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The Crystal Structure of a Novel Copper(II) Complex with Asymmetric Ligand Derived from L-Histidine

Patrick Deschamps, Prasad P. Kulkarni, and Bibudhendra Sarkar*

Department of Structural Biology and Biochemistry, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada, and Department of Biochemistry, University of Toronto, Ontario M5S 1A8, Canada

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The crystal structure of a novel copper(II) complex with a potentially hexadentate Schiff base ligand derived from L-histidine has been solved by a single-crystal X-ray diffraction method at pH 7.4. The copper(II) ion is coordinated asymmetrically by a tetradentate ligand with the amino and imidazole imido nitrogen atoms on one side versus imino nitrogen and carboxylate oxygen atoms on the other side in a distorted square-planar geometry. The formation of an infinite chain through carboxylate coordination is observed. The novel ligand is obtained by the reaction between the L-histidine molecules coordinated to copper(II) and 4-hydroxy-4-methylpentan-2-one formed by aldol condensation of acetone. This complex provides insights into a possible structural arrangement between copper(II) and L-histidine which is physiologically important and abundantly present in biological systems.

Copper(II)−amino acid complexes are involved in the process of copper transport in humans.[1,2] These complexes and their derivatives are important due to their biochemical and pharmacological properties.[1−4] They are also considered as good models to study metal−ligand interactions in metalloproteins and metalloenzymes.[5] Furthermore, copper(II)−amino acid complexes demonstrate interesting stereochemical properties. Copper(II), as a Jahn−Teller center, when complexed with amino acids, adopts a variety of coordination geometries, from distorted square planar, flattened tetrahedral, and distorted square-pyramidal to distorted octahedral as observed in many crystal structures reported to date.[6−13]

L-Histidine serves as a ligand through the imidazole imido nitrogen atom in most of the copper enzymes and proteins.[14−16] Furthermore, the complex bis(L-histidinato)copper(II), identified as the main copper(II)−amino acid species in human blood serum, plays a pivotal role in the transport of copper in humans.[1] The subcutaneous administration of the copper(II)−L-histidine complex is currently used for the treatment of Menkes disease.[1,3] Because of these varied interests, extensive research has been carried out in many laboratories to characterize the complexation in the copper(II)−L-histidine system.[1,17−28] The mode of L-histidine coordination strongly depends on the solution pH, the composition, and the

* To whom correspondence should be addressed at The Hospital for Sick Children. E-mail: bsarkar@sickkids.ca. Phone: 416-813-5921. Fax: 416-813-5022,

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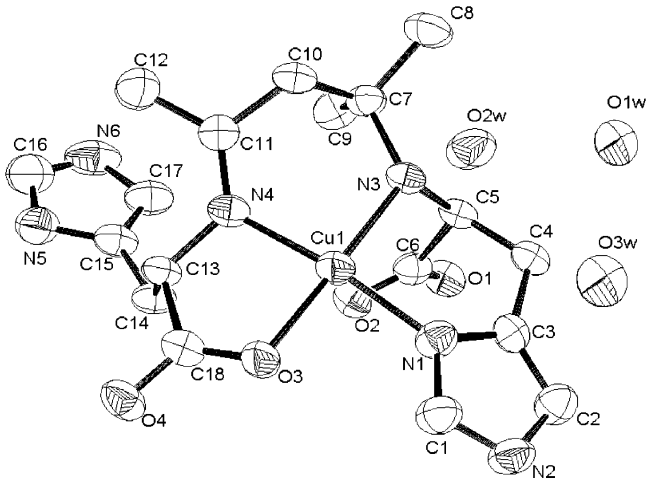


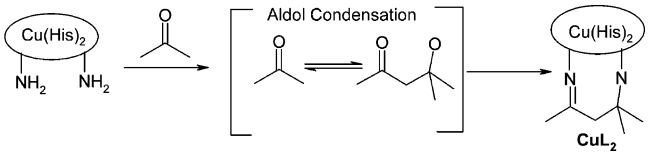
Figure 1. ORTEP diagram of copper(II) complex $\mathbf{CuL_2}$ showing 50% probability thermal ellipsoids. Selected interatomic distances (Å): Cu(1)−O(3) 1.977(3), Cu(1)−N(4) 1.980(4), Cu(1)−N(1) 1.983(4), Cu(1)−N(3) 2.019(3), Cu(1)−O(2) 2.50. Bond angles (deg): O(3)−Cu(1)−N(4) 82.95(13), O(3)−Cu(1)−N(1) 90.45(14), N(4)−Cu(1)−N(1) 173.11(15), O(3)−Cu(1)−N(3) 178.60(14), N(4)−Cu(1)−N(3) 95.75(14), N(1)−Cu(1)−N(3) 90.90(14).

