

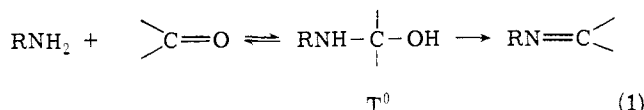
Evidence for Two Concurrent Mechanisms and a Kinetically Significant Proton Transfer Process in Acid-Catalyzed *O*-Methyloxime Formation^{1a}

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Abstract: A mechanism for *O*-methyloxime formation from benzaldehydes in aqueous solution is proposed that involves three sequential kinetically significant steps; namely (1) formation of an unstable zwitterionic tetrahedral intermediate, T^\pm , (2) protonation of T^\pm in a diffusion-controlled reaction, and (3) hydronium ion catalyzed dehydration of a neutral tetrahedral intermediate that is in rapid equilibrium with the protonated species formed in step 2. The following evidence is presented in support of this mechanism. (1) The pH-rate profiles at zero buffer concentration for the reaction of methoxyamine free base with three substituted benzaldehydes show *two* negative breaks in the pH-region below neutrality. (2) A change in rate-determining step that cannot be accounted for by a transition from rate-determining carbinolamine formation to dehydration is observed in the presence of increasing concentrations of general acid catalysts with *p*-methoxybenzaldehyde at pH 2-3. (3) Absolute rates for the hydronium ion catalyzed proton transfer process, calculated from observed rate constants and estimated equilibrium constants for formation of T^\pm , are 7×10^9 - $10^{10} M^{-1} \text{ sec}^{-1}$, in the range expected for a diffusion-controlled proton transfer. Absolute rates for the uncatalyzed conversion of T^\pm to a neutral tetrahedral intermediate are 10^6 - 10^7 sec^{-1} , consistent with a solvent-mediated intramolecular proton transfer. (4) Structure-reactivity correlations for three substituted benzaldehydes are consistent with the proposed mechanism; in particular, a logarithmic plot of the observed rate constants for the hydronium ion catalyzed proton transfer step against the equilibrium constants for formation of the neutral tetrahedral intermediates has a slope of 0.9 in satisfactory agreement with the expected value of 1.0 for a diffusion-controlled reaction of T^\pm . (5) The Brønsted plot for general acid catalysis of the reaction of *p*-methoxybenzaldehyde undergoes a transition from slope 0 to -1.0 at $pK \sim 8.6$, which is in good agreement with the estimated pK' of ~ 9 for the hydroxyl group of the protonated tetrahedral intermediate. In addition to the mechanism involving a stepwise proton transfer, a second, concurrent mechanism for catalysis by the hydronium ion, which is ascribed to a proton transfer that is more-or-less "concerted" with carbon-nitrogen bond formation, is observed at high acidity.

The formation of imines, hydrazones, and related derivatives from carbonyl compounds ordinarily proceeds in two steps, the formation of a carbinolamine intermediate and its dehydration to give the observed product (eq 1). At pH



values below neutrality, most reactions of this type undergo a change in rate-determining step with decreasing pH, from dehydration to formation of the carbinolamine, as the acid-catalyzed dehydration step becomes faster than the uncatalyzed formation of the intermediate.² Evidence has recently been obtained that the addition step in some reactions of this type is itself a stepwise process and involves preliminary formation of a very unstable zwitterionic form of the tetrahedral intermediate, which is trapped by proton transfer in a subsequent kinetically significant step.^{3,4} The present article presents evidence for the existence of such a sequential reaction pathway for the acid-catalyzed addition step in *O*-methyloxime formation from aromatic aldehydes. This evidence includes (1) the existence of two changes in rate-determining step and hence three sequential, kinetically significant steps for *O*-methyloxime formation at pH values below neutrality; (2) both absolute magnitudes and structure-reactivity correlations for the rate constants of the hydronium ion catalyzed proton transfer step that are in accord with expectation for a diffusion-controlled reaction of the zwitterionic intermediate; and (3) a nonlinear Brønsted plot of the type observed by Eigen⁵ for general acid catalysis of the proton transfer process. Catalysis of the addition step in *O*-methyloxime formation by the hydronium

ion also proceeds by a separate, concurrent pathway having only one kinetically significant step. The latter pathway involves a mechanism of proton transfer that we believe is in some sense "concerted" with the attack of the nucleophile on the carbonyl group. A portion of this work has been described in a preliminary communication.⁶

Results

The pH-rate profiles for the reaction of methoxyamine free base with aromatic aldehydes at 25° are complex and show more than a single break between pH 0 and 6, as indicated in Figure 1. The presence of two breaks (at pH ~ 1.0 and 3.5) is most apparent for *p*-chlorobenzaldehyde; however, small but definite breaks at pH ~ 1.0 and 4.0 are also observed for *p*-methoxy- and *p*-nitrobenzaldehyde, in addition to the more pronounced breaks at pH ~ 4.5 and 1.0, respectively, exhibited by these compounds. The break in the pH-rate profile at low pH for *p*-methoxybenzaldehyde is more clearly seen in a linear plot of the rate constant against h_0 or antilog ($-\text{pH}$) as a significant negative deviation of the rate constants at high acidity from the straight line determined by the observed rate constants at lower acidity. This small break between pH 0.0 and 2.0 occurs *in addition* to a more pronounced break at pH ~ 4 (Figure 1) that is ascribed to the normal^{2,7} transition from rate-limiting carbinolamine formation at low pH to dehydration at higher pH. Values of k_{ad}^0 , the second-order rate constant for the addition step (extrapolated where necessary to zero methoxyammonium ion concentration), are plotted against acidity in Figure 2. The correction for the contribution of the dehydration step at these low pH values never exceeded 5% of the observed rate constants.

A similar small break in the pH-rate profile for *p*-nitrobenzaldehyde occurs at pH ~ 4.0 , such that the rate con-

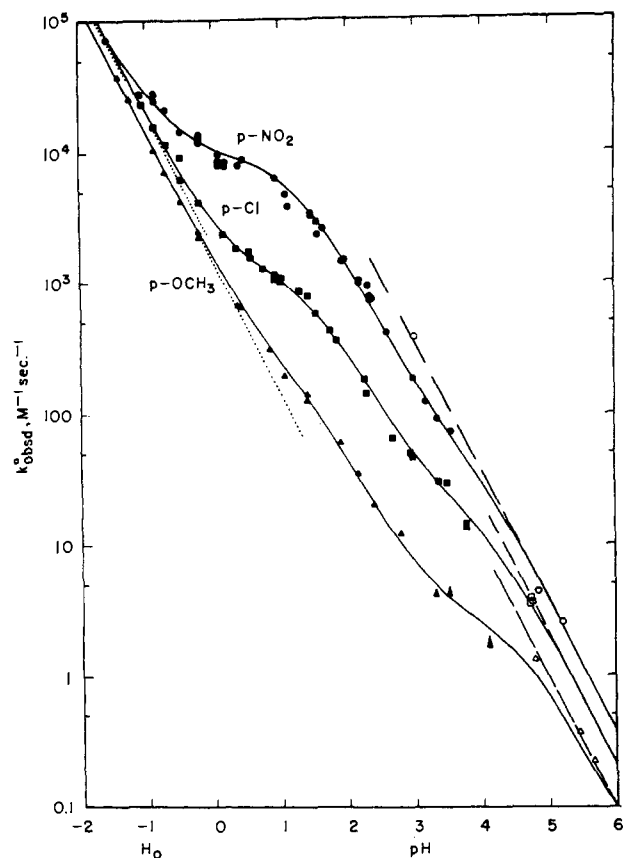


Figure 1. Dependence on pH of the second-order rate constants in terms of amine free base, k_{obsd}^0 , corrected for catalysis by buffers and methoxyammonium ion, for the addition of methoxyamine free base to *p*-nitro- (●), *p*-chloro- (■), and *p*-methoxybenzaldehyde (▲) in aqueous solution at 25°. The open symbols and broken lines indicate the rate constants for the dehydration step at high pH or high buffer concentration, and the dotted lines indicate the rate constants for the hydronium ion catalyzed process (k_1) that is predominant at low pH. The solid lines are theoretical curves for the overall reaction and are calculated from eq 2 and 2a and the kinetic constants of Table I.

stants observed at pH 2–3.5 fall two- to threefold below the line of slope 1.0 determined by the rate constants for the dehydration step near pH 5.0. The occurrence of a change in rate-determining step for *p*-nitrobenzaldehyde in this pH region is confirmed by the nonlinearity of a plot of the second-order rate constant against formate buffer concentration at pH 2.98 (Figure 3). This is a result of the transition from a rate-limiting step that is subject to buffer catalysis to a step that is not buffer catalyzed, as the buffer concentration is increased.^{3b,8,9} The limiting rate constant at high buffer concentration at pH 2.98 is in good agreement with that calculated for the dehydration step (Figure 1, broken line) from the rate constants observed at higher pH. In addition to this small break, a more marked negative break in the pH-rate profile for *p*-nitrobenzaldehyde occurs at pH ~ 1.0 .

The observed pH-rate profiles may be fit by a steady-state rate law having the form of eq 2 and 2a, where k_{obsd}^0 is the second-order rate constant for the overall reaction (extrapolated to zero buffer concentration) in terms of methoxyamine free base, $K_{\text{ad}}k_5$ is the observed rate constant when the dehydration step is rate determining, and k_{ad}^0 is the apparent rate constant for the addition step at zero buffer concentration. Analysis of the kinetic data as described in the Experimental Section yields the kinetic constants summarized in Table I, and substitution of these constants into eq 2 and 2a gives the theoretical pH-rate

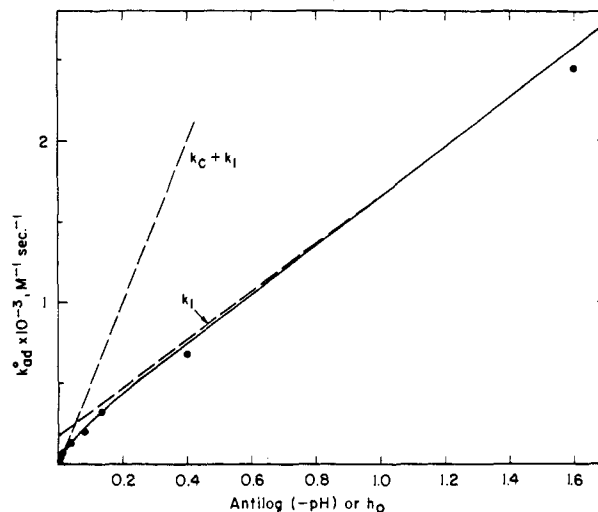


Figure 2. Dependence on acidity of the second-order rate constant, k_{ad}^0 , in terms of methoxyamine free base, for the addition step in *O*-methyloxime formation from *p*-methoxybenzaldehyde in the range pH 2.6 to $H_0 = -0.2$. The solid line is a theoretical curve based on eq 2a and the rate constants of Table I; the broken lines show limiting values for the apparent rate constants at high and low acidity, where k_1 corresponds to the pathway of hydronium ion catalysis that is predominant in strongly acidic solution, and k_C corresponds to the stepwise pathway for proton transfer from the hydronium ion that becomes significant as the pH is increased.

