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Selective binding of chiral molecules of cinchona alkaloid by β- and γ-cyclodextrins and organoselenium-bridged bis(β-cyclodextrin)s

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Abstract

The inclusion complexation behavior of chiral members of cinchona alkaloid with β- and γ-cyclodextrins (**1** and **2**) and 6,6′-trimethylenediseleno-bridged bis(β-cyclodextrin) (**3**) was assessed by means of fluorescence and 2D-NMR spectroscopy. The spectrofluorometric titrations have been performed in aqueous buffer solution (pH 7.20) at 25.0 °C to determine the stability constants of the inclusion complexation of **1**–**3** with guest molecules (i.e., cinchonine, cinchonidine, quinine, and quinidine) in order to quantitatively investigate the molecular selective binding ability. The stability constants of the resulting complexes of **2** with guest molecules are larger than that of **1**. As a result of cooperative binding, the stability constants of inclusion complexation of dimeric β-cyclodextrin **3** with cinchonidine and cinchonine are higher than that of parent **1** by factor of 4.5 and 2.4, respectively. These results are discussed from the viewpoint of the size-fit and geometric complementary relationship between the host and guest.

Keywords: Inclusion complexation; Chiral molecule; Cinchona alkaloid; Cyclodextrins; Fluorescence; 2D-NMR; Stability constants; Molecular recognition; Cooperative binding; Organoselenium

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1. Introduction

The cinchona alkaloids are well known for their broad spectrum of biological and pharmaceutical properties. They can be used as antimalarials, antiarrythmics, and sodium-channel blockers. Recently, members of this family have shown their efficacy in restoring sensitivity towards antitumor drugs in cells expressing the multidrug resistance phenotype [1]. Due to their potential broad range of biological activities [2], the molecular recognition of cinchona alkaloids can help us to understand numerous bioprocesses. Among the cinchona alkaloids, the most often studied are cinchonine, cinchonidine, quinine, and quinidine (Chart 1).

Native cyclodextrins and their derivatives could accommodate a wide variety of inorganic, organic, and biological molecules in their hydrophobic cavity to form stable inclusion complexes in aqueous solution, which can be used to increase the bioavailability of poorly soluble drugs [3], and in chiral separation technologies [4] owing to their fascinating inner cavity with intrinsic chirality. Dimeric cyclodextrins linked with a simple tether possess the two discrimination sites upon complexation with a guest molecule, and show a higher binding ability when compared with native cyclodextrins. Therefore, numerous efforts have been devoted to the design and synthesis of dimeric cyclodextrins for molecular recognition purposes [5–8]. It is well demonstrated that cyclodextrins and their derivatives have been successfully used

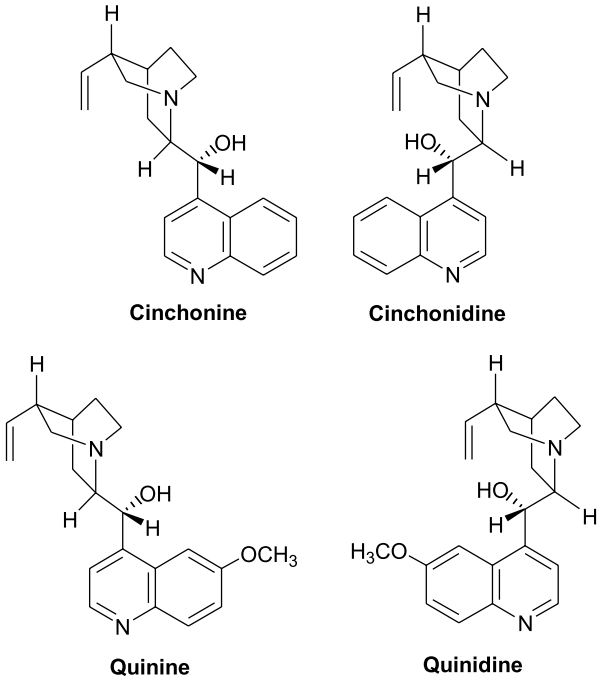

Chart 1.

