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Studies on the Interaction between Derivatives of 9-Aacridinyl Amino Acid as Anticancer Drugs and Functionalized Carbon Nanotubes: ONIOM2-PCM Approach

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Recently, the derivatives of 9-acridinyl amino acid have been synthesized and introduced as the anticancer and antiproliferative agents. In this regard, the functionalized single-wall carbon nanotubes (f-SWCNTs) have been employed as a drug delivery system in the nanomedicine applications. The role of the functionalized armchair (5,5) SWCNT in drug delivery of 9-acridinyl amino acid derivatives, as the anticancer agents, was studied by combining quantum mechanics and molecular mechanics methods. Therefore, the present study was conducted to investigate the binding properties of 9-acridinyl amino acid derivatives, as the anticancer agents, with pristine (5,5) single-walled carbon nanotube (SWCNT) and functionalized SWCNT (COOH-SWCNT) by the ONIOM2 (B3LYP/6-311G:UFF) and ONIOM2-PCM methods. The structural and electronic properties, binding energy, highest occupied molecular orbital and lowest unoccupied molecular orbital of the most stable configuration were also analyzed. Our results displayed that the interaction of the nanotubes with the derivatives of 9-acridinyl amino acid was relatively weak; suggesting that the interaction and adsorption of the anticancer agents with SWCNT can be physical in nature. The interaction of the anticancer agents on the f-SWCNT was stronger than that on the pristine SWCNT. In the aqueous solution, the solubility of the f-SWCNT as the carrier was increased.

Keywords: Drug delivery, Anticancer, 9-Acridinyl amino acid derivatives, Functionalized single-walled carbon nanotube, Two-layer integrated orbital molecular mechanics-polarizable continuum model

INTTRODUCTION

Derivatives of acridine belong to the category of compounds with anticancer, antiproliferative, anti-inflammatory, anti-parasitic, anti-tubercular, antimicrobial, antimalarial, fungicidal, and antiviral properties [1]. Acridine derivatives have conjugated planar structure, making them useful for treating several diseases, such as cancer, bacterial infections, Alzheimer's disease and protozoan inflammation [2]. The action mechanism of acridine derivatives is usually related to the DNA intercalation and the following effects on the biological processes associated with its corresponding enzymes and DNA [3]. Also, several derivatives of acridinyl amino acid have been demonstrated to have suitable anticancer activity. Gellerman synthesized the derivatives of bis-acridine and n-substituted 9-aminoacridine that included the electron-withdrawing or electron-donating groups and amino acid functional groups [4]. 9-Aminoacridine derivatives have shown more antitumor activity than the commercial m-amsacrine and 9-aminoacridine. These derivatives can form the DNA damaging reactive types due to the increase in chelating properties. Lyakhov *et al.* synthesized a series of 9-acridine amino acid derivatives and showed that the antiproliferative activity of these derivatives is related to the selected chain length and its amino acid [5]. Also, these derivatives possess linear aliphatic side chains and display good anticancer activity (Fig. 1). Recently, novel derivatives of acridinyl amino acid with less toxicity and better antitumor activity compared to the amsacrine have

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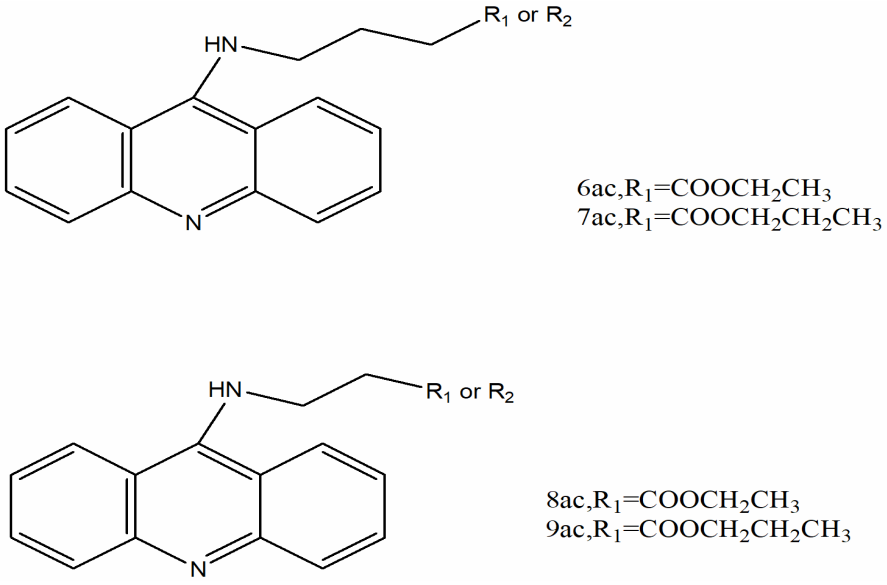

