Kinetics and Mechanism for Addition of Amines to Formyl-1-methylpyridinium Ions[1]

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Abstract: The following lines of evidence establish that semicarbazone, phenylhydrazone, and oxime formation from 2-, 3-, and 4-formyl-1-methylpyridinium ions occurs with rate-determining carbinolamine dehydration under acidic, neutral, and basic conditions. First, plots of first-order rate constants against amine concentration are nonlinear. This nonlinearity reflects carbinolamine accumulation. Second, rate constants for conversion of tetrahedral adducts of substrate and amine to imines are the same as rate constants observed for imine formation from the carbonyl substrate. Third, these reactions occur exclusively with acid catalysis in the pH range investigated; no evidence was found for the usual pH-independent reactions typical of addition of weakly basic amines to the carbonyl function. Finally, low susceptibility of these reactions to general acid catalysis coupled with large values of the Bronsted exponent are suggestive of rate-determining carbinolamine dehydration, not amine attack.

The role of nucleophilic reactions at carbonyl carbon in the chemistry and biochemistry of pyridoxal phosphate[2] has motivated a number of studies of kinetics and mechanism for addition of oxygen and nitrogen nucleophiles to pyridine aldehydes. Particularly well studied is the hydration of these species which has been probed by conventional kinetic techniques[3-7] as well as by the T-jump method.[8] These studies have included investigations of both metal-ion catalysis and enzymatic catalysis for hydration of pyridine aldehydes.[9]

Less well understood are reactions involving addition of amines to the carbonyl group of these complex substrates. Some important early work dealt directly with such reactions for pyridoxal itself[10-12] and with models for this compound.[13] Moreover, equilibrium constants have been measured for addition of a number of amines to pyridine-4-carboxaldehyde to form carbinolamines,[14,15] and rate constants have been measured for addition of piperidine and sarcosine to this substrate.[15] Interpretation of these reactions is complicated by both protolytic and hydration equilibria of the substrates. We have elected to pursue studies of addition of amines to pyridine aldehydes employing conventional carbonyl reagents, hydroxylamine, semicarbazide, and phenylhydrazine, and two series of substrates: the pyridine aldehydes themselves and their cationic *N*-methyl derivatives. The rationale for proceeding in this manner derives from (i) the fact that mechanism and catalysis for reactions of these nucleophiles is rather thoroughly understood;[16-18] (ii) use of the *N*-methyl derivatives provides a model for the protonated pyridine aldehydes and simplifies data interpretation, and (iii) use of the three pyridine aldehydes will permit comparison of structure–reactivity correlations with those previously found for the hydration reactions.

This manuscript reports findings for oxime, semicarbazone, and phenylhydrazone formation from *N*-methylpyridine aldehydes.

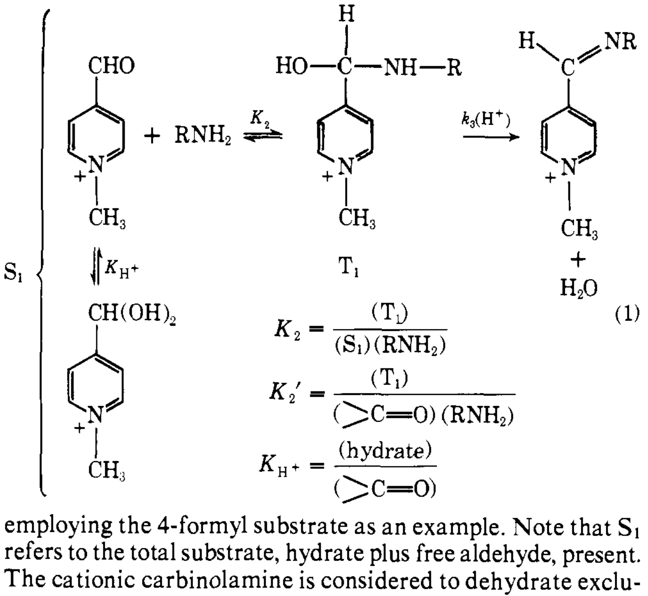
Experimental Section

Materials. 2-, 3-, and 4-formyl-1-methylpyridinium iodides were synthesized from methyl iodide and the appropriate pyridine aldehydes. These materials were carefully recrystallized prior to use in kinetic experiments. Several tetrahedral adducts between these aldehydes and carbonyl reagents were synthesized according to the method of Poziomek et al.[19] Semicarbazide hydrochloride, hydroxylamine hydrochloride, and phenylhydrazine were carefully recrystallized before use in kinetic experiments. Solutions of these reagents were prepared just prior to use. Reagent grade inorganic salts were employed without further purification. Distilled water was used throughout.

Kinetic Measurements. All rate measurements were carried out spectrophotometrically employing Zeiss PMQ II spectrophotometers equipped with thermostated cell holders. Rates of oxime and semicarbazone formation were measured in water at 30 °C; rates of phenylhydrazone formation were measured in 20% aqueous ethanol at 25 °C. Ionic strength was maintained at 0.50 throughout. pH was maintained constant through use of dilute carboxylic acid buffers or by employing the nucleophilic reagents as their own buffer. Values of pH were measured with Radiometer pH meters. First-order rate constants were measured from plots of the difference between optical density at infinite time and optical density against time in the usual manner.