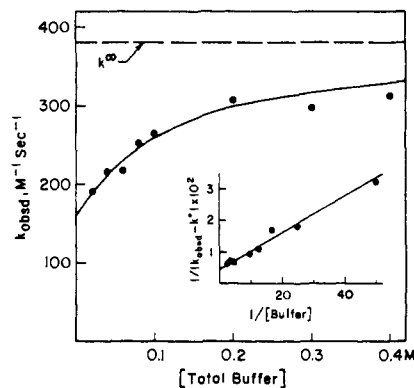


Figure 3. Dependence of the observed second-order rate constant for *O*-methyloxime formation from *p*-nitrobenzaldehyde and 2.5×10^{-3} *M* (total) methoxyamine on the concentration of formate buffer, 79% acid (pH 2.98). The broken line represents the limiting rate constant at high buffer concentration that was determined from a double reciprocal plot (inset) of the experimental points. The solid line is a theoretical curve for limiting rate constants of 160 and 380 $M^{-1} \text{sec}^{-1}$ at zero and high buffer concentrations, respectively, and an apparent catalytic constant of 5400 $M^{-2} \text{sec}^{-1}$ for total formate buffer at pH 2.98.

profiles indicated by the solid lines of Figure 1, which are in good agreement with the experimental points.

$$k_{\text{obsd}}^0 = k_{\text{ad}}^0 K_{\text{ad}} k_5 a_{\text{H}^+} / (k_{\text{ad}}^0 + K_{\text{ad}} k_5 a_{\text{H}^+}) \quad (2)$$

$$k_{\text{ad}}^0 = k_1 a_{\text{H}^+} + \frac{k_2 (k_C a_{\text{H}^+} + k_D)}{k_C a_{\text{H}^+} + k_D + k_2} \quad (2a)$$

According to this formulation, the constants k_1 , k_2 , k_C , and k_D correspond to the kinetically significant processes that are most important in the acid-catalyzed region below pH 0, the uncatalyzed region at low pH, the acid-catalyzed region at pH 2–3, and the uncatalyzed region at pH 3.5–4.0, respectively. The acid-catalyzed process observed above pH 4.5 is assigned to dehydration of the carbinolamine intermediate, $K_{\text{ad}}k_5$ in the steady-state rate law. Carbinolamine dehydration is known to be rate determining at pH

Table I. Kinetic Constants for *O*-Methyloxime Formation from Para-Substituted Benzaldehydes^a

Substituent	<i>p</i> -OCH ₃	<i>p</i> -Cl	<i>p</i> -NO ₂
$k_1, M^{-2} \text{sec}^{-1}$	1500	2070	1930
$k_2, M^{-1} \text{sec}^{-1}$	175 ± 25	1150	1.0 × 10 ⁴
$k_C = K_n k_3, M^{-2} \text{sec}^{-1}$	(3.5 ± 0.5) × 10 ³	4.0 × 10 ⁴	(2.6 ± 0.1) × 10 ⁵
$k_D = K_n k_4, M^{-1} \text{sec}^{-1}$	3.0 ± 0.5	25 ± 5	83 ± 15
$K_{ad} k_5, M^{-2} \text{sec}^{-1}$	9.2 × 10 ⁴	2.1 × 10 ⁵	3.6 × 10 ⁵
K_{ad}, M^{-1}	1.1	13.4 ± 0.6	125 ± 10

^a At 25°. Ionic strength 1.0 (KCl) except at HCl concentrations ≥ 1.0 *M*. Kinetic constants are calculated from the steady-state rate eq 2 and 2a for the processes of Scheme I. Rate constants are based on a pK_a' of 4.73 for methoxyammonium ion and h_0 (ref 16) at [HCl] ≥ 1.0 *M* or $\text{antilog}(-\text{pH})$ at [HCl] < 1.0 *M*.

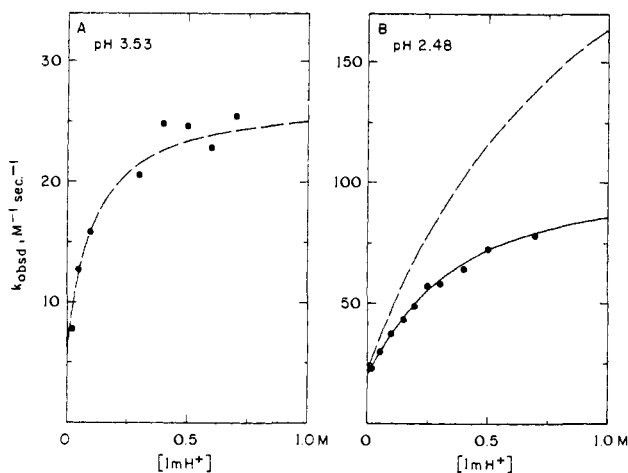


Figure 4. Dependence of the observed second-order rate constant, k_{obsd} , for *O*-methyloxime formation from *p*-methoxybenzaldehyde on the concentration of imidazolium chloride at pH 3.53 and 2.48. The total concentration of methoxyamine was 5×10^{-3} *M* at pH 3.53 and 1.5×10^{-2} *M* at pH 2.48. The broken lines are theoretical curves based on values for the kinetic constants, k_1 , k_C , k_D , and $K_{ad}k_5$, given in Table I, and k_{cat} for methoxyammonium and imidazolium ions from Table II. The broken lines correspond to the limiting rate constants, k^∞ , of 27.1 and 304 $M^{-1} \text{sec}^{-1}$ at pH 3.53 and 2.48, respectively, for rate-limiting dehydration. The solid line at pH 2.48 was calculated from the complete steady-state rate law and corresponds to a value of $k^\infty = 113 M^{-1} \text{sec}^{-1}$, for which k_2 is largely rate determining.

values near neutrality in the reaction of a number of weakly basic nitrogen nucleophiles with aromatic aldehydes,^{2,7-9} and the rapid preequilibrium formation of the carbinolamine from methoxyamine at neutral pH was demonstrated spectrophotometrically.¹⁰ addition of *p*-nitro-, *p*-chloro-, or *p*-methoxybenzaldehyde to solutions of methoxyamine (0.002–0.10, 0.02–0.27, and 0.2–1.0 *M*, respectively) at neutral pH causes an instantaneous decrease in the absorbance of the aldehyde, followed by slower appearance of the *O*-methyloxime product. For *p*-nitrobenzaldehyde, the observed pseudo-first-order rate constants for *O*-methyloxime formation at pH 4.82 and 5.20 show a nonlinear dependence on the concentration of methoxyamine because of the accumulation¹¹ of an intermediate.

General Acid Catalysis. The effect of added buffers and other catalysts on the rate of *O*-methyloxime formation from *p*-methoxybenzaldehyde varies as a function of pH. At pH 5.67 where dehydration is solely rate determining, the observed second-order rate constant is independent of added imidazolium chloride up to 0.5 *M*. Plots (Figure 4) of k_{obsd} against the concentration of imidazolium chloride are nonlinear as a consequence of a change in rate-determining step^{3b,8,9} with increasing concentration of imidazolium ion. The rate constant at pH 3.53 (Figure 4A) approaches a limit at high catalyst concentration which corresponds to the rate constant, $K_{ad}k_5 a_{\text{H}^+}$, for the dehydration step. At pH 2.48 (Figure 4B), the observed curvature in the

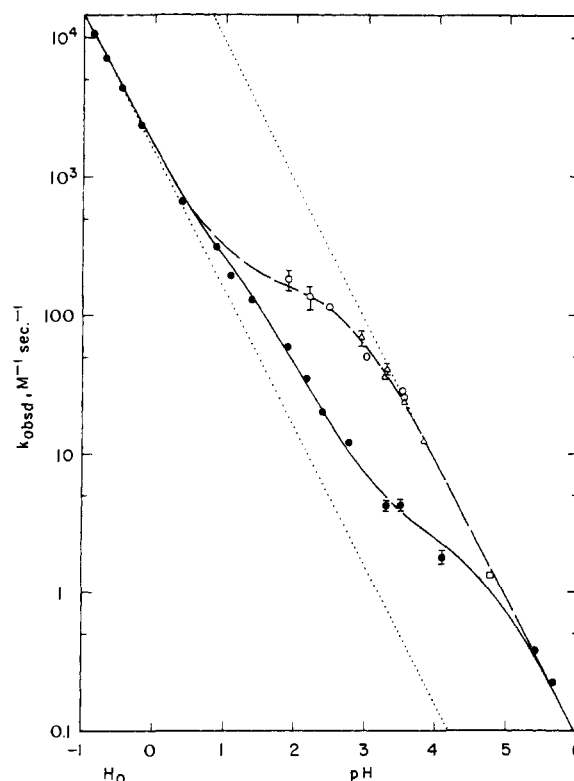


Figure 5. Dependence on pH of the observed second-order rate constants for the reaction of methoxyamine free base with *p*-methoxybenzaldehyde extrapolated to zero (solid symbols) and high (open symbols) concentrations of general acid catalysts. Rates at high catalyst concentration were determined in the presence of imidazolium (O) and methoxyammonium (□) ions and carboxylic and cacodylic acids (Δ). The solid line is theoretical for the overall reaction, k_{obsd}^0 , at zero buffer concentration, from eq 2 and 2a and the rate constants of Table I; the broken line is theoretical for k^∞ (eq 10). The dotted lines indicate the rate constants for the hydronium ion catalyzed attack and dehydration steps at low and high pH, respectively.

plot of k_{obsd} against the concentration of imidazolium ion cannot be accounted for by a transition to rate-determining dehydration at high catalyst concentration. The observed rate constants level off at a value approximately 2.5-fold below that expected for rate-limiting dehydration at this pH, as indicated by the broken line of Figure 4B. Extrapolated values for the limiting rate constants at high concentrations of imidazolium ion and carboxylic and cacodylic acids as a function of pH are shown by the open symbols of Figure 5.

Further evidence for a change in rate-determining step at low pH from a general acid catalyzed process to one that is not general acid catalyzed is provided by the observation that the initial slope of a plot of k_{obsd} against the concentration of imidazolium ion is more than twofold smaller at pH 1.45 than at pH 2.20. At pH 0.36, no catalysis at all is observed with difluoroacetic acid ($pK_a' = 1.13$), a much

Table II. General Acid Catalysis of *O*-Methyloxime Formation from *p*-Methoxybenzaldehyde^a

Catalyst	pK _a '	pH	Concn range, M	k _{ent} , M ⁻² sec ⁻¹	k _{ent} (av), M ⁻² sec ⁻¹
Difluoroacetic acid	1.13 ^b	0.36 ^c	0.0-0.50		≤ 160 ^d
Cyanoacetic acid (CNAc)	2.33 ^b	2.60	0.02-0.40	350	
		2.65	0.02-0.05	330	340
Chloroacetic acid (ClAc)	2.70 ^b	2.62	0.02-0.60	300	
		3.00	0.10-0.35	230	270
Methoxyacetic acid (MeOAc)	3.40 ^b	2.61	0.02-0.70	205	
		3.31	0.02-0.40	190	200
Formic acid (For)	3.56 ^b	3.30	0.01-0.50	220	
		3.82	0.02-0.40	170	200
β-Chloropropionic acid (βCP)	3.93 ^b	2.94	0.0-0.50	170	
		3.41	0.02-0.30	220	200
Acetic acid (Ac)	4.65 ^b	2.65	0.02-0.40	200	
		3.27	0.02-0.50	225	215
Cacodylic acid (Cac)	6.15 ^e	3.53	0.02-0.20		160
Cation of					
Triazole (TrzH ⁺)	2.58 ^f	2.67	0.05-0.70		450
Methoxyamine (MAH ⁺)	4.73	2.73	0.025-0.25	350	
		2.78	0.05-0.25	280	315
Imidazole ^g (ImH ⁺)	7.21 ^g	1.90	0.02-0.70	520 ^h	
		2.20	0.02-0.60	585 ^h	
		2.48	0.02-0.70	320	
		3.01	0.02-0.70	335	
		3.53	0.02-0.70	360	
		3.53	0.02-0.30	330	330
2-Cyanoethylamine (CNEAH ⁺)	8.20 ^e	2.52	0.0-0.40	150	
		2.84	0.0-0.40	153	151
2-Methoxyethylamine (MEAH ⁺)	9.72 ^g	3.02	0.0-0.50		18
3-Methoxypropylamine (MPAH ⁺)	10.46 ⁱ	3.00	0.0-0.50		5.0 ± 1.5
Ethylamine (EAH ⁺)	10.97 ^g	2.96	0.0-0.40		≤ 1.3 ^j

^a At 25°, ionic strength 1.0 (KCl). ^b Reference 9. ^c In the pH region where uncatalyzed attack of the nucleophile (*k*₂) is rate determining for the stepwise pathway. ^d Limit based on the failure to observe any catalysis and the assumption that a 10% increase in rate at the highest concentration of acid would be detectable. ^e M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 8818 (1972). ^f J. Fox and W. P. Jencks, *ibid.*, **96**, 1436 (1974). ^g W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968). ^h Approximate value (accurate within ±30-40%). Not used in calculation of average. ⁱ Determined by potentiometric titration (this work) at 25°, ionic strength 1.00 ± 0.05 (KCl). ^j Limit based on the observation of an approximately 12% increase in the rate at the highest concentration of catalyst used.

stronger acid than imidazolium ion, at acid concentrations up to 0.43 M, although a 20% acceleration of the rate would be expected if the catalytic constant for difluoroacetic acid were equal to that measured at higher pH for imidazolium ion or for cyanoacetic acid (pK_a' = 2.33).

