137 (23), 136 (26), 135 (15), 121 (12), 119 (11), 105 (14), 91 (15), 77 (13), 69 (11).

Anal. Calcd for $C_{15}H_{19}O_4F_3$: C, 56.24; H, 5.97. Found: C, 56.28; H, 5.55.

Repetition of this reaction with **2** labeled with a CD_3 group at C_4[3] gave **5** in which the peak at δ 1.20 (CCl_4) was reduced in area by 25%.

Attempted Hydrolysis of 5. A solution of **5** (46 mg) in 2 mL of 7% potassium carbonate in aqueous methanol (2:5 v/v) was stirred at room temperature for 4 h. Workup gave a quantitative recovery of **5**.

Acknowledgment. We are indebted to the National Institutes of Health (Grant No. GM 15997) for financial support of this research.

Registry No. 1, 73396-38-0; 2, 73396-39-1; 3, 73396-44-8; 4, 2819-86-5; 5, isomer 1, 73396-45-9; 5, isomer 2, 73465-14-2.

General-Acid-Catalyzed Ring Opening of Oxazolidines. Hydrolysis of 2-[4-(Dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine

Thomas H. Fife* and J. E. C. Hutchins

Department of Biochemistry, University of Southern California, Los Angeles, California 90033

Received December 26, 1979

A cationic Schiff-base intermediate is detectable at pH <10 in the hydrolysis of 2-[4-(dimethylamino)-styryl]-*N*-phenyl-1,3-oxazolidine. Thus, ring opening proceeds with C–O bond breaking, i.e., in the direction which gives the most stable carbonium ion intermediate. Ring opening is hydronium ion catalyzed at low pH and only slightly affected by the protonation state of the *p*-dimethylamino group. From pH 5 to 7.5 ring opening occurs in a pH-independent reaction which probably involves unimolecular C–O bond breaking. At higher pH apparent hydroxide ion catalysis is observed in the reversible ring opening, which reflects reclosure of the ring by attack of the neighboring alkoxide ion on the iminium ion. The value of pK_{eq} for ring opening determined both spectroscopically and from the kinetic data is 8.05. General-acid catalysis occurs in ring opening. Proton transfer and C–O bond breaking are concerted, as shown by the Brønsted coefficient α of 0.53. Concerted general-acid catalysis in these reactions is due to the ease of C–O bond breaking brought about by stabilization of the developing carbonium ion in the transition state. The hydrolysis of the intermediate cationic Schiff base is pH independent in the pH range 8–13 and hydronium ion catalyzed at low pH due to protonation of the *p*-dimethylamino group.

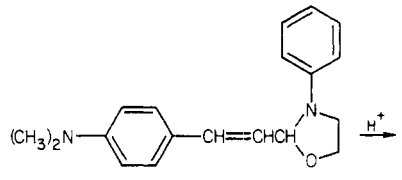
The mechanism of hydrolysis of acetal analogues in which one oxygen is replaced by nitrogen is of considerable importance not only because of the theoretical significance of the general catalysis found in these reactions[1] but also because compounds of this general type are of great biochemical importance. The hydrolysis of glycosylamines[2-4] and nucleosides[2,5-8] has been extensively studied. Glycosylamine hydrolysis appears to proceed via a Schiff-base intermediate,[2,3] but there has been considerable difference of opinion in regard to the mechanism of hydrolysis of nucleosides.[2,5-8]

Oxazolidines (cyclic *N,O*-acetal analogues) hydrolyze rapidly.[1] Ring opening of 2-(substituted phenyl)-*N*-ethyl-1,3-oxazolidines occurs to give a cationic Schiff-base intermediate.[1] Thus, the reaction proceeds with C–O bond breaking even though the nitrogen is quite basic and is protonated at low pH. The ring opening of 2-(*p*-methoxyphenyl)-*N*-ethyl-1,3-oxazolidine was found to be buffer catalyzed,[1] but kinetically equivalent possibilities in those reactions complicated mechanistic interpretation. General-acid catalysis in oxazolidine ring opening would be in accord with the great stabilization of the developing carbonium ion that is possible by the adjoining nitrogen. In the hydrolysis of acetals, ease of bond breaking is a critical feature in giving rise to general-acid catalysis.[9,10] An easily broken C–O bond can be due to a good leaving group[11] or to a highly stabilized carbonium ion,[12] and in both cases general-acid catalysis is found. However, the Schiff-base intermediate in the hydrolysis of 2-(*p*-methoxyphenyl)-*N*-ethyl-1,3-oxazolidine could only be directly observed at pH values less than 4, presumably because at higher pH it is present only at steady-state concentrations. This prevented study of the neutral species reactions. A number of extremely important mechanistic questions remain to be answered. Among these questions are the following. (1) What is the mechanistic significance of the observed general catalysis? (2) Does a neutral-species pH-independent reaction occur at high pH as in the hydrolysis of acetals which are subject to general-acid catalysis?[11,12] Would such a reaction also give a Schiff-base intermediate? (3) How significant is the substituent on nitrogen in directing ring opening? Will a Schiff base also arise from an *N*-phenyl derivative or if there is the possibility of substantial carbonium ion stabilization by the 2-substituent? In order to approach these questions, one must be able to observe oxazolidine ring opening at high pH. The Schiff-base intermediate must therefore be reasonably stable and have a large extinction coefficient, with λ_{max} preferably in the visible portion of the spectrum, so that

