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Computational study of SiCNT interacting with Benidipine

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Benidipine belongs to a class of drugs called calcium channel blockers and is used primarily to treat hypertension (hypertension) and angina pectoris. Carbon nanotube (CNT) properties, such as high surface-to-volume ratio, improved conductivity and durability, biocompatibility, ease of functionalisation, and optics, have led to their evaluation as new drug and gene carriers. We have conducted a theoretical investigation of the interactions of the BEN molecule with SiCNT. To better understand the molecular properties, optimised molecular geometry and reactive parameters were investigated by computational study and calculated using the DFT method and B3LYP/6-31G (d) basis set. The adsorption energies of SiCNT/BEN complexes are in the range of −13.22 kcal mol^{-1} to −36.76 kcal mol^{-1}, which indicates that partial chemisorption has occurred. According to QTAIM analysis, complexes can also be said to be partially covalent due to |VB|/GBCP>1. The decreases in energy gap changes between 75% and 90% and dipole moment of complexes changes between 8.80 and 18.60 Debye were perceived for the SiCNT/BEN drug. The results reveal that the vertical ionisation potential (VIP) of complexes is less than that of the BEN molecule, but their vertical electron affinity (VEA) is larger than that of the BEN molecule.

Keywords: *Benidipine, DFT, QTAIM, Toxicity*

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1. Introduction

Various vectors, such as polymers and nanocomposites, are used for targeted drug delivery [1]. However, these have shortcomings such as the need for surgical excision after drug administration when using polymer hydrogel formulation containing erythropoietin because the polymers are not biodegradable [2], and the rate of dissolution in the stomach is very fast due to acid attack when oral administration is done using natural polysaccharides [3]. These problems can be solved by using CNTs instead of polymers. CNTs are biodegradable and do not require surgical excision after drug administration. The chemical properties of CNTs may allow several molecules to interact simultaneously in the tube. If the drug's water solubility, natural dissolution rate and oral bioavailability are low, its therapeutic applications are limited. A study on Ribavirin drug sensing and detection on the pristine and functionalized single-wall carbon nanotubes were carried

out using the density functional theory (DFT). The electronic properties and interaction mechanisms of Ribavarin with the CNTs were reported [4]. The transformative potential of nanomedicine in preventing and treating various diseases through the interaction of nanomaterials with biological molecules is truly inspiring.

Benidipine, a dihydropyridine derivative calcium channel blocker developed in Japan, is a fascinating case. It blocks L, N, and T calcium channels via a membrane approach and has several unique mechanisms of action [5], making it an intriguing subject for further research and potential applications. Using nanoscale materials allows the change of basic parameters such as immunogenicity, diffusivity, solubility, half-life in the bloodstream, and the release rate of the active substance. In recent years, nanoparticle-based therapeutic agents have been developed to treat asthma, allergies, diabetes, pain, infection, and other diseases [6]. Benipidine taken orally is a BCS class II drug with poor oral bioavailability due to its extensive first-pass hepatic metabolism and high lipophilicity (log P 4.28) [7].

The application of nanotechnology to medicine has led to significant advances in areas such as cancer treatment, medical imaging, implantable materials, and tissue regeneration strategies [8]. Since the Si and C atoms in the six-membered rings of SiC nanotubes (SiCNTs) have different electronegativities, the reactivity of SiCNTs in sensing a wide range of molecules is significant compared to carbon nanotubes [9]

This work aims to use the SiCNT as a carrier for the BEN drug. The electronic properties and molecular properties of the complexes formed by the interaction of SiCNT and BEN molecule interactions between BEN and SiCNT were carried out, and the Quantum theory of atoms in molecules (QTAIM) was also performed with the characteristics of critical Points (CPs) using the Multiwfn package [10].

To understand the antioxidant capacity of the complexes formed by the interaction of the BEN molecule of the SiCNT with different functional groups, the Vertical Electron Affinity (VEA) and Vertical Ionization Energy (VIE) of the complexes were calculated, and the Electron Donor-Acceptor Map (DAM) was drawn by using the VEA and VIE values.

