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Molecular modeling study of β-cyclodextrin complexes with (+)-catechin and (−)-epicatechin

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Abstract

The structural aspects for the complexation of (+)-catechin (CA) and (−)-epicatechin (EC) (an enantiomer) to β-cyclodextrins (CDs) were explored by using a semi-empirical PM3 method. In the β-CD/CA inclusion complex, the orientation in which the aromatic A-ring of CA projects onto the 2-OH/3-OH face of β-CD, and the B-ring projects from the 6-OH face is preferred in the binding energy (BE). In contrast, the inclusion of the B-ring of EC from either the secondary hydroxyl group side or the primary hydroxyl group side gives rise to the two most probable complexes. The molecular modeling results are in agreement with the NMR observations and molecular dynamics (MD) simulations. EC forms a more stable complex with β-CD than the corresponding CA, as judged from the difference in BE. The differential interactions between each enantiomer and the chiral host give rise to the significant structural differences for the corresponding inclusion complexes. Numerous host–guest C–H···O interactions, resulting from induced fit of the hosts toward each of the enantiomeric guests, comprise a third significant component besides the O–H···O hydrogen bonds and the van der Waals contacts.

Keywords: Cyclodextrin; (+)-Catechin; (−)-Epicatechin; PM3; Inclusion complexation; Hydrogen bond interaction

1. Introduction

Catechins are phenolic compounds extracted from plants and present in natural food and drinks, such as green tea [1] or red wine [2]. The role of such molecules in the prevention of cancer and cardiovascular disease has received a great deal of attention [3,4]. Catechins are scavengers of reactive oxygen species, and their resulting anti-oxidant properties are of great interest in dietetics and cosmetology. Furthermore, their antiviral and cancer inhibiting properties could have pharmaceutical applications. However, catechin powders are bitter, brown, and easily oxidized, and hence difficult to use as a natural food additive or medicine. Inclusion in cyclodextrins (CDs) is envisaged in order to mask the nasty aspects (taste, colour...) of such phenolic compounds [5]. Due to their potential applications, and also to their optimal size, these molecules have been widely used as model compounds for inclusion studies with β-CDs and their derivatives.

The flavan-3-ol compound catechins consist of two benzene rings (A- and B-rings) and a pyran ring (called the C-ring) (Fig. 1a). Catechins exist as two geometrical isomers, catechin (CA) in a *trans* form and epicatechin (EC) in a *cis* form, based on different configuration of 3′,4′-dihydroxyphenyl and hydroxyl groups at the 2- and 3-positions of the C-ring. These isomers often exhibit different behavior in terms of pharmacological processes, therapeutic efficacy and biological processes [6]. Thus, seperation of the enantiomers is necessary to meet the increasing demand for evaluation of the pharmacokinetic attributes of each enantiomer and to control the enantiomeric purity of pharmaceutical preparations [7].

CDs (Fig. 1b), which are cyclic glucose oligomers, are well known in supramolecular chemistry as receptors that are capable of including a range of organic, inorganic, and biological molecules into their hydrophobic cavities via noncovalent interactions. One especially important application

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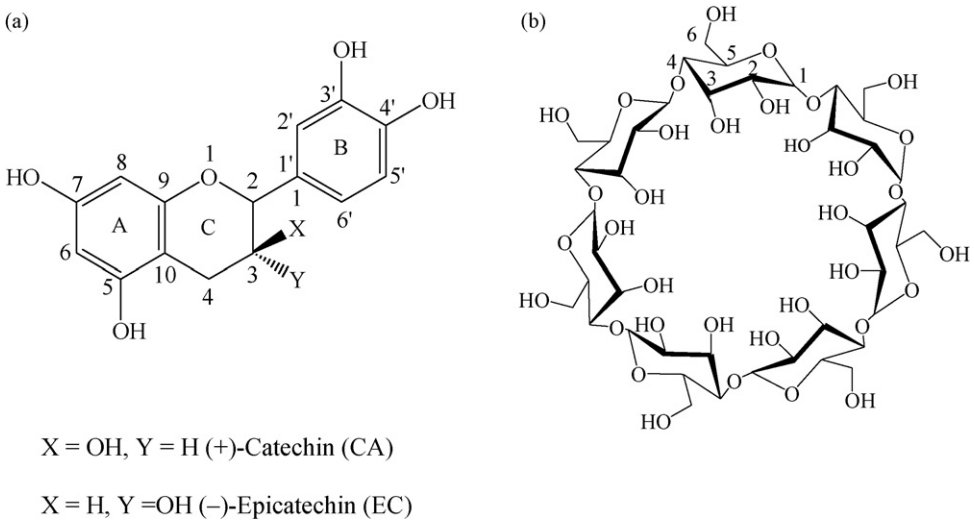

Fig. 1. Schematic representation for the conformations of catechins (a) and β-CD (b).

of CD-based materials has been in the field of separation science. They have been widely used as host compounds in molecular recognition, for separation of enantiomers in racemic mixtures, and as enzyme models [1,7]. The study of the host–guest interactions between CDs and the enantiomers of a chiral molecule should provide a better insight into these interactions and elucidate chiral recognition processes in biological receptor molecules. Therefore, it is important to clarify the structures of the inclusion complexes from a viewpoint of molecular recognition and enzyme-substrates within the hydrophobic cavities of CDs. The driving forces for the complex formation have been attributed to hydrophobic interactions, van der Waals interactions, hydrogen bonding, and release of ring strain in the CD cavity [8]. Due to the limitations of the experimental methods, molecular modeling is frequently used to rationalize experimental findings concerning molecular and chiral recognition by CDs. Molecular modeling methods are valuable tools for detailed information on the geometry and the interaction energy of the inclusion compounds.

