

Aromatic Diamino-bridged Bis(β -cyclodextrin) as Fluorescent Sensor for the Molecular Recognition of Bile Salts

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Binding behavior of 4,4'-diaminodiphenyl ether-bridged-bis (6-amino-6-deoxy- β -cyclodextrin) **2** with four representative bile salts, *i.e.*, cholate (CA), deoxycholate (DCA), glycocholate (GCA) and taurocholate (TCA), has been investigated at 25 °C in phosphate buffer (pH 7.20) by fluorescence, circular dichroism and 2D NMR spectroscopy. The result indicated that the bis(β -cyclodextrin) **2** acts as fluorescent sensor and displays remarkable fluorescence enhancement upon addition of optically inert bile salts. From the induced circular dichroism (ICD) and ROESY spectra, it is deduced that the phenyl moiety in the linker of bis(β -cyclodextrin) **2** is partially self-included in the CD cavity, and is not expelled out of the CD cavity upon complexation with bile guests. Owing to the cooperative host-tether-guest binding mode in which the linker and guest are co-included in the two CD cavities, bis(β -cyclodextrin) **2** significantly enhanced binding ability and molecular selectivity as compared with the native β -cyclodextrin **1** through the simultaneous contributions of hydrophobic, hydrogen bond, and electrostatic interactions. The complex stability constants are discussed comparatively and globally from the viewpoints of multiple recognition between host and guest.

Key Words : Bridged bis(β -cyclodextrin)s, Bile salts, Fluorescence spectroscopy, Inclusion phenomena, Molecular recognition

Introduction

It is well-known that fluorescent spectra are a powerful tool for studying the host-guest inclusion phenomena, which have been widely employed in molecular recognition of cyclodextrins (CDs).¹⁻³ The introduction of fluorophore sidearms to the CD framework not only provides additional binding sites but the sidearms are also capable of acting as fluorescent sensors with some optically silent guest molecules.⁴⁻⁶ Possessing two appropriately located hydrophobic CD cavities in the same molecule, bis(β -CD)s feature very high binding ability and molecular selectivity for specific ditopic guests through the cooperative two-point recognition.^{7,8} However, works on the molecular recognition of bis(β -CD)s with fluorescent linkers are concentrated mostly on the inclusion complexation of rather simple organic guests and amino acids,⁹⁻¹¹ and practically less attempts have

been made on the recognition of optically inert bile salts. Bile salts, on the other hand, are classical surfactant-like biological amphipathic compounds containing a steroid skeleton which have distinctive detergent properties and play a significant role in the metabolism and excretion of cholesterol in mammals.¹²

In the present study, we investigated the selective binding behavior of the bis(β -CD) **2** (Chart 1) containing fluorescent aromatic diamine linker towards four bile salts (Chart 2) by fluorescence, circular dichroism and 2D NMR spectroscopy. It is of particular interest to investigate the molecular recognition behavior of bis(β -CD) **2** toward bile salts from the viewpoint of induced-fit interactions, and the role of the cooperative weak interactions working between host and guest through a fluorescence-sensing mechanism. This approach could serve to further our understanding of this developing but little-investigated area in the field of CD chemistry.

