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Complexes of 3,4-Dihydroxyphenyl Derivatives. I. Copper(II) Complexes of DL-3,4-dihydroxyphenylalanine

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pH-metric, visible, UV and ESR spectral studies of the copper(II)–DL-3,4-dihydroxyphenylalanine (DL-DOPA) and the copper(II)–aminoacid–pyrocatechol systems were used to draw conclusions on the complexes formed in the copper(II)–DOPA system. The stability constants of these complexes were determined from the pH-metric data. It was found that at lower pH(<5) aminoacid type complexes of composition CuH_2A *and* $Cu(H_2A)_2$ *are formed, while at higher pH values (>9) the pyrocatechol type complex* $Cu(HA)_2$ *and its deprotonated species are formed. In the intermediate pH range cyclic and open-chain dimeric species are produced, together with a complex containing both N,O and O,O bonds. The existence of this complex is also supported by the fact that formation of the mixed ligand complex is favoured in the copper(II)–pyrocatechol–alanine and copper(II)–pyrocatechol–phenylalanine systems.*

Introduction

The catecholamines and their derivatives play an important role in various neurological and biochemical reactions[1]. It is known, for example, that oxidative transformations of these compounds are catalyzed by copper(II)-containing enzymes.[2,3] L-3,4-dihydroxyphenylalanine (L-DOPA), one of this group of compounds, has been used for about 15 years in the treatment of Parkinson's disease[4]. Its interaction with metal ions may therefore be an important factor in its biological activity[5].

The metal complexes of DOPA have already been subjected to a number of investigations, from both equilibrium and structural aspects. With metal ions this compound may form an aminoacid type O,N bond via the alanine side-chain, or a pyrocatechol type O,O bond via the *ortho* phenolic hydroxy groups. It has not yet been established, however, whether complexes containing only the same types of bonds are formed in the equilibrium system, or whether various other species are possible, in which both O,N and O,O bonds are found. Gorton and Jameson[6] assumed that at lower pH mononuclear complexes are formed containing only aminoacid type bonds, while in alkaline solutions the bonds are only of the pyrocatechol type. In addition, at a metal–ligand ratio of 1:1 a dinuclear complex was also found, in which the DOPA behaves as a bridging ligand. In a more recent paper[7] they concluded as to the formation of various open-chain polymers. Apart from these complexes, they also took into account a binuclear cyclic species.

Weber *et al.*[8] recently carried out equilibrium studies on the metal complexes of adrenaline and related compounds. As regards the copper(II)–DOPA system, they found that up to pH ~5 complexes of type CuA and CuA_2 are formed, containing only aminoacid-like bonds. It was further assumed that up to the physiological pH value monomeric and polymeric complexes containing O,O bonds as well are not formed in the equilibrium system. Kwik *et al.*[9] came to conclusions contrasting with these findings. On the basis of spectral studies, they suggested the formation of complexes containing both N,O and O,O bonds at the physiological pH.

Pilbrow, *et al.*[5,10] carried out ESR spectral studies on the copper(II)–DOPA system, and concluded that only monomeric complexes are present in solution at room temperature. At a metal–ligand ratio of 1:1 a complex CuA was assumed in which oxygen atoms of the phenolic hydroxy and carboxyl groups are linked to the metal ion. Investigations on frozen solutions proved the formation of a dimeric complex, and it was assumed that the donor atoms of the aminoacid side-chain are involved in the bonding.

It can be seen from the above data that the findings relating to the copper(II)–DOPA system are contradictory. Accordingly, the aim of the present work is to contribute to the clairification of the equilibrium conditions in this complicated system, by means of equilibrium, ESR, UV and visible spectral studies. Also, the possibility of the formation of mixed complexes containing both N,O and O,O bonds should be taken into consideration. As a model experiment, we have also made investigations on the copper(II)–pyrocatechol–phenylalanine and copper(II)–pyrocatechol–alanine systems.

Experimental

Chemicals

The chemicals used were commercial products by REANAL and FLUKA. Alanine and phenylalanine were purified by recrystallization from an ethanol–water mixture, and pyrocatechol by distillation at reduced pressure. DL-3,4-dihydroxyphenylalanine (DL-DOPA), a FLUKA product, was used without further purification. The concentration of the $CuCl_2$ stock solution, prepared from the compound of highest analytical purity, was checked gravimetrically via the oxinate.[11]

pH-metric Measurements

The stability constants of the proton and copper(II) complexes of alanine, phenylalanine and pyrocatechol were determined by pH-metric titrations. The experimental conditions in these investigations were the same as those described earlier[11].

