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Synthesis of Phosphoryl-Tethered β-Cyclodextrins and Their Molecular and Chiral Recognition Thermodynamics

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Two novel phosphoryl-bridged bis- and tris(β-cyclodextrin)s of different tether lengths, i.e., bis[*m*-(*N*-(6-cyclodextryl)-2-aminoethylaminosulfonyl)phenyl]-*m*-(chlorosulfonyl)phenylphosphine oxide (**5**) and tris[*m*-(*N*-(6-cyclodextryl)-8-amino-3,6-diazaoctylaminosulfonyl)phenyl]phosphine oxide (**6**), have been synthesized by reactions of 6-oligo(ethylenediamino)-6-deoxy-β-cyclodextrins with tris[*m*-(chlorosulfonyl)phenyl]phosphine oxide. The complex stability constants (K_S), standard molar enthalpy ($\Delta H°$), and entropy changes ($\Delta S°$) were determined at 25 °C for the inclusion complexation of phosphoryl-modified bis- and tris-cyclodextrins (**5** and **6**, respectively), mono[6-*O*-(ethoxyhydroxyphosphoryl)]-β-cyclodextrin (**2**), mono[6-*O*-(diethylamino-ethoxyphosphoryl)]-β-cyclodextrin (**3**), and mono[6-*O*-(diphenoxyphosphoryl)]-β-cyclodextrin (**4**) with representative alicyclic and *N*-Cbz-D/L-alanine guests in 0.1 M phosphate buffer solution at pH 7.2 by means of titration microcalorimetry. The thermodynamic parameters obtained indicate that the charge−dipole interaction between the phosphoryl moiety and the negatively charged guests, as well as the conformational difference of modified β-cyclodextrins in aqueous solution, significantly contribute to the inclusion complexation and the enhanced chiral discrimination. The interactions and binding modes between the hosts and chiral guests were further studied by two-dimensional NMR spectroscopy to elucidate the influence of the structural features of hosts on their increased chiral recognition ability and to establish the correlation between the conformation of the resulting complexes and the thermodynamic parameters obtained.

Introduction

It has been amply demonstrated that modified cyclodextrins (CDs) possessing nucleophilic or electrophilic substituents significantly alter the original complexation behavior of native CDs toward various guests. For this reason, a considerable amount of effort has been devoted to the design and synthesis of novel CD derivatives with functional substituents, which are of scientific and technological importance.[1−16] Recently, Breslow et al. reported that dimeric β-CD can disrupt the protein−protein aggregation to inhibit the activity of L-lactate dehydrogenase and citrate synthase.[9] Bis-CDs tethered with a linker containing a C═C bond were used as cleavable carriers for the photosensitizer in photodynamic tumor therapy.[10] Bayley and co-workers described a pore-forming protein equipped with two different CDs at the both ends, in which the trapped organic molecule shuttles back and forth between the two CD stations. Such self-assembling nanostructures may be employed in the fabrication of multianalyte sensors.[13,14] Since these applications are essentially based on the interaction between the CD and the guest molecule, the investigations of the structure of modified CDs and their inclusion complexation thermodynamics are of great importance in elucidating the origin of selective binding to a specific guest. It is noted, however, that previous thermodynamic

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studies focused mainly on inclusion complexation of native CDs with conventional guests[17−27] and less attention has been paid to the molecular recognition thermodynamics of chemically modified CDs, in particular bridged oligo(cyclodextrin)s with functional tethers.[18,20] The thermodynamic studies of such systems are expected to provide us with a deeper understanding of the factors governing the supramolecular complexation through cooperative multiple intermolecular interactions.[18,20]

Possessing a chiral hydrophobic cavity surrounded by D-glucopyranose units, native and modified CDs exhibit chiral recognition ability upon complexation with a variety of chiral guests and have been applied in particular to biomimetic chemistry and separation science and technology.[28,29] It has been revealed, however, that the chiral discrimination by native CDs leads, in general, to poor results due to the perfect enthalpy−entropy compensation canceling the originally small differences in $\Delta H°$ and $T\Delta S°$ for two enantiomers.[30] Fortunately, the poor chiral recognition ability can be significantly improved by chemical modification.[26,31,32] Recently, it has been shown that aminated CD strongly binds charged, rather than neutral, guests through the attractive Coulombic interaction, indicating that the charged group in the guest molecule appreciably contributes to the overall complexation thermodynamics.[26] We have also shown that the introduction of a phosphoryl moiety to β-CD enhances the complex stability with some aliphatic amino acids through electrostatic interaction.[33]

In the present study, we synthesized a series of mono-, bis-, and tris-CDs with phosphoryl tethers, i.e., mono[6-*O*-(ethoxyhydroxyphosphoryl)]-β-cyclodextrin (**2**), mono-[6-*O*-(diethylamino-ethoxyphosphoryl)]-β-cyclodextrin (**3**), mono[6-*O*-(diphenoxyphosphoryl)]-β-cyclodextrin (**4**), bis-[*m*-(*N*-(6-cyclodextryl)-2-aminoethylaminosulfonyl)phenyl]-*m*-(chlorosulfonyl)phenylphosphine oxide (**5**), and tris[*m*-(*N*-(6-cyclodextryl)-8-amino-3,6-diazaoctylaminosulfonyl)-phenyl]phosphine oxide (**6**) (Chart 1), and their complexation thermodynamic behavior with representative neutral and negatively charged alicyclic guests and *N*-Cbz-D/L-alanine (Chart 2) was examined by means of microcalorimetric titration. It is of particular interest to investigate how and to what extent the phosphoryl moiety, appended as a functional sidearm or tether, affects the molecular and chiral recognition behavior of mono-, di-, and trimeric CD hosts toward the negatively charged guests.

CHART 1. Host Structure

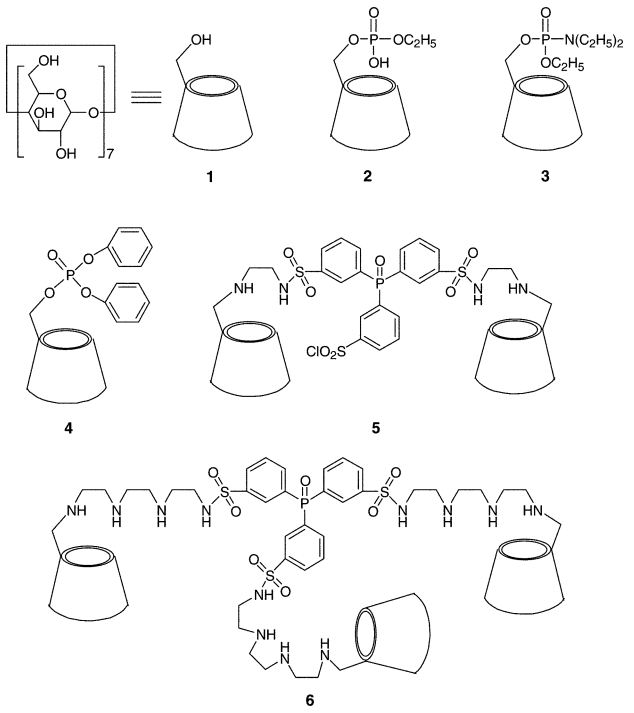
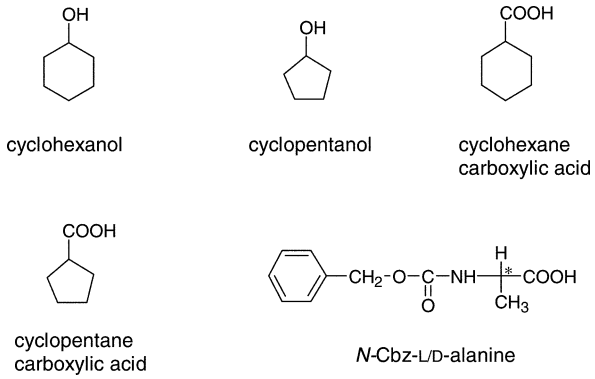


CHART 2. Guest Molecule



Experimental Section

Materials. *N*,*N*-Dimethylformamide (DMF) was dried over calcium hydride for 2 days and then distilled under reduced pressure prior to use. Mono[6-*O*-(ethoxyhydroxyphosphoryl)]-β-cyclodextrin (**2**), mono[6-*O*-(diethylamino-ethoxyphosphoryl)]-β-cyclodextrin (**3**), mono[6-*O*-(diphenoxyphosphoryl)]-β-cyclodextrin (**4**) were synthesized as reported previously.[33,34] Tris(*m*-chlorosulfonylphenyl) phosphine oxide was prepared by a literature procedure.[35] Mono[6-oligo(ethylenediamino)-6-

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deoxy]-β-cyclodextrins were prepared according to the procedures reported by Harada et al.[36] Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.1 M phosphate buffer solution of pH 7.20 for spectral measurements and microcalorimetric titrations.

