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Studies on molecular recognition in supramolecular systems. Part 31: Circular dichroism spectral studies of molecular and chiral recognition of aliphatic alcohols by 6-modified β-cyclodextrins

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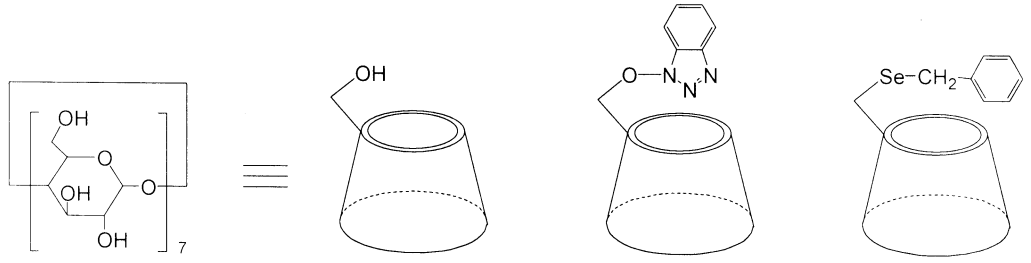
Abstract—The stability constants (K_S) for the inclusion complexation of novel mono[6-*O*-(1- benzotriazole)]-β-cyclodextrin (**2**) and mono(6-benzylseleno-6-deoxy)-β-cyclodextrin (**3**) with a series of chiral and achiral (cyclo)alkanols have been determined at 25°C in aqueous phosphate buffer solution at pH 7.20 by circular dichroism spectral titration. It was revealed that **2** and **3** can fairly strictly recognize not only the size/shape but also the chirality of guest molecules. Thus, the log K_S value, or the Gibbs free energy change ($-\Delta G^0$), increases linearly with increasing number of carbon atoms (N_C) in cycloalkanol, affording comparable increments per methylene unit: $-d\Delta G^0/dN_C$=2.0 and 2.2 kJ mol^{-1} for **2** and **3**, respectively. Furthermore, **2** and **3** displayed moderate to excellent isomer selectivities of up to 15.3 for the guest alcohols examined, while moderate enantioselectivities of 1.1–1.4 were obtained with chiral borneol and menthol guests upon complexation with **2** and **3**. The present results obtained with **2** and **3** elucidate the effects of substituents on the complexation behavior as well as some of the factors governing size, shape, and chiral selectivities. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

As a crucial concept in supramolecular chemistry, the molecular recognition phenomenon has been intensively investigated and discussed for the last three decades particularly in relation to biological substrate–receptor interactions.[1–3] Possessing well-defined hydrophobic cavities which can bind various organic, inorganic, and biological molecules to form stable inclusion complexes or supramolecular species, natural and chemically modified cyclodextrins have been employed as excellent hosts in supramolecular chemistry and chiral selectors in separation science and technology.[4–6] Hence, a great deal of effort has been devoted to the design and syntheses of novel cyclodextrin derivatives which display enhanced molecular binding abilities and selectivities for specific substrates.[7] The preceding studies clearly indicate that the molecular recognition by native and modified cyclodextrins is governed by several cooperatively-working weak forces, which include dipole–dipole, electrostatic, van der Waals,



1 2 3

Chart 1.

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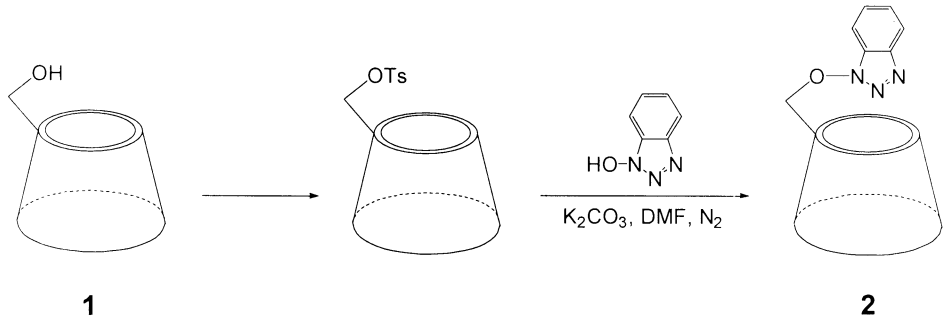

Scheme 1. Synthesis of mono-[6-*O*-(1-benzotriazole)-6-deoxy]-β-cyclodextrin (2).

hydrogen bonding, and hydrophobic interactions.[8–28] Possessing a wide structural diversity and moderate solubility in aqueous solution, aliphatic alcohols have been employed as typical guest molecules in molecular recognition studies, as exemplified by the interesting work of Matsui[19] and Ueno.[13–18] We have also studied the molecular recognition of various guests, including amino acids and aliphatic alcohols, by a series of modified cyclodextrins, and have shown that the structure of the sidearm introduced to cyclodextrin significantly affects not only the molecular recognition ability but also the enantioselectivity for chiral guests.[20–28]

In the present study, we report our study on the syntheses and inclusion complexation of mono[6-*O*-(1-benzotriazole)]-β-cyclodextrin (**2**) and mono(6-benzylseleno-6-deoxy)-β-cyclodextrin (**3**). The complexation behavior of these modified cyclodextrins with a series of acyclic, cyclic, and bicyclic alkanols was studied in aqueous phosphate buffer solution (pH 7.20) at 25°C by differential circular dichroism spectroscopy. The complex stability constants of these aliphatic alcohols with **2** and **3** will promote our understanding of the effects of substituent attached to cyclodextrin on the molecular and chiral recognition, and also contribute to the development of more sophisticated functional cyclodextrins with high molecular and enantiomer selectivities (Chart 1).

