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ORIGINAL PAPER

Chemical reactivity and adsorption properties of pro-carbazine anti-cancer drug on gallium-doped nanotubes: a quantum chemical study

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Abstract

In this study, we propose new armchair single-walled nanotubes (SWNTs) for stable adsorption, increasing drug delivery performance and decreasing side effects of pro-carbazine (Pro-CB) anti-cancer in the framework of B3LYP/6-31 g*/Lanl2DZ level of theory. Indeed, doping gallium (Ga) metal in SWNTs is naturally followed by changing of geometry, increasing dipole moment, and creating one site with high reactivity in order to better adsorption of the drug molecule. Chemical reactivity descriptors show that SWNTs and Pro-CB have electrophile and nucleophile roles in interaction, respectively. More importantly, high local and dual softness in Ga-doped SWNTs indicate improvement of drug adsorption. Parallel and perpendicular complexes result from their interaction in the N and the O sites. Negative values of binding energy (E_{bind}) show that composed complexes are energetically stable especially in the O site in comparison with the N site. On the other hand, more negative value of the E_{bind} in SWCNTs shows that these nanotubes are more effective for drug adsorption than their boron nitride counterparts.

Keywords Pro-carbazine anti-cancer · Chemical reactivity descriptors · Drug delivery · Density of state · Natural bond orbital

Introduction

Single-walled nanotubes (SWNTs) are considered a novel class of carriers with significant efficiency in drug-delivery systems [1]. Thanks to their structural properties, such as high surface area, specific size, highly site-selective delivery, and sensitivity [2–7], SWNTs have the ability to transport drug molecules to target cells without side effects [4, 6–8]. Indeed, this release of drug molecules is due to better adsorption of drug ligands to the in/out side of SWNTs. Nowadays, carbon and boron nitride nanotubes (CNTs and BNNTs) are strong candidates in medical and biological fields [9–17]. Electrostatic potentials of these nanotubes in outer and inner surfaces cause their different behavior in interaction with other molecules [18, 19]. This is why we can see the trace of many research groups in a vast variety of theoretical and experimental studies [2, 3, 20–27].

The in vitro and in vivo studies showed that using SWCNTs causes selective transport of cisplatin (*cis*-DDP) to the tumor cells and reducing side effects [1, 28, 29]. In other words, high efficiency of interaction of SWCNTs and platinum complexes anticancer was showed that this nanotubes have not toxicity [21, 30]. The interaction between SWCNTs and folic acid has been studied experimentally [31]. Using SWCNT carriers results in decreasing interaction of folic acid with other molecules and safe delivery by folate receptors [20]. In another work, adsorption of leflunomide on SWCNTs and SWBNNTs has been determined in order to introduce these nanotubes as multipurpose innovative carriers for better drug delivery and diagnostic application [27].

It has been observed that doping of metal on SWNTs results in better adsorption and reduction of possible toxicity such as the one in platinum-based drugs on Al-doped BNNTs [32, 33]. Sensitivity of gold doped on CNT (AuNPs) to environmental factors such as pH has been investigated [34]. Existence of intermolecular forces between SWNTs and drug molecules conveniently are assigned using quantum chemical calculations.

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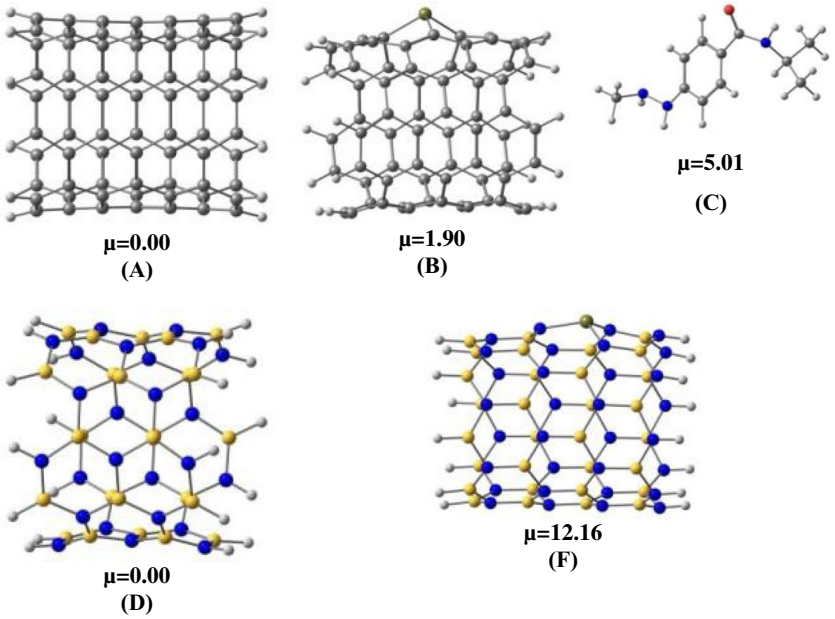

