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Binding Ability and Assembly Behavior of β-Cyclodextrin Complexes with 2,2′-Dipyridine and 4,4′-Dipyridine

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Two channel-type supramolecular aggregations **1** and **2** were prepared by the inclusion complex of β-cyclodextrin with 2,2′-dipyridine and 4,4′-dipyridine, respectively, and their binding ability and assembly behavior were investigated comprehensively by X-ray crystallography, ^{1}H NMR, circular dichroism spectra, and microcalorimetric titration in solution and the solid state. The obtained results revealed that the hydrogen bonds and π−π stacking interactions are crucial factors for the formation of the molecular aggregations containing β-cyclodextrin and dipyridines. The disparity of nitrogen atom position in dipyridines leads not only to the distinct crystal system and space group, i.e., monoclinic system (*C*2) for **1** and triclinic system (*P*-1) for **2**, but also different binding modes and thermodynamical parameters upon complexation of 2,2′-dipyridine and 4,4′-dipyridine with β-cyclodextrin in aqueous solution.

Introduction

Macrocyclic sugars called cyclodextrins (α-, β-, and γ-CDs) could form stable inclusion complexes with a variety of guest molecules, in which the guest molecules are included within the hydrophobic cavity of CDs.[1−4] A commonly accepted model for complex formation suggests that the complex is formed when a suitable hydrophobic molecule displaces water from the cavity.[5,6] Several recent works reported the solution studies of CD upon complexation with amino acids,[7,8] peptides,[9,10] dyes,[11,12] steroids,[13−15] and so on, using different methods such as fluorescence spectrometry, UV−vis spectrometry, and titration microcalorimetry. These studies not only were directed toward an understanding of binding behavior and molecular/chiral recognition of CDs but also provided valuable information on the effects of changes in functionality and chirality of guests. On the other hand, a large number of crystallographic studies on the inclusion complexes of cyclodextrins have been performed during the past 30 years.[16−27] Close examinations of the crystal structures of a variety of inclusion complexes revealed

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that the geometrical complementarity and/or size/shape matching between host and guest is certainly one of the most important factors determining the molecular conformation and packing mode in the crystal.[16a] In the meanwhile, the crystal structure is affected also by other factors, such as the type, length, functional group, and heteroatom position of guest. This in turn implies that the crystal structure of the CD complexes is designable through the precise control of interactions between guest and CD unit. We have recently reported systematic studies on the binding ability and self-assembly behavior of modified β-CDs both in solution and the solid state.[28] The obtained results not only indicated that the pivot heteroatom, through which the aromatic substituent is tethered to β-CD, plays a critical role in determining the helix structure in the solid state but also revealed that the dimerization step in solution is the key to the formation of solid linear polymeric supramolecular architectures. Nevertheless, to the best of our knowledge, there are few studies focused on understanding how the slight difference between guest structures affects the inclusion modes and binding abilities of CD with guests both in solution and the solid state, though it not only provides valuable insight into the intermolecular interactions involving hydrophobic, hydrogen bond, and $\pi-\pi$ interactions in the host−guest systems but also could serve to establish correlation between the conformational feature and the molecular recognition ability of host−guest complexes.

In the present study, we prepared two channel-type supramolecular aggregations **1** and **2** by the inclusion complex of β-cyclodextrin with 2,2′-dipyridine (2-DPD) and 4,4′-dipyridine (4-DPD), respectively, and systematically investigated their binding abilities and assembly behavior in both solution and the solid state by means of X-ray crystallography, ^{1}H NMR, circular dichroism spectra, and microcalorimetric titration. It is of our particular interest to investigate how and to what extent the disparity of heteroatom position affects the conformational feature, binding ability, and assembly behavior of CD with different dipyridine guests and to elucidate the correlations between the binding mode and the thermodynamic parameters of the host−guest complexation.

Experimental Section

Materials and Instruments. 2,2′-Dipyridine and 4,4′-dipyridine were commercially available and used without further purification. Reagent grade β-CD was recrystallized twice from water and dried in vacuo at 95 °C for 24 h prior to use.

The X-ray intensity data were collected on a standard area detector system equipped with a normal-focus molybdenum-target X-ray tube (λ = 0.71073 Å) operated at 2.0 kW (50 kV, 40 mA) and a graphite monochromator at T = 293(2) K. The structures were solved by using direct method and refined, employing full-matrix least squares on F^2 (Siemens, SHELXTL, version 5.04). Elemental analyses were performed on a commercially available instrument. ^{1}H NMR spectra were recorded in D_2O. Circular dichroism (CD) and UV−vis spectra were performed in a conventional quartz cell (light path 10 mm) on a spectropolarimeter or a spectrophotometer equipped with a temperature controller to keep the temperature at 25 °C.