2. Results and discussion

2.1. Syntheses

In this work, the precursor, mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin (6-OTs-β-CD), was prepared in 9% yield by the reaction of β-cyclodextrin with *p*-toluenesulfonyl chloride in aqueous sodium hydroxide solution, according to the literature procedure.[29] Mono-[6-*O*-(1-benzotriazole)-6-deoxy]-β-cyclodextrin (**2**) was synthesized in 50% yield by reaction of 6-OTs-β-CD with 1-hydroxybenzotriazole, possessing an activated hydroxyl group, in the presence of anhydrous K_2CO_3 (Scheme 1). It is indispensable that

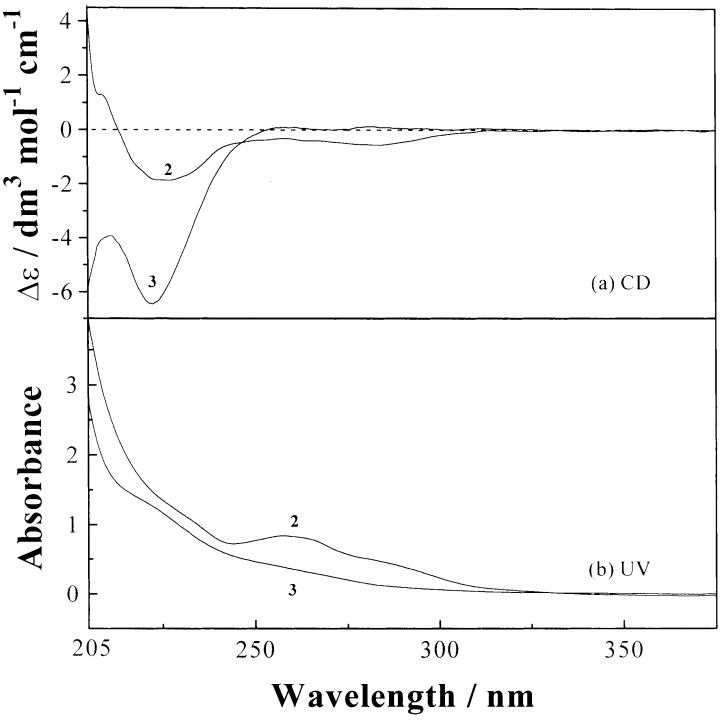

Figure 1. (a) Circular dichroism and (b) absorption spectra of mono-[6-*O*-(1-benzotriazole)-6-deoxy]-β-cyclodextrin (**2**) (0.1 mM) and mono-(6-benzylseleno-6-deoxy)-β-cyclodextrin (**3**) (0.05 mM) in phosphate buffer solution (pH 7.2) at 25°C.

Table 1. Short and/or long fluorescence lifetimes (τ_S,τ_L) and relative quantum yields (Φ_S,Φ_L) for 8-anilino-1-naphthalenesulfonate (ANS) in the presence and absence of host compounds in aqueous phosphate buffer solution (pH=7.20, 0.1 M) at 25.0°C

Guest	Concn. (μM)	Host	Equiv.	τ_S (ns)	Φ_S (%)	τ_L (ns)	Φ_L (%)	χ^2
ANS	10	None		0.4	100			1.42
	500	None		0.4	100			1.46
	10	1	40	0.5	96.5	3.1	3.5	1.00
	250	1	10	1.5	67.6	3.2	32.4	1.24
	10	2	20	0.6	100			1.30
	10	3	23	0.4	100			1.23

compound **2** is purified by column chromatography over Sephadex G-25 because of the highly water-soluble nature of **2**.

2.2. Self-inclusion of 2 and 3

The UV and CD spectra of benzotriazole-β-cyclodextrin (**2**) and benzylseleno-β-cyclodextrin (**3**) in aqueous buffer solution are shown in Fig. 1. The benzyl moiety of **3** was deduced to be shallowly included in the cyclodextrin cavity,[25] on the basis of the negative Cotton effect observed for the ^1L_a band around 225 nm which is in good agreement with Kajtar's sector rule.[30] Possessing a benzotriazole chromophore, host **2** gave significantly different UV and CD spectra. As can be seen from Fig. 1, there are at least three absorption peaks at 225, 264 and 284 nm, for all of which the corresponding negative Cotton effect peaks are observed in the CD spectrum. Therefore, it is reasonable to deduce that all of the three transition moments of the benzotriazole chromophore of **2** lie in the negative region of the sector. Thus, the chromophore is not vertically included in the cavity, but just perching on the rim of the cavity consistent with Kajtar's sector rule and Harata's results.[30–32] Examinations of Corey–Pauling–Koltun (CPK) molecular models confirm this conclusion, since the benzotriazole moiety can only slightly penetrate into the cyclodextrin cavity upon forming a self-inclusion complex.

