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Cooperative self-assembly and molecular binding behavior of cyclodextrin–crown ether conjugates mediated by alkali metal ions

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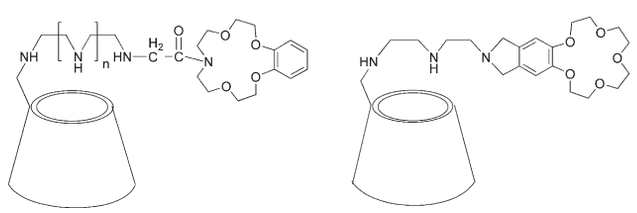
In order to quantitatively investigate their molecular binding ability, a series of cyclodextrin–crown ether conjugates containing β-cyclodextrin (β-CyD) and crown ether units, *i.e. N*-(benzoaza-15-crown-5)acylaminomethylene tethered 6-diethylenetriamino-6-deoxy-β-CyD (**1**), *N*-(benzoaza-15-crown-5)acylaminomethylene tethered 6-triethylenetetraamino-6-deoxy-β-CyD (**2**) and 4′,5′-dimethylene-benzo-15-crown-5 tethered 6-diethylenetriamino-6-deoxy-β-CyD (**3**), have been prepared as ditopic molecular receptors. Their inclusion complexation behavior with four representative fluorescent dyes, *i.e.* ammonium 8-anilino-1-naphthalenesulfonate (ANS), sodium 6-toluidino-2-naphthalenesulfonate (TNS), acridine red (AR) and rhodamine B (RhB), has been comprehensively investigated in aqueous NaH_2PO_4/Na_2HPO_4 or KH_2PO_4/K_2HPO_4 buffer solution (pH 7.20) by means of circular dichroism, fluorescence, and 2D NMR spectra. The results indicate that the self-assembly of crown ether modified β-CyD mediated by potassium ion exhibits a dimeric structure, which significantly enhances the original binding ability and molecular selectivity of parent β-CyD and its derivatives towards guest molecules through the cooperative binding of two hydrophobic CyD cavities with one guest. This cooperative binding mode of K^+/CyD–crown ether systems are further confirmed by Job's experiments and 2D NMR investigations. Attributed to the positive contributions from the metal-ligated crown ether cap and K^+-mediated dimerization of CyDs, the binding constant (*Ks*) values of CyD–crown ether conjugates **1**–**3** toward ANS are 10–83 times higher than that of β-CyD. The increased binding ability and molecular selectivity of CyD–crown ether conjugates are discussed from the viewpoints of size/shape-fit and multiple recognition mechanism.

Introduction

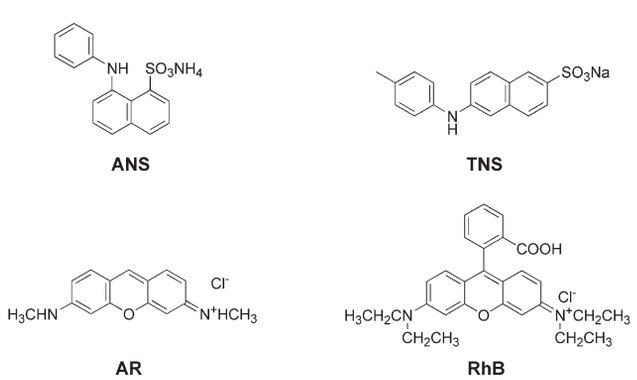
It is well known that crown ethers and cyclodextrins (CyDs) can be taken as molecular receptors to selectively bind ionic and molecular guests respectively forming host–guest complexes or supramolecular species. Therefore, in the past few decades, a lot of effort has been contributed to the design and synthesis of functional crown ethers and CyD derivatives in order to enhance their original ionic/molecular binding affinities and selectivities.[1] Recently, many approaches to appropriately introduce another recognition site, such as a CyD, calixarene or crown ether, to the parent CyD rim have been widely reported.[2–8] For example, it was reported that crown ether capped β-CyDs can mimic the receptor sites of enzymes,[5c] and thus successfully be used as artificial enzyme-mimetic systems to accelerate the hydrolysis of *p*-nitrophenyl ester in the presence of transition metal cations[9] or as stationary-phase selector for chromatography showing excellent enantioselectivity.[10] Moreover, Suzuki *et al.* reported the strong binding of tryptophan by crown ether-tethered CyDs owing to the superiority of the CyD secondary-hydroxyl side modification.[7b] In addition, Lincoln and coworkers reported the inclusion complexation of Brilliant Yellow tetraanion with diazacoronand linked β-CyD dimer and their sodium analogues.[11] These studies significantly advanced our understanding of the factors governing host–guest inclusion complexation from the viewpoints of multiple recognition and induced-fit mechanism between CyD-based synthetic receptors and model substrates. Recently, we reported a preliminary investigation into the molecular recognition behavior of benzo-15-crown-5 tethered β-CyDs, which were found able to remarkably enhance the original binding ability of parent β-CyD towards cyclohexane carboxylates[12] and fluorescent dyes[13] by the cooperative binding of one guest molecule by two closely located binding sites (crown ether and CyD). In the present work, we select three novel benzoaza-15-crown-5 modified β-CyDs, *i.e. N*-(benzoaza-15-crown-5)-acylaminomethylene tethered 6-diethylenetriamino-6-deoxy-β-CyD (**1**), *N*-(benzoaza-15-crown-5)-acylaminomethylene tethered 6-triethylenetetraamino-6-deoxy-β-CyD (**2**) and 4′,5′-dimethylene-benzo-15-crown-5 tethered 6-diethylenetriamino-6-deoxy-β-CyD (**3**) (Chart 1) as ditopic molecular receptors, each of which possesses two different recognition sites, *i.e.* CyD and crown ether, and a flexible oligo(ethylenediamine) linker in a single molecule. The reason for choosing oligo(ethylenediamine) fragments as linker groups is that these flexible groups can appropriately adjust the distance and/or location of the crown ether unit relative to the CyD cavity to fit the size/shape of the guest molecule, therefore enabling us to improve the binding ability of CyD–crown ether conjugates through cooperative multiple recognition. The inclusion complexation behavior of hosts **1**–**3** with some structure-related fluorescent dyes (Chart 2), *i.e.* ammonium 8-anilino-1-naphthalenesulfonate (ANS), sodium 6-toluidino-2-naphthalenesulfonate (TNS),



