

- a Hewlett-Packard Model 5750 apparatus fitted with dual thermal conductivity and hydrogen flame detectors; (b) 150 ft \times 0.02 in. stainless steel capillary column lined with DC-550 oil at 110 °C; (c) 50 ft \times 0.02 in. capillary support coated open tubular (SCOT) column lined with Carbowax 20M mounted in a Perkin-Elmer Mark II flame ionization gas chromatograph.
- (10) Amberlyst-15 resin and literature describing it were obtained from Rohm and Haas Co. This reagent shows considerable promise in effecting acid-catalyzed conversions.
- (11) A Nester/Faust (NFA-100) autoannular spinning band column was used.
- (12) W. M. Harms and E. J. Eisenbraun, *Org. Prep. Proced. Int.*, **4**, 67 (1972).
- (13) Mass spectra were obtained with a Consolidated Electroynamics Corp. Model 21-110B high-resolution mass spectrometer operated under low-resolution conditions at 70 eV. NMR spectra were obtained with a Varian Associates HR-60 or HR-100 spectrometer. Peak positions are reported

- in terms of δ (pPM) downfield from internal standard tetramethylsilane (δ 0). IR spectra were obtained with a Beckman IR-5A spectrometer as films on NaCl plates or as KBr pellets. Melting points were taken in capillary melting point tubes using a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. Cyclohexane used in the reactions was "Baker Analyzed" reagent, spectrophotometric quality. The benzene used was Fisher Certified reagent (thiophene free). Phillips pure grade isoprene was used in all cyclalkylation reactions. The sulfuric acid used was reagent grade. The petroleum ether, bp 60–68 °C, was redistilled before use.
- (14) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **34**, 3571 (1969).
- (15) The ketone **14** (Celestolide) was purchased from International Flavors and Fragrances, New York, N.Y.
- (16) W. Reppe and W. J. Schweckendiek, *Justus Liebigs Ann. Chem.* **560**, 104 (1948).

Internal Acid Catalysis in the Formation of Imines from Isobutyraldehyde and Monoprotonated Diamines¹

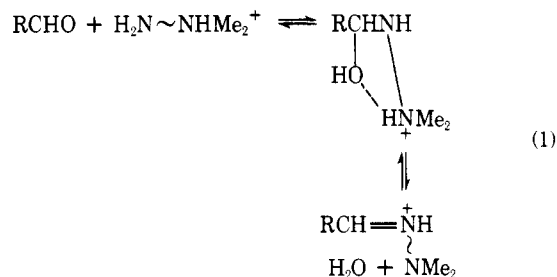
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The reactions of isobutyraldehyde with diamines of the type $\text{Me}_2\text{N}(\text{CH}_2)_n\text{NH}_2$ where $n = 2, 3, 4,$ and 5 have been studied at various pHs by stopped-flow spectrophotometry. A small amount of aldehyde disappears in an equilibrium process whose rate is too fast to measure. Rough equilibrium constants for this rapid reaction (K_r) are determined in the various runs. The K_r values at various pHs are resolved into K_{Ca} , the equilibrium constant for formation of the carbinolamine $i\text{-PrCH}(\text{OH})\text{NH}(\text{CH}_2)_n\text{NMe}_2$, and K_{Cab} , the equilibrium constant for formation of the protonated carbinolamine $i\text{-PrCH}(\text{OH})\text{NH}(\text{CH}_2)_n\text{NHMe}_2^+$. Also determined in the various runs are the equilibrium constants for a slower reaction (K_s), in which equilibrium is not established until about 5–50 s. These are resolved into values of K_{ic} , the equilibrium constants for formation of carbinolamine and imine, and K_{ich} . In all cases K_{ich} covers the formation of protonated carbinolamine and the protonated imine $i\text{-PrCH}=\text{N}(\text{CH}_2)_n\text{NHMe}_2^+$. However, when monoprotonated 2-dimethylaminoethylamine is the reactant much of the product is probably the 1,1-dimethyl-2-isopropylimidazolidinium ion, and when monoprotonated 3-dimethylaminopropylamine is the reactant an analogous six-membered ring heterocyclic cation is probably formed to a significant extent. Approximate first-order rate constants for dehydration of the carbinolamine mixtures are determined in individual runs. The rate constants obtained at various pHs are resolved into k_{co} , the rate constant for dehydration of the unprotonated carbinolamine, and k_{ch} , the rate constant for dehydration of the protonated carbinolamine. In the case of 2-dimethylaminoethylamine there is also a significant term for catalysis of dehydration of the protonated carbinolamine by the unprotonated diamine. The products $K_{\text{Ca}}k_{\text{co}}$ and $K_{\text{Cab}}k_{\text{ch}}$ are reliable second-order rate constants for imination of the aldehyde by the unprotonated and monoprotonated diamine, respectively. The former values give a satisfactory fit to a logarithmic plot against the $\text{p}K_{\text{as}}$ of the protonated primary amino groups that includes data on a number of primary monoamines. The values of $K_{\text{Cab}}k_{\text{ch}}$ for 2-dimethylaminoethylamine and 3-dimethylaminopropylamine are too large by about 7000-fold and 100-fold, respectively, to fit the plot. These deviations are attributed to internal acid catalysis of the dehydration of the intermediate protonated carbinolamine by the dimethylammonio substituent group.

