Kinetics and Mechanism for Pyridine N-Oxide Carboxaldehyde Phenylhydrazone Formation[1]

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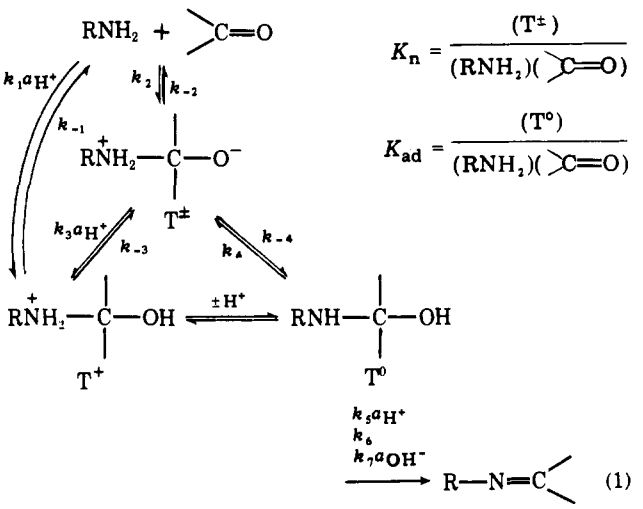
Abstract: Phenylhydrazone formation from the three isomeric pyridine *N*-oxide carboxaldehydes occurs with two breaks in the pH-rate profiles. Under alkaline conditions, nonlinearity between first-order rate constants and amine concentration established that carbinolamine dehydration is rate determining. Under more acidic conditions, structure-reactivity correlations and susceptibility to general acid catalysis, as well as the break in the pH-rate profile, strongly suggest that stepwise formation of carbinolamine becomes the rate-determining step. Finally, the second break in the pH profile is interpreted as reflecting a transition to rate-determining concerted formation of the carbinolamine.

The addition of nitrogen nucleophilic reagents to carbonyl compounds occurs in two general stages: formation of a carbinolamine addition intermediate and subsequent carbinolamine dehydration to yield the imine product.[2,3] Carbinolamine formation occurs by at least three separate routes:[4-6]



concerted addition of amine and protonation of the carbonyl oxygen atom ($k_1a_{H^+}$), a stepwise route involving trapping by proton transfer of a dipolar compound formed by addition of amine to the carbonyl group (k_2 followed by $k_3K_na_{H^+}$ or k_4K_n), and a "spectator" mechanism involving preassociation of acid catalyst with carbonyl oxygen.[7] Carbinolamine dehydration may be simpler but occurs via acid-catalyzed, pH-independent, and base-catalyzed pathways ($k_5a_{H^+}$, k_6, $k_7a_{OH^-}$).

The addition of amines to carbonyl compounds frequently occurs with one or two changes in the rate-determining step as a function of pH.[2-6] Carbinolamine dehydration is usually rate determining at neutral and basic values of pH but becomes more rapid than carbinolamine formation under acidic conditions. A second change in the rate-determining step, from the stepwise route (k_2) to the concerted route (k_1,a_{H^+}) for carbinolamine formation, is sometimes observed under more acidic conditions.[4,5] Changes in the rate-determining step are manifested by breaks in pH-rate profiles, changes in structure–reactivity correlations, nonlinear plots of rate constants against catalyst concentration, and variation of the Brønsted exponent for general acid catalysis.[4-6]

We have begun to explore the kinetics and mechanism for addition of amines to a particular set of carbonyl substrates, pyridine aldehydes and their derivatives, in some detail. An earlier investigation examined the addition of hydroxylamine, phenylhydrazine, and semicarbazide to the three isomeric formyl-1-methylpyridinium ions.[8] It was established that, contrary to most other cases, carbinolamine dehydration is rate determining over the entire pH range from 1 to 11, reflecting the increased reactivity for nucleophile addition resulting from the electron-withdrawing power of the cationic nitrogen function. In continuation of this work, we have now explored the kinetics for addition of phenylhydrazine to 2-, 3-, and 4-pyridine *N*-oxide carboxaldehydes. The *N*-oxides possess a less potent electron-withdrawing ring nitrogen atom and this should be reflected in the kinetics and mechanism for amine addition. Like that for the *N*-methyl compounds, the behavior of the *N*-oxides is not complicated by the possibility of protonation on the heterocyclic ring under the conditions of the experimental measurements. In addition to their intrinsic interest, these studies provide the necessary background for understanding the kinetics of addition of amines to the parent pyridine aldehydes, a case complicated by the protonation of the ring nitrogen. This will be the subject of a future communication.

