Molecular Recognition Study on Supramolecular Systems. 20. Molecular Recognition and Enantioselectivity of Aliphatic Alcohols by L-Tryptophan-Modified β-Cyclodextrin

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L-Tryptophan-modified β-cyclodextrin (L-Trp-β-CD) has been synthesized and its molecular recognition behavior investigated through fluorescence and circular dichroism spectrometry, as well as fluorescence lifetime measurement in the presence and absence of various alcohols as guest molecules. Employing the indolyl group as a spectral probe, spectrofluorometric and spectropolarimetric titrations have been performed in aqueous phosphate buffer solution at pH 7.20 to calculate the complex stability constants for 1:1 inclusion complexation of L-Trp-β-CD with several series of alcohols at 25 °C. The results obtained indicate that L-Trp-β-CD can recognize not only size/shape and hydrophobicity but also the enantiomeric and geometrical isomers of the guest alcohols, showing a 230-fold molecular selectivity (13.5 kJ mol^{-1}) for 2-adamantanol over cyclopentanol among the cyclic alcohols examined. Moderate enantiomeric selectivities of 1.2 and 1.9 for (−)-isomers of borneol and menthol, respectively, and geometrical selectivity of 2.0 for geraniol over nerol have also been observed.

Introduction

Chiral recognition, multiple recognition mechanisms, and the induced-fit interactions are of current interest in supramolecular chemistry.[1] Several weak intermolecular forces between the host and guest, such as dipole−dipole, hydrophobic, electrostatic, van der Waals, and hydrogen-bonding interactions, cooperatively contribute to the molecular recognition process. Many natural and artificial receptor systems have already been investigated in order to elucidate the role of these interactions upon complexation with a wide variety of guest molecules of diverse structures.[2] Among them, native and modified cyclodextrins have been employed as receptor molecules,[3−7] as well as enzyme mimics.[8,9] Recently, we have reported the molecular recognition behavior of β-cyclodextrin derivatives that possess a chromophoric probe.[10] Several modified cyclodextrins bearing a fluorescence probe have been synthesized and their complexation behaviors have been investigated.[11,12] Both Ueno[11] and Corradini[12] have employed the dansyl moiety as a fluorescence probe to investigate complexation and sensing properties of β-cyclodextrin derivatives. Lipkowitz[13] has found that the tryptophan molecule can be included in the α-cyclodextrin cavity with moderate enantioselectivity. Because the indolyl moiety is similar in size to the dansyl group and exhibits strong fluorescence in a hydrophobic environment, it can be utilized as a fluorescence probe. Furthermore, the complexation behavior of L-tryptophan-modified β-cyclodextrin could be analyzed more easily following changes in the circular dichroism spectra.

We wish to report the synthesis of L-Trp-β-CD (Scheme 1) and its self- and guest-inclusion behavior monitored by fluorescence and circular dichroism spectroscopy and fluorescence lifetime measurement. The complex stability constants determined for a series of guest alcohols (Chart 1) are discussed from the viewpoint of the size/shape-fit, structural rigidity, and hydrophobicity of the guest.

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Scheme 1

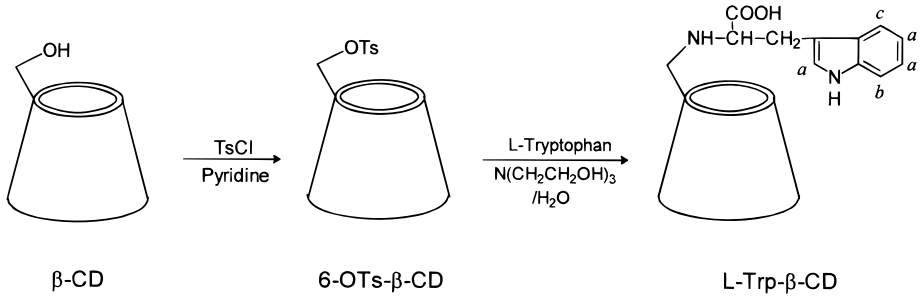
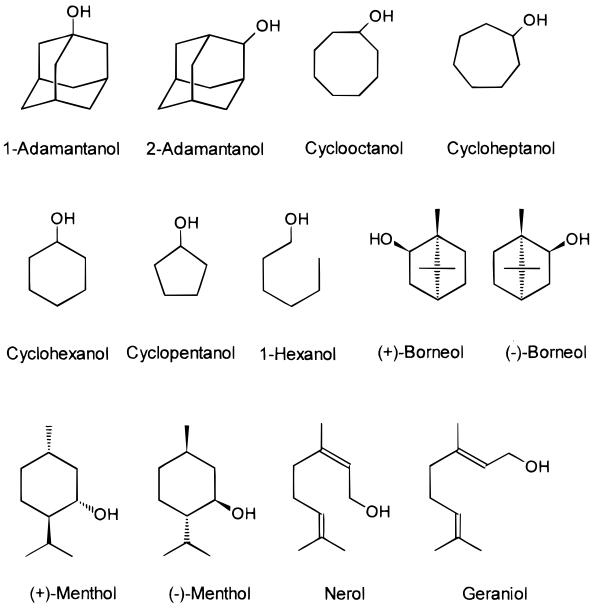


