Steric Effects in the Hydrolysis Reactions of *N*-Acylimidazoles. Effect of Aryl Substitution in the Leaving Group

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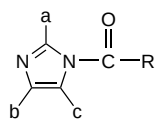
The kinetic and mechanistic effects of aryl substitution in the leaving group have been determined in the hydrolysis reactions of *N*-acylimidazoles. *N*-Acyl derivatives of 2,4,5-triphenylimidazole hydrolyze rapidly in OH^- and water reactions. The latter reactions are pH independent from pH 4 to 9. The *N*-acetyl derivative hydrolyzes with rate constants similar to those of *N*-acetylimidazole in the OH^- reaction but 40-fold *larger* in the pH-independent reaction. *N*-(trimethylacetyl)-2,4,5-triphenylimidazole hydrolyzes at 15 °C with k_{OH}, the second-order rate constant for the OH^- reaction, 26-fold larger than the rate constant for alkaline hydrolysis of the corresponding *N*-acetyl derivative, even though steric hindrance to approach of a nucleophile is extreme in the former reaction. The pH-independent reaction of the *N*-trimethylacetyl compound is 4-fold faster than that of the *N*-acetyl derivative and is characterized by a D_2O solvent isotope effect (k_{H_2O}/k_{D_2O}) of 2.0. A phenyl substituent in the 2-position of the imidazole ring exerts a small rate-retarding effect in the hydrolysis reactions. *N*-(Trimethylacetyl)-4,5-diphenylimidazole hydrolyzes 10- and 55-fold faster in the OH^- and water reactions, respectively, at 15 °C, than *N*-(trimethylacetyl)benzimidazole at 30 °C, although the pK_a of the leaving group is identical in the two cases. The additive nature of the steric rate-accelerating effects in the acyl group and the leaving group indicates an effect on the ease of C−N bond breaking; the hydrolysis reactions very likely proceed in a concerted manner without the formation of a stable tetrahedral intermediate.

The hydrolysis reactions of *N*-acylimidazoles and *N*-acylbenzimidazoles have been actively studied.[1−12] These compounds are amides but possess structural features that give rise to exceptional hydrolytic reactivity. The second-order rate constant k_{OH} for alkaline hydrolysis of *N*-acetylimidazole is 316 M^{-1} s^{-1} at 25 °C,[4] even though the pK_a of the imidazole leaving group is 14.5.[13] *N*-Acylimidazoles can be considered model amides that illustrate the effect of restricted resonance with the carbonyl group in hydrolytic reactions.[5] *N*-Acylimidazoles have been observed as intermediates in bimolecular and intramolecular nucleophilic reactions of imidazole with esters[14−17] and are possible intermediates in enzymatic acyl transfer reactions.[2] Mechanistic understanding of the reactions of *N*-acylimidazoles is, therefore, of both chemical and biochemical significance.

The bimolecular reactions of *N*-acylimidazoles provide highly unusual examples of steric acceleration due to the increased size of the acyl group. Staab[3] found that *N*-(trimethylacetyl)imidazole hydrolyzes faster than *N*-acetylimidazole in conductivity water. The abnormal steric effect also extends to the OH^-, conjugate acid, and imidazole-catalyzed reactions.[6−8] In those reactions the rate constants are approximately 2−8-fold larger for hydrolysis of the trimethylacetyl derivative than the acetyl. In contrast, a normal steric effect in a bimolecular reaction produced by a trimethylacetyl acyl group should give a rate retardation of 50−100-fold, as exemplified by the imidazole and OH^- nucleophilic reactions of *p*-nitrophenyl esters.[6] The Taft steric effects constant E_s for trimethylacetyl is −1.54, whereas that for acetyl is zero.[18]

Electronic effects of substituents in the imidazole leaving group have been determined in the OH^- and water reactions,[9] but steric effects in the leaving group have not previously been investigated. We have therefore in the present work studied the hydrolysis reactions of the *N*-acyl derivatives of 2,4,5-triphenylimidazole, **I** and **II**, with which steric crowding of the carbonyl by the leaving group is extreme. For comparison purposes *N*-acylimidazoles of 4,5-diphenylimidazole **III** and **IV**, 4(5)-phenylimidazole **V**, and 2-phenylimidazole **VI** were also studied.