n = 1, **1**
n = 2, **2**

3

Chart 1 Host structures.



ANS

TNS

AR

RhB

Chart 2 Guest structures.

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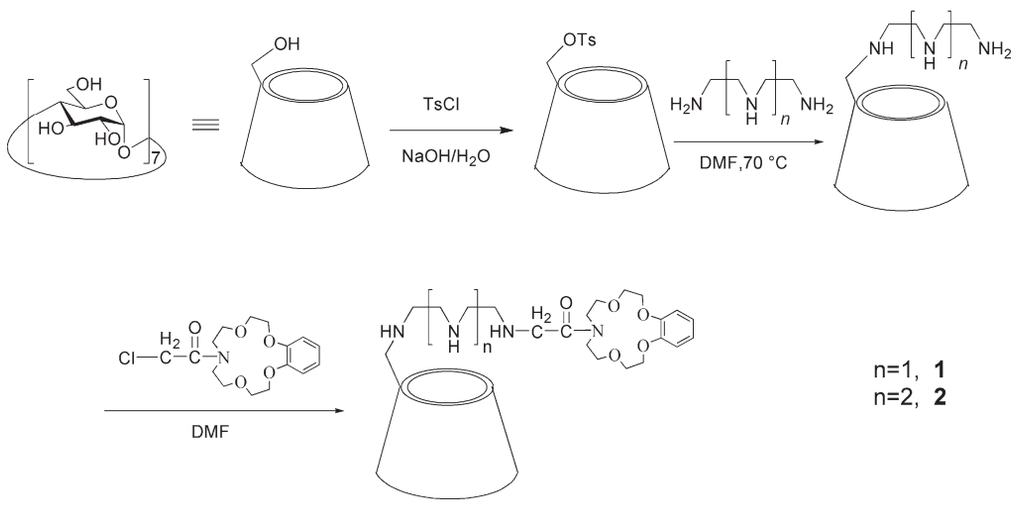


Scheme 1 Synthesis route.

acridine red (AR) and rhodamine B (RhB) is investigated in aqueous NaH_2PO_4/Na_2HPO_4 or KH_2PO_4/K_2HPO_4 buffer solution (pH 7.20) at 25 °C. It is well documented that benzo-15-crown-5 can coordinate with the Na^+ or K^+ cation by 1 : 1 or 2 : 1 stoichiometry respectively.[14] Therefore, we hypothesize that, in the present case, the potassium cation will mediate the dimerization of CyD–crown ether conjugates **1**–**3** through 2 : 1 sandwich complexation of crown ether units with K^+, and thus affect the binding ability and selectivity of CyD–crown ether conjugates towards guest molecules. It is our special interest to examine the molecular recognition mechanism concerning the uncommon CyD–crown ether self-assemblies mediated by alkali metal ions, which will serve our further understanding of this important, but less investigated, area in the field of supramolecular chemistry.

Results and discussion

As shown in Scheme 1, the cyclodextrin–crown ether conjugates **1** and **2** were synthesized in relatively low yields from oligo(ethylenediamine) modified β-CyDs.

