding N-acylimidazoles. These differences can in part reflect the relatively low pK_a of the conjugate acid of an N-acylbenzimidazole. The bend in the profile of Figure 1 at low pH indicates that the pK_a of the N-acetylbenzimidazole conjugate acid is 1.8, whereas that of the N-acetylimidazole conjugate acid is 3.6.[2,4] Thus, the k_H of I is relatively small because $k_H = k_1/K_a$ and the k_1 values are reasonably similar for the two types of compounds (Tables I and II). The differences in the k_H values for the N-acylbenzimidazoles and the N-acylimidazole derivatives (100-fold) are in complete accord with the differences in pK_a. Likewise, the small k_0 values of the N-acylbenzimidazoles are also in accord with a contribution from a mechanism involving attack of OH^- on the protonated species (XI) rather than



the kinetically equivalent attack of H_2O on the neutral species (XII), although it will be noted that in contrast with k_H the differences in k_0 for the benzimidazole and imidazole derivatives are much less than the differences in K_a. Thus, the variation in k_0 for the two types of compounds does not quantitatively reflect the smaller concentration of protonated species in the case of the N-acylbenzimidazole. It can be seen in Tables I and II that the fused benzene ring of the benzimidazole derivatives has little effect not only on the hydrolysis of the protonated species (k_1) but also in the OH^--catalyzed hydrolysis of the neutral species (k_{OH}). Both of these reactions involve nucleophilic attack. Therefore, it is reasonable that the benzene ring would also not greatly affect the ratio of rate constants in the pH-independent reaction if mechanism XI was occurring. Therefore, mechanism XI does not constitute the primary reaction pathway. The pK_a of the benzimidazole leaving group is 12.8 in comparison with 14.5 for imidazole.[26] Consequently, the relatively small magnitude of the

(26) Walba, H.; Isensee, R. W. J. Org. Chem. 1961, 26, 2789.

k_0 values for hydrolysis of the *N*-acylbenzimidazoles also cannot be readily explained in terms of mechanism XII or the related mechanism involving general base catalysis by a second molecule of water. A totally concerted process involving attack of a water molecule and simultaneous transfer of a proton to the leaving group (XIII) is in accord

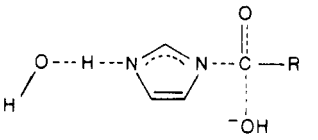


XIII

with the data and is consistent with the moderate effect of substitution on the k_0 values for *N*-(3,3-dimethylbutyryl)-4(5)-substituted-imidazoles (VII–X). In mechanism XIII, the expected rate-accelerating effect of a leaving group of lower pK_a will be compensated by the greater difficulty of proton transfer. A similar mechanism was suggested as a possibility in the hydrolysis of *N*-acetylimidazole,[5] 1-acetyl-1,2,4-triazole,[13b] and *N*-acetylbenzotriazole.[13c,d]

Steric bulk in the acyl group of an *N*-acylimidazole produces a smaller effect on the OH^--catalyzed hydrolysis reaction than in the hydrolysis of analogous *p*-nitrophenyl esters.[6] Branching at the β-carbon of the acyl group of an *N*-acylimidazole produces a relatively small rate retardation, and branching at the α-carbon produces a small rate acceleration in contrast with the large retarding effect of alkyl group substitution at both carbons in ester hydrolysis. It can be seen in Tables I and II that this pattern of effects also occurs with the benzimidazole derivatives; *N*-(3,3-dimethylbutyryl)benzimidazole (III) has a second-order rate constant k_{OH} that is 3-fold less than that of the *N*-acetyl derivative (I), but *N*-(trimethylacetyl)benzimidazole (II) has a k_{OH} that is 3-fold larger than that of I. Thus, the transition state is reached without appreciable steric hindrance to the approach of the nucleophile.

