CHAPTER 5

Theoretical investigation on the interaction of transplatin with DNA: A QM/MM study

IN THIS CHAPTER-

- INTRODUCTION
- METHODOLOGY
- HYBRID QM/MM CALCULATIONS

OUTLOOK-

- ✓ We have studied different interacting species that has been involved during the course of the incoming transplatin complex towards its cellular target DNA.
- ✓ The magnitude of binding energy is maximum for the final Pt-DNA adduct.
- ✓ The interaction energy gradually decreases with decrease of distance and the final adduct attains its most stable configuration.
- ✓ The change in Gibb's free energy signifies the feasibility of the reaction under normal body temperature.

5.1 Introduction

Metal based complexes and metal ions are known for its diverse effect in cellular process and the most influencing metal is the platinum. It has been used over the last decade for the treatment of cancer. The successive progress in the metal based drugs stated with the discovery of *cis*-diaminedichloroplatimum (II) complex, clinically known as cisplatin, in 1970s.[1] Cisplatin is found to be paradigm for the treatment of testicular and ovarian cancer. However, the therapeutic window of cisplatin is exceedingly narrowed as this complex exerted some serious drawbacks including nephrotoxicity, neurotoxicity, and ototoxicity and also undergoes indiscriminate distribution throughout the body during treatment.[2-5] To overcome these issues more than 3,000 platinum drugs were derived and tested against several cancer cell lines.[6] In this systematic evaluation process the second and third generation platinum drugs are also introduced which are the analogs of cisplain *viz.* carboplain and oxaliplatin.[7,8] However, these drugs also suffer from resistance issues and other side effects, which are associated with the parent compound. The basic difference in pharmacokinetic point of view of these drugs is the rate of transformation to their reactive species which will selectively target cellular target DNA. The cytotoxicity profile of these drugs is highly dependent on the nature of the carrier and leaving groups coordinated to the central Pt-atom.[9-11] Thus by simply varying the coordinating ligands the activity can be modulated. The design of more efficient and less toxic platinum chemotherpetic agents constitutes a broad area of research in this field.[10,11] The design of more efficient and less toxic platinum chemotherpetic agents constitutes a broad area of research in this field.

Initially, it has been believed that only *cis*-isomers of the platinum based chemotherpic agents are active against cancer.[12] But it was Farrel et al.[13] who first pointed out that certain transplatin complexes showing higher antitumor activity both *in vitro* as well as *in vivo*.[14-16] These are the bulky carrier ligands which reduces the rate of replacement of the chloro ligands and limit the axial access of the Pt-atom.[17] The first representative of this novel class of *trans*-platinum complexes is *trans*-[$PtCl_2$(dimethylamine)(isopropylamine)], represented in Figure 5.1. The compound is a mixture of aliphatic amines, showing marked activity against *cis*-DDP resistance in Pam212-*ras* tumor cells and can induce cell death through apoptosis.[18]

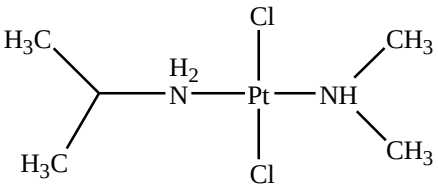

Figure 5.1 Structural formula of *trans*-[$PtCl_2$(dimethylamine)(isopropylamine)]

The cellular targets of platinum based anticancer drugs are N7 atom of the purine bases which are guanine (G) and adenine (A) inside the cell.[19] The tendency of the platinum complexes for the N7 of the purines results from the strong basicity at this position, ability to form hydrogen bond between the amino group of the complex with O6 atom of guanine and the accessibility for the platinum complex, as shown in Figure 5.2.[20,21]

