



Study of Suggested Chemotherapy Agent of bis ((S) -3-methoxy carbamoyl pentanoate) di chloride bis(ethyl amine)platinum (IV)(MPP) using DFT



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Abstract

In this paper, we designed the platinum octahedral complex as an anti-cancer drug by applying it to the Gaussian 09W program. The physical properties were calculated using the DFT / B3LYP density function theory for basis sets (LANL2DZ), we also calculated the ultraviolet-visible spectrum (UV), the infrared spectrum (IR), the stability energy, the HOMO and LUMO orbits, the Global properties, and the difference between them and studied the reduction of the octahedral complex to a flat square and its hydrolysis inside the human body, then compared its association with the nitrogenous bases that make up the DNA through nitrogen atom number (N7) and then its association With DNA strand and the results showed that the designed compound achieved high chemical rigidity when linked to methyl. DNA and this indicates its biological effectiveness towards cancer inhibition and compare this result with the well-known treatment against cancer, which is cisplatin, theoretically using the same method and the same basis.

Keywords: Chemotherapy of platinum complex, DFT, B3LYP, LANL2DZ, IR and geometry optimization, Global Reactivity Descriptors.

1. Introduction

Bladder cancer is one of the cancers of the urinary voices, the most repulsive and vicious of all neoplasms in the world⁽¹⁾, Species are activated as Pt(IV), Pt(IV) octahedral complexes can serve as pro-drugs for agents of Pt(II). reduction under physiological conditions To their counterparts from Pt(II), which is followed by hydrolysis and Electrophilic DNA attacks. The bio-reduction of this of Pt(IV) complexes by endogenous elimination of agents such as Glutathione, ascorbic acid, and proteins of the sulfhydryl group, usually ⁽²⁾ The existence and action of the Equatorial Ligands determine axial ligands, both of which are released. Whereas the two ligands of the axial provide A chance to be able to alter the properties of the final metabolite, Such as potential for reduction, lipophilicity, and complexes' specificity ^(3,4) Cisplatin is a small and remarkably simple molecule made up of one atom of platinum bound to two amides and

two chlorides; it is a very effective drug considering its size. Cisplatin undergoes a mechanism known as an equation in conditions of low chloride concentration, as seen in the cytosol, in which one or two chlorides are substituted by water molecules Cisplatin becomes extremely reactive through the aquation process and binds to several biomolecules within the cell readily⁽⁵⁾ Cisplatin covalently binds to DNA bases in its reactive form, DNA adducts formed. interacts Partly with the nucleophilic N7-sites of the purine base, A double reaction can be covalently reacted to When the purines are placed Adducts are formed by Intrastrand on the same filament, or, alternatively, if the purine is on opposite strands, an interstrand crosslink (ICL) is created⁽⁶⁾ Around 50 percent A platinum drug with all chemotherapy regimens is commonly used. Despite their effectiveness In the field of cancer care, Compounds Based on Pt(II) present two major disadvantages: A panel composed of extreme Side-effects and chemoresistance induction. Additionally, All the platinum medications that are used in clinics are administered Intravenously through debilitating

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perfusion cycles, Acute emesis hampers their oral administration as their oral administration, gastrointestinal tract Low bioavailability, toxicity and. Therefore, until destroying a significant number of Pt(II) clusters, meeting Due to protein In the bloodstream bindings, their final goal, resulting in Unwanted side reactions (7) The use of Pt(IV) compounds is one technique to resolve the limits of Pt(II) complexes. They have an octahedral geometry-related coordination number 6, so they are very inert to substitute, and thus suitable for oral administration, enhancing patient compliance. In the bloodstream, their inertness increases their lifespan and hence the likelihood of meeting the target of the tumor and intact. function As prodrugs after the activation of them Intracellular reduction agents, including GSH, Cytochrome, ascorbic acid, and other bioreductants, by reducing hypoxic conditions typical of the cancer microenvironment. Upon reduction, Complexes of Pt(IV) unlock the relevant cytotoxic complex Drug and two axial ligands of square-planar Pt(II) that may be comparable or distinct (8).

The objective of this paper is to estimate the reactivity of DNA bases toward Cis- Pt complex and the dependence of Pt(IV) complex on theoretical chemical parameters such as the energies of Energy to the highest filled orbit (EHOMO) and Energy to tread an empty orbit (ELUMO), the energy gap (Eg) between E_{HOMO} and E_{LUMO} , the global electrophilicity (ω), softness (σ), electronegativity (χ), electron affinity (A), global hardness (η), ionization potential (I), the total energy (Etot) and the fraction of electrons transferred (ΔN).