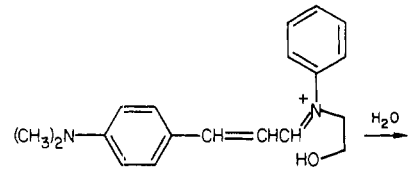
(1) Fife, T. H.; Hagopian, L. *J. Am. Chem. Soc.* **1968**, *90*, 1007.
(2) Capon, B. *Chem. Rev.* **1969**, *69*, 407.
(3) Capon, B.; Connett, B. E. *J. Chem. Soc.* **1965**, 4497.
(4) Simon, H.; Palm, D. *Chem. Ber.* **1965**, *98*, 433.
(5) Shapiro, R.; Kang, S. *Biochemistry* **1969**, *8*, 1806.
(6) Shapiro, R.; Danzig, M. *Biochemistry* **1972**, *11*, 23.
(7) Cadet, J.; Teoule, R. *J. Am. Chem. Soc.* **1974**, *96*, 6517.
(8) Romero, R.; Stein, R.; Bull, H. G.; Cordes, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 7620.
(9) Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264.
(10) Fife, T. H. *Adv. Phys. Org. Chem.* **1975**, *11*, 1.
(11) Fife, T. H.; Jao, L. K. *J. Am. Chem. Soc.* **1968**, *90*, 4081. Fife, T. H.; Brod, L. H. *Ibid.* **1970**, *92*, 1681.
(12) Anderson, E.; Fife, T. H. *J. Am. Chem. Soc.* **1969**, *91*, 7163.

0022-3263/80/1945-2099$01.00/0

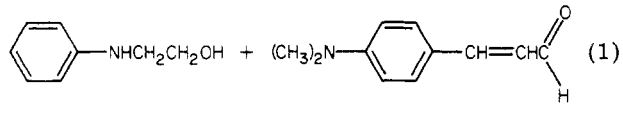
small concentrations might be detected. Oxazolidine derivatives of *p*-(dimethylamino)cinnamaldehyde meet these criteria. The long conjugated system allows both the cationic Schiff-base intermediate in the reaction and the aldehyde product to absorb in the visible portion of the spectrum at well-separated wavelengths so that both ring opening and hydrolysis of the intermediate can be easily monitored. We have, therefore, studied the ring-opening reaction of 2-[4-(dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine (I) and the hydrolysis of the Schiff base II, which can be directly observed as an intermediate at pH values below 10 (eq 1).



I



II



(1)

Experimental Section

Materials. 2-[4-(Dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine was prepared by refluxing *p*-(dimethylamino)cinnamaldehyde (purified by sublimation at 107 °C) and redistilled *N*-phenylethanolamine in benzene containing a trace of *p*-toluenesulfonic acid. Water was continuously removed by azeotropic distillation using a Dean-Stark trap. After removal of the benzene by rotary evaporation, the crude solid residue was recrystallized from dry hexane to yield crystals with a melting point of 118–120 °C. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53. Found: C, 77.19; H, 7.47. The infrared spectrum had medium/strong absorptions at 6.27, 6.67, 7.33, 8.46, 9.49, 10.40, and 13.37 μm. Buffers were made from AR materials. Amine buffer components were freshly distilled immediately prior to use. The dioxane employed was spectral grade (Mallinckrodt) and was refluxed over sodium borohydride for 3 h and distilled prior to use.

Kinetic Methods. All kinetic measurements were made at 30 °C in 50% dioxane–H_2O (v/v) with μ = 0.5 M (KCl). Stock solutions of substrate (5×10^{-3} M) were prepared in dried acetonitrile. To follow the ring opening reaction, we mixed 60 μL of substrate solution with 10 mL of 10^{-3} M KOH in 50% dioxane–H_2O, and this solution was introduced into one of two identical syringes in a Durrum D110 stopped-flow spectrophotometer. The other syringe contained buffer such that on rapid mixing of equal volumes from the two syringes a buffer of desired concentration was obtained. In following ring reclosure, the substrate was introduced into 10^{-3} M HCl (50% dioxane–H_2O) in which the cationic Schiff base is rapidly formed. This solution was used in one syringe of the stopped-flow apparatus while the other contained an appropriate buffer. The slower disappearance of intermediate and the appearance of aldehyde were monitored by conventional spectrophotometry, with either a Beckman 25 or Perkin-Elmer Model 124 spectrophotometer, the latter being equipped with a jacketed, thermostated cell. Reaction solution pH values were measured with a Beckman Model 3500 digital pH meter standardized with Mallinckrodt standard buffer solutions.

UV–Visible Spectra. Spectra were obtained by using a Perkin-Elmer 124 spectrophotometer and 1-cm quartz cells. A solution of the oxazolidine I in acetonitrile showed the following absorptions: λ_{max} 302 nm (log ϵ 4.39), 248 (4.20). A qualitatively similar spectrum was obtained immediately after dissolving the substrate in 10^{-3} M KOH (μ = 0.5, 50% dioxane–H_2O): λ_{max} 303 nm (log ϵ 4.41). This spectrum changed slowly with time to match that of an equivalent amount of *p*-(dimethylamino)cinnamaldehyde: λ_{max} 397 nm (log ϵ 4.54).