Fig. 1 Optimal structures of carbon [C] (**a**), carbon/gallium [C/Ga] (**b**), pro-carbazine [Pro-CB] (**c**), boron nitride [BN] (**d**), and boron nitride/gallium [BN/Ga] (**f**) armchair (5, 5) nanotubes, respectively

The above-reported studies aimed at introducing SWNTs as good deliverers of various drug molecules. However, the reactivity and adsorption of pro-carbazine (Pro-CB) drug on SWNTs carrier have not attracted much attention yet. In this study, we are going to investigate theoretical adsorption of Pro-CB drug as brain anti-cancer on armchair (5, 5) SWXNTs (X = C, BN)]. Geometries of these structures with a single bond are presented in Fig. 1. In order to improve Pro-CB adsorption and increasing chemical reactivity in these nanotubes, one gallium atom was doped in SWNTs. Therefore, our main objective is determination of the ground-state structures, chemical reactivity, and origin of these linkages and nature of adsorptions using density functional theory (DFT) method. In the following, natural bond orbital (NBO) [35] analysis was carried out to identify the underlying nature of events in their interactions.

Computational methods

Geometry optimizations, calculations of chemical reactivity descriptors, electronic analysis of SWXNTs (X = C, BN) and Pro-CB compounds were carried out by using Gaussian 09 program package [36] in the framework of density functional theory (DFT) and 6–31 + g(d)/Lanl2DZ basis set for light/heavy atoms [37–39]. To confirm that the structures refer to the corresponding local minima, vibrational frequencies were calculated and no imaginary frequency was obtained for any structures such as in other reports [40]. Further, the stability of the systems was evaluated through computing energies of binding (E_{bind}):

$$E_{bind} = E_{complex} - \left(E_{SWNT} + E_{drug}\right) \quad (1)$$

In these equations, $E_{complex}$, E_{SWNT}, and E_{drug} are the total energy of the complex, SWNTs, and Pro-CB anti-cancer. Tendency of an electron in a compound to interact with other molecules is called chemical reactivity [41]. In the framework of DFT method, global and local indices of reactivity are calculated using ionization potential (IP) and electron affinity (EA) [42]:

$$IP(SWNT) = E_{tot}(SWNT^{+}) - E_{tot}(SWNT) \quad (2)$$

$$EA(SWNT) = E_{tot}(SWNT^{-}) - E_{tot}(SWNT) \quad (3)$$

Table 1 Calculated ionization potential (IP), electron affinity (EA), chemical potential (μ), global hardness (η), and softness (S), and HOMO-LOMO gap (ΔH-L) at B3LYP/6-31 g (d)/Lanl2DZ level of theory

Molecules	Global chemical reactivity						
	IP	EA	μ	η	S	ΔH-L	$\Delta H_{Pro\text{-}CB}$-L_{SWNTs}
CNT (5, 5)	4.68	2.28	− 3.48	1.20	0.83	2.20	2.66
CNT (5, 5)-Ga	4.35	2.66	− 3.51	0.84	1.18	7.28	2.30
BNNT (5, 5)	6.40	0.09	− 3.24	3.15	0.32	1.67	4.87
BNNT(5, 5)-Ga	6.51	2.36	− 4.44	2.08	0.48	4.74	2.60
Pro-carbazine	4.96	1.81	− 3.39	1.58	0.63	3.64	–

All parameters are in electron volt (eV)

