DFT Study of Boron-Fullerene Carrier for Delivery of Anticancer Drugs

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Abstract
The structures of boron-doped fullerene B-C₅⁹ (1) as a drug delivery system, two derivatives of cyclophosphamide anticancer prodrug (2 and 3) as well as their covalently bonded structures 4 and 5 were optimized by DFT computations at B3LYP level of theory using 6-31G(d) basis set. Comparing compounds 4 and 5 revealed that the bromo derivative (-22.5569 kcal/mol) was more stable than its chloro analogue (22.0483 kcal/mol). The dipole moments of isolated drugs (~ 5.2, 5.1 D) had almost half values compared with those of their related compounds covalently bonded to the B-C₅⁹ (~ 9.7, 9.8 D) reflecting attachment of drugs on the B-C₅⁹ significantly enhanced the polarity of the whole systems which was a desired property for drug delivery in biological media. The HOMO-LUMO band gaps of pristine B-C₅⁹ (1) and isolated drugs 2, 3 were near 2.3 and 2.7 eV, respectively while those of compounds 4, 5 were smaller (2.1 eV) indicating decrease in electrical conductivities of the isolated drugs/B-C₅⁹ upon interactions.

Keywords: DFT Computation; Cyclophosphamide; Drug Delivery; B-C₅⁹ nanocage; Band Gap.

1. Introduction
Since the discovery of the "buckyball" (fullerene C₆₀) in 1985 as a stable allotrope of carbon with a closed cage structure [1] and then macroscopic scale synthesis of C₆₀ [2], fullerenes have attracted great scientific attention for their possible applications particularly as nanomaterial and biomedical species. It was established that fullerenes and their derivatives have various medical applications and are promising as HIV inhibitor [3], photosensitive oxidizing agents against malignant skin cancer [4,5], Magnetic Resonance Imaging contrast agents [6], gene or drug delivery carriers [7,8] and neuroprotection by antioxidant activity for healing neurodegenerative illnesses [9]. Accordingly, they can be employed as drugs or carriers for different biological molecules. A number of computational approaches have often been performed on the interaction between fullerenes and different species [10-12]. First-principles density functional and quantum Monte Carlo calculations on light-element B and Be doped fullerences exhibited considerably enhanced molecular H₂ binding [13]. Cyclophosphamide (CP, CAS 50-18-0) is a well-known anticancer prodrug which is activated by cytochrome P-450 in the liver [14] and shows therapeutic activity against several human cancers [15-18]. Literature review supports

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that there is not any report about the attachment of cyclophosphamide derivatives on the boron-doped fullerene surface.

The aim of this work is to predict the structural and electronic properties of compounds formed between two chemically attached anticancer prodrug analogues of cyclophosphamide and boron-doped fullerene BC$_{59}$ (as a drug carrier). For this purpose, DFT computations were carried out at B3LYP level on five compounds including isolated drugs and also their compounds with B-C$_{59}$ nanocage.

2. Computational Details

The structures of compounds 1-5 (Fig. 1) were drawn and optimized in Hyperchem 7.0 program. The quantum chemical calculations were performed to fully optimize the geometries of the structures by Gaussian 98 program [19] using density functional theory (DFT) at B3LYP level and standard 6-31G(d) basis set. The optimizations were followed by computations of the harmonic and the vibrational frequencies, so that no imaginary frequencies were obtained at these computations. The natural bond orbital (NBO) calculations were performed to obtain the HOMO-LUMO band gap energies.

3. Results and Discussion

In order to investigate the electronic and structural properties of boron-doped fullerene B-C$_{59}$ (1) and two derivatives of cyclophosphamide prodrug (2 and 3) as well as those of their covalently bonded structures 4 and 5 (Fig. 1), DFT computations were performed at B3LYP level of theory using 6-31G(d) basis set. The stabilization and binding energies for the isolated and covalently bonded drug-B-fullerene compounds were calculated from the equations $E_{\text{stabilization}} = E(\text{molecule}) - E(\text{atom or ion})$ and $E_{\text{binding}} = E(\text{complex}) - [E(\text{drug}) + E(\text{fullerene})]$, respectively. The $E$ values (kcal/mol) for compounds 1-5 are given in Table 1.

![Figure 1](https://example.com/figure1.png)

Figure 1. The molecular structures of compounds 1-5 indicating atom numbering.

It can be seen that between compounds 2 and 3 that only differ in the halogen atoms of C-X bond (X = Cl, Br), compound 2 is more stable having a greater negative $E_{\text{stabilization}}$ (-2688.45 kcal/mol). Comparing compounds 4 and 5 reveals that the bromo derivative (-22.5569 kcal/mol) is more stable than its chloro analogue (-22.0483 kcal/mol). The optimized structures of the compounds 4 and 5 at B3LYP level are presented in Fig. 2 displaying the chemical attachment of the drugs through the phosphoryl oxygen atom onto the boron atom of B-C$_{59}$ nanocage.

