# Bifunctional Catalysis of the Dedeuteration of Acetone-d_6 by 3-Dimethylaminopropylamine, 2-(Dimethylaminomethyl)cyclopentylamines, and Polyethylenimines[1a,b]

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Abstract: Catalysis constants for the dedeuteration of acetone-d_6 by six electrically neutral amines of the type RCH_2NMe_2, where R contains sp^3-hybridized carbon at its point of attachment, give a fairly good Brønsted correlation with a β of 0.60. The catalysts $Me_2N^+HCH_2CH_2NMe_2$ and $Me_3N^+(CH_2)_nNMe_2$, where n is 2 and 3, are somewhat too reactive to fit this correlation. Catalysis by species of the type $Me_2N(CH_2)_nNH_2$, where n is 2–5, at various pH's was divided into catalysis by the unprotonated and by the monoprotonated species. The catalysis constants for the unprotonated species fit the Brønsted correlation, those for the monoprotonated species where n is 2, 4, and 5 are somewhat too large, and that for the monoprotonated form of 3-dimethylaminopropylamine is much too large to fit. In the case of the latter catalyst much of the acetone-d_6 that reacts is transformed to acetone-d_4 and acetone-d_3 without passing through acetone-d_5 as an intermediate; the deuterium exchange data may be treated in terms of Scheme I to obtain the rate constants for imine formation in fair agreement with the value obtained previously by capturing experiments using hydroxylamine. Thus most of the reaction arises from bifunctional catalysis in which acetone-d_6 is transformed to the iminium ion $(CD_3)_2C=N^+H(CH_2)_3NMe_2$, which, at comparable rates, hydrolyzes back to acetone and undergoes rate-controlling internal deuteron transfer to the dimethylamino group to give the enamine $CD_2=C(CD_3)NH(CH_2)_3NDMe_2^+$, whose $-NDMe_2^+$ group rapidly exchanges with the solvent to give a $-NHMe_2^+$ group, which transfers its proton internally to give the exchanged iminium ion. The two most stable conformers of the cyclic transition state, in which the carbon–deuterium bond being broken is held almost parallel to the p orbital on the adjacent carbon atom, have eclipsed conformations with respect to carbon 1 and carbon 2 from the diamine catalyst. The 2-(dimethylaminomethyl)cyclopentylamines, in which the analogous carbon atoms are kept nearly eclipsed, are much better catalysts, the cis isomer being as much as 150 times as effective as would be expected if it were acting only as a simple basic catalyst. With these compounds there is cocatalysis by external bases, which catalyze exchange of the $-NDMe_2^+$ group in the intermediate enamine, an exchange that is comparable in rate with the internal deuteron transfer that regenerates unexchanged iminium ion. On a weight basis, both the cis and trans isomers are comparable in catalytic activity to an enzyme whose ability to catalyze the hydrogen exchange of acetone is a part of its natural biological function.

Several previous papers in this series have described searches for bifunctional catalysis of the deuterium exchange of isobutyraldehyde-2-d by catalysts of the type $B-R-NH_2$, which should transform the aldehyde to an iminium ion from which the basic group B may remove the deuterium internally *via* a transition state like **1**. Although catalysts of the type $H_3N^+(CH_2)_nCO_2^-$

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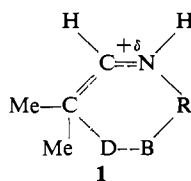
and $Me_2N(CH_2)_nNH_2$, where n was 1–5 and 2–5, respectively, gave no evidence for bifunctional activity,[2,3] compounds such as polyethylenimines[4,5] and

1-dimethylamino-8-amino-2-octyne,[3] in which there are basic groups more widely separated from the primary amino groups, do act as bifunctional catalysts for isobutyraldehyde-2-d. Apparently, transition states like **1**, in which there is cis stereochemistry around the carbon–nitrogen multiple bond, are strained enough to make bifunctional catalysis by the smaller catalysts undetectable. When the catalyst is large enough that the basic group can reach the deuterium atom in the trans form of the intermediate iminium ion, bifunctional catalysis of the dedeuteration of isobutyraldehyde-2-d may be observed.

In order to observe bifunctional catalysis *via* a cis transition state it seemed desirable to study a less hindered compound than isobutyraldehyde, *e.g.*, a compound with only hydrogen atoms on the α-carbon atom(s). Acetone seemed an attractive possibility since in any iminium ion formed from it three α-hydrogen atoms will be cis to the R group from the amine. A preliminary description of bifunctional catalysis of the dedeuteration of acetone-d_6 has already appeared.[6]

Results

All the catalysts used were known compounds except *N*,*N*-dimethyl-2,2-difluoroethylamine, which was pre-

(1) (a) This investigation was supported in part by Public Health Service Grants AM10378 from the National Institute of Arthritis and Metabolic Diseases and GM18593 from the National Institute of General Medical Sciences. Part XV in the series Catalysis of α-Hydrogen Exchange. (b) For part XIV, see J. Hine, K. W. Narducy, J. Mulders, F. E. Rogers, and N. W. Flachskam, *J. Org. Chem.*, **38**, 1636 (1973). (c) National Institutes of Health Postdoctoral Fellow (No. F02 GM-41309), 1969–1971. (d) National Science Foundation Undergraduate Research Participant, Summer, 1972.

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(6) J. Hine, M. S. Cholod, and J. H. Jensen, *J. Amer. Chem. Soc.*, **93**, 2321 (1971).

pared from ethyl difluoroacetate[7] by transformation to the N,N-dimethylamide, followed by reduction with sodium borohydride in the presence of aluminum chloride.[8] The 2-(dimethylaminomethyl)cyclopentylamines, previously reported only as a mixture of geometric isomers,[9] were separated by fractional crystallization of their oxalates into material taken to be the trans isomer, more than 98% pure, and material taken to be 81% cis and 19% trans. The strongest evidence for our stereochemical assignments are the pK values for the conjugate acids of the amines, which were 9.80 and 7.59 for the trans isomer and 9.44 and 7.00 for the 81:19 cis-trans mixture. Interpretation of any one of these values is complicated by the possibility of stabilization of the monoprotonated amines by internal hydrogen bonding. The equilibrium constant K_{12} for the forma-

$$K_{12} = [\text{H}^+]^2[\text{Am}]/[\text{AmH}_2{}^{2+}]$$

tion of the neutral diamine from the diprotonated species, however, may be seen to be $10^{-16.44}$ for the largely cis material, nine times as large as the value $(10^{-17.39})$ for the trans isomer. The diprotonated form of the cis isomer would be expected to be relatively destabilized because the two positively charged nitrogen atoms cannot get as far apart as they can in the diprotonated form of the trans isomer.[10]

The dedeuteration of 0.52 M acetone-d_6 in aqueous solution at 35° was studied by the method described previously,[11] in which the deuterium content of the acetone is determined by mass spectral measurements. In most kinetic runs the reactions were treated as simple consecutive dedeuterations, as shown in eq 1. Values of

$$d_6 \xrightarrow{k_6} d_5 \xrightarrow{k_5} d_4 \xrightarrow{k_4} \text{etc.} \quad (1)$$
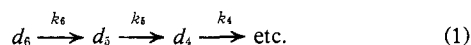
k_6 were taken as the slopes of least-squares plots of ln f_6 vs. time, where f_6 is the fraction of acetone-d_6 in the acetone. These values and eq 2, in which $(f_5)_0$ and

$$f_5 = (f_5)_0 e^{-k_5 t} + \frac{k_6(f_6)_0}{k_6 - k_5}(e^{-k_5 t} - e^{-k_6 t}) \quad (2)$$

$(f_6)_0$ are the fractions of acetone-d_5 and acetone-d_6 at zero time, were used to calculate k_5. Values of k_6 and k_5 obtained using a number of amine catalysts in aqueous solution at 35° and various pH's are listed in Table I. Except where noted each run consisted of 7–9 points and the standard deviations of the f_6 and f_5 values from those calculated from k_6 and k_5 were less than 4.5 and 9%, respectively. Most of the runs were carried from $f_6 > 0.9$ to $f_6 < 0.2$ and only the four runs noted were not carried to $f_6 < 0.4$. In these four runs k_5 is relatively unreliable. The ratio k_6/k_5 was in the range 1.06–1.33 in all other runs except one, where it was 1.01. We are not confident that any of these values are significantly different from 1.20, the value that should be obtained in the absence of secondary deuterium isotope effects.

The isotopic content of deuterated acetone may be expressed in terms of a bar graph of f_6, f_5, etc., such as

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(10) *Cf.* G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 9.
(11) J. Hine, J. C. Kaufmann, and M. S. Cholod, *J. Amer. Chem. Soc.*, **94**, 4590 (1972).

