Steric Effects in the Hydrolysis of N-Acylimidazoles and Esters of p-Nitrophenol
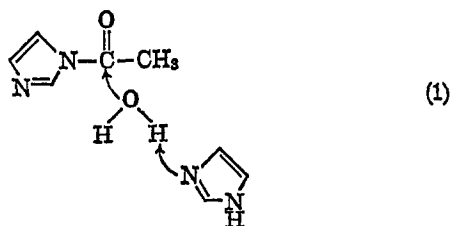
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The imidazole- and hydroxide ion-catalyzed hydrolysis of a series of N-acylimidazoles and the imidazole-catalyzed hydrolysis of a similar series of p-nitrophenyl esters was studied in water at 30°. In the ester series increased alkyl group branching in the acyl group, at both the α- and β-carbons, results in decreased rates for nucleophilic catalysis by imidazole. The hydrolysis of the N-acylimidazoles, involving classical general base catalysis by imidazole, does not show any rate retardation due to branching at the α-carbon. A small accelerating effect is actually observed. Branching at the β-carbon does result in a rate decrease but to a much smaller extent than is the case for the hydrolysis of the similarly substituted p-nitrophenyl esters. Hydroxide ion catalysis and general acid catalysis of the hydrolysis of the N-acylimidazoles are influenced by steric effects in much the same manner as general base catalysis.

It has been shown that the imidazole-catalyzed hydrolysis of phenyl acetates proceeds with nucleophilic attack by imidazole at the ester carbonyl, N-acetylimidazole being formed as an intermediate in the reaction.[1,2] The hydrolysis of N-acetylimidazole is also catalyzed by imidazole,[3] with the mechanism of this reaction most likely involving proton abstraction by imidazole from a water molecule in the transition state.

$$(1)$$

Steric effects in the catalyzing base have been studied for reactions exemplifying both nucleophilic and classical general base mechanisms. Nucleophilic catalysis of ester hydrolysis is strongly retarded by substitution of large groups at the 2-position of imidazole.[4] General base catalysis, involving proton transfer in the transition state, however, would appear generally to be only moderately affected by substitution in the catalyzing base.[5] No systematic study has yet been made of the effects on rate of bulky substituents in the substrate. To determine whether a difference in susceptibility to steric hindrance, produced by alkyl group

branching in the acyl group, might be exhibited by the two mechanisms, the imidazole-catalyzed hydrolysis of a series of sterically hindered N-acylimidazoles was studied as well as the hydrolysis of a similar series of p-nitrophenyl esters.

Experimental Section

Materials. The imidazole employed was from Eastman Kodak Co. (White Label). Dioxane was purified by the method of Fieser.[6] Acid chlorides were either commercially obtained (Matheson Coleman and Bell) or, in the case of 3,3-dimethylbutyryl chloride and triethylacetyl chloride, prepared from the commercially obtained carboxylic acids (K & K Laboratories) by reaction with thionyl chloride.

The N-acylimidazoles were prepared by dissolving 2 equiv. of imidazole in refluxing benzene and slowly adding 1 equiv. of the appropriate acid chloride dissolved in benzene. The mixture was protected from moisture with a calcium chloride drying tube and was generally refluxed for 2 to 3 hr. The precipitated imidazole hydrochloride was removed by filtration. The filtrate was then flash evaporated, and the residual material was purified by distillation or by recrystallization from either hexane or an ether–hexane mixture. The physical constants of the products matched closely the values reported by Staab.[7] N-3,3-Dimethylbutyrylimidazole had m.p. 69–69.5°. *Anal.* Calcd. for $C_9H_{14}N_2O$: C, 65.06; H, 8.43; N, 16.87. Found: C, 65.33; H, 8.66; N, 16.72. N-Triethylacetylimidazole had b.p. 102.5° at 1.5 mm. *Anal.* Calcd. for $C_{11}H_{18}N_2O$: C, 68.04; H, 9.28; N, 14.43. Found: C, 67.76; H, 9.34; N, 14.32.