Experimental Section

Materials. 4-Pyridinecarboxaldehyde *N*-oxide (I), 3-pyridinecarboxaldehyde *N*-oxide (II), and 2-pyridinecarboxaldehyde *N*-oxide (III) were prepared by the following sequence of reactions: the appropriate pyridine carboxaldehydes were transformed to the corresponding diethyl acetals according to the procedure of Felder and Pitre;[9] the acetals were oxidized to the corresponding *N*-oxides as described by Craig and Purushothaman;[10] pyridine *N*-oxide acetals were hydrolyzed to liberate the pyridine *N*-oxide carboxaldehydes. Compound, mp: I, 150-151 °C (lit.[11] 151-152 °C); II, 139 °C (lit.[11] 138 °C); III, 91-92 °C (lit.[11] 92 °C). All other reagents employed were obtained commercially and, with the exception of reagent grade inorganic salts, were either redistilled or recrystallized prior to use. Solutions of phenylhydrazine were prepared just prior to use, as were those of carboxylic acids in 20% ethanol, to avoid esterification.

Kinetic measurements[12-14] were carried out spectrophotometrically at 25 °C with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder. The reaction of phenylhydrazine with the aldehydes was followed by observing the appearance of product at the following wavelengths: I, 393 nm; II, 365 nm; III, 376 nm. The initial concentration of aldehydes was 3.3×10^{-5} M. In all cases, a sufficient excess of nucleophilic reagent was employed so that pseudo-first-order rate behavior was observed. First-order rate constants were evaluated from slopes of plots of log ($OD_\infty - OD_t$) against time in the usual manner. Second-order rate constants were obtained by dividing the first-order rate constants by the concentration of nucleophilic reagent in the reactive, free-base form. In the region in which carbinolamine formation is principally rate determining, rate constants have been corrected for the influence of the rate of carbinolamine dehydration as described by Sayer and Jencks.[15] Catalytic (third order) rate constants were evaluated from the slope of plots of second-order rate constants against the concentration of the catalyst.

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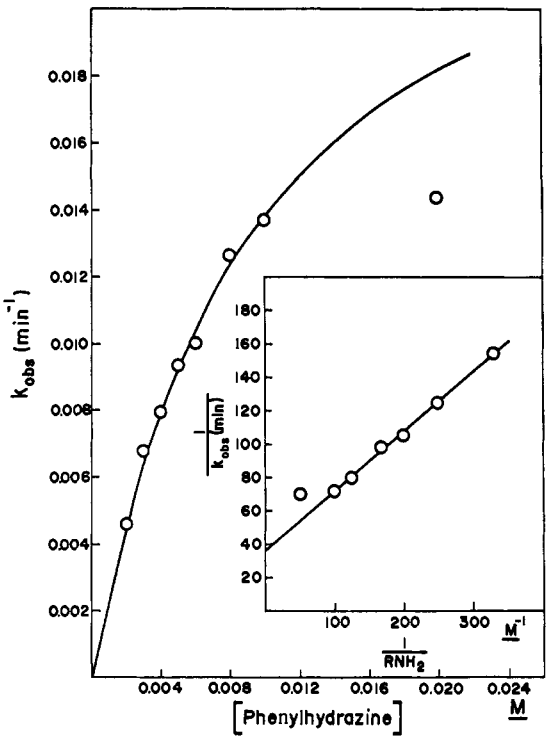


Figure 1. First-order rate constants for 2-pyridinecarboxaldehyde *N*-oxide phenylhydrazone formation at pH 10.4 plotted against the concentration of phenylhydrazine. The solid line is a theoretical one calculated using values of K_{ad} (105 M^{-1}) and the first-order rate constant (0.027 min^{-1}) for carbinolamine dehydration derived from the double reciprocal plot of this data as shown in the insert as described in the text.

