Hindawi Publishing Corporation
Journal of Nanomaterials
Volume 2015, Article ID 380348, 6 pages
http://dx.doi.org/10.1155/2015/380348

Research Article

Carboxylated Capped Carbon Nanotubes Interacting with Nimesulide Molecules: Applied Electric Fields Effects

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Received 20 August 2015; Accepted 2 November 2015

Academic Editor: Yuan Chen

Interactions of carboxylated capped carbon nanotubes with nimesulide molecules under electric fields were investigated by *ab initio* simulations. Repulsive forces between the nimesulide molecules and the carboxyl group of the carbon nanotubes, except for the nimesulide radical configuration, were observed. To keep the original molecule in the pristine form, electric fields with different intensities were applied, where changes in the behavior of the interactions between the molecules were noticed. It was shown that the intensity of the interaction between the nimesulide and the hydrophilic carboxylated capped carbon nanotube can be modulated by the action of the external electric fields making promising systems for drug delivery applications.

1. Introduction

In the world of nanotechnology, carbon nanotube (CN) represents one of the most promising materials for applications in several knowledge areas, because of its exceptional electronic, mechanical, and thermal properties [1]. Due to their susceptibility to chemical interactions, CNs are very favorable for biomedical applications; besides they have dimensions comparable to many biological species.

As nanomaterial for biomedical applications, the use of CN includes biological sensors [1] and drug delivery systems [2], among other possibilities [3]. Until now, it is known that pristine CN presents certain toxicity, but the functionalized one can overcome this problem and could present good biocompatibility, which is crucial for applying this material in biomedical area [4]. Another point to take into account for the successful application of nanotubes in biomedical devices is the fact that, in pristine form, they are hydrophobic and biological fluids are aqueous [3]. It is reported that the introduction of functional groups on the tube surface can surpass these difficulties, and the carboxyl group is the most used one for this goal [5]. In addition to the functionalization of CNs, some interactions may be facilitated by the application of electric fields, which polarizes the system inducing a dipolar momentum, changing the nonpolar character of the tube [6].

Nimesulide is a nonsteroidal anti-inflammatory drug belonging to the class of sulfonamides with anti-inflammatory, antipyretic, and analgesic effect. Despite a wide range of applications, the nimesulide may cause some gastrointestinal disorders [7]. In toxicity studies, it presents essentially liver, renal, and gastrointestinal damage. In Switzerland [8], based on the number of cases reported, it was considered the most hepatotoxic anti-inflammatory drug. Due to studies like this, the use of nimesulide was discontinued in some countries, such as Ireland and many other European countries [9]. Moreover, nimesulide can cause other effects when in higher dose than therapeutic concentrations, which can occur in tissues where the drug is adsorbed, for example, antioxidant activity. The direct delivery of nimesulide molecules to specific tissues could maximize and enhance the positive effects of the drug on the human body as well as avoid the undesirable side effects. The possibility here proposed is the interaction of nimesulide molecules with carboxylated capped carbon nanotubes (CCCN). These nanomaterials can provide an alternative route of drug delivery to a specific part of the body and the carboxyl group may represent a way to control the insolubility and incompatibility of CN [10].

The interactions of nimesulide with pristine and Si-doped capped CN were previously studied by Zanella et al. [11] through first principles calculations, where a physisorption regime was observed. In this paper, repulsive forces were found in the studied interactions, and we proposed overcoming the drawbacks by the application of an electric field, which changes the binding energy values. Previous studies show that the applied electric field can polarize the system, increasing the interactions of CN with polar molecules or even allowing covalent bonds between these systems [6, 12, 13].

2. Methodology

The structural and energetic results for CCCN interacting with nimesulide were performed by *ab initio* density functional theory (DFT) calculations [14, 15]. The SIESTA code [16] was used to execute the simulations and interactions between ionic cores and valence electrons using norm-conserving pseudopotentials (Troullier-Martins) [17]. The double-zeta basis set plus polarization functions (DZP) were employed for all atomic species. The exchange-correlation potential was adjusted by the local density approximation (LDA), according to the parameterization proposed by Perdew and Zunger [18]. A cutoff of 200 Ry for the grid integration in the real space was used, to represent the charge density. The structural optimizations were achieved through the conjugate gradient algorithm [16] until the residual forces were smaller than 0.05 eV/Å.

