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# Conformational stability, spectroscopic and computational studies, highest occupied molecular orbital, lowest unoccupied molecular orbital, natural bond orbital analysis and thermodynamic parameters of anticancer drugs on nanotube - A review

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**Abstract**

Today the use of nanotubes (CNTs) is widely spread a versatile vector for drug delivery that can officiate as a platform for transporting a variety of bioactive molecules, such as drugs. In the present study, the interaction between the nanotube and anticancer drugs is investigated. Density functional theory (DFT) calculations were using the Gauss view and the complexes were optimized by B3LYP method using B3LYP/6-31G (d, p) and B3LYP/6-311++G (d, p) basis set in the gas phase and water solution at 298.15K. The calculated highest occupied molecular orbital (HOMO) and the lowest unoccupied (LUMO) energies Show that charge transfer occurs within the molecule. Furthermore, the effects of interactions on the natural bond orbital analysis (NBO) have been used to a deeper investigation into the studied compounds. These factors compete against each other to determine the adsorption behavior of the tube computer simulation is seen to be capable to optimize anticancer drug design. This review article mainly concentrates on the different protocols of loading anticancer drugs onto CNTs as well as how to control the anticancer drug release and cancer treatment.

***Key words:*** Anticancer drugs, DFT, NBO, HOMO–LUMO.

## Introduction

The application of nanotechnology in disease treatment, monitoring, diagnosis and in the mastery of biological systems in the single molecule or molecular group area is denoted to as nano drug. The major aim of nano drug is the design of the substance capable of forking up and target pharmaceutical, therapeutic and diagnostic factors (1-5). The kind of drug delivery system carbon nanotube was discovered by Iijma in 1990 (6). Surgery and X-ray therapy provided the only way of attacking a malignant disease in the past. The current medical literatures show that chemotherapy is employed in almost all the cases, despite the agony that all the antineoplastic agents are non-specific and highly toxic to the patient. A variety of antineoplastic agents are in clinical use, for example, alkylating agents, antimetabolites, nitrosoureas, plant alkaloids, antibiotics, enzymes, hormones and radioactive isotopes. These are chemically different compounds and their modes of action are also varied (7). Anticancer genes act in a dominant fashion: when ectopically over expressed, they specifically destroy tumor cells without harming normal cells. This cell destruction can occur in several ways such as programmed cell death, and mitotic catastrophe followed by apoptosis or necrosis, and autophage anticancer genes have only lately emerged from works on cancer cells (8). The various computational tools such as Density Functional Theory (DFT) and Car-Parrinello molecular dynamics simulations can be used in order to conduct the calculations. Density functional quantum chemical calculations have recently provided a relatively consistent image on base pair action and reaction energies and geometries. This may lead to more detailed information on structure, energy of the base pair and charge distribution (9-12). Density functional methodology has been found to be really useful in explaining the chemical reactivity, resistance and site selectivity of such intricate systems which makes use of the quantum molecular descriptors whit similar hardness, chemical potential and electrophilicity indices (13).

DFT is used in a lot of research, to study, for example the interaction of particles with the pristine; Al-, Ga-doped BN nanotubes (14). Drug delivery with nano materials is an active emergent research area and CNT draws noticeable potential use owing to its unique quasi one-dimensional structure and electronic properties (15). In this article, the adsorption energies, optimized parameters, the molecular orbital properties like HOMO, LUMO, chemical potential, hardness, their energy gap and NBO calculations are used to gain insights into the influence of anticancer drugs adsorption on the electronic properties, and the geometrical structure of nanotubes (16).