The formation of an imine from an aldehyde or ketone and a primary amine in neutral or basic solution ordinarily involves the reversible formation of a carbinolamine, which, in the rate-controlling step, loses a hydroxide ion to give an iminium ion, whose equilibration with the corresponding imine is established very rapidly.^{2,3} This loss of hydroxide ion is uncatalyzed in strongly basic solution but becomes acid catalyzed as the pH is lowered. Nevertheless, increases in the acidity of the reaction solution do not necessarily increase the rate of iminium ion formation, because they decrease the fraction of the amine present in the reactive (unprotonated) form. We thought that relatively rapid iminium ion formation under mild conditions, which is desirable in bifunctional catalysts that are being investigated in this laboratory,⁴ could be achieved by internal acid catalysis. We have therefore investigated imine formation from isobutyraldehyde and ω -dimethylaminoalkylamines and learned that with monoprotonated forms of such diamines there may be internal acid catalysis of the dehydration of the intermediate carbinolamine (eq 1). After this work was completed, similar internal acid



catalysis in iminium ion formation from acetone and various monoprotonated diamines was discovered.^{5,6}

Results

Equilibrium Constants for Carbinolamine and Imine Formation. Stopped-flow mixing of aqueous solutions of isobutyraldehyde and amines of the type $\text{Me}_2\text{N}(\text{CH}_2)_n\text{NH}_2$ where $n = 2, 3, 4,$ and 5 showed that a small but significant amount of the aldehyde was used up in an equilibrium process that was too fast to measure and that a larger amount of al-

Table I. Equilibrium Constants for Reactions of Isobutyraldehyde with Diamines^a

Registry no.	Diamine	K_{Ca} , M ⁻¹	K_{Cah} , M ⁻¹	K_{ic} , M ⁻¹	K_{ich} , M ⁻¹	K'_{ich} , M ⁻¹
108-00-9	Me ₂ N(CH ₂) ₂ NH ₂	2.0 (0.3)	5.1 (0.2)	49.7 (0.6)	14.4 (0.4)	38
109-55-7	Me ₂ N(CH ₂) ₃ NH ₂	0.9 (0.2)	1.2 (0.2)	103 (9)	20 (7)	67
3529-10-0	Me ₂ N(CH ₂) ₄ NH ₂	2.4 (0.2)	0.8 (0.2)	99 (1)	15.6 (0.7)	47
3209-46-9	Me ₂ N(CH ₂) ₅ NH ₂	1.8 (0.1)	0.4 (0.1)	100 (2)	24 (2)	114

^a In water at 35 °C. The parenthesized figures are standard deviations.

dehyde was then used up in a slower equilibrium process. Similar observations had been made earlier in the reactions of isobutyraldehyde with methylamine⁷ and other primary amines,⁸ and evidence was described that the rapid equilibrium involved addition of the amine to the aldehyde to give carbinolamine and in the slower equilibrium imine is also formed; the equilibrium concentrations of protonated carbinolamine and of iminium ion were too small to detect. In the present case the situation is complicated by the fact that the tertiary–primary diamines (TP) upon protonation may give either a tertiary protonated (HTP⁺) or primary protonated (TPH⁺) species, as well as a diprotonated form (HTPH²⁺). Furthermore, the carbinolamine formed may exist as an electrically neutral form (Ca) or with the dimethylamino substituent protonated (HCa⁺). The equilibrium constant for the rapidly established equilibrium (K_r) may be expressed in terms of total carbinolamine and total diamine as

$$K_r = \frac{[Ca] + [HCa^+]}{[Al]([TP] + [HTP^+] + [TPH^+] + [HTPH^{2+}])} \quad (2)$$

in which Al is the free (unhydrated) aldehyde. K_r is an “apparent” equilibrium constant, whose value will be a function of the pH at which it is measured. In determining K_r allowance must be made for hydration of the aldehyde, which occurs to the extent of about 30.6% at equilibrium at 35 °C.⁹ Rate constants for establishment of equilibrium between the aldehyde and its hydrate were estimated as described previously.^{7,8} For about half the runs, including all those carried out above pH 10.3, more than 2 half-lives for establishment of the dehydration–hydration equilibrium had passed before the first of the transmittance measurements that were extrapolated to zero time to obtain the “initial” transmittance, from which K_r was calculated. In these runs it was assumed that the dehydration–hydration equilibrium was fully established. In most of the other half of the runs, including all those carried out below pH 9.6, the dehydration–hydration equilibrium was estimated to be less than 20% established during the time when the transmittance measurements used for extrapolation were made. In these runs it was assumed that no net aldehyde hydration or hydrate dehydration took place during the establishment of the carbinolamine equilibrium. Five runs on 3-dimethylaminopropylamine were carried out at pH 9.67 where the dehydration–hydration equilibrium was estimated to be about 50% established at the time of the first of the transmittance measurements used in extrapolation. In these runs K_r was calculated by assuming that the dehydration–hydration equilibrium was fully established.

The values of K_r obtained for 2-dimethylaminoethylamine are plotted against the pH in Figure 1. The variation of K_r with pH may be understood in terms of

$$K_r = K_{Ca}f_u + K_{Cah}f_m \quad (3)$$

in which it is written as a function of K_{Ca} , the equilibrium constant for formation of carbinolamine from unprotonated diamine, K_{Cah} , the equilibrium constant for formation of monoprotected carbinolamine from monoprotected diamine, f_u , the fraction of diamine that is unprotonated, and

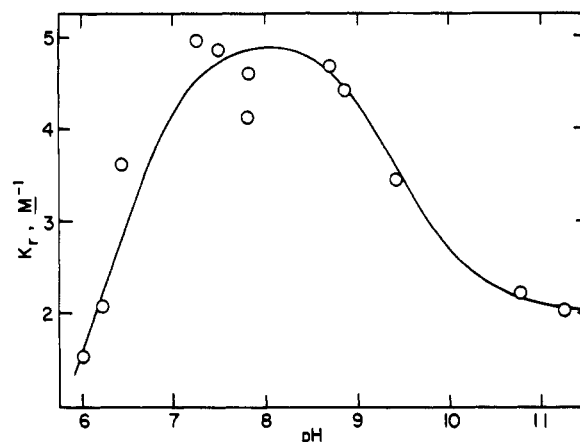


Figure 1. Plot of K_r for isobutyraldehyde and 2-dimethylaminoethylamine in water at 35 °C and ionic strength 0.002–0.43 vs. pH. The line is based on the values of K_{Ca} and K_{Cah} in Table I and an ionic strength of 0.10.

