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Isothermal Titration Calorimetry and Theoretical Studies on Host-guest Interaction of Ibuprofen with α-, β- and γ-Cyclodextrin

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Abstract Thermodynamic parameters for formation of the inclusion complexes of α-, β- and γ-cyclodextrin (α-, β- and γ-CD) with ibuprofen (BF) in Tris-HCl buffer solutions (pH = 7.0) have been determined by isothermal titration calorimetry (ITC) with nanowatt sensitivity, and the inclusion structures have been investigated by using ^{1}H-NMR spectra at 298.15 K. A theoretical study on the inclusion processes between BF and CDs has been performed with the B3LYP/6-31G*//PM3 method in order to investigate the formation mechanism of the inclusion complexes. An analysis of the thermodynamic data indicates that the stoichiometries of α-, β- and γ-CD with BF are all 1:1 and formation of the inclusion complexes α-CD·BF and β-CD·BF are driven by enthalpy and entropy, whereas formation of γ-CD·BF is an entropy driven process. The ^{1}H-NMR spectra provide clear evidence for the inclusion phenomenon, and show that the isobutyl group and aromatic ring of the guest molecule are trapped inside the cavity of the CDs. Theoretical calculations suggest that the complex formed by the BF molecule entering into the cavity of the CD molecule from the wide side is more stable than that from the narrow side.

Keywords Cyclodextrin · Ibuprofen · Inclusion complex · Isothermal titration calorimetry · ^{1}H-NMR · DFT · PM3

1 Introduction

Cyclodextrins (CDs), the most prominent host molecules used in supramolecular chemistry up to now [1, 2], are cyclic oligosaccharides composed of glucopyranose units and can

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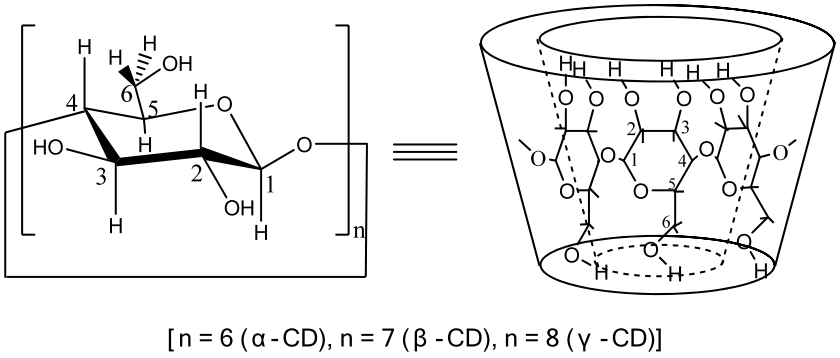

Fig. 1 Molecular structure of cyclodextrin

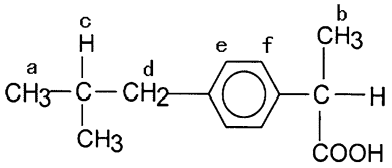

Fig. 2 Molecular structure of ibuprofen. Letters a, b, c, d, e and f are used to label the different H atoms of ibuprofen and the *C is used to express the relative position between BF and the CDs in the theoretical calculations

be characterized by a truncated cone structure with a hydrophobic interior and hydrophilic exterior [3] as shown in Fig. 1. The most common CDs are α-, β-, and γ-CD, which consist of six, seven, and eight D-glucose units, respectively. They possess the remarkable property of forming inclusion complexes with many organic, inorganic and biological compounds without covalent bonds, and the resultant inclusion complexes can induce modification of the physicochemical properties of guest molecules (such as increasing water solubility and solution stability) [4, 5]. In addition, CDs can mediate many organic reactions in which the CDs represent good models for mimicking enzymes [6, 7]. Consequently, CDs are widely used in analytical chemistry, organic synthesis and the pharmaceutical industry [8–13].

Ibuprofen (BF, see Fig. 2) is a typical example of a molecule whose physicochemical properties can be modified by CDs. BF is a member of a group of drugs called nonsteroidal anti-inflammatory drugs. It is widely used to reduce fever and treat pain or inflammation caused by many conditions such as headache, back pain, arthritis, chronic laryngitis and bronchiolitis. However, its application in the pharmaceutical field is limited by its low aqueous solubility, bad taste as well as increasing risk of serious effects on the stomach and intestines [14–16]. Fortunately, CDs can improve its solubility and taste by reacting with BF to form inclusion complexes.

