General Acid Catalyzed Imidazolidine Hydrolysis. Hydrolysis of 2-(*tert*-Butyl)-*N,N'*-dimethyl-1,3-imidazolidine and 2-(*p*-Methoxyphenyl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine

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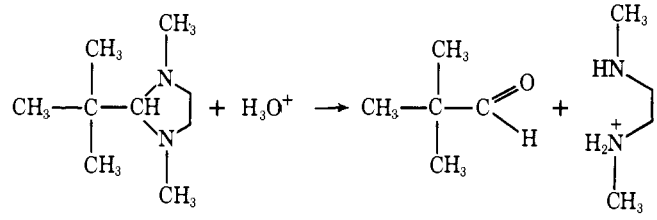
Abstract: The rates of hydrolysis of 2-(*tert*-butyl)-*N,N'*-dimethyl-1,3-imidazolidine and 2-(*p*-methoxyphenyl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine have been determined in H_2O at 30 °C. Both compounds have similarly shaped pH–log rate constant profiles for aldehyde formation. In both cases there is a pH-independent reaction at high pH (>12). As pH is progressively lowered there are successively encountered a hydronium ion catalyzed reaction, another nearly pH independent reaction commencing at the high pK_a of the imidazolidine ring, and at low pH (2–5) a second hydronium ion catalyzed reaction which most likely reflects protonation of the acyclic nitrogen subsequent to ring opening. In hydrolysis of the 2-(*tert*-butyl) derivative at pH values less than 6, two well-separated steps can be observed in the reaction by employing stopped-flow rate measurements. The reactions correspond to aldehyde formation and subsequent hydration of the aldehyde product. The pH–rate constant profile for the initial step is bell shaped with a maximum at about pH 2. At low pH a monoprotonated species exists as a discrete intermediate prior to the observed reaction. Kinetic general acid catalysis occurs in the initial reaction. This most likely results from the kinetically equivalent general base catalyzed hydrolysis of an intermediate protonated Schiff base, a possibility which is supported by a Brønsted coefficient α for general acid catalysis of 0.76. Two steps can be observed at 330 nm in the hydrolysis of 2-(*p*-methoxyphenyl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine at pH values below 3.5. These steps are ring opening to give a cationic Schiff base and hydrolysis of the Schiff base to *p*-methoxybenzaldehyde. From spectral considerations it is probable that the Schiff-base intermediate observed in ring opening is the *N*-alkyl Schiff base arising from expulsion of the least basic nitrogen and formation of the most stable iminium ion. The ring-opening reaction is pH independent in the pH range 0–3.5 (k_{open} = 188 s^{-1}), indicating reaction of the monoprotonated imidazolidine, but the reaction is much slower in D_2O than H_2O (k_{H_2O}/k_{D_2O} = 2.5). Thus proton transfer is possibly taking place in the critical transition state. The reaction must involve proton transfer to the least basic nitrogen with cleavage of the C–N phenyl bond. The most significant factor in determining the direction of ring opening of unsymmetrical imidazolidines must be the amount of stabilization of the incipient carbonium ion in the transition state. The implications of these results for reactions of N^5,N^{10}-methylenetetrahydrofolic acid are discussed.

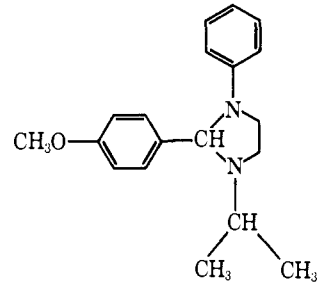
In reactions of the important enzyme cofactor N^5,N^{10}-methylenetetrahydrofolic acid, the imidazolidine ring must open, possibly with general acid catalysis by an appropriate functional group in the active site of the enzyme. Knowledge of the manner in which imidazolidines may be cleaved is therefore crucial in understanding the mechanism of action of the cofactor. There have been several kinetic studies of the formation of an imidazolidine ring from formaldehyde and various diamines,[2-5] and buffer catalysis is observed in this reaction.[2] The hydrolysis of 2-(substituted phenyl)-*N,N'*-dimethyl-1,3-imidazolidines proceeds with rate-determining hydrolysis of a cationic Schiff-base intermediate.[6] This Schiff base can be observed spectrophotometrically at pH values less than 4.7, but the ring-opening process is too rapid to be directly observed even with a Durrum stopped-flow instrument. N^5,N^{10}-Methylenetetrahydrofolic acid is an imidazolidine derivative of an aliphatic aldehyde. However, there have been no previous mechanistic studies of the hydrolysis of imidazolidines of aliphatic aldehydes. It is, therefore, important to determine whether significant mechanistic differences exist in the hydrolysis reactions of such compounds in comparison with the imidazolidines of aromatic aldehydes previously studied;[6] the reduced carbonium ion stability provided by an aliphatic group at the 2 position might be expected to have a profound effect on both rate and mechanism in the ring-opening reaction. In this paper we report work on the hydrolysis of 2-(*tert*-butyl)-*N,N'*-dimethyl-1,3-imidazolidine (I).

A feature of N^5,N^{10}-methylenetetrahydrofolic acid that is undoubtedly of critical importance is its unsymmetrical structure, which gives rise to a large difference in pK_a values for the N(5) and N(10) nitrogens.[7] To determine the mechanistic effects of dissymmetry we have studied the hydrolysis



I (1)

reactions of the unsymmetrical imidazolidine 2-(*p*-methoxyphenyl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine (II).



II

Experimental Section

Materials. 2-(*tert*-Butyl)-*N,N'*-dimethyl-1,3-imidazolidine (I) was prepared by refluxing equimolar amounts of freshly distilled pivaldehyde (J. T. Baker) and *N,N'*-dimethylethylenediamine (Aldrich) in benzene with water being continuously removed by azeotropic distillation. After removal of benzene the product was distilled at atmospheric pressure, and the fraction boiling at 165 °C, n^{23}_D 1.4453,

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Table I. Observed Rate Constants for Hydrolysis of 2,2,*N*,*N*′-Tetramethyl-1,3-imidazolidine and 2-(*tert*-Butyl)-*N*,*N*′-dimethyl-1,3-imidazolidine in Alkaline Solution at 30 °C (μ = 1.0)[a]

Imidazolidine	KOH, M or pH	k_{obsd}, s^{-1}
2,2-Dimethyl	0.50	0.0094
	0.10	0.012
	0.02	0.014
	pH 10.88[b]	0.022
	pH 10.80[b]	0.031
2-(*tert*-Butyl)	0.50	0.000 15
	0.30	0.000 23
	0.20	0.000 23
	0.10	0.000 28
	0.01	0.000 39
	0.004	0.000 99

[a] With KCl. [b] Carbonate buffer.

was collected, lit.[8] bp 168–170 °C. NMR analysis gave a spectrum identical with that previously reported.[8]

2-(*p*-Methoxyphenyl)-*N*-isopropyl-*N*′-phenyl-1,3-imidazolidine (II). *N*-Isopropyl-*N*′-phenylethylenediamine was prepared by the general procedure of Shepherd and Wilkinson[9] (method C). In the present case, 0.048 mol of *N*-phenylethylenediamine was added to 0.1 mol of acetone in 100 mL of dry ethanol. Over a period of 45 min $NaBH_4$ (0.15 mol) was added. The resulting mixture was refluxed for 3 h, yielding a clear yellow solution over excess solid borohydride. The ethanol was then removed by rotary evaporation, and 40 mL of aqueous 10 N NaOH was added. The aqueous solution was extracted with benzene, and the benzene extracts were dried over Na_2SO_4. The benzene was removed by rotary evaporation, and the residual liquid was distilled, boiling at 155 °C (15 mm) (lit.[9] bp 149–153 °C (15 mm)).

The imidazolidine II was prepared from *p*-methoxybenzaldehyde and *N*-isopropyl-*N*′-phenylethylenediamine by a procedure identical with that for I. The material crystallized from an ether/hexane solvent mixture. After recrystallization the compound melted at 72–73 °C. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 77.03; H, 8.11; N, 9.46. Found: C, 77.01; H, 8.14; N, 9.62.

