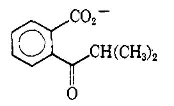
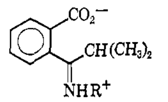
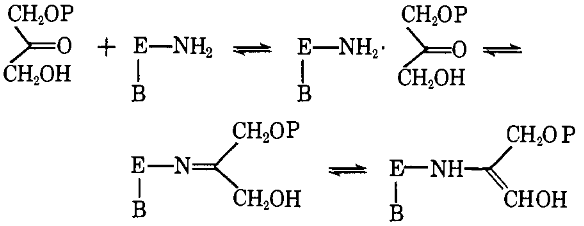
Table V. Comparison of Aldolase-Catalyzed α-Hydrogen Exchange of Dihydroxyacetone Phosphate with Some Intramolecular Enolizations

System	k, sec^{-1}	Ref
	50×10^{-7}	21
	500	See text
Aldolase-N$=$CR$_2$ + H$_2$O	690	38

lysis by external water, as assumed above. Therefore, it is of interest to compare the rate constant of this intramolecular catalysis of enolization with the rate constant of aldolase-catalyzed enolization. This comparison is shown in Table V. Since protonated ketimines enolize 10^8-fold faster than corresponding ketones (Table IV) the rate of the hypothetical intramolecular carboxylate ion catalyzed enolization of a protonated ketimine may be calculated from that of the corresponding ketone. From Table V it is seen that the rate of the hypothetical intramolecular carboxylate ion catalyzed enolization of a protonated ketimine compares very favorably with that of the aldolase-catalyzed enolization. Although the chemical analogy is far from complete it can be tentatively suggested that the aldolase-catalyzed enolization involves Schiff base formation, followed by proton abstraction to produce the corresponding enamine, as shown in eq 14.


(14)

Studies on the Mechanism of Oxime and Ketimine Formation[1]

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Abstract: The rate constant for ketimine formation from acetone and methylamine has been determined using two independent methods: by direct spectrophotometric observation and by determination of the rate of acetoxime formation from acetone and hydroxylamine in the presence of methylamine. The two methods yield equivalent rate constants. The pH dependence of ketimine formation indicates a reaction which is dependent only on free methylamine concentration. This result is in agreement with previous suggestions for the mechanism of this reaction. The rates of oximation of benzaldehyde and acetone were determined from approximately pH 6 to 12. With both substrates, a reaction dependent on oxonium ion and a reaction dependent on hydroxide ion were observed. In the acetone reaction, a reaction independent of pH was also observed. The oxonium ion catalysis and pH-independent reactions are interpreted as general acid catalyses by oxonium ion and water, respectively, on the basis of the fit of these data to a Brønsted plot, with $\alpha = 0.6$. The hydroxide ion reaction is interpreted as a specific hydroxide ion catalysis on the basis of its deuterium oxide isotope effect.

The rate of formation of the ketimine between methylamine and acetone was of interest in studies of enolization involving ketimine as possible intermediates.[3] Some of the kinetics of ketimine formation studied here were carried out by direct spectrophotometric measurements. However, since the equilibrium constant of ketimine formation from methylamine and acetone is very poor ($K_1 = 0.22\ M^{-1}$), the technique of using the oximation reaction to follow the formation of ketimine, developed by Cordes and Jencks, has also been used.[4] In this method hydroxylamine reacts very rapidly with the protonated ketimine and the rate of oximation is limited by the rate of formation of the ketimine. As background for our studies on ketimine intermediates in enolization reactions, studies on both ketimine formation and oxime formation are reported here.

Experimental Section

Materials. Acetone, benzaldehyde, hydroxylamine, and acetonitrile were of analytical reagent grade. Methylamine hydrochloride was an Eastman Kodak Co. product and was recrystallized from ethanol. Deuterium oxide (99.64%) was obtained from the Volk Radiochemical Co. The deuterium oxide buffers were prepared directly from heavy water and the protium buffer. For example, 0.1 M hydroxylamine hydrochloride will exchange with heavy water to give 0.2 M water, a dilution of the heavy water which is negligible for the purposes of our experiments. The ionic strength of the buffer solution was kept constant at 0.11 in the oximation of benzaldehyde and 0.2 in the other reactions. The pH of the buffers was adjusted in a Radiometer pH-Stat using 12 M sodium hydroxide. This treatment did not affect the ionic strength of the solutions and had a negligible effect on the concentrations. pD was calculated from the equation[5]

$$\text{pD} = \text{pH meter reading} + 0.4$$

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(1) This research was supported by a grant from the National Science Foundation.

