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Density Functional Theory Calculations of Functionalized Carbon Nanotubes with Metformin as Vehicles for Drug Delivery

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ABSTRACT

Drug delivery by nanomaterials is an active emergent research area and CNTs draws considerable potential application owing to its unique quasi one-dimensional structure and electronic properties. Single walled carbon nanotubes and carbon fullerenes can be used in drug delivery due to their mechanical and chemical stability. The past few years, increasing attention by several reputed groups has been devoted on functionalization of carbon nanotube s (CNT s).In this paper, we reported the effects of covalently binding isoniazid, an metformin molecule to functionalized carbon nanotube. In this work, binding energies, energies of solvation, computational-chemistry molecule descriptors with use density function theory(DFT) method and 6-31G*,6-31G** basis set were calculated. The results show to covalently bind isoniazid to functionalized carbon nanotubes suitable for carrier's metformin molecule. We have performed DFT calculations for f-SWCNTs in order to assess their roles as nanovectors for drug delivery of metformin.

Keywords: Functionalized CNT; Metformin; Drug Delivery

INTRODUCTION

Toxicity of CNTs represents a hot topic. It relates to the health care of researchers working with this nanomaterial's but it is also an issue concerning all their future applications [1]. The common opinion that chemical f-CNTs do not exert cytotoxicity and in particular and surprisingly, that covalent f-CNTs are better than non-covalent functionalized ones, depending on the degree of functionalization [2].

Functionalized carbon nanotubes offer enormous potential as components of Nano scale electronics and sensors. In the first category, O, Connell et al [3].showed evidence for the formation of water-soluble SWNTs by wrapping with various polymers. Similarly, Zheng et al [4].have reported DNA wrapping on to SWNTs through relatively weak p-stacking. The functionalization of CNT is an effective way to prevent nanotube aggregation, Which helps to better disperse and stabilize the CNT's with in a polymer matrix [5].

There are several approaches for functionalization of CNTs including defect functionalization, covalent functionalization and non-covalent functionalization [6].Isoniazid, also known as isonicotinyl hydrazide (INH), is an antibiotic used as a first-line agent for the prevention and treatment of both latent and active tuberculosis [7]. It is effective against mycobacteria, particularly Mycobacterium tuberculosis. It is also active against some atypical types of mycobacteria, such as M. kansasii and M. xenopi. Isoniazid is an organic compound that is available in tablet, syrup, and injectable forms.The anti-proliferative and proapoptotic effect of Metformin in in

vitro studies was observed in concentrations that are usually seen in diabetic patients treated with Metformin (approximately 1.5 grams per day). However, there is inter-individual variation in drug response and the role of drug-metabolizing enzymes and drug transporters are starting to form the focus of these research projects [8].

COMPUTATIONAL METHODS

In this work, the carriers metformin drug molecule with covalently functionalized CNT (5,0) towel length by computational methods. We considered a (5,0) CNT of 60 carbon atom and 10 hydrogen atom. The optimizations of metformin and F-SWCNT were individually in gas and water phases. Metformin molecule loaded with F-WCNT was geometrically optimized (Fig1).The electronic and structural properties of the (5,0) zigzag single-walled carbon nanotube (SWCNT) and metformin adsorbed on SWCNT were derived by means of density functional theory (DFT) method (Hohenberg and Kohn, 1964; Parr andYang, 1989) with the B3LYP functional (Becke's three-parameter hybrid exchangeFunctions using the Lee–Yang–Parr gradient-corrected correlation) (Becke,1993; Lee Met al., 1988). For all systems, a geometry optimization calculation was Performed using 6-311G(d) basis set. All calculations were carried out using the Gaussian 09 program [9]. The binding energy was calculated using the following equation [10].

$$Eb=E(FM/SWCNT)-E(SWCNT)-E(FM) \quad (1)$$

where E(FM/SWCNT) is the total electronic energy of the adsorbed metformin

Molecule on the f-SWCNT after full geometry optimization. E(SWCNT) and E(FM) are the electronic energies of the SWCNT with functionalized group, and the metformin molecule respectively. The energy corresponding to HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) respectively indicate the ionization potential of the molecule and electron affinity value. It is known that DFT methods give lower LUMO–HOMO gapsthan HF methods, and that is why we use a hybrid method B3LYP for the calculation of the LUMO–HOMO gaps [11]. A high LUMO–HOMO energy gap represents greater stability and low reactivity of the chemical species. Also using the Koopmans' theory I= -EHOMO is the first vertical ionization energy and A= -ELUMO is the electron affinity of the molecule [12].

