Qualitative Determination of Bile Acids by Fluorescence Responses of Disubstituted γ -Cyclodextrins Having 2-(1-Naphthyl)propanoyl Residues

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Eight γ -cyclodextrin (γ -CyD) derivatives having two optically active (R)- or (S)-2-(1-naphthyl)propanoyl residues at the primary hydroxyl sides, which are 6A,6B-, 6A,6C-, 6A,6D-, and 6A,6E-positions (RR-AB, RR-AC, RR-AD, RR-AE, SS-AB, SS-AC, SS-AD, and SS-AE, respectively), were synthesized for investigating their fluorescence responses towards bile acids in a 10 vol.% ethylene glycol aqueous solutions. Strong intramolecular excimer fluorescence observed for RR-AD, RR-AE, SS-AD, and SS-AE is varied either strengthened or weakened direction based on the guest species. Although RR-AB, RR-AC, SS-AB, and SS-AC showed weak or no excimer fluorescence, some bile acids changed the monomer fluorescence intensity decreased, with excimer fluorescence being induced. By taking the fluorescence intensity changes as a sensitivity factor for detecting the guests, together with the shift in peak positions of the excimer fluorescence, one may qualitatively determine the type of bile acids in a solution at 50 mmol dm⁻³. No simple correlation is observed between the 1:1 host-guest binding constants and the sensing factors, which indicated that not only the binding strength but also the binding conformation governed the sensitivity and selectivity of the hosts.

Key Word : modified- γ -cyclodextrin, 2-(1-naphthyl)propanoic acid, fluorescence, chemosensor, bile acids.

1. Introduction

During the last decade, many studies have appeared on chemosensors based on the readily measurable spectral changes (ultraviolet-visible absorption, fluorescence, and circular dichroism) induced by the presence of the target compounds.¹⁻⁴⁾ Although cyclodextrins (CyDs),⁵⁾ which are water soluble oligosaccharides composed only of glucopyranose units, are spectroscopically inert compounds, if they are modified with a lumophore such as pyrenyl,⁶⁾ *p*-dimethylaminobenzoyl,⁷⁾ and dansyl⁸⁾ moieties, they can show guest-responsible fluorescence changes owing to environmental changes forced to the pendant groups by complexing with external guest species. The pattern of the fluorescence responses of CyDs having one lumophore is simple; only the intensity of the fluorescence is increased or decreased. On the other hand, CyDs having two lumophores exhibited the wide variety of responses in fluorescence because of the interactions among a CyD cavity and two lumophores involving excimer formation and excitation energy transfer.⁹⁻¹²⁾ This suggests that they have possibility on detection of the guest species

both in qualitative and quantitative manners. On the basis of this aspect, we have synthesized the eight γ -CyD derivatives having (R)- or (S)-2-(1-naphthyl)propanoyl moieties at the primary hydroxyl groups of the two different glucopyranose residues, which are 6A,6B-, 6A,6C-, 6A,6D-, and 6A,6E-positions (RR-AX; X=B, C, D, or E, respectively; Fig. 1a), and have investigated their molecular recognition and sensing abilities toward biologically important bile acids (Fig. 1b).

2. Experimental

2.1. Syntheses of RR-AX and SS-AX (X=B, C, D, or E)

Synthetic procedures of RR-AE and SS-AE were described elsewhere.¹³⁾ The other hosts were synthesized with a similar manner from corresponding ditosylated- γ -CyD¹⁴⁾ (150 mg, 0.093 mmol) and (R)- or (S)-sodium 2-(1-naphthyl)propanoate (100 mg, 0.45 mmol), which was prepared with the reported procedure.^{15,16)} The $[\alpha]_D^{25}$ values of (R)- and (S)-2-(1-naphthyl)propanoic acid were -119.7 or +118.6°, respectively (literature values¹⁵⁾ were -120.1 and +120.3°, respectively). Spectral data and results of elemental

analyses of RR-AB, RR-AC, RR-AD, SS-AB, SS-AC, and SS-AD are summarized as follows.

