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Theoretical investigation of Melphalan as a Drug Carrier by Carbon Nanotube

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Many studies have been conducted as the scientific community increasingly seeks targeted drug delivery for specific diseases. This type of medication has many side effects for the patient. In order to better understand and optimize the laboratory process for evaluating the efficacy of drug carriers, the application of theoretical and computational methods plays an important role. Nanocarriers improve drug performance and reduce side effects by altering the pharmacokinetic properties of the drug. In this study, the role of a carbon nanotube as a drug carrier for melphalan, a drug used to treat cancer, was investigated using quantum calculations based on density functional theory at the B3LYP level of theory and the 6-311G basis set. To observe the effects of carbon nanotubes on the nature of the drug, the melphalan molecule was bound to the carbon atoms of the wall surface of the carbon nanotube through its most chemically active sites. Density functional theory calculations, were used to examine the adsorption behavior and electronic sensitivity of a carbon nanotube for the drug melphalan. The drug tends to be adsorbed on the nanotube via its O atom with adsorption energies of about -94.84 kJ mol^{-1}.

Keywords: Melphalan, Nanotube, DFT, Chemical activity

INTRODUCTION

The introduction of melphalan (p-(bis(chloro-2-ethyl) amino)-Lphenylalanine) (MEL), known to be alkylating, dates back to the late 1950s, after which it was extensively studied as an antitumor agent. This drug has broad applications in treating multiple myeloma, ovarian and breast cancers, neuroblastoma, malignant melanoma with regional spread, and localized soft tissue carcinoma. Melphalan possesses alkylating properties as it forms carbonium ion intermediates with extreme reactivity that transfer alkyl groups to cellular macromolecules by forming covalent bonds. The poor solubility of melphalan in aqueous media means its practical insolubility in water. In addition, oral administration of melphalan leads to its different bioavailability characteristics. The rapid hydrolysis (degradation) of melphalan at physiological pH leads to more complications, as its short half-life in the bloodstream (90 min) causes it to rapidly disappear from the systemic. Therefore, the therapeutic properties of melphalan should be improved to achieve lower toxicity [1-2]. This agent has the highest chemotherapeutic activity and can be used to treat myeloma. It has been shown that there is a correlation between drug dose and response to disease [3-5]. Accordingly, the incorporation of higher doses of melphalan, as well as autologous stem cell transplantation in consolidation therapy has been considered in a large number of patients over the past 3 decades, resulting in a median overall survival benefit of more than one year [6]. Although it is possible to achieve longer survival with the addition of new immunomodulatory and proteasome inhibitory agents [7], high doses of melphalan along with autologous stem cell transplantation are still considered in qualified patients after induction therapy [8-10]. SWCNTs are capable of delivering bioactive molecules through cell membranes and surprisingly into the cell nuclei because they have a considerably high specific

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surface area [11-12]. As the hydrophobic carbon nanotubes (CNTs) don't show solubility in aqueous culture, modifying CNTs may be effective in overcoming the mentioned restriction. Besides, as evidence shows, CNTs' pristine surface is inert; in other words, making the attachment of biomolecules to the underlying surface more challenging. The present work has examined the interactions of MEL and nanotube using the DFT technique by B3LYP/6-311G level of theory to perform melphalan-targeting drug delivery [13-21].

COMPUTATIONAL METHOD

The study carried out full geometry optimizations of equilibrium geometries, total energies, as well as electronic densities in the framework of DFT at B3LYP/6-311G level of theory. Calculation of the adsorption energies of MEL on nanotube through the site with the highest activity was performed with the use of the relation below:

$$E_{ads} = E_{T(MEL/NT)} - (E_{NT} + E_{MEL}) \quad (1)$$

where $E_{T(MEL/NT)}$ represents the overall energy of the MEL adsorbed on the nanotube, $E_{(NT)}$ is the melphalan energy, and E_{MEL} indicates the overall nanotube energy. Investigation of the DFT-based reactivity descriptors was carried out through Frontier molecular orbital theory. Moreover, the calculation of the energy surface of molecular electrostatic potential (MEP) was performed to describe the distribution of the total molecular charge. Calculation of DFT-based chemical reactivity and stability descriptors, including electronic chemical potential (μ), chemical hardness (η), chemical softness (S), as well as electrophilicity (ω), was performed through Eqs. ((2)-(5)) based on Koopmans theorem:

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{V(r),T} \quad (2)$$

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{V(r),T} \quad (3)$$

$$\omega = \mu^2/2\eta \quad (4)$$

$$S = 1/\eta \quad (5)$$

where μ, η, S, and ω designate chemical potential, chemical hardness, chemical softness, and global electrophilicity index, respectively.

