furans were carried out at 25.0 ± 0.1 °C under pseudo-first-order conditions with OsO_4 the limiting reagent. The progress of the reaction was monitored by ultraviolet absorption spectroscopy with a Perkin-Elmer Model 552 spectrophotometer equipped with a thermoelectric cuvette holder. Kinetics were generally followed at 315 nm for OsO_4/bpy solutions and at 450 nm for OsO_4/pyridine solutions. Plots of $\log[(A_\infty - A_0)/(A_\infty - A_t)]$ vs. time were linear over at least 4 half-times, except in the case of kinetin riboside plus OsO_4/pyridine, in which curvature became apparent after 2–3 half-times. The initial concentrations of substrate (furan) and ligand (pyridine or bpy) were varied to establish the rate law and to evaluate rate constants.

In the case of a furan that produced only a 1:1 Os/furan adduct, the rate of appearance of UV-absorbing osmate groups was exactly equal to the rate of disappearance of the furan. In the case of a furan that produced a 2:1 Os/furan adduct, the rate of formation of individual UV-absorbing osmate groups was twice the rate of disappearance of furan, so $d[OsO_4]/dt = 2(d[KR]/dt)$, assuming the intermediate monoadduct did not accumulate (i.e., d[monoadduct]/dt = 0). Since we monitored osmate appearance and not furan disappearance, the rate constants for furan disappearance were calculated by using the relationship in eq 5.

$$-d[KR]/dt = k_{obsd}[OsO_4]/2 \quad (5)$$

Combining eq 1 and 5 gives eq 6. An examination of the validity

$$k_{obsd} = 2(k_0[KR] + k_1[KR][bpy]) \quad (6)$$

of applying the steady-state approximation to the intermediate monoadduct in the case of kinetin, as described above, follows.

There are three observations that suggest that the use of the steady-state approximation is valid in these kinetics experiments. First, the NMR experiments failed to reveal the existence of the monoadduct even when the furan was present in excess and OsO_4 was added slowly and with vigorous stirring. Second, the enol ether 2,3-dihydrofuran, an analogue of the $\alpha\beta$ monoadduct, is orders of magnitude more reactive than furan itself. Third, the following kinetics experiment provided an independent evaluation of the rate constants for addition of OsO_4/bpy to kinetin without use of the steady-state approximation, and the results of both methods agreed.

The kinetics of addition of OsO_4/bpy to kinetin were carried out with OsO_4/bpy in excess and kinetin as the limiting reagent. This assured that the final product would be the 2:1 Os/furan adduct, which was verified experimentally on the basis of the magnitude of the absorbance increase of the solution. In this experiment kinetin disappears via a pseudo-first-order process, as does the intermediate $\alpha\beta$-type monoadduct. The data, plotted as absorbance vs. time, were fitted by an iterative procedure based on a published computer program.[21] Reasonable values for the extinction coefficients (at 315 nm) of kinetin, the monoadduct (1.2×10^4 M^{-1} cm^{-1}), and the diadduct (2.5×10^4 M^{-1} cm^{-1}) were selected. Then the two variables, the pseudo-first-order rate constants for addition of OsO_4/bpy to kinetin and to the monoadduct, were calculated by minimizing the deviation of the calculated absorbances from the observed absorbances. With OsO_4 at 0.72 mM, bpy at 2.0 mM, and kinetin at 0.03 mM initially, we found the pseudo-first-order rate constants to be 0.021 min^{-1} and >5 min^{-1} for the first and second step, respectively. This allows k' to be estimated at 73 M^{-1} min^{-1}, in good agreement with the value 71 M^{-1} min^{-1} obtained by using the steady-state approximation (OsO_4 limiting). Thus, use of the steady-state approximation appears to be justified in the case of kinetin. Taken together, these three reasons argue strongly that the approximation is valid for the other furans that ultimately produce a 2:1 Os/furan adduct. The results obtained using the approximation, displayed in Table III, are inherently more accurate and easier to obtain than those obtained by the curve-fitting method.

Bis(osmate ester) of 2-Acetylfuran. A solid bis(osmate ester) was prepared from an aqueous solution containing 20 mM OsO_4, 20 mM bpy, and 10 mM 2-acetylfuran (freshly distilled). The solid was collected by suction filtration, washed with water and ethyl acetate, finely ground, rewashed, and dried in vacuo. Anal. Calcd for $C_{26}H_{22}Os_2N_4O_{10}$: C, 33.55; H, 2.38; N, 6.02. Found: C, 33.90; H, 2.73; N, 5.89.

Acknowledgment. We thank Dr. J. Witschel for excellent technical assistance. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, to the Arizona State University Research Council, and to the NIH (Grant No. R01GM27886). This research was assisted by an instrument grant from the NSF (Grant No. CHE76-05506).

