Synthesis of Novel Bis(β-cyclodextrin)s Linked with Glycol and Their Inclusion Complexation with Organic Dyes

by **Yong Zhao**[a]), **Yong Cun Yang**[a]), **Hao Shi**[a]), **Hong You Zhu**[b]), **Rong Huang**[c]), **Chao Ming Chi**[a]), and **Yan Zhao***[a])

[a]) College of Chemistry and Chemical Engineering, Yunnan Normal University, Kunming 650092, P. R. China (phone/fax: +86-871-5516061; e-mail: zhaooyann@163.com)

[b]) School of Chemical Science and Technology, Yunnan University, Kunming 650091, P. R. China

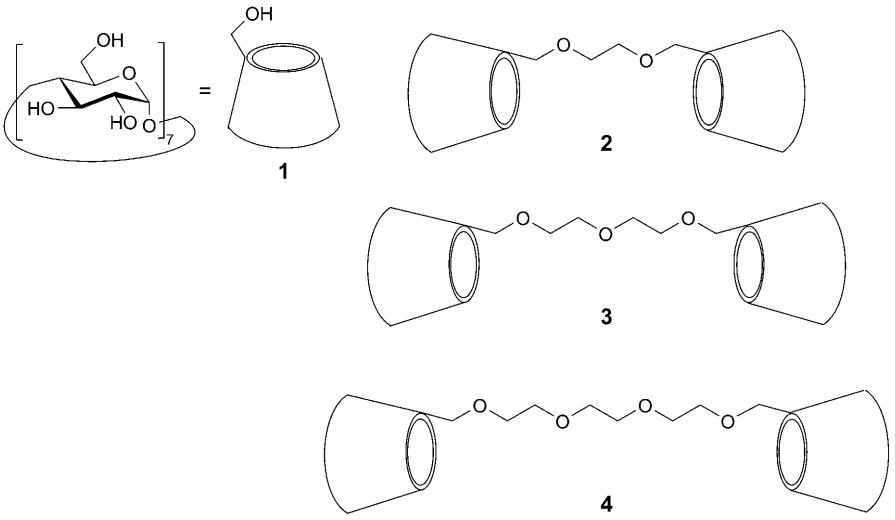
[c]) Experimental Center, Yunnan University, Kunming 650091, P. R. China

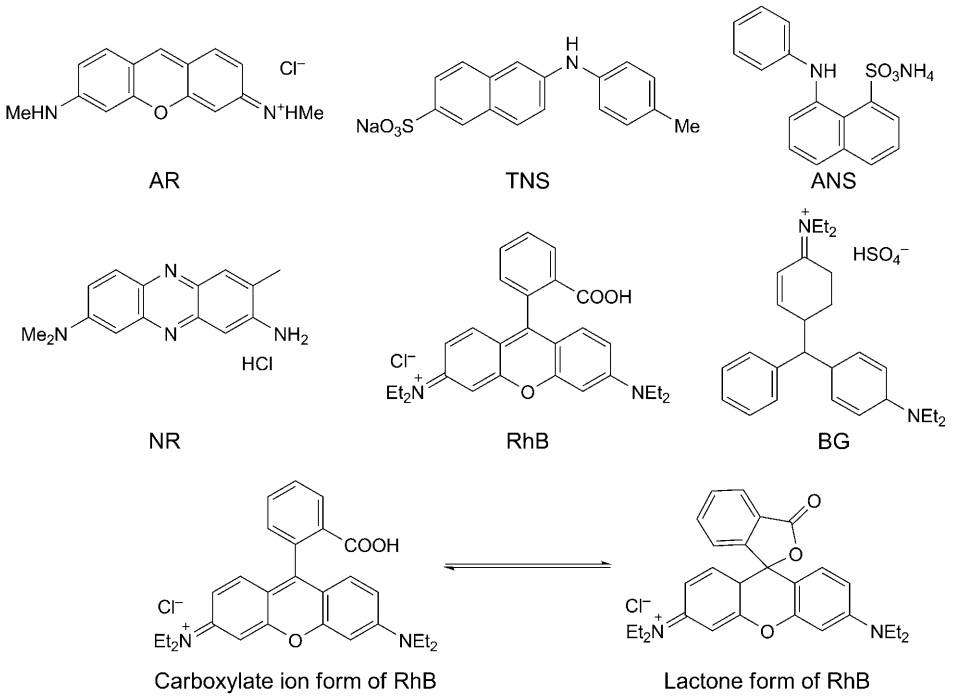
Three novel bis(β-cyclodextrin (CD))s with flexible glycol linkers, *i.e.*, ethylene glycol-bridged bis(6-hydroxy-6-deoxy-β-CD) (**2**), diethylene glycol-bridged bis(6-hydroxy-6-deoxy-β-CD) (**3**), and triethylene glycol-bridged bis(6-hydroxy-6-deoxy-β-CD) (**4**) have been synthesized by the reaction of mono[6-*O*-(*p*-toluenesulfonyl)]-β-CD with corresponding materials. The inclusion complexation behaviors of these compounds **2**–**4** with organic dyes; that is, acridine red (= *N*-[(3*Z*)-6-(methylamino)-3*H*-xanthen-3-ylidene]methanaminium chloride; AR), neutral red (= N^8,N^8,3-trimethylphenazine-2,8-diamine hydrochloride; NR), ammonium 8-anilinonaphthalene-1-sulfonate (ANS), sodium 6-(*p*-toluidinyl)-naphthalene-2-sulfonate (TNS), rhodamine B (RhB) and brilliant green (= *N*-(4-{[4-(diethylamino)cyclohexa-2,5-dien-1-yl](phenyl)methyl}cyclohex-2-en-1-ylidene)-*N*-ethyl-ethanaminium hydrogen sulfate; BG), have been investigated at 25° in phosphate buffer (pH 7.20) by ultraviolet, fluorescence, and 2D-NMR spectroscopy. The results indicate that the two linked CD units may cooperatively bind a guest, and the molecular binding ability toward dye guests, especially bent ANS, T-shaped RhB, and triangular BG, can be extended. This cooperative binding mode is confirmed by *Job*'s experiments and 2D-NMR investigations. Furthermore, the complex stability depends greatly on the linker length of these glycol-bridged bis(β-CD)s and the size and shape of guest. The higher binding ability and selectivity of dye molecules by bis(β-CD)s **2**–**4** are discussed from the viewpoint of size/shape-fit concept and multiple recognition mechanism.

