Effect of Copper(II) Ternary Complex Formation on the Co-ordination Behaviour of Dipeptides in Aqueous Solution

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By evaluating the multiple equilibria involved in the copper(II)–glycylglycine (GlyGly) or glycinamide (Glam) (A)–DL-2-aminobutyric acid (2-aba), DL-3-aminobutyric acid (3-aba), DL-2,3-diaminopropionic acid (dapa), DL-2,4-diaminobutyric acid (daba), and DL-ornithine (Orn) (B), and also copper(II)–GlyGly (A)–Glam (B) ternary systems under biologically important conditions by potentiometry using advanced computer techniques, the tendency to complexation of dipeptides in the ternary complex species of the type CuABH, CuAB, $CuABH_{-1}$, and $CuABH_{-2}$ is discussed. It appears that the extra proton in the CuABH complexes in copper(II)–GlyGly or Glam (A)–dapa, daba, and Orn (B) systems resides with the ligand B. In the CuABH and CuAB types of complexes, co-ordination of the dipeptides (A) gives a five-membered chelate ring involving a terminal amino-moiety and an oxygen of the neighbouring amide group. The present investigation shows that the amide-deprotonated dipeptides (AH_{-1}) are bidentate in the $CuABH_{-1}$ and $CuABH_{-2}$ ternary complexes when the ligand B is bidentate or tridentate.

In recent years, considerable attention has been paid to the co-ordination behaviour of dipeptides in their copper(II) binary and ternary complexes, towards a better understanding of metal ion–enzyme–substrate complexes.[1,2] It was generally accepted[1-12] that initial complex formation between a dipeptide and copper(II) in both the binary and ternary systems results in a chelate involving a terminal amino-moiety and oxygen of the neighbouring amide group. At higher pH values, the dipeptide undergoes deprotonation of the amide group and it becomes tridentate *via* *N*-amino, *N*-peptido, and *O*-carboxylate groups as in the $CuAH_{-1}$ glycylglycinate (GlyGlyO) binary complex species.[3,4,8]

TABLE 1

Stability constant data for the copper(II)–2-aba, 3-aba, dapa, daba, Orn, GlyGly, and Glam binary systems at 37 °C and $I = 0.15$ mol dm^{-3} ($Na[ClO_4]$). Standard deviations are given in parentheses

	Ligands B						
	2-aba [a]	3-aba [a]	dapa [b]	daba [b]	Orn [b]	GlyGly [c,d]	Glam [c,d]
log β_{HB}	9.43(1)	9.95(1)	9.37(2)	9.93(2)	10.22(1)	7.99(1)	7.89(1)
log β_{H_2B}	11.54(1)	13.30(1)	15.98(3)	18.02(4)	18.85(2)	11.26(1)	—
log β_{H_3B}	—	—	17.37(5)	19.88(6)	20.99(4)	—	—
log β_{CuBH}	—	—	15.37(4)	16.99(3)	17.67(2)	—	—
log β_{CuB}	8.10(2)	7.16(2)	10.61(4)	10.94(3)	—	5.70(8)	5.53(5)
log $\beta_{CuB_2H_2}$	—	—	30.16(5)	32.92(4)	34.32(3)	—	—
log β_{CuB_2H}	—	—	25.32(6)	26.89(4)	26.12(6)	—	—
log β_{CuB_2}	15.13(4)	12.90(5)	20.18(5)	19.15(6)	—	—	—
log $\beta_{CuBH_{-1}}$	—	—	—	—	—	1.62(2)	−1.14(9)
log $\beta_{CuB_2H_{-1}}$	—	—	—	—	—	5.50(10)	3.18(9)

[a] Refs. 19 and 20. [b] Ref. 13. [c] Refs. 8 and 20. [d] GlyGly and Glam become primary ligands A in the ternary systems (Tables 2 and 3). However, Glam is the secondary ligand B in the copper(II)–GlyGly (A)–Glam (B) ternary system.