Currently, there is great interest in the theoretical study of supramolecular systems. For this purpose, molecular mechanics (MM) [9] or semiempirical methods [10,11] 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 are unable to fully account for the inherent quantum mechanical effects, as the molecular mechanics and dynamics methods are based on the classical physics of balls and springs. With no representation of electron density, many chemically important quantum based effects are missed [12]. Semiempirical methods, like *ab initio* methods, are based on an inherent quantum mechanical description of the electronic structure, but are efficient enough for practical calculations on systems of this size.

The inclusion of CA and EC with native β-CDs has been studied and an inclusion complex with a stoichiometry of 1:1 in solid state and in aqueous solution, was attained [5,13,14]. Furthermore, the probable structures of the inclusion complexes of β-CD with CA and EC have been proposed on the basis of NMR and molecular dynamics simulations [5,13]. However, to our best knowledge, quantum mechanical studies on the inclusion complexation of β-CD with CA and EC, two rather flexible molecules, have been scarcely reported by far. Preliminary NMR studies on the inclusion of CA by β-CD yielded contradictory results for both the evaluation of the affinity constant and the proposed geometry of the complex. Furthermore, the studies of noncovalent interactions involving aromatic substrates are pivotal to both chemical and biological recognition, as reviewed and evaluated by Meyer et al. [15].

As applied by Liu et al. [16], Parametric Model 3 (PM3) has been chosen to study host–guest complexes between β-CD and CA or EC. Due to the molecular size, PM3 is a powerful technique which can be currently applied and performs better than Austin Model 1 (AM1) in biochemical systems due to its improved description of the interactions between non-bonded atoms, e.g. hydrogen bond and steric effects [17]. It has high computational efficiency and its precision is comparable to that of *ab initio* calculations with medium-sized basis sets. By using the PM3 method, we have successfully studied β-CD/quercetin interactions [18], and found that intermolecular O–H···O hydrogen bond interaction plays an important role in the bound β-CD/quercetin complex. Such hydrogen bonds have attracted substantial interest in the fields of chemistry and biology. Depending on the type of the interaction, the strength of the hydrogen bond can vary from well over 10 kcal/mol (termed as strong hydrogen bonds) to a few kcal/mol (weak hydrogen bonds). Though the stabilization energy of the weak hydrogen bond is generally quite small, it has been pointed out that such a weak intermolecular interaction is of potential importance in structures and functions of biological macromolecules. One type of weak interaction that has attracted considerable attention recently in the structural biology community is the

interaction involving the C–H group [19]. C–H···O contacts have been found in a number of CD inclusion complexes. These C–H···O contacts show the stereochemical features and directionality of conventional hydrogen bonds (H bonds), and are called C–H···O bonds. It is believed that the C–H···O bonds can make energetically favorable contributions to the stability as well as to the strength of host–guest interactions [20]. The aim of theoretical studies is to discover why and how the chiral recognition takes place, taking into account that the nature of the forces responsible for one enantiomer binding to a chiral surface is the same as that for its optical isomer. To study the enantiodifferentiation of CA and EC by β-CD we first determine the interaction energy between the chiral host and each enantiomer, then establish the differences in the corresponding inclusion complexes.

2. Computational methods

2.1. System studied and single point calculations

The atomic coordinates of the β-CD molecule, refcode POBRON of the Cambridge structural database (CSD) as determined by X-ray diffraction [21], have been selected as starting geometry for a complete optimization with PM3. The starting structures of the CA and EC were constructed with the help of CS Chem3D Ultra (Version 6.0, CambridgeSoft.com) and were fully optimized with PM3. These geometries were always used in all calculations of host–guest complexes.

The coordinate system used to define the process of complexation is shown in Fig. 2. The construction method was reported in [18]. 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 CA or EC molecule was docked into the cavity of β-CD with the B- 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 the $-Z$ (complex named by R_{in}) or the $+Z$ (complex named by R_{out}) space were built. The relative position between the host and the guest was measured by the *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 the *Z*-axis, at 20° intervals from −180° to 180° and scanning the *Z*-coordinate at 1 Å intervals. For the PM3-optimised equilibrium geometries of the β-CD/CA and β-CD/EC complexes, DFT/B3LYP and HF single point calculations with the split-valence 6-31G* basis set and thermodynamic analysis were performed in vacuo.

