statement derives from our finding that the value obtained for k_{OH} (eq 17) falls on the plot of σ_I *vs.* log k_{OH} constructed from the data of Bell and Coller (references provided in footnote 17) for alkaline hydrolysis of α-substituted ethyl acetates. The difference in the mechanisms of hydrolysis of ethyl cyanoacetate and III is attributable to the large difference in leaving tendency of ethoxide and *o*-nitrophenoxide ions. One might argue that the evidence for an E1cB mechanism in the hydrolysis of V is not totally conclusive but we believe it to be quite compelling for III. It should be noted that the ylide of ethyl dimethylsulfonium acetate has been isolated[8] as a stable material. It may be concluded that the ρ values associated with the leaving group for the BAc2 mechanism is less positive than that for the E1cB mechanism.

Sacher and Laidler[21] have studied the hydrolysis of *p*-nitrophenyl acetate (*p*-NPA) at high pH (pH 8–10) and concluded that the mechanism is of the form of eq 13. In attempts to detect the plateauing of the rate with increasing hydroxide ion concentration we have restudied the hydrolysis of *p*-NPA measuring the spectrophotometric rate for *p*-nitrophenol release to as high as 0.5 *M* KOH. As Table V shows the second-order rate constant for hydroxide remains constant from pH $\approx$6 to $\approx$13.5 so that the kinetics are described by $k_{obsd} = k_{OH}[HO^-]$. This result is not surprising since the pK_a of *p*-NPA is at least greater than 14.0 and only kinetically insignificant quantities of the carbanion would be formed in the pH ranges investigated.

Acknowledgment. This work was supported by a grant from the National Institutes of Health.

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Catalytic Reactions Involving Azomethines. XI.[1] The Kinetics of Condensation of Histamine with 3-Hydroxypyridine-4-aldehyde. An Intramolecular Mannich Reaction

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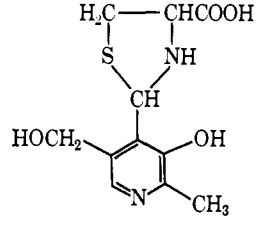
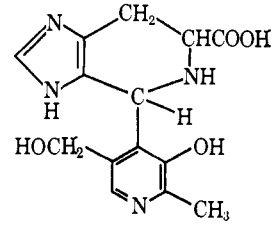
Abstract: The kinetics of the condensation of the pyridoxal analog 3-hydroxypyridine-4-aldehyde with histamine to yield VII have been investigated. It has been established that the reaction proceeds *via* rapid imine formation followed by a much slower ring-closure step. Under the conditions in which total histamine concentration far exceeds that of aldehyde, the rate-limiting step of imine formation changes from carbinolamine formation to carbinolamine dehydration. From the pH dependence of the observed first-order rate constants for conversion of imine species to final product, values of rate constants for ring closure of each imine species have been determined. Two favored mechanisms of product formation are provided. These are, nucleophilic attack of the 5 position of the neutral imidazolyl group on the unprotonated imine linkage and a like attack of the anionic imidazolyl group; both paths being assisted by proton donation from the phenolic hydroxyl group.

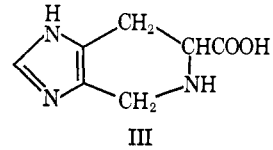
In aqueous solutions pyridoxal reacts with amino acids to provide pyridoxamine and the corresponding α-keto acids.[1,2] The transamination reaction has been clearly established to occur through imine formation followed by a general base catalyzed[1] prototropic shift and hydrolysis of the resultant ketimine. In the case of the amino acids histidine and cysteine, intramolecular condensation reactions successfully compete with prototropy to provide cyclic products (I and II) rather than ketimine.[3] Structure II resembles closely that of the condensation product of formaldehyde with histidine (III).[4] The reactions leading to the formation of II and III may be placed in the category of Mannich-type reactions.



