Reaction Kinetics of the Metal Ion Catalyzed β-Phenylserine–Pyridoxal Model System

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Abstract: Both β-elimination and dealdolation reactions were found to occur in the vitamin B-6 catalyzed reactions of β-phenylserine. The products of the reactions were found to consist of benzaldehyde, pyridoxylideneglycine (or glycine and pyridoxal), and phenylpyruvic acid. The reaction rate constants for the parallel elimination and dealdolation reactions in D_2O were determined by proton NMR over pD ranges of 4–10 for metal-free systems and 3–10 for metal-catalyzed systems. The observed (overall) rate constants in the metal-free systems for the disappearance of phenylserine are $k_{obsd} = 5.4 \times 10^{-6}$ s^{-1} M^{-1} at low pD to 3.1×10^{-4} s^{-1} M^{-1} at neutral pD. For the dealdolation and elimination reactions the rate constants varied from $k_{obsd_2} = 3 \times 10^{-6}$ s^{-1} and $k_{obsd_3} = 2 \times 10^{-6}$ s^{-1}, respectively, at neutral pD to $k_{obsd_2} = 1.4 \times 10^{-4}$ s^{-1} and $k_{obsd_3} = 8.3 \times 10^{-5}$ s^{-1} at higher pD. Further rate enhancement in the presence of metal ions at low pD was 60-fold for Al(III) and 50-fold for Zn(II), while at high pD it was only 2.3-fold for Al(III) and 1.4-fold for Zn(II). The ratios of dealdolation to β elimination are about 2:1 in metal-free systems and 4:1 and 5:1 in Al(III) and Zn(II) systems, respectively. The significance of these results relative to proposed reaction mechanisms is discussed.

In a general mechanism for the vitamin B-6 catalyzed reactions, Metzler et al.[1b] described the β-elimination and dealdolation reactions of Schiff bases of α-amino acids with a β-hydroxyl substituent. The amino acids previously investigated for the pyridoxal-catalyzed dealdolation reaction are serine (converted to glycine and formaldehyde), threonine (converted to glycine and acetaldehyde[2,3]), and β-hydroxyvaline (converted to glycine and acetone[4]). The nonenzymatic elimination reactions of hydroxyl-substituted α-amino acids were reported[2,5] for serine (converted to pyruvic acid and ammonia) and threonine (converted to 2-oxobutanoic acid and ammonia).

The question arises as to which factors determine the relative rates of these two pyridoxal-catalyzed reactions of β-hydroxy-α-amino acids. It has been determined that the choice of β substituent as a leaving group is very critical to determining the rates of β-elimination reactions.[6,7] The hydroxyl group seems to be the poorest leaving group present in any of the amino acids for which pyridoxal-catalyzed β elimination has thus far been studied. Thomas et al.[8] and Longenecker and Snell[6] have studied the β-*O*-sulfate and β-*O*-phosphate esters, respectively, and have shown that the rates of β elimination are slower for the threonine esters than for the serine esters. These rates seem to illustrate that alkyl β substituents also affect rates of reaction. A conclusion resulting from previous work is that a β substituent possessing an inductive electron-releasing effect, such as the methyl group, favors dealdolation, as shown by comparison of threonine with β-hydroxyvaline. Conversely, the dealdolation rate should be reduced and the fraction of β elimination increased by increasing the electron-withdrawing tendencies of the β substituents. To test these predictions experimentally, it was decided to employ β-phenylserine as a substrate. This paper reports the kinetics of the nonenzymatic pyridoxal and metal ion catalyzed reactions of β-phenylserine.

Experimental Section

Pyridoxal hydrochloride was obtained from Mann Laboratories as Mann Analyzed grade, DL-β-phenylserine and β-phenylpyruvic acid sodium salt, were obtained from United States Biochemical Corp., and glycine was obtained from Sigma Chemical Co. and used without further purification. NaOD, D_2O, and DCl were obtained from Diaprep Corp.; the purity of D_2O was 99.7%. NaOD (40%) and DCl (20%) were diluted to the appropriate concentration under dry nitrogen. Stock solutions of aluminum(III) and zinc(II) were prepared by dissolving $Al_2(SO_4)_3$ and $Zn(NO_3)_2$ in D_2O and evaporating to dryness. After this procedure was repeated several times, to remove residual H_2O, the solutions were diluted to the appropriate concentration and standardized by conventional chelatometric titration.[9] The gallium(III) solution was prepared by dissolving a specific amount of gallium metal in DCl and diluting to the appropriate volume.

