Modelling Pt^{II}(Ligand) – Amyloid-β Interactions: Prediction of Ligand Effects

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Alzheimer's disease (AD) is a neurodegenerative condition associated with progressive cognitive decline in patients. The causes and development of AD are poorly understood, but one hallmark of AD is the presence of amyloid plaques. The early stages of the Aβ aggregation process have therefore become a target for the development of AD-therapeutics [1]. The N-terminal domain of Aβ contains His-rich high-affinity metal binding sites, responsible for physiological coordination of Cu^{II}/Zn. One route to AD-therapeutics involves disrupting coordination by using compounds that occupy these binding sites, hindering the Aβ aggregation process. Recently, Barnham *et al.* showed that Pt^{II}(phenanthroline) complexes inhibit Aβ aggregation and limit its neurotoxicity *in vitro* [2].

In this work, Ligand Field Molecular Mechanics (LFMM), DFT and semi empirical methods are applied to a series of Pt^{II}-Ligand systems binding to the N-terminal domain of the Aβ peptide. Molecular dynamics (LFMM/AMBER) is used to explore the conformational freedom of the peptide fragment, and identifies favourable Pt^{II}-binding modes and peptide conformations. Pt^{II} coordination depends on the nature of the ligand, providing evidence that binding mode may be controlled by ligand design. Structural analysis of the sampled Pt^{II}-Aβ conformations shows that platinum coordination disrupts existing secondary structure in Aβ and promotes formation of ligand-specific turn-type secondary structure. [3][4]

References:

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