Table 2 Local reactivity descriptors for SWNTs and pro-carbazine, all parameters are in electron volt (eV)

CNT	s^+	s^-	Δs	CNTGa	s^+	s^-	Δs
C52	0.007	0.006	0.001	C52	0.021	0.020	0.001
C63	0.007	0.006	0.001	C63	0.021	0.020	0.001
C73	0.003	0.004	− 0.001	C73	0.091	0.011	0.080
				Ga	0.378	0.004	0.374
BNNT				BNNTGa			
N33	0.003	0.005	− 0.002	N35	0.011	0.012	− 0.001
N36	0.003	0.000	0.003	N43	0.011	0.012	− 0.001
N41	0.003	0.008	− 0.005	N45	0.013	0.003	0.010
				Ga	0.269	0.009	0.260
Pro-CB							
N1	0.003	0.106	− 0.103	–	–	–	–
N13	0.003	0.005	− 0.002	–	–	–	–
N20	0.005	0.003	0.002	–	–	–	–
O12	0.002	0.066	− 0.064	–	–	–	–

Global descriptors are electronic chemical potential (μ), chemical hardness (η), chemical softness (S), and electrophilicity (ω), respectively. Escaping tendency of electrons from the equilibrium systems is called chemical potential [41]:

$$\mu = -\frac{(\mathrm{IP} + \mathrm{EA})}{2} \tag{4}$$

Resistance of a system to electron transfer is hardness; its large value shows that the system is harder and more stable or less reactive [41, 43]:

$$\eta = \frac{(\mathrm{IP} - \mathrm{EA})}{2} \tag{5}$$

Reverse of hardness is global softness and its large value indicates less stability and high tendency to reacts with other molecules [41]:

$$S = \frac{1}{\eta} \tag{6}$$

Exchange of electrons is local electrophilicity (ω) [44]:

$$\omega = \frac{\mu^2}{2\eta} \tag{7}$$

Favorable site of SWNTs in interaction with Pro-CB anticancer are predicted by investigation of local descriptors such as Fukui function (***f***), softness (***s***), philicity (***ω***), dual softness (Δ***s***), and dual philicity (Δ***ω***). Sensitivity of the chemical potential of a system to a local external potential is called Fukui function (***f***); it is used in order to characterize reactivity of an atom in a compound [41]. Finite difference approximation has been applied to determine nucleophilic (f^+) and electrophilic (f^-) attacks [41]:

$$f_k^+ = q_k^{N+1} - q_k^N \tag{8}$$

$$f_k^- = q_k^N - q_k^{N-1} \tag{9}$$

where q_k^N, q_k^{N+1} , and q_k^{N-1} are electronic populations of the *N*, (*N* + 1) and (*N*-1) electron systems on selected atom, respectively. Role a site in a compound in electrophilic (nucleophilic) attacks identify by using local softness and philicity [45]:

$$s_k^\alpha = f_k^\alpha \cdot S \tag{10}$$

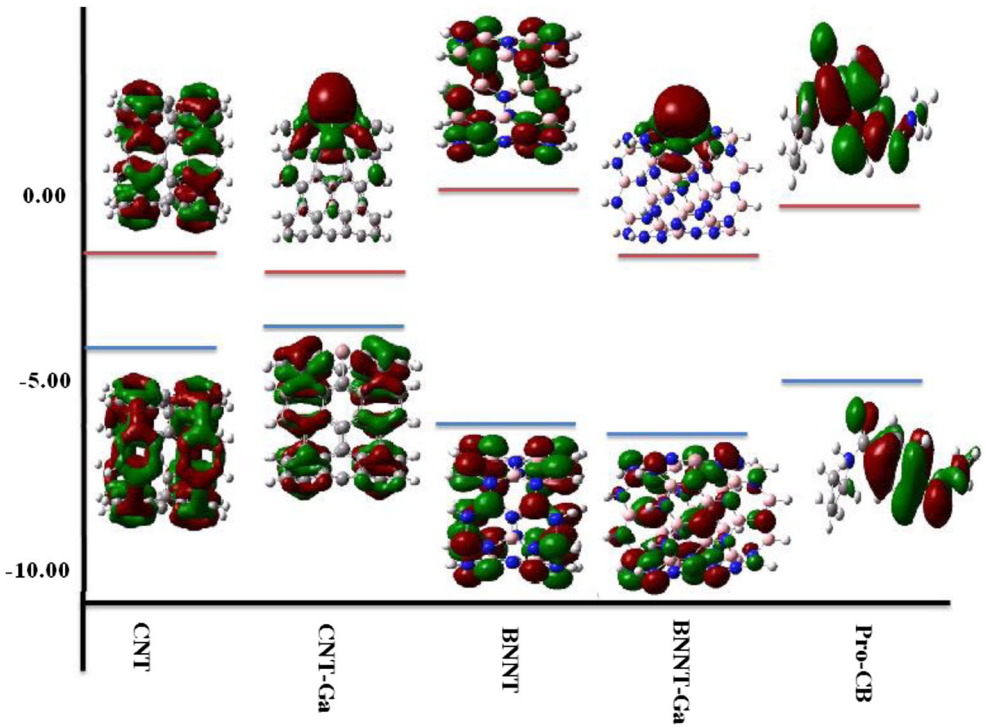

Fig. 2 HOMO-LUMO gap of SWXNTs (X = C, BN) compounds are obtained using B3LYP/6-31 g*/Lanl2DZ level of theory

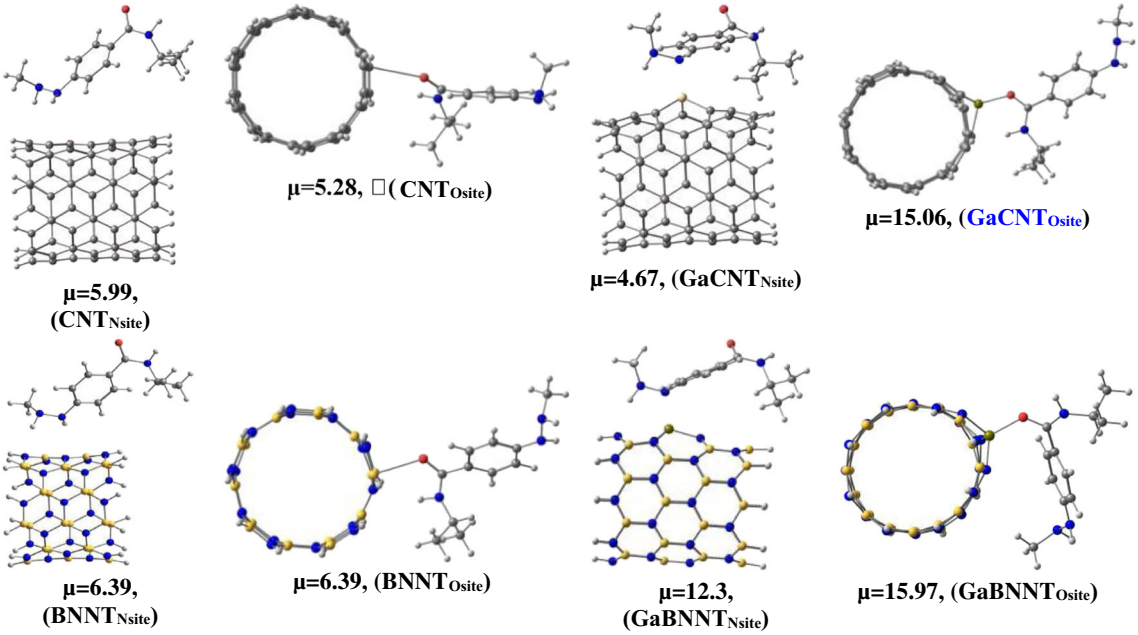

Fig. 3 Low-lying structures of SWNT/Pro-carbazine complexes with dipole moment (μ, Debye), dihedral angle (°, degrees), distances of nitrogen (N) and oxygen (O) sites with SWNTs (d, Å), respectively

when $\alpha = +, -$ means nucleophilic, electrophilic attacks; maximum positive value of local softness in the k site indicate that this site has most electrophile property in compound and it is favorable for nucleophilic attack in reaction with Pro-CB. Selectivity of the ***k*** site in nucleophilic (electrophilic) attacks is evaluated by dual local softness [46, 47]:

$$\Delta s_k = s_k^+ - s_k^- \tag{11}$$

the $\Delta s_k > 0$ and $\Delta s_k < 0$ mean site ***k*** is favorable for nucleophilic and electrophilic attacks, respectively.