RESULTS AND DISCUSSIONS

The optimal structure of the melphalan molecule can be seen in Fig. 1. The negative charge on each atom indicates chemically active points, the negative charge on the surface indicates the place of connection to the positive points of the nanotube, and the positive points indicate the position of connection to the negative points. In Fig. 2, the conventional charge of the nanotube molecule is also shown, where the surface carbon atoms act as active molecular points.

The electronegativity difference between nitrogen and chlorine atoms in the melphalan molecule with carbon atoms on the nanotube surface is less than the difference between the electronegativity of carbon atoms in melphalan and carbon in the nanotube. This electronegativity difference can create the best position for interaction on the nanotube surface with negative carbon atoms in melphalan. Table 1 shows the length of the bonds related to the drug complex

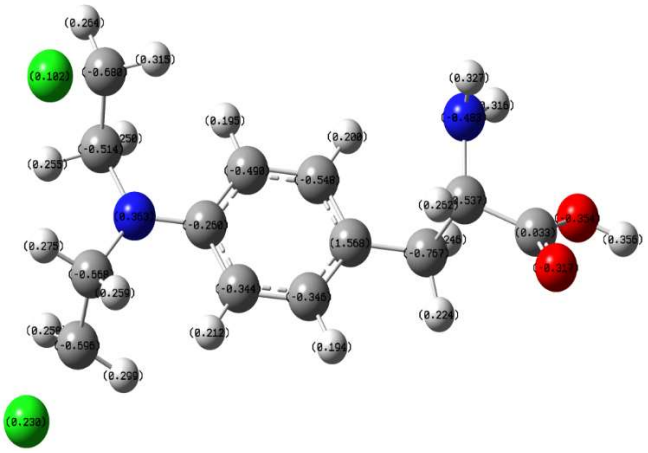

Fig. 1. Melphalan's conventional charge values.

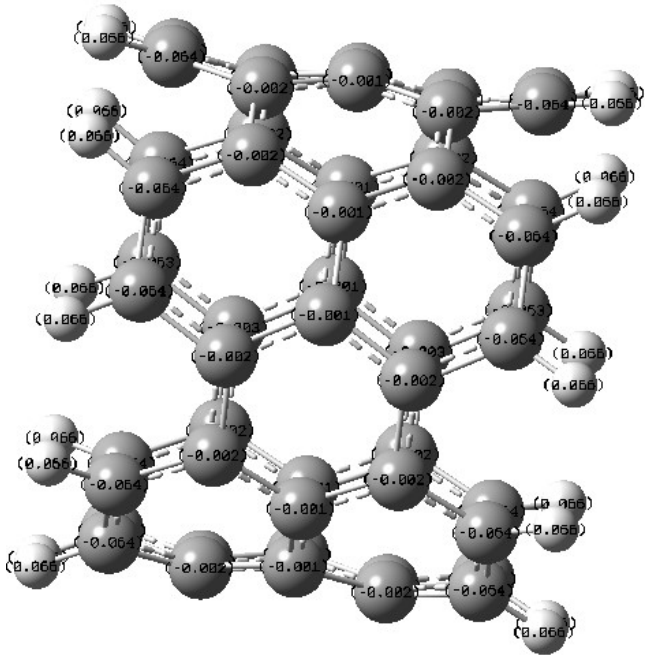

Fig. 2. Conventional charges of carbon nanotube atoms.

Table 1. The Bond Length in the Binding of Melphalan to Carbon Nanotubes

	bond length (angstrom)
R(38,107)	2.54
R(39,107)	2.77
R(63,108)	2.53
R(66,106)	3.17
R(66,108)	2.6

with the nanotube; the length of the bonds shows that the nanotube is a very favorable carrier for melphalan.

