Coordination Selectivity in the Mixed-Ligand Formation of Copper(II)–Glycyl-DL-Serine with some Amino Acids

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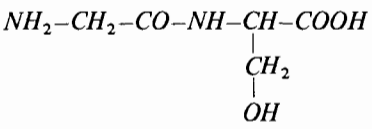
Binary and ternary complexes of Cu(II) with dipeptides containing amide carbonyl, alcoholic hydroxy and carboxy groups in the side chain have been studied. The peptide (X ligand) was glycyl-DL-serine (gly-ser) and one of the amino acids, glycine, alanine, valine, threonine, serine, asparagine, tyrosine, aspartic and glutamic acids, was used as Y ligand. In the mixed-ligand complexes containing aspartic acid, it has been pointed out that the amino acid occupies one equatorial and one axial site in the coordination sphere of the copper(II) and at higher pH the carboxylate oxygen of the peptide glycyl-DL-serine is replaced by the deprotonated alcoholate (O^-).

Considerable attention has been paid in recent years to the coordination behaviour of dipeptides in their copper(II) binary and ternary complexes [1, 2]. The main interest is the influence of side chain donor groups on complex formation [3, 4]. Martin and co-workers [5] have established that in basic solution the side-chain amide of glycyl-asparagine undergoes hydrogen ionization, followed by amide nitrogen bonding to copper(II). No such effect was observed for the alcoholate group of glycyl-DL-serine. Glycyl-DL-serine, (glycyl-2-amino-3-hydroxy propionic acid),



is of interest for complexation studies, as it contains five bonding sites, thus exhibiting a number of possibilities for the formation of complexes of different bonding types. On the basis of our previous studies [6] and in an attempt to clarify the nature of dipeptide–cation interaction, we have studied the mixed-ligand complexes of copper(II)–dipeptides–amino acids [7–11], particularly the interaction of the aromatic group with metal ion glycyl-phenyl alanine complexes [7]. We undertook this work to study the effect of the hydroxy group on the complexation equilibria and the mode of binding of glycyl-serine in binary and ternary complex species.

Experimental

The peptide (glycyl-DL-serine) was purchased from Sigma Chemical Co. as Sigma grade. The amino acids, glycine, α-alanine, valine (E. Merck, Germany), serine, threonine, asparagine, tyrosine (B.D.H., AnalaR), glutamic and aspartic acids (Fluka, purum) were of the highest purity available from each Chemical Co. and were used without further purification. Copper was taken as perchlorate and its concentration estimated as described previously [6, 12]. Glass-distilled water was used in the preparation of solutions.

Copper complex formation constants were evaluated from potentiometric titration curves of glycyl-DL-serine and amino acids in the absence and presence of copper(II). Changes in pH were followed using glass and calomel electrodes and a ELICO Digital pH meter (L1-10 No. 1275). The accuracy of the pH meter was ±0.01 pH unit. The pH meter was standardised before each titration using a buffer solution of potassium hydrogen phthalate (pH 4.01 at 30 °C). The glass electrode was calibrated in terms of hydrogen ion concentrations and titrations were carried out at 30 °C with an ionic background of 0.10 mol dm^{-3} ($NaClO_4$). Calculations were made with the aid of a computer program outlined in our earlier papers [7, 10]. All computations were carried out at the Tata Institute of Fundamental Research, Bombay.

Results and Discussion

The numerical methods used to evaluate the acid dissociation constants of glycyl-DL-serine and the formation constants of the corresponding binary complexes with copper(II) have been described in earlier publications [7, 10]. The stability constant data reported in Table I for these complexes agree well with the literature data, after making allowances for the changes in experimental conditions. The formation constants for $CuXYH_{-1}$ are an average of 10 sets and are accurate to ±0.05 log units. The accuracy of Δ log K would, therefore, be within the same range.

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TABLE I. Acidity Constants of Glycyl-DL-serine Peptide and Corresponding Copper(II) Binary Complexes. T = 30 °C; μ = 0.1 mol dm^{-3} ($NaClO_4$). (Standard deviations are given in parentheses).

