Molecular Recognition Studies on Supramolecular Systems. 25. Inclusion Complexation by Organoselenium-Bridged Bis(*β*-cyclodextrin)s and Their Platinum(IV) Complexes

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A series of novel bis(*β*-cyclodextrin)s connected by organoselenium linkers, i.e., 6,6′-trimethylenediseleno-bridged bis(*β*-cyclodextrin) (**2**), 2,2′-trimethylenediseleno-bridged bis(*β*-cyclodextrin) (**3**), 6,6′-*o*-phenylenediseleno-bridged bis(*β*-cyclodextrin) (**4**), and the corresponding platinum(IV) complexes (**5**−**7**) were synthesized from *β*-cyclodextrin (**1**). The inclusion complexation behavior of **1**−**7** with some fluorescent dyes, i.e., ammonium 8-anilino-1-naphthalenesulfonate, sodium 2-(*p*-toluidinyl)naphthalenesulfonate, Methyl Orange, and Mordant Orange 1, was investigated in aqueous phosphate buffer solution (pH 7.20) at 25 °C by fluorescence and circular dichroism spectrometry, as well as fluorescence lifetime measurements. The spectrofluorometric and spectropolarimetric titrations gave the complex stability constant (K_S) and Gibbs free energy change ($\Delta G°$) for the stoichiometric 1:1 inclusion complexation of **1**−**7** with the fluorescent dyes. The bis(*β*-cyclodextrin)s **2**−**4** showed higher affinities toward these guests than native *β*-cyclodextrin, and the binding abilities of **5**−**7** were further enhanced by incorporating Pt(IV). The cooperative binding abilities of these bis(*β*-cyclodextrin)s are discussed from the viewpoints of the size/shape-fit concept, the induced-fit interaction, and the multiple recognition mechanism.

Introduction

It is well documented that native and modified cyclodextrins, having fairly rigid and well-defined hydrophobic cavities, act as molecular receptors (hosts) to bind substrates (guests), forming host−guest complexes or supramolecular species in aqueous solutions.[1−4] Possessing dual hydrophobic cavities in a close vicinity, bridged cyclodextrin dimers have been demonstrated to greatly enhance the original molecular binding ability of the parent cyclodextrin through the cooperative binding of one guest molecule in the closely located two cyclodextrin cavities,[5−8] which provide an excellent model system mimicking the substrate-specific interaction of enzymes.[9,10] Consequently, a variety of bridged bis(cyclodextrin)s have recently been synthesized in order to examine and compare the molecular binding abilities of cyclodextrin and bridged bis(cyclodextrin)s and also to gain insights into factors governing the inclusion complexation from the viewpoints of multiple recognition and induced-fit interaction between the host bis(cyclodextrin)s and guest molecules. Recently, the molecular recognition behavior of cyclodextrin dimers has been reviewed comprehensively by Breslow and co-workers.[11] Unfortunately, the synthetic and molecular recognition studies on organoselenium-bridged cyclodextrin dimers are still rare, except for recent studies by Liu et al.[12] and Shen et al.[13]

We have recently shown that *o*-phenylenediseleno-bridged *β*-cyclodextrin dimers form more stable complexes with 8-anilino-1-naphthalenesulfonate (ANS) than native *β*-cyclodextrin through the cooperative binding of one ANS molecule by two cyclodextrin moieties. Furthermore, a platinum(IV) complex of the bis(*β*-cyclodextrin) showed yet stronger binding to ANS.[12] These results advanced our understanding of the several weak interactions working in the multipoint recognition and induced-fit processes involving two adjacent receptor units (host) and a substrate molecule (guest) and also prompted us to further investigate the inclusion complexation behavior of a series of organoselenium-bridged bis(*β*-cyclodextrin)s.

We now wish to report our study on the syntheses and molecular recognition behavior of organoselenium-bridged *β*-cyclodextrin dimers (**2**−**4**) and their complexes with platinum(IV) (**5**−**7**), shown in Chart 1. The inclusion complexation behavior has been investigated at 25 °C in aqueous phosphate buffer solution (pH 7.20) by means of fluorescence and circular dichroism spectroscopy as well as fluorescence lifetime measurement. The complex stability constants (log K_S) and Gibbs free energy changes

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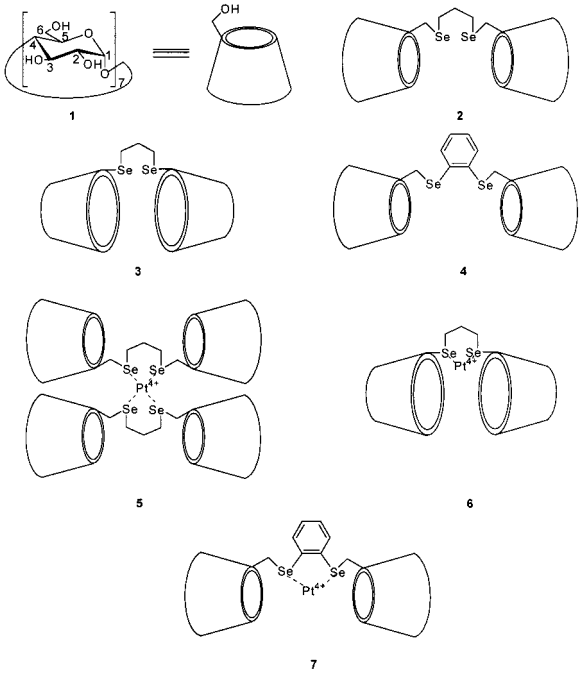
Chart 1