Different primary geometries such as drug distribution near the nanotube surface were examined to identify nanotube complexes that showed stability. According to Table 2, atom charge possesses a positive electrostatic potential making atoms good candidates for nucleophilic attacks. Ultimately, the site of nanotube complexes for the adsorption of molecules from C29, N32, and O36,

Table 2. NBO Charge Distribution of Molecules from B3LYP/6-311G Level of Theory

MEL	Charge	NT	Charge	NT/MEL	Charge
N8	0.363	C	-0.001<Q<-0.065	N78	-0.653
Cl15	0.102			Cl77	-0.108
Cl7	0.230			Cl85	-0.095
C16	-0.250			N103	-0.774
C17	-0.490			O108	-0.394
C21	-0.345			O105	-0.530
N32	-0.483				
O35	-0.317				
O36	-0.354				
C29	-0.537				
C26	-0.767				

respectively, was predicted and the results are presented in Table 2. As shown in this table, there is a stronger drug interaction from its head side with an adsorption energy of -94.84 kJ mol^{-1} (interaction distance is 2.00 Å) compared to others. There are lower negative values for Gibbs free energies compared to the values of the adsorption energies, which is related to a decrease in the entropy effect during the process of adsorption.

According to the atom's charge distribution, positive and negative sites of molecules play a role in their interactions. The charge values of C29 and N32 are negative, making them suitable donors in MEL and active sites in interaction with other molecules. On the other hand, N8 and C17 possess the highest positive charges and can be good acceptors in interactions of MEL. Positive as well as negative charges of carbon are observed in the NT wall with lower values compared to the nanotube head charge. Thus, the nanotube head contributes to the interactions of molecules (Figs. 3-6). Even though the electronic features of the nano-complexes show sensitivity to drugs, they have considerably large adsorption energy under the effects of which the desorption

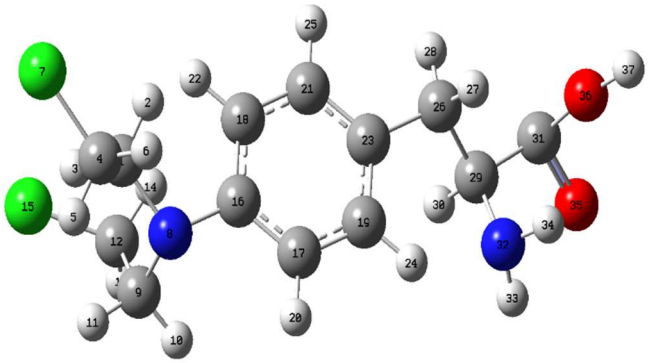

Fig. 3. Geometry structure of MEL.

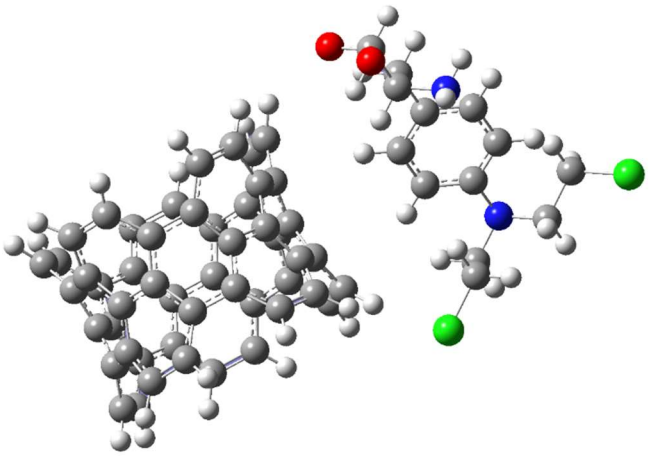

Fig. 5. Geometry structure of MEL/NT.