However, interpretations with regard to the bonding mode of amide-deprotonated dipeptides in the ternary complex systems of copper(II) differ. Several workers[4,9,10] are of the view that the amide-deprotonated dipeptides are bidentate *via* *N*-amino- and *N*-peptido-groups in the copper(II) ternary complex systems. Others[9,11,12] favour the tridentate binding through *N*-amino, *N*-peptido, and *O*-carboxylate groups in the ternary systems, as is also the case with the $CuAH_{-1}$ GlyGlyO binary complex species. By considering these points, I thought it worthwhile to study the stability and structure of various ternary complex species for some copper(II)–glycylglycine (GlyGly) or glycinamide (Glam) (A)–amino-acid (B) systems. The compound Glam resembles a dipeptide without a carboxyl group. The amino-acids (B) chosen are DL-2-aminobutyric acid (2-aba), DL-3-aminobutyric acid (3-aba), DL-2,3-diaminopropionic acid (dapa), DL-2,4-diaminobutyric acid (daba), and DL-ornithine (Orn). In addition to these ten ternary systems, the copper(II)–GlyGly (A)–Glam (B) system was also studied. All these investigations were carried out by potentiometry at 37 °C and $I = 0.15$ mol dm^{-3} ($Na[ClO_4]$) in aqueous perchlorate media.

EXPERIMENTAL

Solutions of all the ligands (Fluka Puriss) were prepared immediately before use in doubly-distilled water from materials dried under vacuum over P_2O_5. Copper(II) perchlorate solution was prepared by neutralising copper(II) carbonate with perchloric acid. The concentration of the metal stock solution was determined by titration with ethylenediaminetetra-acetate. Acid-washed glassware and reagent grade chemicals were used throughout the work.

Examinations by potentiometry were made at 37 °C under nitrogen with 0.15 mol dm^{-3} $Na[ClO_4]$ as background electrolyte. The equipment and electrode standardisation procedures have been described elsewhere.[13-17] The stability constants for the ternary systems were computed from titrations in which total concentrations of the metal, ligand A, and ligand B were in 1 : 1 : 1 and 1 : 2 : 2 molar ratios.

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The potentiometric data were treated with the MINIQUAD-75 computer program [18] on an IBM-370 computer. While refining the ternary complex constants, the values of overall protonation constants of the ligands A and B, and the overall association constants of the parent binary complex species [8,13,19,20] measured at 37 °C and $I = 0.15$ mol dm^{-3} (Na[ClO$_4$]) by potentiometry using MINIQUAD-75 (Table 1), were fixed without further refinement. The ionic product of water, *i.e.* the pK_w value of 13.62 at 37 °C, was also treated as a non-refinable parameter. The model selected was that which gave the best statistical fit, consistent with chemical logic, to the titration data without giving any systematic drifts in the magnitudes of various residuals as described elsewhere.[18] The results obtained are listed in Tables 2 and 3. The charges of all the complex species reported in this paper are omitted for clarity.

RESULTS AND DISCUSSION

The copper(II)–GlyGly or Glam (A)–2-aba and 3-aba (B) systems showed the presence of two ternary complexes (CuAB and CuABH$_{-1}$) in addition to the binary complex species [HA, CuA, CuAH$_{-1}$, CuA$_2$H$_{-1}$, HB, H$_2$B, CuB, CuB$_2$, and also H$_2$A in the GlyGly (A) ligand systems]. In the copper(II)-GlyGly or Glam (A)-dapa, daba, and Orn (B) systems, three ternary complex species of stoicheiometry CuABH, CuAB, and CuABH$_{-1}$ were evident in addition to the binary species [HA, CuA, CuAH$_{-1}$, CuA$_2$H$_{-1}$, HB, H$_2$B, H$_3$B, CuBH, CuB$_2$H$_2$, CuB$_2$H; also H$_2$A in the GlyGly (A) ligand systems, and CuB and CuB$_2$ in the dapa, daba (B) ligand systems]. The CuAB, CuABH$_{-1}$, and CuABH$_{-2}$ ternary complexes were detected in the copper(II)–GlyGly (A)–Glam (B) system in addition to the binary complexes (HA, H$_2$A, CuA, CuAH$_{-1}$, CuA$_2$H$_{-1}$, HB, CuB, CuBH$_{-1}$, and CuBH$_{-2}$).

