Catalysis of α-Hydrogen Exchange. II. Isobutyraldehyde-2-*d* Exchange *via* N-Methyliminium Ion Formation[1]

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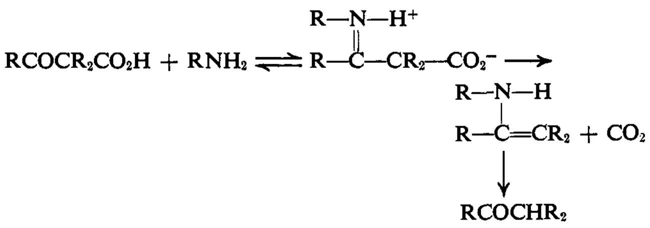
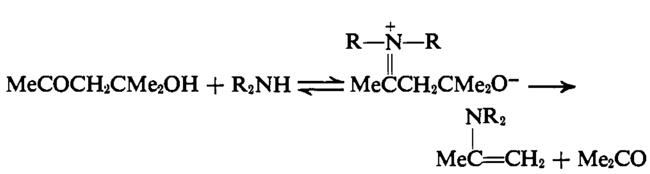
Abstract: In the presence of a moderate excess of free methylamine, isobutyraldehyde-2-*d* exists largely in the form of its N-methylimine. The deuterium exchange of the imine under such conditions was found to be largely proportional to the concentration of methylammonium ions at methylammonium ion concentrations of 0.1 *M* or larger. It was therefore concluded that the most important reaction path under such conditions involves the rate-controlling removal of deuterium by methylamine from the conjugate acid of the imine. When corrections were made for the exchange due to the attack of hydroxide ions on the aldehyde, a significant fraction of the reaction remained unaccounted for. This part of the reaction, which is simply first order in imine, may be due to the attack of hydroxide ions on the conjugate acid of the imine or to the kinetically equivalent attack of methylamine on the aldehyde.

In 1934 Pedersen suggested that primary amine catalysis of the decarboxylation of β-keto acids is due to the formation of the zwitterionic form of the β-imino acid, which then loses carbon dioxide to give an enamine.[3] Westheimer pointed out that analogous



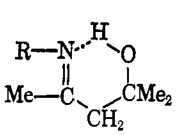
$$RCOCR_2CO_2H + RNH_2 \rightleftharpoons R\text{—}\overset{\overset{\displaystyle R\text{—}N\text{—}H^+}{\|}}{C}\text{—}CR_2\text{—}CO_2^- \longrightarrow R\text{—}\overset{\overset{\displaystyle R\text{—}N\text{—}H}{|}}{C}{=}CR_2 + CO_2 \longrightarrow RCOCHR_2$$

intermediates could explain the specific catalysis of the dealdolization of diacetone alcohol by primary and secondary but not by tertiary amines.[4] However, for



$$MeCOCH_2CMe_2OH + R_2NH \rightleftharpoons Me\overset{\overset{\displaystyle R\text{—}\overset{+}{N}\text{—}R}{\|}}{C}CH_2CMe_2O^- \longrightarrow Me\overset{\overset{\displaystyle NR_2}{|}}{C}{=}CH_2 + Me_2CO$$

the case of primary amine catalysis, at least, a mechanism in which the zwitterion intermediate is replaced by a somewhat similar chelate intermediate



was preferred,[4,5] in view of the relative insensitivity of the reaction rate to changes in the ion-solvating power of the medium.[5]

Other work has strengthened the evidence that reactions involving removal from a carbonyl compound of an α substituent without its bonding electron pair are catalyzed by primary and secondary amines because the amines transform the carbonyl group into the more strongly electron-withdrawing iminium ion group ($>C{=}NR_2^+$)[6] or perhaps to a chelated imine.[7,8] Such catalysis appears to be important in such enzymic reactions as those catalyzed by transaldolases[9] and decarboxylases.[10]

We are interested in catalysis of the α-deprotonation reactions of aldehydes and ketones. Shilov, Yasnikov, and co-workers have studied the catalysis of such reactions a number of times in their series "Catalytic Action of Aminoacids and Amines in Organic Reactions," of which 15 papers have appeared to date.[11] They have secured evidence that primary amine catalysis of certain α-deprotonation reactions involves the formation of an iminium ion and its transformation to an enamine. Although certain of the reaction mechanisms suggested in this series of papers seem implausible to us, their discussion will be deferred to a later article in which we hope to discuss our own related work.

The interpretation of much of the existing data on primary amine catalysis of decarboxylations of β-keto acids, dealdolization reactions, and α-deprotonation reactions is complicated by the polyfunctional character of many of the catalysts and substrates and by the fact that the intermediate imine was formed only at very low concentrations as a reaction intermediate. In most of the reactions that have been studied kinetically it is not clear whether the rate-controlling step is the formation of the imine, formation of the enamine, or some other step. For this reason we have investigated the deuterium exchange of isobutyraldehyde-2-*d*, a reaction whose catalysis by tertiary amines and oxygen bases has already been studied,[1b] in the presence of methylamine–methylammonium ion buffers, conditions under which much of the amine is transformed to imine.

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[1] (a) This investigation was supported in part by Public Health Service Research Grant AM 06829 MCB, from the National Institute of Arthritis and Metabolic Diseases. (b) For the preceding paper in this series see J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **87**, 5050 (1965).

[2] Department of Chemistry, The Ohio State University, Columbus, Ohio.

[3] K. J. Pedersen, *J. Phys. Chem.*, **38**, 559 (1934).

[4] F. H. Westheimer, *Ann. N. Y. Acad. Sci.*, **39**, 401 (1940).

[5] F. H. Westheimer and W. A. Jones, *J. Am. Chem. Soc.*, **63**, 3283 (1941).

[6] No one name has been generally accepted for these species, which are also called immonium ions and imonium ions.

[7] K. J. Pedersen, *J. Am. Chem. Soc.*, **60**, 595 (1938).

