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Theoretical Study of the Inclusion Processes of Ibuprofen Enantiomers with Native and Modified β-CDs

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Abstract

PM3 calculations in vacuum were performed on the inclusion complexation of β-cyclodextrin (β-CD), heptakis-(2-O-methyl)-β-cyclodextrin (2-Me-β-CD) and heptakis-(6-O-methyl)-β-cyclodextrin (6-Me-β-CD) with ibuprofen (IB) enantiomers. Inclusion process pathways are described and the most probable structure of the 1:1 complex are sought through a potential energy scan. The energy differences between the inclusion complexes and the hosts (native and modified CDs) by calculation show that modified CDs have much more interaction sites with IB and enhance van der Waals interaction and hydrophobic interaction between them, form more stable complexes than native CD does. Stabilization energies of S-IB complexes are higher than that of R-IB complexes both for native and modified CDs.

Introduction

α-, β-, and γ-cyclodextrins are cyclic oligosaccharides consisting of six, seven, and eight glucose units respectively. These compounds, usually characterized as a doughnut or Wreath-Shaped truncated cones with a hydrophobic cavity [1]. They have been widely used as host molecules because of their properties, such as their solubility in water and the cavity created by the rim of oxygen atoms in the glycosidic function [2, 3]. In recent years, they have been subjected to diverse modifications to give wide variety of CD derivatives [4–6]. A variety of CD derivatives have been synthesized in order to modify or enhance the original molecular recognition property of the native CDs. These modified CDs have been widely used, for example, as enzyme mimics, supramolecular receptors and chiral selectors in separation science and technology [7].

Ibuprofen (IB) [8] whose chemical name is D, L-2 (4-isobutylphenyl) propionic acid, is an anti-inflammatory, antipyretic, analgesic drug, widely used in the treatment of arthritis to study the absorption metabolism and excretion of IB. IB shows bad dissolvability in water because of its hydrophobic structure. However, a rapid drug release is preferable, especially for analgesic drugs. Formation of inclusion complexes with CDs can improve the dissolvability of IB. The complexes of IB with native CD and modified CD have been reported [9]. That is the reason we choose IB as guest.

Intensive theoretical works have been performed over the past few years on CDs [10–14]. Most computational studies of CDs involve host–guest complexation, their structures, energies, preferred bonding orientations, and so on, are typically calculated. Early quantum calculations were performed with semi-empirical CNDO methods [15, 16], followed by several semi-empirical quantum calculations, e.g., molecular mechanics (MM) [17–21] and molecular dynamics (MD) [22, 23] with various force field approaches. Recently, at a higher level of quantum calculations, *ab initio* methods at the Hartree–Fock or the density functional theory levels with a minimal basis set were carried out [24, 25]. Calculations are useful for a better understanding of such inclusion processes of CDs. The calculations can strengthen and supply the conclusion from the experiment, and vice versa. However, most of research works focused on the host–guest complexes of native CDs and few have been concerned with the modified CDs so far [26, 27].

In this paper, the semi-empirical PM3 method has been applied to study the inclusion processes of IB enantiomers in β-CD, heptakis-(2-O-methyl)-β-cyclodextrin (2-Me-β-CD) [28] and heptakis-(6-O-methyl)-β-cyclodextrin (6-Me-β-CD) [28], in order to provide further insight into the different complexation properties of IB enantiomers into native and modified β-CDs. The inclusion processes, the geometry of complexes, and the energy differences are computed. This proved the significance of modified CDs in molecular recognition.

Calculation and methodology

The complexation processes of various CDs with IB were studied by using PM3 semi-empirical method (PM3). PM3

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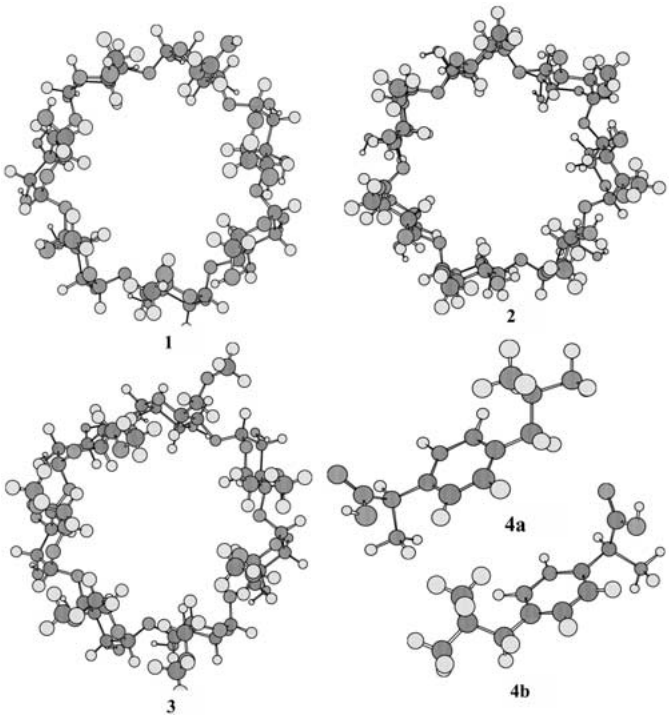

