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ORIGINAL PAPER

Simulations on the possibility of formation of complexes between fluorouracil drug and cucurbit[n]urils: ab initio van der Waals DFT study

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Abstract The binding geometry of fluorouracil/cucurbit[n]urils (CB[n]s) complexes with n=5–8 is investigated using the *first-principles* van der Waals density functional (vdW-DF) method, involving full geometry optimization. Such host-guest complexes are typically calculated using conventional DFT method, which significantly underestimates non-local dispersion forces (or vdW contributions) and therefore affects interactions between respected entities. We address here the role of vdW forces for the fluorouracil and CB[n]s molecules which can form directional hydrogen bonds with each other. It was found that the inclusion of dispersion interactions significantly affects the host-guest binding properties and the hydrogen bonding between the molecules provides the main binding mechanism, while results in the same geometries for the considered complexes. The 0.84 eV binding energy, for the thermodynamically favorable state, reveals that the interaction of fluorouracil with CB[n]s is an exothermic interaction and typical for strong hydrogen bonding. Furthermore, we have investigated the binding nature of these host-guest systems in aqueous solution with ab initio MD simulations adopting vdW-DF method. These findings afford evidence for the applicability of the vdW-DF approach and provide a realistic benchmark for the investigation of the host-guest complexes.

Keywords ab initio MD simulations · Cucurbit[n]urils · Density functional theory · Drug delivery · vdW interactions

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Introduction

Cucurbit[n]urils (n is generally 4–12) have abbreviated CB[n]s, that have features of cavitands and are appropriate for host-guest complex [1]. The commercially accessible shapes of CB[n]s, with molecular formula $C_{6n}H_{6n}N_{4n}O_{2n}$, are obtained by condensation reaction of glycoluril repeating units and formaldehyde molecules during an acid-catalyzed reaction [2]. The initial member of the cucurbit's family (CB[6]) was discovered by Behrend et al. in 1905 [3], but its structure was not determined until 1981 [4]. After two decades, CB[n]s (n=5,7,8) were determined, and also CB[10]s was reported in 2002 [5]. Chemical or physical properties of these inclusion complexes of CB[n] family with a variety of cations and organic substrates through hydrophobic effect, charge-dipole, van der waals (vdW) and hydrogen bonding interaction with the carbonyl-inclosed portals, have focused on a strong deal of consideration in the recent years owning their utility as drug delivery, catalysts, switches, building blocks in supramolecular architectures such as catenanes, rotaxanes and nanomachine [1, 6–8]. There exist some interesting functions of CB[n]s as host-guest complexes, which are essential for drug delivery [8]. Recent studies show that incorporation of platinum anticancer complexes such as oxaliplatin and multinuclear amine complexes inside CB[7] and CB[8] decreases their high cytotoxicity in cancer treatments [9, 10]. Furthermore, several works have concerned the syntheses and antitumor activity of inclusion compounds of CB[n]s with platinum, gold and palladium complexes [11, 12].

5-fluorouracil (5-fu), a fluorinated pyrimidine belongs to the group of antineoplastic antimetabolite drugs that are widely used in the treatment of various cancers such as the

Table 1 Calculated geometrical parameters for the optimized geometries of CB[n]s (n=5–8) in (Å)

	Diameter of oxygen portal (α)	Intramolecular depth of cavity (β)
CB[5]	5.56	6.35
CB[6]	7.30	6.27
CB[7]	8.58	6.30
CB[8]	10.32	6.30

gastrointestinal tract, breast, pancreas, rectum, colorectal, head and neck [13, 14]. It is well known that thymidylate synthase is a key enzyme for DNA replication [13]. 5-fu has similar structure with thymine which acts principally as a thymidylate synthase inhibitor. 5-fluoro-2-deoxyuridine-5-phosphate (FdUMP) as a false predecessor for incorporation into DNA or RNA, inhibits the exchange of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP) [14, 15]. Injection of fluorouracil causes damage to the nervous system behavior even in low concentration [16]. It is well known that when host molecules transform inside the bioenvironment their properties might be altered through oxidation, hydrolysis or reduction phenomena, thus it is needed to control releasing ability, improve bioavailability and reduce their toxic effects [17].

In this work, we present a theoretical study on the possibility of formation of the complex between 5-fu and CB[n]s by means of *first-principles* vdW density functional (vdW-DF) calculations to address the vdW forces in the considered systems. The vdW-DF method is a *first-principles* approach that has already been demonstrated to reliably describes hydrogen-bonded interactions correctly [18], as accurate as the more complicated MP2 method thus it seems a fairly