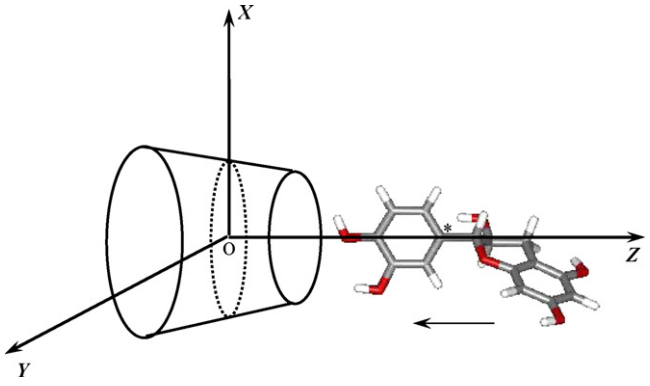

Fig. 2. Coordinate systems used to define the process of complexation. And the scheme for two different approaches of CA/EC, B-ring projecting into either $-Z$ (complex named by R_{in}) or $+Z$ (complex named by R_{out}) space.

2.2. Definition of the binding energy (BE)

In this study, the binding energy (BE) upon complexation between CA or EC and the β-CD calculated for the minimum energy structure is defined in Eq. (1) [22]:

$$\mathrm{BE} = E[C]_{\mathrm{opt}} - E[G]_{\mathrm{opt}} - E[\mathrm{CD}]_{\mathrm{opt}} \quad (1)$$

$$\mathrm{DEF}[G] = E[G]_{\mathrm{sp}}^{\mathrm{opt}} - E[G]_{\mathrm{opt}} \quad (2)$$

where, $E[\mathrm{C}]_{\mathrm{opt}}$, $E[\mathrm{G}]_{\mathrm{opt}}$, and $E[\mathrm{CD}]_{\mathrm{opt}}$ represent the HF energies (heats of formation) of the complex, the free guest and the free β-CD, respectively. DEF[*G*] stands for deformation energy of the guest. $E[G]_{\mathrm{sp}}^{\mathrm{opt}}$ is the single point energy of the guest 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.

2.3. Thermodynamic analysis for the complexation process of β-CD with CA or EC

The geometries of the CA, EC, β-CD and four plausible up and down orientations, having the B-ring in the smaller and larger cavity, respectively, were fully optimized without any geometrical or symmetry constraints using the semiempirical PM3 method, which has been shown to give very reasonable geometrical parameters for CDs. PM3 harmonic frequency calculations were performed for the equilibrium structures, characterizing them as true minima on the potential energy surface. The PM3 frequencies were then used for the evaluation of the internal energy (ΔE_{int}) and thermal energy (ΔG_{T}) corrections, with the aid of the well known formulae of statistical thermodynamics. We calculate the enthalpy (ΔH) and Gibbs free energy (ΔG) of the complexation process between β-CD and CA or EC using the equations below, a procedure that was successfully used in [23].

$$\Delta H = \Delta E_{\mathrm{ele-nuc}} + \Delta E_{\mathrm{int}} \quad (3)$$

$$\Delta G = \Delta E_{\mathrm{ele-nuc}} + \Delta G_{\mathrm{T}} \quad (4)$$

$$\Delta G_{\mathrm{T}} = \Delta E_{\mathrm{int}} - T\Delta S \quad (5)$$

Here, $\Delta E_{\mathrm{ele-'nuc}}$ stands for the electronic plus nuclear repulsion contribution to ΔH and ΔG. All calculations were carried out using the GAUSSIAN 03 quantum mechanical package [24].

3. Results and discussion

3.1. Structure of the β-CD/CA inclusion complex

The analysis of the potential energy surfaces corresponding to this closing-up and rotation of the β-CD/CA complexes shows several energy minima at different combinations of rotation angles and distances. The optimum position and angle for CA into β-CD at R_{in} and R_{out} orientations can be, respectively, determined according to the binding energy. Other possible locations and angles of CA were examined using the PM3 method, but were shown to be energetically less favorable and so they were not listed.

Fig. 3 depicts BE for the approach of CA to β-CD with orientations R_{in} and R_{out}. The complexation process is energetically favorable. The most stable structure is reached at approximately $Z = -2$ Å ($\theta = 30^\circ$) and $Z = -4$ Å ($\theta = 140^\circ$) for the CA for the R_{in} and R_{out} approaches, respectively. At this point the BE energies are -51.38 and -62.74 kJ mol^{-1} (as shown in Table 1), which is favorable, by 10.36 kJ mol^{-1}, to the formation of the complex by the approach of the nonpolar side of CA to the β-CD. The same result is also obtained with the B3LYP/6-31G* and HF/6-31G* single point calculations in vacuo, in which the energy difference becomes 28.14 and 15.69 kJ mol^{-1}, respectively. From Table 1, the BE computed in vacuo with the HF and DFT methods, this does not necessarily 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*. This means that the preferred orientation of the complex is that in which the aromatic A-ring of CA projects onto the 2-OH/3-OH face of β-CD, and the B-ring projects from the 6-OH face. Similar results were reported by using the molecular docking routine and supported by NMR experimental observations [5,13].

For each equilibrium structure, the statistical thermodynamic calculation was performed at 298.15 K at 1 atm. Results are presented in Table 1. From Table 1, we can be seen that the complexation reactions of CA with β-CD are exothermic judged from the negative enthalpy changes. And the negative enthalpy changes suggest that both the inclusion processes are enthalpically favorable in nature. On the other hand, the enthalpy changes for the R_{out} orientation are more negative than for the R_{in} orientation, which is surely attributed to the more tightly van der Waals interactions. The thermodynamic results indicate that the R_{out} structure should be preferred based both on energetic and enthalpy grounds, being the R_{out} complex in perfect agreement with the experimentally proposed structure for the β-CD/CA complexation at the normal pressure and room temperature.

