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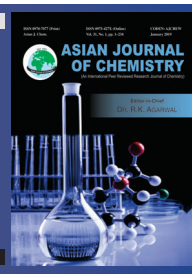

A Comparative Reactivity Study of Adenine *versus* Guanine Base through Transition State Formation with *cis*-Platinum(IV) Complex using DFT

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B3LYP, Lanl2DZ basis sets at density functional theory (DFT) method has been used on a ground state geometry optimized for all proposed structures that have been involved in this study. Structural parameters such as bond lengths, bond angles and dihedral angles have been calculated in the same way to achieve a global reactivity description of Pt(IV) complex. We suggested a minimal energy structure of diamino*bis*((4-hydroxy-4-butanol)oxy)platinum(IV) chloride complex (DOP) as a new chemotherapy formula of *cis*-platinum complex. The reactive site of nucleophilic attachment at DOP occurs on carbon atoms due to their positive charge, while other atoms (nitrogen, oxygen, chlorine) are carried negative charges due to the delocalization of electron pair by a resonance effect. Bonds of Pt-Cl with 2.290 Å are more reactive bounds toward the replacement reactions than other chemical bonds in the DOP complex. Investigation revealed that the thermodynamic functions values are increased due to increasing vibrational intensities of cisplatin complex. The fourth transition state (TS4) is the most probable transition state than other suggested transition states for both guanine and adenine bases. The TS4 of platinum complex binding with guanine is the most probable by a factor of -18.134 a.u. of optimization energy value than other suggested states. TS4-guanine is the most probable than other suggested states by factor 7.354 kcal/mol of zero point energy (ZPE). Hence, platinum complex (DOP) is binded with guanine base of DNA through N7.

Keywords: DFT studies, Adenine, Guanine base, *cis*-Platinum(IV) complex.

INTRODUCTION

Anticancer chemical compounds in the recent years hold potential for their activity as chemotherapies. Platinum (IV) complexes are more inert than platinum (II) complexes due the resistant to unwanted side-reactions at human body [1]. All *cis*-platinum complexes are reactive as prodrugs when starting activation by bioreduction to release the cytotoxic Pt(II) component. These complexes contained two axial ligands, which they could be used to influence the reduction kinetics [2] lipophilic, cellular accumulation [3] and activity [4] of platinum species.

Platinum based drugs are very effective anticancer agents which are widely used at clinic treatments and half of all chemotherapeutic regimens administered to patients include a platinum complex drug [5] as cisplatin, carboplatin and oxaliplatin drugs are triggered cancer cell death by binding to nuclear DNA and they are distorted the structure of DNA [6]. The reactivity and selectivity of the most cisplatin complexes are reacted in the blood as a nucleophile and never reaching the tumour. The limitation of bioavailability of the drug is due to undesirable interactions and preclude oral administration [7]. Attentions have been increased about this chemotherapy agents by academic researchers and investigations are occurs through experimental and computational calculations. Density functional theory (DFT) method is employed to investigate the thermal stability and mechanical properties of Pt(VI) complex [8]. It is believed that the platinum(IV) complexes act as prodrugs that are activated extra- or intracellular *in vivo* by reduction that transforms them to square planar platinum(II) complexes by an elimination of the axial ligands [9]. The preparation of some platinum(IV) complex is given up the anti-proliferative potency of the complexes that are correlated with their lipophilic as well as with their cellular accumulation, but not with their reduction potentials [10,11].

We have suggested a new optimized geometry of diamino-*bis*((4-hydroxy-4-butanol)oxy)platinum(IV) chloride (DOP)

complex and simulated its reactivity toward DNA bases through different suggested transition states. The energetic and structural parameters of Pt(IV) complex and all other suggested structures are calculated to prove our opinion about this new structure of *cis*-platinum complex.