Chart 1



Experimental Section

Materials. *β*-Cyclodextrin, 1-adamantanol, cyclooctanol, cyclohexanol, and 1-hexanol were purchased from Nacalai Tesque, Inc. 2-Adamantanol, cyclopentanol, (−)-borneol, (+)-menthol, (−)-menthol, and nerol were purchased from Tokyo Kasei. (+)-Borneol and cycloheptanol were purchased from Aldrich and Merck-Schuchardt, respectively. Geraniol, disodium hydrogen phosphate dodecahydrate, and sodium dihydrogen phosphate dihydrate were obtained from Wako Pure Chemicals, Inc. L-Tryptophan was purchased from Peptide Institute, Inc. *β*-Cyclodextrin was recrystallized twice from water and dried in vacuo for 12 h at 95 °C before use. Analytical grade pyridine was predried by refluxing over NaOH pellets for 24 h. The pyridine was then decanted and refluxed over powdered CaH_2 for 2 days and fractionally distilled. All other materials were used without further purification. Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.10 mol dm^{-3} phosphate buffer solution of pH 7.20, which was used when taking measurements.

Synthesis of L-Tryptophan-Modified *β*-Cyclodextrin (L-Trp-*β*-CD). L-Tryptophan (0.4 g) and mono[6-*O*-(*p*-toluenesulfonyl)]-*β*-cyclodextrin (1.0 g), which was prepared from *β*-cyclodextrin and *p*-toluenesulfonyl chloride in dry pyridine,[14,15] were dissolved in water (30 mL) containing triethanolamine (20 mL), and the stirred mixture heated to reflux under a nitrogen atmosphere for 24 h. After evaporation of most of the solvent under reduced pressure, the resulting solution was poured into vigorously stirred anhydrous ethanol (500 mL), and the resultant mixture was stored in a refrigerator to produce a pale yellow precipitate. The solid product was collected by filtration and then purified by column chromatography on a hydroxymethylcellulose column with an aqueous ammonium bicarbonate eluent (0.05 mol dm^{-3}), followed by chromatography on a Sephadex G-25 column with deionizated water as eluent, to give pale yellow product (0.25 g) in 21% yield. The product was observed to be very hygroscopic: FAB-MS *m*/*z* 1343.3 ($M^+ + Na - 10H_2O$), 1321.3 ($M^+ + H - 10H_2O$); ^{1}H NMR (D_2O, TMS) δ 2.90−3.86 (m, 45H), 4.85−5.03 (m, 7H,), 7.02−7.18 (m, 3H), 7.31−7.35 (d, 1H), 7.52−7.56(d, 1H); FT-IR (KBr) ν 3373.0, 2909.0, 1626.6, 1555.6, 1456.4, 1399.4, 1223.9, 1144.5, 1073.2, 1019.1, 930.9, 741.7 cm^{-1}; UV $\lambda_{max}(\epsilon)$ 279 nm (3300 dm^3 mol^{-1} cm^{-1}). Anal. Calcd for $C_{53}H_{80}O_{36}N_2 \cdot 10H_2O$: C, 42.40; H, 6.67; N, 1.87. Found: C, 42.04; H, 6.65; N, 1.96.

The sterically hindered base, triethanolamine, was observed to benefit the preparation of L-Trp-*β*-CD, and the hydroxymethylcellucose column was employed in order to remove excess L-tryptophan.

Spectrophotometric Titrations. Concentrated stock solutions of L-Trp-*β*-CD and various guests were prepared in a 0.10 mol dm^{-3} aqueous phosphate buffer at pH 7.20. The titration solutions were prepared in 10.0 mL volumetric flasks with the host/guest molar ratio ranging from 0 to ca. 160.

Fluorescence spectra were measured using a JASCO FP-777 spectrofluorometer, using a conventional 1 × 1 cm quartz cell at 25 °C with the excitation and emission slits of 5 nm width. The sample solutions at a host concentration of approximately 1 × 10^{-5} mol dm^{-3} were excited at 280 nm to give a strong emission, and the fluorescence intensity at the emission maximum was used to determine the complex stability constants.

The circular dichroism spectra were obtained using a JASCO J-720S spectropolarimeter with the temperature of the cell was kept constant at 25.0 °C using a JASCO PTC-348WI temperature controller unit. The response time of the instrument was set at 8 s and the bandwidth at 2 nm in order to obtain highly reproducible spectra upon repeated measurement. All of the spectra recorded in the presence/absence of varying amounts of added guest were recorded, and subsequent spectral subtraction afforded the differential circular dichroism spectra, which were used in the calculation of the complex stability constants.

