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Comparison of drug delivery systems: Nanotube and *p*- Sulphonatocalix[4]arene, by Density Functional Theory

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Abstract

Nowadays, the use of calixarenes and nanotubes are widely spread in the field of drug delivery. In this work, interaction between *p*-sulphonatocalix[4]arene and nanotube(6,6)with Fluorouracil drug is investigated. Density function theory (DFT) calculations have been performed using the Gauss view and Gaussian03 by B3LYP (beck three-parameter hybrid functional combined with Lee-Yang-Parr correlation functional) method and 6-31G (d) standard basis set. The length bond (Å), bond angel (degree), dihedral angel (in degree), hyperconjugation energy, and total energy (KJ mol⁻¹), formation energy (KJ mol⁻¹), moment dipole (in Debye) and occupancy of between nanotube (6,6) and *p*-sulphonatocalix[4]arene with anti-cancer drug are calculated by B3LYP/6-31G (d) method. The results show that composite 2 is more stable than the other composite. The hyperconjugation energy (E^2) in the *p*-sulphonatocalix[4]arene-fluorouracil is higher than that in the other composite. The standard formation energy (ΔE_f°) in the the *p*-sulphonatocalix[4]arene-fluorouracil is more negative value (lower) to composite 1.

Keyword: Single-walled carbon nanotube; DFT; 5-Fluoropyrimidin-2; 4(1H, 3H)-dion; *p*-Sulphonatocalix[4]arene; Drug design; NBO; C_v ; Energy stability

Background

The extensive research on carbon nanotube done to their structural characterization and discovered by Iijima in 1991 year [1,2]. Among the numerous delivery systems currently under investigations, single-walled carbon nanotubes seem to embody a promising option [3]. Single-walled carbon nanotubes are made up of carbon atoms arranged in a series of condensed benzene rings and wrapped into a tubular form (Figure 1b). Nanotubes are two types of: single- walled carbon nanotube (SWCNT) and multi-walled carbon nanotube (MWCNT), respelsitvly. In particular, the application of single-walled carbon nanotube , calixarene, fulouren and cytosine as new carrier for drug delivery, properties became doable soon after the demonstration of cellular uptake of this new material [4-10].

In the paper, the composite of nanotube (6,6)-fluorouracil and *p*-Sulphonato-calix[4]arene)-fluorouracil are

investigated as a drug delivery system. Calixarenes are a group of supramolecule that have basket-like shape which are easily available through the cyclocondensation of para-substituted phenols with formaldehyde [11-15]. The *p*-Sulphonatocalx[4]arene have received considerable attention in recent years because of their selective metal ion binding properties in aqueous solution, the formation of basket- like be layer structures in the solid state, and the observation of H-bonding with aromatic rim. Calixarenes invested in the context of electrochemical selective, sensor, stationary phases, solid phase extraction phases and drug delivery in five decade ago [16-20]. One way to increase the aqueous solubility of drugs is to use complexing agents to form hast- guest complex [21]. *P*-sulphonatocalix[4]arene are react with types of drugs , metals and other gust organic and inorganic from upper rim that inclusion SO_3H group and lower rim that inclusion OH group is not reactivity. They have shown interesting properties of activity against bacteria, fungi, cancerous cells and enveloped viruses, but also against thrombosis or fibrosis diseases [22-25]. Anti-cancer drugs act in a dominant fashion:

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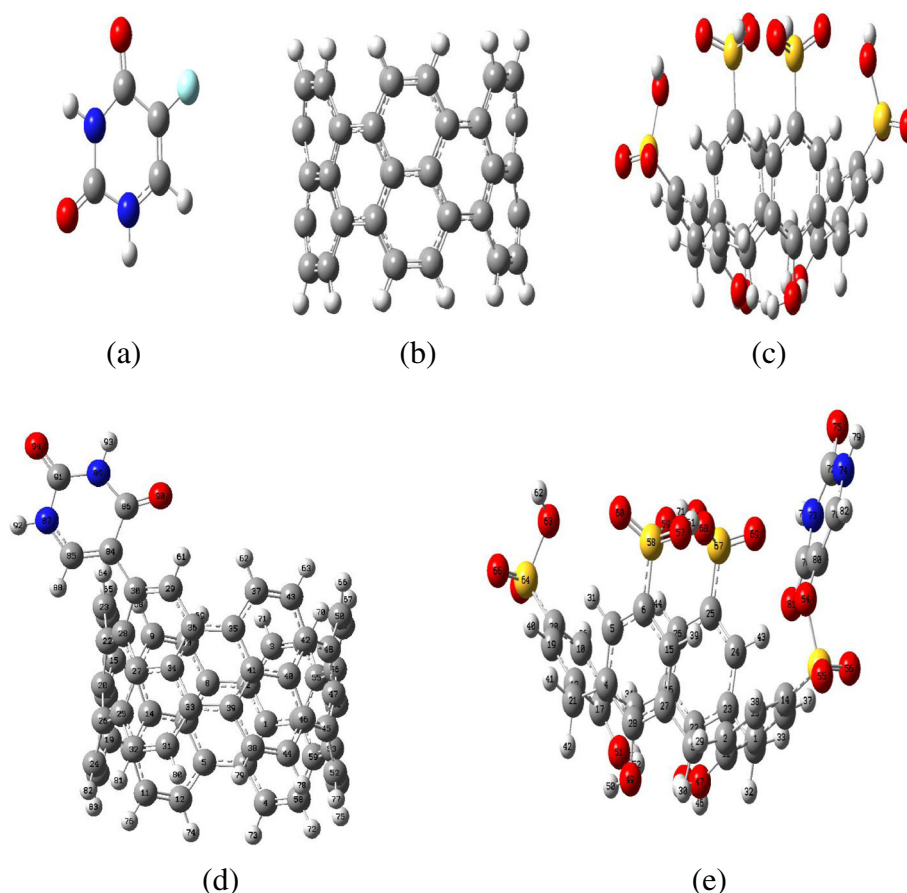


Figure 1 The structures of optimized molecular by B3LYP/6-31G (d) method at 298.15 K. (a) Fluorouracil, (b) Nanotube(6,6), (c) p-Sulphonatocalix[4]arene, (d) Composite1, (e) Composite 2.

when ectopically over expressed they specifically destroy tumor cells without harming normal cells. Anticancer genes have only recently emerged from studies on cancer cells [26,27]. Fluorouracil or 5-Fluoropyrimidin-2, 4 (1H, 3H)-dione is used as anti-cancer drug. Fluorouracil derived of pyrimidine that used as an anti-cancer drug for years ago. The structure of Fluorouracil is observed in Figure 1a. It is anti-metabolite drug and acts in several ways, but principally as synthesis inhibitor [28]. These days there are ways to deliver drug system in the body without side effects. In this paper, we reported types of drug delivery system like single-walled nanotube, p-Sulphonatocalix[4]arene.

Results and discussion

Density Functional Theory (DFT), hybrid QM/MM and Car-Parrinello molecular dynamics simulations can be used in theory investigation. The using computer for drug design and analyzed interaction between drug and receptors (for example: nanotube, fullerenes and calixarene) and give optimal fit [29-32]. The more detailed information on structure, charge distribution, and

energetic of the base pair are study by DFT method. At present, quantum chemical is extensive applicable to the interpretation of physical and chemical properties of drugs. The cellular receptors of many drugs used for medical treatment are react with proteins. By binding to the receptor, drugs either enhance or inhibit its activity. The biological mechanism of a disease then often suggests the types of molecules needed for nanodrugs [33-35]. Figure 1a, b, c, d, e shows the optimized composites fluorouracil, nanotube(6,6), p-Sulphonatocalix [4]arene, and nanotube(6,6)-fluorouracil (composite1), p-Sulphonatocalix[4]arenes-fluorouracil (composite2), respectively, by DFT method at B3LYP/6-31G(d) level.

