to iodine and acyl hypoiodites, the list of iodinating agents must be expanded to include $(HO)_2PO(OI)$ and/or $HOPO_2(OI)^-$. The detailed mechanism of attack of such agents is yet to be elucidated (*cf.* the discussion upon phenol in acetate buffers).

Acknowledgment. We are indebted to the National Science Foundation for generous support of this research and to the Petroleum Research Fund, administered by the American Chemical Society, for a graduate fellowship to J. M. M.

Kinetics of the Formation of Imines from Acetone and Primary Amines. Evidence for Internal Acid-Catalyzed Dehydration of Certain Intermediate Carbinolamines[1a]

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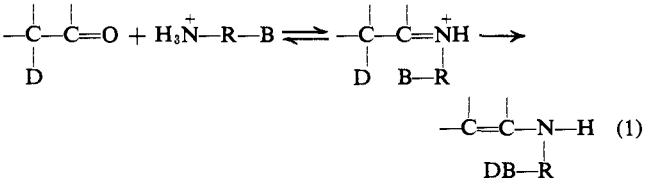
Abstract: The kinetics of the formation of imines from acetone and a number of substituted primary amines have been studied in water at 35° by a method in which trapping of the imine by hydroxylamine permitted the rate of imine formation to be determined by monitoring the rate of acetone disappearance. A plot of the logarithms of the second-order rate constants for primary *n*-alkyl amines with no substituents, ω-methoxy substituents, ω-dimethylamino substituents, and a 2-trimethylammonio substituent *vs.* the pK_a values of the corresponding primary ammonium ions gave a fairly straight line. Rate constants for the monoprotonated (at the tertiary amino group) forms of 2-dimethylaminoethylamine, 3-dimethylaminopropylamine, 4-dimethylaminobutylamine, 5-dimethylaminopentylamine, and *trans*-(2-dimethylaminomethyl)cyclopentylamine were too large to fall on this line by factors of 1000-, 12-, 3-, 2-, and 60-fold, respectively. The enhanced reactivity is attributed to internal catalysis of the dehydration of the intermediate carbinolamines by the $NHMe_2^+$ substituents in the monoprotonated diamines.

The formation of an imine is an important intermediate step in many reactions of aldehydes and ketones.[2] For example, the dedeuteration of isobutyraldehyde-*2-d* in the presence of monofunctional primary amines was found to involve the relatively rapid reversible formation of imine followed by rate-controlling attack of a base on the iminium ion.[3] Certain primary amines with basic substituents (B–R–NH_2) were found to act as bifunctional catalysts for the dedeuteration of isobutyraldehyde-*2-d*[4] and acetone-d_6[5] by the mechanism shown in eq 1. In the



(1)

case of acetone-d_6, the bifunctional catalysts had made the deuterium transfer step so efficient that imine formation had become partly rate controlling. Further increases in the efficiency of the deuterium transfer step will not be able to increase the overall rate of dedeuteration beyond the rate of imine formation. The formation of imines is known to be subject to acid catalysis.[6,7] Hence it was of interest to learn whether an acidic substituent group in a primary amine could act as an internal catalyst and increase the rate of formation of imine. Via observed such internal catalysis in the formation of imines from isobutyraldehyde and the monoprotonated forms of diamines of the type $Me_2N(CH_2)_nNH_2$, where n was 2 and 3.[8] Internal catalysis by phenolic hydroxy groups has also been suggested.[9,10] The present work is an attempt to learn whether internal catalysis can be observed in the formation of imines from monoprotonated diamines and acetone. The equilibrium constants for the formation of imines from acetone are so small that at the concentrations of reagents used only a negligible fraction of the acetone is transformed to imine at equilibrium. Hence the reaction was followed by the method of Williams and Bender, in which the imine is captured by hydroxylamine, which transforms it to acetoxime.[11]

Results

The rate of reaction of acetone with hydroxylamine

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(2) The imines are ordinarily formed *via* the corresponding iminium ions, but equilibrium between the two species is usually established more rapidly than any competing reaction. For this reason, we shall often use a phrase like "formation of imine" as synonomous with "formation of iminium ion" for convenience.

(3) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Amer. Chem. Soc.*, **88**, 3367 (1966).

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(7) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

(8) F. A. Via, Ph.D. Dissertation, The Ohio State University, 1970.

(9) T. C. French, D. S. Auld, and T. C. Bruice, *Biochemistry*, **4**, 77 (1965).

(10) R. L. Reeves, *J. Org. Chem.*, **30**, 3129 (1965).

