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Thermodynamics of the Molecular and Chiral Recognition of Cycloalkanols and Camphor by Modified β-Cyclodextrins Possessing Simple Aromatic Tethers

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The complex stability constants (K_S) and thermodynamic parameters ($\Delta G°$, $\Delta H°$, and $T\Delta S°$) for 1:1 inclusion complexation of β-cyclodextrin (β-CD) derivatives, 6-*O*-phenyl-β-CD (**2**) 6-*O*-(4-formylphenyl)-β-CD (**3**), 6-*O*-(4-nitrophenyl)-β-CD (**4**), 6-*O*-(4-bromophenyl)-β-CD (**5**), 6-*O*-(4-chlorophenyl)]-β-CD (**6**), and 6-*O*-(4-hydroxybenzoyl)-β-CD (**7**) with representative guest molecules, cyclic alcohols (cyclopentanol, cyclohexanol, cycloheptanol, cyclooctanol), (±)-borneol, and (±)-camphor, have been determined by means of titration microcalorimetry in an aqueous phosphate buffer solution (pH = 7.20) at 298.15 K. The results obtained indicate that the introduction to β-CD of an aromatic ring bearing different substituent groups significantly enhances the molecular binding ability and moderately alters the chiral discrimination ability for the guests examined here, displaying the highest enantioselectivity of up to 4.01 for the inclusion complexation of **6** with (±)-camphor. The enhanced molecular/chiral discrimination ability caused by derivatization is attributed solely to increased positive entropy changes due to the expanding hydrophobic interaction and desolvation effects. The binding modes of host−guest interactions derived from ROESY spectroscopy data show that the resulting complex of **4** and (+)-borneol possesses better induced-fit interaction as compared to (−)-borneol, which is responsible for the enhanced molecular/chiral recognition ability.

Introduction

Naturally occurring cyclodextrins (CDs) possessing a hydrophobic central cavity that are linked by α-1,4-glucose bonds can be selectively modified to provide all kinds of exquisite CD derivatives, which are known to significantly alter the original binding ability and molecular selectivity of parent CDs.[1−9] However, thermodynamic investigations on molecular recognition have been mainly focused on the inclusion complexation of native CDs with a great variety of organic, inorganic, and biologic guest molecules,[10−14] and thus the complexation thermodynamics of many CD derivatives are still unknown. Recently, Inoue,[15,16] Kano,[17,18] and Lincoln[19] et al. have reported the complexation and/or chiral recognition thermodynamics of aminated β-CDs possessing a positive charge with neutral/charged guests, respectively, revealing the counterbalance between electrostatic and conventional intracavity interactions. We have investigated the complexation thermodynamics of a series of modified CDs carrying different substituent groups, such as pyridinio, phosphonyl, anilineo, arylseleno, furfuryl, and quinolyl, with guests L-tryptophan, naphthalene derivatives, aliphatic alcohols and so on, with results that indicate electronic effect, the original conformation of modification group-tethered β-CDs, and the size/shape-fitted relationship between the host cavity and the guest diameter directly influence the binding ability.[20−25] How-

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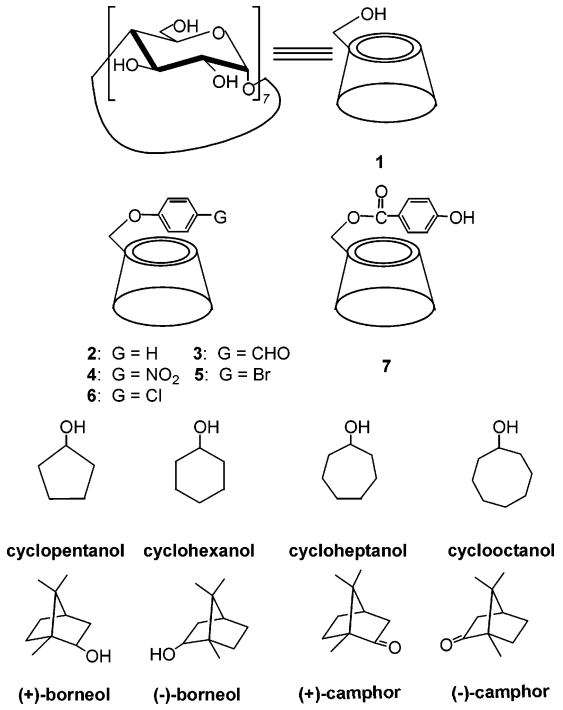
CHART 1. Structures of Host β-CD, Modified β-CDs, and Guest Molecules



ever, the thermodynamic behavior of CD derivatives linked by a rigid aromatic ring has scarcely been reported thus far, although these investigations are very important in understanding the structure-energetics correlation in molecular recognition. In this respect, some representative molecules, such as homologous cycloalkanols, borneol, and camphor, were selected as guests to measure their binding ability with CD derivatives. A simple reason for selecting camphor and borneol as guests is that both these chiral molecules possess an important biological function[26−30] and their size/shape is favorable for examining the effects of sidearms attached to β-CDs upon molecular/chiral recognition with CDs.[31,32]

In the present paper, we wish to report our investigation results on the molecular and chiral recognition thermodynamics of modified β-CDs **2**−**7** typically bearing a hydrophobic aromatic ring with cycloalkanols and camphor/borneol in an aqueous phosphate buffer solution (pH = 7.20) by titration microcalorimetry (Chart 1). In particular, we have examined the effects of the substituent groups attached to parent β-CD upon inclusion complexation with guest molecules and elucidated the correlations between the conformation of the resulting complexes and the thermodynamic parameters obtained.

Experimental Section

Materials. *N*,*N*-Dimethylformamide (DMF) was dried over calcium hydride for 2 days and then distilled under a reduced pressure prior to use. 6-*O*-Phenyl-β-CD (**2**), 6-*O*-(4-formylphenyl)-β-CD (**3**), 6-*O*-(4-nitrophenyl)-β-CD (**4**), 6-*O*-(4-bromophenyl)-β-CD (**5**), and 6-*O*-(4-hydroxybenzoyl)-β-CD (**7**), were prepared according to the procedures reported recently.[33,34] Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.1 mol·dm^{-3} phosphate buffer solution, pH 7.20, for all isothermal calorimetric measurements.

