Theoretical investigation of thioguanine isomers anticancer drug adsorption treatment on $B_{12}N_{12}$ nanocage

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Keywords: $B_{12}N_{12}$ nanocage, thioguanine isomers, solvent effect, drug delivery properties, density functional theory

Supplementary material for this article is available online

Abstract

Density functional theory (DFT) method used to investigate the interaction of thioguanine isomers with $B_{12}N_{12}$ nanocage in several media to earn electronics properties. To achieve this purpose, adsorption of thioguanine isomers on the exterior surface of $B_{12}N_{12}$ investigated in the gas phase and water media. Optical structures, electronic properties, and natural bond orbitals (NBO) analysis display that the adsorption of thioguanine on $B_{12}N_{12}$ nanocage is a strong chemisorption in the gas phase as well as water media. Besides, the electronic conductance of nanocage is significantly altered once the thioguanine isomers molecules are adsorbed. Thus, the energy gap between HOMO and LUMO orbitals is reduced which could be applied as a chemical signal to confirm chemical adsorption. Moreover, the relative dipole moments calculated for obtained configurations suggest that these structures could be solubilized or dispersed in polar mediums like water. Based on results, $B_{12}N_{12}$ nanocage could be a potential carrier for delivering thioguanine isomers in nanomedicine applications.

1. Introduction

Recently with the development of nanoscience, variety of BN nanostructured materials such as nanosheet, nanotubes, nanocones, nanoparticles and nanocage clusters have been applied in different fields. Fullerene and its compounds are interesting chemical sensors since they show high sensitivity towards gaseous molecules [1–7]. Strong affinity of gas molecules for nanostructure surfaces causes the entrapment of some of these gas molecules onto the surface. The boron nitride cages and nanotubes have been extensively studied as isoelectronic counterparts to carbon cages due to high temperature stability, low dielectric constant, large thermal conductivity, wide-band gap, and oxidation resistance [8–11].

Due to the polar nature of boron−nitrogen (BN) bond, BN nanostructure is expected to have high reactivity compared to their carbon analogs. In addition, because of huge charge separation between boron an nitrogen these atoms can act as Lewis acid and base, respectively and BN nanostructures can be seen as a nano-metal catalyst Lewis acid−base pairs. Studies showed that $B_{12}N_{12}$ is the most stable structures [12] compared to other isomers of fullerene like-materials such as $B_{24}N_{24}$ [13], $B_{28}N_{28}$ [14] and $B_{32}N_{32}$ [15]. Oku et al synthesized $B_{12}N_{12}$ nanocage, detected by laser desorption time of the flight mass spectrometry [16]. The synthesized cage had $T_h$ symmetry point group and consisted of 8 hexagon (6-MR) and 6 tetragon (4-MR) B−N rings, with two distinct bonds between B and N atoms.

Cancer is caused by mutations in the cells of the body. Mutant cells multiply at a faster rate than healthy cells, releasing nutrients and oxygen to these cells. Currently, cancer treatment includes invasive techniques such as using cutter to perform chemotherapy, primary chemotherapy to shrink existing cancerous masses, surgery to remove the tumor if possible, and radiation therapy. The goal of chemotherapy and radiation is to kill cancer
cells, which are more sensitive to chemotherapy drugs and radiation because of their much faster growth and division than healthy cells. Existing chemotherapy research seeks to provide pharmaceutical carriers with different drug entry routes, find new therapeutic targets, such as blood vessels that supply tumor tissue, and develop targeted and specific drug forms. The efficacy of a therapy depends directly on its ability to kill cancer cells so that healthy cells are not affected [17]. Targeted drug delivery includes active and passive prototyping. In active targeting, the therapeutic agent or carrier binds to a specific tissue or cell, but inactivated targeting, the drug agent and the carrier inactivates the target cell and tissue. Nanoparticles can be designed to easily cross biological barriers that traditional drugs cannot [18]. Several quantum mechanical studies were reported on adsorption of different molecules including 5-fluorouracil [19, 20], aspirin [21], Sarin [22], mercaptopurine [23] on BN nanostructures.

Thioguanine, also known as thioguanine or 6-thioguanine (6-TG) is an antineoplastic anti-metabolite used in the treatment of several forms of leukemia including acute nonlymphocytic leukemia. Anti-metabolites masquerade as purine or pyrimidine—which become the building blocks of DNA. They prevent these substances becoming incorporated in to DNA during the ‘S’ phase (of the cell cycle), stopping normal development and division. 6-thioguanine is a thio analogue and actually there is a natural purine basic guanine has been proven [24]. Thioguanine substance is toxic for white blood cells like other thiopurines. Although it is incorporated into human bone marrow cells, but as with other thiopurines, crossing the blood-brain barrier for this substance is not known.

