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Ferrocene-Appended Cyclodextrins. The Effects of Temperature, Organic Solvent, Length of Spacer, and Cavity Size on the Complexation Behavior

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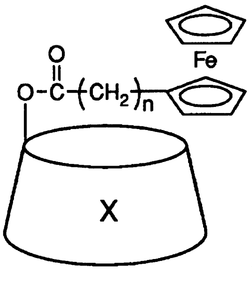
Inclusion phenomena of cyclodextrins (CyDs) bearing a ferrocene moiety, **1**—**4**, which have different cavity sizes and spacer lengths, were investigated by circular dichroism (CD) spectroscopy in pure ethylene glycol (EG) and 20% EG aqueous solution. β-CyD derivatives, **1** and **3**, and a γ-CyD derivative, **4**, form intramolecular complexes, including the ferrocene moiety in the CyD cavity with orientation similar to that in corresponding native CyD–ferrocene complexes, while another γ-CyD derivative, **2**, which has no spacer alkyl chain, takes various conformations. The host–guest binding constants of **1**—**4** for several guests revealed that the ferrocene moiety of **1**—**4** depresses the guest binding, acting as an intramolecular inhibitor in guest binding. In particular, the depression was remarkable for **3** and **4** and the spacer alkyl chain was suggested to stabilize the intramolecular complexes. The ferrocene modified CyDs exhibit similar trends in guest selectivity to those of native CyDs. The effects of EG content on the binding constants of **1** and **2** revealed that hydrophobic effect operated in the guest accommodation. Thermodynamic parameters for the binding processes of **1** and **2** for 1-adamantanol were obtained from the temperature variations in binding constants, the values being $-21.9\ \mathrm{kJ\,mol^{-1}}$ for ΔH° and $2.76\ \mathrm{J\,mol^{-1}\,K^{-1}}$ for ΔS° for **1** and $-25.1\ \mathrm{kJ\,mol^{-1}}$ for ΔH° and $-36.1\ \mathrm{J\,mol^{-1}\,K^{-1}}$ for ΔS° for **2**. These values indicated that the complexation of **1** and **2** for 1-adamantanol was governed both by hydrophobic effect and van der Waals interaction, and the latter was especially important in the case of **1** and 1-adamantanol.

Ferrocene is an organometallic compound composed of two cyclopentadienyl rings and Fe(II). Owing to the presence of Fe(II), ferrocene undergoes oxidation electrochemically or chemically in the presence of appropriate oxidizing agents, and the oxidized form known as ferricinium cation can be reduced to the original form by electron transfer from an electrode or reducing agents. Since this process is fully reversible, ferrocene can act as an electron mediator.[1] From the viewpoint of constructing efficient and selective electron transfer systems on this basis, it is desirable that reactants and the mediator (ferrocene) are present in proximal positions. Ferrocene modified cyclodextrins may be suitable as one of such systems because they have the covalently-linked mediator as well as the cavities in which chemical species can be included.

Cyclodextrins (CyDs) are naturally occurring oligosaccharides composed of glucopyranose units linked by α-1, 4-glycosidic bonds, and have an ability to include a hydrophobic molecule into their cavities, producing host–guest complexes.[2] Among CyDs, α-, β-, and γ-CyD, whose glucopyranose units are six, seven, and eight in the number, respectively, are well-known. Because of the suitable size and favorable molecular shape of ferrocene, α-, β-, and γ-CyD can form host–guest complexes with ferrocene although the stoichiometry and the orientation of ferrocene in the complexes depend on the size of the CyD cavities.[3] The binding is usually very strong and it is reported that complexation occurs not only in aqueous solution but also in organic media such as dimethyl sulfoxide and ethylene glycol.[3,4] In this connection, we reported[5] that ferrocene-appended β- and γ-CyD (**1** and **2**, respectively), in which the ferrocene moiety was covalently connected to CyD framework, form intra- and intermolecular complexes both in aqueous and organic solutions.

We now report the details of the intramolecular complexation and the guest binding behavior of 6-*O*-ferrocenylcarbonyl-β-CyD (**1**), 6-*O*-ferrocenylcarbonyl-γ-CyD (**2**), 6-*O*-(4-ferrocenylbutanoyl)-β-CyD (**3**), and 6-*O*-(4-ferrocenylbutanoyl)-γ-CyD (**4**). The effects of the cavity size, the spacer alkyl chain length, temperature, and content of organic solvent (ethylene glycol (EG)) on the formation of the intra- and intermolecular complexes of **1**—**4** have extensively been studied mainly by using circular dichroism (CD) spectroscopy (Scheme 1).



1: X=β-CD, n=0
2: X=γ-CD, n=0
3: X=β-CD, n=3
4: X=γ-CD, n=3

Scheme 1.

Experimental

Materials. γ-CyD was kindly gifted from Nihon Shokuhin Kako Co., Ltd. and was used as received. β-CyD was purchased from Nacalai Tesque and was recrystallized from water. Ferrocene, succinic anhydride, *p*-toluenesulfonyl chloride, 2-naphthalenesulfonyl chloride, and ferrocenecarboxylic acid were commercially available and were used without further purification. EG for spectroscopic measurements was distilled under reduced pressure. All the guest compounds (cyclohexanol, *l*-borneol, *l*-menthol, 1-adamantanol, and cyclododecanol) were used as received.

Measurements. Ultraviolet-visible (UV-vis) absorption spectra were recorded on a Shimadzu UV-250 spectrophotometer. Circular dichroism spectra were recorded on a JASCO J-400X spectropolarimeter equipped with a JASCO J-501 dataprocessor. During the spectroscopic measurements, the temperature of the cell holders was kept at 25 °C, unless otherwise noted, with circulating water.