1. *Stability and Structure of the* CuABH *Ternary Complexes in Copper*(II)–GlyGly *or* Glam (A)–dapa, daba, *and* Orn (B) *Systems*.—It appears more reasonable to suggest that the extra proton in the CuABH complexes in all the six ternary systems mentioned above resides with the dapa, daba, or Orn secondary ligands (B), because in the copper(II)–GlyGly or Glam (A) binary systems, no protonated species were detected.[8,20] It has already been established [13,21,22] that the site of protonation in the CuBH or CuB$_2$H dapa, daba, and Orn complexes is their respective terminal amino-groups. Hence it may be inferred that in the CuABH complexes detected in the systems also under study, the extra proton is attached to the terminal amino-group of the dapa, daba, or Orn (B) ligands. The same point may further be confirmed by noting that the log β_{CuABH}, pK^{H}_{CuABH}, and log K^{CuA}_{CuABH} values in Tables 2 and 3 follow the trends of the log β_{HB} or log β_{CuBH} values in Table 1 for the copper(II)–dapa, daba, or Orn (B) binary systems. The log K^{CuBH}_{CuABH} values in Table 2 for the copper(II)–GlyGly (A)–dapa, daba, and Orn (B) systems are comparable to the log β_{CuB} value in Table 1 for the copper(II)–GlyGly binary system suggesting that GlyGly is bidentate *via* *N*-amino- and *O*-peptido-groups in these CuABH ternary complexes. Thus, the CuABH complexes in the copper(II)–GlyGly (A)–dapa, daba, and Orn (B) systems would have enhanced stability due to the electrostatic interaction between the terminal $^-NH_3{}^+$ group of the B ligand and the unbound COO$^-$ group of GlyGly (A). However, such interactions are not possible in the CuABH complexes in copper(II)–Glam (A)–dapa, daba, and Orn (B) systems because Glam (A) does not contain a COO$^-$ group.

TABLE 2

Stability constants for the copper(II)-GlyGly(A)-secondary ligand(B) systems at 37 °C and $I = 0.15$ mol dm^{-3} (Na[ClO$_4$]). Standard deviations are given in parentheses

	Secondary ligands B					
	2-aba	3-aba	dapa	daba	Orn	Glam
log β_{CuABH}	—	—	20.92(10)	22.58(5)	23.25(9)	—
log β_{CuAB}	13.40(10)	12.94(17)	16.05(12)	16.11(4)	16.55(10)	11.25(8)
log $\beta_{CuABH_{-1}}$	6.54(7)	5.91(5)	8.79(4)	8.49(4)	8.28(22)	4.19(10)
log $\beta_{CuABH_{-2}}$	—	—	—	—	—	−2.74(15)
pK^{H}_{CuABH}	—	—	4.87	6.47	6.70	—
log K^{CuA}_{CuABH}	—	—	15.22	16.88	17.55	—
log K^{CuBH}_{CuABH}	—	—	5.55	5.59	5.58	—
Δ log K_{CuABH}	—	—	−0.15	−0.11	−0.12	—
log K^{CuA}_{CuAB}	7.70	7.24	10.35	10.41	10.85	5.55
log K^{CuB}_{CuAB}	5.30	5.78	5.44	5.17	—	5.68
Δ log K_{CuAB}	−0.40	0.08	−0.26	−0.53	—	0.02
pK^{H}_{CuAB}	6.86	7.03	7.26	7.62	8.27	7.06
log $K^{CuAH_{-1}}_{CuABH_{-1}}$	4.92	4.29	7.17	6.87	6.66	2.57
log $K^{CuB}_{CuABH_{-1}}$	−1.56	−1.25	−1.82	−2.45	—	−1.34
Δ log $K_{CuABH_{-1}}$	−3.18	−2.87	−3.44	−4.07	—	−2.96
p$K^{H}_{CuABH_{-1}}$	—	—	—	—	—	6.93
Δ log $K_{CuABH_{-2}}$	—	—	—	—	—	−3.22

In order to characterise the stability of the CuABH ternary complex with that of the binary complexes CuA or CuBH, the parameter Δ log K_{CuABH} was calculated using equation (2) for the equilibrium reaction (1). For copper(II) having a square-planar co-ordination sphere to which two bidentate ligands co-ordinate, on statistical grounds [2,23,24] a Δ log K value of −0.6 is expected and

TABLE 3

Stability constants for the copper(II)–Glam (A)–secondary ligand (B) systems at 37 °C and $I = 0.15$ mol dm^{-3} (Na[ClO$_4$]). Standard deviations are given in parentheses

