Molecular recognition study on supramolecular systems. Part 19.† Circular dichroism studies of inclusion complexation of aliphatic alcohols by organoselenium modified β-cyclodextrins

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Complex stability constants for the stoichiometric 1 : 1 inclusion complexation of various aliphatic alcohols with mono[6-(benzylseleno)-6-deoxy]-β-cyclodextrin (**1**), mono[6-(phenylseleno)-6-deoxy]-β-cyclodextrin (**2**), and mono-[6-(*o*-, *m*-, or *p*-tolylseleno)-6-deoxy]-β-cyclodextrin (**3**–**5**) have been obtained by spectrophotometric titrations at 25 °C in phosphate buffer solution (pH = 7.2). The Cotton effects observed indicate that the aromatic moiety penetrates shallowly into the hydrophobic cavity of cyclodextrin. Therefore, the aromatic moiety can be taken as an induced circular dichroism (ICD) probe to investigate the inclusion phenomena. The results obtained demonstrate that the modified β-cyclodextrin (**1**) is highly sensitive to the size/shape and conformational rigidity of guest molecules, giving fairly good molecular selectivity up to 114 for adamantan-1-ol/cyclopentanol and relatively high *E*/*Z* selectivity up to 2.7 for geraniol/nerol. Interestingly, all of the modified β-cyclodextrins employed displayed relatively good enantioselectivity for (+)-enantiomers of borneol and menthol. The molecular recognition ability and enantioselectivity for aliphatic alcohols of the modified β-cyclodextrins (**1**–**5**) are discussed from the viewpoints of the size/shape–fit relationship and the multipoint recognition mechanism.

Introduction

Molecular recognition by modified cyclodextrins is currently a significant topic in supramolecular chemistry. Modification of native cyclodextrins by introducing nucleophilic or electrophilic substituents can alter not only the original molecular binding ability but also the relative molecular selectivity and enantioselectivity.[1–6] Consequently, a wide variety of cyclodextrin derivatives have been designed and synthesized in order to investigate the recognition mechanism controlled by the simultaneous operation of several weak interactions and the factors governing inclusion phenomena of guest molecules by host cyclodextrins.[7–21] Aliphatic alcohols with a variety of structures have been employed as model guest compounds to study systematically the inclusion complexation behavior of natural and modified cyclodextrins. Matsui *et al.*[22] reported the inclusion complexation thermodynamics of natural cyclodextrins with aliphatic alcohols. More recently, Ueno *et al.*[23] have reported the molecular recognition of aliphatic alcohols by modified cyclodextrins carrying a dansyl moiety as fluorescent probe, giving interesting results. These results indicated that, in addition to the size and shape of aliphatic alcohols, the microstructural change of the cyclodextrins apparently governs the inclusion complexation phenomena to some extent. Therefore, the elucidation of the inclusion mechanism is also helpful for our further understanding of the multipoint recognition and the induced-fit interaction hypothesis proposed for the selective binding of specific substrate by biological receptors.

In the present study, we report our synthesis of the series of arylseleno derivatives of β-cyclodextrin (**1**–**5**) shown in Chart 1, and investigation of their inclusion complexation with selected aliphatic alcohols in phosphate buffer solution (pH = 7.2) at 25 °C using differential circular dichroism spectrometry.[24]

