ORIGINAL ARTICLE

Theoretical study for quercetin/β-cyclodextrin complexes: quantum chemical calculations based on the PM3 and ONIOM2 method

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Abstract The inclusion interaction between quercetin and β-cyclodextrin (β-CD) binding site has been investigated, based on PM3 and ONIOM2 methods. The obtained results clearly indicate that the orientation in which the B ring of the guest molecule located near the secondary hydroxyls of the β-CD cavity is preferred in the binding energy. Moreover, Analyses regarding the complex structures suggest that one hydrogen bond between 7-hydroxy group (OH) of quercetin and 6-OH of β-CD is formed. This hydrogen bond interaction plays an important role in the bound quercetin/β-CD complex.

Keywords Cyclodextrin · Quercetin · PM3 · ONIOM · Binding energy · Inclusion interaction

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Introduction

Today, one of the most important research fields in chemistry is the study of large systems. In this sense, one of the most active research areas is the field of supramolecular chemistry, which involves the use of non-covalent interactions to assemble molecules into stable, well-defined structures and which plays an important role in biological processes [1]. Thus, it is crucial to examine the interactions between molecules and their environment. Well known systems include host–guest and protein–substrate complexes, molecular clusters, or simply molecules within their medium [2–4]. Among the best-known hosts are cyclodextrins (CDs). CDs are cyclic oligosaccharides with a small number of glucose units. The most common CDs are α-, β- and γ-CDs that differ in the number of D-glucopyranose ($C_6H_{10}O_5$) units: 6, 7 and 8, respectively [5]. The resultant inclusion complexes can induce modification of the physicochemical properties of the 'guest' molecules, particularly in terms of water solubility and solution stability [6]. Therefore, it is important to clarify the structures of the inclusion complexes from a viewpoint of enzyme-substrates within the hydrophobic cavities of CDs [7].

Currently, there is great interest in the theoretical study of supramolecular systems. For this purpose, molecular mechanics (MM) [8] or semiempirical methods [9, 10] are the most widely used as ab initio and Density Functional Theory (DFT) methods are prohibitively expensive in treating such large systems. Unfortunately, in general, MM methods do not accurately describe the geometries or energetics of intermolecular interactions. With no representation of electron density, many chemically important quantum

based effects are missed. Additionally, intermolecular interactions for a number of MM force fields are known to be poorly reproduced [11]. Semiempirical methods employ approximations to accelerate solution of the Roothan-Hall equations; thus, they are quantum mechanical in nature and are an improvement over MM methods in accounting for quantum phenomena. However, empirical solutions are substituted for the large number of multielectron integrals, and these are parameterized to reproduce experimental observables for a large number of molecules. These approximations sharply limit the precision of semiempirical methods, particularly in treating systems that were not present in the initial parameterization procedure [12].

However, such investigation of larger molecular system is limited by the computational effort required and the accuracy of the method used, theoretical chemistry has turned its interest to the so-called hybrid methods that use multiple approaches of varying accuracy and cost to simultaneously treat different parts of a system. The use of hybrid methods is very important for the study of large molecules or supramolecular systems. Within these schemes the computational cost diminishes considerably and the entire system can be considered without needing to generate simplistic model systems. Among these hybrid approaches, the hybrid ONIOM method developed by Morokuma et al. [13] is especially appealing as it can combine any quantum mechanics/quantum mechanics (QM/QM) or QM/MM method within one other. In CD chemistry, under many circumstances the CD only provides an environment effect and we are more interested in the chemistry of the guest molecules in the CD environment. Therefore, it appears a promising field to use the ONIOM method to study CD chemistry. However, to our best knowledge, very few calculations were performed for CD complexation based on the ONIOM methods.

With an aim toward increasing our knowledge of supramolecular interactions, in this article we focus on the O–H⋯O interactions between host and guest molecules and the conformational changes of the guest molecule. This study is related to a work on β-CD/quercetin interactions [14]. Quercetin (3, 3′, 4′, 5, 7-penthydroxy flavone, Fig. 1a.) is an important constituent of the flavonoid family and is found in many fruits and vegetables, as well as olive oil, red wine, and tea [15–17]. It has been demonstrated to possess many biological effects that are considered beneficial to health, including antioxidation by scavenging free radicals, anticancer, antiviral prevention of atherosclerosis, and chronic inflammation activities [18, 19]. Conformational flexibility of the quercetin molecule