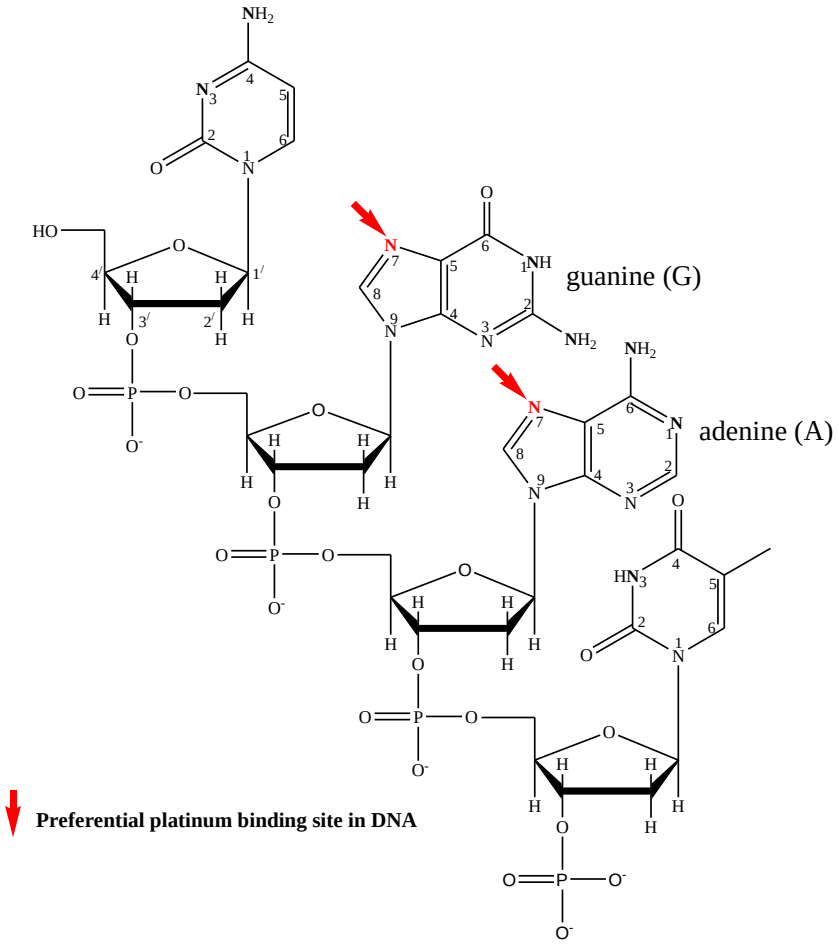

Figure 5.2 Preferential binding site for the platinum based drugs on DNA

Cisplatin adducts in linear DNA include 90% 1,2-d(GpG) or d(ApG) CLs with other lesions including 1,3-d(GpNpG) intrastrand CLs and to a lesser extent interstrand

cross-links (ICLs), monofunctional adducts and various DNA protein CLs.[22] However, transplatin cannot form such intrastrand cross-links instead it will exhibit only monofunctional adducts, 1,3-intrastrand CLs and ICLs.[21] Thus, they will form a kinetically stable Pt-DNA adduct which is generally responsible for biologically activity of such complexes.[23]

5.2 Methodology

5.2.1 Hybrid Quantum Mechanics/Molecular Mechanics (QM/MM) Method:

QM/MM calculations are based on the experimental NMR structure (PDB id:1XRW).[24] The structure has been downloaded from the protein data bank and used for our calculations. The PDB contains a modified site specific octamer in 5′-CCTCG*TCC-3′/3′-GGAGCAGG-5′ fragment where, the asterisk indicates the $[Pt(en)\text{-}ACRAMTU)]^{3+}$ complex (en = ethane-1,2-diamine, ACRAMTU = 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethyl thiourea). In this PDB structure, we have manually replaced the existing complex with our selected *trans*-$[PtCl_2$(dimethylamine)(isopropylamine)] complex.

We have carried out the QM/MM calculation in order to reduce the computational effort since it has a massive structure containing more than 500 numbers of atoms. So, it is quite impractical to perform the density functional calculations in the entire system. For this we have employed the QMERA program[25] incorporated with the Accelrys Materials Studio package. The QM region is treated with the DMol^3, all electron calculation is performed on 'fine grid' using Generalized Gradient Approximation (GGA) including Perdew-Burke-Ernzerhof (PBE), Handy's family of functionals (HCTH) and Perdew-Wang 91 (PW91) level of theories.[26-29] In all the cases, we have used DNP[30] basis set for our calculations. A non-local DFT Hamiltonian is used with Gradient corrected exchange-correlation functional for the QM region,[31] whereas, the MM region is treated with molecular mechanics using GLUP.[32]

We have adopted the hybrid QM/MM method to optimized different possible configurations of the adducts, where, the QM potentials are used for *trans*-$[PtCl_2$(dimethylamine)(isopropylamine)], guanine and cytosine while the remaining DNA bases and sugar phosphate backbone is treated with MM force field.