(2) University of Oxford, Oxford, England.

(3) A. Williams and M. L. Bender, *J. Am. Chem. Soc.*, **88**, 2502 (1966).

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

(5) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

and pOH and pOD were calculated from the autoprotolysis constants of water and deuterium oxide using pH and pD, respectively. The pK_a of hydroxylamine was determined at 25° in water and in heavy water using an ionic strength of 0.2 M in a Radiometer pH-Stat. ND_3OD^+ (pK_a = 6.5) was found to be a weaker acid than NH_3OH^+ (pK_a = 6.03).[6]

Kinetics. In the direct spectrophotometric determination of Schiff base formation, 1 M methylamine hydrochloride was adjusted to pH 10.4 in a Radiometer pH-Stat using 12 M sodium hydroxide solution. Cuvettes containing 3.0 ml of this buffer were placed in the cell compartment of a Cary 14 spectrophotometer and 50 or 75 μl of acetone solution in water (to make 5.8 or 8.7 $\times 10^{-3}$ M) were quickly added and the reaction followed at 235 mμ, the absorption maximum of the acetone–methylamine Schiff base.

In the oximation experiments, buffers containing 0.02 M hydroxylamine hydrochloride and enough sodium chloride to maintain an ionic strength of 0.11 or 0.2 were adjusted to a given pH using 12 M sodium hydroxide solution. Buffer (3.0 ml) was then placed in a cuvette and equilibrated in the cell compartment of a Cary 14 spectrophotometer. Acetone in water or benzaldehyde in acetonitrile was added *via* a lambda pipet. The reactions were followed by the change in absorptivity at 230 (acetone) or 250 mμ (benzaldehyde). Good first-order plots were usually obtained up to *ca.* 90% of the reaction. At high pH's (*ca.* 11–12) the infinity absorption in both acetone and benzaldehyde oximations fell below that at lower pH's. This phenomenon is explained by the ionization of the oxime and has no effect on the first-order rate constants. The absorption of acetone or benzaldehyde was measured in water in the same cell. The absorptions at time zero of the oximation reactions were calculated by extrapolating the first-order plots to zero time.

The kinetics of oximation of benzaldehyde in deuterium oxide buffers were carried out under the same conditions as those in the water buffers. One milliliter of buffer solution at the required pH at 0.11 ionic strength containing 0.1 M hydroxylamine in a 2.0-ml cell was equilibrated in the cell compartment of the spectrophotometer. Then 10 μl of benzaldehyde in acetonitrile was added and the absorption at 250 mμ was recorded immediately on addition.

Results

Formation of Schiff Base from Acetone and Methylamine. The equilibrium constant of this reaction was determined in aqueous solution at pH 10.5 and 12.2 spectrophotometrically. An estimate of the absorption of N-isopropylidenemethylamine in aqueous solution was made on the basis of the absorption of isopropylidene-*n*-butylamine in acetonitrile. The spectrum of the latter system showed a maximum at 235 mμ (ϵ 1.92 $\times 10^2$). As the pH of the methylamine solution was increased from pH 8.5 to 12.2, the absorption peak at 265 mμ, characteristic of acetone, fell slightly in intensity and a new intense peak appeared at *ca.* 235 mμ. A plot of log A_{225}, where negligible acetone absorption occurred, *vs.* pH indicated a pK_a of about 10.6, as expected from the acidity of the methylammonium ion. The equilibrium constant for ketimine formation was calculated from the absorption at 235 mμ, assuming that the extinction coefficient of the ketimine was equivalent to that of the *n*-butylamine ketimine in acetonitrile and assuming that the acetone concentration was constant (the absorption of acetone at 265 mμ indicated that it was indeed constant). The equilibrium constant (K_1 = (ketimine)/(methylamine)$\cdot$(acetone)) was found to be 0.21 at pH 10.5 and 0.23 M^{-1} at 12.2. Although these values may be in error due to the assumption of the extinction coefficient of the ketimine, they agree well with constants of similar reactions found in the literature.[7-9] For example, the equilibrium constant for the formation of ketimine from acetone and *n*-butylamine is 0.08 and that from cyclopentanone and methylamine is 0.125.

