η chain by a flash of intensity I is related to the quantum yield (ϕ_η) by the expression[27]

$$-\ln (1 - P_\eta) \equiv -\ln (\bar{P}_\eta) \propto \phi_\eta I \quad \text{(A6)}$$

Letting the quantum yields for triplet formation in the two subunits be ϕ_1 and $\phi_2 = r\phi_1$ ($0 \leq r \leq 1$), it follows that

$$\bar{P}_2 = \bar{P}_1 r \quad \text{(A7)}$$

Substituting this relation into eq A4, one obtains an implicit formula for calculating $\bar{P}_1$ and consequently P_1 and P_2, given the average excitation level, P, and $\bar{P} = 1 - P$ and an assumed value of r.

$$\bar{P}_1 = \frac{2\bar{P}}{1 + \bar{P}_1^{(r-1)}} \quad \text{(A8)}$$

The value of r is unknown in advance but can be estimated rather well from the initial rate data as is described in the text.

Under initial conditions, namely $k_{i\gamma}t \ll 1$ for all i, eq A3 reduces to a linear form

$$\Delta A_t = \Delta A_0(1 - k_1 t) \quad \text{(A9)}$$

where

$$k_1 = \frac{\sum_{i=1}^{4}\sum_{\gamma} k_{i\gamma} f_{i\gamma}}{\sum_{i=1}^{4}\sum_{\gamma} f_{i\gamma} i} \quad \text{(A10)}$$

The $k_{i\gamma}$ are given in eq 4 and the $f_{i\gamma}$ are defined in terms of the f_l^{jk} of eq A5.

General-Acid Catalysis of Imidazolidine Ring Opening. The Hydrolysis of Ethyl *N,N'*-[1-(*p*-(Dimethylamino)phenyl)propenediyl]-*p*-[((2-tetrahydroquinolinyl)methylene)amino]benzoate

Thomas H. Fife* and August M. Pellino

Contribution from the Department of Biochemistry, University of Southern California, Los Angeles, California. *Received June 30, 1980*

Abstract: Ring opening of ethyl *N,N'*-[1-(*p*-(dimethylamino)phenyl)propenediyl]-*p*-[((2-tetrahydroquinolinyl)methylene)-amino]benzoate in 50% dioxane–H_2O at 30 °C proceeds with formation of a Schiff base having λ_{max} = 539 nm. This Schiff base is that formed by breaking of the C–N(10) bond as indicated by the spectral data; i.e., the most stable Schiff base is formed with expulsion of the nitrogen of lowest pK_a. Ring opening is catalyzed by hydronium ion with the second-order rate constant $k_H = 1.4 \times 10^5$ M^{-1} s^{-1}. The Schiff base intermediate is not detectable at pH values greater than 7, being present only at low steady-state concentrations (pK_{eq} for ring opening is 4.8). Hydrolysis of the Schiff base proceeds 10^5–10^6-fold more slowly than ring opening. Hydronium ion catalysis occurs at low pH with $k_H = 0.13$ M^{-1} s^{-1}. General-acid catalysis by a series of buffer acids was found in ring opening with a Brønsted α coefficient of 0.7. Thus, protonation of nitrogen and C–N bond breaking take place in a concerted manner with proton transfer well advanced in the transition state. General-acid catalysis only occurs in reactions of the neutral species. Addition of a proton to give a monocationic species abolishes general-acid catalysis in ring opening, although the second-order rate constant for hydronium ion catalysis is only reduced sixfold. Thus, carbonium ion stabilization and leaving group effects are much more important in giving rise to general-acid catalysis than basicity considerations. The α of 0.7 for the imidazolidine is higher than that obtained in ring opening of 2-(*p*-(dimethyl-amino)styryl)-*N*-phenyl-1,3-oxazolidine (0.5), which primarily reflects the effect on α of the basicity of the leaving groups (*p*-carbethoxyphenyl-substituted nitrogen vs. oxygen). The α in imidazolidine ring opening is identical with that for hydrolysis of 2-(*p*-(dimethylamino)styryl)-1,3-dioxolane (0.7), which indicates that carbonium ion stabilization, leaving group ability, and basicity factors are compensating in the two reactions in regard to the effect on α. Although basicity of the nitrogens of the imidazolidine ring is very high in comparison with the analogous acetal, general-acid catalysis still occurs because bond breaking is facile, and the same factors are important in the two reactions.

The important enzyme cofactor N^5,N^{10}-methylenetetrahydrofolic acid contains an imidazolidine ring which undergoes ring opening during its enzyme mediated reactions.[1] This ring opening may occur with general-acid catalysis by functional groups in the active sites of the enzymes as has been suggested for thymidylate synthetase.[2] Thus, an understanding of the chemistry of imidazolidine ring opening is of critical importance to understanding the mechanism of action of the cofactor. It is also of great theoretical importance to determine the factors that might facilitate general-acid catalysis in reactions of compounds of relatively high basicity.[3,4]

A Schiff base has been observed spectroscopically in ring opening of 2-(substituted benzaldehyde)-1,3-imidazolidines[5,6] at pH <5, but searches for general-acid catalysis were made difficult by the fact that a Schiff base could not be observed at pH >5, only low steady-state concentrations being present in the hydrolysis reactions. Thus, the effect of weak acids, which offer the best chance for success,[7] could not be studied. Ring opening of *N*-alkylimidazolidines of *p*-(dimethylamino)cinnamaldehyde can be

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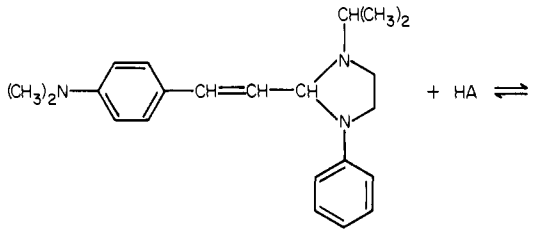
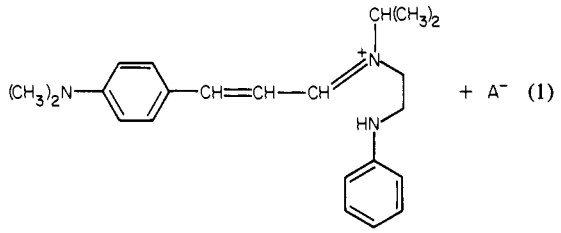
observed[3] at all pH values below 12 because of the stability of the Schiff bases and their large extinction coefficients for absorbance in the visible portion of the spectrum. General-acid catalysis was observed in ring opening of the unsymmetrical 2-(*p*-(dimethylamino)styryl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine (I) to the most stable *N*-alkyl Schiff base (eq 1).[3,8]

