The Mechanism of Nitrone Formation. A Defense of Anthropomorphic Electrons[1]

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Abstract: The rate and equilibrium constants have been compared for the formation of the oxime and the N-methylnitrone of *p*-chlorobenzaldehyde. It was shown by ultraviolet spectroscopy that N-methylhydroxylamine and *p*-chlorobenzaldehyde at alkaline pH rapidly form an intermediate tetrahedral addition compound, which is converted to product in a subsequent slow acid-catalyzed reaction. The rate of α-*p*-chlorophenyl-N-methylnitrone formation exhibits a pH–rate maximum, which is not due to general acid catalysis. The evidence is consistent with a mechanism for nitrone formation in which there is a change in the rate-determining step from a rate-limiting nucleophilic attack of free amine under acidic conditions to a rate-limiting dehydration of the carbinolamine intermediate under neutral and alkaline conditions. It is suggested that the proton transfer associated with the attack step must be intramolecular. The dehydration of the carbinolamine intermediates is subject to general acid catalysis with Brønsted α values of 0.77 for both reactions. The role of the catalyst is discussed and a rule is proposed which states that in general acid–base catalysis of reactions which involve proton transfer to or from nitrogen, oxygen, or sulfur, bases will react with protons which become more acidic and acids will react with atoms which become more basic in the transition state (and products).

Oxime formation has been shown to occur in a two-step process (eq 1) in which acid-catalyzed dehydration of the carbinolamine intermediate is rate determining at neutral and weakly acidic pH and attack of free hydroxylamine on the carbonyl group is rate determining at more acidic pH values.[2] This change in rate-determining step accounts for the characteristic bell-shaped pH–rate profile of this and a number of other reactions of carbonyl groups.[3a] The study of nitrone formation (eq 2) which is reported here was carried out to determine whether this related reaction proceeds by a similar mechanism.[3b]

$$>C{=}O + NH_2OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HO\underset{|}{\overset{|}{C}}\overset{H}{N}OH \xrightarrow{k_2(HA)} >C{=}NOH + H_2O \qquad (1)$$

$$>C{=}O + CH_3NHOH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HO\underset{|}{\overset{|}{C}}\overset{CH_3}{N}OH \xrightarrow{k_2(HA)} >C{=}\underset{CH_3}{\overset{+}{N}}{-}O^- + H_2O \qquad (2)$$

Experimental Section

All organic reagents were commercial products and were recrystallized at least twice before use. Attempts to purify N-methylhydroxylamine hydrochloride by crystallization from ethanol and ether resulted in decomposition of the compound. A purified compound, mp 87–88°, was obtained in the following manner. A yellow contaminant was partially removed by washing with a small volume of cold absolute ethanol on a sintered glass funnel. The residue was extracted several times with 10 volumes of hot acetonitrile. After crystallization in the cold, the product was washed with cold acetonitrile, recrystallized, and finally washed with ethyl acetate. Reagent grade inorganic salts were used without further purification.

Solutions of the aldehyde and nitrogen bases were prepared just prior to use. *p*-Chlorobenzaldehyde was dissolved in 10% ethanol so that the final reaction mixture was, at most, 1.7% in ethanol. Solutions of the nitrogen bases, which contained 10^{-4} *M* ethylenediaminetetraacetic acid, were prepared from their hydrochlorides and were neutralized to the desired pH with potassium hydroxide. Ionic strength was maintained by the addition of potassium chloride. Glass-distilled water was used throughout.

The kinetic and equilibrium measurements were made with a Zeiss PMQ II spectrophotometer equipped with a jacketed cell holder maintained at 25°. Solutions were equilibrated at this temperature prior to mixing and the reaction was initiated by the addition of *p*-chlorobenzaldehyde to the reaction mixture containing the nitrogen base. The pH of the solutions was measured with a glass electrode and the Radiometer PHM 4b pH meter after the measurements were completed.

The ultraviolet spectrum of the product of the reaction of *p*-chlorobenzaldehyde and N-methylhydroxylamine corresponded to the spectrum of an authentic sample of α-*p*-chlorophenyl-N-methylnitrone (mp 127.5–128.5°) which was synthesized according to the procedure of Brady.[4] Ultraviolet spectra were obtained with a Perkin-Elmer Model 350 spectrophotometer.

Rates were followed spectrophotometrically by measuring the increase in absorbance due to product formation at 232 mμ for oxime formation and at 310 mμ for nitrone formation. Kinetic measurements were carried out with the concentration of the nitrogen base in sufficient excess of aldehyde that pseudo-first-order kinetics were obtained.

First-order rate constants for the reaction at neutral and moderately acid pH values were calculated from the half-times of the reaction using the formula $k_{\mathrm{obsd}} = 0.693/t_{1/2}$. The half-time of the reaction was obtained from semilogarithmic plots of the extent of the reaction, $x_\infty - x$, against time. Second-order rate constants, k_2, for the acid-catalyzed dehydration step, were calculated by dividing the observed first-order rate constants by the hydrogen ion activity and r, the fraction of carbonyl compound converted to carbinolamine intermediate; $k_2 = k_{\mathrm{obsd}}/[\mathrm{H}^+]r$. The value of r in each experiment was calculated from the equilibrium constant for

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[2] W. P. Jencks, *J. Am. Chem. Soc.*, 81, 475 (1959).

[3] (a) For a recent compilation of references, see ref 2 of G. E. Lienhard and W. P. Jencks, *ibid.*, 87, 3855 (1965). (b) After the completion of this manuscript, a report by M. Masui and C. Yujima [*J. Chem. Soc., Sect. B*, 56 (1966)] appeared describing the kinetics of the formation of nitrones from a series of aliphatic aldehydes. While the results obtained by these workers are similar to those reported here, the interpretation of the rate constants is different, because the equilibrium formation of an addition intermediate at neutral pH and the decrease in the rate at acid pH below that calculated for rate-determining acid-catalyzed dehydration, indicative of a change in rate-determining step, were not observed under their experimental conditions. It should be noted that the kinetic demonstration of a change in rate-determining step requires a *negative* deviation of the observed rate to a value lower than that predicted by the rate law which holds for the reaction under different experimental conditions. The small decreases in the rate of acetaldehyde formation at acid pH observed by these workers may, in fact, represent the beginning of such a deviation.

[4] O. L. Brady, F. P. Dunn, and R. F. Goldstein, *ibid.*, 2386 (1926).

carbinolamine formation and the concentration of the nitrogen free base using the formula $r = K_1[\text{base}]/(1 + K_1[\text{base}])$. The concentration of the free base was determined from the per cent neutralization of the hydrochloride or was calculated from the measured pH and the pK_a' of the hydroxylammonium ion. The pK_a' values of hydroxylammonium and N-methylhydroxylammonium ions were found to be 6.17 and 6.15, respectively, by electrometric titration at ionic strength 0.5 *M* and 25°.

In acidic solutions nitrone formation does not go to completion at reasonable concentrations of N-methylhydroxylamine hydrochloride, so that the desired pseudo-first-order rate constants, k_f, were obtained from the observed rate constants and the relationships $K' = k_f/k_r = [\text{nitrone}]_{\text{tot}}/[\text{ald}]$ and $k_{\text{obsd}} = k_f + k_r$, where k_f and k_r are the pseudo-first-order rate constants for the forward and reverse reactions, respectively. These constants refer to measurements made at a given concentration of N-methylhydroxylamine hydrochloride and a given acidity, with the concentration of N-methylhydroxylamine hydrochloride in great excess over that of *p*-chlorobenzaldehyde. The values of K' for each run were obtained from the relationship $K' = A/(A_N - A)$, where A is the observed change in absorbance at 310 mμ in a particular run, and A_N is the change in absorbance for complete conversion to the nitrone at the same acidity. The value of A_N was obtained from a plot of the absorbance of the nitrone as a function of acidity, from the data described in the next paragraph. The rate experiments were carried out in 0.01–0.72 *M* hydrochloric acid and 0.02–0.60 *M* N-methylhydroxylamine hydrochloride, which gave values of K' in the range 1.0 to 1.5 in most experiments. The calculated rate constants are based on the measured pH values; a few calculations based on H_0 values[5] gave similar, although not identical, results. The rate of the dehydration step makes a significant contribution to the observed rate even in the most acidic solutions which were examined; consequently the rate constant for the attack of N-methylhydroxylamine on *p*-chlorobenzaldehyde was obtained from the observed rate constants and the steady-state rate eq 4.

