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### COMPLEX FORMATION IN THE TERNARY SYSTEMS: COPPER(II)-GLYCYL-PHENYLALANINE-AMINO ACIDS

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# COMPLEX FORMATION IN THE TERNARY SYSTEMS: COPPER(II)-GLYCYL-PHENYLALANINE-AMINO ACIDS

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The coordination chemistry of amino acids and peptides is of considerable interest, due to its biological importance. In the case of glycine and phenylalanine, extensive studies have been made of the thermodynamic and kinetic condition of complex formation with  $3d^5-3d^{10}$  transition metal ions and of structural features of the resulting complexes.<sup>1-6</sup> Fairly abundant knowledge is available on the complexes of glycyphenylalanine with transition metal ions, primarily, copper(II), zinc(II) and nickel(II).<sup>1,7-9</sup> Because of their roles in the storage and transport in the neurotransmitters,<sup>10</sup> attention has been focused on the study of the interactions with transition metal ions.<sup>11</sup>

It is interesting to note that although ligands such as phenylalanine, glycy-phenylalanine and glycy-tyrosine contain aromatic substituent groups that appear to interact with metal ions, particularly copper ion, they do not promote significant stereoselectivity in simple binary complexes.<sup>11,12</sup> However, there is evidence that in ternary complexes these substituent groups can promote stereoselectivity.<sup>13</sup>

In the course of previous studies performed in this laboratory the coordination behaviour of potentially tridentate amino acids and peptides towards copper ion has been widely investigated.<sup>14,17</sup> Glycy-phenyl alanine contains more than two donor groups, and thus in principle there are a number of possibilities for the formation of complexes of different bonding types. Accordingly, in the present work we set out to determine the stability constants of mixed-ligand complexes of copper ion with glycy-phenylalanine and some amino acids. A further aim of the present work to explore the preferential formation of ternary complexes and the mode of bonding of glycy-phenylalanine in binary bis complex and ternary species involved.

## EXPERIMENTAL

The peptide (glycy-L-phenylalanine) was obtained from the Sigma Chemical Co. as Sigma grade. The amino acids such as glycine,  $\alpha$ -alanine,  $\beta$ -alanine, valine, serine, threonine, asparagine, tyrosine, glutamic and aspartic acid were of B.D.H. (AnalaR) and E. Merck (Germany) biochemical grade. These ligands were purified by repeated crystallization from water alcohol. Doubly distilled water was used in the preparation of solutions. The details regarding the other chemicals are given in earlier papers.<sup>18,19</sup>

Copper complex formation constants were evaluated from potentiometric titration curves of glycy-phenylalanine and amino acid in absence and presence of copper. Changes in pH were followed using glass and calomel electrodes and ELICO Digital pH meter (L1-10 No. 1275). The accuracy of pH meter was  $\pm 0.01$  pH unit. The pH meter was standardized before

each titration by buffer solution of potassium hydrogen phthalate with pH value 4.01 at 30°C. Titrations were carried out at various metal ligand ratio from 1 : 1 to 1 : 5. The system were titrated with a 0.44 N NaOH solution. All investigations were carried out under nitrogen atmosphere at 30°C and ionic strength 0.1 M (NaClO<sub>4</sub>). The experimental condition for a mixed ligand systems was 1 : 1 : 1 (copper ion : glycyl-phenylalanine : amino acid). From the evaluation of the formation constants a Fortan computer programme was used in putting at least 150 experimental data for each system. All computations were carried out at IBM computer of the Tata Institute of Fundamental Research, Bombay.

## RESULTS AND DISCUSSION

The acid dissociation stability constants of glycyl-phenylalanine and their stability constants with Cu(II) were measured under these experimental conditions to the constant for the ternary complexes to permit the reliable calculation of  $\Delta \log K$ . The error in the data obtained for the formation constant of (CuXY H-1) can be estimated as  $\pm 0.05$  log unit since beside the direct experimental errors, this value also contains the errors of at least 10 previously determined formation, taken into consideration in the calculations. The experimental accuracy for the evaluation of  $\Delta \log K$  values was also  $\pm 0.05$  since,  $\Delta \log K$  values were determined from the formation constants.

