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Research paper

A DFT investigation on interactions between asymmetric derivatives of cisplatin and nucleobase guanine

Truong Ba Tai [a,b], Pham Vu Nhat [c,*]

[a] Computational Chemistry Research Group, Ton Duc Thang University, Ho Chi Minh City, Viet Nam
[b] Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City, Viet Nam
[c] Department of Chemistry, Can Tho University, Viet Nam

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ABSTRACT

The interactions of hydrolysis products of cisplatin and its asymmetric derivatives *cis*- and *trans*-[$PtCl_2$(*i*Pram)(Mepz)] with guanine were studied using DFT methods. These interactions are dominated by electrostatic effects, namely hydrogen bond contributions and there exists a charge flow from H-atoms of ligands to the O-atoms of guanine. The replacement of NH_3 moieties by larger functional groups accompanies with a moderate reaction between Pt^{II} and guanine molecule, diminishing the cytotoxicity of the drug. The asymmetric and symmetric NH_2 stretching modes of complexes having strong hydrogen bond interactions are red shifted importantly as compared to complexes without presence of hydrogen bond interactions.

1. Introduction

Cisplatin or *cis*-diamminedichloroplatinum(II) is a widely-used antitumor drug which particularly successes in treatment of various fatal diseases, including testicular, ovarian, head and neck cancers [1,2]. Unfortunately, it also presents some disadvantages, for example, several side effects such as nausea, ear damage, vomiting and both intrinsic and acquired resistances [3,4]. During the past decades much effort has been therefore devoted to limit these drawbacks by exploiting alternative platinum complexes. However, the search for analogous compounds that outperform cisplatin is an extremely difficult task, not only because of the diversity of the compositions, structures and properties of replaced ligands, but also due to the lack of quantitative atomic level information about the factors controlling Pt-DNA interactions. Although thousands of platinum compounds were synthesized so far, only few new agents such as oxaliplatin, carboplatin and nedaplatin were registered worldwide and have entered clinical practice [5–7]. A thorough understanding of interactions between platinum and DNA building blocks plays a crucial role and is helpful in designing new cisplatin analogues.

Since DNA was found to be the primary target of the drug, numerous theoretical and experimental studies were devoted to reveal the nature of cisplatin–DNA interactions [8,9]. In this context, quantum chemical calculations have widely been used and made significant contributions to deeper understanding on these interaction mechanisms [10]. From the early time, using Hartree-Fock (HF) model in conjunction with the minimal basis set STO-3G, Kozelka and co-workers were able to reproduce some structural patterns of *cis*-DDP–base DNA [11,12]. Other primarily remarkable results on structural aspects of the complexes between platinum and biomolecules came from the Carloni's research group, based on the density functional theory (DFT) calculations [13,14]. More recently, the hydrolysis of cisplatin and some features in their electronic structures were intensively studied at different levels of theory [15–17]. The combined experimental and theoretical approaches were also used to describe more accurately the interactions of cisplatin and base purines [18,19]. The first-principles calculations were employed to study not only cisplatin–DNA complexes, but also other non-Pt and Pt- transition metal complexes [20,21].

In this report, we carried out a detailed examination on the interactions between an asymmetric derivative of cisplatin, *cis*-[$PtCl_2$(*i*Pram)(Mepz)] (where *i*Pram is isopropylamine and Mepz is 1-methylpyrazole), and the DNA base guanine by using DFT calculations. The derivative was formed by replacing two —NH_3 groups of cisplatin with larger functional groups, including isopropylamine and 1-methylpyrazole as shown in Scheme 1. The cytotoxicity of this complex in several human cell lines was found to be lower than that of cisplatin [22], but further information is

* Corresponding author at: Department of Chemistry, Can Tho University, Viet Nam.
E-mail addresses: truongbatai@tdt.edu.vn (T.B. Tai), nhat@ctu.edu.vn (P.V. Nhat).

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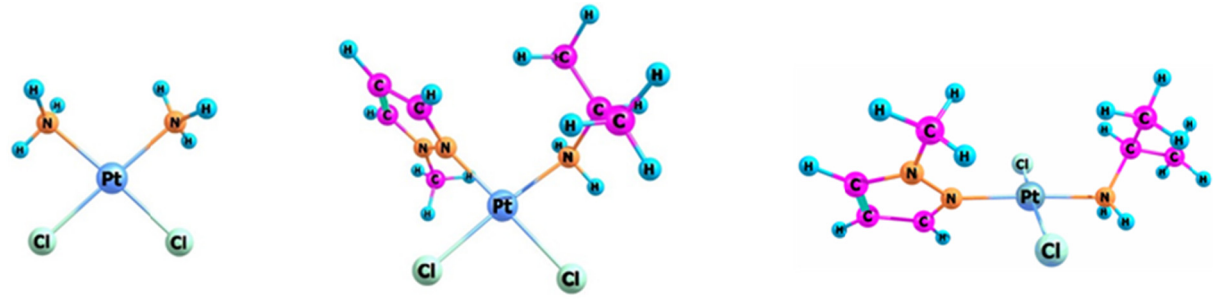

Scheme 1. Optimized geometries of *cis*-[$PtCl_2(NH_3)_2$] (left), *cis*-[$PtCl_2$(*i*Pram)(Mepz)] (middle) and *trans*-[$PtCl_2$(*i*Pram)(Mepz)] (right).

still not unambiguous. In addition, Reedijk et al. [23] interestingly showed that the asymmetric *trans*-amine(azole)dichloridoplatium complexes possess cytotoxicity profiles comparable to cisplatin and are particularly promising as alternatives to cisplatin in second line treatment due to their higher activities in the resistant A2780res cell line. Thus the interactions between *trans*-[$PtCl_2$(*i*Pram)(Mepz)] and the nucleobase are also examined.