Results

As is developed in detail below, oxime, semicarbazone, and phenylhydrazone formation from formyl-1-methylpyridinium ions proceed with rate-determining carbinolamine dehydration over the entire pH range investigated. The kinetics for these reactions is complicated by the hydration equilibria of the substrates. The reaction scheme is formulated in eq 1,



$$K_2 = \frac{(T_1)}{(S_1)(RNH_2)} \qquad K_2' = \frac{(T_1)}{(>C{=}O)(RNH_2)} \qquad K_{H^+} = \frac{(\text{hydrate})}{(>C{=}O)} \tag{1}$$

employing the 4-formyl substrate as an example. Note that S_1 refers to the total substrate, hydrate plus free aldehyde, present. The cationic carbinolamine is considered to dehydrate exclusively with acid catalysis, in accord with results presented below. In terms of rate and equilibrium constants defined in eq 1, the first-order rate constants for this reaction are given by:

$$k_{obsd} = k_3K_2(RNH_2)(H^+)/[1 + K_2(RNH_2)] \tag{2}$$

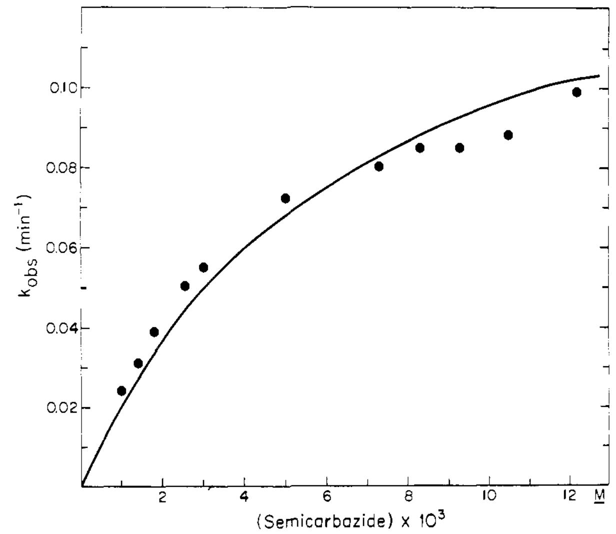


Figure 1. First-order rate constants for 4-formyl-1-methylpyridinium semicarbazone formation plotted as a function of the concentration of semicarbazide free base. Kinetic measurements were carried out at 30 °C and ionic strength 0.50, pH 4.02 maintained with 0.04 M oxalate buffer. The points are experimental; the solid line was calculated on the basis of the rate and equilibrium constants collected in Table II.

Table I. Rate Constants for 4-Formyl-1-methylpyridinium Semicarbazone Formation in Aqueous Solution at 30 °C and Ionic Strength 0.50[a]

pH	(Semicarbazide)$_{fb}$, M	k_{obsd}, min^{-1}	k_2^{app},[b] M^{-1} min^{-1}	k_2^{cor},[c] M^{-1} min^{-1}
1.53	0.00011	0.522	4745	4834
	0.000148	0.701	4736	4855
	0.00022	0.929	4223	4381
	0.00031	1.26	4065	4279
	0.00045	1.63	3622	3899
2.03	0.00012	0.189	1575	1607
	0.00020	0.391	1955	2021
	0.00032	0.470	1469	1549
	0.00042	0.686	1633	1750
	0.00054	0.785	1454	1587
	0.00073	0.952	1304	1466
	0.00092	1.109	1205	1393
	0.0021	1.835	874	1186
	0.0032	2.31	722	1115
	0.0042	2.33	555	951
2.53	0.00031	0.181	584	615
	0.00065	0.336	517	574
	0.00086	0.402	467	535
	0.0011	0.475	432	513
	0.0021	0.790	376	510
	0.0033	0.931	282	440
3.03	0.00031	0.062	200	
	0.00065	0.120	185	
	0.00082	0.137	167	
	0.00106	0.195	184	

[a] All reactions were carried out in 0.04 M oxalate buffers, and the rate constants have not been corrected to zero buffer concentration. [b] Apparent second-order rate constants calculated by dividing first-order rate constants by the concentration of semicarbazide free base. [c] Second-order rate constants corrected for the extent of carbinolamine formation: $k_2^{cor} = k_2^{app}[1 + K_2(RNH_2)]$

1-Formyl-4-methylpyridinium Iodide Semicarbazone Formation. In Figure 1 first-order rate constants for 1-formyl-4-methylpyridinium semicarbazone formation at 30 °C, pH 4.02, and ionic strength 0.5 are plotted as a function of the concentration of semicarbazide free base. The crucial observation is that the rate constants deviate from linearity at the higher amine concentrations, consistent with accumulation of significant amounts of carbinolamine.[20,21] This deviation from linearity cannot be accounted for in terms of a transition in the rate-determining step from carbinolamine dehydration to rate-determining dehydration of the aldehyde hydrate; on the basis of the data of Cabani et al.[3] concerning rates of hydration and dehydration of pyridine aldehydes, one can estimate that the rate constant for aldehyde hydrate dehydration is near 3 min^{-1}, more than an order of magnitude greater than the apparent limiting value of the observed rate constants. Consequently, the data in Figure 1 provide strong evidence that carbinolamine dehydration is rate determining for this reaction at pH 4.

This conclusion has been directly corroborated by measurement of the rate constant for formation of the semicarbazone from the tetrahedral adduct of semicarbazide and 4-formyl-1-methylpyridinium iodide at 30 °C, pH 4.12, in the presence of 0.3 M total semicarbazide. A first-order rate constant of 0.0875 min^{-1} was obtained. From this value and the concentration of hydrated protons, a value for k_3 (eq 1) of 1150 M^{-1} min^{-1} may be calculated. This value is in reasonable agreement with one of 1400 M^{-1} min^{-1} based on a more extensive collection of data employing the aldehyde as substrate and assuming rate-determining carbinolamine dehydration. Were amine attack rate determining under these conditions, one would have observed a much more rapid collapse of the tetrahedral compound to the semicarbazone.

