Kinetics and Mechanism of the Hydrolysis of N-Isobutylidenemethylamine in Aqueous Solution[1]

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Abstract: Measurements on the kinetics of hydrolysis of N-isobutylidenemethylamine from pH 0.3 to 8.2 have been combined with earlier kinetic measurements on the formation of this imine between pH 7.6 and 11.5 to give a fairly complete rate–pH profile at 35°. The rate constant for hydrolysis increases from pH 0.3, where decomposition of the zwitterion $i\text{-PrCH(O}^-\text{)NH}_2\text{Me}^+$ is rate controlling, up to around pH 4.5, where it begins to level off as hydration of the iminium ion *via* attack of water becomes rate controlling. The rate constant then falls around pH 7 as the equilibrium protonation of the imine begins to be significantly incomplete. Above about pH 8 the rate again levels off as attack of hydroxide ions on the iminium ion becomes rate controlling. The pK_a value for the iminium ion obtained from the pH profile agrees well with the value 6.88 ± 0.08 determined by an indicator method on a stopped-flow spectrophotometer. Several rate and equilibrium constants for the individual steps of the reaction were determined directly, and others could be estimated rather reliably. It is estimated that below about pH 4.5 the principal form of the reactant is probably the conjugate acid of the carbinolamine, $i\text{-PrCH(OH)NH}_2\text{Me}^+$, rather than the iminium ion.

A study of the kinetics of the hydrolysis of N-isobutylidenemethylamine was of interest to us for reasons given in the previous paper, in which a kinetic study of the formation of this imine from isobutyraldehyde and methylamine in aqueous solutions between pH 7.6 and 11.6 was described.[2]

In solutions that are so basic that neither the amine nor imine is protonated to an appreciable extent, isobutyraldehyde is transformed largely to the imine by excess methylamine at concentrations above about 0.02 *M*.[3] However, since the amine is considerably more basic than the imine, in acidic aqueous solutions no directly measurable fraction of the aldehyde can be transformed to imine or iminium ion at equilibrium. In solutions acidic enough that both the imine and amine are essentially completely protonated, the reaction whose kinetics we have studied has the stoichiometry shown in eq 1. The pK_a of the iminium ion

$$i\text{-PrCH{=}NHMe}^+ + \text{H}_2\text{O} \longrightarrow i\text{-PrCHO} + \text{MeNH}_3^+ \qquad (1)$$

has been estimated[4] to be around 7 or less. To aid in the interpretation of the kinetic results at various pH's, we have determined a more reliable value directly. We have also studied the kinetics of hydrolysis between pH 0.3 and 8.2 and drawn conclusions about the mechanism of establishment of the aldehyde–imine (or iminium ion) equilibrium over the entire pH range.

Results

pK_a for the Iminium Ion. Significant concentrations of imine and iminium ions may coexist only near pH 7, where hydrolysis to isobutyraldehyde is quite rapid. Therefore, stopped-flow spectrophotometric measurements had to be used in the pK_a determination. One of the two syringes of the apparatus was filled with an aqueous solution of methylamine to which enough isobutyraldehyde had been added to transform most of the amine to imine. The second syringe was filled with a dilute aqueous solution of the indicator bromothymol blue and enough perchloric acid to neutralize all the amine and carbinolamine [i-PrCH(OH)NHMe] and part of the imine in the first solution. For reasons to be described later, it was assumed that when the two solutions were mixed the small amount of carbinolamine present was transformed instantaneously to aldehyde and methylammonium perchlorate. Thus, mixing the two solutions gave a solution with known initial concentrations of imine and iminium ion. Although spectrophotometric measurements made much before 0.1 sec after mixing seemed to be relatively unreliable, after this time the pH of the solution may be calculated from the pK of bromothymol blue and the absorbance of its basic form at 6150 Å. In each run the initial pH was calculated by extrapolation of the values determined between about 0.1 and 0.3 sec, during which time the pH increased by about 0.25. In three sets of runs, the initial pH's were about 6.38, 6.52, and 6.65, respectively. From these pH's and the known initial concentrations of imine and iminium ion, pK_a values[5] of 6.97 ± 0.02, 6.86 ± 0.03, and 6.80 ± 0.02 could be calculated. The overall average value was 6.88 ± 0.08. For each of the experimental points the concentrations of imine and iminium ions may be calculated if the first-order rate constant for hydrolysis is known. From these concentrations and the known pH, the pK_a of the iminium ion may be calculated. The rate constant that had to be used to get the same pK_a value at a given time as that calculated by extrapolation to zero time fell somewhat as the reaction proceeded (and the pH increased). From the points taken between about 0.1 and 0.3 sec, k values of 2.10 ± 0.10, 1.69 ± 0.14, and 1.49 ± 0.12 sec^{-1} were obtained from the three sets of runs. These values were taken as first-order rate constants for hydrolysis at pH's 6.56 ± 0.18, 6.69 ± 0.17, and 6.85 ± 0.20, respectively.

