### Investigation Study of Molecular Modeling for New Pt(Iv) Complex Using Density Functional Theory

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#### **KEYWORDS**

Theoretical study, structural properties, B3LYP, Lanl2DZ, Cis platinum complexes and DFT.

### ABSTRACT

Investigation study has been carried out to find a new geometry optimization
structure of octahedral platinum complex (diaminobis ((hydroxyl carbamoyl)
Oxy) platinum(IV) chloride) (DHOP) by using density functional theory
(DFT) method /B3LYP/Lanl2DZ basis set that's implemented into Gaussian
09 program. Structural and energetic properties have been investigated, such as
total energy, $\Delta G$ , $\Delta H$ , $\Delta S$ , EHOMO, ELUMO, Egap and the rate constant for
all chemical reaction.
This study shows that the energy gap value of DHOP complex is high with low
value of ZPE and positive imaginary frequency, this refers to higher stability of

دراسة تحقق للنمذجة الجزيئية لمعقد البلاتين (IV) الجديد باستخدم نظرية دالة الكثافة

Platinum complex formation.

لقاء حسين كاظم\*1 و عباس عبد علي دريع 1

1 قسم الكيمياء ، كلية العلوم ، جامعة بابل ، الحلة ، بابل ، العراق

المُستلخص	
اجريت دراسة التحقق لايجاد التركيب الهندسي الامثل لمعقدت البلاتين ((IV الثمانية السطوح (ثنائي امينو بس(هيدروكسيل كاربوميل )اوكي بلاتين (IV) كلوريد (DHOP) بوساطة استخدام طريقة نظرية دالة الكثافة المعتمدة على الدالة القاعدية /B3LYP/LanL2DZ المتضمنة في برنامج كاوسين 09. اجري التحقق من الخصائص الطاقية والتركيبية مثل الطاقة الكلية وطاقة كيبس والانثاليي والانتروبي	رقم المسودة: (2872) تاريخ استلام المسودة: 04/02/2017 تاريخ المسودة المُعَذَلة: 10/09/2018 *الباحث المراسل: لقاء حسين كاظم بريد الكتروني: liqaa.aljailawi@uokufa.edu.iq
ولا الموجيك المسطى المصوع بالمسروك ولك المتورجين متوجي المرح والك المبرد والمبرد السرعة للتفاعلات الكيميائية . تبدن من الديار قربان قربة الله ترالنار قربال قر DILOP تكان ذرقته قرمالية القترنتان	الكلمات الدالة
نبيل من الدراسة بال فيمة طافة الفجوة الخاصة بالمعقد DHOP لحون ذو قيمة عالية وطافة نقطة الصفر واطنة القيمة أضافة الى ان أشارة التردد الخيالي موجبة دلالة على الاستقرارية العالية لتكون معقد البلاتين.	در اسة نظرية والخصائص التركبية و B3LYP,LanL2DZومعقد سز بلاتين و نظرية دالة الكثافة

### Introduction

Metals are used in medicinal application can be traced back almost 5000 years (Orving, 1999). Development of modern medical inorganic chemistry centers of positive metals charged are favored to bind negatively charged biomolecules; the constituents of proteins and nucleic acid as good complexes for binding to metal ions (Christiana, et al, 2003), Simulated by the serendipitous discovery of cisplatin. Cisplatin therapy is associated with at least temporary infertility in the majority of patients (Perry, et al, 1992). Among males receiving cisplatin for testicular cancer, almost all became azoospermia within the first two cycles of therapy. Metals are ubiquitous and some are essential for cellular processes. Depending on their availability, metals were selected during the process of evolution to improve biochemical processes involved in cellular processes. While metals have specific characteristics that include redox activity, variable coordination modes, and reactivity towards organic substrates, there intracellular availability is tightly regulated. Thus, aberrant metal ion concentrations are associated with various pathological disorders, including cancer. Nevertheless, metal compounds are potential candidates as anticancer agents (Frezza, et al 2010). Cisplatin is one of the most potent chemotherapy drugs widely used for cancer treatment. The discovery of cisplatin, cis-[Pt (II) (NH3) 2Cl2], ([PtCl2 (NH3)2] or CDDP), was a cornerstone which triggered the interest in platinum (II) - and other metalcontaining compounds as potential anticancer drugs. Clinical use of CDDP determined that many patients with different types of cancer have been successfully treated, including: sarcoma cancers, cancers of soft tissue, bones, muscles, and blood vessels. Such cancers received better prognosis and therefore became less life threatening these days (Rosenberg, et al 1980 and Desoize et al 2002). The clinical success of CDDP and its derivatives determined considerable effort to develop other effective metal-based anticancer compounds (Che et al 2010 and Chen et al 2009). However, its use is limited due to side effects in normal tissues. The cytotoxic effect of cisplatin its food and drug administration (FDA) approval in 1978, Pt (IV) compound was used in clinics worldwide (carboplatin, oxaliplatin, nedaplatin, lobaplatin,

