Journal of Inclusion Phenomena and Macrocyclic Chemistry **42:** 115–120, 2002.

Inclusion Complexation Thermodynamics of Acridine Red and Rhodamine B by Natural and Novel Oligo(ethylenediamine) Tethered Schiff Base β-Cyclodextrin

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(Received: 2 April 2001; in final form: 28 June 2001)

Key words: dye molecules, inclusion complexation, Schiff base β-cyclodextrins, thermodynamics

Abstract

A series of Schiff base β-cyclodextrin derivatives **2**–**5** with an oligo(ethylenediamine) tether have been newly synthesized and their inclusion complexation behavior has been assessed and discussed thermodynamically, employing acridine red (AR) and rhodamine B (RhB) as representative guests. Fluorescence spectrophotometric titrations have been performed in methanol-water (1 : 2) phosphate buffer solution (pH = 7.20) at 25.0–45.0 °C in order to obtain the complex stability constants (K_S) and the thermodynamic parameters (ΔH° and $T\Delta S^\circ$) for the stoichiometric 1 : 1 inclusion complexation of two guests with the native and modified β-cyclodextrins (**1** and **2**–**5**). As compared with the parent β-cyclodextrin **1**, all of the chemical modifications to the primary side of β-cyclodextrins examined led to substantial decreases for rhodamine B and marked increases for acridine red in complex stability, which are elucidated in terms of the induced-fit interaction and the complementary geometrical relationship between the host β-cyclodextrins and guest molecules, as well as the length of the linking chain of β-CD derivatives. The induced circular dichroism spectral analyses of these β-cyclodextrin derivatives indicated that the aromatic moiety in modified β-cyclodextrins is not embeded into the hydrophobic cavity of cyclodextrin. The inclusion complexation of **2**–**5** with acridine red possess higher binding constants than that with rhodamine B, which are solely attributed to the increased enthalpic gain. Thermodynamically, the inclusion complexation with the modified β-cyclodextrins **2**–**5** is absolutely enthalpy-driven for acridine red, while for complexation with rhodamine B is mainly entropy-driven.

Introduction

Cyclodextrins having fairly rigid and well-defined hydrophobic cavities can act as the molecular receptor to selective binding of substrates forming host–guest or supramolecular complexes [1–3], which is currently a significant topic in chemistry and biochemistry [4–7]. Possessing the specific functional groups as compared with the parent β-cyclodextrin (**1**), the chemically modified β-cyclodextrins can alter not only the original molecular binding ability but also the relative molecular selectivity significantly through further ligation or stereochemical complement of the functional sidearm located in the cyclodextrin cavity [8–11]. Therefore, a large number of cyclodextrin derivatives have been designed and synthesized in order to investigate their molecular recognition behavior [12]. However, the study on the molecular recognition thermodynamics for a wide variety of organic as well as inorganic guest molecules has been concentrated mainly on natural cyclodextrins. So far, few thermodynamic studies have been undertaken for inclusion complexation with chemically modified cyclodextrins [13]. We have recently reported the syntheses of a series of modified cyclodextrins and their inclusion complexation thermodynamics with model substances such as amino acids [14], naphthalene derivatives, and other aromatic compounds [8b, 15], and found that the type of substituent introduced to the cyclodextrin drastically affects the molecular recognition ability and enantioselectivity, giving insight into the thermodynamic factors involved, which can be used to govern the inclusion complexation phenomena by chemically modified cyclodextrin from the thermodynamic point of view.

In the present study, we synthesized a series of β-cyclodextrin derivatives, i.e., mono-[6-[[(benzylideneamino)ethyl]amino]-6-deoxy]-β-cyclodextrin (**2**), mono-[6-[[(benzylideneamino)propyl]amino]-6-deoxy]-β-cyclodextrin (**3**), mono-[6-[[(cinnamylideneamino)ethyl]amino]-6-deoxy]-β-cyclodextrin (**4**), and mono-[6-[[(cinnamylideneamino)propyl]amino]-6-deoxy]-β-cyclodextrin (**5**), shown in Chart 1, and investigated their thermodynamics of molecular binding behavior with the selected guest acridine Red (AR) and rhodamine B (RhB) in methanol-water (V/V = 1 : 2) buffer solution (pH = 7.20) at 25.0–45.0 ± 0.1 °C, using the fluorometric titration technique. The simple reason for choosing these dye molecules as spectral probe is that these fluorescent dyes are known to be very sensitive to environmental changes, which will enable us to investigate their inclusion complexation