Catalytic constants for a series of carboxylic acids and ammonium ions (Table II) were determined from plots of the second-order rate constants as a function of catalyst concentration, corrected for the contribution of the buffer-independent step that is rate limiting at high catalyst concentrations, as described in the Experimental Section. Typical plots of the observed and corrected rate constants are shown in Figure 6. That the catalytic species is the conjugate acid was shown by the identity, within experimental error, of the slopes of *k*_{corr} against the concentration of the acidic species at varying pH values near or below the pK_a' of the catalysts. Salt or medium effects caused by the addition of substituted ammonium salts to the reaction mixture are probably insignificant, as shown by the observation that the rate of the reaction at pH 2.84 changes by less than 2% upon substitution of up to 1.0 M tetramethylammonium chloride for potassium chloride at a total ionic strength of 1.0.

No evidence for significant nucleophilic catalysis of *O*-methyloxime formation, *via* an intermediate alkylimmonium ion,¹² was detected with cyanoethylammonium ion under the experimental conditions used. The reaction catalyzed by 0.2 M cyanoethylammonium ion at pH 2.85 was found to be first order in methoxyamine at 0.015 and 0.03 M total methoxyamine. If the reaction were to involve nucleophilic catalysis, with rate-limiting attack of methoxyamine on an intermediate alkylimmonium ion, formation of

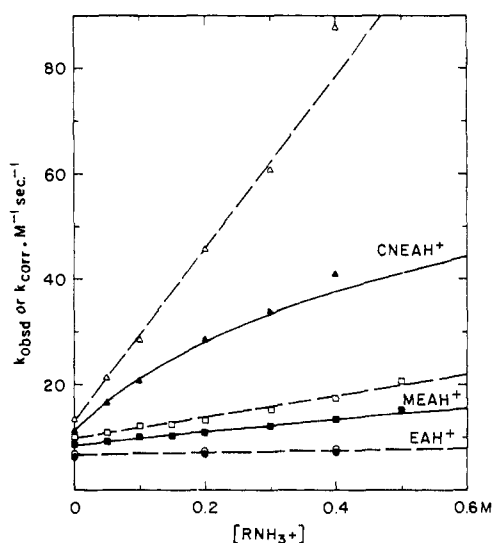


Figure 6. Catalysis of *O*-methyloxime formation from *p*-methoxybenzaldehyde by cyanoethyl- (CNEAH⁺), methoxyethyl- (MEAH⁺), and ethylammonium (EAH⁺) ions. Solid symbols are experimental points; open symbols are corrected for a change in rate-determining step according to eq 12, as described in the Experimental Section. The solid lines are theoretical curves based on the catalytic constants of Table II, with the limiting rate constant at high catalyst concentration defined by eq 10. Catalytic constants were determined from the slopes of the broken lines through the corrected points.

the immonium ion must be faster than the observed rate under these conditions. That this is not true is shown by the observation that the pseudo-first-order rate constant for the

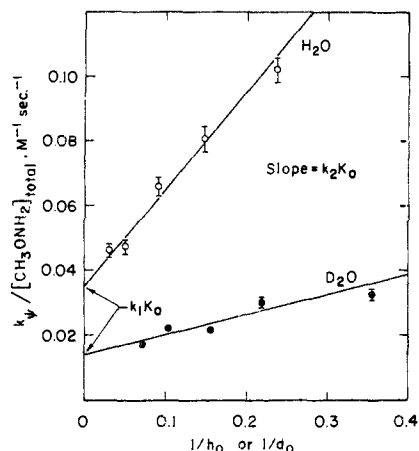


Figure 7. Deuterium isotope effect on the observed pseudo-first-order rate constants, divided by total methoxyamine concentration, for *O*-methyloxime formation from *p*-nitrobenzaldehyde in aqueous H_2SO_4 (O) and D_2SO_4 (●).

reaction of 0.03 *M* total methoxyamine with *p*-methoxybenzaldehyde, catalyzed by 0.2 *M* cyanoethylammonium ion at pH 2.85, is $5.47 \times 10^{-3} \text{ sec}^{-1}$, more than twice as fast as the measured rate constant (see Experimental Section) for imine formation from *p*-methoxybenzaldehyde and 0.2 *M* cyanoethylammonium ion. We conclude that nucleophilic catalysis by cyanoethylammonium ion makes no significant contribution to the observed catalytic constants at low pH, and that the observed catalysis is of the general acid type, as found for tertiary amines and carboxylic acids. The curvature in a plot of observed rate constants against cyanoethylammonium ion concentration (Figure 6) is also consistent with the same change in rate-determining step at high catalyst concentration that is observed with other general acid catalysts and is unlikely to occur for a nucleophilic mechanism in which the carbinolamine derived from the aldehyde and methoxyamine is not an intermediate. For less acidic primary ammonium ions, the catalysis is small (Figure 6), and, even if some contribution from the nucleophilic mechanism occurs, the observed catalytic constants represent upper limits for the general acid catalyzed mechanism. The significant observation for these compounds is the small magnitude of the catalysis by weakly acidic, relative to more strongly acidic ammonium ions.

Deuterium Isotope Effects. The isotope effect, $K_a^{\text{H}}/K_a^{\text{D}}$, on the dissociation constant of methoxyammonium ion at 25° and ionic strength 1.0 was determined spectrophotometrically using 2,5-dinitrophenol as an indicator and is equal to 3.24 ± 0.10 , based on a value of $K_a^{\text{H}}/K_a^{\text{D}}$ of 3.4 for the indicator.¹³ The isotope effect determined from the stoichiometric buffer ratios and observed values of pH or pD (where pD is obtained by adding 0.40 to the pH meter reading in D_2O solution)¹⁴ is 3.17 ± 0.10 . The use of an earlier value of $K_a^{\text{H}}/K_a^{\text{D}} = 3.32$ for the indicator¹⁵ gives $K_a^{\text{H}}/K_a^{\text{D}}$ for methoxyammonium ion of 3.17, which is in exact agreement with the results obtained from pH measurements. The value of $K_a^{\text{H}}/K_a^{\text{D}}$ for methoxyammonium ion is taken as 3.2 ± 0.1 . Hence, the $\text{p}K_a'$ of methoxyammonium ion in D_2O is 5.23 ± 0.02 . Figure 7 shows the second-order rate constants for the reaction of methoxyammonium ion with *p*-nitrobenzaldehyde in protiated and deuterated aqueous sulfuric acid, as a function of $(1/h_0)$ ¹⁶ or $(1/d_0)$.¹⁷ The isotope effect, $k_1^{\text{H}}/k_1^{\text{D}}$, of 0.8 ± 0.15 on the rate constant for the acid-catalyzed process that is predominant under strongly acidic conditions is obtained by dividing the ratio of the intercepts, $k_1^{\text{H}}K_a^{\text{H}}/k_1^{\text{D}}K_a^{\text{D}}$, by the isotope effect of 3.2 ± 0.1 on the dissociation constant of

methoxyammonium ion. The isotope effect, $k_2^{\text{H}}/k_2^{\text{D}}$, on the uncatalyzed process that occurs at low pH is equal to 1.5 ± 0.2 , from $K_a^{\text{H}}/K_a^{\text{D}}$ and the ratio of the slopes, $k_2^{\text{H}}K_a^{\text{H}}/k_2^{\text{D}}K_a^{\text{D}}$.

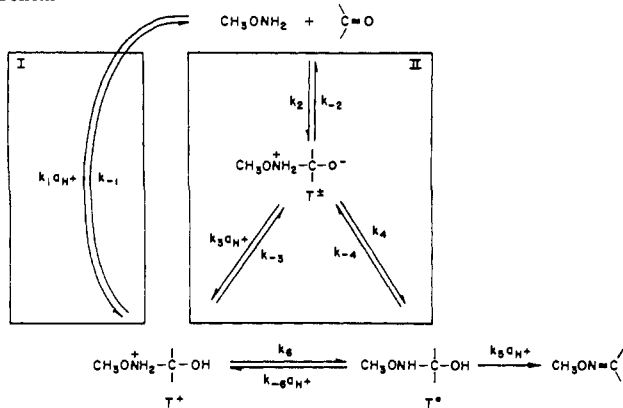
Discussion

Addition reactions of nitrogen nucleophiles to the carbonyl group ordinarily proceed by a two-step mechanism involving formation of a tetrahedral intermediate, T^0 , followed by its dehydration to give the observed product, an imine, oxime, or hydrazone (eq 1). For many of these reactions, a break in the pH-rate profile with decreasing pH is observed.^{2,8,9} This is a consequence of a change in rate-determining step, from rate-determining dehydration to formation of the intermediate, T^0 , that occurs because the acid-catalyzed dehydration step becomes faster than uncatalyzed formation and breakdown of T^0 as the pH is decreased. The pH-rate profiles (at zero buffer concentration) for *O*-methyloxime formation from aromatic aldehydes (Figure 1) exhibit a break at $\text{pH} \sim 4$, corresponding to this change in rate-determining step.

In addition to the break at $\text{pH} \sim 4$, corresponding to a change in rate-determining step from rate-limiting dehydration to formation of T^0 , the pH-rate profiles for *O*-methyloxime formation from the present series of substituted benzaldehydes show a second change in rate-determining step, manifested by a second negative break in the pH-rate curve, as the pH is decreased still further. This second negative break becomes apparent near $\text{pH} 1.0$ and hence is not an artifact resulting from the use of the H_0 function below pH zero. Furthermore, the absence of any unusual activity coefficient effects on methoxyamine in strongly acidic solution is indicated by the observation that the pH-rate profile for the reaction of acetone with methoxyamine is linear, with a slope, $\Delta \log k_{\text{obsd}}/\Delta \text{pH}$, of -1.0 in the region between $H_0 -1.0$ and $\text{pH} 1.5$, where breaks occur with the aromatic aldehydes.⁶ That the observed negative deviation at low pH is not a consequence of a salt effect on the aldehyde is indicated by the absence of any negative break in the H_0 region for the reaction of *p*-methoxybenzaldehyde with semicarbazide.¹⁸ The observation of two negative breaks in the pH-rate profile is inconsistent with a simple two-step mechanism involving rate-determining dehydration at high pH and a single transition state for acid-catalyzed carbinolamine formation below pH 3. Hence, the overall reaction must consist of at least three sequential, kinetically significant steps.

