Molecular Recognition Studies on Supramolecular Systems. 22. Size, Shape, and Chiral Recognition of Aliphatic Alcohols by Organoselenium-Modified Cyclodextrins

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A novel cyclodextrin derivative, mono[6-(*p*-methoxyphenylseleno)-6-deoxy]-*β*-cyclodextrin (**2**), has been synthesized and characterized by elemental analysis and mass, FT-IR, and ^{1}H NMR spectroscopy. The stability constants (K_S) of the inclusion complexation of **2** and mono[6-(*p*-tolylseleno)-6-deoxy]-*β*-cyclodextrin (**3**) with a series acyclic and cyclic alcohols have been determined in phosphate buffer solution (pH 7.20) at 25 °C by using the circular dichroism spectral titration method. Although the stability constants obtained for the inclusion complexation of **2** and **3** with aliphatic alcohols are generally smaller than those for native *β*-cyclodextrin, the modified cyclodextrins can recognize both the size and chirality of the guest molecules. Interestingly, the complex stability constants (log K_S), or the Gibbs free energy change ($-\Delta G°$), increase linearly with increasing number of carbon atoms in the guest molecule (N_C), irrespective of the topological differences of acyclic, cyclic, and bicyclic guests. The unit increment of complex stability per methylene ($-\mathrm{d}\Delta G°/\mathrm{d}N_C$) is not appreciably affected by the difference of the host's substituent but is a critical function of the guest topology, affording distinctly different $-\mathrm{d}\Delta G°/\mathrm{d}N_C$ values of 2.4 and 2.9 kJ mol^{-1} for alkanols and cycloalkanols, respectively. In the complexation of chiral guests with **2** and **3**, the observed enantioselectivities, as measured by the stability difference ($\Delta\Delta G°$), are mostly in the range of 1−2 kJ mol^{-1}.

Introduction

Studies on molecular recognition have received much attention in supramolecular chemistry involving natural and artificial host−guest systems.[1,2] Cyclodextrins, composed of six, seven, or eight D-glucopyranose units, possess truncated cone-shaped hydrophobic cavities which are capable of binding various organic, inorganic, and biological molecules to form stable host−guest inclusion complexes. Hence, they have been extensively used as supramolecular receptors and chiral selectors in separation science and technology.[3−7] To improve or enhance the original molecular binding abilities of the native cyclodextrins, a great deal of effort has been concentrated on the design and syntheses of novel cyclodextrin derivatives in recent years.[8,9] In fact, a wide variety of native and chemically modified cyclodextrins have been employed in the studies of their molecular recognition behavior with various guest molecules.[10−15] It has been demonstrated that several weak forces, including van der Waals, hydrophobic, electrostatic, dipole−dipole, and hydrogen-bonding interactions, cooperatively govern the inclusion complexation behavior of cyclodextrin hosts. We have reported the syntheses and molecular recognition of a series of modified cyclodextrins in the previous study and found that the type of substituent introduced to cyclodextrin drastically affects the molecular recognition ability, including enantioselectivity for chiral guests.[16−18]

We wish now to report our study on the syntheses and inclusion complexation of novel mono[6-(*p*-methoxylphenylseleno)-6-deoxy]-*β*-cyclodextrin (**2**) and its analogue mono[6-(*p*-tolylseleno)-6-deoxy]-*β*-cyclodextrin (**3**) (Chart 1). The complexation behavior of these two organoselenium-modified cyclodextrins with a series of acyclic, cyclic, and bicyclic alkanols was studied in phosphate buffer solution (pH 7.20) at 25 °C by differential circular dichroism spectroscopy.