Synthesis of 6-*O*-(4-Chlorophenyl)]-β-CD (6). To a solution of 4-chlorophenol (0.4 g, 3 mmol) in DMF (10 mL) was added anhydrous K_2CO_3 (0.4 g, 3 mmol). The mixture was stirred for 2 h at room temperature under nitrogen, after which 6-(*p*-toluenesulfonyl)-β-CD[35] (1.9 g, 1.5 mmol) in dry DMF (20 mL) was added dropwise with stirring, and then the whole solution was heated at 80 °C for 24 h. The resultant solution was evaporated under reduced pressure to give a light yellow powder, which was dissolved in a minimum amount of hot water, and then the solution was poured into acetone (200 mL). The crude product obtained was purified on a Sephadex G-25 column, recrystallized twice from water, and then dried in vacuo to give a pure sample of **6** (20%). ^{1}H NMR (D_2O, TMS, ppm): δ 3.4−4.4 (m, 42H); 4.9−5.0 (m, 7H); 6.9−7.0 (d, 2H); 7.2−7.3 (d, 2H). UV−vis (H_2O) λ_{max} (ϵ): 279 nm (1470 M^{-1} cm^{-1}). Anal. Calcd for $C_{48}H_{73}ClO_{35}\cdot 6H_2O$: C, 42.59; H, 6.33. Found: C, 42.77; H, 6.48.

Isothermal Microcalorimetric Titration. All calorimetric experiments were performed using a thermostated and fully computer-operated VP-ITC calorimeter. The VP-ITC instrument was calibrated chemically by performing a complexation reaction of β-CD with cyclohexanol, and the thermodynamic parameters obtained were shown to be in good agreement with literature.[10] In this study, all microcalorimetric titrations were performed in an aqueous phosphate buffer solution (pH = 7.20) at atmospheric pressure and 298.15 K. Each solution was degassed and thermostated using a ThermoVac accessory before titration. Each microcalorimetric titration experiment consisted of 25 or 29 successive injections. A constant volume (5 μL/injection for cycloheptanol, 10 μL/injection for other guests) of guest solution (1.0−2.0 mM for chiral guests, 14.9−33.0 mM for cyclic alcohols) in a 0.250 mL syringe was injected into the reaction cell (1.4227 mL) charged with a native or modified β-CD solution (0.1−1.0 mM) in the same buffer solution. A representative titration curve is shown in Figure 1.

A control experiment to determine the heat of dilution was carried out with each run by performing the same number of injections with the same concentration of guest compound as used in the titration experiments into a pure buffer solution without the host compound. The dilution enthalpies determined in control experiments were subtracted from the enthalpies measured in the titration experiments to obtain the net reaction heat.

The ORIGIN software (Microcal Inc.), which was used to simultaneously compute the equilibrium constant (K_S) and

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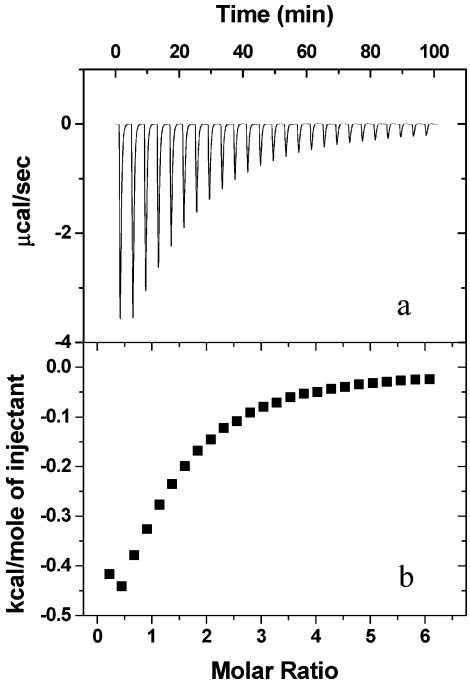

FIGURE 1. Calorimetric titration of host **4** with cyclohexanol in a phosphate buffer solution (pH = 7.20) at T = 298.15 K. (a) Raw data for 25 sequential injections (10 μL per injection) of cyclohexanol solution (33.00 mM) injected into host **4** solution (1.07 mM). (b) Reaction heat obtained from the integration of the calorimetric traces.

standard molar enthalpy of reaction ($\Delta H°$) from a single titration curve, gave a standard deviation based on the scatter of the data points in the titration curve. The net reaction heat in each run was calculated by the "one set of binding sites" model. Additionally, the first point was removed from the titration curve acknowledging that the concentration of host in the cell far exceeded the concentration of the guest.

A typical titration curve and the fitted results for the complexation of (−)-borneol with host **5** are shown in Figure 2. The knowledge of the binding constant (K_S) and molar reaction enthalpy ($\Delta H°$) enabled calculation of the standard free energy of binding ($\Delta G°$) and entropy changes ($\Delta S°$), according to the equation

$$\Delta G° = -RT \ln K_S = \Delta H° - T\Delta S°$$

where R is the gas constant and T is the absolute temperature.

In our experiments, the complexation of host **3** with (−)-camphor gives a relatively larger deviation of 9%. Such relatively large uncertainties may be encountered when microcalorimetric experiments are performed under circumstances where only a low guest affinity is obtained and/or a very low concentration is used. Experiments under improved conditions, using higher concentrations, could not be performed because of the poor water solubility of both host and guest compounds. To check the accuracy of the observed thermodynamic quantities, two independent titration experiments were carried out; the average values obtained for the complex stability constant (K_S), standard free energy ($\Delta G°$), enthalpy ($\Delta H°$), and entropy changes ($T\Delta S°$) for 1:1 inclusion complexation of various guest molecules with β-CD **1** and modified β-CDs **2**−**7** are listed in Table 1.

