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Fluorescence Properties, Induced-Fit Guest Binding and Molecular Recognition Abilities of Modified γ-Cyclodextrins Bearing Two Pyrene Moieties

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γ-Cyclodextrin (γ-CD) derivatives bearing two pyrene moieties at AB, AC, AD, and AE glucose units (**1–4**), were prepared as chemosensors for detecting molecules by their guest-responsive excimer emission intensity. All these hosts exhibited predominant excimer emission and remarkable induced circular dichroism (ICD) in a 20% dimethyl sulfoxide aqueous solution. The excimer emission and the ICD intensities mostly decreased upon addition of a variety of organic guests. The result indicates that **1–4** undergo an induced fit conformational change upon complex formation, excluding the pyrene moieties from inside to outside the γ-CD cavity in guest binding. The guest-induced fluorescence variations were analyzed by 1:1 host–guest stoichiometry and the obtained binding constants were roughly correlated with the guest-induced fluorescence variations. The binding and fluorescence data revealed that **1–4** have remarkable molecular recognition abilities for bile acids and other guests.

Molecular recognition by artificial systems is a great desire of many chemists and has been intensively investigated. Recently, many chromophore-modified hosts have been prepared as chemosensors for detecting ions or molecules. In many of these systems, spectroscopic variations associated with guest binding have been utilized for the sensing purpose.[1] Cyclodextrins (CDs) are cyclic oligosaccharides which have six or more of D-(+)-glucopyranose units. Among them, the members composed of six (α-CD), seven (β-CD), and eight (γ-CD) D-(+)-glucopyranose units are most popular and they have remarkable abilities to form inclusion complexes in aqueous solution by accommodating a guest molecule in their central cavity.[2] We have prepared a variety of fluorescent CDs which have one or two fluorophore units as fluorescent chemosensors for detecting molecules.[3] Pyrene is well-known to exhibit excimer emission and the guest-induced variation in the pyrene excimer emission intensity has been used in some of chemosensors for detecting metal cations[4] or molecules.[5] Inclusion of pyrene in the CD cavity may also be interesting, but such inclusion may be limited to γ-CD because the cavity sizes of α-CD and β-CD are too small to include the pyrene ring.[6] The γ-CD derivatives with an appending pyrene ring form an association dimer that exhibits a strong excimer emission arising from the face-to-face interaction between the two pyrene rings in the dimer.[7] This system exhibits the guest-induced reduction in the excimer emission intensity upon guest addition, due to the conversion from the dimer to 1:1 host-guest complexes, and was used as a sensory system for detecting organic compounds.[7b] However this system has one demerit as a sensor from the practical point of view, because the formation of the association dimers depends on the concentration of the γ-CD derivatives. In the present study, γ-CD derivatives **1**–**4** bearing two pyrene moieties (Chart 1) were synthesized to avoid this demerit and thereby to construct more effective sensory systems. Since γ-CD consists of eight glucose units, there are four isomers (**1**:AB, **2**:AC, **3**:AD, and **4**:AE) when its glucose residues are abbreviated as A, B, C, D... in clockwise order. In these systems, the two pyrene moieties are located at different positions on one γ-CD unit and it is interesting how the geometrical isomers of **1**–**4** respond differently to the added guest species. In the preliminary study on modified CDs bearing two pyrene units, the chromophores are directly attached to the primary hydroxy groups by ester bond.[7d] In such a case, the mobility of pyrene units is restricted because of the short linker between γ-CD and pyrene moieties. γ-CD derivatives **1**–**4** prepared in this study have a longer linker between γ-CD and the pyrene moiety and improved flexibility of the appending moiety may be expected. Their abilities as fluorescent chemosensors and

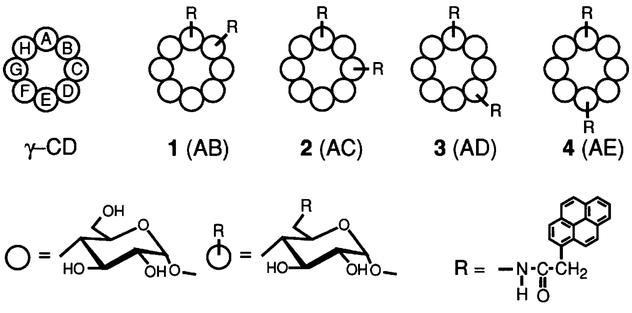


Chart 1.

guest-induced conformational changes are described in this paper.

Results and Discussion

Fluorescence Spectra of 1–4. Figure 1 shows the fluorescence spectra of **1–4** (1.5 × 10^{-7} M) in a 20% DMSO aqueous solution excited at 344 nm (M = mol dm^{-3}). All derivatives show weak normal emission with the peaks around 380 and 400 nm, and extremely strong excimer emission with the peak around 490 nm. The result indicates that the two pyrene rings of **1–4** can interact with each other in a face-to-face fashion. From the measurement of UV spectra of **1–4** at different concentrations, we found that the absorption intensities at 346 nm are proportional to their concentrations and there is no concentration dependency. This result confirms that the excimer emission shown by **1–4** arises not from the intermolecular pyrene-pyrene interaction but from the intramolecular one.