Isothermal titration calorimetry (ITC) is an extremely powerful and highly sensitive technique that is very helpful for investigating weak interactions between molecules, yielding both thermodynamic and kinetic information [17]. It has been applied to determine stability constants, stoichiometry, interaction enthalpies, entropies, Gibbs energies and heat capacity changes. Thus, ITC has been applied in many areas such as cyclodextrin chemistry, polymer chemistry, cellular biology and biochemistry [18–22]. To our knowledge, there have been no reports of the direct investigation of the complexes of CDs with BF in Tris-HCl buffer solutions (pH = 7.0) using nanowatt sensitivity ITC. Thus, the purpose of this report is to investigate the thermodynamic properties from reaction of CDs with BF by utilizing isothermal titration calorimetry. In addition, a quantum-chemical study has also been done

on the structures of the inclusion complexes as well as the inclusion processes between CDs and BF.

2 Materials and Methods

2.1 Materials

The α- and γ-CDs were bought from Aldrich and β-CD was purchased from the Shanghai Chemical Reagent Company (Shanghai China). They were purified twice by recrystallization in redistilled water and then dried under reduced pressure at 353 K for 48 h prior to use. The reagents were stored over P_2O_5 in a vacuum desiccator at room temperature. BF was obtained from Fluka Chemical Company and was $\geq$99% pure. NaOH (GR) and tris(hydroxymethyl)aminomethane (Tris, BR) were purchased from the Sinopharm Chemical Reagent Co. Ltd. (China).

2.2 Isothermal Titration Calorimetry

The nanowatt isothermal titration microcalorimeter is supported by a Thermometric Activity Monitor (TAM) Thermometric 2277 (Thermometric, Sweden) and controlled by Digitam 4.1 software [23]. This instrument has a precision of electrical calibration better than $\pm 1\%$, and its accuracy was checked by measuring the dilution enthalpy of a concentrated sucrose solution [24]. A BFNa solution (titrant, 1.5×10^{-2} mol·dm^{-3}), which was prepared from the same quantities of BF and NaOH in Tris-HCl buffer solutions (pH = 7.0), is injected into the 1.0 cm^3 stainless steel ampoule containing 0.5 cm^3 of CDs solution (titrand, 5.00×10^{-3} mol·dm^{-3}), in 40 aliquots of 12 μL each, using a 500 μL Hamilton syringe controlled by a 612 μL Lund Syringe Pump. The interval between two injections varied from 35 to 45 min, which is sufficiently long for the signal to return back to the baseline. The stirrer in the ampoule was operated at a constant speed of 30 rpm. All the experiments were performed at 298.15 ± 0.01 K. The enthalpies of dilution of BFNa and the CDs solutions were determined in separate experiments. No significant heat effect was found so that the dilution heats are negligible.

2.3 ^{1}H-NMR Measurements

^{1}H-NMR spectra were recorded on a FT-NMR 1500A model 400M superconductive Nuclear Magnetic Resonance Instrument (USA, Varian Company). The spectra were acquired at 298.15 K and the center of the solvent signal (D_2O, at 4.640 ppm) was used as the reference point.

2.4 Computational Methods

Besides the experimental measurements, molecular modeling is very popular for investigating CD chemistry in order to calculate the binding energy (ΔE) as well as the geometrical structure of the inclusion complex and it has proved to be a very useful tool [25, 26]. In this paper the inclusion models used have been successfully employed by Liu and co-workers [25], as shown in Fig. 3. In the models, the glycosidic oxygen atoms of CDs are placed in the XY plane and their center is defined as the center of the whole system. BF approaches and passes through the cavity of CDs in the $+Z$ to $-Z$ direction, and the distance between the