(11) A. Williams and M. L. Bender, *J. Amer. Chem. Soc.*, **88**, 2508 (1966); *cf.* E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 826 (1962).

in aqueous solution at 35° with and without added primary amines was followed by spectral measurements at 275 nm. The kinetics were interpreted in terms of a reaction scheme that may be abbreviated as shown in eq 2–4, in which the symbols to be used for various

$$\underset{\text{Ac}}{Me_2CO} + \underset{\text{Hx}}{H_2NOH} \xrightarrow{k_{ox}} \underset{\text{Ox}}{Me_2C{=}NOH} \quad (2)$$

$$Me_2CO\ (+\ \underset{\text{Am}}{RNH_2}) \underset{k_{-im}}{\overset{k_{im}}{\rightleftharpoons}} \underset{\text{Im}}{Me_2C{=}NR} \quad (3)$$

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

species are written below the formulas. Since the amine is regenerated in the reaction, its constant concentration (in a given run) is absorbed into k_{im}, which is therefore a first-order rate constant. The equilibrium constant for the formation of acetoxime from acetone and hydroxylamine in water is 10^6 M^{-1} at 25°.[12,13] If it is not too much smaller at 35° then in most of our runs, where at least 0.01 M excess hydroxylamine was used, well over 99.9% of the acetone should be used up at equilibrium. If the concentrations of intermediates, such as the imine, carbinolamine [Me_2C(OH)NHR], and Me_2C(OH)NHOH, are neglected and the imine assumed to be captured quantitatively by hydroxylamine (*i.e.*, k_{hx}[Hx] $\gg$ k_{-im}), the rate of disappearance of acetone may be expressed as shown in eq 5. If the concentration of hydroxylamine is

$$-d[Ac]/dt = k_{im}[Ac] + k_{ox}[Hx][Ac] \quad (5)$$

constant, the entire process is simply a first-order reaction of acetone. The observed first-order rate constant obtained from a plot of ln $[(A_0 - A_\infty)/(A_t - A_\infty)]$ *vs.* time (where the A's are absorbances) may then be expressed as shown in eq 6.

$$\frac{1}{t} \ln \frac{A_0 - A_\infty}{A_t - A_\infty} = k_{obsd} = k_{im} + k_{ox}[Hx] \quad (6)$$

In order to evaluate k_{ox}, the reaction of acetone with 0.03 and 0.10 M hydroxylamine was first studied in the absence of primary amines, where k_{im} will be zero. Runs between pH 6.65 and 8.36 were buffered with *N*-methylmorpholine; those between pH 8.40 and 10.68 were buffered with trimethylamine. Runs using 0.03 M hydroxylamine were followed only to about 50% completion in order to minimize the drop in the first-order rate constants resulting from the decrease in hydroxylamine concentration. Values of k_{obsd} and of k_{ox}, the latter obtained by dividing k_{obsd} by the initial hydroxylamine concentration, are listed in Table I. The fact that the average concentration of hydroxylamine present during the runs was smaller than the initial concentration should make the recorded k_{ox} values about 8% smaller than they should be in the 0.03 M hydroxylamine runs and about 4% smaller in the 0.10 M hydroxylamine runs. If the equilibrium constant for addition of hydroxylamine to acetone to give Me_2C(OH)NHOH is 1.0 M^{-1} at 35°, as it is at 25°,[14] the values of k_{ox} in the 0.03 M hydroxylamine runs will be made about 3% too small and those in the 0.10 M hydroxylamine runs about 9% too small.

(12) A. Ölander, *Z. Phys. Chem.*, **129**, 1 (1927).
(13) J. B. Conant and P. D. Bartlett, *J. Amer. Chem. Soc.*, **54**, 2881 (1932).
(14) W. P. Jencks, *ibid.*, **81**, 475 (1959).

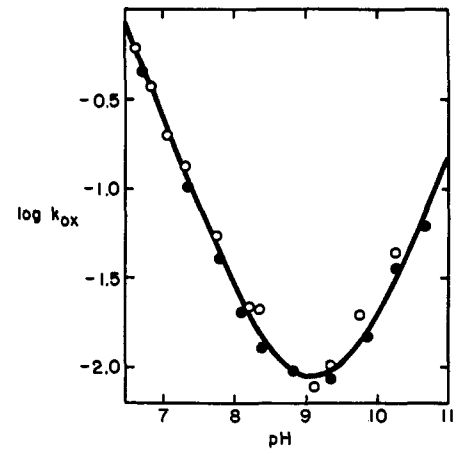

Figure 1. Experimental values of log k_{ox} and curve calculated from eq 7: (●) 0.10 M H_2NOH; (○) 0.03 M H_2NOH, initial rates.

Table I. Kinetics of the Reaction of Acetone[a] with Hydroxylamine in Water at 35° [b]

pH[c]	$[H_2NOH]_0$,[d] M	$10^3 k_{obsd}$, sec^{-1}	$10^3 k_{ox}$, M^{-1} sec^{-1}
6.65	0.030	15.2	573
6.70	0.100	38.0	425
6.83	0.030	10.0	362
7.07	0.030	5.6	196
7.31	0.030	3.88	133
7.35	0.100	9.85	101
7.75	0.030	1.62	54.6
7.80	0.100	4.00	40.4
8.12	0.100	2.08	20.9
8.21	0.030	0.676	22.6
8.36	0.030	0.64	21.6
8.40	0.100	1.32	13.2
8.82	0.100	0.983	9.84
9.11	0.030	0.239	7.97
9.33	0.100	0.883	8.83
9.35	0.030	0.311	10.4
9.77	0.030	0.617	20.6
9.86	0.100	1.50	15.0
10.25	0.100	3.67	36.7
10.26	0.030	1.32	44.0
10.68	0.100	6.36	63.6

[a] Initial concentration, 0.0100 M. [b] Sodium chloride added to bring the ionic strength to 0.30 N. [c] Trimethylamine buffers above pH 8.38 and *N*-methylmorpholine buffers below this pH. Total buffer concentrations 0.100 M. [d] Total initial concentrations including both states of protonation.

