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Rates of Formation of Iminium Ions from Acetone and Monoprotonated 2-[(Dimethylamino)methyl]pyrrolidine[1]

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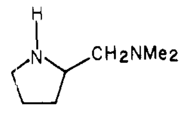
The kinetics of the reaction of 2-[(dimethylamino)methyl]pyrrolidine (1) with acetone has been studied by experiments in which the reversibly formed iminium ion is captured irreversibly by hydroxylamine. From experiments over the pH range 8.5–10.6 rate constants for iminium ion formation from 1 and 1-H$^+$ were obtained. These rate constants were smaller than the corresponding rate constant for pyrrolidine, but the value for 1-H$^+$ was large enough to show that the intermediate carbinolamine was undergoing internal acid-catalyzed dehydration to give the iminium ion.

Pyrrolidine reacts with acetone to give an iminium ion in aqueous solution about 80 times as fast as dimethylamine[2] and more than 40 times as fast as any primary amine, other than a monoprotonated diamine, that has been studied.[3,4] However, a number of monoprotonated primary-tertiary diamines react with acetone to give iminium ions much more rapidly than do primary amines of comparable basicity or the corresponding unprotonated diamines.[3,4] This is attributed to internal acid-catalyzed dehydration of the intermediate carbinolamine, as shown in Scheme I.

For the monoprotonated forms of diamines of the type $Me_2N(CH_2)_nNH_2$, the most reactive was the one where $n = 2$, even though this one was the least basic and rates of imination by primary monoamines increase with increasing basicity.[3] To combine the advantageous effects of forming an iminium ion at pyrrolidine nitrogen and having a dimethylamino substituent β to that nitrogen, we have studied the reaction of acetone with 2-[(dimethylamino)methyl]pyrrolidine (1).



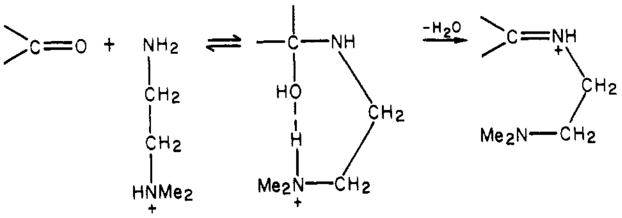
1

Results

Lithium aluminum hydride reduction of *N*,*N*-dimethyl-5-oxo-2-pyrrolidinecarboxamide gave 1, which has also been prepared by reduction of the *N*,*N*-dimethylamide of proline.[5] Its thermodynamic pK_a values in water at 35 °C were found to be 9.82 and 5.77.

Equilibrium constants for iminium ion formation from acetone and secondary amines in aqueous solution are so small that it is not practical to follow the reactions directly. Therefore we have used hydroxylamine to capture the iminium ions as they are formed. When moderate concentrations of hydroxylamine capture the iminium ions quantitatively this method is relatively simple.[6] With secondary amines, however, the capture is less efficient[2] and with 1 there is the added complication that imination by the unprotonated and monoprotonated species must both be taken into account. We measured the rate of transformation of acetone to its oxime (which is essentially irreversible for present purposes) in the presence of various concentrations of 1 and hydroxylamine and at various pH's at ionic strength 0.27 ± 0.03. The results were treated in terms of eq 1–5. Equation 1 is for the background reaction, for which k_{ox} has been found to obey eq 6.[2]

Scheme I



$$Me_2CO + H_2NOH \xrightarrow{k_{ox}} Me_2C{=}NOH + H_2O \quad (1)$$

$$Me_2CO + 1 \underset{k_d}{\overset{k_{im}}{\rightleftharpoons}} Me_2C{=}NR_2^+ + OH^- \quad (2)$$

$$Me_2CO + 1\text{-}H^+ \underset{k_d'}{\overset{k_{imh}}{\rightleftharpoons}} Me_2C{=}NR_2^+ + H_2O \quad (3)$$

$$Me_2C{=}NR_2^+ + H_2NOH \xrightarrow{k_0} Me_2C{=}NOH + 1\text{-}H^+ \quad (4)$$

$$Me_2C{=}NR_2^+ + H_2NOH + OH^- \xrightarrow{k_0'} Me_2C{=}NOH + 1 \quad (5)$$

$$k_{ox} = (1.64 \times 10^6[H^+] + 80[OH^-] + 5.66 \times 10^{-3})\ M^{-1}\ s^{-1} \quad (6)$$

