Iminium-Ion Formation and Deuterium Exchange by Acetone in the Presence of Pyrrolidine, Pyrazolidine, Isoxazolidine, and Their Acyclic Analogues[1]

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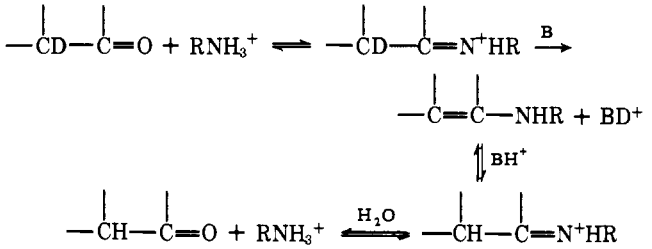
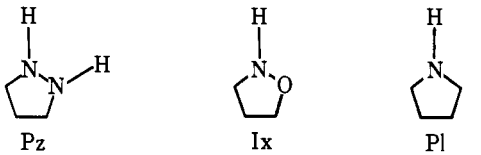
Abstract: Equilibrium constants for iminium-ion formation in the reaction of acetone in aqueous solution at 35 °C with pyrazolidinium, isoxazolidinium, *O,N*-dimethylhydroxylammonium, and *N,N'*-dimethylhydrazinium ions were found to be 9.33, 8.96, 0.117, and 0.057 M^{-1}, respectively. The kinetics of hydrolysis of the iminium ions were studied in every case except that of the *N*-isopropylidene-*O,N*-dimethylhydroxylammonium ion, whose hydrolysis is too fast to follow by the techniques used with the other iminium ions. The rate of hydrolysis of the *N*-isopropylidenepyrazolidinium ion is independent of the pH from about pH 3 to 6; it is hydrogen ion catalyzed at lower pHs and hydroxide ion catalyzed at higher pHs. The rate of hydrolysis of *N*-isopropylidenisoxazolidinium ions is pH independent from pH 0.5 to about 2, increases until about pH 4, remains pH independent until pH 6.5, and has become too fast to measure above pH 8. Both reactions are general base catalyzed in all the buffers studied. A mechanism is described to fit the kinetics of each of these reactions. The dedeuteration of acetone-d_6 was studied in pyridine buffers in the presence of each of the four hydrazine and hydroxylamine derivatives and also in the presence of the dimethylammonium and pyrrolidinium ion (which was also studied in 3-dimethylaminopropionitrile buffers). All six of these secondary ammonium ions catalyze the dedeuteration by transforming the acetone-d_6 to an iminium ion that is dedeuterated by pyridine more rapidly than the ketone is. The iminium-ion formation is a relatively rapid equilibrium in all cases except that of pyrrolidinium ions, where the intermediate iminium ion loses deuterium and hydrolyzes at comparable rates, and possibly the case of dimethylammonium ions, where the amount of catalysis via iminium-ion formation is too small to reveal mechanistic details. The effect of structure on the efficiency of catalysis of dedeuteration via iminium-ion formation is discussed.

Previous papers in this series[2] have dealt with catalysis of α-dedeuteration of aldehydes and ketones by primary amine salts that transform them to iminium ions whose α-deuterium atoms are more acidic than those of the original carbonyl compound (Scheme I). An analogous mechanism may be written for salts of secondary amines. In such a case the iminium double bond would have an additional hydrocarbon substituent, which might have a stabilizing effect, as such substituents do with carbon–carbon and carbon–oxygen double bonds.[3] Another possible way to facilitate iminium-ion formation by stabilizing the iminium ion would be to use the α effect. Hydrazine and hydroxylamine react with aldehydes and ketones to give carbon-double-bond-nitrogen products with much larger equilibrium constants than simple primary amines do.[4] However, dedeuteration of carbonyl compounds in the presence of such catalysts would be hampered by the tendency of most of the limiting reagent to be tied up as oxime or hydrazone (nonproductive binding). For this reason we decided to study hydrazine and hydroxylamine derivatives containing secondary but not primary nitrogen atoms. In view of the particular rapidity of iminium-ion formation from acetone and pyrrolidine,[5] where the carbon–nitrogen double bond is exo to a five-membered ring, we chose pyrazolidine (Pz) and isoxazolidine (Ix) as possible catalysts. For comparison purposes, pyrrolidine (Pl) and the acyclic analogues *N,N'*-dimethylhydrazine, *O,N*-dimethylhydroxylamine, and dimethylamine were also studied. Both iminium-ion formation and catalysis of dedeuteration were investigated. An earlier

Scheme I



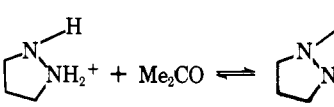


MeNHNHMe MeNHOMe Me_2NH

study of the dedeuteration of isobutyraldehyde-*2-d* in the presence of dimethylamine, piperidine, piperazine, and morpholine revealed no detectable amount of dedeuteration via intermediate iminium ions.[6] This has been attributed to steric effects that should be much smaller with acetone than isobutyraldehyde. In at least some other cases, including decarboxylation of β-keto acids[7-9] and dealdolization of β-hydroxy ketones,[10-12] where iminium ions are intermediates, secondary amines have been found to be catalysts, although poorer ones than closely related primary amines.

Results

Equilibrium in Iminium-Ion Formation. When acetone is added to aqueous pyrazolidine buffers, the pH increases, the absorption maximum of acetone at 265 nm is replaced by a stronger new maximum at 235 nm, and the ^1H NMR spectrum shows peaks attributable to the *N*-isopropylidenepyrazolidinium ion (**1**). From concentrated solutions **1** was isolated as



(1)

1

its perchlorate. We also isolated isopropylidene derivatives of isoxazolidinium, *N,N'*-dimethylhydrazinium, and *O,N*-dimethylhydroxylammonium ions, all as perchlorates.