Peptide	$pK^{H}_{H_2X}$	pK^{H}_{HX}	MX	M(X–H) ($CuXH_{-1}$)	MX(X–H) (CuX_2H_{-1})
Glycyl-DL-serine	2.99(2)	8.14(1)	5.66(2)	1.65(2)	4.64(3)
	2.99[a]	8.14[a]	5.66[a]		
		8.09[b]	5.66[b]	1.64[b]	4.64[b]
	2.978[c]	8.16[c]			

[a]Ref. 23. [b]Ref. 3. [c]Ref. 24.

It can be stated from Table I that the pK value of the glycyl-D-serine carboxy group decreases to some extent, because of the electron withdrawing effect of the hydroxy group. The side chain shows a distinct influence of the equilibrium constants of the complexes. Increasing the side chain leads to lower stability of the complex which is also shown by the commencement of complex formation at higher pH values. Complex formation with glycyl-DL-serine begins with the coordination of the donor atom of the terminal NH_2 group and carbonyl oxygen of the neighbouring amide group. It has been established that the metal ion and three donor atoms are virtually coplanar [13] and the complex CuX(X-H) has a basically planar structure [14–16] so will bond through its amino and deprotonated amide nitrogen atoms and the carboxyl oxygen. Brookes and Pettit [17, 18] as well as Gergely and Nagypal [15, 19] describe further species CuX, $CuXH_{-1}$, $CuXH_{-2}$ and CuX_2H_{-1} in which one or two peptide protons are dissociated. Brookes and Pettit [17] tried to find a comprehensive model which would hold for a wide range of pH. They suggested three models, among which no further selection seemed to be possible, at least in the case of binary bis complexes of the dipeptides.

In ternary complexes with increase in pH, the amide group of the dipeptide (glycyl-DL-serine) becomes deprotonated and $CuXYH_{-1}$ ternary complexes are formed. Regarding the mode of bonding of the peptide, one may expect bidentate and tridentate bonding of glycyl-DL-serine in the $CuXYH_{-1}$ complexes also, as in the binary bis complexes. This may be easily accounted for by considering the bidentate bonding of the amide-deprotonated glycyl-DL-serine *via* the N-amino and N-peptide group in the $CuXYH_{-1}$ complexes (structure I) and its bonding in a tridentate manner (II) *via* N-amino, N-peptide and O-carboxylate groups in the $CuXH_{-1}$ binary complex [17, 19], *i.e.* for computing $\Delta \log K^{CuX_2H_{-1}}_{CuXYH_{-1}}$ and $\Delta \log K^{CuXH_{-1}}_{CuXYH_{-1}}$ using equations (1–4).

$$CuX_2H_{-1} + Y \rightleftharpoons CuXYH_{-1} + X \quad (1)$$

$$\Delta \log K^{CuX_2H_{-1}}_{CuXYH_{-1}} = \log \beta\, CuXYH_{-1} - \log \beta\, CuX_2H_{-1} \quad (2)$$

$$CuXH_{-1} + Y \rightleftharpoons CuXYH_{-1} \quad (3)$$

$$\Delta \log K^{CuXH_{-1}}_{CuXYH_{-1}} = \log \beta\, CuXYH_{-1} - \log \beta\, CuXH_{-1} \quad (4)$$

The log β $CuXH_{-1}$ value used was that for tridentate bonding of the amide-deprotonated glycyl-DL-serine in its $CuXH_{-1}$ binary complex irrespective of its bidentate bonding in the $CuXYH_{-1}$ ternary complex species. Thus $\Delta \log K^{CuX_2H_{-1}}_{CuXYH_{-1}}$ value is reduced by *ca.* 3 log units with respect to $\Delta \log K^{CuXH_{-1}}_{CuXYH_{-1}}$ in all the systems.