The pH values of the solutions used for kinetic studies were measured with a Corning Model 101 digital electrometer fitted with a Beckman miniature combination glass electrode, and pH values were adjusted with NaOD. The instrument was calibrated before and after each kinetic run by the use of standard buffers and corrected by the use of activity coefficients to read $-\log [H^+]$ directly. In the case of D_2O solutions, the deuterium ion concentration was computed by adding 0.40 to the observed reading. The temperature of the reaction was maintained at 31.5 ± 1.0 °C, the ambient temperature of the NMR probe. The ionic strength was maintained at $\mu = 1.0$ with potassium nitrate.

All kinetic runs were carried out in homogeneous systems. In the metal-free pyridoxal–amino acid systems, the analytical concentrations of amino acid and pyridoxal were 0.10 M. In the metal–pyridoxal–amino acid systems, the analytical concentrations of amino acid and pyridoxal were 0.10 M, and the concentrations of metal ions were set at 0.10 and 0.05 M to achieve amino acid:pyridoxal:metal ion molar concentration ratios of 1:1:1 and 2:2:1, respectively.

^1H NMR spectra were obtained with a Varian HA-100 nuclear magnetic resonance spectrometer. The chemical shifts are reported in hertz with respect to the resonance of tetramethylsilane (Me_4Si), which was inserted into the reaction mixture in a coaxial tube. Carbon-13 decoupled spectra were obtained with a Jeol PS-PFT-100 spectrometer and Nicolet data system in the T1 program mode. The chemical shifts were recorded in parts per million with respect to tetramethylsilane (Me_4Si). The D_2O solvent was the source of an internal deuterium lock; a 6410-kHz range and 8K words of memory were used, giving a digital resolution of 0.996 Hz.

To determine reaction products, the sample solutions used for the kinetic runs were acidified to ensure the cleavage of the Schiff base complexes, consolidated to 0.20 M concentration, and ^{13}C NMR spectra were taken, and compared with the analogous spectra of authentic compounds. The fraction of Schiff base in the experimental solutions was determined by taking the sum of the integrals of the resonances of the 6-H, 4-CH, and 2-CH_2 groups of pyridoxal. The ratios of benzaldehyde and phenylpyruvic acid concentrations were determined for each experimental NMR spectrum over the first 2 half-lives of the reaction.

Results and Discussion

Resonance Assignments. The carbon-13 chemical shifts of pyridoxal and other compounds involved in the reactions studied are listed in Table I. The assignments correspond closely to the previously reported shifts for pyridoxal[10] and values listed for other compounds involved in the reaction correspond to those of related compounds.[11] The carbon-13

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Table I. Carbon-13 NMR Chemical Shifts (ppm vs. Me_4Si)[a]

compounds	C		COH	CO_2H, C=O			C-1	C-2	C-3	C-4	C-5
benzaldehyde					190.6		134.7	127.8	127.2	132.5	
pyridoxal	$2CH_3$	15.4	71.1	hemiacetal	99.6	C-6	126.7	145.2	150.2	141.0	139.3
phenylserine	C—N	60.2	71.6		170.9		139.0	130.2	130.2	127.0	
phenylpyruvic											
keto	CH_2	45.8		C=O	181.5						
				CO_2	175.3		135.6	131.5	130.0	128.5	
diol	CH_2	46.2	96.1		175.3		136.0	131.0	130.5	128.7	
enol			76.7								
glycine	CH_2	44.0			177.3						

[a] Reference 10; assignment C-3 → C-5.

