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Evaluation of absorption behavior of Streptozocin anti-cancer drug on Cr doped Carbon Nanotube (5,5) using DFT theoretical method

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Abstract: In this study, the physicochemical characteristics of the adsorption of the anticancer drug Streptozocin (STZ, Zanosar) on the extern surface of Cr-doped carbon nanotube (CNTCr) have been investigated. Optimization all structures were performed using the DFT method at the mpw1pw91/6-311G level of theory. The energies, the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), the density of states (DOS), the distribution of electric charges, and the dipole moments have been calculated to investigate the physical chemistry behaviors of the structures. As well as, the molecular descriptors such as electrophilicity (ω), chemical potential (μ), chemical hardness (h) and chemical softness (S) of compounds were investigated. Examination of the intramolecular and intermolecular bonds indicates that the adsorption of the drug on the nanotube surface has been taking place. Also, the calculated adsorption energy was negative and indicates that the adsorption is thermodynamically possible. All the obtained results of the theoretical calculations have shown that CNTCr is suitable for delivering the anti-cancer drug STZ.

Keywords: Streptozocin, Cr-doped CNT, DFT, adsorption energy, DOS

1. Introduction

Drug delivery systems are engineered technologies for the targeted delivery and, or controlled and prolonged release of therapeutic agents. Although biomolecules are more commonly used in the clinical therapies, but recently the use of nano carriers has attracted much more attention [1-4]. High surface-volume ratio, targeted delivery of compounds to the intended tissue, binding of a large number of drug molecules to the nano-carrier surface, and use of a lower dose of the drug are the important factors in the use of these nano structures [5-8]. Many theoretical studies have been conducted on the use of carbon nanotubes as drug delivery carriers for the targeted treatment of diseases such as cancer [9-12]. The adsorption of anti-cancer drugs by doped nanotubes and fullerenes were conducted and their results were reported [13-15]. For instance, the interaction of carbon nanotube with the skin anticancer drug has also been investigated by Hesabi et al. [11]. The adsorption of Carmustine on carbon nanotubes contaminated with boron metal and hydrogen atoms was also investigated using the density functional theory method [16]. The potential of BN, AlN, and CN nanotubes as the drug delivery systems of Tegafur drug was investigated by the density functional theory [17]. Streptozocin (STZ) is in the category of anti-cancer drugs and a natural compound produced by the Streptomyces bacteria. This compound has broad antibacterial properties and is used in the treatment of pancreatic cancer [18]. Some authors have reported that STZ is an anti-betagenic and induces diabetes and it has been used to cause diabetes in laboratory animal specimens since its finding [19,20]. This compound has been used as an inhibitor of DNA synthesis in bacterial and mammalian cells. STZ is toxic to pancreatic beta cells and its side effects are seen after seventy-two hours after use and according to

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the dose used [21]. The compound is stable at pH=7.4 and 37 degrees Celsius for about an hour. The biological half-life of this compound is about 5 to 15 minutes [18]. STZ can methylate DNA in the open oxygen position of guanine, resulting in DNA damage and so the cell will death by necrosis. STZ can also cause the methylation of proteins [22]. Based on the above results and the possibility of damaging non-target cells by this drug, targeted delivery of Streptozocin to cancerous cells for example, pancreatic beta cells can be very important. Therefore, it is important to study the adsorption of Streptozocin on the surface of nanocarriers, including carbon nanotubes, to deliver the drug to the target cells of cancerous tissue. The reshearches show that, the adsorption capability of nanotunes can be enhanced through forming active sites in nanotube surface. Also, doping CNTs with transition metals increases their electronic properties and chemical reactivities. Therfore, the high reactivity of transition metals makes them suitable candidates for doping nanotubes [23]. Based on the results of the above studies, the adsorption of this drug on the surface of carbon nanotubes doped by a metallic atom has given more suitable results. Therefore, in this study, physical chemistry characteristics of the adsorption of the anticancer drug STZ on the surface of Cr-doped carbon nanotubes (CNTCr) were investigated. In this way, after optimizing the structure of the drug, the interaction of the anticancer drug STZ on the surface of carbon nanotubes was investigated. Then, a stable structure and optimal energy was obtained for STZ, CNTCr and CNTCr/STZ complex and the physical chemistry characteristics of these structures were investigated using DFT method.

