# The Chemistry of a Platinum Anticancer Drug: A Theoretical Study

Saksham Malik

**Abstract**— The paper gives a full detailed account of the discovery and development of *{cis-diamminedichloro Platinum}* or cis-DDP. The development of the famous anticancer drug is described with a possible explanation of its biomolecular chemistry. Cisplatin is widely used for cancer treatment and this study on its biomolecular mechanism will help in the development and synthesis of improved anticancer drugs.

**Index Terms**— anti-cancer drug, biochemistry, cancer, cisplatin,coordination compounds, drug, platinum, transplatin

## 1 Introduction

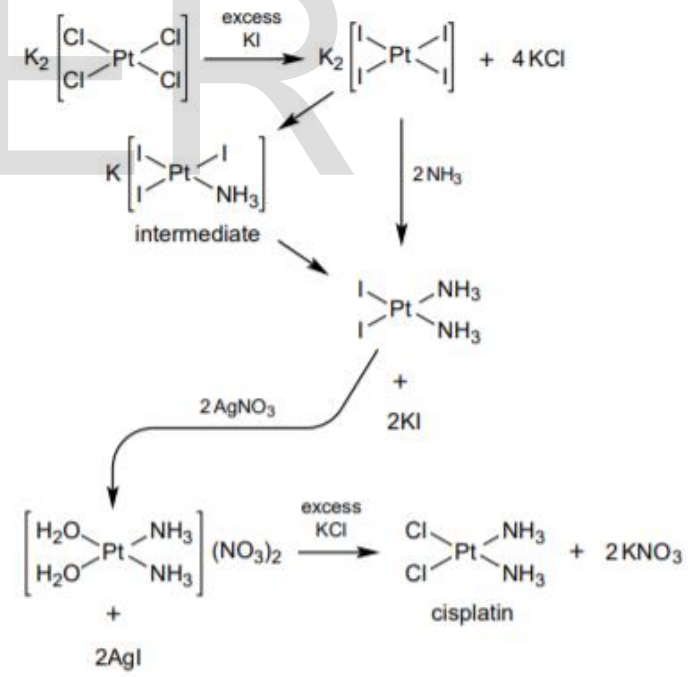
Cisplatin [$Pt(NH_3)_2Cl_2$], "the Penicillin of cancer drugs" was first synthesized by Michael Peyrone in 1845 and is hence historically known as Peyrone's Chloride. The discovery subsequently led to fervent debate about its structure until Alfred Werner discussed it in his theory of Coordination Compounds in 1893. He correctly predicted its square planar geometry and distinguished between the cis and trans isomers: cisplatin and {*trans*-[$Pt(NH_3)_2Cl_2$]}. Werner was awarded the Nobel Prize for his work in 1913.

In the early 1960s, Barnett Rosenberg, a professor of biophysics and chemistry at the Michigan State University, began a series of experiments with *Escherichia Coli* (E coli.) bacteria and an electric field to study its effect on bacterial growth. The mitotic spindles in a dividing cell, similar to the magnetic field lines of a bar magnet, sparked the curiosity in Rosenberg's mind. He observed the growth of E.coli in Ammonium Chloride buffer through Platinum electrodes. These experiments started to recognise the medicinal power of cisplatin. After much investigation, it was found that the phenomenon was not due to electric current, instead the Platinum electrodes were responsible. A range of transition metals were then tested and found to also result in elongation of E coli cells. It was also found by Rosenberg that the trans complex of cisplatin was found to be ineffective.

Rosenberg's study generated interest in the use of metal compounds in cancer treatment. Since then, thousands of platinum compounds have entered clinical use and drugs like carboplatin {cis-[$Pt(NH_3)_2(CBDCA)$], CBDCA=1,1 cyclobutane dicarboxylic acid} have complemented cisplatin. Cisplatin has been instrumental in the cure of over 90% of testicular cancer cases and it plays an important role in the treatment of cancer such as cervical cancer, neck cancer, bladder cancer as well as many others.

## 2 Synthesis

Majority of cisplatin synthesis use $K_2[PtCl_4]$ as starting material and convert it into $K_2[PtI_4]$ using KI, which after addition of ammonium hydroxide gives the yellow precipitate of cis-[$Pt(NH_3)I_2$]. After treatment with $AgNO_3$ in water and treatment with excess of chloride ion, cisplatin can be synthesized. This method was suggested by Dhara in 1970.




