β-Cyclodextrin Inclusive Interaction Driven Separation of Organic Compounds

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A novel selective separation method for organic compounds, especially thermosensitive substances, has been proposed using unsubstituted β-cyclodextrin (β-CD) as a host and some alcohols and aldehydes as model guests in aqueous solution. The separation factors were evaluated from the extraction of an equimolar mixture of alcohol and aldehyde compounds. The inclusion equilibrium constants for several alcohols and aldehydes over β-CD have been calculated through their UV-vis spectra. The Gibbs free energy changes of β-CD/substrates complexes (ΔG) have been calculated combined B3LYP/6-31G(d)//ONIOM2(B3LYP/6-31G(d):PM3) with semicontinuum solvation model. The difference of Gibbs free energy changes (ΔΔG) for the inclusion complexes formed via the intermolecular weak interactions e.g., hydrogen bond and electrostatic interaction was the reason why alcohol and aldehyde compounds could be selectively separated. © 2010 American Institute of Chemical Engineers *AIChE J,* 57: 2341–2352, 2011
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Introduction

To get pure compound, separation is vital for organic synthesis, and separation methods are gathering continuous attention.[1] Traditional separation process e.g., distillation,[2] liquid membrane permeation,[3] chromatography,[4] and supercritical CO_2 extraction[5] are different from the methods based on molecular recognition that stresses interaction between host compounds (cyclodextrins, crown ethers, and calixarenes) and guest compounds (anions, cations, and neutral molecules).

As supramolecular host compounds, cyclodextrins (CDs) are directly obtained from starch by enzymatic digestion and purification. They are a series of natural cyclic oligosaccharides consisting of glucoside bonds.[6] With 6, 7, and 8 glucose units, CDs are usually called as α-, β-, and γ-CD, respectively. They all possess a hollow truncated cone with a nonpolar cavity and two hydrophilic rims containing hydroxyl groups. Because of its hydrophobic interior and hydrophilic exterior, CDs and their derivatives are well known to form inclusion complexes with many organic

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compounds.[7–9] CDs can form complex through two kinds of intermolecular interactions: (A) ''inner interaction,'' usually Van der Waals force, hydrophobic-lipophilic interaction and dispersion interaction etc. (B) ''external interaction,'' mainly hydrogen bond. These intermolecular interactions are helpful to obtain high affinity binding for hydrophobic guest.[10] Not only have CD derivatives been widely used as functional monomer in molecularly imprinting,[11] stationary phase in HPLC,[12] selectors for capillary electrophoretic,[13] selective extraction for some isomers,[14,15] but also have been applied for the separation of compounds with highly similar chemical structures, e.g., structural and optical isomers, in chromatography and capillary electrophoretic.[16] However, the CD derivatives used in these experiments have special structure, so they are expensive and only suitable for very small scale production.

With the rapid development of theoretical studies on supramolecular chemistry, theoretical methods have widely been employed for describing geometries and thermodynamic properties of such inclusion complexes.[17–21] Recently, hybrid ONIOM method that applies multiapproaches (QM/QM or QM/MM) to treat different parts of system simultaneously has captivated many researchers' interest and is effective to investigate the β-CD/guest inclusion processes.[22–24]

β-Cyclodextrin (β-CD) is the cheapest among the CD family, it can catalyze the substrate-selective oxidation of oxygen, sulfur and nitrogen-containing compounds in water,[25,26] and was able to selectively form inclusion complexes with these substrates, which was favorable for separating products from reactants, especially some thermosensitive materials. In this work, we applied β-CD for selective separation of several alcohols and aldehydes. PM3 and ONIOM2 methods were simultaneously employed to analyze intermolecular weak interactions between β-CD and hydrates of various aldehydes and alcohols (as shown in Figure 1), optimized structures of inclusion complexes, solvent effects on inclusion processes and mechanisms for selective separation. To the best of our knowledge, it was the first instance to use only β-CD for selective separation of some organic compounds with similar boiling points or chemical structures.

Experimental Method and Calculation Details

Extraction of single substrate

β-CD (1 mmol) was dissolved in 25 mL deionized water at 60°C, and 1 mmol substrate was added while stirring. When the solution was clear (after 1 h), it was cooled to 4°C and kept for 24 h and then centrifugated. The supernatant was extracted with ethyl acetate (50 mL) and the amount of substrate in extract was measured by GC with naphthalene as internal standard. This process was regarded as Process 1 and the obtained substrate in water phase was marked as P1.

The white precipitation was redissolved in 25 mL of deionized water at 60°C and extracted with ethyl acetate (50 mL). The amount of substrate in extract was measured by GC also with naphthalene as internal standard. This process was regarded as Process 2 and the obtained substrate in the inclusion complexes was marked as P2.

β-CD (1 mmol) was dissolved in 25 mL deionized water at 60°C and 1 mmol substrate was added while stirring. After 1 h, when the mixture was completely clear, it was directly extracted with ethyl acetate (50 mL). The amount of substrate in extract was measured by GC with naphthalene as an internal standard. This process was regarded as Process 3 and the obtained substrate was marked as P3.

All the extraction experiments were carried out for three times and the reproducibility for all the data was within 5%.

Measurement of inclusion equilibrium constants

A typical procedure for measurement of the inclusion equilibrium constant of benzyl alcohol on HITACHI U-3010 UV-vis spectrometer was as follows. First, the absorbance curve of β-CD (5.0 mmol/L) was measured within 190–650 nm at room temperature. The optimal detection wavelength was found to be 217 nm. Then, with β-CD (5.0 mmol/L) as reference, the absorbencies of different concentrations of benzyl alcohol (0.0, 0.5, 1.0, 2.0, and 3.0 mmol/L) have been measured. The corresponding absorbencies were found to be 0, 2.525, 2.806, 2.961, and 3.035, respectively.

The experiments for the binding constants measured were carried out in triplicate. Inclusion equilibrium constant data were averaged.

Extraction of two different substrates

β-CD (1 mmol) was dissolved in 25 mL deionized water at 60°C, and equimolar amounts of two different substrates (1 mmol) was added while stirring. P1, P2, and P3 for both substrates were measured as Process 1-3 described. The reproducibility for all the data was within 5%.

Extraction rate and separation factor

To illustrate selective separation of alcohols and aldehydes with the β-CD system, extraction rate and separation factor have been defined as:

Extraction rate (E) = P2/the total amount of substrate

Here the total amount of substrate was 1 mmol, hence E = P2.

Separation factor (K) = P2 of the substrate with higher P2/P2 of the other substrate.

If K was more than 1, it suggested that two different substrates could be separated. Generally, the greater K is, the better their separation. For two-component mixture (guest1 + guest2), it was considered that they have completely been separated when the content of a guest in another guest was less than 1%. Namely, to get a substrate with purity >99%, it would mean that

$$\frac{1}{K^n} \leq 1\% \tag{1}$$

Here K was separation factor, n was extraction steps.