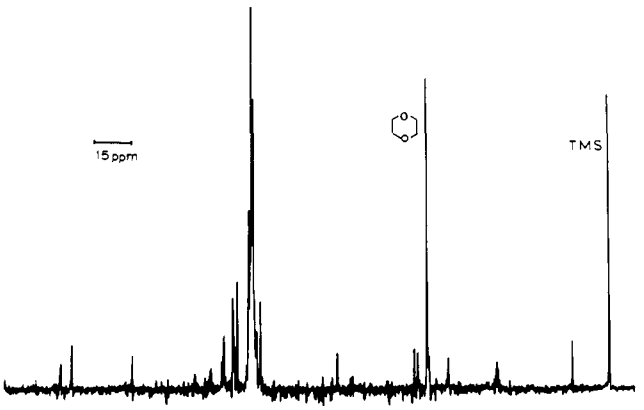


Figure 1. The carbon-13 NMR spectrum of the system consisting of 0.10 M pyridoxal and 0.10 M β-phenylserine at low pD showing the formation of products, benzaldehyde, phenylpyruvic acid, and glycine, and reactants; frequencies are reported in parts per million.

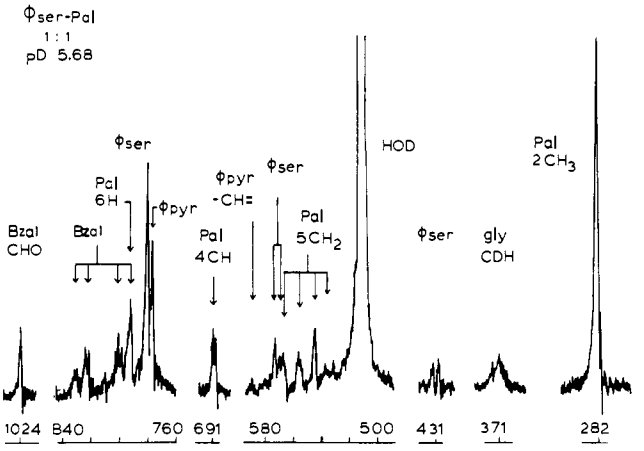


Figure 2. The 100-MHz NMR spectrum of 0.10 M pyridoxal and 0.10 M β-phenylserine at pD 5.68 showing the formation of products benzaldehyde and phenylpyruvic acid at 113 h 30 min after mixing; frequencies are reported in hertz with respect to Me_4Si.

spectra of products of the kinetic run exhibited the resonances of pyridoxal, benzaldehyde, glycine, and keto and diol forms of phenylpyruvic acid, as shown in Figure 1. The chemical shifts for pyridoxal, reported in Table I, are for the hemiacetal form. Not all of the assignments for the enol form of phenylpyruvic acid are listed in Table I because of the fact that (1) the resonances of benzene ring carbons could not be individually assigned, (2) the olefinic carbon resonance was not observed, and (3) only the alcoholic carbon resonance was observed at 76.7 ppm.

The proton chemical shifts of pyridoxal resonances have been assigned and discussed in detail elsewhere.[12] The resonances for β-phenylserine, glycine, benzaldehyde, and β-phenylpyruvic acid have been assigned and are listed in Sadtler