Registry No. 1, 110-00-9; 2, 534-22-5; 3, 625-86-5; 4, 1192-62-7; 5, 98-01-1; 6, 88-14-2; 7, 6141-57-7; 8, 525-79-1; 9, 4338-47-0; 10, 3238-40-2; 11, 3387-26-6; 12, 5076-10-8; 13, 30614-73-4; 14, 67-47-0; 15, 30614-77-8; 16, 1883-75-6; thymidine, 50-89-5; 2-acetylfuran bis(bipyridylosmate ester), 78685-52-6; OsO_4, 20816-12-0.

(21) K. B. Wiberg, "Physical Organic Chemistry", Wiley, New York, 1964, pp 567–572.

Kinetic Analysis of the Ring Opening of an *N*-Alkyloxazolidine. Hydrolysis of 2-(4-Methylphenyl)-2,3-dimethyl-1,3-oxazolidine

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Received February 12, 1981

Hydrolysis of the title oxazolidine, III, occurs in two separate reaction stages, reversible ring opening to a cationic Schiff base, IV, followed by a considerably slower formation of hydrolysis products. The ring opening occurs in an H^+-catalyzed reaction and in a pH-independent reaction, with the crossover between the two occurring at about pH 5. A general acid catalyzed pathway ($\alpha = 0.70$) is also observed. The equilibrium constant (pK_{I^+}) for IV ⇄ III + H^+ is 7.45, this number being obtained spectroscopically and in a kinetic analysis. The kinetic analysis also furnishes a dissociation constant (pK_{SH^+}) for the protonated oxazolidine of 6.19, the difference between pK_{SH^+} and pK_{I^+} showing that after attainment of equilibrium the conjugate acid of III is a 19:1 mixture of cationic Schiff base and protonated oxazolidine. The formation of hydrolysis products involves rate-limiting addition of water or hydroxide ion to IV, although a small percentage of a reaction via an oxocarbonium ion derived from C–N cleavage of the protonated oxazolidine cannot be ruled out. Rate constants for the water and hydroxide addition are slower than their intramolecular counterparts, this being particularly true in comparing hydroxide ion reactions. This occurs despite the fact that the ring closure is a supposedly disfavored 5-endo-trigonal process.

Oxazolidines are cyclic acetal analogues with one oxygen replaced by nitrogen. These heterocycles hydrolyze relatively rapidly, even in basic media, producing the corresponding carbonyl compound and β-amino alcohol. A feature of their hydrolysis is that a ring-opened cationic Schiff base is often observed as an intermediate in acid

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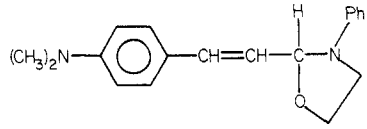
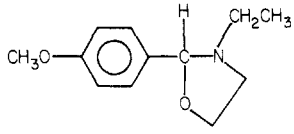
solutions.[1,2] The study of this system is of importance in the investigation of the nature of catalysis in acetal hydrolyses and related reactions[3] and also because of the analogy to the hydrolysis of glycosylamines and nucleosides,[4] reactions of considerable biological significance. The opening and closing of an oxazolidine ring has also been observed in some natural product chemistry.[5]

A detailed kinetic investigation of the ring opening has recently been reported for the oxazolidine I.[2] General-acid



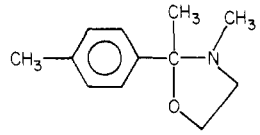
I



II

catalysis is observed, as is usually the case in the hydrolysis of acetals where a C–O bond is easily broken due to the formation of a highly stabilized carbonium ion.[3] Buffer catalysis is also observed with the oxazolidine II, but the analysis is complicated by kinetic ambiguity.[1]

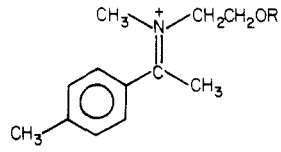
We report here a study of the hydrolysis of 2-(4-methylphenyl)-2,3-dimethyl-1,3-oxazolidine (III). A detailed kinetic analysis is possible with this system, since the ring opening is kinetically well separated from the subsequent hydrolysis. One of the questions which can be addressed concerns the effect of making the oxazolidine ring nitrogen more basic. In the case of I the protonation of this nitrogen is apparently obscured by protonation of the dimethylamino group.