Figure 1. The structures of β-CD(**1**), 2-Me-β-CD(**2**), 6-Me-β-CD(**3**) and IB enantiomers(R- IB (**4a**) , S- IB (**4b**)).

has highly computational efficiency that permits the modeling of large systems beyond the capacity of *ab initio* methods. The precision is comparable to that of *ab initio* with medium-sized basis sets. PM3 also performs better than AM1 in biochemical systems due to its improved description of the interaction between non-bonded atoms. Compared with an AM1-optimized CD, the MM-optimized CD was found far from stable [29]. Hence, it is convenient to choose PM3 method to calculate our systems.

Semi-empirical quantum calculations with the use of PM3 method are performed with the aim to reproduce the potential energy scan of the inclusion processes. The initial structure of β-CD constructed with the help of X-ray crystallographic data [30]. Methyl group was added at the 2- or 6-positions of β-CD. The geometry of β-CD, modified β-CDs, and IB enantiomers were fully optimized with PM3 methods. Their structures are shown in Figure 1.

The coordinate of the inclusion process is situated by the distance between a dummy atom located at the center of the glycosidic oxygen atoms of theβ-CD and a second dummy atom located at the center of benzene is illustrated in Figure 2. The secondary hydroxyl groups ofβ-CD were placed pointing toward the positive Z-axis. The inclusion complexation was emulated by entering the guest molecule from one end of β-CD and then letting it pass through the host molecule in steps. In each step, the geometry of the complex was fully optimized by PM3 without any restriction. Two possible complexation orientations were considered. For simplicity, the orientation in which the carboxyl of IB points toward the primary hydroxyls of the β-CD was called head down, while the other in which carboxyl points toward the secondary hydroxyls of the β-CD was named head up.

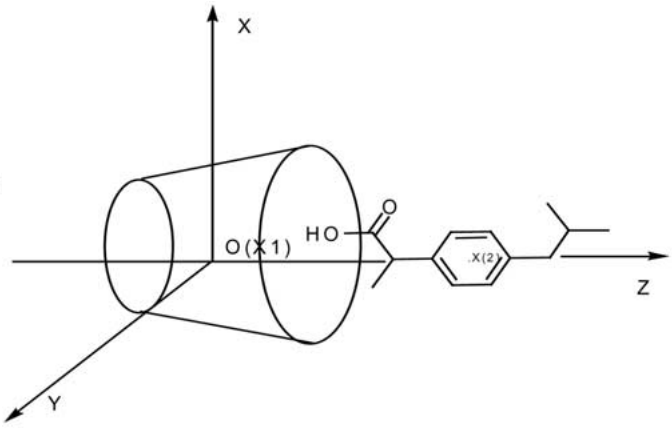

Figure 2. Coordinate system used to define the process of complexation β-CD with R/S-IB.

Results and discussion

The penetrations of IB enantiomers in cavity of CDs were studied. The results are summarized in Figure 3, Figure 4 and Table 1. Figure 3 depicts the stabilization energy variation of the inclusion processes of R- and S-IB into native and modified-CDs at different distances. Such results suggest that the penetration from the secondary face needs probably more energy to overcome the energy barrier and the penetration pathway predicts two penetration levels. The energy variation involved in the inclusion emulation indicates that the complexes prefer to adopt inclusion geometry with the guest inside the host cavity, in order to increase the van der Waals attraction, dipole–dipole interaction, hydrophobic interaction and hydrogen-bonding interaction between host and guest.