2. Computational Method

All computations have been performed using Gaussian 09 software package [24]. The structure of STZ, CNTCr and CNTCr/drug complex was obtained using Gaussview software and DFT theoretical method was used to optimize the structures [25,26]. The interaction energies, the HOMO-LUMO energy gap, density of states (DOS), the electric charge distribution and dipole moments were computed at mpw1pw91/6-311g level of theory. In addition, electrophilicity (ω), chemical potential (μ), chemical hardness (η), chemical softness (S) and bond length changes in drug binding to carbon nanotubes in the complex were calculated [27,28]. All the mentioned calculations were performed in the gas phase.

3. Results and discussion

3.1 Optimization of structures

The drug and complex optimization energy were performed in a gradual and step-by-step process using the DFT method at the mpw1pw91/6-311g level of theory. Figure 1 shows that the optimization process is performed correctly and the structures energetically gained a stable position. Figure 1 shows the optimized structure of STZ (a), CNTCr (b), and the CNTCr/drug complex (c).

3.2 Electronic energies and relative stability

The orbital energies of HOMO and LUMO, the energy gap (Eg), Fermi level (EF), system energy and adsorption energy related to the structure of carbon nanotubes, STZ, and their complex has reported in Table 1. The results have been shown that the highest value of HOMO energy has related to STZ (-5125.7 eV) and the lowest value has related to the CNTCr (-9520.5 eV). Furthermore, the highest energy gap due to the difference between the HOMO and LUMO orbitals energy also belongs to STZ. These results indicate the low reactivity of STZ. Fermi-Level energy refers to the highest energy state that an electron has at absolute zero temperature [29]. The calculated values of this energy for CNTCr, STZ and CNTCr/drug complex have found -5.8350 eV, -5.7829 eV and 6.1035 eV, respectively (Table 1).

The drug adsorption energy on the Cr doped carbon nanotube has calculated according to the following equation:

$$E_{ads} = E_{CNTCr}/\text{drug} - (E_{drug} + E_{CNTCr}) \qquad (1)$$

Where E_{ads} is the adsorption energy, $E_{CNT_{Cr}}$ / drug is the total energy of CNT_{Cr}/drug complex, $E_{CNT_{Cr}}$ is the energy of CNT_{Cr} and E_{drug} is the drug energy, respectively. The calculated value of E_{ads} was -0.189 eV. This is a significant negative value that indicates the absorption of the drug on the CNT_{Cr}.

3.3 Frontal molecular orbitals

HOMO and LUMO molecular orbitals significantly affect electrical and optical properties as well as chemical properties. The energy difference between the HOMO and LUMO orbitals, namely the gap

energy, indicates the state of stability of the structure and the activity of the molecule. The HOMO molecular orbital, the LUMO molecular orbital, and the density of states diagram (DOS) of STZ drug have shown in Figure 2. As can be seen, the distribution of HOMO and LUMO orbitals in the drug structure is mostly upon the atoms with high reactive potentials including O1, N1, N2 and O2. Moreover, the DOS plot in Figure 2 has shown that the energy difference between the occupied and unoccupied molecular orbitals was 3.4591 eV. This difference is large enough to conclude that the structure of the drug is energetically stable. Figure 3 shows the two-dimensional representation of the density of the electrical charge on the STZ drug from two different angles of view. As expected, this figure shows that the distribution of electrical charge in the reactive parts of the molecule, including on nitrogen and oxygen atoms, is higher than in other parts of the molecule. This charge distribution can be attributed to the polarization ofthe molecule by the oxygen and nitrogen atoms in the structure of STZ.

