afforded 479 mg (87% yield) of ketone **14b** after recrystallization from CH_2Cl_2/hexane: mp 125–126 °C; IR (mull, Nujol), 1695 (s), 1610 (m), 1495 (m), 1245 (s), 1025 (m) cm^{-1}; NMR δ 2.37–3.56 (5 H, m), 6.02 (2 H, s), 6.72 (1 H, s), 7.10 (1 H, s), 7.22 (5 H, s); UV λ_{max} nm (ϵ) 231 (22 320), 267 (9280), 319 (11 070). Anal. ($C_{17}H_{14}O_3$) C, H.

2-(3,4-Methylenedioxybenzyl)-α-indanone (15b) was prepared in a manner identical with that described for 2-(3,4-dimethoxybenzyl)-indanone (**15a**) using $AlCl_3$ (300 mol %) in CH_2Cl_2. From 0.568 g (2.0 mmol) of the methylenedioxypropionic acid **13b** was obtained a 3/2 mixture of the ketones **15b** and **14b**. The desired product **15b** was isolated by chromatography (SiO_2, CH_2Cl_2/EtOAc) and recrystallized from CH_2Cl_2/hexane: mp 118–119 °C; IR (mull, Nujol) 1695 (s), 1525 (s), 1250 (s, b), 1160 (s), 1045 (m) cm^{-1}; NMR δ 2.35–3.52 (5 H, m), 5.78 (2 H, s), 6.77 (3 H, s), 6.60–7.75 (4 H, m); UV λ_{max} nm (ϵ) 252 (12 950), 277 (sh). Anal. ($C_{17}H_{14}O_3$) C, H.

Acknowledgments. This research was supported in part by the National Institute on Drug Abuse.

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General-Acid-Catalyzed Imidazolidine Ring Opening. Hydrolysis of Symmetrical and Unsymmetrical 1,3-Imidazolidines of *p*-Dimethylaminocinnamaldehyde

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Abstract: Rate constants have been obtained for ring opening of a series of symmetrical and unsymmetrical 1,3-imidazolidines of *p*-dimethylaminocinnamaldehyde in H_2O at 30 °C. Ring opening of the *N,N'*-diphenyl derivative is catalyzed by hydronium ion (k_H = 2290 M^{-1} s^{-1}), and gives rise to a cationic Schiff base with λ_{max} 505 nm. The reaction is considerably slower in D_2O than in H_2O, k_H/k_D = 3.0. At pH greater than 6 ring opening is pH independent (k_0' = 1.8 × 10^{-2} s^{-1}). Ring opening of the *N,N'*-dimethylimidazolidine to a species with λ_{max} 480 nm is hydronium ion catalyzed (k_H = 2 × 10^9 M^{-1} s^{-1}) and pH independent at pH values above 11.5. The unsymmetrical *N*-isopropyl-*N'*-phenyl derivative opens to give a species with λ_{max} 480 nm and with rate constants that are similar to those for the *N,N'*-dimethyl substituted compound (k_H = 4 × 10^7 M^{-1} s^{-1}). Consequently, this species must be the *N*-isopropyl Schiff base resulting from breaking of the C–N phenyl bond. General acid catalysis of ring opening was observed in trimethylamine buffer. Only at pH values less than 6 does C–N isopropyl bond breaking become competitive, giving the *N*-phenyl Schiff base (λ_{max} 512 nm). The interconversion of Schiff bases (480 → 512 nm) is general acid catalyzed by buffer acids or a kinetic equivalent. Thus, ring-opening reactions of imidazolidines have been directly monitored, and general acid catalysis has been observed. It can be concluded that, in reactions of the neutral species and hydronium ion, or a general acid, the imidazolidine ring opens preferentially to give the most stable carbonium ion with expulsion of the least basic nitrogen. In the reaction of the unsymmetrical imidazolidine at low pH when there are two protons in the transition state, either C–N bond may break, and the C–N phenyl Schiff base is the favored product. These results are discussed in relation to reactions of N^5,N^{10}-methylenetetrahydrofolic acid.

In reactions of the important enzyme cofactor N^5,N^{10}-methylenetetrahydrofolic acid, the imidazolidine ring must open,[1] 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-(aryl or alkyl)-N,N'-disubstituted 1,3-imidazolidines to the corresponding aldehyde proceeds with ring opening followed by rate-determining hydrolysis of a cationic Schiff-base intermediate.[6,7] With 2-(*p*-methoxyphenyl)-1,3-imidazolidines this Schiff base can be observed spectrophotometrically at pH values less than 4.7.

A question of considerable theoretical interest is whether concerted general-acid-catalyzed reactions will occur when basicity of the substrate is high.[6,8] Since ease of bond breaking is a critical feature in giving rise to such reactions in acetal hydrolysis,[9,10] it might be expected that general acid catalysis will occur in the hydrolysis of acetal analogues of high basicity

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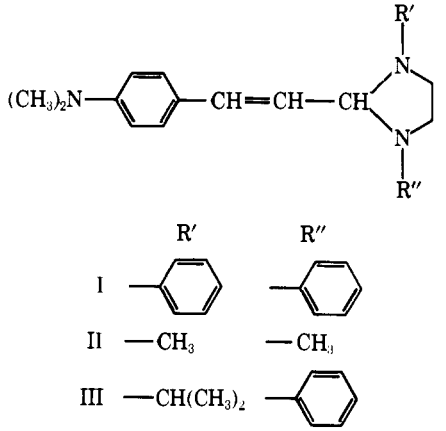
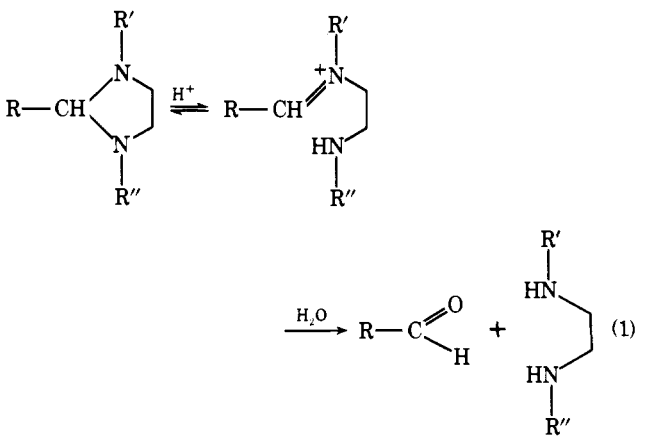
if bond breaking is sufficiently facile. In fact, if a protonated intermediate has a lifetime of less than 10^{-13} s, the reaction *must* be concerted. The demonstration of general acid catalysis in the ring opening of imidazolidines would allow a rigorous assessment of the structural features required for such catalysis to be effective.

In a search for observable general acid catalysis in imidazolidine ring opening, both basicity and carbonium ion stabilization effects must be taken into account. *N,N'*-Dialkyl-1,3-imidazolidines possess high basicity (pK_{app} = 7-9) and provide a high degree of stabilization of the incipient carbonium ion during ring opening to the cationic Schiff base, so that the reactions are extremely rapid. *N,N'*-Diphenyl substitution provides an advantageous low basicity, but nitrogen may not then sufficiently stabilize the incipient carbonium ion for C-N bond breaking to be sufficiently easy for general acid catalysis to occur. Therefore, an unsymmetrical imidazolidine (*N*-alkyl-*N'*-phenyl) might provide the maximum opportunity for observation of general acid catalysis in ring opening. The unsymmetrical nature of N^5,N^{10}-methylenetetrahydrofolic acid must play a key role in reactions of that cofactor derivative. There is a large difference in the pK_a values of theN(5) and N(10) nitrogens of tetrahydrofolic acid.[11] To determine the mechanistic effects of dissymmetry in the hydrolysis of simple 1,3-imidazolidines, we have studied the hydrolysis reactions of the symmetrical and unsymmetrical 1,3-imidazolidines of *p*-dimethylaminocinnamaldehyde (I-III). With these compounds a large measure of stabilization of the developing carbonium ion is provided by the conjugated substituent at the 2 position. In previous studies[6,7] of imidazolidine hydrolysis a cationic Schiff base could not be directly observed at pH values greater than 5, presumably because the intermediate is then present only at low steady state concentrations. This has presented a serious obstacle in the search for general acid catalysis of ring opening, since, in view of the expected facile hydronium ion catalysis, the most favorable opportunity for observation of buffer catalysis is with weak buffer acids at high pH,[12] above the high pK_a of the ring. For ring opening to be observable at high pH it is necessary that the cationic Schiff-base intermediate have a large extinction coefficient, with λ_{max} preferably in the visible region of the spectrum, and possess reasonable stability so that low concentrations can be detected. These conditions are met with I-III. The long conjugated system allows both the cationic Schiff-base intermediate in the reaction (eq 1) and the aldehyde product to absorb in the visible portion of the spectrum at well-separated wavelengths, so that both ring opening and hydrolysis of the intermediate can be easily monitored at all pH values in the case of III.