Moreover, geometrical information is completed by the results of NBO analysis [35]. Type of bonds, depletion of occupancies, percent of Lewis and non-Lewis, and stabilization energies [35, 48] are obtained by NBO analysis. The stabilization energy (E^2_{ij}) in Eq. (12) includes interaction Hamiltonian $\hat{H}$, orbital energies E_j and E_i and also $\langle i|\hat{H}|j\rangle$ that is the matrix element.

$$E^2_{ij} = \frac{\left|\langle i|\hat{H}|j\rangle\right|^2}{E_j - E_i} \tag{12}$$

Results and discussion

Geometric and energetic results

Starting point theoretical studies is determination most stable geometries. Therefore, armchair (5, 5) single-walled nanotubes (SWXNT, X = C and BN) with finite length and hydrogen saturation in both ends were optimized without any symmetry constrains to obtain local minimum of structures (see Fig. 1). There is no imaginary frequency in any of the SWNTs structures, so they are in real minima.

Doping of gallium metal in SWNTs is naturally followed by a change of carbon and boron NT geometries; for example, C—Ga and N—Ga bonds length average 2.01 and 1.84 Å,

Table 3 Bond lengths (Å) and bond and dihedral angles (°), and binding energy (E_{bind}, kcal mol^{-1}) in the nanotube–drug complexes calculated at B3LYP/6-31 g (d) level of theory

Nanotubes	Distance		Bond angle	Dihedral angle	E_{bind}	
	N1(2) site	O site	∠C (Ga)—N (O)—C (Ph)	∠C (M)—N (O)—Ph	N site	O site
CNT (5, 5)	3.948	3.132	152.2 (157.1)	78.1 (137.3)	− 3.7	− 4.6
CNT (5, 5)-Ga	(2.080)	(1.956)	108.8 (127.6)	12.3 (179.8)	− 127.8	− 138.2
BNNT (5, 5)	3.517	2.760	135.7 (156.5)	20.9 (137.5)	− 3.1	− 4.0
BN(5, 5)-Ga	(2.069)	(1.986)	108.8 (128.9)	28.0 (98.2)	− 40.0	− 45.6

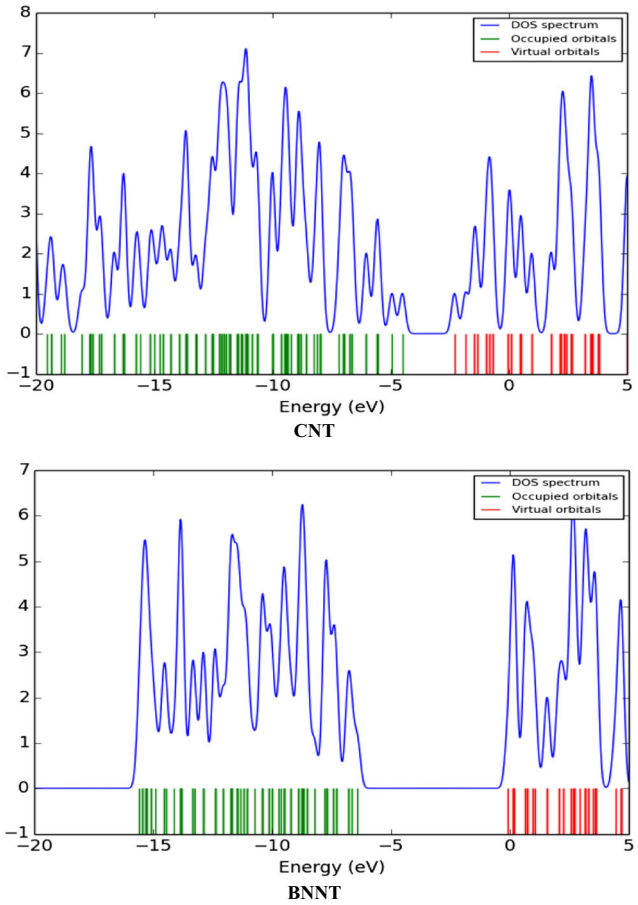

Fig. 4 Calculated electronic density of states (DOS) for the SWXNTs (X = C, BN) and pro-carbazine (Pro-CB) drug as a function of the energy