Thioguanine was first synthesized and entered into clinical trial more than 30 years ago. It is a 6-thiopurine analogue of the naturally occurring purine bases hypoxanthine and guanine [25]. The advantage of the present work is introducing a pristine nanostructure to detect two isomers of thioguanine molecule, avoiding the necessity of doping, functionalizing, and in general manipulating of its structure.

2. Computational details

The geometric structure of examined systems is completely optimized by theoretical methods. The optimization of structures in this study has been carried out using density functional theory (DFT). Although the B3LYP is a common method of studying nanostructures [26–28] it’s not a successful method for non-covalent calculations, so it’s necessary to use other methods. The function of the M06-2X can be a non-local function with a twofold amount of (2 ×) non-local exchange for the understanding of the scattering forces [29]. This function is used in the study of numerous nano-sized molecular structures as an acceptable method, due to its higher percentage of Hartree–Fock exchange (34%) [30, 31]. Therefore, desired geometric structures are totally optimized with exchange-correlation functional M06-2X with basis set 6–31 G (d,p). The harmonic vibration frequencies also calculated to indicate that the obtained structures are in the minimum level of energy. The frequency calculation result shows that all structures have a real frequency. The analysis of natural bond orbitals (NBO) [32] is done at the same computational level too. All the calculations are done using Gaussian09 software [33].

In this research, quantum molecular descriptors [34] including energy gap (E_g) and Fermi level (E_f) are also calculated. Energy gap (E_g) is the difference between energy levels of HOMO (the highest occupied molecular orbital) and LUMO (the lowest unoccupied molecular orbital).

Following the common convention, E_f stands approximately in the middle of the energy gap at 0 K. Also, the total density of states (TDOS) on nanostructure and the composed complexes for desired systems are computed at the same computational level through GaussSum software [38].

Time-dependent density functional theory (TD-DFT) calculations are also done to gaining excited states and UV-vis spectrum at the same computational level [36].

According to the equation below, E_{ads} and BSSE has been calculated for the above configurations in the gas phase.

\[
E_{\text{ads}} = E_{\text{complex}} - E_{\text{Thioguanine isomer}} - E_{\text{nanocage}} + E_{\text{BSSE}}
\]  

(1)

Wherein \(E_{\text{complex}}, E_{\text{Thioguanine isomer}}, \) and \(E_{\text{nanocage}}\) are the final energy of composed complex between thioguanine isomers (Isomer I and II) and nanocage, separate energy of thioguanine isomer and cage in the gas phase, respectively. The basis set superposition error (BSSE) [37] is evaluated to remove the overlay effect of the basis function, using the Counterpoise keyword.

Thermodynamic properties such as Gibbs free energy (\(\Delta G_{\text{ads}}\)) and enthalpy (\(\Delta H_{\text{ads}}\)), have been investigated in accordance with the following equations, for thioguanine isomers adsorption on the external surface of \(B_{12}N_{12}\) at a temperature of 298.14 K and atmospheric pressure:

\[
\Delta H_{\text{ads}} = H_{\text{complex}} - H_{\text{Thioguanine isomer}} - H_{\text{nanocage}}
\]  

(2)
Where H and S are enthalpy and entropy, respectively.

\[
\Delta G_{ads} = \Delta H_{ads} - T \Delta S_{ads} = \Delta H_{ads} - T(S_{complex} - S_{thioguanine isomer} - S_{nanocage})
\]  

(3)
To investigate the effect of water solvent on desired systems, geometrical structures of B$_{12}$N$_{12}$ nanocage, thioguanine isomers, and configurations obtained in the gas phase with the same method completely optimized. All calculations have been done in water media of 78.3553 dielectric constant, using the self-consistent reaction field (SCRF) polarized continuous model (PCM). Based on the equation below, $E_{\text{ads}}$ amounts for obtained configurations are calculated.

$$E_{\text{ads}} = E_{\text{complex}} - E_{\text{thioguanine isomer}} - E_{\text{nanocage}}$$

Where $E_{\text{complex}}$, $E_{\text{thioguanine isomer}}$, and $E_{\text{nanocage}}$ are the final energy of composed complex between thioguanine isomers and nanocage, separate energy of thioguanine and cage in the water media.

