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Synthesis of Novel Bis(β-Cyclodextrin)s and Metallobridged Bis(β-Cyclodextrin)s with 2,2′-Diselenobis(benzoyl) Tethers and Their Molecular Multiple Recognition with Model Substrates

Yu Liu,* Li Li, Heng-Yi Zhang, and Yun Song

Department of Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

yuliu@public.tpt.tj.cn

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To investigate quantitatively the cooperative binding ability of β-cyclodextrin dimers, a series of bridged bis(β-cyclodextrin)s with 2,2′-diselenobis(benzoyl) spacer connected by different lengths of oligo(ethylenediamine)s (**2**−**5**) and their platinum(IV) complexes (**6**−**9**) have been synthesized and their inclusion complexation behavior with selected substrates, such as Acridine Red, Neutral Red, Brilliant Green, Rhodamine B, ammonium 8-anilino-1-naphthalenesulfonate, and 6-*p*-toluidino-2-naphthalenesulfonic acid, were investigated by means of ultraviolet, fluorescence, fluorescence lifetime, circular dichroism, and 2D-NMR spectroscopy. The spectral titrations have been performed in aqueous phosphate buffer solution (pH 7.20) at 25 °C to give the complex stability constants (K_S) and Gibbs free energy changes ($-\Delta G°$) for the inclusion complexation of hosts **2**−**9** with organic dyes and other thermodynamic parameters ($\Delta H°$ and $T\Delta S°$) for the inclusion complexation of **2**−**5** with fluorescent dyes ANS and TNS. The results obtained indicate that β-cyclodextrin dimers **2**−**5** can coordinate with one or two platinum(IV) ions to form 1:1 or 1:2 stoichiometry metallobridged bis(β-cyclodextrin)s. As compared with parent β-cyclodextrin (**1**) and bis(β-cyclodextrin)s **2**−**5**, metallobridged bis(β-cyclodextrin)s **6**−**9** can further switch the original molecular binding ability through the coordinating metal to orientate two β-cyclodextrin cavities and an additional binding site upon the inclusion complexation with model substrates, giving the enhanced binding constants K_S for both ANS and TNS. The tether length between two cyclodextrin units plays a crucial role in the molecular recognition with guest dyes. The binding constants for TNS decrease linearly with an increase in the tether length of dimeric β-cyclodextrins. The Gibbs free energy change ($-\Delta G°$) for the unit increment per ethylene is 0.32 kJ·mol^{-1} for TNS. Thermodynamically, the higher complex stabilities of both ANS and TNS upon the inclusion complexation with **2**−**5** are mainly contributed to the favorable enthalpic gain ($-\Delta H°$) by the cooperative binding of one guest molecule in the closely located two β-cyclodextrin cavities as compared with parent β-cyclodextrin. The molecular binding ability and selectivity of organic dyes by hosts **1**−**9** are discussed from the viewpoints of the multiple recognition mechanism and the size/shape-fitting relationship between host and guest.

Introduction

β-Cyclodextrin is a toroidally shaped polysaccharide made up of seven D-glucose monomers linked by α-1,4-glucose bonds. Its exterior, bristling with hydroxy groups, is fairly polar, whereas the interior of the cavity is nonpolar. These structural features enable β-cyclodextrin to accommodate bicyclic aliphatic and aromatic compounds to form host−guest or supramolecular complexes in aqueous solutions.[1−3] As compared with parent β-cyclodextrin, the bridged bis(β-cyclodextrin)s tethered by some simple functional groups can enhance the original molecular binding ability and selectivity through cooperative binding of one guest molecule in the closely located two cyclodextrin cavities. Hence, a variety of dimeric cyclodextrins with a considerable structural diversity have been designed and synthesized to understand the recognition process controlled by the simultaneous operation of several weak interactions and also to gain insights into the factors and mechanism governing the inclusion complexation behavior of bridged cyclodextrin dimers.[4−10] Recently, some functional organosele-

* To whom correspondence should be addressed. Tel: +86-22-23503625. Fax: +86-22-2350-4853.

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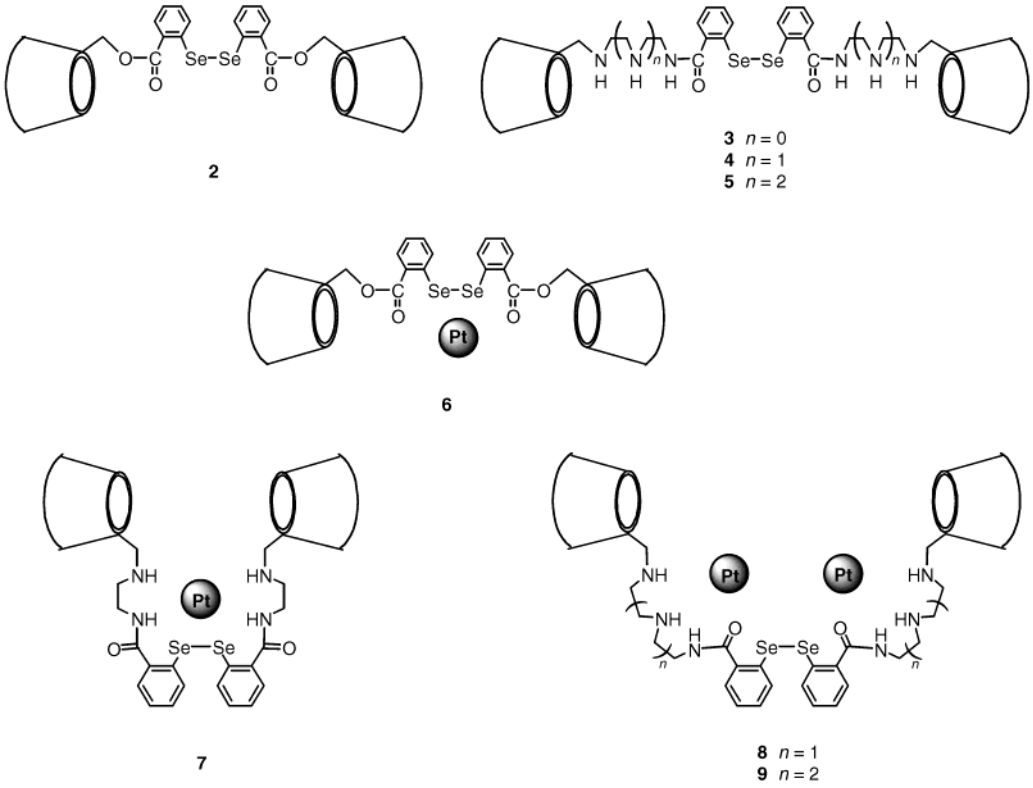
CHART 1



nium bridged bis(*β*-cyclodextrin)s have been applied successfully to enzyme-mimetic chemistry and nanostructure supramolecular assembly.[11,12] Therefore, the molecular recognition studies on bridged bis(*β*-cyclodextrin)s are one of the crucial topics in supramolecular chemistry and biochemistry.[13,14]

We have recently demonstrated that the organoselenium- and oligoethylenediamine-bridged bis(*β*-cyclodextrin)s can form more stable complexes with some fluorescent dyes than native *β*-cyclodextrin through the cooperative binding, and their metal complexes show yet stronger abilities to bind to guest molecules.[15−17] These results will promote our understanding of the multiple recognition and the induced-fit interaction hypothesis proposed for the binding of specific substrates by biological receptors. Unfortunately, the thermodynamics and the role of linker length in molecular recognition have rarely been investigated so far upon the inclusion complexation with organoselenium-bridged bis(*β*-cyclodextrin)s.[18,19] In the present study, we wish to report the inclusion complexation behavior of a series of novel synthesized bis(*β*-cyclodextrin)s linked by 2,2′-diselenobis(benzoyl) tether with the selective dye molecules (Chart 1) and their complexation thermodynamics with guest dyes such as ANS and TNS (Chart 2). It is of our special interest to elucidate the molecular recognition behavior of guest dyes by organoselenium-bridged bis(*β*-cyclodextrin)s with ligated platinum ions. The results obtained indicate that the oligo(ethylenediamine) tethers incorporated in the organoselenium *β*-cyclodextrin dimers not only adjust the linker length between the two cyclodextrin moieties but also ligate to metal ions, which enables us to modify and potentially switch the original molecular binding ability through the metal ligation.