includes the orientation of the linkage between ring B and ring C. We theoretically studied this host–guest system using PM3 methods. We found one intermolecular O–H⋯O bond between quercetin and the β-CD in which quercetin was encapsulated [14]. In general, semiempirical methods underestimate the strength of hydrogen bonds giving too long distances and too small energies for H-bonded systems. A very limited body of work regarding the treatment of intermolecular O–H⋯O interactions using semiempirical methods was found in the literature. To this purpose, we have performed an ONIOM study of the complex reactions of β-CD with quercetin. The complexes were divided into two layers. The inner layer (the quercetin molecule) was treated by the density functional method (DFT) B3LYP and ab initio Hartree-Fork (HF) employing the 6-31G* basis set, respectively, while the outer layer (β-CD) by the semiempirical PM3 method. Liu and coworkers [20] suggested PM3 should be advantageous in direct structure optimization of β-CD. The inclusion of the outer layer was important for obtaining reasonable results for the proposed complexes configuration. The results offer significant insights into the inclusion interactions between β-CD and quercetin.

Computational methods

System studied and single point calculations

The initial structures of β-CD and quercetin were constructed with the help of CS Chem3D Ultra (Version 6.0, CambridgeSoft.com) from the crystal structure [21, 22] and were fully optimized with PM3. As shown in Fig. 1b, a conformation for quercetin was obtained with a minimum energy, where the dihedral angle 6′-1′-2-3 is equal to 64.5°. The coordinate system used to define the process of complexation is shown in Fig. 2. The construction method was reported in [14]. Briefly, the β-CD ring was constructed with seven identical glucose units positioned symmetrically around the Z-axis, such that all the glycosidic oxygens are in the XY plane and their center was defined as the center of the coordination system. The 2-OH and 3-OH groups of each glucose project into –Z space. The quercetin molecule was docked into this β-CD model with the B-ring to C-ring bond coincident with the Z-axis. Multiple starting positions were generated by movement of the bond along the Z-axis, and complexes with the B-ring projecting into either –Z (complex named by ring up) or +Z (complex named by ring down) space were built. The relative position between the host and the guest was measured by the

Fig. 1 Molecular structures of (**a**) quercetin and PM3-optimized quercetin (**b**)
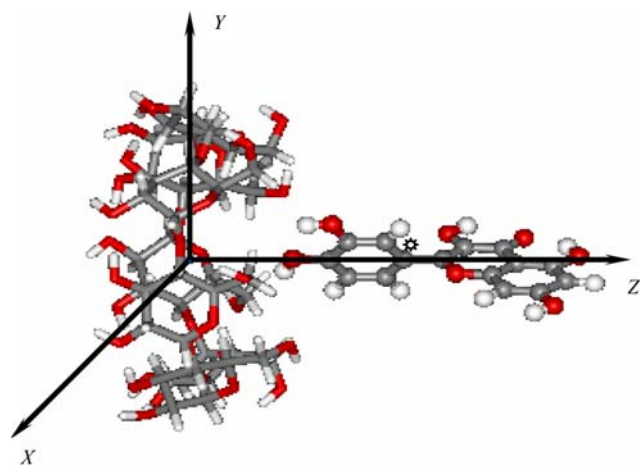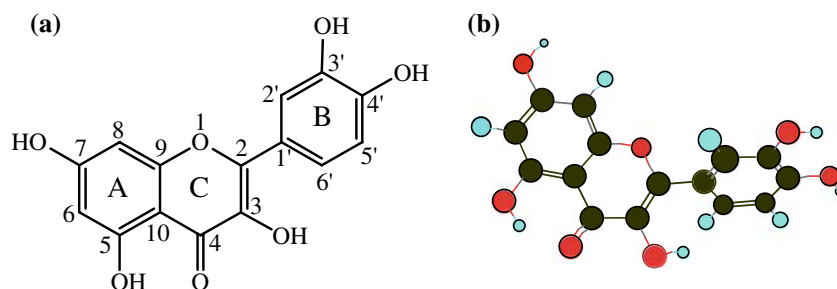

Fig. 2 Coordinate systems used to define the process of complexation

Z-coordinate of the labeled carbon atom of the guest (Fig. 2). In order to find an even more stable structure of the complex, each guest molecule was calculated for all of the structures obtained by scanning *θ*, circling around *Z*-axis, at 20° intervals from 0 to 360° and scanning *Z*-coordinate at 1 Å intervals. Each complex was energy minimized in vacuo, and the lowest energy complexes were used as the starting geometries for single point calculation and ONIOM analysis.