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TABLE 1. Crystal Data and Experimental and Refinement Parameters of 1 and 2

	crystal **1**	crystal **2**
molecular formula	$C_{104}H_{201}N_4O_{92.5}$	$C_{104}H_{194}N_4O_{89}$
M_r (g mol^{-1})	2987.69	2924.63
crystal system	monoclinic	triclinic
space group	*C*2	*P*-1
Z	4	1
a (Å)	19.427(6)	15.364(3)
b (Å)	24.100(8)	15.497(3)
c (Å)	33.457(11)	18.115(3)
α (deg)	90	99.463(4)
β (deg)	103.783	113.195(3)
γ (deg)	90	103.022(3)
V (Å^3)	15213(8)	3705.0(11)
ρ_{calcd} (g cm^{-3})	1.304	1.311
F (000)	6372	1558
T (K)	293(2)	293(2)
μ (Mo Kα)/mm^{-1}	0.116	0.116
crystal dimensions (mm)	0.34 × 0.24 × 0.20	0.36 × 0.34 × 0.30
range scanned θ (deg)	1.61−25.00	1.96−25.00
index range	$-12 < h < 23$ $-28 < k < 22$ $-39 < l < 39$	$-18 < h < 17$ $-14 < k < 18$ $-21 < l < 20$
no. of reflections collected	34320	19120
no. of unique reflections	21582	15431
R_{int}	0.0789	0.0179
R_1 ($I > 2\sigma(I)$)	0.1032	0.0907
wR_2 (all data)	0.2016	0.2432
($\Delta\rho$) max (e Å^{-3})	0.642	0.835
($\Delta\rho$) min (e Å^{-3})	−0.336	−0.535

The microcalorimetric titrations were performed by an isothermal titration microcalorimeter at the atmospheric pressure and 25 °C in aqueous solution. In each run, a solution of host in a 0.250 mL syringe was sequentially injected with stirring at 300 rpm into a solution of guest in the sample cell (1.4227 mL volume). All thermodynamic parameters reported in this work were obtained by using the one set of binding sites model. Two independent titration experiments were performed to afford self-consistent parameters and give the averaged values.

Preparation of Crystal 1. An ethanol solution of 2-DPD (1 mmol, 10 mL) was added dropwise to an aqueous solution of β-CD (1 mmol, 30 mL) and stirred at 30 °C for 5 h. The solution was cooled to room temperature, and the formed precipitate was filtrated to give white powder. The crude product was dissolved in hot water to make a saturated solution and then cooled to room temperature. After removing the precipitates by filtration, a small amount of water was added to the filtrate. The resultant solution was kept at room temperature for 2 weeks. The colorless crystal formed was collected along with its mother liquor for the X-ray crystallographic analyses. Data for **1**: yield 72%. ^{1}H NMR (600 MHz, D_2O, TMS, ppm): δ 3.42∼3.79 (m, 42H); 4.91∼4.92 (d, 7H); 7.38∼7.40 (m, 2H); 7.87∼7.89 (m, 2H); 7.97∼7.98 (d, 2H); 8.52∼8.53 (d, 2H). Anal. Calcd for $C_{52}H_{78}O_{35}N_2{\cdot}6H_2O$: C, 44.64; H, 6.48; N, 2.00. Found: C, 44.61; H, 6.44; N, 2.05.

Preparation of Crystal 2. Crystal **2** was prepared by the reaction of β-CD with 4-DPD in aqueous solution.[19] CCDC-203243 for **2** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Results and Discussion

Crystal Structures. The crystal data and experimental and refinement parameters of **1** and **2** are shown in Table 1. In the crystal structures of **1** and **2**, each β-CD has an approximate 7-fold axis and maintains the round shape of the macrocycle, and each glucose residue of β-CD has a $^4C_1$ chair conformation. The crystals of **1** were monoclinic with the space group *C*2, Z = 4 and the unit