Results and Discussion

Synthesis. As illustrated in Scheme 1, organoselenium-bridged bis(*β*-cyclodextrin) **2** was synthesized in 19% yield from 2,2′-diselenobis(benzoic acid) and *β*-cyclodextrin according to our recently reported procedures,[20] while oligo(ethylenediamino)-tethered organoselenium-bridged bis(*β*-cyclodextrin)s **3**−**5** were prepared in satisfactory yields starting from 6-*O*-monotosyl-*β*-cyclodextrin, which was converted to mono[6-oligo(ethylenediamino)-6-deoxy]-*β*-cyclodextrins according to procedures similar to those described for **2**. And then, metallobridged bis(*β*-cyclodextrin)s **6**−**9** were prepared from oligo(ethylenediamino)-tethered organoselenium-

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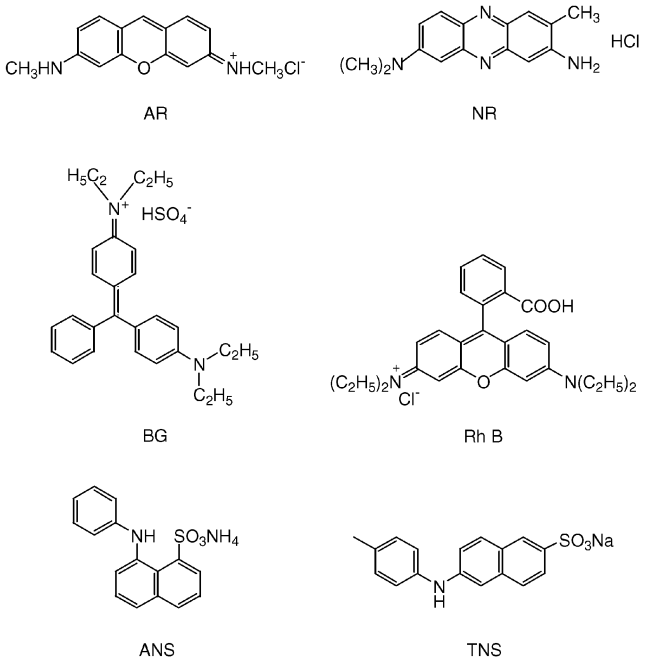
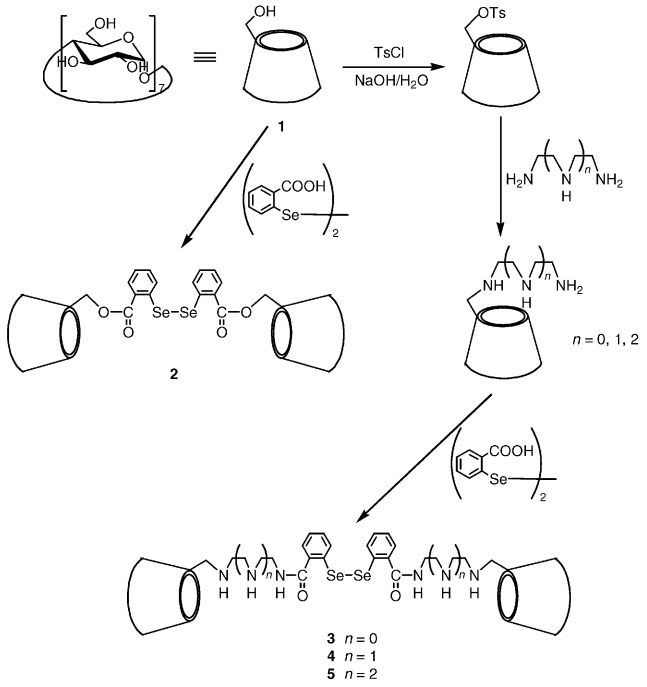
CHART 2



SCHEME 1



bridged bis(β-cyclodextrin)s **2**−**5**, respectively, by the coordination reaction with $PtCl_4$ in aqueous solution. The complex formation of the metallobis(β-cyclodextrin)s was validated by the elemental analysis data, IR spectra, and ^{1}H NMR spectra, and the conductivity measurements showed that the complex stoichiometry was 1:1 for both **2**−Pt(IV) (**6**) and **3**−Pt(IV) (**7**) complexes, while it was 1:2 for both **4**−Pt(IV) (**8**) and **5**−Pt(IV) (**9**), respectively. A representative Job plot for the 1:1 and 1:2 complexation of bis(β-cyclodextrin)s **2** and **4** with Pt(IV) is shown in Figure 1.

Circular Dichroism Spectra of β-Cyclodextrin Dimers 2−5. Circular dichroism (CD) is an essential spectral property for probing chirality[21,22] and has been widely employed to elucidate the absolute conformation of achiral compound enclosed in chiral cavity. Therefore, circular dichroism spectra are a convenient method for investigating the conformations of chromophoric tethers attached to two cyclodextrin units.[16,20] In this work, the CD spectra of **2**−**5** were taken at a low concentration of 1×10^{-4} in aqueous buffer solution at pH 7.20 in order to investigate the initial conformation of β-cyclodextrin dimers with a chromophoric organoselenium tether.

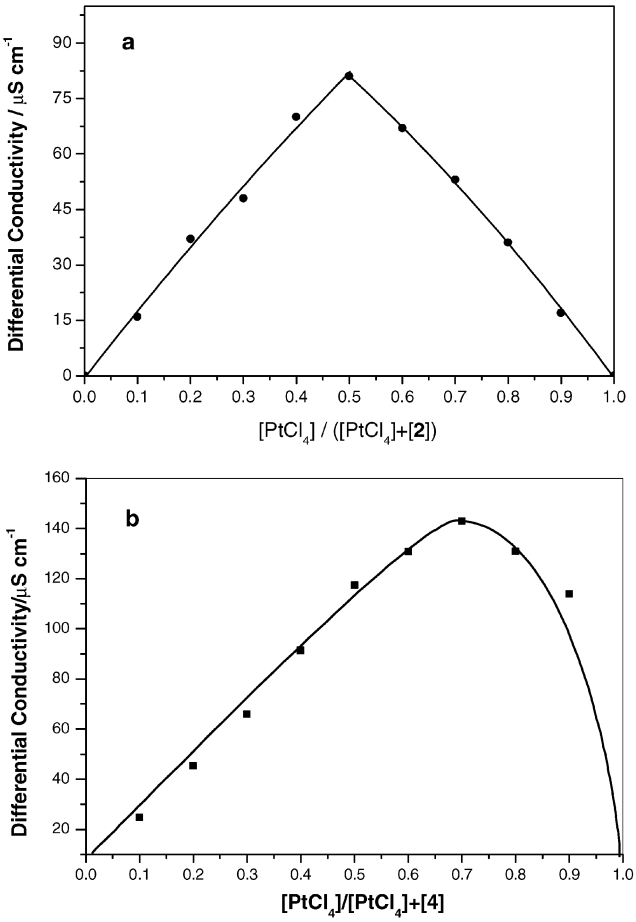


FIGURE 1. Job plots of (a) the **2**/Pt(IV) system ([**2**] + [Pt(IV)] = 5.0×10^{-4} mol·dm^{-3}) and (b) the **4**/Pt(IV) system ([**4**] + [Pt(IV)] = 5.0×10^{-4} mol·dm^{-3}).