First-order rate constants for 4-formyl-1-methylpyridinium semicarbazone formation were measured as a function of semicarbazide concentration at 30 °C at several additional values of pH. Representative data are collected in Table I. Apparent second-order rate constants obtained by dividing first-order constants by the concentration of semicarbazide free base are relatively constant at low amine concentrations and then decrease with increasing amine concentration; results are qualitatively similar to those shown in Figure 1. In those cases in which first-order rate constants exceed unity, at least a portion of the decrease in apparent second-order rate constant may be attributed to increasing influence of the rate of aldehyde hydrate dehydration on the reaction rate (see below). The remainder of the departure of first-order rate constants from linearity with amine concentration reflects carbinolamine accumulation, as at pH 4.02 (Figure 1). True (as opposed to apparent) second-order rate constants for semicarbazone formation at each value of pH were estimated from the slopes of plots of first-order rate constants against amine concentration (not shown) employing data for low amine concentrations only. Logarithms of these rate constants are plotted against pH in Figure 2. The data are well correlated by a single straight line of slope −1, indicating that the reaction is subject to specific acid catalysis over the pH range investigated. No break in the pH-rate profile suggestive of a change in rate-determining step is observed. Consequently, it is concluded that carbinolamine dehydration is the rate-determining step down to at least pH 1.5.

The data presented in Figures 1 and 2 accord with the rate law expressed in eq 2. For the purposes of evaluation of rate and equilibrium constants, it is convenient to rearrange this rate law:

$$\frac{1}{k_{obsd}} = \frac{1}{(RNH_2)}\left[\frac{1}{k_3K_2(H^+)}\right] + \frac{1}{k_3(H^+)} \qquad (3)$$

A plot of $1/k_{obsd}$ against $1/(RNH_2)$ for 4-formyl-1-methylpyridinium semicarbazone formation at pH 4.02, an alternative way of displaying the data shown in Figure 1, yields an excellent straight line (Table I, plot not shown). From the slope of this line and the measured pH, a value of k_3K_2 of 2.7 × 10^5 M^{-2} min^{-1} is calculated. This value is in sensible agreement

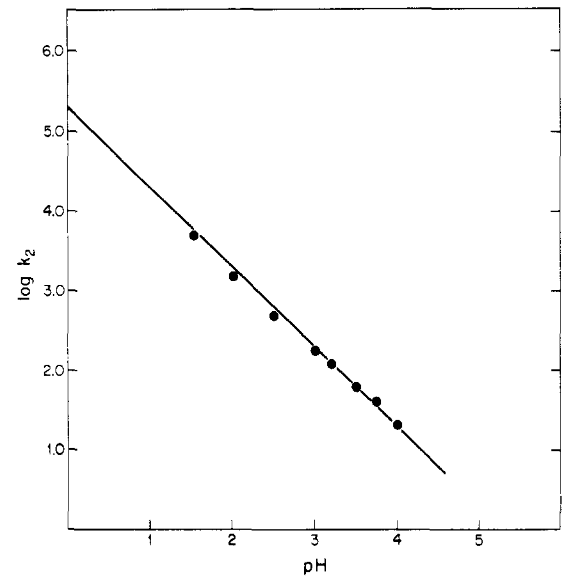
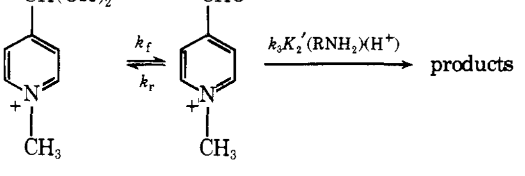


Figure 2. Logarithms of second-order rate constants, in units of M^{-1} min^{-1}, for 4-formyl-1-methylpyridinium semicarbazone formation plotted against pH. The solid line has a slope of −1.

with a result of 2.0×10^5 M^{-2} min^{-1} obtained for the same quantity from the ordinate intercept in Figure 2. A value of 2.4×10^5 M^{-2} min^{-1} has been adopted for this quantity. This value also accords with one based on a double reciprocal plot of the data at pH 3.53 (Table I, plot not shown) and is probably accurate to within ±25%. From the ordinate intercept, a value of k_3 of 1.4×10^3 M^{-1} min^{-1} is obtained. From this value and that for k_3K_2, a value of K_2 of 170 M^{-1} was calculated. The solid line in Figure 1 is a theoretical line based on these values. Sander and Jencks have measured a value of 110 M^{-1} for the equilibrium constant for addition of semicarbazide to pyridine-4-carboxyaldehyde, K_{eq} = (adduct)/(hydrated plus unhydrated aldehyde)(RNH_2), in water at 25 °C and ionic strength 1.0.[14] If one assumes that the influence of N-methylation is quantitatively similar for the addition of water and semicarbazide to the carbonyl function, then our value for K_2 is in accord with that previously measured.

With a reasonably reliable value for the equilibrium constant for carbinolamine formation (K_2) now in hand, it is possible to return to the original data and correct the apparent second-order rate constants for the extent of carbinolamine formation: $k^{cor} = k^{app}[1 + K_2(RNH_2)]$. The corrected values have been included in Table I. Note that values of corrected second-order rate constants decrease significantly with increasing amine concentration, establishing that the rate of aldehyde dehydration must make a partial contribution to the overall rate at high concentrations of amine at low values of pH. This is entirely reasonable since, as noted above,[3] one can estimate the first-order rate constant for hydrate dehydration to be near 3 min^{-1}. It is possible to attempt to account for the influence of the rate of aldehyde dehydration on the overall rate. We can write the reaction as:



(4)

with the corresponding rate law, assuming that low concentrations of amine are employed or that carbinolamine accumulation has been corrected for:

Table II. Summary of Rate and Equilibrium Constants for 4-Formyl-1-methylpyridinium Semicarbazone Formation[a]

Constant	Value
k_3	1.4×10^3 M^{-1} min^{-1}
K_2	170 M^{-1}
K_2'	9.0×10^3 M^{-1}
k_f	5.9 min^{-1}
K_{H^+}	69

[a] All constants are defined in eq 1 and 4.