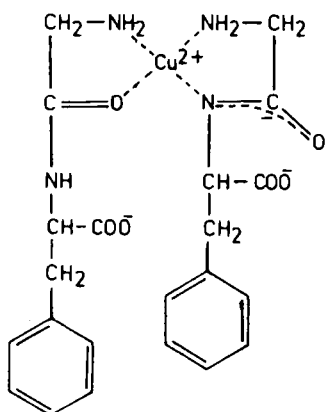
In most of the cases the formation constants are close to comparable values reported in the literature but the values differ at different experimental conditions. In Table I  $K_{H_2L}^H$  refers to the protonation of carboxyl group and  $K_{HL}^H$  to that of amine nitrogen. The value for  $K_{HL}^H$  indicates that the amino nitrogen atom in the peptide is less basic than the corresponding amino acid. The copper complexes with glycyl-phenylalanine are more stable than those of other peptides.<sup>15,16</sup> The structures of the complexes of Cu(II) with simple dipeptides have been reasonably well elucidated, the major species being [CuX]<sup>+</sup>, [Cu(X-H)], [Cu(X-2H)]<sup>-</sup>. It has been established that in [CuX]<sup>+</sup> complex Cu(II) coordinates to the amino nitrogen and amide oxygen. The metal ion and the three donor atoms are known to be virtually coplanar in the solid state<sup>20</sup> and it can be assumed that this will also be true in solution. Two axial water molecule will be relatively loosely bound in a tetragonally distorted position. The complex [CuX(X-H)] has basically planar structure and will bond through its amino and deprotonated amide nitrogen atoms and the carboxyl oxygen. The suggestions have been made as to the structure of bis [CuX(X-H)] complex. One is five coordinate<sup>21,22</sup> and other is planar.<sup>8,23</sup> As glycyl-phenylalanine is a bidentate as well as tridentate ligand, there is a rearrangement of the donor centres to give the structure I and II in planar and five coordinate complexes respectively.

It is interesting to compare the present results with those obtained by Brookes and Pettit<sup>8</sup> for Cu<sup>2+</sup> complexes of other dipeptides. The comparison shows a different stability of

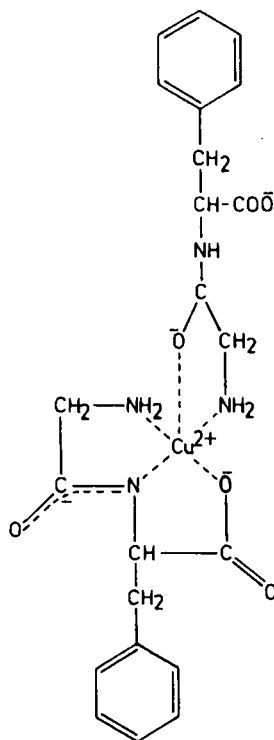
TABLE I  
Acidity constants of glycyl-phenylalanine peptide and corresponding binary copper complexes  
 $t = 30^\circ\text{C}$  and  $\mu = 0.1\text{M}$  (NaClO<sub>4</sub>)  
(Standard deviations are given in parentheses)

Peptide	$\text{p}K_{H_2L}^H$	$\text{p}K_{HL}^H$	[MX] <sup>+</sup>	M(X-H)	[MX(X-H)] <sup>-</sup>
Glycyl-phenylalanine	2.98(3)	3.16(2)	5.83(1)	1.93(2)	5.23(4)
	2.987 <sup>a</sup>	8.157 <sup>a</sup>	5.82 <sup>a</sup>	1.934 <sup>a</sup>	5.23 <sup>a</sup>
	3.12 <sup>b</sup>	8.16 <sup>b</sup>	5.45 <sup>b</sup>	1.59 <sup>b</sup>	4.77 <sup>b</sup>
	3.09 <sup>c</sup>	8.10 <sup>c</sup>	5.36 <sup>d</sup>		3.16 <sup>d</sup>

<sup>a</sup>= Ref. 8, <sup>b</sup>= Ref. 29, <sup>c</sup>= Ref. 30, <sup>d</sup>= Ref. 1.