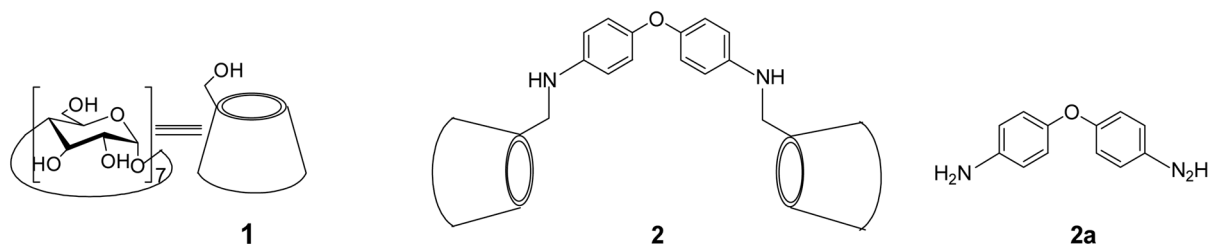


Chart 1

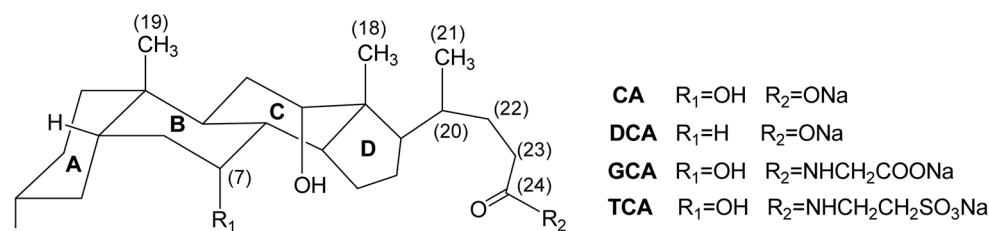


Chart 2

Experimental Section

Materials. All bile salt guests, *i.e.*, cholate (CA), deoxycholate (DCA), glycocholate (GCA) and taurocholate (TCA), were purchased from Sigma and used as received. Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.1 M phosphate buffer solution of pH 7.20 for spectral measurements. 4'-diaminodiphenyl ether-bridged-bis (6-aimino-6-deoxy- β -CD) **2** was prepared as previously reported.¹³

Instruments. 1H NMR spectra were recorded on a Bruker AV. DRX5 instrument operated at 500 MHz. UV and Circular dichroism spectra were performed on a Shimadzu UV2401 PC spectrometer and a JASCO 810 spectropolarimeter, respectively. Fluorescence spectra were measured in a conventional quartz cell ($10 \times 10 \times 45$ mm) at 25 °C on a Hitachi F-4500 spectrometer equipped with a constant-temperature water bath, with the excitation and emission slits of 10 nm width at an excitation wavelength 300 nm.

Results and Discussion

Original conformation of bridged bis(β -CD) **2.** The CD cavity can provide a chiral microenvironment where achiral group complexed by CDs show the induced circular dichroism (ICD) signal(s) in corresponding transition band(s), and thereby, circular dichroism spectrometry has become a convenient method for the elucidation of the structure features of CD derivatives and complexes.^{14,15} The circular dichroism spectrum and corresponding UV/vis absorption spectrum of bridged bis(β -CD) **2** are shown in Figure 1. As can be seen from Figure 1, the bis(β -CD) **2** presents a strong negative Cotton effect peak at 225 nm ($\Delta\epsilon = -3.27 \text{ dm}^3 \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$) and a weak positive Cotton effect peak at 287 nm ($\Delta\epsilon = +0.61 \text{ dm}^3 \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$), attributed to the 1L_a and 1L_b transition bands of phenyl chromophore, respectively. According to the generally accepted empirical rule,^{16,17} the sign of ICD signal depends on the orientation of the transition dipole moment of the chromophore with respect to the dipole moment of the CD. For the chromophore located inside the CD cavity, its electronic transition parallel to the CD axis gives a positive ICD signal, whereas the perpendicular transitions gives a negative signal, but this situation is reversed for the chromophore located outside the CD cavity. We propose that the phenyl chromophore in the linker of bis(β -CD) **2** might shallowly include in the β -CD cavity with an acclivous orientation to form self-included complex.

