Imines, Imidazolidines, and Imidazolidinium Ions from the Reactions of Ethylenediamine Derivatives with Isobutyraldehyde and Acetone[1a,b]

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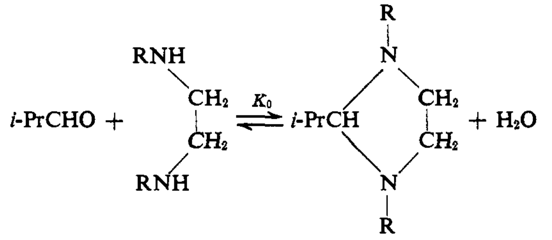
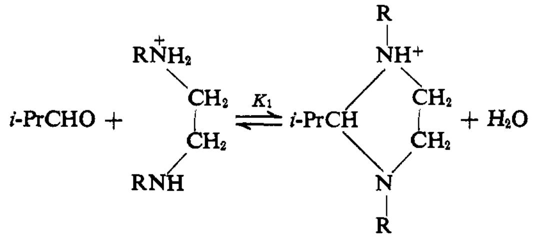
Abstract: Equilibrium constants for the formation of 2-isopropylimidazolidine and its 1,3-dimethyl and 1,3-diethyl derivatives from isobutyraldehyde and ethylenediamine or the appropriate *N,N'*-dialkylethylenediamine in water at 35° were found to be 2240, 799, and 64.7 M^{-1}, respectively. Equilibrium constants for the formation of the respective imidazolidinium ions from the monoprotonated ethylenediamines are 658, 13.2, and 2.27 M^{-1}. These lead to pK values for the three imidazolidinium ions of 9.15, 7.95, and 8.42, respectively. Equilibrium constants of 1.54 and 0.63 M^{-1} for the formation of 2,2-dimethylimidazolidine and 1,2,2,3-tetramethylimidazolidine from acetone and the appropriate diamine were determined. The reaction of isobutyraldehyde with various amounts of ethylenediamine in dimethyl sulfoxide was shown to give the diimine or the imidazolidine but no significant amounts of monoimine. The nmr spectra of a number of alkyl-substituted imidazolidines were measured, and the AA'BB' patterns in the spectra of 2-isopropyl- and 2-*tert*-butyl-1,3-dimethylimidazolidine were analyzed for coupling constants and chemical shifts.

In a study of the catalysis of the deuterium exchange of isobutyraldehyde-*2-d* by polyethylenimines[2] it seemed likely that the results were complicated by the transformation of much of the aldehyde to imidazolidines. Since we found no quantitative studies of equilibria in the formation of imidazolidines in the literature,[3] and since the formation of imidazolidines has been used in distinguishing aldehydes from ketones[6,7] and appears to be important in the physiological action of certain folic acid derivatives,[5,8-10] we thought it worthwhile to determine equilibrium constants for some reactions of this type.


(1)

Results

Equilibrium Constants for Formation of Imidazolidines and Imidazolidinium Ions in Water. When an aldehyde or ketone is treated with an ethylenediamine derivative having at least one hydrogen atom on each nitrogen atom, a derivative of imidazolidine may be formed as shown in eq 1. If the reaction conditions are sufficiently acidic, the formation of an imidazolidinium ion, as shown in eq 2, may also take place to a significant extent. In our calculations the concentration of water will be taken as constant and absorbed into the equilibrium constants K_0 and K_1, which will hence have the dimensions M^{-1}. If an apparent equilibrium constant is defined, as shown in eq 3, in terms of total concentrations of diamine $[\mathrm{Da}]_t$ and imidazolidine $[\mathrm{Imid}]_t$ regardless of their states of protonation, it should have a constant value at a given pH. If the formation of diprotonated imidazolidine may be neglected, K_{app} will vary with the acidity of the solution as shown in eq 4,


(2)

$$K_{\mathrm{app}} = [\mathrm{Imid}]_t/([\mathrm{Da}]_t[i\text{-PrCHO}]) \tag{3}$$

$$K_{\mathrm{app}} = f_0K_0 + f_1K_1 \tag{4}$$

where f_0 is the fraction of diamine present in the unprotonated form and f_1 is that present in the monoprotonated form.

Values of K_{app} were determined in aqueous solution at 35° by absorbance measurements at the isobutyraldehyde (285.0 nm) or acetone (264.8 nm) absorption maxima. The absorbance of the imidazolidines was taken as zero at these wavelengths, an assumption that is supported by the absence of any clear trend in the values of K_{app} obtained with increasing ratios of amine to aldehyde. Many values of K_{app} obtained using isobutyraldehyde were so large that the formation of imidazolidine was very nearly complete at moderate

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[1] (a) This investigation was supported in part by Public Health Service Research Grants AM 10378 from the National Institute of Arthritis and Metabolic Diseases and GM 18593 from the National Institute of General Medical Sciences. (b) Abstracted largely from the Ph.D. Dissertation of K. W. Narducy, The Ohio State University, 1971. (c) National Institutes of Health Predoctoral Fellow (No. F01 GM-41963), 1968-1971.

[2] J. Hine, F. E. Rogers, and R. E. Notari, *J. Amer. Chem. Soc.*, **90**, 3279 (1968).

[3] During the final stages of our work a study of the transformation of glyoxylate ions to imidazolidines appeared,[4] and we learned of a study of the reaction of formaldehyde with tetrahydrofolic acid.[5]

[4] A. Hilton and D. L. Leussing, *J. Amer. Chem. Soc.*, **93**, 6831 (1971).