For the equilibrium geometries of the quercetin/*β*-CD complexes, DFT/B3LYP or ab initio HF single point calculations with the split-valence 6-31G* basis set were performed for the PM3-optimized complexes both in vacuo and in water solution by using Onsager continuum solvation model based on the self consistent reaction field (SCRF) method. Onsager continuum solvation model has been successfully applied in the inclusion complexation of *β*-CD with the ground singlet and excited triplet xanthones or 4,4′-benzidine and o-tolidine [23, 24]. HF and DFT *BE*s computed in vacuo have been corrected for basis-set superposition error (BSSE) using the counterpoise method.

Definition of the binding energy

In this study, the binding energy (*BE*) upon complexation between quercetin and the *β*-CD calculated for the minimum energy structure are defined as equal (1) [25]:

$$BE = E[C]_{opt} - E[S]_{opt} - E[CD]_{opt} \qquad (1)$$

$$DEF[S] = E[S]_{sp}^{opt} - E[S]_{opt} \qquad (2)$$

here, $E[C]_{opt}$, $E[S]_{opt}$, and $E[CD]_{opt}$ represent the total optimized energy (heats of formation) of the complex, the free substrate and the free *β*-CD, respectively. $DEF[S]$ stands for deformation energy of the substrate. $E[S]_{sp}^{opt}$ is the single point energy of the substrate on the configuration taken from the optimized complex geometry. The magnitude of the energy change would be a sign of the driving force towards complexation. The more negative the binding energy is, the more thermodynamically favorable is the inclusion complex.

ONIOM calculations

For a deeper understanding of the molecular recognition, the equilibrium geometries of both quercetin/*β*-CD complexes were also completely optimized using the ONIOM method. The ONIOM method is a hybrid computational method that allows different levels of theory to be applied to different parts of a molecular system. In the two-layered ONIOM method, the molecular system under study is divided into an inner and an outer layer. The inner layer consists of the most critical elements of the system, and the rest of the system comprises the outer layer. In the terminology of Morokuma and co-workers [4, 13], the full system is called "real" and is treated with a low level of theory. The inner layer is termed "model" and is treated with both the low level of theory and a high level of theory. The total ONIOM energy E^{ONIOM} is given by

$$E^{ONIOM} = E(high, \ model) + E(low, \ real)$$
$$- E(low, \ model) \qquad (3)$$

where E(high, model) is the energy of the inner layer at the high level of theory (the quercetin molecule), E(low, real) is the energy of the entire system at the low level of theory (the complexes), and E(low, model) is the energy of the model system at the low level of theory (β-CD). Thus, the ONIOM method allows one to perform a high-level calculation on just a small, critical part of the molecular system and incorporate the effects of the surrounding elements at a lower level of theory to yield a consistent energy expression with similar accuracy to a high-level calculation on the full system. A variety of combinations of theoretical methods have been compared in the present study. All calculations were carried out using the $G_{AUSSIAN}$ 03 package [26].

