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Investigating Stability and Solubility Properties of Cyclophosphamide-Functionalized (8,0) and (4,4) CNT Complexes in Water: Computational Studies

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ABSTRACT

Stabilities and quantum molecular descriptors of cyclophoshphamide (an anticancer drug)-functionalized (8,0) zigzag and (4,4) armchair carbon nanotubes (CNTs) complexes in water were studied using density functional theory (DFT) calculations. Two attachments namely the sidewall- and tip-attachments are considered for the model constructions. Calculations of the total electronic energy (E_t) and binding energy (E_b) of all complexes indicates better thermodynamic stabilities for the sidewall-attachment of cyclophosphamide than the tip-attachment. On the other hand, results from chemical hardness show that drug-functionalized (8,0) zigzag and (4,4) armchair complexes in the tip-attachment configuration possess the smallest and greatest chemical hardness, respectively. By computing the solvation energy, it is found that the solution of the drug and all complexes are spontaneous in water. Furthermore, chirality and attachment configuration have no effects on solvation energy of complexes.

Keyword: Carbon nanotubes; Cyclophosphamide drug; Density functional theory; Drug delivery; Quantum molecular descriptors.

1. INTRODUCTION

The main purpose of chemotherapy is to destroy the cancer cells whilst minimizing the side effects to healthy tissues [1]; however, chemotherapy with anti-cancer drugs is often unsuccessful due to the toxic and side effects. Moreover, the method is not sufferable for patients either [2]. Therefore, finding the methods on drug delivery systems (DDSs) has gained increasing at-tention in recent years. In this technique, the cancerous tissues are selectively targeted with minimal damage to normal tissues [3, 4]. With development of nanotechnology, it has been found out that few nanomaterial-based products could have the ability to be used as drug carriers in DDSs [5, 6]. The current DDSs are mainly liposomes [7], dendrimers [8], polymers [9], virus-
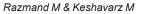
Int. J. Bio-Inorg. Hybd. Nanomat., Vol. 3, No. 1 (2014), 49-55

Razmand M & Keshavarz M

based systems [10], cyclodextrins [11], nanoparticles [13], fullerences [14], and nanotubes [15]. Carbon nanotubes (CNTs) are the most advanced nanovectors for favorable drugs and biomulecules deliveries in living systems [16, 17]. Compared to other nanomaterials, CNT possesses interesting properties such as large surface area and distinct optical features like strong Raman shift and high absorption in the near infrared (NIR) region, which make possible biomedical applications in detections and imaging processes [18]. Because of large surface area of CNT, multiconjugations of different molecules are allowed to be loaded on the CNT sidewalls through chemical or physical bonds [19]. CNT is recognized as a novel efficient drug transporter; therefore, there is demand to accelerate its optimum development, which requires a better understanding of the structural properties of drug-CNT complexes. Density function theory (DFT) is widely used to predict the structural and spectroscopic parameters of molecules [20].

DFT plays as a very useful tool to describe the chemical reactivity, stability and site selectivity of complex systems using properties such as chemical hardness, chemical potential, and electrophilicity indices. The obtained DFT information enables comprehension of features of molecules with respect to their stability [21]. Cyclophpsphamide is a widely used chemotherapy drug with high selectivity and a wide spectrum of activities [22]. With respect to CNT drug delivery systems, different complexes such as 2-methylheptyl-isonicotinate (MHI)-CNT [23], isoniazid-CNT [24], $Sn(CH_3)_2$(N-acetyl-L-cysteinate)-CNT [25], doxorubicin-CNT, RNAs (siRNAs)-CNT [26] have been reported. Within this work, the stability, solubility, and quantum molecular descriptors of the nanovector-azomethine ylide-cyclophosphamide complex are investigated using DFT calculations. The representative models of (8,0) zigzag and (4,4) armchair CNTs are considered for the combinations with the cyclophosphamide.

2. COMPUTATIONAL DETAILS

Investigation of the stabilities and quantum mechanical descriptors of two complex systems are per-
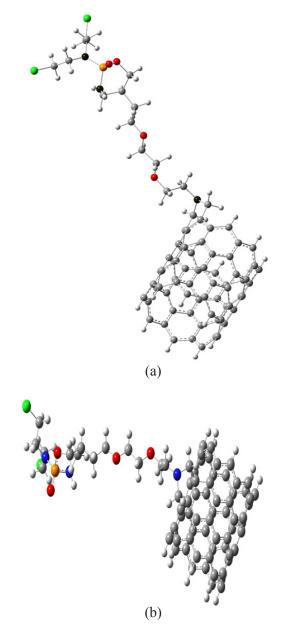

(a)

(b)

Figure 1: (8,0) Zigzag CNT-azomethine ylide-cyclophosphamide: (a) tip-attachment configuration; (b) sidewall-attachment configuration.