RESULTS AND DISCUSSION:

In Tables 1 and 2, the quantum molecular descriptors of all structures for both sidewall-attachment and tip-attachment configurations have been listed. The properties include the HOMO-LUMO energy gap, chemical hardness, and electrophilicity index. Chemical hardness is defined as the reactivity index. This reactivity is related to the resistance to change in the electron number or deformation of the electron in molecules.

In contrast to hard molecules, molecules or materials with small chemical hardness possess a high chemical reactivity. In the tip-attachment configuration, chemical hardness values of cyclophosphamide, complexes I and II are given by 3.54, 0.27 and 1.09 eV, respectively. Thus, it is clearly realized that the chemical hardness of the cyclophosphamide drug is greater than the chemical hardness of complexes. From the chemical viewpoint this indicates that the drug molecule is more stable. Hence, the reactivity of the complexes is higher than that of the drug molecule. Furthermore, since the armchair (4,4) nanotube-based complex has the greatest

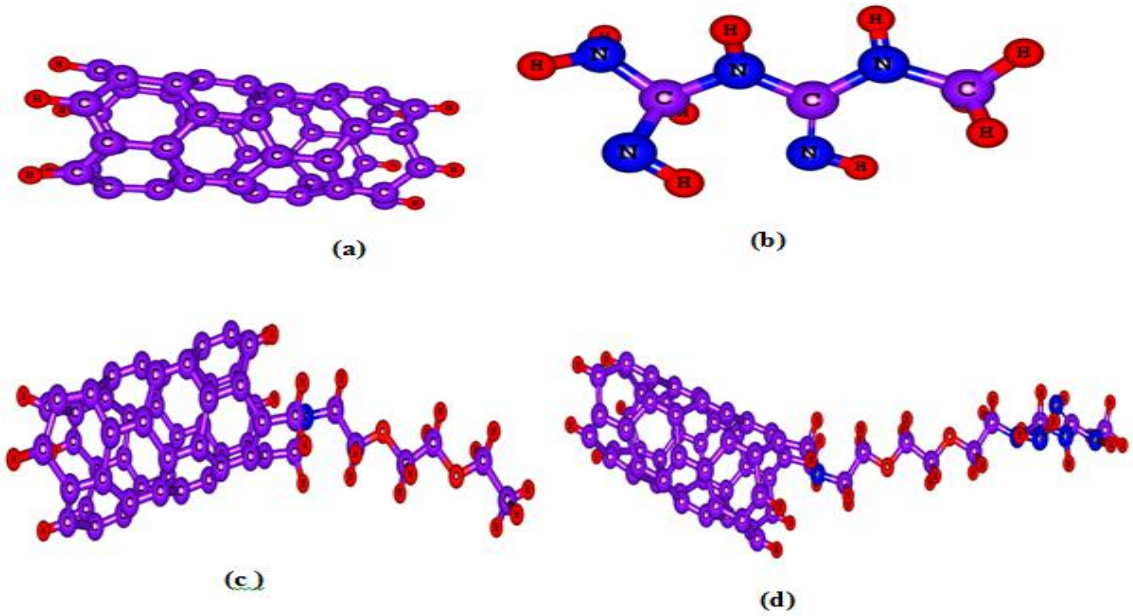

Fig.1. Optimized geometries of (a) (5,0) zigzag SWCNT, (b) metformin drug molecules, (c) (5,0)-SWCNT functionalized (d) functionalized (5,0)-SWCNT with one and one FM drug molecules.

chemical hardness among the complexes, it has the lowest chemical reactivity. In contrast, the zigzag (8,0) nanotube-based complex stays completely in the opposite side, it has the lowest chemical hardness and the greatest chemical reactivity. Then, charge transfer takes place between the functional group and tip of nanotube.

Density-of-states (DOS) is an important concept of solid physics, which represents the number of states in unit energy interval, since energy levels are contiguous, so DOS can be plotted as curve map. In isolated system (such as molecule), the energy levels are discrete, the concept of DOS is questionable and some people argued that DOS is completely valueless in this situation. However, if the discrete energy levels are broadened to curve artifically, DOS graph can be used as a valuable tool for analyzing the nature of electron structure.

