



Carbazochrome carbon nanotube as drug delivery nanocarrier for anti-bleeding drug: quantum chemical study

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Abstract

The interaction between drugs and single-walled carbon nanotubes is proving to be of fundamental interest for drug system of delivery and nano-bio-sensing. In this study, the interaction of pristine CNT with carbazochrome, an anti-hemorrhagic or hemostatic agent, was investigated with M06-2X functional and 6-31G* basis set. All probable positions of related adsorption for these kind drugs were thought-out to find out which one is energetically suitable. Based on the achieved data, the stronger interactions appeared the oxygen atom of C=O group and nitrogen atom of imine groups. The topology analysis of QTAIM (quantum theory of atoms in a molecule) method was accomplished to understand the properties of interactions between the CNT and carbazochrome. Frontier molecular orbital energies of all systems, global index including stiffness, softness, chemical Gibbs energies, and electrophilicity parameters, as well as some other important physical data such as dipole moment, polarizability, anisotropy polarisability, and hyperpolarizability were calculated, evaluated, and then compared together. The essence of the formed bonding model progress along the reaction roots was further validated using electron localization function (ELF) calculations. The highest values of adsorption energies were determined in the range of 18.24 up to 22.12 kcal mol⁻¹ for these kind systems. The acceptable recovery time of 849 s was obtained for the desorption of carbazochrome from the CNT surface under UV-light. The final results exhibit that carbazochrome can serve as a promising carrier and also as sensitive sensors in any kind of practical application.

Keywords CNT · Carbazochrome · Drug delivery · ELF · QTAIM

Introduction

Spontaneous bleeding control is a concern for surgeons, anesthetists, hematologists, and the patient. The spontaneous cessation of bleeding caused by rupture of blood vessels is called hemostasis. Extravasation would be stopped if any holes can be blocked in the system or if the pressure becomes lower than the pressure outside the bleeding vessel [1]. Carbazochrome, an antihemorrhagic or hemostatic agent, causes blocking of blood flow by forming a

platelet plug of platelets in the blood. Due to the unique property of the molecule, the drug can be used to prevent excessive blood flow during surgical operations and to treat hemorrhoids [2]. IUPAC name of carbazochrome is (3,6-dihydroxy-1-methyl-2,3-dihydroindol-5-yl)iminourea. They analyzed thermodynamically stable crystal packs of carbazochrome conformers from the stability and properties of the global minimum carbazochrome produced from lattice energy optimisation applying in the repulsion/attraction or dispersion potential field, hydrogen bond analysis, and second derivative properties [3].

Carbon nanotubes (CNTs) are used in biology and medicine as drug delivery systems due to their unique properties such as high tensile strength, high stacking efficiency, low toxicity, elasticity, ultralightweight, excellent chemical and thermal stability, high surface area and non-immunogenicity [4, 5]. Due to their intrinsic properties and high dynamism, they have recently been applied as drug adsorbents in the medical and pharmaceutical industries [6]. Because of their characteristic surface

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properties and their capsule and needle-like shape, they can encapsulate drugs and a variety of biomolecules such as DNA molecules.

Among the numerous delivery systems currently under investigation, single-walled carbon nanotubes seem to hold a promising option, consisting of carbon atoms arranged and tubularly wound in a series of condensed benzene rings [7]. In particular, single-walled carbon nanotubes, calixarene, as new carriers for drug delivery, application of fulourene, and cytosine properties became feasible soon after the cellular uptake of this new material was demonstrated [8–11]. It also brings with it the solubility problem, which can be considered as the main obstacle to the applications of fullerene and carbon nanotube molecular systems as sensors and drug carriers. It has been shown that the solubility problem can be overcome by substitution of heteroatoms [12].

They investigated interaction and bond properties of anticancer drug doxorubicin (DOX), armchair single-walled carbon nanotube (SWCNT), and hydroxyl- and carboxyl-functionalized SWCNT (f-SWCNT) based on DFT theory to design, improve, and expand carbon nanotube (CNT) drug carriers which is applied in biomedical systems such as drug delivery systems [13].

The physical chemistry data and also pharmacological properties of the bioactive product can be affected through the physiological situation [14]. A drug delivery system (DDS) can be used to increase the effectiveness of drugs and prevent them from being deactivated to the target areas [15]. Various categories of carriers have been studied, containing lipids, PEGs, and polypeptides [16, 17]. Among the many delivery systems, (*n, n*) single-walled carbon nanotubes, composed of armchair atom arranging in a tubular form, appear to represent a promising option [18]. Findings regarding the SWNT-(streptavidin protein) of conjugates to human promyelocytic leukemia (HL60) and human T cells, have been reported by this work [19].

It has been reported that useful information about the interaction of nanostructures and drug molecules can be obtained using density functional theory (DFT) calculations [20, 21].

They examined the (6,6) single-walled carbon nanotube-SWCNTs-fluorouracil and p-sulphonato-calix aren [4]-fluorouracil composite with DFT method in view point of drug delivery [11]. They investigated the potentiality of SWCNTs as a carrier for droksidopa by quantum mechanical calculation and also by molecular dynamics simulation in both gas and water phases [22]. With the bibliography searching, we know, there is no earlier report about using CNT as a nano-carrier for carbazochrome drug. Therefore, the goal of this study is to investigate the quantum-chemical aspects of the interaction of this drug with SWCNTs.

Computational details

Through a theoretical quantum calculation, equilibrium geometries optimization, total energies, and electronic densities were accomplished in the DFT framework with M062X functional and 6-31G* basis set were made using the Gaussian 09 program package [23].

The adsorption behavior of carbazochrome on a zigzag (4,0)SWCNTs (40atom) was investigated. The adsorption energies of carbazochrome on SWCNTs via the different active sites were calculated using the following relationship:

$$E = E_{\text{complex}} - (E_{\text{drug}} + E_{\text{CNT}}) \quad (1)$$

where E_{drug} is the energy of the free drug, E_{CNT} is the energy of the free carbon nanotube. The binding energy has been corrected using the basis set superposition error (BSSE).

Also, the relaxed CNT-drug system strength is defined as the difference between the energy of interaction (E_{int}) with the energy of the complex and the drug molecule bonded to the SWCNTs in the optimized complexes

$$E_{\text{int}} = E_{\text{complex}} - (E_{\text{drugincomplex}} + E_{\text{CNTincomplex}}) \quad (2)$$

If E_{int} is negative, it indicates pull between drug and CNT, if E_{inter} is positive, it indicates push between drug and CNT.

E_{def} , can be denoted as the used energy for changing the molecule from its ideal configuration to the relaxed molecule-surface system.

$$E_{\text{def}} = E_{\text{def-drug}} + E_{\text{def-CNT}} \quad (3)$$

where $E_{\text{def-CNT}}$ is the energy of the deformed CNT surface after drug adsorption. $E_{\text{def-drug}}$ is the energy of the drug form molecule with deformed geometry after its adsorption on CNT. The counter-poise (CP) method of Boys and Bernardi was used to correct the E_{ads} and E_{int} based on BSSE [24].

The nature of intermolecular energies between drug and CNT surfaces is investigated by using Bader's QTAIM theory using MULTIWFN software [25]. QTAIM theory is used to examine the bond critical points (BCP) between two adjacent atoms: their electron densities and Laplacians [26].