formed using DFT calculations with hybrid functional B3LYP and a 6-31G* basis set implemented in the Gaussian 03 software [27]. These complexes include the (8,0) zigzag CNT-azomethine ylide-cyclophosphamide (complex I; Figure 1) and the (4,4) armchair CNT-azomethine ylide-cyclophosphamide (complex II; Figure 2). The tubular ending atoms of CNTs are saturated with hydrogen atoms to achieve the sp^2 hybridizations for the atomic valance shells. Two softwares of Nanotube Modeler [28] and GaussView were used for our structural visualizations [29]. To
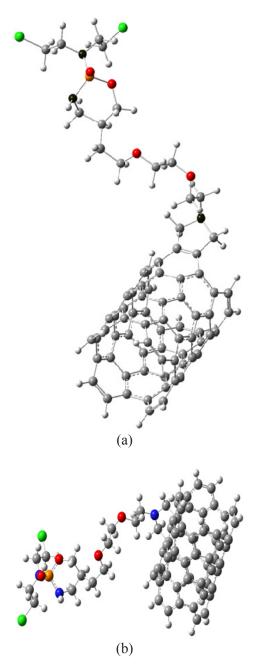
(a)

(b)

Figure 2: *(4,4) Armchair CNT-azomethine ylide-cyclophos-phamide: (a) tip-attachment configuration; (b) sidewall-at-tachment configuration.*

make the complex structures, the cyclophosphamide anticancer drug is separately attached to the sidewall and tip of CNTs through a molecular linker of azomethine yilde (as a functional group). The model structures including the individual and complex molecules are geometrically optimized in the gas and solvent phases. From the optimized structures, the parameters of total energies, binding energies, and HOMO-LUMO energy gaps have been evaluated. Moreover, the

quantum molecular descriptors of ionization potentials, electron affinities, chemical hardnesses, chemical potentials, and electrophilicities are estimated using E_{HOMO} and E_{LUMO} for all optimized structures.

The binding energies of the complexes are evaluated using eq. (1):

$$E_b = E_t(\text{Complex}) - E_t(f-\text{nanovectors}) - E_t(\text{drug}) \qquad (1)$$

where, E_t (Complex), E_t (f-nanovectors) and E_t (drug) define the total electronic energy of the complexes, functionalized nanovectors (nanotube), and drug, respectively.

Chemical hardness of an N-electron system can be expressed as eq. (2):

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(r)} \qquad (2)$$

where, E and v(r) are the total energy and external potential, respectively. The finite difference approximation is used to acquire the operational definition of hardness:

$$\eta = \frac{1}{2}(I - A) \qquad (3)$$

in which I indicates the ionization potential, and A indicates the electron affinity of the system. Further approximation can be imposed on the equation by the Koopmans Theorem [30]. Therefore one arrives at:

$$\eta = \frac{1}{2}\left(E_{LUMO} - E_{HOMO}\right) \qquad (4)$$

where HOMO means the highest occupied molecular orbital and LUMO means the lowest unoccupied molecular orbital.
The electrophilicity index is calculated as [31]:

$$\omega = \frac{\mu^2}{2\eta} \qquad (5)$$

The property of free Gibbs energy of solvation has been also evaluated with respect to the energy differences of optimized structures in gaseous and in watery phases. To include the water salvation effects, we used the Polarizable Continuum Model (PCM) as implemented in the Gaussian software. It is noted that because of chemical functionalization, we did not

Int. J. Bio-Inorg. Hybd. Nanomat., Vol. 3, No. 1 (2014), 49-55

Razmand M & Keshavarz M

Table 1: *Total electronic energy (E_t), binding energy, and quantum molecular descriptors of all structures for tip-attachment configuration in the solvent phase.*

Parameters	Drug	Complex I	Complex II
E_t/eV	-48913.85	-129629.38	-129626.93
E_b/eV	-	-32.38	-32.38
E_{HOMO}/eV	-6.80	-3.81	-4.63
E_{LUMO}/eV	0.27	-3.27	-2.45
E_{LUMO}-E_{HOMO}/eV	7.07	0.54	2.18
I=-E_{HOMO}/eV	6.80	3.81	4.63
A=E_{LUMO}/eV	-0.27	3.27	2.45
η/eV	3.54	0.27	1.09
μ/e	3.27	3.54	3.54
ω	1.51	23.22	5.74

include basis set super position error calculations in our work, which is important to be calculated for the physical interactions. Moreover, the used basis set of this work is acceptable as a proper one to yield reliable results.