In the pH-metric study of DOPA the ligand concentration was 4×10^{-3} or 8×10^{-3} mol/dm^3, and the metal ion–ligand ratio was 1:1, 1:2, 1:3.5 or 1:5 (at a ratio of 1:1 a precipitate was observed at pH ~6.2, but this dissolved at higher pH). KOH solution with a concentration of 0.2 mol/dm^3 was used for titrations. The dissociation constant of the second phenolic hydroxy group of DOPA was determined at a ligand concentration of 8×10^{-2} mol/dm^3. This dissociation constant can be obtained only with appreciable inaccuracy, because its value lies close to the ionic product of water[12].

The potentiometric measurements were made on a Radiometer PHM 4 instrument, as described earlier[11].

Spectral Studies

Visible and UV spectrophotometric measurements were used to study the spectra of the copper(II)–alanine, copper(II)–pyrocatechol and copper(II)–alanine–pyrocatechol systems at metal–ligand ratios of 1:2. In addition, the spectrum of the copper(II)–DOPA system was recorded at various pH values in the range ~4.5–8 at a metal–ligand ratio of 1:1, and in the range ~5–11.5 at a metal–ligand ratio of 1:2. These measurements were made on a Beckmann DB-GT double-beam recording spectrophotometer.

In the room-temperature ESR spectral studies, the metal ion concentration was 2×10^{-2} mol/dm^3 in all cases, the solvent being water or a 1:1 mixture of water and methanol. The parameters of spectra obtained at room temperature were independent of the solvent. An ESR tube drawn out to a capillary ~1.5 mm in diameter was used to record the solution spectra.

In measurements on solutions frozen to the temperature of liquid nitrogen, the metal ion concentration was 1×10^{-2} mol/dm^3 and the solvent was a 1:1 mixture of water and methanol. In the case of the copper(II)–pyrocatechol system, water and a 2:1 mixture of ethylene glycol and water were used to study the solvent effect. Normal ESR tubes were employed to examine the frozen solutions. The other experimental conditions were the same as those described for the visible and UV spectral studies.

ESR spectra were recorded on a JES-ME-lX ESR spectrometer. The g values were determined by comparison with the signal of Mn^{2+} in MgO. Recordings were made with the utmost exclusion of air, and the solutions were always freshly prepared in order to avoid oxidation of the ligands.

Calculations

The species of various compositions formed in the copper(II)–DOPA system can be characterized by the following general equilibrium process:

$$qM + pH + nA \rightleftharpoons M_qH_pA_n \qquad (1)$$

The stability constants of the species are given by:

$$\beta_{qpn} = \frac{[M_qH_pA_n]}{[M]^q[H]^p[A]^n} \qquad (2)$$

Calculations relating to the copper(II)–DOPA and the other systems examined were performed in the manner reported previously[13, 14].

Results and Discussion

First a study was made of whether formation of a mixed complex containing O,O and N,O bonds is favoured in the copper(II)–DOPA system. For this, model experiments were carried out in systems in which the potential donor groups of DOPA occur in different ligands. The ligands used were alanine, phenylalanine and pyrocatechol.

The protonation constants of the ligands and the stability constants of their parent and mixed complexes with copper(II) are listed in Table I.

It can be seen from the Table that the mixed ligand complex has enhanced stability ($\Delta\log\beta_{CuAB}$ ~0.5); this is well illustrated by Figure 1, in which the concentration distribution of the complexes formed in the copper(II)–alanine–pyrocatechol system at a metal–ligand–ligand ratio of 1:1:1 is plotted as a function of pH.

Our data for the mixed ligand complexes are in good agreement with the results of Sigel *et al.*[16] These authors investigated complexes in which various amines acted as ligand A, with pyrocatechol as ligand B. They claimed that the enhanced stability of the mixed ligand complexes is affected by the interaction between the π electron system of the pyrocatechol and the d orbitals of the copper(II). Additionally, formation of the pyrocatechol parent complex of type CuA_2 is sterically hindered ($\log K_1/K_2 \sim 3$), which similarly promotes

TABLE I. Stability Constants of the Proton Complexes and the Copper(II) Parent and Mixed Ligand Complexes of Alanine (A), Phenylalanine (A), and Pyrocatechol (B). I = 0.2 mol/dm^3 (KCl); t = 25° C.

	pK_1	pK_2	$\log\beta_{CuL}$	$\log\beta_{CuL_2}$
Alanine[a]	2.35 ± 0.01	9.68 ± 0.01	8.04 ± 0.02	14.73 ± 0.02
Phenylalanine[a]	2.18 ± 0.01	9.08 ± 0.01	7.76 ± 0.02	14.56 ± 0.02
Pyrocatechol	9.28 ± 0.01	13.00 ± 0.10	13.82 ± 0.10	24.69 ± 0.10
Copper(II)–Alanine–Pyrocatechol	$\log\beta_{CuAB}$	20.54 ± 0.04	$\Delta\log\beta_{CuAB}$[b]	0.53 ± 0.04
Copper(II)–Phenylalanine–Pyrocatechol	$\log\beta_{CuAB}$	20.37 ± 0.04	$\Delta\log\beta_{CuAB}$[b]	0.44 ± 0.04

[a] See reference 15. [b] $\Delta\log\beta_{CuAB} = \log\beta_{CuAB}^{exp} - 1/2\,(\log\beta_{CuA_2} + \log\beta_{CuB_2} + \log 4)$.