Parameters related to HOMO and LUMO energies such as stiffness, softness, chemical Gibbs energies, electronegativity, chemical potential and electrophilicity index, nucleofugality, electrofugality, and maximum electron flow were calculated using the following equations [27, 28].

$$\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}} \quad (4)$$

$$\mu = -\chi \cong \left(\frac{E_{\text{HOMO}} + E_{\text{LUMO}}}{2} \right) \quad (5)$$

$$\eta = \frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2} \quad (6)$$

$$\sigma = \frac{\eta}{2} \quad (7)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (8)$$

$$\Delta E_n = \pm \frac{(\mu + \eta)^2}{2\eta} \quad (9)$$

$$\Delta E_e = \frac{(\mu - \eta)^2}{2\eta} \quad (10)$$

$$\Delta N_{\text{ideal}} = -\frac{\mu}{\eta} \quad (11)$$

Current electron density, ELF, and LOL functions

The current densities can be formulated as follows:

$$\rho(r) = \eta_i |\varphi_i(r)|^2 = \sum_i \eta_i |\sum_l C_{li} \chi_l(r)|^2 \quad (12)$$

That χ , η_i , and C are the basis function for orbitals, occupation number, and a coefficient matrix. Bader [29, 30] illustrated regions of large electron localization have a wide value of Fermi-hole. Becke and coworkers [31] illustrated that spherically average like-spin pair has suitable correlation with the Fermi hole. Consequently, they introduced a new function as “electrons localization functions” [32, 14].

$$(\text{ELF}).\text{ELF}(r) = \frac{1}{1 + [D(r)/D_{0(r)}]^2} \quad (13)$$

where

$$D(r) = \frac{1}{2} \sum_i \eta_i |\nabla \varphi_i|^2 - \frac{1}{8} \left[\frac{|\nabla \rho_\alpha|^2}{\rho_\alpha(r)} + \frac{|\nabla \rho_\beta|^2}{\rho_\beta(r)} \right] \quad (14)$$

and

$$D_{0(r)} = \frac{3}{10} (6\pi^2)^{\frac{2}{3}} [\rho_\alpha(r)^{\frac{5}{3}} + \rho_\beta(r)^{\frac{5}{3}}] \quad (15)$$

for closed-shell systems, since $\rho_\alpha(r) = \rho_\beta(r) = \frac{1}{2}\rho$, D and D_0 terms can be simplified as

$$D(r) = \frac{1}{2} \sum_i \eta_i |\nabla \varphi_i|^2 - \frac{1}{8} \left[\frac{|\nabla \rho|^2}{\rho(r)} \right] \quad (16)$$

and

$$D_{0(r)} = \frac{3}{10} (3\pi^2)^{\frac{2}{3}} \rho(r)^{\frac{5}{3}} \quad (17)$$

Savin et al. [33] showed, $D(\mathbf{r})$ parameter as the excess kinetic energies due to the Pauli repulsion, while $D_0(\mathbf{r})$ is known as Thomas–Fermi kinetic term. Here the ELF can be interpreted in view point of kinetic energies among Kohn–Sham DFT’s wave-functions. And it would be in the range of [0,1], which means for a large ELF value, electrons are strongly localized. Although ELF can be used for the wide varieties of molecules, localized orbital locator (LOL) is the other important function that has been investigated by Becke and coworkers instead of ELF for some special molecules [34].

$$\text{LOL}(r) = \frac{\tau(r)}{1 + \tau(r)}, \text{ where } \tau(r) = \frac{D_0(r)}{\frac{1}{2} \sum_i \eta_i |\nabla \varphi_i|^2} \quad (18)$$

$D_0(r)$ is used synonymously with ELF for spin polarized and closed shell systems.

Jacobsen showed that the kinetic energies of LOL can be interpreted much better than ELF, since LOL provides a more precise and clear image than ELF. LOL can also be interpreted in terms of localized orbitals. LOL’s range of values is between zero and 1, as with ELF [0, 1].

Result and discussion

Various computational tools can be used, such as DFT, Car–Parrinello MD simulations, and hybrid QM/MM approximations for any further calculations. Quantum molecular calculations has been provided recently as a relatively consistent phenomenon of the interaction forces and geometries about the structure, charge distribution, and energy of these kind interacting molecules. As drug carriers, the administration, absorption, and transportation of CNTs must be considered for obtaining the desired treatment effects. The studied routes of CNT administration include oral and injections such as subcutaneous injection, abdominal injection, and intravenous injection. There are different ways of absorption and transportation when CNTs are administered by different routes. Various interaction orientations considered for the interacting drug molecule (N1, O2, N3, N4, which are the semicarbazide group, and the interactions between the O5, N6, and O7 atoms belonging to the indole group) and the CNT were calculated with DFT method in level M062X/6-31G (d) and given in Fig. 1 that exhibits the optimized compound carbazochrome, a zigzag CNT (4,0) (40atom), and carbazochrome–CNT(4,0) complexes (complex1–complex6). From Fig. 1, it can be concluded that carbazochrome has various sites for interaction.

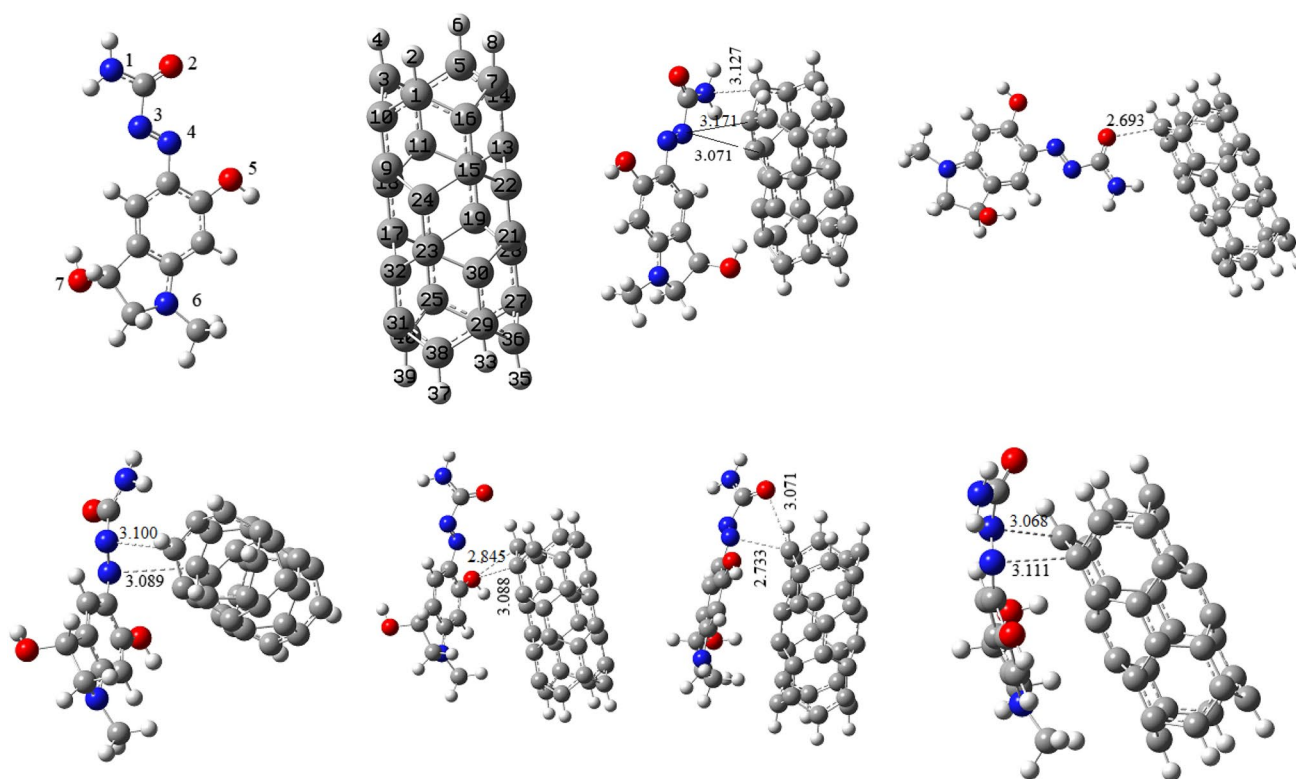


Fig. 1 The optimized compound carbazochrome, nanotube (4×0), nanotube (4×0)-carbazochrome complexes (complex1–complex6) calculated by M062X/6-31G (d) level

The calculated equilibrium binding distance between carbazochrome and CNT for the complex1–complex6 are given in Table 1 and the calculated interaction, adsorption, and deformation energies of complex1–complex6 are given in Table 2.