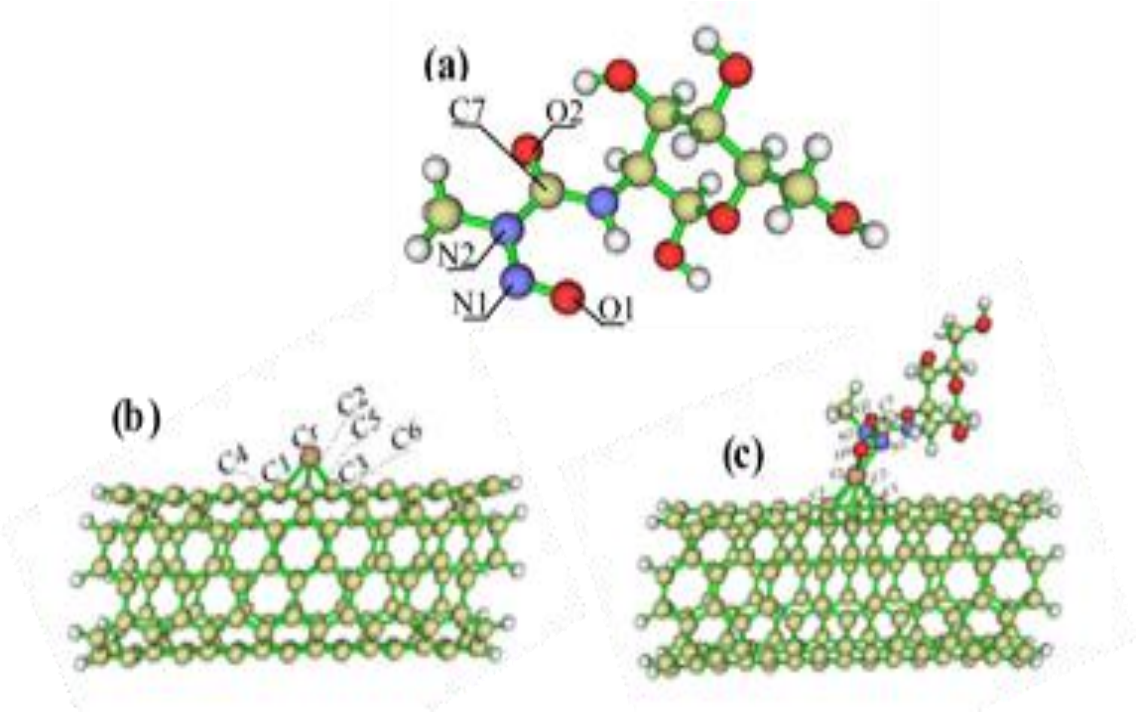

Figure 1. The optimized structures of STZ (a), CNTCr (b) and CNTCr/drug (c)

Table. 1. HOMO, LUMO, gap, Fermi level, system and adsorption energies that have calculated for the optimized structures of CNT_C, STZ, and CNT_{Cr}/drug.

Energy	**CNT_{Cr}**	**STZ**	**CNT_{Cr}/STZ**
E_{HOMO} (eV)	-5.9520	-7.5125	-6.2400
E_{LUMO} (eV)	-5.7181	-4.0533	-5.9670
E_g (eV) [a]	0.2340	3.4591	0.2729
E_F (eV) [b]	-5.8350	-5.7829	6.1035
Energy (keV)	-184.2561	-27.1914	-211.6366
E_{ads} (eV) [c]	-	-	-0.189

[a]Eg (Gap energy) [b]E_F (Energy of Fermi level) [c]Adsorption energy

Then, the structure of CNTCr has optimized to use as a carrier to deliver STZ drug in the gaseous phase (Figure 1). Figure 4 shows HOMO, LUMO and DOS plot of CNTCr after optimization. At the DOS plot shows, the energy gap between the HOMO orbital and the LUMO orbital is 0.2340 eV. The low energy gap in CNTCr structure has indicated the reactivity of its structure. Figure 4 shows an approximately uniform distribution HOMO orbital throughout the CNTCr structure. While the distribution of LUMO orbital is more around the carbons bonded to Cr. This can be attributed to the tendency of CNTCr to react in this position. Moreover, the two-dimensional illustration of the

electrical charge distribution on CNTCr (Figure 5) shows that this structure has a uniform and homogeneous charge distribution. This can be attributed to the nearly uniformity of CNTCr atoms and approximately non-polarity of its structure. Figure 6 shows the HOMO, LUMO orbitals and the DOS plot of the CNTCr/drug complex after optimization. As deduced from Figure 1, STZ has bonded by nitrogen (N1) and oxygen (O1) atoms to the Cr atom on the CNT. The energy gap between the HOMO and the LUMO orbitals in CNTCr/drug complex, as can see in the DOS plot, is 0.2729 eV (Figure 6). This small amount of the energy gap can indicate the instability of the complex and its capability to release the drug. In terms of targeted delivery of the drug carrier, this characteristic is very important. Studying the distribution of HOMO and LUMO orbitals on the complex structure have shown that the highest distribution of HOMO orbitals on the structure was in the position of Cr doped atom on SWCNT (Figure 6). While, LUMO orbitals have distributed almost uniformly throughout of carbon nanotubes in the complex. This indicates the interaction of occupied orbitals of drug at the position of reactive atoms N1 and O1 with the unoccupied orbitals of Cr doped SWCNT to form CNTCr/drug complex (Figure 6). Also, studying of the distribution of electric charge on the complex has shown that by binding the drug to the nanotube, a uniform distribution of electrical charge has been performed on the nanostructure of the complex (Figure 7).