Equilibrium constants for iminium-ion formation in the reactions of acetone with isoxazolidinium ions and *O,N*-dimethylhydroxylammonium ions were determined by UV measurements in dilute aqueous solution, as described in more detail in the Experimental Section and Appendix. The *K* value

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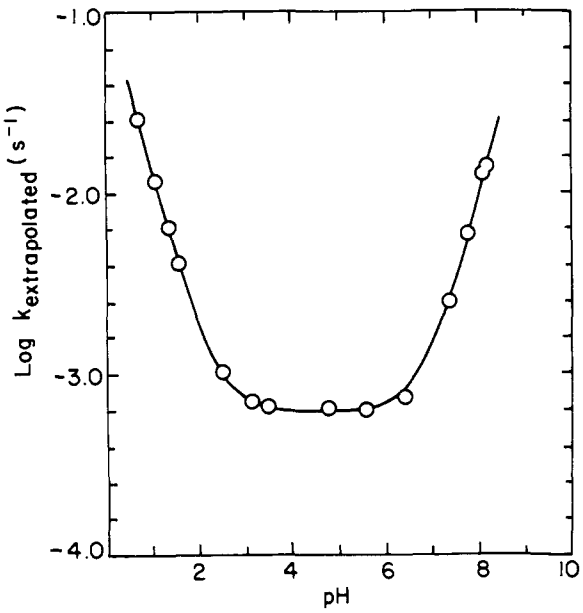

Figure 1. Log k for hydrolysis of *N*-isopropylidenepyrazolidinium ions in water at 35 °C and zero buffer concentration vs. pH.

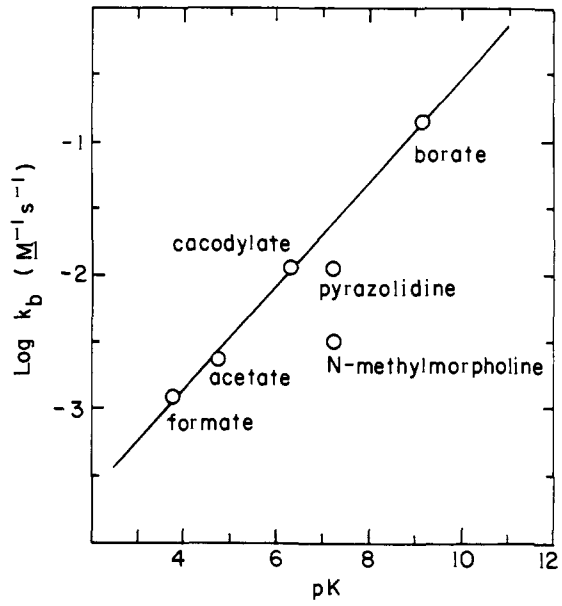

Figure 2. Brønsted plot for general base catalysis of hydrolysis of *N*-isopropylidenepyrazolidinium ions in water at 35 °C.

Table I. Equilibrium Constants for Iminium-Ion Formation from Acetone and $R_2NH_2^+$ Ions in Water[a]

$R_2NH_2^+$	K, M^{-1}	σ,[b] M^{-1}	pK_a
IxH^+	8.96[c,d]	0.36	4.73
$MeONH_2Me^+$	0.117[c,e]	0.005	4.48
	0.11[f]		
PzH^+	9.33[g]	0.57	7.25
$MeNHNH_2Me^+$	0.057[f]		7.32

[a] At 35 °C unless otherwise noted. [b] Estimated standard deviations.[13] [c] From UV measurements. [d] $\epsilon_{Im} = 0.22\ M^{-1}\ cm^{-1}$; $\sigma = 0.22\ M^{-1}\ cm^{-1}$. [e] ϵ_{Im} assumed to be zero. [f] From NMR measurements using acetone-d_6 at 33 °C in concentrated solutions extrapolated to dilute solution in deuterium oxide. [g] From the kinetics of the forward and reverse reactions.

Table II. Catalysis Constants for Hydrolysis of *N*-Isopropylidenepyrazolidinium Ions[a]

catalyst	10^3k, $M^{-1}\ s^{-1}$	$10^3\sigma$,[b] $M^{-1}\ s^{-1}$
HCO_2^-	1.2	0.7
AcO^-	2.4	0.4
$Me_2AsO_2^-$	11.4	0.5
pyrazolidine	10.2	4.3
N-methylmorpholine	2.5	1.2
borate ion	147	38
OH^-	2 740 000	84 000
H^+	93.5	2.7
none	0.64[c]	0.02[c]

[a] In water at 35 °C. [b] Estimated standard deviations. [c] This is the k_w value, whose dimensions are s^{-1}.

for reaction of *N,N'*-dimethylhydrazinium ions was too small to be determined reliably by UV measurements in aqueous solution.

Equilibrium constants for iminium-ion formation in the reactions of *N,N'*-dimethylhydrazinium ions and *O,N*-dimethylhydroxylammonium ions with acetone were determined by NMR measurements. To avoid interference from the peaks for ordinary water and acetone, deuterium oxide and acetone-d_6 were used. In order to get large enough concentrations of iminium ions for reliable measurements, reactant concentrations had to be so high that the solutions could not be considered just aqueous solutions. Therefore the results, which are listed in the Appendix, were extrapolated to pure deuterium oxide solution by plotting K and log K against the molar concentration of deuterium oxide, the mole fraction of deuterium oxide, and the percentage deuterium oxide by weight. For *N,N'*-dimethylhydrazinium ions the highest correlation coefficient was obtained in the plot of K vs. mole fraction deuterium oxide. For *O,N*-dimethylhydroxylammonium ions the best plot was of log K vs. mole fraction deuterium oxide. The resulting K values are listed in Table I.

Kinetics of Iminium-Ion Formation and Hydrolysis. The equilibrium constant for iminium-ion formation from acetone and pyrazolidinium ions in aqueous solution is such that the reaction can be studied in both directions. Addition of about 10^{-4} M *N*-isopropylidenepyrazolidinium perchlorate to water is followed by essentially complete hydrolysis, the absorbance at 235 nm dropping to about 1% of its initial value. Using various buffers, 36 runs were made over the pH range 0.7–9.0. For each set of runs at a given pH using a given buffer a plot of k_{obsd} vs. the buffer concentration gave a satisfactory straight line. Rate constants extrapolated to zero buffer concentration plus those obtained below pH 2, where only hydrochloric acid was present to control the pH, are plotted logarithmically against the pH in Figure 1. Assumption of general acid and base catalysis and least-squares treatment of the data gave small negative constants for the general acids. The 36 values of k_{obsd} were therefore fit to the equation

$$k_{obsd} = k_w + k_H[H^+] + \sum_i k_{b_i}[B_i] \qquad (2)$$

in which general acid catalysis is neglected. The rate constants and standard deviations obtained are listed in Table II. The values for k_w, k_H, and k_{OH} were used to draw the line in Figure 1. The other values, plus one for the base pyrazolidine obtained from the kinetics of the iminium-ion-forming reaction, are plotted against the pK values for the conjugate acids of the bases involved in Figure 2. The least-squares line through the four points for oxygen bases has a slope and intercept of 0.39 and −4.4, respectively.