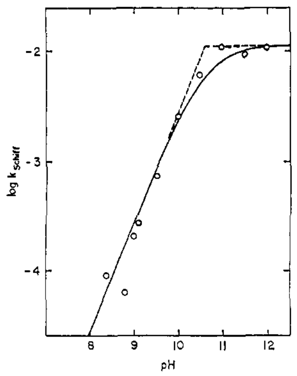

Figure 1. The effect of pH on the oximation of acetone in the presence of methylamine using 0.1 M methylamine hydrochloride, 0.02 M hydroxylamine hydrochloride, 1.57 $\times 10^{-3}$ M acetone, at 25.0°, and ionic strength 0.2. The rate constants are k_{imine} of Table I. The solid line is calculated using eq 2 and the pK_a of methylamine, 10.6.

The rate constant of ketimine formation from acetone and methylamine, defined by eq 1, was determined by direct spectrophotometric measurement. Reaction is

$$\text{acetone} + \text{methylamine} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \text{ketimine} \qquad (1)$$

very fast and thus, only an approximation to the rate constant may be made, namely that the half-life of the reaction is 2 ± 0.2 sec. From this rate constant which measures the sum of the two first-order (or pseudo-first-order) processes, the known equilibrium constant and the known excess concentration of methylamine, it was possible to calculate $k_1 = 7 \pm 1 \times 10^{-2}$ M^{-1} sec^{-1}.

The rate constant of ketimine formation from acetone and methylamine was also determined by following the formation of acetoxime from acetone and hydroxylamine in the presence of methylamine. The results of these oximation experiments are given in Table I. In order to determine the rate constant of ketimine formation the observed rates must be corrected for background oximation due to catalysis by water, hydroxide ion, or methylamine acting as general bases. The first-order ketimine formation rate constants are plotted *vs.* pH in Figure 1. The experimental data fit the following equation indicating dependence only on free methylamine concentration. The solid line of Figure 1 was calculated on the basis of eq 2 and

$$k_{\text{imine}} = 11.4 \pm 3.6 \times 10^{-2}\,(\text{methylamine})\ M^{-1}\,\text{sec}^{-1} \qquad (2)$$

the pK_a of methylamine, 10.6. Thus, the second-order rate constant of ketimine formation, $k_i = k_{\text{imine}}/$(methylamine), determined from oximation studies, agrees well with that determined from direct spectrophotometric observations.

The "background" oximation mentioned above was investigated at pH 10 by determining the rate of oximation of acetone by hydroxylamine in the presence of constant methylamine. The experimental data are

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(6) T. C. Bissot, R. W. Parry, and D. H. Campbell, *J. Am. Chem. Soc.*, **79**, 796 (1957), give pK_a of NH_3OH^+ = 5.97 at 25°.

(7) M. Brezina and P. Zuman, *Chem. Listy*, **47**, 975 (1953); *Chem. Abstr.*, **48**, 5674 (1954).

(8) P. Zuman, *Collection Czech. Chem. Commun.*, **15**, 839 (1950).

(9) R. E. Van Atta and D. R. Jamieson, *Anal. Chem.*, **31**, 1217 (1959).

Table I. Oximation of Acetone in the Presence of Methylamine from pH 8.5 to 12.5

pH	Obsd rate constant × 1000, sec^{-1} (A)	Background[b] × 1000, sec^{-1} (B)	$[MeNH_2]$ (free) × 100, *M*	k_{imine}[c] × 1000, sec^{-1} (A − B)	$k_{imine}/[MeNH_2]$[d] × 100, M^{-1} sec^{-1}
8.4	0.35	0.26	0.0625	0.09	14.4
8.8	0.302	0.24	0.156	0.062	3.97
9.0	0.443	0.235	0.245	0.208	8.49
9.11	0.505	0.230	0.312	0.275	8.81
9.5	0.96	0.22	0.735	0.74	10.1
10.0	2.82	0.24	2.01	2.56	12.7
10.5	6.88	0.32	4.42	6.06	13.7
11.0	13.50	2.5	7.15	11.0	15.4
11.5	16.50	7.0	8.9	9.5	10.7
12.0	34.80	24.0	9.6	10.8	11.3
12.5	87.50	85.0	9.9	2.5	...