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. The emission from the sample was passed through an appropriate filter (Toshiba UV-33) placed before the detector in order to eliminate scattered excitation light. Maximum counts of up to 10 000 were collected for each measurement. The accumulated signals were then processed and the lifetimes determined by deconvolution with nonlinear least-squares fit.

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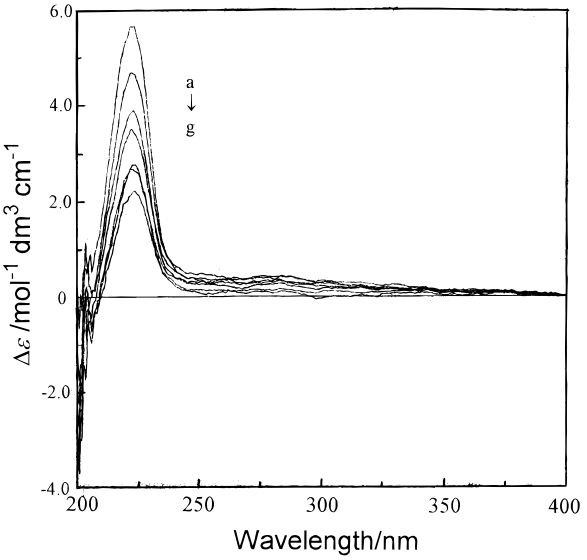

Figure 1. Circular dichroism spectra of L-Trp-β-CD (5.28×10^{-5} mol dm^{-3}) in the presence and absence of cycloheptanol (mmol dm^{-3}): (a) 0; (b) 0.858; (c) 1.717; (d) 3.433; (e) 5.150; (f) 8.583; (g) 13.73, in aqueous phosphate buffer solution (pH 7.20) at 25.0 °C.

Results and Discussion

Spectroscopic Study on the Self-Inclusion of L-Trp-β-CD in Aqueous Phosphate Buffer. As can be seen from the circular dichroism spectra of L-Trp-β-CD in Figure 1, an interaction exists between the L-tryptophan moiety and the chiral cyclodextrin cavity. In this case, the sector rule proposed by Kajtár et al.[16] cannot be applied to the present system, since the rule was derived from the spectra of inclusion complexes of a number of simple achiral aromatic compounds with cyclodextrins. The circular dichroism spectrum of L-Trp-β-CD (Figure 1) shows a positive Cotton effect peak at 222 nm ($\Delta\epsilon = +5.64$), whereas L-tryptophan shows a similar peak at 220 nm ($\Delta\epsilon = +8.50$). Furthermore, the molar circular dichroism ($\Delta\epsilon$) decrease upon the addition of guest alcohols, as exemplified in Figure 1. It may be concluded that the L-tryptophan residue perches on the edge of cyclodextrin cavity or appreciably penetrates into chiral hydrophobic cavity.

In an aqueous phosphate buffer solution, upon excitation at 280 nm, L-Trp-β-CD afforded a much stronger emission at 352 nm than L-tryptophan under the same chemical and optical conditions. This observation indicates that the indolyl moiety of the L-tryptophan residue is located in a more hydrophobic environment, i.e., within the cyclodextrin cavity, rather than in the bulk aqueous solution. This argument is based on the basis of the general interpretation of the enhanced fluorescence observed with aromatic fluorophores included in the cyclodextrin cavity. Furthermore, the fluorescence intensity of L-Trp-β-CD decreased consistently (Figure 2) upon gradual addition of the guest alcohols, demonstrating that the guests compete with the tryptophan residue for occupancy of the cyclodextrin cavity and expel the fluorescent residue out of the hydrophobic cavity into the bulk aqueous solution. The observed fluorescence behavior confirms that the indolyl moiety of L-tryptophan residue is initially accommodated in the cyclodextrin cavity.

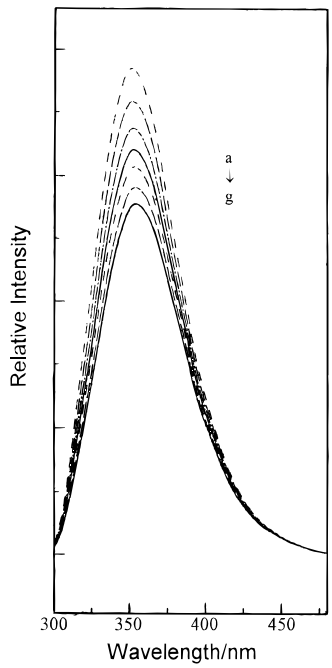

Figure 2. Fluorescence spectra of L-Trp-β-CD (1.03×10^{-5} mol dm^{-3}) in the presence and absence of (−)-menthol (mmol dm^{-3}): (a) 0; (b) 0.211; (c) 0.422; (d) 0.633; (e) 0.844; (f) 1.267; (g) 1.689, in aqueous phosphate buffer solution (pH 7.20) at 25 °C.