Synthesis of Bis[*m*-(*N*-(6-cyclodextryl)-2-aminoethylaminosulfonyl)phenyl]-*m*-(chlorosulfonyl)phenylphosphine Oxide (5). Mono[6-(2-aminoethylamino)-6-deoxy]-β-cyclodextrin (1.6 g, 1.4 mmol) was dissolved in DMF (50 mL) containing two drops of triethylamine, to which tris(*m*-chlorosulfonylphenyl)phosphine oxide (0.1 g, 0.18 mmol) in DMF (20 mL) was added dropwise at 5 °C under nitrogen. The resultant mixture was stirred for 3 days in an ice bath and then for an additional 7 days at 70 °C. The reaction mixture was evaporated under reduced pressure to dryness. The residue was dissolved in water, and the resultant solution was poured into acetone to give a precipitate. The crude product obtained was collected by filtration and purified by column chromatography over Sephadex G-25 with distilled deionized water as an eluant to give a pure sample 0.23 g, in 40% yield: ^{1}H NMR (D_2O, TMS) δ 3.0−4.0 (m, 92H), 4.7−4.9 (m, 14H), 7.4−8.0 (m, 12H); ^{13}C NMR (D_2O) δ 144.34, 144.18, 134.39, 131.56, 130.27, 128.24, 101.95, 99.52, 81.24, 76.71, 73.15, 71.86, 60.37; FT-IR (KBr) ν 3344, 3060, 2929, 1660, 1587, 1548, 1433, 1332,1301, 1185, 1153, 1079, 1032, 944, 846, 801, 754, 691, 617, 578, 534 cm^{-1}; UV−vis (H_2O) λ_{max} (ε) 276.2 (4820), 269.6 (5010), 263.0 nm (4470 M^{-1} cm^{-1}). Anal. Calcd for $C_{106}H_{162}O_{78}N_4S_3PCl\cdot 18H_2O$ (MW = 3227.3): C, 39.45; H, 6.18; N, 1.74; Cl, 1.10. Found: C, 39.31; H, 5.86; N, 2.04; Cl, 0.88.

Synthesis of Tris[*m*-(*N*-(6-cyclodextryl)-8-amino-3,6-diazaoctylaminosulfonyl)phenyl]phosphine Oxide (6). The bridged tris(β-cyclodextrin) (**6**) was synthesized in 10% yield from the reaction of mono[6-(8-amino-3,6-diazaoctylamino)-6-deoxy]-β-cyclodextrin with tris(*m*-chlorosulfonylphenyl)phosphine oxide, according to procedures similar to those employed in the synthesis of **5**: ^{1}H NMR (D_2O, TMS) δ 2.3−3.76 (m, 162H), 4.87−5.20 (m, 21H), 7.60−7.64 (m, 6H), 7.92−7.98 (m, 6H); ^{13}C NMR (D_2O) 144.49, 144.33, 134.62, 131.62, 130.41, 128.49, 102.05, 81.33, 73.26, 72.20, 72.00, 71.36, 60.46, 52.02, 51.87; FT-IR (KBr) ν 3348, 3065, 2927, 1660, 1433, 1332, 1299, 1227,1154, 1078, 1032, 1079, 1032, 944, 847, 801, 755, 697, 616, 578, 535 cm^{-1}; UV−vis (H_2O) λ_{max} (ε) 276.8 (3390), 269.4 nm (4160 M^{-1}cm^{-1}). Anal. Calcd for $C_{162}H_{267}O_{109}N_{12}S_3P\cdot 27H_2O$ (MW = 4740.5): C, 41.05; H, 6.82; N, 3.55. Found: C, 40.70; H, 6.41; N, 3.34.

Microcalorimetric Titration. An isothermal calorimeter was used for all microcalorimetric experiments. The instrument was calibrated chemically by performing the complexation reaction of β-CD with cyclohexanol, which gave thermodynamic parameters in good agreement with literature data.[26,37]

The microcalorimetric titrations were performed at atmospheric pressure and 25 °C in aqueous phosphate buffer solution (pH 7.20). At this pH, the carboxylic acid guests (pK_a 4.9−5.0) are fully ionized as |pH − pK_a(guest)| > 2.

All solutions were degassed and thermostated using a ThermoVac accessory before the titration experiment. In each run, a buffer solution of organic guest in a 0.250 mL syringe was sequentially injected with stirring at 300 rpm into a phosphate buffer solution of cyclodextrin (0.9−3.3 mM) in the sample cell (1.4227 mL volume). Each titration experiment was composed of 25 successive injections (10 μL per injection). A typical titration curve is shown in Figure 1.

A control experiment was performed to determine the heat of dilution by injecting a guest buffer solution into a pure buffer solution, containing no CD. The dilution enthalpy was subtracted from the apparent enthalpy obtained in each titration run, and the net reaction enthalpy was analyzed by using the "one set of binding sites" model, as exemplified in Figure 2 for the complexation of Cbz-L-alanine with host **3**.

The ORIGIN software (Microcal) allowed us to simultaneously determine the binding constant (K_S) and reaction enthalpy (ΔH°) with the standard derivation on the basis of the scatter of data points from a single titration experiment. All thermodynamic parameters reported in this work were obtained by using the one set of binding sites model. Two to three independent titration experiments were performed to afford self-consistent parameters, and the averaged values are reported in Table 1.

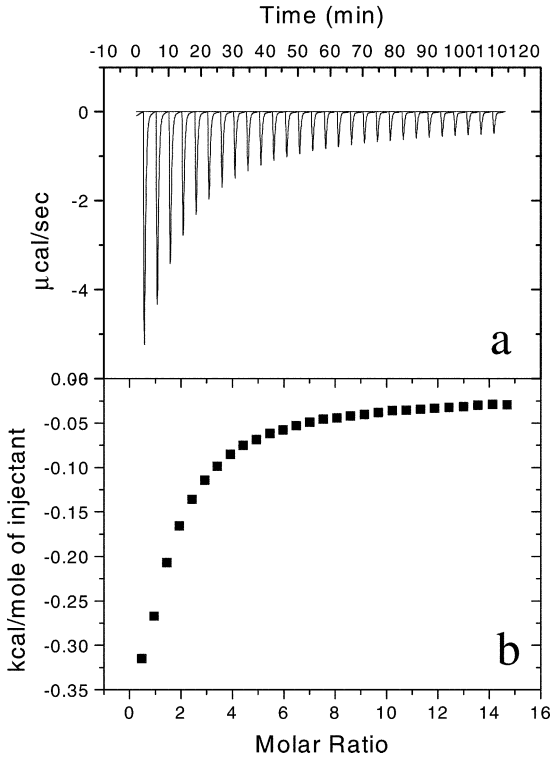

FIGURE 1. Calorimetric titration of host **2** with cyclohexanol in phosphate buffer (pH 7.2) at 25 °C. (a) Raw data for sequential 10 μL injections of cyclohexanol solution (71.39 mM) into host **2** solution (1.05 mM). (b) Heats of reaction as obtained from the integration of the calorimetric traces.

For further validation of the reliability of the whole system and the calculation procedures, the thermodynamic parameters obtained for β-cyclodextrin (Table 1) are compared with the reported values in Table 2, showing satisfactory agreement in each case. The slight differences observed may be attributed to the differences in pH and/or ion strength of the buffer solution used.

