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Six-at-Once Dedeuteration of Acetone-d_6 in the Presence of 3-*exo*-[(Dimethylamino)methyl]-2-*exo*-norbornanamine[1]

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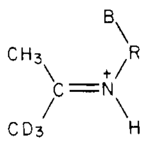
3-*exo*-[(Dimethylamino)methyl]-2-*exo*-norbornanamine (**2**) was prepared and used as a catalyst in aqueous solution at 35 °C for the dedeuteration of acetone-d_6. Monoprotonated **2** acts as an effective catalyst by transforming the ketone to an iminium ion and then using its dimethylamino group to dedeuterate the iminium ion by internal basic catalysis. At pH 9.95 the most common result of iminium-ion formation is the exchange of all six deuterium atoms. This requires a mechanism for cis–trans isomerization of the intermediate iminium ion. The *gem*-diamine mechanism proposed earlier for iminium ions derived from cyclopentanone helps explain why **2** gives six-at-once exchange while some rather similar diamines do not. The kinetics of iminium-ion formation from **2** and acetone were studied by the hydroxylamine-capture technique. The rates of iminium-ion formation thus obtained are reasonably consistent with those obtained in the deuterium exchange experiments.

In previous papers in this series we have studied four types of exchange of the α-hydrogen atoms of ketones. The first type is the one at a time stereorandom exchange brought about by simple bases, which chemists have observed for decades. A second type, which proceeds through the iminium-ion mechanism shown in Scheme I when the divalent R group is appropriately chiral and the deuterium atom is prochiral, is stereoselective exchange.[2,3] A third type, proceeding through Scheme I in certain cases where k_2 is larger than k_{-1} and k_3 is larger than k_{-2}, gives removal of all the deuterium atoms on one side of the carbonyl group as the most common result of iminium-ion formation.[4-6] This occurs because, after the iminium ion (shown as **1** in a case where the ketone is acetone-d_6) has exchanged all the deuterium atoms that are cis to the basic group B from the catalyst, the remaining deuterium atoms are too far away to be reached by B (which is separated from N by only three carbon atoms in the catalysts for which this type of exchange has been seen). The fourth type of exchange, in which exchange of all the α-deuterium atoms on both sides of the carbonyl group is the most common result of iminium-ion formation, was discovered in the dedeuteration of cyclopentanone-2,2,5,5-d_4 in the presence of 3-(dimethylamino)propylamine.[1b,7] In this case, cis–trans isomerization of the intermediate iminium ion is faster than exchange or hydrolysis back to ketone.



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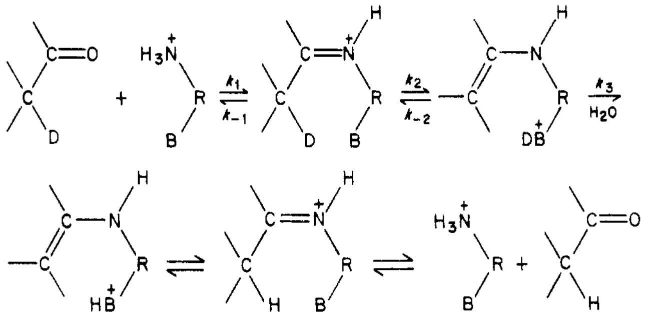
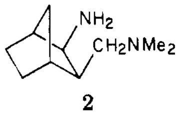
Scheme I



We decided to study 3-*exo*-[(dimethylamino)methyl]-2-*exo*-norbornanamine (**2**), because the C–NH_2 bond is eclipsed with the C–CH_2NMe_2 bond, just as it is in the cases of the endo–endo compounds **3**[5,6] and **4**[2], which are the most efficient catalysts for dedeuteration of acetone-d_6 that we have found to date. We discovered that **2** can give the fourth type of exchange (all-at-once exchange) with acetone-d_6, even though type 3 (all on one side) exchange occurs with **3**[5,6] and **4**.[8]



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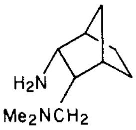

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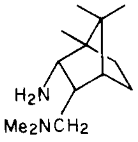

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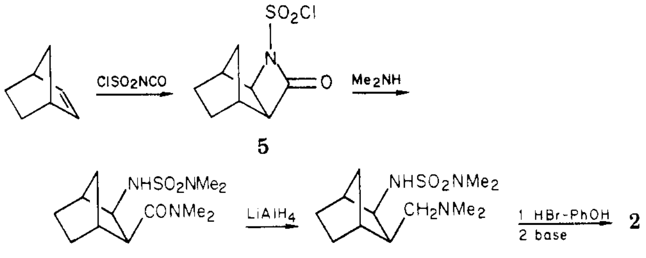
Results and Discussion

The synthesis of **2** started with the known exo addition of chlorosulfonyl isocyanate (CSI) to norbornene.[9-12] The product, **5**, reacts with 2 mol of dimethylamine in manner



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7

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[1] (a) Part 23 in the series "Catalysis of α-Hydrogen Exchange". (b) For part 22, see: Hine, J.; Miles, D. E.; Zeigler, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 4374–9. (c) Abstracted in part from the MS Thesis of H.-M. T., The Ohio State University, 1982.

[2] Hine, J.; Li, W.-S. *J. Am. Chem. Soc.* **1975**, *97*, 3550–1; Hine, J.; Li, W.-S.; Zeigler, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 4403–9.

[3] Hine, J.; Zeigler, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 7524–9.