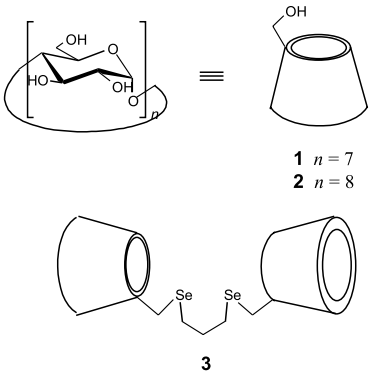

Chart 2.

in the enantioselective recognition of L/D-amino acids [9–11] and in sequence recognition of oligopeptides [12–15]. These studies solidly suggest that cyclodextrins may form inclusion complexes with small biological molecules in aqueous solution. Unfortunately, there has been little studied on the inclusion complexation of bis(β-cyclodextrin)s with chiral biological molecules, and the molecular recognition mechanism for this system is still disputed.

Here, we report the inclusion complexation behavior of cinchona alkaloids by native β-, γ-cyclodextrins and bis(β-cyclodextrin)s, shown in Chart 2. The guest molecules, such as cinchonidine, cinchonine, quinine, and quinidine (Chart 1), exhibit intense fluorescence in aqueous solutions and are sensitive to environmental changes, and which enable us to use them as spectral probes to investigate the inclusion complexation with cyclodextrins. In addition, 2D-NMR spectroscopy has been used to study the inclusion complexation of β-cyclodextrin **1** with cinchonine in order to understand the binding model and inclusion complexation behavior. Furthermore, the 2D-NMR spectroscopic results also serve to explain the molecular recognition mechanism with bridged bis(β-cyclodextrin). The complexation stability constant and binding model show weak interaction between host cyclodextrin and guest, and elucidate the selective binding mechanism of chiral molecule for cinchona alkaloids.

2. Experimental

2.1. Materials

β- and γ-cyclodextrin (**1**, **2**) were purchased from Ensuiko Seito. The 6,6′-trimethylenediseleno-bridged bis(β-cyclodextrin)s (**3**) were synthesized according the procedures reported previously [16]. Cinchonidine, cinchonine, quinine, and quinidine were commercially available from Aldrich Chemicals. Sodium dihydrogen phosphate and disodium hydrogen phosphate were dissolved in doubly distilled, deionized

water to make a 0.10 M buffer solution of pH 7.20, which was used as solvent throughout the measurements.

2.2. Spectral measurements

Fluorescence spectra were measured in a conventional quartz cell ($10 \times 10 \times 40$ mm) on a JASCO-FP-750 spectrofluorimeter. The excitation and emission slits were 10 nm for all the cinchona alkaloids. The excitation wavelengths for cinchonine, cinchonidine, quinine, and quinidine were 329 nm. The maximum emission wavelength of aqueous solution of all the guest molecules is at 387 nm. The sample solution containing cinchona alkaloids (1.0×10^{-5} mol dm^{-3} for cinchonine, cinchonidine, quinidine, and 1.7×10^{-7} mol dm^{-3} for quinine) and various concentration of hosts ($0–4 \times 10^{-3}$ mol dm^{-3}) was maintained at 25.0 ± 0.1 °C for spectral measurements by a circulating thermostated water-jacket. NMR spectra were obtained on a Varian Mercury VX300 spectrometer. Nuclear Overhauser Effect Spectroscopy (NOESY) experiments were recorded using a 1.0 mM solution of cinchonine in the presence of 3.0 eq of β-cyclodextrin and bis(β-cyclodextrin)s in 99% D_2O and 1% methanol. As the solubility of cinchonidine is lower than that of cinchonine, the 0.1 mM cinchonidine and 5.0 equivalents dissolved in the mixture solvent of 50% D_2O and 50% methanol. The effect of methanol on the inclusion complexation is very weak. All these experiments were carried out with a mixing time of 600 ms.

