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Effects of carbon nanotubes on properties of the fluorouracil anticancer drug: DFT studies of a CNT-fluorouracil compound

ABSTRACT

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Density functional theory (DFT) calculations were performed to investigate the effects of a carbon nanotube (CNT) on the properties of the fluorouracil (F-Uracil) anticancer drug. To achieve the purpose, a molecular model including both of F-Uracil and CNT molecules was created to represent the CNT@F-Uracil compound. The optimized parameters indicated that the new compound could show new properties different from the original F-Uracil. The obtained chemical shielding parameters also indicated that the electronic properties of oxygen and fluorine atoms could detect notable changes whereas those of carbon and hydrogen atoms are almost negligible. Moreover, the most changes of properties were observed for nitrogen atom number one, in which make the connection link of the CNT group to the F-Uracil molecule. The changes of properties of other nitrogen atom are almost negligible.

Keywords: *Carbon nanotube; Fluorouracil; Density Functional Theory; Chemical Shielding.*

INTRODUCTION

Since the discovery of carbon nanotubes (CNTs), considerable efforts by numerous researchers have indicated that novel properties and applications could be expected for the carbon based nanomaterials [1-3]. Medicinal and pharmaceutical applications of CNTs among their various applications have been drastically highlighted due to their importance in the fields of life sciences [4-6]. Earlier studies demonstrated that the CNTs could be chemically or physically functionalized by other atoms or molecules, in which the combined structures could show new properties [7-9]. The works also indicated that the molecular structures of drugs could be attached to the CNTs for their better delivery processes into the living systems [10].

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Fluorouracil (F-Uracil) is an anticancer drug, which is constructed by a 5-fluorouracil structure of the di-keto form of pyrimidine uracil nucleobase [11]. For a long time, F-Uracil has been used in treatments of cancers such as colorectal cancer, pancreatic cancer, and breast cancer [12-14]. Since it has a pyrimidine structure, nitrogen number one of the ring is a proper atomic site for connecting to other atoms or molecules, in which it is connected to the pentose sugar group in the original uracil nucleotide [11]. Using this property, we attached a F-Uracil molecule to a molecular CNT group through nitrogen number one of the pyrimidine ring to detect the effects of CNTs on properties of the F-Uracil structure for the possible drug delivery processes.

Within this work, we performed density functional theory (DFT) calculations to investigate the properties of the F-Uracil anticancer drug in combination with a CNT group. To systematically achieve the purpose of study, the individual structure of F-Uracil was optimized at the first step of calculations and then the combined structure including the F-Uracil and the CNT group was optimized (Figure 1). To detect the effects of CNT on the properties of F-Uracil, the properties of F-Uracil were evaluated before and after combinations (Tables 1 and 2). Nuclear magnetic resonance (NMR) properties for F-Uracil have been reproduced by calculations to better detect the electronic properties of F-Uracil during the combination process. It is noted that the major question of this work is to investigate the effects of attached CNT on the properties of F-Uracil anticancer drug, which is important in better clarifying the roles of CNTs for drug delivery processes in living systems.

EXPERIMENTAL

Through this work, DFT calculations were performed using the B3LYP exchange-correlation functional and the 6-31G* standard basis set as implemented in the Gaussian 98 package [15]. All atomic optimization processes were performed to minimize the structures of individual F-Uracil and the combined CNT@F-Uracil structures (Figure 1). The representative CNT is a (5,0) zigzag nanotube with the stoichiometry of $C_{40}H_{10}$, in which the

hydrogen atoms saturate the carbon atoms of the tubular tips. To attach the CNT to the F-Uracil, one hydrogen atom of CNT and the hydrogen atom of nitrogen number one of F-Uracil were removed to make possible the molecular connection (Figure 1, panel b). It is important to note that the tip of CNT is a proper site for the molecular attachments in order to keep the original sp^2 hybridization of carbon atoms. By optimization processes, dipole moments, energy levels of the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO), and binding energies were obtained. It is noted that the value of binding energy was obtained by the equation $E_{\text{Binding}} = E_{\text{CNT}} + E_{\text{F-Uracil}} - E_{\text{CNT@F-Uracil}}$. For better achieve the purpose, isotropic and anisotropic chemical shielding parameters were also obtained for the F-Uracil counterpart of the optimized structures. The chemical shielding parameters could define the NMR properties of matters, which are important elements in determining the electronic properties of matters [16]. The gauge-independent atomic orbital approach (GIAO) [17] was employed to generate the chemical shielding parameters. The calculated parameters of this work are summarized in Tables 1 and 2.