f_m , the fraction of diamine that is monoprotected (eq 4–7).

$$K_{Ca} = [Ca]/([Al][TP]) \quad (4)$$

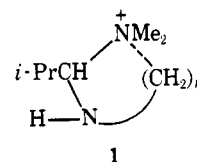
$$K_{Cah} = \frac{[HCa^+]}{[Al]([HTP^+] + [TPH^+])} \quad (5)$$

$$f_u = [TP]/([TP] + [HTP^+] + [TPH^+] + [HTPH^{2+}]) \quad (6)$$

$$f_m = \frac{([HTP^+] + [TPH^+])}{([TP] + [HTP^+] + [TPH^+] + [HTPH^{2+}])} \quad (7)$$

Values of K_{Ca} and K_{Cah} were calculated from eq 3 using the experimentally determined values of K_r and f_u and f_m values calculated from the ionization constants of the diamines.^{10,11} The values obtained are listed in Table I, and those for 2-dimethylaminoethylamine were used to draw the line in Figure 1. We suspect that the reliability of these K_{Ca} and K_{Cah} values is considerably poorer than is indicated by the standard deviations shown. This unreliability arises from the rather small differences in absorbances upon which the values are based and upon the uncertainties in extrapolating absorbances to zero time, especially in the case of such rapid reactions as some of those involving 2-dimethylaminoethylamine.

The equilibrium constant for the slower reaction, in which equilibrium is not reached until 5–50 s, is denoted K_s . It covers the formation of both the protonated and unprotonated carbinolamine, an electrically neutral imine (Im), an imine whose tertiary amino substituent is protonated (HIm⁺), and possibly a heterocyclic cation (Het⁺) of the type 1. By analogy to earlier



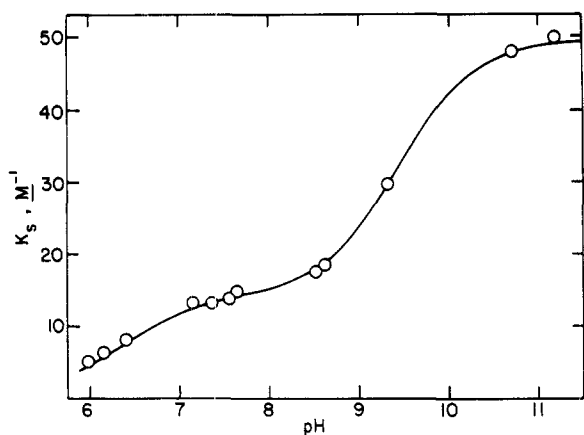


Figure 2. Plot of K_s for isobutyraldehyde and 2-dimethylaminoethylamine in water at 35 °C and ionic strength 0.002–0.43 vs. pH. The line is based on the values of K_{ic} and K_{ich} in Table I and an ionic strength of 0.10.

work⁸ we assume that iminium ions will be present in negligible concentrations. Thus the pH-dependent equilibrium constant K_s , defined by

$$K_s = \frac{[Ca] + [HCa^+] + [Im] + [HIm^+] + [Het^+]}{[Al]([TP] + [HTP^+] + [TPH^+] + [HTPH^{2+}])} \quad (8)$$

may be expressed in terms of pH-independent equilibrium constants as shown by

$$K_s = K_{ic}f_u + K_{ich}f_m \quad (9)$$

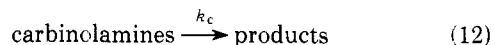
in which K_{ic} , the equilibrium constant for formation of imine and carbinolamine, and K_{ich} , the equilibrium constant for formation of protonated imine, protonated carbinolamine, and heterocyclic cation, are defined in

$$K_{ic} = ([Im] + [Ca])/([Al][TP]) \quad (10)$$

$$K_{ich} = \frac{[HIm^+] + [HCa^+] + [Het^+]}{[Al]([HTP^+] + [TPH^+])} \quad (11)$$

Values of K_s for 2-dimethylaminoethylamine and 4-dimethylaminobutylamine are plotted against pH in Figures 2 and 3, respectively. The values of K_{ic} and K_{ich} obtained by the method of least squares for all four diamines are listed in Table I. Those for 2-dimethylaminoethylamine and 4-dimethylaminobutylamine were used to draw the lines in Figures 2 and 3, respectively.

Kinetics of the Reactions of Isobutyraldehyde with ω -Dimethylaminoalkylamines. To interpret the reaction kinetics the transformations of carbinolamines to iminium ions have been assumed to be the rate-controlling steps, as appears to be the case with monoamines,^{2,3,7,8} and changes in pH during a given run (which exceeded 0.25 only in the case of 3-dimethylaminopropylamine at pH 9.91 ± 0.18 , where it was 0.36) were neglected. Within a given run the reaction is treated as a first-order reaction of total carbinolamine (eq 12).



Adding the assumption that establishment of equilibrium between the aldehyde and aldehyde hydrate is rapid relative to imine formation we obtain

$$k_c t = \left(\frac{2K_s - 2K_r}{K_s} - \frac{\beta}{\alpha} \right) \ln \frac{K_s \gamma a_0 + \alpha}{K_s \gamma a + \alpha} + \frac{\beta}{\alpha} \ln \frac{a_0}{a} \quad (13)$$

