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## Probing the Effect of Bipyridine Derivatives on the Reduction of Platinum(IV) Complexes by 5'-dGMP

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In previous studies, the mechanism for the reduction of tetrachloridoplatinum(IV) complex with 5'-dGMP has been investigated. In this research, two platinum(IV) complexes [PtCl<sub>4</sub>(N-N)] (N-N = 4,4'-dimethyl-2,2'-bipyridine, A and 5,5'-dimethyl-2,2'-bipyridine, B) were considered and theoretically compared with Pt<sup>IV</sup>dach (dach = diaminocyclohexane), by means of the Becke3LYP DFT functional calculations. The mechanism of two electron reduction was thoroughly followed for three compounds. The relative Gibbs energies for all intermediate, transition states and products were calculated and compared. LUMO-HOMO energy gap was also determined, where this energy gap was 3.5 eV in complexes A and B; and 4.5 eV in Pt<sup>IV</sup>dach. The overall calculated Gibbs energy for the formation of corresponding Pt<sup>II</sup> complex is 30.0 kJ mol<sup>-1</sup> in A, 28.5 kJ mol<sup>-1</sup> in B and 43.2 kJ mol<sup>-1</sup> in Pt<sup>IV</sup>dach. Thus compounds A and B illustrated more favorability for the proposed two electron reduction, interestingly. The results demanded that the hydrogen bonds play a critical role in the stability of intermediates and transition states in Pt<sup>IV</sup>dach. The effective parameters in the mechanism were also discussed.

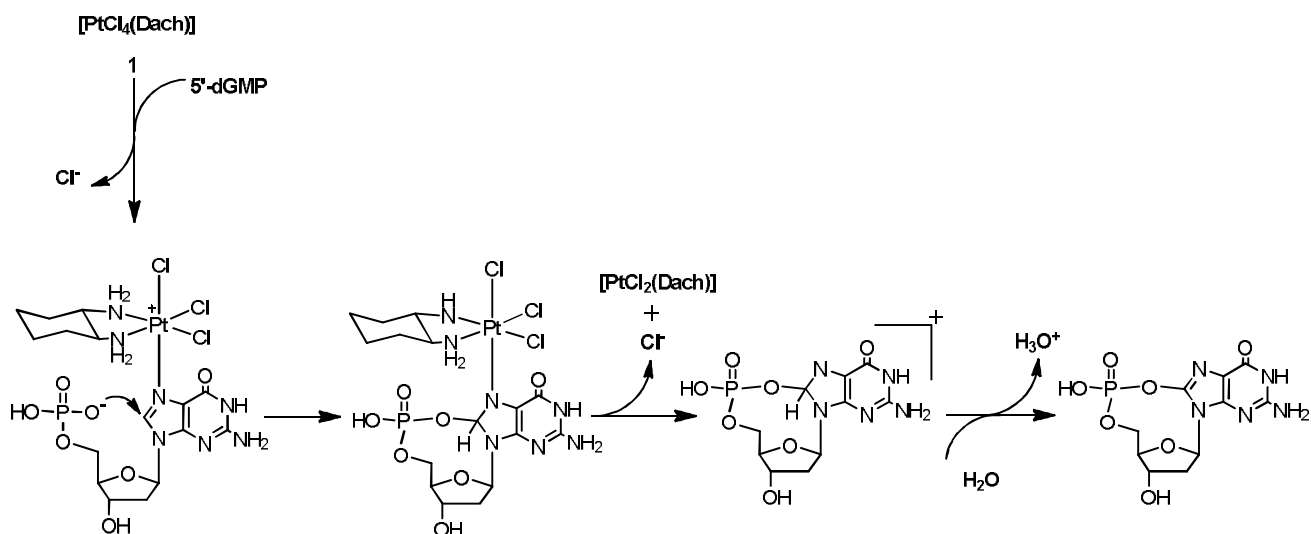
**Keywords:** Bipyridine derivative, Platinum complex, DFT, Guanosine