Correspondingly, time-resolved fluorescence decay measurements provided us with more direct information about the environment around the indolyl moiety of the L-tryptophan residue. When fitting the obtained fluorescence decay data to the equation

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

it was observed that the decay curve for L-Trp-β-CD in the presence and absence of guest adamantanols could not be fitted to a single-exponential function but could be fitted well to a linear combination of two exponential functions. In contrast, the decay curve of L-tryptophan in aqueous solution gave a good fit to a single-exponential function. The fluorescence lifetimes (τ) and relative quantum yields (Φ) for L-Trp-β-CD in the presence and absence of alcohols and for L-tryptophan in aqueous phosphate buffer are summarized in Table 1. The two-component decay observed for L-Trp-β-CD in the presence and absence of guest molecules indicates that the indolyl moieties of the L-tryptophan residue are located in two different environments, one of which is polar and the other nonpolar, and also that the interconversion of the two species is much slower than the fluorescence decay, which occurs on the ns time scale. The shorter lifetimes ($\tau_S = 2.8$ ns for L-Trp-β-CD, 2.9 ns for L-Trp-β-CD + 1-adamantanol, and 3.1 ns for L-Trp-β-CD + 2-adamantanol) are close to that of L-tryptophan in water (3.0 ns), indicating that those indolyl moieties are exposed to the bulk aqueous solution.

Since higher fluorescence intensity is correlated with an increase in the relative quantum yield (Φ_L) of the τ_L

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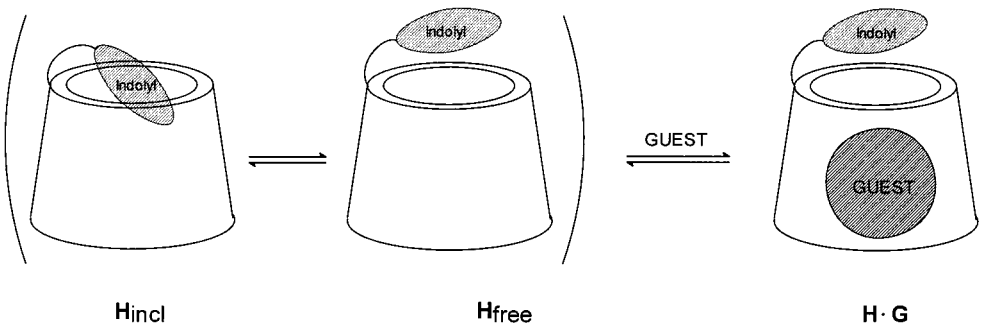
Table 1. Fluorescence Lifetimes (τ) and Relative Quantum Yields (Φ) for L-Trp-β-CD in the Presence and Absence of Guest Molecules and L-Tryptophan in Aqueous Phosphate Buffer Solution (pH = 7.20, 0.10 mol dm^{-3})

compd	concn × 10^5/mol dm^{-3}	guest	equiv	τ_S/ns	Φ_S/%	τ_L/ns	Φ_L/%	χ^2
L-Trp-β-CD	1.23			2.8	25	8.6	75	1.41
L-Trp-β-CD	1.23	1-adamantanol	130	2.9	50	8.7	50	1.17
L-Trp-β-CD	1.23	2-adamantanol	66	3.1	51	9.0	49	1.30
L-Trp	0.107			3.0	100			1.42

Scheme 2



component, the fluorophore included in the cyclodextrin cavity is considered to be protected from attack by water molecules, increasing the contribution of the τ_L component to the fluorescence intensity. The longer fluorescence lifetimes for L-Trp-β-CD in the presence and absence of guest adamantanols are also essentially the same; i.e., 8.6, 8.7, and 9.0 ns for L-Trp-β-CD, L-Trp-β-CD + 1-adamantanol, and L-Trp-β-CD + 2-adamantanol, respectively. From this we may conclude that the indolyl moieties are located in an identical hydrophobic environment, i.e., within the cyclodextrin cavity.

If we consider the relative quantum yields listed in Table 1, it is clear that the guest adamantanol competes with the self-included indolyl moiety for the cyclodextrin cavity and expels the indolyl moiety from the cavity, resulting in the increase of the τ_S component.

The spectroscopic evidence is compatible with the complexation mechanism shown in Scheme 2, where the free and self-included indolyl moieties are in a dynamic equilibrium and the addition of a guest leads to further equilibrium with the inclusion complex. Examination of CPK space-filling molecular models reinforces this argument.