where

$$a = [Al] - [Al]_{eq}$$

$$\alpha = \sqrt{(\delta K_s + \gamma)^2 + 4K_s \gamma [Al]_0}$$

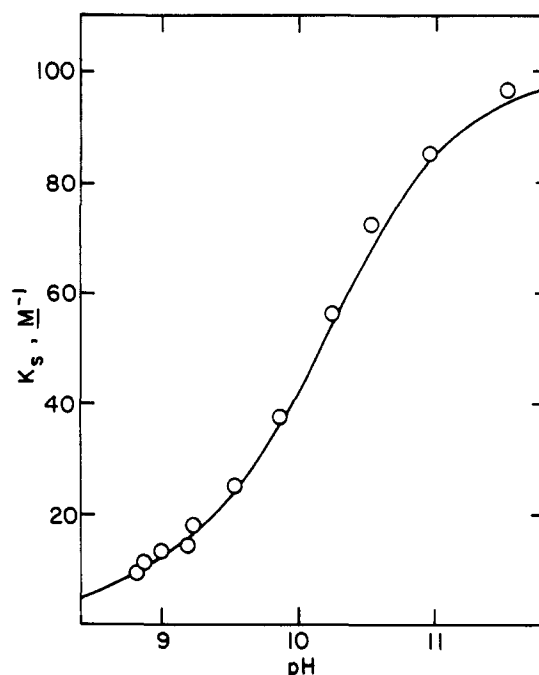


Figure 3. Plot of K_s for isobutyraldehyde and 4-dimethylaminobutylamine in water at 35 °C and ionic strength 0.005–0.15 vs. pH. The line is based on the values of K_{ic} and K_{ich} in Table I and an ionic strength of 0.10.

$$\beta = \frac{K_s - K_r}{K_r} \left(\gamma + \delta K_r + \frac{K_r(\alpha - \delta K_s - \gamma)}{K_s} \right)$$

$$\gamma = 1 + K_h$$

$$K_h = [Ah]/[Al]$$

$$\delta = [TP] + [HTP^+] + [TPH^+] + [HTPH^{2+}] - [Al] - [Ah]$$

which is similar to the rate equation for monoamines.⁸ In this equation Ah is the aldehyde hydrate, a_0 is the value of a at time (t) zero, $[Al]_0$ is the initial concentration of aldehyde, and $[Al]_{eq}$ is that at equilibrium. Equation 13 was used in all cases in which the first-order rate constant for approach to equilibrium in hydration was more than five times as large as the rate constant for approach to equilibrium in imine formation (e.g., in all runs made above pH 10). When imine formation was more than five times as fast as hydration, the equation was modified in accordance with the assumption that there was no net hydration of aldehyde or dehydration of aldehyde hydrate during the formation of imine. This modification consists of setting γ equal to 1.0 and setting δ equal to $[TP] - [Al]$. $[Al]_{eq}$ is set equal to the concentration of aldehyde that would be present if carbinolamine and imine formation were at equilibrium but the concentration of aldehyde hydrate had not changed since the solutions were mixed. When neither hydration nor imine formation could be considered to be fast relative to the other, the rate constant was calculated in each of the two possible ways and the two values (which differed by about 15%, with the rapid-hydration rate constant being larger) were averaged. The values of K_r and K_s used in eq 13 were not those obtained in the given run, but were the values calculated from eq 3 and 9 using the equilibrium constants listed in Table I.

For monoamines the values of k_c obtained at high pH, where the reaction consists of uncatalyzed ionization of the carbinolamine to give hydroxide and iminium ions, were found to be independent of the pH; however, if the amine studied was weakly enough basic to permit measurements to be made in sufficiently acidic solution a hydrogen ion catalyzed reaction became prominent.⁸ In the present case the uncatalyzed

Table II. Rate Constants for Dehydration of Carbinolamines Derived from Isobutyraldehyde and Diamines^a

Diamine	pK _{AmH} ^b	f _t ^b	k _{co} , s ⁻¹	k _{ch} , s ⁻¹	% std dev of k _c
Me ₂ N(CH ₂) ₂ NH ₂ ^c	9.30	0.38	3.64 (0.40)	25.2 (1.0)	11
Me ₂ N(CH ₂) ₃ NH ₂	9.91	0.30	18.5 (1.3)	41.2 (1.3)	9
Me ₂ N(CH ₂) ₄ NH ₂	10.17	0.33	12.8 (0.6)	11.4 (0.5)	8
Me ₂ N(CH ₂) ₅ NH ₂	10.44	0.21	20.7 (0.7)	18.5 (0.8)	6

^a In water at 35 °C. The parenthesized numbers are standard deviations. Unless otherwise stated the values shown were obtained using eq 15. ^b From ref 10. ^c Using eq 16; the k_g value also obtained was 1553 ± 165 M⁻¹ s⁻¹.

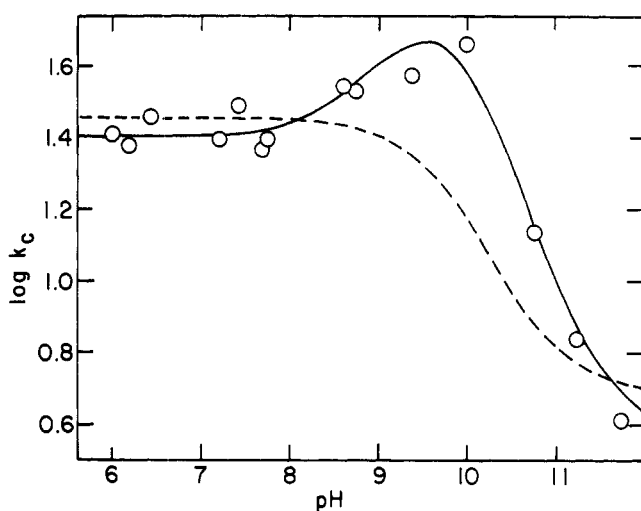


Figure 4. Plot of log k_c for dehydration of carbinolamines vs. pH in the reaction of 2-dimethylaminoethylamine with isobutyraldehyde in water at 35 °C. The dashed line is a fit of the data to eq 15 and the solid line a fit to eq 16 as described in the text.

reaction would correspond to a first-order reaction of the unprotonated carbinolamine and the hydrogen ion catalyzed reaction would correspond to a first-order reaction of the protonated carbinolamine; that is, k_c would follow

$$k_c = k_{co}f_u' + k_{ch}(1 - f_u') \quad (14)$$

in which k_{co} is the rate constant for the unprotonated carbinolamine, k_{ch} is the rate constant for the protonated carbinolamine, and f_u' is the fraction of the carbinolamine that is unprotonated. Values of f_u' were calculated from

$$f_u' = \frac{K_{Ca}K_{AmH}}{K_{Ca}K_{AmH} + K_{Cah}[H^+]} \quad (15)$$

in which K_{AmH} is the acidity constant of total monoprotonated diamine.