## Computational methods

Many computational tools, such as density functional theory (DFT) and Car-Parrinello molecular dynamics simulations may be used for calculations. Density functional quantum chemical calculations have recently provided a relatively consistent image on base pair interaction energies and geometries. This can lead to more detailed information on the structure, charge distribu-

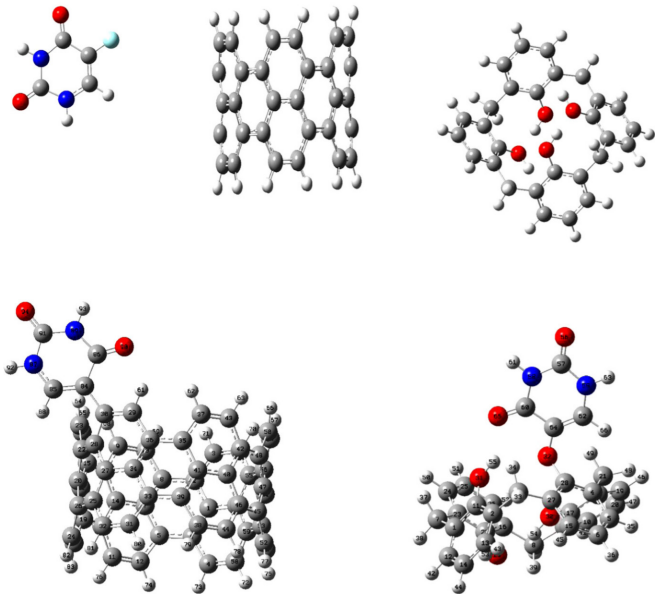

**Figure 1.** The structures of optimized using $B_3$LYP/6-31G (*d*) method at 298.15K (8).

tion, and energy of the base pair (17-20). Now, quantum chemical is almost universally applicable to the explanation of physical and chemical properties of different compounds (21). Understanding the biochemical mechanism of an illness usually suggests the types of molecules necessary for new drugs. In whole instances, the end of using the computer is in order to break down the drug design, the action and reaction between the drug and receiver sites and to design drugs that yield a suitable optimal (22-24).

## Methods

An investigation is taken out utilizing a personal computer nanotube- anticancer drug (with different atom number) which reacts with anticancer drug. In this article, the drug delivery properties are investigated by NBO analysis and DFT method. The DFT calculations have been performed using the nanotube modeler (25) Gauss view (26) and Gaussian (27) using B3LYP method and 6-31 G (*d*) standard basis set NBO analysis (28,29). Computations have been also performed for all composites using B3LYP method and the standard 6-31G (*d*) basis set. Complexes between anticancer drug and nanotube (6,6) are optimized, then bond length (Å), bond angle (deg), dihedral angle (deg), hyperconjucation energy, as well as total energy ($KJmol^{-1}$) moment dipole (Debye), occupancy, total energy and HOMO-LUMO are investigated between nanotube (6,6) and anti-cancer drug using $B_3$LYP/6- 31G (*d*) method.

## Results and discussion

Researchers have carried out a series of DFT calculations on anticancer drugs using both the B3LYP/6-311++G (d, p) and 6-31G (d, p) methods. Figure 1 for instance, shows the optimized compound fluorouracil, nanotube (6,6) -fluorouracil (complex1), and calix (4) aryan-fluorouracil (complex2) by the DFT method in level B3LYP/6-31G (*d*) (8).

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), (30), and the HOMO-LUMO bond gap have been found as a quantity of the structural stability properties (31). The parameters of bond length (Å), natural bond orbital (NBO) and bond angle (deg), distances of the analyzed models of the nanotube (6,6) and calyx (4) arene are calculated by DFT at the level of $B_3$LYP and 6-31G (*d*) standard basis set and are shown in Table 1. The DFT calculated geometric parameters for complex1, and 2 are compared in Table 1. The bond lengths $C_{30}$-$C_{84}$/ $O_{84}$ calculated for complex 1,2 at the DFT level range from 1.47 to1. 40 Å, at the B3LYP/6-31G (*d*) level (8).