I: R = CH_3; a = phenyl; b = phenyl; c = phenyl

II: R = $C(CH_3)_3$; a = phenyl; b = phenyl; c = phenyl

III: R = CH_3; a = H; b = phenyl; c = phenyl

IV: R = $C(CH_3)_3$; a = H; b = phenyl; c = phenyl

V: R = CH_3; a = H; b = phenyl; c = H

VI: R = CH_2CH_2phenyl; a = phenyl; b = H; c = H

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(1) Gerngross, O. *Chem. Ber.* **1913**, *46*, 1908.
(2) (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill; New York, 1969. (b) Bruice, T. C.; Benkovic, S. *Bioorganic Mechanisms*; W. A. Benjamin: New York, 1966.
(3) Staab, H. A. *Chem. Ber.* **1956**, *89*, 1927, 2088; **1957**, *90*, 1320.
(4) Jencks, W. P.; Carriuolo, J. *J. Biol. Chem.* **1959**, *234*, 1272, 1280.
(5) Fife, T. H. *Acc. Chem. Res.* **1993**, *26*, 325.
(6) Fife, T. H. *J. Am. Chem. Soc.* **1965**, *87*, 4597.
(7) Fee, J. A.; Fife, T. H. *J. Org. Chem.* **1966**, *31*, 2343.
(8) Fee, J. A.; Fife, T. H. *J. Phys. Chem.* **1966**, *70*, 3268.
(9) Fife, T. H.; Natarajan, R.; Werner, M. H. *J. Org. Chem.* **1987**, *52*, 740.
(10) Hogg, J. L.; Phillips, M. K.; Jergens, D. E. *J. Org. Chem.* **1977**, *42*, 2459.
(11) Kogan, R. L.; Fife, T. H. *Biochemistry* **1984**, *23*, 2983.
(12) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 4631.
(13) Walba, H.; Isensee, R. W. *J. Org. Chem.* **1961**, *26*, 2789.
(14) Bender, M. L.; Turnquest, B. W. *J. Am. Chem. Soc.* **1957**, *79*, 1656,. Bruice, T. C.; Schmir, G. L. *J. Am. Chem. Soc.* **1957**, *79*, 1663.
(15) Bruice, T. C.; Sturtevant, J. M. *J. Am. Chem. Soc.* **1959**, *81*, 2860.
(16) Bruice, T. C. *J. Am. Chem. Soc.* **1959**, *81*, 5444.
(17) (a) Fife, T. H.; Bambery, R. J.; DeMark, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 5500. (b) Fife, T. H.; DeMark, B. R. *J. Am. Chem. Soc.* **1979**, *101*, 7379.
(18) Taft, R. W., Jr. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 13, p 556.

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Experimental Section

Materials. *N*-Acetyl-2,4,5-triphenylimidazole (**I**) was prepared by mixing 2,4,5-triphenylimidazole (1.48 g, 0.005 mol) and acetic anhydride (0.51 g, 0.005 mol) in 100 mL of ethyl acetate and adding sodium methoxide (0.27 g). The mixture was stirred at room temperature for 24 h. The solvent was then removed by rotary evaporation. The residue was taken up in 150 mL of dry ether, stirred for 30 min, and then filtered. The ether was removed from the filtrate by rotary evaporation. After recrystallization from an ether−hexane mixture, the compound melted at 275 °C. Anal. Calcd for $C_{23}H_{18}N_2O$; C, 81.62; H, 5.36; N, 8.28. Found: C, 81.49; H, 5.48; N, 8.18.

The *N*-acylimidazole derivatives **II**, **III**, and **IV** were prepared by the same general method as that for **I**. After recrystallization from an ether−hexane mixture, **II** melted at 272 °C. Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.06; H, 6.36; N, 7.37. Found: C, 82.19; H, 6.45; N, 7.21. After recrystallization from an ether−hexane mixture, **III** melted at 182 °C. Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.86; H, 5.34; N, 10.69. Found: C, 77.99; H, 5.18; N, 10.73. After recrystallization from ether−hexane, **IV** melted at 150 °C. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.90; H, 6.63; N, 9.21. Found: C, 78.76; H, 6.70; N, 9.09.

In the preparation of *N*-acetyl-4(5)-phenylimidazole (**V**), 4(5)-phenylimidazole (2.88 g, 0.02 mol) was suspended in 100 mL of ethyl acetate containing pyridine (1.58 g). The mixture was stirred for 30 min, and 1.6 g of acetyl chloride was added. The mixture was stirred overnight and then filtered. The filtrate was transferred to a 200 mL round bottomed flask, and the solvent was removed by rotary evaporation. The residue was recrystallized from an ethyl acetate, cyclohexane mixture and then melted at 107 °C. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.21; H, 5.56; N, 14.86. Compound **III** was also prepared by this general method.