[8] J. C. Speck, Jr., and A. A. Forist, *ibid.*, **79**, 4659 (1957).

[9] *Cf.* J. C. Speck, Jr., P. T. Rowley, and B. L. Horecker, *ibid.*, **85**, 1012 (1963), and references cited therein.

[10] F. H. Westheimer, *Proc. Chem. Soc.*, 253 (1963).

[11] For the latest paper in this series see N. V. Volkova, E. A. Shilov, and A. A. Yasnikov, *Ukr. Khim. Zh.*, **31**, 56 (1965).

Results and Discussion

The nmr spectra of aqueous solutions to which more free methylamine than isobutyraldehyde has been added show that the absorption due to the aldehyde and its hydrate has been largely replaced by the absorption characteristic of isobutyraldehyde N-methylimine. That is expected in view of the fact that the equilibrium constant for the formation of the imine is 90.7 M^{-1} in aqueous solution at 35°[12]

$$K = \frac{[\mathrm{ImH}]}{[\mathrm{AH}][\mathrm{MeNH_2}]} \qquad (1)$$

where ImH is the protium form of the imine and [AH] is the concentration of the protium form of isobutyraldehyde (including both the free and the hydrated forms). Although equilibrium in imine formation is reached within 1–2 min, if not much sooner, the existence of separate peaks in the nmr spectra for the nitrogen-bound methyl groups of the imine and the methyl groups of the excess methylamine places an upper limit on the rate at which the imine is formed under our conditions.

When isobutyraldehyde-2-*d* is used instead of the protium compound, the doublet due to the carbon-bound methyl groups of the imine is replaced by a more closely spaced triplet centered at the same frequency. When such a solution is permitted to stand, the intensity of this triplet diminishes, while the doublet due to the protium compound appears and grows in intensity, surrounding the triplet. This is essentially the same change in nmr spectrum that accompanies the deuterium exchange of isobutyraldehyde-2-*d*.[1b]

In preliminary runs the kinetics of deuterium exchange were followed by nmr measurements on the aqueous reaction solutions. In the runs on which data are given herein the reaction was stopped by addition of an excess of acetic acid; this transformed the imine into the aldehyde, which was then extracted with chloroform. The deuterium content of the aldehyde dissolved in chloroform was then determined as described previously[1b] and it was assumed that the imine from which the aldehyde was generated had the same deuterium content.

Within any given run the reaction was found to be satisfactorily first order in isobutyraldehyde-2-*d*-N-methylimine. However, since the equilibrium between the imine and the aldehyde (and its hydrate) is established at a rate much faster than that of the deuterium exchange reaction, the reaction could equally well be interpreted as being a first-order reaction of isobutyraldehyde-2-*d*, or to be more general, as containing terms first order in each of the suggested species.

The rate of reaction *via* the aldehyde should contain a term in each of the bases present, hydroxide ions, methylamine, imine, and water. However, since earlier experiments[1b] have shown that the water term is *much* too small to contribute significantly to a reaction of the rate being observed, only the first three terms can be of appreciable importance. Deuterium exchange *via* the aldehyde will decrease the deuterium content of both the aldehyde and the imine in equilibrium with it. The extent to which it affects the imine will be proportional to f_I, the fraction of material present as imine

$$f_I = \frac{[\mathrm{ImH}] + [\mathrm{ImD}]}{[\mathrm{ImH}] + [\mathrm{ImD}] + [\mathrm{AH}] + [\mathrm{AD}]}$$

where ImD is the deuterioimine and AD is isobutyraldehyde-2-*d* (free and hydrated). Thus the rate of imine exchange *via* aldehyde may be expressed

$$-\left(\frac{\mathrm{d}[\mathrm{ImD}]}{\mathrm{d}t}\right)_{via\ \mathrm{aldehyde}} = f_I(k_m[\mathrm{MeNH_2}] + k_i[\mathrm{Im}] + k_h[\mathrm{OH^-}])[\mathrm{AD}] \qquad (2)$$

where k_m is the second-order rate constant for transformation of isobutyraldehyde-2-*d* to its conjugate base by the action of methylamine, k_h (whose value is known[1b]) is the corresponding constant for hydroxide ions, k_i is the corresponding constant for the imine, and [Im] is the total concentration of imine, protio and deuterio. Use of the term k_i[Im] involves a neglect of secondary deuterium kinetic isotope effects in this reaction.

One may also envision exchange through the imine, which would be expected to be much less reactive than the aldehyde but which is present in considerably higher concentrations. Inasmuch as water cannot compete significantly with the stronger bases present in bringing about the deuterium exchange of the aldehyde under basic conditions such as we have employed, it is assumed that we may also neglect attack of water on the imine, which should be less reactive and hence more selective than the aldehyde. Thus, the rate of exchange *via* the imine is expressed

$$-\left(\frac{\mathrm{d}[\mathrm{ImD}]}{\mathrm{d}t}\right)_{via\ \mathrm{imine}} = f_I(k_m''[\mathrm{MeNH_2}] + k_i''[\mathrm{Im}] + k_h''[\mathrm{OH^-}])[\mathrm{ImD}] \qquad (3)$$

where k_m'', k_i'', and k_h'' are rate constants for attack of the bases in question on the deuterium atom of the imine.