An interesting feature of the chosen guests is conformational flexibility. This flexibility can favor the host–guest interaction as the guest can modify its conformation to ensure a better penetration. The influence of the flexibility of the guest on increasing the stability of CD complexes was previously discussed by Rekharschy and Inoue [25]. They stated that flexibility enhanced the complexation entropy since ‘‘more possible conformers can fit properly into the cavity’’. Conformational flexibility of the CA molecule includes the

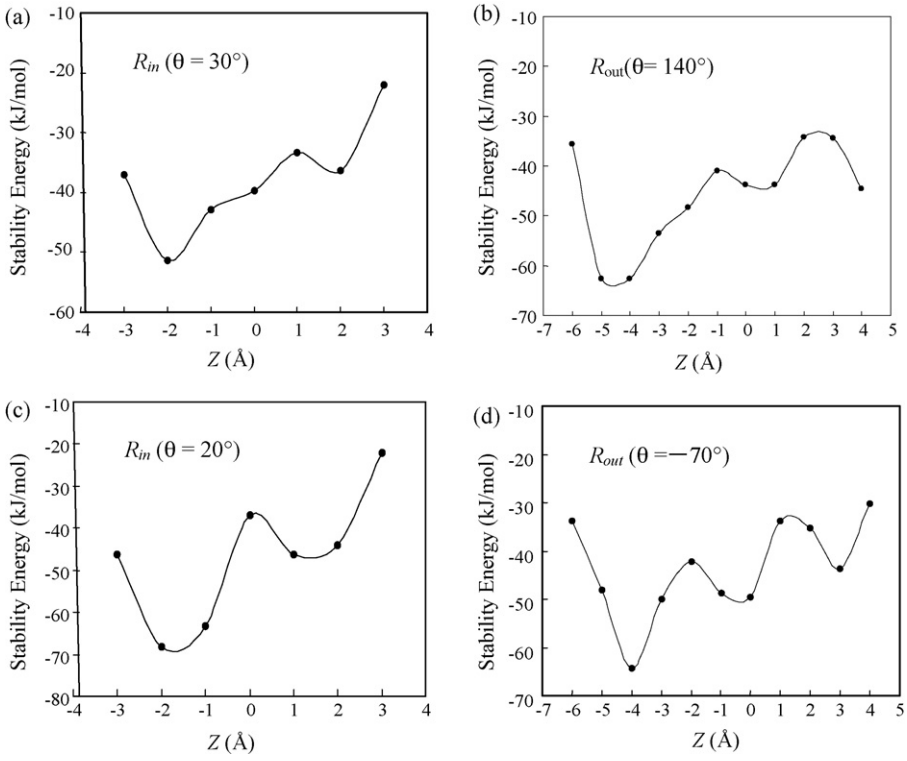

Fig. 3. Stability energies of the inclusion complexation of the guests into β-CD at different positions (Z) and orientations: (a) R_{in} for β-CD/CA complexes; (b) R_{out} for β-CD/CA complexes; (c) R_{in} for β-CD/EC complexes; (d) R_{out} for β-CD/EC complexes. The position of the guest was determined by the Z-coordinate of the labeled carbon atom (*) in the phenyl group from the center of the glycosidic oxygens. θ is the angles with each guest molecule circling around the Z-axis of the system.

Table 1
The binding energy and thermodynamic characteristics upon the inclusion complexation of β-CD with CA or EC by the PM3 methods

Species	β-CD/CA		β-CD/EC	
	R_{in}	R_{out}	R_{in}	R_{out}
PM3				
E[a] (kJ mol^{-1})	−7029.63	−7040.98	−7046.95	−7042.93
BE[a] (kJ mol^{-1})	−51.38	−62.74	−68.23	−64.21
DEF[a] [G] (kJ mol^{-1})	2.23	1.51	2.11	1.97
ΔH° (kJ mol^{-1})	−36.03	−55.06	−59.07	−56.66
ΔG° (kJ mol^{-1})	33.23	28.83	22.04	24.69
ΔS° (J mol^{-1} K^{-1})	−232.32	−281.39	−272.03	−272.86
B3LYP/6-3 1G*(in vacuo)				
E[a] (kJ mol^{-1})	−13931924.08	−13931952.22	−13931939.40	−13931924.18
BE[a] (kJ mol^{-1})	21.63	−6.51	−0.27	14.95
HF/6-31G* (in vacuo)				
E[a] (kJ mol^{-1})	−13853063.26	−13853082.95	−13853064.22	−13853047.05
BE[a] (kJ mol^{-1})	65.97	50.28	60.96	77.83

[a] E is the HF energy based on various methods, DEF is the deformation energy, BE is the binding energy upon complex, BE = $E[C]_{opt} - E[G]_{opt} - E[CD]_{opt}$.

orientation of the linkage between ring B and ring C, and the puckering of the pyran ring (C ring). Investigation of the deformation energy of the guest by PM3 methods (as shown in Table 1), interestingly, demonstrated that the CA molecule for R_{in} orientation requires slightly more energy for conformation adaptation upon binding within the cavity of β-CD than that of the R_{out} orientation as indicated by the DEF[G] of about 2.23 and 1.51 kJ mol^{-1}, respectively.