Results and Discussion

It is well-known that the "size-fitted" combination of host CDs and guest molecules yields 1:1 inclusion complexes and that the binding ability depends on the fitting efficiency of the size and shape of a guest into a CD cavity.[20] As can be seen from Table 1, all of the resulting complexes of β-CD **1** with homologous cycloalkanols, (±)-camphor, and (±)-borneol have a 1:1 stoichiometry, but their binding ability and thermodynamic parameters are entirely different from each other. Borneol possesses a relatively rigid skeleton and a fitted-size/shape and can therefore be more tightly wrapped in the host cavity than other guest molecules, giving stronger hydrophobic and

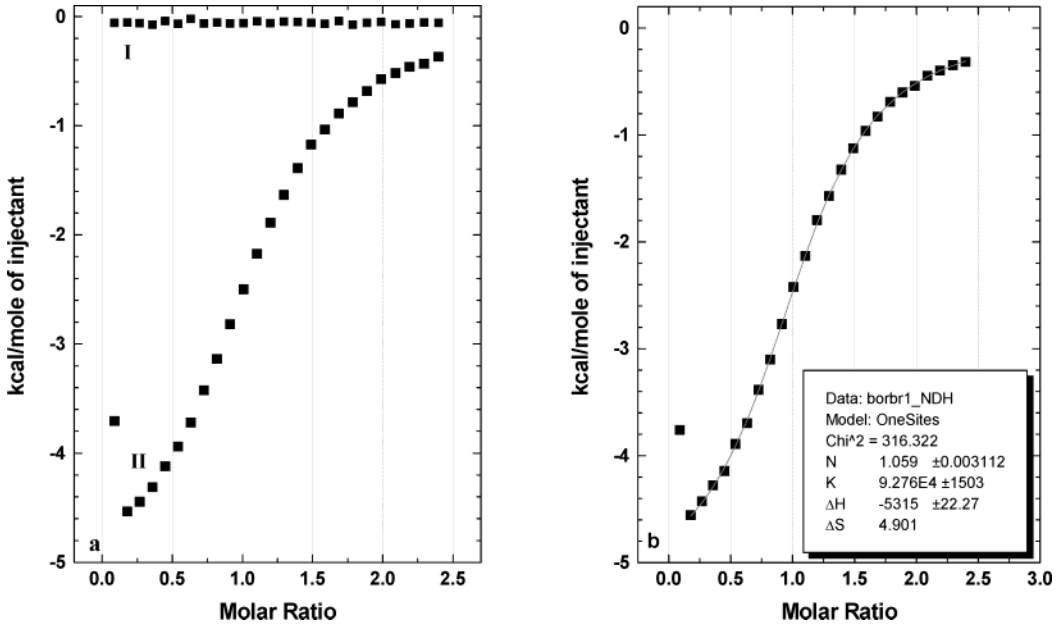

FIGURE 2. (a) Heat effects of the dilution (I) and the complexation reaction (II) of (−)-borneol with host **5** for each injection during titration microcalorimetric experiments. (b) "Net" heat effects of complexation of (−)-borneol with host **5** for each injection, obtained by subtracting the dilution heat from the reaction heat, which was fitted by computer simulation using the "one set of binding sites" model.

TABLE 1. Complex Stability Constant (K_S) and Thermodynamic Parameters for 1:1 Inclusion Complexation of Cycloalkanols, (±)-Camphor, and (±)-Borneol with β-CD 1 and Monomodified β-CDs 2−7 in a Phosphate Buffer Solution (pH 7.20) at T = 298.15 K

