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Molecular Recognition and Cooperative Binding Ability of Fluorescent Dyes by Bridged Bis(β-cyclodextrin)s Tethered with Aromatic Diamine

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Abstract

A novel bridged bis(β-cyclodextrin), *m*-phenylenediimino-bridged bis(6-imino-6-deoxy-β-cyclodextrin) (**2**), was synthesized by the reaction of *m*-phenylenediamine and 6-deoxy-6-formyl-β-cyclodextrin. The inclusion complexation behavior of the novel bridged bis(β-cyclodextrin) **2**, as well as native β-cyclodextrin (**1**), *p*-phenylenediamino-bridged bis(6-amino-6-deoxy-β-cyclodextrin) (**3**) and 4,4′-bianilino-bridged bis(6-amino-6-deoxy-β-cyclodextrin) (**4**) with representative fluorescent dye molecules, i.e., acridine red (AR), neutral red (NR), Rhodamine B (RhB), ammonium 8-anilino-1-naphthalenesulfonate (ANS) and sodium 6-toluidino-2-naphthalenesulfonate (TNS), was investigated at 25 °C in aqueous phosphate buffer solution (pH 7.20) by means of fluorescence, and circular dichroism, as well as 2D NMR spectrometry. The spectrofluorometric titrations have been performed to calculate the complex stability constants (K_S) and Gibbs free energy changes (ΔG°) for the stoichiometric 1 : 1 inclusion complexation of **1–4** with fluorescent dye molecules. The results obtained demonstrated that bis(β-cyclodextrin)s **2–4** showed much higher affinities toward these guest dyes than native β-cyclodextrin **1**. Typically, dimer **2** displayed the highest binding ability upon inclusion complexation with ANS, affording 35 times higher K_S value than native β-cyclodextrin. The significantly enhanced binding abilities of these bis(β-cyclodextrin)s are discussed from the binding mode and viewpoints of size/shape-fit concept and multiple recognition mechanism.

Introduction

As a very important family of cyclodextrin derivatives, bridged bis(cyclodextrin)s are known to greatly enhance the original molecular binding ability and selectivity of native cyclodextrins through the cooperative binding of a single model substrate by two hydrophobic cavities located in a closely vicinity [1–4], and therefore provide an excellent model system mimicking the substrate-specific interaction of enzymes [5–6]. Consequently, a wide variety of bridged bis(β-cyclodextrin)s have been synthesized in order to examine and compare the molecular binding abilities of native cyclodextrin and bridged bis(cyclodextrin)s and also to gain insights into factors governing the inclusion complexation phenomena between the host bis(β-cyclodextrin)s and guest molecules [7–16]. Recently, we have shown that some bridged β-cyclodextrin dimers linked by organoselenium, oligoethylenediamine, and 2,2′-bipyridine-4,4′-dicarboxy tethers can form more stable complexes with guest molecules, displaying the higher molecular binding ability and selectivity [17–23]. Studies on molecular recognition of bis(β-cyclodextrin)s in turn help us understand the multiple recognition mechanism and the induced-fit interaction working between the biological acceptor and substrates [22].

In the present paper, we wish to report our investigation results on the synthesis of bridged bis(β-cyclodextrin)s tethered through aromatic diamine (Chart 1) and their molecular binding ability with fluorescent dyes. The inclusion complexation behavior of bis(β-cyclodextrin)s **2–4** has been investigated at 25 °C in aqueous phosphate buffer solution (pH 7.20) by means of fluorescence, circular dichroism, and 2D NMR spectrometry. The complex stability constants (K_S) and Gibbs free energy changes (ΔG°) obtained for some structurally related fluorescent guest molecules (Chart 2) are compared with parent β-cyclodextrin in order to elucidate the inclusion complexation mechanism with bridged bis(β-cyclodextrin)s. It is our special interest to examine and discuss the effects of chain length and/or rigidity of tether moieties in bridged bis(β-cyclodextrin)s upon the inclusion complexation with fluorescent guest molecules.