[a] 0.1 *M* methylamine hydrochloride, 0.02 *M* hydroxylamine hydrochloride, 1.57×10^{-3} *M* acetone, at 25° and ionic strength 0.2. [b] See oximation experiments, Table IV, Figure 4. [c] k_{Schiff} is a pseudo-first-order rate constant = $k_1'[MeNH_2]$. [d] The least-squares mean of these determinations is $11.4 \pm 3.6 \times 10^{-2}$ M^{-1} sec^{-1}.

shown in Figure 2. The intercept of this plot reflects the oximation which proceeds through rate-determining ketimine formation and which thus is not dependent on hydroxylamine concentration.[10] On the other hand, the slope of Figure 2, 11.1×10^{-3} M^{-1} sec^{-1}, contains the rate constants for oxime formation which are dependent on hydroxylamine concentration, and which presumably proceed with (general) base-catalyzed dehydration of the carbinolamine by methylamine, water, or hydroxide ion. Using the data of Table III, an experimental value for the water and hydroxide ion contribution can be obtained (assuming oxonium ion catalysis is negligible at pH 10). This contribution is found to be equal to the slope of Figure 2 (12×10^{-3} M^{-1} sec^{-1}). Thus, the sole function of methylamine in catalyzing oxime formation is to act as a nucleophilic catalyst (*via* ketimine formation) rather than to act as a general basic catalyst.

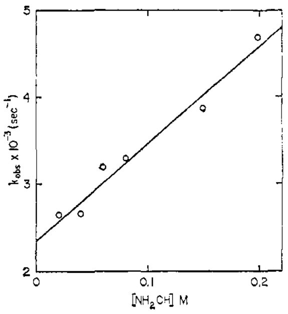

Figure 2. The effect of hydroxylamine concentration on the oximation of acetone at pH 10, μ = 0.2, 0.1 *M* methylamine and 1.57×10^{-3} *M* acetone.

The rate of oximation of benzaldehyde was measured from pH 6 to 13 (Figure 3 and Table II). The observed rate constant was found to vary with pH according to oxonium ion and hydroxide ion catalysis in this range, although below pH 6, the observed rate constant is expected to level off and then decrease as the pH is lowered in proportion to the free hydroxylamine concentration.[11] The catalytic rate constants for oxonium and hydroxide ion catalysis obtained from Figure 3 are collected in Table III.

Table II. Oximation of Benzaldehyde[a]

pH	$[C_6H_5CHO]$ × 10^4 *M*	[Boric acid] × 10^2 *M*	k_{obsd} × 10^3 sec^{-1}	$E_{25°}^{obsd}$ (in water)	$E_{25°}^{obsd}$ (init)	K[c,e,f] × 10^2 *M*
6.0	0.734	0	40.3	0.65	0.46	11.6
6.5	0.734	0	15.1	0.65	0.28	5.9
7.05[b]	0.88	0	4.17	1.01	0.37	5.4
7.1 (pD)[b]	0.88	0	6.6	1.01	0.53	8.9
7.7	0.734	1	0.892	0.65	0.27	6.95
8.55	0.734	1	0.467	0.65	0.25	6.25
9.0	0.734	1	1.21	0.65	0.22	5.1
9.5[b]	2.2	1	2.56	1.95[d]	0.52	3.6
9.9 (pD)[b]	2.2	1	1.12	1.95[d]	0.61	4.55
10.2	0.734	0.5	14.6	0.65	0.24	5.85
10.28	0.734	1	14.0	0.65	0.19	4.15
11.08	0.734	1	71.0	0.65	0.25	6.25

[a] 25°, followed at 250 mμ, ionic strength 0.11, 0.1 *M* hydroxylamine. [b] 1 ml of solution. [c] For a comparison see ref 11. [d] Calculated from the dilution of the same volume of benzaldehyde solution in 3 ml of water. [e] Relatively large errors in *K* probably due to volume deviations in adding the benzaldehyde. $E_{25°}$ (in water) was determined once for each concentration of benzaldehyde employed. [f] *K* was determined according to Jencks:[11] $K = [carbonyl] \cdot [NH_2OH]/[carbinolamine] = E_{25°}\,(init),\ [NH_2OH]/E_{25°}\,(in\ water) - E_{25°}\,(init)$.