I



II



III

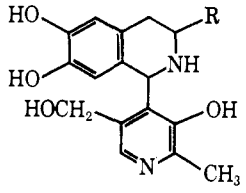
(1) For previous papers in this series see (a) T. C. Bruice and R. M. Topping, *J. Amer. Chem. Soc.*, **85**, 1480 (1963); (b) *ibid.*, **85**, 1488 (1963); (c) *ibid.*, **85**, 1493 (1963); (d) T. C. Bruice, *Biochemistry*, **3**, 1589 (1964); (e) T. C. French, D. S. Auld, and T. C. Bruice, *ibid.*, **4**, 77 (1965); (f) J. W. Thanassi, A. R. Butler, and T. C. Bruice, *ibid.*, **4**, 1463 (1965); (g) D. S. Auld and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2083 (1967); (h) *ibid.*, **89**, 2090 (1967); (i) *ibid.*, **89**, 2098 (1967); (j) J. R. Maley and T. C. Bruice, *ibid.*, 90, 2843 (1968).

(2) For a critical review see: T. C. Bruice and S. J. Benkovic "Bioorganic Mechanisms," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 8.

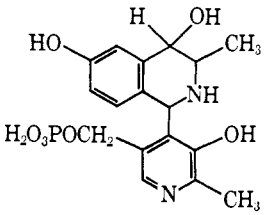
(3) D. Heyl, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, 70, 3429 (1948).

(4) J. Wellisch, *Biochem. Z.*, **49**, 173 (1913).

Mannich-type cyclic condensation products are also obtained when pyridoxal or pyridoxal phosphate are allowed to react with 3,4-dihydroxyphenethylamine (to produce IVa)[5] and 2-amine-1-(3′-hydroxyphenyl)-propanol (to yield V).[6] Tryptophan has been shown

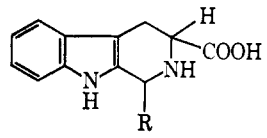


IVa, R = H
b, R = COOH



V

to condense with formaldehyde and both aliphatic and aromatic aldehydes to yield compounds of general structure VI[7,8] and a like condensation reaction has



VI

been suggested to occur with pyridoxal phosphate.[6] 3,4-Dihydroxyphenyl-L-alanine (DOPA) decarboxylase exhibits substrate inhibition which has been established as due to the reaction of L-DOPA with enzyme bond pyridoxal phosphate to presumably yield the phosphate ester of IVb.[6]

The "Mannich" condensation products of pyridoxal and pyridoxal phosphate are formed best at alkaline pH in contrast to the acidic conditions which are optimum for the syntheses of tetrahydroisoquinolines, tetrahydro-β-carbolines, etc., *via* the condensation of an aldehyde with a β-arylethylamine (Pectet–Spengler reaction).[9] The purpose of this study is the determination of the kinetics for the condensation of L-histamine with 3-hydroxypyridine-4-aldehyde (to yield VII) in order to determine the nature of the intermediates undergoing the condensation reaction. Apparently no attempt has been made previously to interpret in mechanistic terms the kinetics of this type reaction.[10]

Experimental Section

Materials. 3-Hydroxypyridine-4-aldehyde was prepared by the method of Heinert and Martell[11] as modified by French, Auld, and Bruice.[1e] The twice-sublimed aldehyde was stored in a desiccator in the dark at 0°. Histamine dihydrochloride (Cyclo Chemical Corp. grade 1), was purified by recrystallization according to the following procedure. Approximately 15 g of solid was placed in 100 ml of absolute ethanol which was allowed to come to a boil. Water was then added dropwise until complete solution was effected. After filtering, a sufficient amount of ether was added to the hot solution to initiate precipitation. The recrystallization procedure was repeated until the material was pure white and a constant melting point was reached (mp 245–246°, lit.[12] 244–246°). Ethylenediaminetetraacetic acid (EDTA) was used as its disodium salt (Fisher Scientific Co. reagent grade) without further purification.

Apparatus. Kinetic studies of the cyclization reaction were carried out on a spectrophotometer consisting of a Beckman DU monochromator and a Gilford Model 2000 multiple-sample absorbance recorder. The spectrophotometer was equipped with four thermospacers through which water at 30 ± 0.1° was circulated, and a dual wavelength selector which allowed observation of the reaction at two wavelengths simultaneously. Rates of imine formation were measured on a Durrum-Gibson stopped-flow spectrophotometer Model 13001, equipped with a Kel-F cell and valve block through which water at 30 ± 0.2° was circulated. Ultraviolet and visible spectra were determined on a Perkin-Elmer Model 350 double-beam recording spectrophotometer. A repetitive scan accessory was used for preliminary rate studies. All pH measurements were made on a Radiometer Model 22 pH meter equipped with a Model PHA 630 Pa scale expander and a combined glass-calomel electrode.