3. Results and discussion

3.1. Structural and geometrical optimization of B$_{12}$N$_{12}$ nanocage in the gas phase and water media

In this study, the optimization of structures has been accomplished using the DFT method with exchange-correlation functional M06-2X/6-31 G (d,p). Firstly, the B$_{12}$N$_{12}$ nanocage structure in the gas phase was optimized.
investigated. This nanocage has consisted of 8 hexagonal and 6 tetragonal rings with $T_h$ symmetry. In $B_{12}N_{12}$ nanocage structure two types of nonequivalent $B$–$N$ bonds are visible, one between two six-membered rings with 1.438 Å bond lengths and another between a six-membered ring and a four-membered ring with 1.483 Å bond lengths (figure 1(a)). NBO analyze illustrates that natural charge on nitrogen in the nanocage is equal to $-1.189 |e|$ which expresses the electronegative difference between boron and nitrogen atom. The result emphasizes that the $B$–$N$ bond is slightly ionic. The electron properties of this nanocage are also investigated. The energy of boundary molecular orbitals and energy gap have been calculated in the same computational level, listed in table 1. The calculated energy gap of $B_{12}N_{12}$ is about 9.56 eV. The total density of states spectrum (TDOS) and distribution display of HOMO and LUMO orbitals for this structure is shown in figure 1(b). As shown above, HOMO orbital is concentrated on N atoms, while LUMO orbital is placed on B atoms. The optimized structures of thioguanine isomers have been also displayed in figures 2(a) and (c). The total energy of isomer I and II is equal to $-865.302$ and $-865.310$ Hartree, respectively. It seems that the isomer II is more stable.

Moreover, geometrical structures of $B_{12}N_{12}$ nanocage and thioguanine isomers with the same method in water media with the dielectric constant of 78.3553 are optimized using a polarizable continuum model (PCM). At first, the $B_{12}N_{12}$ nanocage structure was investigated (figure 3(a)). According to mentioned figure, there is no noticeable change between nanocage structure in the gas phase and water media. NBO analysis reveals that the natural charge of the nitrogen atom in the water media is equal to $-1.194 |e|$. It indicates electronegativity
difference between a boron atom and nitrogen atom in water media has increased in comparison to the gas phase. Boundary molecular orbitals energy and energy gap are investigated at the same computational level and the results are listed in table 1. The obtained value of the energy gap is about 9.61 eV. The total density of states (TDOS), distribution display of HOMO and LUMO orbitals for this structure in figure 2 confirming that small effects also derived from the presence of the water media. In addition, the optimized structures of thioguanine isomers are shown in figures 2(b) and (c). The structures in water media have no remarkable difference with the gas phase.

3.2. Thioguanine isomers adsorption on B\textsubscript{12}N\textsubscript{12} nanocage in the gas phase

To find the most stable configurations of adsorbed thioguanine isomers (I and II) on the external surface of B\textsubscript{12}N\textsubscript{12} nanocage, different situations were investigated in the gas phase. Molecular electrostatic potential (ESP)
distribution of thioguanine isomers can be seen in figures 2(b) and (d) respectively. According to these figures, electron density (the red color on figure) is placed on the top of S and some N atoms of thioguanine isomers. Therefore, both structures can approach to the nanocage using these atoms. Eventually, ten configurations of isomer I and eight configurations of isomer II were observed (figures 4, S1 and S2 is available online at stacks.iop.org/MRX/6/1250g2/mmedia). The most favorable structures are displayed in figure 4 which three of them belong to isomer I: (A), (B) and (C). In structure A, nitrogen atom of 5-membered ring of thioguanine has been established on a bond with boron atom of nanocage. Also, hydrogen atom connected to nitrogen in the para position beside sulfur has interacted with nitrogen atom of nanocage. According to figure 4(a) desired nitrogen and boron atoms are in bond between a 6-membered and a 4-membered rings of nanocage and have composed a
new 6-membered ring with thioguanine molecule. Structure B is almost similar to structure A. Thioguanine has interacted with boron and nitrogen atoms placed on the bond between two 6-membered rings of nanocage (see figure 4(c)). In structure C, nitrogen atom stood on 5-membered ring of thioguanine molecule (see figure 4(e)). In structure A of isomer II, nitrogen atom in the para position beside sulfur has established a bond with boron atom of nanocage. In addition hydrogen atom connected to nitrogen in 5-membered ring of thioguanine molecule has interacted with the nitrogen atom of nanocage. It should be noted that desired nitrogen and boron atoms are in bond between a 6-membered and a 4-membered rings of nanocage and have formed a new 6-membered ring with thioguanine (see figure 4(g)). In structure B, nitrogen atom placed on 5-membered ring of thioguanine molecule has founded a bond with boron atom of nanocage. Also, hydrogen atom connected to carbon atom in 5-membered ring of thioguanine has interacted with the nitrogen atom of nanocage. These