Experiment

Design Drug The design drug contains three methods as shown in Fig.1: Reaction paths (symmetric and asymmetric) for forming dual Complexes of platinum (IV). Oxidation of platinum (II) with an enormous Carboxylic acid excess and a small additional suitable peroxide for the processing of platinum (IV) monocarboxylate complex 1. Method 2 includes the use of a typical carbodiimide reagent coupling to produce platinum (IV) complex 2 monocarboxylates, after A distinct group of carboxylates is injected Usage of another activated carboxylate to develop platinum (IV) complex 5 in situ mixed carboxylates. Method 3 Usage of a particular one includes reaction R-group (HOCOCH₂CHC₂H₅CONHOCH₃) with an expected Platinum (IV) and Carboxylate complex 3 to produce Complex (IV) 4 dicarboxylates (9).

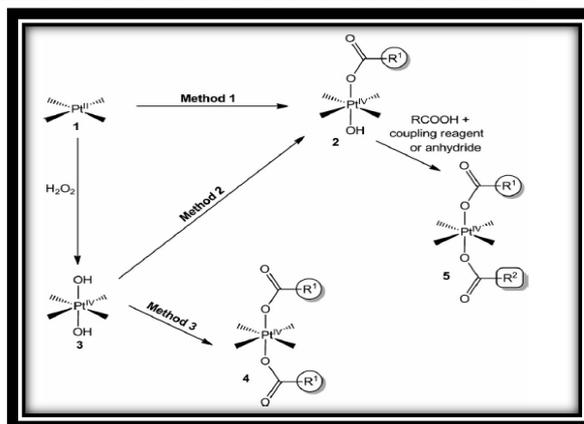


Fig.1: Reaction pathways for forming platinum(IV) complexes

Computational methods

Using the Gauss View program, we drew the platinum complex and performed calculations on it using Gaussian 09⁽¹⁰⁻¹²⁾ using functional density DFT / P3LYB in the basis set LANL2DZ⁽¹³⁾ in which the engineering optimization structure was designed, and the Mulliken charge was determined. As well as determining the total energy of the complex and the energy of the transition between the LUMO and the highest electron-occupied orbit HOMO and determining the energy difference between the orbitals⁽¹⁴⁾ The chemical potential (μ) is defined in theoretical chemistry as defined the negative of the Electronegativity (χ)⁽¹⁵⁾ as:

$$\chi = \frac{1}{2} (E_{LUMO} + E_{HOMO}) \dots \dots \dots 1$$

$$\mu = -\chi = \frac{1}{2} (E_{LUMO} - E_{HOMO}) \dots \dots \dots 2$$

The quantitative description of the hardness (η) An N-electron device with total energy power E can be articulated as⁽¹⁶⁾

$$\eta = \frac{1}{2} (E_{LUMO} - E_{HOMO}) \dots \dots \dots 3$$

The global index of electrophilicity (ω)⁽¹⁷⁾ In terms of is conveyed as:

$$\omega = -\frac{\mu^2}{2\eta} \dots \dots \dots 3$$

Where the First potential for vertical ionization and electrons affinities are IP and EA, respectively, of the

system of chemicals. The above parameters can be expressed as a further approximation using Koopmans' theorem⁽¹⁸⁾.

$$I = -E_{\text{Homo}} \dots\dots\dots 4$$

$$A = -E_{\text{Lumo}} \dots\dots\dots 5$$

Where the energy of the lowest unoccupied molecular orbital is ELUMO, and the energy of EHOMO is the energy of the highest occupied orbital molecular. Moreover, the maximum wavelength of the platinum complex was theoretically measured by computing the visible UV spectrum and diagnosing the complex by computing the infrared spectrum.

RESULTS AND DISCUSSION

Geometry optimization of Pt(IV)Complex

The optimized geometries structure of the octahedral complex Pt(IV) Fig.2, Table (1), DFT /B₃LYP /LANL2DZ addresses all the practical findings of the current analysis.