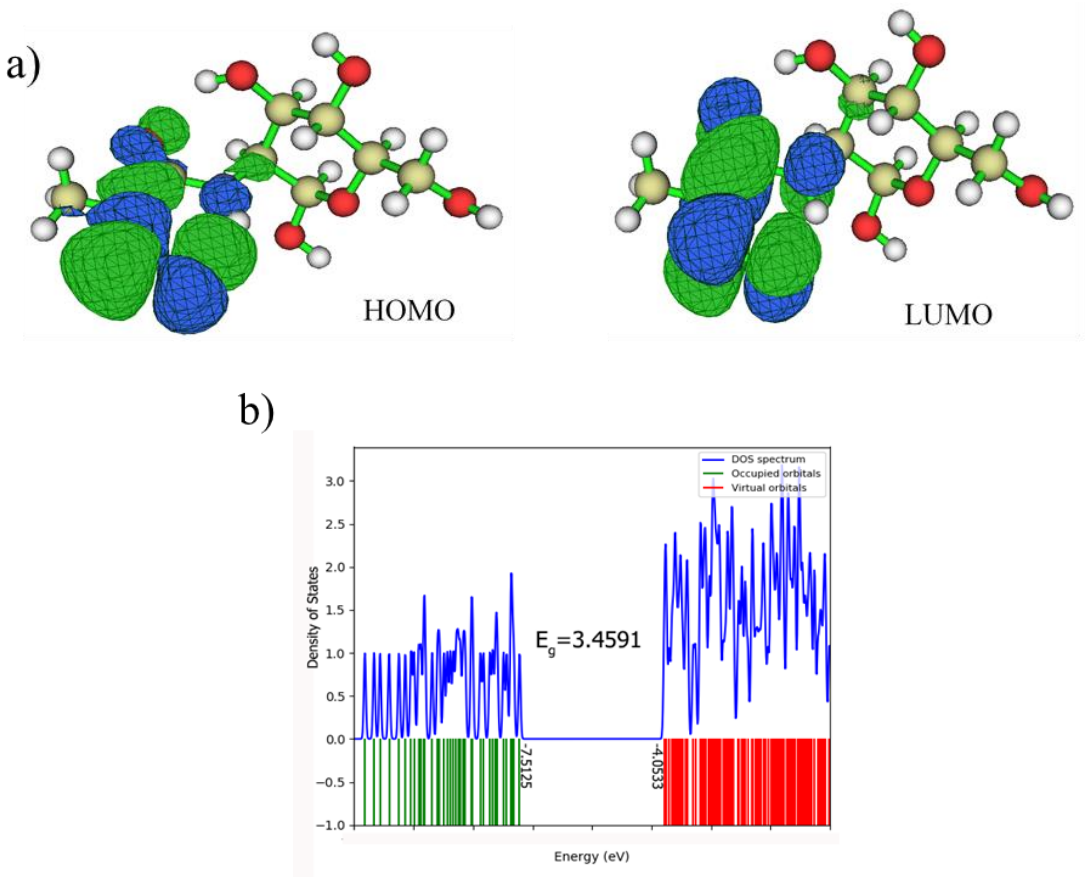

Figure 2. a) Charge distribution of HOMO-LUMO orbitals and b) DOS plot of STZ after optimization