Figure 4. (Continued.)
desired atoms are in bond between a 6- and 4-membered ring and have created a new 5-membered ring with thioguanine molecule, whereas S-H function is placed on top of 6-membered ring of thioguanine (see figure 4(i)). Although structure C is almost similar to structure B, but S-H function has interaction with nitrogen atom of nanocage situated in bond between 6- and 4-membered rings of thioguanine (see figure 4(k)). $E_{\text{ads}}$ values are calculated for these configurations and have been reported in tables 2 and S2. Negative adsorption energy indicates that the composed complexes are stable. Adsorption energy ($E_{\text{ads}}$) values for mentioned configurations in the gas phase, are in a range of $-18.55$ to $-146.75 \text{kJ.mol}^{-1}$ and $-30.27$ to $-150.76 \text{kJ.mol}^{-1}$ for isomers I and II respectively (tables 2 and S2). The results of these tables demonstrated that the composed configurations have a negative value of adsorption energy and as a result, those structures are stable especially for isomer II. Besides, interaction between both isomers of thioguanine and B$_{12}$N$_{12}$ nanocage is strong. $E_{\text{ads}}$ of A, B and C configurations in both of them implied strong chemisorption on the exterior surface of B$_{12}$N$_{12}$ nanocage.

In isomer I, B–N distance of configuration A, is calculated about 1.591 Å whereas in B and C are about 1.595 and 1.586 Å, respectively (figure 4). N ··· H interaction distance in A and B configurations are also obtained 2.121 and 2.086 Å. While in configuration of isomer II, B–N distance is calculated about 1.599 Å whereas in B and C are almost obtained 1.610 and 1.618 Å, respectively. As reported in table 2, charge transfers from molecule to nanocage are observed after thioguanine adsorption on the external surface of nanocage. Based on this table, the charge transfer value of A and B configurations is equal to 350 [me], while transferred charge from thioguanine to nanocage is about 364 [me] in the C configuration in isomer I. Also, in isomer II charge transfer value of A, B and C configurations is equal to 365, 364 and 344 [me], respectively. These facts are confirmed strong electrostatic interaction between thioguanine and nanocage. In addition, adsorption of thioguanine on the external surface of nanocage is indicated strong chemisorption. It can be said, thioguanine acts as Lewis acid while nanocage acts as Lewis base. Also, obtained dipole moment values of nanocage and configurations are registered in the upper table. Whereas this nanocage is completely symmetric (Th$_{5}$ symmetry), the dipole moment of nanocage value is zero before thioguanine adsorption. But according to table 2, dipole moment of three configurations in isomer I are obtained in range of 2.07–2.12 Debye whereas, in another isomer these results are between 4.52 to 10.33 Debye. Consequently, these configurations are able to be solubilized in polar media, like water. Therefore, mentioned configurations can be a promising candidate for drug delivering.

On the other configurations (isomers I, D–J structures in figure S1 and also isomer II, D–H structures in figure S2) interaction distances were calculated. These values were in a range of 1.651 to 3.251 Å for isomer I, and 1.627–2.763 Å for isomer II. Besides, the transferred charge from thioguanine isomers to nanocage in these configurations were obtained in the range of 328 to 654 [me] for isomer I and in the range of 56 to 418 [me] for isomer II respectively (table S2). But about the configuration J in isomer I, 7 [me] electrical charge from the nanocage is transmitted to thioguanine molecule. As can be seen from the results of the mentioned table, the adsorption energy value is also very small ($-18.55 \text{kJ.mol}^{-1}$) which is confirmed as a weakly physisorption in this configuration. Also, dipole moments of the above structures have been reported in the range of 5.36 to 13.34 Debye for isomer I and also in the range of 5.10 to 14.51 Debye for isomer II respectively (see table S2).

Therefore, it can be concluded that these obtained configurations could be solubilized in polar media, like water.

To check the effect of thioguanine isomers adsorption on the electronic properties of nanocage, some parameters such as energy gap ($E_{\text{g}}$) and Fermi energy ($E_{\text{F}}$) for thioguanine isomers/nanocage systems in the gas phase were calculated. The results have been collected in tables 1 and S1 that demonstrating remarkable changes.