2,2,*N*,*N*′-Tetramethyl-1,3-imidazolidine (III) was prepared from acetone and *N*,*N*′-dimethylethylenediamine by a procedure identical with that for I. The product boiled at 145–146 °C, n^{25}_D 1.4494 (lit.[8] bp 134–136 °C).

The Schiff-base derivatives of *p*-methoxybenzaldehyde and aniline or isopropylamine were prepared by refluxing equivalent amounts (0.1 mol) of freshly distilled aldehyde and freshly distilled amine in benzene (100 mL) with water being continuously removed by azeotropic distillation. After removal of the benzene by rotary evaporation the products were distilled or recrystallized. *N*-(*p*-Methoxy)benzylideneaniline had mp 62–63 °C after recrystallization from ether (lit.[10] mp 58–59 °C). The Schiff base hydrolyzed rapidly in moderately concentrated acid solutions. However, it was sufficiently stable in 12 M HCl that an accurate UV spectrum could be obtained: λ_{max} 368 nm (ϵ 3.4 × 10^4 M^{-1} cm^{-1}). *N*-(*p*-Methoxy)benzylideneisopropylamine had bp 70–72 °C (0.3 mm), n^{23}_D 1.5407. Its λ_{max} value in 5 M HCl was 318 nm (ϵ 3 × 10^4 M^{-1} cm^{-1}) and in 12 M HCl λ_{max} was 323 nm (ϵ 4 × 10^4 M^{-1} cm^{-1}). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.20; H, 8.42; N, 7.95.

Kinetic Methods. In studies employing a Zeiss PMQ11 or Beckman 25 spectrophotometer, 1 drop of I was added directly to 3 mL of buffer in the cuvette with a calibrated dropping pipet, and the reaction was monitored at 280 nm after thorough mixing. With II, 25 μl of a 0.004 M solution in dry acetonitrile was added to 3 mL of buffer in the cuvette, and the reaction was followed at 283 or 330 nm. Temperature was controlled at 30 ± 0.1 °C, and the ionic strength of buffers was maintained constant at 1.0 or 0.5 M with KCl.

Reactions too rapid to be monitored with a conventional spectrophotometer were followed using a Durrum-Gibson stopped-flow spectrophotometer (Model D 110). The substrate was dissolved at the desired concentration in aqueous 0.002 M sodium hydroxide, where it is reasonably stable. This solution was introduced into one of two identical drive syringes. The other syringe contained a lower pH buffer, such that on rapid mixing of equal volumes from the two syringes a reaction solution at the required pH was obtained. The drive syringes, mixing chamber, and cuvette were suspended in a water trough whose temperature was maintained at 30 ± 0.1 °C. Optical density changes after mixing were recorded on a Hewlett-Packard storage oscilloscope (Model 1207B). With each buffer, four to six reactions were tabulated. Reaction solution pH values were measured with a Radiometer pH meter Model 22 and GK 2303C combined electrode standardized with Mallinckrodt standard buffer solutions. Pseudo-first-order rate constants were calculated with an IBM 360 computer or an Olivetti-Underwood Programma 101.

Determination of the Extent of Initial Protonation of I at pH 2. The extent of protonation of I at pH 2.02 and 30 °C was determined by rapid mixing, using a Durrum stopped-flow, of equal volumes of two solutions, the first of which contained 0.0378 M substrate dissolved in 0.002 M KOH (μ = 1.0), and the second containing 2.76 × 10^{-5} M thymol blue in 0.078 M HCl (μ = 1.0). The initial absorbance on mixing (after 2 ms) at 545 nm was 0.22. This decreased to 0.18 in an exponential manner ($t_{1/2}$ = 46.6 ms). The final pH was 2.39. On mixing two identical solutions lacking substrate the initial absorbance at 545 nm was 0.44, showing that an absorbance drop of 0.22 occurred instantaneously on mixing the solution containing substrate. In a separate experiment, using a Beckman Model 25 spectrophotometer, the quantity of 3.43 M KOH needed to give the *same* absorbance decrease at 545 nm in 3 mL of an identical solution lacking substrate was determined. The base concentration necessary was found to be 0.0274 M, and the pH of this solution was 2.02. Thus, 0.0189 M substrate and 0.0274 M hydroxide ion cause identical decreases in absorbance at 545 nm in the presence of 1.38 × 10^{-5} M thymol blue. Consequently, at pH 2.02 each substrate molecule has an average of 1.45 protons.

Results

N,*N*′-Dimethyl-1,3-imidazolidines of aliphatic aldehydes hydrolyze to their respective aldehydes in H_2O at high pH in a pH-independent reaction. Rate constants are given in Table I for these reactions with I and 2,2,*N*,*N*′-tetramethyl-1,3-imidazolidine. At pH values below 9 the rates become too fast to measure conveniently with conventional equipment. For a detailed study employing a Durrum stopped-flow instrument, the *tert*-butyl derivative (I) was selected since stock solutions made up at high pH have reasonable stability.

At pH values less than 6, two steps can be detected in the hydrolysis of I. At 280 nm there is a rapid increase in absorbance followed by a much slower decrease. These two processes are both first order and are of sufficient difference in velocity that rate constants for both steps can be accurately obtained. The absorbance change in the first step is much larger than that of the second step. In Figure 1 a typical oscilloscope trace for these reactions is shown. The spectrum of the product after the second reaction is that of pivaldehyde. In Figure 2 a plot is presented of log k_0 for the first step vs. pH where k_0 is the rate constant at zero buffer concentration. The ascending arm of the bell-shaped profile with slope of −1.0 at pH values greater than 2.5 indicates hydronium ion catalysis with k'_H = 4.5 × 10^4 M^{-1} s^{-1}. The maximum in the profile is at approximately pH 2.5. At pH values greater than 6, only one reaction is observed. This reaction is formation of pivaldehyde. From pH 6 to 8.5 the reaction is pH independent with k_0 = 1.25 × 10^{-1} s^{-1}. Again, k_0 is the rate constant obtained by extrapolation to zero buffer concentration. At pH values greater than 9, the slope of the plot is −1.0, indicating hydronium ion catalysis (k_H = 1.1 × 10^8 M^{-1} s^{-1}). Above pH 12 the reaction again becomes pH independent with k'_0 = 2.3 × 10^{-4} s^{-1}.

Buffer catalysis is observed in both steps of the reaction. A plot is presented in Figure 3 of k_{obsd} for the initial reaction vs. total formate buffer concentration. The slopes increase as the pH is decreased showing that the catalysis is general acid catalysis. Rate constants for general acid catalysis (k_{HA}) are given in Table II. A Brønsted plot of log k_{HA} vs. the pK_a of the catalyst acid is shown in Figure 4. The slope is −0.76 (r = 0.989). Two discrete steps in the reaction were not observed in cacodylate buffer. The point for dichloroacetic acid, which was determined at a pH on the descending arm of the pH–rate

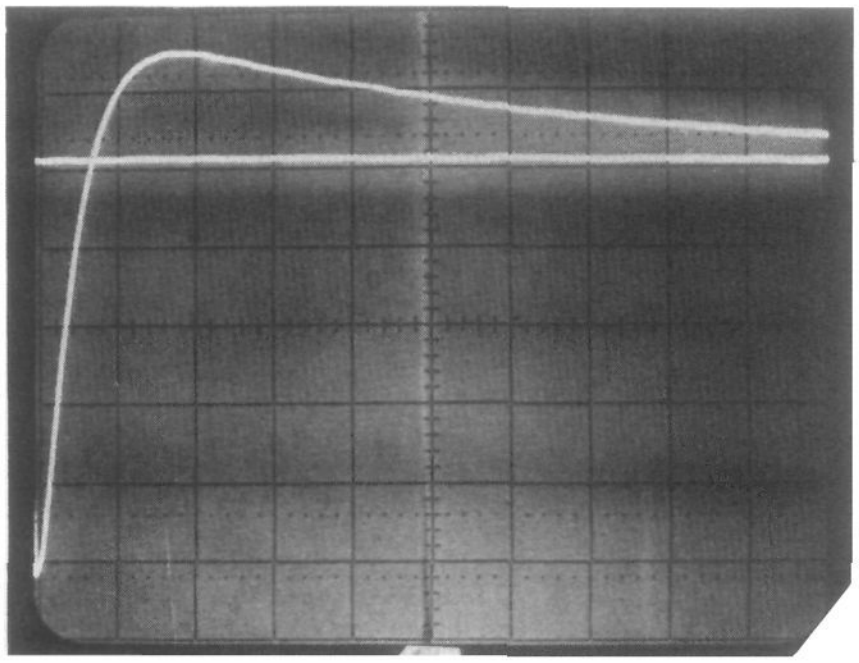


Figure 1. Oscilloscope trace at 283 nm for the hydrolysis of 2-(*tert*-butyl)-*N,N'*-dimethyl-1,3-imidazolidine in 0.34 M total formate buffer at pH 4.36, 30 °C, and μ = 1.0. The substrate concentration was 0.019 M. The time scale (horizontal axis) is 1 s per division. The horizontal line was obtained after 30 s (t_∞).