Spectrofluorometric Titrations. In fluorometric titration experiments, the fluorescence intensity of the chromophore that is attached to the edge of the β-cyclodextrin cavity gradually decreases with increasing guest concentration (Figure 2). Assuming a 1:1 stoichiometry, the inclusion complexation of the alcohol (G) with the β-cyclodextrin derivative (H) is expressed by eq 1 and the complex stability constant (K_s) is given by eq 2

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

$$K_s = \frac{[H\cdot G]}{[H][G]} \qquad (2)$$

$$\Delta F = \Delta\epsilon[H\cdot G] \qquad (3)^{17}$$

where ΔF and $\Delta\epsilon$ denote the changes in the fluorescence intensity and molar extinction coefficient of the chromophoric β-cyclodextrin derivative upon inclusion complexation of the alcohol.

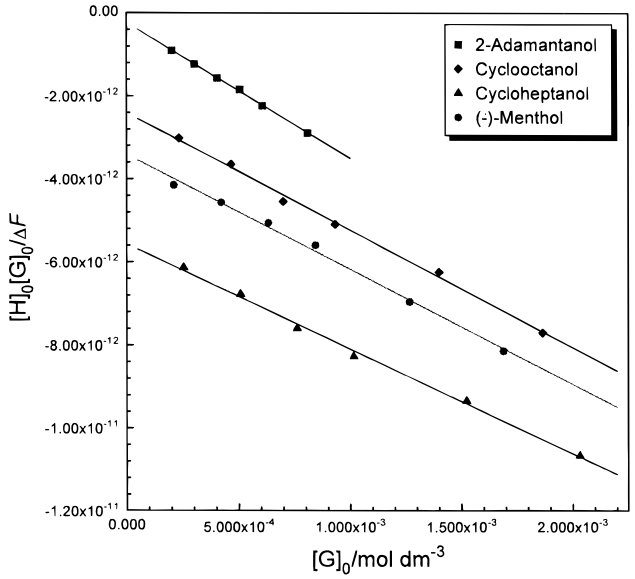


Figure 3. Typical plots of $[H]_0[G]_0/\Delta F$ versus $[G]_0$ for the inclusion complexation of L-Trp-β-CD with 2-Adamantanol (■), cyclooctanol (◆), cycloheptanol (▲), and (−)-menthol (●) in aqueous phosphate buffer solution (pH = 7.20) at 25 °C.

Under the conditions employed, the initial concentration of the guest alcohol is much larger than that of L-Trp-β-CD, i.e., $[G]_0 \gg [H]_0$. Therefore, the combination of eqs 2 and 3 leads to the extended Benesi−Hildebrand equation (eq 4), which is used to calculate the complex stability constants (K_s) (eq 2) from the slope and intercept of $[H]_0[G]_0/\Delta F$-versus-$[G]_0$ plots.

$$\frac{[H]_0[G]_0}{\Delta F} = \frac{1}{K_s\Delta\epsilon} + \frac{[G]_0}{\Delta\epsilon} \qquad (4)$$

Figure 3 illustrates some results of such a treatment for the inclusion complexation of L-Trp-β-CD with 2-adamantanol, cyclooctanol, cycloheptanol, and (−)-menthol, where the calculated $[H]_0[G]_0/\Delta F$ values are plotted against the $[G]_0$ values, affording an excellent linear relationship.

The complex stability constants (log K_s) and the free energy changes calculated from the slope and intercept are listed in Table 2.

Table 2. Stability Constants (log K_s) and the Gibbs Free Energy Changes ($-\Delta G$) for the Inclusion Complexation of Some Cyclic Alcohols with L-Trp-β-CD in Aqueous Phosphate Buffer Solution (pH = 7.20) at 25 °C

host	guest	K_s	log K_s	$-\Delta G$/kJ mol^{-1}	$\Delta\Delta G^c$/kJ mol^{-1}
L-Trp-β-CD	1-adamantanol	4730[a]	3.67	21.0	
	2-adamantanol	13900[a]	4.14	23.7	2.7
	cyclooctanol	1180[a]	3.07	17.5	
	cycloheptanol	453[a]	2.66	15.2	
	cycloheptanol	451[b]	2.65	15.2	
	cyclohexanol	96.8[b]	1.99	11.3	
	cyclopentanol	60[b]	1.78	10.2	
	(+)-borneol	1950[a]	3.29	18.8	
	(−)-borneol	2410[a]	3.38	19.3	0.5
	(+)-menthol	429a	2.63	15.0	
	(−)-menthol	810[a]	2.91	16.6	1.6
	nerol	197[a]	2.30	13.1	
	geraniol	384[a]	2.58	14.8	1.7
	1-hexanol	28[b]	1.48	8.3	

[a] Determined by spectrofluorometric titration. [b] Determined by spectropolarimetric titration. [c] The differences in ΔG values for the isomers.