As can be seen, energy gap of A, B and C configurations of isomer I is 6.14 eV while for the other configurations is

| Isomer | Configuration | Dipole moment | $Q_{\text{m}}$ (me) | $E_{\text{ads}}$ (kJ/mo) | $\Delta H_{\text{ads}}$ (kJ/mo) | $\Delta G_{\text{ads}}$ (kJ/mo) |
|---------|---------------|---------------|-------------------|-----------------|--------------------------|------------------|
| Gas Phase | B$_{12}$N$_{12}$ | I | A | 2.07 | 350 | -146.75 | -155.79 | -106.58 |
| | | | B | 2.12 | 350 | -145.08 | -154.20 | -106.48 |
| | | | C | 2.10 | 364 | -135.90 | -145.37 | -100.72 |
| | II | A | 4.52 | 365 | -150.76 | -162.88 | -115.09 |
| | | | B | 10.33 | 364 | -129.35 | -139.03 | -87.06 |
| | | | C | 9.93 | 344 | -123.34 | -133.18 | -80.83 |
| Water Media | B$_{12}$N$_{12}$ | I | A | 2.76 | 369 | -159.84 | — | — |
| | | | B | 2.45 | 368 | -159.60 | — | — |
| | II | A | 5.94 | 382 | -162.57 | — | — |
| | | | B | 13.58 | 388 | -158.18 | — | — |
| | | | C | 13.31 | 377 | -151.31 | — | — |
in the range of 6.14 to 6.28 eV. On the other hand, energy gap of A, B and C configurations of isomer II is 6.97, 6.95 and 6.94 eV, respectively. And also, for others configurations in this isomer E_g value is in the range of 6.64 to 7.08 eV. The remarkable reduction of energy gap (ΔE_g) during the adsorption process is due to the strong adsorption of thioguanine isomers on the external surface of B_{12}N_{12} nanocage. TDOS spectrum and graphical presentation of HOMO and LUMO orbitals in the A, B, and C configurations from both isomers are shown in figure 4. The interaction of thioguanine and nanocage leading to the formation of a new HOMO level with higher energy and a new LUMO level with lower energy. These energy levels have caused a deduction of the

Figure 5. (a), (c), (e), (g) and (i) Optimized structures and (b), (d), (f), (h) and (j) total density of states (TDOS) of the B_{12}N_{12}/thioguanine isomers configurations in water media. (Bonds are in Å).
energy gap. So that the $E_g$ value of these configurations is remarkably reduced by 35.70% in isomer I and about 27% in isomer II. Therefore, the conductivity of these systems is significantly changed. Based on these results, we expected that these configurations can be a suitable candidate to act as a sensor for the thioguanine molecule.

In the next step, thermodynamic properties such as Gibbs free energy changes ($\Delta G_{ads}$) and enthalpy changes ($\Delta H_{ads}$) of configurations are obtained from frequency calculation and equations (2) and (3). The achieved results reported in tables 2 and S2. In table 2, values of $\Delta H_{ads}$ for A, B, and C configurations in isomer I are equal to $-155.79$, $-154.20$, and $-145.37$ kJ.mol$^{-1}$, respectively. On the other hand, enthalpy changes for A, B, and C configurations of isomer II are obtained $-162.88$, $-139.03$ and $-133.18$ kJ.mol$^{-1}$, respectively. In addition, $\Delta G_{ads}$ amounts for mentioned configurations are calculated $-106.58$, $-106.48$, and $-100.72$ kJ.mol$^{-1}$, respectively for isomer I and $-115.09$, $-87.06$ and $-80.83$ kJ.mol$^{-1}$ for isomer II. These results confirmed that the strong chemisorption of
thioguanine on the exterior surface of B$_{12}$N$_{12}$ nanocage in the gas phase. Also, obtained results in table S2 were shown strong chemisorption for other configurations. But for J structure in isomer I ($\Delta G_{\text{ads}} = 14.54 \text{ kJ.mol}^{-1}$ and $\Delta H_{\text{ads}} = -16.20 \text{ kJ.mol}^{-1}$) and also G and H structures in isomer II ($\Delta G_{\text{ads}} = 10.01$ and $11.76 \text{ kJ.mol}^{-1}$ and $\Delta H_{\text{ads}} = -34.29$ and $-37.06 \text{ kJ.mol}^{-1}$, respectively), were demonstrated a weakly physisorption.