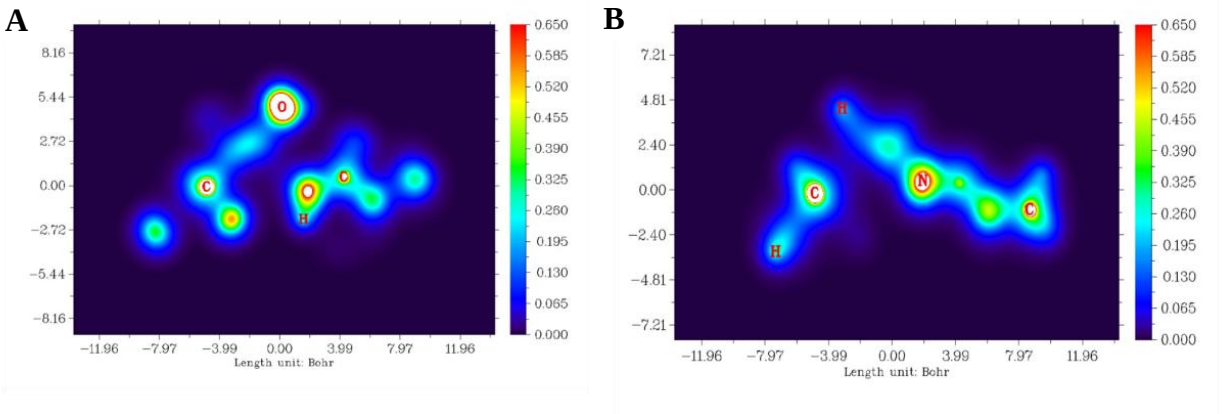

Figure 3. Two-dimensional representation of the density of electrical charge of the optimized structure of STZ from two different angles of view A and B

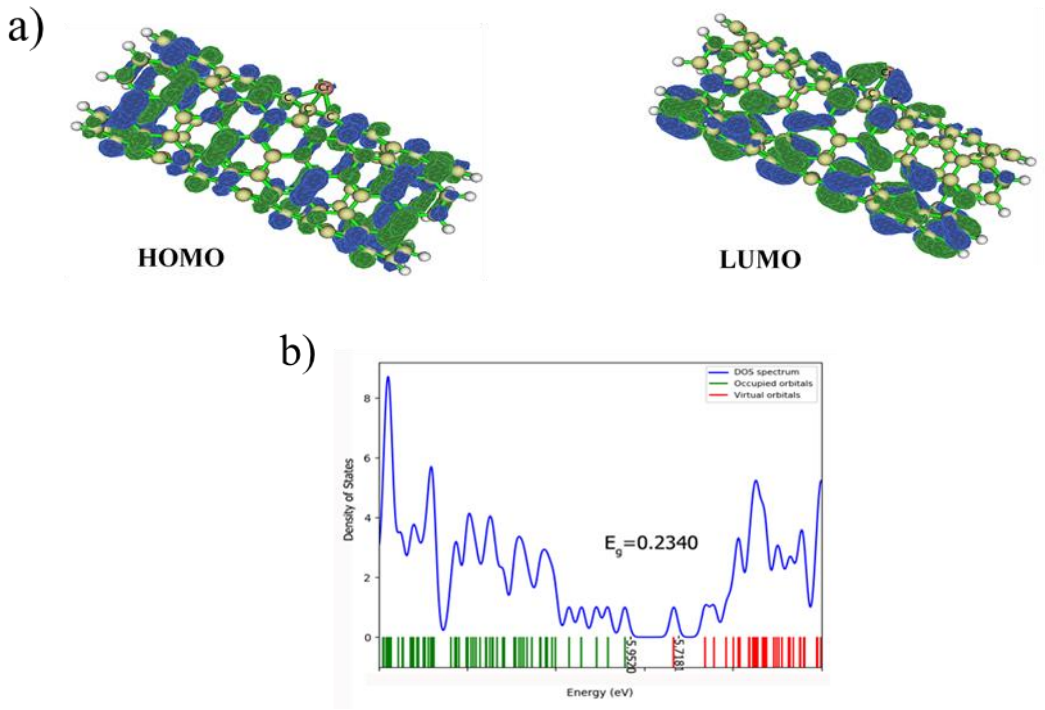

Figure 4. a) Charge distribution of HOMO-LUMO orbitals and b) DOS plot of CNT_{Cr} after optimization