Deferent complexation orientations of native and modified β-CDs have different stabilities (Figure 3). The head-down orientations of native β-CD and 2-Me-β-CD were more favorable than the head-up ones. This agrees with the viewpoint that the anti-parallel arrangement of the dipoles of the host and guest molecules was preferable in CD complexation [31]. The unexpected orientation of 6-Me-β-CD was probably caused by van der Waals interaction and hydrophobic interaction between host and guest, when iso-butyl group located at the narrower rim, which means that there is significant van der Waals interaction and hydrophobic interaction. Hence, to 6-Me-β-CD the head-up orientation is more stable.

Figure 4 shows the energy minimum structures of both the head-down and -up orientations, which can be explicitly understood that IB have been included into the cavities of native and modified CDs.

It can also be found by the energy change in the course of inclusion that modified CDs also seem to show better complex behavior and greater potential in the formulation of complexes than native CD. In order to provide further insight into it, we calculated the stabilization energy difference (ΔE) between the complexes and their original compounds, and also the energy difference ($\Delta\Delta$E) between R-IB and S-IB complexes.

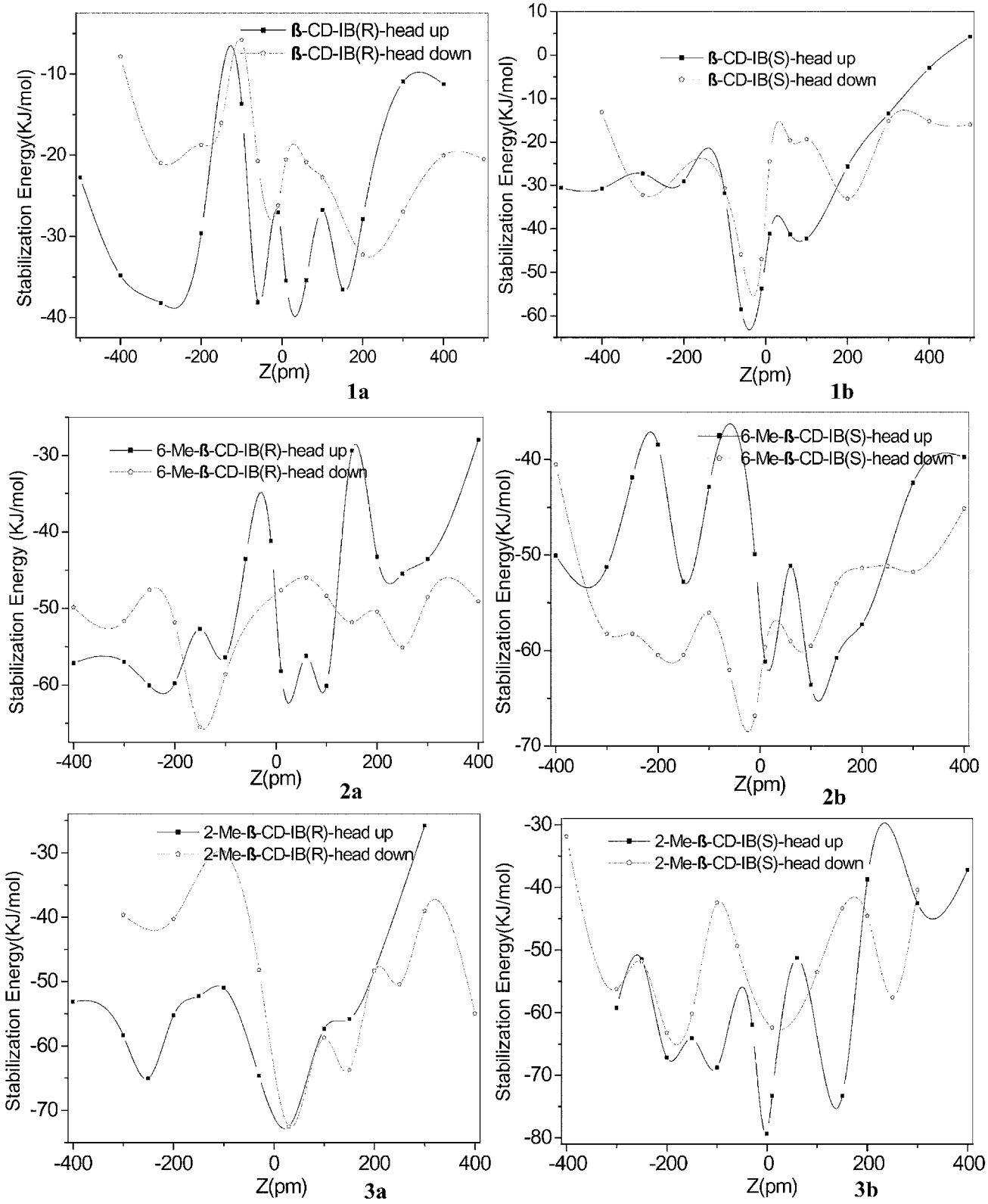

Figure 3. Graphic for the emulation of the inclusion complexation of IB enantiomers into β-CD, 2-Me-β-CD and 6-Me-β-CD cavity. The position of the guest was determined by the Z coordinate of the dummy atom in the center of phenyl. R-IB penetrate β-CD from two sides (**1a**), and S-IB penetrates β-CD from two sides (**1b**). R-IB penetrates 2-Me-β-CD from two sides (**2a**), and S-IB penetrates 2-Me-β-CD from two sides (**2b**). R-IB penetrates 6-Me-β-CD from two sides (**3a**), and S-IB penetrates 6-Me-β-CD from two sides (**3b**).