The total energy function used in this approach is given as:

$$E = E_{QM} + E_{MM} + E_{QM/MM} \tag{5.1}$$

Here, E_{QM} and E_{MM} are the energies for the QM and the MM regions. The last term, $E_{QM/MM}$, describes the interaction between the QM and MM parts and typically contains the terms for electrostatic, van der Waals and bonding interactions across the region.

In this work, we have calculated binding energy (BE) of the final adduct, expressed as

$$BE_{Pt-DNAadduct} = \left[\left(E_{DNA}^{QM/MM} + E_{product}^{QM}\right) - E_{transDNAadduct}^{QM/MM}\right] \tag{5.2}$$

We have also calculated the change in Gibb's free energy (ΔG) with respect to temperature in order to check the feasibility of the incoming drug molecule towards the DNA strand at different distances. The value of ΔG is given as:

$$\Delta G_{Pt-DNAadduct} = \left[\left(\Delta G_{DNA}^{QM/MM} + \Delta G_{product}^{QM}\right) - \Delta G_{transDNAadduct}^{QM/MM}\right] \tag{5.3}$$

5.3 Results and Discussion

5.3.1 Hybrid QM/MM Calculation:

In this part, we have optimized and calculated the values of QM/MM energies of Pt-DNA adduct, DNA at different version of the Generalized Gradient Approximation (GGA) *i.e.* PBE, HCTH and PW91 with DNP basis set using Accelrys Materials Studio QMERA module. The transplatinum complex is free from DNA molecule, therefore, its energy calculated using QM method with the help of DMol[3] programme. The energies of different species are presented in the Table 5.1.

Table 5.1 Calculated values of energies at different levels

Species	Theory level	QM/MM Energy (Hartee)
Pt-DNA Adduct	PBE/DNP	-15.605
	HCTH/DNP	-14.955
	PW91/DNP	-15.638
DNA	PBE/DNP	-12.369
	HCTH/DNP	-11.844
	PW91/DNP	-12.398
		QM Energy
Transplatin complex	PBE/DNP	-4.0093
	HCTH/DNP	-3.8599
	PW91/DNP	-4.038

From this table, it has been found that all the energy values show similar trend, however, PW91/DNP level of theory gives the lowest energy values for all the species in each case. We have also calculated binding energy of the platinum-DNA adduct under different levels to confirm the trend. The binding energy is calculated using the data that has been presented earlier (Table 5.1), with the help of the formula that has been described in the computational details part. The values of the binding energy of the final Pt-DNA adduct are given in Table 5.2.

Table 5.2 Binding energies of the final transDNA adduct

Species	Theory level	Binding Energy (kcal/mol)
Pt-DNA adduct	PBE/DNP	-485.28
	HCTH/DNP	-469.86
	PW91/DNP	-500.58

From the reported data in the Table 5.2 it is has been found that, the binding energy of the adduct at PW91/DNP level of theory is more negative in magnitude compared to that of the other levels. This signifies that at this level of theory, the adduct attains its most stable configuration. The binding energy also follows similar trend that has been observed in case of the individual species *i.e*. PW91/DNP level gives the lowest energy in each case. Therefore, we have chosen this functional in order to study the effect of incoming drug molecule towards the DNA stand. The optimized geometry of the final adduct at PW91/DNP level of theory are shown in the Figure 5.3.