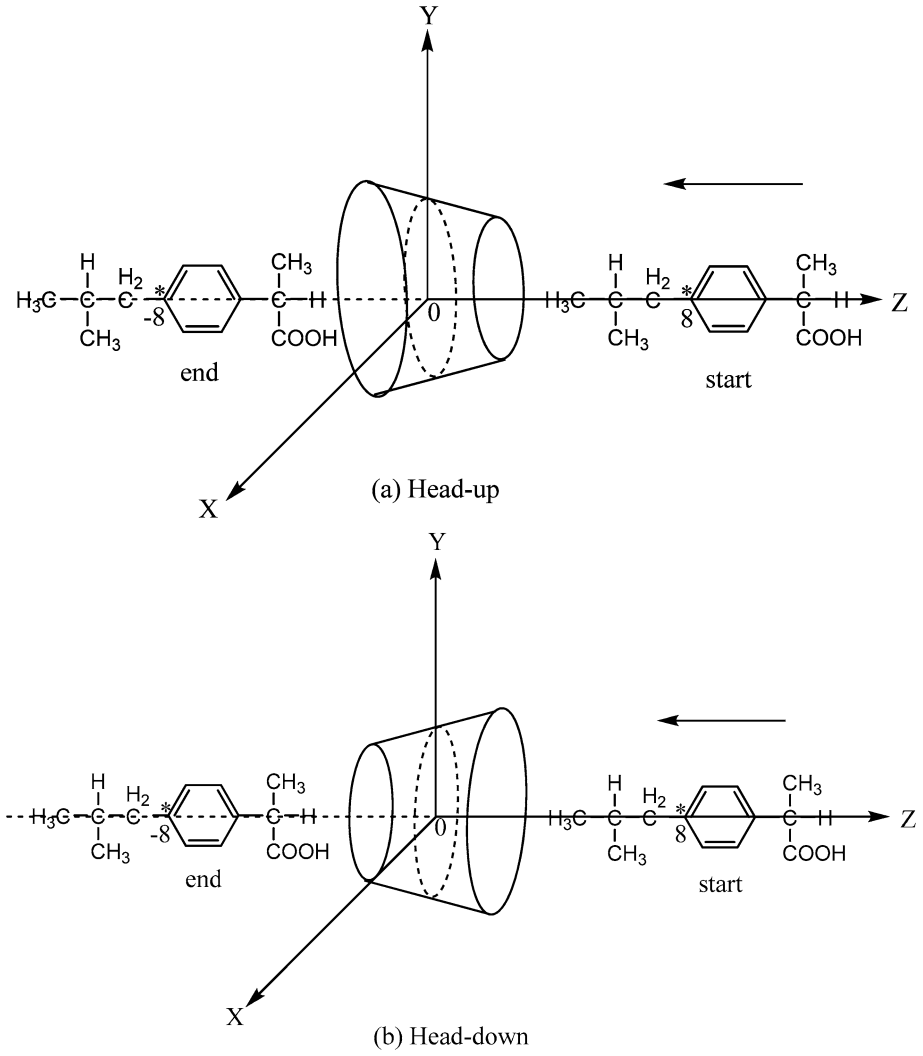

Fig. 3 Coordinate systems used to define the inclusion processes: (**a**) head-up and (**b**) head-down

labeled carbon atom (C*) of BF and the Z-coordinate origin was varied in 1 Å steps from $+8$ to -8 Å. For convenience, the BF passing through the cavity of CDs from the narrow side (Fig. 3a) and the wide side (Fig. 3b) are defined as "Head-up" and "Head-down" configurations, respectively. For each step, the geometry of the complex was fully optimized by the PM3 method [26] without imposing any symmetrical restrictions. Harmonic frequency analysis was used to ensure that the located stationary point is the true minimum. The single point energies of the inclusion complexes were calculated at the B3LYP/6-31G* level. All of the calculations were performed with the Gaussian 98 software package [27].

3 Results and Discussion

3.1 Thermodynamic Data Analysis

In order to analyze the standard enthalpies ΔH_i° of the inclusion complexes of BF with α-, β- and γ-CD, the apparent equilibrium constant (β_i) for overall reaction has been defined as follow:

$$\mathrm{M} + i\mathrm{L} \underset{\leftarrow}{\rightarrow} \mathrm{ML}_i; \qquad \beta_i = \frac{[\mathrm{ML}_i]}{[\mathrm{M}][\mathrm{L}]}; \qquad \Delta H_i^{\circ} \tag{1}$$

where $i = 1, 2$ or 3, and M or L, respectively, represent the host (CDs) and guest (BF) molecules. Therefore, there are five possible reaction models.

The total concentration of M and L can be obtained by the formulas Eq. 2 and Eq. 3:

$$[\mathrm{M}]_{\mathrm{t}} = [\mathrm{M}]\left(1 + \sum_i \beta_i [\mathrm{L}]\right) \tag{2}$$

$$[\mathrm{L}]_{\mathrm{t}} = \left(1 + [\mathrm{M}] \sum i\beta_i [\mathrm{L}]^{i-1}\right) \tag{3}$$

The relationship between the overall equilibrium constants (β_i) and the stepwise equilibrium constants (K_i) is given by the formula

$$\beta_i = \Pi K_i \tag{4}$$

The thermodynamic parameters, ΔH_i° and β_i(or K_i), can be derived by the regression method [28], which was performed with the Ligand Binding Analysis routine of the Digitam 4.1 software [23]. By comparing the simulation curves for the five possible reaction models with the experimental titration curve, we confirmed that the most reasonable stoichiometries of α-, β- and γ-CD with BF are all 1:1 (see Fig. 4) in these systems. Then, the standard Gibbs energy changes (ΔG°) and standard entropy changes ($T\Delta S^{\circ}$) of the interaction processes were calculated and are listed in Table 1.