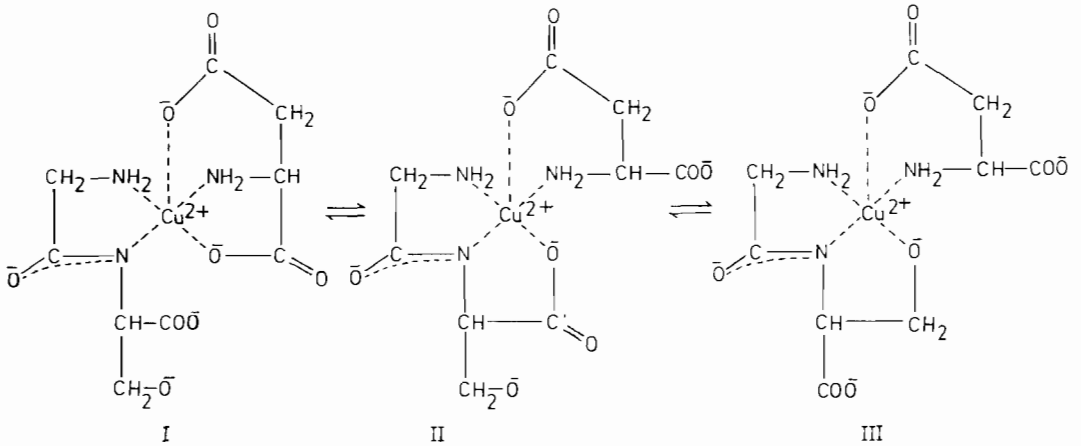

TABLE II. Stability Constants and Derived Constants of the Mixed-Ligand Complexes of the Copper(II)–Glycyl-DL-serine(X)–amino acid(Y) Systems. T = 30 °C; μ = 0.1 mol dm^{-3} ($NaClO_4$) (standard deviations are given in parentheses).

Amino acid	log β $CuXYH_{-1}$	$\Delta \log K^{CuX_2H_{-1}}_{CuXYH_{-1}}$	$\Delta \log K^{CuXH_{-1}}_{CuXYH_{-1}}$
Glycine	4.98(1)	0.34	3.33
DL-α-Alanine	4.94(2)	0.30	3.29
DL-Valine	4.89(2)	0.25	3.24
L-Threonine	4.73(3)	0.09	3.08
DL-Serine	4.78(2)	0.14	3.13
L-Asparagine	4.68(2)	0.04	3.03
L-Tyrosine	4.80(2)	0.16	3.15
L-Aspartic	5.38(3)	0.74	3.73
L-Glutamic	4.99(2)	0.35	3.34

Table II gives the stability constants for mixed-ligand complexes ($CuXYH_{-1}$) and derived constants relating to the substitution and addition process. Further analysis of the tabulated data suggests several final details of mixed-ligand formation.

(*i*) Δ log K values in all the systems indicate that the ternary complexes are more stable than the corresponding binary ones. It is clear from Table II that the derived constants relating to the processes (1 and 3) are smaller for asparagine than for the other amino acids. This observation supports the assumption that mixed-ligand complex formation with asparagine is less favoured.

(*ii*) The data in Table II was used to plot complex stability (Δ log K) against ligand basicity (ΣpK). A straight line relationship of positive slope was observed. These conclusions have been confirmed in subsequent studies of mixed-ligand complexes [20].

(*iii*) The experimental data relating to the mixed-ligand complex of glycine show that it forms more stable mixed complexes than those of other amino acids.

The absence of the alkyl chain in glycine indicates its relatively high stability [21].

(*iv*) Aspartic acid exhibits enhanced stability in mixed ternary complexes with dipeptides [19] including glycyl-phenylalanine [7]. The enhanced stability of the ternary aspartic–Cu(II)–glycyl-serine complex over the binary Cu(II)–glycyl-serine is consistent with the principle of mixed-ligand complex formation. An additional factor favouring complexation of this system is the presence of the hydroxy group in the peptide, which appears to interact with copper(II). The only effects the substituents can have will be through their inductive effect and the influence of the hydroxy group in glycyl-serine complexes would be expected to be greater in complex (II) than in (I), because, in the former, the ligand is held more rigidly.

Kozłowski and Siatacki [22] concluded that at high pH the carboxylate oxygen is replaced by the deprotonated alcoholate (O^-) donor atom in bonding to copper(II) at least in the case of alanyl-serine. Sigel *et al.* [23] also suggested the participation of the hydroxy group in complex formation on the basis of stability constant data.

The significantly higher value, *i.e.* 0.74, for complex stability of the glycyl-serine–Cu(II)–aspartic acid system accompanied by high stability of the ternary complex may be due to the replacement of the carboxylate oxygen by the deprotonated alcoholate donor atom with the formation of a mixed complex (III) at high pH as a result of the subsequent structural rearrangement. These findings are supported both by the data to be found in the literature [22, 23] and by the equilibrium constant data in Table II as well as in our earlier work [10].

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