	Secondary ligands B				
	2-aba	3-aba	dapa	daba	Orn
$\log \beta_{CuABH}$	—	—	20.07(43)	21.82(4)	22.11(8)
$\log \beta_{CuAB}$	12.64(9)	11.89(9)	15.30(8)	15.58(3)	14.95(7)
$\log \beta_{CuABH_{-1}}$	5.71(5)	4.89(4)	8.14(4)	8.10(2)	6.65(8)
$\mathrm{p}K^{H}_{CuABH_{-1}}$	—	—	4.77	6.24	7.16
$\log K^{CuA}_{CuABH}$	—	—	14.44	16.29	16.58
$\log K^{CuBH}_{CuABH}$	—	—	4.70	4.83	4.44
$\Delta \log K_{CuABH}$	—	—	−0.83	−0.70	−1.09
$\log K^{CuA}_{CuAB}$	7.11	6.36	9.77	10.05	9.42
$\log K^{CuB}_{CuAB}$	4.54	4.73	4.69	4.64	—
$\Delta \log K_{CuAB}$	−0.99	−0.80	−0.66	−0.89	—
$\mathrm{p}K^{H}_{CuAB}$	6.93	7.00	7.16	7.48	8.30
$\log K^{CuAH_{-1}}_{CuABH_{-1}}$	6.85	6.03	9.28	9.24	7.79
$\log K^{CuB}_{CuABH_{-1}}$	−2.39	−2.27	−2.47	−2.84	—
$\Delta \log K_{CuABH_{-1}}$	−1.25	−1.13	−1.33	−1.70	—

values greater than this indicate higher stability of the

$$\mathrm{CuA} + \mathrm{CuBH} \rightleftharpoons \mathrm{CuABH} + \mathrm{Cu} \qquad (1)$$

$$\Delta \log K_{CuABH} = \log \beta_{CuABH} - (\log \beta_{CuA} + \log \beta_{CuBH}) \qquad (2)$$

ternary complexes than the binary complexes. The $\Delta \log K_{CuABH}$ values in Table 2 for the copper(II)–GlyGly (A)–dapa, daba, and Orn (B) systems follow this trend. However, the same parameter in Table 3 for the CuABH complexes in the ternary systems with (A) = Glam suggest that they do not have marked stabilities.

2. *Stability and Structure of* CuAB *Ternary Complexes in the Systems under Study.*—As in the monoprotonated ternary complexes CuABH discussed above, it is clear from the $\log K^{CuB}_{CuAB}$ values in Tables 2 and 3 that in the CuAB complexes in all these ternary systems the GlyGly or Glam (A) ligand binds the metal in a bidentate mode *via* *N*-amino- and *O*-peptido-groups. The $\log K^{CuA}_{CuAB}$ values in Tables 2 and 3 for the systems with (B) = 2-aba and 3-aba agree closely with the corresponding $\log \beta_{CuB}$ values in Table 1 for the copper(II)–2-aba and 3-aba (B) binary systems, demonstrating that bonding of 2-aba and 3-aba in the CuAB ternary complexes in the presence of GlyGly or Glam (A) ligands involves respectively five- and six-membered chelate rings. Thus, the copper(II)–GlyGly or Glam (A)–2-aba and 3-aba (B) systems would respectively contain five- and five-, and five- and six-membered chelate rings, of which the latter would be more preferred [2,19,20,23-25] due to the fact that the rings of different sizes introduce more ligand-field asymmetry and stabilize the ternary complexes. Also, it may be concluded from the $\log K^{CuA}_{CuAB}$ values in Tables 2 and 3 for the copper(II)–GlyGly or Glam (A)–dapa, daba, and Orn (B) systems that all these secondary ligands (B) are tridentate in their CuAB complexes. The $\log K^{CuB}_{CuAB}$ and $\log K^{CuA}_{CuAB}$ values in Table 2 for the copper(II)–GlyGly (A)–Glam (B) system clearly indicate that both GlyGly (A) and Glam (B) are bidentate in the CuAB complex resulting in two five-membered chelate rings. Thus, the copper(II)–GlyGly or Glam (A)–2-aba and 3-aba, and also copper(II)–GlyGly (A)–Glam (B) ternary systems would have a square-planar geometry, and hence a $\Delta \log K_{CuAB}$ value [equations (3) and (4)] of −0.6 is expected. However, in the copper(II)–GlyGly or Glam (A)–dapa, daba, and Orn (B) systems, the statistically expected value [2,19,24] of $\Delta \log K_{CuAB}$ is −0.9, because the co-ordination sphere of copper(II) in these complexes becomes distorted due to the tridentate binding of the dapa, daba, or Orn (B) ligands. Comparison of the $\Delta \log K_{CuAB}$ values for the copper(II)–GlyGly (A)–secondary ligand (B) systems in Table 2 with the above statistically expected values clearly demonstrates that the CuAB complexes in all these six ternary systems do have marked stabilities. However, the $\Delta \log K_{CuAB}$ values in Table 3