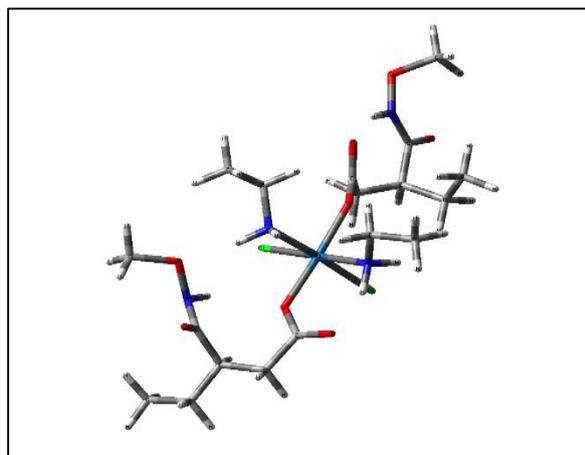


Fig. 2 Geometry optimized for Pt(IV)complex by DFT/ B₃Lyp basis set LanL2DZ (5d,7f).

Also, the measured geometry parameters obtained for the compound and in comparison the available

Table 1 Measure the length of the bond experimentally and theoretically by DFT/B₃LYP/LANL2DZ of platinum complex

Bond type	length by x-ray data	length by calculations DFT
Pt-CL	2.37 Å ⁰	2.43 Å ⁰
Pt-N	2.09 Å ⁰	2.10 Å ⁰
Pt-O	2.02 Å ⁰	2.04 Å ⁰

evidence for X-ray.

It appears that the lengths of the links are consistent with what was measured experimentally⁽¹⁹⁾. We also note from the measurements of the angles between the atoms of the complex (CL-Pt-CL) is 94.53°, (N-Pt-N) is 97.47°, and (O-Pt-O) is 174.18°. The structure of this complex is the distorted shape of an octahedral because the angles of the bonds between the atoms are not of uniform sizes.

Properties of Pt(IV) complex

Mulliken charges distribution

The populations of Mullikan represent the straightforward depictions of the distribution of costs. Charges from Mullikan render in a molecule, net atomic populations are available when electrostatic capabilities produce the electrical field outside of a molecule formed by an internal distribution of charge. We note that carbon atoms with numbers 22,35,40,45 and 51 show a positive charge due to their presence next to high electronegativity groups, which are oxygen and nitrogen and the H₁₁ molecule of hydrogen. The uppermost positive is connected to Nitrogen (N7) As Table (2), Fig (3).

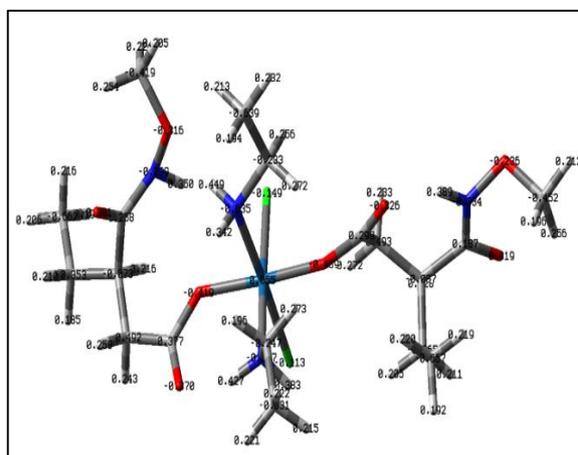


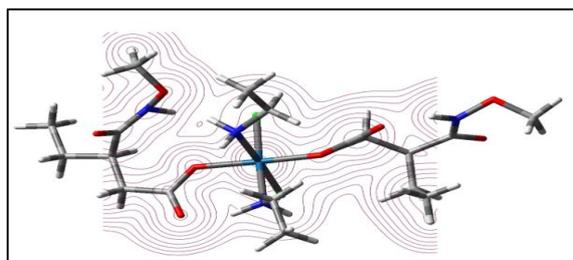
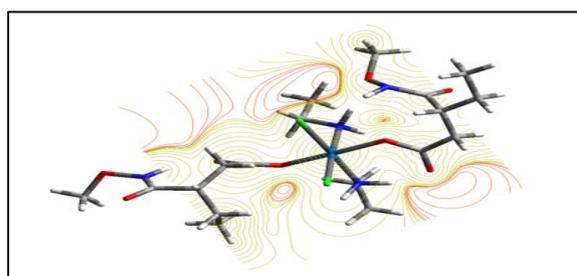
Fig.3 Mulliken charges of 2D for Pt (IV) complex by DFT/ B₃Lyp basis set LanL2DZ (5d,7f).