Equilibrium constants for the formation and protonation of *p*-chlorobenzaldehyde nitrone were calculated from spectra of solutions of 6×10^{-5} *M* *p*-chlorobenzaldehyde in 0.01, 0.25, 1.0, and 4.0 *M* sulfuric acid which had been allowed to reach equilibrium at each of five different concentrations of N-methylhydroxylamine hydrochloride in the range 0.1–1.0 *M* (0.03 to 0.3 *M* in 0.01 *M* sulfuric acid). Apparent equilibrium constants for nitrone formation at each acidity were obtained from the reciprocal of the negative slope of plots of ΔA against $\Delta A/[CH_3NH_2OH^+]$, where ΔA is the change in absorbance compared to aldehyde alone. From these equilibrium constants and the observed spectra the absorbance of the nitrone at 270 mμ was calculated at each acidity and from the change in this absorbance with pH and H_0 a value of $pK_{PH^+} = 0.35$ for the acid dissociation of the protonated nitrone was calculated. Values of H_0 and h_0 were taken from Paul and Long.[5] Values of $K_{PH^+} = 0.42$ ($pK_{PH^+} = 0.38$) and $K_{H^+} = 1.54$ M^{-1} were obtained from the negative slope and 1/intercept, respectively, of plots of $1/K_{\text{app}}$ against $1/K_{\text{app}}h_0$, where K_{app} is the apparent equilibrium constant for formation of (total) nitrone at each acidity and $K_{H^+} = [{>}C{=}N(CH_3)OH^+]/[{>}C{=}O][CH_3NH_2OH^+]$. The formation of protonated nitrone was found to be more favored in 4 *M* ($K_{\text{app}} = 5.9$ M^{-1}) than in 1 *M* ($K_{\text{app}} = 1.75$ M^{-1}) sulfuric acid, presumably because of changes in the activity of water and in activity coefficients in strong acid, and the former value was not used in the calculations. The equilibrium constant for formation of the free nitrone, $K_{\text{ov}} = [{>}C{=}\overset{+}{N}(CH_3)O^-]/[{>}C{=}O][CH_3NHOH] = 9.4 \times 10^6$ M^{-1}, was calculated from the apparent equilibrium constant under conditions in which the nitrone is not protonated and from the dissociation constant for N-methylhydroxylamine hydrochloride, $pK_a' = 6.15$.

The value of $pK_a' = -1.25$ for the dissociation of the conjugate acid of *p*-chlorobenzaldehyde oxime, reported by Koehler, *et al.*[6] was confirmed by spectrophotometric measurements in the presence of 0.6 *M* hydroxylamine hydrochloride and 0.5–7.0 *M* sulfuric acid. The spectra revealed no hydrolysis to the aldehyde under these conditions. Rate constants for oxime formation were obtained from nine experiments in 0.01–1.0 *M* hydrochloric acid and 0.01–0.04 *M* hydroxylamine hydrochloride in the same manner as described above for nitrone formation, except that it was not necessary to correct for a change in absorbance caused by protonation of the oxime under these conditions. The second-order rate constant for the attack of hydroxylamine on *p*-chlorobenzaldehyde was obtained by dividing k_f by the concentration of free hydroxylamine; in the acidic solutions the dehydration rate does not have a significant influence on the observed rate. The over-all equilibrium constant for oxime formation, $K_{\text{ov}} = [{>}C{=}NOH]/[{>}C{=}O][NH_2OH] = 6.1 \times 10^7$ M^{-1}, was obtained from the ratio of oxime to aldehyde at the end of the reaction in these experiments and from the concentration of free hydroxylamine, based on a pK_a' of hydroxylamine hydrochloride of 6.17 and pH values which were measured with a glass electrode standardized at pH 4.0 with standard buffer and at pH 1.10 with 0.1 *M* hydrochloric acid. From these constants the value of $K_{H^+} = [{>}C{=}NHOH^+]/[{>}C{=}O][NH_3OH^+]$ was calculated to be 2.3 M^{-1}.

The equilibrium constant for addition compound formation was determined from the decrease in the absorption of pyruvate anion at 320 mμ immediately after the addition of N-methylhydroxylamine to six different concentrations between 0.067 and 0.88 *M* in 0.03 *M* phosphate buffer, pH 7.7. The rate of dehydration of the adduct was determined from rate measurements between pH 5.4 and 6.7 with 0.05 *M* total N-methylhydroxylamine, in which the formation of nitrone was followed at 260 mμ; the rate constant was calculated in the same manner as described above for the reaction with *p*-chlorobenzaldehyde.

Attempted Rearrangement of α-*p*-Nitrophenyl-N-ethylnitrone. This nitrone was prepared by the addition of excess *p*-nitrobenzaldehyde dissolved in hot absolute ethyl alcohol to an alcoholic solution of N-ethylhydroxylamine hydrochloride, obtained as a syrup from the reduction of nitroethane.[7] The reaction mixture was shaken with excess solid sodium bicarbonate and allowed to stand at room temperature overnight, followed by refrigeration. The yellow crystals were recrystallized from benzene–petroleum ether, mp 124–125° (lit.[7] mp 122–123°). *Anal.* Calcd for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.70; H, 55.35; N, 14.33. When this nitrone was dissolved in water and heated at 80–90° for 1 hr,[7] only the starting material (74%) crystallized from the reaction mixture. The mother liquor was concentrated on a rotatory evaporator and analyzed by ascending chromatography on Whatman 3MM paper, developed with 0.1 *M* disodium phosphate in water. The spots were visualized with ultraviolet light. Only the nitrone (R_f 0.69) was found in the reaction mixture and there was no indication of the formation of oxime (R_f 0.42).

Results

When either hydroxylamine[2,8] or N-methylhydroxylamine is added to *p*-chlorobenzaldehyde at pH 8.0 there is an immediate drop in the ultraviolet absorbance of the aldehyde, which is caused by its partial conversion to the carbinolamine addition product (eq 1). The dehydration of this intermediate to the oxime or nitrone is slow at this pH, so that with a small extrapolation of the absorbance to the time of mixing, the extent of this initial reaction at different nitrogen base concentrations and, hence, the equilibrium constants for formation of the intermediates may easily be measured. In Figure 1 are shown reciprocal plots of the absorbance change as a function of base concentration; at extrapolation to infinite base concentration the absorbance change corresponds to essentially complete disappearance of the aldehyde absorption at 260 mμ. The equilibrium constants, $K_1 = [HO\overset{|}{\underset{|}{C}}NROH]/[RNHOH][{>}C{=}O]$, for formation of the adducts of *p*-chlorobenzaldehyde with hydroxylamine and N-methylhydroxylamine are 23.5 and 6.6 M^{-1}, respectively (Table I).

The pH–rate profiles for oxime and nitrone formation from *p*-chlorobenzaldehyde in the presence of 0.01 *M* hydroxylamine or 0.2 *M* N-methylhydroxylamine are both bell shaped (Figure 2). The plateau and descending limbs of the curves at high pH are a measure of the amount of carbinolamine formed and the rate

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[5] M. A. Paul and F. A. Long, *Chem. Rev.*, 57, 1 (1957).

[6] K. Koehler, W. Sandstrom, and E. H. Cordes, *J. Am. Chem. Soc.*, 86, 2413 (1964).

[7] G. W. Watt and C. M. Knowles, *J. Org. Chem.*, 8, 540 (1943).

