

Secondary Amine Catalysis of the Oximation of Acetone^{1a}

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The equilibrium constants for addition of hydroxylamine to acetone to give a carbinolamine and for oxime formation have been found to be 0.59 and $4.65 \times 10^5 \text{ M}^{-1}$, respectively, in water at 35 °C. The pK_a of the protonated oxime is 1.54. The kinetics of oxime formation have been studied over the pH range 4.5–12.7 and the reaction found to be catalyzed by pyrrolidine, dimethylamine, and morpholine. These secondary amines act as catalysts by transforming acetone to iminium ions that then react with hydroxylamine to give acetoxime. Over the pH range studied (~8.5–10.3) the amines are in rapid equilibrium with intermediates of the type $\text{Me}_2\text{C}(\text{OH})\text{NR}_2$, which then undergo uncatalyzed loss of hydroxide ions to give iminium ions. The efficiency of capture of the iminium ion derived from pyrrolidine was observed to increase with increasing concentrations of hydroxylamine, above pH 9, at least. Under the conditions used, capture of the iminium ions derived from dimethylamine and morpholine was almost complete. Rate constants for formation of iminium ions from pyrrolidine, dimethylamine, and morpholine are 4.25, 0.0504, and $0.00109 \text{ M}^{-1} \text{ s}^{-1}$ in water at 35 °C. These relative reactivities are rationalized in terms of polar effects and steric effects that are similar to those seen in the solvolysis of tertiary chlorides, another reaction in which an atom at the reaction center acquires a positive charge and changes its hybridization from sp^3 to sp^2 .

Several publications from this laboratory have described bifunctional catalysis of the removal of α hydrogen from an aldehyde or ketone.² All the bifunctional catalysts used contain a primary amino group, whose function is to transform the carbonyl compound into the iminium ion, whose α -hydrogen atoms are more acidic than those in the original carbonyl compound. Secondary amines should also give iminium ions and should not have the disadvantage that primary amines have in some cases, of transforming most of the carbonyl compound into imine ("nonproductive binding"). The ability of alkyl substituents to stabilize double bonds, well known in the cases of carbon-carbon and carbon-oxygen double bonds,³ might make equilibrium constants for iminium ion formation larger for secondary than for primary amines if steric effects are not too unfavorable. Under conditions where primary amines catalyze the dedeuteriation of isobutyraldehyde-2-*d* largely via iminium ion formation,⁴ dimethylamine, morpholine, piperazine, and piperidine gave no evidence for such catalysis, acting only as simple bases.⁵ However, it was suggested that this result may reflect a steric effect arising from the branching at the α -carbon atom of isobutyraldehyde. Accordingly, we are interested in learning how rapidly acetone is transformed to an iminium ion by simple secondary amines and whether such iminium ions lead to significant amounts of α -hydrogen exchange.

Many reactions at or near carbonyl groups are catalyzed by primary and secondary amines and seem to involve the intermediate formation of iminium ions.^{6,7} Cordes and Jencks showed that moderate concentrations of semicarbazide or hydroxylamine are sufficient to capture almost all the intermediate imine formed from some primary amines and *p*-chlorobenzaldehyde under at least some conditions.⁸ This provides a method for determining the rate of imine formation that is particularly valuable when the equilibrium constant for imine formation is so small that the amount of imine present at equilibrium in aqueous solution is too small to measure reliably. Hydroxylamine has been used as the capturing agent in studying the kinetics of imine formation from acetone and a number of primary amines.^{9–11} We are not aware of hydroxylamine or semicarbazide capture having been used to measure the rate of formation of iminium ions from a secondary amine and a carbonyl compound. In fact, the rate of morpholine-catalyzed semicarbazone formation by pyridoxal was found to be linear in semicarbazide concentration up to the highest concentration (0.1 M) used, showing that this concentration is nowhere near enough for complete capture of the intermediate iminium ion.¹² Nevertheless, pyridoxal

has certain special structural features that might make it an exceptional case. Therefore we have studied hydroxylamine capture as a method of measuring the rate of iminium ion formation from acetone and secondary amines.

Results and Discussion

Equilibrium Constants for Carbinolamine and Oxime Formation. In previous studies we ignored the amounts of acetone and hydroxylamine that were tied up as carbinolamine in the relatively rapid equilibrium that precedes direct oxime formation.^{10,11}



A value of 1 M^{-1} was obtained for K_{Ca} for acetone at 25 °C and ionic strength 3.2 by spectral measurements extrapolated to zero time.¹² This value promised that the fraction of reactants present as carbinolamine would probably be small at the reactant concentrations we used. However, the oximation of acetone is so fast that the extrapolation used to determine K_{Ca} at 25 °C was rather large, so that the value obtained was said to be less reliable than those obtained for other carbonyl compounds.¹³ Furthermore, it was necessary to use larger concentrations of hydroxylamine in the present study than we had used previously. We therefore determined K_{Ca} under our conditions, 35 °C and ionic strength 0.3. The reactants were mixed in a stopped flow spectrophotometer and absorbance measurements over about the first second were extrapolated to zero time. The K_{Ca} value of 0.59 M^{-1} obtained had a standard deviation of 0.13 M^{-1} . The formation of carbinolamine involves the transformation of two molecules to one molecule and must therefore be accompanied by a large negative change in entropy. Hence, K_{Ca} could be as large as the reported values only if the reaction is exothermic. Therefore K_{Ca} should decrease with increasing temperature. Our value at 35 °C is smaller than the value obtained at 25 °C¹³ and also smaller than a value (1.0 M^{-1}) determined by flow UV spectroscopic measurements at 30 °C and ionic strength 1.96,¹⁴ which was reported after our experiments were completed.

