Equilibrium in Formation and Conformational Isomerization of Imines Derived from Isobutyraldehyde and Saturated Aliphatic Primary Amines[1]

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Abstract: The following dimensionless equilibrium constants were determined for the formation of imines and water from isobutyraldehyde and saturated aliphatic primary amines in aqueous solution at 35°: *i*-PrCH=NMe, 4950; *i*-PrCH=NEt, 3490; *i*-PrCH=NPr-*n*, 4180; *i*-PrCH=NBu-*n*, 4040; *i*-PrCH=NPr-*i*, 1840; *i*-PrCH=NBu-*t*, 200. Two of the experimental methods used were based on ultraviolet measurements at the aldehyde and imine absorption maxima (at 2850 and about 2300 A, respectively). These measurements gave satisfactory agreement with a pH method based on the fact that addition of isobutyraldehyde to primary amine buffers decreases the pH by transforming the amine to the much less basic corresponding imine. Largely on the basis of nuclear magnetic resonance data it is concluded that all the imines are very largely *trans* compounds and that in the principal conformations one of the carbon–methyl bonds of the isobutylidene group eclipses the carbon–nitrogen double bond. Both the nmr data and the equilibrium constants for imine formation may be rationalized semiquantitatively by the assumption that rotation around the carbon–nitrogen single bond so as to eclipse the carbon–nitrogen double bond with a carbon–hydrogen bond yields a conformation that is about 2.0 kcal/mole more stable than a conformation in which the carbon–nitrogen double bond has been eclipsed by a carbon–carbon bond.

Rates, equilibria, and reaction mechanisms have been studied carefully in many reactions of the type

$$RNH_2 + R'COR'' \rightleftharpoons RN{=}CR'R'' + H_2O$$

where RNH_2 is a hydroxylamine or hydrazine derivative.[3] Several studies have also been made of the reactions of aromatic aldehydes with aromatic[3] and aliphatic amines[3-8] (and of the reverse reactions). Quantitative studies of the reaction in cases where R, R′, and R″ are all hydrogen atoms or saturated alkyl groups are less common. In his review on imines, which covers their chemistry from the time of their discovery by Schiff in 1864 through Sept 1962, Layer describes no such studies.[9] Zuman reported the polarographic determination of the equilibrium constant for imine formation in the reaction of ammonia and several amino acids with pyruvic acid and several aldehydes and ketones,[10] and Březina and Zuman described a similar investigation of the reaction of cyclopentanone and cyclohexanone with ammonia, methylamine, glycine, and other aliphatic amines.[11] More recently Le Bris, Lefebre, and Coussement have studied the reaction of acetone with isopropylamine,[12] and Williams and Bender have studied the reaction of acetone with methylamine.[13] We have not been able to find any measurements of the equilibrium constant for imine formation from a saturated aliphatic aldehyde and an aliphatic amine.

For this reason, as part of a study of reactions involving the formation of imines as intermediates,[14] we have investigated the formation of imines from several saturated aliphatic amines and isobutyraldehyde, an aldehyde whose equilibrium constant for aldolization is rather unfavorable[15] and whose aldol cannot undergo simple dehydration to an α,β-unsaturated aldehyde.

Determination of *K*

Ultraviolet Measurements at the Aldehyde Maximum. The addition of primary amines to aqueous solutions of isobutyraldehyde causes a decrease in the intensity of absorption at the aldehyde maximum (2850 A). By measurements of the absorption at 2850 A in the presence of known initial concentrations of isobutyraldehyde and amine, the equilibrium constant for the reaction

$$i\text{-PrCHO} + RNH_2 \rightleftharpoons i\text{-PrCH}{=}NR + H_2O$$

may be calculated.

If I is the concentration of imine, W the concentration of water, B the concentration of amine, and A' the concentration of isobutyraldehyde in the free (unhydrated) form

$$K' = IW/A'B \qquad (1)$$

Isobutyraldehyde is about 30% hydrated at equilibrium in aqueous solution at 35°.[15] Inasmuch as equilibrium is quite rapidly established between the free aldehyde

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[2] The Ohio State University, Columbus, Ohio.

[3] W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

[4] G. Vavon and P. Montheard, *Bull. Soc. Chim. France*, **7**, 560 (1940).

[5] R. L. Hill and T. I. Crowell, *J. Am. Chem. Soc.*, **78**, 2284 (1956).

[6] E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 826 (1962).

[7] E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963).

[8] R. W. Green and P. W. Alexander, *Australian J. Chem.*, **18**, 329 (1965).

[9] R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

[10] P. Zuman, *Collection Czech. Chem. Commun.*, **15**, 839 (1950).

[11] M. Březina and P. Zuman, *Chem. Listy*, **47**, 975 (1953).

[12] A. Le Bris, G. Lefebre, and F. Coussement, *Bull. Soc. Chim. France*, 1366 (1964).

[13] A. Williams and M. L. Bender, *J. Am. Chem. Soc.*, **88**, 2508, (1966).

[14] J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *ibid.*, **88**, 3367 (1966).

[15] J. Hine, J. G. Houston, and J. H. Jensen, *J. Org. Chem.*, **30**, 1184 (1965).

and its hydrate,[16,17] it is convenient for many purposes to treat the equilibrium mixture of aldehyde and hydrate as a single substance. The total concentration of free aldehyde and hydrate may be referred to as the apparent aldehyde concentration and denoted A. The apparent equilibrium constant is then

$$K = IW/AB \qquad (2)$$

where K is equal to $K'A/A'$.

The absorbance D of a solution containing aldehyde, amine, and imine may be expressed

$$D = A\epsilon_A + B\epsilon_B + I\epsilon_I \qquad (3)$$

where the ϵ's are the respective extinction coefficients. Substitutions and rearrangement lead to the expression

$$A_0/(A_0\epsilon_A + B_0\epsilon_B - D) = 1/(\epsilon_A + \epsilon_B - \epsilon_I) + W/[KB(\epsilon_A + \epsilon_B - \epsilon_I)] \qquad (4)$$

where $A_0 = A + I$ and $B_0 = B + I$. The value of A_0 is simply equal to the concentration of aldehyde added initially. The value of B_0, however, is equal to the initially added, titrimetrically determined concentration of amine *minus* the concentration of substituted ammonium ion (conjugate acid of the amine).