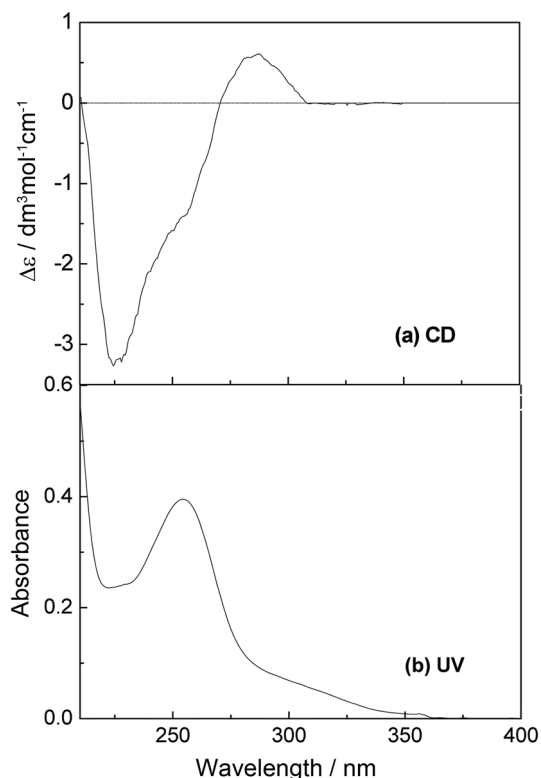


Figure 1. (a) Circular dichroism spectrum and (b) absorption spectrum of bis(β -CD) **2** (1.0×10^{-4} M) in phosphate buffer (pH 7.20) at 25 °C.

2D NMR spectroscopy has recently become an essential method in the study of the conformation of the CD derivatives and the interaction between host CDs and guest molecules, since one can conclude that two protons are closely located in space if an NOE cross-peak is detected between the relevant protons in the NOESY or ROESY spectrum. Therefore, it is possible to estimate the orientation of the tether moiety in the CD cavity using the assigned NOE correlations. It is well-known that only H3, H5, and H6 of CDs can give cross-peaks for analyzing host-guest interactions, as H2 and H4 are not facing to the inner cavity and H1 is affected by D_2O . If the tether moiety is self-included in the CD cavity, the NOE correlations between the protons of the tether moiety and the H3/H5/H6 protons of the CD should be observed. To this end, to obtain further evidence about the initial geometry of the self-included model of host **2**, the ROESY spectrum of bridged bis(β -CD) **2** was measured in D_2O . As shown in Figure 2(a), the ROESY spec-

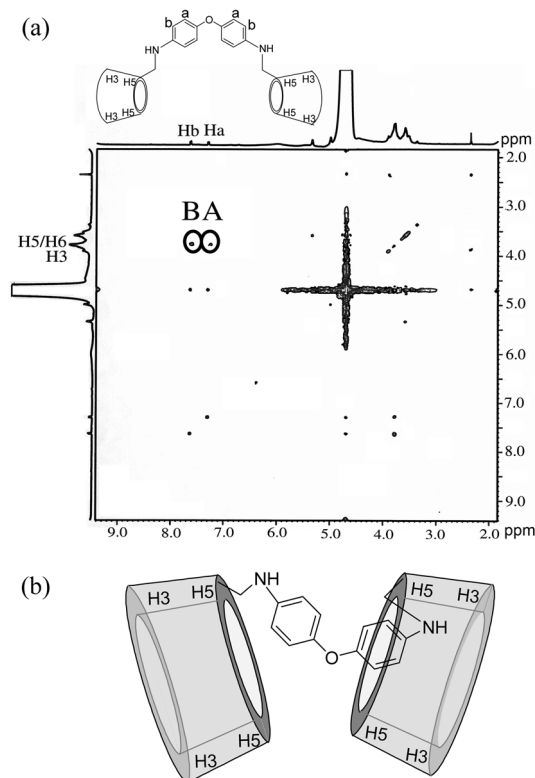


Figure 2. (a) ^1H ROESY spectrum of bis(β -CD) **2** (1.0×10^{-3} M) in D_2O at 25°C with a mixing time of 400 ms, (b) possible conformation of **2**.

trum of bis(β -CD) **2** displays clear NOE cross-peaks between the H5/H6 of CD cavity and Ha of the aromatic protons (peaks A), as well as between the H5/H6 and the Hb protons (peaks B). Since the H5/H6 protons are located near to the narrow opening of the CD cavity, while the H3 protons are near to the wide opening, we can conclude that the aromatic moiety of the CD tether is not entirely but partially self-included into the hydrophobic cavity from the narrow opening. The self-included binding mode of bis(β -CD) **2** obtained from the ROESY experiment is in excellent agreement with the result obtained from the previous circular dichroism experiment. Based on the above facts, we propose a possible conformation of bridged bis(β -CD) **2** (Figure 2(b)).