(Δ*G*°) obtained for some structurally related fluorescent guest molecules (Chart 2) are discussed in terms of the cooperative binding and the complementary geometrical relationship between the dimeric host and guest. It is another point of interest to compare the complexation behavior of the 6,6′- and 2,2′-bridged dimers (**2** and **3**), in which two cyclodextrin moieties are linked with each other at the primary or secondary side, respectively.

Experimental Section

Materials. Methyl Orange and Mordant Orange 1 were purchased from Aldrich. Ammonium 8-anilino-1-naphthalenesulfonate (ANS) and sodium 2-(*p*-toluidinyl)naphthalene-6-sulfonate (TNS) were purchased from Tokyo Kasei. All chemicals were reagent grade and used without further purification unless noted otherwise. *β*-Cyclodextrin of reagent grade (Shanghai Reagent Works) was recrystallized twice from water and dried in vacuo at 95 °C for 24 h prior to use. *N*,*N*-Dimethylformamide (DMF) was dried over calcium hydride for 2 days and then distilled under a reduced pressure prior to use. 6,6′-*o*-Phenylenediseleno-bridged bis(*β*-cyclodextrin) (**4**) and its platinum(IV) complex (**7**) were prepared according to the reported procedures.[12] Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.10 M phosphate buffer solution of pH 7.20, which was used in the spectral measurements.

Synthesis of 6,6′-Trimethylenediseleno-Bridged Bis(*β*-cyclodextrin) (2). 1,2-Diselenacyclopentane[14] (0.2 g) was dissolved in absolute ethanol (60 mL) containing sodium hydroxide (0.12 g) and sodium borohydride (0.114 g). After the ethanol solution became colorless, mono[6-*O*-(*p*-toluenesulfonyl)]-*β*-cyclodextrin[15] (2.64 g) in *N*,*N*-dimethylformamide (40 mL) was added to the solution at 80 °C under a nitrogen atmosphere, and the resultant mixture was stirred for 5 h at that temperature. Then the solvent was evaporated under a reduced pressure to dryness. The residue was dissolved in water, and then acetone was added to the solution to give a light yellow precipitate. After drying, the precipitate was purified on a column of Sephadex G-25 to give 1.5 g (53% yield) of **2** as a light yellow solid: FAB-MS *m*/*z* 2436 (M^+); ^{1}H NMR (D_2O) *δ* 1.89−2.16 (m, 6H), 3.19−3.92 (m, 84 H), 5.01−5.23 (m); IR (KBr) *ν* 3389, 2912, 1645, 1574, 1409, 1381, 1347, 1308, 1150, 1072, 1023, 941, 853, 819 cm^{-1}. Anal. Calcd for $C_{87}H_{144}O_{68}Se_2 \cdot 8H_2O$: C, 40.50; H, 6.25. Found: C, 40.25; H, 6.30.

Synthesis of 2,2′-Trimethylenediseleno-Bridged Bis(*β*-cyclodextrin) (3). *β*-Cyclodextrin dimer **3** was prepared in 19% yield from mono[2-*O*-(*p*-toluenesulfonyl)]-*β*-cyclodextrin[16] and 1,2-diselenacyclopentane according to the similar procedures described above, except for the extension of the reaction period to 20 h: FAB-MS *m*/*z* 2436 (M^+); ^{1}H NMR (DMSO-d_6, TMS) *δ* 1.95 (m, 6H), 3.1−4.0 (m), 4.31−4.72 (m), 4.9 (m, 14 H), 5.53−6.0 (m); ^{13}C NMR (D_2O): *δ* 104.3, 100.5, 84.0, 83.4, 76.1, 75.1 74.7, 71.8, 62.5, 52.0, 33.1, 28.0; IR (KBr) *ν* 3351, 2902, 1646, 1404, 1360, 1332, 1253, 1145, 1071, 1021, 938, 852, 795 cm^{-1}. Anal. Calcd for $C_{87}H_{144}O_{68}Se_2 \cdot 12H_2O$: C, 39.36; H, 6.38. Found: C, 39.19; H, 6.57.

