Schiff's Bases as Intermediates in the Hydrolytic Decomposition of 2-Alkyl-3-methyl-1,3-oxazolidines in Aqueous Acid

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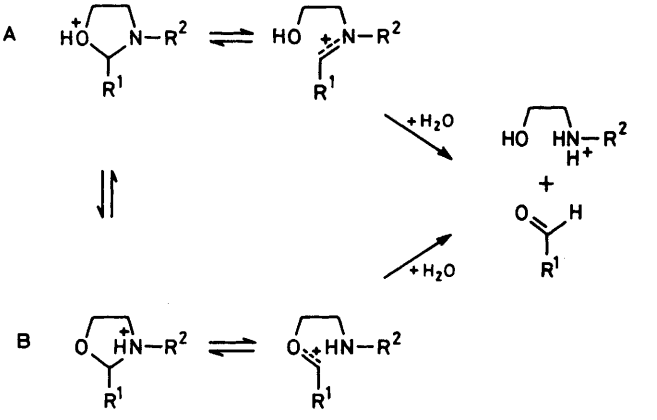
The kinetics for the hydrolysis of 2-alkyl-3-methyl-1,3-oxazolidines have been examined spectrophotometrically in acidic solutions. The decomposition of the substrates to 2-methylaminoethanol and the corresponding aldehydes have been shown to proceed *via* stable intermediates which are kinetically and u.v.-spectroscopically very similar to the acyclic cationic Schiff's base derived from isobutyraldehyde and 2-methoxyethylmethylamine. The mechanisms for the formation and breakdown of the Schiff's base intermediate are discussed on the basis of pH–rate profiles, activation parameters, salt effects, and solvent deuterium isotope effects.

While the mechanisms for the hydrolytic reactions of cyclic acetals have been extensively studied,[1] data on the hydrolysis of the corresponding N,O-heterocycles, 1,3-oxazolidines and 1,3-perhydro-oxazines, are quite limited. Under neutral and slightly acidic conditions the latter compounds rather rapidly decompose to the corresponding carbonyl compounds and amino-alcohols. Two alternative mechanisms can be tentatively written for the hydrolysis reaction. Either protonation of ring-oxygen is followed by formation of a cationic Schiff's base intermediate (route A in Scheme 1), or the substrate protonated at the nitrogen atom undergoes a rate-limiting cleavage to an acyclic oxocarbenium ion, as in the hydrolysis of acetals (route B in Scheme 1). 1,3-Oxazolidines derived from aromatic aldehydes have been shown to utilize pathway A.[2-4] We now report on our studies with oxazolidines derived from aliphatic aldehydes and suggest that the same route may also be extended to the hydrolysis of these compounds, in spite of the fact that 2-alkyl-1,3-oxazolidines can be expected to form considerably more stable oxocarbenium ions than their 2-aryl counterparts. The mechanisms for the formation and decomposition of the Schiff's base intermediate are elucidated by pH–rate profiles, electrolyte effects, solvent deuterium isotope effects, activation parameters, and structural effects.



Scheme 1.

Results and Discussion

Figure 1 shows the time-dependent u.v. spectrum of 2-isopropyl-3-methyl-1,3-oxazolidine undergoing hydrolysis in aqueous perchloric acid. The pK_a value of the conjugate acid of the substrate is unknown, but obviously the ring nitrogen is almost completely protonated in the markedly acidic solutions employed in the present study. The absorption maximum of the protonated substrate at *ca.* 190 nm (log ε *ca.* 3.4) initially increases and then slowly disappears with concomitant formation of a weak maximum at 284 nm (log ε *ca.* 1). Accordingly, hydrolysis seems to proceed *via* a relatively stable intermediate, the decomposition of which produces isobutyraldehyde as the final product. The latter compound is responsible for the absorbance at 284 nm. The u.v. spectrum of the intermediate, in turn, closely resembles that of the trifluoromethanesulphonate salt of the acyclic Schiff's base cation (I).

The first-order rate constants for the formation and decomposition of the intermediate are plotted in Figure 2 against the acidity of the reaction solution. Formation occurs *ca.* 100 times faster than decomposition. The consecutive steps of the oxazolidine hydrolysis are thus kinetically fairly well separated. Figure 2 also includes the rate profile for the hydrolysis of the cationic Schiff's base (I). This compound is in fact a mixture of two geometric isomers. However, first-order kinetics were observed to be well obeyed. Presumably the two isomers are in rapid equilibrium, since the hydrolysis of Schiff's bases is known [5] to proceed under acidic conditions by reversible addition of water to the substrate. Comparison of the pH–rate profiles in Figure 2 reveals that the breakdown of the intermediate in the oxazolidine hydrolysis and the decomposition of the acyclic Schiff's base (I) respond in the same manner to changes in the oxonium ion concentration. This fact, together with the similarity of the u.v. spectra, strongly suggests that hydrolysis of 2-isopropyl-3-methyl-1,3-oxazolidine takes place *via* the acyclic cationic Schiff's base described in Scheme 1.