Compound **VI** was prepared by adding β-phenylpropionyl chloride in tetrahydrofuran (THF) dropwise to a solution of 2-equiv of 2-phenylimidazole in THF. The mixture was refluxed for 48 h. The mixture was then filtered, and the solvent was removed by rotary evaporation. The residual oil was vacuum distilled and boiled at 190−192 °C (0.01 mm), $n^{22}_D = 1.6121$. Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.15; H, 6.00; N, 10.08.

Acetonitrile was Eastman-Kodak Spectro-Grade. All other chemicals were reagent grade. The water employed was deionized and distilled. Imidazole was obtained from Aldrich and was sublimed prior to use.

Kinetic Methods. The rates of hydrolysis of compounds **I**−**VI** in H_2O were measured with a Pye-Unicam SP8-100 or Beckman-25 recording spectrophotometer, by following the spectral changes at 290−300 nm. Buffer solutions were maintained at a constant ionic strength of 0.5 M with KCl. A typical kinetic run was initiated by injecting 20−30 μL of a 2 $\times 10^{-2}$ M stock solution of the substrate in acetonitrile into 3 mL of buffer maintained at the appropriate temperature. The buffers employed were formate, acetate, cacodylate, imidazole, Tris, *N*-ethylmorpholine, and carbonate. The hydrolysis reactions are catalyzed by buffer. Therefore, rate constants were obtained by extrapolation to zero buffer concentration.

Reaction mixture pH values were measured with a Radiometer type PHM 22r or a Beckman 3500 digital pH meter. The values of pD were calculated by employing the glass electrode correction equation of Fife and Bruice.[19] In calculating second-order rate constants for the reaction with OH^-, the ion product of water (K_w) was taken to be 4.47×10^{-15} at 15 °C, 1.0×10^{-14} at 25 °C, and 1.47×10^{-14} at 30 °C.

Molecular modeling of the *N*-acylimidazoles was carried out with a Silicon Graphics Indigo 2 workstation. The software programs that were employed were Spartan 3.1 from Wavefunction, Inc., and Quanta 4.0 − Charmm from Molecular Simulations. With the Quanta-Charmm program, energy minimization was by the method of steepest descent and by the method of Newton-Raphson until a constant value was obtained. A Sybyl minimizer was employed with the Spartan 3.1 program; MM2 and MM3 failed. The energy minimized structures were determined in the absence of solvent.

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

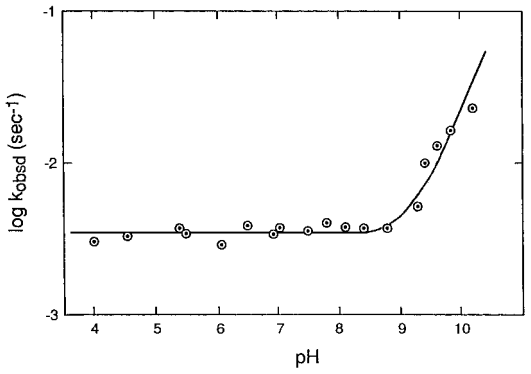


Figure 1. Plot of log k_{obsd} vs pH at 25 °C and $\mu = 0.5$ M (with KCl) for hydrolysis of *N*-acetyl-2,4,5-triphenylimidazole.

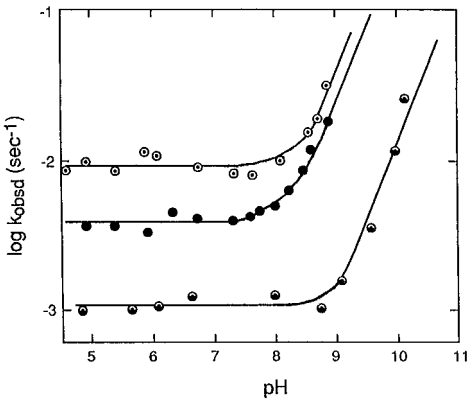


Figure 2. Plots of log k_{obsd} vs pH at 15 °C and $\mu = 0.5$ M (with KCl) for hydrolysis of *N*-acetyl-2,4,5-triphenylimidazole (◒), *N*-(trimethylacetyl)-2,4,5-triphenylimidazole (●), and *N*-(trimethylacetyl)-4,5-diphenylimidazole (⊙).