To assure that reversibility in oxime formation may be neglected under our conditions in aqueous solution at 35 °C (as had been assumed to be the case previously^{9,10} on the basis of an equilibrium constant determined at 25 °C^{15,16}), the equilibrium constant was determined. With the abbreviations Ox, Ac, and Hx for acetoxime, acetone, and hydroxylamine,

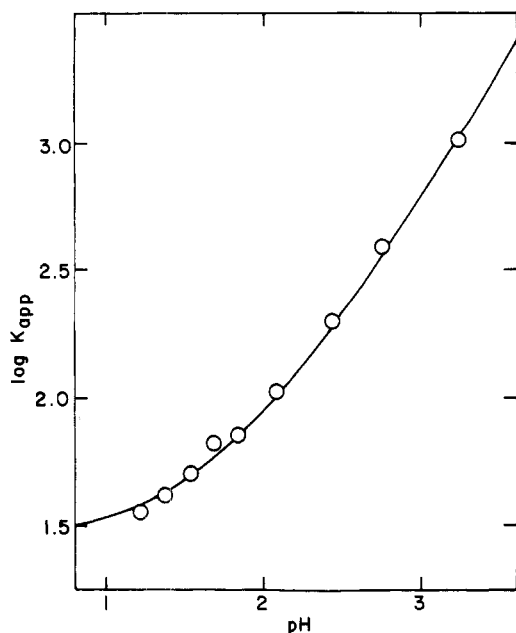


Figure 1. Plot of $\log K_{app}$ for the oximation of acetone in water at 35 °C vs. pH.

respectively, the equilibrium constant sought is defined by

$$K_{Ox} = [Ox]/([Ac][Hx]) \quad (2)$$

The constant determined directly in a given experiment, however, is K_{app} , which is defined by

$$K_{app} = [Ox]_t/([Ac][Hx]_t) \quad (3)$$

in which the subscript t refers to all states of protonation of the species in question. Values of K_{app} were determined by dissolving known amounts of acetoxime in water at various pH's from 1.2 to 3.2 and measuring the absorbance at 277 nm, where the oxime absorbs negligibly, but acetone absorbs almost as strongly as at its 264-nm absorption maximum. The resulting values are plotted logarithmically against the pH in Figure 1. The value of K_{Ca} we have obtained shows that under the present conditions, where less than 1% of the hydroxylamine is ever present in the unprotonated form, the formation of carbinolamine may be neglected. Analogy with studies of the addition of protonated and unprotonated amines to formaldehyde¹⁷ shows that the formation of protonated carbinolamine may also be neglected. Therefore, K_{app} may be expressed as shown in

$$K_{app} = \frac{K_{Ox}K_{HxH}(K_{OxH} + [H^+])}{K_{OxH}(K_{HxH} + [H^+])} \quad (4)$$

in terms of K_{Ox} and of K_{HxH} and K_{OxH} , the thermodynamic acidity constants for hydroxylammonium ions and protonated acetoxime. Values of pK_{HxH} over the ionic strength range 0.06–0.24 used in the experiments were obtained by interpolation between the values 5.73 and 5.76 reported for ionic strengths 0.00 and 0.25, respectively.¹⁸ Least-squares treatment of the K_{app} values obtained gave values of $4.65 \times 10^5 M^{-1}$ and 1.54 for K_{Ox} and pK_{OxH} , with standard deviations of $0.30 \times 10^{-5} M^{-1}$ and 0.05, respectively. The line in Figure 1 is based on these values and an average ionic strength of 0.15.

Oximation in the Absence of Amines. The previous study¹⁰ of the kinetics of the reaction of acetone with hydroxylamine in water at ionic strength 0.3 and 35 °C had been limited to the pH range 6.6–10.7, and had neglected the transformation of part of the reactants to carbinolamine; also, the first-order rate constants obtained using an excess of hy-

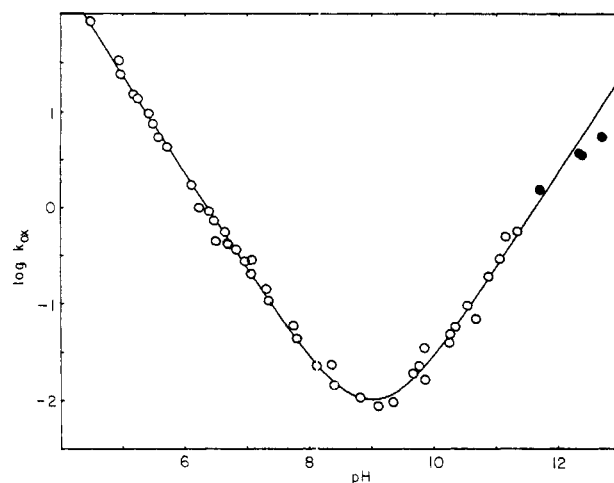


Figure 2. Plot of $\log k_{ox}$ vs. pH for the oximation of acetone in water at 35 °C and ionic strength 0.3. The solid circles are for points not used in the least-squares treatment for the values of the rate constants in eq 6 on which the line is based.

droxylamine had been transformed to second-order rate constants by dividing by the initial hydroxylamine concentration. By use of stopped flow kinetic measurements we have now extended the pH range to 4.5–12.7. The total initial concentration of hydroxylamine, in all states of protonation, was 7.5–12 times that of the acetone. Hence the hydroxylamine concentration was taken as a constant $[Hx]$ equal to its average value during the kinetic run. Then the second-order rate constant for oximation in a given run, k_{ox} , may be expressed in terms of the observed first-order rate constant, k_{obsd} , as shown by

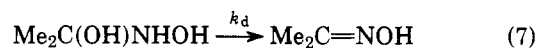
$$k_{ox} = k_{obsd}(1 + K_{Ca}[Hx])/[Hx] \quad (5)$$