Circular dichroism spectra

Circular dichroism (CD) spectrometry has become a convenient and widely employed method for the elucidation of the absolute conformation of chiral organic compounds in the past three decades.[15,16] Moreover, achiral organic compounds can also show an induced circular dichroism (ICD) signal in the corresponding transition band in cases where there is a chiral microenvironment. CyDs, which possess inherent chiral cavities, may provide such a microenvironment for the included achiral chromophore. Therefore, if a chromophoric group is closely attached to the CyD rim, the corresponding ICD signal should be observed due to the interaction between the appended chromophore and the chiral CyD cavity. This phenomenon may be consequently used to elucidate the location and orientation of the appended moiety. In this context, in order to obtain information about the original conformation of CyD–crown ether conjugates, we measured the CD spectra of hosts **1**–**3** in dilute buffer solution. The results show that hosts **1**–**3** display fairly weak ICD signals ($\Delta\varepsilon \leq 0.5$ dm^3 mol^{-1}cm^{-1}) for the transitions of aromatic chromophores in either NaH_2PO_4/Na_2HPO_4 or KH_2PO_4/K_2HPO_4 buffer solution (Fig. 1). According to the empirical rules that interpret the ICD observed for a chromophore inside or outside of the CyD cavity proposed by Kajtar,[17] Harata,[18] and Kodaka[19] *et al.*, we can deduce that the aromatic rings in **1**–**3** are located distantly from the CyD cavity. This conformation will provide a free CyD cavity for the penetration of the guest molecule upon inclusion complexation.

Binding mode

The complexes of CyD–crown ether conjugates **1**–**3** with Na^+ or K^+ cation were prepared *in situ* in aqueous solution. Conductivity measurements of CyD–crown ether/NaCl (or KCl) systems

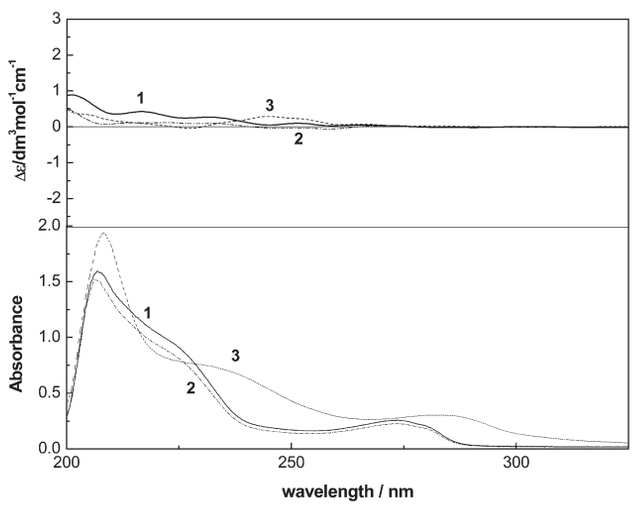


Fig. 1 Circular dichroism spectra of **1**–**3** (1.0×10^{-4} mol dm^{-3}) in NaH_2PO_4/Na_2HPO_4 buffer solutions (pH 7.20).

indicate that the coordination stoichiometry is 1 : 1 for CyD–crown ether/Na^+ complexes and 2 : 1 for CyD–crown ether/K^+ complexes, respectively. Fig. 2 shows a representative conductivity titration curve for the 2 : 1 coordination of host **1** with KCl. Through an approximative calculation based on the relatively high concentration of Na^+ or K^+ ion ([Na^+] = [K^+] = 0.344 M) in the phosphate buffer solution and the low host concentration employed in all of the spectral experiments ([host] = 0–230 μM) as well as the reported association constant between benzo-15-crown-5 and Na^+ or K^+ in aqueous solution,[20] we deduce that most of the benzo-crown ether units in hosts **1**–**3** are coordinated with Na^+ or K^+ ion forming CyD–crown ether/Na^+ (K^+) complexes.

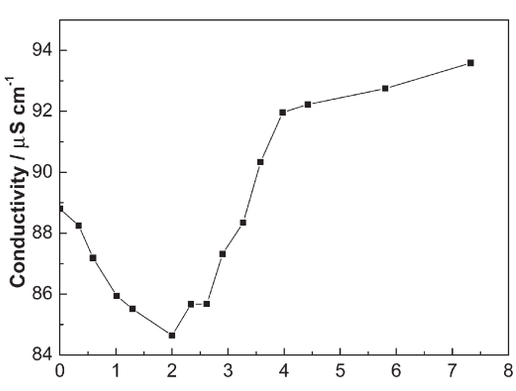
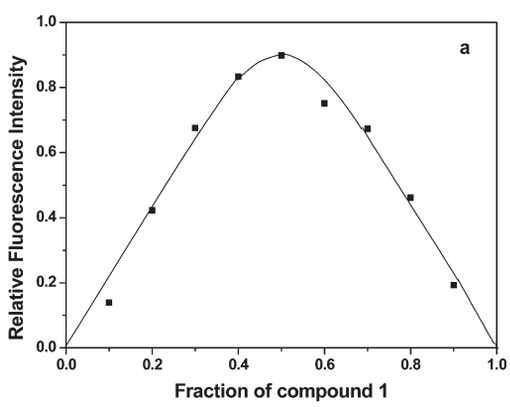


Fig. 2 Conductivity of KCl (5×10^{-4} M) in the aqueous solution of host **1** at 25 °C.

