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STUDY OF STRUCTURAL AND ELECTRONIC PROPERTIES OF BC_2N NANOTUBE INTERACTING WITH ANTI INFLAMMATORY DRUGS[1]

ESTUDO DAS PROPRIEDADES ESTRUTURAIS E ELETRÔNICAS DO NANOTUBO DE BC_2N INTERAGINDO COM FÁRMACOS ANTIFLAMATÓRIOS

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ABSTRACT

Interaction between BC_2N nanotube armchair (3,3), nimesulide, and acetylsalicylic acid were studied by first principles calculations based on Density Functional Theory (DFT). Usually used for the treatment of acute and chronic inflammatory conditions, these drugs have anti-inflammatory activity, but can cause many adverse reactions. BC_2N nanotube could be used as carrier of nimesulide and acetylsalicylic acid because the interaction of drugs with nanostructure materials could minimize side effects and aid these drugs to act in target sites. Results found indicate a weak (physical adsorption) interaction between BC_2N nanotube and nimesulide with binding energies that range from -0.13 eV to -0.27 eV. Binding energies found for the interaction between acetylsalicylic acid and BC_2N nanotube range from -0.24 eV to -0.45 eV, characterizing the interaction as weak (physical adsorption). These results indicate the possibility of use BC_2N nanotubes as carrier for nimesulide and acetylsalicylic acid.

Keywords: acetylsalicylic acid, carrier, Density Functional Theory, nanostructure, nimesulide.

RESUMO

A interação entre o nanotubo de BC_2N do tipo armchair (3,3), nimesulida e o ácido acetilsalicílico foram estudados por cálculos de primeiros princípios com base na Teoria do Funcional da Densidade (DFT). Utilizados no tratamento de condições inflamatórias agudas e crônicas, esses fármacos têm atividade anti-inflamatória, porém, podem causar inúmeras reações adversas. O nanotubo de BC_2N pode ser usado como carreador da nimesulida e do ácido acetilsalicílico, pois a interação de fármacos com nanomateriais pode minimizar os efeitos colaterais e auxiliar esses medicamentos a atuarem nos órgãos alvos. Os resultados encontrados indicam uma interação fraca (adsorção física) entre o nanotubo de BC_2N e nimesulida, com energias de ligação que variam de -0,13 eV a -0,27 eV. As energias de ligação encontradas para a interação entre o ácido acetilsalicílico e o nanotubo de BC_2N variam de -0,24 eV a -0,45 eV, caracterizando a interação como fraca (adsorção física). Estes resultados indicam a possibilidade de utilizar o nanotubo de BC_2N como carreador para a nimesulida e o ácido acetilsalicílico.

Palavras-chave: *ácido acetilsalicílico, carreador, Teoria do Funcional da Densidade, nanoestrutura, nimesulida.*

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INTRODUCTION

The discovery of carbon nanotubes (IIJIMA, 1991) led researchers to investigate the possibility to form nanotubes from other chemical elements, such as Boron (B) and Nitrogen (N), where the hybridization is similar to Carbon (C). Nanotubes composed of B, N and C (BCNNTs) were theoretically proposed (MIYAMOTO et al., 1994) and experimentally synthesized (YIN et al., 2005). Ciofani et al. (2009) studied the interaction between living cells and BNNTs, their study highlighted the potential application of these nanotubes in magnetic treatment, physically guided delivery of drugs and drug targeting. Among BNNTs the BC_2N NT is considered the most stable due to the several C-C and B-N bonds, presenting four sites of interaction (C_I, C_{II}, N and B) (ROSSATO; BAIERLE; ORELLANA, 2007). Previous studies have proposed nanostructures as carrier to minimize nimesulide side effects (ZANELLA et al., 2007).

Nimesulide is an anti-inflammatory non-steroid drug with anti-inflammatory, analgesic and antipyretic actions (BEVILACQUA; MAGNI, 1993), similar to acetylsalicylic acid. Acetylsalicylic acid is commonly known as aspirin, used as anti-inflammatory, antipyretic, analgesic and antiplatelet (VANE; BOTTING, 2003). These drugs can present several side effects, including abdominal cramps, nausea, vomiting, headache and dizziness. Thus, the combination of these molecules with BC_2N NTs could minimize their side effects.