EXPERIMENTAL

Computations were performed using Gaussian 09 [12] and molecular structures were plotted with Gauss View program [13]. Our calculations were carried out with the B3LYP density functional [14,15]. All optimizations were calculated without any symmetry constraints using Lanl2DZ basis set [16]. Charges obtained from natural bond orbitals (NBO) [17] procedure were determined to verify the trends of Mulliken population analysis. MO analyses were performed to *ab initio* calculations used to study model systems mimicking interactions in a polar solvent or crystal. The reason is that the polar solvent and counter ions very efficiently compensate for the electrostatic effects associated with ions.

To understand better the coordination properties, the total energy, electronic and nuclear energies were calculated for DOP complex, like HOMO, LUMO orbitals and their energies. The electronic transition energy of DOP complex and the single point were obtained by using time-dependent density functional theory TD/DFT with B3LYP calculations [18]. The electronic spectra of diamino*bis*((4-hydroxy-4-butanol)oxy)platinum(IV) chloride (DOP) complex were calculated.

RESULTS AND DISCUSSION

The geometry structure of diamino*bis*((4-hydroxy-4-butanol)-oxy)platinum(IV) chloride (DOP) complex under optimized relaxation is covered by total energy equal to -1024.415 a.u. Fig. 1 shows the orientation of bonded atoms, each one labelled by a number that represents the ordered in the optimized structure [13,19]. These atoms bonded with each other's according to equilibrium distance and angles as represented in Table-1.

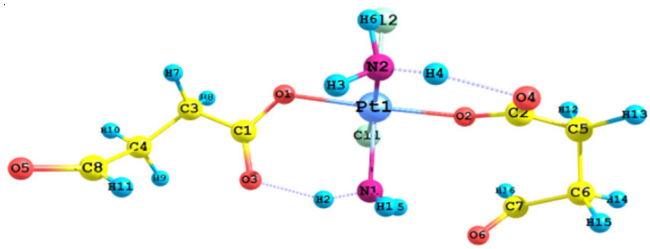

Fig. 1. Geometry optimized structure of DOP complex

A good agreement is found between our calculated values and X-ray diffraction study by Milburn and Tru [20] of bond length and bond angles, respectively. The difference of Pt-N3 bond is equal to 0.034 Å, is also found in good agreement [21]. The same thing is also found for the bond lengths of Pt-O6, Pt-Cl2, which are 0.04 and 0.02 Å, respectively. The differences in bond angle, like Pt1-O6-C7 angle is equal to 2º. Other angles are ranged from 0 to less than 2º for Pt1-N3-O6, N5-Pt1-N3, Pt1-Cl2-N3 and Cl4-O13-Pt1, respectively. The values are in good closer between present calculation and experimental values.The dihedral angle in the molecule (Cl4-O13-Pt1-Cl2), (C9-C7-O6-Pt1), (C16-C14-O13-Pt1), (C17-C16-C14-O13) and (C10-C9-C7-O6) are (180º, 90º, 180º, 90º, 180º) respectively, and these dihedral angles provided a stable structure for the DOP complex.

Mullikan atomic charge calculation has an important role in the application of quantum chemical calculation of molecular system because of atomic charge effect dipole moment, molecular polarizability, electronic structure and more properties of molecular systems [18]. The atomic charge values were obtained by the Mullikan population analysis. The Mullikan atomic charges of DOP complex are listed in Table-2. The Mullikan charges on the atoms in molecules computed with a B3LYP method and Lanl2DZ basis set (Fig. 2). The carbon, oxygen, nitrogen and chlorine atoms exhibit a substantial negative charge, which is donor atom is shown in Fig. 3, hydrogen atom exhibits a positive charge, which is an acceptor atom.

TABLE-1
CALCULATION OF BOND LENGTH AND BOND ANGLE OF DOP COMPLEX

Bonds	Bond length (Å)		Angle	Bond angles (°)		Dihedral angle	Dihedral (°)
	Calcd.	Exp. [20]		Calcd.	Exp. [20]		
Pt_1-N_3	1.96	2.01	Pt_1-O_6-C_7	120	122	Cl_4-O_{13}-Pt_1-Cl_2	180
Pt_1-Cl_2	2.29	2.330	Pt_1-N_3-O_6	90	89	C_9-C_7-O_6-Pt_1	90
Pt_1-O_6	1.94	1.960	N_5-Pt_1-N_3	82.2	82	C_{10}-C_9-C_7-O_6	180
			Pt_1-Cl_2-N_3	180	180	C_{16}-C_{14}-O_{13}-Pt_1	90
			Cl_4-O_{13}-Pt_1	120	122	C_{17}-C_{16}-C_{14}-O_{13}	180

