Molecular modeling of platinum (IV) complex as new drugs for anticancer chemotherapy

Abbas A-Ali Drea

Department of Chemistry- College of Science
University of Babylon, Hilla, Babylon, Iraq

Lekaa Hussain Khdaim

Department of Chemistry- College of Science
University of Babylon, Hilla, Babylon, Iraq

Abstract- Molecular modeling through theoretical calculation have been done to synthesis a new drugs for anticancer chemotherapy. Complex of (bis((4- methoxy -4- oxobutanoyl) oxy) bis methoxy amine)platinum (IV) chloride have been modeled synthesis as Prodrug molecule theoretically using density functional theory, DFT, B3LYP/LanL2DZ at level of theory. Geometry optimization have been calculated for all chemical species that's participate in the modulation. Energetic properties and all other characteristics properties have been calculated to estimate the general features of complex reactivity and stability toward the biochemical reactions.

They found that total energy value of geometry optimized structure equal to -1482.398 a.u. The reactivity measurement by energy gap value 0.01141 kCal mol^{-1}. Prodrug molecule have positive value of imaginary frequency, evidence for their stable complex is achieved through calculus of vibrational transition spectrum. Electronic transition calculation gave a clear view about the nature of chemical bonding and back donation of ligands.

Keywords – Molecular modeling, platinum (IV) complex, anticancer chemotherapy DFT, Theoretical calculation, Geometry optimization, Surface potential energy, and transition state.

I. INTRODUCTION

A lot of chemical compounds have been fabricated for medical uses, epically for Cancer diseases treatments. One of the famous chemical compounds as anticancer chemotherapy are Cis-platinum complexes and its derivatives of carboplatin [1, 2] .Also oxaliplatin [3], nedaplatin[4] have been used widely in anticancer chemotherapy [5-6]. Square planer platinum(II)complex are acting as prodrugs containing two carrier ligands and two leaving groups, the two leaving group are exchanged in the cell platinum complex(IV) are possess ant malignant properties and can act as prodrugs. Novel platinum complex is large group in both Cis and Trans form with different donor ligand [7].Cisplatin is treatment small cell lung, ovarian, testicular, head, and neck tumors [8].The primary target of cisplatin is genomic DNA, specifically the N7 position of guanine bases [9]. Higher level of theory basis set into DFT calculation, that's implemented in package programs like Hyperchem program and Gaussian program been used to achieve a new model of drags or to proposed mechanism respect complex acting as prodrug for anticancer chemotherapy [10-14].

In the present work, modulation anew prodrug anticancer of platinum complex (IV) based on theoretical calculation that's will be done depending on DFT calculations. Geometry optimization process are proceed to get on physiochemical properties such as Mullikan charge ,EHOMO,ELUMO ,energy gap ΔE ,dipole moment (µ),total density, electrostatic potential ,Absolut electronegativity (X) ionization potential(I) chemical hardness (η) ,chemical softness(S) and electron affinity(A) [15-17].

II. COMPUTATIONAL DTAIL

Different theoretical MO method have been used, that's implemented onto G09W [18] running on windows XP work station with core i7 .The geometry optimization of platinum complexes at DFT /B3Lyp [Becke's three parameter exchange functional along with the Lee-Yang-Parr nonlocal correlation functional [19-20]. Frequencies of vibration and electronic transitions have been calculated for platinum (IV) complexes using B3Lyp /LanL2DZ method. Calculus are done using restricted and unrestricted Hartree Fock respectively [21]. All characteristic properties of complexes, like ionization potential, Electron affinity, and others labeling phenomena have been calculated using Koopmans's theorem [22, 23].