$$dP/dt = k_3K_2'(RNH_2)(H^+)(>C{=}O) \qquad (5)$$

Note specifically that this law is written in terms of K_2' (eq 1). The concentration of free aldehyde can be approximated assuming the steady-state approximation: $(>C{=}O) = k_fS_t/[k_r + k_3K_2'(RNH_2)(H^+)]$ in which it has been assumed that the concentration of hydrate is equal to the total substrate concentration, S_t. Now the expression for the observed first-order rate constants takes the form:

$$k_{obsd} = \frac{k_fk_3K_2'(RNH_2)(H^+)}{k_r + k_3K_2'(RNH_2)(H^+)} \qquad (6)$$

or, in double reciprocal form:

$$\frac{1}{k_{obsd}} = \frac{k_r}{k_fk_3K_2'(H^+)}\frac{1}{(RNH_2)} + \frac{1}{k_f} \qquad (7)$$

First-order rate constants for 4-formyl-1-methylpyridinium semicarbazone formation at pH 1.53 were corrected for the extent of carbinolamine formation as described above, and the reciprocals of these constants were plotted against the reciprocal of the amine concentration. A satisfactory straight line is obtained from which a value for k_f of 5.9 min^{-1} is calculated from the ordinate intercept. This value is in satisfactory agreement with a value estimated on the basis of published data for the rate of dehydration of the protonated pyridine-4-carboxaldehyde hydrate at this pH, 3.2 min^{-1}.[3] Due to the small value of the intercept, our value for k_f may be in error by a factor of 2.

The slope of the double reciprocal plot of corrected first-order rate constants against amine concentration (eq 7) is 1.85×10^{-4} and is equal to $k_r/k_fk_3K_2'(H^+)$. K_2' may be estimated from our value for K_2 and an evaluation of K_{H^+} based on the value of 52 for the equilibrium constant for hydration of protonated pyridine-4-carboxaldehyde: $K_2' = K_2(1 + K_{H^+}) = 170 \times 53 = 9 \times 10^3$ M^{-1}. Employing this value and the measured pH, we can calculate a value for $k_r/k_f = K_{H^+}$ from the slope of the line; a value of 69 is obtained, in satisfactory agreement with the hydration equilibrium constant for the protonated species.

A summary of rate and equilibrium constants defined in eq 1 for 4-formyl-1-methylpyridinium semicarbazone formation is provided in Table II.

Second-order rate constants for 4-formyl-1-methylpyridinium semicarbazone formation at pH 2.81 are plotted against the concentration of chloroacetate buffer in Figure 3. Rate constants increase slightly but significantly with increasing buffer concentration, strongly suggesting that carbinolamine dehydration is subject to general acid catalysis: $K_{cat}^{ClCH_2COOH} = 2.2$ M^{-1} min^{-1}.

4-Formyl-1-methylpyridinium Iodide Oxime Formation. In Figure 4, first-order rate constants for oxime formation from 4-formyl-1-methylpyridinium iodide are plotted as a function of the concentration of hydroxylamine free base at pH 3.95 and 5.23, 30 °C, and ionic strength 0.50. At both values of pH, rate constants level off and eventually become independent of amine concentration, as in the case of semicarbazone formation from

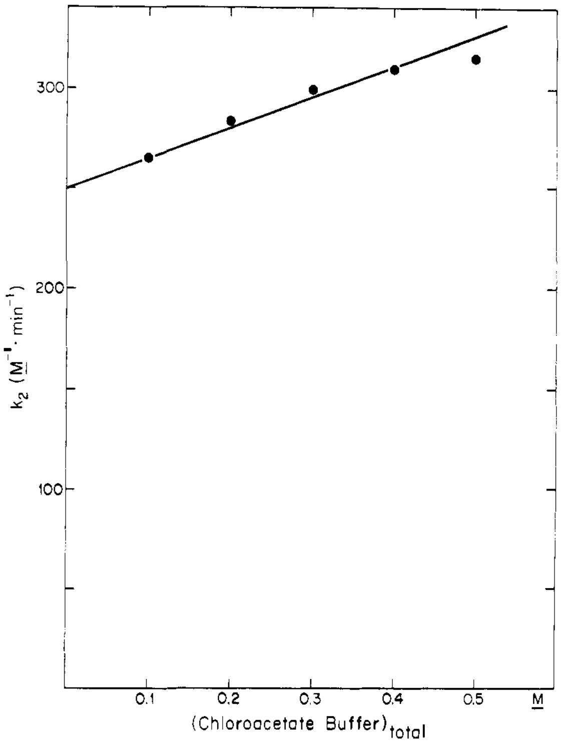


Figure 3. Second-order rate constants for 4-formyl-1-methylpyridinium semicarbazone formation at pH 2.81 plotted against the concentration of a chloroacetate buffer.