TABLE-2
MULLIKAN CHARGES DISTRIBUTION ON THE MOLECULAR STRUCTURE OF DOP COMPLEX

Atoms	Mullikan charge values DFT	Atoms	Mullikan charge values DFT	Atoms	Mullikan charge values DFT	Atoms	Mullikan charge values DFT
Pt1	0.051	H10	0.445	H26	0.242	C22	0.040
Cl2	-0.105	H11	0.400	H27	0.261	H28	0.227
Cl3	-0.118	O12	-0.382	H28	0.227	O25	-0.284
N4	-0.824	C16	0.387	H29	0.225	H31	0.236
N7	-0.813	O14	-0.377	H30	0.191	H32	0.243
H5	0.354	C18	-0.456	O13	-0.381	H33	0.225
H6	0.445	C19	-0.362	C17	0.382	H34	0.229
H8	0.367	C23	0.047	O15	-0.371	H35	0.199
H9	0.434	O24	-0.221	C21	-0.404	–	–

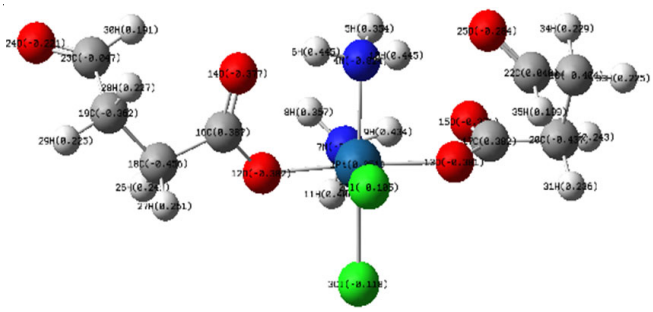

Fig. 2. Geometry optimization of DOP complex

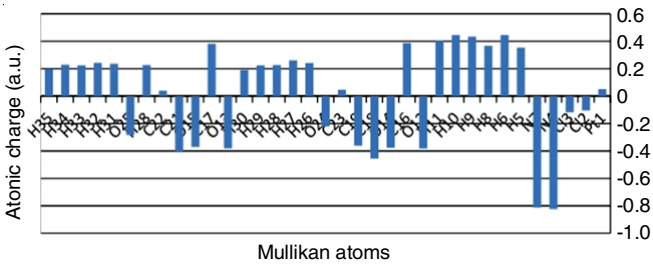

Fig. 3. Mullikan atomic charges for DOP complex

The electron density was calculated by DFT/B3LYP/Lanl2DZ using ESP with SCF density matrix. Fig. 4 shows carbon atoms carried a lower electron density therefore expected to be the site for nucleophilic attach in DOP complex. While around nitrogen, oxygen, chlorine and platinum atoms carried high electron density due to delocalization of electron pair on the nitrogen, oxygen and chlorine atoms by a resonance effect [21]. Fig. 5 shows a red colour is referred to the high distribution of electron density and the green colour is refers to a low distribution of electron density on the molecular structure of DOP complex.