To use eq 4 for the determination of K, ϵ_A and ϵ_B were determined by measurements on solutions containing only isobutyraldehyde or only amine. Then, for solutions containing various amounts of aldehyde and amine, absorbances (D) were determined and values of A_0 were calculated from the volumes and concentrations of the standard solutions that had been used. From this point the method of successive approximations was used. Values of B_0 and B were estimated from data on the solutions used to prepare the equilibrium solution, from the approximate equation $D = A\epsilon_A$ (the last two terms in eq 3 are relatively small), and from estimates of the concentration of ammonium ions based on the ionization constant of the amine and the concentration of isobutyric acid determined titrimetrically to be present in the isobutyraldehyde solutions used. A knowledge of the concentration of the ammonium ions is of even greater importance in the determination of K by ultraviolet measurements at the imine maximum and by pH measurements. Therefore the basis for the calculations will be treated in some detail here, using the formation of the N-methylimine as a specific example.

Everett and Wynne-Jones determined the acidity constant of the methylammonium ion in water at ionic strengths (due to potassium chloride) 0.05, 0.10, 0.15, 0.20, and 0.25 M at 10° intervals from 10 to 50°.[18] Plots were made of the log K_a values at each ionic strength (and also the values extrapolated to zero ionic strength) *vs.* temperature. From these plots, values of log K_a at 35° at the various ionic strengths were determined and a plot of log K_a *vs.* ionic strength at 35° made. At any desired ionic strength a value of log K_a may be read off this plot and combined with the value of the ion-product constant of water at the same ionic strength[19] to give the ionization constant of methylamine.

The value of W, the water concentration, was calculated from the partial molar volumes of the amines used, which were determined by measuring the densities of amine solutions of known concentrations, and from the partial molar volume of isobutyraldehyde, which was assumed to be equal to the molar volume of the pure material. Except in the case of the measurements made using *t*-butylamine, where W was as low as 50.5 M, W was in the range 53.2–55.1 M in all our reaction solutions.

In this manner we obtained the values (or first approximations of the values) required for a plot of $A_0/(A_0\epsilon_A + B_0\epsilon_B - D)$ against W/B, using the D values obtained experimentally;[21] in some cases, where W was essentially the same for all points, the abscissa in the plot was $1/B$ rather than W/B. According to eq 4, the intercept of the best possible[22] straight line through the points is equal to $1/(\epsilon_A + \epsilon_B - \epsilon_I)$, and K (or K/W in plots against $1/B$) is equal to the intercept divided by the slope. From the preliminary value for K thus obtained, values of B_0 and B were calculated with increased accuracy and the entire process for the calculation of K repeated until no further changes were found in the values obtained. In the later plots the best line was determined by the method of least squares.

This method for determining K was used for a careful study of the reaction of methylamine with isobutyraldehyde and for preliminary studies using other amines. From the final plot obtained in one run on methylamine the value 4900 ± 160 was obtained.

Ultraviolet Measurements at the Imine Maxima. The decrease in absorbance at 2850 A brought about by the addition of saturated aliphatic primary amines to aqueous solutions of isobutyraldehyde is accompanied by an increase in absorbance around 2300 A. In hexane solution unsubstituted aliphatic aldimines have been reported to have absorption maxima around 2460 A with extinction coefficients of about 80 M^{-1} cm^{-1}.[23,24] On going to the more polar solvent, ethanol, these extinction coefficients increase somewhat and the maxima shift to around 2380 A. The extinction coefficients of the imines at their absorption maxima in water are about ten times as large as the apparent extinction coefficient of the aldehyde at its maximum. For this reason the equilibrium constants for the formation of some of the higher imines of isobutyraldehyde, which separate from aqueous solution at the concentrations most suitable for measurements at the absorp-

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[16] L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5224 (1963).

[17] J. Hine and J. G. Houston, *J. Org. Chem.*, **30**, 1328 (1965).

[18] D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc.* (London), **A177**, 499 (1941).

[19] These values were obtained from the data listed by Harned and Owen.[20] Values for the ion-product constant of water (K_w) in the presence of potassium chloride, sodium chloride, and sodium bromide are listed in terms of molalities. These values were converted to molarities and plotted against the square root of ionic strength. Inasmuch as the values obtained for the three different salts are identical, within the experimental uncertainty, up to an ionic strength of 0.06 M, a single line was drawn through the three set of points. The use of this line is equivalent to the assumption that the substituted ammonium salts that are responsible for the ionic strength in our reaction solutions have the same effect on K_w that the three alkali-metal salts do at a given ionic strength. The highest ionic strengths used were about 0.015 M.

[20] H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, pp 638, 725, 752–754.

[21] In all cases equilibrium was shown to be established in a much shorter time than had elapsed when our equilibrium D values were measured.

[22] The intercept cannot be smaller than $1/(\epsilon_A + \epsilon_B)$, a known quantity.

[23] R. Bonnett, N. J. David, J. Hamlin, and P. Smith, *Chem. Ind.* (London), 1836 (1963).

[24] R. Bonnett, *J. Chem. Soc.*, 2313 (1965).

tion maximum for isobutyraldehyde, may be determined conveniently by measurements at the absorption maxima of the imines.

Although the extinction coefficients of the amines at about 2300 A are considerably smaller than those of the imines, the concentration of amine is often considerably larger than that of imine. For this reason it was convenient to use in the reference cell an amine solution of about the same strength as that in the sample cell instead of using pure water as was done in the measurements at 2850 A. When this is done the term B_0 in eq 4 must be replaced by $B_0 - B'$, where B' is the concentration of amine in the reference cell. In order to avoid working with negative numbers, the equation is also multiplied by -1 to give

$$A_0/[D - A_0\epsilon_A - (B_0 - B')\epsilon_B] = 1/(\epsilon_I - \epsilon_A - \epsilon_B) + W/[KB(\epsilon_I - \epsilon_A - \epsilon_B)] \quad (5)$$

Equation 5 was used to determine K graphically by the method of successive approximations, as described in the preceding section. The necessary ionization constants at 35° and various ionic strengths were obtained from the literature for methylamine,[18] ethylamine,[25] *n*-propylamine,[25] and *t*-butylamine[26] (in the first four cases by interpolation between data at higher and lower temperatures) and determined in the present investigation for isopropylamine. The values of K determined by use of eq 5 are listed in Table I.