As shown in Figure 2, the substantially different CD spectra of organoselenium bridged bis(β-cyclodextrin)s **2**−**5** indicate that there exists significant, but different, degrees of interaction between the aromatic tether and the two chiral cavities of β-cyclodextrin dimer. In our recent investigation,[20] the CD spectrum of dimeric host **2** in aqueous solution shows two negative Cotton effect peaks at 233 nm ($\Delta\epsilon = -4.03$) and 266 nm ($\Delta\epsilon = -0.32$) and a weak positive peak at 325 nm ($\Delta\epsilon = 0.35$). The bridged bis(β-cyclodextrin)s **3**−**5**, possessing similar tethers appended to β-cyclodextrin, display very similar patterns on the circular dichroism spectra, but they give the opposite Cotton effects to **2**, i.e., a positive Cotton

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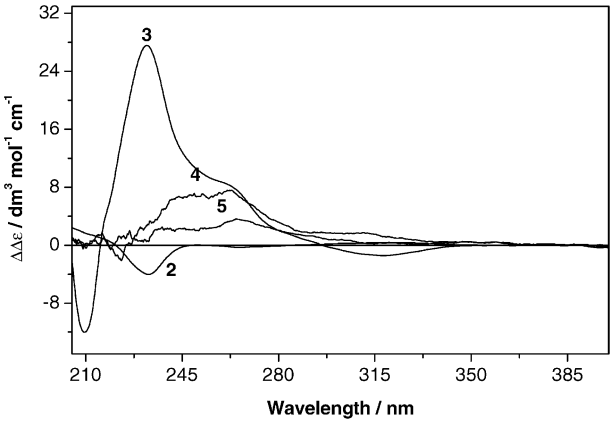

FIGURE 2. Circular dichroism spectra of hosts **2**−**5** (1×10^{-4} mol dm^{-3}) in aqueous solution at 25 °C.

effect peak at 232 nm ($\Delta\epsilon = 27.6$) with a shoulder at 260 nm ($\Delta\epsilon = 8.64$) and a weak negative peak at 318 nm ($\Delta\epsilon = -1.43$) for **3**, two moderate positive Cotton effect peaks at 242 nm ($\Delta\epsilon = 6.40$) and at 261.4 nm ($\Delta\epsilon = 7.57$) for **4**, and at 234.8 nm ($\Delta\epsilon = 2.0$) and at 264.8 nm ($\Delta\epsilon = 3.61$) for **5**, respectively. On the basis of the Kajtar's sector rule and Harata's results,[23,24] we deduce that the benzene ring in the tether of **2** does not penetrate deeply into the cavity of β-cyclodextrin but is shallowly self-included in the cavity. However, it is difficult to be self-included into the cavity for the benzene ring in **3**−**5** tethered by longer linkers. Consequently, the transition moments of the ^1L_a and ^1L_b bands for **3**−**5** become perpendicular to the axis of β-cyclodextrin, affording two positive Cotton effects. The negative Cotton effect at 318 nm indicates that the transition dipole moment of the Se−Se bond in host **3** is inferred to be parallel to the host axis while the transition dipole moment of Se−Se bonds in hosts **4** and **5** is deduced to be perpendicular to the axis of host, since there are no negative Cotton effects at corresponding bands. On the other hand, the 2D-NOESY spectrum of host compound **4** in D_2O (see Supporting Information) shows no signal of correlation between the protons of the bridged chain and H-3 and H-5 of β-cyclodextrin. This result indicates that the bridged chain is not located inside cyclodextrin cavities and corresponds with the circular dichroism spectrum analysis.

Fluorescence Lifetime. It is well-documented that the inclusion complexation of fluorescent dyes by cyclodextrin hosts not only induces the fluorescence enhancement and peak shift[16] but also leads to significantly elongated fluorescence lifetimes in the hydrophobic environment, as demonstrated by Bright[25] and Reinsborough.[26] In this study, we measured the lifetime of ANS in aqueous buffer solution (pH 7.20) in the presence and absence of β-cyclodextrin **1** and bis(β-cyclodextrin)s **2**−**5** in order to assess the microenvironmental polarity around the included ANS and to understand the inclusion complexation behavior of bridged bis(β-cyclodextrin)s.

TABLE 1. Fluorescence Lifetime (τ) and Relative Quantum Yield (Φ) of ANS in the Presence and Absence of Natural β-Cyclodextrin and Bis(β-cyclodextrin)s 1−5 in Aqueous Buffer Solution (pH 7.20) at 25.0 °C

ANS/μM	host	equiv	τ_S/ns	Φ_S/%	τ_L/ns	Φ_L/%	χ^2	ref
10	none		0.4	100			1.42	a
500	none		0.4	100			1.46	b
10	**1**	40	0.5	96.5	3.1	3.5	1.00	a
250	**1**	10	1.5	67.6	3.2	32.4	1.24	b
10	**2**	20	0.6	88.1	7.4	11.9	1.04	c
10	**3**	20	1.2	75.2	10.1	24.8	1.46	c
10	**4**	20	2.0	61.8	10.3	38.2	1.47	a
10	**5**	20	2.4	62.6	9.95	37.4	1.36	a

[a] This work. 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. [b] Reference 15. [c] Reference 20.

The short and long fluorescence lifetimes (τ_S and τ_L) and relative quantum yields (Φ) observed for ANS in the presence of β-cyclodextrin or bis(β-cyclodextrin) **2**−**5** are summarized in Table 1. From the data listed in Table 1, we can see that ANS itself exhibits a very short lifetime of 0.4 ns in aqueous solution but two lifetimes of 0.5 and 3.1 ns in the presence of β-cyclodextrin. The two decay lifetimes indicates that the ANS molecule is located in two distinctly different environments, one of which is polar and the other is nonpolar. The shorter lifetime is consistent with the initial lifetime, while the elongated lifetime of 3.12 ns in the presence of β-cyclodextrin clearly indicates that the environment around the ANS molecule is more hydrophobic than that in the bulk water. Judging from the different lifetime (τ_S and τ_L) observed for ANS in the presence of bis(β-cyclodextrin)s (**2**−**5**), we infer that the short- and long-lived fluorescing species are assigned to free and included ANS, respectively. It is noted that, although the short lifetimes (τ_S) are practically the same as native and bis(β-cyclodextrin)s, the distinctly different long lifetimes (τ_L) are obtained for native (3.2 ns) and bis(β-cyclodextrin)s (7.4−10.3 ns), reflecting the critical difference in microenvironmental hydrophobicity of the host cavity. Interestingly, despite possessing various tether lengths, the host compounds **3**−**5** give only slightly different τ_L (10.1 ± 0.2 ns), while the host compound **2** has a shorter τ_L (7.4 ns). As we demonstrated in previous reports,[17] the shorter lifetime upon inclusion complexation with bis(β-cyclodextrin)s is ascribed to the interaction of the anilino moiety of ANS with the β-cyclodextrin cavity, and the much longer lifetime (10.1 ± 0.2 ns) is attributed to the naphthalene group of ANS partly penetrating into an adjacent β-cyclodextrin cavity of the dimers. Therefore, the self-inclusion of the benzene ring for host compound **2** is unfavorable for inclusion complexation with ANS, giving the τ_L shorter than bis(β-cyclodextrin)s **3**−**5**. This hydrophobic difference between parent β-cyclodextrin and bridged bis(β-cyclodextrin)s will subsequently result in the dramatically different stability of the complex upon inclusion complexation with guest molecules.