ICD Spectra of 1–4. An achiral guest like a pyrene molecule included in a chiral CD cavity may exhibit an induced circular dichroism (ICD) in its absorption regions. Figure 2 shows the ICD spectra of **1–4** (2.0 × 10^{-5} M) in a 20% DMSO aqueous solution. Pyrene shows an absorption spectrum including ^1L_a and ^1B_b transition bands around 350 and 280 nm, respectively.[8,6b] For AB, AC, and AD, the ICD spectra exhibit a positive ICD in the ^1B_b transition region around 280 nm and a negative one in the ^1L_a transition region around 350 nm. For AE, the spectrum shows a negative ICD in the ^1L_a transition region around 350 nm, like other isomers, but shows a negative one in the ^1B_b transition region around 280 nm, and the ICD intensities in both transition regions are smaller than those of the other isomers. Since these hosts show ICD spectra, their pyrene units may exist inside the cavity, but it is not easy to suppose the exact locations for these isomers due to the complicated ICD spectra.

Temperature and Organic Solvent Effects on Fluorescence Spectra. Figure 3-a shows the fluorescence spectra of **3** (2.0 × 10^{-5} M) in a 20% DMSO aqueous solution at various temperatures. The intensities of both monomer and excimer emissions decrease with rising temperature. To get the detailed information, we plot the excimer (490 nm) to monomer (378 nm) fluorescence ratio (I_{ex}/I_m) of **1–4** against temperature in Fig. 4-a. For all hosts, the ratio of the excimer decreases with increasing temperature to a greater or a lesser extent depending on the host species, and this suggests that the pyrene moieties,

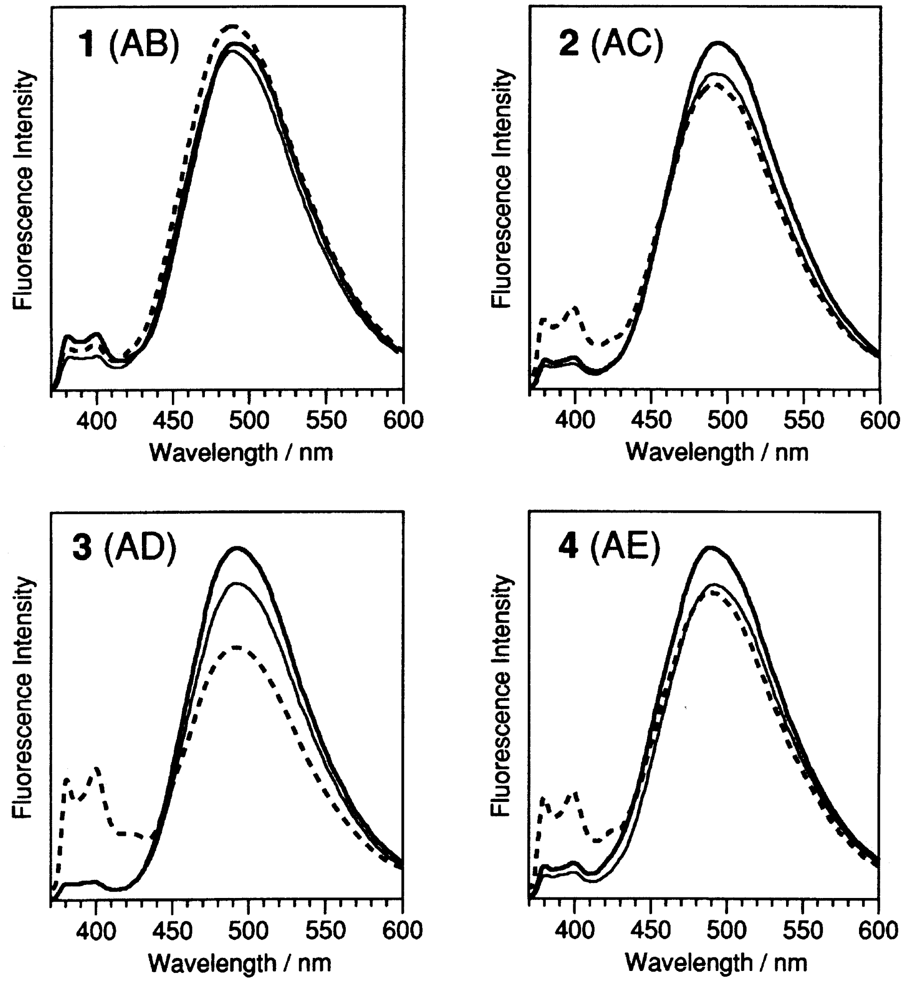


Fig. 1. Fluorescence spectra of **1**, **2**, **3**, and **4** alone (0.15 μM; ——), in the presence of (+)-borneol (1 mM; ——) and lithocholic acid (20 μM; - - -) in a 20% DMSO aqueous solution at 25 °C. Excitation wavelength was 344 nm.