Table 1. Rate Constants for the Hydrolysis of *N*-Acylimidazoles with $\mu = 0.5$ M with KCl

compound	k_{OH} (M^{-1} s^{-1})	k_0 (s^{-1})	T (°C)
I	180	1.1×10^{-3}	15
	250	3.5×10^{-3}	25
N-acetylimidazole[a]	316	8.3×10^{-5}	25
II	4720	4.0×10^{-3}	15
N-(trimethylacetyl)imidazole[b]	533	1.1×10^{-3}	30
III	1580	1.5×10^{-3}	15
N-acetylbenzimidazole[c]	204	3.0×10^{-5}	30
IV	6400	9.3×10^{-3}	15
N-(trimethylacetyl)benzimidazole[c]	612	1.7×10^{-4}	30
V	850	5.6×10^{-4}	30
VI	290		30

[a] Reference 4. [b] Reference 6. [c] Reference 9.

Results

Figure 1 is a plot of log k_{obsd} at zero buffer vs pH for hydrolysis of *N*-acetyl-2,4,5-triphenylimidazole in H_2O at 25 °C, $\mu = 0.5$ M with KCl. A hydroxide ion promoted reaction is observed at pH > 9; k_{OH}, the second-order rate constant, is 250 M^{-1} s^{-1}. At pH < 9 the reaction is pH independent ($k_0 = 3.5 \times 10^{-3}$ s^{-1}). The rate constants for the pH-independent reaction were also obtained at 15 and 30 °C.

In Figure 2 the plot is shown of log k_{obsd} vs pH for hydrolysis of **I**, **II**, and **IV** at 15 °C ($\mu = 0.5$ M with KCl). Rate constants for these reactions are given in Table 1. The D_2O solvent isotope effect (k_{H_2O}/k_{D_2O}) for the pH-independent reaction is 2.0 ($k_{D_2O} = 5.4 \times 10^{-4}$ s^{-1}) with

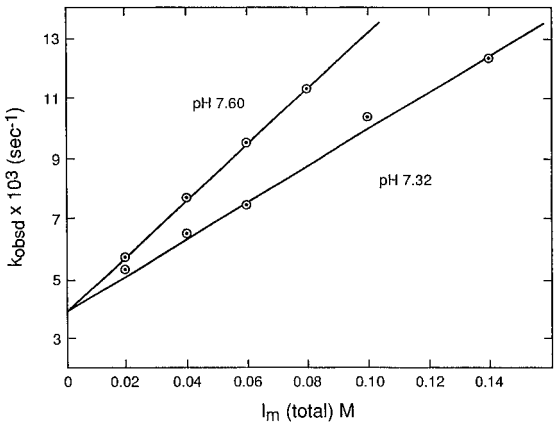


Figure 3. Plot of k_{obsd} for hydrolysis of *N*-(trimethylacetyl)-2,4,5-triphenylimidazole at 15 °C (μ = 0.5 M) vs the total concentration of imidazole (B + BH^+).

Table 2. Second-Order Rate Constants for the Base-Catalyzed Reactions of *N*-Acetyl-2,4,5-triphenylimidazole in H_2O at 25 °C, μ = 0.5 M with KCl

base[a]	pK_a	k_B (M^{-1} s^{-1})
imidazole	7.05	0.031
Tris	8.10	0.04
N-ethylmorpholine	7.80	0.05

[a] Total buffer concentration was varied from 0.02 to 0.4 M at constant pH.

I, 2.0 (k_{D_2O} = 2.0 × 10^{-3} s^{-1}) with **II**, and 2.1 (k_{D_2O} = 4.5 × 10^{-3} s^{-1}) with **IV**.

N-Acetyl-4(5)-phenylimidazole (**V**) hydrolyzes at 30 °C with k_{OH} = 850 M^{-1} s^{-1} and k_0 = 5.6 × 10^{-4} s^{-1}. These constants are less than those for **III**, even though the pK_a values for the substituted imidazole leaving groups are similar,[13] and there is less steric hindrance to approach of a nucleophile with **V**.

