New Ligand Topologies for Complexation/Artificial Nuclease Mimics

Thesis submitted for the degree of

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Statement of Originality

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Brendan Griggs

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Date
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**Figure 6.11**: Gel electrophoresis for DNA cleavage by 1:1 copper(II) complexes of aminoalcohols [0.6 μg/L plasmid, 0.95 mM complex, 37°C pH 7.6, HEPES buffer, 2 hr incubation]: duplicate measurements of the complexes of 7.2 at various concentration 1.88 mM (lanes 1–2), 0.94 mM (lanes 3–4), 0.47 mM (lanes 5–6), 0.235 mM (lanes 7–8), 0.1175 mM (lanes 9–10), and (for comparison) of the highly active cleavage agent aqua(cyclohexane-1,3,5-triamine)copper(II) (lanes 11). Also shown are untreated water control (lane 12) in which a small amount of circular plasmid is present, untreated circular plasmid (lane 13) and linearised plasmid (lane 14). Column M represents a molecular weight marker.

**Figure 6.12**: Possible mechanism for the phosphodiester cleavage of dsDNA using the copper complex of aminoalcohol 6.2

**Figure 6.13**: Gel electrophoresis for DNA cleavage by metal(II) complexes of the tetraaza ligand 6.8 [0.6 μg/IL plasmid, 37°C, pH 7.6, HEPES buffer, 2 hr incubation]. (Lanes 2–3) 1.88 mM 2:1 Cu:L; (lane 4) 0.95 mM 2:1 Cu:L; (lane 5) 1.88 mM 1:1 Cu:L; (lane 6) 1.88 mM 2:1 Ni:L; (lane 7) 0.95 mM 2:1 Ni:L; (lane 8) 1.88 mM 1:1 Ni:L; (lane 9) 1.88 mM 2:1 Co:L; (lane 10) 0.95 mM 2:1 Co:L; (lane 11) 1.88 mM 1:1 Co:L. Also shown are a positive control marker Cu(tacen) (lane 12), catalyst-free H₂O-only control marker (lane 13), untreated supercoiled plasmid in which a small amount of circular plasmid is present (lane 14), and linearised plasmid (lane 15). Column 1 contains a molecular weight marker.......

**Figure 6.14**: DNA cleavage for several metal(II) complexes of ligand 6.8; results after 2 hr incubation under conditions described in Figure 6.13

**Figure 6.15**: (a). Gel electrophoresis for DNA cleavage by Cu(II) complexes of tetraaza ligands 6.9 and 6.10 [0.6 μg/L plasmid, 37°C, pH 7.6, HEPES buffer, 2
hr incubation]: (lanes 2, 3) 1.88 mM 1:1 Cu:(6.9); (lanes 3, 4) 1.88 mM 2:1 Cu:(6.9); (lanes 5, 6) 1.88 mM 2:1 Cu:(6.10). Also shown are catalyst-free H₂O-only control marker (lane 7), a positive control marker Cu(tacn)²⁺ (lane 8), untreated supercoiled plasmid in which a small amount of circular plasmid is present (lane 9), and linearised plasmid (lane 10). Column 1 contains a molecular weight marker.

**Figure 6.16**: Proposed active dinuclear copper(II) complex of a semi-rigid tetraamine ligand. It is possible that 6.9 may be able to achieve the same type of binding.

**Figure 6.17**: Molecular structure for the proposed active species resulting from metal-promoted decomposition of 6.11 and responsible for the cleavage of plasmid dsDNA.

**Figure 6.18**: (a). Gel electrophoresis for DNA cleavage by mixed transition metal complexes of the pyridine containing ligands 6.12 and 6.13 [0.6 µg/L plasmid, 37°C, pH 7.6, HEPES buffer, 2 hr incubation]: (lanes 2, 3) 1.88 mM 1:1 Zn:(6.12); (lanes 4, 5) 1.88 mM 1:1 Cu:(6.12); (lanes 6, 7) 1.88 mM 1:1 Ni:(6.12) (lanes 8, 9) 1.88 mM 1:1 Co:(6.12) (lane10,11) 1.88 mM 2:1 Cu:(6.13). Also shown are the positive control marker Cu(tacn)²⁺ (lane 12) catalyst-free H₂O-only control marker (lane 13), untreated supercoiled plasmid in which a small amount of circular plasmid is present (lane 14), and linearised plasmid (lane 15). Column 1 contains a molecular weight marker; lane numbering is from left to right.

**Figure 6.19**: (a). Gel electrophoresis for DNA cleavage by dinuclear copper(II) complexes of ligands 6.21, 6.22, 6.23 and 6.24 [0.6 µg/L plasmid, 37°C, pH 7.6, HEPES buffer, 2 hr incubation; Cu conc. 1.88x10⁻³ M]: (lanes 2, 3) 1.88 mM 2:1 Cu:(6.21); (lanes 4, 5) 1.88 mM 2:1 Cu:(6.22); (lanes 6, 7) 1.88 mM 2:1 Cu:(6.23) (lanes 8, 9) 1.88 mM 2:1 Cu:(6.24). Also shown are the positive control marker Cu(tacn)²⁺ (lane 10) catalyst-free H₂O-only control marker (lane 11), untreated supercoiled plasmid in which a small amount of circular plasmid is present (lane 12), and linearised plasmid (lane 13). Column 1 contains a molecular weight marker.

