X-Ray Crystal Structure of a Schiff's Base Complex of Copper(II)

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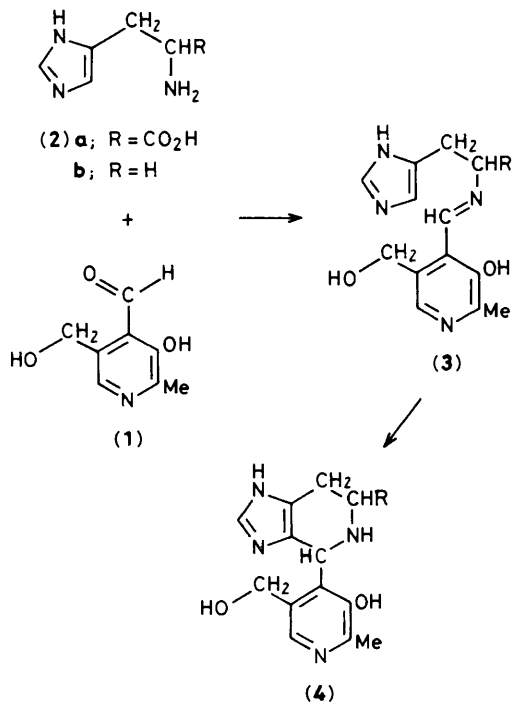
X-Ray structural analysis of the copper(II) complex of the pyridoxylidenehistamine Schiff's base, $[Cu(C_{13}H_{16}N_4O_2)Cl_2]$, shows that the copper atom is square-pyramidally co-ordinated by the tridentate Schiff's base through the imino and imidazole nitrogens and the phenolate oxygen, and by a chlorine atom; another chlorine atom occupies a fifth, axial site.

Pyridoxal phosphate–amino acid Schiff's bases are key intermediates in a variety of metabolic reactions of amino acids such as decarboxylation, transamination, racemization, and C–C bond cleavage, which are catalysed by enzymes that require pyridoxal phosphate as a cofactor. Many nonenzymic model reactions also proceed by similar mechanisms in the presence of pyridoxal (**1**) and suitable metal ions.[1] However, only a limited number of crystal structures of pyridoxal–amino acid–metal Schiff's base complexes have been reported,[2] despite the importance of the stereochemistry about the α-carbon atom of the amino acid residue in controlling the activity of the Schiff's bases.[3] Among these only one example involving histidine is known[2g] in spite of the biological importance of this amino acid: it is a complex formed between the metal ion and the *cyclised* Schiff's base, 1,2,3,4-tetrahydroimidazo[4,5-*c*]pyridine. The ternary pyridoxal–histidine or histamine–metal ion system is also of interest because metal ions like Cu^{2+} and Zn^{2+} inhibit[4] the cyclisation reactions between pyridoxal and histidine[5–7] (**2a**) or histamine[7,8] (**2b**); in metal-free systems, these cyclisation reactions proceed through the formation of Schiff's base intermediates (**3**) to give 1,2,3,4-tetrahyroimidazo[4,5-*c*]pyridine compounds (**4**).

We report here the preparation of the Schiff's base complex of pyridoxal, histamine as a histidine derivative, and copper(II), the crystal structure of which shows that the pyridoxylidenehistamine Schiff's base co-ordinates to the metal atom through the imino and imidazole nitrogens and the phenolate oxygen and that the imidazole co-ordination is responsible for the inhibition of the cyclisation reactions by metal ions. The structure gives important conformational parameters that provide a basis for the understanding of stereochemical aspects of vitamin B_6 model reactions involving histidine.



A 10 ml methanol solution containing 20 mg (1.0×10^{-4} M) pyridoxal·HCl, 18 mg (1.0×10^{-4} M) histamine·2HCl, and 20 mg (1.0×10^{-4} M) $Cu(OAc)_2 \cdot H_2O$ was heated gently (*ca.* 60 °C) to reduce the volume to *ca.* 5 ml, and brought to pH *ca.* 5 with one drop of NaOH. Crystals (deep-green plates) suitable for *X*-ray analysis were isolated from the solution after a few days at room temperature. *Crystal data:* $[Cu(C_{13}H_{16}N_4O_2)Cl_2]$, M = 394.74, monoclinic, space group $P2_1/n$, a = 16.667(3), b = 10.293(4), c = 8.966(1) Å, β = 91.16(1)°, Z = 4, U = 1537.8(7) Å^3, D_m = 1.70(1), D_c = 1.705 g cm^{-3}. The structure was solved by heavy atom methods and refined by the block-diagonal least-squares method (the non hydrogen atoms were treated anisotropically and the hydrogen atoms isotropically) to the current R and R_w of 0.058 and 0.047, respectively, for 2070 reflections [$2\theta \leq 55°$, $F_o > 3\sigma(F_o)$; Rigaku diffractometer, Mo-K_α radiation].†