The hydrolysis of **VI** at 30 °C proceeds with k_{OH} = 2.9 × 10^2 M^{-1} s^{-1}, which is 3.0-fold less than the k_{OH} for hydrolysis of *N*-(β-phenylpropionyl)imidazole at 30 °C (8.6 × 10^2 M^{-1} s^{-1}).[9]

The hydrolysis reactions of **I**−**VI** are markedly catalyzed by the base species of the buffer. Figure 3 is a plot of k_{obsd} for hydrolysis of **II** at 15 °C vs the concentration of total imidazole buffer (Im + ImH^+). The second-order rate constant k_{Im} is 0.10 M^{-1} s^{-1}. There is no evidence for a general acid catalyzed reaction. Second-order rate constants for the base-catalyzed reactions of **I** are given in Table 2.

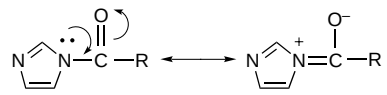
Discussion

The observed rate constants for hydrolysis of *N*-acylimidazoles in H_2O follow eq 1, where K_a is the dissociation constant of the conjugate acid (the pK_a of *N*-acetylimidazolium ion is 3.6).[4] Thus, there is a reaction

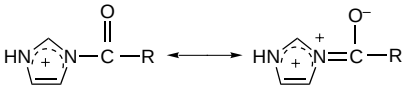
$$k_{obsd} = k_1\left[\frac{a_H}{(K_a + a_H)}\right] + [k_0 + k_{OH}(K_w/a_H)]\left[\frac{K_a}{(K_a + a_H)}\right] \quad (1)$$

of the conjugate acid and also pH-independent and OH^- reactions of the neutral species.

Resonance involving N-1 and the carbonyl group (eq 2) will deactivate the carbonyl towards attack of a nucleophile by reducing the partial positive charge on carbon. Steric inhibition of this resonance is clearly not responsible for the rate-enhancing effect of acyl group


(2)

branching in the hydrolysis of *N*-acylimidazoles.[5−7] Protonation of N-3 would greatly diminish such a resonance effect (eq 3),but the order of reactivity for a large series


(3)

of *N*-acylimidazole conjugate acids is the same as in the OH^- reaction. The differences in the magnitudes of the rate constants for the compounds in the series are also nearly the same in the two reactions.[7] *N*-Acetyl-*N*′-methylimidazole is a good model for reactions of the protonated *N*-acetylimidazole,[20] which indicates that in the conjugate acid the proton is on N-3.

An early transition state in which there is little bond making with a nucleophile would be consistent with the absence of large rate-retarding steric effects in the acyl group of *N*-acylimidazoles.[5−7] An early transition state could not explain a rate-enhancing effect of increased acyl group branching. However, the ease of C−N bond breaking could be increased greatly by the relief of steric strain. The observed steric effects are, therefore, in accord with a transition state that involves C−N bond breaking.[6]

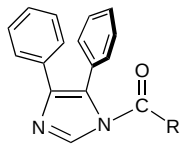
Triphenyl substitution in the imidazole leaving group has a large accelerating effect on the pH-independent water reaction. *N*-Acetyl-2,4,5-triphenylimidazole (**I**) at 25 °C has a k_{OH} that is similar to that for hydrolysis of *N*-acetylimidazole. The water reaction, on the other hand, is enhanced 40-fold by the triphenyl substitution, which results in pH independence of the hydrolysis reaction from at least pH 4 to 9. *N*-(Trimethylacetyl)-2,4,5-triphenylimidazole (**II**) hydrolyzes 26-fold faster than the corresponding acetyl derivative (**I**) in the hydroxide ion reaction and 4-fold faster in the water reaction, even though steric hindrance to approach of a nucleophile at the carbonyl is extreme. Likewise, **II** hydrolyzes 9-fold and 4-fold faster, respectively, in the two reactions at 15 °C than *N*-(trimethylacetyl)imidazole does at 30 °C. The pK_a of the triphenylimidazole leaving group is less than that of imidazole,[21] but the steric bulk due to the phenyl group substitution is large.

A phenyl group in the 2-position of the imidazole ring exerts only a small rate-retarding steric effect in the hydrolysis reactions; **VI** has a k_{OH} that is 3-fold less than that of the corresponding imidazole derivative. Accordingly, *N*-(trimethylacetyl)-4,5-diphenylimidazole (**IV**) hydrolyzes 2-fold faster than the 2,4,5-triphenyl derivative (**II**) in the water reaction and 4−6-fold faster than **III** in the OH^- and water reactions. Thus, **IV** is the most reactive *N*-acylimidazole that has been investigated kinetically.