3.2 Thermodynamics Parameters

From Table 1, one can see that: (i) the overall equilibrium constants (β_i) are 0.65×10^3, 1.27×10^4 and 0.14×10^3 $\mathrm{dm^3 \cdot mol^{-1}}$ for the inclusion complexes, α-CD·BF, β-CD·BF and γ-CD·BF, respectively. These data indicate that the inclusion complex β-CD·BF is more stable than the others, which can be explained by β-CD having the optimal size for its internal cavity (8 Å) to encase the BF molecule. (ii) The standard formation enthalpies (ΔH°) of the complexes α-CD·BF and β-CD·BF are -3.20 and -14.11 $\mathrm{kJ \cdot mol^{-1}}$, respectively, which indicate that the formation reactions for these two complexes are weak exothermic processes. However, the ΔH° value for γ-CD·BF is 3.49 $\mathrm{kJ \cdot mol^{-1}}$ which indicates that formation of this complex is an endothermic process. (iii) Negative values for the standard Gibbs energy changes (ΔG°) indicate that the formation of all of the complexes are spontaneous processes. (iv) The entropy effects ($T\Delta S^{\circ}$) for formation of the inclusion complexes are positive and make a smaller contribution to the negative value of the standard Gibbs energy than the heat effect. The positive entropy effect may be due to the combined results of the host-guest reaction (negative contribution to entropy) and releasing of water molecules from the cavity (positive contribution to entropy). Finally, formation of the inclusion complexes α-CD·BF and β-CD·BF are enthalpy-entropy synergistically driven processes, whereas that of γ-CD·BF is an entropy-driven process.