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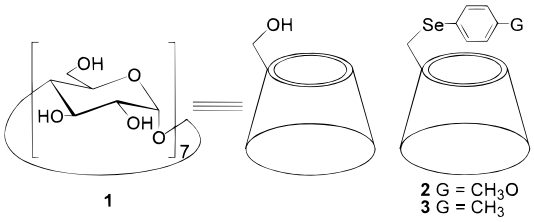
Chart 1



Experimental Section

Materials. All guest alcohols were commercially available and used without further purification. β-Cyclodextrin of reagent grade (Suzhou Monosodium Glutamate Works) was recrystallized twice from water and dried in vacuo at 95 °C for 24 h prior to use. *N*,*N*-Dimethylformamide (DMF) was dried over calcium hydride for 2 days and then distilled under a reduced pressure prior to use. Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.1 mol dm^{-3} phosphate buffer solution of pH 7.20 for CD spectral measurements.

Mono[6-(*p*-methoxylphenylseleno)-6-deoxy]-β-cyclodextrin (**2**) was synthesized by the reaction of mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin (6-OTs-β-CD)[19] with di(*p*-methoxylphenyl) diselenide[20] according to a similar procedure described previously for mono[6-(*p*-tolylseleno)-6-deoxy]-β-cyclodextrin (**3**).[21] Sodium borohydride (0.037 g, 1 mmol) was added to the yellow solution of di(*p*-methoxylphenyl) diselenide (0.164 g, 0.5 mmol) in dry ethanol (50 cm^3) with stirring under nitrogen at room temperature. After the solution turned to colorless, a solution of mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin (1.29 g, 1 mmol) in dry DMF (75 cm^3) was added dropwise into the solution and heated to 80 °C for 5 h with stirring. The resultant solution was evaporated under a 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 cm^3). The precipitate formed was filtrated to give white powder. The crude product was recrystallization three times from water and dried in vacuo to give a pure sample in 50% yield: FAB-MS (NaI) *m*/*z* 1327 ($M + Na^+ - 3H_2O$), 1305 ($M + H^+ - 3H_2O$); UV−vis λ_{max} (H_2O)/nm (ϵ/dm^3 mol^{-1} cm^{-1}) 232.2 (12500), 268.2 (3030); FT-IR (KBr) ν/cm^{-1} 3388, 2914, 1630, 1602, 1509, 1406, 1339, 1284, 1242, 1150, 1073, 1022, 941, 749; ^{1}H NMR δ 7.43 (d, 2H), 6.85 (d, 2H), 5.6−5.9 (m), 4.83 (m, 7H), 4.5 (m), 3.0−4.0 (m). Anal. Calcd for $C_{49}H_{76}O_{35}Se{\cdot}3H_2O$: C, 43.33; H, 6.09; Se, 5.81. Found: C, 43.49; H, 6.55; Se, 5.87.

Spectrometric Measurements. Absorption and induced cirular dichroism measurements were performed in a conventional quartz cell (light path 1 cm) on a Shimadzu UV-2401 or JASCO V-550 spectrophotometer and on a JASCO J-720W spectropolarimeter equipped with a temperature controller, respectively.

The inclusion complexation by the organoselenium-modified β-cyclodextrins was best detected by circular dichroism (CD) spectrometry, since the absorption spectrum did not show any significant changes even upon addition of a large excess of the guest.[22] The CD spectra of β-cyclodextrin derivatives **2** and **3** ($0.5-1.0 \times 10^{-4}$ mol dm^{-3}), were measured at 25 °C in the presence of varying concentrations of guest in the phosphate buffer. The differential CD spectra were obtained by subtracting the original CD spectrum, recorded in the absence of a guest, from those recorded in the presence of a guest.