Experimental Section

Materials. 2-(*p*-Dimethylaminostyryl)-*N,N'*-diphenyl-1,3-imidazolidine (I) was prepared by refluxing overnight in benzene equimolar amounts of freshly sublimed *p*-dimethylaminocinnamaldehyde (Aldrich) and recrystallized *N,N'*-diphenylethylenediamine (Aldrich). Water was continuously removed from the reaction mixture by azeotropic distillation with the benzene. The benzene was removed by rotary evaporation. The residue was suspended in ether, and benzene was added to dissolve the mass. After 1 h at 4 °C, crystals formed which were collected and recrystallized from benzene-ether. The yellow needles melted at 174-175 °C. Anal. Calcd for $C_{25}H_{27}N_3$: C, 81.32; H, 7.35; N, 11.41. Found: C, 81.20; H, 7.33; N, 11.27. The ring-closed product was indicated by the NMR spectrum (Varian EM-360) in deuteriochloroform, showing a peak at δ 5.75 ppm,[2,13] and the absence of peaks at δ 9.6 ppm due to aldehyde. Me_4Si (δ 0 ppm) was employed as an internal standard.

2-(*p*-Dimethylaminostyryl)-*N,N'*-dimethyl-1,3-imidazolidine (II) was prepared by reacting in benzene sublimed *p*-dimethylaminocinnamaldehyde with a slight excess of freshly distilled *N,N'*-dimethylethylenediamine by a procedure identical with that for synthesis of I. The stoichiometric amount of water was recovered. The NMR spectrum was consistent with an imidazolidine. Since this imidazolidine reacts readily with water, precautions were taken during its isolation and purification to avoid hydrolysis. After removal of most of the benzene solvent by distillation directly from the reaction flask, the minimum volume of benzene solution was transferred to an Erlenmeyer flask with dry hexane. The Erlenmeyer was sealed with a tight fitting rubber septum, and crystallization occurred when the flask was allowed to stand in the cold. The thoroughly dried pale yellow crystals were then sublimed at 1 mm (70-80 °C), yielding a homogeneous, pale yellow sublimate melting at 94-96 °C. Anal. Calcd for $C_{15}H_{23}N_3$: C, 73.41; H, 9.46; N, 17.13. Found: C, 73.52; H, 9.59; N, 16.94.

2-(*p*-Dimethylaminostyryl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine (III). *N*-Isopropyl-*N'*-phenylethylenediamine was prepared employing the general procedure of Shepherd and Wilkinson[14] (method C) as modified by Fife et al.[7] The imidazolidine III was prepared from *p*-dimethylaminocinnamaldehyde and *N*-isopropyl-*N'*-phenylethylenediamine by a procedure identical with that for synthesis of I. The material crystallized from a benzene-ether mixture. After recrystallization the compound melted at 126-127 °C. Anal. Calcd for $C_{22}H_{29}N_3$: C, 78.76; H, 8.71; N, 12.53. Found: C, 78.48; H, 8.73; N, 12.40.

2-Styryl-*N,N'*-diphenyl-1,3-imidazolidine (IV) was prepared by reacting in benzene freshly distilled cinnamaldehyde with an equivalent amount of *N,N'*-diphenylethylenediamine by a procedure identical with that for synthesis of I. The benzene was removed by rotary evaporation. After recrystallization from benzene/hexane, the white needles melted at 121-123 °C. Anal. Calcd for $C_{23}H_{22}N_2$: C, 84.66; H, 6.75; N, 8.59. Found: C, 84.37; H, 6.69; N, 8.60.

The Schiff-base derivatives of *p*-dimethylaminocinnamaldehyde and aniline or isopropylamine were prepared by refluxing equivalent amounts (0.006 mol) of once-sublimed aldehyde and freshly distilled amine in benzene (150 mL) with water being continuously removed by azeotropic distillation. After removal of the benzene by rotary evaporation, the products were crystallized from chloroform/hexane or dry benzene/hexane. After recrystallization, *N*-(*p*-dimethylamino)cinnamylideneisopropylamine (V) had mp 79-80 °C. Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.71; H, 9.34; N, 12.95. Found: C, 77.39; H, 9.14; N, 13.39. *N*-(*p*-Dimethylamino)cinnamylideneaniline (VI) had mp 131-133 °C. Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.55; H, 7.26; N, 11.19. Found: C, 81.36; H, 7.38; N, 10.95.

Table I. Spectral Data for *p*-Dimethylaminocinnamaldehyde, Imidazolidines, and Schiff Bases of *p*-Dimethylaminocinnamaldehyde

compd	solvent	λ_{max}, nm	$\epsilon \times 10^{-4}$, M^{-1} cm^{-1}
p-dimethylamino-cinnamaldehyde	acetonitrile	378	
	H_2O (pH 10.5)	396	
	H_2O (pH 6.83)[a]	398	3.1
	H_2O (pH 5.8)	376	
	H_2O (pH 1.45)	281	
I	acetonitrile	303	2.33
		255	3.72
	acetonitrile + acid[b]	512	5.72
II	acetonitrile	297	2.03
	acetonitrile + acid[b]	480	3.99
III	acetonitrile	300	2.62
	acetonitrile + H_2O[c]	480	2.70
	acetonitrile + acid[d]	512	5.49
IV	acetonitrile	253	4.75
V	acetonitrile	348	2.64
	acetonitrile + acid[b]	458	4.63
	12 M HCl	312	2.95
	H_2O (pH 7.24)[e]	454	4.49
VI	acetonitrile	382	4.10
	acetonitrile + acid[b]	520	5.92
	12 M HCl	364	2.95

[a] M. F. Dunn and S. J. Hutcheson, *Biochemistry*, **12**, 4882 (1973). [b] 1 μL of 2 M HCl was added to 1.5 mL of solution. [c] 0.19 mL of H_2O was added to 1.5 mL of solution. [d] After 0.19 mL of H_2O was added, giving a peak at 480 nm, 2 μl of 2 M HCl was added resulting in formation of an intense absorbance at 512 nm. This peak subsequently decreased with addition of 1 μL of 2 M HCl with concomitant formation of a peak at 380 nm due to aldehyde. [e] Tris buffer (0.5 M).

Kinetic Methods. In studies measuring the rate of aldehyde formation employing a Beckman 25 spectrophotometer, 100 μL of a 0.005 M solution of substrate in dry acetonitrile was added to 3 mL of buffer in the cuvette, and the reaction was followed at 398 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.

Ring-opening 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 at 505, 480, 303, or 254 nm after mixing were recorded on a Hewlett-Packard storage oscilloscope (Model 1207B). With each buffer, four to six reactions were tabulated. In no case did pH vary by more than 0.04 pH units within the series of buffers in the buffer dilution experiments. Reaction solution pH values were measured with a Radiometer pH-meter Model 22 and GK 2303 C combined electrode standardized with Mallinckrodt standard buffer solutions. The values of pD were calculated employing the glass electrode correction equation of Fife and Bruice.[15] Pseudo-first-order rate constants were calculated with an IBM 370 computer.

Spectral Data. Absorption maxima and extinction coefficients for compounds I-VI and *p*-dimethylaminocinnamaldehyde, the product of the hydrolysis reactions, are given in Table I. No significant hydrolysis to aldehyde occurred in the acetonitrile solutions in any case during the time period of the spectral measurements. The λ_{max} values (I-III) in the presence of H_2O and acid correspond closely with those obtained for the intermediate Schiff bases in the hydrolysis reactions of the respective imidazolidines. It will be noted that upon addition of 1 μL of 2 M HCl to 1.5 mL of acetonitrile, compound VI exhibited a λ_{max} of 520 nm, compared to λ_{max} of 458 nm for compound V under identical conditions. In 12 M HCl both VI and V have λ_{max} values at considerably lower wavelengths owing to protonation of the dimethylamino group, but λ_{max} for VI is still greater than that of V.