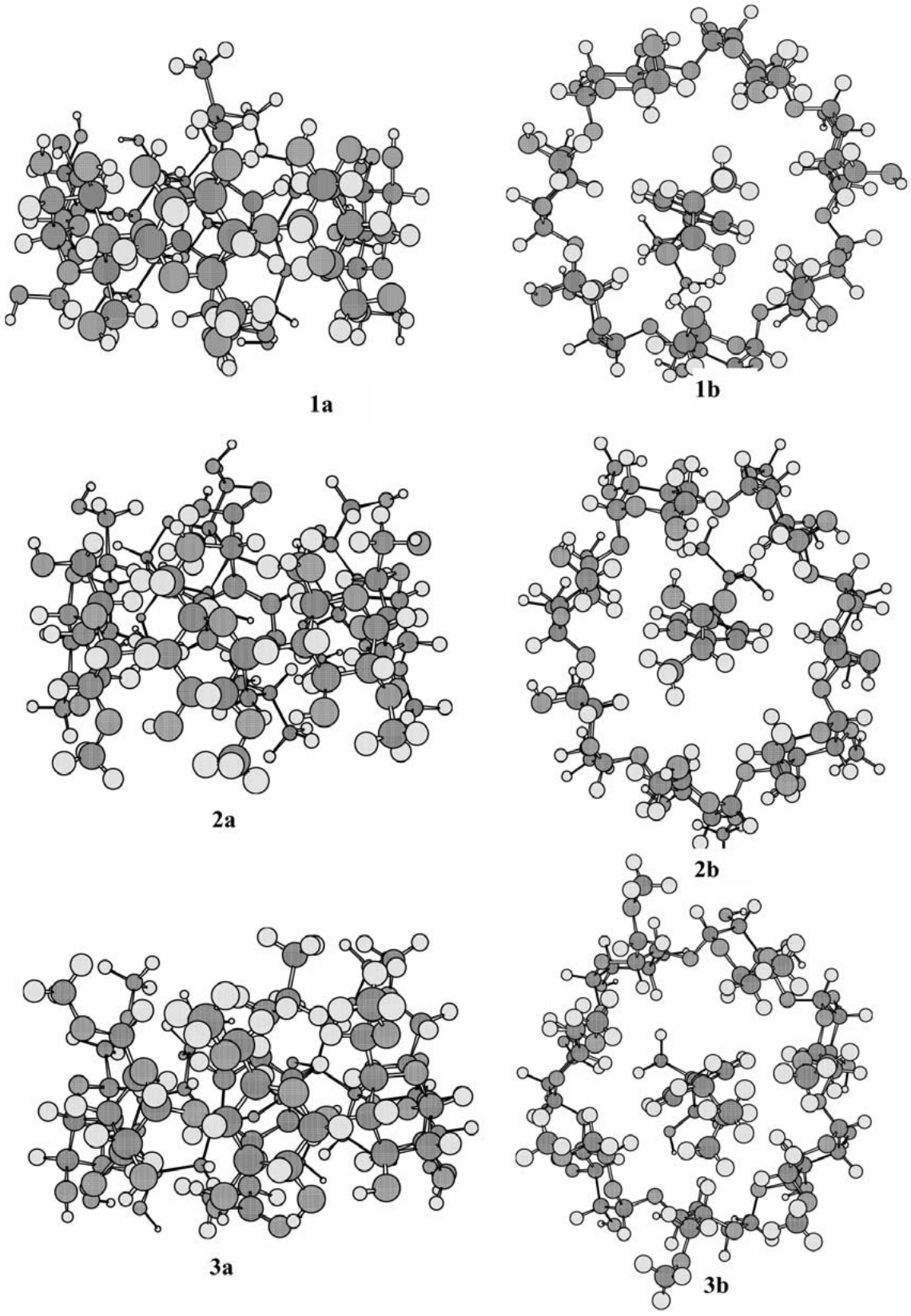

Figure 4. Structures of the energy minimum obtained by the PM3 calculation for complexation of IB enantiomers with β-CD, 2-Me-β-CD and 6-Me-β-CD. S-IB with β-CD from the sides of the β-CD wall (**1a**) and S-IB with β-CD from the sides of the primary hydroxyl rim of the β-CD cavity (**1b**). S-IB with 2-Me-β-CD from the sides of the β-CD wall (**2a**) and S-IB with 2-Me-β-CD from the sides of the primary hydroxyl rim of the β-CD cavity (**2b**). S-IB with 6-Me-β-CD from the sides of the β-CD wall (**3a**) and S-IB with 6-Me-β-CD from the sides of the primary hydroxyl rim of the β-CD cavity (**3b**).

Table 1. Energies of the inclusion complexes of IB enantiomers with β-CD, 2-Me-β-CD, and 6-Me-β-CD.

Species	Heat of formation (kJ/mol)	Stabilization energy upon complexation (kJ/mol) ΔE	$\Delta\ \Delta E = \Delta E_R - \Delta E_S$ (kJ/mol)
IB (R)	−421.1	–	–
IB (S)	−421.1	–	–
β-CD	−6046.9	–	–
β-CD+IB (R)	−6085.1	−38.2	20.2
β-CD+IB (S)	−6105.4	−58.5	
2-Me-β-CD	−5779.3	–	–
2-Me-β-CD+IB (R)	−6272.6	−72.5	6.9
2-Me-β-CD+IB (S)	−6279.5	−79.4	
6-Me-β-CD	−5908.0	–	–
6-Me-β-CD+IB (R)	−6389.2	−60.1	3.5
6-Me-β-CD+IB (S)	−6392.7	−63.6	

All minima obtained in the different potential energy curves of the penetration process are summarized in Table 1. It has been noted that the van der Waals interaction, steric crowding, hydrogen-bonding interaction and hydrophobic interaction contribute most to the stabilization in the complexes [32]. Table 1 shows that modified β-CD can form more stable complexes than β-CD itself, because modified CDs have much more interaction sites with IB and enhance the interaction between host and guest. It agrees with the experimental results [9], the substituent methyl groups expand the hydrophobic region by capping the cavity and increase substrate bonding via a hydrophobic effect [33]. For modified CDs, the number, size and position of substituent groups have