III. EXPERIMENT AND RESULT

Geometry optimized structure of complexes have been calculated using DFT based on B3Lyp /LanL2DZ at level of theory in vacuumed. Figure 1. Represent the geometry optimized structure of complex A. Table 1. Represent the theoretical parameters of optimize geometry as bond length and bond angle of Pt(IV)complex.
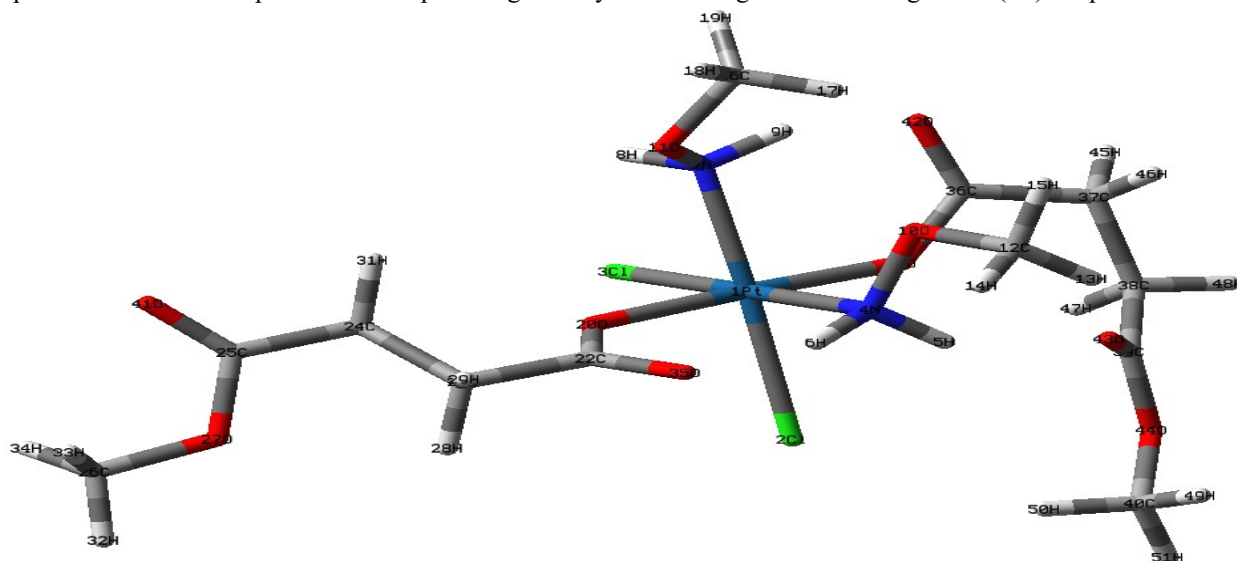

Figure 1. Geometry optimized for Pt (IV) complex by DFT/ B3Lyp/LanL2DZ (5d, 7f) at Level of theory.

Table 1. Theoretical parameter of bond length and bond angle Pt (IV) complex by using DFT/B3Lyp/LanL2DZ at level of theory.

Bond type	Length bond nm	Angle type	Bond angle Å	Dihedral Type	Dihedral
Pt_1-N_{21}	1.97	$Pt_1-N_{21}-O_{22}$	120	$Pt_1-N_{21}-O_{22}-C_{23}$	-180
Pt_1-Cl_{17}	2.29	$Pt_1-N_{18}-O_{19}$	120	$Pt_1-N_{18}-O_{19}-C_{20}$	-180
Pt_1-O_3	1.94	$N_{21}-Pt_1-N_{18}$	90	$Pt_1-O_3-C_5-C_7$	90
		$N_{21}-Pt_1-O_3$	90	$Pt_1-O_2-C_{11}-O_{12}$	-90
		$Cl_4-Pt_1-N_{18}$	180	$Pt_1-O_2-C_{11}-C_{13}$	90
		$Cl_4-Pt_1-O_3$	90	$Pt_1-O_3-C_5-O_6$	-90

The symmetry of complex A form is C1 refer to asymmetrical distribution in the Pt(IV)complex .The output of this complex A gave C1 symmetry which is wrong symmetry [24].The dipole moment (µ) vary from 3 to 15 due to complex A is quite polar complex [5],the dipole moment values of complex for I.R and UV-Vis spectra is different 8.0922,6.2402 respectively. The imaginary frequencies is positive and the energy values is negative ,therefore stable complex A .The physical an thermodynamic properties of complex A were calculated such as energy (kCal mol^{-1}), heat of formation ΔH, Gibbs free energy ΔG, entropy ΔS, thermal energy .

