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

F. R. Nikmaram[*] and M. Khan Ahmadi

F. R. Nikmaram and M. Khan Ahmadi

Department of Chemistry, Faculty of Science, Islamic Azad University,Yadegar - e- Imam Khomeini (RAH) Branch, Tehran, Iran

ABSTRACT

The binding energy and Thermodynamic Parameters of *cis*- Platinum Di Ammino Chlorine (*cis*-$[Pt(NH_3)_2Cl]^+$) and *trans*- Platinum Di Ammino Chlorine *(trans*- $[Pt(NH_3)_2Cl]^+$) complexes with Guanine has been studied by density functional theory (DFT) calculations in water. The binding energies (E_{bin}) of *cis*- and *trans*-$[Pt(NH_3)_2ClG]^+$ are calculated to be 79.38 kcal/mol and 74.98 kcal/mol, respectively. The binding energy (E_{bin}) of *cis*-$[Pt(NH_3)_2ClG]^+$ turns out to be energetically more favorable by about 1.88 kcal/mol than the *trans*-$[Pt(NH_3)_2Cl]^+$. At the point of thermodynamic, the formation of *cis*-$[Pt(NH_3)_2ClG]^+_{(aq)}$ with ΔG (Solv) equal to -10.36 kcal/mol is more favorable than *trans*-$[Pt(NH_3)_2ClG]^+_{(aq)}$ 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 N_7 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 $Pt(NH_3)_2Cl^+$ (Platinum Di Ammino Chlorine : PDAC)[4]. The results have shown that the N_7 site on guanine has been identified as a preferred site. Basch *et al.* have studied on binding of $Pt(NH_3)_3^{2+}$ to nucleic acid bases by *ab initio* calculation [5]. They have reported that the binding energy of N_7 site of the guanine is found to be greater than O_6 site.

COMPUTATIONAL METHODS

In the present work, we describe

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[*]Corresponding author: Nikmaram87 @yahoo.com

theoretically the connection of *cis*- and *trans*- isomers of PDAC to guanine at solvent. We consider monoaqua complex $[Pt(NH_3)_2Cl(H_2O)]^+$. In the results reported below, solution calculations were carried out at a dielectric constant of 80.37 for water. The N_7 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 B_3lyp 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*-$[Pt(NH_3)_2ClG]^+$). The optimum Pt-N_7(G) distance in the *cis*-$[Pt(NH_3)_2ClG]^+$ 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*-$[Pt(NH_3)_2ClG]^+$) that the optimum Pt-N_7(G) distance is calculated to be 2.238 Å. The total energies for each compound and binding energies for $[Pt(NH_3)_2ClG]^+$ complexes are summarized in Table 1. As shown in Table 1, the *cis*-$[Pt(NH_3)_2Cl]^+$ is calculated to be energetically more favorable by about 1.88 kcal/mol than the *trans*-$[Pt(NH_3)_2Cl]^+$. The isomeric energy may play a role in relative reactivity. On the other hand, it is found for the $[Pt(NH_3)_2ClG]^+$, where the *trans*-conformation (*trans*-$[Pt(NH_3)_2ClG]^+$) is more favorable by about 2.51 kcal/mol than that of *cis*-$[Pt(NH_3)_2ClG]^+$, 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*-$[Pt(NH_3)_2ClG]^+$ are calculated to

be 79.38 kcal/mol and 74.98 kcal/mol in solvent, respectively, by Eq1.

$$E_{bin} = E_{[Pt(NH_3)_2ClG]_{aq}^+} - (E_{[Pt(NH_3)_2Cl]_{aq}^+} + E_{guanine_{aq}})$$ (1)

In the calculation, the E_{bin} of *cis*-$[Pt(NH_3)_2ClG]^+$ turns out to be energetically more favorable by about 4.4 kcal/mol than that of E_{bin} of *trans*-$[Pt(NH_3)_2ClG]^+$. The result obtained in this study suggests that the *cis*-PDAC bind more strongly to the guanine base than *trans*-PDAC.

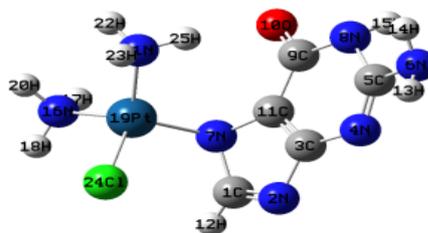**Fig. 1.** Optimized structure of *cis*-$[Pt(NH_3)_2ClG]^+$.

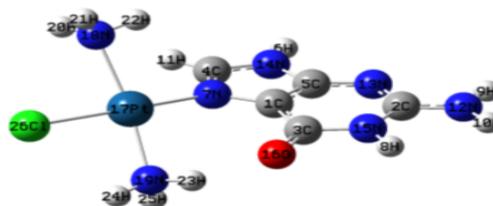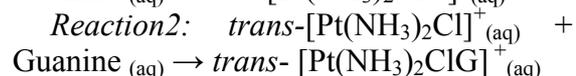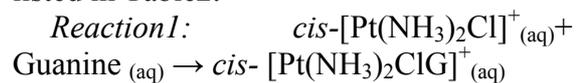**Fig. 2.** Optimized structure of *trans*-$[Pt(NH_3)_2ClG]^+$.