Preparation of Pt (IV) Complexes of Bis(*β*-cyclodextrin)s. The complexes of bis(*β*-cyclodextrin)s **2**-**4** with Pt(IV) were prepared in situ in aqueous solution. Conductivity measurements of the CD dimers/$PtCl_4$ systems indicated that the complex stoichiometry was 2:1 for **2**−Pt(IV) complexes and 1:1 for **3**−Pt(IV) and **4**−Pt(IV),[12] respectively. Figure 1 shows a representative conductivity titration curve for the 2:1 complexation of bis(*β*-cyclodextrin) **2** with $PtCl_4$. The ^{1}H NMR of bis(*β*-cyclodextrin) **2** in the absence and presence of $PtCl_4$ was measured, and from the spectra shown in Figure 2, we can see that the propanyl protons of **2** move downfield upon addition of $PtCl_4$, while the cyclodextrin protons do not show appreciable shifts, indicating the complex between bis(*β*-cyclodextrin) **2** and $PtCl_4$ was formed. Just as we reported in the previous work,[12] the IR spectral changes of **5** and **6** also support the complex formation, since the coupled poly O−H antisymmetric vibration of the complexes shifted to smaller wavenumbers accompanying the peak broadening, and the peaks were broadened obviously with strength decreasing, in the wavelength from 1200 to 1400 cm^{-1}.

Measurement. Circular dichroism (CD) spectra were measured in a conventional quartz cell (10 × 10 × 45 mm) on a JASCO J-720S spectropolarimeter equipped with a PTC-348WI temperature controller to keep the temperature at 25 °C. Fluorescence spectra were recorded in a conventional quartz cell (10 × 10 × 45 mm) at 25° C on a JASCO FP-750 fluorescence spectrometer with the excitation and emission slits of 5 nm width.

Fluorescence lifetimes were determined by the time-correlated single-photon-counting method using a Horiba NAES-550 instrument with a time resolution of 0.5 ns. A self-oscillating discharge lamp filled with hydrogen gas was employed as the pulsed light source, and the excitation light was made monochromatic by a 10 cm monochromator. The emission from the sample was passed through an appropriate filter (Toshiba UV-33) placed before the detector unit in order to eliminate scattered excitation light. Maximum counts of up to 10 000 were collected for each measurement. The accumulated signals were then processed and the lifetime determined by deconvolution with nonlinear least-squares fit.

Results and Discussion

Syntheses. As shown in Scheme 1, the organoselenium-bridged bis(*β*-cyclodextrin)s **2** and **4** were synthesized in satisfactory yields from mono[6-*O*-(*p*-toluenesulfonyl)]-*β*-cyclodextrin and 1,2-diselenacyclopentane, while the bridged bis(*β*-cyclodextrin) **3** was similarly synthesized from mono[2-*O*-(*p*-toluenesulfonyl)]-*β*-cyclodextrin. In this study, the latter starting material, *β*-cyclodextrin 2-tosylate, was prepared through an unconventional route, employing a reaction of *β*-cyclodextrin with *p*-toluenesulfonyl chloride in aqueous sodium hy-

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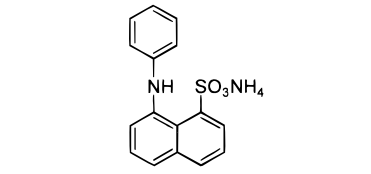
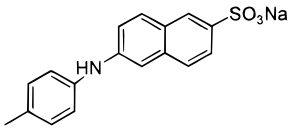
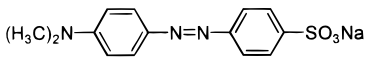
Chart 2



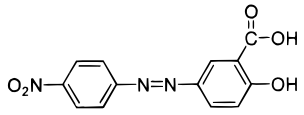
ANS



TNS



Methyl Orange



Mordant Orange 1

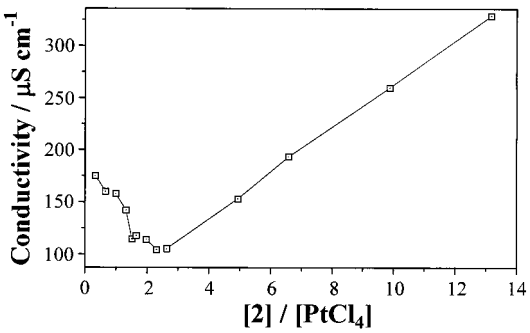


Figure 1. Conductivity of 0.4 mM $PtCl_4$ in 6,6′-trimethylenediseleno-bridged bis(*β*-cyclodextrin) **2** solution at 25 °C.

