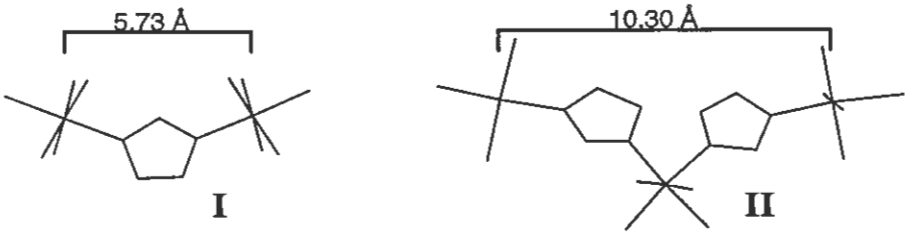
Design, Syntheses and Functional Studies of DNA Binding Metal Complexes

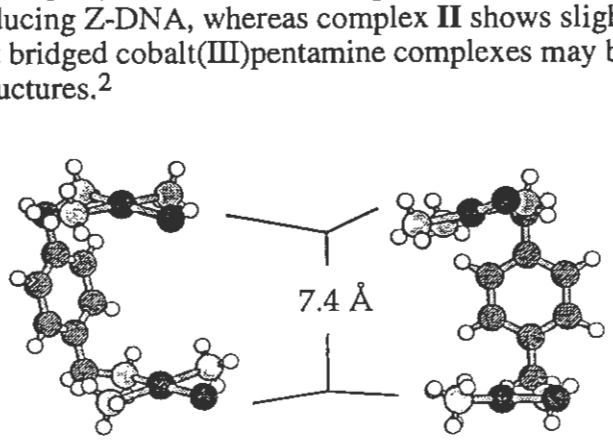
Cornelia Bauer Final Seminar April 10, 1998

Antitumor activity of many anticancer drugs is based on their interaction with DNA. Five basic interaction types are observed: electrostatic interactions of an ionic drug with the negative DNA backbone, intercalation of aromatic parts of a drug between base pairs, covalent binding of the drug to DNA bases, binding in the minor grove and DNA cleavage. Many effective anticancer drugs combine two or more interaction sites and/or types. The interactions of several metal complexes with oligonucleotides were investigated using NMR, circular dichroism (CD) and X-ray crystallography. Using molecular modeling new metal complexes were designed and then synthesized.



I II

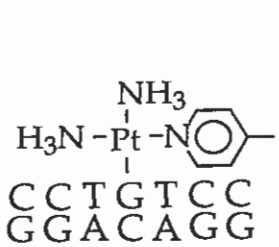
$[Co(NH_3)_6]^{3+}$ is known to facilitate the transition of B- to Z-DNA or B- to A-DNA by electrostatically interacting with the DNA.[1] Bridged cobalt(III)pentamine complexes should enhance this effect by occupying simultaneously two of the $[Co(NH_3)_6]^{3+}$ binding sites. Two imidazole bridged cobalt(III)pentamine complexes, complex **I** and complex **II**, were synthesized and their interactions with DNA oligonucleotides investigated by CD and NMR spectroscopy and X-ray crystallography. Titration studies show showed that the complex **I** is indeed more effective than $[Co(NH_3)_6]^{3+}$ in inducing the transition from B- to A-DNA and similarly efficient in inducing Z-DNA, whereas complex **II** shows slightly smaller effectively. The studies suggest that bridged cobalt(III)pentamine complexes may be useful agents for probing nucleic acid structures.[2]



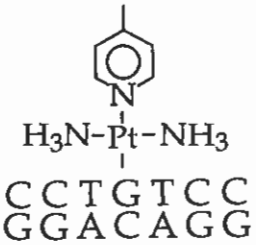
III IV

The family of diamino alkane linked platinum(II) complexes is a series of very potent anticancer drug.[3] Similar to cisplatin they covalently bind to the nucleobase guanine.

Replacing the flexible aliphatic backbone with a more rigid one, thereby introducing a larger conformational change in the lesioned DNA, may improve the activity of the drug. Bivalent transplatin and cisplatin complexes with several organic aromatic amines as a rigid backbone were modeled. The p-xylylene diamine bridged derivatives of transplatin (complex **III**) and cisplatin (complex **IV**) were synthesized. Anticancer activity studies showed that the bis-transplatin (**III**) complex showed similar activity against normal and cisplatin-resistant HeLa cell lines, indicating that it may have a different mode of action from that of cisplatin. However, the overall activity is not high.



V



VI

Both *cis*- and *trans*-$[Pt(NH_3)_2(4\text{-Me-Py})Cl]^+$ bind DNA covalently at the N7-site of the guanines forming a mono dentate adduct, but only the *cis*-isomer shows anticancer activity.[4] The interactions of both, the *cis*- (**V**) and the *trans*- platinum (**VI**) complexes with the DNA-heptamer d(CCTGTCC):d(GGACAGG) were examined and a NMR based high resolution structure was determined. Surprisingly both platinum DNA complexes do not form a very stable complex with its complementary strand. Over time the platinum-DNA complex decomposes and either the 2-methyl-pyridinium group or the platinum complex itself is detached. No interstrand crosslinking was observed.

References

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