The Crystal Structures of Two Copper(II) Complexes of 6-Aminohexanoic Acid: Models of Copper–Protein Interactions

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Summary The crystal structures of two Cu^{II} complexes of 6-aminohexanoic acid (HA) have been determined by *X*-ray diffraction analysis: the copper of Cu(HA)$_4$·2ClO$_4$ is co-ordinated to the oxygens of four carboxylate groups forming four short and four long bonds, whereas the copper of CuA$_2$·2H$_2$O is co-ordinated to two nitrogens and four oxygens.

IT is generally assumed that the Cu$^+$–Cu^{2+} couple is involved in reactions of copper enzymes. The change in oxidation state between Cu^I and Cu^{II} appears consistent with an almost tetrahedral symmetry of the copper site in these proteins,[1] even though the steric arrangements around Cu^{II} in low-molecular-weight models have been found to be octahedral or square pyramidal.[2] One reason for this might be that most of the compounds investigated[2] form chelates through their α-amino, amide, and/or imidazole nitrogen atoms. 6-Aminohexanoic acid, (HA), was chosen as a model for the study of the possible role of unidentate complexing (6-amino-nitrogen and carboxyl oxygen) in copper–protein interactions.

In solution, 6-aminohexanoic acid and copper(II) form two major complexes, CuHA^{2+} and CuH$_2$A$_2$$^{2+}$, and probably also two minor complexes,[3] Cu$_2$H$_4$A$_4$$^{4+}$ and CuH$_4$A$_4$$^{2+}$. The last complex can be isolated from solution as its perchlorate. The structure of this complex has now been established by *X*-ray crystal structure analysis of CuH$_4$-A$_4$·(ClO$_4$)$_2$.

The crystals are tetragonal, of space group $P\bar{4}$. The copper atom occupies the $\bar{4}$ site and is co-ordinated to a very slightly tetrahedrally distorted square of oxygen atoms coming from four different ligands, Cu–O(1) = 1·93 Å; ∠ O(1)–Cu–O(1″) = 90·0°, ∠ O(1)–Cu–O(1′) = 179·1°, (Figure 1). The second oxygens of the carboxylic groups, O(2), describe an elongated tetrahedron at 2·88 Å from the copper. Each of these oxygens is hydrogen bonded to the amino-nitrogen of another ligand, O(2)–N = 2·81 Å. The nitrogen atoms also describe an elongated tetrahedron and are 3·76 Å from the copper. A second hydrogen bond may be formed by each nitrogen atom to a perchlorate oxygen, O(3)–N = 3·02 Å, forming a three-dimensional network through the structure. In the direction of the third hydrogen of each amino-group there are two interactions at 2·84 Å, N–O(2), and 2·90 Å, N–O(1). Calculations indicate that a N–O(2) hydrogen bond exists rather than a, O(1)–N–O(2), bifurcated hydrogen bond. This leads to the formation of dimers, "head to tail," between neighbouring ligands in the same *xy* plane.

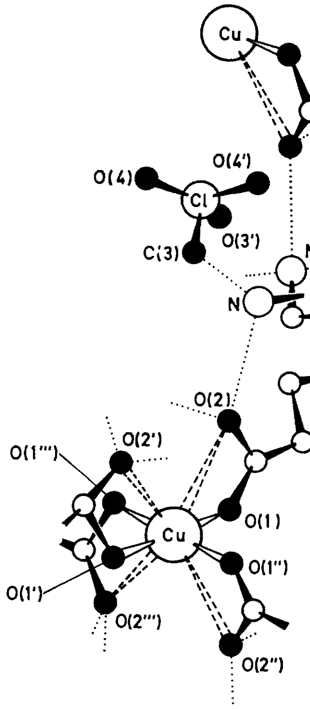

FIGURE 1

Structure analysis shows that the co-ordination to copper is different from that suggested by previous investigators[4,5] (co-ordination through nine-membered chelate rings formed by the amino-nitrogen and the carboxyl oxygen atoms;[4] unidentate co-ordination formed by four ligands through their nitrogen atoms[5]). On the other hand, the co-ordination is similar to that recently reported for $\text{CaCu(OAc)}_4\cdot 6\text{H}_2\text{O}$.[6] The co-ordination polyhedron of this structure was described as a distorted dodecahedron having four short bonds, Cu–O = 1·97 Å and four long bonds, Cu–O = 2·79 Å.

