Original Research Article

Adsorption of melphalan anticancer drug on the surface of boron nitride cage (B₁₂N₁₂): A comprehensive DFT study

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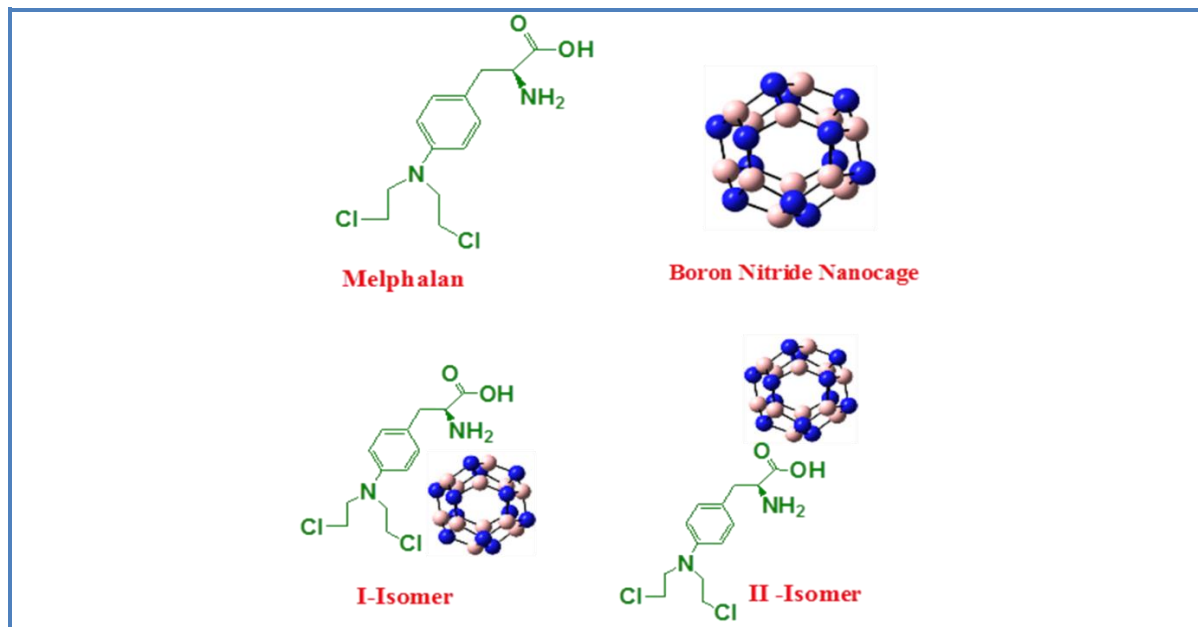
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ABSTRACT

In this study, boron nitride cage ($B_{12}N_{12}$) adsorption with Melphalan anticancer agent in solvent phase (water) was studied using the density function theory (DFT) method. First, the structure of the Melphalan, $B_{12}N_{12}$ and their derivatives were geometrically optimized in two different configurations, with a base set of 6-31G* and hybrid B3LYP functions. Then, IR calculations, frontier molecule orbital (FMO) studies, and molecular orbital analysis were performed. In addition, thermodynamic parameters including, Gibbs free energy (ΔG_{ad}) and enthalpy (ΔH_{ad}) variations indicated that the adsorption of Melphalan with $B_{12}N_{12}$ is intense, spontaneous, one-way and non-equilibrium. The effect of temperature was studied as well. The results proved that at K 305.15 the highest efficiency was achieved.

