That this assumption is warranted was initially indicated by the similarity in K_{eq} values obtained from each of the three line pairs at a given temperature. Further verification was obtained by use of the gated ^{1}H-noise decoupling technique for the suppression of the nuclear Overhauser effect (NOE)[13] at −56 °C (67.9 MHz), which yielded percent **ee** values within 1% of the normally obtained data at this temperature. Use of long delay times (e.g., 80 s, 90° pulse), such that essentially complete relaxation of each nucleus was achieved, and NOE suppression yielded percent **ee** values with considerably more scatter (±4%) due to low signal/noise but with a mean identical with that obtained in the other methods at −56 °C.

Acknowledgment. We thank the National Science Foundation for the support of this research, both through research grants and the major instrument program. We also thank Dr. D. F. Hillenbrand for assistance with ^{13}C NMR instrumentation.

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Bifunctional Catalysis of the Dedeuteration of Acetone-d_6 by Conformationally Constrained Derivatives of *N*,*N*-Dimethyl-1,3-propanediamine[1]

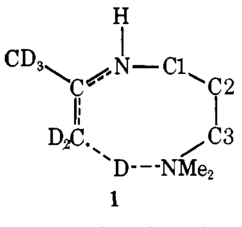
Jack Hine* and Wu-Shyong Li

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210.
Received March 28, 1975

Abstract: Bifunctional catalysis of the dedeuteration of acetone-d_6 by the monoprotonated forms of nine primary–tertiary diamines has been studied. Each catalyst uses its primary amino group to transform the ketone to an iminium ion from which the deuterium is removed internally by the tertiary amino group to give an enamine with a $-NDMe_2^+$ substituent. The deuterium is then removed from the $-NDMe_2^+$ group by attack of a base. Rate constants have been obtained for formation of the iminium ions, as have rate and equilibrium constants for the formation of enamines and rough relative rate constants for removal of deuterium from the $-NDMe_2^+$ groups. In the case of the eight 1,3-diamines studied, the transition state for enamine formation is most stable relative to acetone-d_6 and monoprotonated diamine when there is eclipsing around the bond between the carbon atom to which the primary amino group is attached and the adjacent carbon atom, especially when the C–NH_2 bond is eclipsed with the C–$CNMe_2$ bond. Bifunctional catalysis is also observed with a monoprotonated 1,4-diamine, *o*-(dimethylaminomethyl)benzylamine, but it is much less effective than it would otherwise be because the reactant is so highly stabilized by simultaneous coordination of the added proton with both amino groups. Such internal hydrogen bonding in a monoprotonated diamine, which makes *N*,*N*,*N'*,*N'*,2,2-hexamethyl-1,3-propanediamine and *o*-bis(dimethylaminomethyl)benzene much more basic than they would otherwise be, does not increase the rate at which such diamines remove deuterons from acetone-d_6 and hence results in large deviations from the Bronsted equation for the monofunctional base-catalyzed reaction.

Studies of the dedeuteration of acetone-d_6 in the presence of diamines of the type $Me_2N(CH_2)_nNH_2$, where *n* is 2, 3, 4, and 5, and of the conjugate acids of such diamines showed that monoprotonated *N*,*N*-dimethyl-1,3-propanediamine is the best catalyst.[2,3] This was attributed to internal attack by the dimethylamino group on deuterium in the intermediate iminium ion.

There are two conformers for the transition state **1** for such a process in which the carbon–deuterium bond being broken is approximately perpendicular to the plane described by the three carbon atoms from acetone and the iminium nitrogen atom. In what appears to be the more stable of these two conformers, the C(1)–N bond from the diamine is approximately eclipsed with the C(2)–C(3) bond. In the other conformer the



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C(1)–N bond is approximately eclipsed with a C(2)–H bond. To obtain catalysts in which such eclipsing was approximated in the reactants, *cis*- and *trans*-2-(dimethylaminomethyl)cyclopentylamine were prepared and their monoprotonated forms found to be considerably better catalysts than monoprotonated 3-dimethylaminopropylamine.[2,3] In order to learn more about

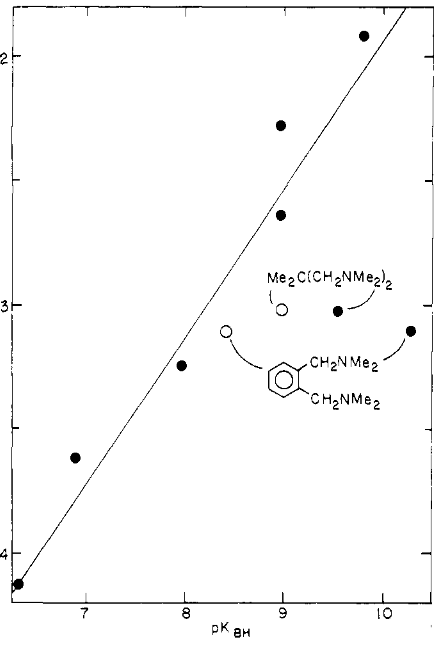


Figure 1. Bronsted plot for dedeuteration of acetone-d_6 in water at 35 °C by bases of the type RCH_2NMe_2.

Table I. Catalysis Constants for the Dedeuteration of Acetone-d_6 in Aqueous Solution

Base	$pK_a{}^a$	Temp, °C	$10^5 k_6$,^{b} $M^{-1} s^{-1}$
$Me_2C(CH_2NMe_2)_2$	9.84	35	189
o-$C_6H_4(CH_2NMe_2)_2$	10.58	35	158
n-$BuNMe_2$	10.73^c	0	47.1
$Me_2NCH_2CH_2CN$	7.46^c	0	0.641
NaOH	15.07^d	0	270

^{a} Acidity constant of the monoprotonated form of the base indicated at zero ionic strength and the temperature shown. ^{b} Rate constant for the transformation of acetone-d_6 to acetone-d_5. ^{c} Extrapolated from a value determined at 1 °C or below in the present investigation and a value determined previously at 35 °C. ^{d} See Experimental and Data Treatment Section.

the relationship between bifunctional catalytic activity and conformation, we have studied several additional conformationally constrained derivatives of 3-dimethylaminopropylamine, including some that are more rigid than cyclopentane derivatives. We have also sought to learn whether bifunctional catalysis can be obtained with a compound in which the two amino groups are separated by four carbon atoms.