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

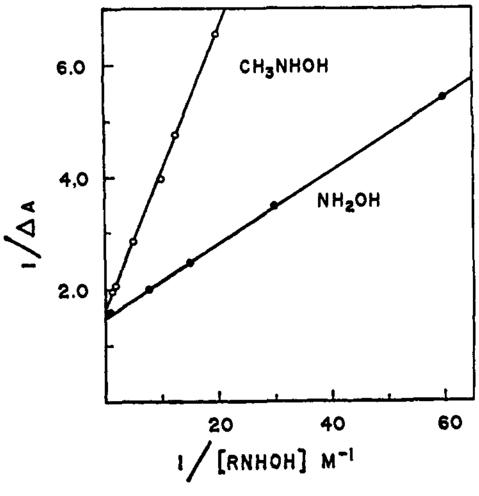

Figure 1. A reciprocal plot of the decrease in *p*-chlorobenzaldehyde absorbance at 260 mμ observed immediately upon the addition of increasing concentrations of hydroxylamine and N-methylhydroxylamine at pH 8.0 and 25°. The reaction mixtures contained for NH_2OH addition 4×10^{-5} *M* *p*-chlorobenzaldehyde, 0.03 *M* phosphate buffer, ionic strength 0.38; for CH_3NHOH addition 2×10^{-4} *M* *p*-chlorobenzaldehyde, 0.05 *M* phosphate buffer, ionic strength 0.49, path length 0.2 cm.

of its acid-catalyzed dehydration. The specific rate constants for dehydration of the carbinolamine adducts, calculated from the observed rates and the equilibrium concentrations of carbinolamine according to the rate law of eq 3, are 3.6-fold smaller for nitrone than for oxime formation (Table I). The calculated rates, based on these rate and equilibrium constants, with a small correction for general acid catalysis by N-methylhydroxylammonium ion, are shown as the dashed lines in Figure 2, and agree satisfactorily with the observed rate constants in this pH region.

$$\text{rate} = k[\text{RNHOH}][\text{>C=O}][\text{H}^+] =$$

$$\frac{k}{K_1}[\text{HO}\overset{|}{\underset{|}{\text{C}}}\text{NROH}][\text{H}^+] = k_2[\text{HO}\overset{|}{\underset{|}{\text{C}}}\text{NROH}][\text{H}^+] \quad (3)$$

Table I. Rate and Equilibrium Constants for the Reaction of Hydroxylamine and N-Methylhydroxylamine with *p*-Chlorobenzaldehyde at 25°[a]

	NH_2OH	CH_3NHOH
K(over-all, M^{-1}) = [P]/[A][N]	6.1×10^7	9.4×10^5
K_1 (M^{-1}) = [C]/[A][N]	23.5	6.60
K_2 = [P]/[C] = K_0/K_1	2.6×10^6	1.42×10^5
k_1, M^{-1} min^{-1}	2.31×10^6	2.5×10^6
k_{-1} (min^{-1}) = k_1/K_1	9.8×10^4	3.8×10^5
k_2, M^{-1} min^{-1}	3.33×10^6	9.2×10^5
k_{-2} (M^{-1} min^{-1}) = k_2/K_2	1.28	6.9
K_{NH^+} (M) = [N][H$^+$]/[NH$^+$]	7.1×10^{-7}	6.8×10^{-7}
K_{PH^+} (M) = [P][H$^+$]/[PH$^+$]	17.8	0.42
K_{H^+} (M^{-1}) = [PH$^+$]/[A][NH$^+$]	2.3	1.54

[a] [P] = $ClC_6H_4CH{=}NOH$ or $ClC_6H_4CH{=}N^+(CH_3)O^-$, [A] = ClC_6H_4CHO, [N] = NH_2OH or CH_3NHOH, [C] = $ClC_6H_4CH(OH)NHOH$ or $ClC_6H_4CH(OH)N(CH_3)OH$.

The equilibrium constant for the formation of the addition compound from N-methylhydroxylamine and pyruvate anion and the rate constant for its dehydration were determined in a similar manner to be 4.4 M^{-1} and 4.1×10^6 M^{-1} min^{-1}, respectively.

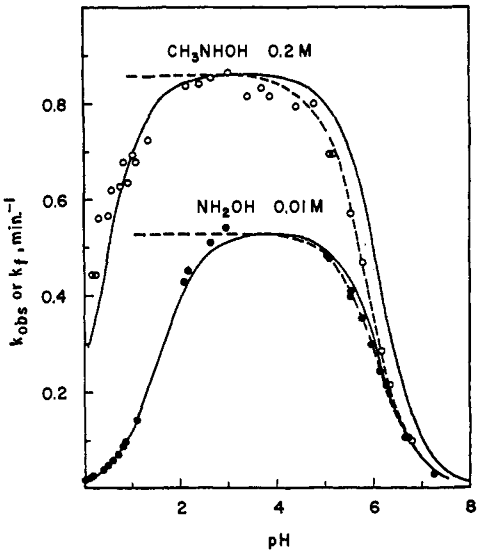

Figure 2. Reaction rates of 0.01 *M* hydroxylamine and 0.2 *M* N-methylhydroxylamine with *p*-chlorobenzaldehyde as a function of pH at 25°. pH 0–2, HCl or H_2SO_4; pH 2–3.5, 0.05 *M* potassium phosphate buffer; pH 3.5–5.0, 0.1 *M* sodium acetate buffer; above pH 5, no added buffer; *p*-chlorobenzaldehyde, 0.7–1.5 $\times$ 10^{-4} *M*; ionic strength 0.5 except in the acid solutions. The rate constants below pH 2 (k_f) were calculated as described in the text; calculated for rate-limiting dehydration of the carbinolamine addition compound (- - - -); calculated for dilute solutions from the steady-state rate eq 4 (———).

At pH values below 2.0 there is a decrease in the rate of nitrone and oxime formation from *p*-chlorobenzaldehyde below that calculated for the equilibrium formation and rate-determining dehydration of the carbinolamine. This is attributed in the nitrone reaction, as in the hydroxylamine reaction,[2] to a change to rate-determining attack of the free nitrogen base on the aldehyde in acid solution. At the lowest pH values examined the rates of oxime formation are directly proportional to the concentration of free nitrogen base and no acid catalysis of the addition step[2,9] was detected. The rates of nitrone formation are more difficult to measure in acid solution because of the relatively unfavorable over-all equilibrium for this reaction (see the Experimental Section). However, the rate of nitrone formation does not appear to fall off as rapidly as the concentration of free N-methylhydroxylamine at the lowest pH values, which suggests that an acid-catalyzed path for the addition of the nitrogen base is significant in this reaction. This conclusion was supported by the observation that the nitrone undergoes rapid hydrolysis in 4 *M* sulfuric acid; since the equilibrium constant is 5.9 M^{-1} at this acidity, an acid-catalyzed condensation reaction must also take place at a significant rate. The rate constant, k_1, for the attack of free N-methylhydroxylamine on *p*-chlorobenzaldehyde is very similar to that for hydroxylamine (Table I). Equation 4, in which N_T is the

$$\frac{\text{rate}}{[N_T][\text{>C=O}]} = \frac{k_{\text{obsd}}}{[N_T]} = \frac{k_1k_2}{\left(\frac{k_{-1}}{[\text{H}^+]} + k_2\right)\left(1 + \frac{[\text{H}^+]}{K_{\text{NH}^+}}\right)} \quad (4)$$

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(9) E. Barrett and A. Lapworth, *J. Chem. Soc.*, **93**, 85 (1908); R. B. Martin, *J. Phys. Chem.*, 68, 1369 (1964).

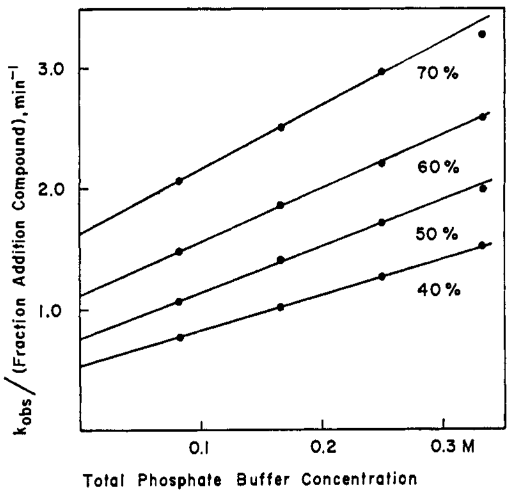

Figure 3. Catalysis by potassium phosphate buffers of the dehydration step of *p*-chlorobenzaldoxime formation at 25°, ionic strength 0.8. The fraction of buffer present as the monoanion is indicated.