Many studies about the interaction between nanostructures and nimesulide, and acetylsalicylic acid are found in literature (ABBASI; JAHANBIN-SARDROODI, 2016; BUKKITGAR et al., 2016; JAURIS et al., 2017; VESSALLY et al., 2017; ZHANG et al., 2010). Zanella et al. (2007) investigated the use of pristine and Si-doped capped SWNTs to be used in a delivery system to nimesulide. The results found indicated nimesulide interacts with pristine capped SWNTs under a physiosorption regime, and interaction of nimesulide with Si-doped SWNTs is strong. These results show capped carbon nanotube could be a promising drug delivery system for nimesulide. Another theoretical study found a stable interaction between nimesulide and carbon nanotubes. This stability is assigned by the authors to the nanotube curvature, which increases the adsorption between the molecule and the nanotube (JAURIS et al., 2015). Also, experimental studies found feasible to load acetylsalicylic acid onto carbon nanotubes using sonication method in order to study the release of this drug (YUSOF et al., 2009). To our knowledge, this is the first study of the interaction of BC_2N NT and these drugs.

Therefore, the aim of this study is to investigate by means of first principles calculations based on Density Functional Theory (DFT) the interaction of nimesulide, and acetylsalicylic acid, with BC_2N NT armchair (3,3). Structural and electronic properties from different configurations of these molecules interacting with BC_2N NT were analysed. These investigations could predict BC_2N nanotube as a possible carrier for nimesulide and acetylsalicylic acid.

MATERIAL AND METHODS

Structural and electronic properties of nimesulide and acetylsalicylic acid molecules interacting with BC_2N nanotube were obtained by first-principles calculations based on DFT, which describes properties of the systems based on its electronic density (HOHENBERG; KOHN, 1964). DFT associated with pseudopotential method is implemented on SIESTA code (SOLER et al., 2002), which performs self-consistent calculations. Using a numerical base obtained from the pseudo-atomic orbitals SIESTA code describes the wave functions of the systems under study. To describe the exchange-correlation term the Local Density Approximation (LDA) (CEPERLEY; ALDER, 1980) was used and the double-ξ bases plus polarization function (DZP) is incremented. The norm-conserving pseudopotentials of Troullier-Martins (TROULLIER; MARTINS, 1991) describes the interaction between the electrons of the valence level.

BC_2N NT armchair type (3,3) of 288 atoms was used to perform our calculations. Optimizations of geometry were conducted with total relaxation of BC_2N NT and molecules atoms. Binding energy (E_B) was calculated using basis set superposition error (BSSE) (BOYS; BERNARDI, 1970) (1):

$$E_B = [\, E_T\,(BC_2N + drug) - E_T\,(BC_2N + drug_{ghost}) - E_T\,(BC_2N_{\,ghost} + drug)] \quad (1)$$

where E_T (BC_2N + *drug*) is the total energy of the system, which is the total energy of the interaction between BC_2N NT and the molecule; E_T ($BC_2N + drug_{ghost}$) is the total energy of the interaction between BC_2N NT and the ghost molecule; $E_T(BC_2N_{ghost} + drug)$ is the total energy of the interaction between ghost BC_2N NT and the molecule. The 'ghost' term corresponds to additional basis wave functions without atomic potential centered at the position of the drugs or at the BC_2N.