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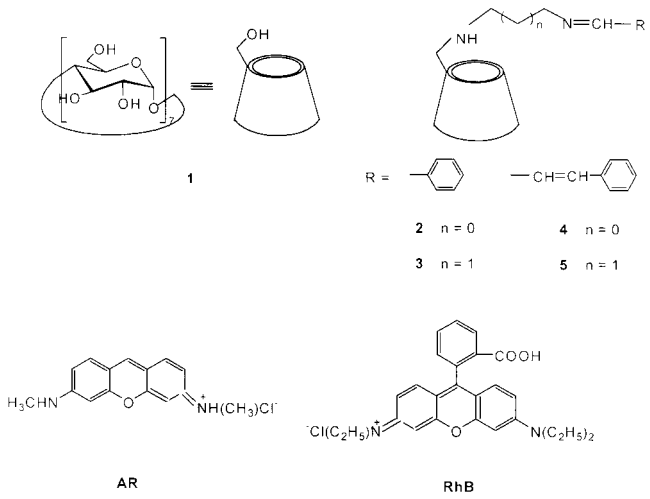

Chart 1.

behavior with native and modified cyclodextrins using the fluorometric titration method. From this investigation we can discuss the molecular binding ability of the modified β-cyclodextrins **2–5** for representative guest molecules from the thermodynamic point of view according to the size/shape-fit concept and the role of cooperative weak interactions working between the host and guest.

Experimental

Apparatus

Elemental analyses were performed on a Perkin-Elmer 240 instrument. Mass spectra were recorded on a Bruker Biflex III MALDI-TOF spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM 200 spectrometer. FT-IR and UV spectra were obtained on a Nicolet FT-IR 5DX and Shimadzu UV-2401PC spectrometer, respectively. Fluorescence spectra of the guests in the presence/absence of varying concentration of the host were obtained on a JASCO FT-750 spectrometer. Circular dichroism (CD) spectra were recorded on a JASCO J-720 spectropolarimeter.

Materials

Acridine red (AR) and rhodamine B (RhB) were purchased from Tianjin Chemical Reagent Plant. All chemicals were reagent grade and used without further purification. β-Cyclodextrin of reagent grade (Shanghai Reagent works) was recrystallized twice from water and dried in vacuo at 95 °C for 24 h prior to use. Mono[6-deoxy-6-(*p*-tolysulfonyl)]-β-cyclodextrin, mono[6-(ethylenediamino)-6-deoxy]-β-cyclodextrin and mono[6-(propylenediamino)-6-deoxy]-β-cyclodextrin were prepared according to the reported procedures [16, 17]. Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water and methanol [$CH_3OH : H_2O$(V/V) = 1 : 2] to make a 0.10 M phosphate buffer solution of pH 7.20, which was used in the spectral measurements.

Syntheses

*Mono-[6-[[(benzylideneamino)ethyl]amino]-6-deoxy]-β-cyclodextrin (**2**)*

To a methanol solution (20 mL) containing 0.08 mL phenyl aldehyde was added 0.5 g of mono[6-(ethylenediamino)-6-deoxy]-β-cyclodextrin and 5 drops of glacial acetic acid. The resultant mixture was stirred under reflux for 3 h, and another 3 h at room temperature. After evaporation of methanol, the residue was dissolved in acetone (ca. 100 mL) and stirred for 1 h, then filtered and acetone was added again. This procedure was repeated two times to eliminate phenyl aldehyde and glacial acetic acid. The resulting solid was dissolved in ethanol and stirred for 1 h, and insoluble materials were removed with filtration. The filtrate was evaporated to dryness to give a yellow solid (yield, 22%) MALDI-TOF MS m/z: 1264.5(M^+ + H-5H_2O). ^{1}H NMR (D_2O, TMS), δ: 2.65–3.17 (m, 4H), 3.53–3.77 (m, 42H), 4.98 (s, 7H), 7.45–7.87 (m, 6H). FT-IR (KBr) ν/cm^{-1} 3401, 2927, 1636, 1598, 1560, 1387,1300, 1254, 1156, 1079, 1032, 945, 756, 704, 580. UV-vis λ_{max} ($CH_3OH : H_2O$ = 1 : 2)/nm (ϵ/dm^3 mol^{-1} cm^{-1}) 305(4100) Anal. Calc. For $C_{51}H_{80}O_{34}N_2 \cdot 5H_2O$, C 45.2, H 6.69, N 2.06; Found: C 44.98, H 7.02, N 1.94.

