(7) (a) J. D. Roberts, W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3329 (1950); (b) H. G. Richey, Jr., and N. C. Buckley, *ibid.*, **85**, 3057 (1963); P. R. Story and S. R. Farenholtz, *ibid.*, **86**, 527 (1964).
(8) E. N. Peters and H. C. Brown, *J. Am. Chem. Soc.*, **97**, 7454 (1975).
(9) H. C. Brown and E. N. Peters, *J. Am. Chem. Soc.*, **97**, 7442 (1975).
(10) H. C. Brown, E. N. Peters, and M. Ravindranathan, *J. Am. Chem. Soc.*, **97**, 7449 (1975).
(11) P. D. Bartlett and M. R. Rice, *J. Org. Chem.*, **28**, 3351 (1963).
(12) H. C. Brown, F. J. Chloupek and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 1248 (1964).
(13) H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1972, Chapter 11.
(14) P. D. Bartlett and W. P. Giddings, *J. Am. Chem. Soc.*, **82**, 1240 (1960).
(15) W. P. Giddings and J. Dirlam, *J. Am. Chem. Soc.*, **85**, 3900 (1963).
(16) D. V. Braddon, G. A. Wiley, J. Dirlam, and S. Winstein, *J. Am. Chem. Soc*, **90**, 1901 (1968).
(17) H. Tanida, H. Ishitobi, and T. Irie, *J. Am. Chem. Soc.*, **90**, 2688 (1968).
(18) H. Tanida, T. Irie, and T. Tsushima, *J. Am. Chem. Soc.*, **92**, 3404 (1970).
(19) H. C. Brown and G. L. Tritle, *J. Am. Chem. Soc.*, **90**, 2689 (1968).
(20) H. C. Brown and G. L. Tritle, *J. Am. Chem. Soc.*, **86**, 4904 (1964).
(21) H. Tanida, T. Tsuji, and H. Ishitobi, *J. Am. Chem. Soc.*, **86**, 4904 (1964).
(22) H. Tanida, Y. Hata, S. Ikegami, and H. Ishitobi, *J. Am. Chem. Soc.* **89**, 2928 (1967).
(23) H. Tanida, T. Tsuji, and S. Teratake, *J. Org. Chem.*, **32**, 4121 (1967).
(24) H. C. Brown and K. Takeuchi, *J. Am. Chem. Soc* **90**, 2691 (1968).
(25) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Am. Chem. Soc.*, **74**, 1113 (1952).
(26) M H. Rei and H. C. Brown, *J. Am. Chem. Soc.* **88**, 5335 (1966).
(27) P. v. R. Schleyer, *J. Am. Chem. Soc.*, **89**, 701 (1967).
(28) For example, the acetolysis rate of *anti*-9-benzonorbornenyl brosylate is faster than that of 7-norbornyl by a factor of 5×10^5 as compared with the 10^{11} factor assigned to the 7-norbornenyl derivative.[21]
(29) See discussion in ref 9.
(30) H. Tanida, H. Ishitobi, T. Irie, and T. Tsushima, *J. Am. Chem. Soc.*, **91**, 4512 (1969).
(31) This is equivalent to a plot against σ^+ for the 2-aryl derivatives, but allows the inclusion of the 2-CH_3 and 2-H derivatives in the plot.
(32) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958).
(33) G. L. Tritle, Ph.D. Thesis, Purdue University, West Lafayette, Indiana, 1966.
(34) H. C. Brown and M.-H. Rei, *J. Org. Chem.*, **31**, 1090 (1966).

General Acid Catalysis of the Hydrolysis of Acetal Analogues of High Basicity. The Hydrolysis of 2-(Substituted phenyl)-*N,N*-dimethyl-1,3-imidazolidines

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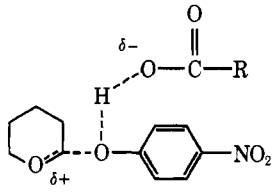
Abstract: The rates of hydrolysis of a series of 2-(substituted phenyl)-*N,N*-dimethyl- and -diphenyl-1,3-imidazolidines to the corresponding aldehydes have been measured in H_2O at 30 °C. With 2-(*p*-methoxyphenyl)-*N,N*-dimethyl-1,3-imidazolidine, a cationic Schiff base intermediate can be observed at pH values below 4.7 (λ_{max} 330 nm). This Schiff base hydrolyzes rapidly in moderately concentrated HCl solutions in comparison with analogous intermediates formed during hydrolysis of 2-(*p*-methoxyphenyl)-*N*-ethyloxazolidine and -thiazolidine. High reactivity is due to lack of reversibility of the ring-opening reaction after protonation of the nitrogen leaving group subsequent to ring opening. The order of reactivity for intramolecular nucleophilic attack on a cationic Schiff base is SH > OH > $N^+H_2CH_3$. The rate of cationic Schiff base hydrolysis decreases with increasing acidity in moderately concentrated HCl solutions. From pH 2–4, formation of *p*-methoxybenzaldehyde is pH independent. Kinetic general base catalysis occurs in that pH region. At pH values greater than 4.7, a Schiff base intermediate can no longer be observed, and the rate of aldehyde formation decreases with increasing pH. A plot of log k_{obsd} vs. pH is linear from pH 8.5–11 with slope of −1.0. At pH values greater than 11, the reaction again becomes pH independent ($k_0^{H_2O}/k_0^{D_2O} = 1.5$). The acid-catalyzed reaction involves rapid acid-catalyzed ring opening (at near diffusion-controlled rates) followed by rate-limiting Schiff base hydrolysis. Kinetic general acid catalysis is observed. An intermediate is not observed because of facile reversibility of the ring-opening reaction. That this interpretation is correct is shown by the behavior of the analogous open-chain compound *N,N,N′,N′*-tetramethyl-*p*-methoxytoluenediamine. This compound gives a cationic Schiff base at rates too fast to measure at all pH values. The Schiff base hydrolyzes to *p*-methoxybenzaldehyde in a pH-independent reaction which involves proton transfer in the critical transition state ($k_{H_2O}/k_{D_2O} = 2.39$). General base catalysis is observed with $\beta = 0.42$. Hydroxide ion catalysis takes place at pH values greater than 7. 2-(*p*-Methoxyphenyl)-*N,N*-diphenylimidazolidine hydrolyzes slowly to aldehyde in an acid-catalyzed reaction which is $\sim 10^7$-fold slower than in the case of the *N,N*-dimethyl derivative. The reaction is considerably faster in D_2O than H_2O ($k_D/k_H = 2.9$). Thus, it is likely that the ring is opening in an A-1 reaction involving preequilibrium protonation of the substrate by hydronium ion. The relative unreactivity of this compound is due to the low basicity of the ring nitrogens ($pK_a < 1$). Therefore, protonation is not appreciable, and the nitrogen does not readily release electrons to stabilize a carbonium ion intermediate.

