Analytical Procedures. Gas chromatographic analysis procedures were described previously.[7] Gaseous products were analyzed at room temperature on either a 2-ft Porapak Q or a 15-ft 30% Dowtherm on firebrick; C_5–C_8 hydrocarbons on a 12-ft SF 96 column at 80°; acetone, *t*-alcohols, and *t*-alkyl ethers on a 9-ft FFAP at 90°, a 12-ft didecyl phthalate column at 100°, a 12-ft SF 96 at 135°, and an 8-ft Carbowax 20M column at 40°. Mixtures of the cyclopropylcarbinyl, homoallyl and cyclobutyl ethers, and alcohols were analyzed on all four of the above columns. Carboxylic acids were analyzed on a 4-ft XF 1150 column at 200°. Methyl esters of cyclopropylacetic, cyclobutanecarboxylic, and allylacetic acids were analyzed on a 12-ft didecyl phthalate column at 140°.

Quantum Yield Measurements. Aliquots (3 ml) of a 0.3 *M* solution of perester were transferred from a standard flask to 10 × 1 cm tubes. The solutions were degassed with a slow stream of helium and the tubes tightly sealed with rubber septa. The solutions were photolyzed in a merry-go-round apparatus (F. Moses Co., Wilmington, Del.) which maintained an ambient temperature of 28° in the reaction cell. Aliquots (3 ml) of degassed solutions of the actinometer (either chloroacetic acid or potassium ferrioxalate) were photolyzed at the same time as the perester solutions. The reaction was allowed to proceed to about 5% conversion (approximately 30 min) and the yield of carbon dioxide was determined by gas chromatography. A value of 0.34 was used for the quantum yield of chloride ion from chloroacetic acid[70] and a value of 1.25 for the quantum yield of ferrous ion from potassium ferrioxalate.[71] There was negligible dark reaction for the peresters under these conditions. A helical low-pressure mercury resonance lamp[72] was used as the light source and the quartz tubes were covered with aluminum foil except for the window being irradiated. The relative values of the quantum yields listed in Table XIII are accurate to within at least 10%, but the absolute values may be less reliable.

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(72) Mr. Charles Shott, Department of Chemistry, University of Alberta, Edmonton.

Kinetics of the Formation of N-Isobutylidenemethylamine from Isobutyraldehyde and Methylamine in Aqueous Solution[1]

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Abstract: Stopped-flow spectrophotometric measurements on the reaction of isobutyraldehyde with methylamine in water at 35° over the pH range 10.1–11.5 gave a value of 8.5 ± 0.5 M^{-1} for K_{ca}, the equilibrium constant for addition of the amine to the aldehyde, and a value of 6.2 ± 0.7 sec^{-1} for k_e, the rate constant for dehydration of the carbinolamine to N-isobutylidenemethylamine. Kinetic studies of methylammonium chloride catalysis of the oximation of isobutyraldehyde at pH 8.5–9.8 gave values of k_eK_{ca} in agreement with the stopped-flow measurement, but at pH 7.6 larger values were obtained, suggesting acid catalysis of the dehydration of the carbinolamine. The equilibrium constant for the addition of hydroxylamine to isobutyraldehyde was found to be 105 ± 11 M^{-1}, and the rate constant for dehydration of the adduct to give oxime fit the equation $k_d = (6.5 \times 10^5[\mathrm{H^+}] + 3.2 \times 10^{-12}/[\mathrm{H^+}] + 4.6 \times 10^{-3})\ \mathrm{sec^{-1}}$. A kinetic study of the hydration of isobutyraldehyde in the presence of N-methylmorpholine buffers showed that the reaction was fast enough that the hydration–dehydration equilibrium could be treated as continually established throughout the studies of the reaction of isobutyraldehyde. Structural effects on equilibrium constants for addition to isobutyraldehyde are discussed.

The kinetics and mechanism of the formation and hydrolysis of a number of imines derived from aromatic carbonyl compounds and/or aromatic amines have been studied previously. Many of these and similar studies of oximes, hydrazones, semicarbazones, etc., have been reviewed by Jencks.[2] Several studies of imines derived from acetone[3,4] and from aliphatic amino acids and keto acids[5] have been carried out. We are aware of no previous studies of the kinetics of the formation or hydrolysis of an unsubstituted aliphatic aldimine, but the studies of Stewart and coworkers on formocholine[6] and on iminium ions[7] are closely related. Such a study on an aldimine was needed in connection with studies of the deuterium exchange of isobutyraldehyde-2-*d* in the presence of primary amine salts.[8] These amine salts appear to catalyze the exchange by forming iminium ions that lose deuterium to some base in the rate-controlling step of the reaction (eq 1). In

$$\mathrm{Me_2CDCHO} + \mathrm{RNH_3^+} \rightleftharpoons \mathrm{Me_2CDCH{=}NHR^+} \rightleftharpoons \mathrm{Me_2CDCH{=}NR} + \mathrm{H^+}$$

$$\mathrm{Me_2CDCH{=}NHR^+} + \mathrm{B} \longrightarrow \mathrm{Me_2C{=}CHNHR} + \mathrm{BD^+} \quad (1)$$

order to understand this reaction more completely, in particular to learn under what conditions, if any, a change in the rate-controlling step may be expected, a knowledge of the kinetics and mechanisms of the imine-forming reaction is necessary. We have there-

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(5) D. L. Leussing and C. K. Stanfield, *ibid.*, **88**, 5726 (1966); D. L. Leussing and L. Anderson, *ibid.*, **91**, 4698 (1969).

(6) T. D. Stewart and H. P. Kung, *ibid.*, **55**, 4813 (1933).

(7) H. G. Reiber and T. D. Stewart, *ibid.*, **62**, 3026 (1940).

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fore studied the formation of the imine derived from methylamine, the primary amine used most often in previous studies of the deuterium exchange reaction. In an accompanying report the kinetics of the hydrolysis of this imine are described.[9]

Equilibrium measurements have shown that in the presence of concentrations of isobutyraldehyde and methylamine above about 0.02 *M* the formation of imine proceeds past 50% completion.[10] Preliminary measurements showed that the reaction was too fast to study by the methods then available to us. The rate of formation of imine may be decreased by the addition of acid to transform the amine to its unreactive conjugate acid, but the extent of reaction at equilibrium is also decreased, and when enough acid is added to protonate all the methylamine the amount of aldehyde transformed to imine at equilibrium is too small to detect. However, it seemed possible to circumvent this difficulty by use of a kinetic method based on the observation of Cordes and Jencks that imine formation is the rate-controlling step in the aniline-catalyzed formation of semicarbazones from various carbonyl compounds.[11] Such a method was used by Williams and Bender, who determined the rate of formation of the N-methylimines of benzaldehyde and acetone by measuring the extent to which methylamine catalyzed the formation of benzaldoxime and acetoxime.[4] Therefore we measured the rate of formation of imine from isobutyraldehyde and methylamine by capturing the imine with hydroxylamine as it was formed. Later, having obtained a stopped-flow spectrophotometer, we studied the kinetics of imine formation in more basic solutions by direct measurements.