In order to investigate the effects of self-inclusion of **2** and **3** on their complexation behavior, time-resolved fluorescence decay of 8-anilino-1-naphthalenesulfonate (ANS) was investigated in the presence and absence of the β-cyclodextrin derivatives to assess the micro-environmental polarity around the included ANS. Since the rates of complexation/decomplexation are much slower than that of the fluorescence decay, the decay profile of fluorescence intensity ($F(t)$) can be described as a sum of unimolecular decays for all fluorescing species present in the solution:

$$F(t) = \sum_{i=1}^{n} A_i \exp(-t/\tau_i) \qquad (n = 1, 2, \text{ etc.})$$

where A_i and τ_i represent the initial abundance and lifetime of the ith fluorescing species.

In the absence of the host, the observed decay profile of ANS fluorescence was absolutely single-exponential in the aqueous phosphate buffer, giving a short lifetime of 0.4 ns for free ANS in the bulk solution. In contrast, the decay profile in the presence of native β-cyclodextrin (**1**) was successfully analyzed only by a linear combination of two exponential functions, affording a short (0.5–1.5 ns) and long (3.1–3.2 ns) lifetimes assignable to free and included ANS, respectively.[33] However, the decay curve obtained with added **2** or **3** was well fitted to a single-exponential function, giving short lifetimes (0.4–0.6 ns). The fluorescence lifetimes and relative quantum yields thus obtained are summarized in Table 1. The longer lifetime of ANS (3 ns) in the presence of **1** is reasonably accounted for in terms of a more hydrophobic environment around the ANS molecule included in the cavity. Interestingly, the addition of an excess amount of either **2** or **3** does not appreciably alter the original lifetime (0.4 ns) obtained in the bulk solution. This somewhat unexpected result clearly indicates that the benzotriazole or benzylseleno group self-included in the cavity of **2** or **3** prevents the inclusion of ANS. It is well known that the emission wavelength of TNS or other similar molecules act as a solvatochromic probe for monitoring the extent of its encapsulation.[34] Although the λ_{max} of ANS did not show any significant changes upon addition of **2**, the addition of **3** led to a slight blue shift of λ_{max}, indicating a weak interaction between the receptor and guest ANS. Therefore, the self-included appendant does not seem to enhance the original binding ability of β-cyclodextrin, but rather affords much weaker interaction with large-sized guest molecules such as ANS.

2.3. CD spectral titration

The use of CD spectral changes upon guest inclusion is a less-common technique for the determination of stability constants.[35,36] The quantitative 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 molecular binding ability and selectivity for various guests. When a guest was added to an aqueous solution of **2** or **3**, significant changes in shape and intensity were induced in the CD spectrum, although practically no change was observed in the conventional UV spectrum. As can be seen from Fig. 2, the stepwise addition of 2-ethyl-1-butanol of 16.3 mM to a dilute aqueous buffer solution of **2** (0.1 mM) causes a gradual increase of the CD intensity at longer wavelengths and a decrease at shorter wavelengths with an accompanying isobestic point at 246 nm. The CD spectral changes and the saturation behavior are more clearly seen from the differential CD spectra (Fig. 2b), which are used for the quantitative analysis to determine the stability constant of the complex (K_S).