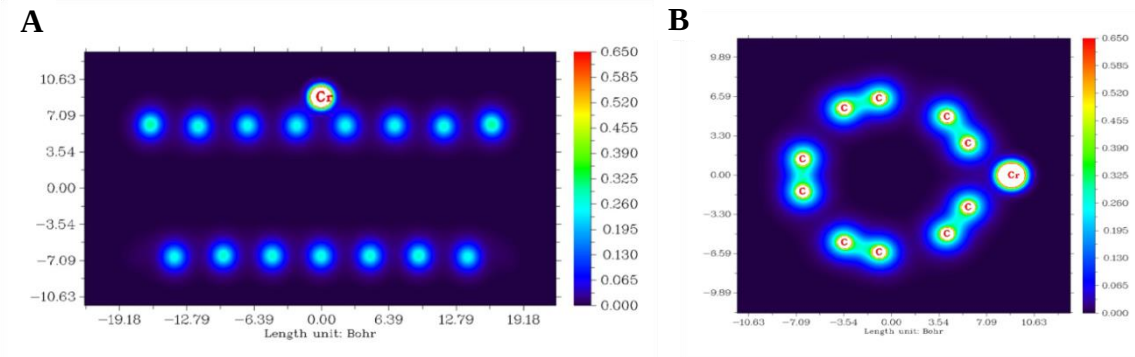

Figure 5. Two-dimensional representation of the density of electrical charge of the optimized structure of CNT_{Cr} from two different angles of view A and B

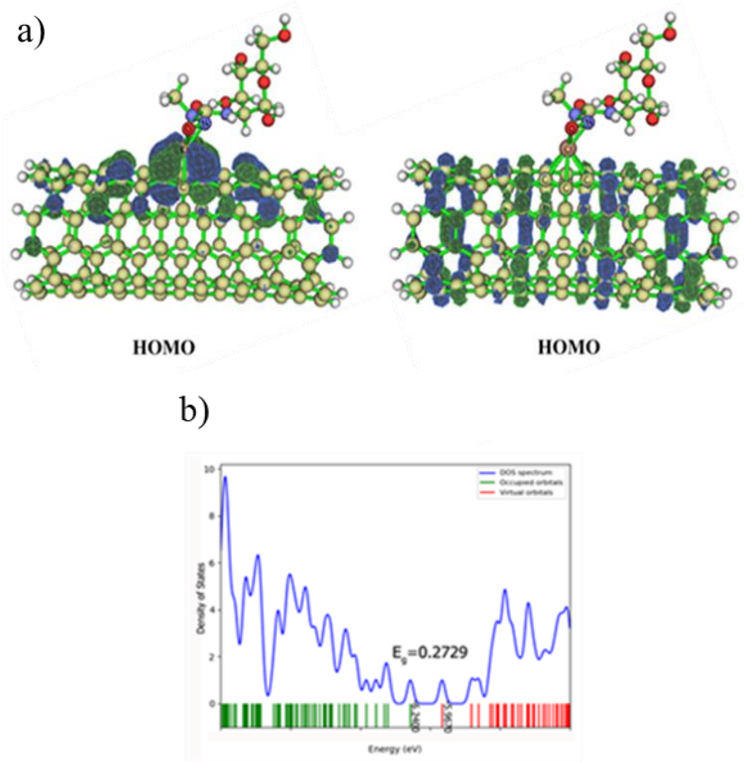

Figure 6. Charge distribution of HOMO-LUMO orbitals and b) DOS plot of of CNT_{Cr}/drug complex after optimization

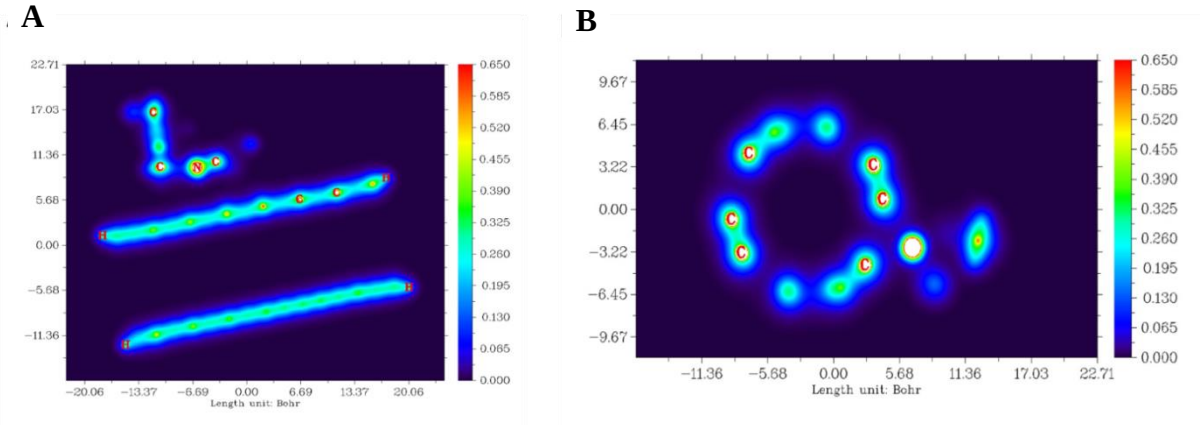

Figure 7. Two-dimensional representation of the density of electrical charge of the optimized structure of CNT_{Cr}/drug from two different angles of view A and