Values of log k_c for the reaction of 2-dimethylaminoethylamine with isobutyraldehyde are plotted against pH in Figure 4. A least-squares fit to eq 14 gave values of k_{co} and k_{ch} of 5.0 ± 1.1 and 28.4 ± 2.7 s⁻¹, respectively, where the ± figures are standard deviations. These values fit the k_c values with a standard deviation of 30%. This fit is illustrated by the dashed line in Figure 4, which was calculated from the given k_{co} and k_{ch} values and an ionic strength of 0.10. Although the experimental measurements were made at ionic strengths ranging from 0.002 to 0.43 (with only the two points below pH 6.4 being at ionic strengths above 0.13), this has no significant effect on how well the dashed line fits the points. The positive deviations seen for the points taken between pH 8 and 11 suggested that there is catalysis of dehydration of the protonated carbinolamine by unprotonated diamine, that is, that k_c should be expressed as shown in

$$k_c = k_{co}f_u' + k_{ch}(1 - f_u') + k_g(1 - f_u')[TP] \quad (16)$$

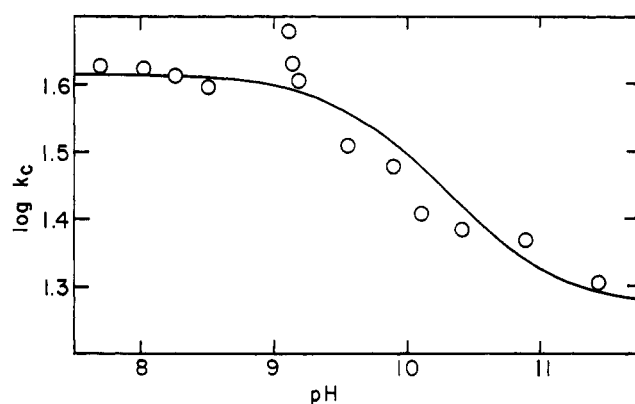


Figure 5. Plot of log k_c for dehydration of carbinolamines vs. pH in the reaction of 3-dimethylaminopropylamine with isobutyraldehyde in water at 35 °C. The line is based on eq 15, the k_{co} and k_{ch} values in Table II, and an ionic strength of 0.10.

A least-squares fit of the data to eq 16 gave k_{co}, k_{ch}, and k_g values of 3.64 ± 0.40 s⁻¹, 25.2 ± 1.0 s⁻¹, and 1553 ± 165 M⁻¹ s⁻¹, respectively. These values fit the observed k_c values with a standard deviation of 11%. This fit can be illustrated only approximately by a single line in Figure 4, because in eq 16, unlike eq 15, the value of k_c depends on the diamine concentration, and total diamine concentrations ranging from 0.021 to 0.174 M were used in the points shown in the figure. However, the k_g term in eq 16 is almost negligible below pH 7.7, where the free amine concentration was always less than 0.0005 M, and above this pH the total diamine concentration was always between 0.041 and 0.051 M except at pH 9.978, where it was 0.079 M. Hence the solid line in Figure 4 was based on a total diamine concentration of 0.050 M, an ionic strength of 0.10, and the values of k_{co}, k_{ch}, and k_g given. The apparent agreement is not quite as good as the real agreement of eq 16 with the data, which we believe is within the experimental uncertainty.

Application of eq 15 to the data obtained on each of the other three diamines gave k_{co} and k_{ch} values that reproduced the k_c values used with a standard deviation of less than 9%. In each case use of eq 16 gave a negative value for k_g. The data obtained with 3-dimethylaminopropylamine are plotted against the pH in Figure 5; the line shown is based on an ionic strength of 0.10 and the least-squares values of k_{co} and k_{ch} obtained using eq 15. In Table II are the values of k_{co} and k_{ch} obtained for 2-dimethylaminoethylamine using eq 16 and those obtained for the three higher diamines using eq 15.

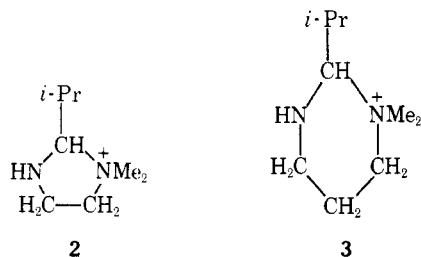
Discussion

The values of K_{Ca} and K_{Cah} we have obtained show no clear trend with the structures of the species involved, although the values obtained with monoamines decreased monotonically with decreasing basicity of the amines.⁸ This fact plus the experimental difficulties involved in obtaining the K_{Ca} and K_{Cah} values make us uncertain that the differences among the values are experimentally significant.