I



II

$[\text{CuL}]^+$  as the nature of the substituent changed. In other words the highest stability of  $[\text{Cu}(\text{X}-\text{H})]$  and  $[\text{CuX}(\text{X}-\text{H})]$  is observed for  $\text{Cu}^{2+}$  complex of glycyl-phenylalanine, due to the presence of aromatic group. Aromatic groups appear to confer extra stability to certain complexes by a weak association over the ionic centre of the complex, giving a dipole-induced dipole interaction. Such interaction has recently been confirmed by visible and epr spectroscopy.<sup>24</sup> These interactions have been found in  $\text{Cu}(\text{II})$ -dipeptide systems but not in  $\text{Cu}(\text{II})$ -amino acid systems.<sup>25</sup>

Table II gives the formation constants for the mixed complexes  $[\text{CuXYH}_{-1}]$  and equilibrium constants relating to the substitution process. Further analysis of the tabulated data suggests several finer details of the mixed-ligand formation.

1) In all the systems  $\Delta \log K$  is negative, suggesting that the ternary complexes are very much stable relative to their binary analogues. However, the value of  $\Delta \log K$  in the system corresponding to asparagine as secondary ligand is close to zero i.e.  $-0.06$  indicates the destabilized nature of the mixed complex.  $\Delta \log K$  values for the other systems show the smaller deviations from the expected values.

2) According to the data in Table II, glycine forms stable mixed complex than those of other amino acids. The absence of alkyl chain in glycine shows the relative higher stability. These investigations have proved unambiguously.<sup>6,26</sup>

3) Copper parent complex of  $\beta$ -alanine is substantially less stable than  $\alpha$ -amino acids. The stabilities of the mixed complexes of  $\beta$ -alanine and aspartic acid are relatively higher than those amino acids. The phenomenon is explained by the assumption that similar to the

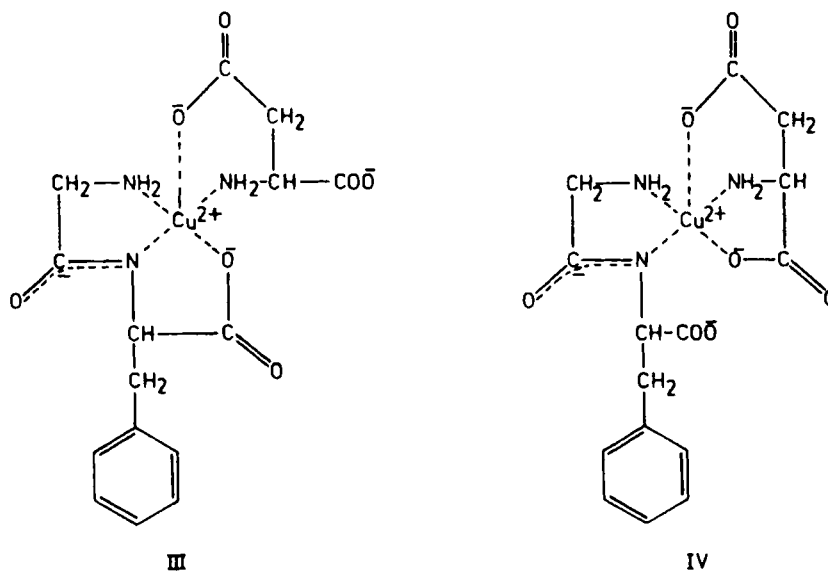
TABLE II  
 Formation constants of the copper(II)-glycyl-phenylalanine-amino acid complexes and equilibrium constants of the substitution process  
 $(\text{CuX}_2\text{H}^- + \text{Y} \rightleftharpoons \text{CuXYH}^- + \text{X})$   
 $t = 30^\circ\text{C}$  and  $\mu = 0.1 \text{ M (NaClO}_4\text{)}$   
 (Standard deviations are given in parentheses)