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Graphical Abstract

Introduction

Since the development of boron nitride (BN) nanotubes [1], various types of BN nanostructured materials have been reported due to their great potential to be used with low dimensions in an isolated environment. Many studies have been reported on BN nanomaterials and single crystals such as nanotubes, bundled tubes, nano corns, nano capsules, nanoparticles, BN cluster, and BN metallofullerenes. These materials are expected to be useful as electronic devices, field-effect transistors, high heat-resistant semiconductors, insulator lubricants, nanowires, magnetic nanoparticles, gas storage materials, and optoelectronic applications including ultraviolet light emitters [2, 3]. Theoretical calculations on BN nanomaterials such as nanotubes, cluster-included nanotubes, BN clusters, BN metallofullerenes, cluster solids, and hydrogen storage have also been carried out for prediction of the properties. By controlling the size, layer numbers, helicity, compositions, and included clusters, these cluster-included BN Nano cage structures with bandgap energy of ~6 eV and no magnetism are expected to show various electronic, optical, and magnetic properties. $B_{12}N_{12}$ exceptionally strong and inert materials [8] are non-toxic as long as their length does not exceed a few microns [9]. These properties make boron nitride an appealing candidate for encapsulation and delivery applications. By locating specific ligands on the surface of the $B_{12}N_{12}$, it can be used to connect to specific cell receptors, and thus target drug delivery to a specific cell. In general, the goal of surface optimization of the $B_{12}N_{12}$ nanoparticle is to increase the likelihood of drug delivery to tumor the cells and reduce the side effects of drugs. The use of chemicals in the treatment of cancer goes back to late World War II, when it was determined that nitrous Mustard and their derivatives have anti-tumor properties. Alkaline agents (pseudo alkaline) are named because they have the ability to pair the alkaline group with a large number of electronegative

groups in the cellular environment and to link them. Alkylating drugs connect a C_nH_{2n+1} alkyl group to DNA [17-18]. Melphalan are one of these drugs. This drug acts by chemical change in the DNA of the cell. Usually, the alkyl group binds two strands of DNA through the guanine nitrogen 7 and prevents DNA from being replicated. Melphalan is an alkylating agent that eliminates the division of tumor cells and is used in certain types of cancer. Melphalan is an anticancer drug preventing the growth of cancer cells in body. Melphalan is used to treat certain types of cancer including multiple myeloma, ovarian cancer, and breast cancer [19-21]. Some characteristics that make $B_{12}N_{12}$ notable are solubilizing properties, high thermal stability, and good solubility in biological fluids [22-25]. Previously, a report by Isaacs showed that alkylating agents can be efficiently solubilized by the supramolecular solubilizing agent, which are very versatile in the binding of several molecules of biomedical relevance. So drug delivery can play a decisive role in promoting the safety of this drug. To estimate the capability of $B_{12}N_{12}$ as a nano drug carrier for the Melphalan, it is very important to evaluate the $B_{12}N_{12}$ of this nanostructure on the chemical properties of the drug in advance. This study, for the first time has examined the effect of $B_{12}N_{12}$ adsorption on the properties of Melphalan in a computational manner. The chemical structure of the Melphalan is depicted in Figure 1.

Figure 1. Chemical structure of Melphalan, Boron Nitride Nano Cage structure, I-Isomer and II-Isomer
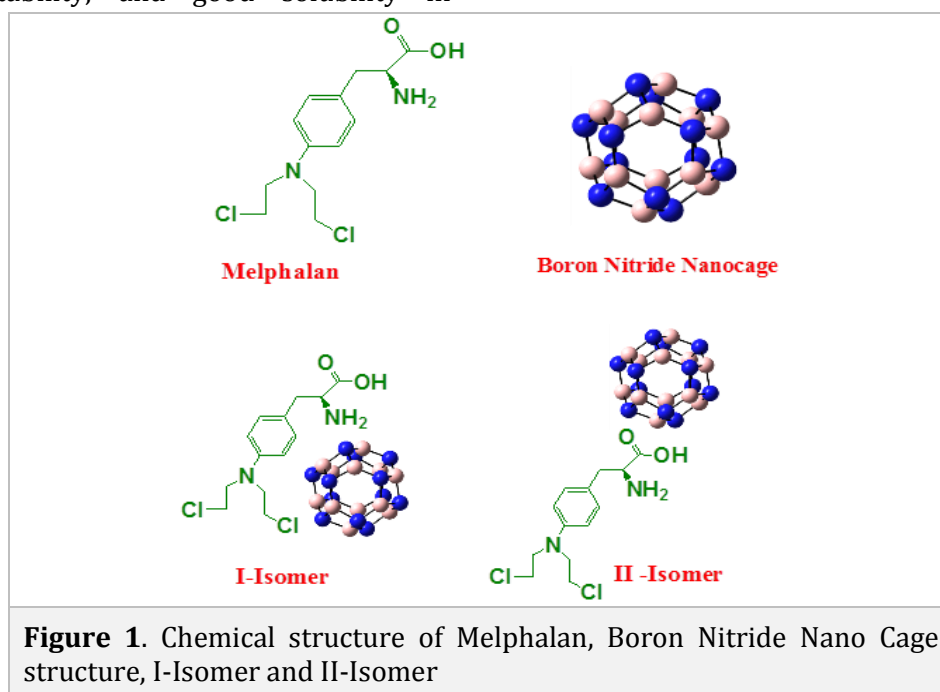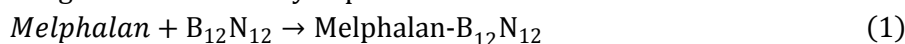
Computational methods