RR-AB: Yield 35%. FAB-MS m/z 1661 ($[M+H]^+$). IR (KBr) 1720 cm^{-1} (C=O). $^1\text{H-NMR}$ (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 1.48-1.54 (m, 6H, CH_3), 3.07-3.09 (m, 2H, CH), 3.3-3.9 (m, others, overlapped with H_2O), 4.05-4.46 (m, 6H, $\text{C}_6\text{-OH}$), 4.50-4.93 (m, 8H, $\text{C}_1\text{-H}$), 5.43-5.64 (m, 16H, $\text{O}_2\text{-H}$ and $\text{O}_3\text{-H}$), 7.39-7.57 (m, 14H, aromatics); Anal. Calcd for $\text{C}_{74}\text{H}_{100}\text{O}_{42} \cdot 5\text{H}_2\text{O}$: C, 50.74; H, 6.33%. Found: C, 50.71; H, 6.29%.

RR-AC: Yield, 38%. FAB-MS m/z 1661 ($[M+H]^+$). IR (KBr) 1720 cm^{-1} (C=O). $^1\text{H-NMR}$ (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 1.51-1.57 (m, 6H, CH_3), 3.00-4.00 (m, others, overlapped with H_2O), 4.26-4.60 (m, 6H, $\text{C}_6\text{-OH}$), 4.72-4.91 (m, 8H, $\text{C}_1\text{-H}$), 5.47-5.63 (m, 16H, $\text{O}_2\text{-H}$ and $\text{O}_3\text{-H}$), 7.40-8.07 (m, 14H, aromatics). Anal. Calcd for $\text{C}_{74}\text{H}_{100}\text{O}_{42} \cdot 10\text{H}_2\text{O}$: C, 48.26; H, 6.57%. Found: C, 48.26; H, 6.46%.

RR-AD: Yield 22%. FAB-MS m/z 1661 ($[M+H]^+$). IR (KBr) 1720 cm^{-1} (C=O). $^1\text{H-NMR}$ (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 1.48-1.54 (m, 6H, CH_3), 3.08-3.12 (m, 2H, CH), 3.3-4.0 (m, others, overlapped with H_2O), 4.18-4.44 (m, 6H, $\text{C}_6\text{-OH}$), 4.50-4.93 (m, 8H, $\text{C}_1\text{-H}$), 5.47-5.66 (m, 16H, $\text{O}_2\text{-H}$ and $\text{O}_3\text{-H}$), 7.37-8.04 (m, 14H, aromatics). Anal. Calcd for $\text{C}_{74}\text{H}_{100}\text{O}_{42} \cdot 12\text{H}_2\text{O}$: C, 47.33; H, 6.66%. Found: C, 47.12; H, 6.24%.

SS-AB: Yield 30%. FAB-MS m/z 1661 ($[M+H]^+$). IR (KBr) 1720 cm^{-1} (C=O). $^1\text{H-NMR}$ (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 1.51-1.57 (m, 6H, CH_3), 2.88-3.01 (m, 2H, CH), 3.3-3.9 (m, others, overlapped with H_2O), 4.00-4.59 (m, 6H, $\text{C}_6\text{-OH}$), 4.81-4.92 (m, 8H, $\text{C}_1\text{-H}$), 5.10-5.90 (m, 16H, $\text{O}_2\text{-H}$ and $\text{O}_3\text{-H}$), 7.35-8.09 (m, 14H, aromatics). Anal. Calcd for $\text{C}_{74}\text{H}_{100}\text{O}_{42} \cdot 5\text{H}_2\text{O}$: C,

50.74; H, 6.33%. Found: C, 50.71; H, 6.29%.

SS-AC: Yield 27%. FAB-MS m/z 1661 ($[M+H]^+$). IR (KBr) 1720 cm^{-1} (C=O). $^1\text{H-NMR}$ (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 1.51-1.57 (m, 6H, CH_3), 3.03-3.06 (m, 2H, CH), 3.3-4.1 (m, others, overlapped with H_2O), 4.16-4.40 (m, 6H, $\text{C}_6\text{-OH}$), 4.58-4.91 (m, 8H, $\text{C}_1\text{-H}$), 5.44-5.61 (m, 16H, $\text{O}_2\text{-H}$ and $\text{O}_3\text{-H}$), 7.40-8.13 (m, 14H, aromatics). Anal. Calcd for $\text{C}_{74}\text{H}_{100}\text{O}_{42} \cdot 7\text{H}_2\text{O}$: C, 48.72; H, 6.43%. Found: C, 49.72; H, 6.45%.