host	guest	N[a]	K_S (M^{-1})	$\Delta G°$ ($kJ·mol^{-1}$)	$\Delta H°$ ($kJ·mol^{-1}$)	$T\Delta S°$ ($kJ·mol^{-1}$)
1	cyclopentanol	2	168 ± 3	−12.70 ± 0.04	−3.90 ± 0.10	8.80 ± 0.10
	cyclohexanol	2	707 ± 4	−16.26 ± 0.01	−6.08 ± 0.01	10.19 ± 0.02
	cycloheptanol	2	2344 ± 92	−19.23 ± 0.10	−11.61 ± 0.26	7.63 ± 0.36
	cyclooctanol	2	4425 ± 1	−20.8 ± 0.00	−15.70 ± 0.01	5.10 ± 0.02
	(+)-camphor	2	8261 ± 261	−22.36 ± 0.07	−13.82 ± 0.55	8.54 ± 0.62
	(−)-camphor	2	4988 ± 60	−21.11 ± 0.03	−23.84 ± 0.60	−2.74 ± 0.58
	(+)-borneol	2	18640 ± 110	−24.38 ± 0.01	−20.86 ± 0.54	3.52 ± 0.55
	(−)-borneol	2	19750 ± 580	−24.52 ± 0.07	−23.16 ± 0.07	1.34 ± 0.16
2	cyclopentanol	2	392 ± 29	−14.80 ± 0.07	−1.53 ± 0.08	13.27 ± 0.15
	cyclohexanol	2	835 ± 12	−16.68 ± 0.03	−6.08 ± 0.33	10.60 ± 0.29
	cycloheptanol	2	3537 ± 31	−20.25 ± 0.02	−10.40 ± 0.01	9.85 ± 0.03
	cyclooctanol	2	6753 ± 23	−21.86 ± 0.01	−13.54 ± 0.01	8.32 ± 0.02
	(+)-camphor	2	13715 ± 55	−23.61 ± 0.01	−12.64 ± 0.07	10.97 ± 0.06
	(−)-camphor	2	5800 ± 167	−21.48 ± 0.07	−14.24 ± 0.59	7.24 ± 0.65
	(+)-borneol	2	35300 ± 1170	−25.96 ± 0.08	−19.29 ± 0.01	6.61 ± 0.01
	(−)-borneol	2	32240 ± 940	−25.74 ± 0.07	−18.96 ± 0.02	6.78 ± 0.04
3	cyclopentanol	2	618 ± 4	−15.94 ± 0.01	−0.15 ± 0.03	15.79 ± 0.04
	cyclohexanol	2	964 ± 78	−17.06 ± 0.30	−2.01 ± 0.14	15.06 ± 0.45
	cycloheptanol	2	3438 ± 21	−20.19 ± 0.02	−7.52 ± 0.01	12.66 ± 0.03
	cyclooctanol	2	6720 ± 82	−21.85 ± 0.04	−10.74 ± 0.02	11.11 ± 0.05
	(+)-camphor	2	12330 ± 490	−23.35 ± 0.10	−13.18 ± 0.38	10.17 ± 0.28
	(−)-camphor	2	8799 ± 810	−22.50 ± 0.23	−17.97 ± 0.55	4.54 ± 0.32
	(+)-borneol	2	41140 ± 1390	−26.34 ± 0.09	−20.24 ± 0.24	6.10 ± 0.32
	(−)-borneol	2	45530 ± 305	−26.59 ± 0.02	−22.58 ± 0.11	4.01 ± 0.13
4	cyclopentanol	2	834 ± 50	−16.36 ± 0.17	−1.04 ± 0.09	15.32 ± 0.25
	cyclohexanol	2	1432 ± 16	−18.05 ± 0.03	−3.44 ± 0.03	14.61 ± 0.00
	cycloheptanol	2	5025 ± 163	−21.12 ± 0.08	−9.92 ± 0.04	11.21 ± 0.13
	cyclooctanol	2	9992 ± 59	−22.83 ± 0.02	−13.11 ± 0.02	9.73 ± 0.02
	(+)-camphor	2	33775 ± 185	−25.85 ± 0.01	−10.44 ± 0.01	15.41 ± 0.01
	(−)-camphor	2	10640 ± 851	−22.98 ± 0.20	−15.43 ± 0.65	7.55 ± 0.84
	(+)-borneol	2	106750 ± 350	−28.70 ± 0.01	−16.91 ± 0.37	11.80 ± 0.38
	(−)-borneol	2	50505 ± 4065	−26.77 ± 0.28	−23.00 ± 0.75	3.77 ± 0.48
5	cyclopentanol	2	362 ± 17	−14.85 ± 0.13	−2.00 ± 0.01	12.85 ± 0.12
	cyclohexanol	2	1625 ± 11	−18.35 ± 0.07	−3.44 ± 0.07	14.91 ± 0.00
	cycloheptanol	2	7449 ± 185	−22.11 ± 0.07	−9.29 ± 0.23	12.82 ± 0.30
	cyclooctanol	2	16080 ± 110	−24.01 ± 0.02	−13.14 ± 0.02	10.87 ± 0.04
	(+)-camphor	2	23160 ± 160	−24.92 ± 0.02	−13.85 ± 0.16	11.07 ± 0.18
	(−)-camphor	2	11400 ± 220	−23.18 ± 0.03	−12.37 ± 0.58	10.81 ± 0.60
	(+)-borneol	2	86490 ± 4780	−28.18 ± 0.13	−23.97 ± 0.01	4.22 ± 0.13
	(−)-borneol	2	92440 ± 300	−28.35 ± 0.00	−22.09 ± 0.06	6.26 ± 0.15
6	cyclopentanol	2	629 ± 3	−15.94 ± 0.01	−1.93 ± 0.01	14.01 ± 0.00
	cyclohexanol	2	1253 ± 62	−17.68 ± 0.12	−5.82 ± 0.02	11.86 ± 0.11
	cycloheptanol	2	7925 ± 32	−22.25 ± 0.01	−10.56 ± 0.01	11.69 ± 0.01
	cyclooctanol	2	15880 ± 155	−23.98 ± 0.03	−13.55 ± 0.02	10.43 ± 0.01
	(+)-camphor	2	49760 ± 490	−26.80 ± 0.02	−10.94 ± 0.26	15.86 ± 0.30
	(−)-camphor	2	12405 ± 545	−23.36 ± 0.11	−14.15 ± 0.38	9.21 ± 0.27
	(+)-borneol	2	133450 ± 2450	−29.26 ± 0.05	−18.92 ± 0.40	10.33 ± 0.44
	(−)-borneol	2	89570 ± 750	−28.27 ± 0.02	−22.53 ± 0.00	5.73 ± 0.02
7	(+)-camphor	2	18660 ± 990	−24.37 ± 0.13	−13.50 ± 0.08	10.87 ± 0.05
	(−)-camphor	2	14595 ± 325	−23.77 ± 0.06	−15.91 ± 0.21	7.86 ± 0.26
	(+)-borneol	2	83385 ± 2855	−28.09 ± 0.08	−24. 25 ± 0.11	3.84 ± 0.20
	(−)-borneol	2	92250 ± 245	−28.34 ± 0.00	−22.43 ± 0.07	5.91 ± 0.07

[a] N is the number of independent titration experiments performed.

van der Waals interactions leading to the highest enthalpy, which is directly related to the inclusion complex stability. A discussion of the molecular and chiral recognition by monomodified β-CD is interesting from the viewpoint of an induced-fit interaction between the modified β-CD cavity and guest molecule, because simple aromatic compounds bearing different substituent groups attached on the edge of a β-CD significantly alter not only the molecular binding ability but also the chiral selectivity.

