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UNIQUE BINDING BEHAVIOR OF γ-CYCLODEXTRIN BEARING A FERROCENE MOIETY

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The analysis of circular dichroism variations induced by guests reveals that the binding ability of γ-cyclodextrin bearing a ferrocene moiety is much lower in water (<10%) but higher in ethylene glycol (>300%) than that of the corresponding β-cyclodextrin derivative.

KEYWORDS ——— γ-cyclodextrin; inclusion complex; host-guest complex; ferrocene; circular dichroism; solvent effect

Cyclodextrins (CDs) form inclusion complexes with a variety of guest molecules in water. On this basis, they have been widely used as a model of enzymes.[1)] Much effort has been devoted also to studying their abilities as drug carriers or stabilizers.[2,3)] The CDs, which are commercially available, are α, β and γ consisting of six, seven and eight D-glucopyranose units, respectively. In comparison with smaller α- and β-CDs, γ-CD has not been used frequently due to its large cavity size. However, γ-CD has recently been shown to include two guest molecules in its large cavity.[4)] When a naphthalene moiety is covalently attached to γ-CD, the moiety acts as a spacer which enables the cavity to accommodate one guest molecule by narrowing the large cavity.[5)] This is a report on the way the binding behavior changes when ferrocene, which is too bulky to act as a spacer, is attached to γ-CD as shown by **1**. We also describe the effect of the solvent on the binding ability of **1**. We found that the binding ability of **1**, which is much poorer than that of the corresponding β-CD derivative **2** in water, is better than that of **2** in ethylene glycol.[6)]

The γ-CD derivative **1** was prepared by the reaction of 6-O-2-naphthylsulfonyl γ-CD (0.665 mmol) with potassium ferrocenecarboxylate (1.73 mmol) in dimethyl sulfoxide (20 ml) at 80 °C for 3 h. Repeated recrystallization of the crude product from the mixed solvent of n-BuOH, ethanol, and water (5:4:3 by volume) afforded pure **1** as a pale brown powder (24% yield). **1** was characterized by ^{1}H NMR, UV, IR spectroscopy and elemental analysis (Found: C, 43.38; H, 6.14. Calcd for $C_{59}H_{88}O_{41}Fe \cdot 7H_2O$: C, 43.33; H, 6.29). Rf 0.42 (n-PrOH, H_2O 3:1).

1: γ-CD

2: β-CD

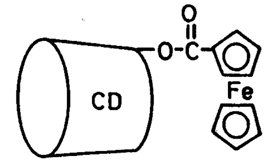

Figure 1 shows the circular dichroism spectra of **1** and **2** in three solvent systems of water, ethylene glycol and 1:1 ethylene glycol-water. A positive peak at 475 nm is seen for **2** in all solvent systems (only the spectra of **2** in water are shown in Fig. 1). The circular dichroism pattern of **1** in water is virtually the same as that of **2** with a slight shift of the positive peak to 465 nm while the patterns of **1** in ethylene glycol and 1:1 ethylene glycol-water are different from that in water, exhibiting a peak at 440-455 nm and a trough at 500-510 nm. Since the absorption band in the 400-550 nm region has been assigned to the d-d transition of iron which contains two components with absorption maxima at shorter and longer wavelengths in the region,[7)] the peak and trough can be interpreted in terms of the induced circular dichroism bands corresponding to the two absorption components. On addition of guests, the circular dichroism intensity simply decreases for the aqueous solution of **1** and all the solutions of **2** while the circular dichroism pattern changes to one with a negative band in the 475-480 nm region for **1** in ethylene glycol and 1:1 ethylene glycol-water. This suggests that the ferrocene moiety changes its location by guest binding, being excluded almost completely from the cavity in the former case and being moved inside the cavity toward the rim of CD in the latter case.

Table I shows the binding constants of 1:1 complexes of **1** and **2** for various guests, which were obtained by analyzing the guest-induced variations of the circular dichroism intensities at appropriate wavelengths. The binding constants of **1** in water are much smaller than those of **2**, ranging from 3.2 to 9.9% of the values for **2**. Of the guests examined, both **1** and **2** bind (-)-borneol most strongly, so (-)-borneol was used as a guest to study the binding abilities of **1** and **2** in different solvent systems. For both hosts, the binding is particularly dependent on the solvent composition. It becomes weaker for **2** in the order water>1:1 ethylene glycol-water>ethylene glycol, but for **1** it changes in the complicated order 1:1 ethylene glycol-water>water>ethylene glycol. Since water plays an important role in cyclodextrin complexation, it is readily understandable that ethylene glycol tends to weaken the binding of **1** and **2**. The curious result is that **1** gives the largest binding constant in 1:1 ethylene glycol-water. Perhaps ethylene glycol participates in the complexation

Table I. Binding Constants of Ferrocene-Appended Cyclodextrins[a)]

Guest	Solvent[b)]	Binding constant (K/mol^{-1} l) **1**	**2**	100[K(**1**)/K(**2**)]
Cyclohexanol	H_2O	4.3	135	3.2
Nerol	H_2O	33.3	337	9.9
Benzyl alcohol	H_2O	0.61	17.4	3.5
Cyclohexanone	H_2O	4.4	48.7	9.1
(-)-Borneol	H_2O	193	2785	6.9
(-)-Borneol	H_2O-EG(1:1)	210	594	35
(-)-Borneol	EG	71	22.6	314

a) Measured at 25 °C. Errors are within ±5%. b) EG: ethylene glycol.