SS-AD: Yield 28%. FAB-MS m/z 1661 ($[M+H]^+$). IR (KBr) 1720 cm^{-1} (C=O). $^1\text{H-NMR}$ (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 1.46-1.53 (m, 6H, CH_3), 3.02-3.07 (m, 2H, CH), 3.3-3.8 (m, others, overlapped with H_2O), 4.03-4.30 (m, 6H, $\text{C}_6\text{-OH}$), 4.50-4.93 (m, 8H, $\text{C}_1\text{-H}$), 5.45-5.65 (m, 16H, $\text{O}_2\text{-H}$ and $\text{O}_3\text{-H}$), 7.38-8.11 (m, 14H, aromatics). Anal. Calcd for $\text{C}_{74}\text{H}_{100}\text{O}_{42} \cdot 10\text{H}_2\text{O}$: C, 45.17; H, 6.86%. Found: C, 45.35; H, 6.60%.

2.2. Measurements

Spectroscopic measurements were performed in a 10 vol.% Gethylene glycol aqueous solution (pH 7.4) owing to the poor solubility of the γ -CyD derivatives into pure water. Fluorescence spectra were recorded on a Jasco FP-770 spectrofluorophotometer. Circular dichroism spectra were recorded on a Jasco J-720 spectropolarimeter. All measurements were performed at 25 $^{\circ}\text{C}$. To obtain the sensing parameters ($\Delta I/I^0$) as well as the binding constants (K), a stock solution of the guests (5.0-0.005 mol dm^{-3} in ethylene glycol or MeOH) was added stepwise to the Gsolution containing the host. The sensing parameters were Gacquired at the constant guest concentration (50 mmol dm^{-3}). When the fluorescence intensity changes were not large enough to obtain binding constants, we used guest-induced circular dichroism spectral changes to obtain binding constants. The 1 : 1 host-guest binding constants were calculated with a non-linear least-square regression method.¹⁷⁾

3. Results and Discussion

3.1. Fluorescence and Circular Dichroism Spectra

Figure 2 shows the fluorescence spectra of the RR-AX and SS-AX types in a 10 vol.% ethylene glycol aqueous solutions. Apparent excimer fluorescence was observed for RR-AD, RR-AE, SS-AC, SS-AD, and SS-AE around 390-400 nm together with normal fluorescence around 330-340 nm. SS-AC also exhibited excimer fluorescence around 400 nm, but its peak position was obscure. The relative intensity of the excimer fluorescence was in the order of $\text{RR-AE} > \text{SS-AE} > \text{SS-AD} > \text{RR-AD} > \text{SS-AC}$. No excimer fluorescence was observed for RR-AB, RR-AC, and SS-AB. These facts indicate that the possibility of the formation of excimer would be governed by the distance between the carbonyl groups at the γ -CyD rim; the farther the inter-distance of the carbonyl groups, the higher the possibility of the formation of the excimer.

Figure 3 shows fluorescence spectral changes of RR-AE induced by deoxycholic acid (2) or hyodeoxycholic acid (3) as typical examples. As the concentrations of 2 or 3 increased, the monomer as well as the excimer fluorescence intensities changed. The stability of the excimer species is dependent on a type of the guests, as suggested by the decrease or increase in the excimer fluorescence intensities.

Figure 4 shows the circular dichroism spectra ($^1\text{B}_u$ region) of the hosts in a 10 vol.% ethylene glycol aqueous solutions. A negative trough and positive peak are observed around 227 and 217

Figure 1. Structures of γ -CyD derivatives used in this study (a), and bile acids used as guests (b).

nm, respectively, for RR-AX type and those are observed around 220 and 230 nm, respectively, for SS-AX type. The addition of bile acids changed the circular dichroism spectra of RR-AX type and SS-AX type (data not shown), which indicates that 2 should be bound by the cavities of the hosts with the location of the naphthyl moieties being changed.