The binding energies (E_b) were calculated using the basis set superposition error (BSSE) [19]. This correction is done through the counterpoise method using "ghost" atoms within the following equation:

$$E_b = \left[E_T\left(\mathrm{CCCN} + \mathrm{X}\right) - E_T\left(\mathrm{CCCN} + \mathrm{X}_{\mathrm{ghost}}\right) - E_T\left(\mathrm{CCCN}_{\mathrm{ghost}} + \mathrm{X}\right)\right], \quad (1)$$

where X corresponds to the nimesulide molecule and E_T(CCCN + X) is the total energy of CCCN interacting with nimesulide. The "ghost" CCCN/X corresponds to additional basis wave functions centered at the position of the CCCN/X but without any atomic potential.

In order to change the interactions between nimesulide molecules and CCCN, electric fields with different intensities were applied, with the same criteria as studied by de Menezes et al. [6] that considered values of electric field within a range considered practicable not to promote the breakage of the carbon bonds of the nanotubes. The relative energy (E_r) was calculated as the difference between the total energies of the system with/without the applied electric field (E_E)/(E_0):

$$E_r = E_E - E_0. \quad (2)$$

All the calculations were performed using periodic-boundary conditions and supercell approximations. A lateral separation of 40 Å between tube centers was used in order to guarantee that there was no interaction among the periodic images in the perpendicular direction to the tube axis. The unity cell had 120 carbon atoms plus the carboxyl radical, and the tube was (10, 0), with a diameter suitable for closing the tube ends with fragments of fullerene C_{60}. All geometry optimizations were done without any symmetry constraints.

Table 1: Distances and binding energies for the configurations of Figure 1.

System	Bond distance (Å)	E_b (eV)
(i)	1.99 (O-O_{tube})	2.09
(ii)	2.15 (O-O_{tube})	0.62
(iii)	1.36 (C-O_{tube})	−3.85

3. Results

Three configurations were analyzed of the nimesulide moving toward the carboxyl group of the CCCN by the following: (i) oxygen of the -NO_2 group (same configuration studied by Zanella et al. [11], Figure 1(c)), labeled nime-N; (ii) the -SO_2 group (Figure 1(d)), labeled nime-S; and (iii) the -CH_2 nimesulide radical (removing one hydrogen from the -CH_3 group) (Figure 1(e)).

Table 1 shows the values of binding energy (calculated by (1)) and smaller distance between both molecules (CCCN and nimesulide), for the considered configurations. One can observe that the interaction between the oxygen of the nimesulide and the carboxyl group of the tube tends to be repulsive, resulting in a positive binding energy.

Figure 2 shows the energy levels and the plot of the local density of states (LDOS) for all systems of Figure 1. For pristine nimesulide (Figure 2(a)), the plot of electronic charge densities for HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) indicates that there is no contribution of the charge from -CH_3 group. That indicates that this group in the original form is the less reactive part of nimesulide, and to change this scenario, we functionalized the nimesulide molecule removing one hydrogen from this group, forming a dangling bond. For the configuration of the interacting systems in which the -CH_3 group is functionalized by removing one hydrogen, a covalent bond is observed. In this configuration, the HOMO and LUMO energy difference (ΔHL) is almost closed (Figure 2(e)). From the plot of LDOS, as shown in Figure 2(e), a small contribution of the charge from the region of the interaction in the HOMO and a major contribution of this region in the LUMO are observed. In HOMO, the major contribution is in the opposite side to the interaction region, as in the CCCN without the nimesulide (Figure 2(b)). In the nime-N configuration, a charge contribution occurs mainly from the interaction region in the HOMO (Figure 2(c)).

Considering the fact that nimesulide interacts only covalently when functionalized, we apply an external uniform electric field in the CCCN axis direction in order to modulate the intensity of the interaction in the nime-N and nime-S arrangements. For a drug delivery system, a physisorption regime is appropriate due to the possibility of attaching/detaching molecules from a nanostructure, and a covalent bond is too strong to allow this mechanism. Because of that, configuration (iii) (functionalized nimesulide) is