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

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

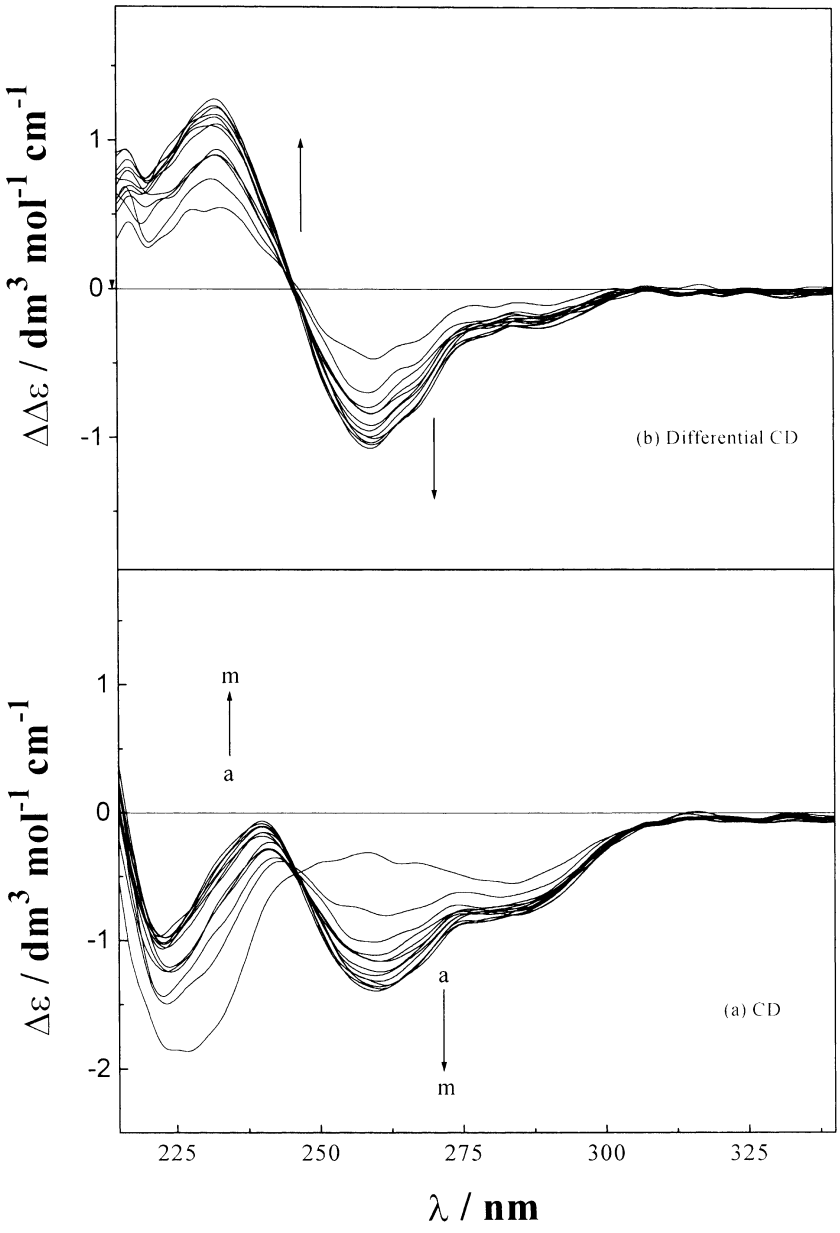

Figure 2. (a) CD and (b) differential CD spectral changes of phosphate buffer solution of mono-[6-*O*-(1-benzotriazole)-6-deoxy]-β-cyclodextrin (**2**) (0.1 mM) in the presence of 2-ethyl-1-butanol, added as a guest. The concentration of 2-ethyl-1-butanol (from a to m): 0, 1.4, 2.7, 4.1, 5.4, 6.8, 8.1, 9.5, 10.8, 12.2, 13.5, 14.0, and 16.3 mM.

The stability constant (K_S) can be determined using a non-linear least-squares method according to the curve fitting Eq. (2).[21]

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

where $[G]_0$ and $[H]_0$ refer to the total concentrations of aliphatic alcohol and β-cyclodextrin derivative, respectively, α is the proportionality coefficient for the effective CD intensity change induced by guest complexation, which may be taken as a sensitivity factor for the CD change, and $\Delta\Delta\epsilon$ denotes the change in CD intensity upon stepwise addition of the guest. For each host compound examined, the plot of $\Delta\Delta\epsilon$ as a function of $[G]_0$ gave an excellent fit to the theoretical curve, verifying the validity of the 1:1 complex stoichiometry assumed above. As shown in Fig. 3, the observed $\Delta\Delta\epsilon$ values (open circle) are plotted against $[G]_0$ to give an excellent fit without any serious deviations from the calculated values (small dots). In the repeated measurements, the K_S values were reproducible within an error of ±5%, which corresponds to an estimated error of 0.15 kJ mol^{-1} in the free energy of complexation (ΔG^0). The K_S and α values obtained by the curve fitting are listed in Table 2, along with the free energy change of complex formation ($-\Delta G^0$).

2.4. Molecular recognition (guest's size)

Although the simultaneous operation of several weak interactions is essential in general for molecular recognition in supramolecular system, the data obtained in the present and

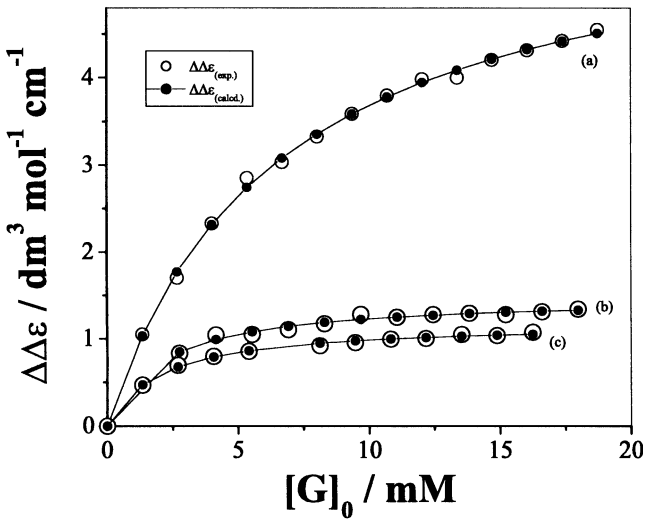

Figure 3. Least-squares curve-fitting analyses for complexations of 3,3-dimethyl-1-butanol (a), cycloheptanol (b), and 2-ethyl-1-butanol (c) with mono-[6-*O*-(1-benzotriazole)-6-deoxy]-β-cyclodextrin (**2**).