[4] Hine, J.; Cholod, M. S.; King, R. A. *J. Am. Chem. Soc.* **1974**, *96*, 835–45.

[5] Hine, J.; Li, W.-S. *J. Am. Chem. Soc.* **1976**, *98*, 3287–94.

[6] Hine, J. *Acc. Chem. Res.* **1978**, *11*, 1–7.

[7] Zeigler, J. P. Ph.D. Dissertation, The Ohio State University, 1978.

[8] Li, W.-S., unpublished observations, The Ohio State University, 1974.

[9] The addition of CSI to norbornene was mentioned in Graf's review of the reactions of CSI[10] but it was not told whether the product was endo or exo, and the reaction could not be found in the literature cited.[11] The reaction was described and the stereochemistry established by Moriconi and Crawford.[12]

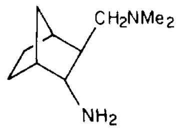
[10] Graf, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 172–82.

[11] Graf, R. *Justus Liebigs Ann. Chem.* **1963**, *661*, 111–57.

[12] Moriconi, E. J.; Crawford, W. C. *J. Org. Chem.* **1968**, *33*, 370–8.

0022-3263/83/1948-3797$01.50/0

analogous to that observed for other CSI adducts[9-11] to give **6**. Reduction of **6** to **7**, followed by cleavage with hydrogen bromide and phenol,[13] gave **2**. The ^{1}H NMR spectra of **2**, **6**, and **7** give additional evidence for their exo stereochemistry. Each has a doublet ($J \approx 8$ Hz) for the hydrogen on the nitrogen-bound methinyl group at carbon 2. If this methinyl hydrogen atom were exo there would be easily detectable coupling with the vicinal bridgehead hydrogen,[14] as there is for the analogous hydrogen of **3** ($J \approx 4.5$ Hz).[15] Furthermore, the coupling constants of ~8 Hz are nearer the range (5.8–7.7 Hz)[14] characteristic of norbornane endo–endo coupling constants than the ranges characteristic of exo–exo or endo–exo coupling constants (8.9–11.4 and 2.2–5.8 Hz, respectively).[14] They are smaller than the corresponding coupling constants for **3** and **4** ($J = 9.5$[15] and 10.2 Hz,[2] respectively) and larger than the coupling constants for the endo–exo isomer **8** ($J \approx 4.5$ Hz).[15]



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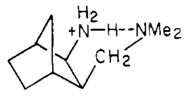
The pK's of mono- and diprotonated **2** were found to be 10.34 and 6.56, respectively. This is a larger equilibrium constant for the monoprotonation of the amine and a smaller equilibrium constant for the second protonation than observed for **3** (pK = 9.78 and 6.82),[16] **4** (pK = 9.84 and 6.59),[2] or **8** (pK = 9.92 and 7.61).[16] This would be expected if monoprotonated **2** were more highly stabilized by internal hydrogen bonding (**9**). When the method of estimation described previously is used,[16] the fraction of monoprotonated **2** existing in the cyclic hydrogen bonded form (f_c) is calculated to be 0.825, compared to 0.36 and 0.15 for **3** and **8**, respectively. Since the monoprotonated diamine is the effective species in bifunctional catalysis of α-hydrogen exchange and in internal acid-catalyzed iminium-ion formation,[6] the stabilization of monoprotonated **2** in a way not possible for the transitions state for exchange and iminium-ion formation will make **2** a poorer catalyst than it would otherwise be.



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Dedeuteration of acetone-d_6 in aqueous **2** buffers was studied at four pH's ranging from 6.54 to 9.95. At the highest pH, the exchange was seen to follow a pattern not observed before for acetone-d_6. As shown in Figure 1, after the d_6 concentration had dropped enough that d_6 was no longer the most abundant species, d_0 became the most abundant. There was never a time at which either the d_5, d_4, d_3, d_2, or d_1 species was the most abundant. This contrasts with the one at a time exchange observed with simple bases, in which first d_6 is the most abundant species, then d_5, then d_4, etc. through d_3, d_2, d_1, and d_0.[5] It also contrasts with the all on one side exchange observed in the presence of **3**, for example, in which first d_6 is the most abundant species, then d_3, and then d_0.[4-6] The behavior of acetone-d_6 in the presence of **2** is analogous to that of cyclopentanone-2,2,5,5-d_4 in the presence of 3-(dimethylamino)propylamine, where d_4 is initially the most abundant, followed by d_0, with none of the intermediates d_3, d_2, or d_1 ever being the most abundant species.[1b,7]

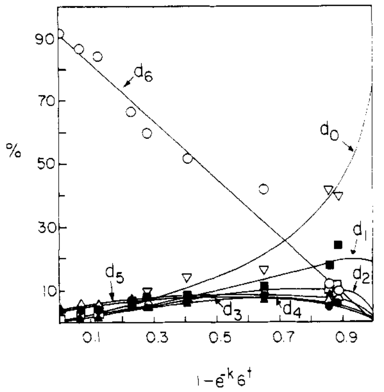
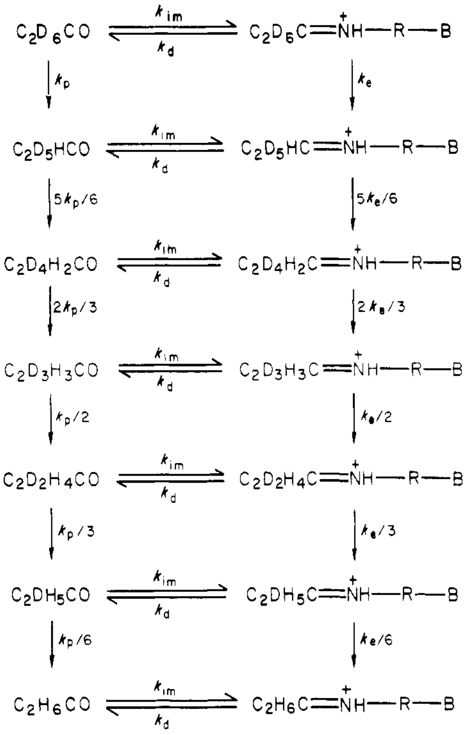