Spectral Titrations. In the fluorescence spectral titration experiments, the original fluorescence intensities of guest molecules were relatively weak, especially for ANS and TNS, but the stepwise addition of a known amount of host compound caused significant successive enhancement in fluorescence intensity with appreciable

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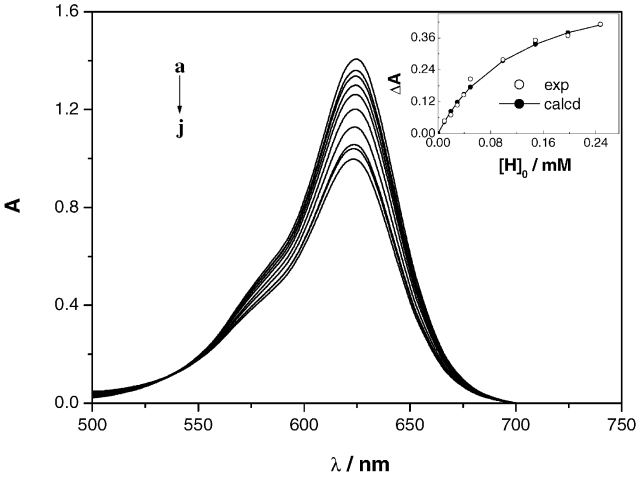

FIGURE 3. UV−vis spectral changes of Brilliant Green (19 μM) and the nonlinear least-squares analysis (inset) of the differential intensity (ΔA) to calculate the complex stability constant (K_S) upon addition of **4** (0−250 μM from a to j) in aqueous buffer solution.

hypsochromic shifts. The hypsochromic shift of fluorescence peak for AR was relatively small as compared with NR, RhB, ANS, and TNS. These phenomena suggested that the fluorophore experienced a less polar environment and the inclusion complex was formed by adding host compound. On the other hand, the bridged bis(β-cyclodextrin)s **3**−**5** with long spacers would quench the fluorescence of RhB, which is consistent with the case of β-cyclodextrin or modified β-cyclodextrins.[27] It is unexpected that the bis(β-cyclodextrin) **2** tethered by a shorter linker effectively enhanced the original fluorescence intensity of RhB. These results indicated that the functional tether of bridged bis(β-cyclodextrin)s not only influenced the host−guest binding ability but also changed the fluorescence behavior of guest molecule to some extent. Actually, the enhanced fluorescence intensity of RhB upon associating with **2** is attributed to the inclusion complexation of the fluorescent acid form of RhB in the pseudocavity formed by the dicarboxylate linker between two β-cyclodextrin units,[28] while the hosts **3**−**5** tethered by the longer spacers prefer to bind with the colorless lactonic form of RhB through hydrogen-bonding, thus resulting in the quenched fluorescence of RhB.

To further investigate the molecular binding ability and selectivity, the binding constants of bis(β-cyclodextrin)s with Brilliant Green (BG) were determined by means of ultraviolet spectroscopy. As can been seen from Figure 3, the absorption maximum of BG is considerably decreased upon increasing the concentration of bis(β-cyclodextrin)s **4**, indicating the inclusion complex formed between **4** and BG.

If a 1:1 stoichiometry is assumed, where the two β-cyclodextrin moieties in **2**−**5** are treated as a host unit, the inclusion complexation of a guest (G) with a host (H) is express by eq 1.

$$H + G \overset{K_S}{\rightleftharpoons} H\cdots G \qquad (1)$$

The effective stability constant (K_S)[29] can be obtained

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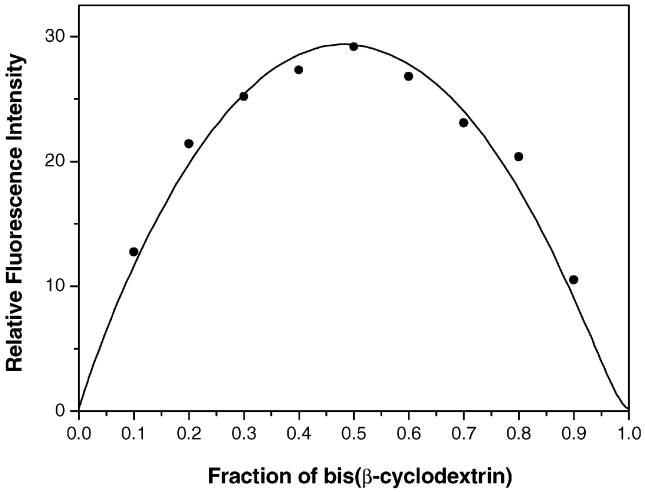

FIGURE 4. Continuous variation plot of the **4**/AR system ([bis(β-cyclodextrin) unit] + [AR] = 2.0×10^{-5} mol dm^{-3}).

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 2[30]

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

where $[G]_0$ and $[H]_0$ refer to the total concentrations of the guest and host, and α is 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 $[H]_0$ gave an excellent fit; the experimental data do not show any significant deviations from the theoretical curve in each case. In the repeated measurements, the K_S values were reproducible within an error of ±5%. Furthermore, the stoichiometry of the host−guest inclusion complexation was determined by the continuous variation method. A representative Job plot is given in Figure 4, showing the 1:1 stoichiometry for the inclusion complexation of **4** with AR. The K_S values obtained are listed in Table 2, along with the free energy change of complex formation ($-\Delta G°$). The complex stability constants (K_S) are also plotted against the host examined in Figure 7.

Binding Model. To infer the binding model of the organoselenium-bridged bis(β-cyclodextrin)s with guest dyes, we recorded the 300-MHz NOESY spectrum of RhB (5.0 mM in D_2O) in the presence of 1 equiv of **4**. As shown in Figure 5, the NOESY spectrum displays clear NOE cross-peaks between the H-3 and H-5 of β-cyclodextrin and the methyl protons of diethylamino groups in RhB (peaks A) as well as those between the H-3 and H-5 and the aromatic protons of diethylaminophenyl in RhB (peaks B). Furthermore, the cross-peaks C were observed between the aromatic protons of linker in **4** and the aromatic protons of the benzoate moiety in RhB. These results indicate that the cooperative interaction exists

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TABLE 2. Complex Stability Constant (K_S) and Gibbs Free Energy Change ($-\Delta G°$) for the Inclusion Complexation of Dye Molecules with β-Cyclodextrin 1 and Bis(β-cyclodextrin)s 2−9 in Aqueous Buffer Solution (pH 7.20) at 25.0 °C

host	guest	K_S	K_S(**X**)/ K_S(**1**)[a]	log K_S	$-\Delta G°$ (kJ·mol^{-1})	methods[b]	ref
1	AR	2089	≡1	3.32	18.90	FL	c
	NR	480	≡1	2.68	15.30	FL	d
	BG	2187	≡1	3.34	19.10	UV	e
	RhB	4240	≡1	3.63	20.70	FL	c
	ANS	103	≡1	2.01	11.49	FL	f
	TNS	3670	≡1	3.56	20.35	FL	f
2	AR	3320	1.6	3.52	20.10	FL	d
	NR	2350	4.9	3.37	19.24	FL	d
	BG	3060	1.4	3.49	19.90	UV	e
	RhB	11870	2.8	4.07	23.26	FL	d
	ANS	1200	11.7	3.08	17.59	FL	d
	TNS	13770	3.8	4.14	23.66	FL	d
3	AR	2440	1.2	3.39	19.30	FL	d
	NR	3040	6.3	3.48	19.88	FL	d
	BG	13300	6.1	4.12	23.50	UV	e
	RhB	5590	1.3	3.75	21.39	FL	d
	ANS	1370	13.3	3.14	17.90	FL	d
	TNS	12900	3.5	4.11	23.46	FL	d
4	AR	4320	2.1	3.63	20.80	FL	d
	NR	1830	3.8	3.26	18.62	FL	d
	BG	9500	4.3	3.98	22.70	UV	d
	RhB	5060	1.2	3.70	21.14	FL	d
	ANS	2570	25.0	3.41	19.46	FL	d
	TNS	10220	2.8	4.01	22.89	FL	d
5	AR	24800	11.9	4.39	25.10	FL	d
	NR	2570	5.4	3.41	19.46	FL	d
	BG	5150	2.4	3.71	21.20	UV	d
	RhB	4500	1.1	3.65	20.85	FL	d
	ANS	1570	15.2	3.20	18.24	FL	d
	TNS	9740	2.7	3.99	22.77	FL	d
6	ANS	3270	31.7	3.51	20.06	FL	d
	TNS	20700	5.6	4.32	24.63	FL	d
7	ANS	4390	42.1	3.64	20.79	FL	d
	TNS	50200	13.7	4.70	26.83	FL	d
8	ANS	5820	56.5	3.76	21.49	FL	d
	TNS	24500	6.7	4.39	25.05	FL	d
9	ANS	2480	24	3.39	19.37	FL	d
	TNS	15330	4.2	4.18	23.89	FL	d

