DFT analysis of interaction between a Carbon nanotubes and anti-cancer drugs

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Abstract- Carbon nanotubes (CNTs) have been attracting attention in the pharmaceutical industry because they have characteristic mechanical properties. Due to discovery of carbon nanotubes (CNTs), several research efforts indicate the possibility of exotic properties and subsequent applications of carbon based nanomaterials. Moreover, CNT can also be highly scene-changing in the field of medicine and pharmaceutical. CNTs could be chemically functionalized by other atoms or molecules resulting in new structures thereby providing excellent properties, related density functional theory (DFT) calculations have been reported in literature with different structures of CNTs and anticancer drugs.
In this work, interaction of carbon nanotube (6, 6) armchair and (6, 0) zigzag with Fluorouracil drug is being investigated. The DFT calculations have been performed using Gaussian 09 in B3LYP method and 6-31G (d, p) standard basis set at 298K.The nanotube can be a useful tool for better delivery of this drug. Also, NBO analysis shows that there exist hyper conjugative effects arising from an overlap between occupied orbital in the drug and unoccupied orbital in carbon nanotubes.

Keywords – Drug delivery, Nanotube, DFT, Fluorouracil, NBO, Formation energy

I. INTRODUCTION

The ability to investigate substances at the molecular level has boosted the search for materials with outstanding properties for use in medicine. The application of these novel materials has generated the new research field of nanomedicine. The major goal of nanomedicine is the design of material capable of delivery and targeting of pharmaceutical, therapeutic, and diagnostic agents [1-3]. In 1991, Dr. Iijima discovered thin and long straw- shaped carbon nanotubes during a TEM analysis of carbon clusters synthesized by the arc-discharge method [4]. Carbon nanotubes (CNTs) are essentially cylindrical molecules made of carbon atoms. CNTs are graphene sheets rolled into a seamless cylinder that can be open ended or capped, having a high aspect ratio with diameters as small as 1nm and a length of several micrometers. CNTs made from a single graphene sheet results in a single-walled nanotubes (SWNT) while several graphene sheets make up multi-walled carbon nanotubes (MWNTs) [5]. Carbon nanotubes (CNTs) having unique electronic, mechanical, photonic and chemical properties [6-8], qualifying them to be used in biological and medical research.
The idea of using hallows cylindrical structure as a transporter or container has been proposed for many years [9]. In this paper, complex formed between the Fluorouracil and single walled carbon nanotubes (6, 6) armchair/ (6, 0) zigzag are investigated as drug delivery system. Fluorouracil or Fluoropyramidin-2, 4(1H, 3H)-dion is one of the most commonly used drug to treat cancer. Fluorouracil is a part of a group of chemotherapy drugs. It is anti-metabolite drug and acts in several ways. These days there are ways to deliver a drug in the body without side effects [10].In the paper, we investigated types of drug delivery system such as nanotubes.

II. MATERIALS AND METHODS

The two Single walled CNTs models considered here are (6, 6) armchair and (6, 0) zigzag with their ends saturated by hydrogen atoms. Nanotubes are generated by nanotube structure generator (TubeGen 3.4). [11] The SWCNT (6, 6) model consists of 96 atoms and SWCNT (6, 0) model formed by 72 atoms. All geometries have been fully optimized at the Density functional theory with hybrid functional B3LYP and basis set 6-31G (d, p) level by using Gaussian 09 suite of programs[12] at temperature 298.15 K.In order to study the possible interaction between SWCNT (6, 6)/ (6, 0) with fluorouracil anti- cancer drug .

