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Armchair BN nanotubes—levothyroxine interactions: a molecular study

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Abstract The density functional theory has been applied to investigate the structural and electronic properties of single-wall boron nitride nanotubes (SW-BNNT) of (5,5) chirality, with surface and ends functionalized by the drug levothyroxine ($C_{15}H_{11}NI_4O_4$). The exchange-correlation energies have been modeled according to the Hamprecht-Cohen-Tozer-Handy functional within the generalized gradient approximation (HCTH-GGA) and a base function with double polarization has been used. The (5,5) BNNT-Levothyroxine structural optimization has been done considering the minimum energy criterion in nine possible atomic structures. Simulation results indicate that the preferential adsorption site (chemical adsorption) of the levothyroxine fragment is at the nanotube ends. The BNNT-Levothyroxine system polarity increases which indicates the possible dispersion and solubility both non-solvated and solvated in water. The BNNT-Levothyroxine solvated in water modifies its chemical reactivity which may allow the drug delivery within the biological systems. On the other hand, the decrease in the work function is important for the optoelectronic device design, which also makes these materials suitable to improve the field emission properties.

Keywords Boron nitride nanotubes · DFT theory · Levothyroxine · Solvatation · Work function

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Introduction

The theoretical prediction reported by Rubio et al. [1] and the experimental realization by Chopra et al. [2] of the boron nitride nanotubes (BNNTs) synthesis have motivated scientists a little to investigate these systems as in the case of carbon nanotubes (CNTs). However BNNTs have been only a little bit explored for applications in medicine or in the fabrication of optoelectronic devices. The limited use of BNNTs is because of the low solubility and the difficulty to have clean surfaces. Recently have been reported studies of the water functionalized nanotubes [3], as well as applications in biology as anti-cancer drug when toxicity is reduced [4]. When the nanotubes are polymer functionalized it is possible to apply them as biosensors to measure glucose [5] and as visible light emitting devices [6]. Therefore it is important to investigate the functionalization of BNNTs at the surface and ends (unsaturated dangling bonds) with different functional groups or molecules in order to modify the nanotube electronic and structural properties. We shall mention the theoretical reports [7–13] on the electronic and magnetic properties of BN nanotubes and nanosheets when they are interacting with organic molecules or functional groups which in turn indicate the method to explore properties at the nanometer scale.

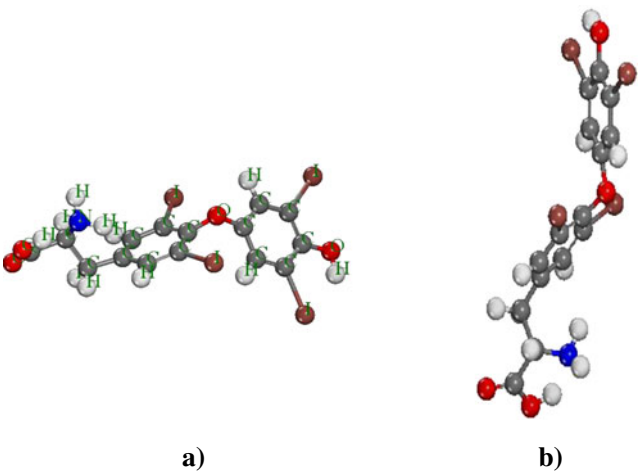
Recall that levothyroxine [14] is as drug which may be employed in the treatment of hyperthyroidism [15, 16] provided that this molecule is adsorbed on the duodenum with high efficiency in the interval of 40 and 80 %. Therefore it is interesting to investigate the drug transportation and delivery within the biological systems in order to improve the efficiency. It is also important to detect the functionalization effects in order to search for optoelectronic applications as suggested by the reports in the literature of the interactions of nanotubes with molecules [6, 17–20].