Further evidence for two changes in rate-determining step is provided by the behavior of the reaction in the presence of general acid catalysts. Plots of the observed second-order rate constant for *O*-methyloxime formation from *p*-methoxybenzaldehyde against catalyst concentration are nonlinear (Figure 4). At $\text{pH} 3.53$, this nonlinearity is satisfactorily accounted for by a change in rate-determining step with increasing catalyst concentration from formation to dehydration of the carbinolamine.^{3b,8,9} The limiting rate constants at intermediate pH values and high concentrations of general acid catalysts are directly proportional to the hydronium ion activity (Figure 5) and correspond to the expected rate for hydronium ion catalyzed carbinolamine dehydration. At lower pH, plots of the observed rate constant against the concentration of general acid catalysts for the reaction of methoxyamine with *p*-methoxybenzaldehyde level off much more sharply than predicted for rate-limiting dehydration at high catalyst concentrations (Figure 4B, broken line), and the limiting rate constants approach a pH-independent rate (Figure 5). This requires that some process that is slower than carbinolamine dehydration and

Scheme I



that proceeds through a neutral (rather than a cationic) transition state be partially rate determining at low pH and high concentrations of general acid catalysts.

Since there are only two processes that involve making and breaking of bonds to carbon, the observation of two changes in rate-determining step and three kinetically significant steps for *O*-methyloxime formation requires that one step must involve a proton transfer process. A mechanism consistent with the experimental observations is given by Scheme I. According to this formulation, the addition step proceeds by two concurrent mechanisms, one of which (pathway I) involves a single, hydronium ion catalyzed step that is kinetically significant, whereas the other (pathway II) involves two steps, an uncatalyzed attack of the nucleophile to form a highly unstable zwitterionic intermediate, T^\pm , and a proton transfer process that is required to "trap" this intermediate,³ by converting it to T^+ or T^0 , in order for the intermediate to undergo further reaction to products. The empirical rate constants for the stepwise pathway, k_2 , k_C , and k_D of eq 2a, correspond to k_2 , $K_n k_3$, and $K_n k_4$, respectively, where $K_n = k_2/k_{-2}$ is the equilibrium constant for formation of T^\pm from starting materials. Five regions are observed as a result of the two breaks in the pH-rate profile, as illustrated schematically for *p*-chlorobenzaldehyde in Figure 8. These correspond to significant contributions from the following rate-determining processes, in order of decreasing pH: (E) hydronium ion catalyzed dehydration ($K_{ad}k_5$) of the neutral carbinolamine intermediate, T^0 ; (D) water-mediated proton transfer ($K_n k_4$) between the nitrogen and oxygen atoms of T^\pm ; (C) diffusion-controlled proton transfer ($K_n k_3$) from the hydronium ion to T^\pm ; (B) uncatalyzed attack (k_2) of methoxyamine on the aldehyde; and (A) hydronium ion catalyzed attack (k_1) of methoxyamine, *via* pathway I.

At pH values near neutrality (region E of the pH-rate profile), the dehydration step, $K_{ad}k_5$, is rate determining. As the pH is decreased, a change in rate-determining step occurs, and at intermediate values of pH the proton transfer steps $K_n k_4$ and $K_n k_3$ leading to the conversion of T^\pm to T^0 or T^+ are rate determining, in regions D and C, respectively. At still lower pH, diffusion-controlled protonation of T^\pm by the hydronium ion becomes faster than the uncatalyzed formation and breakdown of T^\pm , and the pH-rate profile shows a second break, corresponding to a change in rate-determining step to a neutral transition state for uncatalyzed formation and breakdown of T^\pm (k_2), in region B. If no additional mechanism were available, the pH-rate profile should level off at low pH, at a rate corresponding to k_2 . The observed increase in rate below pH 0 (region A) is ascribed to the existence of a separate mechanism (pathway I) that involves a single kinetically significant step for hydronium ion catalyzed conversion of starting materials to

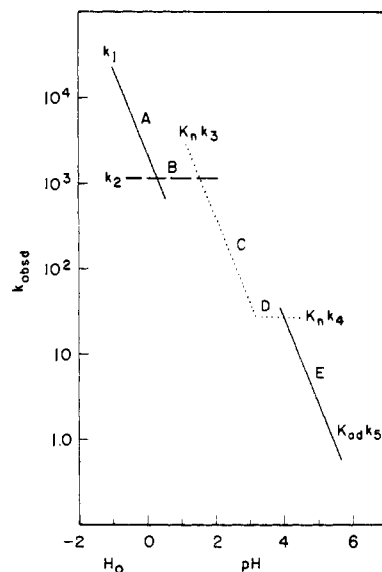


Figure 8. Diagram illustrating the contributions of the kinetic processes of Scheme I to the observed pH-rate profile for *O*-methyloxime formation from *p*-chlorobenzaldehyde in different regions of pH. The solid curve is calculated for the overall reaction (eq 2 and 2a).

T^+ . This pathway becomes most important at low pH where the rate-determining step for the sequential pathway II is not subject to acid catalysis.

The proton transfer process that traps T^\pm is catalyzed by general acids as well as by the hydronium ion. In the presence of sufficiently high concentrations of general acid catalysts, the proton transfer process becomes faster than the uncatalyzed attack and the expulsion of methoxyammonium ion from T^\pm , and a change in rate-determining step for the *addition* process *via* pathway II, from proton transfer to attack of the nucleophile, occurs as the catalyst concentration is increased, with a limiting rate constant equal to k_2 . As the pH is increased, the hydronium ion catalyzed dehydration step, $K_{ad}k_5 a_{\text{H}^+}$, becomes slower than k_2 . Thus the single change in rate-determining step at pH ~ 2.5 in the presence of very high concentrations of general acid catalysts (Figure 5, upper line) corresponds to a transition with increasing pH from rate-limiting formation of T^\pm (k_2) to dehydration of T^0 ($K_{ad}k_5$).

Based on the proposed mechanism, two specific predictions were made with regard to structural effects on reactivity and to catalysis of the reaction. (1) The hydronium ion catalyzed proton transfer process that is kinetically significant at intermediate pH values should be accelerated by electron-withdrawing substituents on the aldehyde and should exhibit a sensitivity to substituents that is equal to that of K_n , the equilibrium constant for formation of the zwitterionic carbinolamine. (2) The Brønsted plot for general acid catalysis of the proton transfer process should be nonlinear,⁵ with a slope close to 0 for strongly acidic catalysts and 1.0 for weakly acidic catalysts, and a relatively sharp transition near the $\text{p}K_a$ of T^\pm . The experimental observations are in agreement with both of these predictions.

Structure-Reactivity Correlations. The observed rate constant for the hydronium ion catalyzed proton transfer process at intermediate pH is $K_n k_3$, from the steady-state rate eq 2a. Since k_3 is diffusion controlled, the effect of aldehyde structure on the magnitude of the observed rate constant should only reflect differences in K_n . This equilibrium constant is equal to $K_{ad}K_z$ (eq 3). K_z should be essentially independent of substituents on the central carbon atom since substituent effects on ammonium and alcoholate ion formation should be equal and opposite, as indicated by

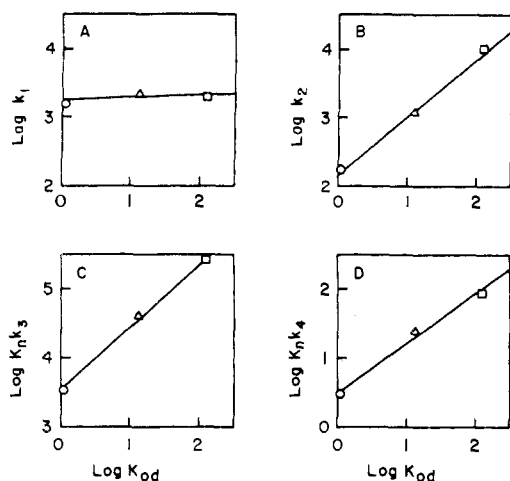
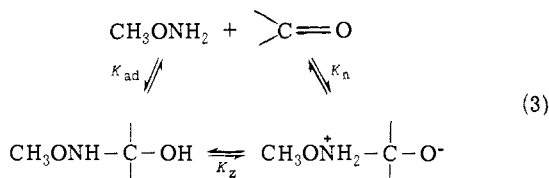


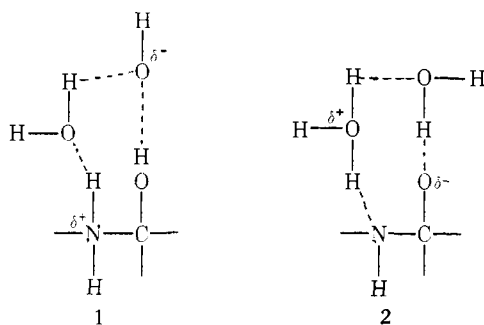
Figure 9. Relationship between the rate constants for the individual processes in *O*-methyloxime formation from *p*-methoxy- (O), *p*-chloro- (Δ), and *p*-nitro- (\square) benzaldehyde (Scheme I) and the equilibrium constants, K_{ad} , for neutral carbinolamine formation: (A) hydronium ion catalyzed attack, k_1 (slope 0.04); (B) uncatalyzed attack, k_2 (slope 0.85); (C) hydronium ion catalyzed proton transfer, $K_n k_3$ (slope 0.95); (D) water catalyzed proton transfer, $K_n k_4$ (slope 0.7).

the fact that the dissociation constants for benzylammonium ions¹⁹ and 1-phenyl-2,2,2-trifluoroethanols²⁰ show equal sensitivities to aromatic substituents. Hence, the prediction is made that $K_n k_3$ should show the same dependence on aldehyde substituents as K_{ad} ; *i.e.*, a plot of $\log K_n k_3$ against $\log K_{ad}$ for different aldehydes should have a slope of 1.0. The experimentally observed structure-reactivity relationship (Figure 9C) has a slope of 0.9, consistent with this prediction.



The slope of a plot of $\log K_n k_4$ against $\log K_{ad}$ (Figure 9D) is 0.7, indicating that for the water-mediated proton transfer the effect of substituents on K_n is partially offset by a decrease in k_4 with electron-withdrawing substituents. This is consistent with the α value of 0.5 observed in an analogous system, the solvent mediated proton transfer between the oxygen atoms of carboxylic acids,²¹ which suggests that k_4 should show some sensitivity to the acidity or basicity of T^\pm . Such an effect is to be expected if the intramolecular "proton switch," through one or two water molecules, is a stepwise²² process.

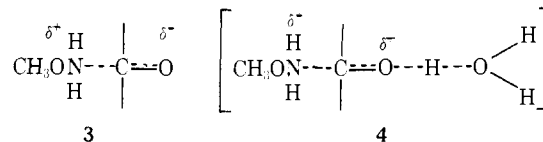
The observation that k_4 is decreased by electron-withdrawing substituents is consistent with transition state **1** in which proton donation to oxygen is further advanced than



proton abstraction from nitrogen, and the carbinolamine moiety possesses a partial positive charge. Transition state **2**, in which proton transfer from nitrogen is further advanced than proton donation to oxygen, requires a partial negative charge on the carbinolamine and is not consistent with the experimental observations. This observation is consistent with a mechanism for the solvent-mediated "proton switch" in which the initial proton transfer process involves the more favorable of the two possible proton transfers between T^\pm and water. Based on estimated pK_a values (see below) for the hydroxyl and ammonium groups of T^+ and T^\pm , respectively, proton transfers from water to T^\pm to give T^+ and a hydroxide ion (*cf.* transition state **1**) are expected to be more favorable than the alternative proton transfers to give T^- and a hydronium ion (*cf.* transition state **2**) by factors of 4, 60, and 600 for the *p*-nitro-, *p*-chloro-, and *p*-methoxybenzaldehyde derivatives, respectively. A similar result has been obtained for the "proton switch" between the nitrogen and oxygen atoms of the zwitterionic tetrahedral intermediate in the aminolysis of alkyl acetates.²³

The rate constant, k_2 , for the uncatalyzed attack of methoxyamine (transition state **3**) should be increased by electron-withdrawing substituents on the aldehyde. In agreement with this prediction, a plot of $\log k_2$ against $\log K_{ad}$ (Figure 9B) has a slope of 0.85. The large magnitude of this slope suggests a relatively late transition state, with extensive C-N bond formation, for the uncatalyzed attack step.