Kinetics. All kinetic runs were carried out at 30 ± 0.1° in glass-distilled water at a calculated ionic strength of 1.0 (with KCl) under the pseudo-first-order conditions of a large excess of histamine. The external buffers and the pH values at which they were used follow: phosphate (7.10, 7.79), Tris (7.79, 8.56), triethanolamine (8.56), carbonate (9.19), and borate (9.19). Below pH 7 and above pH 9.5, histamine served as its own buffer. Solutions of the aldehyde were refrigerated and never kept for more than 1 week. All kinetic runs were done in the presence of 5.0×10^{-3} *M* EDTA.

Rate studies of the cyclization reaction included histamine dilutions. The concentrations employed in combination with the buffers where necessary were 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.10, 0.12, and 0.14 *M* in the pH range 6.52–7.79, and 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, and 0.10 *M* in the pH range 8.56–10.94. In a typical run, the histimine solutions were equilibrated in standard taper stoppered cuvettes (3-ml capacity) for *ca.* 10 min in the cell housing of the spectrophotometer. Reaction was then initiated by adding one drop of aldehyde solution (6 mg/2 ml in 1 *M* KCl) to each of the histamine solutions, stoppering, inverting twice to mix, and placing the cell block back into the spectrophotometer. In the lower pH range (slower reaction) the rate was monitored at 305 mμ (appearance of the cyclized product) and 390 mμ (disappearance of imine) simultaneously. The rate constants obtained at both wavelengths were virtually identical for each individual run. In the higher pH ranges, the reaction was followed at 305 mμ.

In the stopped-flow kinetic studies of imine formation, a single concentration of histamine (0.15 *M*) was employed. Half dilution of random 0.30 *M* histamine stock solutions at various pH values produced a negligible pH drift. The aldehyde solution used was made up with 1.1 mg of 3-hydroxypyridine-4-aldehyde per 25 ml of 1 *M* KCl. Imine formation was monitored at 392 mμ. Scale expansions of 5×, 10×, and 20× were necessary because the starting aldehyde has a significant absorbance at that wavelength.

In the rate studies of *both* the cyclization reactions and imine formation buffer dilutions were performed at the pH values which required external buffering. Plots of k_{obsd} against total concentration of buffer were always horizontal indicating no catalysis of either reaction by any of the buffers at any pH.

pK_a' Values of histidine (30°) were determined titrimetrically (pK_{a_1} = 6.00; pK_{a_2} = 10.22) employing the apparatus previously described[13] and the calculation procedures described by Albert and Sargeant.[14]

Results

All reactions were carried out with histamine (H) in great excess over 3-hydroxypyridine-4-aldehyde (PCHO). In this manner all reactions were pseudo first order (eq 1). In Figure 1 is provided a representa-

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(6) H. F. Schott and W. G. Clark, *J. Biol. Chem.*, 196, 449 (1952).
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(10) G. Rotilio and B. Mondovi, *Arch. Biochem. Biophys.*, 114, 598 (1966).
(11) D. Heinert and A. E. Martell, *J. Amer. Chem. Soc.*, 81, 3933 (1959).
(12) P. G. Stecher, Ed., "The Merck Index," 7th ed, Merck & Co., Inc., Rahway, N. J., 1960.
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(14) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley & Sons, Inc., New York, N. Y., 1962, pp 37, 39.