Furthermore, Job's experiments by fluorescence spectrometric methods were also performed to explore the stoichiometry for the inclusion complexation of metal-ligated CyD–crown ether conjugates with representative guests. Fig. 3 illustrates the Job's plots for the **1**/AR system in NaH_2PO_4/Na_2HPO_4 or KH_2PO_4/K_2HPO_4 buffer solution. In the measurement concentration range, the plot for the **1**/AR system in NaH_2PO_4/Na_2HPO_4 buffer (Fig. 3a) shows a maximum at a molar fraction of 0.5, indicating 1 : 1 inclusion complexation between CyD–crown ether host and guest molecule. On the other hand, the plot for the **1**/AR system in KH_2PO_4/K_2HPO_4 buffer (Fig. 3b) displays a maximum at 0.67, which corresponds to 2 : 1 **1**/AR stoichiometry. This result indicates that two CyD–crown ether components actively participate in the binding of one guest molecule. Similar results are obtained in the case of the inclusion complexation of other metal-ligated CyD–crown ether conjugates with guest molecules. Therefore, we can deduce that the CyD–crown ether conjugates **1**–**3** may adopt different binding modes in NaH_2PO_4/Na_2HPO_4 and KH_2PO_4/K_2HPO_4 buffer solution. In a NaH_2PO_4/Na_2HPO_4 buffer solution, the CyD–crown ether conjugate adopts a conventional 1 : 1 binding mode upon inclusion complexation with the guest molecule, where the Na^+ ligated crown ether unit acts as a positively charged cap near the narrow rim of CyD cavity and provides additional binding interactions towards the accommodated guest through the electrostatic attraction or repulsion between the metal-ligated crown ether cap and charged guest molecule (Fig. 4a). However, these CyD–crown ether conjugates prefer a sandwich binding mode upon complexation with the guest molecule in a KH_2PO_4/K_2HPO_4 buffer (Fig. 4b). In this mode, the guest molecule is cooperatively bound by two CyD cavities, and K^+ acts as not only a recognition site for the charged guest but also a metal bridge to link the two adjacent CyD units forming the self-assembled dimer.

The different binding modes of Na^+ or K^+-coordinated CyD–crown ether conjugates are further validated by 2D ROESY experiments. Fig. 5 shows 2D ROESY spectroscopy for the inclusion complexation of host **1** with TNS in both NaH_2PO_4/Na_2HPO_4 and KH_2PO_4/K_2HPO_4 buffers. Fig. 5a shows the clear correlations



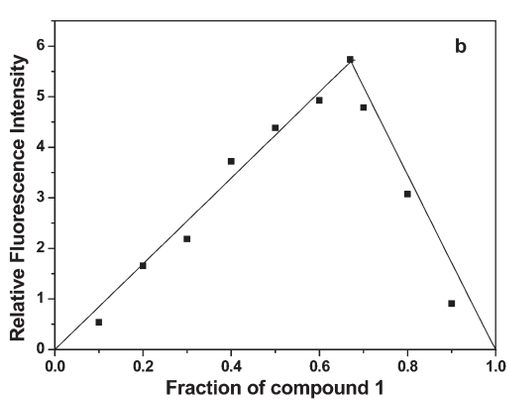


Fig. 3 Job's plots for **1**/AR system in (a) NaH_2PO_4/Na_2HPO_4 and (b) KH_2PO_4/K_2HPO_4 buffers. ([**1**] + [AR] = 1.0×10^{-5} mol dm^{-3}).