1. Introduction. – It is well-known that native and modified cyclodextrins (CDs), having fairly rigid and well-defined hydrophobic cavities, act as molecular receptors (hosts) to bind substrates (guests), forming host–guest complexes in aqueous solutions [1][2]. This fascinating property enables them to be successfully used as drug carriers, separation reagents, enzyme mimics, and photochemical sensors in science and technology. However, the native and mono-modified CDs possess a relatively low molecular binding ability and selectivity upon inclusion complexation with guest molecules [3]. Bridged bis(β-CD)s, as a very important family of CD derivatives, have been known to alter significantly the molecular binding ability and selectivity toward a variety of guests in comparison with the native β-CD through the cooperative binding of a single model substrate by two hydrophobic cavities located in a close vicinity, and therefore provide an excellent model system mimicking the substrate-specific interaction of enzymes [4][5]. Hence, a variety of dimeric CDs with a considerable

structural diversity have been synthesized to understand the recognition process controlled by the simultaneous operation of several non-covalent interactions and also to gain insights into the factors governing the inclusion complexation behavior of bridged CD dimers [6–8]. We have recently demonstrated that some aromatic diamine-bridged bis(β-CD)s can form more stable complexes with dyes, bile salts, and aliphatic oligopeptides, displaying the higher molecular-binding ability and selectivity [9][10]. These results will help us understanding the multiple recognition and the induced-fit interaction hypothesis proposed for the binding of specific substrates by biological receptors, and prompt us to further investigate the inclusion complexation behavior of other bridged bis(β-CD)s.

In the present study, we report our study on the synthesis and molecular recognition behavior of three novel glycol-bridged bis(β-CD)s **2**–**4**. The reason for choosing glycol fragments as linker groups is that these flexible groups can appropriately adjust the distance and/or orientation of two CD cavities to fit the size/shape of the guest molecule, therefore improving binding ability of bridged bis(β-CD)s **2**–**4** through cooperative multiple recognition. Since the above glycol bis(β-CD)s **2**–**4** are spectroscopically inert, the inclusion phenomena have been observed by using spectroscopically active guests that exhibit changes in fluorescence spectra upon complexation with bis(β-CD)s. Here, six organic dye guests, acridine red (= *N*-[(3*Z*)-6-methylamino)-3*H*-xanthen-3-ylidene}methanaminium chloride; AR), neutral red (= N^8,N^8,3-trimethylphenazine-2,8-diamine hydrochloride; NR), ammonium 8-anilinonaphthalene-1-sulfonate (ANS), sodium 6-(*p*-toluidinyl)-naphthalene-2-sulfonate (TNS), rhodamine B (RhB), and brilliant green (= *N*-(4-{[4-(diethylamino)cyclohexa-2,5-dien-1-yl](phenyl)methyl}cyclohex-2-en-1-ylidene)-*N*-ethylethanaminium hydrogen sulfate; BG), which are usually as the spectral probes, were employed. The inclusion complexation behaviors of these novel bridged bis(β-CD)s **2**–**4** with six dye guest molecules have been investigated by fluorescence, ultraviolet, as well as 2D-NMR spectroscopy in phosphate buffer (pH 7.20) at 25°. The effect of linker length of