Table III. Dehydration Rate Constants of Carbinolamines from Hydroxylamine at 25°

Carbonyl compd	Catalyst	k_2, M^{-1} sec^{-1}	Solvent
Acetone[b]	Hydroxide ion	1.25×10^{2}	Water
	Water	1.27×10^{-4}[a]	Water
	Oxonium ion	1.52×10^{6} [11]	Water
Benzaldehyde[c]	Hydroxide ion	3.03	Water
	Deuteroxide ion[d]	4.23	Deuterium oxide
	Oxonium ion	2.77×10^{3}	Water
	Deuteroxonium ion[d]	9.2×10^{3}	Deuterium oxide

[a] The concentration of water is considered to be 55.5 *M*. [b] The equilibrium constant of carbinolamine formation used in the calculation of the dehydration rate constant was taken as 1.0 M^{-1}.[11] [c] The equilibrium constants of carbinolamine formation used in the calculation of the dehydration rate constant were those of Table II. [d] The equilibrium constants of carbinolamine formation were quite similar in water and D_2O (see Table II).

The rate of oximation of acetone was also measured over the same pH range (Figure 4 and Table IV). Again the rate constant was found to depend on the

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(10) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, 84, 832 (1962).
(11) W. P. Jencks, *ibid.*, 81, 475 (1959).

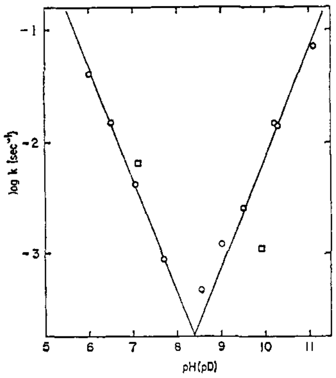


Figure 3. The oximation of benzaldehyde at 25.0°, μ = 0.11, 0.1 M hydroxylamine, 0.734–2.2 × 10^{-4} M benzaldehyde. The squares are reactions in deuterium oxide solvent. The solid lines have slopes of −1 and +1.

oxonium and hydroxide ion concentrations. However, in this oximation, there is also a region where the rate constant is independent of pH (pH 8–10). The catalytic rate constants of the oxonium ion, hydroxide ion, and water catalyses obtained from Figure 4 are also collected in Table III.

Table IV. The Oximation of Acetone at 25°[a]

pH	Borate concn × 10^2 M	k' sec^{-1} × 10^3
6.5	...	8.2
7.0	...	3.48 (3.29)[11]
7.7	...	0.835
8.5	3	0.246
9.0	3	0.233
9.22	6	0.32
9.55	3	0.214
10.0	3	0.24
10.15	6	0.456
11.0	2	2.52
11.5	2	6.95
12.0	2	24.9
12.0	4	18.9
12.5	2	86.0

[a] 0.02 M hydroxylamine, ionic strength 0.2.

The effect of deuterium oxide on the oxonium ion and hydroxide ion catalyzed oximations of benzaldehyde were carried out at pH(D) 7.1 and 9.5, respectively. Benzaldehyde was used in the oximation experiments conducted in heavy water since under the conditions of the reactions, acetone would undergo considerable deuterium exchange on its α-carbon atoms and thus lead to the confusion of a secondary isotope effect. The oximation reaction at neutrality or above can be expressed in terms of eq 3, where K is the equilibrium constant for carbinolamine formation = $(R_2CO)\cdot(NH_2OH)/(\text{carbinolamine})$ and k_2 is either $k_2^{H^+}$ or $k_2^{OH^-}$ depending on the catalysis of the dehydration

$$R_2CO + NH_2OH \underset{}{\overset{K}{\rightleftarrows}} \text{carbinolamine} \xrightarrow{k_2} \text{oxime} \quad (3)$$

step. Thus, the rate of dehydration of the carbinolamine to produce oxime under either oxonium or hydroxide ion catalysis can be calculated knowing the equilibrium constant of carbinolamine formation.

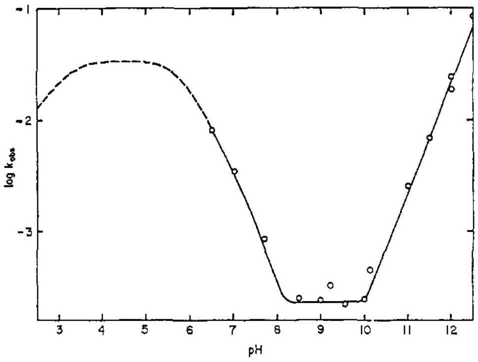


Figure 4. The oximation of acetone at 25.0°, μ = 0.2, 0.02 M hydroxylamine. The solid line from 7 to 8 has a slope of −1 and the line from 10 to 12.5 has a slope of +1.

