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Application of $C_{30}B_{15}N_{15}$ heterofullerene in the isoniazid drug delivery: DFT studies

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ABSTRACT

Using density functional theory, we have investigated the potential application of a $C_{30}B_{15}N_{15}$ heterofullerene in anti-cancer isoniazid drug delivery. It was found that isoniazid prefers to attach via its $-NH_2$ group to a boron atom of the $C_{30}B_{15}N_{15}$ with releasing a large energy of about 21.91 kcal/mol. Our partial density of states analysis demonstrates that the boron atoms significantly contribute in generation of virtual orbitals of $C_{30}B_{15}N_{15}$ fullerene, indicating that these atoms will be suitable for nucleophilic attack rather than carbon atoms. In addition to the large released energy, the electronic properties $C_{30}B_{15}N_{15}$ are significantly sensitive to the isoniazid attachment which can recognize the drug trajectory by affecting the fluorescence emission properties. Unlike, different nanostructures whose structures need to be manipulated to be suitable for drug delivery, the $C_{30}B_{15}N_{15}$ fullerene can be used in the pristine form. We proposed a drug release mechanism in cancer tissues, representing that in the low pH of the cancer cells the drug and $C_{30}B_{15}N_{15}$ fullerene are considerably protonated, thereby separating the drug from the surface of the fullerene. The reaction mechanism of the drug with the fullerene is changed from covalence in natural environment to hydrogen bonding in acidic cancer cells.

1. Introduction

Heterofullerenes which are made by substitutional doping in the fullerene shell and inorganic fullerenes have attracted great attention recently [1–15]. The most prominent heterofullerenes contain boron and nitrogen instead of carbon atoms. For B- and N-doped C_{60} fullerenes, the possible incorporation of dopants at several positions of the cage must be considered [16]. In 1991, Guo and coworkers stated that there should be no B-B or N-N bonds in the B- and N-doped C_{60} fullerene structures [17]. One year later, Xia *et al.* showed that $B_{30}N_{30}$ heterofullerenes are theoretically stable and they can be synthesized from borazine [18]. In 2004, Erkoç investigated $C_{30}B_{15}N_{15}$ heterofullerenes by semi-empirical molecular orbital calculations [19]. They suggested a stable structure with a frontier molecular orbital energy gap value of about 1 eV [19].

Isoniazid molecule was prepared for the first time by Meyer and Mally in 1912, while they were entirely unaware of its potential for treating tuberculosis [20]. After 40 years of no attention to this compound, Bernstein *et al.* discovered that isoniazid is an anti-tubercular drug [21]. Despite the widely used and the efficient effects of isoniazid in tuberculosis treatment, it can cause severe side effects such as peripheral neuropathy and hepatotoxicity which confines the doses that can be used clinically [22,23]. Drug delivery systems offer some advantages including the possibility to target specifically the tumor cells and protect the drug from degradation [24]. Thus, it can enhance the therapeutic efficiency and reduce the toxicity of the drug. On the other hand, when bacteria are treated with antibiotics, the drug resistance increases and higher concentrations of antibiotic are needed for affecting on the bacteria. Hence, a system that facilities delivery of high doses of drug to the bacteria sites is highly desirable [24]. By advent of nanotechnology, different nanostructures have found promising applications in gas sensors, electronic, gas removal, drug delivery, etc [25–41]. Recently, much attention has been paid to delivery of anti-cancer drugs such isoniazid by nanostructures [42–44]. Although, an effective carrier to reduce the side effects associating with isoniazid therapies is still lacking.

B- and N-doped heterofullerenes have been already known as noncytotoxic nanostructures which can be functionalized with several molecules for biological applications [45,46]. Saikia et al. have studied the structure and electronic properties of the noncovalent functiona-

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lization of BN nanotubes with isoniazid [47]. Furthermore, Judge and coworkers have synthesized a C_{60}/isoniazid conjugate and successfully tested it for antimycobacterial activity [48]. In this work, we investigate the potential utility of $C_{30}B_{15}N_{15}$ heterofullerene as a drug carrier for isoniazid anti-tubercular drug by means of density functional theory (DFT) calculations. The adsorption and release mechanisms of the drug will be considered.

2. Computational details

The B3LYP exchange-correlation functional [49,50] and 6–31G (d) basis set were performed to study the interaction between the $C_{30}B_{15}N_{15}$ fullerene and the isoniazid drug. The B3LYP is a commonly used density functional which frequently has been jointed with 6–31G (d) basis set to explore different properties of nanostructures [51–65]. Geometry optimizations, adsorption energies (E_{ad}), molecular electrostatic potential (MEP), natural bond orbitals (NBO) and electronic properties such as the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO) and the HOMO-LUMO energy gaps (E_g) were carried out using GAMESS program package at the same level of theory [66]. GaussSum program [67] was used to draw density of states (DOS) plots.

We have done vibrational frequency calculations to make sure that all optimized structures correspond to the global minima on the potential energy surface. The values of E_{ad} for the optimized complexes were obtained by following equation:

$$E_{ad} = E(\text{Isoniazid } /C_{30}B_{15}N_{15}) - E(\text{Isoniazid}) - E(C_{30}B_{15}N_{15}) + \text{BSSE} \quad (1)$$

where E(Isoniazid /$C_{30}B_{15}N_{15}$) is the energy of the complex between isoniazid and the $C_{30}B_{15}N_{15}$ heterofullerene. The counterpoise method of Boys and Bernardi was used to calculate the basis set superposition error (BSSE) energy for all studied complexes [68]. Moreover, to predict the charge transfer between the isoniazid molecule and $C_{30}B_{15}N_{15}$, we accomplished NBO analysis.