*Mono-[6-[[(benzylideneamino)propyl]amino]-6-deoxy]-β-cyclodextrin (**3**)*

This compound was prepared by the reaction of phenyl aldehyde and mono[6-(propylenediamino)-6-deoxy]-β-cyclodextrin by the same method as for **2**. MALDI-TOF MS m/z: 1279.2(M^+ + H-5H_2O). ^{1}H NMR (D_2O, TMS), δ: 3.14 (m, 6H), 3.55–3.79 (m, 42H), 4.99 (s, 7H), 7.3–7.9 (m, 6H). FT-IR (KBr) ν/cm^{-1} 3399, 2929, 1638, 1561, 1409, 1335, 1156, 1079, 1032, 945, 756, 579. UV-vis λ_{max} ($CH_3OH : H_2O$ = 1 : 2)/nm (ϵ/dm^3 mol^{-1} cm^{-1}) 291(1334) Anal. Calc. For $C_{52}H_{82}O_{34}N_2 \cdot 5H_2O$, C 45.61, H 6.77, N 2.05; Found: C 45.32, H 7.01, N 1.94.

*Mono-[6-[[(cinnamylideneamino)ethyl]amino]-6-deoxy]-β-cyclodextrin (**4**)*

This compound was prepared by the reaction of phenylacrolein and mono[6-(ethylenediamino)-6-deoxy]-β-cyclodextrin by the same method as for **2** (yield, 24%). MALDI-TOF MS m/z: 1291.2(M^+ + H-4H_2O). ^{1}H NMR (D_2O, TMS), δ: 2.67–3.15 (m, 4H), 3.44–3.67 (m, 42H), 4.97 (s, 7H), 6.8–7.39 (m, 8H). FT-IR (KBr) ν/cm^{-1} 3412, 2929, 1637, 1561, 1410, 1335, 1246, 1155, 1080, 1032, 946, 849, 755, 704, 580. UV-vis λ_{max} ($CH_3OH : H_2O$ = 1 : 2)/nm (ϵ/dm^3 mol^{-1} cm^{-1}) 290(6258) Anal. Calc. for $C_{53}H_{82}O_{34}N_2 \cdot 4H_2O$, C 46.69, H 6.65, N 2.05; Found: C 46.57, H 6.91, N 2.31.

*Mono-[6-[[(cinnamylideneamino)propyl]amino]-6-deoxy]-β-cyclodextrin (**5**)*

This compound was prepared by the reaction of phenylacrolein and mono[6-(propylenediamino)-6-deoxy]-β-cyclodextrin by the same method as for **2** (yield, 19%). MALDI-TOF MS m/z: 1305.3 (M^+ + H-4H_2O). ^{1}H NMR (D_2O, TMS), δ: 2.83 (m, 6H), 3.62–3.9 (m, 42H), 5.03

(s, 7H), 6.8–7.7 (m, 8H). FT-IR (KBr) ν/cm^{-1} 3400, 2929, 1686, 1639, 1406, 1370, 1331, 1238, 1156, 1079, 1031, 945, 756, 704, 578. UV-vis λ_{max} ($CH_3OH:H_2O$ = 1 : 2)/nm (ϵ/dm^3 mol^{-1} cm^{-1}) 292(4348) Anal. Calc. for $C_{54}H_{84}O_{34}N_2{\cdot}4H_2O$, C 47.09, H 6.73, N 2.03; Found: C 46.81, H 7.02, N 2.08.