Addition of around 10^{-3} M acetone to 0.05–0.1 M solutions of pyrazolidinium perchlorate is followed by an increase in absorbance at 235 nm that provided a basis for studying the kinetics of the imination reaction:

$$\mathrm{Ac} + \mathrm{PzH}^+ \underset{k_d}{\overset{k_f}{\rightleftharpoons}} \mathrm{Im}^+ + \mathrm{H_2O} \qquad (3)$$

Because the concentration of pyrazolidinium ions (PzH^+) changes only very little during the reaction, in the rate equation

$$d[\mathrm{Im}^+]/dt = k_f[\mathrm{PzH}^+][\mathrm{Ac}] - k_d[\mathrm{Im}^+] \qquad (4)$$

the product $k_f[PzH^+]$ may be treated as a first-order rate constant. The observed first-order rate constants for the reversible reaction will then be equal to the sum $k_f[PzH^+] + k_d$ of the first-order rate constants for the forward and reverse reaction:

$$k_{obsd} = k_f[\mathrm{PzH}^+] + k_d \qquad (5)$$

The equilibrium constant K is equal to k_f/k_d; hence, k_f in eq 5 may be replaced by Kk_d. The concentration of pyrazolidinium ions may be expressed in terms of $[Pz]_t$, the total concentration of pyrazolidine in all states of protonation. These two substitutions give

$$k_{obsd} = \left(\frac{K[\mathrm{Pz}]_t[\mathrm{H}^+]}{K_{PzH} + [\mathrm{H}^+]} + 1\right)k_d \qquad (6)$$

in which K_{PzH} is the acidity constant for pyrazolidinium ions.

Over the pH range 0.76–8.56, 29 kinetic runs were made with the pH being controlled by the presence of hydrochloric acid, an acetate buffer, or a pyrazolidine–pyrazolidinium buffer. In applying eq 6 to these data it should be noted that k_d is the rate constant for the iminium-ion hydrolysis reaction, which we had already studied kinetically. Hence k_d may be calculated except for the contribution of general base catalysis by pyrazolidine. If k_{pz} is the catalysis constant for pyrazolidine and k_d' is defined as $k_d - k_{pz}[Pz]$, eq 6 may be rewritten as

$$k_{obsd} = \left(\frac{K[\mathrm{Pz}]_t[\mathrm{H}^+]}{K_{PzH} + [\mathrm{H}^+]} + 1\right)\left(k_d' + k_{pz}[\mathrm{Pz}]\right) \qquad (7)$$

This equation contains two unknowns, K and k_{pz}, whose values (and standard deviations) were found by a least-squares treatment to be 9.33 (0.57) M^{-1} and 0.010 (0.004) M^{-1} s^{-1}, respectively.

The kinetics of hydrolysis of *N*-isopropylidenisoxazolidinium ions were followed by spectrophotometric measurements of the concentration of acetone formed. Initial concentrations of 10^{-3} M were used, which should cause the reaction to go to about 99% completion at equilibrium. The acidity was controlled by added hydrochloric acid up to pH 2.5. Above this pH formate, acetate, and cacodylate buffers were used, with two different buffer concentrations used for each buffer ratio. Rate constants extrapolated to zero buffer concentration are plotted logarithmically vs. pH in Figure 3 over the pH range 0–7. In borate buffers, above pH 8, the reaction was too fast to follow. We did not obtain very reliable catalysis constants for the buffers because most of the rate was independent of the buffer concentration and because only two concentrations per buffer ratio were studied. However, we did calculate catalysis constants (standard deviations) of 0.03 (0.03), 0.03 (0.02), and 0.05 (0.02) M^{-1} s^{-1} for formate, acetate, and cacodylate ions, respectively, assuming that the reaction is general base catalyzed. The assumption of general acid catalysis gave *much* larger standard deviations in the catalysis constants obtained.

Studies made on the reaction of *N,N'*-dimethylhydrazinium ions with acetone and on the hydrolysis of the resulting iminium ion showed that establishment of equilibrium was accompanied by a slower side reaction that produced strong absorbance in the ultraviolet. This made it impossible for us to get very reliable kinetic data. However, we did make some rather crude studies in which the absorbance at 240 nm was followed after enough acetone to give a concentration of 0.03 M was added to four dimethylhydrazinium chloride solutions. From the equilibrium constant obtained by NMR measurements, the acetone concentration may be shown to change by less than 2% in any run. Hence, the observed first-order rate constants are equal to the sum $k_f[Ac] + k_d$ (cf. eq 5). From the K value (which is k_f/k_d) of 0.057 M^{-1}, it follows that k_d constitutes more than 99% of k_{obsd}. The four k_{obsd} values obtained with 0.01, 0.15, 0.20, and 0.25 M dimethylhydrazinium chloride were all in the range 0.010–0.015 s^{-1}. The products giving rise to the extraneous UV absorption were not formed in amounts large enough to be seen in the ^1H NMR spectra.

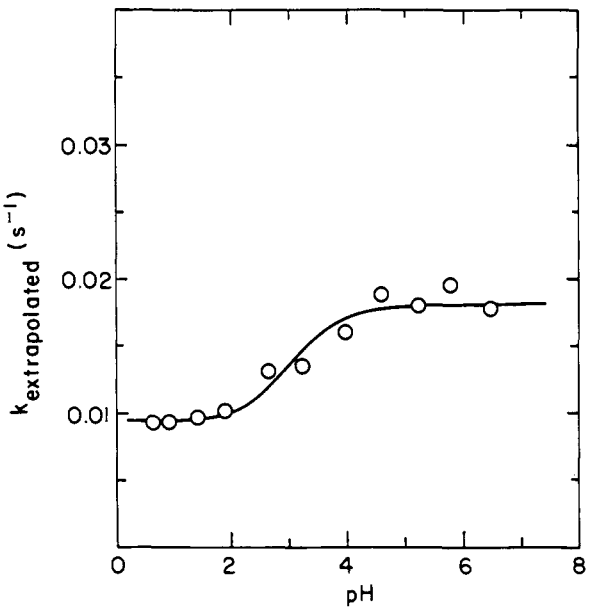

Figure 3. Log k for hydrolysis of *N*-isopropylidenisoxazolidinium ions in water at 35 °C and zero buffer concentration vs. pH.