3. Results and discussion

3.1. Spectral titrations

The cinchona alkaloids, (i.e., cinchonine, cinchonidine, quinidine, and quinine), are strongly fluorescent in aqueous solution but are sensitive to environmental changes, which enable us to use them spectral probes to investigate the inclusion complexation with cyclodextrin **1**–**2** and bis(β-cyclodextrin)s **3**. Figs. 1 and 2 depict the fluorescence quenching of cinchonidine by β-cyclodextrin **1** and bis(β-cyclodextrin)s **3**. The photophysical behavior observed appears to be in distinct contrast to that of many fluorescent guest molecules upon inclusion complexation. The fluorescence intensity of cinchonidine gradually decreases upon increasing the β-cyclodextrin concentration. It clearly indicates that part of cinchonidine was embedded into the hydrophobic cavity of β-cyclodextrin apart from bulk water. It is interesting to note that bis(β-cyclodextrin)s **3** exhibits somewhat different fluorescence behavior upon inclusion complexation with the cinchonidine. As can be seen in Fig. 2, with the addition of host **3**, the fluorescence of cinchonidine gradually decreases, and is accompanied by a significant red shift (15, 387–402 nm). This phenomenon was ascribed to the cooperative binding of one guest molecule by two β-cyclodextrin moieties. As compared with the native β- and γ-cyclodextrins, the relative larger shift for dimeric (β-cyclodextrin)s is due to its higher sensitivity toward changes in the polarity of its environment. The above observation supports the idea that the cinchona

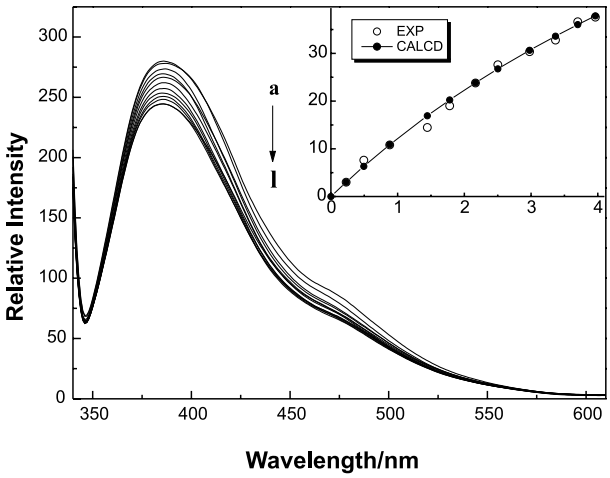

Fig. 1. Fluorescence spectral changes of cinchonidine (10 μM) and the nonlinear least-squares analysis (inset) of the differential intensity (ΔF) used to calculate the complex stability constant (K_S) upon addition of **1** (0–4000 μM from a to l) in aqueous buffer solution.

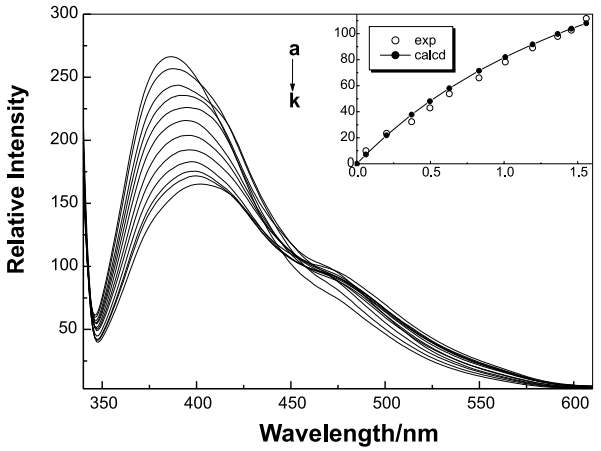

Fig. 2. Fluorescence spectral changes of cinchonidine (10 μM) and the nonlinear least-squares analysis (inset) of the differential intensity (ΔF) used to calculate the complex stability constant (K_S) upon addition of **3** (0–4000 μM from a to k) in aqueous buffer solution.

alkaloids are shielded from the aqueous environment and most probably are located in the cyclodextrin cavities.