3.3. Adsorbed thioguanine on B$_{12}$N$_{12}$ nanocage in a water media

To find the most stable configurations of absorbed thioguanine isomers on the external surface of B$_{12}$N$_{12}$ nanocage in water media, different positions obtained in the gas phase, are optimized again through MO6-2X/6-31 G(d,p) in this phase with 78.3553 dielectric constant. Finally, nine stable configurations for isomer I and seven stable configurations for isomer II were observed (figures 5, S3 and S4). The most favorable structures are shown in figure 5 which contains two structures for isomer I: A and B configurations that are similar to B and A configurations in the gas phase, respectively, and also three structures for isomer II: A, B and C configurations that are similar to A, B and C configurations in the gas phase, respectively.

$E_{\text{ads}}$ values for obtained configurations were calculated according to equation (4) and reported in tables 2 and S4. The value of adsorption energy ($E_{\text{ads}}$) for above configurations in the water media is in the range of $-17.33$ to $-159.84 \text{ kJ.mole}^{-1}$ for isomer I and $-42.95$ to $-162.57 \text{ kJ.mole}^{-1}$ for isomer II (see tables 2 and S4). Results demonstrated that the composed configurations have a negative value of adsorption energy therefore, they are stable and interaction between thioguanine isomers and B$_{12}$N$_{12}$ nanocage is strong especially for isomer II. Among them, $E_{\text{ads}}$ of five configurations that mentioned is implied to strong chemisorption.

From isomer I of thioguanine, in configuration A, B–N bond distance is about 1.584 Å whereas it’s 1.583 Å in B configuration (figures 5(a) and (c)). From isomer II, in configuration A, B–N distance is about 1.590 Å, but they’re 1.590 and 1.597 Å in B and C configurations, respectively. The shorter B–N bond in the above-obtained configurations in a water media related to obtained configurations in the gas phase is also evidence of stronger adsorption on the external surface of nanocage. As can be seen in table 2, there is also charge transfer from molecule to nanocage after thioguanine isomers adsorption on the external surface of nanocage. According to this table, a charge transfer of 369 and 368 $|\text{me}|$ can be seen in A and B configurations from isomer I, while transferred charge from isomer II of thioguanine to nanocage in the A, B, and C configurations is about 382, 388 and 377 $|\text{me}|$, respectively. These results indicated that there is a strong electrostatic interaction between thioguanine isomers and nanocage in these configurations. Also, adsorption of thioguanine on B$_{12}$N$_{12}$ nanocage is chemisorption. In addition, the values of dipole moments as an important factor for are registered, due to nanocage introduces as a nanocarrier. The dipole moment value of nanocage with $T_h$ symmetry before thioguanine adsorption is equal to zero. But the results in table 2 displayed that, calculated dipole moment for two configurations of isomer I are equal to 2.76 and 2.45 Debye, whereas for three configurations of isomer II are

![Figure 5.](image)
In other configurations (C–I structures of isomer I in figure S3 and D–G structures of isomer II in figure S4) interaction distance is in 1.633–3.215 Å and 1.626–2.550 Å range for isomer I and II, respectively. In these configurations, the transferred charge from thioguanine to nanocage is in the range of 375–700 and 58–495 |me| for both isomers, respectively (table S4). The obtained results illustrated that the interaction between nanocage and molecule is chemical adsorption. On the other hand, in the configuration I of isomer I, 7 |me| amount of electrical charge transfers from nanocage to thioguanine. As can be seen in the above table, in this configuration adsorption energy value is very small (−17.33 kJ.mole$^{-1}$) which is implied to weakly physisorption between nanocage and thioguanine in water media.

In this section, we studied the effect of thioguanine adsorption on the electronic properties of B$_{12}$N$_{12}$ nanocage in the water media (see tables 1 and S3). Looking at the results of these tables, we can see that energy gap of A and B configurations are equal to 6.41 eV, and in range of 6.18–6.66 eV for other configurations of isomer I. Whereas this energy is obtained 6.93 eV for A configuration and 6.94 eV for B and C configurations in isomer II, and also in the range of 6.65–7.05 eV for others. A significant reduction of energy gap ($\Delta E_g$) implied to the strong adsorption of thioguanine isomers on the external surface of B$_{12}$N$_{12}$ nanocage. The total density of states (TDOS) and graphical presentation of HOMO and LUMO orbitals in five mentioned configurations are shown in figure 5. According to this figure, the interaction of thioguanine and B$_{12}$N$_{12}$ nanocage results in decreasing between the valance and

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**Table 3.** Selected excitation energies ($\Delta E$), Wavelength ($\lambda$), Oscillator strength ($f_0$), and relative orbital contributions calculated of B$_{12}$N$_{12}$ and configurations (both isomers) in the gas phase and water media.