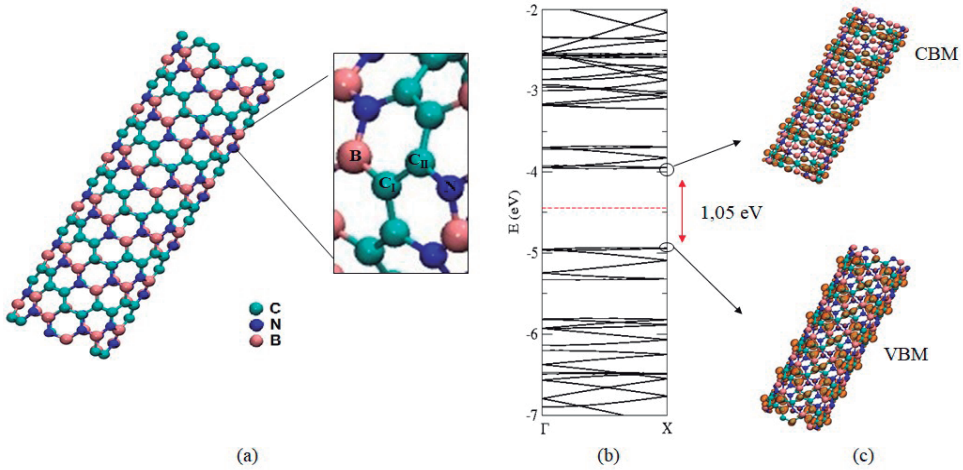
RESULTS AND DISCUSSION

BC_2N NANOTUBE

Geometry of equilibrium for BC_2N NT, its electronic band structure and the local density of states (LDOS) associated to valence band maximum (VBM) and conduction band minimum (CBM) are presented in figure 1 (a), (b) and (c), respectively. Also, in figure 1 (a) we can show the zoom of the structure with the four sites of interaction specified, where C_I is bonded to two carbon atoms and one boron, and C_{II} is bonded to two carbon atoms and one nitrogen. As shown in figure 1 (b), the calculated band gap is 1.05 eV, which characterizes BC_2N NT as a semiconductor material, this value is in good agreement with the literature (PAN; FENG; LIN, 2006; ROSSATO; BAIERLE; ORELLANA, 2007). Charge density for VBM is more concentrated on C_I site and for CBM is more

concentrated on C_{II} site. These results are also in agreement with the literature data (PAN; FENG, LIN, 2006).

Figure 1 - Geometry of equilibrium (a), electronic band structure (b) and LDOS (c) associated to the VBM and CBM of the BC_2N nanotube.

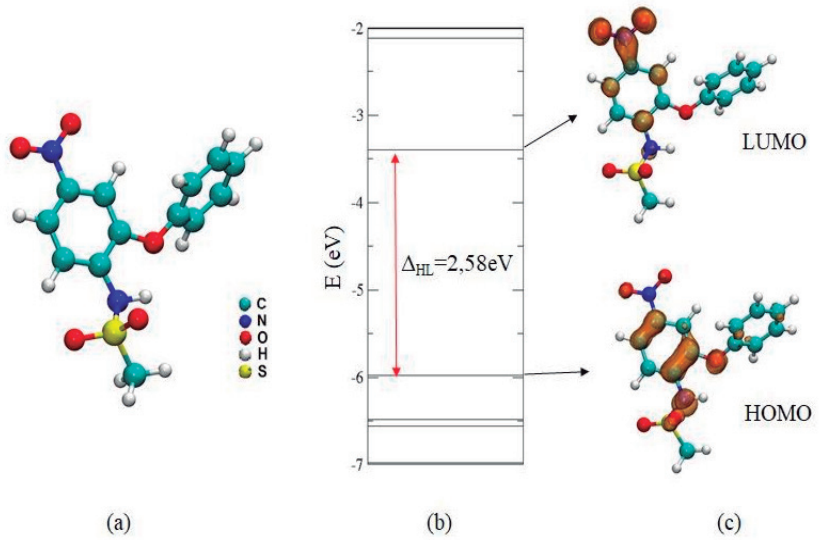


BC_2N nanotube (3,3) has a diameter of 8.34 Å and 48 atoms in its unit cell. The bond lengths of the C-C, B-N, C-N and C-B were found to be on average, 1.44 Å, 1.44 Å, 1.39 Å and 1.54 Å, respectively, which is in agreement with the literature (MIYAMOTO et al., 1994).

NIMESULIDE AND ACETYLSALICYLIC ACID

In figure 2 (a)-(c) we can show the nimesulide optimize geometry, its energy levels and LDOS associated with the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO).

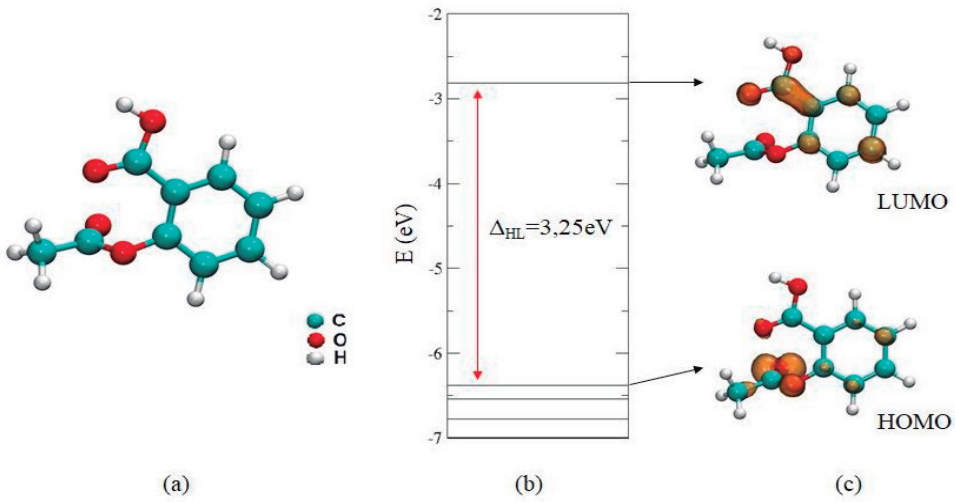
Figure 2 - Optimized geometry (a), energy levels (b) and LDOS (c) for HOMO and for LUMO of nimesulide.