### INTRODUCTION

Platinum-based anticancer drugs have been proved to play an important role in the treatment of various cancers, including prostate, bladder, lung, ovarian, head and neck carcinomas [1-4]. Cisplatin, alone or in conjunction with other anticancer drugs has been used in treatment of nearly 50% of all kinds of tumors [2]. The successful usage of carboplatin and oxaliplatin as anticancer drugs has attracted much attention to the discovery of a new generation of Platinum-based anticancer drugs [5]. Severe toxic side effects like neurotoxicity, nephrotoxicity, ototoxicity, tinnitus, vomiting and nausea, along with drug resistance are the main disadvantage of the usage of cisplatin [6,7]. It seems that platinum(IV) complexes are promising alternatives to tackle these problems [8]. These compounds are an important category of materials that can be acted as prodrugs. Because of inertness, they have less toxicity

outside of the cancerous cell [9]. It should be noted that the oxidative damage of DNA which can motivate the processes such as aging, mutagens and carcinogens, can be overcome and controlled by using intermediate metal complexes, like platinum(IV) complexes [10-13]. One of the platinum(IV) complexes that can oxidize DNA, is [PtCl<sub>4</sub>(dach)] (dach = diaminocyclohexane) [10]. Choi *et al.* suggested that this platinum(IV) complex is a reactive agent with high potential for the guanine moiety oxidation of DNA. They showed that only guanine nucleotides with a phosphate or hydroxyl group as a nucleophile at their position five, can be oxidized by platinum(IV) center. Choi *et al.* experimentally investigated the mechanism of the oxidation of 5'-dGMP by [PtCl<sub>4</sub>(dach)] (Pt<sup>IV</sup>dach) [14,15]. In this regard, Ariaifard *et al.* examined the above-mentioned oxidation mechanism theoretically [16]. According to the aforesaid studies, the following mechanism was proposed for guanine oxidation (Scheme 1). This scheme shows a targeted mechanism for 5'-dGMP oxidation by Pt<sup>IV</sup>dach. In this mechanism, the first step of

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Scheme 1. Proposed mechanism for two electron reduction of Pt<sup>IV</sup>dach by 5'-dGMP

the reaction is through the coordination of N7 from guanine to Pt(IV). Subsequently, with the nucleophilic attack of group 5'-phosphate at the C8 position of guanine, two electrons from guanine were transferred to Pt(IV), and eventually the Pt(II) complex and a phosphor-diester ring intermediate were obtained [16].

In 2011, we synthesized the Pt<sup>IV</sup>-based compounds, [Pt(4,4'-dmbipy)Cl<sub>4</sub>] (A) and [Pt(5,5'-dmbipy)Cl<sub>4</sub>] (B), as shown in Scheme 2 (where 4,4'-dmbipy is the abbreviation for 4,4'-dimethyl-2,2'-bipyridine and 5,5'-dmbipy for 5,5'-dimethyl-2,2'-bipyridine); and examined the cytotoxic effects of these compounds and compared them with cisplatin, with acceptable results [17]. In this study, the density functional theory (DFT) was used to examine the two electron reduction of the title compounds by 5'-dGMP. Pt<sup>IV</sup>dach complex which is a known platinum(IV) compound, has been utilized for comparison with compounds A and B. In this complex, the ligand has an aliphatic amino nature, while in compounds A and B, the bipyridine ligands were aromatic. The aim of the present paper is to find out what might be the effective parameters in the reduction mechanism for platinum(IV) compounds as prodrugs and their conversion to corresponding Pt(II) ones.