The calculated equilibrium-binding distance for N1-C38, N1-C31, N3-C32, and O6-C2 at complex1 are 3.127,

3.171, 3.071, and 3.055 Å, respectively, and adsorption energy is $-14.96 \text{ kcal mol}^{-1}$. The energy of adsorption and equilibrium-binding distance between O2 and C atom belonging to CNT for the complex2 are determined to be respectively $7.13 \text{ kcal mol}^{-1}$ and 2.693 Å ; for complex3, C23-N4, C38-N3 distances are 3.089 and 3.100 Å , and calculated adsorption energy is $-8.14 \text{ kcal mol}^{-1}$ for complex

Table 1 The calculated equilibrium binding distance between carbazochrome and CNT for the complex1–complex6

	Atom	Bond length	Atom	Mulliken charges		Atom	Mulliken charges		Charge
				CNT	Comp		Drug	Comp	
1	C38-N1	3.127	C38	-0.205	-0.196	N1	-0.815	-0.796	-0.02296
	N3-C31	3.171	C31	0.045	0.0558	N3	-0.339	-0.316	
	C32-N3	3.071	C32	-0.014	0.0092	N3	-0.339	-0.316	
	C3-O7	3.055	C3	-0.205	-0.169	O7	-0.645	-0.666	
2	C38-O2	2.693	C38	-0.205	-0.153	O2	-0.482	-0.507	0.004935
	O2-H37	2.556	H37	0.189	0.215	H	0.392	0.368	
	H-C23	2.277	C23	-0.014	-0.104				
3	C23-N4	3.089	C23	-0.014	0.008	N4	-0.227	-0.216	0.007103
	C38-N3	3.100	C38	-0.205	-0.171	N3	-0.339	-0.315	
4	C38-O5	2.845	C38	-0.205	-0.160	O5	-0.632	-0.653	0.029106
	C31-O5	3.088	C31	0.045	0.030				
5	N4-C38	2.733	C38	-0.205	-0.178	N4	-0.216	-0.250	0.002562
	O2-C38	3.071				O2	-0.482	-0.525	
6	N4-C31	3.111	C31	0.045	0.047	N4	-0.227	-0.279	0.002217
	N3-C38	3.068	C38	-0.205	-0.062	N3	-0.339	-0.297	

Table 2 The calculated interaction, adsorption, and deformation energies of carbazochrome, CNT, and complex1–complex6 (kcal mol^{−1})

Complex	$E_{\text{ads/inter/def}}$	SEZPE	SETE	SETEn	SETFE
1	E_{ads}	− 14.96	− 14.05	− 14.65	− 1.72
	E_{inter}	− 16.45	− 15.53	− 16.13	− 2.59
	E_{def}	1.49	1.48	1.48	0.87
2	E_{ads}	− 7.13	− 5.91	− 6.51	3.54
	E_{inter}	− 7.55	− 6.26	− 6.85	3.95
	E_{def}	0.42	0.34	0.34	− 0.41
3	E_{ads}	− 8.14	− 6.99	− 7.58	3.81
	E_{inter}	− 10.29	− 8.96	− 9.56	2.33
	E_{def}	2.15	1.97	1.97	1.48
4	E_{ads}	− 18.24	− 17.11	− 17.71	− 5.64
	E_{inter}	− 21.28	− 20.21	− 20.81	− 7.99
	E_{def}	3.04	3.10	3.10	2.35
5	E_{ads}	− 22.25	− 21.50	− 22.09	− 8.25
	E_{inter}	− 24.23	− 23.33	− 23.93	− 9.84
	E_{def}	1.98	1.84	1.84	1.59
6	E_{ads}	− 22.12	− 21.50	− 22.09	− 8.11
	E_{inter}	− 24.11	− 22.76	− 23.35	− 10.13
	E_{def}	1.99	1.26	1.26	2.01

SEZPE, sum of electronic and zero-point energies; SETE, sum of electronic and thermal energies; SETEn, sum of electronic and thermal enthalpies; SETFE, sum of electronic and thermal free energies

2. Calculated adsorption energies for complex4–complex6 are − 18.24, − 22.25, and − 22.12 kcal mol^{−1}, respectively. Our results suggest that considering only three positions is more energetically important; via −O–H attached to the phenyl ring (complex4), via the O atom of the carbonaceous group and a nitrogen atom of the imine group (complex5), and two nitrogen atoms of imine group (complex6). It was found that the complex5 gives the strongest adsorption energy in the other configurations.

Interaction and deformation energy of complex5 are − 24.23 and 1.98 kcal mol^{−1}. The values show that the interaction between CNT and carbazochrome is physical adsorption. They reported that the calculated adsorption energy was approximately − 0.405 eV with an equilibrium distance of approximately 3.167 Å and stated the presence of physical absorption in the interaction [35].

Computing the free energy change of any reaction is a useful approach to assessing its thermodynamic feasibility. A large negative change in free energy as it passes from reagents to products creates a quantitative spontaneous (and exothermic) reaction. SETE in interaction for complex1–complex6 are − 2.59, 3.54, − 1.72, 2.33, − 7.99, − 9.84, and − 10.13 kcal mol^{−1}. It was found that the complex6 gives the strongest spontaneous (and exothermic) reaction in the other configurations. It can be said that the weak intermolecular interference between CNT and carbazochrome is an alternative, and the CNT favors the suitability of the

carbazochrome molecule as a drug, resulting in desorption [36, 37].

From the thermodynamic quantities calculated in the gas phase, it is seen that the formation of all complexes is exothermic, and all except complex2 and complex3 are thermodynamically applicable under ambient conditions. Charge population analysis using the Mulliken approach shows that there is − 0.02295 $\bar{e}$ charge flow from CNT to carbazochrome in complex1, whereas in complex2–complex6, there was a charge flow of 0.004935, 0.007103, 0.029106, 0.002562, and 0.002217 $\bar{e}$ from the carbazochrome to the CNT.

According to the Mulliken charge population analysis with the Mulliken approach, the Mulliken charge of the C38 atom in CNT, which was − 0.205 $\bar{e}$, was − 0.196 $\bar{e}$ in complex1. The Mulliken charge, which was − 0.815 $\bar{e}$ in carbazochrome, was − 0.796 $\bar{e}$ in complex1. The negative charge densities of the C38 and N1 atoms in the interaction of CNT and carbazochrome show that they decrease to 0.009 $\bar{e}$ and 0.019 $\bar{e}$, respectively. However, the fact that there is a charge density flow from CNT to carbazochrome during the interaction indicates that the charge densities are distributed over other atoms.

In complex5, which has the highest adsorption and interaction energy in the studied complexes, the charge transfer from carbazochrome to CNT was 0.002562 $\bar{e}$, and in this interaction, the Mulliken charge density of C38 decreased to 0.027 $\bar{e}$, and the N4 and O2 atoms increased to 0.034 and 0.043 $\bar{e}$. It shows that it is distributed over other atoms. In order to clarify the binding nature in these complexes, we evaluated the total electron density maps of carbazochrome, CNT, and complexes. Regions with high electron density are shown in red and yellow. In the carbazochrome molecule, it is seen that the phenyl group has a negative potential, while in the complexes, it is concentrated in the binding groups, as can be seen in Fig. 2.