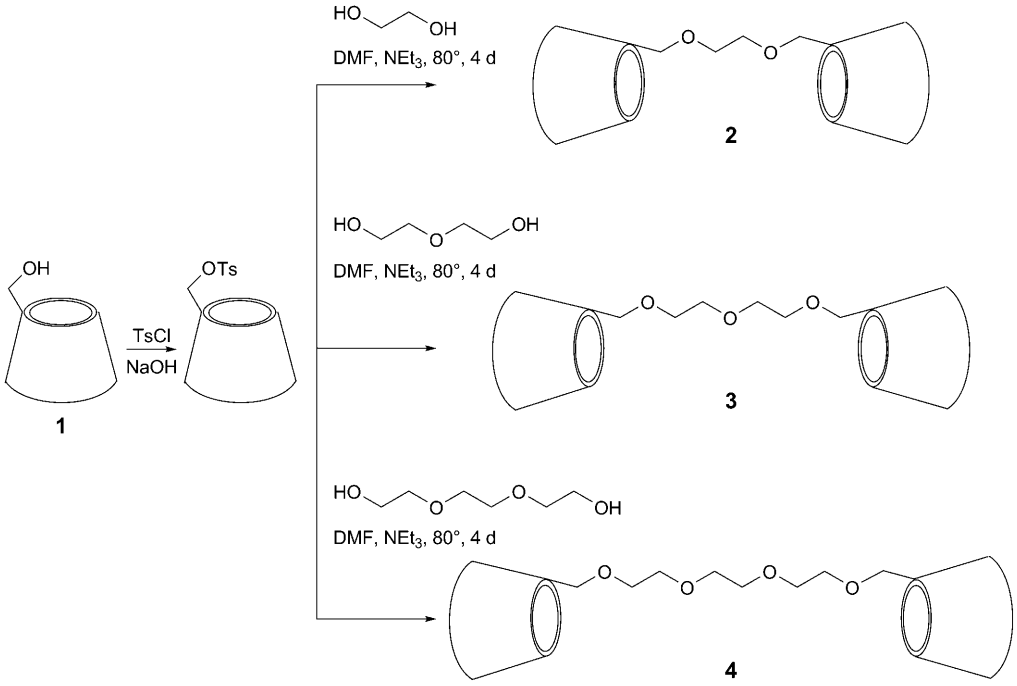


two CD moieties in the inclusion complexation according to the multipoint recognition and induced-fit concept between the dimeric host and model substrate is discussed.

2. Results and Discussion. – 2.1. *Synthesis.* As illustrated in the *Scheme*, ethylene glycol-bridged bis(6-hydroxy-6-deoxy-β-CD) (**2**), diethylene glycol-bridged bis(6-hydroxy-6-deoxy-β-CD) (**3**), and triethylene glycol-bridged bis(6-hydroxy-6-deoxy-β-CD) (**4**) were synthesized from mono[6-*O*-(*p*-toluenesulfonyl)]-β-CD.

2.2. *Fluorescence Titration*. The quantitative molecular-binding ability and selectivity of bis(β-CD)s **2**–**4** toward representative structurally related dyes were investigated in aqueous buffer solution at 25° by ultraviolet and fluorescence spectral titration methods. In the case of the addition of bis(β-CD)s **2**–**4**, the fluorescence intensities of ANS, TNS, AR, and NR increase. Representative spectral changes are shown in *Fig. 1*,*a* for the inclusion complexation of host **2** with TNS. As a guest, TNS is the typical fluorescence probe, which is very sensitive to the environment and exhibits strong fluorescence in a hydrophobic environment in which its fluorescence intensity becomes weak in bulk H_2O [11]. As can be seen from *Fig. 1*,*a*, TNS alone exhibits a weak fluorescence spectrum in the phosphate buffer solution (pH 7.20), but the addition of bis(β-CD) **2** dramatically enhances the fluorescence intensity, and leads to a large hypsochromic shift to 445 nm of the fluorescence peak. These results clearly indicate that the aromatic group of TNS is embedded into the hydrophobic cavity of CDs. However, the inclusion complexation behavior of RhB with host **2** shows the

Scheme



opposite spectral changes as compared with ANS, TNS, AR, and NR (*Fig. 1,b*), which may be attributed to the balance between fluorescent acid-form and the colorless lactone form. In the present investigation, the interaction between the benzoate moiety in RhB and the bulk H_2O is shielded in the resulting complex, which makes the equilibrium shift from the hydrophilic, fluorescent carboxylate ion form of RhB to the hydrophobic nonfluorescent lactonic neutral form, which leads to the fluorescence quenching [12]. Further study indicates that the pH value of the solution does not change significantly during the experimental procedure.

2.3. *Inclusion-Complexation Stoichiometry.* The stoichiometry for each of the inclusion complexation of bis(β-CD)s **2**–**4** with dye guests is determined by *Job*'s method of continuous variation to the stoichiometry of host–guest complexes. *Fig. 2* illustrates the *Job*'s plot for **3**/ANS system. In the concentration range examined, the plot for ANS shows a maximum at a molar fraction of 0.5, indicating 1:1 sandwich complexation. The same results are obtained in the cases of the inclusion complexation of other hosts with selected guest molecules.

Validating the 1:1 host–guest inclusion complexation stoichiometry by *Job*'s method, the inclusion complexation of a guest (G) with a host (H) was expressed by *Eqn. 1* and the complex stability constant (K_s) is given by *Eqn. 2*.