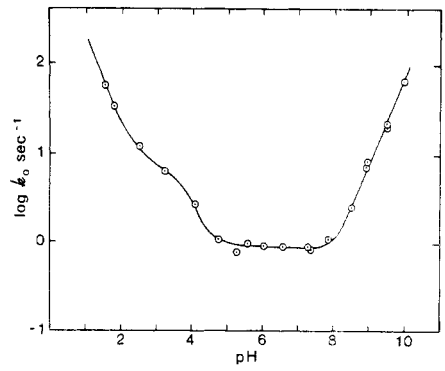


Figure 1. Plot of log k_0 vs. pH for the ring opening of 2-[4-(dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine to a cationic Schiff base in 50% dioxane–H_2O (v/v) at 30 °C and μ = 0.5 (KCl).

Introduction of I into acidic solutions resulted in the rapid formation of an intense red color. In half-neutralized 0.01 M formic acid (μ = 0.5, 50% dioxane–H_2O, pH 4.82) λ_{max} was 498 nm (log ϵ 4.81). Essentially the same spectrum was obtained after sufficient 1 M HCl was rapidly added to substrate just previously dissolved in 10^{-3} M KOH to make the solution 10^{-3} M in HCl. Introduction of substrate into buffers of various pHs (μ = 0.5, 50% dioxane–H_2O) at 30 °C and measurement of the absorbance at 498 nm immediately after mixing showed that the absorbance fell sigmoidally with increasing pH, allowing an apparent pK_{eq} value of 8.05 to be determined. In each case the absorbance at 498 nm decreased with time, and a spectrum was eventually obtained corresponding to that of an equivalent concentration of *p*-(dimethylamino)cinnamaldehyde.

Results

The introduction of 2-[4-(dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine into 50% dioxane–H_2O (v/v) at pH 1–9 (μ = 0.5 M with KCl) gives rise to the rapid formation of an intermediate with λ_{max} = 498 nm. This intermediate must be a cationic Schiff base. The initial value of the absorbance at 498 nm decreases sigmoidally with increasing pH, giving an apparent pK_{eq} value of 8.05 (see Experimental Section). Rate constants were obtained both for intermediate formation at 498 nm and substrate disappearance at 302 nm and were identical. The logarithms of rate constants obtained for intermediate formation at zero buffer concentration (k_0) are plotted in Figure 1 vs. pH. At low pH, hydronium ion catalysis is observed (k_H = 1630 M^{-1} s^{-1}). There is an inflection in the profile near pH 3.5, and from pH 3.5 to 4.5 the slope is again −1.0 (k_H' = 2×10^4 M^{-1} s^{-1}). A pH-independent reaction is observed from pH 5.5 to 7.5 (k_0' = 0.938 s^{-1}), and at pH values greater than 7.5 apparent hydroxide ion catalysis occurs. The data give a good fit to eq 2, where K_a is the apparent

$$k_0 = \frac{k_H a_H^3 + k_H' K_a a_H^2 + k_0' K_a a_H + k_{OH} K_a K_w}{K_a a_H + a_H^2} \quad (2)$$

dissociation constant of the *p*-dimethylamino group (pK_a = 3.35). Included in Figure 1 are data obtained by rapidly mixing equal volumes of buffer and preformed *intermediate* dissolved in 10^{-3} M HCl (50% dioxane–H_2O, μ = 0.5) and monitoring the appearance of the oxazolidine I at 302 nm. At pH 8.9 and 9.4 the identity of the rate constants for Schiff-base formation from oxazolidine and oxazolidine formation from Schiff base was established. At high pH

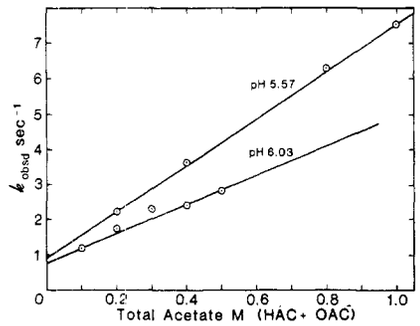


Figure 2. Plot of k_{obsd} vs. total acetate concentration for the appearance of cationic Schiff base (λ_{max} = 498 nm) in the ring opening of 2-[4-(dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine in 50% dioxane–H_2O (v/v) at 30 °C and μ = 0.5 (KCl).

Table I. Second-Order Rate Constants for General-Acid-Catalyzed Ring Opening of 2-[4-(Dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine in 50% Dioxane-H_2O at 30 °C (μ = 0.5)

acid catalyst	pK_a[a]	k_{HA}, M^{-1} s^{-1}
H_3O^+		2×10^{4}[b]
chloroacetic	4.13	82.4[c]
formic	4.76	32.3[c]
succinic	5.29	39.6,[c] 19.8[c,d]
acetic	6.03	7.6[e]

[a] Determined under the same reaction conditions as the ring-opening reactions. [b] Catalysis of the reaction of the neutral species (pH 3.5–5). [c] Determined in half-neutralized buffer. [d] Statistically corrected. [e] Determined at two buffer ratios (pH 5.57 and 6.03).

values a Schiff-base intermediate could not be observed, although aldehyde formation, measured at 397 nm, could be followed.