Topology analysis

Topology analysis based on Bader's QTAIM method has been employed with MULTIWFN program. It has been applied for the selected complexes with the strong interaction energy and more negative adsorption energy values given in Table 1. Thus, the property of intermolecular interactions between CNT and drug is determined in terms of electron densities at bond critical points (BCPs).

In QTAIM analysis, mostly, laplacian $\nabla^2\rho(r)$ characteristics and the electron density of $\rho(r)$ are widely used to understand the bonding interactions property. However, the total energy density of $H(r)$ and $|V(r)|/G(r)$ are more remarkable parameters on bonding characteristics. It has been noted that for weak and medium-strength hydrogen bonding and van der Waals interactions due

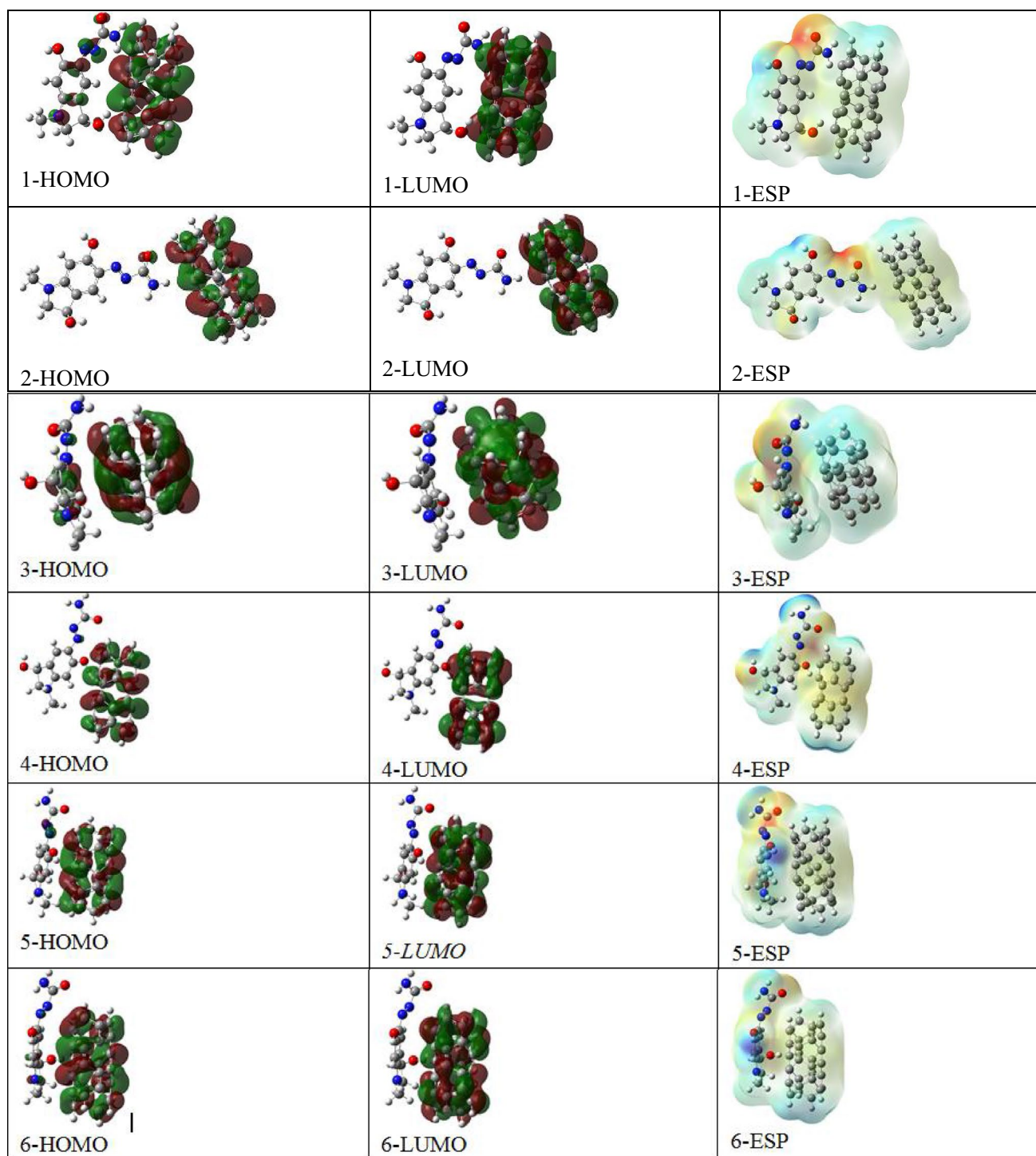


Fig. 2 HOMO, LUMO, and ESP form of carbazochrome complexes (complex1–complex6)

to the $\nabla^2\rho(r) > 0, H(r) > 0, |V(r)|/G(r) < 1$. The strong hydrogen bonds as the intermediate type of interaction related to $\nabla^2\rho(r) > 0, H(r) < 0, 1 < |V(r)|/G(r) < 2$. The covalent bonding characteristics correspond to

$\nabla^2\rho(r) < 0, H(r) < 0, |V(r)|/G(r) > 2$. The calculated parameters related to QTAIM are represented in Table 3. All the BCP parameters for the selected two complexes are given in Table 3.

Table 3 The QTAIM parameters of selected complexes at the BCPs. ($\rho(r)$), ($\nabla^2\rho(r)$), $y(G(r))$, ($V(r)$) ($H(r)$), the ratio $|V_{BCP}|/G_{BCP}$

	BCP drug-CNT	ρ_{BCP}	$\nabla^2\rho_{BCP}$	G_{BCP}	V_{BCP}	H_{BCP}	$\frac{ V_{BCP} }{G_{BCP}}$
Complex1	O58-C3	0.0089953	0.02864881	0.00637412	−0.00558601	0.78810E-3	0.876359
	H60-C10	0.0064457	0.20480840	0.00408164	−0.00304308	0.00103856	0.745553
	H51-C9	0.0086487	0.02789399	0.00568965	−0.00440579	0.00128385	0.774353
	H62-C18	0.0168489	0.05058477	0.01218945	−0.01173273	0.45673E-03	0.962531
	H43-C32	0.0058093	0.01999599	0.00391383	−0.00282866	0.00108517	0.722735
	H69.C23	0.0084599	0.02777012	0.00574151	−0.00454049	0.00120102	0.790818
	N45-C32	0.0095906	0.02925069	0.00637501	−0.00543734	0.93766E-03	0.852916
	N41-C38	0.0092201	0.02648873	0.00598239	−0.00534261	0.63979E-03	0.893055
Complex5	O66-C35	0.0062120	0.02545403	0.00519646	−0.00402941	0.00116705	0.775415
	O66-H37	0.0127652	0.04707427	0.01073079	−0.00969302	0.00103777	0.903290
	N62-C38	0.0151947	0.05264539	0.01149667	−0.00983199	0.00166467	0.855204
	O61-C31	0.0075404	0.02455781	0.00533510	−0.00453076	0.80435E-03	0.849235
	O61-C23	0.0065634	0.01884586	0.00399188	−0.00327229	0.71958E-03	0.819738
	C49-C23	0.0062352	0.01745302	0.00369054	−0.00301782	0.67272E-03	0.817719
	C48-C23	0.0066979	0.01813392	0.00384244	−0.00315139	0.69104E-03	0.820155
	H58-C24	0.0121040	0.03648692	0.00816775	−0.00721377	0.95398E-03	0.883201
	H47-C24	0.0059264	0.01831454	0.00372119	−0.00286374	0.85745E-03	0.769577

The computed molecular topographical map of complex1 and complex5 with critical points and atom labels are also illustrated in Fig. 3.