Table I. Kinetics of the Exchange of Acetone-d_6 in Aqueous Amine Solutions at 35°

Amine	[Am]$_t$,^{a} M	pH	$10^6 k_6$, sec^{-1}	$10^6 k_5$, sec^{-1}
n-BuNMe$_2$	0.0979	9.42	271	248
n-BuNMe$_2$	0.0977	10.60	955	872
MeOCH$_2$CH$_2$NMe$_2$	0.0503	9.38	64.3	57.6
MeOCH$_2$CH$_2$NMe$_2$^{b}	0.0500	9.96	116^c	74.0
(EtO)$_2$CHCH$_2$NMe$_2$	0.0964	8.81	45.7	40.5
HC≡CCH$_2$NMe$_2$	0.0961	7.94	56.3	47.2
NCCH$_2$CH$_2$NMe$_2$	0.1441	6.35	7.04	6.01
NCCH$_2$CH$_2$NMe$_2$	0.1441	7.82	27.1	22.9
F$_2$CHCH$_2$NMe$_2$	0.1442	6.30	4.40	3.90
F$_2$CHCH$_2$NMe$_2$	0.1442	7.16	8.76	7.71
F$_3$CCH$_2$NMe$_2$^{d}	0.2391	3.92	0.244	0.182
F$_3$CCH$_2$NMe$_2$	0.2909	5.29	0.992	0.873
F$_3$CCH$_2$NMe$_2$^{e}	0.1926	5.65	0.447	0.299
Me$_2$NCH$_2$CH$_2$NMe$_2$	0.0477	6.58	4.72	4.05
Me$_2$NCH$_2$CH$_2$NMe$_2$	0.0496	8.12	43.4	87.1
Me$_2$NCH$_2$CH$_2$NMe$_2$	0.0471	8.65	87.1	81.9
H$_2$NCH$_2$CH$_2$NH$_2$	0.0989	8.53	27.2^f	21.7
H$_2$NCH$_2$CH$_2$NH$_2$	0.0488	9.55	36.2	30.4
H$_2$NCH$_2$CH$_2$NH$_2$	0.0482	10.3	77.9	65.6
Me$_2$NCH$_2$CH$_2$NH$_2$^{g}	0.0489	7.94	26.3	20.5
Me$_2$NCH$_2$CH$_2$NH$_2$	0.0485	8.55	58.8	49.3
Me$_2$NCH$_2$CH$_2$NH$_2$	0.0477	9.79	175	140
Me$_2$N(CH$_2$)$_4$NH$_2$	0.0491	9.40	335	331
Me$_2$N(CH$_2$)$_4$NH$_2$	0.0470	10.05	424	400
Me$_2$N(CH$_2$)$_4$NH$_2$	0.0489	11.06	615	532
Me$_2$N(CH$_2$)$_5$NH$_2$	0.0478	9.84	479	418
Me$_2$N(CH$_2$)$_5$NH$_2$	0.0475	10.27	722	613
Me$_2$N(CH$_2$)$_5$NH$_2$	0.1895	11.12	3233	2850
Me$_2$N(CH$_2$)$_5$NH$_2$	0.0474	11.20	642	580
Me$_3\overset{+}{\text{N}}$CH$_2$CH$_2$NMe$_2$	0.1451	6.24	8.75	7.89
Me$_3\overset{+}{\text{N}}$CH$_2$CH$_2$NMe$_2$	0.1451	5.66	4.71	4.18
Me$_3\overset{+}{\text{N}}$(CH$_2$)$_3$NMe$_2$	0.0966	7.73	54.3	47.3
Me$_3\overset{+}{\text{N}}$(CH$_2$)$_3$NMe$_2$	0.0966	8.26	104	83.8
PEI-1800^h	0.107^i	3.60	2.4	1.9
PEI-1800^h	0.102^i	5.32	16.1	13.3
PEI-1800^h	0.098^i	7.05	86	79
PEI-1800^h	0.101^i	8.01	184	
PEI-1800^h	0.103^i	8.51	185	164
PEI-1800^h	0.102^i	9.22	137	126
PEI-1800^h	0.097^i	9.90	85	75
PEI-1800^h	0.118^i	10.51	76	66
PEI-600^h	0.099^i	8.49	152	129
PEI-190^{h,j}	0.099^i	8.54	41	32

^{a} Total amine concentration, not allowing for protonation or imine or imidazolidine formation. ^{b} Followed to $f_6 = 0.42$. ^{c} Standard deviation of f_6 values, 5.0%. ^{d} Followed to $f_6 = 0.76$. ^{e} Followed to $f_6 = 0.55$. ^{f} Standard deviation of f_6 values, 6.1%. ^{g} Followed to $f_6 = 0.62$. ^{h} PEI-X is polyethylenimine with an average molecular weight of X. ^{i} Normality (in equivalents of amino group per liter). ^{j} Technical tetraethylenepentamine, referred to as a PEI because it is a mixture of a number of similar compounds.

those shown in Figure 1. When acetone-d_6 is dedeuterated by the path shown in eq 1 with no secondary kinetic isotope effects, this bar graph changes with time in a unique way, the only difference between kinetic runs being the time scale for the change. For all the runs covered by Table I the change in bar graphs closely followed the theoretical pattern which is illustrated on the left side of Figure 1 for the cases where f_6 has fallen to 0.690, 0.351, and 0.139. In the presence of certain diamine catalysts under certain conditions the pattern is much different. Bar graphs from runs in the presence of 3-dimethylaminopropylamine and *trans*-2-(dimethylaminomethyl)cyclopentylamine are shown in the middle
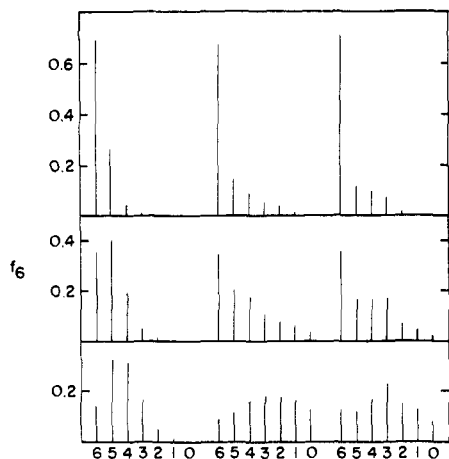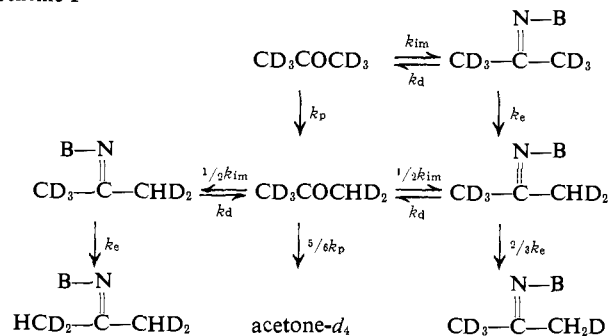
Figure 1. Bar graphs of f_6, f_5, f_4, etc., for deuterated acetone. The three on the left are theoretical graphs for eq 1, those in the middle are for 3-dimethylaminopropylamine, and those on the right for 2-(dimethylaminomethyl)cyclopentylamine. For the top three $f_6 \sim 0.69$, for the middle three $f_6 \sim 0.35$, and for the bottom three $f_6 \sim 0.12$.

Figure 2. Plot of rate constants for dedeuteration of 0.52 M acetone-d_6 in the presence of 0.1 M PEI-1800 in water at 35° $vs.$ pH.

and right side, respectively, of Figure 1. Especially in the latter case it seems likely that, in addition to the path shown in eq 1, acetone-d_6 is transformed directly to the d_4 and d_3 but not to the d_2, d_1, and d_0 species. The contrast to the patterns expected from eq 1 is so great that in some runs there is no time at which acetone-d_5 is the most abundant species.

This behavior in the presence of certain bifunctional catalysts was interpreted in terms of the abbreviated reaction scheme (Scheme I), in which the bifunctional

Scheme I

$$\frac{df_5}{dt} = qk_6 f_6 - \left(1 - \frac{q}{6}\right)k_6 f_5 \qquad (5)$$

which q is defined in eq 6. Substitution for f_6 in terms

$$q = [2r(k_p/k_6) + 3]/(2r + 3) \qquad (6)$$

of $(f_6)_0$, k_6, and t and integration gives eq 7. The value

$$f_5 = [6(f_6)_0 + (f_5)_0]e^{-(1-q/6)k_6 t} - 6(f_6)_0 e^{-k_6 t} \qquad (7)$$

of k_6 already obtained in the given run and an iterative computer process gave the q value from which the experimental f_5 values may be calculated with the smallest sum of the squares of the deviations. If very little of the reaction proceeds via the imines ($i.e.$, if $k_p \sim k_6$) or if the imines hydrolyze much more rapidly than they lose deuterium ($i.e.$, if $r \ll 1$), q is essentially equal to 1.00 and eq 7 reduces to eq 2 [with k_5 expressed as $(5/6)k_6$]. Calculations of the optimum value of q for all the runs in Table I by a method that does not allow q to be larger than 1.00 gave values ranging from 0.96 to 1.00. The standard deviation of the f_5 values calculated from these q values and the corresponding k_6 values from the experimental f_5 values were never larger than 10%. The fact that these f_5 values could thus be fit almost as well by eq 7, in which k_5 is set at $(5/6)k_6$, as when k_5 is treated as a disposable parameter (eq 2), is further evidence that the deviations of k_6/k_5 ratios from 1.2 are not experimentally significant.

