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## Supramolecular Chemistry

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### Molecular binding behaviours of bile salts by bridged and metallobridged bis( $\beta$ -cyclodextrin)s with naphthalenecarboxyl linkers

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## Molecular binding behaviours of bile salts by bridged and metallobridged bis( $\beta$ -cyclodextrin)s with naphthalenecarboxyl linkers

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A bridged bis( $\beta$ -cyclodextrin) **1** bearing a fluorescent naphthalenecarboxyl linker and its complexes with Cu(II) and Ni(II) (**2** and **3**) were synthesised and comprehensively characterised. The experiments of circular dichroism and  $^1\text{H}$  rotating frame nuclear Overhauser effect spectroscopy (ROESY) indicated that the naphthyl groups in **1–3** were shallowly included in the  $\beta$ -cyclodextrin cavities but excluded from the cavities upon inclusion complexation with guest molecules. The fluorescence titration experiments in Tris–HCl buffer solution (pH 7.4) showed that both **1** and its complexes **2** and **3** gave higher binding constants ( $K_b$ ) than the corresponding values of the native and mono-modified  $\beta$ -cyclodextrins. The significantly enhanced binding abilities of bridged and metallobridged bis( $\beta$ -cyclodextrin)s were discussed in the viewpoint of cooperative binding and multiple recognition of dimeric host with guest molecule.

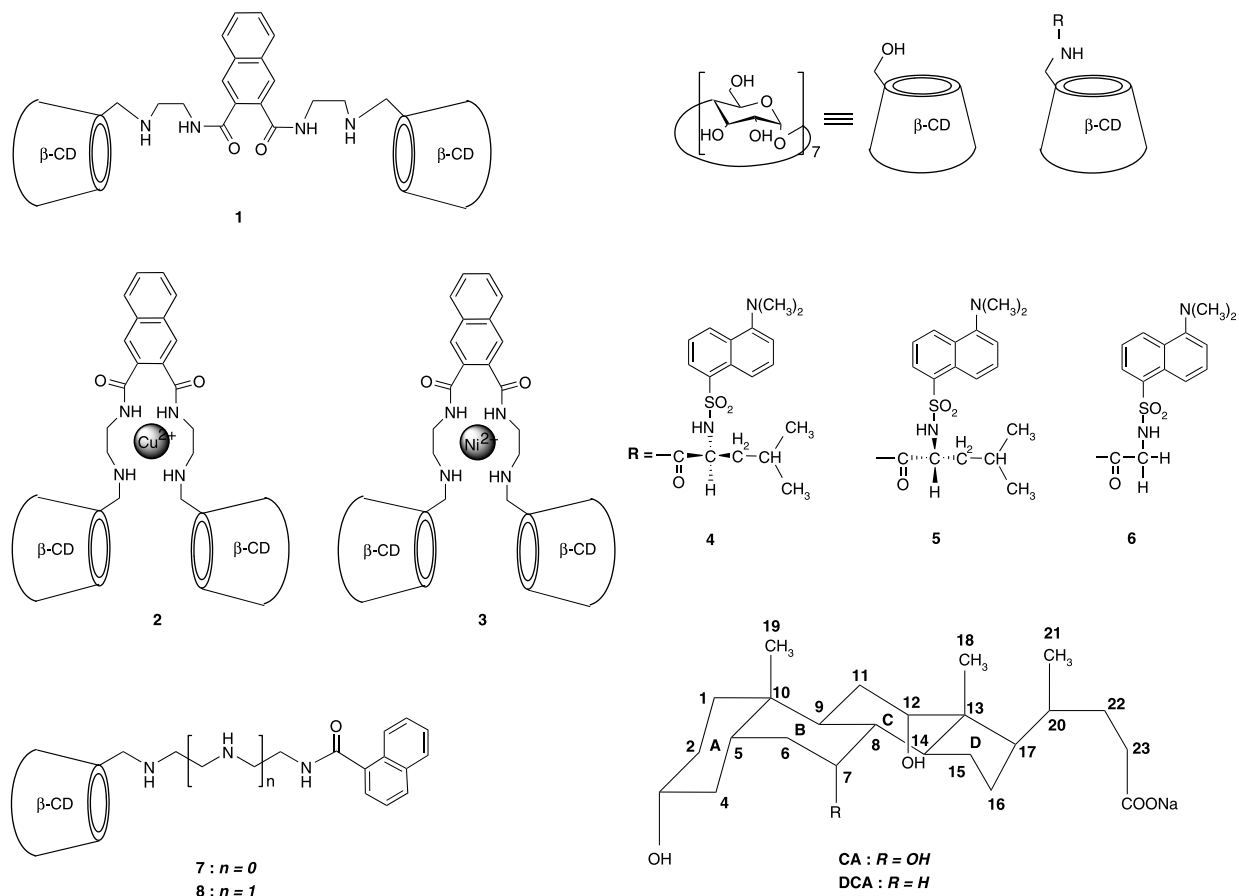
**Keywords:** cyclodextrin; bile salts; fluorescence spectroscopy; molecular recognition