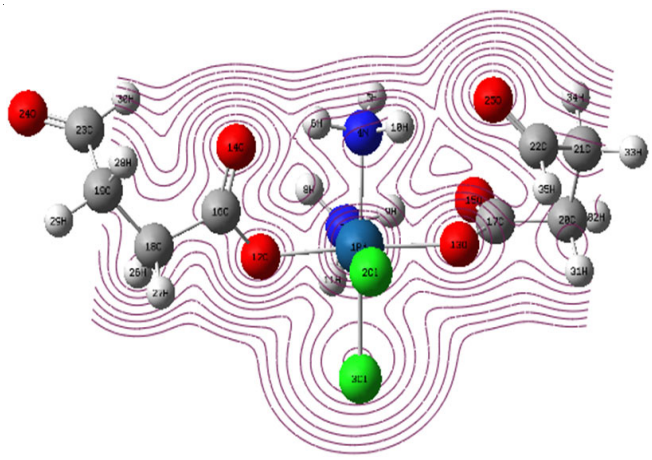

Fig. 4. Total density of 2D for DOP complex

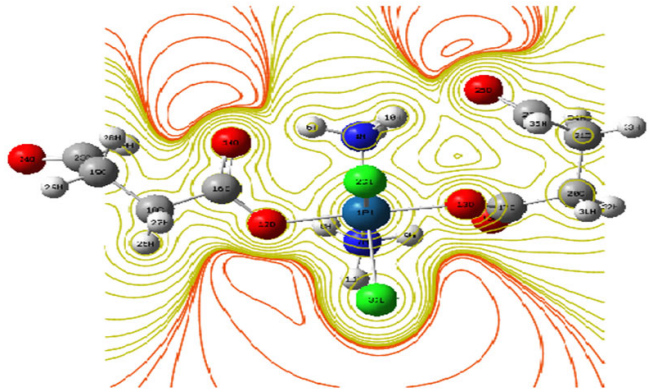

Fig. 5. Two-dimensional view of an electrostatic potential distribution of DOP complex

The relative reactivity of DOP complex depends on energy gap (ΔE) value as important parameters. Table-3 shows the energetic values of DOP complex, since the energy value of HOMO and LUMO are equal to 0.02873 and -0.00024 kcal/mol, respectively, Thus indicate that energy gap value of DOP complex is equal to 0.02873 kcal/mol and implies a low electronic stability and high reactivity [21].

Fig. 6a shows a molecular orbital (HOMO and LUMO) calculation in three dimensions and Fig. 6b is two dimensions that appear in green and red colour respectively, where red colour is the negative part to the wave function, which is attacked by an electrophile while green colour is the positive part of wave function that would be attacked by a nucleophile. The E_{HOMO} value indicates a tendency to lower donate electrons (Lewis base) to suitable acceptor molecule with low empty molecular orbital energy. The value of the E_{LUMO} also indicate a tendency to accept electrons (Lewis acid) from the metal [22].

According to Koopmans theorem [23], it was possible to calculate the energy value of the electronic affinity (A), ionization potential (I), electronegativity (χ), chemical potential (μ), hardness (η), softness (S) and electrophilic index (ω) [24,25] for DOP complex.

Table-4 shows the small value of electronegativity of DOP complex leads to a polar covalent bond.The electron affinities are negative because the energy of this system is reduced, while the chemical potential measures the tendency of electrons to flow from a region of higher chemical potential to lower chemical potential becomes uniform throughout [26,27].

Cisplatin is a square planar d^8 platinum(II) complex with two coils chloride ligands and two amine ligands. The bonds of Pt-N are kinetically inert and thermodynamically stable, while the bonds of Pt-Cl are semi-labile and the bonds of Pt-OH_2 are very reactive. The chloride ligands can be slowly exchanged by water (aquatint) or by other nucleophiles. Platinum

TABLE-3
ENERGETIC PROPERTIES OF DOP COMPLEX

LUMO energy	HOMO energy	Dipole moment (Debye)	Nuclear energy (a.u.)	Electronic energy (a.u.)	Kinetic energy (a.u.)	Total energy (a.u.)
0.02849	-0.00024	7.0610	671.8075	-3403.7616	542.4594	-1024.415
ΔH	ΔG	ΔS	ZPE	Imaginary frequencies	Degree of freedom	Point group
181.416	128.8993	176.144	165.5022	+	99	C_1

*units of kcal mol^{-1}

TABLE-4
GLOBAL INDEXES VALUES OF DOP COMPLEX BY DFT/B3LYP/LanL2DZ AT 298.150 K AT LEVELS OF THEORY

Global indexes	-X (ev)	μ (ev)	-μη (ev)	-σ	-σ	-S (1/ev)	ΔN	I (kJ mol^{-1})	-A (kJ mol^{-1})
Values	0.0144	0.0144	0.0287	34.81	3.594×10^{-3}	17.40	0.5	0.0002	0.0285