Determination of Binding Constants. The 1:1 host–guest binding constants of **1**—**4** for several guests were determined from the guest-induced CD intensity variations by the digital simulation analyses based on the following expression;[6)]

$$K = \frac{\theta^{\circ} - \theta_{\mathrm{X}}}{(\theta_{\mathrm{X}} - \theta_{\mathrm{S}})[\text{Guest}] - [\beta\text{- or }\gamma\text{-Fc-CyD}]\dfrac{\theta^{\circ} - \theta_{\mathrm{X}}}{\theta^{\circ} - \theta_{\mathrm{S}}}},$$

where θ°, θ_{x}, and θ_{s} denote the molecular ellipticities for host alone, sample, and host–guest complex, respectively. The spectral displacement method reported by Eftink et al.[7)] was used to determine the binding constants of β- and γ-CyD for several guests, using phenolphthalein as a dye.

Syntheses. 6-*O*-Ferrocenylcarbonyl-β-CyD (1). This compound was synthesized from 6-*O*-tosyl-β-CyD by the reported procedure.[5b)] Found: C, 43.44, H, 6.39%. Calcd for $C_{53}H_{78}O_{36}Fe \cdot 7H_2O$: C, 43.21; H, 6.29%.

6-*O*-Ferrocenylcarbonyl-γ-CyD (2). This compound was synthesized from 6-*O*-(2-naphthylsulfonyl)-γ-CyD[8)] by the reported procedure.[5b)] Found: C, 43.71, H, 6.17%. Calcd for $C_{59}H_{88}O_{41}Fe \cdot 6H_2O$: C, 43.82; H, 6.23%.

3-(Ferrocenylcarbonyl)propanoic Acid (5). To a solution of ferrocene (1.86 g, 0.01 mol) and succinic anhydride (1.0 g, 0.01 mol) in 1,2-dichloroethane (50 mL), anhydrous aluminum chloride (2.67 g, 0.02 mol) was added and refluxed for 3 h. After cooling the solution, water (50 mL) and concd HCl (50 mL) were added to acidify the solution, and then the organic layer was separated and dried with Na_2SO_4. The solvent was removed in vacuo, the resultant mixture was led to SiO_2 column chromatography with the hexane–AcOEt–AcOH (50:50:1) as an eluent. Yield; 1.87 g (65%).

4-Ferrocenylbutyric Acid (6). The mixture of zinc powder (6.0 g), $HgCl_2$ (0.60 g), concd HCl (0.3 mL) and water (10 mL) was stirred for 5 h at room temperature. Then, to the filtrate of the mixture, water (3.75 mL), concd HCl (8.75 mL), toluene (5.0 mL), and **5** (4.0 g) were added and refluxed for 30 h. After cooling the mixture, the organic layer was separated, and the aqueous layer was extracted with ether (40 mL×3). The organic layers were combined and washed with water (3 times), followed by the drying with $CaCl_2$. After evaporating the solvent in vacuo, the resultant mixture was purified by SiO_2 column chromatography with hexane–AcOEt–AcOH (85:45:1) as an eluent, afforded **6** as a pale brown powder. Yield; 2.45 g (56%). Found: C, 61.78; H, 5.92%. Calcd for $C_{13}H_{16}Fe$: C, 61.79; H,5.93%. Compound **6** was converted into the sodium salt (**7**) by the addition of equimolar of sodium hydroxide in an ethanol solution, followed by evaporation.

6-*O*-(4-Ferrocenylbutanoyl)-β-CyD (3). Sodium salt **7** (1.45 g, 0.005 mol) and 6-*O*-tosyl-β-CyD (4.4 g, 0.0034 mol) were dissolved in 30 mL of DMSO and stirred at 80 °C for 5 h. The solution was allowed to stand still until becoming cool and poured into acetone (1 L). The precipitate formed was filtrated and recrystallized repeatedly from 1-butanol–ethanol–water (5:4:3), affording **3**. Yield; 3.45 g (27%). MS (FAB) *m*/*z* 1388 ($[M+H]^+$); IR (KBr) 1720, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6; 500 MHz) δ=1.50—1.78 (m, 2H), 2.15—2.41 (m, 2H), 3.12—3.81 (m), 3.95 (t, 4H), 4.10—4.25 (m, 5H), 4.41—4.69 (m, 6H), 4.80—5.01 (m, 7H), 5.63—6.01 (m, 14H); Found: C, 43.95, H, 6.48%. Calcd for $C_{56}H_{84}O_{36}Fe \cdot 8H_2O$: C,43.87, H, 6.57%.

6-*O*-(4-Ferrocenylbutanoyl)-γ-CyD (4). Sodium salt **7** (0.42 g, 0.00202 mol) and 6-*O*-(2-naphthylsulfonyl)-γ-CyD (1.0 g, 0.00672 mol) were dissolved in DMSO (10 mL) and stirred at 80 °C for 5 h. The mixture was allowed to stand becoming cool and poured into acetone (200 mL). The precipitate formed was collected and purified by Sephadex G-15 column chromatography using water as an eluent, affording pure **4**. Yield; 0.24 g (21%). MS (FAB) *m*/*z* 1550 ($[M+H]^+$); IR (KBr) 1720, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6; 500 MHz) δ=1.65—1.78 (m, 2H), 2.15—2.39 (m, 4H), 3.12—3.82 (m), 3.98 (t, 4H), 4.05—4.16 (m, 5H), 4.53—4.62 (m, 7H), 4.81—5.01 (m, 8H), 5.63—5.96 (m, 16H); Found: C, 43.75, H, 6.68%. Calcd for $C_{62}H_{94}O_{41}Fe \cdot 8H_2O$: C,43.92, H, 6.54%.

Results and Discussion

CD Spectra in 20% Ethylene Glycol Aqueous Solutions. Firstly, we attempted to study intra- and intermolecular complexation behavior of **1**—**4** in aqueous solutions. Since solubility of **3** and **4** to pure water was poor, we used 20% EG aqueous solutions of **1**—**4** for spectroscopic measurements. When an achiral chromophore is accommodated in a chiral CyD cavity, induced CD was observed in the absorption region of the chromophore. Absorption and CD spectra above 300 nm of **1**—**4** are shown in Fig. 1[#] together with the CD spectra of **1**—**4** in the presence of *l*-borneol. All hosts **1**—**4** exhibited the CD bands associated with the d–d transition of Fe(II) of ferrocene moieties around 460 nm, indicating the formation of intramolecular complexes between the ferrocene moieties and the CyD cavity. Possibility for the intermolecular complexation of **1**—**4** could be negligible because

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[#] In our previous papers concerning the sensing ability of **1** (*Makromol. Chem., Rapid Commun.*, **12**, 113 (1991) and *Anal. Chem.*, **64**, 1650 (1992)), the UV-vis spectrum of **1** between 350 and 300 nm was mistakenly shown with the values in ϵ two fold larger than those of original one. Corrected spectrum of **1** is shown here.