Table I. Equilibrium Constants for the Formation of Imines from Isobutyraldehyde and Primary Amines in Water at 35°

	K^a	
Primary amine	Ultraviolet measurements at imine max	pH measurements
$MeNH_2$[b]	5050 ± 190	4910 ± 110
$EtNH_2$	3560 ± 170	3420 ± 120
n-$PrNH_2$	4210 ± 50	4140 ± 70
i-$PrNH_2$	1830 ± 20	1850 ± 70
n-$BuNH_2$	4060 ± 80	4010 ± 40
t-$BuNH_2$	199 ± 4	

[a] These are the dimensionless equilibrium constants defined by eq 2, in which W is the actual molar concentration of water. [b] Ultraviolet measurements at the aldehyde maximum gave a K value of 4900 ± 160.

pH Measurements. When isobutyraldehyde is added to a primary amine–amine hydrochloride buffer the pH decreases. It is plausible that this is due to the transformation of some of the primary amine to aldimine, which is considerably less basic. Although we have found no report of the determination of the ionization constant of an aliphatic aldimine, there are sound theoretical reasons why the sp^2 nitrogen atom of such an imine should be less basic than the saturated nitrogen atom of the corresponding amine. Furthermore the available data on aromatic aldimines and on aliphatic ketimines support the argument that aliphatic aldimines are significantly less basic than the corresponding amines. Cordes and Jencks, for example, found that the ionization constants of substituted N-benzylidene-*t*-butylamines vary from 5×10^{-7} for the *p*-methoxy compound to 2.5×10^{-9} for the *p*-nitro compound.[7] Březina and Zuman reported that the imines derived from methylamine and cyclohexanone and cyclopentanone have ionization constants of 2.7×10^{-5} and less than 10^{-6}, respectively.[11] On the basis of data on related compounds it has been estimated[14] that the ionization constant of N-isobutylidenemethylamine is around 10^{-7} or less. In comparison, typical unsubstituted saturated primary and secondary amines have ionization constants in the range 4×10^{-4} to 1.5×10^{-3}.

If it is assumed that the imine formed is protonated to a negligible extent, the effect of adding isobutyraldehyde to a primary amine buffer is to remove some of the amine and thus increase the ratio $[RNH_3^+]/[RNH_2]$. The concentration of amine present after the addition of isobutyraldehyde to an amine buffer may be expressed

$$[RNH_2] = \frac{[RNH_2]_0[RNH_3^+][OH^-]K_b^0}{[RNH_3^+]_0[OH^-]_0K_b} \quad (6)$$

where the subscript and superscript zeros refer to concentrations before the addition of aldehyde and the ionization constant at the initial ionic strength, and the concentrations and ionization constant after the addition of aldehyde are written without zeros. The concentrations of hydroxide ion are calculated from the observed pH's and the ion-product constant of water at the proper ionic strength.[19] The concentration of ammonium ions is equal to the sum of the buffer anion concentration and the hydroxide ion concentration. The concentration of imine may be expressed

$$I = (V_0/V)([RNH_3^+]_0 + [RNH_2]_0) - [RNH_3^+] - [RNH_2] \quad (7)$$

where V_0 is the volume of buffer solution before the aldehyde solution is added and V is the volume afterwards. From eq 6 and 7 and the concentration of aldehyde known to have been added, the equilibrium concentration for imine formation may be calculated.

From 14 to 31 different measurements were made for each of the amines studied, with the ratio of amine to aldehyde added being varied by at least fourfold and the hydrogen ion concentration being varied by an even larger factor. The results obtained are listed in Table I. Preliminary measurements were made using *t*-butylamine, but the equilibrium constant for imine formation is so small that the pH changes observed were not large enough to permit reliable results to be obtained.

Properties of N-Isobutylidenealkylamines

The various N-isobutylidenealkylamines were isolated from the reaction of isobutyraldehyde with the primary amine. The nmr spectra of the imines isolated are summarized in Table II.

The ultraviolet absorption spectrum of each of the imines isolated was measured in 2,2,4-trimethylpentane solution, and the spectra of three imines were measured in acetonitrile. The wavelength of the absorption maxima and extinction coefficients at the maxima thus obtained are listed in Table III. Also listed

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

(26) H. B. Hetzer and R. G. Bates, *J. Phys. Chem.*, **66**, 308 (1962).

Table II. Nmr Spectra of N-Isobutylidenealkylamines

Chemical shifts, τ, and types of proton A	B[a]	C	D	E	F	G	Coupling coustants, cps J_{AB}	J_{BC}	J_{CD}	J_{DE}	J_{EF}
$(CH_3)_2CH—CH=N—CH_2—CH_2—CH_2—CH_3$											
8.96		2.51	6.70	~8.5	*b*	*b*	7.0	4.0	1.3	6.0	
$(CH_3)_2CH—CH=N—CH_2—CH_2—CH_3$											
8.94		2.52	6.75	8.48	9.18		6.8	4.3	1.4	6.4	6.9
$(CH_3)_2CH—CH=N—CH_2—CH_3$											
8.94		2.51	6.72	8.91			7.2	3.9	1.3	7.5	
$(CH_3)_2CH—CH=N—CH(CH_3)_2$											
8.98		2.49	6.80	8.92			6.2	4.1	<0.5	6.3	
$(CH_3)_2CH—CH=N—CH_3$											
8.95		2.50	6.84				7.0	4.2	1.6		
$(CH_3)_2CH—CH=NC(CH_3)_3$											
8.91		2.54	8.85				6.9	4.1			

[a] The absorption by type B protons was too broad and weak to permit a reliable assignment of the chemical shift, but in all cases τ was about 7.7. [b] The peaks due to these protons were obscured by other absorption.