Results and Discussion

Circular Dichroism Spectra. The absorption and circular dichroism spectra of mono[6-(*p*-metholxylphenylseleno)-6-deoxy]-β-cyclodextrin (**2**) and mono[6-(*p*-tolylseleno)-6-deoxy]-β-cyclodextrin (**3**) are shown in Figure 1. Possessing similar aromatic chromophores appended to cyclodextrin, the circular dichroism spectra of **2** and **3** are very similar in shape. Thus, the ^1L_a and ^1L_b bands of both **2** and **3** show moderate negative and positive extrema, respectively. On the basis of the Kajtar's sector rule and Harata's results,[23−25] we deduce that the aromatic substituents of **2** and **3** do not penetrate deeply into the cavity of cyclodextrin but are shallowly included in a direction perpendicular to the cavity axis. Examination with Corey−Pauling−Koltun (CPK) molecular models also indicates that the *p*-substituted phenyl group cannot deeply intrude into the cyclodextrin's cavity, since the linker group is not long enough to allow full penetration of the aryl group into the cavity. Interestingly, the relative CD intensity of the ^1L_a and ^1L_b bands is obviously inverted between **2** and **3**, affording a more negative extrema for the ^1L_a of **3** but a more positive extrema for the ^1L_b band of **2**. The less negative ^1L_a and more positive ^1L_b bands observed for **2** may indicate the slightly shallower but more perpendicular penetration of the anisyl group in **2** as compared with the tolyl group in **3**.

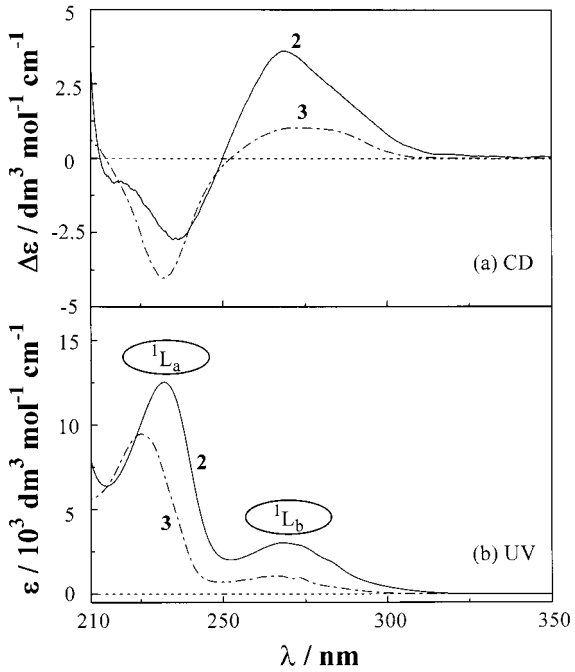


Figure 1. (a) Circular dichroism and (b) absorption spectra of 6-(*p*-methoxylphenylseleno-6-deoxy)-β-cyclodextrin (**2**) (50 μmol dm^{-3}) and 6-(*p*-tolylseleno-6-deoxy)-β-cyclodextrin (**3**) (50 μmol dm^{-3}) in pH 7.2 phosphate buffer solution at 25 °C.

Complex Stability Constant. The CD spectral study with modified cyclodextrins enables us not only to elucidate the conformation of the aromatic moiety in the hosts but also to determinate the complex stability constants. When a guest was added to an aqueous solution of **2** or **3**, significant changes were observed in the CD spectrum, although practically no change was observed in the absorption spectrum. Typical changes in the CD and differential CD spectra are shown in Figure

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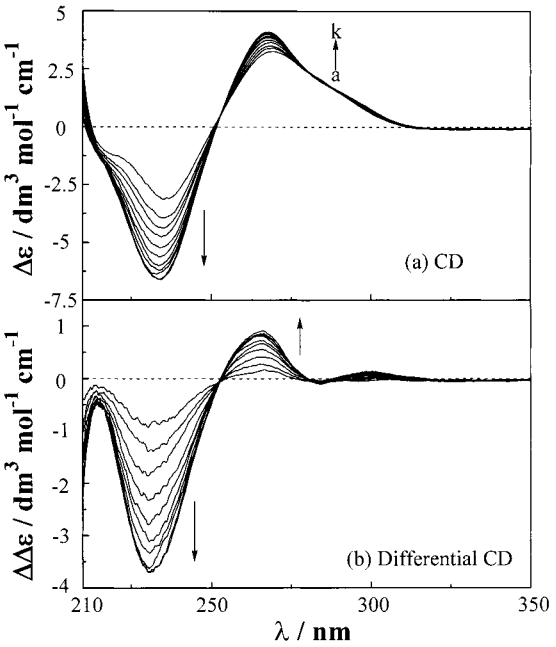