## COMPUTATIONAL METHODS

Gaussian 09 [18] was utilized completely at the B3LYP

level of density functional theory (DFT) for fully optimization of all structures reported in this paper [19]. The 6-31G(d) basis set was used for atoms other than Pt and the effective core potential of Hay and Wadt with a double- $\xi$  valence basis set (LANL2DZ) was chosen for describing Pt [20-22]. A polarization function of  $\xi_f = 0.993$  was also added to Pt [23]. This basis set combination will be referred to as BS1. Frequency calculations were performed at the same level of theory as that for structural optimization. Transition structures were situated using the Berny algorithm. To corroborate the connectivity between transition and minima, we used Intrinsic Reaction Coordinate (IRC) calculations [24]. Single-point energy calculations were accomplished for all of the structures with a larger basis set (BS2) in water using the CPCM solvation model [25] with the M06 [26] level to further correction on the energies obtained from B3LYP/BS1 optimization. BS2 was picked to apply the quadruple- $\zeta$  valence def2-QZVP [27] basis set on Pt and the 6-311+G(2d,p) basis set on other atoms. To assess the corresponding Gibbs free energies,  $\Delta G$ , the entropy corrections were computed at the B3LYP/BS1 level and were finally adjoined to the M06/BS2 total energies. Recent studies have demonstrated that M06 predictions are more accurate than B3LYP [28], so it has prompted us to choose this function for all single-point calculations.