The original total DOS (TDOS) of isolated system can be written as:

$$TDOS(E) = \sum_i \delta(E - \varepsilon_i)$$

Where $\{\varepsilon\}$ is eigenvalue set of single-particle Hamilton, δ is Dirac delta function. If δ is replaced by broadening function F(x), such as Gaussian, Lorentzian and pseudo-Voigt function, we get broadened TDOS. Let us see an example, from which we can know what new information can be revealed by DOS map. This is a water molecule under HF/6-31G* wavefunction in ground state, the orbitals are canonical MOs; fragment 1 is defined as P-shells of oxygen (correspond to 2p atomic orbitals), fragment 2 is defined as two hydrogens, both original and broadened TDOS/PDOS/OPDOS are shown in the graph below. Notice that the height is only meaningful for lines (original data) but not for curves, left-axis and right-axis correspond to TDOS/PDOS and OPDOS respectively. The vertical dashed line indicates the position of HOMO level. The original DOS graph is discrete comb-like lines, from which we cannot obtain any additional information other than energy level distribution, it is impossible to distinguish different type of

lines and degenerate energy levels owing to the overlapping. However if the discrete lines are broadened, from the height of black curve (TDOS) we can clearly know how dense the energy levels are distributed everywhere. Besides, the curves corresponding to TDOS, PDOS (red line for fragment 1, blue line for fragment 2) and OPDOS (green line) no longer overlap, we can clearly identify characters of each orbital by observing these curves. For example, the red curve is high and nearly approach's black line in the region of -0.9 a.u. to -0.3 a.u., so we can be concluded that 2p atomic orbitals of oxygen have significant contribution to corresponding Mos. Since the green curve is greater than or less than zero respectively denote corresponding MOs are favorable or unfavorable for forming chemical bond between oxygen 2p orbitals and hydrogen's, it is shown that the orbital pointed by the leftmost arrow is very helpful for bonding, while the high-energy state orbitals (> 0.1 a.u.) are not conducive for bonding (namely anti bonding character), fortunately they haven't been occupied, otherwise the molecule must be broken. These conclusions can be confirmed further by observing is surfaces of corresponding MOs.

Table 1. Binding energies of FM, functionalized (5,0) zigzag SWCNT with one FM drug molecules, respectively

Parameters	metformin	F-SWCNT	FM-SWCNT
Binding energy in gas phase (ev)	-10717	-66112.5	-76806.8
Binding energy in water phase(ev)	-10722.2	-66114.1	-1799098
Dipole moment in gas phase (ev)	3.9561	6.6482	6.6925
Dipole moment in water phase(ev)	4.9612	3.6506	10.2663

Table 2. Quantum molecular descriptors for functionalized (5.0) zigzag SWCNT, FM, and Functionalized SWCNT with FM drug molecules in gas phase (eV)

states	$E_{ads(ev)}$	$I=-E_{HOMO/ev}$	$A=-E_{LUMO/ev}$	$Egap=E_{LUMO}-E_{HOMO}$	$\mu=-(I+A)/2$	$\eta=(I-A)/2$	$S=1/2\eta$	$W=\mu^2/2\eta$
Metformin	------	5.90446	1.938583	3.965877	-3.921521	1.982938	0.991469	15.24714
F-CNT	-------	3.935944	2.983796	0.952148	-3.45987	0.476074	0.238037	2.849469
FM-CNT	0.8326	4.141666	2.845287	1.29638	-3.49348	0.64819	0.324095	3.955377

Table 3. Quantum molecular descriptors for functionalized (5.0) zigzag SWCNT, FM, and functionalized SWCNT with FM drug molecules in solvation phase(water) (eV)

states	$E_{ads(ev)}$	$I=-E_{HOMO/ev}$	$A=-E_{LUMO/ev}$	$Egap=E_{LUMO}-E_{HOMO}$	$\mu=-(I+A)/2$	$\eta=(I-A)/2$	$S=1/2\eta$	$W=\mu^2/2\eta$
Metformin	-----	6.08161	2.413432	3.668178	-4.24752	1.834089	0.917044	16.5448
F-CNT	-----	4.293509	2.941073	1.352436	-3.61729	0.676218	0.338109	4.424088
FM-CNT	1.0551	4.292149	2.938352	1.353797	-3.61525	0.676899	0.338449	4.423543