[5] R. G. Kallen, *Methods Enzymol.*, **18**, 705 (1971).

[6] J. H. Billman, J. C. Y. Ho, and L. R. Caswell, *J. Org. Chem.*, **17**, 1375 (1952).

[7] H.-W. Wanzlick and W. Løchel, *Chem. Ber.*, **86**, 1463 (1953).

[8] R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5851 (1966).

[9] S. J. Benkovic, P. H. Benkovic, and D. R. Comfort, *J. Amer. Chem. Soc.*, **91**, 1860, 5270 (1969).

[10] S. J. Benkovic, P. H. Benkovic, and R. Chrzanowski, *ibid.*, **92**, 523 (1970).

concentrations of reactants. Initial aldehyde concentrations were around 0.01 *M*, and 10-cm cells were used in measurements carried out in the presence of excess aldehyde. At higher concentrations the equilibrium concentration was too nearly equal to the excess of aldehyde over diamine, and in shorter cells the absorbance was too small to measure reliably. In the presence of excess diamine, aldehyde concentrations around 0.1 *M* were used (still in 10-cm cells) so that the small *fraction* of free aldehyde present at equilibrium was a large enough *amount* to give reliable absorbances.

In calculating values of K_{app} the free aldehyde and its hydrate were treated as a single species. Since isobutyraldehyde is 30% hydrated at 35°,[11] the values we report should be divided by 0.7 to be put on a free-aldehyde basis. Acetone is known to be less than 1% hydrated under these conditions.[12]

Values of log K_{app} for the reaction of isobutyraldehyde with ethylenediamine, *N,N'*-dimethylethylenediamine, and *N,N'*-diethylethylenediamine are plotted *vs.* pH in Figure 1 as the open circles, solid circles, and triangles, respectively. We do not know why the values for the unsubstituted and the dimethyl compound, for which we took many experimental precautions and made many repetitions of measurements, are not as reproducible as those for the diethyl compound. The acidity constants for the diprotonated (K_{a2}) and monoprotonated (K_{a1}) substituted ethylenediamines at 35° were determined potentiometrically. The pK_a values for ethylenediamine at 35° were calculated using the equations of Robinson and Stokes[13] relating temperature and pK_a values at zero ionic strength. This permitted the calculation of the values of f_0 and f_1 at any given pH and ionic strength. Ionic strength effects were approximated by the Davies equation.[14] We then calculated the values of K_0 and K_1 such that the sum of the squares of the fractional deviations of eq 4 (shown in eq 5) was a minimum. The lines in Figure 1

$$\sum(\text{fractional deviation})_i^2 = \sum\left(1 - \frac{f_{0_i}K_0 + f_{1_i}K_1}{K_{\text{app}_i}}\right)^2 \quad (5)$$

were obtained by use of eq 4 with these values, which are listed in Table I. The experimental values of K_{app} may be calculated from these K_0 and K_1 values with standard deviations of 17.0, 17.1, and 4.2% for ethylenediamine and its *N,N'*-dimethyl and *N,N'*-diethyl derivatives, respectively.

Table I. Equilibrium Constants[a] for the Formation of Imidazolidines and Imidazolidinium Ions in Water at 35°

Diamine	Isobutyraldehyde K_0	Isobutyraldehyde K_1	Acetone K_0
$H_2NCH_2CH_2NH_2$	2240	658	1.54
$MeNHCH_2CH_2NHMe$	799	13.2	0.63
$EtNHCH_2CH_2NHEt$	64.7	2.27	

[a] In M^{-1}.

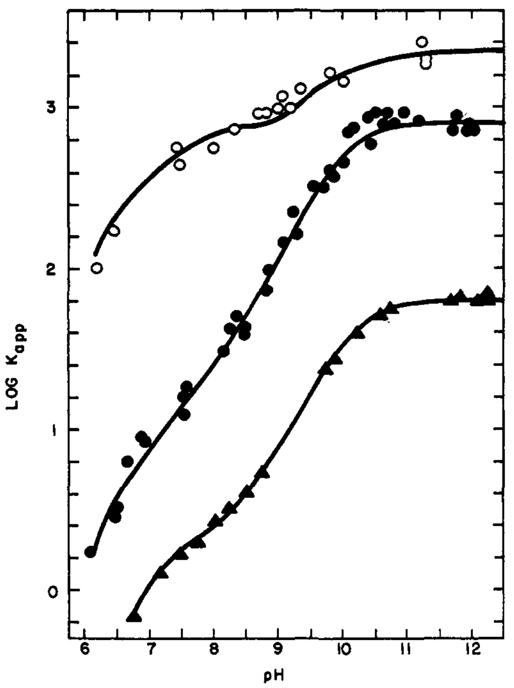

Figure 1. Plot of log K_{app} *vs.* pH for the formation of imidazolidine derivatives from isobutyraldehyde and (○) ethylenediamine, (●) *N,N'*-dimethylethylenediamine, and (▲) *N,N'*-diethylethylenediamine.

Preliminary measurements showed that the equilibrium constants for the formation of imidazolidines from acetone were so much smaller than those for imidazolidines formed from isobutyraldehyde that the values of K_1 would probably be too small to measure by the techniques used for isobutyraldehyde. The relatively small K_0 values were determined using about 0.1 *M* solutions of acetone and 1-cm cells at high pH. Values obtained in reactions with ethylenediamine and its *N,N'*-dimethyl derivative are listed in Table I.