The appearance of intermediate (λ_{max} = 498 nm) was monitored in HCl solutions and in chloroacetate, formate, succinate, cacodylate, *N*-methylmorpholine, and trimethylamine buffers from pH 1.5 to 9.4. In solutions of the carboxylic acid buffers appreciable buffer catalysis was observed with rate constants linearly increasing with buffer concentration. In Figure 2 k_{obsd} is plotted vs. total acetate concentration at two constant pH values, the results showing kinetic general-acid catalysis. Values of the second-order rate constants k_{HA} for general-acid catalysis of intermediate formation are given in Table I. A Brønsted plot of log k_{HA} vs. the pK_a of the catalyzing acid is shown in Figure 3. The slope is −0.53.

Disappearance of the intermediate was monitored from pH 1 to 9 at 498 nm, and the appearance of *p*-(dimethylamino)cinnamaldehyde at 397 nm was followed over the pH range 1–13. First-order behavior was obtained in all cases, with rate constants for intermediate disappearance or aldehyde formation being identical in the pH range 1–9. In Figure 4 log k_0 is plotted vs. pH, where k_0 is the rate constant obtained by extrapolation to zero buffer concentration. The rate constant for pH-independent aldehyde formation at high pH was found to be 2.2×10^{-3} s^{-1}. The value of k_H is 0.331 M^{-1} s^{-1}, and the rate constant for the water reaction (pH 4–7) is 2.9×10^{-4} s^{-1}.

Discussion

The intermediate in the hydrolysis of 2-[4-(dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine with λ_{max} = 498 nm must correspond with the Schiff base II. The Schiff base produced by ring opening of 2-[4-(dimethylamino)-styryl]-*N*,*N*′-diphenyl-1,3-imidazolidine has λ_{max} = 505 nm, and the protonated Schiff base of *p*-(dimethylamino)-cinnamaldehyde and aniline has λ_{max} = 520 nm.[13] Thus,

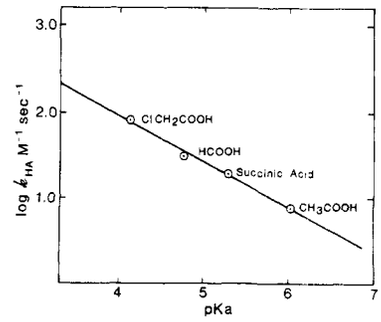


Figure 3. Brønsted plot of log k_{HA} vs. the pK_a of the catalyst acid in ring opening of 2-[4-(dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine to a cationic Schiff base in 50% dioxane–H_2O (v/v) at 30 °C and μ = 0.5 (KCl).

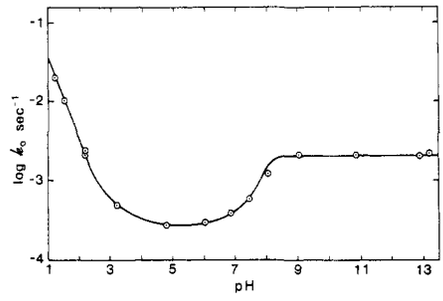


Figure 4. Plot of log k_0 vs. pH for the appearance of *p*-(dimethylamino)cinnamaldehyde in the hydrolysis of the cationic Schiff base derived from 2-[4-(dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine in 50% dioxane–H_2O (v/v) at 30 °C and μ = 0.5 (KCl).

a λ_{max} of 498 nm is a reasonable value for the Schiff base II. It is apparent that ring opening is proceeding with C–O bond breaking, in spite of the fact that the oxazolidine nitrogen is of much higher basicity than oxygen and would be protonated preferentially in the hydronium ion catalyzed reaction. The direction of ring opening is such as to take advantage of the greater carbonium ion stabilization by nitrogen in the transition state, even though it is phenyl substituted and substantial stabilization by the 2-substituent is possible. Ring opening is occurring in the direction governed by carbonium ion stability.[14] In the related ring-opening reactions of unsymmetrical imidazolidines,[13,16] ring opening also occurs to give the most stable iminium ion with expulsion of the best leaving group.

The pH–log k_0 profile for ring opening of 2-[4-(dimethylamino)styryl]-*N*-phenyl-1,3-oxazolidine shows hydronium ion catalysis in the pH range 1–5. The slope of the plot is −1.0 at pH 1–3 and at pH 3.5–4.5, with a small plateau between these regions. The break in the plot near pH 3.5 probably corresponds with the pK_a of a protonated nitrogen. The pK_a of the *p*-dimethylamino group of various derivatives of *p*-(dimethylamino)cinnamaldehyde ranges from 3 to 4.8.[17,18] Thus, the reaction at pH 3.5–5

(13) Fife, T. H.; Pellino, A. M. *J. Am. Chem. Soc.*, in press.

