

Stereoselectivity in the Formation of the Metal Complexes of *O*-Phosphoserine

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Stability constants are reported for the bis complexes of *O*-phospho-DL-serine and *O*-phospho-L-serine with the metal ions Co(II), Zn(II), Cu(II), and Ni(II). For the cases of Co(II), Ni(II), and Cu(II), LL complexes and DL complexes have virtually the same stabilities. In the case of Zn(II), however, stereoselectivity favoring the LL complex approaches the theoretical maximum. The steric and Coulombic effects in bis complex formation are considered in the light of available evidence, and it is suggested that the Zn(II) complex is formed by meridional coordination of the ligands. It is further suggested that, in the absence of unusual steric effects, bis six-coordinate binding of optical isomers of the same tridentate ligand should lead to DL stereoselectivity for facial coordination while LL (or DD) stereoselectivity would be expected in the event of meridional coordination.

Introduction

Stereoselective coordination is always possible when two chiral ligands bind a metal ion. In the past, the majority of studies of stereoselective effects have dealt with the kinetically inert complexes of Co(III) and Pt(IV) with optically active diamines. These effects have been explained by Corey and Bailar¹ on the basis of the puckering of the chelate rings. Studies with kinetically inert complexes have the disadvantage of often not revealing the source—kinetic or thermodynamic—of the stereoselectivity. With kinetically labile complexes studied by static methods, stereoselective effects must be essentially thermodynamic in origin. In practice, however, relatively few kinetically labile systems have been reported. Studies of bidentate amino acids like alanine, phenylalanine, valine, leucine, tyrosine, and tryptophan with the metal ions Cd(II), Co(II), Ni(II), Pb(II), and Zn(II) have shown that there are negligible differences in the stabilities of the optically pure (MLL) and the mixed (MDL) complexes.²⁻⁶ However, when the amino acid has a third binding site, as in histidine and penicillamine, stereoselective complex formation has often been observed. Significant effects have been observed in the formation of the bis complexes of histidine with Co(II), Ni(II), and Zn(II).⁷⁻⁹ In these systems the MDL (racemic) complexes were found to be more stable than the MLL complexes. More pronounced stereoselective effects favoring the MDL complexes were found with histidine derivatives having methyl and benzyl substituents.^{10,11} Stereoselectivity in the metal complexes of other tridentate amino acids has been recently reviewed.¹² We are investigating the occurrence of stereoselective effects in the metal complexes of biologically important molecules, as a part of a project involving the study of how conformation can affect reactivity. These model studies may also be useful in understanding the high degree of specificity that metalloenzymes exhibit toward substrates of a particular structural type or optical conformation.¹³ In the present study the interaction of *O*-phospho-L-serine and *O*-phospho-DL-serine with Co(II), Ni(II), Cu(II), and Zn(II) has been investigated. A large stereoselective effect was observed in the formation of the bis complexes of Zn(II). This and reflections on the patterns of stereoselectivity in six-coordinate complexes are discussed below.

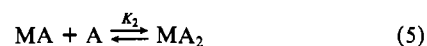
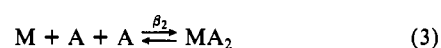
Experimental Section

Materials. The ligands *O*-phospho-L-serine and *O*-phospho-DL-serine were obtained from Sigma Chemical Co. Metal ion solutions were standardized by titration with the disodium salt of EDTA.¹⁴ Carbonate-free sodium hydroxide was prepared and standardized by titration with potassium hydrogen phthalate. Double-distilled water

was used in the preparation of all stock and experimental solutions.

Methods. Proton association constants for *O*-phospho-L-serine and *O*-phospho-DL-serine and the association constants for the metal complexes were determined by potentiometric titration with standard carbonate-free sodium hydroxide in the absence and the presence of the metal ions, respectively. The concentration ratio of metal to ligand was 1:2 in all cases. Multiple titrations were carried out for each system. The glass electrode was calibrated in terms of hydrogen ion concentration. All titrations were carried out under an atmosphere of nitrogen at 15 °C and $\mu = 0.15$ (KNO₃). The reason for utilizing this reduced temperature was to avoid any chance of metal-catalyzed phosphate hydrolysis. At 15 °C no significant free phosphate ion could be detected in the time required to obtain stable pH values. Other experimental details are similar to those reported in an earlier publication.¹⁵