The hydronium ion catalyzed mechanism of pathway I (Scheme I) is expected to have a smaller dependence on aldehyde substituents since for this pathway (transition state **4**) the favorable effect of electron-withdrawing substituents



on carbon-nitrogen bond formation will be partially or completely offset by their unfavorable effect on the protonation of oxygen in the transition state. The observed values of k_1 (Figure 9A) are insensitive to substituents, with a slope of $\log k_1$ against $\log K_{ad}$ of 0.04. This large difference in sensitivity to substituents of the acid-catalyzed processes that are observed at low and intermediate pH provides a dramatic demonstration (Figures 9A and 9C) that the reaction proceeds through qualitatively different transition states in these two pH regions.

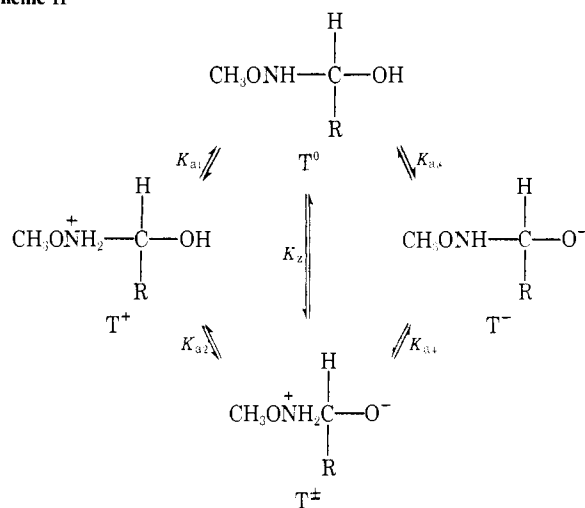
If estimates are made for the equilibrium constants interrelating the different ionic forms of the tetrahedral intermediate (Scheme II), approximate values for each individual rate constant of Scheme I may be calculated. The estimation of these equilibrium constants is illustrated for the carbinolamine derived from *p*-chlorobenzaldehyde.

(i) Following considerations discussed in detail elsewhere,^{3b} pK_{a1} is estimated to be 2.0 ± 0.3 from the observed $pK_{a'}$ of 4.88 for *N,O*-dimethylhydroxylammonium ion²⁴ and an average ΔpK_a of 2.9 ± 0.3 for substitution of a methyl group by *p*-ClC₆H₄CH(OH).

(ii) pK_{a2} is estimated to be 8.5. Starting with the estimated²⁵ pK_a of 9.98 for CH₃N⁺H₂CH₂OH, replacement of a hydrogen on the central carbon atom by *p*-ClC₆H₄ should give a ΔpK^{3b} of -0.45 or $pK_a = 9.53$ for the *N*-methyl derivative. Substitution of CH₃O ($\sigma_1 = 0.25$)²⁶ for CH₃ on nitrogen gives a ΔpK of $-8.4(0.25/2) = -1.05$ if ρ_1 for alcohol and amine ionization²⁷ is taken as 8.4, and the fall-off factor for transmission of substituent effects through nitrogen²⁸ is taken as 2.0. Hence $pK_{a2} = 8.5$.

(iii) The value of pK_{a3} is estimated to be 13.8. Given the

Scheme II



pK_{a1} of 2-chloroethanol²⁹ of 14.31, a σ_1 value of 0.17 for ClCH_2 ²⁶ and an estimated²⁷ σ_1 value of 0.18 for CH_3ONH , substitution of CH_3ONH for ClCH_2 should give a pK_a of 14.23. Replacement of a hydrogen by $p\text{-ClC}_6\text{H}_4$ should further decrease pK_{a3} by 0.45 unit,^{3b} to 13.8.

(iv) From the interrelationship among the four equilibrium constants of Scheme II, $pK_{a4} = pK_{a1} + pK_{a3} - pK_{a2} = 2.0 + 13.8 - 8.5 = 7.3$.

(v) $\log K_z$ for the conversion of T^0 to T^\pm may be estimated from the relationship $\log K_z = pK_{a1} - pK_{a2} = -6.5$.

With the foregoing estimates for the ionization constants for the tetrahedral intermediate derived from p -chlorobenzaldehyde, the effect of substituents on the aromatic ring was calculated using $\rho = 1.06$ for dissociation of the ammonium ion¹⁹ and $\rho = 1.11$ for ionization of the alcohol group, based on the ρ value for dissociation of trifluoroacetophenone hydrates.²⁰ Values of the individual rate constants of Scheme I were calculated from observed rate constants and the relationships $K_n = K_{ad}K_7$ (see eq 3), $k_{-2} = k_2/K_n$, $k_{-1} = k_1K_{a1}/K_{ad}$, $k_{-3} = k_3K_{a2}$, $k_{-4} = k_4K_z$, $k_{-6} \approx 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$ for a thermodynamically favorable proton transfer,⁵ and $k_6 = k_{-6}K_{a1}$, and are listed in Table III. The values of k_3 for the hydronium ion catalyzed proton transfer are 1.1×10^{10} , 1.0×10^{10} , and $6.8 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$ for p -methoxy-, p -chloro-, and p -nitrobenzaldehyde, respectively, in good agreement with the expected values for diffusion-controlled proton transfers from the hydronium ion.⁵ The values of k_4 between 10^6 and 10^7 sec^{-1} are consistent with the rate constants for a cyclic, solvent-mediated proton transfer process.^{30,31}

Values of k_{-2} for breakdown of T^\pm to starting materials are large, as required by a mechanism for which trapping of this intermediate by diffusion-controlled proton transfer is kinetically significant at moderate pH values. A value of k_{-2} of $5 \times 10^{11} \text{ sec}^{-1}$ has been estimated for the breakdown of the intermediate T^\pm derived from p -chlorobenzaldehyde and the less basic amine 2-methyl-3-thiosemicarbazide^{3b} ($pK_{a'} = 1.2$), and the rate constant for amine expulsion from the corresponding intermediate derived from pyridine-4-carboxaldehyde and piperazine⁴ is $\geq 10^7 \text{ sec}^{-1}$. For derivatives of a single aldehyde, the increased leaving ability of methylthiosemicarbazide relative to methoxyamine probably results from both the lower pK_a of methylthiosemicarbazide and the steric factors that are reflected in an approximately 60-fold smaller value of K_{ad} for this amine. The assumption made in deriving the steady-state rate eq 2 and 2a, that at moderate pH values the equilibration of T^+ and T^0 (k_6 and k_{-6}) is fast relative to the other possible routes for reaction of T^+ and T^0 (k_{-1} , k_{-3} , k_{-4} ,

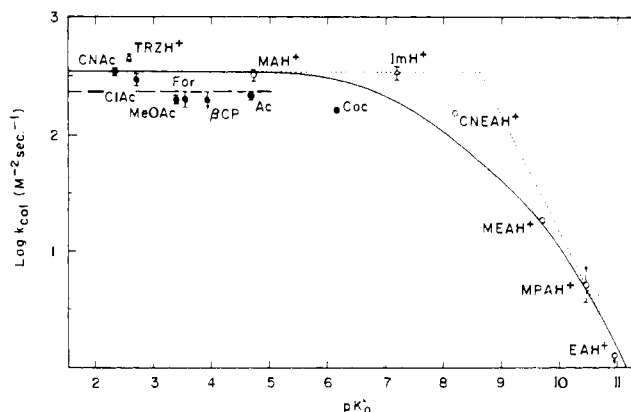


Figure 10. Brønsted plot for general acid catalysis of the formation of p -methoxybenzaldehyde O -methyloxime by carboxylic and cacodylic acids (●) and primary (○) and heterocyclic (Δ) amines. The shape of the solid line through the points for primary amines is based on the data of Eigen for proton transfers from ammonium ion to oxygen bases (ref 5). The dotted lines indicate limiting slopes of 0 and -1.0 .

Table III. Summary of Calculated Rate and Equilibrium Constants for the Individual Processes of Schemes I and II

	$p\text{-OMe}$	$p\text{-Cl}$	$p\text{-NO}_2$
pK_{a1}	2.5	2.0	1.4
pK_{a2}	9.05	8.5	7.9
pK_{a3}	14.35	13.8	13.2
pK_{a4}	7.8	7.3	6.7
K_{ad}, M^{-1}	1.10	13.4	125
K_z	3×10^{-7}	3×10^{-7}	3×10^{-7}
K_n, M^{-1}	3.3×10^{-7}	4.0×10^{-6}	3.8×10^{-5}
$k_1, M^{-2} \text{ sec}^{-1}$	1500	2070	1930
k_{-1}, sec^{-1}	4.4	1.5	0.6
$k_2, M^{-1} \text{ sec}^{-1}$	175	1150	1×10^4
k_{-2}, sec^{-1}	5.3×10^8	2.9×10^8	2.6×10^8
$k_3, M^{-1} \text{ sec}^{-1}$	1.1×10^{10}	1.0×10^{10}	6.8×10^9
k_{-3}, sec^{-1}	9.8	32	86
k_4, sec^{-1}	9.1×10^6	6.2×10^6	2.2×10^6
k_{-4}, sec^{-1}	2.7	1.9	0.66
$k_5, M^{-1} \text{ sec}^{-1}$	8.4×10^4	1.57×10^4	2.9×10^3
k_6, sec^{-1}	3×10^7	10^8	4×10^8
$k_{-6}, M^{-1} \text{ sec}^{-1}$	$\sim 10^{10}$	$\sim 10^{10}$	$\sim 10^{10}$

and k_5) and hence is not kinetically significant, is consistent with these calculations.

General Acid Catalysis. In the pH region where the proton transfer step is the predominant kinetically significant process, O -methyloxime formation is subject to general acid catalysis. The second prediction of the mechanism of Scheme I for O -methyloxime formation involves the shape of the Brønsted plot for this catalysis. If a simple proton transfer is rate determining for the general acid catalyzed process, the considerations of Eigen⁵ predict that the Brønsted slope, α , should be near zero when this proton transfer is in the thermodynamically favorable direction and should show a transition to a slope approaching -1.0 as the reaction becomes thermodynamically unfavorable with increasing pK_a of the acid catalyst. For a proton transfer in which reactants and products are symmetrical with respect to charge, the break in the Brønsted plot should occur at a pK_a equal to that for the hydroxyl group of T^+ .

Figure 10 shows the Brønsted plot for general acid catalysis of O -methyloxime formation from p -methoxybenzaldehyde in the pH range 1.9–3.8. Statistical corrections were not applied to the rate or dissociation constants for these acids.³² For strongly acidic catalysts, the Brønsted slope, α , is ≤ 0.1 (for carboxylic acids) and ≤ 0.05 (for ammonium ions). Strongly basic primary ammonium ions show a much steeper slope, with $\alpha \geq 0.9$. Fitting the experimental points for ammonium ions to the shape of the Brønsted curve re-

ported by Eigen⁵ for a simple diffusion-controlled proton transfer (between the ammonium ion and oxygen bases) gives a break between the limiting slopes of $\alpha = 0$ and $\alpha = 1$ at $\text{p}K_a = 8.6$, which is in good agreement with the estimated $\text{p}K_a$ of 9.05 for the hydroxyl group of T^+ .

The positive deviations of triazolium, methoxyammonium, and imidazolium ions from the line determined by carboxylic and cacodylic acids may reflect a small electrostatic effect, and in the case of triazolium and imidazolium ions could also involve an orientational or statistical factor. The 1.5-fold deviation of methoxyammonium ion from the line for carboxylic acids is smaller than the three- to fivefold acceleration of diffusion-controlled proton transfers observed by Eigen for oppositely charged reactants,⁵ and suggests that electrostatic effects are relatively unimportant in this system, probably as a result of shielding of the negative charge in T^\pm by the high ionic strength of the medium and the positively charged ammonium group of the zwitterion.

