Internal Catalysis in Imine Formation from Acetone and Acetone-d_6 and Conformationally Constrained Derivatives of *N,N*-Dimethyl-1,3-propanediamine

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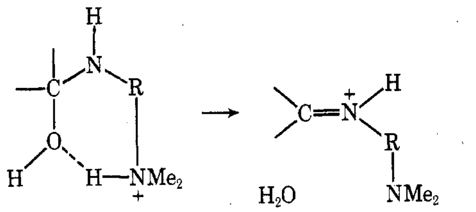
The kinetics of the reactions of 3-*exo*-dimethylaminomethyl-2-*endo*-norbornanamine (1), *cis*-2-(dimethylaminomethyl)cyclohexylamine (2), and 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine with acetone, and of these three diamines, neopentylamine, and 2-*endo*-norbornanamine with acetone-d_6 to give imines have been studied at 35° and various pH's by use of hydroxylamine to capture the imines as they are formed. Acetone-d_6 was more reactive than acetone in the reactions with hydroxylamine alone as well as in the reactions with each of the diamines; the average k^D/k^H was 1.2. The rate constants for the monoprotonated diamines were so large relative to those for the unprotonated diamines that reliable values for the latter could not be obtained. The dominant reaction mechanism appears to be a reversible formation of the carbinolamine derived from the tertiary-protonated form of the monoprotonated diamine followed by rate-controlling internal acid-catalyzed formation of the iminium ion. The rate constants are compared with those obtained as a by-product of deuterium exchange studies of reactions of **1**, **2**, **3**, and five other monoprotonated diamines by the same mechanism. The comparisons show that structural features that destabilize conformations in which the two amino groups are far apart may decrease the reactivity by relative stabilization of a cyclic hydrogen-bonded form of the monoprotonated diamine as well as increasing the reactivity by relative stabilization of the transition state. Freezing the H_2N–C–C–CH_2NMe_2 dihedral angle of 1,3-diamines at values near 0, 60, and 120° does not give large differences in reactivity. Comparison of the rate constants for reactions of unprotonated neopentylamine and 2-*endo*-norbornanamine with those obtained previously for amines of the type $XCH_2CH_2NH_2$ gives no evidence for steric hindrance.

Imine formation in the reactions of isobutyraldehyde[2] and acetone[3] with the monoprotonated forms of certain diamines is much faster than would be expected from data on primary amines with similar basicities and steric properties but without acidic substituents. This has been explained in terms of internal acid catalysis of the dehydration of the intermediate carbinolamine. Monoprotonated *trans*-2-(dimethylaminomethyl)cyclopentylamine, which may be considered a derivative of monoprotonated 3-dimethylaminopropylamine in which rotation around the C-1–C-2 bond has been constrained, reacts with acetone to give imine more than four times as rapidly as monoprotonated 3-dimethylaminopropylamine does. To learn more about how such conformational constraints influence internal acid catalysis in imine formation we have studied additional derivatives of 3-dimethylaminopropylamine using more rigid compounds than used previously and constraining the dihedral angle between the C-1–N and C-2–C-3 bonds to values of about 0, 60, and 120°.



Rates of imine formation are useful in interpreting data on bifunctional catalysis of the dedeuteration of acetone-d_6 by derivatives of 3-dimethylaminopropylamine.[4] For this reason we have studied the kinetics of formation of imines from acetone-d_6 as well as ordinary acetone.

Results

The equilibrium constants for imine formation from acetone and most primary amines in aqueous solution are too small for reliable rate constants to be obtained by direct measurements on the reaction. Hence we used the method described previously, in which the imine is captured as rapidly as it is formed by hydroxylamine, which transforms it to the oxime almost irreversibly.[3] That is, the kinetics of oxime formation are studied in the presence of the primary amines as catalysts. In order to determine the extent of such catalysis we must know how fast the oximation is in the absence of the catalyst. The oximation of acetone-d_6 in the absence of primary amines was carried out under conditions similar to those used for acetone of normal isotopic composition.[3] The reaction was studied in water at 35° using 0.010 M acetone d_6, 0.097 M hydroxylamine, and an ionic strength of 0.297. Trimethylamine buffers were used between pH 7.24 and 10.51 and N-methylmorpholine buffers in the overlapping pH range 6.68–7.87. Since no general acid or base catalysis had been found with acetone, there was assumed to be none for acetone-d_6. The first-order rate constant obtained in a given run was divided by the initial concentration of unprotonated hydroxylamine to obtain a second-order rate constant. These second-order rate constants are probably made about 4% too small by neglect of the decrease in hydroxylamine concentration during the reaction and perhaps as much as another 9% too small by neglect of the small amount of hydroxylamine that was tied up as $Me_2C(OH)NHOH$. However, these uncertainties will have little effect on comparisons of the resulting rate constants with those obtained for ordinary acetone, which were calculated in the same way, or in using the rate constants to correct data obtained using primary amine catalysts for the "background" reaction rate, which is subject to essentially the same uncertainties. The second-order rate constants (k_{ox}) obtained are listed in Table III[5] and plotted logarithmically against the pH in Figure 1. They are fit by eq 1 with a standard deviation of 3.7%.[6] However, the reliability of this division of the total reaction rate into three terms is reduced by the fact that the third term never contributed more than about 50% to the overall reaction rate, and in the low pH region where the first term dominates the reaction rate and the high pH region where the second term does, the reaction is so fast that the observed values of k_{ox} are of reduced reliability. Comparison of eq 1 with the