Table 2. Thermodynamic calculation of Pt(IV)complex by using DFT/B3Lyp/Lan2DZ at 298.150K at levels of theory

Total energy	-1482.398 a.u
Enthalpy ΔH	268.8867 Kcal/Mol
Gibbs free energy	202.4278 Kcal/Mol
Entropy	222.9042 Kcal/Mol
Zaro point energy	237.0818 Kcal/Mol
Imaginary frequencies	+
Time of calculation	IR=1h:17m:27s and UV=8h:46m:8s
Degree of freedom	147
Kinetic energy	1.375159960421D+03
E-N energy	-9.549360577589D+03

N-N energy	3.059532181679D+03

High electron density distribution on oxygen in carbonyl groups and nitrogen in amine group because the high value of electronegativity [25].The electrostatic potential in Figure 2,3, the negative charge are remarked by red color are distribution on the oxygen atoms in carbonyl groups and the nitrogen in amine group due to high value of electronegativity .The positive charge are remarked by green color are distribution on Carbone atoms[26].The Mullikan atomic charges give a positive value for C and H and negative values for O, N, S, Cl atoms .Figure 4.
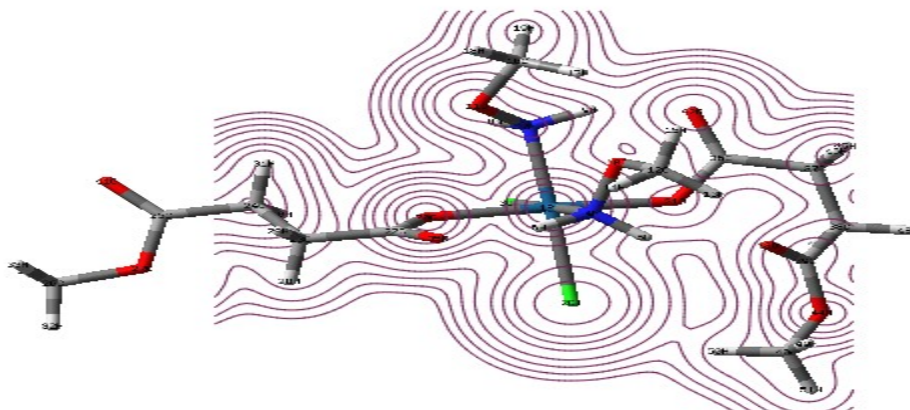

Figure 2. Total charge density for Pt(IV)complex by using DFT/B3Lyp/Lan2DZ at levels of theory.
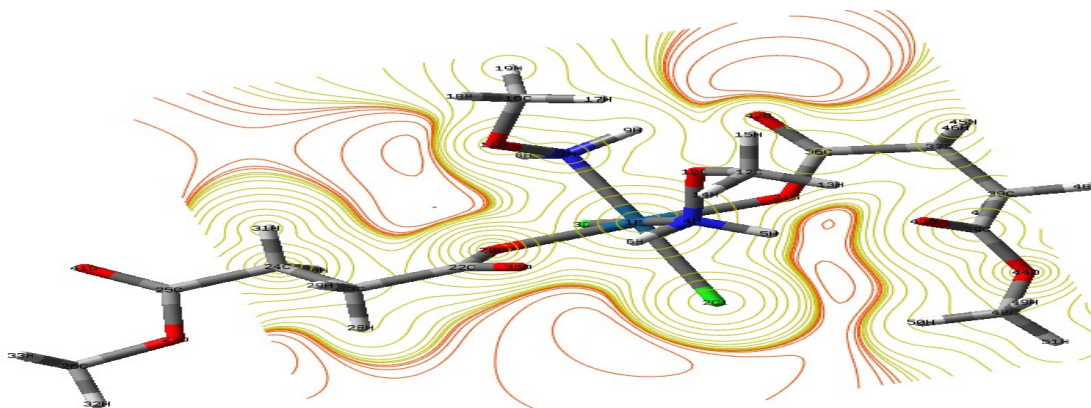