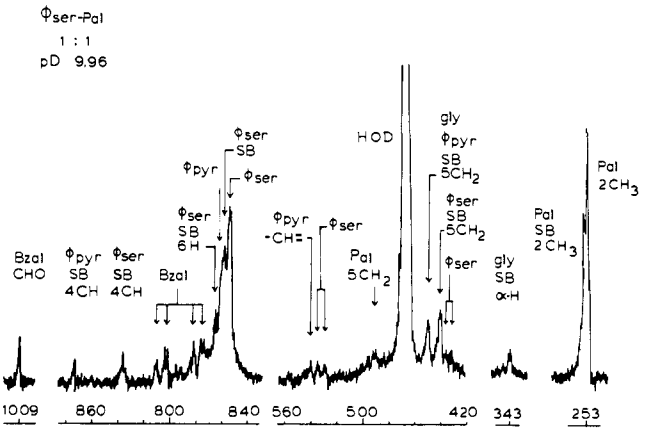
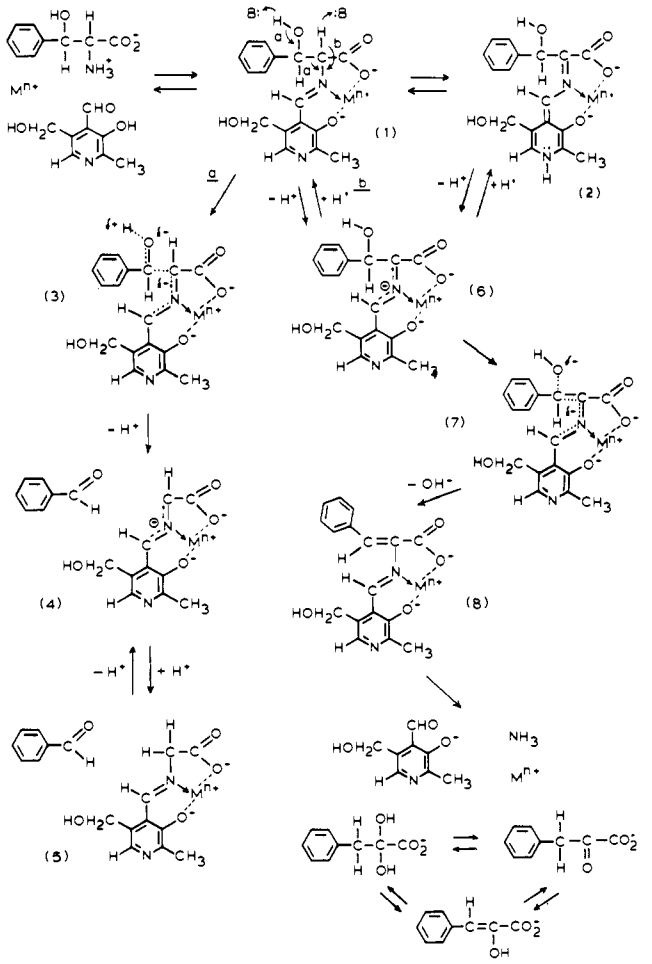


Figure 3. The 100-MHz NMR spectrum of 0.10 M pyridoxal and 0.10 M β-phenylserine at pD 9.96 showing the intermediate Schiff base formation at 80 min after mixing; frequencies are reported in hertz with respect to Me_4Si.

tables.[13] At pD values less than 5 in the presence of metal ions and at pD values less than 6 in the absence of metal ions, the NMR spectra of equimolar solutions of pyridoxal and β-phenylserine consists of resonances attributable entirely to the two components. As shown in Figure 2 for pD 5.68 with metal ions absent, the resonances at lower pD values taken at 113 h 30 min after mixing are separate and distinct and can thus be easily assigned.

All resonances shift to higher field with increasing basicity. As the pD is increased above 6, Schiff base resonances become apparent; they are labeled SB in Figure 3. In this figure are seen resonances of initial components and final products as well as Schiff bases of phenylserine and glycine, and the β-eliminated Schiff base intermediate (**8**) in Scheme I, which is a possible component. Figure 3, taken 80 min after mixing the components, illustrates the complexity of the spectra. The resonances are assigned in the order of appearance. Initial spectra consisted of pyridoxal, β-phenylserine, and its Schiff base (**1**). Benzaldehyde and the Schiff bases of glycine (**5**) and phenylpyruvic acid (**8**) appeared next, and finally free phenylpyruvic acid appeared. Figure 4, which shows the phenylserine–pyridoxal–aluminum (2:2:1) system at pD 10.26, taken 80 min after mixing, indicates the complexities encountered in assigning resonances, especially in the 720–800 Hz and 220–280 Hz ranges. In the 720–800 Hz range, the resonances of individual peaks were assigned according to the order of their appearance. In the 220–280 Hz range, the 2-CH_3 resonances were assigned as follows: the phenylserine Schiff base (**1**) 2-CH_3 peak was present in the initial spectrum and the glycine Schiff base (**5**) 2-CH_3 peak appeared soon after. The phenylpyruvic acid Schiff base (**8**) 2-CH_3 peak appeared much later, and was followed by appearance of the pyridoxal 2-CH_3 peak. The pyridoxal 2-CH_3 peak was confirmed by spiking the reaction mixture with pyridoxal at the conclusion of the kinetic run.