At first, the structures of Melphalan, $B_{12}N_{12}$, and the Melphalan- $B_{12}N_{12}$ complexes were designed by Gauss View 3.1 and nanotube modeller 1.3.0.3 software. Afterward, geometrical optimizations, IR and Frontier molecular orbital computations were performed on them by using the density functional theory method in the B3LYP/6-31G (d) level of theory. This basis set was selected because in former studies, it had produced results which were in an admissible agreement with the experimental data [31-40]. All of the

calculations were done in the temperature range from 278.15 to 305.15 K over the temperature range from 3°-3° by Spartan software, in the aqueous phase. The investigated processes were as follows:

$$Melphalan + B_{12}N_{12} \rightarrow Melphalan\text{-}B_{12}N_{12} \tag{1}$$

Equations 2-4 were used to calculate the adsorption energy values (E_{ad}) and thermodynamic parameters of the evaluated process including enthalpy changes ($\mathbf{\Delta}H_{ad}$), Gibbs free energy variations ($\mathbf{\Delta}G_{ad}$).

$$E_{ad} = \left(E_{(\text{Melphalan-B}_{12}N_{12})} - \left(E_{(Melphalan)} + E_{(B_{12}N_{12})} \right) \right) \tag{2}$$

$$\Delta H_{ad} = \left(H_{(\text{Melphalan-B}_{12}N_{12})} - \left(H_{(Melphalan)} + H_{(B_{12}N_{12})} \right) \right) \tag{3}$$

$$\Delta G_{ad} = \left(G_{(\text{Melphalan-B}_{12}N_{12})} - \left(G_{(Melphalan)} + G_{(B_{12}N_{12})} \right) \right) \tag{4}$$

In the aforementioned equations, E represents the total electronic energy of each structure; H denotes the sum of the thermal enthalpy and total energy of the evaluated materials. The G also stands for the sum of the thermal Gibbs free energy and total energy for each of the studied structures. R and T are also the ideal gas constants and temperature respectively. Frontier molecular orbital parameters such as band gap (HLG), chemical hardness (η), chemical potential (μ), electrophilicity (ω) and the maximum transferred charge (ΔN_{max}) were calculated via Equations 5-9.

$$\text{HLG} = E_{LUMO} - E_{HOMO} \tag{5}$$

$$\eta = \frac{(E_{LUMO} - E_{HOMO})}{2} \tag{6}$$

$$\mu = \frac{(E_{LUMO} + E_{HOMO})}{2} \tag{7}$$

$$\omega = \frac{\mu^2}{2\eta} \tag{8}$$

$$\Delta N_{max} = -\frac{\mu}{\eta} \tag{9}$$

E_{LUMO} and E_{HOMO} in Equations 5 to 7 denote the energy of the lowest unoccupied molecular orbital and the energy of the highest occupied molecular orbital respectively.