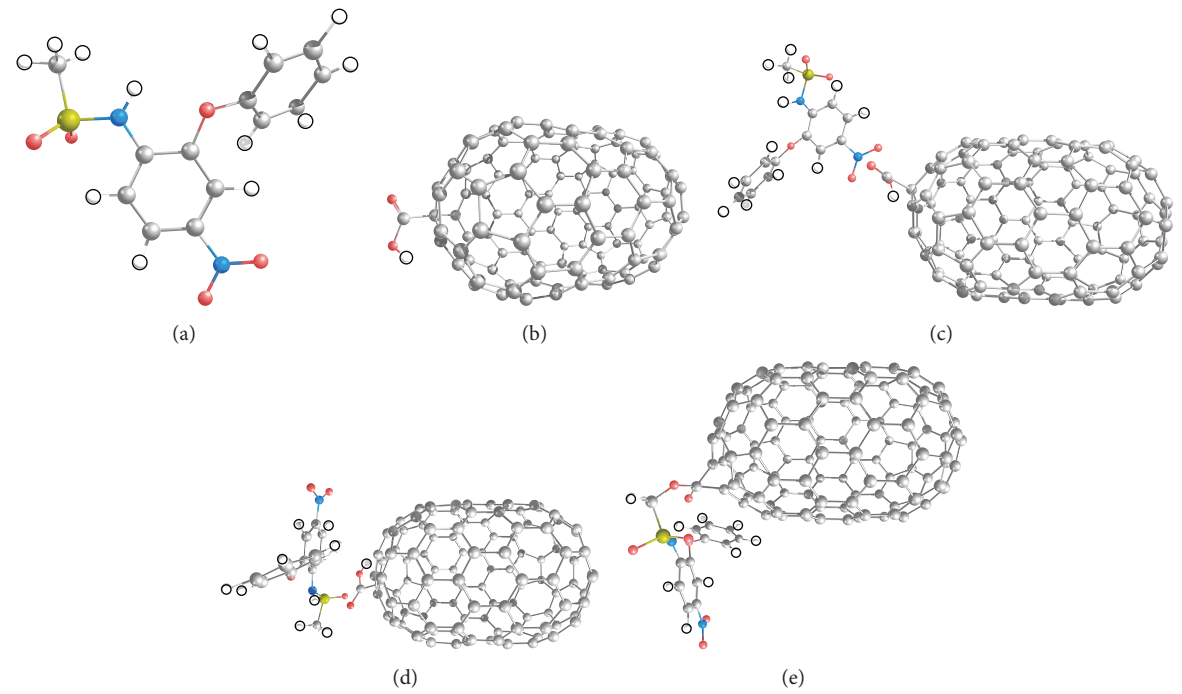

Figure 1: Optimized geometry of (a) isolated nimesulide, (b) isolated CCCN, (c) nime-N, (d) nime-S, and (e) functionalized nimesulide interacting with the nanotube by the -CH_2 group. Grey: carbon; white: hydrogen; blue: nitrogen; red: oxygen; and yellow: sulfur.

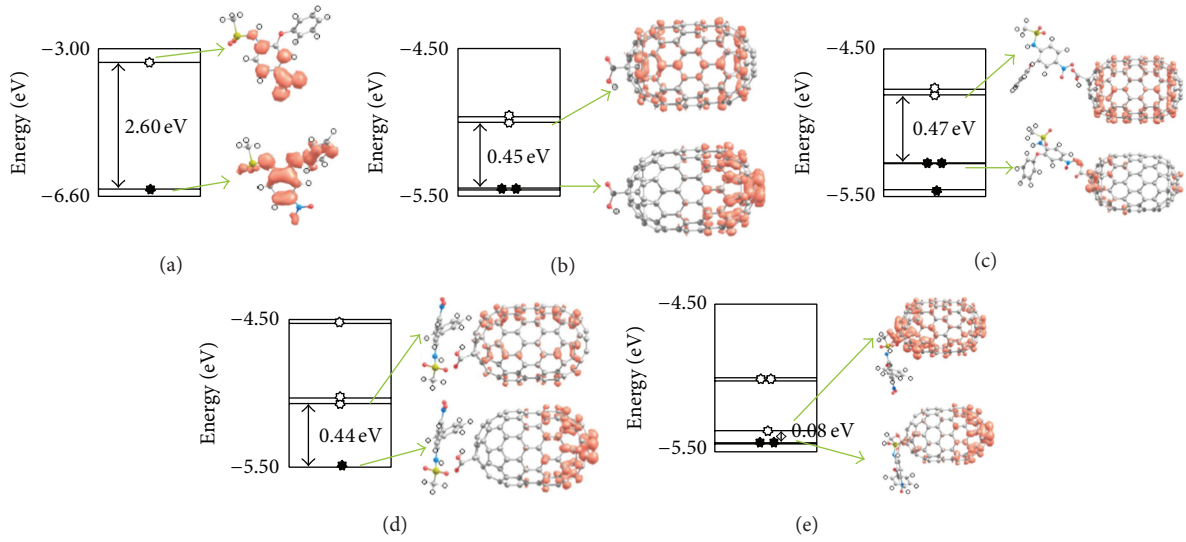

Figure 2: Energy levels and plots of the electronic charge densities (LDOS) for HOMO and LUMO for (a) isolated nimesulide, (b) isolated CCCN, (c) nime-N, (d) nime-S, and (e) nimesulide radical interacting with the CCCN by the -CH_2 group. Filled circles are valence electrons and empty circles are conduction electrons. The isodensity used for the charge density plots was 0.0005 e/Bohr^3.

