Studies on the Mixed Ligand Complexes Involving Ligands of Biological Importance
(Ni(II)/Zn(II)/Cd(II)-1,10-phenanthroline-2,2'-bipyridyl-phenylalanine)

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Formation Constants, Mixed Ligand Derivatives

pH-metric studies on the interaction of Ni(II), Zn(II) or Cd(II) with 1,10-phenanthroline (Phen) or 2,2'-bipyridyl (Bipy) in the presence of phenylalanine (Phe) indicate the formation of 1:1:1 mixed ligand chelates and their monohydroxo derivatives. The addition of Phe takes place after the combination of Phen or Bipy with the metal ion is complete. The formation constants of the resulting complexes have been determined at 30 ± 1 °C and ionic strength (μ) = 0.1 KNO₃ and the ternary complexes involving Phen are found to be more stable than the corresponding complexes involving Bipy as primary ligand.

Solution equilibria studies for the formation of mixed ligand complexes in the ternary systems Ni(II)/Zn(II)/Cd(II)-1,10-phenanthroline-glycine/a-alanine/norleucine/histidine and Ni(II)/Zn(II)/Cd(II)-2,2'-bipyridyl-histidine have been reported by us in earlier communications¹⁻² and their formation constants have been determined potentiometrically. Such studies have now been extended to other ternary systems involving these metal ions, 1,10-phenanthroline (Phen) or 2,2'-bipyridyl(Bipy) as primary ligands and phenylalanine (Phe) as secondary ligand, since phenylalanine is an important essential amino acid and an interesting anomaly of metabolism is connected with it in feeble-minded childrens called phenylketonuria (PKU). In this disorder phenylalanine is converted into phenylpyruvic acid and phenyllactic acid. Latter is also responsible for the mental aberrations of PKU³⁻⁴. The concept is also supported by the fact that if phenylalanine intake is restricted in infant with PKU, the mental symptoms do not develop. Conversion of phenylalanine into harmless, soluble and stable complexes.

From the view point of the role of metal complexes in biological systems, the information about the concentration of different species of a metal complex in equilibrium mixtures is of considerable importance and can be predicted on the basis of their formation constants. So the present studies were aimed at determining the formation constants of the mixed ligand complexes involving phenylalanine.

**Experimental**

Stock solutions of metal nitrates (AnaR BDH) were prepared and standardized as described previously¹⁻². Aqueous solutions of 1,10-phenanthroline hydrochloride, 2,2'-bipyridyl hydrochloride and phenylalanine were prepared by direct weighing and their strengths were checked by pH-metric titrations against a standard solution of potassium hydroxide. The pH-titrations were carried out at 30 ± 1 °C with a Systronics pH-meter standardized against a 0.05 M solution of potassium hydrogen phthalate (AnaR BDH). The ionic strength of the reaction mixtures was kept approximately constant (μ = 0.1 KNO₃) using requisite amount of potassium nitrate and low concentrations (5 × 10⁻³ M) of ligands and metal ion in case of the systems involving Ni(II) and Zn(II) and (2.5 × 10⁻³ M) in the systems involving Cd(II) on account of the low solubility of its complexes.

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Results and Discussion

Curves 1–3 (Figs. 1–3) represent the pH-metric titrations of phenylalanine, 1,10-phenanthroline and 2,2'-bipyridyl, respectively. The dissociation constant of Phe, \( (pk = 9.05) \) was calculated using the method of Chaberek and Martell, and those of Phen and Bipy have been taken from the literature. Reaction mixtures containing equimolar proportions of Ni(II) and Phe (curve 4, Fig. 1); Ni(II), Zn(II) or Cd(II) and Phen (curve 5, Figs 1–3, respectively) or Bipy (curve 6, Figs 1–3, respectively) give a sharp inflexion at \( m = 1 \), (where \( m = \) moles of base added per mole of metal ion or ligand) followed by a buffer region in the high pH range indicating the formation of 1:1 binary complexes and their conversion into the corresponding hydroxo derivatives. However, in the Zn(II) (curve 4, Fig. 2) and Cd(II) (curve 4, Fig. 3) systems only one ill-defined inflexion at \( m \sim 2 \) is obtained.

