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<th>Inclusion behavior of -cyclodextrin with bipyridine molecules : factors governing host-guest Inclusion geometries</th>
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<td>Author(s)</td>
<td>Zhao, Yanli; Benítez, Diego; Yoon, II.; Stoddart, J. Fraser</td>
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<td>2009</td>
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Inclusion Behavior of β-Cyclodextrin with Bipyridine Molecules: Factors Governing Host-Guest Inclusion Geometries

Yan-Li Zhao, [b] Diego Benítez,[b] Il Yoon,[b] and J. Fraser Stoddart*[a, b]

Abstract: The 1:1 complexation of β-cyclodextrin (β-CD) with structurally similar bipyridine guests which lead to the formation of six inclusion complexes (1–6) of β-CD with 4,4′-vinylenedipyridine, 2,2′-vinylenedipyridine, 1-(2-pyridyl)-2-(4-pyridyl)ethylene, 4,4′-ethylene-dipyridine, 4,4′-dithiodi-pyridine, and 2,2′-dithiodipyridine has been investigated comprehensively by X-ray crystallography in the solid state and by 1H NMR spectroscopy and microcalorimetric titration in aqueous solution. The complex formation constants (KS) for the stoichiometric 1:1 host–guest inclusion complexation of β-CD with the bipyridine derivatives were determined in aqueous solution by microcalorimetry and the host–guest inclusion geometries of the complexes were deduced from 1H ROESY NMR spectroscopy. It transpires that the guest bipyridine molecules are included in the β-CD cavity with a range of different inclusion geometries. In the solid state, the crystal superstructures for the β-CD complexes 1, 4, and 5 are characterized by the triclinic crystal system (space group P1) commensurate with AAAA type supramolecular aggregation. By contrast, the β-CD complexes 2, 3, and 6 display either monoclinic (space group P21) or orthorhombic (space group C2221) crystal systems, characteristic of ABAB type supramolecular aggregation. The results demonstrate that the relative locations of the nitrogen atom positions and the bridge-bond links between the two pyridine rings in these bipyridine guests, not only lead to distinct crystal systems and space groups, but also to different binding geometries and thermodynamical parameters on complexation of the bipyridines with β-CD. The knowledge obtained from this research improves our understanding of the molecular recognition and self-assembly processes exhibited by β-CD, both in the solid state and in aqueous solution.

Keywords: crystal structures · cyclodextrins · host–guest systems · inclusion compounds · NMR spectroscopy

Introduction

As naturally abundant cyclic oligosaccharides, cyclodextrins (CDs) have been applied in the fields of molecular recognition and supramolecular assembly.[1–6] Indeed, CDs can form stable inclusion complexes in aqueous solution with various guest molecules through the simultaneous contributions of several noncovalent bonding interactions by which the guest molecules are included within their hydrophobic inner cavities. The commonly accepted model for CD complex formation suggests that a CD complex forms when a suitable hydrophobic molecule displaces “high energy” water from the CD cavity.[7] In the inclusion complexation process, besides several weak intermolecular noncovalent forces, such as dipole–dipole (ion), hydrophobic, electrostatic, van der Waals, and hydrogen bonding interactions, the solvent, environment, and geometries of hosts and guests also affect the stabilities of the inclusion complexes. The strong binding affinity of CDs to hydrophobic molecules in aqueous solution enables these hosts to be effective receptors for organic, inorganic, and biological substrates.[8–10] Therefore, the findings of the researchers who have investigated the geometrical properties associated with the binding of guest molecules by CDs during the past two decades have attracted a lot of attention. For example, several research groups have reported solution studies of CDs upon complexation with amino
acids,[11,12] peptides,[13,14] drugs,[15,16] surfactants,[17,18] steroids,[19] and so forth, using different methods such as microcalorimetry in addition to NMR, UV/Vis, and fluorescence spectrometry. Through these studies, which were directed toward an understanding of the binding behavior and molecular/chiral recognition of CDs, these research groups have provided valuable information on the effects of changes in the functionality and chirality of guests that is not revealed in the crystal superstructures of the inclusion complexes. Nonetheless, it is much more valuable if the crystal superstructures of inclusion complexes can be obtained because they can provide direct insight into the binding mechanisms of substrates by CDs. Indeed, a number of crystallographic studies on inclusion complexes of CDs with guest molecules have been performed during the past decade. Close examination of the crystal superstructures of a variety of inclusion complexes reveals that steric matching of the host and guest is certainly one of the most important factors determining the molecular geometry of a complex and its packing in the solid state.[20a] It is obvious that crystal superstructures can be affected by other factors, such as the type, length, functional group, and heteroatom content of the guests. This situation implies that the crystal superstructures of the CD complexes are designable through the precise control of interactions between the guests and CD hosts. Nevertheless, there are very few investigations focused on understanding how small differences in the structures of the guests affect the inclusion geometries and binding abilities of CDs, both in solution and the solid state. The nature of these variations could provide valuable insights into the complexity of the intermolecular interactions involving hydrophobic, hydrogen bonding, and π–π stacking interactions in the host–guest systems and serve to establish a correlation between the host–guest geometrical relationships and the molecular recognition abilities of CDs towards guests.

Herein, we report the preparation of six inclusion complexes (1–6 in Scheme 1) of β-CD with 4,4′-vinylenedipyridine, 2,2′-vinylenedipyridine, 1-(2-pyridyl)-2-(4-pyridyl)ethylene, 4,4′-ethylenedipyridine, 4,4′-dithiodipyridine, and 2,2′-dithiodipyridine, respectively.