Results and Discussion

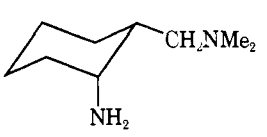
Simple Basic Catalysis. In order to treat the data obtained with bifunctional catalysts, it is necessary to estimate how much of the observed dedeuteration of acetone-d_6 arises from monofunctional catalysis. A satisfactory Bronsted plot was obtained previously using six tertiary amines of the type RCH_2NMe_2.[3] However, evidence has been described that the monoprotonated forms of some of the primary–tertiary diamines used in the present study exist largely as cyclic hydrogen-bonded species in which the added proton is coordinated with both amino groups simultaneously.[4] There should be steric and other difficulties in forming such a species as the *immediate* product of attack of the diamine on acetone-d_6. Hence, the measured basicity of such a diamine should give an exaggerated estimate of the effectiveness of the diamine in the direct removal of a deuteron from acetone-d_6. To test this hypothesis we studied the dedeuteration of acetone-d_6 in the presence of two ditertiary amines that yield largely cyclic, internally hydrogen-bonded species upon monoprotonation. The second-order rate constants obtained for N,N,N',N',2,2-hexamethyl-1,3-propanediamine and o-bis(dimethylaminomethyl)benzene, which are listed in Table I and represented (after being corrected statistically) by solid circles in Figure 1, are too small, by sevenfold and 20-fold, respectively, to fall on the Bronsted line shown. It is unlikely that these deviations arise largely from simple steric hindrance, since the larger deviation occurs with the less hindered amine. We believe that the deviations may be explained by the product stability principle,[5] but that the immediate product of their reaction is a less stable noninternally hydrogen-bonded species (which we shall denote DTT) rather than the more stable internally hydrogen-bonded TDT. From our previous estimates[4] that the monoprotonated forms of N,N,N',N',2,2-hexamethyl-1,3-propanediamine and o-bis(dimethylaminomethyl)benzene are internally hydrogen bonded to extents of 77 and 98.6%, respectively, pK values for the open HTT forms of these species of 9.28 and 8.71, respectively, may be obtained. Use of these pK values gives (after statistical corrections) the two open circles, whose deviations from the Bronsted line are much smaller. We believe that these remaining deviations may well arise largely from simple steric hindrance.

To serve as reference data for studies of bifunctional catalysts at 0 °C, we also determined catalysis constants for N,N-dimethylbutylamine, 3-dimethylaminopropionitrile, and hydroxide ions at 0 °C, with the results shown in Table I. The rate constants obtained for the two amines give a Bronsted β of 0.57, which is within the experimental uncertainty of the value 0.60 obtained at 35 °C.

Rate Constants for Imine Formation by Monoprotonated Diamines. We have studied catalysis of the dedeuteration of acetone-d_6 in water at 35 °C by six primary–tertiary diamines having three carbon atoms between the amino groups: N,N,2-trimethyl-1,3-propanediamine (**2**), N,N,2,2-tetramethyl-1,3-propanediamine (**3**), *cis*-2-(dimethylaminomethyl)cyclohexylamine (**4**), *trans*-2-(dimethylaminomethyl)cyclohexylamine (**5**), 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine (**6**), and 3-*exo*-dimethylaminomethyl-2-*endo*-norbornanamine (**7**), and by one, o-(dimethylaminomethyl)benzylamine (**8**), that has four carbon atoms between the amino groups.

$Me_2NCH_2CHMeCH_2NH_2$
2

$Me_2NCH_2CMe_2CH_2NH_2$
3



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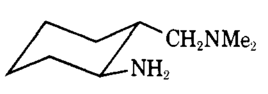

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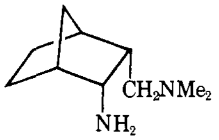

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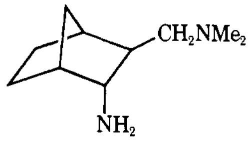

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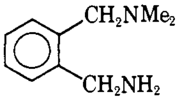

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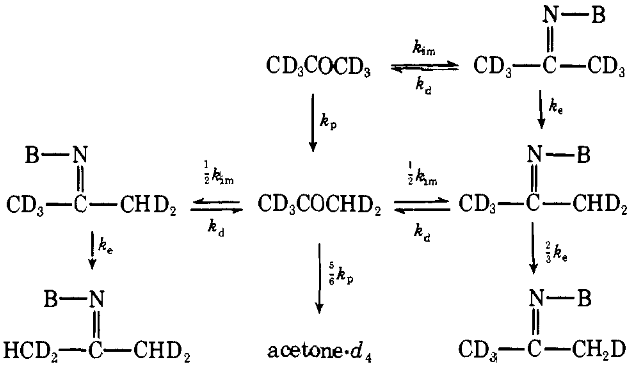
Our results were treated in terms of the mechanism proposed previously,[3] which is shown in an abbreviated form in Scheme I, in which the bifunctional catalyst is $B-NH_2$, with B being the dimethylamino substituent. The steady-state assumption for the intermediate imines gives:

$$k_6 = k_p + k_{im}k_e/(k_e + k_d) \tag{1}$$

for k_6, the first-order rate constant for disappearance of ace-

Scheme I



tone-d_6. The rate of formation of acetone-d_6 follows the equation

$$\frac{df_5}{dt} = qk_6f_6 - \left(1 - \frac{q}{6}\right)k_6f_5 \qquad (2)$$

in which f_5 and f_6 are the fractions of acetone-d_5 and -d_6, respectively, present in the acetone and q, like k_6, is a constant that can be obtained directly from the experimental data in any given run. The rate constant k_p for direct dedeuteration will always contain the terms shown in

$$k_p = k_B[\mathrm{Am}] + k_B'[\mathrm{AmH}^+] + k_h[\mathrm{OH}^-] \qquad (3)$$

and will also contain additional terms if any extra bases in addition to the diamine catalyst are present. The rate constants for imine formation and hydrolysis follow the equations

$$k_{im} = k_a[\mathrm{Am}] + k_{ah}[\mathrm{AmH}^+] \qquad (4)$$

$$k_d = k_{do}[\mathrm{Im}] + k_{dh}[\mathrm{ImH}^+] \qquad (5)$$

Exchange by the imine is assumed to take place only by internal attack of the dimethylamino group of the iminium ion to give enamine, so that k_e is equal to the rate of such attack multiplied by y, the fraction of the enamine that gives dedeuterated imine (rather than reverting to undedeuterated imine). Combination of these relationships with eq 1 gives

$$k_e = k_i[\mathrm{ImH}^+]y \qquad (6)$$

$$k_6 = k_p + \frac{k_aK_{AH}(k_a[\mathrm{Am}] + k_{ah}[\mathrm{AmH}^+])[\mathrm{H}^+]ay}{k_aK_{AH}(1 + ay[\mathrm{H}^+]) + k_{ah}[\mathrm{H}^+]} \qquad (7)$$

in which a is $k_i/(k_{do}K_{IH})$, K_{AH} is the acidity constant of the monoprotonated diamine, and K_{IH} is the acidity constant of the iminium ion. The constant q may be expressed as

$$q = \frac{(2k_ak_pK_{AH}ay + 3k_{ah}k_6)[\mathrm{H}^+] + 3k_ak_6K_{AH}}{(2k_aK_{AH}ay + 3k_{ah})k_6[\mathrm{H}^+] + 3k_ak_6K_{AH}} \qquad (8)$$