Kinetics of Imine Hydrolysis. The kinetics of hydrolysis of the N-isobutylidenemethylamine were studied at

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[1] This investigation was supported in part by Public Health Service Research Grant No. AM 10378 from the National Institute of Arthritis and Metabolic Diseases.

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

[3] J. Hine and C. Y. Yeh, *ibid.*, **89**, 2669 (1967).

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

[5] All the ± values listed are standard deviations.

35° by adding solutions of acid to equilibrium mixtures of aldehyde, imine, and amine and following the increase in absorbance due to the aldehyde at 2850 Å. Below about pH 2 the reaction was slow enough to follow using an ordinary recording spectrophotometer. In this pH range both the reacting imine and the amine that is formed are practically completely protonated, so that the pH does not change during a kinetic run. Furthermore, the rate constants for hydration of the aldehyde[2,6] are so much larger than those for its formation that the aldehyde may be treated as being equilibrated with its hydrate instantaneously on formation. Hence rate constants were calculated from plots of log ($A_\infty - A$) *vs.* time (where A is the absorbance). The values[5] obtained are listed in Table I.

Table I. Rate Constants for Hydrolysis of N-Isobutylidenemethylamine in Water at 35°

HB	[HB] + [B]	pH	k_{obsd}, sec^{-1}
H_3O^+ [a]		0.30	$(1.21 \pm 0.13) \times 10^{-4}$
H_3O^+ [a]		0.77	$(8.59 \pm 0.06) \times 10^{-4}$
Cl_2CHCO_2H	0.247	1.39	3.08×10^{-3}
$ClCH_2CO_2H$	0.342	2.24	$(2.15 \pm 0.06) \times 10^{-2}$
$ClCH_2CO_2H$	0.123	2.62	$(4.88 \pm 0.23) \times 10^{-2}$
$ClCH_2CO_2H$	0.246	2.66	$(5.41 \pm 0.17) \times 10^{-2}$
$ClCH_2CO_2H$	0.127	2.74	$(6.28 \pm 0.25) \times 10^{-2}$
HCO_2H	0.237	3.18	$(2.03 \pm 0.03) \times 10^{-1}$
HCO_2H	0.124	3.70	$(5.4 \pm 0.9) \times 10^{-1}$
AcOH	0.238	4.29	1.73 ± 0.02
AcOH	0.119	4.77	2.58 ± 0.07
AcOH	0.067	5.65–5.70	3.56 ± 0.11
[b]		6.38–6.74	2.10 ± 0.10
[b]		6.52–6.86	1.69 ± 0.14
$NmmH^+$ [c]	0.357	6.54–6.58	2.26 ± 0.10
[b]		6.65–7.05	1.49 ± 0.12
$NmmH^+$ [c]	0.146	6.87–6.97	1.62 ± 0.08
$NmmH^+$ [c]	0.168	6.92–7.02	1.61 ± 0.02
$NmmH^+$ [c]	0.148	7.00–7.11	2.83 ± 0.04
$NmmH^+$ [c]	0.102	7.25–7.43	1.37 ± 0.03
$NmmH^+$ [c]	0.204	7.32–7.42	1.38 ± 0.05
$NmmH^+$ [c]	0.085	7.38–7.65	1.02 ± 0.02
$NmmH^+$ [c]	0.074	7.50–7.90	1.03 ± 0.01
$NmmH^+$ [c]	0.066	7.65–8.25	1.07 ± 0.02

[a] From perchloric acid. [b] No added buffer. Rate constants calculated from change of pH with time. [c] N-Methylmorpholinium perchlorate.

Above pH 2 the reaction was so fast that it was followed with a stopped-flow spectrophotometer. Above about pH 4 the absorbance did not increase monotonically from its initial value to its final equilibrium value as it did in more acidic solutions. Instead, the absorbance increased to a maximum and then decreased to the final equilibrium value. This behavior is believed to be related to the fact that isobutyraldehyde is 30% hydrated in aqueous solution at 35°.[7] The initial increase in absorbance is due to the formation of the aldehyde by hydrolysis of the imine. When the concentration of aldehyde has become large enough and that of imine small enough, hydration of the aldehyde becomes faster than hydrolysis of the imine, and the absorbance decreases. Rate constants for hydrolysis (Table I) were determined from plots of log ($A_{\max} - A$) *vs.* time, and in a few runs rate constants for hydration were determined from plots of log ($A - A_\infty$) *vs.* time. In order to minimize complications arising from the hydration reaction, only points taken during about the first half of the hydrolysis reaction were used in calculating rate constants for hydrolysis. Analogously, no points were taken for the hydration reaction until the hydrolysis reaction could be calculated to be more than 99% complete. Since the hydration reaction is reversible, the first-order rate constant obtained from the plot of log ($A - A_\infty$) is the sum of the rate constants for hydration and dehydration.