Hence the recorded values of k_{ox} are probably 10–15% smaller than the actual values. However, we shall use k_{ox} only as a correction term in the determination of k_{im} from eq 6, and in this case such an error will be almost completely canceled. The values of k_{ox} from Table I are plotted in Figure 1 along with a plot of eq 7 for which the numerical values were calculated

$$k_{ox} = (2.34 \times 10^6 a_{H^+} + 1.50 \times 10^{-12} / a_{H^+} + 5.20 \times 10^{-3})\ M^{-1}\ sec^{-1} \quad (7)$$

by the method of least squares. Treatment of k_{ox} in terms of eq 7 assumes specific hydrogen ion and hydroxide ion catalysis. This treatment is supported by the lack of evidence for general catalysis in the reaction in this pH range at 25°[9] and by the fact that at pH 5.9 the dihydrogen phosphate ion, which is a stronger acid than any of our buffer components, increased the rate by only about 20% at a concentration of 0.2 M.[14]

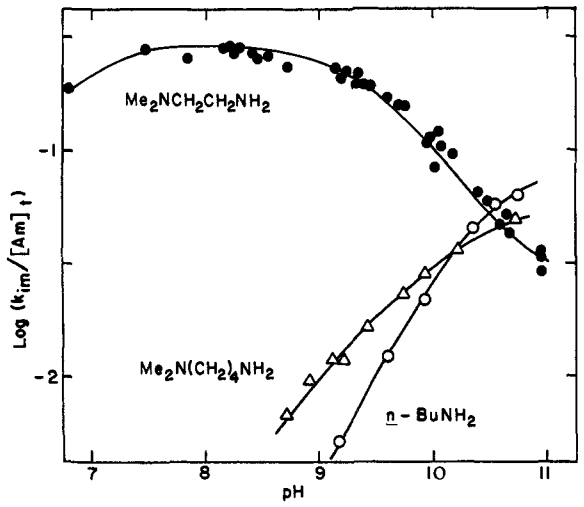

Figure 2. Plot of log ($k_{im}/[Am]_t$) *vs.* pH: (●) 2-dimethylaminoethylamine; (○) *n*-butylamine; (△) 4-dimethylaminobutylamine.

Table II. Rates of Formation of Acetoxime in the Presence of 2-Dimethylaminoethylamine[a]

pH	$[Am]_t$,[b] *M*	$[H_2NOH]$, *M*	$10^3 k_{obsd}$, sec^{-1}	$k_{im}/[Am]_t$,[c] M^{-1} sec^{-1}
9.23	0.0192	0.0200	4.00	0.199
9.26	0.0200	0.0400	4.50	0.206
9.23	0.0192	0.0500	4.67	0.219
9.23	0.0200	0.0500	4.67	0.211
9.27	0.0200	0.0800	5.17	0.221
9.27	0.0192	0.100	5.05	0.215
9.27	0.0192	0.120	5.22	0.214
9.32	0.0200	0.0500	4.52	0.202
9.38	0.0200	0.0300	4.20	0.195
9.35	0.100	0.0300	22.0	0.217
9.69	0.0200	0.0500	3.83	0.159
9.75	0.0600	0.0500	9.93	0.154
10.08	0.0200	0.0500	3.38	0.110
10.07	0.0600	0.0500	7.42	0.104

[a] With an initial acetone concentration of 0.0100 *M* and an ionic strength of 0.30 *N* in aqueous solution at 35.0°. [b] Total concentration including all states of protonation. [c] Obtained by subtracting $k_{ox}[H_2NOH]$, calculated using eq 7, from k_{obsd} and then dividing by $[Am]_t$.

To learn what concentrations of hydroxylamine are required for essentially complete capture of the intermediate imines, the rate of reaction of 0.01 *M* acetone with hydroxylamine at various concentrations was studied in the presence of 2-dimethylaminoethylamine, 3-dimethylaminopropylamine, and *trans*-2-(dimethylaminomethyl)cyclopentylamine. The monoprotonated forms of these amines formed imines particularly rapidly. There is no reason to expect the equilibrium constants for their imine formation to be unusually large. Hence their imines must undergo hydrolysis especially rapidly. Therefore concentrations of hydroxylamine sufficient to capture these imines quantitatively in competition with their relatively rapid hydrolysis should certainly suffice for the capture of the other imines whose formation was studied. In such reactions the amount of acetone tied up as carbinolamine [$Me_2C(OH)NHR$] or imine may be neglected. Primary alkyl amines have much smaller equilibrium constants for addition to carbonyl groups than hydroxylamine does.[15] The equilibrium constant for the formation of imine from acetone and methylamine at 35° is 0.26 M^{-1}.[16] Judging by analogy to isobutyraldehyde,[17,18] all the amines used in the present study should have considerably smaller equilibrium constants for imine formation. Hence, probably no more than 1% of the acetone was ever present as imine in our runs.