The rate constants k_2 were calculated in this manner under conditions of oxonium ion catalysis at pH 7.1 and under conditions of hydroxide ion catalysis at pH 9.5 (see Figure 3). These rate constants, k_2, were compared with the k_2's of corresponding reactions carried out in deuterium oxide at pD 7.1 and 9.5. In order to get comparable values of $k_2^{OH^-}$ and $k_2^{OD^-}$, the pH and pD must be transformed to concentrations of OH^- and OD^- (see Table III) and the dehydration constants must be converted to second-order constants. When this is done, it is found that $k_2^{OH^-} = 3.03$ M^{-1} sec^{-1} and $k_2^{OD^-} = 4.23$ M^{-1} sec^{-1}. Thus $k_2^{OD^-}/k_2^{OH^-} = 1.40$. Likewise, for the oxonium ion catalyzed reactions, $k_2^H = 2.77 \times 10^3$ M^{-1} sec^{-1} and $k_2^D = 9.2 \times 10^3$ M^{-1} sec^{-1}, and $k_2^D/k_2^H = 3.3$.

Discussion

Ketimine Formation. The direct spectrophotometric determination of the rate constant of ketimine formation from acetone and methylamine yields a value which is equivalent to the rate constant determined by following the formation of acetoxime from acetone and hydroxylamine in the presence of methylamine according to the method of Cordes and Jencks.[4] The equivalence of these rate constants is a confirmation of the validity of the latter procedure.

From the hydrolysis of N-benzylidene-1,1-dimethylmethylamine, the microscopic reverse of ketimine formation, dehydration of the carbinolamine may be concluded to be rate-determining above pH 4.[13] Thus at the alkaline pH's studied here, the rate-determining step of the formation of ketimine would be expected to again be the dehydration of the carbinolamine. That is, in the formation of the ketimine shown in eq 4, $k_{-1} > k_2$, k_1/k_{-1} is a fast preequilibrium,

$$(CH_3)_2CO + CH_3NH_2 \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} (CH_3)_2CH(OH)NHCH_3 \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} (CH_3)_2C{=}NCH_3 + H_2O \quad (4)$$

and k_2 is the rate-determining step of the reaction. Thus, when methylamine is in great excess over acetone

$$\text{rate} = K_{\text{imine}}(\text{acetone})$$

and

$$K_{\text{imine}} = \frac{k_1}{k_{-1}}k_2(\text{methylamine})$$

The plot of k_{imine} *vs.* pH shown in Figure 1 shows dependence on a single basic group of $pK_a = 10.6$, the pK_a of methylamine. Thus, it appears that neither the equilibrium constant, k_1/k_{-1}, nor the dehydration rate constant, k_2, is pH dependent. Therefore, the dehydration of the carbinolamine can be neither hydroxide ion nor oxonium ion catalyzed. The reaction can, however, be either a water-catalyzed reaction or a spontaneous reaction.

Jencks[12] considers that the predominant pathway for dehydration of the carbinolamine formed from a strongly basic amine involves the direct expulsion of a hydroxide ion.

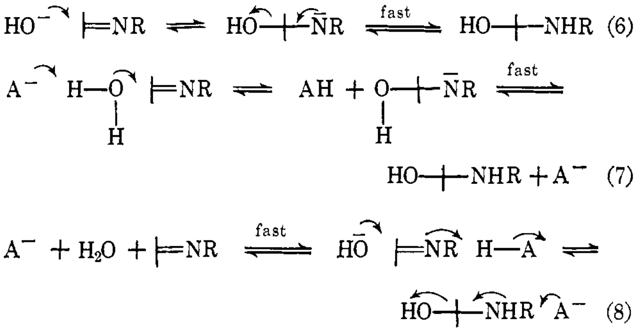
$$H_2O + {>}{=}NR \overset{\text{fast}}{\rightleftharpoons} HO^- + {>}{=}\overset{+}{N}HR \rightleftharpoons HO{-}{>}{-}\ddot{N}HR \qquad (5)$$

The electron pair on the nitrogen atom provides the driving force for this reaction. This mechanism is borne out in experiments on the hydrolysis of benzylidene-1,1-dimethylethylamine and benzhydrylidenedimethylammonium ion at alkaline pH.[13,14] The rate-limiting formation of carbinolamine in these reactions occurred by the attack of hydroxide ion on the protonated ketimine and not by water attack on the unprotonated base. These hydrolyses are the microscopic reverse of the ketimine formation investigated in this work. The analogy between the two reverse reactions is further strengthened since the amines in both reactions are strongly basic. It may therefore be concluded that the mechanism of the dehydration of the carbinolamine intermediate from acetone and methylamine in the pH range 8 to 12 involves the direct expulsion of hydroxide ion (eq 5) and does not involve water as a general basic catalyst.

