Applied Surface Science 462 (2018) 720–729

Contents lists available at ScienceDirect

Applied Surface Science

journal homepage: www.elsevier.com/locate/apsusc

Full Length Article

Comprehensive quantum chemical insight into the mechanistic understanding of the surface functionalization of carbon nanotube as a nanocarrier with cladribine anticancer drug

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ARTICLE INFO

Keywords:
Quantum chemical calculations
Drug delivery
Pristine and functionalized carbon nanotubes
Cladribine
Functionalization mechanisms

ABSTRACT

Using molecular models for pristine (NT) and COOH (FNT) functionalized carbon nanotube, ten noncovalent configurations and four mechanisms of covalent functionalization of NT and FNT with cladribine anticancer drug (CDA) were studied. Quantum molecular descriptors, free energies of solvation and binding energies of non-covalent interactions were investigated in H_2O and DMF solvents and gas phase. The calculation of binding energies confirmed the energetic stability of all CDA/NT and CDA/FNT configurations. The free energies of solvation show that NT and FNT solubility increases in all drug-nanotube configurations which is a main factor for its applicability in the drug delivery. Quantum molecular descriptors of drug such as global hardness and HOMO-LUMO energy gap are higher than those of drug-nanotube complexes, showing the reactivity of the drug increases. The AIM analysis for the most stable configuration (CDA/FNT2) demonstrated that the intermolecular hydrogen bonding plays a main role in this system. For the covalent functionalization COOH (FNT) and COCl (NTCOCl) functionalized carbon nanotubes were considered. Cladribine may bond to FNT and NTCOCl through NH_2 and OH groups. The activation parameters of all pathways were calculated, indicating the activation energies and Gibbs free energies related to FNT mechanisms are higher than those of NTCOCl mechanisms.

1. Introduction

Due to their unique mechanical, photonic, chemical and electrical properties [1–4], carbon nanotubes (CNTs) have the capacity, to be applied in the fields such as biological and medical research [5–7]. An increasing amount of attention has been paid to the functionalization of CNTs with DNA, polymers, peptides, and drugs [6,8–14]. CNTs were used as drug carrier for anticancer drugs such as doxorubicin [15,16], cisplatin [17,18], paclitaxel [19], methotrexate [20] and carboplatin [21]. Typical methods including ozonization [22], hydrogenation [23], cycloaddition [24], fluorination [25], amidation and esterification [26,27] have been utilized to functionalize CNTs.

Contrary to some of the defects such low solubility and that they will not be easily discharged from the body, they have advantages such high drug loading capacities and good cell penetration qualities [28] which make them appropriate candidates for being used in drug delivery [29–33]. For this reason, there has been increasing interest in medical applications of CNTs.

Chemotherapy is one of the effective ways to treat cancer. The greater the dose of anticancer drug, the greater the side effects [34,35]. Due to reasons mentioned above CNTs are more suitable to be used for drug delivery than systems such as polymers, dendrimers, and liposomes, which are being used at present [36,37]. CNTs become covalently and noncovalently functionalized with anti-cancer drugs and this causes the dosage of the prescribed medicine and consequently their side effects, such as vomiting, hair loss, cardio-toxicity and breathing difficulties, to be decreased [38,39]. Cladribine or 2-chlorodeoxyadenosine (CDA) has anticancer activities and is effective in the treatment of hairy cell leukemia, chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), non-Hodgkin's lymphomas, Langerhans cell histiocytosis and Waldenstrom macroglobulinemia [40–42]. CAD is toxic to healthy cells, because it is prescribed at high doses [43,44]. It is therefore of great importance that this drug is targeted to the cancerous tumours. For this purpose, various nanocarriers such as carbon nanotubes and polymeric nanoparticles have been used [45–47].

Physical functionalization such as hydrogen bonding and van der Waals interaction does not cause any important perturbation in CNTs [48,49], but covalent bonding increases the solubility and compatibility

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https://doi.org/10.1016/j.apsusc.2018.08.151
Received 20 May 2018; Received in revised form 10 August 2018; Accepted 18 August 2018
Available online 20 August 2018
0169-4332/

of CNTs [50]. Parallel with the experimental methods based on trial and error, an important approach in the study of drug delivery systems is the use of quantum calculations [51–55]. In 2016, the Chemistry Nobel Prize was given to the design and manufacture of molecular machines, an important application of which is in the drug delivery [56–58].

In this work, quantum calculations have been used to analyze noncovalent interactions and different mechanisms of covalent functionalization of CNTs with cladribine drug. So far, few researches has been done on the mechanism of covalent functionalization of CNTs with drugs and therefore this work could inspire the researchers in the design and manufacture of new drug delivery systems [5,59].

2. Computational method

All calculation have been done using B3LYP [60–62] level of theory and 6-31G(d, p) basis set in GAUSSIAN 09 package [63]. All degrees of freedom for all geometries in gas and solution phases (H_2O and DMF) were optimized. For noncovalent interactions in gas phase, the calculations were repeated by M06-2X functional [64,65] which describes the dispersion interactions [66].

The solvent has a key role in different chemical and biological systems explicitly [67,68] or implicitly. Polarized continuum model (PCM) [69,70] was employed to consider the implicit effects of the solvent. For the calculation of the free energy of solvation (ΔG_{solv}), SMD solvation model was used [71]. In this model, $\Delta G_{solv}$is obtained by Eq. (1):

$$\Delta G_{solv} = (E_{solv} + \Delta G_{nonelectrostatic}) - E_{gas} \quad (1)$$

where E_{solv} and E_{gas} show the total energies in the solution and gas phases, respectively, and $\Delta G_{nonelectrostatic}$ is the nonelectrostatic energy.