The first seven entries in Table II show that 0.02 *M* hydroxylamine captures about 90% of the imine formed from 0.02 *M* total 2-dimethylaminoethylamine (including all states of protonation) at pH 9.25 ± 0.02. Six runs at pH 8.26 ± 0.04 showed that 0.04 *M* hydroxylamine was about as effective as any higher concentration. Sets of at least six runs on 0.100 *M* 3-dimethylaminopropylamine at pH 9.56 ± 0.06 and at pH 9.66 ± 0.04 showed that 0.01 *M* hydroxylamine was as efficient as larger concentrations. Seven runs on 0.02 *M* *trans*-2-(dimethylaminomethyl)cyclopentylamine at pH 9.22 ± 0.04 showed that 0.02 *M* hydroxylamine was only about 75% efficient, but that 0.06 *M* hydroxylamine was about as efficient as larger concentrations. For comparison purposes, it may be noted that 0.005 *M* hydroxylamine gave almost complete capture of the imine formed in the reaction of methylamine with isobutyraldehyde.[19]

On the basis of these data, it was concluded that 0.03 *M* hydroxylamine will be sufficient to capture more than 90% of the imine formed from any of the amines studied except *trans*-2-(dimethylaminomethyl)cyclopentylamine, for which 0.08 *M* hydroxylamine will be sufficient. Because of the acetone tied up as $Me_2C(OH)NHOH$ and because of the incompleteness of capture of the imines, the values of k_{im} we have obtained are probably too low by an amount that may reach 20% in the case of the cyclopentane derivative.

The last seven entries in Table II consist of three sets of points that show that k_{im} is proportional to the total concentration of amine present at a given pH (±0.03).

Values of k_{obsd} were determined for the three diamines already referred to, two other ω-dimethylamino alkyl amines, and five primary monoamines with a range of basicities but with no acidic or basic substituents. The values obtained with 2,2,2-trifluoroethylamine were within the experimental uncertainty of the corresponding values of $k_{ox}[Hx]$, showing that imine formation was too slow to study by the method employed. Values of $k_{im}/[Am]_t$ are plotted logarithmically against the pH in Figure 2 for 2-dimethylaminoethylamine, 4-dimethylaminobutylamine, and *n*-butylamine. Data on the other compounds are listed in Table III. The reactivity of the 2-trimethylammonioethylamine cation was so low that even though a considerably larger concentration of amine was used than in any other case, imine formation contributed only 32–51% to the total reaction. Most of the other reactions studied consisted largely of imine formation; only in two runs at pH 10.95 on 2-dimethylaminoethylamine and in the last run in Table III did $k_{ox}[Hx]$ exceed 55% of k_{obsd}.

(15) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, 90, 6154 (1968).
(16) M. S. Cholod, unpublished observations.
(17) J. Hine and C. Y. Yeh, *J. Amer. Chem. Soc.*, 89, 2669 (1967).
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(19) J. Hine, F. A. Via, J. K. Gotkis, and J. C. Craig, Jr., *J. Amer. Chem. Soc.*, 92, 5186 (1970).

Table III. Rates of Primary Amine Catalyzed Oximation of Acetone[a]

Primary amine	pH	10^3k_{obsd}, sec^{-1}	$10^3k_{im}/[Am]_t$, M^{-1} sec^{-1}
$MeO(CH_2)_2NH_2$	8.56	0.667	3.0
	8.88	0.781	5.0
	9.65	1.41	10.4
	9.89	1.84	13.2
	10.20	2.19	13.1
$MeO(CH_2)_3NH_2$	9.06	0.755	4.9
	9.38	1.37	10.7
	9.64	1.75	13.8
	9.73	1.85	14.4
	10.07	2.91	22.1
	10.41	4.75	35.9
	10.43	4.54	31.5
$Me_3N^+(CH_2)_2NH_2$[b]	8.45	0.85	1.6
	8.48	0.83	1.6
	9.71	0.59	0.7
	9.71	0.76	1.3
	9.83	0.72	0.9
$Me_2N(CH_2)_3NH_2$	8.21	2.00	14.1
	8.54	2.35	19.8
	9.31	3.29	30.1
	9.53	3.87	35.4
	9.80	3.85	34.0
	10.04	4.93	42.7
	10.26	4.92	39.3
	10.40	6.00	47.0
	10.44	6.07	46.5
	10.61	6.28	42.6
$Me_2N(CH_2)_5NH_2$	9.05	1.15	8.8
	9.59	2.83	24.8
	9.75	2.53[c]	32.0
	9.98	4.63	40.3
	10.17	3.68[c]	55.8
	10.52	5.17[c]	78.3
trans-2-(Dimethylaminomethyl)-cyclopentylamine[d]	8.17	3.17	74
	8.49	3.07	100
	8.87	2.97	110
	9.25	3.20	123
	9.38	3.06	114
	9.63	3.03	102
	9.97	3.17	80
	10.26	3.77	56

[a] Initial acetone concentration 0.0100 *M*, ionic strength 0.3 *N*, temperature 35.0°, total amine concentration 0.100 *M* except where otherwise stated. [b] Total amine concentration 0.27 *M*. [c] Total amine concentration 0.0660 *M*. [d] Total amine concentration 0.0200 *M*.