$$k_{ox} = (2.71 \times 10^6 a_{H^+} + 2.20 \times 10^{-12}/a_{H^+} + 6.83 \times 10^{-3})\ M^{-1}\ \text{sec}^{-1} \quad (1)$$

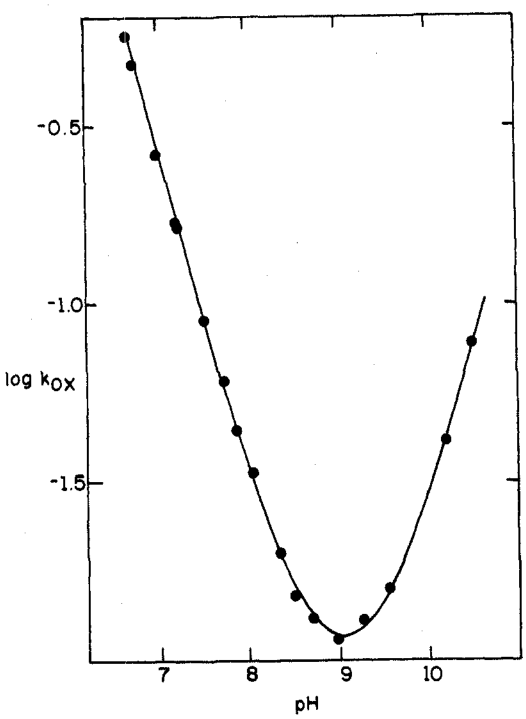


Figure 1. Plot of rate constants for oxime formation by acetone-d_6 vs. pH. Curve calculated from eq 1.

analogous equation obtained previously for ordinary acetone gives k^{D}/k^{H} values of 1.16, 1.47, and 1.31 for the first, second, and third terms, respectively.

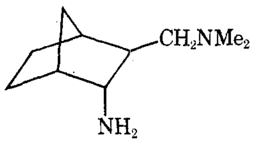
In the presence of a primary amine the reaction may be represented as shown in eq 2–4.

$$\mathrm{Me_2CO} + \mathrm{H_2NOH} \xrightarrow{k_{ox}} \mathrm{Me_2C{=}NOH} \quad (2)$$

$$\mathrm{Me_2CO} + \mathrm{H_2NR} \underset{k_{-im}}{\overset{k_{im}}{\rightleftharpoons}} \mathrm{Me_2C{=}NR} \quad (3)$$

$$\mathrm{Me_2C{=}NR} + \mathrm{H_2NOH} \xrightarrow{k_{hx}} \mathrm{Me_2C{=}NOH} + \mathrm{RNH_2} \quad (4)$$

If $k_{hx}[\mathrm{H_2NOH}]$ is much larger than k_{-im} capture of the imine will be essentially quantitative and the only effect of increases in the hydroxylamine concentration on the reaction rate will arise from the k_{ox} term. If $k_{hx}[\mathrm{H_2NOH}]$ is comparable to or smaller than k_{-im} increases in hydroxylamine concentration will increase the rate both because of the direct reaction (the k_{ox} term) and because of increased efficiency of capturing the imine. Evidence was described that 0.08 M hydroxylamine was enough to capture essentially all the intermediate imine in the case of all the diamines studied previously, and 0.03 M was enough for the monoamines.[3] Hence these concentrations were used in the present study. In addition, runs were made in the presence of 3-*exo*-dimethylaminomethyl-2-*endo*-norbornanamine (**1**) at pH 9.1 using 0.04 and 0.15 M hydroxylamine and in the presence of *cis*-2-(dimethylaminomethyl)cyclohexylamine (**2**) using 0.15 M hydroxylamine at pH 8.7 and 10.1



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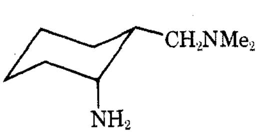

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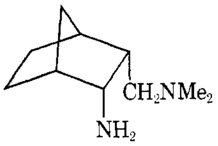
and the dependence of the observed reaction rate on the concentration of hydroxylamine found to be within the experimental uncertainty of that expected from the k_{ox} term alone.