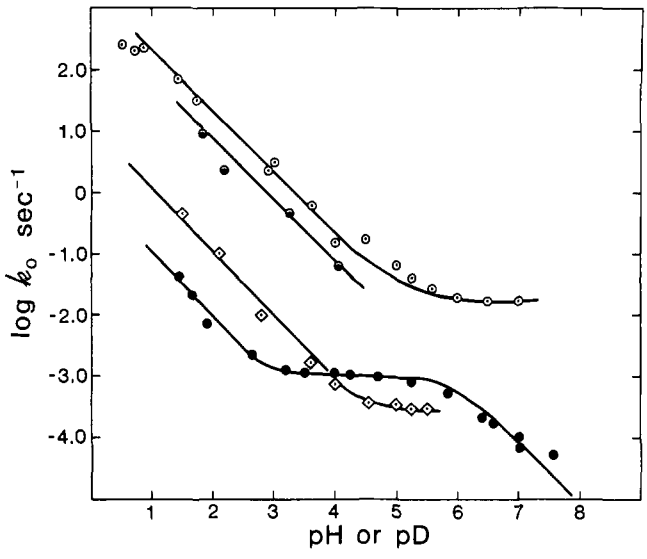


Figure 1. Plots of log k_0 vs. pH for ring opening reactions of 2-(*p*-dimethylaminostyryl)-*N,N'*-diphenyl-1,3-imidazolidine (I) in H_2O (⊙) and D_2O (⊖), μ = 1.0, and hydrolysis of the intermediate cationic Schiff base in H_2O (◇) and 50% dioxane-H_2O (v/v) (●) at 30 °C, μ = 0.5. Rate constants for aldehyde formation were obtained by extrapolation to zero buffer concentration.

Addition of I to 50% dioxane-H_2O (pH 8.22) gives a solution with a UV spectrum having λ_{max} 300 nm, indicative of the ring-closed compound, as seen in dry acetonitrile. This absorbance is stable. Upon addition of HCl to the pH 8.22 buffer containing I, the solution changes from water white to brilliant red-orange (λ_{max} 516 nm). Concurrent with this is disappearance of the 300-nm absorbance and appearance of a peak at 400 nm due to aldehyde. The rate of aldehyde formation coincides with the rate of disappearance of the absorbance at 516 nm. The above behavior is paralleled in acetonitrile where λ_{max} is 300 nm in dry solution and 515 nm in acidified acetonitrile.

Addition of III to 50% dioxane-H_2O (pH 8.22) gives a solution with a UV spectrum having a strong absorbance with λ_{max} 480 nm. Thus, III opens immediately. A very small peak at 300 nm is also observed. Addition of III to H_2O (pH 6.0) gives a solution with a spectrum having λ_{max} 480 nm. Acidification with concentrated HCl shifts the absorbance maximum to 516 nm (trough at 480 nm). In dry acetonitrile III has a λ_{max} 300 nm, indicative of the ring-closed compound. Addition of H_2O to the acetonitrile gives a solution having λ_{max} 480 nm. Addition of acid leads to a spectrum with λ_{max} 512 nm with no loss of peak height. In pH 1.66 50% dioxane-H_2O, III has a spectrum with λ_{max} 532 nm.

Results

In the hydrolysis reactions of 2-(*p*-dimethylaminostyryl)-*N,N'*-diphenyl-1,3-imidazolidine (I) in H_2O at 30 °C at pH values less than 6, a rapid increase in absorbance at 505 nm can be observed. This reaction must correspond with ring opening to a cationic Schiff base. The rates of the reactions were followed with stopped-flow measurements, and in Figure 1 is presented a plot of log k_0 vs. pH where $k_0 = k_{obsd}$ at zero buffer concentration. The slope from pH 1.5 to 4.0 is −1.0, indicating hydronium ion catalysis with a second-order rate constant ($k_H = k_0/a_H$) of 2290 M^{-1} s^{-1} at 30 °C. The ring-opening reaction is slower in D_2O than in H_2O (k_H/k_D = 3.0). A pH-independent reaction occurs at pH values greater than 6 (k_0' = 1.8 × 10^{-2} s^{-1}). Buffer catalysis was not observed in formate or chloroacetate buffers at total buffer concentrations ranging from 0.125 to 0.5 M.

After completion of the initial phase of the reaction, the absorbance at 505 nm slowly declines owing to hydrolysis of the cationic Schiff base to aldehyde. Rate constants for this reaction were determined by following the decrease in absorbance at 505 nm or the increase in absorbance at 398 nm due to formation of aldehyde. Rate constants determined at

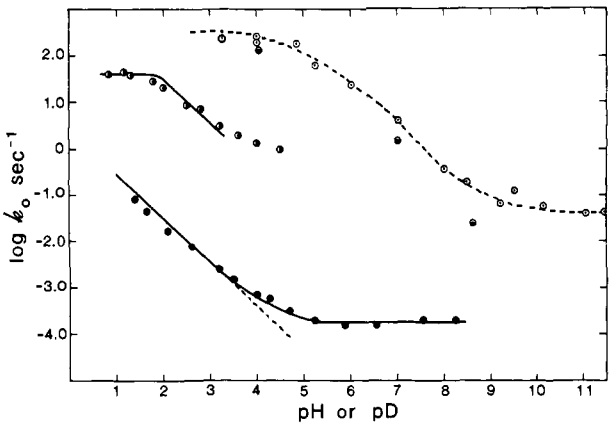


Figure 2. Plots of log k_0 vs. pH for ring opening reactions of 2-(*p*-dimethylaminostyryl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine (III) in H_2O (⊙) and D_2O (◒) to give a species with λ_{max} 480 nm (pH >6), the 480 to 512 nm transition (◑) in H_2O, μ = 1.0, and hydrolysis in 50% dioxane-H_2O of the intermediate cationic Schiff base (●) at 30 °C, μ = 0.5. Rate constants for aldehyde formation were obtained by extrapolation to zero buffer concentration.

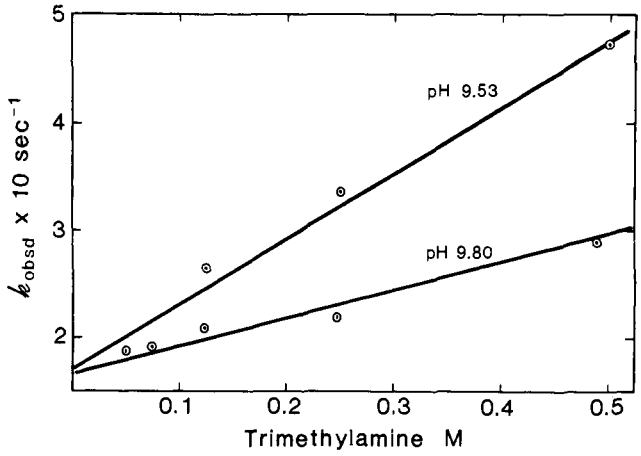


Figure 3. A plot of log k_{obsd} vs. the total concentration of trimethylamine buffer in the ring opening of 2-(*p*-dimethylaminostyryl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine at 30 °C in H_2O and μ = 1.0 (with KCl).

the two wavelengths were identical. The pH-log k_0 profile for aldehyde formation in H_2O or 50% dioxane-H_2O (v/v) is also shown in Figure 1. At pH values below 3 the reaction is hydronium ion catalyzed (k_H = 10 M^{-1} s^{-1} in H_2O and 1.0 M^{-1} s^{-1} in 50% dioxane-H_2O), while at higher pH the reaction is pH independent (k_0 = 10^{-3} s^{-1} in 50% dioxane-H_2O), followed by a further decline in k_0 with increase in pH (k_H' = 10^3 M^{-1} s^{-1}). Rate constants k_0 for aldehyde formation were obtained by extrapolation to zero buffer concentration. A Schiff-base intermediate cannot be observed spectrophotometrically at pH values greater than 7.5. The species absorbing at 303 nm is present, and when the solution is acidified it gives the intermediate with λ_{max} 505 nm.

2-(*p*-Dimethylaminostyryl)-*N,N'*-dimethyl-1,3-imidazolidine (II) reacts very rapidly in H_2O at 30 °C to give a species with λ_{max} 480 nm. Rate constants for this reaction were determined in the pH range 9-13. At pH values less than 11.5 the reaction is hydronium ion catalyzed (k_H = 1.8 × 10^9 M^{-1} s^{-1}). At pH values greater than 11.5 a pH-independent reaction was observed (k_0' = 5.6 × 10^{-3} s^{-1}). At low pH values the reaction was much too fast to measure even with a Durrum stopped-flow apparatus. Hydrolysis of the cationic Schiff-base intermediate to aldehyde in 50% dioxane-H_2O at 30 °C proceeds with H_2O catalysis (k_0' = 2.2 × 10^{-4} s^{-1}), and hydronium ion catalysis (k_H = 0.01 M^{-1} s^{-1}). Rate constants were measured by following the decrease in absorbance at 480 nm (disappearance of Schiff base) or the increase at 398 nm (appearance of aldehyde) and were identical at the two wavelengths.

