

Kane-Maguire Group Research Projects

My background training is in the inorganic chemistry area (in particular, transition metal chemistry). The field is very broad, and depending on one's interests may include significant components of organic, analytical, physical, or biochemistry. Over the last six years my research interests have increasingly evolved into the bioinorganic area. Research students in my group typically spend a considerable amount of time on synthesis and characterization of new transition metal complexes, and then investigate their interaction with biological species such as DNA. These studies include the use of a range of spectroscopic probes such as uv-visible, emission (the latter involving both steady-state and pulse laser excitation), nmr, and circular dichroism (for optical activity measurements).

The Interaction of Chromium(III) Compounds with DNA

The biopolymer DNA (deoxyribonucleic acid) normally consists of two complementary strands intertwined in a double helix (duplex). Following helix uncoiling, each separate strand acts as a template for building a new complementary strand. Effective anti-tumor agents in chemotherapy frequently suppress this replication process, either by preventing uncoiling of the double helix and /or causing strand cleavage (i.e. loss of part of a strand due to a drug activated chemical reaction). As part of a collaborative effort with the group of Dr. John Wheeler, we recently initiated a program to explore the possible development of a new class of such drugs based on molecules of chromium(III) of the type $[\text{Cr}(\text{diimine})_3]^{3+}$. In these complexes, diimine is the generic name for ligands based on the parent 1,10-phenanthroline (abbreviated as phen – see Figure 1), which bind to Cr via the lone pair electrons on the two N atoms. Upon light absorption these Cr species become potent oxidizing agents, and we have compelling evidence that they subsequently cause oxidation of the DNA base guanine.¹⁻³ Since guanine oxidation has been shown in other systems to serve as the genesis point for DNA strand cleavage, our Cr molecules show potential as light promoted antitumor agents. Importantly, the requirement for light activation provides an avenue for selective destruction of DNA in cancer cells. Our studies on Cr/diimine systems will continue next summer on two different but related fronts:

Goal 1. Investigate $[\text{Cr}(\text{diimine})_3]^{3+}$ systems capable of H-bonding to DNA

A major focus of present literature drug research is to design molecules that target specific DNA base sequences. The four DNA bases are guanine (G), adenine (A), cytosine (C), and thymidine (T). A strong AT binding predilection has been widely documented in the literature for drug/duplex DNA interactions. For this and other reasons, there has been considerable biochemical interest in developing molecules with a GC base recognition signature. One approach has been to design molecules with specific DNA H-bonding capabilities – a popular H-bonding target being the 2-amino group of the guanine base (see Figure 2), which protrudes in the minor groove of duplex DNA. To our knowledge, only one example has been reported for preferential GC binding in the transition metal/DNA area. For all our previously examined $[\text{Cr}(\text{diimine})_3]^{3+}$ /DNA systems, an AT base binding preference was observed.¹⁻⁴ It is noteworthy that in these prior studies, the diimine groups utilized were incapable of DNA H-bonding.

We therefore propose to continue efforts begun last summer to synthesize and characterize complexes of the type $[\text{Cr}(\text{DPA})_2(\text{diimine})]^{3+}$ and $[\text{Cr}(\text{DPQ})_2(\text{diimine})]^{3+}$ (see Figure 1 for the structures of DPA and DPQ). We anticipate that these Cr compounds will exhibit spectroscopic properties typical of $[\text{Cr}(\text{diimine})_3]^{3+}$ systems, and will thus retain the highly desirable excited state oxidizing power observed for such species. However, both DPA and DPQ should also provide opportunities for DNA H-

bonding to the 2-amino group of guanine, utilizing the lone pair electrons available on the additional N atoms present in the DPA and DPQ ligands.

Goal 2. Cr-DNA covalent bond formation studies

Currently, one of the three most widely prescribed antitumor agents is the platinum drug *cisplatin*, $cis\text{-}[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$. A key to this molecule's remarkable therapeutic success is the formation of a direct *covalent* (i.e. permanent) bond between the Pt and the N-7 atom (Figure 2) of the guanine DNA base. Direct metal-DNA bonding is not likely with our present $[\text{Cr}(\text{diimine})_3]^{3+}$ systems. This limitation is associated with the strength of the Cr-diimine bonds present, several of which would have to be broken to permit subsequent Cr-guanine covalent bond formation.