For nimesulide molecule the difference found between HOMO/LUMO ($_{HL}$) was of 2.58 eV, in LDOS presented in figure 2 (c), one can observe a higher concentration of charge on NO_2, benzene and SO_2 of the molecule. These results are in good agreement with literature data ($_{HL}$=2.55 eV) (ZANELLA et al., 2007).

Figure 3 (a)-(c) presents acetylsalicylic acid optimize geometry, its energy levels and LDOS associated with HOMO and LUMO.

Figure 3 - Optimized geometry (a), energy levels (b) and LDOS (c) for HOMO and for LUMO of acetylsalicylic acid.

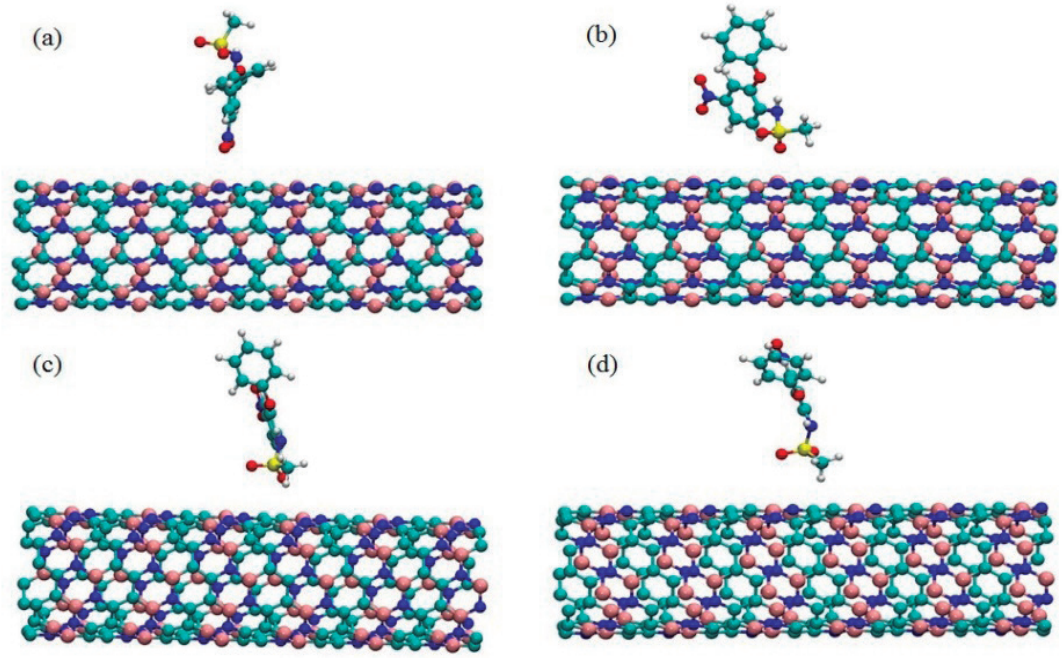


For acetylsalicylic acid molecule the $_{HL}$ found was of 3.25 eV. In LDOS presented in figure 3 (c), it is observed a higher concentration of charge density on CO_2, O and benzene of the molecule. These results are in agreement with literature data (ABBASI; JAHANBIN-SARDROODI, 2016).

BC_2N INTERACTING WITH NIMESULIDE AND ACETYLSALICYLIC ACID MOLECULES

To analyze the interaction between nimesulide and BC_2N NT, four groups of the molecule (CH_3, NO_2, SO_2 and C_6H_5) were place to interact with the four atomic sites of BC_2N NT, totalizing in 16 configurations. Figure 4 (a)-(d) presents only the most stable configurations obtained from interactions between BC_2N NT sites and nimesulide: N_{tube}-NO_2, B_{tube}-SO_2, C_{Itube}-SO_2 and C_{IItube}-CH_3.

Figure 4 - Relaxed structure for (a) N_{tube}-NO_2, (b) B_{tube}-SO_2, (c) C_{Itube}-SO_2 and (d) C_{IItube}-CH_3.



To analyze the interaction between acetylsalicylic acid and BC_2N NT, three acetylsalicylic acid groups (CH_3, OH and C_6H_4) were placed to interact with the four atomic sites of BC_2N NT, totalizing in 12 configurations. Figure 5 (a)-(d) presents only the most stable configurations obtained from the interaction between the BC_2N NT sites and acetylsalicylic acid: N_{tube}-OH; B_{tube}-OH; C_{Itube}-C_6H_4 and C_{IItube}-OH.