Cisplatin is then purified by recrystallization using hot water containing 0.1M HCl. However, it is important to check the stereochemistry of compounds after crystallization. Kurnakow test is a widely used method for the same. By adding thiourea(tu) in excess, cis-[$Pt(NH_3)_2(tu)_2$]$Cl_2$ separates out as a yellow soluble complex whereas a white powdered, water soluble complex is observed in the form of trans-[$Pt(NH_3)_2(tu)_2$]$Cl_2$.

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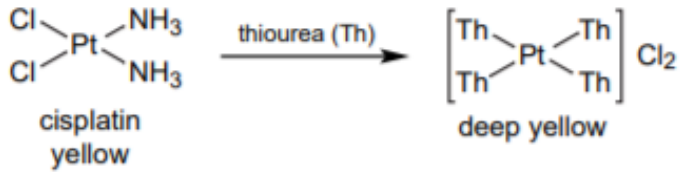
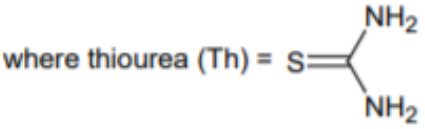
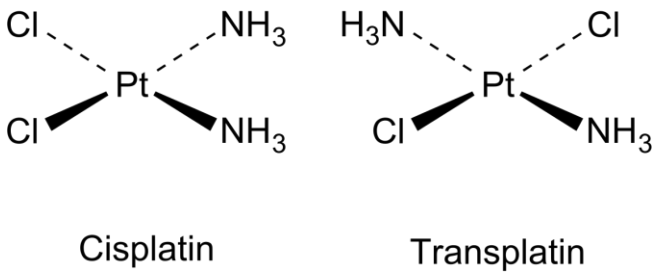




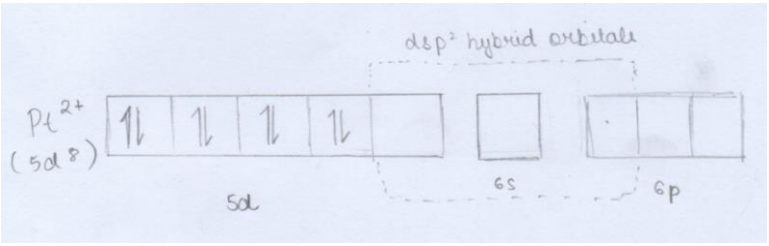



## 3 Bonding & Structure

Werner's coordination theory in 1893 was the first attempt to explain bonding in coordination complexes. It was Werner who first suggested the geometry of $[Pt(NH_3)_2Cl_2]$ including both cis and trans isomers. Werner postulated that a complex having Coordination Number 4 could only be square planar and tetrahedral. After considering the dipole moments of each isomer, he concluded the structure was square planar.




In the 1930s, Pauling developed the Valence Bond theory(VBT). The theory considers the atomic orbitals that are used for bonding by metals and postulates that ligands form coordinate bonds to the metal. The empty orbitals are hybridised to give a set of four equivalent hybrid orbitals. A ligand orbital containing a lone pair of electrons forms a coordinate bond by overlapping with an empty hybrid orbital on the metal ion, thus forming a sigma bond.



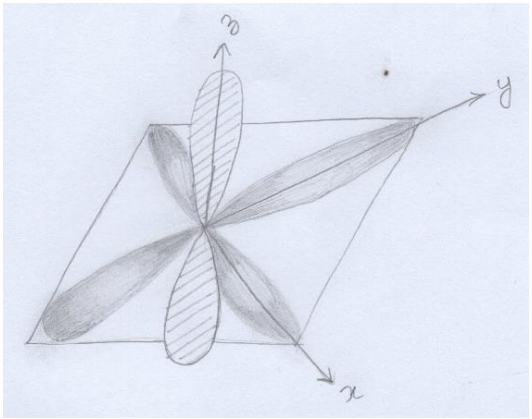

The shortcomings of VBT were superseded by the Crystal Field Theory (CFT), proposed by Bethe and van Vleck. In this, the attraction between the central metal and ligand is considered purely electrostatic, resulting in ion-ion interactions and ion-dipole interactions. The CFT is unable to account for structures of some compounds and hence when some allowance for covalency is made, it is called the ligand field theory which consider sigma overlap of orbitals, π overlap, pπ-dπ bonding (back bonding).