Results

Kinetics of Hydration of Isobutyraldehyde. Isobutyraldehyde exists in the form of its hydrate to an extent of 30% at equilibrium in aqueous solution at 35°.[12] We needed to know something about the rate at which this equilibrium is established under the conditions used in our studies of imine formation in order to understand the mechanism of imine formation better. The catalytic constant for the hydrogen ion catalyzed hydration reaction had been determined,[13] but no measurements in neutral or basic solutions had been reported.

The hydration reaction was studied by injecting isobutyraldehyde into a buffer solution and making spectrophotometric measurements of the rate of decrease of absorbance that results from the hydration of 30% of the added aldehyde. First-order rate constants were calculated from a plot of log $(A - A_\infty)$ *vs.* time, where A and A_∞ are the absorbances at the given time and at equilibrium, respectively. The reactions were so fast that the precision of the rate constants obtained is not very high, but we tried to compensate somewhat for this by making a rather large number of runs. The results obtained using N-methylmorpholine buffers are listed in Table I.[14] It was assumed that the hydration of isobutyraldehyde, like that of other aldehydes,[15] is subject to general acid and base catalysis so that the first-order rate constant may be expressed as shown in eq 2 where Nmm is N-methylmorpholine.

Table I. Kinetics of Hydration of Isobutyraldehyde in the Presence of Aqueous N-Methylmorpholine Buffers at 35° [a]

[Nmm], *M*	[NmmH$^+$], *M*	pH	100k, sec^{-1}	No. of runs
0.00082	0.0071	6.49	1.19 ± 0.25	5
0.00204	0.0177	6.49	1.41 ± 0.04	2
0.0102	0.088	6.49	2.64 ± 0.45	10
0.0060	0.0138	7.04	2.11 ± 0.77	5
0.0120	0.0275	7.04	2.88 ± 0.13	5
0.0301	0.069	7.04	4.60 ± 0.25	9
0.0075	0.0118	7.18	2.73 ± 0.09	5
0.0150	0.0236	7.18	3.61 ± 0.25	5
0.0374	0.059	7.18	5.42 ± 0.12	5
0.0104	0.0098	7.44	3.89 ± 0.10	4
0.0208	0.0197	7.44	4.87 ± 0.41	5
0.052	0.049	7.44	6.98 ± 0.36	8
0.0138	0.0059	7.79	6.81 ± 0.27	4
0.0276	0.0118	7.79	8.13 ± 0.70	5
0.069	0.0295	7.79	10.73 ± 1.06	5

[a] Sodium chloride present as necessary to bring the ionic strength to 0.10 *M*

$$k = k_0 + k_{\mathrm{H}}[\mathrm{H}^+] + k_{\mathrm{Nmm}}[\mathrm{Nmm}] + k_{\mathrm{Nmmh}}[\mathrm{NmmH}^+] + k_{\mathrm{OH}}[\mathrm{OH}^-] \quad (2)$$

The values listed in Table I are the rate constants for approach to equilibrium and hence the sums of the rate constants for the forward and reverse reactions. From the sum of the hydrogen ion catalytic constants for the forward and reverse reactions (1.4×10^3 M^{-3} sec^{-1})[13] it may be calculated that hydrogen ion catalysis never contributes as much as 4% to any of the total first-order rate constants listed in Table I. Since the present data would therefore be of no use in obtaining an independent determination of k_{H}, we used the experimental values of k and the value of k_{H} determined previously[13] in a least-squares[16] calculation of the values of the other constants in eq 2. The resultant values were multiplied by 0.30 and 0.70 to give the catalytic constants for the hydration and dehydration reactions, respectively, and these catalytic constants are listed in Table II.

Table II. Catalytic Constants for the Hydration of Isobutyraldehyde in Aqueous Solution at 35°

Constant	k_{cat} (hydration)	k_{cat} (dehydration)
k_0	2.3×10^{-3} sec^{-1}	5.4×10^{-3} sec^{-1}
k_{H}[a]	4.4×10^{2} M^{-1} sec^{-1}	1.0×10^{3} M^{-1} sec^{-1}
k_{Nmm}	0.22 M^{-1} sec^{-1}	0.51 M^{-1} sec^{-1}
k_{Nmmh}	3.0×10^{-2} M^{-1} sec^{-1}	6.9×10^{-2} M^{-1} sec^{-1}
k_{OH}	9.6×10^{3} M^{-1} sec^{-1}	2.2×10^{4} M^{-1} sec^{-1}

[a] Values from ref 13.

Kinetics of the Methylamine-Catalyzed Oximation of Isobutyraldehyde.[17] The determination of the rate of

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(14) All the ± figures for rate and equilibrium constants given in this paper are standard deviations.

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(16) In this least-squares treatment, it was not the sum of the squares of the deviations but the sum of the squares of the fractional deviations $(|k_{\mathrm{obsd}} - k_{\mathrm{calcd}}|k_{\mathrm{obsd}})$ that was minimized.

(17) Most of the material in this section is described in more detail in the M.S. Thesis of J. K. Gotkis, The Ohio State University, Columbus, Ohio, 1969. Considerable amounts of recalculation have been carried out, however, largely on the basis of a subsequent determination of the value of K_{ad}.

imine formation from isobutyraldehyde and methylamine *via* measurements on methylamine catalysis of the reaction of hydroxylamine with isobutyraldehyde to give isobutyraldoxime is based on the following reaction mechanism. Written below various of the species involved is the abbreviation that will be used for that species.

$$\underset{\text{Al}}{i\text{-PrCHO}} + \text{H}_2\text{O} \overset{K_h}{\rightleftharpoons} \underset{\text{Ah}}{i\text{-PrCH(OH)}_2}$$

$$i\text{-PrCHO} + \underset{\text{Hx}}{\text{H}_2\text{NOH}} \overset{K_{ad}}{\rightleftharpoons} \underset{\text{Ad}}{i\text{-PrCH(OH)NHOH}}$$

$$i\text{-PrCHO} + \underset{\text{Am}}{\text{MeNH}_2} \overset{K_{ca}}{\rightleftharpoons} \underset{\text{Ca}}{i\text{-PrCH(OH)NHMe}}$$

$$i\text{-PrCH(OH)NHMe} \underset{k_{-c}}{\overset{k_c}{\rightleftharpoons}} \underset{\text{Im}}{i\text{-PrCH{=}NMe}} + \text{H}_2\text{O}$$

$$i\text{-PrCH(OH)NHOH} \xrightarrow{k_d} \underset{\text{Ox}}{i\text{-PrCH{=}NOH}} + \text{H}_2\text{O}$$

$$i\text{-PrCH{=}NMe} + \text{H}_2\text{NOH} \xrightarrow{k_{hx}} i\text{-PrCH{=}NOH}$$