Results and Discussion

Synthesis. Mono[6-oligo(ethylenediamino)-6-deoxy]-β-cyclodextrins with varied tether lengths unexpectedly displayed different behavior upon reaction with tris(*m*-chlorosulfonyl)phosphine oxide, thus solely giving bis-CD **5** from mono(ethylenediamino)-β-CD and tris-CD **6** from tris(ethylenediamine)-β-CD (Scheme 1). This contrasting result may be rationalized in terms of efficient intramolecular "self-inclusion" of the unreacted *m*-chlorosulfonylphenyl moiety by the closely located CD cavity in **5**, which prevents the third condensation reaction leading to tris-CD. On the other hand, the intramolecular self-

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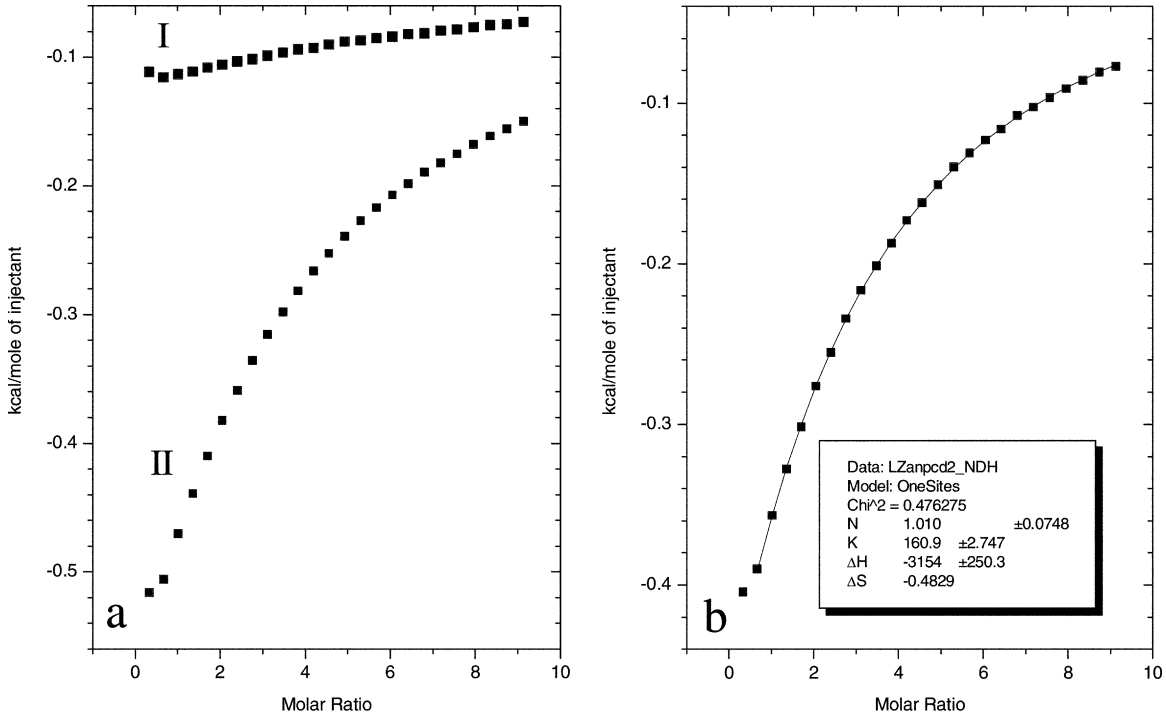


FIGURE 2. (a) Heat effects of dilution (I) and of complexation (II) of Cbz-L-alanine with host **3** for each injection during titration microcalorimetric experiment. (b) "Net" heat effect obtained by subtracting the heat of dilution from the heat of reaction, which was analyzed by computer simulation using the one set of binding sites model.

TABLE 1. Complex Stability Constant (K_S) and Standard Enthalpy ($\Delta H°$) and Entropy Changes ($T\Delta S°$) for 1:1 Inclusion Complexation of Alicyclic and Chiral Guests with β-Cyclodextrin 1 and Modified Mono-, Bis-, and Tris-β-cyclodextrins 2−6 in Phosphate Buffer Solution (pH 7.20) at T = 298.15 K

guest[a] (charge)	host[b]	N[c]	K_S, M^{-1}	$\Delta G°$, kJ/mol	$\Delta H°$, kJ/mol	$T\Delta S°$, kJ/mol
cyclohexanol (0)	1	2	707 ± 4	−16.26 ± 0.01	−6.08 ± 0.01	10.19 ± 0.02
	2	2	680 ± 15	−16.17 ± 0.05	−2.78 ± 0.04	13.40 ± 0.02
	3	2	834 ± 9	−16.67 ± 0.03	−4.0 ± 0.1	12.7 ± 0.1
	4	2	179 ± 2	−12.86 ± 0.03	−6.69 ± 0.03	6.162
	5	2	763 ± 7	−16.45 ± 0.02	−5.3 ± 0.1	11.2 ± 0.1
cyclopentanol (0)	1	2	168 ± 3	−12.70 ± 0.04	−3.9 ± 0.1	8.8 ± 0.1
	2	2	385 ± 8	−14.76 ± 0.05	−0.65 ± 0.04	14.10 ± 0.09
	3	2	296 ± 19	−14.10 ± 0.16	−1.9 ± 0.1	12.2 ± 0.3
	4	2	74 ± 2	−10.67 ± 0.07	−2.4 ± 0.1	8.3 ± 0.2
	5	2	200 ± 6	−13.13 ± 0.08	−7.8 ± 1.3	5.3 ± 1.3
cyclohexanecarboxylic acid (−1)	1	2	259 ± 6	−13.77 ± 0.06	−2.4 ± 0.2	11.4 ± 0.3
	2	2	195 ± 18	−13.06 ± 0.22	−2.7 ± 0.3	10.3 ± 0.5
	3	2	196 ± 7	−13.08 ± 0.08	−7.6 ± 0.9	5.5 ± 1.0
	4	2	189 ± 7	−13.00 ± 0.09	−10.7 ± 0.3	2.3 ± 0.4
	5	2	127 ± 3	−12.01 ± 0.05	−34.0 ± 3.1	−22.0 ± 3.1
cyclopentanecarboxylic acid (−1)	1	2	d			
	2	2	421 ± 16	−14.98 ± 0.09	−0.40 ± 0.06	14.6 ± 0.2
	3	2	403.7 ± 0.3	−14.91	−2.1 ± 0.5	12.8 ± 0.5
	4	2	835 ± 44	−16.67 ± 0.13	−5.49 ± 0.17	11.18 ± 0.04
	5	2	∼80	∼−10.86		
N-Cbz-L-alanine (−1)	1	1	158 ± 6	−12.55 ± 0.09	−12.03	0.53
	2	2	125 ± 3	−11.97 ± 0.06	−4.7 ± 0.3	7.2 ± 0.4
	3	2	157 ± 4	−12.54 ± 0.06	−13.12 ± 0.07	−0.59 ± 0.02
	4	2	30 ± 2	−8.43 ± 0.17	−16.4 ± 0.4	−8.0 ± 0.6
	5	2	115 ± 3	−11.76 ± 0.07	−24.2 ± 1.2	−12.4 ± 1.2
	6	2	93.8 ± 0.2	−11.26	−11.41 ± 0.01	−0.15
N-Cbz-D-alanine (−1)	1	1	152 ± 6	−12.45 ± 0.10	−8.67	3.78
	2	3	138 ± 5	−12.21 ± 0.09	−10.95 ± 0.06	1.37 ± 0.03
	3	2	205 ± 5	−13.19 ± 0.06	−4.9 ± 0.1	8.3 ± 0.2
	4	2	∼62	∼−10.23		
	5	2	154 ± 3	−12.48 ± 0.05	−7.9 ± 0.4	4.6 ± 0.4
	6	2	205.8 ± 0.2	−13.20	−5.62 ± 0.03	7.58 ± 0.02

[a] [Guest] = 27.5−71.4 mM. [b] [Host] = 0.9−3.3 mM. [c] Number of titration runs performed. [d] K_S or $\Delta H°$ was too small to determine by titration microcalorimeter.