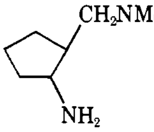
The value of k_p in any run was calculated via eq 3 using k_B and k_B' values estimated from data on similar compounds. For a set of runs using a given diamine at various concentrations and pH's, this leaves k_a, k_{ah}, and the value of ay in each run as the only unknowns in eq 7 and 8. In principle, these unknowns could be assigned the values that best fit the observed k_6 and q values. In practice, however, this fit is relatively insensitive to the value used for k_a. Therefore the k_a values used were calculated from

$$\log k_a = 0.606\mathrm{p}K_{TPH} - 7.19 \qquad (9)$$

which is based on the linear relationship observed between log k_a for a number of primary amines and the pK values of the conjugate acids of the amines[6,7] and on the observation that acetone-d_6 is about 20% more reactive than ordinary acetone in such processes.[7] The acidity constant K_{TPH} refers to that form of the monoprotonated diamine in which the added proton is on the primary amino group; values of K_{TPH} for the amines used have been estimated recently.[4]

The experimental data, "observed" ay values, and calculated values of k_6 and q obtained for diamines **2**, **3**, **5**, and **8** are listed in Table II. 3-Dimethylaminopropionitrile was added in some of the runs carried out with **4**, **6**, and **7**, and with **6** *N*,*N*-dimethyl-2,2-difluoroethylamine or *N*,*N*-dimethyl-2,2-diethoxyethylamine was also added in some runs. The data on these diamines are listed in Tables III, IV, and V, respectively. The agreement of the calculated with observed values of k_6 and q became poor at the high concentrations of tertiary amine used in some of the runs with **6**, perhaps because of a solvent effect. Therefore, data on the two runs with more than 7 wt % added tertiary amine were not used in the least-squares treatment. In one of the other runs was more than 4 wt % amine present.

In Tables VI and VII are data obtained at 0 °C using *trans*-2-(dimethylaminomethyl)cyclopentylamine (**9**) and *N*,*N*-dimethyl-1,3-propanediamine (**10**), which were studied



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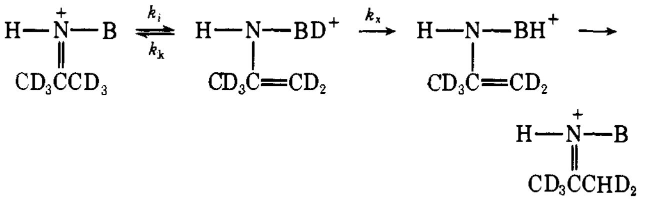
$\mathrm{Me_2NCH_2CH_2CH_2NH_2}$

10

previously at 35 °C.[3] Since the kinetics of imine formation have not been studied at 0 °C, k_a for **10** was determined as a parameter of the least-squares treatment. Compound **10** is the most suitable compound to treat in this way because it is the one for which the k_a pathway for imine formation is largest relative to the k_{ah} pathway. For compound **9** k_a was obtained by assuming an entropy of activation equal to that for **10**. The values of k_a, k_B, and k_B' used and the resulting values of k_{ah} for **2–10**, including values for **9** and **10** at 35 °C obtained by the slightly different method of calculation used in the present paper, are listed in Table VIII.

Transformation of Imine to Enamine and Exchange. The variation in y with varying reaction conditions is explained in terms of Scheme II, which was proposed previously.[3] This

Scheme II



scheme is an amplification of the step governed by k_e in Scheme I and by k_i in eq 6. The exchange step, whose rate constant is k_x, is assumed to involve rate-controlling removal of a deuteron from the BD$^+$ group by a base. In the equation

$$k_x = k_s + k_m[\mathrm{AmH}^+] + k_u[\mathrm{Am}] + k_l[\mathrm{OH}^-] + k_t[\mathrm{T}] \qquad (10)$$

AmH$^+$ and Am are the monoprotonated and unprotonated diamine, T is any added tertiary amine that may be present, and k_s is the rate constant for the water-catalyzed and uncatalyzed reactions. This leads to

$$ay = \frac{(s + m[\mathrm{AmH}^+] + u[\mathrm{Am}] + l[\mathrm{OH}^-] + t[\mathrm{T}])a}{1 + s + m[\mathrm{AmH}^+] + u[\mathrm{Am}] + l[\mathrm{OH}^-] + t[\mathrm{T}]} \qquad (11)$$

in which s is k_s/k_k, m is k_m/k_k, etc. In principle, values of s, m, u, l, a, and if appropriate, t, could be determined for a given diamine by a regression analysis of the ay values. In practice, however, the concentrations of the appropriate species were not varied widely enough (and it is not clear that such variation would have been feasible) for this to be practical. Least-squares treatment gave estimated standard deviations that were less

Table II. Dedeuteration of Acetone-d_6 in the Presence of 2, 3, 5, and 8[a]

Amine	$[\mathrm{Am}]_t$,[b] M	pH	$10^5 k_6$, s^{-1} Obsd	$10^5 k_6$, s^{-1} Calcd	q Obsd	q Calcd	$10^{-9} ay$, M^{-1} Obsd[c]	$10^{-9} ay$, M^{-1} Calcd
2	0.0113	7.389	12.4	12.5	0.719	0.727	6.99	7.20
2	0.0451	7.520	77.5	75.7	0.554	0.541	15.7	14.6
2	0.0118	8.618	40.6	41.0	0.523	0.528	17.2	17.3
2	0.0474	8.686	179	179	0.472	0.471	21.7	21.0
2	0.0474	9.882	140	143	0.589	0.603	21.2	22.6
3	0.0225	8.012	21.9	20.4	0.390	0.319	16.7	11.2
3	0.0449	8.070	36.6	37.5	0.373	0.390	12.3	13.9
3	0.0449	10.023	48.5	53.7	0.445	0.565	19.0	18.1
5	0.0114	6.818	0.810	0.810	1.000	0.983	0.733	0.777
5	0.0455	6.920	8.17	8.18	0.880	0.948	2.18	1.92
5	0.0119	8.290	11.3	11.3	0.898	0.867	5.99	4.73
5	0.0477	8.430	44.9	44.8	0.883	0.869	5.93	5.83
5	0.0455	10.327	39.1	39.4	0.843	0.939	6.52	6.46
8	0.0432	6.010	4.91	4.87	0.795	0.741	4.26	4.26
8	0.0510	7.322	17.1	17.2	0.651	0.664	6.19	6.20
8	0.0510	9.482	23.6	23.7	0.622	0.628	10.3	10.3
8	0.0236	10.071	11.4	11.4	0.784	0.778	11.1	10.8
8	0.0510	10.090	22.7	22.6	0.777	0.768	10.8	11.4
8	0.0510	10.374	21.8	21.8	0.835	0.845	11.8	11.6
8	0.0510	10.687	20.7	20.8	0.907	0.928	12.3	11.8

[a] Using 0.52 M acetone-d_6 in aqueous solution at 35 °C. [b] Total concentration of diamine. [c] The estimated standard deviations for the observed ay values were ~4% for 2, 30–55% for 3, 5–9% for 5, and ~4% for 8.