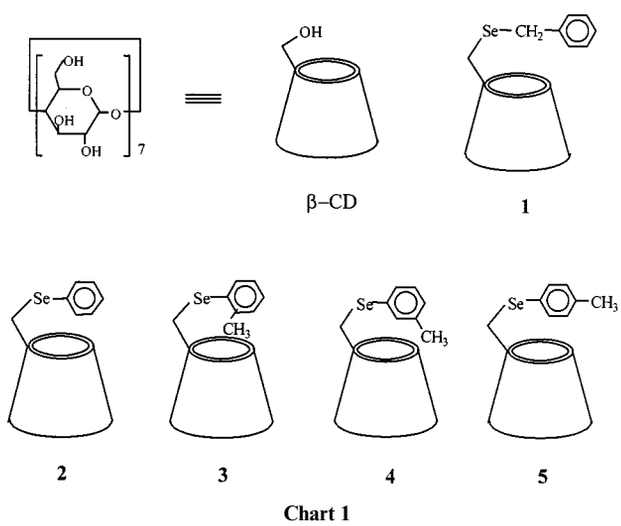

Chart 1

One important reason for choosing organoselenium-modified cyclodextrins as hosts is that selenium, possessing a larger atomic radius and lower electronegativity than carbon, can lead to a C–Se bond which is longer and more flexible than a C–C bond. The series of aliphatic alcohols shown in Chart 2 are employed as guest molecules in order to examine the possible participation of several weak interactions working in the complexation with the organoselenium-modified β-cyclodextrins. Under such circumstances, we can discuss the molecular recognition ability and enantioselectivity upon complexation of aliphatic alcohols by β-cyclodextrin derivatives **1**–**5** in terms of the size–fit and the complementary geometrical relationship between the host cyclodextrins and guest aliphatic alcohols. The complex stability constant (log K_s) and Gibbs free energy changes ($-\Delta G°$) obtained will provide further understanding

† For Part 18, see ref. 30.

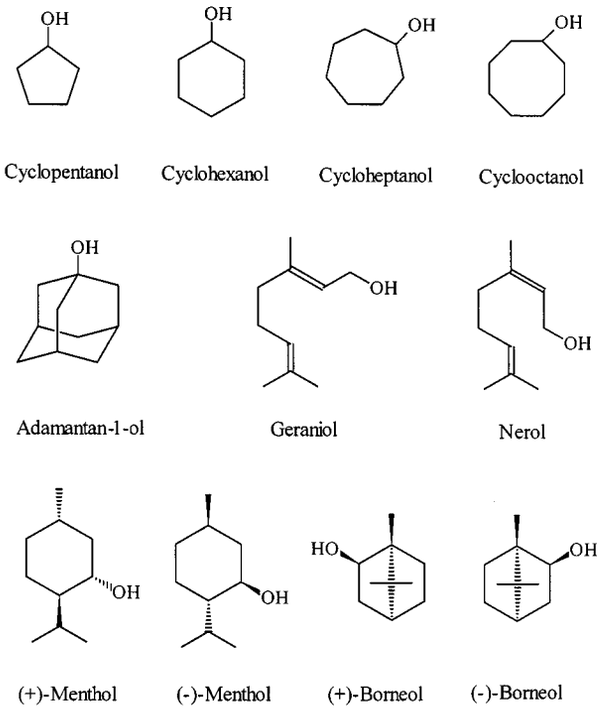

Chart 2

of the potential importance of such studies in discussing the relevant stereochemical complementary geometrical relationship between the biological receptor (host) and substrate (guest) interaction.[1]

Experimental

Spectroscopy

Circular dichroism (CD) spectra were recorded on a JASCO J-720 spectropolarimeter.

Materials

Guest aliphatic alcohols employed were commercially available and were used as received. Adamantan-1-ol, cyclohexanol and cyclooctanol were purchased from Nacalai Tesque, Inc. Cyclopentanol, (−)-borneol, (+)-menthol, (−)-menthol, and nerol were purchased from Tokyo Kasei. (+)-Borneol, cycloheptanol, and geraniol were purchased from Aldrich, Merck and Wako, respectively. A series of organoselenium-modified β-cyclodextrins, bearing benzylseleno (**1**), phenylseleno (**2**), and *o*-, *m*- and *p*-tolylseleno (**3**–**5**) groups were synthesized in 40–55% yields, respectively, by the reaction of mono[6-*O*-(*p*-tolylsulfonyl)]-β-cyclodextrin with the corresponding aromatic selenide anions in DMF, according to the procedures reported recently.[25] A representative synthetic procedure and characterization of modified cyclodextrin (**1**) is as follows.

Mono[6-*O*-(*p*-tolylsulfonyl)]-β-cyclodextrin (6-OTs-β-CD) was prepared by a reaction of β-cyclodextrin with toluene-*p*-sulfonyl chloride in dry pyridine.[26] Compound **1** was synthesized by the reaction of mono[6-*O*-(*p*-tolylsulfonyl)]-β-cyclodextrin (6-OTs-β-CD) with dibenzyl diselenide[27] according to the following procedure. Sodium borohydride (0.037 g, 1 mmol) was added to the yellow solution of dibenzyl diselenide (0.17 g, 0.5 mmol) in dry ethanol (50 ml) with stirring under nitrogen at room temperature. Once the solution became colorless, a solution of mono[6-*O*-(*p*-tolylsulfonyl)]-β-cyclodextrin (1.29 g, 1 mmol) in dry DMF (75 ml) was added dropwise into the solution, which was then heated to 60 °C for 2 h with stirring. The resultant solution was evaporated under reduced pressure to give a light yellow powder, which was then dissolved in a minimum amount of hot water, and poured into acetone (100 ml).