Equations 2 and 3 are for the two methods of iminium-ion formation, eq 4 is for simple capture of the iminium ion by hydroxylamine, and eq 5 is for hydroxide ion catalyzed capture. All the rate constants except k_{ox} are defined as being pH independent, but the four rate constants in eq 2 and 3 are not independent of each other. Hence k_d' will be expressed as shown in eq 7 and 8, in which K_w

$$k_d' = k_d k_{imh} C / k_{im} \quad (7)$$

$$C = K_w/(\gamma^2 K_{1\text{-}H}) \quad (8)$$

is the autoprotolysis constant of water, γ is the activity coefficient of a singly charged ion (which we calculated from the Davies equation),[7] and $K_{1\text{-}H}$ is the acidity constant of 1-H$^+$. The hydroxylamine concentration was always at least three times as large as the acetone concentration (0.01 M) and the reactions were not followed past the disappearance of more than 16% of the hydroxylamine. Hence the hydroxylamine concentration was always within 8%

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[1] Research supported in part by Grant GM 18593 from the National Institute of General Medical Sciences. Abstracted in part from the Ph.D. Dissertation of Ramon A. Evangelista, The Ohio State University, 1978.

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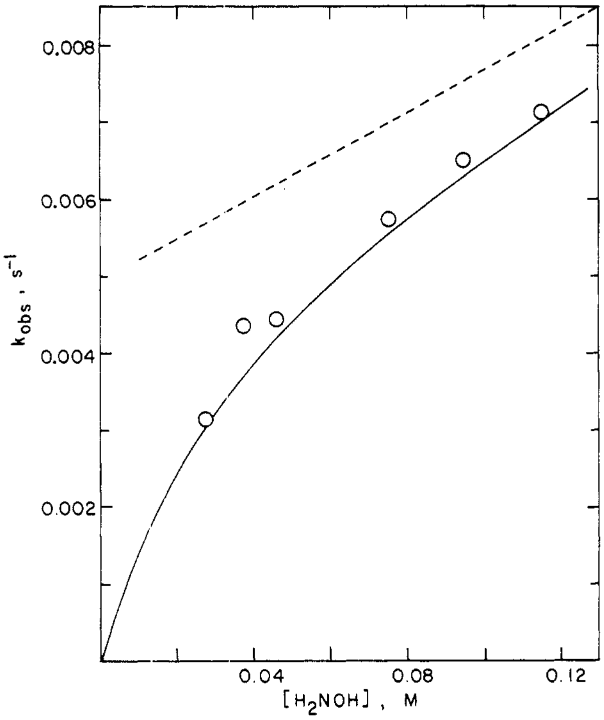

Figure 1. Plot of k_{obsd} vs. hydroxylamine concentration for the oximation of 0.01 M acetone in the presence of 0.100 M total 1 at pH 9.96 in water at 35 °C.

of its average value, which was treated as a constant throughout the run. The pH and concentration of 1 do not change during the reaction, which is therefore treated as solid first-order process with a rate constant k_{obsd}. Values of k_{obsd} in 35 runs are given in the experimental section. Application of the steady-state treatment to eq 1-4 followed by substitution from eq 7 and rearrangement gives eq 9-11 for k_{obsd}. Nonlinear least-squares treatment[8]

$$k_{obsd} = \frac{(k_{im}[1] + k_{imh}[1\text{-H}^+])[H_2NOH](1 + z[OH^-])}{(y[OH^-] + k_{imh}C/k_{im}) + [H_2NOH](1 + z[OH^-])} + k_{ox}[H_2NOH] \quad (9)$$

$$y = k_d/k_0 \quad (10)$$

$$z = k_0'/k_0 \quad (11)$$

of the data gave the values and parenthesized estimated standard deviations shown in eq 12-15 for the four disposable parameters in eq 9.

$$k_{im} = 0.0327\ (0.0121)\ M^{-1}\ s^{-1} \quad (12)$$

$$k_{imh} = 0.0660\ (0.0071)\ M^{-1}\ s^{-1} \quad (13)$$

$$k_d/k_0 = 46.4\ (14.9) \quad (14)$$

$$k_0'/k_0 = 912\ (927)\ M^{-1} \quad (15)$$

These parameter values fit the observed rate constants with an estimated standard deviation of 9.45%, which is not much larger than the average deviations found in pairs of duplicate runs. The fit to on values at pH 9.96 ± 0.03 and 0.100 ± 0.001 M 1 with varying concentrations of hydroxylamine is shown by the solid line and open circles in Figure 1. The dashed asymptote that the solid line is approaching represents the k_{obsd} that would have been obtained if capture of the iminium ions by hydroxylamine had been complete. The points are the averages of the k_{obsd} values obtained at a given hydroxylamine concentration. The solid line tends to run slightly below the points; it is based on parameters obtained from data at all pH's, not just the points shown in the figure.