| Isomer | Configuration | Excited state | $\Delta E$ (eV) | $\lambda$ (nm) | $f_0$ | Assignment |
|--------|---------------|---------------|-----------------|----------------|------|------------|
| Gas Phase B$_{12}$N$_{12}$ | I | A | 11 | 7.1275 | 173.95 | 0.0585 | HOMO−1 $\rightarrow$ LUMO |
| | | | (16) | (7.5667) | (163.86) | (0.0435) | (HOMO−1 $\rightarrow$ LUMO) |
| | | | (40) | (8.2676) | (149.96) | (0.0313) | (HOMO−1 $\rightarrow$ LUMO) |
| | | | (4) | (5.1960) | (238.62) | (0.1282) | (HOMO−5 $\rightarrow$ LUMO) |
| | | | (6) | (5.5442) | (223.63) | (0.0975) | (HOMO−1 $\rightarrow$ LUMO + 2) |
| | | B | 2 | 4.2794 | 289.72 | 0.4844 | HOMO−1 $\rightarrow$ LUMO |
| | | | (32) | (7.2063) | (172.05) | (0.1526) | (HOMO−5 $\rightarrow$ LUMO + 2) |
| | | | (4) | (5.1993) | (238.46) | (0.1258) | (HOMO−1 $\rightarrow$ LUMO) |
| | | C | 2 | 4.2984 | 288.44 | 0.4900 | HOMO−1 $\rightarrow$ LUMO |
| | | | (25) | (7.0007) | (177.10) | (0.1311) | (HOMO−5 $\rightarrow$ LUMO + 2) |
| Water Media B$_{12}$N$_{12}$ | II | A | 11 | 6.4232 | 191.43 | 0.3525 | HOMO $\rightarrow$ LUMO + 1 |
| | | | (3) | (5.4288) | (228.38) | (0.2931) | (HOMO−4 $\rightarrow$ LUMO) |
| | | | (1) | (4.6649) | (265.78) | (0.2301) | (HOMO $\rightarrow$ LUMO) |
| | | B | 6 | 5.9600 | 208.03 | 0.3038 | HOMO $\rightarrow$ LUMO + 1 |
| | | | (16) | (6.6883) | (185.38) | (0.2796) | (HOMO−9 $\rightarrow$ LUMO) |
| | | | (1) | (4.6732) | (265.31) | (0.1619) | (HOMO $\rightarrow$ LUMO) |
| | | C | 16 | 6.6870 | 185.41 | 0.2957 | HOMO−13 $\rightarrow$ LUMO |
| | | | (6) | (5.9372) | (208.83) | (0.2983) | (HOMO−1 $\rightarrow$ LUMO + 1) |
| | | | (1) | (4.6541) | (266.40) | (0.1636) | (HOMO $\rightarrow$ LUMO) |
| | I | A | 2 | 4.0011 | 309.87 | 0.7072 | HOMO−1 $\rightarrow$ LUMO |
| | | | (18) | (6.7514) | (183.64) | (0.4109) | (HOMO−2 $\rightarrow$ LUMO + 3) |
| | | | (3) | (4.8880) | (253.65) | (0.3571) | (HOMO−2 $\rightarrow$ LUMO) |
| | | B | 2 | 4.0003 | 309.94 | 0.7051 | HOMO−1 $\rightarrow$ LUMO |
| | | | (18) | (6.7489) | (183.71) | (0.5051) | (HOMO−2 $\rightarrow$ LUMO + 3) |
| | | | (3) | (4.8917) | (253.46) | (0.3580) | (HOMO−2 $\rightarrow$ LUMO) |
| | II | A | 8 | 6.2918 | 197.06 | 0.4463 | HOMO−7 $\rightarrow$ LUMO |
| | | | (1) | (4.4491) | (278.67) | (0.4395) | (HOMO−1 $\rightarrow$ LUMO) |
| | | | (3) | (5.3035) | (233.78) | (0.3165) | (HOMO−3 $\rightarrow$ LUMO) |
| | | B | 4 | 5.8392 | 212.33 | 0.6227 | HOMO−1 $\rightarrow$ LUMO + 3 |
| | | | (12) | (6.5792) | (188.45) | (0.5122) | (HOMO−12 $\rightarrow$ LUMO) |
| | | | (1) | (4.4676) | (277.52) | (0.3215) | (HOMO $\rightarrow$ LUMO) |
| | C | 4 | 5.8474 | 212.03 | 0.5746 | HOMO−1 $\rightarrow$ LUMO + 3 |
| | | | (11) | (6.5617) | (186.95) | (0.5335) | (HOMO−12 $\rightarrow$ LUMO) |
| | | | (1) | (4.4678) | (277.51) | (0.3228) | (HOMO $\rightarrow$ LUMO) |
conduction levels. TDOS analysis reveals that interaction between thioguanine isomers and nanocage leads to a reduction of band gap up to 33.40% in isomer I and about 27% in isomer II. It is related to nanocage, and as a result conductivity of system changes significantly. So, this nanocage is sensitive enough to thioguanine molecule.