All kinetic experiments were carried out at 25.0 ± 0.1 °C in 20% aqueous ethanol at an ionic strength of 0.50 maintained with KCl unless otherwise indicated, in the presence of 2.0×10^{-4} M EDTA. Values of apparent pH were recorded with a Radiometer Model PHM 4d pH meter equipped with a glass electrode. Calculations of the concentration of phenylhydrazine free base and undissociated carboxylic acids were made employing the Henderson-Hasselbalch equation, and values of pK_a determined earlier.[16]

Results

Since light absorption by phenylhydrazine makes direct determination of the equilibrium constants for carbinolamine formation, K_{ad}, from phenylhydrazine and pyridine *N*-oxide carboxaldehydes very difficult, these constants were evaluated from the dependence of first-order rate constants on phenylhydrazine concentration under conditions in which carbinolamine dehydration is expected to be rate determining. A typical example is shown for the case of 2-pyridinecarboxaldehyde *N*-oxide phenylhydrazone formation at pH 10.4, 0.04 M carbonate buffer, in Figure 1. Note that the rate constants increase less rapidly than the phenyhydrazine concentration, consistent with accumulation of carbinolamine. Under the conditions of this experiment, the rate law for phenylhydrazone formation has the form

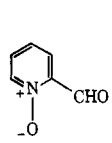
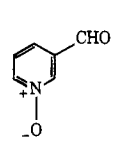
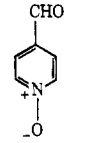
$$k_{obsd} = k_5^{app}K_{ad}(RNH_2)/(1 + K_{ad}(RNH_2)) \quad (2)$$

in which $k_5^{app} = k_5a_{H^+} + k_6 + k_7(OH^-)$. In double reciprocal form, eq 2 may be written

$$1/k_{obsd} = 1/k_5^{app} + (1/(RNH_2))(1/k_5^{app}K_{ad}) \quad (3)$$

A plot of $1/k_{obsd}$ against $1/(RNH_2)$ yields $1/k_5^{app}$ as the intercept and $1/k_{ad}k_5^{app}$ as the slope. Such a plot is shown in the insert in Figure 1. From this plot, values of K_{ad} of 105 M^{-1} and of k_5^{app} of 0.027 min^{-1} were calculated. The solid line in Figure 1 is a theoretical one calculated using these values. It gives good agreement with experimental data except for the point at the highest phenylhydrazine concentration. Values for K_{ad} for the 3- and 4-aldehydes were evaluated in the same manner from the data collected in Table I (supplementary material). The results are summarized in Table II. Note that equilibrium constants for carbinolamine formation are quite insensitive to the position of substitution of the pyridine ring with the aldehyde function.

Table II. Rate and Equilibrium Constants for Phenylhydrazone Formation from Three Pyridine *N*-Oxide Carboxaldehydes in 20% Aqueous Ethanol at 25 °C and Ionic Strength 0.50[a]

			
k_1, M^{-2} min^{-1}	7×10^5	7×10^5	5×10^5
k_2, M^{-1} min^{-1}	6×10^5	2.5×10^5	3×10^5
k_3K_n, M^{-1} min^{-1}	1.7×10^7	5.0×10^6	4.2×10^6
k_{-3}, M^{-1} min^{-1}	1.6×10^5	4.5×10^4	4.5×10^4
k_4K_n, M^{-1} min^{-1}	200	200	100
k_{-4}, min^{-1}	1.9	1.8	1.06
k_5, M^{-1} min^{-1}	5.0×10^5	5.4×10^5	6.6×10^5
k_5K_{ad}, M^{-2} min^{-1}	5.2×10^7	6.0×10^7	6.2×10^7
k_6, min^{-1}	0.027	0.073	0.085
k_7, M^{-1} min^{-1}	3.0		
K_{ad}, M^{-1}	105	112	94

[a] Rate and equilibrium constants are defined in eq 1.

Under acidic conditions, the rate of phenylhydrazone formation from the three pyridine *N*-oxide aldehydes was observed to be linear in phenylhydrazine concentration. Although this observation validates the treatment of the kinetic data employed, it does not distinguish between rate-determining carbinolamine formation and dehydration under acidic conditions since the concentrations of phenylhydrazine free base employed were not sufficiently great so as to have elicited carbinolamine accumulation.

In Figure 2 are provided pH–rate profiles for phenylhydrazone formation for all three isomeric pyridine *N*-oxide carboxaldehydes. Where necessary, rate constants have been corrected for carbinolamine accumulation employing the values of K_{ad} derived as described above. However, phenylhydrazine free base concentration was always maintained at 0.005 M or below so that such corrections did not amount to more than 40% in any case and were usually much smaller than this and were frequently negligible. In addition, rate constants were measured as a function of buffer concentration and extrapolated to zero buffer concentration. Note that the pH–rate profiles for all three substrates show the break in the pH range 4–6 characteristic of a transition from rate-determining carbinolamine formation at more acidic values of pH to carbinolamine dehydration at more basic values. In addition, all three compounds show a substantial rate of uncatalyzed carbinolamine dehydration which becomes important near pH 8. Dehydration of the carbinolamine derived from the 2 isomer also shows a modest base-catalyzed reaction.

