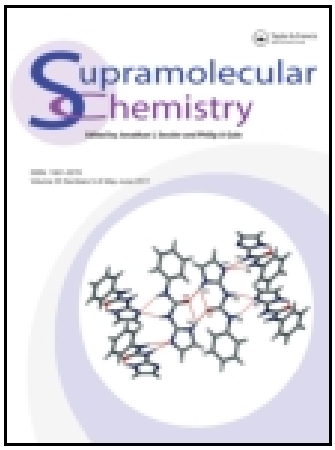

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Molecular Recognition of Aliphatic Alcohols and Carboxylic Acid by Chromophoric Cyclodextrins*

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Molecular recognition behavior of eight cyclodextrin derivatives, *i.e.* mono(6-pyridinio-6-deoxy)-α-cyclodextrin (**1α**), mono(6-pyridinio-6-deoxy)-β-cyclodextrin (**1β**), mono(6-pyridinio-6-deoxy)-γ-cyclodextrin (**1γ**), mono[6-(*p*-picolinio)-6-deoxy]-β-cyclodextrin (**2β**), mono(6-anilino-6-deoxy)-β-cyclodextrin (**3β**), mono[6-(*m*-toluidino)-6-deoxy]-β-cyclodextrin (**4β**), mono[6-*O*-(8-quinolyl)]-β-cyclodextrin (**5β**), and novel mono[6-(2-naphthylamino)-6-deoxy]-β-cyclodextrin (**6β**), with a series of aliphatic alcohols and carboxylic acid has been investigated spectroscopically. Using the appended aromatic group as a spectral probe, spectrofluorometric or spectropolarimetric titrations have been performed at 25 °C in aqueous phosphate buffer solution (pH 7.20, 0.1 M) to determine the complex stability constants (K_s) and Gibbs free energy changes ($-\Delta G°$) for the stoichiometric 1:1 inclusion complexation of cyclodextrin derivatives with the guests. The results obtained demonstrate that the modified cylclodextrins are highly sensitive to the size/shape and hydrophobicity of guest molecules, and particularly **5β** gives an excellent molecular selectivity up to 215 for 1-adamantanol/cyclohexanol. The binding ability and selectivity of the modified cyclodextrins (**1α**, **1γ**, and **1β-6β**) are discussed from the view points of size/shape-fit concept, induced-fit interaction, and the multiple recognition mechanisms.

Keywords: Molecular recognition, modified cyclodextrin, aliphatic alcohol, inclusion complexation

INTRODUCTION

As cyclic oligosaccharides built up from D-glucopyranose units connected through α-1,4-glycoside linkages, cyclodextrins possess hydrophobic truncated cone-shaped cavities which can recognize a wide variety of organic and inorganic molecules, forming host-guest or supramolecular inclusion complexes in aqueous solution [1, 2]. Therefore, native cyclodextrins and their derivatives have been employed widely as enzyme mimics and supramolecular receptors in separation science and technology [3 – 7]. It is well known that substituents introduced to cyclodextrin can alter the original molecular selectivity and enantioselectivity through the microenvironmental changes of cyclodextrin cavity. In fact, diverse cyclodextrin derivatives have hitherto been synthesized and their molecular binding abilities with various guest compounds have been investigated in order to gain insights into the mechanism of the molecular recognition [8, 9]. Among them,

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chromophore-appended cyclodextrin constitutes one of the most important categories of cyclodextrin derivatives, since their complexation behavior is evaluated conveniently by spectrometric methods such as absorption, circular dichroism, and fluorescence spectroscopy. Ueno *et al.* prepared a series of fluorescent cyclodextrins as sensitive indicators for molecular recognition and found that the substituent is self-included initially in the cyclodextrin cavity, but is readily excluded from the cavity upon accommodation of a guest molecule [10 – 13]. It was thus shown that the binding ability and molecular selectivity of modified cyclodextrins depend not only on the size and hydrophobicity of cyclodextrin cavity itself, but also on the substituents. We have reported the syntheses and molecular recognition of a series of modified cyclodextrins in the previous studies, where we found that the type of substituent introduced to cyclodextrin drastically affects the molecular recognition ability as well as the enantioselectivity for chiral guests [14 – 16].

In this paper, we wish to report the results of our study on the inclusion complexation of several cyclodextrin derivatives, carrying pyridinio (**1**α, **1**β, **1**γ), *p*-picolinio (**2**β), anilino (**3**β), *m*-toluidinio (**4**β), quinolyl (**5**β), and naphthylamino (**6**β) moieties in the side chain, with aliphatic alcohol and carboxylic acid guests in phosphate buffer solution at 25 °C, which is assessed by spectropolarimetric and spectrofluorometric titrations. We will discuss the influence of the substitution and the structure of guest upon inclusion complexation of the modified cyclodextrins **1–6** with these guests from the viewpoints of size/shape-fit relationship, multipoint recognition and induced-fit mechanism. The complex stability constants obtained will contribute to further understanding of several weak forces, such as hydrophobic, van der Waals, electrostatic, and hydrogen-bonding interactions, which cooperatively to govern the inclusion complexation phenomenon by cyclodextrin.