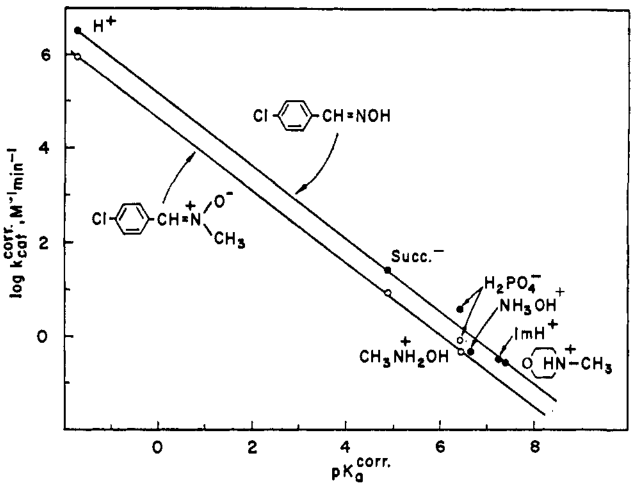

Figure 4. Brønsted plot of the catalytic constants listed in Table II for general acid catalyzed oxime (●) and nitrone (○) formation from *p*-chlorobenzaldehyde at 25°; abbreviations: succ, succinate monoanion; ImH$^+$, imidazolium ion.

total concentration of nitrogen base and K_{NH^+} = [RNHOH][H$^+$]/[RNH$_2$OH$^+$], is the steady-state rate equation for these reactions according to the mechanism of eq 1 and 2 and should describe the rate in dilute solutions over the entire range of pH. The calculated rates from this equation are shown as the solid lines in Figure 2. The calculated lines are in reasonable agreement with the observed rate constants. The positive deviations in the most acid solutions are attributed to acid catalysis of the attack step in the nitrone reaction. In the most alkaline region, the concentration of free nitrogen base is sufficiently large that an appreciable fraction of the aldehyde is converted to the carbinolamine addition compound. Under these conditions the steady-state approximation does not hold and the rates are better described simply by the rate and equilibrium constants of eq 3 and Table I (dashed lines in Figure 2).

The over-all equilibrium constants were calculated from the amount of product formation at equilibrium at acid pH values (Table I). With this information the equilibrium constants and rate constants in both directions for both steps of the reaction were calculated (Table I). The acid dissociation constants for the conjugate acids of the oxime and nitrone of *p*-chlorobenzaldehyde were determined spectrophotometrically. The equilibrium constant, K_{H^+}, for formation of the protonated nitrone from *p*-chlorobenzaldehyde and N-methylhydroxylamine hydrochloride (eq 5) was determined spectrophotometrically and the corresponding constant for protonated oxime formation was calculated from the equilibrium constant for reaction of the uncharged compounds and the acid dissociation constants of hydroxylamine hydrochloride and of the protonated oxime (Table I).

$$RNH_2OH^+ + {>}C{=}O \rightleftharpoons {>}C{=}NROH^+ + H_2O \qquad (5)$$

Oxime[2] and nitrone formation are subject to general acid catalysis under conditions in which the dehydration step is rate-determining; catalysis by phosphate buffer at a number of buffer ratios is illustrated in Figure 3. Changes in pH were observed with increasing concentration of some of the phosphate buffers, but these changes were in a direction which would cause a slight underestimation of the catalytic constants. Catalytic constants for a series of general acids for both reactions were measured at different buffer concentrations and buffer ratios as shown in Table II. The catalytic constants are expressed for the dehydration of the carbinolamine intermediate (eq 6) and were calculated from the

$$\text{rate} = k_{cat}\left[{>}C{<}\begin{matrix}OH\\NROH\end{matrix}\right][HA] \qquad (6)$$

slopes of plots of k_{obsd}/r against the concentration of the catalytically active species of the buffer. The catalytic constants, corrected for statistical effects,[10] are summarized in the form of a Brønsted plot in Figure 4. No statistical correction was made for the hydrated proton because of uncertainty as to the structure of the catalytically active species. Catalysis is observed with both cationic and anionic acids and both classes of acid give catalytic constants which fall near a line with a slope (α) of 0.77. This steep slope makes the determination of catalytic constants difficult in the face of the marked catalysis by the solvated proton and no general acid catalysis could be detected at pH values at which acids as strong as acetic acid exist in the acidic form. Oxalate dianion has no effect on the rate and the rates were insensitive to ionic strength between ionic strength 0.5 and 1.8 at pH 6.18 ± 0.03, which supports the conclusion that it is true general acid catalysis and not a salt effect which is observed in the presence of anionic catalysts. In each case, except for catalysis by hydroxylammonium ion, rate increases of more than 50% of the uncatalyzed rate were observed at the highest catalyst concentrations; with hydroxylammonium ion only a 22% rate increase was observed.

The reaction with methoxyamine is also subject to general acid catalysis by phosphate monoanion. The pseudo-first-order rate constants for the reaction of 10^{-4} *M* *p*-chlorobenzaldehyde with 0.05 *M* methoxylamine were found to increase progressively from 0.064 to 0.106 min^{-1} with increasing phosphate buffer con-

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[10] S. W. Benson, *J. Am. Chem. Soc.*, 80, 5151 (1958); D. Bishop and K. J. Laidler, *J. Chem. Phys.*, 42, 1688 (1965). These two procedures give identical results for the acids examined in this study.

Table II. Catalytic Constants of Acids for the Dehydration Step of Oxime and Nitrone Formation from *p*-Chlorobenzaldehyde at 25°

Catalyst	Concn range, M	Buffer ratio, A^-/HA	pH	No. of detmn	Ionic[a] strength	pK_a	p$K_a^{cor\,b}$	k,[c,d] M^{-1} min^{-1}	k_{cat},[e] M^{-1} min^{-1}	k_{cat}^{cor},[b] M^{-1} min^{-1}
Oxime Formation										
Hydrated proton			5.54	1	0.5	−1.74	−1.74		3.28×10^6	3.33×10^6
			5.79	1					3.42×10^6	
			6.14	1					3.30×10^6	
			6.68	1					3.30×10^6	
Succinate monoanion	0.15–0.45	4/1	5.94	4	1.0	5.48	4.88	5.2	26	26
Phosphate monoanion	0.083–0.33	3/7	6.24	4	0.8	6.60	6.43	5.3	7.6	3.7
		2/3	6.45	4				4.4	7.3	
		1/1	6.63	4				3.8	7.5	
		3/2	6.86	4				3.0	7.4	
Hydroxylamine HCl	0.20–0.60	7/3	6.60	6	1.0	6.17	6.65	0.40	1.3	0.45
Imidazole HCl	0.25–1.00	1/9	6.13	4	1.0	6.95	7.25	0.57	0.63	0.31
		1/1	7.13	4				0.30	0.61	
N-Methylmorpholine HCl	0.25–1.00	1/4	7.17	4	1.2	7.41	7.41	0.23	0.29	0.27
		2/3	7.65	4				0.16	0.25	
Nitrone Formation										
Hydrated proton			5.19	1	0.5	−1.74	−1.74		8.9×10^5	9.2×10^5
			5.54	1					8.8×10^5	
			5.78	1					9.4×10^5	
			6.17	1					9.2×10^5	
			6.35	1					9.2×10^5	
			6.80	1					9.9×10^5	
Succinate monoanion	0.066–0.533	7/3	5.79	4	1.5	5.48	4.88	2.6	8.6	8.8
		4/1	6.03	3				1.8	8.9	
N-Methylhydroxylamine HCl	0.075–0.50	7/3	6.55	4	0.5	6.15	6.45	0.28	0.92	0.46
Phosphate monoanion	0.083–0.333	2/3	6.53	3	0.8	6.60	6.43	0.97	1.62	0.81
		1/1	6.67	4				0.80	1.60	
Oxalate dianion	0.066–0.533	1/0	5.50	3	1.25	4.19		0		0
		1/0	5.90	3				0		0