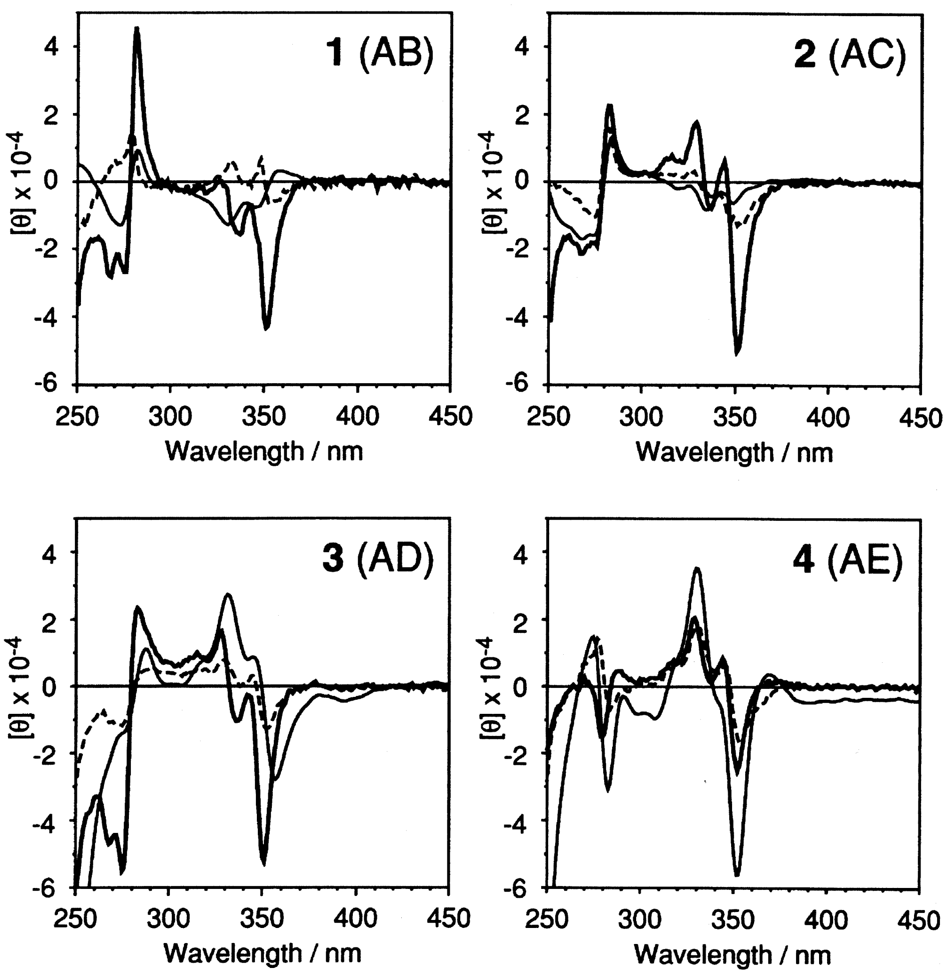


Fig. 2. Circular dichroism spectra of **1**, **2**, **3**, and **4** alone (20 μM; ——), and in the presence of cyclododecanol (300 μM; ——) and lithocholic acid (**1** : 40 μM, **2**–**4** : 100 μM; - - -) in a 20% DMSO aqueous solution at 25 °C.

which form the stable excimer inside the CD cavity, tend to be excluded to outside the cavity at high temperatures, resulting in the depressed excimer formation. However, we note that there is another possibility: that the temperature effect of fluorescence spectra can also be explained by inactivation of the excimer state at high temperature. Figure 3-b shows the fluorescence spectra of **3** at different contents of DMSO in aqueous solutions. The monomer emission intensity increases with increasing DMSO content, while the excimer intensity increases below ca. 60% DMSO content and is almost constant above the DMSO content. The excimer (490 nm) to monomer (378 nm) intensity ratios (I_{ex}/I_m) of **1**–**4** are plotted against the DMSO content in Fig. 4-b. In 0.1% DMSO content, **3** has the largest ratio among the hosts, implying that **3** has a conformation favorable for forming an excimer. In the cases of **2**, **3**, and **4**, the excimer ratio decreases with increasing DMSO content, indicating that DMSO weakens the hydrophobic interaction between the two pyrene units. The locational change of the two pyrene units from inside to outside the cavity occurring with the cancellation of stacking between the two pyrene units may be reflected in the decrease of the excimer intensity ratio. In contrast to **2**–**4**, the excimer ratio of **1** is almost constant over the whole range of DMSO content due to the neighboring location of the two pyrene units in **1**. On the other hand, the result that the excimer emission intensity is still remarkable in 100% DMSO solution of **1**–**4** demonstrates that the two pyrene units can interact with each other both inside and outside of the γ-CD cavity, based on the proximal locations.

Temperature and Organic Solvent Effects on ICD Spectra. Figure 5-a shows the ICD spectra of **3** at various temperatures. At low temperature (10 °C) the ICD intensities are large, and the intensities decreased with increasing temperature. The intensity of ICD at 85 °C becomes one third of that at 10 °C. This temperature effect is explained in terms of limited mobility and restricted conformation of the pyrene moieties included in the γ-CD cavity at lower temperatures. On the other hand, when the temperature is high, the mobility of pyrene moieties may be high enough to be excluded from the CD cavity, resulting in the weak ICD that reflects the relatively free movement of the chromophores. This tendency was observed for all isomers, and the ICD intensities of **1**–**4** at 351 nm are plotted against the temperature in Fig. 6-a. For all isomers, the intensities of ICD at 85 °C become less than one-third the values at 10 °C. Figure 5-b shows the ICD spectra of **3** at different