Figure 1. Kinetic plot for dedeuteration of acetone-d_6 in the presence of 0.0050 M 3-*exo*-[(dimethylamino)methyl]-2-*exo*-norbornanamine at pH 9.953 and 35 °C: (○) d_6, (●) d_5, (△) d_4, (▲) (d_3, (□) d_2, (■) d_1, (▽) d_0.

Scheme II



The explanation for these results appears to be the same as that suggested for the dedeuteration of cyclopentanone-2,2,5,5-d_4 in the presence of 3-(dimethylamino)propylamine;[1b] cis–trans isomerization of the intermediate iminium ion is at least comparable in rate to hydrolysis of the iminium ion back to ketone. If cis–trans isomerization is fast compared to hydrolysis and exchange, the mixture of cis and trans iminium ions may be treated as a single species and Scheme II may be used. Neglecting secondary deuterium kinetic isotope effects, we also treat the different isomeric species of a given isotopic content (such as CD_3COCH_3 and CD_2HCOCH_2D) as one species (e.g., $C_2D_3H_3CO$).

The value of k_p, the rate constant for simple base-catalyzed dedeuteration, was estimated from Brønsted plots for related compounds, as described previously[4] and as described in more detail in the Appendix. Since the k_p term never accounts for more than 4% of the total reaction rate, even an error of a factor of 2 in the estimation of k_p

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[13] Cf. Snyder, H. R.; Heckert, R. E. *J. Am. Chem. Soc.* **1952**, *74*, 2006–9.
[14] Laszlo, P.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1964**, *76*, 1171–9.
[15] Hine, J.; Li, W.-S. *J. Org. Chem.* **1975**, *40*, 289–92.
[16] Hine, J.; Li, W.-S. *J. Org. Chem.* **1975**, *40*, 1795–800.

Table I. Kinetics of Dedeuteration of Acetone-d_6 in the Presence of 3-*exo*-[(Dimethylamino)methyl]-2-*exo*-norbornanamine[a]

pH	10^6k_6,[b,c] s^{-1}	10^6k_p, s^{-1}	10^6k_{im},[b,d] s^{-1}	r[b,d]	standard deviation[e]
6.540	17.1 (0.3)	0.27	484[f]	0.033	0.016
7.077	42.9 (0.2)	0.48	213 (26)	0.25 (0.03)	0.017
9.325	363 (26)	10.5	494 (32)	3.17 (0.27)	0.031
9.953	525 (43)	22.1	604 (26)	6.36 (0.41)	0.022

[a] Using 0.00504 ± 0.00002 M total diamine in water at 35 °C. [b] The parenthesized figures are estimated standard deviations. [c] Based on d_6 values only. [d] Based on d_6, d_5, d_4, d_3, d_2, d_1, and d_0 values. [e] Of the calculated fractions d_6, d_5, ..., d_0 from the observed values. [f] Assigned value; see text.

would not give a serious error in the rest of our data treatment. Taking k_p as known, the data for any run can be used to obtain k_{im} and r, where $r = k_e/k_d$. The iterative nonlinear least-squares treatment did not converge for the data obtained at pH 6.54. This is because the rate of exchange depends on the product $k_{im}r/(1 + r)$, and when r is small compared to 1.0, this becomes essentially equal to the product $k_{im}r$. A value can be obtained for this product but not for its individual factors. Hence, in this case we arbitrarily set k_{im} equal to 484×10^{-6} s^{-1}, the value that may be calculated from the results of a study of the kinetics of imination that will be described later in this paper. The treatment converged for the data obtained at pH 7.077, and the product $k_{im}r$ that may be calculated from the results is probably reliable. The resulting value of r, however, is so small that we believe that the estimated standard deviations for k_{im} and r, obtained by standard methods,[17] are much smaller than the actual uncertainties in the values of these parameters. The resulting k_{im} and r values are shown in Table I, along with k_p values, standard deviations of the fit to the observed d_6, d_5, ..., d_0 values, and values of k_6, the first-order rate constants for disappearance of acetone-d_6. These k_6 values were calculated from d_6 values only but, according to Scheme II, may be expressed as shown in eq 1. The k_6 values that may

$$k_6 = k_p + k_{im}r/(1 + r) \qquad (1)$$

be calculated from the k_p, k_{im}, and r values in Table I, which are based on all the d_6, d_5, ..., d_0 values deviate from those based on d_6 values only by an average 5%. Secondary deuterium kinetic isotope effects may contribute to these small differences. The agreement of the experimental data at pH 9.953 with Scheme II is illustrated in Figure 1, in which the lines are based on this scheme and the values of k_p, k_{im}, and r shown in Table I.

