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Carbon and BN nanocones as nano carriers for 5-Fluorouracil, a DFT study

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ABSTRACT: 5-Fluorouracil (5-FU) is an anticancer drug. In this work, we have investigated the electronic properties and topological analysis of interaction between 5-FU and carbon nanocone and BN nanocone. The structural stability of isomer complexes of 5-FU with carbon nanocone and BN nanocone have been investigated for two position of interactions. We have found that the most stable complexes are formed of O8 of 5-FU (oxygen that is placed between two nitrogen) connection to nanocones. The factors of E_{int} and $\%\Delta E_{gap}$, electron mobility, electron density (ρ) and Laplacian of electron density ($\nabla^2\rho_b$) show a more favorable interaction between the 5-FU drug and BN nanocone due to connection of O8 from 5-FU and Boron atom of BN nanocone. BN nanocone is more sensitive for complex formation with 5-FU drug. It can be concluded that BN nanocone as pharmaceutical nano carrier is an efficient drug carrier. All calculations were performed at M06/6-31+G* level of DFT method embedded in the Gaussian 03 program.

Keywords: *BN Nano cone; Carbon Nano cone; DFT; 5-Fluorouracil; Nano Carrier*

INTRODUCTION

5-fluorouracil (5-FU) is known as one of the chemotherapeutic regimens for patients with metastatic colorectal cancer (IWAMOTO 2014). 5-FU is an anticancer drug and an intercepter of cancer cells activities for colon cancer, esophageal cancer, stomach cancer, pancreatic cancer, breast cancer, and cervical cancer, (Fig. 1a) (Dorr 1994, Chu 2007, Longley *et al.*, 2003). The role of carbon nanotubes as drug carrier of 5-FU anticancer drug were said at different researches (Dresselhaus *et al.*, 1996, Kong *et al.*, 2000, Zare and Shadmani 2013). In this paper, the complex of carbon nanocone with 5-fluorouracil and BN nanocone with 5-FU are investigated as drug carrier systems. The nanocones are the type of nano materials that observed as caps on the ends of nanotubes, and also as free standing nanostructures, Fig.1.b (Iijima, *et al.*, 1992). The nanocone structure is characterized by its cone angle (Ge and Sattler, 1994). More recently, a theoretical study by Alfieri and Kimoto have indicated that nanocones with angles 60º, 120º, 240º and 300º are stable (Alfieri and Kimoto, 2011). Carbon nanocones have also been observed, since 1968 or even earlier on the surface of naturally occurring graphite (Gillot, *et al.*, 1968). Carbon nanocones are produced in an industrial process that decomposes hydrocarbons into carbon and hydro-

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gen with a plasma torch having a plasma temperature above 2000°C (Naess, *et al.*, 2009). A research on the complex of carbon nanotube with 5-FU shown that the carbon nanotube as drug delivery of 5-FU is better than the p-sulphonatocalix-[4]-arene, due to the large energy gap (Zare and Shadmani, 2013). Therefore, the study of electronic properties of nanostructures is important for investigation of complex formation and electronic translations. The electronic properties have been described by Natural Bond Orbital (NBO) analysis (Nagarajan, *et al.*, 2001). In addition to illustrate the bond characteristics, we have calculated the electron density and Laplacian of electron density of bonded interactions in the framework of QTAIM (Popelier, 2001, Gillespie and Popelier, 2001).

MODEL AND SIMULATION DETAILS

We have modeled and simulated drug delivery complexes of 5-FU with Carbon nanocone and BN nanocone. In this work, the interaction of 5-FU with Carbon nanocone and BN nanocone were studied by M06 level of DFT that it is a hybrid-meta DFT method. The M06 functional is suitable for application in noncovalent interactions (Zhao and Truhlar, 2008, Truhlar and Zhao, 2008). All calculations in this article were performed with 6-31+G* basis set (Frisch, *et al.*, 1984) embedded in the Gaussian 03 package (Frisch, *et al.*, 2003). A small cluster of nanocone with disclination angle equal to 240º and height equal to 4 have been created by Nanotube Modeler 2014 software. The optimized complexes of 5-FU with Carbon nanocone and BN nanocone were shown in Figs. 5, 6, 8, 9. The main aim of this work is to investigate the structural stability and electronic properties of complexes of Carbon and BN nanocone with 5-FU. Therefore, we have obtained the interaction energies. The interactions were considered at the two orientations. We have recommend orientations as:

Position 1: O8 from 5-FU to C and or B of nanocones.
Position 2: F from 5-FU to C and or B of nanocones.