The bond lengths calculated at $C_{36}$--- $C_{29}$ for complex 1 (in ring nanotube), 1.44 Å and, for complex 2, 1.40 Å, are within the range (in ring calixarene). The bond lengths calculated

$C_{85}$--- $C_{87}$ for complex 1, 1.37 Å, and complex 2 are ranged 1.38 Å. The $C_{88}$--- $C_{92}$ bond length is lower than $C_{36}$--- $C_{29}$bond length in complex 1 and 2. With that reason, there is more electronegativity of nitrogen than carbon. The angles for $N_{87}$-$C_{91}$=$O_{94}$ are 123/41° and 123/77° for complexes 1 and 2. The angles for $C_{84}$-$C_{86}$=$O_{90}$ are 126/9° and 124/4° for complex 1 and 2, respectively. The angles for $C_{84}$-$C_{86}$=$O_{90}$ is larger than the angel for $N_{87}$-$C_{91}$=$O_{94}$ in complexes 1 and 2. The interaction of between non-bonding and bonding pairs on the nitrogen atom of the angle is reduced in $N_{87}$ - $C_{91}$=$O_{94}$. The dihedral angles for C/$H_{30}$- $C_{28}$-- $C_{27}$-- $C_{34}$ for complex 1and 2 range from −26/01° to 35/84° (in dihedral 6). The dihedral angles 1, 2, 3, 4, 5 and 6, are observed in Table 1 and Figure 2 (8).

**Table 1.** Parameters of in $B_3$LYP/6-31 G (*d*) method optimized by complexes 1 and 2at 298.15K

| Agent | Complex1 | Complex2 |
|---|---|---|
| $C_{30}$ – $C_{84}$/$O_{84}$ | 1.47 | 1.40 |
| $C_{30}$ = $C_{20}$ | 1.37 | 1.35 |
| $C_{36}$… $C_{29}$ | 1.43 | 1.40 |
| $C_{28}$ – $C_{30}$ | 1.47 | 1.46 |
| $C_{85}$… $N_{87}$ | 1.37 | 1038 |
| $N_{87}$ – $C_{91}$ | 1.39 | 1.40 |
| $C_{91}$ = $O_{94}$ | 1.22 | 1.23 |
| $C_{30}$ = $C_{28}$… $C_{27}$ | 116.02 | 121.62 |
| $C_{84}$ = $C_{85}$ – $H_{88}$ | 121.36 | 122.70 |
| $C_{85}$… $N_{87}$ – $H_{92}$ | 120.82 | 120.48 |
| $N_{87}$ – $C_{91}$ =$O_{94}$ | 123.42 | 123.77 |
| $C_{91}$ – $N_{89}$ – $H_{93}$ | 115.60 | 115.47 |
| $O_{90}$ = $C_{86}$ – $C_{84}$ | 126.90 | 124.39 |
| $C_{30}$ – $C_{84}$ = $C_{85}$ …$N_{87}$ [1] | 178.86 | - |
| $H_{87}$ – $C_{84}$ – $N_{86}$ …$H_{91}$ [2] | 0.79 | 0.52 |
| $C_{90}$ – $N_{88}$ – $C_{85}$ = $O_{89}$ [3] | - 178.64 | - 179.12 |
| $H_{61}$ – $C_{29}$ = $C_{30}$ – $C_{28}$ [4] | 172.74 | - |
| $O_{94}$ = $C_{91}$ – $N_{89}$ – $C_{86}$ [5] | 179.16 | 173.95 |
| C/$H_{30}$– $C_{28}$ … $C_{27}$ … $C_{34}$ [6] | − 26.01 | 35.84 |

Bond distances (Å), Bond Angles (deg) and dihedral Angles(deg) (8).