hepaplatin, miriplatin and dicycloplatin (Wheat, et al 2010, Tanaka et al 2011 and Yang, et al, 2012). After the discovery of Cisplatin as anticancer drugs, used different of Pt (IV) complex and almost 50% of all anticancer chemotherapy (Galanski, 2005). Cisplatin complex is used also as therapy for small cell lung, ovarian, testicular, head and neck tumors (Schornagel, 1996 and Adjei, 1999). The computational study of Pt (IV) complex using DFT and Lanl2DZ has been formally described in the literature (Picazo, et al 2007). This study showed that the M-N, and M-O bonds are formed by the electron ion pair association between Nitrogen and Oxygen atoms within the metal atom, indicating Covalence bond and binding M-Cl using the same level of computation (Picazo, et al 2009)

Our team has recently suggested a new PT (IV) complex provided with energetic structural evidence, such as total energy, EHOMO, ELUMO, agape and some other stability factors of the complex.

#### **Computation methods**

Geometry optimization of suggested chemical structures is performed through package program, Gaussian 09 (Pan et al 2013). Density functional theory (DFT) has employed for all our calculations. (Parr, et al 1989 and Zeiglar, 1991), Beck three parameter hybrid functional in conjunction with Lee-Yang-Parr correlation functional (B3LYP) method (Becke, 1988 and Stephens, et al, 1994). Basis set of Lanl2DZ (Pan, et al 2013) level of theory. HOMO and LUMO energy levels and then the Egap value were calculated only for minimum energy for DHOP complex (diaminobis ((hydroxycarbamoyl) Oxy) platinum (IV) chloride). Measurements of Vibrational frequencies are carried out thorough same computational method to characterize the nature of stationary points with zero point energy. Calculation of total energy stability had been performed at the B3LYP / Lanl2DZ level of theory to estimate bond length, bond angle and dihedral for DHOP complex. Reaction rate constant has been calculated by DFT /Lanl2DZ to estimate the reaction rate of determining reaction step.

### **Results and Discussion**

The results of bond lengths and bond angles and dihedral angle (Pan, et al 2013) are represented in Fig.1, most of bond length values are slightly larger than the experimental values. Theoretical calculations are perfect for an isolated molecular structure in vacuum (Lewis et al 1994). The differences of bond length for DHOP complex as Pt-Cl, Pt-O, and Pt-N are (2.290, 1.950, 1.99), experimental values of bond length(2.280,1.945,1.88) respectively and the bond angle as(Cl10-Pt1-Cl11), (Cl11-Pt1-N2), (O13-Pt1-N3), (N2-Pt1-O12) and (N5-Pt1-N3) are (90°,180°,89°,90°,82°) respectively. The dihedral angle in molecule (C17-O13-Pt1-Cl11), (N15,C14,O12,Pt1) and ,(N16,C17,O13,Pt1) are (180°,90°,90°) respectively, predicting a drastic decrease of dihedral angle (Urmila, et al 2013).