**Abstract in Chinese:**

为了系统地研究β-CD和结构相近的联吡啶类客体的分子识别能力和聚集行为，我们制备了6个分子识别配合物，即，β-CD和4,4′-乙烯联吡啶（配合物1）、β-CD和2,2′-乙烯联吡啶（配合物2）、β-CD和4,4′-乙烯联吡啶（配合物3）、β-CD和4,4′-乙烯联吡啶（配合物4）、β-CD和4,4′-乙烯联吡啶（配合物5）和β-CD和二硫联吡啶（配合物6），并将它们用X射线晶体衍射分析、核磁共振波谱测定等方法对这些配合物进行了全面的研究。在溶液中，β-CD和联吡啶类客体能够形成1:1的1:1客体包合物。微量滴定实验给出了这些包合配合物的解离常数(κa)和热力学参数。二维核磁共振结果进一步验证了这些配合物能够以不同的模式包合在β-CD空腔中。在此基础上，包合物1、4和5的晶体结构属于单斜晶系(P1空间群)，能够形成AAAA型的超分子聚集体。包合配物2、3和6则给出了单斜(222)空间群或正交(C2221)空间群的晶系，进而形成ABAB型的超分子聚集体。这些研究结果还表明，联吡啶类客体中的电子云位置和联吡啶联吡啶间的π-π相互作用是影响这些配合物解离常数和热力学的因素。此外，X射线晶体衍射和热力学参数，以及这些包合配合物在溶液中的聚集行为，为分子识别提供了重要的实验依据。

**Results and Discussion**

**Preparation of Inclusion Complexes and Their Crystal Structures**

Bipyridine molecules have very interesting coordination properties and therefore are frequently used as building blocks to construct supramolecular architectures,[33-37] In the present work, we chose 4,4′-vinylenedipyridine, 2,2′-vinylenedipyridine, 1-(2-pyridyl)-2-(4-pyridyl)ethylene, 4,4′-ethylenedipyridine, 4,4′-dithiodipyridine, and 2,2′-dithiodipyridine as guests in order to prepare inclusion complexes with β-CD. These bipyridine guests vary in their constitutions, resulting in broad variations in their inclusion geometries and in the binding behavior of the complexes. The inclusion complexes 1–6 of β-CD with all six bipyridine guests were prepared in aqueous ethanol solution using a simple method, that is, an EtOH solution (10 mL) of
each guest (1 mmol) was added dropwise to an aqueous solution (40 mL) of β-CD (1 mmol). The turbid solutions were stirred and heated to 50°C, in order to attain complete dissolution. After cooling down to room temperature, the precipitates which formed were isolated by filtration and washed with H2O. The resulting solids were dried under vacuum to give powder-like samples. The inclusion complexes of β-CD were characterized by 1H NMR spectroscopy and MALDI time-of-flight mass spectrometry. The inclusion geometries and binding behaviors of the complexes were investigated by 1H ROESY (Rotating frame Overhauser Effect Spectroscopy) NMR spectroscopy and microcalorimetric titrations. Crystals of the complexes were then grown from saturated aqueous solutions. Single crystals of appropriate quality were chosen for X-ray crystallographic analyses.

**Solution Investigation**

In order to investigate the binding behavior of β-CD with bipyridine guests in aqueous solution, we have performed 1H NMR spectroscopic experiments on the host–guest system at 25°C in D2O. First of all, the stoichiometries of the host–guest systems were determined by 1H NMR spectroscopy employing experiments where the molar ratios of guest and β-CD were varied, while the overall molar concentrations of the two components were held constant. A typical Job plot for the β-CD/4,4′-ethylenedipyridine system at 25°C in D2O reveals (Figure 1) a minimum at 0.50, indicating the formation of a 1:1 host–guest inclusion complex between β-CD and 4,4′-ethylenedipyridine. Very similar results were obtained in the case of the inclusion complexes of β-CD containing the other guests.

Next, the changes of chemical shifts of proton probes in the guest molecules in the presence of β-CD were varied using the 1H NMR titration method at 25°C in D2O. The changes (Δδ) in chemical shifts of the Hα protons on 4,4′-ethylenedipyridine, x is the molar fraction of 4,4′-ethylenedipyridine.

![Figure 1. Job plot obtained for β-CD/4,4′-ethylenedipyridine ([β-CD]+[4,4′-ethylenedipyridine]=5.0×10⁻³ mol dm⁻³) in D2O at 25°C.](image)

The changes (Δδ) in chemical shifts of the Hα protons on 4,4′-ethylenedipyridine in the presence of β-CD display downfield shifts (Δδ) of up to +0.02 and +0.07 ppm, respectively, while the Hβ protons reveal upfield shifts (Δδ) of up to –0.05 ppm under the same conditions. A possible explanation for these observations is that the interaction between the Hα protons of 4,4′-ethylenedipyridine and the wall of β-CD is stronger than that between Hα or Hβ and the wall. Furthermore, we have also performed the 1H NMR titration experiments of β-CD in the presence of guests at 25°C in D2O. Typical 1H NMR titration spectra of β-CD on addition of 4,4′-ethylenedipyridine are shown in Figure 3. The H3 and the H5 protons in β-CD experience upfield shifts (Δδ) of about 10⁻³ mol dm⁻³). The H4 and Hα protons in 4,4′-ethylenedipyridine.