### Introduction

Possessing the hydrophobic interior and hydrophilic surface, cyclodextrins (CDs), a class of cyclic oligosaccharides with six, seven or eight D-glucose units linked by  $\alpha$ -1,4-glucose bonds, have the abilities to accommodate various guest molecules within their truncated cone-shaped cavities to form host–guest inclusion complexes or supramolecular species (1–4). Therefore, CDs and their derivatives have been widely applied in the fields of analytical chemistry (5), enzymology (6), pharmaceuticals (7), food industry (8, 9) and so on. Superior to native and mono-modified CDs, bridged bis(CD)s can greatly enhance the original binding abilities and molecular selectivities of native CDs through cooperative binding of two adjacent hydrophobic cavities as well as additional binding interactions from the functional linker. Moreover, metal ions that are introduced into the bridged bis(CD)s can also act as an efficient binding site in multiple recognition (10). On the other hand, bile salts are a class of important surfactant-like molecules possessing a steroid structure and have crucial properties in the digestion of cholesterol and human metabolism (11). In the past two decades, the selective binding and molecular recognition of bile salts by bis(CD)s have attracted increasing attention. For example, Breslow et al. (12) reported the efficient recognition and binding of cholesterol by short-linked bis(CD)s. Reinhoudt et al. studied bis(CD)s as receptor molecules for steroid sensors, showing enhanced binding abilities towards cholate and deoxycholate (13).

Ueno and co-workers reported the fluorescence sensing behaviours of dansyl-modified bis(CD)s towards bile salts (14). Recently, we also reported the stoichiometric 1:1 and 1:2 binding of bridged bis( $\beta$ -CD)s with bile salts by means of fluorescence spectroscopy and microcalorimetry, showing the strong binding abilities and high molecular selectivities (15–17). However, the comparative studies on the molecular binding behaviours of bridged bis( $\beta$ -CD)s and metallobridged bis( $\beta$ -CD)s with bile salts are still rare (15–17), to the best of our knowledge. In the present work, we wish to report the syntheses and molecular binding behaviours of a naphthalenecarboxy-bridged bis( $\beta$ -CD) and its metal complexes with two bile salts, i.e. sodium cholate acid (CA) and sodium deoxycholate acid (DCA) (Scheme 1). The inclusion complexation behaviours were investigated in aqueous buffer solution (pH 7.4) by means of fluorescence, circular dichroism spectroscopy and two-dimensional NMR. There are some obvious advantages to choose naphthalenecarboxy-bridged bis( $\beta$ -CD) and its metal complexes as host molecules. Firstly, the flexible naphthalenecarboxyl linker can adjust to the orientation and distance of two  $\beta$ -CD cavities for the size of guest molecules. Secondly, the coordinated metal centre can also provide additional electrostatic attraction with negatively charged bile salts. These studies will help us deeply examine the role of cooperative binding and multiple recognition mechanism in the selective binding of bridged and metallobridged bis( $\beta$ -CD)s, which will

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Scheme 1. Molecular structures of host and guest.

enrich our further understanding of this developing, but little investigated, area of supramolecular chemistry.

## Experimental section

### General

$^1\text{H}$  NMR spectra were performed in  $\text{D}_2\text{O}$  on a Varian Mercury VX300 instrument. Elemental analyses were performed on a Perkin-Elmer 2400C instrument. UV-vis spectra and circular dichroism were recorded in a conventional quartz cell ( $10 \times 10 \times 45$  mm) on a Shimadzu UV-2401PC spectrophotometer and a JASCO J-715S spectropolarimeter, respectively. Fluorescence spectra were recorded in a conventional quartz cell ( $10 \times 10 \times 45$  mm) at  $25^\circ\text{C}$  on a JASCO FP-750 spectrometer with excitation and emission slits of 10 nm.

### Materials

$\beta$ -CD of reagent grade was recrystallised twice from water and dried *in vacuo* at  $95^\circ\text{C}$  for 24 h, prior to use. *N,N*-Dimethylformamide (DMF) was dried over calcium hydride for 2 days and then distilled under reduced pressure, prior to use. Dicyclohexylcarbodiimide (DCC),

CA and DCA were commercially available and used without further purification. Mono(6-aminoethylamino-6-deoxy)- $\beta$ -CD was prepared according to previously reported methods (18,19). Tris-HCl buffer solution (pH 7.4) was used as solvent for all spectrophotometric measurements.