The observed hydrolysis of 2-(*p*-dimethylaminostyryl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine (III) in H_2O at 30 °C proceeds in three distinct phases. Upon addition to water there is a rapid decrease in absorbance at 303 nm and formation of a species with an absorbance maximum at 480 nm. Rate constants measured at the two wavelengths were identical (pH >6). At pH values less than 5.5 a species with λ_{max} 512 nm is also formed in the ring-opening reaction of III, and at pH <3 it becomes the only species detected. At pH <5 the rate of decrease in absorbance at 303 nm (disappearance of substrate) was followed. A plot of log k_0 vs. pH for ring opening is shown in Figure 2. At high pH there is a pH-independent reaction (k_0' = 0.045 s^{-1}). In the pH range 7-10 hydronium ion catalysis is observed (k_H = 4.0 × 10^7 M^{-1} s^{-1}). Rate constants for the ring-opening reaction again become pH independent near pH 5 with k_0 = 260 s^{-1}. Pronounced buffer catalysis of ring opening at pH >9.5 was observed in trimethylamine buffers.

Table II. Rate Constants for Buffer Catalysis of the Interconversion of Cationic Schiff Bases Produced from III in H_2O at 30 °C (480 → 512 nm)

acid	buffer concn, M (total)	pK_a[a]	k_{HA}, M^{-1} s^{-1}
H_3O^+		−1.74	3160
chloroacetic	0.125-0.50	2.74	36.7[b]
formic	0.125-0.50	3.60	10.0[c]
acetic	0.125-0.50	4.60	2.7[d,e]

[a] Determined under the same conditions as the catalyzed reactions. [b] Determined in half-neutralized buffer and at pH 3.20. [c] Determined at pH 3.60, 4.00, and 4.50. [d] Determined at pH 5.00 and 4.48. [e] General base catalysis was also detected in formate and acetate buffers with rate constants k_B of 1.8 M^{-1} s^{-1} and 6.3 M^{-1} s^{-1}, respectively.

A plot of k_{obsd} vs. total trimethylamine buffer is shown in Figure 3. The second-order rate constant k_{HA} has a value of 0.73 M^{-1} s^{-1}. Large buffer catalysis was not detected at other pH values, presumably because of the very rapid hydronium ion catalyzed and pH-independent reactions. Only a small catalytic effect was observed in piperidine buffers.

When a solution of the species with λ_{max} 480 nm at pH 6 is rapidly mixed with an equal volume of a lower pH solution, an absorbance increase occurs at 512 nm. The pH-log k_0 profile for this transformation is presented in Figure 2. The reaction is catalyzed by hydronium ion (k_H = 3160 M^{-1} s^{-1}) and by buffer. Rate constants are given in Table II. The slope of a Brønsted plot of log k_{HA} vs. the pK_a of the catalyzing acid is −0.4. The species with λ_{max} 480 nm and that with λ_{max} 512 nm are both present after attainment of equilibrium in this step at pH >3; ratios of OD_{480}/OD_{512} progressively decrease from 2.2 at pH 5.6 to 0.5 at pH 3.3. The ratio is 1.05 at pH 4.5. Rate constants for aldehyde formation were determined by measuring the decrease in absorbance at 512 nm or the increase at 398 nm. In Figure 2 is also shown a plot of log k_0 vs. pH for aldehyde formation in 50% dioxane-H_2O. At low pH there is hydronium ion catalysis (k_H = 3.16 M^{-1} s^{-1}) while at pH >5 the reaction is pH independent (k_0 = 1.78 × 10^{-4} s^{-1}).

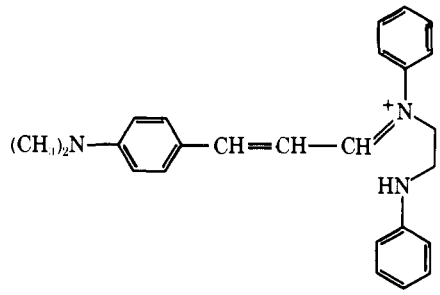
The hydrolysis reactions of 2-styryl-*N,N'*-diphenyl-1,3-imidazolidine (IV) at 30 °C in H_2O proceed with a large decrease in absorbance at 254 nm followed by a much slower increase in absorbance at the same wavelength to give a final spectrum characteristic of cinnamaldehyde. The logarithms of k_{obsd} for the first stage of the reaction (ring opening) are a linear function of pH in the pH range 2-6 with a slope of −1.0. The second-order rate constant k_H for hydronium ion catalysis

is 1030 M^{-1} s^{-1}. Buffer catalysis was not observed in this reaction in cacodylate buffer at pH 6.0 or acetate buffer at pH 4.61 at total buffer concentrations ranging from 0.20 to 1.0 M. The second step in the reaction (hydrolysis of the cationic Schiff base) is considerably slower than ring opening. At pH 4.61 k_{obsd} has the value 1.53×10^{-4} s^{-1}, which is 52-fold less than k_{obsd} for ring opening. At pH <5 Schiff-base hydrolysis is hydronium ion catalyzed (k_H = 10.8 M^{-1} s^{-1} at 30°C in 50% dioxane-H_2O).

Discussion

Hydronium Ion Catalysis of Ring Opening. The hydrolysis of 2-(*p*-methoxyphenyl)-*N*,*N*′-diphenyl-1,3-imidazolidine to *p*-methoxybenzaldehyde proceeds with hydronium ion catalysis in the pH range 1-6 at a rate that is 10^7 less than that for the corresponding *N*,*N*′-dimethyl derivative.[6] This relatively slow rate is brought about by the low basicity of the imidazolidine nitrogens and by the relative inability of a phenyl-substituted nitrogen to release electrons to stabilize the incipient carbonium ion in the transition state. The acid-catalyzed hydrolysis reaction undoubtedly occurs via a ring-opened species, although formation of a cationic Schiff-base intermediate could not be directly observed.[6]

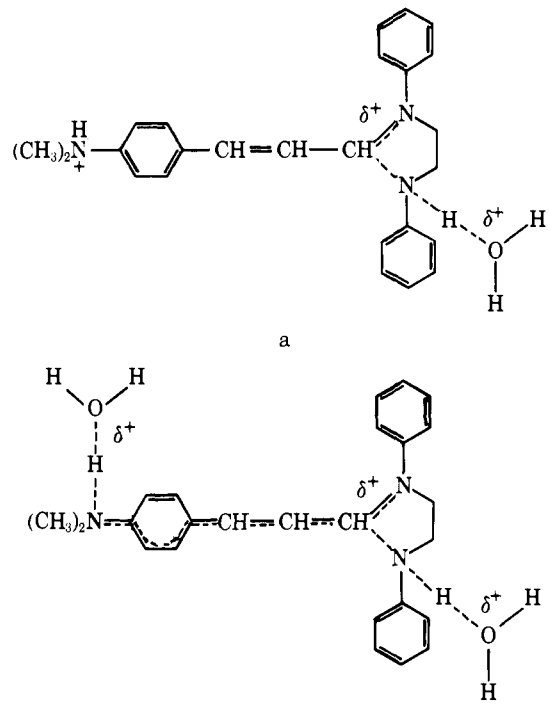
In the present work, the hydrolysis of I proceeds with formation of an intermediate having λ_{max} 505 nm. This intermediate must be the iminium ion (VII) resulting from ring



VII

opening. The ring-opening reaction is catalyzed by hydronium ion with a second-order rate constant k_H of 2290 M^{-1} s^{-1} at 30 °C. The pH-log (rate constant) profile for ring opening of I is reasonably linear with slope of −1.0 in the pH range 1-4, indicating that the ionization state of the *p*-dimethylamino group is not changing in that pH region. The pK_a of the *p*-dimethylamino group conjugate acid of less reactive analogues is 3-4.8.[16,17] A spectrophotometric titration of I at 303 nm gave evidence for a pK_a around 4.5. This titration was not as quantitatively precise as desired because of the rapid rate of ring opening at low pH and reduced water solubility of the compound at pH >5.5. Nevertheless, hydronium ion catalyzed ring opening must involve catalysis of the reaction of a protonated species. The leaving-group nitrogen will undergo protonation prior to or during ring opening, but the other proton in the kinetically reactive species could be on either the *p*-dimethylamino group or an *N*-phenyl nitrogen. Protonation of the *p*-dimethylamino group would be expected to slow the reaction by reducing basicity of the ring nitrogens and by decreasing resonance stabilization of the developing carbonium ion. The second-order rate constant for hydronium ion catalyzed hydrolysis of the analogous 1,3-dioxolane is reduced 160-fold by protonation of the *p*-dimethylamino group.[17]