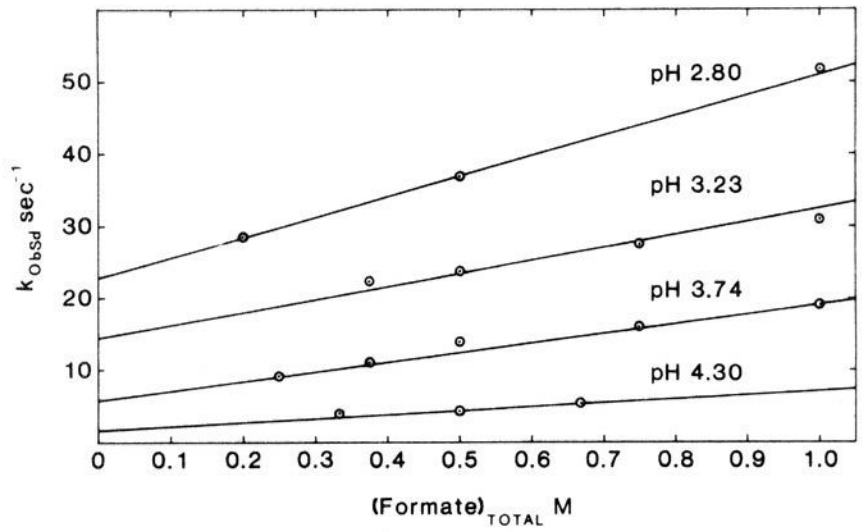


Figure 3. Plot of k_{obsd} vs. total formate buffer concentration for the first step in the hydrolysis of 2-(*tert*-butyl)-*N,N'*-dimethyl-1,3-imidazolidine in H_2O at 30 °C (μ = 1.0).

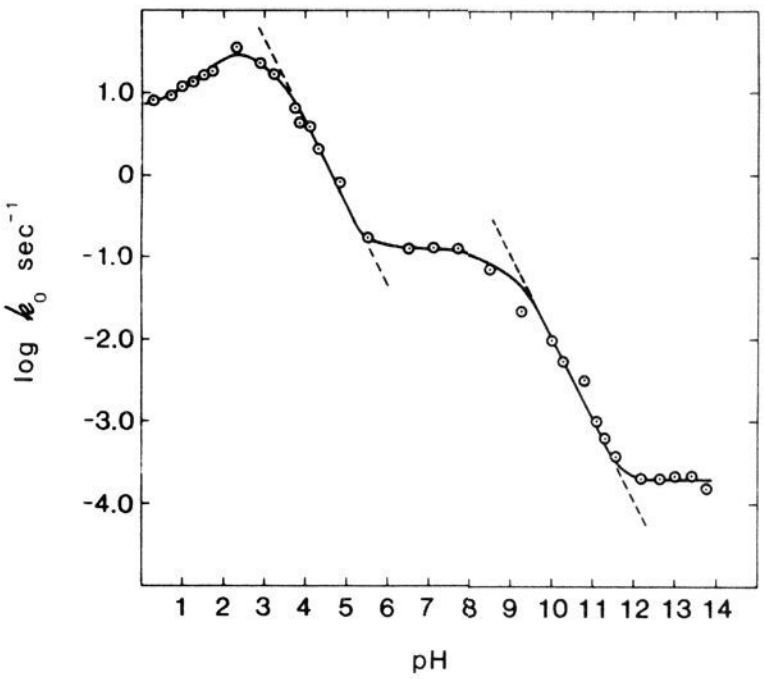


Figure 2. Plot of log k_0 vs. pH for hydrolysis of 2-(*tert*-butyl)-*N,N'*-dimethyl-1,3-imidazolidine in H_2O at 30 °C (μ = 1.0). The line was constructed from eq 2 employing appropriate values of the constants. The lines at pH 2–5 and 9–12 have slopes of −1.0. At pH values less than 6, k_0 is k_{obsd} for aldehyde formation (the initial step in the reaction). The values of k_0 in buffered solutions were obtained by extrapolation to zero buffer concentration.

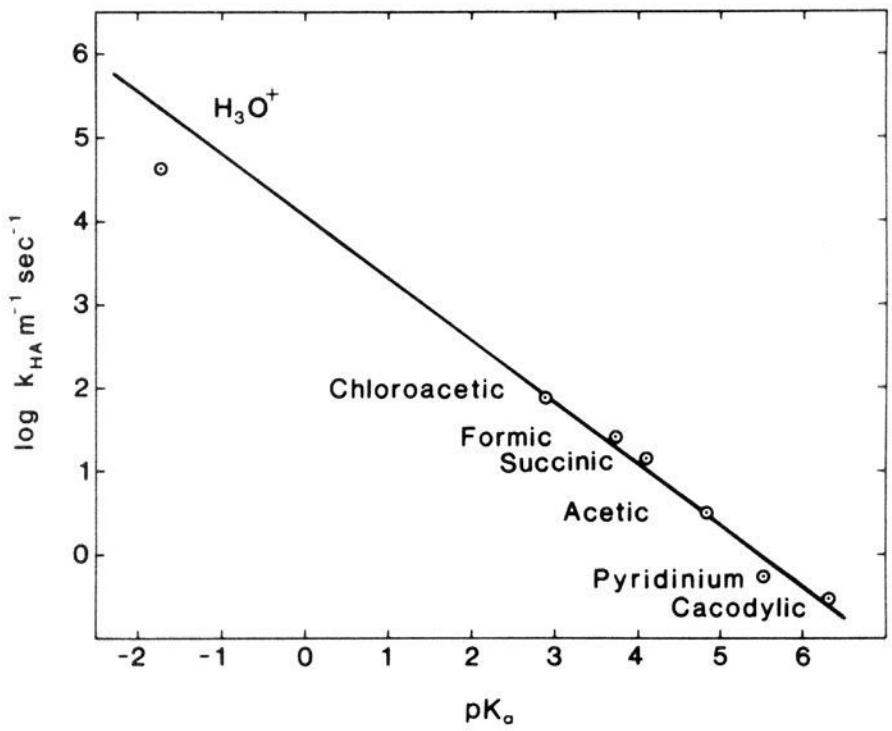


Figure 4. Brønsted plot of log k_{HA} for general acid catalysis of the first step in hydrolysis of 2-(*tert*-butyl)-*N,N'*-dimethyl-1,3-imidazolidine in H_2O at 30 °C (μ = 1.0) vs. the pK_a of the acid catalyst.

Table II. Second-Order Rate Constants for General Acid Catalyzed Hydrolysis of 2-(*tert*-Butyl)-*N,N'*-dimethyl-1,3-imidazolidine in H_2O at 30 °C (μ = 1.0)

Acid catalyst	pK_a	k_{HA}, M^{-1} s^{-1}
H_3O^+	−1.74	4.50×10^4
Dichloroacetic	1.49	33.9
Chloroacetic	2.88	68.5
Formic	3.74	24.5
Succinic	4.08	13.92
Acetic	4.80	3.10
Pyridine	5.50	0.512
Cacodylic	6.28	0.272

constant profile at low pH, falls considerably below the line of Figure 4 and was omitted from the correlation. In view of the high concentration of I required to obtain suitable absorbance changes (0.02 M), it was necessary to employ buffers of high concentration to avoid pH changes due to introduction of the substrate. Therefore, in studies of buffer catalysis, work was confined to reasonably concentrated buffers (up to 1 M). Rate constants for the second step in the hydrolysis of I are given in Table III. Data are not as extensive as for the first step in the reaction because of the smaller absorbance changes with resulting lower accuracy of the rate measurements.