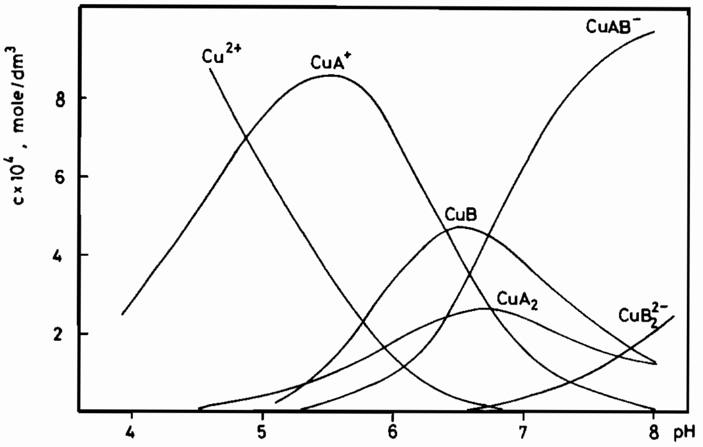


Figure 1. Concentration distribution of complexes formed in the copper(II)–alanine–pyrocatechol system as a function of pH, at a metal–ligand ratio of 1 : 1 : 1.

formation of the mixed ligand complex. On the basis of the data obtained for the model systems, therefore, it may be assumed that a complex containing both N,O and O,O bonds may be formed in the copper(II)–DOPA system too.

In the equilibrium studies relating to DOPA, the protonation constants were first determined. The results are given in Table II, together with some of the literature data.

Comparison of our values for the protonation constants with those determined by other authors, allowance being made for the differing ionic strengths, reveals a reasonably good agreement. As a check, we back-titrated with HCl a solution of the ligand titrated to pH ~10.6 with KOH. The pK values determined in the two ways coincided within 0.01 log unit. Accordingly, oxidation of the ligand during the titration can be excluded.

In the copper(II)–DOPA system a study was first made of whether the equilibrium processes in the usual range of formation of the copper(II)–aminoacid complexes can be described by the formation of complexes containing only aminoacid type bonds. In this case the phenolic hydroxy groups are protonated, thus the H_2A^- species was regarded as the free complexing agent. The formation curves calculated with this assumption for the different metal–ligand ratios can be seen in Figure 2.

TABLE II. Protonation Constants of DOPA.

pK_1	pK_2	pK_3	pK_4	I mol/dm^3	t° C	Reference
2.22 ± 0.01	8.80 ± 0.01	9.83 ± 0.01	13.40 ± 0.20	0.2 KCl	25	Present work
2.31 ± 0.04	8.71 ± 0.02	9.74 ± 0.01	13.40 ± 0.20	1.0 KNO_3	25	6
2.04 ± 0.04	8.81 ± 0.05	9.87 ± 0.05	11.80 ± 0.09	0.37 $NaNO_3$	20	8

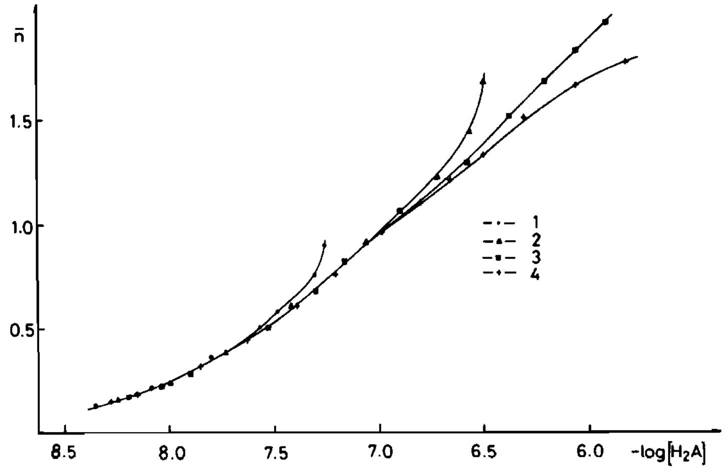


Figure 2. n̄ *vs.* -log[H_2A] formation curves for the copper(II)–DOPA system at metal–ligand ratios of (1) 1 : 1; (2) 1 : 2; (3) 1 :3.5; (4) 1 : 5.