We also treated the data by a scheme in which no cis–trans isomerization of the intermediate iminium ions was permitted, so that only deuterium atoms on one side of the carbonyl group could be exchanged as the result of the formation of a given iminium ion (see Appendix). This scheme fits the data at pH 6.54 and 7.077, where the small r values show that most of the deuterium exchange occurs by a one at a time path, almost as well as Scheme II does. However, the alternative scheme gives standard deviations from d_6, d_5, ..., d_0 values 83% larger than Scheme II at pH 9.325 and 3.4 times as large at pH 9.953. Moreover, the resulting k_{im} and r values give, via eq 1, k_6 values that are about 37% larger than the values in Table I at each of these two higher pH's.

The kinetics of iminium-ion formation from acetone and 2 were studied spectrophotometrically by the hydroxylamine-capturing technique used previously.[18-23] Oxime formation is essentially irreversible, but iminium-ion and imine formation do not proceed to a directly detectable extent at equilibrium under the conditions used. Since 0.1 M hydroxylamine did not seem to give essentially complete capture of the iminium ions formed in the present case, we did not make the simplifying assumption that we made for most of the primary amines studied previously. Instead, we used a more detailed mechanism similar to that used for secondary amines.[22] In Scheme III the rate constants are all composite. The rate constant for the "background" reaction, k_{ox}, contains a hydrogen-ion-catalyzed term, a hydroxide-ion-catalyzed term, and an uncatalyzed term, whose values in water at 35 °C have been found to be 1.64×10^6 M^{-2} s^{-1}, 80 M^{-2} s^{-1}, and 5.66×10^{-3} M^{-1} s^{-1}, respectively.[22] The first-order rate constant for iminium-ion formation, k_{im}, contains terms for the unprotonated diamine and the monoprotonated diamine, as shown in eq 2. The reverse rate constant, k_d, allows for

$$k_{im} = k_{am}[Am] + k_{amh}[AmH^+] \qquad (2)$$

reversibility of both the k_{am} and k_{amh} paths. However, the four rate constants, k_{am}, k_{amh}, k_{-am}, and k_{-amh}, are not all independent of each other, and from the principle of microscopic reversibility, k_d may be expressed as shown in eq 3, in which K_w is the autoprotolysis constant of water,

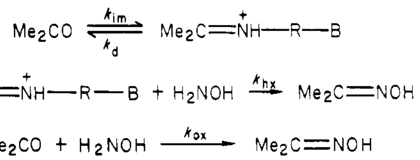
$$k_d = k_{am}[OH^-] + k_{amh}K_w/(k_{am}K_a) \qquad (3)$$

and K_a is the acidity constant of monoprotonated diamine. As shown in eq 4, we allow for uncatalyzed, hydroxide-

$$k_{hx} = k_0 + k_b[OH] + k_a[H^+] \qquad (4)$$

ion-catalyzed, and hydrogen-ion-catalyzed capture of the iminium ions by hydroxylamine. The k_a term was not used with monoamines; it corresponds to capture of those iminium ions derived from the diamine in which the dimethylamino group is also protonated. The data treatment used for the imination of cyclopentanone[23] gives, for each run, a value of k_1, which is defined in eq 5, in which [Hx] is the average concentration of hydroxylamine present during the run,[24] a is k_a/k_0, b is k_b/k_0, d is k_{am}/k_0, and C is K_w/K_a.

Scheme III



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[17] Hamilton, W. C. "Statistics in Physical Science"; Ronald Press: New York, 1964; sections 4-1, 5-3.

[18] Cf. Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 826–31.

[19] Williams, A.; Bender, M. L. *J. Am. Chem. Soc.* **1966**, *88*, 2508–13.

[20] Hine, J.; Cholod, M. S.; Chess, W. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 4270–6.

[21] Hine, J.; Li, W.-S. *J. Org. Chem.* **1975**, *40*, 2622–6.

[22] Hine, J.; Dempsey, R. C.; Evangelista, R. A.; Jarvi, E. T.; Wilson, J. M. *J. Org. Chem.* **1977**, *42*, 1593–9.

[23] Hine, J.; Zeigler, J. P.; Johnston, M. *J. Org. Chem.* **1979**, *44*, 3540–5.

[24] Since the hydroxylamine was always used in substantial excess over the acetone, its concentration did not vary greatly during a given run.

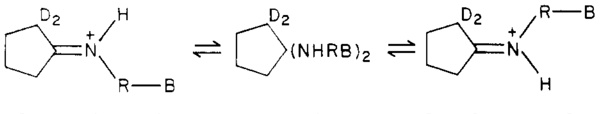
$$k_1 = \frac{(k_{am}[\mathrm{Am}] + k_{amh}[\mathrm{AmH}])[\mathrm{Hx}](1 + a[\mathrm{H^+}] + b[\mathrm{OH^-}])}{[\mathrm{Hx}](1 + a[\mathrm{H^+}] + b[\mathrm{OH^-}]) + d([\mathrm{OH^-}] + k_{amh}C/k_{am})} \qquad (5)$$

As was the case with **3**, **8**, and several other of the catalysts that have been studied, monoprotonated **2** forms iminium ions so rapidly (via internal acid-catalyzed dehydration of the intermediate carbinolamine) that imination via unprotonated **2** never constitutes a large enough fraction of the reaction for the value of k_{am} to be determined directly. Hence, as with such catalysts, the value of k_{am} was estimated to be 0.021 M^{-1} s^{-1}, the same value used for **3**.[21]