RESULTS AND DISCUSSION

To determine the effects of CNTs on the properties of F-Uracil, which is important in the drug deliveries, we performed DFT calculations to evaluate the structural and electronic properties of F-Uracil in two states of before and after combination. Two models of this work are F-Uracil and CNT@F-Uracil structures (Figure 1), which were optimized at the first step and their properties were evaluated after optimization (Tables 1 and 2). In the original F-Uracil, nitrogen atom number one of the pyrimidine ring has one hydrogen atom. The atoms at the tubular tips of original CNT are also saturated by the hydrogen atoms. To make possible the combination of CNT and F-Uracil molecules, the hydrogen atom of nitrogen atom number one and also one hydrogen atom of the tubular tip were removed. By doing these removals, the combined model was constructed as the CNT@F-Uracil compound (Figure 1, panel b). The optimization process yielded a length of 1.39 Å for the

connecting length between the carbon atom of the tubular tip and the nitrogen atom number one of the pyrimidine ring. For this molecular connection, a value of 3.89 eV was obtained by calculating energies for the structures of the combined compound and the individual counterparts. Moreover, comparing the optimized bond lengths of F-Uracil in panels (a) and (b) of Figure 1 reveals that the lengths were slightly changed in the CNT@F-Uracil model. Among the obtained optimized lengths, the most notable changes could be observed for C2-N1 and C6-N1 bonds, in which both are located close to the linking region. Looking at the contents of Table 1 reveals that the value of dipole moment is notably larger for the CNT@F-Uracil model than the F-Uracil model. The values of energy levels of HOMO and LUMO also detected notable changes in the two models, in which their Δ values are smaller in the combined model. The trend means that the levels of HOMO and LUMO are closer in the CNT@F-Uracil compound than the original F-Uracil molecule. It is important to note that the energy difference between HOMO and LUMO is dominant in conducting properties of matters, in which smaller differences could yield better conducting properties. The obtained properties by optimization processes indicated that the properties of F-Uracil are changed from the individual molecule to the combined compound, in which the expected new properties could be observed for the CNT@F-Uracil compound with respect to the original F-Uracil.

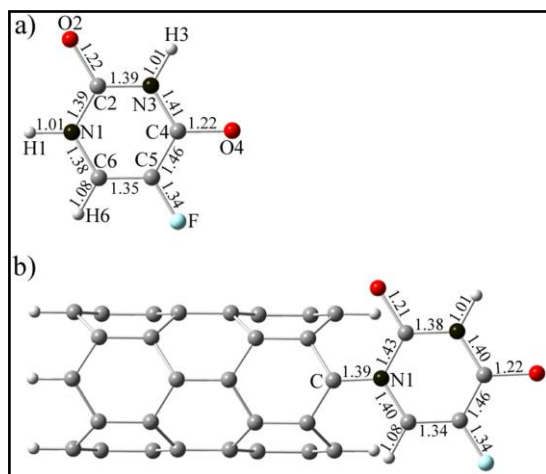


Fig. 1. The models of study are F-Uracil (a) and CNT@F-Uracil (b). The optimized bond lengths of F-Uracil are included in panels (a) and (b).

Table 1. Optimized properties*

Property	F-Uracil	CNT@F-Uracil
Stoichiometry	C ₄ H ₃ FN ₂ O ₂	C ₄₄ H ₁₁ FN ₂ O ₂
Dipole Moment /Debye	3.90	5.78
HOMO /eV	- 6.78	- 4.26
LUMO /eV	- 1.38	- 3.09
Δ (HOMO-LUMO) /eV	5.40	1.17
Binding Energy /eV	—	3.89

* See Figure 1 for the models.