At pH values below 3.5, two steps are discernible in the hydrolysis in H_2O of 2-(*p*-methoxyphenyl)-*N*-isopropyl-*N'*-phenylimidazolidine (II) at 30 °C and μ = 1.0 M at 330 nm. An oscilloscope trace of the reaction is shown in Figure 5. The first step, characterized by an increase in absorbance at 330 nm, must correspond with ring opening to a cationic Schiff base. This reaction is pH independent from pH 0 to 3.5 and has a rate constant k_{open} of 188 ± 8 s^{-1}. The reaction is 2.5 times slower in D_2O than in H_2O ($k_{open}^{D_2O}$ = 74 ± 7 s^{-1}). There is no significant buffer catalysis by chloroacetate or formate buffer at concentrations ranging from 0 to 0.5 M. The second step, characterized by a decrease in absorbance at 330 nm, must correspond with hydrolysis of the intermediate Schiff base to aldehyde. Rate constants measured at 330 or 283 nm are identical. At pH values greater than 5.0 an intermediate cannot be detected. The reaction then occurs with an increase in absorbance at 283 nm to give a product with the spectrum of *p*-methoxybenzaldehyde. In Figure 6 is shown a plot of log k_0

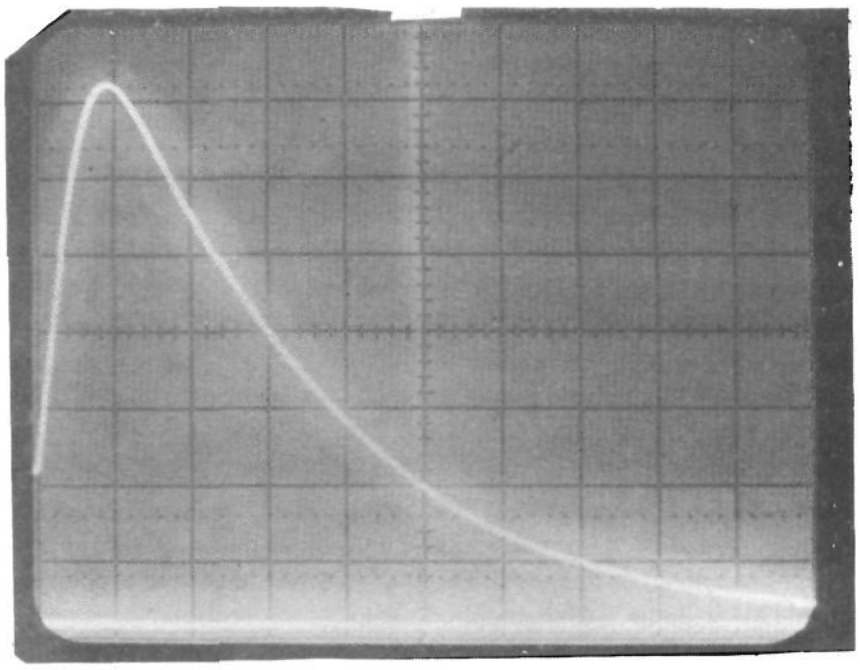


Figure 5. Oscilloscope trace at 330 nm for the hydrolysis of 2-(*p*-methoxyphenyl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine at pH 1.34 (μ = 1.0 M) and 30 °C. The time scale (horizontal axis) is 0.05 s per division.

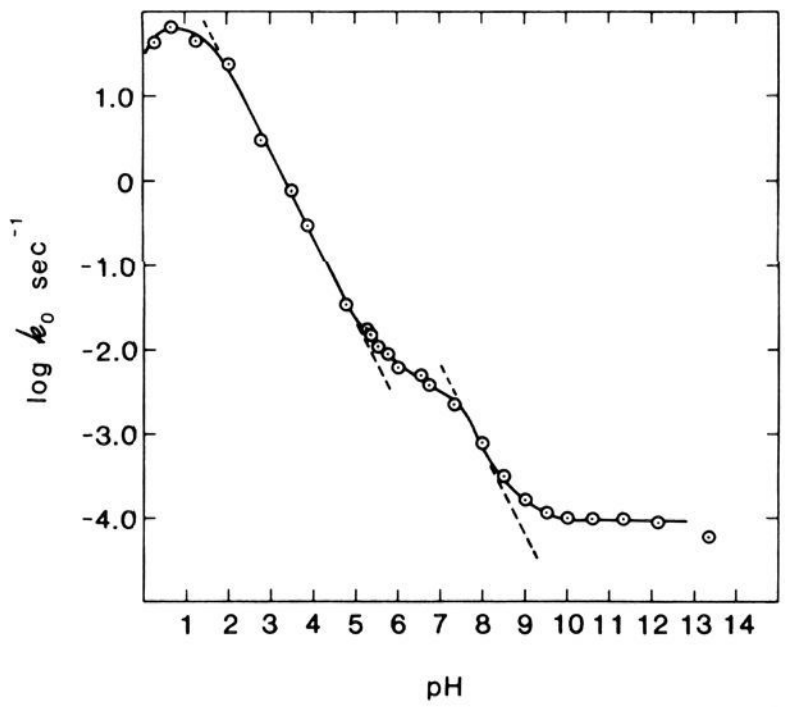


Figure 6. Plot of log k_0 vs. pH for formation of *p*-methoxybenzaldehyde from 2-(*p*-methoxyphenyl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine at 30 °C and μ = 1.0 M with KCl in H_2O. The line was constructed from eq 2 employing appropriate values of the constants. The lines at pH 2–5 and 7–10 have slopes of −1.0. The values of k_0 in buffered solutions were obtained by extrapolation to zero buffer concentration.

Table III. Rate Constants for the Second Stage in the Hydrolysis of 2-(*tert*-Butyl)-*N,N'*-dimethyl-1,3-imidazolidine at 30 °C (μ = 1.0)

Buffer	pH	k_0,[a] s^{-1}	k_2[c] $M^{-1}\,s^{-1}$
Chloroacetate[b]	2.87	1.2	3.0
Formate	3.74[b]	0.16	0.94
	3.22		2.2
Succinate[b]	4.07	0.09	0.88
Acetate[b]	4.81	0.06	0.24

[a] Rate constant obtained by extrapolation to zero buffer. [b] Half-neutralized buffer. [c] Slope of a plot of k_{obsd} vs. total buffer concentration.

vs. pH for the formation of *p*-methoxybenzaldehyde from II. The linear portions of the plot at pH 2–5 and 7–10 have slopes of −1.0 indicating hydronium ion catalysis. The values of k'_H and k_H are 2.4×10^3 and 6.3×10^4 $M^{-1}\,s^{-1}$, respectively. At pH values greater than 10 the reaction again becomes pH independent with $k'_0 = 9.5 \times 10^{-5}$ s^{-1}. The data for aldehyde formation from both I and II give a satisfactory fit to eq 2 at pH values above 2,