The optimized geometries for both models, R_{in} and R_{out}, of the inclusion complexes are presented in Fig. 4. The binding geometry in the two complexes is different, but it is affected in both by numerous host–guest C–H···O interactions, resulting from induced fits of the hosts toward the guests. Starikov et al. have found structural evidence for C–H···O hydrogen bonding in a number of CD inclusion complexes, and confirmed that the C–H···O bond energies were around 2–8 kJ mol^{-1} depending

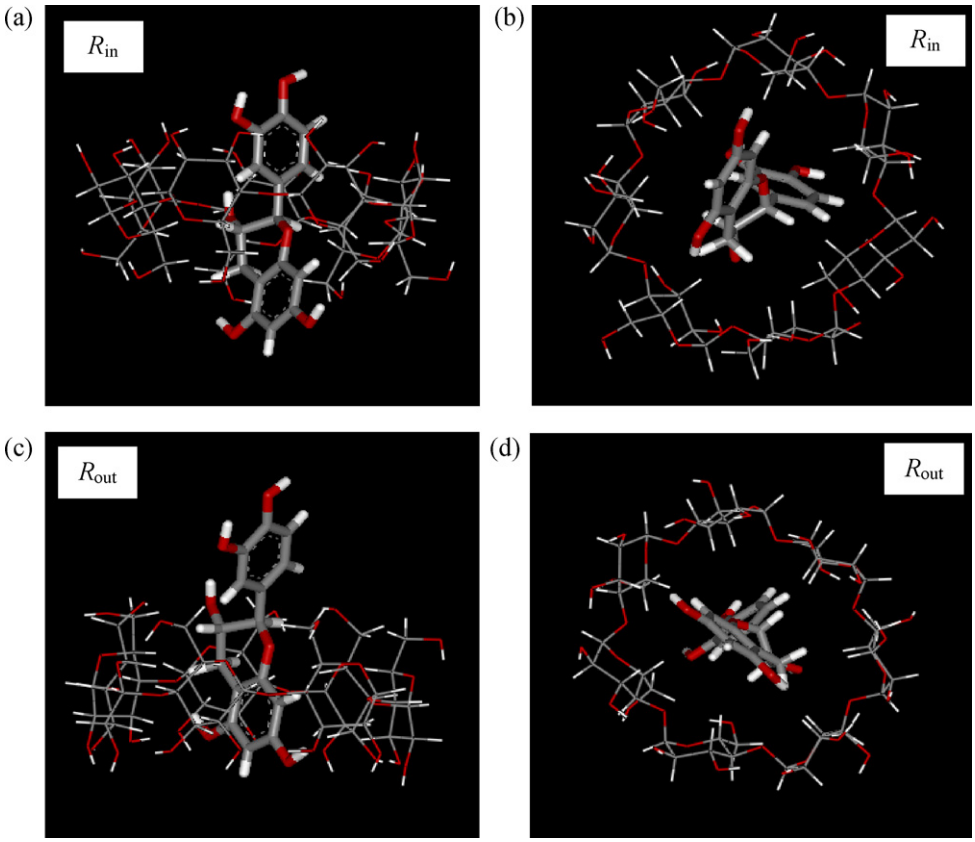

Fig. 4. Energy-minimized structure obtained by PM3 calculations for the β-CD/CA complexes. (a) R_{in} seen from the side of the β-CD wall; (b) R_{in} seen from the primary hydroxyl rim of the β-CD cavity; (c) R_{out} seen from the side of the β-CD wall; (d) R_{out} seen from the secondary hydroxyl rim of the β-CD cavity.

on the nature of the C–H donor [26,27]. Quantum mechanical calculations have been performed to determine the energetics of the C–H···O bonds in the complexes of small molecules, which are far below values of conventional hydrogen bonding (16–25 kJ mol^{-1} for O–H···O hydrogen bonds in carbohydrates) [28], but appreciably above energies of van der Waals contacts. The detailed intermolecular hydrogen bonds interaction for the two inclusion complexes are listed in Table 2 and shown in Fig. 5 as dotted lines. From Table 2, we see that the number of intermolecular hydrogen-bond interactions correlates with the orientation of the guest molecule. In the R_{in} structure, the B-ring of CA projects onto the 2-OH/3-OH face of β-CD, and the A-ring projects from the 6-OH face. There are four short host–guest C–H–O interactions: two C(5)H groups of the inner cavity lining donate hydrogen bonds ($d_{H\cdots O}$ = 2.61 and 2.49 Å, respectively) to O(3)H of CA, and the CA molecule accepts two C–H···O bond from C(6)H group and C(3)H group ($d_{H\cdots O}$ = 2.73 and 2.75 Å) located on the rim of β-CD. Five C–H···O bonds are formed in the R_{out} complex: CA accepts four C–H···O hydrogen bonds from C(3)H, C(5)H and C(6)H donors, respectively. Besides the hydroxyl of CA, the C(3)H atom of CA donates one hydrogen bond ($d_{H\cdots O}$ = 2.61 Å) to O(6)H of β-CD. It was suggested that the contribution of the C–H···O interactions to the structural stability is more substantial in R_{out} orientations than in R_{in} orientations. Unexpectedly, the optimized geometries reveal that there is no O–H···O hydrogen bond interactions between β-CD and the guests examined here as described in the systematic docking studies [13]. These observations clearly show that, numerous C–H···O hydrogen bonds are formed. The resulting host–guest interactions therefore comprise a third significant component besides the O–H···O hydrogen bonds and the van der Waals contacts.