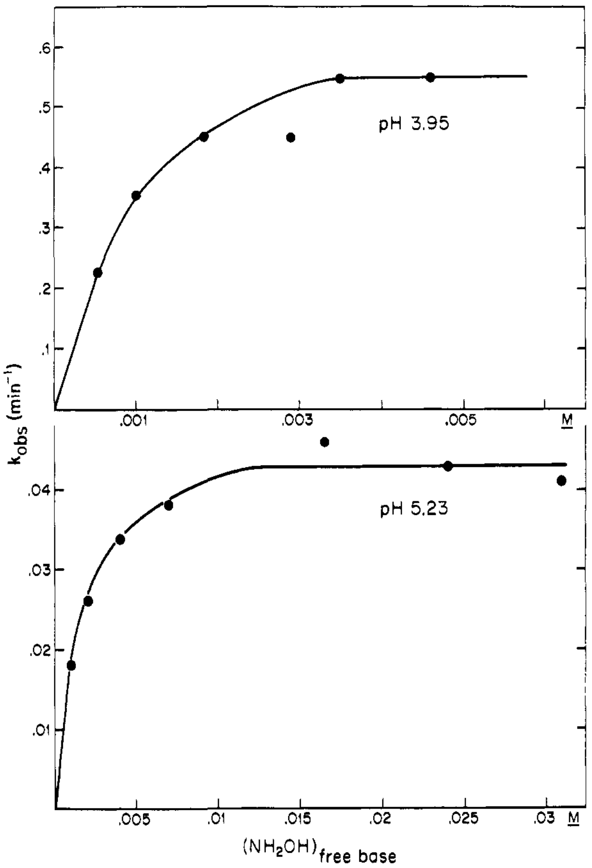


Figure 4. First-order rate constants for 4-formyl-1-methylpyridinium oxime formation plotted as a function of the concentration of hydroxylamine free base at pH 3.95 and 5.23; measurements made at 30 °C and ionic strength 0.50.

the same substrate (Figure 1). Note that independence of amine concentration is achieved at values of k_{obsd} well below those at which aldehyde hydrate dehydration significantly influences the overall rate (see above). Consequently, the data shown in Figure 4 offers strong evidence that oxime formation occurs with rate-determining carbinolamine dehydration under these conditions. Double reciprocal plots of k_{obsd} against amine concentration yield straight lines having ordinate intercepts too small to permit evaluation of k_3 and, hence, of K_2 independent of k_3. Examination of the concentrations of amine required to achieve half-maximal velocities at pH 3.95 and 5.23 (Figure 4) suggest that K_2 must fall in the range 500 to 1500 M^{-1}.

Since K_2 was not directly measured, it was estimated in the following manner. First, it is assumed that protonated pyridine-4-carboxaldehyde is a good model for the N-methyl derivative. Second, it is assumed that protonation (or methylation) of the pyridine nitrogen atom will have the same effect on the equilibrium constant for addition of hydroxylamine as it does on that for water. The relative extents of hydration of protonated and unprotonated pyridine-4-carboxaldehyde is 34.6 = K_{H^+}/K_H;[3] Sander and Jencks have measured the equilibrium constant for addition of hydroxylamine to pyridine-4-carboxaldehyde, $K_1' = 1500$ M^{-1}.[14] Finally, since $K_2' = 53 \times K_2$, as developed above, it follows that K_2 is near 980 M^{-1}, five–six-fold greater than the corresponding value for semicarbazide (Table II). This value is used in subsequent calculations. If first-order rate constants in Figure 4 are corrected for accumulation of carbinolamine by the equation: $k_{obsd}^{cor} = k_{obsd}[1 + 980(RNH_2)]$, the corrected constants are linear in the concentration of hydroxylamine. That is, the value of K_2 of 980 M^{-1} accounts quantitatively for the deviations from linearity observed in Figure 4.

First-order rate constants for 4-formyl-1-methylpyridinium oxime formation at lower values of pH are collected as a function of hydroxylamine concentration in Table III. At the lower amine concentrations employed, rate constants are linear in amine concentration as revealed by the constancy in apparent values of second-order rate constants. At pH 1.5 and 2.05, the concentration of hydroxylamine free base is too low to cause deviations from linearity; that observed at high amine concentrations at pH 1.5 reflects influence of the rate of aldehyde hydrate dehydration on the rates. At pH 3.01, significant concentrations of carbinolamine accumulate and second-order rate constants have been corrected as described above.

The logarithms of second-order rate constants for oxime formation plotted as a function of pH yield a straight line with a slope of −1, indicating that acid catalysis of dehydration of the cationic carbinolamine is the only important route under these conditions. k_3 was evaluated from the limiting rate constant for oxime formation at high hydroxylamine concentrations at pH 5.23. A value of 7.3×10^3 M^{-1} min^{-1} was obtained. In addition, k_3 was measured as the rate constant for conversion of the adduct between 4-formyl-1-methylpyridinium ion and hydroxylamine to oxime at pH 4.5. This method gave a value of 6.6×10^3 M^{-1} min^{-1}. We have chosen a value of 7.0×10^3 M^{-1} for this constant. Using this value, one can estimate K_2 to be 790, slightly smaller than that estimated as described above.

Finally, a plot of the reciprocal of first-order rate constants for oxime formation at pH 1.5 against the reciprocal of amine concentration yields an approximate value of k_f from the ordinate intercept of 2.9 min^{-1}. k_f was also measured from the rate constant at high hydroxylamine concentrations at pH 1.50, and a value of 2.44 min^{-1} was obtained. These values are in excellent agreement with that estimated from the data of Cabani et al.,[3] 3.2 min^{-1}, and are about twofold smaller than that obtained from related data on semicarbazone formation, as detailed above.

Table III. Rate Constants for 4-Formyl-1-methylpyridinium Oxime Formation in Aqueous Solution at 30 °C and Ionic Strength 0.50