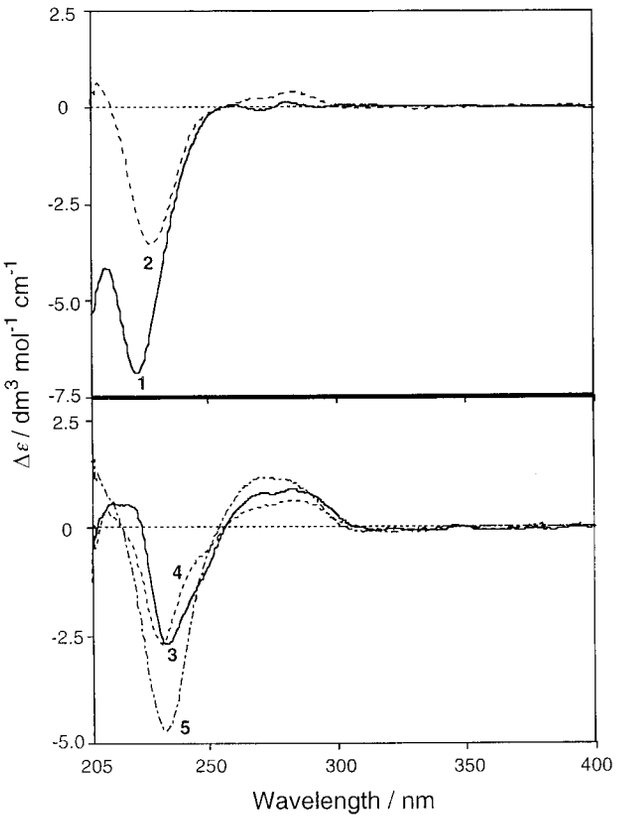

Fig. 1 Circular dichroism spectra of β-cyclodextrin derivatives **1** and **2** (top) and **3**–**5** (bottom) (6×10^{-5} mol dm^{-3}) in phosphate buffer solution at 25.0 °C.

The precipitate formed was filtered to give a white powder. The crude product was purified by three recrystallizations from water and dried *in vacuo* to give a pure sample (yield 50%). ^{1}H NMR (200 MHz, [$^2H_6$]DMSO, 25 °C, TMS): δ 3.1–3.9 (m, 40H), 4.1–4.6 (m, 8H), 4.8–5.2 (9H), 5.3–5.8 (m, 14H), 7.3 (m, Ar 5H). IR (KBr) ν/cm^{-1} 3369.0, 2912.5, 1730.9, 1701.5, 1638.6, 1615.4, 1574.6, 1536.7, 1514.6, 1398.6, 1365.0, 1336.5, 1302.9, 1273.9, 1235.1, 1149.4, 1127.1, 1073.8, 1022.3, 938.4, 885.6, 789.7, 769.3, 692.7, 658.7. UV/vis (water) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 260.2 (613). $C_{49}H_{76}O_{34}Se{\cdot}6H_2O$ (1396.2): calcd. C, 42.15; H, 6.35. Found: C, 42.12; H, 6.10%.

Spectral measurements

The binding constants for the inclusion complexation of modified β-cyclodextrins (**1**–**5**) with some selected aliphatic alcohols were determined using differential circular dichroism (CD) spectrometry. The sample solutions containing modified β-cyclodextrins **1**–**5** (0.06 mmol dm^{-3}) and varying concentrations of guests (0.6–9.6 mmol dm^{-3}) were kept 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 guest from that in the presence of a guest on computer memories. Simultaneous examination of each sample solution by UV spectrometry did not show any significant change upon addition of the guests.