![Figure 2. 1H NMR spectra of 4,4′-ethylenedipyridine (1.03×10⁻³ mol dm⁻³) recorded following the stepwise addition of β-CD (a–h: 0–2.37×10⁻³ mol dm⁻³) in D2O at 25°C.](image)

![Figure 3. 1H NMR spectra of β-CD (1.02×10⁻³ mol dm⁻³) recorded following the stepwise addition of 4,4′-ethylenedipyridine (a–h: 0–2.06×10⁻³ mol dm⁻³) in D2O at 25°C.](image)
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−0.13 and −0.21 ppm, respectively. In the cases of the other guests, the upfield shifts (Δδ) for the H3 and the H5 protons of β-CD are in the order of −0.08 to −0.15 ppm and −0.13 to −0.24 ppm, respectively. These results indicate that the inclusion of an aromatic guest inside the CD cavity can cause major upfield shifts of the H3 and/or the H5 protons on account of the ring currents generated by the aromatic portions of the guests and/or hydrogen bonding interactions between the host and guests.[41]

It is also interesting to note that the complexion of guests with β-CD produces larger upfield shifts for H5 than those for H3. An investigation by Goldberg and co-workers[41] has suggested that the magnitude of the upfield shifts for H3, An investigation by Goldberg and co-workers[41] has suggested that the magnitude of the upfield shifts for H3 and those for H5. An investigation by Goldberg and co-workers[41] has suggested that the magnitude of the upfield shifts for H3 and (peak A) and H, (peak B) protons, indicating distinctly that the 2,2'-vinylene-

dipyridine guest is also included inside the β-CD cavity. The fact that the correlation (peak E) of H3 with the H2 protons is slightly weaker than the others suggests that the H2 protons in 2,2'-vinylene-dipyridine should be removed from H3. A possible inclusion geometry for 2 is shown in Figure S2b of the Supporting Information. For complex 3 (4.6 × 10⁻³ mol dm⁻³), the NOE cross-peaks between the H3/H5 protons of β-CD and the Hg/Hg (peak A) and H, (peak C) protons of 1-(2-pyridyl)-2-(4-pyridyl)ethylenediyldithiophosphate molecule, and between the H3 protons and the H2 protons (peak B) are shown in the ROESY spectrum (Figure S3a of the Supporting Information), indicating that the 1-(2-pyridyl)-2-(4-pyridyl)ethylenediyldithiophosphate molecule is included in the cavity of β-CD. Notably, it shows the interaction between the H3 and the H2 protons (peak B), implying the 2-pyridyl moiety of 1-(2-pyridyl)-2-(4-pyridyl)ethylenediyldithiophosphate molecule is located on the secondary side of the β-CD cavity. This interesting result indicates that the β-CD can direct the orientation of the 1-(2-pyridyl)-

2-(4-pyridyl)ethylenediyldithiophosphate molecule inside the cavity. According to the results of the ROESY NMR experiment, a possible geometry of β-CD with 1-(2-pyridyl)-2-(4-pyridyl)ethylenediyldithiophosphate is given in Figure S3b of the Supporting Information.

The nonconjugated guests, 4,4'-ethylenedipyridine, 4,4'-di-
diethylenedipyridine, and 2,2'-dithiodiethylenedipyridine have more flexible skeletons than those of the conjugated guests, that is, 4,4'-viny-

lenedipyridine, 2,2'-vinylene-dipyridine, and 1-(2-pyridyl)-

2-(4-pyridyl)ethylenediyldithiophosphate molecule. Thus, the nonconjugated guests can be included in the cavity of β-CD with better matching geometries. In the case of the complex 4 (4.7 × 10⁻³ mol dm⁻³), its ROESY spectrum (Figure S4a of the Supporting Information) reveals NOE cross-peaks between the H3/H5 protons of β-CD and the Hg (peak A), H, (peak B), and H, (peak C) protons of 4,4'-ethylenedipyridine molecule. Simi-

larly, the ROESY spectrum (Figure S5a of the Supporting Information) of the complex 5 (3.4 × 10⁻³ mol dm⁻³) shows NOE cross-peaks between the H3/H5 protons of β-CD and the Hg (peak A) and H, (peak B) protons of 4,4'-dithiodi-
diethylenedipyridine molecule. For the complex 6 (2.5 × 10⁻³ mol dm⁻³), the ROESY spectrum (Figure S6a of the Supporting Information) reveals NOE cross-peaks between the H5 protons of β-CD and the Hg (peak A) and H, (peak B) protons of 2,2'-dithiodiethylenedipyridine molecule, as well as between the H3 protons and the H2 (peak C) protons. Based on the results of these ROESY NMR experiments, possible inclusion geometries of β-CD with the three nonconjugated guests are shown in Figures S4b, S5b, and S6b of the Supporting Information, respectively. Although a series of complex geometries may be present in the β-CD inclusion complexes in aqueous solution,[62,63] the inclusion geometries in the sys-
tem under investigation should be an optimum one for the various host–guest geometries adopted between β-CD and the bipyridine guests. Therefore, the results of the 1H ROESY NMR experiments serve to establish the corre-
lation between the geometrical features of the inclusion
complexes and the molecular recognition mechanism of β-CD toward bipyridine guests. The different inclusion geometries and strict size/shape fitting relationships between the host and guest explain reasonably well the different binding affinities and guest selectivities of β-CD.