Experimental

Materials

Ammonium 8-anilino-1-naphthalenesulfonate (ANS) and sodium-6-toluidino-2-naphthalenesulfonate (TNS) were

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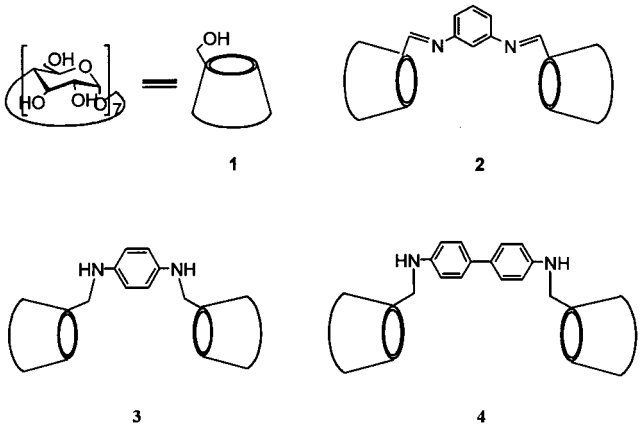
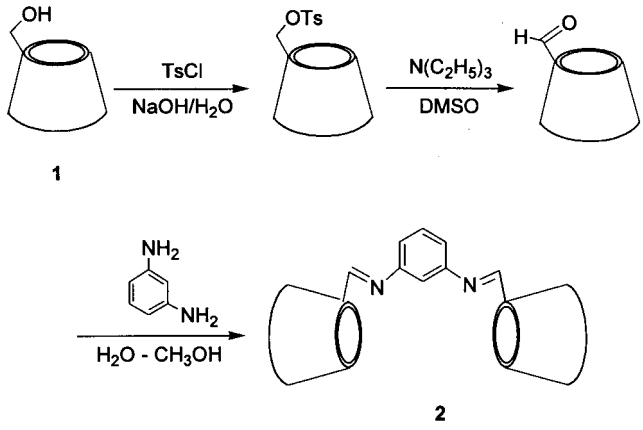


Chart 1.



Scheme 1.

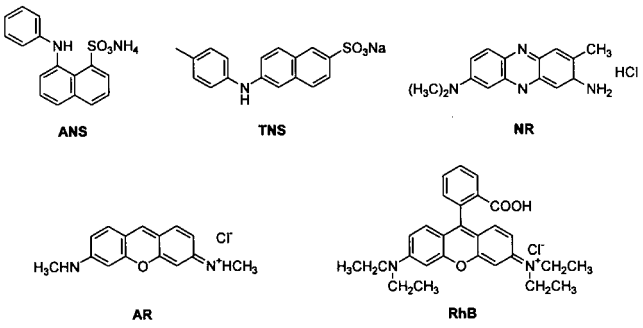


Chart 2.

purchased from Wako. Acridine Red (AR), Neutral Red (NR) and Rhodamine B (RhB) were purchased from Tianjin Chemical Reagent Plant. 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. Mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin was prepared by the reaction of β-cyclodextrin with *p*-toluenesulfonyl chloride in aqueous alkaline solution [24]. 6-Deoxy-6-formyl-β-cyclodextrin was prepared according to the reported procedure [25]. *p*-phenylenediamino-bridged bis(6-amino-6-deoxy-β-cyclodextrin) (**3**) and 4,4′-bianilino-bridged bis(6-amino-6-deoxy-β-cyclodextrin) (**4**) were prepared according to our previous report [26a].

Synthesis of *m*-phenylenediimino-bridged bis(6-imino-6-deoxy-β-cyclodextrin) (**2**).