Fluorescence measurements

The fluorescence titrations using a series of solutions containing AR/RhB (5.0×10^{-6} mol dm^{-3}) and varying amounts of β-cyclodextrin derivative (**2**, **3**, **4** and **5**) (0–2.8×10^{-4} mol dm^{-3}) were carried out in aqueous buffer solution (pH = 7.20, CH_3OH : H_2O(V/V) = 1 : 2). The quartz cells (1 cm) were kept at constant temperature (25.0 ± 0.1 °C) with circulating water from a constant-temperature water bath. In order to determine thermodynamic parameters for the complexation equilibria, the spectral titrations were repeated at 25.0, 30.0, 35.0, 40.0 and 45.0 °C, respectively.

Results and discussion

CD spectra

In order to examine the original conformation of the modified β-cyclodextrins in dilute solution, the circular dichroism (CD) spectra have been performed at a concentration of 4.5 $\times 10^{-4}$ mol dm^{-3}. As can be seen from Figure 1a and 1b, the induced circular dichroism (ICD) spectrum of modified β-cyclodextrins **3** and **5** in methanol–water buffer solution (pH 7.20) showed two weak positive Cotton effect peaks for ^1L_a at 228.2 nm and 228.8 nm ($\Delta\epsilon$ = 0.356 dm^3 mol^{-1} cm^{-1} for **3**, $\Delta\epsilon$ = 0.335 dm^3 mol^{-1} cm^{-1} for **5**) and for ^1L_b at 252.8 nm and 274.2 nm ($\Delta\epsilon$ = 0.078 dm^3 mol^{-1} cm^{-1} for **3**, $\Delta\epsilon$ = 0.134 dm^3 mol^{-1} cm^{-1} for **5**), respectively. According to the sector rule proposed by Kajtar [18] and Harata *et al.*'s empirical rule [19], the Cotton effect observed for the ^1L_a and ^1L_b bands indicates that the aromatic group moiety is not embedded into the hydrophobic cavity of cyclodextrin [6, 20], and shows only very small ICD changes upon addition of guest molecules. These results demonstrate that the chromophoric groups originally perched on the edge of β-cyclodextrin do not suffer substantial conformational change upon guest inclusion, and are not suitable as spectral probe to determine the complex stability constant. Therefore, the selected guest AR and RhB as a probe for fluorescence spectrometry determines the stability constant (K_S) of inclusion complexation with modified β-cyclodextrin host. Furthermore, ICD spectra and the fluorimetric titrations were performed in a MeOH/H_2O mixture because of the low solubility of modified β-cyclodextrin host.

Fluorimetric titration

In the titration experiments using fluorescence spectrometry, the fluorescence intensity of AR/RhB gradually changed with increasing concentration of modified β-CDs **2**, **3**, **4** and **5**. Typical fluorescence spectral changes upon addition of **2** to the AR solution are shown in Figure 2. These results indicate the formation of inclusion complexes of these CDs with AR/RhB. By assuming a 1 : 1 complex stiochiometry, the inclusion complexation of guest (G) with β-CD derivative (H) is expressed by Equation (1).