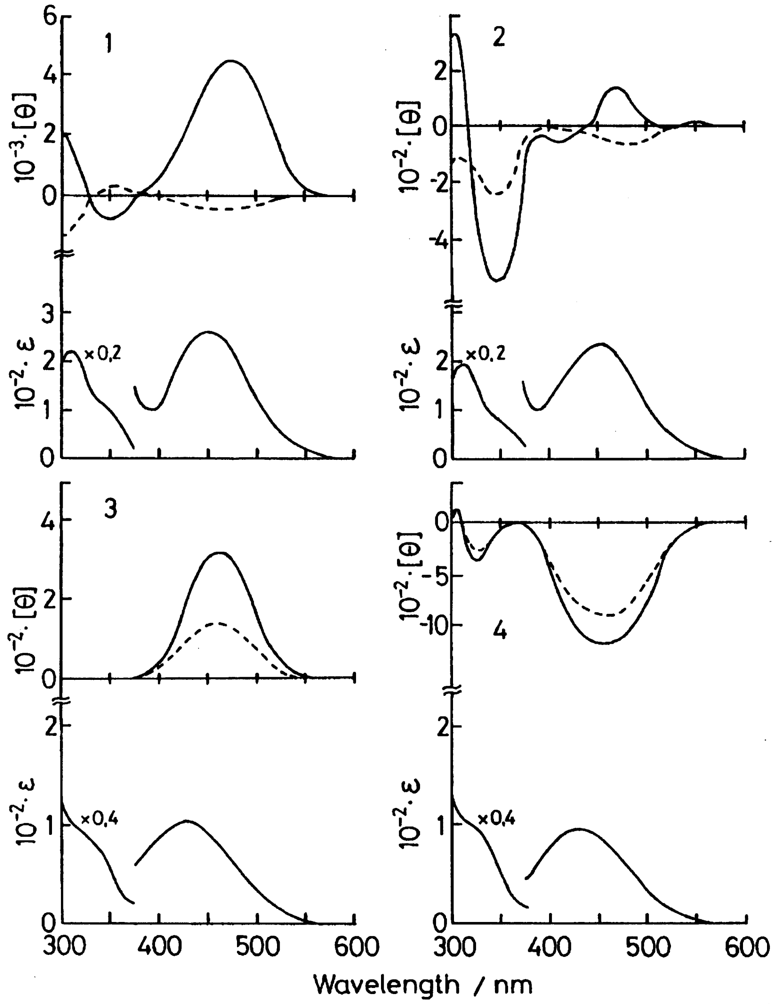

Fig. 1. UV-visible absorption (bottom) and CD spectra (top) of **1**—**4** in 20% EG aqueous solutions at 25 °C, alone (—, **1**; 2.44×10^{-4} mol dm^{-3}, **2**; 2.56×10^{-3} mol dm^{-3}, **3**; 6.21×10^{-4} mol dm^{-3}, **4**; 2.56×10^{-3} mol dm^{-3}) or in the presence of *l*-borneol (---, **1**; 4.14×10^{-3} mol dm^{-3}, **2**; 4.34×10^{-3} mol dm^{-3}, **3**; 6.56×10^{-3} mol dm^{-3}, **4**; 5.31×10^{-3} mol dm^{-3}).

no change in the CD spectra of **1**—**4** was obtained as compared with the spectra shown in Fig. 1 when their solutions were diluted 1/10-fold. It is known that a sign of CD bands reflects the conformation of a host–guest complex.[9] The positive CD bands at the d–d transition region observed for **1** and **3** are consistent with the results of β-CyD–ferrocene complexes reported by Harata et al.[3c] They observed positive and negative CD bands around 460 nm for β-CyD–ferrocene and γ-CyD–ferrocene complexes, respectively, and concluded that the conformation of the β-CyD–ferrocene complex is an axial inclusion as shown in Fig. 2 A, while that of the γ-CyD–ferrocene complex is equatorial as shown in Fig. 2 B. On the same basis, the conformation of the intramolecular complexes of **1** and **3** are assumed to be axial while that of **4** is to be equatorial. However, it is noted that there exists risk to determine an exact conformation of **1**—**4** from CD spectra because the theoretical model based on the Kirkwood–Tinocco oscillator strength theory applied so far assumed that the location of the chromophore in the CyD cavity was fixed at the center. Recently, Kodaka[10] et al. experimentally and theoretically demonstrated that the position of the chromophore on CyD molecular Z axis should be taken into account to elucidate the accurate structures of the CyD–guest inclusion complexes from the CD spectral data. This suggests again that some other spectroscopic data or X-ray analysis may be needed to determine a correct orientation of the ferrocene moiety of the modified CyDs. The CD spectrum of **2**, however, was too complicated to estimate the conformation of the intramolecular complex.

