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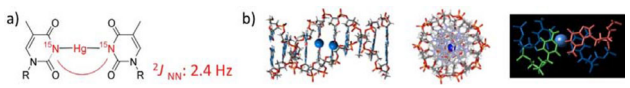
We have studied structures of metal-mediated base-pairs, Hg^{II}-mediated T–T (T–Hg^{II}–T) and Ag^{I}-mediated C–C (C–Ag^{I}–C). We have definitely determined the chemical structure of the T–Hg^{II}–T base-pair with Hg^{II}-mediated ^{15}N–^{15}N *J*-coupling ($^{2}J_{NN}$) [1]. Based on this chemical structure, we further determined 3-dimensional (3D) structure of a DNA duplex with tandem T–Hg^{II}–T base-pairs [2]. The T–Hg^{II}–T base-pairs well mimics Watson–Crick base-pairs, which explains why DNA polymerase elongated a DNA chain using the T–Hg^{II}–T base-pair [3]. Within the duplex, Hg atoms are located along with the helical axis of the DNA duplex, and are shielded from bulk water solvent by the thymine bases and the stacked Watson–Crick base-pairs. This structural feature well explains positive entropy (ΔS) for the formation of a T–Hg^{II}–T base-pair within a DNA duplex [4], which is known as a dehydration-entropy. In addition, a recently determined crystal structure of a DNA duplex with tandem T–Hg^{II}–T base-pairs [5] showed the Hg–Hg distance (3.3 Å) is close enough to suggest the existence of the metallophillic attraction between heavy elements [6].



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IL 23

DNA cleavage ability and cytotoxicity of mono- and dinuclear copper complexes

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Since the discovery of cisplatin, metal-based drugs for cancer therapy is a rapidly growing field of medicinal chemistry. Cisplatin is one of the most widely used anticancer drugs, although its high toxicity and severe side-effects are significant limitations. Consequently, the attention has shifted to less toxic transition metal ions, such as copper which is an essential biometal. Cu complexes can interact with DNA via intercalation or groove binding, cause oxidative DNA damage, induce apoptosis and a range of Cu complexes were found to exhibit promising anticancer activity.

This lecture presents our recent work aimed at the development of Cu-based DNA cleavage agents. As an example, the X-ray structure of $[Cu_2\{bcmp(-H)\}(\mu\text{-}OH)](ClO_4)_2$ (bcmp = 2,6-bis(1,4,7-triazacyclonon-1-ylmethyl)-4-methylphenol is shown below. The Cu complex cleaves DNA in the presence of reducing agents and exhibits promising in vitro antitumor activity against pancreatic cancer cell lines.

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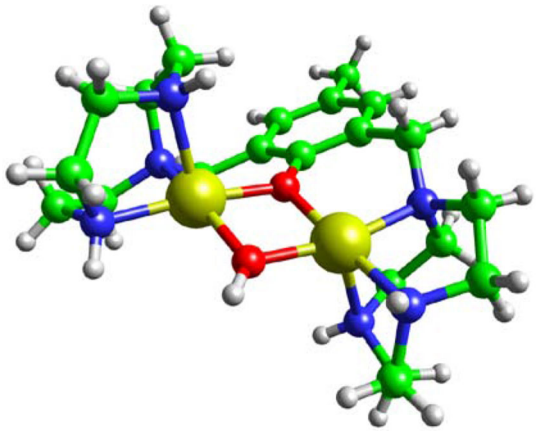

IL 24

How much "wrong" metal can a metallothionein fold take?

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The small, cysteine-rich metallothionein (MT) proteins are thought to be intrinsically disordered in the absence of metal ions, and to only adopt an ordered structure upon metal-binding. Generally, MTs can, in vitro, bind both mono- (Cu(I)) and divalent (Zn(II) and Cd(II)) metal ions. For Cys-only coordination, Cu(I) prefers linear/diagonal and trigonal planar coordination geometries, and Zn(II) and Cd(II) adopt tetrahedral geometry. In absolute thermodynamic terms, Cu(I) always binds more strongly than either Cd(II) or Zn(II), but it is inevitable that the protein backbone must adopt different conformations to allow for different coordination geometries. Since the backbones of MTs tend to be highly flexible, it is a common assumption that either M(I) or M(II) can be accommodated equally well, but more recently, this idea has been questioned [1]. It is suggested that at least some MTs have evolved to best accommodate either M(I) or M(II), with others showing no clear preference, leading to a new classification system based on which metal ion is "preferred" [2]. We hypothesise that the observed preferences are mediated through protein folding—with an ordered structure observed only for the "correct" metal ion. We explore this idea using a prototypical Zn-MT, SmtA from the cyanobacterium *Synechococcus* PCC7942. Zn_4SmtA has a very well-defined 3D structure. Multinuclear NMR spectroscopy and native ESI–MS have been used to characterise the products of reconstitution of the apo-protein with Cu(I), as well as mixed-metal species generated during metal replacement titrations. SmtA formed species with a range of M(I), M(II) stoichiometries, with some retaining at least partially ordered structures, whilst complete replacement with Cu(I) led to fully disordered protein. In addition, SmtA expressed recombinantly in the