Ternary Complexes of Substituted Catechols and Dipeptides with Copper(II)

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The formation constants of the ternary complexes [CuA(L)], where A refers to the monoanions of glycylglycine (A^1), glycyl-L-alanine (A^2), or glycyl-L-leucine (A^3) and L to the dianions of catechol (L^1), pyrogallol (L^2), 4,5-dihydroxybenzene-1,3-disulphonic acid (L^3), or naphthalene-2,3-diol (L^4), were determined by potentiometric titration in aqueous medium at 30°C and I = 0.2 mol dm^{-3} ($NaClO_4$) using the SCOGS computer program. The enhanced stability of the ternary complexes is attributed to possible hydrogen bonding between the two ligands through a water molecule.

Laccase is an enzyme containing one molecule of Type I, one molecule of Type II copper, and two molecules of antiferromagnetically coupled Type III copper. The enzyme catalyses the oxidation of *o*- and *p*-dihydroxyphenols to quinones. In such copper-containing proteins, exhibiting polyphenol oxidase activity, there may be intermediate formation of ternary complexes of Cu^{II} containing phenolate and protein.[1] In order to mimic such biological systems, ternary complexes involving amino acids and substituted catecholates have been developed.[2] It was thought of interest to study a closer laccase model, *i.e.* ternary systems involving dipeptides and substituted catechols.

It is generally accepted[3-13] that initial complex formation between a dipeptide and copper(II) in the binary system results in a chelate, involving a terminal amino group and oxygen of the neighbouring amide group. At higher pH values the dipeptide undergoes deprotonation of the amide group and it becomes tridentate co-ordinating through N-amino, N-peptido, and O-carboxylate groups. Ternary complexes involving dipeptides have been studied and a similar type of co-ordination of the dipeptides has been observed,[5,12,14,15]

Yamauchi *et al.*[16] showed that intramolecular aromatic ring stacking exists in ternary palladium(II) complexes [PdL(L–L)], where L refers to a dipeptide with the N-terminal aromatic amino acids tyrosylglutamate, tyrosylglycinate, tryptophylglutamate, or phenylalanylglycinate and L–L to 2,2′-bipyridine (bipy), 4,7-diphenyl-1,10-phenanthroline-4′,4″-disulphonate, or ethylenediamine (en). Gergely and co-workers[17] studied the stability constants of mixed-ligand complexes of manganese(II), cobalt(II), nickel(II), copper(II), and zinc(II) ions with 3-(3′,4′-dihydroxyphenyl)-L-alanine (L-dopa), dopamine [4-(2-aminoethyl)benzene-1,2-diol], L-adrenaline {4-[1-hydroxy-2-(methylamino)ethyl]benzene-1,2-diol}, L-noradrenaline [4-(2-amino-1-hydroxyethyl)benzene-1,2-diol] as ligand A and L-alanine, L-histidine, glycylglycine, and adenosine triphosphate (ATP) as ligand B. Ternary complexes [CuA(L)] and [$CuAH_{-1}L$] involving intramolecular interligand interactions have been studied by us, where L = an amino acid with non-co-ordinating side groups,[18,19]

This paper deals with the ligand–ligand interactions in copper(II) ternary complexes involving dipeptides and substituted catechols.

Experimental

All the reagents used were of A.R. grade and the titrations were carried out using a digital pH-meter with an accuracy of ±0.01. The proton–ligand formation constants of the dipeptides H_2A and HA and the formation constants of binary complexes [CuA] and [$CuAH_{-1}$] were determined in aqueous media at 30 °C and I = 0.2 mol dm^{-3} ($NaClO_4$) using the SCOGS computer program[20] (charges on the species have been omitted for simplicity). In case of catechol and substituted catechols, proton–ligand formation constants of the binary complexes [CuL] and [CuL_2] were also refined under identical conditions. The values are given in Table 1 and are in agreement with those reported earlier.[21] These refined values were used as fixed parameters for the refinement of the formation constants of the mixed-ligand complexes [CuA(L)] and [$CuAH_{-1}L$]. For the determination of the formation constants of the ternary complexes [CuA(L)], the following sets of solutions (50 cm^3) having Cu:A:L in 1:1:1 and 1:1:2 ratio were prepared and titrated against standard alkali: (1) 0.02 mol dm^{-3} $HClO_4$, 0.004 mol dm^{-3} ligand A, 0.004 mol dm^{-3} ligand L, 0.004 mol dm^{-3} metal perchlorate, and 0.168 mol dm^{-3} $NaClO_4$; (2) 0.02 mol dm^{-3} $HClO_4$, 0.004 mol dm^{-3} ligand A, 0.008 mol dm^{-3} ligand L, 0.004 mol dm^{-3} metal perchlorate, and 0.164 mol dm^{-3} $NaClO_4$. Titrations of each set were carried out twice to check the reproducibility of the data. The formation constants for the ternary species determined by using the SCOGS program are shown in Table 2.