It is clear from this figure that the formation curves coincide up to n̄ ~1 (pH ~4.8–5). Since the solutions have also an intense blue colour, it may be presumed that up to pH ~5 only the aminoacid side-chain takes place in complex formation. In the higher pH range of the titration curve, however, the colour of the solution gradually changes through green to yellow. Electronic excitation spectra of these solutions, with a metal–ligand ratio of 1 : 2, were also recorded at pH values where the phenolic hydroxy groups may be assumed to participate in complex formation. In order to be able to identify the absorption bands, similarly to Gorton and Jameson[6] we recorded not only spectra of the copper(II)–DOPA system, but also those of the copper(II)–alanine, copper(II)–pyrocatechol and copper(II)–alanine–pyrocatechol systems. The data on the individual absorption maxima are contained in Table III.

The band at 15–16 kK can be ascribed to the *d–d* transition of copper(II) complexes, while the band at 23.5–25 kK, of medium intensity, is presumably characteristic of the copper(II)- O,O bonds[9,17]. *o*-Quinones also possess absorption maxima nearly in this energy range. In the case of the copper(II)–DOPA system, however, this band already appears at pH ~5.5, when oxidation of the ligand can be neglected on account of the careful exclusion of oxygen.

TABLE III. Spectral Data on Copper(II) Complexes in Aqueous Solution; t = 25° C.

	pH	Visible and UV Absorption Maxima kK
Cu(II) : alanine 1 : 2	8.0	16.26
Cu(II) : pyrocatechol 1 : 2	8.5	14.88; 25.05
Cu(II) : alanine : pyrocatechol 1 : 1 : 1	8.5	15.67; 24.1
Cu(II) : DOPA 1 : 2	5.5	15.95; 23.5
Cu(II) : DOPA 1 : 2	7.0	15.75; 23.8
Cu(II) : DOPA 1 : 2	10.5	15.48; 24.3

On the basis of the literature data published so far[6,7,9], and of the equilibrium and spectral studies on the model systems in the present work, it is likely that the parent complexes CuA, CuA_2, CuA′ and CuA'_2 (A is the ligand binding in an aminoacid-like manner, and A′ that binding like pyrocatechol) and the species CuAA′ containing mixed bonds are formed in the copper(II)–DOPA system. However, our titration data in the pH range ~5–8 could not be evaluated with the assumption of only these species, for there was a significant difference between the experimental and the calculated titration curves.

ESR spectral examinations also were carried out to identify the species formed in the copper(II)–DOPA equilibrium system. For comparison, ESR spectra were also recorded for the copper(II)–alanine, copper(II)–pyrocatechol and copper(II)–alanine–pyrocatechol systems. The ESR parameters determined from measurements at room temperature and 77 K are listed in Table IV.

Comparison of the data in Table IV reveals that the parameters of the ESR spectrum of the copper(II)–DOPA system with a metal–ligand ratio of 1 : 2 agree with those of the copper(II)–alanine system at pH ~6, and with those of the copper(II)–pyrocatechol system at pH ~ 11. On this basis it may be concluded that primarily aminoacid-like CuA_2 is formed at pH ~6 in the copper(II)–DOPA system, and pyrocatechol type CuA'_2 at pH ~11. In the intermediate pH range a mixed spectrum was obtained; we shall return to the evaluation of this below.

TABLE IV. ESR Spectral Parameters of Copper(II) Complexes.

	pH	Solvent[a]	g_o	$g_{\parallel}$	$g_{\perp}$	10^4A_o cm^{-1}	$10^4A_{\parallel}$ cm^{-1}	$10^4A_{\perp}$ cm^{-1}
Cu(II) : alanine 1 : 1	6.0	A	2.15	2.31	2.07	60	160	10
Cu(II) : alanine 1 : 2	8.0	A	2.12	2.25	2.06	69	179	20
Cu(II) : pyrocatechol 1 : 2	6.2	C	2.15	2.31	2.07	68	170	22
	8.5	A	2.12	2.28 2.24	2.04 2.05	81	178 199	34 24
	8.5	B	2.12	2.25	b	80	198	b
	8.5	C	2.12	2.28 2.24	2.03 2.06	83	182 206	33 24
Cu(II) : alanine : pyrocatechol 1 : 1 : 1	8.0	A	2.12	2.26	2.05	77	184	31
Cu(II) : DOPA 1 : 2	6.0	A	2.12	2.25	2.06	66	179	10
Cu(II) : DOPA 1 : 2	11.0	A	2.12	2.28 2.25	2.04 2.06	81	177 198	34 23
Cu(II) : DOPA 1 : 1	6.4	A	b	2.36	2.06	b	171	b

[a] A = 1 : 1 methanol–water mixture; B = water; C = 2 : 1 ethylene glycol–water mixture.

[b] No direct experimental data.