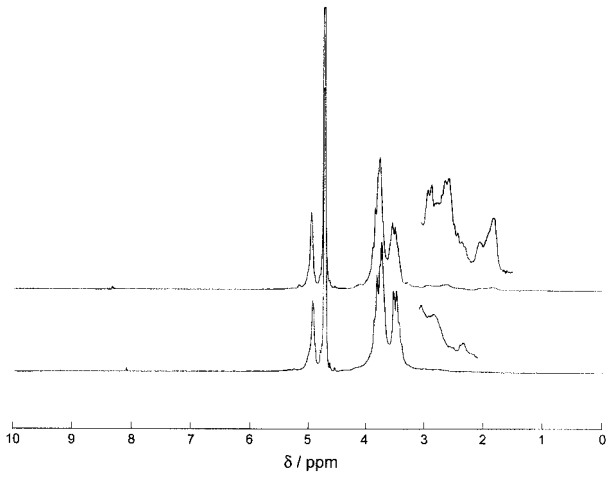
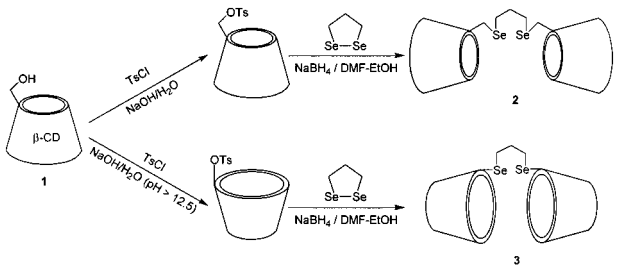


Figure 2. ^{1}H NMR spectra of 6,6′-trimethylenediseleno-bridged bis(*β*-cyclodextrin) **2** in the absence (the upper) and presence (the lower) of $PtCl_4$.

droxide solution. It is believed that aqueous sodium hydroxide as base is not strong enough to ionize the 2-OH of cyclodextrin, and therefore, the 2-tosylate cannot be prepared in aqueous sodium hydroxide solution.[17] However, Shen and co-workers repeated the experiment, which was reported originally by Toda et al,[18,19] to find that the 2-*O*-tosylate can be obtained by employing modified reaction conditions and different separation procedures.

Scheme 1



Breslow et al.[20] have revealed that, even if the 2-tosylate is used as the starting material, both 2- and 3-O-substituted cyclodextrin derivatives are potentially produced through the ring-opening nucleophilic attack to 2,3-epoxycyclodextrin generated in situ from the 2-tosylate under the basic conditions. We therefore seriously checked the position of the substituent introduced in our product. In general, the ^{13}C NMR spectra of N- or S-substituted sugar derivatives are known to show a large upfield shift of the α-carbon, a small upfield shift of the *β*-carbon, and a very small upfield shift of the *γ*-carbon relative to the parent sugar.[21,22] Hence, we can assign the point of substitution from the ^{13}C NMR spectrum of the product. In the ^{13}C NMR spectrum of **3**, the C-2 showed a significant upfield shift up to 24.1 ppm, while moderate shifts of 3.8 and 3.3 ppm for the C-1 and C-3 (*β*-carbons) and a very small shift of 0.6 ppm for the C-4 (*γ*-carbon) were observed. In contrast, if the substitution would take place at the C-3 of a glucose unit of *β*-cyclodextrin, the upfield shift of C-1 (as a *γ*-carbon) should be much smaller and that of C-4 (as a *β*-carbon) should be much larger. We conclude that the 1,3-trimethylenediseleno bridge is introduced at the C-2 of *β*-cyclodextrin.

Circular Dichroism Spectra of Inclusion Complexes. Inclusion of an achiral aromatic guest in chiral cyclodextrin cavity give rise to the induced circular dichroism (ICD) at the wavelengths absorbed by the chromophore. Using the ICD phenomena, the inclusion behavior of the bridged bis(*β*-cyclodextrin)s with the azo dyes was investigated. As shown in Figure 3 (traces b and c), both native *β*-cyclodextrin **1** and the bridged bis-(*β*-cyclodextrin) **3** induce appreciable CD at the $\pi-\pi^*$

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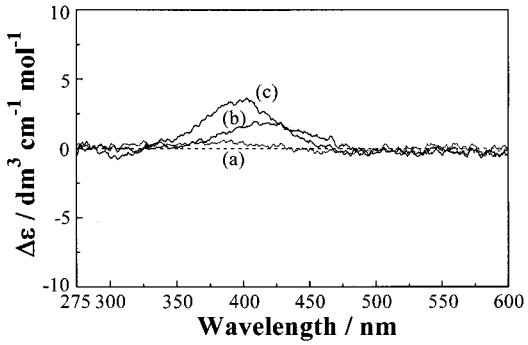

Figure 3. Circular dischroism spectra of Methyl Orange (16.8 μM) (a) in the absence and in the presence of (b) β-cyclodextrin **1** (1.7 mM) and (c) 2,2′-trimethylenediseleno-bridged bis(β-cyclodextrin) **3** (1.6 mM) in aqueous buffer solution at pH 7.20.