3.2. Binding model

If the chiral members of the cinchona alkaloids are in the cyclodextrin cavity, the NOESY spectra of the resulting complexes would show intermolecular cross-peaks

between the protons of the guest and the protons at C-3 and/or C-5 of the host cyclodextrin. Studies on the two inner (H-3 and H-5) hydrogen atoms of cyclodextrin in the presence of a guest molecule could provide the proof of complexation. In order to obtain detailed information about the binding of the β-cyclodextrin with cinchonine from the NOE effect, 2D NMR spectroscopy has been performed in a solution of D_2O and methanol. The spectra showed detectable signals. Cinchonine possesses two distinct functional groups, namely the aromatic ring and the aliphatic ring. Consequently, bimodal binding can occur, and the inclusion complexes formed by cinchonine and cyclodextrins have been considered in two different binding modes. As shown in Fig. 3, cross-peak A was observed between the proton at C-3 and the aromatic ring containing nitrogen and cross-peak B was observed between the protons at C-3 and C-5 and the benzene ring. Moreover, there was no correlative effect between the proton at C-5 and the aromatic ring containing nitrogen, which

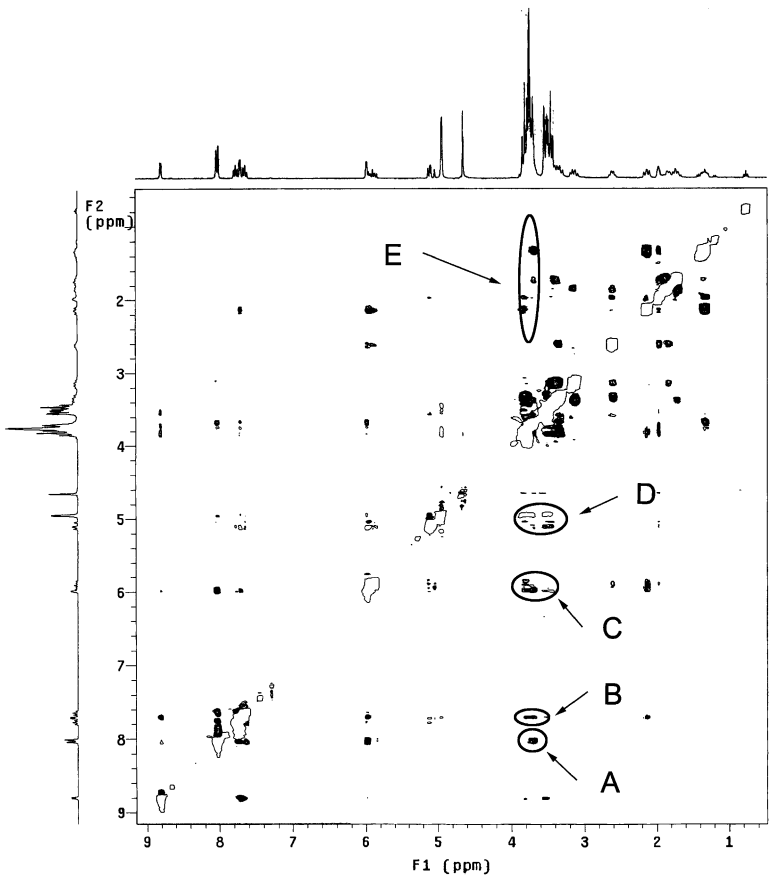

Fig. 3. ^{1}H-NOESY spectrum (300 MHz) of a mixture of **1** with cinchonine ($[\mathbf{1}] = 3.0 \times 10^{-3}$ M, [cinchonine] $= 1.0 \times 10^{-3}$ M) in D_2O (1% methanol) at 298 K with a mixing time of 600 ms.

means that the aromatic ring is only embedded at a slant from the second side of the cavity. Furthermore, the correlations between the proton at the ethenyl moiety and the protons at C-3 and C-5 (peak C) as well as between the protons of the aliphatic ring and the protons at C-3 and C-5 (peaks D and E) indicate that the ethenyl group and the aliphatic ring in cinchonine are included in the cavity of cyclodextrin. These results show that an interaction exists between the β-cyclodextrin and cinchonine in two geometries for the inclusion complexes without an appreciable preference for one, as shown in Fig. 4.

