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Theoretical insights into the encapsulation of anticancer Oxaliplatin drug into single walled carbon nanotubes

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Abstract

The present work was an attempt to evaluate the potentialities of using SWCNTs as nanovectors for drug delivery of anticancer drug Oxaliplatin. First-principles van der Waals density functional (vdW-DF) calculations are used to investigate the incorporation of oxaliplatin inside the typical semiconducting and metallic single wall carbon nanotubes with various diameters (SWCNTs). Adsorption energy is calculated and the results show that oxaliplatin affinity for the semiconducting SWCNTs is stronger than that for the metallic counterparts. The obtained binding energies reveal that oxaliplatin prefers to be encapsulated into the semiconducting and metallic nanotubes with diameter of about 9 and 11 Å, respectively. We also found that vdW forces mainly contribute to the binding of selected drug molecule to SWCNTs. The study of the electronic structures and charge analysis indicate that no significant hybridization between the respective orbital takes place and the small interaction obtained quantitatively in terms of binding energies. Our findings afford not only a molecular insight into understanding of the interaction between oxaliplatin and SWCNTs but also may be instructive to relevant scientists who are attempt to develop effective methods for suitable nanovectors for drug delivery.

Keywords: SWCNTs, Drug delivery, ab initio calculations, oxaliplatin, vdW-DF, Cancer drugs

1.Introduction

Among the top three killers in modern society, cancer is in next to the heart and cerebrovascular diseases [1]. Due to rapid progress of this complicated disease in our modern world, utilization of sophisticated and effective agents/methods that can help diagnose, prevent and manage it, is vital. Oxaliplatin, chemical name [(1R, 2R)-cyclohexane-1, 2-diamine] (ethanedioato-O, O') platinum (II), is one of the platinum-based drugs, used in treatment of advanced colorectal [2-4] and many other type of cancers [5-16]. Figure 1 shows a schematic representation of an oxaliplatin molecule. This compound and its other analoges (cisplatin and carboplatin) are caused cell death by preventing the repetition and transcription of DNA in cancer cell [17]. However, presentation intensive dose-limiting side effects and intrinsic or acquisitive drug resistance are their specifications [18].

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Hence, in recent years, nanovector as a promising area, can improve remedial and pharmacological index of anticancer drugs [19, 20]. Compared with various nanoparticles, carbon nanotubes (CNTs), with their extraordinary physical, chemical, and mechanical properties, have constituted separate realm in nanomedicine applications, particularly for drug delivery [21, 22], vaccine and gene delivery [23-25], protein carriers [26, 27] and in the treatment of broken bones [28]. Due to their high surface area they can conjugate with wide variety of therapeutics and biomolecules and help them to penetrate into the target cells [29, 30]. Functionalized nanotubes also have a role in tumor therapy without inflicting damage to normal body tissue through encapsulation drugs. The structural robustness of these materials is significant factor for holding compounds like acids, amines, polymers [31, 32] and radioactive metal ions [33]. They also have the ability to overcome many limitations that available drug carriers show. The objective of our simulation is to obtain the possibility of using CNTs as nanovectors for the drug delivery of oxaliplatin.

In this work we carried out density functional theory (DFT) calculations on the encapsulation of oxaliplatin molecule into single-walled CNTs. Details of the model as well as the computational methods employed are explained more thoroughly in the next followed by a discussion of our results in the Results and discussion, and a summary in the Conclusions.

1.1 Computational details

The optimization and total energy calculations for the interaction between CNTs and oxaliplatin drug were obtained using self-consistent DFT calculations with the ab initio simulation package SIESTA (Spanish Initiative for Electronic Simulations with Thousands of Atoms) [34, 35]. Siesta solves the standard Kohn–Sham equations and has been indicated to be very effective for large molecular systems [36]. This code uses the description of valence electrons and norm-conserving nonlocal pseudopotentials were adopted for the atomic cores. The pseudopotentials were constructed using the Trouiller–Martins scheme [37] to explain the interaction of valence electrons with the atomic cores. All total energy calculations were performed with triple-ζ polarized (TZP) basis sets. The cutoff energy of 150 Ry for the grid integration was utilized to represent the charge density. The Brillouin zone was sampled by 1×1×5 special k-points using the Monkhorst–Pack scheme for geometry optimization and energy calculations. We employed the first-principles vdW density functional (vdW-DF) calculations within the PBE-GGA method because the intermolecular interactions [38, 39] could be influenced due to the non-local dispersion or vdW interactions [40, 41].