Nmr Spectra of Imidazolidines. The imidazolidines derived from reaction of *N,N'*-dimethyl- and *N,N'*-diethylethylenediamine with isobutyraldehyde or acetone were prepared in pure form and their nmr spectra measured. To aid in the interpretation of the results, the imidazolidines obtained in the reactions of *N,N'*-dimethylethylenediamine with formaldehyde, acetaldehyde, propionaldehyde, and pivaldehyde were synthesized and their nmr spectra measured. The nonaqueous equilibria of ethylenediamine and isobutyraldehyde in dimethyl-d_6 sulfoxide were examined by nmr. The chemical shifts for the various types of protons in these imidazolidines and a few values for related compounds are listed in Table II. The δ values for the imidazolidines formed from acetone and from formaldehyde, for which the peaks due to the H_f type protons are singlets, are obtained readily from first-order theory. In the imidazolidines formed from other aldehydes, however, the chemical shift of the protons of type H_f differs significantly depending on whether they are cis or trans to H_e. A detailed treatment was applied to the spectra of 2-isopropyl-1,3-dimethylimidazolidine and 2-*tert*-butyl-1,3-dimethylimidazolidine. The spectrum of the isopropyl compound in benzene showed a larger number of peaks attributable to protons of the type H_f than any other spectrum. The peaks due to the isopropyl group and the two nitrogen-bound methyl

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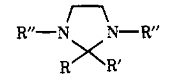
(11) J. Hine, J. G. Houston, and J. H. Jensen, *J. Org. Chem.*, **30**, 1184 (1965); L. R. Green, unpublished observations, The Ohio State University.

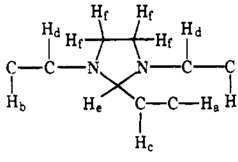
(12) J. Hine and R. W. Redding, *J. Org. Chem.*, **35**, 2769 (1970).

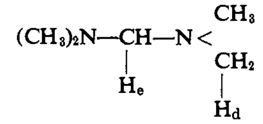
(13) R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," 2nd ed (revised), Butterworths, London, 1968, Appendix 12.1, p 519.

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

Table II. The Nmr Spectra of Imidazolidines[a]





R	R′	R″	a	b	c	d	e	f
			Chemical shifts, δ (ppm), for various types of protons					
H	H	Me[b]				2.38	3.18	2.64
H	Me	Me			1.06	2.33	2.48	2.60[c]
H	Et	Me	0.84		1.40	2.26	2.46	2.65[c]
H	*i*-Pr	Me	0.85		1.6	2.35	2.48	2.66[c]
H	*t*-Bu	Me	0.85			2.47	2.54	2.77[c]
H	Ph	Me[d]				2.1	3.22	2.83[c]
Me	Me	Me			0.88	2.20		2.68
H	*i*-Pr	Et	1.0	1.0	1.5	2.7	2.7	2.7[c]
Me	Me	Et		0.91	1.06	2.44		2.72
H	H	*n*-Bu[e]		*f*		*f*	3.39	2.78
H	Me	*n*-Bu[e]		*f*		*f*	3.20	*f*
H	*i*-Pr	H[g]	0.92		1.5		3.31	2.74[c]
CF_3	CH_2CO_2Et	H[h,i]			2.61			3.05
$CH_2(CH_2)_4CH_2$		H[h,j]			1.45			2.85
 $(CH_3)_2N{-}\underset{H_e}{CH}{-}N{<}^{CH_3}_{CH_2H_d}$						2.16	2.59	

[a] As 20% solutions in carbon tetrachloride with tetramethylsilane as internal reference, unless otherwise noted. [b] Similar values were reported by E. W. Randall, C. H. Yoder, and J. J. Zuckerman, *Inorg. Chem.*, **6**, 744 (1967). [c] Center of AA′BB′ multiplet. [d] Neat; phenyl protons at δ 7.37 ppm: N. Indictor, J. W. Horodniak, H. Jaffe, and D. Miller, *J. Chem. Eng. Data*, **14**, 76 (1969). [e] In $CDCl_3$, concentration not stated: E. M. Wilson, *Tetrahedron*, **21**, 2561 (1965). [f] Not given. [g] In DMSO-d_6; amino protons averaged with water peak. [h] Concentration not stated: M. M. Joullié, G. M. J. Slusarczuk, A. S. Dey, P. B. Venuto, and R. H. Yokum, *J. Org. Chem.*, **32**, 4103 (1967); *cf.* G. M. J. Slusarczuk and M. M. Joullié, *ibid.*, **36**, 37 (1971). [i] The methyl and methylene protons of the ethyl group absorbed at δ 1.26 and 4.15 ppm, respectively, and the amino protons at δ 1.16 ppm. [j] From cyclohexanone. Amino protons absorbed at δ 1.16 ppm.