### Synthesis of 2,3-naphthalenedicarboxy-bridged bis(6-aminoethylamino-6-deoxy- $\beta$ -CD) (1)

Mono(6-aminoethylamino-6-deoxy)- $\beta$ -CD (2.4 g) was dissolved in DMF (50 ml), and then 2,3-naphthalenedicarboxylic anhydride (0.2 g), DCC (0.5 g) and 4 Å molecular sieves were added. The reaction mixture was stirred for 2 days in an ice bath, followed by another 2 days at room temperature. The precipitate was removed by filtration, and the filtrate was evaporated under reduced pressure. After the residue obtained was dissolved in a minimal amount of water, acetone (150 ml) was added to the solution to give a light yellow precipitate. This procedure was repeated twice. The crude product obtained was purified on Sephadex C-25 and G-25 columns with distilled water as the eluent. After drying *in vacuo*, a pure sample was obtained in

23% yield as a yellow solid.  $^1\text{H NMR}$  ( $\text{D}_2\text{O}$ , TMS, ppm):  $\delta$  2.9–4.4 (m, 92H), 5.0 (m, 14H), 7.6–8.2 (m, 6H); UV/vis (water):  $\lambda_{\text{max}}(\epsilon) = 235 \text{ nm}$  ( $22,270 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$ ), 268 nm ( $2440 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$ ); elemental analysis (%) calcd for  $\text{C}_{100}\text{H}_{156}\text{O}_{70}\text{N}_4\cdot 9\text{H}_2\text{O}$ : C 44.54, H 6.50, N 2.01; found: C 44.55, H 6.21, N 2.09.

## Results and discussion

### Metal coordination and stoichiometry

Naphthalenedicarboxy-bridged bis( $\beta$ -CD) **1** was prepared in a moderate yield by the reaction of mono(6-aminoethyl-amino-6-deoxy)- $\beta$ -CD with 2,3-naphthalenedicarboxylic anhydride. Furthermore, coordination reaction of **1** with copper(II) and nickel(II) in aqueous solution gave metallobridged bis( $\beta$ -CD)s **2** and **3** *in situ*. To investigate the metal coordination behaviour, UV titrations of **1** with  $\text{Cu}^{2+}$  or  $\text{Ni}^{2+}$  ions were performed at  $25^\circ\text{C}$  in aqueous solution. The absorbance intensities of **1** at 235 and 268 nm gradually increased with the addition of  $\text{Cu}^{2+}$  or  $\text{Ni}^{2+}$ . In the control experiment, the UV–vis spectrum of  $\text{Cu}^{2+}$  or  $\text{Ni}^{2+}$  within the measurement concentration range displayed no appreciable changes at 200–350 nm under the same experimental conditions. These results indicated that the metal ion was coordinated to **1** to form the metallobridged bis( $\beta$ -CD)s. Moreover, the conductivity measurements were used to explore the coordination stoichiometry of metallooligo( $\beta$ -CD)s in aqueous solution since the conductivity of the system decreased upon complex formation. As shown in Figure 1, the plot of  $1/\text{Cu}^{2+}$  system showed a minimum at a concentration ratio of 1.0, which corresponded to the 1:1 coordination

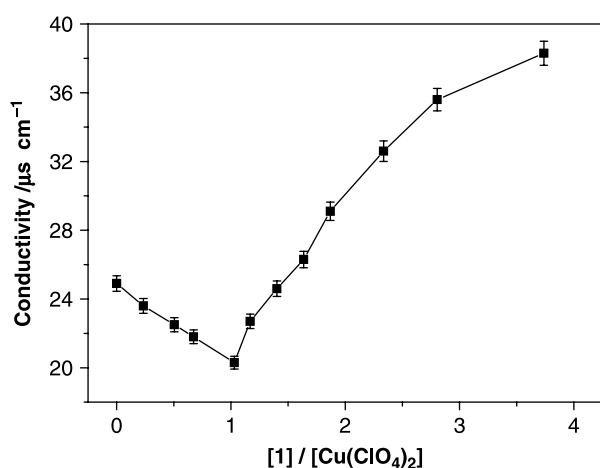


Figure 1. The dependence of conductivity of  $\text{Cu}(\text{ClO}_4)_2$  ( $1.07 \times 10^{-4} \text{ mol dm}^{-3}$ ) on the concentration of **1** ( $0, 0.25 \times 10^{-4}, 0.54 \times 10^{-4}, 0.72 \times 10^{-4}, 1.1 \times 10^{-4}, 1.25 \times 10^{-4}, 1.5 \times 10^{-4}, 1.75 \times 10^{-4}, 2.0 \times 10^{-4}, 2.5 \times 10^{-4}, 3.0 \times 10^{-4}$  and  $4.0 \times 10^{-4} \text{ mol dm}^{-3}$ ) in aqueous solution at  $25^\circ\text{C}$ .

stoichiometry. The same stoichiometry was also found in the  $1/\text{Ni}^{2+}$  system.