Injection of acetonitrile solutions of *N*-isopropylidene-*O,N*-dimethylhydroxylammonium perchlorate into water followed by UV measurements at 275 nm showed that equilibrium was already essentially established when the first measurement was made after 14 s. The reaction is therefore too fast to follow by standard techniques.

Kinetics of Dedeuteration of Acetone-d_6. The dedeuteration of acetone-d_6 in the presence of secondary amine salts was interpreted in terms of Scheme II, which is analogous to that used before for primary amine salts.[2] According to this scheme, k_6, the first-order rate constant for disappearance of acetone-d_6, may be expressed as

$$k_6 = k_p + k_{im}k_e/(k_e + k_d) \qquad (8)$$

The fraction of acetone-d_5 present at any given time (f_5) may be expressed as

$$f_5 = [6(f_6)_0 + (f_5)_0]e^{-(1-q/6)k_6t} - 6(f_6)_0e^{-k_6t} \qquad (9)$$

Scheme II

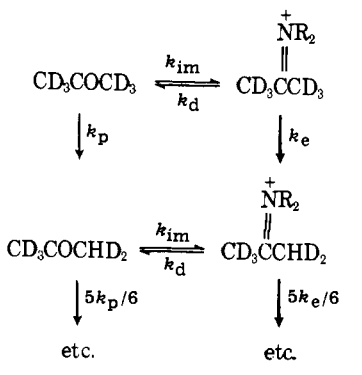

Table III. Acetone-d_6 Dedeuteration in the Presence of Pyrrolidinium Ions and 3-Dimethylaminopropionitrile Buffers[a]

pH	$[PlH^+]_t$,[b] M	$[DPN]_t$,[c] M	μ[d]	10^6k_6 (σ),[e] s^{-1}	q (σ)[e]
6.325	0.1998	0.2007	0.360	2.17 (0.17)	0.41 (0.03)
6.400	0.2007	0.2009	0.361	2.43 (0.15)	0.46 (0.06)
7.075	0.1997	0.2005	0.290	8.92 (0.29)	0.43 (0.03)
7.080	0.1997	0.2009	0.290	9.80 (0.23)	0.41 (0.02)
7.920	0.2016	0.2012	0.216	35.1 (1.8)	0.60 (0.05)
8.045	0.2019	0.2008	0.216	32.1 (1.6)	0.60 (0.05)

[a] Using 0.52 M acetone-d_6 in water at 35 °C. [b] Total pyrrolidinium chloride. [c] Total 3-dimethylaminopropionitrile. [d] Ionic strength. [e] Estimated standard deviation.

Table IV. Acetone-d_6 Dedeuteration in the Presence of $R_2NH_2^+$ and 1:1 Pyridine Buffers[a]

pH	$[R_2NH_2^+]$, M	$R_2NH_2^+$	10^7k_{6obsd}[b] (σ), s^{-1}	q (σ)[c]
5.060	0	none	5.04 (0.30)	0.88 (0.06)
5.080	0	none	5.08 (0.09)	0.94 (0.02)
5.055	0.0957	$Me_2NH_2^+$	5.67 (0.10)	0.93 (0.02)
5.060	0.0956	$Me_2NH_2^+$	5.65 (0.12)	0.91 (0.02)
5.040	0.0964	PlH^+ [d]	25.2 (0.6)	0.66 (0.03)
5.060	0.1000	PlH^+	26.5 (0.5)	0.65 (0.05)
5.060	0.0962	$MeNHNH_2Me^+$	57.6 (0.6)	0.96 (0.01)
5.060	0.0967	$MeNHNH_2Me^+$	57.1 (0.8)	0.96 (0.01)
5.090	0.0962	PzH^+ [e]	281 (8)	0.92 (0.03)
5.020	0.0963	PzH^+	280 (6)	0.92 (0.03)

[a] Using 0.52 M acetone-d_6 in water at 35 °C with a total pyridine concentration in the range 0.3858 ± 0.0034 and an ionic strength (NaCl) of 0.30. [b] This is the "observed" value of k_6, not corrected for the fraction of acetone present as iminium ion, a correction that is necessary for the runs in which pyrazolidine was present. [c] Estimated standard deviations. [d] Pyrrolidinium. [e] Pyrazolidinium.

where the subscript zeroes refer to the fractions at zero time and q is defined by eq 10. The change in f_6, the fraction of acetone-d_6 in the acetone, with time gives the value of k_6. The only unknown in eq 9 is then q, for which a value is determined by least squares in each run.

$$q = \frac{5(k_e/k_d)(k_p/k_6) + 6}{5(k_e/k_d) + 6} \quad (10)$$

Values of k_6 and q obtained using pyrrolidinium ions and 3-dimethylaminopropionitrile buffers are listed in Table III. Under these conditions only a negligible amount of free pyrrolidine is present. Similarly, only a negligible amount of any free amine except pyridine is present in any of the runs listed in Table IV, where 1:1 pyridine buffers were used with pyrrolidinium, dimethylammonium, pyrazolidinium, or *N,N'*-dimethylhydrazinium ions added. A similar pH was used for the runs shown in Table V, where pyridine buffers were also present, but at this pH a significant fraction of the isoxazolidinium or *O,N*-dimethylammonium ions also added exist in the free amine form.

Only in the runs using pyrazolidinium and isoxazolidinium salts was a substantial fraction of the acetone transformed to iminium ions. This transformation could have disturbed the first-order character of the reaction if the imine formation had not been so much faster than the dedeuteration reaction. (In each run the first-order rate constant for approach to equilibrium in imination was at least 40 times as large as k_6.) In Table VI are listed the equilibrium concentrations of iminium ions and the true or corrected values of k_6 for the runs described in Tables IV and V in which pyrazolidinium or isoxazolidinium ions were present. The corrected k_6 values are obtained by dividing the observed values by the fraction of the acetone-d_6 that was present in that form rather than in the iminium-ion form. The iminium-ion concentrations were calculated from the equilibrium constants in Table I.