First-order rate constants for the formation of oxime from acetone or acetone-d_6 in the presence of **1**, **2**, or 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine (**3**)



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are listed in Tables IV–VIII.[5] The observed first-order rate constants may be expressed as shown in eq 5

$$k_{obsd} = k_{ox}[\mathrm{H_2NOH}] + k_{a}[\mathrm{Am}] + k_{ah}[\mathrm{AmH^+}] \quad (5)$$

in which k_{ox} is given by eq 1 for acetone-d_6 or an analogous equation[3] for acetone, k_a is the second-order rate constant for imine formation from the unprotonated diamine, and k_{ah} is the corresponding rate constant for monoprotonated diamine. Values of k_a and k_{ah} obtained from the data in Tables IV–VIII by least-squares fits[6] to eq 5 gave k_{calcd} values that differed from the k_{obsd} values by standard deviations of 5.1–10.7%. However, some of the values of k_a obtained were implausible. One value was zero and would have been negative if the method of treating the data had permitted it. In no run was the calculated value of $k_a[\mathrm{Am}]$ as much as 21% as large as k_{obsd}. Hence it was decided that the k_a values could be estimated more reliably than they could be determined. A plot of the values of log k_a for six electrically neutral amines of the type $\mathrm{XCH_2CH_2NH_2}$ vs. the pK_a values of the corresponding $\mathrm{XCH_2CH_2NH_3^+}$ was earlier found[3] to closely approach a straight line of slope 0.59. In view of the possibility that the primary amino groups presently being studied are too hindered to be expected to give k_a values that would fall near this line, we studied the kinetics of imine formation of neopentylamine and 2-*endo*-norbornanamine using acetone-d_6. From the rate constants obtained in the individual runs, which are listed in Tables IX and X,[5] and the values of pK_a at 35° for the conjugate acids of these amines, which are 9.83 (calculated from data at 16–25°) and 10.03 for the neopentyl and norbornyl compounds, respectively,[7] second-order rate constants of 0.085 and 0.080 M^{-1} sec^{-1} were obtained. The latter value, referring to the norbornanamine, is essentially that required to fit on the plot of log k_a values for $\mathrm{XCH_2CH_2NH_2}$ compounds vs. the corresponding pK_a values, when allowance is made for the ~20% greater reactivity of acetone-d_6 than ordinary acetone that may be seen in our other results. Even when allowance is made for this secondary deuterium kinetic isotope effect the value 0.085 M^{-1} sec^{-1} for the reaction of neopentylamine with acetone-d_6 is about 50% too large to fit the plot of log k_a values for $\mathrm{XCH_2CH_2NH_2}$ compounds.

Having found no evidence for steric hindrance in the rate constants for imine formation we assumed that the values of log k_a for **1**, **2**, and **3** would fall on the plot for $\mathrm{XCH_2CH_2NH_2}$ that we have referred to. This assumption and the pK_a values that have been estimated for the forms of the monoprotonated diamines that are protonated at the primary amino groups (that is, the pK_{TPH} values, which are 9.70, 9.55, and 9.24, respectively[7]) gave k_a values of 0.040, 0.032, and 0.021 M^{-1} sec^{-1}, respectively. The k_a values for reaction with acetone-d_6 were then obtained by multiplying these rate constants by a k^{D}/k^{H} value of 1.2 (the average of the values for k_{ah}). These estimated k_a values were used to calculate the corresponding k_{ah} values by the method of least squares.[6] The resulting k_{ah} values, which are listed in Table I, give the k_{calcd} values listed in Tables IV–VIII, whose standard deviations from the k_{obsd}

Table I
Kinetics of Imine Formation from Acetone or Acetone-d_6 and 2-Dimethylaminomethyl Cyclic Amines[a]

	CH_3COCH_3		CD_3COCD_3		
Amine	10^3 k_a[b]	10^3 k_{ah}	10^3 k_a[b]	10^3 k_{ah}	k^D_{ah}/k^H_{ah}
1	40	147	48	151	1.03
2	32	172	39	206	1.20
3	21	307	25	394	1.28

[a] In water at 35°. All rate constants in M^{-1} sec^{-1}. [b] Estimated as described in the text.

values ranged from 7.2 to 10.7% for the six sets of values. These standard deviations are very little larger than those obtained using k_a values obtained from the regression analysis. In fact, the k_a term in eq 5 may be completely neglected without changing the resultant k_{ah} values by more than 10% from those listed in Table I and without raising any standard deviation of the k_{calcd} values from a set of k_{obsd} values above 13.5%. Hence the values obtained for k_{ah} are relatively independent of the uncertainties in the k_a values.