The interaction energies (ΔE_{int}), the change of Dipole moment ($\Delta\mu$) and $\%\Delta E_{gap}$ of studied complex systems have been obtained by Eq. 1, Eq. 2 and Eq. 3, respectively.

$$\Delta E_{int} = E_{complex} - (E_{nanocone} + E_{5-Fluorouracil}) \tag{1}$$

$$\Delta\mu = \mu_{complex} - (\mu_{nanocone} + \mu_{5-Fluorouracil}) \tag{2}$$

$$\%\Delta E_{gap} = \frac{(E_{gap_{complex}} - E_{gap_{nanocone}})}{E_{gap_{nanocone}}} \times 100 \tag{3}$$

The first term in Eq. 1 is the energy of the complex system and the next two terms are the energies of the

Table 1. Dipole moment, ΔDipole moment of interaction (in bracket), Energy of structures, ΔE int (in bracket), E_{Lumo}, E_{HOMO} , E_{gap} and $\%\Delta E_{gap}$

Structure		**μ/ Debye** **[Δμ]**^{i}	**a.u E/** **[ΔE_{int}/kcal.mol^{-1}]**^{ii}	**E_{LUMO} (eV)**	**E_{HOMO} (eV)**	**E_{gap} (eV)**	**$\%\Delta E_{gap}$**
5-Fluorouracil		4.4811	-513.796	-2.02	-7.78	5.76	-
Carbon nanocone		0.0002	-303.9720	-4.75	-7.45	2.7	-
5-Fluorouracil with Carbon nanocone	P1	10.7906 [6.3095]	-817.856 [-55.2279]	-3.67	-5.22	1.55	-42.59
	P2	5.8340 [1.3529]	-817.781 [-8.15867]	-4.14	-5.99	1.85	-31.48
BN nanocone		4.8011	-318.1707	-4.13	-7.38	3.25	-
5-Fluorouracil with BN nanocone	P1	13.3358 [4.0536]	-832.203 [-148.299]	-3.61	-4.73	1.12	-65.53
	P2	3.6305 [-5.6517]	-832.176 [-131.354587]	-3.6	-5.52	1.92	-40.92

i: ΔDipole moment of interaction; ii: ΔE of interaction free nanocone molecule and bare 5-FU, respectively. The harmonic vibrational frequencies of the fully optimized structures have been calculated to confirm the stationary point as local minima with all positive frequencies. The electronic properties of nanostructures have been described by lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO).

The major classification of bonded interactions in the framework of quantum theory of atoms in molecules (QTAIM) has been proposed based on the sign of electron density (ρ_b) and Laplacian of electron density ($\nabla^2\rho_b$) at the Bond Critical Points (BCPs) (Bader and Essen, 1994). The Electron Density at the BCP has been shown to be strongly correlated with the binding energy for several types of bonding interaction (Bader, 1998, Domagala and Grabowski, 2005). Because the Laplacian is essentially a second derivative, its sign indicates regions of local electronic charge concentration or depletion with respect to the immediate neighborhood. As is known, $\nabla^2\rho_b$ identifies whether the charge of the region is shared interactions as covalent ($\nabla^2\rho_b > 0$ and $\rho b \approx 10^{-1}$) or closed shell interactions as van der walls ($\nabla^2\rho_b < 0$ and $\rho_b \approx 10^{-2}$). The AIM analyses for the optimized structures (Figs. 5, 6, 8, 9) have been performed to obtain the topological properties of the bonds.

RESULTS AND DISCUSSION

The structural stability of nano structures can be described by calculated energy. To evaluate the stability of structures, we first optimized the complexes between 5-FU and nanocones, by Gussian 03 program and then the interaction energy (Eint) of the considered systems was calculated using the equation1. In this work, the interactions between 5-FU and nanocones have been studied for two positions of connection. Table 1 presents the dipole moments, interaction

Fig. 1. 5-Fluorouracil

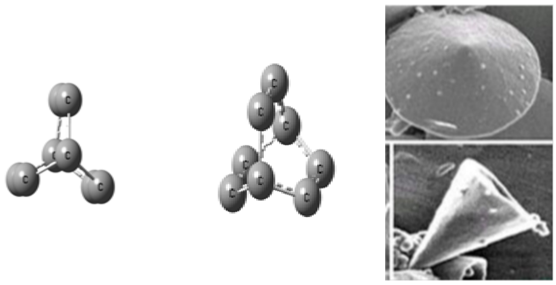
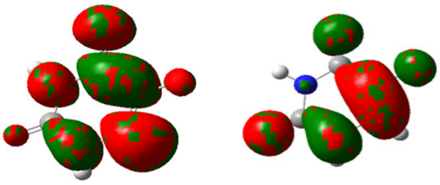
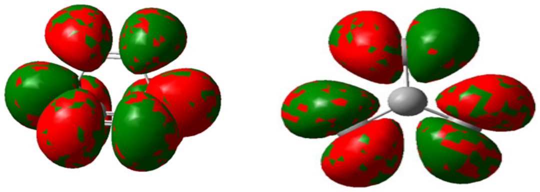