It may also be seen in Table II that the pK_a of the leaving group has only a moderate effect on the magnitude of k_{OH}, regardless of whether the leaving group is imidazole (pK_a = 14.50),[26] benzimidazole (pK_a = 12.8),[26] or 4-nitroimidazole (pK_a = 9.1).[22] When the acyl group is 3,3-dimethylbutyryl, nitro substitution in the imidazole ring increases k_{OH} only 31-fold in comparison with the unsubstituted compound (X). This corresponds to a β_{lg} (slope of a plot of log k_{OH} vs. the pK_a of the leaving group) of −0.28. Similarly, with the β-phenylpropionyl acyl group β_{lg} is −0.3. Consequently, there is little or no C–N bond breaking in the transition state. The β_{lg} of −0.28 is quite similar to that of −0.30 for acetate esters of substituted phenols,[27,28] with which it has been considered that nucleophilic attack at the carbonyl is the rate-determining step.[2] Likewise, the β_{lg} of −0.44 for alkaline hydrolysis of *N*-aryl-β-lactams has been attributed to rate-limiting formation of a tetrahedral intermediate.[29] It can be concluded that the transition state for OH^--catalyzed hydrolysis of *N*-acylimidazoles must resemble the reactants regardless of whether nucleophilic attack is concerted with C–N bond breaking or a tetrahedral intermediate is formed. Therefore, leaving group departure must be a facile process (nucleophilic attack will be rate determining if the reaction is concerted or if the leaving group departs from a tetrahedral intermediate faster than the intermediate reverts back to reactants). It is likely that the ease of C–N bond breaking is being enhanced by hydrogen bonding of water to N-3 (XIV).



XIV

A plot of log k_{OH} for hydrolysis of the *N*-(3,3-dimethylbutyryl)-4(5)-substituted imidazoles vs. σ_p, the Hammett substituent constant[25] for para substituent groups (Figure 2), is also nicely linear with a slope of 1.9 (r = 0.99) employing σ = 0.778 for NO_2. The meta substituent constants also provided a reasonable fit to the data (r = 0.896), although the correlation was not as good as that provided by the para substituent constants. The σ_I constants gave a still poorer fit. The ρ value for OH^--catalyzed hydrolysis of acetate esters of substituted phenols was found to be 1.1.[30] The Hammett treatment was, of course, developed for reactions of meta- and para-substituted benzene derivatives.[25,31,32] There is no reason to expect it to be applicable to other types of ring systems.[31] Nevertheless, the imidazole ring has aromatic properties,[33] and the linear relationship between the logarithms of the rate constants for hydrolysis of the *N*-acyl-4(5)-substituted-imidazoles and the σ constants is therefore of considerable interest. Such a relationship indicates that the substituent groups are influencing the reactions of the substituted *N*-acylimidazoles through a polar effect. Note in Figure 2 that there is no indication of a variable resonance or steric effect by the substituent group nor is the mechanism changing within the series. The ρ value must reflect a large influence of inductive electron withdrawal from the carbonyl. The Hammett relationship has been used previously to correlate the pK_a values of substituted imidazoles.[34,35]

***N*-(3,3-Dimethylbutyryl)-4(5)-nitroimidazole.** The plots of log k_{obsd} vs. pH for hydrolysis of the β-phenylpropionyl (VI) and 3,3-dimethylbutyryl (VII) derivatives of 4-nitroimidazole are characterized by pH-independent regions that extend from pH 6–7 to at least pH 1. Even at pH 1 there is no indication of any reaction of the protonated species. Therefore, the pK_a of the conjugate acid is less than 1.0. The value of k_0 for VI (10^{-2} s^{-1}) is fairly large in comparison with that of *N*-(β-phenylpropionyl)-imidazole (3.0×10^{-4} s^{-1}).[15] The rate-accelerating effect of a 4(5)-nitro group is smaller but still substantial with VII in comparison with X. Protonation of the leaving group by water, as in mechanism XIII, is clearly not as important as the increased ease of nucleophilic attack in the reactions of the nitro-substituted derivatives. The fast rate of the pH-independent reactions must also be due in part to the relatively low pK_a of the leaving group. Thus, the strong electron withdrawal in the leaving group will

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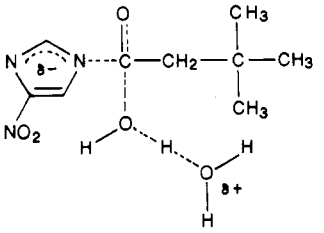
(28) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622.
(29) Procter, P.; Gensmantel, N. P.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1185.
(30) Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1963**, *85*, 1.
(31) Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191.
(32) Wells, P. R. *Chem. Rev.* **1963**, *63*, 171.
(33) Hofmann, K. *Imidazole and Its Derivatives*; Interscience Publishers: New York, 1953.
(34) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1980**, *27*, 241 and references therein.
(35) Charton, M. *J. Org. Chem.* **1965**, *30*, 3346.