The structural features in acetals that will allow general acid catalysis in their hydrolytic reactions have been determined.[2] General acid catalysis by buffer acids will be observed in cases where the leaving group is good (a phenol) and the intermediate carbonium ion is of moderate stability.[3] General acid catalysis will also occur when the leaving group is poor (an aliphatic alcohol) if the intermediate is of exceedingly great stability, approaching that of an alkoxytropylium ion,[4] or if there is steric strain in the ground state which is relieved in the transition state of the reaction.[5] In all of these cases, ease of bond breaking is the key factor in facilitating general acid catalysis, with basicity considerations apparently of secondary importance. That even very low basicity of the substrate will not by itself permit general acid catalysis was shown by the fact that general acid catalysis could not be observed in hydrolysis of benzaldehyde methyl *S*-phenyl thioacetals where thiophenol is the leaving group in the reaction.[6] The exactly analogous oxygen acetals are subject to general acid catalyzed hydrolysis.[7]

In an early discussion of general acid catalyzed hydrolysis of orthoesters,[8] low basicity was stressed as the primary cause. However, it was later demonstrated that with orthoesters, as with acetals, ease of bond breaking is of greater importance in facilitating general acid catalysis.[9]

Jencks[10] has recently proposed that concerted general acid catalysis will be seen in cases where the pK_a of the sub-

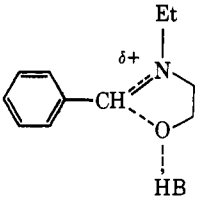
strate and the product are widely separated with basicity of the transition state and the pK_a of the catalyst being intermediate. In this manner, a thermodynamically unfavorable proton transfer in the ground state will be converted to a favorable proton transfer in the transition state. Acetal hydrolysis appears to fit this criterion nicely. A reasonable estimate of the pK_a of 2-(*p*-nitrophenoxy)tetrahydropyran would be −10, whereas that of the product *p*-nitrophenol is 7. The reaction is best considered to be a concerted process (I) in which proton transfer and bond breaking occur simul-



I

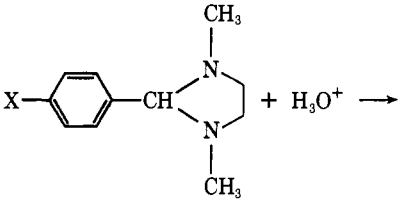
taneously.[2,3] Again, however, the stress on basicity appears to be at variance with the predominant importance of ease of bond breaking and the lack of general acid catalysis in the hydrolysis of thioacetals.[6]

If ease of bond breaking is indeed of overwhelming importance in leading to general acid catalysis, then it might be expected that such catalysis would be observed in cases where substrate basicity is quite *high* if bond breaking is sufficiently facile. An adjoining nitrogen will greatly stabilize a carbonium ion through electron release. Thus, acetal analogues in which an oxygen atom is replaced by nitrogen should, and do, hydrolyze relatively rapidly.[11] It is probable that it is this great carbonium ion stability that makes ring opening of phenyl *N*-ethyl-1,3-oxazolidines to a positively charged Schiff base so facile and which in turn leads to the observed general catalysis[11] (II). We have therefore studied

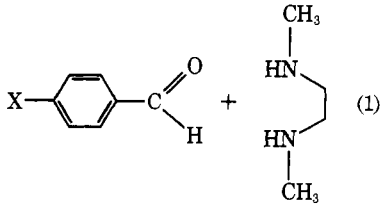


II

the hydrolysis reactions of the 2-(substituted phenyl)-*N,N*-dimethyl-1,3-imidazolidines III–VII (eq 1) since basicity is

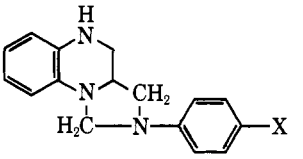


III, X = OCH_3
IV, X = CH_3
V, X = H
VI, X = Cl
VII, X = NO_2



(1)

high and bond breaking should be relatively easy. Little previous work has been reported on the hydrolysis of imidazolidines. Benkovic et al.[12] found buffer catalysis in the synthesis of the methylenetetrahydrofolic acid models VIII in



VIII

aqueous dioxane from the corresponding tetrahydroquinoxaline analogues and formaldehyde. General base catalysis was the preferred mechanism. From this it might be inferred that general acid catalysis would occur in ring-cleavage reactions of VIII and *N*(5),*N*(10)-methylenetetrahydrofolic acid. An understanding of the manner in which the imidazolidine ring can open is of critical importance in the elucidation of the mechanism of action of tetrahydrofolic acid derivatives.

Experimental Section

Materials. 2-(Substituted phenyl)imidazolidines were prepared by refluxing in benzene equivalent amounts of the appropriately substituted benzaldehyde and *N,N*-disubstituted-ethylenediamine. Water was continuously removed from the reaction mixture by azeotropic distillation with the benzene. After collection of a theoretical amount of water, the benzene was removed by rotary evaporation, and the residue was either distilled or recrystallized. 2-(*p*-Methoxyphenyl)-*N,N*-dimethylimidazolidine (III) had bp 93–95 °C (0.6 mm), n_D^{24} 1.5315; lit.[13] bp 83 °C (0.2 mm), n_D^{20} 1.5326. An NMR spectrum was identical with the reported spectrum.[13] 2-(*p*-Methylphenyl)-*N,N*-dimethylimidazolidine (IV) had bp 73.5–74 °C (0.4 mm), n_D^{24} 1.5232; lit.[13] bp 68 °C (0.2 mm), n_D^{20} 1.5248. 2-Phenyl-*N,N*-dimethylimidazolidine (V) had bp 63–64 °C (0.8 mm), n_D^{25} 1.5241; lit.[13] bp 65 °C (0.6 mm), n_D^{20} 1.5271. 2-(*p*-Chlorophenyl)-*N,N*-dimethylimidazolidine (VI) had bp 97 °C (0.7 mm), n_D^{23} 1.5395; lit.[13] bp 74 °C (0.23 mm), n_D^{20} 1.5404. 2-(*p*-Nitrophenyl)-*N,N*-dimethylimidazolidine (VII) had bp 126 °C (0.5 mm), n_D^{25} 1.5560. Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.72; H, 6.78. Found: C, 59.76; H, 6.74. 2-(*p*-Methoxyphenyl)-*N,N*-diphenylimidazolidine (IX) had mp 163–164 °C; lit.[14] mp 163–164 °C. *N,N,N',N'*-Tetramethyl-*p*-methoxytoluenediamine (X) was prepared by the method of Milakofsky[15] and boiled at 131–133 °C (10 mm); lit.[15] 120–121 °C (6 mm).

Kinetic Methods. Stock solutions of substrate (1×10^{-2} M) were made up in anhydrous acetonitrile. In studies employing a Zeiss PMQ 11 or Gilford Model 2000 spectrophotometer, 25 μl of the substrate stock solution was injected into the reaction cuvette containing 3 ml of buffer, and the reaction was monitored at the appropriate wavelength after stirring. Temperature was controlled at 30 ± 0.1 °C, and the ionic strength of the buffers was kept constant at either 0.5 or 1.0 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.