The values obtained previously were recalculated using this equation and all the k_{ox} values are plotted logarithmically against pH in Figure 2. The variation of k_{ox} with pH was assumed to follow

$$k_{ox} = k_H[H^+] + k_h[OH^-] + k_w \quad (6)$$

which allows for hydrogen ion catalyzed, hydroxide ion catalyzed, and uncatalyzed reactions. A least-squares treatment of the values obtained below pH 11.4 gave k_H , k_h , and k_w values of $1.64 \times 10^6 M^{-1} s^{-1}$, $80 M^{-1} s^{-1}$, and $5.66 \times 10^{-3} s^{-1}$ with standard deviations of 4.2, 7.2, and 19.4%, respectively. The line in Figure 2 is based on these values. The points obtained above pH 11.6 were not included in the least-squares treatment because the increase in transmittance used to obtain the rate constant was preceded by a rapid unexplained decrease in transmittance, and because in calculating $[Hx]$ a correction had to be made for that part of the hydroxylamine present as its conjugate base. To make this correction the pK value of 13.74 at 25 °C¹⁹ was assumed to change with temperature in the same way that pK_w does, giving a hydroxylamine pK of 13.42 at 35 °C. The values of k_H and k_w are near those obtained previously,¹⁰ but the previous k_h value was 36% smaller than the present one.

The second-order rate constant k_{ox} is the product of the equilibrium constant for carbinolamine formation and k_d ,



the rate constant for dehydration of the carbinolamine. The k_H and k_h terms in eq 6 correspond to hydrogen ion and hydroxide ion catalysis of the dehydration of the carbinolamine. Jencks showed that dehydration of this carbinolamine is subject to general acid catalysis by $H_2PO_4^-$ but not signifi-

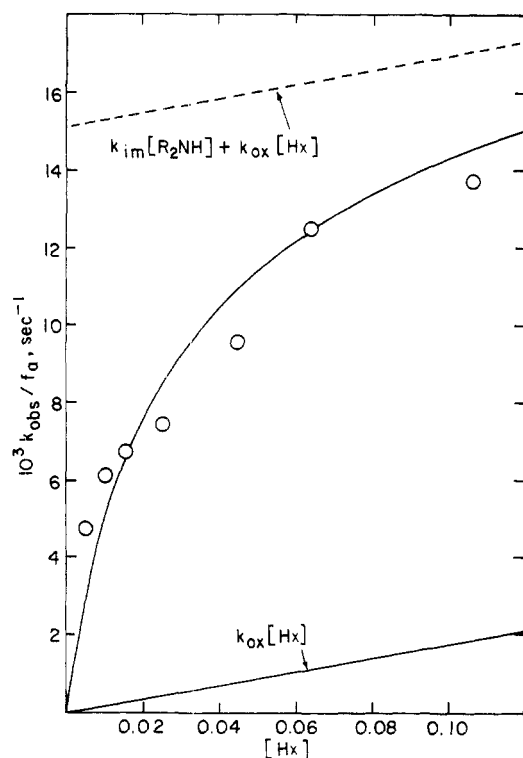


Figure 3. Plot of k_{obsd}/f_a for the oximation of acetone at pH 9.70 ± 0.01 in the presence of 0.103 ± 0.004 M total pyrrolidine vs. the average concentration of hydroxylamine present in the run.

cantly by hydroxylammonium ions (even though these are more acidic than H_2PO_4^-); no evidence for general base catalysis was found.¹³ This is consistent with our lack of evidence for catalysis by the components of the triethylamine, trimethylamine, *N*-methylmorpholine, and hydroxylamine buffers used. It is inconsistent with a recently reported flow-NMR study of the reaction of acetone with hydroxylamine, in which the carbinolamine was observed directly and the rate constant for its dehydration said to increase by more than 110% as the total hydroxylamine concentration was increased from 0.2 to 0.5 M at 30 °C and pH 7.70.¹⁴ However, these rate constants seem clearly to have been miscalculated. They appear to be first-order rate constants for overall disappearance of carbinolamine, but when the carbinolamine is in equilibrium with substantial concentrations of acetone and hydroxylamine the rate of its disappearance depends on the equilibrium constant for carbinolamine formation and the concentrations of acetone and hydroxylamine as well as on the rate constant for dehydration. This error accounts for the value of k_d extrapolated to zero phosphate concentration being reported as 0.012 s^{-1} in the flow-NMR study at 30 °C¹⁴ in contrast to Jencks' value of 0.03 s^{-1} at 25 °C and our value of 0.09 s^{-1} at 35 °C. Recalculation of all the k_d values in the flow-NMR report gives results consistent with the present study and the work of Jencks. It might be mentioned that the same method of calculation seems to have been used in a flow-NMR study of the reaction of hydroxylamine with acetaldehyde.²⁰ However, the equilibrium constant for carbinolamine formation in that case appears to be so large that the limiting reactant is transformed almost entirely to carbinolamine, so that the resulting error in k_d is small.