Figure 2. (a) CD and (b) differential CD spectral changes of phosphate buffer solution of 6-(*p*-methoxylphenylseleno-6-deoxy)-*β*-cyclodextrin (**2**) (0.1 mmol dm^{-3}) in the presence of cyclopentanol, added as a guest. The concentration of cyclopentanol is (from a to k): 0, 3.1, 6.1, 9.2, 15.3, 21.4, 27.6, 36.8, 45.9, 61.3, and 76.6 mmol dm^{-3}, respectively.

2 for the complexation of cyclopentanol with **2**. Similar spectral changes were observed with **3** upon addition of guests.

Assuming the 1:1 host:guest stoichiometry, the complexation of guest (G) with host cyclodextrin (H) is expressed by eq 1.

$$H + G \overset{K_S}{\rightleftharpoons} H\cdot G \qquad (1)$$

The CD spectral change ($\Delta\Delta\epsilon$) upon addition of guest, where $\Delta\Delta\epsilon = \Delta\epsilon$ (with guest) $- \Delta\epsilon$ (without guest), is assumed to be proportional to the concentration of inclusion complex produced, i.e. $\Delta\Delta\epsilon = \alpha[H\cdot G]$. The proportionality coefficient α is taken as a sensitivity factor for the CD change induced by the addition of one molar guest, or a quantitative measure of the conformational changes upon complexation.[22,26] Then, the complex stability constant (K_S) is expressed by eq 2:

$$K_S = \frac{[H\cdot G]}{[H][G]} = \frac{\Delta\Delta\epsilon/\alpha}{([H]_0 - \Delta\Delta\epsilon/\alpha)([G]_0 - \Delta\Delta\epsilon/\alpha)} \qquad (2)$$

where $[H]_0$ and $[G]_0$ denote the initial concentrations of host and guest, respectively. Equation 2 is solved for $\Delta\Delta\epsilon$ to give eq 3.

$$\Delta\Delta\epsilon = \{\alpha([H]_0 + [G]_0 + 1/K_S) \pm \sqrt{\alpha^2([H]_0 + [G]_0 + 1/K_S)^2 - 4\alpha^2[H]_0[G]_0}\}/2 \qquad (3)$$

Using the nonlinear least squares curve-fitting method,[26] we obtained the complexation stability constant for each host−guest combination. Figure 3 illustrates some representative plots of experimental and calculated data obtained by using eq 3, in which no serious deviations are observed. The excellent curve fits indicate not only that the stability constants obtained are reliable but also that the host−guest complexation by the cyclodextrin derivatives proceeds through the 1:1 stoichiometry. The isobestic points observed in each CD titration plot further confirm the simple one-step transformation from free host to the final 1:1 complex.

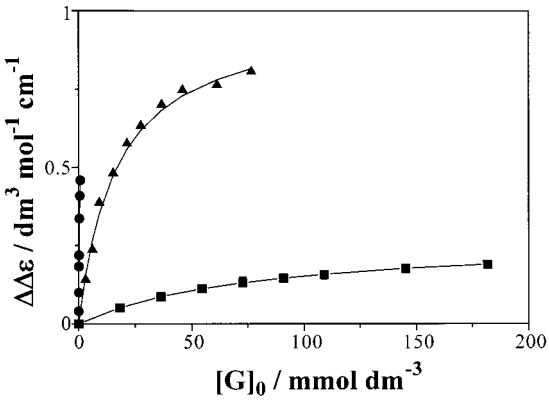

Figure 3. Curve-fitting analyses for complexations of cyclopentanol (▲) and (+)-menthol (●) with **2** and *n*-butanol (■) with **3**.