The thermodynamic pK_a of compounds III–VII could not be measured because of the rapid rates of ring opening. However, a plot of initial absorbance utilizing the stopped-flow spectrophotometer vs. pH for a series of identical concentrations of III yielded a sigmoidal curve with a midpoint at pH 4.1. This apparent pK_a is most likely a complex constant representing a combination of ring opening of the imidazolidine and addition of a proton to the

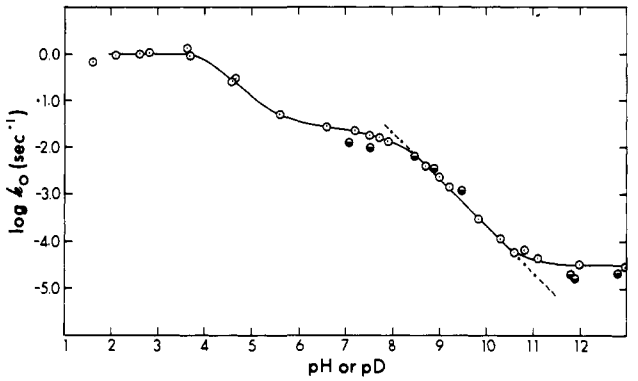


Figure 1. Plot of log k_0 vs. pH for the formation of *p*-methoxybenzaldehyde (measured at 283 nm) from 2-(*p*-methoxyphenyl)-*N,N*-dimethyl-1,3-imidazolidine at 30 °C and μ = 1.0 with KCl in H_2O (⊙) and in D_2O (⊖).

Table I. Values of k_{obsd} for Aldehyde Formation from Rapidly Formed Cationic Schiff Bases in Moderately Concentrated HCl Solutions at 30 °C

Compd	HCl concen, M	k_{obsd}, s^{-1}
III	0.499	0.52
	1.999	0.18
	2.91	0.12
	4.00	0.046
	5.83	0.0167
IV	5.83	0.050
V	5.83	0.131

Table II. Second-Order Rate Constants for General Base and General Acid Catalyzed Hydrolysis of 2-(*p*-Methoxyphenyl)-*N,N*-dimethylimidazolidine in H_2O at 30 °C (μ = 1.0)[a]

Catalyst	pK_a	k_B, M^{-1} s^{-1}	k_{HB}, M^{-1} s^{-1}
Chloroacetate	2.6	1.18	
Formate	3.6	1.31	
Acetate	4.7	1.44	
Tris (H_2O)	8.3		0.79
Tris (D_2O)			0.41
Ethanolamine	9.6		0.137
Piperidine (H_2O)	11.3		0.0059
Piperidine (D_2O)	11.8		0.0046

[a] Where buffer catalysis was measured at more than one pH value, the reported second-order rate constant is the average.

free acyclic amine group produced by ring opening (see Discussion)

Results

In Figure 1 is shown a plot of log k_0 vs. pH for appearance of *p*-methoxybenzaldehyde from 2-(*p*-methoxyphenyl)-*N,N*-dimethylimidazolidine (III) in H_2O at 30 °C with μ = 1.0. The points were obtained by extrapolation to zero buffer concentration with the exception of those determined in HCl or NaOH solutions. A cationic Schiff base intermediate can be observed at pH values below 4.7. This intermediate has a λ_{max} at 330 nm which is similar to the λ_{max} at 323 nm for the cationic Schiff base derived from 2-(*p*-methoxyphenyl)-*N*-ethyloxazolidine and protonated *p*-methoxybenzilidine-ethanolamine.[11] The rates of formation of the cationic Schiff base were too rapid to be measured. Rate constants for Schiff base hydrolysis in moderately concentrated HCl solutions are given in Table I. Rate constants for disappearance of Schiff base at 330 nm and appearance of aldehyde at 283 nm were identical.

In the pH range where the substrate is completely protonated, general base catalysis by buffer bases is observed.

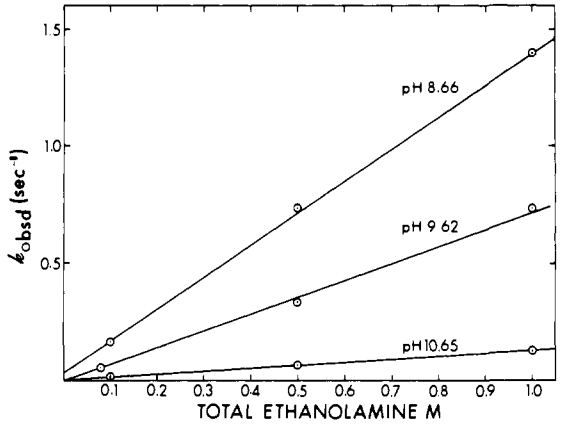


Figure 2. Plot of $k_{obsd} \times 10$ vs. total ethanolamine concentration (B + BH^+) for the formation of *p*-methoxybenzaldehyde from 2-(*p*-methoxyphenyl)-*N,N*-dimethyl-1,3-imidazolidine in H_2O at 30 °C with μ = 1.0 with KCl.

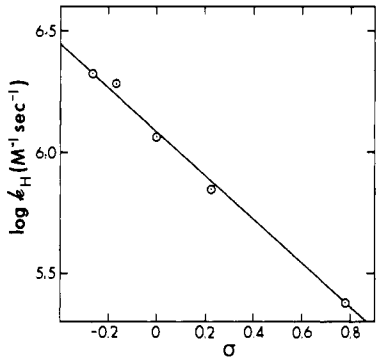


Figure 3. Plot of log k_H for acid-catalyzed hydrolysis of 2-(para-substituted phenyl)-*N,N*-dimethyl-1,3-imidazolidines to the appropriate aldehydes in H_2O at 30 °C (μ = 0.5) vs. σ.

Rate constants for general base catalysis are given in Table II. At pH values greater than 4.7, *p*-methoxybenzaldehyde is the product, but a Schiff base intermediate is not observed. At pH 6.5–7.5, catalysis by imidazole cannot be detected, with total imidazole concentration varying from 0.1 to 2.0 M.

An acid-catalyzed reaction occurs at pH values greater than 8 ($k_H = 2 \times 10^6$ M^{-1} s^{-1} for III). The slope of the plot of log k_{obsd} vs. pH (Figure 1) is −1.0. This reaction is faster in D_2O than in H_2O (k_D/k_H = 1.8 at zero buffer concentration) and is subject to general acid catalysis. Second-order rate constants for general acid catalysis are given in Table II. A plot of k_{obsd} vs. total ethanolamine concentration at three pH values is presented in Figure 2. The D_2O solvent isotope effect (k_{HA}/k_{DA}) for the Tris buffer-catalyzed reaction is 1.93. In Figure 3 is given a plot of log k_H vs. σ, the Hammett substituent constant,[16] for a series of 2-(*p*-substituted phenyl)-*N,N*-dimethylimidazolidines. The value of ρ is −0.93. The second-order k_H values given in Table III were calculated from rate constants determined by extrapolation to zero buffer concentration in borate buffer at pH 9.05.