Binding Ability for Cycloalkanols. The complex stability constants obtained clearly indicate that the affinity of all β-CD derivatives examined here toward cyclic alcohols is substantially enhanced 1.2−4.9 times as compared with that of native β-CD. Although the magnitudes of enthalpy and entropy changes for each β-CD derivative vary considerably, the trend seems to be similar in each case. The enhanced binding constant (K_S) for the complexation of **4** with cyclopentanol (CP) is increased from 168 to 834, which is 4.9 times higher than that for β-CD. Apparently, the enhanced binding ability can be attributed to the geometric complementarity between host and guest, since the relatively small CP molecule more easily produces the co-inclusion complex with aromatic sidearm in **4**, which is also supported by the ROESY experiment of the complex **4**-cyclopentanol (Figure 3) and the examination of the CPK models. To further understand the origin of the enhanced binding

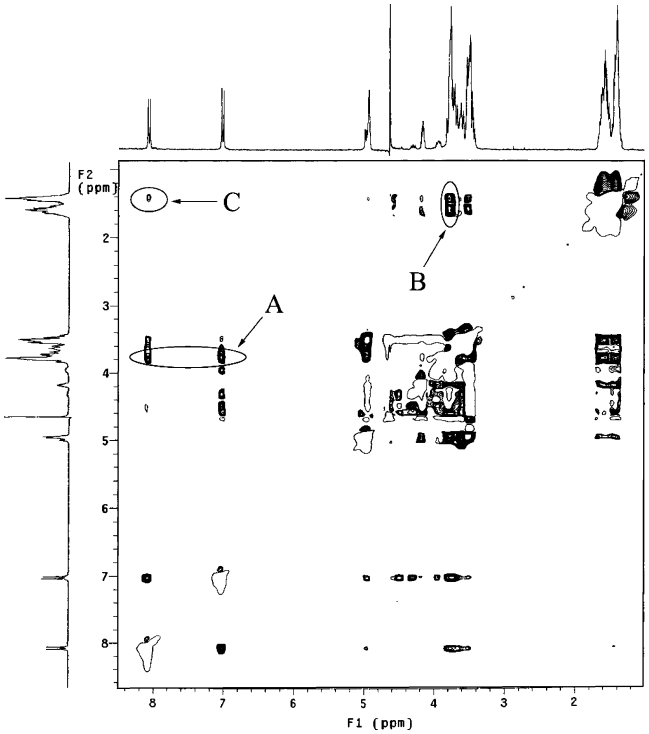

FIGURE 3. ROESY spectrum of a complex of host **4** (1×10^{-3} mol·dm^{-3}) and cyclopentanol (1.4×10^{-3} mol·dm^{-3}) with a mixing time of 400 ms in D_2O solution. In the spectrum, cross-peaks A represent the correlations of the aromatic ring of CD and CD cavity, cross-peaks B correspond to those of guest CP and CD cavity, and cross-peak C displays that of guest CP and the aromatic ring of CD.

ability from the thermodynamics point of view, differential reaction enthalpy ($\Delta\Delta H° = \Delta H°_{\text{host 2–6}} - \Delta H°_{\beta\text{–CD}}$) and entropy ($T\Delta\Delta S° = T\Delta S°_{\text{host 2–6}} - T\Delta S°_{\beta\text{–CD}}$) were computed. The calculated results exhibit that hosts **2**−**6** give smaller reaction enthalpy changes ($\Delta\Delta H° = 0$−4.96 kJ·mol^{-1}) and more favorable entropy changes ($T\Delta\Delta S° = 0.41$−6.99 kJ·mol^{-1}) than native β-CD. The decreased enthalpy change ($\Delta\Delta H°$) for **2**−**6** is overcompensated for by the differential entropy change gain, ultimately leading to the enhancement of binding constants. Therefore, we can conclude that the contribution of the entropy change undoubtedly plays a crucial role in increasing the complex stability for modified β-CDs. It should be noted that the complexation thermodynamic behavior of modified β-CDs **3**−**6** with cycloheptanol (CH′) as well as host **3** with cyclooctanol (CO) is different from that of native β-CD, showing that inclusion reactions are mainly driven by larger entropic changes ($\Delta H° < 0$; $T\Delta S° > 0$; $|\Delta H°| < |T\Delta S°|$). Undoubtedly, the introduction of a hydrophobic aromatic ring to β-CD expands the hydrophobic cavity of a parent β-CD to some extent, and thus judging from the thermodynamic parameters obtained, cooperative van der Waals and hydrophobic interactions must occur in inclusion complexation with modified β-CDs.

To visualize the comprehensive influence on the complexation process of both the sidearm attached to parent β-CD and the shape/size of the guest, the changing profiles of binding constants (K_S) upon complexation of cycloalkanols with hosts **1**−**6** are shown in Figure 4.

As can be seen from Figure 4, β-CD derivatives **2**−**6** for the inclusion complexation with the same guest

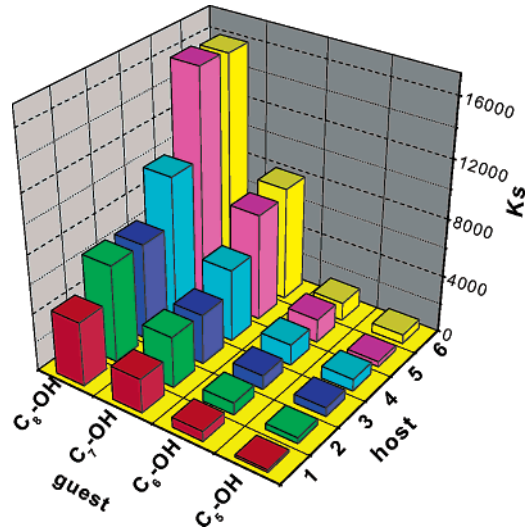

FIGURE 4. Binding constants (K_S) as a function of cyclic alcohol for the inclusion complexation of hosts **1**−**6** in a phosphate buffer solution (pH = 7.20) at 298.15 K.

exhibit different host selectivity sequences, such that **1** < **5** < **2** < **3** < **6** < **4** for the complexation with CP and **1** < **2** < **3** < **6** < **4** < **5** for that with cyclohexanol (CH). The binding selectivity of hosts **2**−**6** by the guest molecule is increased with decreasing molecular size of the cyclic alcohol. Cyclooctanol displays the weakest host selectivity for the inclusion complexation with hosts **2**−**6**, as it possesses a relatively larger size as compared with other guest molecules although its affinity toward these hosts is enhanced moderately compared with parent β-CD. To discuss the effect of guest ring size on the inclusion complexation from the viewpoint of thermodynamics, the slope of the linear fit of $-\Delta G°$, $-\Delta H°$, and $-T\Delta S°$ for hosts **2**−**6** against the number of methylenes in the guest (N_c) are calculated, respectively, and their average values have been computed as 2.48, 4.10, and 1.56 kJ·mol^{-1}. As compared with native β-CD ($-d\Delta G°/dN_c = 3.5$ kJ·mol^{-1}),[10] modified hosts **2**−**6** give a large reduction in $-d\Delta G°/dN_c$, indicating that the modified groups increase the binding ability of β-CD with the smaller guest molecules. Thermodynamically, the $-d\Delta H°/dN_c$ difference between β-CD (4.8 kJ·mol^{-1} of $-d\Delta H°/dN_c$)[10] and modified β-CD is very small, and thus the large decrease of the hosts **2**−**6** in $-d\Delta G°/dN_c$ caused by $-dT\Delta S/dN_c$ must be attributable to the expanded host hydrophobic effect by the sidearm and the extensive desolvation in the complexation process.