Fig. 2. Carbon nanocone from three view



LUMO HOMO

Fig. 3. HOMO and LUMO orbitals of 5-Fluorouracil



LUMO HOMO

Fig. 4. HOMO and LUMO orbitals of Carbon nanocone

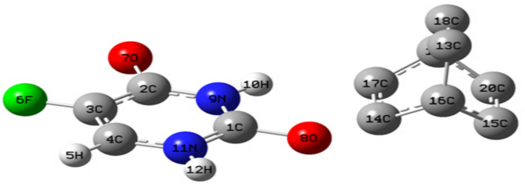


Fig. 5. Optimized structure of 5-Fluorouracil and Carbon nanocone: P1

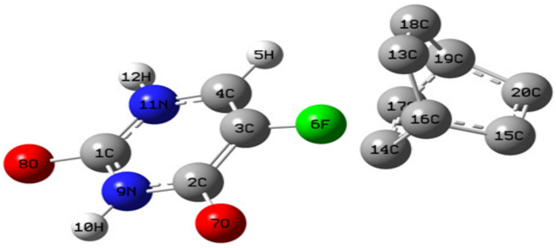
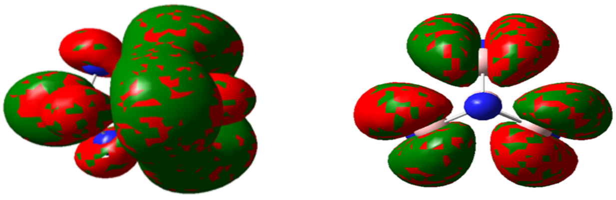


Fig. 6. Optimized structure of 5-Fluorouracil and Carbon nanocone: P2



LUMO HOMO

Fig. 7. HOMO and LUMO orbitals of BN nanocone

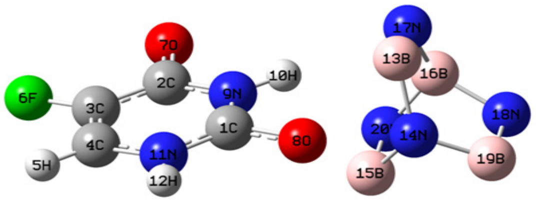


Fig. 8. Optimized structure of 5-Fluorouracil and BN nanocone: P1

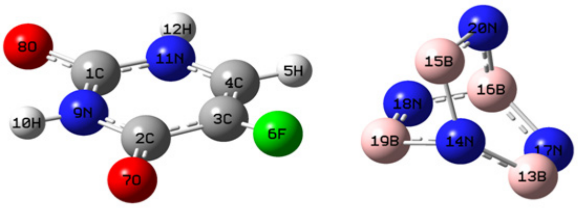


Fig. 9. Optimized structure of 5-Fluorouracil and BN nanocone: P2

energies (ΔE_{int}), Gap of Energy (E_{gap}) and $\%\Delta E_{gap}$ for all the interacting systems. The polarity of a molecule describes its dipole moment. Dipole moment gives clear information about the arrangement of charges in nano structures. The result of dipole moment may indicate that the type effect of atom is important and asymmetry in charge distribution in nanocones can be explained the different electronic properties. Table 1 shows that the complex of 5-FU with BN nanocone at P1 position has the highest value of dipole moment at gas phase. Therefore, it can be extrapolated that solvation of this complex in water is more than other complexes at Table 1.

The values of energies of isomer complexes in Table 1 show that the position of P1 complex due to connection of O8 to carbon nanocone (-817.856 a.u.) is more stable than P2 isomer (-817.781 a.u.). Also, P1 complex of 5-FU with BN nanocone (-832.203 a.u.) is more stable than P2 isomer (-832.176 a.u.). The calculated ΔE_{int} by Eq.1 in Table1 show that connection between the O8 atom of 5-FU with carbon nanocone, P1 complex (-55.228 kcal.mol^{-1}) is energetically more suitable than P2 complex (-8.158 kcal.mol^{-1}). The values of ΔE_{int} show that the connection between the O8 atom of 5-FU with Boron atom of BN nanocone (-148.299 kcal.mol^{-1}) is energetically favored over P2 complex (-131.354 kcal.mol^{-1}).