In Table 1, it is obvious that composite 2 has formed higher hyperconjugation energy than the composite 1. Also, the results show by increasing *P* share in hybrid of atoms, the occupancy decreases. The *S* orbital share in hybrid of carbon in composite 2 is more than that in composite 1. If combined with the most stable hyperconjugation energy, the occupancy coefficient becomes smaller. Composite 2 is more stable than the composite 1. The hyperconjugation energy composite 2

Table 1 Parameters of NBO analysis of composite 1 and 2 by B3LYP/6-31G (d) method at 298.15 K

Agent	Donor	Occupancy	Acceptor	Occupancy	Hybrid	E ²	Σ E ²
Composite 1	BD(1)C30- C84	1.96631	BD*(1)C27-C28	0.02586	SP ^{1.98}	1.48	35.5
			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*(2)C84-C85	0.23733	BD*(1)C85-N87	0.01939	SP ^{2.51}	3.76	3
			BD*(2)C29-C30	0.2195	SP ^{99.99}	17.59	
Composite 2	BD(1)O54- C80	1.98809	BD*(1)N73-C76	0.07349	SP ^{1.77}	1.32	46.3
			BD*(1)N74-C78	0.01797	SP ^{1.69}	2.00	
			BD*(1)C78-C80	0.02461	SP ^{1.58}	1.19	
	LP(1)O54	1.95049	BD*(1)C78- C80	0.024241	SP ^{1.58}	2.71	
			BD*(2)C78- C80	0.024241	SP ^{99.99}	3.67	
	LP(2)O54	1.90929	BD*(1)C76-C80	0.07057	SP ^{1.72}	8.76	
			BD*(1)C78-C80	0.02461	SP ^{1.58}	5.14	
	BD*(2)C78-C80	0.38376	BD*(1)S53-O54	0.24241	SP ^{4.81}	21.57	9

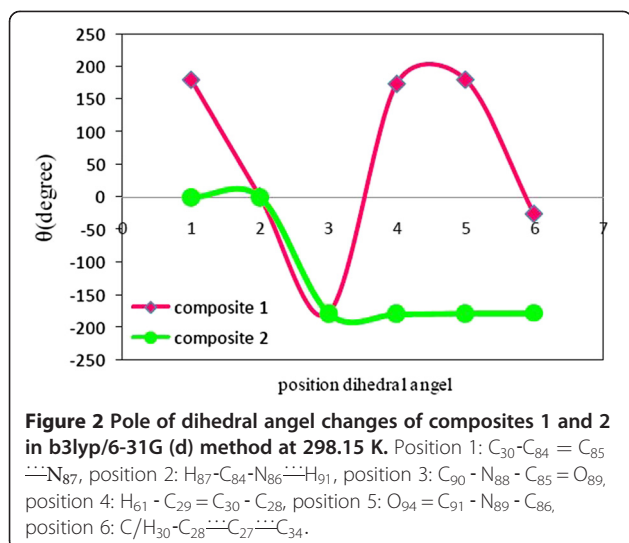
(46.39) is larger than that of composite1. If the S orbital hybrid of a compound is lower, the occupancy becomes larger. In composite 2, hybrid and occupancy are SP^{99.99} and 0.024241(acceptor) and 1.90929(donor), respectively. For example, in composite 2, hybrid and occupancy are SP^{4.81} and 0.24241(acceptor) and 0.38278 (donor), respectively. In Table 1, the Mulliken charges of electronegative O₈₄ donor atoms and C₃₀ acceptor atom are negative and positive, respectively. The energy gap of composite 2 is larger than that of composite1; therefore, composite 2 is more stable.

We measured the parameters, such as bond length (Å), natural bond orbital (NBO) and bond angle (degree), dihedral angle (degree), distances of analysed models, of the single-walled nanotube in this paper, and the end of the nanotube that was saturated by hydrogen atoms in them were examined by DFT at the level of B3LYP and 6-31G (d) standard basis set and shown in Table 2. The DFT-calculated geometric parameters for composite 1 and 2 are compared in Table 2. The bond lengths C₃₀-C₈₄/O₈₄ calculated for composite 1 and 2 by the DFT method are 1.47 and 1.37 Å, respectively, at the B3LYP/6-31G (d) level. The bond distance of composite 2 decreased toward that of composite 1 because the O atom in composite 2 is more electronegative than the C atom.