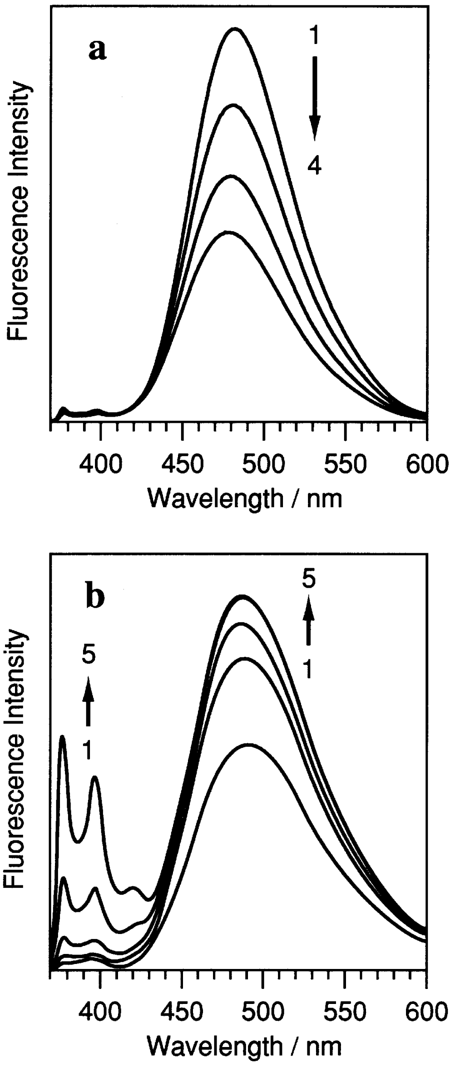


Fig. 3. Fluorescence spectra of **3** (0.15 μM) (a) in a 20% DMSO aqueous solution at different temperatures (1, 10; 2, 25; 3, 40; 4, 55 °C) and (b) in aqueous solutions with different DMSO contents (1, 0; 2, 20; 3, 40; 4, 60; 5, 80%) at 25 °C. Excitation wavelength was 344 nm.

contents of DMSO in aqueous solution. Similarly to the temperature effect on the ICD intensities, the ICD intensity decreases with increasing DMSO content. When the DMSO contents is 20%, the ICD intensity around 350 nm is strong, but the intensity becomes very small in an 80% DMSO aqueous solution. The organic solvent cancels the hydrophobic interaction between CD cavity and pyrene moieties, as reflected by the decrease in ICD, and this is consistent with the results of the observations in fluorescence spectra. The ICD intensities of **1**–**4** at 351 nm are plotted against the DMSO content in Fig. 6-b. The results indicate that all isomers show very weak ICD in 80% DMSO aqueous solution. Both high temperature and high DMSO concentration can change the pyrene location of **1**–**4** from inside to outside the cavity and this result is consistent with that obtained from the fluorescent data.

Guest Induced ICD Changes. Figure 2 shows the ICD spectra of **1**–**4** alone and in the presence of two kinds of guests which have quite different structures. One is lithocholic acid, which has a bulky rigid frame, and the other is cyclododecanol, which has a cyclic flexible frame. The peak intensity at 350 nm decreases upon addition of the guests for **1** and **2**. However the spectral changes for **3** and **4** are different from those of **1** and **2**. For **3**, the peak intensity decreased like the former two hosts when lithocholic acid was added, but a decrease of the intensity and a shift of the peak were observed when cyclododecanol was added. For **4**, a slight reduction in the intensity was observed upon addition of lithocholic acid, while a considerably larger enhancement of the peak intensity was observed upon addition of cyclododecanol. Such results suggest that the complexes of **3** and **4** exhibit different ICD patterns depending on the guest species. This finding demonstrates that these hosts recognize the shape of the guests and form complexes with the guests with distinctly different structures.

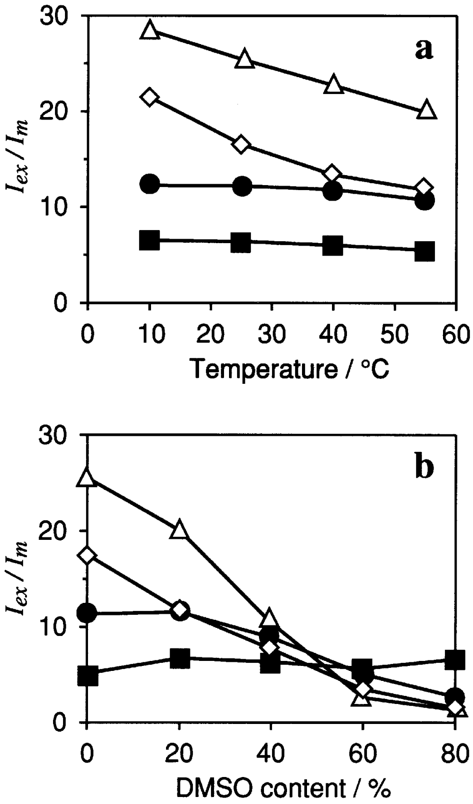


Fig. 4. The excimer to monomer fluorescence intensity ratios (I_{ex}/I_m) of **1**–**4** (0.15 μM; ■, **1**; ●, **2**; △, **3**; ◇, **4**) as a function of (a) temperature (DMSO content: 20%) and (b) DMSO content (25 °C). Excitation wavelength was 344 nm. I_{ex} and I_m were measured at 490 and 378 nm, respectively.