Table III. Ultraviolet Spectral Data on N-Isobutylidenealkylamines

Imine	Me_3CCH_2-$CHMe_2$ λ_{max}, mμ	ϵ	CH_3CN λ_{max}, mμ	ϵ	Water λ_{max}, mμ	ϵ
i-PrCH=NMe	2425	67			2265	146
i-PrCH=NEt	2420	83	2450	108	2300	127
i-PrCH=NPr-*n*	2450	91			2300	155
i-PrCH=NPr-*i*	2410	85	2400	110	2250	187
i-PrCH=NBu-*n*	2440	88	2410	108	2200	144
i-PrCH=NBu-*t*	2500	84			2260	163

are the extinction coefficients and absorption maxima determined in water by the measurements in which the equilibrium constants for imine formation were also determined. The increase in extinction coefficients and shift of the absorption maxima to shorter wavelengths noted on going from saturated hydrocarbons to the more polar solvent ethanol[23] also occur on going to acetonitrile and to the even more polar solvent, water.

Each of the imines studied had a strong absorption band in the infrared at 1670 ± 5 cm^{-1} due to the carbon–nitrogen double bond. This is in agreement with several Raman observations[27–29] and with previous infrared studies.[30,31] Densities, boiling points, and refractive indices are listed in Table IV.

Table IV. Physical Properties of $(CH_3)_2CHCH=NR$ Compounds

R	d_4	nD	Temp, °C	Bp, °C (mm) Obsd	Lit.
Methyl	0.7388[a]	1.4041[a]	12.5	69.5	69.5[a]
Ethyl	0.7325[b]	1.3979[b]	35	87	90[a]
n-Propyl	0 7518[a]	1.4158[a]	13.5	115	115[a]
Isopropyl	0.7269[c]	1.3934[c]	35	97	100[a]
n-Butyl	0.7580	1.4090[d]	35	139–140	142.7[f]
t-Butyl	0.7453	1.4055[g]	25	115–116	51–53 (83)[e]

[a] R. T. Tiollais, *Bull. Soc. Chim. France*, 708, 716 (1947). [b] Lit.[a] d^{15}_4 0.7395, n^{15}D 1.4072. [c] Lit.[a] $d^{13.5}_4$ 0.7341, $n^{13.5}$D 1.4064. [d] Lit.[e] n^{20}D 1.4151. [e] W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957). [f] G. E. Coates and L. E. Sutton, *J. Chem. Soc.*, 1187 (1948). [g] Lit.[e] n^{20}D 1.4078.

Discussion of Results

The formation of an imine from an aldehyde and a primary amine almost undoubtedly involves the intermediate formation of an α-hydroxyamine.[3]

$$RCHO + R'NH_2 \rightleftharpoons \underset{\displaystyle OH}{\underset{|}{RCHNHR'}} \rightleftharpoons RCH=NR'$$

It seems extremely unlikely that either of the two products shown would be formed to the complete exclusion of the other. Therefore, it seems probable that the equilibrium constants we have measured are for the formation of a mixture of imine and α-hydroxyamine. Some of the methods we have used give little information as to the composition of this mixture. All the methods, as employed, give evidence that one molecule of aldehyde reacts with one molecule of primary amine to give one molecule of product, but this does not distinguish between imine and α-hydroxyamine formation. In principle, a distinction could be based on the fact that a molecule of water is a by-product in the formation of imine but not in the formation of α-hydroxyamine. In practice, however, the concentration of water in our reaction mixtures was never varied by so much as 10%, so this distinction cannot be made.

The determination of *K* by pH measurements is based on the assumption that a product is being formed whose basicity is negligible in comparison to that of the primary amine being studied. If this assumption is in error the values of *K* determined should show a tendency to decrease as increasing amounts of aldehyde are added to a given buffer. No such tendency may be seen in the experimental results. Evidence that imines should be relatively weakly basic has already been described.[7,11,14] However, it is not unlikely that α-hydroxyamines are also significantly weaker bases than the primary amines from which they are formed. From Hall's correlation of the basicities of aliphatic amines[32] it may be estimated that an α-hydroxy substituent will decrease the ionization constant of an amine by 50–100-fold. Such a decrease will be partially offset by the greater basicity (by about twofold) usually observed for secondary amines, compared to primary amines. Thus an α-hydroxyamine would probably be a weaker base than the primary amine from which it was formed, and it *might* be so weak as to be protonated to a negligible extent in the presence of the primary amine buffer.

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(27) A. Kirrmann and P. Laurent, *Bull. Soc. Chim. France*, 1657 (1939).

(28) L. Kahovec, *Acta Phys. Austriaca*, **1**, 307 (1948); *Chem. Abstr.*, **42**, 6665 (1948).

(29) R. Cantarel, *Compt. Rend.*, **210**, 480 (1940).

(30) L. J. Bellamy, "Infrared Spectra of Complex Molecules," 2nd ed, Methuen and Co., London, 1958, Chapter 15.

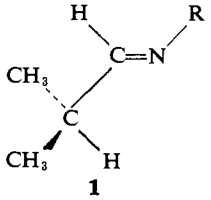
(31) F. H. Suydam, *Anal. Chem.*, **35**, 193 (1963).

(32) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

The ultraviolet measurements at 2850 A showed that a product is formed that absorbs almost negligibly at this wavelength, a property that is at least as plausible for the α-hydroxyamine as for the imine. The measurements around 2300 A, however, show that a product is being formed with an absorption maximum and an extinction coefficient greater than 120 M^{-1} cm^{-1} at about this wavelength. Such properties are quite implausible for a saturated α-hydroxyamine but are quite reasonable for an aldimine. Therefore, it seems clear that the product whose formation we are studying is largely an imine. Nevertheless, the spectral properties to be expected of our imines cannot be predicted with enough quantitative reliability to rule out the possibility that some α-hydroxyamine may also be present in our product mixtures in aqueous solution.