Molecular modeling reveals that in the energy-minimized structures of the 2,4,5- and 4,5-phenyl-substituted *N*-acylimidazoles the phenyl substituents cannot be coplanar with the imidazole ring; in a coplanar system there is direct steric interaction of the *ortho* hydrogens of the 4- and 5-phenyl groups. Therefore, the phenyl groups are each twisted out of the plane of the imidazole

(20) Wolfenden, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1961**, *83*, 4390.
(21) The pK_a values for 2,4-diphenylimidazole and 4,5-diphenylimidazole are 12.53 and 12.80, respectively.[13]

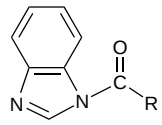
ring so that the alignment is propeller like, with nearly an edge to face alignment of the rings in the 4- and 5-positions. The steric interactions with the acyl group are thereby increased and become pronounced with bulky acyl groups (trimethylacetyl). The carbonyl group of the acyl derivatives abuts the face of the phenyl group in the 2- or 5-position (**VII**). Steric distortion of an amide has



VII

been found to give rise to enhanced rates of hydrolysis,[22,23] and that is a possible explanation for the rapid hydrolysis of the 4,5-diphenylimidazole derivatives **III** and **IV**.[24]

With benzimidazole derivatives the increased reactivity of the trimethylacetyl acyl group compared to acetyl is maintained,[9] but the rate constants for both the OH^- and water-promoted reactions of *N*-acylbenzimidazoles are much less than those for the corresponding 4,5-diphenyl-substituted compounds **III** and **IV**. *N*-(Trimethylacetyl)-benzimidazole hydrolyzes with a k_0 that is 55-fold less at 30 °C than k_0 for the pH-independent hydrolysis of *N*-(trimethylacetyl)-4,5-diphenylimidazole (**IV**) at 15 °C. Likewise, k_{OH} for the benzimidazole derivative is 10-fold less at 30 °C than k_{OH} for **IV** at 15 °C. Benzimidazole has a pK_a of 12.8 (25 °C),[13] which is identical with that of 4,5-diphenylimidazole. Therefore, the relative reactivities do not reflect electronic differences but must be steric in origin. The benzimidazole leaving group of *N*-acylbenzimidazoles is a planar system (**VIII**),in con-

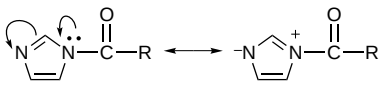


VIII

trast to the 4,5-phenyl-substituted imidazole **VII**. Steric accelerating effects in the acyl group and the leaving group are additive, which indicates an effect on the ease of C−N bond breaking.

Water Reactions. The large plateaus in the pH−rate constant profiles for hydrolysis of **I**−**IV** provide an opportunity for characterizing the water reactions since observed rate constants can be measured that are not influenced by the OH^- and conjugate acid reactions. The pH-independent reactions of the 2,4,5-triphenylimidazole and 4,5-diphenylimidazole *N*-acyl derivatives proceed more slowly in D_2O than in H_2O ($k_{H_2O}/k_{D_2O} = 2.0$), which indicates proton transfer in the transition state. A similar D_2O solvent isotope effect was found in the hydrolysis of *N*-acetylimidazole ($k_{H_2O}/k_{D_2O} = 2.7$).[4] The solvent isotope effect is consistent with a water reaction.

The restriction of water in the reactant would be an important kinetic factor because the translational entropy of water molecules required for solvation of the transition state would not then be lost. The resonance of eq 4 will place partial negative charge on N-3,[25] which



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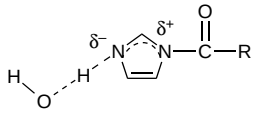
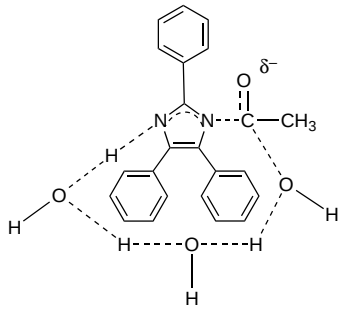
will promote hydrogen bonding of a water molecule (**IX**).[26]



IX

The structuring of solvent could be further enhanced by a large hydrocarbon residue in the acyl group.[8] Steric effects are normal in the aminolysis reactions of *N*-acylimidazoles in tetrahydrofuran,[3] which suggests that the solvent is important in determining the order of reactivity.