At pH values greater than 11–12, k_{obsd} for aldehyde formation becomes pH independent. Rate constants are given in Table IV, and in Figure 4 is shown a plot of log k_0 vs. σ. The ρ value is −0.35. The D_2O solvent isotope effect $k_0^{H_2O}/k_0^{D_2O}$ for pH-independent hydrolysis of III is 1.5 at 30 °C and 1.8 at 50 °C. As shown in Figure 5, the conjugate acid of piperidine is a general acid catalyst for reaction of the *p*-methoxy derivative III in the pH region where the reaction is pH independent with a second-order rate con-

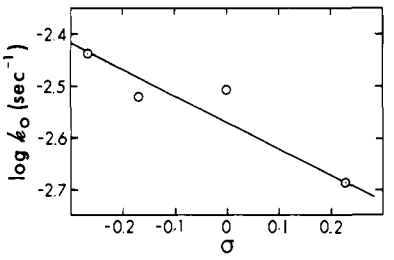


Figure 4. Plot of log k_0 + 1.0 for pH-independent hydrolysis of 2-(para-substituted phenyl)-*N,N*-dimethyl-1,3-imidazolidines to the appropriate aldehydes in H_2O at 50 °C (μ = 0.5) vs. σ. The rate constants were obtained in 0.1 M NaOH.

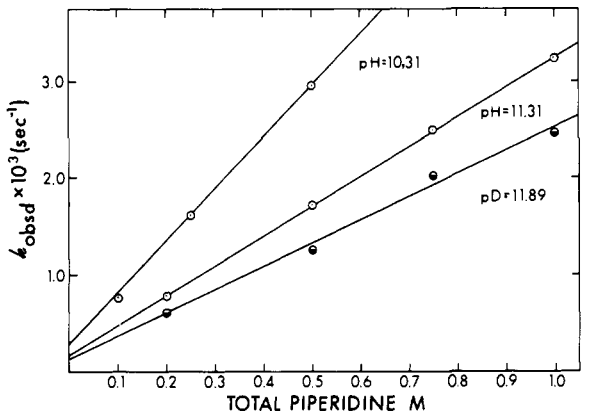


Figure 5. Plot of k_{obsd} vs. total piperidine concentration (B + BH^+) for the formation of *p*-methoxybenzaldehyde from 2-(*p*-methoxyphenyl)-*N,N*-dimethyl-1,3-imidazolidine in H_2O at 30 °C with μ = 1.0 with KCl (⊙) and in D_2O (◒).

Table III. Values of the Rate Constants for Hydrolysis of 2-(Para-substituted phenyl)-*N,N*-dimethyl-1,3-imidazolidines in H_2O at pH 9.05 (μ = 0.5) and 30 °C

p-Substituent	$k_{obsd} \times 10^3$ s^{-1} [a]	$k_H \times 10^{-6}$ M^{-1} s^{-1}
OCH_3	1.90	2.12
CH_3	1.72	1.93
H	1.05	1.17
Cl	0.635	0.71
NO_2	0.215	0.24

[a] Rate constants were obtained by extrapolation to zero buffer concentration.

Table IV. Values of $k_{obsd} \times 10^4$ s^{-1} for Hydrolysis of 2-(Para-substituted phenyl)-*N,N*-dimethyl-1,3-imidazolidines in NaOH Solutions at 50 °C (μ = 0.5)

Para-substituent	NaOH concn, M			
	0.001	0.01	0.1	0.06 (NaOD)
OCH_3	4.58	3.31	3.45	1.96
CH_3	6.28	4.21	3.03	
H	4.48	3.13	3.12	
Cl		2.43	2.07	

stant k_{HA} = 5.9 × 10^{-3} M^{-1} s^{-1}. However, catalysis was not observed when triethylamine buffers were employed.

A cationic Schiff base (λ_{max} 312 nm) is formed from *N,N,N',N'*-tetramethyl-*p*-methoxytoluenediamine in H_2O at rates that are too fast to measure. Hydrolysis of the cationic Schiff base was monitored by following disappearance at 325 nm and appearance of *p*-methoxybenzaldehyde at 283 nm. The reaction is pH independent at pH values below 7 with a rate constant, k_0, of 9.4 × 10^{-3} s^{-1} at 30 °C. Hydrolysis is slower in D_2O than H_2O, k_{H_2O}/k_{D_2O} = 2.39, as

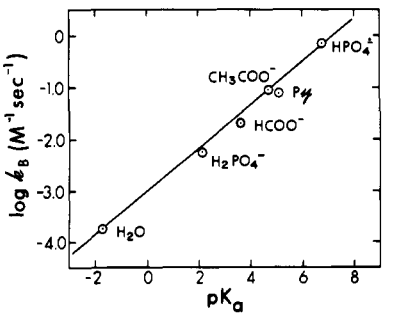


Figure 6. Plot of log k_B for general base catalyzed hydrolysis of the cationic Schiff base derived from *N,N,N',N'*-tetramethyl-*p*-methoxytoluenediamine in H_2O at 30 °C (μ = 0.5) vs. the pK_a of the catalyzing bases. The point for H_2O was calculated as $k_0/55.5$.

Table V. Rate Constants for Hydrolysis of the Cationic Schiff Base Derived from *N,N,N',N'*-Tetramethyl-*p*-methoxytoluenediamine at 30 °C (μ = 0.5 with KCl)

Buffer	pH	$k_0 \times 10^3$ s^{-1} [a]	$k_B \times 10^3$ M^{-1} s^{-1}
HCl (1 M)		2.18	
HCl (0.1 M)	1.10	9.2	
HCl (0.01 M)	2.10	9.1	
DCl (0.01 M)		3.8	
HCl (0.002 M)	3.00	9.1	
$H_2PO_4^-$	2.08	12.2	5.83
Formate	3.60	9.6	20.7
Acetate	4.70	7.7	92.5
Pyridine	5.21	9.8	78.3
HPO_4^{2-} (H_2O)	6.79	10.0	698.3
HPO_4^{2-} (H_2O)	5.82	9.3	766.6
HPO_4^{2-} (D_2O)	7.26 (pD)	7.5	250.0

[a] Rate constants obtained by extrapolation to zero buffer concentration.

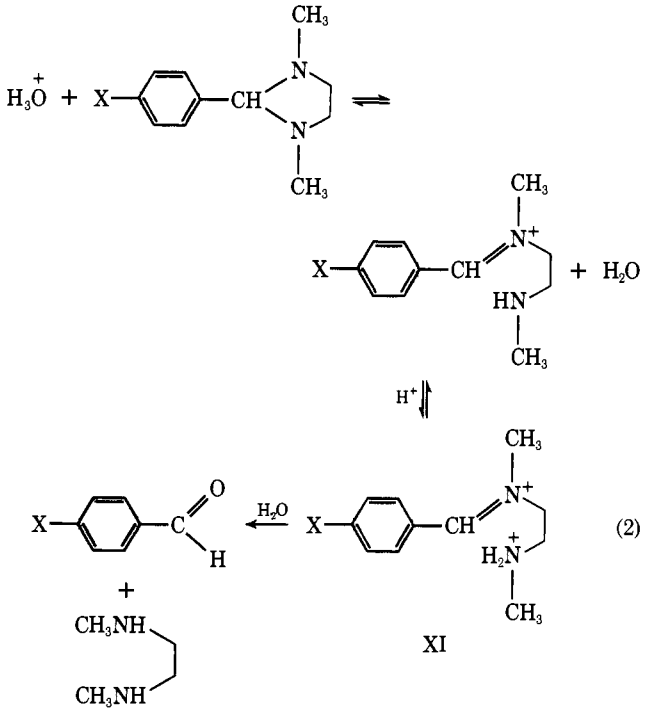
determined in HCl and DCl or by extrapolation to zero buffer concentration in acetate buffers in H_2O and D_2O. The hydrolysis reaction of the cationic Schiff base is catalyzed by general bases. The second-order rate constants are given in Table V, and in Figure 6 a plot of log k_B vs. pK_a is presented. The Brönsted coefficient β is 0.42. At pH values greater than 7, hydroxide ion catalysis can be observed: k_{OH} = 5 × 10^4 M^{-1} s^{-1}.