Table 2
Geometric parameters of the D–H···A host–guest contacts with $d_{H\cdots O} < 3.0$ Å and $\alpha_{C-H\cdots O} > 90^\circ$ by quantum chemical calculations

Contact	H···A	D···A	D-H···A
β-CD/CA			
R_{in}			
C-6-H···O-7-H	2.73	3.54	129.4
C-5-H···O-3-H	2.61	3.63	144.3
C-5-H···O-3-H	2.49	3.46	124.1
C-3-H···O-3′-H	2.75	3.63	135.3
R_{out}			
C-3-H···O-7-H	2.62	3.75	174.6
C-3-H···O-5-H	2.47	3.58	169.0
C-5-H···O-3-H	2.92	3.78	128.3
H-6-0···H-3-C	2.60	3.61	149.1
C-6-H···O-3′-H	2.72	3.65	141.6
β-CD/EC			
R_{in}			
C-5-H···O-5-H	2.73	3.62	134.6
C-3-H···O-3-H	2.76	3.86	164.5
H-6-O···H-7-O	1.82	2.75	160.9
R_{out}			
C-3-H···O-7-H	2.68	3.70	150.2
C-3-H···O-5-H	2.49	3.62	176.4
H-6-O···H-3-C	2.70	3.76	157.2

O···O distances <3.2 Å suggestive of O–H···O hydrogen bonding between guest molecules are also given.

3.2. Structure of the β-CD/EC inclusion complex

Fig. 3 depicts BE for the EC inclusion in β-CD. Complexation with both orientations is energetically favorable. The most stable structure is reached at approximately $Z = -2$ Å ($\theta = 20^\circ$) and $Z = -4$ Å ($\theta = -70^\circ$) for the EC for the R_{in} and R_{out} approaches, respectively. EC totally penetrates into the CD cavity in both structures. The quantum mechanical PM3 calculations show that the R_{in} orientation is preferred by 4.02 kJ mol^{-1} with respect to the R_{out} orientation. It is thus difficult to choose between the preferential approaches (R_{in} or R_{out}) of the guest, the BE energies being almost similar. These results suggest that PM3 calculations cannot allow for establishing the preferential ways of the guests penetrating the CD cavity, and these two orientations are all possible structures of the β-CD/EC inclusion complex. Judging from the 1H NMR spectra and Corey–Pauling–Koltun (CPK) atomic models, Ishizu et al. [5] reported previously two possible β-CD/EC inclusion modes, R_{in} and R_{out}. In this study, the structure of the β-CD/EC inclusion complex was made more clear by using PM3 methods. But, the BE values computed in vacuo with the HF and DFT method are positive. This does not necessarily 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*. It is also suggested that the PM3 method is a powerful technique which can be currently applied to study host–guest complexes between β-CD and CA or EC. The same results are also obtained with the statistical thermodynamic calculation at 1 atm and 298.15 K in vacuo by PM3, in which the enthalpy change, the thermal Gibbs free energy (AG) and entropy contribution (ΔS) do not show large gap, and the energy difference becomes 2.41, 2.65 and 0.83 kJ mol^{-1}, respectively. The deformation energy values of EC are reported in Table 1. The energies found for both R_{in} and R_{out} models are practically the same as indicated by the DEF[G] of about 2.11 and 1.97 kJ mol^{-1}, respectively. It revealed that these two complexes require almost the same energy for conformation adaptation to its bound pocket. The proposed favorable structures are graphically presented in Fig. 6. Our results show that upon the β-CD/EC inclusion complex formation, the B ring of EC is included deeply in the β-CD cavity from the wide secondary hydroxyl group to form the inclusion mode R_{in} (Fig. 6). The B and C rings of EC did not incline to the molecular axis of β-CD, but were positioned at the center of the cavity along the molecular axis of β-CD in order to avoid the steric hindrance and the hydrophilic character due to the axial 3-OH group of EC. As shown in Table 2 and Fig. 5, a strong O–H···O hydrogen bond ($d_{O\cdots O}$ = 2.75 Å) between O-6 of CD and O-7 of the A-ring is predicted to occur in R_{in} modes. At the same time, EC accept two C–H···O hydrogen bonds from C(3)H and C(5)H donors in the large, hydrophilic face of the β-CD. In the R_{out} complex, three C–H···O hydrogen bonds are formed: one –CH group of the pyran