Discussion

Iminium-Ion Formation and Hydrolysis. From the equilibrium constant for the formation of acetoxime and the acidity constants of hydroxylammonium and *N*-isopropylidenehydroxylammonium ions[5] a value of 29 M^{-1} may be calculated for K. The K value 0.117 M^{-1} for *O,N*-dimethylhydroxylammonium ions listed in Table I shows that the two added methyl groups *destabilize* the iminium ion relative to the ammonium ion. Steric repulsions between these methyl groups and the carbon-bound methyl groups in the iminium ion almost undoubtedly play a major role in this destabilization. The oxygen atom and nitrogen-bound carbon atom in isoxazolidine are held away from the reaction center by the five-membered ring, so that decreased steric repulsions in the iminium ion would be expected. The importance of conformational restrictions produced by the five-membered ring[14] on the ease of changing the hybridization of the nitrogen atom from sp^3 to sp^2 is harder to assess. The extra hydrogen atom in *N,N'*-dimethylhydrazinium ions (relative to *O,N*-dimethylhydroxylammonium ions) might make steric repulsions in the iminium ion slightly larger. This is a possible explanation for why five-membered ring formation in the hydrazine series (to give pyrazolidine) increases K somewhat more than it does in the hydroxylamine series.

By analogy to the work of Sayer and co-workers on the reactions of methoxylamine with acetone and benzaldehydes,[15,16] we propose Scheme III for the hydrolysis of the *N*-isopropylidenisoxazolidinium ion. Assumption that steps 12 and 15 are rapid equilibria leads to eq 16 for the observed first-order rate

Table V. Acetone-d_6 Dedeuteration in the Presence of Pyridine, Isoxazolidine, and *O,N*-Dimethylhydroxylamine Buffers[a]

pH	$[Py]_t$,[b] M	$[RNHOR]_{total}$, M	RNHOR	10^6k_{6obsd}[c] (σ),[d] s^{-1}	q (σ)[d]
5.00	0.3868	0.0968	Ix[e]	13.3 (0.2)	0.98 (0.02)
5.25	0.3855	0.0968	Ix	14.4 (0.4)	0.98 (0.03)
5.23	0.3809	0.1922	Ix	34.0 (0.6)	0.98 (0.02)
5.56	0.3913	0.1936	Ix	39.5 (0.8)	0.99 (0.02)
5.12	0.3844	0.1937	Ix	32.5 (0.6)	0.97 (0.02)
5.00	0	0.1922	Ix	8.23 (0.19)	0.97 (0.02)
5.86	0	0.1866	Ix	9.83 (0.30)	0.98 (0.03)
5.28	0.3856	0.1912	MeNHOMe	66.1 (0.3)	1.01 (0.03)
5.03	0.3846	0.2868	MeNHOMe	146 (3)	1.00 (0.02)
4.11	0	0.1912	MeNHOMe	23.1 (0.3)	0.98 (0.02)
4.95	0	0.2860	MeNHOMe	60.8 (1.5)	0.99 (0.02)

[a] Using 0.52 M acetone-d_6 in water at 35 °C and ionic strength (NaCl) 0.30. [b] Total pyridine concentration. [c] This is the "observed" value of k_6, not corrected for the fraction of acetone present as iminium ions, a correction that is necessary only for the runs in which isoxazolidine was present. [d] Estimated standard deviation. [e] Isoxazolidine.

Table VI. Iminium-Ion Concentrations and Corrected k_6 Values for Runs Using Pyrazolidinium or Isoxazolidinium Ions

pH[a]	$[Im^+]_{eq}$,[b] M	10^6k_6,[b] s^{-1}
5.09[c]	0.0774	33.0
5.02[c]	0.0775	32.9
5.00[d]	0.0574	15.0
5.25[d]	0.0511	16.0
5.23[d]	0.0940	41.5
5.56[d]	0.0689	45.5
5.12[d]	0.1054	40.8
5.00[d,e]	0.1132	10.5
5.86[d,e]	0.0477	10.8

[a] pH is listed to identify the run from Table IV or V. [b] Calculated as described in the text. [c] Pyrazolidine used in this run. [d] Isoxazolidine used in this run. [e] No pyridine buffer used.

Scheme III

$$R_2C{=}NR_2^+ + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_2\overset{OH}{\overset{|}{C}}NR_2 + H^+ \qquad (11)$$

$$R_2\overset{OH}{\overset{|}{C}}NHR_2^+ \overset{K_a}{\rightleftharpoons} R_2\overset{OH}{\overset{|}{C}}NR_2 + H^+ \qquad (12)$$

$$R_2\overset{OH}{\overset{|}{C}}NHR_2^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R_2CO + R_2NH + H^+ \qquad (13)$$

$$R_2\overset{OH}{\overset{|}{C}}NR_2 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} R_2\overset{O^-}{\overset{|}{C}}NHR_2^+ \qquad (14)$$

$$R_2\overset{O^-}{\overset{|}{C}}NHR_2^+ \overset{fast}{\rightleftharpoons} R_2CO + R_2NH \qquad (15)$$

constant for hydrolysis of our iminium ion. Nonlinear least-squares treatment[13] of our data gives a k_1 value of 0.0181 (0.0006) s^{-1}, a k_3K_a/k_2 value of 2.19 (0.78) $\times 10^{-3}$ M, and a $k_{-1}K_a/k_2$ value of 0.905 (0.081), where the parenthesized values are standard deviations. These values were used to draw the line in Figure 3.

$$k_{obsd} = \frac{k_1[H^+] + k_1k_3K_a/k_2}{(1 + k_{-1}K_a/k_2)[H^+] + k_3K_a/k_2} \qquad (16)$$

