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Kinetics and Mechanism for Oxime Formation from Pyridine-2-, -3-, and -4-carboxaldehydes[1]

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Oxime formation from pyridine-2-, -3-, and -4-carboxaldehydes occurs with rate-limiting carbinolamine dehydration under both acidic and neutral conditions. Carbinolamine dehydration of pyridine-2-carboxaldehyde occurs *via* a transition state bearing a single positive charge, unlike the corresponding reaction for formyl-1-methylpyridinium ion and the reaction under acidic conditions for pyridine-3- and -4-carboxaldehydes.

Although certain equilibrium constants[2,3] and rate constants[3] for addition of amines to pyridinecarboxaldehydes and to structurally related aldehydes including pyridoxal phosphate[4–6] have been determined, much remains to be revealed about the mechanism of addition of nitrogen nucleophiles to pyridine aldehydes in general.

Understanding the kinetics for nucleophilic addition reactions of pyridine aldehydes is complicated by two factors: (i) protonic equilibria of the substrates and (ii) pH-dependent substrate hydration. This series of investigations was initiated with examination of the addition of semicarbazide, hydroxylamine, and phenylhydrazine to *N*-methylpyridinium aldehydes, substrates for which the first factor does not enter and for which the second is less troublesome since the extent of substrate hydration becomes almost independent of pH.[7] We have elected to continue this work with an investigation of the addition of hydroxylamine to pyridine-2-, -3-, and -4-carboxaldehydes, consistent with the goal of understanding the mechanism and catalysis for imine formation from pyridine aldehydes.

Experimental Section

Pyridine-2-, -3-, and -4-carboxaldehydes were obtained commercially and were redistilled. Hydroxylamine hydrochloride was recrystallized from ethanol. Solutions of these reagents were prepared just prior to use to minimize the possibility of decomposition. Distilled water was employed throughout.

All kinetic measurements were carried out spectrophotometrically at 30 °C as previously described.[7] Ionic strength was maintained at 0.5 throughout by the use of potassium chloride. pH was maintained constant through use of dilute carboxylic acid buffers. Values of pH were measured with Radiometer potentiometer Model 26. 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 and Discussion

Previous investigations in this laboratory have revealed that semicarbazone, oxime, and phenylhydrazone formation from 2-, 3-, and 4-formyl-1-methylpyridinium ions occurs with rate-determining carbinolamine dehydration under acidic, neutral, and basic conditions.[7]

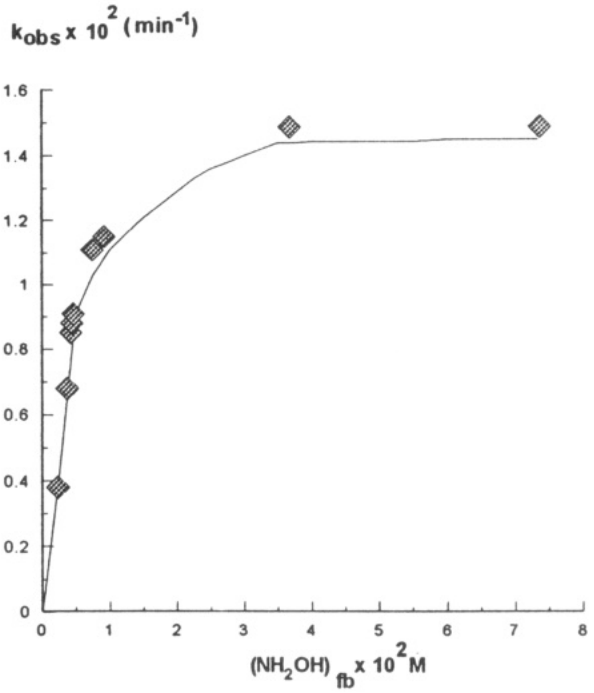

Figure 1. First-order constants for pyridine-2-carboxaldehyde oxime formation plotted as a function of hydroxylamine free base concentration. The rate constants were measured at 30 °C and ionic strength 0.50, pH 7.04.

Since pyridine-2-, -3-, and -4-carboxaldehydes are protonated under acidic conditions, pK_{app} = 3.80, 3.80, and 4.77,[8] respectively, and hence should be closely related in reactivity to the respective 2-, 3-, and 4-formyl-1-methylpyridinium ions, it is reasonable to anticipate that the corresponding reactions for these substrates will occur with the same rate-determining step.