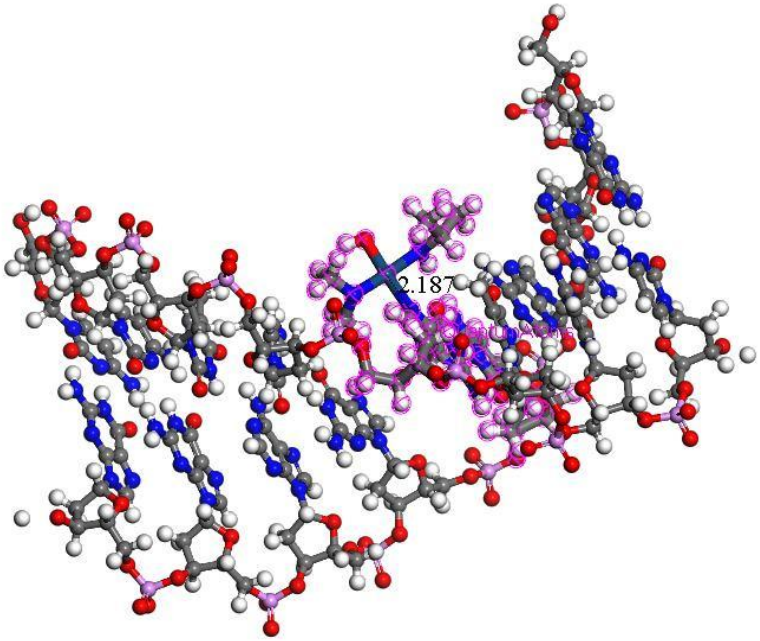

Figure 5.3 Optimized structure of the final Pt-DNA adduct

Here, the *trans*-[$PtCl_2$(dimethylamine)(isopropylamine)] complex, guanine and cytosine is treated as QM level (highlighted in pink colour) and the rest part of the DNA is treated with MM force field. In this optimized structure, the distance between the Pt complex and the DNA *i.e.* Pt–N (from N in the DNA molecule) bond distance is found to be 2.187 Å.

In this chapter, we have also study the structural changes along with the change in thermochemical property of the incoming drug molecule into the DNA strand. For this, we have manually put the title complex at two different distances (near and far) and obtained the binding affinities. Fist we have put the transplatin complex at maximum distance (O-N greater than 5.0 Å) and tried to optimize the whole system. At the optimized geometry, we observe a shift from the original distances, the optimized distance is observed at 4.56 Å, at the same time distance between Pt–O is found to be 2.108 Å. The optimized structure of the combined species is shown in the Figure 5.4.

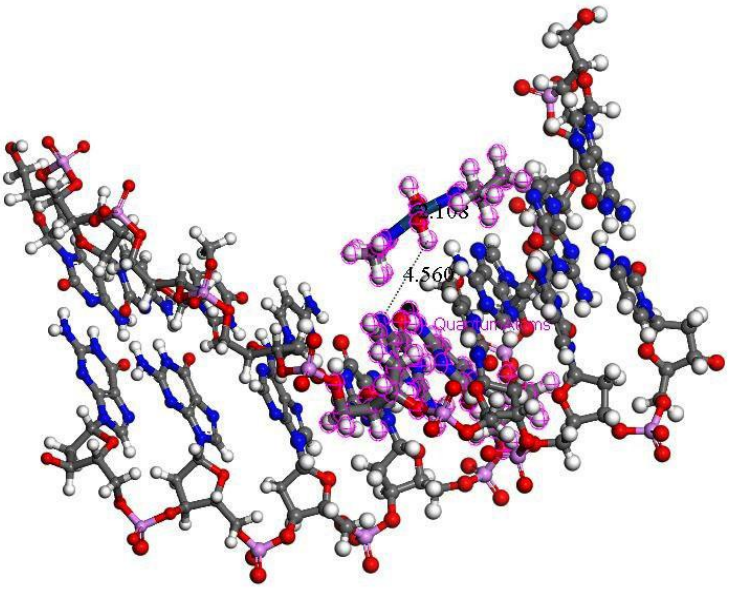

Figure 5.4 Optimized interacting structure of the complex with DNA at 5.0 Å apart

Secondly, we have also studied the interactions between these two species at a minimum possible distance, placing the drug molecule at 3.5 Å away from the DNA duplex. In this case, we have notice a very small shortening of distances, the drug is coming close to the DNA strand and the optimized distance in this case is found to be 3.407 Å between the drug and the DNA system. The distance between Pt–O is at the distance equal to 2.081 Å. The optimized structure of the whole system is shown in Figure 5.5.