According to Table 3, the highest electron density at BCP between the nitrogen atom (N62) of the drug and the carbon atom (C38) of the CNT, which indicates more accumulation of charge from the computational results presented in Table 2, the all interactions in the both complex structures indicate the typical electrostatic interactions according to QTAIM classification with the topology parameters as $\nabla^2\rho(r) > 0$, $H(r) > 0$, $|V(r)|/G(r) < 1$.

QTAIM analysis shows that the majority of the interactions of drug with the surface of CNT can be defined as non-covalent nature. One of the important measurements of chemical stability is the energy gap between HOMO and LUMO, and if a molecule is little or no HOMO–LUMO gap, it can be chemically reactive.

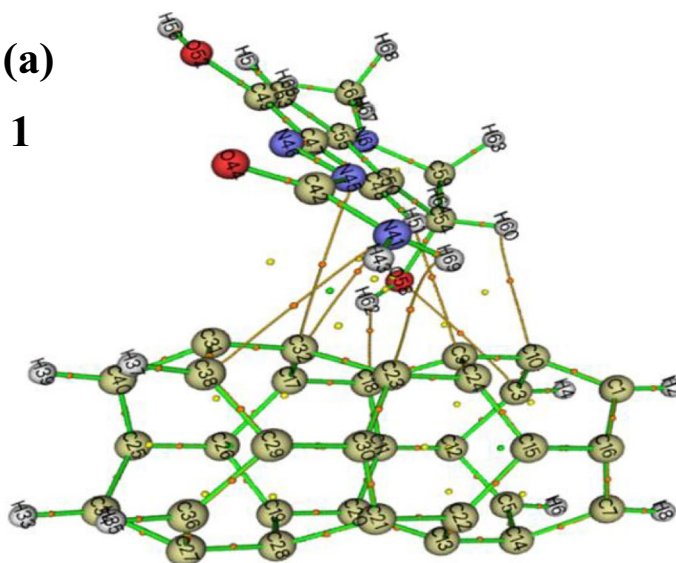
Atomic and bond critical points are presented by atom labels and orange spheres, respectively. The cage and ring critical points are due to green and yellow circles. The lines are bond paths.

Tables 4 and 5 summarize HOMO–LUMO energies and the parameters like such as hardness (η), softness (σ), electronegativity (χ), the maximum amount of electronic charge transfer ΔN_{maks} , chemical potential (μ) and electrophilicity index (ω), nucleofugality, electrofugality related to E_{HOMO} and E_{LUMO} , and thermal energy, heat capacity, and entropy values of carbazochrome, CNT, and complex1–complex6 calculated with M062X/6-31 g* level. It is notable, in single-electron excitation process, an electron leaves one space

function to the real space functions that can be perfectly described as HOMO $\rightarrow$ LUMO transition. However, in most practical cases, this single-orbital pair model is not suitable, and the excitations have to be represented as the transition of multiple MO pairs with proper weighting coefficients. Intermolecular orbital overlap integral is important in discussions of intermolecular charge transfer. In this study, we calculate HOMO–HOMO and LUMO–LUMO overlap integrals between carbazochrome, CNT, and complex1–complex6 calculated. The wavefunction level we used is M062X functional and 6-31 g (d) basis set correspond to HOMO and LUMO, respectively. Consequently, we examine which transport routes are the most favorable due to the atom with larger contribution to HOMO/LUMO) which is more likely to be the preferential site of electrophilic/nucleophilic attack, respectively. The concepts of absolute electronegativity ($\chi = \frac{(I+A)}{2}$) and absolute hardness ($\eta = \frac{I-A}{2}$), are related as ($I = \chi + \eta$), where I and A are the ionization potential and electron affinity of our system (Table 4). The usefulness of χ and η lies in their ability to help predict chemical behavior. The value of η for different systems does correlate with chemical hardness and softness defined empirically. The theoretical basis for the new quantities lies in the density functional formalism. Since molecular orbital (MO) theory is by far the most widely used by chemists, it is important to place χ and η in a MO framework. Within the validity of Koopmans' theorem, the frontier orbital energies are given by $-\epsilon_{\text{HOMO}} = I$ and $-\epsilon_{\text{LUMO}} = A$. The stability of chemical compounds against deformation in an electric field can be related by its hardness. The hardness of CNT

Fig. 3 The computed molecular topographical map of **a** complex1 and **b** complex5 with all critical points

(a)
Complex 1



(b)
Complex 5

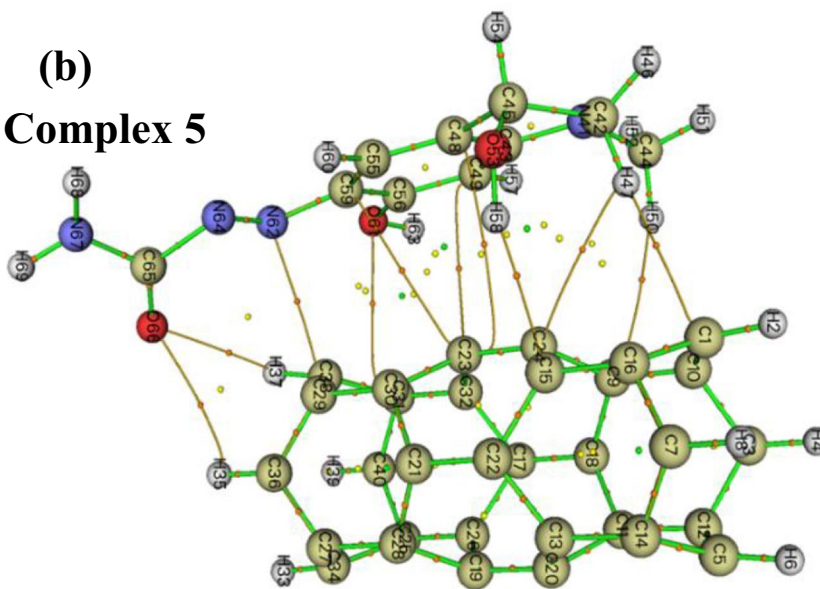


Table 4 E_{HOMO} , E_{LUMO} , ΔE_g , hardness, softness, the maximum amount of electronic charge transfers of carbazochrome, CNT and complex1–complex6 calculated with M062X functional, and 6-31 g (d) basis set. $\% \Delta E_g$ represents the percentage of band gap of complex with respect to the bare CNT

Molecules	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE_g (eV)	$\% \Delta E_g$	η (eV)	σ (eV ⁻¹)	ΔN_{maks}
Carbazome	−6.753	−0.896	5.856		2.928	0.171	1.306
CNT	−6.220	−2.304	3.916		1.958	0.255	2.177
1	−6.283	−2.382	3.902	−0.36	1.951	0.256	2.221
2	−6.064	−2.158	3.905	−0.28	1.953	0.256	2.105
3	−6.227	−2.352	3.875	−1.05	1.938	0.258	2.214
4	−6.077	−2.160	3.917	0.025	1.958	0.255	2.103
5	−6.139	−2.232	3.907	−0.22	1.953	0.256	2.143
6	−6.262	−2.346	3.915	−0.02	1.958	0.255	2.199

Table 5 Chemical potential, electronegativity, electrophilicity, nucleofugality, electrofugality values of carbazochrome, CNT, and complex1–complex6 calculated with M062X/6-31 g (d) level

Molecules	χ (eV)	μ (eV)	ω (eV)	ΔE_n (eV)	ΔE_e (eV)	K
Carbazochrome	3.825	− 3.825	2.498	0.137	7.786	
CNT	4.262	− 4.262	4.639	1.356	9.880	
1	4.333	− 4.333	4.811	1.454	10.119	1.82×10^1
2	4.111	− 4.111	4.328	1.193	9.415	2.53×10^{-3}
3	4.290	− 4.290	4.749	1.428	10.007	1.60×10^{-3}
4	4.118	− 4.118	4.330	1.191	9.428	1.37×10^4
5	4.186	− 4.186	4.484	1.275	9.646	1.13×10^6
6	4.304	− 4.304	4.731	1.406	10.014	8.95×10^5

being 1.958 eV is decreased to 1.951, 1.953, 1.951, 1.938, and 1.953 eV for complex1, complex3, and complex5, and it is the same for complex2 and complex5. When the hardness values are compared, the stability of complex4 and complex6 is the same as that of the CNT (Table 4).