[a] Relative selectivity for each dye, where host **X** = **1**−**9**. [b] CD, circular dichroism; UV, ultraviolet/visible; FL, fluorescence. [c] Reference 36. [d] This work. [e] Reference 20. [f] Reference 15.

between **4** and RhB. It is well-known that the extensive aggregation of RhB exist in the higher concentration region.[31] We investigated the fluorescence spectra of concentrated RhB in the presence of β-cyclodextrin and compound **4** to confirm the binding model of the inclusion complexation of RhB with compound **4** in the 2D-NMR experiment. The results obtained indicate that the fluorescence intensity of RhB was dramatically quenched in the higher concentration region and shows two separate fluorescence peaks at 575 and 640 nm, respectively, belonging to the free and aggregated RhB deduced by the excitation spectrum of two emission peaks individually. When β-cyclodextrin was added to the concentrated RhB solution, the fluorescence intensity of RhB was significantly enhanced, being greater at longer wavelength than at shorter wavelength. Therefore, it is considered that the dissociation of RhB dimers, upon addition of β-cyclodextrin to concentrated RhB solution, is attributed to the binding of the monomer to the β-cyclodextrin cavity

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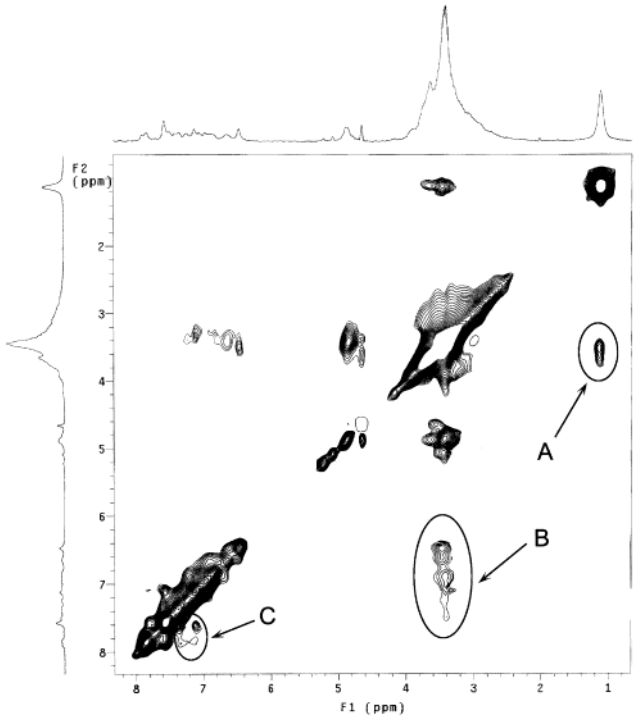

FIGURE 5. ^{1}H−NOESY spectrum (300 MHz) of a mixture of **4** with RhB ([**4**] = [RhB] = 5.0 × 10^{-3} M) in D_2O at 298 K with a mixing time of 600 ms.

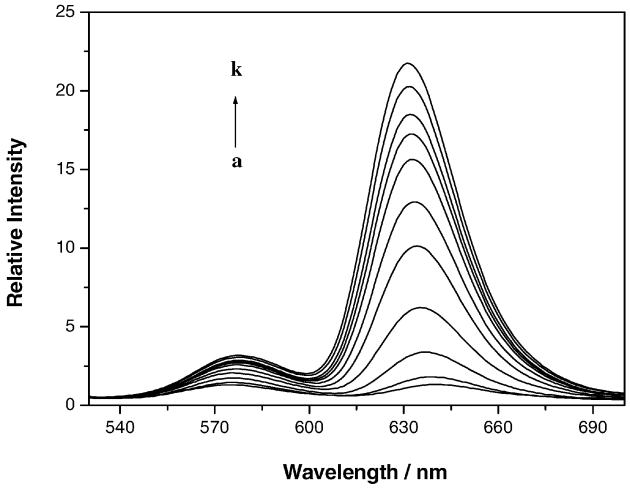

FIGURE 6. Fluorescence spectral changes of RhB (5.0 mM) upon addition of **4** (the concentration of host **4**: 0−6.7 mM from a to k).

maintaining a low concentration of free RhB in solution. Similar phenomena were observed when compound **4** was added to the concentrated RhB solution (Figure 6), which would confirm that the monomer of RhB is included in **4** at the higher concentration, and the 2D-NMR spectrum under the experimental conditions used also reflects the reality of the binding model upon inclusion complexation with bridged bis(β-cyclodextrin)s.

Binding Ability of Bridged Bis(β-cyclodextrin)s 2−5. Studies on molecular multiple recognition by the cyclodextrin dimers indicated that the functional bridged chain spacer between two cyclodextrin units plays a crucial role in determining the inclusion complex sta-

bility,[15−17,32−35] since the conformation, length, flexibility, and additional coordination site of the functional group tether may control how the dual cyclodextrin cavities adjust their orientation and conformation to cooperatively binding one guest molecule through the simultaneous operation of several weak forces such as ion−dipole, dipole−dipole, dipole−induced dipole, van der Waals, electrostatic, hydrogen bonding, and hydrophobic interactions according to the size/shape−fit concept between host and guest. As can be seen from Table 2, guest dyes AR and NR, possessing a similar heterocycle anthracene moiety, gave entirely different binding constants upon inclusion complexation with native β-cyclodextrin (**1**), displaying K_S values of 2089 and 480 for the AR and NR, respectively.[36] This result seems reasonable, since examination with CPK (Corey−Pauling−Koltum) molecule models indicates that AR, which has small substituent, can be well-embedded in the cavity of β-cyclodextrin in the longitudinal direction, while NR can partly penetrate into the cyclodextrin cavity to form a weaker inclusion complex due to the steric hindrance. As compared with parent **1**, bridged bis(β-cyclodextrin)s **2**−**5** form much more stable inclusion complexes with AR and NR through cooperative binding by two β-cyclodextrin units, displaying a binding affinity sequence of AR > NR, except for host compound **3**. It is significantly noted that the enhanced molecular binding abilities of host **5** are much greater for AR than that for NR, thus exhibiting **a** remarkably high AR/NR molecular selectivity of 10. The stability sequence of inclusion complexation of bridged bis(β-cyclodextrin)s for AR does not coincide with that for NR, which depends on how bridged bis(β-cyclodextrin)s with flexible/rigid tether fit to the size/shape of guest molecules. As compared with the linear AR and NR molecules, the triangular BG and the T-shaped RhB guest molecules seem unable to fully enjoy cooperative binding of the two β-CD moieties upon inclusion complexation with bis(β-cyclodextrin)s **2**−**5**. As can be seen from Figure 7, the enhanced molecular binding ability (1.1−2.8) is a relatively flat pattern for inclusion complexation of RhB with **2**−**5**. However, closed examination of molecular binding ability toward the BG/RhB pair demonstrates that the tether length between two β-cyclodextrin units can change the original molecular selectivity. The natural β-cyclodextrin **1** and the short-tethered **2** showed relatively good molecular selectivity up to 1.9 and 3.9, respectively, for the RhB/BG pair, but the moderate-tethered **3** and long-tethered **4** and **5** exhibited inverted molecular selectivity, giving the general BG/RhB selectivity of 2.4, 1.9, 1.1, respectively. It is also noted that the inclusion complex stability of bis(β-cyclodextrin)s **2**−**5** with linear guest TNS is higher than that of ANS, but the enhanced molecular binding ability for TNS is less than for ANS, showing weak molecular selectivity for the TNS/ANS pair. These results indicate that the tether length between two β-cyclodextrin units