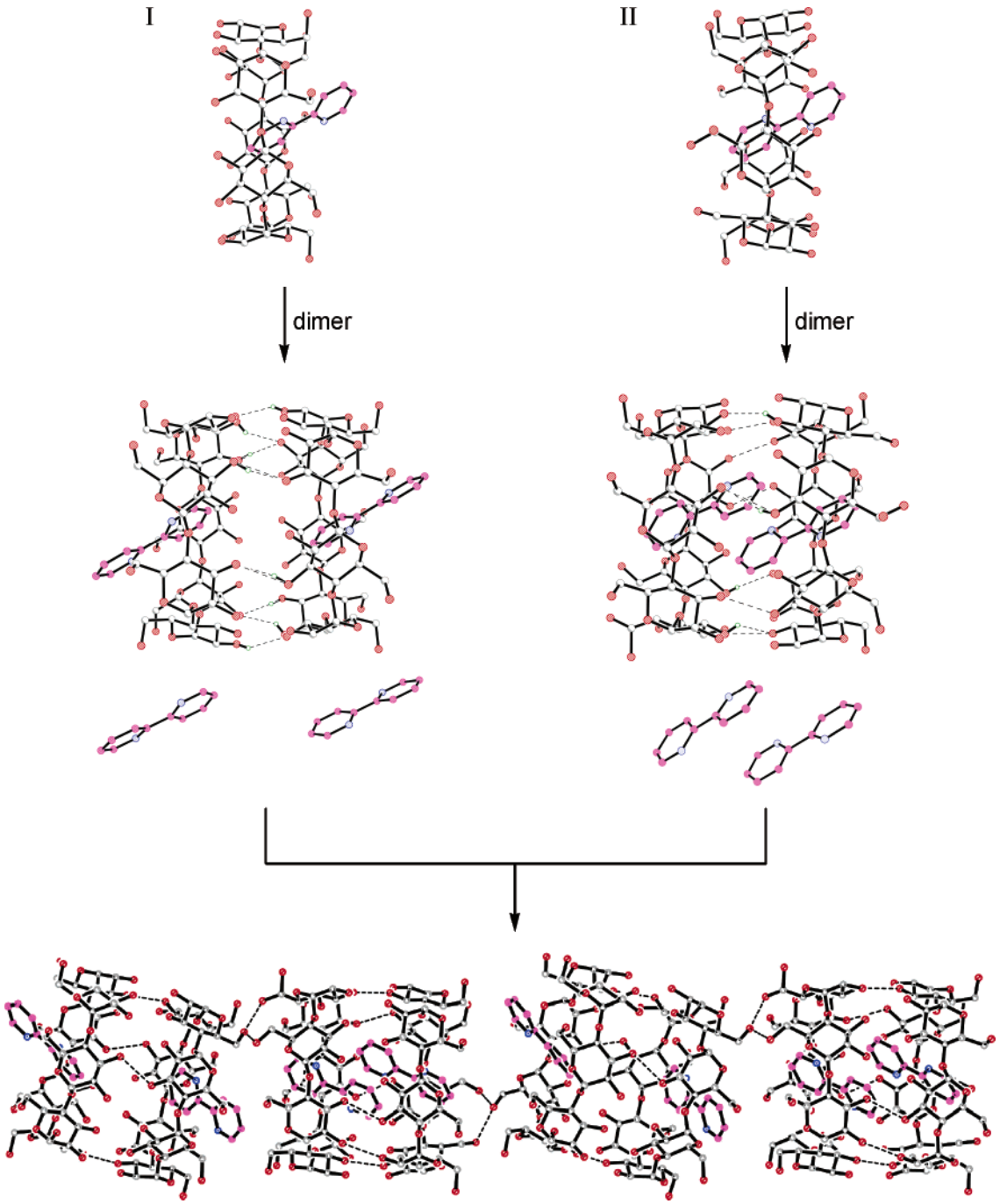

FIGURE 1. The head-to-head channel structure of **1** by the packing of the differently oriented dimer I and dimer II. The 2-DPD molecules are colored by atom type: pink, carbon atoms; blue, nitrogen atoms. The β-CDs are also colored by atom type: gray, carbon atoms; red, oxygen atoms; green, hydrogen atoms involved in hydrogen bond interactions.

cell parameters a = 19.427 Å, b = 24.100 Å, and c = 33.457 Å, whereas those of **2** were triclinic with the space group P-1, Z = 1 and the unit cell parameters a = 15.364 Å, b = 15.497 Å, and c = 18.115 Å. In the structure of **1** (Figure 1), the 2-DPD molecules occurred in the β-CD cavities by two different orientations, i.e., type I and type II. For type I, the 2-DPD molecule, in which the dihedral angle between the two pyridine rings (angle A) was 171.3°, is partially embedded in a β-CD cavity with a 58.8° angle between the 2-DPD molecular axis and the heptagons composed of seven glycosidic oxygen atoms in β-CD (angle B). For type II, the 2-DPD molecule is deeply included in a cavity with the angle A of 174.1° and the dihedral angle B of 58.6°. Furthermore, two I or two II form the head-to-head dimer structures, in both of which two β-CDs are connected by 10 hydrogen bonds from the hydroxyl groups in the secondary sides of β-CDs. The two 2-DPD molecules in dimer I are directed to the outside of the dimer from the primary sides of the β-CDs, and those in dimer II point to the inside of the dimer with $\pi-\pi$ interactions between two adjacent pyridine rings of the two 2-DPD molecules (0.2° dihedral angle and 4.018 Å of centroid separation), which are infrequent in the crystal structures of the inclusion complexes between CDs and guest molecules. The head-to-head dimers I and II could further self-assemble to form a channel-type