Computational model

All calculations were performed with Gaussian 03 D.01 program.[27] β-CD was used as host, and different compounds e.g., benzyl alcohol, benzaldehyde, 1-phenyl ethanol, 2-phenyl ethanol and cinnamaldehyde were selected as model guests. The initial structures of β-CD and guests were

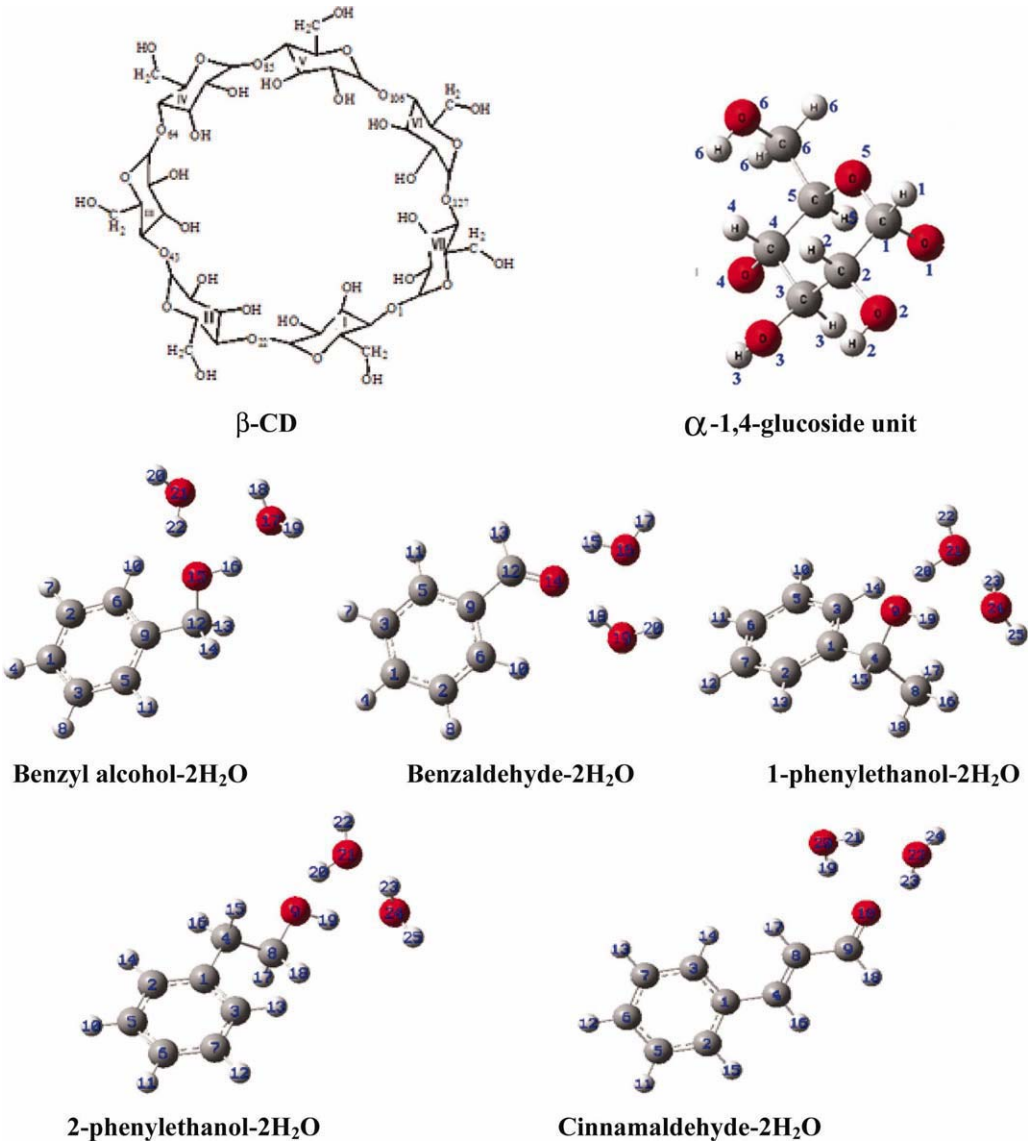

Figure 1. Molecular structures optimized by PM3 and atom number of β-CD, glucose unit connected via α-1, 4 bonds, and substrate-2H_2O hydrates.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

constructed using CS Chem3D Ultra (Version 8.0), and they were fully optimized using PM3 method without any symmetry constraint. Then, the models of inclusion complexes were built on the basis of PM3-optimized host and guests. The coordinate systems for describing the inclusion process of β-CD with guests were shown in Figure 2. The guests penetrating from the side of the primary hydroxyl groups was named 'head up' and penetrating from the side of the secondary hydroxyl groups was named 'head down'.

As reported in references,[28] the glycosidic oxygen atoms were placed onto the *XY* plane, their center was designated as the coordination origin, and the longer dimension of guests was placed onto the Z axis. The initial position of the guests in hydrophobic cavity was defined by *Z* coordinate of C* atom (Z_{C*}) in Figure 2, and the angle between plane of benzene ring and *XZ* plane was defined as the docked angle (θ). The inclusion processes of putting substrate or its hydrate through β-CD cavity were emulated by changing Z_{C*} from +8 to −6 (head up) or −8 to +6 (head down) at 1 interval, and by changing θ from 0 to 360° at 15° intervals.

For the global minima found, the geometries were optimized by two-layer ONIOM2 method (B3LYP/6-31G (d) for guest and PM3 for β-CD). The binding energy (BE_2) could be expressed as

$$BE_2 = E_{complex} - (E_{guest} + E_{host}) \quad (2)$$

$E_{complex}$ was the energy of complex, E_{guest} was the total energy of guests, and E_{host} was the total energy of host.

To obtain accurate computational results, explicit solvation model[29] and semicontinuum solvation model[30] (consisting of Onsager continuum solvation model and explicit solvation model) have been used to investigate solvent effects on binding energies of inclusion complexes. Here, the

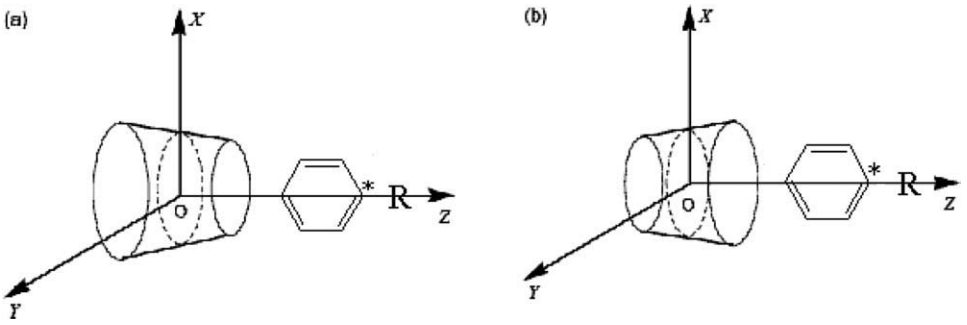

Figure 2. Coordinate systems for describing the inclusion process of β-CD with substrate or its hydrate: (a) head up (b) head down.

explicit solvation effect was considered by placing two water molecules (H_2Os) around aldehyde group or hydroxyl of substrates to create the hydrates.

Computational methods

The geometry structure of every point on the potential energy surface of the inclusion process was optimized by PM3 method, and multilocalized minima were found. For these localized minima obtained, θ was changed from 0 to 360° at 15° intervals to locate the global minima. To obtain more accurate results, the global minima were further reoptimized by hybrid ONIOM2 (B3LYP/ 6-31G(d): PM3) method.