In order to interpret the results obtained with the diamines we needed to know the relative basicities of the two different amino groups. These have been determined by a proton magnetic resonance (pmr) spectral method for the ω-dimethylamino alkyl amines.[20] We have applied the same method to *trans*-2-(dimethylaminomethyl)cyclopentylamine. We found δ_t, the chemical shift of the methyl hydrogen atoms in the diprotonated ion,[21] to be 45.3 cps. For δ_p, the chemical shift of the methyl hydrogen atoms in diamine that has been monoprotonated at the primary amino group, the same value (0.9 Hz) was taken as had been used for 3-dimethylaminopropylamine, in which there are also three carbon atoms between the two amino groups. The chemical shifts of partly protonated diamine then give a value of 0.36 for f_t, the fraction of monoprotonated diamine that is protonated at the tertiary group.

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

(21) Downfield from the methyl hydrogen atoms in the free diamine.

Discussion

The decreases in values of $k_{im}/[Am]_t$ for *n*-butylamine, 2-methoxyethylamine, and 3-methoxypropylamine that accompany decreasing pH must be due to the decreasing fraction of amine present in the unprotonated form. The data for these compounds were fit to eq 8, in which f_0 is the fraction of amine that is unprotonated and f_1 is the fraction monoprotonated. Transformation of eq 8 to 9 makes it clear that k_{am} is the rate constant for uncatalyzed imine formation. This reaction is expected[6,7,11,19] to involve reversible addition of the amine to acetone to give a carbinolamine that rate controllingly ionizes to give a hydoxide ion and an iminium ion (eq 10). The second term refers

$$k_{im}/[Am]_t = f_0k_{am} + f_1k_{amh} \quad (8)$$

$$k_{im} = k_{am}[Am] + k_{amh}[AmH^+] \quad (9)$$

$$Me_2CO + RNH_2 \rightleftharpoons Me_2\overset{OH}{\overset{|}{C}}NHR \rightleftharpoons Me_2C{=}\overset{+}{N}HR + OH^- \quad (10)$$

to acid catalysis of the dehydration of the carbinolamine. For the three amines mentioned this second term was too small to detect. The values of k_{am} obtained by a least-squares fit[22] of the k_{im} values with k_{amh} set equal to zero are listed in Table IV. In this fit the pK_a values 10.33, 9.82, and 9.09 were used for the conjugate acids of *n*-butylamine,[23] 3-methoxy-

Table IV. Rate Constants for Formation of Imines from Acetone and Primary Amines[a]

Amine	pK_a[b]	10^3k_{am}, M^{-1} sec^{-1}	Deviation,[c] %
$n\text{-}C_4H_9NH_2$	10.33	94.7	3.9
$MeO(CH_2)_2NH_2$	9.09	15.8	8.4
$MeO(CH_2)_3NH_2$	9.82	47.8	8.3
$Me_3N^+(CH_2)_2NH_2$	6.7	0.9[d]	24
$Me_2N^+H(CH_2)_2NH_2$	6.71	797	9.8
$Me_2N(CH_2)_2NH_2$	9.27	21[d]	
$Me_2N^+H(CH_2)_3NH_2$	8.50	108	6.7
$Me_2N(CH_2)_3NH_2$	9.75	51.5	
$Me_2N^+H(CH_2)_4NH_2$	9.23	69.4	7.0
$Me_2N(CH_2)_4NH_2$	10.00	66.7	
$Me_2N^+H(CH_2)_5NH_2$	10.06	159	9.1
$Me_2N(CH_2)_5NH_2$	10.34	84.4	
$Me_2N^+HC_6H_{10}NH_2$[e]	8.33	388	5.0
$Me_2NC_6H_{10}NH_2$[e]	9.61	19[d]	

[a] In aqueous solution at ionic strength 0.3 *N* and 35°. [b] K_a is the equilibrium constant for loss of a proton from the primary-protonated derivative of the amine indicated at 35° and ionic strength 0.3 *N*. [c] Standard deviation from the fit to the observed k_{im} values. [d] Relatively unreliable; see text. [e] The tertiary-protonated and unprotonated forms of *trans*-2-(dimethylaminomethyl)cyclopentylamine.

(22) The sums of the squares of the *fractional* deviations were minimized.

(23) Data at 20 and 40° and ionic strengths 0.0497, 0.0991, and 0.1976 *N*[24] were first interpolated to 35° and then extrapolated to ionic strength 0.30 *N*.

(24) A. G. Evans and S. D. Hamann, *Trans. Faraday Soc.*, 47, 34 (1951).

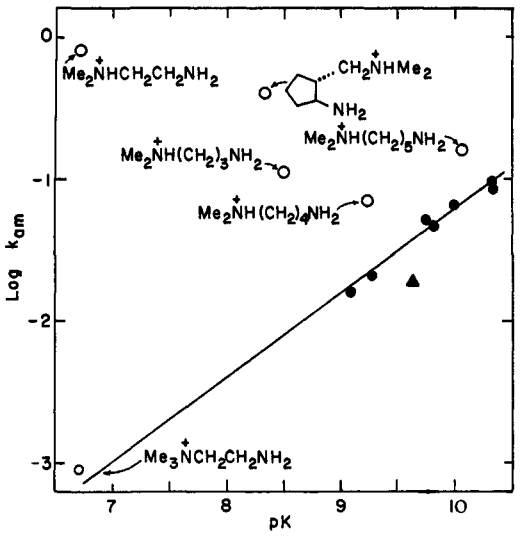


Figure 3. Plot of logarithms of second-order rate constants for the formation of imines from acetone and various species of the type RNH_2 in water at 35° and ionic strength 0.3 *N* *vs.* pK_a for the corresponding RNH_3^+ species under the same conditions: (●) amines of the type $XCH_2CH_2NH_2$ without acidic substituents; (○) Me_2N^+H or Me_3N^+ substituted primary amines; (▲) *trans*-2-(dimethylaminomethyl)cyclopentylamine.

propylamine,[25] and 2-methoxyethylamine,[25] respectively. The fact that the data could be fit to eq 8 satisfactorily shows that the reaction was not largely general acid or base catalyzed, but it does not rule out significant contributions of such catalysis.