$$\mathrm{CuA} + \mathrm{CuB} \rightleftharpoons \mathrm{CuAB} + \mathrm{Cu} \qquad (3)$$

$$\Delta \log K_{CuAB} = \log \beta_{CuAB} - (\log \beta_{CuA} + \log \beta_{CuB}) \qquad (4)$$

for the systems with (A) = Glam do not deviate much from their statistically expected values. The positive $\Delta \log K_{CuAB}$ values obtained in the copper(II)–GlyGly (A)–3-aba and Glam (B) ternary systems (Table 2) suggest that 3-aba or Glam (B) prefers to add to the CuA GlyGly binary complex rather than to aquated copper(II). Again, it may be noted from Tables 2 and 3 that $\Delta \log K_{CuAB}$ values for the copper(II)–GlyGly or Glam (A)–3-aba (B) systems are more positive compared to those values for the copper(II)–GlyGly or Glam (A)–2-aba (B) systems. This may be attributed to the preference for five- and six-membered chelate rings in the former systems compared to the five- and five-membered chelate rings in the latter as described earlier.

3. *Stability and Structure of* CuABH$_{-1}$ *Ternary Complexes.*—With rise in pH, the amide group of the dipeptides [GlyGly or Glam (A)] becomes deprotonated and CuABH$_{-1}$ ternary complexes are formed. A question arises with regard to the mode of bonding of these amide-deprotonated dipeptides (AH$_{-1}$) and the secondary ligands (B). Regarding the mode of bonding of the secondary ligands (B), one may expect the bidentate binding of 2-aba and 3-aba, and tridentate binding of

dapa, daba, and Orn (B) in the $CuABH_{-1}$ complexes also, as their binding in CuAB complexes in the copper(II)–GlyGly or Glam (A)–2-aba, 3-aba, dapa, daba, and Orn (B) systems described above. If so, the log K^{CuA}_{CuAB} and log $K^{CuAH_{-1}}_{CuABH_{-1}}$ values in each of these systems must be comparable. But it may be noted from Tables 2 and 3 that the copper(II)–Glam (A)–(B) systems follow this trend, while in the copper(II)–GlyGly (A)–(B) systems the log $K^{CuAH_{-1}}_{CuABH_{-}}$ values in all the systems are *ca.* 3 log units less than the corresponding value for log K^{CuA}_{CuAB}. This may be easily accounted for by considering the bidentate binding of the amide-deprotonated GlyGly *via* *N*-amino and *N*-peptide groups in the $CuABH_{-1}$ complexes unlike its binding in a tridentate manner *via* *N*-amino, *N*-peptide, and *O*-carboxylate groups in the $CuAH_{-1}$ GlyGly binary complex; [4,8] *i.e.* for computing log $K^{CuAH_{-1}}_{CuABH_{-1}}$ using equation (5), the log $\beta_{CuAH_{-1}}$ value used was that for the tridentate binding of the amide-deprotonated GlyGly in its $CuAH_{-1}$ binary complex irrespective of its bidentate binding in the $CuABH_{-1}$ ternary complex species. Thus, log $K^{CuAH_{-1}}_{CuABH_{-1}}$ values get reduced by *ca.* 3 log units in all the systems. This bidentate binding of the amide-deprotonated GlyGly in the ternary systems under study may further be confirmed by noting that the pK^{H}_{CuAB} values in all the copper(II)–GlyGly (A)–(B) systems in Table 2 are nearly identical within the limits of experimental error to those values in Table 3 for the corresponding copper(II)–Glam (A)–(B) ternary systems, *i.e.* the bonding modes of amide-deprotonated GlyGly and Glam are same in the $CuABH_{-1}$ complexes in all the ternary systems reported here. If the carboxylate group of amide-deprotonated GlyGly is also co-ordinated with the metal in its $CuABH_{-1}$ ternary species, then it should have been reflected in the pK^{H}_{CuAB} value as is the case with pK^{H}_{CuA} values in the copper(II)–GlyGly and Glam (A) binary systems.[4,8]

$$\log K^{CuAH_{-1}}_{CuABH_{-1}} = \log \beta_{CuABH_{-1}} - \log \beta_{CuAH_{-1}} \qquad (5)$$