Results and discussion

CD Spectra

As can be seen from Fig. 1, the CD spectrum of modified β-cyclodextrin **2** in aqueous solution showed a strong negative Cotton effect peak, corresponding to the ^1L_a band, at 232 nm ($\Delta\varepsilon = -3.41$) and a weak positive Cotton effect for the ^1L_b band at 279 nm ($\Delta\varepsilon = 0.99$). The other modified cyclodextrins also showed such a strong negative Cotton effect peak for the ^1L_a

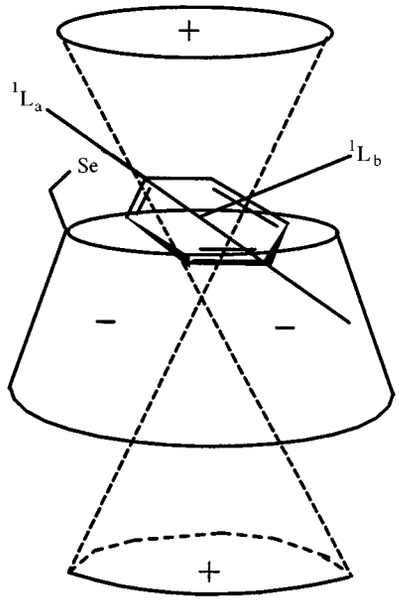

Fig. 2 Kajtar's sector rule applied to transition moments of ^1L_a and ^1L_b bands of the phenylseleno moiety in modified β-cyclodextrin **2**.

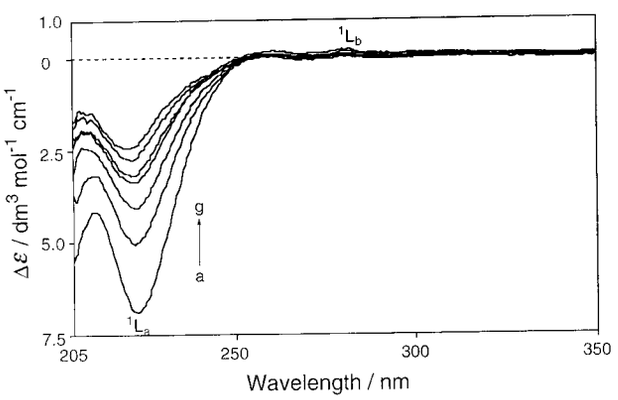

Fig. 3 The circular dichroism spectrum of β-cyclodextrin derivative **1** in the presence of cyclooctanol at various concentrations at 25.0 °C. The concentration of **1** is 6×10^{-5} mol dm^{-3}. The concentrations of cyclooctanol increase in the range of 0–9.6×10^{-3} mol dm^{-3} from a to g.

band and a weak positive Cotton effect for the ^1L_b band. According to the sector rule proposed by Kajtar *et al.*,[28] these negative and positive Cotton effects observed respectively for the ^1L_a and ^1L_b bands indicate that the aromatic moiety penetrates shallowly into the hydrophobic cavity of cyclodextrin. As illustrated schematically in Fig. 2, the transition moment of the ^1L_a band lies in the negative region, while that of the ^1L_b band is in the positive region, coinciding with the Cotton effect observed. It is thus inferred that the arylseleno moiety is only shallowly included in the cyclodextrin cavity. Hence, we can use the aromatic moiety as a CD probe to investigate the inclusion behavior.

CD spectral titrations

As can be seen from Fig. 3, in the titration experiments using differential CD spectrometry, gradual addition of a known concentration of cyclooctanol to a dilute host solution (0.06 mmol dm^{-3}) in phosphate buffer solution caused significant decreases in intensity in the ^1L_a band, while the change in the ^1L_b band was minimal at this host concentration. This result indicates that the aromatic moiety, initially perching on the edge of the cyclodextrin cavity, suffers substantial conformational changes upon guest inclusion, probably moving out of the chiral hydrophobic cavity, This substantial CD spectral change

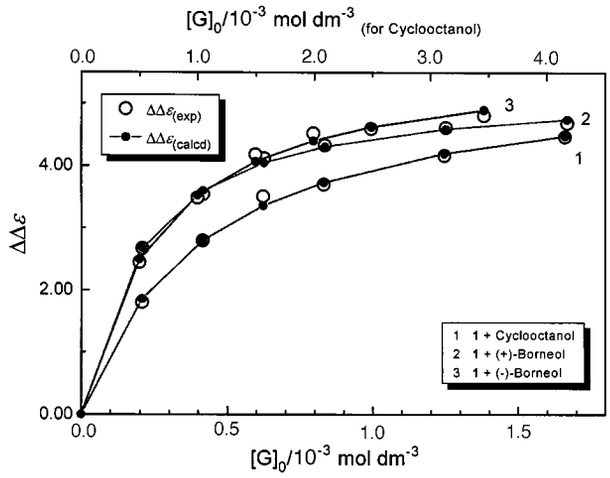

Fig. 4 Curve fitting analyses, according to eqn. (2), for complexations of cyclooctanol, (+)-borneol, and (−)-borneol with **1** at 25.0 °C.