Microcalorimetric titration (ITC) experiments have been performed in aqueous phosphate buffer solutions (pH 7.0) at 25°C. The formation constants ($K_f$) and the thermodynamic parameters of the bipyridine guests upon complexation with β-CD are listed in Table 1. The formation constants ($K_f$) for the inclusion complexation of host with guest decrease in the following order—4,4′-dithiodipyridine > 1-(2-pyridyl)-2-(4-pyridyl)ethylene > 4,4′-ethylenedipyridine > 4,4′-vinylene-dipyridine > 2,2′-dithiodipyridine > 2,2′-vinylene-dipyridine. We note that the association of β-CD with 4,4′-dithiodipyridine affords the highest formation constant of 1102 ± 58 M$^{-1}$, a value which is 7.7 times more than that for 2,2′-vinylene-dipyridine (144 ± 29 M$^{-1}$). This relatively good molecular selectivity can be attributed to strict size/shape matching and hydrophobic interactions between the host and guest. The guests, 4,4′-ethylenedipyridine, 4,4′-dithiodipyridine, and 2,2′-dithiodipyridine, have more flexible skeletons than those of 4,4′-vinylene-dipyridine and 2,2′-vinylene-dipyridine. They can find a match with the β-CD cavity more easily by changing their geometries, leading to higher formation constants except in the case of 2,2′-dithiodipyridine. Furthermore, the guests with nitrogen atoms in the 2,2′-positions afford lower formation constants compared with guests which have nitrogen atoms in their 2,4′- and 4,4′-positions, most likely because of their lower hydrophobicities.

The thermodynamic parameters listed in Table 1 show that complex formation of bipyridine guests with β-CD in phosphate buffer solution is accompanied by favorable enthalpic changes and positive entropic contributions, except in the case of 2,2′-dithiodipyridine ($TΔS^o = −16.0 ± 0.4$ kJ mol$^{-1}$). It is well-known that the negative enthalpy changes can be accounted for by the hydrogen bonding and van der Waals interactions arising from the size/shape matching between the host and guest. When the guests are embedded in the cavity of β-CD, the previously existing hydrogen bonding between the nitrogen atoms and water molecules will become weaker or even non existent as a result of the hydrophobicity inside the β-CD cavity. Furthermore, the larger $K_f$ values for the guests with nitrogen atoms in their 2,4′- and 4,4′-positions as compared with the guests which have nitrogen atoms in their 2,2′-positions mean that there exists a more extensive desolvation effect for the guests with nitrogen atoms in their 2,4′- and 4,4′-positions upon complexation with β-CD. The difference in desolvation effect of the guests with nitrogen atoms in their 2- and 4-positions can be ascribed to their differing orientations within the β-CD cavity, cf., the ROESY experiments. In the case of 2,2′-dithiodipyridine with β-CD, the larger entropy loss ($TΔS^o = −16.0 ± 0.4$ kJ mol$^{-1}$) may be attribute to the smaller geometrical change and/or weaker desolvation effect between the host and guest as compared with other complexes. These results help us understand the thermodynamic origins at work in the process of the molecular inclusion.

### Crystal Superstructures

Direct evidence for the formation of inclusion complexes 1-6 has been obtained in the solid state. Single crystals of the β-CD complexes 1, 4, and 5 were triclinic and had space group $P1$. The single crystal for the complex 2 was monoclinic and had space group $P2_1$. The single crystals for the complexes 3 and 6 were orthorhombic and had space group $C221$. The crystal data and experimental and refinement parameters for the superstructures 1–6 are listed in Table 2 and their unit cells are shown in Figure 4 and Figure S9 of the Supporting Information. In these crystal superstructures, the skeleton of β-CD with its approximate seven-fold axis and toroidal shape, as well as the coplanarity of the seven glycosidic oxygen atoms, are not significantly changed with the inclusion of the bipyridine molecules. There is a little conformational variability in the β-CD torus, that is, the two primary OH groups for complexes 1 and 2 and one primary OH group for complex 4 are disordered over two sites, one site a (+)-gauche conformer (the primary OH groups point toward the interior of β-CD), and the other a (−)-gauche conformer (the primary OH groups point toward the exterior of β-CD). Some H$_2$O molecules are distributed throughout the unit cells of crystals 1–6, and these H$_2$O molecules are almost located on the exterior of the β-CD cavities, an observation which indicates the presence of strong hydrophobic interactions between the β-CD cavities and guests.

In the unit cell of 1 (Figure 4a and Figure S9a of the Supporting Information), two 4,4′-vinylene-dipyridine molecules with the trans configuration are embedded into two β-CD cavities in different directions, forming a head-to-head dimer arrangement, which is somewhat different from the inclusion complexes produced by β-CD and guests in the solid state.[20b] In particular, there is an H-bonding interaction between an ortho-hydrogen atom (H$_2$) in pyridine ring A of 4,4′-vinylene-dipyridine molecule and an O atom on the...
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Table 2. Crystal data, experimental and refinement parameters for crystals 1–6.

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<tr>
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<th>Crystal 3</th>
<th>Crystal 4</th>
<th>Crystal 5</th>
<th>Crystal 6</th>
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<td>0.2407</td>
<td>0.2343</td>
<td>0.2853</td>
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</table>