Secondary Amine Catalysis of Oximation. The oximation of acetone in the presence of secondary amines was usually carried out with substantial excesses of hydroxylamine over acetone and treated as a first-order reaction of acetone in any given run. Equilibrium constants for addition of simple amines to carbonyl groups are so much smaller than for ad-

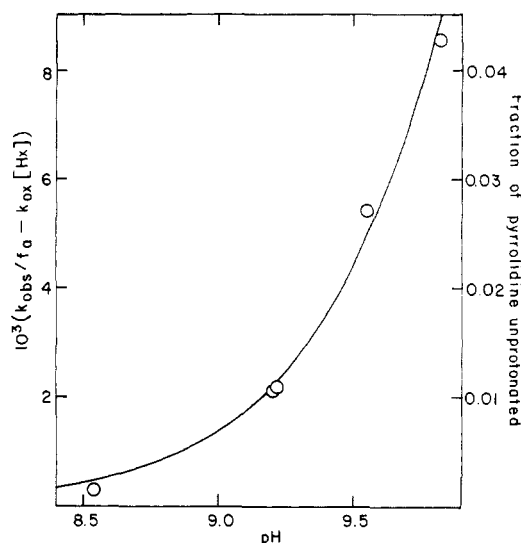


Figure 4. Kinetics of oximation of acetone in the presence of 0.156 M hydroxylamine and 0.049 M total pyrrolidine. The scale for the points is on the left-hand side and the scale for the line is on the right-hand side of the graph.

dition of hydroxylamine²¹ that the amount of reactants tied up by such addition may be neglected. If the secondary amine is transforming acetone to an iminium ion with the second-order rate constant k_{im} , and if the iminium ion is being transformed quantitatively to oxime by the hydroxylamine present, the first-order rate constant for the disappearance of acetone could be expressed as shown in

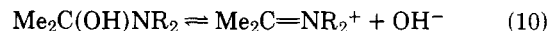
$$k_{\text{obsd}}/f_a = k_{\text{im}}[\text{R}_2\text{NH}] + k_{\text{ox}}[\text{Hx}] \quad (8)$$

in which f_a , the fraction of acetone present as such, rather than in the form of the carbinolamine derived from hydroxylamine, may be expressed as shown in

$$f_a = 1/(K_{\text{Ca}}[\text{Hx}] + 1) \quad (9)$$

The value of f_a was always between 0.88 and 1.00, so that k_{obsd}/f_a is just a slightly "corrected" form of k_{obsd} . According to eq 8, at a given concentration of secondary amine and a given pH, a plot of k_{obsd}/f_a vs. the hydroxylamine concentration should give a straight line of slope k_{ox} and intercept $k_{\text{im}}[\text{R}_2\text{NH}]$. In Figure 3 data obtained at pH 9.70 in the presence of 0.10 M total pyrrolidine are plotted. The points do not describe a straight line and the best straight line through the points would certainly have a much larger slope than k_{ox} ; the straight line at the bottom of the figure is a plot of the first-order rate constant for the uncatalyzed oximation reaction and has a slope of k_{ox} . The experimental points suggest that capture of the intermediate iminium ion by hydroxylamine is incomplete but that increasing hydroxylamine concentrations are making such capture more nearly complete.

In Figure 4 is a plot of k_{obsd}/f_a for 0.049 M pyrrolidine in the presence of 0.156 M hydroxylamine, which is enough to make capture of the iminium ion almost complete. The line shown, whose ordinates refer to the scale on the right-hand side of the graph, is the fraction of pyrrolidine present in the unprotonated form. The close agreement between the points and the line shows the iminium ion formation is largely a reaction of the free amine, that is, that dehydration of the intermediate carbinolamine is largely uncatalyzed.



This conclusion is supported by studies of the pyrrolidine-catalyzed dedeuteriation of acetone- d_6 , which show that even at pH 7 there is no significant acid catalysis of iminium ion

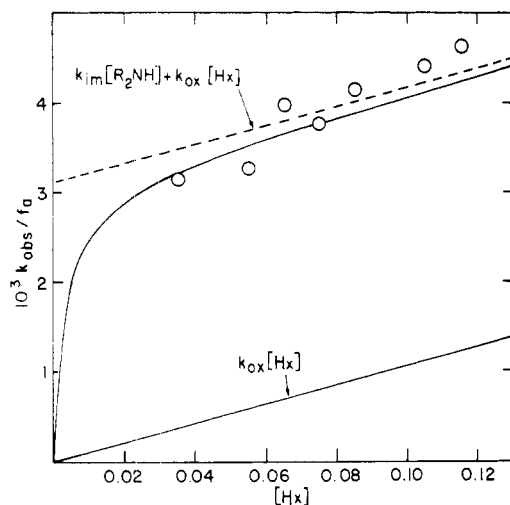
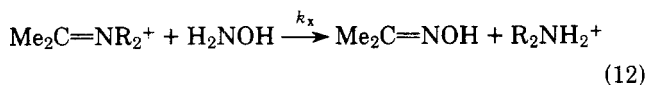
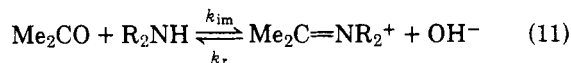


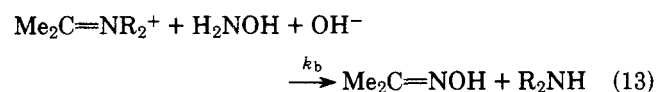
Figure 5. Plot of k_{obsd}/f_a for the oximation of acetone at pH 8.83 \pm 0.01 in the presence of 0.150 M total pyrrolidine vs. the average concentration of hydroxylamine in the run.

formation from acetone and pyrrolidine.²² Application of the principle of microscopic reversibility to eq 10 shows that, in capturing the iminium ion, hydroxylamine must compete with hydroxide ions. In this regard let us examine Figure 5, a plot of k_{obsd}/f_a vs. hydroxylamine concentration in the presence of 0.15 M total pyrrolidine at pH 8.83, where there are less than one-seventh as many hydroxide ions as at pH 9.70. The experimental points describe a line almost parallel to the line at the bottom of the figure, which refers to the rate of uncatalyzed oximation. This shows that capture of the iminium ions by hydroxylamine is almost complete. Such capture was much less complete at pH 9.70 (Figure 3). Apparently the hydroxylamine captures the iminium ion more efficiently at pH 8.83 than at pH 9.70 because it has fewer hydroxide ions to compete with.