It is of interest that the catalytic constants for the most acidic carboxylic acids show small positive deviations from a line of slope 0 (broken line, Figure 10), and cacodylic acid shows a negative deviation. The points for carboxylic and cacodylic acids may be fit reasonably well by a Brønsted line of slope 0.08. Eigen's data for simple proton transfer reactions⁵ indicate that the slopes approach but do not reach the theoretical limiting values of 0 and 1.0 several units above and below $\Delta\text{p}K_a = 0$. That the transition to a slope of 0 is very gradual for carboxylic acids and may not be complete even for a large favorable $\Delta\text{p}K$ is suggested by the observation that the Brønsted plot for the reaction of carboxylic acids with acetate ion has a slope close to 0.5 over a $\text{p}K_a$ range of nearly 5 units.³³ These considerations suggest a cautionary note in the interpretation of small but nonzero Brønsted slopes over a limited range of catalyst $\text{p}K$; unless other factors are considered, it is probably impossible to base an assignment of a "concerted" mechanism of catalysis on such slopes.

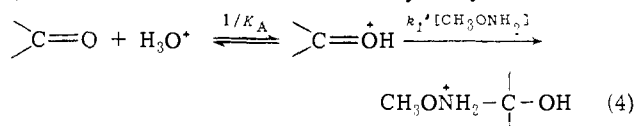
The positive deviation by hydronium ion (not shown) of approximately an order of magnitude from the limiting Brønsted line for catalysis by acidic ammonium ions is of the magnitude expected from the data of Eigen⁵ for simple diffusion-controlled proton transfers, and from experimental observations for other systems believed to involve rate-limiting simple proton transfers to unstable reaction intermediates.^{31,34} Water shows a 2000-fold positive deviation (based on a concentration of 55 M) from the line of slope 1.0 for weakly acidic primary ammonium ions and presumably exerts its catalytic effect *via* a different mechanism (the "proton switch" of transition state **1**) that does not require diffusion away of the hydroxide ion before a second proton transfer occurs to give T^0 . The kinetically indistinguishable stepwise mechanisms for the pH-independent reaction that involve protonation of T^- by hydronium ion or deprotonation of T^+ by hydroxide ion in the rate-determining step are excluded since, based on the $\text{p}K_a$ values of Table III, such mechanisms require rate constants for the rate-determining proton transfer step between 8.6×10^{11} and $6 \times 10^{14} M^{-1} \text{sec}^{-1}$, two to five orders of magnitude greater than the diffusion-controlled limit.

Isotope Effects and the Mechanism of the Acid-Catalyzed k_1 Process. The solvent isotope effect, $K_a^{\text{H}}/K_a^{\text{D}}$, on the dissociation constant of methoxyamine is 3.2 ± 0.1 . This is similar to the isotope effects measured for the dissociation constants of semicarbazide⁸ and weakly basic anilines.¹⁷

According to the mechanism of Scheme I, the transition state for the uncatalyzed addition step, k_2 , does not involve a proton transfer, and hence only a secondary isotope effect should be observed. In accordance with this prediction, the

observed isotope effect, $k_2^{\text{H}}/k_2^{\text{D}}$, of 1.5 ± 0.2 is small and is in the same range as the isotope effects of 0.9–1.9 observed for reactions of nucleophiles with acyl compounds.³⁵

The acid-catalyzed addition process (k_1) that is significant at low pH may involve either of two kinetically equivalent mechanisms: (1) general acid catalysis by the hydronium ion, *via* a transition state such as **4** in which proton transfer is in some sense "concerted" with carbon-nitrogen bond formation or (2) specific acid catalysis involving attack of methoxyamine on the fully protonated aldehyde (eq 4). The absence of observable catalysis by difluoroacetic



acid for the reaction of *p*-methoxybenzaldehyde in the low pH region is consistent with either mechanism 2 or mechanism 1 with an α value for general acid catalysis >0.3 , where catalysis by high concentrations of hydronium ion "swamps out" catalysis by comparable concentrations of weaker acids. The observed dependence of $\log k_1$ on H_0 with a slope of 1.0 does not permit an unequivocal assignment of mechanism since both general and specific acid catalyzed processes have been observed to follow H_0 with slopes close to or slightly greater than unity.³⁶ The observed solvent isotope effect, $k_1^{\text{D}}/k_1^{\text{H}}$, of 1.25 ± 0.2 for the reaction of methoxyamine with *p*-nitrobenzaldehyde also cannot be used to distinguish between mechanisms 1 and 2. This inverse isotope effect is significantly smaller than the inverse isotope effects of 2–3 ordinarily observed for acetal hydrolysis and other reactions that are known to proceed by a specific acid catalyzed mechanism,³⁷ but it is not inconsistent with such a mechanism if the solvent isotope effect on K_A for the aldehyde is small, as has been reported for another weakly basic carbonyl compound, benzalacetophenone.¹⁷ An inverse isotope effect of the magnitude observed is also consistent with general acid catalysis. An inverse isotope effect of 1.4 is observed for the hydronium ion catalyzed hydrolysis of ethyl orthocarbonate, a reaction that is also catalyzed by general acids,³⁸ and an inverse isotope effect as large as 2.3 has been reported for general acid catalyzed formation of a carbonium ion from tri-*p*-anisylmethanol.³⁹

The following two lines of evidence support the conclusion that the process corresponding to k_1 involves true general acid catalysis by the hydronium ion. (1) General acid catalysis by the hydronium ion occurs for carbinolamine formation from more weakly basic amines such as thiosemicarbazide⁹ and 2-methyl-3-thiosemicarbazide^{3b} since for these compounds the hydronium ion lies on the same Brønsted line as buffer catalysts. Evidence that the mechanism for hydronium ion catalyzed carbinolamine formation from these weakly basic amines is identical with that for the process corresponding to k_1 for methoxyamine is provided by the following observations.¹⁸ (a) $\log k_1$ for methoxyamine falls on the same correlation line as the corresponding rate constants for thiosemicarbazide and 2-methyl-3-thiosemicarbazide in a linear correlation of $\log k_H$ for hydronium ion catalyzed carbinolamine formation from different amines and *p*-chlorobenzaldehyde with $\log K_n$ for the equilibrium formation of T^\pm . (b) The rate constants, k_1 , for methoxyamine show the same low sensitivity to polar substituents on the aldehyde as do the rate constants for hydronium ion catalyzed carbinolamine formation from 2-methyl-3-thiosemicarbazide. Given that k_1 for methoxyamine represents the same process as acid-catalyzed carbinolamine formation from weakly basic amines, it is unlikely

that this process for methoxyamine ($pK_a' = 4.73$) would require complete protonation of the aldehyde (specific acid catalysis), whereas only partial protonation is needed for the attack of the more weakly basic thiosemicarbazide ($pK_a' = 1.88$) and 2-methyl-3-thiosemicarbazide ($pK_a' = 1.20$).

(2) The conjugate acid of *p*-nitrobenzaldehyde, required as an intermediate in the specific acid catalyzed mechanism of eq 4, is probably too unstable to account for the observed magnitude of k_1 . The rate constants, k_1' , for the attack of methoxyamine on *p*-nitrobenzaldehyde, calculated from eq 5 and the value of -8.1 for pK_A for this aldehyde deter-

$$k_1' = k_1 K_A \quad (5)$$

mined by Arnett and coworkers^{40,41} is $2.4 \times 10^{11} M^{-1} \text{sec}^{-1}$, approximately two orders of magnitude faster than the rate constants for most diffusion-controlled reactions in water.⁵ Even if pK_A is as high as -5.6 (based on the H_A scale),⁴⁶ the calculated value of k_1' is $8 \times 10^8 M^{-1} \text{sec}^{-1}$, close to the diffusion-controlled limit. The sensitivity to polar substituents of k_1' for the (hypothetical) attack of methoxyamine on the protonated aldehyde is large and is comparable to that for the attack on the unprotonated aldehyde (k_2), a result that is unexpected for a reaction whose rate approaches the diffusion-controlled limit. Furthermore, a plot of k_1' against pK_A (in terms of H_0 or H_A)⁴⁷ for *p*-nitro-, *p*-chloro-, and *p*-methoxybenzaldehyde is linear up to (or beyond) the diffusion-controlled limit; the curvature expected as this limit is approached does not appear.

Two points demonstrated in this work are of particular interest. (1) A "concerted" mechanism of general acid or base catalysis is possible and provides a kinetic advantage under some circumstances, even when the intermediate T^\pm in the stepwise pathway is stable enough to have a finite lifetime. This means that the limiting hypothesis⁴⁸ "... that concerted catalysis occurs *only* when intermediates are too unstable to exist for a finite time or to give products at a significant rate without requiring rate constants larger than ... diffusion-controlled ..." is incorrect. (2) We believe that the hydronium ion catalyzed reaction represents the first example of a reaction involving rapid proton transfer to or from an electronegative atom that has been observed to proceed by concurrent, kinetically distinct "concerted," and stepwise pathways for proton transfer, with a single catalyst. The fact that the two distinct pathways I and II of Scheme I are observed means that there is a barrier that separates the pathway for the "concerted" from that for the stepwise process on the three-dimensional free energy surface⁴⁸ for the reaction. Such a barrier should exist for proton transfer from carbon, and the existence of distinct stepwise and concerted pathways for an olefin-forming elimination reaction has been discussed in this context by More O'Ferrall.⁴⁹ In the present case, the barrier separating the two pathways may not be a "chemical" one because of the extremely low activation energy for thermodynamically favorable proton transfers to or from electronegative atoms. Instead this barrier may well consist primarily of the free energy of activation for diffusion together of T^\pm and the hydronium ion.

This point is illustrated by the energy contour diagram of Figure 11, which represents the two possible pathways for formation of T^+ from *p*-methoxybenzaldehyde and methoxyamine, catalyzed by $1.0 M$ hydronium ion. The portion of the diagram to the right of the dotted line represents events occurring within a termolecular encounter complex of aldehyde, methoxyamine, and hydronium ion, and the "concerted" process that occurs within this complex is shown by the solid line. The free energy barrier for for-

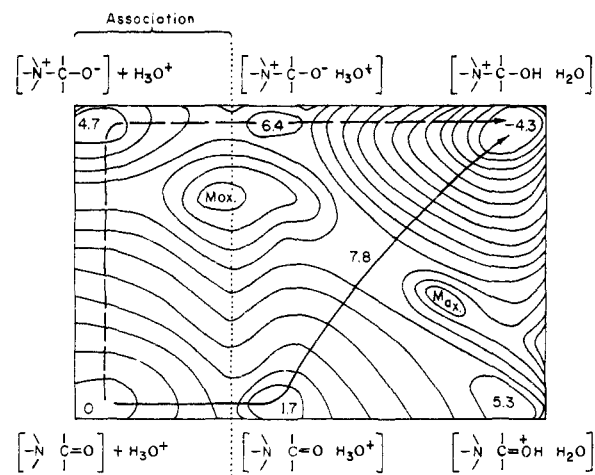


Figure 11. Energy contour diagram for catalysis of carbinolamine formation from *p*-methoxybenzaldehyde and methoxyamine by $1.0 M$ hydronium ion, including the free energy barrier corresponding to an association step involving the catalyst. Bracketed species represent encounter complexes. Each contour line equals 1 logarithmic unit.

mation and breakdown of an encounter complex with the catalyst, corresponding to a rate constant for diffusion of $\sim 10^{10} M^{-1} \text{sec}^{-1}$ in the forward (k_f) direction and $5 \times 10^{11} \text{sec}^{-1}$ in the reverse (k_r) direction,⁵⁰ is represented by a ridge (dotted line) separating the bimolecular and termolecular encounter complexes. The maximum in the upper lefthand part of the diagram that separates the concerted (solid line) and stepwise (broken line) pathways arises from this ridge and is a consequence of the small but significant kinetic barrier to the diffusion process.