Figure 5 - Relaxed structure for (a) N_{tube}-OH, (b) B_{tube}-OH, (c) C_{Itube}-C_6H_4 and (d) C_{IItube}-OH.

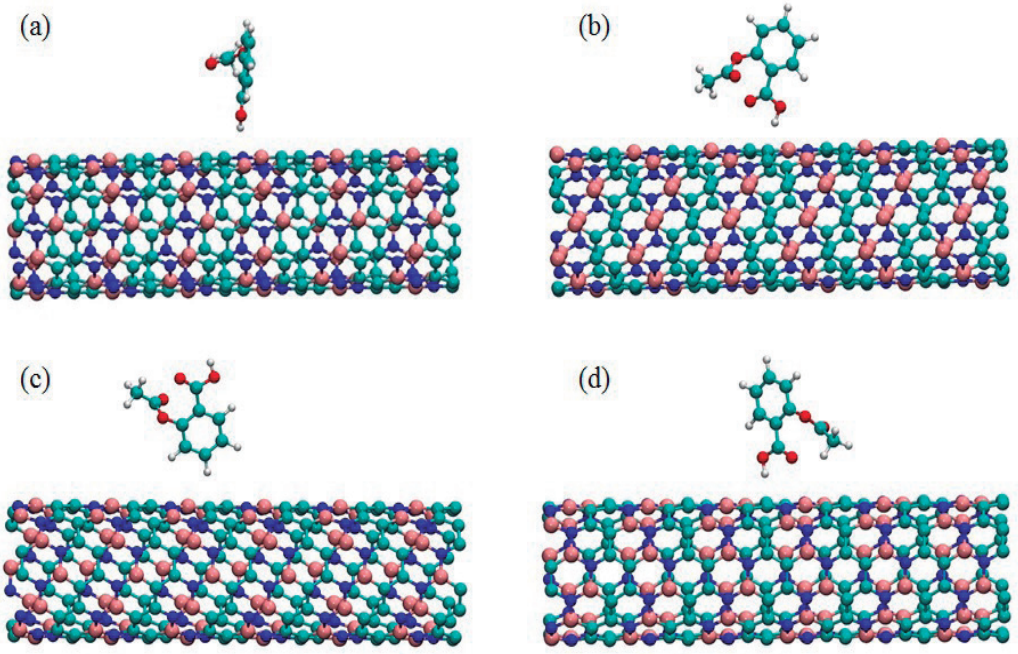


Table I shows the values of smaller distance (D), binding energy (E_B) and charge transfer (Δq) obtained for configurations presented in figure 3 and figure 5. Binding energies for all systems were calculated using equation (1).

Table 1 - Smaller distance (D), binding energy (E_B), and charge transfer (Δq) for the most stable interactions between molecules and BC_2N NT sites.

Configurations	Bond sites	D(Å)	E_B (eV)	Δq (e)
BC_2N- Nimesulide	$\mathbf{N}_{BCN}$-N$\mathbf{O}_{2nimesulide}$	2.80	-0.15	+0.08
BC_2N- Nimesulide	$\mathbf{B}_{BCN}$-S$\mathbf{O}_{2nimesulide}$	2.43	-0.27	+0.07
BC_2N- Nimesulide	$\mathbf{C}_{\mathbf{I}BCN}$-S$\mathbf{O}_{2nimesulide}$	2.80	-0.15	+0.02
BC_2N- Nimesulide	$\mathbf{C}_{\mathbf{II}BCN}$-C$\mathbf{H}_{3nimesulide}$	2.28	-0.13	-0.06
BC_2N- Acetylsalicylic Acid	$\mathbf{N}_{BCN}$-O$\mathbf{H}_{acetylsalicylic\ Acid}$	1.95	-0.24	-0.11
BC_2N- Acetylsalicylic Acid	$\mathbf{B}_{BCN}$- O$\mathbf{H}_{acetylsalicylic\ Acid}$	2.22	-0.34	-0.20
BC_2N- Acetylsalicylic Acid	$\mathbf{C}_{\mathbf{I}BCN}$-$C_6\mathbf{H}_{4acetylsalicylic\ Acid}$	2.26	-0.45	-0.08
BC_2N- Acetylsalicylic Acid	$\mathbf{C}_{\mathbf{II}BCN}$- O$\mathbf{H}_{acetylsalicylic\ Acid}$	2.00	-0.24	-0.11

The smallest distances between nimesulide atoms and BC_2N NT site range from 2.23 to 2.80 Å. Binding energies between BC_2N NT and nimesulide range from -0.13 eV to -0.27 eV. Binding energies between BC_2N NT and acetylsalicylic acid range from -0.24 eV to -0.45 eV. These values are in agreement with the literature data for interactions of nanostructures with anti-inflammatory drugs. Jauris et al. (2016) reported binding energies values of -0.4 eV and -1.0 eV for the interaction of nimesulide with fullerene and carbon nanotubes.