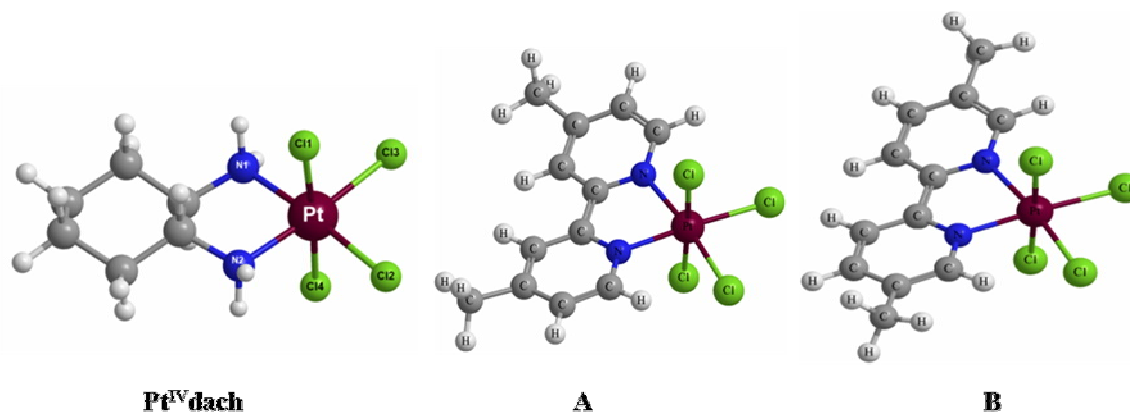

 Scheme 2. Optimized structures for studied Pt<sup>IV</sup> compounds

Table 1. Bond Distances (Å) and Bond Angles (°) for Complex A

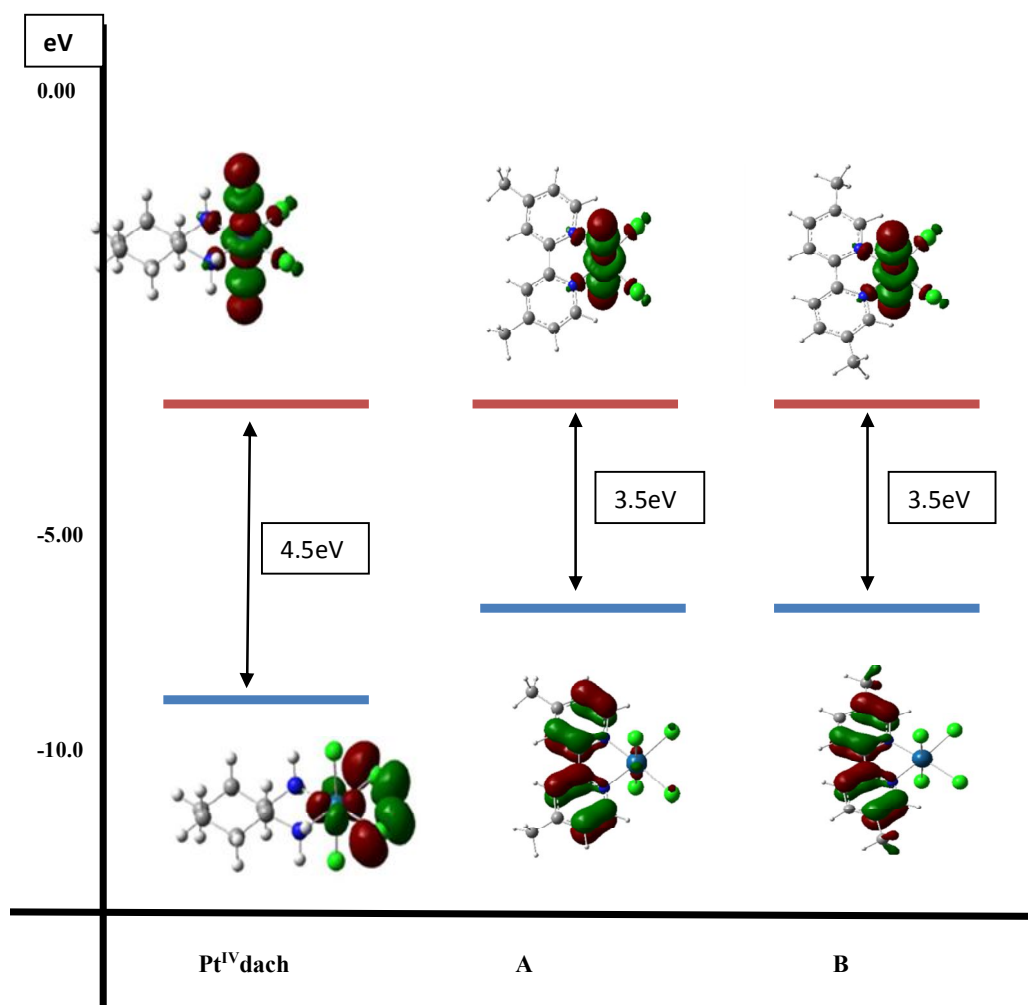
Distances	(Exp.)	(B3LYP)	Angles	(Exp.)	B3LYP
Pt-Cl1	2.401	2.396	N2-Pt-N1	88.533	79.984
Pt-Cl4	2.393	2.396	N1-Pt-Cl3	92.188	96.034
Pt-Cl2	2.383	2.383	N2-Pt-Cl2	92.188	96.034
Pt-Cl3	2.383	2.383	Cl3-Pt-Cl2	87.082	87.948
Pt-N1	2.060	2.054	N2-Pt-Cl1	90.289	89.000
Pt-N2	2.060	2.054	N1-Pt-Cl1	90.286	90.932
SD		±0.004	Cl3-Pt-Cl1	89.031	90.928
			Cl2-Pt-Cl1	89.028	90.928
			N2-Pt-Cl4	89.607	89.020
			N1-Pt-Cl4	89.609	89.021
			Cl3-Pt-Cl4	91.075	89.000
			Cl2-Pt-Cl4	91.078	90.932
			SD		±3.271

## RESULTS AND DISCUSSIONS

We chose two different Pt-based compounds, A and B (Scheme 2) to compare them with Pt<sup>IV</sup>dach. The synthesis of these complexes had previously been reported by us [17]. They illustrated acceptable cytotoxic effects on cancerous cell lines. All complexes reported here are Pt<sup>IV</sup> complexes

with different chelate ligands (Scheme 2).

In the first step of our study, we evaluated the DFT/B3LYP method to optimize structure parameters as well as electronic structure. The evaluation was performed on compound A (as a sample) and the coordinates of its crystal structure were used as input data. Table 1 lists the experimental and calculated results and, as can be seen, low