Unlike copper(I), copper(I) ions apparently do interact with 6-amino-groups in solution.[7] Data obtained from e.m.f. measurements using constant-current electrolysis of a two-phase copper amalgam[8] indicate that a single four-nuclear complex $\text{Cu}_4{}^{\text{I}}\text{A}_4$ exists.[7] Attempts to crystallize this species produced violet, green, and colourless phases. One of the violet phases has been identified as the Cu$^{\text{II}}$ phase, $\text{CuA}_2\cdot 2\text{H}_2\text{O}$. The *X*-ray structure analysis shows that the four closest ligand atoms are two carboxyl oxygens and two amino-nitrogens arising from four different molecules bonded in *trans*-positions, Cu–O(1) = 1·96 Å, Cu–N = 1·98 Å; ∠ O(1)–Cu–N(1) = 93·6°, ∠ O(1)–Cu–N(1′) = 86·4° (Figure 2). Each ligand is bonded to two different copper atoms, and so forms a three-dimensional network of infinite chains. The other two carboxyl oxygens form two weak bonds, Cu–O(2) = 2·67 Å (Figure 2). There are also two oxygens belonging to the water molecules at 3·60 Å from copper: these oxygens are hydrogen bonded to one nitrogen, N–O(3) = 2·96 Å, and two carboxylic oxygen atoms, O(3)–O(2‴) = 2·70 Å; O(3)–O(2″) = 2·87 Å (Figure 2). The nitrogen atom also appears to be hydrogen bonded to a carboxylate oxygen, N–O(2) = 2·98 Å. However, the bond is somewhat longer than the corresponding bond (0·17 Å) in the first structure.

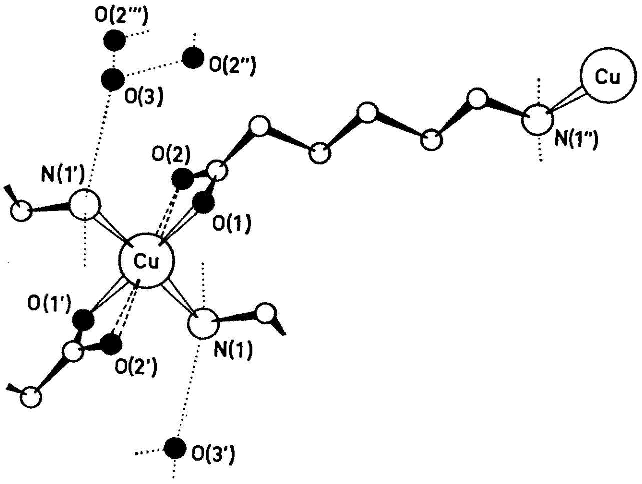

FIGURE 2

Regarding the possible biological significance of these results, Cu$^{\text{II}}$ ions apparently become co-ordinated to the 6-amino-nitrogen atoms after first being reduced and then re-oxidized. This parallels the reconstitution of native Cu$^{\text{II}}$-proteins from apoprotein and Cu ions, which is best achieved by the addition of Cu$^{\text{I}}$ to the apoprotein and then subsequent oxidation.[9]

Crystal data: Tetra-(6-aminohexanoic acid)copper(II) diperchlorate is tetragonal with $a = 10{\cdot}60$, $c = 7{\cdot}72$ Å, $D_m = 1{\cdot}51$, $D_c = 1{\cdot}51$ g cm^{-3}, $Z = 1$ for $\text{CuC}_{24}\text{H}_{52}\text{N}_4\text{O}_8\cdot 2\text{ClO}_4$; space group $P\bar{4}$; the collected data consist of 937 independent reflexions (138 unobservably weak).

Bis-(6-aminohexanoato)copper(II) dihydrate is monoclinic with $a = 8{\cdot}3$, $b = 20{\cdot}0$, $c = 5{\cdot}15$ Å, $\beta = 107{\cdot}7°$, $D_m = 1{\cdot}41$, $D_c = 1{\cdot}47$ g cm^{-3}, $Z = 2$ for $\text{CuC}_{12}\text{H}_{24}\text{N}_2\text{O}_4\cdot 2\text{H}_2\text{O}$; space group $P2_1/n$; the collected data consist of 949 independent reflexions (175 unobservably weak).

The two sets of data were recorded using equi-inclination Weissenberg photographs and Cu-K_α radiation, the reflexions being estimated visually. The structures were solved by three-dimensional Patterson and heavy-atom Fourier methods, and were then refined by full-matrix least-squares techniques. At the present stage of refinement, the residuals R are $\text{Cu(HA)}_4(\text{ClO}_4)_2$, 0·086; $\text{CuA}_2\cdot(\text{H}_2\text{O})_2$, 0·094.

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