$$H + G \overset{K_s}{\rightleftharpoons} G \cdot H \tag{1}$$

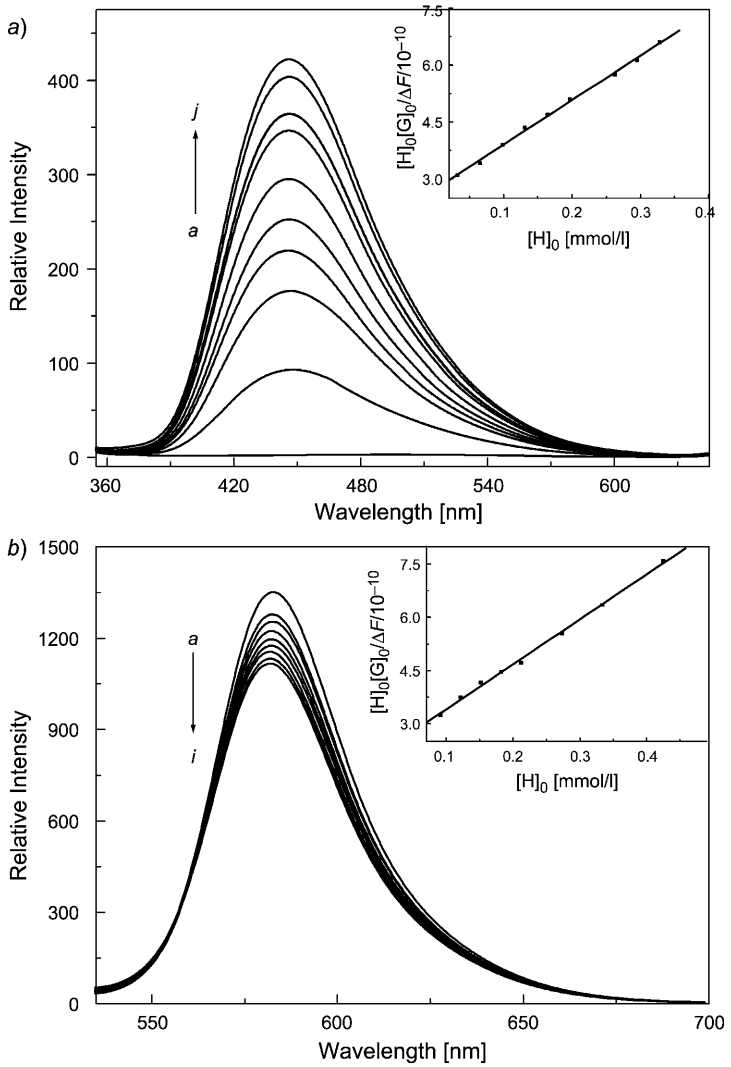


Fig. 1. *Changes in the fluorescence spectra of* a) *TNS* (8.58×10^{-6} M) *upon addition of bis(β-CD)* **2** (from *a* to *j:* 0, 0.33, 0.66, 0.99, 1.32, 1.65, 1.98, 2.64, 2.97, 3.33×10^{-4} M; $\lambda_{ex} = 388$ nm), *and* b) *RhB* (5.10×10^{-6} M) *upon addition of bis(β-CD)* **2** (from *a* to *i:* 0, 0.90, 1.20, 1.50, 1.80, 2.10, 2.70, 3.30, 4.20×10^{-4} M; $\lambda_{ex} = 520$ nm) *in phosphate buffer* (pH 7.20) *at 25°. Insets:* Typical plots of $[H]_0[G]_0/\Delta F$ *vs.* $[H]_0$ for the inclusion complexation of bis(β-CD) **2** with TNS and RhB.

$$K_s = \frac{[H \cdot G]}{[H][G]} \tag{2}$$

$$\Delta F = \Delta\varepsilon[H \cdot G] \tag{3}$$

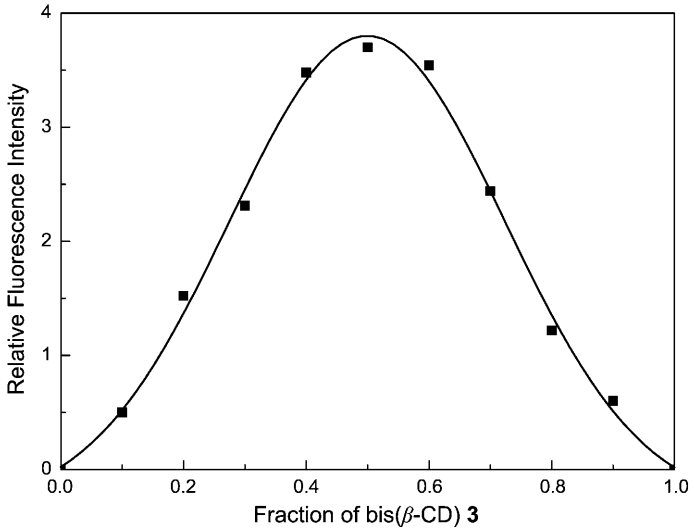


Fig. 2. *Continuous variation plot of the complexation of* **3** *with ANS in phosphate buffer* (pH 7.20) *at 25°* ($[\mathbf{3}]+[\mathrm{ANS}]=4.20\times10^{-5}$ M) *produced with data taken from fluorescence spectra* ($\lambda_{ex}=388$ nm)

where ΔF and $\Delta\varepsilon$ denote the sequential changes of fluorescence intensity and the differential molar extinction coefficient of dye guest in the absence and presence of bis(β-CD). Under the conditions employed, the initial concentration of the bis(β-CD)s is much larger than that of guest molecules, *i.e.*, $[\mathrm{H}]_0 \gg [\mathrm{G}]_0$. Therefore, the combination of *Eqns. 2* and *3* leads to the extended *Benesi–Hildebrand* equation (*Eqn. 4*), which is used to calculate the complex stability constants (K_s) (*Eqn. 2*) from the slope and intercept of $[\mathrm{H}]_0[\mathrm{G}]_0/\Delta F$ *vs.* $[\mathrm{H}]_0$ plots.

$$\frac{[\mathrm{H}]_0[\mathrm{G}]_0}{\Delta F} = \left(\frac{1}{K_s \Delta F}\right) + \frac{[\mathrm{H}]_0}{\Delta F} \tag{4}$$

Fig. 1 (insets) illustrates the result of such a treatment for the inclusion complexation of host **2** with TNS and RhB, where the calculated $[\mathrm{H}]_0[\mathrm{G}]_0/\Delta F$ values were plotted *vs.* the $[\mathrm{H}]_0$ values, generating an excellent linear curve. The complex stability constants (K_s) and the free-energy changes ($-\Delta G^\circ$) calculated from the slope and intercept are listed in the *Table*.

