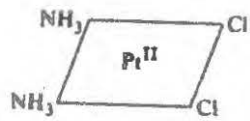
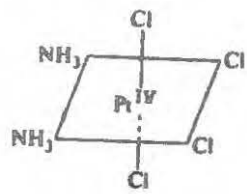
The Chemistry of cis-dichlorodiammineplatinum(II): An Anticancer Drug

David W. Conrad Literature Seminar May 15, 1986

The neutral platinum coordination complex, cis-dichlorodiammineplatinum(II), Peyrone's chloride, was first synthesized in 1845 [1]. It was separated from the corresponding trans isomer by Werner as early as 1898 [1], but it was not until 1969 that its potent anticancer activity was reported. Rosenberg et al. [2,3] found that an electric field applied to a suspension of E. coli prevented cell division, but induced filamentous growth. This effect was finally traced to the presence of two coordination complexes: cis-dichlorodiammineplatinum(II) and cis-tetrachlorodiammineplatinum(IV) which were produced electrolytically at the platinum electrodes.



cis-dichlorodiammineplatinum(II)
Cisplatin
cis-DDP

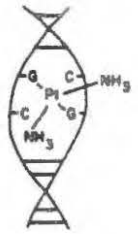


cis-tetrachlorodiammineplatinum(IV)

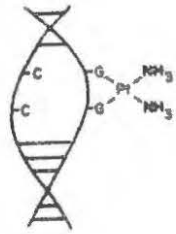
The initial animal studies revealed that both these complexes had antineoplastic activity, while the corresponding trans isomers were inactive [4]. The platinum(II) complex was found to be the more potent and was subjected to clinical trials in 1972. This complex, called cisplatin, is now widely used in the treatment of solid tumors of the head, neck, testes, and ovaries [5].

In order to understand the chemical reactions that occur when cisplatin is injected intravenously, one must consider the aqueous chemistry of the complex. The species formed are highly dependent on the chloride ion concentration in both the plasma and cytoplasm [6]. At sufficiently low chloride ion concentration, cisplatin undergoes a series of stepwise hydrolysis reactions [7]. It is believed that the aquated species are the physiologically active forms. Hydroxo-bridged dimers and trimers can also be formed, but are unlikely to be a major intracellular component due to the low platinum concentration under physiological conditions [8,9,10].

There is currently considerable evidence that DNA is the principal intracellular target for cisplatin [2,3,11]. Inhibition of cell division implies interference with DNA replication, but concomitant cellular growth indicates that RNA and protein synthesis are proceeding normally. Several types of possible DNA-cisplatin adducts have been proposed. These include both DNA interstand(I) and DNA intrastrand(II) crosslinks. Current evidence from both NMR studies [12] and X-ray crystal structures [13] favors an intrastrand crosslink between N(7) on adjacent guanines as the critical platinum binding lesion. The corresponding trans isomer, due to stereochemical restraints, would be unable to form such a crosslink.



(I)



(II)

Recent kinetics data by Lippard [14] suggest that different Pt-DNA lesions occur for the cis- and trans-isomers. These studies also point to differential repair of these lesions as being responsible for the greatly increased cytotoxicity of the cis- vs. the trans-isomer.

Elucidation of the specific repair mechanisms along with an understanding of the structure activity relationship is leading to the design of more efficient inorganic anticancer drugs.

References

1. Lippard, S. J., "New Chemistry of an Old Molecule: cis-$[Pt(NH_3)_2Cl_2]$," Science **1982**, 218, 1075 and references therein.

2. Rosenberg, B.; Van Camp, L.; Grimley, E. B.; Thomson, A. T., "The Inhibition of Growth or Cell Division in Escherichia coli by Different Ionic Species of Platinum(IV) Complexes," J. Biol. Chem. **1969**, 242, 1347.

3. Rosenberg, B.; Van Camp, L.; Krigas, T., "Inhibition of Cell Division in Escherichia coli by Electrolysis Products from a Platinum Electrode," Nature **1965**, 205, 698.

4. Prestayko, A. W.; Crooke, S. T., "Cisplatin: cis-diamminedichloroplatinum(II)," Cancer Treat. Rev. **1979**, 6, 17.

5. Cisplatin, Current Status and New Developments. A. W. Prestayko, S. T. Crooke and S. K. Carter, Ed.; Academic Press, New York, 1980.

6. Reishus, J. W.; Martin, D. S., "Cis-Dichlorodiammineplatinum(II). Acid Hydrolysis and Isotopic Exchange of the Chloride Ligands," J. Am. Chem. Soc. **1971**, 83, 2457.

7. Lee, K. W.; Martin, D. S., "cis-Dichlorodiammineplatinum(II). Aquation Equilibria and Isotopic Exchange of Chloride Ligands with Free Chloride and Tetrachloroplatinate(II)," Inorg. Chim. Acta **1976**, 17, 105.

8. Lim, M. C.; Martin, R. B., "The Nature of cis Amine Pd(II) and Antitumor cis Amine Pt(II) Complexes in Aqueous Solutions," J. Inorg. Nucl. Chem. **1976**, 38, 1911.

9. Taggiani, R.; Lippert, B.; Lock, C. J. L.; Rosenberg, B., "Hydroxo-Bridged Platinum(II) Complexes. Di-μ-hydroxo-bis[diammineplatinum(II)] Nitrate, $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2](NO_3)_2$. Crystalline Structure and Vibrational Spectra," J. Am. Chem. Soc. **1977**, 99, 777.

10. Taggiani, R.; Lippert, B.; Lock, C. J. L.; Rosenberg, B., "Hydroxo-Bridged Platinum(II) Complexes. Crystallographic Characterization and Vibrational Spectra of cyclo-tri-μ-hydroxo-tris[cis-diammineplatinum(II)] Nitrate," Inorg. Chem. **1977**, 16, 1192.

11. Harder, H. C.; Rosenberg, B., "Inhibitory Effects of Anti-Tumor Platinum Compounds on DNA, RNA, and Protein Synthesis in Mammalian Cells in Vitro," J. Cancer **1970**, 6, 207.

12. Polissiou, M.; Viet, M. T.; St.-Jacques, M.; Theophanides, T., "Binding Study of the Drug cis-dichlorodiammineplatinum(II) to Gp^5 and dGp^5 by High Resolution Proton and Carbon-13 NMR Spectroscopy," Inorg. Chim. Acta **1985**, 107, 203.

13. Lippard, S.; Sherman, S. E.; Gibson, D.; Wang, H. J.; "X-ray Structure of the Major Adduct of the Anticancer Drug Cisplatin with DNA: cis-$[Pt(NH_3)_2$-{d(pGpG)}]," Science **1985**, 230, 412.

14. Ciccarelli, R. B.; Solomon, M. J.; Varshavsky, A.; Lippard, S. L., In Vivo Effects of cis- and trans-Diamminedichloroplatinum(II) on SV40 Chromosomes: Differential Repair, DNA-Protein Cross-Linking, and Inhibition of Replication," Biochemistry **1985**, 24, 7533.