Figure 2. Fluorescence spectra, excited at 280 nm, of RR-AX ($3.75 \text{ mmol dm}^{-3}$; left panel) and SS-AX (ca. $3.75 \text{ mmol dm}^{-3}$; right panel) in a 10 vol.% ethylene glycol aqueous solutions at 25°C .

Figure 3. Fluorescence spectra, excited at 280 nm, of RR-AE, alone ($3.75 \text{ mmol dm}^{-3}$) or in the presence of 50 mmol dm^{-3} of 2 or 3 in a 10 vol.% ethylene glycol aqueous solutions at 25°C .

Figure 4. Circular dichroism spectra of RR-AX (left panel) and SS-AX (right panel) in a 10 vol.% ethylene glycol aqueous solutions at 25°C .

Table 1. Sensing Factors ($\Delta I/I^0$) of RR-AX and SS-AX for Common Six Bile Acids at Their Concentration of $50 \mu\text{mol dm}^{-3}$

Host	$\Delta I/I^0$ ^{a)}					
	1	2	3	4	5	6
RR-AB (monomer)	-0.02	-0.01	-0.01	-0.02	-0.01	-0.07
(excimer)	0.14	0.31	0.16	0.20	0.13	-0.07
RR-AC (monomer)	-0.07	-0.10	-0.05	-0.08	-0.05	-0.10
(excimer)	0.48	0.92	0.68	0.66	0.53	0.14
RR-AD (monomer)	-0.09	-0.13	0.01	-0.06	-0.01	-0.06
(excimer)	0.30	0.59	-0.03	0.23	0.01	-0.15
RR-AE (monomer)	-0.12	-0.14	0.17	-0.09	0.10	0.02
(excimer)	0.03	0.13	-0.26	0.06	-0.26	-0.33
	(+7.0 nm) ^{b)}	(+8.5 nm) ^{b)}	(0 nm) ^{b)}	(+8.0 nm) ^{b)}	(+1.5 nm) ^{b)}	(0 nm) ^{b)}
SS-AB (monomer)	-0.12	0.00	-0.09	-0.06	-0.10	-0.28
(excimer)	0.00	0.02	0.17	0.12	0.07	0.00
SS-AC (monomer)	-0.02	-0.03	-0.04	-0.03	-0.09	-0.22
(excimer)	0.23	0.30	-0.47	-0.13	-0.35	-0.45
SS-AD (monomer)	0.13	0.18	0.01	0.09	-0.01	-0.13
(excimer)	-0.20	-0.32	-0.43	-0.29	-0.30	-0.54
SS-AE (monomer)	0.19	0.26	0.05	0.13	0.03	-0.04
(excimer)	-0.29	-0.42	-0.46	-0.38	-0.36	-0.59

a) Positive and negative signs indicate an increase and a decrease of the fluorescence intensities.

b) The values in parentheses are magnitude of shift in excimer fluorescence in the presence of bile acids. A positive sign indicates the shift to longer wavelength region.

3.2. Discrimination of Bile Acids by RR-AX and SS-AX (X = B, C, D, and E)

In order to check the sensing capabilities of RR-AX and SS-AX types, we measured their monomer and excimer fluorescence intensity in the presence of the bile acids at 50 mmol dm^{-3} . Fluorescence intensity changes ($\Delta I = I - I^0$, where I and I^0 denote the fluorescence intensity in the presence and absence, respectively, of 50 mmol dm^{-3} of bile acids) which were divided by I^0 for normalization were chosen as a sensing factor.

Tables 1 shows the sensing factors $\Delta I/I^0$ of RR-AX and SS-AX types obtained at 340 (normal fluorescence) and 390 nm (excimer fluorescence) for the bile acids. For RR-AE, the shifts in the excimer fluorescence are also compiled in Table 1. The positive and negative signs indicate increases and decrease in the fluorescence intensities, respectively.

From these data, one can qualitatively determine the type of bile acids.

