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 to 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]. Atentions 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) complex [9]. 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) complex 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)

**Keywords:** DFT studies, Adenine, Guanine base, cis-Platinum(IV) complex.
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 energy, electronic and nuclear energies were calculated for DOP complexes very efficiently 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 complex, like HOMO, LUMO orbitals and their energies. The Mullikan charges on the atoms in molecules computed with Mullikan population analysis. The atomic charge values are calculated to prove our opinion about this new structure of cis-platinum complex.

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 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.

<table>
<thead>
<tr>
<th>Bonds</th>
<th>Bond length (Å)</th>
<th>Bond angle (°)</th>
<th>Dihedral angle</th>
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<tbody>
<tr>
<td></td>
<td>Calcd.</td>
<td>Exp. [20]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pt1-N1</td>
<td>1.96 (0.051)</td>
<td>2.01 (0.284)</td>
<td>120 (0.222)</td>
</tr>
<tr>
<td>Pt1-Cl2</td>
<td>2.29 (0.015)</td>
<td>2.330 (0.382)</td>
<td>90 (0.236)</td>
</tr>
<tr>
<td>Pt1-O6</td>
<td>1.94 (0.034)</td>
<td>1.960 (0.382)</td>
<td>82.2 (0.034)</td>
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</table>

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-C12, which are 0.04 and 0.02 Å, respectively. The differences in bond angle, like Pt1-O6-C7 angle is equal to 2°. Other angles are ranged from 0 to less than 2° for Pt1-N3-O6, N5-Pt1-N3, Pt1-C12-N3 and Cl14-O13-Pt1, respectively. The values are in good closer between present calculation and experimental values. The dihedral angle in the molecule (Cl4-O13-Pt1-C12), (C9-C7-O6-Pt1), (C16-C14-O13-Pt1), (Cl1-C16-C14-O13) and (C10-C9-C7-O6) are (180°, 90°, 180°, 90°, 180°) 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.
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 (\(\Delta E\)) 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].

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 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**

<table>
<thead>
<tr>
<th>LUMO energy</th>
<th>HOMO energy</th>
<th>Dipole moment (Debye)</th>
<th>Nuclear energy (a.u.)</th>
<th>Electronic energy (a.u.)</th>
<th>Kinetic energy (a.u.)</th>
<th>Total energy (a.u.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02849</td>
<td>-0.00024</td>
<td>7.0610</td>
<td>671.8075</td>
<td>-3403.7616</td>
<td>542.4594</td>
<td>-1024.415</td>
</tr>
<tr>
<td>(\Delta H)</td>
<td>(\Delta G)</td>
<td>(\Delta S)</td>
<td>ZPE</td>
<td>Imaginary frequencies</td>
<td>Degree of freedom</td>
<td>Point group</td>
</tr>
<tr>
<td>181.416</td>
<td>128.8993</td>
<td>176.144</td>
<td>165.5022</td>
<td></td>
<td>+</td>
<td>99</td>
</tr>
</tbody>
</table>

*units of kcal mol\(^{-1}\)
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 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

![TABLE-4](image)

Table 4: Global Indexes Values of DOP Complex by DFT/B3LYP/LanL2DZ at 298.150 K at Levels of Theory

<table>
<thead>
<tr>
<th>Global indexes</th>
<th>-X (ev)</th>
<th>µ (ev)</th>
<th>-μη (ev)</th>
<th>-σ</th>
<th>-σ</th>
<th>-S (1/ev)</th>
<th>ΔN</th>
<th>I (kJ mol⁻¹)</th>
<th>-A (kJ mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values</td>
<td>0.0144</td>
<td>0.0144</td>
<td>0.0287</td>
<td>34.81</td>
<td>3.594 (× 10^{-3})</td>
<td>17.40</td>
<td>0.5</td>
<td>0.0002</td>
<td>0.0285</td>
</tr>
</tbody>
</table>

![LUMO](image)

- LUMO = 0.02849
- ΔE\(_{gap}\) = 0.02873
- HOMO = -0.00024

**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(NH3)2(H2O)2 and similarly for the amino group at C6 position in adenine base. Both oxo and amino groups at the C6 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.

![Energy diagram](image)

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

**TABLE-5**

<table>
<thead>
<tr>
<th>Complex</th>
<th>Configuration interaction of guanine</th>
<th>Configuration interaction of adenine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TS1(N1)</td>
<td>TS2(N3)</td>
</tr>
<tr>
<td>Total energy</td>
<td>-644.288</td>
<td>-792.29</td>
</tr>
<tr>
<td>ΔG (kcal mol⁻¹)</td>
<td>91.177</td>
<td>78.313</td>
</tr>
<tr>
<td>ΔS (kcal mol⁻¹)</td>
<td>119.96</td>
<td>123.75</td>
</tr>
<tr>
<td>ΔH (kcal mol⁻¹)</td>
<td>126.945</td>
<td>115.211</td>
</tr>
<tr>
<td>ZPE (kcal mol⁻¹)</td>
<td>94.91</td>
<td>96.23</td>
</tr>
</tbody>
</table>
CONFLICT OF INTEREST

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

REFERENCES

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