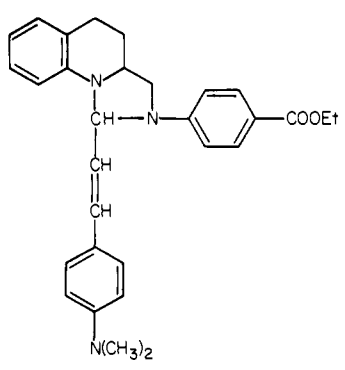


I



II

However, an extensive study of the general-acid-catalyzed reaction could not be accomplished because of competition from the facile hydronium ion catalyzed reaction ($k_H = 4 \times 10^7$ M^{-1} s^{-1}) and the pH-independent reaction at pH >9.5. It was thought that a suitable variation in the pK_a values of the two nitrogens might allow the determination of rate constants for a series of general acids and, consequently, determination of the Brønsted α coefficient. This would then give information on transition-state structure and the influence of the nitrogen pK_a values. Maximizing basicity and incipient carbonium ion stabilization with the *N,N'*-dimethyl derivative[3] leads to a hydronium ion catalyzed reaction that is nearly diffusion controlled ($k_H = 2 \times 10^9$ M^{-1} s^{-1}). Decreasing basicity and incipient carbonium ion stabilization greatly with the *N,N'*-diphenyl derivative gives greatly reduced reactivity ($k_H' = 2 \times 10^3$ M^{-1} s^{-1}), but general-acid catalysis was not observed.[3] Thus, a nitrogen pK_a is required which is less than that of the *N*-isopropyl group of I but more than that of *N*-phenyl, so that the developing carbonium ion will still be reasonably well stabilized but not to the same extent as in I. The leaving group pK_a should then be as low or lower than that of *N*-phenyl. In this paper we report a study of the formation and hydrolysis of a Schiff base from ethyl *N,N'*-[1-(*p*-(dimethylamino)phenyl)-propenediyl]-*p*-[((2-tetrahydroquinolinyl)methylene)amino]-benzoate (III) with which the above conditions are met. The



III

parent diamine has been studied previously in its reactions with formaldehyde,[9] and buffer catalysis was observed in formation of an imidazolidine ring. The diamine is extremely appropriate because its pK_a values are almost identical with those of the N(5) and N(10) nitrogens of tetrahydrofolic acid.[9,10] The finding of marked general-acid catalysis in ring opening of III in this study allows a more detailed knowledge of the transition state in reactions of this type and has permitted comparison with the similar reactions of analogous cyclic *O,O*-acetals and *O,N*-oxazolidines, so that the factors influencing general-acid catalysis in reactions of these various analogues can be assessed.

Experimental Section

Materials. Quinoline 2-carboxaldehyde was prepared by treatment of dibromoquinaldine with $AgNO_3$ in H_2O by the method of Hammick[11] and melted at 69–70 °C (lit.[11] mp 71 °C). Dibromoquinaldine was prepared from tribromoquinaldine, employing the procedure of Sharp;[12] mp 120–121 °C (lit.[12] mp 120 °C). The tribromoquinaldine was prepared according to the method of Hammick.[13] This compound melted at 128–129 °C (lit.[13] mp 128 °C). The preparation of ethyl *p*-[((2-tetrahydroquinolinyl)methylene)amino]benzoate from quinoline 2-carboxaldehyde followed closely the procedure of Benkovic et al.[9] The compound melted at 96–97 °C (lit.[9] mp 93–94 °C). The UV–vis and NMR spectra of the compound corresponded exactly with those previously reported.

The synthesis of ethyl *N,N'*-[1-(*p*-(dimethylamino)phenyl)-propenediyl]-*p*-[((2-tetrahydroquinolinyl)methylene)amino]benzoate (III) from *p*-(dimethylamino)cinnamaldehyde and ethyl *p*-[((2-tetrahydroquinolinyl)methylene)amino]benzoate was accomplished by refluxing equimolar amounts of the reactants in benzene with continuous removal of water by azeotropic disillation. No reaction occurred until addition of 2 equiv of morpholine. An overnight reflux did then give the imidazolidine as evidenced by the NMR of the residue. In this spectrum, peaks due to aldehyde were absent. A benzene solution of the residue was further refluxed for 48 h. After removal of benzene by rotary evaporation, the mass was recrystallized from tetrahydrofuran and petroleum ether to give pale yellow needles, mp 121–123 °C. Anal. Calcd for $C_{30}H_{33}N_3O_2$: C, 77.09; H, 7.07; N, 8.99. Found: C, 77.50; H, 7.21; N, 9.03. The important peaks in the NMR spectrum (Varian EM-360) were a doublet centered at 7.9 ppm (2 H), a complex multiplet centered at 6.9 ppm (11 H), a complex triplet centered at 5.85 ppm (1 H), a quartet centered at 4.3 ppm (2 H), a sharp singlet at 2.9 ppm (6 H), and a triplet centered at 1.4 ppm (3 H). There were no aldehyde peaks. Me_4Si was the standard (0 ppm).

N-(*p*-(Dimethylamino)cinnamylidene)-*p*-carbethoxyaniline (IV) was prepared by refluxing equimolar amounts of *p*-(dimethylamino)cinnamaldehyde and ethyl *p*-aminobenzoate in benzene. Water was continuously removed by azeotropic distillation employing a Dean Stark trap. After removal of the benzene by rotary evaporation, the residue was crystallized from a tetrahydrofuran–hexane mixture. After recrystallization the compound melted at 145–147 °C. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.53; H, 6.83; N, 8.69. Found: C, 74.27; H, 7.11; N, 8.55. In 50% dioxane–H_2O (v/v) with μ = 0.5 M at pH 2.6, the UV spectrum had λ_{max} at 568 nm.