Figure 3. Electrostatic potential (ESP) for Pt (IV) complex by using DFT/B3Lyp/LanL2DZ at levels of theory.
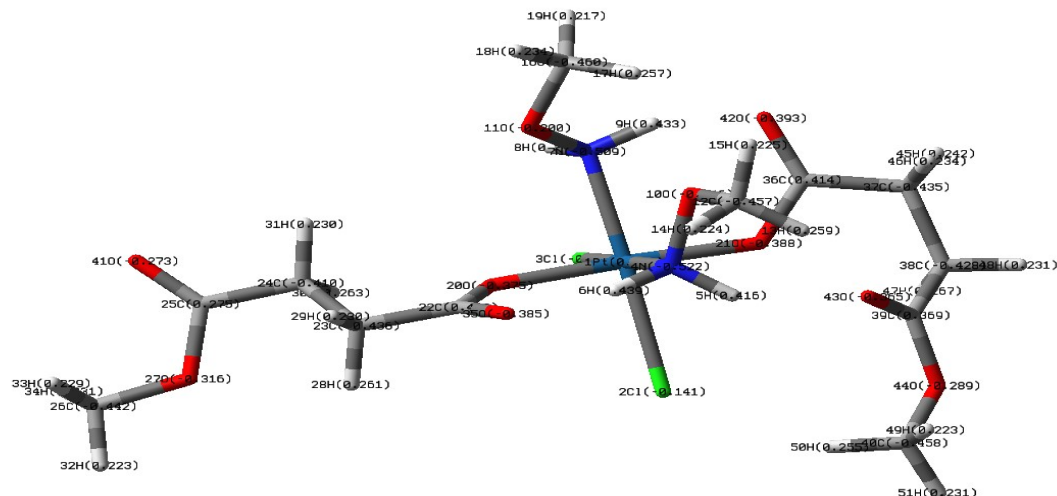
Figure 4. Mullikan atomic charge for Pt(IV)complex by using DFT/B3Lyp/LanL2DZ at levels of theory

C-HOMO-LUMO Calculation

Geometry optimization form for platinum (IV) complex described the frontal orbital's is useful to explore the interaction of surface metal's atoms and adsorption centers of the inhibitor molecule [27].The value of HOMO energy is often associated with electron donating ability of complex ,but the energy of LUMO is ability to acceptor electron [28].The energy of HOMO =-0.00239,while the of LUMO =0.00902, low energy gap candidates this complex to be a good semiconductor and solar material .The reason behind this small gap is the extended of the metallic element platinum due to their availability in the HOMO energy level[29] , table 2 .Figure5 .

Table 2. Physical properties for Pt (IV) complex at DFT/B3LYP/LanL2DZ (5D, 7F) at levels of theory.

Type of calculation	Value of properties calculation
HOMO energy	-0.00239 Kcal/Mol
LUMO energy	0.00902 Kcal/Mol
Energy gap	0.01141 Kcal/Mol
ionization potential	0.26692
Electron affinity	0.12087
electronegativity	0.193895
chemical hardness	0.073025
chemical softness	13.69394