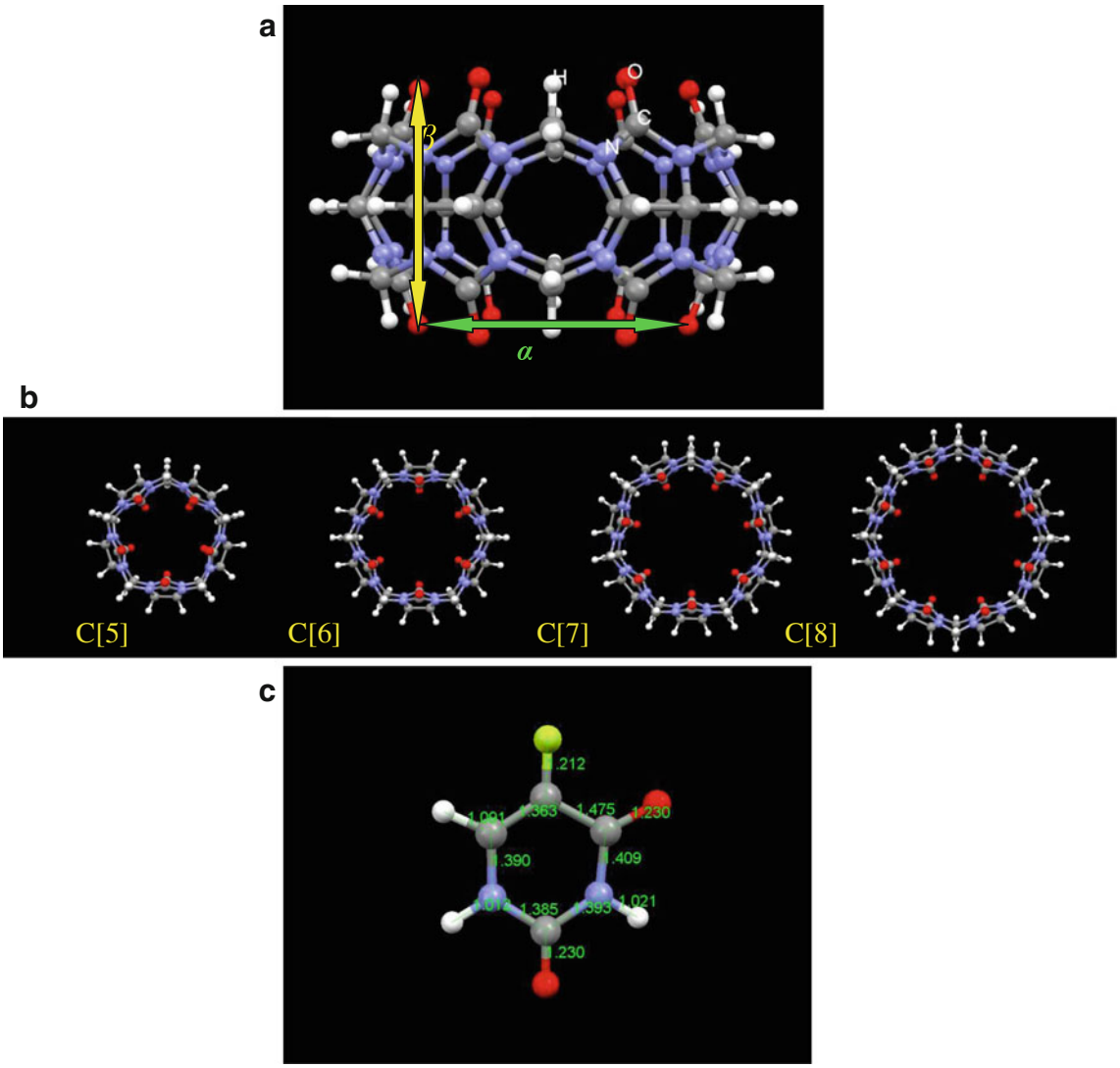

Fig. 1 DFT optimized structure for isolated CB[n]s, n=5–8, (**a**) diameter of oxygen portal (α) and intramolcular depth of cavity of cucurbit (β), (**b**) CB[5] - CB[8] and (**c**) 5-fu molecules

accurate computational approach for the present system. However, standard DFT method describes the dispersion forces less accurately [19], which is important in hydrogen-bonded complexes. As far as we know, no *first-principles* quantum mechanical calculations within vdW-DF approach were performed for these host-guest systems. Therefore, to understand the mechanism of fluorouracil/CB[n]s interaction accurately, it is essential to clarify the role of the vdW forces, which provide remarkable achievements on the field of biotechnological applications. We demonstrate that the vdW forces are solely responsible for the binding of the fluorouracil to CB[n]s and that the inclusion of dispersion forces via the vdW-DF method results in enhancements to the host-guest molecules binding.

Theoretical approach

Conventional density functional theory (DFT) has become an invaluable tool in studying hydrogen-bonded complexes such as DNA bases [20–25]. This failure of conventional DFT is attributed to the fact that it is inherently local and does not include accurate descriptions of long-range attractive contributions to vdW interactions, so-called London dispersion forces [26, 27]. All calculations were performed using the SIESTA simulation package which is based on localized basis set and the method of pseudopotentials [28]. In our calculations we use Norm-conserving pseudopotentials of Troullier and Martins [29] with the valence electron configurations of all atoms. We used soft confinement potentials [30] to generate triple-ζ double polarized (TZDP) basis set for all species with the confinement regions corresponding to the energy shift of 20 meV which is essential for preventing ruthless overestimation of binding [31, 32]. For all structures considered in the present work, all atoms were allowed to optimize unconstrained until the forces on each atom were less than 0.02 eV/Å. We have considered the correction for basis set superposition error (BSSE) via the counterpoise correction (CP) method [33] to further correct the obtained binding energy values in all cases. In order to estimate the binding energy of the interacting molecules we use the expression

$$E_b = E(\mathrm{CB[n]/5{-}fu}) - \left[E\left(\mathrm{CB[n]_{ghost}/5{-}fu}\right) + E\left(\mathrm{CB[n]/5{-}fu_{ghost}}\right)\right], \quad (1)$$

where the E (CB[n]/5-fu) is the total energy of the cucurbit with the fluorouracil. The 'ghost' molecule corresponds to additional basis wave functions centered at the position of the fluorouracil or the cucurbit, but without any atomic potential. In such a definition, $E_b<0$ corresponds to a stable optimized configuration.

We employed both the vdW-DF [34, 35] and the conventional DFT within Perdew-Burke-Ernzerhof (PBE) [36] GGA to compare the effects of dispersion interactions on the binding of fluorouracil molecule to CB[n]s. Note that the dispersion interaction is to some extent dependent on the choice of implemented exchange functionals [37, 38]. Previous calculation results revealed that in systems where the hydrogen bonding is dominate the PBE exchange functional is favorable while for the systems with the vdW interactions, the choice of the revPBE [39] exchange functional provided better accuracy. The interaction between the fluorouracil and CB[n]s involves the hydrogen bonding forces; therefore, we performed all the vdW-DF calculations with the PBE approximation. It was found that the vdW forces lead to a significant difference of about 0.2 eV in binding energy and also affects our conclusions.