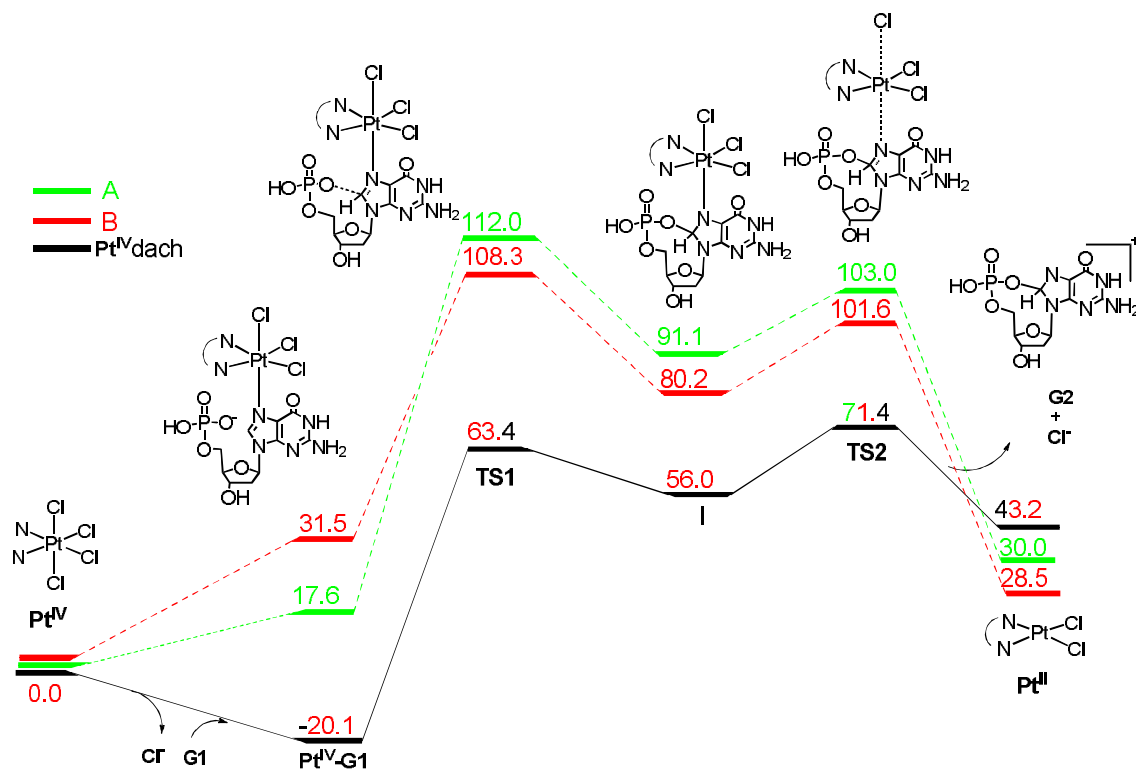
**Fig. 1.** HOMO-LUMO gap and optimized structures of HOMO and LUMO for  $\text{Pt}^{\text{IV}}\text{dach}$ , A and B.

standard deviation for distances ( $\pm 0.004 \text{ \AA}$ ) and angles ( $\pm 3.271^\circ$ ) demands that DFT/B3LYP be a proper method to calculate our desired parameters.

The frontier molecular orbitals (the highest occupied molecular orbital,  $E_{\text{HOMO}}$  and the lowest unoccupied molecular orbital,  $E_{\text{LUMO}}$ ) are the crucial factors to exhibit the stability of a compound. Lower HOMO-LUMO gap results in more reactivity due to easier charge transfer [29]. As shown in Fig. 1, the charge density distribution shows that in all complexes, the LUMO density is concentrated on anti-bonding orbital of  $d_{z^2}$  of platinum and  $p_z$  of axial chloro ligands where its energy level is around  $-3.7 \text{ eV}$ . But there is some distance between HOMO density distribution of platinum complexes with pyridine ligands and those with

dach ligand. In complexes A and B, HOMO localization is mostly on nonbonding orbital of aromatic pyridine ligand, with a LUMO-HOMO energy gap of  $3.5 \text{ eV}$ . However, in  $\text{Pt}^{\text{IV}}\text{dach}$  with no aromatic ligand, HOMO density is located on bonding orbital of  $d_{xy}$  of platinum and  $p_x/p_y$  of equatorial chloro ligands where it causes the energy gap of  $4.5 \text{ eV}$ . These calculated data revealed a relatively more reactivity for complexes A and B.