The pH-independent reaction of **I** can be considered analogous to that of *N*-acetylbenzimidazole[9] and *N*-acetylimidazole[20,27] in which proton transfer from water to N-3 is concerted with nucleophilic attack at the carbonyl carbon and C−N bond breaking (**X**). A similar



X

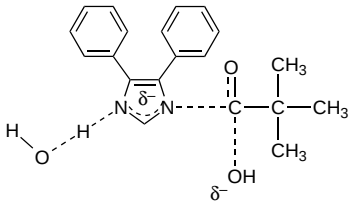
mechanism was suggested in the hydrolysis of *N*-acetyl-1,2,4-triazole and *N*-acetylbenzotriazole.[28] Concerted nucleophilic attack and C−N bond breaking in the reactions of *N*-acylimidazoles would be in accord with the additive steric rate-accelerating effects in the acyl group and the leaving group; the transition state would then be achieved with stretching of the C−N bond and incomplete formation of a bond with the nucleophile.

Concerted Reactions. Breakdown of a tetrahedral intermediate is not likely rate determining in the OH^- and conjugate acid reactions of *N*-acylimidazoles, in view of the lack of significant ^{18}O incorporation into the carbonyl group when the hydrolysis reactions are carried out in water enriched with ^{18}O.[29,30] The β_{1g} value of −0.28 in the OH^- reaction for substitution in the imidazole leaving group[9] (slope of a plot of log k_{OH} vs the pK_a of the

(22) Bennet, A. J.; Wang, Q. P.; Slebocka-Tilk, H.; Somayaji, V.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1990**, *112*, 6383.
(23) Curran, T. P.; Borysenko, C. W.; Abelleira, S. M.; Messier, R. J. *J. Org. Chem.* **1994**, *59*, 3522.

(24) The computed C−N bond length of the amide function determined in the modeling studies was dependent on the program employed.
(25) Pullman, B.; Pullman, A. *Quantum Biochemistry*; Wiley Interscience: New York, 1963; p 381. Molecular orbital calculations on *N*-acetylimidazole indicate that N-3 has a net negative charge of 0.23$^-$.
(26) A water molecule forms a hydrogen bond to imidazole with considerable stability (5.6 kcal/mol). Del Bene, J. E.; Cohen, I. *J. Am. Chem. Soc.* **1978**, *100*, 5285.
(27) Hogg, J. L.; Phillips, M. K. *Tetrahedron Lett.* **1977**, 3011.
(28) Patterson, J. F.; Huskey, W. P.; Hogg, J. L. *J. Org. Chem.* **1980**, *45*, 4675. Gopalakrishnan, G.; Hogg, J. L. *J. Org. Chem.* **1981**, *46*, 4959. Reboud-Ravaux, M. *J. Am. Chem. Soc.* **1980**, *102*, 1039.
(29) Bunton, C. A. *J. Chem. Soc.* **1963**, 6045.
(30) Fee, J. A. Ph.D. Thesis, University of Southern California, 1967. The ratio of the rate constants for hydrolysis and exchange (k_{hyd}/k_{ex}) in the alkaline hydrolysis of *N*-(3,3-dimethylbutyryl)imidazole at 50% hydrolysis is >60.

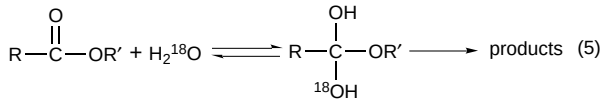
substituted imidazole) is consistent with rate-determining nucleophilic attack by OH^-.[31−33] Therefore, if the enhancement of C−N bond breaking is a factor in producing the abnormal steric acceleration effects, as is likely, then the hydrolysis reactions are concerted (**XI**), and a stable tetrahedral intermediate does not exist.



XI

Likewise, the reactions of *N*-acetylimidazole and *N*-acetylimidazolium ion with trifluoroethoxide ion are either concerted or, if a tetrahedral intermediate is formed, the intermediate cannot be sufficiently stable to be at equilibrium with respect to proton transfer.[34]

It is generally accepted that most hydrolytic reactions of acyl derivatives proceed via tetrahedral intermediates, i.e., the reactions involve addition of a nucleophile to the carbonyl group to give the intermediate followed by elimination to give products or to regenerate the reactants.[35] Reactions of esters of aliphatic alcohols in water enriched with ^{18}O give ^{18}O incorporation into the carbonyl group of the ester.[35−37] Incorporation of ^{18}O is consistent with the formation of a symmetrical tetrahedral intermediate that undergoes breakdown to reactants (eq 5).[35−37] It must also be shown that the tetrahedral