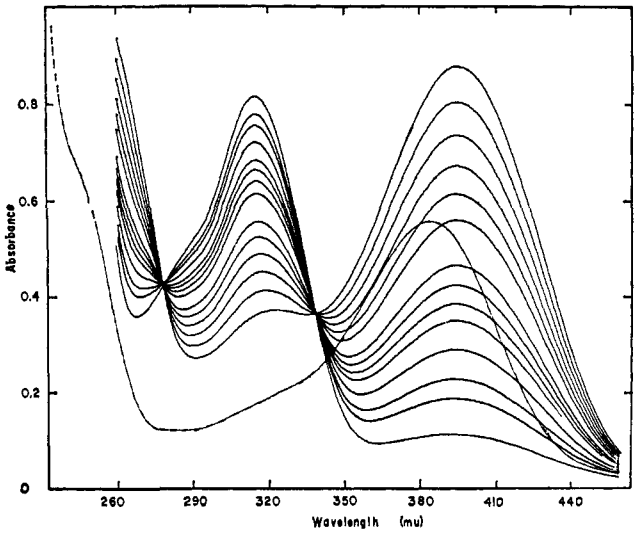


Figure 1. The change of absorbance with time of a solution *ca.* 10^{-4} *M* in 3-hydroxypyridine-4-aldehyde and 0.06 *M* in histamine. Decreasing absorbance at 390–400-mμ range. Dashed line is absorbance of 3-hydroxypyridine-4-aldehyde.

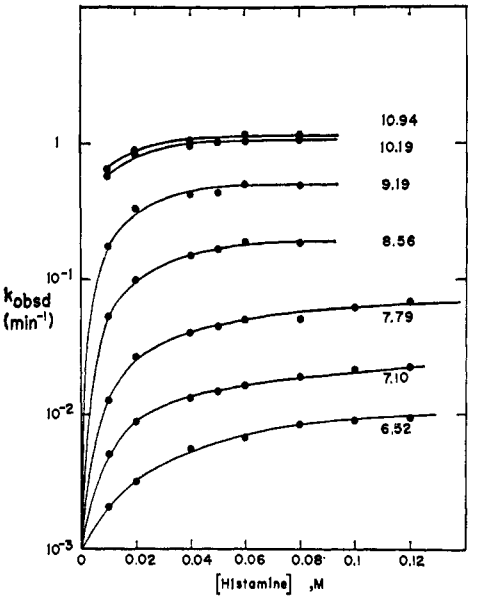


Figure 2. Dependence of the pseudo-first-order rate constant for disappearance of exocyclic unsaturation upon the concentration of histamine at various pH values.

tive repetitive scan of absorbance change of a solution *ca.* 10^{-4} *M* in $PCHO_T$ and 0.06 *M* in H_T (pH 7.16 with phosphate buffer). Inspection of Figure 1 re-

$$-\frac{d[PCHO_T]}{dt} = k_2'[PCHO_T][H_T]$$

$$-\frac{d[PCHO_T]}{dt} = k_{obsd}[PCHO_T] \qquad (1)$$

veals a constant decrease in λ_{max} at 392 (exocyclic unsaturation to pyridine ring) and increase in absorbance at 316 mμ (condensation product) with tight isosbestic points at 288 and 339 mμ. The presence of tight isosbestic points establishes that in the time course of the scans, an intermediate does not build up and then disappear.

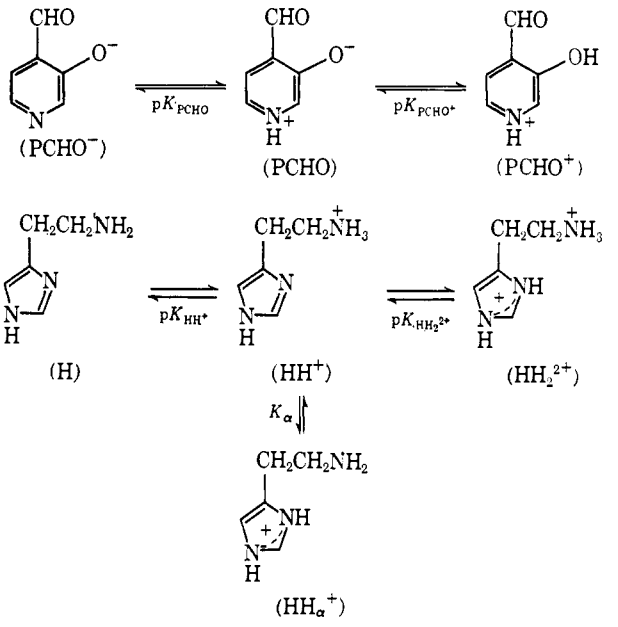
Figure 2 is a plot of k_{obsd} *vs.* $[H_T]$ at a series of pH values. From the results of Figure 2 it is apparent that: (a) the over-all rate of the condensation reaction first increases with increase in $[H_T]$ and then becomes independent of $[H_T]$ at its higher value; and (b) the initial increase in k_{obsd} with increase in $[H_T]$ as well as the value of k_{obsd} at high $[H_T]$ both increase with pH. These experimental results are in accord with the mechanism of eq 2, where C_T and I_T represent carbinol-

