Metallobiology of Amyloid Beta Peptides by Ligand Field Molecular Mechanics

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Amyloid beta (AB) peptides are a major constituent of the senile plaques observed in the brains of patients with Alzheimer's disease (AD). Naturally occurring metals in the brain, such as copper and zinc, can coordinate to several residues at the N-terminus of AB and it has long been suggested that they contribute to aggregation of these peptides and therefore play a role in the onset of AD. [1] Non-natural metals, such as platinum, can also coordinate to similar sites, as such they are potential anti-Alzheimer's agents through a disruption of the native metal coordination. [2] Ligand field molecular mechanics (LFMM) offers a powerful tool to study systems such as these by utilising a small number of transferable parameters that capture the key d-orbital effects, and is an alternative for expensive quantum simulations or molecular mechanics with ad hoc metal parameters. We report results using LFMM to study several AB transition metal systems, with a particular focus on copper and platinum coordination. Several smaller fragments of AB have been considered as model test systems, such as AB1-16, as shown in figure 1, as well as the full 42 residue peptide. The effect of metal coordination on the secondary structure and other structural aspects have also been explored.

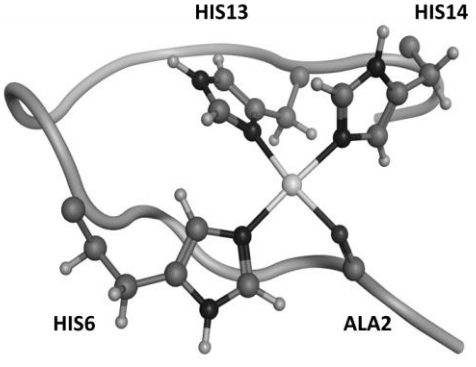

Figure 1: Cu(II)–AB1–16 with the [Oc^{A2},$N\varepsilon^{H6}$,$N\delta^{H13}$,$N\varepsilon^{H14}$] copper binding mode [3]

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