The energy profile for the reduction of three complexes  $\text{Pt}^{\text{IV}}\text{dach}$  [ $\text{Pt}(\text{dach})\text{Cl}_4$ ], [ $\text{Pt}(4,4'\text{-dmbipy})\text{Cl}_4$ ] (A) and [ $\text{Pt}(5,5'\text{-dmbipy})\text{Cl}_4$ ] (B) by 5'-dGMP were calculated and presented in Fig. 2. The process starts by substitution of an axial Cl ligand by 5'-dGMP. As stated in previous studies, this reaction starts with the binding of  $\text{Pt}(\text{IV})$  with the N7 of



**Fig. 2.** The relative Gibbs energy profile for reduction mechanism of Pt<sup>IV</sup>dach (line), A and B (dashed) by 5'-dGMP, obtained from the M06/BS2//B3LYP/BS1 calculations (in kJ mol<sup>-1</sup>).

5'-dGMP in an inner-sphere mechanism [30-32]. The reduction mechanism of Pt<sup>IV</sup>dach was reviewed and then compared with the complexes A and B.

As stated previously, dach, (1R,2R)-1,2-(Diaminocyclohexane), is from the family of aliphatic amines. In this category of amines, there are N-H groups that can cause a double sustainability on transition states (TS1) during their reaction with DNA. This stability is due to hydrogen bond between O atom of 5'-phosphate and NH<sub>2</sub> of dach [16]. Figure 3 reveals the position of the above-mentioned hydrogen bonding. In spite of dach ligand, bipyridine derivatives with a lack of aliphatic amine are not able to interact with 5'-dGMP by hydrogen bonding. Consequently, the complexes A and B exhibit less stability in first stage.

The comparative calculated energy profile for the reaction of 5'-dGMP with Pt<sup>IV</sup>dach and complexes A and B is shown in Fig. 2. The results of this study have been summarized in Table 2. According to this table, it is evident that for Pt<sup>IV</sup>dach with an aliphatic amine-based ligand, all

barriers are lower than those found in other complexes with bipyridine derivatives. The barriers of two transition states including TS1 and TS2 for Pt<sup>IV</sup>dach are 63.4 and 71.4 kJ mol<sup>-1</sup>, respectively, whereas for complexes A and B are higher (112.0 and 103.0 kJ mol<sup>-1</sup> for A; 108.0 and 101 kJ mol<sup>-1</sup> for B). It shows more stability on transition states in Pt<sup>IV</sup>dach complex, due to the presence of hydrogen bonding between N-H group in amine with O atom of 5'-phosphate group (Fig. 3).

In a more detailed investigation, as brought in Fig. 4 for compound A, the reaction starts with the dissociation of an axial chloride and the introduction of guanosine, consequently. 5'-dGMP was employed because this conformer results in the most stable product in coordination with tetraplatin ([PtCl<sub>4</sub>(N-N)]; N-N = 1,2-diaminocyclohexane), among guanosine derivatives [33]. Thus, our proposed pathway proceeded by the coordination of N7 of 5'-dGMP with platinum center to produce a Pt<sup>IV</sup>-G1 complex. This process is thermodynamically