2. Materials and Method

The DFT calculations at Becke's three-parameter hybrid one [11] with the correlation functional of Lee, Yang and Parr [12] together with 6-31G(d) basis sets were used for geometry optimisation for all different positions of the BEN, SiCN, and BEN/SiCNT complex structures.

Frequency calculations were also performed using similar level theory to determine the optimised structures' stability and verify that all stationary points are consistent with a minimum point passing through the potential energy surface. All of the calculations, including geometry optimisation and single-point energy calculations, were performed by the Gaussian 09 package [13]. In order to perform quantum theory of atoms in molecule (QTAIM) analysis, the Multiwfn program was employed. The Principal Set Superposition Errors (BSSE) method of Boys and Bernardi is used to correct the interaction energies [14].

3. Results and Discussions

The possible interactions of the functional groups of BEN with SiCNT were investigated. Tthe geometrically optimized structures of BEN, SiCNT with the atomic numbers, and their complexes obtained which was given in **Fig. 1** with the interaction of BEN molecule and SiCNT.

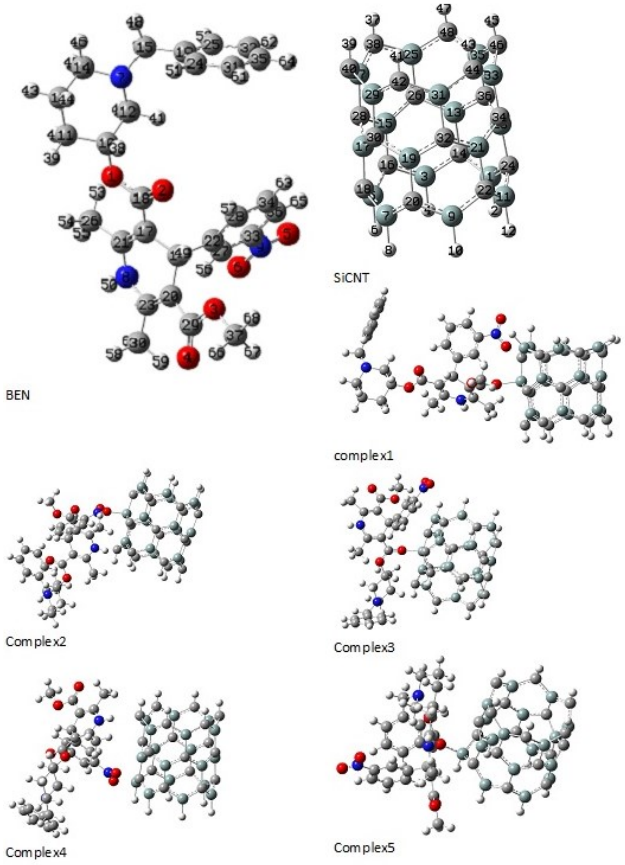

Fig.1. Optimized structures of BEN, SiCNT and their complexes

In **Fig. 2**, the highest occupied molecular orbital (HOMO) and the lowest occupied molecular orbital (LUMO) graphs of BEN/SiCNT complexes are given.