Fluorescent Sensors Using Excimer Emission. As described in the previous section, **1**–**4** show remarkably strong excimer emission and change the emission intensity associated with the formation of intermolecular inclusion complexes with guest molecules. Figure 7 shows the fluorescence spectra of **3**, alone and in the presence of various concentrations of litho-

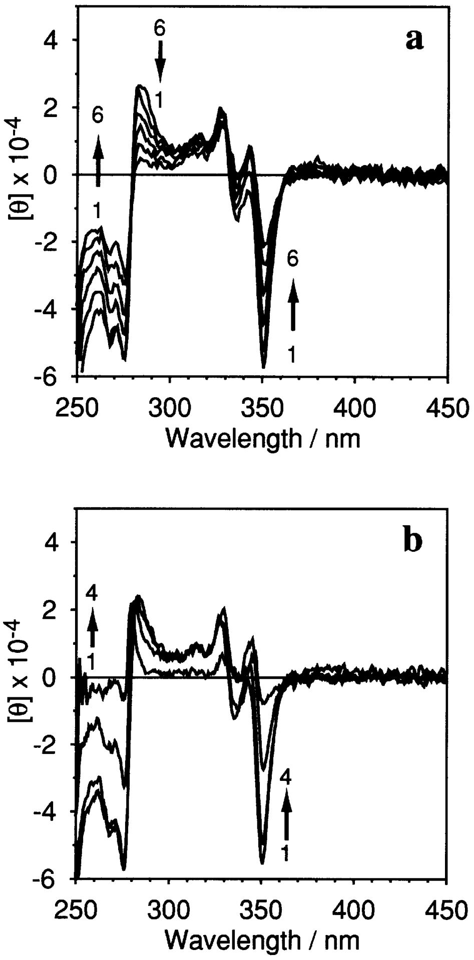


Fig. 5. Induced circular dichrosim spectra of **3** (20 μM) (a) in a 20% DMSO aqueous solution at different temperatures (1, 10; 2, 25; 3, 40; 4, 55; 5, 70; 6, 85 °C) and (b) in aqueous solution with different DMSO contents (1, 20; 2, 40; 3, 60; 4, 80%) at 25 °C.

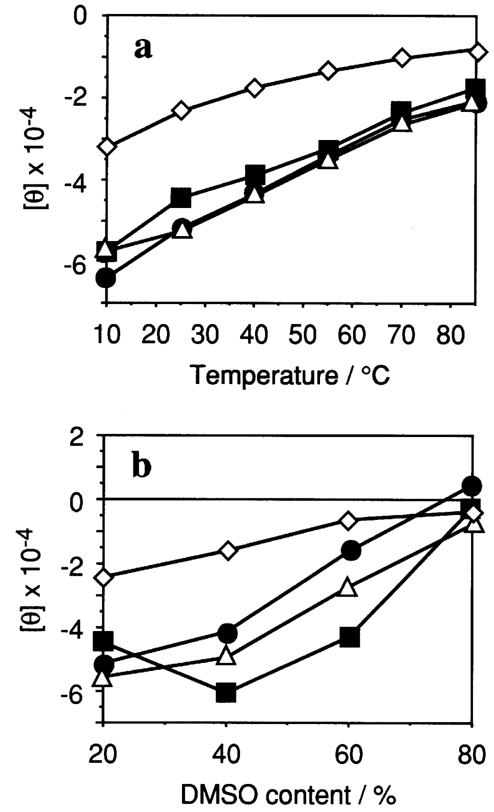


Fig. 6. The circular dichroism intensities of **1**–**4** (20 μM; ■, **1**, ●, **2**; △, **3**; ◇, **4**,) at 351 nm in aqueous solution as a function of (a) temperature (DMSO content: 20%) and (b) DMS0 content (25 °C).

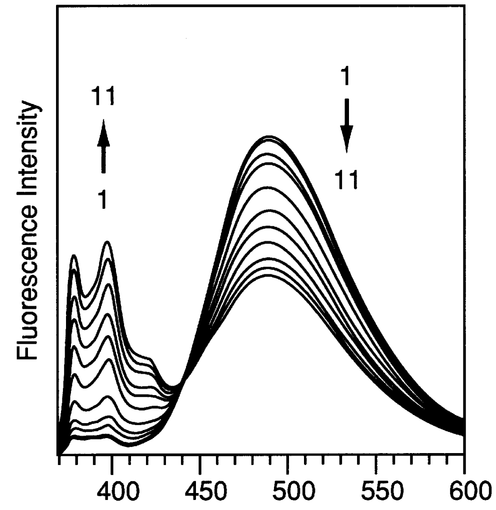


Fig. 7. Fluorescence spectra of **3** (0.15 μM) in a 20% DMSO aqueous solution at various lithocholic acid concentrations (1, 0; 2, 1; 3, 3; 4, 5; 5, 10; 6, 15; 7, 20; 8, 25; 9, 30; 10, 35; 11, 40 μM). Excitation wavelength was 344 nm.

