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Complex Formation in the Ternary Systems: Copper(II)–glycylsarcosine–Amino Acids

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Great attention has been paid to elucidating and identifying the equilibrium constants and the species present in the mixed-ligand complexes of biological systems. The mixed-ligand complexes of Cu^{2+} peptides–amino acids have been studied by Gergely and Nagypal [1]. In the recent years, the mixed-ligand complexes of Cu^{2+} 2,2′ bipyridyl with some dipeptides are reported by Sigel [2] and the stabilities of these complexes are discussed on the basis of substitution of the alkyl group in the peptide. More recently, however, Tamburro *et al.* [3] have studied the metal complexes of cyclo-L-methionyl methionine.

Glycyl sarcosine differs from the others in incorporating a secondary nitrogen into the peptide bond. In spite of numerous studies [4–8] of different copper(II)–dipeptide complexes no systematic study has been made of the complexes formed between a particular dipeptide and the amino acids.

In our laboratory studies on the interaction of metal ions with amino acids, peptides, thiodicarboxylic and pyridine dicarboxylic acids have been undertaken in order to contribute to the mapping of binding sites in metal–dipeptide interactions [9–11]. We report here, in addition to the few data for binary complexes already reported [10], the equilibrium studies on the mixed-ligand complex formation occurring when copper(II) is mixed with glycyl sarcosine and amino acids and to examine the mode of bonding in the complex species involved.

Experimental

The peptide (glycyl sarcosine) was obtained from the Sigma Chemical Co. as Sigma grade. The amino acids such as glycine, α-alanine, β-alanine, phenyl alanine, valine, norvaline, serine, threonine, tyrosine, asparagine, tryptophan, aspartic and glutamic acid were of B.D.H. (AnalaR) and E. Merck (Germany) biochemical grade and purified by repeated crystallization from water alcohol. All standard solutions were prepared in doubly distilled water. The ionic strength was kept constant at 0.1 *M* by the addition of $NaClO_4$. The details regarding the other chemicals and measurements of pH are given in an earlier paper [9, 11].

Results and Discussion

The dissociation constants of the ligands and stability constants of their corresponding copper complexes were evaluated by Irving and Rossotti's method [12] and are reported in Tables I and II together with some literature values. In Table I $K^H_{H_1L}$ refers to protonation of the amine nitrogen aton and $K^H_{H_2L}$ to that of carboxyl group. The value for K^H_{HL} demonstrates that the amino nitrogen atom in glycyl sarcosine is less basic than in the corresponding amino acids. The copper complexes with glycyl sarcosine are less stable than predicted from the results of the other peptides [13]. However, the alkyl group it contains in place of one of the amino hydrogen atoms probably gives rise to a steric effect in the complex formation. The chelation occurs through nitrogen of amino group and oxygen of the peptide, thus glycyl sarcosine acts as bidentate ligand, in agreement with earlier findings [2, 4]. Formation constants for the parent complexes (Table II) were measured under identical experimental conditions as the constants for

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TABLE I. Acidity Constants of Glycyl Sarcosine Peptide and of the Corresponding Binary Copper Complexes (t = 30 °C and μ = 0.1 $NaClO_4$).

Peptide	$pK^H_{H_2L}$	pK^H_{HL}	log K_1 [c]	log K_2 [c]
Glycyl sarcosine	2.77 ± 0.01	8.67 ± 0.03	6.41	5.13
	2.78[a]	8.59[a]	6.34[a]	5.14[a]
	2.98[b]	8.57[b]	6.50[b]	5.14[b]

[a] Ref. 2, 4. [b] Ref. 17. [c] Log K values evaluated by the method of least squares.

TABLE II. Formation Constants (log K) for the Parent Binary Complexes of Copper(II) at 30 °C and μ = 0.1 *M* ($NaClO_4$) Standard deviations are given in parentheses.

Ligand/Acids	Log K_1	Log K_2
Glycine	8.07(2)	6.79(3)
	8.07[a]	6.77[a]
α-alanine	8.09(3)	6.72(4)
	8.07[c]	6.72[c]
	8.04[b]	6.69[b]
β-alanine	7.10(1)	5.40(2)
	7.11[c]	5.40[c]
β-phenylalanine	7.93(3)	6.92(3)
	7.93[d]	6.90[d]
Valine	8.05(2)	6.86(1)
	8.04[d]	6.87[d]
Norvaline	8.05(4)	6.80(2)
	8.07[a]	6.75[a]
Serine	7.85(1)	6.58(3)
	7.85[d]	6.57[d]
Threonine	7.95(4)	6.67(3)
	7.94[d]	6.67[d]
Tyrosine	7.86(2)	6.85(3)
	7.68[b]	6.81[b]
Asparagine	7.80(5)	6.56(1)
	7.86[c]	6.56[c]
Tryptophan	8.00(2)	7.54(3)
	8.02[d]	7.54[d]
Aspartic	8.40[e]	6.75[e]
Glutamic	7.85[e]	6.30[e]

[a]Ref. 15. [b]Ref. 18. [c]Ref. 17. [d]Ref. 4. [e]Ref. 11.