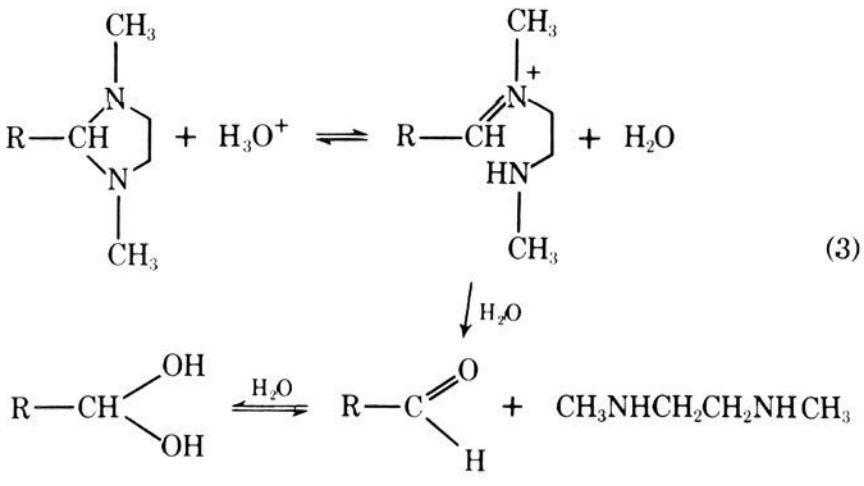
$$k_0 = [k_0' + k_H a_H]\left[\frac{K_{a1}}{K_{a1} + a_H}\right] + k'_H a_H \left[\frac{K'_a}{K'_a + a_H}\right] \quad (2)$$

where k_0 is k_{obsd} at zero buffer concentration, K_{a1} is the apparent dissociation constant of the imidazolidine ring, and K'_a is a complex dissociation constant pertaining to the acyclic nitrogen produced by ring opening. With compound II the apparent pK_a values determined from the pH–log rate constant profile are pK_{a1} = 7.2 and pK'_a = 1.5. The thermodynamic pK_a values for I and II could not be determined because of the rapid rates of hydrolysis. Equation 2 is based on the assumption that the reactions governed by k_H and k_H' represent rate-determining attack of H_2O on unprotonated and protonated cationic Schiff-base intermediates produced by ring opening of the protonated imidazolidine (see Discussion section). The data for both I and II are not fit by eq 2 at pH <2; the decline in k_0 with increasing acid concentration is very likely the result of a change in rate-determining step which cannot be described by an additional term in the equation.

Weak buffer catalysis is observed in the hydrolysis of II (283 nm) in chloroacetate, acetate, cacodylate, and phosphate buffer, which is kinetic general acid catalysis. Second-order rate constants k_{HA} are 3.48, 0.10, 0.013, and 0.012 $M^{-1}\,s^{-1}$, respectively. The second-order rate constant for chloroacetic acid catalysis determined at pH 2.78 by monitoring the decrease in absorbance at 330 nm is 3.17 $M^{-1}\,s^{-1}$, which is in reasonable agreement with that obtained by following the increase in absorbance at 283 nm. Buffer dilution studies were routinely carried out at constant pH in the concentration range 0.05–0.50 M total buffer.

Discussion

2-(*tert*-Butyl)-*N,N'*-dimethyl-1,3-imidazolidine. Two consecutive reactions can be monitored in the hydrolysis of 2-(*tert*-butyl)-*N,N'*-dimethyl-1,3-imidazolidine at pH values below 6. These reactions are characterized by a rapid increase in absorbance at 280 nm followed by a slower decrease in absorbance at the same wavelength. The overall reaction undoubtedly is ring opening to a cationic Schiff base and subsequent hydrolysis of the Schiff base to pivaldehyde followed by hydration of the aldehyde product. It is likely that the observed second stage of the reaction is hydration of the rapidly formed aldehyde product as in eq 3. Hydration of pivaldehyde is considerable in aqueous solution; equilibrium constants for hydration are 0.47 and 0.21 at 0 and 30.8 °C.[11] The rate of hydration was found to be enhanced by hydronium ion, hydroxide ion, and buffer.[11] In support of the scheme of eq 3 in hydrolysis of I, it was found that injection of pivaldehyde into acetate buffer solutions containing an equivalent amount of *N,N'*-



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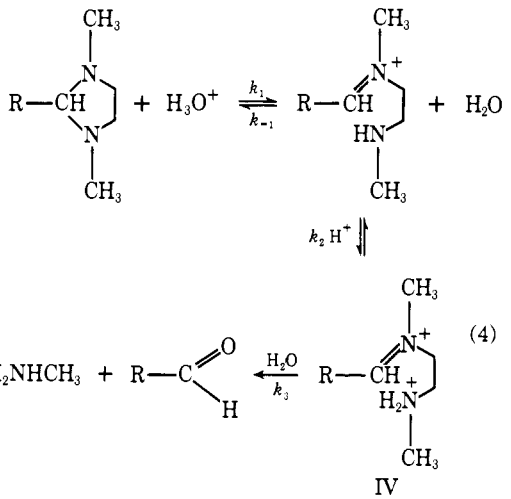
dimethylethylenediamine gave rate constants in good agreement with those measured for the second reaction in hydrolysis of I (Table III). The alternative possibility that the two steps in the reaction at 280 nm are formation and hydrolysis of a cationic Schiff base is not likely.[12,13] If the observed initial step in the reaction were ring opening then the observed general acid catalysis would of necessity be acid catalysis of ring opening of a protonated species.

The experiments with thymol blue indicator described in the Experimental Section show conclusively that protons are taken up by the imidazolidine (I) prior to the observed reactions. The demonstration that at pH 2 the molecule has on the average 1.45 protons before the observed hydrolysis reaction proves conclusively the existence of a monoprotonated species and suggests the possibility of a diprotonated intermediate at high acid concentrations (pH <2). If a cationic Schiff-base intermediate reverts rapidly to imidazolidine so that Schiff base is present only at steady state concentrations then this proton uptake indicates preequilibrium formation of a protonated imidazolidine. If, on the other hand, the cationic Schiff base is formed rapidly and is present at a high concentration at low pH then the fast proton uptake must reflect the ring-opening process. There is no spectral evidence for the presence of high concentrations of a Schiff-base intermediate at pH > 3. It was argued from the observed rates of hydrolysis of 2-(*p*-methoxyphenyl)-*N,N'*-dimethyl-1,3-imidazolidine that a discrete protonated intermediate possibly does not exist in the ring-opening reaction of that compound, the rate-determining step involving bond breaking in concert with partial proton transfer from hydronium ion to nitrogen. It was considered that the great ease of bond breaking brought about by the highly stabilized carbonium ion intermediate in the reaction would allow the transition state to be reached when proton transfer is only partial. In the present case, the aliphatic aldehyde derivative I will give rise to an intermediate carbonium ion that is much less stable, and a monoprotonated imidazolidine ring could exist.[14]

The initial reaction in hydrolysis of I is characterized by a bell-shaped plot of log k_0 vs. pH with a maximum at about pH 2. The ascending arm of the profile with decreasing pH indicates a catalytic effect for hydronium ion. Since the apparent pK_a of the imidazolidine ring is high (9.0), it is likely that hydronium ion catalysis represents protonation of the acyclic nitrogen produced by ring opening (eq 4). Such protonation



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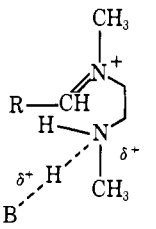
IV

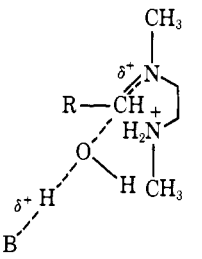
would inhibit reclosure of the ring and would thereby produce a catalytic effect on the rate of aldehyde formation. The descending arm of the pH–rate constant profile at pH values less than 2 might correspond with double protonation of the imidazolidine ring; the diprotonated species would be relatively unreactive because a protonated nitrogen would not readily release electrons to stabilize an incipient carbonium ion during ring opening. However, it will be noted in Figure 2 that the slope at pH < 2 is less than 1.0, contrary to what would be expected if that effect were due to a pK_a of the imidazolidine ring.

The formation and hydrolysis of Schiff bases has been extensively studied,[15-21] and the mechanisms of these reactions are reasonably well understood.[18,20,21] The principal conclusions follow: (1) The pH-independent hydrolysis reaction which occurs under basic conditions probably involves rate-determining attack of hydroxide ion on the protonated Schiff base. (2) At pH values where the Schiff bases are predominantly protonated, attack of water on the protonated Schiff base takes place. (3) Under still more acidic conditions, the decrease in first-order rate constants with decreasing pH is due to a change in rate-determining step with carbinolamine decomposition becoming rate limiting. Therefore, the simplest explanation of the pH–rate constant profile for hydrolysis of I is that Schiff-base hydrolysis is rate determining with the rate-determining step changing at about pH 2, presumably from attack of water on the cationic Schiff base to decomposition of a carbinolamine intermediate.

