Enhanced Binding Ability of β-Cyclodextrin Bearing Seven Hydrophobic Chains Each with a Hydrophilic End Group

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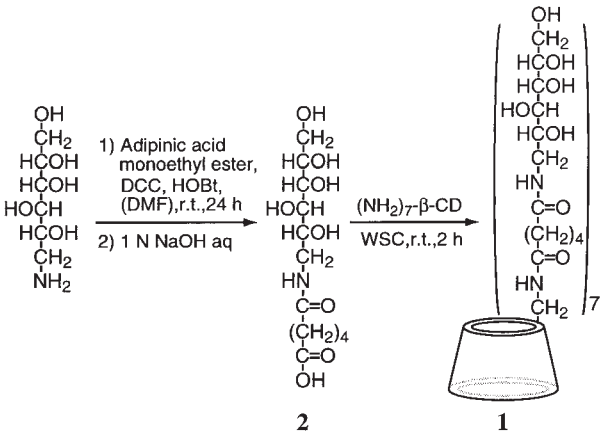
Seven adipic acid units each with a D-glucamine unit at the end were introduced to primary hydroxyl side of β-cyclodextrin to enlarge the hydrophobic cavity. The modification remarkably enhanced the binding ability for larger guests.

Cyclodextrins (CDs) play an important role in supramolecular chemistry, because CDs are soluble in water with a well-defined hydrophobic molecular cavity, and can be modified with various functional groups.[1–4] The kinds of guests to be bound by CDs are limited by the shape and size of the CD cavity and modification to enlarge the CD cavity is required for application of CDs to larger guests. Introduction of both hydrophobic and hydrophilic units to CDs is essential for enlargement of the cavity, because modification only with hydrophobic unit causes diminishment in their solubility in water. Here we report a new water-soluble modified CD that has seven adipic acid units and seven D-glucamine units as hydrophobic and hydrophilic parts, respectively.

The desired compound (**1**) was synthesized as shown in Scheme 1. D-Glucamine was connected with adipic acid monoethly ester by dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) followed by the hydrolysis of the ester with 1N NaOH aqueous solution to obtain a carboxylic acid (**2**). **2** and 6-heptaamino-β-CD was reacted with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) at pH 4.5–6.0 at room temperature for 2 h to form **1**. The product was purified by Sephadex G-25. The desired compound (**1**) was identified by elemental analysis, ^{1}H NMR spectra including 2D NMR, and mass spectrum.[5]



Scheme 1. Synthesis of **1**.

The binding behavior of **1** for 2-anilinonaphthalene-6-sulfonic acid (2,6-ANS) was studied. The fluorescence intensity of 2,6-ANS around 440 nm increases upon addition of **1** as shown in Figure 1. The continuous-variation method (Job plot) was used to determine the stoichiometry, while the total concentration of 2,6-ANS and **1** was kept constant of 0.1 mM.[6,7] The Job plot indicates that **1** forms 1 : 1 complex with 2,6-ANS as shown in Figure 2. The binding constant of **1** for 2,6-ANS was obtained to be $2.97 \times 10^3\ M^{-1}$ by the host-induced variations in the fluorescent intensity of 2,6-ANS based on the Benesi-Hildebrand type equation for the 1 : 1 host-guest complex formation.[6,7] The ROESY spectrum of the complex of **1** and 2,6-ANS shows NOE between ^{1}H of the naphthyl unit of 2,6-ANS and ^{1}H of β-CD, and

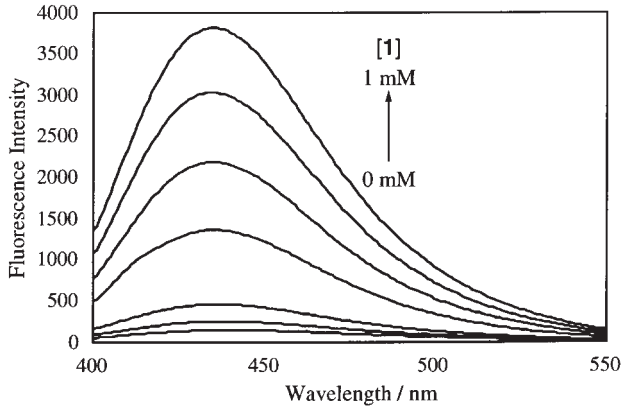


Figure 1. Fluorescence spectra of 2,6-ANS in the presence of various concentrations of **1**; [2,6-ANS] = 5 mM, λ_{ex} = 330 nm.

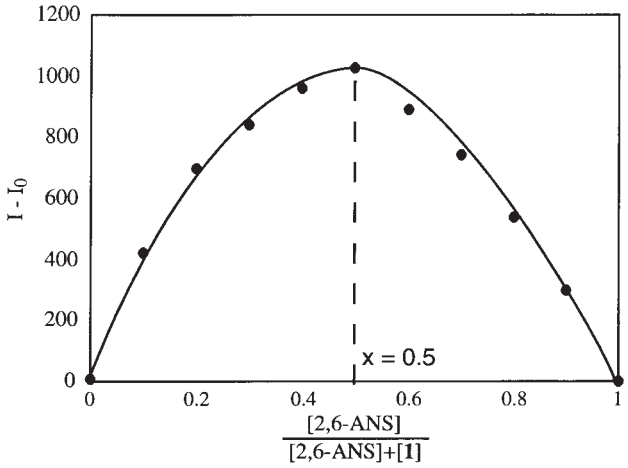


Figure 2. Job plots of **1** and 2,6-ANS : λ_{ex} = 320 nm, λ_{em} = 440 nm; I and I_0 are the fluorescence intensity of 2,6-ANS in the presence and absence of **1**, respectively; [**1**] + [2,6-ANS] = 0.1 mM.

between ^{1}H of the phenyl unit of 2,6-ANS and ^{1}H of the alkyl chain of the adipic acid unit of **1**. This spectrum suggests that the naphthyl unit of 2,6-ANS is located in the β-CD cavity and the phenyl unit of 2,6-ANS is located near the adipic acid unit.