N-(*p*-(Dimethylamino)cinnamylidene)-1,2,3,4-tetrahydroquinoline (V) could not be directly synthesized by the above procedure. However, it was generated in quantities sufficient for purposes of obtaining spectra by adding 1.05×10^{-4} mol of *p*-(dimethylamino)cinnamaldehyde and 1,2,3,4-tetrahydroquinoline to 50% dioxane–H_2O (μ = 0.5 M) and adjusting the pH to 2.4 with HCl. This gave a red solution of Schiff base with λ_{max} = 535 nm. A modification of the above experiment was also carried out in benzene. To a cuvette filled with benzene was added equimolar amounts of *p*-(dimethylamino)cinnamaldehyde and tetrahydroquinoline hydrochloride. This solution was initially yellow but turned red-purple upon addition of HCl. The λ_{max} was 530 nm. The color was stable at 50 °C, but the solution became yellow when cooled.

The dioxane used in these studies was spectral grade (Mallinckrodt) and was refluxed over sodium borohydride for 3 h and distilled prior to use.

Kinetic Methods. All kinetic studies were carried out at 30 °C by employing 50% dioxane–H_2O (v/v), μ = 0.5 M with KCl. Ring-opening reactions were followed employing a Durrum-Gibson stopped-flow spectrophotometer (Model D-110). The substrate was dissolved at the

(8) Buffer acid catalysis was observed in trimethylamine buffers with ionic strength held constant with either KCl or tetramethylammonium chloride. The D_2O solvent isotope effect in the hydronium ion catalyzed reaction (k_H/k_D) was 3.2.

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(12) Sharp, L. K. *J. Pharm. Pharmacol.* **1949**, *1*, 395.
(13) Hammick, D. L. *J. Chem. Soc.* **1923**, *123*, 2882.

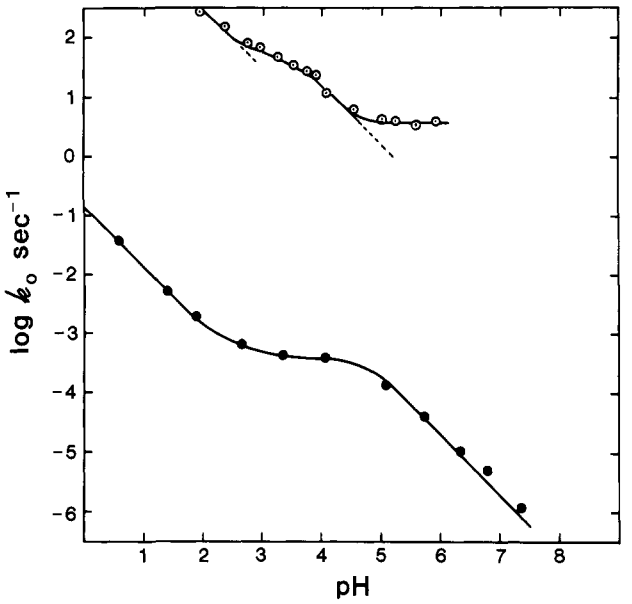


Figure 1. Plots of log k_0 vs. pH for ring opening of ethyl *N,N'*-[1-(*p*-(dimethylamino)phenyl)propenediyl]-*p*-[((2-tetrahydroquinolinyl)-methylene)amino]benzoate (III) (⊙) and hydrolysis of the intermediate Schiff base (●) in 50% dioxane–H_2O (v/v) at 30 °C and μ = 0.5 M with KCl.

desired concentration in pH 8.5–9.5 50% dioxane–H_2O. 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. Ring opening was followed by monitoring an increase in absorbance at 539 nm or a decrease at 304 nm. Rate constants determined at the two wavelengths were identical. The hydrolysis reaction was followed employing a Beckman 25 recording spectrophotometer. The reaction was monitored by following the decrease in absorbance at 539 nm after ring opening was complete or the increase in absorbance at 398 nm due to production of aldehyde. Reaction solution pH values were measured with a Radiometer Model 22 pH meter and GK 2303 C combined electrode standardized with Mallinckrodt standard buffer solution. Pseudo-first-order rate constants were calculated with an IBM 370 computer.

Results

In the hydrolysis of ethyl *N,N'*-[1-(*p*-(dimethylamino)-phenyl)propenediyl]-*p*-[((2-tetrahydroquinolinyl)methylene)-amino]benzoate in 50% dioxane–H_2O (v/v) at 30 °C and μ = 0.5 M, an intermediate is produced with λ_{max} = 539 nm. The log k_0–pH profile for ring opening to this intermediate is presented in Figure 1, where k_0 is k_{obsd} at zero buffer concentration. The slope is −1.0 from pH 4.5–3.5 and from pH 3–2 with a small plateau between these regions. The break in the plot at pH ~3.5 is very likely due to a nitrogen pK_a. The equation for k_0 is given in eq 2, where k_H' and k_H are second-order rate constants for

$$k_0 = \frac{k_H' a_H^2 + k_H K_{app} a_H + k_0' K_{app}}{K_{app} + a_H} \quad (2)$$

hydronium ion catalyzed reaction of the protonated and neutral species, respectively, and k_0' is the rate constant for the pH-independent reaction at pH >5. Equation 2 gives an excellent fit to the data with k_H' = 2.2 × 10^4 M^{-1} s^{-1}, k_H = 1.4 × 10^5 M^{-1} s^{-1}, k_0' = 3.8 s^{-1}, and pK_{app} = 3.3. At pH >7 an intermediate in the reaction can no longer be observed. There is then a continuous increase in absorbance at 398 nm corresponding to formation of aldehyde. In Figure 1 is also shown the plot of log k_0 vs. pH for appearance of aldehyde, where again k_0 is k_{obsd} extrapolated to zero buffer concentration. This reaction could be followed at 398 or 539 nm (disappearance of intermediate), and rate constants determined at the two wavelengths were identical. The hydrolysis reaction is hydronium ion catalyzed at low pH (k_H = 0.13 M^{-1} s^{-1}) and pH independent at pH >3 (k_0' = 4 × 10^{-4} s^{-1}) followed by a further decline in k_0 at pH >5 (k_H'' = 20 M^{-1} s^{-1}).