2.4. *Binding Mode*. To examine the binding mode operative in these bis(β-CD)s upon cooperative binding with dye guests, we performed a ROESY experiment at 298 K. *Fig. 3,a* illustrates a typical ROESY spectrum for the inclusion complexation of bis(β-CD) **3** with TNS. As can be easily recognized, this spectrum presents three distinct cross-peaks (peaks *A*, *B*, and *C*) between the H-atoms of TNS and the interior H-atoms (H3/H5/H6) located in the cavity of CD, which indicates that TNS should be included into the cavity of host **3**. Peak *B* represents the correlations between the aromatic H-atoms of the toluene moiety in TNS and the H3/H5/H6 H-atoms of CD, implying that the toluene moiety of TNS resides in the cavity of CD. On the other hand,

Table. *Complex Stability Constant* (K_s) *and* Gibbs *Free Energy Change* ($-\Delta G^\circ$) *for 1:1 Inclusion Complexation of Organic Dyes with β-CD* **1** *and Bis(β-CD)s* **2**–**4** *in Aqueous Buffer Solution* (pH 7.20) *at 25°*

Host	Guest	K_s	log K_s	$-\Delta G^\circ$ [kJ mol^{-1}]	Methods	Ref.
1	AR	2630	3.42	19.5	Fluorescence	[5e]
	NR	480	2.68	15.3	Fluorescence	[5f]
	ANS	103	2.01	11.5	Fluorescence	[5f]
	TNS	3670	3.56	20.3	Fluorescence	[5e]
	RhB	4240	3.63	20.7	Fluorescence	[5d]
	BG	2190	3.34	19.1	Ultraviolet	This work
2	AR	3420	3.53	20.2	Fluorescence	This work
	NR	750	2.88	16.4	Fluorescence	This work
	ANS	290	2.46	14.1	Fluorescence	This work
	TNS	4360	3.64	20.8	Fluorescence	This work
	RhB	5890	3.77	21.5	Fluorescence	This work
	BG	4830	3.68	21.0	Ultraviolet	This work
3	AR	4980	3.70	21.1	Fluorescence	This work
	NR	660	2.82	16.1	Fluorescence	This work
	ANS	440	2.64	15.1	Fluorescence	This work
	TNS	4500	3.65	20.8	Fluorescence	This work
	RhB	6280	3.80	21.7	Fluorescence	This work
	BG	6720	3.83	21.8	Ultraviolet	This work
4	AR	3670	3.56	20.3	Fluorescence	This work
	NR	610	2.79	15.9	Fluorescence	This work
	ANS	420	2.62	15.0	Fluorescence	This work
	TNS	3910	3.59	20.5	Fluorescence	This work
	RhB	14670	4.17	23.8	Fluorescence	This work
	BG	10770	4.03	23.0	Ultraviolet	This work

peak *C* displays the interactions between the naphthalic H-atoms near the sulfonic group and the H3/H5/H6 H-atoms of CD, indicating that the naphthalene ring moiety includes into another CD cavity. Furthermore, peak *A*, representing the correlation between the Me H-atoms of TNS and the H3/H5/H6 H-atoms of CD, provides the information that the Me group of TNS is also included into the cavity of CD. It can also be observed from crosspeaks *A*, *B*, and *C* that the corresponding TNS H-atoms all show stronger correlations with the CD's H5/H6 H-atoms than with the H3-atoms. Since the H5/H6 H-atoms are located close to the narrow opening of the CD cavity but the H3-atoms are near to the wide opening. Therefore, we can deduce that the toluene and naphthalene units of TNS are respectively included in two CD cavities from the narrow side to give the sandwich inclusion complex (*Fig. 4*,*a*). In addition, the ROESY spectrum of the **3**/RhB system (*Fig. 3*,*b*) further confirms the cooperative binding mode of the glycol bridged bis(*β*-CD)s toward guests. As shown in *Fig. 3*,*b*, the spectrum displays clear crosspeaks (peak area *A′*) between the H3 and H5/H6 (comparable intensities) of CD and the Me H-atoms of the Et_2N groups in RhB, and the other significant corresponding crosspeaks (peak area *B′*) between the aromatic H-atoms of the diethylaminophenyl groups in RhB and the H3 (weak) and H5/H6 of CD, suggesting that the alkyl group in RhB must be deeply included into the cavity of the