Fig. 1. Derivatives of 9-acridine amino acid.

been synthesized [6]. In this study, compounds with side chain lengths and the most activity (compounds 6ac, 8ac and 9ac), and compound with longer side chains and the most lipophilicity (compound 7ac) were selected.

Drug carrier is essential for more selectivity and intelligence of the drugs. Single-walled carbon nanotubes (SWCNTs) are made of a cylindrical structures of graphite sheets and have high sensitivity and site-selective delivery [7]. Since, they have high specific surface area and aspect ratios, their interaction with biomolecules could be through chemical attachment, adsorption, or encapsulation. These conjugations with drugs cause carrying the bioactive molecules across the cell membranes and the cell nuclei [8, 9]. SWCNTs can be used as the first carriers to deliver the drug to the cells, because of their stability, capability to penetrate into the cell membranes, and high drug carrying capacity properties [10].

However, SWCNTs are toxic and their toxicity can be controlled by the functionalized structure and size [11]. Functionalized-SWCNTs are capable of delivering and carrying one or more therapeutic agents as suitable and essential nanovectors [12]. Also, these small enough particles are able to pass the biological barriers and deliver the biomolecule to the cells. Purposeful and selectable delivery of the functionalized CNTs is appropriate for encapsulation of the remedial compounds [13]. Interaction of the anticancer drug molecules like carboplatin [14], cisplatin [15], doxorubicin [16,17], methotrexate [18] and paclitaxel [19] with carbon nanotubes has also been studied. Hamedani *et al.* studied the interaction of the folic acid drug on the SWCNT by the density functional theory (DFT) method [20]. Shojaee *et al.* studied the interaction of the f-SWCNT (5,5) with mitoxantrone [21]. Also, Athira *et al.* investigated the SWCNT and papain interactions for developing a biosensor [22]. Castillo *et al.* investigated the interaction between the SWCNTs and folic acid through the computational and experimental methods [23]. Also, the interaction between a SWCNT (6,6) and Carmustine as an anti-cancer agent has been studied by the DFT/natural bond orbital (NBO) analysis [24]. Shaki et al. investigated the interaction of penicillamine as an anticancer agent with the pristine SWCNT and f-SWCNT through DFT calculations [25]. Also, the interaction of Cisplatin with pristine SWCNT (5,5) has been investigated using the quantum mechanics [26].

In this paper, the potential of pristine SWCNT and f-SWCNT by COOH functional group will be shown for interaction with the novel 9-acridinyl amino acid derivatives in both gaseous and solution phases through the ONIOM2 approach. The quantum molecular descriptors, frontier

molecular orbitals, and binding energy of the 9-acridinyl amino acid derivatives and f-SWCNT (5,5) complexes were also analyzed. Investigation of this chemical interaction can be used as a new method for drug delivery.

COMPUTATIONAL METHODS

An own two N-layer integrated orbital molecular mechanics (ONIOM2) method was used to implement the geometry optimization of the structures. This method is based on partitioning a sizable molecular system into different layers that can be accompanied by lower computational cost and better accuracy compared to the pure DFT method [27]. Morokuma *et al.* proposed and implemented the ONIOM methodology [28,29]. The ONIOM approach is an effective method for investigation of large molecular systems as biomolecules and drug delivery system. In the ONIOM2 approach, the whole molecule (real) is partitioned into two parts, a small part of the system (model) is treated at a high level of theory, and then, the broader surrounding region is treated at a high level of theory.