Based on the optimized structure of ONIOM2, solvent effects have been investigated by Onsager continuum solvation model[31] on the level of B3LYP/6-31G(d). Zero point energy (ZPE) has also been calculated using B3LYP/6-31G(d) with a scale factor of 0.9614.[32] The binding energy, entropy, enthalpy and Gibbs free energies were calculated at 298.15 K and 1 atm.

Results and Discussion

β-CD inclusion separation owns some unique advantages e.g., (a) β-CD is water-soluble and its host-guest inclusion complexes are easily formed under mild conditions. (b) β-CD can selectively recognize and bind guests due to the size, rigidity and chirality of its hydrophobic cavity and different host-guest interactions, and the various inclusion complexes can be easily obtained with different affinity binding. (c) The interactions between β-CD and guest are fast and reversible, then the inclusion complexes can be redissolved in organic solvent and the guest can be re-released from the inclusion complexes to achieve selective separation.

Extraction rate of several alcohols and aldehydes

The strength of the interactions between β-CD and guests could be concluded via extraction results of alcohol or aldehyde from β-CD and their inclusion complexes. Table 1 showed the results for different alcohols and aldehydes.

According to the above description about Process 1, Process 2, and Process 3, P1 plus P2 should be equal to P3 in theory. However, because of the interactions between β-CD and guests, it made that P1 plus P2 was no more than P3. The greater the interaction, the smaller the extraction rate (P2). From Table 1, it could be found that some alcohols and aldehydes couldn't be extracted completely, which indicated that β-CD/guest inclusion complexes were formed and the host-guest interactions were different for different guests. To obtain the difference on extraction rate and the host-guest interactions, UV-vis spectra[33] have been used for measuring the inclusion equilibrium constants.

The relationship between extraction rate and inclusion equilibrium constant

If β-CD: guest complex was formed with 1: 1 stoichiometry, the inclusion of β-CD and guest could be expressed as

$$\mathrm{H} + \mathrm{G} \overset{K_a}{\rightleftharpoons} \mathrm{H-G} \tag{3}$$

According to Hildebrand- Benesi formula, the following equation could be concluded:

$$[\mathrm{H}]_0/\Delta\mathrm{A} = 1/K_a\Delta\varepsilon[\mathrm{G}]_0 + 1/\Delta\varepsilon \tag{4}$$

Here K_a was the inclusion equilibrium constant, $[G]_0$ was the concentration of guest, $[H]_0$ was the concentration of β-CD, ΔA was the changes of absorbance for the inclusion complex and $\Delta\varepsilon$ was extinction coefficient difference of β-CD before and after inclusion. By means of the linearity between $[H]_0/\Delta A$ and $1/[G]_0$, K_a and $\Delta\varepsilon$ could be calculated.

When the concentration of β-CD was given, the change of absorbance for different concentration of guests in the β-CD solution was recorded. From the aforementioned Eq. 4, $[H]_0/\Delta A$ had good linearity with the reciprocal concentration of the guest compound, which suggested β-CD/guest complex

Table 1. Extraction of Different Alcohols and Aldehydes

	Amount of Substrate (mmol)			
Substrate	P1	P2	P3	The Relation of P1, P2, and P3
Benzyl alcohol	0.381	0.537	0.968	P1 + P2< P3<1
Benzaldehyde	0.327	0.631	1.000	P1 + P2< P3 = 1
1-Phenylethanol	0.202	0.717	0.930	P1 + P2< P3<1
2-Phenylethanol	0.187	0.809	1.000	P1 + P2< P3 = 1
Cinnamaldehyde	0.162	0.776	1.000	P1 + P2< P3 = 1

Table 2. Extraction Rates, Linearity and Inclusion Equilibrium Constants for Different Alcohols and Aldehydes

Substrate	Extraction Rate	$[H]_0/\Delta A = 1/K_a\Delta\varepsilon[G]_0 + 1/\Delta\varepsilon$ (R)	K_a
Benzyl alcohol	0.537	$Y = 1.58479 \times 10^{-3} + 0.19779 \times 10^{-6}X$ (R = 0.99974)	8012 ± 573
Benzaldehyde	0.631	$Y = 0.01318 \times 10^{-3} + 0.01235 \times 10^{-6}X$ (R = 0.99986)	1067 ± 76
1-Phenylethanol	0.717	$Y = 0.03785 \times 10^{-3} + 0.05998 \times 10^{-6}X$ (R = 0.99891)	631 ± 45
2-Phenylethanol	0.809	$Y = 0.00892 \times 10^{-3} + 0.02380 \times 10^{-6}X$ (R = 0.99961)	375 ± 10
Cinnamaldehyde	0.776	$Y = 0.0171 \times 10^{-3} + 0.04714 \times 10^{-6}X$ (R = 0.99999)	363 ± 10

was formed with 1:1 stoichiometry, and K_a could be obtained. The results have been listed in Table 2.

The stability of the CD host-guest inclusion complex mainly depends on the nature of guest as well as the shape and size of the host cavity. In other words, it mainly relies on the host-guest interactions. The inclusion equilibrium constant is determined by the strength of the interaction. The greater the inclusion equilibrium constant, and the lower the extraction rate of guest separation from the inclusion complex. The results in Table 2 show that the inclusion equilibrium constants for different guests are in the order of:

Benzyl alcohol > benzaldehyde > 1-phenyl ethanol > 2-phenyl ethanol > cinnamaldehyde

While the extraction rates for different guests:

Benzyl alcohol < benzaldehyde < 1-phenyl ethanol < cinnamaldehyde < 2-phenyl ethanol

Except for cinnamaldehyde, other alcohols and aldehydes were in good agreement with the rule for extraction rate and inclusion equilibrium constant. The aldehyde group of cinnamaldehyde was a little far from benzene ring and the oxygen atom of the aldehyde group was difficult to form hydrogen bond with hydroxyl of β-CD, which would lead to the β-CD/cinnamaldehyde complexes formed mainly via the inner interaction e.g., Van der Waals force and hydrophobic interaction. However, besides the inner interaction, the external interaction (hydrogen bond) between β-CD/other substrates complexes also exists. Moreover, the inclusion equilibrium constant of benzyl alcohol was greater than that of benzaldehyde, it could be because alcohol was easier to form strong hydrogen bonds with β-CD than aldehyde.

Binding energies of the inclusion complexes

The relationship between binding energies of β-CD/hydrate complexes and reaction coordinates (Z_{C^*}) were presented in Figure 3.

As shown in Figure 3, multiple local minima on the potential energy surfaces have been localized in the inclusion processes that guests entered its hydrophobic cavity, due to the flexible conformation of host β-CD.[34,35] For example, five local minima for β-CD/benzyl alcohol-$2H_2O$ head up have been obtained. Similarly, four for β-CD/benzyl alcohol-$2H_2O$ head down, four for β-CD/benzaldehyde-$2H_2O$ head up, four for β-CD/benzaldehydel-$2H_2O$ head down, five for β-CD/1-phenylethanol-$2H_2O$ head up, five for β-CD/1-phenylethanol-$2H_2O$ head down, four for β-CD/2-phenylethanol-$2H_2O$ head up, five for β-CD/2-phenylethanol-$2H_2O$ head down, three for β-CD/cinnamaldehyde head up, five for β-CD/cinnamaldehyde head down. These localized minima were further optimized by scanning θ from 0 to 360° at 15° intervals. When considering the effects of Z_{C^*} and θ on the inclusion processes, the global minima could be found. Binding energies (E_{bind}) and the corresponding initial positions (defined by parameters Z_{C^*} and q) in hydrophobic cavity of β-CD were listed in Table 3.