Our results may be summarized by stating that the equilibrium constant for the isobutylidenation of methylamine is rather larger than those for ethylamine, *n*-propylamine, and *n*-butylamine, and the constants for the three latter amines are more than twice as large as that for isopropylamine, which is almost nine times as large as the constant for *t*-butylamine. This variation in equilibrium constants seems most plausibly attributed to steric hindrance. Before discussing such steric hindrance, however, we should discuss the detailed structure of the imines we have studied.[32a]

By analogy with the extensive studies that have been made on olefins and carbonyl compounds[33] it would be expected that our imines would exist in a conformation with the carbon–nitrogen double bond eclipsed by the α-hydrogen atom, **1**, or one of the methyl substituents of the isobutylidene group, **2**. We would expect the coupling constant between the α-hydrogen of the isopropyl group and the hydrogen attached to sp^2 carbon (J_{BC} in Table II) in **1** to be intermediate between the value 11.5 cps reported as characteristic for such *trans* coupling constants in analogous olefins[34] and the value 6.8 cps estimated for such *trans* coupling constants in analogous aldehydes.[35] Although we have not found any clearly relevant published data on imines, Leonard and Paukstelis found a coupling constant of 10.0 cps between the two corresponding hydrogen atoms of the 2-ethylbutylidene group in N-2-ethylbutylidenepyrrolidinium perchlorate,[36] where steric effects would be expected to cause the compound to exist principally in a conformation like **1**. For conformation **2**, where these two hydrogens are *gauche* to each other, a value intermediate between the olefin value 3.7 cps[34] and the aldehyde value −0.3 cps[35] would be expected. The assumption of coupling constants for the imines exactly halfway between those for the analogous olefins and aldehydes (9.2 and 1.7 cps for *trans* and *gauche* coupling, respectively) plus the observed values of J_{BC} (4.1 ± 0.2 cps) leads to calculation of a 29–35% content of conformation **1** and a 65–71% content of conformation **2** in the imines studied. In view of the uncertainty in *trans* and *gauche* coupling constants used, this estimate of the relative fractions of the two conformations present is not highly reliable. We feel that the presence of significant amounts of conformation **2** is rather well established, and the simultaneous presence of significant amounts of conformation **1** is probable. Although conformation **2** appears to be the more abundant conformation, this abundance is not necessarily any greater than would be explained by the fact that there are two methyl groups that can eclipse the carbon–nitrogen double bond (as in **2**) but only one hydrogen atom that can.



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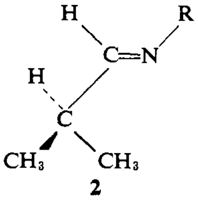

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There is good evidence that aldimines in which the carbon–nitrogen double bond is conjugated with one or more aromatic rings exist preferentially in the *trans* form[37] (by the *trans* form we refer to the isomer in which the isopropyl group from the aldehyde is *trans* to the R group of the amine). In the *cis* forms of such compounds there would be steric interference with the coplanarity required for the maximum resonance stabilization. For imines derived from saturated aliphatic aldehydes and amines, however, little convincing evidence as to the relative stabilities of the two forms seems to have been published. The high rate of formation and hydrolysis of the imines studied under the conditions of their preparation makes it seem likely that the more stable forms were obtained. Conformations **1** and **2** have been written as *trans* isomers because of several lines of evidence that our compounds are *trans* isomers and that they are more stable than the corresponding *cis* isomers. Even in the case of N-isobutylidenemethylamine, the imine for which the *cis* isomer should be least strained, it may be pointed out that with the analogous hydrocarbons, the 4-methyl-2-pentenes, equilibration studies show that the *trans* isomer is about 1.2 kcal/mole more stable than the *cis* isomer at 55°.[40] The differences in stability between the *cis* and *trans* isomers are probably larger in the case of the imines than in the case of the olefins. If we assume carbon–nitrogen single- and double-bond distances of 1.44 and 1.30 A and a C=N—C bond angle of 116.9° as reported for N-methylenemethylamine,[41] a C—C= angle equal to the C—C=C angle in propylene (124.3°),[42] and an sp^3-carbon–sp^2-carbon bond distance of 1.501 A, like that in propylene, an internuclear distance of 2.80 A may be calculated for the two carbon atoms attached to sp^2 carbon and sp^2 nitrogen in the *cis* isomer of an aldimine. The same assumptions

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(32a) NOTE ADDED IN PROOF. Dr. N. J. Leonard has kindly brought to our attention the similar conclusions concerning conformational and geometric isomerization in imines reached by W. J. Musliner, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1965.

(33) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1966, Sections 1–3b

(34) A. A. Bothner-By, C. Naar-Colin, and H. Günther, *J. Am. Chem. Soc.*, **84**, 2748 (1962).

(35) G. J. Karabatsos and N. Hsi, *ibid.*, **87**, 2864 (1965).

(36) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).

(37) In derivatives of N-benzylideneaniline, for example, dipole measurements provide evidence that the compounds ordinarily obtained are *trans* isomers,[38] and flash photochemical studies show that these ordinarily obtained materials may be photoisomerized to less stable isomers that rapidly isomerize back to the starting materials.[39]

(38) V. de Gaouck and R. J. W. Le Fèvre, *J. Chem. Soc.*, 741 (1938).

(39) D. G. Anderson and G. Wettermark, *J. Am. Chem. Soc.*, **87**, 1433 (1965).

(40) A. Schriesheim and C. A. Rowe, Jr., *ibid.*, **84**, 3160 (1962).

(41) K. V. L. N. Sastry and R. F. Curl, *J. Chem. Phys.*, **41**, 77 (1964).

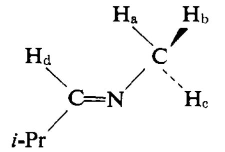
(42) D. R. Lide and D. Christensen, *ibid.*, **35**, 1374 (1961).

plus a 1.336-A carbon–carbon double-bond distance, as in propylene, lead to an internuclear distance of 3.03 A for the two carbon atoms attached to sp^2 carbon and *cis* to each other in a *cis* olefin. The difference of 0.23 A should be sufficient to make the *cis* imine considerably more destabilized (with respect to the *trans* isomer) than the corresponding *cis* olefin. It should also be noted that the difference in stabilities of the two geometric isomers of the 4-methyl-2-pentenes is related to the difference between an isopropyl–methyl *cis* interaction and an isopropyl–hydrogen *cis* interaction, whereas the difference in stabilities of the geometric isomers of our imines is related to the difference between an isopropyl–R *cis* interaction and an isopropyl–unshared pair *cis* interaction.

Furthermore, if our argument that there are significant amounts of both conformations **1** and **2** is correct, the relative amounts of these conformations and hence the magnitude of the J_{BC} values in Table II would be expected to vary markedly as the R group attached to nitrogen is changed from methyl through ethyl and isopropyl to *t*-butyl if any or all the imines studied existed to a significant extent as *cis* isomers. The essentially constant character of J_{BC} therefore provides evidence that the imines are practically all *trans*.