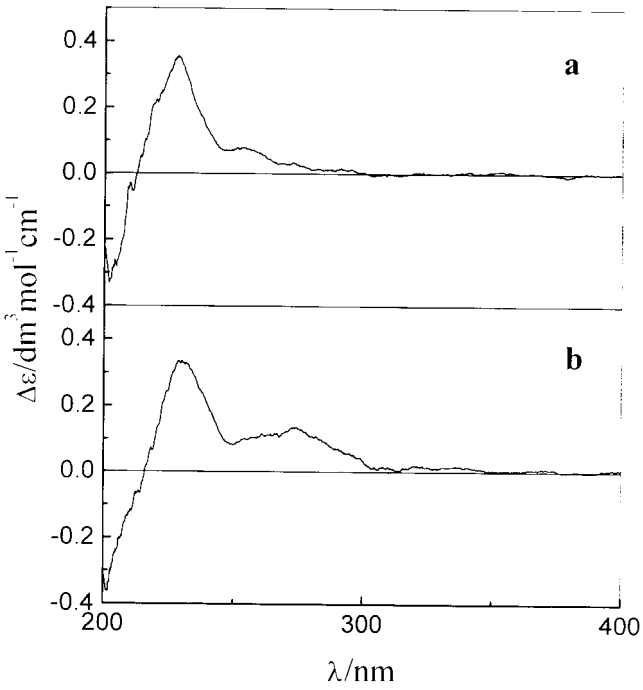

Figure 1. Circular dichroism spectrum of β-cyclodextrin derivatives **3** (0.45 mmol dm^{-3}) (a) and **5** (0.45 mmol dm^{-3}) (b) in methanol–water buffer solution (pH 7.20) at room temperature.

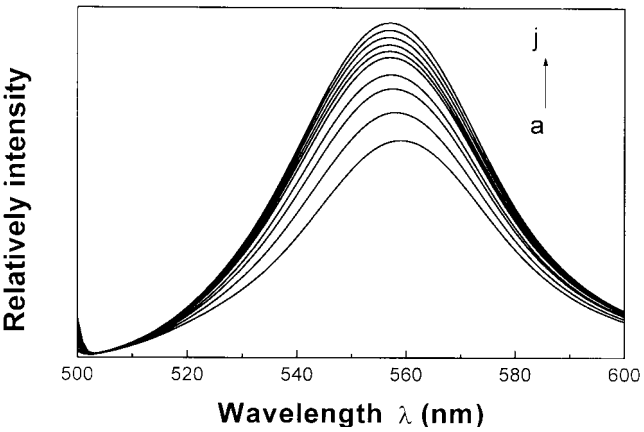

Figure 2. The fluorescence spectra of AR (5.0×10^{-6} mol/L) in phosphate buffer solution (pH 7.20) in the presence of **2** at various concentrations. The concentration increase of **2** from a to j are 0, 0.028, 0.056, 0.084, 0.112, 0.140, 0.168, 0.196, 0.224, 0.280 mmol/dm^3, respectively. The excitation wavelength was 490 nm.

$$H + G \overset{K_S}{\rightleftharpoons} G \cdot H. \quad (1)$$

The stability constant (K_S) of the inclusion complex formed was determined from the gradual changes in fluorescence intensity (ΔF) upon stepwise addition of H, using a non-linear least squares method according to the curve fitting Equation (2) [21].

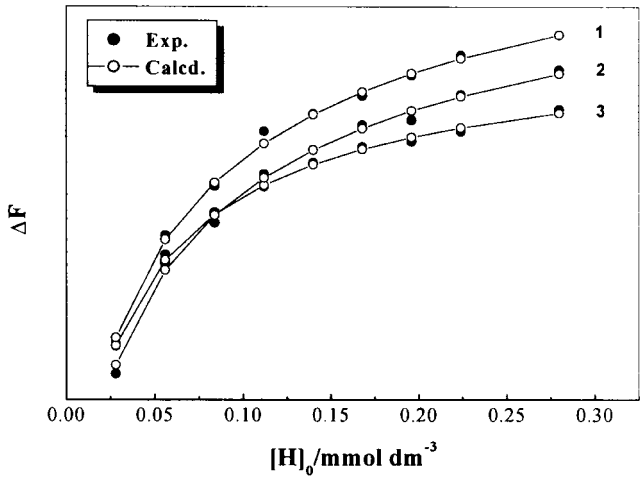

Figure 3. Curve-fitting analyses for complexation of **2**, **3** and **4** with AR at 25 °C according to Equation (2).

Table 1. Stability constants (K_S) for 1 : 1 host–guest complexation of the guest with modified β-cyclodextrin derivatives **1**–**5** at 25–45 °C (pH7.20 phosphate buffer)

log K_S						
Host	Guest	25.0	30.0	35.0	40.0	45.0
1	AR	3.32	3.17	3.08	2.93	
	RhB	3.81	4.25	4.70	4.98	
2	AR	3.87	3.84	3.73	3.71	3.65
	RhB	3.07	3.83	4.31	4.58	4.81
3	AR	3.79	3.68	3.65	3.55	3.45
	RhB	3.03	3.45	3.97	4.59	4.88
4	AR	4.04	3.89	3.79	3.71	3.66
	RhB	3.13	3.88	4.20	4.58	
5	AR	4.13	4.06	3.97	3.92	3.82
	RhB	3.29	3.67	4.04	4.28	4.57