According to Table 3, it could be found that the inclusion position of guests in hydrophobic cavity of β-CD depended on entering approach and nature of guest. For the obtained global minima, Z_{C^*} ranged from −2 to 2 and θ ranged from 0 to 135°, indicating that phenyl group has completely penetrated into hydrophobic cavity. The global minima were in turn found at approximately $Z = 1$ Å and $\theta = 45°$ for β-CD/Benzyl alcohol-$2H_2O$ head up, $Z = -1$ Å and $\theta = 60°$ for β-CD/Benzyl alcohol-$2H_2O$ head down, $Z = 2$ Å and $\theta = 30°$ for β-CD/Benzaldehyde-$2H_2O$ head up, $Z = 0$ Å and $\theta = 135°$ for β-CD/Benzaldehyde-$2H_2O$ head down, $Z = 1$ Å and $\theta = 120°$ for β-CD/1-phenyl ethanol head up, $Z = -1$ Å and $\theta = 0°$ for β-CD/1-phenyl ethanol head down, $Z = 1$ Å and $\theta = 60°$ for β-CD/2-phenyl ethanol head up, $Z = -2$ Å and $\theta = 45°$ for β-CD/2-phenyl ethanol head down, approximately $Z = 0$ Å and $\theta = 60°$ for β-CD/Cinnamaldehyde head up and $Z = -1$ Å and $\theta = 0°$ for β-CD/Cinnamaldehyde head down, respectively.

Generally, the binding energy (E_{bind}), calculated as the energy difference between the total energy of inclusion complexes and the sum of the total energies of β-CD and guests, is closely correlative with the stability of β-CD/guests inclusion complexes. The more negative the binding energy is, the more stable the corresponding β-CD/guest complex is. The negative binding energies in Table 3 for the global minima showed that β-CD could interact with hydrates to form stable inclusion complexes. Corrected by explicit solvation effects, the binding energies calculated on the level of PM3 ranged from −5.29 to −18.49 kcal mol^{-1} that was consistent with those of the previously reported α-CD/acetophenone inclusion processes.[36] The binding energies for these β-CD/hydrates complexes were in sequence of β-CD/Benzyl alcohol-$2H_2O$ head down (−18.49 kcal mol^{-1}) > β-CD/Benzaldehyde-$2H_2O$ head down (−15.82 kcal mol^{-1}) > β-CD/1-phenyl ethanol head down (−14.33 kcal mol^{-1}) > β-CD/Benzyl alcohol-$2H_2O$ head up (−13.67 kcal mol^{-1})> β-CD/2-phenyl ethanol head down (−12.88 kcal mol^{-1}) > β-CD/Benzaldehyde-$2H_2O$ head up (−12.56 kcal mol^{-1}) > β-CD/1-phenyl ethanol head up (−10.67 kcal mol^{-1}) > β-CD/2-phenyl ethanol head up (−10.39 kcal mol^{-1}) > β-CD/ Cinnamaldehyde head down (−6.30 kcal mol^{-1}) > β-CD/ Cinnamaldehyde head up (−5.29 kcal mol^{-1}).

However, since PM3 method neglects diatomic difference overlap (NDDO) model[37] and reproduces molecular properties rather than intermolecular properties, it often fails to describe action model of intermolecular hydrogen bonds and optimized structure of host-guest complexes.[38] To improve the computational accuracy, the β-CD/substrat-$2H_2O$ complexes were further reoptimized by ONIOM2(B3LYP/6-31G(d):

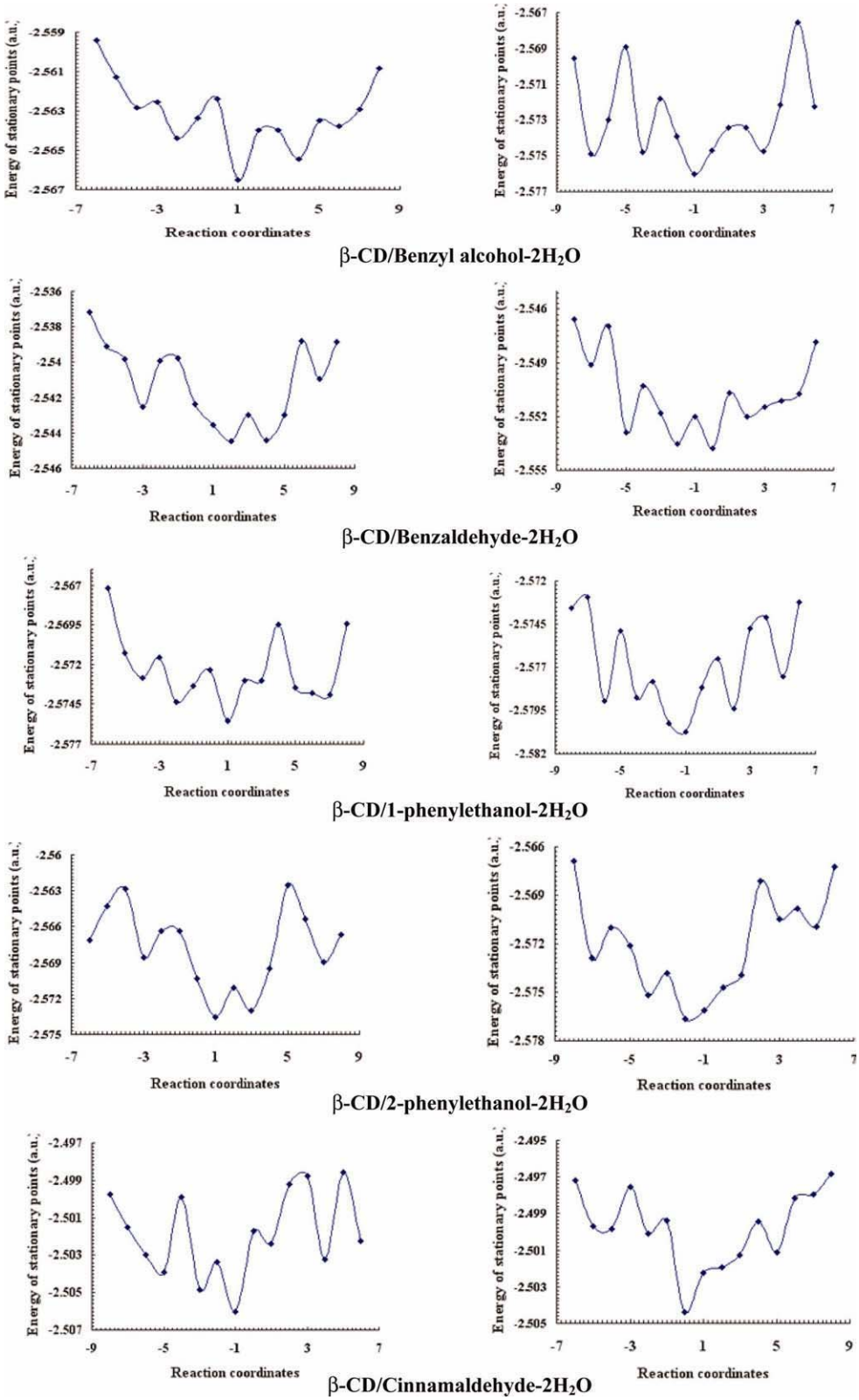

Figure 3. Energy graphs for inclusion processes of β-CD with hydrates consisting of substrates and $2H_2O$ by varying reaction coordinate (Z_{C^*}).