can be used to determine the complex stability constants. Assuming 1 : 1 stoichiometry, the inclusion complexation of aliphatic alcohols (G) with modified β-cyclodextrins (H) is expressed by eqn. (1).

$$H + G \overset{K_s}{\rightleftharpoons} G{\cdot}H \quad (1)$$

The stability constant (K_s) of the inclusion complex formed can be determined using a non-linear least squares method according to the curve fitting eqn. (2),[29] where $[G]_0$ and $[H]_0$

$$\Delta\Delta\varepsilon = \{a([H]_0 + [G]_0 + 1/K_s) \pm \sqrt{a^2([H]_0 + [G]_0 + 1/K_s)^2 - 4a^2[H]_0[G]_0}\}/2 \quad (2)$$

refer to the total concentration of aliphatic alcohols and β-cyclodextrin derivatives, respectively; a is the proportionality coefficient, which may be taken as a sensitivity factor for the CD change; $\Delta\Delta\varepsilon$ denotes the change in the CD spectrum of β-cyclodextrin derivative upon stepwise addition of the guest alcohol. For each host compound examined, the plot of $\Delta\Delta\varepsilon$ as a function of $[G]_0$ gave an excellent fit, verifying the validity of the 1 : 1 complex stoichiometry assumed above. As shown in Fig. 4, where the $\Delta\Delta\varepsilon$ values are plotted against the $[G]_0$ values to give an excellent fit, no serious deviations are found in the curve fitting. When repeated measurements were made, the K_s value was reproducible within an error of ±5%, which corresponds to an estimated error of 0.15 kJ mol^{-1} in the free energy of complexation ($\Delta G°$). The complex stability constants (K_s) and the sensitivity factor a obtained by the curve fitting are listed in Table 1, along with the free energy change of complex formation ($-\Delta G°$).

Molecular recognition ability and enantioselectivity

Extensive studies on molecular recognition by cyclodextrins[2] have shown that an important characteristic of the complexation is the simultaneous operation of several weak forces working between the guest and host. In the present case, the relative size and stereochemical complementary relationships between host and guest, hydrogen-bonding and hydrophobic interactions, and the induced dipole of the functional sidearm perching on the edge of cyclodextrin cavity are considered to be important. The results obtained indicate that the self-inclusion of the β-cyclodextrin's sidearm plays an important role in determining how the guest molecule fits into the host cavity, according to the sidearm's size, shape, dipole, charge, and functional group.

As can be seen from Table 1, all of the modified β-cyclodextrins except **2** show relatively high molecular binding ability

Table 1 Complex stability constants (log K_s), Gibbs free energy changes ($-\Delta G°$) and sensitivity factors a for the inclusion complexation of modified β-cyclodextrins **1**–**5** with aliphatic alcohols in phosphate buffer solution (pH = 7.20) at 25 °C

Host	Guest	K_s	log K_s	$-\Delta G°$/ kJ mol^{-1}	$a/10^2$
1	Cyclopentanol	68	1.83	10.5	730
	Cyclohexanol	138	2.14	12.2	815
	Cycloheptanol	470	2.67	15.3	869
	Cyclooctanol	996	3.00	17.1	962
	Adamantan-1-ol	7760	3.89	22.2	1020
	Geraniol	857	2.93	16.7	538
	Nerol	317	2.50	14.3	1060
	(+)-Menthol	887	2.95	16.8	800
	(−)-Menthol	835	2.92	16.7	929
	(+)-Borneol	5740	3.76	21.5	924
	(−)-Borneol	4350	3.64	20.7	1130
2	Cyclooctanol	386	2.59	14.8	35.1
3	Cyclooctanol	1670	3.22	18.4	2010
	(+)-Menthol	2270	3.36	19.2	1630
	(−)-Menthol	1720	3.24	18.5	1820
	(+)-Borneol	26300	4.42	25.2	1900
	(−)-Borneol	20700	4.32	24.6	1910
4	Cyclooctanol	6520	3.81	21.8	1030
	(+)-Menthol	2140	3.33	19.0	778
	(−)-Menthol	2000	3.30	18.8	658
	(+)-Borneol	39200	4.59	26.2	1030
5	Cyclooctanol	4440	3.65	20.8	452
	(+)-Menthol	2470	3.39	19.4	111
	(+)-Borneol	14300	4.16	23.7	668

