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Investigating Chitosan–Curcumin Nanorings for Containing Fluorouracil

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Abstract: Density functional theory (DFT) calculations have been performed to investigate formation possibilities and properties of chitosan–curcumin (Chit–Cur) nanorings for containing fluorouracil (FU) anticancer drug. The B3LYP exchange–correlation functional and the 6–31G* standard basis set have employed for performing DFT calculations. In this case, first, all individual structures have been optimized, then; nanorings have been constructed by the covalent attachments of Chit–Cur counterparts. To this aim, three complexes including FU–Chit2–Cur2, FU–Chit4–Cur2 and FU–Chit6–Cur2 have been constructed by physically locating FU inside the nanorings. The atomic and molecular scales results in isolated gas phase and water solvated systems indicated that the FU–Chit2–Cur2 complex could be expected as a good container for the FU anticancer drug.

Keywords: *Chitosan, Curcumin, Fluorouracil, Nanoring, Density functional theory.*

1. Introduction

Fluorouracil, or 5-fluorouracil, (FU) has been used for several years as an efficient anticancer agent to treat several types of cancers [1]. However, the unwanted side effects made the FU as an unsuitable medicine for the patients [2]. Therefore, several efforts have been dedicated to optimize the usage of FU for the patients with minimum side effects [3]. In this case, designing new carriers to contain and to carry FU until reaching the specific target could be a useful method of modifications of FU usage [4]. Chitosan (Chit) and curcumin (Cur) have been considered as good carriers or complementary materials to carry drugs inside the living systems for some years [5–10]. However, each of Chit and Cur compounds itself may have some deficiencies for the required role of drug carrier [11, 12]. Combining different portions of Chit and Cur together may help to improve the efficiency of using of this material as a better carrier comparing with each individual structure [13]. Solubility is an important task to be considered for carriers, in which it is also important for both of Chit and Cur individual counterparts [14, 15]. In addition to physico–chemical properties, size of carrier is also very much important for the purpose of investigating new drug carriers [16]. After the discovery of nano science and technology, considerable attempts have been done to characterize nano–sized materials for specific

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purposes in living systems [17]. Targeted drug delivery systems based on nanostructures have been expected to be very much useful for the purposes of carrying drugs up to the specified targets [18]. In this case, investigations of various types of nanostructures have become one of first aims or researcher of different fields [19]. It is important to note that the nanostructures are such complicated structures to be investigated in the laboratories; therefore, computational chemistry methodologies could help researchers to significantly investigate the formation possibilities and properties of nano based materials [20–22].

Within this work, possibilities of formation for a type of Chit–Cur nanoring to contain FU (Figs. 1 and 2) have been investigated based on density functional theory (DFT) calculations employing the B3LYP exchange–correlation functional and the 6–31G* standard basis set. Optimizations of structural models have been investigated by different numbers of repeating Chit and Cur counterparts. Optimized geometries in addition to atomic/molecular scales properties have been evaluated to achieve the purpose of this work. It is important to note that chemical bonds are used to construct Chit–Cur structures, but FU is kept through physical interactions in the center of constructed nanoring.

2. Computational Method

Within this work, DFT based calculations have been performed employing the standard B3LYP/6–31G* method to investigate formation possibilities and properties for types of Chit–Cur nanorings to contain FU anticancer drug. To achieve this purpose, individual molecular models of Chit, Cur and Fu (Fig. 1) have been firstly optimized to achieve the minimum–energy starting structures to construct hybrid systems. Subsequently, nanorings have been constructed and optimized based on combinations of already optimized Chit and Cur counterparts including Chit2–Cur2, Chit4–Cur2, and Chit6–Cur2 systems (Fig. 2). At the last step, the FU counterpart has been located in the center of nanorings and the complex structures have been optimized again. As a result, there are three individual starting structures: Chit, Cur and FU, three nanorings: Chit2–Cur2, Chit4–Cur2 and Chit6–Cur2, and three complex structures: FU–Chit2–Cur2, FU–Chit4–Cur2, and FU–Chit6–Cur2 (Figs. 1 and 2). The calculations have been performed in two systems of isolated gas phase and water solvated (based on polarizable continuum model, PCM) to obtain molecular and atomic properties. Molecular properties including total energies, binding energies, energies of the highest occupied and the lowest unoccupied molecular orbitals, energy gaps, and dipole moments are summarized in Table 1. Additionally, atomic scale quadrupole coupling constants (QCC) [23] have been calculated for all FU counterparts in the individual and complex forms to see the effects of nanoring on the initial properties of FU (Table 2). It is important to note that QCC parameters are very good elements to investigate the electronic properties of matters [24–26]. These parameters could be obtained by the solid–state nuclear magnetic resonance (NMR) technique, in which reproducing reliable values of QCC is an advantage of computational chemistry [27]. Moreover, it is not easy to perform NMR experiments on the complicated nano systems. All calculations of this work have been performed by the Gaussian 09 program [28].