To investigate the selective binding mechanism for chiral molecules, the two different binding models of cinchonine and cinchonidine with bis(β-cyclodextrin) **3** have been delineated from the NOESY spectrum. As can be seen from the Fig. 5, cross-peak A displayed an interaction between the protons of the benzene ring of cinchonine and the proton at C-5 of the cyclodextrin cavity. This result showed that the aromatic ring of cinchonine was shallowly embedded into the first side of the cavity. Cross-peak B was observed between the protons of the ethenyl group and the protons at C-5. Cross-peak C showed the correlative effect between the end protons of the ethenyl group and the protons at C-5 and C-3. These observations indicate that this portion of the guest is deeply embedded into the first side of the cavity. Cross-peak D displayed an interaction between the proton of the aliphatic ring of the guest and the proton at C-5 of bis(β-cyclodextrin). Thus, it is clear that the aromatic ring of cinchonine can be slightly included in one cavity of bis(β-cyclodextrin), while the aliphatic ring of cinchonine can be deeply included in the other cavity of bis(β-cyclodextrin). Fig. 6 exhibits the correlative effect of bis(β-cyclodextrin) with cinchonidine. The cross-peak A was observed between the proton of the aromatic ring containing nitrogen and the proton at C-5 of the cyclodextrin cavity. Cross-peak B indicated an interaction between the benzene ring of cinchonidine and the protons at C-3 and C-5 of the cyclodextrin cavity. Cross-peak C showed the correlative effect of the protons of the ethenyl group and the protons at C-3 and C-5 protons of another cyclodextrin cavity. Cross-peak D represented the correlative effect of the proton of the aliphatic ring of cinchonidine and the proton at C-5 of the cyclodextrin cavity. These results indicated that the quinoline ring and the ethenyl group of cinchonidine can be deeply included in the two cyclodextrin cavities, respectively. The different binding model of bis(β-cyclodextrin) with cinchonine and cinchonidine indicated that bis(β-cyclodextrin) could recognize the chiral guest members of the cinchona alkaloids.

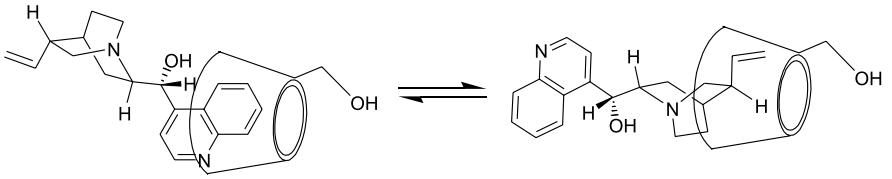

Fig. 4. Two binding models of β-cyclodextrin with cinchonine.

