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Computational study on mechanisms of the anticancer drug: Cisplatin and novel polynuclear platinum(II) interaction with sulfur-donor biomolecules and DNA purine bases

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ABSTRACT

In this paper, we explore the monofunctional substitution reactions between cisplatin and novel polynuclear platinum(II) (BBR3005 and BBR3464) hydrolyzed complexes and sulfur-donor biomolecules (glutathione, methionine and cysteine) and purine bases (guanine and adenine) in DNA with two different DFT-B3LYP/M06 functional methods and IEF-PCM solvation model. The computed activation energy barrier of chloroaqua-Pt (BBR3464) and diaqua-Pt (BBR3464) complexes binding to guanine (G), adenine (A), and glutathione (GSH) in the aqueous solution with B3LYP functional method is 17.9/17.9 kcal/mol, 19.9/19.8 kcal/mol, and 13.2/14.6 kcal/mol, respectively. What is more, the computed activation energy barrier for substitution reaction of diaqua-cisplatin with DNA by B3LYP functional method is 20.1 kcal/mol (11.2 kcal/mol for M06 functional method) for guanine (G) (experimental value = 18.3 kcal/mol) and 22.3 kcal/mol (15.5 kcal/mol for M06 functional method) for adenine (A), which shows that the B3LYP functional method may be more suitable for platinum–DNA system calculation compared with M06 functional method. Our calculation demonstrates that GSH is more favorable intracellular targets than Met, Cys and DNA purine bases for BBR3464, which is also consistent with the results that platinum(II) has high affinity for binding to S-donors biomolecules especially glutathione compared with N-donors biomolecules such as DNA purine bases.

The calculated activation energies barrier of interaction of polynuclear platinum(II) with purine bases are lower than those of cisplatin no matter we use B3LYP or M06 functional method, which confirms that anticancer activity of polynuclear platinum(II) is higher than cisplatin as suggested by experiment.

1. Introduction

Cisplatin, discovered to have cytotoxic activity by Rosenberg in 1960, is one of the most widely used anti-cancer drugs [1]. However, cisplatin has some side effects on clinical uses, which limit its large dose and clinic usage to some extent. Therefore, great efforts have been made to reduce the toxic side effects and overcome resistance in order to discover new drugs [2–5].

In the past decades, with an understanding of the mechanism of action of anticancer platinum drugs [6–12], some new 'non-classical' platinum complexes containing polynuclear platinum were discovered and tested. Polynuclear platinum complexes contain two or more reactive platinum coordination centres linked by aliphatic diamine chains, which can form various DNA adducts such as long-distance intra- and interstrand cross-links compared with cisplatin and its analogues [13–15]. Consequently, many researchers have turned to design and synthesize novel polynuclear platinum complexes. BBR3005 and BBR3464 (as seen in Scheme 1) are representative dinuclear and trinuclear platinum complexes, respectively. BBR3464 is the first polynuclear platinum anticancer drug to enter clinical trials, which has undergone phase II clinical trials in humans [16–19]. Even in the cisplatin resistant cancer cells, BBR3464 is more cytotoxic than cisplatin, which is attributed to the formation of various types of DNA adduct, such as 1,4-and 1,6-interstrand cross-links [20–23]. Although it is now generally considered that cellular DNA is the primary target of platinum drugs [24–26], many details of the mechanism of reaction of platinum with biological target leading to antitumor activity still remain unclear. As we all know, there are a lot of biological molecules of competitive reaction with platinum complexes in cells. Then, the anticancer activity of platinum-based anticancer drugs is also regarded as to be related with reaction with a variety of biomolecules [27]. Glutathione (GSH) is a cellular tripeptide