Table. 2. The values of the moment of inertia of CNT_{Cr}, STZ and the CNT_{Cr}/STZ complex

Element	CNT_{Cr} (kg.m^2)	STZ (kg.m^2)	CNT_{Cr}/STZ (kg.m^2)
Dipole moment	7.139	0.557	2.223
Moment of Inertia	$I_a = 3.8072 \times 10^{-35}$	$I_a = 1.2659 \times 10^{-36}$	$I_a = 6.2774 \times 10^{-35}$
	$I_b = 1.0515 \times 10^{-34}$	$I_b = 3.1722 \times 10^{-36}$	$I_b = 1.1250 \times 10^{-34}$
	$I_c = 1.0701 \times 10^{-34}$	$I_c = 3.5768 \times 10^{-36}$	$I_c = 1.3697 \times 10^{-34}$

3. 4 Dipole moment and moment of inertia

The dipole moments of the nanotube, STZ and CNTCr/drug complex have calculated at mpw1pw91/6-311g level of theory and data have reported in Table 2. The higher dipole moment indicates more displacement in electron clouds, so the higher the dipole moment, the higher the absolute value of the bond energy. The calculated

total dipole moment values at mpw1pw91/6-311g level of theory for drug, CNTCr and CNTCr/drug complex are 0.5566, 7.1389 and 2.2234 Debye (D), respectively. As can be seen in Table 2, the CNTCr has the highest dipole moment. This may explain the adsorption of the drug on the Cr atom of CNTCr. Moment of inertia represents the resistance against the rotation of the molecule and its value is a matrix of numbers per axis X, Y and Z, and provides an estimation of the structure of the molecule. These parameters have been calculated for the drug, CNTCr and CNTCr/drug complex and data have reported in Table 2.

As expected, the highest values of the moment of inertia for Ia, Ib and Ic are related to the CNTCr/drug structure

3. 5 Some physical chemistry properties

Some significant physical chemistry properties related to STZ, CNTCr and CNTCr/drug structures have also calculated using DFT method. Ionization potential (I), electron affinity (A), chemical hardness (η), chemical potential (μ), chemical softness (S), electrophilicity (ω) and maximum electronic charge (ΔNmax) have calculated and studied using DFT method. The values of these parameters have reported in Table 3.

Table. 3. Ionization potential (IP), electron affinity (EA), chemical hardness (η), chemical potential (μ), chemical softness (S), electrophilicity (ω) and maximum electronic charge (ΔN_{max}) CNT_{Cr}, STZ and the CNT_{Cr}/STZ complex

Property	CNT_{Cr}	STZ	CNT_{Cr}/STZ
[IP] (eV)	7.8126	9.0298	8.0372
[EA] (eV)	3.3368	2.2546	3.4986
[η = (I - A) / 2] (eV)	0.1170	1.7295	0.1364
[μ = -(I + A) / 2] (eV)	-5.8350	-5.7829	-6.1035
[S = 1 / 2η] (eV)	4.2735	0.2891	3.6643
[ω = μ^2 / 2η] (eV)	145.5010	9.6678	136.5068
[ΔNmax = -μ / η]	5.7180	4.0534	5.9671

Table. 4. The bond length of the optimized structure of CNT_{Cr}, STZ and the CNT_{Cr}/STZ complex

Modify Bond	CNT_{Cr}(Å)	STZ(Å)	CNT_{Cr}/STZ(Å)
Cr-C1	**2.06779**		**2.14055**
Cr-C2	**2.20894**		**2.38226**
Cr-C3	**2.06779**		**2.15927**
Cr-C4	**2.06676**		**2.07801**
Cr-C5	**2.20698**		**2.32125**
Cr-C6	**2.06676**		**2.15155**
***Cr-O1**			**1.84368**
***Cr-N1**			**1.91053**
O1-N1		**1.17572**	**1.34390**
N1-N2		**1.32636**	**1.47777**
N2-C7		**1.41695**	**1.43650**
C7-O2		**1.20225**	**1.22277**