FUNCTION	ΔH*	ΔG*	ΔS**	ZPE**	Imaginary frequencies	Total energy A.u	Degree of freedom	Full point group
DHOP	116.152	72.01	148.06	99.43	+	-642.76	69	C1
Complex								





The energy difference between HOMO and LUMO orbital is called agape (energy gap) which is important for stability of DHOP complex (Sudha, et al 2011). And 3D and 2D plots HOMO & LUMO and energy as shown in Table 1, Fig.2, and Fig.3 respectively. The molecule which has large dipole moment ( $\rho$ ) of DHOP complex is more reactive and is quite polar (Bourass, et al 2015) on the other side, the DHOP complex has high value of the pi (0.01316) therefore its electron donor, the electronegativity of DHOP complex is small due to their ability to donate to the electron. The DHOP complex has a low value of  $\eta$  this indicates easy to liberate the electrons, finally, the complex has highest capability to donor electron.

Physical properties	Values	Physical properties	Values
HOMO energy	-0.22604 kCal/ Mol	Chemical softness (S)	4.4037
LUMO energy	0.00104 kCal/ Mol	Chemical potential (Pi)	0.225 ev
Energy Gap (Egap)	0.00825 kCal/ Mol	Absolute softness ( $\sigma$ )	8.8075 ev
Ionization potential (IP)	0.22604 KJ/Mol	Global electrophilicity (ω)	0.22293
Electron affinity (EA)	-0.00104 KJ/Mol	Additional electronic	1.031x10-3
Absolute hardness (η)	0.11354ev	charge ( $\Delta N$ )	

Table 1	I. P	hysical	pro	nerties	of	DHOP	complex.
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Figure 2. Frontal molecular orbital's of 3D for DHOP complex.



Figure 3. Frontal molecular orbital of 2D for DHOP complex.

The electron density is typically shown a comparison of the identified electron density with that predictable by spherical models of the atoms and is called distortion electron density. The negative charge is remarked by red color or distribution of the oxygen atoms in carbonyl groups and the nitrogen in the amine group due to the high value of electronegativity (Obi-Eghedi, 2011) The positive charge is remarked by green color or distribution of Carbone atoms (Muhammed, 2014). The Mullikan atomic charges give a positive value for C and H and negative values for O, N, Cl atoms. The electron density represented through Fig. 3, and Fig.4 that's described Mullikan charge, electron density respectively



Figure 4. Mullikan charge for DHOP complex.



Figure 5. Total density of 2D for DHOP complex.

Atomic charge distribution of DHOP complex of Mullikan charge. The most negative values are those present at nitrogen and oxygen (N2, N5, N16, N15, O12, O13, O18, O19, O20, O21). The carbon atom C14 is attached to both atoms of nitrogen and oxygen. The C14 becomes a more positive charge due to the inductive effect of charge compared with C17.The chemical reaction of PtCl4 with NH3 can be passed by multistep to give a final product. Table 2 and Scheme 1 they are shows the total energy values of chemical species that's participating in the reaction. The net equation is consisted from one molecule of PtCl4 with two molecules of NH3. The reaction is exothermic  $\Delta$ Hnet= -3.0899 kCal. Mol-1.

Chemical species	Total energy	IR-Freq.	ZPE	ΔΗ	ΔG	ΔS
PtCl <sup>4</sup>	-178.039	-	2.741	7.241	-16.92	81.04
NH <sup>3</sup>	-55.87	+	21.74	25.03	11.32	45.98
PtCl4 (NH3) <sup>2</sup>	-292.28	-	46.25	58.03	19.55	129.06
PtCl2 (NH3) <sup>2</sup>	-262.29	+	49.85	57.98	29.65	95.02
Cl2	-918.87	+	0.704	2.941	-13.05	53.63
H <sup>2</sup> O <sup>2</sup>	-150.69	-	16.28	19.33	3.06	54.58
PtCl <sup>2</sup> (NH3) <sup>2</sup> (OH) <sup>2</sup>	-412.58	+	51.55	61.57	28.18	111.99
HOCONHOH	-318.37	-	35.94	40.81	20.46	66.93
PtCl2 (NH3) <sup>2</sup> (OCONHOH) <sup>2</sup>	-642.76	+	99.43	116.152	72.01	148.06
H <sub>2</sub> O	-37.79	+	13.13	16.00	2.585	44.99

Table 2. Energy's value of chemical reaction of DHOP complex.