Values of k_6 and q calculated from eq 7 for 3-dimethylaminopropylamine and the 2-(dimethylaminomethyl)-cyclopentylamines are listed in Table II. From these values, the experimental f_5 values may be calculated with standard deviations that exceed 8% only in the two cases noted. When eq 2 is applied to those runs for which q values less than 0.6 were obtained the resulting k_5 values were between 0.32 and 0.49 times the corresponding k_6 values, and the experimental f_5 values could not be calculated with standard deviations less than 20%.

catalyst is B–NH$_2$, with B being a basic substituent. This scheme neglects secondary deuterium kinetic isotope effects and assumes that the intermediate imines lose deuterium only from the methyl group cis to B (as would be expected for internal catalysis by the catalysts used). According to Scheme I the first-order rate constant for disappearance of acetone-d_6 may be expressed as shown in eq 3, in which r is the rate constant

$$k_6 = k_p + k_{im}r/(1 + r) \qquad (3)$$

ratio k_e/k_d, if the steady-state assumption is made for the intermediate imines. The rate of formation of acetone-d_5 may be expressed as shown in eq 4. Substitution of a

$$\frac{df_5}{dt} = k_p f_6 - \frac{5}{6}k_p f_5 + k_{im}\left(\frac{r}{1+r}\right)\left(\frac{3}{2r+3}\right) \times$$

$$f_6 - k_{im}\left(\frac{r}{2r+3}\right)f_5 - \frac{1}{2}k_{im}\left(\frac{r}{1+r}\right)f_5 \qquad (4)$$

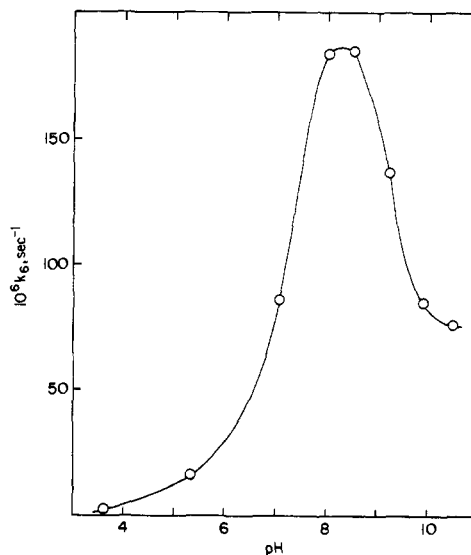value for k_{im} from eq 3 and rearrangement gives eq 5, in

Discussion

Catalysis by Polyethylenimines. Figure 2 is a plot of

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Table II. Kinetics of the Exchange of Acetone-d_6 in the Presence of 3-Dimethylaminopropylamine and 2-(Dimethylaminomethyl)cyclopentylamines

Amine	[Am]$_t$, M	pH	$10^6 k_6$, sec^{-1}	q
Me$_2$N(CH$_2$)$_3$NH$_2$	0.0483	5.84	5.22	a
	0.0477	7.56	250	0.49
	0.0482	8.05	548	0.48
	0.0469	8.52	847	0.48
	0.0468	8.88	989	0.50
	0.0243	8.90	497	0.52
	0.0474	8.97	1020	0.49
	0.0968	9.65	2000	0.60
	0.0244	9.99	553	0.74
	0.0487	10.01	1170	0.73
	0.0482	10.57	915	0.89
	0.1922	11.13	2630	0.95
	0.0479	11.15	671	1.00
trans-2-(Dimethyl-	0.00481	7.63	91.4	0.79
aminomethyl)-	0.00962	7.74	280	0.83
cyclopentylamine	0.0192	7.83	665	0.77
	0.00481	8.65	343	0.68
	0.00962	8.73	1030	0.60
	0.0192	8.76	2370	0.54
	0.00481	9.76	437	0.49
	0.00962	9.76	884	0.45
	0.0192	9.85	1790	0.43
cis-2-(Dimethyl-	0.00818	7.21	97.6	0.92
aminomethyl)-	0.0192	7.35	375	0.87
cyclopentylamine	0.00847	8.31	817	0.69
	0.0192	8.45	2420	0.61
	0.00866	9.65	1090	0.44
	0.0192	9.71	2200	0.38

^{a} Since the reaction was followed only to f_6 = 0.69, no reliable value of q could be obtained.

k_6 vs. pH for the exchange of acetone-d_6 in the presence of 0.1 N PEI-1800 (polyethylenimine with an average molecular weight of 1800). Just as in the case of iso-butyraldehyde-2-$d^{4,5}$ there is a rate maximum near pH 8. This provides convincing evidence that the PEI is not just acting as a simple base. Although the catalytic activity of the PEI's is not as large, relative to that of such model compounds as ethylenediamine and its various N-methylated derivatives, as in the dedeuteration of isobutyraldehyde-2-d, it seems quite likely that polyfunctional catalysis is important in the present case as well. Since q values of 1.0 were obtained when eq 7 was applied to the data the intermediate imines formed in the reaction must be hydrolyzed back to acetone considerably more rapidly than they are dedeuterated by transformation to iminium ions followed by internal attack by the amino groups of the polymer.

Simple Basic Catalysis. Catalysis by water and hydrogen ions[11] never contributed as much as 0.2% to the total reaction rate in any run carried out above pH 5. The rate constant for hydroxide ion catalysis[11] shows that such catalysis never contributed more than 18% to any reaction carried out below pH 11 except for the ethylenediamine run at pH 10.3 where about half the reaction arises from hydroxide ion catalysis. Since acetate ions are about three times as effective as acetic acid molecules in catalyzing the enolization of acetone in aqueous solution at 25°,[12] we have neglected simple acid catalysis by the acid members of our acid–base pairs, all but one of which are more weakly acidic than acetic acid by more than 40-fold. The exception, the N,N-dimethyl-2,2,2-trifluoroethylammonium ion, may well have significant catalytic activity. However, the runs in

(12) R. P. Bell and P. Jones, *J. Chem. Soc.*, 88 (1953).

which it was present were so slow that the resulting rate constants were of reduced reliability.

For the tertiary monoamines studied catalysis constants were calculated by dividing the first-order rate constants, corrected for hydroxide ion catalysis, by the concentrations of free amine. Both the unprotonated and monoprotonated forms of N,N,N',N'-tetramethylethylenediamine were assumed to be catalysts, and catalysis constants were calculated by the method of least squares. In Table III are the catalysis constants

Table III. Catalysis Constants for the Dedeuteration of Acetone-d_6 in Water at 35°

Catalyst	pK^a	$10^5 k_B$, M^{-1} sec^{-1}	Std dev, %
n-BuNMe$_2$	9.80	1220	7.0
MeOCH$_2$CH$_2$NMe$_2$	8.96	230	0.6
(EtO)$_2$CHCH$_2$NMe$_2$	7.96	58.1	b
HC≡CCH$_2$NMe$_2$	7.21	64.7	b
NCCH$_2$CH$_2$NMe$_2$	6.89	24.1	4.0
F$_2$CHCH$_2$NMe$_2$	6.32	7.59	0.4
F$_3$CCH$_2$NMe$_2$	4.54	0.4^c	40
Me$_2$NCH$_2$CH$_2$NMe$_2$	9.26^d	1160	13.6
Me$_2$ṄHCH$_2$CH$_2$NMe$_2$	5.34^e	9.2^c	
Me$_2$NCH$_2$CH$_2$NH$_2$	9.30^d	498^c	13.5
Me$_2$NCH$_2$CH$_2$NH$_3^+$	5.98^e	42.6^c	
Me$_2$N(CH$_2$)$_3$NH$_2$	9.91^d	1270^c	16.0
Me$_2$N(CH$_2$)$_3$NH$_3^+$	7.67^e	2250^c	
Me$_2$N(CH$_2$)$_4$NH$_2$	10.17^d	1060^c	1.5
Me$_2$N(CH$_2$)$_4$NH$_3^+$	8.44^e	778^c	
Me$_2$N(CH$_2$)$_5$NH$_2$	10.44^d	1150^c	21.4
Me$_2$N(CH$_2$)$_5$NH$_3^+$	9.07^e	1440^c	
H$_2$NCH$_2$CH$_2$NH$_2$	9.68^d	99.6^c	5.1
H$_2$NCH$_2$CH$_2$NH$_3^+$	6.58^e	23.8^c	
Me$_3$ṄCH$_2$CH$_2$NMe$_2$	5.57	7.79	4.8
Me$_3$Ṅ(CH$_2$)$_3$NMe$_2$	7.54	146	6.1

^{a} Thermodynamic pK in water at 35°. ^{b} Based on only one kinetic run. ^{c} Relatively unreliable (see text). ^{d} This is the gross pK for total monoprotonated diamine without regard to the position of protonation. ^{e} This is the gross pK for the diprotonated diamine without regard to the position from which the proton is lost.