The p-nitrophenyl esters were prepared by adding an equivalent amount of the appropriate acid chloride, dissolved in anhydrous ether, to a solution of equivalent amounts of p-nitrophenol and pyridine in anhydrous ether. The mixture was protected with a calcium chloride drying tube and was generally stirred for 2–3 hr. at room temperature. After standing overnight, the mixture was filtered to remove pyridine hydrochloride. The filtrate was flash evaporated, and the residual material was purified by recrystallization from an ether–hexane mixture or by distillation. The physical constants matched the literature values.[8] p-Nitrophenyl 3,3-dimethylbutyrate had m.p. 34–35°. *Anal.* Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.33; N, 5.91. Found: C, 60.83; H, 6.54; N, 5.83.

Kinetic Measurements. The kinetics of the hydrolysis of the N-acylimidazoles and the p-nitrophenyl esters

(1) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, 79, 1652, 1656 (1957).
(2) T. C. Bruice and G. L. Schmir, *ibid.*, 79, 1663 (1957).
(3) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, 234, 1272, 1280 (1959).
(4) T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, 80, 148 (1958).
(5) F. Covitz and F. H. Westheimer, *ibid.*, 85, 1773 (1963); J. A. Feather and V. Gold, *J. Chem. Soc.*, 1752 (1965).

(6) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 284.
(7) H. A. Staab, *Chem. Ber.*, 89, 1927, 2088 (1956).
(8) S. Kreisky, *Acta Chem. Scand.*, 11, 913 (1957); C. Huggins and J. Lapides, *J. Biol. Chem.*, 170, 467 (1947).

were studied in water, utilizing imidazole buffers at 30° and employing a constant ionic strength of 1.0 M made up with KCl. The N-acylimidazoles were each studied at three or four different buffer ratios, while the p-nitrophenyl esters were each studied at two buffer ratios. The rates were measured spectrophotometrically with a Zeiss PMQ 11 spectrophotometer by following the decrease in absorption at 245 mμ in the case of the N-acylimidazoles and by following, in the case of the p-nitrophenyl esters, the increase in absorption at 400 mμ due to formation of the p-nitrophenolate ion. The p-nitrophenyl esters were first dissolved in dioxane, and then one drop of solution was added from a calibrated dropping pipet to the preheated (30°) buffer solution in the thermostated cuvette. The solution was then stirred vigorously. The N-acylimidazoles were added directly with vigorous stirring to the thermostated buffer solution in the cuvette by means of a microspatula. The rates were generally followed to 75% of completion. Infinity points were taken at 10 half-lives. The pseudo-first-order constant (k_{obsd}) for ester hydrolysis at each buffer concentration was obtained from the slope of a plot of log (O.D.$_\infty$ − O.D.$_i$/O.D.$_\infty$ − O.D.$_t$) vs. time, while k_{obsd} for N-acylimidazole hydrolysis at each buffer concentration was obtained from a plot of log (O.D.$_i$/O.D.$_t$) vs. time. The pH of each solution was measured on a Model 22 Radiometer pH meter. Constant temperature was maintained in the kinetic runs by circulating water at 30 ± 0.1°, from a Haake Model F constant-temperature circulating bath, through a Zeiss constant-temperature cell holder.

In work utilizing 99.8% D$_2$O as the solvent, the glass electrode correction formula of Fife and Bruice[9] was employed in the determination of a_D. The pK_a of imidazole in D$_2$O at 30° is 7.54 as determined by the method of half-neutralization.

The rates of alkaline hydrolysis of the N-acylimidazoles were measured titrimetrically with a Radiometer TTT-1 Autotitrator and Radiometer Titrigraph. A Metrohm EA 115-X electrode was employed. The procedure and equipment were the same as previously described.[10] The rates were followed to completion, and the pseudo-first-order rate constants were obtained by the method of Guggenheim.[11] At the very low concentrations which were used, catalysis by product was negligible since identical rate constants were obtained when the initial concentration of substrate was varied over a 2-3-fold range. Rate measurements were made at several pH values with each compound. The observed rate constants were directly proportional to the hydroxide ion concentration in the pH range studied titrimetrically.