The isolated carbazochrome has a large HOMO–LUMO energy gap of 5.856 eV, where E_{HOMO} is − 6.753 eV, and the E_{LUMO} is − 0.896 eV. The isolated CNT has 3.916 eV HOMO–LUMO energy gap, where the HOMO energy is − 6.220 eV, and the LUMO energy is − 2.304 eV. As can be seen in Table 3, after adsorption of carbazochrome on CNT, the HOMO–LUMO energy gap of system decreases to 3.902, 3.905, 3.875, 3.907, and 3.915 eV, respectively for complex1–complex6 and, however, increases slightly to 3.917 for complex4.

In order to understand the sensing mechanism of the CNT to drug, the variation of ΔE_g gap during the adsorption process is taken into account by the following equation.

$$\% \Delta E_g = 100(\Delta E_{g2} - \Delta E_{g1}) / \Delta E_{g1} \quad (19)$$

where ΔE_{g1} and ΔE_{g2} are the ΔE_g values of CNT and complex, respectively.

Sensors are concerned with the change of their electrical conductivity after drug adsorption due to electron exchange between the drug and the sensor. In this line, the drug sensitivity of CNT is based on the HOMO and LUMO energies.

The percentage change values, of $\% \Delta E_g$ for each complex is given in Table 3. As reported energies of E_{HOMO} and E_{LUMO} and energy gap (E_g) in Table 3, the electronic properties of CNT are affected by the adsorption of carbazochrome drug. The decreasing order of percentage change values are obtained for complex3, complex1, complex2, complex5, and complex6 as 1.05%, 0.36%, 0.28%, 0.22%, and 0.022%, but for complex4, it is about 0.025 by increasing.

The lower E_g values indicate higher electrical conductivity, reactivity, and sensitivity. Therefore, decreased E_g through adsorption of carbazochrome drug indicates the

CNT can detect the drug. Except complex4, all studied geometries of complex structures can be detected the drug material. The density of states (DOS) diagram of each complex was also calculated in order to better understanding the stability of the system. The change in E_g by DOS analysis can be confirmed as shown in Fig. 4.

The DOS diagrams of CNT and selected complexes are calculated in the energy range of − 15 to 0 eV have been shown in Fig. 4. In these plots, we have selected the complexes with the significant $\% \Delta E_g$ values given in Table 3, as complex3 and complex1.

The ionization potential of the system may decrease when carbazochrome is adsorbed (complex2, complex4, and complex5) or increase (complex1, complex3, and complex6) depending on the adsorption site; but these variations are not noticeable.

ELF current-densities image obtained from DFT studies of carbazochrome carbon nanotube as drug delivery nano-carrier for anti-bleeding drug are represented in (Fig. 5) and the currents consist of HOMO contributions (Table. 4).

In a ring having “ $4n$ ” electrons, HOMO–LUMO is derived from a split degenerate ($\lambda = n$), whereas in a ring with a “ $4n + 2$ ” system such as carbazochrome, HOMO–LUMO is associated with “ $n + 1$ ” and “ n ”. λ is zero when $n = 4$. The diatropic contribution and the paratropic contribution consist of transitions with $\Delta \lambda = +1$ and $\Delta \lambda = 0$, respectively [38, 39]. In Huckel’s theory, $\{\pi\}$ energies are calculated using coulomb and resonance parameter $\{\beta\}$ [40]. Therefore, for higher symmetry $4n + 2$ systems, HOMO–LUMO transitions cause to diatropic currents. For the “ $4n$ ” ring (subsytmetry), the HOMO–LUMO transition leads to paratropic contribution, and the second HOMO–LUMO + 1 transition causes to tropic contributions [41].

The chemical hardness (η) and chemical potential (μ) for the investigated structures are the parameters used to predict the reactivity of the molecules. Since compounds with lower chemical hardness and higher chemical potential values will be more reactive, the electron transfer required for the implementation of the chemical reaction can be easier [29]. As can be seen in Table 5, in complex2 and complex5, when

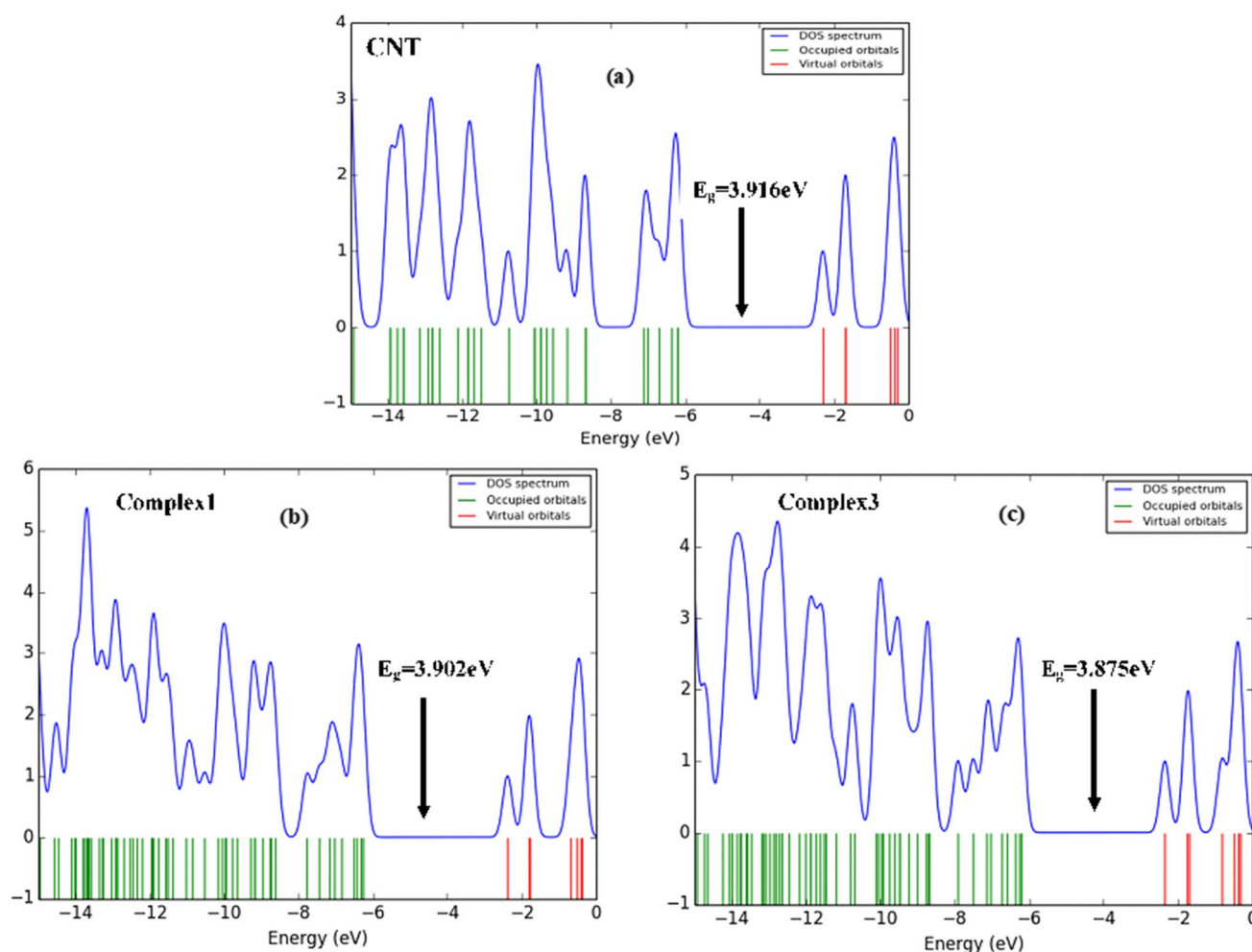


Fig. 4 TDOS graphs for **a** pristine CNT, **b** complex1, and **c** complex3 structures

carbazochrome is adsorbed to CNT surfaces, the hardness decreases, and the chemical potential increases in both configurations, indicating that the reactivity of carbazochrome increases after its adsorption to the CNT surface [42].