$$PCHO_T + H_T \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_T \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} I_T \xrightarrow{k_3} \text{products} \qquad (2)$$

amine and imine species, respectively. Appearance of isosbestic points in Figure 1 suggests that C_T and I_T are formed rapidly and reversibly and that the disappearance of $PCHO_T$, C_T, and I_T at equilibrium is being observed. The dependence of k_{obsd} upon H_T at the latter's lower concentrations may then be attributed to the equilibrium concentration of C_T and I_T as being H_T dependent. The lack of dependence of k_{obsd} upon H_T at the latter's higher concentrations must then be due to the fact that all $PCHO_T$ is in the form of C_T and I_T.

If the rate-determining step at high $[H_T]$ is the dehydration of C_T then the increase of k_{obsd} with pH at constant $[H_T]$ might then be related to the difference in reactivity of the various ionic species of $PCHO_T$, H_T, and I_T and possible involvement of OH^- catalysis. Important ionic species of initial reactants which must be considered for imine formation are provided in Scheme I.

Scheme I



The pseudo-first-order constants for formation of intermediates were determined with the aid of the stopped-flow spectrophotometer. The values of k_{obsd} are provided by eq 3. At high $[H_T]$, $k_1[H_T] \gg k_{-1}$

$$k_{obsd} = k_1[H_T] + k_{-1} \qquad (3)$$

and k_{obsd} is provided by eq 4. In Figure 3, k_1 is plotted

$$k_{obsd} = k_1[H_T] \qquad (4)$$

vs. pH. The points of Figure 3 are experimental and the curve theoretical being derived from an expression developed in the following discussion.

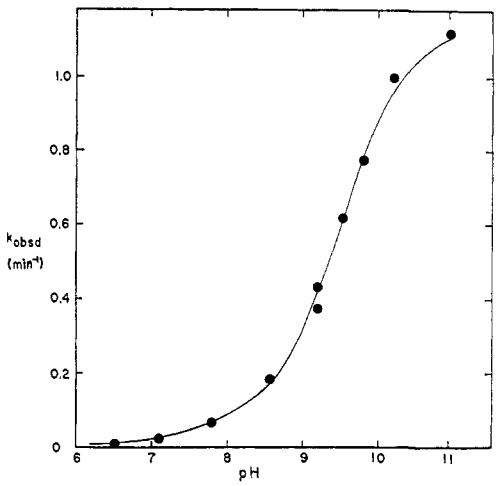


Figure 3. The pH dependence of the rate constant for formation of imine species from 3-hydroxypyridine-4-aldehyde and histamine.

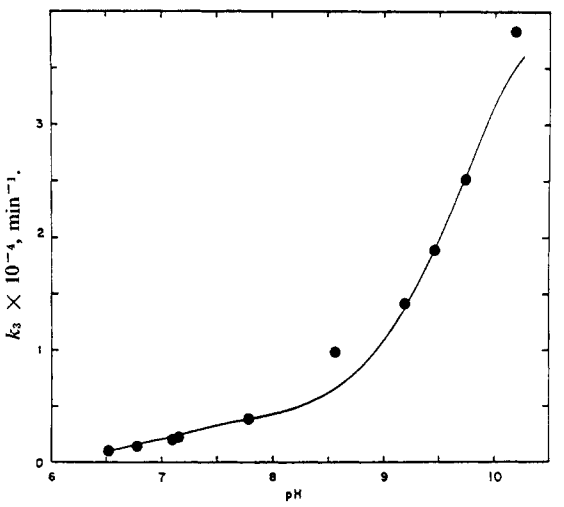
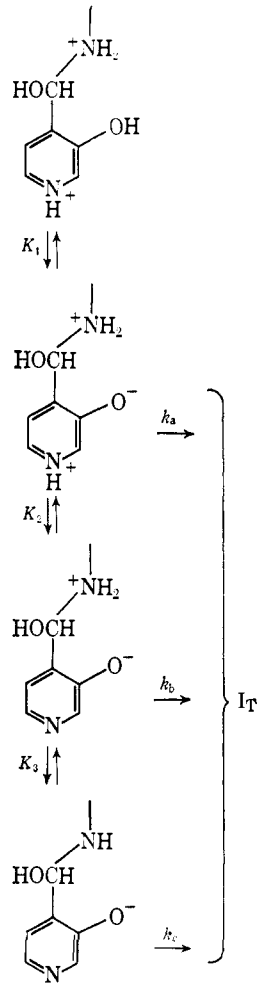