After addition of *l*-borneol as a guest, the CD spectra of **1**—**4** were changed, indicating that the guest was inserted into the CyD cavities with induction of a change in location of the ferrocene moiety. For **1** and **2**, both of which have the ferrocenecarbonyl moiety directly connected to a primary hydroxyl group of CyD, a positive peak at 470 nm (**1**) or 460 nm (**2**) changed drastically to a negative trough on guest binding with a shift in

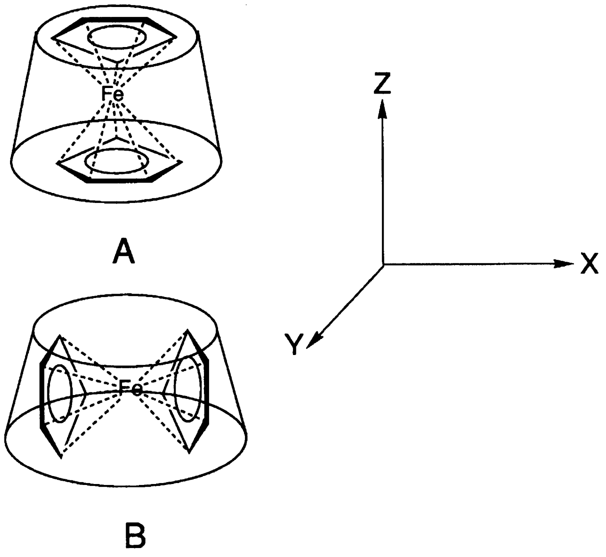

Fig. 2. The structure of axial inclusion (A) and equatrial inclusion (B) for CyD–ferrocene complexes.

peak maximum to 460 nm for **1** and 480 nm for **2**. On the other hand, **3** and **4**, which have a propyl chain between ferrocene and CyD, exhibited only slight decreases in CD intensity without any significant shift in their peak maxima. The absorption band around 400—550 nm of ferrocene is known as the absorption comprising two components with peak maxima at shorter and longer wavelength region,[11] and the complicated CD behavior of **1** and **2** on guest binding may be related to the nature of the absorption.

Binding Constants of 1—4 in 20% Ethylene Glycol Aqueous Solutions. From the guest concentration dependent CD spectral variations, the binding constants (K) of the host–guest complexation were determined for **1**—**4** based on 1 : 1 complexation stoichiometry. The K values of **1**—**4** obtained for several guests are summarized in Table 1 together with those of native β- and γ-CyD determined by spectroscopic displacement method.[7] At a first glance, one can be aware of the markedly small K values of **1**—**4** compared to those of corresponding native CyDs. This strongly indicates that the ferrocene moiety of **1**—**4** acts as an intramolecular inhibitor[12] in binding guest rather than as an effective hydrophobic cap.[13] This tendency was strengthened in the case of **3** and **4**. The binding constants of **1** for *l*-borneol and cyclohexanol were 31 and 6.3% of those values of β-CyD, respectively, while the binding constants of **3** were much smaller with the values of 2.6 and 4.9% of those of β-CyD for *l*-borneol and cyclohexanol, respectively. A similar trend was observed for 1-adamantanol. For the γ-CyD derivatives of **2** and **4**, the binding constants for *l*-borneol were 591 and 191 $\text{mol}^{-1}\,\text{dm}^3$, respectively, being small compared to those of native γ-CyD whose binding constants for *l*-borneol and 1-adamantanol were 3700 and 3100 $\text{mol}^{-1}\,\text{dm}^3$, respectively. Obviously, the presence of the alkyl chain in **3** and **4** has the effect of decreasing the guest binding ability. The reason for the difference in the binding ability between **1** or **2** and **3** or **4** may be explained by taking into account the remarkable stability of the intramolecular ferrocene–CyD complexes of **3** and **4**; the alkyl chain increases the freedom of the movement of the ferrocene moiety, thus allowing the moiety to behave like a free ferrocene molecule in the intramolecular ferrocene–CyD complexes. It is well known that γ-CyD accommodates two aromatic guests simultaneously,[14] forming a 1 : 2 host–guest complex. This characteristic feature relates to one guest accommodation of modified γ-CyDs,[15] in which the modified residue narrows the wider γ-CyD cavity on binding guests, acting as an effective spacer. It seems, however, to be difficult for **4** to accommodate an additional guests such as *l*-borneol to form a stable host–guest complex because of the bulkiness and the freedom of the ferrocene moiety. Thus, **4** had a markedly small binding constant relative to native γ-CyD. On the other hand, **2** exhibited a relatively large binding ability for the guests. Since the ferrocene moiety of **2** was restricted with respect to the freedom in and out of the γ-CyD cavity owing to the absence of the alkyl chain, the ferrocene moiety could take a conformation suitable for accommodating a guest as a hydrophobic cap or a spacer.

Table 1 also shows another characteristic feature on a molecular recognition ability of **1**—**4** in guest binding. When comparing the data between **1** and **2**, the β-CyD derivative of **1** has larger binding constants for *l*-borneol, 1-adamantanol, *l*-menthol, and cyclohexanol than the γ-CyD derivative of **2**, although **2** binds cyclododecanol 1.20-fold more strongly than **1**.This result may be related to the fact that cyclododecanol, which is the largest molecule among the guests listed in Table 1, is too large to be accommodated in the β-CyD cavity while it can be included in the large γ-CyD cavity. However, the degrees of the differences in the binding constants between **1** and **2** are rather small in comparison with the case of pyrene-appended CyDs[16] in a 10% DMSO aqueous solution, where the β-CyD derivative exhibited no complexation with cyclododecanol while the γ-CyD derivative forms a stable complex with the same guest. Native β-CyD binds *l*-borneol and *l*-menthol 2.3- and 3.2-fold more strongly than γ-CyD, respectively. This feature is consistent with the result of molecular model considerations that β-CyD can bind those guests more snugly than γ-CyD whose cavity is too large to bind the guests tightly. The driving forces for the formation of CyD–guest complexes are believed to be hydrophobic and van der Waals interactions. The latter force acts effectively when the contact area between molecules is large. In this context, the stronger binding affinities of β-CyD to *l*-borneol, 1-adamantanol, and *l*-menthol than those of γ-CyD are reasonable. This intrinsic feature of CyDs for guest binding is preserved

Table 1. The 1 : 1 Host–Guest Binding Constants (K) of CyDs for Several Guests in 20% Ethylene Glycol Aqueous Solutions at 25 °C