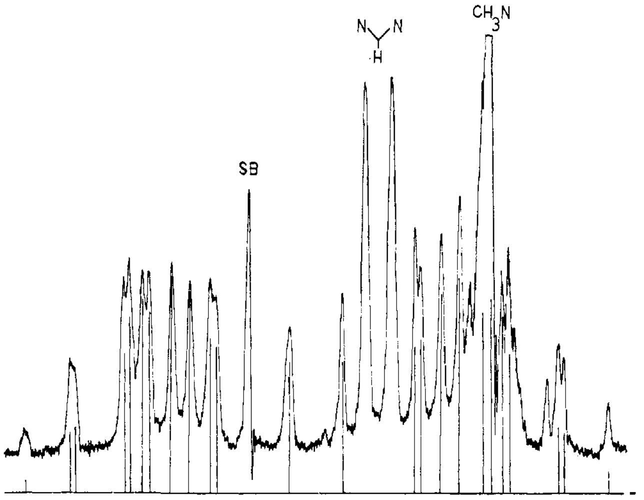


Figure 2. Calculated peak positions and relative intensities for the AA′BB′ part of the 60-MHz pmr spectrum of 1,3-dimethyl-2-isopropylimidazolidine and the experimental spectrum from about δ 2.15 to 3.20 ppm in benzene solution.

groups were easily identified. It was then seen that when the two largest remaining peaks (neglecting sidebands) in the complex multiplet stretching from δ 2.0 to 3.2 ppm were attributed to H_e (*cf.* Table II), the rest of the multiplet was symmetrical, as would be expected for an AA′BB′ spectrum.[15] A search of the literature for examples of AA′BB′ spectra to aid in the analysis of our own brought to light the work of Abraham on 2-methyl-1,3-dioxolane.[16] His calculated spectra of the dioxolane greatly resembled our spectrum of 2-*tert*-butylimidazolidine in carbon tetrachloride. His method of analysis, in which $J_{AA'}$ and $J_{BB'}$ are taken to be equal, was applied to our spectra to provide estimates of coupling constants and chemical shift differences for use in the more complicated and thorough procedure of Garbisch,[17] in which no restrictions need be placed on coupling constants or chemical shifts. The values resulting from this procedure were used as part of the input for the computer program NMRIT.[18] The resulting calculations of the program produced a listing of transitions whose frequencies and intensities match closely those observed in the experimental spectrum. The transition numbers were then assigned to the experimentally observed frequencies and computer program NMREN[18] was used to calculate the energy levels and errors necessary for iterative fitting with NMRIT. Generally, ten iterations were sufficient to bring about convergence.

The spectrum of the isopropyl derivative in benzene was analyzed by averaging the frequencies of five experimental spectra. The iterative fit in this case was the best of the four we examined (isopropyl and *tert*-butyl derivatives in benzene and carbon tetrachloride), reproducing the average experimental spectrum with an average deviation of 0.068 Hz. The values calculated are shown in Table III and a comparison of experi-

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(15) J. R. Dyer, "Applications of Absorption Spectroscopy to Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 108.

(16) R. J. Abraham, *J. Chem. Soc.*, 256 (1965).

(17) E. W. Garbisch, Jr., *J. Chem. Educ.*, **45**, 480 (1968).

(18) J. D. Swalen in "Computer Programs for Chemistry," Vol. 1, D. F. DeTar, Ed., W. A. Benjamin, New York, N. Y., 1961, Chapter 4.