From the well-known expression for calculating the molecular binding energies, Eb are obtained for various cases of our study.

$$Eb = E(oxal/CNT) - E(CNT) - E(oxal) \quad (1)$$

where E(oxal/CNT) is the total energy of the CNT interacting with the oxaliplatin drug and E(CNT) and E(oxal) are the total energy of the isolated CNT/oxaliplatin alone.

2. Results and discussion

To find the most energetically favorable complex between oxaliplatin and single walled CNTs, we first selected various types of SWCNTs with different diameters, namely metallic (6, 6), (7, 7), (8, 8), (9, 9), (10, 10) and (11, 11) and semiconducting (10, 0), (11, 0), (12, 0), (13, 0), (14, 0) and (15, 0) nanotubes. The formation energy (binding energy (Eb) of encapsulated oxaliplatin inside the selected SWCNTs are calculated. After full structural optimization of the considered systems, the calculated results with the vdW-DF method indicate that the oxaliplatin/CNT (8, 8) and oxaliplatin/CNT (14, 0) complexes are energetically favorable complexes with the binding energies about -0.62 eV (-14.30 kcal/mol) and -0.99 eV (-22.82 kcal/mol), respectively. We also evaluate the effect of non-vdW forces using conventional DFT method for oxaliplatin/CNT (8, 8) as well as oxaliplatin/CNT (14, 0) complexes. The obtained results are represented in Table 1 for all the considered complexes.

Table 1: Binding energy (Eb) of encapsulated oxaliplatin into the considered SWCNTs

oxaliplatin/CNT	E_b(eV)
6,6	1.34
7,7	-0.33
8,8	-0.62 (-0.65)*
9,9	-0.29
10,10	-0.33
11,11	-0.18
10,0	2.40
11,0	0.24
12,0	-0.81
13,0	-0.90
14,0	-0.99 (-0.97)*
15,0	-0.79
16,0	-0.71