$$\Delta F = \{\alpha([\mathrm{H}]_0 + [G]_0 + 1/K_S)\}$$

$$\pm\sqrt{\alpha^2([\mathrm{H}]_0 + [G]_0 + 1/K_S)^2 - 4\alpha^2[\mathrm{H}]_0[G]_0}/2, \quad (2)$$

where $[G]_0$ and $[\mathrm{H}]_0$ refer to the total concentration of AR/RhB and β-CD derivative, respectively, and α the proportionality coefficient, which may be taken as a sensitivity factor for the fluorescence change upon complexation. For each host examined, the ΔF values were plotted as a function of $[\mathrm{H}]_0$ to give an excellent fit, validating the 1 : 1 stoichiometry assumed above. Typical plots are shown for inclusion complexation of AR with β-CDs **2**, **3**, and **4** in Figure 3. In the repeated measurements, the K_S value was reproducible within an error of ±5%. The experiments were performed at 25.0, 30.0, 35.0, 40.0, and 45.0 °C and the stability constants (log K_S) obtained by the curve fitting are listed in Table 1. In order to compare with the case of native β-CD **1** and investigate in detail how the modified residue affects the guest molecule, we also determined the binding constants of **1** for Ar and RhB under our experimental conditions and listed the data in Table 1.

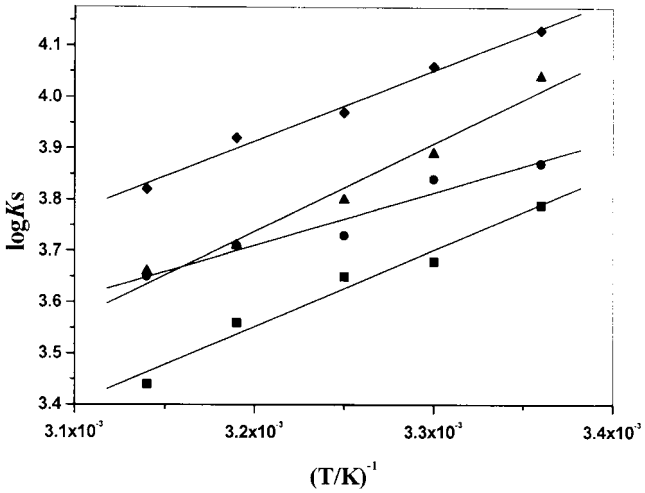

Figure 4. Typical plots of log K_S versus 1/T in spectrophotometric titrations of **2** (●), **3** (■) **4** (▲) and **5** (♦) with AR guest.

Thermodynamic parameters

The free-energy change ($\Delta G°$) for inclusion complexes formed by modified β-cyclodextrins and guest is calculated from the equilibrium constants K_S by Equation (3) and is related to the enthalpic and entropic

$$\Delta G° = -\mathrm{RT}\ln K_S, \quad (3)$$

$$\Delta G° = \Delta H° - T\Delta S° \quad (4)$$

changes ($\Delta H°$ and $\Delta S°$) through the Gibbs–Helmholtz equation (4). Combining Equations (3) and (4), we obtain Equation (5) which describes the

$$\log K_S = (1/2.303\mathrm{R})(\Delta S° - \Delta H°/\mathrm{T}) \quad (5)$$

temperature dependence of K_S. Thus, plots of the log K_S values, shown in Table 1, as a function of the inverse of temperature gave good linear relationships. Typical plots for host compounds **2**, **3**, **4** and **5** with AR are shown in Figure 4. The thermodynamic parameters obtained for each modified β-cyclodextrin inclusion complexation with guests are listed in Table 2.

Molecular binding ability

Although a wide variety of weak interactions are known to be involved in the inclusion complexation with cyclodextrin, the most important are the van der Waals and hydrophobic interactions, both of which depend on how the size and/or shape of a guest molecule fit into the host cavity [22]. In the present case, the hydrophobic, as well as van der Waals, interactions are considered to play important roles in determining the complex stability. Simultaneously, the results obtained indicate that the shallow self-inclusion of the sidearm of β-CDs also plays a crucial role in the inclusion complexation of the guest molecule in the host cavity.