In the reactions in which water appears, its essentially constant concentration will be absorbed into the appropriate rate or equilibrium constants. The formation of oxime is written as irreversible because the transformation of aldehyde is believed to be essentially complete under the conditions used. The equilibrium constant for the formation of acetoxime from acetone and hydroxylamine at 19° in aqueous solution[18,19] is $10^6\ M^{-1}$. The value for isobutyraldehyde would be expected to be higher in view of the fact that the equilibrium constant for the reaction of methylamine with isobutyraldehyde to give the N-methylimine[10] is about 400 times as large as the equilibrium constant for the corresponding reaction of methylamine with acetone.[4] However, even if the equilibrium constant for the formation of isobutyraldoxime is only $10^6\ M^{-1}$, the transformation of aldehyde to oxime will be about 99.99% complete in the presence of the 0.009 *M* excess of hydroxylamine present in most runs. The equilibrium constant K_{ca} for the addition of methylamine to isobutyraldehyde, whose determination will be described later, is so small that the concentration of the carbinolamine is negligible compared to that of the aldehyde under all the conditions under which oximation was studied. The equilibria governed by K_{ad} and K_{ca} are established quite rapidly relative to the oximation reactions being studied. Equilibrium in the hydration of the aldehyde was also assumed to be established rapidly relative to the reaction being studied, but this assumption may not be warranted in certain runs that will be referred to later.

If k_{-c} is small compared to $k_{hx}[\text{Hx}]$, as will be shown subsequently, the rate of formation of oxime may be expressed

$$\frac{d[\text{Ox}]}{dt} = (k_cK_{ca}[\text{Am}] + k_dK_{ad}[\text{Hx}])[\text{Al}] \qquad (3)$$

The observed first-order rate constants were calculated from a plot of log $(A_\infty - A)$, where *A* is the absorbance at 2200 Å, largely due to the oxime, *vs.* time. This procedure is equivalent to using eq 4.

$$\frac{d[\text{Ox}]}{dt} = k_{obsd}([\text{Ox}]_\infty - [\text{Ox}]) \qquad (4)$$

If $[\text{Al}]_0$ is defined as the total concentration of aldehyde originally added, then eq 5 follows from the fact that the reaction goes to completion and eq 6 follows from the fact that

$$[\text{Al}]_0 = [\text{Ox}]_\infty \qquad (5)$$

concentrations of carbinolamine and imine are always small compared to $[\text{RCHO}]_0$. Combination of eq 3–6

$$[\text{Al}]_0 = [\text{Al}] + [\text{Ah}] + [\text{Ad}] + [\text{Ox}] \qquad (6)$$

gives eq 7. Rearrangement and substitution of equilibrium constants gives eq 8.

$$k_{obsd} = \frac{(k_cK_{ca}[\text{Am}] + k_dK_{ad}[\text{Hx}])[\text{Al}]}{[\text{Al}] + [\text{Ah}] + [\text{Ad}]} \qquad (7)$$

$$k_{obsd} = \frac{k_cK_{ca}[\text{Am}] + k_dK_{ad}[\text{Hx}]}{1 + K_h + K_{ad}[\text{Hx}]} \qquad (8)$$

The observed rate constants for the formation of oxime may be seen to consist of two terms, the k_cK_{ca} term for reaction *via* imine and the k_dK_{ad} term for direct reaction. In order to learn the magnitude of the direct term, the reaction was studied in the absence of methylamine. Spectrophotometric measurements on the appearance of the oxime between pH 7 and 10 were made, usually in the presence of buffers. The initial concentrations of hydroxylamine and aldehyde used were about 0.01 and 0.001 *M*, respectively. Because of the excess of hydroxylamine present, the first-order rate equation used is a good approximation. The observed rate constants are listed in Table III.

Table III. Kinetics of the Reaction of Isobutyraldehyde with Hydroxylamine in Water at 35° [a]

Buffer base	$[\text{B}] + [\text{BH}^+]$, *M*	pH	10^3k_{obsd}, sec^{-1}	10^3k_d
None		7.08	17.2	43.5
None		7.22	18.4	46.2
N-Methylmorpholine	0.0720	7.23	17.9	44.9
N-Methylmorpholine	0.0364	7.28	16.6	41.7
N-Methylmorpholine	0.0235	7.48	12.9	32.1
N-Methylmorpholine	0.0470	7.53	12.5	30.9
None		7.54	9.6	22.7
N-Methylmorpholine	0.0470	7.69	8.7	21.6
N-Methylmorpholine	0.0720	7.71	6.8	16.8
N-Methylpyrrolidine	0.0370	7.85	5.2	12.8
Trimethylamine	0.0390	8.00	5.7	14.1
$\text{MeN(CH}_2\text{CH}_2\text{OH)}_2$	0.0420	8.19	4.7	11.6
Trimethylamine	0.0390	8.32	3.0	7.3
Trimethylamine	0.0390	8.60	3.4	8.5
Trimethylamine	0.0390	8.75	2.8	6.8
Trimethylamine	0.0390	8.76	2.7	6.5
Trimethylamine	0.0390	9.02	3.5	8.6
N-Methylpyrrolidine	0.0370	9.12	3.7	9.1
Trimethylamine	0.0390	9.22	4.1	10.0
Trimethylamine	0.0390	9.38	5.6	13.8
Trimethylamine	0.0390	9.38	6.3	15.4
N-Methylpyrrolidine	0.0370	9.67	7.7	18.9
N-Methylpyrrolidine	0.0370	9.80	9.7	23.9

[a] Initial concentrations of hydroxylamine and isobutyraldehyde 9.9×10^{-3} and $9.5 \times 10^{-4}\ M$, respectively. Sodium chloride added to give an ionic strength of 0.2 *M*.

Stopped-flow spectrophotometric measurements were used to determine the value of K_{ad} ($105 \pm 11\ M^{-1}$).[14] From this value and the average concentration of

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[18] A. Ölander, *Z. Phys. Chem.*, **129**, 1 (1927).