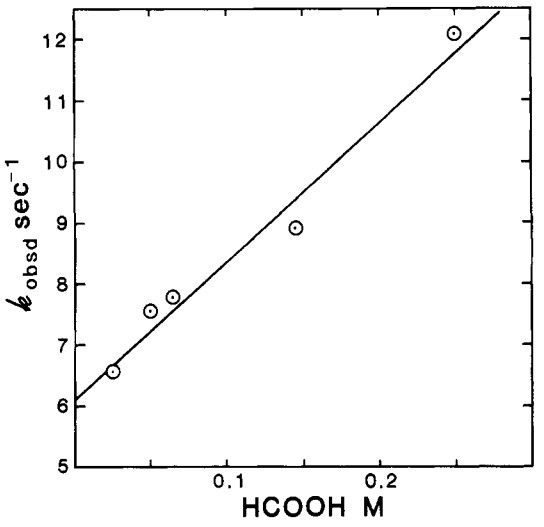


Figure 2. Plot of k_{obsd} for ring opening of III vs. the concentration of formic acid at pH 4.64 in 50% dioxane–H_2O (v/v) at 30 °C and μ = 0.5 M with KCl.

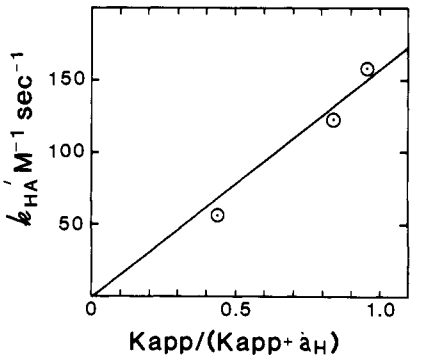


Figure 3. Plot of k_{HA}' (slope of a plot of k_{obsd} vs. chloroacetic acid concentration) vs. $K_{app}/(K_{app} + a_H)$ for chloroacetic acid catalyzed ring opening of III in 50% dioxane–H_2O (v/v) at 30 °C and μ = 0.5 M with KCl.

Table I. Rate Constants k_{HA} for General-Acid Catalysis of Ring Opening of III in 50% Dioxane–H_2O at 30 °C (μ = 0.5 M with KCl)

acid	pK_a[a]	k_{HA}, M^{-1} s^{-1}
H_3O^+		1.4 × 10^5 [b]
maleic	2.38	2.6 × 10^3 [c,d]
chloroacetic	4.04	156
formic	4.64	29.0[d]
benzoic	5.62	21.8
acetic	5.95	8.6[d]

[a] Determined by half neutralization with experimental conditions the same as in the ring opening reactions. [b] Reaction of the neutral species. [c] Calculated assuming no catalysis of the reaction of the protonated species. [d] Average of rate constants obtained at 2 pH values.

The ring-opening reaction to give the species with λ_{max} = 539 nm is markedly catalyzed by buffer acids as shown in Figure 2 where k_0 is plotted vs. formic acid concentrations. Such plots for various buffer acids at more than one pH showed that catalysis is by the acid species of the buffer. At pH values close to the pK_{app} the slopes of plots of k_0 vs. HA decrease with decreasing pH. A plot of k_{HA}' for chloroacetic acid vs. $K_{app}/(K_{app} + a_H)$ is presented in Figure 3. The plot shows that only the neutral species is subject to general-acid-catalyzed ring opening with a second-order rate constant given by the intercept at $K_{app}/(K_{app} + a_H)$ = 1.0. Values of the rate constants for a series of general acids are given in Table I. A Brønsted plot of log k_{HA} vs. the pK_a of the catalyzing acid is given in Figure 4. The slope is −0.70 (r = 0.98).

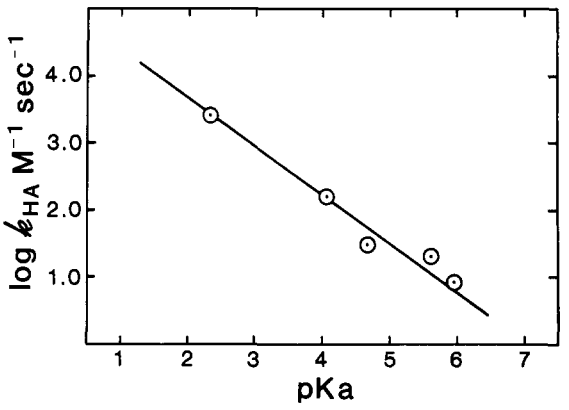
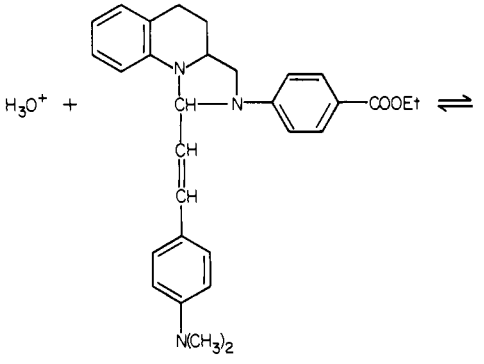


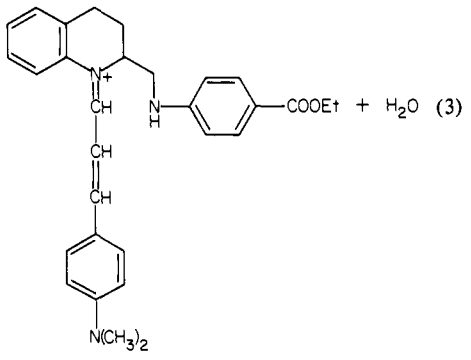
Figure 4. Brønsted plot of log k_{HA} vs. pK_a for general-acid catalysis of ring opening of III in 50% dioxane–H_2O (v/v) at 30 °C and μ = 0.5 M with KCl.

