Metal-Binding in Chelation Therapy: *X*-Ray Crystal Structure of a Copper(I)–Copper(II) Complex of D-Penicillamine

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Summary The purple complex formed by copper with D-penicillamine at physiological pH is shown to be a $[Cu^{I}_{8}Cu^{II}_{6}L_{12}Cl]^{5-}$ cluster [$L = {}^{-}S\text{-}C(Me_2)\text{-}CH(NH_2)CO_2{}^{-}$] in which the eight S_3-co-ordinated Cu^I atoms surround a central chloride ion; each of the six Cu^{II} atoms is N_2S_2-co-ordinated by two chelating L ligands whose carboxy-groups are on the surface of the cluster.

THE structure of the intensely purple complex formed by copper and D-penicillamine is of interest in relation to the use of the ligand in the treatment of Wilson's disease (hepatolenticular degeneration). We have crystallised the complex as a highly hydrated thallium(I) salt. The unit-cell is cubic, $a = 50{\cdot}847(2)$ Å, space group $F432$. The absence of *X*-ray reflections beyond a limit of $\sin\theta/\lambda = 0{\cdot}372$ for Cu-K_α radiation suggested that the crystals were seriously disordered. The intensities of only 1077 independent reflections could be recorded.

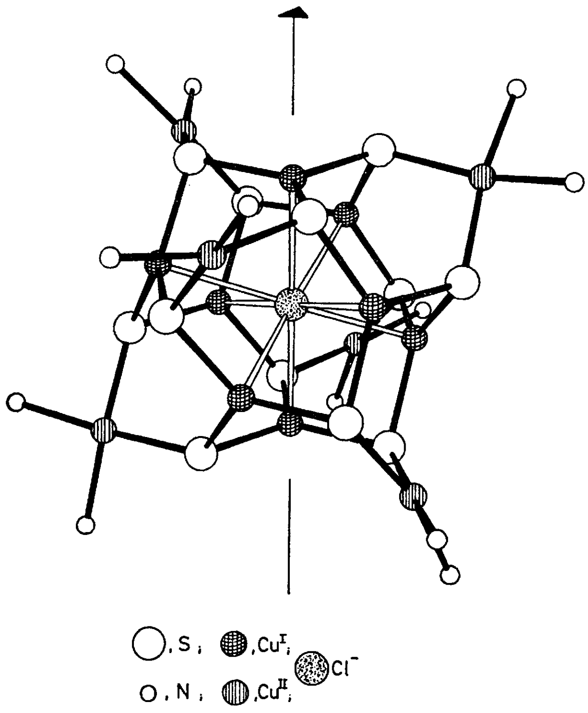

FIGURE 1. The Cu–Cl–N–S framework of the copper–penicillaminate cluster, showing the three-fold axis through two Cu^I atoms and the central Cl.

The structure consists of mixed-valence clusters with composition $[Cu^{I}_{8}Cu^{II}_{6}L_{12}Cl]^{5-}$ surrounded by Tl^+ ions and water molecules. There are 32 symmetry-related clusters in the unit cell. In each cluster (see Figures 1 and 2) there are eight Cu atoms which are each co-ordinated by three penicillamine S(thiol) atoms in an approximately trigonal planar geometry. These eight metal atoms are thereby identified as Cu^I. Two of the Cu^I sites, as well as the Cl^- ion at the centre of the cluster, lie on a three-fold rotation axis. The remaining six Cu atoms can be identified as Cu^{II} by their approximately square-planar co-ordination geometries. The donor atoms in each case are the N(amino) and S(thiol) atoms of two *cis* chelating penicillamine ligands. Every S(thiol) atom in the structure is thus bonded to one Cu^{II} and two Cu^I atoms. The configuration of the S–C and three S–Cu bonds about the S(thiol) atoms is approximately tetrahedral. The penicillamine carboxylate groups are located on the exterior of the cluster.

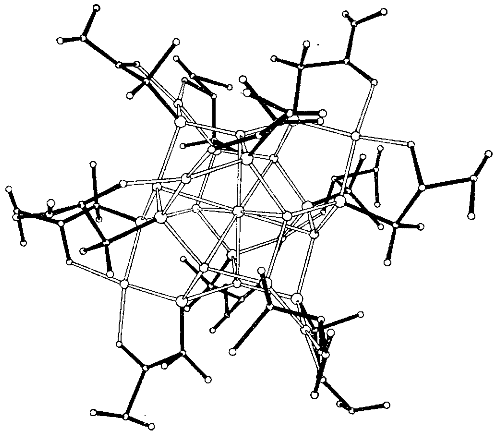

FIGURE 2. The $[Cu^{I}_{8}Cu^{II}_{6}(\text{penicillaminate})_{12}Cl]^{5-}$ cluster in the same orientation as in Figure 1. The nature of the atoms in the ligand molecules is self-explanatory.

The crystals prepared by us contain 5 Tl^+ ions (confirmed by elemental analysis) and about 55 water molecules (calculated from the measured density) per $[Cu^{I}_{8}Cu^{II}_{6}L_{12}Cl]^{5-}$ cluster. The Tl^+ ions and water molecules are disordered and we have not been able to refine all their positions. The disorder accounts for the poor quality and low resolution of our diffraction data. There is, however, strong supporting evidence that the structure here reported for the cluster is correct. Wright and Frieden have reported that the copper–penicillamine complex in solution is a polymeric anion with molecular weight 2600.[1] The formula weight of the clusters in the present compound is 2668. We have prepared solid derivatives of the same anion with $Co(NH_3)_6{}^{3+}$ and Cd^{2+} as the counter-ions. In both cases the elemental analyses lead to the correct counter-ion : Cu ratios. Finally, a cationic cluster compound with a similar $Cu^I:Cu^{II}$: ligand stoicheiometry and with similar co-ordination at Cu^I and Cu^{II}, N–S chelation, and bridging S atoms, has been prepared from $HS\text{-}CMe_2\text{-}CH_2\text{-}NH_2$.[2]

Several structural features of the complex seem to be important for its observed stability in solution: (i) the ligands are able to chelate the Cu^{II} atoms as well as to provide $Cu^{I}\text{-}S\text{-}Cu^{II}$ bridges, (ii) the locations of the methyl groups of the ligands are such that they protect the Cu^I atoms against chemical attack from the surrounding medium; the essential role of the methyl groups is supported by the observation that a similar complex, which is stable in solution, can be prepared with β,β-dimethylcysteamine ($^-S-CMe_2-CH_2-NH_2$)[2,3] but not with cysteamine ($^-S-CH_2-CH_2-NH_2$) or cysteine [$^-S-CH_2-CH(CO_2^-)NH_2$],[3] and (iii) a chloride ion is located at the centre of the cluster, with the eight Cu^I atoms as nearest neighbours (mean Cu^I-Cl distance = 2·7 Å). The requirement for a chloride ion in the cluster is consistent with the observation made by others and by us that the purple copper–penicillamine complex is not formed unless chloride or bromide ion is present in solution,[1] and that small amounts of chloride are always present in the purified solid products.[4]

Diffraction data were recorded on an Enraf–Nonius CAD-4/F diffractometer. The crystal specimen was sealed in a capillary to prevent loss of water and consequent loss of diffracting power. The structure was solved by a combination of Patterson, direct phasing, and Fourier methods, and was refined by full-matrix least-squares. The present residual R is 0·187.

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