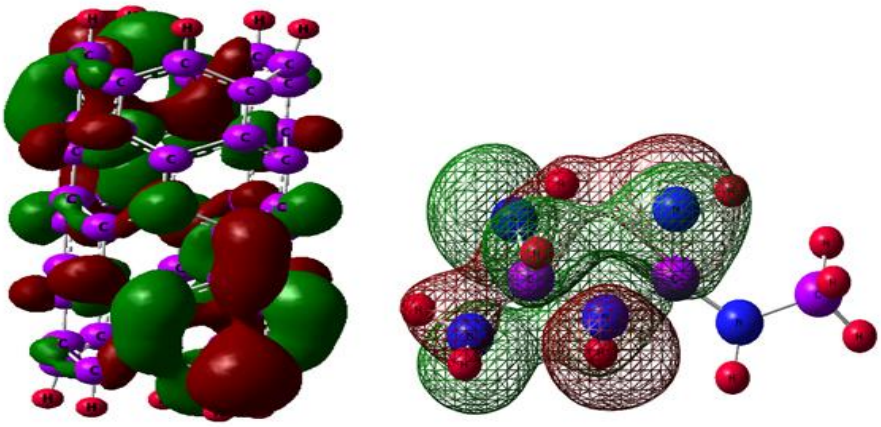

Fig. 2. DFT calculated HOMO and LUMO orbitals for (5,0)-SWCNT and FM drug Molecules.

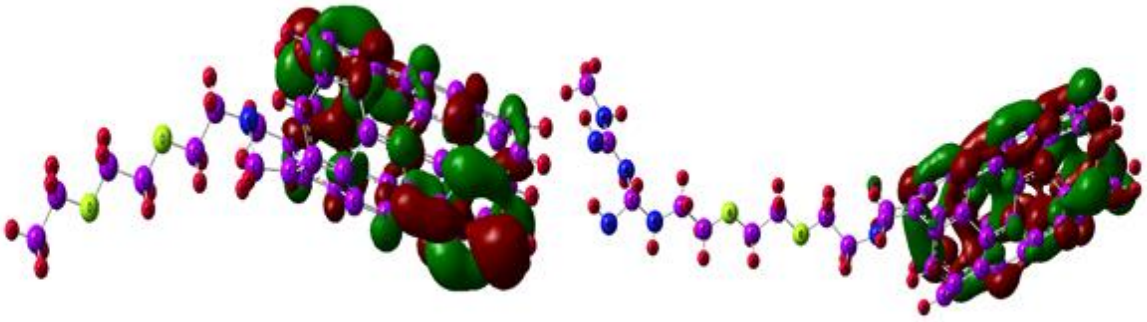

Fig. 3. DFT calculated HOMO and LUMO orbitals for functionalized (5,0)-SWCNT with one F-M drug molecules.

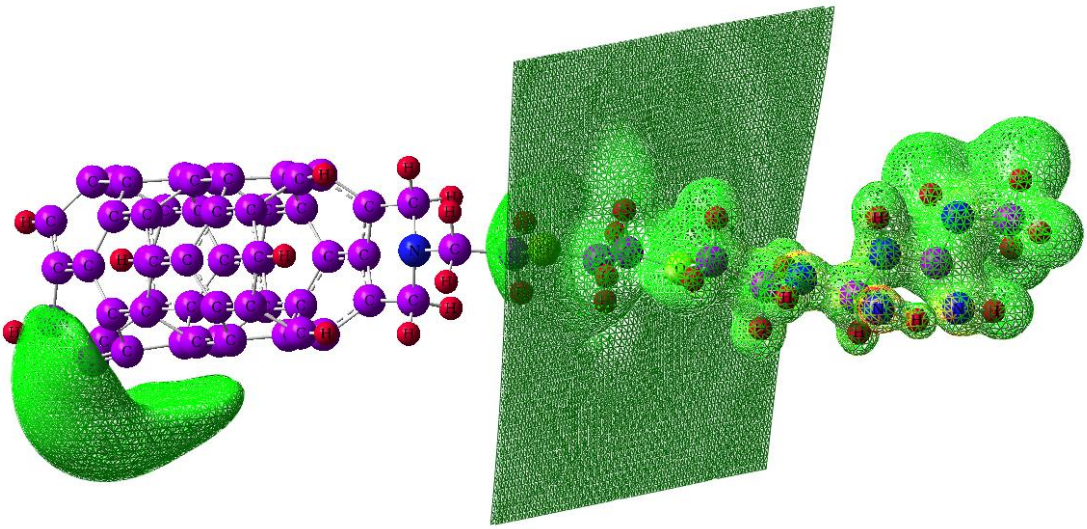

Fig. 4. The molecular electrostatic potential surface of metformin on the SWCNT.

