



Adsorption behavior of 5-fluorouracil on pristine, B-, Si-, and Al-doped C60 fullerenes: A first-principles study



Mehrnoosh Khodam Hazrati, Nasser L. Hadipour*

Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran

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ABSTRACT

Since C60 fullerene has been enormously studied as a drug delivery vehicle, we investigated the interaction between C60 and 5-fluorouracil drug using density functional theory calculations. The electronic and structural properties were explored in terms of binding energies, frontier molecular orbitals, DOS and NBO. To manipulate 5-fluorouracil adsorption properties on the C60, we substituted a carbon atom with boron, silicon and aluminum. In contrast to the pristine C60, the binding energy of 5-fluorouracil to the doped fullerenes is much more negative and the HOMO–LUMO gaps are significantly enlarged. Our results suggest that doping may improve C60 drug delivery properties.

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1. Introduction

In recent years, nanotechnology plays a significant role in industry and medicine, exclusively in cancer therapy [1–7]. Drug delivery as one of the most challenging issues in cancer therapy employs nanostructures to improve the drug solubility as well as *in vivo* life time, and eventually lead to design of safe and effective drug nano delivery systems [8–10].

5-fluorouracil (hereafter 5-FU) which belongs to the class of widely used chemotherapy drugs, is exploited to treat several types of cancer including breast, colon, skin, head and neck cancers [11–13]. Although 5-FU prevents the growth of cancer cells and finally results them to be wiped out [14], it causes unwanted side effects such as myelotoxicity, hand–foot syndrome, stomatitis, neurotoxicity, and cardiotoxicity [15]. Thus far, several efforts have been carried out to enhance the bioavailability of 5-FU and reduce its side effects [16–18], but an efficient vehicle to deliver 5-FU is still lacking.

Among miscellaneous nanostructures, fullerenes are known as suitable candidates for drug delivery regarding their appropriate properties such as hydrophobic characteristic, unique spherical structure, efficient drug loading and less side effects in biological media [19–24]. So far, a great deal of experimental and theoretical studies have been carried out on C60 [20–24] as a first fullerene type discovered by Kroto et al. [25]. The mentioned drug nanocar-

rier is potentially appropriate to promote the therapeutic efficiency of drug, since it can be engineered to moderate the release and the stability of drug in order to prolong the spread time of drug, protecting it from elimination by phagocytic cells or premature degradation [20,23,24].

Despite the notable advantages of experimental researches, the application of computational methods has been increasingly extended since the empirical methods are expensive and time consuming. In the present work, density functional theory (DFT) method has been used to examine the ability of C60 to adsorb 5-FU as a promising candidate for carrying this drug. Furthermore, the interactions of drug with doped fullerenes have been studied to improve the electron acceptor character of C60 fullerene [26–29].

2. Computational details

DFT method has been applied to study the interaction and specifically the formation possibility of a stable complex between 5-FU and pristine, B-, Si-, and Al-doped C60 fullerenes. To evaluate the most stable structure of 5-FU:C60 and its energy, B3LYP, the series of Minnesota 06 functionals and Martin Head-Gordon, ω B97x-D, a semi-empirical, range-separated hybrid functional [30], with 6-31G(d) basis set were used in GAMESS program suite [31]. GaussSum program [32] has been used to obtain the density of states (DOS). Also, the most stable configurations between 5-FU and doped-C60 fullerenes and their energies were performed using M06-2X functional with same level of basis set. Binding energies

* Corresponding author.

E-mail address: nasserhadipour@gmail.com (N.L. Hadipour).

(E_b) for the complexes in order to define the relative stability with respect to the nanostructures–drug interactions were calculated by equation (1):

$$E_b = E_{\text{Complex}} - (E_{\text{Cage}} + E_{5\text{-FU}}) \quad (1)$$

where E_{Complex} is the total electronic energies of fullerenes loaded with 5-FU drug after full geometry optimization. Vibrational frequencies were calculated at the same level of theory to confirm that all of the stationary points correspond to true minima on the potential energy surface. In order to gain additional details, we computed the electrophilicity index (ω). This index measures the stabilization in energy when the system acquires an additional electronic charge from the environment. In our work, we were interested in electrophilicity index as a descriptor for the charge transfer direction. Higher value of ω indicates higher electrophilic power of the structure [32]. Electrophilicity index given by equation (4):

$$\mu = (E_{\text{HOMO}} + E_{\text{LUMO}})/2 \quad (2)$$

$$\eta = [-E_{\text{HOMO}} - (-E_{\text{LUMO}})]/2 \quad (3)$$

$$\omega = \mu^2/2\eta \quad (4)$$

which μ is electronic chemical potential and η chemical hardness of the ground state [33].