The global electrophilicity index measures the total ability to attract electrons. CNT can be accepted as a strong electrophile due to possessing a high electrophilicity index at B3LYP (4.639), and carbazochrome possesses a lower electrophilicity index at B3LYP (2.498) (Table 5). Therefore, in the interaction of the carbazochrome with the CNT, the electron density flows from the carbazochrome to the CNT [43].

The fractional number (ΔN) of the electron transferred between two molecules is determined by Eq. 12. Electron transfer parameter determines the direction of spontaneous electron flow, as well as the fraction of electrons transferred from system A to system B [37, 44]

$$\Delta N = \frac{\mu_B - \mu_A}{\eta_A + \eta_B} \quad (20)$$

where, η_A and η_B chemical hardness of the acceptor (A) and donor (B) systems, and μ_A is chemical potential of the acceptor (A) and μ_B is those of donor (B) systems. If ΔN is positive, the charge transfer occurs spontaneously from B to A, and if negative, the charge transfer occurs in the opposite direction. ΔN value of 0.09 in the equation $\Delta N = \frac{\mu_{\text{carbazochrome}} - \mu_{\text{CNT}}}{\eta_{\text{carbazochrome}} + \eta_{\text{CNT}}}$ supports that the charge flow from carbazochrome to CNT supports that CNT treats as electron acceptor and carbazochrome treats as electron donor.

The thermodynamic equilibrium constants of the reaction are also calculated by placing the values of Gibbs free energy changes in the following equation. In this formula, R denotes the ideal gas constant and T the temperature. As can be seen from the Table 4, complex5 has the largest K value among the studied complexes.

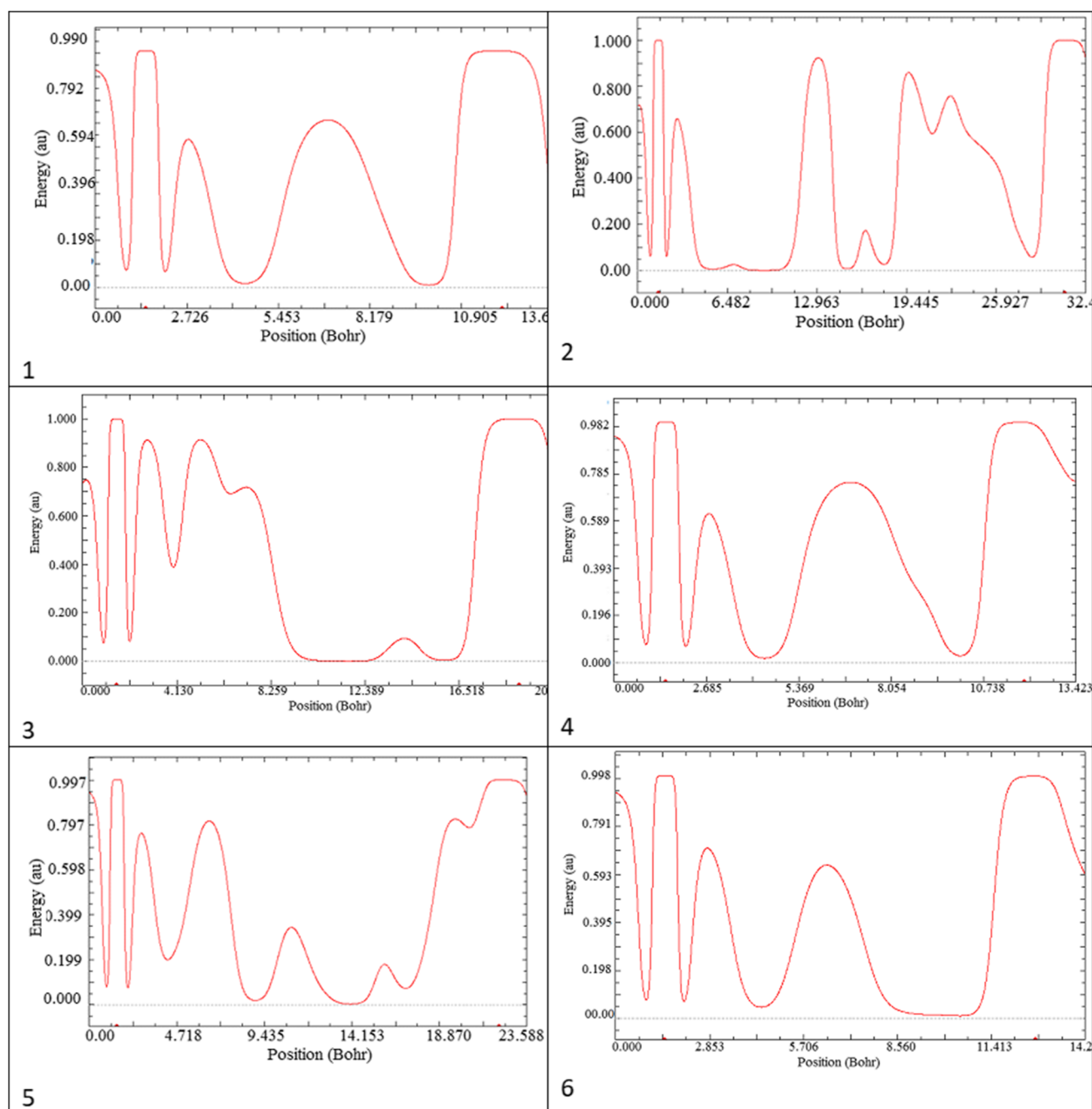


Fig. 5 ELF current–density map from DFT calculations of carbazochrome carbon nanotube as drug delivery nanocarrier

$$K = \exp\left(-\frac{\Delta G_{\text{ads}}}{RT}\right) \quad (21)$$

As seen in Table 5, equilibrium constants order are complex3 < complex2 < complex1 < complex4 < complex6 < complex 5. Complex1, complex4–complex6, is exergonic and thus thermodynamically favorable.

The results of the dipole moments (μ), static and dynamic polarizability (α), anisotropic polarisability, and first hyperpolarizability (β) of carbazochrome, CNT, and complexes obtained by the interaction of different functional groups with M062X6-31G (d) are given in Table 6.