Calculations. The proton association constants for the free ligands and the cumulative formation constants for the protonated and normal 1:1 and 1:2 metal-ligand complexes formed according to the equilibria (1)–(3) were calculated from the potentiometric titration data with



the aid of a corrected version of the computer program SCOGS.¹⁶

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Table I. Stability Constants^a (True for LL, Apparent for DL) of Metal Complexes of *O*-Phosphoserine with Co(II), Ni(II), Cu(II), and Zn(II) at 15 °C and $\mu = 0.15$ (KNO₃)

metal complex	$K_{\text{MHA}}^{\text{log}}$	$\log K_1$	$\log K_2^b$	$\log \beta_2^b$	$K_{\text{MA}_2}^{\text{log}}$
Co(II)					
DL	1.86	5.44	3.72	9.16	1.6 ± 0.2
LL	1.88	5.41	3.80	9.21	2.1 ± 0.2
Ni(II)					
DL	2.31	6.50	4.68	11.18	1.7 ± 0.3
LL	2.31	6.48	4.74	11.22	2.0 ± 0.1
Cu(II)					
DL	4.67	9.56	6.25	15.81	
LL	4.67	9.57	6.31	15.88	
Zn(II)					
DL	1.91	5.86	4.21	10.07	1.7 ± 0.2
LL	2.00	5.89	4.46	10.35	2.2 ± 0.2

^a Constants are accurate to ±0.02. ^b K_2 and β_2 for the metal-*O*-phospho-DL-serine complexes refer to $K_{2,\text{rac}}$ and $\beta_{2,\text{rac}}$. K_2 and β_2 for the metal-*O*-phospho-L-serine complexes refer to $K_{2,\text{LL}}$ and $\beta_{2,\text{LL}}$.

Stepwise formation constants for the equilibria (4) and (5) could be readily calculated from the proton and cumulative association constants. Formation of bis monoprotonated-metal complexes, MHA₂ (equilibrium 6), were also considered in processing the data with SCOGS. While in the Cu(II) system no constant could be obtained, the equilibrium constants for the other metal ions were found to be quite small with comparatively large standard deviations (Table I). These species are not further considered as they are evidently present in low concentrations. It should be noted that the constants for the MA₂ complexes obtained from titration data with *O*-phospho-L-serine are true constants for the formation of MLL species (eq 7). When

$$\beta_{2,\text{LL}} = [\text{MLL}] / ([\text{M}][\text{L}][\text{L}]) = \beta_{2,\text{DD}} \quad (7)$$

O-phospho-DL-serine (racemic form) is used, the titration data yield apparent (or mixed) stability constants for the bis complexes (eq 8).

$$\beta_{2,\text{rac}} = ([\text{MDL}] + [\text{MLL}] + [\text{MDD}]) / \{[\text{M}](\text{[D]} + [\text{L}])^2\} \quad (8)$$

The true stability constant for the formation of the MDL species (eq 9) was calculated with use of the relationship⁷ in eq 10. K_2 , the stepwise

$$\beta_{2,\text{DL}} = [\text{MDL}] / ([\text{M}][\text{D}][\text{L}]) \quad (9)$$

$$K_{2,\text{DL}} = 4K_{2,\text{rac}} - 2K_{2,\text{LL}} \quad ([\text{L}] = [\text{D}]) \quad (10)$$

addition constant, is defined as shown in eq 11.

$$K_2 = \beta_2 / \beta_1 \quad (\beta_{1,\text{D}} = \beta_{1,\text{L}} = K_{1,\text{L}} = K_{1,\text{D}}) \quad (11)$$

Results

The protonation constants for the amine nitrogen, phosphate oxygen, and the carboxylate oxygen moieties of *O*-phospho-L-serine and *O*-phospho-DL-serine were found to be 9.98 (±0.003), 3.64 (+0.004), and 2.12 (±0.006), respectively. The stability constants for the formation of the MHA and MA complexes are listed in Table I. Since stereoselectivity is not expected for the protonation of the free ligands and in the formation of the 1:1 metal-ligand complexes, the protonation constants and the stability constants for the MHA and MA complexes of *O*-phospho-L-serine *O*-phospho-DL-serine are in very good agreement. The stability constants (true for LL, apparent for DL) of the MA₂ complexes are listed in Table I. The true stability constants for the formation of the MDL species have been calculated (eq 10) and listed in Table II.