Highlighted atoms in table 1 represent the atoms that were placed the closest of BC_2N NT. In all cases which hydrogen (H) is the closest of the BC_2N NT site, the charge transfer is negative, indicating charge transfer occurs from the molecule to BC_2N NT. All interactions in which oxygen (O) atom is the closest of the BC_2N NT site, the charge transfer is positive, indicating charge transfer occurs from BC_2N NT to the molecule.

Figures 6 and 7 shows the calculated electronic band structure for BC_2N NT, energy levels of the molecules and electronic band structures for the configurations presented in table 1.

Figure 6 - Electronic band structure of BC_2N nanotube (a), energy levels of nimesulide (b) and electronic band structures for N_{tube}-NO_2 (c), B_{tube}-SO_2(d), C_{Itube}-SO_2 (e) and C_{IItube}-CH_3 (f).

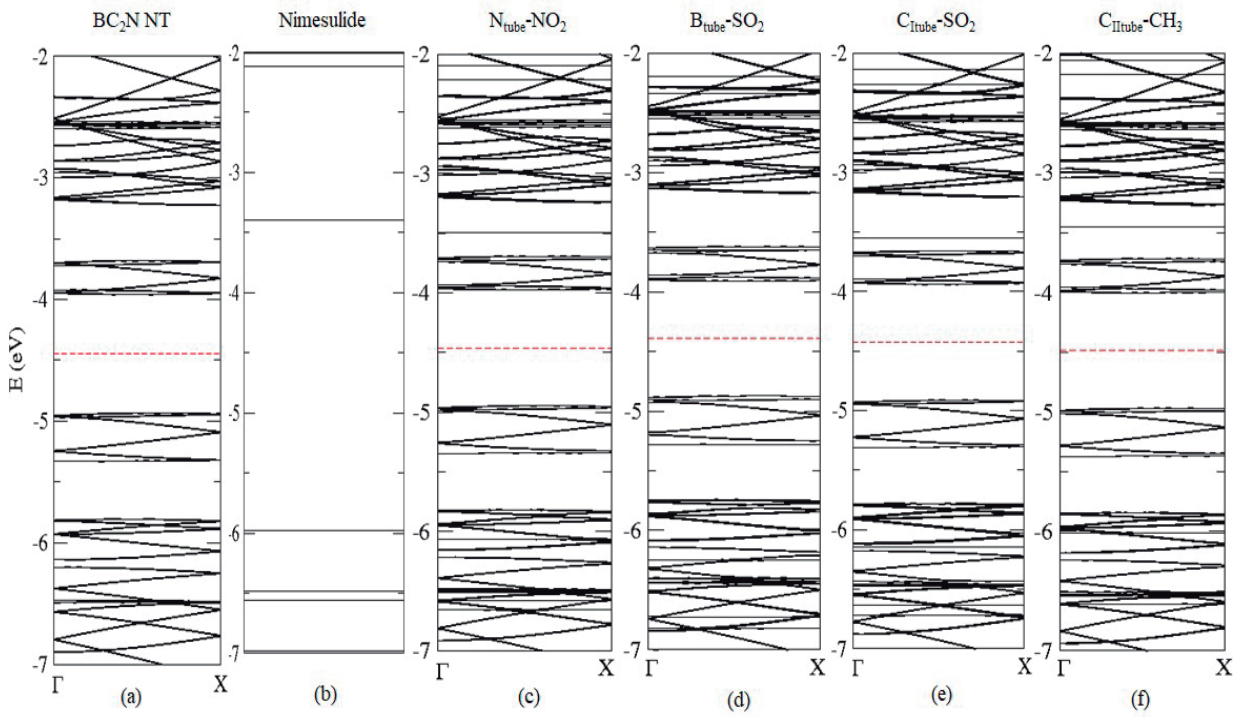
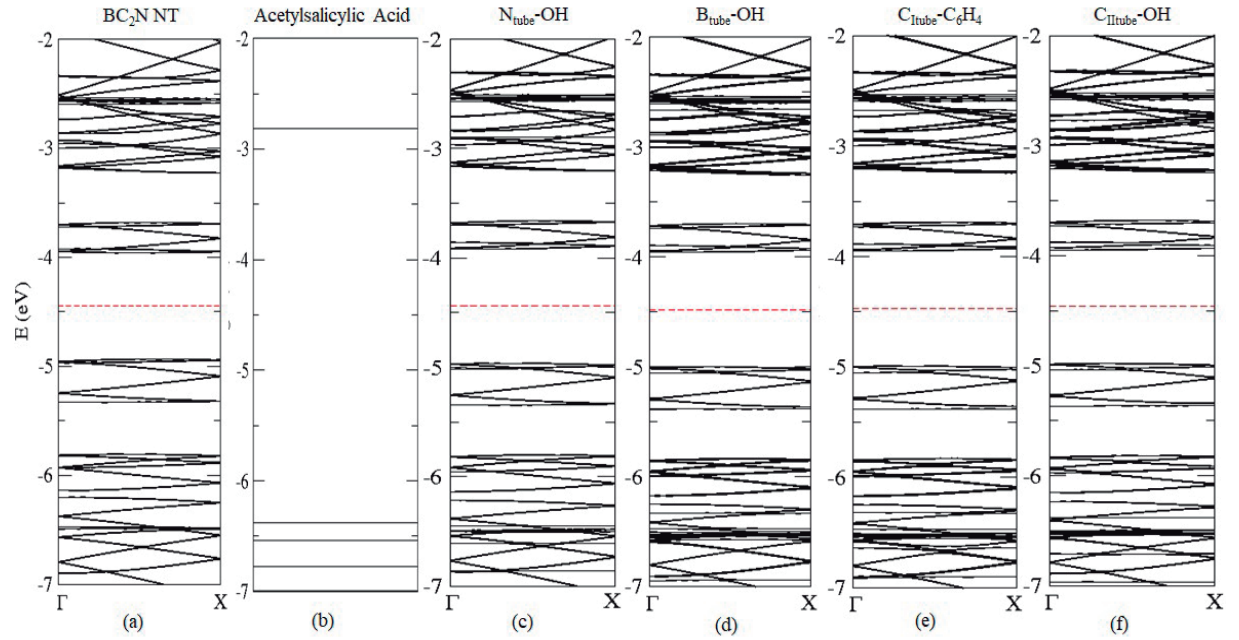