to borneol and adamantan-1-ol, which may be attributed to the strict size–fit relationship between the host and the spherical guests. The aromatic substituent on the sidearm attached to the edge of cyclodextrin also plays a crucial role in guest inclusion. Thus, the K_s value for cyclooctanol increases from 386 for **2** (phenyl) to 996 for **1** (benzyl) and then to 1670–6520 (tolyl) for **3**–**5** with increasing hydrophobicity of the substituent introduced. This clearly indicates that the aromatic substituent, initially perching in the cavity in the absence of the guest, is driven out of the cavity upon guest inclusion, expanding the original hydrophobic cavity to the primary side.

As can be readily recognized from the data for **1** (Table 1), the binding constant is highly sensitive to the size/shape and rigidity of the guest molecules, giving moderate molecular selectivity up to 14.6 for cyclooctanol/cyclopentanol and fairly good *E*/*Z* selectivity up to 2.7 for geraniol/nerol. For the hosts **3**–**5**, the combined effect of size/shape–fit and substituent led to the enhanced molecular recognition ability and isomer selectivity. However, most of the host compounds display only relatively low enantioselectivities of 1.1–1.3. It seems reasonable that modified β-cyclodextrins show high recognition ability for guests possessing distinctly different size/shape, but only low enantioselectivity for enantiomers possessing small structural differences.

Mono[6-(benzylseleno)-6-deoxy]-β-cyclodextrin (1)

In order to evaluate the inclusion complexation behavior of **1** with the aliphatic alcohols from a more quantitative point of view, the free energy change ($-\Delta G°$) was plotted against the formal number of carbon atoms (N_C) in the guest molecule in Fig. 5. As has been observed frequently with native and modified cyclodextrins,[2] the plot gives a good straight line at least with the cycloalkanols to give a unit increment in $\Delta G°$ per methylene of 2.2 kJ mol^{-1}, which is somewhat smaller than the typical unit increment of 2.8 ± 0.8 kJ mol^{-1} observed in the complexation of a wide variety of cycloalkanols with β-cyclodextrin.[2] It is noted that the plot for adamantan-1-ol falls exactly on the regression line when it is treated as a C_{10} cycloalkanol. In contrast, the other terpenoid alcohols employed (formal N_C = 10), gave much lower complex stabilities, as shown

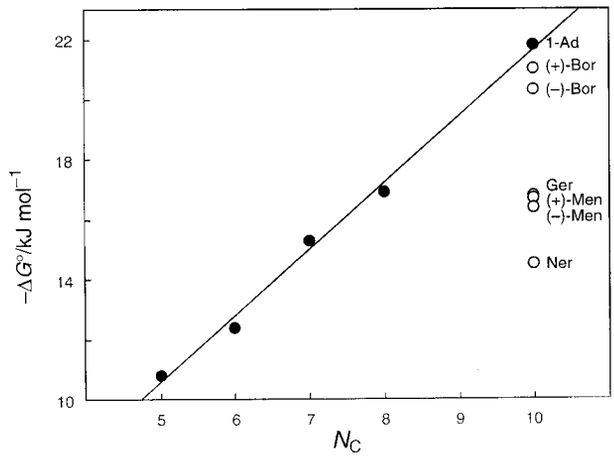

Fig. 5 Gibbs free energy changes ($-\Delta G°$) of complexation of cycloalkanols (C_5–C_8), adamantan-1-ol (1-Ad), (+)- and (−)-borneol (Bor), (+)- and (−)-menthol (Men), geraniol (Ger), and Nerol (Ner) with mono[6-(benzylseleno)-6-deoxy]-β-cyclodextrin as a function of number of carbon atoms (N_C) in the guest molecule.