Results and Discussion

The second-order rate constants for the imidazole-catalyzed hydrolysis of the p-nitrophenyl esters and the imidazole- and imidazolium ion-catalyzed hydrolysis of the N-acylimidazoles are presented in Tables I and II. The constants for the hydrolysis of the p-nitrophenyl esters (k_{Im}) were obtained from the slopes of plots of k_{obsd}, at constant pH and ionic strength, vs. the

(9) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).
(10) T. H. Fife, *J. Am. Chem. Soc.*, **87**, 271 (1965).
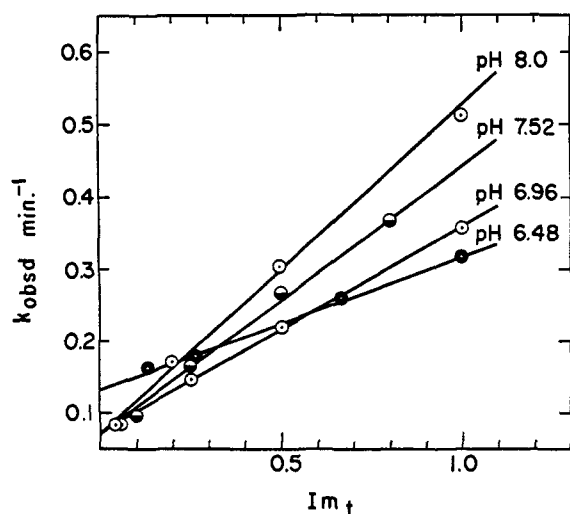(11) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

concentration of imidazole present as the free base. When pH was varied, the slopes of such plots were found to be nearly parallel lines, showing the base form of imidazole to be the catalyst in the reaction in accordance with the data for p-nitrophenyl acetate.[1,2]

Table I. Rate Constants for the Imidazole-Catalyzed Hydrolysis of p-Nitrophenyl Esters at 30° and μ = 1.0 M

Ester	k_{Im}, l. mole^{-1} min.$^{-1}$	$k_{Im}^{D_2O}$	$k_{Im}/k_{Im}^{propionate}$
Propionate	56.8		1.0
Isobutyrate	40.3		0.71
Trimethylacetate	0.55	0.48	0.01
Butyrate	31.8		0.56
3,3-Dimethylbutyrate	0.39		0.007

Table II. Rate Constants for the Imidazole-[a] and Imidazolium Ion-Catalyzed Hydrolysis of N-Acylimidazoles at 30° and μ = 1.0 M

N-Acyl group	pH	k_{Im_t}	k_{ImH}	k_{Im}	$k_{Im}/k_{Im}^{propionyl}$
		——l. mole^{-1} min.$^{-1}$——			
Acetyl				0.14[b]	
Propionyl	6.47	0.065	0.034	0.16	1.0
	7.07	0.11			
	7.54	0.153			
Isobutyryl	6.47	0.105	0.056	0.26	1.6
	7.07	0.178			
	7.54	0.246			
Trimethylacetyl	6.48	0.185	0.11	0.39	2.4
	6.96	0.283			
	7.52	0.388			
	8.0	0.453			
Butyryl	6.48	0.0475	0.025	0.12	0.75
	7.08	0.084			
	7.54	0.113			
3,3-Dimethyl-butyryl	6.47	0.009	0.0045	0.023	0.14
	7.08	0.0152			
	7.51	0.021			
Triethylacetyl	7.08	0.00016	0.00007	0.0002	0.0012
	7.54	0.00020			
	8.0	0.00023			

[a] The pK_a of imidazole at 30° was found to be 7.10 by the method of half-neutralization. [b] Reference 3, 25°, μ = 0.2 M.