Discussion

The values of k^D/k^H show that acetone-d_6 is more reactive than acetone in each of the three pathways for oxime formation covered by eq 1 and in imine formation by each of the three monoprotonated diamines studied. All these reactions are believed to involve relatively rapid reversible addition to the carbonyl group to give a carbinolamine whose dehydration is rate controlling.[8] The oximation of acetone-d_6 has also been found to be faster than that of acetone in acidic solution where attack of hydroxylamine on the carbonyl group is the rate-controlling step.[9] Our results are consistent with a steric explanation based on the smaller effective van der Waals radius of covalently bonded deuterium relative to protium.[9-12] A probable uncertainty of about 10% in our k^D/k^H values makes it unclear which of the differences among our k^D/k^H values are experimentally significant. Therefore discussion of whether any of the additional factors suggested to account for secondary deuterium kinetic isotope effects are important in our reactions is not warranted.

Values of k_{ah} for reactions of acetone-d_6 with a number of dimethylamino-substituted primary amines are listed in Table II. These include the three values obtained in the present work and values obtained less directly for some other 1,3-diamines and a 1,4-diamine as a by-product of studies of diamine catalysis of the deuterium exchange of acetone-d_6.[4,13] Also listed are values for compounds of the type $Me_2N(CH_2)_nNH_2$, where n is 2, 3, and 4, obtained from data on the reaction with acetone[3] and the assumption that the ratio k_{ah}^D/k_{ah}^H equals 1.2. The values of k_{ah} obtained from dedeuteration studies, which are parenthesized, deviate from those obtained (under slightly different conditions) from oximation rate measurements by an average of 22%. We do not believe that these deviations are large enough to mask any significant trends in the k_{ah} values listed.

According to the plot of log k vs. pK values referred to earlier, even the most basic of the monoprotonated diamines having three carbon atoms between the two amino groups should not have a k value larger than about 0.003 M^{-1} sec^{-1} if there were no internal acid catalysis of dehydration of the intermediate carbinolamine. Hence the k_{ah} values for all these amines probably arise largely from such catalysis.

The values of k_{ah} listed are second-order rate constants for reaction of acetone-d_6 with the *average* monoprotonated diamine. However, since the rate-controlling step is believed to be a first-order reaction of the carbinolamine arising from addition of the tertiary-protonated diamine to the acetone, we believe that it is more meaningful to compare second-order rate constants based on tertiary-protonated diamines. These, which are denoted k'_{ah}, are obtained by dividing k_{ah} by f_t, the fraction of the monoprotonated diamine that is protonated at the tertiary amino group. The values of f_t estimated previously[7,14] are listed in Table II. The largest variation in f_t values does not arise from variations in the ratio of f_t to f_p (the fraction of primary-protonated diamine); instead it arises from variations in f_c, the fraction of the monoprotonated diamine that exists as a cyclic hydrogen-bonded species in which the proton is attached to both amino groups at the same time.

The transition state for the internally acid-catalyzed transformation of the carbinolamine to an iminium ion and a molecule of water is presumed to be subject to the con-

Table II
Rate Constants for Imine Formation from Acetone-d_6 and Some Monoprotonated Diamines[a]

Diamine	10^3 k_{ah}[b] M^{-1} sec^{-1}	100 k'_{ah} M^{-1} sec^{-1}	pK_1[c]	f_t[c]	f_c[c]
3	394 (406)	113	9.78	~0.35	~0.36
$Me_2NCH_2CH_2NH_2$	364[d]	96	9.30[e]	0.38[e]	0.0[e]
2	206 (176)	103	10.02	0.20	0.46
trans-(2-Dimethylaminomethyl)cyclopentylamine	168[d] (219)	51	9.80	0.33	~0.11
1	151 (214)	61	9.92	~0.25	~0.15
$Me_2NCH_2CHMeCH_2NH_2$	(63)	23	9.87	0.28	0.24
trans-(2-Dimethylaminomethyl)cyclohexylamine	(51)	46	10.29	0.11	0.71
$Me_2N(CH_2)_3NH_2$	39[d] (32)	13	9.91	0.30	0.0
$Me_2N(CH_2)_4NH_2$	27[d]	8	10.17[e]	0.33[e]	0.0[e]
$Me_2NCH_2CMe_2CH_2NH_2$	(~13)	~12	10.03	0.11	0.71
o-(Dimethylaminomethyl)benzylamine	(8)	37	10.07	0.022	0.934