The primary side of the β-CD (d₁-₄−₁₀ = 2.41 Å), which fixes the orientation of the guest molecule inside the β-CD cavity, This dimerization can be attributed to the cooperative interactions of ten H-bonding interactions between the secondary OH groups of two adjacent β-CD units, as well as the π-π stacking of two pyridine rings B and B' (13° dihedral angle and 3.72 Å centroid–centroid separation) in the two guest molecules. Furthermore, the dihedral angles between the plane of these pyridine rings A (A') or B (B') in 4,4'-vinylenedipyridine and the heptagons composed of seven glycosidic oxygen atoms (O4-heptagon) in β-CD are 67° (101°) or 89° (84°), and the centroid-centroid separations between them are 1.43 (3.63) Å or 5.19 (3.73) Å, indicating that one 4,4'-vinylenedipyridine molecule with pyridine rings A and B is included shallowly in a β-CD cavity while the other one with pyridine rings A' and B' is deeply included in the cavity. The dihedral angle between the pyridine rings A (A') and B (B') in 4,4'-vinylenedipyridine is 40° (39°). However, the crystal superstructure of 4,4'-vinylenedipyridine (Figure 5), obtained from H₂O, shows that the dihedral angle between the pyridine rings A and B is 20°. The 4,4'-vinylenedipyridine molecules are self-assembled through three H-bonding interactions linked by H₂O molecules.
(\(d_{\text{C-H-O}}=2.39\) Å, \(d_{\text{O-H-N}}=2.00\) Å, \(d_{\text{O-H-N}}=2.05\) Å). No \(\pi-\pi\) interactions can be found in the superstructure. These results indicate that the geometry and packing mode of the host molecule can be altered by the complexation inside the cavity of \(\beta\)-CD.

In the case of complexes 4 and 5 with nonconjugated guests (Figures 4d and 4e and Figures S9d and S9e of the Supporting Information), although their crystal system and space group are the same as that for complex 1, the inclusion geometry of host and guest in the superstructures 4 and 5 have several differences compared with that in 1. Two 4,4'-ethylenedipyridine or two 4,4'-dithiodipiridine molecules with the cis configuration are included inside the cavities of \(\beta\)-CD in two different directions, forming dimeric superstructures. Some key dihedral angles and centroid-centroid separations in the dimers are listed in Tables 3 and 4, respectively, indicating that the two 4,4'-ethylenedipyridine molecules are included shallowly in the cavities, whereas one 4,4'-dithiodipiridine molecule with A and B pyridine rings is included shallowly, while the other one with A' and B' pyridine rings is located almost in the middle of the cavity. In the unit cell of 4, the two \(\beta\)-CDs of the dimer are connected by ten H-bonding interactions between the OH groups on the secondary faces of the \(\beta\)-CD rings. In particular, there are three H-bonding interactions between the host and guest, that is, an H atom (H1) in 4,4'-ethylenedipyridine and a glycosic O atom in the \(\beta\)-CD ring (\(d_{\text{C-H-O}}=2.55\) Å), a N atom in 4,4'-ethylenedipyridine and a secondary OH group in the \(\beta\)-CD ring (\(d_{\text{O-H-N}}=2.61\) Å), and the N atom and an H atom in a glucopyranose ring of adjacent \(\beta\)-CD (\(d_{\text{O-H-N}}=2.45\) Å)—and a weak \(\pi-\pi\) interaction between two pyridine rings B and B' in a face-to-face arrangement (17° dihedral angle and 3.89 Å centroid–centroid separation). Hydrogen bonding interactions involving glycosic O atom are not common in crystal superstructures of \(\beta\)-CD with guest molecules. In the unit cell of 5, the two \(\beta\)-CD rings in the dimer are connected by five H-bonding interactions between the OH groups on the secondary sides of the \(\beta\)-CD rings. There are two H-bonding interactions between the host and guest, that is, a N atom in 4,4'-dithiodipiridine and a secondary OH group in an adjacent \(\beta\)-CD ring (\(d_{\text{O-H-N}}=2.53\) Å), as well as an S atom in 4,4'-dithiodipiridine and an H atom in a glucopyranose ring of \(\beta\)-CD (\(d_{\text{C-H-S}}=2.93\) Å) and the \(\pi-\pi\) interaction of two pyridine rings B and B' in a face-to-face arrangement (4° dihedral angle and 3.76 Å centroid–centroid separation). We attribute the different guest orientations to the stabilization afforded by the H-bonding interaction between the guest and host \(\beta\)-CD.

Superstructure 2 belongs to monoclinic crystal system (Figure 4b and Figure S9b of the Supporting Information). Two 2,2'-vinylenedipyridine molecules with \(\text{trans}\) configurations are included inside two \(\beta\)-CD cavities, forming a head-to-head dimer arrangement. The seven H-bonding interactions between secondary OH groups in two adjacent \(\beta\)-CD units and the \(\pi-\pi\) stacking between two pyridine rings B and B' (1° dihedral angle and 3.73 Å centroid–centroid separation) in the 2,2'-vinylenedipyridine molecules can be found in the dimer. The dihedral angles between the plane of the pyridine rings A (A') or B (B') in the 2,2'-vinylenedipyridine molecule and the 4,4'-heptagon in \(\beta\)-CD are 64° (65°) or 65° (65°), and the centroid–centroid separations between them are 2.92 (3.46) Å or 2.67 (3.04) Å, which values which indicate that the two 2,2'-vinylenedipyridine molecules are located almost at the middle of the \(\beta\)-CD cavities. This result is different from that in superstructure 1.