[19] J. B. Conant and P. D. Bartlett, *J. Amer. Chem. Soc.*, **54**, 2881 (1932).

hydroxylamine present during the kinetic runs (9.3 × 10^{-3} M minus the concentration of hydroxylammonium ions), values of k_d were calculated using eq 8. These experimental values of k_d are also listed in Table III. Partly on the basis of previous studies,[2,4] it was assumed that k_d is the sum of three terms, one due to hydrogen ion catalysis, one due to hydroxide ion catalysis, and one due to an uncatalyzed reaction. Application of

$$k_d = k_H[H^+] + k_{OH}K_w(1/[H^+]) + k_0 \qquad (9)$$

the method of least squares[16] to the values of k_d in Table III gave the following values for the constants in eq 9. From these values, log k_d may be expressed as

$$k_H = 6.5 \times 10^5$$

$$k_{OH}K_w = 3.2 \times 10^{-12}$$

$$k_0 = 4.6 \times 10^{-3}$$

a function of pH, as shown by the solid line in Figure 1, in which the data in Table III are also plotted. Comparison of runs made at differing buffer concentrations reveals no significant correlation between the amount or direction of deviation of the experimental points from the line in Figure 1 and the concentration of buffer used. Thus, in the oximation of isobutyraldehyde, like that of the other aldehydes and ketones that have been studied,[2] general acid or base catalysis does not appear to be important. In the first two runs in Table III, the rate constant for attainment of the aldehyde hydration–dehydration equilibrium (neglecting catalysis by hydroxylamine) is comparable to k_{obsd}. This is a possible explanation for the fact that the value of k_d for the first run deviates more than any other point from the line in Figure 1.

With a value of k_d it was possible to use eq 8, correct for the rate of direct formation of oxime, and learn the rate of oximation *via* imine formation. First, however, it was necessary to establish the validity of the assumption that k_{-c} is small compared to $k_{hx}[Hx]$ used in deriving eq 8. The kinetics of the formation of isobutyraldoxime were studied in the presence of constant concentrations of isobutyraldehyde and essentially constant concentrations of methylamine and varying concentrations of hydroxylamine at pH 9.43 ± 0.07 with the results shown in Table IV. From these results, the known values of K_h, k_d, and K_{ad}, and the average concentrations of hydroxylamine and methylamine present during the run, the values of k_cK_{ca} also shown were calculated. These calculations are of reduced reliability for the first three runs, in which there is not a very large excess of hydroxylamine over aldehyde. The values of k_cK_{ca} obtained at hydroxylamine concentrations above 0.003 M are probably within the experimental uncertainty of each other. This uncertainty is rather large because the reactions were rather fast, but the data seem to ensure that at the higher concentrations used the hydroxylamine was capturing almost all of the intermediate imine. From a more detailed treatment of the data it may be estimated that $k_{hx} \geq 10^4k_{-c}$ M^{-1} under the conditions of Table IV.

Table IV. Effect of Changing Hydroxylamine Concentration on Rate of Formation of Isobutyraldoxime in Water at 35° [a]

pH	$10^3[H_2NOH]_0$, M	10^3k_{obsd}, sec^{-1}	k_cK_{ca}, sec^{-1}
9.41	1.00	91	28
9.50	1.00	108	27
9.42	3.00	104	35
9.42	5.00	116	43
9.36	6.00	103	45
9.44	7.99	141	58
9.39	8.00	94	42
9.41	8.00	94	41
9.43	10.00	131	60

[a] $[RCHO]_0 = 9.5 \times 10^{-4}$ M; $[MeNH_2] + [MeNH_3^+] = 0.050$ M; sodium chloride added to bring the ionic strength to 0.20 M.

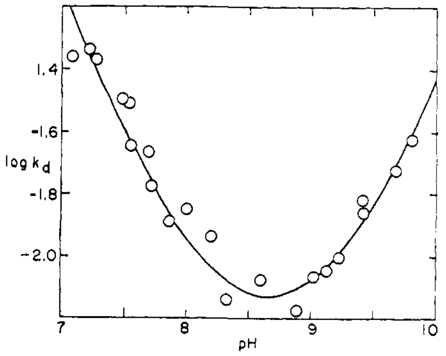

Figure 1. Experimental values of log k_d and curve calculated from eq 9.

A number of runs were made in methylamine–methylamine hydrochloride buffers with a total buffer concentration of 0.0503 M. Only in solutions more acidic than pH 10 was the reaction slow enough to follow. Rate constants and values of k_cK_{ca} calculated from eq 8 are listed in Table V.

Table V. Oximation of Isobutyraldehyde in the Presence of Aqueous Methylamine Buffers at 35° [a]

pH	10^3k_{obsd}, sec^{-1}	k_cK_{ca}, sec^{-1}
7.62	13.3	140
7.62	14.3	167
7.62	14.5	173
8.48	14.6	45
8.48	13.8	41
8.48	13.9	42
8.57	20.3	54
8.57	17.1	44
8.57	18.9	50
8.81	20.1	31
8.81	31.0	51
8.96	33.0	39
8.96	33.4	40
8.96	33.6	40
9.34	75.6	41
9.34	66.6	35
9.43	133	60
9.43	131	59
9.82	287	62

[a] $[MeNH_2] + [MeNH_3^+] = 0.0503$; $[H_2NOH]_0 = 9.9 \times 10^{-3}$ M; $[RCHO]_0 = 9.5 \times 10^{-4}$ M; sodium chloride added to bring the ionic strength to 0.20 M.

Stopped-Flow Measurements on the Reaction of Isobutyraldehyde with Methylamine.[20] Above pH 10 equilibrium in the transformation of isobutyraldehyde to its N-methylimine lies far enough to the right to make

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[20] Abstracted largely from the M.S. Thesis of F. A. Via, The Ohio State University, Columbus, Ohio, 1968.

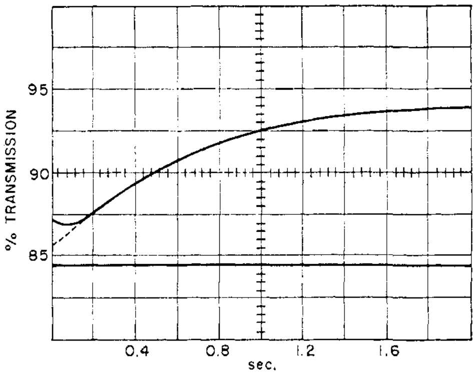

Figure 2. Stopped-flow measurements at 2850 Å, mixing 0.006 *M* isobutyraldehyde and 0.0416 *M* methylamine.