(k_B) obtained and the standard deviations of the fits of the rate constants in Table I to these k_B values. The value of k_B for N,N-dimethyl-2,2,2-trifluoroethylamine is seen to be relatively unreliable. The other values for electrically neutral amines of the type RCH$_2$NMe$_2$, where R is attached via an sp^3-hybridized carbon atom, give a satisfactory Brønsted plot of slope 0.60, as shown by the solid circles in Figure 3. This is considerably smaller than the value 0.88 obtained by Bell and Lidwell in a study of the iodination of acetone in the presence of carboxylate ions at 25°.[13] This difference in β values is in the right direction to be explained by the greater basicity of our catalysts relative to those of Bell and Lidwell, but it is so large as to suggest that other factors are also important.

The point for N,N-dimethylpropargylamine, which is a somewhat less hindered amine than those upon which the line is based, falls slightly above the line, suggesting that steric hindrance is significant. This suggestion is supported by the fact that the points for trimethylamine and 1,4-diazabicyclo[2.2.2]octane, whose catalysis constants were determined previously,[11] also fall above the

(13) R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc., Ser. A*, **176**, 88 (1940).

line. However, steric hindrance does not explain why the points for $Me_3N^+(CH_2)_nNMe_2$, where n is 2 and 3, and the monoprotonated form of N,N,N',N'-tetramethylethylenediamine, lie above the line. These deviations for cationic amines are reminiscent of those observed in the general base catalyzed decomposition of nitramide, where the catalysis constants for bases of a given strength tend to increase with increasing positivity of the charge on the base.[14] Kresge and Chiang have attributed such deviations to electrostatic interactions between the positively charged substituent and the negative charge being placed on the substrate in the transition state.[15] The deviations of our three points for cationic tertiary amines from the line for the electrically neutral amines would be less than half as large if pK values at the average ionic strengths of the kinetic runs had been used in making the plot. However, such a method of plotting would increase most of the deviations between species of different charge type observed by Kresge and Chiang. It should be noted that if activity coefficients depend only on the ionic strength and the electrical charge type of the species, as in the Davies equation or the limiting form of the Debye–Hückel equation, then if an acid or base fits a Brønsted equation for species of a different charge type at a given ionic strength it must deviate from that equation at other ionic strengths.

Catalysis by ω-Dimethylaminoalkylamines. None of the compounds with primary amino groups should be tied up as imines to a significant extent. The equilibrium constants for the formation of imidazolidines,[16] however, are large enough to show that the data for ethylenediamine are probably complicated by the transformation of as much as one-third of the amine to an imidazolidine.

The compounds having primary amino groups should be capable of catalyzing the hydrogen exchange of acetone not only by acting as simple bases but also by transforming the acetone to iminium ions, which would donate α hydrogen to bases more rapidly than acetone would. Extrapolation from data on catalysis by methylamine[11] indicates that attack by an external base on an iminium ion should not be the major pathway for reaction in any of our runs (where the amine concentrations were relatively low), but that small amounts of reaction by such a mechanism were probably occurring. Studies of the ω-dimethylaminoalkylamines having two, four, and five methylene groups between the amino groups did not give enough evidence for bifunctional catalysis to warrant making the number of runs required for reliable measurement of the extent of reaction via iminium ions. Hence the k_B values listed for these compounds in Table III were obtained from eq 8,

$$k_6 - k_h[OH^-] = k_B[Am] + k_B'[AmH^+] \qquad (8)$$

in which rate-controlling attack of amines on iminium ions is neglected. Values 2–32% smaller are obtained if a term of the form $k[Am][AmH^+]$ is added to eq 8 to allow for catalysis via the formation of iminium ions. Interpretation of these k_B values in terms of the Brønsted equation is complicated by the fact that both the primary and tertiary amino groups contribute to both

(14) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, Chapter Vc.
(15) A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, **95**, 803 (1973).
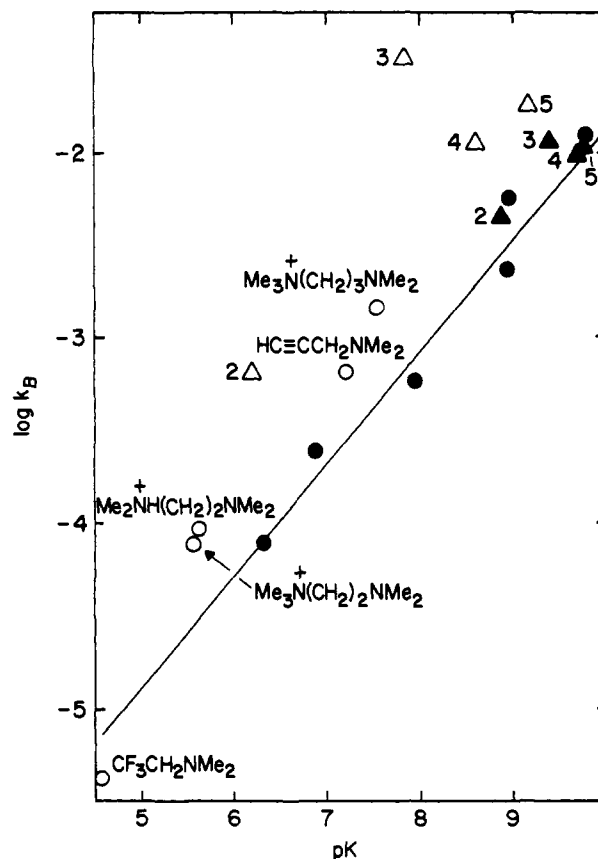(16) J. Hine and K. W. Narducy, *J. Amer. Chem. Soc.*, **95**, 3362 (1973).

Figure 3. Brønsted plot of the amine-catalyzed dedeuteration of acetone-d_6: (▲) $H_2N(CH_2)_nNMe_2$, labeled with the value of n; (△) $H_3N^+(CH_2)_nNMe_2$, labeled with the value of n; (●) other electrically neutral amines of the type RCH_2NMe_2 where R has an sp^3-hybridized carbon atom at its point of attachment; (○) as labeled. For treatment of the data on ω-dimethylaminoalkylamines and their conjugate acids, see text.

k_B values and pK values, although primary and tertiary amines are not expected to fall on the same Brønsted line. We have focused our attention on catalysis by the dimethylamino groups; this should be the major contributor to simple basic catalysis in view of the observation that the catalysis constant for trimethylamine is seven times as large as that for methylamine in spite of the fivefold greater basicity of methylamine.[11] Accordingly, we have taken the catalysis constants for the dimethylamino groups as being seven-eighths of the k_B values for the $Me_2N(CH_2)_nNH_2$ compounds listed in Table III. The logarithms of these values have been plotted in Figure 3 against the pK values for the cations $Me_2N^+H(CH_2)_nNH_2$[17] rather than the pK values for total monoprotonated diamine listed in Table III. The resulting points are seen to give satisfactory agreement with the Brønsted line for electrically neutral bases of the type RCH_2NMe_2.

The k_B values for the monoprotonated diamines were treated analogously. Each $Me_2N(CH_2)_nNH_3^+$ was taken to be seven times as reactive as the corresponding $Me_2N^+H(CH_2)_nNH_2$. The points were then plotted in Figure 3 allowing for the fraction of the monoprotonated diamine that is protonated at each of the two amino groups and the appropriate pK values.[17] The points for the ions with two, four, and five meth-

(17) J. Hine, F. A. Via, and J. H. Jensen, *J. Org. Chem.*, **36**, 2926 (1971).

ylene groups between the two nitrogen atoms lie above the line for amines of the type RCH_2NMe_2 shown in the figure, but perhaps by no more than would be accounted for by experimental uncertainty, iminium ion catalysis, and the cationic nature of these species. We do not feel we have enough evidence to tell whether any of these species are acting as bifunctional catalysts to a significant extent.