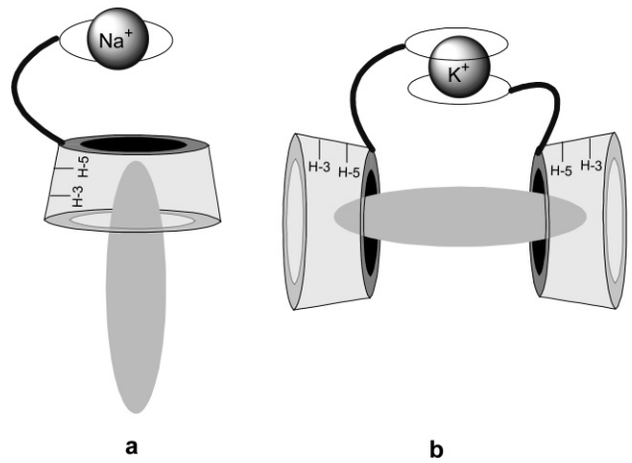


Fig. 4 Binding mode of guest molecule with CyD–crown ether conjugate in (a) NaH_2PO_4/Na_2HPO_4 and (b) KH_2PO_4/K_2HPO_4 buffers.

between TNS protons and the interior protons (H-3, H-5) of the CyD cavity. Through the ascription of these correlations, we can find that the cross-peaks A correspond to the correlations between the methyl protons of TNS and the interior protons of CyD, and the cross-peaks B correspond to the correlations between the protons in the phenyl moiety (Ha, Hb) of TNS and the interior protons of CyD, while cross-peaks C correspond to the correlations between the naphthalene protons (Hg, Hh) of TNS and the interior protons of CyD. Moreover, it can be observed from the cross-peaks A, B and C that the corresponding TNS protons (Ha, Hb, Hg, Hh) all show stronger correlations with the H-5 protons of CyD than with the H-3 protons. Since the H-3 protons are located near the wide side of the CyD cavity, while the H-5 protons are near the narrow side, we can deduce that the toluene and naphthalene units of TNS are respectively included in two CyD cavities from the narrow side as illustrated in Fig. 4. One possible explanation for these phenomena is that the CyD–crown ether conjugate forms a dimeric self-assembly through the mediation of a coordinated potassium center, which subsequently adopts a cooperative binding mode upon inclusion complexation with TNS. On the other hand, Fig. 5b merely exhibits one set of cross-peaks (peaks D) assigned to the correlations between the Hg, Hh protons of TNS and the interior protons of CyD, while the correlations with the H-3 protons are stronger than those with the H-5 protons. This means that only the naphthalene unit of TNS penetrates into the CyD cavity from the wide side but the toluene unit locates outside, which is consistent with the hypothesized structure in Fig. 4. On the other hand, a kinetic investigation by the time-dependent UV spectra of guest dyes in the presence of host **1** (or **2**) using a reported method[21] indicates that the rate of dyes entering the CyD cavities are much faster than those of dyes leaving the CyD cavities. This means that the resulting complexes of hosts **1**–**2** with guest dyes are stable in aqueous solution.

Binding ability and molecular selectivity

After validating the host–guest binding mode, we performed fluorescence titration experiments to quantitatively investigate the molecular binding ability and selectivity of hosts **1**–**3** with guest molecules. Fig. 6 illustrates the typical fluorescence changes of AR upon gradual addition of host **1** in an NaH_2PO_4/Na_2HPO_4 buffer solution. As can be seen from Fig. 6, with the addition of host **1**, the fluorescence intensity of AR gradually increases, accompanied by slight hypsochromic shifts (3 nm, 559→556 nm from trace a to trace m) of the emission peaks, which may be ascribed to the increased microenvironmental hydrophobicity around the accommodated AR upon inclusion complexation. The stability constant (*Ks*) of the inclusion complex formed can be calculated from the gradual changes in fluorescence intensity of guest (ΔI_f) upon stepwise addition of host using a curve fitting method.[22] In the repeated measurements, the *Ks* values are reproducible within an error of ±5%. The complex stability constants (*Ks*) obtained by curve fitting are listed in Table 1, along with the free energy change ($-\Delta G°$) of complex formation.