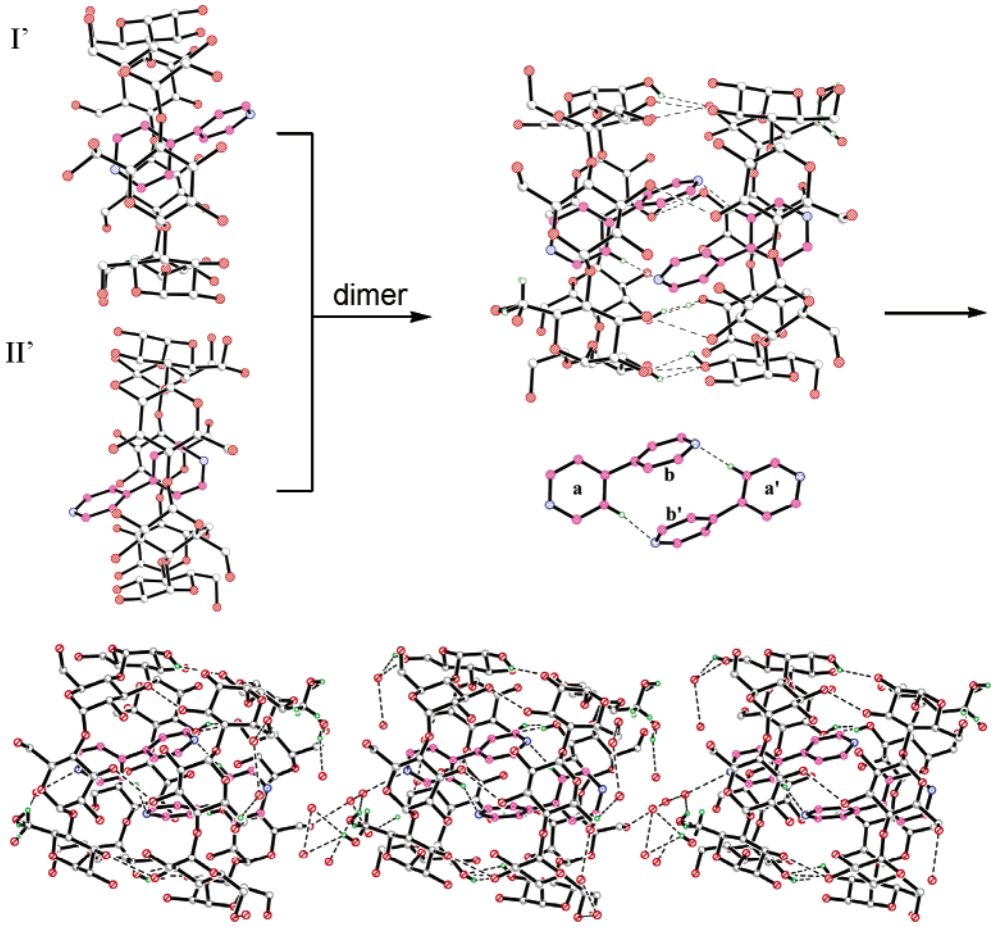

FIGURE 2. The head-to-head channel structure of **2** by the packing of the differently oriented I′ and II′. The 4-DPD molecules are colored by atom type: pink, carbon atoms; blue, nitrogen atoms. The *β*-CDs are also colored by atom type: gray, carbon atoms; red, oxygen atoms; green, hydrogen atoms involved in hydrogen bond interactions.

polymeric supramolecule through two hydrogen bonds between dimers I and II.

In the structure of **2** (Figure 2), two 4-DPD molecules are also embedded into the *β*-CD cavities by two different directions (type I′ and type II′), and the angles between the 4-DPD molecular axis and the heptagons composed of seven glycosidic oxygen atoms in *β*-CD are 63.3° and 71.1°, respectively. In sharp contrast to **1**, one I′ and one II′ in **2** form the head-to-head dimer arrangement. The pyridine ring *a* (or *a*′) of the 4-DPD molecule in each dimer is deeply included in a *β*-CD cavity and another pyridine ring *b* (or *b*′) is only shallowly embedded into the cavity, with a dihedral angle of 94.5° (or 75.6°) between rings *a* (or *a*′) and *b* (or *b*′). The two *β*-CDs in the dimer are connected by 13 hydrogen bonds (11 of them come from the hydroxyl groups on the secondary sides of the *β*-CDs and 2 of them involve a nitrogen atom in the *b* (and *b*′) ring and a *meta* hydrogen atom in the *a*′ (and *a*) ring) and the $\pi-\pi$ interaction of two pyridine rings in a face-to-face arrangement (dihedral angle of 42.2°, centroid separation between *b* and *b*′ of 3.634 Å). Furthermore, the head-to-head dimer also could self-assemble to form channel-type polymeric supramolecules through hydrogen bonds between dimers using the nitrogen atom in *a* ring.

According to the crystal structures of **1** and **2**, it could be demonstrated that the different crystal arrangements of two DPDs in *β*-CD cavities are ascribed to the disparity of nitrogen atom position on aromatic rings. 4-DPD molecules not only participate in the formation of hydrogen bonds but also provide an aromatic ring for the $\pi-\pi$ stacking interactions, accordingly leading to their ordered arrangement in the cavities. Inversely, 2-DPD molecules utilize only the weak hydrophobic and $\pi-\pi$ interactions to give the "unordered" arrangement.[29−31] Therefore, these interesting results provided the valuable insight for understanding spatial arrangement rule of biotic acceptor with different model substrates in the solid state, and molecular recognition mechanism of *β*-CD with functional guests.