Table III. Dedeuteration of Acetone-d_6 in the Presence of *cis*-2-(Dimethylaminomethyl)cyclohexylamine (4)[a]

$[\mathrm{Am}]_t$,[b] M	$[\mathrm{DPN}]_t$,[c] M	pH	$10^5 k_6$, s^{-1} Obsd	$10^5 k_6$, s^{-1} Calcd	q Obsd	q Calcd	$10^{-9} ay$, M^{-1} Obsd[d]	$10^{-9} ay$, M^{-1} Calcd
0.0242	0	6.040	0.732	0.732	0.991	0.975	1.86	1.79
0.0452	0	6.211	2.54	2.55	0.934	0.962	2.87	2.25
0.0123	0	6.290	0.661	0.661	0.980	0.978	1.64	1.81
0.0124	0	7.170	6.78	6.78	0.970	0.953	3.57	3.50
0.0128	0.0459	7.220	13.6	13.5	0.922	0.915	7.05	7.13
0.0249	0	7.230	15.9	15.8	0.998	0.944	4.26	4.86
0.0462	0.3559	7.231	71.4	71.3	0.847	0.841	14.7	11.9
0.0454	0.1750	7.270	70.9	70.7	0.870	0.848	13.4	10.8
0.0122	0.1768	7.280	19.0	18.9	0.914	0.896	10.0	10.6
0.0497	0	7.308	54.4	54.4	0.918	0.901	7.87	6.79
0.0249	0	8.543	89.2	89.1	0.847	0.846	13.2	11.3
0.0499	0	8.581	188	190	0.796	0.834	14.3	12.4
0.0124	0	9.752	35.1	35.1	0.856	0.868	13.1	13.5
0.0249	0	9.782	71.6	71.3	0.901	0.863	13.6	13.7
0.0497	0	9.798	136	136	0.857	0.869	12.9	13.8

[a] Using 0.52 M acetone-d_6 in aqueous solution at 35 °C. [b] Total concentration of diamine. [c] Total concentration of 3-dimethylaminopropionitrile. [d] Estimated standard deviations ~3%.

Table IV. Dedeuteration of Acetone-d_6 in the Presence of 3-*endo*-Dimethylaminomethyl-2-*endo*-norbornanamine (6)[a]

$[\mathrm{Am}]_t$,[b] M	R_3N[c]	$[R_3N]_t$,[d] M	pH	$10^5 k_6$, s^{-1} Obsd	$10^5 k_6$, s^{-1} Calcd	q Obsd	q Calcd	$10^{-9} ay$, M^{-1} Obsd[e]	$10^{-9} ay$, M^{-1} Calcd
0.0090			6.985	10.2	10.2	0.968	0.961	5.84	5.87
0.0096	DFE[f]	0.0967	7.342	34.1	34.1	0.912	0.911	14.3	15.3
0.0090	DFE[f]	0.2740	7.362	49.5	50.3	0.756	0.858	24.7	23.5
0.0090			7.406	29.3	29.3	0.916	0.922	12.1	11.6
0.0123	DPN[g]	0.0958	8.272	248	250	0.549	0.554	117	81.8
0.0123			8.325	195	195	0.668	0.665	72.0	83.3
0.0120	DPN[g]	0.4640	8.331	215	243	0.480	0.591	108	114
0.0123	DPN[g]	0.9625	8.375	222[h]	261	0.432[h]	0.611	109[h]	152
0.0048	DEE[i]	0.2378	8.658	122	131	0.425	0.458	212	219
0.0046	DEE[i]	0.4631	8.658	116[h]	133	0.442[h]	0.530	194[h]	301
0.0048	DEE[i]	0.1185	8.689	114	118	0.462	0.478	174	167
0.0094			9.297	249	227	0.306	0.298	348	337
0.0123			9.767	245	233	0.222	0.219	570	527
0.0246			9.802	507	455	0.225	0.220	564	612
0.0094			10.177	123	113	0.240	0.233	642	601

[a] Using 0.52 M acetone-d_6 in aqueous solution at 35 °C. [b] Total concentration of diamine. [c] Tertiary amine added. [d] Total concentration of added tertiary amine. [e] Estimated standard deviations 10–18%. [f] *N,N*-Dimethyl-2,2-difluoroethylamine. [g] 3-Dimethylaminopropionitrile. [h] Not used in the least-squares treatment. [i] *N,N*-Dimethyl-2,2-diethoxyethylamine.

Table V. Dedeuteration of Acetone-d_6 in the Presence of 3-*exo*-Dimethylaminomethyl-2-*endo*-norbornanamine (7)[a]

[Am]$_t$,[b] M	[DPN]$_t$,[c] M	pH	10^5k_6, s^{-1} Obsd	10^5k_6, s^{-1} Calcd	*q* Obsd	*q* Calcd	$10^{-9}ay$, M^{-1} Obsd[d]	$10^{-9}ay$, M^{-1} Calcd
0.0103	0.1915	7.592	39.4	37.6	0.726	0.673	32.2	29.4
0.0045	0.3288	7.618	20.0	19.9	0.796	0.785	26.4	29.9
0.0047	0.1074	7.637	19.2	18.9	0.744	0.713	27.1	28.6
0.0203	0.1888	7.645	74.8	73.1	0.683	0.656	32.1	29.4
0.0051	0	7.678	9.15	9.15	0.870	0.876	8.12	7.95
0.0103	0	7.743	22.0	22.0	0.840	0.852	9.87	10.4
0.0206	0	7.804	58.4	58.5	0.787	0.797	14.5	13.8
0.0103	0	8.705	73.0	74.3	0.667	0.711	23.3	24.4
0.0050	0	8.707	36.3	36.6	0.684	0.709	23.6	22.2
0.0202	0	8.722	152	153	0.670	0.691	25.7	26.5
0.0051	0	9.897	28.9	29.3	0.686	0.722	28.7	29.6
0.0103	0	9.950	58.3	58.9	0.681	0.705	31.2	30,0
0.0206	0	9.950	115	117	0.653	0.703	31.0	30.2

[a] Using 0.52 M acetone-d_6 in aqueous solution at 35 °C. [b] Total concentration of diamine. [c] Total concentration of 3-dimethylaminopropionitrile. [d] Estimated standard deviations 5–10%.