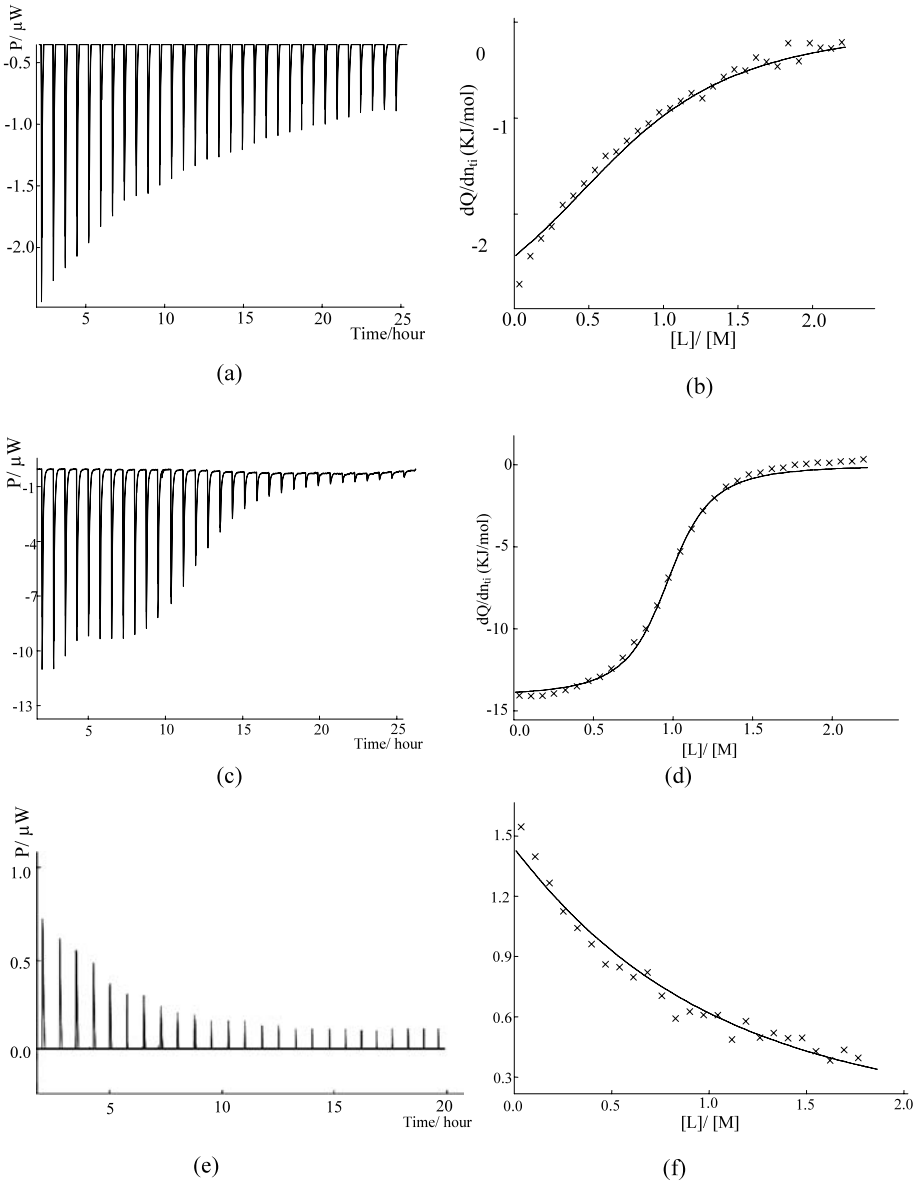

Fig. 4 Curves (**a**, **c** and **d**), variation of the heat-flow/electrical power P as a function of time t (titrant: BFNa, 1.5×10^{-2} mol·dm^{-3}; titrand: α-, β-, γ-CDs, 5.00×10^{-3} mol·dm^{-3}); (**b**, **d** and **f**) rate of reaction heat changes with the amount of M versus the ratio of concentrations [BFNa]/[CDs] (the *line* is the result of simulation and the *points* are experimental values)

3.3 ^{1}H-NMR Spectroscopy

^{1}H-NMR spectroscopy has been used to obtain information about the microscopic structures of inclusion complexes [29, 30]. The induced shift, $\Delta\delta$, is defined as the difference between the chemical shifts in the presence and absence of the other reactants

Table 1 Stability constants (β_i), standard changes of enthalpy (ΔH°), Gibbs energy change (ΔG°) and of the temperature-entropy products ($T\Delta S^\circ$) for the complexes formed by the host (α-, β-, γ-CD) with the guest (BF) in aqueous solution at 298.15 K

	$10^3\beta_i/(\mathrm{dm^3\cdot mol^{-1}})$	$\Delta H^\circ/(\mathrm{kJ\cdot mol^{-1}})$	$\Delta G^\circ/(\mathrm{kJ\cdot mol^{-1}})$	$T\Delta S^\circ/(\mathrm{kJ\cdot mol^{-1}})$
α-CD·BF	0.65	−3.20	−16.00	12.80
β-CD·BF	12.71	−14.11	−23.35	9.24
γ-CD·BF	0.14	3.49	−12.21	15.70

Table 2 ^{1}H chemical shifts of ibuprofen protons in the inclusion complexes ($\Delta\delta = \delta_{\mathrm{complex}} - \delta_{\mathrm{free}}$)

Different H atoms of ibuprofen	Number of H protons	$\Delta\delta$ (ppm)		
		α-CD·BF	β-CD·BF	γ-CD·BF
H(a)	6	+0.046	+0.023	−0.055
H(b)	3	−0.006	+0.001	−0.007
H(c)	1	+0.049	−0.012	−0.078
H(d)	2	+0.040	−0.013	−0.041
H(e)	2	+0.013	−0.179	−0.086
H(f)	2	+0.009	−0.022	−0.016

Table 3 ^{1}H chemical shifts of glucopyranose-unit protons of the CD molecule in the inclusion complexes ($\Delta\delta = \delta_{\mathrm{complex}} - \delta_{\mathrm{free}}$)

	$\Delta\delta$ (ppm)					
	1-H	2-H	3-H	4-H	5-H	6-H
α-CD	0.002	0.001	0.013	0.004	0.002	−0.002
β-CD	−0.032	−0.036	−0.113	−0.015	−0.086	−0.085
γ-CD	−0.034	−0.032	−0.050	−0.027	−0.026	−0.025

($\Delta\delta = \Delta\delta_{(\mathrm{complex})} - \Delta\delta_{(\mathrm{free})}$). The ^{1}H chemical shifts of the ibuprofen protons and glucopyranose unit protons of the CD molecule in the studied host-guest\systems are shown in Tables 2 and 3, respectively.

From Table 2 one can see that the ^{1}H chemical shifts of H(a) (0.046 ppm), H(c) (0.049 ppm) and H(d) (0.040 ppm) of the BF molecule in the α-CD·BF system are much larger than those of H(b) (−0.006 ppm), H(e) (0.013 ppm) and H(f) (0.009 ppm). The chemical shifts of protons in the D-glucose-unit of the α-CD molecule are very small, except for 3-H (which is in the cavity of α-CD) as given for the α-CD·BF system in Table 3. These data suggest that perhaps only the isobutyl group of the BF molecule is included in the cavity of α-CD. In the β-CD·BF system, the chemical shifts of H(a), H(e), H(f) are very large (the shift of H(e) is especially large, extending to −0.179 ppm). The data in Table 3 clearly show that the ^{1}H chemical shifts of 3-H, 5-H and 6-H in β-CD are much larger than those of 1-H, 2-H and 4-H. Therefore, it can be generalized that the cavity of β-CD accommodates the isobutyl group and part of the aromatic ring of the BF molecule. In the γ-CD·BF system, the chemical shifts of all H atoms of the BF molecule are very large except for H(b) in the γ-CD·BF system, and the chemical shifts of 3-H and 5-H (in the cavity of γ-CD) obviously