3. RESULTS AND DISCUSSION

3.1. Stability of complexes
The data from sidewall-attachment and tip-attachment configurations in solvent phase are shown in Tables 1

and 2, which display the total electronic energy (E_t), binding energy (E_b), and quantum molecular descriptors. The tables show that the chirality of the nanotubes does not influence on the substantial effects on the total electronic energy; both the (4,4) armchair nanotube-based complex (Figure 2) and the (8,0) zigzag nanotube-based complex (Figure 1) seemed to have approximately the same total values of electronic energy, E_t = (~-129626 eV). Negative values of E_t for three complexes from thermodynamic consideration imply for the stabilities of these complexes. Comparing the E_t values of Tables 1 and 2 shows that the to-

Table 2: *Total electronic energy (E_t), binding energy, and quantum molecular descriptors of all structures for sidewall-attachment configuration in the solvent.*

Parameters	Drug	Complex I	Complex II
E_t/eV	-48913.85	-129657.6	-129657.68
E_b/eV	-	-32.33	-32.34
E_{HOMO}/eV	-6.80	-3.89	-3.84
E_{LUMO}/eV	0.27	-3.16	-3.18
E_{LUMO}-E_{HOMO}/eV	7.07	0.63	0.66
I=-E_{HOMO}/eV	6.80	3.89	3.84
A=E_{LUMO}/eV	-0.27	3.16	3.18
η/eV	3.54	0.31	0.33
μ/e	3.27	3.53	3.51
ω	1.51	20.10	18.66

Razmand M & Keshavarz M

Int. J. Bio-Inorg. Hybd. Nanomat., Vol. 3, No. 1 (2014), 49-55

tal electronic energies of the complexes are affected by the attachment configurations. The total electronic energy values for the two complexes in the sidewall-attachment configurations were lower than the corresponding values in the tip-attachment configurations. Therefore, the stability of the sidewall-attachment is due to the decreasing E_t value of the complexes. In the tip-attachment configuration, complex I and II had binding energy values of -32.38 and -32.38 eV. In addition, binding energies of the two complexes in the sidewall-attachment configurations were -32.33 and -32.34 eV. Similar to the total electronic energy, the chirality of nanotubes had no effect on the binding energy. Hence, from at thermodynamic point of view attachment of cyclophosphamide to both armchair and zigzag CNT could be expected.

3.2. Quantum molecular descriptors

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 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.

Table 3: Solvation energy of two complexes in both tip-attachment and sidewall-attachment configuration; all values are in eV/ unit.

Configuration	Complex I	Complex II
Tip-attachment	-0.81	-0.81
Sidewall-attachment	-0.80	-0.81

Table 2 illustrates the chemical hardness value of the two complexes in the sidewall-attachment configuration as 0.32 and 0.31eV respectively. The chemical hardness of complex I is slightly increased in the sidewall-attachment configuration that mentions a small decrease in chemical reactivity of the two complexes. As a result, the charge transfer between the functional group and the nanovector is increased. On other hand, the chemical hardness of complex II is decreased considerably. This decrease implies for high charge transfer between the functional group and the nanotube sidewall that results in increasing the complex reactivity.

Tables 1 and 2 show that the complex I possesses a bigger electrophilicity in the tip-attachment configuration. Hence, complex tends to behave as an electrophil agent. The comparison of electrophilicity in Tables 1 and 2 expresses that, in the sidewall-attachment configuration, the electrophilicity indexes of complex I and II are lower than its corresponding values in the tip-attachment configuration. However, the value of electrophilicity of complex II in the sidewall-attachment configuration is significantly larger than its value in the tip-attachment configuration. This shows that the complex II behaves more electrophilic in the sidewall-attachment than the tip-attachment.

3.3. Solubility in water

The solvation energies of the cyclophosphamide drug and two complexes in both attachment configurations were calculated with attention to the difference between the total electronic energy in the gas phase and in the presence of water. The solvation energy value of drug obtained as -0.5 eV and solvation energy of the two complexes for both attachment configurations is depicted in Table 3. It is clear from this Table that chirality or attachment configuration has no effects on solvation energy of complexes. In both of the attachment configurations, all complexes possess negative

solvation energies; this fact implies that the solvation of drug and all complexes in water are spontaneous. Consideration of the solvation energies of the cyclophospamide drug and complexes in this study reveals that the solubility of the cyclophosphamide anticancer drug in water is increased by functional carbon nanotube and nanocone with cyclophosphamide as a nanovector for drug.

4. CONCLUSIONS

Effects of nanotube chiralities (zigzag or armchair) and drug attachment configuration on thermodynamic stability, quantum descriptors, and solubility in water of cyclophosphamide-azomethine-nanovector complexes were theoretically performed using DFT calculations. The results of this investigation indicate some trends. First, total electronic energy is affected by the attachment configuration. Complexes with the sidewall-attachment have lower total electronic energy, so possess greater thermodynamic stability. However, the attachment configuration does not have any effects on the binding energy of complexes. Also, both total electronic energy and binding energy are not influenced by chirality of nanotubes. Second, chirality types have considerable effects on chemical hardness. In contrast, the attachment configuration has slight effects on chemical hardness, except armchair (4,4) CNT-based complex. The greatest and smallest chemical hardness belong to drug-functionalized zigzag (8,0) and armchair (4,4) complexes respectively in tip-attachment configuration. Third, solvation energy of drug and all complexes is negative, and then the solution of these complexes is spontaneous in water. In addition, the solvation energy of complexes is not affected by chirality or attachment configuration.

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