Table VI. Dedeuteration of Acetone-d_6 in the Presence of *trans*-2-(Dimethylaminomethyl)cyclopentylamine (9) at 0 °C[a]

pH	10^5k_6, s^{-1} Obsd	10^5k_6, s^{-1} Calcd	*q* Obsd	*q* Calcd	$10^{-9}ay$, M^{-1} Obsd[b]	$10^{-9}ay$, M^{-1} Calcd
8.235	1.34	1.34	0.855	0.851	418	379
8.811	2.95	2.96	0.830	0.848	429	452
8.930	3.46	3.45	0.856	0.839	459	485
9.890	9.15	9.05	0.672	0.654	1273	1126
10.190	9.68	9.52	0.632	0.613	1532	1374
10.617	7.59	7.78	0.600	0.623	1502	1625

[a] In aqueous solution using 0.52 M acetone-d_6 and 0.00934 M total diamine. [b] Estimated standard deviations ~4%.

Table VII. Dedeuteration of Acetone-d_6 in the Presence of *N,N*-Dimethyl-1,3-propanediamine (10) at 0 °C[a]

pH	10^5k_6, s^{-1} Obsd	10^5k_6, s^{-1} Calcd	*q* Obsd	*q* Calcd	$10^{-9}ay$, M^{-1} Obsd[b]	$10^{-9}ay$, M^{-1} Calcd
8.800	2.97	3.03	0.659	0.705	113	116
9.244	5.43	5.43	0.637	0.635	155	119
9.902	6.55	6.44	0.686	0.662	144	120
10.503	5.10	5.12	0.751	0.771	99	120
10.951	5.36	5.27	0.832	0.778	128	120

[a] In aqueous solution using 0.52 M acetone-d_6 and 0.0491 M total diamine. [b] Estimated standard deviations were ~8%.

Table VIII. Rate Constants for Direct Dedeuteration and Iminium Ion Formation by Acetone-d_6 and Diamines[a]

Diamine	10^5k_B,[b] M^{-1} s^{-1}	$10^5k_B'$,[b] M^{-1} s^{-1}	10^3k_a,[b] M^{-1} s^{-1}	10^3k_{ah},[c] M^{-1} s^{-1}
2	435	45.2	39	63.3 (1.1)
3	124	6.05	27	12.6 (1.9)
4	435	31.1	39	176 (8)
5	435	14.4	39	51 (16)
6	435	22.0	25	393 (16)
7	435	79.7	48	215 (15)
8	90.3	1.84	12	8.2 (0.3)
9	435	77.1	39	229 (7)
10	791	152	62	29.9 (0.9)
9[d]	15.7	2.23	1.3	24.6 (0.7)
10[d]	30.8	4.78	2.21	3.01 (0.17)

[a] In water at 35 °C unless otherwise noted. [b] Estimated as described in the text. [c] The parenthesized figure are estimated standard deviations. [d] At 0 °C.

Table IX. Kinetic Constants for Enamine Formation and Exchange[a]

Diamine	10^{-9}, *a* M^{-1}	$10^{-3}l$, M^{-1}	*m*, M^{-1}	*s*	*dpn*,[b] M^{-1}
2	22.9	92	71	0	
	(1.4)	(52)	(11)		
3	18.4	67	52[c]	0	
	(4.4)	(84)			
4	14.0	120	31	0.11	24
	(1.5)	(141)	(12)	(0.02)	(11)
5	6.5	374	14	0	
	(1.2)	(296)	(8)		
6[d]	781	7.1	0.6	0.002	0.12
	(117)	(2.1)	(1.1)	(0.005)	(0.07)
7	30.6	144	25	0.12	155
	(1.4)	(49)	(16)	(0.05)	(198)
8	12.2	12.5	15	0.28	
	(0.6)	(6.4)	(3)	(0.06)	
9	110	11.1	9.1	0.053	
	(16)	(3.7)	(3.3)	(0.014)	
9[e]	1920	39	0	0.23	
	(357)	(26)		(0.05)	
10	8.15	1800	170	1.25	
	(0.46)	(14500)	(2620)	(0.84)	
10[e]	120	7000	0	0	
	(15)	(47000)			

[a] Values of the constants in eq 11 at 35 °C, unless otherwise noted, in aqueous solution obtained as described in the text. The values of *u* are $^1/_{30}$th of the corresponding values of *l*. The figures in parentheses are estimated standard deviations. [b] Values of *t* for the tertiary amine 3-dimethylaminopropionitrile. [c] Relative values of *l*, *u*, *m*, and *s* were assumed to be the same as for **2**. [d] Values of *t* of 0.07 (0.02) and 1.4 (0.5) M^{-1} were obtained for *N,N*-dimethyl-2,2-difluoroethylamine and *N,N*-dimethyl-2,2-diethoxyethylamine, respectively. [e] At 0 °C.

than 25% of the *a* values for every catalyst, but for very few of the other parameters were the estimated standard deviations this small. To increase the probable reliability of these other parameters, we added to our least-squares treatment the requirement that *l* equal 30*u*. This requirement is based on the fact that the removal of the acidic deuteron from the enamine by unprotonated diamine must have an equilibrium constant rather near 1.0. Various observations such as those of Eigen and co-workers on proton transfers from various acids to ammonia[8] show that such proton transfers tend to be about ¹⁄₃₀th as fast as deprotonation of the given acid by hydroxide ions. Imposition of this requirement did not significantly affect the precision with which the *ay* values could be correlated, nor did it change any *a* value by as much as 5.0%. For **3**, for which only three runs were made, the added assumption was made that the relative values of *l*, *u*, *m*, and *s* were the same as for **2**, whose structure was taken to be the closest to **3** of all the other catalysts. Least-squares treatment yielded the values of *a*, *l*, *m*, *s*, and the estimated standard deviations listed in Table IX, from which the *ay* values in the last columns of Tables II–VII were calculated. The poorest agreement in *ay* values is seen

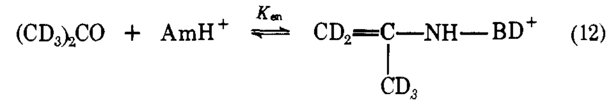
Table **X**. Equilibrium Constants for Enamine Formation from Acetone-d_6 and Related Data[a]