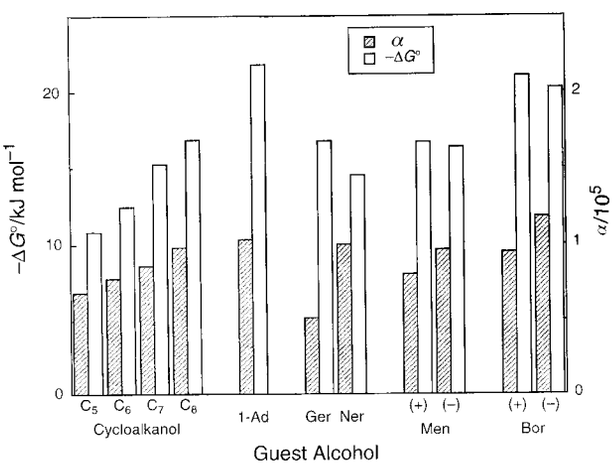

Fig. 6 Sensitivity factor (a) and Gibbs free energy changes ($-\Delta G°$) upon complexation of cycloalkanols (C_5–C_8), adamantan-1-ol (1-Ad), geraniol (Ger), Nerol (Ner), (+)- and (−)-menthol (Men), and (+)- and (−)-borneol (Bor) with mono[6-(benzylseleno)-6-deoxy]-β-cyclodextrin **1**; compare the different changing profiles of a and $-\Delta G°$ for the terpenoid alcohols.

in Fig. 5. This result may be attributed to less-efficient van der Waals interactions of these acyclic or branched C_{10} alcohols as well as the larger entropic losses of acyclic alcohols upon complexation.

It is also interesting to compare the changing profiles of $-\Delta G°$ value and of sensitivity factor a, both of which are shown in Fig. 6. As far as the cycloalkanols and adamantanol are concerned, both values behave quite similarly, indicating that the larger guests, which are bound more strongly, induce more extensive conformational changes. This result seems to imply that the a value can be taken as a quantitative measure of the conformational change induced by guest inclusion in the host cavity, at least for the cycloalkanol series. However, this idea cannot immediately be extended to the complexation behavior of the other guest series even in a qualitative sense, since the highest K_s value does not always accompany the most drastic CD change or the highest a value with the acyclic and more complicated alcohols employed. This apparent discrepancy may be rationalized by taking into account that the CD spectral change only represents fairly local conformational changes around the chromophore, while the binding constant reflects more global changes in the cooperative weak interactions between the host and guest. Hence, these results are helpful to our further understanding of the multipoint

recognition mechanism. In general, the value of sensitivity factor a only represents the microstructural change on inclusion complexation, which mainly depends on the depth of guest penetration into the cavity, which is, however, not the only factor that influences the inclusion complexation. It has been extensively verified that the stability of an inclusion complex with modified cyclodextrin is governed by several cooperative weak forces working between host and guest, including hydrophobic, hydrogen-bonding, dipole–dipole, electrostatic and van der Waals interactions.[2] Therefore, it is not particularly curious that the sensitivity factor a shows only a poor positive correlation (correlation coefficient r 0.46, for the inclusion complexation of host **1** with the aliphatic alcohols examined) with the complex stability.

It is more interesting that host **1** shows the strongest binding ability for adamantan-1-ol and gives the highest molecular selectivity up to 114 for adamantan-1-ol/cyclopentanol. One reasonable explanation is that adamantan-1-ol, possessing a large rigid hydrophobic spherical structure, can induce the strongest hydrophobic interaction and establish the best size–fit relationship between the host and guest. Furthermore, owing to its most rigid and hydrophobic structure, adamantan-1-ol forms the most stable complex with modified β-cyclodextrin **1** of the seven C_{10} aliphatic alcohols.

As can be seen from Table 1, modified β-cyclodextrin **1** can recognize not only the size of the aliphatic alcohols, but also the shape and chirality of the isomers. For borneol, menthol, nerol and geraniol, possessing obviously different shape and rigidity, modified β-cyclodextrin **1** displays fairly good isomer separation: (+)-borneol > (−)-borneol > geraniol > (+)-menthol > (−)-menthol > nerol, giving highest isomer selectivity up to 18.1 for (+)-borneol/nerol. This order of complex stability is mostly determined by the rigidity and size/shape of the guests. Therefore, possessing the most rigid molecular structure, borneol forms the most stable complex with host **1**, while the most flexible, least bulky nerol with an (*E*)-double bond gives the least stable complex. It is somewhat unexpected that geraniol and menthol form complexes of comparable stability, which might be attributable to the more bulky structure imposed by the (*E*)-double bond. Host **1** shows relatively low enantioselectivity for borneol, the enantioselectivity calculated from the K_s values is 1.3 for (+)-borneol/(−)borneol. However, owing to their distinctly different shape, the geometrical isomers, nerol and geraniol, show substantially different K_s values; the *E*/*Z* selectivity calculated from the K_s values amount to 2.7 for geraniol/nerol.