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 N_7 lone-pair orbital of the guanine reactant and the empty Pt-based $d_{x^2-y^2}$ 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 π^*-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 (Solv) and cannot be separated when a continuum model is used.

Thus, it is convenient to introduce a new energy $\Delta H(Sol) = \Delta H(SCF) + \Delta G(Solv)$, 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 Table2.

Reaction1: cis-[Pt(NH$_3$)$_2$Cl]$^+_{(aq)}$+ Guanine $_{(aq)} \rightarrow$ cis- [Pt(NH$_3$)$_2$ClG]$^+_{(aq)}$

Reaction2: $trans$-[Pt(NH$_3$)$_2$Cl]$^+_{(aq)}$ + Guanine $_{(aq)} \rightarrow$ $trans$- [Pt(NH$_3$)$_2$ClG] $^+_{(aq)}$

We found a more differential result of cis-[Pt(NH$_3$)$_2$Cl]$^+$ and $trans$- [Pt(NH$_3$)$_2$Cl]$^+$. At the point of thermodynamic, the formation of cis-[Pt(NH$_3$)$_2$ClG]$^+_{(aq)}$ with $\Delta G(Solv)$ equal to -10.36 kcal/mol is more favorable than $trans$-[Pt(NH$_3$)$_2$ClG]$^+_{(aq)}$ with 16.21 kcal/mol. Also, on the base of value of ΔH (Sol) in Table 2, the reaction 1 for cis-[Pt (NH$_3$)$_2$ClG]$^+_{(aq)}$, is more exothermal with -80.71 kcal/mol with respect to reaction 2 for $trans$-[Pt(NH$_3$)$_2$ClG] $^+_{(aq)}$ 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-N$_7$/ Å	E $_{total}$ / (a.u.)	*E $_{relative}$ / kcal.mol^{-1}	E $_{bin}$ / 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	74.98

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

Table 2. *Thermodynamic properties at 298k in solvent

structure	H(SCF)	G(Solv)	
cis-[Pt(NH$_3$)$_2$Cl]$^+$ $_{(aq)}$	-434474.01	-59.84	
$trans$- [Pt(NH$_3$)$_2$Cl]$^+$ $_{(aq)}$	-415027.86	-19.51	
Guanine $_{(aq)}$	-340575.51	-27.21	
cis -[Pt(NH$_3$)$_2$ClG]$^+$ $_{(aq)}$	-775119.87	-97.41	
$trans$- [Pt(NH$_3$)$_2$ClG]$^+$ $_{(aq)}$	-755620.70	-30.50	
	$\Delta H(SCF)$	$\Delta G(Solv)$	$\Delta H(Sol)$
Reaction1	-70.35	-10.36	-80.71
Reaction2	-17.33	16.21	-1.12

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

C_6-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*-$[Pt(NH_3)_2ClG]^+_{(aq)}$ and *trans*-$[Pt(NH_3)_2ClG]^+_{(aq)}$, respectively. As expected, the oxo group at *cis*-$[Pt(NH_3)_2ClG]^+_{(aq)}$ is a much better hydrogen-bond acceptor than the *trans*- $[Pt(NH_3)_2ClG]^+_{(aq)}$, and the stronger interaction is reflected in $\Delta G(Solv)$, Table2.

REFERENCE

[1] B. Mansy, B. Rosenberg, A. J. Thomson, J. Am. Chem. Soc. 95 (1973) 1633-1637.

[2] B. Rosenberg, Biochemie. 60 (1975), 859-863.

[3] A. T. M. Marcelis, J. Reedijk, Recl. Trav. Chim. Pays Bas. 102(1983)121-126.

[4] [4] J. P. Caradonna, S. J. Lippard, M. J. Gait, M. Singh, J. Am. Chem. Soc. 104 (1982) 5793-5799.

[5] H. Basch, M.Krauss, W. J. Stevens, D.Cohen, Inorg.Chem. 25 (1986) 684-690.

[6] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K.N. Kudin, J. C. Burant, J. M. Millam, S.S. Iyengar, J. Tomasi, O. Yazyev, A.J. Austin, R. Cammi, C. Dannenberg, V.G. Zakrzewski, S. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J.A. Pople, Revision B.03 ed., Gaussian, Inc., Pittsburgh PA,, 2003.

[7] I. M. Alecu, J. Zheng, D. G. Truhlar, J. Chem. Theory Comput. 6 (2010), 2872.

[8] J. Tomasi, M. Persico, Chem. ReV. 94 (1994), 2027.

[9] C. Cramer, D. G. Truhlar, Chem. ReV. 99 (1999) 2161.