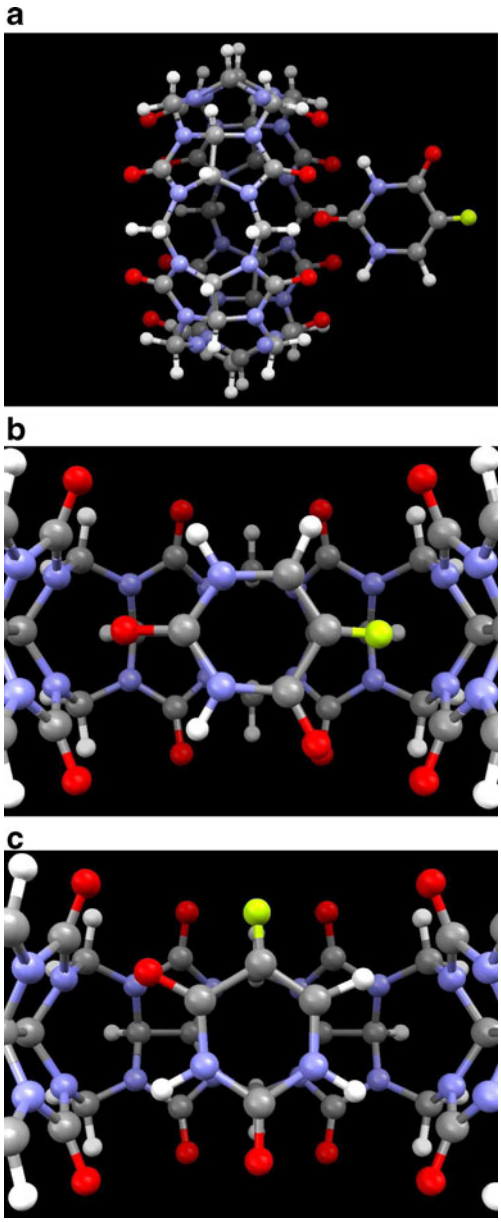

Fig. 2 Three different states of the fluorouracil molecule interacting with the CB[n]s (**a**) the exterior state and the interior states, (**b**) the parallel orientation and (**c**) the perpendicular orientation

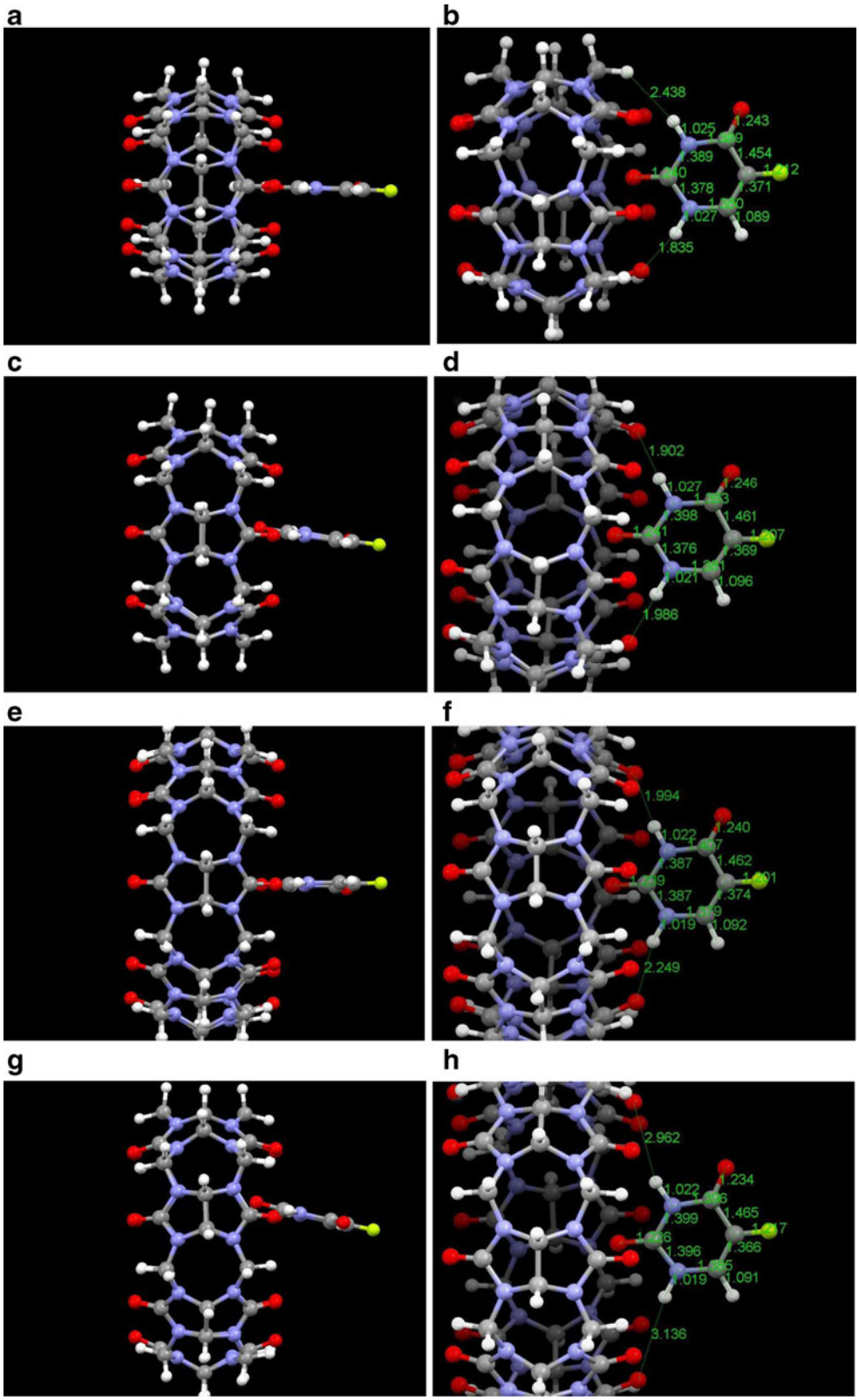

Fig. 3 The optimized geometric structures of the considered configuration for the fluorouracil/CB[n]s complexes in exterior state by using GGA method. **a**, (**b**) 5-fu/CB[5] (**c**), (**d**) 5-fu/CB[6] (**e**), (**f**) 5-fu/CB[7] (**g**), (**h**) 5-fu/CB[8] complexes

Results and discussion

To evaluate the geometry and stability of the CB[n]/5-fu complex, we first carried out full structural optimization of 5-fu molecule and CB[n]s with n=5–8 by the GGA approach. The resulting structure demonstrates that the average intramolecular depth of cavity is about 6.30 Å for the respected CB[n]s, but the calculated diameter of oxygen portals for

Table 2 Calculated binding energies and diameter of oxygen portals of cucurbits and calculated Mulliken charges for 5-fu/CB[n] systems (n=5–8) by using GGA method

Binding energy	Exterior state	Interior state	
		Par	Perp
CB[5]-fluorouracil	−0.50	1.77	2.61
CB[6]-fluorouracil	−0.67	−0.03	−0.3
CB[7]-fluorouracil	−0.54	−0.06	−0.02
CB[8]-fluorouracil	−0.49	−0.06	−0.02
Diameter of oxygen portals of CBs for complexes			
CB[5]-fluorouracil	7.18	8.19/7.84	7.85/7.83
CB[6]-fluorouracil	7.55	8.18/7.35	8.21/8.10
CB[7]-fluorouracil	8.13	8.74/8.44	8.42/8.46
CB[8]-fluorouracil	9.90	10.38/10.38	9.84/10.20
Calculated Mulliken charges for complexes			
CB[5]-fluorouracil	0.13	0.52	0.66
CB[6]-fluorouracil	0.13	0.15	0.37
CB[7]-fluorouracil	0.09	0.05	0.33
CB[8]-fiuorouracil	0.02	0.00	0.30

CB[5], CB[6], CB[7] and CB[8] are 5.56, 7.30, 8.58 and 10.32 Å, respectively (Table 1) which are consistent with insightful chemical expectations and also other theoretical studies [40]. The schematic representation of the optimized structures for CB[n]s and 5-fu molecules are given in Fig. 1.