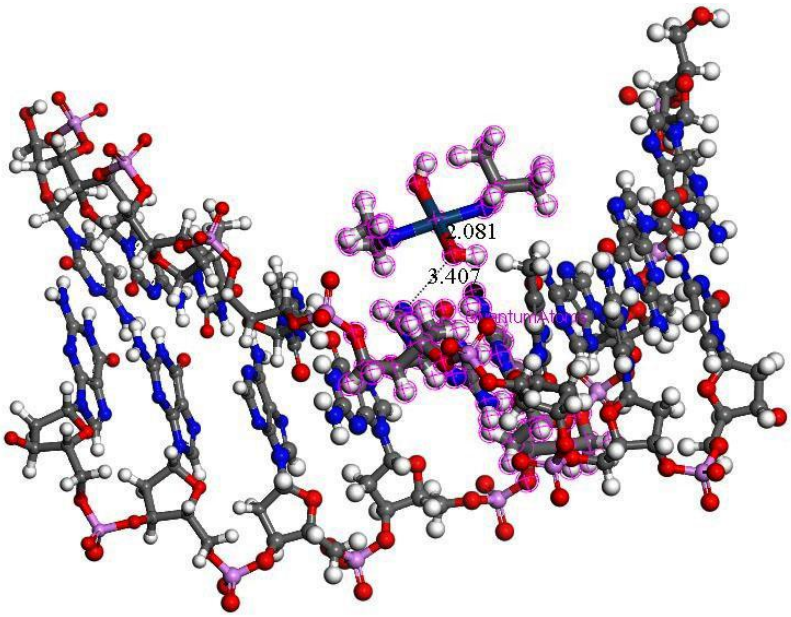

Figure 5.5 Optimized interacting structure of the complex with DNA at 3.5 Å apart

We have also evaluated the interaction energy of the species at these two distances. The QM/MM energies along with the interaction energies of the incoming tranplatin complex are presented in the Table 5.3. The results show that the interaction energy gradually decreases with decrease of distance and the final Pt-DNA adduct attains its most stable configuration.

Table 5.3 Overall energy of the interacting species at different distances

Species	**QM/MM Energy (au)**	**Energy (kcal mol^{-1})**
At a distance 4.560Å		
Pt-DNA adduct	-16.178	-161.815
At a distance 3.425 Å		
Pt-DNA adduct	-16.114	-202.080
At a distance 2.187 Å		
Pt-DNA adduct	-15.638	-500.58

Table 5.4 Change in Gibb's free energy (ΔG) at different temperature

Temperature (K)	**ΔG (kcal mol^{-1})** At 4.56 Å Distance	**ΔG (kcal mol^{-1})** At 3.407 Å Distance	**ΔG (kcal mol^{-1})** After Binding
298.15	7.126	3.544	-0.44
300	7.033	3.414	-0.547
325	5.764	1.635	-2.002
350	4.484	-0.169	-3.473
375	3.192	-2	-4.962
400	1.89	-3.855	-6.468
425	0.576	-5.734	-7.989
450	-0.749	-7.636	-9.526
475	-2.085	-9.56	-11.078
500	-3.431	-11.506	-12.644

Lastly, we have checked the feasibility of the adduct, before and after binding with the help of changes in thermodynamic parameter, Gibb's Free energy (ΔG). At a given temperatures the feasibility of a reaction increases with a decrease in Gibb's free

energy, more negative value of ΔG implies more feasibility. The value ΔG are calculated at temperature ranges (298 K to 500 K) and reported in Table 5.4. From this table, it has been observed that at maximum interacting distance (4.56 Å), the feasibility of the interacting species is found to be at 450 K and above, however, at minimal distance (3.407 Å), the feasibility of the species increases at much lower temperature *i.e.* starts at 350 K. The value of ΔG for the platinum-DNA adduct after binding is negative within the whole temperature range. This will signifies the possibility of the formation of the adduct under normal human body temperature and the feasibility of the reaction (formation of adduct) is increasing when the drug molecule is approaching towards the DNA strand.

5.4 Conclusion

In this chapter, we have studied different interacting species that has been involved during the course of the incoming drug molecule towards its cellular target DNA. We have optimized all the interacting species as well as the final Pt-DNA adduct and calculated the binding affinities at PW91/DNP level of theory. From the results, it has been observed that the magnitude of binding energy is maximum for the final adduct. The interaction energy of the incoming drug molecule towards the DNA is also evaluated. The results show that the interaction energy gradually decreases with decrease of distance and the final adduct attains its most stable configuration. The feasibility of the species is ascertained with the help of the change in Gibb's free energy at different temperature ranges. The change in Gibb's free energy at a particular temperature also shows similar trend and signifies the feasibility of the reaction under normal body temperature. The work presented in the manuscript will be very much useful for the investigation of stability as well as the feasibility of the various species that has been generated during the interaction of the drug molecule with cellular DNA. This initial work will paves the way to explore the different interacting possibilities, which eventually lead to the development of drug with higher success rates.

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