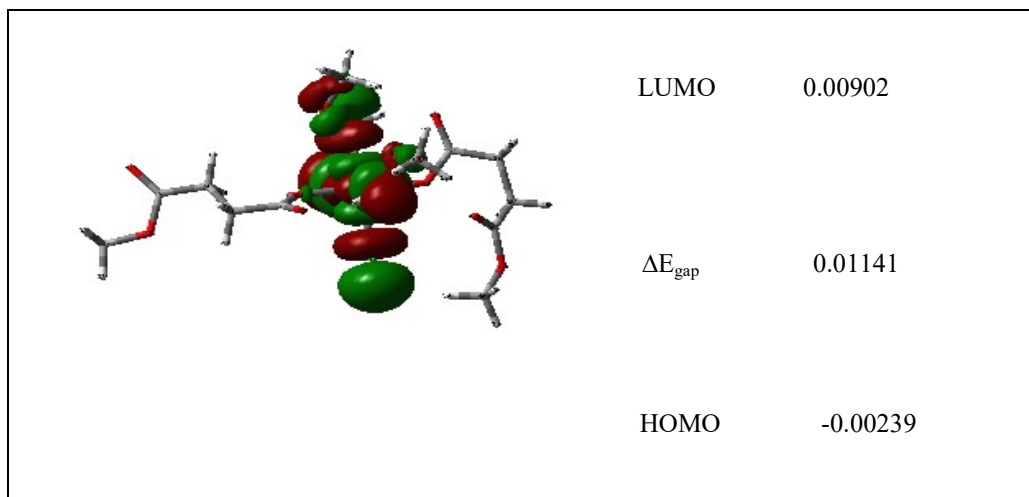|		
LUMO	0.00902	
ΔE_{gap}	0.01141	
HOMO	-0.00239	

Figure 5. HOMO-LUMO of the geometry optimized Pt(IV)complex by DFT/B3LYP/LanL2DZ at levels of theory.

D-Infrared spectroscopy study

The theoretical I.R data for platinum (IV) complex was calculation by using DFT/B3LYP/LanL2DZ , table 3show vibrational frequencies for complex A ,the limited refer to high intensity in IR spectra also description of type frequencies in complex A .The spectrum of complex shows band 2850-3000cm^{-1} which due to (C-H) aliphatic ,the spectrum of complex show band 3300-3500cm^{-1} which due to (N-H)stretching, the band in IR of complex at 1705-1725cm^{-1} which due to (C=O) ,the band at 1000-1300cm-1which due to(C-O)stretching , the two band 1515-1560 & 1345-1385 which due to (N-O)stretching . New bands have been occurred around (Pt-O) ,(Pt-Cl) (Pt-N)at 710cm^{-1} , 320cm^{-1} , 568cm^{-1} respectively as shown at Figure 6.

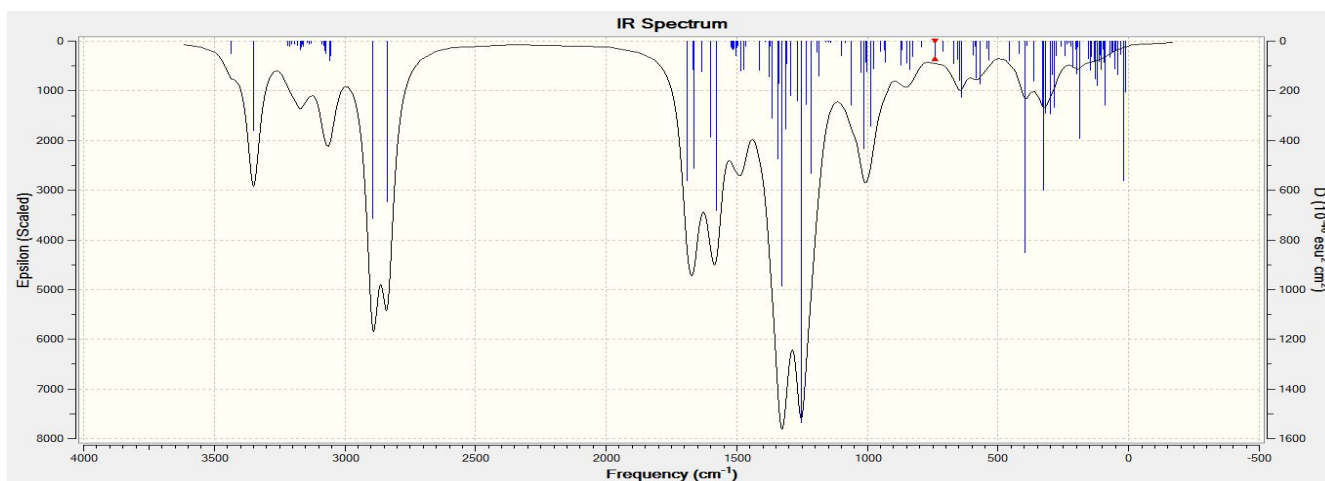

Figure 6. I.R.- frequencies calculated for Pt (IV) complex at DFT/B3LYP/LanL2DZ at levels of theory.