The preceding evidence suggests eq 11 and 12



for the secondary amine catalyzed oximation of acetone. Inasmuch as reaction of hydroxylamine with acetone is subject to base catalysis, the possibility of hydroxide ion catalysis of the capture of iminium ions by hydroxylamine is also included in the proposed mechanism (eq 13).



This mechanism, and allowance for that fraction of the acetone tied up as $\text{Me}_2\text{C}(\text{OH})\text{NHOH}$, gives

$$k_{\text{obsd}}/f_a = \frac{k_{\text{im}}[\text{R}_2\text{NH}][\text{Hx}](k_x/k_r + (k_b/k_r)[\text{OH}^-])}{[\text{OH}^-] + [\text{Hx}](k_x/k_r + (k_b/k_r)[\text{OH}^-])} \quad (14)$$

for the observed first-order rate constants. Least-squares treatment of 78 values of k_{obsd} for 0.048–0.150 M total pyrrolidine and 0.0055–0.244 M hydroxylamine over the pH range 8.54–9.81 using values of k_{ox} and f_a calculated from eq 6 and 9, respectively, gave values of $4.25 \pm 0.11 \text{ M}^{-1} \text{ s}^{-1}$, 0.0065 ± 0.0047 , and $2.1 \pm 30 \text{ M}^{-1}$ for k_{im} , k_x/k_r , and k_b/k_r , respectively, where the \pm figures are standard deviations. From these values the k_{obsd} values can be calculated with a standard deviation of 11.0%. There is obvious doubt as to the reality of base ca-

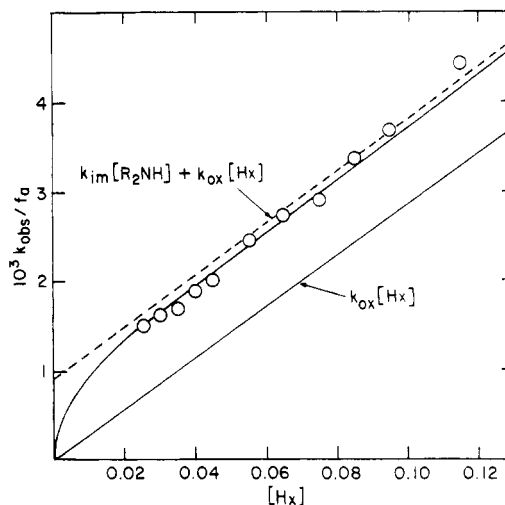


Figure 6. Plot of k_{obsd}/f_a for oximation of acetone at pH 9.98 \pm 0.03 in the presence of 0.100 M total dimethylamine vs. the average concentration of hydroxylamine present during the run.

talysis of the hydroxylamine reaction because k_b/k_r is so much smaller than its standard deviation. When k_b/k_r was set equal to zero the least-squares treatment gave k_{im} and k_x/k_r values of $4.24 \pm 0.10 \text{ M}^{-1} \text{ s}^{-1}$ and 0.0068 ± 0.0006 , respectively, which also fit the k_{obsd} values with a standard deviation of 11.0%. When k_x/k_r was set equal to zero k_{im} rose only to $4.44 \pm 0.17 \text{ M}^{-1} \text{ s}^{-1}$, k_b/k_r became $47 \pm 6 \text{ M}^{-1}$, and the standard deviation in the fit to the k_{obsd} values was 12.6%. Thus there is great uncertainty as to the details concerning the capture of iminium ions by hydroxylamine, i.e., as to the values of k_b/k_r and k_x/k_r , but this results in little uncertainty in k_{im} , whose value was the principal objective of the study. The solid curved lines in Figures 3 and 5 are based on the k_{im} , k_x/k_r , and k_b/k_r values of $4.25 \text{ M}^{-1} \text{ s}^{-1}$, 0.0065 , and 2.1 M^{-1} , respectively. They are, therefore, samples of how the proposed mechanism fits all 78 values of k_{obsd} . The dashed lines at the top of the figures are plots of $k_{\text{im}}[\text{R}_2\text{NH}] + k_{\text{ox}}[\text{Hx}]$, the rate constants for oximation that would be observed if capture of the iminium ions by hydroxylamine were perfect, vs. the hydroxylamine concentration. These lines are asymptotes that are approached by the solid curved lines.

Dimethylamine catalysis of oximation was also studied, as illustrated by the plot in Figure 6 of k_{obsd}/f_a vs. hydroxylamine concentration for 0.10 M total amine at pH 9.98. Dimethylamine is so much poorer than pyrrolidine as a catalyst that for none of the points shown in the figure does the added amine as much as double the reaction rate. From inspection of the points in the figure it is not clear whether iminium ion capture is essentially complete or not. Application of eq 14 to 120 values of k_{obsd} for 0.10 or 0.20 M total dimethylamine and 0.026–0.116 M hydroxylamine over the pH range 8.97–10.33 gave plausible values for k_{im} and k_b/k_r but a small negative value for k_x/k_r . Hence, k_x/k_r was set equal to zero and least-squares values of $0.0504 \pm 0.0029 \text{ M}^{-1} \text{ s}^{-1}$ and $313 \pm 235 \text{ M}^{-1}$ obtained for k_{im} and k_b/k_r , respectively. These values fit the 120 k_{obsd} values with a standard deviation of 9.0% and were the basis of the solid curved line in Figure 6. Since this curve fits the experimental points only slightly better than the dashed line does (and the situation is similar at other pH's), we have not learned anything very reliable about how hydroxylamine captures the iminium ion derived from acetone and dimethylamine. This does not affect the reliability of the k_{im} value obtained, however.