In this work we investigate structural (bond lengths and nanotubes diameter) and electronic (polarity, chemical poten-

tial and work function) properties of single-wall boron nitride nanotubes (SW-BNNT) with (5,5) chirality when the surface and ends are functionalized by the levothyroxine drug. We use the tubular models reported in the literature [21, 22]. The choice of the BNNT (5,5) chirality is because this structure exhibits strain energy of 0.123 eV/atom, which is low as compared with other chiralities. The energy value indicates that the nanostructure may easily phase transform from 2D to 1D [23]. We have also analyzed the solvation in water using the molecular simulation within the density functional theory. The theory yields good results for 1D and 2D nitrides as reported in the literature [24–29]. Studies reported in this work are devoted to exploring the possible applications in one-dimensional nitrides for the drug transportation and delivery within the biological systems to treat hyperthyroidism or to fabricate optoelectronic devices.

Simulation models and methods

First principles total energy calculations have been performed to study the interaction between the molecule levothyroxine (Fig. 1), with chemical composition $C_{15}H_{11}NI_4O_4$, and boron nitride nanotubes (BNNTs) with (5,5) chirality. Calculations have been done using the Hamprecht-Cohen-Tozer-Handy (HCTH) functional [30] within the generalized gradient approximation (GGA) and a DNP base function with double polarization (a H-*p* orbital, B-, N-, O-, C-*d* orbital, and I-*f* orbital is used) [31] as implemented in the DMol^3 [32] quantum chemistry code. Nine geometries have been explored to determine the most stable structure of the BNNT-drug system (Fig. 2) according to the molecule symmetry. In the *first* the levothyroxine is oriented perpendicularly to the nanotube (NT), in this case the molecule oxygen atoms are closer to the boron atoms of the NT hexagon. The *second* geometry displays the molecule oriented perpendicularly to the NT with the OH group near the NT hexagon. In the *third* configuration the molecule is oriented perpendicularly to the NT with the OH group close to the B atom of the NT. In the *fourth* atomic structure the levothyroxine is oriented parallel to the NT. The *fifth* geometry shows the molecule perpendicular to the NT with the iodine atom being close to the nitrogen atom of the NT. The *sixth* atomic configuration displays the molecule perpendicular to the NT with the OH group being close to the nitrogen atom of the NT. In the *seventh* geometry the levothyroxine is perpendicular to the NT with O atoms pointing towards the boron atom. The *eighth* atomic structure exhibits the levothyroxine molecule perpendicular to one NT end with the molecule oxygen atoms close to the NT, and in the *ninth* configuration the molecule is oriented perpendicular to the NT end with the OH group being close to the nanotube.



a) **b)**

Fig. 1 In this figure we show the Levothyroxine. **a** top view, **b** side view

Studies of the interactions between the levothyroxine molecule and the (5,5) chirality BNNT have been done considering a NT of length 1.32 nm and diameter of 0.76 nm. The monohydrogenated nanotubes at the ends (open NTs) contain a total of 120 atoms (50 N, 50 B and 20 H atoms, Fig. 3a) and the levothyroxine molecule is with the chemical composition of $C_{15}H_{11}NI_4O_4$. Solvation effects have been included by using the polarized continuum model (conductor-like screening model) [33–35], a dielectric constant of 78.4 is used to account for water as a solvent. To analyze the solvent effects we have calculated the solvation energy differences using the formula $Esolv_1=E[(BNNT_{solv}) - E(BNNT_{vaccum})]$ and $Esolv_2= E[(BNNT - Levothyroxine)_{solv} - E(BNNT - Levothyroxine)_{Vaccum}]$. Energy gaps have also been obtained considering the HOMO and LUMO frontier orbitals. The levothyroxine adsorption energy on the nanotube is obtained with the formula $Ead=E_{BNNT + Levothyroxine} - E_{BNNT} - E_{Levothyroxine}$. The chemical potential is determined as the average (HOMO+LUMO)/2 provided that in the electron gas this is equal to the Fermi energy and it is placed at the center of the energy gap. The work function is calculated as the energy difference between vacuum level (LUMO) and the Fermi level (chemical potential), it represents the minimum energy required to remove an electron from the Fermi level. The molecular electrostatic potential (MEPs) is obtained as reported in the literature using the Coulomb formula [36]. We have used a cut radius of 0.30 nm for the orbital (of the Levothyroxine, and BNNT-Levothyroxine pristine and solvated systems) of the base function with a tolerance of 2.0×10^{-5} Ha for the total energy convergence. The structural stability has been obtained taking into account non-complex vibration frequencies [37].