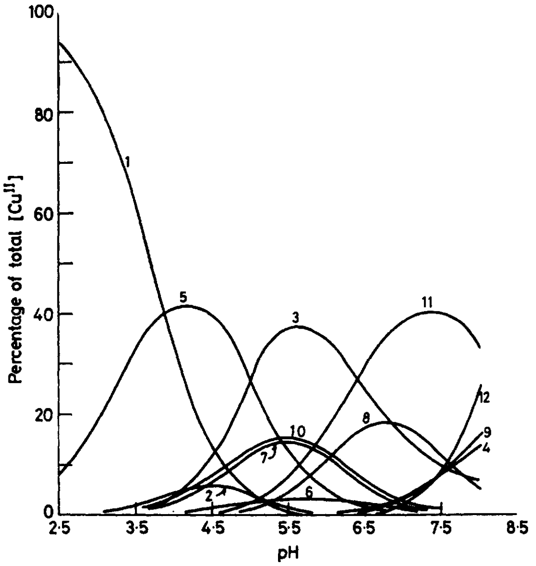

FIGURE 1 Species distribution for the copper(II)–GlyGly(A)–daba (B) ternary system at a metal : A : B ratio 1 : 1 : 1: (1) unbound copper(II), (2) CuA, (3) $CuAH_{-1}$, (4) CuA_2H_{-1}, (5) CuBH, (6) CuB, (7) CuB_2H_2, (8) CuB_2H, (9) CuB_2, (10) CuABH, (11) CuAB, and (12) $CuABH_{-1}$

The different mode of bonding of amide-deprotonated GlyGly in the $CuAH_{-1}$ binary and $CuABH_{-1}$ ternary complex species is also reflected in the Δ log $K_{CuABH_{-1}}$ values in Table 2; *i.e.* this parameter is negative with high magnitude which may be explained by considering the fact that for calculating Δ log $K_{CuABH_{-1}}$ using equation (7), the log $\beta_{CuAH_{-1}}$ value used was that for the tridentate binding of the amide-deprotonated GlyGly in

$$CuAH_{-1} + CuB \rightleftharpoons CuABH_{-1} + Cu \qquad (6)$$

$$\Delta \log K_{CuABH_{-1}} = \log \beta_{CuABH_{-1}} - (\log \beta_{CuAH_{-1}} + \log \beta_{CuB}) \qquad (7)$$

its $CuAH_{-1}$ binary complex, although it is bidentate in the $CuABH_{-1}$ ternary complex species.

With regard to the ternary complexes, $CuABH_{-1}$ and $CuABH_{-2}$ in the copper(II)–GlyGly (A)–Glam (B) system, it seems that the $CuABH_{-1}$ complex is formed due to the deprotonation of the amide group of GlyGly (A) because the discrepancies described above in the log $K^{CuAH_{-1}}_{CuABH_{-1}}$ and Δ log $K_{CuABH_{-1}}$ values in copper(II)–GlyGly (A)–2-aba, 3-aba, dapa, daba, and Orn (B) systems are also seen in these values in Table 2 for the copper(II)–GlyGly (A)–Glam (B) ternary system. In the $CuABH_{-2}$ species in this system, one may easily suggest that the amide group of both GlyGly (A) and Glam (B) is deprotonated and thus this complex species would have a square-planar geometry where the four positions would be filled up by the amino- and peptido-nitrogens of GlyGly (A)

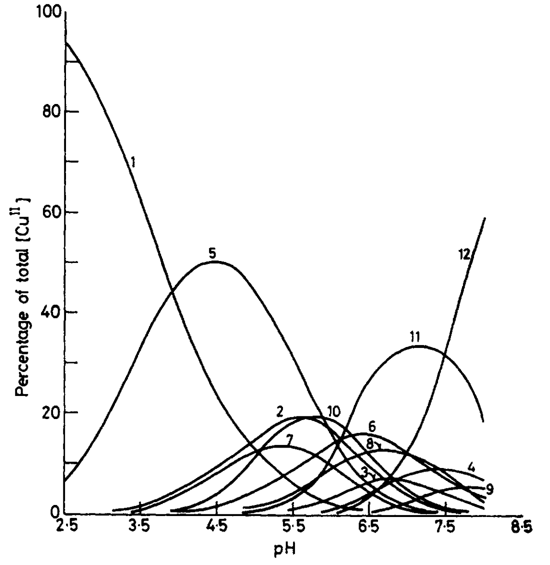

FIGURE 2 Species distribution for the copper(II)–Glam (A)–daba (B) ternary system at a metal : A : B ratio of 1 : 1 : 1. Species as in Figure 1