Discussion

The intermediate formed in hydrolysis of ethyl *N,N'*-[1-(*p*-(dimethylamino)phenyl)propenediyl]-*p*-[((2-tetrahydroquinolinyl)methylene)amino]benzoate is undoubtedly a Schiff base. The λ_{max} of 539 nm is similar to those of the Schiff bases formed from 2-(*p*-(dimethylamino)styryl)-*N,N'*-diphenyl-1,3-imidazolidine (λ_{max} = 505 nm) and from 2-(*p*-(dimethylamino)styryl)-*N*-phenyl-1,3-oxazolidine (λ_{max} = 498 nm).[14] The cationic Schiff base of *p*-(dimethylamino)cinnamaldehyde and tetrahydroquinoline (V) has λ_{max} = 535 nm, whereas the λ_{max} of the corresponding *p*-carbethoxyaniline Schiff base (IV) is considerably greater, λ_{max} = 568 nm. Therefore, the Schiff base formed from III must be the most stable Schiff base (VI) in eq 3. This reaction is the first observed imidazolidine ring opening



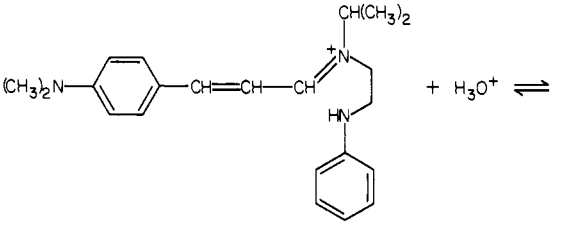
III



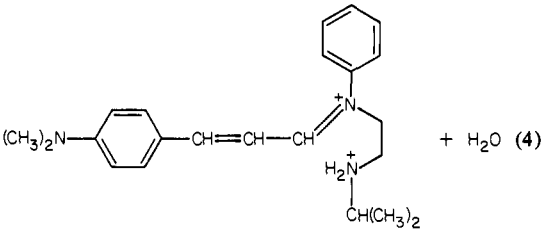
VI

where the nitrogen pK_a values are similar to those of tetrahydrofolic acid.[9,10] The pK_a values of N(1) and N(10) in the diamine are 2.58[9,15] and −1.10,[9,16] respectively. The nitrogen of highest pK_a can release electrons most readily to stabilize the incipient carbonium ion. The reaction is therefore proceeding with production of the most stable Schiff base and expulsion of the best leaving group. This is analogous to the ring opening reaction of 2-(*p*-(dimethylamino)styryl)-*N*-isopropyl-*N'*-phenyl-1,3-imidazolidine (I) at pH >6 which also gives the most stable *N*-alkyl Schiff base (II).[3]

In ring opening of the unsymmetrical imidazolidine I in H_2O at pH <6, the *N*-phenyl Schiff base is also formed.[3] A rearrangement of Schiff bases is observed when preformed II at pH 6 is subjected to a rapid lowering of pH (eq 4). The formation

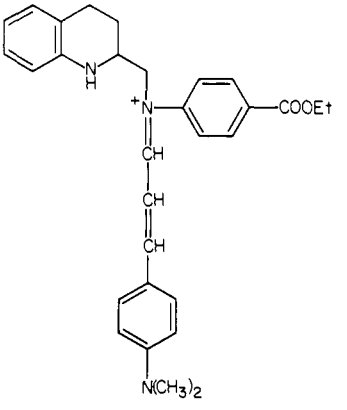


II



VII

of VII from I at low pH is due to the presence of the *p*-dimethylamino group which permits a dication intermediate at moderate pH (pK_1 = 4.7); it would be expected that VII might be formed rapidly from a dication. The greater stability of VII at low pH must arise from the difference in pK_a values of the exocyclic nitrogens of II and VII. The pK_a of II should be less than 2. The pK_a of the exocyclic nitrogen of VII would be much higher (>5), and protonation of that nitrogen would prevent ring reclosure. Thus, as pH is lowered below 6, Schiff base VII is observed as a product. However, formation of the alternate Schiff base VIII from III is not observed at any pH. This is very likely