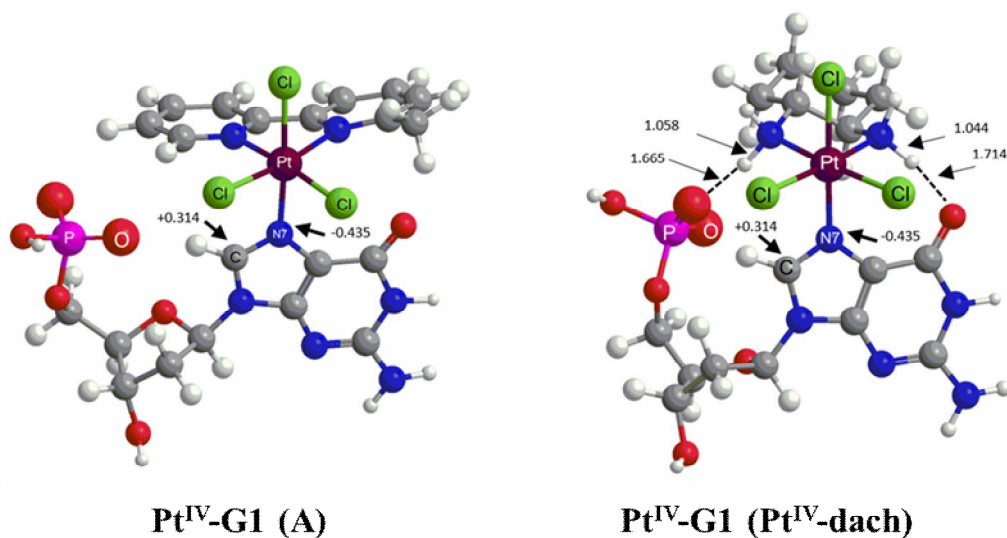


Fig. 3. Optimized structures that show the hydrogen bonding.

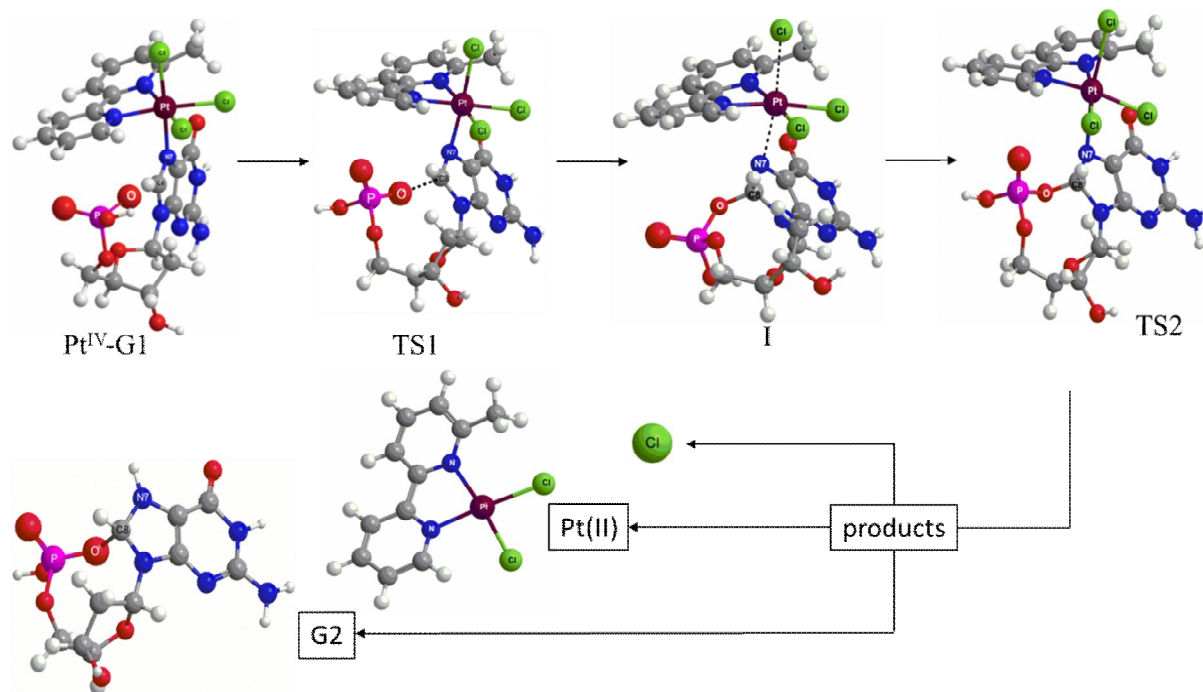
**Table 2.** The Relative Gibbs Energy Profile for Reduction Mechanism of Four Pt<sup>IV</sup> Complexes by 5'-dGMP, Obtained from the M06/BS2//B3LYP/BS1 Method (in kJ mol<sup>-1</sup>)

Complex	Structure	Pt <sup>IV</sup> -G1	TS1	I	TS2	Pt <sup>II</sup>
Pt <sup>IV</sup> dach		-20.1	63.4	56.0	71.4	43.2
A		17.6	112.0	91.1	103.0	30.0
B		31.5	108.3	80.2	101.6	28.5

favorable for Pt<sup>IV</sup>dach, contrary to the other two compounds A and B (Fig. 2).