Table II. True Stability Constants of MLL and MDL and the Ratio of Diastereoisomers, α , of the Co(II), Ni(II), Cu(II), and Zn(II) Complexes with *O*-Phosphoserine at 15 °C and $\mu = 0.15$ (KNO₃)

metal	$\log K_{2,\text{LL}}$	$\log K_{2,\text{DL}}$	α
Co(II)	3.80	3.92	0.66
Ni(II)	4.74	4.91	0.74
Cu(II)	6.31	6.40	0.74
Zn(II)	4.46	3.86	0.13

Stereoselectivity in the formation of bis complexes¹¹ can be expressed in terms of α , which represents the ratio of the concentration of the mixed (MDL) complexes to those of the optically pure complexes (eq 12). The value of α is obtained

$$\alpha = [\text{MDL}] / ([\text{MLL}] + [\text{MDD}]) \quad (12)$$

from eq 13. $\alpha > 1$ indicates that stereoselectivity favors the

$$\alpha = K_{2,\text{DL}} / 2K_{2,\text{LL}} \quad (13)$$

formation of MDL complexes over the MLL and MDD complexes. $\alpha < 1$ represents the case wherein the optically pure complexes are preferentially formed. $\alpha = 1$ indicates a statistical formation of the diastereoisomers and the absence of stereoselectivity. In Table II the values of α for the formation of bis complexes of *O*-phosphoserine with Co(II), Ni(II), Cu(II), and Zn(II) are tabulated. The most striking feature of these values is the low value for Zn(II) ($\alpha = 0.13$), indicating a large stereoselective effect in favor of the optically pure species.

Discussion

For the data in Table II, values of α less than unity are observed for all systems. Owing to the methods of calculation, the differences between $K_{2,\text{LL}}$ and $K_{2,\text{DL}}$ cannot be considered significant for the cases of Co(II), Ni(II), and Cu(II). In the case of Zn(II), however, a large, significant stereoselectivity is observed. Here the magnitude of stereoselectivity is large and approaches the theoretical maximum expected for such an effect. The basis for this statement is that the apparent constant observed for the racemic ligand ($\log K_{2,\text{DL}} = 4.21$) is nearly half the magnitude of the true constant observed for the optically pure ligand ($\log K_{2,\text{LL}} = 4.46$). If the reaction were perfectly stereoselective so that in a racemic mixture only the MLL and MDD complexes were formed, the apparent constant observed would be exactly half the value obtained for the optically pure case.

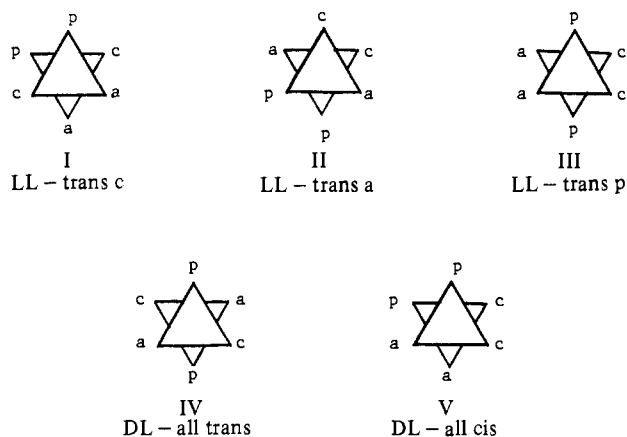
The failure to observe stereoselectivity in the Cu(II), Ni(II), and Co(II) cases is not surprising. In an earlier paper, we showed that the 2:1 complexes of *O*-phosphoserine with these metal ions are bisbidentate.¹⁹ The bidentate amino acid bis complexes generally do not display stereoselectivity.²⁻⁶ In our previous work, it was impossible to show whether or not the phosphate group is bound to Zn(II) in the bis complex. Since tridentate amino acids display stereoselective coordination and since a large stereoselective effect is observed with this *O*-phosphoserine and Zn(II), we presume that phosphate coordination has occurred and that the ligands are tridentate in the bis complex.