This interpretation of observed absorption maxima in terms of initially predominant imine hydrolysis and subsequently predominant aldehyde hydration is supported by several independent bits of evidence. The final absorbance in all cases was essentially equal to that expected from the transformation of all the imine and carbinolamine originally present into 30% hydrated aldehyde. The maximum absorbance was essentially that expected from the transformation of the imine and carbinolamine to unhydrated aldehyde in those cases in which the hydrolysis and hydration reactions were fairly cleanly separated. In the run in Table I carried out with an N-methylmorpholine buffer at pH 7.38–7.65, the observed rate constant for hydration (0.3 of the rate constant for approach to hydration equilibrium) of the aldehyde was 0.025 sec^{-1}. From the catalysis constants determined using N-methylmorpholine buffers in a direct study of the hydration of isobutyraldehyde[2] a rate constant of 0.027 sec^{-1} may be calculated at pH 7.65, neglecting catalysis by methylamine whose concentration was very small and by methylammonium ion, which should be a very poor catalyst. Although the hydration of isobutyraldehyde does not appear to have been studied in the presence of acetate buffers, the rate constant 0.038 sec^{-1} obtained for hydration in the run at pH 4.77 listed in Table I is plausible, in view of the observed catalytic constants for acetic acid and acetate ion in the hydration of acetaldehyde and the fact that catalysis constants for acetaldehyde hydration[8] tend to be somewhat larger than those for isobutyraldehyde hydration.[2,6]

The first-order rate plots for imine hydrolysis runs above pH 3 usually showed some curvature corresponding to falling rate constants. Curvature before 0.1 sec was attributed to mixing processes, and this part of the reaction was ignored. Around pH 4 the curvature may relate to the fact that the aldehyde hydration reaction is comparable in rate to the imine hydrolysis reaction. Above about pH 6 the pH increases appreciably during the reaction, and the rate constant is known to decrease with increasing pH in this range. Hence, most of the rate constants in Table I, which are the averages of the results of several runs under the given conditions, are probably less reliable than might be indicated by the standard deviations listed.

Some runs were also made around pH 7 using phosphate buffers, usually giving larger rate constants than the runs at the same pH listed in Table I. However, these runs were rather poorly reproducible, perhaps partly because the aldehyde hydration reaction

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(6) J. Hine and J. G. Houston, *J. Org. Chem.*, **30**, 1328 (1965).

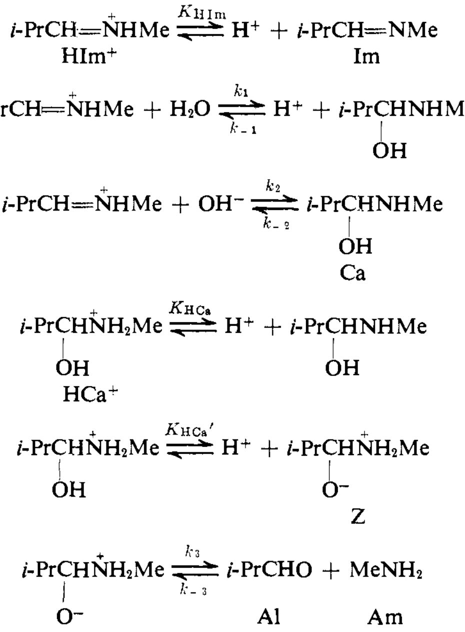
(7) J. Hine, J. G. Houston, and J. H. Jensen, *ibid.*, **30**, 1184 (1965).

(8) R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956).

was considerably faster than in the runs listed in Table I, and this phase of our work was dropped.

Discussion

The hydrolysis of N-isobutylidenemethylamine is similar to that of the N-benzylidene-*t*-butylamines, which has been studied by Cordes and Jencks.[9] By adding certain details[10] that did not require attention in their study we may arrive at mechanism 2 for our reaction. If the various proton-transfer equilibria



$$\underset{\text{HIm}^+}{i\text{-PrCH}{=}\overset{+}{\text{N}}\text{HMe}} \underset{}{\overset{K_{\text{HIm}}}{\rightleftharpoons}} \text{H}^+ + \underset{\text{Im}}{i\text{-PrCH}{=}\text{NMe}}$$

$$i\text{-PrCH}{=}\overset{+}{\text{N}}\text{HMe} + \text{H}_2\text{O} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{H}^+ + i\text{-PrCH(OH)NHMe}$$

$$i\text{-PrCH}{=}\overset{+}{\text{N}}\text{HMe} + \text{OH}^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{\text{Ca}}{i\text{-PrCH(OH)NHMe}} \qquad (2)$$

$$\underset{\text{HCa}^+}{i\text{-PrCH(OH)}\overset{+}{\text{N}}\text{H}_2\text{Me}} \overset{K_{\text{HCa}}}{\rightleftharpoons} \text{H}^+ + i\text{-PrCH(OH)NHMe}$$