not considered for the application of the external electric field. The scheme of Figure 3 illustrates how electric fields of 0.05 V/Å were applied on the systems with the isolated nimesulide; similar methodology was previously used by de Menezes et al. [6]. It is relevant to point out that no spin polarization was observed for the most stable configurations.

Different intensities and directions of the applied electric field (−0.05, 0, and 0.05 V/Å) were checked for the configurations nime-N and nime-S. The results for the relative energy (see (2)) show that the stability of the systems occurs with applied electric field parallel [antiparallel] to the tube axis for nime-N [nime-S].

In this way, we consider for nime-N [nime-S] high intensities of the applied electric fields in parallel [antiparallel] direction to the nanotube axis, with the results presented in Table 2. It is not surprising that different configuration requires field applied on opposite orientations. Similar behavior was described by de Menezes et al. [6] when which

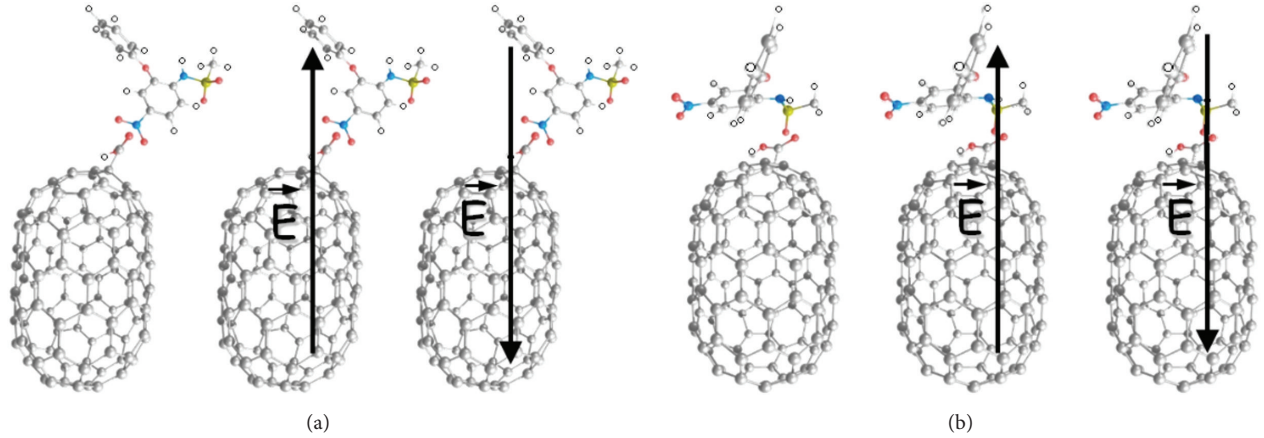

Figure 3: Illustration of the electric field applied to the systems (a) nime-N and (b) nime-S configurations.