2-(*p*-Methoxyphenyl)-*N,N*-diphenyl-1,3-imidazolidine hydrolyzes in an acid-catalyzed reaction with a second-order rate constant at 30 °C (k_H) of 0.06 M^{-1} s^{-1} in H_2O. The reaction is faster in D_2O than H_2O (k_D/k_H = 2.9). Low solubility at pH values where a significant fraction of the compound is unprotonated prevented an extensive study in H_2O. With 50% dioxane-H_2O (v/v) as the solvent a plot (not shown) of log k_{obsd} at 30 °C vs. pH is linear with a slope of −1.0 in the pH range 2.10–5.95. The second-order rate constant k_H for hydronium ion catalysis in 50% dioxane-H_2O is 16.6 M^{-1} s^{-1}. Buffer catalysis by chloroacetate or formate buffer could not be detected in 50% dioxane-H_2O.

Discussion

Hydrolysis in Moderately Concentrated Acid. In moderately acidic HCl solutions, a Schiff base intermediate can be observed spectrophotometrically in the hydrolysis of the 2-(substituted phenyl)-*N,N*-dimethyl-1,3-imidazolidines III–VI. In all cases when the compound is introduced into aqueous solution, an absorbance maxima is detected at a wavelength corresponding closely to that of the positively charged Schiff base derived from the appropriate 2-(substituted phenyl)-*N*-ethyl-1,3-oxazolidine[11] or the protonated benzilidine ethanolamine Schiff base.[11] Formation of the

Schiff base is too rapid to be measured even with a Durrum stopped-flow instrument. The good leaving group and stable carbonium ion intermediate will give rise to a facile ring opening. In contrast, Schiff base formation could be easily monitored in hydrolysis of the analogous *N*-ethyloxazolidines.[11] The intermediate Schiff base then hydrolyzes rapidly to give a substituted benzaldehyde as the product as depicted in eq 2. The rates of Schiff base disappearance and



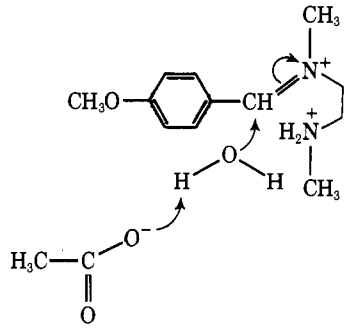
(2)

XI

aldehyde formation at the appropriate wavelengths are identical. An observed decrease in rate constant with increasing acidity is characteristic of Schiff base hydrolysis in acidic media.[11,17]

The Schiff bases derived from the phenyl-*N,N*-dimethyl-1,3-imidazolidines hydrolyze rapidly in acid solutions in comparison with those from corresponding *N*-ethyloxazolidines[11] or thiazolidines.[18] The relative rate ratios at 30 °C in 4.0 M HCl for the para-methoxy substituted benzilidene compounds are: aminoethanethiol, 1; *N*-ethylethanolamine, 10; and *N,N*-dimethylethylenediamine, 700. Differences in inductive effects should not cause such large rate differences. The relatively rapid rate of hydrolysis of the imidazolidine at low pH must be due to the fact that a protonated amine neighboring group cannot react with the Schiff base XI (stabilized carbonium ion) to recyclize the compound (see eq 2). Reversal of the reaction would greatly slow the apparent rate of Schiff base disappearance and aldehyde formation. Such reversal would be expected to occur with neighboring OH and SH functional groups. Thus, the order of reactivity with a Schiff base center (stabilized carbonium ion) is SH > OH > $H_2{}^+NCH_3$.

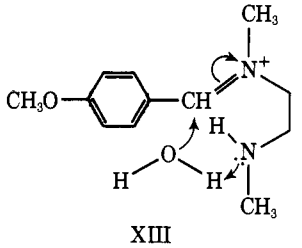
Hydrolysis at pH 2.0–8.0. At pH values greater than 4.7, a Schiff base intermediate from III can no longer be observed. Absorbance at the appropriate wavelengths increases to give a final spectrum characteristic of the aldehyde. In Figure 1 is shown a pH–log rate constant profile for the formation of *p*-methoxybenzaldehyde from III. The profile is complex and can be most conveniently discussed in terms of individual pH regions. At pH 2–4 the reaction is pH independent, and rapid ring opening is followed by rate-limiting reaction of the cationic Schiff base intermediate with water (eq 2). Acid catalysis is not observed in the overall reaction because the concentration of hydronium ion is sufficient to completely convert all of the substrate to the protonated intermediate XI. Protonation of amine in the intermediate XI will facilitate hydrolysis by inhibiting reclosure of the ring. Therefore, as the extent of amine protonation decreases, the rate of the reaction falls. It will be noted in Figure 1 that the change in slope occurs at pH 4, corresponding closely to the apparent pK_a of 4.1 determined spectrophotometrically (see Experimental Section). General base catalysis by acetate, formate, and chloroacetate occurs in this pH region as in XII or a kinetic equivalent.



XII

There is only a small dependence of the second-order rate constants in Table II on basicity of the catalyzing base, which must result from little proton transfer in the transition state for attack of water on the highly reactive cationic Shiff base center.

At higher pH values where the amine function of the cationic Schiff base from III is unprotonated, k_0 again becomes nearly pH independent. The difference in k_0 values in the plateau regions of the pH–log rate constant profile at pH 2–4 and 5.5–7.5 is a factor of 40 which reflects the rate-slowing effect of dissociation of a proton from the neighboring amine group. Hydrolysis is twofold faster in the pH range 5.5–7.5 ($k_0 = 2 \times 10^{-2}$ s^{-1}) than in the water reaction of the cationic Schiff base from *N,N,N′,N′*-tetramethyl-*p*-methoxytoluenediamine (X), in spite of the possibility of rapid reclosure of the ring. In D_2O, k_0 is considerably less than in H_2O ($k_{H_2O}/k_{D_2O} = 1.8$). The reaction could therefore involve intramolecular general base catalysis (XIII). This is supported by the fact that bimolecular