NMR and ICD Spectra. To further investigate the binding behavior of *β*-CD with DPD molecules in solution state, the NMR experiments were performed for their inclusion complexation at 25 °C in D_2O. In general, while the complex is examined by ^1H NMR technique, the inclusion complexation of a guest molecule into the CD cavity will result in changes of the chemical shifts of guest protons.[32−34] It is found that the chemical shifts of all protons of the 2-DPD molecule changed in the presence of *β*-CD, i.e., H_g1 and H_g2 protons' signals shift to downfield about 0.06 and 0.05 ppm respectively, and signals of H_g3 and H_g4 shift to downfield about 0.05 ppm.

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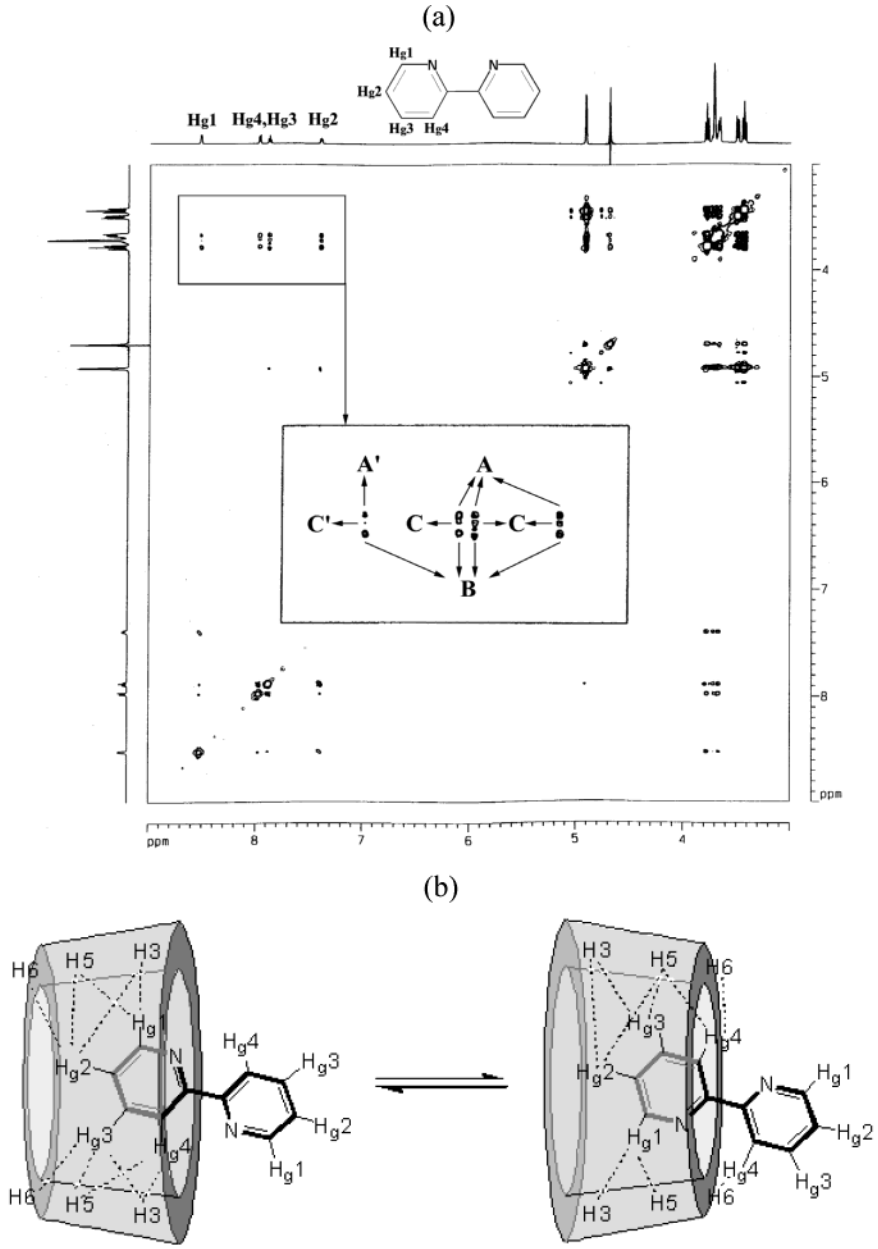

FIGURE 3. (a) ^{1}H ROESY spectrum of **1** (4.8×10^{-3} mol dm^{-3}) in D_2O at 293.2 K with a mixing time of 200 ms. (b) Possible structure of **1** in aqueous solution.

A change in the chemical shift of all protons of the 4-DPD molecule is also observed in the presence of β-CD: the signals of *meta* protons shift upfield (ca. 0.02 ppm) and the signals of *ortho* protons shift downfield (ca. 0.09 ppm). The results obtained validated the formation of inclusion complexes in solution for β-CD with DPD.