As shown in Scheme 1, 6-deoxy-6-formyl-β-cyclodextrin (1.0 g) and *m*-phenylenediamine (0.5 g) were dissolved in 1 : 2 (V/V) H_2O—CH_3OH (30 mL), and several drops of acetic acid were added to catalyze the reaction. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 5 days, and then the mixed solvent was evaporated under reduced pressure to dryness on a rotary evaporator. The residue was dissolved in a small amount of water, and subsequently the resultant solution was poured into acetone with vigorous stirring to produce a brown-yellow precipitate. After collected by filtration, the crude product was purified by column chromatography on Sephadex G-25 with the distilled, deionized water as eluent to give a pure sample (0.3 g, yield 29%). Anal. Calcd for $C_{90}H_{140}O_{68}N_2 \cdot 12H_2O$: C, 42.17; H, 6.15; N, 1.13. Found: C, 42.32; H, 6.47; N, 1.09. ^{1}H NMR (D_2O, 300 MHz, TMS, ppm): δ 3.4–4.0 (m, 84 H), 4.99 (m, 14 H), 6.4–6.6 (m, 4 H), 7.8 (s, 2 H). FT-IR (KBr) ν/cm^{-1}: 3284, 2935, 1727, 1662, 1606, 1529, 1409, 1349, 1268, 1152, 1079, 1028, 935, 850. UV/vis (H_2O) λ_{max}/nm (ϵ/dm^3 mol^{-1} cm^{-1}: 214 (20140), 293 (3327).

Measurements

Elemental analyses were performed on a Perkin–Elmer-2400C instrument. NMR spectra were recorded on a Varian Mercury VX300 instrument. FT-IR spectra were obtained on a Nicolet FT-IR 5DX. Circular dichroism (CD) and UV-Vis spectra were recorded in a conventional quartz cell (light path 10 mm) on a JASCO J-715S spectropolarimeter and a Shimadzu UV-2401PC spectrophotometer equipped with a PTC-348WI temperature controller to keep the temperature at 25 °C, respectively. Fluorescence spectra were measured in a conventional quartz cell (10 × 10 × 45 mm) at 25 °C on a JASCO FP-750 spectrometer equipped with a constant-temperature water bath, with the excitation and emission slits of 5 nm width for all the fluorescent dyes. The excitation wavelengths for ANS, TNS, NR, AR, and RhB were 350, 366, 510, 490 and 520 nm, respectively. In the fluorescence titration experiments, the concentration ranges of dyes and cyclodextrin dimers were 1 $\sim$ 10 μM and 30 $\sim$ 400 μM, respectively. Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in deionized, distilled water to make a 0.10 M aqueous phosphate buffer solution of pH 7.20, which was used as solvent for all spectral measurements.

Results and discussion

Circular dichroism spectra

The induced circular dichroism (ICD) spectra of **2–4** have been performed at a concentration of 1 × 10^4 mol dm^{-3} in aqueous buffer solution at pH 7.20 in order to obtain information about the original conformation of bridged

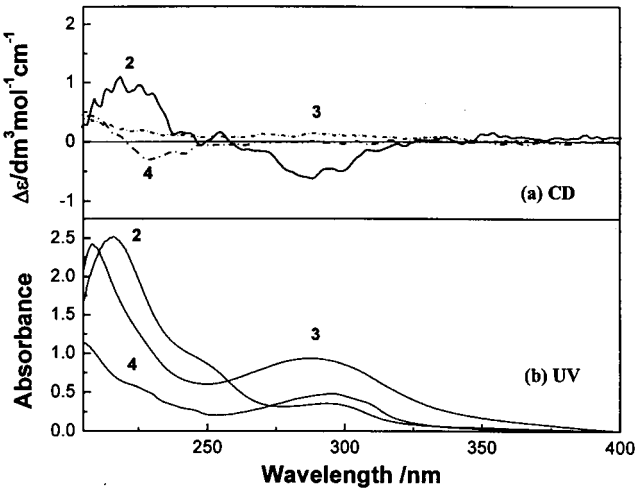


Figure 1. (a) Circular dichroism spectra and (b) absorption spectra of β-cyclodextrin derivatives **2–4** (1.0×10^{-4} M) in aqueous phosphate buffer solution (pH 7.20) at 25 °C.