There is significant buffer catalysis in the initial reaction which is kinetic general acid catalysis. Thus, as in the hydronium ion catalyzed reaction, the general acid catalyzed reaction may be looked upon as either partial proton transfer to the acyclic nitrogen subsequent to ring opening (V), or general base catalysis of the hydrolysis of a protonated Schiff base (VI). In both cases, protonation of nitrogen would aid the re-



V



VI

action by inhibiting reclosure of the ring. If it is assumed that Brønsted coefficients of 1.0 and 0 are indicative of rate-determining proton transfer reactions,[22] whereas Brønsted coefficients between 0 and 1.0 imply proton transfer concerted with bond making or breaking, then the α value of 0.76 obtained from the plot of Figure 4 gives support to a concerted mechanism for the general acid catalyzed reaction. Rate-determining protonation of the acyclic nitrogen by relatively weak acids subsequent to ring opening (V) would be expected to lead to a Brønsted α close to unity.

In order for protonation of the acyclic nitrogen of the cationic Schiff-base intermediate (k_2 in eq 4) to be rate determining, it would be necessary for k_2 (HA) to be less than k_{-1}, the rate constant for reclosure of the ring. Since with strong acids (H_3O^+), k_2 will be the rate constant of a diffusion-controlled reaction (10^{10} M^{-1} s^{-1}), k_2 should be greater than k_{-1}. It is likely that protonation of the acyclic nitrogen is an equilibrium process and that Schiff-base hydrolysis is rate limiting. The observed general acid catalysis would then actually correspond with general base catalysis of the hydrolysis of the protonated Schiff base (VI) with $\beta = 0.24$ ($\alpha = 1 - \beta$). A Bronsted β of 0.24 for such a reaction is in accord with the β of 0.4 found for general base catalyzed hydrolysis of the cationic Schiff base derived from *N,N,N',N'*-tetramethyl-*p*-methoxytoluenediamine[6] and the low sensitivity of the reaction to basicity of the catalyst in hydrolysis of the cationic Schiff base produced in ring opening of 2-(*p*-methoxyphenyl)-*N,N'*-dimethyl-1,3-imidazolidine.[6] The Brønsted β value for

general base catalyzed attack of water on benzhydrylidenedimethylammonium ion is 0.27.[20]

At pH values greater than 6 an intermediate is not detected, the observed reaction being the formation of pivaldehyde. The pH–log rate constant profile for this reaction is a plateau until pH 9.0 where there is a change of slope to −1.0. This acid-catalyzed reaction has a second-order rate constant $k_H = 1.1 \times 10^8\ M^{-1}\ s^{-1}$. The bend in the profile probably corresponds to the high pK_a of the imidazolidine ring, and the acid-catalyzed reaction is most likely rapid hydronium ion catalyzed ring opening followed by rate-limiting attack of H_2O on the intermediate cationic Schiff base. If ring opening were rate determining and the reaction occurred with unimolecular breakdown of the conjugate acid, then the second-order rate constant for hydronium ion catalysis would be given by $k_H = k_{open}/K_a$, where K_a is the dissociation constant of the conjugate acid (10^{-9}) and k_{open} is the rate constant for unimolecular ring cleavage of the protonated imidazolidine. A value of $1.1 \times 10^{-1}\ s^{-1}$ can thereby be calculated for k_{open}. This value is improbably low considering the resonance stabilization of the developing carbonium ion provided by the adjoining nitrogen. Rate constants for unimolecular breakdown of protonated acetals are much greater. For example, that for benzaldehyde diethyl acetal must approximate $10^8\ s^{-1}$.[6]

The mechanistic possibilities for the pH-independent reaction at high pH are (1) rate-determining uncatalyzed or water-catalyzed breakdown of the imidazolidine to a cationic Schiff base followed by fast hydrolysis of the Schiff base, or (2) hydronium ion catalyzed ring opening of the imidazolidine followed by rate-determining hydroxide ion catalyzed hydrolysis of the Schiff base (eq 5). Cationic Schiff-base hydrolysis has been shown to proceed with hydroxide ion catalysis at high pH, and evidence was presented that this step is rate limiting in the pH-independent hydrolysis of 2-(*p*-methoxyphenyl)-*N*,*N*′-dimethylimidazolidine at high pH.[6] Imidazolidine I, with an aliphatic substituent at the 2 position, hydrolyzes sevenfold faster than the derivative with a *p*-methoxyphenyl substituent at the 2 position even though the *p*-methoxyphenyl group should provide greater stabilization of the incipient carbonium ion in the transition state for ring opening than is possible by an alkyl substituent. A *p*-methoxyphenyl substituent can release electrons through a resonance effect to stabilize a carbonium ion, which contributes to a faster rate of hydrolysis for diethyl acetals or dioxolanes of *p*-methoxybenzaldehyde than in the case of acetals where such resonance stabilization is not possible.[23] The faster pH-independent hydrolysis of I relative to 2-(*p*-methoxyphenyl)-*N*,*N*′-dimethyl imidazolidine must be due to (1) the slightly greater basicity of the imidazolidine nitrogens (apparent pK_a values are 9.0 and 8.0, respectively), and (2) a compensation of effects in which increased carbonium ion stabilization will permit a larger equilibrium concentration of cationic Schiff base but may decrease reactivity of the Schiff base toward attack by ^-OH. The acid-catalyzed hydrolysis reaction of I at pH 9–12 ($k_H = 1.1 \times 10^8\ M^{-1}\ s^{-1}$) is also nearly two orders of magnitude faster than that of the corresponding *p*-methoxyphenyl derivative as can be seen from the rate constants in Table IV.

Table IV. Rate Constants for Imidazolidine Hydrolysis to Aldehydes in H_2O at 30 °C

Compd	$k'_H \times 10^{-4}$, $M^{-1}\ s^{-1}$	$k_H \times 10^{-4}$, $M^{-1}\ s^{-1}$	$k'_0{}^a \times 10^4$, s^{-1}
2-(*p*-Methoxyphenyl)-*N*,*N*′-dimethyl-1,3-imidazolidine[b]	1.0	200	0.34
2-(*tert*-Butyl)-*N*,*N*′-dimethyl-1,3-imidazolidine	4.50	11 000	2.3
2-(*p*-Methoxyphenyl)-*N*-isopropyl-*N*′-phenyl-1,3-imidazolidine	0.235	6.3	0.95
2-(*p*-Methoxyphenyl)-*N*,*N*′-diphenyl-1,3-imidazolidine[b]		0.000 006	

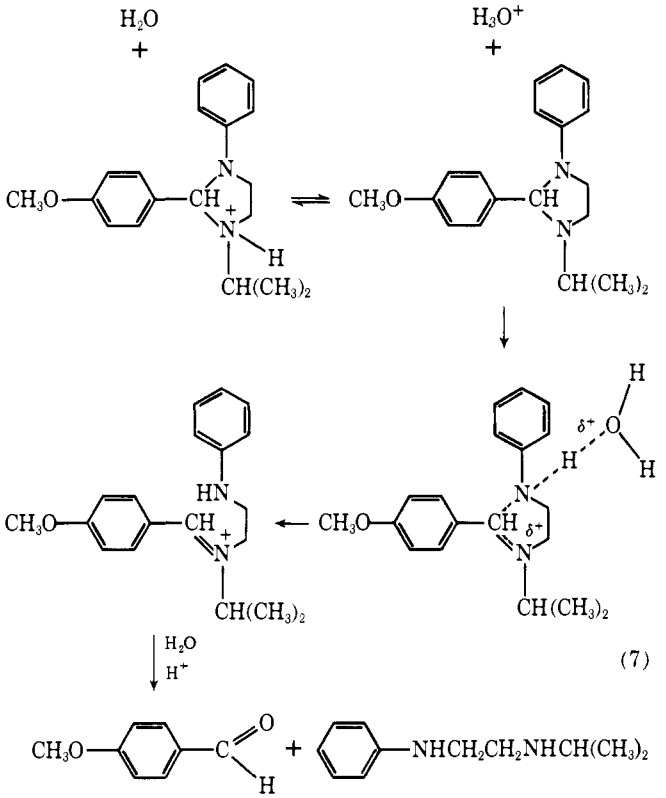
[a] Rate constant for the pH-independent reaction at high pH (>11). [b] Reference 6.