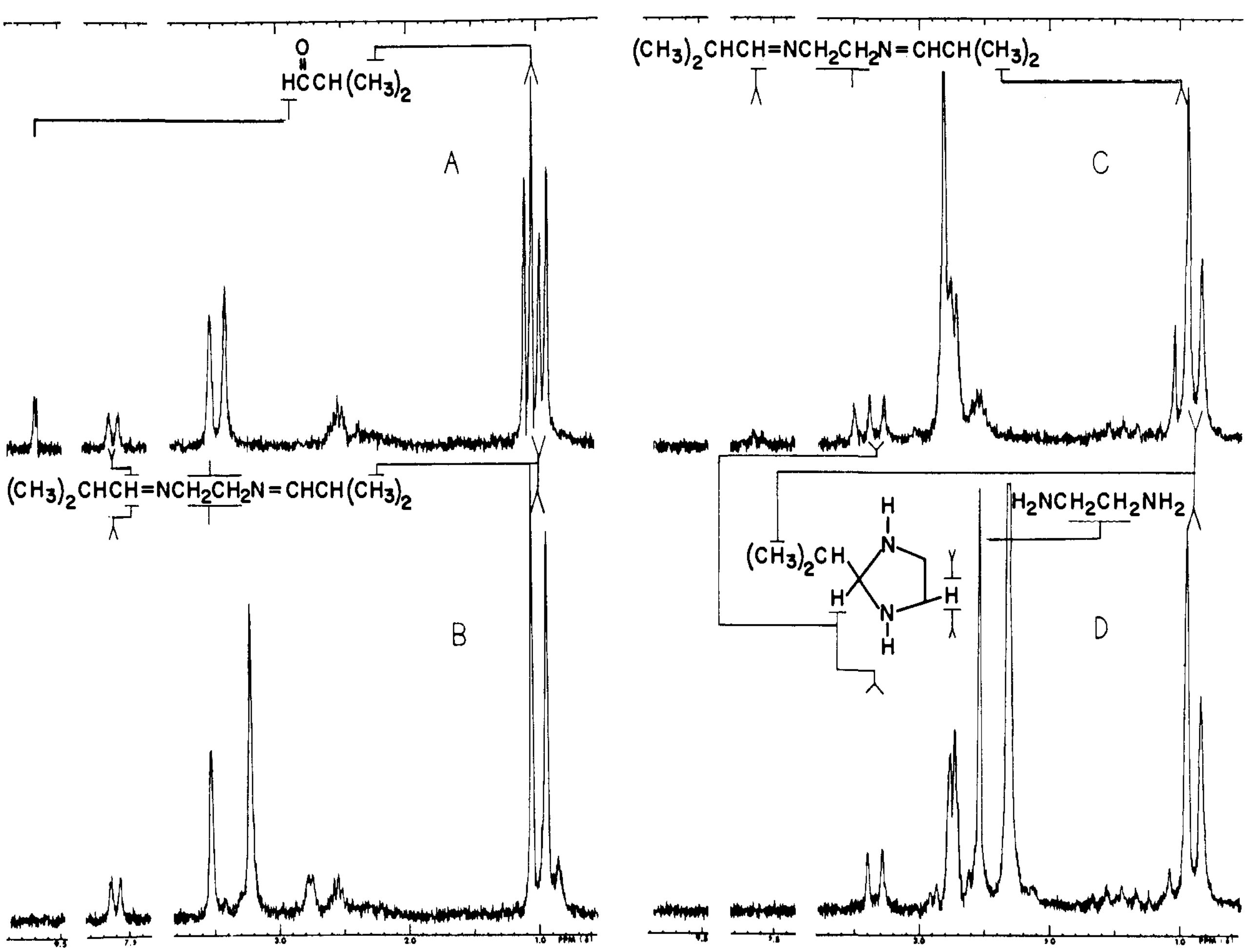

Figure 3. Proton magnetic resonance spectra of 0.5 mmol of isobutyraldehyde and (A) 0.15 mmol, (B) 0.30 mmol, (C) 0.45 mmol, and (D) 0.75 mmol of ethylenediamine in dimethyl-d_6 sulfoxide (60 MHz).

Table III. Coupling Constants and Chemical Shift Differences for the AA′BB′ Spectra of 1,3-Dimethyl-2-R-imidazolidines at 60 MHz

R (solvent)	Coupling constants,[a] Hz: $J_{AA'}$	J_{AB}	$J_{AB'}$	$J_{BB'}$	$\nu_0 \delta$	Av dev[b]
i-Pr (C_6H_6)	6.47 ± 0.08	−9.51 ± 0.05	6.17 ± 0.05	5.85 ± 0.08	35.21	0.068
i-Pr (CCl_4)	6.22 ± 0.23	−9.58 ± 0.16	5.96 ± 0.16	6.22 ± 0.23	29.02	0.164
t-Bu (C_6H_6)	5.67 ± 0.38	−10.23 ± 0.27	6.22 ± 0.27	6.25 ± 0.38	29.28	0.340
t-Bu (CCl_4)	5.89 ± 0.15	−9.97 ± 0.11	6.30 ± 0.11	5.90 ± 0.15	20.90	0.107

[a] Uncertainties listed are the errors as calculated by NMRIT: J. D. Swalen and C. A. Reilly, *J. Chem. Phys.*, 37, 21 (1962). [b] Average deviation of observed and calculated frequencies.

mental and calculated spectral intensities is presented in Figure 2. This spectrum shows all 24 transitions of the AA′BB′ system,[17] except for a pair of peaks hidden under the *N*-methyl absorbance. It should also be noted that unlike the dioxolanes, where $J_{AA'} = J_{BB'}$, the imidazolidines we examined showed additional splitting due to the inequality of the vicinal cis coupling constants. This effect, however, was observed in benzene solution but not in carbon tetrachloride and hence may be attributable to solvation factors. The values in the last three lines of Table III are less reliable because they are based on spectra in which, for various reasons, a significantly smaller number of separate peaks could be observed than in the case of the isopropyl derivative in benzene solution.

Ethylenediamine and Isobutyraldehyde in Dimethyl-d_6 Sulfoxide. The nmr spectra of various mixtures of isobutyraldehyde and ethylenediamine were examined in DMSO-d_6 (Figure 3). The isobutyraldehyde methyl doublet (J = 6 Hz) was at δ 1.05, the α-hydrogen multiplet at δ 2.5, and the aldehyde hydrogen doublet (J = 1 Hz) at δ 9.67 ppm in a solution of 0.5 mmol of aldehyde in 0.5 ml of DMSO-d_6. The intensities of these peaks were decreased by the addition of 0.15 mmol of ethylenediamine which was accompanied by the appearance of new doublets at δ 1.00 (J = 6 Hz) and 7.62 ppm (J = 5 Hz) and new singlets at δ 3.42 and 3.52 ppm (Figure 3A). We believe that these new peaks are due to formation of the diimine **1** and water. If the added di-