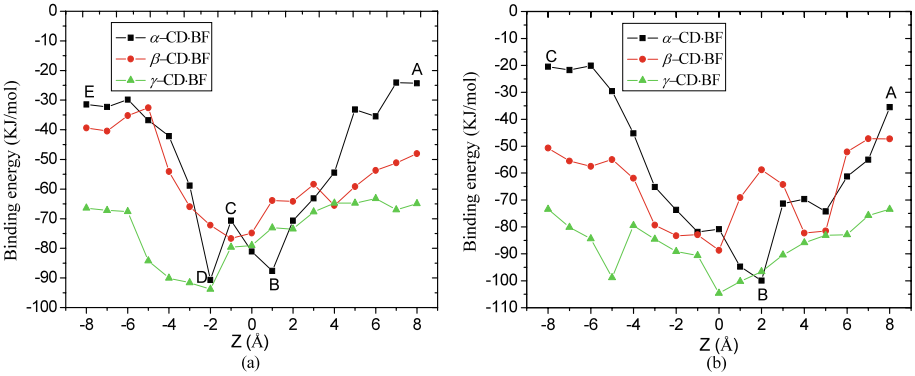

Fig. 5 Energy curves obtained by BF passing through the cavity of α-, β- and γ-CD: head-up (**a**) and head-down (**b**)

change from the values given in Tables 2 and 3. This indicates that the isobutyl group and aromatic ring of the BF molecule are trapped in the cavity of γ-CD. The chemical shifts of specific protons in the CDs systems provide direct evidence for the formation of inclusion complexes, which indicates that NMR is a very useful tool for investigating the host-guest interaction in CD chemistry.

3.4 Theoretical Investigation

As described above, interactions between CDs and BF have been studied experimentally with isothermal titration calorimetry (ITC) and ^{1}H-NMR spectroscopy, which provide evidence for the formation of inclusion complexes. However, the geometries and stabilities of the complexes, as well as the inclusion energetics for formation of the complexes, are still unclear. Therefore, a theoretical study of the energies and inclusion processes for formation of the inclusion complexes has also been done.

By using the simulation models as shown in Fig. 3, the binding energy change curves for BF passing through the cavity of α-, β- and γ-CD are shown in Figs. 5a (for Head-up) and 5b (for Head-down), respectively. As shown in Fig. 5a, taking the α-CD·BF system as an example, the energy decreases sharply from the starting point **A** ($Z_{\mathbf{A}} = 8$ Å; $Z_{\mathbf{A}}$ being the Z-coordinate of point **A**) until it reaches point **B** ($Z_{\mathbf{B}} = 1$ Å), which is a local minimum. Then, the energy increases rapidly and achieves a local maximum at point **C** ($Z_{\mathbf{C}} = -1$ Å). After that, the energy decreases again until it reaches point **D** ($Z_{\mathbf{D}} = -2$ Å), the global minimum for the whole curve. This indicates that BF and α-CD could form the most stable inclusion complex in the Head-up pattern. Lastly, the energy increases until point **E** ($Z_{\mathbf{E}} = -8$ Å).

Similarly, we give a simple presentation of the energy changes obtained from BF passing through the cavity of α-CD from the wide side (Head-down). In Fig. 5b, the energy decreases sharply from the starting point **a** until reaching point **b** ($Z_{\mathbf{b}} = 2$ Å), which is the global minimum of the whole curve and indicates that BF and α-CD could form another stable inclusion complex in the Head-down pattern. Subsequently, the energy increases rapidly until reaching point **c** ($Z_{\mathbf{c}} = -8$ Å). The energy change curves of BF passing through the cavity of β-CD and γ-CD are also shown in Figs. 5a and 5b. It can be seen that BF and β- and γ-CD can also form stable inclusion complexes both for Head-up and Head-down interactions.

Table 4 Thermodynamic parameters of the inclusion complexes of α-CD·BF, β-CD·BF and γ-CD·BF calculated by the PM3 method[a]