Experimental Section

Materials. All organic reagents (with the exception of formic and acetic acids) were recrystallized, distilled, or sublimed before use. 2,5-Dinitrophenol, mp 106° , was a gift from M. Gresser. D_2O (99.8 atom % D) was redistilled; 98% D_2SO_4 (99.5 atom % D) and DCI (20% in D_2O , 99+ atom % D) were commercial products and were used without further purification. Glass-distilled water was used in all experiments.

Solutions of *p*-methoxybenzaldehyde were prepared in ethanol, immediately diluted with glass-distilled water, and stored under argon. Such solutions were stable for at least 2 weeks, as indicated by the absence of any absorbance change at 290 nm. Solutions of *p*-chlorobenzaldehyde were prepared under argon in approximately 60% aqueous ethanol and used on the same day, as were solutions of *p*-nitrobenzaldehyde in water containing approximately 1% ethanol. Partially neutralized solutions of methoxyamine hydrochloride were also prepared within 24 hr of use.

Equilibrium Constants for Carbinolamine Formation. Equilibrium constants, K_{ad} , at 25° and ionic strength $1.0 M$ (KCl), for formation of the neutral carbinolamine intermediates from methoxyamine were determined spectrophotometrically⁹ in $0.02 M$ phosphate buffer, 78% dianion, from the absorbance change, extrapolated to time zero, at 260 or 290 nm respectively, upon mixing a solution of *p*-chloro- or *p*-methoxybenzaldehyde with known concentrations of methoxyamine. The total concentration of aldehyde plus adduct in the reaction mixtures was $7.5 \times 10^{-5} M$. Six amine concentrations between 0.02 and $0.27 M$ and five amine concentrations between 0.2 and $1.0 M$ were used with *p*-chloro- and *p*-methoxybenzaldehyde, respectively. The equilibrium constant for *p*-nitrobenzaldehyde was measured in $0.02 M$ imidazole buffer, 35% acid, at 268 nm using $6.6 \times 10^{-5} M$ *p*-nitrobenzaldehyde and nine concentrations of methoxyamine between 0.002 and $0.10 M$. The change in absorbance resulting from complete conversion of the aldehyde to the carbinolamine, determined from the ordinate intercept of a double reciprocal plot of ΔA against amine concentration, was ca. 30% of the initial absorbance of the aldehyde. The equilibrium constant for carbinolamine formation was determined from the negative abscissa intercept of the above double reciprocal

plot or from the negative reciprocal of the slope of a plot of ΔA against $\Delta A/[\text{amine}]$.

Kinetics. Rates of reaction at $25.0 \pm 0.3^\circ$ were followed on a Gilford Model 2000 or a Zeiss PMQ II spectrophotometer by observing the disappearance of aldehyde (*p*-methoxybenzaldehyde, 290 nm) or the appearance of *O*-methyloxime (*p*-chlorobenzaldehyde, 296 nm; *p*-nitrobenzaldehyde, 305 nm). Under the experimental conditions used ($[\text{CH}_3\text{ONH}_2]_{\text{total}}/[\text{RCHO}] \geq 16$), the reactions followed pseudo-first-order kinetics. Aldehyde concentrations of 3×10^{-4} , 5×10^{-5} , and $7.5 \times 10^{-5} M$ were ordinarily used in experiments with *p*-chloro-, *p*-nitro-, and *p*-methoxybenzaldehyde, respectively. In experiments with *p*-chlorobenzaldehyde using total concentrations of methoxyamine $< 5 \times 10^{-3} M$, a concentration of $3 \times 10^{-5} M$ aldehyde in 5-cm path length cells was used. An ionic strength of 1.0 was maintained with potassium chloride in all reactions at $\text{pH} > 0$. Final concentrations of ethanol, introduced with the aldehyde solutions, in the reaction mixtures did not exceed 0.6%. The pH was measured immediately after completion of the reactions or in some cases both before and after each reaction. In the latter cases, kinetic runs showing a variation in $\text{pH} > 0.03$ unit during the reaction were discarded. Second-order rate constants were calculated by dividing the observed pseudo-first-order rate constants, k_ψ , by the concentration of methoxyamine free base, calculated from a $\text{p}K_a'$ of 4.73 for methoxyamine and the measured pH (for acid concentrations $< 1.0 M$) or the H_0 values of Paul and Long¹⁶ (for acid concentrations $\geq 1.0 M$). The second-order rate constants were extrapolated to zero buffer and zero methoxyamine concentration by one of the following procedures.

(a) In the region of the pH-rate profile where the addition step is predominantly rate determining at low buffer concentrations the observed second-order rate constants, k_{obsd} , were corrected for the contribution of the hydronium ion catalyzed dehydration step, $K_{\text{ad}}k_5a_{\text{H}^+}$, using the formula of eq 6, and were then extrapolated

$$k_{\text{ad}} = k_{\text{obsd}} / (1 - k_{\text{obsd}} / K_{\text{ad}}k_5a_{\text{H}^+}) \quad (6)$$

to zero buffer concentration to give k_{ad}^0 , the rate constant for the uncatalyzed addition step. The composite rate constant at zero buffer concentration was then calculated as previously described⁹ from k_{ad}^0 and $K_{\text{ad}}k_5a_{\text{H}^+}$. The reactions of *p*-chloro- and *p*-methoxybenzaldehyde are catalyzed by both methoxyammonium ion and external buffers. With these aldehydes, the methoxyamine and buffer concentrations were varied independently, and values of k_{ad} were extrapolated to zero buffer and zero methoxyamine concentration as described above.

(b) At low methoxyamine concentrations, where catalysis by methoxyammonium ion is small compared with the baseline rate, an empirical linear extrapolation of the observed second-order rate constants for the overall reaction to zero methoxyamine concentration was made. The value of the rate constant, k_{obsd}^0 , for the overall reaction obtained in this way agreed within 5% with that obtained by method a for the reaction of *p*-chlorobenzaldehyde and 0.001–0.005 *M* methoxyamine at $\text{pH} 3.76$. This method was also used with *p*-methoxybenzaldehyde with methoxyamine concentrations $\leq 0.02 M$. Catalysis by low concentrations of methoxyammonium ion was insignificant below $\text{pH} 1.0$ for *p*-methoxy- and *p*-chlorobenzaldehyde, and no corrections for such catalysis were made in this pH region. The reaction of *p*-nitrobenzaldehyde does not exhibit significant catalysis at any pH by the concentrations of methoxyammonium ion used in our experiments.

(c) In the pH range where the dehydration step is rate determining, catalysis by buffers and methoxyammonium ion was shown to be insignificant under our experimental conditions. Observed second-order rate constants were corrected when necessary for accumulation of the tetrahedral intermediate, using eq 7, where $[\text{N}]$ is the concentration of methoxyamine free base.

$$k_{\text{obsd}}^0 = k_{\text{obsd}}(1 + K_{\text{ad}}[\text{N}]) \quad (7)$$

Under strongly acidic conditions (*i.e.*, below $\text{pH} 0$), *O*-methyloxime formation from *p*-chloro- and *p*-methoxybenzaldehyde does not go to completion at all concentrations of methoxyamine used. For reactions under these conditions, k_f , the second-order rate constant for the forward reaction, was obtained from the slope of plots of the pseudo-first-order rate constant, k_ψ , against the

concentration of methoxyamine (eq 8). For *p*-methoxybenzal-

$$k_\psi = k_f[\text{N}] + k_r \quad (8)$$

dehyde at the highest acidity used ($H_0 = -1.4$), the correction required by this equilibrium was 15% of the apparent second-order rate constant observed in the presence of 0.40 *M* total methoxyamine.

Limiting rate constants, k^∞ , for buffer-independent steps at high buffer concentration were determined from plots of $1/(k_{\text{obsd}} - k_{\text{obsd}}^0)$ against $1/[\text{buffer}]$, as described in a previous publication.^{3b}

Analysis of pH-Rate Data. The following detailed analysis of the kinetic data is based on the assumption that the addition step proceeds by two concurrent, *additive* pathways, one of which involves a single kinetically significant step (k_1), which is subject to catalysis only by the hydronium ion, and which is the principal process observed at high acidity. The second pathway involves a sequential process and a change in rate-determining step with increasing pH, from a process that is uncatalyzed (k_2) to one that proceeds through both hydronium ion catalyzed (k_C) and uncatalyzed (k_D) transition states. The steady-state rate law for the complete mechanism is given by eq 2 and 2a. The value of $K_{\text{ad}}k_5$ for the dehydration step was determined from the dependence on pH of the observed rate constants at pH values above the second break in the pH-rate profile, where this step is entirely rate determining, and from extrapolated values of the limiting rate constants (k^∞) at high buffer concentrations (Figure 1, open symbols). At intermediate pH values, these extrapolated values for $K_{\text{ad}}k_5a_{\text{H}^+}$ are in good agreement with those obtained for rate-limiting dehydration at high pH. Rate constants, k_{ad}^0 , for the addition step were calculated, using eq 6, from values of k_{obsd}^0 or from plots of k_{ad} against buffer concentration (see above) in the pH region ($\text{pH} < 4.2$, Figure 1) where the addition step makes a significant contribution to the overall rate.

The rate constant, k_1 , for the acid-catalyzed process that predominates at low pH was determined from the slopes of plots of k_{ad}^0 against h_0 below $H_0 = -0.50$.

The rate constant, k_2 , for the uncatalyzed process that is observed at low pH was obtained by one of two methods. The first was by analysis of pH-rate data at zero buffer concentration and was used in the analysis of the pH-rate profiles for *p*-chloro- and *p*-nitrobenzaldehyde. Subtraction of $k_1a_{\text{H}^+}$ from both sides of eq 2a gives a composite rate constant, k_{seq} , for the sequential pathway of addition (eq 9). The rate constant k_1 was evaluated inde-

$$k_{\text{seq}} = k_{\text{ad}}^0 - k_1a_{\text{H}^+} = k_2(k_Ca_{\text{H}^+} + k_D) / (k_2 + k_Ca_{\text{H}^+} + k_D) \quad (9)$$

pendently from data in the H_0 region (see above). Since for the compounds studied k_2 is much larger than k_D , the apparent rate constant for the second pH-independent process that is observed at higher pH, the limiting value of k_{seq} at low pH is k_2 . This rate constant was obtained from plots of $\log(k_{\text{seq}})$ against pH. The foregoing method was satisfactory for *p*-nitro- and *p*-chlorobenzaldehydes, for which the contribution of k_1 does not represent a large fraction of k_{ad}^0 at intermediate pH values, but not for *p*-methoxybenzaldehyde where $k_1a_{\text{H}^+}$ is large relative to the rate constants for the sequential process. As a result, the process represented by k_2 for this compound is kinetically significant only over a narrow pH range at zero buffer concentration. In this system advantage was taken of the observation that the step corresponding to k_2 is not subject to general acid catalysis, whereas buffer catalysis is observed when the step corresponding to k_C is rate determining, and the observed second-order rate constants at high buffer concentration approach a buffer-independent limit, k^∞ (Figure 5, open symbols), which is given by eq 10. Values of k^∞ were deter-

$$k^\infty = K_{\text{ad}}k_5a_{\text{H}^+}(k_1a_{\text{H}^+} + k_2) / (K_{\text{ad}}k_5a_{\text{H}^+} + k_1a_{\text{H}^+} + k_2) \quad (10)$$

mined in a series of imidazolium chloride solutions between $\text{pH} 1.90$ and 3.53 from plots of $1/(k_{\text{obsd}} - k_{\text{obsd}}^0)$ against $1/$

[ImH⁺].^{3b} The best value for k_2 was then determined from eq 10, using known values (see above) of k_1 and $K_{ad}k_5$ and successive approximations for k_2 to obtain the best fit to the observed values of k^∞ .