Results and Discussion

The formation constants for the binary copper(II)–dipeptide systems were computed taking into account the species H_2A, HA, A, Cu, [CuA], and [$CuAH_{-1}$]. The equilibria corresponding to the binary constants are as in equations (1) and (2).

$$Cu + A \rightleftharpoons [CuA], \quad K^{Cu}_{CuA} = [CuA]/[Cu][A] \quad (1)$$

$$[CuA] \rightleftharpoons [CuAH_{-1}] + H^+, \quad K^{CuA}_{CuAH_{-1}} = [CuAH_{-1}][H]/[CuA] \quad (2)$$

The formation constants of the ternary copper(II)–dipeptide–catechol systems were evaluated by taking into account the species mentioned above and also H_2L, HL, L, [CuL], and the mixed-ligand complex species [CuA(L)] and [$CuAH_{-1}L$]. In cases where the metal, ligand A, and ligand L were in the ratio 1:1:2, the species [CuL_2] was also considered. However, consideration of the latter in the case where metal:A:L are in 1:1:1 ratio did not give refinement since the concentration of [CuL_2] is very low. The constants for the ternary species correspond to the equilibria (3) and (4).

$$Cu + A + L \rightleftharpoons [CuA(L)], \quad K^{Cu}_{CuAL} = [CuA(L)]/[Cu][A][L] \quad (3)$$

$$[CuA(L)] \rightleftharpoons [CuAH_{-1}L] + H^+, \quad K^{CuAL}_{CuAH_{-1}L} = [CuAH_{-1}L][H^+]/[CuA(L)] \quad (4)$$

Table 1. Proton-ligand and complex formation constants in aqueous media at 0.2 mol dm^{-3} $NaClO_4$ and 30 °C with standard deviations in parentheses

(*a*) Dipeptides

Ligand	K_1^H	K_2^H	Copper(II) complex: $\log K_{CuA}^{Cu}$	$\log K_{CuA}^{CuAH_{-1}}$
Glycylglycinate (A^1)	7.99	3.04	5.78	4.47
	(0.02)	(0.03)	(0.19)	(0.06)
Glycyl-L-alaninate (A^2)	8.07	3.03	5.84	4.41
	(0.03)	(0.04)	(0.22)	(0.07)
Glycyl-L-leucinate (A^3)	8.07	3.10	5.93	4.86
	(0.03)	(0.04)	(0.12)	(0.06)

(*b*) Catechol and derivatives

Ligand	K_1^H	K_2^H	Copper(II) complex: K_{CuL}^{Cu}	$K_{CuL_2}^{CuL}$
Catecholate (L^1)	13.06	8.94	13.66	11.30
	(0.05)	(0.04)	(0.04)	(0.05)
Pyrogallolate (L^2)	10.86	9.17	12.80	—
	(0.02)	(0.01)	(0.06)	
4,5-Dihydroxybenzene-1,3-disulphonate (L^3)	11.97	7.69	13.82	11.19
	(0.01)	(0.01)	(0.04)	(0.04)
Naphthalene-2,3-diolate(L^4)	10.90	8.34	11.78	9.08
	(0.05)	(0.08)	(0.03)	(0.04)

Table 2. Formation constants of mixed-ligand complexes and Δ log *K* in aqueous media, $I = 0.2$ mol dm^{-3} ($NaClO_4$) at 30 °C. Standard deviations are given in parentheses

Complex	$\log K_{CuAL}^{Cu}$	$\Delta \log K_{CuAL}$	$\log K_{CuAL}^{CuAH_{-1}L}$
$[CuA^1(L^1)]$	18.15	−1.29	8.12
	(0.24)		(0.13)
$[CuA^1(L^2)]$	17.68	−0.90	8.56
	(0.02)		(0.03)
$[CuA^1(L^3)]$	18.34	−1.26	8.75
	(0.05)		(0.08)
$[CuA^1(L^4)]$	16.56	−1.00	8.70
	(0.20)		(0.12)
$[CuA^2(L^1)]$	18.26	−1.24	8.17
	(0.20)		(0.11)
$[CuA^2(L^2)]$	17.79	−0.85	8.57
	(0.02)		(0.02)
$[CuA^2(L^3)]$	18.43	−1.23	8.88
	(0.05)		(0.08)
$[CuA^2(L^4)]$	16.40	−1.22	8.28
	(0.32)		(0.13)
$[CuA^3(L^1)]$	18.38	−1.21	8.37
	(0.14)		(0.12)
$[CuA^3(L^2)]$	17.81	−0.92	8.66
	(0.04)		(0.04)
$[CuA^3(L^3)]$	18.40	−1.35	8.78
	(0.05)		(0.08)
$[CuA^3(L^4)]$	16.49	−1.22	8.59
	(0.15)		(0.10)