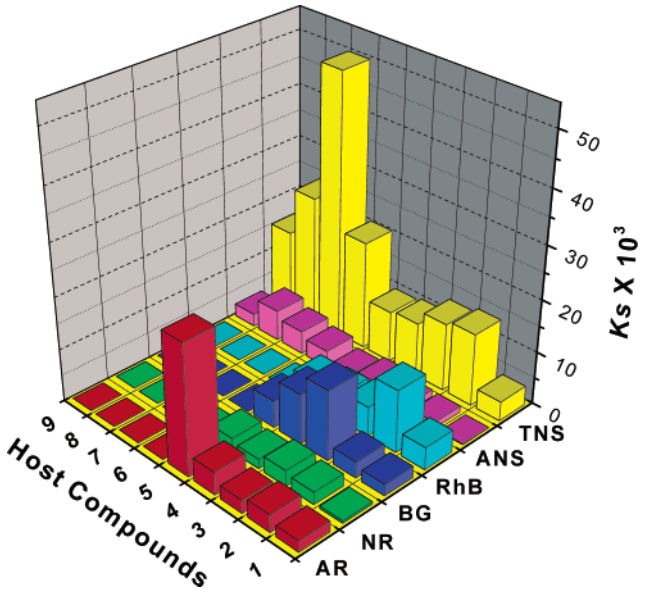

FIGURE 7. Complex stability constants (K_S) for the inclusion complexation of hosts **1**−**9** with guest molecules in aqueous solution.

can control the molecular recognition behavior of bis(β-cyclodextrin)s to some extent. As can be seen from Table 2 and Figure 7, the importance of tether length in molecular recognition is more clearly demonstrated by comparing the host selectivity sequence obtained for six guest dyes. The K_S values for the inclusion complexation of six dyes by host compounds **1**−**5** decrease in following the order:

AR **5** > **4** > **2** > **3** > **1**

NR **3** > **5** > **2** > **4**> **1**

BG **3** > **4** > **5** > **2** > **1**

RhB **2** > **3** > **4** > **5** > **1**

ANS **4** > **5** > **3** > **2** > **1**

TNS **2** > **3** > **4** > **5** > **1**

The complex stability order may be attributed to the distance and contacting surface area between host bis(β-cyclodextrin)s and guest dyes. Typically, the distance between the two cavities in host **2** is too short to appropriately accommodate the triangular BG but is better for the T-shaped guests, giving the higher binding constant for RhB. Further investigation indicated that the Gibbs free energy change ($-\Delta G°$) decreases linearly with an increasing number of ethylene units in the tether (N_E) for the inclusion complexation of bis(β-cyclodextrin)s **2**−**5** with TNS. Using previously reported[17] and present data, the Gibbs free energy changes ($-\Delta G°$) for the inclusion complexation with TNS were plotted against the number of ethylene units in the tether, giving good linear relationships. As shown in Figure 8, the free energy changes ($-\Delta G°$) decrease linearly and afford the unit decrement of complex stability per ethylene ($-d\Delta G°/dN_E$) as 0.44 kJ·mol^{-1} for oligo(ethylenediamino)-bridged bis(β-cyclodextrin)s and 0.32 kJ·mol^{-1} for **2**−**5**. One possible explanation for the unit decrement of complex

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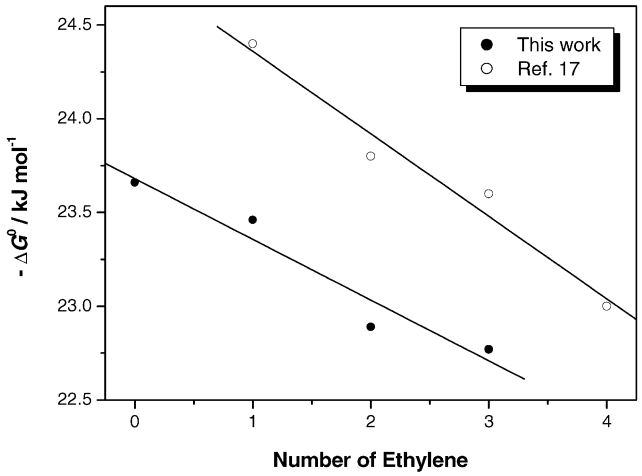

FIGURE 8. Plot of Gibbs free energy changes ($-\Delta G°$) versus the ethylene number in the tether for the inclusion complexation of dimeric β-cyclodextrins **2**−**5** (●) and oligo(ethylenediamino)-bridged bis(β-cyclodextrin)s (○) with TNS.

stability per ethylene unit of the latter is that the flexibility of **2**−**5** linked by rigid polyamine tether is lower than that of the bridged bis(β-cyclodextrin)s linked by olig(ethylendiamine) groups, and then the unit decrement of complex stability per ethylene of former is higher than that of latter. However, careful examination also noted an interesting odd−even effect from the straight lines drawn in Figure 8; i.e. the points for one and three ethylenes are systematically higher and that for two lower than the line. We do not have direct evidence yet whether this effect may be contributing to the relative orientation of cyclodextrin units.

Binding Ability of Metallobridged Bis(β-cyclodextrin)s 6−9. To further extend the original binding ability of modified cyclodextrin, much work has been devoted to the design and syntheses of cyclodextrin derivatives possessing a coordinated metal center. Indeed, metal ions were introduced to the functional groups of a cyclodextrin tether, giving a variety of metallobridged cyclodextrins, which can alter not only the original binding ability of cyclodextrin derivatives but also the molecular selectivity.[37−40] As can be seen from Chart 1 and Table 2, the coordination of Pt(IV) to functional tethers **2**−**5** gave a series of metallobridged bis(β-cyclodextrin)s **6**−**9,** but bis(β-cyclodextrin)s with shorter tethers (**2** and **3**) ligated one metal ion and the bis(β-cyclodextrin)s with longer tethers (**4** and **5**) ligated two metal ions, therefore showing significantly different molecular binding ability for ANS and TNS. This result seems reasonable, since the N and Se atoms in long-tethered **4** and **5** can be jointly ligated to Pt(IV), giving the metallobridged bis(β-cyclodextrin)s with two Pt(IV). Compared to the parent β-cyclodextrin **1** and dimeric β-cyclodextrins **2**−**5**, metallobridged bis(β-cyclodextrin)s **6**−**9** can afford much more stable inclusion complexes with model substrates, attributed to the cooperative association of two tethered hydrophobic cavities with model substrates, the conformation fixed by metal ligation, as well as the additional electrostatic and/or electron-transfer interaction between ligated metal and accommodated guest molecule. As a result of cooperative binding, the binding constant of bis(β-cyclodextrin) **4** with ANS is higher than that of native β-cyclodextrin by a factor of 25, while that of the corresponding metallo-bridged bis(β-cyclodextrin) **8** is greater by a factor of 56.5. This result may point to a mechanism concerning molecular multiple recognition behavior; i.e. two hydrophobic binding sites (cyclodextrin cavities) and one (or two) metal coordination center(s) in metallobridge bis(β-cyclodextrin)s jointly contribute to the cooperative binding toward model substrates. By comparing the enhancement effect for each guest, we can see that the highest enhancement given by metallobridged bis(β-cyclodextrin)s for each guest dye (with the observed enhancement factors shown in the parentheses) is with **8** ($\times$56.5) for ANS and with **7** ($\times$13.7) for TNS, respectively. From a comparison of the enhancement factor, we may conclude that the bent guest ANS is able to fully enjoy the cooperative binding of metallobridged bis(β-cyclodextrin)s compared to the linear guests TNS.

TABLE 3. Thermodynamic Parameters for 1:1 Inclusion Complexation of Guest Molecules with β-Cyclodextrin 1 and Bis(β-cyclodextrin)s 2−5 in Aqueous Solution at 25 °C

host	guest	$-\Delta G°$/kJ·mol^{-1}	$-\Delta H°$/kJ·mol^{-1}	$T\Delta S°$/kJ·mol^{-1}	ref
1	ANS	11.7	6.9	4.8	a
	TNS	19.0	4.0	15.0	b
2	ANS	17.6	22.5	4.9	c
	TNS	23.7	11.8	11.9	c
3	ANS	17.9	45.0	26.9	c
	TNS	23.5	18.9	4.6	c
4	ANS	19.5	11.8	7.7	c
	TNS	22.9	24.3	1.4	c
5	ANS	18.2	26.1	7.9	c
	TNS	22.8	22.0	0.8	c

[a] Reference 25. [b] Reference 26. [c] This work.