Table I. Reaction of Acetone with Hydroxylamine in the Presence of 1[a]

pH	$[H_2NOH]_{ave}$, M	$10^3 k_{obsd}$, s^{-1}	$10^3\sigma$,[b] s^{-1}
9.94	0.0460	4.44	0.05
9.94	0.0459	4.67	0.10
9.99	0.0750	5.82	0.04
9.99	0.0751	5.66	0.06
9.94	0.0274	3.62	0.30
9.94	0.0275	2.68	0.44
9.97	0.115	7.22	0.07
9.97	0.115	7.07	0.07
9.99[c]	0.0948	6.53	0.05
9.97[c]	0.0367	4.36	0.16
9.95	0.0459	4.13	0.12
9.95	0.0459	4.54	0.05
8.93	0.0848	5.77	0.03
8.90	0.0458	4.42	0.05
8.90	0.0459	4.27	0.03
8.88	0.114	6.24	0.03
8.89[d]	0.0275	4.01	0.15
8.89[d]	0.0273	3.83	0.16
8.78[d]	0.0274	3.14	0.14
8.78[d]	0.0275	4.16	0.15
8.62	0.0274	3.81	0.17
8.62	0.0272	3.57	0.10
8.46	0.114	6.95	0.03
8.46	0.114	7.01	0.04
9.43	0.0747	4.84	0.05
9.43	0.0751	4.87	0.03
10.30[e]	0.0273	3.79	0.02
10.30[e]	0.0274	3.75	0.25
10.64	0.0748	9.98	0.09
9.93[f]	0.0275	4.28	0.46
9.93[f]	0.0275	5.02	0.17
9.96[f]	0.0746	9.46	0.04
9.96[f]	0.0745	9.02	0.05
9.96[f]	0.115	10.8	0.1
9.96[f]	0.115	10.4	0.1

[a] Using an initial acetone concentration of 0.01 M, a total 1 concentration of 0.099 M, and an ionic strength of 0.297 ± 0.002 in water at 35 °C unless otherwise noted. [b] Estimated standard deviation (ref 8). [c] Total 1 concentration 0.101 M. [d] Ionic strength 0.238. [e] Ionic strength 0.248. [f] Total 1 concentration 0.198 M.

The fact that the standard deviation for k_0'/k_0 is slightly larger than the value makes it uncertain whether the k_0' term ever contributes significantly under our reaction conditions. When this term is dropped from eq 9, least-squares values (and standard deviations) of 0.0423 (0.0079), 0.0605 (0.0043), and 51.5 (13.5) were obtained for k_{im}, k_{imh}, and k_d/k_0, respectively, and the standard deviation from the k_{obsd} values was 9.64%. This again shows that the value of k_0'/k_0 is highly uncertain, but the new values obtained for k_{im}, k_{imh}, and k_d/k_0 are all within the estimated standard deviations of the values shown in eq 12-14.

Discussion

The value of k_{im} for 1 is less than one-hundredth as large as the value (4.25 M^{-1} s^{-1})[2] for pyrrolidine itself. This is probably the result of both polar and steric factors. Since pyrrolidine (pK_a 10.99)[9] is about 25 times as basic as trimethylamine (pK_a 9.58),[10] the basicity of 1 (p$K_{1\text{-H}}$ = 9.82)

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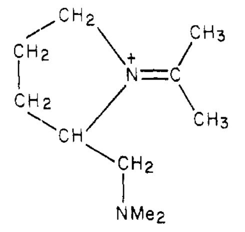
is probably largely due to the pyrrolidine nitrogen atom. A plot of log k_{im} vs. pK_a for primary amines in which steric effects are reasonably constant has a slope of 0.59.[3] Assuming that a similar relationship would hold for equally hindered pyrrolidines, we estimate that polar effects decrease k_{im} by about fivefold. We then take the remaining 20-fold decrease to be a steric effect. Much of the particularly great reactivity of pyrrolidine was attributed to the decreased steric repulsions in the iminium ion formed from the pyrrolidine relative to those present in an iminium ion formed from a secondary amine in which the two R groups attached to nitrogen are not held together in a five-membered ring. However, in **2**, the iminium ion formed from **1** and acetone, there should be strong repulsions between the (dimethylamino)methyl group from **1** and a methyl group from acetone.



2

The rate constant for imination by **1**-H$^+$ (k_{imh}) is about twice as large as that for **1** (k_{im}) in spite of the fact **1** is far more basic than **1**-H$^+$. Hence the reaction of **1**-H$^+$ is being speeded by the internal acid catalysis of dehydration of the intermediate carbinolamine. However, the rate constant for monoprotonated *N*,*N*-dimethylethylenediamine (0.30)[3,11] is more than four times as large as the value for **1**-H$^+$. One reason for this is the hindrance present in the iminium ion **2**. Another reason is based on the fact that the reactive form of monoprotonated diamines of the type we are considering must have the tertiary amino group protonated and the primary or secondary amino group free. Since pyrrolidine is considerably more basic than a primary amine, a significantly smaller fraction of the tertiary amino groups is probably protonated in **1**-H$^+$ than in monoprotonated *N*,*N*-dimethylethylenediamine.