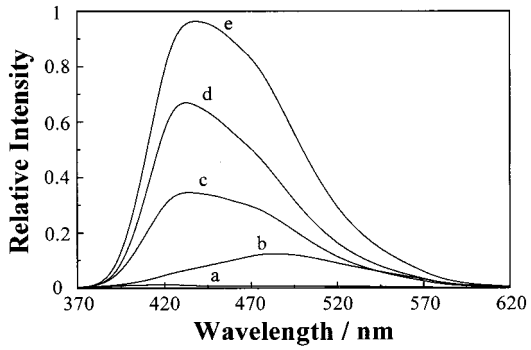

Figure 4. Fluorescence spectra of TNS (10 μM) (a) in the absence and in the presence of (b) β-cyclodextrin **1** (450 μM), (c) 2,2′-trimethylenediseleno-bridged bis(β-cyclodextrin) **3** (24 μM), (d) 6,6′-trimethylenediseleno-bridged bis(β-cyclodextrin) **2** (26 μM), and (e) 6,6′-*o*-phenylenediseleno-bridged bis(β-cyclodextrin) **4** (26 μM) in aqueous buffer solution at pH 7.20. Excitation wavelength was 315 nm.

transition band of the azo group in Methyl Orange, while no CD is seen in the absence of cyclodextrin (Figure 3, trace a). These results clearly indicate that the Methyl Orange molecule is included in the chiral cyclodextrin cavity. The ICD spectrum of Methyl Orange (17 μM) included by **1** (1.7 mM) showed a positive Cotton effect peak at 420 nm ($\Delta\epsilon = +1.84$ M^{-1} cm^{-1}). Possessing the dual hydrophobic cavities, the bridged bis(β-cyclodextrin) (**3**) at an even lower concentration (1.6 mM) induces a stronger Cotton effect at 403 nm ($\Delta\epsilon = +3.64$ M^{-1} cm^{-1}). This may be attributed to the enhanced binding ability and/or to the more efficient ICD upon inclusion by **3** than by **1**. The induced molar circular dichroism ($\Delta\epsilon$) gradually increased upon further addition of **1** and **3**. From the geometrical requirement, Methyl Orange molecule is inferred to be incorporated longitudinally into the cavities.[23,24] In such situation, only the dimethylaminophenyl group is accommodated in the cavity of **1**, while both aromatic rings are cooperatively included in the adjacent two cavities of **3**, as indicated by the hypsochromic shift of the complex with **3** rather than **1**.

Fluorescence Spectra. TNS and ANS are known to be very sensitive to environmental changes, which enables us to use the fluorescent dye as a spectral probe to investigate the inclusion complexation with β-cyclodextrin **1** and the bridged bis(β-cyclodextrin)s **2**−**7**. As exemplified in Figure 4, the fluorescence of TNS itself was extremely weak in the aqueous buffer solution (pH 7.20), but the addition of the cyclodextrin hosts **1** (45-fold excess) and **2**−**4** (2.5-fold excess) dramatically enhanced the fluorescence intensity by factors of 15−100 and caused significant bathochromic shifts of the fluorescence peak. It should be noted that the degrees of fluorescence enhancement and bathochromic shift depend critically on the host structure, affording a moderate fluorescence enhancement and extensive bathochromic shift for native β-cyclodextrin but significant enhancements and less-extensive shifts for the bis(β-cyclodextrin)s. These observations clearly indicate that, upon complexation with **1**−**4**, the TNS molecule is certainly included in the cyclodextrin cavity, but the hydrophobic environment around the TNS molecule differs substantially, depending on the mode and depth of penetration. The binding ability of the hosts with TNS may be judged as **4** > **2** > **3** > **1** from the extent of fluorescence enhancement.

Fluorescence Lifetime. The inclusion complexation of fluorescent dyes by cyclodextrin hosts not only induces the fluorescence enhancement and peak shifts[12] but also leads to significantly elongated fluorescence lifetimes in the hydrophobic environment, as demonstrated by Bright[25] and Reinsborough.[26] In the present study, we performed the nanosecond time-resolved fluorescence experiments with ANS in aqueous buffer solution (pH 7.20) in the presence or absence of β-cyclodextrin **1** or the bridged bis(β-cyclodextrin)s **3**, **4**, **6**, and **7** in order to assess the microenvironmental polarity around the included ANS.

Since the rates of complexation/decomplexation are much slower than that of the fluorescence decay, the decay profile of fluorescence intensity ($F(t)$) can be described as the sum of unimolecular decays for all fluorescing species present in the solution:

$$F(t) = \Sigma A_i \exp(-t/\tau_i)\ (i = 1, 2, ...) \qquad (1)$$

where A_i and τ_i represent the initial abundance and lifetime of the ith species. In the absence of the host, the fluorescence decay curve observed for ANS in aqueous buffer solution was perfectly fitted to a single-exponential function. In contrast, the decay profile of ANS in the presence of β-cyclodextrin or bis(β-cyclodextrin)s could be analyzed only by a linear combination of two exponential functions. The short and long fluorescence lifetimes (τ_S and τ_L) and relative quantum yields (Φ) observed for ANS in the presence of **1**, **3**, **4**, **6**, and **7** are summarized in Table 1. The elongated lifetimes in the presence of the hosts clearly indicate that the environment around the ANS molecule is more hydrophobic than the bulk water. Furthermore, the two-component decay indicates that the ANS molecule is located in two distinctly different environments, one of which is polar and the other nonpolar. However, the shorter lifetimes (τ_S = 1.3−2.9 ns) in the presence of hosts do not agree with the original lifetime (0.4 ns) of ANS in water. Then, the two lifetimes (τ_S and τ_L) observed in the presence of the host should originate from two different fluorescing species. For native cyclodextrin, the 1:1 and 2:1 host−guest complexes may be responsible for the short- and long-lived species,

