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A computational study of PAMAM dendrimer interaction with trans isomer of picoplatin anticancer drug

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ABSTRACT

In this study, the interaction of zero generation (G0) of polyamidoamine (PAMAM) dendrimer with trans isomer of Picoplatin anticancer drug (AMD) has been investigated by density functional theory. According to the structure of dendrimer and drug, two types of dendrimer cavities that can interact with the drugs can be formed in drug-loaded PAMAM dendrimer in which AMD drug can be located inside the PAMAM cavities through Cl and NH_3 heads. The results have indicated that the interaction of PAMAM dendrimer with picoplatin anticancer drugs is physisorption. Relevant information about geometry, adsorption energy and molecular orbitals and quantum molecular descriptor, the most stable site for drug loading corresponds to the core of the dendrimer. The PAMAM-AMD complexes have shown a significant improvement of structural and electronic properties according to the results obtained from different arrangement of PAMAM G0-AMD complexes; a [G0-AMD (Cl-1)] complex is the preferred adsorption arrangement. As a result, it seems that the zero generation PAMAM dendrimer being combined with the AMD drug is suitable for use in drug delivery.

1. Introduction

According to the latest research in the pharmaceutical area, refining the drug properties that treat different diseases are more important than novel drugs synthesis [1]. The elements that indicate the drug treatment effectiveness are adequacy, solubility, toxicity, biocompatibility and bioavailability [2]. Many drugs are not suitable for the treatment of diseases due to lack of one of the above elements. The use of nanocarriers such as polymeric micelles, liposomes, carbon nanotubes, nanospheres and dendrimers to transport a drug can be a solvent of the problems just specified. Not only do these nanocarriers make the drug chemical structure not to change. But they also reduce drugs side effects, which can improve targeting and controlled release of medications [1].

The structure of polymers is classified in to four categories: linear, cross-linked, branched and dendrimer [3]. Nanoparticles of cationic polymers called dendrimers are a suitable vehicle for transferring drugs and genes. Special features of the dendrimers include high solubility in aqueous media, chemically controllable structure as well as symmetric and spherical molecular shape. The multitude of surface groups which are varied in their chemical structure, and which can be useful in changing the properties of dendrimers [4]. As can be seen in Fig. 1 In the structure of particular kind of dendrimers called polyamidoamine (PAMAM) dendrimers, there are three permanent features: ethylenediamine core, branches attached to amide group of the core and primary amine end groups [5].

Inner cavities are one of the characteristics of high generation dendrimers which are very useful in transferring anticancer drug to the target area of treatment [6]. Interaction of drug compounds with the dendrimers is possible in two ways: covalent and non-covalent. The covalent interaction of the drug occurs with the superficial functional groups of dendrimer through the binding. Non-covalent interaction occurs due to the physical interaction of the drug with internal dendrimer cavities or dendrimer external surfaces [7]. These physical encapsulations of the drug-dendrimer complexes are due to three types of interactions including hydrogen binding, hydrophobic and electrostatic interaction [8]. The electrostatic interactions of dendrimers have made them good candidate as drug delivery systems in recent years [9,10].

Medications which are based on platinum are one of the most effective drugs in chemotherapy for various types of cancers. Cisplatin (*cis*-[$PtCl_2$ (NH_3)] or *cis*-DDP) is one of the platinum drugs that acts against cancer tumors for more than 30 years [11]. But the

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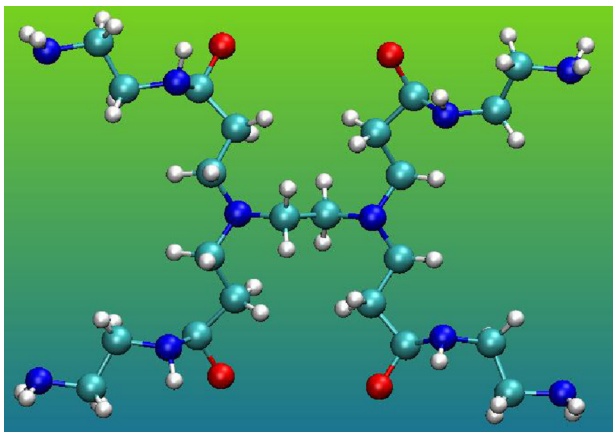

Fig. 1. Structure of PAMAM-NH_2 G0 dendrimer.

serious limitations of this drug such as insolubilization in aqueous solution, side effects and bad resistance make it impossible to use it [12]. As a result of further research next generations of platinum drugs were discovered. The second generation solves the cisplatin toxicity problem and the third generation resolves the cisplatin resistance. AMD or picoplatin is a *cis*- isomer of the third generation of platinum drugs [13]. The use of theoretical and computational methods to evaluate the loading of the drug in the carrier and its release process in the target area has advantages over experimental methods [14,15].

PAMAM dendrimer requires a computational method that is highly accurate. DFT calculations eliminate empirical method errors and also greatly reduce the cost of the analysis. In addition they give us a very detailed insight on the changes in structural geometries, energies of interaction and the charge distribution in the process of encapsulation [2,16].