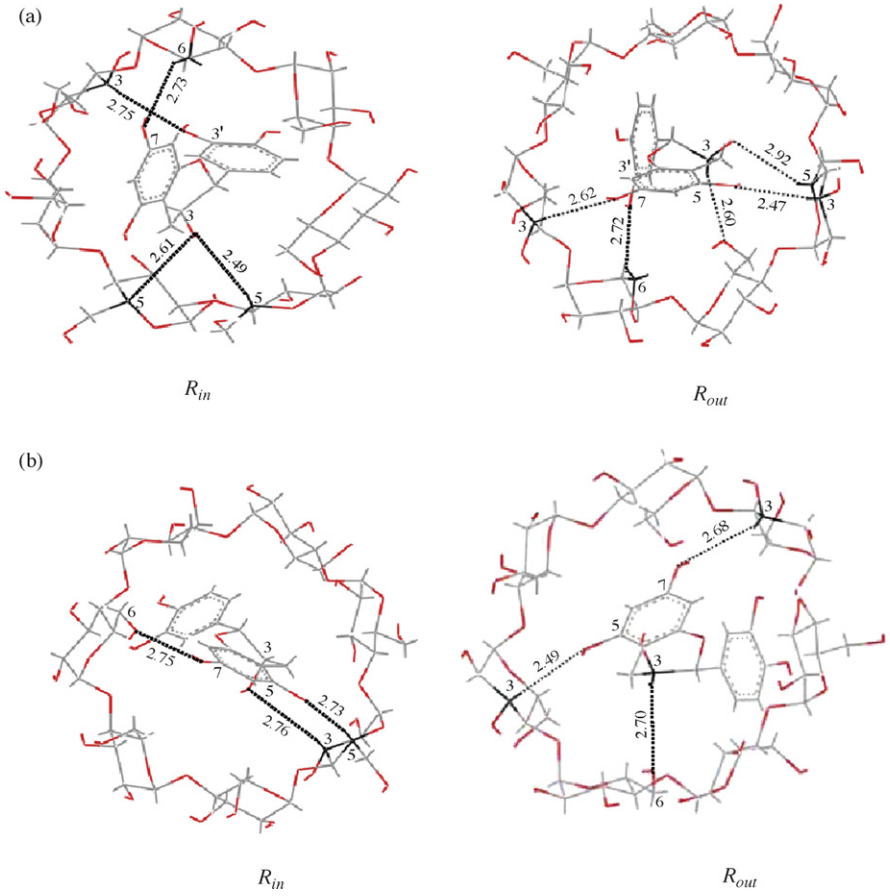

Fig. 5. Host–guest C–H···O interactions in β-CD inclusion complex. (a) β-CD/CA complexes; (b) β-CD/EC complexes. Dotted lines are C–H···O hydrogen bonds with $d_{H\cdots O} < 3.0$ Å, and the C–H groups forming C–H···O bonds are drawn with dark color.

ring (C-3-H atom) close to H-6-O of a glucopyranose unit, the distances of H···O was 2.70 Å. Two C–H···O hydrogen bonds are displayed between C-3-H and O-7 or O-5 of the A-ring, and $d_{O\cdots O}$ is 2.68 and 2.49 Å, respectively. So intermolecular hydrogen bonds also play a pivotal role for this conformational exchange.

3.3. Comparison of complexations to form β-CD/CA and β-CD/EC

Insights into the structural parameters of CD complexes can be obtained by analyzing the predicted binding energy for optimized CDs-guest complexes obtained from molecular quantum calculations and comparing host–guest interaction. The negative BE changes upon complexation clearly demonstrate that β-CD can form stable complexes with CA and EC, which is observed in the experiments. It can also be seen that the β-CD/EC inclusion was significantly more favorable than the β-CD/CA inclusion by a negligible energy difference of -16.85 kJ mol^{-1} (R_{in}) and -1.47 kJ mol^{-1} (R_{out}), respectively. This suggests that EC fits tightly with β-CD based on the PM3 calculation. It seems to contradict the experimental findings according to the evaluation of the affinity constant. Ishizu et al. [5] thought that CA fits tightly with β-CD because of smaller steric hindrance from the equatorial 3-OH group of CA than that from the axial 3-OH group of EC. The results may be that our calculations were carried out in a vacuum, and solvation effects were not considered. However, the obtained results are qualitatively useful. In a previous study of ours [18], we theoretically studied β-CD/quercetin system using PM3 methods and found that it can form complexes with β-CD with a less favorable energy as compared with β-CD and CA or EC complexes. This may be contributed to the puckers of C-ring of CA or EC. Considering structural and BE information of the complex structures, it can be suggested that the β-CD/CA or β-CD/EC complexation enhances favorable contacts (van der Waals interaction and hydrogen bond interaction) of the C ring of the guest, increasing the stability of guest binding.

In β-CD/CA or EC inclusion complexes, numerous host–guest C–H···O hydrogen bonds are observed. These can be donated not only by –CH_2 and –CH groups of the inner cavity lining of β-CD to guest molecules but also from a guest to O atom of a glucopyranose unit in the face of β-CD. Although they are weak, we consider the C–H···O bonds as a third, direct cohesive host–guest interaction besides van der Waals contacts and O–H···O hydrogen bonds, and they will contribute to the overall stability and structure of the inclusion complexes of the CDs. The enantiospecificity exhibited by the described systems reveals the subtle differences of the weak intermolecular forces involved in the selective binding of the two optical antipodes by the two hosts. The binding geometry in the two complexes is