RESULTS

CD spectra

It is known that achiral chromophoric guests, when accommodated in the chiral cavity of cyclodextrin, produce induced circular dichroism (ICD). Similarly the chromophoric substituents appended to cyclodextrin produce ICD, which can be used as a convenient probe to determining its conformation in the cavity and also for detecting the inclusion complexation with various guests. As shown in Figure 1, the CD spectra of these pyridinio-substituted cyclodextrins, **1**α, **1**β, **1**γ, and **2**β, are similar in shape but appreciably different in intensity. Thus, these modified cyclodextrins **1** and **2** exhibit a positive CD at the ^1L_b band around 260 nm and a negative CD at the ^1L_a band around 230 nm. Kajtar *et al.* [17] and Harata [18] *et al.* elucidated that, if the transition moment of guest chromophore is parallel to the axis of symmetry of the cyclodextrin, *i.e.* the axis of the cyclodextrin cavity, then the sign of the induced Cotton effect for that transition will be positive. On the contrary, if the transition moment is perpendicular to the cavity axis, the sign will be negative. Based on the above empirical rule, we can deduce that the aromatic substituents of **1**α, **1**β, **1**γ and **2**β do not deeply penetrate but are shallowly included in the cavity in a direction perpendicular to the cavity axis. Figure 2 illustrates the result of Kajtar's sector rule [17] applied to the *p*-picolinio moiety in **2**β. Examinations with Corey-Pauling-Koltun (CPK) molecular models also indicate that the pyridinio group cannot deeply enter into the cavity, since the linker is not long enough to allow full penetration into the cavity. However, it is interesting that the ICD intensity increases with increasing ring size for the homologous cyclodextrins in the order **1**α < **1**β < **1**γ. This may be attributed to the deeper penetration of the pyridinio group into the cavity of larger-sized cyclodextrins.

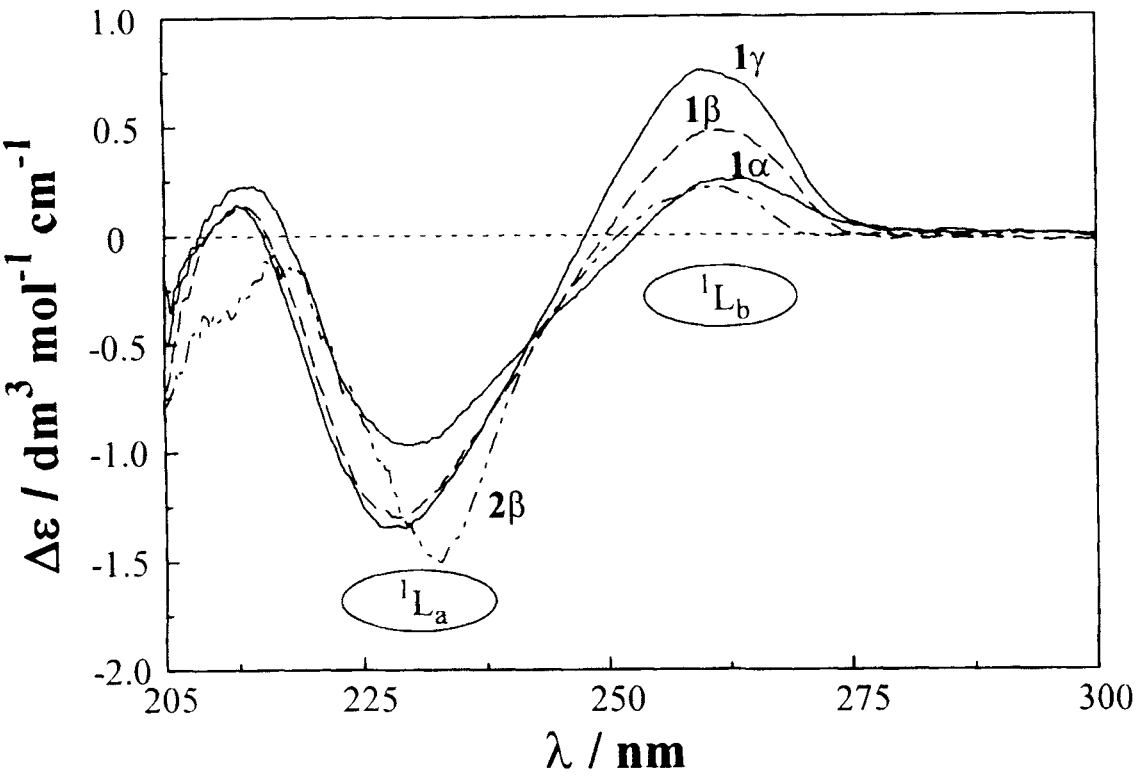

FIGURE 1 Circular dichroism spectra of 6-(pyridinio-6-deoxy)-α-cyclodextrin (**1α**) (50 μM), 6-(pyridinio-6-deoxy)-β-cyclodextrin (**1β**) (50 μM), 6-(pyridinio-6-deoxy)-γ-cyclodextrin (**1γ**) (50 μM) and 6-[(*p*-picolinio)-6-deoxy]-β-cyclodextrin (**2β**) (50 μM) in phosphate buffer solution (pH 7.2) at 25 °C

Spectral Titration

In order to study quantitatively the interaction of the hosts (**1α**, **1γ** and **1β-6β**) with guest molecules, differential CD or fluorescence spectral titrations were performed at 25 °C in aqueous phosphate buffer solution. As exemplified in Figure 3, gradual addition of a known concentration of guest compound (cyclopentanol) to a dilute host solution of **4β** (0.2 mM) caused significant change in CD intensity.