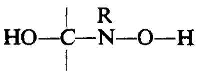
[a] No variation in rates was observed with changes in ionic strength from 0.5 to 1.8 at pH 6.18 ± 0.03. [b] Statistical corrections were made by the method of Benson;[10] no corrections were made for the hydrated proton. [c] $((k_{obsd} - k_{intercept})/(\text{fraction addition compound}))/[\text{total buffer}]$. [d] k_{obsd} for nitrone formation was corrected for N-methylhydroxylammonium ion catalysis. [e] $((k_{obsd} - k_{intercept}))/(\text{fraction addition compound}))/[\text{catalytic species}]$.

centration from 0.1 to 0.5 M at pH 6.09 ± 0.01, ionic strength 1.0 M, measured at 232 mμ; the catalysis was much less at pH 6.7. This suggests that the similar catalysis which is observed with the hydroxylamine and N-methylhydroxylamine reactions does not require the presence of a proton on the hydroxylamine oxygen atom.

It has been reported that the nitrone formed from ethylhydroxylamine and *p*-nitrobenzaldehyde undergoes hydrolysis to *p*-nitrobenzaldoxime and ethyl alcohol.[7] We were anxious to examine this interesting reaction in more detail, but were not able to detect the formation of *p*-nitrobenzaldoxime from this nitrone.

Discussion

In all of its major characteristics, the mechanism of nitrone formation appears to be the same as that for oxime formation, and the differences which do exist are those which might be expected from the differences in the properties of the reactants and products. Nieman, Maimind, and Shemyakin have shown by the use of ^{18}O-labeled N-phenylhydroxylamine that the oxygen atom of the nitrone is derived from the hydroxylamine and not from the aldehyde.[11] These workers further suggest that the reaction proceeds by a radical mechanism similar to that for azoxybenzene formation in alkaline solution[12] and argue that a carbinolamine intermediate, I, would undergo N–O rather than C–O



$$HO{-}\overset{|}{\underset{|}{C}}{-}\overset{R}{N}{-}O{-}H$$

I

cleavage because of the smaller bond energy of the N–O than of the C–O bond.[11] However, there is no necessary correlation between bond energies, dissociation energies, and activation energies for heterolytic cleavage of a bond[13] and, furthermore, the formation of a stable product by N–O cleavage would also require the energetically difficult cleavage of a C–H bond, whereas C–O cleavage can proceed independently to form the relatively stable $>C{=}\overset{+}{N}<$ group. The similarity in the properties of the nitrone- and oxime-forming reactions, the many characteristics of oxime formation and related reactions which can be explained on the basis of an ionic mechanism,[14] and the absence of any compelling evidence for a radical mechanism lead us to conclude that nitrone formation occurs by an ionic mechanism similar to that for oxime formation[2] (eq 1 and 2). Although there is strong evidence that the

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(11) L. A. Neiman, V. I. Maimind, and M. M. Shemyakin, *Tetrahedron Letters*, 3157 (1965).

(12) G. A. Russell and E. J. Geels, *J. Am. Chem. Soc.*, **87**, 122 (1965).

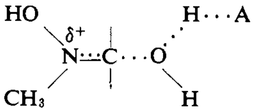
(13) M. Szwarc and M. G. Evans, *J. Chem. Phys.*, **18**, 618 (1950).

(14) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

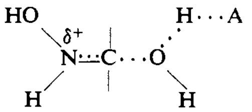
related reaction of azoxybenzene formation occurs by a radical mechanism in alkaline solution, there is no such evidence for the neutral or acid-catalyzed reaction pathways, for which an ionic mechanism has been suggested,[15a] and the possibility that the mechanism of azoxybenzene formation under these conditions is similar to that for nitrone formation deserves further consideration.

The fact that the rapid formation and accumulation of the carbinolamine intermediate may be demonstrated spectrophotometrically at neutral pH and that the further reaction to form nitrone is acid catalyzed establishes that acid-catalyzed dehydration of the carbinolamine intermediate is the rate-determining step of nitrone formation in this pH region. This mechanism accounts for the alkaline limb and the plateau of the pH–rate profile; in the plateau region below the pK of N-methylhydroxylamine the increase in the rate of acid-catalyzed dehydration of the addition intermediate is balanced by the decrease in the equilibrium concentration of the addition intermediate with increasing acidity (caused by the decrease in the concentration of free N-methylhydroxylamine), so that the observed rate of nitrone formation is independent of pH. This mechanism predicts that the rate should remain constant with decreasing pH, but it is observed that the rate of both nitrone and oxime formation drops off sharply below pH 2. Such a *decrease* in rate cannot be accounted for by an additional reaction pathway and is, therefore, attributed to a change in rate-determining step in a two-step reaction mechanism, such that attack of the small concentration of free nitrogen base becomes rate determining in acid solution as the rate of acid-catalyzed dehydration of the carbinolamine intermediate becomes very fast. (This situation could be described somewhat differently in terms of a pH-independent dehydration of a cationic steady-state intermediate, $>C(OH)NHROH^+$ or a tautomer thereof, but there does not appear to be any special advantage to such a description). In the case of oxime formation the attack step becomes almost completely rate determining in the most acid solutions, while in the nitrone reaction the rate decrease occurs in more acid solution in the face of an unfavorable over-all equilibrium so that the attack step is only partly rate determining. The calculated pH dependencies of the rates according to this mechanism (eq 3 and 4 and Table I) agree satisfactorily with the observed rates of nitrone and oxime formation over the range of experimental conditions examined (Figure 2). No evidence for a pH-independent dehydration reaction above neutrality was detected. (It is possible that the trend in the values of k_{H^+} for nitrone formation with increasing pH reflects a small contribution of the latter reactions; this was not investigated in detail because of experimental difficulties caused by the decomposition of N-methylhydroxylamine.)[15b]

The 3.6-fold smaller equilibrium constant for formation of the carbinolamine addition compound from N-methylhydroxylamine than from hydroxylamine is of the magnitude expected from the increased steric requirements of the methyl group in the former compound. The larger difference of 13-fold for the comparable reactions with pyruvate[2] (57 and 4.4 M^{-1}) reflects the larger steric requirements of a ketone compared to an aldehyde. The 13-fold slower rate of nitrone than of oxime formation from *p*-chlorobenzaldehyde at pH values above 2 is caused in equal part by this difference and by a 3.6-fold smaller rate of acid-catalyzed dehydration of the intermediate formed from N-methylhydroxylamine; a similar difference is observed for the dehydration catalyzed by general acids (Table II). This difference is attributed to less favorable solvation of the developing positive charge on the nitrogen atom in the transition state for nitrone formation (II) than in that for oxime formation (III). There is a good deal of evidence which suggests that such solvation provides a significant amount of stabilization of cationic nitrogen compounds, which is lost upon alkyl substitution,[16,17] and the fact that $CH_3ONH_3^+$ is 20 times stronger as an acid than $HONH_3^+$ suggests that this solvation effect[18] may be exerted over a greater distance from the center of positive charge than is any electron-donating effect of the methyl group. The solvation effect per hydrogen atom appears to be greatest for those amine cations with the smallest number of hydrogen atoms.[17] No difference is observed in the rates of the dehydration steps for oxime[2] (4.0×10^6 M^{-1} min^{-1}) and nitrone (4.1×10^6 M^{-1} min^{-1}) formation from pyruvate, in which the transition states have no net charge. The fact that there is no *large* difference between the rates of dehydration of the hydroxylamine and N-methylhydroxylamine adducts confirms an earlier conclusion that there is not a large amount of breaking of the N–H bond in the transition state,[8] because such bond breaking is not possible in the case of the nitrone. The similar rates of attack of N-methylhydroxylamine and of hydroxylamine on the carbonyl group (k_1) suggest that the greater nucleophilic reactivity of secondary than of primary amines[19] is almost exactly balanced by the steric hindrance of the methyl group in the former reaction. The similar rates of the attack step and the differences in the rates under conditions in which dehydration is rate determining account for the slightly different shapes of the pH–rate profiles for the two reactions.