cholic acid in a 20% DMSO aqueous solution at 25 °C. The peak intensity of the excimer emission around 490 nm decreases with increasing concentration of lithocholic acid, while the monomer emission peaks around 380 and 400 nm are enhanced by the presence of the guest. This observation indicates that two pyrene rings, which are included in the cavity and form the excimer, are excluded from the cavity associated with the guest accommodation and tend to be separated from each other (Fig. 8). The isoemissive point was observed at 445 nm, which indicates the existence of equilibrium between the self-inclusion complex and the 1 : 1 host–guest complex. The binding constants (K) of **1**–**4** for several guests were obtained from the guest-induced variations in excimer emission intensity using the same procedure as reported previously.[9,10] Figure 9 shows the guest-induced change in emission intensity at 490 nm for **3** as a function of concentration of cyclododecanol. A typical saturation curve for **3** and cyclododecanol was obtained by a nonliner least squares fitting procedure. The same curve-fitting analysis could be applied to other hosts and guests with good fitting. The value of $\Delta I/I_0$ was used as the measure of the sensitivity of **1**–**4**, where $\Delta I = I_0 - I$, and I_0 and I are the excimer emission intensities in the absence and presence of guests, re-

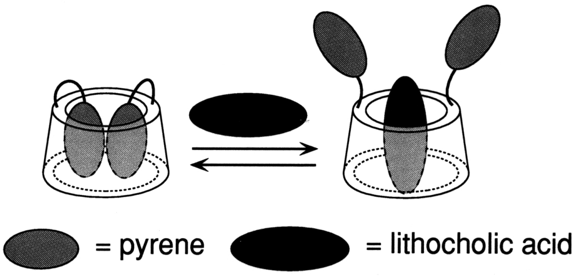


Fig. 8. Schematic illustration of the equilibrium between intramolecular and intermolecular inclusion complexes.

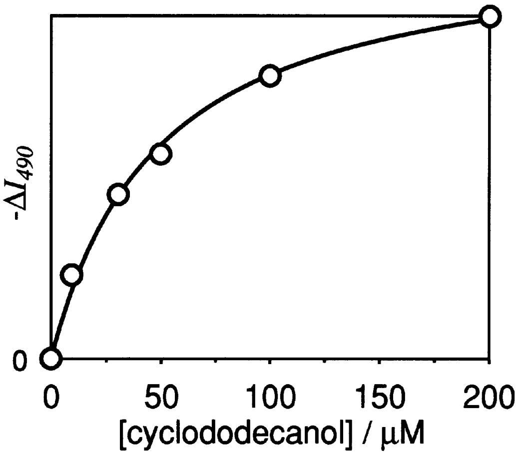


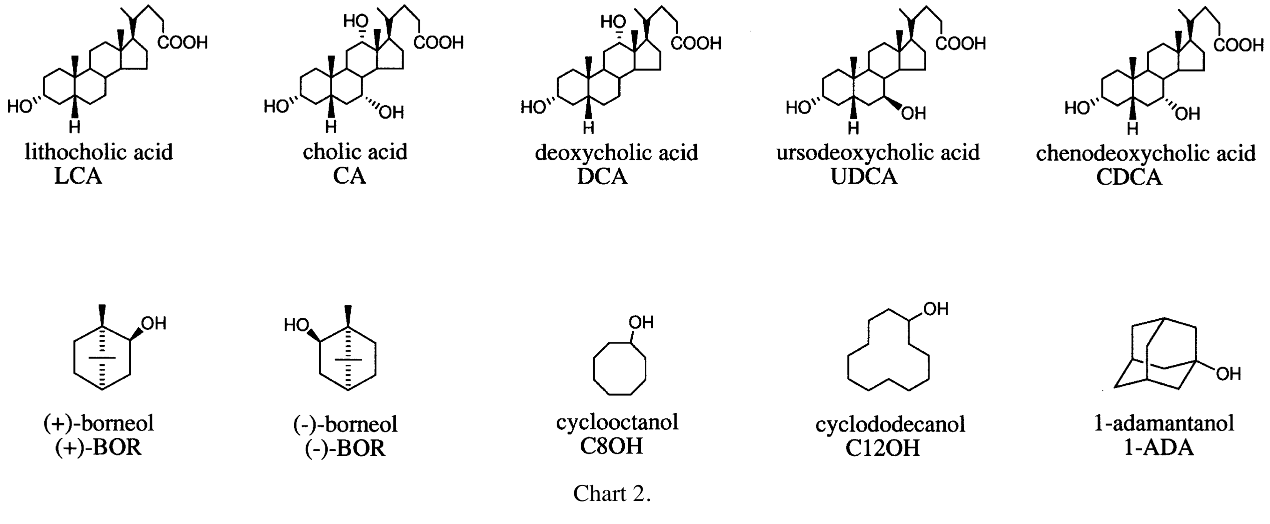
Fig. 9. Curve-fitting data for the fluorescence intensitites of **3** (0.15 μM) at 490 nm at different concentrations of cyclododecanol at 25 °C.