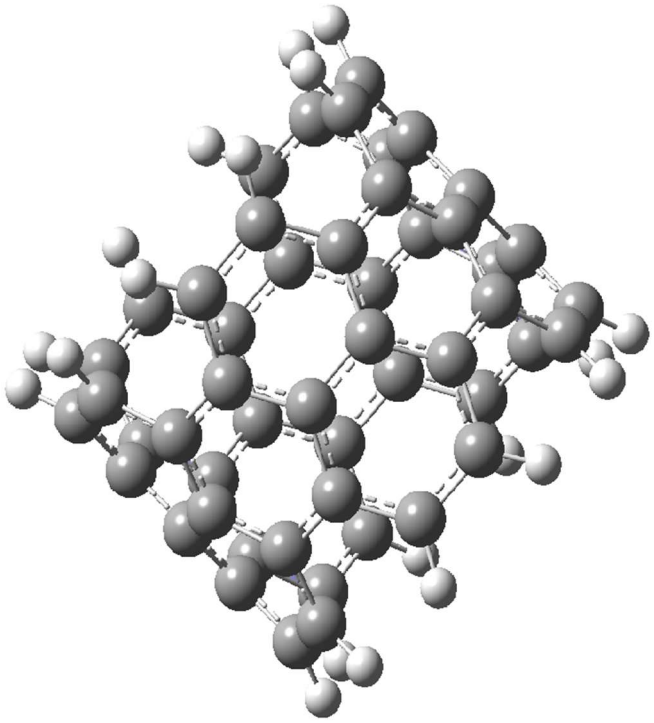

Fig. 4. Geometry structure of NT.

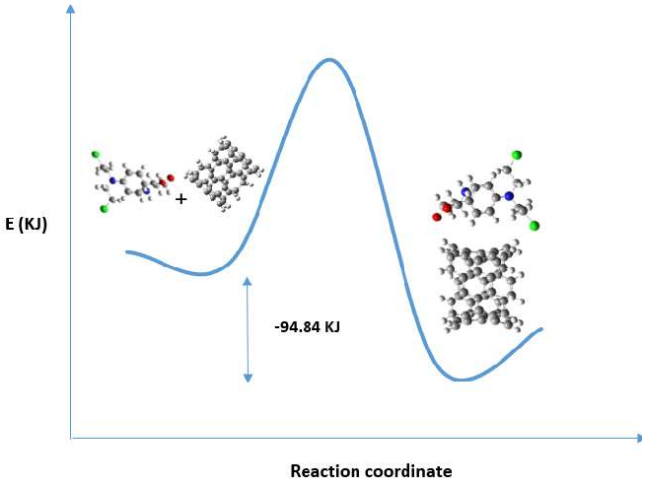

Fig. 6. Diagram of adsorption energy.

process can be hindered. The calculation of electronics parameters, as shown in Table 3, aimed at providing an in-depth analysis of this issue.

HOMO energy represents the molecular capability of donating electrons, which means that bigger values of HOMO energy lead to the higher probability of electron donation by the molecule. The energy of LUMO represents the ability of molecules to accept electrons, which means that lower LUMO energy values lead to a higher probability of electron acceptance by the molecule. One of the significant parameters is the energy gap of the HOMO and LUMO energy levels of the molecule since it is a function of the reactivity of the molecules. A basic description of the atoms' chemical reactivity is ionization potential. The molecules with higher IP show high stability. A hard molecule possesses larger energy gaps while soft molecules indicate higher reactivity compared to hard molecules because of easier

Table 3. Molecular Parameters of all Compounds and Complexes

Molecular parameter	MEL	NT	NT/MEL
HOMO energy	-0.28817	-0.11502	-0.27723
LUMO energy	-0.16539	0.11213	-0.22872
ΔE HOMO-LUMO	-0.12278	-0.22715	-0.04851
Ionization energy (IP)	0.28817	0.11502	0.27723
Electron affinity (EA)	0.16539	-0.11213	0.22872
Electronegativity (χ)	0.22678	0.00145	0.25298
Chemical potential (μ)	-0.22678	-0.00145	-0.25298
Chemical softness (s)	16.28900	8.80470	20.61430
Chemical hardness (η)	0.06139	0.11358	0.04851
Global electrophilicity index (ω)	0.00158	1.18000E-7	0.00155

electron offering to acceptors. The electrophilicity index can help describe the molecules' electron acceptance abilities.

Based on Table 3, MEL donates electrons to NT. Thus, MEL can start biological and chemical reactions. NT plays the role of an acceptor in chemical interactions. Data on the distribution of charge confirms this finding. According to the band gap of energy, MEL has reactivity in chemical media. Electronics data show the structural stability of the MEL/NT complex and the ability to act as targeted carriers of nanostructures.

CONCLUSION

DFT calculation was carried out to investigate interactions between MEL drug with nanotube while employing B3LYP functional. Based on the results, there is an exponential increase in the conduction electrons' population, unlike the carbon nanotubes.

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