Results and discussion

As seen in Figure 1, it approaches $B_{12}N_{12}$ from two situations. To understand more easily, each derivative of the Melphalan derivate with $B_{12}N_{12}$ is named with an abbreviation, which will be explained, the Melphalan is approaching the two positions to the $B_{12}N_{12}$. The links between nitrogen atoms as well as the links between nitro groups and carbon and nitrogen atoms in the structure of Melphalan can play a key role in the effectiveness of synthesized. In other words, as these links are looser and easier to disassociate, Melphalan can react more easily. Thus, after geometric optimization was performed on all compounds, the length of B-NH bonds, in the pure Melphalan, as well as their derivatives with $B_{12}N_{12}$ was measured and the values obtained in Table 1. As the data in Tables 1 indicate, after NH attachment to $B_{12}N_{12}$, the length of the bonds OH and NH-B bonds have increased, meaning that these bonds become looser and these derivatives can more easily enter the process of effectiveness. Density is another parameter that has a direct and special relationship with effective power. As is seen in the data in the tables, the Melphalan density has decreased after the connection to the pure $B_{12}N_{12}$.

Table 1. Adsorption Energy, Minimum Frequency, Density, Weight, and Bond Length of Melphalan and Its Derivatives with $B_{12}N_{12}$

	Melphalan	I-Isomer	II -Isomer
Adsorption energy (KJ/mol)	---	-2545.10	-2544.11
Lowest frequency (cm-1)	15.20	9.2258	3.2618
OH– B_{38} (Å)	-----	1.48248	2.46772
NH– B38 (Å)	-----	1.38542	2.48778
Area (Å²)	305.99	487.94	514.57
Orbital p participation	---------	2.91	2.92
Weight (amu)	307.21	588.006	588.102
Volume (Å³)	281.61	519.71	519.80
Density (amu/Å³)	1.09	1.13	1.14

Thermodynamic parameters of the adsorption process

The adsorption enthalpy changes (ΔH_{ad}) and Gibbs free energy variations (ΔG_{ad}) were calculated using Equations 3 and 4 respectively. In Equation 3, H represents the sum of the thermal enthalpy and total energy and in the equation 4, G stands for the sum of the thermal Gibbs free energy and total. As depicted in Table 2, $B_{12}N_{12}$ reaction is done by exothermic Melphalan, and energy is transferred from the system to the environment, as the values of ΔH_{ad} are obtained for all the derivatives are negative. However, this phenomenon cannot have an effect on the reaction run, because, despite this increase, the enthalpy changes remain negative. Moreover, to examine the effect of temperature on $B_{12}N_{12}$ substituent process, all thermodynamic parameters were calculated at the temperature range from 278.15 K to 305.15 K in the 3°-3° range and the values were reported. As is seen in Table 2, the temperature of the enthalpy changes gradually increases with increasing temperature. Thus, the process of forming the desired compounds becomes warmer with increasing temperature, and the optimum temperature for the surface adsorption of all derivatives is 278 K.

Table 2. Values of changes in adsorption enthalpy for Melphalan adsorption and Gibbs free energy variations (ΔG_{ad}) at the temperature range of 278.15 K to 305.15 K

ΔH_{ad} (KJ/mol)		
Temperature (K)	I-Isomer	II-Isomer
278.15	-2866.3212	-2932.4044
281.15	-2866.4478	-2932.3668
284.15	-2862.3054	-2933.3288
287.15	-2864.1244	-2932.2923
290.15	-2863.1752	-2932.2552
293.15	-2866.7410	-2932.2177
296.15	-2866.2411	-2932.1797
299.15	-2866.2471	-2932.1393
302.15	-2866.2574	-2933.0990
305.15	-2866.1730	-2932.0584
ΔG_{ad} (KJ/mol)		
Temperature (K)	I-Isomer	II-Isomer
278.15	-2599.2802	-2736.2107

281.15	-2596.5494	-2736.0910
284.15	-2596.7981	-2735.9704
287.15	-2597.0477	-2735.8528
290.15	-2597.2951	-2735.7363
293.15	-2597.5444	-2735.6199
296.15	-2597.7935	-2735.5025
299.15	-2598.0395	-2735.3862
302.15	-2598.2850	-2735.2689
305.15	-2598.5303	-2735.1537

Calculation and determining the specific heat capacity (CV)