Scheme I



Kinetic Treatment. The rate measurements were based on the appearance of the products, benzylaldehyde and phenylpyruvic acid, as well as the disappearance of the amino acid, phenylserine. For the metal-free systems, the rate equations are based on the following reaction scheme:

$$\text{Pal} + \text{PhSer} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{SB} \begin{cases} \xrightarrow{k_2} \text{Bzal} + \text{GlySB} \\ \xrightarrow{k_3} \text{PhPyr} + \text{Pal} + \text{NH}_3 \end{cases} \quad (1)$$

For the metal–Schiff base 1:1 and 1:2 systems, the following scheme was employed:

$$\text{Pal} + \text{PhSer} + \text{M}^{n+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{SBM} \begin{cases} \xrightarrow{k_2} \text{Bzal} + \text{GlySBM} \\ \xrightarrow{k_3} \text{PhPyr} + \text{Pal} + \text{NH}_3 + \text{M}^{n+} \end{cases} \quad (2)$$

where PhSer = phenylserine; Pal = pyridoxal; SB or SBM = phenylserine Schiff base with or without metal ion; Bzal = benzaldehyde; PhPyr = phenylpyruvic acid; GlySB = glycine Schiff base; GlySBM = glycine Schiff base metal chelate. The following rate equation is obtained for the metal-free system in the absence of an appreciable amount of Schiff base:

$$\frac{\text{d[PhSer]}}{\text{d}t} = \left(\frac{k_{-1}k_1}{k_2 + k_3 + k_{-1}} - k_1\right)[\text{Pal}][\text{PhSer}] = k_{\text{obsd}}[\text{Pal}][\text{PhSer}] \quad (3)$$

Similarly, for the metal-Schiff base (1:1) systems:

$$\frac{\text{d[PhSer]}}{\text{d}t} = \left(\frac{k_{-1}k_1}{k_2 + k_3 + k_{-1}} - k_1\right)[\text{Pal}][\text{PhSer}][\text{M}^{n+}] = k_{\text{obsd}}^{\text{M}}[\text{Pal}][\text{PhSer}][\text{M}^{n+}] \quad (4)$$

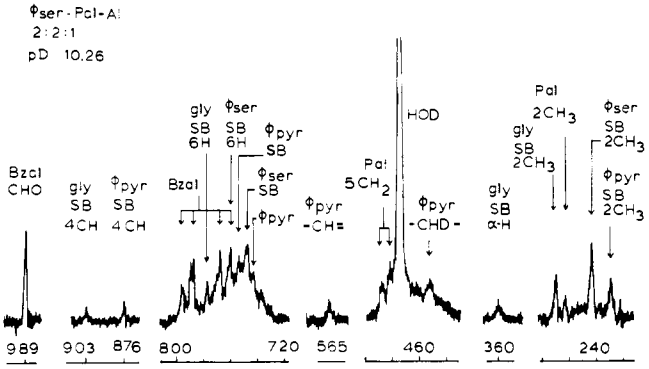


Figure 4. The 100-MHz NMR spectrum of 0.10 M pyridoxal, 0.10 M β-phenylserine, and 0.05 M metal ion at pD 10.26 showing complexity of the spectrum and all the possible Schiff bases at 80 min after mixing; frequencies are reported in hertz with respect to Me_4Si.

When the steady-state assumption is not applicable to Schiff base formation (i.e., when the accumulation of Schiff base in the solution is appreciable), the concentration changes of the Schiff base of phenylpyruvic acid can be followed by NMR. Thus, the following equations are employed:

$$\frac{\text{d[Bzal]}}{\text{d}t} = k_{\text{obsd}_2}[\text{SBM}] \quad (5)$$

$$\frac{\text{d[PhPyr]}}{\text{d}t} = k_{\text{obsd}_3}[\text{SB}] \quad (6)$$

The reaction stoichiometry, assuming no other by-products, gives the following relationship:

$$[\text{PhSer}]_0 = [\text{PhSer}] + [\text{Bzal}] + [\text{PhPyr}] + [\text{SB}]$$

where $[\text{PhSer}]_0$ is the initial concentration of the amino acid.