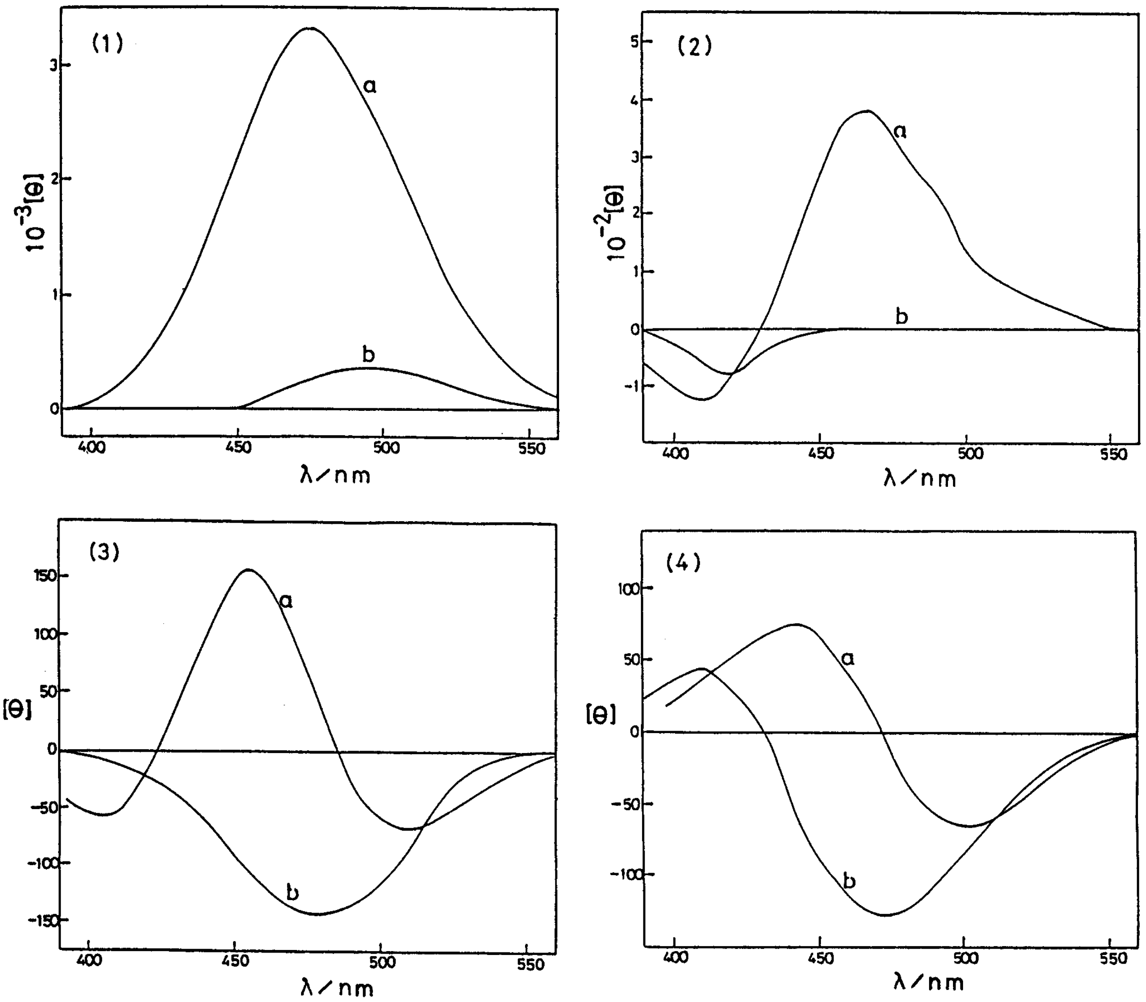

Fig. 1. Circular Dichroism Spectra of Ferrocene-Appended Cyclodextrins, Alone (a) or in the Presence of Guests (b)
(1) host: **2** (0.247 mmol l^{-1}); guest: cyclohexanol (26.9 mmol l^{-1}); solvent: water, (2) host: **1** (1.26 mmol l^{-1}); guest: cyclohexanol (133 mmol l^{-1}); solvent: water, (3) host: **1** (1.34 mmol l^{-1}); guest: (-)-borneol (4.46 mmol l^{-1}); solvent: 1:1 ethylene glycol-water, (4) host: **1** (2.69 mmol l^{-1}); guest: (-)-borneol (28.4 mmol l^{-1}); solvent: ethylene glycol.

of **1** in a manner not yet well characterized.

Detailed examination of the results reveals that the binding constant of **1** in ethylene glycol is 37% of that value in water while the binding constant of **2** in ethylene glycol is only 0.8% of the value in water. Thus, the binding ability of **1** in ethylene glycol is 3-fold higher than that of **2**, while in water the binding ability of **1** is only 6.9% of that of **2**. The difference in binding in **1** and **2** may be related to their different cavity sizes. The ferrocene moiety is most likely to be axially included in the smaller cavity of **2**, but it may be allowed to take both axial and equatorial orientations in the larger cavity of

1.[8)] The circular dichroism patterns of **1** in water are similar to those of **2**, suggesting that in water the axial inclusion of the ferrocene moiety takes place in **1**. On the other hand, the different circular dichroism patterns of **1** in 1:1 ethylene glycol-water and in ethylene glycol are probably related to the equatorial inclusion of the ferrocene moiety.[6b)]

These results reveal that the binding ability of the γ-CD derivative **1** is much lower in water but higher in ethylene glycol than that of the β-CD derivative **2**. This unique property of **1** is probably related to its large γ-CD cavity in which the ferrocene moiety is allowed to take different orientations. Further work is needed to determine how ethylene glycol influences the binding and the circular dichroism of **1**.

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