Electronic Effect of the Substituting Group. Connors,[36] Guo,[37] and Davies[38] et al. have previously employed the Hammett's σ values as a major parameter to predict the stability constants for resulting complexes of β-CD with guests. In this context, hosts **2**−**6** that bear a very similar structure except for the *para* substituent group exhibit significantly distinct behavior upon complexation with cyclic alcohols. To investigate the influence of the electronic effect from the substituent group of CD

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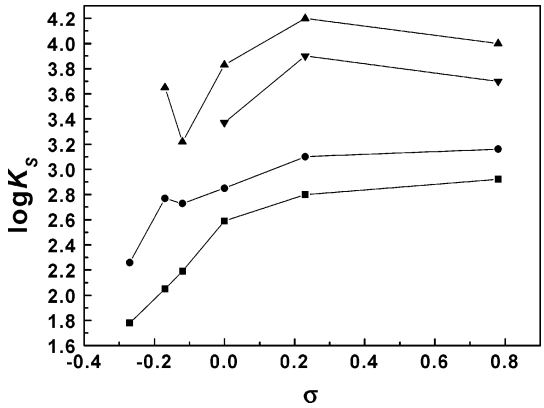

FIGURE 5. The stability constants (log K_S) of the host−guest complex plotted as a function of the Hammett's value of the host's substituting group, for complexation with (■) cyclopentanol, (●) cyclohexanol, (▼) cycloheptanol, and (▲) cyclooctanol, respectively.

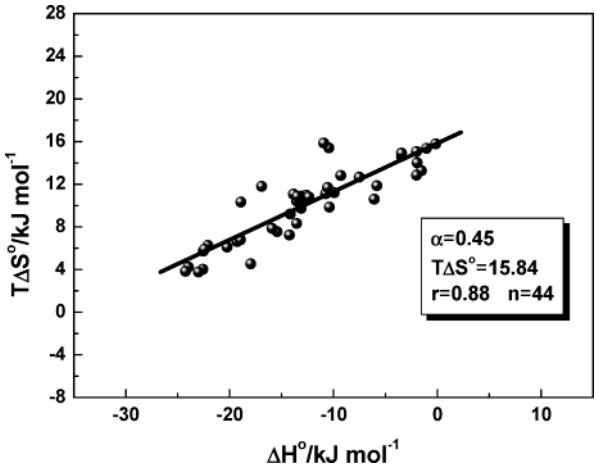

FIGURE 6. Enthalpy−entropy compensation plot for inclusion complexation with modified β-CDs **2**−**7**.

on the inclusion process with guests, the complex stability constants upon inclusion complexation with cyclic alcohols are plotted in Figure 5 as a function of the Hammett's σ value of the substituent group of the aromatic ring using current and previously reported data.[39] Neglecting the difference of the pivot atom, the complex stability constants are gradually enhanced with an increased σ value, indicating that the electron density affects the complex stability significantly. A reasonable explanation for this observation is that the charge and relative Hammett σ-values of the substituent group at the sidearm determine the orientation of the substituent group linked to the dipolar CD cavity, which influences the hydrophobic microenvironment of the CD cavity.[40]

Structural Effect of the Guest Molecules. Camphor and borneol enantiomers show higher negative enthalpy values for inclusion complexation with hosts **2**−**6** as compared with homologous cyclic alcohols, as they possess a rigid bicyclic framework with branch chains. This indicates that the guests with double rings are more suitable for the cavity of the modified β-CD linked by a simple aromatic ring, as they have higher cooperative interactions between modified β-CDs and guests. On the other hand, the stronger interaction between borneol and **2**−**7** gives a larger negative enthalpy change over 4.61−10.12 kJ·mol^{-1} than that between camphor and **2**−**7**, which is probably attributable to intermolecular hydrogen bond formation between borneol and CDs because guests lacking a hydroxyl group give the relevant lower enthalpic changes upon inclusion complexation with CD.[41−44] This confirms again that the hydrogen bonding and van der Waals interactions cooperatively contribute to the recognition process of the modified β-CDs.

