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Inclusion complexes between cisplatin and oxidized carbon nanostructures: A theoretical approach

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ABSTRACT

The toxicity of inclusion compounds formed by carbon nanostructures depends on its functionalized surface, use of solvents, dosage and other properties. Molecular modeling has potentially contributed to the understanding of the chemical nature of the formation of these systems and allows advancement in studies of the mechanism of transport, release of drugs and their biological implications. This work reports a quantum chemical investigation of the inclusion complexes formation between oxidized carbon nanotube (CNTox)/nanocone (CNCox) structure and cisplatin molecule, using the density functional theory (DFT) with the B3LYP functional and 6–31G(d,p)/LanL2DZ standard basis sets. Our results indicate that the cDDP@CNTox (inclusion complex – cisplatin into oxidized carbon nanotube) and cDDP@CNCox (inclusion complex – cisplatin into oxidized carbon nanocone) systems form stable molecular complexes that can be used as drug delivery devices. Our theoretical simulation of molecular spectra (IR, Raman and ^{1}H NMR) reveals substantial changes due to complex formation that can be easily experimentally observed.

1. Introduction

Cisplatin (cDDP) is one of the most used drugs in the solid tumors treatment due to its high anticancer activity. Recent studies show that its toxicity can be minimized [1–6]. In addition, research has been conducted to reduce drug resistance problems [7,8] that appear with its continued use and also through new proposals of drug transport in the biological environment [9,10]. The search for new cisplatin-based drugs delivery systems (DDS) aims to improve the pharmacology of bioactive drug by preserving them from parallel reactions that can avoid reaching the biological target. The most studied DDS models involve mainly liposomes [11–13], dendrimers [14,15], polymers [16–18], cyclodextrins [19–22], nanoparticles [15,23–25] and carbon nanocomposites [26–35]. Important biological factors such as the transport mechanism, tolerance, biodistribution and toxicity of these systems are essential for clinical use approval [36–40]. Regarding carbon nanocomposites such as carbon nanotubes (CNTs) and nanocones (CNCs), toxicity depends mainly on the amount of metallic impurities, surface functionalization, use of solvents, dispersants and surfactants, in addition to the length, type, aggregation state, and dosage of the nanostructure employed [40]. Surface functionalization may increase the solubility and/or dispersion in water or in other solvents allowing their use as nanovectors of drugs, vaccines and other biomolecules. Tahara et al. [38] studied the toxicity and biodistribution by intravenous administration in mice of three types of oxidized carbon nanocones (CNCox), which were obtained (i) in the slow combustion (550 °C) and presence of dry air flow followed by natural cooling to room temperature, (ii) dispersed H_2O_2 at 100 °C under light irradiation and (iii) by dispersion with H_2O_2 and chemical functionalization with bovine serum albumin. Oxygen-containing functional groups, such as carboxyl groups, at the hole edges generated were observed. The authors observed that the oxidized nanocones did not show high toxicity and did not cause serious anomalies in animal tissues. The oxidized species in the slow combustion accumulated primarily in the lungs and those treated with peroxide with slightly higher hydrophilicity distributed in the lungs, liver and spleen. Recently, De Souza et al. [41] using density functional theory (DFT) calculations proposed theoretical models of carbon nanotubes and nanocones functionalized with organic groups such as carbonyl, hydroxyl and carboxyl. The holes generated on the surface of the oxidized nanostructures are able to release antitumor drugs of small molecular structure such as cisplatin to medium-sized as the organic drug busulfan. The authors believe that these structures can

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be better dispersed in polar biological fluids such as the bloodstream, and thus, through future biological trials, it is expected that nanostructures of this type can be considered promising drug carrier agents.

Kazemi-Beydokhti et al. [30] investigated the thermal conductivity of a new nanofluid, which can be used as a DDS using oxidized carbon nanotubes (CNTox) with a carboxyl group involved with two types of phospholipids applied as a carrier of cisplatin. Cisplatin molecules were covalently linked to the nanotubes through carboxyl groups distributed along their oxidized surface. The authors show that the increase in temperature and a decrease in pH results in improvement of the drug release. In addition, the authors suggested that the strong binding forces between CNTox and cDDP molecules help maintain the complex structure by improving the half-life of the drug in the blood vessels without being deactivated by other biomolecules. Hosni et al. [35] studied a variety of capped and opened pristine carbon nanotubes diameters in order to verify the maximum encapsulation capacity of cisplatin molecules as a function of tube length. The authors showed through theoretical calculations of ^{195}Pt NMR chemical shift (δ) at the Hartree-Fock (HF) level that the δ ^{195}Pt decreased when the diameter of the nanotube increases. In addition, through signal intensity analysis, it is possible to predict the relationship between tube diameter and drug confining energy. In the last six years, our group has investigated through theoretical [27,28,41,42] and theoretical-experimental [26] studies DDS formed by pristine carbon nanotubes/nanocones and cisplatin drug. We evaluated the structural aspects of nanostructures that are favorable to the drug encapsulation process, and also employed DFT calculations of Raman and NMR spectroscopies that allow the characterization of the inclusion complex. Recently, we reported our first theoretical-experimental work [26] on the encapsulation of cisplatin into carbon nanotubes and we are moving towards to the in vitro biological trials of these and other inclusion compounds formed by carbon nanostructures. In the Ref. [26], the inclusion process of cDDP into CNT was analyzed by means of thermogravimetry, electron microscopy and Raman spectroscopy, with the aid of DFT calculations. Our experimental results clearly demonstrated that the inclusion of the drug in pristine CNTs was achieved at about 7.8% wt., a high value compared to estimates from studies related to inclusion of cDDP in CNT, which are conducted with oxidized CNT samples. TG analysis showed that the thermal stability of the single walled carbon nanotube (SWCNT) was modified by the incorporation of cDDP. Our results show that the G/D intensity ratio varied from 10.9 (pristine nanotube) to 4.8 (inclusion complex) due to the decrease of the tube structural order upon the drug inclusion and our calculations showed a decreasing of 7.4 to 4.8, in line with experimental data.