2D NMR spectroscopy has recently become an important method for the investigation of the interaction between host CDs and guest molecules,[28b,35] since the NOE cross-peaks between the protons that are closer than 0.4 nm in space will be observed in ROESY spectrum and the relative intensities of these cross-peaks depend on the spaces between the corresponding protons. The height and the diameter of the β-CD cavity are about 0.79 ± 0.01 nm and 0.60−0.65 nm,[36] respectively. Therefore, while the guest molecule is included into the β-CD cavity, the NOE correlations between the protons of the guest and the protons of the β-CD cavity (H-3 and H-5) will be determined by means of ROESY experiment. According to the relative intensity of these cross-peaks, it is possible to estimate the orientation of the guest molecule within the β-CD cavity. To obtain further evidence about the geometrical conformation of **1** and **2** in solution, 2D NMR experiments of **1** and **2** have been performed in D_2O. As shown in Figure 3a, the ROESY spectrum of **1** displayed clear NOE cross-peaks between

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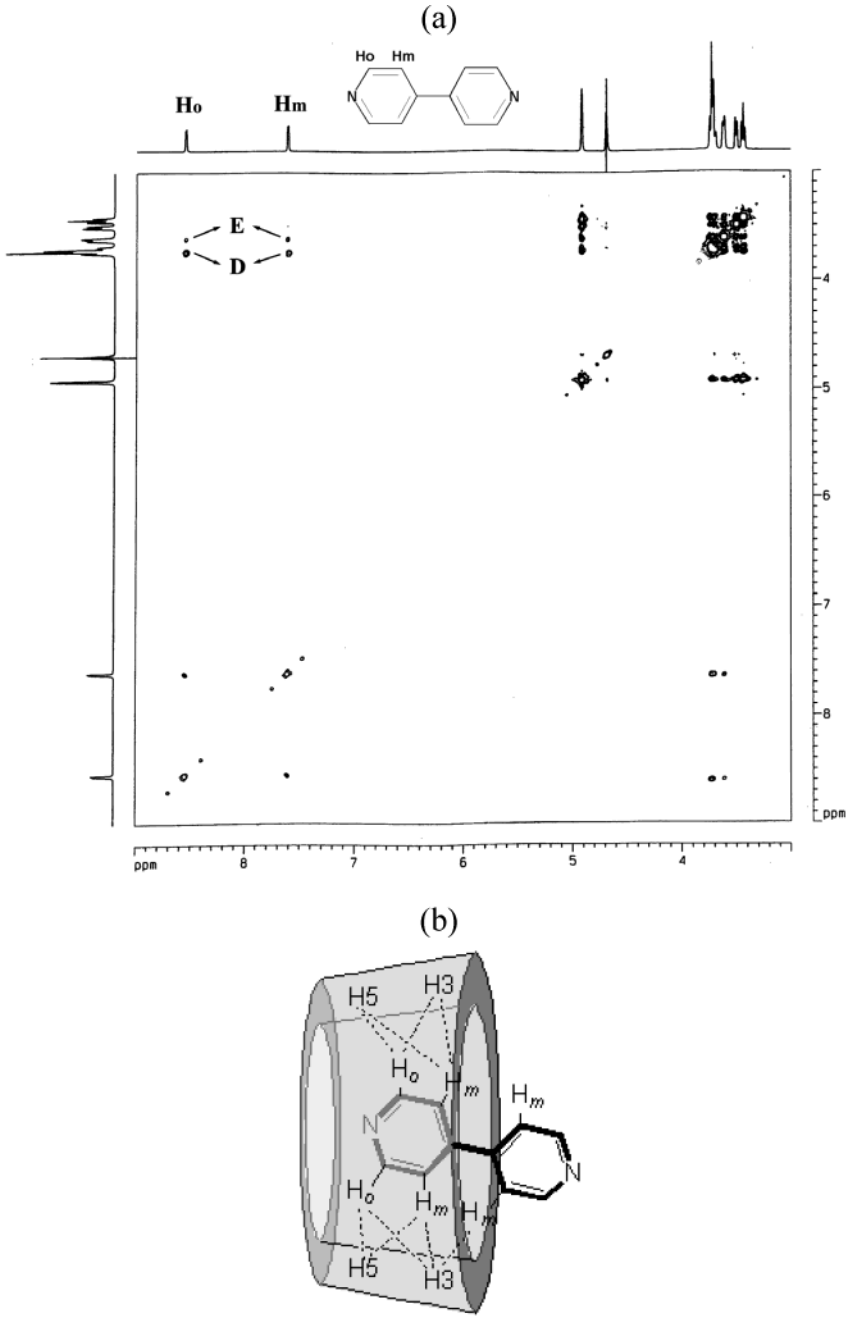

FIGURE 4. (a) ^{1}H ROESY spectrum of **2** (4.8×10^{-3} mol dm^{-3}) in D_2O at 293.2 K with a mixing time of 200 ms. (b) Possible structure of **2** in aqueous solution.