When k_{amh}, a, b, and d in eq 5 were all treated as disposable parameters, a nonlinear least-squares treatment of 15 values of k_1, obtained over the pH range 7.55–10.42 using 0.0155–0.076 M **2**, 0.03–0.10 M initial hydroxylamine, and 0.002–0.006 M initial acetone, did not converge. The values for a, b, and d climbed steadily, but the value for k_{am} remained near 0.2 M^{-1} s^{-1}. An argument that a should be in the range $10^{7.29}$–$10^{8.8}$ is in the Appendix. When a was set at the geometric mean value $10^{8.04}$, the treatment converged to give values (standard deviations) of 0.24 (0.04) M^{-1} s^{-1}, 8 (7) × 10^4 M^{-1}, and 12 (5) for k_{amh}, b, and d, respectively. We attach no significance to the values for b and d, which were considerably different when values for a of $10^{7.29}$ and $10^{8.8}$ were used. However, these upper and lower limits for a gave k_{amh} values (standard deviations) of 0.23 (0.03) and 0.25 (0.04) M^{-1} s^{-1}, respectively. These values are larger than the k_{amh} values that may be calculated from the k_{im} values in Table I and a k_{am} value of 0.21 M^{-1} s^{-1}. The most reliable such value is 0.15 M^{-1} s^{-1}, which is obtained from the run at pH 9.953, where the most reliable k_{im} value was obtained. The value obtained from the dedeuteration studies need not agree perfectly with that obtained from oximation studies because the former refer to acetone-d_6 and to a solution that is 0.52 M in acetone (4% by volume), whereas ordinary acetone was used at concentrations below 0.01 M in the latter studies. Nevertheless, it is significant that if an intermediate k_{amh} value of 0.19 M^{-1} s^{-1} is used to calculate k_{im} values for the dedeuteration runs shown in Table I and least-squares values for r are obtained, the d_6, d_5, ..., d_0 values are fit with standard deviations of 0.015, 0.022, 0.045, and 0.026 for the runs at pH 6.54, 7.077, 9.324, and 9.953, respectively. These values are small enough and close enough to the values in Table I to show that a k_{amh} value of 0.19 M^{-1} s^{-1} is also consistent with the dedeuteration data.

This intermediate k_{amh} value of 0.19 M^{-1} s^{-1} for **2** is about half as large as the value for **3** (0.40 M^{-1} s^{-1}).[21] It appears that the value for **2** is smaller because the reactant, monoprotonated **2**, is more highly stabilized by internal hydrogen bonding than monoprotonated **3** is. In fact, if we calculate a k'_{amh} value based on tertiary monoprotonated diamine by dividing k_{amh} by the estimated fraction of monoprotonated diamine that is HTP, we get values of 2.0 and 1.1 M^{-1} s^{-1} for **2** and **3**, respectively.

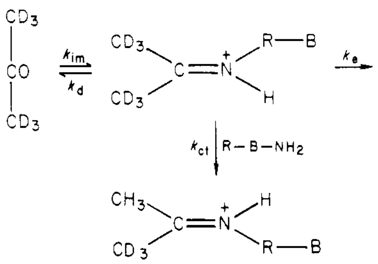
Evidence has been described that relatively rapid cis–trans isomerization of the iminium ion formed from 3-(dimethylamino)propylamine and cyclopentanone occurs via a *gem*-diamine (eq 6). Can this mechanism explain



(6)

why **2** gives six-at-once exchange and **3** does not? The three relevant possible reaction paths available to an iminium ion, cis–trans isomerization, hydrolysis to ketone, and exchange, are shown in Scheme IV. Only if k_{ct}, the rate constant for cis–trans isomerization, and k_e, the rate constant for dedeuteration of the iminium ion, are comparable to or larger than k_d, the rate constant for hydrolysis, can there be substantial amounts of six-at-once exchange. Steric repulsions in the transition state leading to the intermediate *gem*-diamine should make k_{ctx} for the exo isomer **2** larger than k_{ctn} for the endo isomer **3**. Steric effects should also make the equilibrium constant k_{imx}/k_{dx} for iminium-ion formation by **2** larger than k_{imn}/k_{dn}, the corresponding equilibrium constant for the iminium-ion formation by **3**. Since k_{im} is dominated by the k_{amh} term when significant amounts of monoprotonated **2** or **3** are present and since k_{amh} for **3** is 0.4 M^{-1} s^{-1},[20] k_{imn} is about twice as large as k_{imx} in the pH range where six-at-once and three-at-once exchange is observed. The rate constant ratio k_{ct}/k_d for **2** may be compared to that for **3** as shown in eq 7, which shows that the ratio for **2** is equal to that

Scheme IV



$$\frac{k_{ctx}}{k_{dx}} = \left(\frac{k_{ctx}}{k_{ctn}}\right)\left(\frac{k_{imx}/k_{dx}}{k_{imn}/k_{dn}}\right)\left(\frac{k_{imn}}{k_{imx}}\right)\frac{k_{ctn}}{k_{dn}} \qquad (7)$$

for **3** multiplied by three factors, each of which is larger than 1.0 (k_{ctx}/k_{ctn} probably being the largest). This is presumably why cis–trans isomerization of the iminium ion is large enough, relative to hydrolysis, for six-at-once exchange to be important in the case of **2** but not in the case of **3**. The rate of cis–trans isomerism via the *gem*-diamine mechanism should increase with increasing catalyst concentration. The dedeuteration of acetone-d_6 was studied at concentrations of **3** as high as 0.0246 M,[5] almost five times as large as the **2** concentrations used in the present study, but apparently this was not enough to make k_{ct} comparable to k_d.