3. Results and discussion

3.1. Structure and properties of isoniazid and $C_{30}B_{15}N_{15}$

The $C_{30}B_{15}N_{15}$ heterofullerene consists of four types of hexagonal and three types of pentagonal rings which are shown as H1-H4 and P1-P3 in Fig. 1. It is a polar molecule with a dipole moment about 3.39 D. The calculated equilibrium C–C bond lengths in $C_{30}B_{15}N_{15}$ are about 1.42 Å, being comparable with those of C60 fullerene (~1.41 Å [69]). The average C–B, C–N and B–N bond lengths are about 1.54 Å, 1.44 Å and 1.47 Å, respectively. Depending on the position of atoms in the structure of $C_{30}B_{15}N_{15}$ fullerene, there are three types of boron atoms called A, B, and C and highlighted in Fig. 1 by red, green and orange circles, respectively. The MEP plot for the optimized structure of isoniazid with a formula $C_6H_7N_3O$ depicted in Fig. 1. It shows the most likely reaction sites of isoniazid which are a carbonyl oxygen, a nitrogen atom of hexagon and a $-NH_2$ group as numbered from 1 to 3 in this work. Hence, there are 9 main interaction states between the isoniazid molecule and the $C_{30}B_{15}N_{15}$ fullerene.

3.2. The isoniazid adsorption on $C_{30}B_{15}N_{15}$

The optimized structures of the 9 studied complexes of isoniazid and $C_{30}B_{15}N_{15}$ are presented in Fig. 2. The bond lengths between the interaction sites are about 1.60, 1.64 and 1.65 Å for different involving heads of isoniazid. The distances are almost identical for all three types of boron atoms. The values of E_{ad} and the BSSE corrected E_{ad} are listed in Table 1, indicating that the adsorptions from $-NH_2$ head group of isoniazid on the boron atoms are the most favorable interaction between isoniazid and $C_{30}B_{15}N_{15}$ molecules. The nitrogen in $-NH_2$ group has a lone pair and tends to react with boron atom as a Lewis base. The values of E_{ad} as well as the bond lengths show that there is a negligible chemical difference between boron atoms in the $C_{30}B_{15}N_{15}$. Therefore, we assumed that all boron atoms are identical and focused on the boron type **C**. The BSSE corrected E_{ad} values are about −7.58, −17.70 and −21.91 kcal mol^{-1} for **C1**, **C2** and **C3** complexes, showing that there are relatively strong interactions between the reactants. Complex **C3** with the most negative value of E_{ad} is the most stable complex between all the studied complexes. Table 1 indicates that the effect of the BSSE correction on the weaker interaction is larger.

3.3. The electronic properties

The results of DFT calculations reported in Table 1 and partial DOS plot in Fig. 3 show that $C_{30}B_{15}N_{15}$ heterofullerene is a semiconductor with an E_g value about 0.96 eV in which the HOMO and LUMO energies are about −4.52 and −3.56 eV, respectively. This is in good agreement with the previously reported value [10]. Interestingly, PDOS plot demonstrates that the N atoms which are much more electronegative atoms with a lone pair (Lewis base) significantly contribute in the generation of occupied orbitals. While the electron deficient boron atoms are mainly responsible of virtual orbital creation which is in consistence their Lewis acid character. Carbon atoms with a moderate electronegativity contribute in both occupied and virtual orbitals.

In complex **C1,** after the interaction, the HOMO level of the cage is slightly shifted to more positive value and the LUMO level is shifted from −3.56 to −4.03 eV. Thus, the E_g is decreased by about 11% from 0.96 to 0.88 eV. The changes in HOMO, LUMO and E_g in complex **C2** are similar to those in the complex **C1**. For the complex **C3**, while HOMO level is slightly shifted to higher positive value, there is a

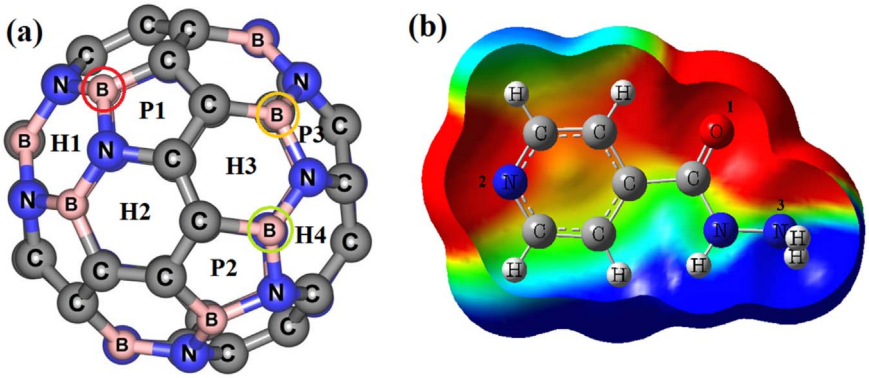

Fig. 1. (a) The optimized structure of $C_{30}B_{15}N_{15}$ heterofullerene consists of four types of hexagonal (H1-H4) and three types of pentagonal (P1-P3) rings. Different types of boron atoms (A, B and C) are marked by red, green and orange circles. (b) The optimized structure of the isoniazid molecule and its MEP plot. Different active sites are determined by 1, 2 and 3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).