bis(β-cyclodextrin)s linked by aromatic diamine tether in dilute aqueous solution [27]. As shown in Figure 1, possessing similar aromatic chromophoric tether appended to β-cyclodextrin, the hosts **2–4** display different ICD spectra in the absence of guest. Host **3** showed very weak positive Cotton effect broad peaks. However, the ICD spectra of host **4** showed only a weak negative cotton effect peak at 228 nm ($\Delta\epsilon = -0.302$ dm^3 mol^{-1} cm^{-1}). This weak negative Cotton effect observed for ^1L_a band of **4** would be better analyzed as an ordinary CD induced by the distant chiral cyclodextrin moieties, although a shallow binding or perching model is not rigorously ruled out. β-cyclodextrin dimer **2** exhibits moderate positive cotton effect peak ($\Delta\epsilon = +1.1$ dm^3 mol^{-1} cm^{-1}) at 219 nm and a weak negative cotton effect peak ($\Delta\epsilon = -0.62$ dm^3 mol^{-1}cm^{-1}) at 288 nm, which belong to the ^1L_a band and ^1L_b band, respectively. According to the sector rule proposed by Kajtar [28] and Harata *et al.*'s empirical rule [29, 30], it is deduced that the aromatic tether cannot deeply include into its hydrophobic cavity of β-cyclodextrin, but shallowly perching over the rims of two β-cyclodextrin cavities, which may favor inclusion complexation with guest molecule.

Binding model

Since two protons located closely in space can produce an NOE cross-peak between the relevant protons in the NOESY or ROESY spectra, two-dimensional NMR spectroscopy has recently become an important method for the investigation of the interaction between host cyclodextrins and guest molecules. In order to deduce the binding model and molecular recognition mechanism upon inclusion complexation with bridged bis(β-cyclodextrin)s, two-dimensional NMR spectroscopy experiments were performed on a Varian Mercury VX300 spectrometer. In our previous reports, we have investigated the binding model of bridged bis(β-cyclodextrin)s with the different relative longer spacer upon inclusion complexation with T-shape guest dye molecule [21, 23], indicating the sandwich-type conformation and the operation of the cooperative binding mode in the complexation of RhB by bis(β-cyclodextrin). In order to further expand our research, bridged bis(β-cyclodextrin)s (**2**) with shorter and/or rigid spacer is chosen as host to examine the cooperative binding behavior of two more adjacent cavities upon inclusion complexation with T-shape guest. Under our experimental condition, the carboxyl group of RhB using as guest molecule in aqueous solution is not protonated and should exist as a carboxylate anion [21a]. We recorded the NOESY spectrum of a 5.0 mM solution of RhB in D_2O in the presence of an equimolar **2** and obtained experimentally detectable species signals (Figure 2). It is well known that there is a balance between inclusion and dissociation of modified cyclodextrins in solution, so the cross-peaks arising from space correlations between host and guest present both inside protons and outside protons of the cyclodextrin in the NOESY spectra. As shown in Figure 2, 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), it means that the methyl protons of diethylamino groups could be deeply embedded in the cavities of β-cyclodextrin dimers. Further information about how the diethylamino groups were included into the hydrophobic cavity of cyclodextrin may be reasonably deduced according to the cross-peaks B. The cross-peaks between H-5 and all aromatic protons of diethylamino-phenyl in RhB (peaks B except for B′) together with that between H-3 and only *ortho* protons of diethylamino (peak B′) imply that the aromatic ring jointing diethylamino groups should be located near to H-5, and the *ortho* protons enter shallowly the primary hydroxyl side of cyclodextrin. Therefore, the diethylamino groups in RhB must be included into the hydrophobic cavities of cyclodextrin dimer from the primary hydroxyl side. Unlike the bonding model between 2,2′-bipyridine-4,4′-dicarboxy-bridged bis(6-*O*-β-cyclodextrin) and RhB [23], the NOE cross-peaks between the aromatic protons of the linker in **2** and the aromatic protons of the benzoate moiety in RhB were not observed, which indicates that benzoate moiety in RhB must be away from the aromatic protons of *m*-phenylenediimine in **2**. These results show that the cooperative interaction only exists between the two cavities of **2** and RhB as deduced binding model in Figure 3.