Experimental Section

3-*exo*-(Dimethylcarbamido)-2-*exo*-[(dimethylsulfonamido)amino]norbornane (6). A solution of 25 g (0.556 mol) of dimethylamine in 100 mL of dry ether was added dropwise with stirring to a solution of 40.3 g (0.171 mol) of *N*-(chlorosulfonyl)-*exo*-3-aza-4-ketotricyclo[4.2.1.0^{2,5}]nonane[9-12] in 200 mL of dry ether. After an additional hour of stirring, the resulting white precipitate was collected on a filter, washed with water to remove dimethylamine hydrochloride, and dried to give 49.2 g (99.6%) of crude **6**, mp 140–144 °C. Recrystallization from absolute ethanol gave pure product: mp 145–146 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.13–2.13 (m, 6), 2.23–2.43 (m, 3), 2.77 (s, 6, $SO_2N(CH_3)_2$], 2.93 (s, 3, 1 $CONCH_3$), 3.07 (s, 3, 1 $CONCH_3$), 3.68 (d, 1, J = 8 Hz, CHNHS). Anal. Calcd for $C_{12}H_{23}N_3SO_3$: C, 49.80; H, 8.01; N, 14.52; S, 11.08. Found: C, 49.78; H, 8.17; N, 14.37; S, 11.00.

3-*exo*-[(Dimethylamino)methyl]-2-*exo*-[(dimethylsulfonamido)amino]norbornane (7). A solution of 32.7 g (0.113 mol) of **6** in 320 mL of dry tetrahydrofuran (THF) was added with stirring to 8.2 g (0.216 mol) of lithium aluminum hydride in 80 mL of dry THF. After 6 days at reflux, the solution was cooled to 0 °C, and water (23 mL) was added dropwise until gas was no longer evolved. The solution was filtered, the precipitate was washed with 260 mL of ether, and the filtrate and washing were

Table II. Oximation of Acetone in the Presence of 2[a]

pH	$10^2[2]_t$,[b] M	$10^2[\mathrm{Hx}]_{av}$,[c] M	$10^3 k_{obsd}$,[d] s^{-1}	$10^3 k_{calcd}$,[d] s^{-1}
7.551	1.55	2.88	4.0	3.7
7.604	1.55	5.87	7.3	5.9
7.872	3.80	9.72	7.6	9.4
8.400	2.35	2.88	2.8	2.2
8.486	2.35	2.89	2.2	2.2
8.806	4.70	2.86	3.8	4.4
8.945	7.60	9.69	13	13
9.052	3.80	9.73	8.1	7.5
9.226	2.35	2.88	3.2	3.2
9.295	3.80	9.77	9.4	8.1
9.618	3.80	9.75	10	8.8
10.204	3.80	9.83	7.4	10
10.268	2.35	5.91	7.7	6.5
10.391	2.35	2.91	5.9	5.0
10.420	1.55	2.92	5.7	4.0

[a] At 35 °C in water at ionic strength (NaCl) 0.3. [b] Total 2 concentration, in all degrees of protonation. [c] Average concentration of hydroxylamine. [d] $k_1 + k_{ox}[\mathrm{Hx}]_{av}$.

combined. The combined solutions were washed with 200 mL of brine and dried over $MgSO_4$, and the solvent was removed in vacuo, giving 20.4 g (66%) of white solid, mp 89–92 °C. Recrystallization from absolute ethanol gave pure **7**: mp 96–8 °C; ^1H NMR (CCl_4, 90 MHz) δ 1.0–1.73 (m, 6), 1.73–1.93 (m, 3), 2.28 [s, 6, $SO_2N(CH_3)_2$], 2.60 (m, 2, CH_2N), 2.70 [s, 6, $CN(CH_3)_2$], 3.23 (d, 1, J = 8 Hz, CHNHS). Anal. Calcd for $C_{12}H_{25}N_3SO_2$: C, 52.33; H, 9.15; N, 15.26; S, 11.64. Found: C, 51.94; H, 9.15; N, 14.95; S, 11.54.

3-*exo*-[(Dimethylamino)methyl]-2-*exo*-norbornanamine (2) Dihydrochloride. After 270 mL of 48% hydrobromic acid (0.239 mol) was added to a mixture of 16.3 g (0.059 mol) of **7** and 8 g (0.085 mol) of phenol, the solution was refluxed for 17 h and cooled to 0 °C. The cooled solution was made very basic using NaOH solution and extracted with three 160-mL portions of ether. After two washings with 30-mL portions of water and drying over $MgSO_4$, the ether was evaporated to give 7 g (71%) of yellow oil. Saturated HCl in ether was added to a solution of the oil in ether to give a sticky pinkish white solid, which was recrystallized from absolute ethanol to yield pure white **2**·2HCl: mp 221–223 °C; ^1H NMR (300 MHz, D_2O/DSS) δ 1.26–1.82 (m, 6), 2.3–2.45 (m, 3), 2.95 (s, 6, NCH_3), 3.1–3.22 (m, 2, CH_2N), 3.5 (d, 1, J = 7.9 Hz, $CHNH_2$). Anal. Calcd for $C_{10}H_{22}N_2Cl_2$: C, 49.80; H, 9.19; N, 11.61; Cl, 29.40. Found: C, 49.61; H, 9.18; N, 11.48; Cl, 29.12.

p*K* and Kinetic Measurements. Methods described previously were used to calculate acidity constants from data on the potentiometric titration of **2**·2HCl with standard sodium hydroxide,[23] to obtain d_6, d_5, ..., d_0 values at various times by mass spectral means in the dedeuteration of acetone-d_6,[25] and to follow the reaction of acetone with hydroxylamine spectrophotometrically.[19-21] The kinetic data on the reaction of acetone with hydroxylamine in the presence of **2** are shown in Table II, in which k_{obsd} and k_{calcd} are values of $k_1 + k_{ox}[\mathrm{Hx}]_{av}$.