Diamine	$10^{-4}k_k$, s^{-1}	$10^{-9}b$, M^{-1}	10^7K_{en}, M^{-1}	$10^7K_{en}'$, M^{-1}
2	22	12	5.6	20
3	30	5.0	1.6	14
4	17	47	3.1	16
5	5.4	25	2.4	22
6	282	95	11	33
7	14	37	13	51
8	160	8.0	0.078	3.5
9	180	37	3.8	12

[a] In water at 35 °C.

to have been obtained with **3**, for which the smallest number of runs was made, and **2** at 0 °C, where less reference data were available and where the largest amounts of reaction by mechanisms other than bifunctional catalysis probably occurred. The tendency of the *ay* values for **2** to increase with increasing base concentrations is so slight that the estimated standard deviations listed in Table IX for most of the parameters other than *a* are larger than the parameters. This did not prevent reliable values being obtained for *a*, however.

Since proton transfers between oxygen and nitrogen in aqueous solution ordinarily take place at essentially every properly oriented collision when they have equilibrium constants significantly larger than 1.0, the removal of deuterium from the -$NDMe_2^+$ group of the first enamine in Scheme II by hydroxide ions should be diffusion controlled. For this reason we estimate that k_l at 35 °C is about 2×10^{10} M^{-1} s^{-1}, a value estimated from Eigen's rate constants for proton transfers,[8] for each of the compounds studied. This gives us values for k_k, the first-order rate constant for regeneration of the iminium-d_6 ion from the enamine, since k_k is equal to k_l/l. From k_k the equilibrium constant k_{en} for formation of enamine from acetone-d_6 and monoprotonated diamine (eq 12)



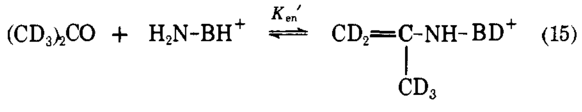
$$(CD_3)_2CO + AmH^+ \overset{K_{en}}{\rightleftharpoons} CD_2{=}\underset{\displaystyle CD_3}{\underset{|}{C}}{-}NH{-}BD^+ \qquad (12)$$

may be calculated, using eq 13, in which *b* is defined, as previously,[3] by eq 14,

$$K_{en} = k_{ah}a/k_kb \qquad (13)$$

$$b = \frac{k_{dh}}{k_{do}K_{IH}} = \frac{k_{ah}}{k_aK_{AH}} \qquad (14)$$

in which K_{IH} is the acidity constant of the iminium ion. From the values of k_a and k_{ah} in Table VIII and of K_{AH} (the acidity constant of the monoprotonated diamine), *b* values were obtained. These and eq 13 gave the K_{en} values that are listed with k_k and *b* values in Table X. (Data on **10**, the only compound whose *l* value had an estimated standard deviation that was much larger than the value, are not included.) Only the K_{en} value for **8** differs by more than a factor of 3 from 4.5×10^{-7} M^{-1}. It may be that much of the deviation by **8** arises from the existence of about 93.4% (more than for any of the other diamines) of the monoprotonated form of this diamine as an internally hydrogen-bonded species.[4] If K_{en} is divided by f_t, the fraction of the monoprotonated diamine in which the proton is on the tertiary amino group only, we obtain K_{en}', in which the reactants are now more nearly analogous for each of the diamines being compared. The K_{en}' value for **8** in Table X is much nearer the other values than was the case for the K_{en} values. The remaining deviation may be significant; it would not be surprising for the only unsaturated diamine (which is also the only one with four carbon atoms between its two amino groups) to behave somewhat differently from the others. Since the polar properties of the other diamines are all rather similar and molecular models do not show any major steric interactions in the various enamines, the values of K_{en}' would be expected to be similar. Considering the uncertainty in the *l* values used in the calculation, the fact that the K_{en}' values for **2**–**7** and **9** are all within a factor of 2 of 25×10^{-7} M^{-1} shows that this expectation is supported by the data. The rough constancy of the K_{en}' values also shows that the values of *l* in Table IX are probably roughly correct. The rough validity of the other parameter values listed at 35 °C is supported by the fact that of the 32 values of *l, u, m, dpn*, etc., the values for each diamine increase monotonically with the basicity of the species involved (hydroxide ion, unprotonated diamine, etc.), except for the *m* value for **6** (which is less than half as large as its estimated standard deviation). The fact that the value of *s* relative to *l* is five times as large for **8** as for any other diamine may be related to the much greater tendency for internal hydrogen bonding in monoprotonated **8** than in any of the other monoprotonated diamines. That is, removal of D^+ from the $NDMe_2^+$ group of the enamine derived from **8** may involve the action of the enamine nitrogen atom as a base.



$$(CD_3)_2CO + H_2N\text{-}BH^+ \overset{K_{en}'}{\rightleftharpoons} CD_2{=}\underset{\displaystyle CD_3}{\underset{|}{C}}\text{-}NH\text{-}BD^+ \qquad (15)$$

The effect of structure on efficiency of bifunctional catalysis is usefully discussed in terms of a second-order rate constant for the formation of enamine from ketone and monoprotonated diamine. This avoids the problem of the variability of *y*, whose value is a function of the pH of the solution and the concentrations of various bases present as well as the structure of the catalyst. If we also neglect the terms in the kinetic equations we have used that allow for equilibrium between the various states of protonation of the diamine and for reaction pathways involving these other states of protonation, we may define k_{en} as

$$k_{en} = \frac{k_{ah}k_i}{k_i + k_{dh}} = \frac{k_{ah}a}{a + b} \qquad (16)$$

Inasmuch as *a* and *b* are of comparable magnitude for the diamines we have studied, the rate of enamine formation depends on the energy of the transition state for iminium ion formation as well as on that for enamine formation. Since we have already discussed the effect of structure on the rate of iminium ion formation,[7] let us consider only the stability of the transition state for enamine formation. This stability, relative to the stabilities of acetone-d_6 and total monoprotonated diamine, is measured by $k_{ah}a/b$, which is the value k_{en} would have if the energy barrier for iminium ion formation were lowered sufficiently without changing the energy of any other transition state or species. The stability of total monoprotonated diamine, which includes primary-protonated, tertiary-protonated, and internally hydrogen-bonded forms, is so complicated that we have also calculated values for k_{en}', as defined in eq 17, which is a measure of the stability of the transition state for enamine formation relative to that of acetone-d_6 and tertiary-protonated diamine.