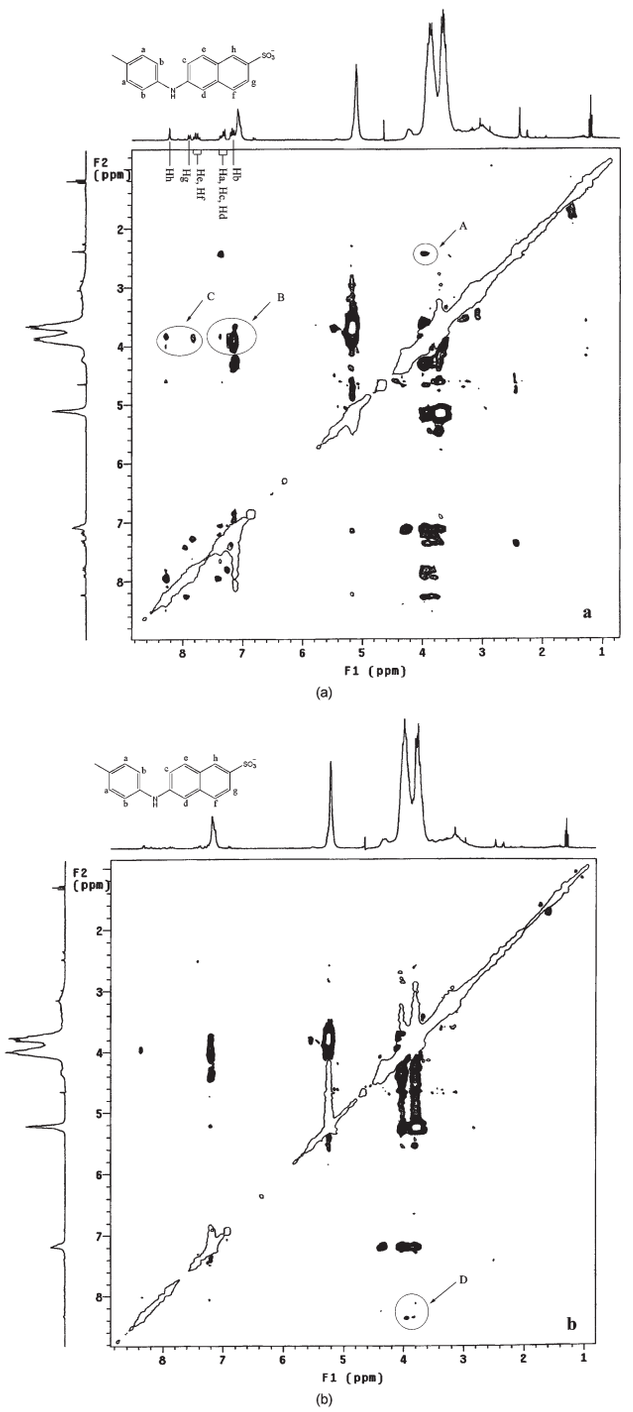


Fig. 5 2D ROESY spectra of a mixture of host **1** with TNS in (a) KH_2PO_4/K_2HPO_4 and (b) NaH_2PO_4/Na_2HPO_4 buffers.

By comparing the enhancement effects for each guest, we can see that the metal-ligated CyD–crown ether conjugates which gives the highest enhancement for each guest dye (with the observed enhancement factors shown in the parentheses) are **3**–K^+ (× 83) for ANS, **1**–Na^+ (× 12.6) for TNS, **3**–K^+ (× 8.4) for RhB, and **2**–K^+ (× 2.6) for AR, respectively. From a comparison of these enhancement factors, we may conclude that the negatively charged guest ANS and TNS are able to more fully exploit the cooperative binding of CyD–crown ether conjugates. This should be reasonable, since the certain electrostatic attraction between the metal-ligated crown ether cap and anionic guest provides a positive contribution to host–guest inclusion complexation and thus leads to high binding affinities. On the other hand, as can be readily recognized from Table 1, the *Ks* values for the inclusion complexation of CyD–crown ether hosts with guest molecules increases in the following order:

Table 1 Complex stability constants (*Ks*) and Gibbs free energy changes ($-\Delta G°$) for the inclusion complexation of organic dyes with CyD–crown ether conjugates **1**–**3** in different buffer solutions (pH 7.20)

Host	Guest	*Ks*	log*Ks*	$-\Delta G°$(kJ mol^{-1})	Ref.
β-CyD	ANS	102	2.01	11.5	*a*
	TNS	3700	3.57	20.4	*a*
	AR	2630	3.42	19.5	*a*
	RhB	5100	3.71	21.2	*a*
1–Na^+	ANS	3260	3.51	20.05	*b*
	TNS	46500	4.67	26.64	*b*
	AR	1880	3.27	18.69	*b*
	RhB	6880	3.84	21.90	*b*
2–Na^+	ANS	1720	3.23	18.47	*b*
	TNS	7200	3.86	22.02	*b*
	AR	1330	3.12	17.83	*b*
	RhB	9460	3.98	22.69	*b*
3–Na^+	ANS	1680	3.22	18.41	*b*
	TNS	6560	3.82	21.79	*b*
	AR	3200	3.50	20.01	*b*
	RhB	8680	3.94	22.48	*b*
1–K^+	ANS	3430	3.53	20.18	*c*
	TNS	10620	4.03	22.98	*c*
	AR	1570	3.20	18.24	*c*
	RhB	18100	4.26	24.30	*c*
2–K^+	ANS	1015	3.01	17.16	*c*
	TNS	22100	4.34	24.80	*c*
	AR	6740	3.83	21.85	*c*
	RhB	13000	4.11	23.48	*c*
3–K^+	ANS	8500	3.93	22.43	*c*
	TNS	26600	4.42	25.26	*c*
	AR	2730	3.44	19.61	*c*
	RhB	42900	4.63	26.44	*c*

[a] Reference 23. [b] In NaH_2PO_4/Na_2HPO_4 buffer solution. [c] In KH_2PO_4/K_2HPO_4 buffer solution.