As can be seen from Table 1, the molecular binding ability is affected drastically by several structural factors

Table 2. Thermodynamic parameters (in kcal mol^{-1}) for 1 : 1 host–guest complexation of guests with modified β-cyclodextrins **1**, **2**, **3**, **4** and **5** at 25 °C in aqueous solution (pH 7.20, 0.10 mol dm^{-3} phosphate buffer)

Host	Guest	$-\Delta G$	$-\Delta H$	$-T\Delta S$
1	AR	4.5	10.3	5.8
	RhB	5.2	−32.3	−37.5
2	AR	5.3	4.8	−0.5
	RhB	4.2	−35.6	−39.8
3	AR	5.2	6.9	1.75
	RhB	4.1	−40.2	−44.3
4	AR	5.5	8.0	2.5
	RhB	4.3	−38.3	−42.6
5	AR	5.6	6.3	0.67
	RhB	4.5	−26.3	−30.8

of modified β-CDs and the dye guests. At the temperature of 25 °C, the modified β-CDs **2**–**5** gave significantly higher K_S for AR than for RhB. This may be attributed to the strict size-fit relationship and relatively stronger hydrophobic interaction between host and guest. Possessing a hydrophilic carboxyl group, RhB is more hydrophilic and sterically hindered than AR, which jointly reduces the hydrophobic interaction and the extent of desolvation upon complexation. Examination of CPK space-fitting molecular models indicated that the AR and RhB molecules are too large to be included completely in the β-CD cavity.

In spectral titration, the fluorescence intensity of guest compounds AR and RhB gradually changes upon the addition of β-CDs, indicating that guest molecules can form inclusion complexes with modified β-CDs, even if their thermodynamic properties are quite different. It is noted that the molecular binding ability, the free-energy change ($-\Delta G°$) as well as the enthalpy change ($-\Delta H°$) and the entropy change ($-T\Delta S°$) for inclusion complexation with host β-CD derivatives are highly sensitive to the molecular type and size of the guest molecule. Meanwhile, the functional groups, attached to the edge of CD, are embedded into the cavity of CD, preventing the guest inclusion at least in part, so they are expected to affect the inclusion behavior of these modified β-CDs. To visualize the molecule binding behavior of the native and modified β-CDs (**1**–**5**) from the thermodynamic point of view, the free energy ($-\Delta G°$), enthalpy ($-\Delta H°$), and entropy changes ($T\Delta S°$) for the inclusion complexation of AR and RhB are plotted for the host β-CDs in Figure 5. As a consequence of compensation between these positive or negative $T\Delta S°$ and $\Delta H°$ values, the molecular binding ability may be more explicitly understood in term of the size- or shape-fit and the hydrophobicity of the guest molecules, as discussed below.

Acridine red (AR)

As can be seen from Table 1 and Figure 4a, the ΔH values for the inclusion complexation of β-CDs with AR guest are all negative, arising from the stronger hydrophobic in-