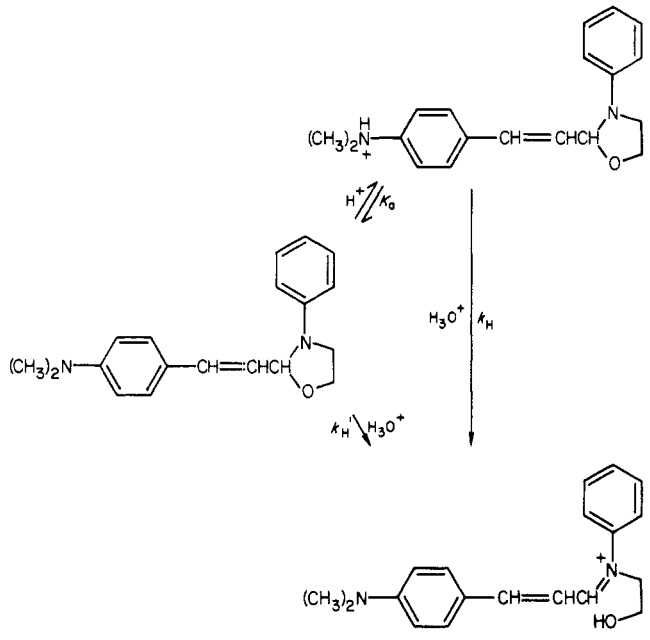
(14) The possibility cannot be ruled out that nitrogen expulsion occurs rapidly to form an oxocarbonium ion which undergoes still more rapid reversal to regenerate reactant. This would have no effect on the observed kinetics of ring opening in which the iminium ion (C–O bond breaking) is the observed product. Open-chain α-amino ethers have also been found[15] to give rise to iminium ions in acidic solution, and in those cases reversibility will not be a factor. This is also the case with glucosylamines.[3]

(15) (a) Ross, D. Ph.D. Thesis, University of Washington, 1964. (b) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 464.

(16) Fife, T. H.; Hutchins, J. E. C.; Pellino, A. M. *J. Am. Chem. Soc.* **1978**, *100*, 6455.

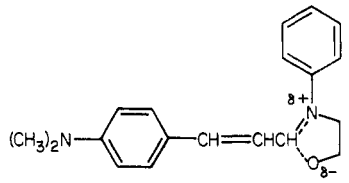
(17) A pK_a of 3 was reported for the *p*-dimethylamino group of *p*-(dimethylamino)cinnamaldehyde at 25 °C: Dunn, M. F.; Hutcheson, J. S. *Biochemistry* **1973**, *12*, 4882.

Scheme I



involves hydronium ion catalyzed reaction of the neutral species (Scheme I), whereas at pH <3 hydronium ion catalyzed reaction of a protonated species is occurring. Protonation of the *p*-dimethylamino group would be expected to decrease the rate of reaction by decreasing the basicity of the ring oxygen and by reducing the ease of stabilization of the developing carbonium ion. However, there is only a 10-fold difference in k_H and k_H'. Similarly, the second-order rate constant for hydronium ion catalyzed hydrolysis of the analogous 1,3-dioxolane of *p*-(dimethylamino)cinnamaldehyde is reduced 16-fold by protonation of the *p*-dimethylamino group.[18] An alternative to Scheme I for the reaction with two protons in the transition state would place a proton on the oxazolidine ring nitrogen. In that case all of the stabilization of the incipient carbonium ion in ring opening would come from the [*p*-(dimethylamino)phenyl]ethylene substituent at the 2-position.

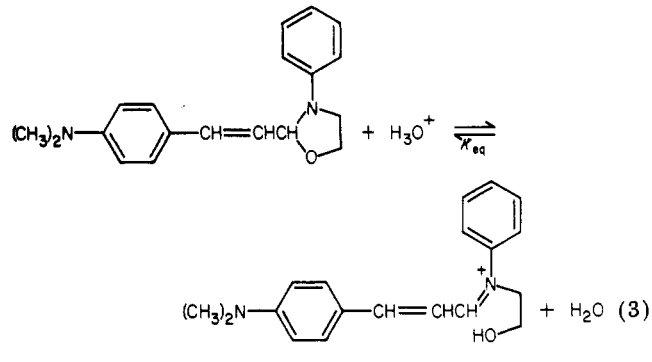
At pH values greater than 5, ring opening of I becomes pH independent. This reaction could be either a unimolecular decomposition to the Schiff base or a water-catalyzed reaction. Reactions independent of pH are also found in the hydrolysis of acetals subject to general-acid catalysis[11,12] and in the hydrolysis of thioacetals.[19,20] In those cases the reactions involve unimolecular decompositions. Evidence included ΔS^* values near zero and D_2O solvent isotope effects close to unity. If the pH-independent hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran[11] were considered to be a water-catalyzed reaction, it would be characterized by a value of log (k_0/55.5 M) which lies ~4 logarithmic units above the line in a Brønsted plot for general-acid catalysis. A unimolecular mechanism (e.g., III), in common with the mechanism of pH-independent breakdown of acetals, is preferred because the reverse reaction (ring closure) can then be viewed as attack of alkoxide ion on the cationic Schiff base. If ring opening



III

was a water-catalyzed reaction in the forward direction with water acting as a general acid partially donating a proton to the leaving group in the transition state, then the microscopic reverse reaction would involve hydroxide ion partially abstracting a proton from the alcohol as oxygen attacks at carbon. An equilibrium involving the alkoxide ion and hydroxide ion would be established at a diffusion-controlled rate. Consequently, spontaneous reclosure of the ring should proceed through the alkoxide ion, and, therefore, by microscopic reversibility ring opening at pH >5 must be a unimolecular breakdown.