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 3. Binding Energies (E_{bind}) of β-CD/Substrate-2H_2O Complexes Calculated by PM3 and the Corresponding Z_C* and θ[a]

Host-Guest Inclusion Complexes		Z_C*	θ	E_{bind}
β-CD/Benzyl alcohol -2H_2O	Head up	1	45	−13.67
	Head down	−1	60	−18.49
β-CD/Benzaldehyde-2H_2O	Head up	2	30	−12.56
	Head down	0	135	−15.82
β-CD/1-phenylethanol-2H_2O	Head up	1	120	−10.67
	Head down	−1	0	−14.33
β-CD/2-phenylethanol-2H_2O	Head up	1	60	−10.39
	Head down	−2	45	−12.88
β-CD/Cinnamaldehyde-2H_2O	Head up	0	60	−5.29
	Head down	−1	0	−6.30

[a]The center of glycosidic O atoms was defined as coordinate origin, the binding energies included in the explicit solvent effect. E_{bind} in kcal mol and θ was in degree. The unit of E_{bind} is kcal mol^{-1}.

PM3). The binding energy (E_1) corrected by explicit solvation model, the binding energy (E_2) corrected by semicontinuum solvation model and the Gibbs free energy change (ΔG) with B3LYP/6-31G(d)//ONIOM2(B3LYP/6-31G(d):PM3) method were listed in Table 4.

As shown in Table 4, the negative binding energies and Gibbs free energy changes (ΔG) of β-CD/substrates-2H_2O complexes further demonstrated that β-CD could interact with these aldehydes or alcohols to form stable inclusion complexes. When considering the entropy contributions, Gibbs free energies were obtained, and the values of the Gibbs free energy changes (ΔG) were a little smaller than the corresponding binding energy. Corrected by explicit solvation effects, the ΔG calculated on the level of B3LYP/6-31G(d)//ONIOM2 were within −4.67 to −17.91 kcal mol^{-1}. Except for the inclusion complexes of β-CD/cinnamadehyde-2H_2O, the ΔG_1 of the other head down were a little more than the ΔG_1 of the corresponding head up. From an energetic point of view, it could be concluded that benzyl alcohol, benzaldehyde, 1-phenylethanol and 2-phenylethanol penetrating the hydrophobic cavity from the side of secondary hydroxyl (S-OH) were more favorable than penetrating from the side of primary hydroxyl (P-OH), while cinnamaldehyde entering hydrophobic cavity from the side of P-OH were more advantaged than entering from the side of S-OH. The Gibbs free energy changes (ΔG_1) for these β-CD/dihydrate complexes including in the explicit solvation effects that were calculated by B3LYP/6-31G(d)//ONIOM2 method were in sequence of β-CD/Benzyl alcohol-2H_2O head down (−17.91 kcal mol^{-1}) > β-CD/Benzaldehyde-2H_2O head down (−11.12 kcal mol^{-1}) > β-CD/Benzyl alcohol −2H_2O head up (−11.08 kcal mol^{-1}) > β-CD/Benzaldehyde −2H_2O head up (−8.51 kcal mol^{-1}) > β-CD/1-phenyl ethanol-2H_2O head down (−7.52 kcal mol^{-1}) > β-CD/1-phenyl ethanol-2H_2O head up (−6.00 kcal mol^{-1}) > β-CD/Cinnamaldehyde-2H_2O head up (−5.89 kcal mol^{-1}) > β-CD/2-phenyl ethanol-2H_2O head down (−5.07 kcal mol^{-1}) > β-CD/Cinnamaldehyde-2H_2O head down (−4.92 kcal mol^{-1}) > β-CD/2-phenyl ethanol-2H_2O head down (−4.67 kcal mol^{-1}).

Similarly, when being corrected by semicontinuum solvation effects, the Gibbs free energy changes (ΔG_1) calculated by B3LYP/6-31G(d)//ONIOM2 method for the obtained complexes were in sequence of β-CD/Benzyl alcohol-2H_2O head down (−16.91 kcal mol^{-1}) > β-CD/Benzyl alcohol-2H_2O head up (−10.70 kcal mol^{-1}) > β-CD/Benzaldehyde-2H_2O head down (−8.85 kcal mol^{-1}) > β-CD/ Benzaldehyde-2H_2O head up (−7.52 kcal mol^{-1}) > β-CD/1-phenyl ethanol-2H_2O head down (−6.68 kcal mol^{-1}) > β-CD/1-phenyl ethanol-2H_2O head up (−5.53 kcal mol^{-1}) > β-CD/Cinnamaldehyde-2H_2O head down (−4.47 kcal mol^{-1}) > β-CD/2-phenyl ethanol-2H_2O head down (−4.02 kcal mol^{-1}) > β-CD/Cinnamaldehyde-2H_2O head up (-3.86 kcal mol^{-1}) > β-CD/2-phenyl ethanol-2H_2O head down (−3.45 kcal mol^{-1}).

The solvation Gibbs free energy (ΔG_{sol}) was defined as the difference between ΔG_1 of explicit solvation model and ΔG_2 of semicontinuum solvation model. Generally, ΔG_{sol} represents the solvent effect on charge distribution of solute and electrostatic interaction between solvent and solute. The greater ΔG_{sol} is, the greater solvent effect on the inclusion process is. According to Table 4, ΔG_2 was a little lower than the corresponding DG_1, which indicated that semicontinuum solvation effects disfavored the inclusions of aldehyde or alcohol hydrates with β-CD in water. The calculated ΔG_{sol} ranged from 0.38 to 2.27 kcal mol^{-1}, the positive ΔG_{sol} might be attributed to the different magnitude between weak interaction of substrates with H_2Os and the corresponding one of substrate-dihydrates with β-CD. The solvent effect on the inclusion process of β-CD/ Benzaldehyde-2H_2O head down was the strongest (2.27 kcal mol^{-1}), while that of β-CD/Benzyl alcohol-2H_2O head up was the weakest (0.38 kcal mol^{-1}).