The binding constants of **1** for some guests were obtained by competition assay using 2,6-ANS.[6,7] The fluorescence intensity of the solution containing 2,6-ANS and **1** decreased by addition of 1-nonanol as shown in Figure 3. The binding constant of **1** for 1-nonanol was obtained to be $1.66 \times 10^4\ M^{-1}$ from the guest-induced variations in the fluorescent intensity of 2,6-ANS by the usual curve-fitting method.[6,7] The binding constants of **1** and β-CD for other guests were also obtained by the same method (Table 1). The binding constant of **1** for 1-octanol is three times larger than that of β-CD. The binding constant of **1** for

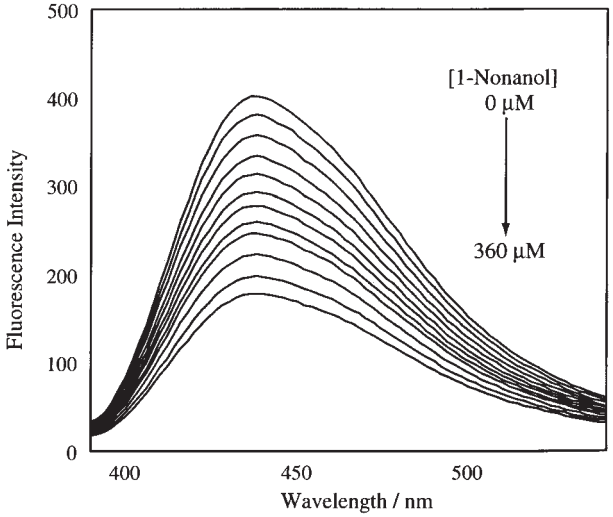


Figure 3. Fluorescence spectra of 2,6-ANS in the presence of **1** and various concentrations of 1-nonanol; [**1**] = 200 μM, [2,6-ANS] = 5 μM, λ_{ex} = 320 nm.

Table 1. Binding constants of β-CD and **1** for various guests

Guest	Binding Constant/M^{-1}	
	β-CD	**1**
1-Heptanol	2600 ± 100	1500 ± 200
1-Octanol	3000 ± 600	9400 ± 100
1-Nonanol	6500 ± 100	16600 ± 400
1-Decanol	21200 ± 300	67100 ± 3400
Cyclohexanol	3100 ± 100	10200 ± 500
Cyclooctanol	5900 ± 500	22600 ± 700
Cyclododecanol	8100 ± 600	18600 ± 700
1-Adamantanol	34500 ± 400	58800 ± 700
1-Adamantan carboxylic acid	44200 ± 400	57400 ± 1300
(+)-Camphor	15700 ± 300	7300 ± 200
(−)-Camphor	7600 ± 200	7800 ± 200
(+)-Borneol	35500 ± 3600	45200 ± 1500
(−)-Borneol	48500 ± 1900	41300 ± 1600

cyclooctanol is four times larger than that of β-CD. These results indicate that the hydrophobic alkyl chain of adipic acid unit expands the hydrophobic cavity of β-CD. The binding constants of **1** for adamantanol and adamantanecarboxylic acid are also larger than those of β-CD. It suggests that the hydrophobicity of the β-CD cavity itself also increases by the presence of the alkyl chain. The binding constant of **1** for (+)-borneol is larger than that of β-CD, whereas the binding constant of **1** for (−)-borneol is smaller than that of β-CD. This alteration of binding constant caused the change of enantioselectivity for borneol from (−)-selectivity to (+)-selectivity. The binding constant of **1** for (+)-camphor is half of that of β-CD, whereas the binding constant of **1** for (−)-camphor is almost the same as that of β-CD. The depths of inclusion for guests might be changed by addition of the adipic acid unit and the modification by the hydrophobic units affects enantio-selectivity for borneol and camphor. The alkyl chain of the adipic acid unit may inhibit the binding ability of **1** due to the insertion of the alkylchain into the CD cavity. This might be the reason why the binding constant of small-sized guests such as 1-heptanol is smaller for **1** than for β-CD.

In conclusion, the introduction of both adipic acid unit and D-glucamine unit to β-CD caused enlargement of the cavity without decrease of solubility in water. The modification increased the binding constants for larger guests and influenced the enantios-electivity for chiral guests.

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References and Notes

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5 Anal. Calcd for $C_{126}H_{224}O_{77}N_{14}\cdot H_2O$: C, 47.51; H, 7.15; N, 6.16%. Found: C, 47.74; H, 7.56; N, 5.76%. TOF-MS (*m*/*z*): 3187.8 (calcd for $[M+Na]^+$, 3188.4). ^{1}H NMR (500 MHz, D_2O, δ) 1.53 (m, 28H, $COCH_2CH_2$), 2.21 (m, 28H, $COCH_2CH_2$), 3.20 (dd, J = 8.06, 13.93, 7H, H-6 of glucamine), 3.38 (m, 14H, H-6' of glucamine and H-6 of CD), 3.44 (m, 7H, H-6' of CD), 5.00 (d, J = 2.68, 7H, H-1 of CD).
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