Fluorescence titrations

For a more quantitative assessment of the inclusion complexation behavior of β-cyclodextrin **1** and its dimers **2–4** with fluorescent dye molecules, i.e., ANS, TNS, AR, NR and RhB, fluorescence titrations have been performed at 25 °C in aqueous phosphate buffer solution (pH 7.20). Figure 4 illustrates the typical fluorescence changes of TNS upon gradual addition of host **2**. As can be seen from Figure 4, the stepwise addition of a known amount of the host **2** to a dilute TNS solution (10 μM) caused significant enhancement in fluorescence intensity, accompanying appreciable bathochromic shift of the fluorescence peak. Since TNS, just like ANS, is only weakly fluorescent in highly polar media such as water but becomes extremely fluorescent in nonpolar environments; therefore, the increase in fluorescence intens-

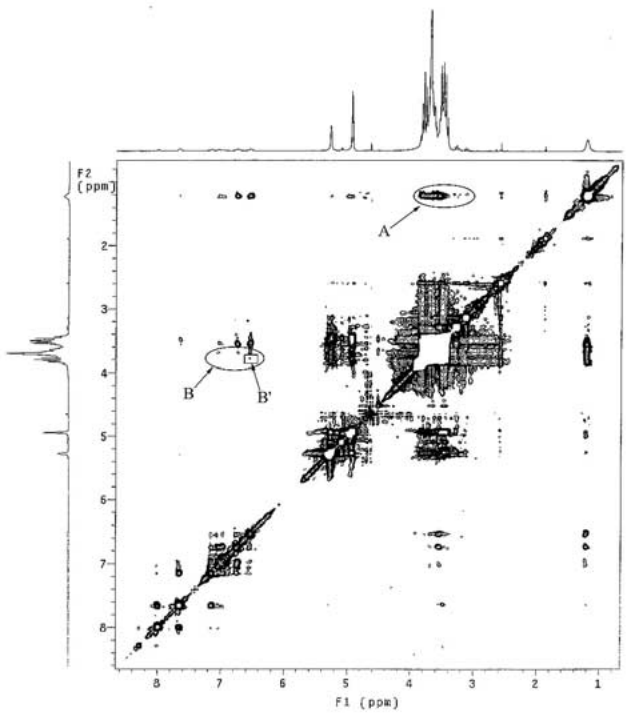


Figure 2. ^{1}H-NOESY spectrum (300 MHz) of a mixture of **2** with RhB ([**2**] = [RhB] = 5.0×10^{-3} M) in D_2O at 298 K with a mixing time of 600 ms.

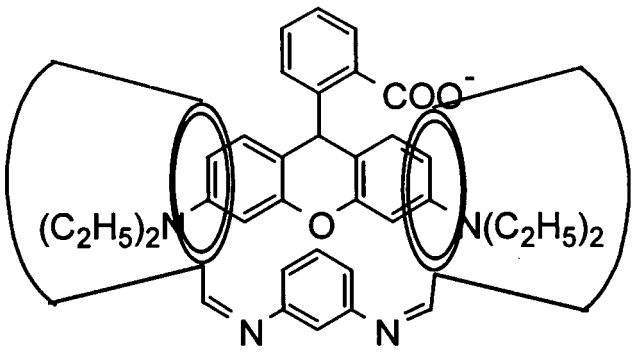


Figure 3. Plausible inclusion complexation mode of RhB with **2**.

ity of TNS observed is attributed to the incorporation of the TNS aromatic group into the nonpolar cavities of bridged bis(β-cyclodextrin) **2**. Therefore, this enhancement is due to a combination of effects resulting from a specific host-guest inclusion complex formation including the protection of the bound fluorophore from external quenchers such as oxygen, the inhibition of the "free rotor" effect for the bound fluorophore, and the exposure of the bound fluorophore to a less polar environment [31].