1: $C_{30}$ – $C_{84}$ = $C_{85}$ …$N_{87}$ dihedral Angles, 2: $H_{87}$ – $C_{84}$ – $N_{86}$ …$H_{91}$ dihedral Angles, 3: $C_{90}$ – $N_{88}$ – $C_{85}$ = $O_{89}$ dihedral Angles, 4: $H_{61}$ – $C_{29}$ = $C_{30}$ – $C_{28}$ dihedral Angles, 5: $O_{94}$ = $C_{91}$ – $N_{89}$ – $C_{86}$ dihedral Angles, 6: C/$H_{30}$– $C_{28}$ … $C_{27}$ … $C_{34}$ dihedral Angles

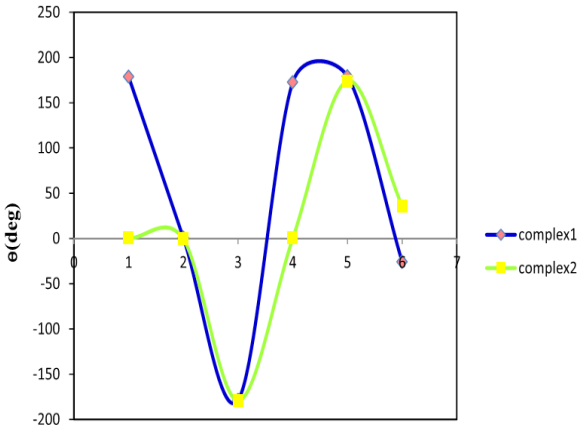


**Figure 2.** Pole of change dihedral angle of complexes 1, and 2 using methods B $_3$LYP/6-31 G (*d*) at 298.15 k (8).

The computations of the total energies, hyperconjoucation energy ($E_2$) of the optimized structures, dipole moments (μ), occupancy and hybrid at B3LYP/6-31G (*d*) levels are shown in Tables 2 and 3. In Table 2, the Mulliken charges in donor atoms electronegative $O_{84}$ and acceptor$C_{30}$ are negative and positive, respectively. Complex 1 has gap of energy that is larger than complex 2; therefore, complex 1 is stable. In Table 2, it becomes obvious that the complex 1 has formed higher hyperconjugation energy than complex 2. Also, the results show that by increasing p part in hybrid of atoms, the occupancy decreases. The S orbital part in hybrid of carbon in complex 2 is more than the S orbital part in hybrid of in complex 1. Combined with the most of hyperconjugation energy is stable. The occupancy coefficient is smaller. Complex 1 is more stable than complex 2.

The hyperconjugation energy complex1 at 37.34 is larger than that in complex 2. The S hybrid orbital of a compound is lower. Table 2 shows the HOMO and LUMO energies for complexes. By evaluating HOMO/LUMO gap energies, it is obvious that if the gap becomes bigger, the complex will be stable; therefore, complex 1 is the more stable of the two complexes. The results of the present work were obtained using DFT optimization and formation energy ($\Delta E°_f$ in $KJmol^{-1}$) calculation of the $B_3$LYP/6-31G (*d*) level. $\Delta E°_f$ is calculated using the formula $\Sigma E°_{product} - \Sigma E°_{reactant} = \Delta E°_f$ Values in complexes 1 and 2 are in the range of −13.275 and +46.902 $KJmol^{-1}$; therefore, complex1 has the lowest formation energy than the others. The energy (KJ $Mol^{-1}$) and dipole moments (Debye) indicate the consistency between the two complex calculations in DFT method. The gap energies and total energy, $\Sigma E_2$, HOMO and LUMO complexes 1and 2 were calculated using the $B_3$LYP method and 6-31G (*d*) basis set. The total energy sum of energy transitional, energy rotational and energy vibration in level $B_3$LYP/6-31G (*d*) for complexes 1 and 2 was calculated. The obtained results are shown in Table 3 (8).