XIII

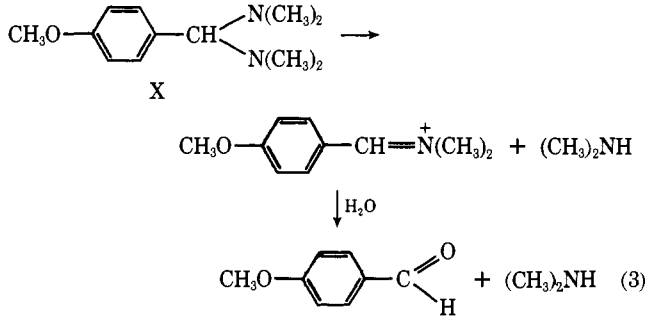
general base catalysis by imidazole cannot be detected. It would not be expected that bimolecular catalysis by relatively weak bases would compete with a reasonably facile intramolecular reaction. In contrast, imidazole is a good catalyst for hydrolysis of the cationic Schiff base derived from *N,N,N′,N′*-tetramethyl-*p*-methoxytoluenediamine.[15]

Hydrolysis at pH 8.0–11.0. At pH 8.0 a unit change in slope occurs in the plot of log k_0 vs. pH (Figure 1), probably corresponding to the pK_a of the imidazolidine nitrogens of III. An acid-catalyzed reaction is observed in the pH range 8–11, k_{obsd} decreasing with increasing pH. This acid-catalyzed reaction proceeds with large rate constants, k_H for III being 2×10^6 M^{-1} s^{-1} at 30 °C. Acid catalysis most likely reflects initial protonation of the substrate by hydronium ion. The linear Hammett σ–ρ plot in Figure 3 shows that the mechanism does not change with increased electron withdrawal by substituents. The ρ value of −0.93 reflects

the importance of ease of protonation and carbonium ion stabilization since electron withdrawal by substituents will decrease both. Nucleophilic attack of H_2O on the cationic Schiff base should be enhanced by increased electron withdrawal, and the ρ value is considerably more positive than found for acid-catalyzed acetal hydrolysis ($\rho = -3.35$ for hydrolysis of substituted benzaldehyde diethyl acetals).[19]

A question of importance is whether a change in rate-determining step to ring opening has taken place in the pH region where the rate begins to decline with increasing pH. There is a large D_2O solvent isotope effect ($k_D/k_H = 1.8$). If rate-determining C-N bond breaking were occurring after preequilibrium protonation, it would be expected that the reaction would be faster in D_2O than H_2O as in the case of A-1 acid-catalyzed acetal hydrolysis reactions,[2,19] but in acetal hydrolysis the ratio k_D/k_H is normally greater than 1.8, being usually in the range 2.7-3.0. Also, the much more positive ρ value in acid-catalyzed imidazolidine hydrolysis than in acetal hydrolysis argues against an A-1 mechanism as does the observed general species catalysis. Ring opening could only be rate limiting if the rate constant for Schiff base hydrolysis was much greater than that for reclosure of the ring. This is unlikely in the pH range where the Schiff base hydrolysis is a water reaction. The faster acid-catalyzed reaction in D_2O indicates that the equilibrium constant for ring opening must be larger in D_2O than in H_2O, and it will be noted in Figure 1 that the pK_{app} of the imidazolidine is shifted in D_2O. Apparent general acid catalysis was observed with amine buffers, but general base catalysis of the hydrolysis of the Schiff base intermediate formed in a rapid hydronium ion catalyzed ring opening would be consistent with this observation. Jencks and Cordes[17] found no catalysis by buffers in the same pH range in hydrolysis of *p*-methoxybenzilidine-2,2-dimethylethylamine, a Schiff base of high basicity. Catalysis was found in acetate buffer which was interpreted as general base catalysis.

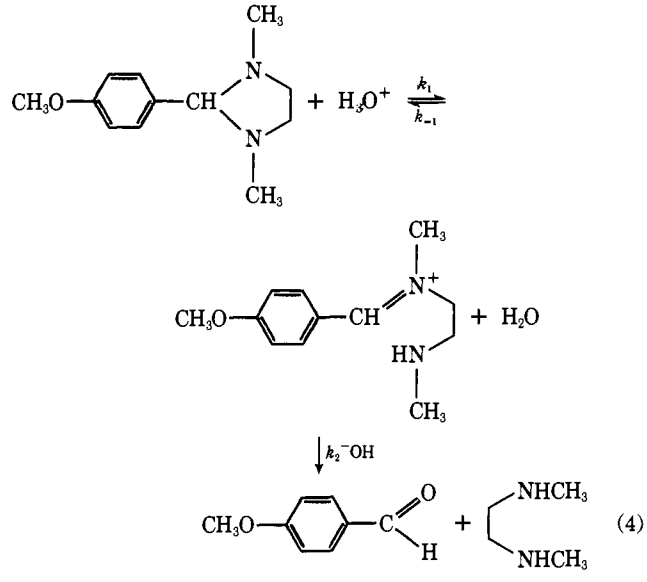
That ring opening of the imidazolidines must be rapid in comparison with Schiff base hydrolysis at pH values greater than 4.7 can be inferred from the behavior of the analogous open chain *N,N,N',N'*-tetramethyl-*p*-methoxytoluenediamine (X). This compound gives rise to a cationic Schiff base at rates that are too fast to measure conveniently. Thus, the reason that a Schiff base intermediate in imidazolidine hydrolysis is not observed at pH >4.7 must be that reversal of the ring-opening reaction occurs readily when the amine substituent of the intermediate Schiff base is unprotonated. It will be noted that hydrolysis of the cationic Schiff base derived from *N,N,N',N'*-tetramethyl-*p*-methoxytoluenediamine (X) is pH independent over much of the pH range.



(3)

This represents a reaction with water and is characterized by a D_2O solvent isotope effect $k_{H_2O}/K_{D_2O} = 2.4$. The hydrolysis of the cationic Schiff base is subject to general base catalysis by a series of bases with a Brönsted coefficient β of 0.42. Therefore, proton transfer is occurring in the critical transition state. These results are in substantial agreement with those obtained by Milakofsky.[15] Hydroxide ion catalysis is observed at pH values greater than 7.

Hydrolysis at pH 11-13. At pH values greater than 11, formation of aldehyde from the substituted imidazolidines becomes pH independent. Possible mechanisms for the pH-independent reaction are: (1) rate-limiting unimolecular ring opening to a cationic Schiff base which then hydrolyzes rapidly; (2) water-catalyzed ring opening which is rate limiting; and (3) an acid-catalyzed ring opening to a cationic Schiff base, followed by rate-determining attack of hydroxide ion on the Schiff base. Reactions independent of pH have been observed in the hydrolysis of acetals which are subject to general acid catalysis.[2-4] These reactions are unimolecular as shown by D_2O solvent isotope effects near unity, ΔS^* values close to zero, and rate constants many orders of magnitude greater than expected for water catalysis. These unimolecular reactions are brought about by ease of bond breaking due either to a good leaving group or a highly stabilized carbonium ion intermediate. In the case of imidazolidine hydrolysis, however, the ratio $k_0^{H_2O}/k_0^{D_2O}$ is 1.5 at 30 °C and 1.8 at 50 °C. Also, unimolecular ring opening would be expected to be markedly susceptible to electronic substituent effects in the phenyl group since charge would be developed during the reaction, but the values of k_0 show only small variation with changing substituent. Thus, a unimolecular rate-determining ring opening can be ruled out. Ring opening must be either a water-catalyzed reaction that is rate determining or a hydronium ion catalyzed reaction. The Hammett ρ value close to zero for the pH-independent reaction might be taken to indicate compensating electronic effects in consecutive reactions as would be the case in an acid-catalyzed ring opening, followed by hydroxide ion attack on the cationic Schiff base (eq 4).