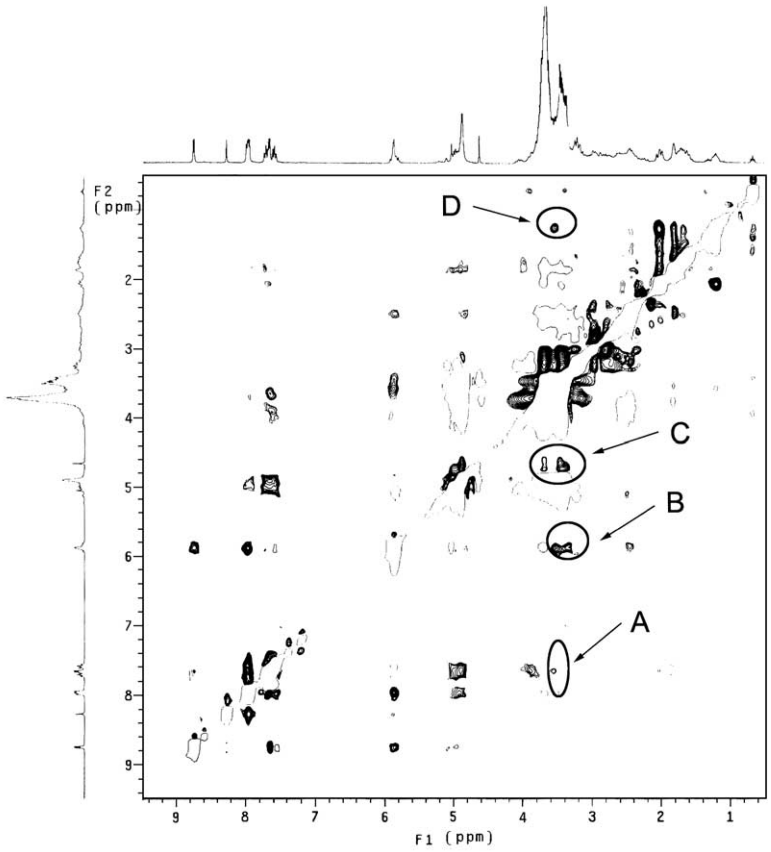

Fig. 5. ^{1}H-NOESY spectrum (300 MHz) of a mixture of **3** with cinchonine ([**3**] = 3.0×10^{-3} M, [cinchonine] = 1.0×10^{-3} M) in D_2O (1% methanol) at 298 K with a mixing time of 600 ms.

3.3. Fluorescence quenching

The quenching phenomena resulting from the interaction of α-cyclodextrin with specific azo dyes have been previously reported by Matsui and Mochida [17]. Warner et al. [18] investigated the basis for quenching of acridine by β-cyclodextrin, and pointed out that the specific interaction of lone-pair electrons between the unprotonated nitrogen heteroatom and the high electron density of the cyclodextrin interior cavity resulted in the quenched fluorescence. In view of this observation, such an interaction could deactivate the guest molecule and result in a decrease of the number of fluorescing species in solution. The cinchona alkaloids molecules have similar structures, so that the fluorescence changes will be comparable. The NOE effect between the proton at C-3 and the aromatic ring containing nitrogen clearly indicates that there is an interaction between the nitrogen atom and the cyclodextrin cavity. In this case, the hydrogen bond of nitrogen with the hydroxyl

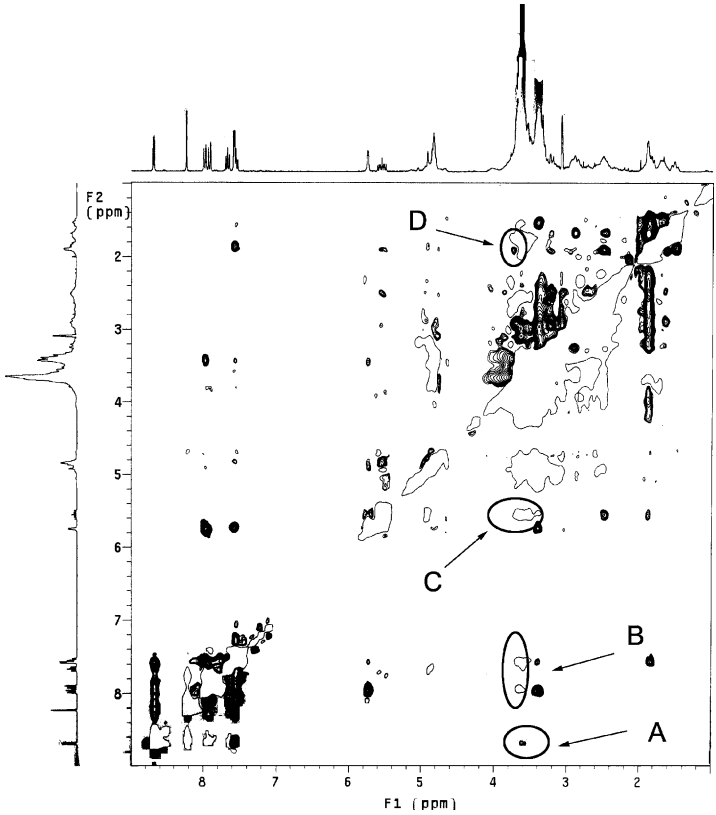

Fig. 6. ^{1}H-NOESY spectrum (300 MHz) of a mixture of **3** with cinchonidine ([**3**] = 5.0×10^{-4} M, [cinchonidine] = 1.0×10^{-4} M) in D_2O (50% methanol) at 298 K with a mixing time of 600 ms.

group of cyclodextrin cavity is weaker than that with bulk water, leading to the guest molecule deactivating, and diminishing the number of fluorescing species in solution. These reasons cause in the quenching of the fluorescence of cinchona alkaloids.