### Conformation analysis of bridged and metallobridged bis( $\beta$ -CD)s

It has been widely demonstrated that the circular dichroism spectrometry is a convenient method for investigating the conformation of CD systems. Generally, the inclusion of a chromophoric achiral guest/ moiety in a chiral CD cavity produces the induced circular dichroism (ICD) signals (20, 21). In this work, both bis( $\beta$ -CD) **1** and metallobridged bis( $\beta$ -CD)s **2–3** displayed positive ICD signals for the  $^1\text{L}_a$  and  $^1\text{L}_b$  transitions of the naphthyl chromophore. The observed Cotton effect peaks were  $\Delta\epsilon = 6.33 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 237 nm and  $4.04 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 252 nm for **1**,  $\Delta\epsilon = 5.89 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 234 nm and  $5.86 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 244 nm for **2**, and  $\Delta\epsilon = 4.90 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 232 nm and  $4.99 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 243 nm for **3**. According to the pioneering studies on the ICD phenomena of modified CDs (22–24), we deduced that the naphthyl groups in hosts **1–3** were shallowly included in the  $\beta$ -CD cavities with an acclivous orientation to form self-included complexes. This shallow self-included conformation was further confirmed by the 2D-NMR results. Generally, the nuclear Overhauser effect (NOE) cross-peaks between the protons that are closer than 0.4 nm in space will be observed in the nuclear Overhauser enhancement spectroscopy (NOESY) or rotating frame nuclear Overhauser effect spectroscopy (ROESY) spectrum. Therefore, if the substituent group is self-included into the  $\beta$ -CD cavity, the NOE correlations between the protons of the substituent group and the inner protons of the  $\beta$ -CD cavity (H-3/H-5/H-6) will be measured. It should be noted that only the cross-peaks with H3, H5 and H6 protons of CDs can be considered when the 2D-NMR results of CD systems are analysed because the H2 and H4 protons are located outside the cavity and the H1 protons are disturbed by  $\text{D}_2\text{O}$ . Figure 2 shows the clear NOE cross-peaks (peaks a and b) between the  $\text{H}_a/\text{H}_b$  protons of the naphthyl group in **1** and the H3/H5/H6 protons of  $\beta$ -CD cavity. Further comparison showed that the  $\text{H}_a/\text{H}_b$  protons of the naphthyl group gave the stronger NOE cross-peaks with the H5/H6 protons than those with the H3 protons. Since the H5/H6 protons were located near the narrow opening of the  $\beta$ -CD cavity while the H3 protons near the wide opening, these NOE correlations indicated that the naphthyl unit of linker group was self-included in the  $\beta$ -CD cavity from the narrow opening, which was consistent with the deduced conformation from the circular dichroism experiments. A similar result was also observed in the 2D-NMR experiments of **3**. However, due to the paramagnetic disturbance caused by the copper(II) ion, the 2D-NMR spectrum of **2** was impossible to measure.