Spectropolarimetric Titrations. With some guest molecules, the spectrofluorometric titration did not afford satisfactory results, and thus, we decided to follow the titration experiment by circular dichroism spectroscopy. Although an approximation approach (using the extended Benesi−Hildebrand equation for circular dichroism)[18] could evaluate the stability constants (K_s) for the inclusion complexation of L-Trp-β-CD with guest alcohols, our results were obtained using the nonlinear curve-fitting approach, which is a more accurate fitting method.[19] For the equilibrium eq 1, the intensity changes ($\Delta\Delta\epsilon$) in the circular dichroism of L-Trp-β-CD upon the addition of guest molecules are assumed to be proportional to the concentration of inclusion complex (H·G) produced in the solution

$$\Delta\Delta\epsilon = \alpha[\mathrm{H{\cdot}G}] \tag{5}$$

where α denotes a sensitivity factor for the circular dichroism change, or a quantitative measure of the conformational change upon complexation. From this, eq 6 can be derived.

$$\Delta\Delta\epsilon^2 - \alpha\left([\mathrm{H}]_0 + [\mathrm{G}]_0 + \frac{1}{K_s}\right)\Delta\Delta\epsilon + \alpha^2[\mathrm{H}]_0[\mathrm{G}]_0 = 0 \tag{6}$$

Solving eq 6 for $\Delta\Delta\epsilon$, we obtain eq 7.

$$\Delta\Delta\epsilon = \left[\alpha\left([\mathrm{H}]_0 + [\mathrm{G}]_0 + \frac{1}{K_s}\right) \pm \sqrt{\alpha^2\left([\mathrm{H}]_0 + [\mathrm{G}]_0 + \frac{1}{K_s}\right)^2 - 4\alpha^2[\mathrm{H}]_0[\mathrm{G}]_0}\right]/2 \tag{7}$$

The complex stability constant K_s and the sensitivity factor α were calculated by nonlinear fitting using the value of $\Delta\Delta\epsilon$ observed at each initial guest concentration $[\mathrm{G}]_0$. Typical curve-fitting plots are shown in Figure 4

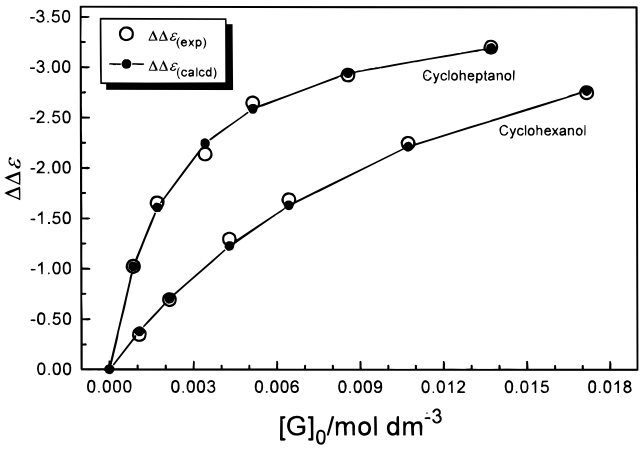


Figure 4. Typical plots of curve-fitting of $\Delta\Delta\epsilon$ versus $[\mathrm{G}]_0$ for the inclusion complexation of L-Trp-β-CD with cycloheptanol and cyclohexanol in aqueous phosphate buffer solution (pH = 7.20) at 25 °C.

for cycloheptanol and cyclohexanol. The results are also listed in Table 2. As can be seen in Table 2, very similar K_s values for cycloheptanol were obtained from spectrofluorometric and spectropolarimetric titrations.

Complex Stability Constants and Molecular Recognition. Extensive studies have revealed that the size/shape-fit concept plays a crucial role in the formation of inclusion complexes with guest molecules of various structures. On the basis of the size/shape-fit concept, weak intermolecular forces such as ion−dipole, dipole−dipole, dipole−induced dipole, van der Waals, electrostatic, hydrogen bonding and hydrophobic interactions are known to cooperatively contribute to inclusion complexation. Previous work and examination of CPK space-filling molecular models suggest that adamantane's rigid spherical skeleton is the best size/shape-fitted to the β-cyclodextrin cavity.[20] Consequently, L-Trp-β-CD shows the highest K_s values for 1- and 2-adamantanols among the acyclic and (poly)cyclic guest molecules examined. It should be noted that size/shape-matching leads to optimum distances between the adamantanol molecular surface and the interior of the cavity, affording strong hydrophobic interactions. In this context, it is reasonable that L-Trp-β-CD gives a smaller K_s for the rigid, but smaller, borneols than for adamantanols, showing molecular selectivities ranging from 2 to 7 for adamantanol vs borneol inclusion. Furthermore, L-Trp-β-CD has much lower ability to include monocyclic and acyclic alcohol guests.