Another noteworthy experimental finding is that a double ESR signal can be observed in the spectra recorded at 77 K for complexes of both pyrocatechol and DOPA of type CuA'_2. A similar phenomenon was observed in the investigation by ESR of copper(II) complexes of acetylacetone[18], tropolone and similar compounds[19] in solvent mixtures. This phenomenon was interpreted by Porte *et al.*[19] in terms of a weak axial and H-bond interaction between one of the solvent components and the complex. This seems to be supported by the fact that in the case of the copper(II)–pyrocatechol system in pure water as solvent a single broad signal was obtained in our work; this might be ascribed to a complex containing water molecules in the axial positions. At the same time, we observed a double signal in water–methanol and water–ethylene glycol solvent mixtures, the intensity relation depending to a small extent on the composition of the solvent mixture. Further investigations in pure solvents are necessary, however, for a more exact interpretation of this phenomenon.

The spectra recorded at room temperature and 77 K for the copper(II)–DOPA system with a metal–ligand ratio of 1 : 1 at pH ~6.4 are presented in Figure 3.

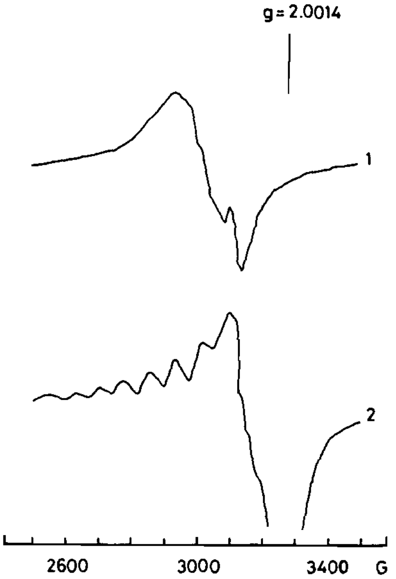


Figure 3. ESR spectra of the copper(II)–DOPA system at a 1 : 1 metal–ligand ratio in a 1 : 1 methanol–water mixture at pH 6.4 (1) At room temperature; (2) at 77 K.

The spectrum at room temperature differs significantly in shape from the ESR spectra of both CuA and CuA′. The intensity of the spectrum did not vary appreciably between pH 4 and 8. With the assumption of dimeric species, the intensity of the signal would be expected to decrease, because of the dipole–dipole interaction[20]. A similar experimental result was obtained by Smith *et al.*[10], who suggested on this basis that the spectrum can be ascribed to a complex CuA coordinated one of the phenolic O^- atoms and the chain-terminating COO^- group. In our view, however, it is difficult to accept such a structure, because of the considerable steric hindrance involved. On the lower field side of the 77 K spectrum in Figure 3, assigned to the transition $\Delta M_s = \pm 1$, a well-resolved seven-line signal can be observed, with an intensity relation of approximately 1 : 2 : 3 : 4 : 3 : 2 : 1. This proves the presence of a dimeric species in significant concentration[21]. A low-field signal corresponding to the transition $\Delta M_s = \pm 2$ could not be observed at the concentrations used, since the ESR tube itself had a fairly intense signal at ~1500 G. In frozen solution, of course, different associations may also exist besides those at room temperature. Thus, unambiguous conclusions cannot be drawn from the results obtained at 77 K. Nevertheless, it is highly probable that a dimeric species is also formed in solution in the copper(II)–DOPA system. The reason why the decrease in intensity of the room temperature signal cannot be observed is that the triplet state of the copper(II) appears in the spectrum[22].

ESR spectra recorded in the frozen solution for copper(II)–DOPA and the other comparative systems at a metal–ligand ratio of 1 : 2 are given in Figure 4.

The spectrum shown in Figure 4 for the copper(II)–DOPA system at pH 7.2 can be interpreted as indicating that neither CuA_2 nor CuA'_2 is formed in significant concentration. The spectrum is primarily a superposition of the spectra of the mixed ligand complex CuAA′ and the dimeric species identified at a metal–ligand ratio of 1 : 1. At the same time our ESR measurements did not confirm the formation of the complex CuA′ assumed by Gorton and Jameson[6] on the basis of electronic excitation spectral and pH-metric studies.