The composition of the equilibrium mixture formed in pre-equilibrium ring-opening of 1,3-oxazolidines cannot be estimated from the available data. In other words, the concentration of the unchanged starting material, which is in equilibrium with the intermediate, may be relatively large during the heterolysis of the latter. Consequently, the rate constants obtained for the decomposition stage may be smaller than the real rate constants for heterolysis. This is a possible explanation for the observed difference in reactivity between the intermediate of the oxazolidine hydrolysis and the acyclic Schiff's base (I). For the same reason, the rate constants obtained for the formation of the intermediate may deviate from the real rate constants for the rupture of the CO bond.

The acidity of the reaction solution does not markedly affect the concentration of the oxygen-protonated substrate. This species is in equilibrium with the nitrogen-protonated substrate, the proportion of the unprotonated substrate being negligible. Accordingly, the concentrations of the two monocations are controlled only by the difference in their pK_a values. However, as seen from Figure 2, the formation of the

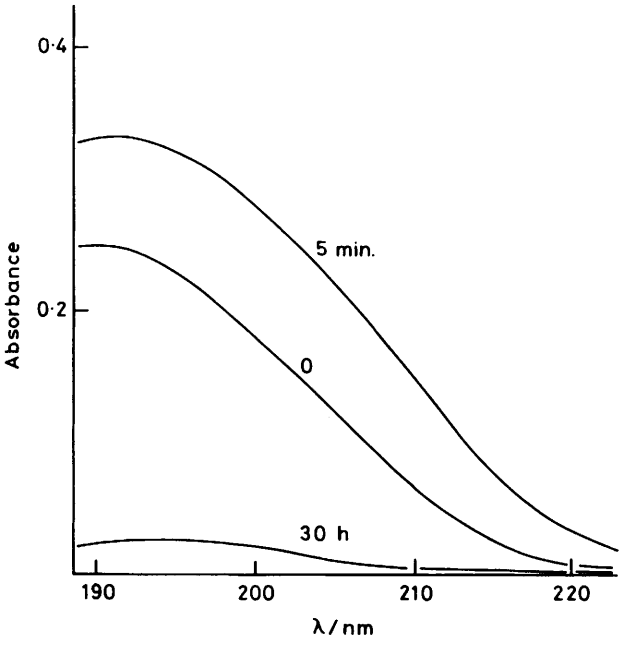
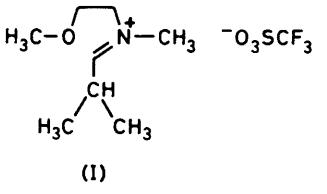


Figure 1. Time-dependent u.v. spectrum for 2-isopropyl-3-methyl-1,3-oxazolidine allowed to hydrolyse in 2 mol dm^{-3} perchloric acid at 283.2 K



(I)

Schiff's base intermediate is considerably retarded at high acid concentrations. This retardation reflects common salt effects rather than the influence of acidity on reactivity. As seen from Figure 3, sodium perchlorate exerts comparable effects on the rate of formation of the intermediate. Similar decelerations in the corresponding reactions of 2-aryl-3-ethyl-1,3-oxazolidines have been suggested to result from the decrease of the activity of water on going to concentrated electrolyte solutions.[2] Accordingly, water would participate in the transition state for the initial ring-opening.[2] It should be noted, however, that the rate retardations are far greater than the changes in the activity of water. The ratio of water activities in 1 and 5 mol dm^{-3} perchloric acid, for example, is only 1.6.[6] Alternatively, the negative salt effects may be accounted for by changes in the charge distribution on going from the initial to the transition state.[7] In the protonated substrate the positive charge is more localized than in the transition state leading to the cationic Schiff's base. Consequently, high salt concentrations stabilize the ionic initial state more effectively and thus retard the reaction. The situation is the same if protonation of the ring oxygen takes place in concert with CO bond cleavage. Again the initial state, consisting of the neutral substrate and oxonium ion, is more ionic than the transition state, and the negative salt effects are understandable.