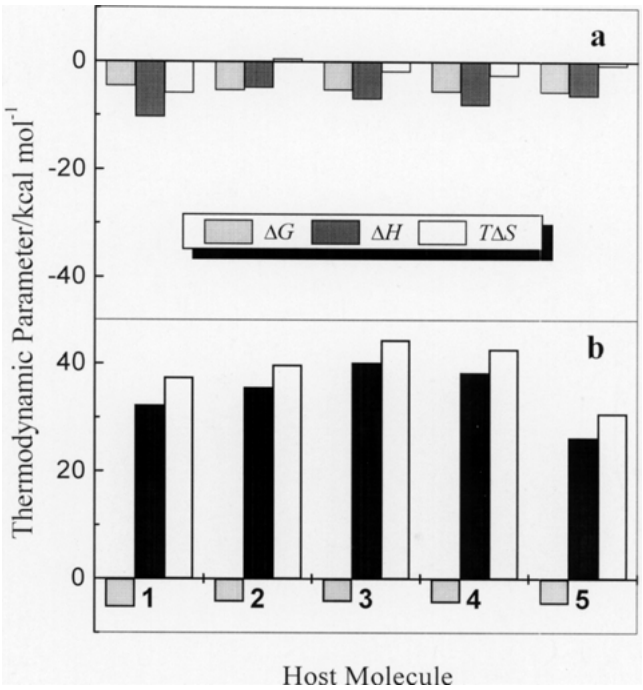

Figure 5. Free energy (ΔG^0), enthalpy($-\Delta H^0$), and entropy changes ($T\Delta S^0$) for the inclusion complexation of AR (a) and RhB (b) with β-cyclodextrin derivatives (**1**–**5**) in aqueous solution (pH 7.20) at 25 °C.

teraction, whereas the $T\Delta S$ values are either negative or slightly positive, indicating inclusion complexation with AR without accompanying extensive desolvation. This means that these inclusion reactions for AR are primarily enthalpy-driven processes. All the modified β-CDs (**2**–**5**) have larger Ks values as compared with the parent β-cyclodextrin **1**, and the combination of AR with β-CD derivatives **4** and **5** gives the strongest inclusion complexes (log K_S = 4.04, 4.13). We can see that the complex stability constants (K_S) of **4** and **5** with AR are larger by roughly 2–4 order of magnitude than those for **2** and **3**. The above results indicated that these β-CDs offered a different microenvironment upon guest addition, even though they possessed very similar structures except for the length of the side arm chain. Compared with **2** or **3**, the compound **4** or **5** was just extended the chain of a C=C bond, and have higher complex stability. One possible explanation is that **4** and **5** have a longer and flexible chain, and are expected to move rather freely from the cavity of the β-CDs to the bulk water, while the compounds **2** and **3**, which both have a shorter chain, form a more rigid conformation and discourage the replacement inclusion of the guest. The order of the binding ability of the β-CDs for AR is **5**> **4**> **2**, **3**> **1**. On the other hand, the inclusion complexation of **2**–**5** with AR gives higher binding constants than with RhB, which are attributed to the increased enthalpic gain due to the hydrophobic and van der Waals interactions.

Rhodamine B (RhB)

For the RhB guest molecule, the β-CDs gave different results, and the modified β-cyclodextrins **2**–**5** show lower complex stability than the parent β-cyclodextrin **1**. Apparently, when the RhB molecule is free in solution, it seems to

allow for a stronger solvent shell. Upon binding, this solvent shell is broken up, leading to the partly unfavorable enthalpy change (ΔH). Furthermore, the inclusion complexation demands fairly extensive desolvation of both RhB and **2**–**5**, affording the highly positive entropy change upon complexation, as observed actually (Figure 5). On the other hand, the inclusion complexation of RhB with the modified CDs gave entirely positive enthalpy change (ΔH), indicating that these inclusion reactions for RhB are mainly entropic-driven processes. It suggests that the β-CDs form a suitable conformation favorable to the complexation with RhB from the viewpoint of entropy, but unfavorable to the complexation from the adjusted induced-fit concept, giving lower stability constants. The above results indicate that modified CDs are suitable for the linear AR molecule, and unfavorable for the larger triangular RhB molecule to inclusion complexation, and relative adding the length of linking chain of β-CD derivatives may enhance complex stability. Therefore, the size/shape fit concept between the host CDs and guest dye molecules plays crucial roles in determining inclusion complex stability.

In conclusion, Schiff base groups attached to β-cyclodextrin gives a series of functionalized β-cyclodextrin derivatives, which alter not only the original binding ability, but also the molecular selectivity. In sharp contrast to the parent β-CD to the inclusion complexation of AR and RhB, the modified CDs **2**–**5** show high binding ability to AR, giving the inverted molecular selectivity for AR and RhB. Thermodynamically, the inclusion complexation with the modified β-cyclodextrins **2**–**5** is absolutely enthalpy-driven for AR, while for complexation with RhB is mainly entropy-driven.

Acknowledgements

This work was supported by Natural Science Foundation (No. 29992590-8 and 29972029) of China, and the Foundation of Ministry of Education, which are gratefully acknowledged.

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