$$i\text{-PrCH(OH)}\overset{+}{\text{N}}\text{H}_2\text{Me} \overset{K_{\text{HCa}}'}{\rightleftharpoons} \text{H}^+ + \underset{\text{Z}}{i\text{-PrCH(O}^-\text{)}\overset{+}{\text{N}}\text{H}_2\text{Me}}$$

$$i\text{-PrCH(O}^-\text{)}\overset{+}{\text{N}}\text{H}_2\text{Me} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \underset{\text{Al}}{i\text{-PrCHO}} + \underset{\text{Am}}{\text{MeNH}_2}$$

in this mechanism are established rapidly relative to the rates of the other reactions shown, and if the steady-state assumption may be made for the free and protonated carbinolamine (Ca and HCa$^+$) and the zwitterion (Z), eq 3, which is analogous to the expression used by Cordes and Jencks, may be derived for the observed first-order rate constant for disappearance of imine (and iminium ion). In eq 3, K_w is the autoprotolysis constant of water.

$$k_{\text{obsd}} = \frac{k_3K_{\text{HCa}}'(k_1[\text{H}^+] + k_2K_w)}{([\text{H}^+] + K_{\text{HIm}})(k_{-1}K_{\text{HCa}}[\text{H}^+] + k_{-2}K_{\text{HCa}} + k_3K_{\text{HCa}}')} \qquad (3)$$

Equation 4, which is a

$$\frac{k_1k_{-2}}{k_{-1}k_2} = K_w \qquad (4)$$

result of the principle of microscopic reversibility, may be solved for k_{-1}, the solution substituted in eq 3, and the result rearranged to give eq 5, in which q is defined as shown in eq 6. Equation 5 should be applicable

$$k_{\text{obsd}} = \frac{k_1[\text{H}^+] + k_2K_w}{([\text{H}^+] + K_{\text{HIm}})(k_1q[\text{H}^+] + k_2K_wq + 1)} \qquad (5)$$

$$q = \frac{k_{-1}K_{\text{HCa}}}{k_1k_3K_{\text{HCa}}'} \qquad (6)$$

not only to the kinetic data reported in the present paper but also to the kinetic data on the formation of the imine from methylamine and isobutyraldehyde reported in the preceding paper.[2] In that paper the reaction rate was expressed as shown in eq 7 in terms of

$$\frac{d([\text{Im}] + [\text{HIm}^+])}{dt} = k_cK_{\text{ca}}[\text{Al}][\text{Am}] \qquad (7)$$

K_{ca}, the equilibrium constant for carbinolamine formation from aldehyde and imine, and k_c, the first-order rate constant for dehydration of the carbinolamine. The equilibrium constant for the formation of total imine (K_t) from aldehyde and amine may be expressed

$$K_t = \frac{[\text{Im}] + [\text{HIm}^+]}{[\text{Al}][\text{Am}]} = K_{\text{im}}\left(1 + \frac{[\text{H}^+]}{K_{\text{HIm}}}\right) \qquad (8)$$

as shown in eq 8, where K_{im} is defined in eq 9. If the

$$K_{\text{im}} = \frac{[\text{Im}]}{[\text{Al}][\text{Am}]} \qquad (9)$$

assumptions used in deriving eq 5 are correct, k_{obsd} has the meaning shown in eq 10. Equation 11 then

$$-\frac{d([\text{Im}] + [\text{HIm}^+])}{dt} = k_{\text{obsd}}([\text{Im}] + [\text{HIm}^+]) \qquad (10)$$

follows from the fact that at equilibrium k_cK_{ca} [Al] [Am] must equal k_{obsd} ([Im] + [HIm$^+$]). Values of k_{obsd} at

$$k_{\text{obsd}} = \frac{k_cK_{\text{ca}}K_{\text{HIm}}}{K_{\text{im}}(K_{\text{HIm}} + [\text{H}^+])} \qquad (11)$$

various pH's were calculated from the values of k_c, K_{ca}, and K_{im} reported in the preceding paper[2] and the value of K_{HIm} determined here.[11]

Values of log k_{obsd} are plotted *vs.* pH in Figure 1; to avoid cluttering, only the average of the k_{obsd} values determined by oximation measurements at a given pH is plotted. Since the hydrogen ion concentration is known for every kinetic run, eq 5 may be treated as containing four unknown constants, k_1, k_2K_w, K_{HIm}, and q. Since k_2 is the rate constant for a reaction between two oppositely charged ions, its magnitude should change considerably with changing ionic strength, but to the extent to which the Debye–Hückel limiting law is valid, the product k_2K_w should be independent of the ionic strength. The values of k_{obsd} for all the points plotted in Figure 1 except the point at pH 0.3, which is at the beginning of the region of acid concentrations where acidity functions are commonly used instead of pH, were used simultaneously to calculate the optimum values of these unknowns by the method of least squares.[12,13] From the resultant values of 3.02 sec^{-1}, 4.18 × 10^{-8} *M* sec^{-1}, 1.04 × 10^{-7} *M*, and 7.75 × 10^3 *M*$^{-1}$ sec for k_1, k_2K_w, K_{HIm}, and q, respectively, the 42 values of k_{obsd} may be calculated with a standard deviation of 19%. The line in Figure 1 was drawn from eq 5 and these values of the four unknowns. Since the term k_2K_wq is equal to 3 × 10^{-4}, it follows that eq 5 may be simplified by dropping this

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[9] E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **85**, 2843 (1963).