(4)

From the scheme of eq 4, assuming steady-state concentrations for Schiff base:

$$k_{obsd} = \frac{[k_1(H_3O^+)k_2(OH^-)]}{[k_{-1}(H_2O) + k_2(OH^-)]} \quad (5)$$

For attack of hydroxide ion on the Schiff base to be rate determining, $k_{-1}(H_2O) \gg k_2(OH^-)$. In that case:

$$k_{obsd} = K_{eq}(H_3O^+)k_2(OH^-)$$

$$k_{obsd} = K_{eq}K_w k_2 \quad (6)$$

The D_2O solvent isotope effect for the pH-independent reaction at high pH would be given by eq 7. The value of K_w

$$\frac{k_0^{H_2O}}{k_0^{D_2O}} = \frac{(K_{eq}K_w k_2)^{H_2O}}{(K_{eq}K_{D_2O}k_2)^{D_2O}} \quad (7)$$

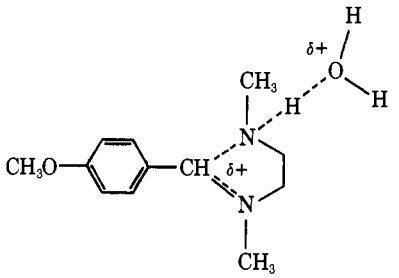
at 30 °C is 1.47×10^{-14}, while K_{D_2O} at 30 °C is 0.22×10^{-14} [20] From the solvent isotope ratio for the acid-catalyzed reaction $k_D/k_H = 1.8$, the ratio $K_{eq}^{D_2O}/K_{eq}^{H_2O} = 4.3$ can be calculated, assuming that water attack on the cationic Schiff base would have the ratio $k_{H_2O}/k_{D_2O} = 2.4$ found for the water reaction of the Schiff base from X. The reported[15] solvent isotope effect k_{OH}/k_{OD} for hydroxide ion catalyzed hydrolysis of the cationic Schiff base from X is 1.25 and should be similar for that from III. A theoretical solvent isotope effect $k_0^{H_2O}/k_0^{D_2O} = 1.9$ can then be calculated which is in good agreement with that observed. Deuteroxide ion is a stronger base than ^-OH; it might therefore be expected that k_2 would be greater in D_2O. If this were the case the calculated ratio would be reduced accordingly.

Jencks and Cordes[17] found that at high pH, attack of ^-OH on protonated Schiff bases of aliphatic amines was rate determining. The rate constant for *p*-methoxybenzilidine-2,2-dimethylethylamine is 10^6 M^{-1} s^{-1}. The rate constant for attack of hydroxide ion on the cationic Schiff base derived from *N,N,N′,N′*-tetramethyl-*p*-methoxytoluenediamine (X) is 5×10^4 M^{-1} s^{-1} at 30 °C. It is a reasonable assumption that k_2 from eq 4 would be of similar magnitude. Therefore, employing the value of k_{obsd} at 30 °C for the methoxy derivative III in 0.1 M base (3×10^{-5} s^{-1}) K_{eq} can be calculated to be 4×10^4. Since $k_{-1}(H_2O) \gg k_2(OH^-)$, $k_{-1}(H_2O) \gg 5 \times 10^3$ s^{-1}. Consequently, $k_{-1}(H_2O)$ must be at least 5×10^4 s^{-1}. Thus, since $K_{eq} = k_1/k_{-1}$, k_1 would necessarily be at least 4×10^7 M^{-1} s^{-1}. This is only slightly less than a value characteristic of diffusion-controlled reactions and illustrates the great facility of ring opening.

The mechanism of the ring-opening step for III cannot be specified unambiguously, and either preequilibrium protonation or a concerted reaction involving proton transfer from hydronium ion as the C–N bond breaks must be regarded as possibilities. The great facility of ring opening at near diffusion-controlled rates does, however, lend support to the latter possibility. If ring opening involved preequilibrium protonation, then the rate constant for Schiff base formation would be given by

$$k_{open} = (k_r/K_{SH^+})(a_H) \quad (8)$$

where k_r is the rate constant for ring opening of the protonated species and K_{SH^+} is the dissociation constant of the imidazolidine. Since k_{open}/a_H is equal to k_1 in eq 4, which is at least 4×10^7 M^{-1} s^{-1}, k_r can be calculated to be $<10^3$ s^{-1}. This is an improbably low value considering the good leaving group and highly stabilized carbonium ion being produced. Values of the rate constant for unimolecular cleavage of protonated compounds that would be expected to be less reactive are often much greater than 10^3 s^{-1}. For example, benzaldehyde diethyl acetal has a second-order rate constant for A-1 hydronium ion catalyzed hydrolysis in H_2O at 30 °C of 225 M^{-1} s^{-1}.[21] The measured dissociation constant for the conjugate acid of benzaldehyde diethyl acetal[22] is $10^{5.7}$. Therefore, k_u is 1.1×10^8 s^{-1}. In a typical A-1 reaction (eq 9) where $k_{obsd}/a_H = k_1k_u/(k_{-1}(H_2O) + k_u)$, the value of $k_{-1}(H_2O)$ must be much greater than k_u. The magnitude of k_{-1} cannot, however, be greater than that for a diffusion-controlled reaction (10^{10}–10^{11} M^{-1} s^{-1}). Thus, it is clear that if k_u is only slightly greater (100–1000-fold) than for decomposition of the conjugate acid of benzaldehyde diethyl acetal, because of either a more stable carbonium ion intermediate or a better leaving group, then proton transfer from hydronium ion will *necessarily* be part of the rate-limiting step regardless of the basicity of the compound. It is thus probable that proton transfer to nitrogen is only partial in the transition state for ring opening in acid-catalyzed imidazolidine hydrolysis. A concerted reaction (XIV) is likely in which proton transfer