[a] In water at 35°. [b] Parenthesized values were obtained from studies[4,13] of diamine catalysis of the dedeuteration of acetone-d_6. The other values were obtained from studies of diamine catalysis of oximation. [c] K_1 is the acidity constant of the monoprotonated diamine, which exists as a cyclic internally hydrogen-bonded species to the extent f_c and as a tertiary protonated species to the extent f_t. These data are from ref 7 unless otherwise noted. [d] From data on acetone of normal isotopic composition and the assumption that k^D_{ah}/k^H_{ah} equals 1.2. [e] From ref 14.

Table III

Kinetics of the Reaction of Acetone-*d*$_6$ with Hydroxylamine in Water at 35°[a]

pH	10^3k_1 (sec^{-1})	10^3k_{ox} (M^{-1} sec^{-1}) obsd	10^3k_{ox} (M^{-1} sec^{-1}) calcd
6.679	49.7	564	574
6.747	42.3	475	492
7.006	24.2	263	274
7.211	16.2	170	174
7.242[b]	15.6	164	162
7.521	8.78	90.5	88.6
7.735[b]	5.92	60.6	56.8
7.872	4.33	44.2	43.4
8.049	3.29	33.6	31.3
8.351	1.96	19.9	19.4
8.500	1.48	15.1	16.1
8.697	1.29	13.0	13.4
8.980	1.12	11.4	11.8
9.266	1.27	12.9	12.4
9.561	1.53	15.8	15.6
10.201	3.93	41.2	41.9
10.507	7.48	78.0	77.6

[a] Initial concentrations of hydroxylamine and acetone, 0.0971 ± 0.0014 and 0.0100 *M*, respectively. Sodium chloride added to bring the ionic strength to 0.297 ± 0.003. Trimethylamine buffers were used in all runs above pH 8 and *N*-methylmorpholine buffers in all runs below pH 8 unless otherwise noted. Total buffer concentrations were 0.10 *M*
[b] Trimethylamine buffer used.

Table IV

Oximation of Acetone in the Presence of 3-*exo*-(Dimethylaminomethyl)-2-*endo*-norbornanamine (**1**)[a]

[Diamine]$_t$ *M*	[H$_2$NOH]$_t$ *M*	pH	10^3k_{obsd} sec^{-1}	10^3k_{ox}[H$_2$NOH] sec^{-1}	10^3k_{calcd} sec^{-1}
0.0196	0.0806	7.601	5.32	5.08	5.80
0.0197	0.0808	7.652	5.40	4.58	5.37
0.0212	0.0815	7.681	4.37	4.35	5.25
0.0212	0.0815	8.042	4.04	2.16	3.65
0.0212	0.0815	8.245	2.78	1.52	3.36
0.0212	0.0815	8.697	2.77	0.87	3.30
0.0212	0.0875	8.882	3.39	0.82	3.39
0.0386	0.1543	9.080	6.70	1.38	6.19
0.0199	0.0375	9.082	3.38	0.34	2.82
0.0399	0.0375	9.090	6.26	0.34	5.32
0.0196	0.1562	9.102	4.21	1.40	3.84
0.0212	0.0815	9.266	3.49	0.75	3.40
0.0212	0.0814	9.395	3.28	0.80	3.42
0.0212	0.0815	9.575	3.48	0.93	3.46
0.0212	0.0815	9.772	3.46	1.18	3.55
0.0212	0.0815	9.970	4.02	1.58	3.76
0.0212	0.0815	10.142	4.04	2.13	4.12
0.0392	0.0805	10.258	5.95	2.67	6.07
0.0394	0.0808	10.458	7.07	3.91	7.00
0.0394	0.0808	10.695	9.21	6.43	9.17
0.0394	0.0808	11.075	16.0	14.8	17.2

[a] In water at 35° with an initial acetone concentration of 0.0100 *M*. Sodium chloride present to bring the ionic strength to 0.286 ± 0.006 unless otherwise noted.