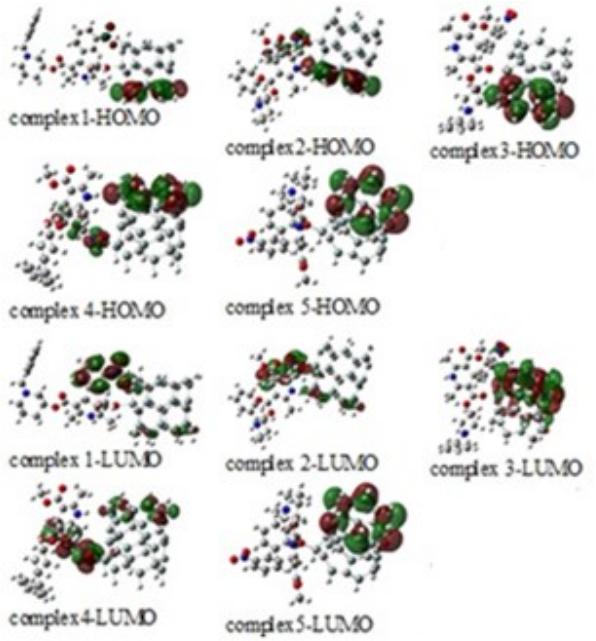

Fig.2. HOMO, LUMO frontier orbitals of BEN/ SiCNT complexes

The contribution of atoms orbitals to HOMO and LUMO for complexes is tabulated in Table 1 and Table 2, respectively. In Fig. 2 and Table 1, the HOMO for complex1, complex3, complex5 and are localized on the SiCNT belonging to mainly C38, C40, C42, C44, C46, C48 atoms.

Table 1 Contribution of atoms orbitals to HOMO for complexes

Struc	Atoms	1	2	3	4	5
SiCNT	Si25	2.4		2.4	2.0	2.7
	Si27	2.3	1.2	2.2	1.3	2.4
	Si29	1.8	2.1	1.1	1.5	2.2
	Si31	2.5	2.5	2.5	2.0	2.3
	Si33	2.5	2.6	2.9	2.5	2.5
	Si35	2.5	2.2	2.9	2.5	2.9
	C38	12.8	9.0	12.4	9.0	14.5
	C40	12.8	11.3	11.3	8.3	11.8
	C42	12.5	13.7	12.0	9.4	11.3
	C44	14.3	15.9	15.9	13.8	13.2
	C46	13.0	14.3	16.6	15.2	16.4
	C48	13.1	11.4	16.0	13.4	17.0
BEN	N9		3.3		5.3	
	05		3.1		4.9	
	C27				1.6	
	C28				1.9	
	C36				1.6	
	O6				1.5	

The contributions of the mentioned atoms are 12.8, 12.8, 12.5, 14.3, 13.0, and 13.1, respectively, for the first complex in percentage,12.4, 11.3, 12.0, 15.9, 16.6 and 16.0, for the 3rdcomplex in percentage and 9.0, 8.3, 9.4, 13.8, 15.2 and 13.4, for the third complex in percentage. and for complex2 and complex4 is also localized on the SiCNT belonging to mainly C38, C40, C42, C44, C46 atoms and localized on the the N9 (3.3 % for complex2 and 5.3 % for complex 5) and O5 (3.1 % for complex2 and 4.9 % for complex5) atoms of the BEN molecule.

As listed in Table 2, the LUMO density is concentrated on the drug moiety, mainly C27, C28, N8, C36, O5, and O6 atoms for complex 1, C27, C36, O1, O6, H54 atoms for complex 2, and LUMO is distributed as C18, C23, C27, C28, C36, O1, O6 and H54 atoms of BEN molecule as 17.8 %, 7.6 %, 7.4 %, 8.9 %, 24.7 %, and 7.6 %, respectively for complex4, while LUMO s distributed SiCNT nanotube for complex 5.

Table 2 Contribution of atoms orbitals to LUMO for complexes

Struc	Atm	1	2	4			3	5
SiCNT	Si17		1.4			Si1	11.2	13.9
	C18	2.7				Si3	7.0	8.1
	C30		1.1			Si5	7.0	6.0
	C38		1.0	2.3		Si7	6.7	1.6
	C40		1.5	1.3		Si9	7.7	6.3
	C42	1.4	2.6	1.5		Si11	10.8	8.3
	C44	1.2	1.8	2.6		Si13	2.5	3.7
	C46			3.2		C14	3.3	3.8
	C48			3.7		Si15	1.8	2.5
BEN	C17				*SiCNT*	C16	2.8	2.8
						Si17		1.8
	C18			17.8		C18	2.8	
	C23			7.6		Si19	2.0	1.6
	C27	6.5	7.7	7.4		C20	2.7	
	C28	9.0		8.9		Si21	2.5	2.6
	N8	1.4				C22	3.5	2.8
	C36	25.0	26.3	24.7		Si23	3.6	3.8
	O1	7.9	7.8	7.6		C24	3.9	4.0
	O6	22.1	24.1	22.5		C26		2.1
	H54	13.1	9.1	7.5		C28		1.1
						C34	1.9	2.3
						C36	1.9	2.2
					BEN	C18		2.8
						C21		3.1