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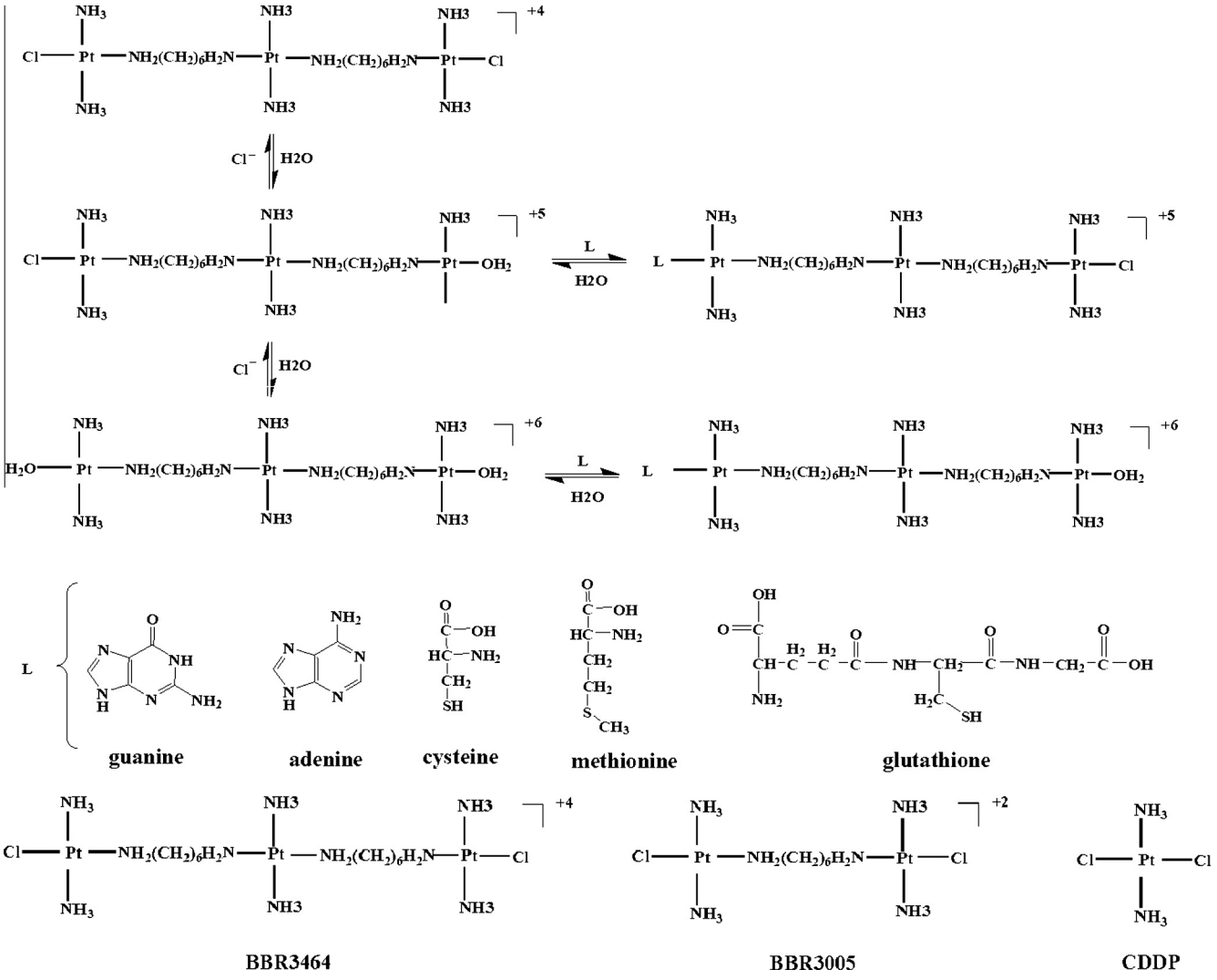

Scheme 1. The monofunctional substitution reactions of the monoaquated and diaquated platinum(II) complexes with sulfur-donor biomolecules and DNA purine bases, respectively.

including cysteine residues and is generally considered as an important role in the metabolic interactions of platinum drugs [28,29]. Furthermore, since the concentration of glutathione and cysteine inside the cell is about 0.1–10 mM [30], a conventional hypothesis is that most of the Pt drug interaction with sulfur-biomolecules before it enters cell nucleus to bind to DNA [31]. Hence, the GSH, Met and Cys are chosen as the primary sulfur-biomolecules for investigation.

In recent years, although theoretical studies on platinum drugs mainly focus on the mechanism of reaction with DNA purine bases [32–37], a few theoretical studies have been investigated, concerning the mechanism of reaction of novel polynuclear platinum(II) anticancer drugs with biological targets. In addition, other aspects of DNA damages have been reported. For example, secondary low-energy electrons can cause single and double-strand breaks in DNA, further result in the fragmentation of DNA bases thereby initiate chemical reactions that can eventually lead to cell apoptosis [38–40]. Moreover, Boudaïffa et al. [41] reported that strand breaks in DNA by low-energy electrons at energies well below the ionisation threshold (<10 eV).

In the present study, we perform different DFT methods to investigate the possible pathways for reactions of polynuclear platinum(II) with S-containing (glutathione, methionine and cysteine) and N-containing biomolecules (purine bases) as its intracellular targets, which will provide a better understanding of the anticancer mechanisms of polynuclear platinum drug in cell. The monoaquated and diaquated complexes of cisplatin and novel polynuclear platinum(II) binding to nucleophiles L are systematically studied (Scheme 1).

2. Computational method

In the gas phase, all geometry optimizations and frequency calculations are accomplished with B3LYP [42–44] and M06 [45,46] functional methods of the density functional theory (DFT). Meanwhile, the LanL2DZ [47–49] effective core potential basis set are employed for transition metal platinum atom and 6-31G (d, p) Pople basis set are used for all nonmetal atoms. At this same level of theory, the harmonic frequency analysis based on analytical second derivatives is carried out to confirm that the stationary point is the local minimum (NIMAG = 0) on the potential energy surface (PES) [50] for the reactants and products and the first saddle point (NIMAG = 1) for transition states, respectively. Meanwhile, we can