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Table 1. Fluorescence Lifetime (τ) and Relative Quantum Yield (Φ) of Ammonium 8-Anilino-1-naphthalenesulfonate (ANS) in the Presence and Absence of Native β-Cyclodextrin (1) and Bis(β-cyclodextrin)s (1, 3, 4, 6, and 7) in Aqueous Buffer Solution (pH 7.20) at 25° C[a]

ANS/μM	host	equiv	τ_S/ns	Φ_S/%	τ_L/ns	Φ_L/%	χ^2
500	none		0.4	100			1.46
250	**1**	10	1.5	67.6	3.2	32.4	1.24
10	**3**	24	2.6	17.9	13.0	82.1	1.47
10	**4**	40	2.9	45.6	9.9	54.4	1.11
10	**6**	24	1.3	50.4	7.3	49.6	1.46
10	**7**	20	2.0	45.5	9.0	54.5	1.46

[a] In the presence of host, the fluorescence decay was not single but double exponential with short and long lifetimes, indicated by subscripts S and L, respectively.

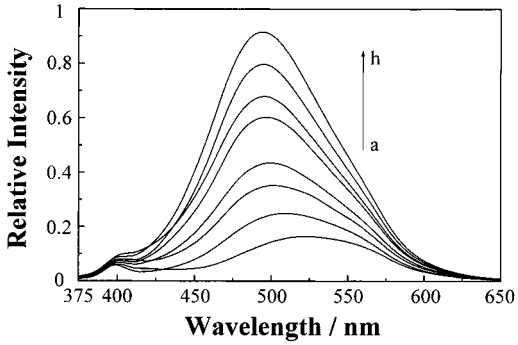

Figure 5. Fluorescence spectral changes of ANS (10 μM) upon addition of 6,6′-trimethylenediseleno-bridged bis(β-cyclodextrin) **2** in aqueous buffer solution at pH 7.20; [**2**] = 0, 52, 104, 156, 260, 312, 364, and 468 μM (a−h). Excitation wavelength was 350 nm.

respectively. For bis(cyclodextrin)s, the two fluorescing species may be assigned to the equilibrating "intramolecular" 1:1 and 2:1 host−guest complexes, in which the ANS molecule is accommodated in one and two cavities. This idea is compatible with the fact that the longer τ_L is always accompanied by the higher Φ_L, since the stabilization of the inter/intramolecular 2:1 complex leads in general to a more hydrophobic environment and therefore to an elongated lifetime as a result of more efficient protection from the attack of water. It is also interesting to note that, although the τ_S for mono- and bis(cyclodextrin) falls in a relatively narrow range 1.3−2.9 ns, the τ_L varies more widely in a range 3.2−13.0 ns, probably depending on the exaggerated difference in the microenvironmental hydrophobicity of the hypothetical cavity formed upon 2:1 complexation. From the tendency of τ_L, it is inferred that the 2,2′-bridged host **3** affords the most hydrophobic cavity among the bis(cyclodextrin)s, while β-cyclodextrin forms the least hydrophobic cavity upon 2:1 complexation with ANS. The other bis(cyclodextrin)s are located between these two extremes and give diverse hydrophobicity, reflecting the mode and depth of penetration.

Spectral Titrations. To study quantitatively the complexation behavior of hosts **1**−**7**, fluorescence spectral titrations of guest dyes were performed at 25 °C in aqueous phosphate buffer solution at pH 7.20. As shown in Figure 5, the stepwise addition of a known amount of the host to a dilute ANS solution (10 μM) caused significant enhancement in fluorescence intensity.

Assuming the 1:1 stoichiometry, where the two β-cyclodextrin moieties in **2**−**7** are treated as a unit,[27] the