Spectral titration. Many investigations have demonstrated that a chromogenic group originally accommodated in the CD cavity may undergo substantial conformational changes upon guest inclusion, with accompanying appreciable spectral changes. The binding ability of a fluorescent-labeled CD can be quantitatively assessed by analysis of the spectral changes induced by guest inclusion. As can be seen from Figure 3, the fluorescence intensity of bis(β -CD) **2**, is much larger than that of reference compound **2a** under the identical conditions. Since the fluorescence intensity of the phenyl moiety is sensitive to changes in its microenvironment and is greater in hydrophobic microenvironment than in a hydrophilic one, the above result suggest that phenyl moiety of bis(β -CD) **2** was included into the hydrophobic cavities, leading to more

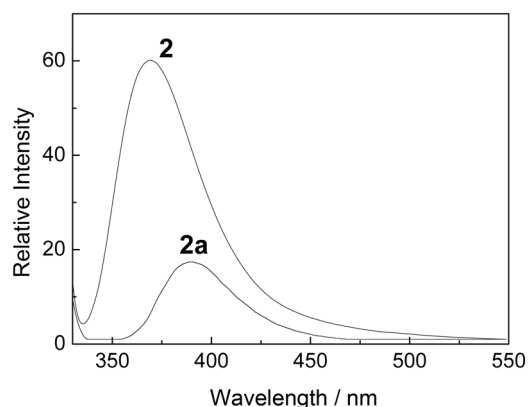


Figure 3. Fluorescence spectra of **2a** and bis(β -CD) **2** at the same concentration of 5.0×10^{-6} M in phosphate buffer (pH 7.20) at 25°C ; $\lambda_{\text{ex}} = 300$ nm.

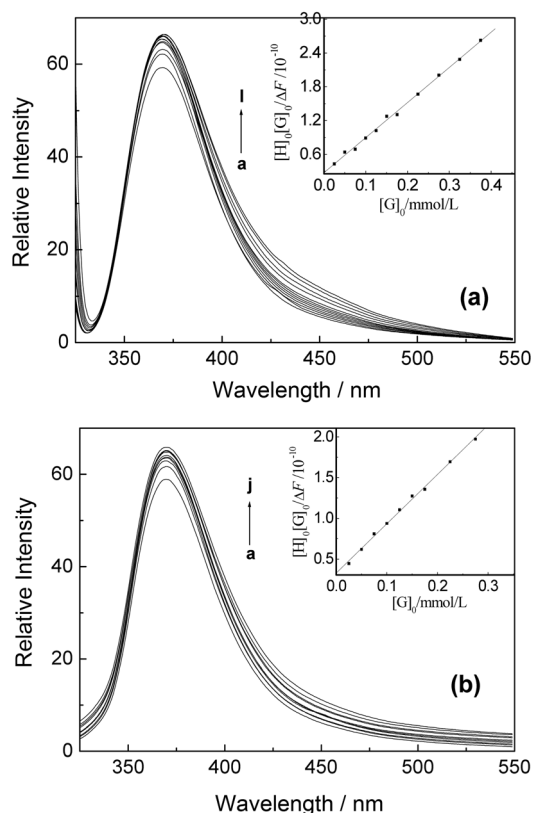


Figure 4. Fluorescence spectral changes of bis(β -CD) **2** ($5.0 \mu\text{M}$) upon addition of (a) DCA (from a to l = 0, 25, 50, 75, 100, 125, 150, 175, 225, 275, 325, 375 μM), and (b) TCA (from a to j = 0, 25, 50, 75, 100, 125, 150, 175, 225, 275 μM) in phosphate buffer (pH 7.20) at 25°C ; $\lambda_{\text{ex}} = 300$ nm; inserts: Typical plots of $[\text{H}]_0[\text{G}]_0/\Delta F$ versus $[\text{G}]_0$ for the inclusion complexation of bis(β -CD) **2** with DCA and TCA.

effective shielding of the fluorophore from the deactivating water attack. The result is in good agreement with the ICD and 2D NMR spectral study described above.