Neither eq 2 nor 3 provides an explanation for the fact that at essentially constant concentrations of imine and methylamine the rate of deuterium exchange increases with increasing concentration of methylammonium ions (Tables I and II). It seems quite im-

Table I. Rate of Deuterium Exchange of $Me_2CDCH{=}NMe$ in the Presence of Aqueous $MeNH_2$–$MeNH_3ClO_4$ Buffers at 35°[a]

M					$10^5\cdot$
$[MeNH_2]$	$[MeNH_3^+]$	$10^4\,[OH^-]$	μ	$10^5 k_p$, sec^{-1}	k_{cor}, sec^{-1}
0.270	0.460	6.4	0.460	18.2	18.9
0.270	0.459	6.4	0.459	18.5	19.2
0.270	0.368	7.7	0.368	14.5	15.0
0.270	0.277	9.7	0.277	10.0	10.3
0.269	0.185	13	0.185	8.55	8.8
0.270	0.0939	21	0.0939	6.05	6.0
0.267	0.0329	49	0.0329	4.32	3.9
0.264	0.00706	212	0.0217[b]	5.84	3.3
0.266	0.00475	338	0.0342[b]	7.77	3.8
0.268	0.00242	756	0.0759[b]	12.1	3.0

[a] Sum of the concentrations of aldehyde and imine 0.0540 ± 0.0008 *M*. Concentration of isobutyrate anions 0.0008 ± 0.0006 *M*. f_I is equal to 0.958 ± 0.001. [b] Sodium hydroxide added to reduce the concentration of methylammonium ions.

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(12) C. Y. Yeh, M.S. Thesis, Georgia Institute of Technology, 1965.

Table II. Rate of Deuterium Exchange of $Me_2CDCH{=}NMe$ in the Presence of $MeNH_2$–$MeNH_3Cl$ Buffers at 35°[a]

Run	$[MeNH_2]$, M	$[MeNH_3^+]$, M	$10^4\cdot$ $[OH^-]$, M	$10^4\cdot$ $[RCHO]$, M	$10^4[Im]$, M	10^5k_p, sec^{-1}	10^5k_{cor}, sec^{-1}
1	0.347	0.509	7.5	30	942	17.6	18.1
2	0.289	0.508	6.3	36	936	16.0	16.6
3	0.230	0.508	5.0	45	927	16.0	16.7
4	0.109	0.508	2.4	89	883	17.0	18.8
5	0.109	0.508	2.4	91	900	15.5	17.0
6	0.109	0.508	2.4	46	455	15.0	16.4
7	0.109	0.508	2.4	18	179	14.7	16.1
8	0.347	0.390	9.8	30	942	14.4	14.8
9	0.347	0.271	14	30	942	10.8	11.0
10	0.346	0.153	25	30	942	7.89	7.90
11	0.343	0.0815	46	30	931	5.57	5.31
12	0.343	0.0815	46	30	942	5.96	5.70
13	0.343	0.0830	46	15	466	5.60	5.35
14	0.343	0.0815	46	5.7	178	5.51	5.25
15	0.343	0.0815	46	5.7	178	5.27	5.01
16	0.107	0.0815	15	94	914	5.58	5.68
17	0.107	0.0815	15	94	914	5.68	5.78
18	0.110	0.0815	15	88	884	5.66	5.76
19	0.110	0.0815	15	46	458	5.49	5.57
20	0.110	0.0815	15	15	150	5.43	5.51
21	0.340	0.0417	90	30	942	4.70	3.96

[a] NaCl added as necessary to bring the ionic strength to 0.508 ± 0.005 M; isobutyrate ions were present in concentrations ranging from 0.6 to 2.9% of the imine concentration.

plausible to explain this fact in terms of general acid catalyzed exchange of the aldehyde since in the presence of an acetate buffer, where the acid is much stronger than methylammonium ions and the base much weaker than methylamine, catalysis of deuterium exchange is essentially entirely due to the basic component of the buffer.[1b] It would appear, then, that an acid-catalyzed reaction of the imine, specifically, a reaction of the iminium ion, is occurring.

Like the aldehyde and the imine, the iminium ion should be capable of losing its α-deuterium atoms to any of the four bases present in the reaction solution. Unlike the imine the iminium ion would be expected to be more reactive than the aldehyde and hence perhaps less selective. For this reason catalysis by the most weakly basic, but most abundant, base water will be considered, initially, at least. With these assumptions exchange *via* rate-controlling attack of bases on the iminium ion should obey the rate equation

$$-\left(\frac{d[\mathrm{ImD}]}{dt}\right)_{via\ \mathrm{iminium\ ion}} = f_I(k_m'[\mathrm{MeNH_2}] + k_i'[\mathrm{Im}] + k_h'[\mathrm{OH^-}] + k_w'[\mathrm{H_2O}])[\mathrm{HImD^+}] \quad (4)$$

where $\mathrm{HImD^+}$ is $\mathrm{Me_2CDCH{=}NHMe^+}$ and k_m', k_i', k_h', and k_w' are the rate constants for removal of the deuterium from it by the action of the four bases.

The total reaction rate will be equal to the sum of the rates by the three paths. Equilibrium between the imine and the aldehyde is known to be established at a rate that is rapid compared to the deuterium exchange reaction. It seems highly likely, and will be assumed, that equilibrium between the imine and its conjugate acid is also established relatively rapidly. Neglecting a deuterium isotope effect on the equilibrium constant for imine formation

$$[\mathrm{AD}] = [\mathrm{ImD}]/K[\mathrm{MeNH_2}] \quad (5)$$

If K_{IH} is the acidity constant of the conjugate acid of the imine

$$[\mathrm{HImD^+}] = [\mathrm{H^+}][\mathrm{ImD}]/K_{IH} \quad (6)$$

Equations 5 and 6 may be combined with eq 2 and 4 and the two resulting equations may be added to eq 3 to give

$$-\frac{d[\mathrm{ImD}]}{dt} = f_I\{(k_m[\mathrm{MeNH_2}] + k_i[\mathrm{Im}] + k_h[\mathrm{OH^-}])\frac{[\mathrm{ImD}]}{K[\mathrm{MeNH_2}]} + (k_m'[\mathrm{MeNH_2}] + k_i'[\mathrm{Im}] + k_h'[\mathrm{OH^-}] + k_w'[\mathrm{H_2O}])\frac{[\mathrm{H^+}][\mathrm{ImD}]}{K_{IH}} + (k_m''[\mathrm{MeNH_2}] + k_i''[\mathrm{Im}] + k_h''[\mathrm{OH^-}])[\mathrm{ImD}]\} \quad (7)$$