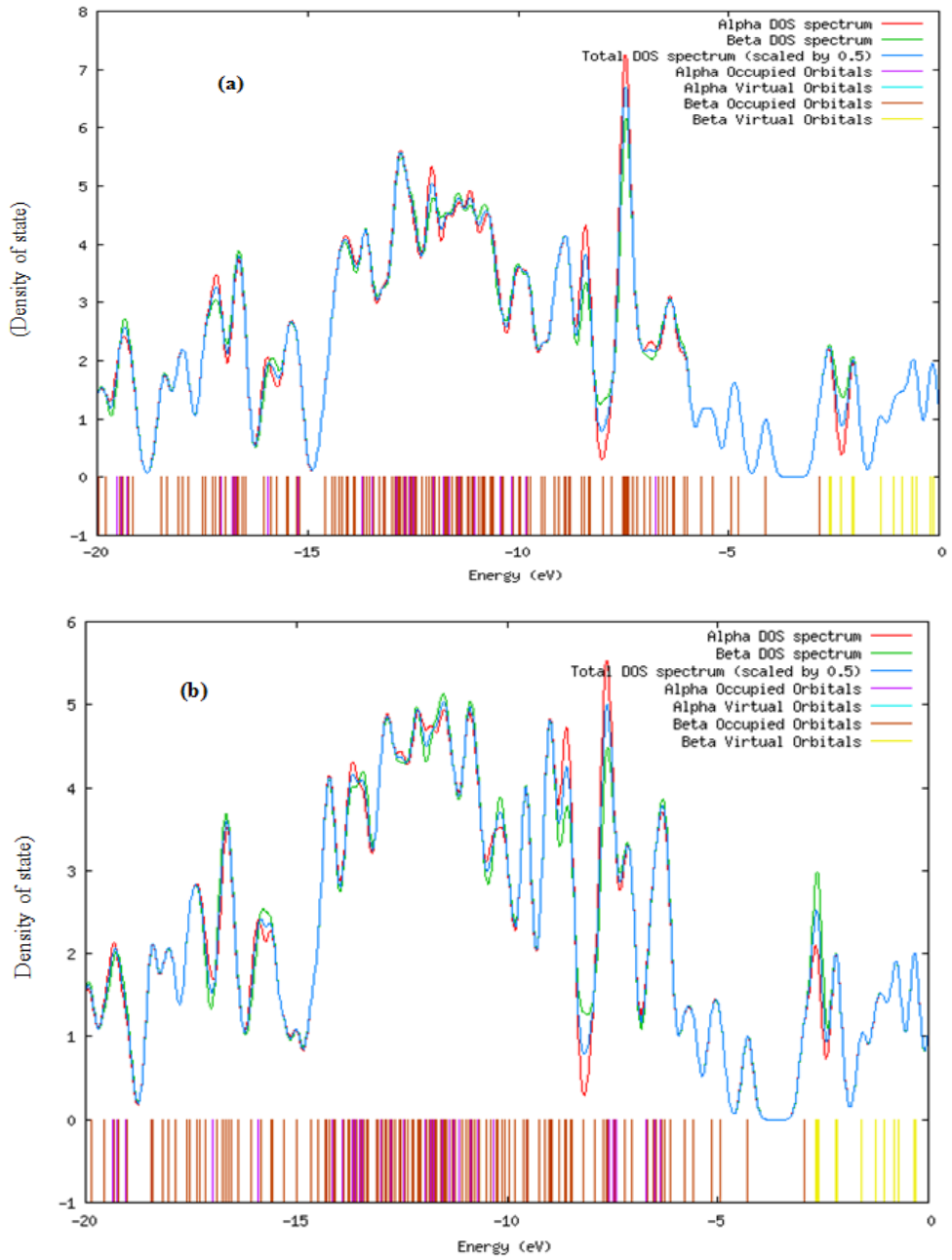

Fig. 5. Total densities states (**TDOS**) for interaction of functionalized (5,0)-SWCNT with metformin drug molecules in ☹a) gas phase, (b) water phase

CONCLUSION:

We have performed DFT calculations for f-SWCNTs in order to assess their roles as nanovectors for drug delivery of metformin. Our results from binding energies (to covalently bind metformin to f-SWCNTs) establish that binding f-SWCNTs in water phase is easier than binding in gas phase. From Tables 1and 2, we can conclude that increasing metformin substitution in functionalized CNT in solution results in decreasing in global hardness, which means that their stability decreases.

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