the H5 (peaks A and A′) and H3 (peaks B) of *β*-CD and the H_g1-H_g4 protons of 2-DPD, which indicates distinctly that the pyridine ring in 2-DPD is deeply included into the hydrophobic cavity of CD. The correlation between the H6 of *β*-CD and the H_g2-H_g4 of 2-DPD (peaks C), as well as very weak correlation between H6 and H_g1 (peak C′), would provide us further information about the orientation of the pyridine ring in the cavity of the CD. Despite that, we cannot yet present a reasonable single illustration to explain these observations. Considering the relative weaker intensity of peak A′ and much the same intensity of other cross-peaks, one may reasonably deduce that 2-DPD molecules are included into the cavity of CD in two different modes, as illustrated in Figure 3b. In the case of **2** (Figure 4a), strong correlations (peaks D) of H3 with the H_m and H_o protons of 4-DPD, as well as the relatively weak cross-peaks (peaks E) between H5 and the H_m and H_o protons, unequivocally indicate that the 4-DPD is accommodated in the cavity from the secondary side, as illustrated in Figure 4b. On the other hand, as can been seen from Figure 5, the UV−vis spectrum of **1** in aqueous solution shows low-energy absorption bands at about 280 nm with extinction coefficients on the magnitude of 10^4 dm^3 mol^{-1} cm^{-1}, which are assigned as a bigger conjugated system occurring between two pyridine rings in 2-DPD; that is to say, the two pyridine rings are almost located in the same plane. However, only weak low-energy absorption bands at about 270 nm with extinction coefficients on the magnitude of 10^3 dm^3 mol^{-1} cm^{-1} is observed in the UV−vis

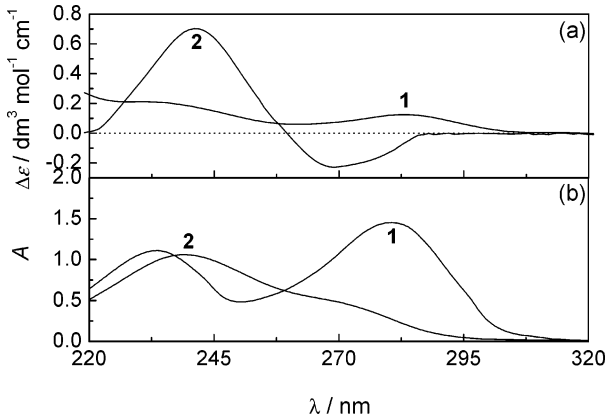

FIGURE 5. (a) Circular dichroism and (b) absorption spectra of **1** (8.2×10^{-5} mol dm^{-3}) and **2** (7.9×10^{-5} mol dm^{-3}) in aqueous solution at 25 °C.

spectrum of **2**, which suggests that conjugation degree between two pyridine rings in 4-DPD is much lower than that in 2-DPD; in other words, the two pyridine rings array in an approximately vertical manner. Therefore, the results of 2D NMR experiments and UV−vis spectra well validate the structural consistency of **1** and **2** in the solid state and in solution.

Achiral organic compounds can show an induced circular dichroism (ICD) signal around their corresponding transition band in cases where there is a chiral microenvironment. Therefore, to deduce the conformation of interaction between the achiral chromophoric compound and the β-CD chiral cavity, ICD spectra of **1** and **2** were measured at 25 °C in aqueous solution. As can be seen from Figure 5, the circular dichroism spectrum of **1** showed two positive Cotton-effect peaks at 231 nm ($\Delta\epsilon = 0.21$ dm^{-3} mol^{-1} cm^{-1}) and at 283 nm ($\Delta\epsilon = 0.12$ dm^{-3} mol^{-1} cm^{-1}) respectively, while **2** displayed a positive Cotton-effect peak at 241 nm ($\Delta\epsilon = 0.70$ dm^{-3} mol^{-1} cm^{-1}) and a negative Cotton-effect peak at 269 nm ($\Delta\epsilon = -0.23$ dm^{-3} mol^{-1} cm^{-1}). According to the pioneering studies of Kajtár and Nau et al. on the ICD phenomena of cyclodextrin complexes,[37,38] we could deduce that the 4-DPD molecules in **2** entered the β-CD cavity with an acclivitous orientation in aqueous solution. However, these empirical rules do not work any more in rationalizing the two positive Cotton-effect peaks observed for the complex **1**. One possible explanation for this spectral phenomenon was that the 2-DPD included in the cavity from the primary or secondary side of β-CD might give two different ICD signals and therefore the apparent ICD signals of their kinetic equilibrium are observed.

Binding Thermodynamics. To quantitatively investigate the binding behavior of **1** and **2** in solution, microcalorimetric titration (ITC) has been performed at 25 °C in aqueous solution to give the binding constants (K_S) and the thermodynamic parameters of 2-DPD and 4-DPD upon complexation with β-CD. A typical titration curve of β-CD with 2-DPD was shown in Figure 6. The thermodynamic parameters listed in Table 2 shows that the complex formation of 2-DPD or 4-DPD with β-CD in aqueous solution is accompanied with a favorable enthalpic change and a positive entropic contribution.