III

Results

The hydrolysis of the oxazolidine III proceeds quantitatively to 4-methylacetophenone (λ_{max} = 257 nm) and 2-(*N*-methylamino)ethanol. The Schiff base IV ($\lambda_{max} \approx$ 290 nm) is observed as an intermediate in solutions with pH <8. The assignment of the Schiff base structure can be made on the basis of previous studies.[1,2] We have also prepared and characterized the *O*-methyl analogue V, and this cation does produce a similar UV spectrum. The Schiff bases IV and V can exist in two different geometrical forms, and the NMR spectrum of V does show that both are in fact present. Excellent first-order kinetics were found, however, for the hydrolysis of both this cation and IV, this observation suggesting that the two isomers have very similar reactivity.[6]



IV, R = H
V, R = Me

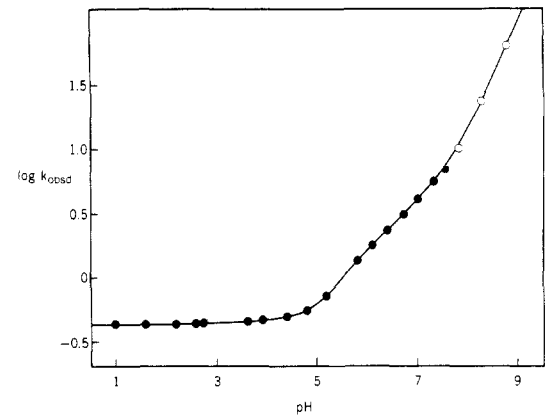


Figure 1. Rate constants for the appearance of Schiff base IV from oxazolidine III (●), and for the disappearance of Schiff base (○; see text for explanation). The rate constant (■) was obtained in both directions. Rate constants at pH >2.5 are based on extrapolation to zero buffer concentration. Conditions are 25 °C and an ionic strength of 0.1.

As mentioned previously the rate of formation of the Schiff base IV is much larger than its subsequent hydrolysis (compare rates in Figures 1 and 3), so that the kinetic behavior for both processes can be accurately analyzed. This feature is not present with 3-alkyloxazolidines derived from benzaldehydes, where except in strong acids the rates of the two processes are much closer.[1] For example, we find with II that the rate of Schiff base formation in dilute acid is only twice the rate of decay. With the oxazolidine III, on the other hand, there is a 100-fold difference.

Rate constants for the formation of the Schiff base are shown in Figure 1. These rate constants for the most part were obtained by adding the oxazolidine III to a dilute base (0.002 M NaOH) and mixing this solution in a stopped-flow spectrophotometer with an appropriate acid or buffer, the appearance of the Schiff base being monitored from the increase in absorbance at 290 nm. In solutions with pH >8 little or no Schiff base is observed (see Figure 4), but it is possible to carry out the experiment in the opposite sense. Thus, oxazolidine was added to a dilute acid (0.002 M HCl), and after the Schiff base forming reaction was complete (30 s), the solution was mixed with an appropriate buffer and the disappearance of the Schiff base monitored. The product in this experiment is predominantly, if not exclusively, oxazolidine, and not ketone,[7] so that the process being studied here is the ring closure. In the pH 7–8 region rate constants were obtained in both directions, ring opening from a base solution and ring closing from acid, and the rate constants were found to be the same within experimental error. Buffer catalysis is also observed. A detailed study was carried out by using chloroacetate, formate, and acetate buffers in the region pH 2.5–5.2; the catalysis in this region is found to be apparent general-base catalysis (Figure 2). The catalytic coefficients for CH_3COO^-, $HCOO^-$, and CH_2ClCOO^- are

(1) Fife, T. H.; Hagopian, L. *J. Am. Chem. Soc.* **1968**, *90*, 1007–1014.
(2) Fife, T. H.; Hutchins, J. E. C. *J. Org. Chem.* **1980**, *45*, 2099.
(3) Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264.
(4) Capon, B. *Chem. Rev.* **1969**, *69*, 407.
(5) Pelletier, S. W.; Mody, N. V. *J. Am. Chem. Soc.* **1979**, *101*, 492.

(6) (a) This can be contrasted with the behavior of some (*E*)- and (*Z*)-phenyl-*N*-methylacetamidates.[6b] (b) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7045.
(7) An accurate determination of the products is made difficult because some ketone forms from the Schiff base in the acid solution before the pH jump is made.

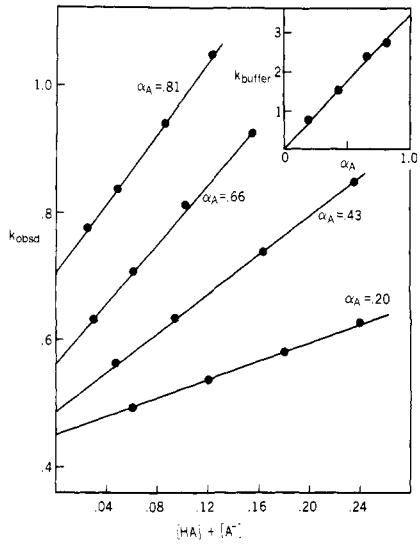


Figure 2. Rate constants for appearance of Schiff base IV in acetic acid buffers. The insert plots the slopes of the lines of the main figure vs. the fraction of buffer in ionized form.