In addition to the optimized properties, NMR properties including isotropic and anisotropic chemical shielding parameters were also generated for the atoms of F-Uracil in the original and combined states (Table 2). Since the chemical shielding parameters are arisen from the electronic sites of atoms, they could reveal insightful information about the electronic properties of matters in the atomic scales. The isotropic term implies for the average value of chemical shielding tensors whereas the anisotropic term implies for the deviation of chemical shielding tensors from the spherical orientations [16]. It is important to note that the NMR parameters could be measured by experiments and they could also be reproduced by quantum computations [18].

Table 2 presents the atomic scale NMR properties for F-Uracil in the original and combined states. Nitrogen atom number one is the most important atom of F-Uracil because it makes possible the connection between the CNT and F-Uracil counterparts in the CNT@F-Uracil compound. Since the environments of N1 in the original and combined structures are completely different, the values of NMR properties for this atom in the two structures show significant changes. Decreasing the value of isotropic term of nitrogen atom number one in the CNT@F-Uracil compound indicates that the strength of C-N bond is more than the strength of N-H bond. Due to these differences, the anisotropic term of nitrogen atom number one also detects the effects of being in the new structure. For nitrogen number three, which is located farther than the region of connection, the changes of chemical shielding parameters in the

original F-Uracil and CNT@F-Uracil are almost negligible. As seen by the values of chemical shielding parameters for hydrogen atoms numbers one, three, and six, the magnitudes of parameters are smaller than other atoms because of the low electronic densities of hydrogen atoms. Due to the mentioned behavior, the changes of chemical shielding parameters between the original and combined models are negligible for the hydrogen atoms. Examining the values of chemical shielding parameters for carbon atoms of F-Uracil in the original and combined models indicates that the properties of carbon atoms are almost remained unchanged during the combination process.

Table 2. NMR properties for F-Uracil*

Atoms	F-Uracil	CNT@F-Uracil
N ₁	141; 52	99; 114
H ₁	27; 8	—
C ₂	53; 65	52; 71
O ₂	29; 399	19; 492
N ₃	99; 51	98; 48
H ₃	26; 5	26; 5
C ₄	43; 83	44; 80
O ₄	59; 613	72; 639
C ₅	53; 73	52; 72
F	352; 109	341; 119
C ₆	72; 117	68; 104
H ₆	26; 4	24; 12

* See Figure 1 for the models and atomic numbers. Isotropic and anisotropic chemical shielding /ppm are respectively written in each row, which are separated by “;”.

Interestingly, notable changes are observed for the chemical shielding parameters of oxygen atoms in the two structures, in which both isotropic and anisotropic terms detect the effects of attached CNT. The oxygen atoms has excess of electrons in comparison with hydrogen, carbon, and nitrogen atoms; therefore, the changes of its chemical shielding parameters are more notable, which defines the effects of CNT on the electronic properties of oxygen atoms. The electronic properties of fluorine atom, which is the symbol of F-Uracil structure, also detect the effects of attached CNT as could be seen by changes the values of chemical shielding parameters from the

original structures to the combined compound. It is important to remember that the chemical shielding parameters could well describe the electronic properties of atoms, in which they are considered as proper elements to study the electronic properties of matters.

CONCLUSIONS

Our DFT study indicated that the structural and electronic properties of F-Uracil could detect the effects of attached CNT. The values of dipole moment, HOMO, LUMO, and bond lengths detect the effects of attached CNT. Moreover, NMR properties indicated that the properties at the atomic sites of F-Uracil also detect the effects of attached CNT, in which the properties of oxygen and fluorine atoms detect the most significant effects whereas those of carbon and hydrogen atoms detect the most negligible effects. For nitrogen atoms, the properties of nitrogen number one, which makes the connection between the F-Uracil and CNT structures, detect notable changes whereas the changes of properties of nitrogen number three are almost negligible. And as a final note, new properties for F-Uracil in the CNT@F-Uracil could yield new application for this anticancer drug.

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