The HOMO and LUMO energy distributions depend on the drug's chemical structure. The HOMO and LUMO are related to the reactive sites and the electrophilic and nucleophilic behavior of a molecule. The HOMO and LUMO for the studied drug, Carbon nanocone and BN nanocone in the gas phase are shown in Figs. 3, 4 and 7, respectively. Fig. 3 reveals

Table 2. Mobility of electrons (E^2) and Charge (q) of Donor and Acceptor Bonds

Donor NBO (i)	Acceptor NBO (j)	E^2 (kcal/mol)	q
5-Fluorouracil with Carbon nanocone, P1			
BD(1) C14-C16	BD*(1) C1-O8	48.60	0.0940
5-Fluorouracil with Carbon nanocone, P2			
BD(1) C14-C16	BD*(1) C3-F6	40.45	0.0763
5-Fluorouracil with BN nanocone, P1			
BD(1) C1-O8	BD*(1) N14-B15	53.81	0.1096
5-Fluorouracil with BN nanocone, P2			
BD(1) C3-F6	BD*(1) N14-B15	9.36	0.0205

that the HOMO is distributed on the O8 and Fluorine of 5-FU, while the LUMO is distributed on the nitrogens of this molecule. Fig. 4 shows that the distributions of HOMO and LUMO on the all of atoms of Carbon nanocone are symmetric and same. Fig. 7 reveals that the HOMO and LUMO of BN nanocone are distributions on nitrogen and Boron of this molecule, respectively. Therefore, the B atom is the electrophilic site of the BN nanocone in gas phase. For an interacting system, the O8 and Fluorine sites of 5-FU are electron donors and suitable for electrophilic attack. The results of optimization of complexes show that interaction between nanocone and 5-FU drug has occurred from O8 and or Fluorine sites of 5-FU with Boron site of BN nanocone.

The values of percent changes of E_{gap} show that the 5-FU interacts to carbon nanocone from O8 position, that is consistent to result of ΔE_{int}. The value of $\%\Delta E_{gap}$ for BN nanocone complexe at P1 position is great distinctively. The Egap of 5-FU with BN nanocone complex (P1) has changed from 3.25 to 1.12 by -65.53% change. While, the calculated $\%\Delta E_{gap}$ for complex of 5-FU with BN nanocone, P2 is -40.92. This result reveals that interaction of 5-FU from O8 site with Boron site of BN nanocone (P1 position) distinctively is more suitable than P2 position.

The electron resonance (E^2) in Table 2 is a factor of electron mobility. Thus, the narrow band gap (1.12 eV) between the HOMO and LUMO levels for 5-FU-BN nanocone complex (P1) results in easy transition of electrons from HOMO level to LUMO and easy mobility of electrons (E^2= 53.81) at this complex. This means that the 5-FU drug molecule is coupled to the BN nanocone that have effected on the electronic charge distribution of atoms of nanocone. Also, a large charge transfer (q= 0.1096) takes place between the drug molecule and nanocone.

Table 3 presents the results for the values of the charge density (ρ_b), the Laplacian at the bond critical points obtained ($\nabla^2\rho_b$) by the M06/6-31+G* level of DFT theory. At all of the complexes the values of $\nabla^2\rho_b$ are positive and the values of ρ_b are at the range of 10^{-2}. These results reveal that 5-FU binds to carbon and BN nanocones with Van der walls interactions. Also, BN nanocone provides suitable condition as nano Carrier for 5-FU.

Table 3. Charge density (ρ_b) and Laplacian of electron density ($\nabla^2\rho_b$)

Position	**Bond**	ρ_b	$\nabla^2 \rho_b$
5-Fluorouracil with Carbon nanocone			
P1	O8-C14	0.07721	+0.00022
P2	F6-C14	0.03860	+0.01499
5-Fluorouracil with BN nanocone			
P1	O8-B15	0.09253	+0.00014
P2	F6-B19	0.04022	+0.01633

CONCLUSIONS

In this research, we have compared the effect of carbon and BN nanocone as nano carriers on the 5-FU anticancer drug. The electronic properties and topological analysis were performed with M06/6-31+G* level of DFT method. We have found that the BN nanocone is more sensitive for complex formation with 5-FU drug due to its E_{int} and $\%\Delta E_{gap}$. The factors of electron mobility, electron density and Laplacian of electron density show a more favorable interaction between the 5-FU drug and BN nanocone due to O8 from 5-FU and BN nanocone. It can be concluded that BN nanocone as pharmaceutical nano carrier is an efficient drug carrier.

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