Compared with complexes 1, 2, 4, and 5, the unit cells for superstructures 3 and 6 (Figures 4c, 4f, and Figures S9c and S9f of the Supporting Information) show only one inclusion geometry between the host and the guests. Although they do not form dimers in the unit cells, their complexes self-assemble to form the dimeric superstructures as shown in Figure 6 and Figure S10 of the Supporting Information. In the case of complex 3, the 1-(2-pyridyl)-2-(4-pyridyl)ethylene molecule with \(\text{trans}\) configuration is located on one side of the 4,4'-ethylenedipyridine molecule, forming a head-to-head dimer arrangement. The seven H-bonding interactions between secondary OH groups in two adjacent \(\beta\)-CD units and the \(\pi-\pi\) stacking between two pyridine rings B and B' (1° dihedral angle and 3.73 Å centroid–centroid separation) in the 4,4'-ethylenedipyridine molecules can be found in the dimer. The dihedral angles between the plane of the pyridine rings A (A') or B (B') in the 4,4'-ethylenedipyridine molecule and the 4,4'-heptagon in \(\beta\)-CD are 64° (65°) or 65° (65°), and the centroid–centroid separations between them are 2.92 (3.46) Å or 2.67 (3.04) Å, which values which indicate that the two 4,4'-ethylenedipyridine molecules are located almost at the middle of the \(\beta\)-CD cavities. This result is different from that in superstructure 1.

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**Table 3. Some dihedral angles in the pyridine rings A (A') and B (B'), and 4,4'-heptagon of crystal superstructures 1–6.**

<table>
<thead>
<tr>
<th>Dihedral Angle [*]</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/B</td>
<td>40</td>
<td>1</td>
<td>23</td>
<td>51</td>
<td>80</td>
<td>99</td>
</tr>
<tr>
<td>B/A'</td>
<td>39</td>
<td>15</td>
<td>47</td>
<td>77</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>A (A')/O4-heptagon</td>
<td>67</td>
<td>101</td>
<td>64</td>
<td>65</td>
<td>85</td>
<td>18</td>
</tr>
<tr>
<td>B (B')/O4-heptagon</td>
<td>89</td>
<td>64</td>
<td>65</td>
<td>90</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>B/B'</td>
<td>13</td>
<td>1</td>
<td>21</td>
<td>17</td>
<td>4</td>
<td>32</td>
</tr>
</tbody>
</table>

**Table 4. Some centroid-centroid separations in the pyridine rings A (A') and B (B'), and 4,4'-heptagon of crystal superstructures 1–6.**

<table>
<thead>
<tr>
<th>Centroid–Centroid Separation [Å]</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (A')/O4-heptagon</td>
<td>1.43</td>
<td>3.63</td>
<td>3.92</td>
<td>3.46</td>
<td>3.71</td>
<td>0.94</td>
</tr>
<tr>
<td>B (B')/O4-heptagon</td>
<td>5.19</td>
<td>3.75</td>
<td>2.67</td>
<td>3.04</td>
<td>4.01</td>
<td>3.84</td>
</tr>
<tr>
<td>B/B'</td>
<td>3.72</td>
<td>3.73</td>
<td>3.80</td>
<td>3.89</td>
<td>3.89</td>
<td>3.76</td>
</tr>
</tbody>
</table>

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**Figure 6. The dimeric superstructures of the inclusion complexes a) 3 and b) 6.** The H atoms and H\(_2\)O molecules are omitted for the sake of clarity. The \(\beta\)-CD rings are colored orange and the bipyridine guests are colored blue, except for the sulfur atoms which are highlighted in yellow.
of the β-CD cavity. The dihedral angles between the plane of the pyridine rings A or B in the 1-(2-pyridyl)-2-(4-pyridyl)ethylene molecule and the O4-heptagon in β-CD are 85° or 90°, respectively, and the centroid–centroid separations between them are 3.71 or 4.01 Å. There are 12 H-bonding interactions between secondary OH groups of two adjacent β-CD units and a weak π–π stacking between the two pyridine rings B and B’ (21° dihedral angle and 3.80 Å centroid–centroid separation) of 1-(2-pyridyl)-2-(4-pyridyl)ethylene in the dimeric superstructure. For the complex 6, the 2,2’-dithiodipyridine molecule with cis configuration is located almost at the middle of the β-CD cavity. The dihedral angle between the plane of the pyridine rings A or B in the 2,2’-dithiodipyridine molecule and the O4-heptagon in β-CD is 125° or 52°, and the centroid–centroid separations between them are 2.96 or 3.16 Å. There are 16 H-bonding interactions between secondary OH groups of two adjacent β-CD units and no π–π stacking between the two pyridine rings B and B’ (32° dihedral angle and 3.02 Å centroid–centroid separation) of the 2,2’-dithiodipyridine molecules in the dimer. Interestingly, two H-bonding interactions \( (d_{C-H-S} = 2.82 \text{ Å} \) and \( d_{C-H-S} = 2.82 \text{ Å} \)) between the S atoms and H atoms (Hₜ) in the 2,2’-dithiodipyridine molecules are present in the dimeric superstructure.

The head-to-head dimers of the complexes 1–6 self-assemble to form polymeric supermolecules, by means of an H-bonding network (see Figure 7 and Figure S11 of the Supporting Information). For superstructures 1, 4, and 5, each dimer connects tightly with the adjacent dimers through a relatively complicated inter dimer H-bonding system involving the β-CD’s C6-OHs, the guest molecules, and H₂O molecules. Notably, there is a kind of H-bonding interaction \( (d_{O-H-N} = 1.83 \text{ Å} \) between a N atom in the pyridine ring A of 4,4’-vinylenedipyridine in the dimer and a primary OH group in adjacent dimers in the superstructure 1. These interconnections enable the dimers to form a linear supramolecular aggregate (AAAA type) in the solid state of the complexes 1, 4, and 5. In the case of complex 2, the adjacent head-to-head dimers self-assemble, resulting in the formation of wave-like polymeric supermolecules (ABAB type) involving inter dimer H-bonding interactions. In particular, there is a kind of H-bonding interaction between an H atom (Hₜ) in the pyridine ring B of 2,2’-vinylenedipyridine molecule in the dimer and a primary O atom in the adjacent dimer \( (d_{C-H-O} = 2.43 \text{ Å} \) ). In the case of the superstructures 3 and 6, the adjacent head-to-head dimers self-assemble to form large wave-like polymeric supermolecules (ABAB type) involving inter dimer H-bonding interactions. Moreover, the strong H-bonding network formed by the OH groups of β-CD, guest molecules, and intervening H₂O molecules stabilize the aggregations 1–6 and further extend the aggregations to a higher architecture level. That is to say, H-bonding interactions play a central role in the formation of the polymeric supermolecules.