Table 2: Mulliken charges distribution of platinum complex by DFT/B3LYP/LANL2DZ

No.	Atoms	values	No.	Atoms	values	No.	Atoms	values
1	Cl	-0.113254	24	C	-0.072852	47	H	0.218668
2	Cl	-0.148980	25	H	0.215733	48	C	0.187162
3	N	-0.597364	26	C	-0.353030	49	C	-0.451715
4	H	0.383030	27	H	0.185048	50	H	0.212005
5	H	0.427432	28	H	0.210261	51	H	0.256407
6	N	-0.634933	29	C	-0.662331	52	H	0.195827
7	H	0.341541	30	H	0.197486	53	O	-0.419208
8	H	0.448975	31	H	0.215572	54	O	-0.438894
9	C	-0.247380	32	H	0.206406	55	O	-0.370141
10	H	0.195686	33	C	0.258222	56	O	-0.326331
11	C	-0.630991	34	C	-0.418903	57	O	-0.300679
12	H	0.215099	35	H	0.224323	58	O	-0.319349
13	H	0.220852	36	H	0.205484	59	O	-0.315861
14	H	0.222430	37	H	0.254459	60	O	-0.235974
15	C	-0.233234	38	C	0.298799	61	N	-0.333686
16	H	0.255800	39	C	-0.493047	62	H	0.389364
17	C	-0.639374	40	H	0.233051	63	N	-0.299059
18	H	0.232141	41	C	-0.086721	64	H	0.350055
19	H	0.193650	42	H	0.227970	65	H	0.271929
20	H	0.212705	43	C	0.227970	66	H	0.219896
21	C	0.376518	44	H	0.210679	67	H	0.272541
22	C	-0.492288	45	H	0.205483	68	H	0.272454
23	H	0.242937	46	C	-0.667497	69	Pt	0.055312

Total density and ESP

It is clear from Fig.4. The Carbon atom carries the positive charge. The site for nucleophiles is also expected to be attacked in the MMP complex. But (nitrogen, oxygen, chloride) carries negative charge due to decentralization of the nitrogen, oxygen, chloride, electron pair by resonance⁽²⁰⁾ Fig.5. Show the red color is high electron density but green color is low electron density disturbance on the atoms in the molecular structure.

**Fig.4** Total density of 2D for Pt (IV) complex**Fig.5** ESP of 2D for Pt (IV) complex by DFT/ B3Lyp basis set LanL2DZ (5d,7f).

Energy levels: The energy of the frontal molecular orbital such as E_{HOMO} , E_{LUMO} , and E_{gap} for MMP chloride was calculated by the DFT with B3LYP/LanL2DZ. The energy of electron-donating potential of E_{HOMO} is frequently related to the molecules, Whereas E_{LUMO} energy is correlated With the potential to accept electrons of the molecules⁽²¹⁾.

The high-value E_{HOMO} shows a heavy inclination to donate Electrons with low empty molecular orbital energy to a sufficient acceptor molecule, also the LUMO value shows a high propensity to accept metal electrons. The results are given in Table (3), Fig (6), show which the MPP chloride has the higher energy of LUMO.. The energy gap between the HOMO and LUMO energy levels of MPP chloride (20). Low energy gap values mean low electronic stability and high reactivity after that When low values mean that removing an electron from the HOMO orbital to LUMO would be simple, which can be a positive thing. result in reactivity The energy units of the Hartree are converted to electron volts by the relation (1) Hartree = (27.211 e.v).

Table 3. Energy levels for MPP chloride at DFT/B3LYP/LanL2DZ (5D, 7F) at levels of theory.

Functions	E_{LUMO}	E_{HOMO}	ΔE gap
MPP chloride	-3.72	-6.17	2.45

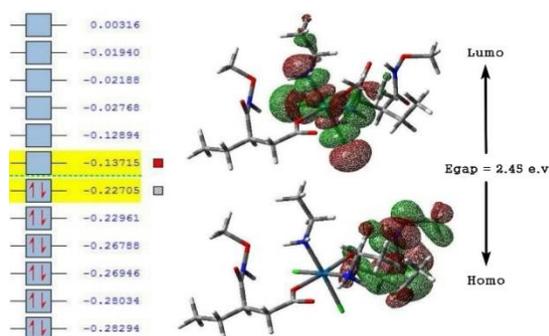


Fig. 6. The energy of molecular orbitals LUMO and HOMO of the complex Pt (IV) by DFT/ B3Lyp basis set LanL2DZ (5d,7f).