Experimental Section

2-[(Dimethylamino)methyl]pyrrolidine. *N*,*N*-Dimethyl-5-oxo-2-pyrrolidinecarboxamide[13] (47 g) was reduced with 14.3 g of lithium aluminum hydride in 700 mL of refluxing tetrahydrofuran for 18 h. To the cooled solution was added 16 mL of 15% aqueous sodium hydroxide, 35 mL of water, and 240 mL of tetrahydrofuran and the mixture was refluxed for 30 min. Then the mixture was filtered and the filtrate was dried over potassium carbonate and distilled. The major fraction (9.6 g), bp 100–105 °C (80 mm), was redistilled to give 8.2 g of colorless liquid, bp 105–110 °C (80 mm) [lit.[5] bp 133–135 °C (760 mm)], which was 99.9% pure by GLC on a Carbowax-KOH column, containing two impurities with shorter retention times: 300-MHz ^{1}H NMR[14] (D_2O, shifts upfield from HOD) δ 1.73 (quintet, 1, J = 7 Hz, $CHCH_2NMe_2$), 2.01 (d of t, 1, J = 10, J' = 7 Hz, CHHNH), 2.13 (d of t, 1, J = 10, J' = 7 Hz, CHHNH), 2.50 (m, 2, CH_2NMe_2), 2.66 (s, 6, CH_3), 2.95 (m, 1, $CHHCH_2NH$), 3.15 (m, 2, $CHHCH_2NH$ and $CHHCHCH_2NMe_2$), 3.58 (d of q, 1, J = 13, J' = 8 Hz, $CHHCHCH_2NMe_2$); IR (neat) 3250 (NH), 2750–2950 (CH), 1420 cm^{-1} (CNH); mass spectrum (70 eV), m/z (relative intensity) 128 (1), 84 (2), 83 (3), 82 (2), 72 (2), 71 (6), 70 (100), 69 (2), 68 (4), 59 (38), 58 (62).

Both the dihydrochloride and dihydrobromide of **1** were prepared and found to be too hygroscopic to be handled conveniently.

Kinetics. The kinetics was followed by spectrophotometric measurements at 275 nm, near the absorption maximum of acetone, as described previously.[2-4] The results obtained are listed in Table I.

Registry No. 1, 70754-93-7; 2, 74420-39-6; hydroxylamine, 7803-49-8; *N*,*N*-dimethyl-5-oxo-2-pyrrolidinecarboxamide, 74420-40-9; acetone, 67-64-1.

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[11] This is the value for total monoprotonated diamine. It is obtained by multiplying the value for tertiary-protonated diamine[3] by the fraction of monoprotonated diamine that is protonated at the tertiary amino group (0.38).[12]

[12] Hine, J.; Via, F. A.; Jensen, J. H. *J. Org. Chem.* **1971**, *36*, 2926–9.

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[14] The NMR assignments are based in part on decoupling experiments.

Vinyl Cation Intermediates in Solvolytic and Electrophilic Reactions. 1. Solvolysis of α-Arylvinyl Derivatives

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The solvolysis of 16 α-arylvinyl tosylates, bromides, and chlorides has been investigated in various alcohol–water mixtures and in acetic acid at several temperatures. All substrates were substituted with either 2-methyl or 2,6-dimethyl groups to accelerate the rates of reaction. The major or exclusive product isolated in most cases was the acetophenone arising from hydrolysis of the expected enol ethers or acetates during workup. The kinetics were simple first order in the vast majority of cases, with excess base added to prevent side reactions. Leaving group effects, Winstein–Grunwald m values, Schleyer Q values, and effects of solvent nucleophilicity all point to a limiting S_N1 ionization generating a vinyl cation intermediate, in which there is little rear-side nucleophilic assistance by solvent. Substituent effects led to ρ values in the range −3.9 to −5.3 vs. σ^+. Activation parameters are typical for an S_N1 process, and ΔS^* is insensitive to the presence of zero, one, or two o-methyl groups, as are the effects of solvent polarity on the rates. The results should therefore be directly comparable with other solvolytic or electrophilic reactions generating formally similar vinyl cation intermediates.

Vinyl cations are now well established as organic reaction intermediates, due to considerable activity in this area over the past 10 years.[1] Probably the two most common ways these intermediates are generated are by solvolytic or

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