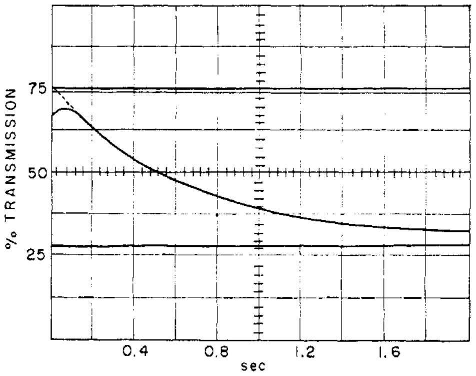

Figure 3. Stopped-flow measurements at 2265 Å, mixing 0.006 *M* isobutyraldehyde and 0.0416 *M* methylamine.

it convenient to study the reaction directly. This was done by stopped-flow spectrophotometric measurements, mostly at 2850 Å, the absorption maximum of the aldehyde. A sample oscilloscope trace is shown in Figure 2 for the case in which one of the mixing syringes contained 0.006 *M* total aldehyde (free and hydrated) and the other contained 0.0416 *M* total methylamine (free and ionized). Because of the rapid initial decrease in transmittance observed and because of experience obtained in studying other reactions, it was assumed that the transmittance values obtained much before 0.1 sec are not reliable. Therefore that part of the experimental trace obtained after about 0.1 sec was extrapolated to zero time, as shown by the dotted line. Both the experimental initial transmittance and the extrapolated initial transmittance were considerably higher than the transmittance observed when pure water was used instead of the methylamine solution. Hence it appears that a significant fraction of the aldehyde disappears by a reaction that is too fast to measure by stopped-flow spectrophotometry. Figure 3 shows the results of measurements on the same solutions at 2265 Å, the absorption maximum for N-isobutylidenemethylamine. The extrapolated initial transmittance when methylamine and isobutyraldehyde are mixed is the same as when pure water is used instead of the aldehyde solution (which absorbs negligibly at this wavelength). Thus the initial rapid reaction of some of the aldehyde does not yield imine. Instead, it was assumed that it yielded the carbinolamine *i*-PrCH(OH)-NHMe. This assumption was supported by the fact that values of K_{ca} calculated from extrapolated initial transmittances and transmittances obtained when pure water was used instead of an amine solution averaged 8.5 ± 0.5 M^{-1} when the concentrations of amine, aldehyde, and hydroxide ions present in the solution were each varied by about threefold or more. In making these calculations, it was assumed that the hydration–dehydration equilibrium of isobutyraldehyde was also established too rapidly to measure under the conditions used. Calculations based on the catalytic constants for hydration show that in the least basic solutions studied (pH 10.15) the half-time for establishment of this equilibrium could have been[21] as long as 0.04 sec. Thus hydration might be slow enough to affect the results obtained at this pH slightly, but results at higher pH should be unaffected.

The initial very rapid disappearance of some of the aldehyde that we have attributed to the formation of carbinolamine is followed by a slower disappearance of considerably more aldehyde in a reaction with a half-life of several tenths of a second. In view of the results shown in Figure 3 and other evidence, this slower reaction is taken to be imine formation. The equilibrium constant for the formation of 1:1 adducts from isobutyraldehyde and methylamine has been reported previously.[10] Although it was recognized that both imine and carbinolamine were being formed, it was argued that the imine was the predominant product, and the constants were written in terms of the formation of imine and water. If the water concentration (about 55 *M*) is absorbed into the equilibrium constant, the reported value of 4950 ± 220 becomes 90 ± 4 M^{-1}. Since this constant represents the formation of both carbinolamine and imine and since the concentrations of free and hydrated aldehyde were combined in its calculation, we may write eq 10. The measurements made

$$\frac{[\mathrm{Ca}] + [\mathrm{Im}]}{([\mathrm{Al}] + [\mathrm{Ah}])[\mathrm{Am}]} = 90 \pm 4\ M^{-1} \qquad (10)$$

in the stopped-flow kinetic studies gave the value 89 ± 3 M^{-1} for this constant. By use of the value of K_{ca} that we have determined and the value of K_h determined previously, this constant may be dissected to give K_{im}.[14]

$$K_{im} = \frac{[\mathrm{Im}]}{[\mathrm{Al}][\mathrm{Am}]} = 118 \pm 5\ M^{-1}$$

In terms of the mechanism for imine formation written in connection with the treatment of the kinetic study of oxime formation, we may note that the aldehyde initially added is always present as the free aldehyde, the aldehyde hydrate, the carbinolamine, or the imine. (The solutions used were too basic for any significant fraction of the carbinolamine or imine to be protonated.) It follows that the total rate of disappearance of these four species must always be zero. Since the

$$\frac{d[\mathrm{Al}]}{dt} + \frac{d[\mathrm{Ah}]}{dt} + \frac{d[\mathrm{Ca}]}{dt} + \frac{d[\mathrm{Im}]}{dt} = 0 \qquad (11)$$

change in the concentration of methylammonium ions that takes place in a given run is always small compared to concentrations of methylamine and aldehyde used, and since the aldehyde and amine react with 1:1 stoichiometry whether they form carbinolamine or imine,

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[21] The catalysis constant for methylamine does not appear to have been determined but was estimated.

it follows that the difference in concentration of amine and free-plus-hydrated aldehyde is a constant, which we shall call δ. The concentration of carbinolamine,

$$\delta = [\mathrm{Am}] - [\mathrm{Al}] - [\mathrm{Ah}] \qquad (12)$$

which is in equilibrium with aldehyde and imine, may be expressed in terms of this constant as shown in eq 13.

$$[\mathrm{Ca}] = K_{\mathrm{ca}}(1 + K_{\mathrm{h}})[\mathrm{Al}]^2 + K_{\mathrm{ca}}\delta[\mathrm{Al}] \qquad (13)$$

The rate of formation of imine may be expressed (eq 14)

$$\frac{\mathrm{d}[\mathrm{Im}]}{\mathrm{d}t} = k_{\mathrm{c}}[\mathrm{Ca}] - k_{-\mathrm{c}}[\mathrm{Im}] \qquad (14)$$

in terms of the mechanism written earlier. Eq 15,

$$[\mathrm{Al}]_0 = [\mathrm{Al}] + [\mathrm{Ah}] + [\mathrm{Ca}] + [\mathrm{Im}] \qquad (15)$$

which defines $[\mathrm{Al}]_0$, may be combined with the relationship between free aldehyde and aldehyde hydrate concentrations, solved for imine concentration, and substituted into eq 14 to give a relation that may be combined with eq 13 and the expression for $k_{-\mathrm{c}}$ in terms of k_{c}, K_{ca}, and K_{im} to give eq 16. Implicit differentiation

$$\frac{\mathrm{d}[\mathrm{Im}]}{\mathrm{d}t} = k_{\mathrm{c}}K_{\mathrm{ca}}(1 + K_{\mathrm{h}})[\mathrm{Al}]^2 + k_{\mathrm{c}}K_{\mathrm{ca}}\delta[\mathrm{Al}] - \frac{k_{\mathrm{c}}K_{\mathrm{ca}}}{K_{\mathrm{im}}}\{[\mathrm{Al}]_0 - (1 + K_{\mathrm{h}})[\mathrm{Al}] - K_{\mathrm{ca}}(1 + K_{\mathrm{h}})[\mathrm{Al}]^2 - K_{\mathrm{ca}}\delta[\mathrm{Al}]\} \qquad (16)$$