Figure 1 shows the molecular structure of the complex, in which the pyridoxal group forms a Schiff's base with histamine, as expected. The Schiff's base exists as a neutral ligand with the phenolic oxygen O(3′) of the pyridoxal group deprotonated, and the pyridoxal ring nitrogen N(1) protonated instead. The tridentate Schiff's base co-ordinates to the copper atom through the phenolate O(3′) [1.922(5) Å], the

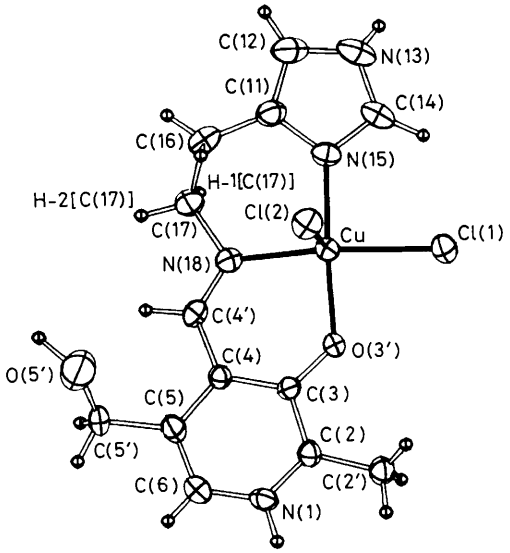


Figure 1. The molecular structure of [Cu(pyridoxylidenehistamine)Cl_2].

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

imino nitrogen N(18) [2.031(5) Å], and the imidazole nitrogen N(15) [1.975(5) Å], and square-pyrimidal co-ordination is completed by the chlorine atom Cl(1) [2.369(2) Å]. Another chlorine atom Cl(2) co-ordinates axially [2.635(2) Å]. The pyridoxal imine [pyridoxal + imino nitrogen N(18)] group and the α-carbon atom C(17) lie almost in the square plane from which the metal atom significantly deviates [0.409(7) Å towards Cl(2)].

The present structure is equivalent to a proposed model[9] for complexes that are responsible for metal inhibition in the cyclisation of histidine or histamine Schiff's bases. Apparently, co-ordination of the imidazole group to the metal ion leads to suppression of the cyclisation of histamine Schiff's base by the metal ion because attack by carbon atom C(12) on the azomethine carbon atom C(4′) is impossible. Moreover, the present *X*-ray analysis, together with the finding[9] that the extent of metal inhibition is almost the same for histamine and histidine, strongly suggest imidazole co-ordination occurs in histidine. Thus this copper chelate provides some important structural parameters for predicting metabolic reactions of the amino acid in the pyridoxal–L–histidine–metal ion system on the basis of the stereochemistry about the α-carbon atom of the amino acid residue, since, in accordance with Dumathan's hypothesis[3] the bond to be cleaved (or formed) must be perpendicular to the plane of the extended π-system to optimize σ—π overlap.

The crystal of the complex, of course, contains both conformers (δ and λ) with respect to the conformation of the chelate ring Cu–N(15)–C(11)–C(16)–C(17)–N(18) because of a crystallographic inversion centre. Figure 1 shows a δ conformation with torsion angles around the C(17)–C(16) and C(16)–C(11) bonds of 73.4(7) [N(18)–C(17)–C(16)–C(11)] and −47.8(9)° [C(17)–C(16)–C(11)–N(15)], while its mirror-image corresponds to the λ conformer. In analogy[10] with histamine-like bound histidine residues where the δ conformation is preferred the carboxy group in the present complex occupies the position H-1 [C(17)] (Figure 1), which is almost perpendicular to the pyridoxal imine plane with a torsion angle C(4′)–N(18)–C(17)–H-1 [C(17)] of −109(4)°, while H-2 [C(17)] is almost in the plane with a torsion angle C(4′)–N(18)–C(17)–H-2 [C(17)] of 3(4)°. Consequently, this conformer is expected to decarboxylate easily but to suffer difficulty in the cleavage of the C_α–H bond, the first step in racemization, transamination, and β-elimination reactions. Among these, β-elimination may be most unfavourable due to the additional co-ordination of the imidazole group. Research is underway to examine this prediction.‡

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‡ For metabolic reactions of L-histidine in the presence of pyridoxal and metal ions, we know of only two relevant papers[7,10] which deal with the conformational properties of Zn^{II} and Cu^{II} complexes with Schiff's bases obtained from pyridoxal and histidine derivatives.