All three pH–rate profiles for phenylhydrazone formation from the pyridine *N*-oxide aldehydes also exhibit a second break under more acidic conditions. The second break presumably reflects a transition from acid-catalyzed stepwise formation of carbinolamine, $k_3K_na_H$, under conditions more basic than pH 1–2, to uncatalyzed addition of amine, k_2, between about pH 0 and 1 and, finally, to the concerted addition mechanism, k_1a_H, under even more acidic conditions.[4,5] The only evident alternative explanation is the possibility of protonation of a significant fraction of the substrates at the *N*-oxide function. This possibility appears remote: the pK_a for the conjugate acid of pyridine *N*-oxide is 0.79.[17] The electron-

withdrawing aldehyde function will surely decrease this value considerably. For example, values of pK_a for the conjugate acids of 3-carboxy- and 4-carboxypyridine *N*-oxides are 0.09 and −0.48 respectively.[17] Since the aldehyde function is a stronger electron-withdrawing group that the carboxyl one, it follows that the basicities of the pyridine *N*-oxides must be quite low. Since the second break in the pH–rate profile becomes evident at pH 1, substrate protonation does not appear to be a viable explanation for this observation.

Since the amount of kinetic data collected at low values of pH is limited, the values for k_1 and k_2 indicated in Table II are to be considered as estimates only.

Steady-state treatment of the scheme shown in eq 1 yields the following rate law for product formation in the region of rate-determining carbinolamine formation:[5]

$$k^0_{ad} = k_1 a_{H^+} + \frac{k_2(k_3 K_n a_{H^+} + k_4 K_n)}{k_3 K_n a_{H^+} + k_4 K_n + k_2} \quad (4)$$

The rate law for rate-determining carbinolamine dehydration is

$$k^0_{deh} = K_{ad}(k_5 a_{H^+} + k_6 + k_7 a_{OH^-}) \quad (5)$$

The solid lines shown in Figure 2 have been calculated employing the rate laws in eq 4 and 5 together with the rate constants collected in Table II. The fit of experimental points to the theoretical lines is acceptable in all three cases.

Under conditions in which carbinolamine formation is the rate-determining step, second-order rate constants, k_{ad}, for phenylhydrazone formation from the 3- and 4-pyridine *N*-oxide aldehydes were observed to increase with increasing concentrations of carboxylic acid/carboxylate buffers. Plots of k_{ad} against buffer concentrations were usually linear up to a buffer concentration near 0.125 M; at higher concentrations the rate constants increased less rapidly than expected on the basis of data collected at lower concentrations. This behavior presumably reflects increasing contribution of k_1, which is insensitive to buffer catalysis, to the rate of the overall reaction.[4,13]

The slopes of linear regions of plots of second-order rate constants against the concentration of carboxylic acid decreased with increasing pH; similar behavior was noted for slopes of plots of rate constants against the concentration of carboxylate ions. This behavior, which has been noted for addition of phenylhydrazine to carbonyl groups earlier,[18] suggests that the reaction is subject to catalysis by carboxylic acids and inhibition by carboxylate ions. The qualitative character of the data is not altered by (1) correction for the contribution of the rate of carbinolamine dehydration to the overall rate; (2) moderate adjustments of values of pK_a for either the conjugate acid of phenylhydrazine or carboxylic acids in either direction; or (3) replacement of KCl as supporting electrolyte by KNO_3 or $NaClO_4$. We do not have a satisfactory explanation for the apparent inhibition by carboxylate ions. Uncertainties introduced by this behavior make calculation of Brønsted coefficients for the general-acid-catalyzed reaction unreliable.