previous studies indicates that the hydrophobic and van der Waals interactions are the dominant factors governing the molecular binding and selectivity of (cyclo)alkanols by native and modified cyclodextrins. As can be seen from Table 2, the native and modified cyclodextrins display much higher binding abilities for cycloalkanols than for the corresponding 1-alkanols, giving the highest K_S for the spherical guests such as adamantanol and borneol. This may be attributed to the strict size/shape-fit relationship between the host cavity and the spherical guests of high hydrophobicity and rigidity. Thus, **2** binds (−)-borneol ca. 2000 times stronger than 1-butanol, and **3** binds 1-adamantanol ca. 600 times stronger than 1-butanol, recognizing the size and shape of the guests.

Like the native and modified cyclodextrins reported previously,[21,25,26,29] the present β-cyclodextrins (**2** and **3**) can recognize the chain length of 1-alkanols and the ring size of cycloalcohols with moderate selectivities, giving K_S increasing gradually with increasing number (N_C) of methylene units in the guest molecule. These results indicate that predominantly the guest's size and/or hydrophobicity govern the inclusion complexation. For all host–guest combinations examined, the complex stability increases with extending the chain length of 1-alkanols or enlarging the ring size of cycloalkanols. In order to visualize the global profiles of the inclusion complexation, the $-\Delta G^0$ values are plotted as a function of N_C for the complexation of 1-alkanols and cycloalkanols with native and modified β-cyclodextrins **1**–**3**.

As can be seen from Fig. 4, the complex stabilities ($-\Delta G^0$) for the inclusion complexation of 1-alkanols and cycloalkanols with **1**, **2**, and **3** increase practically linearly with increasing N_C for all host–guest combinations, except for a few specific points. Similar tendencies are found for many other cyclodextrins in the literature,[21,25–27] unequivocally confirming that the hydrophobic and van der Waals interactions are the origin of size–fit relationship, as these two forces are extremely distance-dependent. In order to quantitatively compare the effect of guest size, the unit increments of ΔG^0 per methylene ($-d\Delta G^0/dN_C$) are calculated from the data listed in Table 2. With host **2**, the unit increments obtained are 1.5 kJ mol^{-1} for 1-alkanols and 2.0 kJ mol^{-1} for cycloalkanols; with host **3**, 1.9 kJ mol^{-1} for 1-alkanols and 2.2 kJ mol^{-1} for cycloalkanols. These values are appreciably smaller than the relevant values obtained with native β-cyclodextrin **1**, i.e. 3.1 and 3.5 kJ mol^{-1} for 1-alkanols and cycloalkanols, respectively.[22] It is noted that, despite the smaller $-d\Delta G^0/dN_C$ values for **2** and **3**, the difference in $-d\Delta G^0/dN_C$ between acyclic and cyclic alcohols is kept constant at 0.3–0.5 kJ mol^{-1} for **1–3**, probably reflecting the inherent entropic disadvantage of the acyclic guests.

Interestingly, the $-\Delta G^0$ value for complexation of (−)-menthol with **2**, if plotted as a cyclic C_{10} alcohol at N_C=10 in Fig. 4, smoothly fits on the extrapolated regression line for cycloalkanols. This means that (−)-menthol behaves like cyclodecanol upon complexation with **2**. 1-Adamantanol, a tricyclic C_{10} alcohol, displays exactly the same behavior upon complexation with **3**. More interestingly, the geometrical isomers of acyclic C_{10} dienol (geraniol and nerol) afford distinctly different $-\Delta G^0$ values. Thus, the (*E*)-isomer (i.e. geraniol) behaves like 1-decanol, whereas the (*Z*)-isomer (nerol) gives a much smaller $-\Delta G^0$ value than that expected for an acyclic C_{10} alcohol. This unusually low affinity for nerol may be attributed to its bent structure around the (*Z*)-double bond. In this context, the low $-\Delta G^0$ values obtained for menthols with **3**, which are incidentally comparable to that for acyclic geraniol, are unexpected and could be attributable to the steric hindrance of the benzyl sidearm of **3** upon accommodation of menthol as a branched cyclohexanol.

2.5. Isomer recognition (guest's shape)

As exemplified above, the size/shape complementarity between the host and guest appears to substantially affect the complex stability and guest selectivity. Hence, we next compare the complexation behavior of isomeric alcohols with modified cyclodextrins. As can be seen from Table 2, hosts **2** and **3** are very sensitive to the shape of guests, giving fairly good isomer selectivities. Thus, the isomer selectivity of **2** for acyclic alkanols, as measured by relative K_S, varies from 1.5 for 2-methyl-2-butanol/3-pentanol (N_C=5) to 4.9 for 2-methyl-2-heptanol/4-methyl-4-heptanol (N_C=8). Host **3** cannot discriminate the isomeric C_4 alkanols at all, but shows an isomer selectivity as high as 7.4 for 1-octanol/2,2-dimethyl-3-hexanol (N_C=8).