II



III

The addition of hydroxylamine to an aldehyde is described in more detail in eq 7. The equilibrium constant for the formation of the initial dipolar product of the reaction, K_a, is equal to K_1/K_bK_c, where K_1 is 23.5 M^{-1} and the subscripts refer to the reactions of eq 7. Reasonable estimates for K_b and K_c (approximately 10^{10} M^{-1} and 10^{-4} M, respectively) indicate that the equilibrium K_a is unfavorable and that k_{-a} is large ($k_{-a} = k_a/K_a \approx 2.3 \times 10^6/2.35 \times 10^{-5} = 10^{11}$ min^{-1} $\approx 2 \times 10^9$ sec^{-1}). The protonation of the dipolar adduct [k_b(H$^+$)] is presumably diffusion con-

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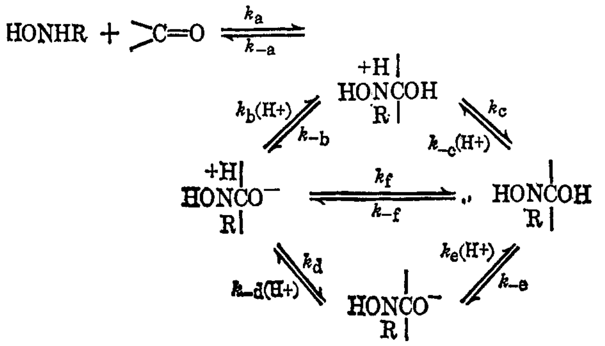
(15) (a) Y. Ogata, M. Tsuchida, and Y. Takagi, *J. Am. Chem. Soc.*, **79**, 3397 (1957). (b) Masui and Yujima[3b] have observed a pH-independent dehydration pathway in the dehydration step of nitrone formation from aliphatic aldehydes.

(16) (a) A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1293 (1949); (b) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

(17) F. E. Condon, *ibid.*, **87**, 4481, 4485 (1965).

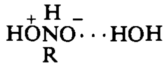
(18) T. C. Bissot, R. W. Parry, and D. H. Campbell, *ibid.*, **79**, 796 (1957).

(19) H. K. Hall, Jr., *J. Org. Chem.*, **29**, 3539 (1964).



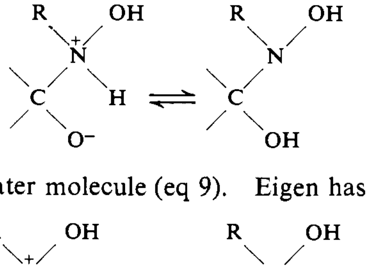
(7)

trolled,[20] but will become slower than k_{-a} as the pH increases. The step which involves the removal of a proton from the dipolar adduct is presumably diffusion controlled in the reverse direction (k_{-d}) and will proceed in the forward direction[20] with a rate constant $k_d = K_d k_{-d} \approx 10^{10} K_d \ll 10^{10}$ sec^{-1}. Other possible pathways for stepwise proton transfer would be expected to proceed at even slower rates. Thus, the rates of these proton transfer steps are not adequate to account for the over-all rate of reaction if the attack of hydroxylamine on the aldehyde is the rate-determining step. (The requirement that hydroxylamine attack be rate determining is that k_{-a} be smaller than the rate constant for subsequent proton transfer at a given pH value.) The situation is not materially changed if it is assumed that water is hydrogen bonded to the carbonyl group to give



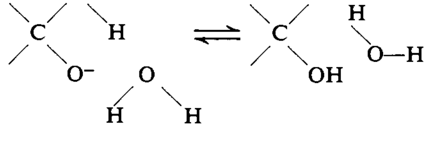
$$\mathrm{HO}\overset{+\,\mathrm{H}}{\underset{\mathrm{R}}{\mathrm{N}}}\overset{-}{\mathrm{O}}\cdots\mathrm{HOH}$$

as the initial product; in this case the diffusion-controlled separation of hydroxide ion from this complex will be relatively slow. The rate constant for the first step, k_a, cannot be much larger than the observed over-all rate constant, because it is limited by the equilibrium constant for this step and by k_{-a}, which is close to the limit for the rate of a diffusion-controlled reaction; furthermore, the absence of general acid–base catalysis[2] and the kinetics of this step, which require a transition state with no net charge, also suggest that proton transfer is not rate determining. The only obvious solution to this dilemma is that proton transfer does not occur in separate steps, but rather occurs in a rapid intramolecular reaction either directly (eq 8) or



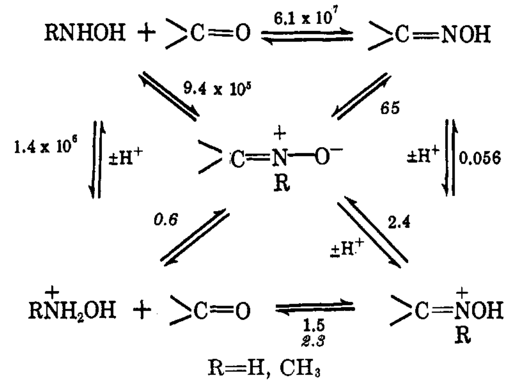
(8)

through a water molecule (eq 9). Eigen has used similar considerations to show that proton transfer processes in the general acid catalyzed hydration of acetaldehyde, and related reactions must occur during a single encounter with the catalyst molecule, rather than in a stepwise process.[21]



(9)

The interrelationships of the equilibrium constants for the formation of the oxime and nitrone of *p*-chlorobenzaldehyde and their conjugate acids are summarized in eq 10, in which calculated equilibrium constants are shown in italic. All constants are given as association constants. The equilibrium constants for the formation of the two conjugate acids are very similar, which reflects the fact that the structure of the two compounds differs only by the substitution of a methyl group for hydrogen. The equilibrium constant for the formation of the free nitrone is $^{1}/_{65}$ as large as that for the free oxime. If it is again assumed that substitution of a methyl group for hydrogen has little effect, the equilibrium constant for isomerization of the oxime to the dipolar form ($>C{=}\overset{+}{N}HO^-$) should be approximately $^{1}/_{65}$, *i.e.*, the dipolar structure is some 2400 cal/mole less stable than the neutral structure and 1–2% of the oxime should normally exist in the dipolar form. This is a conservative estimate, because solvation of the N^+H group by water would be expected to stabilize the dipolar form of the oxime, compared to the nitrone. It is presumably the dipolar form that undergoes reaction when the neutral form of an oxime acts as a nucleophilic reagent to give a product which is substituted on oxygen; it has previously been suggested that the dipolar species is the reactive form in analogous reactions of hydroxylamine.[22] The dipolar form is strongly stabilized by resonance and it would be expected that this fraction would be increased by *para* substituents on the benzene ring which are either strongly electron donating or electron withdrawing by resonance. The difference in the stabilities of the two isomers is also evident in the fact that the conjugate acid of the nitrone is some $^{1}/_{44}$ as strong as an acid than the conjugate acid of the oxime; this difference is a measure of the relative ease with which a proton is lost from the oxygen compared to the nitrogen atom of the protonated oxime.



(10)

General Acid Catalysis and Anthropomorphic Electrons. The kinetic observation of general acid catalysis of the dehydration of a carbinolamine or its microscopic reverse, the attack of water on an imine, can correspond to transition states of the general form of IV or V in which the precise position of the proton is

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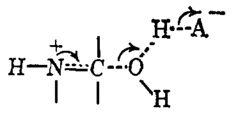
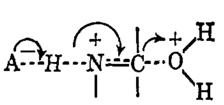
[20] M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

[21] M. Eigen, *Discussions Faraday Soc.*, **39**, 7 (1965).