Appendix

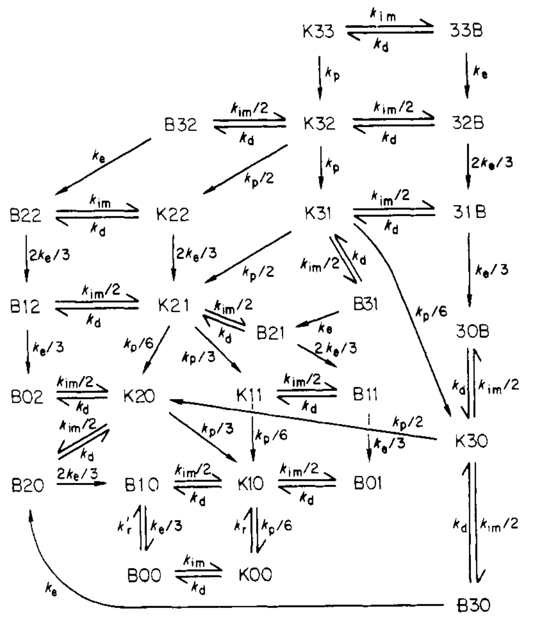
The rate constant k_p for monofunctionally catalyzed exchange of acetone-d_6 may be expressed as shown in eq 8, since hydroxide ions and the unprotonated and monoprotonated forms of **2** are the only significant bases present in the solution. The value of k_h has been found to be 0.0722 M^{-1} s^{-1}.[25] It has been shown that other diamines whose basicities are thought to be increased substantially by internal hydrogen bonding of the monoprotonated form dedeuterate acetone-d_6 considerably more slowly that would be expected from a Brønsted plot of data on monoamines and diamines whose monoprotonated forms are not thought to be internally hydrogen bonded to a substantial extent.[5] When a diamine deprotonates acetone, the monoprotonated diamine that is the immediate product must not be the internally hydrogen-bonded species. Hence, any stability characteristic of the internally hydrogen-bonded species is not reflected in the reaction rate. It was found that when the value that had been estimated for the noninternally hydrogen-bonded species was used in constructing the Brønsted plot, the points for diamines were monoprotonated forms were internally hydrogen bonded fell much nearer the line described by points for analogous monoamines.[5] The acidity constants of the tertiary-protonated (HTP) and primary-protonated (TPH) forms of **2**[26] were assumed to be the same as the values ($pK_{HTP} \approx 9.32$ and $pK_{TPH} \approx 9.24$) estimated previously for **3**.[16] This gives the same k_B (0.00435 M^{-1} s^{-1}) used previously for **3**.[5] It also permits us to estimate that 7.9% of monoprotonated **2** is TPH, 9.6% is HTP, and 82.5% is THP.[26] The latter form was assumed to be catalytically inactive, and k_B' was calculated from eq 9.

$$k_p = k_B[\mathrm{Am}] + k_B'[\mathrm{AmH^+}] + k_h[\mathrm{OH^-}] \qquad (8)$$

$$k_B' = 0.079k_{TPH} + 0.096k_{HTP} \qquad (9)$$

The rate constant for TPH was calculated, like those for other monopositively charged tertiary amines,[5] by assuming that the point fell on a Brønsted line through the point for $Me_2N(CH_2)_3NMe_3^+$ and having the same slope as the Brønsted line for electrically neutral amines of the type RCH_2NMe_2. As before, the rate constant for the primary amine (k_{HTP}) was assumed to be one-seventh as large as for the corresponding tertiary amine. This gives a k_{TPH} value of 0.0014 M^{-1} s^{-1} and a k_B' value of 0.00013 M^{-1} s^{-1}.

Scheme V



Scheme V was used for the dedeuteration of acetone-d_6 assuming no cis–trans isomerization of the intermediate iminium ions. In this scheme the ketones (K's) and iminium ions (B's) are represented by abbreviations including the number of deuterium atoms on each side of the carbonyl group or carbon–nitrogen double bond. Thus, K33 is CD_3COCD_3, K32 is CD_3COCD_2H, K21 is HCD_2COCH_2D, K10 is DCH_2COCH_3, etc. In the iminium ion abbreviations, the location of the B indicates the set of deuterium atoms that are cis to the basic dimethylamino

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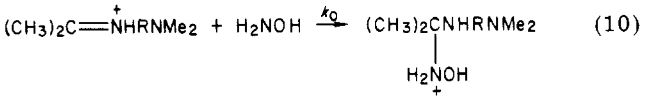
(25) Hine, J.; Kaufmann, J. C.; Cholod, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 4590–5.

(26) The internally hydrogen-bonded form is denoted THP.