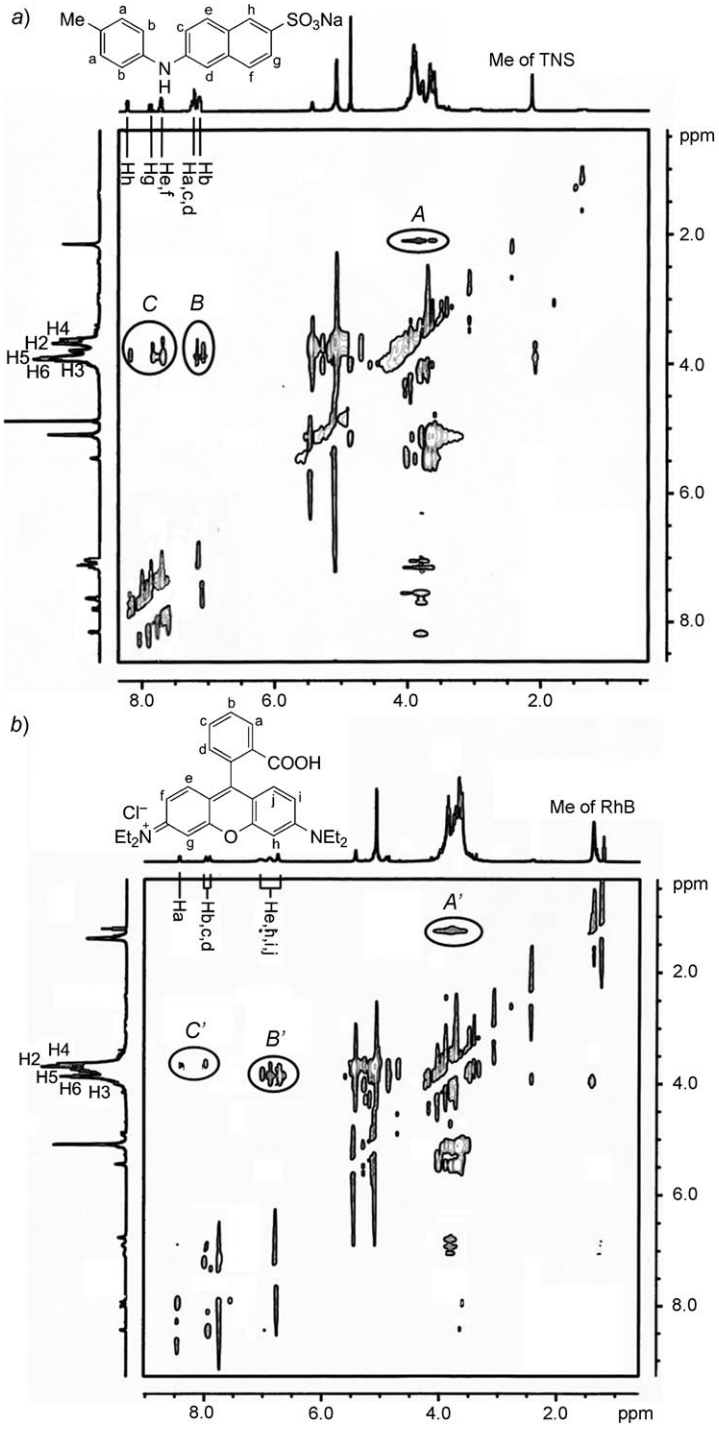


Fig. 3. *ROESY Spectra of host* **3** *in the presence of* a) *TNS, and* b) *RhB in* D_2O ([Host] = [guest] = 5.00×10^{-3} M) *with a mixing time of 400 ms at 298 K*

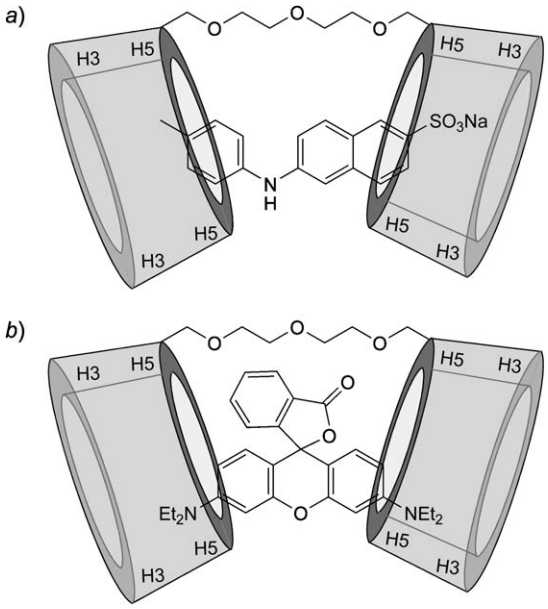


Fig. 4. *Possible inclusion binding modes of host* **3** *with* a*) TNS, and* b*) RhB*

CD. Moreover, the crosspeaks (peak area *C′*) clearly demonstrate the close distance between the CH_2 H-atoms of the glycol linkers in bis(β-CD) **3** and the aromatic H-atoms of the benzoate lactone moiety in RhB. Therefore, we can conclude that the two diethylaminophenyl groups of RhB are included in the hydrophobic CD cavities from the narrow side to form a 'face-to-face' sandwich inclusion complex, while the benzoate lactone branch of RhB is located partially or entirely in the *pseudo*-cavity formed by the linker groups of the host (*Fig. 4*,*b*). In this mode, the guest molecule is more efficiently shielded from the attack of solvent H_2O by the cooperative inclusion complexation with the CD cavities and the formation of the sandwich host–guest complex.

2.5. *Molecular Binding Ability and Molecular Selectivity.* In the present study, the binding constants of glycol-bridged bis(β-CD)s **2**–**4** with all guests investigated are higher than those of the native β-CD **1** by a factor of 1.1–4.9. In addition, by comparing the enhancement effects for each guest, we can see that the bis(β-CD)s **2**–**4** which give the highest enhancement for each guest dye (with the observed enhancement factors shown in the parentheses) are **3** ($\times$1.9) for AR, **2** ($\times$1.6) for NR, **3** ($\times$4.3) for ANS, **3** ($\times$1.2) for TNS, **4** ($\times$3.5) for RhB, and **4** ($\times$4.9) for BG. That is, the triangular BG, bent ANS, and T-shaped RhB, rather than linear guests AR, NR, and TNS, are able to more fully exploit the cooperative binding of bis(β-CD)s **2**–**4**.

