Thermodynamic Parameters of Cis-Platin and Trans-Platin Complexes with Guanine in Water, A DFT Study

F. R. Nikmaram* and M. Khan Ahmadi
Department of Chemistry, Faculty of Science, Islamic Azad University, Yadegar-e-Imam Khomeini (RAH) Branch, Tehran, Iran

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ABSTRACT
The binding energy and Thermodynamic Parameters of cis- Platinum Di Ammino Chlorine (cis-[Pt(NH3)2Cl]+) and trans- Platinum Di Ammino Chlorine (trans- [Pt(NH3)2Cl]+) complexes with Guanine has been studied by density functional theory (DFT) calculations in water. The binding energies (E_{bin}) of cis- and trans-[Pt(NH3)2ClG]+ are calculated to be 79.38 kcal/mol and 74.98 kcal/mol, respectively. The binding energy (E_{bin}) of cis-[Pt(NH3)2ClG]+ turns out to be energetically more favorable by about 1.88 kcal/mol than the trans-[Pt(NH3)2Cl]+. At the point of thermodynamic, the formation of cis-[Pt(NH3)2ClG]^{(aq)} with ΔG (Solv) equal to -10.36 kcal/mol is more favorable than trans-[Pt(NH3)2ClG]^{(aq)} with 16.21 kcal/mol.

Keywords: cis-Pt; trans-Pt; Guanine; Binding Energy; Thermodynamic Parameters

INTRODUCTION
Cis-platinum is used as a popular remedy against a variety of solid tumors to chemotherapy. Despite the considerable success, it has been achieved several restrictions. The search for similar drugs that are covered by these shortcomings, carbo-platin and cis-platin resulted in cross linking within between interdisciplinary part of the complex of platinum (II) and the N7 atom of the purine DNA formed. The binding of Pt(II) complexes to DNA bases has been the subject of extensive experimental and theoretical studies in recent years after the discovery of Rosenberg et al. of the antitumor activity of cis-diammine dichloro platinum(II) (cis-DDP or cis-platin) [1, 2]. The many results of investigation have shown that cis-platin attacks DNA base and it inhibits DNA replication [3]. The mono functional binding sites of the neutral base guanine have been investigated for the Pt(NH3)2Cl+ (Platinum Di Ammino Chlorine : PDAC)[4]. The results have shown that the N7 site on guanine has been identified as a preferred site. Basch et al. have studied on binding of Pt(NH3)3^{2+} to nucleic acid bases by ab initio calculation [5]. They have reported that the binding energy of N7 site of the guanine is found to be greater than O6 site.

COMPUTATIONAL METHODS
In the present work, we describe
theoretically the connection of cis- and trans- isomers of PDAC to guanine at solvent. We consider monoaqua complex $[\text{Pt(NH}_3\text{)}_2\text{Cl(H}_2\text{O})]^+$. In the results reported below, solution calculations were carried out at a dielectric constant of 80.37 for water. The N7 site is considered for binding of guanine to PDAC. The minimum energy geometries of cis- and trans- isomers of PDAC, guanine, and PDAC complexes of guanine are optimized by density functional theory (DFT). DFT calculations are carried out at B3lyp level of theory with the LANL2DZ basis set for Pt and 6-31G* for other atoms using the Gaussian 03 program [6].

Discussions

The optimized geometrical structure is shown in Figure 1 for the cis-PDAC with guanine complex (cis-$[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+$). The optimum Pt-N7(G) distance in the cis-$[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+$ complex is found to be 2.200 Å. The optimized geometric structure is shown in Figure 2 for the trans-PDAC with guanine complex (trans-$[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+$) that the optimum Pt-N7(G) distance is calculated to be 2.238 Å. The total energies for each compound and binding energies for $[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+$ complexes are summarized in Table 1. As shown in Table 1, the cis-$[\text{Pt(NH}_3\text{)}_2\text{Cl}]^+$ is calculated to be energetically more favorable by about 1.88 kcal/mol than the trans-$[\text{Pt(NH}_3\text{)}_2\text{Cl}]^+$. The isomeric energy may play a role in relative reactivity. On the other hand, it is found for the $[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+$, where the trans-conformation (trans- $[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+$) is more favorable by about 2.51 kcal/mol than that of cis- $[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+$, as can be seen in Table 1. We investigate the binding energy values in order to compare the binding strength of PDAC isomers to guanine. The binding energies ($E_{bin}$) of cis- and trans-$[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+$ are calculated to be 79.38 kcal/mol and 74.98 kcal/mol in solvent, respectively, by Eq1.

$$E_{bin} = E_{[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+_{aq}} - (E_{[\text{Pt(NH}_3\text{)}_2\text{Cl}]^+_{aq}} + E_{\text{guanine}_{aq}}) \quad (1)$$

In the calculation, the $E_{bin}$ of cis-$[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+$ turns out to be energetically more favorable by about 4.4 kcal/mol than that of $E_{bin}$ of trans-$[\text{Pt(NH}_3\text{)}_2\text{ClG}]^+$. The result obtained in this study suggests that the cis-PDAC bind more strongly to the guanine base than trans-PDAC.

The electrostatic interaction between the metal center and its closest atoms of the guanine is a magnitude subject. The molecular orbital interactions are unusually complicated. Intuitively, a donor-acceptor interaction between the N7 lone-pair orbital of the guanine reactant and the empty Pt-based $d_{xy}^2$ orbital is expected. These processes involve metal-based orbitals that are orthogonal to the molecular plane of the Pt fragment and have been said as π-back-donation components of the Pt-N
bond, implicating electron density flow from the metal center to the $\pi^*$-orbital of the guanine ring.