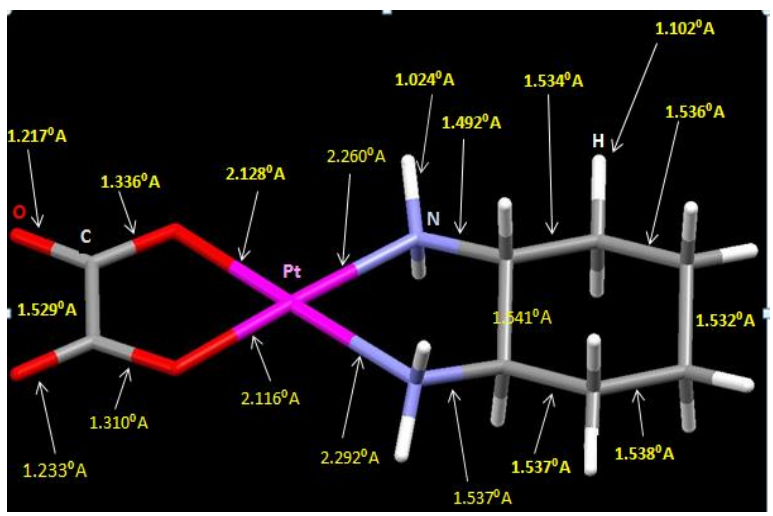
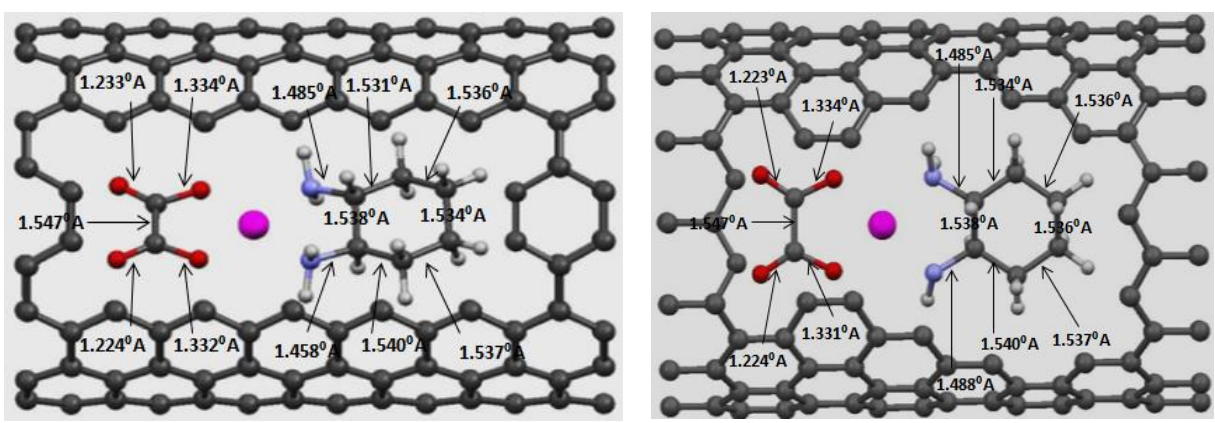
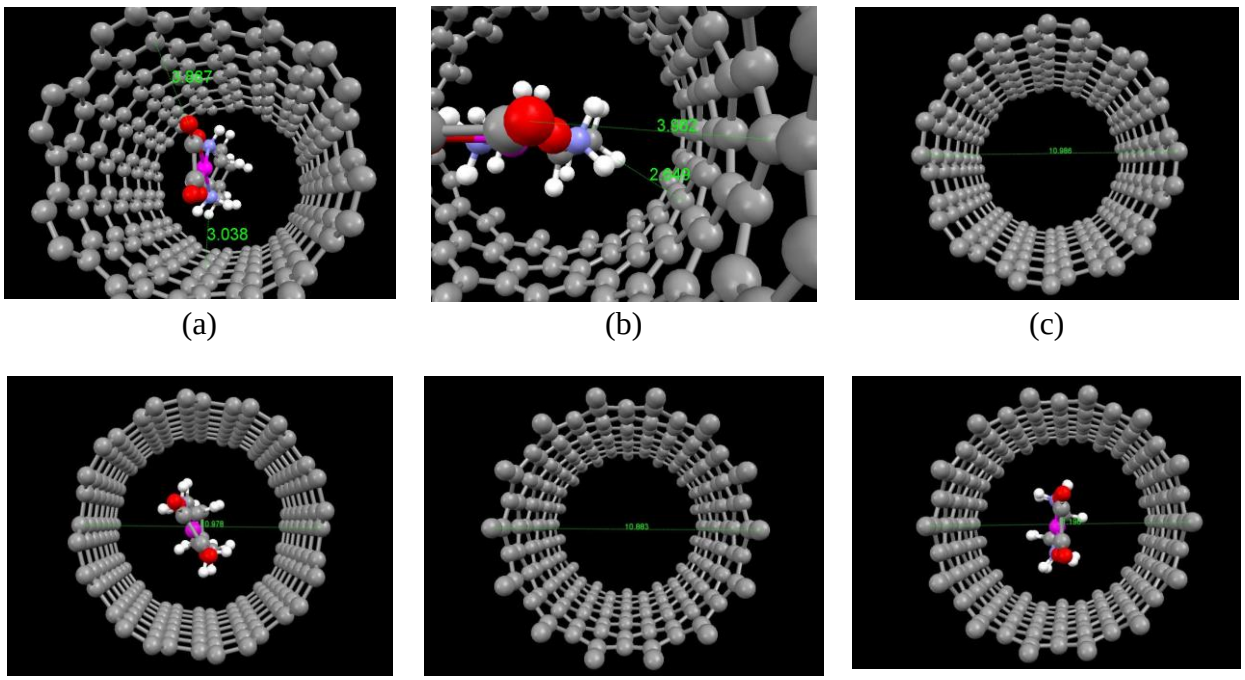


Figure 1. Optimized geometric structure of oxaliplatin molecule. Atom colors: grey–carbon, white–hydrogen, blue–nitrogen, pink–platin and red–oxygen.



(a) (b)

Figure 2. Geometric parameters of the optimized structure of the most stable oxaliplatin/CNTs complexes, (a) oxaliplatin/CNT (8, 8) and (b) oxaliplatin/CNT (14, 0).



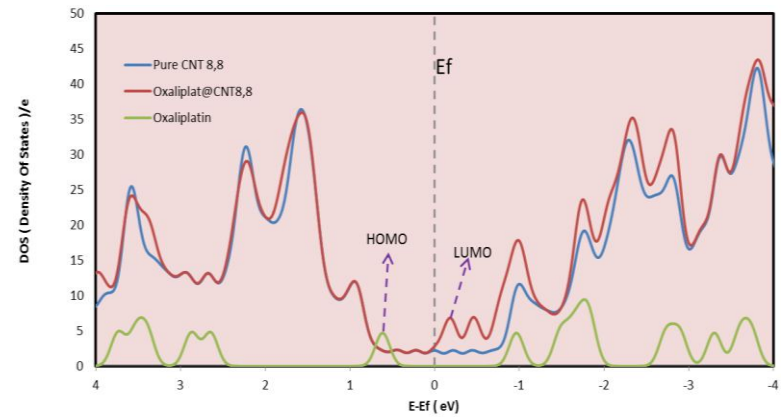
(a) (b) (c)