Assuming the 1:1 stoichiometry, the inclusion complexation of guest molecule (G) with cyclodextrin derivative (H) can be expressed by Eq. (1).

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

The complex stability constant (K_S) can be determined using a non-linear least squares method according to the curve-fitting Eq. (2) [19]:

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

where $[G]_0$ and $[H]_0$ refer to the total concentration of the guest and cyclodextrin derivative, respectively; α is the proportionality coefficient, which may be taken as a sensitivity factor for the CD change; ΔΔε denotes the change in CD intensity upon stepwise addition of guest. For each host examined, the plot of ΔΔε as a function of $[G]_0$ gave an excellent fit, verifying the validity of the 1:1 complex stoichiometry assumed. Typical curve-fitting plots are shown in Figure 4 for the complexation of **1α**, **3β**, and **4β** with

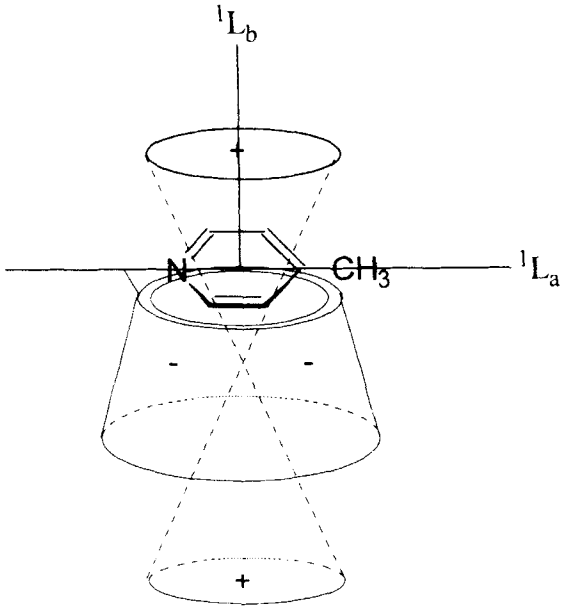

FIGURE 2 Kajtar's sector rule applied to transition moments of ^1L_a and ^1L_b bands of the *p*-picolinio moiety in **2β**

cyclopentanol. When repeated measurements were made, the K_S value was reproducible within an error of ±5%, which corresponds to an estimated error of 0.12 kJ mol^{-1} in the free energy of complexation (ΔG°). The complex stability constants (K_S) obtained by the curve-fitting are listed in Table I, along with the free energy change of complex formation (-ΔG°).

Since the quinoline- and naphthalene-containing cyclodextrins **5β** and **6β** are fluorescent, the K_S values were determined by the fluorometric titration. As shown in Figure 5, the fluorescence spectrum of **5β** suffered significant changes upon gradual addition of 1-adamantanol to the host solution, from which the K_S value was calculated according to the method reported previously [20]. The results are listed in Table I.

DISCUSSION

Extensive studies on molecular recognition by cyclodextrins have shown that several noncovalent intermolecular forces such as hydrophobic, dipole-dipole, van der Waals, electrostatic, and hydrogen-bonding interactions cooperatively contribute to inclusion complexation. In the present case, the relative size and stereochemical complementary relationships between the host and guest, hydrogen-bonding and hydrophobic interactions are considered to be important. The results obtained indicate that the self-inclusion behavior, which is a critical function of the charge, shape, and hydrophobicity of the chromophoric substituents, also plays a crucial role in determining the complex stability and guest selectivity.

Pyridiniocyclodextrins (1α, 1β, and 1γ)

Possessing different cavity sizes, pyridinio-modified cyclodextrins (**1α**, **1β**, **1γ**) showed contrasting binding abilities toward cyclopentanol and cyclohexanol. As can be seen from Table I, **1α** affords much larger binding constants for cyclopentanol (K_S = 740 M^{-1}) and cyclohexanol (K_S = 634 M^{-1}) than those reported for native α-cyclodextrin, *i.e.* K_S = 36 and 62 M^{-1}, respectively [21, 22]. This may be attributed to the expanded hydrophobic cavity formed by the substituent perching over the cavity upon guest inclusion. Somewhat unexpectedly, **1α** prefers cyclopentanol to cyclohexanol in contrast to the general tendency reported for native α-cyclodextrin (Table I). On the contrary, **1β** affords smaller binding constants for cyclopentanol (K_S= 64 M^{-1}) and cyclohexanol (K_S= 165 M^{-1}) than those reported for native β-cyclodextrin, *i.e.* K_S = 170 and 680 M^{-1}, respectively [21, 22]. Probably, the self-included substituent may interfere, or compete, with the full penetration of cycloalkanol guests into the β-cyclodextrin cavity. Accordingly, the unit increment of Gibbs free energy per methylene ($-d\Delta G°/dN_C$ = 2.4 kJ/mol) calculated for **1β** is appreciably smaller than the average value ($-d\Delta G°/dN_C$ = 3.5 kJ/mol) reported for native β-cyclodextrin [23]. Unfortunately, no significant CD spectral changes were