$$k_{en}' = k_{ah}a/(bf_t) \qquad (17)$$

Values of all three of these measures of the stabilities of the transition states for enamine formation for compounds **2**–**10** at 35 °C and of the first two measures for **9** and **10** at 0 °C (no f_t values being available at 0 °C) are listed in Table XI. None of the measures of transition-state stability is significantly correlated with K_{en} or K_{en}', which measure the product stability. Instead, it appears to be the effect of substituents on the stability of the ring that has been formed in the transition state that is important. Molecular mechanics calculations of the

Table XI. Measures of the Stability of the Transition State for Enamine Formation for Acetone-d_6 and Monoprotonated Diamines[a]

Diamine	10^3k_{en}, $M^{-1}\,s^{-1}$	$10^3k_{ah}a/b$, $M^{-1}\,s^{-1}$	10^3k_{en} , $M^{-1}\,s^{-1}$
2	41.5	121	431
3	9.91	46.4	422
4	40.2	52.1	260
5	10.3	12.9	117
6	351	3240	9260
7	96.9	176	706
8	4.95	12.5	566
9	171	681	2060
10	20.2	62.2	207
9[b]	13.4	29.7	
10[b]	1.30	2.28	

[a] In water at 35 °C unless otherwise noted. [b] At 0 °C.

stabilities of these transition states are under way.[9] A more qualitative discussion may be based on consideration of molecular models of the transition state for reaction of **10**, for which there appear to be two relatively stable conformers, each having an approximately eclipsed conformation around the C(1)-C(2) bond of the diamine moiety. In what appears to be the more stable conformer the iminium nitrogen atom is eclipsed by C(3). It is therefore noteworthy that compound **6**, which is the only diamine studied in which there is already such a conformation in the catalyst itself, is the most effective of the catalysts studied. *cis*-2-(Dimethylaminomethyl)cyclopentylamine, in which such a conformation is more loosely approximated, has been studied only at a purity of 81%[3] but was found to be more reactive than **9** and hence more reactive than any catalyst except **6**. The second most stable conformer of the transition state derived from **10** has the iminium nitrogen atom eclipsed with a C(2) hydrogen atom from the diamine. This is the type of conformation loosely approximated in **9** and more rigidly approximated in **7**, the next two most efficient catalysts. The relative unreactivity of the parent compound **10** probably arises from the existence of extended conformations containing few destabilizing gauche interactions. The methylation of C(2) to give diamines **2** and **3** introduces significant gauche destabilization into even the most stable conformations of the catalyst, thus *relatively* stabilizing the transition state. Simultaneously, however, the new methyl groups can interact destabilizingly with the acetone moiety of the transition state. The situation with respect to the cyclohexane catalysts **4** and **5** is rather similar except that with these compounds it is even more difficult than it is with **2** and **3** to get the desired eclipsing in the transition state. The relative values of k_{en}' for **3** and **10** show that the *gem*-dimethyl effect[10] does stabilize the cyclic transition state relative to open-chain monoprotonated diamine; the relative values of $k_{ah}a/b$, however, show that it does not stabilize the cyclic transition state relative to cyclic internally hydrogen-bonded monoprotonated diamine. The value of k_{en}' for **8**, the only compound with four carbon atoms between the amino groups, shows that this compound would have a larger value of $k_{ah}a/b$ than most of the three-carbon diamines if it were not for the strong tendency for monoprotonated **8** to exist as an internally hydrogen-bonded species. Such internal hydrogen bonding could cause many apparently promising diamines to be much poorer bifunctional catalysts than would otherwise be the case. However, molecular models show that in compounds with the two amino groups held rather rigidly in relative geometries that seem optimum for bringing about enamine formation they are too far apart and improperly oriented for simultaneous coordination to the same proton. Nevertheless, such compounds need not be much better catalysts for α-hydrogen exchange than some of the compounds studied here, for which the exchange rate is already limited largely by the rate of iminium ion formation and, under some conditions, by the rate of loss of deuterium from the $NDMe_2^+$ group in the intermediate enamine. To increase the rates of these steps we may need to go to trifunctional or tetrafunctional catalysts.

Table XII. Enthalpies and Entropies of Reaction and Activation[a]

Reactant(s)	Rate or equil constant	ΔH° or $\Delta H^\ddagger$, kcal/mol	ΔS° or $\Delta S^\ddagger$, eu
n-$BuNHMe_2^+$	K_a	10.2	−11.6
$NCCH_2CH_2NHMe_2^+$	K_a	6.3	−11.2
$9\cdot H^+$	K_a	13.0	−3.2
$9\cdot H_2^{2+}$	K_a	9.0	−5.8
$10\cdot H^+$	K_a	12.4	−4.7
$10\cdot H_2^{2+}$	K_a	9.6	−3.7
n-$BuNMe_2$[b]	k_B	15.0	−19
$NCCH_2CH_2NMe_2$[b]	k_B	16.8	−21
OH^-[b,c]	k_B	15.1	−15
$9\cdot H^+$[b]	k_{ah}	10.1	−29
$10\cdot H^+$[b]	k_{ah}	10.4	−32
$9\cdot H^+$[b]	$k_{ah}a/b$	14.4	−13
$10\cdot H^+$[b]	$k_{ah}a/b$	15.2	−15

[a] In water, based on data at 0 and 35 °C. [b] Acetone-d_6 is a coreactant. [c] Based on data at 0, 25, and 35 °C.

Division of the k_{en}' value for **6** by the third-order rate constant for transformation of acetone-d_6 to enamine by the action of methylamine and methylammonium ions[11] gives a quotient of 2300 M. Dividing by 7 to allow for the tertiary character of the amino group that removes deuterium when **6** acts as a bifunctional catalyst gives 330 M as the "effective concentration" of the internal dimethylamino group in removing protons in the iminium ion derived from acetone-d_6 and tertiary-protonated **6**.

It may be noted that in our treatment of the data we have ignored dedeuteration via the attack of external bases on the iminium ions. Arguments against significant amounts of attack of amine on iminium ion were described previously for **10**.[3] Since there is no reason for any of the other diamines to be any more reactive than **10** by such a mechanism and since all are more reactive as bifunctional catalysts as judged by values of k_{en}/f_t, the *relative* amount of such exchange should be less for the other diamines at the same total diamine concentration and still less at the smaller total diamine concentrations used with most of the other catalysts. Estimates based on data on isobutyraldehyde-*2-d*[12,13] as well as on acetone-d_6[11] suggest that several percent of the dedeuteration we have observed with the poorest bifunctional catalysts below pH 7 may arise from attack of water on the intermediate iminium ion. The amount of such exchange is believed to be too small to affect any of the conclusions we have drawn from our observations.