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

[11] The values of k_{obsd} obtained are relatively insensitive to the value of K_{HIm} used; since [H$^+$] was always considerably smaller than K_{HIm}, the right-hand side of eq 11 almost reduces to $k_cK_{\text{ca}}/K_{\text{im}}$.

[12] In this treatment, it was not the sum of the squares of the absolute deviations but of the fractional deviations ($k_{\text{obsd}} - k_{\text{calcd}})/k_{\text{obsd}}$ that was minimized.

[13] The equations resulting from this least-squares treatment were too complicated for us to solve analytically, so they were solved by an iterative procedure, using a computer. The pH used in the calculations was the average value for the given run.

term from the denominator. The value of pK_{HIm} is 6.98, which is within the experimental uncertainty of the value 6.88 determined directly. From the value 13.68 for pK_w at 35° and infinite dilution,[14] the value $2.0 \times 10^6\ M^{-1}\ \text{sec}^{-1}$ may be calculated for k_2 under the same conditions. In spite of the satisfactory agreement obtained between eq 5 and the experimental data, we believe that the value obtained for q does not have the meaning given by eq 6 because the steady-state assumption for the protonated carbinolamine (HCa^+) becomes a poor approximation below about pH 5.

In order to understand the validity and consequences of the steady-state assumption for the protonated carbinolamine, let us consider why the rate of hydrolysis of imine changes with pH in the way that it does. Below pH 4 the rate-controlling step of the reaction is the decomposition of the zwitterion Z, with the rate constant k_3. Since the reactant is mainly in the more highly protonated forms HIm^+ and HCa^+, the fraction present as the zwitterion, and hence the reaction rate, increases with increasing pH. Above pH 4 the formation of zwitterion from iminium ion *via* protonated carbinolamine, whose rate is independent of the pH, is no longer fast enough to overcome the increasing rate of heterolysis of the zwitterion and maintain equilibrium between the iminium ion and the zwitterion. Therefore, starting around pH 4 the rate-controlling step of the reaction moves back to the hydration of the iminium ion with the rate constant k_1. Before k_{obsd} has a chance to become completely pH independent the pH has become too high for the protonation of the imine to be essentially complete, and the rate begins to decrease with increasing pH. This decrease has not become very large before the increasing concentration of hydroxide ions has made a new mode of attack on the iminium ion, *via* rate constant k_2, the principal reaction path. Above about pH 9, the decrease in the fraction of reactant present as the iminium ion is just compensated by the increase in concentration of hydroxide ions, and k_{obsd} is independent of the pH. Thus, above about pH 5.5, the protonated carbinolamine is formed after the rate-controlling step of the reaction and is in equilibrium with isobutyraldehyde and methylammonium ions. Since we know that larger concentrations of methylammonium ions than those present in the kinetic runs do not transform any detectable fraction of isobutyraldehyde to anything, it follows that above pH 5.5 the concentration of protonated carbinolamine is always small and the steady-state assumption applicable. Below pH 4, however, the protonated carbinolamine is in equilibrium with the iminium ion, and the equilibrium ratio may be expressed as shown in eq 12. The values of

$$\frac{[HCa^+]}{[HIm^+]} = \frac{k_1}{k_{-1}K_{HCa}} = \frac{K_{HIm}K_{ca}}{K_{HCa}K_{im}} \qquad (12)$$

K_{HIm}, K_{ca}, and K_{im} are all known and that of K_{HCa} may be estimated fairly reliably. Kallen and Jencks have determined acidity constants for the conjugate acids of four simple hydroxymethylammonium ions for which the acidity constants of the corresponding unhydroxylated species are known.[15] The hydroxy substituent decreased pK_a by 1.88 ± 0.11 (relative to hydrogen). Since the acidity constant of the diisobutylammonium ion is almost identical with that of the dimethylammonium ion at 21°,[16] we assume that the acidity constant of the isobutylmethylammonium ion will also be identical with that of the dimethylammonium ion, both at 21 and 35°. Correction of the resultant value for the effect of the α-hydroxy substituent gives an estimate of 8.61 for pK_{HCa} at 35°, which yields a $[HCa^+]/[HIm^+]$ ratio of 3.8. Unless this estimate is much too large, the protonated carbinolamine is the principal form of the reactant below pH 4.