Carbinolamine dehydration is normally rate-determining under neutral and basic conditions.[9] Data presented below establish that this expectation is fulfilled.

First-order rate constants for pyridine-2-, -3-, and -4-carboxaldehyde oxime formation were measured as a function of amine concentration at several values of pH

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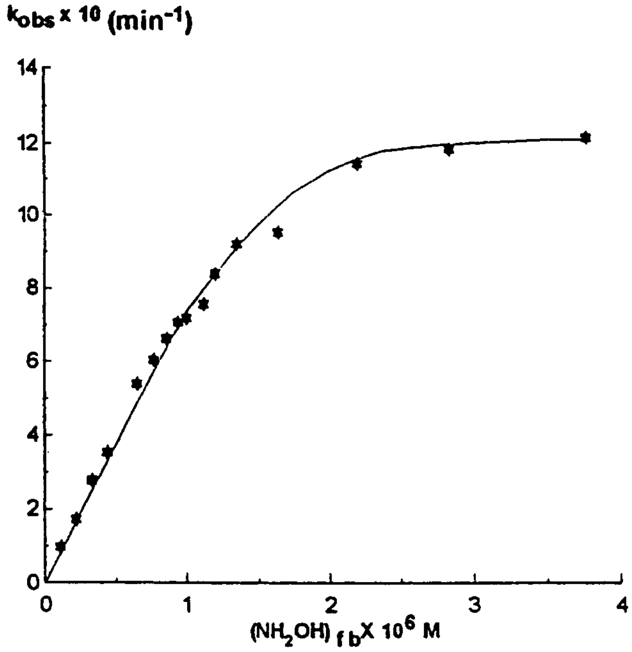


Figure 2. First-order constants for pyridine-3-carboxaldehyde oxime formation plotted as a function of hydroxylamine free base concentration. The rate constants were measured at 30 °C and ionic strength 0.50, pH 1.00.

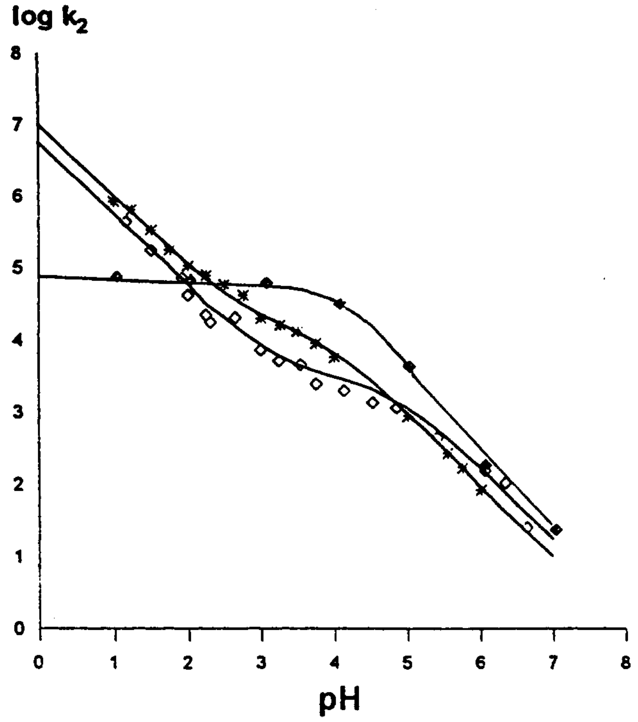
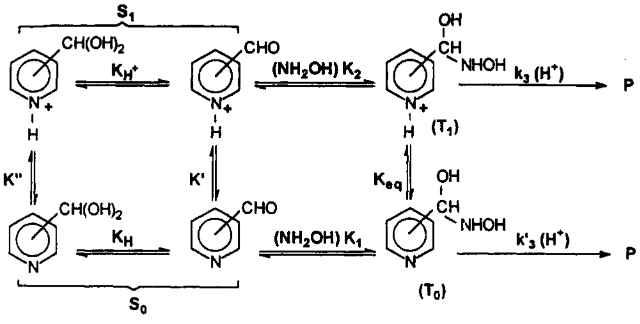


Figure 3. Logarithms of second-order rate constants for pyridine-2-carboxaldehyde (♦), pyridine-3-carboxaldehyde (✱), and pyridine-4-carboxaldehyde (◇) oxime formation plotted as a function of pH.