For a qualitative assessment of the inclusion complexation behavior of bis(β -CD) **2**, the spectral titrations of this compound with CA, DCA, GCA and TCA were performed at 25°C in phosphate buffer (pH 7.20) by fluorescence spectroscopy. Figure 4 shows the typical spectral changes of **2** upon

gradual addition of DCA and TCA, respectively. As can be seen, the relative fluorescent intensities of **2** present a continuous enhancement upon the addition of DCA and TCA, which are distinct from most cases of CD appended with fluorescent groups.^{18,19} In general, the fluorescent intensities of sidearms of CD derivatives undergo an obvious decrease when suitable guests are added because of the competitive inclusion. That is, the preferred binding of guests into the cavity of CD excludes their own fluorescent sidearms out of the cavity. And then the transfer of the fluorescent groups from hydrophobic region to hydrophilic region makes their fluorescence rationally be quenched. The increased fluorescence intensity of bis(β -CD) **2** upon addition bile salts can be rationalized by the increased micro-environmental hydrophobicity and/or steric shielding around the fluorophore arising from the cooperative guest-tether-host interactions. This property might allow the bis(β -CD) **2** application as fluorescence sensor for the molecular recognition of bile salts.

The stoichiometry for the inclusion complexation of bis(β -CD) **2** with bile salts were determined by the continuous variation method. As shown in Figure 5, the plot for bis(β -CD) **2** unit peaked at a molar fraction of 0.5, suggesting a 1:1 inclusion complexation between bis(β -CD) **2** and CA guest. The same results were obtained in the other cases of the inclusion complexation of bis(β -CD) **2** with bile salts.

With the 1:1 stoichiometry for the inclusion complexation of bile salts guest (G) with CDs (H), where the two CD moieties in bis(β -CD) are treated as a single unit, the inclusion complexation is expressed by eq 1 and the complex stability constant (K_s) is given by eq. (2).



$$K_s = [H \cdot G]/[H][G] \quad (2)$$

$$\Delta F = \Delta \varepsilon [H \cdot G] \quad (3)$$

where ΔF and $\Delta \varepsilon$ denote the sequential changes of fluorescence intensity and the differential molar extinction coefficient of host β -CDs in the absence and presence of guest molecule. Under the conditions employed, the initial con-

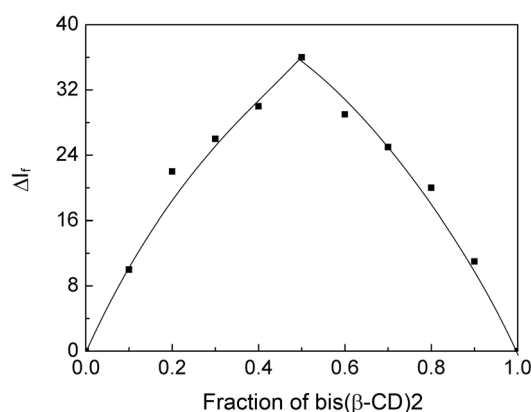


Figure 5. Continuous variation plot of **2**/CA system at 369 nm ([bis(β -CD) unit] + [CA] = 2.3×10^{-5} M).

Table 1. stability constant (K_s) and Gibbs free energy change ($-\Delta G^\circ$) for the inclusion complexation of bis(β -CD) **2** with bile salts in phosphate buffer (pH 7.20) at 25 °C

Host	Guest	K_s (M ⁻¹)	Log K_s	$-\Delta G^\circ$ (kJ/mol)
1	CA	4068 ± 84^{20}	3.6	20.6
	DCA	4844 ± 16^{20}	3.7	21.0
	GCA	2394 ± 69^{20}	3.4	19.3
	TCA	2293 ± 13^{20}	3.4	19.2
2	CA	27050 ± 510	4.4	25.1
	DCA	22930 ± 340	4.4	25.1
	GCA	7200 ± 110	3.9	22.2
	TCA	17610 ± 290	4.2	23.9

centration of guest molecules is much larger than that of the host β -CDs, *i.e.*, $[G]_0 \gg [H]_0$. Therefore, the combination of eqs. (2) and (3) leads to the extended Benesi-Hildebrand equation (eq. 4), which is used to calculate the K_s (eq. 2) from the slope and intercept of $[H]_0[G]_0/\Delta F$ versus $[G]_0$ plots.