As can be seen from the *Table*, the complexation stability constants for a certain host with dye guests are variable according to the guest structure. Therefore, it is interesting to investigate the relationship between the complex stability and guest structure. The K_s value for the complexation of each dye by hosts **1**–**4** increases in the order:

1: RhB > TNS > AR > BG > NR > ANS

2: RhB > BG > TNS > AR > NR > ANS

3: BG > RhB > AR > TNS > NR > ANS

4: RhB > BG > TNS > AR > NR > ANS

As a T-shaped molecule, RhB is very similar to triangular guest BG in structure. It is noted that RhB and BG give different binding constants upon inclusion complexation with the native β-CD **1**, displaying K_s values of 4240 and 2190 M^{-1}, respectively. This should be reasonable, since the hydrophobic lactonic neutral form of RhB matches the size of the native β-CD cavity and thus gives the relatively high binding constant. Comparing with RhB, BG has only one benzene ring that can be penetrated into the β-CD cavity according to the topology. It is well known that a single benzene ring can not fill the space of the β-CD cavity. Hence, the binding ability of the native β-CD **1** with BG is lower than that with RhB. Possessing two hydrophobic cavities, bis(β-CD)s **2**–**4** have a stronger binding ability toward RhB and BG than toward other guests. This may be attributed to not only the cooperative binding of dual β-CD units but also the additional binding site supported by the formation of the sandwich inclusion complex between bis(β-CD)s and guest molecule. According to a recent study of *Liu et al.*, the linker group of bis(β-CD)s can supply a well-organized *pseudo*-cavity which in turn provides additional binding interaction with the benzoate branch of RhB and BG by forming a sandwich inclusion complex [12]. In the present case, bis(β-CD)s **2**–**4** can afford suitable *pseudo*-cavities through the adjustment and orientation of the flexible glycol linker group, in which the branch fragment of RhB and BG can be appropriately accommodated. This consequently leads to a stronger binding ability of bis(β-CD)s **2**–**4** for RhB and BG. On the other hand, although AR and NR possess a similar linear structure with a heterocyclic anthracene center, hosts **1**–**4** show much a stronger binding ability towards AR than NR (K_s (AR-**1**)/K_s (NR-**1**) = 5.5, K_s (AR-**2**)/K_s (NR-**2**) = 4.6, K_s (AR-**3**)/K_s (NR-**3**) = 7.5, K_s (AR-**4**)/K_s (NR-**4**) = 6.0). This result seemed reasonable, since the examination with a CPK molecule model indicates that AR, which possesses two small methylamino substituents, can be well included in the β-CD cavity from the longitudinal direction, while NR can only partly penetrate into the β-CD cavity to form a weaker inclusion complex due to the steric hindrance from the relatively big end groups. In a further investigation, the binding constants for inclusion complexation of hosts **1**–**4** with TNS are roughly 9.4–15.0 times of magnitude larger than that with ANS. Although TNS and ANS possess similar frameworks (naphthalene-ring moiety), TNS is substituted at 2- and 6-position, but ANS at 1- and 8-position. Upon complexation with hosts, the hydrophobic naphthalene part of TNS can be embedded deeply into the CD cavity in the longitudinal direction. While the naphthalene moiety of ANS cannot penetrate in the longitudinal or lateral direction, only the aniline group can be embedded into the cavity. Therefore, all hosts show a stronger binding ability to TNS than to ANS. These results further demonstrate that the size and shape of guest molecules are very important factors for enhancing the binding ability of glycol bridged bis(β-CD)s.

Another interesting fact is that the molecular-binding ability of bis(β-CD)s **2**–**4** towards T-shaped RhB and triangular BG enhance with a sequence of **4** > **3** > **2** > **1**, which is well in agreement with the increasing linker length of these bis(β-CD)s. The glycol linkers of bis (β-CD)s **2**–**4** can adjust the distance and the orientation of the two CD units to form a stable sandwich type complex with a guest molecule. In a comparison among bis(β-CD)s **2**–**4**, the linker of bis(β-CD) **4** possesses the most suitable size/shape to form a sandwich inclusion complex with T-shaped RhB or triangular BG, and therefore gives the strongest binding towards these two substrates. In a sharp contrast, the two CD moieties of bis(β-CD) **2** is too closely located in space to form a stable sandwich inclusion complex with RhB or BG. As a result of such a poor matching in distance between the two cavities, bis(β-CD) **2** shows the lowest K_s values upon inclusion complexation with RhB or BG. Bis(β-CD) **3** is located between these two extremes and gives moderate binding ability. Therefore, the enhanced linker length or the increased relative molecular flexibility can control the binding behavior of bis(β-CD)s with T-shaped RhB or triangular BG molecule, and increase the complex stability. Unexpectedly, the molecular binding ability of bis(β-CD)s **2**–**4** towards the linear guests AR, NR, and TNS, and bent guest ANS do not always increase with increasing host linker length, but vary in an order of **3** > **4** > **2** > **1** for AR, **2** > **3** > **4** > **1** for NR, **3** > **2** > **4** > **1** for TNS, and **3** > **4** > **2** > **1** for ANS. These results indicate that the match of size/shape between the host and the guest dominates the stability of the incluison complex formed to some extent [13]. In this context, the linker length of host **3** is suitable for the cooperative binding of AR, TNS, and ANS, while host **2** gives the most stable complex with NR. Furthermore, close examination of molecular binding ability demonstrates that the linker length between two β-CD units can change the original molecular selectivity. The native β-CD **1** shows a molecular selectivity up to 1.2 and 1.7 for AR/BG and TNS/BG, but bis(β-CD)s exhibit inverted the molecular selectivity, giving BG/AR and BG/TNS selectivity of 1.4 and 1.1 by host **2**, 1.3 and 1.5 by host **3**, 2.9 and 2.8 by host **4**, respectively.