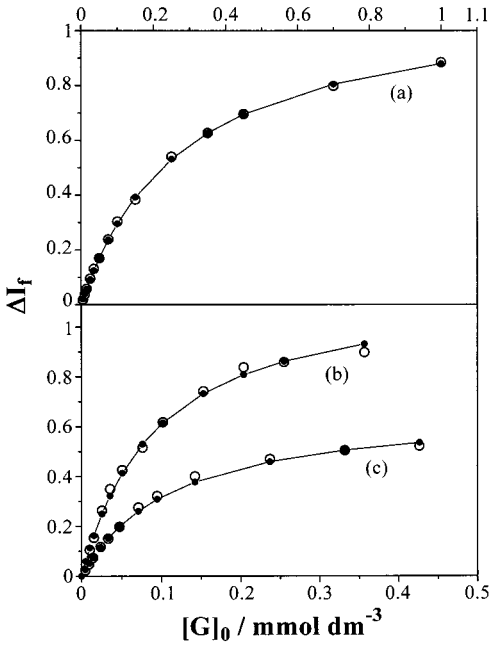

Figure 6. Curve-fitting analyses of fluorescence spectral titrations of TNS with (a) β-cyclodextrin **1**, (b) 6,6′-trimethylenediseleno-bridged bis(β-cyclodextrin) **2**, and (c) 2,2′-trimethylenediseleno-bridged bis(β-cyclodextrin) **3** in aqueous buffer solution at pH 7.20. Differential fluorescence intensity ΔF (open circle) was fitted to the theoretical value (closed circle) calculated for the stoichiometric 1:1 complexation.

inclusion complexation of a guest (G) with a host (H) is expressed by eq 2.

$$H + G \overset{K_S}{\rightleftharpoons} H\cdot G \qquad (2)$$

The effective stability constant (K_S)[28] can be obtained from the analysis of the sequential changes of fluorescence intensity (ΔF) at various host concentration, using a nonlinear least-squares method according to the curve-fitting eq 3[12,29]

$$\Delta F = [\alpha([H]_0 + [G]_0 + 1/K_S) \pm \sqrt{\alpha^2([H]_0 + [G]_0 + 1/K_S)^2 - 4\alpha^2[H]_0[G]_0}]/2 \quad (3)$$

where $[G]_0$ and $[H]_0$ refer to the total concentrations of the guest and host and α the proportionality coefficient, which may be taken as a sensitivity factor for the fluorescence change. For each host examined, the plot of ΔF as a function of $[G]_0$ gave an excellent fit, verifying the validity of the 1:1 complex stoichiometry assumed above. Figure 6 illustrates the typical curve-fitting plots for the titrations of TNS with β-cyclodextrin (**1**) and bridged bis(β-cyclodextrin)s (**2**−**3**). There are no serious diversions between the experimental and calculated data of β-cyclodextrin/TNS system, indicating 1:1 complexation only throughout the concentration range of β-cyclodextrin (0−1 mM). The complex stability constants (K_S) obtained are listed in Table 2, along with the free energy change of complex formation ($-\Delta G°$). The data

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Table 2. Complex Stability Constant (K_S) and Gibbs Free Energy Change ($-\Delta G°$) for 1:1 Inclusion Complexation of Various Guest Dyes with β-Cyclodextrin 1 and Organoselenium-Bridged Bis(β-cyclodextrin)s (2−7) in Aqueous Buffer Solution (pH 7.20) at 25 °C

host	guest	K_S	log K_S	$-\Delta G°$/ kJ mol^{-1}	method[a]	ref
1	Methyl Orange	3560	3.55	20.27	CD	*b*
	Methyl Orange		3.65	20.8	UV	*c*
	Methyl Orange		3.29	18.8	UV	*d*
	Mordant Orange 1	602	2.78	15.87	CD	*b*
	ANS	103	2.01	11.49	FL	*e*
	ANS		2.06	11.8	FL	*f*
	TNS	3670	3.56	20.35	FL	*b*
	TNS		3.2	18.3	CON	*g*
	TNS		3.45	19.7	FL	*f*
	TNS	4000	3.60	20.56	FL	*h*
2	Methyl Orange	17400	4.24	24.20	CD	*b*
	Mordant Orange 1	4900	3.69	21.06	CD	*b*
	ANS	674	2.83	16.15	FL	*b*
	TNS	11680	4.07	23.22	FL	*b*
3	Methyl Orange	37200	4.57	26.09	CD	*b*
	Mordant Orange 1	8100	3.91	22.31	CD	*b*
	ANS	1680	3.23	18.41	FL	*b*
	TNS	9480	3.98	22.70	FL	*b*
4	ANS	1280	3.11	17.73	FL	*b*
	TNS	23800	4.38	24.98	FL	*b*
5	ANS	5960	3.77	21.55	FL	*b*
	TNS	24700	4.39	25.07	FL	*b*
6	ANS	13900	4.14	23.65	FL	*b*
	TNS	17900	4.25	24.27	FL	*b*
7	ANS	4020	3.60	20.57	FL	*e*
	TNS	37300	4.57	26.09	FL	*b*

[a] Method employed: CD, circular dichroism; UV, spectrophotometry; FL, fluorimetry; CON, conductometry. [b] This work. [c] Reference 31, in H_2O. [d] Reference 32, in an aqueous buffer solution at pH 7.5. [e] Reference 12. [f] Reference 26, in an aqueous buffer solution at pH 1.95. [g] Reference 27, in H_2O. [h] Reference 34, in H_2O.

obtained by the spectropolarimetric titrations[30] are also listed in Table 2.