Oximation. The oximation of benzaldehyde and acetone has been studied from approximately pH 6 to 12. In both the benzaldehyde and acetone reactions, a reaction dependent on oxonium ion and a reaction dependent on hydroxide ion have been observed. In the acetone reaction, a reaction independent of pH has been observed. Each of these reactions will be discussed.

Acid Catalysis. Around neutral pH abundant evidence indicates that the rate-determining step in oxime formation involves the dehydration of the carbinolamine (whereas the formation of the carbinolamine is rate determing at low pH's).[15] The dehydration of the carbinolamine is catalyzed by both hydronium ion and general acids.[11] The carbinolamine under consideration here is derived from a nitrogen base with a strongly electron-withdrawing group. Even in the dehydration of such carbinolamines, general acid catalysis is observed,[12] although the fact that it is not very important in comparison to oxonium ion catalysis suggests that the value of the Brønsted α may be large for such reactions. The observation here of an inverse deuterium isotope effect in the acid-catalyzed dehydration of the carbinolamine derived from benzaldehyde and hydroxylamine and the similar observation in the acid-catalyzed dehydration of the carbinolamine derived from *p*-chlorobenzaldehyde and semicarbazide are very difficult to reconcile with the general acid character of these reactions. In general acid catalyzed reactions, a rate-determining proton transfer occurs which usually gives rise to a normal isotope effect. On the other hand, a specific oxonium ion catalysis can be shown to lead to an inverse isotope effect, as observed here. Thus, a conflict appears to exist between the fact that this reaction is known to be catalyzed by general acids and the fact that the deuterium isotope effect is an inverse one. Because predictions of kinetic isotope effects are less certain at the moment than direct observation of general catalysis, the latter must be given more weight.[16,17]

Base Catalysis. At alkaline pH's, oxime formation is catalyzed by hydroxide ion.[15] In the present studies, dependence of the oximation reaction on the hydroxide ion concentration is seen above pH 8.5 in the benzaldehyde reaction and above pH 10 in the acetone reaction. No investigations concerning the nature of this reaction have been made but Jencks has suggested three mechanisms for the base-catalyzed dehydration of the carbinolamine (and its reverse) when this step is rate limiting.[12] These mechanisms involving specific hydroxide ion and general base catalysis are shown below.



(6)

(7)

(8)

No general base catalysis has previously been found for the dehydration of carbinolamines. In the oximation of *d*-carvone,[18] a levelling off in rate was observed as the pH was decreased, but an explanation other than general base catalysis was given. Furthermore, the system was complicated by a conjugated unsaturated group.

One may ask whether the hydroxide ion catalysis is best described as a general basic catalysis, or whether it corresponds to a specific hydroxide ion catalysis. This question can be decided by a consideration of the effect of deuterium oxide on the hydroxide ion catalyzed reaction.[19] For mechanism 8, the deuterium oxide isotope effect may be calculated in the following way. The rate-determining step involves abstraction of a proton (or deuteron) from the carbinolamine by hydroxide ion (or deuteroxide ion). Breaking an N–H bond in the rate-determining step of a reaction is 8.5-fold faster than breaking an N–D bond.[20] On

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[12] W. P. Jencks, "Progress in Physical Organic Chemistry," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1965, pp 96, 98.

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

[14] K. Koehler, W. Sandstrom, and E. H. Cordes, *ibid.*, **86**, 2413 (1964).

[15] See ref 12, p 63.

[16] B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, **82**, 1773 (1960).

[17] A general acid catalysis could yield an inverse deuterium oxide isotope effect for oxonium ion if the proton of the catalyst were largely transferred in the transition state. This interpretation may be valid since its prediction, a large Brønsted α, is found (see later). *Cf.* A. J. Kresge and R. J. Preto, *ibid.*, **87**, 4596 (1965).

[18] G. Baddeley and R. M. Topping, *Chem. Ind.* (London), 1963 (1958).