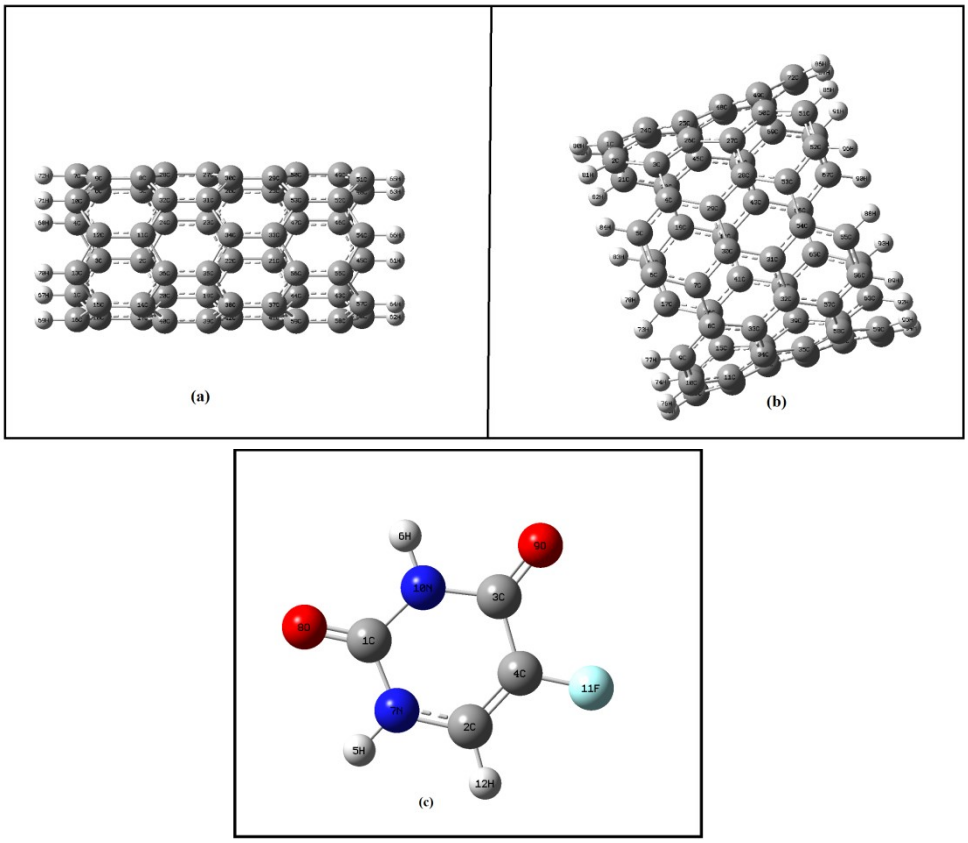

Figure1. The structures of optimized a) Nanotube (6, 0), b) Nanotube (6, 6), c) Fluorouracil

III. RESULTS AND DISCUSSION

3.1 Molecular electrostatic potential (MEP)

The molecular electrostatic potential (MEP) is related to the electron density and is a very useful descriptor in understanding sites for electrophilic and nucleophilic reactions as well as hydrogen bonding interactions [13]. To predict reactive sites of electrophilic or nucleophilic attacks for the investigated molecule, MEP at the B3LYP and 6-31G (d, p) level optimized geometry was calculated.

The molecular electrostatic potential (MEP) plot of Drug molecule was used in order to find the most stable configurations of interaction Fluorouracil (Fig. 2). MEP plot and structural parameters show that the electron density of O atoms of the Fluorouracil molecule is reactive sites (partial negative charge, red and yellow) and provides the possibility for an Fluorouracil molecule to approach the functionalized carbon nanotube (positive charge, blue color)[14]. Therefore, the Fluorouracil molecule is able to approach the single-walled CNT with different orientations.

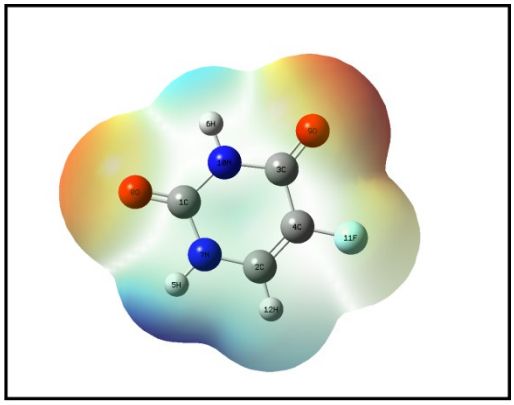

Figure2. Molecular electrostatic potential (MEP) plot of fluorouracil drug at B3LYP/6-31G (d, P) level

3.2. HOMO-LUMO analysis and Formation energy

The interaction between the SWCNT and Fluorouracil was investigated by DFT, HOMO-LUMO and NBO analysis. The optimized structures of SWCNT (6, 0) / (6, 6) and fluorouracil are shown in Fig.1 (a, b, c) and Fluorouracil–SWCNT complexes (1 and 2) are shown in Fig 3.