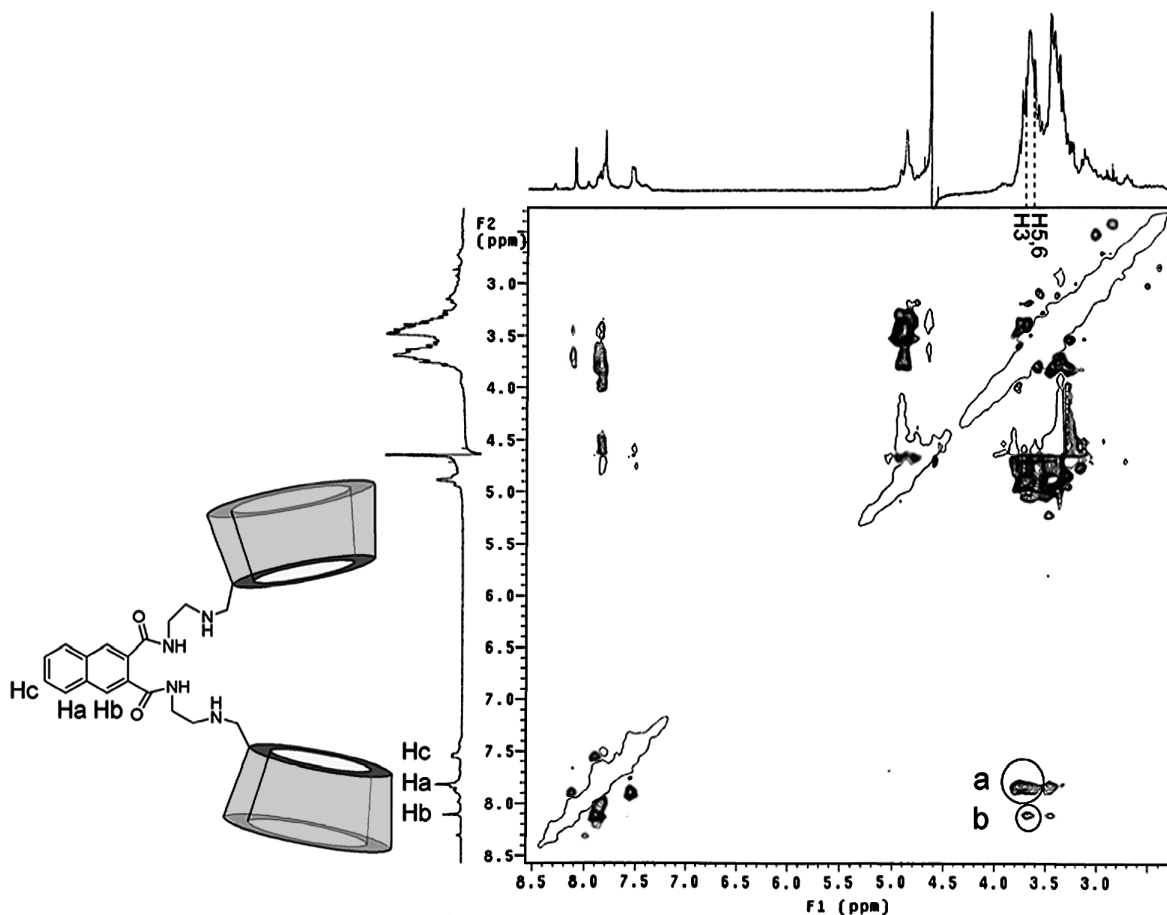


Figure 2. ROESY spectrum of **1** ( $5.0 \times 10^{-3} \text{ mol dm}^{-3}$ ) in  $\text{D}_2\text{O}$  at  $25^\circ\text{C}$  with a mixing time of 300 ms.

### Spectral titration

The inclusion complexations of hosts **1–3** with the selected bile salts were quantitatively investigated in Tris-HCl buffer solution (pH 7.4) by means of fluorescence titrations. As illustrated in Figure 3, the fluorescence intensity of **1** gradually increased with the stepwise addition of CA. The stoichiometry for the inclusion complexation between **1–3** and bile salts were determined by the Job's experiment. The Job's plot for **1/CA** system is shown in Figure 4. In the examined concentration range, there is a maximum at a molar fraction of 0.5, indicating 1:1 inclusion complexation between host and guest. Similar 1:1 stoichiometry was also observed for other cases of inclusion complexations between **2** and **3** of bile salts.

After validating the 1:1 stoichiometry by Job's experiments, the stability constants ( $K_s$ ) for the complexation of bridged bis( $\beta$ -CD) and metallobridged bis( $\beta$ -CD)s (host) with bile salts (guest) could be calculated by analyzing the sequential changes in fluorescence intensity ( $\Delta I_f$ ) of hosts, which occurred with the changes in guest concentration. This analysis was carried out using a