To explain our data on the hydrolysis of *N*-isopropylidenepyrazolidinium ions we added to Scheme III the steps shown in Scheme IV. With the rate-controlling steps being (19) below pH 2, (13) from pH 3 to 6, and (17) above pH 7, the rate constants in Table II correspond to values of 6.4×10^{-4} s^{-1}, 2740 M^{-1} s^{-1}, and 0.0935 M^{-1} s^{-1} for k_1, k_h, and k_a/K_{a2}, respectively. Arguments for the plausibility of the proposed mechanisms are given in the Appendix.[28]

Structural Effects on Reactivity. When the dedeuteration of acetone-d_6 in pyridine buffers was studied in the presence of pyrazolidinium and isoxazolidinium ions and their acyclic analogues, the rate of establishment of the iminium-ion equilibrium was faster than the subsequent removal of deuterium from the iminium ion. Thus the dedeuteration step was fairly cleanly rate controlling and the rate constant for dedeuteration via iminium-ion formation is Kk_n, where K is the equilibrium constant for iminium-ion formation and k_n is the rate constant for removal of deuterium from the iminium ion by pyridine. With pyrrolidinium ions hydrolysis of the iminium ion back to acetone was comparable in rate to the dedeuteration step, which was therefore not cleanly rate controlling. Although the product Kk_n is then larger than the rate constant for deuteration via iminium-ion formation, it is just as good a measure

Table VII. Kinetic Results in $R_2NH_2^+$ Catalysis of the Dedeuteration of Acetone-d_6[a]

$R_2NH_2^+$	10^5k_{amh},[b] M^{-1} s^{-1}	10^5Kk_n,[c] M^{-2} s^{-1}	10^5k_n,[c] M^{-1} s^{-1}	pK_a
pyrazolidinium	600	1100	120	7.25
$MeNHNH_2Me^+$	~70	31	540	7.32
isoxazolidinium	16 000	540	60	4.73
$MeONH_2Me^+$		830	7100	4.48
pyrrolidinium	3.7	21		10.99
$Me_2NH_2^+$	>0.03	>0.3		10.49

[a] In water at 35 °C and about pH 5. [b] Second-order rate constant for iminium-ion formation from ketone and $R_2NH_2^+$. [c] K is the equilibrium constant for iminium-ion formation and k_n is the rate constant for removal of deuterium from that iminium ion by pyridine.

Scheme IV

$$RNHN{=}CR_2 + OH^- \underset{}{\overset{k_h}{\rightleftharpoons}} RNHN{-}CR_2 \qquad (17)$$

$$RNH_2N{=}CR_2 \overset{K_{a2}}{\rightleftharpoons} RNHN{=}CR_2 + H^+ \qquad (18)$$

$$RNH_2N{=}CR_2 + H_2O \overset{k_a}{\rightleftharpoons} RNH_2N{-}CR_2 + H^+ \qquad (19)$$

$$RNH_2NH{-}CR_2 \rightleftharpoons RNH_2NHR + R_2CO + H^+ \qquad (20)$$

of the stability of the transition state for removal of deuterium from the iminium ion by pyridine as it is in the case of the hydrazinium and hydroxylammonium ions. Therefore values of Kk_n as well as k_n, pK_a, and k_{amh}, the rate constant for iminium-ion formation from acetone and $R_2NH_2^+$, were calculated as described in detail in the Appendix and are listed in Table VII. The data obtained for dimethylammonium ions gave only lower limits for k_{amh} and Kk_n.

The k_{amh} value for the pyrrolidinium ion is smaller than those for its α-oxa and α-aza derivatives, but the latter two ions are much more acidic and it is known that k_{amh} values tend to increase with increasing acidity in the reaction of primary ammonium ions of the type $RCH_2NH_3^+$ with isobutyraldehyde[17] (see Appendix). The increases in k_{amh} in Table VII are not necessarily larger than would be expected from the increases in acidity and therefore there is no evidence for an α effect on k_{amh}.

The k_n values show that all the iminium ions are more reactive toward pyridine than acetone is. The extra reactivities range from 230-fold for the iminium ion derived from isoxazolidinium ions to 27 000-fold for the iminium ions derived from *O,N*-dimethylhydroxylammonium ions. None of these figures is as large as the 40 000-fold extra reactivity that was estimated for the *N*-methyliminium ions of acetone,[18] even though the hydrazine and hydroxylamine derivatives, being less basic than methylamine, would be expected to give *more* reactive iminium ions if simple polar effects were the only significant factor. We believe that the same ability of alkoxy and amino substituents to stabilize the carbon–nitrogen double bond that makes the equilibrium constants for iminium-ion formation particularly large decreases the reactivity in processes in which the carbon–nitrogen double bond is lost. When the iminium carbon–nitrogen double bond is stabilized by being exocyclic to a five-membered ring, as it is in the case of the iminium ions derived from isoxazolidinium and pyrazolidinium ions, the reactivity falls even farther short of that which

would be expected if only simple polar effects were operating.

The pyrazolidinium ion is the best catalyst for deuterium exchange of the species studied, as measured by Kk_n, and, although its Kk_n values are only slightly larger than those for the two hydroxylammonium ion derivatives, the greater basicity of pyrazolidine makes its conjugate acid the predominant form over a wider pH range than in the case of the hydroxylamine derivatives. This means that catalysis via iminium-ion formation can be brought about in more basic solutions, where stronger bases, for example, can exist in large enough quantities for cocatalysis.

Experimental Section

The iminium salts were prepared by a method similar to that of Leonard and Paukstelis.[19] *Caution.* The structures of these compounds suggest that they may be dangerous explosives. We handled them with care, never heating them above 50 °C, all heating being done behind safety shields, trying to avoid mechanical shocks, etc.