respectively. Elongation of bonds rather than C─C (1.44 Å) and N─B (1.45 Å) [49, 50] partly result in an increase of dipole moment and creation of a favorable active site in order to better adsorption and more effective interaction with Pro-CB drug. Therefore, chemical reactivity descriptors can set the stage to understand the behavior of SWNTs in their interactions.

Global reactivity descriptors can be used in order to describe stability and role of molecules in reaction (see Table 1. According to global reactivity indexes, more negative values of the μ in SWNTs structures rather than Pro-CB

Table 4 Calculated net charge of atoms in the complexes according to population analysis

Molecules	Pro-carbazine		Ga
	N	O	N (O) sites
CNT (5, 5)	− 0.548	− 0.584	–
CNT (5, 5)-Ga	− 0.627	− 0.533	+ 0.180 (+ 0.246)
BNNT (5, 5)	− 0.560	− 0.537	–
BNNT(5, 5)-Ga	− 0.634	− 0.519	+ 0.408 (+ 0.482)
Pro-carbazine	− 0.704	− 0.668	–

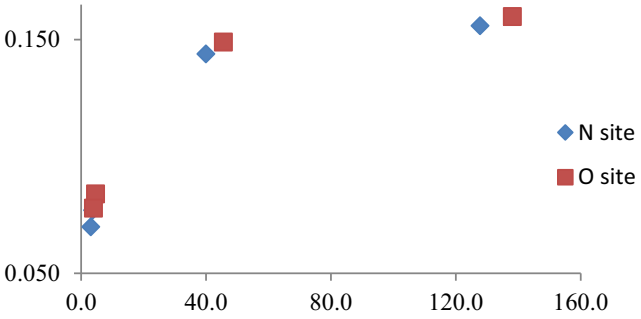

Fig. 5 Correlation of charge transfer (CT) and binding energy (E_{bind}) in the N and O sites of adsorption in the complexes

showing easily electron acceptance and playing an electrophile role in interactions; so, Pro-CB acts as a nucleophile. On the other hand, the η and **S** decreases and increases by doping of gallium in SWNTs, so doped-SWNTs have less stability and more reactivity than pure SWNTs. In addition, Ga-SWNTs have better ability for acceptation of electron due to increasing the ω in comparison with SWNTs.

Awareness of active sites in SWNTs and Pro-CB helps to better understand interactions. Therefore, we have investigated active sites in nucleo (electro) phile using local softness ($s^+$and s^-). Our results show that more positive value of s^+ and Δs in the Ga doped SWNTs centers, especially Ga atom cause Pro-CB attacks with positive value of the s^- to these centers from the N and O sites, see Table 2. According to this table, nucleophile attacks of Pro-CB to Ga-SWNTs carried out from the O site due to high local softness and dual softness in this center.

One of the other significant factors to show stability of SWNTs is highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) gap. Increasing HOMO–LUMO gap with gallium doping partly results in decreasing of $HOMO_{Pro\text{-}CB}$-$LUMO_{SWNTs}$ gaps (see Table 1 and Fig. 2). Consequently, charge transfer, interaction, and delivery of Pro-CB anti-cancer drug probably carried out better than pure SWNTs.

In the following, SWNTs has interacted with Pro-CB molecules at parallel and perpendicular orientation from the nitrogen (N) and oxygen (O) sites, respectively, as shown in Fig. 3. Optimized structural parameters of SWNTs-Pro-CB complexes are given in Table 3. The O─X (X = C, B, and Ga) distances in perpendicular configurations are lower than N─X (X = C, B, and Ga) the planar ones, which reflected by the corresponding higher binding energies. Low bond length results in better adsorption of drug on SWNTs, low side effects, and better drug delivery.