Guest	K/mol^{-1} dm^3					
	1	2	3	4	β-CyD[a)]	γ-CyD[a)]
l-Borneol	2630 ± 50	591 ± 3	225 ± 5	191 ± 5	8500	3700
1-Adamantanol	2880 ± 10	405 ± 3	223 ± 5	172 ± 5	14500	5160
Cyclododecanol	893 ± 7	1070 ± 20	—[b)]	—[b)]	—[b)]	—[b)]
l-Menthol	255 ± 5	128 ± 5	—[b)]	—[b)]	3980	1260
Cyclohexanol	58.5 ± 2.5	6.95 ± 0.15	45.3 ± 4.7	—[b)]	930	—[b)]

a) Binding constants were obtained in pH 10.02 (reading value in pH meter) in EG–0.1 M carbonate buffered solution (2 : 8) with the errors being estimated within ±10%. b) The values could not be obtained accurately.

in the ferrocene appended CyDs. The binding constants of **1** for *l*-borneol and *l*-menthol were 4.45- and 2.07-fold larger than those of **2**, indicating that **1** was a better host to bind such relatively small molecules than **2**. Similar trend was also observed in **3** and **4** although the extent was small; **3** exhibits slightly larger binding constants than **4** for *l*-borneol and 1-adamantanol. This result indicates that the difference in the intrinsic binding affinities between β- and γ-CyD is also preserved for **3** and **4**. Although we attempted to obtain the binding constants of **3** and **4** for other guests, owing to the tiny variations in CD intensity and poor solubilities of the guests, the values could not be obtained accurately except for the case of **3** and cyclohexanol, the value being 45.2 mol^{-1} dm^3, which was almost comparable with the value of **1** for cyclohexanol and was smaller 20 times than that of β-CyD.

Temperature Effect. Fig. 3 showed the CD spectra of **1**—**4** in 20% EG aqueous solutions at various temperatures. The compounds **1**, **3**, and **4** decreased their CD intensities in the whole wavelength region with increasing temperature, while the shape of the CD spectrum of **2** was changed drastically depending on temperature, possessing an isoellipticity point at 425 nm. The decrease in the CD intensity of **1**, **3**, and **4** at high temperature may be attributable to the depression in the formation of intramolecular complexes. The complicated spectral change of **2** means that **2** takes various conformations and that the most stable conformation of **2** depends strongly on temperature. The results of guest-induced and temperature dependent CD spectral changes indicate that the conformation of the intramolecular complexes of **2** is sensitive to external stimuli.

Host–guest complexation processes of β-CyD for adamantane derivatives are well-investigated[17)] and are characterized to be driven by van der Waals interaction with relative contribution of hydrophobic interaction by detail exploration in the thermodynamic parameters (ΔH°, ΔS°) for the processes. It is interesting what forces primarily govern the formation of host–guest complexes between ferrocene-appended CyDs and guest compounds. So, we investigated the temperature effect on the host–guest complex formation of **1** and **2** for 1-adamantanol because **1** and **2** exhibit the prominent CD band around 470 nm and 1-adamantanol has an adamantane framework, which induced large variations in the CD spectra of **1** and **2**.

Table 2 shows the binding constants of **1** and **2** for 1-adamantanol at various temperature. For both hosts, the binding constants were decreased as raising temperature. The van't Hoff's plots ($\ln K$ vs. $1/T$) were applied to the data and the results were demonstrated in Fig. 4. Standard enthalpy and entropy changes (ΔH° and ΔS°, respectively), which were calculated from the intercepts and slopes of the straight lines obtained by least square analyses, were −21.9 kJ mol^{-1} and 2.76 J mol^{-1} K^{-1} for ΔH° and ΔS°, respectively, for **1**, and −25.1 kJ mol^{-1} and −36.1 J mol^{-1} K^{-1} for ΔH° and ΔS°, respectively, for **2**. These values revealed that the complexation between **1** and 1-adamantanol was enthalpically driven with a small contribution of entropy, and that between **2** and 1-adamantanol was also enthalpically driven although it was entropically unfavorable. It is known that a hydrophobic effect, which is believed to be a primary binding force for the complexation of CyD with a guest, is characterized by positive ΔS° and nearly zero ΔH°.[17e)] As described in the next section, a hydrophobic effect was actually operated in the guest accommodation of **1** and **2**. Thus, judging

Table 2. Binding Constants of **1** and **2** for 1-Adamantanol in 20% Ethylene Glycol at Various Temperatures

Temperature / °C	K/mol^{-1} dm^3	
	1	2
5	6580 ± 20	624 ± 4
15	5180 ± 15	420 ± 4
25	2880 ± 10	405 ± 3
35	2810 ± 10	234 ± 4
45	2510 ± 20	184 ± 8
55	1780 ± 30	151 ± 12
65	1330 ± 40	73.3 ± 15.7
75	820 ± 31	—[a)]

a) The value could not be obtained due to the small changes in the CD spectrum.