The total electric dipole moments composed of electric dipole moment components (μ_x, μ_y, μ_z), the averaged (isotropic) dipole polarizabilities (α), anisotropy polarizability

Table 6 The dipole moment, polarizability, anisotropic polarizability, and hyperpolarizability values of carbazochrome, pristine CNT, and complex1–complex6 molecules calculated with the M062X/6-31 g(d) level

Complex	μ D	α 10^{-24}cm^3	Kappa	$\Delta\alpha$	β $10^{-30}\text{cm}^5\text{esu}^{-1}$
1	8.57	70.63	0.02986	41.17	16.42
2	14.02	74.93	0.04623	54.48	62.49
3	13.67	70.36	0.01064	40.14	22.96
4	4.81	71.25	0.03356	53.97	15.56
5	5.04	69.25	0.02567	44.32	13.03
6	21.63	69.07	0.02570	45.42	15.10
Carbazochrome	11.89	23.54	0.11460	24.19	25.42
CNT	0.00	47.71	0.08584	41.93	0.01

a.u. (Bohr-electron) = 2.541765 Debye, polarizability: (α) 1
a.u. = 0.148184709 10^{-24}cm^3 ; First-hyperpolarizability (β): 1
a.u. = 8.639418 $10^{-33}\text{cm}^5\text{esu}^{-1}$

($\Delta\alpha$), and total first static hyperpolarizability from the polarizability components are evaluated as follows respectively [45, 46].

$$\mu = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2} \quad (22)$$

$$\alpha = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \quad (23)$$

$$\Delta\alpha = \left[\frac{(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2 + 6(\alpha_{xz}^2 + \alpha_{xy}^2 + \alpha_{yz}^2)}{2} \right]^{1/2} \quad (24)$$

$$\begin{aligned} \beta_x &= \beta_{xxx} + \beta_{xyy} + \beta_{xzz} \\ \beta_y &= \beta_{yyy} + \beta_{yzz} + \beta_{yxx} \\ \beta_z &= \beta_{zzz} + \beta_{zxx} + \beta_{zyy} \\ \beta &= (\beta_x^2 + \beta_y^2 + \beta_z^2)^{1/2} \end{aligned} \quad (25)$$

A dipole moment is a mathematical calculation dealing with unequal distribution of charge in a compound. In other words, the higher the dipole moment of a compound, the more polar the compound is. On the other hand, polarizability is the tendency of a compound to form a dipole when an external electric field is encountered.

In an applied electric field, the energy of a system is a function of the electric field. The first hyperpolarizability is the third-order tensor with a $3 \times 3 \times 3$ matrix. The 27 components of the 3-dimensional matrix can be decreased to 10 components by means of Kleinman symmetry [47]. The μ of pure model CNT is 0, and the symmetry is very

high; therefore, its corresponding β value is very small ($0.01 \times 10^{-30}\text{cm}^5\text{esu}^{-1}$). The value of the dipole moment increases in the adsorbed configurations relative to the free CNT (0.00 Debye), which can be attributed to the the perturbation in the electron density. The dipole moment of complex1 (8.57), complex4 (4.81), and complex5 (5.04) is smaller than that of the single drug and the dipole moment of complex2 (14.02), complex3 (13.67), and complex6 (21.63) is higher than that of the single carbazochrome which shows that adsorption of carbazochrome on the CNT in these three complexes enhances the polarity of the system that is a good feature for drug delivery in biological environments [48].

When carbazochrome is adsorbed to CNT, the symmetry is broken. The μ and β values both increased, and the variation of β value is very apparent. The β values of complex1–complex6 are 16.42, 62.49, 22.96, 15.56, 13.03, and $15.10 \times 10^{-30}\text{cm}^5\text{esu}^{-1}$. When we compare the different interaction ways, the hyperpolarisability value of complex1, which is formed by the interaction of CNT and carbazochrome with the carbonyl group, is the largest of the complexes formed by the interaction of CNT and carbazochrome with the other groups. It has been reported that a large initial hyperpolarizability ($4.187944 \times 10^{-30}\text{esu}$) value is a prerequisite for it to behave like a good NLO material [49].

Recovery time

We have calculated recovery time of the drug from the studied CNT surfaces. It is known that the recovery time gives an information about the time interval (short or long) of the deformation process. It can be predicted as follows

$$\tau = v^{-1} \exp\left(-\frac{E_{\text{ads}}(\text{BSSE})}{kT}\right) \quad (26)$$

where, v is the attempt frequency, E_{ads} is the BSSE corrected adsorption energy, k is the Boltzmann constant and T is temperature. If the vacuum UV light ($v \sim 3 \times 10^{16}\text{s}^{-1}$) is applied to recover of the drug from the studied surfaces, $E_{\text{ads}}(\text{BSSE})$ values are obtained data with the DFT calculations. The CP corrected binding energy values are used in the above Eq. (14) that obtained for complex1–complex6 : $-13.59\text{ kcal mol}^{-1}$, $-7.43\text{ kcal mol}^{-1}$, $-6.55\text{ kcal mol}^{-1}$, $-15.177\text{ kcal mol}^{-1}$, $-21.036\text{ kcal mol}^{-1}$, and $-21.069\text{ kcal mol}^{-1}$. The calculated recovery time values at 298 K for each complex are $2.98 \times 10^{-7}\text{ s}$, $9.18 \times 10^{-12}\text{ s}$, $2.098 \times 10^{-12}\text{ s}$, $4.348 \times 10^{-6}\text{ s}$, 0.0849 s , and 0.0897 s for complex1–complex6, respectively. Those recovery time values for complex1–complex3 are too short; other values for complex5 and complex6 indicate that desorption of drug from the CNT surface is possible. Thus, the CNT surface

can be a proper sensor material for carbazole drug under UV light frequency and room temperature.

In addition under the UV-light frequency ($\nu \sim 3 \times 10^{12} \text{ s}^{-1}$), which is used for the drug 12 s^{-1} desorption from nanosurfaces [50]. Here, the recovery time of 849 s for complex5 was calculated under the UV-light. It is an acceptable value for the desorption process of carbazochrome drug from CNT surfaces.

Conclusions

In this study, we perused the carbazochrome molecule adsorption on the CNT by various functional groups performing DFT calculations and provided valuable information on structural properties, adsorption energy, orientation, and charge transfer between CNT and carbazochrome drug in CNT/carbazochrome complexes.

CNTs have been used because of in several research, it can be exhibited that cell viability decreases significantly in human bronchial epithelial cells. The trend also shows how DNA damage increases considerably with dose concentration of SWCNTs due to the non-functionalised SWCNT. Therefore, using CNTs needs to be studied carefully for any further drug delivery systems. QTAIM analysis shows that drug's interactions with the CNT surface are non covalent. The global electrophilicity index measures the overall ability to attract electrons. Since CNT has a high electrophilic index and carbazochrome has a lower electrophilic index, electron density shifts from carbazochrome to CNT in the interaction of carbazochrome with CNT.

The formation of all gas-phase complexes is exothermic, and all are thermodynamically feasible under ambient conditions except for complex2 and complex3. The results indicated that when carbazochrome adsorbed on CNT, the hyperpolarizability for adsorbed nanotubes increases many times, which indicates that organic chromophore adsorbed to nanotube enhances the non-linear optical properties. It has been shown that the interaction with different functional groups changes the geometric structure and charge distribution and affects the electrical properties, dipole moment, and polarization. On this line, based on the percentage values of band gap of complexes with respect to the bare CNT, the CNT (4,0) can be used to detect carbazochrome drug as an electrochemical sensor. Furthermore, first-order hyperpolarizability of the complex2 shows that it is an attractive object for future studies of nonlinear optical properties. The nature of the formed bonding mode analysis along the reaction pathways was further approved via electron localization function (ELF) calculations.

Author contribution The first draft of the manuscript was written by Fatma Kandemirli and Hakan S. Sayiner, and all authors commented on previous versions of the manuscript. All authors contributed to the study conception and design, material preparation, data collection, research design, the acquisition, analysis, and interpretation of data. All authors read and approved the final manuscript.

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Data availability All data generated or analyzed during this study are included in this published article.

Code availability N/A.

Declarations

Conflict of interest The authors declare no competing interests.

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