The stability of the ternary complex [CuA(L)] can be quantified by the parameter Δ log *K* [equation (5) and (6)].

$$\log K_{CuAL}^{CuA} = \log K_{CuAL}^{Cu} - \log K_{CuA}^{Cu} \quad (5)$$

$$\Delta \log K_{CuAL} = \log K_{CuAL}^{CuA} - \log K_{CuL}^{Cu} \quad (6)$$

However, for the second species $[CuAH_{-1}L]$ only the deprotonation constant can be obtained. Hence the deprotonation of A

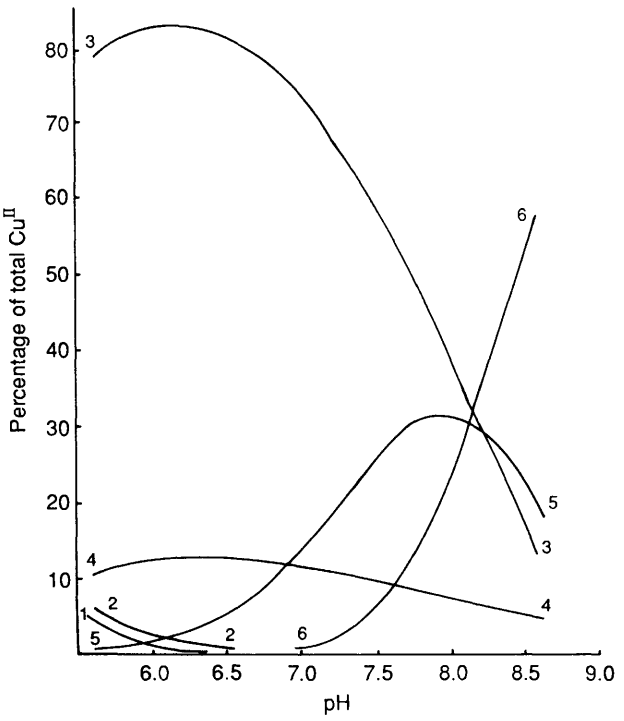

Figure. Species distribution of the copper(II)-glycylglycine(A)–catechol-(L) ternary system at metal:A:L ratio of 1:1:1. Species: 1 = unbound copper, 2 = [CuA], 3 = $[CuAH_{-1}]$, 4 = [CuL], 5 = [CuA(L)], and 6 = $[CuAH_{-1}L]$

in the ternary complex can be compared with the deprotonation in the binary complex [CuA].

From the consideration that in the complex [CuAL] one of the ligands L^{2-} is a dianion and the other ligand A^- is a monoanion, Δ log *K* should have an intermediate value of (log K_2 − log K_1) between those of $[CuA_2]$ where A = salicylaldehydate (= −1.69) with two monoanions and A = catecholate (= −2.34) with two dianions. However, the values in the present complexes are of the order of 1.20. A similar less negative value has been observed for log K_2 − log K_1 in case where A = alaninate (= −1.09). A probable reason is intramolecular interligand hydrogen bonding. However, direct hydrogen bonding between phenolate O^- and a NH or NH_2 group of a dipeptide is less likely from steric considerations. The greater stabilisation of the present [CuA(L)] complexes and less negative Δ log *K* value may be due to hydrogen bonding between the two ligands through a solvent water molecule. Such hydrogen bonding has been suggested in ternary copper(II) complexes involving tertiary amines like phenanthroline.[22]

In case of ternary species $[CuAH_{-1}L]$ it is found that deprotonation of the dipeptide N–H bond is very much reduced. This is also due to two reasons. First, the peptide group on deprotonation forms a dianion and there is strong repulsion between it and the catechol dianion. This inhibits the co-ordination of the dipeptide from the peptide end and hence reduces the deprotonation. Secondly, in the binary copper(II)–dipeptide complex at high pH the peptide group is deprotonated and the species $[CuAH_{-1}]$ is formed, where co-ordination involves the amino nitrogen, peptide nitrogen, and carboxylate oxygen, in equatorial positions. Hence in the ternary complex $[CuAH_{-1}L]$ the ligand L has to occupy one equatorial and one axial position as in Cu-phen-glycyl complex (phen = 1,10-phenanthroline).[13] Occupation of the axial position should destabilise the ternary $[CuAH_{-1}L]$ complex due to Jahn–Teller

distortion. This may also inhibit the formation of $[CuAH_{-1}L]$ with co-ordination from the peptide nitrogen and hence deprotonation of dipeptide N–H.

The distribution of the various ternary species (as a percentage of the total metal) as a function of pH is shown in the Figure.

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