Table 4. Binding Energies (E_1 or E_2) and Gibbs Free Energy Changes (ΔG_1 or ΔG_2) in Solution for β-CD/Substrates-2H_2O Complexes Calculated by ONIOM2 (B3LYP/6-31G (d):PM3) Method[a]

	E_1	ΔG_1	E_2	ΔG_2	ΔE_{sol}	ΔG_{sol}
Head up						
β-CD/Benzyl alcohol-2H_2O	−12.59	−11.08	−11.96	−10.70	0.63	0.38
β-CD/Benzaldehyde-2H_2O	−9.73	−8.51	−8.32	−7.52	0.41	0.99
β-CD/1-Phenylethanol-2H_2O	−7.69	−6.00	−6.95	−5.53	0.74	0.47
β-CD/2-Phenylethanol-2H_2O	−6.80	−4.67	−6.02	−3.45	0.78	1.22
β-CD/Cinnamaldehyde-2H_2O	−7.06	−5.89	−5.11	−3.86	1.95	2.03
Head down						
β-CD/Benzyl alcohol-2H_2O	−18.78	−17.91	−18.25	−16.91	0.53	1.00
β-CD/Benzaldehyde-2H_2O	−12.76	−11.12	−10.34	−8.85	2.42	2.27
β-CD/1-Phenylethanol-2H_2O	−8.93	−7.52	−8.20	−6.68	0.73	0.84
β-CD/2-Phenylethanol-2H_2O	−5.72	−5.07	−4.48	−4.02	1.24	1.05
β-CD/Cinnamaldehyde-2H_2O	−5.55	−4.92	−5.03	−4.47	0.52	0.45

[a]ΔG_1 and ΔG_2 were the Gibbs free energy changes corrected by explicit solvation model and semi-continuum solvation model, respectively. The solvation Gibbs free energies (DG_{sol}) was the difference between ΔG_1 and ΔG_2, and ΔE_{sol} was the difference between E_1 and E_2. The unit of energy is kcal mol^{-1}.

Table 5. Extraction Rates (*E* or P2) of Compounds, Difference of Gibbs Free Energy Changes ($\Delta\Delta G$), Separation Factors (K) and Extraction Steps of Mixtures[a]

Entry	Substrate	P1	P2	P3	$\Delta\Delta G$	*K*	*N*
1	Benzyl alcohol	0.403	0.468	0.896	8.06	1.71	9
	Benzaldehyde	0.196	0.799	1.000			
2	Benzaldehyde	0.366	0.559	0.905	4.28	1.27	19
	Cinnamaldehyde	0.232	0.713	0.942			
3	Benzyl alcohol	0.508	0.273	0.715	12.89	2.12	6
	2-phenylethanol	0.393	0.578	1.000			
4	Benzyl alcohol	0.431	0.402	0.852	10.23	1.57	11
	1-phenylethanol	0.301	0.623	0.940			
5	1-phenylethanol	0.469	0.461	1.000	2.66	1.07	68
	2-phenylethanol	0.502	0.496	1.000			

[a]The meaning of P1, P2 and P3 were described and the definition of the extraction rate (*E*) and separation factor (*K*) were given in Experimental method. $\Delta\Delta G$ is the difference of between $\Delta G2$ of two head down complexes in Table 4. The unit of $\Delta\Delta G$ is kcal mol^{-1}.

Selective separation of mixtures

It is important to pay attention to the difference of interaction between β-CD and different alcohols or aldehydes. The difference for E_{bind} means that we could selectively separate the alcohols and aldehydes. The extraction rates, difference of Gibbs free energy change ($\Delta\Delta G$), separation factor (K) and extraction steps for different compounds has been shown in Table 5.

As shown in Table 5, all separation factors were more than 1, thus these mixtures could be separated. The separation factor for benzyl alcohol and benzaldehyde was 1.71, and benzaldehyde was easier to be extracted than benzyl alcohol. This might be because the electron cloud density of the oxygen atom in alcohols was higher, which led to the strength of the hydrogen bond between β-CD and alcohols was stronger than that for aldehydes. For benzaldehyde and cinnamaldehyde, because the distance between the oxygen atom and the phenyl ring in benzaldehyde was shorter than that of cinnamaldehyde, it was possible to separate them due to the difference of interaction between β-CD and them. The mixture of benzyl alcohol and 1-phenyl ethanol could also be separated selectively for the same reason, and the separation factor reaches up to 2.12. Although the distance between the oxygen atom of 1-phenyl ethanol and the phenyl ring was shorter than that of 2-phenyl ethanol, the steric hindrance of methyl group in 1-phenyl ethanol could interfere with the extraction of 1-phenyl ethanol from the inclusion complex. Benzaldehyde and 1-phenyl ethanol could be selectively separated, for their separation factor was 1.57. However, for isomers e.g., 1-phenyl ethanol and 2-phenyl ethanol, their separation was not efficient and the corresponding separation factor was only 1.07.

It wasn't difficult to find that the difference of Gibbs free energy ($\Delta\Delta G$) obtained by B3LYP/6-31G(d)//ONIOM2 calculations was closely related to the separation factors of mixtures, namely a greater $\Delta\Delta G$ corresponded to a greater separation factors. For example, the $\Delta\Delta G$ (12.89 kcal mol^{-1}) between β-CD/benzyl alcohol-$2H_2O$ and β-CD/2-phenyl ethanol-$2H_2O$ was the greatest among five $\Delta\Delta G$s, and the corresponding separation factor (2.12) was also the greatest one. To get a purity of >99% for benzyl alcohol from the mixtures of benzyl alcohol and 2-phenyl ethanol, six extraction steps were necessary (n=6). Similarly, the $\Delta\Delta G$ (2.12 kcal mol^{-1}) between β-CD/1-benzylethanol-$2H_2O$ and β-CD/1-benzylethanol-$2H_2O$ was the least, which corresponded the least separation factor (1.07), and required 68 extraction steps ($n = 68$) to reach >99% purity.

Optimized structures of the inclusion complexes and action mechanisms of hydrogen bonds

Geometries of the most stable inclusion complexes optimized by ONIOM2(B3LYP/6-31G(d): PM3) were displayed in Figure 4. The number, type, bond length and bond angle of intermolecular hydrogen bonds between b-CD and guests were listed in Table 6, and numbering of atoms or glucose units were shown in Figure 1.

Two types of hydrogen bond interactions e.g., O—H…O and C—H…O have been considered. The cut-off criteria of hydrogen bonds interaction was the O…O distance ($\leq$3.2Å),[39] the C…O distance ($\leq$3.5Å)[40,41] and the bond angle ($\geq$90°). The glucose units in β-CD labeled as I~VII, O atoms in every glucose unit were accordingly defined as 2O, 3O, 4O, 5O, and 6O, secondary hydroxyl groups were named as 2-OH, 3-OH and primary hydroxyl group was named as 6-OH. For example, when the hydrogen bond of O21-H20···6O (I) was formed in the β-CD/Benzyl alcohol-$2H_2O$ head up, the O21-H20 covalent bond of benzyl alcohol-$2H_2O$ acted as hydrogen-donor and 6O atom of glucose unit I of β-CD acted as hydrogen-acceptor.