Table V

Oximation of Acetone-*d*$_6$ in the Presence of 3-*exo*-(Dimethylaminomethyl)-2-*endo*-norbornanamine (**1**)[a]

pH	10^3k_{obsd} sec^{-1}	10^3k_{ox}[H$_2$NOH] sec^{-1}	10^3k_{calcd} sec^{-1}
7.601	6.89	5.94	6.71
7.681	5.50	5.10	6.06
8.042	4.92	2.57	4.15
8.245	4.04	1.84	3.78
8.697	3.44	1.09	3.66
9.266	3.80	1.01	3.78
9.395	3.41	1.09	3.82
9.575	3.87	1.29	3.91
9.772	4.50	1.65	4.09
9.970	4.60	2.25	4.45
10.142	5.40	3.06	5.04
10.258	7.51	3.77	7.16
10.458	8.35	5.66	8.62
10.695	11.6	9.36	11.9
11.075	21.5	21.7	23.8

[a] In water at 35° with an initial acetone-*d*$_6$ concentration of 0.0100 *M*. The concentrations of diamine and hydroxylamine are the same as in the runs at the same pH listed in Table IV. Ionic strengths are 0.283 ± 0.006.

Table VI

Oximation of Acetone in the Presence of *cis*-2-(Dimethylaminomethyl)cyclohexylamine (**2**)[a]

[Diamine]$_t$ *M*	[H$_2$NOH]$_t$ *M*	pH	10^3k_{obsd} sec^{-1}	10^3k_{ox}[H$_2$NOH] sec^{-1}	10^3k_{calcd} sec^{-1}
0.0207	0.0815	7.462	7.49	6.87	8.48
0.0206	0.0813	7.752	5.33	3.76	5.94
0.0205	0.0808	8.143	4.55	1.79	4.59
0.0207	0.0812	8.383	4.45	1.24	4.30
0.0206	0.0811	8.437	4.49	1.15	4.24
0.0207	0.0815	8.636	4.12	0.92	4.13
0.0203	0.1481	8.702	4.72	1.57	4.74
0.0206	0.0813	8.833	4.01	0.78	4.03
0.0206	0.0810	9.067	4.52	0.72	3.96
0.0207	0.0815	9.172	4.17	0.73	3.95
0.0206	0.0813	9.393	3.93	0.80	3.89
0.0206	0.0812	9.751	3.64	1.14	3.89
0.0206	0.0814	9.830	3.51	1.28	3.92
0.0201	0.1583	10.145[b]	6.30	4.20	6.28
0.0206	0.0810	10.197	4.30	2.35	4.43
0.0207	0.0815	10.335	5.40	3.08	4.95
0.0206	0.0813	10.512	6.36	4.46	6.00

[a] In water at 35° with an initial acetone concentration of 0.0100 *M*. Ionic strength 0.297 ± 0.017 unless otherwise noted. [b] Ionic strength 0.353.

Table VII

Oximation of Acetone-*d*$_6$ in the Presence of *cis*-2-(Dimethylaminomethyl)cyclohexylamine (**2**)[a]

pH	10^3k_{obsd} sec^{-1}	10^3k_{ox}[H$_2$NOH] sec^{-1}	10^3k_{calcd} sec^{-1}
7.462	9.89	8.02	10.09
7.752	7.06	4.42	7.21
8.143	5.71	2.14	5.71
8.437	5.25	1.40	5.33
8.702	5.74	1.97	5.98
8.833	4.98	1.00	5.08
9.172	4.98	0.97	4.93
9.393	5.38	1.09	4.79
9.751	4.58	1.60	4.63
10.145	7.55	5.98	7.85
10.197	5.17	3.37	5.14

[a] In water at 35° with an initial acetone concentration of 0.0100 *M*. The concentrations of diamine and hydroxylamine and the ionic strengths are the same as in the runs at the same pH listed in Table VI.

Table VIII

Oximation of Acetone and Acetone-*d*$_6$ in the Presence of 3-*endo*-Dimethylaminomethyl-2-*endo*-norbornanamine (**3**)[a]