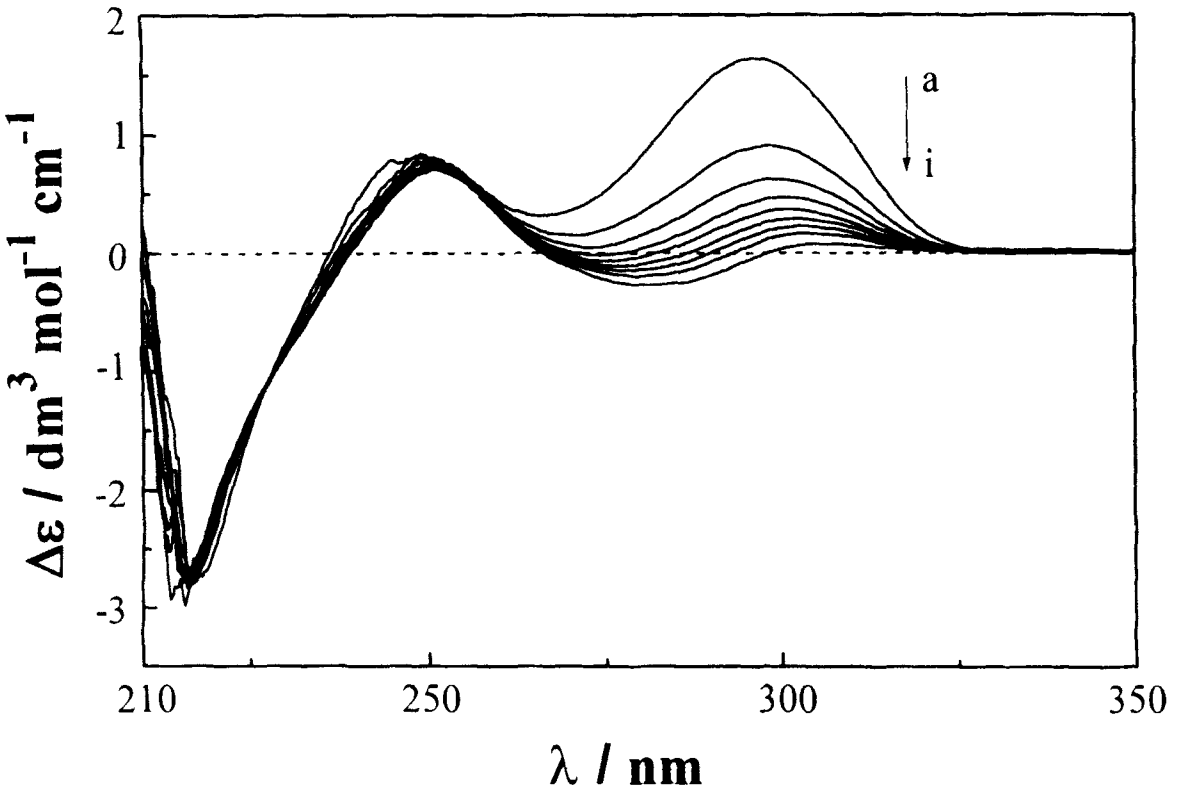

FIGURE 3 CD spectral changes of phosphate buffer solution of 6-(*m*-toluidino-6-deoxy)-β-cyclodextrin (**4β**) (0.2 mM) in the presence of cyclopentanol added as a guest. The concentration of cyclopentanol (from a to *i*): 0, 1.8, 3.6, 5.5, 7.3, 14.6, 18.2, 29.2, and 61.3 mM, respectively

observed with **1γ** upon addition of cyclohexanol under the comparable titration conditions. This result may be rationalized by the poor size-fit relationship between the γ-cyclodextrin and cycloalkanols.

Possessing a charged group, cyclopentanecarboxylate is bound more weakly by **1α** than neutral cyclopentanol. In view of the reduced hydrophobicity of cyclopentanecarboxylate, this result is quite reasonable, but it seems interesting **1γ** can bind cyclopentanecarboxylate stronger than cyclohexanol, although the K_S is fairly small. The carboxylate group would be hydrogen-bonded to peripheral hydroxyl groups of cyclodextrin to overcome the lower hydrophobicity.