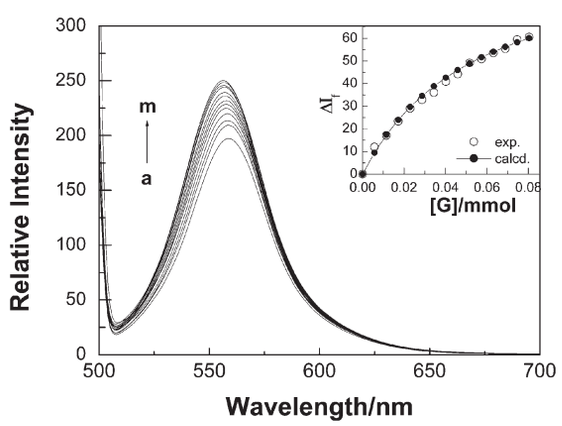


Fig. 6 Fluorescence spectral changes of AR (1.2 μM) and nonlinear least-squares analysis (inset) of the differential intensity (ΔI_f) used to calculate the complex stability constant (*Ks*) upon addition of **1** (0–90 μM from a to m) in NaH_2PO_4/Na_2HPO_4 buffer solution (pH 7.20).

1–Na^+: AR < ANS < RhB < TNS
2–Na^+: AR < ANS < TNS < RhB
3–Na^+: ANS < AR < TNS < RhB
1–K^+: AR < ANS < TNS < RhB
2–K^+: ANS < AR < RhB < TNS
3–K^+: AR < ANS < TNS < RhB

We can see that the relatively large guest molecules, such as TNS and RhB, are better bound by CyD–crown ether conjugates than the small guests. This may be attributed to the size-fit relationship between these guests and the CyD–crown ether conjugates possessing flexible long linkers, which consequently gives strong van der Waals and hydrophobic interactions between host and guest. Another interesting observation is that the T-shaped RhB is better bound by K^+-ligated CyD–crown ether conjugates than by Na^+-ligated ones. The stronger binding ability of CyD–crown ether conjugates in KH_2PO_4/K_2HPO_4 buffer solution may arise from the K^+-mediated dimeric self-assembly of CyD–crown ether conjugates. In our previous work, we have demonstrated that the

linker group of bis(CyD)s can supply a well-organized pseudo cavity which in turn provides additional binding interaction with the benzoate branch of RhB by forming a sandwich inclusion complex, and thus showing high binding affinity toward RhB.[24] In the present case, K^+-mediated CyD–crown ether conjugates can also be regarded as a type of "bis(CyD)s" (Fig. 4b). Upon inclusion complexation with guest molecules, these "bis(CyD)s" can afford suitable pseudo cavities through the adjustment and orientation of the flexible linker group, in which the branch fragment of T-shaped guests, such as RhB, can be appropriately accommodated. This consequently leads to the strong binding ability of K^+-ligated CyD–crown ether conjugates for RhB and their high molecular selectivity for the RhB/AR pair. Typically, native β-CyD only gives moderate binding ability for RhB (Ks = 5100 M^{-1}) and relatively low molecular selectivity (Ks_{RhB}/Ks_{AR} = 1.9) for the RhB/AR pair. However, benefiting from the cooperative binding of two CyD cavities, the **3**–K^+ assembly system displays significantly enhanced binding ability for RhB and molecular selectivity for the RhB/AR pair; that is 8.4 and 8.2 times higher than the corresponding values of native β-CyD, respectively.

In summary, we succeeded in preparing a series of CyD–crown ether conjugates as ditopic molecular receptors. Further investigations demonstrated that the high binding ability and molecular selectivity of CyD–crown ether conjugates come not only from the electrostatic interactions between the metal-ligated crown ether cap and the charged guest molecules, but also the K^+-mediated self-assembly of CyD–crown ether conjugates. Significantly, this concept opens an efficient channel to the design of new multi-site hetero receptors involving crown ethers and/or CyDs. Based on the uncommon self-assembly behavior of CyD–crown ether conjugates mediated by alkali metal ions, further studies are currently in progress concerning the cooperative, multisite/multimode recognition of sophisticated systems.