Mono[6-(phenylseleno)-6-deoxy]-β-cyclodextrin (2), mono-[6-(*o*-tolylseleno)-6-deoxy]-β-cyclodextrin (3), mono[6-(*m*-tolyl-seleno)-6-deoxy]-β-cyclodextrin (4) and mono[6-(*p*-tolylseleno)-6-deoxy]-β-cyclodextrin (5)

As can be seen from Table 1, the five modified β-cyclodextrins display drastically different K_s values for the inclusion complexation with cyclooctanol: *i.e.* **4** > **5** > **3** > **1** > **2**. As compared with the modified β-cyclodextrin **2**, the isomers of **1**, **3**, **4** and **5**, possessing a methylene or methyl substitution in the arylseleno sidearm attached to the edge of the β-cyclodextrin, must produce substantially different conformational change induced by the same guest, which can be further proved by the drastic change of the values of the sensitivity factor a. Somewhat unexpectedly, *m*-isomer **4** displays much higher, nearly four-fold calculated from K_s values, binding stability for cyclooctanol than *o*-isomer **3**. One possible explanation for the enhanced binding ability of host **4** with cyclooctanol is that the self-inclusion of the *m*-tolyl moiety attached to the primary edge of **4** caused more strict complementary geometrical relationship between the cavity of modified β-cyclodextrin **4** and cyclooctanol.

As for borneol and menthol, hosts **3**–**5** show much higher molecular binding ability than **1**, probably due to the more hydrophobic expanded cavity. These hosts display enhanced molecular recognition ability and enantioselectivity for borneol and menthol over **1** or **2**. Host **3** shows relatively high isomer selectivity calculated from the K_s values up to 15.3 for (+)-borneol/(−)-menthol and relatively good enantioselectivities of 1.3 for (+)-borneol/(−)-borneol and 1.3 for (+)-menthol/(−)-menthol. Similarly, host **4** shows fairly good isomer selectivity up to 19.6 for (+)-borneol/(−)-menthol. However, host **5** displays much lower isomer selectivity than **3** and **4**, giving the isomer selectivity of 5.8 for (+)-borneol/(+)-menthol. Although the hosts **3**–**5**, possessing isomeric tolyl substituents, generally exhibit similar binding constants for most guest alcohols, the *o*-tolyl host **3** gives a much smaller K_s value only for cyclooctanol and higher enantioselectivities of 1.3 for borneol and menthol. These somewhat puzzling results would be accounted for in terms of the original penetration of the *o*-methyl group in the cavity, which interferes with the inclusion of larger-sized cyclooctanol but discriminates more precisely the enantiomeric isomers included in the cavity.

Conclusions

The present study indicates that a series of modified β-cyclodextrins possessing a single arylseleno moiety as a CD probe can recognize minimal differences between aliphatic alcohols based on their size, shape, rigidity and chirality. The chromophoric probe perching on the edge of the β-cyclodextrin cavity can produce conformational change induced by guest inclusion, which is useful in determining complex stability constants. Especially, the benzylseleno moiety of cyclodextrin derivative **1** is most sensitive to the microstructural difference of guest molecules among the hosts **1**–**5**. Although all of the modified β-cyclodextrins show low to moderate enantioselectivities for (±)-borneol and (±)-menthol, they display relatively high molecular recognition ability for cyclic alcohols and fairly good isomer separation and *E*/*Z* selectivity for C_{10} alcohols. Moreover, the host compounds **3**–**5** bearing a tolylseleno moiety can enhance both molecular binding ability and selectivity. Experimentally, adamantan-1-ol and (+)-borneol, possessing the most rigid and hydrophobic structures, have the best-fitted size and shape among the aliphatic alcohols examined. These results demonstrate that the size/shape–fit, induced-fit, and substituent effect as well as the multipoint recognition mechanism play crucial roles in the inclusion complexation.

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