Zinc Fingers as Templates for Platinum-Metal Coordination Chemistry

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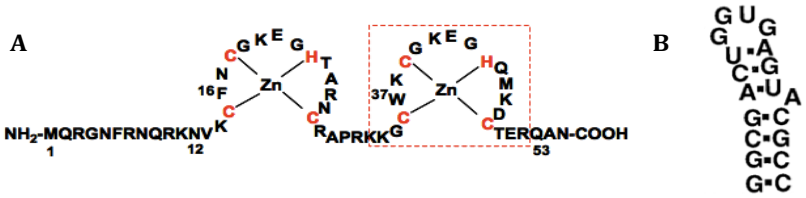
This lecture summarises our work on the fundamental chemistry and biology of platinum-metal (Pt, Pd and Au) complexes with zinc finger proteins. Zinc finger proteins are involved in a host of biological processes such as transcription and DNA repair and they are important targets for therapeutic intervention in viral diseases and cancer. A specific focus will be on the HIV NCp7 nucleocapsid protein (NC), a small basic nucleic acid chaperone containing two zinc finger (or zinc knuckle) Cys_3His motifs and its interaction with RNA. Conceptual analogies between alkylation and metallation in biology have been especially useful in suggesting new patterns of platinum-metal and platinum-nucleobase chemistry. These patterns include molecular recognition and electrophilic attack by platinum-metal compounds on zinc-thiolate bonds. Protonation, alkylation or coordination to a metal ion, such as Pt(II) or Au(III) of a nucleobase generally decreases the energy of its lowest unoccupied molecular orbital (LUMO), thereby improving the potential for π-stacking interactions with the highest occupied molecular orbital (HOMO) in aromatic aminoacids such as N-acetyl tryptophan [1,2]. This effect has been used to target platinum-metal-nucleobases to the tryptophan-containing "full" zinc finger and its single C-terminal peptide. Fluorescence quenching assay, NMR and Circular Dichroism (CD) spectroscopy, ESI-Mass Spectrometry (ESI-MS) and gel-shift electrophoresis show that these small molecules may be effective inhibitors of the nucleocapsid-nucleic acid interaction. X-Ray Absorption Spectroscopy studies can distinguish between Au(I) and Au(III) binding to the peptide. The factors affecting selective "non-covalent" ligand-biomolecule recognition through enhanced π-π stacking between metallated nucleobases and the tryptophan-containing nucleocapsid will be examined. In a second step, such recognition can lead to formation of the "covalent' metal-thiolate bond and subsequent zinc ejection. These findings and others suggest that zinc finger proteins are excellent templates for metal ion exchange and ligand reactivity [3].



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