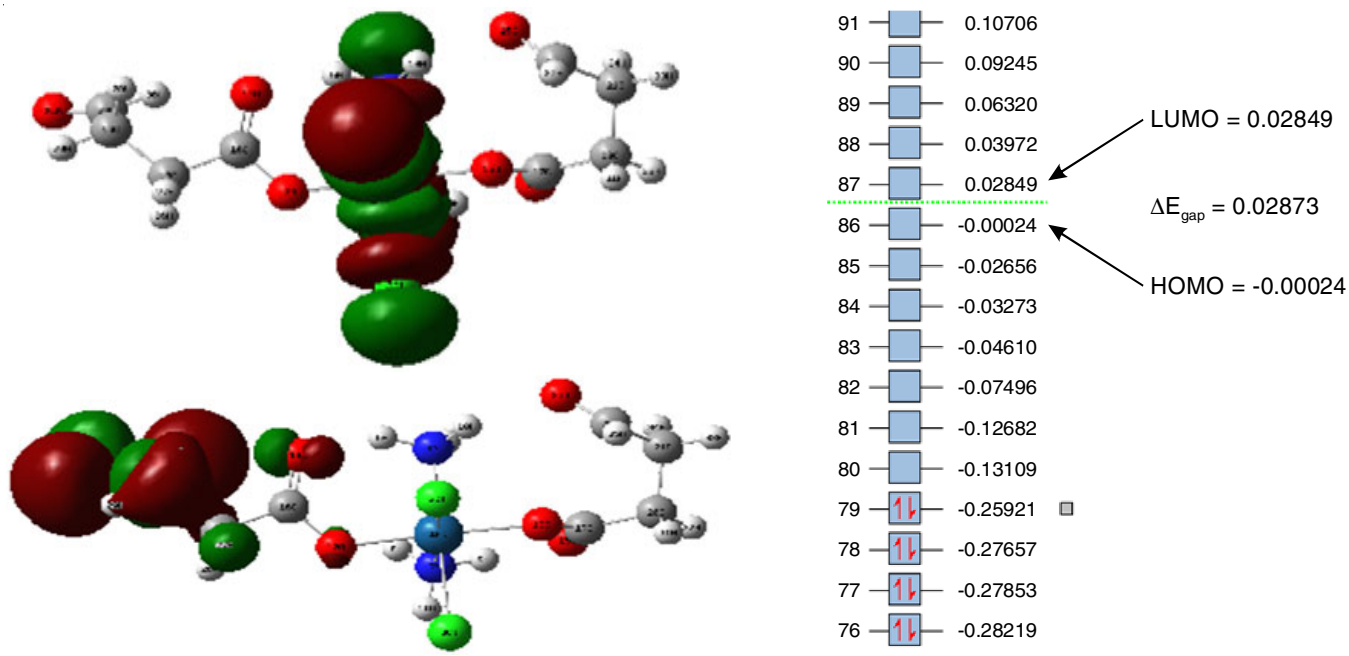

Fig. 6a. Three dimension view molecular orbitals (HOMO-LUMO) of 3D for DOP complex