If the pseudo-unimolecular rate constant k_p is defined

$$-\frac{d[\mathrm{ImD}]}{dt} = k_p[\mathrm{ImD}] \quad (8)$$

it follows that

$$\frac{k_p}{f_I} = \frac{k_m}{K} + \frac{k_i[\mathrm{Im}]}{K[\mathrm{MeNH_2}]} + \frac{k_h[\mathrm{OH^-}]}{K[\mathrm{MeNH_2}]} + \frac{k_m'[\mathrm{H^+}][\mathrm{MeNH_2}]}{K_{IH}} + \frac{k_i'[\mathrm{H^+}][\mathrm{Im}]}{K_{IH}} + \frac{k_h'K_w}{K_{IH}} + \frac{k_w'[\mathrm{H^+}][\mathrm{H_2O}]}{K_{IH}} + k_m''[\mathrm{MeNH_2}] + k_i''[\mathrm{Im}] + k_h''[\mathrm{OH^-}] \quad (9)$$

where K_w is the autoprotolysis constant of water.

The value of k_p is determined in each run, and f_I may be calculated from K and the concentrations of aldehyde and amine used. Inasmuch as k_h is known from previous work[1b] to be 0.031 M^{-1} sec^{-1} the known terms may be assembled by transferring the k_h term to the left side of the equation. When this has been done and substitutions made from the acidity constant expression for methylammonium ions

$$K_{MH} = \frac{[\mathrm{H^+}][\mathrm{MeNH_2}]}{[\mathrm{MeNH_3^+}]}$$

the following equation results

$$k_{\mathrm{cor}} = \frac{k_{\mathrm{m}}}{K} + \frac{k_{\mathrm{i}}[\mathrm{Im}]}{K[\mathrm{MeNH_2}]} + \frac{k_{\mathrm{m}}'K_{\mathrm{MH}}[\mathrm{MeNH_3^+}]}{K_{\mathrm{IH}}} + \frac{k_{\mathrm{i}}'K_{\mathrm{MH}}[\mathrm{Im}][\mathrm{MeNH_3^+}]}{K_{\mathrm{IH}}[\mathrm{MeNH_2}]} + \frac{k_{\mathrm{h}}'K_{\mathrm{w}}}{K_{\mathrm{IH}}} + \frac{k_{\mathrm{w}}'K_{\mathrm{MH}}[\mathrm{H_2O}][\mathrm{MeNH_3^+}]}{K_{\mathrm{IH}}[\mathrm{MeNH_2}]} + k_{\mathrm{m}}''[\mathrm{MeNH_2}] + k_{\mathrm{i}}''[\mathrm{Im}] + \frac{k_{\mathrm{h}}''K_{\mathrm{w}}[\mathrm{MeNH_2}]}{K_{\mathrm{MH}}[\mathrm{MeNH_3^+}]} \quad (10)$$

where

$$k_{\mathrm{cor}} = \frac{k_{\mathrm{p}}}{f_{\mathrm{I}}} - \frac{k_{\mathrm{h}}K_{\mathrm{w}}}{KK_{\mathrm{MH}}[\mathrm{MeNH_3^+}]}$$

In Table I are the results of a series of experiments in which the deuterium exchange reaction was carried out in the presence of a methylamine–methylammonium perchlorate buffer. The ionic strength varied widely, as shown in the table, inasmuch as no other salt was added to maintain constant ionic strength; in several runs, however, sodium hydroxide was added to give a lower concentration of methylammonium ions and a higher concentration of hydroxide ions. According to the equations resulting from the combination of the Debye–Hückel equation with transition state theory[13] there will be a salt effect on a reaction rate only if it is a reaction between two ions. The only rate constant in eq 10 that governs such a reaction is k_{h}'. To a first approximation there should be a salt effect on an equilibrium process only if the process involves a change in the number of ions. The only equilibrium constant in eq 10 that governs such a process is K_{w}. The only terms on the right-hand side of eq 10 in which k_{h}' or K_{w} appears are the terms $k_{\mathrm{h}}'K_{\mathrm{w}}/K_{\mathrm{IH}}$ and $k_{\mathrm{h}}''K_{\mathrm{w}}[\mathrm{MeNH_2}]/K_{\mathrm{MH}}[\mathrm{MeNH_3^+}]$. Since k_{h}' should decrease with increasing ionic strength in approximately the same manner that K_{w} should decrease (in exactly the same manner if the simplest form of the Debye–Hückel equation is applicable), the former term should not change greatly with changing ionic strength. Thus, only the last term on the right-hand side of eq 10 should change greatly with ionic strength. One may attempt to minimize salt effects by keeping the ionic strength constant. This was done in the runs for which data are reported in Table II where methylamine–methylammonium chloride buffers were used and sodium chloride was present in the concentrations necessary to keep the ionic strength 0.508 ± 0.005 *M*. There is no guarantee that this procedure eliminates salt effects, however, since their magnitude is known to depend on the specific nature of the salt(s) present as well as on the ionic strength.

To calculate the equilibrium concentrations of methylamine, methylammonium ions, and hydroxide ions present throughout the various runs and listed in Tables I and II, it was necessary to have values for the ionization constant of methylamine. Values at 35° and ionic strengths up to 0.2 *M* were calculated by interpolation from the data obtained by Everett and Wynne-Jones at 0, 10, 20, 30, 40, and 50°.[14] The acidity constant of the methylammonium ion (K_{MH}) was determined in the presence of 0.555 *M* methylammonium chloride and also in the presence of 0.462 *M* sodium chloride–0.050 *M* methylammonium chloride, using a Beckman research pH meter. The $\mathrm{p}K_{\mathrm{MH}}$ values obtained were 10.446 and 10.450, respectively. Interpolation between these values and those of Everett and Wynne-Jones gave values of 10.444 and 10.450, respectively, at an ionic strength of 0.508 *M*. Since the value of $\mathrm{p}K_{\mathrm{MH}}$ is thus the same, within the experimental uncertainty, at this ionic strength regardless of whether the ionic strength is entirely due to methylammonium chloride or 90% due to sodium chloride, it was assumed that the autoprotolysis constant of water is the same under both sets of conditions as it is when the ionic strength is entirely due to sodium chloride. The appropriate value, obtained by interpolation from the data tabulated by Harned and Owen[15] (and converted from a molality to a molarity basis), was combined with an average $\mathrm{p}K_{\mathrm{MH}}$ value of 10.447 to give an ionization constant of 11.0×10^{-4} *M* for methylamine in water at 35° and 0.508 *M* ionic strength. Ionization constants at ionic strengths between 0.2 and 0.508 *M* were determined by interpolation.