Table 1. Binding Constants of **1**, **2**, **3**, and **4** for Various Guests[a)]

	K/M^{-1}			
Guests	**1** (AB)	**2** (AC)	**3** (AD)	**4** (AE)
LCA	b)	89600	19300	87600
CA	c)	c)	18900	14800
DCA	c)	28600	38800	46900
UDCA	c)	c)	19200	51200
CDCA	c)	32500	23500	70000
(+)BOR	c)	3550	2240	4540
(−)BOR	c)	4300	2720	12600
C8OH	b)	b)	9980	6630
C12OH	9300	17400	20700	69600
1-ADA	748[d)]	144[d)]	347[d)]	433[d)]

a) The binding constants of **1**–**4** (0.15 μM) were measured in a 20% DMSO aqueous solution at 25 °C. b) Fluorescence variations did not show the typical saturation curve. c) Fluorescence variations were too small to be measured accurately. d) These binding constants were determined by circular dichroism variations.

spectively, measured at 490 nm. The structures of the guests used in this study are shown in Chart 2. The binding constants are listed in Table 1, and the sensitivities are shown in Fig. 10. For **1**, the binding constants to most of the guests were not obtained because of subtle variations of excimer intensity. This result suggests that the two pyrene moieties in **1** are unlikely to be kept separated from each other even if they are excluded from the cavity, since the two fluorophores are proximally located. When five biologically important steroidal compound; lithocholic acid (LCA), cholic acid (CA), deoxycholic acid (DCA), ursodeoxycholic acid (UDCA), and chenodeoxycholic acid (CDCA) were used as guests to **1**, remarkable differences in sensitivities among them were observed in spite of the fact that their structures are similar and all of them have a steroidal framework. For CA and DCA, which have a hydroxy group at C-12 of the steroidal framework, the excimer emission decreased upon addition of the guests and the $\Delta I/I_0$ values of the sensitivities are minus. On the other hand, for LCA, UDCA, and CDCA, which have no hydroxy group at C-12, the excimer emission increased with the plus values of $\Delta I/I_0$. These increases of the excimer emission intensity were seen only for pairs of these three guests and **1**. Among the five steroidal guests, LCA, which has the least hydroxy group, was detected with the largest sensitivities by **1**–**4**. This observation suggests that the polarity of the guests, in addition to size, is an important factor for



lithocholic acid
LCA

cholic acid
CA

deoxycholic acid
DCA

ursodeoxycholic acid
UDCA

chenodeoxycholic acid
CDCA

(+)-borneol
(+)-BOR

(-)-borneol
(-)-BOR

cyclooctanol
C8OH

cyclododecanol
C12OH

1-adamantanol
1-ADA

Chart 2.

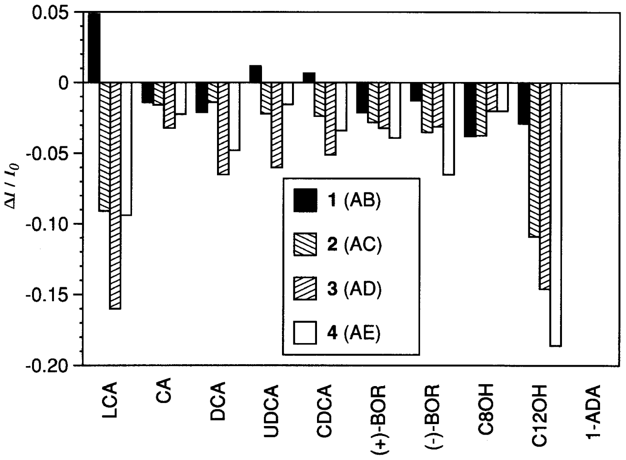


Fig. 10. The sensitivity values ($\Delta I/I_0$) of **1**–**4** (0.15 μM) in a 20% DMSO aqueous solution for various guests measured at 490 nm. [LCA], [CA], [DCA], [UDCA], [CDCA] = 10 μM. [(+)-BOR], [(−)-BOR], [1-ADA], [C8OH], [C12OH] = 100 μM.

the sensitivities to be determined. The sensitivity values of **3** for these five steroidal guests were larger than any other hosts, but **3** does not show the largest binding constants for these guests. In case of cyclododecanol, the binding constants and the sensitivity values have good correlations. The binding constants of **1** and **2** for cyclooctanol were not obtained because they do not show the typical saturation curves for determining the binding constants. The binding constants of **3** and **4** for cyclododecanol are much larger than those for cyclooctanol, indicating that the cavity size is appropriate for cyclododecanol but too large for cyclooctanol. This result is in good agreement with the data of their sensitivity values. It is interesting to examine the ability of **1**–**4** in chiral recognition. The data for (+)- and (−)-borneol may be used as a measure for it. Although the binding constants of **2** and **3** for the enantiomers are almost the same, appreciable chiral recognition with 3-fold (−)-isomer preference was observed for **4** and this result is consistent with the data of their sensitivity values. The binding constants and sensitivities of the hosts to 1-adamantanol, which is known to be a good guest to β-CD, have not been determined because no variations were induced in the fluorescence spectra upon addition of 1-adamantanol. However the binding constants were determined from the analysis of the circular dichroism spectra. All binding constants for 1-adamantanol were less than 1000 M^{-1}, and these values were much smaller than those of β-CD and its derivatives reported previously.[3] This indicates that the shape of the adamantane unit is not appropriate to be snugly accommodated in the cavity of γ-CD.

Conclusions

The hosts **1**–**4**, which have two pyrene moieties at different positions of the primary hydroxy side of γ-CD, exhibit a strong excimer emission and mostly decreased its emission intensity upon addition of various guest compounds. The dichroism intensity of **1**–**4** also decreased upon guest addition. The spectral behavior of the fluorescence and circular dichroism spectra revealed that **1**–**4** change the location of the pyrene moieties from inside to outside the γ-CD cavity upon guest accommodation. The inside-to-outside conformational change of the hosts was also induced by increasing temperature or by increasing DMSO content in aqueous solution. The analysis of the guest-induced variations in the excimer emission intensity gave binding constants of the 1 : 1 host–guest stoichiometry, and the values are reflected in the sensitivity value of $\Delta I/I_0$. All these results demonstrate that **1**–**4** can be used as fluorescent chemosensors for detecting wide-range molecules in aqueous solution.