(d) (e) (f)

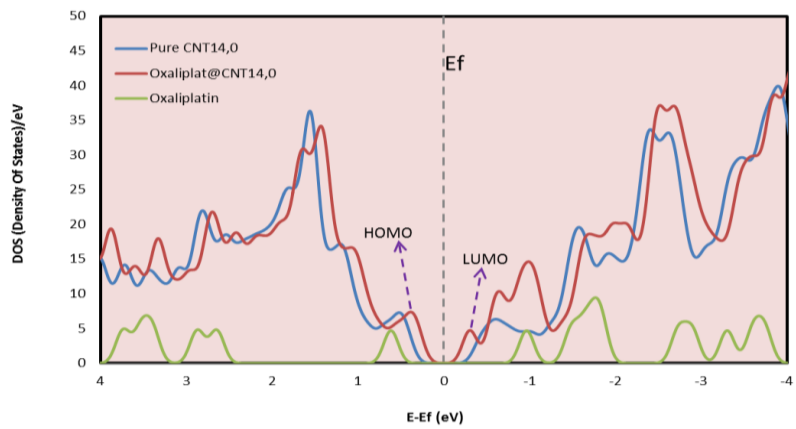
Figure 3. Calculated bonding distances between two closest atoms of the interacting entities for the (a) oxaliplatin/CNT (8, 8) and (b) oxaliplatin/CNT (14, 0) complexes. Diameters for (c) CNT (8, 8), (d) oxaliplatin/CNT (8, 8) complex, (e) CNT (14, 0) and (f) oxaliplatin/CNT (14, 0) systems.

The equilibrium distance between the closest atoms of oxaliplatin (O and H atoms) and CNTs (C atom) are 3.89 Å (dO…C) and 3.04 Å (dH…C) for CNT (8, 8). In the case of the CNT (14, 0) the corresponding values are determined to be about 3.98 Å and 2.65 Å, respectively. The schematic representation of the optimized geometry structure for the most stable complexes is given in figure 2. As it can be seen from the figure the bonds length in the isolated oxaliplatin in comparison with those of the encapsulated molecule for the most stable states change very small in adsorption process. We also compared the CNTs diameters before and after the incorporation of the oxaliplatin. The obtained diameters after full structural optimization of the isolated CNTs, oxaliplatin/CNT (8, 8) and oxaliplatin/CNT (14, 0) complexes reveals that nanotube diameters were increased/decreased after the encapsulation for metallic/semiconducting nanotubes (see Fig. 2). Comparison between C–C bond length of CNTs before and after the encapsulation of oxaliplatin shows that the average C–C bonds length in the perfect nanotube (0.142 nm) is slightly smaller than those in the oxaliplatin/CNT (8, 8) (0.144 nm) and oxaliplatin/CNT (14, 0) complexes (0.419 nm). The small adsorption energies, the rather far equilibrium distance of the adsorbed molecule from the interior surface of the tubes and the small change of bonds length of the incorporated oxaliplatin and SWCNT are all the factors that suggest the involvement of only non-covalent interactions in the incorporation process (physisorption [42-50]). Indeed, weak interaction between the oxaliplatin and SWCNTs in the thermodynamically favorable complexes is an important factor in drug delivery technique. This can be attributed to this fact that the slight change in the molecular structure of a drug may considerably change its specificity hence most drugs are usually burdened onto CNTs carrier's trough physical adsorption.

To further interpret the binding nature in the present complexes, we next study the electronic structures of the thermodynamically most stable state systems. For this purpose, the density of states (DOS) for the combined system of oxaliplatin/SWCNTs was calculated and compared with those of the individual parts, i.e., SWCNTs and oxaliplatin molecule. Fig. 4 shows the total electronic DOS for free oxaliplatin, pristine CNT (8, 8)/(14, 0) and oxalipltin/CNT (8, 8)/(14, 0) systems. We can find from the figures that for both oxalipltin/CNT (8, 8) and oxalipltin/CNT (14, 0) complexes the DOS near the Fermi level is affected by the adsorption of drug.



(a)



(b)

Figure 4. Calculated density of states (DOS) for the most stable in oxaliplatin/CNTs systems at equilibrium geometry, (a) oxaliplatin/CNT (8, 8) and (b) oxaliplatin/CNT (14, 0) complexes.