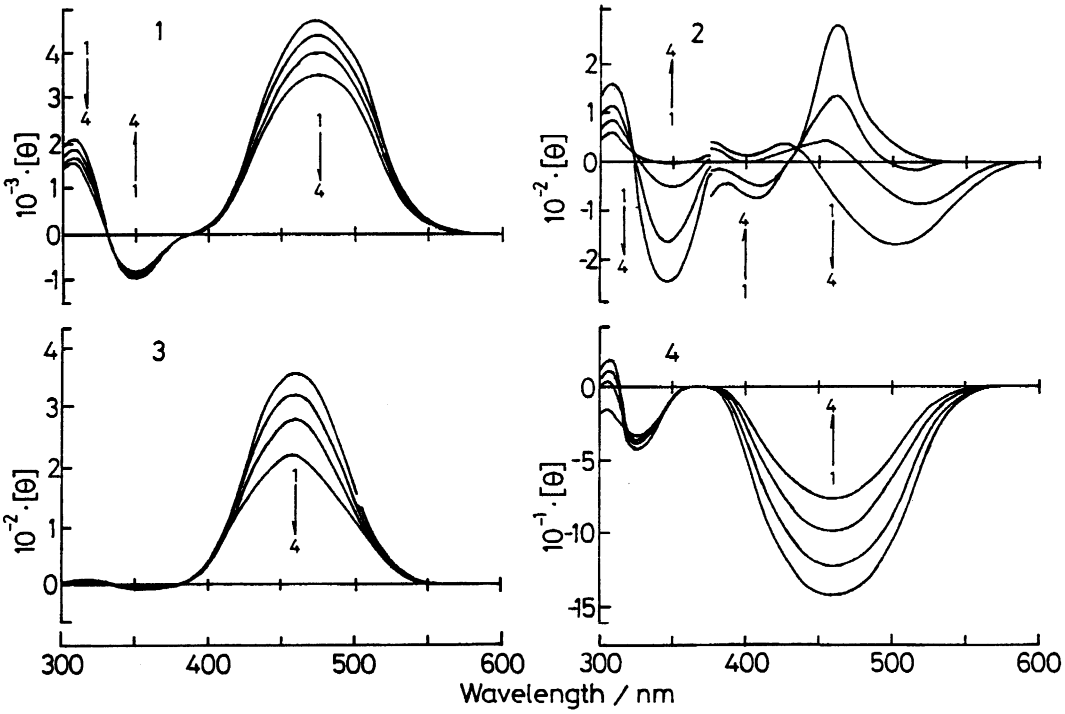

Fig. 3. CD spectra of **1**—**4** in 20% EG aqueous solutions at various temperatures (1; 5 °C, 2; 25 °C, 3; 45 °C, 4; 75 °C). Concentrations of **1**—**4** were the same as in Fig. 1.

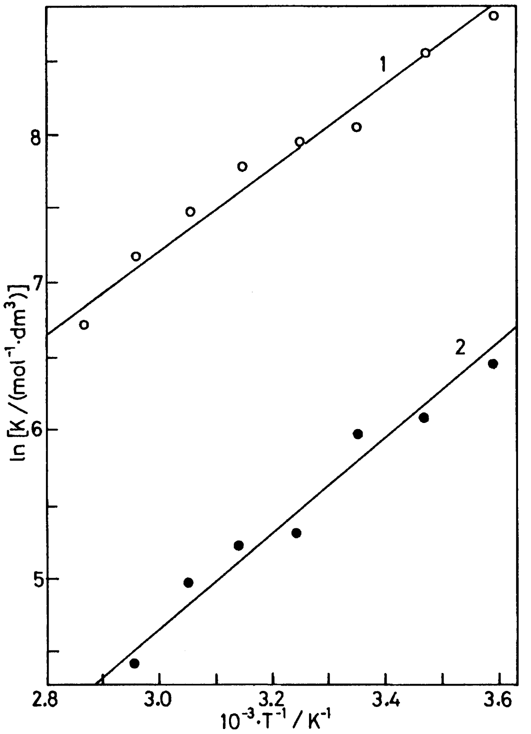

Fig. 4. The van't Hoff's plots of **1**–1-adamantanol (O) and **2**–1-adamantanol (●).

from the thermodynamic parameters, another binding force causing negative ΔH° and ΔS° would participate in the binding process of **1** and **2** for 1-adamantanol and would be masked by the large positive ΔS° given by the hydrophobic effect. Eftink et al.[17d)] regarded the uncertain force as van der Waals interaction in a complexation of native CyDs with adamantane derivatives. The values of ΔH° and ΔS° of the complexation of **1** and 1-adamantanol were consistent with those between β-CyD and 1-adamantanecarboxylate. Thus, we attributed the uncertain force causing negative ΔH° and ΔS° to van der Waals interaction. In comparison of ΔH° and ΔS° values between **1** and **2** for 1-adamantanol, the complexation of **2** was markedly suppressed entropically although the process was enthalpically more favorable than the process of **1**. This strongly indicates that van der Waals interaction was a primary binding force and hydrophobic interaction contributed as an minor factor for the complexation of **2** and 1-adamantanol, whereas both van der Waals and hydrophobic interactions cooperatively effected in the complexation of **1** and 1-adamantanol. This cooperation compensates the inherent thermodynamic parameters of van der Waals and hydrophobic interactions each other, leading relatively large negative ΔH° and small positive ΔS° values.

As mentioned above, the ΔH° and ΔS° values for the complexation of **1** and 1-adamantanol are consistent with those of native β-CyD, suggesting the ferrocene moiety of **1** did not alter the binding nature of β-CyD. On the other hand, the results obtained for **2** and 1-adamantanol were inconsistent with those of native γ-CyD and 1-adamantanecarboxylate,[17d)] for which hydrophobic effect operated (large positive ΔS° value was