TABLE III. Formation Constants of the Copper (II)–Glycyl-sarcosine–amino acid Complexes, and Equilibrium Constants of the Substitution Process ($CuX_2^- + Y \rightleftharpoons CuXY^- + X^-$) Standard deviations are given in parentheses.

Amino Acids	Log β $CuXY^-$	Δ Log K
Glycine	4.86(2)	−0.27
β-alanine	4.58(3)	−0.55
α-alanine	4.78(2)	−0.35
β-phenylalanine	4.71(1)	−0.42
Valine	4.80(3)	−0.33
Norvaline	4.73(2)	−0.40
Serine	4.64(1)	−0.49
Threonine	4.83(4)	−0.30
Tyrosine	4.69(3)	−0.44
Asparagine	4.66(4)	−0.47
Tryptophan	4.73(2)	−0.40
Aspartic	4.91(3)	−0.22
Glytamic	4.72(2)	−0.41

the ternary complexes to permit the reliable calculations for Δ logK values. The stability constants are close to the comparable value reported in the literature but the values differ at different experimental conditions. The equilibrium constants of the mixed complexes (Table III) were evaluated by the method of Ramamoorthy and Manning as outlined in our earlier paper [9, 11].

Tables I–III give formation constants for the binary and mixed complexes and the equilibrium constants relating to the substitution process (1).

$$CuX_2 + Y^- \rightleftharpoons CuXY^- + X^- \quad (1)$$

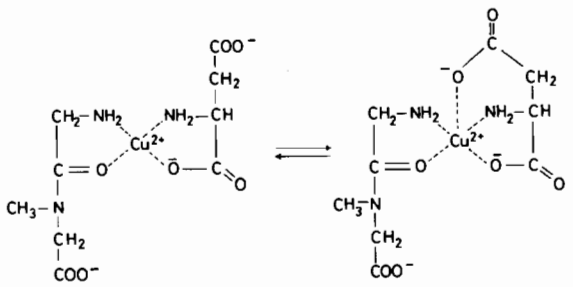
The following conclusions may be drawn from the tabulated data.

i) Glycyl sarcosine does not contain an ionizable protein on its peptide nitrogen atom, hence this nitrogen is essentially non-co-ordinating. As a result the copper(II) glycyl sarcosine equilibrium is much simpler than other peptides.

ii) Considering the steric effects, the copper(II) parent complex of β-alanine is less stable than the complexes of α-amino acids. The stability of the mixed complex follows the same pattern as those of the α-amino acid complexes. The behaviour may be explained by the assumption that the amino acids occupy one equatorial and one axial co-ordination site in the mixed complexes [1].

iii) The relative higher mixed ligand stability, *i.e.* 4.86, is observed in the copper(II) glycyl sarcosine–glycine system than those of the other systems. This phenomenon can be explained by the absence of the alkyl chain, in agreement with the earlier work reported in the literature [14].

iv) In the present investigation, aspartic acid forms mixed complex with glycyl sarcosine peptide, attributed to the fact that this ligand is capable of both glycine and β-alanine co-ordination. Aspartic acid is reported in the literature both as bidentate and tridentate ligand [15]. In our earlier work on mixed ligand complexes of metal ions, we also reported the tridentate nature of the dipicolinic and aspartic acids [11]. Taking into account the above considerations, therefore, it may be assumed that in the CuX_2-type aspartic acid parent complex the donor atoms occupy five co-ordination sites of the copper(II) ion. On the basis of statistical considerations, a higher number of co-ordination possibilities is associated with the stability increase. As glycyl sarcosine, bidentate ligand occupies equatorial position and for aspartic acid, β-alanine like equatorial-axial co-ordination, there is a change in the structural rearrangement, resulting in the highest stability of the mixed complex.



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v) A method for the estimation of stability constants by the relation between ligand basicity and complex stability has been also thoroughly discussed by Sigel [16]. In the present work, the plot of $\Delta\log K$ *vs.* Σ pK gave an inverse relationship between these two quantities. However, the points corresponding to alanine, serine, threonine and glutamic acid deviated from the straight line.

vi) On the basis of equilibrium constant data for mixed complexes of serine, tyrosine, aspargine, threonine and glutamic acid do not influence the equilibrium conditions to any appreciable extent as they contain the third potential donor groups.

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