Scheme 1 Formation of DHOP complex.

The suggested rate determining step depends on the steady state approximation. Scheme.2, represents the determination of effective concentration on the reaction rate. The net rate is equal to zero for intermediates (Drea et al 2012).

$$PtCl_4 + 2NH_3 \xrightarrow{k_1} PtCl_4(NH_{3)2.} 4-27 \qquad Rate=k_1[PtCl_4][NH_3]^2 \\ =k_1[PtCl_4(NH_3)_2]$$

$$PtCl_4(NH_3)_2 \xleftarrow{k_2} PtCl_2(NH_3)_2 + Cl_2 \qquad 4-28$$

$$Pt(NH_3)_2Cl_2 + H_2O_2 \xrightarrow{k_3} Pt(NH_3)_2Cl_2(OH)_2. \quad 4-29$$

$$\mathsf{PtCl}_2(\mathsf{NH}_3)_2(\mathsf{OH})_2 + 2\mathsf{OHCONHOH} \xrightarrow{k_4} \mathsf{PtCl}_2(\mathsf{NH}_3)_2(\mathsf{OCONHOH})_2 + 2\mathsf{H}_2\mathsf{O} 4-30$$

=k<sub>3</sub>[[PtCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>][Cl<sub>2</sub>] Rate=k<sub>3</sub>[PtCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>][H<sub>2</sub>O<sub>2</sub>]  $\sim$  =k<sub>3</sub>[PtCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>(OH)<sub>2</sub>] Rate=k4[PtCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>(OH)<sub>2</sub>][(HOCONHOH]<sup>2</sup>  $= \overset{\scriptstyle \sim}{k_4} [PtCl_2(NH_3)_2(OCONHOH)_2] [H_2O]^2$ 

 $=k_1[PtCl_4(NH_3)_2]$ 

Rate=k3[PtCl4(NH3)2]

The reaction rate law of DHOP is represented as in equation 11.

k2

$$\frac{D [ptCl4 (NH3) 2)}{dt} = k_1 [ptCl_4] [NH_3]^2 - k_2 [ptCl_4 (NH_3)_2] - k_3 [ptCl_4 (NH_3)_2] + k_4 [ptCl_2 (NH_3)_2] [Cl_2] = 0 \dots (5)$$

$$\frac{d [ptCl2 (NH3) 2}{dt} = k_3 [ptCl_4 (NH_3)_2] - k_4 [ptCl_2 (NH_3)_2] [Cl_2] - k_5 [ptCl_2 (NH_3)_2] [H_2O_2] + k_6 [ptCl_2 (NH_3)_2 (OH)_2] = 0 \dots (6)$$

$$\frac{d [ptCl2 (NH3) 2 (OH) 2}{dt} = k_5 [ptCl_2 (NH_3)_2] [H_2O_2] - k_6 [ptCl_2 (NH_3)_2 (OH)_2] - k_7 [ptCl_2 (NH_3)_2 (OH)_2] [HOCONHOH]^2 + k_8 [ptCl_2 (NH_3)_2 (OCONHOH)_2] [H2O]^2 = 0 \dots (7)$$