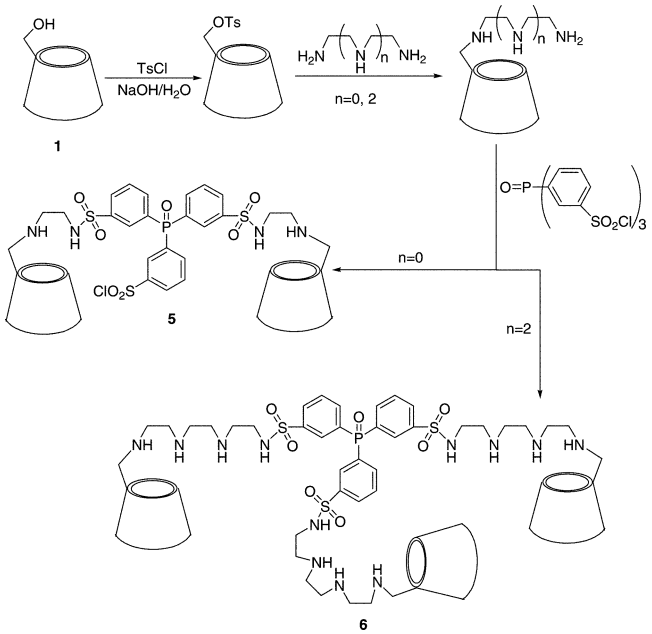
inclusion is not so efficient in the precursor to **6**, and then further condensation with tris(ethylenediamine)-β-CD can occur at a reasonable rate. Indeed, the NOESY examination with host **5** (Figure 3) revealed that the *m*-chlorosulfonylphenyl moiety of **5** is included in the CD cavity, displaying the cross-peaks between the aromatic protons and the H3 and H5 protons of CD (marked "A" in Figure 3).

TABLE 2. Thermodynamic Parameters K, $\Delta G°$, $\Delta H°$, and $T\Delta S°$ Reported for the Inclusion Complexation of the Same Guests with β-Cyclodextrin

guest (charge)	K, M^{-1}	$\Delta G°$, kJ/mol	$\Delta H°$, kJ/mol	$T\Delta S°$, kJ/mol	method[a]	source
cyclohexanol (0)	701 ± 6	−16.24 ± 0.02	−6.3 ± 0.1	9.9 ± 0.1	cal	ref 26
cyclopentanol (0)	172 ± 5	−12.76 ± 0.08	−4.56 ± 0.05	8.20 ± 0.03	cal	ref 38
cyclohexanecarboxylic acid (−1)	263	−13.8	−4.6 ± 1.7	9.2 ± 1.5	pot	ref 39
N-Cbz-L-alanine (−1)	147 ± 4	−12.37 ± 0.07	−10.0 ± 0.2	2.4 ± 0.2	cal	ref 26
N-Cbz-D-alanine (−1)	149 ± 4	−12.40 ± 0.07	−8.9 ± 0.2	3.5 ± 0.2	cal	ref 26

[a] Cal = calorimetry; pot = potentiometry.

SCHEME 1. Synthetic Routes to Hosts 5 and 6



Calorimetry. All complex stability constants (K_S) and molar enthalpies ($\Delta H°$) reported in this paper were calculated successfully by using the one set of binding sites model even for bis-CD **5** and tris-CD **6**. In principle, **5** and **6**, possessing two or three hydrophobic cavities, respectively, may bind the corresponding number of guest molecules upon inclusion complexation. Hence, the calculations were performed by using the two sets of binding sites model as well as the sequential binding model in addition to the one set of binding sites model. However, the parameters calculated by the latter two binding models gave large uncertainties and the quality of fit was not improved. In the case of host **5**, this result is reasonable, since one of the two cavities in **5** is occupied intramolecularly in part by the adjacent *m*-chlorosulfonylphenyl group, which makes it difficult for **5** to bind two guests. However, it is rather surprising that the thermograms obtained with host **6** are much better analyzed by the one set of binding sites model than by the other binding models. The titration curve of host **6** with Cbz-L-alanine is shown in Figure 4. It is considered that, although each of the three cavities of host **6** binds one guest, the binding ability of each cavity should be identical, and hence the binding by each CD moiety can be treated as an independent process that can be analyzed by the one set of binding sites model. For further validation of this data treatment, we examined the same data by the ORIGIN program, using the 3-fold value of the actual concentration of host **6**, and obtained the same results (except for the complex stoichiometry N) as those obtained by using the original concentration described above. Thus, the K_S value represents the binding ability of each cavity of tris-CD **6** toward the guest.

The thermodynamic parameters obtained for the complexation of alicyclic and amino acid guests with hosts **1**−**6** are listed in Table 1. It is noted that the modified cyclodextrins **2**, **3**, **5**, and **6** give more or less increased binding abilities for all guests employed. In contrast, host **4** consistently shows significantly lower *K*s for most of the guests used, except for cyclopentanecarboxylic acid, probably due to the strong intermolecular inclusion of one of the phenyl groups in the sidearm. The inclusion complexations of alicyclic guests with **1**−**5** afford negative $\Delta H°$ and positive $T\Delta S°$ values, with an exception of the combination of **5** and cyclopentanecarboxylic acid. It has been demonstrated that the large negative enthalpy change is attributable mostly to the remarkable van der Waals interactions through the good size/shape fit between the host and the guest, and the large positive entropy change is attributable to the extensive desolvation from the hydrophilic moieties of host and guest and also the relatively high flexibility of the guest accommodated in the cavity.[26,30,40] In the present case, considering the highly positive entropy changes with equally or less favorable enthalpic gains ($|\Delta H°| \leq |T\Delta S°|$), we may conclude that these inclusion reactions are driven by both enthalpy and entropy, with larger contributions from the latter. This means that for these alicyclic guests, the driving force for complexation is mainly the van der Waals interaction and the desolvation of the host and guest. Typically, hosts **2** and **3** possess more hydrophilic substituents than **4**, and hence the hydrophilic moieties surrounded by solvent molecules may cause extensive desolvation upon complexation with the guest with the hydrophilic moiety, giving larger positive entropy gains for alicyclic guests to exceed the inherent entropy losses arising from the molecular association and conformational fixation upon complexation.

Binding Ability and Molecular Selectivity Toward Cycloalkanol. First, we discuss the inclusion complexation of cyclohexanol (CH) and cyclopentanol (CP) with hosts **1**−**5**, since these neutral guests are most suitable for elucidating the fundamental complexation thermodynamics in the absence of more complicated electrostatic and hydrogen-bonding interactions. As can be seen from Table 1, hosts **1**−**5** consistently give higher K_S for CH than for CP, which is attributable to the better

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(39) Gelb, R. I.; Schwartz, L. M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989**, *7*, 465−476.
(40) Hauser, S. L.; Johanson, E. W.; Green, H. P.; Smith, P. J. *Org. Lett.* **2000**, *2*, 3575−3578.

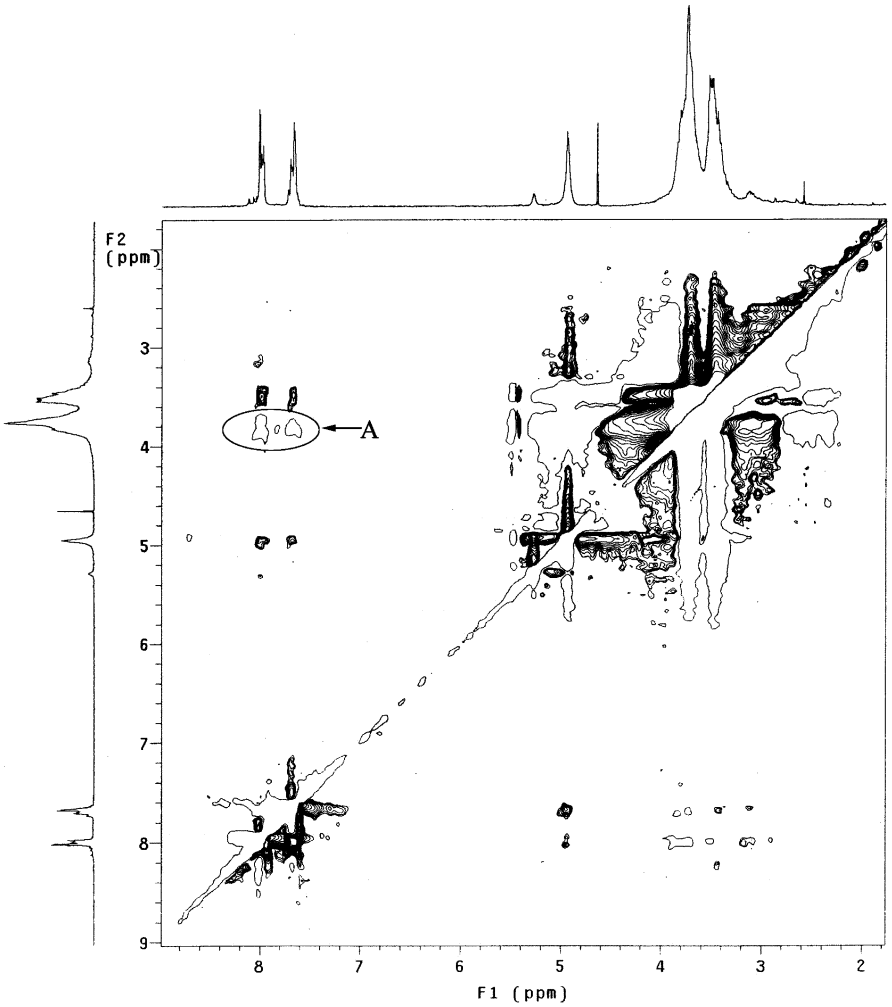

FIGURE 3. NOESY spectrum of host **5** (1.0 mM) in D_2O.