Our group has produced studies on the DDS molecular modeling and, in this work, we show DFT results of structural and spectroscopic properties of inclusion compounds formed by cisplatin antitumor drug with oxidized carbon nanotubes (cDDP@CNTox) and nanocones (cDDP@CNCox). We discuss here the structural influence in the oxidized region of the theoretical models of nanotubes proposed in our previous work [41] due to the formation of inclusion complex with the drug. The infrared (IR), Raman and ^{1}H NMR spectra assignments are presented for the compounds proposed.

2. Computational details

All calculations were performed with the Gaussian 09 package [43] employing the DFT methodology [44] and the B3LYP [45] functional using the LanL2DZ [46] effective core potential (ECP) for platinum atom and the 6-31G [47] basis set for C, H, O, N and Cl atoms. The geometries of the oxidized nanostructures and cDDP molecule were optimized separately and then used to build the molecular complexes I (cDDP@CNTox) and II (cDDP@CNCox). cDDP molecule was included under the axis that passes through the center of mass of each nanostructure, so that the drug was located in the middle of the tube region (Fig. 1). The B3LYP/6-31G/LanL2DZ geometries of all molecules (free monomers and inclusion complexes I and II) were then used for the vibrational harmonic frequency calculations to derive theoretical vibrational IR and Raman spectra. The complexes formation energies (ΔE_F) were calculated as

$$\Delta E_F = E_{complex} - (E_{CNox} + E_{cDDP}) \quad (1)$$

where $E_{complex}$, E_{CNox} and E_{cDDP} correspond to the total energy of the molecular complex, free oxidized carbon nanostructures and cisplatin molecule fully optimized structure, respectively. The basis set superposition error (BSSE) [48] using the counterpoise (CP) approach [49] was also evaluated at the B3LYP/6-31G/LanL2DZ level to access more realistic calculated formation energies. Finally, the Gauge-Independent Atomic Orbital (GIAO) method implemented by Wolinski et al. [50] was used for the calculation of ^{1}H magnetic shielding constants (σ), with chemical shifts (δ), obtained on a δ-scale relative to the Tetramethylsilane (TMS), taken as reference. Solvent effects on the calculation of ^{1}H NMR chemical shifts was evaluated using the polarizable continuum model (PCM) [51] and water solvent (dielectric constant, ε = 78.3553), through single point calculations on the optimized gas phase structures. In spite of the fact that the 6-31G(d,p) basis set may be considered modest, it has been shown [52] that the B3LYP/6-31G(d,p) level of calculation is very adequate for the evaluation of ^{1}H NMR chemical shifts. A comparison between four DFT functionals (B3LYP, BLYP, PBE and M06-2x) with ab initio MP2 post-Hartree-Fock ^{1}H NMR calculations showed that the B3LYP functional exhibited the best agreement, validating the use of the B3LYP/6-31G(d,p) level of calculation. In addition, various other published works addressing structure or stereochemistry of organic molecules, through the analysis of ^{1}H NMR chemical shifts, have made successful use of the B3LYP/6-31G(d,p) level of calculation [53–56].

3. Results and discussion

The carbon nanotube and nanocone structures used to build the inclusion complexes correspond to the final geometries [41] obtained from the molecular modeling of the oxidation in the cap region. Our calculations revealed that the formation of the CNTox and CNCox topologies oxidized on the cap are more favorable than on the tubular region. Thus, in this work we used these topologies for the inclusion complexes modeling with the cisplatin molecule. The structural properties of the CNTox ($C_{168}H_{18}O_{15}$) and CNCox ($C_{250}H_{32}O_{20}$) free monomers are described in Ref. [41] and here we shall describe the possible changes in the geometry of each oxidized nanostructure after inclusion the drug. The length of isolated units of carbon nanotubes [30] and nanocones [31,57] can be obtained in the range of 40–800 nm. Our models, CNTox and CNCox have about 14.3 Å and 17.4 Å (Fig. 1), respectively, and represent precisely the region where in most cases the drug will be hosted, i.e. near to the closed end of the nanostructure [58] which is the focus of this study. The advantages of shorter nanostructures [26] are related to their low toxicity [40] and greater capacity of direct or by phagocytosis translocation in biological membrane [11,59]. Free cisplatin molecule was found to be square planar, as expected, with average Pt—Cl and Pt—N bond lengths of 2.40 and 2.12 Å, respectively, and the overall calculated structure compares well with the X-ray data [60].

Fig. 2 shows the potential energy curve for the geometry optimization process of inclusion complexes. It can be seen that the energy difference between the initial (starting structure) and fully optimized (final structure) geometries is only 0.04 kcal mol^{-1} and 1.25 kcal mol^{-1} for complex I and II, respectively. This is a result of the slight adjustment of the structural parameters between the intermediate geometries in each complex, being that the oxidized region of the CNTox monomer is structurally more rigid and thus, a smaller value is obtained. B3LYP/6-31G/LanL2DZ fully optimized geometry complexes are depicted in Fig. 3A–D. One can see that the cisplatin is located near the oxidized cap of nanostructures. After the complexes optimization,