	CH$_3$-CO-CH$_3$			CD$_3$-CO-CD$_3$		
pH	10^3k_{obsd} sec^{-1}	10^3k_{ox}[H$_2$NOH] sec^{-1}	10^3k_{calcd} sec^{-1}	10^3k_{obsd} sec^{-1}	10^3k_{ox}[H$_2$NOH] sec^{-1}	10^3k_{calcd} sec^{-1}
7.292	13.4	9.42	12.4	13.7	11.0	14.9
7.817	7.88	3.16	7.66	10.2	3.72	9.64
8.013	6.70	2.17	7.05	9.14	2.58	9.00
8.302	6.88	1.33	6.57	8.63	1.61	8.49
8.608	6.70	0.90	6.28	8.88	1.12	8.18
9.046	5.95	0.70	5.96	7.62	0.91	7.76
9.177	5.93	0.70	5.85	7.63	0.93	7.61
9.489	5.84	0.82	5.54	6.68	1.13	7.16
9.631	4.82	0.95	5.40			
9.678	5.11	1.00	5.35	7.12	1.39	6.89
9.815[b]	9.01	1.20	9.29	10.8	1.68	11.8
10.318	6.47	2.84	5.80	8.28	4.10	7.53

[a] In water at 35°, with total hydroxylamine and diamine concentrations of 0.0778 and 0.0202 *M*, respectively, unless otherwise noted. Sodium chloride was present as needed to give an ionic strength of 0.0283 ± 0.005. Initial concentration of acetone or acetone-*d*$_6$ 0.0100 *M*. [b] Total diamine concentration 0.0403 *M*.

Table IX

Oximation of Acetone-*d*$_6$ in the Presence of Neopentylamine[a]

pH	10^3k_{obsd} sec^{-1}	10^3k_{ox}[H$_2$NOH] sec^{-1}	10^3k_{calcd} sec^{-1}
8.606	0.986	0.432	0.775
8.798	1.04	0.375	0.898
9.250	1.68	0.368	1.70
9.612	3.25	0.495	3.04
9.820	4.16	0.653	4.12
9.930	5.33	0.776	4.78
10.260	5.50	1.410	6.99

[a] In water at 35°, with total initial concentrations of acetone-*d*$_6$, hydroxylamine, and neopentylamine of 0.0100, 0.0300, and 0.100 *M*, respectively. Sodium chloride was present as needed to give an ionic strength of 0.31.

Table X

Oximation of Acetone-*d*$_6$ in the Presence of 2-*endo*-Norbornanamine[a]

pH	10^3k_{obsd} sec^{-1}	10^3k_{ox}[H$_2$NOH] sec^{-1}	10^3k_{calcd} sec^{-1}
8.618	0.513	0.430	0.642
9.152	1.14	0.358	1.04
9.568	2.14	0.473	2.05
9.718	2.78	0.553	2.62
9.912	3.93	0.756	3.57
10.110	4.30	1.06	4.75

[a] In water at 35°, with total initial concentrations of acetone-*d*$_6$, hydroxylamine, and norbornanamine of 0.0100, 0.0300, and 0.100 *M*, respectively. Sodium chloride was present as needed to give an ionic strength of 0.275 ± 0.015.

straints described previously, that the N–H–O angle be fairly near 180°, the C–N–H and C–O–H angles be fairly near 109°, and the four atoms attached to the C–N double bond that is being formed be fairly nearly coplanar.[3] Molecular models meeting these requirements for the carbinolamine derived from $H_2NCH_2CH_2CH_2NHMe_2^+$ can be constructed with H_2N–C–C–CH_2 dihedral angles ranging from about 0° to about 120° without obviously large differences in strain. Of the eight diamines listed that have three carbon atoms between their two amino groups, all five in which this dihedral angle is held between 0° and about 120° have k'_{ah} values of $0.79 \pm 0.34\ M^{-1}\ \sec^{-1}$. The parent compound *N,N*-dimethyl-1,3-propanediamine, which probably exists largely as a trans conformer with a H_2N–C–C–CH_2 dihedral angle of 180°, has a considerably smaller k'_{ah} value. Introduction of a 2-methyl substituent to give *N,N*,2-trimethyl-1,3-propanediamine, for which there is now no conformer that has the advantage of being free from any gauche interaction of the primary amino group with a methylene group, increases k'_{ah} by 70%. A second methyl substituent, which gives *N,N*,2,2-tetramethyl-1,3-propanediamine, causes a decrease in reactivity, however, presumably because of crowding in the transition state. This decrease in reactivity is seen to be merely to the level of reactivity of the parent compound, not to a lower level, as would be implied by the k_{ah} values. The smaller value of k_{ah} for *N,N*,2,2-tetramethyl-1,3-propanediamine arises from the relatively great stability of the cyclic hydrogen-bonded form of the monoprotonated amine.