Results and discussion

Binding energy of the β-CD/quercetin complex

A careful conformational analysis was carried out for the host–guest complex. Different minima were localized for the whole complex. The details of the optimization can also be found in former reports [14]. Graphic representation of the energy changes involved in the inclusion process produced two curves for the two complexation orientations (Fig. 3). Table 1 shows the calculated binding energy (BE) of quercetin complexed with β-CD. The negative BE changes upon complexation clearly demonstrate that β-CD can form stable complexes with quercetin, which is observed in the experiments [27–29]. Our previous study showed that the complexation reactions of quercetin with β-CD are exothermic judged from the negative enthalpy changes, and the enthalpy changes are of similar magnitude to the experimental ΔH data [14]. The ring down orientation is significantly less favorable than the ring up orientation by an energy difference of 5.98 kJ mol^{-1} according to PM3 calculations. The same result is also obtained with the B3LYP/6-31G* and HF/6-31G* single point calculation in vacuo in which the energy difference becomes 41.21 and 42.88 kJ mol^{-1}, respectively. The BE difference with BSSE correction is 27.11 and 23.81 kJ mol^{-1} for the DFT and HF method. While these energy differences may be contribute to intermolecular hydrogen bond formation for the ring up orientation. From Table 1, the BE computed in vacuo with the HF and DFT method with BSSE correction is positive, this does not necessarily
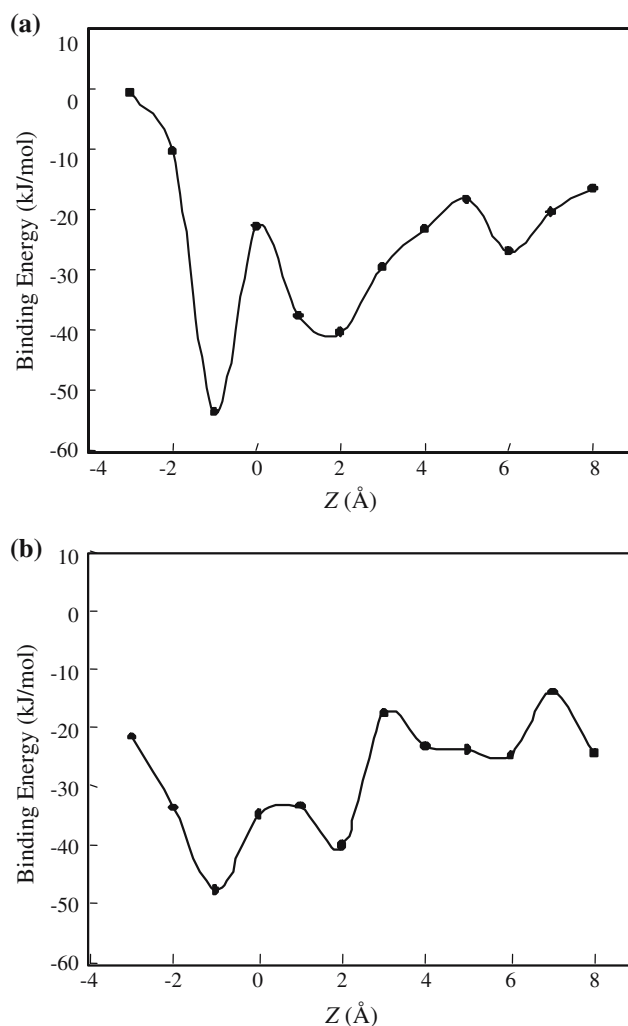

Fig. 3 Binding energies of the inclusion complexation of quercetin into ß-CD at different positions (Z) and orientations: (**a**) Ring up; (**b**) Ring down. The position of the guest was determined by the Z-coordinate of the labeled carbon atom (*) (Fig. 2) in the phenyl group from the center of the glycosidic oxygens

mean that the complexation is unfavorable, for the large complexed system is optimized at the level of PM3 but not HF/6-31G* and B3LYP/6-31G*.

The obtained results indicate that B3LYP/6-31G* single point calculations give more estimated binding energy as compared with HF/6-31G* results. This might be explained by the fact that the B3LYP/6-31G* method can take care of the electrostatic, steric, polarization, and charge transfer interactions between quercetin and β-CD, that occur in the interacting core region [4]. The foundation of the estimated binding energy in the model studied is approximately –72.77 and –10.25 kJ mol^{-1} (BSSE) for the ring up orientation by B3LYP/6-31G* calculations and brings about the stability of this complex systems (Table 1).

Table 1 The binding energy upon the inclusion complexation of β-CD with quercetin and the deformation energy of substrate by PM3 methods

	Quercetin	β-CD	Ring up	Ring down
PM3				
E^a (kJ mol^{-1})	–946.39	–6096.50	–7096.57	–7090.59
BE^a (kJ mol^{-1})			–53.68	–47.70
DEF^a [Quercetin](kJ mol^{-1})			3.01	2.28
HF/6-31G* (in vacuo)				
E^a (kJ mol^{-1})	–2882399.90	–11161192.08	–14043621.32 (–14043567.92)	–14043578.43 (–14043544.11)
BE^a (kJ mol^{-1})			–29.34 (24.06)[b]	13.54 (47.87)[b]
B3LYP/6-31G*(in vacuo)				
E^a (kJ mol^{-1})	–2898944.54	–11224210.51	–14123227.81 (–14123165.30)	–14123186.61 (–14123138.19)
BE^a (kJ mol^{-1})			–72.77 (–10.25)[b]	–31.56 (16.86)[b]
B3LYP/6-31G* (in water)				
E^a (kJ mol^{-1})	–2898967.52	–11224217.68	–14123238.99	–14123189.41
BE^a (kJ mol^{-1})			–74.47	–24.89

[a] E is the total optimized energy (heats of formation), DEF is the deformation energy of the substrate, BE is the binding energy upon complex, $BE = E[C]_{opt} - E[S]_{opt} - E[CD]_{opt}$