From the fluorescence intensity change (ΔF) induced by adding the host molecule, we can determine the complex stability constants (K_S). The stoichiometry for the inclusion complexation of β-cyclodextrin with representative guests was determined by the continuous variation method. A representative plot (Fig. 7), shows the 1:1 stoichiometry for the inclusion complexation of β-cyclodextrin with the guest molecule cinchonine. The inclusion complexation of guest (G) with host (H) is expressed by Eq. (1)

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

The complex stability constants (K_S) [19] were calculated for each host–guest combination from the nonlinear squares fit to Eq. (2) [20],

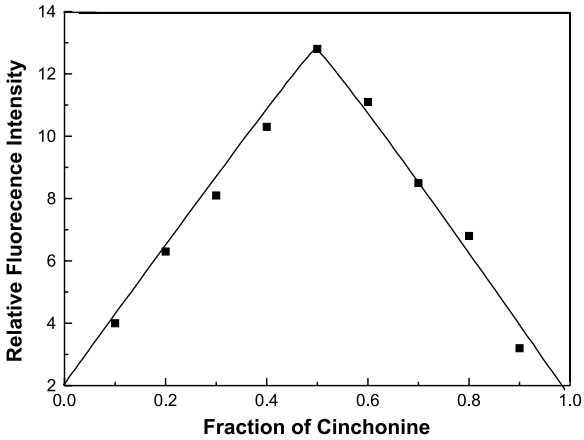

Fig. 7. Continuous variation plot of **1**/cinchonine system. ([β-cyclodextrin] + [cinchonine] = 2.5×10^{-5} mol dm^{-3}).

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

where $[G]_0$ and $[H]_0$ refer to the total concentrations of the guest and host and α is the proportionality coefficient, which may be taken as a sensitivity factor for the fluorescence change. For each host molecule examined, the plot of ΔF as a function of $[H]_0$ gave an excellent fit, verifying the validity of the 1:1 complex stoichiometry assumed above. The experimental data do not show any significant deviations from the theoretical curve in each case. In the repeated measurements, the K_S values were reproducible within an error of ±5%. The K_S values obtained are listed in Table 1, along with the free energy changes of complex formation ($-\Delta G^0$) obtained upon addition of large excess of host. In order to visualize the inclusion complexation behavior of host with the cinchona alkaloid molecules, the changing profiles of free

Table 1
The complex stability constant (K_S) and the Gibbs free energy change ($-\Delta G^0$) for 1:1 inclusion complexation of cinchona alkaloids with β-cyclodextrin **1,** γ-cyclodextrin **2** and bis(β-cyclodextrin)s **3** in aqueous buffer solution (pH 7.20) at 25.0 °C as determined by fluorometric titrations.

Host	Guest	K_S	$\log K_S$	$-\Delta G^0$ (kJ mol^{-1})
1	Cinchonidine	108	2.04	11.61
	Cinchonine	117	2.07	11.82
2	Cinchonidine	321	2.51	14.31
	Cinchonine	462	2.66	15.21
	Quinine	221	2.34	13.38
	Quinidine	206	2.32	13.24
3	Cinchonidine	491	2.69	15.36
	Cinchonine	251	2.40	13.70

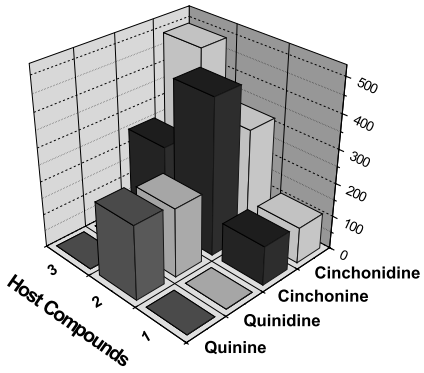

Fig. 8. Complex stability constants (K_S) for the inclusion complexation of hosts **1**–**3** with guest molecules in aqueous solution.

energy changes ($-\Delta G^0$) upon complexation with host compounds **1**–**3** are shown in Fig. 8.