3. Results and Discussion

3.1 Molecular properties

Within this work, formation possibilities and properties have been investigated for a novel design of Chit–Cur (chitosan–curcumin) nanoring for containing FU (fluorouracil) anticancer (Figs. 1 and 2). To achieve this purpose, the individual structures of Chit, Cur and FU have been optimized to reach to the minimum energy levels. Table 1 presents the results for total energies, HOMO and LUMO energies, energy gaps, and dipole moments for isolated gas phase and water solvated systems. Comparing the results shows that the investigated structures have different properties in both systems. In the next step, Chit and Cur counterparts have been attached together by formation of ether bonds to make possible constructions of Chit–Cur nanorings. As indicated by the results of Table 1, HOMO and LUMO are at different levels of energies for the nanorings with corresponding different energy gaps, in which the values of dipole moments also show different parameters. The value of dipole moment for Chit2–Cur2 is very much highlighted among the three available nanorings (11.889 Debye vs. 4.067 and 6.514 Debye), which

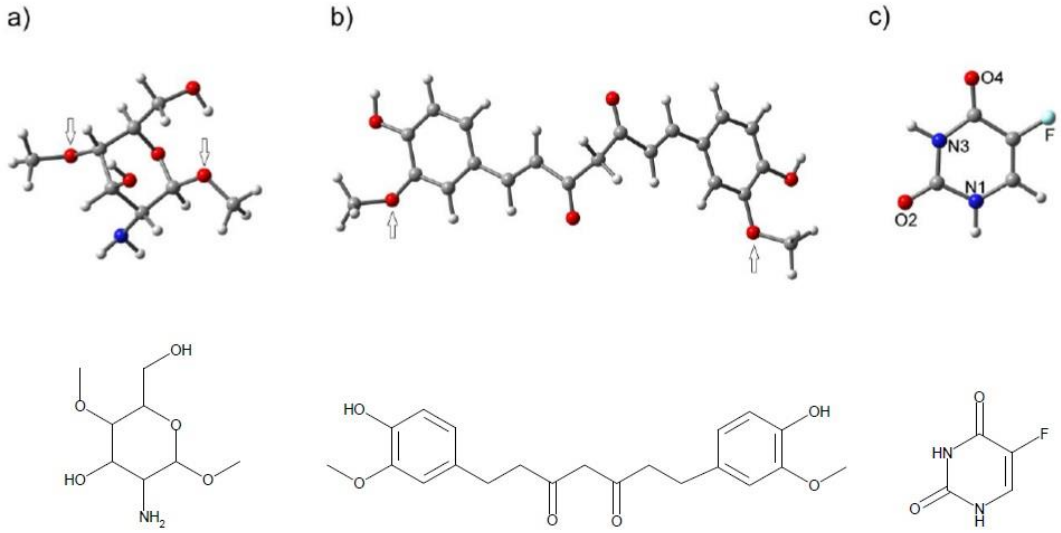

Fig. 1. 3D and 2D views of individual models: a) chitosan (Chit), b) curcumin (Cur), c) fluorouracil (FU). The connecting atomic sites are shown by indicator arrows.