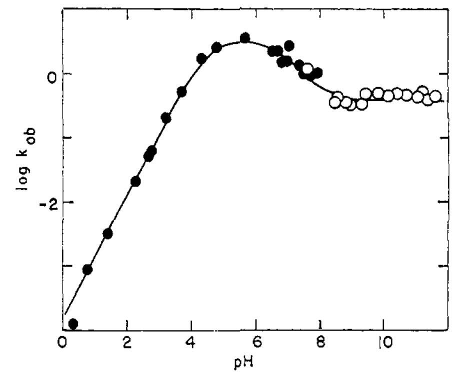

Figure 1. Plot of log k_{obsd} for the hydrolysis of N-isobutylidenemethylamine in water at 35° *vs.* pH: ●, from the rate of hydrolysis of the imine; ○, from the rate of formation of the imine.

If the concentration of the protonated carbinolamine were always negligible compared with that of the iminium ion, then below pH 4 k_{obsd} would be equal to $1/(q[H^+])$. However, if the protonated carbinolamine is present in concentrations comparable to those of the iminium ion, k_{obsd} must be expressed as shown in eq 13.

$$k_{obsd} = \frac{k_1k_3K_{HCa}'}{[H^+](k_1 + k_{-1}K_{HCa})} \qquad (13)$$

Hence we conclude that the value for q that we determined by least-squares treatment of the data in Figure 1, which was controlled largely by the data below pH 4, is actually equal to $(k_1 + k_{-1}K_{HCa})/(k_1k_3K_{HCa}')$. Although eq 13 is applicable below pH 4 and eq 5 is applicable above about pH 5.5, an equation applicable to the entire pH range would be very complicated. In the pH range around 4–5.5, where the rate-controlling step is changing, the reaction should not give clean first-order kinetics. If the protonated carbinolamine is building up to significant concentrations, the reaction should display an induction period before closely approaching a first-order process. We did not notice any such induction period, but the reaction was relatively rapid in this pH range, some of the early part of the reaction was obscured by mixing processes, and in the lower part of the range the rate of hydration of the aldehyde is comparable to its rate of formation.

Available data permit us to determine or estimate reliably all the rate and equilibrium constants of mechanism 2. The rate constant for the dehydration of the carbinolamine, found[2] to be independent of the

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[14] H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, p 754.

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

[16] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965, pp 16, 41.

pH from pH 8.5 to 11.6, must be equal to k_{-2}. From the value of k_1 resulting from the least-squares treatment and the value of $K_{\mathrm{HIm}}K_{\mathrm{ca}}/K_{\mathrm{im}}$, a value of k_{-1} may be calculated by use of eq 12. The value of K_{HCa}' may be estimated from the pK_a value (9.33) determined[17] for the formocholine cation ($Me_3NCH_2OH^+$). Replacement of the hydroxy substituent in glycolic acid by the methylammonio substituent lowers the pK_a 84% as much as replacement by the trimethylammonio substituent does.[18] Assumption that the same is true for the hydroxy substituent in formaldehyde hydrate[19] gives a pK of 9.98 for the hydroxylic hydrogen atom of $MeNH_2CH_2OH^+$, whose acidity is assumed to differ from that of the protonated carbinolamine by the same factor that the acidity of isobutyraldehyde hydrate[7] differs from that of formaldehyde hydrate. This gives an estimate of 10.48 for pK_{HCa}', which may be combined with the values of k_1, k_{-1}, K_{HCa}, and q to give k_3 by use of eq 14. This and the value of k_{-3}

$$k_3 = \frac{k_1 + k_{-1}K_{\mathrm{HCa}}}{qk_1K_{\mathrm{HCa}}'} \qquad (14)$$

calculated from eq 15 are listed in Table II with the

$$k_{-3} = \frac{k_3K_{\mathrm{ca}}K_{\mathrm{HCa}}'}{K_{\mathrm{HCa}}} \qquad (15)$$

other rate constants for mechanism 2. Rate constants for the various proton transfer steps, for which only equilibrium constants are written in mechanism 2, and for analogous proton transfer reactions by the various acids and bases present in the reaction solutions may be estimated fairly reliably from the fact that such reactions are diffusion controlled if their equilibrium constants are significantly larger than 1. Estimates based on data on other proton-transfer reactions between oxygen and nitrogen atoms[20] strongly support the assumption that the proton-transfer equilibria of mechanism 2 are established rapidly relative to the other reactions listed.