When equimolar systems, Ni(II)-Phen/Bipy-Phe (curves 7 and 8, Fig. 1), Zn(II)-Phen/Bipy-Phe (curves 7 and 8, Fig. 2) and Cd(II)-Phen/Bipy-Phe (curves 7 and 8, Fig. 3) systems are studied, the pH curve shows a sharp inflexion at \( m = 1 \), followed by a buffer region in the high pH range indicating the formation of 1:1 binary complexes and their conversion into the corresponding hydroxo derivatives. However, in the Zn(II) (curve 4, Fig. 2) and Cd(II) (curve 4, Fig. 3) systems only one ill-defined inflexion at \( m \sim 2 \) is obtained.

![Fig. 1. Potentiometric titration curves of mixed ligand chelate systems, Ni(II)-Phen/Bipy-Phe. Ionic strength: 0.1 KNO₃; conc.: \((5 \times 10^{-3}) \) M.](image1)

![Fig. 2. Potentiometric titration curves of mixed ligand chelate systems, Zn(II)-Phen/Bipy-Phe. Ionic strength: 0.1 KNO₃; conc.: \((5 \times 10^{-3}) \) M.](image2)

![Fig. 3. Potentiometric titration curves of mixed ligand chelate systems, Cd(II)-Phen/Bipy-Phe. Ionic strength: 0.1 KNO₃; conc.: \((2.5 \times 10^{-3}) \) M.](image3)
(curves 7 and 8, Fig. 3) are titrated, a sharp inflexion at \( m = 1 \), followed by a buffer region is obtained. For the Ni(II)–Phen/Bipy–Phe system another inflexion at \( m = 2 \) is also observed. Comparison of these curves with the corresponding composite curves 9 and 10 (Figs 1–3) (drawn by adding the horizontal distance of Phe curve to the horizontal distance of the M(II)–Phen/Bipy curve at the same pH) inferred that first the 1:1 M(II)–Phen/Bipy complex is formed and then addition of secondary ligand starts at \( m = 1 \) forming the 1:1:1 mixed ligand chelate, MAL, in the ternary systems studied. Further, poor inflexion at \( m = 2 \) in the case of Ni(II)–Phen/Bipy–Phe systems and no inflexion at this stage in other systems probably indicate that the formation of 1:1:1 mixed ligand chelate and its conversion into hydroxo derivative overlap. The formation of the above species is supported by the analysis of the potentiometric data given below.

The formation of 1:1:1 mixed ligand chelate, in the above systems, may be represented as:

\[
\text{MA}^{2+} + \text{L}^- \rightarrow \text{MAL}^+
\]

where \( \text{M}^{2+} \) stands for metal ion, A for Phen or Bipy and \( \text{L}^- \) for the secondary ligand anion. The formation constant, \( K_{\text{MAL}} \) of the ternary chelate may be given by the relation:

\[
K_{\text{MAL}} = \frac{[\text{MAL}^+]}{[\text{MA}^{2+}][\text{L}^-]} \tag{1}
\]

and can be determined by the expression:

\[
K_{\text{MAL}} = \frac{T_M - [\text{L}^-] X}{[\text{L}^-]^2 X} \tag{2}
\]

as derived from the material balance and electroneutrality relations for these systems. In this expression, \( T_M \) represents the total concentration of all the metal species, \( X = [\text{H}^+] / k_1 + 1 \) and

\[
[L^-] = \frac{(2-m)T_M - [\text{H}^+] + [\text{OH}^-]}{[\text{H}^+] / k_1},
\]

where \( k_1 \) is the dissociation constant of the secondary ligand.

**Formation of the hydroxo derivatives of 1:1:1 mixed ligand chelates**

A gradual increase in the values of \( \log K_{\text{MAL}} \) at \( m > 1.5, 1.6 \) and 1.56 in the case of systems, Zn(II)–Phen–Phe, Zn(II)–Bipy–Phe and Cd(II)–Phen/Bipy–Phe, respectively, probably indicates that hydrolysis of the 1:1:1 mixed ligand chelates starts before its formation is complete and the solutions remain more acidic than it would be in the absence of the hydroxo species. The equilibria involved in the formation of monohydroxo derivative of the 1:1:1 mixed ligand chelate may be represented as:

\[
\text{MAL}^+ + \text{OH}^- \rightarrow \text{MAL(OH)} \tag{ii}
\]

and the overall reaction for the formation of monohydroxo derivative may be written as:

\[
\text{MA}^{2+} + \text{L}^- + \text{OH}^- \rightarrow \text{MAL(OH)} \tag{iii}
\]