In contrast to the behavior of the 3- and 4-carboxaldehydes, buffer catalysis for phenylhydrazone formation from the 2 isomer in the region of rate-determining carbinolamine formation could not be reliably established. This may reflect in part the fact that the rate for carbinolamine dehydration for this substrate is only four times more rapid than that for carbinolamine formation; the corresponding rate ratios for the 3 and 4 isomers are near 20. For all three substrates, carbinolamine dehydration was observed to be subject to modest buffer catalysts, as is typical for these reactions.[8] The rate constant for phenylhydrazone formation from the 2-aldehyde increases from 5.5 to 7.1 M^{-1} min^{-1} when the concentration of phosphate buffer is increased from 0.01 to 0.04 M at pH 7. Simi-

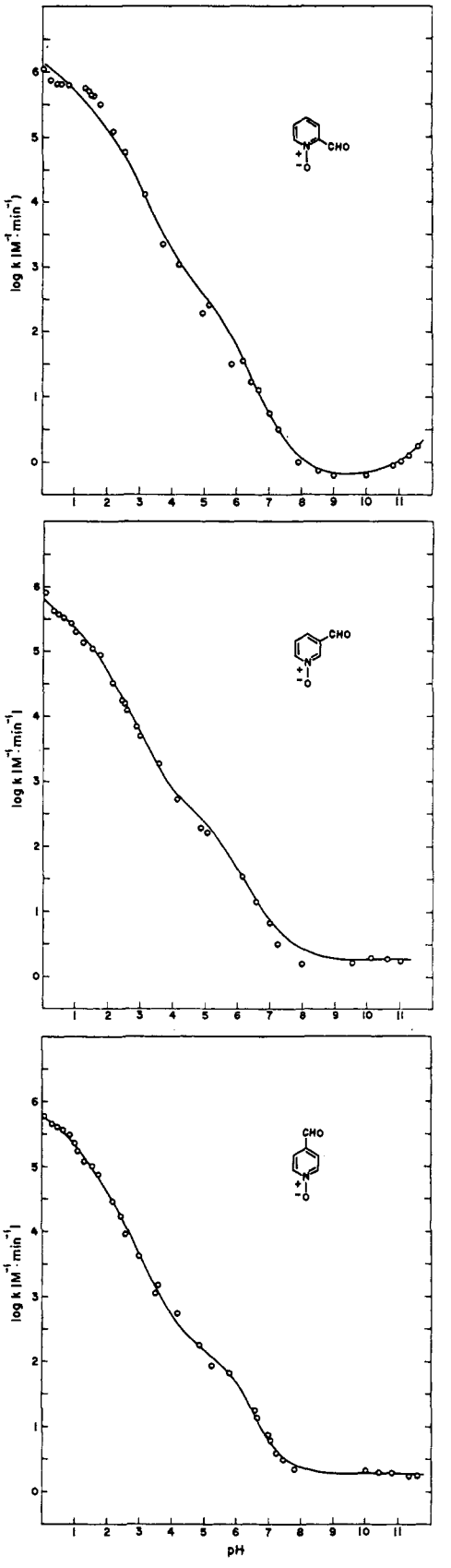


Figure 2. Plots of logarithms of second-order constants, M^{-1} min^{-1}, corrected for carbinolamine accumulation where necessary and extrapolated to zero buffer concentration, for pyridine *N*-oxide carboxaldehyde phenylhydrazone formation plotted as a function of pH or H_0. All measurements were made in 20% aqueous ethanol at 25 °C and ionic strength 0.5. The solid lines in each profile are theoretical ones derived from the rate constants collected in Table II. At the highest concentration of acid employed, values of H_0 in 20% ethanol were taken from M. Sadek, *Suom. Kemistil.*, **39**, 225 (1966), and G. Braude, *J. Chem. Soc.*, 1971 (1948).

larly, second-order rate constants for the 3- and 4-aldehydes increase from 8 to 14 M^{-1} min^{-1} at pH 7 and from 7.2 to 14.8 M^{-1} min^{-1} at pH 7.2 over the same range of phosphate buffer concentration.

Discussion

Pyridinecarboxaldehydes and related substrates are ordinarily hydrated to variable extents in aqueous solution. Pyridine-4-carboxaldehyde is approximately 50% hydrated at equilibrium in water.[19] Conversion of this substrate to the protonated form, 4-formylpyridinium ion, increases the extent of hydration to about 98%.[20] Since the extent of hydration directly influences the measured rate and equilibrium constants for addition of nitrogen nucleophiles, it is important to have the pertinent equilibrium constants for addition of water. From NMR and UV data, it has been estimated that pyridine *N*-oxide 4-carboxaldehyde is 50% hydrated at equilibrium, the 3 isomer 64% hydrated, and the 2 isomer 95% hydrated.[21] These values are not very different from those for the corresponding pyridine aldehydes,[20] suggesting that the *N*-oxide function is about as electron withdrawing as the pyridine ring nitrogen atom itself. All rate and equilibrium constants reported herein refer to the total substrate present, hydrate plus free aldehyde, and not to the free aldehyde itself.