and Glam (B) ligands. The comparable pK^{H}_{CuAB} and $pK^{H}_{CuABH_{-1}}$ values in Table 2 for this system further confirms that both the amide-deprotonated GlyGly (A) and Glam (B) are bidentate in its $CuABH_{-2}$ complex. The parameter $\Delta \log K_{CuABH_{-2}}$ included in Table 2 was computed using equation (9). This value is more negative, which may be accounted by putting forward the same

$$CuAH_{-1} + CuBH_{-1} \rightleftharpoons CuABH_{-2} + Cu \qquad (8)$$

$$\Delta \log K_{CuABH_{-2}} = \log \beta_{CuABH_{-2}} - (\log \beta_{CuAH_{-1}} + \log \beta_{CuBH_{-1}}) \qquad (9)$$

arguments described above for explaining more negative $\Delta \log K_{CuABH_{-1}}$ values in the copper(II)–GlyGly (A)–2-aba, 3-aba, dapa, daba, and Orn (B) ternary systems.

Now it seems to be more interesting to correlate the present results on the bonding mode of the amide-deprotonated dipeptides in the copper(II) ternary complex systems with earlier studies. Martin *et al.*[9] suggested two equilibrium structures for the $CuABH_{-1}$ complex species in the copper(II)–GlyGly (A)–glycine (B) ternary system where in one structure, GlyGly (A) binds the metal in a bidentate mode *via* amino- and peptido-nitrogens, while in the other structure, GlyGly is tridentate through *N*-amino, *N*-peptido, and *O*-carboxylate groups. Glycine (B) in this system is bidentate in the first structure, while it is unchelated in the other. Sigel and co-workers [4,26] showed that the amide-deprotonated dipeptide is bidentate *via* *N*-amino and *N*-peptide groups in the $CuABH_{-1}$ complexes in the copper(II)-dipeptide (A)–2,2′-bipyridyl (B) ternary systems. Brookes and Pettit [27] attributed the absence of $CuABH_{-1}$ ternary complex species in copper(II)–glycyl-L-valine and L-valyl-L-valine (A)–D- or L-histidine (B) systems even at pH 9 to the factor: ' the driving force for the ionization of the amide proton in these dipeptides (A) is drastically reduced due to the tridentate character of histidine (A) ligand '. However, Nair *et al.*[10] reported that in the presence of a bidentate ligand such as histamine or a tridentate ligand such as L-histidine, the amide-deprotonated dipeptides in the $CuABH_{-1}$ ternary species bind in a bidentate mode. The same group of workers [28] predicted that in the presence of a monodentate ligand like unsubstituted imidazole, the amide-deprotonated dipeptide can bind both in bidentate and tridentate modes and two equilibrium structures were postulated. Nagypal and Gergely [11] suggested tridentate binding of the amide-deprotonated dipeptides in the $CuABH_{-1}$ complexes in the copper(II)–dipeptide (A)–amino-acid (B) systems on the basis that $\log \beta_{CuABH_{-1}}$ values in the copper(II)–dipeptide (A)–α- and β-amino-acid (B) systems are comparable. However, the validity of such arguments is doubtful because while comparing the relative stabilities of two ternary complex species, one must take into consideration the basicities of the ligands involved in the complexation. Thus following Sigel [2,23,24] it appears that the parameter Δ log *K*, the difference in stability of the ternary complex with that of the binary complex, is the best way to compare the relative stabilities. The $\Delta \log K_{CuABH_{-1}}$ values in Table 2 for the copper(II)–GlyGly (A)–2-aba and 3-aba (B) ternary systems clearly indicate that the $CuABH_{-1}$ ternary species in the system with B = 3-aba is more stable than that species in the system with B = 2-aba, which is in accordance with the preference for copper(II) ternary chelates containing five- and five-membered rings.[2,19,20,23-25] A recent crystal structure analysis of the $CuABH_{-1}$ (A = GlyGly, B = 1,10-phenanthroline) ternary species by Lim *et al.*[12] indicates that the amide-deprotonated GlyGly is tridentate. On the basis of the visible spectra, these workers suggested that in aqueous solution also, tridentate binding of the amide-deprotonated dipeptides can be expected in the ternary complex systems. However, the interpretation of the absorption spectra of such systems at higher pH is difficult [10,26] due to the many hydrolysed species. Hence without detailed knowledge of the concentrations of all these complexes from their absorption maxima and absorption coefficients, one cannot easily draw any conclusions regarding their solution structures. Thus, the present studies on the copper(II)–GlyGly or Glam (A)–amino-acid (B) systems demonstrate beyond doubt that the amide-deprotonated dipeptides in the presence of bidentate or tridentate ligands in the ternary systems of copper(II) in aqueous solution bind the metal through *N*-amino and *N*-peptido donor groups, which is in agreement with the studies reported previously by Sigel *et al.*[4,26] and also by Nair *et al.*[10] However, one cannot rule out the possibility of the tridentate binding of the amide-deprotonated di-