environment. Despite many efforts in all the laboratories, structural uncertainty still remains for the copper(II)−L-histidine complex because of the lack of the X-ray crystal structure at physiological pH.[1,17−28] During our efforts to crystallize the copper(II)−L-histidine species at physiological pH, we have obtained a novel copper(II) complex with a tetradentate asymmetric Schiff base ligand derived from L-histidine.

A 100 mM aqueous solution of $CuCl_2$ was mixed with a 200 mM aqueous solution of L-histidine so as to give a copper(II)−L-histidine molar ratio of 1:2. The pH of this mixture was adjusted to 7.4 with NaOH (100 mM), as previously reported.[28] The UV−vis spectra and ESR spectra are characteristic of formation of 1:2 copper(II)−L-histidine species.[1,21−22] An equal volume of ethanol was added to make 50/50 vol/vol ethanol/water mixture. The resulting mixture was kept under acetone atmosphere at room temperature for crystallization by the vapor diffusion method. Large blue crystals were obtained from the solution after 5 days. The compound was characterized by using elemental and spectral analyses and a single-crystal X-ray diffraction method.[29,30]

The ORTEP[31] diagram (Figure 1) shows that the L-histidine moieties are joined by a carbon chain formed by

Scheme 1. Pictorial Description for the Formation of $\mathbf{CuL_2}$



the reaction of copper(II) complex with acetone vapors. This is due to self-aldol condensation reaction between acetone forming 4-hydroxy-4-methylpentan-2-one, which further reacts with L-histidine molecules to form a Schiff base ligand, namely 2-[(1,3-dimethylbutylidene)-3-N(1-(1H-imidazol-4-yl) ethanoic acid)]-3-(1H-imidazol-4-yl) propanoic acid ($\mathbf{LH_2}$) (Scheme 1).[32]

Amino acids and zinc−amino acid complexes are known to catalyze such aldol condensation reactions.[33,34] However, this is the first example of aldol reaction involving a copper(II)−amino acid complex. The 4-hydroxy-4-methylpentan-2-one further reacts with copper(II)−L-histidine complex in solution to form $\mathbf{CuL_2}$. Alternatively, it is also possible that first acetone forms a Schiff base ligand L-histidine which undergoes self-aldol condensation reaction since similar reactions have been demonstrated for acetone with aldehydes.[33,35] This reaction is observed over the pH range from 6 to 10 at room temperature.

The $\mathbf{LH_2}$ is a potentially hexadentate Schiff base asymmetric ligand, but in the present case, it acts as tetradentate bianionic ligand toward copper(II) through the amino (N_{am}) and imidazole imido nitrogen (N_{im}) atoms on the one side and the imino nitrogen (N_{imn}) and carboxylate oxygen ($O_{carboxy}$) atoms on the other side of the carbon chain. The Cu−N and Cu−O distances around the copper(II) center range from 1.977 to 2.020 Å. The copper(II) ion is involved in a slightly distorted square planar coordination. The N−Cu−(N/O) angles vary from 82.97° to 95.75°.

Two axial oxygen atoms, O(2) and $O(1)^i$, interact weakly with copper(II) at longer distances of 2.501 and 2.515 Å, respectively. As shown in Figure 2, the O(2) atom originates from the carboxylate group of one of two L-histidine moieties, and the $O(1)^i$ atom is provided by symmetrical ligand [symmetry code: (i) $y - 1, x, -z$]. So the overall chromophore, CuN3OO2, can be described as (4 + 2) distorted octahedral geometry.