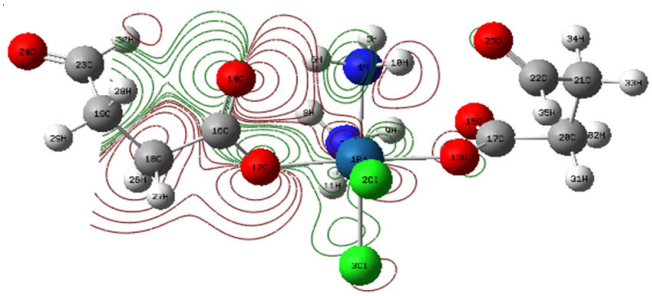

Fig. 6b. Two dimension view of frontal molecular orbital of DOP complex

is a soft metal and according to the hard-soft acid-base (HSAB) theory has a higher affinity toward softer ligands, which rapidly forms strong bonds with Pt(II) center [28]. The suggested bond formation of Pt(II) with nitrogen atoms of guanine and adenine (nitrogen bases) as ligands is readily occurred after complex activation by aquatint process of platinum atom. The simulation of DOP complex binding to the DNA is suggested to be with two N7 atoms for two adjacent bases only (guanines and adenine) on the same DNA strand. The suggested octahedral platinum (IV) complexes are substituted-inert, so reactions with biological nucleophiles, including guanines and adenine are extremely slow [29]. Cisplatin complex binds to plasma proteins and reducing the number of drug molecules that can reach a tumor to deactivate cancer cells [30]. The Pt(II) complex is stable enough to pass through the digestive target. DNA strand contains nucleon bases and cross-linked leading to the formation of asymmetric platinum complex. Fig. 7 shows the suggested reaction mechanism of cisplatin with nitrogen base of DNA as complexation reactions.

Prodrug design is predicated on the assumption that the low spin octahedral d_6 Pt(IV) complexes are inert and will not undergoes hydrolysis or ligand substitutions, therefore conversion of prodrug to the drug is necessary for binding with DNA. Fig. 8 indicated that the lowest value of dissociation energy of first reaction is -5.598 a.u. The enthalpy change of

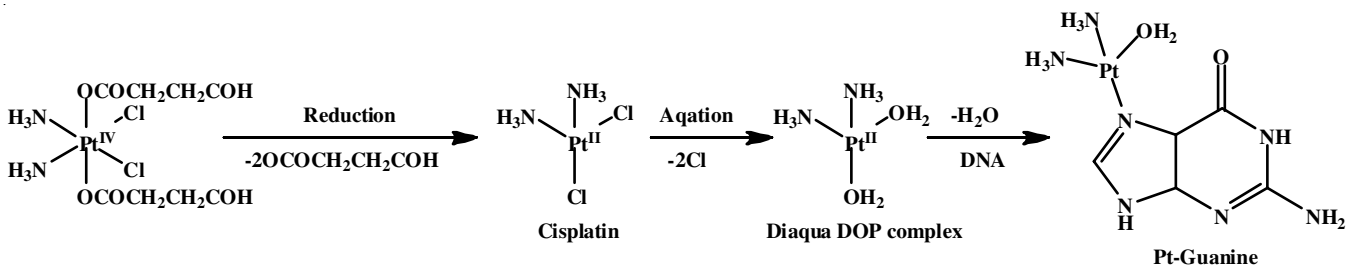

Fig. 7. Suggested mechanism of DOP complex binding with G-DNA

reaction as computed by DFT is an exothermic indication. The high value of Gibb′s free energy for dissociation prodrug Pt(IV) to drug Pt(II) is -61.896 kcal/mol. This indication is more reactive of Pt(II) complex for binding with DNA nucleobases: Adenine (A) and Guanine (G). These results indicated a spontaneous reaction towards DNA nucleobases (guanine) from adenine [31].

The molecular modelling of nucleon bases of guanine and adenine presents four main negative regions corresponds to the four lone electron pairs present on nitrogen atoms (N1, N3, N7 and N9). The results (Table-5) showed that the fourth transition state (TS4) is the most probable transition state than other suggested transition states for both guanine and adenine bases [32]. The lowest total energy value of optimized structure of TS4 at N7 of guanine is equal to -792.613 a.u. and similarly at TS4 of adenine is equal to -774.479 a.u., which means that TS4 of platinum complex binding with guanine is the most probable as compare to TS4 of platinum complex a by factor of -18.134 a.u. of optimization energy value. Another comparison can occur through the different degradable ability of TS4-guanine and TS4-adenine to give up product, which can be found through zero point energy (ZPE). The ZPE of TS4-guanine is equal to 113.326 kcal/mol while the ZPE of TS4-adenine is equal to 121.68 kcal/mol, which means another justification of favourable TS4-guanine by a factor of 7.354 kcal/mol, predicting its more stability and long lifetime.