Scheme 1



$$K_1 = \frac{(T_0)}{(S_0)(NH_2OH)} \qquad K_{eq.} = \frac{(T_0)(H^+)}{(T_1)}$$

$$K_2 = \frac{(T_1)}{(S_1)(NH_2OH)} \qquad K_{app.} = \frac{(S_0)(H^+)}{(S_1)}$$

in the range 1–7 at 30 °C and ionic strength 0.5. At low concentration of amine free base, first-order rate constants increase linearly with increasing amine concentrations. At sufficiently high amine concentrations, the rate constants level off and eventually become independent of this variable. Typical examples of this behavior are provided in Figures 1 and 2.

Second-order rate constants for pyridine-2-, -3-, and -4-carboxaldehyde oxime formation at several values of pH were calculated from slopes of plots of first-order rate constants against the concentration of amine free base over the concentration range for which the reactions were first-order in amine concentration. The logarithms of the second-order rate constants so obtained are plotted against pH in Figure 3.

The data in Figure 3 have been interpreted in terms of the mechanism outlined in Scheme 1, in which carbinolamine dehydration is considered to be the sole rate-determining step. Carbinolamine dehydration of pyridine-3- and -4-carboxaldehydes occurs *via* $(T_1)(H^+)k_3$ and $(T_0)(H^+)k'_3$, but there is no term in the rate law corresponding to an acid-catalized breakdown of the cationic carbinolamine, T_1, for pyridine-2-carboxaldehyde.

The rate law for the mechanism of addition of hydroxylamine to pyridine-3- and -4-carboxaldehydes indicated in Scheme 1 is

$$k_2 = \frac{K_{app}K_1k'_3(H^+) + K_2k_3(H^+)^2}{K_{app} + (H^+) + K_2(NH_2OH)(H^+) + K_{app}K_1(NH_2OH)} \tag{1}$$

At low amine concentrations where the reaction is first-order in amine, this simplifies to

$$k_2 = \frac{K_{app}K_1k'_3(H^+) + K_2k_3(H^+)^2}{K_{app} + (H^+)} \tag{2}$$

Consequently, the second-order rate constant at low pH is given by $K_{app}K_1k'_3 + K_2k_3(H^+)$ and two pH units below the pK_{app} of the substrates the contribution of the first term becomes almost null, so the antilogarithms of the ordinal intercepts of the lines in the acidic zone, in Figure 3, give the values of K_2k_3. The limiting value of k_2, at high values of pH and low amine concentration, is $k_2 = K_1k'_3(H^+)$, and in Figure 3, the antilogarithms of the intercepts at pH 0 of the straight lines of slope −1 in the neutral zone give $k_2 = K_1k'_3$.

A simpler rate law operates with pyridine-2-carboxaldehyde:

$$k_2 = \frac{K_1k'_3K_{app}(H^+)}{K_{app} + (H^+) + K_2(NH_2OH)(H^+) + K_{app}K_1(NH_2OH)} \tag{3}$$

At low amine concentrations, where the reaction is first

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

	substrate		
	2-PyCHO	3-PyCHO	4-PyCHO
K_1 (M^{-1})	220	96	469
K_2 (M^{-1})	650	852	760
K'_1 (M^{-1})	330	106	1184
K'_2 (M^{-1})	5×10^4	5.2×10^3	4×10^4
k_3 (M^{-1} min^{-1})		1.29×10^4	7.4×10^3
k'_3 (M^{-1} min^{-1})	1.6×10^6	7.5×10^7	3.6×10^5

[a] All constants are defined in the text.