At high pH (8–10) the slope of the pH–log k_0 profile of Figure 1 is 1.0; i.e., there is OH^- enhancement of the observed first-order rate constant. Since k_{obsd} is equal to the sum of the rate constants for the forward and reverse reactions, this must reflect the increasing influence of ring reclosure through attack of alkoxide ion on the cationic Schiff base as pH is increased. That this interpretation is correct was shown by monitoring independently at these pH values the increase in absorbance at 302 nm (formation of oxazolidine) from the Schiff base. It was found that the rate of reclosure was identical with the rate of formation of the Schiff base (absorbance increase at 498 nm) in the forward direction. This interpretation demands that as pH is raised further, the equilibrium absorbance at 498 nm due to the Schiff base will decline and finally disappear. That was observed experimentally. Thus, at high pH (>10) the Schiff-base intermediate is present only at low steady-state concentrations. The value of the equilibrium constant for the ring-opening reaction forming a cationic Schiff base (eq 3) was determined spectrophotometrically



(3)

to be 8.91×10^{-9} M (pK_{eq} = 8.05). This value of K_{eq} can also be calculated from the kinetic data by employing eq 4. Taking k_0' (rate constant in the forward direction) to

$$K_{eq} = \frac{k_{OH}K_w}{k_0'} = \frac{[I]a_H}{[\text{Schiff base}]} \quad (4)$$

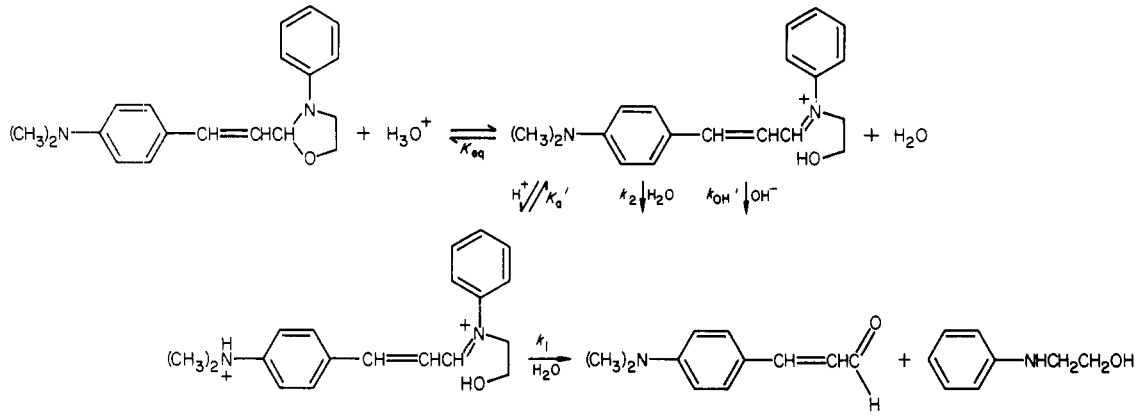
be the rate constant for pH-independent ring opening (k_0' = 0.938 s^{-1}) and obtaining $k_{OH}K_w$ from Figure 1 in the pH range 8–10 ($k_{OH}K_w = 7.94 \times 10^{-9}$ M s^{-1}), K_{eq} is calculated to be 8.46×10^{-9} M (pK_{eq} = 8.07). Consequently, the spectral and kinetic data are highly consistent.

The ring-opening reaction in which the Schiff-base intermediate is formed is general-acid catalyzed by the acid component of the buffer. The fact that ring opening can be observed over a wide range of pH allowed a reasonably extensive study of the buffer-catalyzed reaction, although

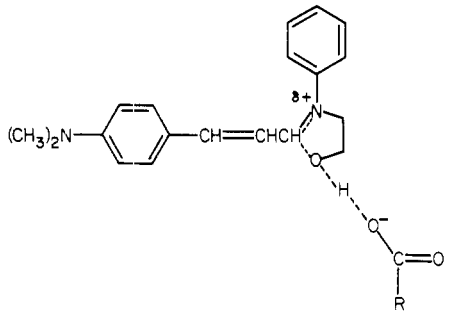
(18) The pH–rate constant profiles for hydronium ion catalyzed hydrolysis of the 1,3-dioxolane and 1,3-oxathiolane of *p*-(dimethylamino)-cinnamaldehyde have significant inflections with pK_{app} values of 4.8 and 4.5 at 30 and 50 °C, respectively. Fife, T. H.; Shen, C. C., unpublished data.

(19) Fife, T. H.; Anderson, E. *J. Am. Chem. Soc.* **1970**, *92*, 5464.
(20) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476.
(21) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1. Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705.