The values of k_{ah} for the two compounds having four carbon atoms between the two amino groups show that freezing the H_2NC–C–C–$CNMe_2$ dihedral angle near 0°, as has been done in *o*-(dimethylaminomethyl)benzylamine, gives an almost threefold *decrease* in reactivity relative to *N,N*-dimethyl-1,4-butanediamine, in which this angle is free to change but is presumably 180° in the most highly populated conformer. The values of k'_{ah}, however, show that the 0° dihedral angle *increases* the reactivity almost sixfold when correction is made for the large fraction of monoprotonated diamine tied up in the cyclic hydrogen-bonded form.

The marked catalytic activity of the monoprotonated form of the highly flexible *N,N*-dimethylethylenediamine suggests that monoprotonated forms of appropriately conformationally constrained 1,2-diamines would be better catalysts for the oximation of acetone than any of the species studied in the present investigation. The differences in relative reactivities as measured by k_{ah} values and those as measured by k'_{ah} values warn us that structural features that disfavor conformers in which the two amino groups are far apart may have the counterproductive result of relatively stabilizing the cyclic hydrogen-bonded form of the monoprotonated diamine as well as the desired result of relatively stabilizing the transition state for iminium ion formation. However, studies with molecular models indicate that when the two amino groups have rigidly been given the optimum relative geometry for internally acid-catalyzed iminium ion formation, their relative geometry is unfavorable for internal hydrogen bonding.

The reactions were not thoroughly tested for general acid and base catalysis. However, several tests, such as the four runs on **1** near pH 9.09, give no indication of general catalysis. Furthermore, none was found previously in similar reactions, where the case of 2-dimethylaminoethylamine was tested several times. Hence, general catalysis is not likely to be very important.

Experimental Section

The synthesis and properties of **1**, **2**, and **3** have been described previously,[15] as have the methods used in following the kinetics of oximation[3] and the pK values used for the amines.

Registry No.—**1**, 53369-68-9; **2**, 53369-73-6; **3**, 53403-34-2; acetone, 67-64-1; acetone-d_6, 666-52-4; hydroxylamine, 7803-49-8; neopentylamine, 5813-64-9; 2-*endo*-norbornanamine, 31002-73-0.

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Oxidation Reactions of 2,2,2-Fluorodinitroethylamine and Some *N*-Alkyl-2,2,2-fluorodinitroethylamines

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2,2,2-Fluorodinitroethylamine is readily oxidized to the hydroxylamine, oxime, and nitrile oxide; further oxidation under forcing conditions leads to cleavage of the carbon–carbon bond. *N-tert*-Butyl-2,2,2-fluorodinitroethylamine behaves similarly, but *N*-alkyl derivatives possessing an α-methylene group are converted to *N*-fluorodinitroethylamides.

Oxidation reactions of β-polynitroalkylamines have apparently not been studied, although many such amines have been prepared by the Mannich reaction of β-polynitroalkanols and aliphatic amines (eq 1).[1,2]

$$XC(NO_2)_2CH_2OH + HNRR' \longrightarrow XC(NO_2)_2CH_2NRR' \quad (1)$$

$$X = \text{halogen, alkyl, } NO_2$$

$$R, R' = \text{alkyl, H}$$

Most of the known β-polynitroalkylamines are secondary and tertiary; primary ones have limited stability and only one has been described.[3]

We report here on a number of oxidation reactions of 2,2,2-fluorodinitroethylamine and some of its derivatives. Since the electronic effects of the dinitroalkyl group appear to determine the reactivity behavior of these materials, many of our observations are probably applicable to oxidations of other β-polynitroalkylamines such as 2,2-dinitropropyl- and 2,2,2-trinitroethylamines as well.

Peracid Oxidations of 2,2,2-Fluorodinitroethylamine (1). The presence of strongly electron-withdrawing substituents in **1** (the fluorodinitromethyl group is reported to have a σ^* of 4.4)[4] decreases its basicity and has a general deactivating effect on its reactivity toward oxidizing agents. Thus, **1** is not affected by hydrogen peroxide in aqueous or methanolic solution, even in the presence of catalysts such as sodium tungstate and molybdate which bring about the rapid oxidation of primary alkyl- and aralkylamines.[5]

Oxidation occurred readily with various peracids, however. One equivalent of *m*-chloroperbenzoic acid (CPB) converted **1** to fluorodinitroethylhydroxylamine (**2**), which was isolated in 69% yield. It is noteworthy that here the oxidation can be halted at the hydroxylamine stage while simple alkylhydroxylamines can usually not be made in good yield by partial oxidation of primary amines.[6] The structure of **2** is supported by its independant preparation by the addition of fluorodinitromethane to formaldoxime (Scheme I).

Scheme I