The data on the 2-trimethylammonioethylamine cation in Table III yield k_{am} and k_{amh} values of 9×10^{-4} and 0.04 M^{-1} sec^{-1}, respectively, with the k_{amh} term contributing as much as half the total value of k_{im}.[28] It is plausible that the k_{amh} term should be relatively more important in this case than with the other monoamines, partly because the measurements were carried into more acidic solutions but mainly because the ratio $K_{AmH}k_{am}/k_{amh}$ (the hydrogen ion concentration at which the k_{am} and k_{amh} terms in eq 8 or 9 are of equal size) increases with increasing amine basicity in the formation of imines from isobutyraldehyde.[29] Nevertheless, these values (especially that for k_{amh}) are uncertain because of the experimental uncertainties in the k_{im} values. Although tests showed that the material used contained no more than 0.2% 2-dimethylaminoethylamine, even this small an amount could account for much of the increase in $k_{im}/[Am]_t$ that seems to accompany decreasing pH. For this reason the calculated value of k_{amh} should be regarded as a maximum.

The values of $k_{im}/[Am]_t$ for the diamines were also fit to eq 8 using pK values determined previously[20] for all the diamines except 2-dimethylaminoethylamine and *trans*-(2-dimethylaminomethyl)cyclopentylamine, for which values were determined in the present study. Activity coefficient corrections were based on the Davies equation.[27] The k_{amh} terms were found to be important. In fact, as shown in Figure 2, protonation of free 2-dimethylaminoethylamine leads to an increase in the rate of imine formation until so much acid has been added that significant amounts of diprotonated diamine are formed. The k_{amh} terms would include hydrogen ion catalyzed imine formation by the unprotonated diamine and uncatalyzed imine formation by the monoprotonated diamine. The fact that these diamines, which are all more than 250 times as basic as the 2-trimethylammonioethylamine cation, all give values of $K_{AmH}k_{am}/k_{amh}$ less than one-fortieth that for 2-trimethylammonioethylamine makes it highly unlikely that hydrogen ion catalyzed imine formation by unprotonated amines is a major contributor to these k_{amh} terms. The k_{amh} terms were therefore taken to represent imine formation from the monoprotonated diamines, and, to make the values obtained more directly comparable with the k_{am} values, AmH^+ in eq 8 and 9 was defined as that form in which protonation has taken place at the tertiary amino group. The resulting values of k_{am} and k_{amh} (which are listed as k_{am} values for the tertiary-protonated diamines) are listed in Table IV with the standard per cent deviations of the fits. The lines in Figure 2 were drawn from these k_{am} and k_{amh} values. Exactly the same goodness of fit would be obtained by defining AmH^+ as total monoprotonated diamine and multiplying the k_{amh} values by the fractions of monoprotonated diamines that are tertiary protonated. The values of k_{am} listed for unprotonated *trans*-2-(dimethylaminomethyl)cyclopentylamine and 2-dimethylaminoethylamine are unreliable because even in the most favorable runs these k_{am} terms contributed 7 and 22%, respectively, to k_{obsd}. For every other k_{am} listed in Table IV there was at least one run in which the term governed by that k_{am} contributed more than 54% to k_{obsd}.

The data on monoamines (including 2,2,2-trifluoroethylamine, for which k_{am} was too small to measure) indicate that k_{am} decreases with increasing electron-withdrawing power of the substituents. A plot of log k_{am} *vs.* pK_a for the monoamines, the free diamines, and the tertiary-protonated diamines (all at 35° and ionic strength 0.3 *N*) is shown in Figure 3. In order to maintain the same definition of pK_a as used with the monoamines, K_a for the free diamines and the tertiary-protonated diamines must be defined as $[H^+][Am]/[HAm^+]$ and $[H^+][AmH^+]/[HAmH^{2+}]$, respectively, where HAm^+ is the primary-protonated, AmH^+ is the tertiary-protonated, and $HAmH^{2+}$ is the diprotonated diamine. These pK_a values, which may be calculated from overall pK_a values determined in the usual ways and f_t values resulting from pmr measurements, are also listed in Table IV. The best line through the points for the six electrically neutral amines of the type $XCH_2CH_2NH_2$ for which reliable k_{am} values were obtained has a slope of 0.59. The amount by which the point for unprotonated 2-(dimethylaminomethyl)cyclopentylamine lies below the line in Figure 3 is no larger than the experimental uncertainty, but it would not be surprising for this RNH_2,

(25) Recalculation of data at 35°[26] taking the observed pH as $-\log a_{H^+}$ and using the Davies equation[27] to calculate ionic activity coefficients gave pK_a values that showed no clear drift with ionic strength from about 0.01 to 0.09 *N*. They were therefore assumed to be the same at ionic strength 0.30 *N*.