Table II. Rate Constants for Mechanism 2 in Water at 35°

n	k_n	k_{-n}
1	$3.0\ \mathrm{sec}^{-1}$	$3.2 \times 10^8\ M^{-1}\ \mathrm{sec}^{-1}$
2	$2.0 \times 10^6\ M^{-1}\ \mathrm{sec}^{-1}$	$6.2\ \mathrm{sec}^{-1}$
3	$\sim 4.9 \times 10^6\ \mathrm{sec}^{-1}$	$\sim 5.6 \times 10^5\ M^{-1}\ \mathrm{sec}^{-1}$

In order to learn whether mechanism 2 is adequate to fit the presently available data or whether it must be amplified in various ways, it would be useful to know whether any of the steps in the reaction are subject to general acid or base catalysis. In the acidic pH range where k_3 governs the rate-controlling step of the reaction, the concentration of chloroacetate buffers used was doubled, with the only change in rate being that expected from the small change in pH (*cf.* Table I). Hence this step is relatively insensitive to general catalysis. No significant general catalysis was observed in the formation of the imine in basic solution.[2] It therefore follows that in this pH range, where k_{-2} governs the rate-controlling step, the hydrolysis of the imine is not significantly general catalyzed. In view of observations on similar reactions[9] general catalysis would be expected in the intermediate pH range, where k_1 governs the rate-controlling step. Although this possibility was not investigated systematically, there seems to be no clear correlation between the magnitude and direction of the deviations of log k_{obsd} from the line in Figure 1 and the concentrations of buffers used. However, it is in this pH range that the rate constants contain the largest experimental uncertainty.

Since even unsubstituted alcohols are more weakly basic than water,[21] and the carbinolamine is an alcohol with an electron-withdrawing substituent, the protonation of the hydroxy group of the carbinolamine by hydrogen ions should have a rate constant significantly below the diffusion-controlled value of about 10^{10} M^{-1} sec^{-1}. The value found for k_{-1} is therefore close enough to the rate constant expected for this protonation reaction to leave open the possibility that essentially every protonation is followed by dehydration or even that the hydroxyl group is removed from the carbinolamine *as* it is protonated.

Experimental Section[22]

Determination of pK_a for Bromothymol Blue. Standard solutions of bromothymol blue at concentrations of about 10^{-5} M were added to 0.05 M perchloric acid, 0.01 M sodium hydroxide, and 0.001 M sodium hydroxide and absorbance measurements made on the basic form of the indicator at 6150 Å. There was no absorbance in the acidic solution, and from the identical absorbances in the two basic solutions the extinction coefficient of the basic form was calculated. Indicator solutions were then added to solutions of N-methylmorpholine–N-methylmorpholinium perchlorate with pH's ranging from 6.68 to 7.10 and ionic strength 0.048 M. The pK of the indicator[5] was then calculated to be 7.105 ± 0.011 from absorbance measurements and the pH's of the solutions, which had been measured using a Beckman Research pH meter, Model 101900. All measurements were made at 35°.

Determination of pK_a for the N-Isobutylidenemethylammonium Ion. In a typical determination, an aqueous solution 0.0974 M in perchloric acid and 1.7×10^{-5} M in bromothymol blue was placed in one syringe of the stopped-flow spectrophotometer and a solution 0.1101 M in methylamine[23] and 0.0867 M in isobutyraldehyde[23] was placed in the other. Photographs of the oscilloscope plot of per cent transmission at 6150 Å *vs.* time showed a smooth curve after about 0.1 sec. Transmittance values recorded much earlier than 0.1 sec after mixing usually did not constitute a continuation of this smooth curve; this fact was attributed to mixing phenomena, and these values were not used in our calculations. In Table III are pH values calculated from transmittances measured between about 0.1 and 0.3 sec and a value at zero time calculated by linear extrapolation.

From the equilibrium constants for the formation of the imine[2] and carbinolamine[2] and for the ionization of methylamine under the conditions used,[24] the concentrations of imine and carbinolamine may be calculated to be 0.0624 and 0.0045 M in the syringe before mixing. In view of the evidence that the hydration of the imine is the rate-controlling step in imine hydrolysis in approxi-

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(21) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

(22) The stopped-flow spectrophotometer used was a Durrum–Gibson instrument. A manually operated flow actuator was used for all except the last few measurements, by which time a solenoid-operated air actuator had been obtained. For other spectral measurements a Cary spectrophotometer, Model 14, was used.

(23) These concentrations are in terms of the amounts of material added and do not take into account the formation of imine, hydration of the aldehyde, etc.

(24) D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc., Ser. A*, **177**, 499 (1941).

Table III. Stopped-Flow Determination of pK_a for the N-Isobutylidenemethylammonium Ion in Water at 35°[a]

Time, sec	pH	[Im], *M*	$[HIm^+]$,[b] *M*	pK_a, assuming k^c is 2.0	2.1	2.2
0.000	6.384[d]	0.00635	0.02483	6.976	6.976	6.976
0.096	6.496	0.00635	0.01916	6.982	6.976	6.971
0.147	6.568	0.00635	0.01654	6.993	6.984	6.975
0.199	6.626	0.00635	0.01420	6.988	6.976	6.963
0.250	6.685	0.00635	0.01208	6.981	6.964	6.947
0.302	6.752	0.00635	0.01020	6.979	6.958	6.936

[a] The initial mixed reaction solution contained concentrations of isobutyraldehyde and methylammonium perchlorate of 0.0122 and 0.0239 *M*, respectively, in addition to the concentrations of imine and iminium perchlorate shown. [b] Values after zero time calculated using a *k* value of 2.1 sec^{-1}. [c] In sec^{-1}. [d] Extrapolated from values determined at later times.