Scheme II



very weak acids could not be employed because of the facile pH-independent reaction at pH >5. The Brønsted plot of Figure 3 for carboxylic acid catalysts has a slope of −0.53. An α value of 0.53 indicates that proton transfer and C–O bond breaking are concerted,[21] as in mechanism IV. The general-acid-catalyzed reaction is brought about



IV

by the ease of C–O bond breaking due to the extensive stabilization of the developing carbonium ion in the transition state. Thus, oxazolidine hydrolysis proceeds analogously to the concerted general-acid-catalyzed hydrolysis reactions of acetals which give Brønsted α values of 0.5–0.7.[11,12,22] Likewise, in those cases, ease of C–O bond breaking is a critical feature in giving rise to general-acid catalysis. Concerted general-acid catalysis has also been observed in elimination of alcohols from carbinolamine ethers[15b] and in the similar dehydration of carbinolamines.[23]

Schiff-Base Hydrolysis. The formation and hydrolysis of Schiff bases has been extensively studied,[23-30] and the mechanisms of these reactions are reasonably well understood.[27,29,30] One of the principal conclusions is that at pH values where the Schiff bases are predominantly protonated, rate-determining attack of water on the protonated Schiff base takes place. Attack of water also occurs in hydrolysis of cationic Schiff bases in the pH range 1–8.[31] At higher pH values hydroxide ion catalysis is observed.[31] Buffer catalysis has been observed in both the formation and the hydrolysis of Schiff bases.[23-31] It is clear from Figure 4 that in 50% dioxane–H_2O Schiff-base hydrolysis is rate determining in the overall reaction of the oxazolidine I at all pH values.

The pH–log k_0 profile for hydrolysis of the Schiff-base intermediate in Figure 4 shows hydronium ion catalysis at low pH. This must reflect protonation of the *p*-dimethylamino group, which would destabilize the iminium ion and thereby increase its rate of hydrolysis. The pK_a of the *p*-dimethylamino group must be quite low in the cationic Schiff-base intermediate since electrons from that nitrogen must be highly delocalized. This is substantiated by the fact that the absorbance maximum of the Schiff base at 498 nm persists at high acidity. Hydronium ion catalysis has also been observed in the hydrolysis of cationic Schiff bases derived from imidazolidines of *p*-(dimethylamino)cinnamaldehyde.[13] In the hydrolysis of the Schiff base II, rate constants are identical for appearance of the aldehyde product, measured at 397 nm, and for disappearance of the Schiff base, measured at 498 nm. The pH–rate constant profile at pH >5 shows an increase in rate with increasing pH followed by a pH-independent region. It will be noted that OH^- catalysis is not observed at high pH, contrary to the pronounced OH^- catalysis seen in the hydrolysis of other types of cationic Schiff bases.[31] The profile can be explained by H_2O and hydroxide ion catalyzed reactions of the cationic Schiff base in terms of Scheme II in which the ring-closure reaction is important in establishing the equilibrium concentration of Schiff base.

The equation for k_0 derived for Scheme II is given in eq 5.

$$k_0 = \frac{k_1 a_H^2 + k_2 K_a' a_H + k_{OH}' K_a' K_w}{a_H^2 + K_a' a_H + K_a' K_{eq}} \quad (5)$$

At high pH the equation simplifies to eq 6. Thus, at

$$k_0 = \frac{k_{OH}' K_w}{K_{eq} + a_H} \quad (6)$$

$K_{eq} > a_H$ the plot of k_0 vs. pH will level off as observed. It is noted from Figure 4 that the reaction becomes pH independent at pH 8, corresponding with the value of pK_{eq} determined spectrophotometrically or calculated from the kinetic data for ring opening.

Nucleoside Hydrolysis. There is considerable evidence suggesting that nucleoside hydrolysis occurs through unimolecular decomposition of protonated and diprotonated species.[32] It was originally suggested that

(22) Anderson, E.; Fife, T. H. *J. Am. Chem. Soc.* **1971**, *93*, 1701.
(23) Sayer, J. M.; Peskin, M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 4277.
(24) Jencks, W. P. *J. Am. Chem. Soc.* **1959**, *81*, 475.
(25) Anderson, B. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1960**, *82*, 1733.
(26) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 832.
(27) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1963**, *85*, 2843.
(28) Willi, A. V. *Helv. Chim. Acta* **1956**, *39*, 1193.
(29) Koehler, K.; Sandstrom, W.; Cordes, E. H. *J. Am. Chem. Soc.* **1964**, *86*, 2413.
(30) Hine, J.; Craig, J. C.; Underwood, J. G.; Via, F. A. *J. Am. Chem. Soc.* **1970**, *92*, 5194.
(31) Fife, T. H.; Hutchins, J. E. C. *J. Am. Chem. Soc.* **1976**, *98*, 2536.

(32) Evidence is briefly summarized in ref 8.