allow both facile nucleophilic attack by the water and C–N bond breaking. Proton transfer does, however, occur in the reaction as shown by the D_2O solvent isotope effect ($k_0^{H_2O}/k_0^{D_2O}$ = 3.5) in the hydrolysis of VI and VII.[2] This very likely indicates that nucleophilic attack by water is being assisted by proton transfer to another water molecule (XV). Broad plateaus due to water-catalyzed reactions

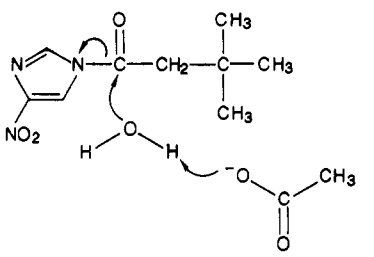


XV

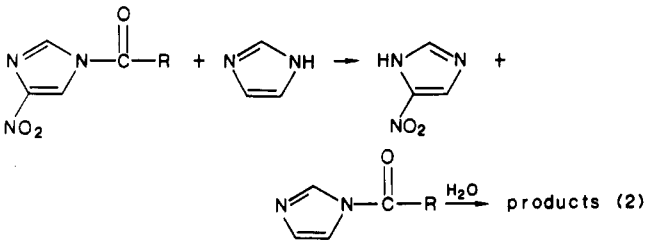
have previously been found in the hydrolysis of acyl activated esters,[2,16-18,36] e.g., di- and trihaloacetates,[16-18] carboxylic acid anhydrides,[2,37] and phenyl esters of picolinic acid.[19,20] In these cases it is very likely the electron deficiency of the carbonyl carbon that is the primary structural feature leading to the water-catalyzed reactions. Thus, the reactions of the nitro-substituted *N*-acylimidazoles can be reasonably regarded as also due to a carbonyl carbon of that type, i.e., one with considerable partial positive charge.

The hydrolysis reactions of VI and VII are markedly catalyzed by buffer. The reactions of VI are too rapid to allow a detailed study, and it was for that reason that the 3,3-dimethylbutyryl derivative was studied. The plot of Figure 5 for catalysis of the hydrolysis of VII by acetate buffer shows that it is only the base component of the buffer (CH_3COO^-) that is catalytically active. The lack of any general acid catalysis illustrates the relative unimportance of protonation of the leaving group in the hydrolysis of the nitro-substituted *N*-acylimidazoles. The general base catalysis can be contrasted with the apparent general acid catalysis in acetate buffers in the hydrolysis of *N*-acetylimidazole,[2,4] a reaction that may involve acetate ion catalysis of the hydrolysis of the N-protonated species. Both general base and general acid catalysis are observed in the imidazole-catalyzed hydrolysis of *N*-acylimidazoles.[6] The Brønsted plot of log k_B vs. the pK_a of the catalyzing base (Figure 6) has the small slope of 0.51, and various types of oxygen and nitrogen bases fit reasonably well on one line. If only the oxygen bases are included in the correlation, the slope is 0.50 (r = 0.98). Brønsted β coefficients of similar magnitude appear to be a characteristic of general base catalyzed ester hydrolysis reactions.[2,16,36] For example, in the general base catalyzed hydrolysis of ethyl dichloroacetate β is 0.47, and again various bases fit well on a single line. In contrast, much larger β values have been noted in nucleophilic reactions of phenolic esters.[28,38] Therefore, it is probable that general base catalysis by oxygen anions (XVI) is occurring in the hydrolysis of VII.

The point for imidazole in Figure 6 deviates positively from the Brønsted plot. This would be the case if imidazole were acting as a nucleophile. Imidazole catalysis occurs in the hydrolysis of *N*-acylimidazoles[2,4,5] by a general base mechanism, possibly because nucleophilic attack would simply regenerate the starting material. In the hydrolysis of VII, however, nucleophilic attack produces a different *N*-acylimidazole (eq 2) which subsequently

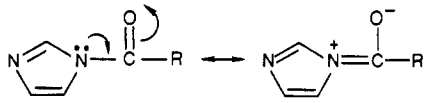


XVI



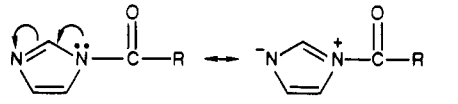
hydrolyzes. The appearance of 4-nitroimidazole was followed at 320 nm. At the conclusion of this reaction a second reaction could be observed at 245 nm, the absorbance maximum of *N*-(3,3-dimethylbutyryl)imidazole. The decline in absorbance at 245 nm gave a second-order rate constant for imidazole catalysis that was nearly identical with that of compound X.[6] Therefore, a nucleophilic mechanism for imidazole in the reactions of VII is conclusively established.