Figure 4. The pH dependence of the rate of formation of cyclic condensation species from imine species.

All attempts to provide a theoretical fit of the experimental points of Figure 3, based on the rates of reaction of the species of Scheme I, were unsuccessful (IBM 1620 computer). Examples of the necessary algebraic manipulations for this purpose are provided in the papers of ref 1 and on p 248 of ref 2.[15] The values of pK_{PCHO} and pK_{PCHO^+} employed were those of Auld and Bruice[1g] and those of pK_{HH^+} and $pK_{HH_2^{2+}}$ are provided in the Experimental Section. Values of K_α were sought by an iteration process. It must be concluded, therefore, that at the high values of $[H_T]$ employed to satisfy eq 4 the rate-determining step for imine formation does not involve the species of Scheme I but alternatively dehydration of carbinolamine (C). At the high $[H_T]$ employed, $k_1[H_T] > k_{-1}$ and $k_2 > k_{-2}$.

Scheme II



In Scheme II there are provided the structures of anticipated carbinolamine species as well as equilibrium and rate steps. From Scheme II the appropriate expression for k_2 is eq 5, where a_H is the hydrogen ion

$$k_2 = \frac{k_a K_1 a_H^2 + k_b K_1 K_2 a_H + k_c K_1 K_2 K_3}{K_1 K_2 K_3 + K_1 K_2 a_H + K_1 a_H^2} \quad (5)$$

activity as determined with the glass electrode. The theoretical line of Figure 3 is generated when a_H and the equilibrium and rate constants of Table I are substituted into eq 5. The closeness of the fit of the line to the points of Figure 3 and the inability to approach a fit when the rate-determining step is assumed to involve reaction of $PCHO_T$ and H_T species is sufficient to establish carbinolamine dehydration as being rate limiting. This being established no attempt was made to further refine the constants of Table I.

Table I. Equilibrium and Rate Constants Employed to Correlate the Rates of Imine Formation

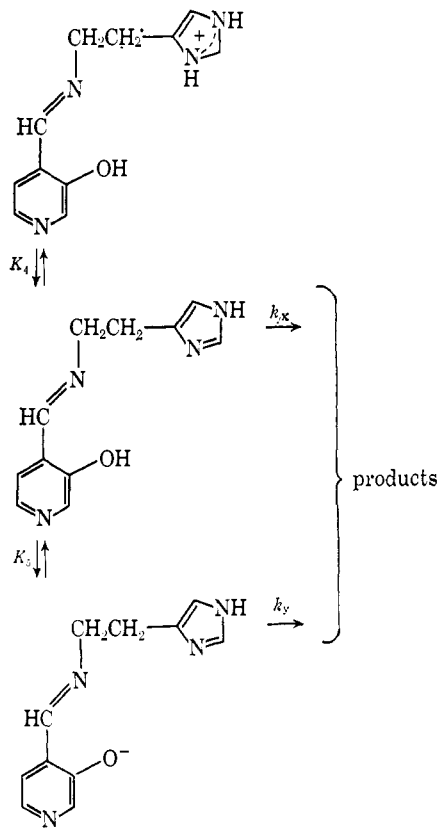
pK_1	3	k_a	1.5×10^2 min^{-1}
pK_2	7	k_b	4.0×10^3 min^{-1}
pK_3	9.7	k_c	4.5×10^4 min^{-1}

Attempts to determine the rates of carbinolamine formation proved inconclusive due to the magnitude of these constants and it was not possible to differentiate carbinolamine formation from the mixing time on the stopped-flow spectrophotometer.