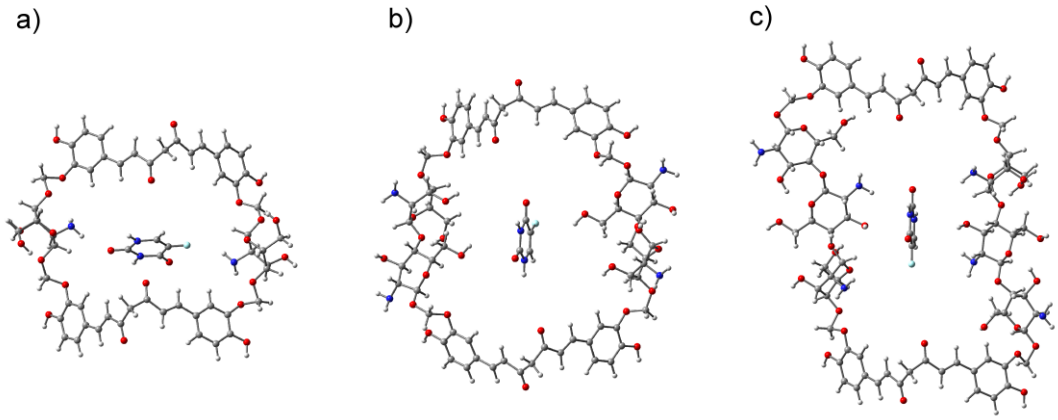

Fig. 2. Complex models: a) FU–Chit2–Cur2, b) FU–Chit4–Cur2, c) FU–Chit6–Cur2.

may refer to more reactivity of this structure than other two ones. At the third step, FU counterparts have been placed at the center of nanorings to construct FU–Chit–Cur complexes. In this case, the values of dipole moments for FU–Chit4–Cur2 and FU–Chit6–Cur2 (4.545 and 7.020 Debye) are increased in comparison with the corresponding Chit–Cur nanorings (4.067 and 6.514 Debye) but the value was decreased for FU–Chit2–Cur2 (8.282 Debye) in comparison with the Chit2–Cur2 nanoring (11.889 Debye). The results of binding energies in both gas and water solvated phases indicate that the most stable complex structure is FU–Chit2–Cur2 among the models (gas phase: 6.190 keV vs. 0.442 and 1.744 keV, water sovlated: 0.871 keV vs. 0.005 and 0.233 keV). It has been already indicated by the values of dipole moments that the reactivity of FU–Chit2–Cur2 could be expected more than other two nanorings, in which it is again confirmed here by the highlighted magnitude of binding energy. Comparing the energies of HOMO and LUMO indicates that the complex structures are more similar to the individual nanorings but not to the individual FU counterparts. Based on the obtained results, the properties of FU and nanorings have been influenced by presenting in the complex systems because of interactions, in which the effects are more significant for the properties of smaller counterpart (FU) than the properties of larger counterpart (nanorings). Earlier studies have been also tried to show the possibility of existence of a

Table 1: Molecular properties*

Model	Total Energy (keV)	HOMO (eV)	LUMO (eV)	Energy Gap (eV)	Dipole Moment (Debye)
Chit	–20.542	–6.323	1.517	7.893	4.907
	[–20.297]	[–6.054]	[2.138]	[8.192]	[6.129]
Cur	–34.384	–5.790	–1.972	3.818	3.833
	[–34.385]	[–5.750]	[–2.023]	[3.727]	[5.121]
FU	–13.988	–6.786	–1.378	5.408	3.902
	[–13.989]	[–6.302]	[0.878]	[7.180]	[5.156]
$Chit_2$–Cur_2	–104.949	–5.611	–1.955	3.656	11.889
	[–104.953]	[–5.618]	[–2.028]	[3.590]	[15.401]
$Chit_4$–Cur_2	–137.107	–5.900	–2.151	3.749	4.067
	[–137.113]	[–5.805]	[–2.050]	[3.755]	[5.668]
$Chit_6$–Cur_2	–169.253	–5.484	–2.146	3.338	6.514
	[–169.259]	[–5.436]	[–2.067]	[3.369]	[7.764]
FU–$Chit_2$–Cur_2	–118.937 (6.190)	–5.622	–2.018	3.604	8.282
	[–118.942 (0.871)]	[–5.616]	[–2.028]	[3.588]	[10.427]
FU–$Chit_4$–Cur_2	–151.096 (0.442)	–5.802	–2.284	3.518	4.545
	[–151.101 (0.005)]	[–5.804]	[–2.053]	[3.751]	[6.349]
FU–$Chit_6$–Cur_2	–183.240 (1.734)	–5.453	–2.135	3.318	7.020
	[–183.247 (0.233)]	[–5.436]	[–2.066]	[3.371]	[7.989]

*See Figs. 1 and 2 for the models. The values in brackets are for the water solvated systems. Energy Gap = LUMO – HOMO. The values in parentheses are for the binding energies (kcal/mol); Binding Energy = $Energy_{\text{FU–Chit–Cur}} - Energy_{\text{Chit–Cur}} - Energy_{\text{FU}}$.

container or carrier for FU counterpart, in which the results are in complementary of each other for the purpose.