We now investigate the interaction between the 5-fu molecule and CB[n]s. In order to explore the approximate stable binding configuration and estimate the corresponding binding energy for the CB[n]/5-fu complex, two configurations, namely; exterior and interior states for the interacting host-guest molecules were considered (Fig. 2). In the case of the exterior state, the oxygen atom between amine nitrogen groups of the guest molecule was positioned at just the center of the oxygen portals and the rest were positioned mainly outside of the cucurbit. We first carried out the full structural optimization of the selected complexes and then calculated the binding energy for the respected systems. Initially we discuss the results obtained from the GGA calculations. After full structural optimization of the considered systems, we found that for the exterior state, the 5-fu molecule prefers to bound to the portal oxygen atoms via its H atoms of the amino nitrogen groups. Furthermore, the oxygen atom between two amino nitrogen groups of the 5-fu moves toward the H atoms of the cucurbit in the CB[7] while in the other complexes the respected oxygen atom remains unchanged, as shown in Fig. 3. This behaviour can be attributed to this fact that in the case of the 5-fu/CB[7] complex, the oxygen atom of the 5-fu interacts with the hydrogen atom of the CB[7] in one direction and the oxygen atom in another one. However, in the case of 5-fu/CB[6], [8] complexes, the oxygen atom of the 5-fu interacts with two of the hydrogen atoms of the CB[6] and two of the oxygen atoms of the CB[8] in opposite direction. As it is clear in the case of 5-fu/CB[5] complex, the

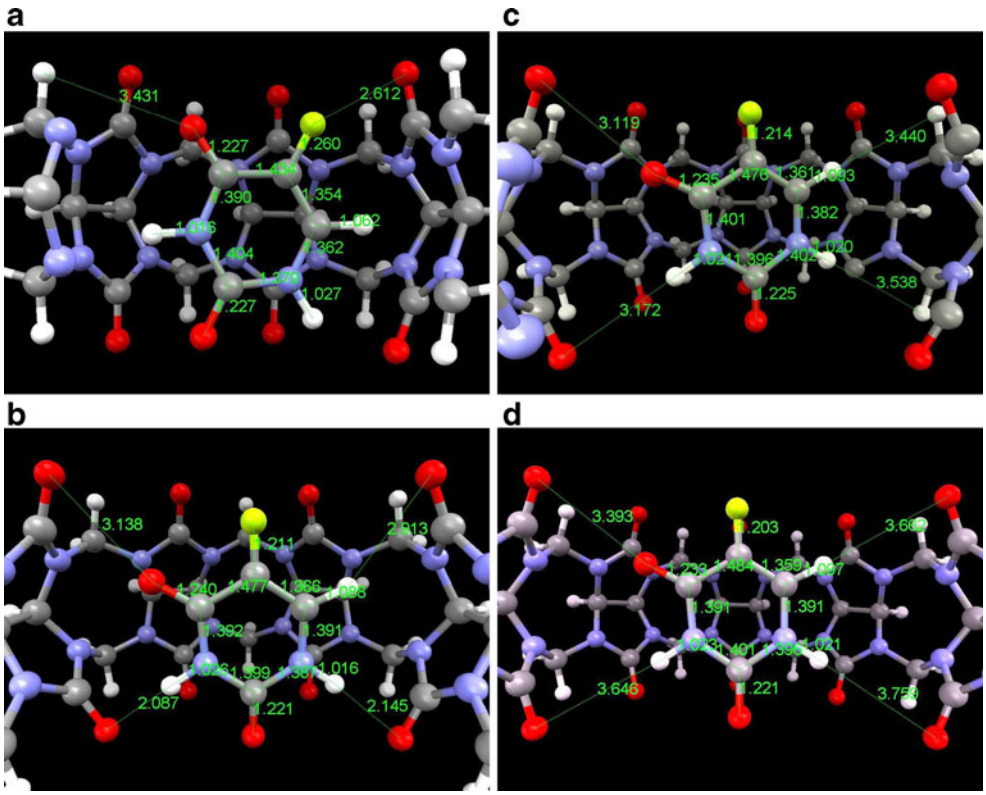

Fig. 4 The optimized geometric structures of the considered configuration for the fluorouracil/CB[8] complexes in the interior-parallel state by using GGA method. **a** 5-fu/CB[5] (**b**) 5-fu/CB[6] (**c**) 5-fu/CB[7] (**d**) 5-fu/CB[8] complexes