6-Pyridinio-6-deoxy- (1β), 6-(p-Picolinio)-6-deoxy- (2β), 6-Anilino-6-deoxy (3β), and 6-(m-Toluidino)-6-deoxy-β-cyclodextrin (4β)

Numerous studies have been performed on the molecular recognition mechanism of chemically modified cylcodextrins. It has been revealed that the substituent appended to cyclodextrin is originally self-included in the cavity in the absence of guest, forming an intramolecular complex, but is expelled out of the cavity upon guest inclusion [12, 13, 15, 16]. Therefore, the molecular recognition by modified cyclodextrin is analogous to competitive inclusion complexation, and the depth of substituent penetration into the cavity significantly affects the binding ability. In a previous report [24], we found that the self-inclu-

sion of β-cyclodextrin's substituent plays an important role in determining how the guest molecule fits into the host cavity. In this context, it is interesting to compare the complexation behavior of the structurally related β-cyclodextrin derivatives **1β-4β**. As can be seen from Table I, the binding abilities of these hosts show quite similar tendencies for both cyclopentanol and cyclohexanol, K_S decreasing in the order **3β** > **4β** > **2β** > **1β**. Thus, the positively charged pyridinio group introduced in **1β** and **2β** does not enhance the original binding ability of β-cyclodextrin, and therefore the electrostatic interaction is not likely to be the major driving force in the inclusion complexation. Instead, the pyridinio group reduces the original hydrophobicity of cyclodextrin cavity, making **1β** and **2β** the poorest binders for cycloalkanols among these four hosts. Judging from the much larger K_S values obtained with **3β** and **4β**, the introduction of an anilino group appears to expand the original cavity and/or enhance its hydrophobicity.

TABLE I The stability constant (K_S) and Gibbs free energy change (-ΔG°) for the inclusion complexation of chemically modified cyclodextrins (**1α**, **1γ**, and **1β-6β**) with some model substrates in phosphate buffer solution (pH 7.20, 0.1 M) at 25 °C

Host	*Guest*	K_S/M^{-1}	$\log K_S$	$-\Delta G°/kJ\cdot mol^{-1}$	$-d\Delta G°/dN_C$[a]	*Method*[b]	*Ref*
α-Cyclodextrin	Cyclopentanol	36	1.56	8.91		Cal	c
	Cyclohexanol	62	1.79	10.2	1.3	Cal	d
β-Cyclodextrin	Cyclopentanol	170	2.24	12.8		Cal	c
		680	2.84	16.2	3.4	Cal	d
1α	Cyclopentanol	740	2.87	16.4		CD	e
	Cyclohexanol	630	2.80	16.0	−0.4	CD	e
	Cyclopentane- carboxylic acid	450	2.65	15.1		CD	e
1β	Cyclopentanol	64	1.80	10.3		CD	e
	Cyclohexanol	165	2.22	12.7	2.4	CD	e
1γ	Cyclohexanol	f				CD	e
	Cyclopentane- carboxylic acid	14	1.15	6.5		CD	e
2β	Cyclopentanol	130	2.11	12.1		CD	e
	Cyclohexanol	400	2.60	14.9	2.8	CD	e
3β	Cyclopentanol	530	2.72	15.5		CD	e
	Cyclohexanol	1980	3.30	18.8	3.3	CD	e
4β	Cyclopentanol	430	2.63	15.0		CD	e
	Cyclohexanol	1250	3.10	17.7	2.7	CD	e
5β	Cyclohexanol	1090	3.04	17.3		Fl	eg
	Cyclohexane- carboxylic acid	650	2.81	16.1		Fl	eg
	Nerol	1920	3.28	18.7		Fl	eg
	(+)-Menthol	25500	4.41	25.2		Fl	eg
	(+)-Borneol	82800	4.92	28.1		Fl	eg
	1-Adamantanol	233800	5.37	30.6		Fl	eg
6β	All alcohols examined	f				Fl	eh

a. Unit increment in ΔG° per methylene in the guest; *i.e.* $-d\Delta G°/dN_C = \Delta G°(\text{cyclopentanol}) - \Delta G°(\text{cyclohexanol})$.
b. Method employed in the determination of KS: Cal: calorimetry; CD: circular dichroism spectrometry; Fl: fluorometry.
c. Value determined at pH 6.9; Ref 23.
d. Value determined at pH 6.9; Ref 24.
e. This work.
f. No significant spectral change could be observed.
g. Excitation at 300 nm.
h. Excitation at 335 nm; too small changes in fluorescence intensity to calculate K_S.