The ionization potential is related to the HOMO energy value (E_{HOMO}) and the electron affinity is related to the LUMO energy (E_{LUMO}) values are written as follows,

$$I = -E_{HOMO} \quad (1)$$

$$A = -E_{LUMO} \quad (2)$$

E_{LUMO} has the lowest electron-empty molecular orbital energy, and E_{HOMO} has the highest electron-occupied

molecular orbital energy. Using parameters such as E_{LUMO} and E_{HOMO} plays an important role in activating many chemical reactions and determining molecular electronic transitions. By using these parameters, properties such as HOMO–LUMO Energy band gap Eg, hardness(η), chemical softness(S), electronic chemical potential(μ), electronegativity(μ), and electrophilicity index (ω) and ΔN_{max} are calculated as given in equations 3-9 [15-17]

$$\eta = \frac{1}{2}(E_{LUMO} - E_{HOMO}) = \frac{1}{2}(I - A) \quad (3)$$

$$Eg = E_{LUMO} - E_{HOMO} \quad (4)$$

$$S = \frac{1}{2\eta} \quad (5)$$

$$\chi = -\frac{1}{2}(E_{HOMO} + E_{LUMO}) \quad (6)$$

$$\mu = -\chi = \frac{1}{2}(E_{HOMO} + E_{LUMO}) \quad (7)$$

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

$$\Delta N_{max} = -\frac{\mu}{\eta} \quad (9)$$

In simple terms, the hardness of an atom, ion, or molecule is a qualitative indicator of how polarizable that species is, that is, how much its electron cloud is distorted in an electric field. Hardness and softness have been proposed to indicate resistance to deformation by mechanical force.

Molecules with a large Eg gap are called hard. The higher the Eg gap, the higher the stability and opposite charge transfer because these molecules resist electron density and distribution changes. Molecules with a small Eg gap require a small energy range for excitation. These types of molecules are called soft molecules and can be easily polarized. In chemical changes, soft molecules are more reactive than hard molecules.

For BEN, Eg is 3.71eV, as shown in Table 3. In the case of complex1, complex2, complex3, complex4, and complex5, $\Delta(E_{LUMO} - E_{HOMO})$ value were 0.55, 0.29, 0.58, 0.79, 0.34eV, which is lower than BEN drug which implies that complexes are easier to polarize The HOMO–LUMO gap for all the complexes decreases in the following order: complex5< complex3< complex2< complex4< complex1. Hence, the highest softness was observed for complex1. It was proposed an electrophilicity index assuming a sea of free electron gas at zero temperature and zero chemical potential [18, 19]. According to Sanderson's principle, when an electrophilic system (atom, molecule or ion) is immersed in the sea, there is a flow of electrons of the amount ΔN from the sea to the system until the chemical potential of the electrophilic system becomes zero (up to the second order [20, 21]. The equation gives the resulting energy change associated with the electron transfer process by

$$\Delta E = \mu \Delta N + \mu \frac{1}{2}\eta(\Delta N) \quad (10)$$

In the case where the system reaches saturation by absorbing the maximum amount of electrons, setting the value of ΔNmax, (ΔE/ΔN) to zero indicates Equation 11

$$\Delta E = \frac{\mu^2}{2\eta} \quad (11)$$

From equations 10, 11 and 9, equation 8 is obtained:

Table 3 E_{HOMO}, E_{LUMO}, energy, Eg, hardness(η), chemical softness(S), electronic chemical potential(μ), electronegativity(μ), and electrophilicity index (ω) and ΔN_{max} for SiCNT, BEN and their complexes (eV units)**.**