Amino acids	$\log \beta \text{ CuXYH}^-$	$\Delta \log K \pm 0.05$
Glycine	5.55 (2)	-0.32
$\alpha$ -alanine	5.49 (1)	-0.26
$\beta$ -alanine	5.61 (4)	-0.38
Valine	5.42 (3)	-0.19
Serine	5.47 (5)	-0.24
Threonine	5.34 (2)	-0.12
Asparagine	5.29 (3)	-0.06
Tyrosine	5.39 (3)	-0.16
Glutamic	5.51 (1)	-0.28
Aspartic	5.74 (4)	-0.51

second peptide ligand in the complex(II), the amino acids occupy one equatorial and one axial coordination sites in the mixed complex.

Aspartic acid exhibits an enhanced stability in mixed ternary complexes with glycyl-glycine, glycylalanine<sup>27</sup> and alanyl methionine<sup>16</sup> including glycyl sarcosine.<sup>15</sup> The enhanced stability of the ternary aspartic- $\text{Cu}^{2+}$ -glycyl-phenylalanine complex over the binary  $\text{Cu}^{2+}$ -glycyl phenylalanine is consistent with the principle of the mixed-ligand complex formation.

An additional factor favouring complexation of this system is due to the presence of aromatic group in the peptide, which appears to interact at least with copper(II). The only effects the substituents can have will be through their inductive effects or through steric interactions. As a result small substituent groups would not be expected to show significant higher stabilities and the influence of the aromatic groups in glycyl-phenylalanine complexes would be expected to be greater in the complex (III) than that of (V) because in the former, the ligand is held more rigidly.



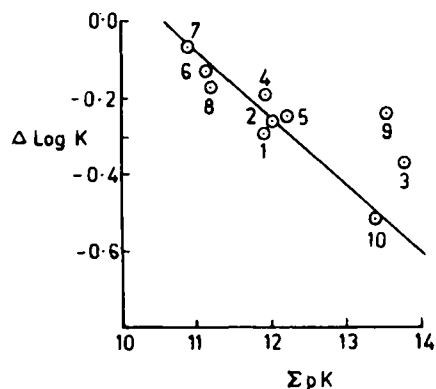


FIGURE 1 Relation between  $\Delta \log K$  and  $\Sigma pK$  for ternary complexes of copper(II)-glycylphenylalanine-amino acids, where amino acids are numbered as same in Table II.

4) On the experimental data relating to the mixed-ligand complex of tyrosine, which contains aromatic substituent group that appears to interact with copper(II). In addition to this, the third potential donor hydroxy group present in aromatic ring of tyrosine do not influence the equilibrium constants of the ternary complex to any appreciable extent.

5) An interesting relationship between complex stability and ligand basicity for estimation of stability constants of ternary complexes is given by Sigel.<sup>28</sup> The relationship has been amply confirmed in subsequent studies involving glycyl-sarcosine and amino acids with copper ion.<sup>15</sup> The plot (Figure 1) gave an inverse relationship between these two quantities, however, the points corresponding to alanine and glutamic acid deviated from straight line.

6) Because exactly the same trends are found in complexes of glycyl-phenylalanine, alanyl-phenylalanine and ternary complexes of these ligands. Certain generalizations are possible. Facially coordinating tridentate ligands in complexes can give efficient three point attachment if the metal ion is not too big, particularly copper(II), in the present investigations. In addition to this, stereoselectivity tends to increase as the degree of substitution increases and as the bulkiness of the substituents increases.

These results taken together, lead to the conclusion that there is strong attractive interaction between copper(II) and the aromatic side chain of glycyl-phenylalanine, particularly in the tridentate nature of the ligand.

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