If the last term in eq 10 may be neglected, then at constant concentrations of imine, methylamine, and water the equation assumes the form

$$k_{\mathrm{cor}} = C + C'[\mathrm{MeNH_3^+}] \quad (11)$$

Hence a plot of k_{cor} *vs.* the concentration of methylammonium ions under such conditions should give a straight line. In Table I the concentrations of imine, methylamine, and water are essentially constant. A plot of the k_{cor} values from this table *vs.* the methylammonium ion concentration (the open circles in Figure 1) is found to be a satisfactory straight line. Runs 1, 8, 9, 10, 11, 12, and 21 from Table II provide a set of points at constant ionic strength and essentially constant concentrations of imine, methylamine, and water; runs 4, 5, 16, 17, and 18 are another such set; and other smaller sets may be seen. A satisfactory straight line may be drawn through each set of points but since the various lines do not differ from each other by more than the experimental uncertainty they are not shown in Figure 1. Instead, one line has been drawn through all the points, although it seems quite possible that the best line through the open circles should be slightly steeper. The linear character of the plot provides good evidence that the last term in eq 10 may be neglected. The best such evidence comes from the points at low methylammonium ion concentration, because it is in these cases that the ratio $[\mathrm{MeNH_2}]/[\mathrm{MeNH_3^+}]$ is the largest and hence it is in these cases that the last term should be the largest. Even with the last three points in Table I, where the hydroxide ion concentration is so large that most of the observed exchange is due to the attack of hydroxide ions on the aldehyde, the attack of hydroxide ions on the imine (*i.e.*, the last term in eq 10) does not occur to a sufficient extent to produce any significant deviations from the best straight line through all the points. If the hydroxide ion is incapable of producing deuterium ex-

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(13) *Cf.* S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Section XV-8.

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

(15) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, p 752.

change by direct attack on the imine under the conditions used, it seems unlikely that the more weakly basic methylamine and imine would be able to do so. For this reason it seems probable that not only the k_h'' term but also the k_m'' and k_i'' terms of eq 10 may be neglected. The data in Table II provide evidence that not only the k_i'' term but all the terms in which the imine concentration appears are small. That is, if we compare various sets of points in which the concentration of methylamine and methylammonium ions has been held constant and the concentration of imine changed, it is found that although k_{cor} tends to increase with increasing imine concentration, in no case is the increase in k_{cor} clearly larger than the experimental uncertainty. This is true in the series of runs 11, 12, 13, 14, 15, where the values of k_{cor} are fairly small so that any change in the terms involving the imine concentration should be more noticeable. It is also true in the series 16, 17, 18, 19, 20, where the values of k_{cor} are equally small and the concentration of methylamine is so small that the k_i term should be relatively large. Finally, it is true with the series of runs 4, 5, 6, 7, where the ratio $[MeNH_3^+]/[MeNH_2]$ is particularly high so that the k_i' term should be relatively large. The tendency of k_{cor} to increase with increasing imine concentration seems to be consistent enough to suggest that the contribution of one or more of the imine terms is real. This tendency is not large enough relative to the experimental uncertainty, however, to permit a meaningful evaluation of the tendency of the imine to attack either of the three species (aldehyde, imine, and iminium ion) under consideration. For this reason we have neglected the terms containing k_i, k_i', and k_i''. It may also be noted in Table II that when the methylamine concentration is increased at constant methylammonium ion and imine concentrations (as in runs 1, 2, 3, 4, and 5 or in runs 11, 12, 16, 17, and 18), k_{cor} shows a small but moderately consistent tendency to decrease. However, this tendency was also too small to permit the evaluation of any of the constants in eq 10 and therefore the terms containing methylamine concentration were neglected.

With the deletion of all the negligible terms, eq 10 takes the form

$$k_{cor} = \frac{k_m}{K} + \frac{k_h'K_w}{K_{IH}} + \frac{k_m'K_{MH}[MeNH_3^+]}{K_{IH}} \qquad (12)$$

and the following mechanism for the reaction (up to and including the rate-controlling step) is seen to contain all the steps needed to explain the experimental results.

$$Me_2CDCHO + MeNH_2 \rightleftharpoons Me_2CDCH{=}NMe + H_2O$$

$$Me_2CDCH{=}NMe + MeNH_3^+ \ (H_2O) \rightleftharpoons Me_2CDCH{=}NHMe^+ + MeNH_2 \ (OH^-)$$

$$Me_2CDCH{=}NHMe^+ + MeNH_2 \xrightarrow{k_m'} Me_2C{=}CHNHMe + MeNH_2D^+$$

$$Me_2CDCH{=}NHMe^+ + OH^- \xrightarrow{k_h'} Me_2C{=}CHNHMe + HOD$$

$$Me_2CDCHO + MeNH_2 \xrightarrow{k_m} Me_2C{=}CHO^- + MeNH_2D^+$$

$$Me_2CDCHO + OH^- \xrightarrow{k_h} Me_2C{=}CHO^- + HOD$$

The enamine and aldehyde anion are then protonated by steps analogous to the reversal of the last four steps shown.