The rates of OH^--catalyzed hydrolysis of *N*-acylimidazoles are remarkably rapid in view of the pK_a of the leaving group. For example, the k_{OH} for OH^--catalyzed hydrolysis of *N*-acetylimidazole[4] is 316.6 M^{-1} s^{-1} at 25 °C, whereas the k_{OH} for hydrolysis of the reactive ester *p*-nitrophenyl acetate[39] is 14.8 M^{-1} s^{-1} at 25 °C, even though the pK_a of the imidazole leaving group is 14.5,[26] over 7 pK_a units greater than that of *p*-nitrophenol. The hydrolytic behavior of substituted *N*-acylimidazoles must be due in part to a large amount of partial positive charge on the carbonyl carbon. This indicates that there is little resonance interaction between N-1 and the carbonyl carbon (eq 3). Such a resonance interaction, which deactivates



(3)

the carbonyl, is typically important with usual types of amides, but in acylimidazoles there will be opposed resonance in which N-3 has net negative charge (eq 4). Mo-



(4)

lecular orbital calculations on *N*-acetylimidazole[40] have indicated that N-3 has a net negative charge of –0.23. On the other hand, it was calculated[40] that N-1 has a net positive charge of +0.475 and the carbonyl carbon has a net positive charge of +0.287.[41] As a consequence, nucleophilic attack at the carbonyl by H_2O, OH^-, or other nucleophiles will be a facile process, and the C–N bond will be easily broken. A partial negative charge on N-3 should promote hydrogen bonding with water, which will in turn facilitate expulsion of the leaving group. It is therefore

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(40) Pullman, B.; Pullman, A. *Quantum Biochemistry*; Wiley Interscience: New York, 1963; p 381.
(41) The net electronic charge will, of course, be influenced by the solvent.

probable that the rapid hydrolysis reactions of *N*-acylimidazoles, in contrast to those of usual amides, are due to the partial positive charges on the carbonyl carbon and N-1 and to the stabilized leaving group of the *N*-acylimidazoles. The importance of these features in the hydrolytic reactions is made clear by the observed effects of variation of the leaving group. Thus, these studies of leaving group effects in *N*-acylimidazole hydrolysis have given considerable insight into the various pathways for the hydrolysis of *N*-acylimidazoles.

Acknowledgment. This work was supported by a research grant from the National Science Foundation.

Registry No. I, 18773-95-0; I·HCl, 103959-14-4; II, 103959-11-1; II·HCl, 103959-15-5; III, 103959-12-2; III·HCl, 103959-16-6; IV, 103959-13-3; IV·HCl, 104013-72-1; V, 62573-86-8; V·HCl, 103959-17-7; VI, 103959-18-8; VII, 103959-23-5; VIII, 103959-19-9; VIII·HCl, 103959-21-3; IX, 103959-20-2; IX·HCl, 103959-22-4; CH_3COCl, 75-36-5; $(CH_3)_3CCOCl$, 3282-30-2; $(CH_3)_3CCH_2COCl$, 7065-46-5; $Phg(CH_2)_2COCl$, 645-45-4; PhCOCl, 98-88-4; H_2O, 7732-18-5; $H_2PO_4^-$, 14066-20-7; OH^-, 14280-30-9; MES, 4432-31-9; *N*-(3,3-dimethylbutyryl)imidazole, 4122-55-8; 4-methylimidazole, 822-36-6; 4-bromoimidazole, 2302-25-2; formate, 71-47-6; acetate, 71-50-1; benzimidazole, 51-17-2; 4-nitroimidazole, 3034-38-6; *N*-benzoylimidazole, 10364-94-0; chloroacetate, 14526-03-5; pyridine, 110-86-1; cacodylate, 75-60-5; 2,6-lutidine, 108-48-5; imidazole, 288-32-4; *N*-ethylmorpholine, 100-74-3.