The process is preceded with a two-electron transfer from guanosine to Pt<sup>IV</sup> center which in an inner sphere mechanism makes one cyclic phosphodiester intermediate. In Pt<sup>IV</sup>-guanosine, the coordination of N7 of guanosine to

Pt center with four positive charges results in a polarization of the C8-N7  $\pi$  bond that increases positive charges of C8 from +0.231 in 5'-dGMP to +0.314 in Pt<sup>IV</sup>-G1 (Fig. 3). Thus, O atom of 5'-phosphate attacks C8 atom easily to make a phosphodiester cycle (I). The transition state (TS1) defined for this cyclization as O-C8 distance is



**Fig. 4.** The optimized structures for two-electron transfers from guanosine to platinum(IV) center in  $[\text{Pt}(4,4'\text{-dmbipy})\text{Cl}_4]$  (A).

1.830 Å showing no covalent bond yet. The imaginary frequency of the O-C stretching in phosphodiester cycle was  $-281.125i$  for this transition state.

The mechanism processes with dissociation of the cyclic phosphodiester ligand and axial Cl from the metal center, resulted in  $\text{Pt}^{\text{II}}$  product, Cl<sup>-</sup> and G2. The imaginary frequency of the second transition structure (TS2) was  $-32.001i$  (for A). In TS2 structure, the Pt-Cl<sub>axial</sub> and Pt-N<sub>G</sub> bond lengths were 2.794 and 2.459 Å (for A), demanding dissociation of axial groups from platinum center. As a result, the two-electron transfer completed through the second transition structure (TS2), and the final product of  $\text{Pt}^{\text{II}}$  complex was achieved. The overall calculated Gibbs energy for the formation of related  $\text{Pt}^{\text{II}}$  complex is  $30.0 \text{ kJ mol}^{-1}$  from A,  $28.5 \text{ kJ mol}^{-1}$  from B and  $43.2 \text{ kJ mol}^{-1}$  from  $\text{Pt}^{\text{IV}}\text{dach}$  (Fig. 3).

Therefore compounds A and B illustrated more favorability for the proposed two-electron reduction than  $\text{Pt}^{\text{IV}}\text{dach}$ . This result is in agreement with this matter, that branched ligands lead to an increase in the cytotoxic activity of the corresponding platinum(IV) prodrugs [34]. The

position of methyl group demands no considerable distance in theoretical thermodynamic data for complexes A and B where both compounds result in close calculated parameters (Table 2).

## CONCLUSIONS

DFT calculations have been carried out to compare the reduction of three platinum(IV) compounds, including  $[\text{PtCl}_4(\text{dach})]$ ,  $[\text{PtCl}_4(4,4'\text{-dmbipy})]$  and  $[\text{PtCl}_4(5,5'\text{-dmbipy})]$  by 5'-dGMP. In the early stages, the HOMO-LUMO gap and calculated energy levels demanded more stability for  $[\text{PtCl}_4(\text{dach})]$ . It seems that the intra-molecular hydrogen bonding is an effective parameter in stability of transition states and intermediate. However, the platinum(II) products with bipyridine derivatives exhibited more stability than those with dach. In summary, our theoretical study revealed that although platinum(IV) compounds with bipyridine derivatives have no N-H group to perform hydrogen bindings, they still show sufficient stability to underlie two-electron reduction easily. Moreover, the

overall Gibbs energy confirmed more favorable reduction for them. This finding can potentially motivate experimentalists to further investigate the pharmacologic properties of these complexes.

## ACKNOWLEDGMENTS

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