In none of our nmr spectra were extra bands that might have been expected from small amounts of *cis* isomer noted. This might be explained by the hypothesis that all the corresponding hydrogen atoms have the same chemical shifts in the two isomers, but nmr data on geometrically isomeric ketimines make this hypothesis implausible.[43,44] It might also be hypothesized that the *cis–trans* equilibrium is estabished so rapidly that the nmr spectra of the two isomers have become fused. However, this hypothesis, too, is implausible. A survey of data on rate of *cis–trans* isomerization of imines shows that all the N-alkyl compounds studied isomerize much too slowly for fusion of nmr spectra.[44] These data also show no detectable tendency for aldimines to isomerize more rapidly than analogous ketimines. Therefore it appears that our imines consist very largely of one isomer.

Yardley, Hinze, and Curl have shown that the carbon–nitrogen double bond in N-methylenemethylamine is eclipsed by one of the hydrogen atoms of the methyl group.[45] By analogy with this observation as well as with the studies on olefins[33,34] and carbonyl compounds,[33,35] we expect N-isobutylidenemethylamine to exist in a conformation like **3**. We suggest



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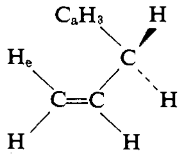
that with the imines derived from ethylamine, *n*-propylamine, and *n*-butylamine the conformation with an alkyl group in place of H_a is considerably less stable than the conformations in which the alkyl group is in the place of H_b or H_c. It is true that such a conformation may be considered to be analogous to conformation **4** for 1-butene, which has been reported to be about as heavily populated as either of the other two conformations, of the type of **5**.[34] However, the same



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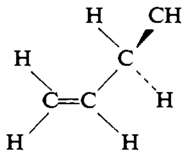

5

assumptions concerning molecular geometry made earlier in this section plus a 1.091-A sp^2-carbon–hydrogen bond distance, 120.5° H—C= bond angles (as in propylene),[42] 1.54-A sp^3-carbon–sp^3-carbon bond distances, and 109.5° bond angles around sp^3 carbon lead to an internuclear distance of 2.06 A between H_d and an sp^3 carbon atom in the place of H_a in conformation **3**, in contrast to a 2.39-A distance between H_e and C_a in conformation **4**. This difference of 0.33 A seems large enough to explain the suggested difference in relative conformational stabilities. The imine derived from isopropylamine would have one relatively stable conformation (with methyl groups in the place of H_b and H_c of **3**) and two unstable conformations (with one methyl group in the place of H_a and another in the place of H_b or H_c). All three conformations of the imine derived from *t*-butylamine would be destabilized by interaction between H_d and a methyl group in the place of H_a.

The nmr spectra of the imines support these suggestions. There is good evidence that coupling constants between pairs of protons analogous to H_a and H_d (in olefins, for example) are much smaller than between pairs like H_b (or H_c) and H_d.[46] It is therefore to be expected that J_{CD} is largest for the methylimine, smaller for the ethyl-, *n*-propyl-, and *n*-butylimines, and smallest for the isopropylimine.

The equilibrium constants for imine formation may be rationalized fairly satisfactorily in terms of steric effects alone if we assume that replacement of H_b or H_c in **3** by an alkyl group leads to a conformation with a free energy content 2.0 kcal/mole (at 35°) lower than when H_a is replaced by an alkyl group. Then relative to an equilibrium constant of about 70 (one-third of the equilibrium constant for the formation of the *t*-butylimine) for the formation of an imine in a conformation with an alkyl group in place of H_a in **3**, the equilibrium constant for the formation of an imine in a conformation that lacks this destabilizing feature should be about 1800. These two figures may be used to calculate the equilibrium constants for the formation of the various imines. For the methylimine, with three stable conformations, the equilibrium constant should be 3×1800 or 5400; for the ethyl-, *n*-propyl-, and *n*-butylimines, with two stable and one unstable conformation, about $(2 \times 1800) + 70$ or 3670; for the isopropylimine, with one stable and two unstable conformations, about $1800 + (2 \times 70)$ or 1940; and for the *t*-butylimine, with three unstable conformations, about 3×70 or 210. This assumed difference in conformational stabilities may also be used to calculate relative populations of conformations, which may be combined with

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[43] H. A. Staab, F. Vögtle, and A. Mannschreck, *Tetrahedron Letters*, 697 (1965).

[44] D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Am. Chem. Soc.*, **88**, 2775 (1966).

[45] J. T. Yardley, J. Hinze, and R. F. Curl, Jr., *J. Chem. Phys.*, **41**, 2563 (1964).

[46] *Cf.* S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

an H_a–H_d type coupling constant of 0.2 cps and an H_b–H_d (or H_c–H_d) coupling constant of 2.3 cps, to calculate values of J_{CD} (Table II) of 1.6, 1.3, 1.3, 1.3, and 0.4 cps for the methyl-, ethyl-, *n*-propyl-, *n*-butyl-, and isopropylimines, respectively. Support for this interpretation of the J_{CD} values is found in the report of a coupling constant of 1.6 cps between the methyl hydrogens and the carbimino hydrogen of N-benzalmethylamine[47] (which we assume to be *trans*), in the report of coupling constants in the range 1.8–2.1 cps between the carbimino hydrogens and the hydrogens attached to nitrogen-bound carbon in the ring of N-alkylidenepyrrolidinium salts[36] (where the relationship between hydrogens is nearer to that between H_d and H_b (or H_c) than to that between H_d and H_a in **3**), in the report of a coupling constant of about 1.5 cps between the boldfaced hydrogen atoms in *t*-BuCH═NCH$_2$-Pr*n*[24] (1.3 cps would be expected from our correlation), and in the reports of no coupling between the boldfaced hydrogens of *t*-BuCH═NCHMeEt[24] and compounds of the type RCH═NCHRAr[43] (where steric effects should favor a conformation like **3**). By analogy with observations on olefins[46] it is presumed that these coupling constants (J_{CD}) are negative.