$$Me_2CHCH{=}NCH_2CH_2N{=}CHCHMe_2$$

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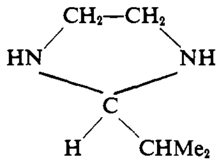
amine was transformed completely to diimine the molar ratio of diimine to aldehyde would be 3:4. This is in agreement with the 3:2 ratio of the area of the doublet at δ 1.00 ppm (attributed to the four methyl groups of the diimine) to that of the methyl doublet of the aldehyde. The doublet at δ 7.62 ppm, which has about the proper area, is attributed to the imine hydrogen atoms, partly by analogy to the imine prepared from isobutyraldehyde and *N*,*N*-dimethylethylenediamine, whose imine hydrogen atom absorbs at δ 7.44 ppm (neat, J = 4.0 Hz).[19] The singlet at δ 3.42 ppm was easily shown to arise from the water produced in the formation of the diimine. The singlet at δ 3.52 ppm is assigned to the methylene groups of the diimine. Because of its complexity, small height, and small changes in chemical shift, the peak for the methinyl hydrogen atoms revealed little about the nature of the reaction. With the addition of another 0.15 mmol of ethylenediamine the peaks attributed to isobutyraldehyde disappeared, the peak attributed to water grew and moved upfield to δ 3.20, a small poorly resolved doublet appeared at 2.74, and a small peak appeared at 0.85 ppm (Figure 3B). Still another 0.15 mmol of diamine decreased the intensity of the peaks attributed to the imine and caused the "water" peak to shift further upfield (Figure 3C). Some new peaks also appeared, and these grew when a final 0.30 mmol of ethylenediamine was added to give a solution that we believe consisted almost entirely of diamine, water, and 2-isopropylimidazolidine (**2**). The spectrum of this mixture (Figure 3D) shows the peaks due to **2** at the positions listed in Table II, the methylene peak of ethylenediamine at δ 2.53 ppm, and at δ 2.34 ppm the "water" peak, which also contains the rapidly exchanging amino protons of the diamine and **2**. The intermediate spectra can be explained in terms of the various species described. For example, the apparent triplet at δ 0.96 ppm in Figure 3C arises from the overlap of the methyl doublet of the diimine at δ 1.00 and the methyl doublet of **2** at 0.92 ppm.



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Discussion

The methods used to obtain the equilibrium constants listed in Table I should actually give the total equilibrium constant for the formation of products from one molecule of carbonyl compound and one diamine (in the case of K_0) or monoprotonated diamine (in the case of K_1). Aside from the imidazolidines and imidazolidinium ions the only other such products that might plausibly be expected to be formed in significant amounts under the reaction conditions are carbinolamines and, in the case of ethylenediamine, imines. From the regularities that have been observed in the formation of carbinolamines and similar adducts from carbonyl compounds,[20] and from the equilibrium constants for the formation of some such adducts from isobutyraldehyde[11,21–23] and acetone,[12] it seems unlikely that carbinolamine formation contributes more than about 1% to any of the total K values listed for isobutyraldehyde or more than about 5% to any of the total K values for acetone. If the equilibrium constant for the formation of imine from isobutyraldehyde and ethylenediamine is the same, per primary amino group, as for *N*,*N*-dimethylethylenediamine, imine formation contributes about 3% to the K_0 value listed in Table I. If the equilibrium constant for imine formation from monoprotonated ethylenediamine may be read from a plot of such constants for amines of the type RCH_2NH_2 *vs.* the pK values of the amines,[19] imine formation contributes less than 2% to K_1 for ethylenediamine and isobutyraldehyde. The conclusion that imine formation is almost negligible in this case is supported by the nmr study of ethylenediamine and isobutyraldehyde in DMSO-d_6, in which no peaks clearly attributable to the monoimine were ever seen.

Estimates of the preceding type may also be used to rationalize the formation of diimine from ethylenediamine in the presence of excess isobutyraldehyde in DMSO-d_6. For this purpose it is convenient to write the equilibrium constant for the formation of the monoimine in the dimensionless form, with the concentration of water included explicitly, as shown in eq 6.

$$K_{\text{im}} = \frac{[i\text{-PrCH}{=}\text{N(CH}_2)_2\text{NH}_2][\text{H}_2\text{O}]}{[i\text{-PrCHO}][\text{H}_2\text{N(CH}_2)_2\text{NH}_2]} \sim 3400 \qquad (6)$$

The estimate of the value shown has already been described. Assuming that the equilibrium constant for transformation of the monoimine to the diimine differs from K_{im} only by symmetry effects[24] leads to a value one-fourth as large (eq 7). Division of the product of K_{im}

$$K_{\text{im-diim}} = \frac{[(i\text{-PrCH}{=}\text{NCH}_2)_2][\text{H}_2\text{O}]}{[i\text{-PrCH}{=}\text{N(CH}_2)_2\text{NH}_2][i\text{-PrCHO}]} \sim 850 \qquad (7)$$

and $K_{\text{im-diim}}$ by K_0', the dimensionless equilibrium constant for the formation of imidazolidine from isobutyraldehyde and ethylenediamine (whose value is 55 × 2240), gives the equilibrium constant for transformation of imidazolidine (Imd) and aldehyde to diimine, as shown in eq 8. If this value, which refers to

$$\frac{K_{\text{im}}K_{\text{im-diim}}}{K_0'} = \frac{[(i\text{-PrCH}{=}\text{NCH}_2)_2][\text{H}_2\text{O}]}{[\text{Imd}][i\text{-PrCHO}]} \sim 23 \qquad (8)$$

aqueous solution, is about the same in DMSO-d_6, a moderately small excess of isobutyraldehyde should transform the imidazolidine fairly completely to diimine in moderately dilute solutions. The large concentration of water present in aqueous solution should make the formation of diimine relatively insignificant under the conditions used in the determination of K_0 and K_1 values. Complications due to the formation of diimine were further minimized by making measurements in the higher pH range only in the presence of excess diamine; excess aldehyde was used only in the lower pH range, where the reaction consisted largely of the formation of imidazolidinium ions.

If the equilibrium constant for the formation of any imine from acetone and a primary amine is about 0.3% as large as for the formation of imine from isobutyraldehyde and the same primary amine, as is the case with methylamine,[25,26] then imine formation contrib-

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(19) J. Hine, C. Y. Yeh, and F. C. Schmalstieg, *J. Org. Chem.*, **35**, 340 (1970).

(20) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968).