There are two lines of evidence which establish that the kinetic results reported in this study are not complicated by the rate of aldehyde hydrate dehydration. First, the measured rate constants for dehydration of pyridine aldehyde hydrates, near 3 min^{-1},[20] are much greater than the first-order rate constants achieved even at the highest concentrations of phenylhydrazine employed. Second, the rate of phenylhydrazone formation under neutral and acidic conditions increases linearly with increasing amine concentration.

To some extent, the observation that rate and equilibrium constants for pyridine *N*-oxide carboxaldehyde formation are strikingly independent of the position of the aldehyde moiety on the heterocyclic ring (Table II, Figure 2) is attributable to partial substrate hydration. The compensation between inherent reactivity and degree of hydration (i.e., the most reactive aldehyde will be the most highly hydrated which, in turn, reduces apparent reactivity) tends to diminish observed differences in reactivity compared to the inherent differences of the free aldehydes themselves. Thus, the fact that the 2 isomer appears about as reactive as the 3 and 4 isomers reflects a greater inherent reactivity of this aldehyde coupled with a much greater extent of conversion of the aldehyde to the unreactive hydrated form.

The pH–rate profiles for phenylhydrazone formation from all three isomeric pyridine *N*-oxide aldehydes show two breaks (Figure 2). This behavior is consistent with a change in the rate-determining step from carbinolamine dehydration to stepwise carbinolamine formation at about pH 5–6, followed by a change in the mechanism of carbinolamine formation, from stepwise to concerted, at about pH 1–2 (eq 1).[4,5] This interpretation is in accord with a number of experimental observations.

First, carbinolamine dehydration is certainly rate determining under basic conditions as revealed by the nonlinear dependence of rate constants on phenylhydrazine concentration (Figure 1). Furthermore, the observation of acid-catalyzed, pH-independent, and base-catalyzed reactions is characteristic of carbinolamine dehydration. The observation that this reaction is only weakly susceptible to buffer catalysis is also consistent with this interpretation.

Second, the existence of a stepwise mechanism for addition of phenylhydrazine to pyridine *N*-oxide aldehydes is consistent with structure–mechanism correlations established earlier.[4,5] The more stable the dipolar addition intermediate, $T^{\pm}$, the more likely the stepwise mechanism becomes. Thus, carbinolamine formation from very weakly basic amines and unreactive aldehydes is usually concerted, although that involving more strongly basic amines and/or more reactive aldehydes is stepwise, reflecting the greater stability of $RN^{+}H_2CO^{-}$.[4,5] On the basis of these simple ideas, one would expect the stepwise mechanism to apply to carbinolamine formation from phenylhydrazine and pyridine *N*-oxide carboxaldehydes. For example, addition of semicarbazide, which is substantially less basic than phenylhydrazine, to *p*-nitrobenzaldehyde, which is less reactive than the pyridine *N*-oxide aldehydes, is stepwise down to a pH near 2.[4]

Third, a comparison of rate constants for pyridine *N*-oxide carboxaldehyde phenylhydrazone formation with those for a closely related reaction, addition of phenylhydrazine-4-sulfonate to *p*-chlorobenzaldehyde,[4] supports a stepwise mechanism. The value of $K_n k_4$ for the latter reaction is 1.2×10^2 M^{-1} min^{-1}; those for the pyridine *N*-oxide aldehydes vary from 1.0 to 2.0×10^2 M^{-1} min^{-1} (Table II). The inherently greater reactivity of the latter substrates is apparently compensated for by an increased extent of substrate hydration as discussed above. $K_n k_3$ for phenylhydrazine-4-sulfonate and *p*-chlorobenzaldehyde is 6×10^5 M^{-2} min^{-1}; values for the isomeric pyridine *N*-oxide aldehydes vary from 4.2×10^6 to 1.7×10^7 M^{-2} min^{-1}. The differences observed presumably reflect the slightly greater basicity of phenylhydrazine as well as differences in carbonyl group reactivity but the values are certainly consistent with a stepwise mechanism. (K_{ad} for addition of phenylhydrazine-4-sulfonate to *p*-chlorobenzaldehyde is about 10^2 smaller than corresponding values for the reactions studied here.)

