Solution and Solid State Interactions between a Potential 'Metal-Protein Attenuating Compound' and Zinc(II): a Bioinorganic Approach towards the Treatment of Alzheimer's Disease

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'Metal-protein attenuating compounds' (MPACs) are an emerging class of therapeutic agents for the treatment of Alzheimer's disease (AD), which withdraw physiological metal ions from Aβ oligomers and decrease oxidative stress. The aim of the present study was to evaluate the interaction, both in solution and solid state, between 2-pyridylcarboxaldehyde isonicotinoyl hydrazone, namely PCIH, a potential MPAC, and Zn^{2+} ions. PCIH was synthesized according to Richardson *et al.*[1], and its Zn^{2+} complex (**1**) was prepared in methanol, with a 1:1 M:L stoichiometry, under reflux for 1 hour. ^{1}H NMR spectra of PCIH, recorded in DMSO-d_6 due to its stability in this solvent, showed an equilibrium between the isomers *E* (ketamine: 85%, enamine: 14%) and *Z* (1%). The solution of **1**, on the other hand, is constituted of a mixture of coordinated (*E*)-isomer in its deprotonated (85%) and protonated (15%) states. The crystal structure of **1** (Figure 1) reflects its solution chemistry: both protonation forms of coordinated PCIH are present, giving rise to a coordination polymer in which zinc is in a square pyramidal geometry. PCIH acts as a tridentate ligand through an N,N,O-system that occupies the metal's equatorial sites, along with a chloro ligand. The coordination sphere of zinc is completed by a pyridine nitrogen from another PCIH molecule. As protonated-PCIH-containing monomers of **1** are cationic, electric neutrality requires the presence of chloride counter-ions (light-green spheres in Figure 1), which partially occupy some voids present in the crystal network.

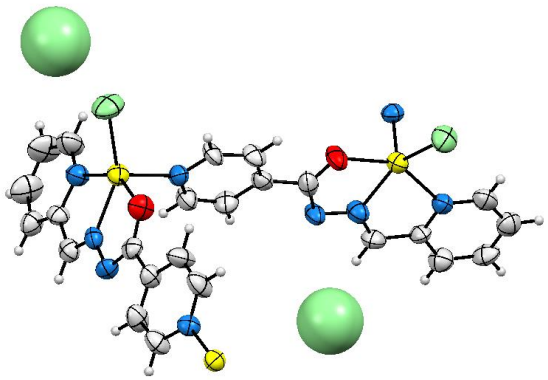

Figure 1. XRD structure showing the asymmetric unit of **1** (partially occupied counter-ion sites are included).

1. Richardson, D.; Bernhardt, P. V.; Becker, E. M.; *PCT/AU2000/001050* **2001**.

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