Assuming stoichiometry 1 : 1 complexation, where the two β-cyclodextrin moieties in bis(β-cyclodextrin) are treated as a single unit [32], the inclusion complexation of guest dye (Dye) with host cyclodextrin (CD) is expressed by Equation (1).

$$\mathrm{CD} + \mathrm{Dye} \overset{K_S}{\rightleftharpoons} \mathrm{CD} \cdot \mathrm{Dye}. \tag{1}$$

The fluorescence spectral change (ΔI_f) upon stepwise addition of host cyclodextrin, where $\Delta I_f = I_f$ (with host) $- I_f$ (without host), is assumed to be proportional

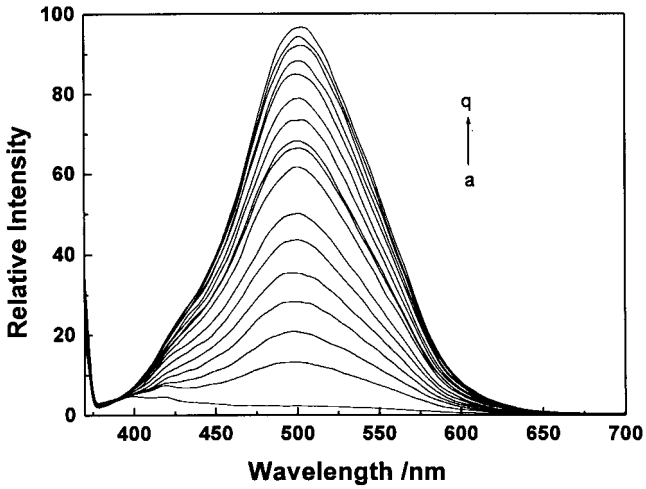


Figure 4. Fluorescence spectral changes of TNS (10 μM) upon addition of *m*-phenylenediamino-bridged bis(6-imino-6-deoxy-β-cyclodextrin) **2** in aqueous buffer solution at pH 7.20; [2] = 0 $\sim$ 228 μM (from a to q). Excitation wavelength was 366 nm.

to the concentration of inclusion complex produced, i.e., $\Delta I_f = \alpha$ [CD · Dye]. Herein α is the proportionality coefficient, which may be taken as a sensitivity factor for the fluorescence change upon complexation. Then the stability constants (K_S) can be calculated using a non-linear least-squares curve-fitting method according to the Equation (2) [26b].

$$\Delta I_f = \{\alpha([\mathrm{CD}]_0 + [\mathrm{Dye}]_0 + 1/K_s) \pm \sqrt{\alpha^2([\mathrm{CD}]_0 + [\mathrm{Dye}]_0 + 1/K_s)^2 - 4\alpha^2[\mathrm{CD}]_0[\mathrm{Dye}]_0}\}/2, \tag{2}$$

where $[\mathrm{Dye}]_0$ and $[\mathrm{CD}]_0$ refer to the total concentrations of fluorescent dye molecule and bis(β-cyclodextrin), respectively. For each host–guest system examined, the ΔI_f values were plotted as a function of $[\mathrm{CD}]_0$ to give an excellent fit, verifying the validity of the 1 : 1 complex stoichiometry assumed above. Figure 5 illustrates the curve-fitting analyses result for the inclusion complexation of bis(β-cyclodextrin) **2** with ANS. As shown in Figure 5, the experimental data do not show any serious deviations from the theoretical curve. In the repeated measurements, the K_S values were reproducible within an error of $\pm 5\%$. The K_S values obtained by the curve fitting are listed in Table 1, along with the free energy changes ($-\Delta G^\circ$) of complex formation.

