The Schiff Base Complex of Pyridoxal, L-Histidine, and Copper(II): An *X*-Ray Study

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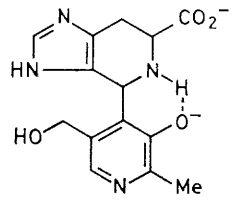
X-Ray structure determination of the 1:1 complex between copper(II) ion and pyridoxylidene-L-histidine reveals a trimeric molecule (with 100—120 waters of crystallisation per cell) where each copper is co-ordinated in a plane by phenolic oxygen, imine nitrogen, and carboxylic oxygen of one Schiff base, and the histidine nitrogen of another ligand, with water in the fifth apical, site.

The absence of information on Schiff base compounds of L-histidine,[1] notwithstanding the biological importance of this amino-acid as a metal binding site, has been noted.[2] The Schiff base with pyridoxal undergoes cyclisation[3] to form the tetrahydropyrido[3,4-*d*]imidazole derivative (**1**), only one of the C(8)† epimers predominating. The pyrido-ring has an 8,9-*trans*† structure with respect to its double bond and the cyclisation is postulated as being important in *in vivo* regulation of pyridoxal-containing enzymes. We present structural information on the pyridoxal intermediate of the cyclised, supposedly 'inactive', form of L-histidine as a complex with copper.

The compound was prepared after initial synthesis of the Schiff base.[3] Pyridoxal and L-histidine, generated from the hydrochloride, were mixed in water and kept for 1 h until the orange colour of the solution faded. The cyclised ligand was precipitated with ether and redissolved in water prior to reaction with a stoicheiometric quantity of copper(II) acetate dissolved in ethanol. The complex was crystallised with great difficulty from aqueous solution by vapour diffusion of ethanol after many abortive attempts under varying conditions. None of the crystals diffracted well and all quickly lost internal order on exposure to the atmosphere but could be stabilised by spraying with polyurethane. This allowed an *X*-ray data set to be collected from one crystal, the standard intensities falling to 74% of their initial value during data collection.



(1)

Crystal data: $C_{14}H_{10}CuN_4O_4 \cdot 8$—10 H_2O, $M = 505.8$ (for 9 H_2O), $a = 18.417(4)$, $b = 17.404(2)$, $c = 23.429(8)$ Å, $\beta = 104.86(3)^\circ$, space group $P2_1$, $Z = 12$, $\lambda(\text{Mo-}K_\alpha) = 0.7107$ Å, $\mu = 10.07$ cm^{-1}. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer, 2890 reflexions with $I > 3\sigma(I)$ being obtained. The water content was estimated from volume considerations.‡

† Numbering as in Figure 1.

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

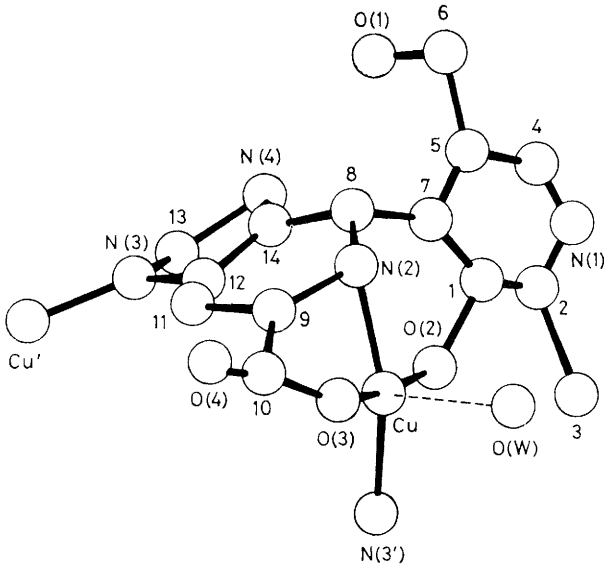


Figure 1. Structure of the ligand–metal unit.

The structure was solved using a combination of direct methods and Patterson analyses followed by application of the heavy atom method. At the current *R*-factor of 0.18 the compound can be seen to be 1 : 1 complex between copper and the cyclised tetrahydropyrido[3,4-*d*]imidazole derivative. The phenolic oxygen O(2),† the secondary amine N(2),† and a carboxylic oxygen O(3)† occupy three planar co-ordinating positions, the fourth being taken by a histidine nitrogen N(3)† from another ligand. Square-pyramidal co-ordination is completed by a water molecule (Figure 1). The structure is trimeric, with three copper atoms in an approximately equilateral triangle bridged by the ligands. The pyridine nitrogens do not bind but form hydrogen bonds with water. A total of 42 such solvent molecules has been located in the asymmetric unit but partial occupancy of sites is indicated for many which approach the liquid state.[1–6] We have found a similar situation using L-isoleucine as the amino-acid, a 1 : 1 copper complex again being present but this time as a polymer. There are six molecules in the triclinic cell (space group *P*1) with 40—50 water molecules also present.

The histidine complex shows the tridentate planar co-ordination observed in other pyridoxylidene-amino-acid complexes[1,7–10] and confirms the cyclisation of the Schiff base. Contrary to the situation in the pyridoxylidene-DL-valine complex and in the L-isoleucine compound referred to above, it is the imidazole nitrogen which occupies the bonding position thus confirming the biological importance of this donor. This supports the recent suggestion[11] that the imidazole group can replace carboxylate as the third donor in a monomeric complex to prevent cyclisation. In all ligands only one of the C(8)† epimers is present and the pyrido-ring is in the 8(*S*), 9(*S*)† or *cis* conformation[2] with respect to its double bond.

Attention has been drawn to the need for axial bonding at the α-carbon atom[12] to ensure reaction.[13,14] With cyclised L-histidine in the *cis*-stereochemistry mentioned above the chelate ring takes the λ-conformation placing the α-hydrogen in the unfavourable equatorial position, and is one way in which histidine ring-closing could influence reactivity.

The large number of water molecules present, 100—120 per unit cell, confirms earlier reports of a high solvent content in some copper and iron complexes with pyridoxal and amino-acids[4] and is contrary to later suggestions.[2]

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