Molecular Binding Ability. Although a wide variety of weak interactions are known to be involved in the inclusion complexation with cyclodextrin, the most important are the van der Waals and hydrophobic interactions, both of which depend on how the size and/or shape of a guest molecule fit into the host cavity. In a study on the inclusion complexation of azonaphthalene dyes with cyclodextrins, Szejtli et al. have shown that the van der Waals interaction is the most important driving force.[35] In the present case, the hydrophobic, as well as van der Waals, interactions are considered to play important roles in determining the complex stability.

As can be seen from Table 2, mono- and bis(β-cyclodextrin)s **1**−**3** gave significantly higher K_S for Methyl Orange than for Mordant Orange 1. This may be attributed to the strict size-fit relationship and relatively stronger hydrophobic interaction between the host and the guest. Possessing the three charged or hydrophilic groups (i.e., carboxyl, hydroxyl and nitro), Mordant Orange 1 is more hydrophilic and sterically hindered than Methyl Orange, which jointly reduces the hydrophobic interaction and the extent of desolvation upon complexation.[36−38] Examinations of CPK space-fitting molecular models indicated that the Methyl Orange and Mordant Orange 1 molecules are too large to be included completely in a single β-cyclodextrin cavity. Hence, the bridged bis(β-cyclodextrin)s **2** and **3** bind these azo dyes much more strongly than the parent β-cyclodextrin, affording 5−8 times higher K_S for **2** and 10−13 times higher K_S for **3** than for native β-cyclodextrin. Again, the 2,2′-bridged bis(β-cyclodextrin) **3** with wider openings gave significantly higher K_S values than the 6,6′-bridged **2**.

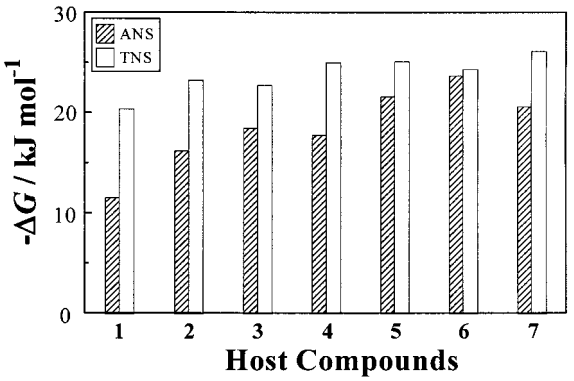

Figure 7. Gibbs free energy changes ($-\Delta G$) upon complexation of ANS and TNS with host **1**−**7** in in aqueous buffer solution at pH 7.20.

Using the common guest molecules (ANS and TNS), the complexation behavior of a series of bis(β-cyclodextrin)s **2**−**7** was quantitatively compared with that of native β-cyclodextrin **1**. In Figure 7, the free energy changes obtained ($-\Delta G°$) were plotted against the hosts. As can be seen from Table 2 and Figure 7, all the mono- and bis(cyclodextrin)s examined form less stable complex with ANS than with TNS. Examinations with CPK molecular models indicate that the hydrophobic naphthalene part of TNS can be embedded deeply into the cavity of β-cyclodextrin in the longitudinal direction, while ANS can penetrate only in part into the cyclodextrin cavity to form a weak inclusion complex due to the steric hindrance. The bridged bis(β-cyclodextrin)s **2**−**4**, possessing two hydrophobic cavities, form more stable inclusion complexes with ANS and TNS than native β-cyclodextrin through the cooperative binding by two β-cyclodextrin units. As can be seen from Figure 7, the platinum(IV) complexes **5**−**7** give yet higher stability constants than the corresponding bis(β-cyclodextrin)s **2**−**4**. However, a close examination of the inclusion complexation of bis(β-cyclodextrin)s **2**−**4** and their Pt(IV) complex **5**−**7** reveals that the stability sequence for ANS, i.e., **6** > **5** > **7** > **3** > **4** > **2**, does not coincide with that for TNS, i.e., **7** > **5** > **4** > **6** > **2** > **3**. It is noted that the 2,2′-bridged bis(β-cyclodextrin) **3** and its Pt(IV) complex **6** show the highest affinities toward ANS among

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the bis(β-cyclodextrin)s **2**−**4** and their Pt(IV) complexes **5**−**7**, respectively. This is attributable to the wider openings of the 2,2′-bridged bis(β-cyclodextrin) derivatives than the 6,6′-bridged counterparts. The increased hydrophobicity of the bridging group (*o*-phenylene) of **4** also favors the inclusion complexation with TNS. On the other hand, the Pt(IV) ion introduced to the bridging chain not only orientates two β-cyclodextrin cavities to fit to the shape of the guest molecule but also acts as an additional site of guest recognition through coordination and/or electrostatic interaction, giving the highest K_S values for both ANS and TNS. Finally, we wish to emphasize that the diseleno bridge introduced is not a passive linker group but acts as a versatile coordinating site that can control the orientation and binding ability/selectivity of bis(cyclodextrin)s.

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