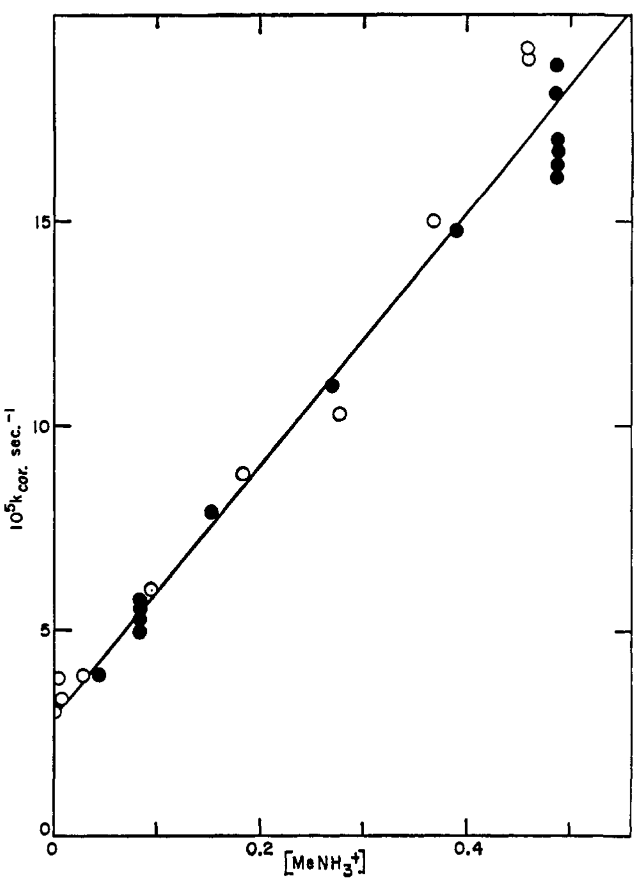

Figure 1. Plot of k_{cor} *vs.* $[MeNH_3^+]$ from data obtained using methylammonium perchlorate and variable ionic strength (open circles) and using methylammonium chloride at ionic strength 0.508 *M* (solid circles).

From eq 12 we conclude that the slope of the plot in Figure 1 (30.6×10^{-5} M^{-1} sec^{-1}) is equal to $k_m'K_{MH}/K_{IH}$ and the intercept (3.0×10^{-5} sec^{-1}) is equal to $k_m/K + k_h'K_w/K_{IH}$. From the slope and the value of K_{MH} quoted earlier the value 8.6×10^6 M^{-2} sec^{-1} may be calculated for k_m'/K_{IH}. In addition to the errors arising from experimental sources, these values may also be somewhat in error (probably slightly too high) because of small contributions from some of the terms in eq 10 that were neglected on going to eq 12. There appears to be no direct method available for separating the intercept into its two component terms; that is, the attack of methylamine on the aldehyde is the kinetic equivalent of the attack of hydroxide ion on the N-methyliminium ion. Hence we can merely determine the maximum value for each term (by assuming the entire intercept is due to the given term).[16] We have also estimated the maximum value for each of the neglected terms by assuming that none of these terms ever contributes as much as 20% to the over-all reaction. The estimated maximum values of k's and k'''s are listed in Table III, as are values and estimated maximum values of $k'K_I/_H$'s (since the value of K_{IH} is not known). These maximum values are of use in studies (currently under way) of the reaction under conditions where only a very small fraction of the aldehyde is present in the imine form.

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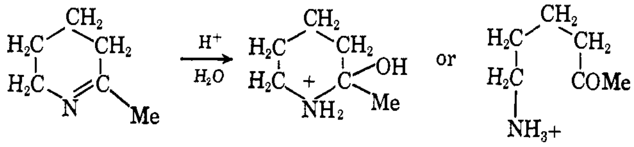
[16] By use of a linear-free-energy relationship, we propose to show in a future paper that the intercept in Figure 1 is determined largely by the attack of methylamine on the aldehyde (*i.e.*, by the k_m term).

Table III. Values for Some of the Constants of Eq 10

Constant	Value
k_m	$<3 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$
k_i	$<1 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$
k_m'/K_{IH}	$8.6 \times 10^{6}\ M^{-2}\ \text{sec}^{-1}$
k_i'/K_{IH}	$<2 \times 10^{6}\ M^{-2}\ \text{sec}^{-1}$
k_h'/K_{IH}	$<8 \times 10^{8}\ M^{-2}\ \text{sec}^{-1}$
k_w'/K_{IH}	$<4 \times 10^{3}\ M^{-2}\ \text{sec}^{-1}$
k_m''	$<2 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$
k_i''	$<9 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$
k_h''	$<2 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$

A value for k_m' could be estimated if we could make a reasonable estimate of the value of K_{IH}. The fact that the addition of acid shifts the imine–aldehyde equilibrium to the side of the aldehyde shows that the imine is a weaker base than the amine, but we do not know how much weaker it is. We have not been able to find an ionization constant listed for any simple N-alkylaldimine of the type RCH=NR′, where R and R′ are both unsubstituted saturated alkyl groups. The most closely analogous compounds for which we have found data are ketimines. The compounds in question are cyclic species that were originally thought to be enamines but, in view of the strong evidence that simple primary and secondary enamines rearrange spontaneously to the more stable imines,[17] are almost undoubtedly very largely imines. A number of 5-substituted (including 5-ethyl) 3,4-dihydro-2H-pyrrolenines have been found to be about $^1/_{1000}$ as basic as the corresponding pyrrolidines.[18] The basicity of 6-methyl-2,3,4,5-tetrahydropyridine is $^1/_{30}$ that of 2-methylpiperidine[19] but the experimental value of the ionization constant of an imine will be caused to be too high by the most probable complications that may accompany protonation in aqueous solution, namely, formation of the salt of the hydrate of the imine or the salt of the open-chain amino ketone (the structure of the cation was not examined in the cases in question[18,19]). We therefore estimate that ketimines are less basic than the corresponding amines by at least 1000-fold. Just as ketones are usually more basic, often by about tenfold, than corresponding aldehydes,[20] ketimines would be expected to be more basic than the corresponding aldimines (although perhaps by a smaller factor since the charge on carbon in a protonated imine is probably smaller than in a protonated aldehyde or ketone). Since the ionization constants of simple saturated secondary aliphatic amines are around 10^{-3} we estimate that the ionization constant of isobutyraldehyde-N-methylimine is around 10^{-7} or less. Thus the value of K_{IH} is 10^{-7} or more and k_m' is equal to 0.86 $M^{-1}\ \text{sec}^{-1}$ or more. Comparison of this value with that for k_m ($<3 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$) shows that methylamine removes deuterium from the N-methyliminium ion about 300 times (or more) as rapidly as it removes deuterium from the aldehyde. This confirms the expectation that the C=NHR$^+$ group should activate α hydrogen atoms more strongly than the carbonyl group does.