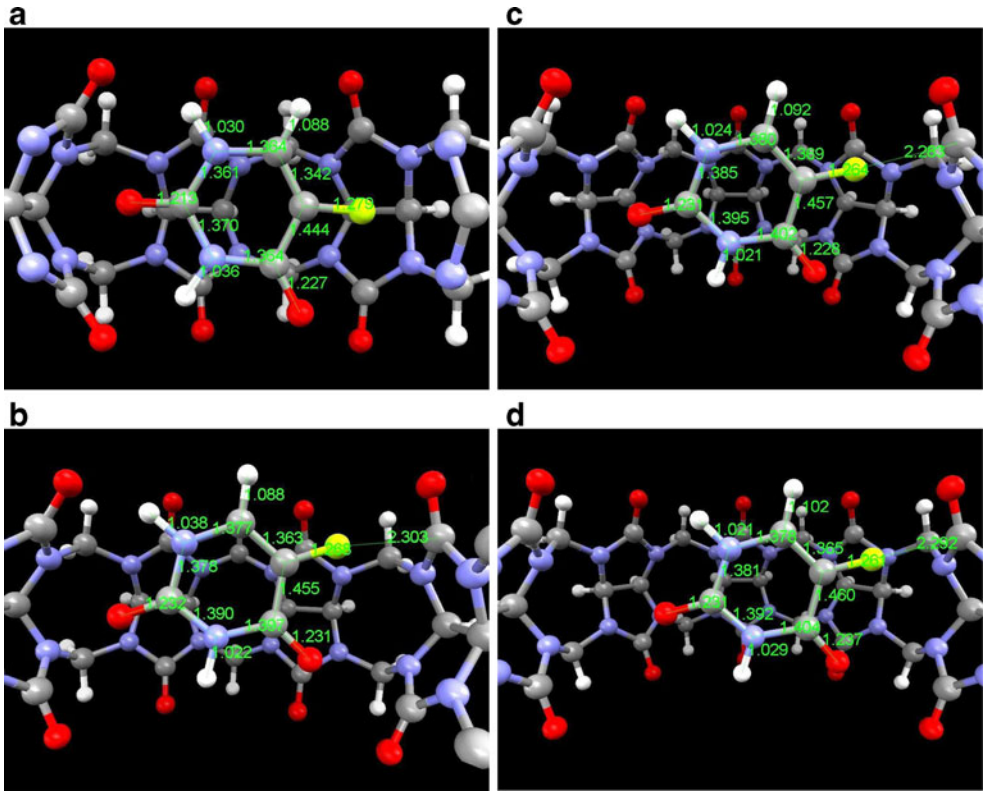

Fig. 5 The optimized geometric structures of the considered configuration for the fluorouracil/CB[n] complexes in the interior-perpendicular state by using GGA method. **a** 5-fu/CB[5] (**b**) 5-fu/CB[6] (**c**) 5-fu/CB[7] (**d**) 5-fu/CB[8] complexes

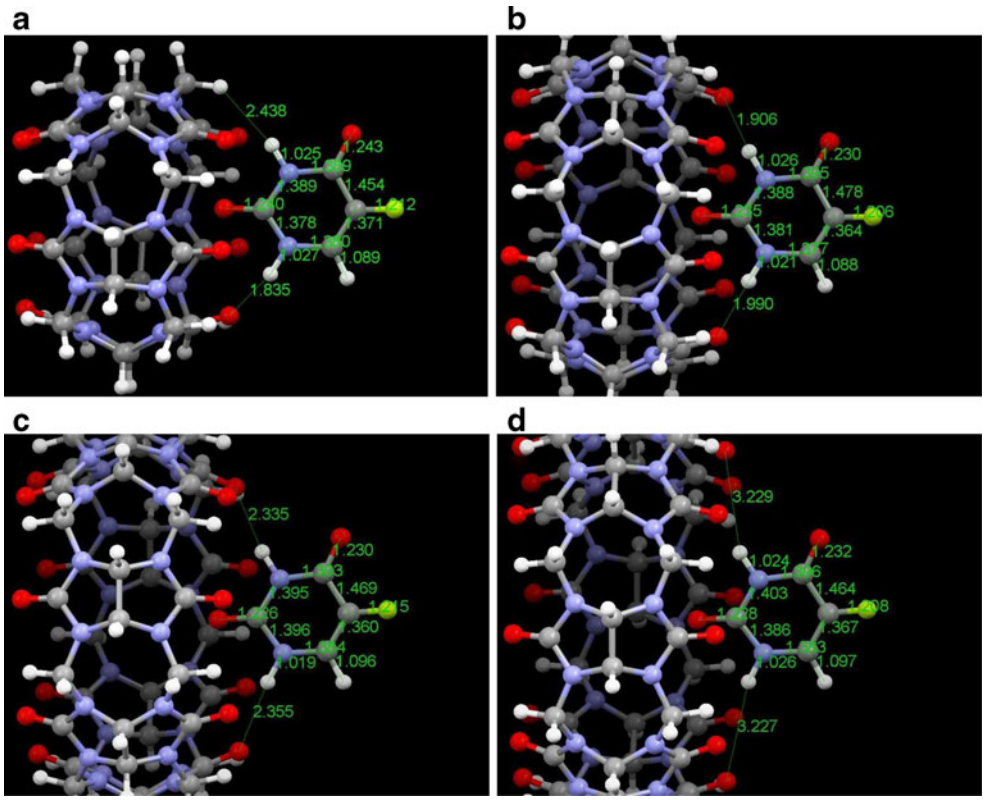

Fig. 6 The optimized geometric structures of the considered configuration for the fluorouracil/CB[n]s complexes in exterior state by the GGA-vdW method. **a** 5-fu/CB[5], (**b**) 5-fu/CB[6], (**c**) 5-fu/CB[7] and (**d**) 5-fu/CB[8] complexes

Table 3 Calculated binding energies and diameter of oxygen portals of cucurbits and corresponding Mulliken charges for 5-fu/CB[n] systems (n=5–8) by using the GGA-vdW method

Binding energy	Exterior state	Interior state	
		Par	Perp
CB[5]-fluorouracil	−0.50	1.92	2.48
CB[6]-fluorouracil	−0.84	−0.22	0.32
CB[7]-fluorouracil	−0.64	−0.06	−0.18
CB[8]-fluorouracil	−0.48	−0.10	−0.26
Diameter of oxygen portals of CBs for complexes			
CB[5]-fluorouracil	5.85	6.43/6.48	5.95/6.43
CB[6]-fluorouracil	7.55	7.77/7.56	7.65/7.16
CB[7]-fluorouracil	8.36	8.65/8.46	8.41/8.52
CB[8]-fluorouracil	10.41	10.37/10.37	10.37/10.40
Calculated Mulliken charges for complexes			
CB[5]-fluorouracil	0.13	0.50	0.67
CB[6]-fluorouracil	0.13	0.07	0.50
CB[7]-fluorouracil	0.06	0.06	0.40
CB[8]-fiuorouracil	0.01	0.00	0.02

oxygen atom of the 5-fu located near the H atom of the CB[5], similar to the 5-fu/CB[7] system, but after the optimization the 5-fu molecule remains unchanged at its initial location. This can be attributed to the oxygen portal area which is larger in the CB[7] than that in the CB[5] and therefore allows the 5-fu molecule to move freely.