2-(*p*-Methoxyphenyl)-*N*-isopropyl-*N*′-phenyl-1,3-imidazolidine (II). An intermediate cationic Schiff base can be directly observed in hydrolysis of II at 330 nm at pH values below 5.0. The absorption maximum of the intermediate at 330 nm is identical with that of the intermediate observed in hydrolysis of 2-(*p*-methoxyphenyl)-*N*,*N*′-dimethyl-1,3-imidazolidine[6] and corresponds closely with that of the cationic Schiff base from 2-(*p*-methoxyphenyl)-*N*-ethyl-1,3-oxazolidine (λ_{max} 324 nm).[24] The protonated Schiff base of *p*-methoxybenzylidine ethanolamine also has its λ_{max} at 324 nm.[24] Furthermore, λ_{max} in 12 M HCl for *N*-(*p*-methoxy)benzylideneaniline is 368 nm whereas that for N-(*p*-methoxy)benzylideneisopropylamine is 323 nm. In 12 M HCl these Schiff bases would be protonated and would therefore be analogous to a cationic Schiff base. Thus, from the spectral data, it is highly probable that the cationic Schiff base observed in the ring opening reaction of II is the more stable *N*-alkyl Schiff base.

The rapid increase in absorbance at 330 nm in hydrolysis of II must correspond to ring opening to a cationic Schiff base. This reaction is pH independent from pH 0 to 3.5. Therefore, the apparent pK_a at pH 1.5 for aldehyde formation (see Figure 6) is not influencing ring opening but must be a factor only in hydrolysis of the intermediate. It can be considered that at pH values below 3.5 the ground state of the molecule is the monoprotonated species. It would be expected that the pK_a of the phenyl substituted nitrogen would be quite low (<2). The pK_a of 2-(*p*-methoxyphenyl)-*N*,*N*′-diphenyl-1,3-imidazolidine is less than 1.[6] Hence, the nitrogen that is predominantly protonated in the reactant ($pK_a = 7.2$)[25] must be the more basic alkyl-substituted nitrogen (eq 6). The phenyl-substituted ni-

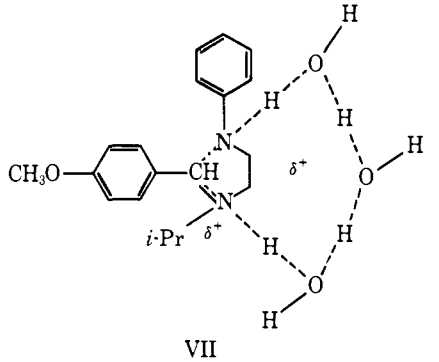
trogen cannot release electrons to stabilize a developing carbonium ion as readily as an alkyl-substituted nitrogen. Consequently, protonation of the *N*-alkyl group could occur to give a protonated imidazolidine intermediate, whereas proton transfer to the *N*-phenyl group might lead to ring opening with concerted proton transfer and C–N bond breaking. It will be noted in Figure 6 that the profile indicates incursion of a hydronium ion catalyzed reaction at pH 7. Since Schiff-base hydrolysis in that pH region involves attack of a water molecule on the cationic Schiff base,[6,18] the inflection in the profile must correspond with the pK_a of the imidazolidine ring, which can be mainly attributed to the alkyl-substituted nitrogen.[25]

Buffer catalysis cannot be detected in the observed ring-opening reaction at low pH. However, the large D_2O solvent isotope effect ($k_{open}^{H_2O}/k_{open}^{D_2O} = 2.5$) shows conclusively that proton transfer is occurring. Thus, the nitrogen that is predominantly protonated in the reactant is not the leaving group in the reaction; the proton is being transferred to the less basic phenyl-substituted nitrogen. Proton transfer in the transition state might occur in a stepwise manner (eq 7), or the reaction might



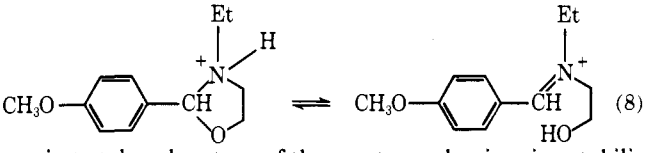
(7)

take place through a concerted internal proton transfer mediated by one or more water molecules (VII). The reaction could



VII

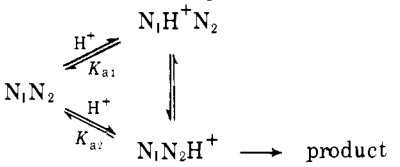
proceed in this manner to take advantage of the much greater stabilization of the developing carbonium ion that is possible by the more basic nitrogen. In a similar manner, 2-(*p*-methoxyphenyl)-*N*-ethyl-1,3-oxazolidine is protonated on nitrogen in the reactant, but ring opening involves proton transfer and C–O bond breaking to give a Schiff base[24] (eq 8)



(8)

again to take advantage of the greater carbonium ion stabilization that results in comparison to the case with C–N bond breaking.

An alternative is given in eq 9 where proton transfer is



(9)

stepwise. The concentration of the relevant monoprotonated species ($N_1N_2H^+$) is given by

$$N_1N_2H^+ = N_T \frac{K_{a1}a_H}{K_{a2}a_H + K_{a1}(K_{a2} + a_H)} \qquad (10)$$

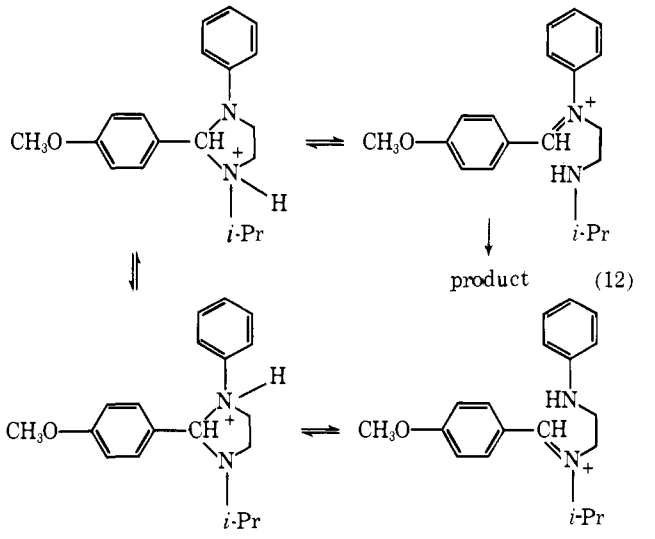
In the pH range 1–3, therefore, since $K_{a2} \gg K_{a1}$,

$$N_1N_2H^+ = N_TK_{a1}/K_{a2} \qquad (11)$$

Thus the reaction would be pH independent, and a D_2O solvent isotope effect might arise if D_2O has different effects on K_{a1} and K_{a2}. Acid dissociation constants are normally reduced in D_2O as compared with H_2O, and this effect can be greater for weaker acids.[26] It is apparent that proton transfer must occur in order to explain the slower rate of ring opening in D_2O than in H_2O regardless of whether such proton transfer occurs in the transition state or in a preequilibrium process. Consequently, the leaving group must be the less basic phenyl-substituted nitrogen in accordance with the conclusion derived from the spectral data.

If the reaction of II follows the scheme of eq 7, it can be calculated from the magnitude of k_{obsd} for ring opening (188 s^{-1}) and the apparent pK_a (7.2) that the second-order rate constant for hydronium ion catalyzed ring opening of the neutral species is 10^9 M^{-1} s^{-1}, approaching that for a diffusion controlled reaction. The lack of buffer catalysis gives some support to the internal proton transfer of VII, although it might simply be a consequence of the relatively high concentration of hydronium ion at low pH. Whether the ring-opening reaction follows the scheme of eq 7 or proton transfer is internal, carbonium ion stability and leaving group ability must be the critical factors in determining the direction of ring opening.