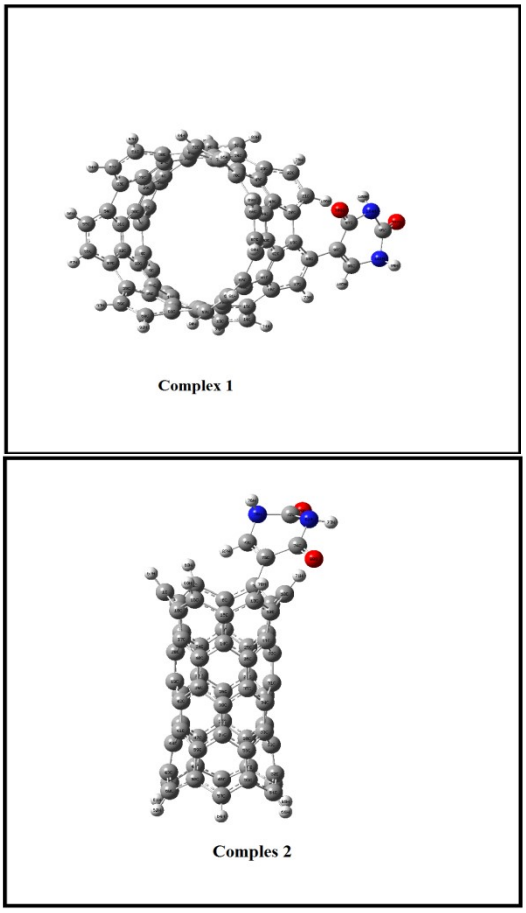

Figure3. The structures of optimized complex 1, interaction of Fluorouracil-Nanotube (6, 6) armchair and complex 2, Fluorouracil – Nanotube (6, 0) zigzag

Fig.3. It is clear that the Fluorouracil–SWCNT complex was formed by the interaction between the fluorouracil and the SWCNT. After fully optimization of the structures of Fluorouracil–SWCNT, the Formation energy (ΔE_f) was obtained by using the following equation-

$$\Delta E_f = \{\Delta E_{(F\text{-}SWCNTs)} - (\Delta E_{SWCNTS} + \Delta E_F)\} \quad (1).$$

Where $\Delta E_{(F\text{-}SWCNTs)}$, ΔE_{SWCNTS} and ΔE_F are the optimized energies of the complexes, SWCNTs and fluorouracil structure respectively. Accordingly the formation energy value was found to be -12.878 $kcalmol^{-1}$(complex 1) and -4.11573 $kcalmol^{-1}$(complex 2).The results obtained from formation energy study reveal that, both the complex 1 and 2 formed from fluorouracil (anti-cancer drug) and mentions nanotubes are negative formation energy. This means the reaction is exothermic and the complex formations (complex 1 and 2) are performed thermodynamically. The gap energies and total energy, HOMO and LUMO complexes 1, 2 were calculated using the B3LYP method and 6-31G (d, p) basis set. The total energy sum of energy transitional, energy rotational and energy vibration in level B3LYP/6-31G (d, p) for complexes 1, 2 was calculated. The obtained results are shown in Table 1.

Table1. Computational data

Molecules	E_{total} ($kcalmol^{-1}$)	ΔE_f ($kcalmol^{-1}$)	HOMO (eV)	LUMO (eV)	Energy Gap (eV)
Complex 1	481.8302	-12.8787	- 4.4904	- 2.7499	1.7405
Complex 2	355.7141	-4.11573	- 3.6841	-3.0155	0.668
CNT_66	445.1186	-	- 4.2536	- 2.5992	1.654
CNTs_60	310.2394	-	- 3.5301	- 2.8612	0.672

Table1. Formation energy, total energy, HOMO, LUMO, Gap of energy are calculated in B3LYP/6-31G (d, p) method at 298.15 K

The Highest occupied molecular orbital (HOMO) and the lowest un-occupied molecular orbital (LUMO) are very important parameters for quantum chemistry. These values help to exemplify the chemical reactivity and kinetic stability of the molecule. The ability of a donor electron is related to the energy of the HUMO (E_{HOMO}) while the accept of an electron implies the energy of the LUMO (E_{LUMO}).The energy gap ($E_{HOMO} - E_{LUMO}$) is an important value which serves as a stability index. In fact, a large HOMO-LUMO gap implies high molecular stability in the sense of its lower reactivity in chemical reactions [15-16]. The calculated energy gaps of pristine (6, 0) and (6, 6) SWCNT are respectively 0.672 and 1.654 eV, whereas in the complexes these values 0.668 and 1.7405 correspondingly. These results indicate that F drug interaction on the pristine (6, 6) armchair SWCNT has more influences on the energy gap compared to pristine (6, 0) zigzag SWCNT.