XIV

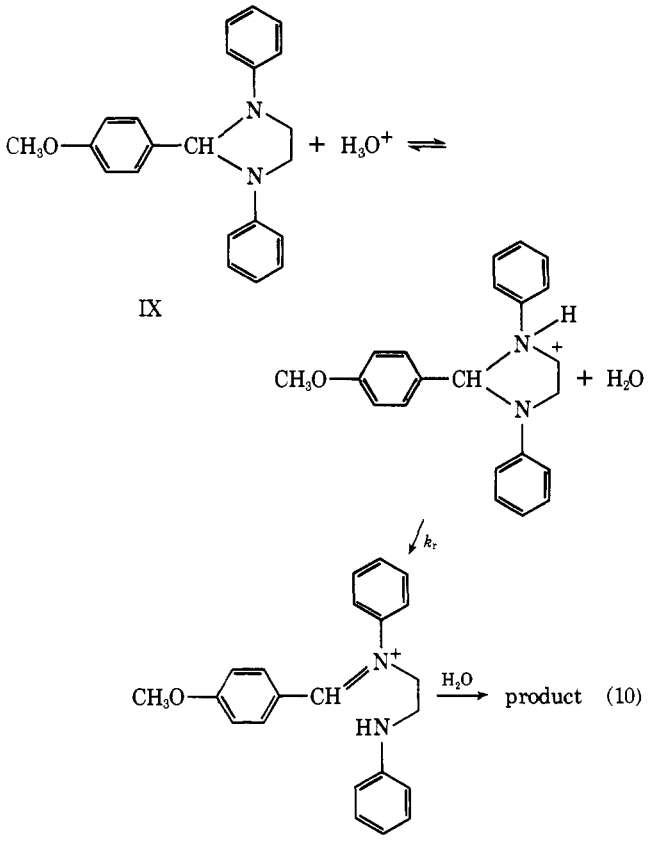
from hydronium ion and C–N bond breaking occur simultaneously. Hydronium ion is probably acting mechanistically as a general acid because of the great facility of the bond-breaking process, partial proton transfer to nitrogen being sufficient to attain the transition state. The above discussion is based on the reasonable assumption that the pH-independent reaction follows the scheme of eq 4, but the same conclusions are arrived at by similarly considering the acid-catalyzed reaction, substituting (H_2O) for (^-OH) in eq 5 and employing 10^{-2} s^{-1} as the value of k_2 for water-catalyzed Schiff base hydrolysis. The observed general acid catalysis in piperidine buffers conceivably could represent catalysis of either step in the reaction, but most likely is nucleophilic attack by the base species on the cationic Schiff base to give a new Schiff base that cannot cyclize. This interpretation is supported by the D_2O solvent isotope effect k_{HA}/k_{DA} of 1.3 (about the same as for ^-OH) and by the lack of observable catalysis by the tertiary amine triethylamine.

$$S + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SH^+ \xrightarrow[\text{slow}]{k_u} C^+ \xrightarrow[\text{fast}]{H_2O} \text{product} \quad (9)$$

Hydrolysis of 2-(*p*-Methoxyphenyl)-*N,N*-diphenyl-1,3-imidazolidine. In an attempt to slow down the ring-opening reaction of substituted imidazolidines so that rates could be measured, the *N,N*-diphenyl derivative IX was prepared and studied. There is a relatively slow reaction of this compound at 30 °C in acid solutions to give a product whose spectrum matches closely that of *p*-methoxybenzaldehyde. The reaction is acid catalyzed with a second-order rate constant k_H which is approximately 10^7-fold less than that of the corresponding *N,N*-dimethyl compound. The reaction is considerably faster in D_2O than H_2O ($k_D/k_H = 2.9$). Thus, it is probable that acid-catalyzed ring opening is occurring by an A-1 mechanism in which preequilibrium protonation by hydronium ion is followed by unimolecular decomposition of the protonated substrate (eq 10). General acid catalysis is not observed in formate buffers in 50% dioxane–H_2O. The slowness of the reaction in comparison with the corresponding *N,N*-dimethyl derivative arises from two factors: (1) basicity of the nitrogens is greatly reduced (by measuring initial absorbance of IX in acid solutions, the pK_a can be estimated to be <1.0); and (2) the ability of nitrogen to release electrons to stabilize an incipient carbonium ion is greatly reduced. It is possibly the latter factor that prevents general acid catalysis from being an effective mechanism in hydrolysis of IX.

Conclusion

It is likely that the unsymmetrical nature of *N*(5),*N*(10)-methylenetetrahydrofolic acid plays a key role in reactions involving this cofactor derivative. The pK_a values of the N(5) and the N(10) nitrogens of tetrahydrofo-



IX

lic acid have been measured and are 4.82 and −1.25, respectively.[23] Such a distribution of pK_a values could facilitate reactions in which ring opening occurs by allowing enzymatic mechanisms involving general acid catalysis. Low basicity of the $N(10)$ nitrogen would favor proton transfer to it in the rate-determining step, while the much higher basicity of the N(5) nitrogen would allow it to readily release electrons to stabilize a carbonium ion intermediate. Thus, both factors would work together to promote general acid catalysis. On the other hand, if both nitrogens had a high pK_a, stability of the ring would be quite low. If both nitrogens had a very low pK_a, carbonium ion stabilization would probably not be sufficient for the ease of bond breaking necessary for general acid catalysis. It would therefore be predicted that in enzymatic reactions of methylenetetrahydrofolic acid in which general acid catalysis takes place, the ring would open on the side of N(10) to give the N(5) methylene derivative.

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References and Notes

(1) Postdoctoral Fellow, Department of Biochemistry, University of Southern California.
(2) T. H. Fife, *Acc. Chem. Res.*, **5**, 264 (1972).
(3) T. H. Fife and L. Jao, *J. Am. Chem. Soc.*, **90**, 4081 (1968); T. H. Fife and L. H. Brod, *ibid.*, **92**, 1681 (1970).
(4) E. Anderson and T. H. Fife, *J. Am. Chem. Soc.*, **91**, 7163 (1969); T. H. Fife and E. Anderson, *J. Org. Chem.*, **36**, 2357 (1971).
(5) E. Anderson and T. H. Fife, *J. Am. Chem. Soc.*, **93**, 1701 (1971); R. F. Atkinson and T. C. Bruice, *ibid.*, **96**, 819 (1974).
(6) T. H. Fife and E. Anderson, *J. Am. Chem. Soc.*, **92**, 5464 (1970).
(7) E. Anderson and B. Capon, *J. Chem. Soc. B*, 1033 (1969).
(8) C. A. Bunton and R. H. De Wolfe, *J. Org. Chem.*, **30**, 1371 (1965).
(9) E. Anderson and T. H. Fife, *J. Org. Chem.*, **37**, 1993 (1972).
(10) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).
(11) T. H. Fife and L. Hagopian, *J. Am. Chem. Soc.*, **90**, 1007 (1968).
(12) S. J. Benkovic, P. A. Benkovic, and D. R. Comfort, *J. Am. Chem. Soc.*, **91**, 5270 (1969).
(13) N. Indictor, J. W. Horodniak, H. Jaffe, and D. Miller, *J. Chem. Eng. Data*, **14**, 76 (1969).
(14) O. Sues and H. Schlesinger, German Patent 1,116,057; *Chem. Abstr.*, **56**, P 10334e (1962).
(15) L. Milakofky, Ph.D. Thesis, University of Washington, 1967.
(16) L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1940, Chapter VII.
(17) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963).
(18) T. H. Fife and J. E. C. Hutchins, unpublished data.
(19) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).
(20) "Handbook of Chemistry and Physics", 54th ed, R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1973, p D131.
(21) T. H. Fife and L. H. Brod, *J. Org. Chem.*, **33**, 4136 (1968).
(22) T. Pletcher and E. H. Cordes, *J. Org. Chem.*, **32**, 2294 (1967).
(23) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5845 (1966).