	E_{HOMO}	**E_{LUMO}**	**Eg**	**η**
SiCNT	-4.21	-3.65	0.55	0.28
1	-3.95	-3.66	0.29	0.15
2	-4.17	-3.59	0.58	0.29
3	-3.80	-3.02	0.79	0.39
4	-4.35	-4.00	0.34	0.17
5	-3.94	-3.03	0.92	0.46
BEN	-5.79	-2.08	3.71	1.85
	S	χ	μ	ω
SiCNT	1.80	3.93	-3.93	27.88
1	3.42	3.80	-3.80	49.52
2	1.72	3.88	-3.88	25.94
3	1.27	3.41	-3.41	14.81
4	2.90	4.18	-4.18	50.60
5	1.09	3.49	-3.49	13.27
BEN	0.27	3.94	-3.94	4.18

The amount of charge transfer in complexations can indicate the adsorption strength between the BEN molecule and SiCNT. The largest charge transfer is seen in complex 5, as given in Table 4. The bond lengths between the SiCNT and BEN molecules, the charge flows between the two molecules, and the electron density between the HOMO and LUMO orbitals of the complexes formed by the interaction of BEN and SiCNT are given in Table 4.

Table 4. Charge transfer, and the bond length between the interacting atoms in complexes

Com plex	Bond	Bond length	CT(BEN-SiCNT)	***ρ***
1	Si17-O4	1.78224	0.031092	0.49791
	Si7-O6	1.90954		
2	Si17-O6	1.85241	0.088783	0.60880
3	Si17-O2	1.87818	0.31202	0.22357
4	Si5-O6	1.79445	0.025896	0.75613
5	Si7-O2	1.79705	0.388067	0.23042

The bond lengths between the SiCNT and BEN molecules, the charge flows between the two molecules, and the electron density between the HOMO and LUMO orbitals of the complexes formed by the interaction of BEN and SiCNT

are given in Table 4. The amount of charge transfer (CT) can be used as an indicator of the adsorption strength between BEN drug and SiCNT for complexations. The amount of CT from BEN to SiCNT in complex1, complex2, complex3, complex4, complex5 is 0.031092, 0.088783, 0.31202, 0.025896, 0.38807 e, respectively.

The adsorption energy of BEN drug is calculated by the following equation:

$$E_{ads} = E_{complex} - (E_{BEN} + E_{SiCNT}) + E_{BSSE} \quad (12)$$

Where E_{BEN}, and E_{SiCNT}, $E_{complex}$ represent the energy of the BEN, SiCNT and complex, respectively. E_{BSSE} represents Base set superposition error energy and was defined as an approximate method estimating of the BSSE [14].

Interaction, deformation and adsorption, and energies of SiCNT/BEN complexes for electronic, enthalpy, and Gibbs free energy terms are given in Table 5. The adsorption energy values are in order: complex4> complex1> complex5> complex2> complex3. The enthalpy values are also for adsorption in the same order. But the order changes for Gibbs free energy in the adsorption.

Table 5 Interaction, deformation and adsorption energies for studied complexes

		ΔE	**ΔH**	**ΔG**
complex1	E_{ads}	-34.09	-34.68	-17.00
	E_{int}	-66.62	-67.21	-54.22
	E_{def}	32.52	32.52	37.22
complex2	E_{ads}	-20.45	-21.04	-5.62
	E_{int}	-33.20	-33.79	-21.37
	E_{def}	12.75	12.75	15.75
complex3	E_{ads}	-13.22	-13.81	-0.44
	E_{int}	-27.76	-28.35	-16.59
	E_{def}	14.54	14.54	16.15
complex4	E_{ads}	-36.76	-37.35	-22.19
	E_{int}	-55.30	-55.89	-44.14
	E_{def}	18.54	18.54	21.95
complex5	E_{ads}	-32.16	-32.76	-18.97
	E_{int}	-49.86	-50.45	-39.31
	E_{def}	17.69	17.69	20.34

Quantum Theory of Atoms in Molecules (QTAIM) analysis

The nature of the interaction was examined by using QTAIM methodology. Bader's atoms in molecules (AIM) analysis for BEN complexes was performed. The bond critical point (BCP) of Si17-O4, Si7—O6 bonds for complex1, Si17-O6 bond for complex2, Si17-O2 bond for complex 3, Si5-O6 bond for complex4 and Si7-O2 for complex 5, For electron density analysis, (3,-1) is commonly called the bond critical point (BCP) because it usually appears between interacting atom pairs. The value of the real space functions in the BCP is of great importance since the value of a and the sign of 2 in the BCP are closely related to the bond strength and bond type, respectively, in the analogous bond type.