3.4. TD-DFT
To obtain critical transition mode with the largest oscillator strength and excitation energy (ΔE) for nanocage and mentioned configurations TD-DFT calculations have executed. These calculations were done at the same level in the gas phase and water media and results have displayed in table 3. The results of upper calculations in the gas phase and water media.

![UV-Vis spectra](image)

Figure 6. UV-Vis spectra of the B$_{12}$N$_{12}$ and configurations (both isomers) with the largest component coefficient marked (a) in the gas phase and (b) water media.
phase illustrated that the critical excited state contains a lot of components. The most component is consisting of HOMO-1 → LUMO for nanocage with excitation energy of 7.127 eV and also in isomer I and II, for three desired configurations with excitation energy between 4.27–4.30 eV and 5.96–6.69 eV, respectively (see figure S5 and table 3). Smaller energy transfer for critical excited states belong to A, B, and C configurations in both isomers than pristine nanocage result in a noticeable decrease in these configurations energy gap related to nanocage. Calculated linear adsorption spectra (the most important adsorption lines with the highest oscillator strength) for B_{12}N_{12} nanocage and three configurations of A, B, and C of both isomers are drawn in figure 6(a). A significant difference between the UV-vis spectrum of nanocage and these configurations are observed. The most important adsorption peak for B_{12}N_{12} nanocage is observed in 173.95 nm in UV area while this peak for the upper configurations, in isomer I, is between 288.44 to 290.54 nm in UV area which is proportional to HOMO-1 → LUMO transition, and also for isomer II is between 185.41 to 208.03 nm in UV area which is related to HOMO → LUMO + 1 or HOMO-13 → LUMO transition. Also, the results of TD-DFT calculations in water media demonstrate that a critical excited state contains a lot of components. The most important component is the HOMO → LUMO + 1 transition for nanocage with excitation energy of 7.13 eV and also HOMO → LUMO transition for two desired configurations with excitation energy of 4 eV in isomer I while in isomer II, HOMO-7 → LUMO or HOMO → LUMO + 3 observed for three mentioned configurations with excitation energy about 5.83 to 6.30 eV (figure S6 and table 3). The small value of excitation energy for critical excited states of these configurations leads to a significant reduction in the energy gap of these configurations in comparison to nanocage. Calculated linear adsorption spectra (the most adsorption lines with the most oscillator power) for B_{12}N_{12} nanocage and mentioned configurations of both isomers are drawn up in figure 6(b). There is a remarkable difference between the UV-vis spectrum of nanocage and five configurations. The most important adsorption peak for B_{12}N_{12} nanocage is 173.87 nm in UV area whereas A and B configurations of isomer I are in 309.87 and 309.94 nm, respectively, in UV area and also three configurations of isomer II have three peaks equal to 197.06, 212.33, and 212.03 nm, respectively, in UV area. The observed shift of peaks in these configurations related to nanocage has resulted in chemical adsorption of thioguanine isomers on the surface of nanocage.

As a result, based on DFT calculations, we have found that the electronic properties of B_{12}N_{12} nanocage interacting with thioguanine isomers were changed significantly. Our study indicated that the adsorption energy of thioguanine isomers in the exothermic process is negative. Therefore, B_{12}N_{12} nanocage is proposed as a promising candidate for drug delivery.

4. Conclusion

In the present study, the DFT method used to do research the interaction of thioguanine isomers molecules and B_{12}N_{12} nanocage in the gas phase and water media. We found that thioguanine isomers tend to be adsorbed on the exterior surface of B_{12}N_{12} nanocage in both states via chemical adsorption. Our results have been shown that the nitrogen atom situated at the 5-membered ring of thioguanine isomers molecules is more reactive than others into the nanocage. On the other hand, according to our obtained, we predicted that isomer II has a stronger interaction with nanocage. The results illustrated that the electrical conductance of B_{12}N_{12} is affected through interaction between B_{12}N_{12} and thioguanine isomers molecules in both media. The energy gap of desired configurations of both isomers changes by about 27.12%–35.70%. These properties as well as high polarity suggested that B_{12}N_{12} can be a good candidate as a nanovehicle in the nanomedicine domain.

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