Qualitatively, 3 and ursodeoxycholic acid (5) caused virtually no change in the fluorescence spectral pattern of RR-AD, the $\Delta I/I^0$ values being less than ± 0.03 . Thus, 3 and 5 can be distinguished from the other bile acids by RR-AD. Discrimination between 3 and 5 is possible by the use of monomer fluorescence of RR-AE, because 5 caused virtually no change in the monomer fluorescence of RR-AE ($\Delta I/I^0 = -0.01$), while the appreciable positive response was induced by 3 ($\Delta I/I^0 = 0.17$). In other words, RR-AE are sensitive to detect the small positional difference of the hydroxyl group of 3 and 5. The sensitivity factors of the other hosts for 3 and 5 were similar, which indicates that 3 and 5 caused similar conformational changes with respect to the two naphthyl moieties of the hosts other than RR-AE. More detailed discussion on differentiation of the positional isomerism of 2-5 will be made latter.

Lithocholic acid (6) is readily differentiated from the other bile acids by SS-AD, because the appreciable negative $\Delta I/I^0$ value (-0.13) at the monomer fluorescence was obtained only by

6. The other bile acids induced positive or no $\Delta I/I^0$ values on the monomer fluorescence of SS-AD.

RR-AC, RR-AD, and RR-AE responded to cholic acid (1), 2, and chenodeoxycholic acid (4) with decreases and increases in the monomer and excimer fluorescence, respectively, though the extent of the changes were different. These guests also induced similar spectral changes on SS-AD and SS-AE fluorescence; namely increases and decreases in the monomer and excimer fluorescence, respectively. It is interesting that among these guests, only 4 slightly depressed the excimer fluorescence of SS-AC, while 1 and 2 increased the excimer fluorescence intensity. Thus, one can differentiate 4 from 1 and 2 by measuring the fluorescence intensity of SS-AC.

Qualitative detection of 1 and 2 seems to be difficult by RR-AX and SS-AX series. However, the fluorescence responses of RR-AX series for 2 were nearly doubled as large as those for 1, except for the cases of the monomer fluorescence of RR-AE where the similar $\Delta I/I^0$ values were obtained for 1 and 2. This means that comparing the magnitude of the responses, one may distinguish 1 and 2. Differences in the fluorescence responses between 1 and 2 are less pronounced in the series of SS-AX, though the larger $\Delta I/I^0$ values are still held for 2.

It is noteworthy that an interesting relationship is found for the changes in the fluorescence response patterns of RR-AD, RR-AE, SS-AD, and SS-AE, all which showed relatively intense excimer fluorescence, induced by deoxycholic acids, 2-5, which possess two hydroxyl groups on the steroid framework. The excimer formation in RR-AD was markedly enhanced by 2 ($\Delta I/I^0 = 0.59$) and 4 ($\Delta I/I^0 = 0.23$), while 3 and 5 induced slight changes in the fluorescence spectra. For SS-AD, all 2-5 decreased the excimer fluorescence. However, 2 and 4 increased the monomer fluorescence intensity while 3 and 5 virtually unchanged the monomer fluorescence intensity of SS-AD. A similar trend was found for SS-AE. The most interesting results may be for RR-AE; 2 and 4 decreased the monomer fluorescence with a concomitant increase in the excimer fluorescence, while 3 and 5 caused no

Table 2. Binding Constants (K) of BR-AX and SS-AX for Common Six Bile Acids in 10% Aqueous Ethylene Glycol Solutions at 25 °C^{2,b)}

Host	K / dm ³ mol ⁻¹					
	1	2	3	4	5	6
RR-AB	— ^{c)}	53000	— ^{c)}	— ^{c)}	— ^{c)}	— ^{c)}
RR-AC	— ^{c)}	29500	40600	— ^{c)}	27900	653000
RR-AD	2210	26000	9700	29400	13800	— ^{c)}
RR-AE	— ^{c)}	124000	12600	65300	7180	866000
SS-AB	— ^{c)}	— ^{c)}	59800	12800	52100	— ^{c)}
SS-AC	— ^{c)}	26500	91200	— ^{c)}	56000	— ^{c)}
SS-AD	22700	209000	39500	98600	27900	96700
SS-AE	44000	130000	38000	74300	25000	74300

a) Determined from guest-induced fluorescence or circular dichroism spectral variations.