(26) C. Y. Yeh, Ph.D. Dissertation, The Ohio State University, 1968.

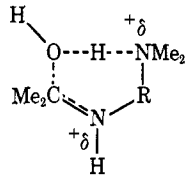
(27) C. W. Davies, *J. Chem. Soc.*, 2093 (1938).

(28) The pK value for the $Me_3N^+CH_2CH_2NH_3^+$ ion was calculated from the thermodynamic value (6.4) determined at ionic strength around 0.03 *N*. Activity coefficients were calculated from the Davies equation.[27]

(29) J. Hine and F. A. Via, *J. Amer. Chem. Soc.*, **94**, 190 (1972).

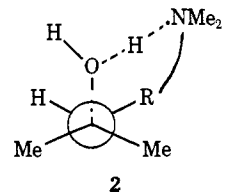
in which R is secondary, to be less reactive than a similar amine in which R is primary.

The points for the five tertiary-protonated diamines all lie above the best line through the points for the electrically neutral amines in Figure 3. In view of the imperfections in the correlation of the data for the electrically neutral amines and the added uncertainties that exist in the values of k_{am} and pK_a for the diamines, it is possible that the deviations for the tertiary-protonated forms of 4-dimethylaminobutylamine and 5-dimethylaminopentylamine are not significant. However, the other three tertiary-protonated diamines are 12–1000 times too reactive to fit the line in Figure 3, and these factors are much larger than the experimental uncertainty and the deviations of other points from the line. It is probably largely coincidence that the point for 2-trimethylammonioethylamine, whose k_{am} value may be uncertain by a factor of 2, lies so near the line in Figure 3. However, this point is certainly known with enough precision to rule out the possibility that cationic substituents in primary amines produce large positive deviations, especially when these substituents are near the amino group. We therefore believe that in the three more deviant tertiary-protonated diamines the dimethylammonio substituent is acting as an internal acid catalyst in the dehydration of the intermediate carbinolamine. Such internal catalysis can be written as a concerted reaction with a transition state like **1**, but it is difficult to rule out possible



1

mechanisms in which the carbon–oxygen and nitrogen–hydrogen bonds are broken in separate steps. The carbinolamine might, for example, ionize reversibly to an intimate ion pair, whose hydroxide ion moiety is neutralized by the dimethylammonio substituent in the rate-controlling step. If **1** is taken as a satisfactory approximation to the transition state, the coplanarity that is going to be required of the four atoms attached directly to the carbon–nitrogen double bond in the iminium ion must influence the stereochemistry of the transition state. The unshared electron pair on nitrogen would be expected to be trans-antiparallel to the adjacent carbon–oxygen bond that is being broken. It also seems reasonable to assume that the three bonds (two of which are partial bonds) to oxygen have about the same bond angles that three bonds to oxygen usually do, and that the O–H–N hydrogen bond prefers to be linear. For these reasons Newman projection **2** is suggested as optimum for the transition state. Examination of molecular models indicates that any of the diamine catalysts that we have studied could give such a transition state without major distortions of bond lengths or bond angles. These transition states would contain varying amounts of torsional strain and van der Waals repulsion, which would be difficult to evaluate even semiquantitatively. The polymethylene chains of the ω-dimethylamino alkyl amine catalysts are presumably most stable in the completely extended conformation. Since such conformations are not suitable for transition states like **2** the longer chain compounds might be expected to be poorer catalysts, and *trans*-2-(dimethylaminomethyl)cyclopentylamine, in which the three carbon atoms between the two amino groups are constrained to conformations more suitable for bifunctional catalysis, might be expected to be a better catalyst than its acyclic analog 3-dimethylaminopropylamine.



2

Catalytic efficiency must be influenced by polar as well as stereochemical factors. The dimethylammonio substituent is acting as an acid catalyst and therefore its activity might be expected to increase with its acidity. The catalyst with the most acidic dimethylammonio group is $Me_2N^+H(CH_2)_2NH_2$ and indeed this is the best catalyst. On the other hand, as the rate constants obtained for the monoamines demonstrate, the catalytic activity increases with the basicity of the primary amino group of the catalyst, largely because electron-withdrawing groups in R decrease the ease of removal of a hydroxide ion from $Me_2C(OH)NHR$. With $Me_2N^+H(CH_2)_3NH_2$ the deactivating effect of the electron-withdrawing substituent is almost as large as the activating effect produced by internal acid catalysis. Thus the catalytic efficiency is not much greater than that shown by *n*-butylamine.

It is not clear that there are any other examples of internal catalysis of imine formation, not counting enzymatic reactions, with which we can compare our results. Internal catalysis by the 3-hydroxy group has been suggested to explain the fact that carbinolamines derived from 3-hydroxypyridine-4-carboxaldehyde are dehydrated much more rapidly than analogous carbinolamines derived from pyridine-4-carboxaldehyde.[9] However, the magnitudes of the rate effects are small enough to be explained as polar substituent effects of an ortho hydroxy or O^- group. Internal catalysis by the *o*-hydroxy substituent in the hydrolysis of *N*-salicylideneaniline and its derivatives has been proposed on the basis of their great reactivity in basic solution.[10] This great reactivity is also observed in the hydrolysis of *N*-salicylidene-2-aminopropane, where additional data provide good evidence that it is merely the result of a large polar substituent effect.[30] On the other hand, no previous attention seems to have been given to the attractive possibility that the relatively high rate of hydrolysis of *N*-(*p*-trimethylammoniobenzylidene)-2-hydroxyaniline around pH 9[9] results from internal acid catalysis by the 2-hydroxy substituent.