3.4. Selectivity binding of chiral molecule

In previous studies [21,22], we examined the inclusion complexation of native and a variety of modified cyclodextrins with diverse guest molecules, and found that an important characteristic of the complexation is the simultaneous operation of several weak forces working between the guest and host. In the present case, it is the size/shape matching between host and guest that dominates the stability of the complexes formed, which indicates that van der Waals and hydrophobic interactions contribute mainly to the formation of supramolecular complexes, as the two forces are closely related to the distance and contact surface area between host and guest. As can be seen from Table 1, β- and γ-cyclodextrins with different size cavity show entirely different binding abilities upon inclusion complexation with cinchona alkaloids. The examination of CPK molecular models indicates that the sizes of cinchonine and cinchonidine are relative large, and are only partially embedded in the β-cyclodextrin cavity, resulting in the relative weak binding constants. However, the cavity of γ-cyclodextrin is larger than that of β-cyclodextrin, so the guest molecules can effectively make contact with the surface of the cavity of γ-cyclodextrin, leading to the higher complex stability than that observed for native β-cyclodextrin. Although cinchonine and cinchonidine share similar structures with quinine and quinidine, the extra methoxyl group on the quinoline ring of quinine and quinidine prevent them from being embedded deeply into the β-cyclodextrin cavity because of the steric hindrance. The other ring containing chiral carbon might be in the β-cyclodextrin cavity, but there is not any fluorescence intensity change when the β-cyclodextrin is added to the quinine solution. This phenomenon further confirms that the interaction between the aromatic nitrogen heterocycle and the inner cavity quenches the fluorescence, but the interaction between the quinine and β-cyclodex-

trin is too weak to calculate the binding constant by fluorescence titration. The aromatic containing the heteroatom ring of quinine, however, can be partly embedded into the cavity of γ-cyclodextrin, giving the relative small binding constant (K_S). The inclusion complexation of β-cyclodextrin with quinidine is similar to that of quinine. Comparing the stability constants of the inclusion complexation of cinchonine, cinchonidine, quinine, and quinidine with γ-cyclodextrin, it is found that the size/shape-fitting combination gives a relatively strong inclusion complexation.

Native cyclodextrins afford only limited binding constants probably due to the weak hydrophobic interactions. Dimeric cyclodextrins, however, are able to enhance the original binding ability of native cyclodextrin through the cooperative binding of single guest molecule by two adjacent cavities. From Table 1 and Fig. 8, we can see that the binding constants of cinchonine and cinchonidine by bis(β-cyclodextrin) are larger than those of the native β-cyclodextrin. As a result of cooperative binding, the stability constants of the resulting complex of dimeric β-cyclodextrin **3** with cinchonidine is higher than that of native β-cyclodextrin by factor of 4.5, while the stability constant with cinchonine is higher than that of native β-cyclodextrin by factor of 2.4.

Investigations on the selective binding of the chiral cinchona alkaloids by receptors would be helpful for understanding the drug–protein binding process [23]. Cyclodextrins, which possess chiral cavities can be taken as excellent molecular receptors that recognize the chiral guest molecules. Unfortunately, native β-cyclodextrin exhibits similar binding ability towards the cinchonidine/cinchonine pair as shown in Fig. 8. Both of the guests are only poorly accommodated in the cavity of **1** due to their large sizes. Therefore, the contribution of the cooperative interaction of second cavity in **3** is more pronounced and enhances K_S. The NOESY experiments show that both of them have a different binding model upon inclusion complexation with host **3**. It is significant that the inclusion complexation of cinchonidine with host **3** is tighter than that of cinchonine and displays a relatively good molecular selectivity up to 2.0 for the cinchonidine/cinchonine pairs. Therefore, cinchonine and cinchonidine can be recognized by the cooperative interaction of two adjacent cavities, preferring cinchonidine to cinchonine. Since γ-cyclodextrin possesses a relative large cavity, the chiral center of guests might be included in its cavity, and can be recognized by γ-cyclodextrin. Intriguingly, γ-cyclodextrin exhibited the inverted molecular selectivity, preferring cinchonine to cinchonidine. This selectivity switching observed for the dimeric β-cyclodextrin and γ-cyclodextrin may be attributed to the chiral microenvironmental changes around the chiral guest molecule.

Acknowledgments

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