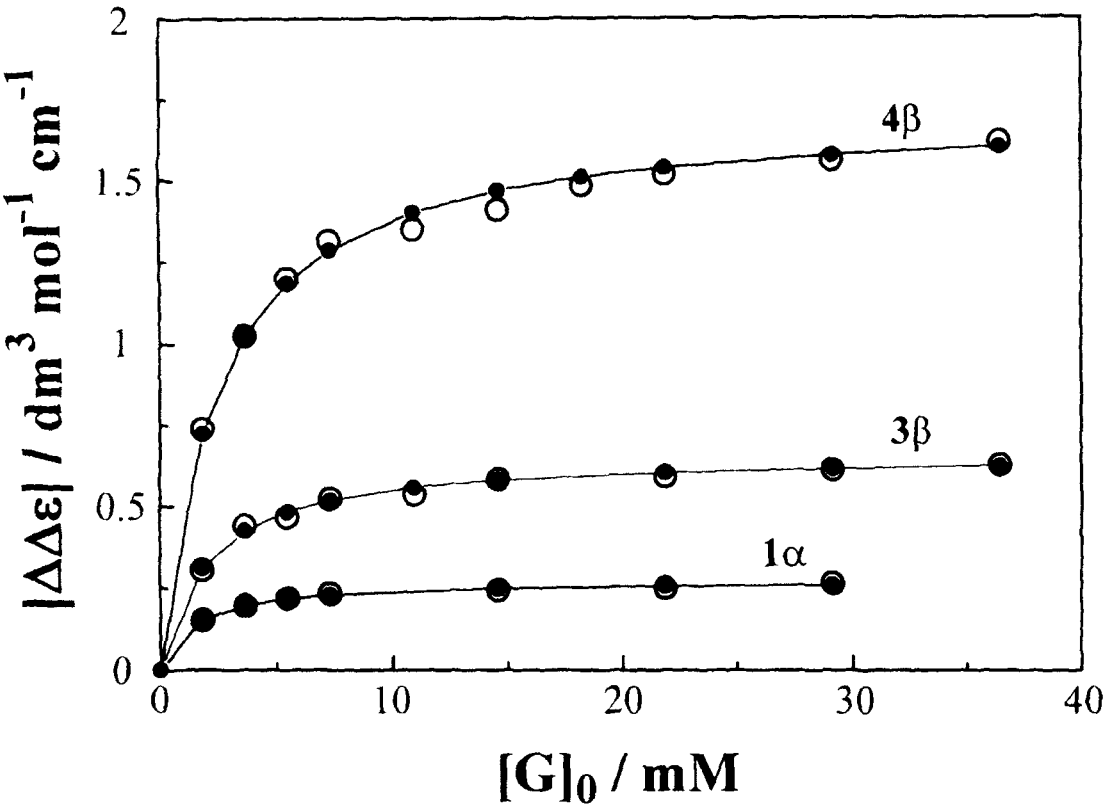

FIGURE 4 Curve-fitting analyses for complexations of cyclopentanol with 1α, 3β, and 4β open circles represent experimental values, while dots denote calculated values

It is also interesting to note that, as shown in Table I, the $-d\Delta G°/dN_C$ value increases from 2.4 kJ/mol for **1β** to 3.3 kJ/mol for **3β**, as the K_S value increases. Although the averaged $-d\Delta G°/dN_C$value of 2.8 kJ/mol is smaller than that reported for native β-cyclodextrin (3.5 kJ/mol), this result indicates that the hydrophobic and van der Waals interactions play the major roles in the complexation of these modified cyclodextrins with cycloalkanols.

6-O-Quinolyl- (5β) and 6-(2-Naphthylamino)-6-deoxy-β-cyclodextrin (6β)

In order to gain further insights into the size/shape-fit concept in the molecular recognition by modified cyclodextrin, spectrofluorometric titrations have been performed to determine the K_S values for complexation of **5β** with a series of aliphatic alcohols of different size, shape and hydrophobicity. Previous work and examination of CPK space-filling molecular models clearly indicate that the rigid spherical skeleton of adamantane is best size/shape-fitted to the β-cyclodextrin cavity [25, 26]. Hence, it is not surprising to observe that **5β** gives the largest K_S for 1-adamantanol as well as the highest molecular selectivity up to 215 for 1-adamantanol/cyclohexanol. Furthermore, as a result of its most rigid and hydrophobic structure, 1-adamantanol forms the most stable complex with modified β-cyclodextrin **5β** among the four C_{10}