The values of the first-order rates k_{obsd_2} and k_{obsd_3} were then found by a plot of d[Bzal]/dt vs. [SB] and d[PhPyr]/dt vs. [SB]. Since it was not possible to obtain a 1:1:1 metal complex above pD 5.50 under the reaction conditions employed, the 2:2:1 metal complex was used for higher measurements. For the case involving Schiff base and metal ion at the stoichiometric ratio of 2:1, no appreciable free pyridoxal or phenylserine was observed. Under these conditions, the first-order rates k_{obsd_2} and k_{obsd_3} were determined in the same manner as described above. Measurement of the change in [SB] was based on the SB 2-CH_3 resonance, since resonances at 720–800 Hz are too complicated and distinct NMR integrations for the various components were not obtained. The concentration of phenylpyruvic acid may be calculated with the following relationship:

$$[\text{PhPyr}] = [\text{PhSer}]_0 - [\text{Bzal}] - [\text{SBM}]$$

since Schiff base formation is essentially complete from the time of the initial spectrum.

Figure 5 presents typical 100 MHz NMR spectra of metal complexes at low pD, showing the variation with time of the resonances of the phenylserine and benzaldehyde used for determination of rate constants for dealdolation and β elimination. The results are summarized in Table II for metal-free systems and Table III for metal-catalyzed systems. Due to turbidity and precipitation during certain kinetic runs, kinetic rates were not determined over the 6–7 pD range for metal-free systems and the 5–8 pD range for metal–complex systems. The broadening of the resonances which occurs at high pD made quantitative integration of the NMR resonance somewhat less accurate in the most alkaline regions of the reaction systems studied.

The rate constants determined in the lower pD range are second order for the metal-free system and third order for the

Table II. Observed Rate Constants for β-Phenylserine-Pyridoxal (1:1)[a]

pD	k_{obsd}, s^{-1} M^{-1}	k_{obsd_2}, s^{-1}	k_{obsd_3}, s^{-1}	[Bzal]/[PhPyr]
4.10	$5.4 \times 10^{-6} \pm 0.2$			1.42
4.33	$6.4 \times 10^{-6} \pm 0.2$			1.59
4.94	$9.9 \times 10^{-6} \pm 0.1$			1.91
5.68	$3.3 \times 10^{-5} \pm 0.1$			1.84
6.05	$4.7 \times 10^{-5} \pm 0.1$			2.00
6.30	$7.2 \times 10^{-5} \pm 0.1$			1.68
7.54	$3.1 \times 10^{-4} \pm 0.1$	$3 \times 10^{-6} \pm 0.6$	$2 \times 10^{-6} \pm 0.6$	1.90
8.02		$1.2 \times 10^{-5} \pm 0.1$	$6.7 \times 10^{-6} \pm 0.1$	1.70
8.47		$2.7 \times 10^{-5} \pm 0.1$	$1.6 \times 10^{-5} \pm 0.1$	1.67
8.94		$8.0 \times 10^{-5} \pm 0.1$	$4.7 \times 10^{-5} \pm 0.1$	1.71
9.38		$1.4 \times 10^{-4} \pm 0.1$	$8.3 \times 10^{-5} \pm 0.1$	1.63
9.96		$1.2 \times 10^{-4} \pm 0.2$	$7.0 \times 10^{-5} \pm 0.2$	1.75

[a] Reference 14; standard deviations.

Table III. Observed Rate Constants for β-Phenylserine-Pyridoxal-Metal Ion

metal	pD	$10^3 k_{obsd}^M$, s^{-1} M^{-2}	$10^4 k_{obsd_2}$, s^{-1}	$10^5 k_{obsd_3}$, s^{-1}	[Bzal]/[PhPyr]
aluminum					
1:1:1	2.91	2.7 ± 0.1			4.7
	3.95	3.3 ± 0.1			4.9
	4.78	5.2 ± 0.1			5.5
2:2:1	9.37		3.2 ± 0.1	6.0 ± 0.1	5.2
	10.26		6.5 ± 0.3	13.0 ± 0.3	5.1
zinc					
1:1:1	2.83	1.8 ± 0.1			3.8
	3.58	2.3 ± 0.1			3.7
	4.23	3.2 ± 0.1			3.6
	4.72	3.8 ± 0.1			3.6
2:2:1	8.87		1.1 ± 0.1	3.3 ± 0.1	3.7
	9.43		2.0 ± 0.1	5.5 ± 0.1	3.7
	10.07		4.5 ± 0.2	12.0 ± 0.2	3.7