[22] W. P. Jencks, *J. Am. Chem. Soc.*, 80, 4585 (1958); W. P. Jencks and J. Carriuolo, *ibid.*, 82, 1778 (1960).



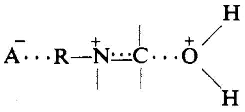
IV



V

unspecified but is different from the starting materials.[13] In IV the general acid donates a proton to the leaving OH group to make it a better leaving group and, in the reverse reaction, a general base removes a proton from water to make it a better attacking group as it attacks the cationic imino group. In V a general base removes a proton from nitrogen to aid the expulsion of water (the hydroxyl group has been protonated in a prior equilibrium step) and in the reverse reaction a general acid donates a proton to the basic nitrogen atom of the imine to make it more susceptible to attack by water. The observation that the dehydration step of nitrone formation is susceptible to general acid catalysis in a manner very similar to oxime formation rules out mechanism V for these reactions, because proton removal from the nitrogen atom is not possible in nitrone formation, and is consistent with mechanism IV. This confirms previous conclusions for related reactions including the hydrolysis of protonated benzylidene-1,1-dimethylethylamines[23] and benzhydrylidenedimethylammonium cation[6] and the formation of 5,10-methylenetetrahydrofolic acid.[24] The values of α for oxime and nitrone formation of approximately 0.77 are similar to the value of 0.73 for the comparable step in the benzhydrylidenedimethylammonium ion reaction[6,25] (β for the reverse of this step = 0.27) and the value of α for the dehydration step of 5,10-methylenetetrahydrofolic acid formation is also large.[24] This is a further indication of the similarity of these reactions.

Swain, Kuhn, and Schowen have recently criticized the type of reasoning which was used (advisedly) in the preceding paragraph as "entirely unsound" in that it attributes anthropomorphic motivation to electrons ("what would I do in that particular situation if I were an unshared pair of electrons") and further suggest that general acid catalysis of this class of reaction may proceed according to transition state VI in which the role of the catalyst is to solvate or stabilize the transition state more than the ground state.[26a] Since the N-H group, when R = H, is presumably less acidic in the transition state than in the ground state, and there is no evidence for the existence of stable hydrogen bonds to structures of this kind in aqueous solution, even in the ground state, these authors propose that there is a special polarizability in the transition state which permits significant stabilization by the catalyzing base.



$\bar{A}\cdots R-\overset{+}{N}{=}C\cdots\overset{+}{O}H_2$

VI

We believe that electrons are at least as well motivated as organic chemists and that the "anthropomorphic" analysis of reaction mechanisms, when properly carried out, is fully compatible with the (tautological) requirement that the most favored mechanism is that in which the free-energy difference between the ground and transition states is smallest.[26b] The arguments concerning this question have been presented in detail by do Amaral, Sandstrom, and Cordes,[25] and only a few points will be emphasized here. Empirically, the finding that the dehydration steps in oxime and nitrone formation show similar sensitivity to catalysis by both cationic and anionic acids effectively rules out mechanism VI for these reactions. If mechanism VI were correct for oxime formation, it would not be expected that similar catalysis would occur by solvation of a proton in oxime formation and a methyl group in nitrone formation, although solvation of the cationic nitrogen atom by an anionic catalyst is conceivable.[26] The fact the catalysis is observed with cationic acids would appear to rule out this mechanism unequivocally because the neutral bases of such acids would not be expected to provide a similar stabilization. This is in agreement with conclusions which have been reached from similar data for the hydrolysis of cationic imines[25] and the formation of 5,10-methylenetetrahydrofolic acid.[24]

The "anthropomorphic" approach can also be defended theoretically, on the ground that electrons, like most anthropoids, will tend to follow the path of least resistance. The problem is one of some importance, because it brings up the questions of why general acid-base catalysis of this kind of reaction should occur at all and what is the role of the catalyst in such reactions. This type of reaction is different from most reactions that have been examined in detail, because it involves the movement of protons as well as the formation and breaking of bonds to carbon; consequently an analysis in terms of transition-state theory must consider the energy profiles for the movement of the proton(s) and of the atoms reacting with carbon and the effects of each of these movements upon the other, in order to specify the lowest energy transition state for the over-all reaction.

Swain, *et al.*, approach this problem by specifying a single transition state, estimating the positions of the atoms in this transition state by application of the "reacting bond" and "solvation" rules, and then placing the catalyst molecule in a position in which it will provide maximum stabilization of this transition state.[26] We suggest that this is an oversimplified approach, because the structure of a transition state will itself be perturbed by the addition of the catalyst molecule and it is necessary to consider the over-all stability of the transition state, not just the stability of the hydrogen bond to the catalyst. Comparisons of various possible catalyzed and uncatalyzed reaction mechanisms must be carried out by comparing the stabilities of the individual transition states for each mechanism.

Consider the pathways for the hydration of a cationic imine or the dehydration of a carbinolamine which are shown in eq 11. The upper and lower pathways are for the attack and expulsion of hydroxide ion and water, respectively, and the middle path involves general

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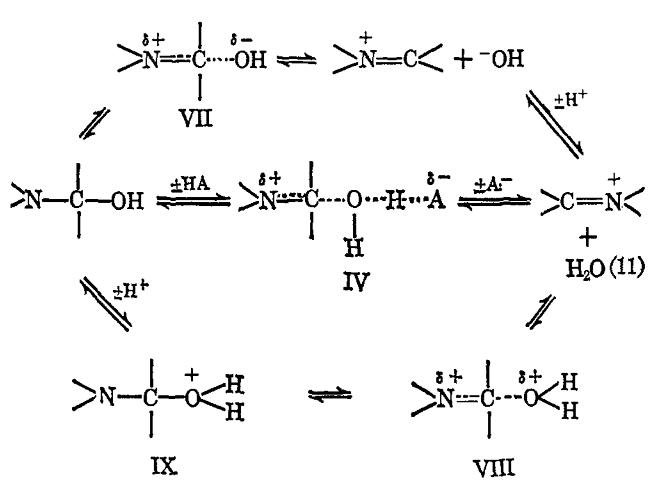
[23] E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, 85, 2843 (1963).

[24] R. G. Kallen and W. P. Jencks, unpublished experiments.

[25] L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *J. Am. Chem. Soc.*, 88, 2225 (1966).

[26] (a) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Am. Chem. Soc.*, 87, 1553 (1965). (b) *Cf.* also the discussion of electrophilia and electrophilicity by J. E. Leffler (in "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956, pp 116–117).



acid catalysis. For a reaction which proceeds at pH 7 (general acid–base catalysis by buffers is usually seen only when the concentration of catalyst is large compared to that of hydroxide ions or protons) the preequilibrium formation of hydroxide ion requires the expenditure of 9500 cal/mole (in the reverse direction) and its expulsion in the forward direction will give an immediate product which is correspondingly unstable relative to the final product. If the basicity of the carbinolamine oxygen atom is similar to that of *n*-butyl alcohol[27] (neglecting the electron-withdrawing effect of the nitrogen atom), the oxonium ion IX will have a pK_a of approximately -2.3 and its formation at pH 7 will require some 12,600 cal/mole. Similarly, the formation of IX from the transition state VIII will give an immediate product with a corresponding instability relative to the final carbinolamine. Clearly, to the extent that the transition states resemble these unstable intermediates,[28-30] these reaction paths will be unfavorable relative to the middle path, in which the formation of these intermediates is avoided by general acid–base catalysis. The free energies required for the formation of these unstable intermediates are a major fraction of the observed free energies of activation for reactions of this type.