As shown in Figure 4, the longer dimension of substrates strongly deviated from *Z*-axis, which suggested that the inclusion complexes were stably formed by intermolecular weak interactions e.g., Van der Waals interaction, electrostatic interaction and hydrogen bonding interaction etc. Generally, the contributions of both hydrogen bonds to binding energy are much greater than that of van der Waals interaction. Generally an O—H…O hydrogen bond interaction contributes a stable energy of 16–25 kJ mol^{-1} to binding energy of complex[42] and a C—H…O hydrogen bond interaction contributes a stable energy of 0.7–2.8 kJ mol^{-1} to binding energy.[43] When forming β-CD/hydrate complexes, phenyl ring was completely inserted into hydrophobic cavity of β-CD and hydroxyl or aldehyde group of substrates strongly interacted with atoms or groups of β-CD, while part of first-shell H_2Os around substrates were still exposed in the surroundings and they could interact with outer solvent molecules.

The results in Table 6 showed that the lengths of O—H…O or C—H…O hydrogen bonds ranged from 2.249 to 3.157 Å or 2.335 to 3.511 Å, and the bond angles of O—H…O or C—H…O hydrogen bonds belonged to 91.4–169.7° or 90.2–159.7°, respectively. Different numbers of hydrogen bonds have been found within these inclusion complexes. In the β-CD/benzyl alcohol-$2H_2O$ head up, there are

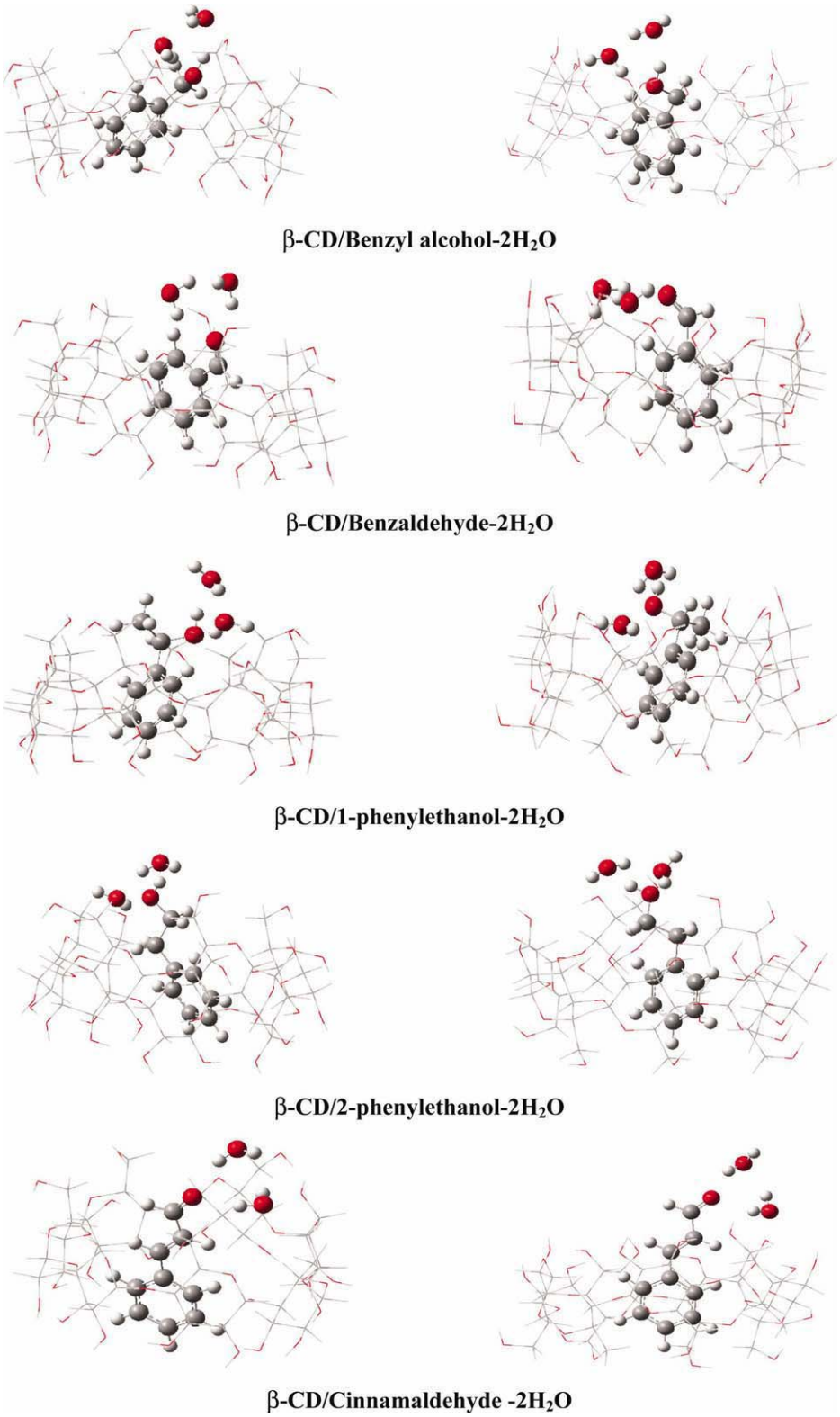

Figure 4. Optimized structure of inclusion complexes obtained by ONIOM2 (B3LYP/6-31G(d):PM3) method.

The "head-up" (left) and "head down" (right) complexes were displayed, respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

one O—H…O hydrogen bond between benzyl alcohol-$2H_2O$ and glucose unit I of β-CD; four C—H…O hydrogen bonds between benzyl alcohol-$2H_2O$ and glucose units II, V, VII. In the β-CD/benzyl alcohol-$2H_2O$ head down, there are three O—H…O hydrogen bonds between benzyl alcohol-$2H_2O$ and glucose units V, VII; two C—H…O hydrogen bonds between

Table 6. Number, Type, Bond Length (*r*) and Bond Angle (*A*) of Intermolecular Hydrogen Bond Between Hydrates and β-CD Calculated by ONIOM2(B3LYP/6-31G(d):PM3)[a]

Inclusion complexes	Number	Type	*r*	*A*
β-CD/Benzyl alcohol-2H_2O head up	5	O21-H20…6O(I)	2.430	98.7
		O17 …6H-6C (II)	3.472	141.8
		C2-H7…4O(VII)	2.969	113.5
		C1-H4…4O(VII)	3.213	97.9
		C5-H11…4O (V)	3.229	136.1
β-CD/Benzyl alcohol-2H_2O head down	5	O21-H20…2O(VII)	2.452	154.3
		O21-H20…3O(VII)	2.876	135.4
		C3-H8…4O(I)	3.266	139.6
		C1-H4…6O(I)	3.384	151.8
		O15 …2-HO(V)	3.164	150.9
β-CD/Benzaldehyde-2H_2O head up	4	O14 …6H-6C(II)	3.225	90.2
		O16-H17…6O (I)	2.922	114.7
		C1-H4…4O (V)	3.335	108.7
		C2-H8…4O(V)	2.794	127.8
β-CD/Benzaldehyde-2H_2O head down	4	O19…3-HO(VI)	2.771	149.5
		O16-H17…4O(I)	2.793	149.0
		C3-H7…4O(IV)	3.429	96.0
		C5-H11…4O(III)	3.323	127.9
β-CD/1-phenylethanol-2H_2O head up	4	C8-H18…6O(I)	2.983	159.7
		C7-H12…4O(I)	3.448	103.2
		O21-H22…6O(IV)	2.778	169.7
		C5-H10…4O(III)	3.373	124.6
β-CD/1-phenylethanol-2H_2O head down	5	O2-H13…4O(IV)	3.485	109.0
		C7-H12…4O(V)	2.653	130.0
		O21-H22…3O(VII)	3.157	135.2
		C8-H18…2O(III)	3.264	115.0
		O21-H22…2O(I)	3.146	101.8
β-CD/2-phenylethanol-2H_2O head up	5	O21-H22…5O(II)	3.110	110.0
		O24-H25…6O(IV)	3.113	152.6
		C7-H12…4O(V)	3.340	137.0
		C5-H10…4O(VI)	3.277	105.5
		O9…H6-6C(II)	3.507	122.2
β-CD/2-phenylethanol-2H_2O head down	3	O24-H25…2O(III)	2.815	127.5
		O21…3-HO(III)	2.466	131.6
		C2-H14…4O(VI)	3.338	110.9
β-CD/Cinnamaldehyde-2H_2O head up	5	O20-H21…6O (IV)	2.656	136.0
		C20…H6-6C(III)	3.220	103.9
		C9-H18…6O(I)	3.275	132.5
		C2-H15…4O(I)	3.181	134.9
		C4-H16…4O(I)	3.431	119.7
β-CD/Cinnamaldehyde-2H_2O head down	4	C8-H17…3O(III)	3.440	106.7
		O20-H19…2O(III)	2.294	91.4
		C3-H14…5O(III)	3.511	145.2
		C8-H17…2O(III)	3.434	153.3