Thermodynamic Parameters. Using the common dyes ANS and TNS as guest molecules, fluorometric titrations have been performed at several temperatures ranging from 25.0 to 40.0 °C to calculate the complex stability constants K_S and the Gibbs free energy changes ($\Delta G°$) at different temperatures for inclusion complexation of organoselenium-bridged bis(β-cyclodextrin)s **2**−**5**. The enthalpic and entropic changes ($\Delta H°$ and $\Delta S°$) of the inclusion complexes formation are obtained from the temperature dependence of the equilibrium constant K_S. The thermodynamic parameters obtained for each inclusion complexation of bridged bis(β-cyclodextrin) with selective guest dyes are listed in Table 3. To compare and discuss the molecular binding behavior of parent β-cyclodextrin **1** and bridged bis(β-cyclodextrin)s **2**−**5** possessing different length spacers from the thermodynamic point of view, the thermodynamic quantities Gibbs free energy ($-\Delta G°$), enthalpy ($-\Delta H°$), and entropy changes ($T\Delta S°$) for the inclusion complexation with ANS and TNS are plotted against the hosts **1**−**5** in Figure 9.

As can be recognized more easily from Figure 9, the inclusion reactions of bridged bis(β-cyclodextrin)s **2**−**5**

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(40) Corradini, R.; Dossena, A.; Galaverna, G.; Marchelli, R.; Panagia, A.; Sartor, G. *J. Org. Chem.* **1997**, *62*, 6283.

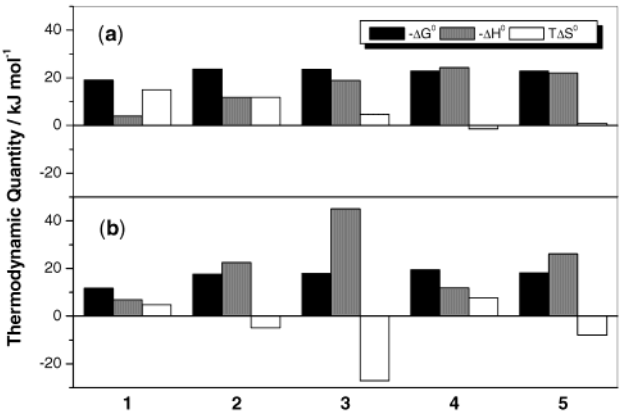

FIGURE 9. Gibbs free energy (−Δ*G*°), enthalpy (−Δ*H*°), and entropy changes (*T*Δ*S*°) for the inclusion complexation of TNS (a) and ANS (b) with β-cyclodextrin and bis(β-cyclodextrin)s **2**−**5** in aqueous buffer solution (pH 7.20) at 25 °C.

with ANS and TNS are all exothermic and give the larger negative enthalpic gain (−Δ*H*°) with positive or negative entropic changes (*T*Δ*S*°), indicating that the inclusion complexes formation is mainly driven by enthalpy. However, the largest enthalpic gain (−Δ*H*°) does not immediately imply the highest complex stability and is often canceled by larger entropic loss, as is the case with bis(β-cyclodextrin) **3** and ANS. It is noted that both ANS and TNS possess a phenyl or naphthyl moiety, but the complexation entropic term of TNS is favorable to that of ANS. Typically, the inclusion complexation of native β-cyclodextrin **1** with TNS shows the entropic driving process, indicating that entropic gain upon extensive desolvation will offset the entropy loss. At the same time, van der Waals or hydrophobic interaction (−Δ*H*° = 11.8 kJ·mol^{-1}) and desolvation (*T*Δ*S*° = 11.9 kJ·mol^{-1}) play almost the same role for **2**, contributing to the Gibbs free energy (−Δ*G*°). One possible explanation for the entropic gain (*T*Δ*S*°) of inclusion complexation with TNS is that the linear TNS allows a more ordered solvent shell, which is broken up upon binding, leading to the favorable entropy term. In view of the structural features of ANS compared with those of TNS, it would appear that an equatorial approach is sterically hindered. The relatively low K_S values appear to support this observation. In the case of ANS, we see that the axial approach is sterically allowed, and this is most likely the mode of complexation.[25] In this case desolvation and van der Waals or hydrophobic interaction jointly contribute to the Gibbs free energy (−Δ*G*°).

Differing from the binding behavior of the parent β-cyclodextrin, the bridged bis(β-cyclodextrin)s **2**−**5** can increase the interaction between the hosts and the guest dyes through the cooperative binding of one guest molecule in the closely located two β-cyclodextrin cavities. Therefore, the inclusion complexation of **2**−**5** with guest dyes as compared with **1** gives the stronger van der Waals and hydrophobic interaction and leads to the higher enthalpy changes (−Δ*H*°), which immediately contribute to the complex stability. As shown in Figure 9, the enhanced binding of ANS by **2**−**5** accompanies a further increase in the originally favorable enthalpic gain (−Δ*H*°) or by a strengthening of the van der Waals or hydrophobic interaction. The reasonable explanation is that the bent guest (ANS) is only poorly accommodated in the cavity of **1** and therefore the contribution of the second cavity in **2**−**5** is much more pronounced to give an enhancement of binding ability. The association process, which leads to the loss of conformational freedom, is inherently accompanied by entropic loss. Therefore, it is not difficult to understand the favorable enthalpic gain (−Δ*H*°) and large entropic loss (*T*Δ*S*°) or less positive entropic gain (*T*Δ*S*°) upon inclusion complexation with bridged bis(β-cyclodextrin)s. The stronger binding of TNS for **2**−**5** than that for **1** is achieved by the exothermic enthalpy changes. Thermodynamically, it may be concluded that the general trend of the enthalpy-driven inclusion complexation for bridged bis(β-cyclodextrin)s **2**−**5** in both cases of ANS and TNS may be ascribed to the cooperative binding mechanism of bridged bis(β-cyclodextrin)s.

Conclusion

In conclusion, bridged bis(β-cyclodextrin)s **2**−**5** tethered by organoselenium bridges significantly extend the original molecular binding ability of parent β-cyclodextrin, and the complex stability constants for the selected guests are larger than native β-cyclodextrin by factors from 1.2 to 56.5 through the cooperative interaction. Furthermore, the complex stability also depends greatly on the tether length of bis(β-cyclodextrin)s and the size/shape of guest. In particular, the coordination of platinum(IV) ion to the tether not only orientates two β-cyclodextrin cavities to fit the shape of guest molecule, but the coordinated Pt also acts an additional site of guest recognition through coordination and/or electrostatic interaction. As an important result, a further enhanced molecular binding ability could be observed for metallobis(β-cyclodextrin)s **6**−**9**. Thermodynamically, the inclusion complexation of **2**−**5** with ANS and TNS is mainly enthalpy driven with a negative or positive entropic contribution. These results further confirm that van der Waals and hydrophobic interaction jointly contribute to the stability of the host−guest inclusion complex.

Experimental Section

Instruments. NMR spectra were performed at 300 MHz. Fluorescence lifetimes were determined by the time-correlated single-photon-counting method 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 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.