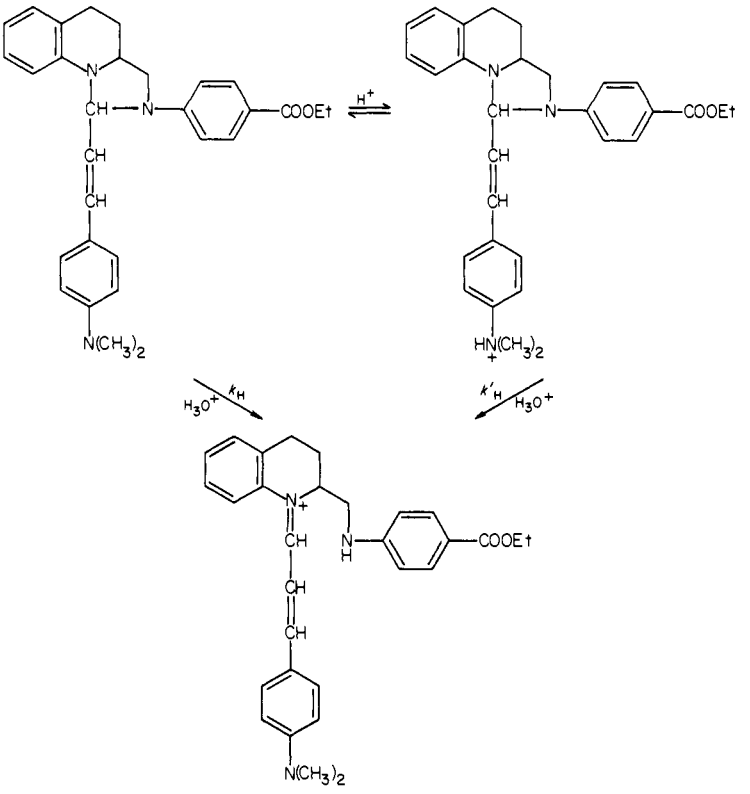


VIII

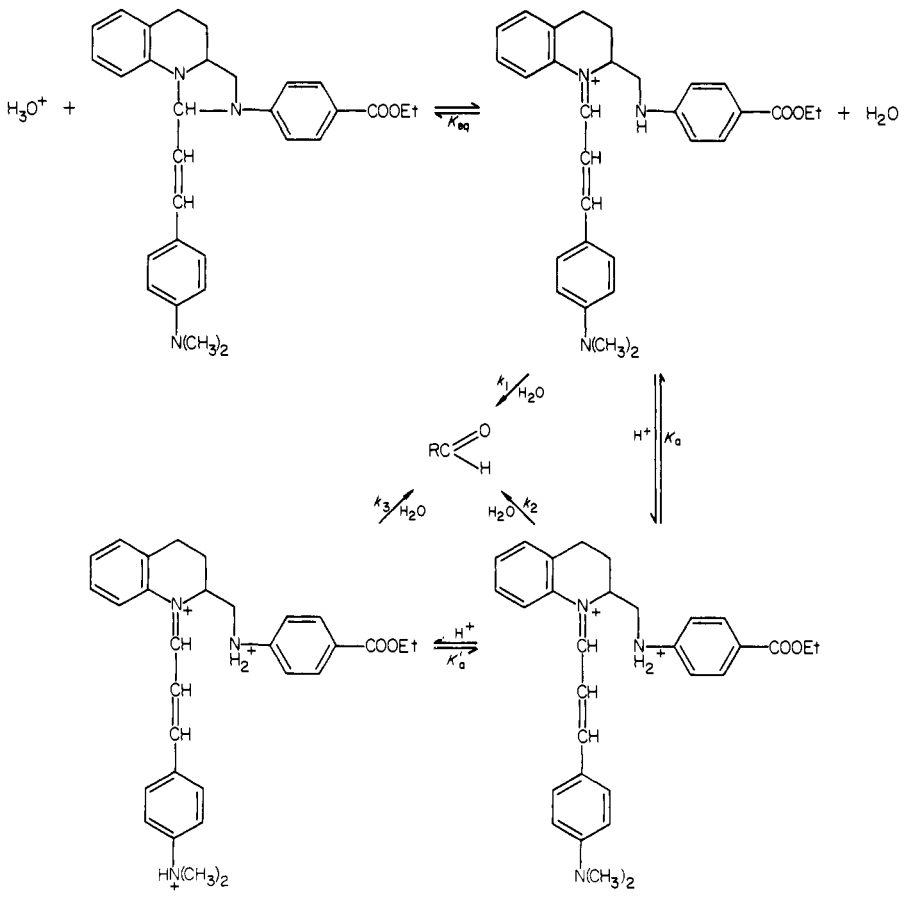
due to the much lower pK_a of N(1) in III and the Schiff base VIII than the isopropyl-substituted nitrogen of I and VII. Thus, in ring opening of III a dication will only be formed at pH values much lower than with I. Since this dication should also occur in a rearrangement of VI → VIII, the formation of VIII from VI or vice versa by this pathway is retarded.[17] Stabilization of

(14) Fife, T. H.; Hutchins, J. E. C. *J. Org. Chem.* **1980**, *45*, 2099.
(15) In 50% dioxane–H_2O at 25 °C.
(16) In H_2O at 25 °C.

(17) The possibility cannot be ruled out that VIII is formed rapidly from III with still more rapid reversal to regenerate reactant via a monocation pathway; i.e., VIII is present at steady-state concentrations. However, this would require a value of k_H for ring opening to VIII much larger than expected[3] considering the pK_a values of the leaving and remaining nitrogens. In bimolecular transimination reactions, however, the more basic nitrogen may be expelled[18] because of concentration effects.



(5)



(6)

VIII to reclosure by protonation of N(1) would only occur at very low pH values (<2). In the solvent employed for study of III (50% dioxane–H_2O) the pK_a values will also be reduced as compared with H_2O. Therefore, there will be little tendency for the Schiff base VIII to form either directly from III or by rearrangement from VI.

As seen in Figure 1, the ring-opening reaction is hydronium

(18) Fischer, H.; De Candis, F. X.; Ogden, S. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 1340.

ion catalyzed from pH 4.5 to 3.5 and pH 3 to 2. The slopes of the plot of log k_0 vs. pH in these ranges are −1.0 with a small plateau between. The break in the profile undoubtedly corresponds with the high pK_a of the molecule. A pK_{app} of 3.3 corresponds with that of 2-(*p*-(dimethylamino)styryl)-*N*-phenyl-1,3-oxazolidine in 50% dioxane–H_2O where the *p*-dimethylamino group is protonated.[14] The pK_a of that group in H_2O with less reactive derivatives has been found to vary from 4.5 to 4.8.[19] Thus, the ring-opening reaction of III proceeds according to the scheme of eq 5. Values of k_H and k_H' are 1.4×10^5 M^{-1} s^{-1} and 2.2×10^4 M^{-1} s^{-1}, respectively. The pK_a of N(1) should be somewhat lower than that of the *p*-dimethylamino group but would not be greatly dissimilar. Therefore, pK_{app}, being a macroscopic constant, could pertain to more than one monoprotonated species. There is no curvature in the profile of Figure 1 at pH ~2, which would signify approach to the dication pK_a, eq 2 giving a good fit to the data with pK_{app} = 3.3.

The values of k_0 for ring opening are nearly pH independent at pH >5. This could reflect a water-catalyzed breakdown of III. However, the pH independence of k_0 in ring opening could also reflect the importance of the reverse reaction. In the ring-opening reaction $k_{obsd} = k_{open} + k_{rev}$. If ring opening is hydronium ion catalyzed, then the reverse reaction (water-catalyzed nucleophilic attack by the acyclic amine) will be pH independent at pH values greater than the acyclic amine pK_a. Therefore, k_{rev} could become the predominant influence on k_0 at high pH. The absorbance due to Schiff base would then decrease and finally disappear as pH is increased, as was observed experimentally. Similar pH-independent reactions were also observed for the other 1,3-imidazolidines of *p*-(dimethylamino)cinnamaldehyde.[3] The reaction of the *N,N'*-diphenyl derivative was pH independent at pH >5, while the reactions of the *N*-alkyl-substituted derivatives do not become pH independent until pH >9.5. Thus, III is ring opening in a manner analogous to the *N,N'*-diphenyl derivative, except that the values of k_0 are 1–2 orders of magnitude greater. As in the case of the *N,N'*-diphenyl derivative, a Schiff base intermediate cannot be observed spectrophotometrically at pH >7. The only reaction that can then be observed is aldehyde formation at 398 nm since the Schiff base is present only at steady-state concentrations.