pH	$(NH_2OH)_{fb}$, M	k_{obsd}, min^{-1}	k_2^{app},[a] M^{-1} min^{-1}	k_2^{cor} [b] $\times 10^{-3}$, M^{-1} min^{-1}
1.50	0.81×10^{-6}	0.151	1.86×10^5	186
	1.69×10^{-6}	0.284	1.68×10^5	168
	3.47×10^{-6}	0.543	1.56×10^5	157
	4.97×10^{-6}	0.826	1.66×10^5	167
	6.47×10^{-6}	0.953	1.47×10^5	148
	1.33×10^{-5}	1.77	1.33×10^5	135
	1.62×10^{-5}	2.07	1.28×10^5	130
	2.13×10^{-5}	2.23	1.05×10^5	107
2.05	6.2×10^{-6}	0.206	3.32×10^4	33.4
	1.09×10^{-5}	0.385	3.57×10^4	35.7
	2.52×10^{-5}	0.784	3.11×10^4	31.9
	3.67×10^{-5}	1.29	3.51×10^4	36.4
	4.29×10^{-5}	1.36	3.17×10^4	33.1
	5.16×10^{-5}	1.58	3.06×10^4	32.2
	5.64×10^{-5}	1.47	2.60×10^4	27.5
	6.01×10^{-5}	1.59	2.64×10^4	28.5
	7.05×10^{-5}	1.94	2.75×10^4	29.1
	8.22×10^{-5}	2.04	2.48×10^4	26.8
3.01	4.26×10^{-5}	0.282	6.62×10^3	6.90
	1.20×10^{-4}	0.519	4.32×10^3	4.84
	2.35×10^{-4}	0.856	3.64×10^3	4.50
	3.36×10^{-4}	1.19	3.54×10^3	4.73
	4.06×10^{-4}	1.55	3.81×10^3	5.33
	4.92×10^{-4}	1.35	2.75×10^3	4.07
	6.73×10^{-4}	1.67	2.48×10^3	4.15
	8.02×10^{-4}	1.81	2.00×10^3	3.77
	9.62×10^{-4}	1.95	2.02×10^3	3.96

[a] Apparent second-order rate constants calculated by dividing first-order rate constants by the concentration of hydroxylamine free base. [b] Corrected second-order rate constants obtained by the equation: $k_2^{cor} = k_2^{app}[1 + 980(RNH_2)]$ as described in the text. This procedure accounts for the influence of accumulation of carbinolamine.

Data for 4-formyl-1-methylpyridinium oxime formation are summarized in Table IV.

2-Formyl- and 3-Formyl-1-methylpyridinium Iodide Oxime Formation. Experiments similar to those described above for 4-formyl-1-methylpyridinium ion were also carried out for the corresponding 2-formyl and 3-formyl compounds. In the case of the former compound, a plot (not shown) of first-order rate constants against the concentration of hydroxylamine at 30 °C and pH 4.02 exhibits saturation (see Figure 4, for example). The limiting first-order rate constant at high hydroxylamine concentration is ca. 0.024 min^{-1}, establishing that the saturation reflects carbinolamine accumulation and not aldehyde hydrate dehydration.

At low concentrations of hydroxylamine, satisfactory straight lines are obtained for plots of first-order rate constants against hydroxylamine concentration for 2-formyl-1-methylpyridinium ion oxime formation. Second-order rate constants were evaluated from the slope of these plots at four values of pH. Logarithms of these second-order rate constants plotted against pH yielded a good linear relationship, the slope of the line is −1.0. Values of K_2 and k_3 were calculated as described previously. These are included in Table IV.

In order to confirm that carbinolamine dehydration is rate limiting for this reaction, the tetrahedral adduct of hydroxylamine and 2-formyl-1-methylpyridinium iodide was synthesized. The rate of formation of the oxime from this adduct was measured at pH 4.03 in the presence of excess hydroxylamine. The value of k_3 obtained is 240 M^{-1} min^{-1}, in excellent agreement with the value obtained employing the carbonyl compound as substrate (see Table IV).

Table IV. Summary of Rate and Equilibrium Constants for 2-, 3-, and 4-Formyl-1-methylpyridinium Oxime Formation[a]

	Substrate		
Constant	2-Formyl	3-Formyl	4-Formyl
k_3, M^{-1} min^{-1}	247	1.05×10^4	7.0×10^3
K_2, M^{-1}	571	676	833
K_2', M^{-1}	4.4×10^4	3.4×10^3	4.3×10^4
k_f, min^{-1}			ca. 2.9

[a] Constants are defined in eq 1 and 4.

2-Formyl-1-methylpyridinium oxime formation is slightly susceptible to buffer catalysis. At pH 4.02, values of first-order rate constants for oxime formation at constant hydroxylamine concentration increase by 50% in the presence of 1.5 M acetate buffer. A satisfactory linear relationship exists between first-order rate constants and buffer concentration.

A plot of first-order rate constants for 3-formyl-1-methylpyridinium oxime formation against the concentration of hydroxylamine at pH 5.02 reveals saturation kinetics with a limiting rate constant of 0.10 min^{-1}. This finding reveals that this reaction also occurs with rate-determining carbinolamine dehydration under mildly acidic conditions.

At low hydroxylamine concentrations, plots of first-order rate constants for oxime formation against hydroxylamine concentration yielded straight lines from whose slopes second-order rate constants were calculated at several values of pH. Logarithms of these rate constants are linearly correlated with pH. Values of k_3 and K_2 were calculated as previously described and are included in Table IV.

Second-order rate constants for 3-formyl-1-methylpyridinium oxime formation were measured as a function of the concentration of formic, acetic, and β-chloropropionic acids. In each case, rate constants increase linearly with increasing buffer concentration. From the slopes of such plots, catalytic constants were calculated: formic acid, 1.01 M^{-1} min^{-1}; acetic acid, 0.26 M^{-1} min^{-1}; β-chloropropionic acid, 7.24 M^{-1} min^{-1}. These values yield an approximate Bronsted exponent of 0.75. The rate constant for catalysis by H_3O^+ falls on this line.

2-Formyl-, 3-Formyl-, and 4-Formyl-1-methylpyridinium Iodide Phenylhydrazone Formation. Data presented above establish that semicarbazone and oxime formation from formyl-1-methylpyridinium ions occurs with rate-determining carbinolamine dehydration under acidic as well as neutral conditions. In a related series of studies with phenylhydrazine as nucleophilic reagent, attention has been directed to the influence of substrate structure on reactivity and to the sensitivity of carbinolamine dehydration to general acid catalysis.