[19] R. Stewart and J. P. O'Donnell, *Can. J. Chem.* **42**, 1682, 1694 (1964).

the other hand, deuteroxide ion is a 1.4-fold better base than is hydroxide ion.[21] Thus, the calculated $k_2^{OD^-}/k_2^{OH^-} = 0.165$. The experimental value of this ratio at pH(D) 9.5 is 1.4, indicating that mechanism 8 cannot be operative. Mechanism 7 can also be eliminated as a description of the hydroxide ion catalysis in a similar fashion, since it contains a preequilibrium proton transfer coupled with a rate-determining proton transfer. On the other hand, mechanism 6 involving specific hydroxide ion catalysis is consistent with the observed "inverse" deuterium oxide isotope effect. The dehydration of the carbinolamine according to mechanism 6 involves a preequilibrium proton transfer followed by a rate-determining decomposition of the conjugate base of the carbinolamine. The over-all rate constant in water and deuterium oxide may therefore be expressed as

$$k_2^{OD^-}/k_2^{OH^-} = \frac{K_w^{H_2O}K_a^{D_2O}k^D}{K_w^{D_2O}K_a^{D_2O}k^H}$$

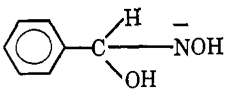
where the K_w's are the autoprotolysis constants of water and deuterium oxide, the K_a's are the ionization constants of the carbinolamine as acids, and the k's are the rate contants of the decomposition of the conjugate bases of the carbinolamine. k^D/k^H can be estimated as 1.4 because the reverse reaction, the attack of hydroxide ion on the ketimine, is estimated to have k^D/k^H *ca.* 1.4[21] and the isotope effect on the equilibrium constant k^D/k^H can be taken as negligible since no proton bond is broken.[22] Furthermore, $K_a^{H_2O}/K_a^{D_2O}$ is approximately 3.[23] Thus $k_2^{OD^-}/k_2^{OH^-}$ can be calculated to be

$$k_2^{OD^-}/k_2^{OH^-} = 6.5(1/3)(1.4) = 3.15$$

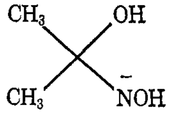
This calculation is in qualitative and reasonable quantitative agreement with the experimental value of 1.4. Considering the assumptions which led to this qualitative agreement and the fact that no other mechanism gives a calculated inverse isotope effect at all, the deuterium oxide isotope effect is a reasonable criterion to specify mechanism 10 for the hydroxide ion catalyzed reaction.[24]

Water Catalysis. An important finding of this work is that the oximation of acetone is independent of pH from 8.5 to 10. This region may be described as a region in which the dehydration of the carbinolamine is catalyzed by water acting either as a general base or general acid. Since the oxonium and hydroxide ion reactions considered above have been described as general acid and specific base catalyses, respectively, the easiest description of the water reaction is a general acid catalysis by water. If the data of the oxonium ion and water catalyses of Table III are interpreted in this fashion together with data for phosphate ion catalysis,[11] a Brønsted plot for general acid catalysis can be constructed which has a slope (α) of approximately 0.6, a reasonable number in the light of the previous discussion. Thus, the Brønsted α of acid catalysis and the inverse deuterium oxide effect of acid catalysis favor general acid catalysis with a transition state close to the fully protonated carbinolamine.

Rate Constants of Dehydration. It is of interest to compare the dehydration rates for the oximation of benzaldehyde and acetone. The carbinolamine of benzaldehyde dehydrates *ca.* 10^3 or 10^2 times more slowly than the carbinolamine of acetone in oxonium ion or hydroxide ion catalysis, respectively (see Table III). Let us consider the hydroxide ion catalyzed reactions. The pK_a's of the two carbinolamines would not be expected to be very different from one another. Therefore, at equivalent hydroxide ion concentrations the species I and II would be expected to be formed in equivalent concentrations. If the dehydration transition states resemble those of the corresponding oxonium ion reactions, they must be close to products and under these conditions I should react faster than II due to the resonance interaction between the incipient carbon–nitrogen double bond and the aromatic ring of I. The observed faster reactivity of II may be explained by saying that the rates are sterically controlled and that the relief of steric strain from II is greater than that from I. A similar argument may be applied to the corresponding oxonium ion catalyses.



I



II

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(20) K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955); R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959.

(21) T. Riley and F. A. Long, *J. Am. Chem. Soc.*, **84**, 522 (1962).

(22) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, Chapter 11.

(23) E. Högfeldt and J. Bigeleisen, *J. Am. Chem. Soc.*, **82**, 15 (1960).

(24) Equation 12 could account for the hydroxide ion catalyzed reaction and its inverse isotope effect if the transition state resembled the products; but see the discussion on water catalysis.