Species	BF	α-CD	β-CD	γ-CD	α-CD·BF	β-CD·BF	γ-CD·BF
$PP_{head\text{-}up}$							
E_{HF} (kJ·mol^{-1})	−418.15	−5238.65	−6117.05	−6981.27	−5747.48	−6611.87	−7493.23
ΔE (kJ·mol^{-1})					−90.68	−76.67	−93.81
H (kJ·mol^{-1})	367.49	−2405.04	−2813.73	−3201.82	−2115.18	−2511.68	−2914.88
ΔH (kJ·mol^{-1})					−77.63	−65.44	−80.55
G (kJ·mol^{-1})	201.54	−2821.93	−3341.40	−776.41	−2616.57	−3114.02	−3576.50
ΔG (k·mol^{-1})					3.82	25.84	−1.63
ΔS (J·mol^{-1}·K^{-1})					−273.18	−304.95	−264.70
$PP_{head\text{-}down}$							
E (kJ·mol^{-1})	−418.15	−5238.65	−6117.05	−6981.27	−5756.75	−6623.89	−7504.01
ΔE (kJ·mol^{-1})					−99.95	−88.69	−104.59
H (kJ·mol^{-1})	367.49	−2405.04	−2813.73	−3201.82	−2124.02	−2518.78	−2924.54
ΔH (kJ·mol^{-1})					−86.47	−72.54	−90.21
G (kJ·mol^{-1})	201.54	−2821.93	−3341.40	−3776.41	−2638.95	−3122.76	−3572.46
ΔG (kJ·mol^{-1})					−18.56	17.10	2.41
ΔS (J·mol^{-1}·K^{-1})					−227.77	−300.65	−310.65

[a] ΔE is the binding energy; $\Delta E = E_{complex} - E_{BF} - E_{CD}$; $\Delta H = H_{complex} - H_{BF} - H_{CD}$; $\Delta G = G_{complex} - G_{BF} - G_{CD}$; $\Delta S = (\Delta H - \Delta G)/T$

Table 5 Single point energies of the inclusion complexes α-CD·BF, β-CD·BF and γ-CD·BF calculated by the B3LYP/6-31G* method

Species	BF	α-CD	β-CD	γ-CD	α-CD·BF	β-CD·BF	γ-CD·BF
E (a.u.)	−656.4185	−3664.3385	−4275.0622	−4885.8013			
Head-up					−4321.0066	−4931.7167	−5542.4727
ΔE (kJ·mol^{-1})					−655.18	−619.54	−664.08
Head-down					−4321.0474	−4931.7315	−5542.4909
ΔE (kJ·mol^{-1})					−762.22	−658.59	−712.02

To investigate the thermodynamics of the inclusion process, the binding energies (ΔE), enthalpy changes (ΔH), Gibbs energy changes (ΔG) and entropy changes (ΔS) for the most stable complexes α-CD·BF, β-CD·BF and γ-CD·BF (both Head-up and Head-down configurations) are summarized in Table 4. From Table 4 it can be seen that: (i) the binding energies (ΔE) of the complexes formed by BF passing through the cavity of α-, β- and γ-CD from its wide side are about 10.0 kJ·mol^{-1} lower than those from approach at the narrow side. The single point energies (in Table 5), calculated by B3LYP/6-31G*, also are much lower for the complexes obtained from Head-down approaches than those from Head-up. Thus, it is predicted that the BF is favored to enter the cavity of CD from its wide side compared to approaching from the narrow side. (ii) The negative ΔH and ΔS values suggest that formation of all these inclusion complexes is an enthalpy-driven processes. However, the experimental data indicate that formation of the inclusion complexes α-CD·BF and β-CD·BF are enthalpy-entropy synergistically driving processes, whereas that of γ-CD·BF is