Molecular binding ability and molecular selectivity

Native and simple modified cyclodextrins afford only very small binding constants probably due to the weak van der Waals and hydrophobic interactions. However, possessing dual hydrophobic cavities, bridged bis(β-cyclodextrin)s **2–4** with simple tethers exhibit the significantly enhanced molecular binding ability through the cooperative binding of two adjacent cavities and multiple recognition towards model substrates. As can be seen from Table 1, the binding constants of bis(β-cyclodextrin)s **2–4** with the guest fluorescent dye molecules are larger than those of native β-cyclodextrin; that is, the K_S values for the dimeric hosts

Table 1. Complex stability constants (K_S) and Gibbs free energy change ($-\Delta G^\circ$) for 1 : 1 inclusion complexation of organic dyes with β-cyclodextrin **1** and bis(β-cyclodextrin)s **2–4** in aqueous buffer solution (pH 7.20) at 25 °C

Host	Guest	λ^F_{max}/nm[a]	K_S	Log K_S	$-\Delta G^\circ$ (kJ/mol)	Ref.
1	NR	576	480 ± 20	2.68	15.30	b
	AR	552	2630	3.42	19.5	d
	ANS	515	103	2.01	11.5	c,d
	TNS	475	3670	3.56	20.3	b
	RhB	572	4240	3.63	20.7	d
2	NR	591	880 ± 40	2.95	16.82	b
	AR	558	9420 ± 400	3.97	22.68	b
	ANS	517	3600 ± 150	3.56	20.30	b
	TNS	500	9020 ± 400	3.95	22.58	b
	RhB	571	5180 ± 200	3.72	21.2	b
3	NR	590	630 ± 30	2.80	15.97	b
	AR	552	45000 ± 1000	4.65	26.6	d
	ANS	515	1470 ± 50	3.17	18.1	b,d
	TNS	476	6200 ± 300	3.79	21.65	b
	RhB	571	6720 ± 300	3.83	21.8	d
4	NR	592	1382 ± 50	3.14	17.93	b
	AR	592	8200 ± 400	3.91	22.3	b,d
	ANS	516	641 ± 30	2.81	16.0	b,d
	TNS	475	5440 ± 200	3.73	21.32	b
	RhB	572	6770 ± 300	3.83	21.9	d

[a] Ultimate fluorescence maximum obtained upon addition of large excess of host, while the λ^F_{max} of AR, NR, ANS, TNS and RhB are 559, 598, 522, 418 and 572 nm, respectively.
[b] This work.
[c] References [17, 26b].
[d] Reference [26a].

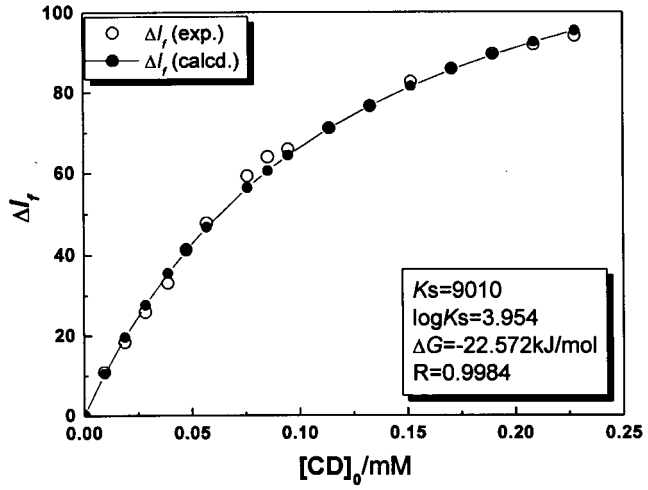


Figure 5. Curve-fitting analyses of fluorescence titration of TNS with *m*-phenylenediamino-bridged bis(6-imino-6-deoxy-β-cyclodextrin) **2** in aqueous buffer solution at pH 7.20.