The entropies of activation obtained for the intial ring-opening of 2-alkyl-3-methyl-1,3-oxazolidines in 5.15 mol dm^{-3} perchloric acid range from −25 to −45 J K^{-1} mol^{-1} (Table 1), *i.e.* less negative than the value of −65 J K^{-1} mol^{-1} reported for 2-phenyl-3-ethyl-1,3-oxazolidine in 5.74 mol

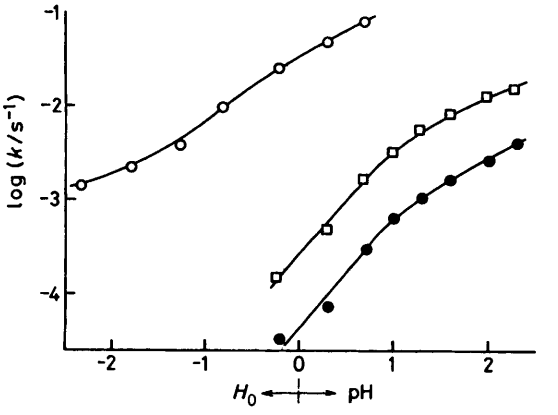


Figure 2. The effect of acidity on the first-order rate constants for the hydrolysis of 2-isopropyl-3-methyl-1,3-oxazolidine at 283.2 K. Open circles refer to the formation and filled circles to the breakdown of the Schiff's base intermediate. Open squares refer to the hydrolysis of the cationic Schiff's base derived from isobutyraldehyde and 2-methoxyethylmethylamine. The ionic strength was adjusted to 0.1 mol dm^{-3} at pH ≥ 1

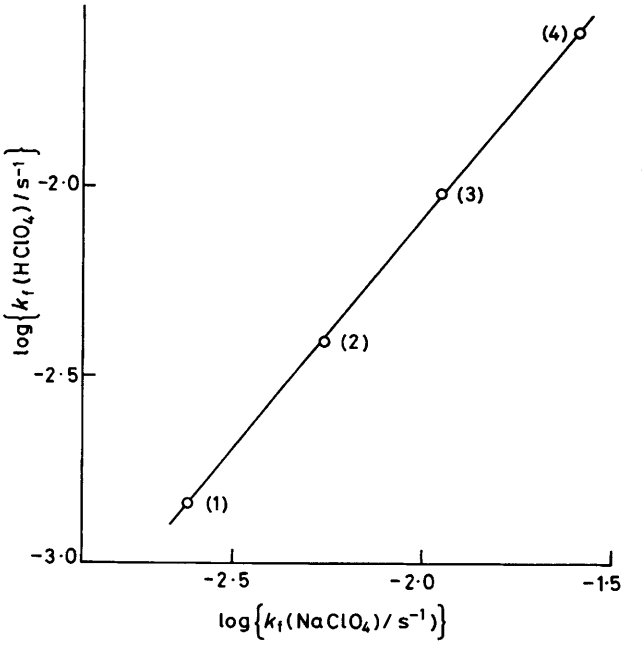


Figure 3. Comparison of the effects that additions of perchloric acid and sodium perchlorate exert on the ring opening of 2-isopropyl-3-methyl-1,3-oxazolidine in 1 mol dm^{-3} acid at 283.2 K. Circles (1)—(4) refer to the ionic strengths of 5, 3, 2, and 1 mol dm^{-3}, respectively

dm^{-3} hydrogen chloride.[2] The $\Delta S^{\ddagger}$ values of this magnitude, while not highly negative are still consistent with participation of solvent in some sense in the transition state preceding the Schiff's base intermediate. For example, proton transfer to the ring oxygen from oxonium ion concerted with ring opening may give rise to slightly negative entropies of activation. However, the $\Delta S^{\ddagger}$ values obtained are not negative enough rigorously to exclude the possibility of unimolecular bond cleavage. Several reactions involving rate-limiting opening of a five-membered ring are characterized by slightly negative entropies of activation, though other experimental data agree with unimolecular heterolysis.[8-11]

Table 1. First-order rate constants at different temperatures, enthalpies, and entropies of activation and solvent deuterium isotope effects for the formation of acyclic Schiff's base intermediates in the hydrolysis of some 2-alkyl-3-methyl-1,3-oxazolidines