The vibrational frequency calculation results based on analytical second derivatives at the B3LYP/6-31G* level of theory were used to confirm proper convergence to local minima geometry and to derive the zero-point-energy (ZPE) and vibrational entropy corrections at room temperature. In the present work, we recommend using the value of 0.974 for scale factor to obtain accurate harmonic frequencies [7]. The thermodynamic properties in water were evaluated by a self-consistent reaction field (SCRF) approach [8,9]. The ZPE corrections, thermal corrections to the enthalpy, entropy terms, and continuum solution energies are added to give Gibbs free energies for the reaction in solution.

The entropy of solution is implicitly included in the solution free energy $G_{\text{Sol}}$ and cannot be separated when a continuum model is used.

Thus, it is convenient to introduce a new energy $\Delta H_{\text{Sol}} = \Delta H_{\text{SCF}} + \Delta G_{\text{Solv}}$, that is the electronic reaction energy as computed directly in the DFT calculation using the self-consistent-field procedure. All energy components are listed in Table 2.

**Reaction 1:** $\text{cis-}[\text{Pt(NH}_3\text{)}_2\text{Cl}]^{+}\text{(aq)}$ + Guanine (aq) → $\text{cis-} [\text{Pt(NH}_3\text{)}_2\text{ClG}]^{+}\text{(aq)}$

**Reaction 2:** $\text{trans-}[\text{Pt(NH}_3\text{)}_2\text{Cl}]^+\text{(aq)}$ + Guanine (aq) → $\text{trans-} [\text{Pt(NH}_3\text{)}_2\text{ClG}]^+\text{(aq)}$

We found a more differential result of $\text{cis-}[\text{Pt(NH}_3\text{)}_2\text{Cl}]^+$ and $\text{trans-} [\text{Pt(NH}_3\text{)}_2\text{Cl}]^+$. At the point of thermodynamic, the formation of $\text{cis-}[\text{Pt(NH}_3\text{)}_2\text{ClG}]^{+}\text{(aq)}$ with $\Delta G_{\text{Solv}}$ equal to -10.36 kcal/mol is more favorable than $\text{trans-}[\text{Pt(NH}_3\text{)}_2\text{ClG}]^{+}\text{(aq)}$ with 16.21 kcal/mol. Also, on the base of value of $\Delta H$ (Sol) in Table 2, the reaction 1 for $\text{cis-} [\text{Pt (NH}_3\text{)}_2\text{ClG}]^{+}\text{(aq)}$, is more exothermal with -80.71 kcal/mol with respect to reaction 2 for $\text{trans-} [\text{Pt(NH}_3\text{)}_2\text{ClG}]^{+}\text{(aq)}$ with -1.12 kcal/mol in water.

We compare the partial charge at the

| Table 1. Bond length, total Energy, relative Energy and binding Energy in solvent |
|-----------------------------|-------------------|------------------|------------------|
| structure                  | Pt-N7 / Å         | $E_{\text{total}}$ / (a.u.) | $E_{\text{relative}}$ / kcal.mol$^{-1}$ | $E_{\text{bin}}$ / kcal.mol$^{-1}$ |
| cis-[Pt(NH$_3$)$_2$Cl]$^+$  | -                 | -262.321         | -                |
| trans-[Pt(NH$_3$)$_2$Cl]$^+$| -                 | -262.318         | 1.882            |
| cis-[Pt(NH$_3$)$_2$ClG]$^+$ | 2.200             | -804.880         | 79.38            |
| trans-[Pt(NH$_3$)$_2$ClG]$^+$| 2.238             | -804.884         | 2.510            |

*E$_{\text{relative}}$ is different of total energy of two structures

| Table 2. *Thermodynamic properties at 298k in solvent |
|-----------------------------|-------------------|------------------|
| structure                  | $H(\text{SCF})$   | $G(\text{Solv})$ |
| cis-[Pt(NH$_3$)$_2$Cl]$^+$  | -434474.01        | -59.84           |
| trans-[Pt(NH$_3$)$_2$Cl]$^+$| -415027.86        | -19.51           |
| Guanine (aq)               | -340575.51        | -27.21           |
| cis-[Pt(NH$_3$)$_2$ClG]$^+$ | -775119.87        | -97.41           |
| trans-[Pt(NH$_3$)$_2$ClG]$^+$| -755620.70        | -30.50           |

$\Delta H(\text{SCF})$, $\Delta G(\text{Solv})$, $\Delta H(\text{Sol})$

| Reaction1                  | -70.35            | -10.36           | -80.71           |
| Reaction2                  | -17.33            | 16.21            | -1.12            |

*All energies are given in kcal.mol$^{-1}$. 

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C6-oxo group of optimized structures of the mono aqua complexes. The charge of oxygen at the oxo group is -0.35 and -0.33 for cis- [Pt(NH3)2ClG]+(aq) and trans- [Pt(NH3)2ClG]-(aq), respectively. As expected, the oxo group at cis- [Pt(NH3)2ClG]+(aq) is a much better hydrogen-bond acceptor than the trans- [Pt(NH3)2ClG]-(aq), and the stronger interaction is reflected in ΔG(Solv), Table2.

REFERENCE