**Figure 6.20**: (a). Gel electrophoresis for the DNA cleavage by Co(III) complexes of ligand 6.30 [0.6 µg/L plasmid, 37°C, pH 7.6, HEPES buffer]: (lanes 2) 5min
Also shown are the catalyst-free H2O-only control marker (lane 15), positive control marker Cu(tacn)2+(lane 16), untreated supercoiled plasmid in which a small amount of circular plasmid is present (lane 17), and linearised plasmid (lane 18). Column 1 contains a molecular weight marker.

**Figure 6.21:** Gel electrophoresis for DNA cleavage by 3:2 copper(II) complexes of polyamine ligand 6.42 [0.6 µg/L plasmid, 37°C pH 7.6, HEPES buffer, 2 hr incubation]: duplicate measurements of the complexes of 7.42 at various concentrations: 0.934mM (lanes 1–2), 0.623 mM (lanes 3–4), 0.311 mM (lanes 5–6), 0.156 mM (lanes 7–8), 0.0779 mM (lanes 9–10), and (for comparison) of the highly active cleavage agent aqua(cyclohexane-1,3,5-triamine)copper(II) (lanes 11). Also shown are untreated water control (lane 12) in which a small amount of circular plasmid is present, untreated circular plasmid (lane 13) and linearised plasmid (lane 14). Column M represents a molecular weight marker.

**Figure 6.22:** Proposed coordination geometry for the copper(II) complex of ligand 6.42.

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**SCHEMES**

**Scheme 4.1:** .................................................................

**Scheme 4.2:** .................................................................
ABSTRACT

This thesis is centred on the organic synthesis of potential metal-binding molecules incorporating different core topologies. The intent, apart from a strong focus on ligand synthesis and characterisation, is to explore in limited ways aspects of their complexation chemistry, and to examine their labile complexes as potential DNA cleavage agents (or synthetic nucleases). This thesis is divided into a number of synthetic chapters (2-5) that deal with different classes of ligands in turn, with a final chapter (6) that explores the potential of a wide range of complexes as artificial nucleases.

Chapter 1 provides an overview of possible ligand topologies for three, four, five and six donor molecules. This provides background information into the defining shapes and coordination modes of these ligand with a series of transition metals.

Chapter 2 concentrates on the development of a suite of new aminoalcohols, with an emphasis on saturated molecules incorporating a piperazine ring, and the introduction of trans-cyclohexanol groups as pendants to originally primary and secondary amines. These molecules were formed from the ring opening reaction of the epoxide cyclohexene oxide with a range of amines using one of two approaches: traditional reflux condensations in the presence of an appropriate solvent; and microwave irradiation in the absence of any solvent. Each of the resulting molecules show differences in topology, reflecting variations in symmetry and rigidity influenced by the choice of amine. These molecules are potentially multidentate ligands for metal ions, and complexation has been probed using potentiometric titrations and by ESI-MS of isolated complexes.

Chapter 3 focuses on the synthesis of a new series of ‘compartment’ ligands incorporating an aromatic p-xylyl benzene core with either amine or imine pendant arm extensions. Attention is focused on the development of synthetic pathways, along with the roles of the shape of the coordinating ligands and of the different metal ions in directing binding totally or preferentially towards di- or poly-nuclear entities. Although complexation of these systems were explored in cursory manner, it was elucidated in general, however, is that each of the two compartments of these ligands, separated as
they are by a rigid core group, tends to bind to metal ions separately. They satisfy their coordination sphere with additional simple ligands (particularly observed for Pt(II) complexation), or else appear to bind an additional ligand in a ‘sandwich’ type arrangement so as to bind a larger number of preferred donors.

The idea of ‘compartment’ ligands incorporating an aromatic benzene core is taken further in Chapter 4 with the synthesis of two classes of ligands from the reaction of 1,2,4,5-tetrakis(bromomethyl)benzene with a array of primary and secondary amine donor groups. The first comprises molecules incorporating chains including nitrogen donors groups extending from the 1,2,4,5-positions on the benzene ring; the second group of ligands comprises those that have undergone additional chemistry involving adjacent pairs of arms leading to the formation of nitrogen-containing heterocyclic or macrocyclic products. These ligands have been designed so as to coordinate at least two metal ions, with control over the inter-metallic distances and relative geometries resulting from the rigid aromatic core. In addition to some coordination chemistry of only selected examples, this family of ligands has also shown promising nuclease activity when screen against dsDNA, as reported in Chapter Six.

In chapter 5, the primary focus is on the development of a novel suite of symmetrically-armed molecules based on a 2,6-diamidopyridine and thioamido core’s that support helicate metal complex formation. This family of new symmetrically-armed compounds can be prepared using either the diester 2,6-bis(methoxycarbonyl)pyridine (L5.9) or the di(acid chloride) 2,6-bis(carboxylic chloride)pyridine (L5.10) with appropriate nucleophilic donor group. The choice of starting material (L5.9 or L5.10) was dependent on the nature of the reacting species and its donor group(s). Although there no evidence supporting the self-assembly into oligomeric helicates in the present examples, these previously unreported and or unexplored polydentate ligands have been shown to form mono and polynuclear metal complexes as confirmed by several spectroscopic techniques.

In the last chapter (Chapter 6) several families of closely related compounds were screened for their ability to promote the hydrolytic cleavage of DNA and secondly probe how apparently minor changes in ligands can influence activity. Several
complexes that may serve as potential ‘lead’ compounds for more detailed examination of their activity and applicability as artificial nucleases have been identified including ligands 6.2, 6.3, 6.8-6.11, 6.21-6.25, 6.28, 6.30 & 6.42.