Chemistry of Dioxiranes. 6. Electronic Effects in the Oxidation of Sulfides and Sulfoxides by Dimethyldioxirane[1]

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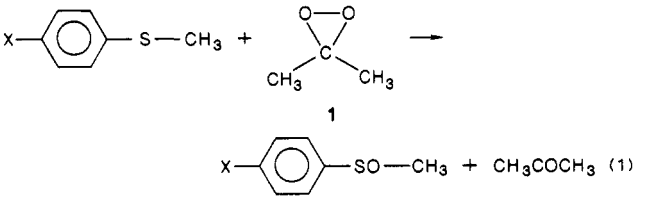
Dimethyldioxirane (1) oxidizes a series of aryl methyl sulfides to the corresponding sulfoxides. In a separate series of reactions the sulfoxides were oxidized by 1 to the corresponding sulfones. The relative rates of oxidation in both series were treated with the Hammett $\rho\sigma$ relationship. The oxidations were found to be electrophilic in character with ρ values for the sulfide and sulfoxide oxidations equal to −0.77 and −0.76, respectively.

Introduction

The availability of pure solutions of dioxiranes[2] has provided an opportunity for a full scale investigation of the chemistry of these interesting peroxides. We have described the reaction of dimethyldioxirane (1) with a number of substrates[2] including, most recently, the remarkable insertion of O atom into carbon–hydrogen bonds of hydrocarbons[3] and nitrogen–hydrogen bonds of amines.[4] The hydrocarbon oxidation work also permitted us to begin a series of investigations directed at understanding the mechanistic details of these interesting oxidations. We have found, for example, that 1 shows a reaction selectivity with one series of hydrocarbon substrates which is quite different from that shown by *tert*-butoxy radical toward the same substrates. Also the primary kinetic isotope effect (k_H/k_D = 4.97) measured[3] for the C–H insertion reaction suggests only a partial breaking of the bond in the transition state. We describe here the results of a study aimed at determining the electronic requirements for oxidation by dimethyldioxirane of a series of sulfides and sulfoxides. The data obtained have been treated with the Hammett linear free energy relationship.

Results and Discussion

During our earlier[2] work exploring the range of oxidations accomplished by 1 we had shown that phenyl methyl sulfide is rapidly and efficiently oxidized to the sulfoxide. Indeed this reaction is so rapid and complete that we frequently use phenyl methyl sulfide to quench oxidations by 1 of less reactive substrates. We have now carried out the oxidation of a series of para-substituted phenyl methyl sulfides in order to determine the influence of electron availability on the rate of oxidation. The relative rate studies were carried out by oxidizing the sulfide substrates in pairs, i.e., each pair contained equimolar amounts of phenyl methyl sulfide and one of the para-substituted materials. The oxidations were carried out at room temperature and with the sulfides in excess. Under these conditions the reactions are complete instantaneously. The reaction solutions were analyzed by capillary GC using an internal standard. The GC conditions were established such that all reactant and product peaks were clearly separated and analysis could be carried out with good precision. In all cases the only products observed were the sulfoxides corresponding to the sulfides used (eq 1). The



relative rates were calculated by comparing initial and final concentrations of the reacting pair of sulfides. The relative rate data were plotted against Hammett σ values[5] and gave a straight line with ρ = −0.77.

In a similar fashion the influence of para substitution on reaction rate was determined by oxidizing pairs of sulfoxides with 1, i.e., phenyl methyl sulfoxide plus one

(1) Part 5: Murray, R. W.; Jeyaraman, R.; Mohan, L. *Tetrahedron Lett.* **1986**, *27*, 2335–2336.

(2) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847–2853. The ^{13}C adsorption at 214 ppm originally assigned to the ring carbon of dimethyldioxirane in this reference has since been found to be an artifact. All other NMR assignments are correct as published. Additional attempts to observe an absorption for the ring carbon using ^{13}C-enriched dioxirane are in progress.

(3) Murray, R. W.; Jeyaraman, R.; Mohan, L. *J. Am. Chem. Soc.* **1986**, *108*, 2470–2472.

(4) Murray, R. W.; Jeyaraman, R.; Mohan, L. *Tetrahedron Lett.* **1986**, *27*, 2335–2336.

(5) The σ values used were taken from Ritchie, C. D.; Sager, W. F. *Progr. Phys. Org. Chem.* **1964**, *2*, 323.

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