#### Therefore, from equation 5-7 get on:

$k_1[ptCl_4][NH_3]^2 - k_2[ptCl_4(NH_3)_2] - k_7[ptCl_2(NH_3)_2(OH)_2][HOCONHOH]^2 + (21) + $	
$k_8[ptCl_2(NH_3)_2(OCONHOH)_2][H2O]^2=0$	
$[ptCl_4(NH_3)_2] = \frac{k1[ptCl4][NH3]_2 + k8[ptCl_2(NH3)_2(OCONHOH)_2]}{k_2 + k7[ptCl_2(NH3)_2(OH)_2][HOCONHOH]_2}$	(8)
Rate = $k_3[ptCl_4(NH_3)_2]$	(9)
By substitution equation 8 in 9 get on :	
Rate =k <sub>3</sub> . $\frac{k1[ptCl4][NH3]2+k8[ptCl2(NH3)2(OCONHOH)2]}{k2+k7[ptCl2(NH3)2(OH)2][HOCONHOH]2}$	
(10)	
The two state of equation (10)	
1- The first probability is to impose $k_7 > k_2$ , the equation will be as follow	
$Rate = \frac{k1[ptCl4][NH3]2+k8[ptCl2(NH3)2(OCONHOH)2]}{k7[ptCl2(NH3)2(OH)2][HOCONHOH]2}$	(11)
2-The secondary probability is to impose $k_2 > k_7$ , the equation will be as follow	
Rate =k <sub>3</sub> . $\frac{k1[ptCl4][NH3]2+k8[ptCl2(NH3)2(OCONHOH)2]}{k2}$	(12)

## Scheme 2. Reaction mechanism according steady state theory of DHOP complex.

### **Spectroscopy of DHOP complex**

The frequencies of bands vibration of PT (IV) complex are shown in Table 3, and Fig. 6. v(Pt-O) Asy=135.9016 Cm-1, v(Pt-Cl)

	Table 3. Vibrational frequencies of DHOP complex.					
	Theoretical Frequencies	Experimental frequencies	Fore. Const.	IR ir		
Г	106 1075		0.10.40			

Theoretical Frequencies	Experimental frequencies	Fore. Const.	IR intensity	Descriptions
496.1075	575	0.1042	22.6979	υ (Pt-O)bend
141.6404	320-330	0.1592	2.1397	υ (Pt-Cl)bend
488.0027	470	0.6856	8.5885	υ (Pt-N)Asy
273.2288	350	0.2377	46.8773	υ (N-O)bend
966.9343	1274	3.1805	52.8592	υ (C-N) Asy
1254.9934	1287	2.0225	236.1001	υ (C-O)Asy
1606.6819	1650	7.6342	302.0211	υ (C=O) sym
3509.8448	3566	7.7322	42.5895	υ (O-H) sym
3638.2339	3283	8.4483	60.9573	υ (N-H) sym
3380.326	3089	6.8962	20.0429	υ (C-H) sym



Figure 6. Theoretical I.R spectrum of DHOP complex

The absorption spectrum of the PT (IV) complex is shown in Fig.7.The excitation energy and U.V/Vis absorption spectra for the singlet-singlet (transition of PT (IV) complex. The spectra is consisted of two bands. The first band occurs at a wavelength of 665 NM is referred to then  $-\pi^*$  transition of the non-bonding electrons present on the nitrogen of the amine group. The second band occurs at a wavelength of 641 NM has been observed referred to the spectrum of the DHOP complex causes red shift due to high electron density in the axial ligand (-OCONHOH), due to a charge transition between pot metal and ligand [Akbari, 2013]



Figure 7. Theoretical UV spectrum for DHOP complex.

Theoretical spectrum of NMR (H1, C13) of PT (IV) complex is represented in Figures of 8 and 9, that's show H1NMR, the singlet- signal at (1.5,2.8,6.7, 8.8 and 7.35 ppm) due to (H3, H22, H23, H24, H25) respectively, Although these protons are

equivalent chemical environments but (H6, H7) as (1.3,1.75 ppm) these protons are equivalent chemical environments. Figure 9, related to C13 NMR, the singlet at (255,490 ppm) for C17, C14 respectively.



Figure 8. Theoretical H<sup>1</sup> NMR spectrum for DHOP complex.



Figure 9. Theoretical H<sup>1</sup> NMR spectrum for DHOP complex.

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