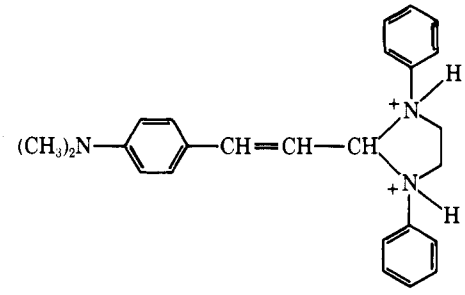
The large D_2O solvent isotope effect (k_H/k_D = 3.0) in the hydronium ion catalyzed reaction may indicate that proton transfer is taking place in the critical transition state. A-1 reactions in which there is preequilibrium formation of a conjugate acid intermediate are normally much faster in D_2O than in H_2O with ratios k_D/k_H of >2.75.[18,19] Proton transfer in the transition state could involve either or both protons as depicted in VIIIa and b where the leaving group is undergoing pro-



a b

VIII

tonation by hydronium ion. C-N bond breaking will lower the pK_a of the *p*-dimethylamino group considerably and therefore necessitate removal of a proton from that group at some stage of the reaction. That the product of the reaction at pH 1-4 is a species having the *p*-dimethylamino group unprotonated is clearly shown by the absorbance maximum at 505 nm, indicating that the same conjugated species is formed as at pH >5. It may be noted that the unsubstituted derivative IV does not give rise to absorbance at 505 nm (λ_{max} 356 nm). A stepwise



VIIIc

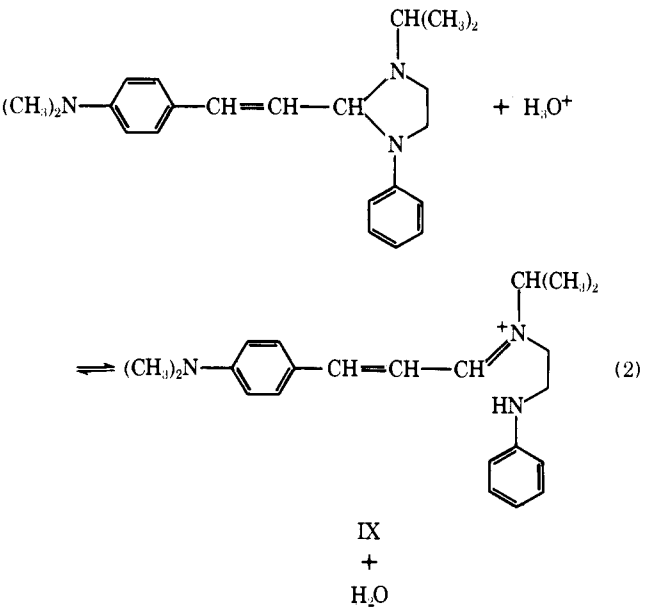
preequilibrium transfer of a proton from the *p*-dimethylamino group to an *N*-phenyl nitrogen, giving VIIIc as the kinetically significant species, might also lead to a slower reaction in D_2O than H_2O if the pK_a of the *p*-dimethylamino group is greater than the pK_a of the *N*-phenyl nitrogen, and correspondingly the pK_a of a dication including the dimethylamino group is greater than that of VIIIc.[7] Acid dissociation constants are normally reduced in D_2O as compared with H_2O, and this effect can be greater for weaker acids. The equilibrium concentration of VIIIc would therefore be dependent upon the relative effects of D_2O and H_2O on the respective dissociation constants. The dimethyl substitution of the para substituent should raise the basicity of that group moderately in comparison to the *N*-phenyl ring nitrogens in the neutral reactant, but the proximity of the positive charges in VIIIc should have a marked acid-strengthening effect. The above possibility is given support by the lack of buffer catalysis in ring opening. If proton transfer to the leaving group is occurring in the transition state, it would be expected that general acid catalysis would be de-

tected, although the pH-independent reaction at pH >6 renders impossible a search for general acid catalysis with weak buffer acids. 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 to obtain a more reactive dication (VIIIc).

The analogous cinnamaldehyde derivative (IV) undergoes hydronium ion catalyzed ring opening at a twofold slower rate than I ($k_H = 10^3\ M^{-1}\ s^{-1}$), even though the protonated *p*-dimethylamino group should slow the reaction of I. This must indicate some resonance interaction between the *p*-dimethylamino group of I and the developing carbonium ion in the transition state, and is explainable in terms of mechanism VIIIb or a reaction via the dication VIIIc. The reaction of IV is faster in D_2O than in H_2O ($k_D/k_H = 3.1$), indicating a mechanism involving a conjugate acid. Thus, the *p*-dimethylamino group of I is of great mechanistic consequence. Its presence in I is directly responsible for the slower reaction in D_2O than H_2O. An A-1 mechanism in ring opening of IV must result from the relative inability of phenyl-substituted nitrogen to stabilize the developing carbonium ion.

The *N,N'*-dialkyl substituted derivative 2-(*p*-dimethylaminostyryl)-*N,N'*-dimethyl-1,3-imidazolidine (II) undergoes a rapid ring-opening reaction which can be monitored by a decrease in absorbance at 288 nm (disappearance of imidazolidine) or an increase in absorbance at 480 nm (appearance of Schiff base). The absorbance maximum at 480 nm for the *N*-alkyl Schiff base is therefore at a lower wavelength in comparison with the corresponding *N*-phenyl derivative (505 nm). The second-order rate constant k_H for the hydronium ion catalyzed reaction is $2 \times 10^9\ M^{-1}\ s^{-1}$, only slightly less than that expected for a diffusion-controlled reaction ($10^{10}\ M^{-1}\ s^{-1}$), showing the great reactivity of the imidazolidine ring when the developing carbonium ion in the transition state is well stabilized and basicity is high.

In ring opening of the unsymmetrical imidazolidine III, a measurable transition (stopped flow) occurs in which the absorbance at 303 nm decreases and a new peak appears with a maximum at 480 nm. Rate constants measured at 303 and 480 nm are identical. The absorbance at 480 nm must correspond with a ring-opened intermediate. A maximum at that wavelength was not found for the iminium ion derived from I or the aldehyde product. Since the *N*-phenyliminium ion of *p*-dimethylaminocinnamaldehyde (VI) has λ_{max} greater than 505 nm (520 nm in acetonitrile), whereas the *N*-isopropyliminium ion V has λ_{max} of 458 nm (Table I), the absorbance at 480 nm is most reasonably attributed to the *N*-isopropyliminium ion (IX). This assignment is strongly supported by the fact that ring opening of the symmetrical *N,N'*-dialkylimidazolidine II only gives rise to a species with λ_{max} 480 nm. The transition at pH values greater than 7 can then be represented by eq 2. The second-order rate constant for hydronium ion catalysis ($k_H = 4 \times 10^7\ M^{-1}\ s^{-1}$) is only 50-fold less than that for ring opening of II. This rate difference must reflect the lower basicity of the leaving-group nitrogen of III. The rate of ring opening of III is considerably less in D_2O than in H_2O ($k_H/k_D = 3.2$). In view of the D_2O solvent isotope effect and the observed general acid catalysis, it is clear that, in the ring-opening reaction at pH >7, proton transfer is occurring in the critical transition state (X). The favored product (IX) is undoubtedly determined by the relative ability of the nitrogens to donate electrons to stabilize the incipient carbonium ion in the transition state and by the relative abilities of the two ring nitrogens to serve as leaving groups. Stabilization of the developing carbonium ion is greater from the alkyl-substituted nitrogen than *N*-phenyl, and the reaction is therefore proceeding with expulsion of the least basic nitrogen.



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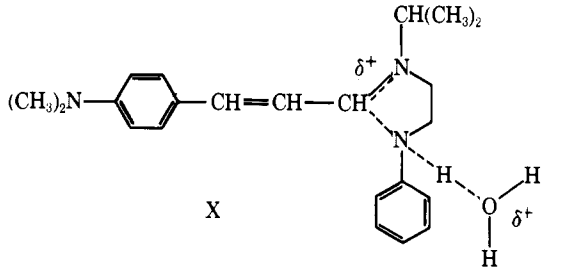
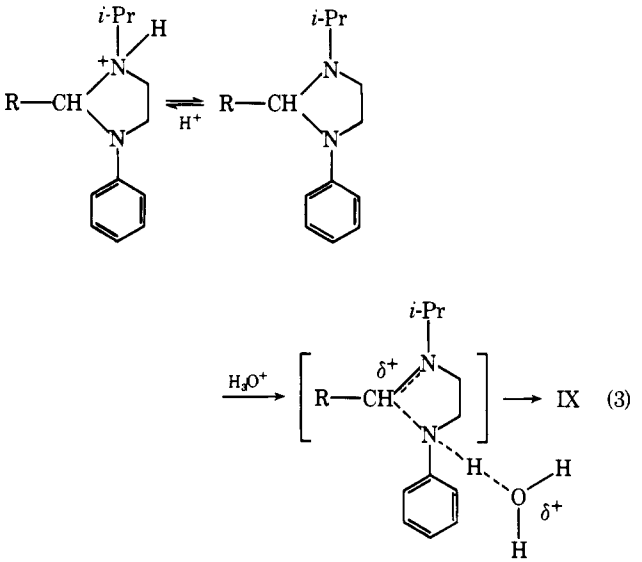
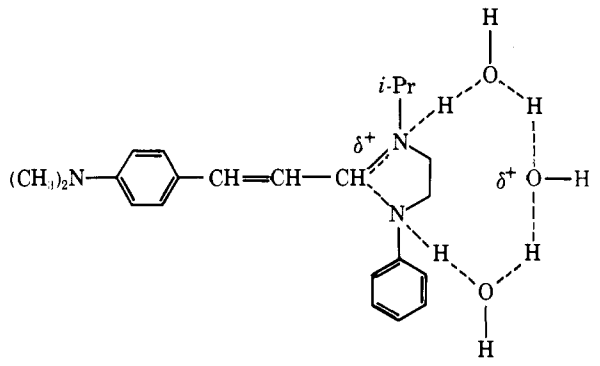