2-Substituent	T/K	$10^3 k_f$/s^{-1} [a]	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1} [b]	$k_f(H_2O)/k_f(D_2O)$ [c]
Methyl	283.2	0.620 ± 0.004	78.5 ± 4.8	−29 ± 16	2.3
	288.2	1.10 0.09			
	293.2	1.71 0.09			
	298.2	2.75 0.13			
	303.2	6.71 0.04			
	308.2	9.52 0.18			
Ethyl	283.2	1.00 ± 0.02	72.3 ± 2.7	−46 ± 9	2.3
	288.2	1.62 0.02			
	293.2	3.04 0.09			
	298.2	5.44 0.01			
	303.2	8.51 0.03			
	308.2	12.1 0.1			
Isopropyl	283.2	1.45 ± 0.01	76.6 ± 1.9	−28 ± 7	2.4
	288.2	2.64 0.03			
	293.2	4.68 0.08			
	298.2	8.43 0.14			
	303.2	12.9 0.1			

[a] Means and standard deviations of four runs in 5.15 mol dm^{-3} perchloric acid. [b] At 298.2 K. [c] Obtained in 2.02 mol dm^{-3} $DClO_4$ and $HClO_4$ at 298.2 K.

Table 2. First-order rate constants at different temperatures, enthalpies, and entropies of activation, and solvent deuterium isotope effects for the decomposition of acyclic Schiff's base intermediates in the hydrolysis of some 2-alkyl-3-methyl-1,3-oxazolidines

2-Substituent	T/K	$10^3 k_d$/s^{-1} [a]	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1} [b]	$k_d(H_2O)/k_d(D_2O)$ [c]
Methyl	283.2	0.434 ± 0.018	74.1 ± 1.9	−47 ± 7	
	288.2	0.837 0.027			
	293.2	1.18 0.04			
	298.2	2.37 0.04			
	303.2	3.70 0.06			
	308.2	5.96 0.26			
	313.2	9.96 0.27			
Ethyl	283.2	0.362 ± 0.005	73.2 ± 2.4	−51 ± 8	3.3
	288.2	0.650 0.004			
	293.2	1.25 0.03			
	298.2	2.15 0.02			
	303.2	3.40 0.12			
	308.2	5.28 0.05			
	313.2	7.61 0.15			
Isopropyl	283.2	0.602 ± 0.017	63.0 ± 1.1	−82 ± 4	4.0
	288.2	1.18 0.06			
	293.2	1.81 0.05			
	298.2	2.89 0.04			
	303.2	4.67 0.11			
	308.2	6.64 0.09			
	313.2	9.71 0.47			
d	283.2	2.95 ± 0.04	52.7 ± 1.0	−106 ± 4	3.2
	288.2	4.78 0.14			
	293.2	6.80 0.10			
	298.2	10.6 0.5			
	303.2	14.6 0.4			
	308.2	20.4 0.7			
	313.2	28.4 0.8			

[a] Means and standard deviations of four runs in 0.10 mol dm^{-3} perchloric acid. [b] At 298.2 K. [c] Obtained in 0.10 mol dm^{-3} $HClO_4$ and $DClO_4$ at 298.2 K. [d] Data for compound (I) (see text)

The solvent deuterium isotope effect of 2.3 (Table 1) is rather small to be consistent with unimolecular heterolysis of the protonated substrate. The spontaneous decompositions of acetals, for example, exhibit values close to unity.[1] In contrast, a marked retardation in D_2O is expected if protonation is concerted with CO bond cleavage, as in the A_{SE}-2 reactions of acetals. The detailed interpretation of the isotope effects of oxazolidine hydrolysis is difficult, however, since replacing H_2O by D_2O may also affect the competitive protonation of oxygen and nitrogen.

As seen from Table 1, the structural effect of the 2-alkyl substituent on the initial ring-opening is small. The slight increment in the reactivity on going from methyl to ethyl and further to isopropyl can probably be accounted for by increasing stabilization of the cationic Schiff's base due to electron donation from the alkyl group attached to the

Table 3. The effect of the ionic strength on the decomposition of the cationic Schiff's base (I) (see text) and the Schiff's base intermediate derived from 2-isopropyl-3-methyl-1,3-oxazolidine

	$k_d/10^{-3}$ s^{-1} [b]	
I/mol dm^{-3} [a]	Compound (I)	Schiff's base intermediate
0.010	19.2 ± 0.2	4.19 ± 0.04
0.050	17.1 0.2	3.70 0.06
0.10	15.5 0.3	3.39 0.11
0.15	15.1 0.2	3.09 0.02
0.20	12.6 0.2	2.80 0.08

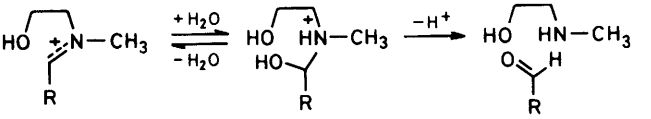
[a] Adjusted with sodium perchlorate. [b] In 0.010 mol dm^{-3} perchloric acid at 283.2 K.

azomethine carbon. A similar stabilization has been observed in the oxocarbenium ion intermediates of the acetal hydrolysis.[1,12]

In summary, all the experimental observations indicated above appear to be consistent with the rate-limiting protonation of the ring oxygen concerted with cleavage of the CO bond. Proton transfer may occur between oxonium ion and the oxygen atom of the unprotonated substrate, or between the nitrogen and oxygen atoms of the protonated substrate through one or more water molecules. These two mechanistic possibilities cannot be distinguished by the present data.