For the C_{10} alcohols, i.e., adamantanols, borneols, menthols, nerol, and geraniol, complexation behavior appears to be governed by the size/shape and rigidity of the guests. The stability constant decreases in the order of structural rigidity: adamantanols > borneols > menthols > geraniol, nerol. The highest molecular selectivity in the C_{10} series amounts to 70 for 2-adamantanol vs nerol inclusion, while the highest selectivity for cyclic C_{10} alcohols, which possess some structural similarity, is 32 for 2-adamantanol vs (+)-menthol inclusion. The excel-

(17) The assumption is valid for the host L-Trp-β-CD existing in either one conformer or two conformers; see ref 11b.

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lent selectivity observed may have a potential application in the separation of these compounds.

For the monocyclic alcohols examined (i.e., menthol, cyclooctanol, cycloheptanol, cyclohexanol, and cyclopentanol), L-Trp-β-CD exhibits good molecular selectivity up to 20 for cyclooctanol vs cyclopentanol inclusion. The structurally flexible cyclooctanol affords the most stable inclusion complex with L-Trp-β-CD, probably via the induced-fit mechanism.

The complexation behavior can be reasonably explained not only by hydrophobicity arguments but also by the geometrical complementary relationship. The hydrophobicity increases with increasing number of carbon atoms in the guest, leading to the following complex stability sequence: cyclopentanol < cyclohexanol < cycloheptanol < cyclooctanol. However, menthols, which possess 10 carbon atoms, gave less stable complexes than cyclooctanol. It is reasonable to consider menthol as a substituted cyclohexanol. The stability constants for (+)- and (−)-menthol, which are larger than that for cyclohexanol but smaller than that for cyclooctanol, may be attributable to the less-effective van der Waals interactions caused by the methyl and isopropyl substituents.

For the three acyclic alcohols, i.e., nerol, geraniol, and 1-hexanol, the former two alcohols gave much more stable complexes than the latter. This is explained simply by the increased hydrophobicity.

For all the guest alcohols examined, the contribution of several structural factors leads to the highest molecular selectivity up to 500 for 2-adamantanol vs 1-hexanol inclusion and 230 for 2-adamantanol vs cyclopentanol inclusion among the cyclic alcohols.

Isomeric Recognition. As can be seen from Table 2, 2-adamantanol affords a more stable complex than 1-adamantanol, indicating that L-Trp-β-CD can recognize the minor difference in substitution position. Although X-ray crystallographic studies clearly indicate that the alcohol's hydroxyl group is located outside of the cyclodextrin cavity near the secondary hydroxyl side,[21] the formation of a hydrogen bond with the cyclodextrin's secondary hydroxyls is more favorable for the adamantanol's hydroxyl group at the 2-position than at the 1-position. The isomer selectivity for 2-adamantanol vs 1-adamantanol amounts to 3.

β-Cyclodextrin, which possesses a chiral microenvironment, has been shown to include L-α-amino acids in preference to D-α-amino acids,[22] and some modified β-cyclodextrins also exhibit a similar enantioselectivity.[10,23] In the present work, we have obtained higher complex stability constants for (−)-borneol and (−)-menthol than those for the corresponding (+)-enantiomers, although the enantioselectivities observed are only moderate: i.e., 1.2 and 1.9 for borneols and menthols, respectively.

L-Trp-β-CD favors geraniol with a trans double bond rather than nerol with a cis double bond, affording the trans/cis selectivity up to 2. This may be attributed to the preferable size/shape fitting interaction with the trans isomer. This is consistent with the inclusion complexation of β-cyclodextrin monobenzoate with cis and trans isomers of cyclooctene and 1-methylcyclooctene.[18]

Although nerol, geraniol, and borneols are isomers with the same formula ($C_{10}H_{17}OH$), these afford good isomer selectivities ranging from 5 to 12 as a result of the cyclic, improved shape-fitted structure of borneol.