Catalysis by 3-Dimethylaminopropylamine. The catalysis constant for the monoprotonated form of 3-dimethylaminopropylamine is the largest listed in Table III and it deviates more than any other from the line in Figure 3. If the data are treated by adding a $k[Am][AmH^+]$ term to eq 8 the value drops by only 4% and the standard deviation of the fit of the k_6 value improves only to 13.8%. It therefore seems unlikely that the particularly strong catalytic activity of this species can be explained in terms of attack of external bases on an intermediate iminium ion. The poor fit of the data to eq 2 in the pH range where the amine is largely monoprotonated gives strong evidence that the monoprotonated amine is not acting just as a simple basic catalyst. Analysis in terms of Scheme I, which includes both simple basic catalysis and bifunctional catalysis *via* an intermediate iminium ion, gave values of k_6 and q that fit the experimental data satisfactorily in each run. In order to tell whether the variations in k_6 and q with pH are consistent with Scheme I a more detailed analysis is needed. The only species capable of giving significant amounts of simple basic catalysis are hydroxide ions and the unprotonated and monoprotonated forms of the diamine. Hence k_p in Scheme I should follow eq 9. Since eq 9 refers to simple basic

$$k_p = k_B[Am] + k_B'[AmH^+] + k_h[OH^-] \quad (9)$$

catalysis, the appropriate values of k_B and k_B' are not those listed in Table III for 3-dimethylaminopropylamine and its monoprotonated derivative. We have estimated the correct values from the k_B values for simple tertiary amines, where the mechanism for catalysis is known unambiguously. Dimethylamino groups were assumed to be seven times as effective as the corresponding primary amino groups, as described previously. The Brønsted line in Figure 3 and the appropriate pK value[17] give an estimate of 6.5×10^{-3} M^{-1} sec^{-1} for k_B in eq 9. The N,N-dimethyl-3-trimethylammoniopropylamine cation was taken as a model for the 3-dimethylaminopropylammonium cation, whose reactivity was calculated from the appropriate pK value $(7.82)^{17}$ and a Brønsted line of slope 0.60 through the point for the N,N-dimethyl-3-trimethylammoniopropylamine cation in Figure 3. (The extrapolation is so short that it makes little difference what Brønsted β is used.) Then, with allowance for the reactivity of the N,N-dimethyl-3-aminopropylammonium cation and the relative amounts of the two monoprotonated forms of 3-dimethylaminopropylamine present[17] a value of 1.6×10^{-3} M^{-1} sec^{-1} is estimated for k_B'. Using the k_h value 7.22×10^{-2} M^{-1} sec^{-1} determined at ionic strengths below 0.05 the values of k_p listed in Table IV were calculated. With these and the corresponding values of k_6 and q the values of r listed in the table were calculated from eq 10, a rearranged form of the definition of q (eq 6).

$$r = k_e/k_d = 3k_6(1 - q)/[2(k_6q - k_p)] \quad (10)$$

Table IV. Kinetic Constants for the Dedeuteration of Acetone-d_6 in the Presence of 3-Dimethylaminopropylamine

pH	$10^6 k_p$, sec^{-1}	r	$10^{-8}a$, M^{-1}	$10^3 k_{ah}$, M^{-1} sec^{-1}
5.84	0.47	a	a	a
7.56	19.5	1.86	95	29.4
8.05	42	1.94	101	29.9
8.52	65	1.89	102	31.8
8.88	83	1.83	105	31.9
8.90	45	1.66	96	31.0
8.97	89	1.87	109	31.2
9.65	301	1.35	116	26.4
9.99	112	0.72	100	33.2
10.01	215	0.75	104	35.4
10.57	314	0.32	123	35.2
11.13	1390	0.19	237	25.9
11.15	470	0	0	∞

a This value could not be calculated because no value of q was determined in this run.

The rate constant for imine formation may be expressed as the sum of a k_a term, which arises from uncatalyzed imine formation by the unprotonated diamine, and a k_{ah} term, which includes acid-catalyzed imine formation by the unprotonated diamine and the formation of imine by the monoprotonated diamine without external catalysis (eq 11).[18,19] From the

$$k_{im} = k_a[Am] + k_{ah}[AmH^+] \quad (11)$$

principle of microscopic reversibility it follows that the rate constant for hydrolysis of the imine may be expressed as shown in eq 12. Dedeuteration of an

$$k_d = k_{do}[Im] + k_{dh}[ImH^+] \quad (12)$$

iminium ion form of the intermediate imine could arise by attack of any base. However, this would also be true for iminium ions derived from the other ω-dimethylaminoalkylamines. The only plausible explanation we have conceived for the markedly enhanced catalytic activity of the monoprotonated form of 3-dimethylaminopropylamine is that in the $(CD_3)_2C=N^+H-(CH_2)_3NMe_2$ cation the dimethylamino group is especially well situated for removing a deuteron internally. Therefore other pathways for dedeuteration of the iminium ion will be neglected and k_e will be expressed as shown in eq 13. Insertion of eq 12 and 13 into the

$$k_e = k_i[ImH^+] \quad (13)$$

definition of r and rearrangement gives eq 14, in which

$$a = r[b + (1/[H^+])] \quad (14)$$

a is $k_i/(k_{do}K_{IH})$, b is $k_{dh}/(k_{do}K_{IH})$, and K_{IH} is the acidity constant of the monoprotonated imine. Application of the principle of microscopic reversibility shows that $k_{dh}/(k_{do}K_{IH})$ is equal to $k_{ah}/(k_aK_{AH})$ where K_{AH} is the acidity constant of the monoprotonated amine. The value of K_{AH} is known and values of k_{ah} and k_a have been determined for the iminization reaction of acetone (not acetone-d_6) in dilute solution at 35°.[19] We shall assume that although the individual values of k_a and k_{ah} may change between the two sets of conditions they will change in the same way. Hence we shall assume that the value of b is equal to $k_{ah}/(k_aK_{AH})$,

(18) J. Hine and F. A. Via, *J. Amer. Chem. Soc.*, **94**, 190 (1972).
(19) J. Hine, M. S. Cholod, and W. K. Chess, Jr., *J. Amer. Chem. Soc.*, **95**, 4270 (1973).

where the rate constants are those determined previously. This and the values of r determined permit the calculation of the values of a listed in Table IV. Except for the runs above pH 11, where the k_p correction constituted half the reaction or more, and the run at pH 5.84, where no value of q was obtained, the values of a are seen to be satisfactorily constant, averaging $(105 \pm 7) \times 10^8\ M^{-1}$.

Substitution of a value of k_{im} from eq 11 and a value of r from eq 14 into eq 3 and rearrangement gives eq 15,

$$k_{ah} = b(k_6 - k_p)(1 + r)/[a[\text{AmH}^+]] \qquad (15)$$

which permits the calculation of a value of k_{ah} for each run. The values listed in Table IV for runs between pH 6 and 11 average $(31.5 \pm 2.0) \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$. This is slightly smaller than the previously obtained value $32.4 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$, which in turn was said to be slightly too small because some of the acetone was tied up as $(\text{CH}_3)_2\text{C(OH)NHOH}$ and because capture of the imine by hydroxylamine was not entirely complete.[19] Imine formation from acetone-d_6 may be somewhat faster than from the protium analog.[20] All things considered the agreement of the k_{ah} values in Table IV with the similar ones obtained previously is believed to be good enough to support the proposed reaction mechanism.

Catalysis by 2-(Dimethylaminomethyl)cyclopentylamines. The data obtained using the 2-(dimethylaminomethyl)cyclopentylamines (DAMCA's) fit eq 8 poorly, standard deviations of 49 and 31% being obtained with the cis and trans isomers, respectively. The efficiency of these catalysts relative to that which would be expected in the absence of bifunctional catalysis is best estimated by comparing the observed values of k_6 with those calculated from estimated k_B and k_B' values for simple basic catalysis. The method of estimation already described for 3-dimethylaminopropylamine gave values of 6.2×10^{-3} and 1.4×10^{-3} $M^{-1}\ \text{sec}^{-1}$ for k_B and k_B', respectively, in the case of trans-DAMCA. The fraction of monoprotonated cis-DAMCA that is protonated at the tertiary amino group (f_t) has not been determined, but if it is taken to be the same as for the trans isomer $(0.36)^{19}$ and if pK values obtained on the 81% cis-19% trans mixture are used, values of 3.8×10^{-3} and $0.62 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$ may be estimated for k_B and k_B', respectively. From these values it is found that the k_6 values obtained for cis-DAMCA are 35-150 times larger and those for trans-DAMCA are 17-75 times larger than would be expected from simple basic catalysis. Since the kinetics of imine formation with acetone have been studied with trans-DAMCA[19] we have assumed that $k_{ah}/(k_a K_{AH})$ has the same value for 0.52 M acetone-d_6 as for its 0.01 M protio analog. The k_a term may be calculated never to contribute more than 5% to the total rate of imine formation in any of the runs on trans-DAMCA listed in Table II. Hence the assumption of a value for the ratio $k_{ah}/(k_a K_{AH})$ may be regarded as a method of correcting for the minor contribution of the k_a term without making significant additional restrictions. This assumption permits the application of eq 14 and 15 to the data in the same way described for 3-di-