At pH values below 5 ring opening of III (disappearance of substrate) becomes pH independent with $k_0^{H_2O}/k_0^{D_2O} = 1.9$. The alkyl-substituted ring nitrogen is the most basic nitrogen and would be protonated at pH values below the high pK_a of the ring as depicted in eq 3, although a pK_a of 5 is lower than



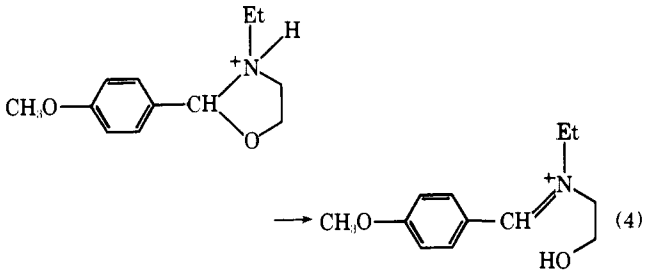
(3)

expected for that nitrogen.[20-22] Existence of a monoprotonated intermediate in this case would depend on the relative inability of the alkyl-substituted nitrogen to serve as a leaving group. Thus, for iminium ion IX to be produced at pH values below the monocation pK_a and above the dication pK_a, a proton transfer must take place which can be either stepwise or concerted through solvent molecules (eq 3 and XI, respectively). Ring opening of the monoprotonated species of 2-*p*-methoxyphenyl-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine to the *N*-alkyl Schiff base is also subject to a large D_2O solvent iso-



XI

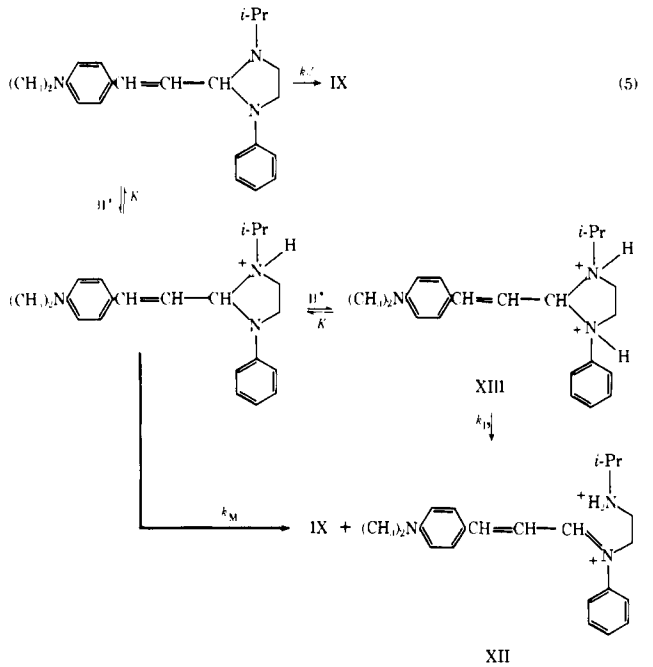
tope effect (k_{H_2O}/k_{D_2O} = 2.5).[7,23] A similar type of reaction must also take place in hydrolysis of 2-(*p*-methoxyphenyl)-*N*-ethyl-1,3-oxazolidine, where nitrogen is protonated at low pH but where ring opening occurs to give a cationic Schiff base (eq 4) (k_{H_2O}/k_{D_2O} = 2.65) to take advantage of the greater



(4)

carbonium ion stabilization by nitrogen in the transition state.[24]

The break in the profile for ring opening at pH 5 could reflect incursion of a reaction of a dicationic species.[22] Either the *p*-dimethylamino group or the *N*-phenyl nitrogen could be protonated, but XIII is depicted as the kinetically reactive species in the scheme of eq 5. It would be predicted that XII



(5)

XII

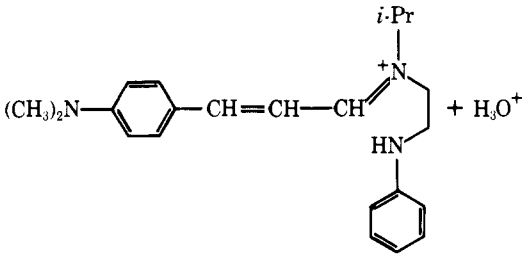
would be a product of a dication reaction via XIII.[25] The product composition after ring opening is highly dependent on pH. At pH values greater than 6, IX is formed exclusively; spectra taken after completion of ring opening have sharp maxima at 480 nm. As the pH is lowered below 5.5 the concentration of a species with λ_{max} 512 nm progressively increases. The species with λ_{max} 512 nm is clearly the *N*-phenyl Schiff base XII, as follows from the λ_{max} values for the Schiff base derived from I (λ_{max} 505 nm) and that for the monoprotonated Schiff base of *p*-dimethylaminocinnamaldehyde and aniline (λ_{max} 520 nm). At pH <4, XII becomes the predominant species. As pH is lowered and it becomes increasingly easy to form a diprotonated species, breaking of the C-N *i*-Pr bond can become increasingly competitive with C-N phenyl bond breaking, i.e., either Schiff base may be produced by breakdown of XIII or a kinetically equivalent reaction. It is probable that pK_2 is greater than 5 and pK_1 less than 5, with the points between representing a transition from a monocation reaction (or kinetic equivalent) to a faster dication reaction. The equation for k_0 (ring opening) derived from the scheme of eq 5 is

$$k_0 = \frac{k_D a_H^2 + k_M K_1 a_H + k_0' K_1 K_2}{a_H^2 + K_1 a_H + K_1 K_2} \quad (6)$$

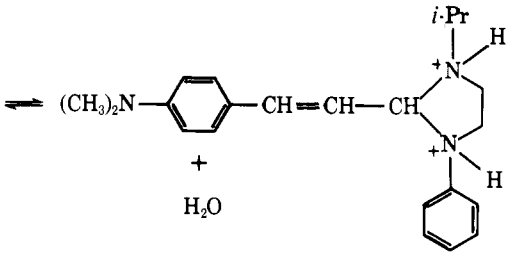
A good fit to the experimental data (dotted line in Figure 2) is provided by k_M = 14 s^{-1}, k_D = 300 s^{-1}, pK_1 = 4.7, and pK_2 = 6.5. The fit to the data is not highly sensitive to the value of pK_2 (±0.5 pK_a units) and the corresponding value of k_M. Employing these values, it is clear that at pH 4.5 the reaction would proceed predominantly via the dication. However, the spectral data at that pH indicate that after ring opening IX and XII are present in comparable amounts. Therefore, IX and XII are both formed by breakdown of a dication and/or rapid reversal of the dication ring-opening reaction occurs to give an equilibrium mixture. The D_2O solvent isotope effect in ring opening at pH <5 shows that proton transfer is occurring either in the transition state or in a stepwise manner.[7,23]

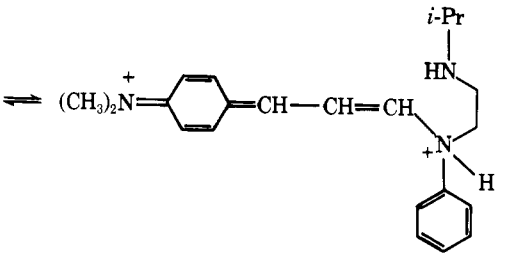
Rapidly lowering the pH of a solution of III at pH 6 in which IX (λ_{max} 480 nm) is at high concentration results in an increase in absorbance at 512 nm. The transformation represents a chemical reaction for which rate constants can be measured in stopped-flow determinations, and the pH-rate constant profile for this reaction is shown in Figure 2. Thus, an equilibrium exists at low pH involving protonated forms of III, IX, and XII. Both IX and XII are present at pH >3.5 after attainment of equilibrium in the second step, as shown by the ratios of OD_{480}/OD_{512}, with the concentration of XII progressively increasing as pH is lowered. Formation of XII only becomes significant at pH values less than 6.