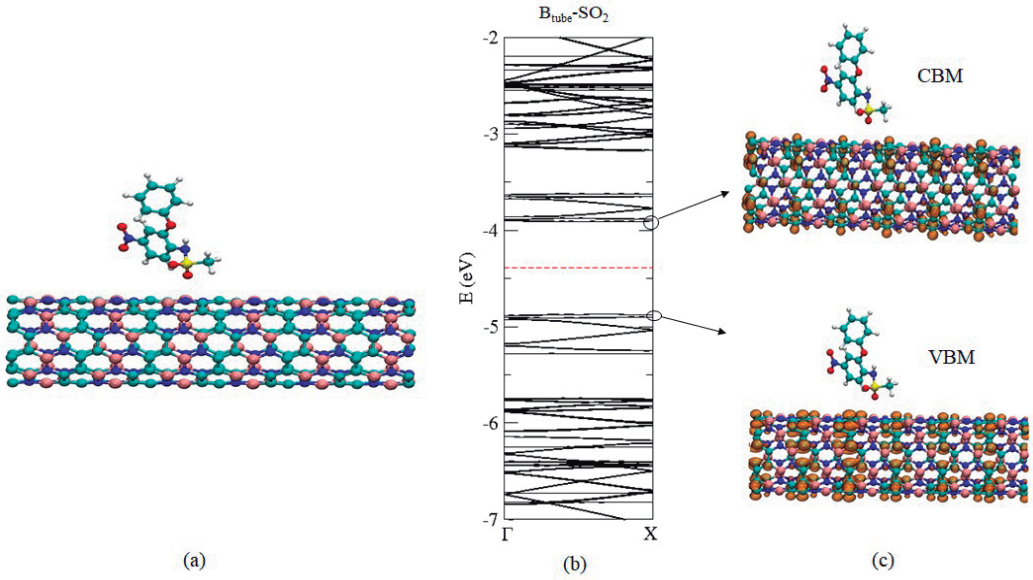
Figure 7 - Electronic band structure of BC_2N nanotube (a), energy levels of acetylsalicylic acid (b) and electronic band structures for N_{tube}-OH (c), B_{tube}-OH (d), C_{Itube}-C_6H_4 (e) and C_{IItube}-OH (f).