Rate constants, k_C and k_D , for the sequential mechanism were determined from k_{seq} and k_2 , using eq 11, which is obtained by

$$k_C a_{H^+} + k_D = k_{seq}/(1 - k_{seq}/k_2) \quad (11)$$

rearrangement of eq 9. A plot of the right-hand side of eq 11 against a_{H^+} in the intermediate pH range (pH 2.50–3.55, *p*-nitrobenzaldehyde; pH 1.53–3.76, *p*-chlorobenzaldehyde) gives a straight line with slope k_C and ordinate intercept k_D . The values of k_C and k_D determined in this way were used to determine a new value of k_2 and the calculations were repeated until a self-consistent set of rate constants, k_2 , k_C and k_D , was obtained. For *p*-methoxybenzaldehyde, k_C and k_D were determined using the complete steady-state rate equation by varying k_C and k_D until the best fit of the observed data to eq 2 and 2a, with the previously determined values (see above) of k_1 , k_2 , and $K_{ad}k_5$, was obtained.

Determination of Catalytic Constants. Catalytic constants for general acid catalysis of *O*-methyloxime formation from *p*-methoxybenzaldehyde were determined from the dependence of the observed second-order rate constants on catalyst concentration. Each catalyst was ordinarily studied in 5–12 kinetic runs at each of two or more pH values. The observed rate constants were corrected for curvature caused by a change in rate-determining step at high concentrations of catalyst using eq 12, where k^∞ was calculated from

$$k_{cor} = k_{obsd}/(1 - k_{obsd}/k^\infty) \quad (12)$$

eq 10 and previously determined values of the buffer independent rate constants, or from double reciprocal plots, as described above. Catalytic constants were obtained from the slopes of linear plots of k_{cor} against the concentration of the acid form of the catalyst.⁵¹

The rate constant for imine formation from *p*-methoxybenzaldehyde and cyanoethylamine buffers (0.05–0.20 *M*) was determined at pH 7.55 and 8.14 in the presence of 0.1 *M* methoxyamine, which forces the reaction to completion by acting as a trapping agent for the imine. The reaction was followed by observing the decrease in absorbance of the aldehyde at 290 nm. The reaction was shown to be zero order in methoxyamine under these experimental conditions by the independence of methoxyamine concentration (0.1 and 0.2 *M*) of the observed pseudo-first-order rate constant in the presence of 0.2 *M* cyanoethylamine. The slope of a plot of the pseudo-first-order rate constants against buffer concentration was determined at each pH, and the rate constant for the reaction of cyanoethylammonium ion was obtained from the intercept at 1.0 of a plot of these observed slopes against the fraction of conjugate acid in the buffer.

Isotope Effects. The isotope effect on the pK_a' of methoxyamine in deuterium oxide solution at ionic strength 1.0 was determined by a modification of the method of Jencks and Salvesen,⁵² using methoxyamine as a buffer and following the absorbance at 540 nm of an added indicator, 2,5-dinitrophenol, for which the isotope effect on the dissociation constant is known.^{13,15} The maximum concentration of H₂O introduced into the D₂O solutions by addition of concentrated aqueous solutions of methoxyamine buffers was 1%. Absorbance measurements were made at a series of eight different buffer ratios from 20 to 90% methoxyamine free base in H₂O and D₂O. Endpoint absorbances of the indicator and its anion were determined in duplicate in 0.1 *N* HCl (DCI) and KOH (KOD) solutions, respectively. Values of K_a^H/K_a^D for methoxyamine were calculated from the observed absorbance of the indicator at each point using eq 13, where A_{OH} (A_{OD}) and A_H (A_D) are the end-

$$(K_a^H/K_a^D)_{MeONH_2} =$$

$$\left(\frac{A_{OH}}{A_{obsd} - A_H} \right) \left(\frac{A_{obsd} - A_D}{A_{OD} - A_{obsd}} \right) \quad (13)$$

point absorbances of the indicator in 0.1 *N* base and acid solutions, respectively. The value of K_a^H/K_a^D was also determined directly from plots of the logarithm of the stoichiometric buffer ratio against pH or pD, where pD was obtained by adding 0.40 to the

pH meter reading in D₂O solution.¹⁴ Experimental verification of this relationship with 8×10^{-3} *M* HCl and DCI at ionic strength 1.0 gave a difference in pH meter reading of 0.41 ± 0.01 .

The solvent deuterium isotope effect on the rate of *O*-methyloxime formation from *p*-nitrobenzaldehyde was determined in a series of five H₂O–H₂SO₄ solutions and five D₂O–D₂SO₄ solutions with H_0^{16} (D_0)¹⁷ values between –0.4 and –1.6. The final concentration of H₂O in the D₂O solutions (from exchange of methoxyamine added as the protio form) was less than 1%. Under acidic conditions, the rate law for the reaction is given by eq 14. If the as-

$$k_\psi = k_1[\text{CH}_3\text{ONH}_2]h_0 + k_2[\text{CH}_3\text{ONH}_2] \quad (14)$$

sumption is made that the dissociation of methoxyammonium ion follows the H_0 acidity function, eq 14 is equivalent to eq 15. Since

$$k_\psi = k_1 K_a [\text{CH}_3\text{ONH}_3^+] + k_2 K_a [\text{CH}_3\text{ONH}_3^+]/h_0 \quad (15)$$

in strongly acidic solutions the concentration of methoxyammonium ion is essentially equal to the total stoichiometric amine concentration, a plot of $k_\psi/[\text{total methoxyamine}]$ against $1/h_0$ should have a slope equal to $k_2 K_a$ and an ordinate intercept equal to $k_1 K_a$. The kinetic isotope effects on k_2 and k_1 were determined from the ratios of the slopes and intercepts, respectively, of these plots for water and deuterium oxide solutions and the independently determined value (see above) of K_a^H/K_a^D for methoxyamine.

References and Notes

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- (47) $pK(H_0)$ values of -9.2 , -7.7 , and -5.7 , obtained by correction of the H_0 values at half-protonation obtained by Yates and Stewart,⁴² to the scale of Jorgenson and Hartter,⁴³ were used for p -nitro-, p -chloro-, and p -methoxybenzaldehyde, respectively. These values should be self-consistent, although each appears to be about 1 pK unit too low based on more recent values.^{40,44} Correction of these values to the H_A scale⁴⁶ gives $pK(H_A)$ values of -5.6 , -4.8 , and -3.7 for p -nitro-, p -chloro-, and p -methoxybenzaldehyde, respectively; an extrapolation of the H_A scale of approximately 1 pK unit was required to estimate $pK(H_A)$ for p -nitrobenzaldehyde.
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- (50) The rate constant for breakdown of the solvation complex between ammonia and water is $6 \times 10^{11} \text{ sec}^{-1}$ (E. Grunwald and E. K. Ralph, *Accounts Chem. Res.*, **4**, 107 (1971)); the use of $k_1 = 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$ and $k_r = 5 \times 10^{11} \text{ sec}^{-1}$ corresponds to an equilibrium constant of 0.02 M^{-1} for encounter complex formation (cf. ref 3b, footnote 31).
- (51) If the dehydration step is entirely rate limiting at high buffer concentrations, the reaction involves a simple change in rate-determining step, from carbinolamine formation to dehydration, with increasing buffer concentration, and, by analogy with other systems,^{3b,9} the slope of k_{cor} against the concentration of the catalytic species is k_{cat} . For the limiting case of the mechanism at low pH, assuming that $K_{\text{ad}}k_5a_{\text{H}^+}$ is large and $k^{\infty} = (k_1a_{\text{H}^+} + k_2)$, a more complex expression for k_{cor} is obtained because of the additivity of the k_1 and sequential pathways of eq 2a, and for this limiting case the slope of k_{cor} against catalyst concentration is $k_{\text{cat}}\{(k_1a_{\text{H}^+} + k_2)/k_2\}^2$. The error introduced by assuming that the slope is equal to k_{cat} would be 6% of k_{cat} at pH 2.5, if the processes represented by $(k_1a_{\text{H}^+} + k_2)$ were entirely rate limiting at high buffer concentration but is actually smaller because of the contribution of the dehydration step at this pH. The error at higher pH values will be even smaller. Since this error is small compared with other experimental uncertainties, the slopes of k_{cor} against the concentration of acid catalyst were taken as equal to k_{cat} in all the buffer catalysis experiments.
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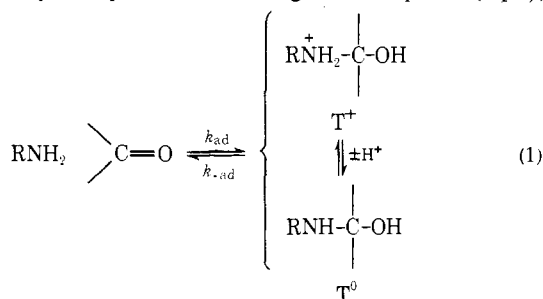
Mechanism of Carbinolamine Formation^{1a}

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Abstract: A general mechanism is described for carbinolamine formation that is consistent with kinetic and structure-reactivity data reported in this paper and elsewhere for the reaction of amines with substituted benzaldehydes. According to this mechanism, the addition reaction that is observed at pH values below neutrality proceeds by two separate and concurrent pathways. These are (I) general acid catalysis of amine attack on the carbonyl group in a more-or-less "concerted" manner and (II) a stepwise process involving the uncatalyzed formation of a zwitterionic intermediate, T^{\pm} , that is subsequently trapped by a kinetically significant proton transfer process involving acids or water. For weakly basic amines and/or aldehydes for which the value of K_{ad} , the equilibrium constant for neutral carbinolamine formation, is small, the predominant pathway of hydronium ion catalyzed carbinolamine formation is the "concerted" pathway, I. This pathway is characterized by rate constants that are relatively insensitive to polar substituents on the aldehyde and the amine. For more strongly basic amines or amines and aldehydes with larger values of K_{ad} , the intermediate T^{\pm} for the stepwise pathway, II, is stabilized, and this pathway is favored relative to the "concerted" process. Contributions of the stepwise pathway to the observed rate of carbinolamine formation are experimentally shown by (a) breaks in pH-rate profiles indicative of changes in rate-determining step that cannot be accounted for by the transition from carbinolamine formation to dehydration and (b) strong sensitivity of the observed rate constants to polar substituents on the amine and the aldehyde under conditions where the stepwise proton transfer processes involving acids or water are kinetically significant. The pH-independent reaction that is ordinarily observed with weakly basic amines at moderately acidic pH values corresponds to a rate determining water-mediated "proton switch" that converts T^{\pm} to T^0 . With hydrazine derivatives possessing an acidic hydrogen in the 2 position, unusually fast rates are observed for the pH-independent process and are attributed to a facile intramolecular proton donation from N-2 of the substituted hydrazine moiety to the alcoholate oxygen atom.

We wish to describe a general mechanism for the formation of tetrahedral addition compounds (carbinolamines) from carbonyl compounds and nitrogen nucleophiles (eq 1),



a process that constitutes the first step in the formation of imines, hydrazones, and related compounds² and is analogous to the formation of tetrahedral intermediates in the aminolysis of acyl compounds.³ At pH values below 13-14, the stable ionization state of the carbinolamine is either T^0 or T^+ , depending on the pH and the pK_a of the parent amine. Hence, carbinolamine formation at neutral or acidic pH values requires both the formation of a carbon-nitrogen bond and the addition of a proton to the oxygen atom, which undergoes a change in pK_a from approximately -5 to -8 in the aldehyde or ketone to $8-9$ in T^+ , or $13-14$ in T^0 . The observed acid catalysis of carbinolamine formation is a consequence of this requirement for protonation of the oxygen atom of the product.