much more effects on complexes stabilization, the bigger (more) the substituent groups are, the more steric crowding is. Hence, 6-methyl have stronger steric crowding than 2-methyl, the stabilization energy upon complexation of 6-Me-β-CD is lower than 2-Me-β-CD, it agrees with the results shown in Table 1. The different interaction between chiral cavity of β-CD and IB enantiomers make the stability of complexes different, it has been used in chiral separation of IB [34]. It is also shown in Table 1 that stabilization energy (ΔE) of β-CD-S-IB is higher than that of β-CD-R-IB, the difference is about 20kJ/mol. The same with modified CDs, the $\Delta\ \Delta$E ($\Delta\Delta E = \Delta E_R - \Delta E_S$) of 2-Me-β-CD-IB is 7 kJ/mol and 6-Me-β-CD-IB is 3.5 kJ/mol, lower than those of native CD with IB enantiomers. The energy difference between enantiomer complexes suggests the strong attraction of modified CD with IB, making the $\Delta\Delta$E smaller than that of native CD. Hence, the substituent group of CD has strong effect on the stability of the complexes.

Conclusion

The semi-empirical PM3 method is suitable to calculate the more stable structures and inclusion processes for R- and S-IB with β-CD and modified β-CDs. The orientation geometry of inclusion complexes of IB enantiomers with native and modified β-CD is predicted with this method. The energy differences for the complexes indicate that methyl modified CDs can form more stable complexes than native CD. The result is in good agreement with the literature [9]. Complexes of S-IB with native and modified CDs are more stable than R-IB complexes. The largest energy difference ($\Delta\Delta E = \Delta E_R - \Delta E_S$) was found between β-CD-IB systems. In the present study, the solvent effect is not yet taken into account and this effect sometimes influences the interaction of the host and guest.

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