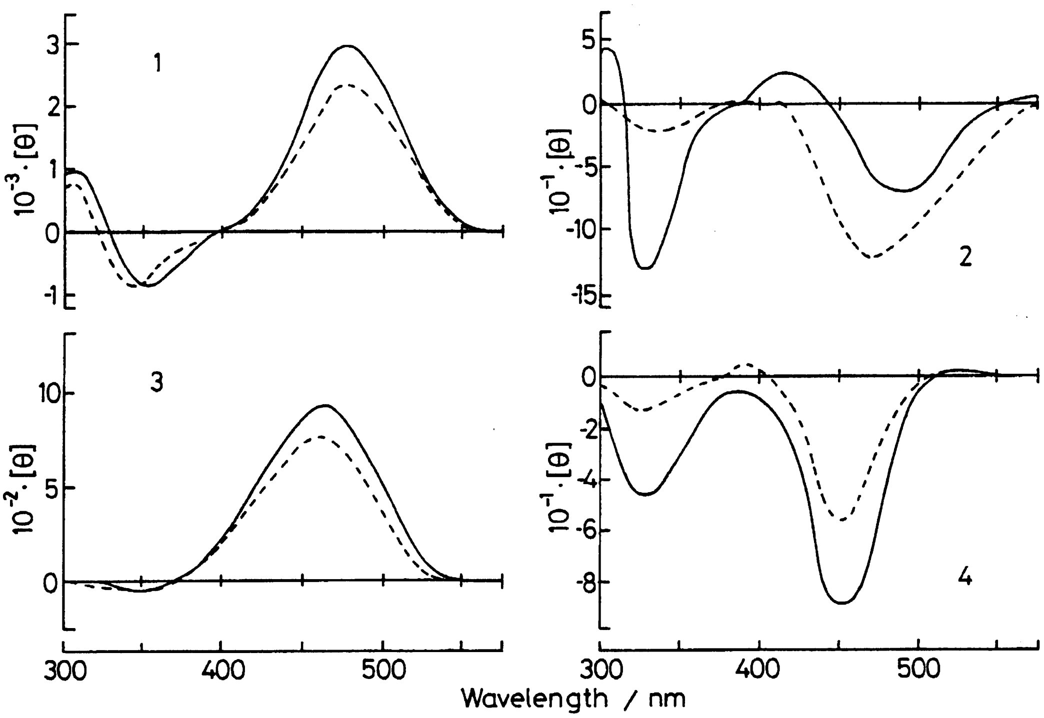

Fig. 5. CD spectra of **1**—**4** in an EG solution at 25 °C, alone (—, **1**; 2.42×10^{-4} mol dm^{-3}, **2**; 2.49×10^{-3} mol dm^{-3}, **3**; 6.21×10^{-4} mol dm^{-3}, **4**; 2.56×10^{-3} mol dm^{-3}) or in the presence of *l*-borneol (---, **1**; 6.13×10^{-3} mol dm^{-3}, **2**; 1.02×10^{-2} mol dm^{-3}, **3**; 1.33×10^{-2} mol dm^{-3}, **4**; 8.18×10^{-3} mol dm^{-3}).

obtained). This indicates that the ferrocene moiety of **2** can change the binding nature of γ-CyD. γ-CyD is more flexible than β-CyD and, thus, when γ-CyD accommodates a guest in its cavity, partial collapse of the γ-CyD molecular structure may occur to adapt the cavity shape to the accommodated guest shape. This partial collapse seems to be endothermic (results in positive ΔH°).[17d] For native γ-CyD, such partial collapse occurs after guest accommodation, while for **2**, the structure of γ-CyD part may be collapsed by the preliminary formation of the intramolecular complex with the ferrocene moiety. After accommodating 1-adamantanol, **2** should preserve the collapsed structure, exhibiting a large negative ΔH° value. The larger contribution of van der Waals interaction in the complexation of **2** and 1-adamantanol, as compared to that of γ-CyD, can be explained by taking into account the presence of the ferrocene moiety. A guest bound to the cavity of **2** can contact the hydrophobic ferrocene moiety which may be accommodated in the cavity, and consequently the guest bound to **2** serves a larger contact area which strengthens the van der Waals interaction than that bound to native γ-CyD. As a result, the complexation of **2** and 1-adamantanol exhibited large negative ΔH° and ΔS° values.

Solvent Effect. If a hydrophobic interaction actually operated in the complex formation of **1**—**4** with various guests, the binding constants should be decreased with increasing organic solvent content in the solution containing **1**—**4** and a guest. Moreover, since ferrocene can form a relatively stable complex with β-CyD in organic solvents such as EG and dimethyl sulfoxide, **1**—**4** are expected to form the intramolecular complexes which result in the ferrocene-induced CD bands. On this basis, we investigated intra- and intermolecular host–guest complexation behavior of **1**—**4** in EG solutions. Figure 5 shows the CD spectra of **1**—**4** in EG solutions with those of **1**—**4** in the presence of *l*-borneol. These spectra apparently indicate that the ferrocene moiety of **1**—**4** interacts with the CyD cavity, and might be accommodated in it. The values of molar ellipticity of **1**—**4** in EG solutions were 2660, −70, 850, and −85 degree mol^{-1} dm^3 cm^{-1} at the peak maximum for **1**, **2**, **3**, and **4**, respectively, being about 0.6-fold smaller than those in 20% EG solutions except for **3** whose value in a 20% EG aqueous solution was 320 degree mol^{-1} dm^3 cm^{-1}, smaller than that in an EG solution with the factor of 0.38. These results indicate that the intramolecular complex of **3** was more stable in an EG solution than in a 20% EG aqueous solution while the other intramolecular complexes were more stable in 20% EG aqueous solutions than in EG solutions. From the viewpoint on spectral patterns in an EG solution, the β-CyD derivatives exhibited the similar spectra to those in 20% EG aqueous solutions, while the spectral patterns of the γ-CyD derivatives in EG solutions were different from those in 20% EG aqueous solutions. In particular, a negative CD band was

Table 3. The 1 : 1 Host–Guest Binding Constants (K) of **1**—**4** for Several Guests in Ethylene Glycol Solutions at 25 °C

	$K/\mathrm{mol^{-1}\ dm^3}$			
Guest	**1**	**2**	**3**	**4**
l-Borneol	22.6 ± 2.0	71.0 ± 0.5	9.7 ± 0.5	—[a)]
1-Adamantanol	73.9 ± 4.4	53.5 ± 0.5	58.3 ± 3.0	—[a)]
Cyclododecanol	50.0 ± 1.0	144 ± 1	18.5 ± 0.8	—[a)]
l-Menthol	6.8 ± 0.4	13.4 ± 0.6	1.9 ± 0.2	—[a)]
Cyclohexanol	4.9 ± 0.1	—[a)]	—[a)]	—[a)]

a) The values could not be obtained accurately.