Comparison of Fluorescent Cyclodextrins. Several fluorescent cyclodextrins have been synthesized previously, and their complexation behavior has been investigated with acyclic and cyclic alcohols, monoterpenes, and cholic acids.[11] It is interesting to compare the molecular recognition abilities of some structurally related fluorescent cyclodextrins in aqueous solution. In particular, Ueno et al. have studied the complexation behavior of modified cyclodextrins bearing fluorescent group(s) at the 2-, 3-, and/or 6-positions,[11] which include dansyl-β-CD,[11b] *N*-dansyl-L-Leu-β-CD,[11c] *N*-dansyl-D-Leu-β-CD,[11c] and *N*-dansyl-Gly-β-CD.[11c] Furthermore, there are some common guests employed in Ueno's and our work, these being cyclopentanol, cyclohexanol, cyclooctanol, 1-adamantanol, (−)-borneol, (+)-menthol, (−)-menthol, nerol, and geraniol. Figure 5 illustrates the profile of the stability constants for each host with these acyclic, cyclic, bicyclic, and tricyclic alcoholic guests, which are arranged tentatively in the order shown above. It is noted that although the stability constant K_s for each guest differs appreciably from host to host, the profiles of K_s are quite similar to each other, at least for the alcohols employed. This observation is normal, since all of the hosts have a β-cyclodextrin cavity of the same size. However, the stability constant for each guest varies by more than 1 order of magnitude, for which the different structure and hydrophobicity of the substituents introduced are jointly responsible. In this context, it is interesting to examine the relative quantum yield (Φ_L) of the τ_L component, since the high Φ_L in the absence of guest is the results of deeper penetration of the dansyl group into the hydrophobic cavity. However, the order of Φ_L, i.e., *N*-dansyl-D-Leu-β-CD (0.77)[11c] > *N*-dansyl-Gly-β-CD (0.71) [11c] > *N*-dansyl-L-Leu-β-CD (0.67) [11c] > dansyl-β-CD (0.26),[11b] does not coincide with that of K_s, i.e., *N*-dansyl-L-Leu-β-CD > dansyl-β-CD > *N*-dansyl-D-Leu-β-CD > *N*-dansyl-Gly-β-CD. This may be attributed to several factors such as the hydrophobicity of the substituent and the length and flexibility of the spacer between the cyclodextrin and the fluorescent probe. Unfortunately, the fluorescence behavior of the present host L-Trp-β-CD with a different fluorophore group cannot be compared directly with the dansyl hosts discussed above, but its high Φ_L value (up to 0.75, Table 1) would also indicate a deep penetration of the Trp group in the cavity. For all hosts examined, the highest K_s values are obtained with 1-adamantanol, indicating that the size/shape-fit relationship plays the determining role in the complexation behavior.

Conclusion

A modified β-cyclodextrin bearing an L-tryptophan residue as a spectral probe has been demonstrated to recognize minimal structural differences in the guest alcohols examined on the basis of their size/shape, rigidity, and hydrophobicity. Fluorescence decay experiments clearly demonstrate the presence of long- and

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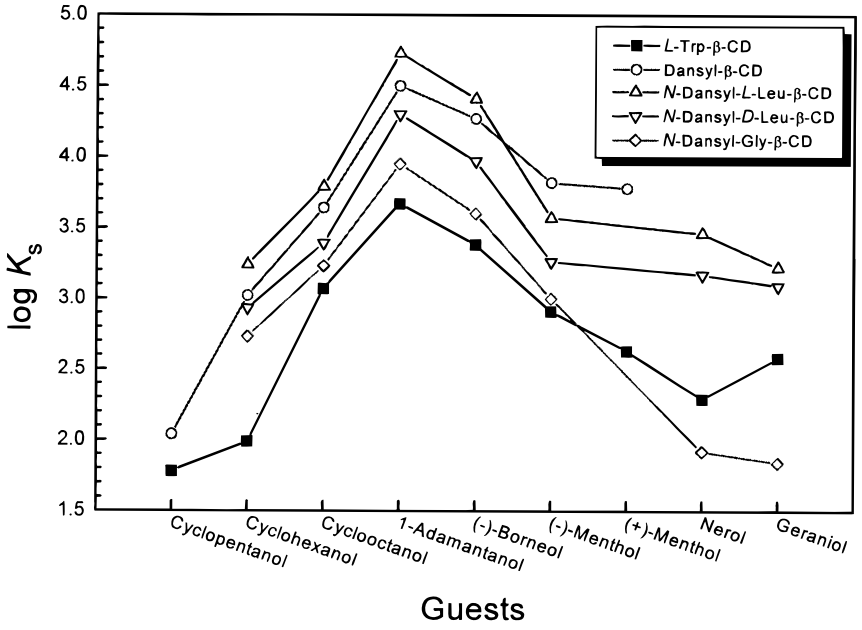

Figure 5. Comparison of the complexation stibility constants of fluorescent cyclodextrins, L-Trp-*β*-CD (■), dansyl-*β*-CD (○), *N*-dansyl-L-Leu-*β*-CD (△), *N*-dansyl-D-Leu-*β*-CD (▽), and *N*-dansyl-Gly-*β*-CD (◇), with several guest alcohols. The data for the last four cyclodextrins were from ref 11b,c.

short-lived species, which correspond to the probe inside and outside of the cavity. These experiments also reveal that part of the tryptophan probe is originally self-included in the cyclodextrin cavity in the absence of guest and is driven out of the cavity upon guest inclusion. Changes in the circular dichroism spectrum that are the result of conformational changes induced by complex formation were employed to determine the complex stability constants. L-Trp-*β*-CD can recognize the guest alcohols, giving good to excellent molecular selectivity and isomer selectivity. Experimentally, 2-adamantanol gives the most stable complex, the origin of which arises from the strongest hydrophobic interactions as a result of the appropriate size and structure, matching which permits the formation of efficient hydrogen bonding interactions.

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