In Figure 5, logarithms of second-order rate constants for phenylhydrazone formation from 2-formyl-, 3-formyl-, and 4-formyl-1-methylpyridinium iodides are plotted as a function of pH. Measurements were carried out in 20% aqueous ethanol at 25 °C and ionic strength 0.50. Second-order rate constants were calculated by dividing first-order rate constants by the concentration of phenylhydrazine free base, calculated employing a value for pK_a of 5.2. In each case, data are correlated by straight lines having slopes of −1, strongly suggesting that carbinolamine dehydration is rate determining over the pH range studied. This conclusion is corroborated by the observation that first-order rate constants for 3-formyl-1-methylpyridinium phenylhydrazone formation at pH 7.35 increase less rapidly than amine concentration over the range 5×10^{-3} to 2.5×10^{-2} M. A similar observation was made for the 2-formyl substrate at pH 6.7 over an amine concentration range from 0.02 to 0.06 M.

Table V. Third-Order Rate Constants for General Acid Catalysis of 2-, 3-, and 4-Formyl-1-methylpyridinium Iodide Phenylhydrazone Formation in 20% Aqueous Ethanol at 25 °C and Ionic Strength 0.5[a]

	Catalyst			
Substrate	Cyanoacetic acid	Chloroacetic acid	Formic acid	Bromoacetic acid
4-Formyl	8.1×10^4	3.5×10^4	6.8×10^3	
3-Formyl	8.8×10^4	4.2×10^4	2.0×10^4	8.8×10^3
2-Formyl	8.6×10^2	3.8×10^2	1.1×10^2	

[a] Rate constants have units of M^{-2} min^{-1}.

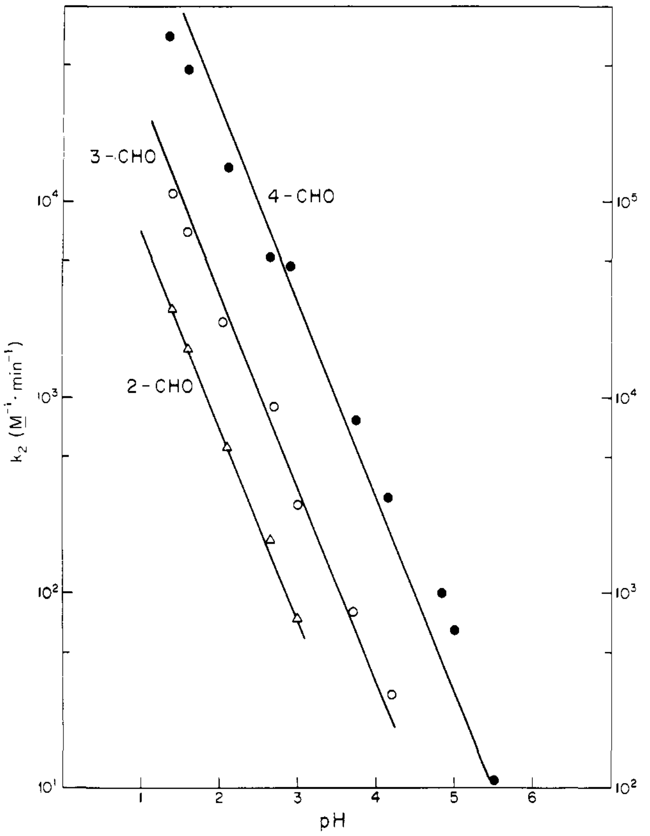


Figure 5. Second-order rate constants for phenylhydrazone formation from 2-formyl-1-methylpyridinium iodide (△), 3 formyl-1-methylpyridinium iodide (○), and 4-formyl-1-methylpyridinium iodide (●) plotted as a function of pH. The ordinate on the left pertains to the 2-formyl and 4-formyl substrates, that on the right to the 3-formyl substrate. Measurements were made at 25 °C and ionic strength 0.5 in 20% aqueous ethanol. All rate constants have been extrapolated to zero buffer concentration.

Values for the equilibrium constants for carbinolamine formation from the cationic aldehydes and phenylhydrazine have not been measured. An approximate value of 400 M^{-1} for the 4-formyl substrate can be obtained on the basis of the corresponding equilibrium constants for reactions with semicarbazide and hydroxylamine (Tables II and IV). In order to avoid significant errors in calculation of second-order rate constants due to carbinolamine accumulation, the concentration of phenylhydrazine free base was never permitted to exceed 2×10^{-4} M and was usually substantially less than this value. Under these conditions, observed first-order rate constants did not exceed 0.2 min^{-1} in any case, a value much lower than the calculated rate for dehydration of the aldehyde hydrates.

From the slopes of plots in Figure 5, values of k_3K_2 (eq 1) were calculated: 2-formyl, 7×10^4 M^{-2} min^{-1}; 3-formyl, 3.5×10^6 M^{-2} min^{-1}; 4-formyl, 3×10^6 M^{-2} min^{-1}. The last value is intermediate between those measured for semicarbazone and oxime formation from the same substrate (Tables II and IV), as expected.

Second-order rate constants for phenylhydrazine formation from the three cationic aldehydes were observed to increase linearly with increasing buffer concentration at constant pH, establishing carbinolamine dehydration for these reactions to be subject to general acid catalysis. Third-order rate constants were calculated from the slopes of plots of second-order rate constants against that concentration of the acidic form of the buffer for several carboxylic acids. Results are collected in Table V. Bronsted plots of third-order rate constants for general acid catalyzed carbinolamine dehydration against pK_a of the catalyst yielded satisfactory straight lines from which the following values of α were calculated: 2-formyl, 0.7; 3-formyl, 0.65; 4-formyl, 0.8.