Results and discussion

Tubular structures have been studied with results indicating that the most stable configuration, according to the energy gap, corresponds to the armchair structure, that is, nanotubes

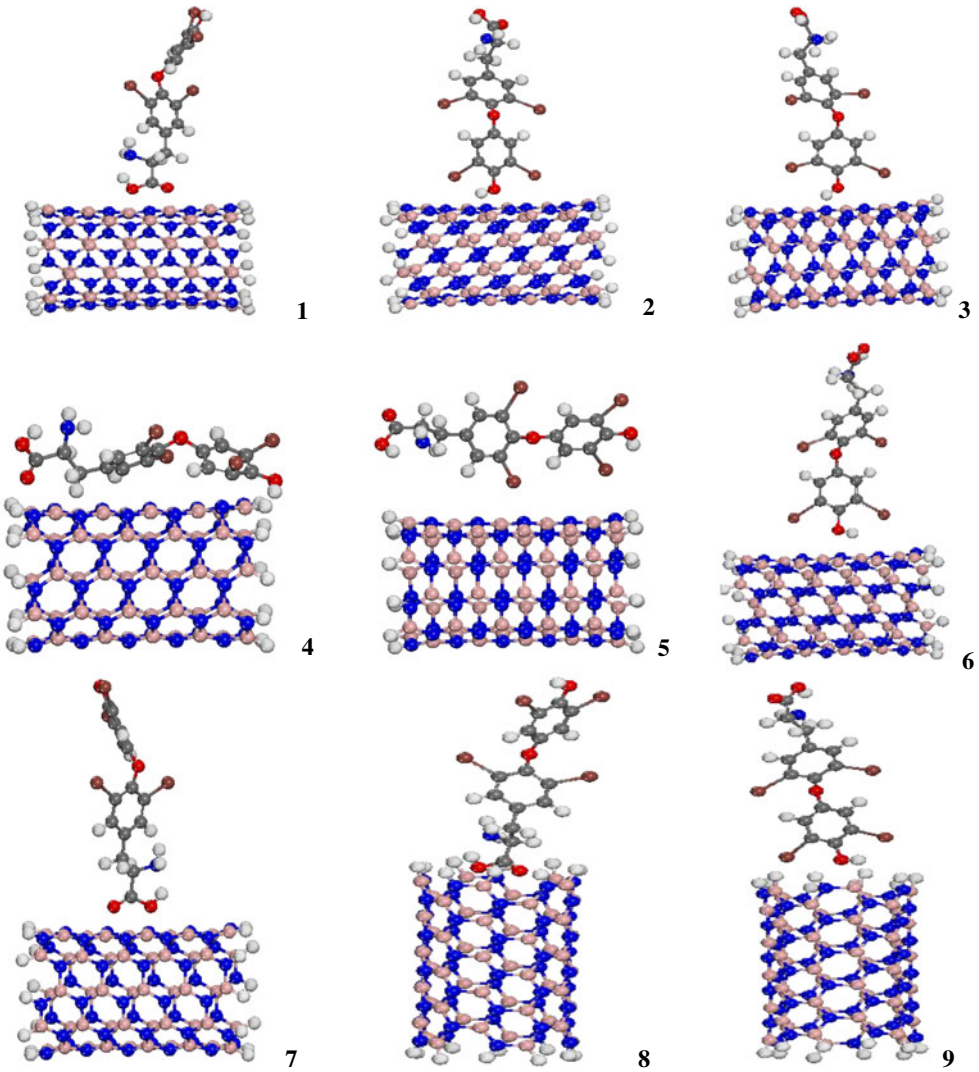


Fig. 2 Geometries used to study the interaction between the BN nanotubes and the drug of levothyroxine

with Hamada index (n,n) [38]. This result is supported by the possible synthesis preparation of nanotubes with open ends as in the boron nitride 1D structures [39]. BN nanotubes are of short length which makes them suitable for functionalization with polymers. These systems may be applied in biomedicine as well as in the synthesis of composites with mechanical resistance [3, 4]. Therefore in this work we have analyzed BN tubular systems to investigate the functionalization. The nanotubes are modeled according to the armchair structure and have open ends with (5,5) chirality (Fig. 3a), as reported in the literature [17–21]. The Levothyroxine is considered to interact with the nanotube surface or ends to explore the changes in the electronic and structural properties of the nanotube and then search for the possible technological applications, as drug delivery in medicine and in optoelectronics.