Binding Ability and Chiral Recognition for Camphor/Borneol. It has been observed that the hosts **2**−**7** enhance not only the molecular binding ability but also chiral selectivity. Compared with native β-CD, modified β-CDs **2**−**7** give larger K_S values, 1.16−6.02 times for complexation with camphor, and 1.63−7.16 times for borneol. The relatively stronger binding ability may come from the co-inclusion of functional groups and guest molecules in the CD cavity by induced-fit interaction, which is well-confirmed by the inclusion modes derived from the following ROESY experiments. From the co-inclusion modes, it is noted that the hydrophobic tether group capping the CD cavity not only enhances the hydrophobic microenvironment of the CD cavity but also effectively shields the accommodated guest from the attack of water, leading to the enhancement of the inclusion complex stability to some extent. Thermodynamically, the enthalpic and entropic changes of the complexation reactions between **2**−**7** and the chiral guests are both favorable ($\Delta H° < 0$; $T\Delta S° > 0$), which is different from the complexation reactions with homologous cycloalkanols. The differential reaction enthalpy and entropy changes calculated by using the data presented in Table 1 reveal that nearly all of the entropy changes ($1.63 < T\Delta S°_{\text{Hosts 2–7}} - T\Delta S°_{\beta\text{–CD}} < 13.55$ for camphor, $0.32 < T\Delta S°_{\text{Hosts 2–7}} - T\Delta S°_{\beta\text{–CD}} < 8.28$ for borneol) are greater than the enthalpy changes ($-0.03 < \Delta H°_{\text{Hosts 2–7}} - \Delta H°_{\beta\text{–CD}} < 11.47$ for camphor, $-3.39 < \Delta H°_{\text{Hosts 2–7}} - \Delta H°_{\beta\text{–CD}} < 4.20$ for borneol). Therefore, the entropy changes apparently control the enhanced binding ability of modified β-CDs as compared to native β-CD. The binding ability of (+)-camphor by hosts **2**−**7** is stronger than that of (−)-camphor. The enthalpic loss for host **2** complexation with (+)-camphor is calculated as $\Delta\Delta H° =$ 1.18 kJ·mol^{-1}, which is 8.42 kJ·mol^{-1} smaller than that of (−)-camphor with host **2**, $\Delta\Delta H° =$ 9.60 kJ·mol^{-1}. However, the significant difference in enthalpic losses for (+)/(−)-isomers is almost completely compensated by the entropic gains ($T\Delta\Delta S°_{(+)\text{–cam}} =$ 2.43 kJ·mol^{-1}; $T\Delta\Delta S°_{(-)\text{–cam}} =$ 9.98 kJ·mol^{-1}), which ultimately gives a modest enhancement in enantioselectivity from K_+/K_- as 1.66 for β-CD to 2.36 for host **2**. Simultaneously, the complexation thermodynamics of other modified β-CDs with (±)-camphor also show an analogical tendency except hosts **3** and **7**. These results indicate that the enhanced chiral discrimination with (±)-camphor should be solely attributable to the increased positive entropy changes

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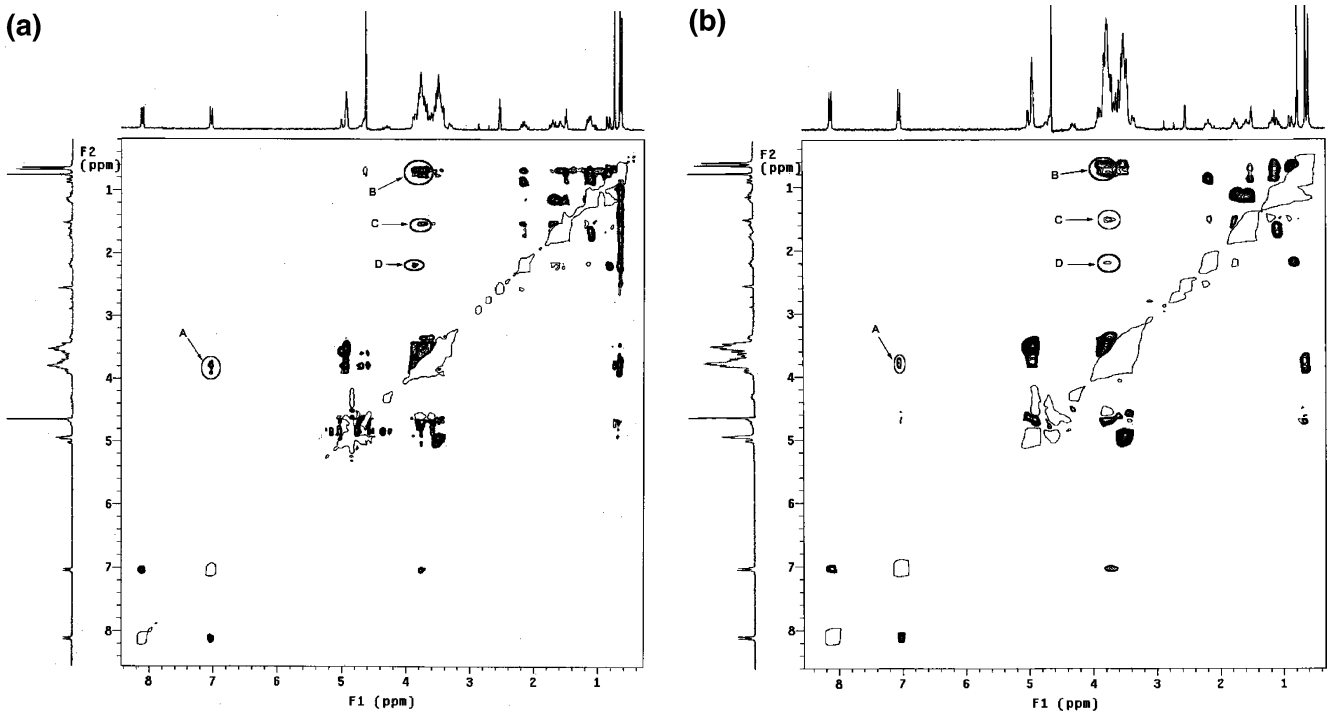

FIGURE 7. ROESY spectra of a complex of host **4** (1×10^{-3} mol·dm^{-3}) and (a) (+)-borneol (1×10^{-3} mol·dm^{-3}) and (b) (−)-borneol (1×10^{-3} mol·dm^{-3}) with a mixing time of 400 ms in 2% DMSO/98% D_2O solution.

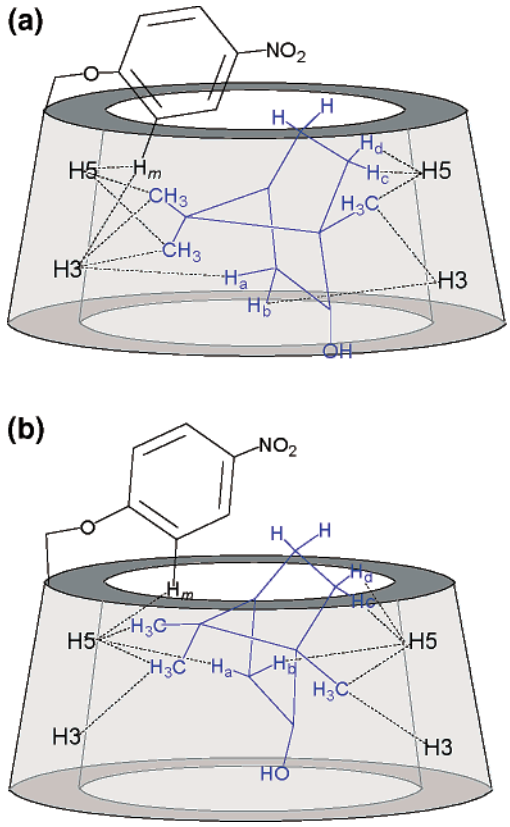

FIGURE 8. Plausible complex structures of (a) (+)-borneol and (b) (−)-borneol with host **4** elucidated from the ROESY experiments.