The high-level of B3LYP/6-311G for derivatives of 9-acridinyl amino acid was used and a universal force field (UFF) level was employed for the low-level real pristine SWCNT and COOH-SWCNT (5,5). Binding energies (BE) should be calculated and evaluated using the small part in the DFT level [30]. Segmentation of the layers in the ONIOM is important in investigating the SWCNTs for drug delivery [31,32]. Also, the polarizable continuum model [33] with the integral equation formalism version [34] is used to evaluate the solvent effects using the ONIOM (ONIOM-PCM) method. In calculation, an armchair (5,5) SWCNT is employed and the SWCNT is capped with hydrogen atoms at either end. This chirality (5,5) is chosen because it is more soluble than the others [35]. The ONIOM2 (B3LYP/6-311G:UFF)-PCM/X method was performed to evaluate the binding energies of SWCNT and f- SWCNT with 9-acridine amino acid derivatives by the Gaussian 09 program [36].

RESULTS AND DISCUSSION

The optimized structures of the derivatives of 9-acridinyl amino acid were obtained by the DFT method and no imaginary negative frequencies for the energy minima were found. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are dependent on the negative and positive Fukui indices, respectively. Table 1 displays the quantum chemical descriptors of the studied derivatives of 9-acridinyl amino acid. These descriptors demonstrate the chemical reactivity of the 9-acridinyl amino acid derivatives. The energy of LUMO describes the ability of the molecule to accept electron; the lower the value of *E*LUMO, the easier the acceptance of electrons. E_{HOMO} denotes the electron donating ability of the molecule. The higher the value of HOMO energy of the molecule, the more trend the donating electrons to a suitable acceptor with a small vacant molecular orbital energy. The binding potential of the 9-acridinyl amino acid derivatives to the pristine SWCNT and f-SWCNT raises through enhancement of HOMO and reduction of LUMO energy values. Regarding the quantum molecular parameters listed in Table 1, 7ac molecule has a low E_{LUMO} and a high E_{HOMO} in contrast to other molecules.

The HOMO–LUMO energy separation (energy gap) is a significant parameter of the chemical reactivity at the most reactive site of the molecule. The results displayed that the 7ac molecule has a low energy gap. Therefore, transferring an electron from the HOMO of the 7ac molecule to its LUMO is more straightforward than that in the other three derivatives indicating that this molecule could have a premier efficiency. Ionization potential, absolute hardness, softness and chemical potential are useful parameters for evaluating the stability and molecular reactivity. The values listed in Table 1 display that the 7ac molecule has the highest softness and the lowest hardness. The capability of the structures to accept the electrons may be illustrated with the electrophilicity parameter. The electrophilicity index is a measure of the tendency of an electrophile to obtain a large amount of electron density. The lowest value of the electrophilicity index was related to the 7ac compound. The dipole moment is expressed as the polarity of a molecule. The highest value of dipole moment in the gas phase was related to the 7ac molecule.

Figure 2 shows the interaction of 9-acridinyl amino acid derivative (7ac), as an anticancer agent, and COOH-

Table 1. Quantum Chemical Descriptors for the Studied Compounds in the Aqueous Solution (eV)

Molecular descriptor	6ac	7ac	8ac	9ac
HOMO	-5.3625	-5.0398	-5.3560	-5.3554
LUMO	-1.9377	-1.6186	-1.9124	-1.9116
Energy gap	3.4228	3.4193	3.4416	3.4418
Ionization potential (IP)	5.3605	5.0379	5.3540	5.3535
Electron affinity (EA)	1.9377	1.6186	1.9124	1.9116
Global hardness (η)	1.7114	1.7096	1.7208	1.7209
Global softness (σ)	432.2950	432.7410	429.9376	429.9036
Electrophilicity (ω)	0.0153	0.0128	0.0153	0.0153
Dipole moment (μ) debye	3.7834	6.3802	5.0154	5.0736