Table 4. The 1 : 1 Host–Guest Binding Constants (K) of **1** for Several Guests in Various EG Aqueous Solutions at 25 °C

	$K/\mathrm{mol^{-1}\ dm^3}$				
Guest	20%EG	50%EG	70%EG	90%EG	EG only
l-Borneol	2630 ± 50	594 ± 52	392 ± 22	54.0 ± 2.0	22.6 ± 2.0
1-Adamantanol	2880 ± 10	1230 ± 30	935 ± 29	205 ± 22	73.9 ± 4.4
Cyclododecanol	893 ± 7	836 ± 15	410 ± 11	332 ± 10	50.0 ± 1.0
l-Menthol	255 ± 5	165 ± 12	75.6 ± 8.6	31.1 ± 2.6	6.8 ± 0.4
Cyclohexanol	58.5 ± 2.5	37.8 ± 2.8	26.2 ± 4.7	13.6 ± 1.1	4.9 ± 0.1

Table 5. The 1 : 1 Host–Guest Binding Constants (K) of **2** for Several Guests in Various EG Aqueous Solutions at 25 °C

	$K/\mathrm{mol^{-1}\ dm^3}$				
Guest	20%EG	50%EG	70%EG	90%EG	EG only
l-Borneol	591 ± 3	430 ± 8	320 ± 16	85.1 ± 2.6	71.0 ± 0.5
1-Adamantanol	405 ± 3	301 ± 11	223 ± 4	75.5 ± 5.5	53.0 ± 0.5
Cyclododecanol	1070 ± 20	810 ± 5	605 ± 6	165 ± 4	144 ± 1
l-Menthol	128 ± 5	89.2 ± 3.5	70.3 ± 3.8	18.0 ± 1.2	13.4 ± 0.6
Cyclohexanol	6.95 ± 0.15	—[a)]	—[a)]	—[a)]	—[a)]

a) The values could not be obtained accurately.

observed for **2** as a maximum one in the d–d transition region with a large (40 nm) bathochromic shift at the peak maximum compared to the most intense band in the same wavelength region in a 20% EG aqueous solution. For **4**, a small (15 nm) bathochromic shift was also seen in the CD spectrum in an EG solution compared to that in a 20% EG aqueous solution, although no change in the CD sign in the d–d transition region was observed. These results suggest that the stable conformations for the intramolecular complexes of **1** and **2** in EG solutions were virtually similar for those in EG solutions, and were substantially different from those in 20% EG aqueous solutions.

All CD spectra of **1**—**4** changed upon guest addition with the intensities being decreased except for **2** whose absolute intensity of the CD band at 505 nm was increased in its intensity with 25 nm of hipsochromic shift in the peak maximum. The thermodynamically stable forms of the intra- and intermolecular complexes of **2** are, therefore, markedly sensitive to external stimuli, such as guest addition, temperature, and polarity around a **2** molecule. This may be due to the fact that, in a γ-CyD cavity, ferrocene can take both axial and equatorial orientations as well as an oblique one. Recent molecular mechanics calculations on a γ-CyD–ferrocene complex suggest[18)] that the most stable conformation was an equatorial type and an oblique one as a follow. The energy difference, however, was found to be less than 0.5 $\mathrm{kcal\,mol^{-1}}$. Additionally, when the ferrocene moiety of **2** was accommodated in the γ-CyD cavity of **2**, the movement was likely to be limited by the γ-CyD molecular wall. Consequently, **2** exhibited the diverse conformations in intra- and intermolecular complexes.

From the guest-induced CD variations, we could obtain the 1 : 1 host–guest binding constants of **1**—**3** for several guests in EG and the results are summarized in Table 3. Although we attempted to obtain the binding constants of **4**, the accurate values could not be obtained. The smaller value of each host- guest set than that in a 20% EG aqueous solution indicates that substantial contribution of the hydrophobic interaction is present in the complexation between **1**—**4** and guests.

Detailed comparison of the values in Table 3 with those in Table 1 allowed to emerge another interesting feature of the complexation. The binding constants of **1** in an EG solution were smaller than those in a 20%

EG aqueous solution with factors ranging from 0.013 to 0.084 while the factors for **2** ranged from 0.105 to 0.136. This difference means that the ability of the guest binding of **1** was markedly depressed in an EG solution in spite of the relative stability of the intramolecular complex, and that the ability of **2** was relatively insensitive to the polarity of a bulk medium. There are two possible mechanisms to explain this difference. One is the co-inclusion[19)] of a solvent EG molecule into the host–guest complex; the wider cavity of **2** can accommodate both a guest molecule and an EG molecule simultaneously while the cavity of **1** is not allowed to accommodate an additional molecule when **1** formed a host–guest complex with a guest molecule. The other explanation is that the binding process of **2** was governed by a van der Waals interaction rather than a hydrophobic effect while there is relatively large contribution of the hydrophobic interaction in the guest binding process of **1**. Although it is difficult to estimate the contributions of the factors for explaining the difference in binding constants between both solutions of **1** and **2**, the thermodynamic parameters suggest that the contribution of the hydrophobic interaction in the host–guest complexation between 1-adamantanol and **1** was larger than that for the case of **2**. Since the binding constants of the hosts in EG solutions actually decreased as compared to those in 20% EG aqueous solutions, it is no doubt that the hydrophobic interaction operated in the complexation processes of the hosts. In addition, co-inclusion of the solvent molecule into the CyD cavity of **2** would not be achieved because of the bulkiness of the ferrocene moiety and the guest molecule. Therefore, the relatively large contribution of the van der Waals interaction in the complexation of **2** resulted in the difference that the relatively large binding constants of **2** in EG solutions. Since γ-CyD is likely to be more flexible than β-CyD, it is suggested that guest-induced ring conformation change occurred, leading adaptation of the shape of **2** to a guest molecule to acquire a large contact area between the molecules.

Detailed experiments on the binding constants of **1** and **2** for the guests in several EG content solutions were performed and the results are summarized in Tables 4 and 5. For each host–guest combination, the binding constants decreased with increasing EG content in the solution containing **1** or **2**, as being expected. These results confirmed the contribution of the hydrophobic interaction of the complexation processes as well as the van der Waals interactions, and might exclude the co-inclusion of the EG molecule into the CyD cavity of **1** and **2** to form a multiple component system.

In conclusion, the ferrocene-appended CyDs of **1**—**4** showed different complexation behavior with respect to the intra- and intermolecular host–guest complexation in 20% EG aqueous and pure EG solutions. The results obtained here will be applicable to constructing artificial redox-enzyme mimics.[20)]

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