(20) In unpublished observations applying the previously described technique,[19] Dr. W.-S. Li has obtained values of k_D/k_H ranging from around 1.0 to around 1.3.
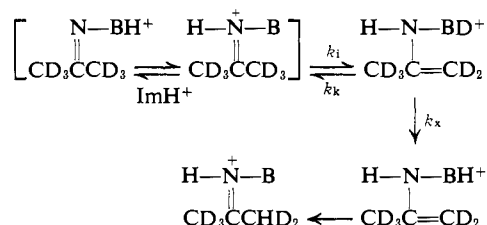
methylaminopropylamine. However, in the present case the value of a was not found to remain reasonably constant over a range of experimental conditions. (See the values of ay in Table V.) Instead it seems to

Table V. Kinetic Constants for the Dedeuteration of Acetone-d_6 in the Presence of trans-2-(Dimethylaminomethyl)cyclopentylamine

pH	$10^6 k_p$, sec^{-1}	r	$10^{-9}ay$, M^{-1} Exptl	Calcd	k_{ah}, M^{-1} sec^{-1}
7.63	3.1	0.42	20	17	0.140
7.74	7	0.32	15	18	0.243
7.83	14	0.45	21	21	0.219
8.65	8	0.72	34	34	0.193
8.73	16	1.00	47	46	0.246
8.78	31	1.30	61	62	0.253
9.76	24	1.77	92	93	0.230
9.76	41	2.07	107	103	0.215
9.85	82	2.16	114	116	0.230

decrease with decreasing concentrations of bases in the reaction solution. We suggest an explanation based on Scheme II for this behavior. This scheme is an ampli-

Scheme II

fication of the step governed by k_e in Scheme I and by k_i in eq 13. In the case of 3-dimethylaminopropylamine k_x is considerably larger than k_k, above pH 7, at least. For this reason eq 13 is applicable. In the present case, however, k_x and k_k are comparable and only a fraction of the intermediate with a $-\text{BD}^+$ group that is formed is then transformed further to the pentadeuterated iminium ion. If this fraction is denoted y, then the term a in eq 14 and 15 must be replaced by ay for these equations to be applicable to the DAMCA's. In Table V are the values of k_p, r, ay, and k_{ah} resulting from the application of eq 9, 10, and the appropriately modified forms of 14 and 15 to the data on trans-DAMCA. The value obtained for k_{ah} is fairly constant, averaging 0.219 ± 0.024 $M^{-1}\ \text{sec}^{-1}$. The experimental value obtained with protio acetone (0.140 $M^{-1}\ \text{sec}^{-1}$) was said to be as much as 20% low because of incomplete capture of the imine and tying up the acetone as $(\text{CH}_3)_2\text{C(OH)NHOH}$.[19] The protio acetone value may therefore be as large as 0.175 M^{-1} sec^{-1}. The difference between these two k_{ah} values is believed to be no larger than the isotope effects, experimental error, etc.

The tendency of ay to increase with the concentrations of bases in the reaction solutions suggests that the deuterium in the $-\text{NDMe}_2^+$ group (the $-\text{BD}^+$ group in Scheme II) is removed by the attack of a base. To treat the matter quantitatively we note that there are four bases present at significant concentrations in the reaction solutions. They are water, monoprotonated amine, unprotonated amine, and hydroxide ions. Therefore y may be represented as shown in eq 16, in

$$y =$$

$$\frac{k_s + k_m[\text{AmH}^+] + k_u[\text{Am}] + k_l[\text{OH}^-]}{k_k + k_s + k_m[\text{AmH}^+] + k_u[\text{Am}] + k_l[\text{OH}^-]} \quad (16)$$

which k_s is the rate constant for solvent-catalyzed (or uncatalyzed, or internally catalyzed) exchange and the other rate constants refer to the bases shown in brackets after them. This equation may be applied to the experimentally determined values of ay by rearrangement to eq 17, in which s is k_s/k_k, m is k_m/k_k, u is k_u/k_k, and

$$ay =$$

$$a\left(\frac{s + m[\text{AmH}^+] + u[\text{Am}] + l[\text{OH}^-]}{1 + s + m[\text{AmH}^+] + u[\text{Am}] + l[\text{OH}^-]}\right) \quad (17)$$

l is k_l/k_k. This permits correlation of the ay values in terms of five parameters. A least-squares treatment gave the parameter values shown in Table VI. The

Table VI. Parameter Values for Eq 17

Parameter	Value
a	$135 \times 10^9\ M^{-1}$
s	0.128
m	0
u	$472\ M^{-1}$
l	$1.11 \times 10^4\ M^{-1}$

relative magnitudes of the parameters are plausible for basic catalysis except for the value of zero for m. However, if m is assigned the value 5 M^{-1} (so that it will differ from u by a factor smaller than the difference in the basicities of the monoprotonated and unprotonated diamine) least-squares treatment gives the equally plausible values of 0.103, 410, and 1.25×10^4 M^{-1} for s, u, and l, respectively, from which the experimental values of ay may be calculated with a standard deviation less than 20% larger than that obtained with the values listed in Table VI. The ability of eq 17 to correlate the experimental ay values satisfactorily with plausible parameter values supports the validity of Scheme II.

The catalytic activity of cis-DAMCA appears to be somewhat greater than that of the trans isomer. However, since the kinetics of imine formation from the cis isomer have not been studied, since the material used in the present study was only 81% pure, and since a smaller number of kinetic runs were made, we shall present no detailed analysis of the data on this isomer.

Our interpretation of the data on trans-DAMCA in terms of Scheme II is unusual in that it requires a deuteron transfer to carbon (the reaction governed by k_k) to compete successfully with a deuteron transfer to oxygen or nitrogen (the reaction governed by k_x). The deuteron transfer governed by k_k is from the weakly acidic $-\text{NDMe}_2^+$ group to a carbon atom at which large changes in bond angles and bond distances must be taking place during the transfer. It may seem surprising that such a process could compete significantly with deuteron transfer reactions between two nitrogen atoms or a nitrogen and an oxygen atom, in view of the evidence that such reactions tend to take place with diffusion control in the favorable direction when the equilibrium constants are significantly larger than 1.0.[21] Our interpretation also requires this in-

(21) M. Eigen, Angew. Chem., Int. Ed. Engl., 3, 1 (1964).

ternal deuteron transfer to compete successfully with deuteron transfers to external bases in the enamines derived from the DAMCA's but not in the enamine derived from 3-dimethylaminopropylamine. To test the plausibility of the interpretation let us see what we can deduce about the magnitude of k_k. If the equilibrium constant for the formation of imine from acetone and amine is K_I, it follows that k_a is equal to $k_{do}K_I$. Then eq 18 follows from the definition of a. If K_E is

$$k_i = ak_aK_{IH}/K_I \quad (18)$$

the equilibrium constant for the formation of enamine from ketimine and if we neglect deuterium equilibrium

$$K_E = [\text{CH}_2\text{=}\text{C}(\text{CH}_3)\text{NH—B}]/[(\text{CH}_3)_2\text{C}\text{=}\text{N—B}] \quad (19)$$

isotope effects and the small difference between the basicity of the dimethylamino (B) group in the enamine and that in the ketimine, K_E may be shown to be equal to k_i/k_k. This gives eq 20. The values of K_{IH} and K_E

$$k_k = ak_aK_{IH}/(K_IK_E) \quad (20)$$

should be about the same for trans-DAMCA as for 3-dimethylaminopropylamine. However, the product ak_a is about eight times as large for the former as for the latter amine. We estimate that K_I is half as large for trans-DAMCA, in which the primary amino group is attached to a secondary carbon atom, as for 3-dimethylaminopropylamine, in which the primary amino group is attached to a primary carbon atom, on the basis of the equilibrium constants for the formation of N-alkylisobutyraldimines from isopropylamine (1840) and n-propylamine (4170).[22] Hence k_k should be about 16 times as large for trans-DAMCA as for 3-dimethylaminopropylamine. Thus even if the rate constants for deuteron transfers are the same in the two cases, s, m, u, and l should be about 16 times as large for 3-dimethylaminopropylamine as for trans-DAMCA. The factor will be larger than 16 if deuteron transfers from the enamine derived from trans-DAMCA are slowed by increased steric hindrance. Even with a factor of 16, y may be calculated to exceed 0.82 in every run made on 3-dimethylaminopropylamine except those at pH 7.56 and 5.84, where it would be 0.71 and 0.67, respectively. Considering that the factor may well be larger, it is plausible that the values of a in Table IV are almost constant but the smallest value is the one obtained at the lowest pH.