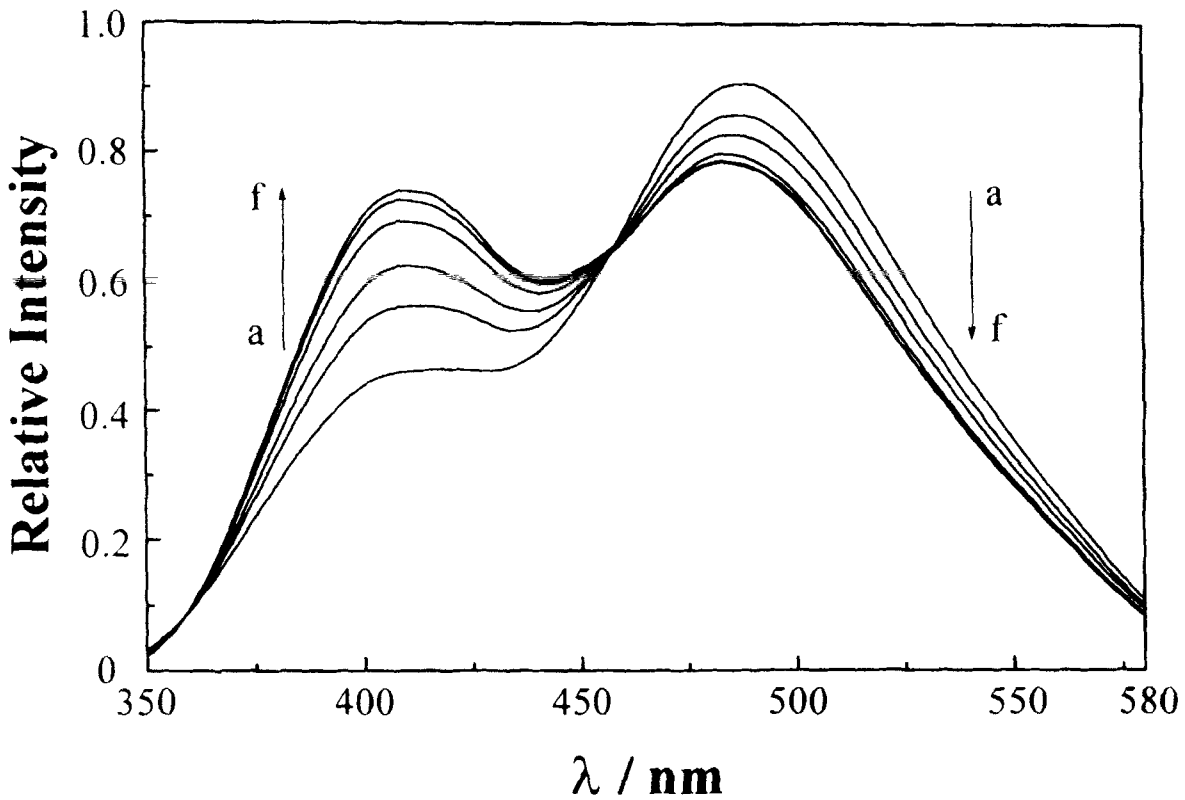

FIGURE 5 Fluorescence spectra of mono[6-*O*-(8-quinolyl)]-β-cyclodextrin (5β) (10 μM) in phosphate buffer solution (pH 7.20) in the presence of various concentrations of 1-adamantanol: (a) 0, (b) 10, (c) 20, (d) 50, (e) 100, (f) 150 μM; excitation wavelength was 300 nm

aliphatic alcohols examined. As can be seen from Table I, 5β can recognize not only the size of aliphatic alcohols, but also the shape of the C_{10} guests (nerol, menthol, borneol, and adamantanol). For the series of acyclic to tricyclic C_{10} alcohols that possess distinctly different shape and rigidity, 5β displays fairly good molecular selectivities of up to 122 for 1-adamantanol/nerol and 43 for (+)-borneol/nerol. This order of complex stability appears to be determined mostly by the rigid molecular structure. Thus, tricyclic adamantanol and bicyclic borneol, both having rigid and bulky skeletons, form the most stable complexes with 5β, while the most flexible, least bulky nerol with a (*E*)-double bond gives the least stable complex.

It should be noted that the fluorescence spectrum of naphthylamino-appended 6β was not affected at all even upon addition of 1-adamantanol. This behavior is consistent with our previous observation that the UV spectrum of mono-[6-(2-naphthylseleno)-6-deoxy]-β-cyclodextrin did not show any changes upon addition of various guests [27]. These results would be attributable either to the spectral insensitivity of 6β or to the insignificant host-guest interaction which are not strong enough to exclude the self-included naphthyl group from the cavity. In this context, it may be emphasized that β-cyclodextrin forms a very stable inclusion complex with 2-naphthalenesulfonate in the phosphate buffer solution, whose K_S is as high as

$2.4\times10^5\ M^{-1}$ [30]. A reasonable explanation for the weak complexation of **6β** is that the naphthyl substituent of **6β** penetrates deeply into the cavity and form an extremely stable self-inclusion complex, which cannot be decomplexed by the guest molecules employed. The result obtained further indicates that the shape, size and hydrophobicity of the subsituent introduced to cyclodextrin play a decisive role in molecular recognition.

EXPERIMENTAL SECTION

Materials

All guest compounds were commercially available and used without further purification. Mono(6-pyridinio-6-deoxy)-α-cyclodextrin (**1α**), mono(6-pyridinio-6-deoxy)-β-cyclodextrin (**1β**), and mono(6-pyridinio-6-deoxy)-γ-cyclodextrin (**1γ**) were synthesized by the reaction of pyridine with corresponding mono-tosylated cyclodextrin, according to the procedures reported by Matsui [29] *et al.* Mono[(6-(*p*-picolinio)-6-deoxy]-β-cyclodextrin (**2β**), mono(6-anilino-6-deoxy)-β-cyclodextrin (**3β**), and mono[6-*O*-(8-quinolyl)]-β-cyclodextrin (**5β**) were prepared as described in the previous paper [14]. Mono[(6-(*m*-toluidinyl)-6-deoxy]-β-cyclodextrin (**4β**) was synthesized by the reaction of *m*-toluidine with mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin in DMF according to the procedure described previously [30]. Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make 0.1 M phosphate buffer solution of pH 7.20 for CD and fluorescence spectral measurements.