E-Ultra –violet spectra

The UV-Vis spectra of the complex A showed abroad band in visible region at 10000cm^{-1} table1 show transition state for complex A was characterized by different beak at high oscillator strength in select cell at (293 and 306) nm refer to (n-δ*) from O4Px,y,z to 1Pt $_{7d}$,1Pt$_{7d+2}$,transition state other from Cl $_{4p\,x,y,z}$ to 1Pt $_{7d}$,1Pt$_{7d+2}$, Figure7 ,and can be assignable to [30].
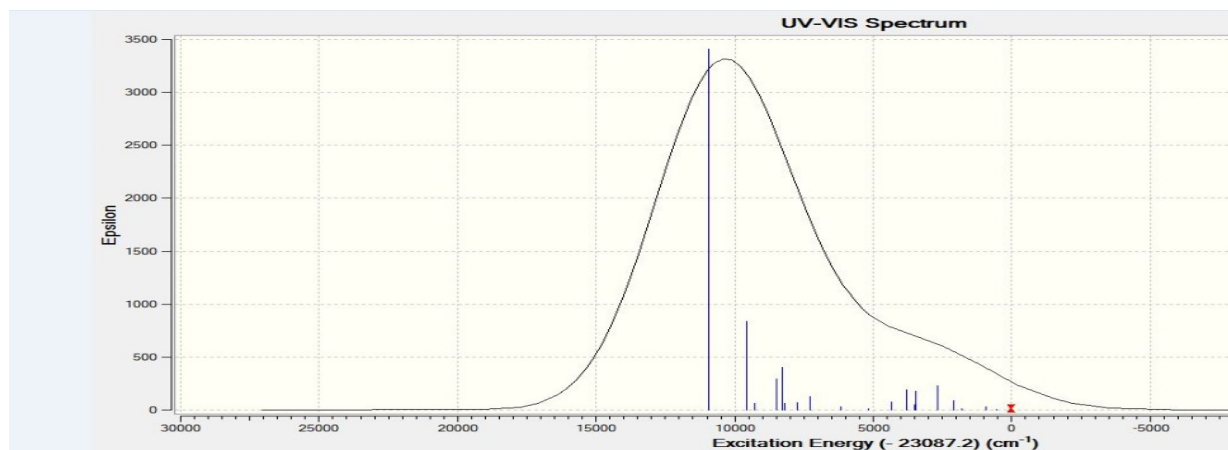
Figure 7. U.V-Vis spectra calculated for Pt(IV) complex at DFT/B3LYP/LanL2DZ at levels of theory

Table 1. Theoretical calculation for UV-Visible transition state for Pt(IV) complex at levels of theory