The plausibility of the absolute values of the rate constants for deuteron transfer are also of interest. The value of k_l, a rate constant for deuteron transfer from an ammonium cation to a hydroxide anion, should be at the diffusion-controlled limit, which we estimate to be $2 \times 10^{10}\ M^{-1}$ sec^{-1}.[21] If this is so, k_u is $9 \times 10^8\ M^{-1}$ sec^{-1}, a reasonable value for a deuteron transfer with an equilibrium constant not far from 1.0 and without the driving force of electrostatic attraction or a highly mobile reactant. It also follows that k_k is about 2×10^6 sec^{-1}. This may be compared with a lower limit for k_k that may be obtained from eq 20. The value of K_{IH} should be larger than the acidity constant for tertiary protonated trans-DAMCA ($4.4 \times 10^{-10}\ M$). The value of K_I is assumed to fall short of the value for methylamine and acetone (0.26 M^{-1})[23] by

(22) J. Hine and C. Y. Yeh, J. Amer. Chem. Soc., 89, 2669 (1967).
(23) M. S. Cholod, unpublished observations, The Ohio State University, 1971.

the same factor that the equilibrium constant for N-alkylisobutyraldimine formation from isopropylamine falls short of the value for methylamine. Since imines with only hydrogen and alkyl substituents have not been found to contain measurable amounts of the corresponding enamines in hydroxylic solvents,[24,25] even in cases like those of isobutyraldimines,[26] where enamine formation leads to an increase in the number of alkyl substituents on the double bond, we believe that K_E must be smaller (probably much smaller) than 0.01. From these estimates and the known values of a and k_a, k_k may be calculated to be larger than 2×10^3 sec^{-1}. This is consistent with the value 2×10^6 sec^{-1} based on the assumption that k_1 governs a diffusion-controlled reaction. In fact, probably the best estimate of K_E is the value 10^{-5} that may be calculated from this value of k_k.

The Ring Size in the Cyclic Transition State. The cyclic transition state in the internal deuteron transfer leading from ketimine to enamine might at first be thought to be most stable when there were five or six atoms (perhaps not counting hydrogen) in the ring because rings of these sizes are commonly the most readily formed. However, further thought reveals that serious stereoelectronic constraints should arise from the demands of the carbon–nitrogen double bond of the reactant and the carbon–carbon double bond of the product. The six atoms kept coplanar by the double bond of the reactant include four that are among the six kept coplanar by the double bond of the product. Newman projection **2** represents the ketimin-

Me$_2$N—
D
CD$_3$——=NH—C
D   D

2
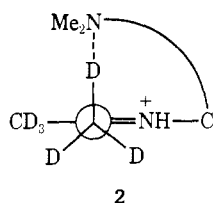
ium ion in a conformation ready to react. Since the plane of the carbon–nitrogen double bond is represented as being horizontal, the bond to the deuteron being transferred is oriented up. This gives the two remaining deuterium atoms the shortest distances to travel to move into coplanarity with the double bond in the enamine. Or, instead of this statement in terms of the principle of least nuclear motion,[27] it may be pointed out that the sp^3 orbital used for bonding to the deuteron being transferred becomes one of the two overlapping p orbitals in the double bond of the product; therefore it should be kept as nearly as possible parallel to the p orbital on the adjacent carbon atom. As the deuteron is being transferred it is the center of a hydrogen bond. In view of the evidence that the most stable orientation of hydrogen bonds is linear, the carbon, deuterium, and nitrogen atoms should be collinear. These restrictions control the relative positions of six of the ring atoms in the cyclic transition state but leave a large gap between the dimethylamino group and the carbon atom to which the primary amino group was attached in the diamine catalyst. Studies

(24) B. Witkop, *J. Amer. Chem. Soc.*, **78**, 2873 (1956).
(25) D. A. Nelson and J. J. Worman, *Chem. Commun.*, 487 (1966).
(26) C.-Y. Yeh, unpublished observations, The Ohio State University, 1967.
(27) J. Hine, *J. Org. Chem.*, **31**, 1236 (1966).

with molecular models seemed to indicate that at least four carbon atoms between the two nitrogen atoms of the diamine would be required to give a conformation like **2** without obvious distortion in bond angles or bond distances. For this reason we had thought that 4-dimethylaminobutylamine might be the best bifunctional catalyst of the ω-dimethylaminoalkylamines. Transition state models like **2** can be constructed based on 3-dimethylaminopropylamine with normal bond distances and bond angles except for the N–D–C hydrogen bond, which must be bent to about 150°. The force constant for bending such a hydrogen bond should not be very large. Another source of instability for the transition state derived from 3-dimethylaminopropylamine is the eclipsing around the bond between carbon-1 and carbon-2 that is present in the two conformers of the transition state that appear to be the most stable. Apparently the diminution in catalytic activity arising from these sources of instability is less than that which accompanies increasing the number of methylene groups in the diamine catalyst. The DAMCA's were studied because if the cyclopentane rings were nearly planar the cis isomer would have about the same conformation around the bond between carbon-1 and carbon-2 as in that conformer of the 3-dimethylaminopropylamine transition state that appears to be the most stable, and the trans isomer would have a conformation like that in the second most stable conformer of this transition state. The enhanced catalytic activities of the DAMCA's support the notion that the catalytic activity of 3-dimethylaminopropylamine is diminished significantly by an increase in eclipsing strain in the transition state relative to that present in the reactants.

The stereoelectronic factors discussed are analogous to those operating in the internal hydrogen migration that takes place in radical cations derived from alkyl vinyl ethers. The principal internal hydrogen shift in the radical cation of n-heptyl vinyl ether proceeds by a transition state containing an eight-membered ring as shown in **3**.[28] If carbon-4 in **3** is replaced by a nitrogen

O—CH$_2$—CH$_2$
HC   CH$_2$
CH$_2$--D--CD
Pr

3
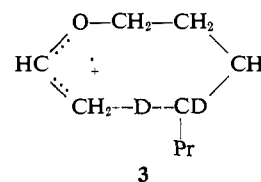
atom and the oxygen atom is replaced by NH the ring becomes the same, including the approximate state of hybridization, as the ring in **2**.

The optimum ring size for internal proton transfers is usually smaller than eight atoms in cases where the double bonds being created and destroyed are not in the ring, as they are in **2** and **3**. In the self-catalyzed iodination of species of the type CH$_3$CO(CH$_2$)$_n$CO$_2^-$ and CH$_3$CO(CH$_2$)$_n$CO$_2$H the rate constants were found to vary with n in the orders $3 > 2 > 4 > 5 \sim 11$ and $3 > 4 > 2$, respectively.[29] If these halogenations take place at the methylene group, as appears to be the case when n is 2, the fastest reactions are those proceeding via a six-atom ring (including hydrogen). In the in-

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(29) R. P. Bell and M. A. D. Fluendy, *Trans. Faraday Soc.*, **59**, 1623 (1963).

ternal proton transfers of the type shown in eq 21 the

$$(O_2N)_2\bar{C}(CH_2)_nCO_2H \longrightarrow (O_2N)_2CH(CH_2)_nCO_2^- \quad (21)$$
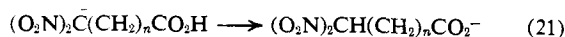
relative rates vary with n in the order $2 > 3 > 4$, corresponding to the fastest reaction being that with a transition state containing a six-membered ring.[30]

Analogies to Enzymatic Catalysis. The DAMCA's and 3-dimethylaminopropylamine act similarly to enzymes. They form a complex (the iminium ion) with the substrate using one functional group (the primary amino group) with internal catalysis of complex formation by a second functional group (the protonated tertiary amino group). They then transform this complex to a second complex (the enamine) by use of an internal group (the free tertiary amino group), and then after several additional steps (in this case, the reverse of the first steps, except for isotopic labeling) release the reaction product. Since the rate-controlling step in the dedeuteration of isobutyraldehyde-2-d and acetone-d_6 in the presence of a monofunctional primary amine is the deuteron transfer that transforms iminium ion to enamine,[11,18,19,31] our catalysts were designed for high efficiency in this step. In some of our reactions this efficiency has become so great that iminium ion formation has become partly rate controlling. Although we had realized that this complication might arise, we had not expected deuterium exchange of the internal $-NMe_2^+$ group also to become partly rate controlling, as it has with the DAMCA's. It would be desirable to add another functional group to catalyze this step to obtain a markedly improved catalyst.