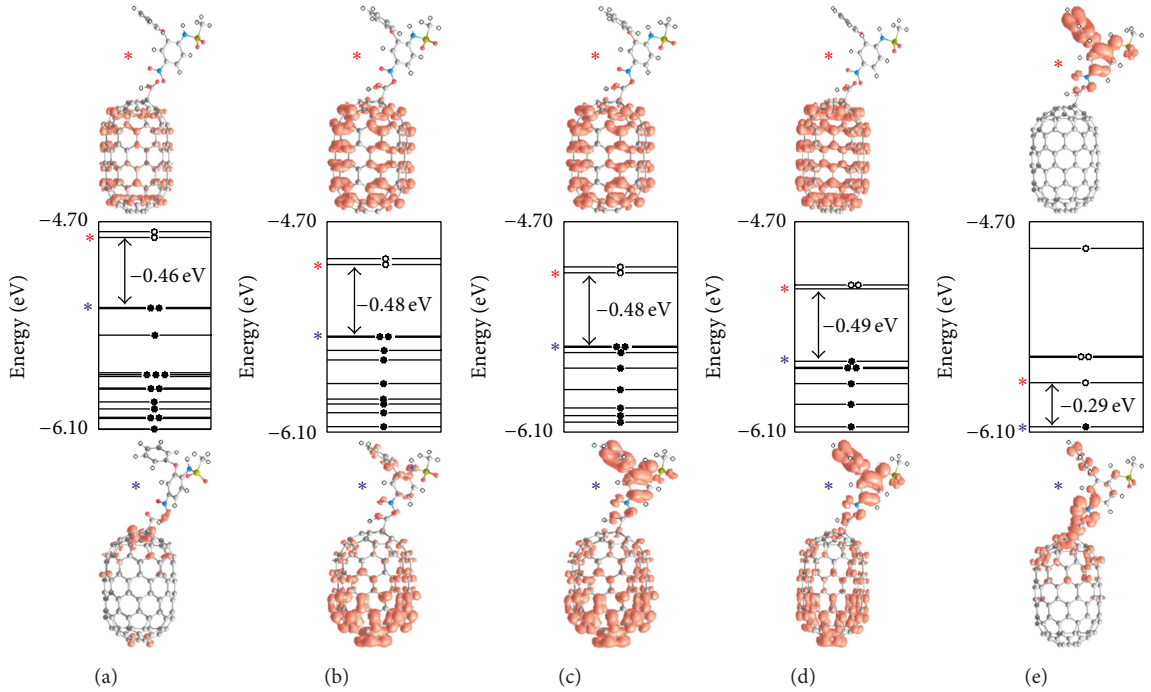

Figure 4: Energy levels and plots of the electronic charge densities for HOMO (assigned by the blue stars) and LUMO (red stars) for the nime-N system under the electric fields of (a) 0, (b) 0.05, (c) 0.10, (d) 0.20, and (e) 0.40 V/Å. For the LDOS plots, the isodensity used was of 0.0005 e/Bohr^3 for all the cases and the energy levels ranges were between −6.10 and −4.70 eV.

orientation of electric field was more favorable to stabilize CN functionalized by amine, amide, hydroxyl, and carboxyl was being determined.

For the nime-N a small rise in the ΔHL of the systems until the electric field is 0.20 V/Å is observed, with an increase in the instability of the systems, as can be observed on the relative binding energies. In case of the nime-S configuration, for all values for the applied electric fields, a reduction on the ΔHL and a growth in the energetic stability are observed.

Figure 4 presents the energy levels and the corresponding LDOS plots for the nime-N configuration with different intensities of applied electric field. A significant reduction of ΔHL around 0.40 V/Å is also observed. In general, the modification on the electronic charge distribution for the HOMO and LUMO levels is observed due to the tendency to polarize the resulting systems. In the specific case of the nime-N under electric field of 0.40 V/Å, the electronic charge in the LUMO moves to nimesulide molecule, mainly in the opposite region of the interaction. In the same case, the electronic charge for the HOMO is located in the region of the interaction between the CCCN and the nimesulide.

For the nime-S, as can be seen in Figure 5, the action of the electric field with intensity of −0.40 V/Å presents the same trend observed for the charge distribution in the LUMO level for the nime-N system. The HOMO level presents