Catalysis of the oximation of acetone by morpholine was studied in less detail than catalysis by pyrrolidine or dimethylamine. Figure 7 is a plot of k_{obsd}/f_a vs. hydroxylamine

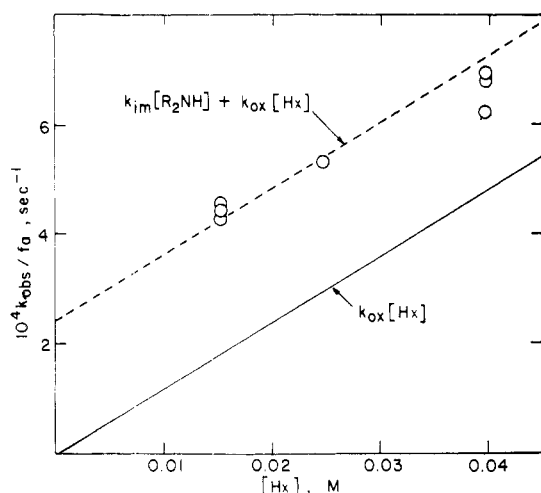


Figure 7. Plot of k_{obsd}/f_a for the oximation of acetone at pH 9.35 in the presence of 0.25 M total morpholine vs. the average concentration of hydroxylamine present in the run.

Table I. Rate Constants for Iminium Ion Formation from Acetone and Secondary Amines in Water at 35 °C^a

Amine	k_{im} , $\text{M}^{-1} \text{s}^{-1}$	Std dev, $\text{M}^{-1} \text{s}^{-1}$	pK
Pyrrolidine	4.25	0.11	10.99
Dimethylamine	0.0504	0.0029	10.49
Morpholine	0.00109	0.00004	8.27

^aAt ionic strength 0.3.

concentration for 0.25 M total morpholine at pH 9.35. As in the case of dimethylamine, much of the total rate observed is seen to be that of the uncatalyzed reaction. The best straight line through the points would certainly not be steeper than the solid line shown, representing the rate constant for uncatalyzed oximation. Capture of the intermediate iminium ions by hydroxylamine was therefore assumed to be complete over the concentration range shown. The data in the figure and nine other k_{obsd} values at pH 9.03–9.77 with a total morpholine concentration of 0.25 M and a hydroxylamine concentration of 0.15 M were fitted to eq 8. The value of k_{im} obtained was $1.09 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ with a standard deviation of $4 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ and the standard deviation of the calculated from the observed rate constants was 6.7%. The dashed line in Figure 7 is based on this k_{im} value.

The values of k_{im} and standard deviations obtained for pyrrolidine, dimethylamine, and morpholine are listed in Table I with the $\text{p}K_a$ values of the protonated amines. The k_{im} values are seen to increase with increasing amine basicity, as might be expected since both iminium ion formation and protonation put a positive charge on the amine nitrogen atom. However, the ability to stabilize a positive charge on nitrogen seems to be an incomplete explanation of the observed structural effects on k_{im} . In Figure 8 $\log k_{\text{im}}$ values for the three secondary amines we have studied are plotted as open circles against the $\text{p}K_a$ values of the conjugate acids of the amines. The solid circles are $\log k_{\text{im}}$ values for primary amines of the type RCH_2NH_2 (also reacting with acetone in water at 35 °C).¹⁰ The points for the primary amines, in which steric effects have been held much more nearly constant, describe a line of slope 0.59. It is plausible that polar effects should give a slope less than 1.0 because only a partial positive charge has been put on the nitrogen atom in the transition state for iminium ion formation. The points for the secondary amines do not lie near any straight line but the best such line would have

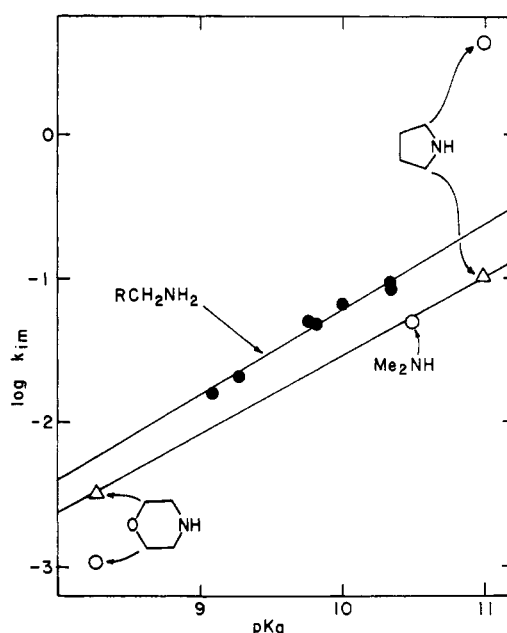


Figure 8. Plot of $\log k_{\text{im}}$ for iminium ion formation from acetone and amines in water at 35 °C vs. $\text{p}K_a$ for the protonated amines: ●, primary amines of the type RCH_2NH_2 ; ○, secondary amines; △, secondary amines corrected for a five- or six-membered ring effect.