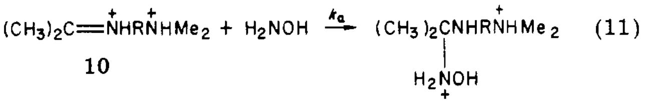
group from the catalyst. Thus, 32B is the iminium ion derived from CD_3COCD_2H in which the dimethylamino group is cis to the CD_2H group. Internal catalysis of dedeuteration changes 32B to 31B. The assumption that protium and deuterium atoms are distributed randomly among the exchangeable positions at equilibrium leads to the calculation that about 15% K10 will be present at equilibrium but no more than 1% of any more highly deuterated species. The rate constants k_r and k_r' in Scheme V allow for reversibility to give the proper equilibrium amount of K10 at infinite reaction. Similar allowance is made in Scheme II.

For both schemes, calculations were made by the differential reaction method, in which the total reaction time is divided up into small increments, and the concentrations of the various species were treated as constants within a given time increment. The size of the time increments was decreased until halving the increments no longer changed the results obtained.

The rate constant k_0 in eq 4 is taken to be the rate constant for the process shown in eq 10, in which R is that part of **2** that is between the primary amino group and the dimethylamino group. Similarly, k_a is taken to be the rate constant for the process shown in eq 11. The reactant in eq 10 is just the conjugate base of the reactant in eq 11, and the immediate reaction product in eq 10 is the conjugate base of that in eq 11. Hence, we may use the concept of the acidity of transition states[27a,28] and treat the transition state for k_0 as the conjugate base of the transition state for k_a. The ratio k_a/k_0 is set equal to the reciprocal of the acidity constant of the dimethylammonio group in the k_a transition state. In the present case, the nitrogen atoms whose basicity we are considering is separated by three carbon atoms and another nitrogen atom from the carbon atom at which nucleophilic attack is taking place. Hence, the state of protonation of the dimethylamino group should have much less effect on where, along the reaction coordinate, the transition state lies than if we were considering the state of protonation of the attacking hydroxylamine, for example.



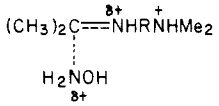
$$(CH_3)_2C{=}\overset{+}{N}HRNMe_2 + H_2NOH \xrightarrow{k_0} (CH_3)_2\underset{H_2\underset{+}{N}OH}{\overset{}{C}}NHRNMe_2 \qquad (10)$$



$$\underset{\mathbf{10}}{(CH_3)_2C{=}\overset{+}{N}HR\overset{+}{N}HMe_2} + H_2NOH \xrightarrow{k_a} (CH_3)_2\underset{H_2\underset{+}{N}OH}{C}NHR\overset{+}{N}HMe_2 \qquad (11)$$

11

Let us represent the transition state for the k_a reaction as 12, in which the δ's have values between 0 and 1.0, and the dashed bonds are somewhere between full bonds and no bonds at all. The acidity of the dimethylammonio group in **12** should be intermediate between the acidity of the dimethylammonio group in **10** and that in **11**. Of course, **10** is just the diprotonated form of **2** (HTPH) with two of the hydrogen atoms on the primary amino group replaced by an isopropylidene group. This transformation of a nitrogen atom four atoms away from the acidic proton from sp^3 to sp^2 hybridization should not have much effect on the acidity (measured by pK_{HTPH}). For diprotonated **2**, pK_{HTPH} is assumed to be the same as the value estimated for diprotonated **3**. Since K_{HTPH} is equal to $K_2 f_p$, pK_{HTPH} is 7.36.[16] To estimate the effect of changing from sp^3 to sp^2 the hybridization of an atom that is four atoms away from the acidic proton we note that ρ^* for $CH_3CH{=}CH$ is 0.48 larger than that for $CH_3CH_2CH_2$[27b], that ρ^* for R_3NH^+ is 3.3,[29] and that an average "fall-off" factor for removing a substituent from the reaction center by an additional atom is 2.8.[27b]. This gives a correction of $(0.48)(3.3)/(2.8)^3$ or 0.07, giving an estimated pK of 7.29 for **10**. To estimate the pK_a of the dimethylammonio group of **11**, we start with the pK_{HTP} for monoprotonated **2** (9.32)[16] and allow for the effect of a positive charge six atoms away by noting that the pK_1 − pK_2 for 1,5-diaminopentane is 1.12,[30] of which 0.60 is a statistical effect. The remaining 0.52 changes 9.32 to 8.80 as an estimated pK_a for **11**.



$$(CH_3)_2\overset{\delta+}{C}{=}{=}{=}NHR\overset{+}{N}HMe_2 \;\vdots\; H_2\underset{\delta+}{N}OH$$

12

Registry No. **2**, 86992-77-0; **2**·2HCl, 86992-78-1; **5**, 14932-21-9; **6**, 86943-98-8; **7**, 86943-99-9; Me_2NH, 124-40-3; acetone-d_6, 666-52-4; hydroxylamine, 7803-49-8.

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(27) (a) Hine, J. "Physical Organic Chemistry", 2nd ed; McGraw-Hill: New York, 1962; section 5-2e. (b) Ref 27a; section 4-4.

(28) Hine, J.; Bayer, R. P. *J. Am. Chem. Soc.* **1962**, *84*, 1989–93.

(29) Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Robert Krieger Publishing Co.: Huntington, NY, 1981; p 163.

(30) Perrin, D. D. "Dissociation Constants of Organic Bases in Aqueous Solution"; Butterworths: London, 1965; p 47.