$$[H]_0[G]_0/\Delta F = (1/K_s \Delta F) + [G]_0/\Delta F \quad (4)$$

Figure 4 (inserts) illustrates the result of such a treatment for the inclusion complexation of bis(β -CD) **2** with DCA and GCA, where the calculated $[H]_0[G]_0/\Delta F$ values were plotted against the $[G]_0$ 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 Table 1.

Binding mode. According to the previous report, bile salts, which possess A, B, C and D rings, are able to penetrate and interact with the hydrophobic CD cavity from either the primary or the secondary side, and bile acids can also enter the CD cavity by either the A-ring of the steroid body or the carboxylate and sulfonate group (tail).²¹⁻²³ Such uncertain penetrating model and binding sites of guests may greatly affect the conformation and binding pattern of the resulting complex of bile salts with CDs, giving different binding constants. Therefore, it is very important to investigate the binding modes between the bis(β -CD) **2** and bile salts for elucidation of the mechanism of molecular recognition. A typical ROESY spectrum of the bis(β -CD) **2** and CA in D₂O is shown in Figure 6(a). The notations used are Hn for CD protons and Pn for steroids protons, where n is the carbon number in CD and steroid. As shown in Figure 6 (a), the ROESY spectrum for the resulting CA/**2** in D₂O displays complicated NOE cross-peaks, which come not only from the intermolecular correlations between the bis(β -CD) **2** and the bile salt, but also from the intramolecular correlations of **2** or CA. Among them, the cross-peak B corresponds to the NOE correlations between CA's P18 protons and CD's H3 protons, and the cross-peak C corresponds to the NOE correlations between the CA's side-chain protons (P21) and the CD's H3/H5/H6 protons. Meanwhile, the cross-peaks D and E correspond to the NOE correlations between CA's D-ring protons (P14 to P17) and CD's H3 protons. In addition, the significant NOE correlations are