There are three potential coordination sites in the L-histidine ligand: the amino nitrogen (N_{am}), the imidazole imido nitrogen (N_{im}), and the carboxylate oxygen ($O_{carboxy}$). The previous crystallographic data for bis copper(II)−histidine reported by Camerman et al.[13] for [Cu(II)(L-histidinato)(D-histidinato)$(H_2O)_2$]·$4H_2O$ at pH 7.4 involves bidentate coordination with the N_{im} and N_{am} atoms in the equatorial position and two oxygen atoms of water molecules at the axial positions giving CuN4O2 chromophore. While

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(29) Anal. Calcd for $C_{18}H_{29}CuN_6O_7$: C, 42.77; H, 5.74; N, 16.63. Found: C, 41.32; H, 5.83; N, 16.60. UV−vis data: λ_{max} = 608 nm, $\epsilon_{\lambda_{max}}$ = 51 M^{-1} cm^{-1}. IR (KBr, cm^{-1}) ν(N−H) = 2972, ν(C=N), and $\nu_{as}(CO_2^-)$ centered around 1590−1615, $\nu_s(CO_2^-)$ = 1393.
(30) Diffraction data (3993 independent reflections) were collected on a Bruker Nonius-Kappa CCD system using Mo Kα radiation. Crystallographic data: $C_{18}H_{29}CuN_6O_7$, fw 505.01 g mol^{-1}, trigonal, space group $P3_12_1$, $a = b$ = 10.9923(4) Å, c = 32.2489(12) Å, V = 3374.6(2) $Å^3$, T = 150(1) K, Z = 6, ρ_{calcd} = 1.491 Mg/m^3, μ = 1.022 mm^{-1}, R1 = 0.0465, wR2 = 0.0941 for $I > 2$. The crystallographic data are similar at pH 7.4 and pH 9.0.
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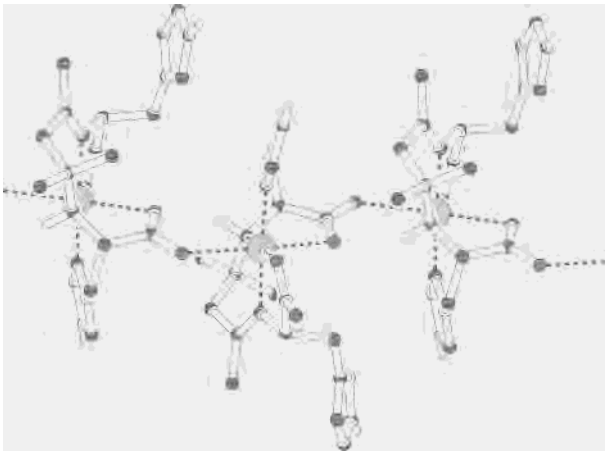

Figure 2. Infinite chain of copper(II) complex **CuL_2** spreading along the [110] direction.

in the structure reported by Evertsson[6] for [Cu(II)(L-histidinato)$_2$(H_2O)$_2$](NO_3)$_2$ at pH 3.7, L-histidine acts as bidentate ligand with two N_{am} along with two $O_{carboxy}$ atoms and two axial waters making CuN2O2O(w)2. In the mixed amino acid complex, [Cu(II)(L-histidinato)(L-threoninato)-(H_2O)]·H_2O, L-histidine acts as a tridentate ligand.[36] With such a great uncertainty related to the coordination mode of L-histidine, the structure of **CuL_2** provides insights into a possible arrangement between copper(II) and L-histidine which resembles one of the many proposed structures for the copper(II)−L-histidine system in solution.[17−23,26]

CuL_2 also provides the opportunity to obtain the structural information for copper(II) coordination with crucial amino acids. For example, in the case of prion protein, copper(II) is bound to histidine along with other amino acids of the octarepeat sequence (PHGGGWGQ) with unknown function.[16] Structural as well as functional properties of such octarepeat coordination can be modeled by **CuL_2** or its analogues which involve L-histidine coordination.

In summary, during our efforts to crystallize the bis L-histidine copper complex we have isolated a novel copper(II) complex with an asymmetric tetradentate Schiff base ligand derived from L-histidine. An aldol reaction using different amino acids and ketones can further be exploited efficiently to synthesize novel complexes with desired structural properties using template synthesis. Such complexes and their analogues will form ideal models for metalloproteins, which can be adapted for various structural analyses as well as tested for their reactivity toward different reactions. Efforts are underway to isolate and crystallize copper(II)−L-histidine species at physiological pH using different conditions and solvents.

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Supporting Information Available: X-ray structural data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org

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