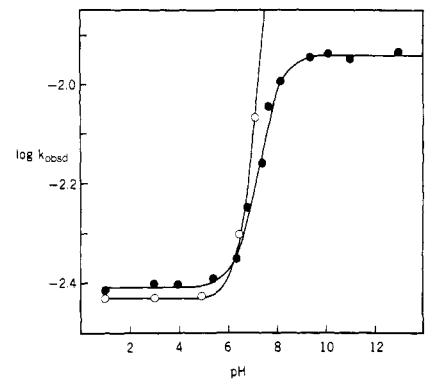


Figure 3. Hydrolysis of oxazolidine III: first-order rate constants for the formation of 4-methylacetophenone, and at pH <8 the disappearance of Schiff base IV (●). First-order rate constants for the hydrolysis of the Schiff base V (○). Between pH 3 and 11 rate constants represent extrapolation to zero buffer concentration.

3.5, 1.8, and 1.0 M^{-1} s^{-1}, respectively. These provide a Brønsted β value of 0.29.

Figure 3 plots rate constants for the formation of the final hydrolysis products, these rate constants being obtained at pH >8 from the appearance of ketone at 257 nm and at pH <8 from both the appearance of ketone and the disappearance of Schiff base, the rates for which are identical within experimental error. First-order rate constants were also obtained for the hydrolysis of the Schiff base V and are also depicted in Figure 3.

With the large difference between the rates of formation and decay of the Schiff base IV, the amount of this cation that is formed in the initial reaction can be determined as a function of pH. The experiment involved the addition of a constant amount of oxazolidine to a series of solutions, with the absorbance at 290 nm being recorded after 5–10 s. This is sufficient time for the Schiff base forming reaction to be essentially complete (Figure 1), while there is very little of the subsequent ketone forming reaction (Figure 3). The behavior that is observed (Figure 4) is typical of an acid–base equilibrium for an acid of dissociation constant 7.44.

Discussion

As in the case of the *N*-phenyloxazolidine I the hydrolysis of the oxazolidine III is separated into two distinct

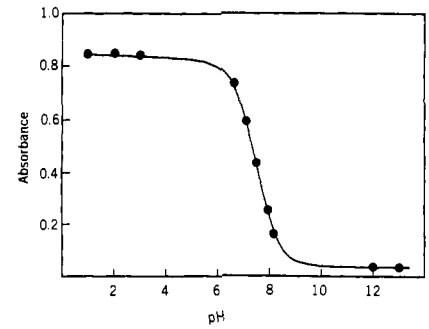
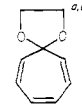


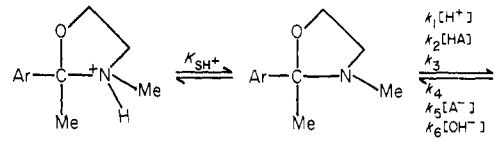
Figure 4. Schiff base absorbance (λ = 290 nm) as a function of pH.

Table I. Rate and Equilibrium Constants

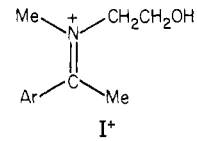
	III[a]	I[b]	
k_1, M^{-1} s^{-1}	6.4×10^5	2×10^4	2.1×10^4
k_3, s^{-1}	3.1	0.938	0.13
$pH^{1/2}$ [d]	5.3	4.3	5.2
k_4, s^{-1}	0.023	0.000 17	0.13
k_6, M^{-1} s^{-1}	1.1×10^7	7.9×10^5	8.0×10^7
pK_{I^+}	7.45	8.07	5.2
pK_{SH^+}	6.19		
k_{H_2O}, s^{-1}	0.0041	~0.0002[e]	0.03
k_{OH^-}, M^{-1} s^{-1}	4.0×10^4	~10^3[e]	2.3×10^4

[a] 25 °C, μ = 0.1. [b] Reference 1, 25 °C, 50% dioxane–water. [c] Reference 10. [d] pH of solution where $k_1[H^+] = k_3$. [e] Estimated from Figure 4 of ref 1.

stages, an initial stage involving equilibration of the oxazolidine form and the Schiff base form followed by a slower stage in which the equilibrium mixture is converted to ketone and amino alcohol. The initial equilibration can be analyzed in terms of eq 1. Ring opening involves



SH⁺ S



I⁺ (1)

hydronium ion catalysis, general-acid catalysis, and water catalysis, while ring closing involves the microscopic reverse of these, water catalysis, general-base catalysis, and hydroxide ion catalysis. These same reactions have also been found with the oxazolidine I.[2] The major variation with III, a variation which is responsible for a completely different form of rate–pH profile, is that the N-protonated oxazolidine is also important. If the assumption is made that the equilibrium between the N-protonated and neutral oxazolidines is rapidly established,[8] eq 2 can be derived

$$k_{obsd} = ((k_6K_wK_{SH^+}/[H^+]) + (k_6K_w + k_4K_{SH^+} + k_3K_{SH^+}) + (k_4 + k_1K_{SH^+})[H^+])/(K_{SH^+} + [H^+]) \quad (2)$$

for the observed rate constant in the absence of buffer. This equation refers to the approach to complete equilibrium in eq 1 and provides the rate constant k_{obsd} independent of the direction of the approach and independent