The bond lengths calculated for C₃₆...C₂₉ in composite 1 (in the nanotube ring) is 1.44 Å and that in composite 2(in the calixarene ring) is 1.39 Å. The bond lengths calculated for C₈₅...C₈₇ in composite 1, 1.37 Å and that in composite 2 is 1.36 Å. The C₈₈...N₉₂ bond length is lower than the C₃₆...C₂₉ bond length in composite1and 2. That is because nitrogen is more electronegative nitrogen than carbon.

Table 2 The parameters of bond and angles propertie in B3LYP/6-31G(d) method for composites at 298.15 K

Agent	Composite 1	Composite 2
Bond length(Å)		
C ₃₀ - C ₈₄ /O ₈₄	1.47	1.37
C ₃₀ = C ₂₀	1.37	1.39
C ₃₆ ...C ₂₉	1.43	1.39
C ₂₈ - C ₃₀	1.47	1.51
C ₈₅ ...C ₈₇	1.37	1.36
N ₈₇ - C ₉₁	1.39	1.38
C ₉₁ = O ₉₄	1.22	1.21
Bond angles (degree)		
C/S ₃₀ -C ₂₈ ...C ₂₇	116.02	118.56
C ₈₄ = C ₈₅ - H ₈₈	121.36	121.65
C ₈₅ ...N ₈₇ -H ₉₂	120.82	120.99
N ₈₇ - C ₉₁ = O ₉₄	123.42	124.32
C ₉₁ - N ₈₉ - H ₉₃	115.60	114.99
O ₉₀ = C ₈₆ - C ₈₄	126.90	123.98
Dihedral angles (degree)		
C ₃₀ -C ₈₄ = C ₈₅ ...N ₈₇ ¹	178.86	-0.063
H ₈₇ -C ₈₄ -N ₈₆ ...H ₉₁ ²	0.79	-0.37
C ₉₀ - N ₈₈ - C ₈₅ = O ₈₉ ³	-178.64	-178.95
H ₆₁ - C ₂₉ = C ₃₀ - C ₂₈ ⁴	172.74	-179.95
O ₉₄ = C ₉₁ - N ₈₉ - C ₈₆ ⁵	179.16	-178.95
C/H ₃₀ -C ₂₈ ...C ₂₇ ...C ₃₄ ⁶	-26.01	-178.72



The bond angle of $N_{87}-C_{91}=O_{94}$ are 123.41° and 124.32° for composites 1 and 2, respectively. The bond angles of $O_{90}=C_{86}-C_{84}$ are 126.9° and 123.9° for composite 1 and 2, respectively. The bond angles $C_{84}-C_{86}=O_{90}$ are higher than those of $N_{87}-C_{91}=O_{94}$ in composite 1 and 2. Thus, the interaction of between nonbonding and bonding pairs on the nitrogen atom of the angle is reduced in $N_{87}-C_{91}=O_{94}$.

The dihedral angels of $C_{30}-C_{84}=C_{85}-N_{87}$ and $C/H_{30}-C_{28}-C_{27}-C_{34}$ for composite 1 and 2 are 178.48° and $-0.06.99^\circ$ (position a), -26.01° and -178.72° (position f), respectively. The different dihedral angel in position a, b, c, d, e and f, are observed in Table 2 and Figure 2.

The electron that is given by the composites in a reaction should be placed on the highest occupied molecular orbital (HOMO), with those which are captured by the composites must be placed on the lowest unoccupied molecular orbital (LUMO) [36], so the atom on which the HOMO is mainly scattered should be able to separated electrons, while the atom by holding the LUMO should achieve electrons on this basis. The energy gap is usually associated with chemical stability against electronic excitation with a larger value like greater stability [37]. Table 3 shows the HOMO and LUMO energy gaps for two composites. By evaluating HOMO/LUMO energy gaps, it is obvious that if that the gap increase, the composite will become stable; therefore, composite 2 is more stable than composite. But, in composite 2 have S and O atoms that

including non bonding pair interaction with C atom fluorouracil, thus gap energies lower than composite 1.