Figs. 8 and 9 show the suggested optimized transition states of platinum complexes with guanine and adenine, respectively. Guanine base contained oxo group on C6 position in their structure gives the ability to form a hydrogen bond with amine or water in $Pt(NH_3)_2(H_2O)_2$ and similarly for the amino group at C_6 position in adenine base. Both oxo and amino groups at the C_6 position for guanine and adenine respectively, are hydrogen-bonded acceptors. However, oxo group in guanine is better hydrogen-bonded acceptor than amino group of adenine, therefore guanine bases are the most probable to form stable structure formation with platinum complex as transition state than adenine [33].

Conclusions

- The bond lengths of Pt atom with O, N, Cl atoms in diamino-*bis*((4-hydroxy-4-butanol)oxy)platinum(IV) chloride (DOP) complex are very important in the load charge transfer of donor and acceptor.
- A small value of energy gap is (0.02873 kcal/mol) implies low electronic stability and high reactivity of complexes toward with nitrogen bases binding.
- The dissociation value indicates that an exothermic reaction (-5.598 a.u.) of prodrug Pt(IV) converted into drug Pt(II).
- The suggested transition state is more probable than other transition states to give up the final reaction product with guanine.

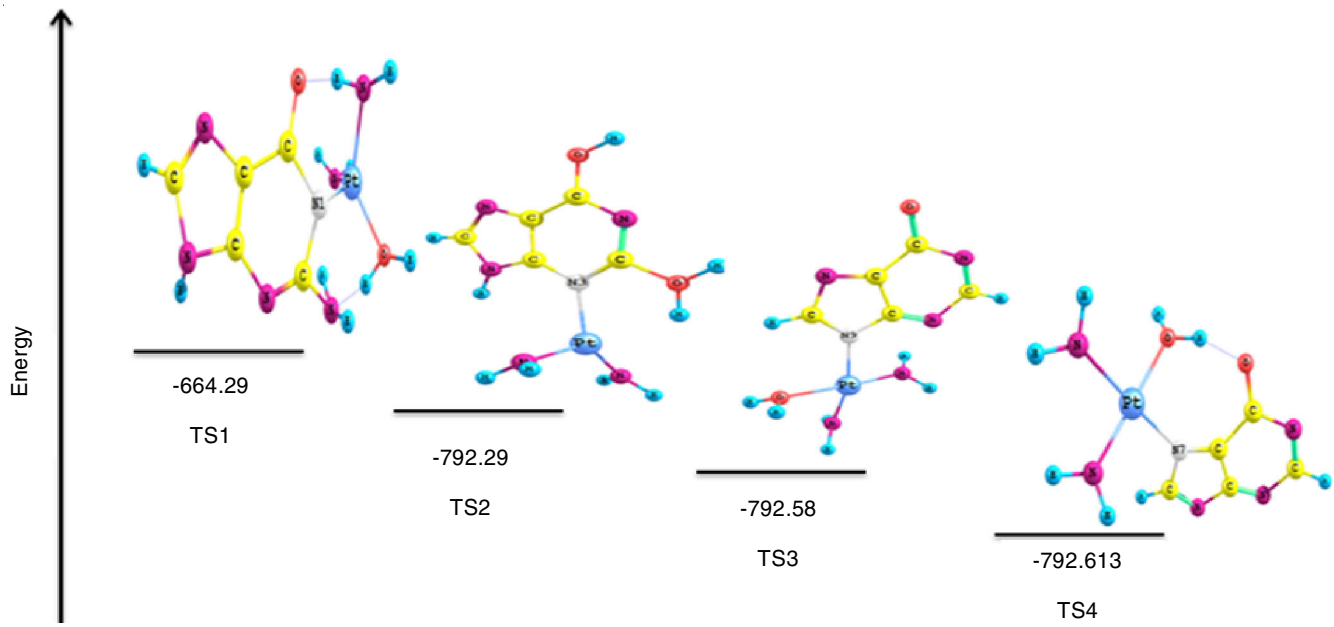

Fig. 8. Configuration interaction of *cis*-platinum(IV) complexes with guanine at different probabilities of the suggested transition state