(8) Eigen, M. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 1.

of the final equilibrium position. This equation has the form shown in eq 3, and the experimental data can be fit

$$k_{obsd} = \frac{a/[H^+] + b + c[H^+]}{d + [H^+]} \quad (3)$$

very satisfactorily to such an equation. (See the line drawn in Figure 1.) This procedure provides the four empirical constants a–d,[9] and although five different constants appear in eq 2, these five are not all independent. An equilibrium constant $K_{I^+} = [S][H^+]/[I^+]$ can be defined; this is related to the rate constants by the expressions $K_{I^+} = k_4/k_1 = k_6K_w/k_3$. Thus there are in fact only four independent constants, K_{SH^+} and, for example, K_{I^+}, k_4, and k_6, and from the values of a–d all the various rate and equilibrium constants of eq 1 can be obtained. These are listed in Table I.

Confirmation that this analysis is correct is provided by the independent observation of the position of the equilibrium of eq 1. This equilibrium can be regarded in an acid–base sense as $(I^+ + SH^+) \rightleftarrows S + H^+$, with an acidity constant given by eq 4. The value calculated for this term

$$K_{app} = K_{I^+}K_{SH^+}/(K_{I^+} + K_{SH^+}) \quad (4)$$

on the basis of the kinetically determined values of K_{I^+} and K_{SH^+} is 7.48, this number being quite close to pK_{I^+} (7.45) since $K_{I^+} < K_{SH^+}$. The spectroscopic value (Figure 4) is 7.44, in excellent agreement.

The rate–pH profile for the ring opening–ring closing (Figure 1) can be analyzed in the following way. (a) In strongly acidic solutions an equilibrium consisting of 95% cationic Schiff base and 5% protonated oxazolidine is established, with a pH-independent rate constant of $k_4 + k_1K_{SH^+}$. The former term represents noncatalyzed ring closure of the Schiff base while the latter represents the H^+-catalyzed ring opening of the neutral oxazolidine present in small concentration in equilibrium with the protonated oxazolidine. (b) The onset of an apparent hydroxide ion catalyzed region at pH 4 represents the same equilibration as in (a) but now with a different kinetic mode of establishment. Ring opening occurs by a noncatalyzed reaction and ring closing by the microscopic reverse, hydroxide ion catalysis. The apparent second-order rate constant in hydroxide ion (which is superimposed on the pH-independent rate constant of a) is given by $k_6 + k_3K_{SH^+}/K_w$. (c) A simple description of the situation between pH 5.5 and 8 is complicated since all three species, SH^+, S, and I^+, are present in amounts varying with pH. However, it can be stated that the ring opening–ring closing reactions in this region are occurring by the k_6 – k_3 pathways as in b. (d) Above pH 8 oxazolidine is the predominant species in the equilibrium. The observed rate constant is equal to $k_6[OH^-]$ and represents hydroxide ion ring closure of the Schiff base.

The preference for ring opening to occur by the noncatalyzed pathway even in acid solutions is also observed with the oxazolidine I[1] and with tropone ethylene ketal,[10] as can be seen in Table I where values of pH are listed at which the H^+-catalyzed and noncatalyzed reactions occur at the same rate. Although comparisons with other species of the oxazolidine type are not at present possible, from results obtained with various tropone ketals[10,11] there would appear to be a special ease associated with the noncatalyzed opening–hydroxide ion closing of five-membered rings. For example, with the acyclic tropone diethyl ketal, $pH^{1/2} = 7.40$,[11] while for tropone trimethylene ketal which contains a six atom ring, $pH^{1/2} = 7.65$.[10] We are currently studying acyclic analogues of III, as well as molecules where there are six-atom rings, to see if the previous conclusion can be extended to the oxazolidine system.