Quantum molecular descriptors were used for the description of chemical reactivity and stability. The global hardness (η) describes the resistance against the change in molecular electronic structure (Eq. (2)).

$$\eta = (\mathrm{I}-\mathrm{A})/2 \quad (2)$$

where $I = -E_{HOMO}$, $A = -E_{LUMO}$, E_{HOMO} and $E_{LUMO}$are the ionization potential, the electron affinity, energy of the lowest unoccupied molecular orbital and energy of the highest occupied molecular orbital, respectively. The electrophilicity index (ω) is formulated as follows [72]:

$$\omega = (I + A)^2/8\eta \quad (3)$$

and the chemical potential (μ) is defined by:

$$\mu = -(I + A)/2 \quad (4)$$

To obtain a better understanding of the nature of the interactions, quantum theory of atoms in molecules (QTAIMs) was used. The AIM computations were performed using the AIMALL package [73]. QTAIM has been based on the topological analysis of the electron density, ρ(r) [74]. The topology of ρ(r) is under the impact of nuclear maxima, bond critical points (BCPs), indicating the lowest point of electron density between two nuclei and lines of maximum density (bond paths) linking the nuclear maxima of bonded nuclei. There are several properties of the electron density at a BCP for distinguishing the nature of the bond. These parameters include the electron density (ρ_b), the Laplacian of the electron density($\nabla^2\rho$), the local electron kinetic (G_b), potential (V_b) and total (H_b) energy densities. The amount of both quantities ρ_b and $\nabla^2\rho$ is related to the strength of the bond between the two nuclei. In addition, the sign of $\nabla^2\rho$ together with the sign of the total energy density (H_b) at the BCP presents more information on the nature of the interactions.

The calculations were performed on a computer cluster for cladribine (CDA), pristine armchair (5,5) single-walled CNT (NT) comprising 110 atoms (10 Å) with the ends terminated by hydrogen atoms, COOH functionalized NT (FNT), COCl functionalized NT (NTCOCl), ten noncovalent configurations of CDA/NT(FNT) and products and transition states of covalent functionalization. Standard convergence criteria for geometry optimization were employed. The transition state obtained was confirmed to have only one imaginary frequency of the Hessian. The optimized structures of reactants and products were checked for minima by second derivative (frequency) calculations. The zero-point corrections were also considered to obtain activation energies. To achieve higher accuracy, approximation methods such as ONIOM [75] were not used.

3. Results and discussion

3.1. Noncovalent interactions

In this section, important quantities have been investigated to accurately determine the nature of the interactions in different configurations.

3.1.1. Binding and solvation energies

The interaction of CDA drug with NT and FNT have been considered from four (CDA/NT1-4) and six (CDA/FNT1-6) different orientations, respectively. Regarding the functional groups of CDA drug such as NH_2 and OH, the drug was put on the exterior surface of the nanotube. The optimized geometries of CDA drug, NT, FNT and different configurations of CDA/NT1-4 and CDA/FNT1-6 in aqueous solution have been presented in Figs. 1–3 (see the Supplementary data to for the Cartesian coordinates of the calculated structures).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.apsusc.2018.08.151.

Table 1 shows the binding energies (Eq. (5)) in H_2O and DMF solvents and gas phase. The binding energies in both H_2O and DMF solvents are less than those of gas phase, however, their values are negative, showing that the adsorption process is favorable and exothermic.

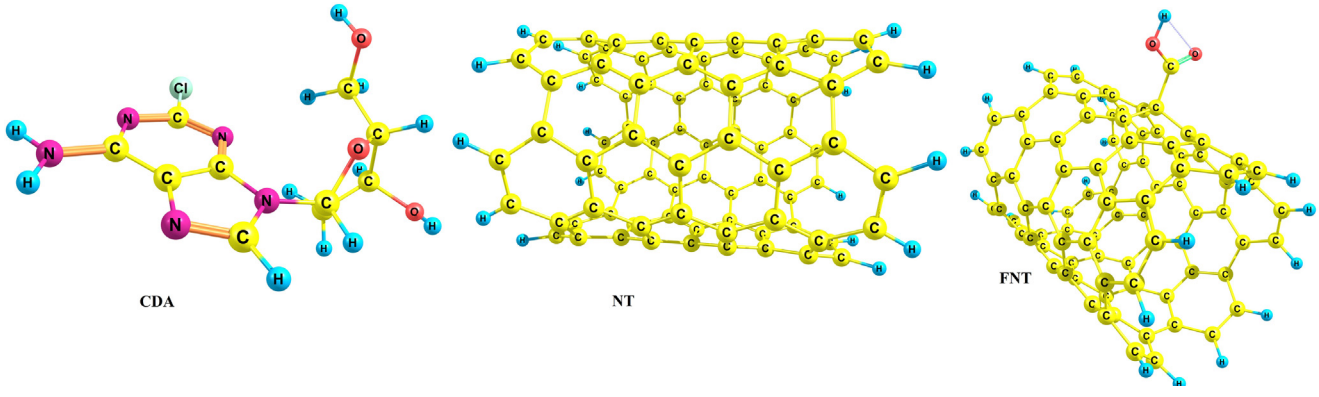

Fig. 1. Optimized structures of CDA, NT and FNT.