Far more attractive candidates for Cr-DNA covalent bonding are molecules of the type $cis\text{-}[\text{Cr}(\text{diimine})_2(\text{CF}_3\text{SO}_3)_2]^+$, where the CF_3SO_3^- ligand is known to be an excellent leaving group. In the presence of DNA, formation of Cr-DNA covalent bonds via guanine displacement of CF_3SO_3^- may occur with some facility. Not only might such species mimic the behavior of *cisplatin*, but it is expected that the Cr complexes formed would be strong photo-oxidants. The destructive power generated upon light absorption would therefore provide the opportunity to selectively damage tumor cells – and thus potentially minimize the serious toxic side-effects associated with *cisplatin* administration. We see this project as long range in scope. Our efforts this summer will be directed towards developing protocols for successfully synthesizing model systems, where the very large DNA molecule is replaced by simpler guanine target species such as 9-methylguanine and 9-ethylguanine (see Figure 2).

The studies described above will be complemented by capillary electrophoresis, mass spectral, equilibrium dialysis, and isothermal titration calorimetry investigations on these same compounds by the Wheeler group. Students will attend regular joint meetings of the two groups to discuss the progress of the work.

Figure 1. Diimine Ligands

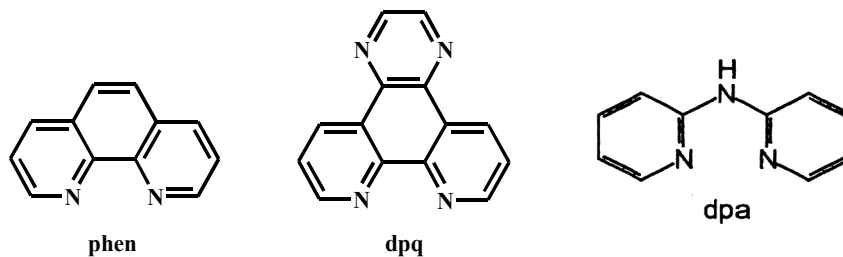
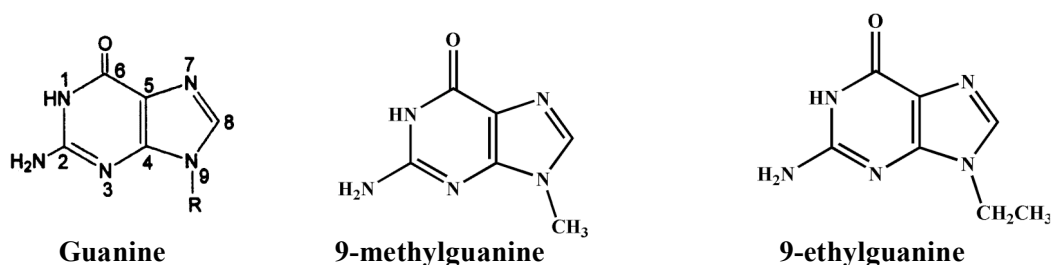


Figure 2.



References:

1. Watson, R.T.; Desai, N.; Wildsmith, J.; Wheeler, J.F.; Kane-Maguire, N.A.P. *Inorg. Chem.* **1999**, *38*, 2683.
2. Kane-Maguire, N.A.P.; Wheeler, J.F. *Coord. Chem. Rev.* **2001**, *211*, 145.
3. Barker, K.D.; Barnett, K.A.; Connell, S.M.; Glaeser, J.; Wallace, A.J.; Wildsmith, J.; Herbert, B.J.; Wheeler, J.F.; Kane-Maguire, N.A.P. *Inorg. Chim. Acta* **2001**, *322*, 74.
4. Schaeper, J.P.; Nelsen, L.A.; Shupe, M.A.; Kane-Maguire, N.A.P.; Wheeler, J.F. *Electrophoresis*, **2003**, *24*, 2704.