Synthesis of Mono[6-(2-naphthylamino)-6-deoxy]-β-cyclodextrin (6β)

Compound **6β** was prepared by the reaction of mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin (2.6 g, 2 mmol) with an excessive 2-aminonaphthalene in *N,N*-dimethylformamide (20 mL) at 80–90 °C for 3 days under nitrogen atmosphere. The reaction mixture was evaporated *in vacuo* at 40 °C to dryness. The residue was washed successively with ethanol and acetone in order to remove unreacted 2-aminonaphthalene. Then, the gray powder obtained was dissolved in a minimum amount of hot water, and the solution was poured into acetone (200 mL). The precipitate formed was filtrated to give white powder. The crude product was recrystallized three times from water and then dried *in vacuo* to give a pure sample of **6β** in 40% yield. UV (H_2O) λ_{max} (log ε) 234.0 (4.40), 268.2 (3.50), 278.2 (3.55), 334.2 nm (3.04); FT-IR (KBr): v 3370, 1927, 1631, 1516, 1409, 1360, 1335, 1302, 1155, 1081, 1032, 941, 843, 753 cm^{-1}; ^{1}H-NMR (DMSO-d_6, TMS) δ 6.9–7.9 (m, 7H, Ar-H), 5.6–5.9 (m, 14H, (O-2)H and (O-3)H), 4.8 (m, 7H, H-1), 4.55 (m, 6H, (O-6)H), 3.1–3.9 (m, 42H, H-3, H-5, H-6, H-2, and H-4); Anal. Calcd for $C_{52}H_{77}O_{34}N\cdot4H_2O$: C, 46.88%; H, 6.39%; N, 1.05%. Found: C, 46.43%; H, 6.51%; N, 1.02%.

Spectral measurements

Binding constants for the inclusion complexation of modified cyclodextrins (**1α**, **1γ**, and **1β-4β**) with guest molecules were determined using circular dichroism (CD) spectrometry on a JASCO J-720S spectropolarimeter. The CD spectra of sample solutions containing a modified cyclodextrin (**1α**, **1γ**, and **1β-4β**) (0.1 – 0.2 mM) and a guest of varying concentrations were measured in a conventional quartz cell maintained at 25.0 ± 0.1 °C by circulating thermostatted water through the jacket. The differential CD spectrum was obtained by subtracting the original CD spectrum in the absence of a guest from that in the presence of a guest on computer memories. The stability constants for inclusion complexation of fluorescent hosts **5β** and **6β** were obtained by using spectrofluorometric titrations. Fluorescence spectra were measured at 25 °C in a conventional quartz cell (1×1 cm) on a JASCO

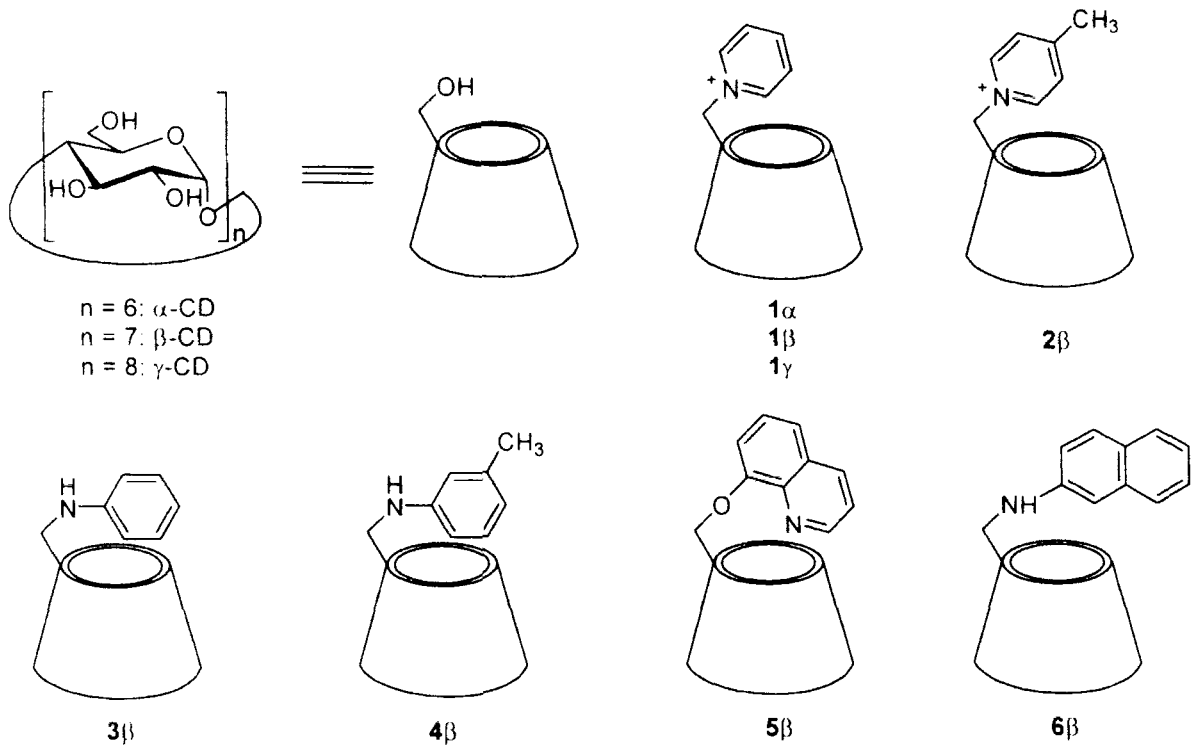

CHART 1

FP-750 spectrofluorometer with excitation and emission slits of 5 nm width. The sample solutions at a host concentration of 10 μM were excited at 300 nm and 335 nm for **5β** and **6β**, respectively, to give strong emission, and the fluorescence intensity at the emission maximum was used to determine the complex stability constants.

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