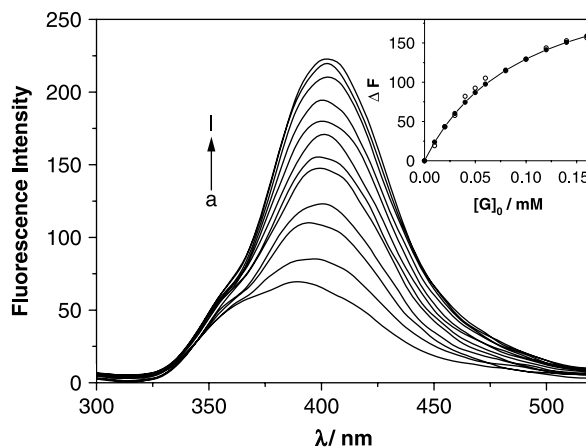


Figure 3. Fluorescence spectral changes of **1** ( $2.0 \times 10^{-6} \text{ mol dm}^{-3}$ ) with the addition of CA ( $0$ ,  $0.1 \times 10^{-4}$ ,  $0.2 \times 10^{-4}$ ,  $0.3 \times 10^{-4}$ ,  $0.4 \times 10^{-4}$ ,  $0.5 \times 10^{-4}$ ,  $0.6 \times 10^{-4}$ ,  $0.8 \times 10^{-4}$ ,  $1.0 \times 10^{-4}$ ,  $1.2 \times 10^{-4}$ ,  $1.4 \times 10^{-4}$  and  $1.6 \times 10^{-4} \text{ mol dm}^{-3}$ ) in Tris-HCl buffer solution (pH 7.4) and the nonlinear least-squares analysis (inset) to calculate the complex stability constant ( $K_s$ ). The excitation wavelength is 268 nm.

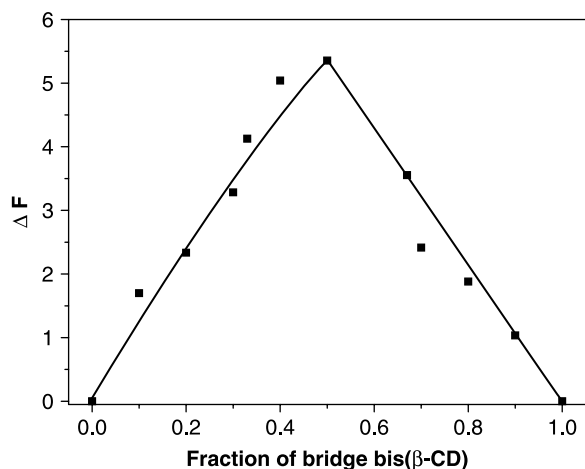


Figure 4. Job's plot of **1**/CA system at 375 nm ( $[1] + [CA] = 1.0 \times 10^{-4} \text{ mol dm}^{-3}$ ).

nonlinear least-squares curve-fitting method (25). For each host examined, the plot of  $\Delta I_f$  as a function of  $[G]_0$  gave an excellent fit (Figure 3, inset). When the measurements were repeated, the  $K_s$  values were reproducible within an error of  $\pm 5\%$ . The  $K_s$  values obtained were listed in Table 1. For comparison, some reported  $K_s$  values for the inclusion complexations of naphthyl-modified  $\beta$ -CD with CA and DCA were also listed in Table 1.

### Binding mode

In order to elucidate the mechanism of molecular recognition, we investigated the inclusion complexation modes between bridged bis( $\beta$ -CD) or metallobridged bis( $\beta$ -CD)s and bile salts. The hosts **1–3** displayed almost reversed ICD signals in the presence of guest bile

salts. Upon addition of CA ( $8.1 \times 10^{-4} \text{ mol dm}^{-3}$ ), the corresponding Cotton effect peaks were  $\Delta\epsilon = -6.44 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 245 nm for **1**,  $\Delta\epsilon = -5.35 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 245 nm for **2**, and  $\Delta\epsilon = -6.10 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 244 nm for **3**. In the case of DCA ( $8.1 \times 10^{-4} \text{ mol dm}^{-3}$ ), the Cotton effect peaks were  $\Delta\epsilon = -7.12 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 245 nm for **1**,  $\Delta\epsilon = -6.00 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 244 nm for **2**, and  $\Delta\epsilon = -6.91 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$  at 244 nm for **3**. According to the generally accepted empirical rule (22–24), the ICD signal is reversed when a chromophore moves from the interior of the  $\beta$ -CD cavity to the exterior, with its orientation of the transition dipole moment with respect to the  $C_7$  axis of the  $\beta$ -CD cavity unchanged. In the previous section, we have demonstrated that the naphthyl groups in **1–3** were shallowly included in the  $\beta$ -CD cavities. Therefore, we can deduce that, upon inclusion complexation with guest bile salts, the naphthyl groups were excluded from the  $\beta$ -CD cavities. Further comparison showed that hosts **1–3** gave the stronger ICD intensities with DCA than CA. This may infer the stronger interactions between hosts **1–3** and DCA, which is basically consistent with the spectral titration results showing that hosts **1–3** gave the higher  $K_s$  values towards DCA. A possible reason for the stronger binding towards DCA may be due to the more hydrophobic steroid skeleton of DCA than that of CA, i.e. DCA lacks the 7-hydroxy group, which consequently strengthens the hydrophobic interactions between host and guest.