The present investigation also furnishes, albeit through a kinetic analysis only, the acidity constant for a protonated oxazolidine, the first such value of which we are aware. The value that is obtained ($pK_{SH^+} = 6.19$) is substantially smaller than values for simple ammonium analogues. Acidity constants for 2-aryl-1-alkylpyrrolidinium ions have been reported and lie around 9.0.[12] The difference with the oxazolidine can be attributed to the presence of the electronegative β ring oxygen atom. The decrease by a factor of 2.8 is about that which would be estimated on the basis of structural correlations devised by Guthrie for tetrahedral adducts such as $^+NHR_2CR_2OR$.[13] Interestingly, a similar decrease in acidity constant is observed when the oxygen in the ring is one atom further removed, as for example in comparing piperidine with morpholine.[14]

The kinetic analysis also reveals that both the cationic Schiff base and the protonated oxazolidine are in fact present in significant amounts after attainment of equilibrium in an acid solution, the ratio being about 19:1 in favor of the former. This ratio is, of course, independent of acidity, but it should be fairly sensitive to changes in oxazolidine structure. In particular, a variation in substituent at the 2-position is likely to effect the stability of the Schiff base considerably more than it will effect the stability of the protonated oxazolidine. Thus N-alkyloxazolidines with 2-substituents which are less carbonium ion stabilizing than in III can be predicted to exist in acids to a greater extent in the N-protonated form.

In terms of eq 1 the buffer catalysis observed for the ring opening–ring closing is expressed by eq 5, with simplifi-

$$k_{Buf} = (k_5K_{SH^+}[A^-] + k_5[H^+][A^-] + k_2K_{SH^+}[HA])/(K_{SH^+} + [H^+]) \quad (5)$$

cation in strong acids where $[H^+] \gg K_{SH^+}$ to eq 6. The

$$k_{Buf} = (k_5 + (k_2K_{SH^+}/K_{HA}))[A^-] \quad (6)$$

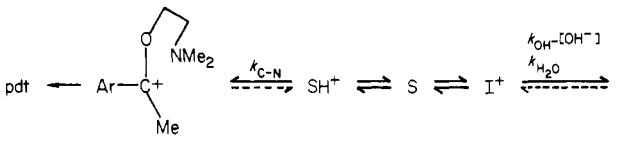
$$= k_5(1 + K_{SH^+}/K_{I^+})[A^-] \quad (7)$$

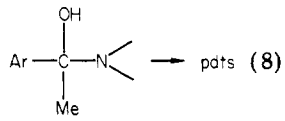
term K_{HA} in eq 6 is the dissociation constant of the buffer acid, and the final equation is obtained from the relationship $K_{I^+} = k_5K_{HA}/k_2$. Equation 7 shows that the catalysis which is observed in acids is apparent general-base catalysis, although in fact it represents the approach to equilibrium catalyzed in the ring closure direction by bases and in the ring opening direction by acids, these acids acting on the neutral oxazolidine. In terms of the actual numbers involved, the catalytic coefficients have a relative contribution of 1:19 from the two terms in eq 6, the k_5 term making the smaller contribution. The observed Brønsted β value (0.3) refers to the ring-closing reaction (k_5). The α value for ring opening (k_2) is $1 - \beta$ or 0.7. This latter value is comparable to those obtained in similar systems. For example, for I a Brønsted α of 0.53 was obtained for ring opening; the C–O cleavage of the amide acetal 4-$CH_3C_6H_4C(OMe)_2NMe_2$ has associated with it an α value of 0.61.[15]

(9) Values of the constants which provide the best fit are $a = 6.95 \times 10^{-14}$, $b = 2.1 \times 10^{-6}$, $c = 0.432$, and $d = 6.4 \times 10^{-7}$.
(10) McClelland, R. A.; Ahmad, M.; Mandrapilias, G. *J. Am. Chem. Soc.* **1979**, *101*, 970.
(11) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7027.
(12) Craig, L. C.; Hixon, R. M. *J. Am. Chem. Soc.* **1931**, *53*, 4367. Craig, L. C. *Ibid.* **1933**, *55*, 2543.
(13) Guthrie, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 3608.
(14) Hine, J. In "Structural Effects on Organic Equilibria in Organic Chemistry"; Interscience: New York, 1975; p 40.

Schiff Base Hydrolysis

The second kinetic stage represents the conversion of the equilibrium mixture of SH^+, S, and I^+ to ketone and amino alcohol. This reaction has been assumed to involve addition of water or hydroxide to the cationic Schiff base I^+,[1,2] but with the protonate d oxazolidine also being present in significant amounts in equilibrium with I^+, the possibility also exists that the hydrolysis proceeds via C–N cleavage,[16] with an intermediate oxocarbonium ion VI (eq 8). There follow two arguments which pertain to this possibility.