For cycloalkanols (N_C=7,8,10), the isomer selectivity of host **2** is 3.3 for cycloheptanol/4-methylcyclohexanol, 1.5 for 2,6-dimethylcyclohexanol/cyclooctanol, and 12.5 for (−)-borneol/(+)-menthol, while the isomer selectivity of host **3** is 1.1 for cycloheptanol/4-methyl-cyclohexanol, 15.3 for cyclooctanol/2,6-dimethyl-cyclohexanol, and 24.5 for 1-adamantanol/nerol. A global examination of the data listed in Table 2 leads to an interesting general trend of K_S for the complexation of cyclic C_{10} alcohols with the cyclodextrin derivatives examined: 2-adamantanol>1-adamantanol>borneol>menthol. This coincides with the order of the rigidity of guest molecule, which may indicate that

Table 2. Stability constant (K_S) and Gibbs free energy change ($-\Delta G^0$) for the inclusion complexation of natural and modified β-cyclodextrin (1–3) with some aliphatic alcohols in phosphate buffer (pH 7.20, 0.1 M) at 25°C

Host	Guest	K_S	log K_s	$-\Delta G^0$ (kJ mol^{-1})	α	Ref.
1	1-Butanol	17	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	12.8	–	[b]
	Cyclohexanol	708	2.85	16.3	–	[b]
	Cycloheptanol	2190	3.34	19.1	–	[b]
	Cyclooctanol	4370	3.64	20.8	–	[b]
2	1-Butanol	22	1.35	7.7	16950	[c]
	2-butanol	74	1.87	10.7	11320	[c]
	1-Pentanol	142	2.15	12.3	13660	[c]
	3-Pentanol	137	2.14	12.2	101680	[c]
	2-Methyl-2- butanol	202	2.31	13.2	14880	[c]
	Cyclopentanol	66	1.82	10.4	18150	[c]
	1-Hexanol	178	2.25	12.8	8380	[c]
	3,3-Dimethyl-2-butanol	491	2.69	15.4	16180	[c]
	2-Ethyl-1-butanol	511	2.71	15.5	11780	[c]
	Cyclohexanol	152	2.18	12.5	9040	[c]
	1-Heptanol	209	2.32	13.2	99850	[c]
	4-Heptanol	119	2.08	11.9	7760	[c]
	2,4-Dimethyl-3-pentanol	214	2.33	13.3	14540	[c]
	4-Methylcyclohexanol	138	2.13	12.2	16690	[c]
2	Cycloheptanol	450	2.65	15.1	13010	[c]
	1-Octanol	396	2.60	14.8	3540	[c]
	2,6-Dimethylcyclohexanol	960	2.98	17.0	15600	[c]
	2,5-Dimethyl-3-hexanol	219	2.34	13.4	13020	[c]
	2,2-Dimethyl-3-hexanol	377	2.58	14.7	17100	[c]
	4-Methyl-4-heptanol	128	2.11	12.0	6790	[c]
	2-Methyl-2-heptanol	633	2.80	16.0	79310	[c]
	Cyclooctanol	639	2.81	16.0	11730	[c]
	(+)-Menthol	5000	3.70	21.1	19430	[c]
	(−)-Menthol	3580	3.55	20.3	18080	[c]
	(+)-Borneol	37600	4.58	26.1	27720	[c]
	(−)-Borneol	44600	4.65	26.5	24540	[c]
3	1-Butanol	13	1.10	6.3	28390	[c]
	2-Butanol	13	1.10	6.3	20540	[c]
	1-Pentanol	37	1.56	8.9	25320	[c]
	3-Pentanol	22	1.35	7.7	23020	[c]
	2-Methyl-2-butanol	37	1.57	9.0	34570	[c]
	Cyclopentanol	68	1.83	10.5	73000	[d]
	1-Hexanol	41	1.61	9.2	49750	[c]
	3,3-Dimethyl-2-butanol	156	2.19	12.5	59310	[c]
	2-Ethyl-1-butanol	42	1.62	9.3	55200	[c]
	Cyclohexanol	138	2.14	12.2	81500	[d]
3	1-Heptanol	143	2.16	12.3	18900	[c]
	4-Heptanol	82	1.92	10.9	14540	[c]
	2,4-Dimethyl-3-pentanol	87	1.94	11.1	330150	[c]
	4-Methylcyclohexanol	411	2.61	14.9	32270	[c]
	Cycloheptanol	470	2.67	15.3	86900	[d]
	1-Octanol	302	2.48	14.2	17630	[c]
	2,6-Dimethylcyclohexanol	65	1.81	10.3	41660	[c]
	2,5-Dimethyl-3-hexanol	127	2.10	12.0	17790	[c]
	2,2-Dimethyl-3-hexanol	41	1.61	9.2	62740	[c]
	4-Methyl-4-heptanol	214	2.33	13.3	108580	[c]
	2-Methyl-2-heptanol	122	2.09	11.9	209120	[c]
	Cyclooctanol	996	3.00	17.1	96200	[d]
	1-Adamantanol	7760	3.89	22.2	102000	[d]
	Geraniol	857	2.93	16.7	53800	[d]
	Nerol	317	2.50	14.3	106000	[d]
	(+)-Menthol	887	2.95	16.8	80000	[d]
	(−)-Menthol	835	2.92	16.7	92900	[d]
	(+)-Borneol	5740	3.76	21.5	92400	[d]
	(−)-Borneol	4350	3.64	20.7	113000	[d]

[a] See Ref. 19.
[b] See Ref. 20.
[c] This work.
[d] See Ref. 25.