Our values of K_{ic} and K_{ich} are much more reliable and show a tendency to decrease with decreasing basicity that is similar to that found previously with monobasic primary amines.¹² In comparing our compounds with the monoamines, however, it should be noted that the linear free energy relationship found with the monoamines related the basicities of the primary amino groups with the equilibrium constants for reaction of the free primary amines with isobutyraldehyde. The pK s of the diamines, however, refer to the basicities of both the primary and tertiary amino groups, and the K_{ich} values in Table I refer to equilibria in which one reactant is a mixture of HTP^+ and TPH^+ , depending on whether the primary or tertiary amino group is protonated at the moment. The fractional extents to which the monoprotonated forms of the four diamines are protonated at each of the two possible positions have been estimated by 1H NMR measurements.¹⁰ Combination of these fractions with the gross acidity constants of the mono- and diprotonated diamines^{10,11} gives the micro-acidity constants, such as K_{HTP} , K_{TPH} , etc. To put them on the same basis as the K_{ic} values and the analogous constants for monoamines,¹³ the K_{ich} values were divided by f_t , the fraction of the monoprotonated diamine that is protonated at the tertiary amino group. This gives a constant we shall call K'_{ich} , which has the meaning

$$K'_{ich} = \frac{[HIm^+] + [HCA^+] + [Het^+]}{[Al][HTP^+]} \quad (17)$$

and the values shown in Table I. The K_{ic} values for primary amines of the type RCH_2NH_2 , where R contains an sp^3 -hybridized carbon atom by which it is attached to the CH_2 group, are plotted logarithmically against the pK_a values of the protonated amines as solid circles in Figure 6. Our values of K_{ic} are plotted as open circles against the corresponding pK_{TPH} values and our values of K'_{ich} are plotted as triangles against the pK_{HTPH} values (the boldfaced hydrogen in pK_{HTPH} being the one whose acidity is referred to). Although the pK_a values for monoprotonated diamines are independent of the ionic strength, to the degree to which the Davies equation or the limiting form of the Debye-Hückel equation for activity coefficients is reliable, the values of pK_{HTPH} are not; the pK_{HTPH} values plotted are at ionic strength 0.10, a rough average of the ionic strengths at which measurements were made. The line shown in Figure 6 is the least-squares best line (slope 0.26) through the 11 points. The points for the species of the type $Me_2N(CH_2)_nNH_2$ fall about as near this line as the monoamine points do, except for the case where $n = 3$, but this corresponds to the K_{ic} value whose standard deviation is more than four times as large as that for any other diamine (see Table I). The points for species of the type $Me_2N^+H(CH_2)_nNH_2$ also fall near the line in the cases where $n = 4$ and 5 , but the point for $n = 3$ may be too high and that for $n = 2$ is certainly too high. These deviations provide strong evidence that the reaction of monoprotonated 2-dimethylaminoethylamine with isobutyraldehyde gives a cationic product mixture containing a large fraction of the 1,1-dimethyl-2-isopropylimidazolidinium ion 2. The analogous reaction of 3-dimeth-



ylaminopropylamine may produce substantial amounts of 3. If the deviation of the point for $Me_2N^+HCH_2CH_2NH_2$ from the line in Figure 6 is exactly due to the formation of 2 then

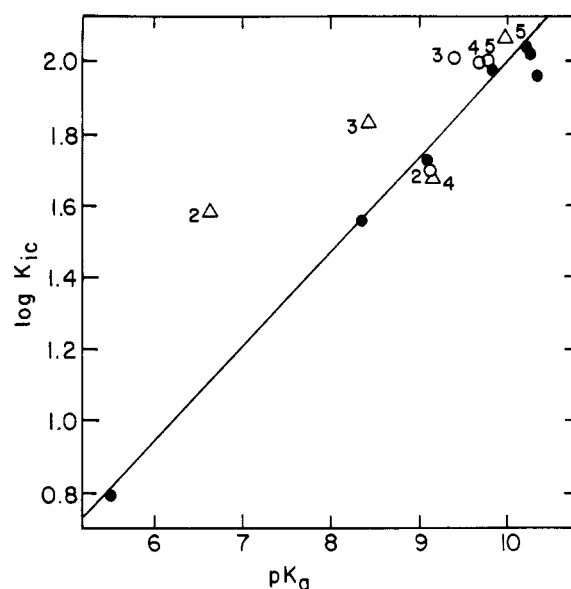


Figure 6. Plot of $\log K_{ic}$ vs. pK_a : ●, primary monoamines of the type RCH_2NH_2 ; ○, diamines of the type $Me_2N(CH_2)_nNH_2$, each point being labeled with the appropriate n ; Δ, protonated diamines of the type $Me_2N^+H(CH_2)_nNH_2$, each point being labeled with the appropriate n .

Table III. Second-Order Rate Constants for Iminium Ion Formation from Isobutyraldehyde and Diamines^a

Diamine	$K_{Ca}k_{co}$, $M^{-1} s^{-1}$	$K_{Cah}k_{ch}$, $M^{-1} s^{-1}$	$K'_{Cah}k_{ch}$, $M^{-1} s^{-1}$
$Me_2N(CH_2)_2NH_2$	7.36	129	338
$Me_2N(CH_2)_3NH_2$	17.2	47.8	159
$Me_2N(CH_2)_4NH_2$	30.3	8.82	26.7
$Me_2N(CH_2)_5NH_2$	37.7	8.16	38.9

^a In water at 35 °C.

the equilibrium constant for formation of 2 is $28 M^{-1}$. This is a plausible value, being within an order of magnitude of the value $19 M^{-1}$ (obtained by multiplying the listed value by $1 + K_h$ to put it on a free-aldehyde basis) for the formation of 1,3-dimethyl-2-isopropylimidazolidinium ions from isobutyraldehyde and monoprotonated N,N' -dimethylethylendiamine.¹⁴

The values obtained for k_c are markedly dependent on the values of K_{Ca} and K_{Cah} used in the calculations and therefore the large uncertainties in these equilibrium constants lead to large uncertainties in k_c . Our reactions, in which only small concentrations of intermediate carbinolamines are ever formed, approach the case in which the concentration of intermediates is too small to detect. In such a case one could determine the products $K_{Ca}k_{co}$ and $K_{Cah}k_{ch}$ (which would simply be second-order rate constants) without being able to separate the products into their component factors. It is therefore not surprising that when we arbitrarily decreased the values of K_{Ca} and K_{Cah} used in the calculations we obtained values of k_{co} and k_{ch} that had increased to about the same extent, so that the products $K_{Ca}k_{co}$ and $K_{Cah}k_{ch}$ remained almost unchanged. Hence we think that the relative magnitudes of these products for the various amines are more meaningful than are those of any of the increment constants. Thus, as in the case of the monoamines,⁸ we shall consider the effect of amine structure on the magnitudes of these products, which are listed in Table III. The $K_{Cah}k_{ch}$ values refer to mixtures of two different forms of the monoprotonated diamine as reactant. They have been divided by f_t to obtain