In our discussion of the nature of the bonds formed by the interaction of the atoms of the nanostructure and BEN, the electron density (ρ_{BCP}), Lagrange kinetic energy (**G_{BCP}**), Potential energy density (**V_{BCP}**), Energy density (H_{BCP}), Laplacian ($\nabla^2\rho_{BCP}$) were analysed and given in Table 6.

If the values of $\nabla^2\rho(r)$ and H(r) are less than zero, the interaction is described as covalent; if the values of $\nabla^2\rho(r)$ are greater than zero and H(r) are less than zero, the interaction is described as partially covalent; and if the values of $\nabla^2\rho(r)$ and H(r) are positive, the interaction is described as non-covalent in nature [22].

In general, for shared (covalent) bonding, $\rho(r)>0.20$ au and for closed-shell interaction, $\rho(r)<0.10$ au [23]. Generally speaking, the larger the electron density value in BCP, the stronger the bond. $\nabla^2\rho(\mathbf{r})$ is positive for Si-O bond for complexes studied.

Table 6. The QTAIM topological parameters of the BEN-adsorbed compounds

Complex	BCPs Drug/NT	ρ_{BCP}	G_{BCP}	V_{BCP}
1	Si17-O4	0.05431	0.06535	-0.07676
	Si7-O6	0.03986	0.02331	-0.03636
2	Si17-O6	0.07641	0.10694	-0.12533
3	Si17-O	0.489624	0.077694	-0.10318
4	Si5-O6	0.029429	0.031468	-0.15895
5	Si7-O	0.049936	0.581967	-0.15895
		H_{BCP}	$\nabla^2\rho_{BCP}$	$\lvert V_{BCP}\rvert/G_{BCP}$
1	Si17-O4	-0.01141	0.21572	1.20325
	Si7-O6	-0.01305	0.04104	0.58485
2	Si17-O6	0.01839	0.35422	1.39955
3	Si17-O2	-0.01249	0.31280	1.37881
4	Si5-O6	-0.01865	0.48657	1.57793
5	Si7-O2	-0.01865	0.48657	1.58605

In Table the value of $\nabla^2\rho_{BCP}$ positive and the value of H_{BCP} negative means that bonds are ionic and coordinate.

According to the $|V_{BCP}|/G_{BCP}$ ratio, if $V_{BCP}|/G_{BCP}<1$, it is for closed-shell interaction, if $|V_{BCP}|/G_{BCP}>2$, it is for shared shell interaction and if |VBCP|/GBCP >1, it is for partially covalent interactions. The interactions. complexes can be said partially covalent due to $|V_{BCP}|/G_{BCP}>1$.

Toxicity

Oxidative stress-induced cellular events and alterations in intracellular calcium homeostasis pathways affect cytotoxicity's biochemical and molecular mechanisms. [24]. Theoretical model studies based on quantum chemical calculations can shed more light on the biochemical and molecular mechanism of this cytotoxicity.

The B3LYP functional was used to calculate the VIP and VEA using Equations (12) and (13), respectively.

$$VEA = \mathrm{E(A)} - E(A^{-1}) \quad (12)$$

$$VIP = E(A^{+1})\text{-E(A)}, \quad (13)$$

Where E(A), E(A+1), and E(A-1) are the natural, cations and anion energies of materials. By considering the single electron transfer process and molecules' ability to accept electrons, it is possible to understand how molecules can scavenge radicals. To make qualitative material comparisons, DAM provides details about the electron accepting and donating power of molecules, as well as the anti-radical potential of molecules and provides a basis for antioxidant studies.