The crystallographic investigations of the inclusion complexes 1–6 of β-CD with bipyridine molecules have demonstrated that the guest molecules are enclosed inside the cavity of β-CD by hydrophobic and H-bonding interactions. In the present examples, the H-bonding interactions (especially for the C–H–O ones) between the host and guest act as a major driving force for the formation of the supramolecular species. It has already been demonstrated that C–H–O interactions are an important consideration in many biological situations and in supramolecular systems. High-level theoretical investigations have provided computational support for interactions of 2–3 kcalmol⁻¹ between α-CH bonds and peptide carboxyl O atoms in neutral systems such as amides, dimerizations, and protein folding. As the complexation of superstructures 1–6 occur in aqueous media, the driving force coming from numerous C–H–O interactions of hydrogen bonding plays a substantial role. Accordingly, we can also deduce that the different arrangements of the guest molecules in the β-CD cavities can be ascribed to the differences of N atom position and bridge-bond links between the two pyridine rings in the bipyridine guests. In the com-

Figure 7. The packing arrangements of the complexes a) 1, b) 2, and c) 3. The H atoms and H₂O molecules are omitted for the sake of clarity. The β-CD rings are colored orange and the bipyridine guests are colored blue.
plexes 1, 4, and 5, the guest molecules possessing N atoms at their 4,4'-positions are included inside the β-CD cavities in two different orientations, thus leading to an “ordered” spatial arrangement of the resultant aggregates (AAAA type). However, in the superstructures 2, 3, and 6, the bipyridine guests, possessing N atoms in their 2,2'- or 2,4'-positions, are included inside the β-CD cavity, which then form a “less-ordered” spatial arrangement of the aggregates (ABAB type). Thus, the present crystal superstructures of the complexes 1–6 not only shed significant light on solution work, but they also imply that structural features discussed in this section may be the essence of the molecular recognition of β-CD with the bipyridine molecules. These results provide valuable insight for the understanding of the spatial topology of biotic acceptors with different model substrates in the solid state, as well as on the inclusion complexation mechanism of β-CD with structurally similar guests.

Conclusions

The binding behavior and geometrical properties of β-CD complexes with structurally similar bipyridine molecules have been investigated in both solution and the solid state. It was of particular interest to us to investigate how and to what extent the difference of heteroatom position and bridge-link bonds on the bipyridine framework of the guests affects the geometrical properties, binding ability, and self-assembly behavior of CD. Therefore, we sought to elucidate the correlations between the binding mode and the thermo-dynamic parameters of the host–guest complexation. The NMR and microcalorimetry investigations indicate that β-CD and bipyridine molecules can form 1:1 host–guest inclusion complexes with moderate complex formation constants. Unexpectedly, however, the guest molecules display different inclusion geometries in the β-CD cavity in aqueous solution, resulting in variable molecular recognition abilities by β-CD. The crystal structures for the complexes 1, 4, and 5 present “ordered” supramolecular aggregates (AAAA type), in which the guest molecules with two orientations are located in the β-CD cavities. By contrast, the complexes 2, 3, and 6 give “less-ordered” supramolecular aggregates (ABAB type). The complexation of β-CD with the guests is driven by H-bonding interactions. The H-bonding interactions between the host and guest result in the remarkable differences of both the guest shape and the location in the cavity, supporting significantly the induced-fit concept. These new observations, along with the easy synthesis of β-CD/bipyridine complexes, indicate that, with judicious design, highly ordered supramolecular arrays can be achieved conveniently in a controllable way, a situation which is useful for understanding of supramolecular recognition and aggregation phenomena on a more global scale.

Experimental Section

Materials and Instruments

β-Cyclodextrin (β-CD), 4,4'-vinylenedipyridine [(pK_a = 4.8 and pK_a = 5.9)], 2,2'-vinylenedipyridine, 1-(2-pyridyl)-2-(4-pyridyl)ethylene, 4,4'-ethylenedipyridine, 4,4'-dithiodipyridine [pK_a = 4.0 and pK_a = 5.1], and 2,2'-dithiodipyridine (pK_a < 1.0 and pK_a = 2.5) were purchased from Aldrich and used as received. Based on the structural similarities of these bipyridine guests, the pH values used for the 1H NMR and microcalorimetric titration experiments were well removed from the pK values at which protonation of the guests occurs. Thus, the complication of having more than one species of guest presented in the solutions was avoided. 1H NMR spectra were recorded on a Bruker Avance 500 spectrometer at 25°C using D_2O as the solvent. The pD values of the solutions in the NMR experiments were determined to be about 6.7. Under the current conditions, the nitrogen atoms in the bipyridine guests will not be protonated. Chemical shifts are reported as parts per million (ppm) downfield from the signal of Me_4Si as internal standard for 1H NMR spectroscopy. High-resolution matrix-assisted laser desorption/ ionization spectra (HR-MALDI) were measured on an AppliedBiosystems DE-STR MALDI time-of-flight mass spectrometer. The reported molecular mass (m/z) values were the most abundant monoisotopic mass. An isothermal calorimeter (MicroCal Inc., Model No.: VP-ITC) was used for all microcalorimetric experiments (pH 7.0). All solutions were degassed and thermostatted using a ThermoVac accessory prior to the titration experiments. The X-ray intensity data were collected on a Bruker Smart 1000 CCD-based diffractometer at T = 100 (2) K. The structures were solved by using the direct method and refined, employing full-matrix least squares on F^2 (Siemens, SHELXTL).