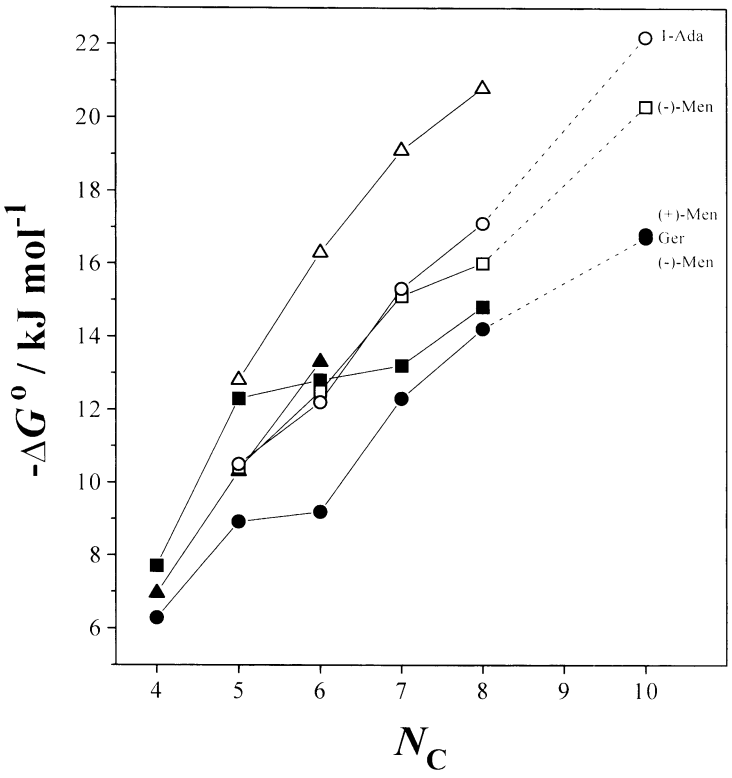

Figure 4. Gibbs free energy change ($-\Delta G^0$) plotted as a function of the number of methylenes (N_C) in the guest molecule for the complexation of a series of 1-alkanol (▲ for 1, ■ for 2, and ● for 3) and cycloalkanols (Δ for 1, □ for 2, and ○ for 3) with 1, 2, and 3 in pH 7.2 phosphate buffer solution.

more rigid isomers loose less entropy upon complexation and hence are bound more strongly. Since these alcohols possess the same number of methyl/methylene/methine units (N_C=10), the isomer selectivity is most probably determined by the small differences in the shape and rigidity of the penetrating hydrophobic part and also the position of the hydroxyl group in guest molecule.

Upon complexation with **2**, branched alkanols of N_C=6 and **7** often give higher K_S values than the corresponding or higher straight-chain 1-alkanols. For example, K_S for 3,3-dimethyl-2-butanol and 2-ethyl-1-butanol (N_C=6) are higher than those for 1-hexanol (N_C=6) and 1-octanol (N_C=8). These results may be rationalized by assuming that the branched alkanols, possessing more compact hydrophobic head groups, can fit more smoothly into the relatively wide cavity of β-cyclodextrin without greatly changing the original conformation as compared with the corresponding 1-alkanol with an extended structure. However, the beneficial branching effect appears to gradually fade out as the chain length of alkanol increases, thus giving almost comparable K_S for all of the examined C_8 alcohols upon complexation with both **2** and **3**. This indicates that yet another important mechanism is operative in isomer recognition by cyclodextrin. It is considered that the hydroxyl group of branched, rather than straight chain, alcohol particularly with short alkyl branches is located more closely to the secondary ahydroxyls of cyclodextrin upon complexation, and therefore has a better chance to form hydrogen bond, stabilizing the resulting complex. Indeed, Harata et al. have verified that the hydroxyl group of guest is usually located near the secondary hydroxyl side in crystalline cyclodextrin complexes.[37,38]

2.6. Enantiomer recognition (guest's chirality)

The data listed in Table 2 also show that the modified β-cyclodextrins can recognize not only the size/shape but also the chirality of guest molecules. Although native β-cyclodextrin does not show any significant enantiomeric discrimination upon complexation with simple chiral guests,[22] modified cyclodextrins may have different, hopefully enhanced, chiral discrimination ability through the altered chiral microenvironment in the cavity, since the introduced substituent is initially self-included but expected to function as a filler to fix the chiral guest included in the cavity. Indeed, hosts **2** and **3** exhibit moderate chiral discrimination abilities for chiral alcohols such as borneol and menthol, affording the $|K^+/K^-|$ ratios of 1.1–1.4, or the $\Delta\Delta G^0$ values of 0.1–0.8 kJ mol^{-1}. Host **2** binds borneol more strongly than menthol but the latter shows a better enantioselectivity; (−)-borneol is more favored than the antipode only by a factor of 1.2, whereas the (+)/(−)-menthol pair gives the highest enantioselectivity of up to 1.4. Host **3** also exhibits moderate preference for the (+)-isomers of borneol and menthol, showing K^+/K^- ratios of 1.1 and 1.3, respectively.