Structural properties

The structural relaxation (see Table 1) and the stability criteria allow obtaining the ground state atomic configuration of the interaction between the Levothyroxine molecule and the boron nitride nanotube in the armchair model which turns out to be configuration nine (Fig. 2c). In this geometry the Levothyroxine molecule interacts, through the OH (a bond length of 2.57 and 5.17 Å, Fig. 3c), with the nanotube end. The NT experiences structural changes as a consequence of the interactions with the molecule in such a way that the diameter increases by 0.05 nm (final value of 0.81 nm) as compared with the pristine BN nanotube of diameter 0.76 nm. The increase in the NT diameter might allow the possible coupling of the NT with the drug in order to be transported through the human body. On the other hand, the tubular structure keeps the B-N bond length at 1.44 Å in agreement with the pristine BNNT, provided that the interaction with the molecule is weak, however the bond length increases by 2×10^{-3} Å, in the vicinity of the interaction, to take the final value of 1.46 Å. Similarly these structural parameters remain unchanged in the BNNT—Levothyroxine system when immersed in a different medium. At the same time the molecule geometrical parameters are unaltered (see Table 2). The molecule adsorption is chemical (−0.67 eV) that depends on the

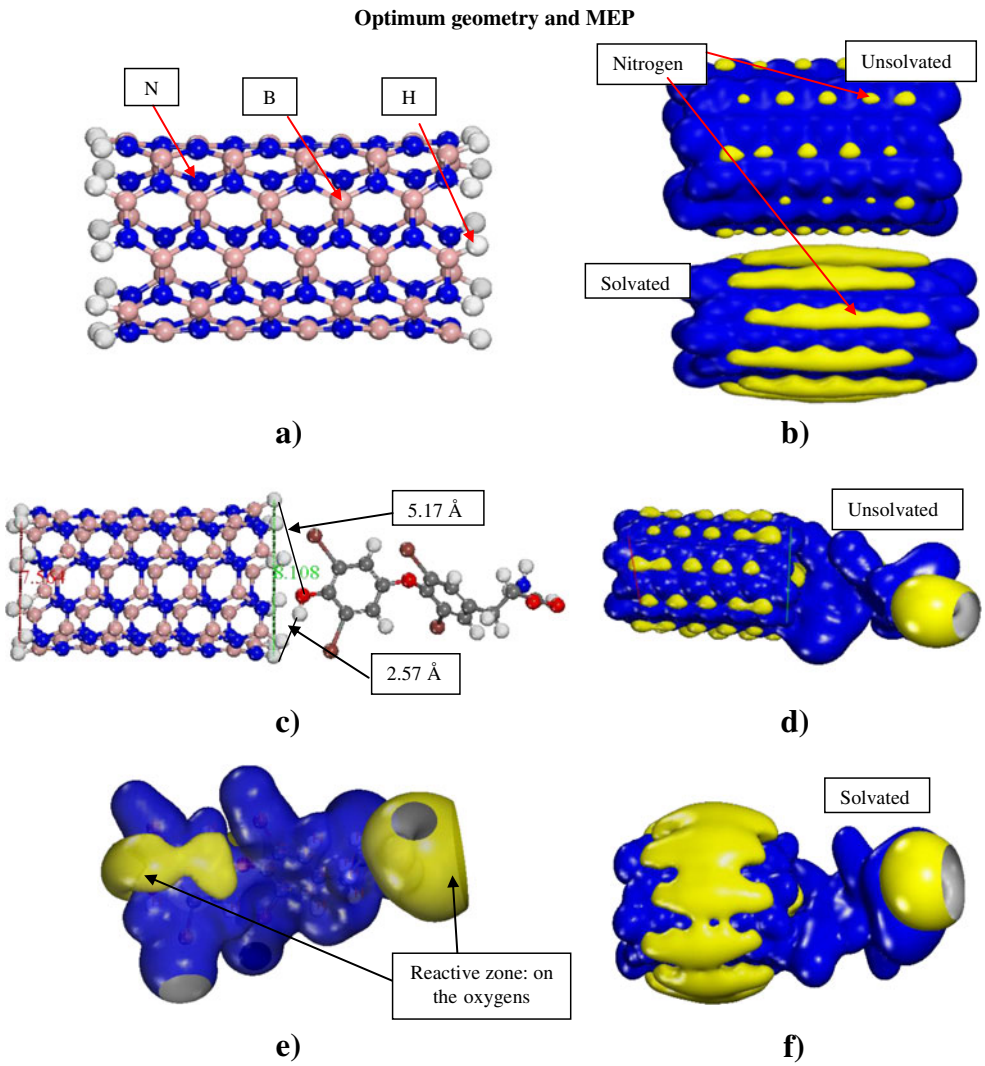


Fig. 3 In this figure we depict the relaxed geometries: **a** BNNT, **b** MEP for BNNT in vacuum and solvated, **c** BNNT-Levothyroxine (configuration 9), **d** MEP for BNNT-Levothyroxine in vacuum, **e** MEP for Levothyroxine, **f** MEP corresponding to the solvated BNNT-levothyroxine system. Blue zone is for the positive charge and yellow zone is for the negative charge

adsorbate which interacts with the far tubular structure of the reactive zone contrary to what is reported in the literature [17].

Electronic properties