Experimental

Materials. γ-Cyclodextrin was kindly provided as a gift by Nihon Shokuhin Kako Co., Ltd and was used after two recrystallizations from water. 1-Pyreneacetic acid and all guest reagents were purchased from chemical suppliers and were used without further purification.

Measurements. Fluorescence measurements were done on a Hitachi 850 fluorescence spectrophotometer and circular dichroism spectra were recorded on a JASCO J-720 spectropolarimeter. The excitation wavelength for fluorescence measurements was 344 nm. The binding constants of 1 : 1 complexation were obtained by the analysis of the guest-induced fluorescence variations using the same procedure as reported previously.[9,10]

Synthesis. The synthesis of bis(2-naphthylsulfonyl)-γ-CD was performed by the same method as reported previously.[11] Diamino-γ-CDs were synthesized from the corresponding bis(2-naphthylsulfonyl)-γ-CDs by the modified method used for monoamino-γ-CD,[10] and the procedures are described below.

6^A, 6^B-Bis(6-deoxy-6-amino)-γ-CD (AB). The corresponding bis(2-naphthylsulfonyl)-γ-CD (131 mg) was dissolved in DMF (4 mL). To this solution, an excess amount of sodium azide (153 mg) was added. The reaction was carried out with stirring at 75 °C for about 10 h. After the mixture was cooled to room temperature, triphenylphosphine (102 mg) was added and the solution was kept stirring for 1 h. To the solution was added 200 μL of concentrated NH_3 aq, and the mixture was stirred at room temperature for about 20 h. The progress of reaction was monitored by TLC (SiO_2; 2-propanol/water/ethyl acetate/NH_3 aq = 5 : 4 : 3 : 1 by volume). After the removal of the precipitate by filtration, the filtrate was poured into 100 mL of acetone and the formed precipitates were collected by filtration. This crude product was used in the next step without further purification.

6^A, 6^X-Bis(6-deoxy-6-amino)-γ-CD (X = C, AC; D, AD; E, AE). These products were synthesized according to the same procedure as used for bis(6-deoxy-6-amino)-γ-CD (AB), and were used in the next step without further purification.

6^A, 6^B-Bis(1-pyreneacetylamino)-γ-CD (1: AB). 1-Pyreneacetic acid (47 mg), dicyclohexylcarbodiimide (DCC, 37 mg), and 1-hydroxybenzotriazole (HOBt, 27 mg) were dissolved in DMF (2 mL) and cooled to 0 °C. To this solution was added the corresponding crude bis(6-deoxy-6-amino)-γ-CD (ca. 60 mg), and the mixture was kept with stirring for 1h at 0 °C, and then for 24 h at room temperature. The progress of the reaction was monitored by TLC (SiO_2; 1-butanol/ethanol/water = 5 : 4 : 3 by volume). This reaction mixture was poured into acetone (100 mL) and the formed precipitates were collected by filtration. The precipitates were dissolved in a small amount of DMF and then the solution was poured into acetone (100 mL) again. The formed precipitates were collected by filtration and this acetone reprecipitation was repeated several times to remove the unreacted 1-pyreneacetic acid. The precipitates were dried in vacuo and then dissolved in a small amount of 50% DMF aqueous solution, and this solution was injected into a HPLC column (YMC ODS A-323, 10 × 250 mm). A linear gradient elution (35% CH_3CN aq–75% CH_3CN aq) was applied, and the UV absorption at 340 nm was monitored. The fractions containing **1** were collected, and after the removal of CH_3CN under reduced pressure, the resultant aqueous solution was lyophilized to give **1** as white powder (6 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.90–4.00 (m), 4.17–4.31 (m, 4H, CH_2CO), 4.81–4.98(m, 8H, C_1H), 7.90–8.38 (m, 18H, aromatic). Anal. Calcd for $C_{84}H_{102}N_2O_{40}\cdot10H_2O\cdot0.2C_3H_7NO$ (DMF): C, 51.46; H, 6.30; N, 1.56%. Found: C, 51.22; H, 5.82; N, 1.67%. TOFMS *m*/*z*: 1802.6. Calcd for $[M+Na]^+$: 1802.7.

6^A, 6^X-Bis(1-pyreneacetylamino)-γ-CDs (X = C, 2; D, 3; E, 4). These products were synthesized according to the same procedure as **1**. The ^{1}H NMR data of **2**–**4** were almost the same as those for **1**. Anal. Calcd for $C_{84}H_{102}N_2O_{40}\cdot10H_2O\cdot0.2C_3H_7NO$ (DMF): C, 51.46; H, 6.30; N, 1.56%. Found: **2**; C, 51.08; H, 5.94; N, 1.76%, **3**; C, 51.37; H, 5.94; N, 1.73%, **4**; C, 50.96; H, 5.97; N, 1.79%. TOFMS *m*/*z*: **2**; 1800.7, **3**; 1804.8, **4**; 1803.4. Calcd for $[M+Na]^+$: 1802.7.

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