Global Reactivity Descriptors

In the table(4), calculate value of chemical potential (μ), electronegativity (χ), global electrophilicity index (ω), global hardness (η), ionization potential(I) and the electronic affinity(A) (22), the results show, the small value of ionization potential indicates high reactivity of the atoms and molecules, the lowest value of hardness indicates a low stable structure. A gain the electrophilicity (ω) is an electrophilic energy calculation of a towards a nucleophile the molecular mechanism. The greater a molecule's electrophilic ability, the greater its reactivity as an electrophile. The designed complex exhibits low hardness and an

electrophilic value indicating that it is a complex with high reactivity (23).

Table 4. Properties of the complex Pt(IV) by DFT/B3LYP/LANL2DZ

MPP	μ (eV)	χ (eV)	ω (eV)	η (eV)	I (eV)	A (eV)
	-4.95	4.955	5.018	2.446	6.179	3.733

Spectroscopy properties

1-UV-Visible spectrophotometer

Fig (7) shows an absorption peak of the maximum wavelength at 558 nm by UV-visible spectroscopy. This leads us to explain that the prepared complex is colored because this wavelength is for the visible region that lies between 380-800 nm.

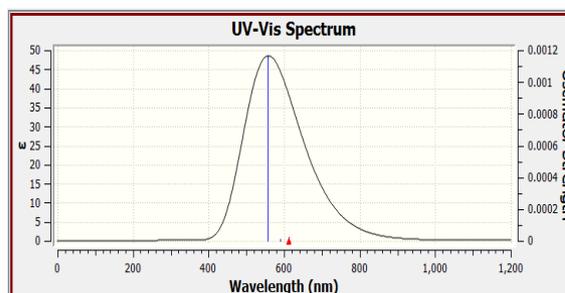


Fig.7. Absorption peak for the maximum wavelength to complex Pt (IV) by DFT/ B3Lyp basis set LanL2DZ (5d,7f).

2-Infrared spectroscopy

For the Pt(IV) complex, at ground state, B3LYP, LANL2DZ base sets shown in Fig (8). the harmonic vibrational frequencies were examined. In addition to asymmetric variants, there were two types of stretching anomalies, including symmetric. The symmetric stretching took place in the same period as the same atoms vibrate, and the asymmetric stretching took place in dissimilar phases as the bonds vibrate. The aliphatic (C-H) stretching vibrations are seen in the region of 3050 cm^{-1} as multiple bands(24) The complex's ν (N-H)amide and ν (N-H) amine stretching vibration measured at $3687, 3215 \text{ cm}^{-1}$ respectively. A new band appears at 1152 cm^{-1} , 1650 cm^{-1} , 1077 cm^{-1} and 1495 cm^{-1} respectively. The ν (C-O), ν (C=O), ν (N-O) and ν (C-N) stretching wavenumber normally appears at 334 cm^{-1} . The ν (Pt-O) at 667 cm^{-1} and ν (Pt-N) band appears at 517 cm^{-1} . The theoretical vibrational decomposition calculations of the platinum complex were carried out using the Gussain09 program (25).

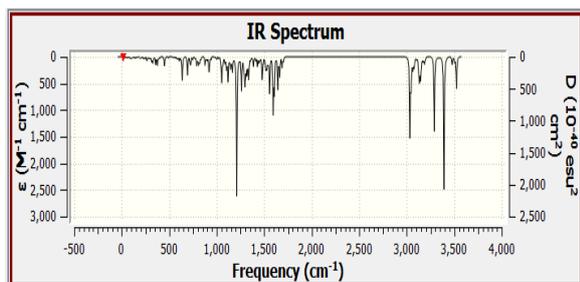


Fig. 8. Infrared spectroscopy of platinum complex by DFT/ B3Lyp basis set LanL2DZ (5d,7f).

Binding with DNA

The octahedral structure of platinum (IV) complexes is less bound to proteins or DNA⁽²⁶⁾, so they are converted within the body to square-level complexes of the cis-type by reducing Pt (IV) to Pt (II)⁽²⁷⁾. Whereas, a relatively high concentration of chloride (about 100 mM) in the blood prevents the ionization of chlorine bonds. It is also evidenced by the fact that this mechanism does not have an ideal pH and is not affected by the presence of structural isotopes⁽²⁸⁾. When compound (II) enters the cell, the chloride ion concentration is much lower (about 4 mM)^(28,29) and then hydrolyses to leave the chloride groups and replace them with aqueous ones. We performed theoretical calculations of the complex association with adenine and guanine once and with human DNA again by mapping part of the DNA. A strand containing three nucleotides arranged in a G-G-T shape, the connection was through the N7 nitrogen atom in both adenine and guanine⁽³⁰⁾. But by