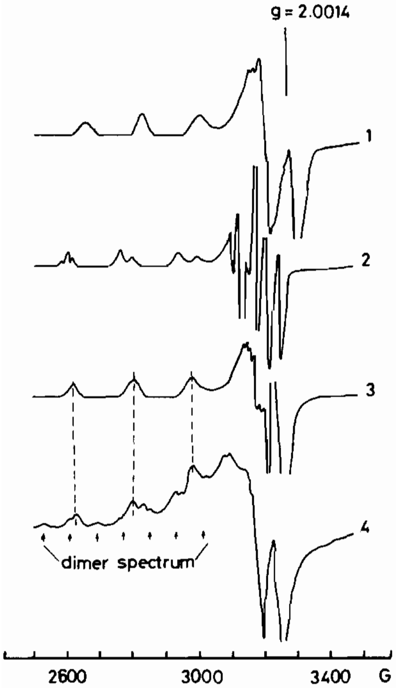


Figure 4. ESR spectra of the following systems in a 1 : 1 methanol–water mixture at 77 K. (1) Copper(II)–alanine at a 1 : 2 metal–ligand ratio at pH 8; (2) copper(II)–pyrocatechol at a 1 : 2 ratio at pH 8; (3) copper(II)–alanine–pyrocatechol at a 1 : 1 : 1 ratio at pH 8; (4) copper(II)–DOPA at a 1 : 2 ratio at pH 7.2.

TABLE V. Stability Data on Copper(II)–DOPA Complexes. I = 0.2 mol/dm³ (KCl), t = 25° C.

Complex	Composition qpn	$\log\beta_{qpn}$
CuH_2A	121	30.75 ± 0.02
$Cu(H_2A)_2$	142	60.61 ± 0.02
$Cu(H_2A)(HA)$	132	53.81 ± 0.04
$Cu(HA)_2$	122	45.33 ± 0.04
$CuHA_2$	112	35.83 ± 0.04
CuA_2	102	25.47 ± 0.04
$Cu_2H_2A_2$	222	53.35 ± 0.05
Cu_2A_2	202	41.90 ± 0.05

In accordance with the above experiments, we assumed that the equilibrium in the copper(II)–DOPA system involves various complexes containing N,O, O,O and mixed bonds, and bi- and possibly polynuclear species. On the basis of this assumption, the stability constants were calculated by the combined treatment of titration curves recorded at two different ligand concentrations and four different metal–ligand ratios. The results are given in Table V.

With these tabulated constants the experimental data give a good fit, within the limits of experimental error. The average value of d(cm³) characterizing the quality of the fit[14] was 0.0056 cm³. If the minor $Cu_2H_2A_2$ species is omitted in the calculation then the goodness of the fit [d(cm³)] of 1 : 1 titration curves will be as high as 0.020 cm³, much higher than the acceptable experimental error. The omission of the other species will cause even more dramatic changes in the d(cm³) values. The data listed in Table V also involve the appropriate protonation constants, from which the required equilibrium constants were derived. These values, together with certain of the literature constants, are listed in Table VI.

The concentration distribution of the complexes formed in the copper(II)–DOPA system at metal–ligand ratios of 1 : 1 and 1 : 2 is plotted in Figures 5 and 6, respectively, as a function of pH.

On the basis of the constants in Table VI and the distribution curves in Figures 5 and 6, and also taking into account the ESR studies, the following statements can be made with regard to the complexes in the copper(II)–DOPA system.

(i) When the metal–ligand ratio is 1 : 1, besides complexes containing aminoacid type bonds two dimeric species of different compositions are also formed, in which the DOPA behaves as a bridging ligand. If the metal–ligand ratio is 1 : 2 or higher, then apart from the mononuclear complexes there is again the possibility of formation of dimeric species, but at higher metal–ligand ratios the concentrations of these

TABLE VI. Equilibrium Constants of Copper(II)–DOPA Complexes at 25° C.

Process	logK	Present work I = 0.2 mol/dm³ (KCl)	References 6, 7 I = 1 mol/dm³ (KNO_3)
$Cu^{2+} + AH_2^- \rightleftharpoons CuAH_2^+$	$logK_1$	7.52 ± 0.02	7.12 ± 0.02
$CuAH_2^+ + AH_2^- \rightleftharpoons Cu(AH_2)_2$	$logK_2$	6.63 ± 0.02	6.29 ± 0.05
$CuAH_2 + CuA^- \rightleftharpoons Cu_2A_2H_2$	$logK_2'$	15.08 ± 0.05	14.605 ± 0.025
$Cu_2A_2H_2 + CuA^- \rightleftharpoons Cu_2A_2^{2-} + CuAH_2^+$	$logK_c$	11.77 ± 0.05	12.435 ± 0.025
$Cu(AH_2)_2 \rightleftharpoons CuA_2H_3^- + H^+$	$logK_2^{-1}$	6.80 ± 0.05	
$CuA_2H_3^- \rightleftharpoons CuA_2H_2^{2-} + H^+$	$logK_2^{-2}$	8.47 ± 0.05	
$CuA_2H_2^{2-} \rightleftharpoons CuA_2H^{3-} + H^+$	$logK_2^{-3}$	9.51 ± 0.05	
$CuA_2H^{3-} \rightleftharpoons CuA_2^{4-} + H^+$	$logK_2^{-4}$	10.35 ± 0.05	