Tables 2 and 3 record the kinetic data for the decomposition of the acyclic Schiff's base (I) and the Schiff's base intermediates formed from the oxazolidines considered above. Entropies of activation, solvent deuterium isotope effects, and salt effects obtained for the acyclic model compound (I) closely resemble those observed for the intermediate derived from the correspondingly substituted oxazolidine. These findings and the similar pH–rate profiles (Figure 2) indicate that both compounds are cleaved by the same pathway. Most probably the mechanism established earlier [5] for the hydrolysis of Schiff's bases in acidic solutions is followed. As depicted in Scheme 2, rapid initial addition of water on the azomethine carbon of the cationic Schiff's base gives a carbinolamine, which subsequently undergoes rate-limiting heterolysis to an amino-alcohol and a carbonyl compound. Since base catalysis is needed to remove the proton from the hydroxy-group of the carbinolamine, the hydrolysis shows an inverse dependence of rate on acidity. The negative entropies of activation are expected. For comparison, the $\Delta S^{\ddagger}$ value for the hydrolysis of 4-methylbenzylidene-1,1-dimethylethylamine is -87 J K^{-1} mol^{-1} under conditions where the decomposition of the carbinolamine is rate limiting.[13] Negative salt effects are consistent with the fact that charged reactants, *i.e.* cationic substrate and hydroxide ion, produce neutral products, aldehyde and amino-alcohol.[6] The observed solvent isotope effect of 3—4 is understandable on the basis of this mechanism as well. The influence of the isotopic nature of the solvent water on the pre-equilibrium addition of water is presumably small, while the abstraction of the proton from the carbinolamine probably exhibits marked retardation in D_2O.

In summary, the hydrolysis of 2-alkyl-3-methyl-1,3-oxazolidines proceeds by formation of an acyclic cationic Schiff's base in a rapid initial stage. Protonation of the ring oxygen concerted with the CO bond cleavage is the most attractive mechanistic possibility for this partial reaction. The breakdown of the intermediate probably occurs with pre-equilibrium formation of a carbinolamine, which in the rate-limiting stage produces 2-methylaminoethanol and the corresponding aldehyde.



Scheme 2.

Experimental

Materials.—2-Alkyl-3-methyl-1,3-oxazolidines were prepared by mixing equal amounts of the appropriate aldehyde and 2-methylaminoethanol in benzene and then removing water by azeotropic distillation.[14] The products exhibited b.p.s consistent with those reported in literature.[14] The cationic Schiff's base (I) derived from isobutyraldehyde and 2-methoxyethylmethylamine was synthesized as its trifluoromethanesulphonate salt by the method described previously [4] for the corresponding derivative of 4-methylacetophenone. The ^{13}C n.m.r. spectrum of the product revealed the presence of two geometric isomers in the proportion of 2 : 3. The more stable isomer exhibited signals at δ ($CDCl_3$) 18.08 [$CH(CH_3)_2$], 31.21 (NCH_3), 40.53 [$CH(CH_3)_2$], 58.93 (OCH_3), 62.94 (NCH_2), 67.42 (OCH_2), and 110.18 p.p.m. (N=CH). The corresponding signals for the less stable isomer were observed at δ 18.40, 31.53, 48.61, 59.04, 54.92, 67.27, and 131.48 p.p.m., respectively.

Kinetic Measurements.—The progress of the hydrolyses was followed spectrophotometrically at 195 and 284 nm, the former wavelength referring to the protonated starting material and the cationic Schiff's base and the latter to the aldehyde formed as the final product. The measurements were performed in stoppered cells on a Cary 17D spectrophotometer. The temperature of the cell housing compartment was kept constant within 0.05 K by water circulating from a thermostatted bath and controlled from the cell with a thermistor. The first-order rate constants were calculated by the method of Guggenheim. The rate constants obtained for the disappearance of the cationic Schiff's base agreed within the limits of experimental error with those for the appearance of the aldehyde.

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