The molecular electrostatic potential (MEP) show that the electronic distribution on the pristine nanotube surface is localized near the nitrogen atom charge (Fig. 3b, unsolvated); however when this is immersed within a different medium such as water, the charge is redistributed near the nitrogen atoms (yellow color, Fig. 3b, solvated). In the ground state structure the interaction between the NT and the molecule induces charge transfer (Fig. 3d) from the OH molecule group to the nanotube end at the adsorption site which is in agreement with the MEP, at the same time this fact indicates the most reactive zones (Fig. 3e). When BNNT-Levothyroxine system is immersed in water the nanotube surface becomes active to allow the charge distribution as shown by the MEP (Fig. 3f). This in turn indicates that the chemical interaction favors a greater charge distribution as compared with the functionalization with different molecules [9, 10]. On the other hand, it is important to remark that the metastable structure (configuration 4), where the NT and the molecule are parallel to each other, shows an energy difference of

Table 1 We report the total energy vs configurations for BNNT-Levothyroxine system

Initial geometry	BNNT-levothyroxine (a.u.)
1	−32628.5007292
2	−32628.5051773
3	−32628.5076562
4	−32628.5156253
5	−32628.5079935
6	−32628.4747841
7	−32628.4993682
8	−32628.5047182
9	−32628.5167611

Table 2 We report bond length (Å), HOMO-LUMO gap, energy Fermi level, dipole moments, work function for BNNT and BNNT-levothyroxine and adsorption energy (all in eV)

Nanotubes	Bond length B-N	HOMO-LUMO gap	Energy Fermi level	Dipolar moment	Work function	Adsorption energy
(5,5) BNNT	1.44	4.59 –LDA [9]	−3.52	0.008	2.3	
		4.70–GGA *	−3.00	0.024	2.35	
(5,5) BNNT	1.44	4.78	−3.65	0.017	2.33	
(5,5) BNNT Solvated water	1.44	4.62	−3.55	0.0	2.3	
Levothyroxine		1.51	−3.24	4.42	1.58	
(5,5) BNNT-levothyroxine	1.44	3.37	−3.55	3.83	1.68	−0.67
(5,5) BNNT-levothyroxine solvated water	1.44	3.19	−4.04	3.55	1.6	

*These values were obtained using the functional Perdew-Burke-Ernzerhof (PBE) [41]

0.031 eV as compared with the ground state structure. In this case there exists charge transfer between the surface and the molecule (Fig. 4), in the vicinity of the molecule charge zone (Fig. 3e). As a result an increase in the polarity inducing a change from a covalent (with 0 D; pristine BNNT) to ionic characteristics (with 3.83 D; BNNT-Levothyroxine) is obtained. This polarity is reduced when the system is water solvated, see Table 2. At the same time we may conclude that the solubility and dispersion of these BNNTs are possible.