(8)

(a) If the C–N cleavage reaction is important, it must complete with Schiff base formation when the neutral oxazolidine is first placed in an acid solution, particularly since the protonated oxazolidine which leads to the C–N cleavage reaction is formed initially. The ratio of C–O cleavage (Schiff base formation) to C–N cleavage (ketone formation) is given by $k_1K_{SH^+}/k_{C-N}$, this equation applying when the acidity is high enough that C–O cleavage involves only H^+ catalysis. This ratio cannot be evaluated exactly. The UV spectrum in acid of the oxazolidine is virtually identical with that of the authentic Schiff base V. This suggests that oxazolidine forms predominantly Schiff base, although a small amount of ketone formation via C–N cleavage cannot be rigorously excluded. If the assumption is made that C–O cleavage occurs to an extent greater than 95% ($k_1K_{SH^+} \geq 20k_{C-N}$), the upper limit on k_{C-N} is 0.02 s^{-1}. This number can then be used to place an upper limit on the contribution of the C–N cleavage reaction to the second stage. In this stage, the C–N cleavage reaction involves SH^+ in equilbrium with I^+, and the observed rate constant in acid is $k_{C-N}K_{I^+}/K_{SH^+}$, the upper limit for which is 0.001 s^{-1}. The observed rate in acid is 0.0039 s^{-1}. Thus we conclude that the C–N cleavage reaction is contributing no more than 25% to the product forming reaction.

(b) In acid solutions the rate constants observed for the disappearance of the Schiff base IV derived from the oxazolidine are quantitatively very similar to those of the Schiff base V (Figure 3), a species which cannot ring close in order to carry out the C–N cleavage reaction. In fact, in acid the hydrolysis of IV is about 10% more rapid than that of V (after correcting the rate for IV for the small concentration of protonated oxazolidine in the equilibrium). This difference is obviously small and could be due to the minor structural difference between IV and V (β-OMe vs. β-OH). If the difference is due to the C–N cleavage reaction, the conclusion must still be reached that its contribution is relatively small.

Interestingly, the rate constant for the C–N cleavage of a protonated amide acetal $ArC(OMe)_2NMe_2H^+$ is of the order of 1 s^{-1}.[17] The effect on this rate of changing to a ketone derivative is difficult to predict. A comparison of benzoate ortho esters[18] and acetophenone ketals[19] where similar oxocarbonium ions are formed shows that the ketone derivatives are in fact more reactive by about an order of magnitude. If the same difference applies to C–N cleavage, the ketone derivative would therefore be expected to undergo this reaction with a rate greater than 1 s^{-1}. As the foregoing analysis has shown, this clearly cannot be the case with the oxazolidine. This raises the possibility that the C–N cleavage of the protonated oxazolidine is rapid but is reversible with a rapid addition of the intramolecular amine group to the oxocarbonium ion. This would, of course, mean that the C–N cleavage could be occurring but, being reversible, not be observed.

The major reaction forming hydrolysis products is therefore the hydrolysis of the cationic Schiff base, and this occurs with rate-determining addition of water and hydroxide ion. This latter conclusion is made on the basis of the observation that rate constants in acid are independent of pH. With other Schiff bases, a change-over occurs in acid solutions, and breakdown of the adduct becomes rate determining,[20] this changeover being accompanied by a definite break in the rate–acidity profile.[21] We are uncertain as to the reason why the Schiff bases derived from the oxazolidines[22] are different, although it is interesting to note that V also shows no sign of a change in rate-determining step.

Rate-limiting water and hydroxide ion addition to the species I^+ in equilibrium with S and SH^+ (eq 8) results in the rate law given in eq 9, where K_{app} is defined in eq 4.

$$k_{obsd} = \frac{\frac{K_{app}k_{H_2O}}{K_{I^+}}[H^+] + \frac{k_{OH^-}K_wK_{app}}{K_{I^+}}}{[H^+] + K_{app}} \quad (9)$$

The experimental data (Figure 3) do fit the form prescribed by eq 9. Curve fitting provides a thrid estimate of pK_{app}; a value of 7.5 is obtained, which is in good agreement with those found previously. Values of k_{H_2O} and k_{OH^-} can also be obtained on substitution of the value of K_{I^+}. These are listed in Table I.

It is interesting to compare these rate constants referring to intermolecular addition to the Schiff base with their intramolecular counterparts, the ring-closure rate constants (k_{H_2O} with k_4 and k_{OH^-} with k_6). In both cases the ring-closing reaction is favored, this being particularly true for the hydroxide ion reactions. Similar behavior is also observed with the oxazolidine I and the cyclic tropone ketal (Table I). Intramolecular reactions, particularly those forming five-membered rings, are often very efficient. However, in the present case this reaction takes the form of what Baldwin[23] has termed a 5-endo-trigonal ring closure, a process which he considers "disfavored". Several other examples of 5-endo-trigonal reactions have recently been observed.[24] The present study shows that the re-

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action can effectively compete even with external solvent addition.

Experimental Section

Materials. 2-(4-Methylphenyl)-2,3-dimethyl-1,3-oxazolidine was prepared by refluxing for 2 weeks in toluene equivalent amounts of 4-methylacetophenone and 2-(methylamino)ethanol, water being continuously removed from the reaction by azeotropic distillation with the toluene. The toluene was removed on a rotary evaporator, and the residual liquid distilled to give III: bp 140 °C (30 mm); NMR ($CDCl_3$, $(CH_3)_4Si$) δ 7.25 (2 H, d), 6.93 (2 H, d), 3.78 (2 H, m), 2.85 (2 H, m), 2.32 (3 H, s), 2.27 (3 H, s), 1.53 (3 H, s).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.2; H, 9.12; N, 7.16.