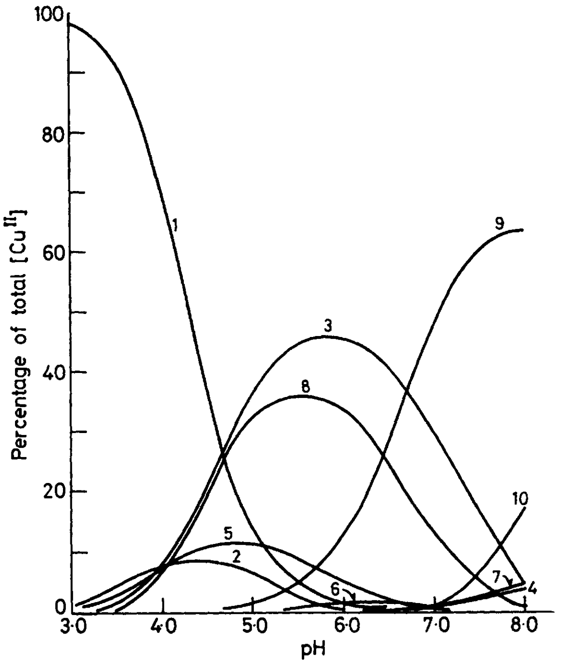

FIGURE 3 Species distribution for the copper(II)–GlyGly (A)–Glam (B) ternary system at a metal : A : B ratio of 1 : 1 : 1; (1) unbound copper(II), (2) CuA, (3) $CuAH_{-1}$, (4) CuA_2H_{-1}, (5) CuB, (6) $CuBH_{-1}$, (7) CuB_2H_{-1}, (8) CuAB, (9) $CuABH_{-1}$, and (10) $CuABH_{-2}$

peptides in the copper(II) ternary chelate systems in presence of a monodentate ligand as reported by Nair *et al.*[28]

4. *Distribution of Species as a Function of* pH *for the Ternary Systems under Study*.—The distribution of various binary and ternary complexes (as percentages of total metal) as a function of pH has been calculated for all the eleven ternary systems reported in this paper. The monoprotonated ternary complexes CuABH in the copper(II)–GlyGly or Glam (A)–dapa, daba, and Orn (B) systems were found to be more favoured in the pH range 4.5—6.5. As expected, the pH region for the predominancy of the CuAB complexes was found to be dependent upon the basicity of the secondary ligand. For example, the CuAB ternary complex species in the system with B = 2-aba attained its maximum concentration at pH 5, while in the system with B = Orn the concentration of the CuAB species did not reach its maximum even at pH 8 and there is a steady increase in its formation with further rise in pH. Again, the concentration of the CuAB complexes in the system with B = 2-aba and 3-aba was found to be only below 10% of the total metal in 1 : 1 : 1 solutions, however they were found in appreciable concentrations in 1 : 2 : 2 solutions. For example, in the 1 : 2 : 2 solution of copper(II)–GlyGly (A)–2-aba (B), about 22% of the total metal was found to be present in the form of CuAB. In all the copper(II)–GlyGly or Glam (A)–secondary ligand (B) systems in this study, the formation of the $CuABH_{-1}$ ternary species began near pH 6.5 and there is a steady increase in its concentration with the rise in pH. The typical distribution pattern of the species for the copper(II)–GlyGly or Glam (A)–daba (B) and also copper(II)–GlyGly (A)–Glam (B) ternary systems are given in Figures 1—3. The diagrams for the other systems in the present investigation showed the qualitative features of Figures 1—3.

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