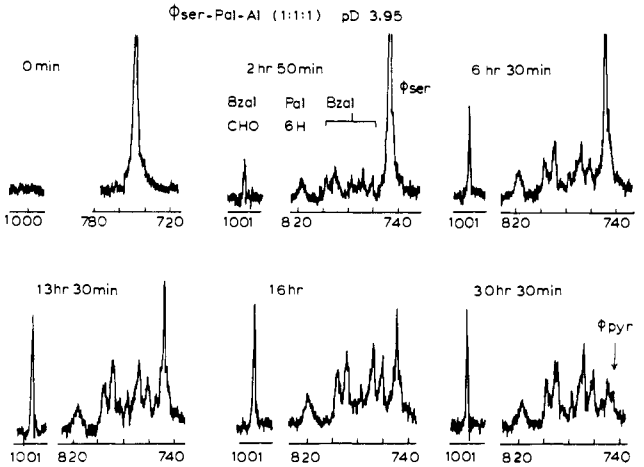


Figure 5. The 100-MHz NMR spectrum of 0.10 M pyridoxal, 0.10 M β-phenylserine, and 0.10 M metal ion at low pD showing the formation of products, benzaldehyde and phenylpyruvic acid, and disappearance of β-phenylserine; frequencies are reported in hertz with respect to Me_4Si.

metal–chelate system, in accordance with the eq 3 and 4. At higher pD, the concentration of Schiff base becomes appreciable so that eq 5 and 6 apply, and first-order rate constants for the Schiff base elimination and dealdolation reactions are obtained. The rate constants thus determined show considerable pD dependence. All three rate constants are reported for the metal-free system at pD 7.54 (Table II). In this case, although there was some Schiff base formation (~8%), the steady-state assumption was still valid; however, since changes in the Schiff base concentration were difficult to measure, k_{obsd_2} and k_{obsd_3} were obtained to only one significant figure.

The factors that influence the rates in the absence of the metal ion are (1) the amount of the Schiff base formation and the degree of protonation of the Schiff base, (2) the ability to labilize the bond between the α proton and α carbon and the α carbon and β carbon of the amino acid moiety, and (3) the contribution from the β substituents of the amino acid moiety. Calculation based on formation constants reported[7,15-17] demonstrates that the fraction of Schiff base in these systems never exceeds 10% of the total substrate below pH 6, and increases at higher pH. This low degree of formation of the Schiff base must be partly responsible for the observed low reaction rate in acidic media.

The labilization of the α-hydrogen or β-carbon atom bound to the α carbon of the amino acid moiety is promoted by the ability of the Schiff base to delocalize the resulting negative charge through the resulting extended conjugated π-bond system. This dissociation is further promoted by the inductive effects of both the metal ion and the heterocyclic nitrogen atom. The latter effect is greatly amplified upon protonation of the pyridine ring. The dissociation of the bond between α and β carbons seems to be favored over α-proton dissociation in view of the observed ratio of products, [Bzal]/[PhPyr] for the reactions run in acidic media (pD 4.94–7.54), which contain low concentrations of Schiff base. The inductive effects favoring α-proton dissociation are counterbalanced in part by the coulombic effect of the metal ion, and by the formation of the intermediate **2**, both of which effects would render the resulting negative charge less available for the withdrawal of the electronegative leaving group **7** required for the completion of the β-elimination reaction.

In the intermediate pH range, it is seen that the first-order rate constants increase with pH, probably because of a change in the nature of the reactive Schiff base species. The observed rate may be considered the summation of the rates of the individual species differing in degree of protonation. Thus:

$$k_{obsd}[SB_T] = k'[H^2SB] + k''[HSB^-] + k'''[SB^{2-}]$$

The concentrations of the three Schiff base species will vary with pH, in accordance with their respective proton affinities. The decrease in the first-order rate constant at higher pH may be accounted for by the deprotonation of the Schiff base at the azomethine nitrogen, resulting in the formation of a much higher proportion of the SB^{2-} species. In the latter form, the catalytic effect of pyridoxal on α-proton dissociation is greatly decreased because of the loss of the inductive effect of the proton bound to the azomethine nitrogen.