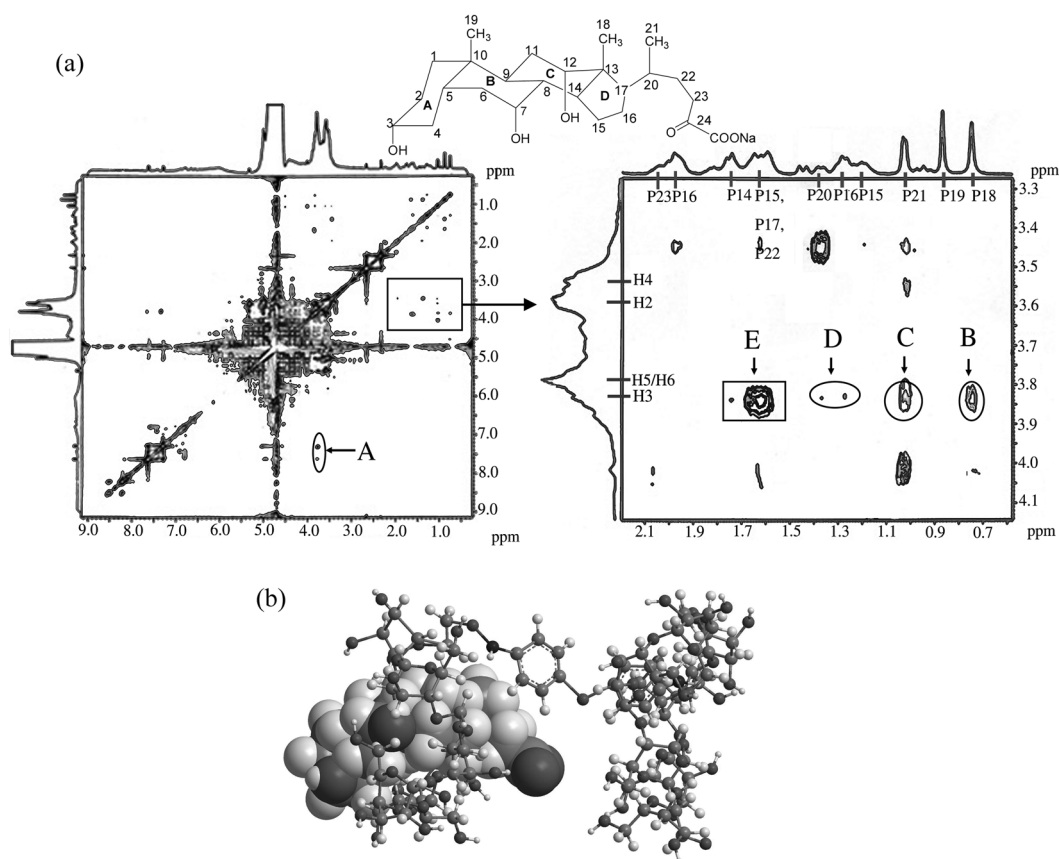


Figure 6. (a) ^1H ROESY spectrum of the **2** with CA (5.0×10^{-3} M each) in D_2O at 25°C with a mixing time of 400 ms, (b) possible binding mode of **2** with CA.

found between CA's side-chain protons and steroid body (P23 with P16, P22 with P16), but no NOE correlations between CA's P19 protons and CD's H3/H5/H6 protons can be observed. We can deduce that the D-ring of CA is wholly include in the CD cavity from the wide opening, while the side-chain is located near the narrow opening of CD cavity and folded toward the steroid body. On the other hand, the obvious cross-peaks (peak A) assigned to the NOE correlations between the phenyl protons of the linker group and H5/H6 protons of CD are also observed, indicating the phenyl moiety is not driven out of the CD cavity even after the guest inclusion. These NOE correlations, along with the 1:1 binding stoichiometry, jointly indicate a host-linker-guest binding mode between the bis(β -CD) **2** and CA. That is, upon complexation with the bis(β -CD) **2**, the carboxylate tail and the D-ring of CA, enter into one CD cavity of **2** from the wide opening, while the phenyl moiety of the CD tether is partially self- included in the other β -CD cavity (Figure 6 (b)). Similar binding mode is also observed in other cases of bis(β -CD) **2**/bile salts complexes. There is an inherent for this binding mode. Under our experimental conditions, the carboxylate (or sulfonate) group in the side-chain of bile salt is not protonated and should exist as a carboxylate (or sulfonate) anion, and the $-\text{NH}-$ fragments in the linker group of bis(β -CD) **2** should be partly protonated. Therefore, the electrostatic interactions between the protonated amino groups ($-\text{NH}_2^+$) in the linker and the anionic carboxylate (or

sulfonate) tail of bile salt may strengthen the inclusion complexations of bis(β -CD) **2** with bile salts. Moreover, the hydrogen bond interactions of the hydroxyl group of CD and the amino fragments in the linker of bis(β -CD) **2** with the carboxylate (or sulfonate) tail of bile salt also contribute to the enhanced binding ability of the bis(β -CD) **2**.

Binding ability and molecular selectivity toward bile salts. It is well documented that, among the several possible weak interactions contributing to the complexation of guests with CDs, the most crucial contributions are made by the van der Waals and hydrophobic interactions, both of which are related to the size/shape matching between the guest and the host cavity. Other intermolecular interactions, such as hydrogen bonding and electrostatic interactions, can also contribute to the inclusion complexation behavior of CDs to some extent. As can be seen from Table 1, the stability constants (K_s) for the inclusion complexation of bis(β -CD) **2** with bile salts are much higher than those values for the native β -CD **1**, that is, the K_s values for the bis(β -CD) **2** are enhanced by factors of 6.6 for CA, 4.7 for DCA, 3.0 for GCA and 7.7 for TCA, respectively. These enhanced binding abilities of bis(β -CD) **2** may be mainly attributed to the cooperative host-linker-guest binding mode between host and guest. In addition to the association of the CD cavity with a guest molecule, the linker group provides some additional binding interactions towards the accommodate guest. These factors jointly contribute to the stronger binding

ability achieved by bis(β -CD) **2** in relation to the native β -CD **1**.