Plots of k_{obsd} vs. total imidazole concentration for the imidazole-catalyzed hydrolysis of the N-acylimidazoles show increasing slopes as the pH is increased, as seen in Figure 1 for N-trimethylacetylimidazole; therefore, the base form is catalytically active. Plots of k_{obsd} vs. base concentration, however, do not yield parallel lines when pH is varied, the slopes decreasing as the pH increases. As a consequence, either a fast imidazole-catalyzed hydrolysis of the protonated amide must also be taking place, or else the imidazolium cation is also catalyzing the reaction of the neutral species. The equation that is followed is

$$k_{obsd} = k_0 + k_H a_H + k_{OH}(OH^-) +$$

$$k_{Im}(Im)_t\left[\frac{K_a}{K_a + a_H}\right] + k_{ImH}(Im)_t\left[\frac{a_H}{K_a + a_H}\right] \quad (2)$$

where k_{Im} is the second-order rate constant for the imidazole-catalyzed reaction, k_{ImH} is the second-order rate constant for an imidazolium cation-catalyzed reaction, (Im)$_t$ is the total concentration of imidazole

Figure 1. Plots of k_{obsd} vs. total imidazole concentration (moles/l.) for the hydrolysis of N-trimethylacetylimidazole in water at 30° and $\mu = 1.0\ M$.
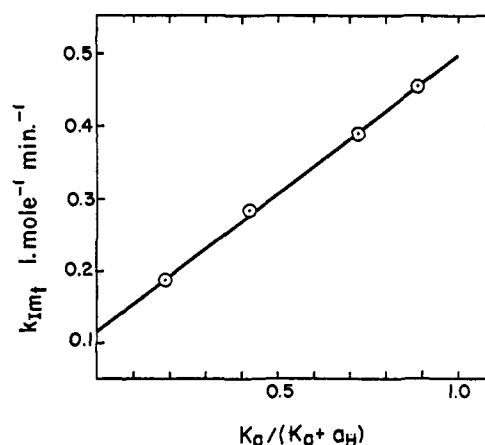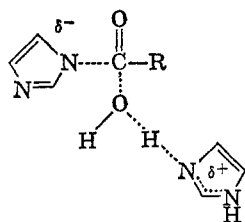

Figure 2. Plot of k_{Im_t} vs. the fraction of imidazole present as the free base, $K_a/(K_a + a_H)$, for the hydrolysis of N-trimethylacetylimidazole in water at 30° and $\mu = 1.0\ M$.

in its free base and conjugate acid form ($Im_t = Im + ImH^+$), K_a is the dissociation constant of the imidazolium cation, and a_H is the activity of hydronium ion as determined by the glass electrode. From eq. 2 it follows that in plots of k_{obsd} vs. (Im)$_t$ the slope will be $k_{Im}K_a/(K_a + a_H) + k_{ImH}a_H/(K_a + a_H)$. By plotting this value (k_{Im_t}) vs. $K_a/(K_a + a_H)$, as in Figure 2, k_{Im} is obtained as the slope and k_{ImH} is the intercept where $K_a/(K_a + a_H)$ is equal to zero. Jencks and Carriuolo[3] have previously found that general acids, such as acetic acid and formic acid, are effective catalysts in the hydrolysis of N-acetylimidazole, but a rate constant for catalysis by the imidazolium cation was not reported.

From the data of Table I it can be seen that increasing the number of methyl groups substituted at both the α- and β-carbon atoms of the acyl group results in large rate retardations in the p-nitrophenyl ester series where catalysis by imidazole is nucleophilic. These steric effects parallel those found in the alkaline hydrolysis of the ethyl esters of these acids[12] and the acid-catalyzed esterification of these acids in methanol.[13] Thus, the rate of the imidazole-catalyzed hydrolysis of p-nitrophenyl trimethylacetate is less by a factor of 103 than that of the corresponding propionate ester. In the alkaline hydrolysis of the ethyl esters in 70% acetone–water at 35°, the trimethylacetate ester hydrolyzes $^1/_{89}$th as fast as the propionate ester.[12] These effects are undoubtedly due primarily to the ability of the alkyl substituent groups to sterically hinder the attack of the nucleophile at the carbonyl carbon. Imidazole is acting as a nucleophilic catalyst in the hydrolysis of p-nitrophenyl trimethylacetate since the rate measured in D_2O is only slightly slower than in H_2O ($k_{Im}^{H_2O}/k_{Im}^{D_2O} = 1.15$).[14] No change in mechanism has occurred, therefore, as a result of the increased steric hindrance.