**Table 2.** The NBO parameters of, Complex 1 and 2 are calculated in $B_3$LYP/6-31G (*d*) method at 298.15K (8).

| Agent | Donor | Occupancy | Acceptor | Occupancy | hybrid | $E^2$ | $\sum E^2$ |
|---|---|---|---|---|---|---|---|
| Complex1 | BD(1)C30- C84 | 1.96631 | BD*(1)C27-C28 | 0.02586 | $SP^{1.98}$ | 1.48 | 35.53 |
| | | | BD*(1)C28-C30 | 0.02920 | $Sp^{2.06}$ | 1.70 | |
| | | | BD*(1)C29-C30 | 0.02033 | $Sp^{1.79}$ | 3.12 | |
| | | | BD*(1)C29-C36 | 0.02164 | $SP^{1.96}$ | 2.51 | |
| | | | BD*(1)C84-C85 | 0.01852 | $SP^{1.88}$ | 3.55 | |
| | | | BD*(1)C84-C86 | 0.06682 | $SP^{2.28}$ | 1.82 | |
| | | | BD*(1)C85-N87 | 0.01939 | $SP^{2.51}$ | 3.76 | |
| | BD*(2)C84-C85 | 0.23733 | BD*(2)C29-C3 | 0.2195 | $SP^{99.99}$ | 17.59 | |
| Complex2 | BD(1)C28-O32 | 1.94416 | BD*(1)C4-C5 | 0.0219 | $SP^{1.9}$ | 1.48 | 22.77 |
| | | | BD*(1)C15-C27 | 0.02108 | $SP^{1.85}$ | 1.6 | |
| | | | BD*(1)C60-C64 | 0.07182 | $SP^{1.71}$ | 1.93 | |
| | | | BD*(2)C62-C64 | 0.24487 | $SP^{1.00}$ | 0.66 | |
| | | | BD*(1)C4-C28 | 0.03327 | $SP^{1.98}$ | 1.88 | |
| | LP(1)O32 | 1.93171 | BD*(2)C27-C28 | 0.37632 | $SP^{1.00}$ | 5.18 | |
| | | | BD*(1)C4-C28 | 0.03327 | $SP^{1.98}$ | 3.86 | |
| | LP(2)O32 | 1.87683 | BD*(1)27-C28 | 0.03258 | $SP^{1.95}$ | 6.15 | |

**Table 3.** Formation energy, total energy, HOMO, LUMO, Gap of energy, moment dipole and heat capacity are calculated in B3LYP/6-31G (*d*) method at 298.15 K (3).

| Agent | $E_{total}$ | $\Delta E°_f$ | HOMO | LUMO | Gap | μ |
|---|---|---|---|---|---|---|
| Complex 1 | 465.7 | −13.27 | −0.158 | −0.089 | −0.069 | 0.52 |
| Complex 2 | 348.0 | +46.9 | −0.199 | −0.054 | −0.145 | 0.59 |

## Conclusion

In this article, the solution shows that complex 1 is more stable than complex 2 between nanotube and fluorouracil (6,6). Thus, complex1 is a better conditioner for drugs than complex 2. NBO analysis shows bigger gap energy in complex1. Complex1 has lower formation energy and is more stable than complex 2. During some years, the rapid advances in computational chemistry have led to an increasingly accurate description of anticancer drugs. Many functional basis sets and corrections thereof have been suggested, which are often optimized to reproduce a specific property with high accuracy. Although the search of finding a universal functional is a prevailing challenge, DFT is yet the method of choice for a large number of theoretical investigations in anticancer drugs because it can provide a number of useful figures that aid to helpful design. Overall, this review provided information about anticancer drugs, which is summed up as follows: Density functional theory calculations at the B3LYP/6-31G (d, p) and 6-311++G** levels were applied to shape the ground state molecular geometry (bond lengths and bond angles), harmonic vibrational wavenumbers, infrared intensities and Raman activities of anticancer drugs. The HOMO–LUMO and NBO analysis provides an efficient method for studying intermolecular and intramolecular interaction in the molecular system. The NBO analysis, analysis of the electrostatic potential map and the HOMO and LUMO analyses, reveal the significant point of charge transfer interactions taking place in the molecules, which is responsible for bioactive property of the biomedical compound.

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