2. Computational methods

All calculations were carried out by using the Gaussian 09 suite of program [24] in the framework of density functional theory [25]. The hybrid B3LYP functional, which was proved to be suitable for platinum–DNA system calculations [26], was employed for geometry optimization and energetic calculations as well. The basis set with an effective core potential (ECP) cc-pVTZ-PP [27] was applied for platinum, while the all electrons cc-pVTZ basis set was used for the non-metals.

The ECP cc-pVTZ-PP basis set includes relativistic effects that are crucial in treatment of heavy elements such as platinum. Harmonic vibrational frequencies were calculated to estimate the zero-point vibrational energy (ZPE) corrections. The natural bond orbital (NBO) charges of atoms were computed using the NBO5.G code [28]. We exploited NBO charges for electron population analysis instead of Mulliken charges because the former are expected to be more reliable [29].

Previous studies confirmed that after entering the cell by passive diffusion through the cell membrane, cisplatin undergoes hydrolysis *via* nucleophilic substitution of chloride with water to form cationic complexes $[Pt(NH_3)_2(H_2O)Cl]^+$ and $[Pt(NH_3)_2(H_2O)_2]^{2+}$ [30]. This process is a fundamental step to determine the anticancer activity of cisplatin since it results in reactive metabolites that ultimately give rise to DNA adducts [31]. Both complexes can be substituted easily by donor ligands such as nitrogen-containing bases of DNA, but it is unclear whether the monoaqua or diaqua species is more important [32].

To gain more insight into these phenomena, we firstly probed the interactions of the monoaqua cation $[Pt(NH_3)_2(H_2O)Cl]^+$ with guanine at various binding sites. Then detailed computations were carried out to examine the interactions between [Pt(*i*Pram)(Mepz)$(H_2O)Cl]^+$ cation and guanine, with emphasis on the dominating preference for initial anchor. The ligand-exchange reaction between these complexes $[PtLL'(H_2O)Cl]^+$ and guanine (G) can be described as following expression:

$$[PtLL'(H_2O)Cl]^+ + G \rightarrow [PtLL'(G)Cl]^+ + H_2O \quad (1)$$

where L = L′ = NH_3 for cation $[Pt(NH_3)_2(H_2O)Cl]^+$ and L = *i*Pram, *L′* = *Mepz* for cation [Pt(*i*Pram)(Mepz)$(H_2O)Cl]^+$.

3. Results and discussion

3.1. Interaction between $[Pt(NH_3)_2(H_2O)Cl]^+$ and guanine

Guanine is one of the four main nucleobases found in both DNA and RNA. The molecule has several possible binding sites with the transition metal, i.e. nitrogen atoms N1, N3, N7 and N9, and the carbonyl oxygen atom [33]. In addition to these traditional anchoring sites, complexes with N1—H tautomers were also considered. The optimized geometries of cisplatin – guanine adducts obtained from these binding sites of guanine are presented as PtGN7, PtGN3, PtGN1, PtGO (Figs. 1).

In agreement with previous prediction [32], the most preferred binding site of guanine is N7, giving rise to structure PtGN7. This form involves one hydrogen bond between hydrogen atom of an ammonia ligand and the carbonyl oxygen at the C6 position. Interestingly, our calculations showed that the stability of these complexes is remarkably affected by formation of hydrogen bonds in systems. As shown in Fig. 1 and Table 1, the hydrogen bond length in the most stable form PtGN7 is 1.757 Å, while there is no presence of any hydrogen bond in the least stable isomer PtGN3. The lengths of hydrogen bonds in PtGN1 and PtGO are 1.859 Å and 1.979 Å, respectively. These observations leave no doubt that hydrogen bond plays a key role on the interaction between cisplatin and guanine. In addition, the N-coordinated sites were found to be more favoured than the O-coordinated position. This is consistent with the hard – soft acid – base (HSAB) rule that the soft acid Pt(II) binds more strongly with the softer base containing nitrogen than harder base containing oxygen.

3.2. Interactions between $[Pt(iPram)(Mepz)(H_2O)Cl]^+$ and guanine

Similar to $[PtCl_2(NH_3)_2]$, the [$PtCl_2$(*i*Pram)(Mepz)] has two stable isomers as shown in Fig. 2. According to our predictions, the *cis* form is less stable than the *trans* counterpart with energy gap of 12.9 kcal/mol.

The optimized geometries of complexes [Pt(*i*Pram)(Mepz)(G)$Cl]^+$ in both *cis*- and *trans*-configurations along with their relative energies computed at the B3LYP/cc-pVTZ-(PP) + ZPE level are displayed in Fig. 3. All configurations were constructed by directly binding Pt-atom of $PtCl_2$(*i*Pram)(Mepz) with N7-atom of guanine. Other configurations in which Pt-atom is bound with other positions of guanine are much less stable and shown in Fig. S1, supplementary Information. Our calculations showed that two conformations *cis*-PtGMpz-1 and *cis*-PtGMpz-2 are almost degenerate with tiny energy gap of 0.7 kcal/mol and are the most stable forms of the complex *cis*-[Pt(*i*Pram)(Mepz)(G)$Cl]^+$. They are only different in orientation of two moieties *i*Pram and Mepz in molecules. Two remaining conformers, namely *cis*-PtGMpz-3 and *cis*-PtGMpz-4, are less stable and are 3.6 and 4.7 kcal/mol higher in