Our *first-principles* results within the GGA approach show that 5-fu prefers to be bound to the CB[6] molecule. The calculated binding energy and the average equilibrium distance between the H atoms of the amino nitrogen groups in the 5-fu and the O atoms of the cucurbit are about −0.670 eV and 1.944 Å, respectively. The obtained results show also that, in the case of 5-fu/CB[6] complex, the bond lengths of $(N-H)_{down}/(N-H)_{up}$ in the 5-fu and $(C-O)_{down}/(C-O)_{up}$, respectively, in the CB[6] changes to 1.027/1.021 Å and 1.221/1.234 Å, which differs slightly from the isolated molecule (1.021/1.012 and 1.214/1.214 Å). From the present results at the GGA level of theory for the exterior state, it can be seen that the 5-fu adsorption capability of the CB[6] is much better than that of other counterparts. The calculated parameters of binding energy and bond length for the considered systems are given in Table 2.

Similar structural optimization and total energy calculations were performed for the interior configurations where two situations called (A) and (B) were considered for the 5-fu molecule: (A) denotes the parallel approach and (B) the perpendicular approach. For the parallel approach, the molecule is placed inside the center of cavity so that the F atom of the 5-fu is located in parallel orientation with respect to the molecular axis while for the perpendicular one, the F atom is located in perpendicular orientation to the molecular axis. After full structural optimization of the considered systems, we found that the 5-fu molecule always locates inside the cavities, regardless of the initial location. Furthermore, the

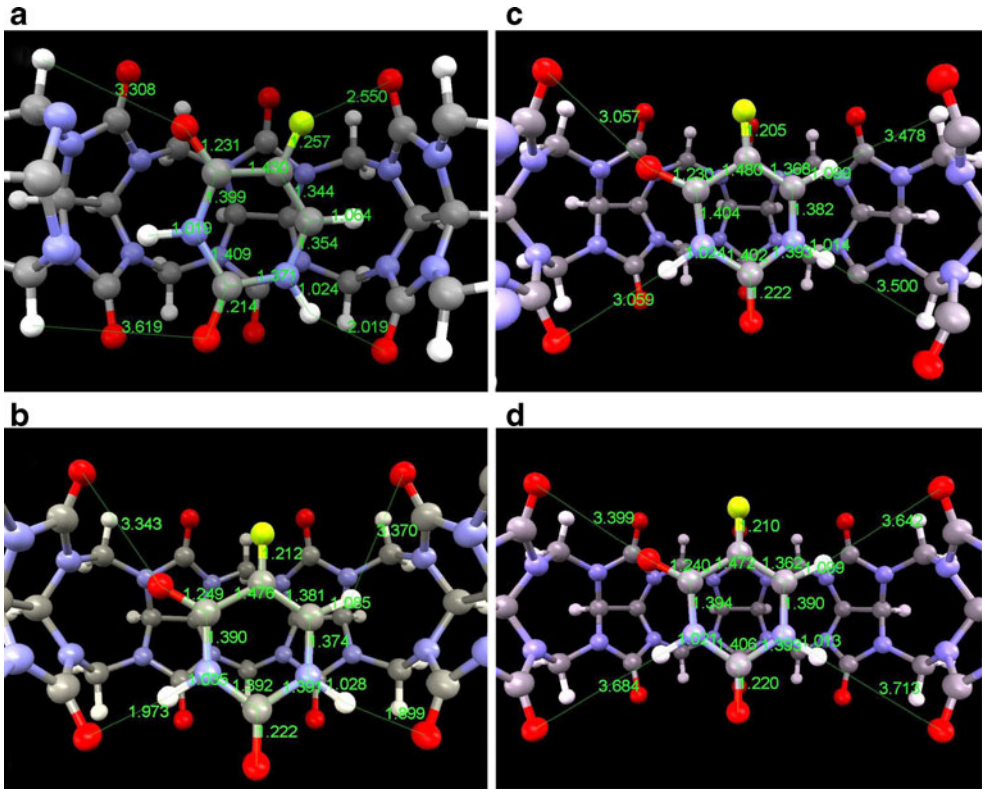

Fig. 7 The optimized geometric structures of the considered configuration for the fluorouracil/cucurbit[n]-complexes in interior-parallel state by using GGA-vdW method. **a** 5-fu/CB[5] (**b**) 5-fu/CB[6] (**c**) 5-fu/CB[7] (**d**) 5-fu/CB[8] complexes

considered molecule rotates so that the F atom positioned close to the C atom of the cucurbit in the case of CB[5] for the parallel state and the CB[6], [7], [8] for the perpendicular states. In Fig. 4 we present the schematic demonstration of the optimized geometric structure and bond length for the binding states of the 5-fu molecule interacting with the selected cucurbits. It was found that the binding energy between the 5-fu and the small-diameter CB[5] (high curvature) is positive, and the optimized geometric structure shows that the symmetrical structure of the CB[5] changed to elliptic configuration. This is due to the repulsion interaction between the 5-fu molecule and the interior side wall of the cucurbit. The obtained results indicate that the 5-fu/CB[5] complex is an energetically unfavorable system with the positive binding energy. The calculated binding energies for the interior states of the other counterparts are reported in Table 2. It is evident that encapsulated 5-fu possess different interaction strengths and binding energies. Our findings reveal that in the case of all cucurbits, especially CB[5], the oxygen portals ribbon of the cucurbit deviate from the circular. The diameter of oxygen portals in cucurbits are also changed during its interaction with the 5-fu molecule where one of them is enlarged and another is depressed in one direction (see Table 2) which indicates that cucurbits are flexible hosts. Furthermore, the 5-fu molecule readily forms more stable binding with the exterior state of the cucurbits in comparison with the interior state.

To further investigate the binding nature between the interacting host-guest molecules, we performed Mulliken charge analyses to estimate the amount of electron transfers between two entities. Charge analysis shows that for the exterior state, the charge transferred from the cucurbit to the 5-fu molecule while for the interior state, the charge transferred from the 5-fu to the cucurbit. Table 2 lists the calculated Mulliken partial atomic charges for the considered 5-fu/CB[n]s complexes (Fig. 5).