In order to get a comprehensible perception of the charge distributions, we also performed natural bond orbitals (NBO) analysis. NBO calculation has been carried out using the same level of theory. The results were described in details in section 3.3 of this manuscript. Furthermore, solvation energies (E_{solv}) were obtained by geometrically optimizing our DFT structures in vacuum and in water.

3. Results and discussion

3.1. Analysis of binding energies and structural parameters

Several possible configurations were selected for 5-FU approaching the side-wall of fullerene. On a C60 fullerene a few highly symmetric adsorption sites can be considered [34]. Pentagons and hexagons of the cage and the top side directly above the carbon atom were chosen as active sites for the C60 nanocage. Computed electrostatic potentials on the molecular surfaces of a single 5-FU molecule are showed that the aromatic ring, O(1), O(2), and F atoms might be considered as probable active sites (Fig. 1). The active sites for BC59, SiC59 and AlC59 according to computed electrostatic potentials, were considered boron, silicon and aluminum atoms, respectively.

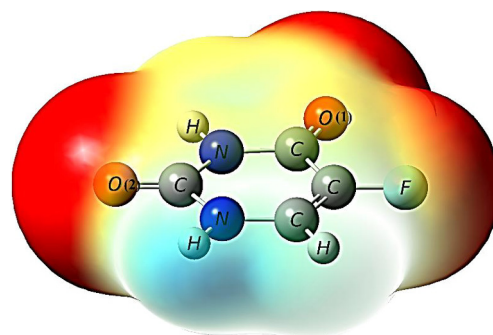


Fig. 1. Computed electrostatic potentials on the molecular surfaces of a single 5-fluorouracil molecule. The surfaces are defined by the 0.0004 electrons/b3 contour of the electronic density. Color ranges, in a.u.: blue, more positive than 0.010; green, between 0.010 and 0; yellow between 0 and -0.010; red, more negative than -0.010. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1 presents the E_b and HOMO–LUMO energy gap (E_g) of the most stable complex of pristine C60 and 5-FU using different functionals. The obtained basic set superposition error (BSSE) corrected E_b for the most stable configuration and equilibrium distance between C60 and 5-FU are about -4.12 kcal/mol and 3.44 Å using M06-2X functional. This weak interaction indicates the existence of physisorption between C60 and 5-FU. The ω B97x-D gives more negative E_b compared to the other functionals which may be originated from the explicit dispersion term. DOS for pristine C60 and the most stable complex of C60:5-FU is shown in Fig. 2. Our findings show that 5-FU prefers to be adsorbed weakly to the C60 via its aromatic ring on the hexagon in nanocage. The preferred orientation is referred to as *parallel displaced π - π stacking* which refers to attractive, noncovalent interactions between two aromatic rings [35].

The values of E_g show that the adsorption of 5-FU on C60 cage decreases the E_g very slightly (0.02 eV). E_g for the pristine C60 were obtained about 1.83 eV using M06L functional, which is in agreement with the experimental amount of 1.8 eV [36]. Since M06 and M06-2X functionals are a hybrid functional with 27% and 54% Hartree–Fock (HF) exchange energy [37], they overestimate the E_g in comparison with M06L functional with no HF exchange energy [38]. While ω B97x-D functional with 22% HF in short range and 100% HF in long range results in values between M06-HF and M06-2X functionals [39]. One can clearly observe the effect of %HF of functional using for calculation of E_g for C60 fullerene in Table 1.

As it is well known the B3LYP is a commonly used functional in the nanostructure studies [40–44], but it is not able to distinguish the weak interaction between two aromatic rings of C60 and 5-FU,

Table 1
The BSSE corrected binding energies (kcal mol⁻¹), HOMO–LUMO energy gap (eV), and the electrophilicity index of the most stable complex, and the perturbation energies (J mol⁻¹) of fullerene using different functionals.

Method	System	E_b	E_{HOMO}	E_{LUMO}	E_g	ΔE_g (%)	ω	ΔE_p
B3LYP	C60	–	–5.98	–3.23	2.76	–	7.71	1349
	C60+drug	0.86	–5.94	–3.19	2.74	0.72	7.57	–
M06-HF	C60	–	–8.97	–1.96	7.01	–	4.26	476
	C60+drug	–4.28	–8.98	–1.99	6.98	0.43	4.31	–
M06-2X	C60	–	–7.25	–2.70	4.55	–	5.43	346
	C60+drug	–4.12	–7.27	–2.75	4.52	0.66	5.55	–
M06	C60	–	–6.23	–3.12	3.11	–	7.02	638
	C60+drug	–2.57	–6.26	–3.17	3.09	0.64	7.19	–
M06-L	C60	–	–5.52	–3.69	1.83	–	11.58	274
	C60+drug	–2.99	–5.56	–3.75	1.81	1.09	11.97	–
ω B97x-D	C60	–	–7.83	–1.78	6.04	–	3.82	679
	C60+drug	–6.43	–7.83	–1.81	6.02	0.33	3.86	–

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