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(22) J. Hine, F. A. Via, J. K. Gotkis, and J. C. Craig, Jr., *J. Amer. Chem. Soc.*, **92**, 5186 (1970).

(23) J. Hine and F. A. Via, *ibid.*, **94**, 190 (1972).

(24) S. W. Benson, *ibid.*, **80**, 5151 (1958).

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utes 10–15% to the total K_0 for ethylenediamine and acetone.

If the formation of products other than imidazolidines and imidazolidinium ions (and water) may be neglected, the acidity constants of the imidazolidinium ions (K_{Imd}) may be calculated from the values of K_0 and K_1 in Table I and the acidity constants of the monoprotonated diamines (K_{a1}). Equation 9 follows from the

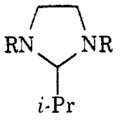
$$K_{\mathrm{Imd}} = K_0 K_{a1}/K_1 \qquad (9)$$

definitions of the four equilibrium constants it contains. The pK values of ethylenediamine, its N,N'-dimethyl and N,N'-diethyl derivatives, and the three imidazolidinium ions derived from these diamines and isobutyraldehyde are listed in Table IV. The pK values of the imidazolidinium ions, which cannot be determined by simple titration of the imidazolidines with aqueous acid because of rapid decomposition under such conditions, may be compared with values that may be estimated by a method based on that of Clark and Perrin.[27] Taking pyrrolidine (pK_a = 11.08 at 35°)[28] as a reference compound for 2-isopropylimidazolidine, the presence of an NHR group one carbon away should decrease pK by ~1.7,[27] an NHR group two carbons away (the same NHR, counting the other way around the ring) should decrease it by 0.8,[27] and the fact that there are two equivalent amino groups should increase it by 0.3. The estimated pK is 8.78, which is 0.37 below the value in Table IV. For 1,3-dimethyl-2-isopropylimidazolidine the reference compound was N-methylpyrrolidine (pK_a = 10.46 at 25°).[29] The same corrections plus a temperature correction[30] of 0.24 (to 35°) give an estimated pK of 7.92, and the generalization that N-methylation decreases pK values by 0.2 relative to other N-alkylations gives an estimate of 8.12 for the pK_a of the conjugate acid of 1,3-diethyl-2-isopropylimidazolidine. The average deviation of the estimated from the experimental pK values (−0.23) is believed to be small enough to support the interpretation we have given our results. The preceding method of estimating pK values may be combined with K_0 and K_1 values we have determined to yield the conclusion that the formation of the diprotonated forms of the imidazolidines we have studied from diamine and carbonyl compound would not occur to a significant extent in aqueous solution at any pH.

Table IV. Acidity Constants of the Conjugate Acids of Diamines and Imidazolidines in Water at 35° [a]

RNHCH$_2$CH$_2$NHR

D



E

R	D, pK_{a2}	D, pK_{a1}	E, pK_a
H[b]	6.58	9.68	9.15
Me	6.56 ± 0.02	9.73 ± 0.03	7.95
Et	6.74 ± 0.02	9.87 ± 0.05	8.42

[a] Uncertainties listed are standard deviations. [b] Values from ref 13.

Smaller values of K_0 and K_1 were obtained for N,N'-diethylethylenediamine than for N,N'-dimethylethylenediamine, probably largely because of steric effects. From examination of molecular models it is clear that in 1,3-diethyl-2-isopropylimidazolidine the ethyl groups have available considerably fewer relatively stable conformations than they do in N,N'-diethylethylenediamine. The equilibrium constants observed for ethylenediamine are larger than those for its N,N'-dimethyl derivative, but it is not clear how important steric effects are in this case. In comparing K_0 values it should be noted that there are four different pairs of hydrogen atoms that can be removed from the amino groups of ethylenediamine to give an imidazolidine but only one such pair in the case of N,N'-dimethylethylenediamine. When the two K_0 values for ethylenediamine in Table I are divided by four to allow for this statistical effect, the corrected values are each slightly smaller than the corresponding values for N,N'-dimethylethylenediamine. However, the corresponding correction in the K_1 values for the formation of 2-isopropylimidazolidinium ions, where there are three times as many paths to the unsubstituted ion as to its 1,3-dimethyl derivative, gives a corrected K_1 value that is still 17 times as large for the unsubstituted as for the dimethylated ion. The preceding anomaly or one like it is an automatic result of the fact that the ratio of K_1 values for ethylenediamine and N,N'-dimethylethylenediamine is considerably larger than the ratio of K_0 values. This, in turn, is an automatic result of the fact that the ratio K_0/K_1 for ethylenediamine is considerably larger than for N,N'-dimethylethylenediamine. Since eq 9 shows that K_0/K_1 is equal to K_{Imd}/K_{a1}, the ratio K_0/K_1 would be expected to be smaller for the transformation of a diprimary ethylenediamine derivative to a disecondary imidazolidine than for the transformation of a disecondary ethylenediamine derivative to an analogous ditertiary imidazolidine. Thus the anomaly would be accounted for by any satisfactory explanation for why simple secondary amines are more basic than either the corresponding primary or tertiary amines.[31]

There are other imidazolidines[32] and heterocyclic analogs of imidazolidines, such as 1,3-dioxolanes[16,33] and 1,3-dithiolanes,[34] that give AA′BB′ patterns in their nmr spectra. We have found no other case in which the AA′BB′ pattern of an imidazolidine has been analyzed to obtain the coupling constants. Among the AA′BB′ patterns in the nmr spectra of 1,3-dioxolanes and 1,3-dithiolanes that have been analyzed, we have found no case in which $J_{AA'}$ and $J_{BB'}$ are different, as they are in the case of 1,3-dimethyl-2-isopropylimidazolidine in benzene solution.