Reactions in which one amino group of a diamine provides internal basic catalysis for reactions of the other amino group[31] are, in a sense, complementary to our reactions, in which the catalyzing amino group becomes protonated and acts as an acid catalyst.

(30) W. Bruyneel, J. J. Charette, and E. De Hoffmann, *ibid.*, **88**, 3808 (1966).
(31) *Cf.* M. I. Page and W. P. Jencks, *ibid.*, **94**, 8818 (1972).

Experimental Section

Kinetics of Amine-Catalyzed Oximation of Acetone. In a typical run stock solutions 1 *M* in hydroxylamine hydrochloride, amine hydrochloride (dihydrochloride in the case of diamines), sodium chloride, and sodium hydroxide were used to prepare the reaction solutions, which were 0.030 *M* in hydroxylamine, 0.100 *M* in amine, 0.30 *N* in ionic strength through addition of sodium chloride, and which contained enough sodium hydroxide solution to give the desired pH. The solutions were prepared using doubly distilled, degassed water with exclusion of oxygen and carbon dioxide. The pH was measured at 35° using a Radiometer pH meter Model 26. A 2.50-ml sample was pipetted into a 1-cm quartz spectrophotometer cell and was placed in the thermostated cell compartment of a Cary 1605 spectrophotometer. The reference cell contained distilled water. Time was allowed for thermal equilibration; the cell was removed, 10 μl of a solution 2.50 *M* in acetone was added by syringe, and the cell was shaken and quickly returned to the sample compartment. The absorbance was monitored at 275 nm, about 10 nm above the absorption maximum of acetone, in order to minimize absorption by species other than acetone. "Infinite" absorption values were measured, and a plot of $\ln [(A_0 - A_\infty)/(A_t - A_\infty)]$ *vs.* time was made based on about 15 points usually covering about 80% of the reaction. The points showed so little scatter that there was little uncertainty in drawing the best straight line as judged by eye. To calculate the concentration of hydroxylamine present in the unprotonated form the p*K* value 5.77 at 35° and ionic strength 0.30 *N* ($NaClO_4$) was interpolated from data obtained under surrounding conditions.[32] In runs on *trans*-2-(dimethylaminomethyl)cyclopentylamine, the material was usually added as its oxalate salt.

Determination of the Ionization Constants. Three samples of *trans*-2-(dimethylaminomethyl)cyclopentylamine were titrated with 0.1 *M* hydrochloric acid at 35° using a Radiometer titrator, and the p*K* values were calculated from the results by the method described previously.[20] Neither the acidity constant of the monoprotonated diamine at zero ionic strength, which was determined largely from data at ionic strengths 0.002–0.023 *N* with an average value of 9.80 ± 0.03 (standard deviation), nor that of the diprotonated diamine, which was determined largely from data at ionic strengths 0.01–0.06 *N* with an average value of 7.59 ± 0.04, showed any clear drift with ionic strength.

The overall p*K* values obtained as described above were dissected into their component micro p*K* values by the pmr method used previously.[12] A series of aqueous solutions 0.10 *M* in methanol and 0.10 *M* in sodium chloride was prepared containing enough *trans*-(2-dimethylaminomethyl)cyclopentylamine to give a strength of 0.103 *M* and enough sodium hydroxide to transform various fractions of the diprotonated amine to the monoprotonated and unprotonated form. The chemical shifts of the methyl protons of the amine were measured relative to those of the internal methanol.

The p*K* of the monoprotonated form of 2-dimethylaminoethylamine was determined by titration with hydrochloric acid at 35° and ionic strength 0.30 *N*. The value obtained (9.48) using activity coefficients calculated from the Davies equation is higher than that obtained previously from a similar determination at lower ionic strength.

The (2-aminoethyl)trimethylammonium chloride hydrochloride used was prepared from 2-dimethylaminoethylamine. The *N*-(2-dimethylaminoethyl)acetamide obtained by acetylation[33] was refluxed for 6–8 hr with 3 equiv of methyl chloride in acetone,[34] and the resulting (2-acetaminoethyl)trimethylammonium chloride was deacetylated by refluxing with methanolic hydrochloric acid. A solution of 50 mg of the resulting (2-aminoethyl)trimethylammonium chloride hydrochloride in 0.50 ml of 50% sodium hydroxide was extracted with 0.50 ml of *o*-dichlorobenzene. No peak at the retention time of 2-dimethylaminoethylamine could be detected on glpc of the extract. Blank experiments showed that similar treatment of 0.1 mg of 2-dimethylaminoethylamine dihydrochloride would give an easily discernible peak (about 1.5 cm high).

Acknowledgment. We thank Mrs. Nancy W. Flachskam for having prepared and tested the purity of the (2-aminoethyl)trimethylammonium chloride hydrochloride.

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(34) *Cf.* C. C. Price, G. Kabas, and I. Nakata, *J. Med. Chem.*, **8**, 650 (1965).