Discussion

The addition of amines to, for example, benzaldehydes is known to occur through formation of a tetrahedral carbinolamine intermediate (eq 1).[16,21] Ordinarily, dehydration of the carbinolamine is the rate-determining step under basic and neutral conditions and addition of the amine is rate determining under acidic conditions.[22] The transition in rate-determining step frequently occurs in the pH range 4–6. These generalizations do not hold true for oxime, semicarbazone, and phenylhydrazone formation for 2-, 3-, and 4-formyl-1-methylpyridinium ions. The following lines of evidence provide convincing evidence that, for these reactions, carbinolamine dehydration is rate determining down to a pH of 1 at least, the limiting pH employed in these investigations. First, plots of first-order rate constants against amine concentration under acidic conditions are nonlinear. This nonlinearity can be accounted for in terms of carbinolamine accumulation or, in some cases, as a combination of carbinolamine accumulation and rate of substrate dehydration. Equilibrium constants for carbinolamine formation calculated from kinetic measurements are in reasonable agreement with estimates based on literature data or related reactions.

Second, rate constants for conversion of tetrahedral adducts of substrate and amines to imines, in the presence of excess amine, are equal to those observed for the conversion of substrate to imine. This requires that carbinolamine dehydration be rate determining. Were this not so, product formation from the tetrahedral adduct would have been faster than product formation from the substrate.

Third, imine formation from the addition of these weakly basic amines to the substrates occurs exclusively with acid catalysis. Experience with the same amines and benzaldehyde reveals that the attack of weakly basic amines on the carbonyl group ordinarily involves pH independent as well as acid-catalyzed reactions. Carbinolamine dehydration, in contrast, shows little or no tendency to occur in the absence of acid catalysis.

Fourth, pH-rate plots for addition of semicarbazide, hydroxylamine, and phenylhydrazine to the pyridine aldehyde substrates do not reveal the break characteristic of a change in rate-determining step.[16,21]

Fifth, formyl-1-methylpyridinium ion semicarbazone and oxime formation exhibit the features of general acid catalysis ordinarily associated with carbinolamine dehydration, not amine attack. For example, semicarbazone formation from 4-formyl-1-methylpyridinium ion is only weakly susceptible to general acid catalysis although attack of semicarbazide on benzaldehydes and certain other substrates is quite susceptible to such catalysis.[16,20,23] Moreover, values of the Bronsted exponent for formyl-1-methylpyridinium ion phenylhydrazone formation are large, in the range 0.7–0.8. Such values are typical of general acid catalysis for carbinolamine dehydration but are larger than values usually observed for amine attack.[16,23,24]

In sum, these lines of evidence provide a convincing case for rate-determining carbinolamine dehydration across the entire pH range investigated (a change in rate-determining step at lower values of pH is not excluded, however). This conclusion is in accord with expectations. It has been previously pointed out by Sayer et al. that increasing reactivity of the aldehyde should cause the pH at which a transition in rate-determining step occurs to diminish.[17] The principal distinction between the reactions probed in this investigation and those considered heretofore is the cationic center on the aldehyde substrates. The positive charge is expected to strongly destabilize the carbonyl function relative to the carbinolamine; the high degree of hydration of these substrates in water[3-6] bears out this expectation. Consequently, one expects facilitation of the addition of amine to carbonyl carbon. On the other hand, the possession of the positive charge may not increase the rate of carbinolamine dehydration: the increased equilibrium constant for formation of carbinolamine may be offset or overridden by the effect of the cationic center on the rate of expulsion of water. Such expulsion requires protonation of the leaving water molecule, and this requires formation of a dicationic species. Overall, the formation of a cationic site on the substrates should increase the rate of amine attack relative to carbinolamine dehydration; this has the effect of pushing the transition in rate-determining step to lower pH values. In the present cases, the pH at which the transition occurs must be below pH 1.

Under conditions of rate-determining carbinolamine dehydration, the overall rate constant for carbonyl addition reactions is given by the product of the equilibrium constant for carbinolamine formation and the rate constant for carbinolamine dehydration, k_3K_2. In Table VI, values of k_3K_2 measured in this investigation are collected. As expected, for a given substrate, reactivity decreases in the order hydroxylamine > phenylhydrazine > semicarbazide. Note, however, that the differences in reactivity are small. For both oxime and phenylhydrazone formation, the 3-formyl and 4-formyl substrates are about equally reactive, within the limits of sensible comparison, and are more reactive than the 2-formyl compound. This difference largely reflects the small rate constants for the dehydration step for the last species, a probable consequence of the proximity of the cationic charge to the site of protonation in the dehydration step.

Table VI. Values of k_3K_2 for 2-, 3-, and 4-Formyl-1-methylpyridinium Ion Oxime, Semicarbazone, and Phenylhydrazone Formation[a]

	Substrate		
Nucleophile	2-Formyl	3-Formyl	4-Formyl
Semicarbazide			2.4×10^5
Phenylhydrazine	7.0×10^4	3.5×10^6	3.0×10^6
Hydroxylamine	1.4×10^5	7.1×10^6	5.5×10^6

[a] Values of k_3K_2 have units of M^{-2} min^{-1}. Values for semicarbazone and oxime formation were measured in water at 30 °C; those for phenylhydrazone formation were measured in 20% aqueous ethanol at 25 °C.

Values of K_2 provide direct measurements of equilibrium constants for addition of nucleophiles to the *unhydrated* aldehydes. Comparison of such equilibrium constants as a function of substrate structure are possible only for addition of hydroxylamine. Data collected in Table IV indicate that the 2-formyl and 4-formyl substrates have about equal affinity for hydroxylamine and that the 3-formyl compound has an affinity about tenfold less. These findings are in excellent agreement with extents and rates of hydration of the corresponding protonated pyridine aldehydes.[3,25] Note that the relative independence of values of K_2 for addition of hydroxylamine simple reflects the fact that equilibrium constants for addition of water and addition of hydroxylamine vary in the same way with substrate structure.

References and Notes

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