Fourth, the observation of (kinetically complex) general acid catalysis for phenylhydrazine formation under mildly acidic conditions provides further evidence for rate-determining carbinolamine formation.

We conclude that the two breaks in the pH–rate profiles can be accounted for in terms of the scheme provided in eq 1.

The pH–rate profiles for pyridine *N*-oxide carboxaldehyde phenylhydrazone formation are quite different from those for addition of phenylhydrazine and other amines to formyl-1-methylpyridinium ions.[8] In the latter case, the pH–rate profiles exhibit no breaks down to pH 1 at least; this behavior reflects rate-determining carbinolamine dehydration over the entire pH range investigated, a consequence of large rate and equilibrium constants for addition of amines due to the strong electron-withdrawing power of the cationic ring nitrogen atom.[8]

The pH-independent route of carbinolamine dehydration is unusually important compared to the acid-catalyzed pathway for these compounds. Rate constants become nearly independent of pH near pH 8; for the corresponding reaction of benzaldehydes, pH independence is achieved only at pH 9.[22] This may reflect destabilization of the cationic carbinolamine relative to the uncharged one by the cationic center at the ring nitrogen.

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Supplementary Material Available: Table I, rate constants for phenylhydrazone formation from three pyridine *N*-oxide carboxaldehydes as a function of phenylhydrazine concentration at pH 10.4, 25.0 °C, and ionic strength 0.50 (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) Supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo.
(2) W. P. Jencks, *Prog. Phys. Org. Chem.*, 2, 63 (1964).
(3) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, 1969.
(4) J. M. Sayer, B. Pinsky, A. Schonbrunn, and W. Washstein, *J. Am. Chem.*

Soc., 96, 7998 (1974).
(5) S. Rosenberg, S. M. Silver, J. M. Sayer, and W. P. Jencks, J. Am. Chem. Soc., 96, 7986 (1974).
(6) W. R. Abrams and R. G. Kallen, J. Am. Chem. Soc., 98, 7777 (1976); J. M. Sayer and C. Edman, Ibid., 101, 3010 (1979).
(7) Equation 1 is taken from ref 4 and does not include the spectator mechanism.[6] The formulation provided is adequate to account for all results presented herein.
(8) P. Sojo, F. Viloria, L. Malave, R. Possomai, M. Caldazilla, J. Baumrucker, A. Malpica, R. Moscovici, and L. do Amaral, J. Am. Chem. Soc., 98, 4519 (1976).
(9) E. Felder and D. Pitre, Gazz. Chim. Ital., 86, 386 (1956).
(10) J. C. Craig and K. K. Purushothaman, J. Org. Chem., 35, 1721 (1970).
(11) W. Mathes and W. Sauermilch, Justus Liebigs Ann. Chem., 618, 152 (1958).
(12) W. P. Jencks, J. Am. Chem. Soc., 81, 475 (1959).
(13) E. H. Cordes and W. P. Jencks, J. Am. Chem. Soc., 84, 4319 (1962).
(14) L. do Amaral, W. A. Sandstrom, and E. H. Cordes, J. Am. Chem. Soc., 88, 2225 (1966).
(15) J. M. Sayer and W. P. Jencks, J. Am. Chem. Soc., 91, 6353 (1969).
(16) R. Moscovici, J. P. Ferraz, E. A. Neves, J. O. Tognoli, M. A. El. Seoud, and L. do Amaral, J. Org. Chem., 41, 4093 (1976).
(17) W. P. Jencks and J. Rogenstein in "Handbook of Biochemistry", H. A. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, 1968.
(18) L. do Amaral and M. P. Bastos, J. Org. Chem., 36, 3412 (1971).
(19) E. Sander and W. P. Jencks. J. Am. Chem. Soc., 90, 6154 (1968).
(20) S. Cabani, P. Gianni, and E. Matteoli, J. Phys. Chem., 76, 2959 (1972).
(21) L. do Amaral, unpublished observations.
(22) L. do Amaral, M. P. Bastos, H. G. Bull, and E. H. Cordes, J. Am. Chem. Soc., 95, 7369 (1973).