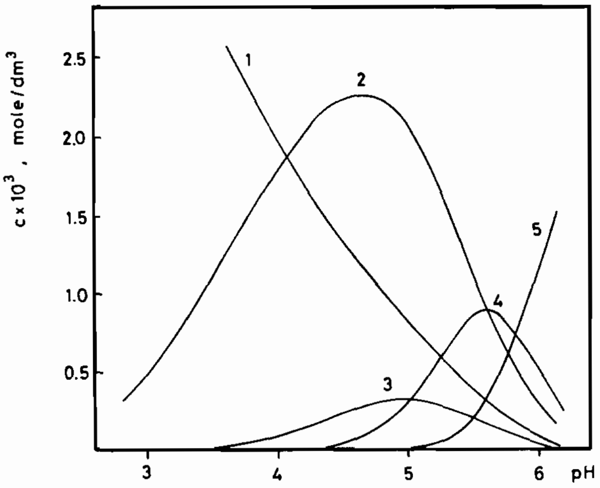


Figure 5. Concentration distribution of the complexes formed in the copper(II)–DOPA system as a function of pH, at a 1 : 1 metal–ligand ratio. (1) Cu^{2+}; (2) CuH_2A^+; (3) $Cu(H_2A)_2$; (4) $Cu_2H_2A_2$; (5) $Cu_2A_2^{2-}$.

decrease considerably. The stepwise deprotonation of $Cu(H_2A)_2$ begins at pH ~5 and, as will be seen later, is accompanied by some structural rearrangement.

The concentration distribution of the protonated ligands is not shown in Figure 6. It is noteworthy, however, that the concentration distribution of the ligand H_3A, unusually, exhibits two maxima and a minimum at pH ~6.6. This can be explained by the fact that at pH > 6.6 the average number of ligands per metal ion decreases compared to that in the lower pH range, due to formation of the dimeric species Cu_2A_2. Similar phenomena have been observed in other systems[23, 24].

(ii) When the differing ionic strengths are taken into consideration, the stability constants of the amino-acid type complexes are in good agreement with the earlier reported data[6]. The larger value obtained for $logK_2$ by Weber *et al.*[8] ($logK_2 = 6.91$) can probably be explained by the fact that formation of dimeric species must be reckoned with even at pH ~5.1, but it was not taken into account by these authors.

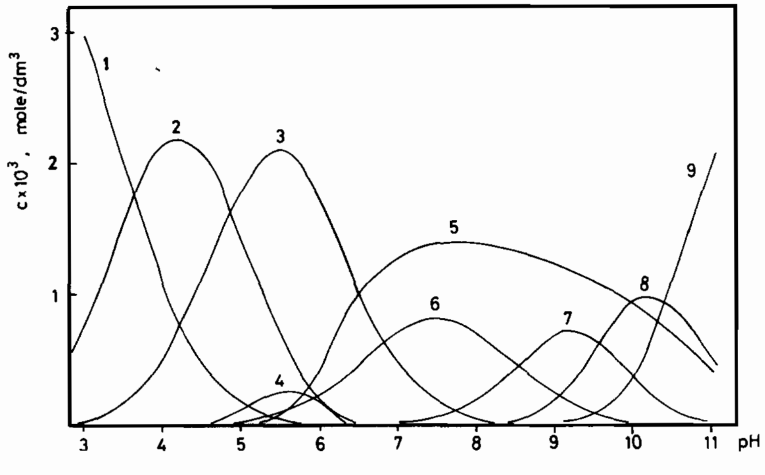
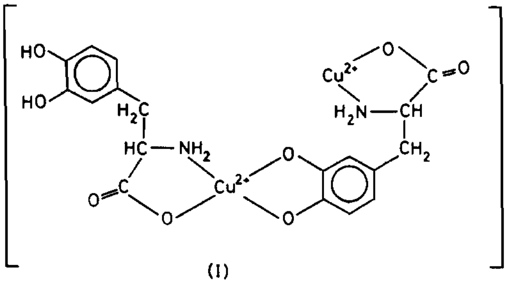


Figure 6. Concentration distribution of the complexes formed in the copper(II)–DOPA system as a function of pH, at a 1 : 2 metal–ligand ratio. (1) Cu^{2+}; (2) CuH_2A^+; (3) $Cu(H_2A)_2$; (4) $Cu_2H_2A_2$; (5) $Cu_2A_2^{2-}$; (6) $Cu(H_2A)(HA)^-$; (7) $Cu(HA)_2^{2-}$; (8) $CuHA_2^{3-}$; (9) CuA_2^{4-}.

(iii) The dimeric species $Cu_2H_2A_2$ is presumably formed by the coupling of two $CuAH_2$ monomers containing aminoacid type bonds. This is accompanied by the formation of a copper(II)–O,O bond.