Experimental Section

Reagents. Reagent grade acetone and isobutyraldehyde were dried overnight over magnesium sulfate and distilled immediately

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[29] S. Searles, M. Tamres, F. Block, and L. A. Quarterman, *J. Amer. Chem. Soc.*, **78**, 4917 (1956).

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[34] L. A. Sternson, D. A. Coviello, and R. S. Egan, *ibid.*, **93**, 6529 (1971).

before use. The *N*,*N*′-dimethylethylenediamine and *N*,*N*′-diethylethylenediamine (Ames Laboratories) were purified by distillation from sodium hydroxide and then from sodium and also by recrystallization of their dihydrochlorides from aqueous methanol. Ethylenediamine containing 1.9% water (Fischer Scientific) was used without further purification.

Instrumentation. Ultraviolet absorbance measurements were made on Cary recording spectrophotometers Model 14 and 1605 using thermostated cell holders. Radiometer glass electrodes (202b or 202c), pH meters (Model 26c), and temperature control equipment were used for pH measurements (with exclusion of oxygen and carbon dioxide). Proton magnetic resonance spectra were determined on a Varian instrument, Model A-60.

Determinations of pK_a. Standard aqueous solutions of the diamines or their dihydrochlorides were titrated potentiometrically at 35.0 ± 0.1° with standard hydrochloric acid or sodium hydroxide. Each diamine was titrated six times. The data obtained, which referred to average ionic strengths ranging from 0.006 to 0.1 *N*, were treated as described previously.[35]

The values of f_0 and f_1 used in eq 5 were calculated from the concentration acidity constants at the appropriate ionic strength, which were calculated from the thermodynamic constants and the Davies equation.[14]

Synthesis of Imidazolidines. Equimolar amounts (60–250 mmol) of carbonyl compound and diamine were dissolved in 35–50 ml of pentane. In method A the solution was refluxed while attached to a Dean–Stark trap to remove the water. In method B the water was removed by allowing the solution to stand over anhydrous magnesium sulfate overnight. In both methods the reaction mixtures were then distilled under nitrogen to give the colorless liquids whose pmr spectra are described in Tables II and III and whose other properties are described in Table V. In the elemental analyses of these compounds, which are sensitive to water, oxygen, and carbon dioxide, the carbon content dropped on successive analysis. The first analyses were satisfactory for 1,3-dimethyl-2-isopropylimidazolidine and 1,2,2,3-tetramethylimidazolidine, but the carbon analyses of the other four new imidazolidines were low by as much as 4%. Nevertheless, we believe that the pmr spectra, method of synthesis, and other properties provide adequate support for the structures assigned.

Determination of Equilibrium Constants. In a typical run various volumes of 1.3427 *M* aqueous *N*,*N*′-dimethylethylenediamine were added to each of eight 50-ml volumetric flasks that already contained about 45 ml of water and 1.000 ml of 0.6826 *M* isobutyraldehyde–0.0013 *M* isobutyric acid and to one such flask containing only water. The small amount of water required to fill these flasks and one containing the aldehyde solution but no diamine caused the loss of very little of the volatile organic compounds. Absorbances of the solutions at 285 nm were measured in 10-cm quartz cells at 35° after constant values (±0.001) had been obtained for at least 5 min. The pH of each solution at 35° was measured. Since the absorbance of the diamine solution without aldehyde was −0.002, each absorbance was increased by 0.002 to correct for absorbance by the reference cell and by any absorption by the diamine solution. The extinction coefficient for isobutyraldehyde was taken as the value (14.59 M^{-1} cm^{-1}) obtained from the absorbance (1.991) of the aldehyde solution that contained no diamine. The results are listed in Table VI.

Table V. Properties of Imidizolidines Synthesized

Imidazolidine	Yield, %	Method	Bp, °C	Lit. bp, °C
1,3-Dimethyl-2-isopropyl-	72	A	83.5 (70 mm)	
1,3-Dimethyl-	63	A	109–110	110–112[a]
1,2,2,3-Tetramethyl-	49	A	134–136	
1,2,3-Trimethyl-	45	A	125–126	65–70 (110 mm)[b]
1,3-Dimethyl-2-*tert*-butyl-	44	B	168–170	
1,3-Dimethyl-2-ethyl-	65	B	136–138	
1,3-Diethyl-2-isopropyl-	60	B	184–185	
1,3-Diethyl-2,2-dimethyl-	59	B	174–176	

[a] C. H. Yoder and J. J. Zuckerman, *J. Amer. Chem. Soc.*, **88**, 4831 (1966). [b] W. J. Rabourn, U. S. Patent 3,236,835 (1966); *Chem. Abstr.*, **64**, 17554c (1966).

Table VI. Formation of 1,3-Dimethyl-2-isopropylimidazolidine from 0.01365 *M* Isobutyraldehyde

$(MeNHCH_2)_2$ 1.3427 *M*, ml	Absorbance	pH	K_{app}, M^{-1}
0.100	1.683	9.72	323
0.200	1.313	10.10	720
0.250	1.153	10.16	755
0.400	0.719	10.39	877
0.500	0.504	10.51	914
0.700	0.271	10.68	907
0.850	0.209	10.78	804
1.000	0.155	10.84	831

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