Molecular Recognition. The stability constant (K_S), Gibbs free energy change ($-\Delta G°$), and sensitivity factor (α) for the inclusion complexation of **2** and **3** with a series of alkanol guests are listed in Table 1. For comparison purposes, the complex stability constants reported for the complexation of native *β*-cyclodextrin with several acyclic and cyclic alkanols are also included in Table 1.

Guest's Size. It is believed that the host−guest complexation by cyclodextrin involves several weak forces, including van der Waals, hydrophobic, electrostatic, dipole−dipole, and hydrogen-bonding interactions. For several years, we have been interested in determining the major contributor(s) to the inclusion and molecular recognition behavior displayed by native and modified cyclodextrin.[13,16−18,21,26,28,29] As can be seen from Table 1, both native (**1**) and modified *β*-cyclodextrins (**2**, **3**) can discriminate the chain length and ring size of guest molecules with moderate selectivities, displaying a gradually increasing tendency in K_S. In other words, the guest's shape and size appear to be the predominant factors that determine the complex stability upon complexation of such simple guests such as alcohols with cyclodextrins. For all hosts examined, the stability constants obtained for a series of acyclic alcohols increase with extending the alkanol's chain length from 4 to 7. The corresponding cyclic alcohols show quite similar complexation behavior but afford binding constants which are greater by a factor of 3 to 5 than those obtained with the corresponding acyclic alcohols. On the basis of these results, we deduce that both van der Waals and hydrophobic interactions mainly contribute to inclusion complexation by cyclodextrins, as these two force are closely related to the distance between host and guest. To visualize the global profiles of the inclusion complexation, the Gibbs free energy

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Table 1. Stability Constant (K_S) and Gibbs Free Energy Change ($-\Delta G°$) for the Inclusion Complexation of *β*-Cyclodextrin (1), 6-(*p*-Methoxylphenylseleno-6-deoxy)-*β*-cyclodextrin (2), and 6-(*p*-Tolylseleno-6-deoxy)-*β*-cyclodextrin (3) with Some Aliphatic Alcohols in Phosphate Buffer (pH 7.20, 0.1 mol dm^{-3}) at 25 °C

host	guest	K_S	log K_S	$-\Delta G°$/ J mol^{-1}	$\Delta\Delta G°$/ J mol^{-1}	α	ref
1	1-butanol	16.6	1.22	7.0			*a*
	1-pentanol	63	1.80	10.3			*a*
	1-hexanol	219	2.34	13.3			*a*
	cyclopentanol	174	2.24	12.76			*b*
	cyclohexanol	708	2.85	16.3			*b*
	cyclooctanol	4365	3.64	20.8			*b*
2	1-butanol	7.4	0.87	4.95		1410	*c*
	1-pentanol	20.6	1.31	7.50		5020	*c*
	1-hexanol	48	1.68	9.60		5790	*c*
	1-heptanol	138	2.14	12.21		6500	*c*
	(*S*)-(+)-2-octanol	291	2.46	14.06	0.26	4680	*c*
	(*R*)-(−)-2-octanol	323	2.51	14.32		4120	*c*
	cyclopentanol	59.8	1.78	10.14		9420	*c*
	cyclohexanol	183	2.26	12.91		11410	*c*
	1-adamantanol	7300	3.86	22.05	1.72	66940	*c*
	2-adamantanol	14600	4.16	23.77		17260	*c*
	(+)-borneol	4330	3.64	20.76	1.06	17340	*c*
	(−)-borneol	6650	3.82	21.82		14020	*c*
	(+)-menthol	1230	3.09	17.64	1.05	18060	*c*
	(−)-menthol	1880	3.27	18.69		23090	*c*
3	1-butanol	12.8	1.11	6.32		1380	*c*
	1-pentanol	42.9	1.63	9.32		1690	*c*
	1-hexanol	80.8	1.91	10.89		1650	*c*
	1-heptanol	276	2.44	13.93		2110	*c*
	cyclopentanol	113	2.05	11.72		1740	*c*
	cyclohexanol	590	2.77	15.82		1690	c
	cyclooctanol	4440	3.65	20.82		4520	*c*
	1-adamantanol	278000	5.44	31.07	1.11	7670	*c*
	2-adamantanol	434600	5.64	32.18		7000	*c*
	(+)-borneol	14300	4.16	23.72	1.31	6740	*c*
	(−)-borneol	24300	4.39	25.03		7430	*c*
	(+)-menthol	2470	3.39	19.36	−2.38	11100	*c*
	(−)-menthol	944	2.97	16.98		13180	*c*