The results of the present work were obtained by DFT optimization and formation energy (ΔE_f° in KJmol^{-1}) calculation at the B3LYP/6-31G (d) level. ΔE_f° is calculated using formula $\sum E_{\text{product}}^\circ - \sum E_{\text{reactant}}^\circ$. The value of ΔE_f° in composite 1 and 2 are -13.275 and $-38.892 \text{ KJmol}^{-1}$, respectively; therefore, composite 2 has lower formation energy than composite 1. The energy gap, total energy, $\sum E^2$, HOMO and LUMO of composites 1 and 2 were also calculated with B3LYP method and 6-31G (d) basis set. The energy (kJ mol^{-1}) and dipole moments (Debye) indicate the consistency between the two composite calculations in the DFT method. The total energy, the sum of is transitional energy, rotational energy and vibration energy, in B3LYP/6-31G (d) level for composite 1 and 2 was calculated. The obtained results are shown in Table 3.

Heat capacity is a measurable physical quantity that specifies the amount of heat required to change the temperature of an object by a given amount. Translation energy, rotation energy, and a combination of the two types of energy in vibration (kinetic and potential) of atoms represent the degrees of freedom of motion which classically contribute to the heat capacity of matter, but loosely bound electrons may also participate. For quantum mechanical reasons, at any given temperature, some of these degrees of freedom may be unavailable, or only partially available, to store thermal energy. Quantum theory can be used to quantitatively predict the specific heat capacity of simple systems.

Conclusions

In this paper, the results show that the complex of *p*-Sulphonatocalix[4]arene and fluorouracil is more stable than nanotube-fluorouracil. Composite 2 is a better conditioner of drugs than composite 1. NBO analysis shows larger energy gap in composite2. Composite2 has lower formation energy, and it is more stable than composite1.

Methods

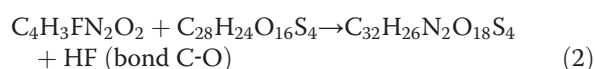
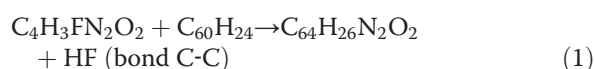
The investigation is carried out using a personal computer which has Intel[®]Pentium[®]dual CPU with 2-GB RAM. Nanotube-fluorouracil (composite 1) and *p*-Sulphonatocalix

Table 3 Parameters of stability composites are calculated by B3LYP/ 6-31G (d) method at 298.15 K

Agent	E_{total} (KJmol^{-1})	ΔE_f° (KJmol^{-1})	HOMO (KJmol^{-1})	LUMO (KJmol^{-1})	Gap (KJmol^{-1})	μ (Debye)	C_v
Composite 1	465.73	-13.275	-0.15877	-0.08918	-0.0696	0.527	191.03
Composite 2	396.25	-38.897	-0.2601	-0.07261	-0.18749	-1.137	186.77

[4]arene-fluorouracil (composite 2) included a calixarene derivation (with different atom number) which reacts with the anti-cancer drug. In this paper, drug delivery properties are investigated by NBO analysis and DFT method. DFT calculations have been performed using the nanotube modeler [38] Gaussview [39] and Gaussian 03 [40] by B3LYP method and 6-31G (*d*) standard basis set. NBO analysis [41] calculations have also been performed for all composites by B3LYP method and 6-31G(*d*) standard basis set. Then complexes of the calix[*n*]arenes derivative and single-walled nanotube with fluorouracil are optimized. The bond length (Å), bond angle (degree), dihedral angle (degree), hyperconjugation energy(E^2), and total energy (E_t in KJ mol⁻¹), moment dipole (μ in Debye), occupancy, and HOMO/LUMO are investigated in the composites by B3LYP/6-31G (*d*) method.

The nanotube (C₆₀H₂₄) and *p*-sulphonatocalix[4]arenes (C₂₈H₂₄O₁₆S₄) and fluorouracil (C₄H₃FN₂O₂) are reacted by Equations 1 and 2, thus is formed products nanotube- fluorouracil (C₆₄H₂₆N₂O₂), *p*-sulphonatocalix [4]arenes- fluorouracil (C₃₂H₂₆N₂O₁₈S₄) and HF in phases gas.



Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KZ and NSH both contributed to this research work. Both authors read and approved the final manuscript.

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