a slope considerably larger than 1.0 and hence would be an implausible description of polar effects. The observed reactivity pattern bears some similarity to that observed in the solvolysis of tertiary chlorides in 80% ethanol at 25 °C. If the $>\text{NH}$ groups of pyrrolidine and dimethylamine are transformed to $>\text{C}(\text{Cl})\text{CH}_3$ groups the compounds become 1-methyl-1-chlorocyclopentane and *tert*-butyl chloride, respectively. In the solvolysis of these compounds the carbon atom acquires a positive charge and changes its hybridization from sp^3 to sp^2 just as the analogous nitrogen atom does in the amines. The cyclopentane derivative hydrolyzes faster than *tert*-butyl chloride does, the log of the ratio of the rate constants being 1.62.²³ If the value of $\log k_{\text{im}}$ for pyrrolidine is corrected for this “five-membered ring effect” by subtracting 1.62 from it the triangular point for pyrrolidine is obtained. Transformation of the $>\text{NH}$ groups of morpholine to $>\text{C}(\text{Cl})\text{CH}_3$ gives 4-methyl-4-chlorotetrahydropyran, whose solvolysis rate does not appear to have been measured. However, we may define the log of the ratio of the rate constant for 1-methyl-1-chlorocyclohexane to that for *tert*-butyl chloride as the “six-membered ring effect”. This value is -0.48 and subtraction from $\log k_{\text{im}}$ for morpholine gives the triangular point shown. The two corrected (triangular) points and the points for dimethylamine, the reference species, describe an excellent straight line whose slope (0.54) is not far from that of the line through the primary amine points. The quality of the line is, no doubt, largely coincidence, but the fact that the corrections gave an improved correlation shows that the factors governing the relative magnitudes of k_{im} are very probably similar to those that govern the relative rates of solvolysis of the tertiary chlorides.

Experimental and Data Treatment Section

Acetoxime was vacuum distilled at 68–70 °C giving white crystals, mp 60–61 °C. Amine hydrochlorides were recrystallized before use. Purities of liquids were checked by GLC. A Radiometer Model 26 pH meter was used to obtain the pH, which was taken to be $-\log a_{\text{H}^+}$. Ionic activity coefficients were calculated from the Davies equation.²⁴ First-order rate constants were calculated from spectrophotometric data by a nonlinear regression that minimized the unweighted sum of the squares of $A_{\text{obsd}} - A_{\text{calcd}}$, where the A 's are absorbances, and

Table II. Pyrrolidine-Catalyzed Oximation of Acetone^a

pH	$10^4 k_{\text{obsd}}$, s ⁻¹	$[\text{R}_2\text{NH}]_t$, ^b M	$[\text{Hx}]$, ^c M	n^d	$10^4 k_{\text{obsd}}/f_a$, s ⁻¹	
					Exptl	Calcd ^e
9.705	61.0	0.1145	0.0104	2	61.3	56.6
9.691	62.2	0.0487	0.0642	4	64.6	64.2
9.697	79.9	0.0503	0.0851	4	83.9	74.0
9.703	80.6	0.0499	0.1053	4	85.6	80.4
9.700	87.6	0.0462	0.1340	4	94.6	82.8
9.702	102.3	0.0503	0.2438	3	117.1	112.5

^aIn water at 35 °C and ionic strength 0.3. ^bIn all states of protonation. ^cAverage hydroxylamine concentration throughout the run. ^dNumber of runs made. ^eFrom eq 14 and the least-squares values of k_{im} , $k_{\text{b}}/k_{\text{r}}$, and $k_{\text{x}}/k_{\text{r}}$.

Table III. Dimethylamine-Catalyzed Oximation of Acetone^a

pH	$10^4 k_{\text{obsd}}$, s ⁻¹	$[\text{Hx}]$, ^b M	n^c	$10^4 k_{\text{obsd}}/f_a$, s ⁻¹	
				Exptl	Calcd ^d
8.971	4.38 ^e	0.026	2	4.44	4.54
8.996	5.22 ^e	0.036	2	5.34	5.47
8.982	6.14 ^e	0.046	3	6.30	6.76
8.983	7.07 ^e	0.056	3	7.30	7.82
8.991	7.74 ^e	0.066	3	8.04	8.91
8.995	8.93 ^e	0.076	4	9.33	9.98
9.615	8.24	0.026	3	8.36	7.96
9.601	11.3	0.026	4	11.5	7.78
9.632	11.2	0.046	3	11.5	11.4
9.616	14.5	0.066	4	15.0	14.7
9.614	15.8	0.066	2	16.4	14.6
9.620	19.2	0.096	2	20.3	19.7
9.629	19.5	0.096	2	20.6	19.9
10.312	29.5	0.026	3	29.9	28.3
10.328	35.6	0.036	2	36.4	35.2
10.326	40.5	0.046	3	41.6	41.0
10.322	47.9	0.056	3	49.4	46.4
10.322	56.2	0.066	3	58.4	52.1
10.322	62.0	0.076	2	64.8	57.8
10.320	67.6	0.086	2	71.0	63.2
10.310	76.5	0.096	3	80.8	67.5

^aIn water at 35 °C and ionic strength 0.3, and, unless otherwise noted, a total dimethylamine concentration of 0.100 M. ^bAverage hydroxylamine concentration throughout the run. ^cNumber of runs. ^dFrom eq 14, a $k_{\text{x}}/k_{\text{r}}$ value of zero, and the least-squares values of k_{im} and $k_{\text{b}}/k_{\text{r}}$. ^e0.200 M total dimethylamine.

Table IV. Morpholine-Catalyzed Oximation of Acetone^a

pH	$10^4 k_{\text{obsd}}$, s ⁻¹	$[\text{Am}]_t$, ^b M	$[\text{Hx}]$, ^c M	n^d	$10^4 k_{\text{obsd}}/f_a$, s ⁻¹	
					Exptl	Calcd ^e
9.030	3.96	0.250	0.016	3	3.99	3.81
9.578	5.02	0.250	0.015	3	5.06	4.85
9.767	5.37	0.252	0.015	3	5.42	5.68

^aIn water at 35 °C and ionic strength 0.3. ^bIn all states of protonation. ^cAverage hydroxylamine concentration throughout the run. ^dNumber of runs. ^eFrom eq 8.

gave values for three parameters, the rate constant and the initial and infinite absorbances.