As was clearly seen, for the oxaliplltin/CNT (8, 8) system new peaks appear above the Fermi level and also the band gap of oxaliplltin/CNT (14, 0) complex reduces hence one can expect a significant enhancement in conductivity of the complexes under study. The DOS of the encapsulated drug molecule into the CNT (14, 0) shifted slightly which clearly shows a weak charge transfer between the respected CNTs and oxaliplatin in the adsorption process. We then performed the Mulliken charge analyses to estimate the amount of electron transfer between SWCNTs and oxaliplatin. Charge analysis revealed a charge transfer of 0.05 and 0.04 e from oxaliplatin molecule to carbon nanotubes for the most favorable oxaliplatin/CNT (8, 8) and oxaliplattin/CNT (14, 0) complexes, respectively. This finding confirms that weak interaction takes place between the respective entities. More insight can be gained from total electron density maps of the electronic densities. Figure 5 represents calculated isosurface maps for the most stable oxaliplatin/CNT complexes. For the energetically favorable complexes, we find that the physically adsorbed oxaliplatin is far from the interior side wall of the tube has almost no effect on the electronic charge distribution of C atoms of the SWCNTs. Thus no charge transfers between the oxaliplatin and SWCNTs molecular orbitals occurs. Figure 5 shows also that the highest occupied molecular orbital (HOMO) being localized on the oxaliplatin while the lowest unoccupied molecular orbital (LUMO) being distributed on SWCNTs. This confirms charge transfer from the oxaliplatin molecule toward the SWCNTs among the encapsulation process. From the obtained results here, we can conclude that the oxaliplatin weakly binds to the interior side wall of the SWCNTs and the small interaction obtained quantitatively in terms of binding energies.

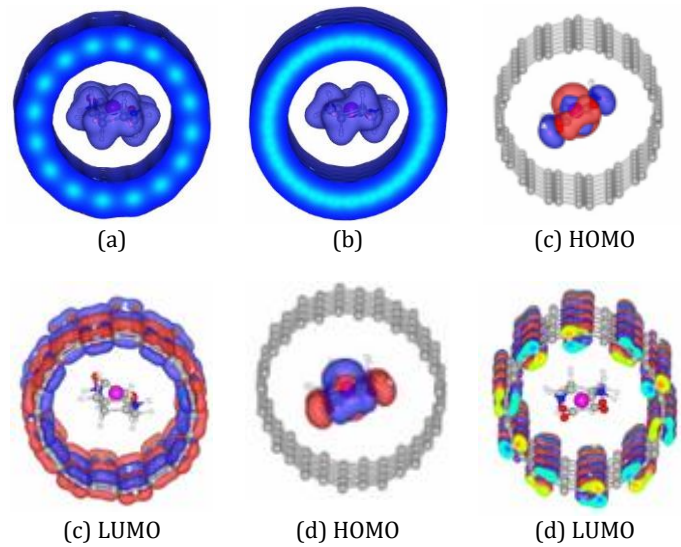


Figure 5. Calculated total electron density for the (a) oxaliplatin/CNT (8, 8) and (b) oxaliplatin/CNT (14, 0) complexes, where 0.05 was used as an isovalue of total electron density. The orbitals localized on the top most valence band (HOMO) and the lowest conduction band (LUMO) for the (c) oxaliplatin/CNT (8, 8) and (d) oxaliplatin/CNT (14, 0) systems (the absolute values of the isosurfaces of the wave functions are 0.02).

3. Conclusion

In summary, we have theoretically investigated the incorporation of oxaliplatin molecule inside the semiconducting and metallic SWCNTs using the first-principles calculations based on vdW-DF methods. Various diameters of SWCNTs from 8 to 15 Å were considered. A full structural relaxation procedure was carried out for all the systems under study. The obtained results indicated that metallic SWCNTs exhibit slightly weaker interaction with the encapsulated oxaliplatin in comparison with the semiconducting one. However, the binding energies value and equilibrium distances obtained from first-principles calculations for the energetically favorable complexes are typical for the physisorption. Our results showed that semiconducting nanotube with diameter of about 11 Å is suitable for the encapsulation of oxaliplatin. In the case of metallic one the corresponding value is determined to be about 9 Å (Fig. 3). A study of the electronic structure indicated that no significant hybridization between the respective orbitals of the host-guest entities takes place that explain the observed small interaction and weak charge transfer between the CNTs and the oxaliplatin. Our first-principles findings provide a molecular insight into understanding of the interaction between oxaliplatin and SWCNTs and hope to be helpful to the relevant experimental researchers who effort to realize suitable nanovectors for drug delivery.

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