[a] Reference 27. [b] Reference 28. [c] This work.

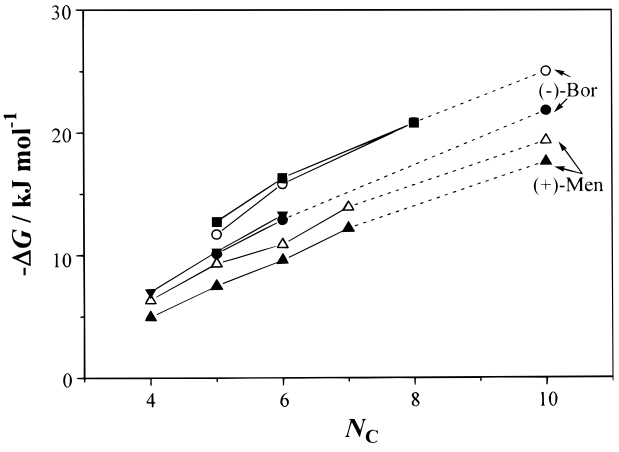


Figure 4. Gibbs free energy change ($-\Delta G°$) plotted as a function of the number of methylenes (N_C) in the guest molecule for the complexation of a series of 1-alkanol (▼ for **1**, ▲ for **2**, and △ for **3**) and cycloalkanols (■ for **1**, ● for **2**, and ○ for **3**) with **1**, **2**, and **3** in pH 7.2 phosphate buffer solution.

changes ($-\Delta G°$) are plotted as a function of the number of methylenes (N_C) in the guest molecule for the complexation of acyclic and cyclic alcohols with native and modified *β*-cyclodextrins **1**−**3**.

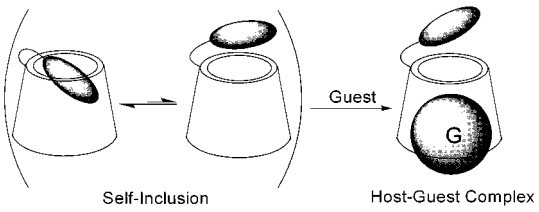
As can be seen from Figure 4, the complex stabilities ($-\Delta G°$) for the complexation of acyclic and cyclic alcohols with **1**, **2**, and **3** increase practically linearly with increasing N_C in all cases. This is often the case in the other host−guest combinations[26,29] and demonstrates that the size−fit relationship between host and guest plays a crucial role in molecular recognition. To quantitatively recognize the guest's size/shape effect, the unit increments per methylene ($-d\Delta G°/dN_C$) are calculated from the data listed in Table 1. Although the substituent introduced and therefore the conformation of two cyclodextrin derivatives **2** and **3** are different considerably, the unit increments are the same for these two cyclodextrins. Irrespective of the hosts employed, the unit increments obtained are 2.4 kJ mol^{-1} for alkanols and 2.9 kJ mol^{-1} for cycloalkanols. These values are somewhat smaller than the corresponding values (3.1 and 3.5 kJ mol^{-1}, respectively) calculated from the thermodynamic data compiled by Rekharsky and Inoue.[29] Although we have no clear explanation for these small but distinct discrepancies, the selenium substitution would affect the van der Waals interaction. Nonetheless, the difference in $-d\Delta G°/dN_C$ between acyclic and cyclic guests remains unchanged at 0.5 kJ mol^{-1}, indicating more intimate interactions for cyclic guests.