3. Conclusions. – In summary, three novel glycol bis(β-CD)s **2**–**4** have been synthesized, and their molecular-recognition behaviors have been studied by ultraviolet, fluorescence, and 2D-NMR spectroscopy. These bis(β-CD)s **2**–**4** significantly extend the original molecular binding ability of the native β-CD **1**, giving relatively strong binding with T-shaped RhB and triangular BG as guests. Furthermore, the complex stability depends greatly on the linker length of the bis(β-CD)s and the size and shape of guest. The appropriate increase of linker length will favor the inclusion complexation of bis(β-CD)s **2**–**4** with RhB and BG. The present results provide a convenient and powerful method, which will be useful for the design and synthesis of new supramolecular systems.

Experimental Part

General. All guest dyes, including AR, NR, ANS, TNS, RhB, and BG, were obtained from commercial sources and used without further purification. β-CD of reagent grade (*Shanghai Reagent Works*) was recrystallized twice from H_2O and dried under vacuum at 95° for 24 h prior to use. DMF was dried over CaH_2 for 2 d and then distilled under reduced pressure. Mono[6-*O*-(*p*-toluenesulfonyl)]-β-CD was prepared from β-CD and TsCl in aq. alkaline soln. [14]. The phosphate buffer (0.10 mol · dm^{-3},

pH 7.20), used in the spectral measurements, was prepared from NaH_2PO_4 and Na_2HPO_4. UV Spectra: *Shimadzu UV2401 PC* spectrometer. FT-IR Spectra: *Bruker FL-IR*. Fluorescence spectra: conventional quartz cell ($10 \times 10 \times 45$ mm) at 25° on a *Hitachi F-4500* spectrometer equipped with a constant-temp. water bath, with the excitation and emission slits of 10 nm width; excitation wavelengths for AR, NR, ANS, TNS, and RhB: 490, 510, 388, 388, and 520 nm, resp.; in the fluorescence titration experiments, the concentration ranges of dyes and bis(β-CD)s were 1 – 10 and 30 – 480 μM, resp. ^{1}H-NMR Spectra: *Bruker AV-DRX5* instrument operated at 500 MHz. Combustion analyses were performed on an *Elementar Vario EL III*.

Ethylene Glycol-Bridged Bis(6-hydroxy-6-deoxy-β-cyclodextrin) (**2**). As shown in the *Scheme*, ethylene glycol (1.5 mmol, 0.09 g) and mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin (3.0 mmol, 3.8 g) were dissolved in 30 ml of anh. DMF containing Et_3N (2 ml), and the mixture was stirred at 80° under N_2 atmosphere for 4 d, followed by evaporation under reduced pressure to dryness. The residue was dissolved in a small amount of H_2O, and the resultant soln. was poured into acetone with vigorous stirring to obtain a yellowish precipitate. The crude product was collected by filtration and chromatographed on a *Sephadex G-25* column with H_2O as eluent to give pure **2** (0.34 g, yield 10%). FT-IR (KBr): 3387, 2928, 2064, 1652, 1418, 1156, 1029, 944, 856, 813, 756, 683, 570. ^{1}H-NMR (D_2O): 3.32 – 3.94 (*m*, H2, H3, H4, H5, H6 of CD, $-OCH_2CH_2O-$); 4.92 – 5.01 (*m*, H1 of CD). FAB-MS: 2297 ($[M+H]^+$). Anal. calc. for $C_{86}H_{142}O_{70} \cdot 12\ H_2O$: C 41.12, H 6.67; found: C 41.49, H 6.50.

Diethylene Glycol-Bridged Bis(6-hydroxy-6-deoxy-β-cyclodextrin) (**3**). Bis(β-cyclodextrin) **3** was prepared similarly to **2** in 12% yield from diethylene glycol and mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin as a brown solid. FT-IR (KBr): 3387, 2982, 1647, 1386, 1029, 848, 571. ^{1}H-NMR (D_2O): 3.33 – 3.94 (*m*, H2, H3, H4, H5, H6 of CD, $-O(CH_2CH_2O)_2-$); 4.91 – 5.03 (*m*, H1 of CD). FAB-MS: 2341 ($[M+H]^+$). Anal. calc. for $C_{88}H_{146}O_{71} \cdot 8\ H_2O$: C 42.55, H 6.57; found: C 42.21, H 6.78.

Triethylene Glycol-Bridged Bis(6-hydroxy-6-deoxy-β-cyclodextrin) (**4**). Bis(β-cyclodextrin) **4** was prepared similarly to **2** in 14% yield from triethylene glycol and mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin as a brown solid. FT-IR (KBr): 3417, 2928, 1646, 1417, 1157, 1030, 851, 572. ^{1}H-NMR (D_2O): 3.33 – 3.95 (*m*, H2, H3, H4, H5, H6 of CD, $-O(CH_2CH_2O)_3-$); 4.92 – 5.04 (*m*, H1 of CD). FAB-MS: 2385 ($[M+H]^+$). Anal. calc. for $C_{90}H_{150}O_{72} \cdot 8\ H_2O$: C 42.76, H 6.62; found: C 43.02, H 6.33.

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