calculating the binding energy, it was found that the energy of guanine binding is less than that of adenine, and this leads us to prefer the bond of the compound with guanine over adenine, and on the other hand, the electronic energy has calculated the energy of the cisplatin complex with the same calculated tape with the compound designed to compare the two results, and it was found that The designed complex has less power, which means that it is more stable. The lower orbital filled with LUMO through which, according to the E_{gap} ⁽³¹⁾, the E_{gap} and chemical hardness (η) are higher for the designed complex than cisplatin and this means a more stable structural structure than cisplatin binding⁽³²⁾, and less electrophilicity(ω) of the designed complex indicating less reactive activity. When binding from cisplatin binding, this leads to the designer complex being more effective in distorting the DNA strand because when it binds to the DNA strand it is more stable and prevents DNA resistance to it. The results are shown in Table (5) and Fig (9).

Table 5. Mathematical comparison between cisplatin and cis dichloro diethanolamine platinum(II)(CEP) using a distribution of DFT/B3LYP/LANL2DZ

Complex type	μ	E gap	η	ω	Electronic energy
CEP	-8.12 e.v	4.48 e.v	2.24 e.v	14.7 e.v	-3.9×10^{-18} K.cal
Cisplatin	-8.31	4.24	2.12	16.2	-3.7×10^{-18} --

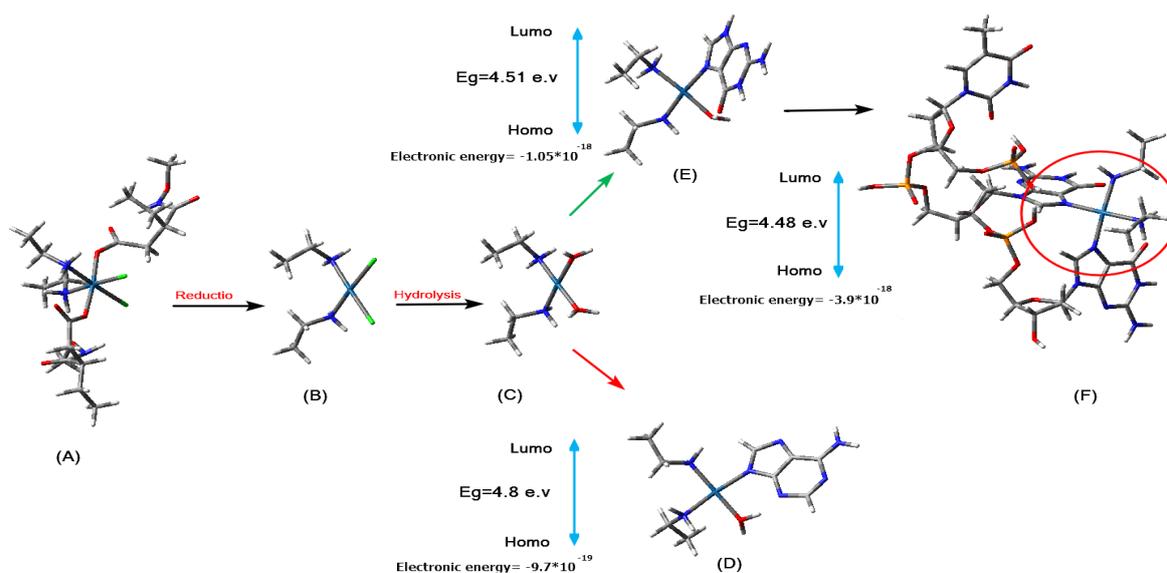


Fig. 9.(A) designer complex by (B) Convert to Pt (II) after reduction (C) Pt (II) complex hydrolysis (D) Pt (II) interaction with the adenine (E) Pt (II) interaction with the guanine (F) Pt (II) interaction with the DNA by DFT/ B3Lyp LanL2DZ.

Conclusion

In this work, theoretical calculations of a new Pt (IV) complex were performed using DFT/B3LYP/LANL2DZ and studied as a potential cancer prodrug, and the potential results were compared with the well-known drug cisplatin, and it was found that the designed complex exhibits a relatively higher chemical stiffness when combined with a piece G-G-T of DNA than that shown by cisplatin when combined with it. The same piece, under the same method and conditions, so this complex may gain an advantage over the resistance of cancer cells to cisplatin due to the stability of its molecular structure when it is in contact with the DNA. This study contributes to the proposal and development of a drug that can be taken orally for both clinical and pharmacological purposes.

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