size matching of CH to the β-CD cavity, as well as the cooperative interaction of different substituents attached to β-CD. Thermodynamically, the inclusion complexation of CH and CP with hosts **1**−**4** is mostly entropy-driven: $|\Delta H°| \leq |T\Delta S°|$. However, the entropic contribution to the enhanced stability observed for CH is not large ($T\Delta S°_{CH} - T\Delta S°_{CP} = 0.5-1.4$ kJ/mol) or even negative (−2.1 kJ/mol), while the enthalpic contribution is much larger ($\Delta H°_{CH} - \Delta H°_{CP} = 2.1-4.3$ kJ/mol). Thus, most of the stability enhancement for CH ($\Delta G°_{CH} - \Delta G°_{CP} = 1.6-3.6$ kJ/mol) arises from the enthalpic gain. This is quite reasonable, as the ring enlargement from CP to CH certainly increases the van der Waals contacts within the CD cavity without significantly altering the degree of desolvation. Except for **2**, all the hosts give the same complex stability sequence toward CH and CP, that is, **3** > **5** > **1** > **4**. CH exhibits smaller enthalpic gains upon complexation with hosts **3** and **5** than with native β-CD **1** ($\Delta H°_{CH-3,5} - \Delta H°_{CH-1} = 0.8-2.1$ kJ/mol), which are "over-compensated" by greater entropic gains of 1.0−2.5 kJ/mol to give the larger K_S values. On the other hand, CH exhibits slightly larger enthalpic gains (0.6 kJ/mol) upon complexation with host **4** than with native **1**, which is, however, canceled out by the much smaller entropic gain, ultimately giving a significantly smaller K_S. The unusual enhancement of CP complexation by host **2** may be rationalized by the slightly more narrow cavity induced by shallow penetration of the phosphate moiety into the cavity, which has been demonstrated in our recent studies.[33,34] The partly occupied hydrophobic cavity prefers smaller guests. According to the induced circular dichroism (ICD) spectrum of host **4** in the aqueous solution,[12] its phosphate moiety is not fully embedded into the hydrophobic cyclodextrin cavity and we deduced that the phenoxy group of host **4** may be included into the hydrophobic cavity of another cyclodextrin from the secondary side. Possessing the partly occupied cavity, host **4** cannot readily bind a guest from the secondary side to form a stable complex, thus giving the smallest entropic changes and the lowest stability constants for both CH and CP among hosts **1**−**4** due to the decreased hydrophobic interaction with cycloalkanols.

Binding Ability and Molecular Selectivity toward Cycloalkanecarboxylic Acid. To examine the role of the charge−dipole interaction between the phosphoryl moiety and negatively charged guest, the complexation behavior of hosts **1**−**5** with cyclohexanecarboxylic acid (CHA) and cyclopentanecarboxylic acid (CPA), which possess the same hydrophobic groups as CH and CP, was investigated to give the results shown in Table 1.

In sharp contrast to the CH and CP pair, the smaller-sized CPA, rather than CHA, afforded the more stable

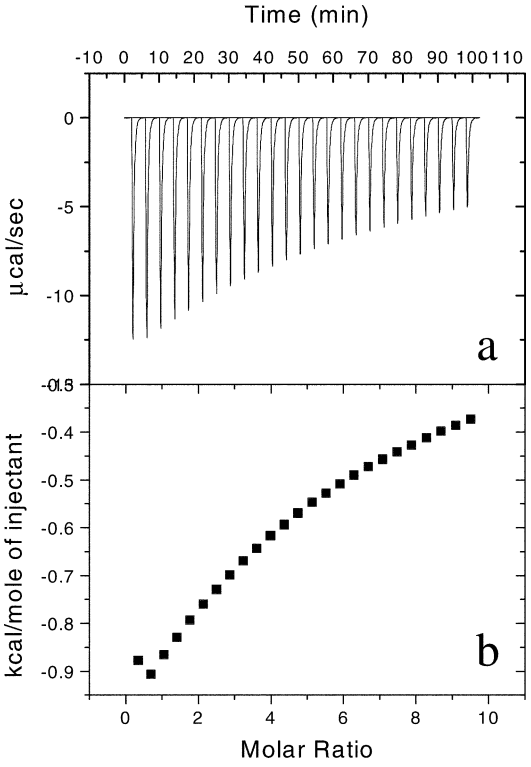

FIGURE 4. Calorimetric titration of Cbz-L-alanine with host **6** at 25 °C in pH 7.2 buffer solution. (a) Raw data for sequential 10 μL injections of Cbz-L-alanine (49.24 mM) into host **6** (0.99 mM). (b) Heats of reaction as obtained from the integration of the calorimetric traces.

complex with most of the hosts examined. If the charge−dipole interaction between the phosphoryl group of host and the carboxylate anion of CPA and CHA is the major driving force for inclusion complexation, the guest should penetrate into the cavity from the more narrow primary side, which discourages the inclusion of the larger-sized CHA and accelerates the inclusion of CPA, eventually inverting the guest selectivity of the native β-CD. In particular, host **4** showed a large enhancement of K_S from 74 M^{-1} for CP to 835 M^{-1} for CPA. Probably, the charge−dipole and van der Waals interactions of CPA with **4** can drive out the self-included phenyl moiety. It is noted also that the combination of host **5** and CHA displays distinctive thermodynamic behavior, giving a very large negative $\Delta H°$ (−33.96 kJ/mol) and $T\Delta S°$ (−21.96 kJ/mol), although the K_S value (127 M^{-1}) is not particularly large. This means that the complexation of host **5** and CHA is highly enthalpy-driven, but the extra enthalpic gain is canceled out by the large entropic loss. This highly negative $T\Delta S°$ value of −21.96 kJ/mol is extraordinary compared to the moderately positive $T\Delta S°$ values obtained for the complexation of CHA with hosts **1**−**4** and of CPA with **1**−**5** and may indicate a dramatic change of complexation mechanism and/or complex structure. One plausible explanation is that the larger-sized CHA molecule penetrates into the cavity of **5** from the wider opening of the secondary side, producing better van der Waals contacts and a larger enthalpic gain, and the charge−dipole interaction takes place between the phosphoryl and distant carboxylate moieties, giving a very rigid complex structure with accompanying additional enthalpic gain and a very large entropic loss.

To further confirm the contribution of charge−dipole interaction, the thermodynamic parameters of the complexation of CPA with hosts **2**−**4** were determined at pH 2.0 (see Supporting Information, Table S2), and the results were compared with those obtained at pH 7.2. Since CPA exists not as an anion [CPA(−1)] but as an acid [CPA(0)] at pH 2.0, there will be no charge−dipole interaction upon complexation with host. It is interesting that the enthalpy becomes the main driving force at pH 2.0 instead of entropy at pH 7.2, which means that the van der Waals, and probably hydrogen-bonding, interactions between the host and CPA(0) are enhanced, while the desolvation no longer plays a major role in the absence of the charged group in the guest. Although CPA(−1) is deduced to be included by cyclodextrins **2**−**4** from the primary side, it is more probable for CPA(0) to be included from the secondary side of **2**−**4**, as the hydrogen-bonding interactions with the secondary hydroxyl groups are expected to occur. Therefore, the difference in driving force could also be ascribed to the different binding modes. The distinctly different binding constants of hosts **2**−**4** toward CPA(0) and CPA(−1) may be attributable to the structural differences.