More interestingly, if the data for (+)-menthol and (−)-borneol are plotted as C_{10} alcohols at $N_C = 10$ in Figure 4, one finds that these data points fall on or near the lines of acyclic and cyclic alkanols, respectively. This means that (−)-borneol has the same stability constant with cyclodecanol and (+)-menthol has a very similar stability constant with *n*-decanol when they form complexes with **2** and **3**. These agreements may be taken as simple coincidence since the antipodes give different binding constants, yet no such coincidence has been reported for the lower homologues up to C_6 acyclic and cyclic alcohols.[29] Then, the present coincidence would imply that acyclic alcohols are folded into a quasicyclic structure in the cyclodextrin cavity, and even the cyclic alcohols are packed in a folded conformation, although the present results would be simply attributable to the differential interactions between the alcohols and the solvent water.

Substituent Effect. As can be seen from Table 1 and Figure 4, the cyclodextrin derivatives **2** and **3**, possessing very similar structures except for the *para* substituent, exhibit significantly different behavior upon complexation with acyclic and cyclic alcohols. Although higher binding constants are obtained with **3** rather than **2**, native cyclodextrin **1** shows still higher binding constants for most guests. These results clearly indicate that the arylselenyl groups introduced at the 6-position do not enhance the complexation ability but rather interfere with guest inclusion in the cavity, probably through the self-inclusion of the aromatic substituents. Judging from the stronger induced CD spectra observed with **2** (Figure 1), the *p*-anisyl group in **2** is self-included more deeply in the cavity than the *p*-tolyl group in **3**, thus interfering with the accommodation of external guests. We may conclude that the introduction of a self-including substituent to cyclodextrin is not favorable to enhancing the cyclodextrin's complexation ability (Scheme 1).

Chiral and Isomer Recognition. The data listed in Table 1 also show that the two modified *β*-cyclodextrins can recognize the differences not only in molecular size and shape of (cyclo)alkanols but also in the enantiomers of chiral guests. We have studied the complexation inclusion of various amino acids with several native and modified cyclodextrins and found that both native and most modified cyclodextrins prefer the L-isomer.[16,30,31] In

Scheme 1



the present study, the enantioselectivities exhibited by **2** and **3** are moderate to good especially for chiral (bi)-cyclic alcohols such as borneol and menthol, affording the $\Delta\Delta G°$ values of 1.1−2.3 kJ mol^{-1} or the $|K^+/K^-|$ ratios of 1.5−2.6. The enantioselectivity of 2.6 is one of the best results ever obtained.[26] In contrast, the enantiomeric pair of acyclic 2-octanol appears to present difficulties in descrimination ($\Delta\Delta G° = 0.26$ kJ mol^{-1} or $|K^+/K^-| = 1.1$), as was the case with other cyclodextrin derivatives.[26] It is inferred that the modification at the rim affects the chiral microenvironment of cyclodextrin cavity and the self-including substituent contributes to the fixation of the included guest, behaving as a spacer.

From the data listed in Table 1, we can see that the complexes of 2-adamantanol with both **2** and **3** are more stable than those of 1-adamantanol, indicating that the cyclodextrins can recognize the minor difference in the substituent position of guest molecules. From the crystal structures of cyclodextrin complexes,[32,33] Harata et al. have verified that the hydroxyl group is usually located near the secondary hydroxyl side, and the hydroxyl group of 2-adamantanol is at a more favorable position to form hydrogen bonding with the secondary hydroxyls than that of 1-adamantanol. Hence, the hydrogen-bonding interaction recognizes the minor difference in the guest structure, and the isomer selectivities up to 1.6−2.0 are accomplished with **2** and **3**.

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