Repulsions by six ligands in an octahedral complex splits the d orbitals on the central metal ion into $t_{2g}$ and $e_g$. Ligands which cause only a small degree of splitting between $e_g$ and $t_{2g}$ are called weak field ligands and ligands causing large splitting are called strong field ligands. The difference in energy between the two d levels is called Δ. Energy required for electron pairing is called Pairing energy(P). If ligands are strong (value of Δ is more), then electrons are paired in $t_{2g}$ before filling begins in $e_g$ orbitals. Similarly weak ligands cause less splitting(higher Δ) which results in filling of electrons in $e_g$ orbitals.

If d electrons are symmetrically arranged, they repel all six ligands equally to form a completely regular octahedron. Asymmetric filling of the $e_g$ orbitals results in some ligands being repelled more than others resulting in tetragonal distortion.

$Pt^{2+}$ - [Xe] $5d^8$

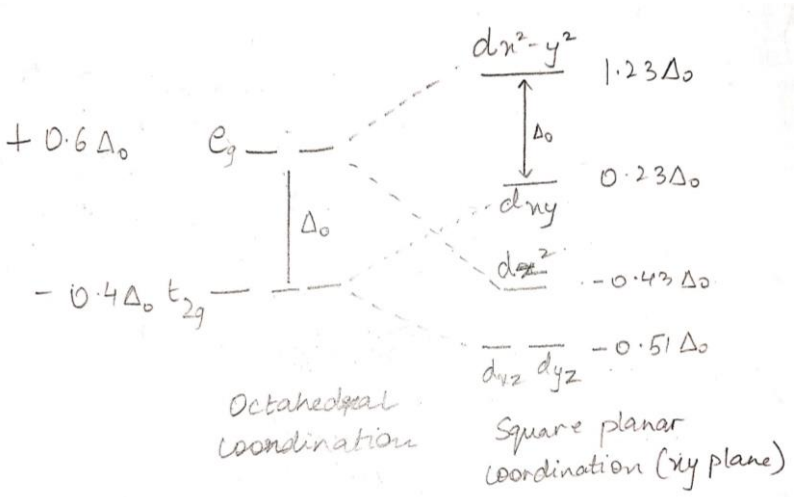
According to CFT, if the central metal ion has a $d^8$ configuration, six electrons will occupy the $t_{2g}$ orbitals and two electrons will occupy the $e_g$ orbitals.




*$d^8$ arrangement ($d_{z^2}$ is full, $d_{x^2-y^2}$ empty)*

The single electron in $d_{x^2-y^2}$ orbital is being repelled by four ligands whereas the ligand in $d_{z^2}$ is only repelled by 2 ligands. Thus, $d_{x^2-y^2}$ rises in energy than $d_{z^2}$ and if the ligand field is

strong enough, the difference in energy between these ligands is greater than the pairing energy. A suitable arrangement in this case is when both electrons pair up and occupy $d_{z^2}$. Hence, the four ligands are free to approach along the x and y axes. This is popularly known as Jahn-Teller Tetragonal Distortion.




## 4 Chemistry of Cisplatin

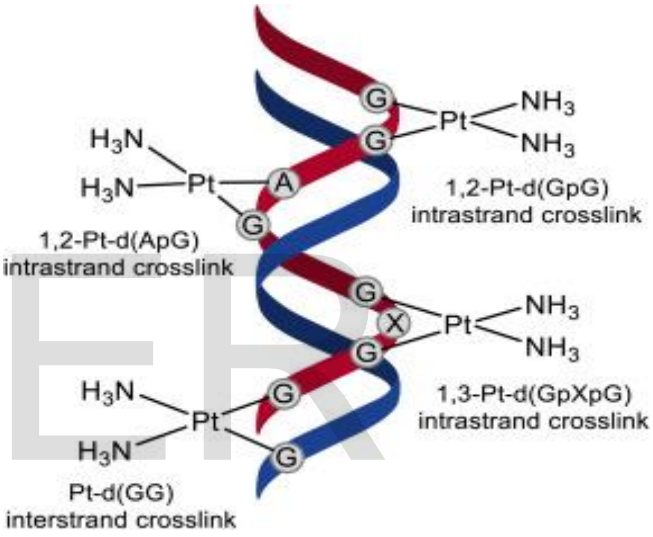
### 4.1 Clinical Use

Dr. Barnett Rosenberg's discovery of the medicinal use of cisplatin led to the "development of immensely important platinum analogues that are today the backbone of solid tumour therapy", in the words of Bruce A. Chabner, who wrote in the memorial issue of cancer research. The fundamental structure of the platinum drugs was elucidated: Pt(II) compounds having two-N donor ligands in a cis-position with atleast one having a N-H group. Compounds showing this structure are expected to play a role against cancer cells. The three most important drugs used in the cancer treatment include Cisplatin, carboplatin, oxaliplatin and their derivatives.