It might also be argued that a scheme such as eq 12 is in



(12)

operation. The rate of hydrolysis of protonated N-(*p*-chloro)-benzilideneaniline is 10^4-fold greater than that of the corresponding *tert*-butylamine Schiff base.[18] Therefore, hydrolysis products might be formed more readily in the present case from the least stable cationic Schiff base. This would demand that the spectrally observed Schiff base (most stable Schiff base) not be directly on the reaction pathway to products, although rate constants for Schiff-base disappearance and aldehyde formation are identical in the pH range (1–3.5). Such a scheme is unlikely at high acidity because protonation of the acyclic nitrogen of the Schiff base would preclude facile reversibility. If the least stable Schiff base were formed preferentially by expulsion of the protonated *N*-alkyl group (most basic amine) then it is highly probable that it would hydrolyze directly to products without significant reversibility to the most stable Schiff base. Ring opening in that case should not have a marked rate-slowing D_2O solvent isotope effect.

An intermediate cationic Schiff base is not detected at pH values greater than 5, probably because the acyclic amine group is then largely unprotonated. When the acyclic amine is in the neutral form reclosure of the ring will be rapid and the Schiff-base intermediate will only be present at low steady-state concentrations. Formation of *p*-methoxybenzaldehyde is then the observed reaction. The log rate constant–pH profile for this reaction in Figure 6 is qualitatively similar to the profiles for hydrolysis of 2-(*p*-methoxyphenyl)-*N,N'*-dimethyl-1,3-imidazolidine[6] and the aliphatic derivative I (Figure 2). It is likely that the reaction involves acid-catalyzed ring opening followed by rate-determining attack of H_2O (pH 7–10) or ^-OH (pH >10) on a cationic Schiff base.

The hydrolysis of cationic Schiff bases derived from *p*-methoxybenzaldehyde has previously been studied.[6] The pH–rate constant profile for hydrolysis of the intermediate obtained from *N,N,N',N'*-tetramethyl-*p*-methoxytoluenediamine shows hydroxide ion catalysis at high pH and a pH-independent reaction from pH 1 to 8. The pH-independent reaction, which involves rate-determining attack of a water molecule on the cationic Schiff base, occurs with a large D_2O solvent isotope effect (k_{H_2O}/k_{D_2O} = 2.4) and general base catalysis (β = 0.42).

Conclusions

N,N'-Dimethyl-1,3-imidazolidines derived from aliphatic aldehydes give pH–rate constant profiles for hydrolysis that are similar in shape to those obtained with imidazolidines of aromatic aldehydes. However, the rate constants for the 2-*tert*-butyl derivative (I) are one to two orders of magnitude greater at 30 °C than those for the 2-(*p*-methoxyphenyl)-substituted compound. With both aliphatic and aromatic imidazolidines, the rate-determining step in the overall reaction at all pH values probably is hydrolysis of an intermediate cationic Schiff base, and general catalysis by buffer takes place in the hydrolysis of the cationic Schiff base derived from both types of imidazolidines.

The unsymmetrical imidazolidine 2-(*p*-methoxyphenyl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine (II) undergoes initial protonation by hydronium ion on the most basic nitrogen, but this does not lead to products. A subsequent proton transfer to the phenyl-substituted nitrogen takes place so that the imidazolidine ring opens to give the most stable carbonium ion intermediate. As in the hydrolysis of acetals,[27] carbonium ion stability is of critical importance in determining mechanism; if the intermediate carbonium ion is highly stable, bond breaking will be sufficiently facile that proton transfer may become part of the rate-limiting step.

The above considerations can be applied to N^5,N^{10}-methylenetetrahydrofolic acid, which must undergo ring opening in biochemically important enzyme-catalyzed processes such as the thymidylate synthetase reaction.[28] The finding of general acid catalysis or a kinetic equivalent in the hydrolysis of I shows that it is a chemically feasible mechanism in reactions of 1,3-imidazolidines of aliphatic aldehydes, and could, therefore, occur in enzymatic reactions of N^5,N^{10}-methylenetetrahydrofolic acid. The unsymmetrical nature of N^5,N^{10}-methylenetetrahydrofolic acid is undoubtedly of critical importance. The pK_a values of N(5) and N(10) in tetrahydrofolic acid are 4.85 and −1.25, respectively.[7] Such a distribution of pK_a values could lead to partially rate-determining protonation of N(10) by a general acid with cleavage of the C–N^{10} bond to take advantage of the low basicity of N(10) and the greater carbonium ion stabilization that would result from electron release by N(5).[6,29]

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References and Notes

(1) Postdoctoral Fellow, Department of Biochemistry, University of Southern California.
(2) S. J. Benkovic, P. A. Benkovic, and D. R. Comfort, *J. Am. Chem. Soc.*, **91**, 5270 (1969); S. J. Benkovic, P. A. Benkovic, and R. Chrzanowski, *ibid.*, **92**, 523 (1970).
(3) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5851, 5864 (1966).
(4) T. H. Barrows, P. R. Farina, R. L. Chrzanowski, P. A. Benkovic, and S. J. Benkovic, *J. Am. Chem. Soc.*, **98**, 3678 (1976).
(5) G. P. Tuszynski and R. G. Kallen, *J. Am. Chem. Soc.*, **97**, 2860 (1975).
(6) T. H. Fife and J. E. C. Hutchins, *J. Am. Chem. Soc.*, **98**, 2536 (1976).
(7) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5845 (1966).
(8) J. Hine and K. W. Narducy, *J. Am. Chem. Soc.*, **95**, 3362 (1973).
(9) R. G. Shepherd and R. G. Wilkinson, *J. Med. Pharm. Chem.*, **5**, 823 (1962).
(10) S. Ikegami and S. Yamada, *Chem. Pharm. Bull.*, **14**, 1389 (1966).
(11) Y. Pocker and D. G. Dickerson, *J. Phys. Chem.*, **73**, 4005 (1969).
(12) The Schiff-base derivative of pivaldehyde and *N*-methylethylenediamine in 5 M HCl has little absorbance at 280 nm. Its absorbance progressively increases with decreasing wavelength in 5 M HCl or in acetonitrile but with no sharp maximum at wavelengths above 230 nm. This is also the case with the di-Schiff base of pivaldehyde and ethylenediamine with which ring closure to an imidazolidine is not possible until the initial hydrolysis reaction has taken place. In 5 M HCl the Schiff bases would be protonated and would, therefore, closely resemble the cationic Schiff base from I. Both Schiff bases hydrolyze in 5 M HCl with a decrease in absorbance at 230 nm and an increase at 280 nm.
(13) The λ_{max} values for a series of Schiff-base derivatives of isobutyraldehyde and aliphatic amines are all less than 235 nm: J. Hine, C. Y. Yeh, and F. C. Schmalstieg, *J. Org. Chem.*, **35**, 340 (1970).
(14) The pK_a of 2-isopropyl-*N,N'*-dimethyl-1,3-imidazolidine has been calculated to be 7.95 (ref 8).
(15) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959).
(16) B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, **82**, 1773 (1960).
(17) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 832 (1962).
(18) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963).
(19) A. V. Willi, *Helv. Chim. Acta*, **39**, 1193 (1956).
(20) K. Koehler, W. Sandstrom, and E. H. Cordes, *J. Am. Chem. Soc.*, **86**, 2413 (1964).
(21) J. Hine, J. C. Craig, J. G. Underwood, and F. A. Via, *J. Am. Chem. Soc.*, **92**, 5194 (1970).
(22) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(23) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).
(24) T. H. Fife and L. Hagopian, *J. Am. Chem. Soc.*, **90**, 1007 (1968).
(25) The pK_a of 7.2 is a macroscopic constant which might involve protonated alkyl and aryl substituted amine groups.
(26) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, p 250.
(27) T. H. Fife, *Acc. Chem. Res.*, **5**, 264 (1972).
(28) J. I. Rader and F. M. Huennekens in "The Enzymes", Vol. 9, 3rd ed, P. D. Boyer, Ed., Academic Press, New York, N.Y., 1973; F. M. Huennekens, *Vitam. Horm.*, **26**, 375 (1968); F. M. Huennekens in "Biological Oxidations", T. P. Singer, Ed., Wiley, New York, N.Y., 1968, p 439.
(29) See also the discussion in S. J. Benkovic and W. P. Bullard, *Prog. Bioorg. Chem.*, **2**, 133 (1972).