The X─O (N)─Ph bond angles in the O site are larger than the N site complexes; this issue indicates that perpendicular complexes are more stable than ones. Besides, the X─O (N)─C─C dihedral angles in the O site are larger than the N site, which can be due to repulsive interaction between N─H bond of Pro-CB and surface of SWNTs in parallel orientation.

Table 5 Donor–acceptor interactions and second-order stabilization energy (kcal mol^{-1})

Nanotubes	Unit 1 → Unit 2 N site	ΔE	Unit 1 → Unit 2 O site	ΔE
Pure CNT	Pro-carbazine → CNT	2.1	Pro-carbazine → CNT	0.3
	CNT → pro-carbazine	0.7	CNT → pro-carbazine	1.0
CNT-Ga	$n_{N18} \rightarrow n^*_{Ga}$	48.9	$n_{O11} \rightarrow n^*_{Ga}$	69.6
Pure BNNT	Pro-carbazine → BNNT	1.4	Pro-carbazine → BNNT	11.6
	BNNT → pro-carbazine	1.5	BNNT → pro-carbazine	2.3
BNNT-Ga	$n_{N1} \rightarrow n^*_{Ga}$	40.0	$n_{O11} \rightarrow n^*_{Ga}$	70.9

Therefore, binding of Pro-CB to SWNTs in the perpendicular complex is more favorable owing to low distances, bond angles, repulsive interaction, and dihedral angles.

Density of state (DOS)

One of the reliable methods to analyze the chemical structures from an electronic viewpoint is density of state (DOS). Adsorption of Pro-CB anti-cancer on SWNTs leads to small modification of drug. We have evaluated the DOS for the best orientation of adsorption in order to confirm preferential adsorption and charge transfers (see Fig. 4 and Fig. S1) (S means Supplementary file). The DOS plots show some discrepancies in the height and slight shifts of energy level of SWNTs; this issue indicates that the drug molecule adsorbs on SWNTs. According to Fig. 4, more discrepancy of occupied and virtual orbitals (≈5.0 eV) in the BNNTs than CNTs (≈3.0 eV) mainly cause low charge transfers and weak chemical adsorption and defective drug delivery than ones.

NBO analysis

Structural and energetical information is completed using natural bond orbital (NBO) theory [35]. Decreasing negative charges of the N and O atoms in both planar and perpendicular complexes show that charge transfer is carried out from Pro-CB to SWNTs (see Table 4). A decrease in the positive charge value of the Ga metal is owing to the delocalization of the N and O lone pairs to the NBO acceptors. Therefore, increasing of electronic charge of metal in the Ga-SWXNTs (X = C, BN) showing drug stabilization on their surfaces in order to better drug delivery. Charge transfer values in perpendicular complexes from O site are more than the N site of parallel ones. There is a relation between the charge transfer and binding energies, shown in Fig. 5. For example, the {Pro-CB[Ga-SWXNT (X = C, BN)]} compounds in the O site with high E_{bind} (− 138.2, − 45.6 kcal mol^{-1}) have maximum charge transfer (69.6, 70.9 kcal mol^{-1}), respectively.

There are two types of weak donation/back-donation interactions in pure SWNT complexes, which consist of Pro-CB → SWNT and SWNT → Pro-CB (as shown in Table 5). Therefore, these donor–acceptor interactions cause weak intermolecular interactions between the Pro-CB anti-cancer and pure nanotubes and very low E_{bind} in this adsorption. Also, NBO results show that the Ga-SWNT-[Pro-CB] complexes have significant donor–acceptor interactions with higher stabilization energies in the O site than in the N site (see Table 5). Therefore, interaction in the O site is stronger than in the N site, which is in good agreement with reducing occupancy, E_{bind}, and DOS analysis.

Conclusions

In this study, SWXNTs (X = C, BN) and Pro-CB structures were optimized and the most favorable orientation in their interactions were investigated. Our results show that doping of gallium atom decreases $HOMO_{Pro\text{-}CB}$ and $LUMO_{SWXNT}$ gap and increases donor–acceptor interactions. These issues indicate better adsorption of Pro-CB on these doped nanotubes, especially Ga-SWCNT. In addition, its E_{bind} value is more negative than SWCNT. Therefore, among SWNTs, Ga-doped SWCNTs is considered as a suitable carrier to transport drug molecules from the O site.

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