2D-NMR experiments gave further information about the binding mode between the host and the guest. Figure 5 illustrated a typical ROESY spectrum of **1**/DCA system, which showed the clear NOE cross-peaks (peaks c) between the C18, C19, C21, C15, C17, C22 protons of DCA, and the interior protons (H3/H5/H6) of the  $\beta$ -CD cavity, and the DCA protons displayed the stronger NOE cross-peaks with H5/H6 protons than H3 protons of  $\beta$ -CD. These NOE cross-peaks unanimously demonstrated that the guest DCA was included in the  $\beta$ -CD cavity with the D-ring and the carboxylic tail located near the narrow opening but the B-ring located near the wide opening. No NOE cross-peaks between the aromatic protons of linker group and the interior protons of the  $\beta$ -CD cavity can be observed, indicating that the naphthyl group was excluded from the  $\beta$ -CD cavity upon inclusion complexation. This result was in well agreement with the one deduced from the circular dichroism spectroscopy. Moreover, Figure 5 also exhibited the clear NOE cross-peaks (peak d) between the methylene protons of linker group and  $\beta$ -CD's H5/H6 protons, which indicated that the ethylenediamino moiety of the linker group was also partially self-included in the  $\beta$ -CD cavity from the narrow opening. According to these NOE signals, we can deduce that bis( $\beta$ -CD) **1** adopted a host-linker-guest co-inclusion

Table 1. Complex stability constants ( $K_s$ ) for 1:1 inclusion complexation of hosts with various guests in Tris-HCl buffer solution (pH 7.4) at 25°C.

Host	Guest	$K_s$ ( $\text{M}^{-1}$ )	Ref.
$\beta$ -CD	CA	4068	(16)
	DCA	4844	(16)
<b>1</b>	CA	10,540	This work
	DCA	12,400	This work
<b>2</b>	CA	15,500	This work
	DCA	15,700	This work
<b>3</b>	CA	31,400	This work
	DCA	95,900	This work
<b>4</b>	CA	1650	(26)
	DCA	2660	(26)
<b>5</b>	CA	500	(26)
	DCA	1520	(26)
<b>6</b>	CA	60.4	(26)
	DCA	1030	(26)

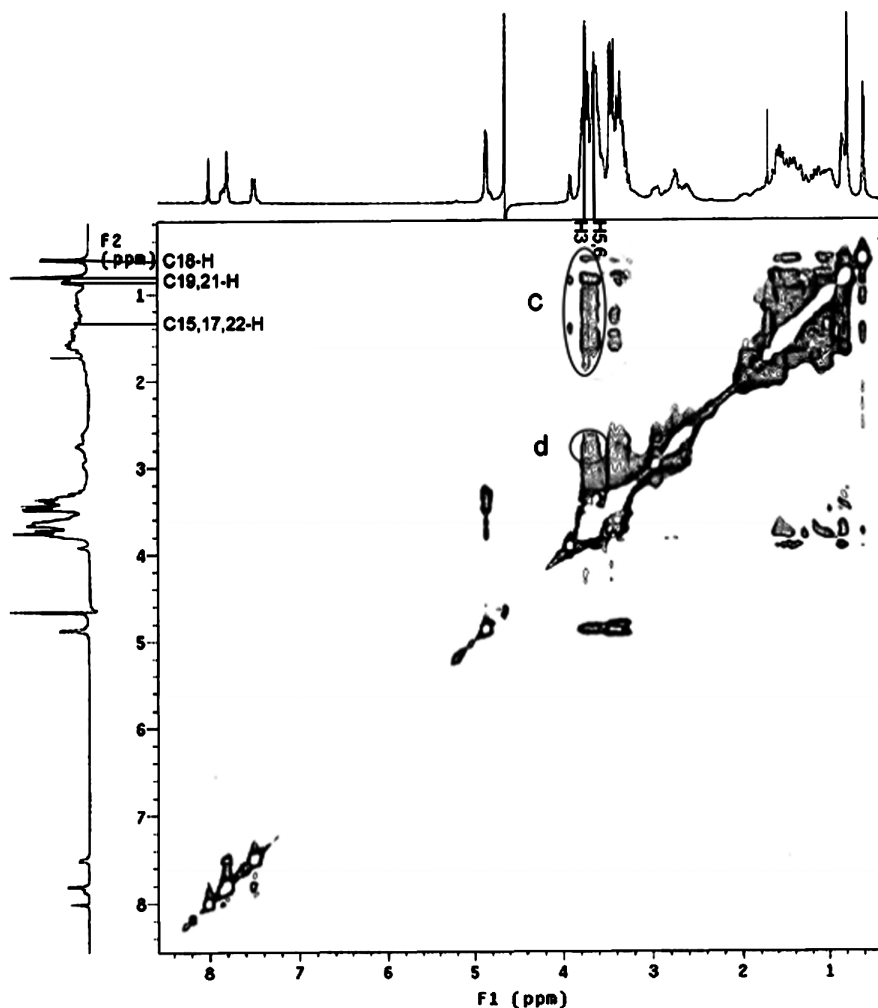


Figure 5. ROESY spectrum of **1**/DCA system ( $[1] = [DCA] = 5.0 \times 10^{-3} \text{ mol dm}^{-3}$ ) in  $\text{D}_2\text{O}$  at  $25^\circ\text{C}$  with a mixing time of 300 ms.