The imine of 4-methylacetophenone and 2-methoxyethylamine was prepared as described for III, with a trace of *p*-toluenesulfonic acid being added to catalyze the addition. This imine had a boiling point of 90 °C (0.1 mm). The cationic Schiff base V, as a trifluoromethanesulfonate salt, was prepared by treatment of this imine dissolved in methylene chloride with an equivalent amount of methyl trifluoromethanesulfonate. The NMR spectrum of this solution showed that the methyl transfer was complete essentially on mixing. The presence of two isomers in about equal proportions was revealed by two NMe peaks (δ 3.96 and 3.76) and two OMe peaks (δ 3.50 and 3.38).

Kinetics. Stopped-flow experiments were carried out on a Durrum-Gibson stopped-flow spectrophotometer; slower kinetic experiments were monitored by using a Unicam sp 1800 spectrophotometer. The ring-opening reaction of III was studied by addition of a small amount of the oxazolidine in CH_3CN to an 0.002 M NaOH solution which had been thermostated in an external water bath. One syringe of the stopped-flow instrument was filled with this solution; while the other syringe was filled with the appropriate aqueous buffer. Six to eight successive mixings were carried out. The data were analyzed directly by using a Tektronix 4051 minicomputer linked to the stopped-flow instrument. First-order rate constants were evaluated by following the increase in absorbance at 290 nm. The ring-closing reaction of the Schiff base was studied in a similar manner. The experiment in this case involved the addition of oxazolidine to 0.002 M HCl, followed by mixing in the stopped-flow apparatus with an appropriate basic buffer. The decrease in UV absorbance at 290 nm was monitored. The formation of hydrolysis products was studied by using conventional spectroscopy, by addition of 1–3 μL of a solution of oxazolidine to a thermostated UV cell. Rate constants were obtained for the increase in absorbance at 257 nm due to the appearance of 4-methylacetophenone or, at pH <8, from the decrease in absorbance at 290 nm. The hydrolysis of the cationic Schiff base V was studied by adding 1 μL of the CH_2Cl_2 solution in which it had been prepared to a thermostated UV cell.

Acknowledgment. Financial support of the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Registry No. III, 78456-50-5; (*E*)-V·$F_3CSO_3^-$, 78456-52-7; (*Z*)-V·$F_3CSO_3^-$, 78456-54-9; 4-methylacetophenone, 122-00-9; 2-(methylamino)ethanol, 109-83-1; *N*-(α,4-dimethylbenzylidene)-2-methoxyethylamine, 78456-55-0; 2-methoxyethylamine, 109-85-3.

Influence of Urea–Water Interactions on the Transition-State Structure for the Hydrolysis of 1-Acetylimidazolium Ion and 1-Acetyl-3-methylimidazolium Ion[1]

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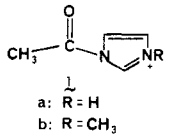
Received June 10, 1981

The hydrolysis of 1-acetylimidazolium ion and 1-acetyl-3-methylimidazolium ion has been investigated in the presence of 3 M urea. Urea significantly reduces the magnitude of the solvent deuterium isotope effect. The transition-state structure for hydrolysis is proposed to involve proton transfer from the nucleophilic water molecule of a water–urea complex. This proposed transition-state structure is consistent with the linear plot of the observed rate constant vs. the atom fraction of deuterium in the solvent. A pH–rate profile has also been determined.

There is general agreement, based on solvent isotope effects,[2,3] Brønsted plots,[2,3] and proton inventories,[4-6] that the hydrolysis of 1-acetylimidazolium ion (**1a**) and 1-acetyl-3-methylimidazolium ion (**1b**) occurs via a transition state containing a catalytic proton bridge between the reorganizing substrate and a water (base) molecule as shown in **2**. This transition-state structure has been suggested on the basis of the proton inventory studies done on **1**.[4-6] Isotope effect contributions from three protons (H_a and both H_b protons) are observed when water is the catalyzing base while a single proton (H_a) exhibits an isotope effect when a base such as imidazole catalyzes the reaction.[4-6]



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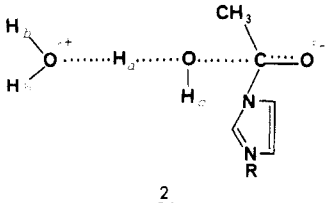

2

Although water–urea systems have been the subject of much study, there is no general agreement as to whether

(1) This work was supported by the National Institutes of Health (Grant No. 1 R01 GM 25433) and, in part, by the Robert A. Welch Foundation.
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