Chiral Discrimination of *N*-Cbz-D/L-Alanine. The complexation of native and modified hosts **1**−**6** with *N*-Cbz-D/L-alanine is clearly enthalpy-driven, differing from the cases with the other alicyclic guests examined above. The enthalpy changes are more negative and the entropy changes less positive or even negative for *N*-Cbz-alanine than for the alicyclic guests, indicating that the van der Waals interaction is stronger but the dehydration is not as extensive upon complexation of *N*-Cbz-alanine. Interestingly, the enantiomer pairs exhibit distinctly different $\Delta H°$ and oppositely signed $T\Delta S°$ values upon complexation with both native and modified CDs **1**−**6**, although apparently the complex stabilities do not greatly differ from each other. Thus, the L-isomer consistently gives more negative $\Delta H°$ and $T\Delta S°$ values, while the D-isomer gives less negative $\Delta H°$ and positive $T\Delta S°$, except for the complexation with **2**. In other words, the complexation of Cbz-L-alanine with **1** and **3**−**6** is driven exclusively by enthalpy, but that of Cbz-D-alanine is driven by both enthalpy and entropy. Most of the enthalpic contribution is attributable to the favorable van der Waals interactions arising from the precise size/shape match of the Cbz phenyl group and the β-CD cavity. However, the closer fit of Cbz-L-alanine to the cavity inevitably causes a greater reduction of complex freedom, giving a negative entropy change. On the other hand, the looser fit of Cbz-D-alanine leads to moderate gains in both enthalpy and entropy, affording higher stability constants not for L- but for D-alanine.

Of the modified CDs **2**−**6**, host **6** afforded the highest enantioselectivity of 2.2 in favor of *N*-Cbz-D-alanine. This seems reasonable, since host **6** possesses long, flexible ethylenediamino chains, which can adjust the conformation of host **6** to fit to the size/shape of the guest and probably serve as an additional binding site upon guest inclusion, leading to enhanced chiral discrimination. It is well-known that native β-cyclodextrins show poor chiral discrimination for amino acids and its derivatives, although the crystal structures show appreciable differ-

ences in the binding mode between the CD complexes of *N*-acetyl-D/L-phenylalanine.[29] As can be seen from Table 1, native *β*-CD affords almost the same K_S values of 152 and 158 M^{-1} for the D- and L-isomers of *N*-Cbz-alanine, respectively. The large negative $\Delta H°$ and the smaller positive $T\Delta S°$ indicate that the complexation of *β*-CD and *N*-Cbz-D/L-alanine is mostly enthalpy-driven with a minor entropy assistance. Although the $\Delta H°$ and $T\Delta S°$ values for the antipodal guest pair are significantly different from each other, the perfect enthalpy−entropy compensation cancels out the differences in $\Delta H°$ and $T\Delta S°$, resulting in poor chiral discrimination. It should be emphasized that the charge−dipole interaction does not appreciably contribute to the binding ability but obviously enhances the enantioselectivity of *β*-CD. The enantioselectivity toward *N*-Cbz-D/L-alanine (K_D/K_L) increases in the following order: 1.0 for **1**, 1.1 for **2**, 1.3 for **3** and **5**, 2.1 for **4**, and 2.2 for **6**. It is interesting to point out that, from the thermodynamic point of view, the charge−dipole interaction and the substituent effect caused by phosphoryl moiety not only alter the original $\Delta H°$ and $T\Delta S°$ values but also disturb the perfect enthalpy−entropy compensation, bringing about the enhancement of the chiral recognition ability of modified CDs **2**−**6**. This is demonstrated in particular by the thermodynamic parameters for host **3**. The complexation of Cbz-L-alanine with **3** gives $\Delta H°$ and $T\Delta S°$ values comparable to those for *β*-CD, and the slightly larger enthalpic gain ($\Delta H°_{L-3} - \Delta H°_{L-1} = -1.1$ kJ/mol) is well compensated by the equally larger entropic loss ($T\Delta S°_{L-3} - T\Delta S°_{L-1} = -1.1$ kJ/mol). In contrast, the complexation of Cbz-D-alanine with **3** gives a smaller enthalpic gain than that for *β*-CD ($\Delta H°_{D-3} - \Delta H°_{D-1} = 3.8$ kJ/mol), which is over-compensated by a larger entropic gain ($T\Delta S°_{D-3} - T\Delta S°_{D-1} = 4.5$ kJ/mol). As a consequence of such opposite behavior of $\Delta H°$ and $T\Delta S°$, the negligible enantioselectivity of *β*-CD ($\Delta\Delta G°_{D/L} = 0.1$ kJ/mol) is substantially enhanced to give a $\Delta\Delta G°_{D/L}$ value of 0.65 kJ/mol for host **3**.

Host **5** exhibited quite interesting complexation thermodynamic behavior with enantiomeric Cbz-alanine. Upon complexation with hosts **3**, **5**, and **6**, Cbz-L-alanine gives much larger enthalpic gains than the antipodal guest, probably due to the closer van der Waals contacts. Such a situation, however, causes severe conformational fixation of the complexed Cbz-L-alanine, which in turn gives the highly negative $T\Delta S°$, ultimately canceling out the enthalpic gain to give a smaller K_S for L-alanine rather than D-alanine.

Two-Dimensional NMR Spectra. To further investigate the unique thermodynamic behavior and the enhanced chiral recognition ability displayed by phosphoryl-modified *β*-CDs, two-dimensional NMR spectral examinations were performed. Although we cannot rigorously rule out the possibility of coexistence of multiple complexes with different structures in the system, we analyzed the obtained NOESY spectra, assuming a single major complex with an *averaged* structure. A comparative NOESY study of different host−guest pairs is expected to reveal the binding mode and the origin of chiral discrimination and also contribute to the elucidation of the relationship between the complex structure and thermodynamic parameters upon inclusion of the CD hosts and *N*-Cbz-D/L-alanine.

Host **5** was examined by two-dimensional NMR spectroscopy in the presence and absence of a guest molecule. As shown in Figure 3, the strong NOE correlation peaks, labeled "A", between the phenyl moiety of **5** and the H3 and H5 inside the CD cavity are seen in the absence of the guest, indicating that the sidearm of host **5** is deeply inserted into the cavity to form a self-inclusion complex in aqueous solution. This is why host **5** forms the 1:1 complex with the guest.

The NOESY spectra of **5** measured in the presence of Cbz-L/D-alanine are shown in Figure 5a,b. In Figure 5a, three sets of NOE correlation peaks are identified, i.e., the cross-peaks between H3 and H5 protons of CD and the phenyl protons of Cbz-L-alanine (peaks B), the cross-peaks between H3/H5 and the methyl protons of Cbz-L-alanine (peaks C), and the cross-peaks between H3/H5 and the phenyl protons of **5** (peaks D). In contrast, the NOE spectrum of the complex of **5** with Cbz-D-alanine (Figure 5b) showed three sets of correlation peaks identified as B1, C1, and D1. Different from Figure 5a, although peaks B1 and C1 show the same information as peaks B and C, peaks D1 indicate that the correlation between H3 and a part of phenyl protons of **5** disappeared by introducing the Cbz-D-alanine. These observations clearly indicate that both of the methyl and phenyl groups of Cbz-D/L-alanine penetrate into the CD cavity-(ies) of **5**, and the self-included *m*-chlorosulfonylphenyl group is partially expelled out of the cavity upon inclusion of Cbz-D-alanine. In view of the CD cavity size, it is likely that Cbz-D/L-alanine molecule is cooperatively bound by two cyclodextrin cavities of host **5**. It is deduced therefore that the enhanced enantioselectivity of host **5** originates from the multiple recognition by two CDs and the tether phosphoryl group. Considering that the *m*-chlorosulfonylphenyl group of host **5** was relaxed through the complexation with Cbz-D-alanine, this complex possesses a relatively looser conformation than that of **5** and Cbz-L-alanine, which consequently caused greater conformational freedom and weaker van der Waals interactions between **5** and Cbz-D-alanine. From this point of view, the thermodynamic parameters are in good agreement with the NMR results. The loose conformation of the complex of **5** with Cbz-D-alanine induced a favorable entropy change but a relatively smaller enthalpy change, while the somewhat fixed conformation of complex of **5** with Cbz-L-alanine caused an unfavorable entropy change and a larger enthalpy change.