We can see that all bile salts examined possess a similar framework containing four rings (A-D) and a side chain (Chart 2). The bile salts CA and DCA only show a small difference in the structure of the C-7 substituent (R1), that is, a hydroxyl group for CA and a hydrogen atom for DCA. On the other hand, different from CA and DCA, guests GCA and TCA possess the more polar side chain (R2).²¹ However, this slight difference will lead to the great distinction in their hydrophobic nature and binding abilities with CDs. As can be seen in Table 1, the *K*s values for the complexation of each host with bile salt guests decreased in the followed order:

- 1: DCA > CA > GCA > TCA
2: CA > DCA > TCA > GCA

Indeed, the binding ability (*K*s = 4844 M⁻¹) of native β -CD **1** with DCA is higher than that with CA (*K*s = 4068 M⁻¹), which should be attributed to the size/shape matching and hydrophobic interactions between host β -CD and guest molecule. According to previous studies on the binding mode between β -CD and bile salts,²² we can deduce that the aliphatic side chain folded toward the steroid skeleton can be included into the cavity of β -CD from the secondary side, and thus the highest affinity for DCA is likely to arise from its more hydrophobic steroid skeleton, lacking the 7-hydroxyl group as compared with CA. However, bis(β -CD) **2** displays higher binding ability for CA than for DCA. One possible reason for the stronger affinity for CA may involve hydrogen bond interactions between the 7-hydroxy group of CA and the 2- and 3-hydroxy group of CD. We have demonstrated that the carboxylate tail and the D-ring of CA enter into the CD cavity through the wide opening. In this binding mode, the 7-hydroxy group of CA is located outside the CD cavity and near to the wide opening of CD, and so can easily interact with the 2- and 3-hydroxy group of CD through hydrogen bond interactions, which subsequently strengthen the host-guest association. Moreover, all the hosts, including the native β -CD **1** and bis(β -CD) **2**, show the weaker binding abilities upon inclusion complexation with GCA and TCA than that of CA and DCA. Attributing to the more hydrophilic tail, which is attached to the end of the D ring, GCA and TCA are unfavorable to insert into the cavity from the second side of CD cavity with their D ring. Meanwhile, host **1** and **2** show different guest selectivity upon binding with these four bile salts. For example, for the native β -CD **1**, the best guest selective is 2.1 for DCA/TCA pair, but the situation is quite different for the bis(β -CD) **2** due to cooperative host-linker-guest binding mode and some additional binding interactions. As a result of multiple recognition mechanism, bis(β -CD) **2** gives higher *K*s values for CA (27050 M⁻¹), DCA (22930 M⁻¹) and TCA (17610 M⁻¹), and the lowest *K*s value for GCA (7200 M⁻¹). Consequently, the higher guest selectivity for bis(β -CD) **2** could reach 3.8 for CA/GCA pair, 3.2 for DCA/GCA pair, 2.4 for TCA/GA pair, respectively.

Conclusion

Aromatic diamino bridged bis(β -CD) **2** successfully used as fluorescent sensor responsive for the molecular recognition of bile salts. The results obtained from ICD and ROESY experiments jointly show that the phenyl moiety in the linker of bis(β -CD) **2** is partially self-included in the CD cavity, and is not expelled out of the CD cavity upon complexation with bile guests. Due to the cooperative host-linker-guest binding mode, bis(β -CD) **2** gives the highest *K*s values up to 27050 M⁻¹ for the complexation with CA, and enhances the original molecular binding ability and molecular selectivity of native β -CD **1** through the simultaneous contributions of hydrophobic, hydrogen bond, and electrostatic interactions. These results will serve our further understanding of the multiple recognition mechanism in supramolecular systems.

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References and Notes

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