Enthalpies and Entropies of Reaction and Activation. In Table XII are enthalpies and entropies of activation calculated from the absolute rate equation

$$k = (\mathbf{k}T/h)\exp(-\Delta H^\ddagger/RT)\exp(\Delta S^\ddagger/R) \qquad (18)$$

and of reaction calculated from the Van't Hoff equation for several of the processes we have studied.

The K_a values for the two tertiary amines give ΔS values near those (∼−12 eu) found for a number of other tertiary amines.[12] The values for the two primary-tertiary diamines are between the values expected for tertiary amines and those expected for primary amines (∼−1 eu).[14]

Enamine formation from acetone-d_6 and monoprotonated **9** or **10** proceeds via a cyclic transition state whereas enolate anion formation by attack of a monofunctional base does not. Nevertheless, the entropy of activation is not as negative for the $k_{ah}a/b$ values as for the k_B values. This is because $k_{ah}a/b$ is a measure of the stability of two species, the transition state *and a water molecule*, while k_B is a measure of the stability of one species, relative to the two reactants. The favorable entropy effect arising from the formation of an extra molecule somewhat more than compensates for the unfavorable entropy of ring formation in the enamine-formation reaction. Changes in the number of species also explain the fact that for **9**·H$^+$ and **10**·H$^+$ the first significant transition state on the path to enamine formation (the one measured by k_{ah}) is 4–5 kcal/mol more stable than the second (measured by $k_{ah}a/b$) as measured by enthalpies but 16–17 eu less stable as measured by entropies. Both transition states are believed to be cyclic and to contain eight-membered rings, but in the first, the transition state for enamine formation, the molecule of water produced as a by-product has not yet been formed, whereas in the second transition state it has. For this reason, decreases in temperature tend to shift rate control from the iminium ion-forming step to the enamine-forming step.

The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for **9**·H$^+$ and **10**·H$^+$ suggest that the increased stability of the transition state for enamine formation by the former arises from both entropy and enthalpy effects, but the uncertainties are large enough to leave open the possibility that only one of these effects is contributing significantly.

The conclusions concerning **9** and **10** that were reached in this section on the basis of $k_{ah}a/b$ values are probably about the same as if k_{en}' values had been available at 0 °C and had been used as the basis. This follows from the similarity in f_t values for **9** and **10** at 35 °C and from the relatively small tendency that either monoprotonated diamine has to exist in a cyclic hydrogen-bonded form.[4]

Experimental and Data Treatment Section

The syntheses of *N,N,N′,N′*,2,2-hexamethyl-1,3-propanediamine, *o*-bis(dimethylaminomethyl)benzene, and compounds **2–8** were described recently.[15] The determination of p*K* values near 0 °C was carried out as described previously for 35 °C except that a Radiometer GK2301C combined electrode was used in order to get a reasonably rapid response. The p*K* values for **9** were 8.46 and 10.92 and those for **10** were 8.49 and 11.09, both at 0 °C and zero ionic strength.

Kinetics of the Dedeuteration of Acetone-*d*$_6$. The method of following the reaction by extraction with chloroform and than mass spectral measurements was described previously.[11] In an early run on *o*-bis(dimethylaminomethyl)benzene, the compound was found to be such a poor catalyst but such a strong base that almost all the reaction was due to the hydroxide ions present. The rate constant listed in Table I comes from runs at pH 9.877 and 9.923 using total amine concentrations of 0.20 and 0.30 M, respectively. Under these conditions the correction for catalysis by hydroxide ions was only about 20% of the total reaction rate. With *N,N,N′,N′*,2,2-hexamethyl-1,3-propanediamine, which was studied at pH 10.062 and a total amine concentration of 0.0376 M, the correction for hydroxide ion catalysis was 26%. In making hydroxide ion corrections (of less than 2%) at 0 °C, pK_w was taken to be increased by 0.124 by the presence of 0.52 M acetone on the same basis described previously for 35 °C.[3]

Values of k_{ah} for each diamine at a given temperature and of ay for each kinetic run were calculated from eq 7 and eq 8 (the values of k_6 used in eq 8 being those calculated from eq 7) so as to minimize the sum of the squares of the fractional deviations from the observed k_6 and q values, with the deviations from q being weighted by the factor $[1 - (f_6)_{last}/0.8]$ where $(f_6)_{last}$ is the last f_6 value determined in the run. This weighting allows for the uncertainty in q resulting from not carrying a reaction far enough. The assumption, for which evidence was described previously,[3] that the tertiary amino groups are seven times as reactive as the primary amino groups was used in estimating values of k_B and k_B'. The values of k_B were estimated using a Bronsted β of 0.60, the value of pK_{HTP} (referring to the tertiary-protonated form of the monoprotonated diamine) for the diamine,[4] and data on a reference compound. The reference compounds used for **3** and **8** were the corresponding ditertiary amines, *N,N,N′,N′*,2,2-hexamethyl-1,3-propanediamine and *o*-bis(dimethylaminomethyl)benzene, and the p*K* values of the open HTT forms of these diamines were used in the Bronsted equation. For the diamines that had a single branch at the carbon β to the dimethylamino group (**2**, **4–7**, and **9**) the similarly branched *N,N*-dimethyl-2,2-diethoxyethylamine was the reference. For **10** the unbranched *N,N*-dimethylbutylamine was the reference. The values of k_B' were estimated similarly except that the presence of a positively charged ammonio substituent three carbons away, as there is in TPH, was assumed to make log *k* larger by 0.40 than it would be for an amine of the same basicity and similar steric properties but without an electrically charged substituent. This factor was calculated from data on *N,N*-dimethylbutylamine, 3-dimethylaminopropionitrile, and 3-trimethylammonio-*N,N*-dimethylpropylamine.[3] Values of k_B and k_B' at 0 °C were calculated from the corresponding values at 35 °C using an activation entropy (−19.8 eu) equal to the average of the values for *N,N*-dimethylbutylamine and 3-dimethylaminopropionitrile. In those runs where tertiary amine was added, the concentrations of protonated and unprotonated amine were calculated from the p*K* values reported earlier, and the catalysis constants determined earlier[3] were used in calculating k_p.

The data were treated by nonlinear least-squares methods.[16] The weighting described for the correlation of k_6 and q values to obtain k_{ah} and ay values gave a variance–covariance matrix whose inverse was used as the weight matrix in obtaining values of *a*, *l*, *m*, *s*, etc. The absolute values of the correlation coefficients between k_{ah} and ay values were usually less than 0.3 and those between various ay values less than 0.1. In the correlation yielding the values of *a*, *l*, *m*, *s*, etc., however, the average correlation coefficient had an absolute value of about 0.5.

References and Notes

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