The rate of ring closure (plateau rate constants of Figure 2; k_3 of eq 2) is much smaller than the rate constants involved in imine formation. In Figure 4 are plotted k_3 values *vs.* pH. The curve of Figure 4 pertains to the reaction paths of Scheme III and was

(15) D. E. Metzler, *J. Amer. Chem. Soc.*, 79, 485 (1957).

Scheme III



generated by substitution of a_H and the constants of Table II into the correct kinetic expression of eq 6.

$$k_3 = \frac{k_x K_4 a_H + k_y K_4 K_5}{K_4 K_5 + K_4 a_H + a_H^2} \quad (6)$$

Table II. Rate and Equilibrium Constants Employed to Correlate Observed Rates of Ring Closure

pK_4	7.15[a]	k_x	5.50×10^{-2} min^{-1}
pK_5	9.48[b]	k_y	1.15 min^{-1}

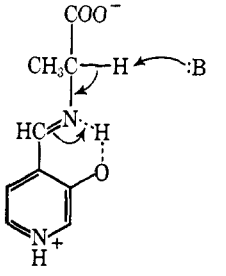
[a] Value of pK_a of 4(5)-methylimidazole. [b] Value of pK_a' determined in ref 1e for imine of valine and 3-hydroxypyridine-4-aldehyde.

Discussion

The results of this investigation reveal that the mechanism of condensation of histidine with 3-hydroxypyridine-4-aldehyde involves the following steps in the sequence: (1) carbinolamine species formation; (2) carbinolamine species dehydration to afford imine species; and (3) ring closure to provide VII.

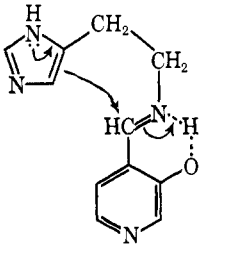
The rate constants for carbinolamine dehydration are very large (Table I) as previously noted for the dehydration of carbinolamines of amino acids and 3-hydroxypyridine-4-aldehyde.[1e,g] The unrefined dissociation constants pK_1 and pK_2 employed for the computer fits of the dehydration rate data are within one unit of the corresponding constants for the imine species formed from alanine and 3-hydroxypyridine-4-aldehyde.

From the pH dependence of the ring-closure step (Scheme III) it may be concluded that formation of VII from azomethine does not proceed through the imidazolium species. Since nucleophilic attack of the neutral imidazole group upon protonated azomethine is kinetically equivalent to attack of imidazolium ion on unprotonated azomethine we may also eliminate this possibility. It is surprising that the imine species, in which the phenolic hydroxyl group is dissociated, is associated with the largest rate constant for ring closure. Thus, from previous studies, an undissociated hydroxyl group assures a greater rate of prototropy in the transamination reaction. It has been suggested that the phenolic group acts in these reactions as a general-acid catalyst[1f,h,i] (eq 7). A similar participation might be



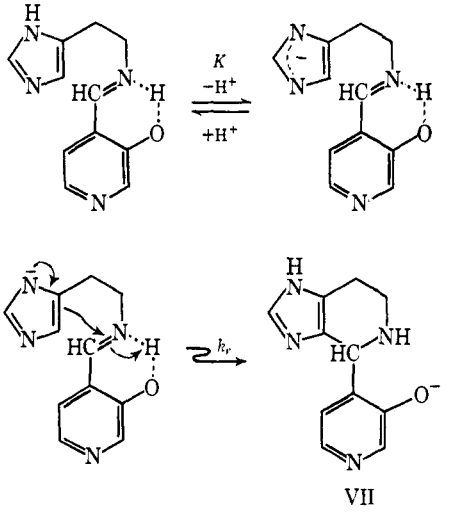
(7)

anticipated for the ring closure step of this study (eq 8).