nucleosides also hydrolyze with formation of a Schiff-base intermediate,[33-35] but this view has been criticized.[2,6,36,37] These reactions may proceed with C–N bond breaking and formation of an oxocarbonium ion intermediate.[32] Stabilization of a developing carbonium ion by nitrogen in nucleoside hydrolysis would be appreciably reduced in comparison with that of glycosylamine[2-4] and oxazolidine hydrolysis, and this could be a critical feature with respect to mechanism. The ease of protonation and leaving-group ability of nitrogen in combination with the ability of oxygen to stabilize a carbonium ion could then lead to rate-determining C–N bond breaking. However, it must be recognized that a reaction involving C–O bond breaking would be reversible as in the hydrolysis of I, and in view of the instability of a Schiff-base intermediate derived from a nucleoside, only low steady-state concentrations would be expected. Thus, the hydrolysis reaction might proceed via an undetectable Schiff base. Even in the case of the highly stabilized iminium ion derived from I, reversibility effects play a significant kinetic role at pH >8. It has recently been reported[7] that both anomerization and furanose → pyranose isomerization occur in the hydrolysis of thymidine and deoxyuridine in 2 M $HClO_4$, thereby removing an objection[2] to C–O bond breaking in the hydrolysis of pyrimidine nucleosides. There is, however, no evidence for anomerization in the hydrolysis of purine nucleosides. Regardless of whether C–O or C–N bond breaking is the predominant pathway in nucleoside hydrolysis, it is clear that an A-1 mechanism, in contrast with a mechanism involving general-acid catalysis in hydrolysis of the oxazolidine I, is due to the great difference in ease of stabilization of a developing carbonium ion with these compounds.

(33) Kenner, G. W. In "The Chemistry and Biology of Purines"; Wolstenholme, G. E. W., O'Connor, C. M., Eds.; Little, Brown, and Co.: Boston, MA, 1957; p 312.
(34) Dekker, C. A. *Annu. Rev. Biochem.* **1960**, *29*, 453.
(35) Micheel, F.; Heesing, A. *Chem. Ber.* **1961**, *94*, 1814.
(36) Shapiro, R. *Prog. Nucleic Acid Res. Mol. Biol.* **1968**, *8*, 73.
(37) Garrett, E. R.; Mehta, P. J. *J. Am. Chem. Soc.* **1972**, *94*, 8532.

Conclusions

In summary, the following conclusions may be drawn from the present work. (1) Ring opening of 2-substituted-1,3-oxazolidines proceeds by C–O bond breaking to give a cationic Schiff base at pH <10, even when there is a phenyl group substituent on nitrogen, and the substituent at the 2-position can significantly stabilize the developing carbonium ion. (2) General-acid catalysis occurs in a concerted process in oxazolidine ring opening (α = 0.5), which is due to the great ease of C–O bond breaking brought about by the highly stabilized carbonium ion in the transition state. (3) Ring opening of the oxazolidine neutral species at pH >5 involves pH-independent C–O bond breaking. (4) Rapid reclosure of the oxazolidine ring occurs at high pH by attack of alkoxide ion on the iminium ion, resulting in only a low steady-state concentration of Schiff base. (5) Apparent hydroxide ion catalyzed hydrolysis of cationic Schiff bases does not occur at high pH when there is an ionizable neighboring group whose attack will reclose the ring.

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

Registry No. I, 73178-24-2; *p*-(dimethylamino)cinnamaldehyde, 6203-18-5; *N*-phenylethanolamine, 122-98-5.

Hydrolysis of the Thiazolium Ion Ring of 1′-Methylthiaminium Ion. Rate and Equilibrium Constants

John A. Zoltewicz* and Georg Uray[1]

Department of Chemistry, University of Florida, Gainesville, Florida 32611

Received December 11, 1979

The reversible hydrolytic cleavage of the thiazolium ion ring of 1′-methylthiaminium ion was studied by a pH-stat method in the forward (ring opening) and reverse (ring closing) directions. At 25.1 °C and 0.2 ionic strength, the observed pseudo-first-order rate constant, k_{obsd}, is given by $117[OH^-] + 1.55 \times 10^5[H^+]$ s^{-1}. The equilibrium is described by the expression $K_a^2 = [H^+]^2$[ring-opened compound]/[thiazolium ion], where $pK_a = 8.56$ at the same temperature and ionic strength used in the kinetic studies. It is estimated that the tetrahedral intermediate which reverts to hydroxide and thiazolium ions can have a half-life no greater than about 20 s.

Hydrolytic cleavage of the thiazolium ion ring of thiamin (vitamin B_1) is part of the characterisitic chemistry of thiamin and was known to the earliest investigators in the field.[2] The ring-opened hydrolysis product has intrinsic interest because it passes through biological membranes more easily than thiamin itself.[3]

In view of the prominent position hydrolytic ring cleavage occupies in the chemistry and biochemistry of thiamin, it is understandable that several groups have studied this process not only for thiamin but also for structurally simpler thiazolium ions.[4-13] All these studies

(1) On leave from the Institut für Organische Chemie, University of Graz, Austria.
(2) R. R. Williams and A. E. Ruehle, *J. Am. Chem. Soc.*, **57**, 1856 (1935).
(3) J. Duclos and P. Haake, *Biochemistry*, **13**, 5358 (1974), and references cited therein.
(4) G. D. Maier and D. E. Metzler, *J. Am. Chem. Soc.*, **79**, 4386, 6583 (1957).
(5) E. Yatco-Manzo, F. Roddy, R. G. Yount, and D. E. Metzler, *J. Biol. Chem.*, **234**, 733 (1959).
(6) J. Crosby and G. E. Lienhard, *J. Am. Chem. Soc.*, **92**, 5707 (1970).
(7) P. Haake and J. M. Duclos, *Tetrahedron Lett.*, 461 (1970).
(8) H. Hogami, J. Hasegawa, and T. Rikihisa, *Chem. Pharm. Bull. (Tokyo)*, **21**, 858 (1973).

0022-3263/80/1945-2104$01.00/0