of the relationship between free and hydrated aldehyde concentrations gives eq 17. Substitution of eq 16, 17,

$$\frac{\mathrm{d}[\mathrm{Ah}]}{\mathrm{d}t} = K_{\mathrm{h}}\frac{\mathrm{d}[\mathrm{Al}]}{\mathrm{d}t} \qquad (17)$$

and the result of implicit differentiation of eq 13 into eq 11 gives eq 18. A more useful variable than the

$$\frac{\mathrm{d}[\mathrm{Al}]}{\mathrm{d}t} = \frac{k_{\mathrm{c}}K_{\mathrm{ca}}\{[\mathrm{Al}]_0 - (K_{\mathrm{im}} + K_{\mathrm{ca}}) \times ((1 + K_{\mathrm{h}})[\mathrm{Al}]^2 + \delta[\mathrm{Al}]) - (1 + K_{\mathrm{h}})[\mathrm{Al}]\}}{K_{\mathrm{im}}\{(1 + K_{\mathrm{h}}) + K_{\mathrm{ca}}(2(1 + K_{\mathrm{h}})[\mathrm{Al}] + \delta)\}} \qquad (18)$$

aldehyde concentration may be defined as the excess of aldehyde over that present at equilibrium and denoted a. To obtain an expression for $[\mathrm{Al}]_{\mathrm{e}}$, we note that at

$$a = [\mathrm{Al}] - [\mathrm{Al}]_{\mathrm{e}} \qquad (19)$$

equilibrium the net rate of formation of aldehyde must be zero, and hence the numerator of the right-hand side of eq 18 must be zero. Equation 20 may be solved for $[\mathrm{Al}]_{\mathrm{e}}$

$$(K_{\mathrm{im}} + K_{\mathrm{ca}})(1 + K_{\mathrm{h}})[\mathrm{Al}]_{\mathrm{e}}^2 + \{\delta(K_{\mathrm{im}} + K_{\mathrm{ca}}) + 1 + K_{\mathrm{h}}\}[\mathrm{Al}]_{\mathrm{e}} - [\mathrm{Al}]_0 = 0 \qquad (20)$$

$$[\mathrm{Al}]_{\mathrm{e}} = \frac{\alpha - \delta(K_{\mathrm{ca}} + K_{\mathrm{im}}) - 1 - K_{\mathrm{h}}}{2(K_{\mathrm{ca}} + K_{\mathrm{im}})(1 + K_{\mathrm{h}})} \qquad (21)$$

where

$$\alpha = \{[\delta(K_{\mathrm{ca}} + K_{\mathrm{im}}) + 1 + K_{\mathrm{h}}]^2 + 4(K_{\mathrm{ca}} + K_{\mathrm{im}})(1 + K_{\mathrm{h}})[\mathrm{Al}]_0\}^{1/2} \qquad (22)$$

Noting that $\mathrm{d}[\mathrm{Al}]/\mathrm{d}t$ is equal to $\mathrm{d}a/\mathrm{d}t$ and substituting the expressions for a and $[\mathrm{Al}]_{\mathrm{e}}$ into eq 18 gives, after some manipulation, eq 23. Further substitution for

$$\frac{\mathrm{d}a}{\mathrm{d}t} = \frac{-k_{\mathrm{c}}K_{\mathrm{ca}}[2(1 + K_{\mathrm{h}})a^2 + \alpha a]}{K_{\mathrm{im}}\{2K_{\mathrm{ca}}(1 + K_{\mathrm{h}})(a + [\mathrm{Al}]_{\mathrm{e}}) + \delta K_{\mathrm{ca}} + 1 + K_{\mathrm{h}}\}} \qquad (23)$$

$[\mathrm{Al}]_{\mathrm{e}}$ and separation of variables transforms eq 23 to 24

$$-\frac{[\beta + 2(1 + K_{\mathrm{h}})K_{\mathrm{im}}a]\mathrm{d}a}{(K_{\mathrm{ca}} + K_{\mathrm{im}})(1 + K_{\mathrm{h}})a^2 + \alpha a} = k_{\mathrm{c}}\mathrm{d}t \qquad (24)$$

where

$$\beta = \frac{K_{\mathrm{im}}}{K_{\mathrm{ca}}}\left[1 + K_{\mathrm{h}} + \delta K_{\mathrm{ca}} + \frac{K_{\mathrm{ca}}(\alpha - 2\delta - 1 - K_{\mathrm{h}})}{K_{\mathrm{ca}} + K_{\mathrm{im}}}\right] \qquad (25)$$

Integration of eq 24 and evaluation of the integration constant from the definition of a_0 as the value of a at time zero gives eq 26. Values of k_{c} calculated using

$$k_{\mathrm{c}}t = \left(\frac{2K_{\mathrm{im}}}{K_{\mathrm{ca}} + K_{\mathrm{im}}} - \frac{\beta}{\alpha}\right) \times \ln\frac{(K_{\mathrm{ca}} + K_{\mathrm{im}})(1 + K_{\mathrm{h}})a_0 + \alpha}{(K_{\mathrm{ca}} + K_{\mathrm{im}})(1 + K_{\mathrm{h}})a + \alpha} + \frac{\beta}{\alpha}\ln\frac{a_0}{a} \qquad (26)$$

eq 26 and values of a determined spectrophotometrically at various pH's as described in the Experimental Section are listed in Table VI.[14]

Table VI. Rate Constants for the Dehydration of the Carbinolamine to Give N-Isobutylidenemethylamine in Water at 35° [a]

$[\mathrm{Al}]_0$	$[\mathrm{Am}]_0$	pH[b]	k_{c}, sec^{-1}	No. of runs
0.0527	0.0785	10.1	6.81 ± 0.10	3
0.0484	0.0835	10.15	6.44 ± 0.29	16
0.0527	0.0788	10.3	6.85 ± 0.14	4
0.0484	0.0835	10.74	6.10 ± 0.23	18
0.0484	0.0819	11.06	6.03 ± 0.14	15
0.0527	0.0785	11.1	6.56 ± 0.51	5
0.0297	0.0200	11.11	5.51 ± 0.90	6
0.0297	0.0285	11.18	7.06 ± 0.43	9
0.0100	0.0583	11.42	5.52 ± 0.34	8
0.0527	0.0778	11.5	6.28 ± 0.34	3
0.0100	0.0990	11.51	5.36 ± 0.44	6

[a] With methylammonium chloride added to adjust the pH. [b] ±0.14 or less.

Discussion

After the completion of our experimental work, a study of the kinetics of hydration of isobutyraldehyde at 0° was published.[22] The relative magnitudes of k_0, k_{H}, and k_{OH} reported are about the same as we have obtained at 35°.