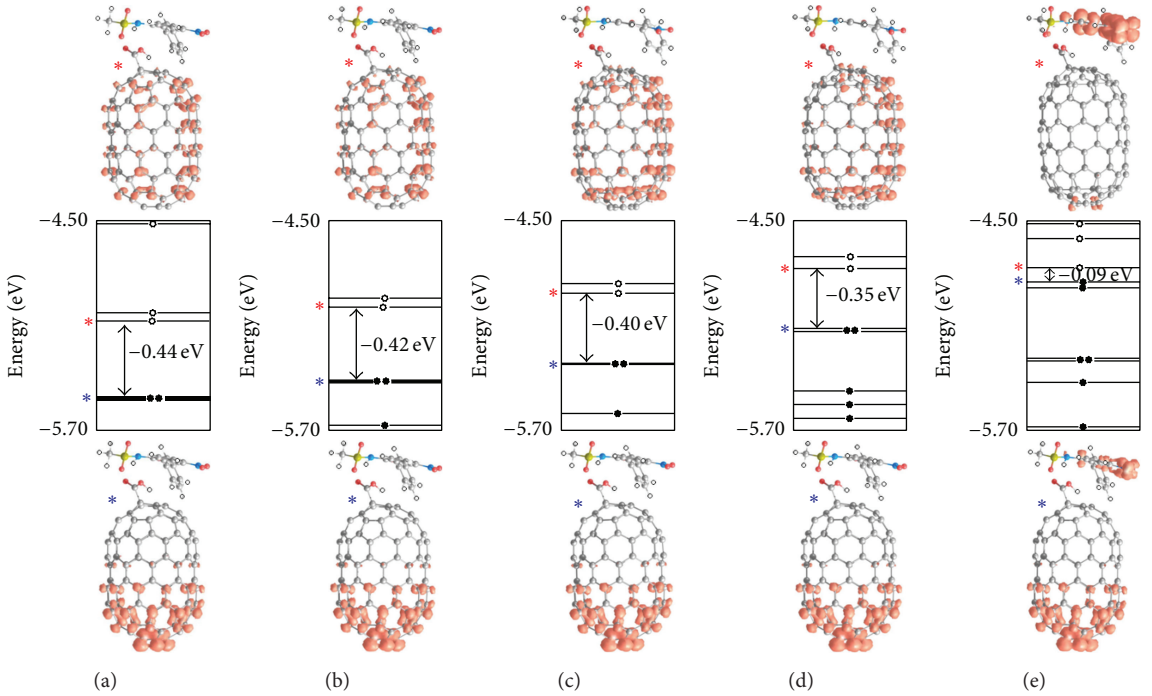

Figure 5: Energy levels and plots of the electronic charge densities for HOMO (assigned by the blue stars) and LUMO (red stars) for the system nime-S under the action of electric fields of (a) 0, (b) −0.05 V/Å, (c) −0.10 V/Å, (d) −0.20 V/Å, and (e) −0.40 V/Å. The isodensity was of 0.0005 e/Bohr^3 for all the cases and the energy levels were between −5.70 and −4.50 eV.

Table 2: Relative energies, binding energies, and ΔHL values for CCCN interacting with the systems nime-N and nime-S under the action of different values of applied electric fields.

	Electric field (V/Å)	E_r (eV)	E_b (eV)	ΔHL (eV)
Nime-N	0	—	2.09	0.46
	0.05	−0.14	2.06	0.48
	0.10	−0.41	1.94	0.48
	0.20	−1.40	1.41	0.49
	0.40	−5.38	−1.02	0.29
Nime-S	0	—	0.62	0.44
	−0.05	−0.07	0.61	0.42
	−0.10	−0.20	0.58	0.40
	−0.20	−0.66	0.49	0.35
	−0.40	−2.34	0.19	0.09

electronic charge in the opposite regions to the interaction, both in the nanotube and in the nimesulide molecule.

Besides, some gas adsorption behavior on carbon based materials has been investigated, where the application of an external electric field can modulate the adsorption/desorption of the molecules being able to act as a reversible switch [20, 21].

The explanation for enhancement (or even weakening) of these interactions is the induction of an extra dipole moment and the appearing of the Stark effect, which causes the spin splitting and degeneracy breaking of energy levels [6, 20, 21]. It is possible to see in [6] a systematic study of the polarization associated with the electric dipole moment of CCCN induced by electric fields of the same intensities here studied. The degeneracy breaking of energy levels in our study is more evident in HOMO levels in both cases (nime-N (Figure 4) and nime-S (Figure 5)), as well as in all cases of functionalized carbon nanotubes studied in [6]. The external electric field can also modulate the bonding properties of van der Waals complexes between π-systems and other species through the polarization of the systems [22, 23].

4. Conclusions

In summary, different arrangements for the nimesulide molecules and CCCN interactions were reported here. However, the trend is that the pristine nimesulide molecule does not present chemical bond with CCCN, these nanostructures being not favorable for carrying out nimesulide in the original form. In both studied configurations of pristine nimesulide interacting with CCCN positive values of binding energies were observed.

Nevertheless, considering carbon nanotubes as component of drug delivery systems, it would be interesting to show the physical interaction between these systems. Then, a way to get the physical adsorption modulated by applying external electric fields was proposed here. We have demonstrated that the interaction between the CCCN and the nimesulide molecule becomes more favorable when exposed to the action of an external electric field, and this knowledge could be extended to interactions with other molecules with

nanotubes. It is important to observe that values out of the applied electric field range considered in this work can produce negative effects associated with break of chemical bonds of the original systems (carbon nanotubes and/or adsorbed molecules), creating structures with different properties that are not of interest for drug delivery.

Then, the studied systems are relevant for biomedical applications because they can combine the hydrophilic properties of the CCCN with the modulation of the intensity of the nimesulide interaction through external physical agents.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

The authors acknowledge CENAPAD-SP for computer time and the Brazilian agencies CNPq and FAPERGS for financial support.

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