Table IV. Equilibrium in the Reaction of Isobutyraldehyde with 3-Dimethylaminopropylamine^a

[Am] _t , ^b M	pH		K _r , M ⁻¹		K _s , M ⁻¹	
	Initial	Final	Obsd	Calcd ^c	Obsd	Calcd ^c
0.0400 ^d	11.512	11.360		0.93	64.3	99.7
0.0400	10.924	10.866	0.85	0.95	109	93.4
0.0400	10.514	10.333	0.81	0.98	91.9	78.2
0.0400	10.204	10.012	0.85	1.01	76.0	63.3
0.0400	10.096	9.731	1.22	1.02	60.9	49.7
0.0400	9.672	9.458	1.57	1.07	47.1	38.0
0.0400	9.292	9.086	0.79	1.08	20.4	27.3
0.0400	9.260	9.017	0.88	1.08	21.5	25.8
0.0200	9.239	9.011	1.97	1.08	20.8	26.2
0.0480	8.582	8.458	0.58	0.93	9.81	16.7
0.0560	8.364	8.208	0.53	0.79	7.98	12.9
0.0720	8.093	7.978	0.34	0.61	5.87	9.4
0.104	7.757	7.646	0.24	0.36	3.62	5.1

^a In water at 35 °C using a total initial aldehyde concentration of 0.0326 M unless otherwise noted. ^b Total initial diamine concentration. ^c From eq 3 or 9 and the equilibrium constants in Table I. ^d Total aldehyde concentration 0.0267 M; 0.0064 M sodium hydroxide added.

Table V. Reaction of Isobutyraldehyde with 4-Dimethylaminobutylamine^a

[Am] _t , ^b M	pH		K _r , M ⁻¹		k _{co} , s ⁻¹	
	Initial	Final	Obsd	Calcd ^c	Obsd	Calcd ^d
0.0400 ^e	11.524	11.515	2.83	2.29	13.7	12.8
0.0400	11.064	10.950	1.49	2.17	13.6	12.8
0.0400	10.682	10.534	1.85	1.96	12.4	12.6
0.0400	10.344	10.243	2.11	1.66	13.1	12.5
0.0400	9.990	9.864	1.07	1.31	10.8	12.2
0.0440	9.688	9.527	0.92	1.03	10.8	12.0
0.0528	9.362	9.217	1.00	0.76	12.4	11.7
0.0560	9.264	9.176	0.85	0.73	11.0	11.7
0.0640	9.156	8.994	0.52	0.64	11.4	11.6
0.0720	8.990	8.862	0.59	0.52	12.7	11.6
0.0800	8.927	8.806	0.29	0.48	12.8	11.5

^a In water at 35 °C with an initial total aldehyde concentration of 0.0258 M. ^b Total amine concentration. ^c From eq 3 and the K_{Ca} and K_{CaH} values in Table I. ^d From eq 14 and the k_{co} and k_{ch} values in Table II. ^e 0.0058 M sodium hydroxide added.

K'_{CaH}k_{ch} values, the second-order rate constants for reactions of tertiary-protonated diamines with isobutyraldehyde.

$$K'_{CaH}k_{ch} = K_{CaH}k_{ch}/f_t \quad (18)$$

In Figure 7 the second-order rate constants for iminium ion formation (which is assumed to be the rate-controlling step in the formation of all the products) from isobutyraldehyde and primary amines are plotted logarithmically against the pK_as of the protonated amines. The values for monoamines were published previously.⁸ The line (slope 0.87) in the figure is based on these data and on the values for the unprotonated diamines. The unprotonated diamines seem to comprise a slightly more reactive family of compounds than the monoamines, but we are not sure that the difference is large enough to be significant. It is clear, however, that the mono-protonated forms of 2-dimethylaminoethylamine and 3-dimethylaminopropylamine, and perhaps 4-dimethylaminobutylamine, are more reactive than would be expected from the data on the other amines. This increased reactivity—about 7000-fold, 100-fold, and 3.8-fold for the mono-protonated forms of 2-dimethylaminoethylamine, 3-dimethylaminopropylamine, and 4-dimethylaminobutylamine, respectively—is attributed to internal acid catalysis of the dehydration of the intermediate carbinolamine. The stabilities of these transition states of the type 4 appear to decrease monotonically as *n* increases from 2 to 5. From studies of

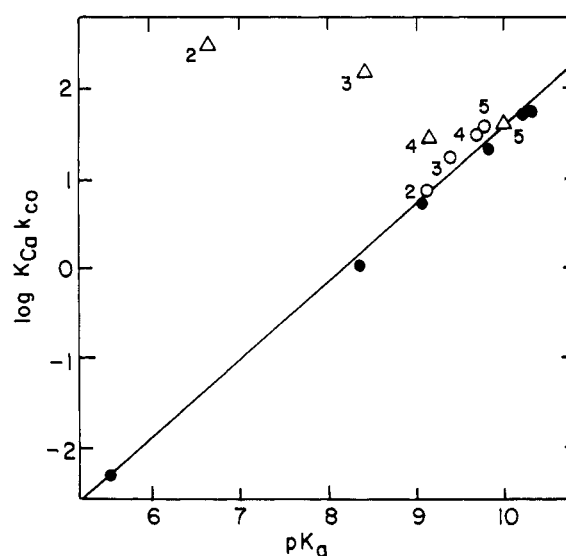
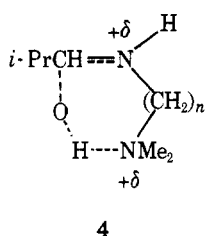


Figure 7. Logarithmic plot of second-order rate constants for iminium ion formation from isobutyraldehyde and primary amines in water at 35 °C vs. the pK_a values of the protonated amines: ●, monoamines of the type RCH₂NH₂; ○, amines of the type Me₂N(CH₂)_nNH₂, each point being labeled with the appropriate *n*; △, amines of the type Me₂N⁺H(CH₂)_nNH₂, each point being labeled with the appropriate *n*. The line is the least-squares line through the circles.