The chemical reactivity indicates the NT structure stability in the NT-Levothyroxine system where the chemical reactivity remains of constant value of −3.55 eV due to the weak interaction. However the NT-Levothyroxine chemical reactivity, immerse in a different medium, decreases by 0.49 eV (taking a final value of −4.04 eV, Table 2) which suggests the potential applications in drug delivery vehicle within biological systems. The semiconductor characteristics are preserved, the energy gap (HOMO-LUMO energy difference) is reduced from 4.78 to 3.37 eV when the drug of levothyroxine interacts with the nanotube. The combined system does not notably modify the nanotube electric conductivity however this gap reduction may be important for the optoelectronic device design. Moreover the polarity increase suggests the possible solubility of these 1D structures in the presence of the levothyroxine molecule. These results are similar to those reported in the literature of the functionalized BNNTs surfaces with methoxy-poly (ethylene glycol)-1, 2-distearoyl-sn-glycero-3-phospoethanolamine-N and solvated in water [3]. Considering that the polarity is solubility dependent we perform first principles total energy calculations taking into account nanotubes solvated in water which display a polarity increase when interacting with levothyroxine having a value in the range of 2.4×10^{-2} to 0 D for the pristine BNNT and of 3.83 to 3.55 D for the BNN-Levothyroxine system. Provided that it is important to investigate these kinds of solvated systems to explore biochemical applications, we determine the energy difference in systems with and without solvation conditions, to determine the solvent effects. We have obtained for the pristine BNNT $E_{solv1}=-227.38$ kcal mol^{-1} and for BNNT-Levothyroxine system $E_{solv2}=-1060.785$ kcal mol^{-1}. Note that the energy becomes more negative which suggests that the conduction electrons have been polarized by the solvation which in turn may favor the dispersion.

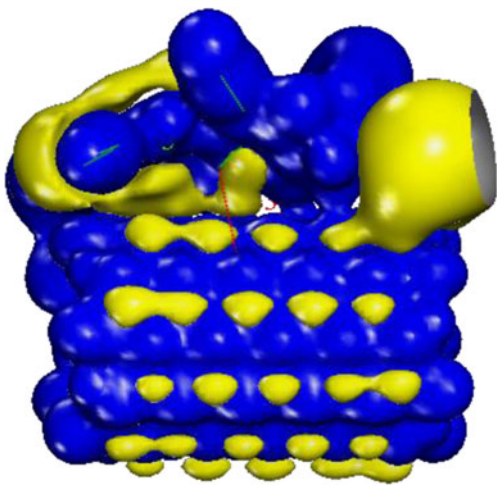


Fig. 4 In this figure we show the MEP of a meta-stable configuration

The functionalized nanotubes work function has the value of 1.68 eV and the corresponding value of the pristine structure is 2.3 eV, which yields an energy decrease of 0.62 eV to favor the charge transport and conditions to develop new devices.

Finally we study the electric conductivity using the formula $\sigma \propto \exp(-E_g/kT)$, where k is the Boltzmann constant and T the temperature [40]. Taking a given temperature for the functionalized tubular structures in the ground state configuration we obtain a high conductivity provided that the energy gap, HOMO-LUMO energy, is small as compared with pristine nanotubes.

Conclusions

We have presented studies of the interaction between the levothyroxine molecule and (5,5) chirality BN nanotubes. Results of the chemical interactions indicate that the

semiconductor behavior of the (pristine and functionalized) nanotube is preserved after the solvation. The polarity increase in the BNNT-Levothyroxine system suggests the possibility to solvate and disperses them for biological applications, as indicated by the more negative energy of the solvated system. The solvation medium induces a better charge distribution on the nanotube surface which reduces the chemical reactivity indicating the possibility of the drug delivery vehicle within biological systems. Finally the work function reduction of the BNNTs makes the systems suitable for technological applications in displays provided that it is possible to modify the field emission properties.

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