[b] The HF and DFT BEs in vacuo using the counterpoise method for correcting the basis set superposition error (BSSE)

When the solvation effect is taken into consideration, the energy difference becomes 49.58 kJ mol^{-1} from the B3LYP/6-31G* SCRF calculation in water. Nevertheless, it should be mentioned that herein the solvent effect is only taken into account on the basis of a continuum solvation model, which considers the solvent as a continuous dielectric with a cavity accurately modeled for the solute. In the model, the solvent reacts against the solute charge distribution, generating a reaction field, and the electrostatic interaction between the solute and the solvent is introduced as a perturbation operator in the solute hamiltonian. Apparently, the solvent reorganization involved in the solvation is not considered in the model. Therefore, the calculation results in solution are only indicative.

Conformational analysis of quercetin upon β-CD/quercetin complexation based on various theoretical methods

By means of a quite exhaustive conformational search using the PM3 method, we found two geometries of the host-guest system that were identified as the most stable conformations. Other possible locations of quercetin were examined using the PM3 method, but were shown to be energetically less favorable (as shown in Fig. 4). Figure 4 depicts these two structures (labeled ring up and ring down), which are both lower in energy than the infinitely separated host and guest molecules. In both geometries the B ring of quercetin is sequestered by β-CD cavity through the secondary or primary rim of the latter. The orientation in which the B ring of quercetin located near the secondary hydroxyls of β-CD cavity is preferred in energy. These results agree with experimental evidence based on H^1-NMR and molecular dynamics (MD) simulations about the overall orientation of the quercetin ligand in the β-CD cavity: the B-ring, C-ring, and part of the A-ring of quercetin display favorable interaction with the hydrophobic cavity of the β-CD [27].

As the β-CD/quercetin complex itself is still too large for ab initio calculations, therefore, we adopted ONIOM2 methods (HF/6-31G*:PM3 and B3LYP/6-31G*:PM3) in order to further understand molecular recognition between the guest and the host. The system was divided into two parts: the most important part, consisting of the guest molecule quercetin for the inner layer; and the minor part, consisting of the remaining part β-CD for the outer layer. Relative energy differences are presented in Table 2. Interestingly, all the methods find the ring up orientation to be more stable than the ring down orientation. Furthermore, all the methods that (probably correctly) predict the ring up orientation as being more stable have energy differences that are separated by no more than 8 kJ mol^{-1}.

Based on the PM3 methods, it was found that there are one hydrogen bonds between 7-hydroxy group (OH) of quercetin and 6-OH of β-CD with the distances between heavy atoms of the hydrogen bonds of 2.73 Å [14]. The quercetin molecule accepts O–H$\cdots$O bond from 6-OH group located on the narrow rim of β-CD. The hydrogen bond here is defined as an
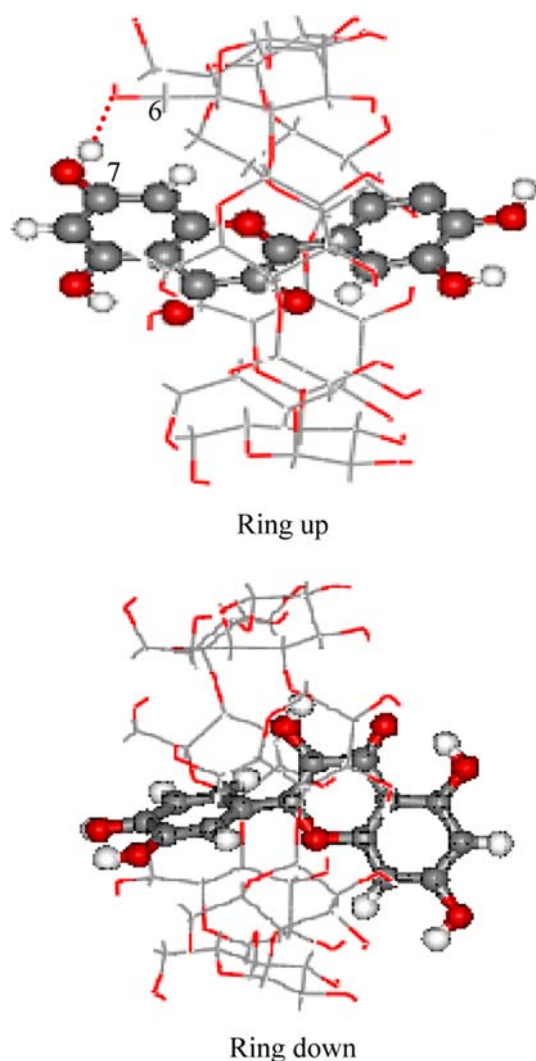
Fig. 4 The two most stable conformations of the phenyl (B ring) structure of quercetin encapsulated in β-CD