Iminium Ion Hydrolysis. The formation and hydrolysis of Schiff bases has been extensively studied,[20-26] and the mechanisms of these reactions are reasonably well understood.[23,25,26] 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[3,5,6] in the pH range 1–8 where hydrolysis of III was studied. It is clear from Figure 1 that in 50% dioxane–H_2O Schiff base hydrolysis is rate determining in the overall reaction at all pH values with values of k_{obsd} 10^5–10^6 less than for ring opening.

The hydrolysis of the Schiff base intermediate is hydronium ion catalyzed at low pH. This catalysis must arise through protonated species involving the exocyclic nitrogen and the *p*-dimethylamino group. Protonation of either nitrogen would greatly destabilize the Schiff base, thereby promoting the hydrolysis reaction. Such hydronium ion catalysis has been observed previously in the hydrolysis of Schiff bases derived from imidazolidines of *p*-(dimethylamino)cinnamaldehyde.[3] The Schiff base VI is more stable in 50% dioxane–H_2O than the Schiff base obtained in ring opening of 2-(*p*-(dimethylamino)styryl)-*N,N'*-diphenyl-1,3-imidazolidine, which hydrolyzes with k_H = 1.0 M^{-1} s^{-1} and $k_0' = 10^{-3}$ s^{-1}. The scheme that must be followed in hydrolysis is given in eq 6. At high acid concentrations a diprotonated species would be obtained, but the pK_a of such a species must be very low. The presence of two positive charges in a molecule can reduce the pK_a of a nitrogen base by 5–7 pK_a units.[27]

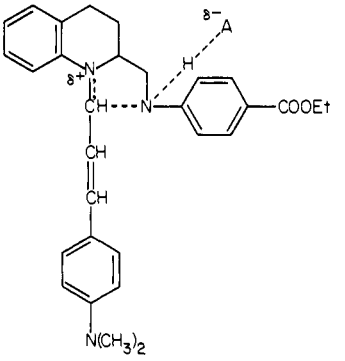
The plateau in Figure 1 followed by a decline in k_0 at pH >5 is very likely a reflection of K_{eq} (eq 6). The equation for k_0 derived from the scheme of eq 6 is given in eq 7. At high pH this equation reduces to eq 8. Thus, at $K_{eq} > a_H$, k_0 will decline with increasing

$$k_0 = \frac{k_1 K_a K_a' a_H + k_2 K_a' a_H^2 + k_3 a_H^3}{a_H^3 + K_a' a_H^2 + K_a K_a' a_H + K_{eq} K_a K_a'} \quad (7)$$

$$k_0 = \frac{k_1 a_H}{K_{eq} + a_H} \quad (8)$$

pH as observed. A pK_{eq} of 4.8 is in agreement with the lack of absorbance due to Schiff base at pH >7. A decline in k_0 because of a change in rate-determining step from formation to breakdown of a carbinolamine is not likely in view of the lack of a downward bend in the profile at pH >5 for hydrolysis of Schiff bases derived from other imidazolidines of *p*-(dimethylamino)cinnamaldehyde or 2-(*p*-(dimethylamino)styryl)-*N*-phenyl-1,3-oxazolidine, where pK_{eq} is much higher.[3,14]

General-Acid Catalysis of Ring Opening. As seen in Figure 2, ring opening of III is markedly catalyzed by general acids. This reaction must involve concerted protonation and C–N bond breaking (IX). The Brønsted plot of Figure 4 has a slope of −0.7.



IX

Thus, proton transfer is probably well advanced in the transition state. The general-acid catalysis must be a consequence of the stabilization of the developing carbonium ion and the good leaving group which thereby makes C–N bond breaking reasonably facile. As a result, the bond can begin to break before proton transfer is complete.

General-acid catalysis was also observed in the conversion of I to II, but in that case an extensive series of general acids could not be studied[3] because of the rapid hydronium ion catalyzed reaction ($k_H = 4 \times 10^7$ M^{-1} s^{-1}). In comparison of III with I, the pK_a of N(1) is less than N-*i*-Pr so that carbonium ion stabilization will be reduced, but *p*-carbethoxyaniline will be a better leaving group than *N*-phenyl. These features result in a hydronium ion catalyzed reaction that is less pronounced ($k_H = 10^5$ M^{-1} s^{-1}) and permit observation of general-acid catalysis over a reasonable range of pK_a. Thus, in a search for observable general-acid catalysis in imidazolidine ring opening, we have been led to a system in which the pK_a values of the two nitrogens are closely similar to those of N(5) and N(10) of tetrahydrofolic acid (4.82 and −1.25 in H_2O).[10] It would be predicted that further increases in developing carbonium ion stabilization and/or leaving group ability would lower the Brønsted α coefficient as in acetal and orthoester hydrolysis reactions.[28,29] When basicity is high and

(19) The pH–rate constant profiles for hydronium ion catalyzed hydrolysis of the 1,3-dioxolane and 1,3-oxathiolane of *p*-(dimethylamino)cinnamaldehyde have significant inflections with pK_{app} values of 4.8 and 4.5 at 30 and 50 °C, respectively. Fife, T. H.; Shen, C. C., unpublished data.

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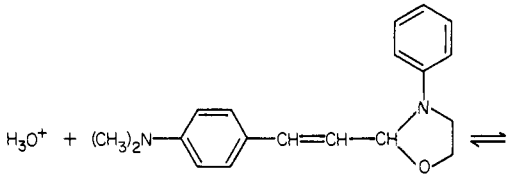
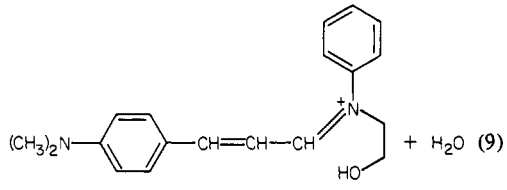
carbonium ion stabilization is maximized, as in the case of *N*,*N'*-dimethyl substitution, ring opening may become diffusion controlled.