[a]The cut-off criteria for the distances of O…O or C…O are accordingly ≤3.2 or ≤3.5 Å, bond angle ranged from 90 to 180°. *r* is in Å, and *A* is in degree.

benzyl alcohol-2H_2O and glucose unit I. In the β-CD/benzaldehyde-2H_2O head up, there are one O—H…O hydrogen bond between benzaldehyde-2H_2O and glucose unit I; three C—H…O hydrogen bonds between benzaldehyde-2H_2O and glucose units II, V. In β-CD/benzaldehyde-2H_2O head down, there are two O—H…O hydrogen bonds between benzaldehyde-2H_2O and glucose units I, VI, two C—H…O hydrogen bonds between benzaldehyde-2H_2O and glucose units III, IV. In the β-CD/1-phenylethanol-2H_2O head up, there are one O—H…O hydrogen bond between 1-phenylethanol-2H_2O and glucose unit IV, three C—H…O hydrogen bonds between 1-phenylethanol-2H_2O and glucose units I, III. In the b-CD/1-phenylethanol-2H_2O head down, there are three O—H…O hydrogen bonds between 1-phenylethanol-2H_2O and glucose units I, IV, VII, two C—H…O hydrogen bonds between 1-phenylethanol-2H_2O and glucose units III, V. In the β-CD/2-phenylethanol-2H_2O head up, there are two O—H…O hydrogen bonds between 2-phenylethanol-2H_2O and glucose units II, IV, three C—H…O hydrogen bonds between 2-phenylethanol-2H_2O and glucose units II, V, VI. In the β-CD/2-phenylethanol-2H_2O head down, there are two O—H…O hydrogen bonds between 2-phenylethanol-2H_2O and glucose units III, III, one C—H…O hydrogen bond between 2-phenylethanol-2H_2O and glucose unit VI. In the β-CD/cinnamaldehyde-2H_2O head up, there are one O—H…O hydrogen bond between cinnamaldehyde-2H_2O and glucose unit IV, four C—H…O hydrogen bonds between cinnamaldehyde-2H_2O and glucose units I, III. In the β-CD/cinnamaldehyde-2H_2O head down, there are one O—H…O hydrogen bond between cinnamaldehyde-2H_2O and glucose unit III, three C—H…O hydrogen bonds between cinnamaldehyde-2H_2O and glucose unit III.

The hydrogen bonds between aldehyde or alcohol hydrates and β-CD played a vital role in inclusion processes. The stabilities of the formed inclusion complexes were closely related to the number, type and strength (bond length and bond angle) of hydrogen bonds. For example, β-CD/benzyl alcohol-2H_2O head down (−18.25 kcal mol^{-1}) was more stable than β-CD/benzaldehyde-2H_2O head down (−10.34

kcal mol^{-1}), which might be because the hydrogen bond strengths in the β-CD/benzyl alcohol-$2H_2O$ head down were stronger than those in β-CD/benzaldehyde-$2H_2O$ head down. In the β-CD/benzyl alcohol-$2H_2O$ head down, the bond lengths of hydrogen bonds of O21-H20…2O (VII), O21-H20…3O (VII) and O15…2OH (V) were in turn 2.452, 2.876, and 3.164 Å, and the corresponding bond angles were in turn 154.3°, 135.4 and 150.9°, and the bond lengths of hydrogen bonds of C3-H8…4O (I) and C1-H4…6O (I) were 3.266 Å and 3.384 Å,and the bond angles were 139.6° and 151.8°, respectively. However, the bond lengths of hydrogen bonds in the b-CD/ benzaldehyde-$2H_2O$ head down were a little longer and the bond angles were a little smaller. The bond lengths of O19 …3HO (VI) and O16-H17…4O (I) were 2.771 and 2.793 Å, bond angle were 149.5° and 149.0°, the bond lengths of hydrogen bonds of C3-H7…4O(IV) and C5-H11…4O(III) were 3.429 Å and 3.323 Å, bond angles were 96.0° and 127.9°. As a result, the different hydrogen bonds between atoms or groups of substrate-$2H_2O$ and glucose units of β-CD can lead to different stabilities of complexes, which explain the different separation factors for the substrates in β-CD.

Recycle of β-cyclodextrin

After the inclusion complexes were redissolved in organic solvent and the guest was released from the inclusion complexes, the white precipitation (β-CD) could be easily recycled by the addition of acetone and centrifugation. When the volume ratio of acetone to water reached 2:1, 95% β-cyclodextrin could be recovered. The recycled β-cyclodextrin could be reused without any loss of separation efficiency. Since the recycled β-cyclodextrin keep unchanged, that is the reason why it could be reused without any loss of separation efficiency. To verify it, the recovered β-cyclodextrin was reused three times, the extraction rates and separation factors remained the same.

Conclusions

CDs have particular inclusion properties and coordination kinetics because they are hydrophilic at the periphery and hydrophobic within the central cavity. Through investigation on the β-CD/aldehyde or alcohol complexes, it has been concluded that weak interactions e.g., hydrogen bonds of O—H…O and C—H…O mostly contributed to the binding energies of the complexes. The solvation Gibbs free energies (ΔG_{sol}) obtained by B3LYP/6-31G(d)//ONIOM2 method indicated that semicontinuum solvent effects on inclusion processes disfavored the formations of inclusion complexes, and the difference between ΔG_2 of two head down complexes was the basis of selective separation for different aldehyde or alcohol compounds via β-CD inclusion. According to the studies on the separation of some alcohol and aldehyde mixtures, it was inferred that selective separation by β-CD inclusion was a novel, simple and efficient method, and might be applied in separation of natural substances and thermosensitive compounds with similar boiling point in the future. Besides, this research provides a method for explaining the separation efficiency based on quantum chemistry with solvation effect for the first time.

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