It is noteworthy that the ability to catalyze the hydrogen exchange reactions of acetone is required for optimal catalytic activity in the case of a certain naturally occurring enzyme. Westheimer and coworkers showed that the decarboxylation of acetoacetic acid by the decarboxylase from Clostridium acetobutylicum involves the intermediate formation of an enamine of acetone, which is then hydrolyzed to acetone.[32] They pointed out that if this hydrolysis is assisted by internal catalysis by the enzyme then enamine formation by acetone must also be so catalyzed. The observation that the enzyme is a powerful catalyst for the deuterium exchange of acetone provides convincing evidence for such catalysis.[33] The reactivities of our catalysts relative to this enzyme vary enormously with the way in which one chooses to make the comparison. A particularly favorable comparison for one of our catalysts relies on the fact that 0.52 M acetone-d_6 exchanges with a first-order rate constant of 2.37×10^{-3} sec^{-1} in the presence of 0.0192 M trans-DAMCA at pH 8.76 and 35°. If we assume that rates increase by twofold between 25 and 35° and that the exchange of 0.5 M acetone-d_6 continues to be first order in enzyme outside the concentration range (3.5×10^{-6}–1.4×10^{-5} M) studied, then the same first-order rate constant could be obtained with 2.6×10^{-4} M enzyme at pH 5.9 (the only pH at which measurements were made).[32] This makes the enzyme 70 times as good a catalyst as trans-DAMCA on a molar basis (taking the molecular weight

of the enzyme as 29,000). On a weight basis, however, the trans-DAMCA would be about three times as effective as the enzyme. There is no reason, of course, why an artificial catalyst cannot be a much better catalyst than an enzyme. The enzyme must ordinarily contain structural features permitting it to be activated or deactivated as needed, it may be as important that an enzyme not catalyze certain reactions as it is that it catalyze a given one, it must be synthesizable by the body and stable toward other cell components, etc. Furthermore, to hypothesize that each enzyme is the best possible catalyst for the reaction in question is a step toward assuming that evolution has come to an end.

If Schemes I and II are correct they show that proton-transfer reactions may take place in aqueous solution without major amounts of exchange with the solvent. The absence of such exchange would therefore be much weaker evidence against a proton-transfer mechanism than has previously been thought.[34] Further work to assess the validity of these schemes is underway.

Experimental Section

N,N-Dimethyl-2,2-difluoroethylamine. A method based on that of Bissell and Finger[8] was used to transform ethyl difluoroacetate[7] to *N,N*-dimethyldifluoroacetamide (bp 155–158°), which was reduced to *N,N*-dimethyl-2,2-difluoroethylamine, isolated as the hydrochloride: pmr (D₂O) δ 3.09 (s, 5.6, CH₃), 3.80 (triplet, $J = 15$ Hz, of doublets, $J = 3.2$ Hz, 2.2, CH₂), 6.48 ppm (triplet, $J = 52.8$ Hz, of triplets, $J = 3.5$ Hz, 1.2, CHF₂), chemical shifts relative to external TMS.

2-(Dimethylaminomethyl)cyclopentylamines. A mixture of isomers was prepared essentially by the method of Nazarov and Kuznetsov: bp 75–76° (15 mm); n^{24}D 1.4623 [lit.[9] bp 92–94° (15 mm)]. Although this mixture gave only one peak on a number of glpc columns, it was separated on a 12-ft column consisting of 20% mannitol and 5% potassium hydroxide on Chromosorb P at 155°. Recrystallization of the oxalate salts from 95% ethanol showed that the more slowly eluted isomer gave the less soluble salt. The amines were obtained from their salts by treatment with aqueous potassium hydroxide, extraction with ether, and removal of the ether. From an original mixture containing comparable amounts of the two isomers the more rapidly and more slowly eluted isomers were obtained in purities of 81 and >98%, respectively.

Other Amines. The appropriate *N,N,N',N'*-tetramethyldiamines were treated with methyl chloride to give 2-dimethylaminoethyltrimethylammonium chloride and 3-dimethylaminopropyltrimethylammonium chloride.[35] The diquaternized compounds whose presence could be detected by pmr in deuterium oxide were removed by recrystallization from chloroform–hydrocarbon mixtures to give products found to be 98 ± 1% pure by acidimetric titration.

The appropriate primary amines were methylated[36] to give *N,N*-dimethylbutylamine, bp 93–95°; *N,N*-dimethyl-2-methoxyethylamine, bp 101–102°; and *N,N*-dimethyl-2,2,2-trifluoroethylamine. Literature methods were used for the preparation of *N,N*-dimethylpropargylamine,[3] *N,N*-dimethyl-1,4-butanediamine,[17] and *N,N*-dimethyl-1,5-pentanediamine.[17] The other amines were commercial products, which (except for the polyethylenimines) were redistilled before use.

Kinetic Runs and Calculations. The catalyst solutions were prepared from the amines and standard hydrochloric acid except for the cases of fluoroamines, whose hydrochlorides were used, and trans-DAMCA, whose oxalate was used in the runs where the initial concentration of total amine was 0.00481 M. When the amine salt was used standard sodium hydroxide was added as required. With the monoamines the concentration of protonated amine was taken as the concentration of added acid (or of added amine salt minus added sodium hydroxide) plus that of hydroxide

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(36) R. N. Icke, B. B. Wisegarver, and G. A. Alles, "Organic Syntheses," Collect. Vol. 3, Wiley, New York, N. Y., 1955, p 723.

ions as calculated from the pH. The pH of the reaction solutions, measured with a Radiometer PHM-26 pH meter and Type G202B electrode, was taken as $-\log a_{H^+}$. The added 0.52 M acetone was assumed to change pK_w by the same amount that the same mole fraction of dioxane would. This amount, calculated by interpolation,[37] increases pK_w at 35° from 13.681 to 13.805. The values of k_B calculated from amine concentrations obtained in this way, which are listed in Table III, differ by an average of 10% from values that were obtained from amine concentrations calculated from the pH of the reaction solution, pK_w, the pK of the protonated amine, and the total concentration of added amine. Values of k_B obtained in the latter way fit the observed k_b values more poorly than do the k_B values for monoamines listed in Table III. However, the former method of calculation of concentrations cannot be used for diamines and so the latter was. For both methods of

calculation activity coefficients were calculated from the Davies equation.[38]

pK Determinations. Potentiometric measurements of pK values were carried out as described previously.[19] All the measurements were carried out at ionic strengths of 0.2 or below except for those on the ω-dimethylaminoalkylamines, which were reported previously,[17] and those on the compounds $Me_3N^+(CH_2)_nNMe_2$ where n is 2 and 3, which were carried out in the ranges of 0.02–0.30 and 0.09–0.30, respectively.

(37) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, pp 662, 754, 756.
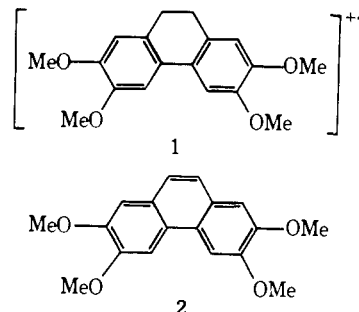
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Anodic Oxidation of Methoxybiphenyls. The Effect of the Biphenyl Linkage on Aromatic Cation Radical and Dication Stability

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Abstract: The biphenyl linkage was shown to have a remarkable stabilizing effect on both cation radicals and dications derived from methoxy-substituted aromatic compounds. In the series of para-substituted compounds $[MeO(C_6H_4)_nOMe]$, maximum stability of ions was observed with $n = 2$ and 3, while the compound with $n = 4$ gave ions more difficultly formed and much less stable. A variety of dimethoxybiphenyls substituted in varying degree and manner with methyl groups have been investigated by voltammetry in acetonitrile, dichloromethane, and trifluoroacetic acid. Steric hindrance to planarity of the two phenyl rings was found to be an important factor in determining ion stability. Slow deprotonation of methoxy-substituted 9,10-dihydrophenanthrene cation radicals and dications was observed although the latter are formally the second conjugate acids of the corresponding phenanthrenes.

In a preliminary communication, we described the intramolecular coupling reaction of 3,3′,4,4′-tetramethoxybibenzyl in acetonitrile to the dihydrophenanthrene and pointed out the unusual stability of the cation radical of the product.[2] The ultimate fate of the cation radical (**1**) was the formation of the phen-

1

2

anthrene (**2**). Thus, the long lifetime of **1** could only be due to a slow deprotonation. The latter provided the first clear evidence for the existence of the ECE mechanism of side chain anodic substitution, a reaction on which differing views had been presented.[3,4] Furthermore, it was pointed out that **1** is formed considerably more easily than **2** is oxidized and that the cation radical of **2** is very short lived. These observations led us to the study of the effect of the biphenyl linkage on the stability and reactions of aromatic cation radicals and dications.

Results

The structures of the methoxybiphenyls which were studied are listed below.

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