Materials. Acridine Red (AR), Neutral Red (NR), Rhodamine B (RhB), Brilliant Green (BG), ammonium 8-anilino-1-naphthalenesulfonate (ANS), and sodium 6-*p*-toluidino-2-naphthalenesulfonic acid (TNS) were commercially available. All chemicals were reagent grade and were used without further purification, unless noted otherwise. β-Cyclodextrin (**1**) of reagent grade 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′-[2,2′-Diselenobis(benzoyloxyl)]-bridged bis(β-cyclodextrin) (**2**) and

6,6′-[2,2′-diselenobis[2-(benzoylamino)ethyleneamino]]-bridged bis(*β*-cyclodextrin) (**3**) were prepared according to the recently reported procedures.[20] 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′-[2,2′-Diselenobis(benzoylamino-3-azapentylamino)]-Bridged Bis(*β*-cyclodextrin) 4. Mono-[6-(5-amino-3-azapentylamino)-6-deoxy]-*β*-cyclodextrin (1 mmol) was dissolved in DMF (30 mL) and then treated with 1 equiv of DCC, 1-hydroxybenzotriazole hydrate (HOBT), and 2,2′-diselenobis(benzoic acid)[41] (0.5 mmol). The mixture was stirred for 12 h in an ice bath and another 18 h at room temperature, and then allowed to stand for 3 days until no more precipitation deposited. The precipitate was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in a minimum amount of hot water and then poured into 150 mL of acetone. The precipitate formed was collected by filtration. This procedure was repeated several times. The crude product thus obtained was purified on a column of Sephadex G-25 with water as eluent. After the residue was dried in vacuo, a pure sample was obtained in 15% yield as a light yellow solid. MS (MALDI-TOF): *m*/*z* 2843 [M + K]+. ^{1}H NMR (D_2O, TMS): 2.7−3.1 (m, 16H), 3.3−3.8 (m, 84H), 4.8 (m, 14H), 7.1−7.9 (m, 8H). IR (KBr) ν/cm^{-1} 3300.6, 2928.0, 1659.0, 1630.1, 1586.5, 1548.7, 1533.9, 1500.0, 1429.7, 1367.0, 1152.6, 1078.8, 1031.4, 943.5, 855.6, 752.8, 704.7. UV/vis (water): λ_{max} (ϵ) = 308.5 nm (5900 mol^{-1} dm^3 cm^{-1}). Anal. Calcd for $C_{106}H_{168}O_{70}N_6Se_2 \cdot 5H_2O$:·C, 43.99; H, 6.20; N, 2.90. Found: C, 44.04; H, 6.07; N, 3.12.

Synthesis of 6,6′-[2,2′-Diselenobis(benzoylamino-3,6-diazaoctylamino)]-Bridged Bis(*β*-cyclodextrin) 5. Bis(*β*-cyclodextrin) **5** was prepared in 12% yield from 2,2′-diselenobis-(benzoic acid)[41] and mono[6-(8-amino-3,6-diazaoctylamino)-6-deoxy]-*β*-cyclodextrin according to a procedure similar to that described above. MS (MALDI-TOF): *m*/*z* 2930 [M + K]$^+$. ^{1}H NMR (D_2O, TMS): 2.5−2.9 (m, 24H), 3.1−3.9 (m, 84H), 4.8 (m, 14H), 7.1−7.9 (m, 8H). IR (KBr) ν/cm^{-1} 3302.0, 2928.2, 1659.6, 1640.3, 1629.5, 1586.9, 1548.8, 1534.1, 1429.6, 1366.3, 1331.5, 1152.9, 1079.0, 1032.1, 943.3, 856.1, 752.5, 704.7. UV/vis (water): λ_{max} (ϵ) = 310.0 nm (6000 mol^{-1} dm^3 cm^{-1}). Anal. Calcd for $C_{110}H_{178}O_{70}N_8Se_2 \cdot 10H_2O$: C, 43.03; H, 6.50; N, 3.65. Found: C, 42.91; H, 6.40; N, 4.06.

Bis(*β*-cyclodextrin)−Pt(IV) Complex 6. The complex **6** was synthesized by the reaction of bis(*β*-cyclodextrin) **2** with $PtCl_4$ in aqueous solution. The complex obtained was purified by column chromatography over Sephadex G-25 with distilled, deionized water to give a pure sample in isolated yields of 70%. ^{1}H NMR (D_2O, TMS) 3.2−3.8 (m, 80H), 4.8−5.2(m, 14H), 7.5−8.1 (m,8H). IR (KBr) ν/cm^{-1} 3302.2, 2931.5, 1708.7, 1690.5, 1663.5, 1636.4, 1586.2, 1409.7, 1298.5, 1152.1, 1078.0, 1028.6, 942.4, 855.8, 750.9, 705.7, 578.4. UV/vis (water): λ_{max} (ϵ) = 317.0 nm (7900 mol^{-1} dm^3 cm^{-1}). Anal. Calcd for $C_{98}H_{146}O_{72}Se_2 \cdot PtCl_4 \cdot 8H_2O$: C, 37.79; H, 5.24. Found: C, 38.03; H, 5.13.

Bis(*β*-cyclodextrin)−Pt(IV) Complex 7. Bis(*β*-cyclodextrin) complex **7** was prepared according to procedures similar to those for the synthesis of **6** in 70% yield. ^{1}H NMR (D_2O, TMS) 3.2−3.7 (m, 84H), 4.8−4.9 (m, 14H), 7.3−8.0 (m, 8H). IR (KBr) ν/cm^{-1} 3298.1, 2929.8, 1649.6, 1592.1, 1412.6, 1367.4, 1331.5, 1258.2, 1152.8, 1078.2, 1028.8, 943.8, 856.6, 753.7, 705.1. UV/vis (water): λ_{max} (ϵ) = 317.0 nm (9900 mol^{-1} dm^3 cm^{-1}). Anal. Calcd for $C_{102}H_{158}O_{70}N_4Se_2 \cdot PtCl_4 \cdot 8H_2O$: C, 38.29; H, 5.48; N, 1.75. Found: C, 37.95; H, 5.40; N, 1.93.

Bis(*β*-cyclodextrin)−Pt(IV) complex 8. Bis(*β*-cyclodextrin) complex **8** was prepared according to procedures similar to those for the synthesis of **6** in 65% yield. ^{1}H NMR (D_2O, TMS) 3.2−3.7 (m, 84H), 4.9−5.2 (m, 14H), 7.2−8.0 (m, 8H). IR (KBr) ν/cm^{-1} 3294.7, 2928.7, 1699.0, 1650.3, 1591.1, 1558.8, 1540.6, 1418.7, 1364.1, 1337.7, 1152.3, 1078.1, 1029.6, 943.8, 854.4, 751.6, 705.0. UV/vis (water): λ_{max} (ϵ) = 288 nm (14 200 mol^{-1} dm^3 cm^{-1}). Anal. Calcd for $C_{106}H_{168}O_{70}N_6Se_2 \cdot 2PtCl_4 \cdot 10H_2O$: C, 34.80; H, 5.18; N, 2.29. Found: C, 34.91; H, 4.99; N, 2.19.

Bis(*β*-cyclodextrin)−Pt(IV) complex 9. Bis(*β*-cyclodextrin) complex **9** was prepared according to procedures similar to those in the synthesis of **6** in 62% yield. ^{1}H NMR (D_2O, TMS) 3.3−3.7 (m, 84H), 4.9−5.2 (m, 14H), 7.2−8.0 (m, 8H). IR (KBr) ν/cm^{-1} 3310.1, 2928.6, 1649.8, 1589.9, 1558.7, 1418.3, 1366.3, 1335.4, 1300.7, 1152.5, 1078.4, 1030.3, 943.8, 855.5, 751.6. UV/Vis (water): λ_{max} (ϵ) = 295 nm (9900 mol^{-1} dm^3 cm^{-1}). Anal. Calcd for $C_{110}H_{176}O_{70}N_8Se_2 \cdot 2PtCl_4 \cdot 8H_2O$: C, 35.63; H, 5.27, N 3.02. Found: C 35.79, H 5.35, N 2.68.

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Supporting Information Available: 2D NOESY spectrum of host compound **4** in D_2O; the method for calculating the thermodynamic parameters and stability constants (K_S) for 1:1 inclusion complexation of ANS and TNS with *β*-cyclodextrin **1** and bis(*β*-cyclodextrin)s **2**−**5**; and typical plots of log K_S versus 1/*T* for the fluorometric titrations of **2**−**5** with TNS. This material is available free of charge via the Internet at http://pubs.acs.org.

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