The overall formation constant, \( K_{\text{MAL(OH)}} \) of the monohydroxo derivative may then be given by:

\[
K_{\text{MAL(OH)}} = \frac{[\text{MAL(OH)}]}{[\text{MA}^{2+}][\text{L}^-][\text{OH}^-]} \tag{3}
\]

Assuming that only mononuclear metal chelate species are formed in the above systems, the following equations are obtained for maintaining the material balance:

\[
T_M = [\text{MA}^{2+}] + [\text{MAL}^+] + [\text{MAL(OH)}] \tag{4}
\]

\[
T_{\text{OH}} + [\text{H}^+] - T_A - [\text{OH}^-] = [\text{MAL}^+] + 2 [\text{MAL(OH)}] + [\text{L}^-] \tag{5}
\]

\[
T_L = [\text{MAL}^+] + [\text{MAL(OH)}] + [\text{HL}] + [\text{L}^-] \tag{6}
\]

where \( T_M, T_A \) and \( T_L \) represent the total concentrations of all the metal, primary and secondary ligand species, respectively, and \( T_{\text{OH}} \) is the concentration of the base added to the reaction mixture during titration. The elimination of MAL(OH) between (4)–(6) gives:

\[
T_M + T_A + T_L - T_{\text{OH}} - [\text{H}^+] - [\text{OH}^-] = [\text{MA}^{2+}] + [\text{MAL}^+] + [\text{HL}] \tag{7}
\]

Since \( T_M = T_A = T_L \) and \( T_{\text{OH}} = m T_M \), equation (7) can be written as:

\[
(3-m)T_M - [\text{H}^+] + [\text{OH}^-] = [\text{MA}^{2+}] + [\text{MAL}^+] + [\text{HL}] \tag{8}
\]

Combining equations (4) and (6) and using the expression for the dissociation constant \( (k_1) \) of the secondary ligand it can be shown that:

\[
[L^-] = \frac{[\text{MA}^{2+}]}{X} \tag{9}
\]

where \( X = [\text{H}^+] / k_1 + 1 \).

Combination of equations (1), (8) and (9) and rearrangement of the terms into the form of a polynomial, give:
a [MA$^{2+}$]$^2 + b [MA$^{2+}$] - c = 0 \tag{10}

where \( a = K_{MAL} \), \( b = 2 [H^+] / k_1 + 1 \), and \( c = (3-m) \cdot T_m - [H^+] + [OH^-] \cdot X \). \( K_{MAL} \) is the formation constant of 1:1:1 mixed ligand chelate. The equilibrium concentration of MA$^{2+}$ present in the reaction mixture may be obtained by solving equation (10) and the concentration of other species involved in the equilibrium relations can then be calculated from the above equations and also the value of formation constant, \( K_{MAL(OH)} \). The formation constants of monohydroxo derivative in case of Ni(II)-Phen/Bipy-Phe could not be calculated due to the appearance of a solid phase at an early stage after the addition of the hydroxyl group starts.

### Table I. Formation constants of the mixed ligand chelates (\( t = 30 \pm 1 \degree C, \mu = 0.1 \text{ KNO}_3 \)).

<table>
<thead>
<tr>
<th>System</th>
<th>log ( K_{MAL} )</th>
<th>log ( K_{MAL(OH)} )</th>
</tr>
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<tbody>
<tr>
<td>Ni(II)-Phen-Phe</td>
<td>4.85 ± 0.11</td>
<td>-</td>
</tr>
<tr>
<td>Ni(II)-Bipy-Phe</td>
<td>4.77 ± 0.11</td>
<td>-</td>
</tr>
<tr>
<td>Zn(II)-Phen-Phe</td>
<td>4.38 ± 0.10</td>
<td>10.07 ± 0.02</td>
</tr>
<tr>
<td>Zn(II)-Bipy-Phe</td>
<td>4.32 ± 0.10</td>
<td>9.54 ± 0.06</td>
</tr>
<tr>
<td>Cd(II)-Phen-Phe</td>
<td>3.66 ± 0.13</td>
<td>8.26 ± 0.07</td>
</tr>
<tr>
<td>Cd(II)-Bipy-Phe</td>
<td>3.52 ± 0.12</td>
<td>7.89 ± 0.01</td>
</tr>
</tbody>
</table>

5. S. Chaberek (Jr.) and A. E. Martell, J. Amer. Chem. Soc. 74, 5052 [1952].