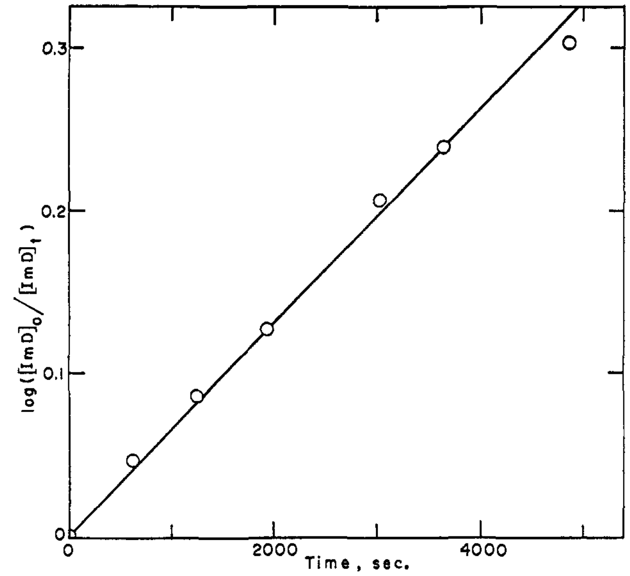


Figure 2. Kinetic plot for run 6 in Table II.

Experimental Section[21]

Nuclear Magnetic Resonance Spectra of Mixtures of Isobutyraldehyde and Methylamine. When a 10–100% excess of methylamine was added to an aqueous solution of isobutyraldehyde at concentrations of 0.1–0.5 *M*, the absorption characteristic of the aldehyde and its hydrate[22] decreases greatly in intensity and new absorption appears. A doublet (J = 7 cps) at τ 8.99 and an unresolved peak at 6.85 with a ratio of areas of 1.9 ± 0.2 to 1.0 were attributed to the carbon-bound and nitrogen-bound methyl groups of N-isobutylidenemethylamine, respectively. Broad multiplets, not much stronger than the background noise levels, near τ 2.4 and 7.6 were attributed to the hydrogen attached to unsaturated carbon and to the tertiary hydrogen atom of the imine. Yeh has found that pure N-isobutylidenemethylamine has doublets at τ 8.95 (J = 7.0 cps) and 6.84 (J = 1.6 cps) and multiplets at τ2.50 and 7.70, which were assigned to the various hydrogen atoms of the molecule in a manner analogous to that described in the preceding sentences.[12] A peak at τ 7.70 (obscuring part of the broad but weak multiplet around τ 7.6) due to the methyl group of the excess methylamine was present in our spectra run on aqueous solutions. When isobutyraldehyde-2-*d* solutions were mixed with methylamine, the τ 8.99 doublet observed with the protium compound was replaced by a triplet ($J \sim$ 1 cps). As the solutions stood this triplet decreased in intensity and was surrounded by the growing doublet of the corresponding protium compound.

Kinetics. The isobutyraldehyde-2-*d* used in the current study was prepared from isobutenyl acetate and deuterium oxide as described previously.[1b] A number of preliminary runs, which gave data roughly like that reported herein but with poorer precision, were carried out by making nmr measurements directly on the reacting solutions. The procedure was analogous to the first of the kinetic procedures described earlier,[1b] except that the measurements were on the imine rather than on the aldehyde.

The data shown in Tables I and II were obtained by use of a procedure of which the following is a specific example. For run 6 of Table II, 5 ml of 1.5220 *M* methylammonium chloride, 5 ml of 0.4650 *M* methylamine, and 5 ml of 0.1504 *M* isobutyraldehyde-2-

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[17] *Cf.* B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

[18] L. C. Craig and R. M. Hixon, *ibid.*, **53**, 4367 (1931); D. F. Starr, H. Bulbrook, and R. M. Hixon, *ibid.*, **54**, 3971 (1932).

[19] R. Adams and J. E. Mahan, *ibid.*, **64**, 2588 (1942).

[20] E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 295, 366 (1963).

[21] All nmr spectra were determined using a Varian A-60 instrument. Chemical shifts are referred to tetramethylsilane for those spectra run in organic solvents and to sodium 3-(trimethylsilyl)-1-propanesulfonate for those spectra run in water.