are enhanced by factors of 1.5-35 for **2**, 1.0-17 for **3**, and 1.5–6.2 for **4**, respectively. Typically, bis(β-cyclodextrin) **2** gives the highest complex stability up to 35 times for ANS as compared with parent β-cyclodextrin upon inclusion complexation. This phenomenon can be arising from the strict size/shape-fit relationship between host and guest, which gives the strongest host–guest hydrophobic interaction. Moreover, further comparison of the molecule structure of the fluorescent dyes examined shows that these pairwise guest molecules for TNS/ANS and AR/NR pairs share some structural similarity; that is, both TNS and ANS possess a naphthalene component, while either AR or NR bears a linear tricyclic aromatic backbone or skeleton. Though these guest molecules possess the structural similarity, the substituent differences will consequently result in their entirely different binding ability with host β-cyclodextrins. As shown in Table 1, the native β-cyclodextrin **1** and bis(β-cyclodextrin)s **2–4** examined form a less stable complex with ANS than with TNS. The examinations with CPK molecular models indicate that ANS can only partly include into the β-cyclodextrin cavity to form a weak inclusion complex as a result of the steric hindrance arising from its bent structure, but the hydrophobic naphthalene fragment of TNS can be embedded deeply into the cavity of β-cyclodextrin in the longitudinal direction [17]. Interestingly, the molecular binding constants of bis(β-cyclodextrin)s **2–4** with ANS and TNS are gradually decreased with the increase of the host tether length, giving a sequence of **2 > 3 > 4**. One possible explanation for the binding ability sequence of host compounds may be the gradually declining chelate effect upon extending the distance between two cyclodextrin moieties. Among the dual β-cyclodextrin hosts examined, bis(β-cyclodextrin) **2** shows the higher K_S values for ANS and TNS but the lowest molecular selectivity for TNS/ANS pair, while host **4** affords the lower K_S value for TNS and ANS but the highest TNS/ANS molecular selectivity up to 8.5 times. This may be attributed to the fact that host **2**, which possesses the shortest and most rigid linker group among dimeric cyclodextrins examined, are most suitable for the inclusion complexation with ANS and TNS. As

compared with host **2**, bis(β-cyclodextrin) **4** possessing the longer chain tether with the slight flexibly jointed chain may be unfavorable for the cooperative binding of the two adjacent cyclodextrin cavities to some extent, making inclusion complex loose. However, host **3** with a tether of moderate length and rigidity gives moderate binding affinity and molecular selectivity.

It is noted that the native β-cyclodextrin **1** and bis(β-cyclodextrin)s **2–4** gave significantly higher K_S for AR than NR. The stronger binding ability for inclusion complexation of AR with **2–4** illuminated reasonably that the linear guest AR with relatively small substituent such as aminomethyl group can be well embedded in the cavity of β-cyclodextrin, while the linear guest NR is only poorly accommodated in the cavity of β-cyclodextrin, attributing to the steric hindrance caused by the larger substituent. Unexpectedly, the molecular binding abilities of bis(β-cyclodextrin)s **2–4** towards AR and NR do not always decrease with increasing host tether length but vary in an order of **3 > 2 > 4** for AR and **4 > 2 > 3** for NR. In the present case, the tether length and flexibility of hosts and size/shape of guests maybe control the inclusion complexation behavior with bis(β-cyclodextrin)s, and determine the complex stability.

The importance of tether length between two β-cyclodextrin units is more clearly demonstrated by comparing the binding ability of RhB with host compounds **2–4**. Different from the linear guest molecules such as AR, NR, and TNS, the K_S value for the inclusion complexation of T-shaped guest RhB by bis(β-cyclodextrin)s **2–4** is increased with increasing host tether length. The investigation results by 2D NMR indicated that the short-tethered **2** can also occur the cooperative binding for inclusion complexation with T-shaped RhB. Therefore, the enhanced tether length or the increased relative molecular flexibility can control the binding behavior of bis(β-cyclodextrin)s with T-shaped RhB molecule, and increase the complex stability.

Conclusion

The bridged bis(β-cyclodextrin)s can enhance the original binding ability of native β-cyclodextrin by the cooperative binding of one guest molecular in the two closely located β-cyclodextrin cavities, giving the highest binding abilities towards ANS up to 35 times higher than native β-cyclodextrin. The inclusion complexation behavior of dimeric hosts mainly depends on the conformation, length, and flexibility of the tether group, which may control how the dual cyclodextrin cavities adjust orientation and conformation to cooperatively bind guest molecule.

Acknowledgements

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