

**THE INFLUENCE OF AMINO ACID SIDE CHAINS ON WATER
BINDING TO THE COPPER(II) IN BIS(*N,N*-DIMETHYL-*L*- α -
ISOLEUCINATO)-COPPER(II): AN EPR AND MOLECULAR
MECHANICS STUDY**

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Abstract: Simulations were done of the electron paramagnetic resonance (EPR) spectra for bis(*N,N*-dimethyl-*L*- α -isoleucinato)copper(II) dissolved in deuterated methanol as a function of temperature. They indicated different behaviour of the complex below and above 300°K. The effect was examined by the conformational analysis of the copper(II) complex with a new molecular mechanics force field.

Key Words: WP-WIN Simfonia Program, Force Field, Amino Acidates

INTRODUCTION

Copper(II) complexes with amino acids and amino acid derivative ligands are potentially good models for mimicking the activity of the superoxide dismutase. To expand our knowledge about the physico-chemical properties of this class of compounds, bis copper(II) complex with *N*-dimethyl-*L*- α -isoleucine was studied by EPR [1], and its structural properties were calculated using the molecular mechanics method.

RESULTS AND DISCUSSION

EPR spectra of bis(*N,N*-dimethyl-*L*- α -isoleucinato)copper(II) [Cu(Met₂Ile)₂] dissolved in deuterated methanol were measured in the temperature interval ranging from 276 to 332°K [1]. The WP-WIN Simfonia program was used to simulate the spectra. The simulations were carried out with the EPR spectral parameters that we measured for the copper(II) amino acid complex with apically bound water in the copper(II) coordination sphere ($g_0=2.119$, $g_{\parallel}=2.219$, $g_{\perp}=2.045$, $a_{Cu}=8.1$ mT, $a_{\parallel}=18.5$ mT, $a_{\perp}=2.95$ mT, and $a_N=0.95$ mT). From the spectral lineshapes, the reorientation correlation time describing the Brownian motion of the complex in solution, τ , was calculated [1], and its dependence on the viscosity of the solvent, η , and temperature, T , was followed. The τ vs. η/T plot was linear in the $(1.8-3.0)\times 10^{-3}$ cPoise K⁻¹ region, but in the $(1.2-1.8)\times 10^{-3}$ cPoise K⁻¹ region it had a very different slope (concurrent with an altered

hydrodynamic volume of the complex). The deviation from the linear τ vs. η/T relationship above 300°K suggested a different conformation of the complex. Also, the spectra recorded above 300°K could only be well simulated with the EPR parameters characteristic for the complex without the apical water [1]. The results led us to conclude that below 300°K the complex behaved as an aqua-complex, while above 300°K it adopted properties characteristic for a copper(II) complex lacking the apically bound water molecule. To examine the influence of the amino acid side chains' conformations on the water binding to the copper(II), a conformational analysis was performed for systems consisting of $\text{Cu}(\text{Met}_2\text{Ile})_2$ alone and together with from 1 to 4 water molecules with a molecular mechanics model [2] and a new force field (unpublished evidence) developed to reproduce and predict the properties of both anhydrous and aqua copper(II) amino acid complexes. (It can be proposed that) each chelate ring of the molecule can have 9 conformers with axial and 9 conformers with equatorial positions of the isoleucine side chains. Among them, three conformations with axial side chain positions (one of them corresponding to the conformation found in the X-ray crystal structure [3]) have potential (strain) energy more than $41.84 \text{ kJ mol}^{-1}$ lower than other axial or equatorial conformations, regardless of whether or not water molecules are present in the studied systems. Via energy minimisation a water molecule initially placed axially to the copper(II) coordination plane only remains in the apical position for the equatorial conformations, while for the axial conformations it moves towards the complex's oxygens and forms hydrogen bonds with them (Fig. 1).

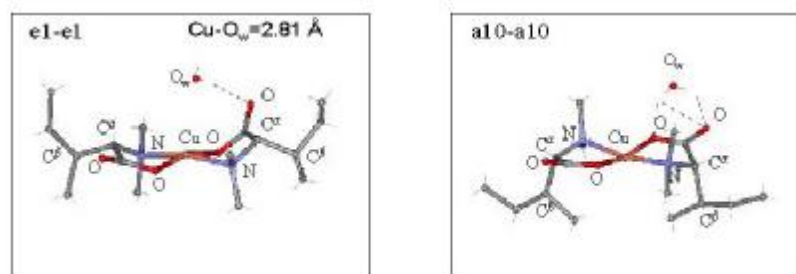


Fig. 1 Two conformations of $\text{Cu}(\text{Met}_2\text{Ile})_2$ with equatorial (e1-e1) and axial (a10-a10) positions of the isoleucine side chains.

Thus, the conformational analysis with the new force field confirms the assumption resulting from the EPR spectra simulations. We can readily suppose that above 300°K increased movements of the $\text{Cu}(\text{Met}_2\text{Ile})_2$ molecules dissolved in methanol make it possible for intramolecular rearrangements to occur giving energetically more preferable axial conformations and the release of the water molecule from the copper(II) coordination sphere.

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