The electron donate tendency (ω-) and the tendency to accept electron-(ω+) were calculated using Equations (14) and (15) and are given in Table 7

$$\omega^{+} = \frac{(VIP+3\,VEA)^2}{16(VIP-VEA)} \quad (14)$$

$$\omega^{-} = \frac{(3VIP+\,VEA)^2}{16(VIP-VEA)} \quad (15)$$

Table 7 VIP and VEA values in eV for BEN and its complexes with SiCNT

	VIP	***VEA***	ω+	ω-
BEN	7.119	0.447	0.670	4.453
1	4.699	3.134	7.942	11.859
2	5.130	2.647	4.299	8.187
3	4.832	2.032	2.667	6.099
4	5.203	3.238	7.075	11.296
5	4.998	2.097	2.745	6.293

The oxidative stress of all systems was determined by donor acceptor map (DAM) [25] using the ω- and the ω+ values and is given in Fig. 5.

If the systems below on the left are good electron donors, they donate electrons by producing reductions of other molecules that gain these electrons. The systems above on the right are good electron acceptors. They oxidize other species by accepting electrons. The (ω-),(ω+) values of the performed complexes are larger than BEN molecules;

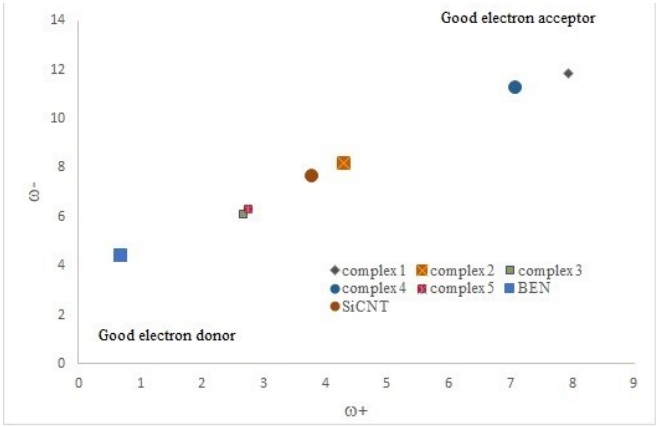

Fig.5 The DAM for BEN drug / SiCNT compounds

The polarizability and hyperpolarizability functions of molecules show nonlinear responses, and the NLO properties of molecules depend largely on their hyperpolarizability. The calculated Dipole Moment polarizabilities, anisotropic polarizability and hyperpolarisibility values [26] for studied BEN molecule and its SiCNT complexes are presented in Table 8.

Table 8 NLO properties of BEN and its complexes (esu)

	Dipole Moment	< α:> (10^{-24} cm^3)	Δα (10^{-24} cm^3)	β (10^{-30} cm^5esu^{-1})
1	18.60	1303	165.5	58751.04
2	8.80	1104	89.43	265.11
3	17.41	947	31.38	134.58
4	10.05	1209	131.85	119.49
5	14.83	929	28.09	75.42
BEN	5.86	346	9.56	0.95

< α >: Polarisibilityi, Δα: Anisotropic polarizability β: first hyperpolarisibility i

The result show that Dipole moment, Polarisibility, anisotropic polarisibility and hyperpolarisibilit values of the complexes are bigger than BEN molecule. Dipole moment is calculated to control the charge separation between the analyte and the adsorbed molecule. Higher dipole moment means more charge separation in a system. Charge separation in complexes is greater than in BEN molecules.

3. Conclusion

This study attempted to explain the chemical reactivity, adsorption, interaction, and deformation energies of BEN on SiCNT using DFT B3LYP/ 6-31G (d) in the gas phase. The

obtained data showed that the drug was active in terms of electronic parameters and the ability to adhere to nanotubes. Dipole moment values show that there are more charge sepation in the complexes than BEN molecule. It was observed that the HOMO of the complex structure are strongly localized on SiCNT. The NLO properties such as dipole moment, polarizability, first hyperpolarizability and increased considerably in the complexes.

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