Comparing the results of isolated gas phase and water solvated systems indicates the significant effects of solvent on molecular properties of the investigated systems. Total energies of the complex systems indicate that the FU–Chit–Cur structures are slightly more stable in the water solvated system than the isolated gas phase. Binding energies indicate that the solvent could separate the FU counterpart from the nanoring. HOMO and LUMO levels also indicate the effects of solvent on electronic properties of the investigated models, which are also seen by the energy gaps in two systems. Dipole moments significantly show the importance of the investigated complex models with highlighted polarization properties in the water solvated systems. Since the solubility is an important factor for the systems related to life sciences, the results of this work indicated that the designed complex models could help for better solubility activities [1, 3].

3.2 Atomic scale quadrupole coupling constants

Atomic scale QCC (quadrupole coupling constants) parameters have been evaluated for nitrogen and oxygen atoms of FU in the individual and complex models for both isolated gas phase and water solvated systems (Table 2). These two types of atoms of FU are the most important ones, which are the responsible for interactions with other molecules and atoms in the populated systems. Both of nitrogen and oxygen have considerable

quadrupole moments and they are very much active for the QCC measurements [23]. Since the magnitudes of QCC are related to the amounts of electric charges at the atomic sites, larger or smaller values indicate the contribution of the atom to interact with other atoms. For nitrogen atoms, the behaviors in FU–Chit4–Cur2 and FU–Chit6–Cur2 are similar with decrease of magnitude of QCC for both nitrogens from FU to complex. However, behavior in FU–Chit2–Cur2 is different, in which the magnitude of N(3) (3724 kHz) is increased whereas the that of N(1) (4069 kHz) is decreased. Interestingly, the changes of magnitudes of QCC for oxygen atoms from individual FU to FU–Chit2–Cur2 are different in comparison with the situations in the two other complexes. The atomic scale results, in addition to molecular results, also indicate that the properties for FU–Chit2–Cur2 are highlighted among three constructed complexes. In this case, FU–Chit2–Cur2 could be proposed as a good container for the FU counterpart. The effects of solvents on the magnitudes of QCC are also obvious to approve the importance of investigated complex models for better solubility in water systems. Lower magnitudes of QCC in the water solvated systems in comparison with isolated gas phase reveal that the FU counterpart could detect the existence of solvent and could detect the effects.

Table 2: Atomic quadrupole coupling constants (kHz) for fluorouracil*

Model	N_1	N_3	O_2	O_4
FU	4121	3690	8247	9440
	[3768]	[3526]	[8109]	[9060]
FU–Chit$_2$–Cur$_2$	4069	3724	8180	9250
	[3786]	[3533]	[8121]	[9022]
FU–Chit$_4$–Cur$_2$	4076	3656	8292	9495
	[3762]	[3509]	[8114]	[9064]
FU–Chit$_6$–Cur$_2$	4035	3643	8359	9461
	[3748]	[3542]	[8178]	[9066]

*See Figs. 1 and 2 for the atoms and models. The values in brackets are for the water solvated systems.

4. Conclusion

Within this work, formation possibilities and properties have been investigated for FU–Chit–Cur complexes as possible containers for FU anticancer drug in isolated gas phase and water solvated systems. Among the constructed complex models, FU–Chit2–Cur2 has been observed as more possible structure than two other FU–Chit4–Cur2 and FU–Chit6–Cur2 ones. The molecular properties indicated that the reactivity of Chit2–Cur2 nanoring is more than other two Chit4–Cur2 and Chit6–Cur2 nanorings. The magnitudes of binding energies also have approved the expected reactivity for Chit2–Cur2 nanoring. Atomic scale QCC properties indicated that the behaviors of nitrogen and oxygen atoms in the FU–Chit2–Cur2 complex are different in comparison with two other FU–Chit4–Cur2 and FU–Chit6–Cur2 complexes, approving again the highlighted behavior of Chit2–Cur2 nanoring. Therefore, FU–Chit2–Cur2 complex could be proposed as a possible container of FU. The effects of water solvent were also significantly observed for both of molecular and atomic properties. As important achievements of this part, the molecular orbital energy levels and dipole moments indicated the most significant effects. Moreover atomic properties of FU also indicated the effects of solvent, in which the magnitudes of effects are still different for the complex structures. Finally, the constructed containers models could be seen as a possible design for FU related applications, in which the FU–Chit2–Cur2 complex could be proposed as the most proper one among the models.

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