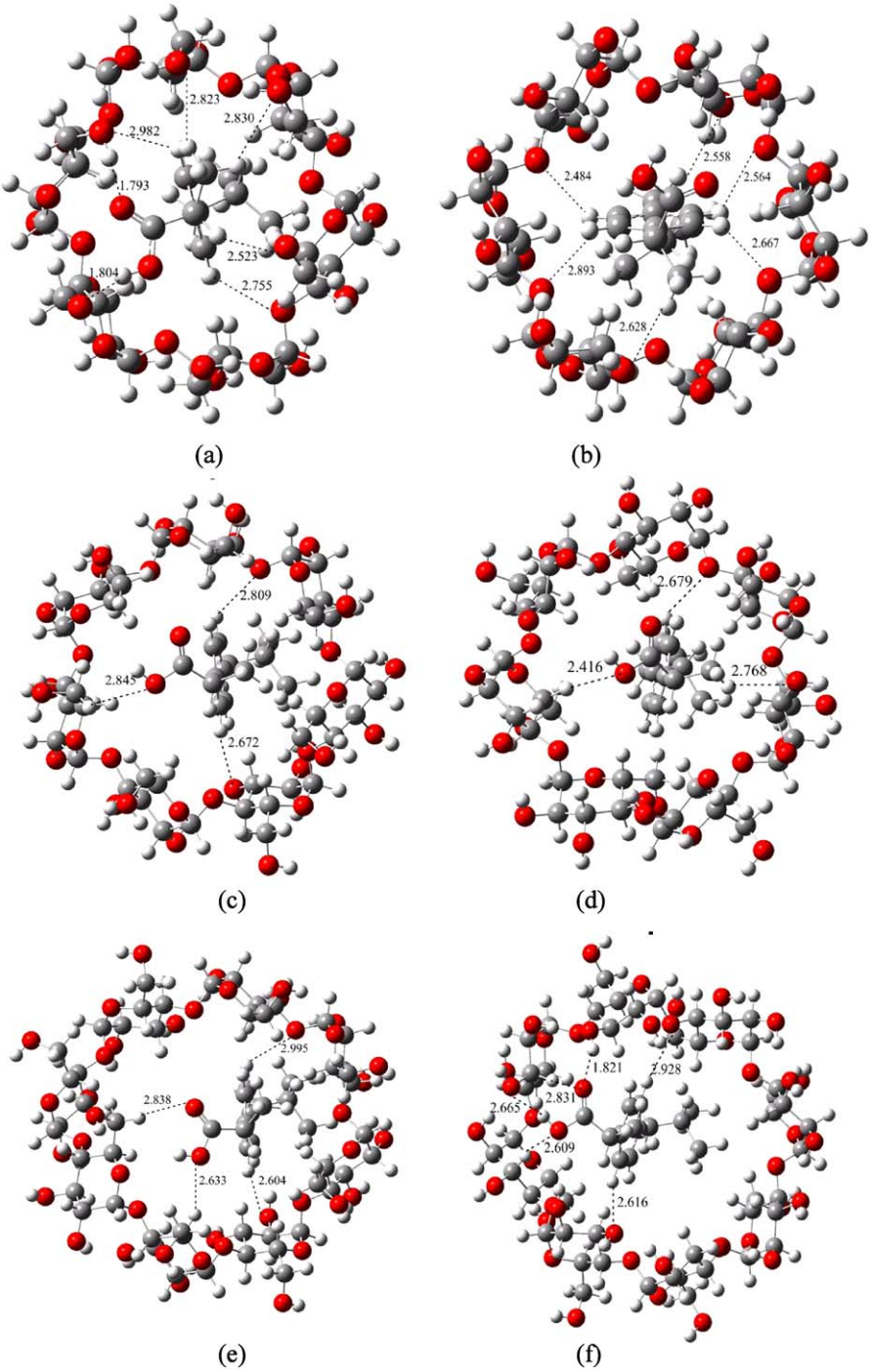

Fig. 6 Structures of the inclusion complexes (α-CD·BF, β-CD·BF and γ-CD·BF) obtained by the PM3 method: the inclusion complexes seen from the narrow side of the CD cavity (**a**, **c** and **e**); complexes seen from the wide side of the CD cavity (**b**, **d** and **f**)

an entropy-driven process. This can be explained by the solvent effect. Unfortunately, because of limitations in the calculation ability of our computer and the large molecular size of cyclodextrins (CDs), calculations for these systems can hardly be performed for aqueous solutions. However, it is observed that the solvent effect on the host-guest interactions easily changes the inclusion reaction from a non-spontaneous process in the gas phase to a spontaneous one in the aqueous phase. The host-guest interaction causes an enthalpy-entropy compensating process in the gas phase whereas the same interaction causes an enthalpy-entropy co-driven process in aqueous solution, because inclusion complexation releases a number of water molecules from the cavity of CDs.

Further studies on the geometrical structures of the inclusion complexes were also made, in order to explore the stability of these complexes and their PM3-optimized structures as shown in Figs. 6(a–f). In Fig. 6 it can be observed that the BF molecule is almost encapsulated in the cavity of a CD molecule. In addition, there are several intermolecular H-bonds in the structures. Here, the H-bond is defined as C–H···O or O–H···O with the distance between O and H being less than 3.0 Å [31]. The H-bond lengths range from 1.79 to 3.00 Å in the structures, which fall just within the reported length range for H-bonds. These data indicate that intermolecular H-bonds play an important role in the stability of these inclusion complexes.

4 Conclusions

The inclusion interactions between α-, β-, γ-CD and BF have been investigated by isothermal titration calorimetry and ^{1}H-NMR spectra measurements at 298.15 K. Analysis of the thermodynamic data indicates that the stoichiometries of all of the CD complexes with BF are 1:1, and that formation of the inclusion complexes α-CD·BF and β-CD·BF is driven by both enthalpy and entropy whereas that for γ-CD·BF is an entropy-driven process. The ^{1}H-NMR spectra data provide clear evidence for the inclusion phenomena indicating that the BF molecule inserts its isobutyl group and aromatic ring into the molecular cavity of the CDs. Theoretical studies suggest that H-bond interaction plays an important role in determining the stability of the inclusion complexes and that the BF is favored to enter into the cavity of the CDs from the wide side rather than the narrow side.

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