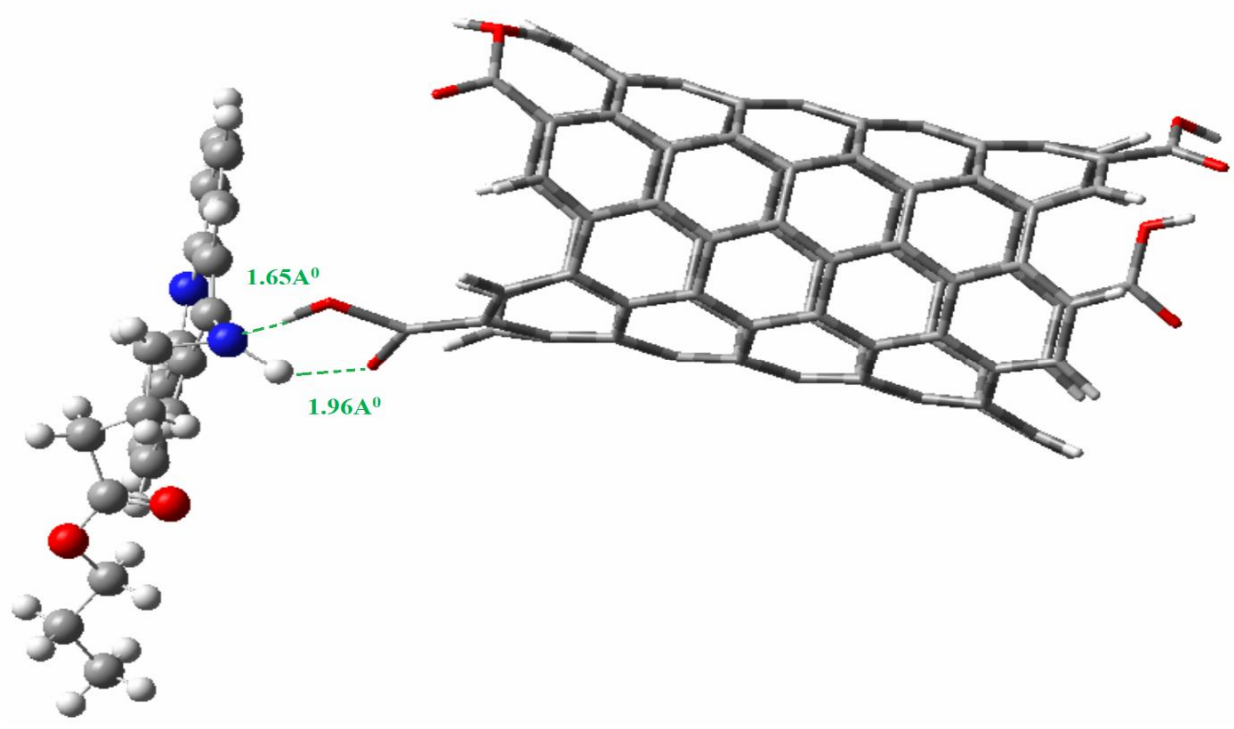

Fig. 2. 9-Aacridinyl amino acid derivative (7ac) and armchair (5,5) functionalized SWCNT (ONIOM2) in the aqueous solution.

SWCNT (5,5) by the ONIOM2-PCM method in the aqueous solution. The non-covalent interactions, such as hydrogen bonds play a critical role in the interaction between 9-acridinyl amino acid derivatives, as the anticancer drugs, and functionalized carbon nanotubes (COOH-SWCNT). Nitrogen (N) atoms of 9-acridinyl amino acid derivatives

have a high reactivity. Two intermolecular H-bonds can be evolved in interaction between 9-acridinyl amino acid derivatives and functionalized carbon nanotubes. The amine's nitrogen atom of the 9-acridinyl amino acid (7ac) is engaged in a strong H-bond with the -COOH proton of SWCNT (5,5) by 1.65 Å length. Also, the proton of the -NH amine group forms a H-bond with the oxygen atom of the carbonyl group of -COOH by 1.92 Å length.

The integrated energy for the ONIOM2 methodology is calculated as:

$$E^{ONIOM\,2} = E^{\mathrm{mod}\,el,\,high} + E^{real,\,low} - E^{\mathrm{mod}\,el,\,low} \quad (1)$$

where 'Real' describes the full system, treated at the 'Low' level, and 'Model' describes the region of the system for which the energy is calculated at both 'High' and 'Low' levels. Accordingly, this approach can be as an extrapolation scheme. The ONIOM methodology authorized an extrapolated energy $^{\mathrm{EONIOM2}}$ for a system segmentation in this approach.