The purpose of this study was to investigate the non-covalent interaction of the zero generation dendrimer with AMD drug. Considering that AMD and PAMAM dendrimer can interact in different directions, in this paper we used a special naming method to determine the interaction side and form of the final complex. Finally by examining and analyzing the result of the computational method, the best mode of interaction between the drug and the dendrimer will be determined. In order to achieve the mentioned results, all the desired structures were optimized. Then considering the capability of DFT method to calculate the amount of molecular and adsorption energies, the best mode of physisorption interaction was determined.

This article will be presented in the following section: in Section 2 we give the details of theoretical methodology was used. In Section 3, we discuss the results obtained from DFT computation. At the end, in section 4 we provide a summary of the main results and conclusions.

2. Computational details

In this study, all of quantum chemical calculations were done by using the Gaussian 03 program package [17]. Full optimization of the geometries were performed without any symmetry constrains at the DFT level of theory with the Becke [18] three parameters hybrid functional and the Lee, Yang and Parr correlation functional B3LYP [19–21] exchange-correlation using a relativistic effective core potential basis set with pseudo potentials for the metal ion, LANL2DZ [22] and the standard6-31G(d) basis set for other atoms (C, H, O, N). After every geometry optimization, the vibrational frequencies are estimated at the above mentioned level. These calculations are used to confirm the fixation of stationary point to true minima on the potential energy surface (PES) and zero point energy (ZPE) values. In the structure that optimized, Single point calculations were performed at B3LYP/6-31G**level of theory to achieve electronic and thermodynamic properties with higher accuracy such as adsorption energies, Density Of State (DOS), Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) energies.

Table 1
Calculated E_{ads} (KJ/mol), and E_{HLG} (eV) of [G0-AMD (Cl-1&2)] and [G0-AMD (NH_3-1&2)] complexes.

Complex	E_{ads}(kJ/mol)	E_{HLG}(ev)
[G0-AMD (Cl −1)]	−21.978	0.138
[G0-AMD (NH3-1)]	21.808	0.152
[G0-AMD (Cl-2)]	−5.903	0.158
[G0-AMD (NH3- 2)]	11.653	0.153

3. Results and discussion

At first we have optimized the structures of zero generation PAMAM dendrimer, picoplatin, and dendrimer-picoplatin**.** The geometrically optimized structures for zero generation (G0) PAMAM dendrimer and trans isomer of picoplatin drug(AMD) have been depicted in (Fig. 2a and b) respectively. Considering the structure of branches and core in Fig. 2a, two types of cavities that can interact with the drugs can be formed in drug-loaded PAMAM dendrimer.It has been observed that there is a very active amine (type III) at the bottom of the first type cavity and (PAMAM) dendrimers with an ethylenediamine (EDA) core at the bottom of the second type that let the drug to interact with them efficiently.

We have studied the non-covalent interaction between zero generation PAMAM and AMD drug by employing two models in which AMD drug can be located inside the first and second type PAMAM cavity through Cl and NH_3 heads. Naming the suggested models is abbreviated in accordance with the following pattern:

[PAMAM generation-drug (drug reaction head- dendrimer cavity type)]

Thereafter, the geometry structures of the four possible states [G0-AMD (Cl-1)], [G0-AMD (Cl-2)], [G0-AMD (NH_3-1)] and [G0-AMD (NH_3-2)] complexes were optimized. For instance, [G0-AMD (Cl-1)] means that AMD drug has been close to the first type cavity zero generation PAMAM dendrimer from Cl head. The adsorption energy (E_{ads}) was calculated employing Equation (1):

$$E_{ads} = E_{(PAMAM\text{-}AMD)} - [E_{(PAMAM)} + E_{(AMD)}] \quad (1)$$

where $E_{(PAMAM\text{-}AMD)}$ refers to the total energy of PAMAM–AMD complex while the $E_{(PAMAM)}$ and $E_{(AMD)}$ refer to the total energy of the PAMAM dendrimer and the total energy of AMD drug, respectively.

It is important to note that these quantities account for relative interaction strength of attachment and not necessarily imply exothermic or endothermic adsorption processes. Therefore, a positive value of E_{ads} indicates weak interactions but not certainly imply an endothermic adsorption process [23]. As can be seen from Table 1; the dendrimer-drug absorbed energy values are in the range of −21 to 22 kJ/mol. The adsorption of AMD drug through Cl head in two types of PAMAM dendrimer cavities is stable energetically ($E_{ads} < 0$) so this is the only case that physical adsorption occurs. By comparing the energy of [G0-AMD (Cl-1)] and [G0-AMD (Cl-2)] complexes, it can be concluded that the drug encapsulated energy in the first type cavity becomes more negative and therefore leads to a stronger physical adsorption. Whereas the amount of energies of [G0-AMD (NH_3-1&2)] are unfavorable, therefore will not be discussed further.