In figures 6 and 7 it is observed little or no significant change around the Fermi energy in the electronic band structures indicating a weak interaction between BC2N NT and molecules, which is in agreement with the values found for binding energies. In figures 8 and 9 we can observe the relaxed

configuration, electronic band structure and LDOS for the most stable configuration of BC2N NT interacting with nimesulide (B_{tube}-SO_2) and acetylsalicylic acid (C_{Itube}-C_6H_4), respectively.

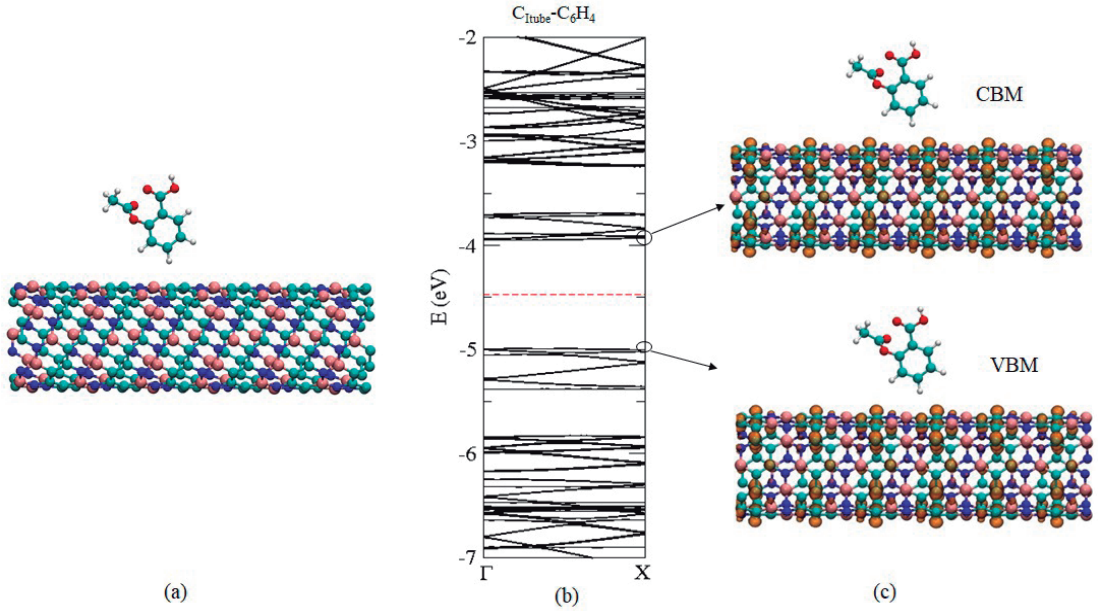
Figure 8 - Geometry of equilibrium (a), electronic band structure (b) and LDOS associated to VBM and CBM for B_{tube}-SO_2.



For B_{tube}-SO_2 the binding energy is -0.27 eV, B-O distance is 2.43 Å and charge is +0.07e.

For this configuration, one can see in Figure 8 (b) that there was no significant change in the electronic band structure around the Fermi energy after the interaction. Also, in figure 8 (c) we can observe that the charge density is concentrated, for VBM and CBM, only on BC2N NT, which indicates weak interaction, a physical adsorption, between BC2N NT and nimesulide.

Figure 9 - Geometry of equilibrium (a), electronic band structure (b) and LDOS associated to VBM and CBM for C_{Itube}-C_6H_4.



For C_{Itube}-C_6H_4 the binding energy is -0.45 eV, distance C_I-H is 2.26 Å and charge is 0.08e. For this configuration, one can see in Figure 9 (b) that there was not there significant change in the electronic band structure around the Fermi energy after the interaction. Also, we can observe that charge density is concentrated, for VBM and CBM, only on BC_2N NT indicating a weak interaction, a physical adsorption, between BC_2N NT and acetylsalicylic acid.

CONCLUSIONS

By means of first-principles simulations the interaction between BC_2N NT and nimesulide and acetylsalicylic acid were studied. The smallest distances between molecules and BC_2N NT range from 2.23 Å to 2.80 Å. In all cases which hydrogen (H) is the closest of BC_2N NT site the charge transfer occurs from the molecule to the nanotube; cases in which oxygen (O) atom is the closest of BC_2N NT site the charge transfer occurs from BC_2N NT to the molecule. Binding energies ranged from -0.45 eV to -0.07 eV and BC_2N NT maintained its semiconductor character. The electronic properties not change significantly after the interactions with the molecules, which characterize a physical adsorption. Also, another indication of physical adsorption is that charge density after the interactions are concentrated only on BC_2N NT. These results show the possibility of using BC_2N NT as drug carriers since its interaction with the different groups of the molecules is weak.

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