The 16 values of $k_{\mathrm{c}}K_{\mathrm{ca}}$ determined from oximation studies between pH 8.48 and 9.82 (Table V) are not believed to differ beyond the experimental uncertainty, which is probably the largest for the values determined at pH 9.43 and 9.82, where k_{obsd} was particularly large. The values of $k_{\mathrm{c}}K_{\mathrm{ca}}$ determined at pH 7.62 are of reduced reliability because the background reaction (the k_{d} term in eq 8) comprised more than half the total reaction in these cases. However it is believed that these

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[22] Y. Pocker and R. G. Dickerson, *J. Phys. Chem.*, 73, 4005 (1969).

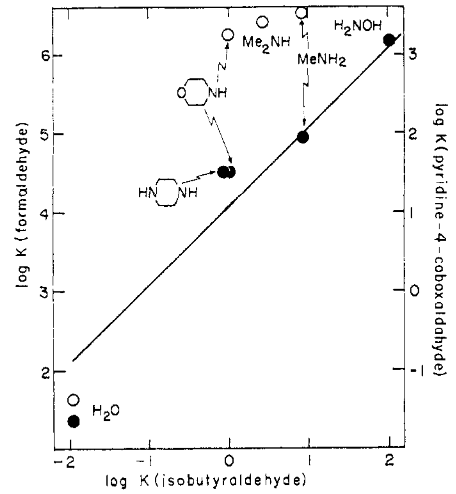

Figure 4. Plot of log K for addition of various reagents to formaldehyde (○) and pyridine-4-carboxaldehyde (●) *vs.* log K for addition to isobutyraldehyde.

Table VII. Equilibrium Constants for Addition to Isobutyraldehyde, Pyridine-4-carboxaldehyde, and Formaldehyde in Aqueous Solution[a]

Addend	K, M^{-1} i-PrCHO	 NC_5H_4CHO[b]	 CH_2O[b]
Water	0.011[c]	0.023	41
Piperazine	0.90[d,e]	32[e]	
Morpholine	1.0[d]	32	1.8×10^6
Dimethylamine	2.7[d]		2.6×10^6[f]
Methylamine	8.5[g]	87	3.4×10^6
Hydroxylamine	105[g]	1500	
Isobutyraldehyde	1.0[c]		

[a] At 20–25° unless otherwise noted. [b] Data from ref 24 unless otherwise noted. [c] Data from ref 12. [d] Data from ref 23, divided by 0.62 to correct the reported value for hydration of the aldehyde. [e] A statistically corrected value obtained by dividing the experimental value by 2. [f] Data from ref 25. [g] At 35°.

values are significantly larger than those determined at higher pH's (because of acid catalysis of the dehydration of the carbinolamine), and this belief is supported by a study of the hydrolysis of N-isobutylidenemethylamine.[9] The values of k_cK_{ca} for pH's above 8 listed in Table V, when divided by the value of K_{ca} determined directly, give a k_c value of 5.4 ± 1.1 sec^{-1}. The values of k_c determined by stopped-flow measurements average 6.2 ± 0.7 sec^{-1}. Although the values of k_c determined in these two different ways are within the experimental uncertainty of each other, it should be noted that the value resulting from oximation measurements may be a little too low because of capture of the imine by oxime being not quite complete.

The oximation experiments do not tell anything about whether general acid or base catalysis of imine formation is occurring, but the k_c values determined by stopped-flow measurements (Table VI) show that general catalysis is not important, if it occurs at all. Of the two runs (pH 11.11 and 11.18) in which much less buffer was used than in the other runs, one gave the highest value of k_c obtained and the other gave the second lowest value. There is therefore no reason to hypothesize any more complicated mechanism for the rate-controlling step of the reaction above pH 8.5 than a simple ionization of the carbinolamine. The overall reaction

$$\underset{\displaystyle\text{OH}}{i\text{-PrCHNHMe}} \xrightarrow{k_c} i\text{-PrCH}{=}\overset{+}{\text{N}}\text{HMe} + \text{OH}^-$$

mechanism will be discussed in detail in connection with the study of the hydrolysis of the imine at various pH's.[9]

The values of the equilibrium constants K_{ad} and K_{ca} for the addition of hydroxylamine and methylamine to isobutyraldehyde should fit plausibly into what is known about equilibrium in addition to carbonyl compounds in general. The only other species for which we have found equilibrium constants for addition to isobutyraldehyde are dimethylamine,[23] morpholine,[23] piperazine,[23] water,[12] and isobutyraldehyde.[12] These data are listed in Table VII with equilibrium constants for addition of the same species to pyridine-4-carboxaldehyde[24] and formaldehyde,[24,25] where available. In Figure 4 the values of log K for the other two aldehydes are plotted against the values of log K for isobutyraldehyde. Sander and Jencks found that such a log–log plot for pyridine-4-carboxaldehyde and *p*-chlorobenzaldehyde gave an excellent straight line of slope 1.0. When log K values for formaldehyde were plotted against those for pyridine-4-carboxaldehyde, however, the points tended to fall in two sets. One set, consisting of those reagents in which the atom that added to the carbonyl group was oxygen or sulfur, fell rather near a straight line of slope 1.0. The other set, consisting of nitrogen reagents, gave somewhat poorer agreement with a different straight line (corresponding to larger equilibrium constants for addition to formaldehyde than would be expected from the data on oxygen and sulfur reagents) whose slope was within the experimental uncertainty of 1.0 but was perhaps larger. The number and variety of points in Figure 4 are not large enough to distinguish between several alternatives. Although the points for water, methylamine, and hydroxylamine in the isobutyraldehyde–pyridine-4-carboxaldehyde plot lie very near a straight line of slope 1.2, it is also true that the latter two points (for relatively unhindered nitrogen bases) lie near the straight line of slope 1.0 shown in the figure, from which the point for water deviates considerably. In either case the deviations by the points for morpholine and piperazine must be explained, most reasonably in terms of steric repulsions in the adducts with isobutyraldehyde, where steric hindrance should be larger than with pyridine-4-carboxaldehyde. This rationalization in terms of steric hindrance finds support in the fact that the deviation of the point for morpholine from a straight line of slope 1.0 through the point for methylamine is larger in the case of formaldehyde than in the case of pyridine-4-carboxaldehyde. In any event the plot in Figure 1 supports the order of magnitude of the values determined for K_{ad} and K_{ca}.

Experimental Section

Kinetics of the Hydration of Isobutyraldehyde. A typical run was begun by adding 3 ml of 0.053 M N-methylmorpholine–0.050 M N-methylmorpholinium perchlorate–0.049 M sodium chloride to

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[23] J. Hine and J. Mulders, *J. Org. Chem.*, **32**, 2200 (1967).