(12) D. P. Evans, J. J. Gordon, and H. B. Watson, *J. Chem. Soc.*, 1439 (1938); G. Davies and D. P. Evans, *ibid.*, 339 (1940).
(13) K. L. Loening, A. B. Garrett, and M. S. Newman, *J. Am. Chem. Soc.*, 74, 3929 (1952).
(14) This ratio can be compared with that obtained in the imidazole-catalyzed hydrolysis of p-nitrophenyl acetate ($k^{H_2O}/k^{D_2O} = 1.0$): M. L. Bender, E. J. Pollock, and M. C. Neveu, *ibid.*, 84, 595 (1962).

It can be seen from Table II that a completely different pattern of effects is obtained in the imidazole-catalyzed hydrolysis of N-acylimidazoles. In the base-catalyzed reaction, branching at the α-carbon produces little effect, the trend on going from the propionyl to the trimethylacetyl derivative actually being one of slight acceleration in rate. Staab[7] has previously found with N-acylimidazoles that increased branching at the α-carbon of the acyl group results in greater rates of "neutral" hydrolysis measured in conductivity water. Branching at the β-carbon does produce rate decreases, but the effects are not nearly as large as in the p-nitrophenyl ester series. Thus, N-3,3-dimethylbutyrylimidazole is only $^1/_7$th as reactive as N-propionylimidazole, while p-nitrophenyl 3,3-dimethylbutyrate is less reactive by a factor of 146 than the corresponding propionate ester. When steric blocking of the carbonyl group is exceedingly great, then large rate decreases do take place in the N-acylimidazole series. N-Triethylacetylimidazole hydrolyzes at an extremely slow rate, even at very high total imidazole concentration ($k_{Im} = 2 \times 10^{-4}$ l. mole^{-1} min.$^{-1}$, approximately $^1/_{800}$th that for N-propionylimidazole).

There are two possible interpretations of the present data for classical general base catalysis: (a) either all rate-retarding effects due to branching at the α-carbon are absent, with branching at the β-carbon producing smaller effects than those observed in nucleophilic catalysis of ester hydrolysis; or (b) branching at both the α- and β-carbons gives rise to a normal rate-retarding effect, due to the blocking of approach to the carbonyl group, which is either wholly or partially compensated for by an accelerating effect caused by the alkyl group substitution. According to the second explanation, slowing of the rate would result when steric hindrance was increased only if the accelerating effect was completely overcome. In the case of explanation (a), it is difficult to see why general base catalysis involving proton abstraction from water would not be subject to some steric retardation due to branching at the α-carbon since attack by an incipient hydroxide ion is occurring at the amide carbonyl. This interpretation would also ignore the accelerating effect actually observed. While this observed effect is

perhaps too small to be considered highly significant, still the trend in the series is certainly real.

The second interpretation would demand an explanation of the accelerating effect. Several possible factors might be responsible. To explain the faster rates of "neutral" hydrolysis for N-acylimidazoles with branching at the α-carbon of the acyl group, Staab[7] postulated that the alkyl groups were forcing the carbonyl out of coplanarity with the imidazole ring, thus causing the loss of much resonance energy and, as a consequence, leading to a more reactive molecule. Staab[7] thought that the "neutral" reaction was a unimolecular decomposition to an acylium ion. This same steric factor, however, might also lead to greater reactivity in a bimolecular reaction. It is unlikely that this possibility could be totally responsible for the observed effects since Staab[7] also found that the rate of aminolysis by diethylamine is strongly retarded by increased branching at the α-carbon. If, however, the hydrolysis reaction involved a mechanism with the transition state lying close to products, then relief of strain might

occur upon entering the transition state, giving rise to a faster rate for the branched compounds. In the alkaline hydrolysis of these compounds, the relative rate ratios (Table III) are very similar to those obtained in