In comparison with the ring opening reaction of 2-(*p*-(dimethylamino)styryl)-*N*-phenyl-1,3-oxazolidine (X) (eq 9) with



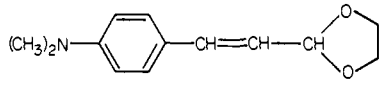
X



(9)

the same reaction conditions (30 °C, 50% dioxane–H_2O),[14] the value of k_H for III is 10-fold larger. Stabilization of the developing carbonium ion may be slightly less in the case of X, but the rate difference must also reflect the much higher basicity of the atom undergoing protonation in the imidazolidine III. In partial compensation, the oxazolidine oxygen must be a better leaving group in a reaction involving concerted proton transfer and bond breaking than the *p*-carbethoxyaniline group of III. Although a fully protonated nitrogen may be a better leaving group than oxygen,[30] in a concerted reaction bond breaking must commence when the proton is still at a distance, and therefore oxygen will normally be a superior leaving group.[31] The key factor in giving rise to a concerted reaction in those cases will be the ease with which the bond can break without the aid of a proton. That the oxygen is the better leaving group is shown by the fact that the oxazolidine ring can break down in a unimolecular process (expulsion of the oxyanion) and by the fact that the oxazolidine pK_{eq} is much higher (8 as compared to 4.8 for III). The Brønsted α coefficient for general-acid catalysis of ring opening is considerably lower with the oxazolidine, 0.5, compared to 0.7 in the case of III. It has been shown in general-acid-catalyzed hydrolysis of acetals[29] and orthoesters[32] that as the leaving group is improved, the α value is reduced, implying that the transition state is reached earlier, i.e., with less proton transfer and less bond breaking.

A further comparison that can be made is with the general-acid catalyzed hydrolysis of the corresponding 1,3-dioxolane (XI).[33]



XI

The hydronium ion catalyzed reaction (k_H = 600 M^{-1} s^{-1} in 50% dioxane–H_2O at 30 °C) is considerably slower than that of III or the oxazolidine X. This must reflect the low basicity of the oxygen leaving group, and the reduced amount of stabilization that the remaining oxygen can provide the developing carbonium ion in comparison to nitrogen. Accordingly, the Brønsted α is 0.7, i.e., higher than that of the oxazolidine X. Replacing *N*-phenyl with O increases α by ~0.2. The comparable α values of the dioxolane and the imidazolidine III may indicate that carbonium ion stabilization, leaving group ability, and basicity factors are nearly compensating in the two reactions in regard to the position of the transition state along the reaction coordinate.

As shown in Figure 3, general-acid catalysis of ring opening only occurs in reactions of the neutral species. With a monocationic species in which the *p*-dimethylamino group is protonated, basicity of the ring nitrogens will be markedly lowered, stabilization of the developing carbonium ion will be reduced, and departure of the leaving group will be retarded in comparison with the neutral species. Lower basicity of the nitrogen undergoing protonation would be expected to be advantageous for general-acid catalysis. Therefore, the fact that such catalysis is not observed in ring opening of the monocation demonstrates that carbonium ion stabilization and leaving group effects are much more important in giving rise to general-acid catalysis than are basicity considerations.[3] In contrast with the total repression of general-acid catalysis by monoprotonation, the hydronium ion catalyzed reaction of III is only retarded by a factor of 6. This is consistent with the expectation that ease of bond breaking will be much more important with a weak acid catalyst than with hydronium ion. Similarly, Hammett ρ values for hydrolysis of substituted benzaldehyde methyl phenyl acetals become more negative as the catalyst acid becomes weaker.[29] Values of ρ 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,[34] clearly showing the greater importance of ease of bond breaking than basicity in the general-acid-catalyzed reactions. That low basicity of the substrate is not the principal factor in leading to general-acid catalysis in reactions of acetals and their analogues is also strikingly shown by the lack of effect of buffer acids in hydrolysis of thioacetals in cases where the C–S bond initially breaks,[35,36] even though pronounced catalysis takes place in hydrolysis of exactly analogous oxygen acetals,[37] and in ring opening of imidazolidines where basicity is relatively high. Although the basicity of the nitrogens of the imidazolidine ring of III is very high in comparison to comparable acetals, general-acid catalysis still occurs because bond breaking is facile, and the same factors are undoubtedly important as in acetal hydrolysis.

It is clear that general-acid catalysis by functional groups in the active sites of enzymes is a chemically reasonable possibility in reactions in which ring opening of the imidazolidine ring of N^5,N^{10}-methylenetetrahydrofolic acid takes place. The unsymmetrical imidazolidine ring of N^5,N^{10}-methylenetetrahydrofolic acid, with resulting divergent pK_a values for the nitrogens, will facilitate general-acid-catalyzed ring opening in enzymatic reactions. The low pK_a of N(10) would favor proton transfer in the rate-determining step while the higher pK_a of N(5) should allow it to sufficiently stabilize a developing carbonium ion so that C–N bond breaking will be facile enough to permit general-acid catalysis. If the nitrogen pK_a's were both low, then electron release to stabilize the incipient carbonium ion would be difficult and general acid catalysis of ring opening might not occur. If, on the other hand, the nitrogen pK_a values were both high, then the imidazolidine ring would be highly unstable in aqueous solution. Thus, the structure of N^5,N^{10}-methylenetetrahydrofolic acid is well designed to permit reasonable stability, so that it can participate in enzymatic reactions but still be subject to general-acid catalysis in ring opening.[38]

Acknowledgment. This work was supported by research grants from the National Institutes of Health.

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(30) Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 489, 499, 507.
(31) The pK_a values of alcohols are, of course, normally much lower than those of amines. The pH-independent reactions of acetals have been shown to involve unimolecular decomposition.[28] In contrast, protonation is normally required for C–N bond breaking.
(32) Anderson, E.; Fife, T. H. *J. Org. Chem.* **1972**, *37*, 1993.
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(38) See also the discussion in ref 2.