To obtain further insight into the mechanism of chiral recognition by mono-*β*-CDs, NOESY spectra of the complexes of Cbz-D/L-alanine with phosphoryl-modified **2** and native **1** (as a reference) were obtained under the comparable conditions; the results are illustrated in Figure 6a−c. As shown in Figure 6c, the NOESY spectrum of the complex of host **1** with Cbz-D-alanine clearly shows the cross-peaks between H3 and H5 of CD and the phenyl protons of the guest (peaks E), as well as the cross-peak between H5 and the methyl protons of Cbz-D-alanine (peak F), but no NOE was found between H3 and the methyl protons of Cbz-D-alanine. It has been reported that the phenyl of Cbz-L-Glu penetrates into the native *β*-CD cavity from the secondary side and the side chain of the guest is located outside.[20] If the same inclusion mode is operative in the present case, the methyl group of Cbz-D-alanine cannot be embedded into the cavity. The simultaneous observation of the cross-

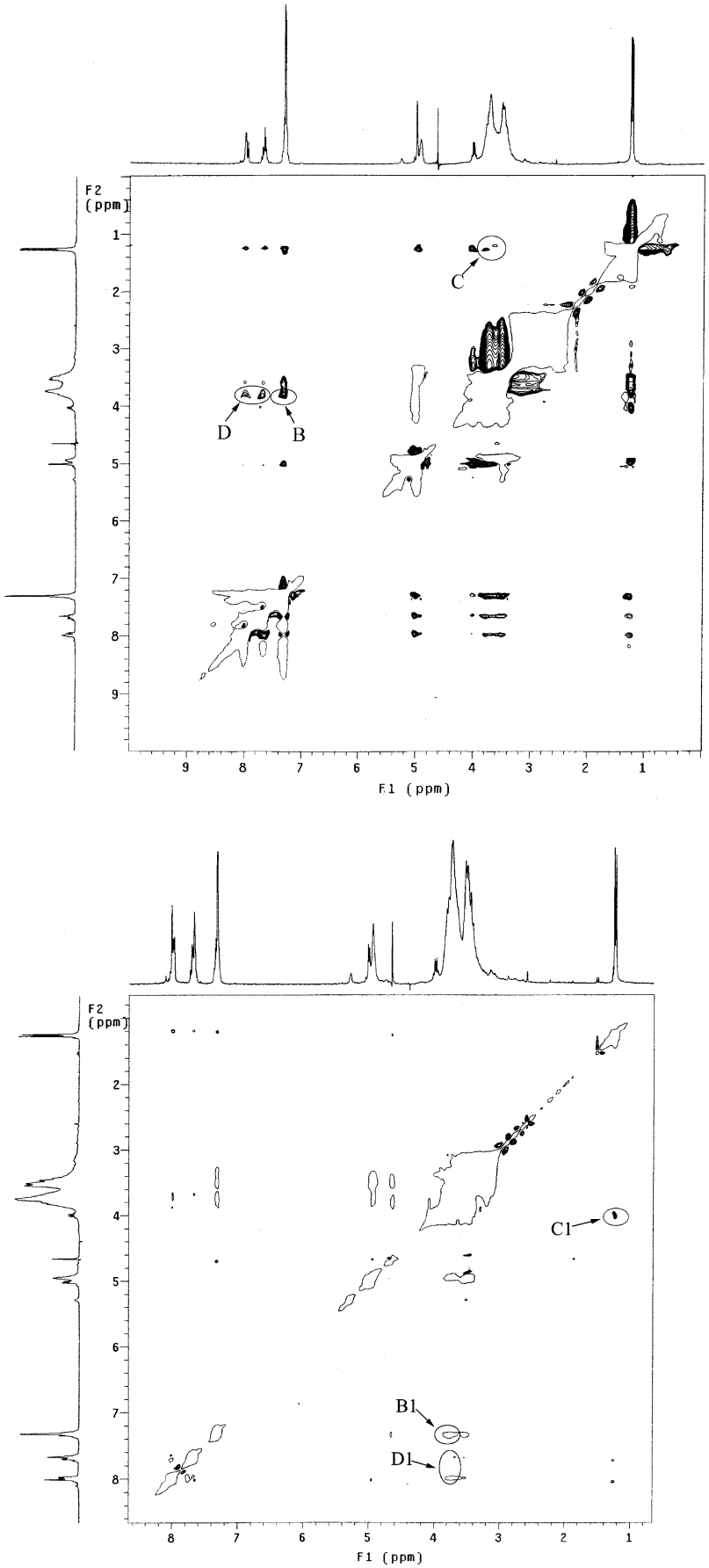

FIGURE 5. (a) NOESY spectrum of host **5** (1.0 mM) and Cbz-L-alanine (2.0 mM). (b) NOESY spectrum of host **5** (1.0 mM) and Cbz-D-alanine (2.0 mM).

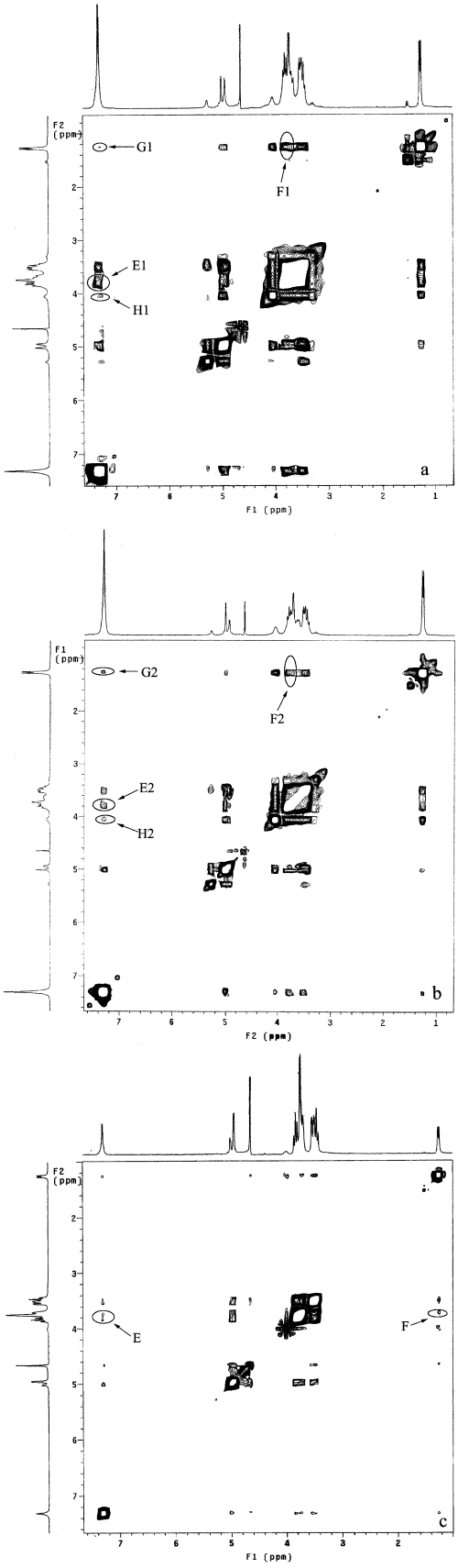

FIGURE 6. (a) NOESY spectrum of host **2** (1.0 mM) and Cbz-D-alanine (2.0 mM). (b) NOESY spectrum of host **2** (1.0 mM) and Cbz-L-alanine (2.0 mM). (c) NOESY spectrum of β-cyclodextrin **1** (1.0 mM) and Cbz-D-alanine (2.0 mM).

peaks for both Cbz phenyl (with CDs H3 and H5; peaks E) and methyl (only with CDs H5; peak F) rather indicates that the phenyl group is deeply included and the methyl shallowly included in the cavity of β-CD from the primary side.

In the NOESY spectra of **2** shown in Figure 6a,b, H3 and H5 display evident cross-peaks with not only the phenyl but also the methyl protons of Cbz-alanine (peaks E1,2 and F1,2, respectively). Furthermore, cross-peaks between the methyl and phenyl groups (peak G1,2) and even between the methylene and phenyl groups (peak H1,2) of Cbz-alanine are clearly observed, indicating that these two moieties are located closely in the same CD cavity. It is likely that the cooperative multiple recognition by cooperative van der Waals and charge−dipole interactions is the origin of the increased chiral discrimination by phosphoryl-modified CDs. However, the relative intensity of E1, G1, and H1 (Figure 6a) differs significantly from that of E2, G2, and H2 (Figure 6b). Thus, peaks G1 and H1 are much weaker than peaks E1, while the peaks E2, G2, and H2 are comparable in intensity. These results indicate that the relative location of the methyl, methylene, and phenyl groups of Cbz-D-alanine inside the cavity of host **2** are appreciably different from that of Cbz-L-alanine. One possible explanation is that the position of the guest carboxylate relative to the phosphoryl substituent of host **2** is fixed by the charge−dipole interaction and the conformation of Cbz-D-alanine is adjusted in the cavity of **2**, maximizing the van der Waals contacts. The stronger NOE cross-peaks E1 and F1 (relative to G1) than E2 and F2 (relative to G2) may indicate closer van der Waals contacts between H3 and H5 with the methyl and phenyl groups of Cbz-D-alanine. These NMR results nicely coincide with the thermodynamic parameters given in Table 1, displaying more negative $\Delta H°$ and less positive $T\Delta S°$ for Cbz-D-alanine. In contrast, the Cbz-L-alanine complex with **2** shows only moderate cross-peaks E2, F2, and G2, indicating the conformational freedom of the guest within the CD cavity. It is interesting and significant that the switching from the enthalpy-driven complexation of Cbz-D-alanine to the entropy-driven complexation of Cbz-L-alanine is adequately reflected in the NOE intensity and, hence, the degree of van der Waals contact is assessed at least qualitatively by two-dimensional NMR experiment.