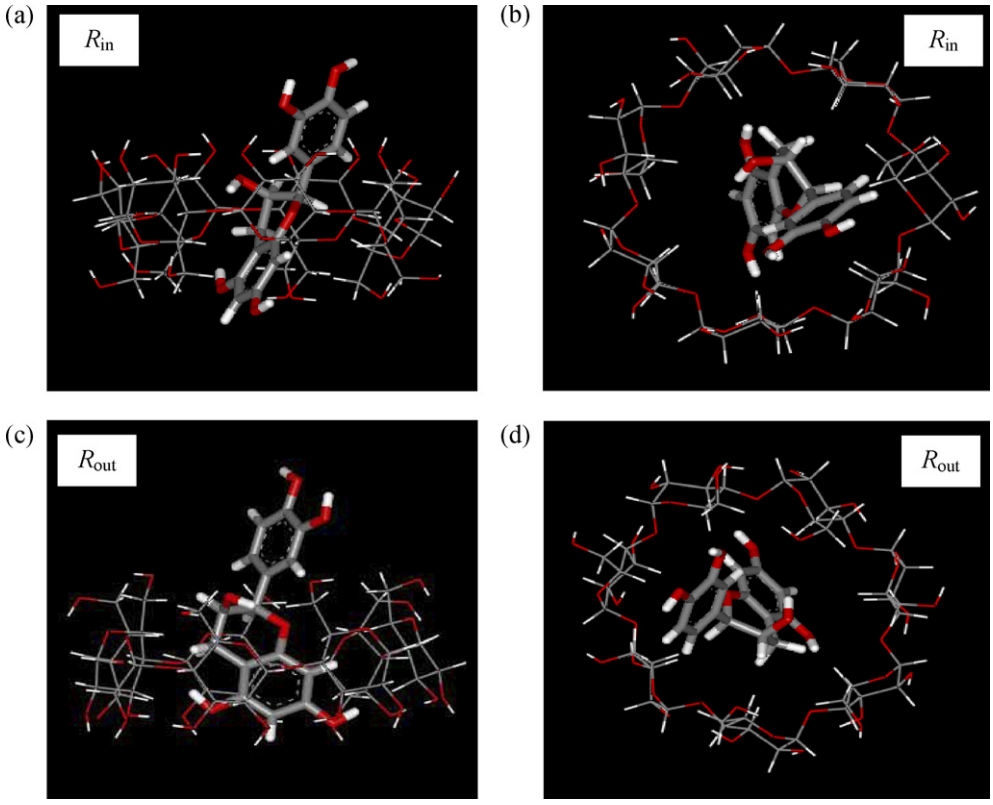

Fig. 6. Energy-minimized structure obtained by PM3 calculations for the β-CD/EC complexes. (a) R_{in} seen from the side of the β-CD wall; (b) R_{in} seen from the secondary hydroxyl rim of the β-CD cavity; (c) R_{out} seen from the side of the β-CD wall; (d) R_{out} seen from the primary hydroxyl rim of the β-CD cavity.

different, but it is affected in both by numerous host–guest C–H···O interactions, resulting from induced fit of the hosts toward each of the enantiomeric guests. Alvira et al. [29] thought that the intermolecular forces responsible for complexation of equol, a chiral molecule, with β-CD establishes a difference between the most stable position of R- and S-equol and hence between their energies. The differential interactions between each enantiomer and the chiral host give rise to different configurations for the corresponding inclusion complexes which give rise to enantiodifferentiation.

3.4. Possible solvent effects on complex stability and hydrogen bond formation

Even though the present calculation does not consider solvent effects, one can postulate possible effects of solvents on the complex. In the 1:1 complex, the four phenolic hydroxyl groups of the A and B rings of CA or EC are left out of the hydrophobic cavity of β-CD because of their hydrophilic characters. On the other hand, 3-OH group of CA or EC is included deeply in the β-CD cavity, and less exposed to solvent molecules. Hence, the 3-OH group of CA or EC in 1:1 complex is much less likely to be affected by solvent molecules than other phenolic hydroxyl groups of CA or EC in the 1:1 complex. Although it was often believed that the geometry of CD inclusion complexes in the crystal lattice reflects their solution structure reasonably well, the binding mode in solution may be different with that in the solid state. Molecular modeling calculations combined with conformational NMR studies confirmed that CA adopts a mixture of A- (with B-ring in a pseudoequatorial position) and *E*-conformers (with B-ring in a pseudoaxial position) in aqueous solution [30]. A very recent NMR study [13] indicated that in aqueous solution two configurations are possible in a 1:1 β-CD/CA complex, which the more extended E-shape may be favored in aqueous solution due to interactions between the hydroxyls of the A-ring and water molecules. Thus, studies on β-CD/CA or EC complexes in solution based on the molecular modeling method must be performed in the future.

4. Conclusions

In this work, we attempt to provide information on the structure of the complexes between (+)-catechin (CA) or (−)-epicatechin (EC) to β-CD using the semiempirical PM3 methods. The orientation in which the B-ring of the guest molecule located near the primary hydroxyls of the β-CD is preferred according to the binding energies in β-CD/CA complexation. The B-ring inclusion from either the secondary hydroxyl group side or the primary hydroxyl group side seems to be the two most probable complex of β-CD/EC. The optimized structures for the CA complexes with β-CD indicate that more defined complexes are formed with CA than with EC. The intermolecular forces responsible for holding the host–guest complex together are primarily weak intermolecular C–H···O interactions, revealing the subtle differences in the binding geometries in the two complexes.

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