O–H···O interaction in which the O···O distance is less than or equal to 3.2 Å and the angle at H is greater than 90° [30]. An intermolecular hydrogen bond which

contributes a stabilization energy of 16–25 kJ mol^{-1} [31] to the complex is formed between quercetin and β-CD. Possible hydrogen bonding is shown in Fig. 4 as a dotted line. The calculated ONIOM2 optimized O···O distance is 2.70 Å smaller than that of the PM3 methods. In general, semiempirical methods underestimate the strength of hydrogen bonds giving too long distances and too small energies for H-bonded systems. From Table 2, it can be seen that the ring down orientation does not seem to be stabilized by such an interaction based on various computational methods. Even though we work in the theoretical treatment in a vacuum, it is known from the literature that secondary OH groups form intramolecular hydrogen bonds and the rate of exchange of protons for ring down orientation is much lower (stronger bonding) than that of ring up orientation. Therefore, it is important to note that the hydrogen bond interactions play an important role in the binding of quercetin in the bound β-CD complex and also may be helpful in increasing the stability of the guest/host complex.

Conformational flexibility of the quercetin molecule includes the orientation of the linkage between ring B and ring C. Investigation on the deformation energy of the substrate by PM3 methods (as shown in Table 1), interestingly, demonstrated that the quercetin molecule for ring up orientation requires slightly more energy than that of the ring down orientation in order to adapt its structure to bind within the cavity of β-CD as indicated by the DEF[S] of about 3.01 kJ mol^{-1}. This can be supported by the fact that flexibility of the guest structure is one of the important structural requirements for β-CD upon complexation. At the same time, interactermolecular hydrogen bonds also play pivotal role for this conformational exchange. The calculational dihedral angle (6′-1′-2-3) was changed to 84.8°, 58.3° and 69.0° for the ring up orientation based on PM3, ONIOM(RB3LYP/6-31G*:RPM3), and ONIOM(RHF/6-31G*:RPM3) method, respectively. And the bond

Table 2 Relative potential energy (kJ mol^{-1}) of the ring up orientation taking the ring down orientation as origin of energies and intermolecular hydrogen bonds with O···O distance (Å) smaller than 3.20 Å

Computational methods	Ring up (kJ mol^{-1})	Ring down (kJ mol^{-1})	ΔE^c
E^a(PM3)	–7096.57	–7090.59	5.98
d(O···O) (H-6-O...H-7-O)	2.73		
E^{ONIOMb}(RB3LYP/6-31G*:RPM3)	–2905138.34	–2905132.78	5.56
d(O···O) (H-6-O...H-7-O)	2.70		
E^{ONIOMb} (RHF/6-31G*:RPM3)	–2888605.07	–2888597.30	7.77
d(O···O) (H-6-O...H-7-O)	2.70		

[a] E is the total optimized energy (heats of formation) for the PM3 method

[b] E^{ONIOM} is the total ONIOM optimized energy based on the PM3-optimized complexes, $E^{ONIOM} = E$(high, model) + E(low, real) – E(low, model)

[c] ΔE is relative energy difference, $\Delta E = E$(Ring down) – E(Ring up)

connected $C_{1'}$ with C_2 is inclined to the molecular axis of β-CD. This also suggests that the quercetin conformation change more largely in order to an interactermolecular hydrogen bonds formation by using the PM3 method. A similar experiment was conducted by using NMR for complexation of (+)-catechin into β-CD [32]. This indicates that the guest conformation is easily affected during CD complexation because of interactermolecular conformation adaptation.

Conclusion

This work has shown that it is now possible to apply the combined high and low quantum chemical methods, based on various approaches such as Hartree Fock, Density Functional Theory, and semiempirical methods, to study β-CD/quercetin complexes using ONIOM2 approach. These results clearly show that the orientation in which the B ring of the guest molecule located near the secondary hydroxyls of the β-CD is preferred according to the binding energies (BE). Comparison of the complex structures suggests that intermolecular hydrogen bond interactions play an important role in the binding of quercetin in the bound β-CD complex and also be helpful in increasing the stability of the guest/host complex.

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