The calculated dipole moments (Debye) for compounds 1-5 are provided in Table 1. The data indicate that B-C$_{59}$ has the smallest polarity with $\mu = 0.5724$ D, but compound 5 reveals the greatest (9.8057 D). It is interesting that the dipole moments of isolated drugs (~ 5.2, 5.1 D) have almost half values compared with those of their related compounds covalently bonded to the B-C$_{59}$ (~ 9.7,
This result illustrates that attachment of drugs on the B-C$_{59}$ greatly enhances the polarity of the whole systems which is a desired property for drug delivery in biological media.

Table 1. The binding energies (kcal/mole), dipole moments (Debye) and band gaps ($E_g = E_{HOMO} - E_{LUMO}$, eV) for compounds 1-5.

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Binding energy</th>
<th>Dipole moment</th>
<th>$E_g$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BFull</td>
<td>-9611.96</td>
<td>0.5724</td>
<td>2.273</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>-2688.45</td>
<td>5.2360</td>
<td>2.733</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>-2674.13</td>
<td>5.1332</td>
<td>2.740</td>
</tr>
<tr>
<td>4</td>
<td>BFull-Cl</td>
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<td>9.6787</td>
<td>2.110</td>
</tr>
<tr>
<td>5</td>
<td>BFull-Br</td>
<td>-22.5569</td>
<td>9.8057</td>
<td>2.113</td>
</tr>
</tbody>
</table>

Figure 2. The structures of compounds 4 and 5 optimized at B3LYP/6-31G* level of theory.

The band gaps ($E_g$) of compounds 1-5 which are the differences of energies between the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) and are measures of electron conductivities are presented in Table 1. It is seen that the band gaps of pristine B-C$_{59}$ (1) and isolated drugs 2, 3 are near 2.3 and 2.7 eV, respectively while those of compounds 4, 5 are smaller (2.11 eV) indicating decrease in electrical conductivities of the isolated drugs/B-C$_{59}$ upon interactions. Moreover, the decrease in the band gaps verifies the interactions between the drugs and B-C$_{59}$ nanoparticle.

The P–O1 and P–O2 bond lengths in compounds 2 and 3 are about 1.49, 1.63 Å but in compounds 4 and 5 they are approximately 1.54, 1.60 Å, respectively, which are between the P=O single bond (1.64 Å) and P=O double bond (1.45 Å) lengths [20] confirming a partial multiple bond character for these P–O bonds. The smaller P–O1 bond lengths in comparison with P–O2 bond lengths display a greater bond order for the phosphoryl bond. Moreover, in compounds 4 and 5, the P–O1 bond lengths are almost 1.54 Å that are longer than those of isolated drug molecules which is due to the attachment of drugs onto the fullerene B-C$_{59}$ surface through their O1 atoms leading to the weakening of P–O1 bonds.

In molecules 2 and 3, the P–N1 and P–N2 bond lengths are about 1.69, 1.68 Å while they are near 1.66, 1.65 Å, respectively, that are close to the P–N single bond length (1.77 Å [20]). The very much slightly smaller P–N bond for the exocyclic groups may be attributed to the electron donation of halogen atoms through resonance effect leading to the more interaction of nitrogen lone pair with the phosphorus atom. All of the C–O and C–N bond lengths are approximately 1.44, 1.47 Å, respectively. The C–X bonds are near 1.39, 1.98 Å for X = Cl, Br, respectively, indicating smaller C–X bond for a smaller, more electronegative halogen atom. The distance measured from the phosphoryl oxygen and B atom of B-C$_{59}$ in compounds 4 and 5 are 1.5942, 1.5969 Å, respectively, confirming a strong interaction (chemisorption) occurs between each drug and B-C$_{59}$ in all thermodynamically favourable compounds.

The HOMO and LUMO molecular orbitals of complexes 4 and 5 are shown in Fig. 3. It is clear that the HOMO and LUMO orbitals of both compounds are mainly observed on the boron-fullerene nanocage but there is practically nothing on the cyclophosphamide anticancer prodrug. Interestingly, the HOMO orbitals of both compounds illustrate that the electron density is placed on boron atom but the LUMO orbitals are not located on this atom.
4. Conclusions

In summary, the covalent bonding of anticancer cyclophosphamide derivatives (2 and 3) drugs through the phosphoryl oxygen atom on the B-C$_{59}$ surface was investigated by DFT computations using B3LYP/6-31G(d) approach. The binding energies were calculated from the equation $\Delta E_{\text{binding}} = E(\text{complex}) - \Sigma [E(\text{drug}) + E(\text{B-fullerene})]$. The $\Delta E$ values show that between compounds 2 and 3 that only differ in the halogen atoms of C-X bond (X = Cl, Br), compound 2 is more stable having a greater negative $\Delta E_{\text{stabilization}}$ (2688.45 kcal/mol). Moreover, in compounds 4 and 5, the $\Sigma$ bond (X = Cl, Br) is more stable than its chloro analogue. Moreover, in compounds 4 and 5, the P=O bond lengths are almost 1.54 Å that are longer than those of isolated drug molecules which is due to the attachment of drugs onto the fullerene B-C$_{59}$ surface through their phosphoryl O atoms leading to the weakening of P=O bonds.

References