Theoretical calculation						
Excitation energy (ev)	Wavelength (nm)	Oscillator strength	Occ MO	Unocc MO	Coefficient	Explanation
3.1939	388.19	0.0039	108 110 111	113 112 113	0.57435 0.11820 0.10744	n-σ* $2Cl_{4px} \longrightarrow 1\ pt_{7d+2}$ $3Cl_{4px} \longrightarrow 1\ pt_{7d0}$ $35O_{4px} \longrightarrow 1\ pt_{7d+2}$
3.2895	376.91	0.0031	106 107 109 109 110 111	112 113 112 113 112 112	0.25360 0.27824 0.10880 0.22106 0.29981 0.36509	n-σ* $35O_{4px} \longrightarrow pt_{7d0}$ $3Cl_{4py} \longrightarrow 1\ pt_{7d+2}$ $2Cl_{3pz} \longrightarrow 1\ pt_{7d0}$ $2Cl_{3pz} \longrightarrow 1\ pt_{7d+2}$ $2Cl_{3px} \longrightarrow 1\ pt_{7d0}$ $35O_{4px} \longrightarrow pt_{7d0}$
3.3308	372	0.0033	107 107 110 111	112 113 113 113	0.12380 0.55124 0.16756 0.16750	n-σ* $3Cl_{4py} \longrightarrow 1\ pt_{7d0}$ $3Cl_{4py} \longrightarrow 1\ pt_{7d+2}$ $3Cl_{4px} \longrightarrow 1\ pt_{7d+2}$ $35O_{4px} \longrightarrow pt_{7d+2}$
3.8906	318.67	0.0069	100 102 103 106	113 112 113 112	0.10286 0.11850 0.27107 0.38060	n-σ* $43O_{4py} \longrightarrow 1\ pt_{7d+2}$ $20O_{4py} \longrightarrow pt_{7d0}$ $21O_{4pz} \longrightarrow 1\ pt_{7d+2}$ $35O_{4px} \longrightarrow 1\ pt_{7d0}$
3.9171	316.52 nm	0.0051	100 102 102 103 105	112 112 113 112 112	0.11546 0.45846 0.15296 0.19809 0.20967	n-σ* $43O_{4py} \longrightarrow pt_{7d0}$ $20O_{4py} \longrightarrow 1\ pt_{7d0}$ $20O_{4py} \longrightarrow pt_{7d+2}$ $21O_{4pz} \longrightarrow pt_{7d0}$ $42O_{4px} \longrightarrow 1\ pt_{7D0}$
4.0511	306.05	0.0144	102 105	113 113	0.49511 0.17929	n-σ* $20O_{4py} \longrightarrow pt_{7d+2}$ $42O_{4px} \longrightarrow pt_{7d+2}$
4.2190	293.87	0.0585	99 100 103	112 112 113	0.33411 0.13319 0.11235	n-σ* $10O_{4px} \longrightarrow 1\ pt_{7d0}$ $43O_{4py} \longrightarrow pt_{7d0}$ $21O_{4pz} \longrightarrow pt_{7d+2}$