For further validation of this relationship between the thermodynamic and NOESY spectral behavior, the two-dimensional NMR spectral examinations of host **3** with enantiomeric Cbz-alanines were performed under identical conditions. Interestingly, the thermodynamic features of the complexation of **3** with the Cbz-alanine pair were in good agreement with the NOESY spectral results, as was the case with host **2**. Thus, the NOESY spectrum of host **3** in the presence of Cbz-D-alanine (Figure 7a) resembles that of host **2** with Cbz-L-alanine, while the NOESY spectrum of **3** with Cbz-L-alanine resembles that of **2** with Cbz-D-alanine. These spectral observations fully agree with the obtained thermodynamic parameters. As can be seen from Table 1, the inclusion complexation of Cbz-D-alanine with host **2** is driven by enthalpy, but the complexation of Cbz-L-alanine with host **2** is mainly driven by entropy with an accompanying small enthalpic gain. In contrast, the inclusion complexation of host **3**

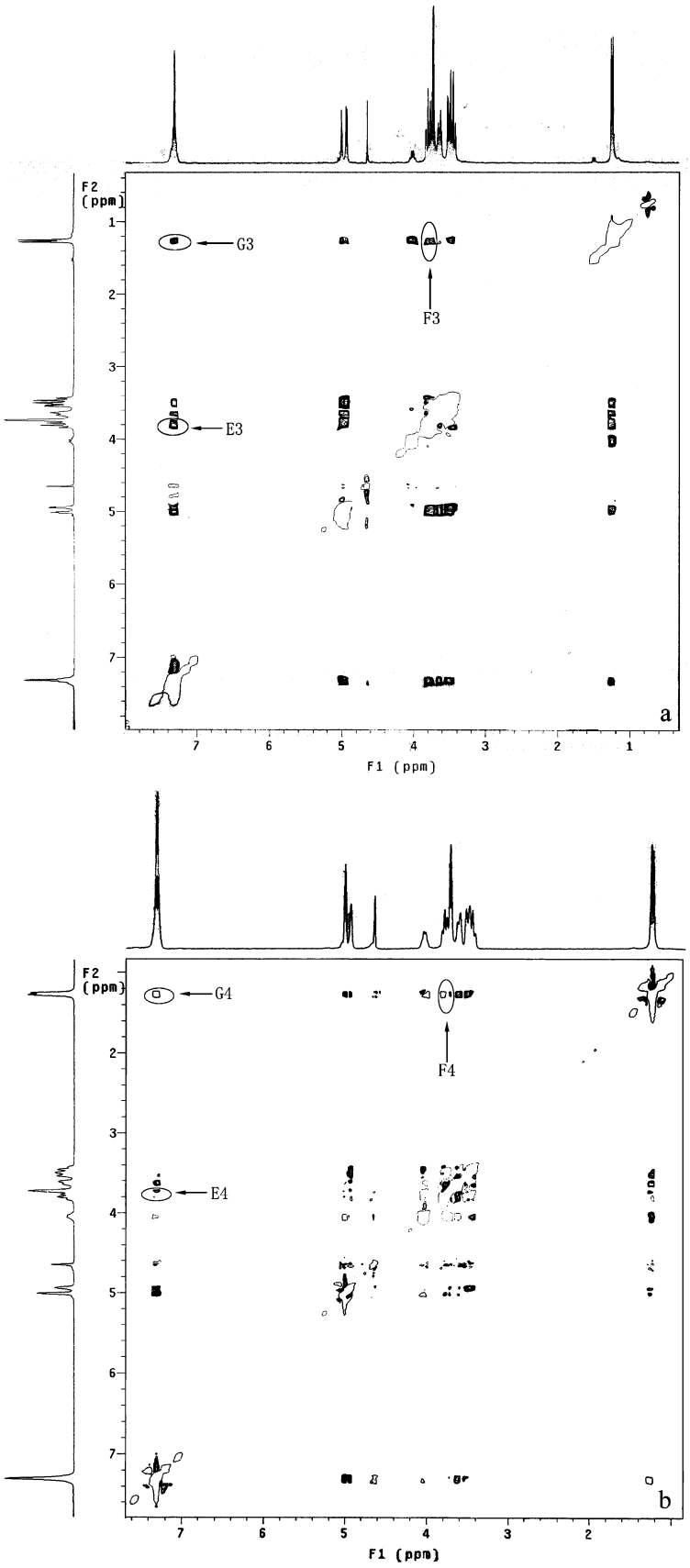

FIGURE 7. (a) NOESY spectrum of host **3** (1.0 mM) and Cbz-D-alanine (2.0 mM). (b) NOESY spectrum of host **3** (1.0 mM) and Cbz-L-alanine (2.0 mM).

with Cbz-L-alanine is an enthalpy-driven process, while the Cbz-D-alanine complexation is driven by the large entropic gains. The NOESY spectral behavior of the complexes of **3** with Cbz-D/L-alanine nicely reflects this

switching of the thermodynamic driving force. It would be puzzling, however, if the apparently trivial change in the sidearm of hosts **2** and **3** could cause the switching of the driving force for complexation. However, it is not unreasonable that the more lipophilic sidearm in **3** enhances the microenvironmental hydrophobicity around the CD cavity, which eventually endows host **3** with a different binding mode. Distinct evidence in support of this hypothesis was obtained from the two-dimensional NMR spectrum of host **3** with Cbz-L-alanine. As can be seen from Figure 7b, the cross-peaks marked E4, arising from the NOE between the host's H3 and H5 and the Cbz's phenyl protons, clearly indicate that the van der Waals interaction of H3 with the phenyl protons are much weaker than that of H5. Similarly, cross-peaks F4 indicate weaker interactions of the host's H3 with the guest's methyl protons than that of H5. These observations indicate that Cbz-L-alanine molecule is located near the rim of the primary side of host **3** without deeply penetrating into the cavity. This complexation behavior is exactly the opposite of that of host **2**, which may rationalize the switching of the thermodynamic driving force between hosts **2** and **3**. The shallow penetration of the guest from the primary side may also contribute to the enhanced chiral discrimination of these phosphoryl-modified β-CDs.

Unfortunately, similar two-dimensional NMR experiments on the complex of host **4** with Cbz-alanine did not give any informative cross-peaks (see Supporting Information), probably as a consequence of the weak binding as revealed by the titration calorimetry experiment.

Conclusion

The introduction of various phosphoryl groups to the primary side of β-CD not only alters the original binding ability and molecular selectivity through the optional charge−dipole interaction but also enhances the chiral recognition ability by finely adjusting the relative position and conformation of the guest molecule accommodated in the CD cavity. It has been demonstrated that the NMR NOESY technique is a powerful tool for elucidating the location and conformation of the guest molecule in the cavity and also correlating the complex structure with the thermodynamic parameters. The combined use of NMR spectroscopy and microcalorimetry revealed the origin of the enhanced chiral recognition exhibited by the phosphoryl-modified β-CDs.

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Supporting Information Available: Differential enthalpies ($\Delta\Delta H°$) and entropies ($T\Delta\Delta S°$) for the complexation of native and modified β-CDs with various guests in phosphate buffer solution (pH 7.2) at 25 °C, thermodynamic parameters of the complexation of hosts **2**−**4** with CPA in pH 2.0 buffer solution, and NOESY spectra of host **4** with Cbz-D/L-alanine. This material is available free of charge via the Internet at http://pubs.acs.org.

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