TABLE-5
ENERGETIC VALUES OF CONFIGURATION INTERACTION OF *cis*-PLATINUM(IV) COMPLEXES AT DIFFERENT SUGGESTED PROBABILITIES OF TRANSITION STATES FORMATION CALCULATED

Complex	Configuration interaction of guanine				Configuration interaction of adenine			
	TS1(N1)	TS2(N3)	TS3(N9)	TS4(N7)	TS1(N1)	TS2(N3)	TS3(N9)	TS4(N7)
Total energy (a.u.)	-644.288	-792.29	-792.58	-792.613	-774.106	-774.113	-774.42	-774.479
ΔG (kcal mol^{-1})	91.177	78.313	69.591	68.606	94.565	94.440	85.090	82.925
ΔS (kcal mol^{-1})	119.96	123.75	121.861	120.932	124.175	124.94	121.02	127.86
ΔH (kcal mol^{-1})	126.945	115.211	105.924	104.662	131.588	131.652	121.172	121.047
ZPE (kcal mol^{-1})	94.91	96.23	105.63	113.326	110.64	111.61	121.66	121.68
Run time (day:hour:min)	5:3:30	6:8:30	6:9:20	5:8:25	4:4:20	4:7:40	4:11:30	4:8:20

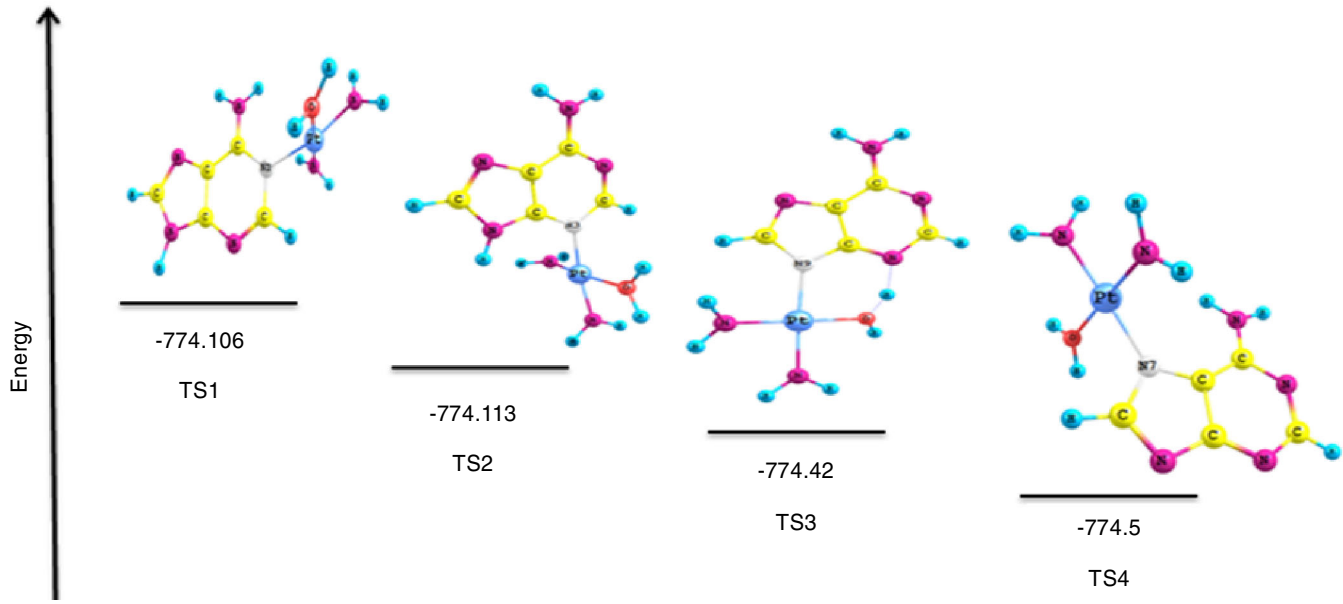

Fig. 9. Configuration interaction of *cis*-platinum(IV) complexes with adenine at different probabilities of the suggested transition state

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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