Although destabilization resulting when a primary alkyl group is put in place of H_a rather than H_b or H_c of conformation **3** provides a plausible rationalization of our observations, there is some uncertainty in the result, 2 kcal/mole, postulated for the amount of this destabilization. The observed coupling constants could be correlated with any amount of destabilization that very largely prevents alkyl groups from taking the place of H_a in **3**; therefore they could be correlated satisfactorily with any amount of destabilization larger than about 1 kcal/mole. The existence of significant nonsteric effects would indicate uncertainty in the result, 2.0 kcal/mole, which is derived from an explanation of the equilibrium constants solely in terms of steric effects. Part of the decrease in equilibrium constants observed in the series Me, Et, *i*-Pr, *t*-Bu could be attributed to decreased stabilization of the carbon–nitrogen double bond by hyperconjugation.[48] It appears that polar effects can be important in imine formation, inasmuch as preliminary observations on amines in which the steric factor has been held essentially constant show that the Taft reaction constant ρ^* is somewhat negative.[1b] However, in view of the increasingly negative substituent constants for the ethyl, isopropyl, and *t*-butyl groups, it may be seen that polar effects would act so as to offset hyperconjugation effects. Evidence against the major importance of hyperconjugation in the present case is provided by the observation that the largest change in log *K* occurs between the isopropyl and *t*-butyl cases. Hyperconjugation seems a poor explanation for most of this change in view of our nmr evidence that the isopropylimine exists very largely in a conformation in which the α-carbon–hydrogen bond is in a plane orthogonal to the π orbitals of the carbon–nitrogen double bond. In addition to the various effects on the stability of the imines being formed, the relative magnitudes of the equilibrium constants for imine formation may also be influenced by effects on the relative stabilities of the amine reactants (that are not balanced by analogous effects on the relative stabilities of the imines). However, we have no evidence for the importance of such effects nor arguments that any such effects should be important. We therefore conclude that steric effects of the type postulated are the predominant factors in bringing about the observed variation in equilibrium constants for imine formation but that other factors are probably significant. A plot of log *K vs.* Taft's E_s values (acyl component)[49] gives a good straight line for the methyl, ethyl, isopropyl, and *t*-butyl compounds, but the equilibrium constants for the *n*-propyl- and *n*-butylimines are almost twice as large as they should be to fall on this line. Our rationalization of the data gives no explanation of why these two equilibrium constants are larger than the equilibrium constant for the formation of the ethylimine.

Experimental Section

Reagents. The isobutyraldehyde and amines used were distilled and stored under nitrogen. The N-isobutylidenealkylamines were prepared from isobutyraldehyde and primary amines by a method based on that of Campbell, Sommers, and Campbell.[50] They were purified by distillation and stored under nitrogen. Their properties are listed in Tables II–IV.

Instrumentation. The ultraviolet spectra were determined using Cary recording spectrophotometers (Model 14). A Beckman Research pH meter (Catalog No. 101900) and glass and calomel electrodes were used for the pH measurements. The infrared spectra were determined with Perkin-Elmer spectrophotometers, Models 21 and 337. The nmr spectra were determined on the neat liquids using Varian A-60 spectrometers. Tetramethylsilane was used as an internal standard.

Ionization Constant of Isopropylamine. The acidity constant of isopropylammonium ions was determined by titration of aqueous solutions of isopropylamine potentiometrically with perchloric acid using a Beckman Research pH meter. The pK_a was calculated from the pH at half-neutralization with due allowance for the concentration of hydroxide ions, which was not negligible in comparison to the concentrations of amine and its conjugate acid. The titration container was thermostated at 35 ± 0.5°. The acidity constant of the isopropylammonium ion was found to be 10.334, 10.309, 10.294, 10.265, and 10.231 at ionic strengths 0.0625, 0.0377, 0.0236, 0.0106, and 0.0030 *M*, respectively, and the value extrapolated to infinite dilution is 10.21. The most nearly comparable value listed in Perrin's compilation is a pK_b of 3.40 for isopropylamine at room temperature.[51] If "room temperature" was 25°, this corresponds to a pK_a of 10.60 for the isopropylammonium ion, from which a value of 10.28 at 35° may be calculated by use of Perrin's methods of correcting for temperature changes.[52] The agreement of this value with ours is as good as could be expected in view of the uncertainty in temperature. The agreement with de Ligny's pK_a of 10.15 for the isopropylammonium ion at 25°[53] is rather poor.

Determination of Equilibrium Constants for Imine Formation. The operations were carried out under nitrogen and solutions were made up using water from which the dissolved air had been replaced by nitrogen. In a typical experiment using the ultraviolet procedure, a volumetric flask was 95% filled with water, a weighed amount of isobutyraldehyde added, and the flask was filled to the mark with water. After the flask had been shaken a sample was titrated with standard base to determine the concentration of isobutyric acid present in the solution. Amine solutions were prepared similarly by weighing except in the case of the more volatile amines, the strength of whose solutions were determined by titration. When ultraviolet measurements were made on such solutions and their mixtures, water at 35° was circulated through the cell

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(47) K. Tori, M. Ohtsuru, and T. Kubota, *Bull. Chem. Soc. Japan*, **39**, 1089 (1966).

(48) *Cf.* R. W. Taft and M. M. Kreevoy, *J. Am. Chem. Soc.*, **79**, 4011 (1957).

(49) R. W. Taft, *ibid.*, **74**, 3120 (1952).

(50) K. N. Campbell, A. H. Sommers, and B. K. Campbell, *ibid.*, **66**, 82 (1944).

(51) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth and Co. (Publishers), Ltd., London, 1965, p 33.

(52) D. D. Perrin, *Australian J. Chem.*, **17**, 484 (1964).

(53) C. L. de Ligny, *Rec. Trav. Chim.*, **79**, 731 (1960).