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

d-0.0018 *M* isobutyric acid (all at 35°) were added to each of eight 25-ml volumetric flasks in a 35° constant-temperature bath. The solutions had all been prepared and stored under nitrogen, the volumetric flasks had been flushed with nitrogen, and the addition was carried out under nitrogen. At recorded times 1 ml of 5 *M* acetic acid was added to stop the reaction and the solution was extracted immediately with 1 ml of spectral grade chloroform. The deuterium content of the isobutyraldehyde in the chloroform extract was determined by measuring the nmr spectra and comparing them with those of known mixtures of isobutyraldehyde and isobutyraldehyde-2-*d*.[23] For each point the deuterium content of the imine was taken as equal to the deuterium content of the aldehyde extracted, and the first-order rate constant was calculated from the slope of a plot of log ($[ImD]_0/[ImD]_t$) *vs.* time as shown in Figure 2. The deuterium content of aldehyde obtained from points taken within a few seconds after the reaction began was found to be essentially the same as that of the aldehyde used in preparing the reaction solutions. Independent measurements show that the addition of excess acetic acid slows the reaction to a rate that may be neglected in the present case. Nmr measurements show that in acidic solution the aldehyde–imine equilibrium is shifted almost entirely to the side of the aldehyde.

p*K* Measurements. Titration of solutions of hydrochloric acid with standard methylamine (with and without added sodium chloride) was carried out using a Beckman research pH meter, Model 101900 and a constant-temperature bath that kept the solution at 35 ± 0.5°. The p*K* values were calculated from the pH at the point where the concentrations of methylamine and methylammonium chloride were equal.

Acknowledgment. We wish to acknowledge our indebtedness to the National Science Foundation for a grant that permitted the purchase of the nuclear magnetic resonance spectrometer used in this investigation.

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[23] A plot of the fraction of deuterated aldehyde *vs.* $d/(d + h)$, where *d* and *h* have the meanings used previously,[1b] was found to be a straight line.

Catalytic Efficiencies in Amide Hydrolysis. The Two-Step Mechanism[1,2]

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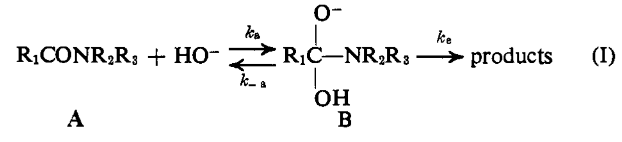
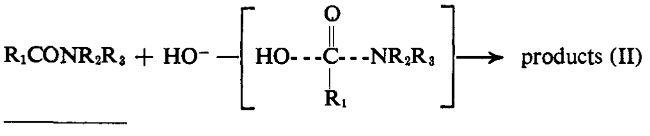
Contribution from the Department of Chemistry, University of Kansas, Lawrence, Kansas. *Received February 14, 1966*

Abstract: The kinetics of hydrolysis of 2,2,2-trifluoro-N-methylacetanilide (I) has been determined in aqueous solution from pH 11.2 to 12.6 at temperatures from 20 to 35°. The kinetic law, shown in eq 1, is consistent with intermediate formation of an adduct of I and hydroxide ion and general base catalyzed conversion of this species to products. The results are not consistent with a single-step conversion of I to hydrolysis products. The activation parameters for the processes corresponding to each rate constant are: (k_a) $\Delta H^* = 5.5$ kcal/mole, $\Delta S^* = -36$ eu; (k_1) $\Delta H^* = 5.9$ kcal/mole, $\Delta S^* = -37$ eu; (k_2) $\Delta H^* = 6.6$ kcal/mole, $\Delta S^* = -21$ eu, for standard states cf 1 *M* aqueous solution for solutes and pure liquid for water. The catalytic efficiency of hydroxide ion relative to water in decomposition of the adduct is thus a purely entropic effect.

Previously available evidence[5] on the mechanism of base-catalyzed amide hydrolysis is consistent with either of two mechanisms: (I) the reversible addition of hydroxide ion to the carbonyl function followed by expulsion of amide ion, and (II) a concerted displacement of amide ion by hydroxide ion in an SN2-like reaction at the carbonyl center. Our observation[2] that the hydrolysis of 2,2,2-trifluoro-N-methylacetanilide exhibits general base catalysis superimposed upon hydroxide ion catalysis is consistent with mechanism I if formation or decomposition of the adduct B is general base catalyzed or with II if attack by hydroxide ion is general base catalyzed.



$$\underset{\textbf{A}}{R_1CONR_2R_3} + HO^- \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \underset{\textbf{B}}{R_1\overset{\displaystyle O^-}{\underset{\displaystyle OH}{C}}\text{—}NR_2R_3} \xrightarrow{k_e} \text{products} \qquad (I)$$



$$R_1CONR_2R_3 + HO^- \longrightarrow \left[HO\cdots\overset{\displaystyle O}{\underset{\displaystyle R_1}{C}}\cdots NR_2R_3 \right] \longrightarrow \text{products} \qquad (II)$$

The finding of Bender and Ginger[6] that the base-catalyzed hydrolysis of benzamide proceeds concurrently with exchange of O^{18} from the substrate carbonyl group is consistent with a scheme in which exchange occurs by the reversible formation of B, which almost always (a fraction $k_{-a}/(k_{-a} + k_e)$ of times) decomposes to reactants, rather than to products, by expulsion of the weaker base hydroxide in preference to the stronger base amide ion ($k_{-a} >> k_e$). Hydrolysis could then result from (II) if its rate constant greatly exceeded $k_e/(k_{-a} + k_e)$. Bender[5a] has pointed out, as an argument against mechanisms such as (II), that no analogous displacement of such a poor leaving group by hydroxide ion is known in saturated carbon systems. However, saturated carbon substrates have no means for stabilization of the concerted-displacement transition state by electron acceptance from the very basic entering and leaving groups because high-energy σ^* orbitals are the

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[1] This research was supported by the National Institutes of Health under Research Grant No. GM-12477-02 and was carried out in part at the Computation Center of the University of Kansas.

[2] Amide Hydrolysis. II. Part I: R. L. Schowen and G. W. Zuorick, *J. Am. Chem. Soc.*, **88**, 1223 (1966). A preliminary account of part of the present work has appeared: R. L. Schowen, H. Jayaraman, and L. Kershner, *Tetrahedron Letters*, 497 (1966).

[3] Fellow of the Institute of International Education.

[4] National Defense Education Act Predoctoral Fellow.

[5] (a) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (b) A. Bruylants and F. Kézdy, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **21**, 213 (1960); (c) S. S. Biechler and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4927 (1957).

[6] M. L. Bender and R. D. Ginger, *ibid.*, **77**, 58 (1955).