Initially, there were problems in the introduction of this drug due to its neurotoxicity, since it caused renal dysfunction in 30% of the patients. This was overcome by Dr. Esteban, a research fellow from Croatia (who later played lead role in the discovery of Oxaliplatin); he recommended sodium chloride diuresis. Later, cisplatin became the major drug for testicular, lung, ovarian and gastric cancer. It is also used as a radiation sensitizer in other cancers including cervical and esophageal.

### 4.2 Mechanism of Action

Almost all mechanisms of action of cisplatin consider DNA to be its primary target. The partial hydrolysis of cisplatin is the first step in which one chloride ligand is replaced by water, forming cis-$[Pt(NH_3)_2(H_2O)Cl]^+$. This product reacts rapidly with DNA (in particular with adenine and guanine), forming a bond with a single nitrogen N7 on a DNA nucleotide. After complete hydrolysis in the second step, the second chloride ligand is replaced by another water molecule forming $[Pt(NH_3)_2(H_2O)_2]^{+2}$ and Platinum binds to a second nucleotide, resulting in a rapid chelation reaction (see figure 7), forming 1,2 adducts. These aquated species readily react since $H_2O$ is a better leaving group than $Cl^-$. The primary bifunctional adducts are of guanine-guanine or adenine-guanine which causes distortion of DNA proteins, signalling DNA repair or cell death. The distortion is seen in the form of bending of the linear DNA structure. It is suggested, however not yet proved, that these 1,2 adducts are responsible for the anti-cancer activity of cisplatin. It has been found that 60-65% of adducts formed by cisplatin are 1,2-d(GpG) intrastrand cross-links and 20-25% d(ApG) intrastrand crosslink.




*Chelate Ring, Intrastrand Crosslinks with DNA*

Solvation is critical in $[Pt(NH_3)_2(H_2O)Cl]^+$ and $[Pt(NH_3)_2(H_2O)_2]^{+2}$. It has been suggested that the strong Hydrogen bonds of N-H…..O between amine and carbonyl groups are the reason for cisplatin's preference for N7 of guanine. A strong H bond can also be found between metal and water molecules. The overlap of lone pairs over the empty $d_{z^2}$ orbital of Platinum also contributes to the overall stability of the complex.

The vast difference in the reactivity of cisplatin and transplatin is the result of the "trans effect." Transplatin hydrolyses four times faster than cisplatin and reacts with ammonia approximately 30 times faster. The high reactivity of the trans isomer leads to side reactions and hence it is not effective as an anticancer drug. The inability of trans isomer to form 1,2 adducts between adjacent purine bases can be attributed to steric reasons. However, it has been discovered recently that trans complexes with bulky amine groups slow the rate of substitution reactions and are sources of potential drugs.

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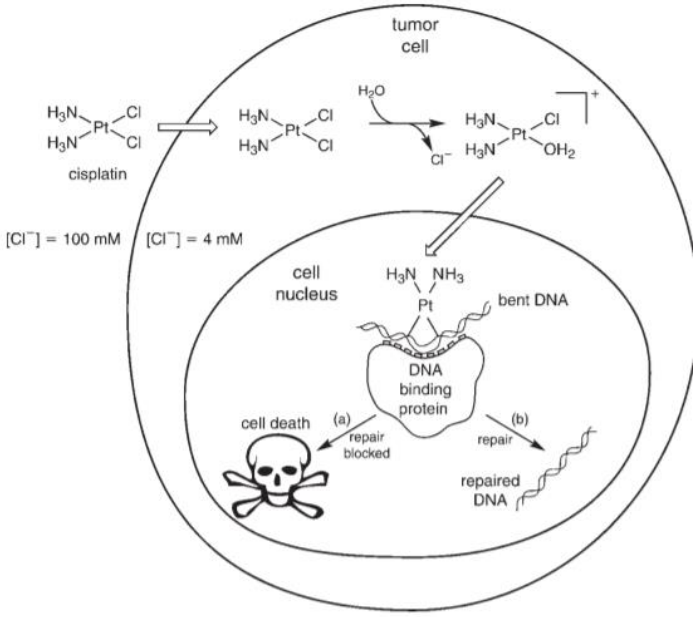
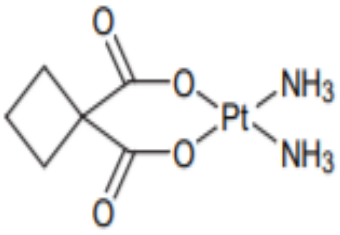