Determination of the Equilibrium Constant for Carbinolamine Formation. In a typical run one syringe of the stopped-flow spectrophotometer contained 0.600 M hydroxylamine hydrochloride and the other 0.600 M sodium hydroxide–0.0100 M acetone. The voltages observed often showed rather random variations as large as 1% in magnitude for about 1 s before settling into a slow increase that was essentially linear in time and amounted to 2–5% over the first 5 s of reaction. Voltages were extrapolated to zero time and compared with similar values obtained when one or the other of the two syringes contained only water or when the first syringe contained sodium hydroxide but no acetone. The assumption that the carbinolamine ab-

sorbs negligibly at the wavelength (275 nm) at which measurements were made gives

$$K_{\text{Ca}} = \frac{\log V_1 V_2 - \log V_3 V_4}{[\text{Hx}] \log (V_4/V_1)} \quad (15)$$

where V_1 is the voltage when the acetone, hydroxylamine hydrochloride, and sodium hydroxide had all been added, V_2 is the voltage when only the sodium hydroxide had been added, V_3 is the voltage when the acetone and sodium hydroxide had been added, and V_4 is the voltage when hydroxylamine hydrochloride and sodium hydroxide had been added.

Determination of the Equilibrium Constant for Oximation. Extinction coefficients for acetoxime in water at 35 °C were deter-

mined in the presence of 0.25 M hydroxylamine–0.25 M hydroxylamine hydrochloride to suppress hydrolysis to acetone. Values of 1.5 and 0.4 M⁻¹ cm⁻¹ were obtained at 264 and 270 nm, respectively, but the value at 277 nm was too small to measure. The values obtained for acetone at these three wavelengths were 18.0, 16.9, and 13.7 M⁻¹ cm⁻¹, respectively. Absorbance measurements were then made on 0.15 M solutions of acetoxime in the presence of 0.013–0.19 M hydrochloric acid and 0.05 M sodium chloride in most cases after 7 h and in all cases after about 13 h. The absorbances after 13 h, which ranged from 0.16 to 0.88, never differed from the values at 7 h by more than 0.011. The pH of the solution was measured after 13 h and ranged from 1.221 to 3.241. The apparent equilibrium constant may be expressed as

$$K_{\text{app}} = \frac{[\text{Ox}]_t - A/\epsilon_{\text{Ac}}}{(A/\epsilon_{\text{Ac}})^2} \quad (16)$$

in which A is the absorbance and ϵ_{Ac} is the extinction coefficient at 277 nm. This equation may be solved to give A as a function of K_{app} and the known quantities $[\text{Ox}]_t$ and ϵ_{Ac} , and then K_{app} may be replaced by the right-hand side of eq 3. A nonlinear least-squares treatment²⁵ was then used to obtain the values of K_{OxH} and K_{Ox} that minimized the sum of the squares of $A_{\text{obsd}} - A_{\text{calcd}}$. Inasmuch as the uncertainty in the absorbance values was thought to be about the same for the various values obtained, all the values were weighted equally.

Stopped-Flow Kinetic Measurements. In a typical run aqueous hydroxylamine hydrochloride was in one syringe and a mixture of acetone and sodium hydroxide and/or a buffer in aqueous solution in the other syringe of the stopped-flow spectrophotometer. The ionic strength of the mixed solution was 0.30, which often required addition of sodium chloride to the solution in one syringe. In the runs below pH 4.95 the initial total concentrations of acetone and hydroxylamine were 0.0020 and 0.0150 M, respectively. In all other runs the acetone concentration was 0.0050 M, with the hydroxylamine concentration being 0.100 M in most of the runs between pH 9.5 and 11.4 and 0.060 M in all the other runs. Most of the rate constants plotted in Figure 2 are the averages of three runs, with about 20 points being taken per run. The buffer was the hydroxylamine in the runs below pH 7, 0.10 M total triethylamine from pH 9.6 to 11.4, and sodium hydroxide at higher pHs.

Oximation of Acetone in the Presence of Added Secondary Amines. These kinetic runs were carried out in essentially the same manner described previously for the reaction in the presence of primary amines. The pH was controlled by the secondary amine buffer except in the dimethylamine runs below pH 9.4 and the pyrrolidine runs around pH 8.8, where a trimethylamine buffer with a total concentration of 0.10 M was used. In the runs using morpholine and most of those using pyrrolidine about 10–20 absorbance values were read from the chart recording. In the runs using dimethylamine and pyrrolidine around pH 8.8 about 40 values were transferred from the Cary 1605 spectrophotometer to a Nicolet Model 1090 digital oscilloscope and later read into the memory of a Hewlett-Packard calculator, Model 9830. In all cases the initial acetone concentration was 0.010 M. The concentrations of hydroxylamine listed and plotted in the various kinetic runs are the average concentrations present over that

part of the reaction that was followed (usually the first 80%, but less than this in the case of the runs using the lowest concentrations of hydroxylamine). The thermodynamic pK_a values used for the conjugate acids of morpholine and pyrrolidine in water at 35 °C were 8.268²⁶ and 10.994,²⁷ respectively. For dimethylamine the value 10.491 was interpolated from measurements at 30 and 40 °C.²⁸ The standard deviations of the rate constants obtained in individual runs were used in the weight matrix when these constants were fit to eq 14 by a nonlinear least-squares treatment.²⁴

Kinetic results not plotted in the various figures are summarized in Tables II, III, and IV for pyrrolidine, dimethylamine, and morpholine, respectively.

Registry No.—Acetone, 67-64-1; acetoxime, 127-06-0; hydroxylamine, 7803-49-8; acetone carbinolamine derivative, 61558-18-7; pyrrolidine, 123-75-1; dimethylamine, 124-40-3; morpholine, 110-91-8.

References and Notes

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