Table VI. Reaction of Isobutyraldehyde with 5-Dimethylaminopentylamine^a

[Am] _i , ^b M	pH		K _r , M ⁻¹		K _s , M ⁻¹		k _c , s ⁻¹	
	Initial	Final	Obsd	Calcd ^c	Obsd	Calcd ^c	Obsd	Calcd ^d
0.0400 ^e	12.338	12.336	1.73	1.80	100.9	98.9	20.5	20.7
0.0400 ^f	11.452	11.408	1.67	1.68	88.5	92.1	21.1	20.7
0.0400	11.004	10.878	1.59	1.49	80.0	77.8	21.6	20.6
0.0400	10.276	10.120	0.92	0.89	39.8	41.6	19.3	20.0
0.0440	9.962	9.802	0.59	0.62	29.6	28.0	19.0	19.6
0.0528	9.643	9.489	0.42	0.40	17.2	17.4	17.4	19.1
0.0640	9.473	9.363	0.12	0.30	11.5	13.6	20.0	19.0
0.0800	9.286	9.155	0.34	0.21	11.8	9.0	20.4	18.8

^a In water at 35 °C with an initial total aldehyde concentration of 0.0232 M. ^b Total amine concentration. ^c From eq 3 or 9 and the constants in Table I. ^d From eq 14 and the k_{co} and k_{ch} values in Table II. ^e 0.0558 M sodium hydroxide added. ^f 0.0026 M sodium hydroxide added.



molecular models it appears that the catalysts, which need not have gauche interactions across carbon-carbon bonds in the ground states, have such interactions in numbers that increase as n increases from 2 to 5. There are also varying amounts of eclipsing strains and nonbonded interactions evident from the models.

As we have mentioned, first-order dehydration of the protonated carbinolamine, whose rate we express as $k_{ch}[CaH^+]$, is kinetically equivalent to hydrogen ion catalyzed dehydration of the unprotonated carbinolamine, whose rate may be expressed as $k_h[H^+][Ca]$. For the amines 2,2,2-trifluoroethylamine, 2,2-dimethoxyethylamine, 3-methoxypropylamine, and methylamine k_hK_{Ca} was found to increase monotonically with increasing amine basicity from 2.9×10^7 to $2.7 \times 10^9 M^{-2} s^{-1}$. Hence, our amines, whose basicities are in this range, should have k_hK_{Ca} values in this range. It may be shown that our values of $K_{Ca}k_{ch}/(K_{Ca}K_{AmH})$, where K_{AmH} is the gross acidity constant of monoprotated diamines, are equivalent to k_hK_{Ca} . Thus the values of k_hK_{Ca} for the diamines range from 5.4×10^{10} to $4.3 \times 10^{11} M^{-2} s^{-1}$ and are much too large to be plausible rate constants for the simple hydrogen ion catalyzed dehydration of unprotonated carbinolamine.

We are not sure why the k_g term in eq 16 is important in the case of 2-dimethylaminoethylamine but not in that of the other diamines. Catalysis of dehydration of monoprotated carbinolamine by unprotonated diamine is kinetically indistinguishable from catalysis of dehydration of unprotonated carbinolamine by monoprotated diamine. We have not formulated the reaction in the latter way because no catalysis by external general acids or bases was observed in the formation of imines from primary aliphatic amines and isobutyraldehyde⁸ or acetone.⁵ However, since it was the values of $K_{Ca}k_{ch}$ that were of principal interest in the present study, we have not carried out the study of additional possible general acid and base catalysts that should be the basis of a detailed discussion of the mechanism of such catalysis.

Experimental and Data Treatment Section

Stopped-flow spectrophotometric measurements were made at the absorption maximum of isobutyraldehyde (285 nm) as described

previously; an aqueous solution of the amine and sodium chloride was in one of the syringes of the apparatus and an aqueous solution of the aldehyde and sodium chloride was in the other.⁷ The sources and properties of the amines were also described previously.¹⁰ Reaction solutions consisted of given amounts of diamine plus the amount of hydrochloric acid, or, in the case of a few runs at high pH, sodium hydroxide, required to give the desired pH. Final pH values were measured immediately after flushing the reaction solutions from the cuvette. Initial pH values were taken as those obtained when an equal volume of distilled water rather than aqueous isobutyraldehyde was mixed with the amine solution. The pH values were taken as $-\log a_{H^+}$. Activity coefficients of electrically neutral species were taken as 1.0 and those of ions were calculated from the Davies equation,¹⁵ which takes the form

$$\log \gamma = -0.5189Z^2 \left(\frac{\sqrt{\mu}}{1 + \sqrt{\mu}} - 0.2\mu \right) \quad (19)$$

at 35 °C, where all the measurements were made.

The absolute uncertainties in K_r and K_s were thought to be relatively independent of the magnitude of K . For this reason, in least-squares treatments of K_r and K_s values it was the sum of the squares of the values of $K_{obsd} - K_{calcd}$ that was minimized. The various rate constants, on the other hand, were thought to be subject to about the same fractional uncertainties. Therefore it was the sum of the squares of the fractional deviations, $1 - k_{calcd}/k_{obsd}$, that was minimized. Standard deviations in the resulting parameters were obtained as described by Hamilton.¹⁶

Data not covered by the figures are listed in Tables IV-VI.

Registry No.—Isobutyraldehyde, 78-84-2.

References and Notes

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