[24] E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6514 (1968).

[25] R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5864 (1966).

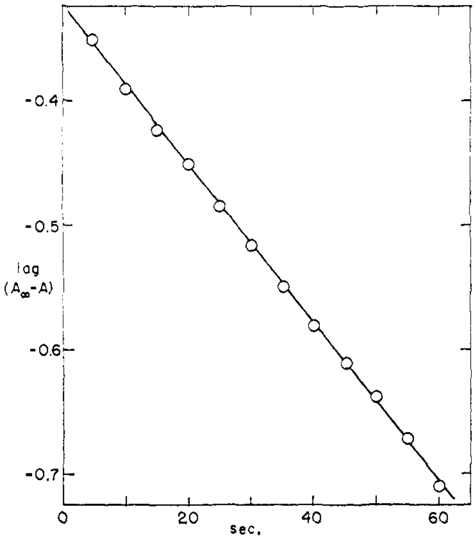

Figure 5. Kinetic plot for the oximation of isobutyraldehyde in the presence of methylammonium chloride at pH 8.48.

each of two 1-cm quartz spectrophotometer cells. (All solutions were made up with exclusion of oxygen.) After 25 μl of tetrahydrofuran was added to the reference cell, both cells were placed in the cell compartment,[26] thermostatted at 35.0°. The reaction was initiated by the addition of 50 μl of an equivolume mixture of isobutyraldehyde and tetrahydrofuran (the purpose of the latter being to bring about instant solution of the aldehyde) by syringe into the sample cell. The cell was shaken and returned to the cell compartment and absorbance measurements begun within about 10 sec. The slope of the plot of log $(A - A_\infty)$ *vs.* time was calculated by the method of least squares.

Kinetics of Formation of Isobutyraldoxime. The appearance of the oxime was followed spectrophotometrically, but not at the oxime absorption maximum near 1900 Å, where there was excessive interference by other species (especially hydroxylamine and the amines used as buffers). Instead, measurements were made at 2200 Å, where the oxime, hydroxylamine, and aldehyde have extinction coefficients of about 550, 7, and 0.5 M^{-1} cm^{-1}. The absorption values at infinite time used in calculating the rate constants were those observed in the given runs. These values often differed considerably from the values that could be calculated, but these differences were attributed to imperfect matching of the buffer in the sample cell by buffer in the reference cell, to the fact that measurements were being made on the side of an absorption band, and to the fact that the slit width chosen automatically by the spectrophotometer varied with the nature of the buffer used.

In a typical run, standard solutions of hydroxylamine, sodium chloride, a buffer, and, if appropriate, methylammonium chloride were used to prepare a solution of the desired pH that had an ionic strength of 0.200 M and was ordinarily 0.0100 M in hydroxylamine (including hydroxylammonium ions). This solution (3 ml) was added to each of two 1-cm cells, which were placed in the thermostatted sample and reference cell holders of the spectrophotometer. After thermal equilibrium had been reached, 0.030 ml of 0.102 M isobutyraldehyde solution was added by syringe to the sample cell, which was shaken and replaced in its holder, and recording of the absorbance was begun (starting about 15 sec after the addition of aldehyde). A typical plot of log $(A_\infty - A)$ is shown in Figure 5.

Equilibrium Constant for the Addition of Hydroxylamine to Isobutyraldehyde. In a typical run, a solution 0.0639 M in hydroxylamine and 0.181 M in sodium chloride was placed in one of the syringes of a Durrum-Gibson stopped-flow spectrophotometer, and a solution 0.0487 M in isobutyraldehyde and 0.221 M in sodium chloride was placed in the other. After the system had reached equilibrium at 35°, the plunger was actuated to mix equal volumes of the solutions from the two syringes in the 2-cm optical cell and the oscilloscope traces of per cent transmission at 2850 Å *vs.* time were photographed. These photographs had to be corrected for parallax since the oscilloscope had been calibrated by eye without any errors of parallax. Changes in transmission before about 0.1 sec were attributed largely to mixing phenomena, and values (which changed rather slowly by stopped-flow standards) recorded after this were extrapolated to 59.3% at zero time. When water was used instead of the hydroxylamine solution the transmittance was 20.2%. The hydroxylamine solution did not absorb appreciably at 2850 Å, and it was assumed that the adduct did not either. Unless hydroxylamine is a much better catalyst for the dehydration of isobutyraldehyde hydrate than is the more basic N-methylmorpholine, the amount of aldehyde used up to form adduct will not be appreciably replenished by dehydration of aldehyde hydrate during the time covered by these stopped-flow measurements on almost neutral solutions. Neglecting such dehydration, a value of 100 M^{-1} may be calculated for K_{ad} from the preceding observations. Seven other similar determinations gave an average K_{ad} value of 105 ± 11 M^{-1}.

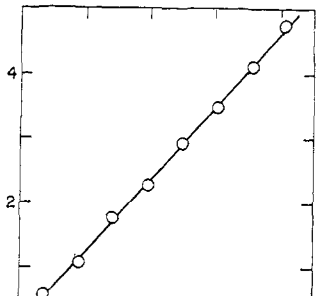

Figure 6. Plot of right-hand side of eq 26 *vs.* time for the reaction of 0.0100 M isobutyraldehyde with 0.0583 M methylamine at pH 11.42 and 35°.

Stopped-Flow Study of the Reaction of Methylamine with Isobutyraldehyde. The stopped-flow spectrophotometer was operated as described in the preceding section. Rate and equilibrium constants were determined from measurements at 2850 Å on solutions that were considerably more concentrated than those used for the runs illustrated by Figures 2 and 3, where the relatively large extinction coefficient for the imine at 2265 Å necessitated the use of rather dilute solutions. On each photograph the extrapolated initial transmittance, eight transmittances at times ranging from about 0.1 sec to about 0.7 sec, when the reaction had gone about two-thirds of the way to equilibrium, and the transmittance at about 1 min, when equilibrium was established, were measured. The concentration of aldehyde was calculated from the absorbance at each point with allowance being made for the small amount of absorbance by the imine (ϵ 0.4 M^{-1} cm^{-1} at 2850 Å); absorption by methylamine was negligible and absorption by the carbinolamine was assumed to be negligible. The value of the right-hand side of eq 26 was calculated for each point using average values of K_{ca} and K_{im} determined from a number of experiments, and k_c was taken as the slope of the least-squares line in plots like the sample shown in Figure 6. In each run the initial and final pH's of the reaction solution were calculated from the ionization constant of methylamine. In some runs the final pH was measured (and found to be within 0.1 of the calculated value). The pH values listed in Table VI are averages of the initial and final values.

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[26] A Cary ultraviolet-visible spectrophotometer, Model 14, was used.