(8)

That the rate of ring closure is greatest for the anionic species, even though the azomethine carbon is less electron deficient, might find interpretation through eq 9 which is kinetically identical with that for k_y of Scheme



(9)

VII

III. The calculated rate constant based on eq 9 is provided by eq 10 and the magnitude of k_r would appear

$$k_r = \frac{k_y K_5}{K} \cong 1.5 \times 10^5 \text{ min}^{-1} \quad (10)$$

reasonable on the grounds that the condensation would involve the intramolecular addition of an enamine anion.[16] Further support for the reasonableness of

(16) The value of K was taken as the second ionization constant of imidazole [T. C. Bruice and J. L. Herz, *J. Amer. Chem. Soc.*, **86**, 4109 (1964)].

the calculated rate constant of eq 10 stems from the resultant Brønsted β of ≈ 0.8 to 0.9, calculated from the rate constants k_x and k_r. Further studies involving other pyridine aldehyde analogs and aromatic aldehydes are essential to firmly establish the mechanism of this step in the condensation reaction and the reason why aromatic aldehydes apparently undergo the Pictet–Spengler reaction best in acidic media.

This study establishes the condensation reaction of histidine with the pyridoxal analog, 3-hydroxypyridine-4-aldehyde, to proceed through azomethine intermediates. Previous workers have established the presence of azomethines[3,5] but not their essential involvement in the condensation reaction. The inability to obtain condensation products when secondary amines are employed has been interpreted[6] as evidence for the necessity of azomethine intermediates. A criticism of this interpretation is the finding that imines are formed from secondary amines and that said positively charged imines undergo addition with greater facility than the neutral imines formed from primary amines.[17]

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Selectivity of C–H Bond Rupture by γ Radiolysis and Hot-Radical Attack in Singly Branched Alkane Glasses[1]

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Abstract: Trapped free radicals are produced in singly branched alkane glasses at 77°K by γ irradiation, hot-radical attack, or photosensitization by aromatic solutes. In contrast to similar activation in the gas and liquid phases, there is a high selectivity for rupture of a particular type of secondary C–H bond, as indicated by the esr spectra of the resultant free radicals. All three methods of activation show the same selectivity. For molecules with branching in the 3 or 4 position, the free radicals formed result predominantly from loss of a hydrogen atom from the secondary carbon atom nearest the end of the longest carbon chain. When branching is in the 2 position, detectable amounts of the radical resulting from loss of a tertiary hydrogen are also found. Identification of the trapped radical formed from 3-methylpentane glass has been made by comparing its esr spectrum with the spectra of the four possible 3-methylpentyl radicals. The latter have been produced by radiolysis of the corresponding iodides and the chlorides. Photolysis of 3-methylpentyl iodides in various organic glasses at 77°K produces, with low quantum yield, radicals formed by abstracting hydrogen atoms from matrix molecules, but no radicals formed by rupture of the carbon–iodine bond of the iodide, illustrating the importance of the cage effect in these systems.

When 3-methylpentane (3MP) is cooled in liquid nitrogen, it readily forms a transparent glassy solid and is widely used as a matrix for studying trapped free radicals, ions, and electrons produced at 77°K by irradiation techniques. In such investigations a signal from radicals produced from the 3MP itself often dominates the esr spectrum. Many authors have reported this spectrum (Figure 1A), which appears to arise from one predominate radical species, but there is not agreement on the identity of the radical.

Staples[2] suggested that the radical results from loss of a secondary hydrogen atom, or of the branching methyl group. Others[3,4] have also proposed removal of the branching methyl group, although no signal attributable to trapped CH_3 radicals is observed, and 3MP at 77°K is known to trap CH_3.

Voevodskii and coworkers[5] generated the six-line signal by a benzene-photosensitized decomposition of 3MP at 77°K. They proposed that it is produced by an equal interaction of the unpaired electron with only five of the seven β-hydrogen atoms in the tertiary 3MP radical, one hydrogen on each of the methylene groups being unable to interact significantly as a result of its orientation, relative to the major axis of the electron orbital.

Skelly, Hayes, and Hamill,[6] and Brocklehurst, *et al.*,[7] noted that the spectrum is composed of four central lines having relative intensities in the ratio of 1:3:3:1 or 1:2:2:1, flanked by two much weaker lines, implying the possibility that it might arise from more than one radical.

Photolysis of HI in 3MP at 77°K[7,8] leads to the same sextet of lines as radiolysis of pure 3MP. This argues against rupture of a C–C bond, and on this basis it was again proposed that the radical formed results from abstraction of a secondary or tertiary hydrogen atom.[9]

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