F-NMR spectra

Chemical shifts of 13C and 1 H -NMR in complex A were investigated by DFT /B3LYP/LanL2DZ (5D,7F) using NMR with GIAO. Calculated chemical shifts of 13C and 1 H -NMR in complex A are shown in Figure 8 (a,b) .The chemical shifts of 13C and 1 H-NMR in complex A as referred by TMS were separated around 28 ppm -192 ppm, and 1.75 ppm – 12.5 ppm, respectively. This behavior was influenced by magnetic shielding effect on the Pt(IV) complex .The separated chemical shifts of 13C and 1H-NMR were caused by nuclear spin interaction in carbon, and proton atoms on Pt(IV) complex .The chemical shift was mainly caused by hybridization of d spin in metal. The chemical shifts of 13C and 1 H NMR Pt (IV) complex depended on the electron density distribution with a slight deviation of charge density on Pt (IV) complex [31]
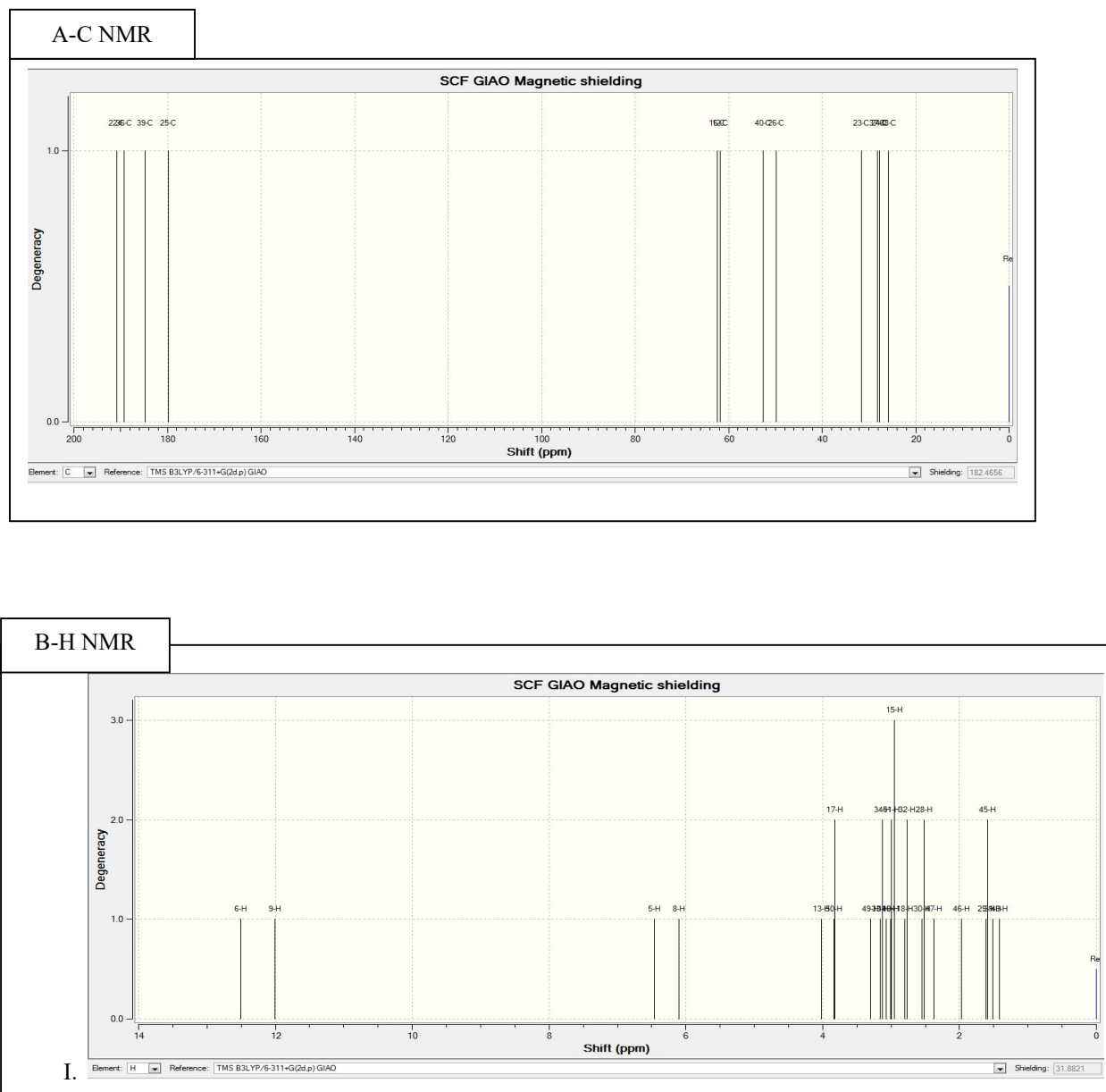
A-C NMR

B-H NMR

Figure 8. NMR spectra calculated for Pt(IV) complex at DFT/B3LYP/LanL2DZ at levels of theory.

IV.CONCLUSION

- The geometry optimized structure of Pt (IV) complex have been calculated using DFT based on B3Lyp /LanL2DZ at level of theory in vacuum.

- The symmetry of complex A form is C1 refer to asymmetrical distribution in the complex A .The output of this complex A gave C1 symmetry which is wrong symmetry
- Thermodynamic calculation of complex A by using DFT/B3Lyp/LanL2DZ which is endothermic and nonspontaneous (268.8867, 202.4278 and energy gap is 0.01141 at k Cal/mole units.
- The stabilized structure of Pt(IV) complex comes out by total energy which equal to -1482.398 a.u units .

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