Hydrogen bonds between acids (HA) and bases (B) have only marginal stability in water. The strength of a hydrogen bond is a function of the acidity of HA and the basicity of B and is ordinarily limited by the fact that the most favorable acid–base pair which can exist is one in which the basicities of A^- and B are equal (*e.g.*, acetic acid–acetate). However, in the course of a reaction which is subject to general acid–base catalysis, there is a large change in the acidity and basicity of the reacting groups. In the absence of proton transfer the basicity of the oxygen atom of the carbinolamine intermediate will increase by some 18 p*K* units if it becomes hydroxide ion or a comparable change in the acidity of water will occur if it becomes the oxonium ion, IX. Now, it is expected that the transition state for the unassisted elimination of hydroxide ion from a carbinolamine will occur far along the reaction coordinate, because hydroxide ion is a poor leaving group.[28,29] Consequently, a considerable basicity should have developed in the incipient hydroxide ion and it would be expected that significant stabilization should occur by interaction with a general acid. Similarly, the transition state for the unassisted attack of water on a cationic imine will occur far along the reaction coordinate in the other direction, because water is a poor nucleophile which will add to a double bond only with difficulty. Thus, the protons of the incipient oxonium ion (IX) will be highly acidic and stabilization will be expected by interaction with a catalyzing base. In both of these situations, the interaction with the catalyst will change the structure of the transition state by changing the nature of the entering and leaving groups, so that the transition state for the catalyzed reaction will approach the center of the reaction coordinate. These interrelationships are shown schematically in Figure 5. The acidity of an N–H group on the cationic imine will *decrease* from a p*K* of about 7 for an imine of *t*-butylamine[23] to about 22 in the carbinolamine, so that this group never becomes thermodynamically unstable at neutrality; it would not be expected that significant stabilization would result from hydrogen bonding to such a group unless special polarizability effects are invoked.[26] The important point in this analysis is that while it is difficult and perhaps meaningless to estimate the hydrogen bond energy in the transition state of the catalyzed reaction, *per se*, an appreciable stabilization is to be expected from the energy of hydrogen bond formation or from actual proton transfer in the catalyzed transition state *compared to* transition states in which no such hydrogen bonding or proton transfer takes place.

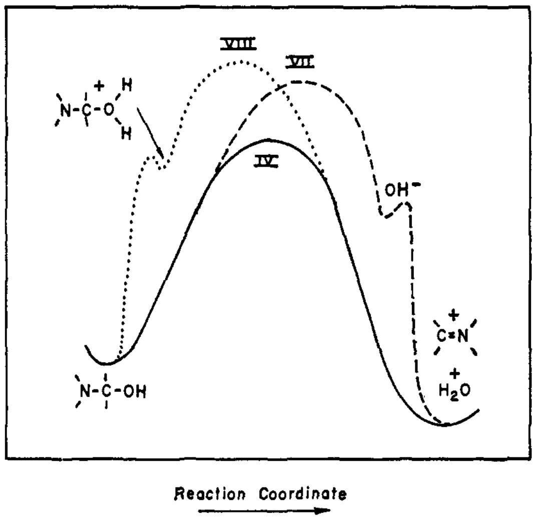


Figure 5. Schematic transition-state diagram for the reaction mechanisms shown in the upper (---------), center (———), and lower (······) lines of eq 11 at neutrality.

In addition to its role in facilitating the reaction by making possible the energetically most favorable location of protons, general acid–base catalysis according to mechanism IV will lower that part of the activation energy barrier which arises from the formation and breaking of C–O and C–N bonds, while hydrogen bonding according to VI will not. The transition state for the expulsion of hydroxide ion from the carbinolamine, the driving force for which is the donation of electrons from the nitrogen atom, is relatively unstable and its stability will be increased by general acid catalysis, which partially converts the leaving

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(27) E. M. Arnett and J. N. Anderson, *J. Am. Chem. Soc.*, 85, 1542 (1963).

(28) J. E. Leffler, *Science*, 117, 340 (1953).

(29) G. S. Hammond, *J. Am. Chem. Soc.*, 77, 334 (1955).

(30) J. E. Gordon, *J. Org. Chem.*, 26, 738 (1961).

group to a water molecule and reduces charge separation. Similarly, the transition state for the attack of the weak nucleophile, water, on the imine (VIII) will be stabilized by a general base which partially converts the water molecule into hydroxide ion and reduces the mutual repulsion of the two positive charges in VIII. It is not clear how hydrogen bonding in transition state VI, which is very similar to VIII, would provide appreciable stabilization of this transition state relative to the ground state or to other possible transition states. Thus, we see no conflict between "anthropomorphic" arguments, as commonly utilized by the organic chemist, and an analysis of a reaction in terms of transition-state theory.

These considerations are consistent with the simple generalizations that catalysis occurs where it is most needed and that reactions of this type generally proceed by pathways which avoid the formation of unstable intermediates.[14] These may be restated in the form of a rule, which we will call the Anthropomorphic rule, as follows. In general acid–base catalysis of reactions which involve proton transfer to or from nitrogen, oxygen, or sulfur, bases will react with protons which become more acidic and acids will react with atoms which become more basic in the transition state (and products). The degree of stabilization by such catalysis will be determined by this change in acidity (or basicity) compared to the basicity (or acidity) of the catalyst and by the stabilization of the transition state for the remainder of the reaction which is brought about by partial proton transfer.

In this discussion we have deliberately avoided discussion of the exact position of the proton in the transition state; this subject will be considered in a future communication. The possibility should be kept in mind that proton transfer proceeds through an intermediate water molecule.[31] In respect to the matters considered here it is only necessary to point out that Brønsted α or β values are measures of the stabilization of the *over-all* transition state by acids and bases of different strength; they are not necessarily exact indicators of the degree to which either proton transfer or the making and breaking of bonds to carbon has taken place in the transition state.

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[31] E. Grunwald, A. Loewenstein, and S. Meiboom, *J. Chem. Phys.*, 27, 630 (1957); A. Loewenstein and S. Meiboom, *ibid.*, 27, 1067 (1957); W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 82, 675 (1960).

Thiol Addition to the Carbonyl Group. Equilibria and Kinetics[1]

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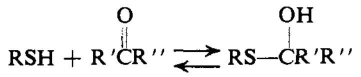
Abstract: Rate and equilibrium constants have been determined for the addition of a series of thiols to acetaldehyde and other carbonyl compounds to form the corresponding hemithioacetals and hemithioketals. The addition reactions occur by specific base catalyzed and general acid catalyzed pathways; no pH-independent reaction was detected. The solvent deuterium isotope effect on the rate of the hydronium ion catalyzed reaction, k_{H_2O}/k_{D_2O}, is 0.59; the isotope effect on the addition equilibrium, K_{H_2O}/K_{D_2O}, is 0.44. The Brønsted α value for general acid catalysis is large, on the order of 0.7. Evidence is presented that the unhydrated carbonyl compound is the reactive species. The acid-catalyzed reactions display a large sensitivity, but the base-catalyzed reactions almost no sensitivity to the basicity of the attacking species. It is suggested that the general acid catalyzed reaction involves proton donation to the carbonyl group and that the base-catalyzed reaction involves attack of the thiol anion on the carbonyl group. Possible roles of the acid catalyst in general acid catalysis are discussed.

In 1885 Baumann[3] reported the reaction of benzenethiol with pyruvic acid in benzene to form a crystalline addition compound, to which he ascribed the structure of a hemithioketal. Since that time a number of stable hemithioacetals and hemithioketals have been prepared by the reaction under mild conditions of thiols with aldehydes and ketones that contain electron-withdrawing groups (eq 1).[4] In the earlier work, the assignment



$$\mathrm{RSH} + \mathrm{R'}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}\mathrm{R''} \rightleftarrows \mathrm{RS{-}}\overset{\overset{\displaystyle OH}{|}}{\mathrm{C}}\mathrm{R'R''} \qquad (1)$$

of the hemithioacetal or hemithioketal structure to such compounds was generally based on their chemical composition and their ready dissociation under certain conditions into the component thiol and carbonyl compounds. More recently, this evidence for the α-hydroxy sulfide structure has been augmented: in the case of crystalline hemithioacetals prepared from phenylglyoxal by an examination of the infrared and nmr spectra of the compounds,[5] and in the case of the

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[3] E. Baumann, *Chem. Ber.*, 18, 258, 883 (1885).

[4] E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. 2, Chemical Publishing Co., Inc., New York, N. Y., 1960, p 205, and Vol. 3, p 320; E. Campaigne in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press Inc., New York, N. Y., 1961, p 134.