Experimental

Materials

All chemicals were reagent grade and used without further purification unless noted otherwise. *N*,*N*-Dimethylformamide (DMF) was dried over calcium hydride for two days and then distilled under reduced pressure prior to use. Mono[6-diethylenetriamino-6-deoxy]-β-CyD and mono[6-triethylenetetraamino-6-deoxy]-β-CyD were prepared according to the literature procedures,[25] and *N*-(chloracetyl)benzoaza-15-crown-5 was synthesized by the reaction of 11,12-benzo-1,7,10,13-tetraoxa-4-aza-cyclopentadec-11-ene (benzoaza-15-crown-5) with chloracetyl chloride in anhydrous acetonitrile.[26] 4′,5′-Dimethylene-benzo-15-crown-5 tethered 6-diethylenetriamino-6-deoxy-β-CyD (**3**) was synthesized according to our previous report.[12]

Apparatus and measurements

Elemental analyses were performed on a Perkin-Elmer-2400C instrument. NMR spectra were recorded on a Varian Mercury VX300 instrument. 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 excitation and emission slits of 5 nm for all the fluorescent dyes. The excitation wavelengths for ANS, TNS, AR, and RhB were 350, 366, 490 and 525 nm, respectively. Disodium hydrogen phosphate dodecahydrate (51.60 g) and sodium dihydrogen phosphate dihydrate (8.85 g) were dissolved in 1000 mL of deionized water to make an aqueous NaH_2PO_4/Na_2HPO_4 buffer solution (0.2 M) of pH 7.20. Moreover, an aqueous KH_2PO_4/K_2HPO_4 buffer solution (pH 7.20, 0.2 M) was similarly prepared by dissolving dipotassium hydrogen phosphate trihydrate (32.86 g) and potassium dihydrogen phosphate (7.6 g) in 1000 mL of deionized water.

Synthesis of *N*-(benzoaza-15-crown-5)-acylaminomethylene tethered 6-diethylenetriamino-6-deoxy-β-CyD (1)

As shown in Scheme 1, mono[6-diethylenetriamino-6-deoxy]-β-CyD (1.8 g) and *N*-(chloracetyl)benzoaza-15-crown-5 (0.688 g) were dissolved in DMF (30 mL), and triethylamine (15 ml) was slowly added over one hour. The reaction mixture was stirred at room temperature overnight and then heated to 75 °C under nitrogen atmosphere for 12 hours. The solvent was removed under reduced pressure on a rotary evaporator. The residue was dissolved in a small amount of hot water, and subsequently the resultant solution was poured into acetone with vigorous stirring to produce a yellow precipitate. After collection by filtration, the crude product was purified by column chromatography on Sephadex G-25 with distilled, deionized water as eluent to give a pure sample (0.50 g, yield 18%). Mp 240 °C (dec.); ^{1}H NMR (D_2O, 300 MHz, TMS, ppm): δ 2.0–3.0 (m, 11H), 3.0–4.0 (m, 58 H), 4.1 (m, 2H), 4.9 (m, 7 H), 6.9 (m, 4 H). IR (KBr): ν 3325, 2927, 1650, 1502, 1455, 1361, 1257, 1155, 1079, 1032, 944, 847, 755, 705, 579 cm^{-1}. Anal. Calcd. for $C_{62}H_{102}O_{39}N_4 \cdot 12H_2O$: C, 42.71; H, 7.28; N, 3.21. Found: C, 42.75; H, 7.14; N, 3.31%. UV/vis (H_2O) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}): 273 (2620).

Synthesis of *N*-(benzoaza-15-crown-5)-acylaminomethylene tethered 6-triethylenetetraamino-6-deoxy-β-CyD (2)

Mono[6-triethylenetetraamino-6-deoxy]-β-CyD (2.0 g) and *N*-(chloracetyl) benzoaza-15-crown-5 (0.688 g) were dissolved in DMF (30 mL), and triethylamine (15 mL) was slowly added over one hour. The reaction mixture was stirred at room temperature under nitrogen atmosphere for one day and then at 80 °C for two days. The solvent was removed under reduced pressure on a rotary evaporator. The residue was dissolved in a small amount of water (15 mL), and subsequently the resultant solution was poured into 2 : 1 (v/v) acetone–ethanol (500 mL) with vigorous stirring to produce a yellow precipitate. The above procedure was repeated twice. After collection 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 (0.24 g, yield 10%). Mp 226 °C (dec.); ^{1}H NMR (D_2O, 300 MHz, TMS, ppm): δ 2.0–2.8 (m, 16H), 3.2–4.0 (m, 58H), 4.2 (m, 2H), 4.9 (m, 7H), 6.8 (m, 4H). IR (KBr): ν 3327, 2928, 1652, 1502, 1455, 1362, 1257, 1203, 1154, 1079, 1032, 941, 847, 754, 705, 580, 407 cm^{-1}. Anal. Calcd for $C_{64}H_{107}O_{39}N_5 \cdot 8H_2O$: C, 44.83; H, 7.23; N, 4.08. Found: C, 44.70; H, 7.17; N, 4.12%. UV/vis (H_2O) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}): 273 (2150).

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