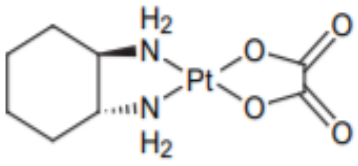

*Overview of Biomolecular Mechanism*

## 5 Development

In spite of the huge success of cisplatin, there continues to be more research on anticancer drugs due to the desire for improved treatment. The effectiveness of cisplatin is undermined by tumour resistance. Some tumour cells have been known to develop resistance against cisplatin after its increased use. The side effects of the use of cisplatin are severe: nausea, vomiting, toxicity to liver, kidney, hearing problems and many others.
Rosenberg and colleagues also developed Carboplatin with the aim of reduced toxicity. Since the bidentate cyclobutanedicarboxylate group is more stable than chloride, it was found show better activity and less toxicity than cisplatin. Oxaliplatin is another Pt(II) complex used in cancer treatment.



*Carboplatin*



*Oxaliplatin*

In recent years, a number of Platinum(IV) complexes have also entered the field. Iproplatin was the first but its use has been abandoned due to no significant advantages over carboplatin. Tetraplatin's use also stopped owing to its high toxicity. The drug satraplatin-{cis,trans-[$PtCl_2$(acetato)$_2$($NH_3$)(cyclohexylamine)]} is currently in its trials and has displayed good activity in cisplatin resistant cells and minimal cytotoxicity in animals.

## 6 Conclusion

The chemistry of platinum anticancer drugs is based on the chemistry of coordination compounds. The influences caused by the geometry can be well illustrated using the trans effect and the differences in the way both isomers react with DNA. The importance of the study of detailed biochemical mechanism of cisplatin is immense to study a wide array of transition metal compounds. The lower toxicity of Pt(IV) indicates the higher stability. The rate of reaction also illustrates the effect of bulky groups and chelating ligands. The effect of Hydrogen bonding should be considered together in the mechanism.
Not only focussed on improving the medical sector but new inventions and discoveries should focus on the environmental effects of the disposal of such toxic inorganic drugs which are non-biodegradable in nature.
A comprehensive study of the most famous drug in the treatment of cancer and its structure opens new doors to this field. It lays the groundwork for further research on improved anticancer drugs. One can expect significant developments in the anticancer industry with use of these metal drugs.

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## Acknowledgment

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## References

[1] Jan Reedijk Increased Understanding of Platinum Anticancer Chemistry- Pure Appl. Chem., Vol. 83, No. 9, pp. 1709–1719, 2011. doi:10.1351/PAC-CON-10-11-03 © 2011 IUPAC, Publication date (Web): 29 March 2011
[2] M. Peyrone. Ann. Chem. Pharm. 55, 205 (1845).
[3] B. Lippert. Cisplatin, "Chemistry and Biochemistry of a Leading Anticancer Drug", Wiley-VCH, Weinheim (1999)
[4] Emanuele Petruzzella, Roman Sirota, Irene Solazzo, Valentina Gandin and Dan Gibson, "Cisplatin Biochemical Mechanism of Action: From Cytotoxicity to Induction of Cell Death Through Interconnections Between Apoptotic and Necrotic Pathways Current Medicinal Chemistry", 2003, 10, 257-266 RSC (2018)
[5] Emanuele Petruzzella, Roman Sirota, Irene Solazzo, Valentina Gandin and Dan Gibson, DOI: 10.1039/c8sc00428e RSC (2018)
[6] J.D. Lee, Concise Inorganic Chemistry
[7] Rebecca A. Alderden, Matthew D. Hall, and Trevor W. Hamble- "The Discovery and Development of Cisplatin" (2006)

[8] Walter Langel, "Molecular Dynamics Studies of Changes In the DNA-Structure As Result of Interactions With Cisplatin" academia.edu
[9]James Platts, "Hydrogen bonding, solvation, and hydrolysis of cisplatin: A theoretical study", Journal of Computational Chemistry, 2004
[10] Barnett Rosenberg: In Memoriam (1924–2009) AACR publications
[11] Wikipedia.org
[12] Inorganic Chemistry, Atkins & Shriver

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