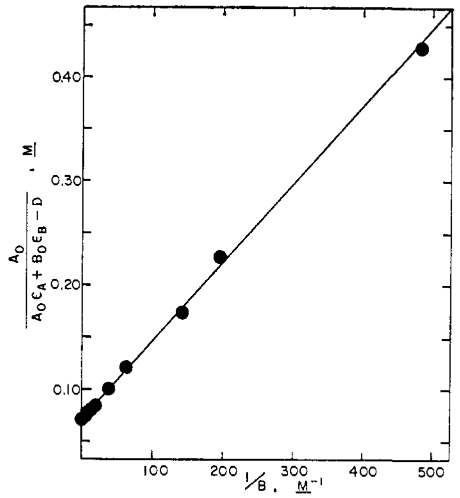

Figure 1. Determination of equilibrium constant for the formation of N-isobutylidenemethylamine by a plot according to eq 4.

compartment and through the thermostatable cell holder. The wavelength of the absorption maximum for the imine was determined by measurements in which the amine was present in large excess.

The data for a run in which measurements were made at the absorption maximum of the aldehyde are shown in Table V and plotted in Figure 1. Those for a run in which measurements were made at the absorption maximum of the imine are shown in Table VI and plotted in Figure 2.

Table V. Measurements on Aqueous Solutions of Isobutyraldehyde and Methylamine at 2850 A

Components of sample soln,[a] ml			
i-PrCHO[b]	$MeNH_2$[c]	H_2O	Absorbance
10.00	0	2.00	1.968
10.00	0	2.00	1.970
10.00	0.100	1.90	1.655
10.00	0.200	1.80	1.375
10.00	0.250	1.75	1.190
10.00	0.40	1.60	0.835
10.00	0.50	1.50	0.637
10.00	0.70	1.30	0.372
10.00	0.85	1.15	0.280
10.00	1.00	1.00	0.243
10.00	1.50	0.50	0.160
10.00	2.00	0	0.120

[a] Reference solution pure water in all cases. [b] 0.1610 *M* (and 0.00173 *M* in isobutyric acid). [c] 3.0100 *M*.

Table VI. Measurements on Aqueous Solutions of Isobutyraldehyde and *n*-Propylamine at 2300 A

Sample soln, ml			Ref soln, ml		
i-Pr-CHO[a]	*n*-Pr-NH_2[b]	H_2O	*n*-Pr-NH_2[b]	H_2O	Absorbance
10.00	0	25.00	0	35.00	0.002
10.00	0	25.00	0	35.00	0.000
10.00	2.00	23.00	2.00	33.00	0.230
10.00	4.00	21.00	4.00	31.00	0.460
10.00	5.00	20.00	5.00	30.00	0.540
10.00	8.00	17.00	8.00	27.00	0.778
10.00	10.00	15.00	10.00	25.00	0.880
10.00	15.00	10.00	15.0	20.00	1.102
10.00	20.00	5.00	20.0	15.00	1.230
10.00	25.00	0	25.0	10.00	1.302

[a] 0.04292 *M* (and 0.00027 *M* in isobutyric acid). [b] 0.07680 *M*.

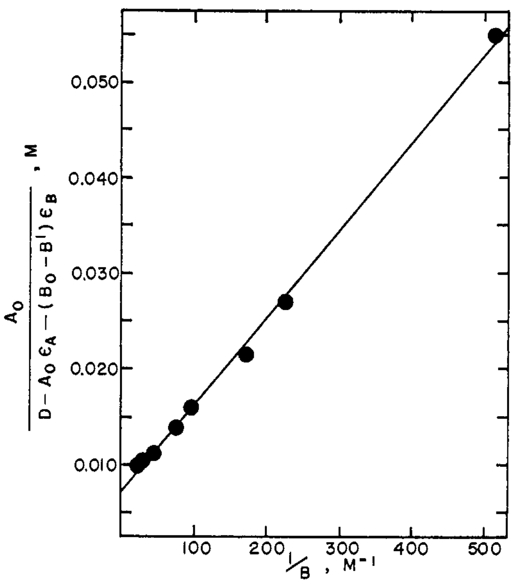

Figure 2. Determination of equilibrium constant for the formation of N-isobutylidene-*n*-propylamine by a plot according to eq 5.

When the equilibrium constant was determined by pH measurements, bromothymol blue was added to the aldehyde solution, to which enough base was then added to turn the indicator green (characteristic of a pH of about 7) in order to neutralize the isobutyric acid present. This aldehyde solution was added from a stoppered buret through a cover (to exclude air) to a beaker of the amine buffer in which the electrodes of the pH meter were immersed. The results obtained with *n*-butylamine are summarized in Table VII.

Table VII. Determination of the Equilibrium Constant for the Formation of N-Isobutylidene-*n*-butylamine by pH Measurements

Sample soln, ml				
i-PrCHO soln	*n*-$BuNH_2$ buffer	pH	$[H_2O]$	*K*
0	70.0[b]	10.432		
15.0[a]	70.0[b]	10.010	54.89	4087
20.0[a]	70.0[b]	9.930	54.84	4036
25.0[a]	70.0[b]	9.868	54.80	3988
30.0[a]	70.0[b]	9.814	54.77	4017
35.0[a]	70.0[b]	9.771	54.73	4009
40.0[a]	70.0[b]	9.733	54.70	4033
45.0[a]	70.0[b]	9.704	54.68	4008
0	70.0[d]	10.446		
15.0[c]	70.0[d]	10.022	54.89	3967
20.0[c]	70.0[d]	9.934	54.84	4024
25.0[c]	70.0[d]	9.880	54.80	3871
30.0[c]	70.0[d]	9.823	54.76	3924
35.0[c]	70.0[d]	9.773	54.73	4003
40.0[c]	70.0[d]	9.734	54.70	4030
45.0[c]	70.0[d]	9.697	54.67	4088
			Av	4006 ± 39

[a] 0.2157 *M*. [b] 0.01387 *M* *n*-$BuNH_2$, 0.00607 *M* *n*-$BuNH_3^+$. [c] 0.2185 *M*. [d] 0.01388 *M* *n*-$BuNH_2$, 0.00607 *M* *n*-$BuNH_3^+$.

Acknowledgments. We wish to acknowledge our indebtedness to the National Science Foundation for grants that made possible the purchase of the nmr spectrometers used and contributed toward the purchase of the ultraviolet spectrophotometers, to the Charles F. Kettering Foundation for a grant that contributed toward the purchase of an ultraviolet spectrophotometer, and to the Eastman Chemical Products Co. for a gift of the isobutyraldehyde used. We also wish to thank Dr. Julien Mulders and Miss Shirley Lee for having made preliminary measurements in this investigation.