***N*-Isopropylidenepyrazolidinium Perchlorate (1).** Preparation of pyrazolidine from hydrazine and 1,3-dibromopropane[20] gave mixtures of reactant, product, 1,5-diazabicyclo[3.3.0]octane, and other by-products from which we found it very difficult to separate pure product. We therefore obtained pyrazolidine by hydrolyzing its *N,N'*-diisobutyryl derivative, which was prepared from *N,N'*-diisobutyrylhydrazine, 1,3-dibromopropane, and potassium ethoxide.[21] Its perchlorate melted at 181–183 °C after two recrystallizations from ethanol–tetrahydrofuran. After a mixture of 3.7 mL of acetone and 0.5 mL of 10 M aqueous pyrazolidinium perchlorate had stood for 1 h, 5 mL of tetrahydrofuran was added and the sample put in a freezer. Several hours later a 70% yield of **1**[22] was collected on a filter as white needles: mp, after recrystallization from 1:1 ethanol–tetrahydrofuran, 139–140 °C; NMR (CD_3CN) δ 6.0 (br s, 1, NH), 4.25 (br t, J = 7 Hz, 2, CH_2N^+), 3.2 (t, J = 7 Hz, 2, CH_2NH), 2.05 (2 s, 6, CH_3), and 2.0 (quintet, J = 7 Hz, CCH_2C); NMR (CD_3SOCD_3) δ 7.2 (br s, 1, NH), 4.2 (br t, J = 7 Hz, 2, CH_2N^+), 3.35 (t, J = 7 Hz, 2, CH_2NH), 2.3 (s, 6, CH_3), and 2.2 (quintet, J = 7 Hz, 2, CCH_2C).

Isoxazolidine. A solution of 11.4 g of hydroxylamine hydrochloride and 33.1 g of 1,3-dibromopropane in 250 mL of 95% ethanol was stirred at 65 °C under nitrogen while 30.4 g of potassium hydroxide in 150 mL of 95% ethanol was added over 45 min. After an additional 90 min the mixture was cooled and filtered, and the solvent removed under reduced pressure. Distillation of the residue at 36 mm gave a liquid (bp 42–72 °C) that was mixed with a saturated solution of hydrogen chloride in ether to give a white solid. Recrystallization from ethanol–tetrahydrofuran gave isoxazolidine hydrochloride, mp 124–125 °C (lit.[23] 124–125 °C). When the hydrochloride was found to be inconveniently hygroscopic the procedure was repeated using hydrogen bromide and a 30% yield was obtained of isoxazolidine hydrobromide:[22] mp 109–111 °C; NMR (D_2O) δ 4.8 (s, 2, HOD), 4.3 (t, J = 7 Hz, 2, CH_2O), 3.7 (t, J = 7 Hz, 2, CH_2N), and 2.5 (quintet, J = 7 Hz, 2, CCH_2C).

Anal. Calcd for C_3H_8NOBr: Br, 51.89. Found: Br, 51.09.

***N*-Isopropylidenisoxazolidinium Perchlorate.** Initial attempts to obtain iminium salts from isoxazolidinium bromide and fluoroborate were unsuccessful. Hence 2.5 mL of 59% isoxazolidine–41% ethanol was mixed with 3.35 mL of 6 M perchloric acid and 10 mL of tetrahydrofuran. The resulting solution was concentrated at room temperature and 0.03 mm pressure but did not crystallize. Addition of 10 mL of acetone, 1 h of standing, and removal of the solvent at reduced pressure gave a wet solid that was recrystallized from 1:1 acetone–tetrahydrofuran to give a 52% yield of *N*-isopropylidenisoxazolidinium perchlorate:[22] mp 99–100 °C; NMR (CD_3SOCD_3) δ 4.5 (t, J = 6.5 Hz, 2, CH_2O), 4.3 (t, J = 6.5 Hz, 2, CH_2N), 2.5 (quintet, J = 7 Hz, 2, CCH_2C), and 2.4 (s, 6, CH_3); NMR (CD_3CN) δ 4.3 (t, J = 7 Hz, 2, CH_2O), 4.05 (t, J = 7 Hz, 2, CH_2N), 2.35 (quintet, J = 7 Hz, 2, CCH_2C), and 2.1 (2 s, 6, CH_3).

***N*-Isopropylidene-*O,N*-dimethylhydroxylammonium Perchlorate.** Essentially the same method used for the isoxazolidine derivative gave a 65% yield of *N*-isopropylidene-*O,N*-dimethylhydroxylammonium perchlorate:[22] mp 186–188 °C; NMR (CD_3SOCD_3) δ 3.95 (s, 3, CH_3O), 3.75 (s, 3, CH_3N), and 2.45 (s, 6, CH_3C); NMR (CD_3CN) δ 4.75 (s, 3, CH_3O), 3.5 (br s, 3, CH_3N), and 2.25 (2 s, 6, CH_3C).

***N*-Isopropylidene-*N,N'*-dimethylhydrazinium Perchlorate.** Essentially the same method used for the isoxazolidine derivative gave a 41% yield of *N*-isopropylidene-*N,N'*-dimethylhydrazinium perchlorate:[22] mp 150–153 °C; NMR (CD_3SOCD_3) δ 6.6 (br, 1, NH), 3.6 (s, 3, $CH_3N{=}C$), 2.65 (d, J = 7 Hz, 3, CH_3NH), 2.5 (s, 3, CH_3C), and 2.4 (s, 3, CH_3C); NMR (CD_3CN) δ 5.3 (br quartet, J = 6 Hz, 1, NH), 3.45 (br s, 3, $CH_3N{=}C$), 2.5 (d, J = 6 Hz, 3, CH_3NH), 2.35 (s, 3, CH_3C), and 2.2 (s, 3, CH_3C).

UV Equilibrium Measurements. In a typical determination 1 mL of 1 M hydrochloric acid and an accurately measured volume of 1.005 M isoxazolidinium bromide were put in each of several 10-mL volumetric flasks, which were then filled to the mark with distilled water. A 3-mL sample from a given flask was then put in both the sample and reference cells of a Cary UV–visible spectrophotometer, Model 1605. After 20 min was allowed for thermal equilibration the spectrophotometer was zeroed and 25 μL of 3.599 M acetone was injected into the sample cell. The absorbance was measured after 30 min was allowed for chemical equilibration.

NMR Equilibrium Measurements. A Varian A-60A spectrometer and external Me_4Si in chloroform were used in all cases. Spectra were determined for the pure $R_2NH_2^+$ salt, for acetone, and for mixtures of $R_2NH_2^+$ salt with acetone and with acetone-d_6, all in D_2O, and for solutions of iminium salts in CD_3SOCD_3 or CD_3CN to which D_2O had been added.