The large magnitude of stereoselectivity observed in the Zn(II) case makes a consideration of the structure of this complex an interesting enterprise. Considering essentially octahedral coordination, the *O*-phosphoserine ligand can coordinate facial or meridional sites. In the case of facial coordination, the possible isomers appear in Chart I. For ligands whose binding sites have different charges, Coulombic repulsions are minimized if all donor groups are trans to one another. The same will be true if the ligands contain bulky

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Chart I. Possible Diastereoisomers for Facial Bis-tridentate Six-Coordinate Complexes As Could Be Formed by *O*-Phospho-DL-serine^a

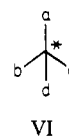


^a Abbreviations: a = amino; c = carboxylate; p = phosphate.

groups and steric effects are considered. The only isomer where all groups are trans is IV. It can only be formed from a D and an L ligand. For the optically active bis complexes, I is the most stable on the basis of Coulombic repulsions between donor sites. It is not obvious to us why this isomer should be sufficiently more stable than IV to account for the large stereoselectivity we observe. It would seem that the usual expectation would be that DL complexes should be favored if the ligands are tridentate and coordinate in a facial fashion.

However, meridional coordination can lead to stereoselectivity of the type we observe. For a tridentate ligand with a chiral center engaging in meridional coordination, three diastereomers are possible for the bis complex. There are two for the LL (or DD) complex and one for the DL complex. The DL complex exists as an enantiomeric pair, and so it may be formed two different ways. In the absence of steric or Coulombic effects the diastereomers would ideally exist in a 1:2:1 ratio. In any real case, however, the chances are that one of the LL isomers will be more stable than the DL isomer. Con-

sider an idealized tridentate ligand, VI, with substituents b



and c on a chiral center and meridional coordination along the line a-d. For a DD or LL complex, two diastereomers are formed. For each ligand of a given diastereomer, the steric or Coulombic interligand interactions of b or c will be the same. In the DL complex, the chiral centers are different and so b on one ligand will not have the same interactions as b on the other ligand. The symmetry is such that a given steric repulsion between two different parts of each ligand will occur twice in the least stable LL isomer, once in the DL isomer, and not at all in the most stable LL isomer. In other words, the DL isomer is always a "steric compromise" between the two LL isomers. When all steric effects are considered, this should generally lead to one of the LL (or DD) isomers being more stable than the DL isomer. Similar arguments can be made in the case of electrostatic repulsions and the *mer* bistridentate coordination should lead to the favoring of LL (or DD) over DL. For a very different system, we have previously demonstrated a number of instances of such stereoselectivity observed for meridional coordination.²⁰

The conclusion that may be drawn is that one would expect that facial bistridentate six-coordinate complexes with one chiral center per ligand should display DL stereoselectivity, if any. Meridional complexes should display DD or LL stereoselectivity.

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Nitrate/Nitrite Chemistry in NaNO₃-KNO₃ Melts

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By chemical analysis of samples taken under carefully controlled conditions, we have been able to show that the only reaction of any consequence that takes place in the equimolar binary NaNO₃-KNO₃ system over the temperature range 500-600 °C is represented by $\text{NO}_3^- \rightleftharpoons \text{NO}_2^- + \frac{1}{2}\text{O}_2$. Over this temperature range there is no evidence of the formation of any anionic oxygen species such as oxide, peroxide, or superoxide at concentrations greater than 10⁻⁵ mol/kg. Equilibrium constants for the above reaction have been determined over the temperature range 500-600 °C. The standard free energy for this reaction [ΔG° (kcal/mol) = 23 000 + 20.6T] has been derived from the experimental data and is in good agreement with similar results for the single salts. A study of the kinetics of the oxidation of nitrite showed the rate of that reaction to be overall second order, first order with respect to both nitrite and oxygen. The rate constants have been measured from 400 to 500 °C, and from their temperature dependence the activation energy for the oxidation of nitrite was calculated: 26.4 kcal/mol.

Introduction

Molten alkali nitrates and, in particular, the equimolar mixture of NaNO₃ and KNO₃ have become attractive candidates for heat transfer and thermal energy storage media

in solar thermal energy systems.¹ As such, they will be subjected to temperatures in the range 500-600 °C, several hundred degrees above their melting point (222 °C for NaNO₃-KNO₃). It is well-known that heating nitrates to

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