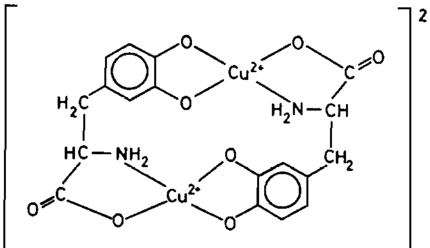
In accordance with this, this formation process is written in such a way in Table VI that the deprotonated form of CuH_2A^+, CuA^-, appears in the equation. In this complex the DOPA behaves as a bridging ligand, by means of its various chelate-forming functional groups, and the open-chain structure (I) proposed by Gorton and Jameson[7] for this complex ($Cu_2H_2A_2$) is probably correct.



(I)

In principle there is also a possibility for the formation of polymers with a higher number of members[7]. In our present investigations calculations were performed with the assumption of species containing three and four nuclei too. With this, the average d(cm^3) characteristic of the quality of the fit improved to a small extent. However, because of the small effect of pH on their formation and also because of the low concentration of the polymeric species, this improvement was within the limits of experimental error. It can be seen from Table VI that the stability constant of the complex $Cu_2H_2A_2$ has a value corresponding to formation of a chelate between the copper(II) and the phenolic hydroxy groups. Gorton and Jameson[6] found logK = 12.99 for the complex CuA′ containing such a bond type. The improbability of formation of this species is also shown by the fact that the calculated value of $\log K_1/K_2$ for these complexes is ~1. In contrast, a value of $\log K_1/K_2$ ~3 is characteristic for complexes between copper(II) and pyrocatechol or its derivatives[25].

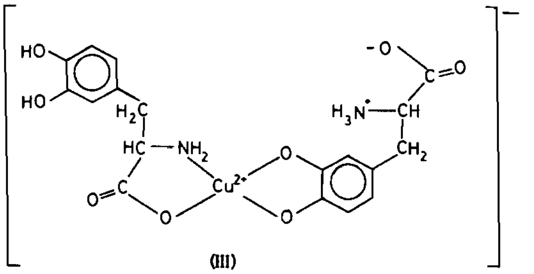
(iv) The species with stoichiometric composition $Cu_2A_2^{2-}$ probably possesses the cyclic structure (II)[7].



(II)

The copper(II)–copper(II) distance can be estimated as 4–5 Å. The dimeric signal in the ESR spectrum can presumably be ascribed to this complex. Because of the favourable spatial arrangement, there is a possibility for dipole–dipole interaction to occur in this species.

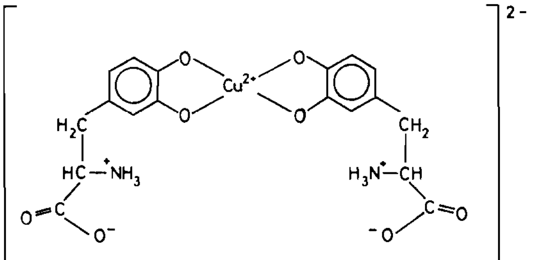
(v) From the value of the deprotonation constant of the species $Cu(H_2A)_2$, it can concluded that this process is accompanied by a structural rearrangement. Its value cannot be ascribed to the dissociation of the phenolic hydroxy group. It may be assumed, therefore, that the mixed ligand complex $Cu(H_2A)(HA)$ with structure (III) is formed, containing both O,O and N,O bonds.



(III)

Apart from the ESR spectral studies, this is also suggested by the fact that, as already mentioned, formation of the mixed ligand complex is very favoured in the copper(II)–alanine–pyrocatechol system.

The constant of the second deprotonation process is about one order smaller than the value of the microconstant ascribable to dissociation of the NH_3^+ group of the ligand ($pk_2 = 9.63$)[26]. On this basis it is probable that a structural rearrangement takes place also in this case, and that the complex $Cu(HA)_2$ (IV) with pyrocatechol-like bonding is formed. This assumption is supported by the fact that the ESR spectrum shows the presence of this complex in significant concentration at pH 9.5. Kwik *et al.*[9] have even prepared a complex with structure (IV) at this pH.



(IV)

On the above basis, the stabilization of the mixed ligand complex $Cu(H_2A)(HA)^-$,

$$\Delta\log\beta_{132} = \log\beta_{132}^{\exp} - {}^1/_2(\log\beta_{142} + \log\beta_{122} + \log 4)$$

is characterized by a value of 0.54, which is in good agreement with the value obtained for the model system in Table I.

The further deprotonation constants K_2^{-3} and K_2^{-4} can presumably be ascribed to the dissociation processes of the NH_3^+ groups of the complex with structure (IV). The gradual increase in the values of these deprotonation constants can in all likelihood be interpreted in terms of the changes taking place in the charge conditions of the complexes.

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