3.3. Natural Bond Orbitals (NBO) analysis

A natural bond orbital (NBO) calculation was performed at the B3LYP/6-31G (d, p) level implemented in Gaussian 09 package. This analysis were performed in order to understand various second order interactions between the filled orbitals of one subsystem and vacant orbitals of another subsystem, in order to have a measure of the intra-molecular delocalization of hyper-conjugation[17]. Hyper-conjugation is the stabilizing interaction that results from the interaction of the electron in an σ-bond (usually C-H or C-C) with an adjacent empty or partially filled p-orbitals or a π-orbital to give an extended molecular orbital that increase the stability of the system. The stabilization energy $E^{(2)}$ associated with i (donor) → j (acceptor) delocalization is estimated from the second-order perturbation approach as given below-

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F^2(i,j)}{\varepsilon_j - \varepsilon_i} \quad (2)$$

Where q_i is the donor orbital occupancy, ε_i and ε_j are diagonal elements (orbital energies) and F (i, j) is the off - diagonal Fock matrix element.

Table2.Computational data .

Model	Donor	(BD)	Occupancy	Acceptor	(BD)	Occupancy	Hybrid	E^2	ΣE^2
	C17- C1 8	σ	1.97200	C 15 - C 16	σ*	0.03293	sp2.40	4.16	
Complex		σ		C 16 - C 17	σ*	0.01650	sp1.77	2.20	
1		σ		C 17 – H 73	σ*	0.01248	sp2.15	1.19	
		σ		C 18 – C 19	σ*	0.02179	sp1.86	3.47	
		σ		C 18 – C 98	σ*	0.02955	sp2.27	1.56	
		π	1.67795	C 16- C 41	π*	0.043742	sp1.00	15.23	51.94
	C 18 -C 19	σ	1.97203	C 17 – C 18	σ*			3.03	
		σ		C 17 – H 73	σ*	0.01248	sp2.15	2.00	
		σ		C 18 – C 98	σ*	0.02955	sp2.27	1.84	
		σ		C 19 – C 20	σ*	0.03413	sp2.37	2.36	
	O 103	LP	1.86287	C 97 – C 98	σ*	0.06140	sp1.63	14.90	
Complex	C 7 – C 9	σ	1.96531	C 6 – C 7	σ*	0.02306	sp2.04	1.24	
2		σ		C 7 – C 75	σ*	0.02622	sp1.87	1.10	
		σ		C 8 – C 9	σ*	0.02938	sp1.76	2.90	
		σ		C 8 – C 32	σ*	0.03932	sp2.15	4.10	
		σ		C 9 – C 10	σ*	0.01840	sp2.08	1.82	
	C 7 – C 9	π	1.53958	C 8 – C 28	π*	0.47353	sp99.99	19.03	47.46
	C 9 – C 10	σ		C 7 - C 9	σ*	0.02321	sp2.10	1.83	
		σ		C 8 – C 9	σ*	0.02938	sp1.76	2.91	
		σ		C 8 – C 28	σ*			4.29	
	C 7 – C 75	σ	1.97377	C 8 – C 9	σ*	0.02938	sp1.76	1.26	
		σ		C 73 – C 75	σ*	0.20915	sp1.60	2.53	
		σ		C 73 – N 78	σ*	0.01434	sp2.68	3.18	
	C 7 – C 9	π	0.52015	C 7 – C 75	σ*	0.02622	sp1.87	1.27	

Table2. The NBO parameters of, Complex 1 and 2 are calculated in B3LYP/6-31G (d, p) method at 298.15K

The larger the $E^{(2)}$ value, the more intensive is the interaction between electron donors and the greater the extent of conjugation of the whole system. Delocalization of electron density between occupied Lewis type (bond or lone pair) NBO orbitals and formally unoccupied (antibonding or Rydberg) non Lewis NBO orbital's correspond to a stabling donor- acceptor interaction. [18]

As can be seen in Table 2, the bond pair donor orbital π C-C → π* C-C in complex 1 and 2 are give more energy stabilization than σ C-C → σ* C-C. In complex1, a very strong interaction has been observed between the lone electron pair LP O (103) and the σ* C (97) – C (98) with an energy of 14.90 kcal mol^{-1}. The hyperconjugation energy values in complex1and 2 are in the range of 51.94 and 47.46 $kcalmol^{-1}$ respectively. The results indicating that these interactions produce a great stabilization in the molecule.

IV.CONCLUSION

In this work , the result shows that the interaction between armchair (6, 6) nanotube with flurouracil anti cancer drug (complex 1) more stable than complex 2.NBO analysis and HOMO- LUMO energy gap shows that complex 1 have largar energy gap (1.7405 eV) and lower formation energy (- 12.8787 $kcalmol^{-1}$) compare to complex 2.Thus, complex1 is a better container for this drug than complex 2.

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