Because of the well-defined potential energy of the ONIOM approach and its correct number of freedom degrees, any theoretical method can be applied with the ONIOM approach for consideration of the potential-energy surfaces. In addition to the potential-energy surface, densities can be gained from the ONIOM methodology. In the ONIOM-PCM method, the integrated charge density, ρ^{ONIOM}, is applied [37]:

$$\rho^{ONIOM\,2} = \rho^{\mathrm{mod}\,el,\,high} + \rho^{real,\,low} - \rho^{\mathrm{mod}\,el,\,low} \quad (2)$$

In the integral equation formalism-polarizable continuum model (IEF-PCM) method, the solute is demonstrated in the sentences of a charge density included by a cavity made in the medium and the solvent is demonstrated by the same polarizable continuum with intermediate permittivity. Regarding the real system, each of the sub-calculations has its own evident surface charge density using one cavity [37].

$$E^{ONIOM-\frac{PCM}{X}} = E^{\mathrm{mod}\,el,\,high}\,(\rho^{\mathrm{mod}\,el,\,high}) + E^{real,\,low}\,(\rho^{real,\,low}) - E^{\mathrm{mod}\,el,\,low}\,(\rho^{\mathrm{mod}\,el,\,low}) \quad (3)$$

Investigation of the binding energy (BE) of the assigned systems revealed the fundamental aspect of the 9-acridinyl amino acid derivatives, as anticancer agents, and COOH-SWCNT (5,5) interactions through the ONIOM2 methodology. Table 2 presents the binding energies computed at the B3LYP/6-311G(d):UFF level of calculation for the optimal structure between 9-acridinyl amino acid derivatives and pristine SWCNT (5,5) and COOH-SWCNT (5,5) in both gas and liquid phases. The results demonstrated that the interactions are exothermic in both phases and 9-acridinyl amino acid derivatives can physically interact on the nanotube surface.

The binding energy was increased in both phases from pristine SWCNT to functionalized SWCNT and values of the calculated binding energy using the ONOIM2-PCM approach were more than those obtained by the ONIOM2 approach. Among the 9-acridinyl amino acid derivatives, compound 7ac led to the most binding energy in both phases. Results displayed that these systems have relatively low stability because of low binding energies, thus COOH-SWCNT (5,5) can be applied for drug delivery.

CONCLUSIONS

In the present work, 9-acridinyl amino acid derivatives, as the anticancer agents, were selected. The interaction of these derivatives on the pristine SWCNT and COOH-SWCNT in gas and water phases was investigated through the ONIOM2 approach. The binding energies demonstrated that these derivatives could be adsorbed on the surface of the COOH-SWCNT better than the pure SWCNT. The results indicated that all the investigated systems are almost stable and the adsorption interaction process is exothermic in gas and water phases. Also, the values of binding energy indicated that the 9-acridinyl amino acid derivatives can interact and be adsorbed physically on the nanotubes surface .The results showed that the 9-acridinyl amino acid derivatives can spontaneously move to the carbon nanotubes due to the attendance of reliable interaction energy between 9-acridinyl amino acid derivatives and SWCNTs. The enhancement in the solubility of derivatives of 9-acridinyl amino acid/SWCNT in the water environment can be caused by functionalization of the SWCNT. Herein, the probability and possibility of using the COOH-SWCNT for

Table 2. Binding Energy ($E_{binding}$, kcal mol^{-1}) Values of Interaction of 9-Acridinyl Amino Acid Derivatives, as the Anticancer Agents, and Carbon Nnanotube (Pristine and Functionalized) in the Aqueous Solution

Compound	SWCNT(pristine)		SWCNT-f(COOH)	
	ONIOM2	ONIOM2-PCM	ONIOM2	ONIOM2-PCM
6ac	-9.6061	-11.4886	-10.5904	-13.7907
7ac	-12.0323	-14.6491	-14.3162	-16.5274
8ac	-9.8265	-11.9756	-13.14333	-14.9506
9ac	-11.1944	-14.3495	-13.2588	-15.7688

drug delivery of 9-acridinyl amino acid derivatives was investigated. Thus, the COOH-SWCNT (5,5) can be an efficient carrier to release these derivatives as the anticancer agents in the diseased cells without causing any drugs side effects. In all systems, the hyperconjugation effect can be realized.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interests regarding the publication of this manuscript.

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