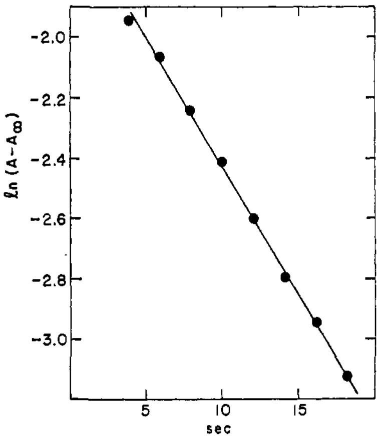

Figure 2. Kinetic plot for the hydration of isobutyraldehyde at pH 7.65 after the formation of the aldehyde by hydrolysis of N-isobutylidenemethylamine.

mately neutral solutions, it was assumed that the carbinolamine was transformed to aldehyde and methylammonium ions almost instantaneously when the two reaction solutions were mixed. From these assumptions the concentrations of imine and iminium ions resulting from mixing equal volumes of the solutions in the two syringes were calculated with the results shown for zero time in Table III. With a first-order rate constant for hydrolysis the concentration of imine and iminium ions may also be calculated for the times between 0.1 and 0.3 sec. First-order rate constants from 1.0 to 3.0 sec^{-1}, at intervals of 0.1 sec^{-1}, were used, and values of pK_a were calculated from the results. In Table III the results for three different values of *k* are shown. For each point, *k*, obtained by interpolation, is taken as that value required to give the same pK_a value as that obtained at zero time.

Kinetics of the Hydrolysis of N-Isobutylidenemethylamine. In a typical run made below pH 2, a mixture of 0.750 ml of 0.0796 *M* methylamine[23] and 0.750 ml of 0.0448 *M* isobutyraldehyde[23] was equilibrated at 35° in a 1-cm spectrophotometer cell. Then 1.500 ml of 0.500 *M* perchloric acid was added rapidly with shaking, and absorbance measurements at 2850 Å were made starting as quickly as possible.

The following is an example of the runs made between pH 2 and 8. A solution made up by diluting 0.7232 g of isobutyraldehyde and 5.2 ml of 5.740 *M* methylamine to 250 ml was used in one syringe of the stopped-flow spectrophotometer and a solution 0.1707 *M* in perchloric acid and 0.1691 *M* in N-methylmorpholinium perchlorate used in the other. Preliminary observations showed that the per cent transmission decreased, passed through a minimum (about 18%) after about 3 sec, and then increased more slowly, reaching a constant value (about 25%) after about 50 sec. To study the faster reaction total oscilloscope sweep times of 0.5 or 1.0 sec were used. Only the line drawn in the first sweep was used for kinetic points, but the transmission minimum was determined from subsequent sweeps. For the slower reaction total sweep times of 20 sec were usually used. The data taken from one photograph of the oscilloscope trace for the rapid reaction are shown in Table IV. Least-squares treatment of a plot of ln $(A_{max} - A)$ *vs.* time for the points after 0.1 sec gave a rate constant of 0.99 sec^{-1}. (Use of all the points gave 0.96 sec^{-1}.) The average value[5] from ten photographs was 1.02 ± 0.02 sec^{-1}. In order to minimize complications due to the slower reaction, only data on about the first half of the rapid reaction were used in calculating the rate constant.

Table IV. A Stopped-Flow Determination of the Rate Constant for Hydrolysis of N-Isobutylidenemethylamine in Water at 35° and pH 7.51 ± 0.14

Time, sec	% transmission[a]	$-\text{Ln}\ (A_{max} - A)$
0.044	60.9	0.655
0.096	59.1	0.680
0.147	56.5	0.720
0.199	54.6	0.768
0.250	50.8	0.819
0.302	48.3	0.871
0.353	45.9	0.925
0.405	44.1	0.969
0.456	43.8	1.027
0.508	40.4	1.075

[a] Minimum % transmission, 18.4.

A plot of ln $(A - A_\infty)$ *vs.* time for the slower reaction is shown in Figure 2. The rate constant for approach to equilibrium obtained from this plot (0.0843 sec^{-1}) was averaged with those obtained from seven other photographs to give[5] 0.0834 ± 0.0008 sec^{-1}. The initial and final pH's of the hydrolysis reaction solution calculated from the acidity constant of N-methylmorpholinium ions (pK_a determined to be 7.28 at 35° and ionic strength 0.15 *M*) are 7.37 and 7.65, respectively. The final pH determined experimentally was 7.74; in most runs the agreement between calculated and experimental pH was better than this.