Table 2. Rate Constants for Pyridine-2-carboxaldehyde Oxime Formation in Aqueous Solution at 30 °C, pH 7.04 and Ionic Strength 0.5

$(NH_2OH)_{fb} \times 10^2$ (M)	k_{obs} (min^{-1})	k_2^{app} [a] (M^{-1} min^{-1})	k_2^{cor} [b] (M^{-1} min^{-1})
0.42	0.85	202	402
0.44	0.88	200	394
0.46	0.91	198	398
0.74	1.11	150	394
0.92	1.15	125	378

[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 $k_2^{cor} = k_2^{app}[1 + 220(NH_2OH)_{fb}]$ as described in the text.

order in amine, this simplifies to

$$k_2 = \frac{K_1 k'_3 K_{app}(H^+)}{K_{app} + (H^+)} \tag{4}$$

and the limiting second-order constant at low pH is $k_2 = K_{app}K_1k'_3$. Note that the reaction under these conditions becomes independent of pH. At low amine concentration and high pH, $k_2 = K_1k'_3(H^+)$, and in Figure 3, the antilogarithm of the intercept at pH 0 of the straight line of slope −1, obtained in the neutral zone, gives the value of $K_1k'_3$.

Independent values of k'_3 were obtained directly from plots of k_{obs} vs $(NH_2OH)_{fb}$, under conditions in which the reactions are independent of amine concentration, at high pH and high hydroxylamine concentration. In these cases the limiting values of observed rate constants are $k'_3(H^+)$ (Figure 1).

This procedure cannot be used to evaluate k_3 because high proton concentrations do not permit carbinolamine accumulation. Therefore, it was necessary to calculate values of K_2. In order to do this, we have assumed that $K_{eq} = K_1K_{app}/K_2$ is equal to K'', the dissociation constant for the conjugate acid of the aldehyde hydrate. Since the aldehyde hydrate and the carbinolamine are closely related structurally, this assumption appears quite reasonable. K'' can be calculated from data present in the work of Cabani *et al.*:[10] 5.34×10^{-5}, 1.78×10^{-5}, and 1.78×10^{-5} M for pyridine-2-, -3-, and -4-carboxaldehydes, respectively. Using this piece of information and the data contained in Figures 1 and 3, values for k_3, k'_3, K_2, and K_1 have been calculated and are collected in Table 1.

In addition, it is possible to calculate equilibrium constants for addition of hydroxylamine to the aldehyde forms of the substrates, specifically

$$K'_2 = (T_1)/(AldH^+)(RNH_2) = K_2(1 + K_{H^+}) \tag{5}$$

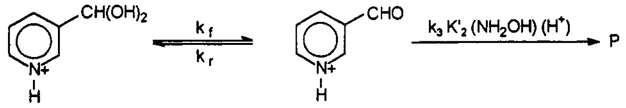
$$K'_1 = (T_0)/(Ald)(RHN_2) = K_1(1 + K_H) \tag{6}$$

since values of $K_{H^+} = (HydrH^+)/(AldH^+)$ and $K_H = (Hydr)/(Ald)$ are known.[10] The values of K'_2 and K'_1 are also included in Table 1.

The solid lines in Figure 3 are calculated based on the rate law of eqs 2 and 4 and the constants in Table 1. The agreement of theory with experimental data result is satisfying.

The saturation effects observed at pH near 6 are strongly suggestive of carbinolamine accumulation, requiring that dehydration of this species be the rate-determining step. This behavior cannot reflect a transition to rate-determining dehydration of the aldehyde hydrates since (i) the substrates are not predominantly hydrated above pH 4[10,11] and (ii) the rate constants for hydrate dehydration are greater than the limiting values observed. For example, at pH 7.00 the first-order rate constant for dehydration of pyridine-2-carboxaldehyde is near 2 min^{-1}.[10] In addition, with reasonably reliable values for the equilibrium constants for carbinolamine formation (K_1 and 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: $k_{corr} = [1 + K_1(RNH_2)]k_{app}$. The corrected values have been included in Table 2. Note that values of corrected second-order rate constants at high values of pH and high concentration of hydroxylamine are constant.