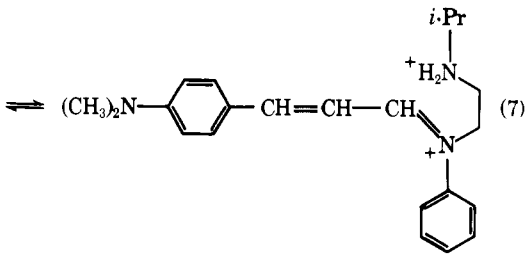
It can be seen in Figure 2 (middle curve) that hydronium ion catalysis occurs in the formation of the species absorbing at 512 nm from IX at pH values less than 3.5. The acid-catalyzed conversion of IX to XII must be a reaction with two protons in the critical transition state. The downward bend in the profile at pH 2 may signify a complex constant representing ring closure and addition of a proton, or it could represent a change in rate-determining step at pH 2 from reclosure of the ring to breakdown of a dication intermediate. The latter possibility is given support by the fact that, whereas there is pronounced buffer catalysis at pH values greater than 2, such catalysis is not detected in maleic acid buffers below pH 2. Hydronium ion catalyzed reclosure of the ring (pH >2) would be rate determining if a dication breaks down more rapidly to XII than to IX. The near pH-independent rearrangement reaction at pH >3.5 would then represent water-catalyzed ring closure. This explanation of the rearrangement profile is also in accord with the observed general acid catalysis, which could then be attributed to concerted C-N bond formation and protonation of the *p*-dimethylamino group or to proton removal by a base from the nucleophilic nitrogen in a reaction of the protonated species. Protonation of the *p*-dimethylamino group of IX would facilitate the reclosure step, and would give rise to the acid catalysis observed at pH <3.5. Upon reopening of the ring an increased percentage of XII would result because protonation of the acyclic nitrogen of XII will be more complete than in the case of IX, thereby stabilizing XII to reclosure



IX





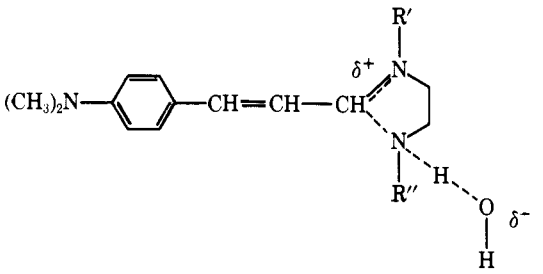


(7)

XII

relative to IX. Assuming that formation of XII must occur through a ring-closed compound, the acid-catalyzed reaction can be depicted as in eq 7 or a kinetic equivalent. The ring opening to XII could occur in this manner since the incipient carbonium ion in the transition state will be well stabilized by the *p*-dimethylaminostyryl substituent at the 2 position.

pH-Independent Ring Opening. The pH-independent ring opening reaction of II and III at pH values greater than 10 can be attributed to a unimolecular, uncatalyzed reaction or to a water-catalyzed reaction (XIV). Departure of an amine anion

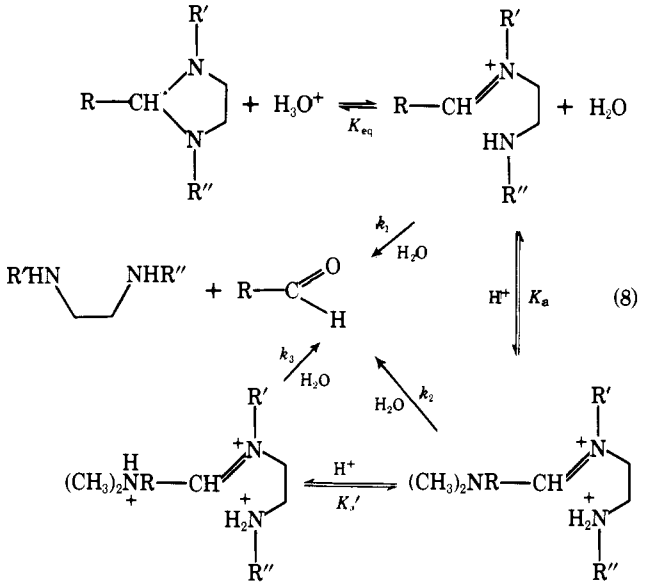


XIV

in a unimolecular decomposition should be energetically quite unfavorable; in nucleophilic reactions of amides protonation of the leaving group is a requirement to avoid expulsion of an unstable amine anion from a tetrahedral intermediate.[26,27] Therefore, in the pH-independent reactions of II and III at high pH, catalysis by H_2O acting as a general acid is a more likely possibility. Reactions independent of pH also occur in the hydrolysis of acetals subject to general acid catalysis;[28-30] however, in those cases the leaving groups are much better and the reactions are unimolecular. In contrast with the smaller k_H (50-fold), k_0' for III is 8-fold larger than that of II, in accord with the different leaving groups (*N*-methyl and *N*-phenyl). Since carbonium ion stabilization will be similar in the two cases, this implies compensating effects on the rate constants in the water-catalyzed reaction due to differences in basicity and leaving-group ability; the more basic nitrogen (*N*-methyl) is protonated most readily but is the poorest leaving group. As the catalyst acid becomes weaker (H_2O) more bond breaking will be required to attain the transition state and leaving-group ability will become relatively more important than in the H_3O^+-catalyzed reaction. Similarly, ρ values for substitution in the phenolic leaving group are positive in general-acid-catalyzed acetal hydrolysis in contrast with negative values in hydronium ion catalyzed reactions.[9,29]

The pH independence of k_{obsd} in ring opening could also reflect the importance of the reverse reaction. In the ring-opening reaction $k_{obsd} = k_{open} + k_{rev}$. If the reaction governed by k_{open} is hydronium ion catalyzed, the reverse reaction (water-catalyzed nucleophilic attack by the acyclic amine) will be pH independent at pH values greater than the intermediate acyclic amine group pK_a. Therefore, k_{rev} could become the predominant influence on k_{obsd} at high pH, although k_{rev} can have no effect on the rate of ring opening at lower pH. At high pH the absorbance due to Schiff base would then disappear as pH is increased. That was observed with I, but the Schiff bases from II and III still display significant absorbance at pH >12.

Cationic Schiff-Base Hydrolysis. Formation of *p*-dimethylaminocinnamaldehyde from the cationic Schiff bases derived from I-III through reaction with water is hydronium ion catalyzed at low pH. These reactions must involve species in which the acyclic amine group of the Schiff base and the *p*-dimethylamino group are protonated (eq 8). The absorbance



(8)

due to the cationic Schiff bases from I-III is maximal at pH values above the range in which acid catalysis occurs in Schiff-base hydrolysis (<3),[31] indicating that the effect of hydronium ion at low pH is not on the concentration of Schiff base. However, protonation of the acyclic nitrogen will destabilize the iminium ion by increasing electron withdrawal and will thereby facilitate the rate of hydrolysis. The hydrolysis of the Schiff base from the cinnamaldehyde derivative IV is also acid catalyzed at low pH, and the reaction in that case must be attributed to protonation of the acyclic nitrogen.

The pK_a of the conjugate acid of the acyclic amine in the Schiff bases should be low. A positive charge separated from a nitrogen conjugate acid by two carbon atoms generally produces an acid-strengthening effect of 1.5-3 pK_a units[11] or greater,[2] in accord with the pK_a values of *N,N'*-diphenylethylenediamine[11,32] in H_2O (2.4 and 3.95). The pK_a of the acyclic amine group of VII in 50% dioxane-H_2O should therefore be <2. The pK_a of the acyclic amine of the Schiff base derived from II should be >5, but acid catalysis is still observed in the pH range 0.5-3.0, thereby indicating an effect of protonation of the *p*-dimethylamino group. Protonation of the *p*-dimethylamino group would also destabilize the iminium ion and, as a consequence, increase the rate of hydrolysis. The pK_a of the *p*-dimethylamino group conjugate acid in the Schiff base VII must be extremely low in view of the strong absorbance at 505 nm even at pH values as low as 0.5. Significant protonation of the para substituent should reduce the absorbance of the Schiff-base derivative appreciably, since the electrons of the dimethylamino nitrogen must be highly delocalized in the Schiff base. The presence of two positive charges in a molecule may depress the most acidic pK_a by 5-7 units.[2]