It is apparent that the substituent introduced to the 6-position significantly affects the inclusion complexation behavior of modified cyclodextrins with aliphatic alcohols, but the detailed mechanism and the factors controlling the chiral discrimination by modified cyclodextrins are not

fully elucidated yet and will be the subjects of future researches.

3. Experimental

3.1. General

Infrared spectra were recorded on a Nicolet FT-IR 5DX instrument. UV and circular dichroism (CD) spectra were measured in a conventional quartz cell (light path 1 cm) on a JASCO J-720W spectropolarimeter equipped with a temperature controller. Elemental analyses were performed on a Perkin–Elmer 2400C instrument. Mass spectra were measured by using a VG ZAB-HS instrument. ^{1}H NMR spectra were recorded on a Bruker AM200 spectrometer at 200 MHz in dimethylsulfoxide-d_6 (DMSO-d_6) solution, using tetramethylsilane as an internal reference.

3.2. 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 two days and then distilled under a reduced pressure prior to use. 1-Hydroxybenzotriazol (Acros, 98%) was used without further purification. 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 spectral measurements.

3.2.1. Mono[6-*O*-(1-benzotriazole)]-β-cyclodextrin (2). To a solution of mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin (6-OTs-β-CD)[29] (2.0 g, 1.5 mmol) in dry DMF (30 cm^3) was added 1-hydroxybenzotriazole (1.0 g, 7.4 mmol) and K_2CO_3 (0.3 g) over 0.5 h with stirring under N_2 at room temperature. The resultant solution was evaporated under reduced pressure to give a light-yellow powder, which was dissolved in minimum amount of hot water, and then the solution was poured onto acetone (200 cm^3). The precipitate formed was filtered to give white powder, which was purified by chromatography on Sephadex G-25 (eluent water) and dried in vacuo to give a pure sample as white powder in 50% yield. FAB-MS: *m*/*z*(%): 1252.6 ($M+H^+$, 100), 1234.6 (12), 1135.6 (17), 843.5 (5); UV (H_2O) λ_{max}/nm (ϵ/dm^3 mol^{-1} cm^{-1}) 210 (11700), 264 (4280), 280 (3200); IR (KBr) ν/cm^{-1} 3320, 2910, 2160, 1652, 1625, 1578, 1503, 1407, 1370, 1328, 1250, 1200, 1153, 1078, 1025, 940, 860, 820, 788, 752, 710; ^{1}H NMR (DMSO-d_6, TMS) δ 3.3–3.9 (m, 40H), 4.4 (d, 2H, J=8.0 Hz), 4.7–5.0 (m, 7H), 5.8 (s, 20H), 7.4–8.2 (m, 4H, Ar); Anal. Calcd for $C_{48}H_{73}O_{35}N_3 \cdot 6H_2O$: C, 42.38; H, 6.25; N, 3.09. Found: C, 42.78; H, 6.59; N, 2.69.

3.2.2. Mono(6-benzylseleno-6-deoxy)-β-cyclodextrin (3). This host was synthesized by the reaction of 6-OTs-β-CD[29] with dibenzyl diselenide,[39] according to the reported procedure.[28]

3.3. Spectrometric titrations

Since the absorption spectra did not show any significant changes even upon addition of a large excess amount of guests the inclusion complexation behavior of the chromophoric β-cyclodextrin derivatives was best determined by the CD spectrometry.[40] The CD spectra of modified β-cyclodextrins **2** and **3** ($0.5–1.0\times10^{-4}$ M), were measured at 25°C in the presence of varying concentrations of a guest in aqueous phosphate buffer solution. The differential CD spectra were obtained by subtracting the original CD spectrum recorded in the absence of guest from those recorded in the presence of guest.

Fluorescence lifetimes were determined by the time-correlated single-photon-counting method using a Horiba NAES-550 instrument with a time resolution of 0.5 ns. A self-oscillating discharge lamp filled with hydrogen gas was employed as a pulsed light source, and the excitation light was made monochromatic by a 10 cm monochromator. Emission from the sample was passed through an appropriate filter (Toshiba UV-33) placed before the detector in order to eliminate the scattered excitation light. Maximum photon counts of up to 10000 were collected for each measurement. The accumulated signals were then processed and the lifetimes were determined by deconvolution using the nonlinear least-squares method.

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