Photochemical and Thermal Rearrangements of Protonated 2,3-Homotropones

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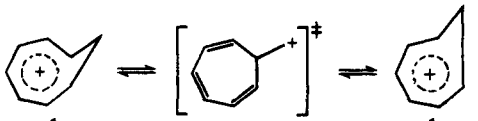
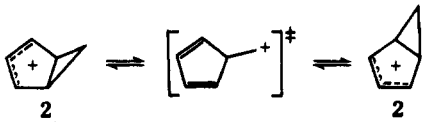
Abstract: The 2-hydroxyhomotropylium cation **10** and 8-*endo*-methyl-, 8-*exo*-methyl-, 8,8-dimethyl-, 1,8,8-trimethyl-, and 3,8,8-trimethyl-2-hydroxyhomotropylium cations, **12, 11, 13, 14,** and **15,** respectively, were prepared by protonation of the corresponding 2,3-homotropones in FSO_3H. On the basis of a comparison of the ^1H NMR spectra of the 2-hydroxyhomotropylium ions with nonaromatic systems it is concluded that they can properly be regarded as homoaromatic cations. Ions **10, 11, 12,** and **13** isomerized when irradiated in FSO_3H to give the corresponding 1-hydroxyhomotropylium cations **19, 21, 22,** and **23,** respectively. The thermal isomerization of these ions has been investigated. Cation **22** was shown to isomerize to **21** at −39.5 °C ($k = 4.3 \times 10^{-4}$ s^{-1}). An equilibrium was set up between these two ions consisting of 6% **22** and 94% **21** at 0 °C. At higher temperatures **21** rearranged to protonated 1-phenylpropanal ($k = 2.5 \times 10^{-4}$ s^{-1} at 37 °C). The 8,8-dimethyl cation **23** isomerized back to **13** ($k = 3.1 \times 10^{-4}$ s^{-1} at −23 °C), which underwent a further series of rearrangements to give eventually protonated 8,8-dimethylbicyclo[3.1.0]octa-3,6-dien-2-one (**29**). The symmetrical 8,8-dimethyl-4-hydroxyhomotropylium cation **32** was observed as an intermediate in the isomerization of **13** to **29**. On the basis of the thermal isomerizations of **14** and **15** it was concluded that the 8,8-dimethyl-3-hydroxyhomotropylium cation must also be an intermediate in the conversions of **13** to **29** and **13** to **32**.

The purpose of this study was to see whether circumambulatory rearrangements could be detected with homotropylium cations,[1] eq 1. Interest in these potential migrations stems from



(1)



(2)

the observation of facile, highly stereoselective, cyclopropyl merrry-go-round reactions of the bicyclo[3.1.0]hexenyl cations, eq 2.[2] The characterization of such rearrangements with **1** would be of value in assessing the importance of homoaromaticity and orbital symmetry in the two systems.

Circumambulatory isomerizations of the bicyclo[3.1.0]-hexenyl cations readily occur. The measured barrier to isomerization of **2** is only 15 kcal/mol[2b] and substituted derivatives of **2** exhibit activation energies which can range down to values which are formally below zero.[2,3]

At the outset of this work, no circumambulatory rearrangements of **1** or its derivatives had been detected. Berson and co-workers[4] had examined deuterated derivatives of the parent cation and concluded that the barrier to such a migration must be greater than 26–27 kcal/mol, a limit set by the onset of rapid decomposition of **1.** Calculations performed by Hehre[5] suggested that the barrier to migration would be of the order of 40 kcal/mol. Since our preliminary communication of these results[6] Scott and Brunsvold[7] have observed a circumambulatory rearrangement with a ring-fused homotropylium cation.

Why should the degenerate rearrangements of **1** have such a larger activation energy than those of **2**? Two primary reasons can be suggested: the constraints put on the system by the dictates of orbital symmetry[8] and the greater homoaromatic stabilization of the ground state of **1** as compared to **2.**

The importance of both factors can readily be seen by comparing the relative stabilities of the ground and formal transition states shown for the migrations in eq 1 and 2. For a concerted migration there are two possible geometries of the transition state and these are not equally attractive. The *bisected* structure which involves inversion at the migrating carbon can be readily attained from either **1** or **2.** The formation of the alternative *eclipsed* structure involves a more difficult non-least-motion movement of the migrating carbon.[9] For orbital symmetry to be conserved in thermally induced migrations, **1** is required to rearrange by the higher energy *eclipsed* transition state, whereas **2** can isomerize by the least motion allowed *bisected* pathway. On the other hand, homoaromatic stabilization of **1** will have the effect of increasing the energy gap between the ground state of **1** and the transition state for migration as compared to the comparable ground and transition states of the nonaromatic **2.**[1,10]

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