The specific heat capacity (CV) values were obtained using the Spartan software at the B3LYP/6-31G* level for the Melphalan derivatives with $B_{12}N_{12}$. As seen in Table 4, there was a tangible gap between the specific heat capacity values of Melphalan and the investigated isomers. Moreover, after the adsorption of Melphalan, a significant increase was observed in the CV values of the evaluated isomers. The CV also had a direct correlation with thermal conductivity [25]. The thermal conductance of $B_{12}N_{12}$ and Melphalan improved after the adsorption of Melphalan. A significant variation in the thermal conductivity of the sensing material plays a key role in the sensitivity of the designed analytical method in the development of thermal biosensors. Therefore, it could be concluded that Melphalan derivatives are a promising sensing material for the construction of thermal biosensors for the detection of Melphalan. Considering that the previous findings in this regard have confirmed the interactions of Melphalan and its derivatives are exothermic, the heat production that is required for the appropriate function of these sensors was implemented spontaneously in the adsorption of Melphalan on $B_{12}N_{12}$. The impact of the changes in the temperature on the specific heat capacity was also assessed in this study. According to the findings, the CV value of each isomer increased by incrementing the temperature; therefore, it could be concluded that thermal conductivity ameliorated at higher temperatures, while drug sensitivity decreased with temperature. By increasing the specific heat capacity of Melphalan derivatives, drug sensitivity reduced depending on temperature, not decomposing by heat.

Table 3. Values of changes in specific heat capacity (CV) Adsorption for Melphalan Adsorption at 278. - 305.15 K

CV (J/mol)			
Temperature(K)	Melphalan	I-Isomer	II-Isomer
278.15	314.6873	468.2602	479.7383
281.15	315.3913	469.8021	481.2545
284.15	316.0958	471.3433	482.7704
287.15	316.8008	472.884	484.286
290.15	317.5063	474.4242	485.8011
293.15	318.2123	475.9637	487.3159
296.15	318.9188	477.5025	488.8303
299.15	319.6258	479.0407	490.3443
302.15	320.3332	480.5782	491.8578
305.15	321.0411	482.1151	493.3708

Calculations of molecular orbitals

The most important frontier molecule orbital cell (FMOS), such as the highest occupied molecule orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) have a decisive role in the chemical stability of the molecule [10]. HOMO shows the ability to give electrons and LUMO has the ability to accept electrons. The energy gap between HOMO and LUMO determines the reactivity, polarization, and hardness-softness of a molecule, which is usually represented by the HLG mark and used to calculate it using Equation 5. In this equation, EH and EL are the energy of HOMO and LUMO orbitals. The energy gap is directly related to the molecular electrical conductivity. In fact, compounds that have small energy gaps can easily pass electrons from the barrier to the conductive strip, which means that materials that have fewer energy bands have more electrical conductivity than molecules with higher energy chats. As demonstrated in Table 4, the energy gap after $B_{12}N_{12}$ connection increased significantly. Indeed, the rate of conductivity of Melphalan has significantly improved after $B_{12}N_{12}$ substituent. The next parameter examined is the chemical hardness (η), whose value can be obtained using Equation 6. Chemical hardness is a good measure to estimate the reactivity of a new compound. This is because molecules that are structurally softer and have low chemical hardness can easily change their electron density. Thus, electronic transmissions essential for chemical reactions are better and easier to use in soft compounds. The data in the table shows that the reaction of Melphalan is reduced after the reaction with $B_{12}N_{12}$ since all the derivatives obtained from the carbon nanotubes subtraction reaction have a higher chemical hardness than the pure drug. The chemical potential (μ) used to obtain the rest of the parameters was calculated using Equation (7). Electrophilicity (ω) and the maximum load transmitted to the system (ΔN_{max}) are both suitable quantities, showing the tendency of a compound to absorb electrons. These two parameters were calculated using Equations (8) and (9), respectively. When two molecules react with each another, one acts as an electrophile while another plays the role of a nucleophile and the compound whose electrophilicity and charge capacity are higher will tend to behave as an electron receptor. On the other hand, a molecule with low electrophilicity and capacity tends to accept the electron system. As shown in the table 4, electrophilicity of Melphalan has been greatly reduced after $B_{12}N_{12}$ binding. Hence, one can be concluded that the desire of Melphalan to absorb electrons has decreased.