Table III. Rate Constants for the Alkaline
Hydrolysis of N-Acylimidazoles at 30° and $\mu = 1.0\ M$

N-Acyl group	k_{OH},[a] l. mole^{-1} min.$^{-1}$	$k_{OH}/k_{OH}^{Propionyl}$
Acetyl	19,000[b]	
Propionyl	32,000	1.0
Isobutyryl	50,000	1.6
Trimethylacetyl	32,000	1.0
Butyryl	28,000	0.9
3,3-Dimethylbutyryl	13,000	0.4
Triethylacetyl	42	0.0013

[a] Second-order rate constant for the hydroxide ion-catalyzed reaction, $k_{obsd} = k_{OH}K_w/a_H$. [b] Reference 3, 25°, $\mu = 0.2\ M$.

the general base catalyzed reaction, the trimethylacetyl and 3,3-dimethylbutyryl derivatives hydrolyzing at rates not greatly different from N-propionylimidazole. Thus, steric factors are affecting the two reactions in the same manner. The alkaline reaction, of course, undoubtedly involves attack of hydroxide ion at the amide carbonyl.

As an additional factor, it is also likely that the presence of alkyl groups will cause water around a molecule to be more highly ordered.[15] With a mechanism involving proton abstraction from water in the transition state, if the water surrounding the substrate

was strongly hydrogen-bonded to other water molecules, the catalyzing base could partially abstract a proton from any point on the water cluster or chain. The effects of such proton abstraction would then be passed rapidly through the chain. Bunton and Shiner[16] have previously discussed the possibility that water catalysis involves proton transfer to or from such a water chain. In the case of general base catalysis, the more highly structured the water surrounding the substrate, the less restricted would be the approach of the catalyzing base. Also, a facilitation in rate might be obtained if the transition state was solvated by several water molecules since such water would already be restricted in the ground state. Attack at the carbonyl should still be retarded by increased branching in the acyl group. Thus, depending on how the opposing effects compromised, either an acceleration or a retardation in rate could be obtained.

Alternative mechanisms that are kinetically equivalent to (1), such as, either an imidazolium cation-catalyzed attack of hydroxide ion or an imidazolium cation-catalyzed decomposition of a tetrahedral intermediate, are also possible and might be expected to show a different susceptibility to branching in the acyl group than was observed in the p-nitrophenyl ester series. Specific base, general acid catalysis was considered by Jencks,[3] however, as a possible mechanism for the imidazole-catalyzed hydrolysis of N-acetylimidazole and was regarded as unlikely since the attack of oxygen anions was found not to be catalyzed by the imidazolium cation.

The hydrolysis of N-acylimidazoles is subject to facile catalysis by general acids, and it will be noted in Table II that this catalysis is more effective in the case of N-trimethylacetylimidazole than with the other compounds in the series. Steric effects on general acid catalysis in this series, therefore, in general, parallel the effects found for general base catalysis. Jencks[3] has suggested that general acid catalysis of the hydrolysis of N-acetylimidazole involves a base-catalyzed reaction of the protonated amide. This observation should also be applicable to the hydrolysis of the present series of compounds.

It is possible that the pattern of steric effects observed in the general base and general acid catalyzed hydrolysis of N-acylimidazoles is a specific feature of the hydrolysis of these compounds rather than a general effect of mechanism. The fact that the hydroxide ion-catalyzed reaction is also influenced by steric factors in a closely similar manner, quite different from that normally encountered in the hydrolytic reactions of esters and amides, necessitates some caution in the interpretation of these results. It is also possible, however, that the observed effects are characteristic of compounds whose hydrolysis reactions are susceptible to general base catalysis. To assess the generality of these effects a study of steric effects in general base catalyzed ester hydrolysis is now in progress in this laboratory.

(15) H. S. Frank and M. W. Evans, *J. Chem. Phys.*, 13, 507 (1945); I. M. Klotz, *Science*, 128, 815 (1958); G. Nemethy and H. A. Scheraga, *J. Chem. Phys.*, 36, 3382, 3401 (1962).

(16) C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, 83, 3214 (1961).