The bend in the pH-log (rate constant) profile at pH 5.4 for hydrolysis of the Schiff base VII in 50% dioxane-H_2O may correspond to the pK_{eq} for the ring-opening step of eq. 8, since the dissociation constants of the phenyl-substituted nitrogens are undoubtedly large. A Schiff-base intermediate could not be observed spectrophotometrically at pH values above 7.5, indicating that only a low steady-state concentration is present. On the other hand, the absorbance of Schiff base at 505 nm is maximal at ~pH 4. Therefore, the pK_{eq} must be close to 5.4. The equation for k_{obsd} derived for the scheme of eq 8 is

$$k_{obsd} = \frac{k_1 K_a K_a' a_H + k_2 K_a' a_H^2 + k_3 a_H^3}{K_{eq} K_a K_a' + K_a K_a' a_H + K_a' a_H^2 + a_H^3} \quad (9)$$

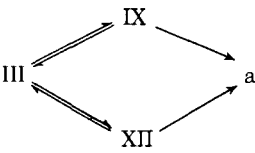
At pH values greater than 5 the equation simplifies to

$$k_{obsd} = \frac{k_1 a_H}{K_{eq} + a_H} \quad (10)$$

An alternative interpretation is that the downward bend in the profile corresponds to a change in rate-limiting step from attack of H_2O on the Schiff base to decomposition of a carbinolamine intermediate. However, such a bend is not observed in hydrolysis of the intermediate derived from II or III with which pK_{eq} is high. The scheme of eq 8 is reasonable, and it is in accord with the spectral data. The rates of aldehyde appearance measured at 398 nm were found to be identical with the rates of disappearance of Schiff base. Thus, a carbinolamine intermediate is not accumulating at detectable concentrations.

The formation and hydrolysis of Schiff bases have been extensively studied,[33-39] and the mechanisms of these reactions are reasonably well understood.[36,38,39] One of the principal conclusions is that, at pH values where the Schiff bases are predominantly protonated, attack of water on the protonated Schiff base takes place. This is also the case for hydrolysis of cationic Schiff bases[6,7] in the pH range 1-8 where hydrolysis of I-III was studied. There is no reason to suspect that the Schiff bases from I-III are not hydrolyzing in accord with expectations derived from the previous work. It is clear from Figure 1 that in H_2O Schiff-base hydrolysis is rate determining in the overall reaction at all pH values.

In hydrolysis of III the cationic Schiff-base intermediates IX and XII should both give the aldehyde product, although XII should hydrolyze more rapidly than IX. Protonated *N*-phenyl Schiff bases hydrolyze much faster than corresponding *N*-alkyl derivatives. For example, the rate of hydrolysis of *N*-(*p*-chloro)benzylideneaniline is 10^4-fold greater than that of the corresponding *tert*-butylamine Schiff base.[36] Also, VI hydrolyzes rapidly in 2 M HCl, whereas V is reasonably stable. Consequently, it is possible that at low pH XII is the direct precursor of the aldehyde product, i.e., the reaction proceeds as in eq 11. At low pH the Schiff bases from I and III hydrolyze

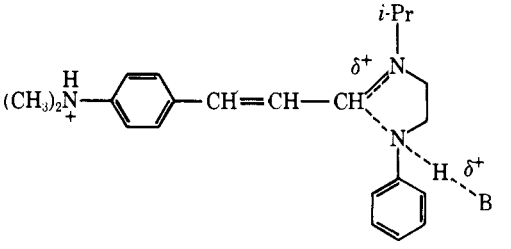


(11)

100-300-fold faster than that from II as reflected in the relative k_H values.

General-Acid-Catalyzed Ring Opening Reactions of III. General acid catalysis was observed in ring opening of III to the species absorbing at 480 nm with trimethylamine buffer (Figure 3). The reactions of I-III constitute the first examples of acid-catalyzed ring opening of imidazolidines where rate constants can be directly measured, and therefore the data of Figure 3 are the first examples of general acid catalysis in such reactions. Bond breaking must be a favorable process because of the stabilization that can be afforded the incipient carbonium ion. A conjugate acid species is therefore not required as an intermediate. Proton transfer to nitrogen is only *partial* in the transition state for ring opening, because the C-N bond can begin to break before proton transfer is complete. In cases where hydronium ion catalysis is facile and a pH-independent reaction takes place, the most favorable pH for observation of buffer acid catalysis will be at the intersection on the pH-rate constant profile between these mechanisms,[12] and accordingly pronounced buffer catalysis was not observed in the reaction of III at pH values considerably above or below 9.50.

Formation of the species with λ_{max} at 512 nm from the species absorbing at 480 nm is also markedly catalyzed by buffer, indicating that a proton is being transferred to or from the substrate in the transition state. This catalysis could be general-base-catalyzed ring closure of a protonated form of IX, as inXV, if that step is rate limiting. General-base-cata-



XV

lyzed ring closure implies general-acid-catalyzed ring opening by microscopic reversibility.

If low basicity of the substrate were the most important factor leading to general acid catalysis in reactions of acetals and acetal analogues, then it would be expected that such catalysis would be observed in the hydrolysis of thioacetals in cases where the C-S bond initially breaks. However, general acid catalysis was not detected in thioacetal hydrolysis even though pronounced catalysis takes place in the hydrolysis of exactly analogous oxygen acetals.[40] Moreover, if basicity of the substrate were the predominant factor leading to general acid catalysis concerted with bond breaking, such catalysis might not be expected when basicity is high. The general acid catalysis of the ring opening of III to IX is undoubtedly a reflection of the great ease of C-N bond breaking due to the effect of the leaving group and the stabilization of the developing carbonium ion. Protonation of the more basic *N*-isopropyl nitrogen does not bring about cleavage of that C-N bond at pH >7. Rather, the alkyl-substituted nitrogen facilitates cleavage of the C-N phenyl bond by stabilizing the developing carbonium ion resulting from expulsion of the least basic nitrogen in a reaction concerted with proton transfer. The

reaction proceeds in such a manner so that the kinetic advantage of expulsion of the best leaving group with maximum carbonium ion stabilization is utilized. Basicity of the atom to which proton transfer is occurring is not the critical factor in giving rise to general acid catalysis in the reactions of III and in the reactions of acetals for which classical general acid catalysis has been observed[9,10] because the bond-breaking process is so facile. The rate constant for unimolecular breakdown of the protonated species of benzaldehyde diethyl acetal must approximate 10^8 s^{-1}.[6] Thus, even with that acetal where the leaving group is poor and the carbonium ion intermediate only of moderate stability, the rate constant for breakdown is almost of the magnitude requiring proton transfer as part of the rate-limiting step. In all cases where general acid catalysis has been observed in acetal hydrolysis, the bond-breaking process is easy because of an extremely good leaving group,[28,29] a highly stabilized carbonium ion in the transition state,[30] or steric strain in the reactant which is relieved in the transition state.[9,10,41,42] When basicity of the ring nitrogens is relatively high and developing carbonium ion stabilization is maximized, as with II, the diffusion-controlled approach of hydronium ion may become rate determining. This possibility is given support by the magnitude of the second-order rate constant k_H for ring opening of II (2×10^9 M^{-1} s^{-1}), which is quite close to the diffusion-controlled limit.

Conclusion

It is likely that the unsymmetrical nature of N^5,N^{10}-methylenetetrahydrofolic acid is an important feature in reactions of the cofactor derivative. The pK_a values of the N(5) and N(10) nitrogens of tetrahydrofolic acid are 4.82 and −1.25, respectively.[11] Enzymatic reactions in which general-acid-catalyzed ring opening occurs would be favored by such a distribution of pK_a values. Low basicity of N(10) would favor C-N(10) bond breaking and proton transfer to N(10) in the rate-determining step, while the higher basicity of N(5) will allow electron release to sufficiently stabilize a carbonium-ion intermediate. Thus, both factors can work together to facilitate general acid catalysis. That such catalysis, involving partially rate-determining proton transfer to nitrogen, is a chemically reasonable possibility for the enzymatic reactions is clearly shown by the present work in which general acid catalysis has been directly observed in the ring opening of the unsymmetrical imidazolidine III. In this transformation the favored reaction involves expulsion of the least basic nitrogen to form the most stable iminium ion. Accordingly, this would also be predicted in reactions of N^5,N^{10}-methylenetetrahydrofolic acid. A competitive expulsion of the most basic leaving group occurs only at pH values close to 4. In order for the most basic nitrogen to serve as a leaving group at low pH, there must be the possibility of a high degree of carbonium ion stabilization by the substituent in the 2 position as with III. This is not the case, however, with N^5,N^{10}-methylenetetrahydrofolic acid, reinforcing the prediction that, in enzymatic reactions of the cofactor in which general acid catalysis takes place, the ring will open on the side of N(10) to give the N(5) methylene derivative.[43]

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