Table 4. The calculated E_H and E_L, HLG, chemical hardness (η) , electrophilicity index (ω), and the maximum amount of electronic charge index (ΔN_{max}), dipole moment for Melphalan and its complexes boron nitride cage

	E_H(eV)	E_L(eV)	HLG(eV)	η(eV)	μ(eV)	ω (eV)	ΔN_{max}(eV)	Dipole moment (deby)
Melphalan	-6.47	7	13.47	6.735	-0.265	0.0052	0.0393	5.97
Boron nitride cage	-8.290	6.690	14.980	7.490	-0.800	0.043	0.107	0.000
I-Isomer	-6.57	4.27	10.84	5.42	-1.15	0.1220	0.2121	5.27
II-Isomer	-6.79	4.02	10.81	5.405	-1.385	3.15	0.2562	5.40

HOMO and LUMO energy analysis

Molecular orbit analysis also proved that $B_{12}N_{12}$ derivatives have less conductivity, electrophilicity, and reactivity compared with that of the pure Melphalan. The $B_{12}N_{12}$ reaction with Melphalan is empirically possible, so the empirical investigation of the synthesis of these derivatives is highly recommended. With the smallest difference in the strip gap, $B_{12}N_{12}$ can be used as a good sensor for Melphalan.

Electrophilicity (ω) and maximum transferred charge (ΔN_{max}) that were calculated using the Equations 8 and 9 consecutively, revealed the tendency of a molecule towards electron. If a material has a great and positive value of ω and ΔN_{max} it will have a greater tendency to absorb an electron. However, if a molecule has a low amount of these indices, it may act as an electron donor [27]. The obtained results in the table 4 revealed that Melphalan can act as a Lewis acid or an electron acceptor because of their high electrophilicity and maximum transferred charge values. While, boron nitride cage can play the role of an electron donor due to its low electrophilicity it can be elicited that the nanostructure and the explosive can take part in electron transfer reactions. Thus, boron nitride cage is an ideal electroactive sensing material for the fabrication of novel Melphalan sensitive electrochemical sensors [36].

Dipole moment was the last investigated parameter. The dipole moment was found to be the key clue which demonstrated the solubility of the investigated structures. A substance with higher dipole moment will have stronger solubility in the polar solvents such as water. However, a low amount of dipole moment indicated the poor solubility in polar solvents. As shown, the dipole moment of $B_{12}N_{12}$ is zero, so, this nanostructure is insoluble in water. This fact is of great importance as many sensors lose

their sensitivity, stability and selectivity after a short period of time because of the leakage of the recognition element from the membrane to the sample solution. In this regard, sensing materials with lower solubility in polar solvents are more suitable for the construction of new sensors. Fortunately, boron nitride cage meets this requirement. Besides, the dipole moment of Melphalan has enhanced significantly after its interaction with $B_{12}N_{12}$. So, it can be deduced that Melphalan has become less soluble in water after the adsorbing on the surface of the $B_{12}N_{12}$ [43-46].

Conclusion

Molecules with high dipole moments have better solubility in water and the compounds with lower bipolar moments will be weaker in polar solvents. The results revealed that, the dipole moment of Melphalan decreased after the $B_{12}N_{12}$ connection. Therefore, nano cage derivatives with Melphalan have less solubility in water compared with the pure Melphalan. Melphalan determination is of a great importance in medical and nutritional fields. In this regard, the performance of the $B_{12}N_{12}$ as a sensing material in the thermal and electrochemical biosensors was investigated using the density functional theory. The obtained results exhibited that the Melphalan adsorption on the surface of the $B_{12}N_{12}$ is exothermic, spontaneous, non-equilibrium and experimentally feasible. However, the adsorption of Melphalan on the $B_{12}N_{12}$ surface was found to be endothermic, non-spontaneous, equilibrium, and experimentally impossible. The calculated band gap, electrophilicity and specific heat capacity parameters show that $B_{12}N_{12}$ can act as an excellent electroactive and thermal sensing material in the construction of Melphalan potentiometric, conduct metric and thermal sensors. In this regard, the experimental use of this nanostructure in the

detection of Melphalan is recommended to be evaluated.

Conflict of interest

We have no conflicts of interest to disclose.

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