This type of correction does not work with the apparent second-order constants at low pH, indicating that the rate of aldehyde dehydration must influence the overall rate. In order to account for this influence, we can write the reaction as



with the corresponding rate law, assuming that low concentrations of amine are employed:

$$dP/dt = K'_2k_3(RNH_2)(H^+)(>\!\!=\!O)$$

Note specifically that this law is written in terms of K'_2 (equilibrium constant for addition of hydroxylamine to the aldehyde forms of the substrates). The concentration of free aldehyde can be approximated assuming the steady-state approximation: $(>\!\!=\!O) = k_fS_t/[k_r + k_3K'_2(RNH_2)(H^+)]$ 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

$$k_{obs} = \frac{K'_2k_3k_f(RNH_2)(H^+)}{k_r + K'_2k_3(RNH_2)(H^+)}$$

or, in double reciprocal form,

$$\frac{1}{k_{obs}} = \frac{k_r}{k_fk_3K'_2(H^+)(RNH_2)} + \frac{1}{k_f}$$

The reciprocal values of first-order rate constants for pyridine-3-carboxaldehyde oxime formation, at pH 1.00, in the zone where the dependence with the hydroxylamine

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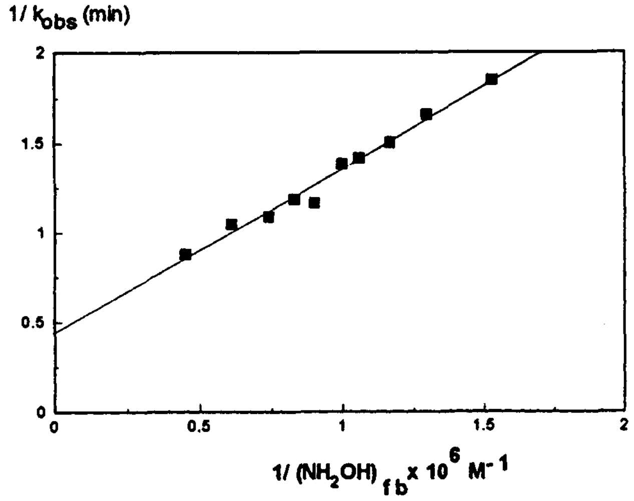

Figure 4. Reciprocal values of first-order rate constants for pyridine-3-carboxaldehyde oxime formation, at pH 1.00, plotted against the reciprocal of amine concentration.

concentration is complex (Figure 2) were plotted against the reciprocal of the amine concentration (Figure 4). A satisfactory straight line is obtained from which a value k_f of 2.3 min^{-1} is calculated from the ordinal 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-3-carboxaldehyde hydrate at the same pH, 9.58 min^{-1}.[10] Due to the small value of the intercept, our value for k_f may be in error by a factor of ~4. The slope of the straight line obtained is equal to $k_r/k_f k_3 K'_2(\mathrm{H}^+)$. An evaluation of $k_r/k_f = K_{\mathrm{H}^+}$, based on the values of K'_2 and k_3 for pyridine-3-carboxaldehyde oxime formation (Table 1) and the measured pH, gives a value for $K_{\mathrm{H}^+} = 6.04$, in satisfactory agreement with the hydration of equilibrium constant for the protonated species ($K_{\mathrm{H}^+} = 5.1$).[10]

The values of K_2 for the addition of hydroxylamine to 2-, 3-, and 4-formyl-1-methylpyridinium ions are 571, 676, and 833 M^{-1}, respectively,[7] close to the values of 650, 852, and 760 M^{-1} measured here for the same reaction with the conjugate acids of pyridine-2-, -3-, and -4-carboxaldehydes, respectively. Thus, the methyl group apparently serves as a reasonable model for a proton in terms of the reactivity of pyridine aldehydes toward nucleophilic reagents.

The greatest difference in the behavior of the conjugate acid of the pyridine-2-carboxaldehyde and both 2-formyl-1-methylpyridinium ion and the conjugate acids of pyridine-3- and -4-carboxaldehydes is that the transition state for dehydration of carbinolamine of the former substrate possesses a single positive charge while the last ones have two. Although pyridine-2-carboxaldehyde is indeed predominantly protonated in acid, it does have a reaction pathway (through the neutral molecule) which is unavailable to the N-methylated derivative and that avoids the proximity of the positive charges. Comparison of $k'_3 = 1.6 \times 10^6$ M^{-1} min^{-1} (pyridine-2-carboxaldehyde) with the values of the same constant of pyridine-3- and -4-carboxaldehydes, 7.5×10^7 and 3.6×10^5 M^{-1} min^{-1}, respectively, suggests the same route of dehydration of neutral carbinolamines.

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