binding mode (10). In this mode, the guest DCA penetrated into one of the  $\beta$ -CD cavities of **1**, and the linker group was partially self-included in the other  $\beta$ -CD cavity. Similar results were also found in other ROESY experiments of hosts **1** and **3** with guest bile salts.

### Binding ability

Many reports have demonstrated that several non-covalent interactions, including van der Waals, hydrogen bonding and electrostatic interactions, simultaneously contribute to the inclusion complexation of CDs with guest molecules. Since the strength of these actions are closely related to the distance and the contact surface area between host and guest, the degree to which the size and shape of a host match those of a guest has a dominant effect on the stability of the complexes formed. According to this mechanism, native and modified monomeric CDs only display limited abilities towards guest molecules

probably because of relatively weak association of one CD cavity with guest molecule. However, bridged bis(CD)s displayed stronger binding abilities than native and modified monomeric CDs owing to cooperative binding of two adjacent CD cavities with a single guest molecule. Significantly, the introduction of metal ions not only alters the original conformation of linker group but also shortens the effective distance of two CD cavities in bridged bis(CD). Moreover, the coordinated metal centre also provides the additional chelation, electrostatic and/or electron transfer interactions with the accommodated guest. As a joint result of these factors, metallobridged bis( $\beta$ -CD)s possess much stronger binding abilities. As shown in Table 1, the binding constants ( $K_s$ ) for the complexation of naphthalenedicarboxy-bridged bis( $\beta$ -CD) **1** and its metal complexes **2–3** with guest bile salts vary in the range of  $1.05 \times 10^4$  to  $9.59 \times 10^4 \text{ M}^{-1}$ . As the reference compounds, native  $\beta$ -CD and naphthyl-modified  $\beta$ -CDs either give limited binding abilities ( $K_s = 60.4$  to  $4.84 \times 10^3 \text{ M}^{-1}$ ) or show

no appreciable binding abilities towards same guests (16,26). For example, naphthalenedicarboxy-bridged bis( $\beta$ -CD) **1** gives the  $K_s$  values towards CA up to 6.4–175 times higher than the corresponding values of naphthyl-modified  $\beta$ -CDs **4–6**. These enhanced binding abilities should be attributed to cooperative binding of the  $\beta$ -CD cavity and the linker group towards the guest molecule, leading to greatly strengthened van der Waals and hydrophobic interactions between host and guest when compared with mono-modified  $\beta$ -CDs. Furthermore, after metal coordination, the metallobridged bis( $\beta$ -CD)s **2** and **3** significantly enhance the original binding ability of native  $\beta$ -CD and naphthyl-modified  $\beta$ -CDs **4–6** by a factor of 3.2–19.8 for native  $\beta$ -CD and 5.9–520 for naphthyl-modified  $\beta$ -CDs. This enhancement may be subjected to a multiple recognition mechanism of metallobridged bis( $\beta$ -CD)s towards model substrates. Firstly, the coordination of a metal ion to the linker group shortens the effective distance of two  $\beta$ -CD cavities to some extent and thus improves the size-fit degree between host and guest. In addition, under the experimental conditions, the carboxylate group of CA or DCA is not protonated and should exist as a carboxylate anion. Therefore, the electrostatic attraction between the anionic carboxyl group of guest bile salt and the coordinated metal ion of metallobridged bis( $\beta$ -CD) may also favour the host–guest binding to some extent. As a cumulative result of these factors, metallobridged bis( $\beta$ -CD)s display significantly enhanced binding abilities towards guest bile salts when compared with parent bis( $\beta$ -CD).

### Conclusion

In summary, naphthalenedicarboxy-bridged bis( $\beta$ -CD) and its metal complexes were successfully synthesised and used as fluorescent sensors for the molecular recognition of bile salts. The coordination of metal ions to bridged bis( $\beta$ -CD)s not only adjusted the conformation of bis( $\beta$ -CD) to fit the size of guest molecule but also provided additional electrostatic interactions with the negatively charged guest molecule, which consequently resulted in the highest  $K_s$  for guest bile salts. These enhanced binding abilities by metal coordination will help us achieve a deeper understanding of the

multiple recognition mechanism often observed in the biological molecular recognition.

### Acknowledgements

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