We now consider the role of vdW forces in the current complexes which have been known to be essential for electronic structure calculations on biomolecules, intermolecular complexes, molecular crystals, and polymers [41]. The long-range nonbonding vdW interactions which influence the stability of such systems have been considered via the vdW-DF method [42, 43]. To this purpose, we carried out a comparative study of the geometries and stable binding configurations for the 5-fu/CB[n] complexes and their individual parts. We compared the results from the vdW-GGA with those obtained using the GGA approach. It should be mentioned that the pure geometries of the 5-fu and the cucurbit molecules were individually optimized by using the vdW-GGA approach. Then, the structural geometries and the binding properties of the 5-fu/CB[n]s complexes are studied by performing the vdW-GGA calculations. We first started by carrying out the optimization procedure for the exterior states. Figure 6 shows the schematic representation of the optimized geometric structures for the

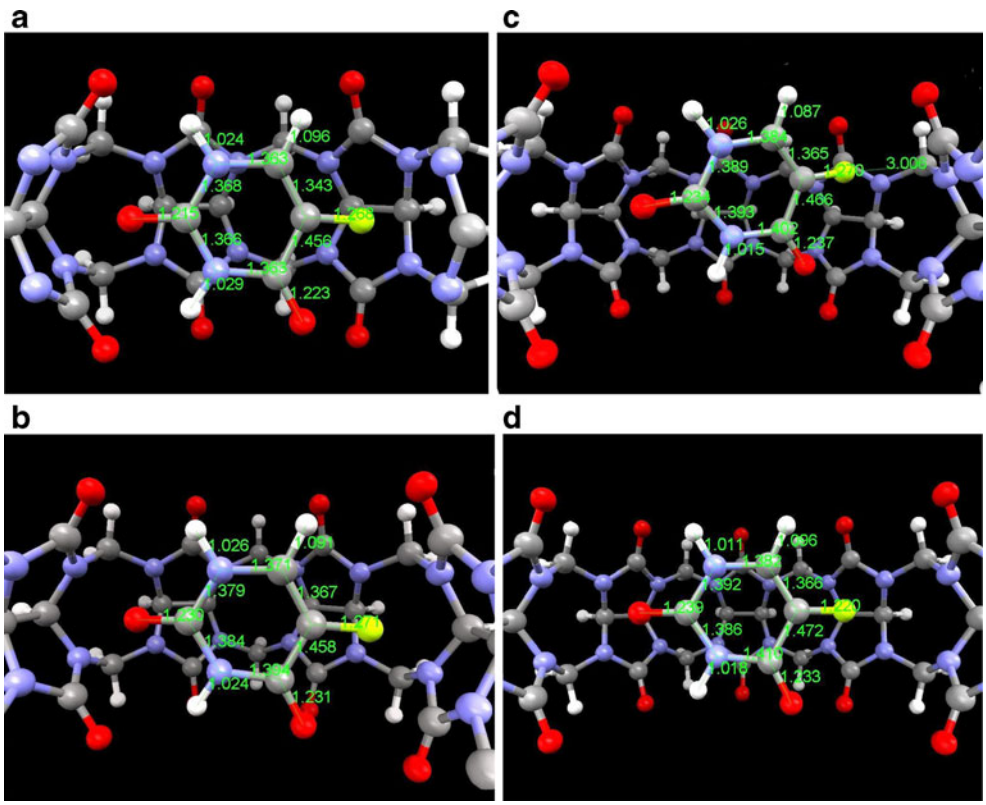

Fig. 8 The optimized geometric structures of the considered configuration for the fluorouracil –cucurbit[n]-complexes in interior-perpendicular state by using GGA-vdW method. **a** 5-fu-CB[5] (**b**) 5-fu-CB[6] (**c**) 5-fu-CB[7] (**d**) 5-fu-CB[8] complexes

exterior configurations. In all the configurations, the 5-fu molecule always locates close to the area of oxygen portals. The calculated binding results indicate that the 5-fu/CB[6] system is the most stable complex. The binding energy for this energetically favorable complex is about −0.84 eV while, the calculated binding energy for the most stable complex obtained by the GGA approach was determined to be −0.67 eV. This difference can be attributed to the consideration of non-local dispersion interactions, which play a key role in the stability of such systems. The calculated binding energies and the structural geometry parameters for all the considered complexes are summarized in Table 3. In the case of 5-fu/CB[6] complex, the average equilibrium distance between the H atoms of amino nitrogen groups from the 5-fu molecule and the O atoms of cucurbits is determined to be about 1.948 Å. In addition, the bond length of $(N-H)_{up}$ in the 5-fu changes from 1.024 Å to 1.026 Å while, the other one, $(N-H)_{down}$, changes from 1.017 Å to 1.021 Å and also the bond lengths of $(C\text{-}O)_{down}/(C\text{-}O)_{up}$ of cucurbit is 1.221/1.230 Å, which is the same as for an isolated molecule. We also evaluated the higher reactivity of the exterior states that performed by the vdW-GGA approach in comparison with the GGA approach. It can be seen from the obtained results that the calculated binding energy for the 5-fu/CB[6] complex by using the vdW-GGA method is higher than that of the GGA one.

To further investigate the interaction between the 5-fu and CB[n]s, the encapsulation of the fluorouracil inside the selected cucurbits was also evaluated. We first incorporated the 5-fu molecule, as mentioned above, inside the cucurbits and then performed full structural optimization within the vdW-GGA method. Figure 7 shows the optimized geometric structure of the considered systems. It was found for the parallel configurations that, the structural geometries for the respected complexes are basically the same as for the GGA approach. Furthermore, the calculated results show that the bond lengths of the fluorouracil changes slightly during its binding to the cucurbits. The calculated binding energies for the 5-fu/CB[5], [6], [7], [8] complexes are about 1.92, −0.22, −0.06 and −0.10 eV, respectively. From the perpendicular configurations, it can be seen that the F atom of the fluorouracil in the 5-fu/CB[7] complex, located adjacent to the C atom of the cucurbit compared to the obtained results by the GGA approach. In comparison with the obtained results from the GGA approach (−0.30 eV) for the 5-fu/CB[6] complex here we observed the binding energy of about +0.32 eV. We can conclude that the vdW-DF approach can fairly represent the repulsion interaction in such systems. For the encapsulated molecule inside the CB[5] both the considered states have positive binding energies which are thermodynamically unfavorable. The calculated binding energies and structural geometry parameters are provided in Fig. 7 and Table 3. We have also performed Mulliken charge analysis for these systems. The obtained values from the charge analysis are similar to those values obtained by the