($T\Delta S°$) accompanying smaller enthalpic losses. It is observed that an analogous tendency to (±)-camphor also exists upon complexation with (±)-borneol, showing that the chiral recognition ability of (±)-borneol by modified β-CDs is also controlled by entropy gains with smaller enthalpy losses. The enantioselectivity increases only slightly for (±)-borneol, but hosts **2**, **4**, and **6** can reverse the chiral selectivity for (±)-borneol as compared with parent β-CD, giving a modest chiral selectivity of up to 2.11 for (+)-borneol versus (−)-borneol upon complexation with host **4**. Apparently, the introduction of the sidearm possessing a strong electron-withdrawing group into β-CD can alter the hydrophobic microenvironment of the CD cavity to a greater extent and afford different induced-fit interaction upon complexation with the chiral guest, leading to an enhanced chiral recognition ability.

Enthalpy−Entropy Compensation. Despite the similarity in structure of the hosts **2**−**7**, we still examined the general enthalpy−entropy compensation effect among the complexation reactions. The entropy changes ($T\Delta S°$) were therefore plotted against the enthalpy changes ($\Delta H°$) using the compiled thermodynamic quantities listed in Table 1 (number of data set (N) = 44). A regression line (correlation coefficient (r) = 0.88) with a small slope (α = 0.45) and a relatively larger intercept ($T\Delta S°$ = 15.84 kJ·mol^{-1}) was obtained and is shown in Figure 6. The slope of the plot for the CD derivatives linked by the rigid aromatic ring is smaller by 0.54 than the reported value for simple modified CDs possessing a flexible hydrophilic sidearm (α = 0.99, $T\Delta S°$ = 17 kJ·mol^{-1}),[10] indicating that the resultant complex of hosts **2**−**7** with guests examined here occurs with minor conformational change during the complexation process. On the other hand, the desolvation effect of the modified CDs investigated here is only slightly smaller than the reported modified CDs linked by flexible hydrophilic groups, deduced from the nearly identical intercept,

which further confirms that an extended hydrophobic cavity is mainly responsible for increased positive entropy changes.

ROESY Spectra. To elucidate the structural features responsible for the high chiral recognition of (±)-borneol upon complexation with modified β-CD **4**, ^{1}H ROESY experiments have also been performed on a Varian Mercury VX300 instrument. As can be seen from Figure 7a, the NOE cross-peaks (peak A) between the H3 and H5 of the CD and *meta* protons (H^m) of the nitrophenyl moiety of CD indicate that the aromatic ring moiety is moderately self-included into the cavity from the β-CD primary side. Simultaneously, NOE cross-peaks (peak B) between the β-CD's H5/H3 and methyl protons of (+)-borneol are also observed. Peaks C and D correspond to the correlations of H_c/H_d of (+)-borneol with H5 of CD and H_a/H_b of (+)-borneol with H3 of CD, respectively. The results suggest that (+)-borneol is completely included into the CD cavity, as illustrated in Figure 8a. The ROESY spectrum of a resulting complex of **4** and (−)-borneol seems the same as in Figure 7a. However after comparing them carefully, we found that only the NOE cross-peak (peak A) between H5 of the CD and *meta* protons (H^m) of the nitrophenyl moiety attached to CD was observed in Figure 7b, indicating that the aromatic ring moiety is located over the cavity. Moreover, the cross-peak D is also different from that of **4** and (+)-borneol, exhibiting the correlations between H_a/H_b of (−)-borneol with H5 of CD instead of H3 of CD. From the results obtained, we may deduce reasonably that the (−)-borneol molecule is located on the primary hydroxyl side of CD cavity, as shown in Figure 8b.

From the above ROESY results, we can deduce that (+)-borneol is accommodated more tightly and deeply in the cavity of host **4**, which results in extensive desolvation, giving more favorable entropy changes of 11.8 kJ·mol^{-1} as compared to 3.77 kJ·mol^{-1} of (−)-borneol. Therefore, the relatively stronger induced-fit interaction between modified β-CDs and guest molecules enhances not only the hydrophobic microenvironment of the CD cavity but also chiral discrimination ability upon inclusion complexation with (±)-borneol.

Conclusion

In the present investigation, we have demonstrated that β-CDs tethered by a rigid aromatic ring possessing different substituent groups can precisely recognize the shape/size of cycloalkanols and enhance or even switch the chiral discrimination ability, giving a highest enantioselectivity of 4.01 for (±)-camphor and 2.11 for (±)-borneol as compared with the parent β-CD. Thermodynamically, the enhanced molecular and chiral recognition abilities by modified β-CDs are consistently controlled by entropy gains with smaller enthalpy losses. The binding modes inferred from the ROESY experiments reveal that the enhanced molecular and chiral recognition ability is mainly attributed to the stronger induced-fit interaction between modified β-CDs and guest molecules.

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Supporting Information Available: Differential standard free energies ($\Delta\Delta G°$) enthalpies ($\Delta\Delta H°$) and entropies ($T\Delta\Delta S°$) for the complexation of modified β-CDs **2**−**7** with homologous cycloalkanols, (±)-camphor, and (±)-borneol in a phosphate buffer solution (pH = 7.20) at 298.15 K. This material is available free of charge via the Internet at http://pubs.acs.org.

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