Kinetics of Hydrolysis of Iminium Ions. In a typical run 6.0 μL of 0.05 M *N*-isopropylidenepyrazolidinium perchlorate in dry acetonitrile was injected into 3.00 mL of a buffer solution in a 1-cm quartz sample cell. The same buffer solution was in the reference cell. Twenty time–absorbance data pairs evenly spaced in absorbance were read from the chart. The rate constant was calculated by nonlinear least-squares treatment of the equation in which the absorbance is expressed as a function of the rate constant and the time. The runs were made in duplicate or triplicate. In some reactions time–voltage data pairs were transferred from the spectrophotometer via a Nicolet calculator Model 191A and a Nicolet digital oscilloscope Model 1090 to a Hewlett-Packard 9830A calculator.

In the hydrolysis of *N*-isopropylidenisoxazolidinium perchlorate 10-cm reaction cells were used in order to make the observed change in absorbance reasonably large at the low concentrations used to make the reaction essentially irreversible.

Deuterium Exchange Kinetics. The reactions were followed by extracting the acetone from the reaction solutions with chloroform and making mass-spectral measurements on the chloroform extracts, as described previously.[24] All the reactions were run under nitrogen. The pH of the solution was always within 1 pH unit of the pK_a of a buffer present in the solution. Sodium chloride was added as needed to bring the ionic strength to 0.3. Ordinarily ten points were taken per run. Attempts were made to take points at such times that the acetone-d_6 concentration would change by 10% increments between points.

pK_a Determinations. The amine salts were titrated potentiometrically with standard sodium hydroxide, in aqueous solution at 35 °C. The pH observed on the Radiometer pH meter and electrode was taken as $-\log a_{H^+}$. Activity coefficients were calculated from the Davies equation.[25] Ionic strengths during the titrations were in the range 0.02–0.10. There appear to be no literature values at 35 °C but values at 25 °C are 7.60 for pyrazolidinium ions,[26] 5.05 for isoxazolidinium ions,[26] 4.75[26] and 4.88 (μ = 1.0)[27] for *O,N*-dimethylhydroxylammonium ions, and 7.52[26] and 7.69 (μ = 1.0)[27] for *N,N'*-dimethylhydrazinium ions. Our values at 35 °C are about 0.25 lower than the dilute solution or 0.40 lower than the ionic-strength-1.0 values at 25 °C.

Supplementary Material Available: An appendix containing raw data on equilibrium in iminium-ion formation; arguments in support of the proposed mechanisms; details on the calculations of K, Kk_n, and k_{amh}; additional discussion of the effect of structure on reactivity (19 pages). Ordering information is given on any current masthead page.

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Thermochemical Identification of the Structural Factors Responsible for the Thermodynamic Instability of 3′,5′-Cyclic Nucleotides

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Abstract: The enthalpies of hydrolysis of several cyclic phosphate diesters which can be considered to be structural analogues of the trans-fused trimethylene phosphate–ribofuranoside ring system of adenosine 3′,5′-cyclic phosphate have been determined by microcalorimetric techniques using the metal-dependent phosphohydrolase from *Enterobacter aerogenes* as catalyst. At pH 7.3 and 25 °C we have obtained the following values (kcal/mol) for sodium salts: *trans*-2-hydroxytetrahydrofuranmethanol cyclic phosphate, −10.6; *trans*-2-hydroxycyclopentanemethanol cyclic phosphate, −7.9; *cis*-2-hydroxycyclopentanemethanol cyclic phosphate, −2.5; 5-methoxytrimethylene phosphate, −4.9; 5-methyltrimethylene phosphate, −3.8. From these values and those determined previously, we can make the following conclusions: (1) the trans-fused trimethylene phosphate–tetrahydrofuran structure is responsible for the 8 kcal/mol more exothermic enthalpy of hydrolysis which cyclic AMP displays relative to trimethylene phosphate; (2) about 5 kcal/mol of the excess enthalpy of hydrolysis of cyclic AMP is the result of geometric distortion due to the trans-ring fusion; (3) about 3 kcal/mol of the excess enthalpy of hydrolysis of cyclic AMP cannot be accounted for by intramolecular effects, suggesting that solvation effects play an important role in the thermodynamic stability of cyclic AMP.

3′,5′-Cyclic nucleotides, e.g., adenosine 3′,5′-cyclic monophosphate (cyclic AMP) and guanosine 3′,5′-cyclic monophosphate (cyclic GMP), are involved in the regulation of many biochemical and biological processes, including hormonal regulation of metabolism, the action of neurotransmitters at synapses, cellular differentiation and malignant transformation, and immunological processes such as the graft vs. host reaction.[3] In essentially all of these processes, the mechanism by which a cyclic nucleotide influences a biochemical reaction is apparently the same: in the case of cyclic AMP, adenylate cyclase catalyzes the formation of cyclic AMP from ATP in response to an extracellular stimulus; the cyclic AMP then activates a cyclic AMP-dependent protein kinase. The activated (and often dissociated) form of protein kinase catalyzes the phosphorylation of an enzyme, thereby altering its catalytic activity and producing the desired cellular response. Cyclic AMP is removed from the system by its hydrolysis to 5′-AMP, which is catalyzed by a specific phosphodiesterase.

Cyclic AMP has been demonstrated to be a "high-energy" phosphate,[4] i.e., the free energy of its hydrolysis to yield 5′-AMP is −11.9 kcal/mol at pH 7.3, pMg 3, and 25 °C. Thermochemical studies reported by Gerlt, Westheimer, and Sturtevant[5] demonstrated that this thermodynamic instability is the result of an unusually exothermic enthalpy of hydrolysis (−12.1 kcal/mol) as compared to those measured for "strain-free" diesters, diethyl phosphate (−2.5 kcal/mol) and trimethylene phosphate[6] (−3.8 kcal/mol); the entropies of hydrolysis of cyclic AMP and "low-energy" phosphate esters appear to be similar and approximately equal to *zero* cal/mol·deg. These studies did not permit an explanation for the enthalpic behavior of cyclic AMP but did suggest that the structural origin of the unusual enthalpic effect was a property of the ribofuranoside–cyclic phosphate portion of the molecule. Also, these studies revealed that the enthalpy of hydrolysis of methyl α-D-glucopyranoside 4,6-cyclic phosphate (−6.9 kcal/mol) was similar to that of ethylene phosphate, a strained five-membered ring phosphodiester; subsequent structural characterization of the glucoside cyclic phosphate[7] revealed no evidence for geometric distortion, i.e., strain. Thus, two

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