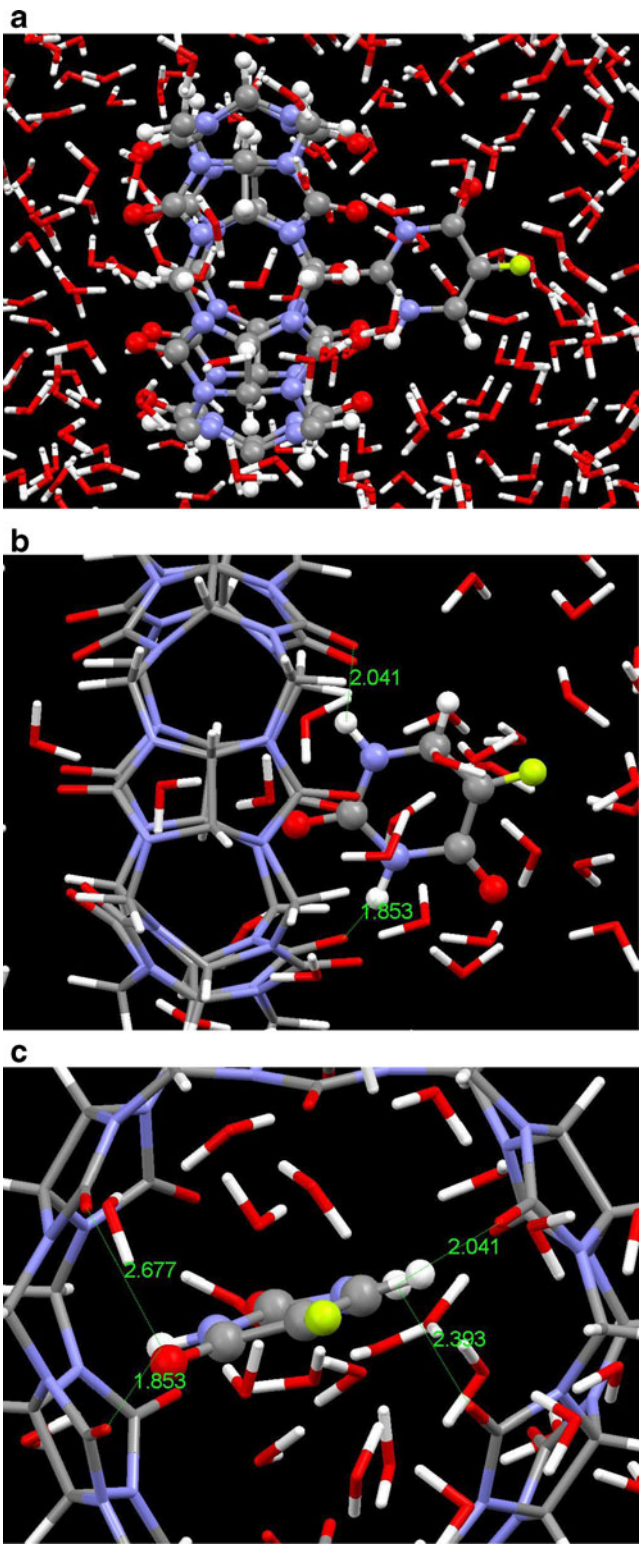

Fig. 9 Schematic representation of (**a**) atomic structures of the most stable complex of 5-fu/CB[6] complex within 120 water molecules. Snapshots of ab initio MD simulation of the 5-fu/CB[6]+120 H_2O system at 310 K for 2.5 ps (**b**) side view and (**c**) front view

GGA approach. It was found that in the case of the exterior state charge transferred from the cucurbits to the 5-fu molecule while, for the interior state, charge transferred from the 5-fu to the cucurbits. The calculated Mulliken partial atomic charges are reported in Table 3.

Our *first-principles* results indicate that the 5-fu molecule incorporated inside the different CB[n]s is weakly bound to the CB[n] in comparison with the exterior state. Furthermore, in the case of interior configurations, the obtained results for the most favorable state by GGA approach differ from those obtained using the vdW-GGA approach. This difference might be related to the non-bonding dispersion interactions in the current DFT calculations, which play an important role in the stability of these systems (Fig. 8).

We have further investigated the binding nature of these host-guest complexes as well as the corresponding geometries in the aqueous solution at environment condition. Ab initio molecular dynamics (MD) simulations were carried out under constant volume and constant temperature conditions (NVT) adopting vdW-GGA within the PBE approach. The temperature effects on the atomic and electronic structures were calculated at the temperature of 310 K. The simulation time t duration of molecular dynamics simulation is 3 ps, the time step used being 1 fs. MD simulations were based on Verlet-type algorithm [44] for integration with Newton's equations of motion and the temperature was controlled by sampling of the canonical ensembles using algorithm of Nose [45]. The simulations were performed in a rectangular box with periodic boundary conditions and filled with the most stable complex of 5-fu/CB[6] and 120 water molecules, as represented in Fig. 9. The volume of the considered simulation box is assigned to be about $(18\times15\times24)$ Å^3. Figure 9 represents the structural parameters calculated by ab inito MD calculation at 310 K. Our *first-principles* results show that the aqueous solution affects the geometries of the 5-fu/CB[6] complex little. The only observed difference is in that the fluorouracil bound slightly closer to the cucurbit due to solvent effect. We also found that the H atoms of -NH in the fluorouracil positioned between the oxygen portal atoms of the cucurbit.

Conclusions

We have investigated the binding processes of fluorouracil molecule to the CB[n]s using two density functional approaches: PBE, which lacks the non-local dispersion interaction, and the vdW-DF, which accounts for this interaction as implemented in the SIESTA code. The results of this study have demonstrated that CB[n]s prefers to be bound to the fluorouracil approaching their portal oxygen atoms in comparison with the encapsulated molecule. It was found that the dispersion interaction dramatically affects, as compared to the PBE based calculations, the binding of the host-guest complexes and is crucial to describe such systems. The only major difference was observed in the binding energy due to vdW interaction, the binding energies increase significantly with the vdW interaction, while geometries of these complexes stay the same as obtained within the PBE functional. We also found that, the orientation of the host molecule with respect to the guest one slightly changes for the considered configurations. Furthermore, the binding nature of these host-guest complexes in the aqueous solution at environment condition have been studied. We performed ab initio MD simulations for the most stable complex under constant volume and constant temperature conditions (NVT) adopting vdW-GGA method. Our *first-principles* finding revealed that the 5-fu/CB[6] complex is quite stable at ambient condition and the aqueous solution affects the geometries of the complex little.

The present results provide some clear reference data to address the role of vdW interactions in such host-guest complexes while the conventional DFT methods do not take into account these interactions and thus the corresponding results would forever remain doubtful unless these interactions are accounted for.

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