For the metal-free system, where the labilization of the bonds around the α carbon is controlled mainly by the inductive effects of the pyridine nitrogen, the β substituents (the hydroxyl group and benzene ring), and the protonation of the azomethine nitrogen, the ratio between the products is less than 2:1 (benzaldehyde to phenylpyruvic acid). The added electron-withdrawing effects of the hydroxyl group and benzene ring seem to be in competition with the effects of the pyridine ring system and the azomethine group. The electron-donating substituents at the β positions of amino acids should favor the dealdolation reaction by reducing the probability of the deprotonation of the α proton (since the labilization of the α proton is the essential first step in β elimination) and by increasing the electron density at the β-carbon atom, thus favoring carbon–carbon cleavage. The electron-withdrawing substituents should favor the β-elimination reaction since the degree of labilization of the α proton would be increased. In β-phenylserine the benzene ring favors β elimination by conjugation and stabilization of the transition state **7** leading to the formation of the unsaturated intermediate **8,** and it also favors dealdolation by conjugation and stabilization of the transition state **3** leading to the formation of benzaldehyde (**4**).

In the presence of metal ions, the dealdolation reaction is promoted to a greater extent than β elimination, as demonstrated by the observed ratios between the concentration of the benzaldehyde and phenylpyruvic reaction products. The ratios are almost 5:1 for alluminum(III) catalysis and nearly 4:1 for zinc(II) catalysis (Tables II and III), indicating that the metal ions favor C–C fission to a greater extent than β elimination. This selectivity, though small in magnitude, is well above experimental error, and it is interesting as another indication that α-proton dissociation is not the only rate-determining step in β elimination, as suggested previously by these authors.[6,7] Apparently, the metal ions may, following α-proton dissociation, stabilize the resulting delocalized negative charge sufficiently to slow down dissociation of the β-electronegative group, as seen in intermediate **6.**

Comparison of the metal-containing and metal-free systems also shows that metal ions have considerable catalytic effects on both reactions. A large rate enhancement is seen in the value $k_{obsd}^{M}[M]$ for aluminum(III) at pD 3.95 where the rate constant is 3.3×10^{-4} s^{-1} M^{-1} compared to the rate constant 5.4×10^{-6} s^{-1} M^{-1} for the pD 4.10 metal-free system. A similar rate enhancement is also observed for zinc(II) at pD 4.23 where the value $k_{obsd}^{M}[M]$ is 3.2×10^{-4} s^{-1} M^{-1} compared to the rate constant 6.2×10^{-6} s^{-1} M^{-1} for the metal-free system at pD 4.33. At high pD (9.4) k_{obsd_2} for zinc(II) is 2.0×10^{-4} s^{-1}, for aluminum(III) it is 3.2×10^{-4} s^{-1}, while the value for the metal-free system is 1.4×10^{-4} s^{-1}. Thus, the rate enhancement at low pD is 60-fold for aluminum(III) and 50-fold for zinc(II), while at high pD it is only 2.3-fold for aluminum(III) and 1.4-fold for zinc(II). Relative rate enhancements of similar magnitude are observed for k_{obsd_3}.

Table III shows the influence of the nature of the metal ion on catalysis of dealdolation and elimination reactions. Trivalent aluminum with higher electron affinity favors the dealdolation reaction more than does divalent zinc, and this is observed in differences in the rate constants as well as in the product ratios. This phenomenon is as expected since the electron flow in dealdolation is through the azomethine nitrogen toward the metal ion. In the β-elimination reaction, however, the zinc(II) ion is a slightly better catalyst than the aluminum(III) ion. Since the electron shift for the breaking of the bond between the β-carbon atom and the electronegative leaving substituent is opposed to the electronic effect of the metal ion, this observation is in conformity with the electronic structure requirements previously suggested for β-elimination reaction.[7]

The study of these systems with gallium(III) was limited to low pD because of the fact that the solution became turbid as the pD was raised. This made it difficult to obtain NMR spectra for this higher pD reaction. The gallium(III) ion caused a greater enhancement in the rates compared to other metal ions for both dealdolation and β-elimination reactions. The reaction produced ratios similar to those of aluminum(III) ion,[18] and seems to verify our statement above concerning the influence of the nature of the metal ion on catalysis.

Further investigations of hydroxyamino acids with a second phenyl group at β carbon, and with other elecronegative substituents at the β carbon, are currently underway. Various metal ions are being studied to determine their relative catalytic effects and their reaction selectivities.

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References and Notes

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