(5)

intermediate lies on the pathway to products, and that has only been accomplished in a few cases.[2,38] A reasonably stable intermediate would very likely be formed when the leaving group is poor. However, if the leaving group is very good, then bond breaking might begin before the intermediate can become symmetrical, as in **XI**. In that case, an anionic tetrahedral intermediate would be metastable or the reaction could be concerted, i.e., nucleophilic attack and bond breaking would occur simultaneously. Williams[39] has suggested that concerted reactions might be more common than supposed. The examples are, however, cases where the leaving group is especially good, such as acyl chlorides.

The pK_a of neutral imidazole is 14.5, which is only slightly less than that of methanol (15.5).[13,40] The high pK_a of the imidazole leaving group would conventionally be thought to require the existence of a tetrahedral intermediate in the OH^- reaction. Staab had suggested in 1956 that *N*-acetylimidazolium ion breaks down via a unimolecular decomposition.[3] That suggestion proved not to be compatible with the D_2O solvent isotope effect, ΔS^* value, and other experimental evidence.[4] Interaction of solvent or other nucleophiles with the developing acylium ion would have a stabilizing effect in the transition state. Thus, a concerted reaction could result. In reactions of a neutral *N*-acylimidazole, a unimolecular decomposition is much less likely than with the protonated species, so reaction with a nucleophile would be of increased importance. A key factor in giving rise to a concerted reaction would then be enhancement of the ease of C−N bond breaking.

Factors must exist which make C−N bond breaking exceptionally favorable; *N*-acetylimidazole undergoes alkaline hydrolysis with a second-order rate constant k_{OH} that is 20-fold larger than that of *p*-nitrophenyl acetate, even though the pK_a of *p*-nitrophenol is only 7.[4,5] The nucleophilic reactions of acyl derivatives are generally dependent on the basicity of the leaving group.[41] Therefore, the large difference in reactivity with these types of compounds, even with a leaving group ΔpK_a of 7.5 pK_a units, indicates that factors other than the pK_a of the leaving group are operative. The partial negative charge on N-3 of *N*-acylimidazoles will facilitate hydrogen bonding of a water molecule (eq 4). Stabilization of the partial negative charge on the leaving group will then enhance C−N bond breaking. The opposed resonance will also restrict the resonance involving N-1 and the carbonyl group,[42] so that the carbonyl is reactive. These factors could, in turn, lead to high reactivity and a concerted process, which would be promoted by relief of strain in the transition state. The novel reactions of these substituted *N*-acylimidazole derivatives have, therefore, provided considerable insight into the structural factors that will permit rapid hydrolysis of acyl derivatives.

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(31) The β_{1g} of −0.28 is similar to that for acetate esters of substituted phenols with which it has been considered that nucleophilic attack of OH^- at the carbonyl is the rate-determining step. Bruice, T. C.; Fife, T. H.; Bruno, J. J.; Brandon, N. E. *Biochemistry* **1962**, *1*, 7. Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622.

(32) Reference 2a, pp 510−513.

(33) The β_{1g} of −0.44 for alkaline hydrolysis of *N*-aryl β-lactams has been attributed to rate-limiting formation of a tetrahedral intermediate. Procter, P.; Gensmantel, N. P.; Page, M. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1185. Blackburn, G. M.; Plackett, J. D. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1366.

(34) (a) Oakenfull, D. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 178. (b) Oakenfull, D. G.; Salvesen, K.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 188.

(35) Reference 2b, pp 22−24

(36) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626.

(37) Bender, M. L.; Thomas, R. J. *J. Am. Chem. Soc.* **1961**, *83*, 4189.

(38) For an example, see: Fedor, L. R.; Bruice, T. C. *J. Am. Chem. Soc.* **1965**, *87*, 4138. Bender, M. L.; Heck, H.d'A. *J. Am. Chem. Soc.* **1967**, *89*, 1211.

(39) Williams, A. *Acc. Chem. Res.* **1989**, *22*, 379. Williams, A. *Adv. Phys. Org. Chem.* **1992**, *27*, 1.

(40) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795.

(41) Reference 2b, pp 58−60. Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 833, 837.

(42) N-1 of *N*-acetylimidazole has a net positive charge of 0.475^+ while the carbonyl carbon has a net positive charge of 0.287^+ according to the molecular orbital calculations of ref 25.