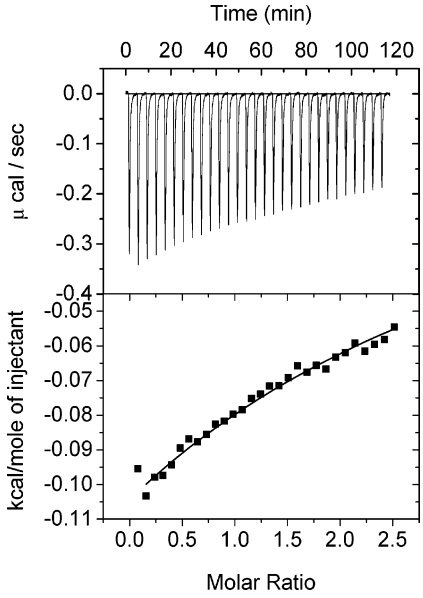

FIGURE 6. Calorimetric titration of 2-DPD with β-CD in aqueous solution at 25 °C: (upper) raw data for sequential 10 μL injections of β-CD solution (12.21 mM) into 2-DPD solution (1.09 mM); (lower) heats of reaction as obtained from the integration of the calorimetric traces.

TABLE 2. Binding Constants (K_S), Standard Enthalpy ($\Delta H°$, kJ mol^{-1}), and Entropy Changes ($T\Delta S°$, kJ mol^{-1}) for 1:1 Inclusion Complexation of β-CDs with 2-DPD and 4-DPD at 25 °C in Aqueous Solution

reaction	DPD (mM)	β-CD (mM)	N^a	K_S	$-\Delta G°$	$-\Delta H°$	$T\Delta S°$
2-DPD + β-CD	1.09	12.21	2	71 ± 12	10.5 ± 0.5	6.4 ± 0.7	4.1 ± 1.2
4-DPD + β-CD	0.66	10.39	2	164 ± 9	12.6 ± 0.2	5.7 ± 0.3	6.9 ± 0.5

[a] Number of microcalorimetric titration experiments performed.

It is well-known that the negative enthalpy changes are accounted for the hydrogen bonds and the van der Waals interactions arising from the size/shape matching between the host and guest. One might deduce reasonably that no other than the hydrogen bonds interactions between the nitrogen atoms in DPD and water molecules lead to their moderate solubility in aqueous solution. When the nitrogen atoms are completely embedded in the cavity of CD, the original hydrogen bonds between the nitrogen atoms and water molecules should become weak or even disappear as a result of the hydrophobicity of the CD cavity. According to the above results of 2D NMR, one of the nitrogen atoms in 4-DPD is more deeply included into the cavity than any of those in 2-DPD, and hence the breaking of these hydrogen bonds upon complexation of 4-DPD and β-CD would cancel the favorable enthalpy changes arising from van der Waals interactions, resulting in the value of 4-DPD upon complexation with β-CD being less enthalpic than that of 2-DPD (5.7 versus 6.4 kJ/mol). Despite that, the slightly larger K_S value for 4-DPD as compared with 2-DPD attributed to its more favorable entropy changes is obtained, which means that there exists the more extensive desolvation effect for 4-DPD upon complexation with β-CD. The

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difference in desolvation effect of 4-DPD and 2-DPD should be ascribed to their different locations within CD cavity as mentioned above and the nature of DPDs. On one hand, according to the presumed binding modes of 4-DPD and 2-DPD in CD cavities by their 2D NMR experiments, it can be deduced that the inclusion of guest from the secondary side (4-DPD and 2-DPD) leads to the larger desolvation effect than from the primary side (2-DPD).[39] On the other hand, the relative strong polarity of 2-DPD[40,41] implies stronger degree of solvation, making their desolvation difficult. These results would help us to understand the thermodynamic origin in the process of the molecular assembly and design the supramolecular systems with more special function.

Conclusions

Two distinct channel-type polymeric supramolecules possessing monoclinic system (*C*2) for **1** and triclinic system (*P*-1) for **2** were constructed by β-CD with 2-DPD and 4-DPD, respectively. The crystallographic studies showed that both 2-DPD and 4-DPD molecules are embedded into the β-CD cavities by two different directions. Two types of symmetrical head-to-head dimer structures are formed by 2-DPD−CD complexes and each dimer possesses two similarly orientated 2-DPD molecules, whereas 4-DPD−CD complexes only form one type of unsymmetrical head-to-head dimer structure but each dimer possesses two differently orientated 4-DPD molecules. Further investigations of their binding behavior elucidated the structural consistency of **1** and **2** in the solid state and in solution. Thermodynamic investigation indicated that the complex formation of DPDs with β-CD is accompanied with a favorable enthalpic change and a positive entropic contribution, and the distinction of binding abilities of β-CD toward 2-DPD and 4-DPD are attributed to the different DPD orientation in the CD cavity and the disparity ofc the nitrogen atom position in DPD. These new observations are useful not only for establishing the correlations between the conformational feature of host−guest complexes and the molecular recognition ability but also for designing novel molecular assembly of CDs and functional guests.

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Supporting Information Available: ORTEP plots of the crystals **1** and **2** and the atomic coordinates, bond lengths, and angles of the crystal **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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