b) The largest error ($\pm 27\%$) was obtained for the complexation between SS-AB and 4. Errors for other host-guest pairs were less than $\pm 15\%$.

c) The binding constants could not be obtained accurately owing to small changes in spectral variations and low solubility of the guests.

change (5) or even an increase in the monomer fluorescence (3) with decreasing the excimer fluorescence. In addition, the peak position of the excimer fluorescence of RR-AE was virtually unchanged by the presence of 3 and 5, while 2 and 4 shifted the peak position by 7-8.5 nm to the longer wavelength region. These facts strongly indicate that the conformations of complexed species of RR-AE with 2 and 4 are similar to each other, and those with 3 and 5 are also similar to each other. On the basis of the spectral variations, RR-AD, SS-AD, and SS-AE may also bind 2 and 4 similarly, and bind 3 and 5 similarly.

All of 2-5 has two hydroxyl groups at the steroid framework, one of which is common for 2-5; namely 3 α -hydroxyl group, which is in an equatorial configuration. The position and configuration of the other hydroxyl groups are follows; 2, 12 α - (axial); 3, 6 α - (equatorial); 4, 7 α - (axial); 5, 7 β - (equatorial). The axial hydroxyl groups together with the 3 α -hydroxyl group of 2 and 4 provides hydrophilicity for the concave surface of the steroid framework (Fig. 5). On the other hand, the equatorial hydroxyl groups of 3 and 5 cannot make the concave surface hydrophilic. RR-AD, RR-AE, SS-AD, and SS-AE, thus, can recognize the hydrophilicity of the concave surface, and hence the presence of the axial hydroxyl groups at the B and C rings of the steroid framework of the deoxycholic acids upon complexing.

3.3 Binding Constants

The 1 : 1 host-guest binding constants of the hosts for the bile acids are summarized in Table 2. There is no simple correlation between the binding constants and the sensing factors. For instance, RR-AE can bind 2 extremely strong ($K = 124000 \text{ dm}^3 \text{ mol}^{-1}$), and this value is nearly 10-times larger than that for 3 ($K = 12600 \text{ dm}^3 \text{ mol}^{-1}$). However, the sensing factors of the excimer and monomer fluorescence of RR-AE for 2 were -0.14 and 0.13, respectively. These values are less intense than the corresponding values for 3 (0.17 and -0.26, respectively). These facts indicate that although RR-AE binds 2 more strongly than 3, the changes in fluorescence of RR-AE induced by 3 is larger than by 2. Therefore, the sensing capability, and hence easiness of detection, is governed by how large conformational changes is induced by guests as well as the binding strength. This is in accord with other chemosensors based on di-functionalized CyDs.⁹⁻¹²⁾

Figure 5. Space filling drawings (energy minimized) of 2-5. Oxygen atoms are specified by black ones.

The binding constants of RR-AD, RR-AE, SS-AD, and SS-AE for 2-5 are categorized into two groups as in the cases of sensing factors. Generally, those hosts bind 2 and 4 more strongly than 3 and 5. This confirms the considerations made in the previous part that 2 and 4 are accommodated by those hosts with the binding conformations being similar to each other, and 3 and 5 are accommodated by those hosts with a similar fashion.

4. Conclusion

We found that RR-AX and SS-AX types were excellent hosts as fluorescent chemosensors for bile acids. When they are used in combination, one can qualitatively determine the type of common six bile acids, based on the changes in monomer and excimer fluorescence intensity and shifts in the peak position of excimer fluorescence. For their sensing capabilities, conformational changes upon guest binding, that is how large conformational changes are induced by guests, is a crucial factor, in addition to the binding strength. Some bile acids can be detected at 50 mmol dm⁻³ by some of those hosts with substantial changes in fluorescence. Since those hosts have optically active moieties at the γ -CyD rim, it is expected that they show discriminating capability towards optical isomers. In relation to this, RR-AE clearly distinguished 4 and 5, the only difference of which is the orientation of the 12-hydroxyl group at the steroid framework. In this regard, we are examining chiral recognition capability of RR-AX and SS-AX types, focusing on terpenes and amino acids.

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