The values of ionization potential (IP) and the electron affinity (EA) are obtained from the equations IP = -0.78E_{HOMO} + 3.17 and EA = -0.65 E_{LUMO} - 0.38, respectively [30]. Chemical hardness (η) can be considered as a measure of the resistance of chemical species to electron arrangement changes. This value has been calculated 1.7295 eV, 0.1170 eV and 0.1364 eV for STZ, CNT_{Cr} and CNT_{Cr}/STZ structures, respectively. On the one hand, chemical softness (S) and chemical potential (μ) can be considered as a measure of the system's tendency to react. Chemical hardness, on the other hand, is the system's response to the external potential for variations in the number of electrons [31]. The electrophilicity index (ω) determines the electrophilic strength of the structure and the amount of energy stability of the system during charge transfer [32]. Finally, the ΔN_{max} parameter

indicates the maximum number of electrons transferred from one system to another. Studying the values of the above-mentioned parameters and indexes indicates that CNT_{Cr} may be a suitable carrier for targeted delivery of STZ.

3. 6 Bond length variations

The bond lengths have calculated at mpw1pw91/6-311g level of theory in the optimized structures of CNT_{Cr}, STZ and the CNT_{Cr}/STZ complex and have reported in Table 4. As can be seen, the length of C1-Cr bonds increased on the adsorption of the STZ on the CNT_{Cr} compared to CNT_{Cr}. Also, two new bonds were formed between Cr atom of nanotube with O1 and N1 atoms of the drug with the distances of 1.84368 A and 1.9553 A, respectively. This binding also has changed the length of the N1-O1, N1-N2, N2-C7, and N1-C8 bonds in the structure of the drug after its binding to the CNTCr. Binding of STZ to CNTCr results in the transfer of charge from of oxygen's nonbonding pair of electrons to two antibonding orbitals of C-Cr in CNTCr. Increasing the electron population of antibonding orbitals and decreasing the electron population of bonding orbitals, and also the more electronegativity of the oxygen atom than that of the carbon atom lead to the weakening of the C-Cr bond and increasing of its bond length.

4. Conclusions

In this study, the absorption of STZ drug on the surface of CNTCr Was investigated using DFT theoretical methods. Firstly, the structures of STZ drug, CNTCr.and the CNTCr/STZ complex has optimized using the density functional theory method. The structural changes have occurred in drug adsorption on the surface of CNTCr including the increase in the length of carbon bonds after adsorption process. The results of the calculations have shown that the highest HOMO energy was related to STZ and the lowest amount of LUMO energy was also related to STZ. As a result, the drug tends to share electrons, which are related to the O1 and N1 atoms in the STZ structure, with the unoccupied orbitals of CNTCr and can be adsorbed on its surface. In addition, the energy gap of the drug also has the highest value, which indicates the stability of its structure. The lower energy of the CNTCr than the drug one also confirms this adsorption interaction. Furthermore, the calculated energy gap for CNTCr./STZ complex indicates that this complex has less energy gap than the CNTCr and the lower energy gap means less stability of the complex and better targeted delivery. The energy obtained for adsorption of the drug on the surface of CNTCr has the negative value, indicating that this process is exothermic. Consequently, this process is thermodynamically possible. Comparing the dipole moments also have shown that due to the formation of the complex the dipole moment has a significant decrease than the CNTCr one. Since the absolute value of energy decreases and the length of the bonds increases with decreasing the dipole moment, the length of the bonds involved also increases with the formation of the complex. The results of studying the change in the length of the bonds of CNTCr as well as the bonds within the drug structure have shown an increase in the lengths of these bonds due to the binding between the drug and CNTCr. In addition, the formation of two bonds between O1 and N1 of the drug and Cr atom of CNTCr has also been demonstrated. Studying other obtained data and especially the adsorption energy; it seems that this adsorption can be considered as a physical adsorption. Furthermore, the results of the interaction of STZ with CNTCr have shown that this adsorption has performed on the surface of the CNTCr. Finally, based on the obtained results, it can be concluded that CNTCr has the capability to carry and delivery the anticancer drug STZ.

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