Syntheses

Inclusion Complex 1 of β-CD with 4,4'-Vinylenedipyridine: An ethanolic solution (10 mL) of 4,4'-vinylenedipyridine (0.18 g, 1 mmol) was added dropwise to an aqueous solution (40 mL) of β-CD (1.13 g, 1 mmol) and the mixture was stirred at 50°C for 5 h. The solution was cooled to room temperature, and the precipitate which formed was filtrated and washed with H_2O. The product was dried in vacuo to give a colorless powder. Inclusion complex 1 (1.02 g, 78%). 1H NMR (500 MHz, D_2O, TMS): δ = 3.46–3.50 (m, 7H), 7.35–7.36 (m, 7H), 3.65–3.68 (m, 7H), 3.75–3.82 (m, 21H), 4.96–4.97 (d, 7H), 7.26 (s, 2H), 7.47–7.48 (d, 4H), 8.42–8.43 ppm (d, 4H); MS (HR-MALDI): calcld for C_{54}H_{80}O_{35}N_{2} M/z = 1317.2054, found m/z = 1316.2837 [M^+].

Inclusion Complex 2 of β-CD with 2,2'-Vinylenedipyridine: The colorless inclusion compound 2 (0.97 g, 74%) was prepared from β-CD (1.13 g, 1 mmol) and 2,2'-vinylenedipyridine (0.18 g, 1 mmol), employing procedures similar to those described above. 1H NMR (500 MHz, D_2O, TMS): δ = 3.34–3.48 (m, 7H), 3.51–3.54 (m, 7H), 3.71–3.77 (m, 21H), 3.81–3.85 (m, 7H), 4.94–4.95 (d, 7H), 7.25–7.29 (m, 2H), 7.43 (s, 2H), 7.58–7.59 (d, 2H), 7.77–7.80 (m, 2H), 8.42–8.43 ppm (d, 2H); MS (HR-MALDI): Calcld for C_{54}H_{82}O_{35}N_{2} M/z = 1317.2054, found m/z = 1316.3521 [M^+].

Inclusion Complex 3 of β-CD with 1-(2-Pyridyl)-2-(4-pyridyl)ethylene: The yellowish inclusion complex 3 (0.89 g, 68%) was prepared from β-CD (1.13 g, 1 mmol) and 1-(2-pyridyl)-2-(4-pyridyl)ethylene (0.18 g, 1 mmol), employing procedures similar to those described above. 1H NMR [500 MHz, D_2O, TMS]: δ = 3.41–3.51 (m, 14H), 3.64–3.79 (m, 21H), 4.91–4.92 (d, 7H), 7.22–7.24 (m, 1H), 7.30–7.31 (d, 2H), 7.46–7.47 (d, 2H), 7.50–7.51 (d, 1H), 7.72–7.75 (m, 1H), 8.37–8.39 ppm (m, 3H); MS (HR-MALDI): calcld for C_{54}H_{80}O_{34}N_{2} M/z = 1317.2054, found m/z = 1316.2469 [M^+].

Inclusion Complex 4 of β-CD with 4,4'-Ethylenedipyridine: The colorless inclusion compound 4 (1.06 g, 81%) was prepared from β-CD (1.13 g, 1 mmol) and 4,4'-ethylenedipyridine (0.18 g, 1 mmol), employing procedures similar to those described above. 1H NMR [500 MHz, D_2O, TMS]: δ = 2.98 (s, 4H), 3.43–3.53 (m, 21H), 3.66–3.73 (m, 42H), 4.92–4.93 (d, 7H), 7.04–7.05 (d, 4H), 8.23–8.24 ppm (d, 4H); MS (HR-MALDI): calcld for C_{65}H_{104}O_{34}N_{4} M/z = 1319.2213, found m/z = 1318.4428 [M^+].
Inclusion Behavior of β-Cyclodextrin with Bipyridine Molecules

Inclusion Complex 5 of β-CD with 4,4′-Dithiodipyridine: The colorless inclusion complex 5 (1.00 g, 74%) was prepared from β-CD (1.13 g, 1 mmol) and 4,4′-dithiodipyridine (0.22 g, 1 mmol), employing procedures similar to those described above. 1H NMR (500 MHz, D2O, TMS): δ = 3.42–3.53 (m, 21H), 3.64–3.67 (m, 21H), 4.10–4.19 (d, 2H), 7.28–7.39 (d, 4H), 8.30–8.33 ppm (d, 4H); MS (HR-MALDI): calcd for C20H32O8N4Ss, m/z = 353.2981, found m/z = 354.3167 [M+].

Inclusion Complex 6 of β-CD with 2,2′-Dithiodipyridine: The colorless inclusion complex 6 (0.97 g, 72%) was prepared from β-CD (1.13 g, 1 mmol) and 2,2′-dithiodipyridine (0.22 g, 1 mmol), employing procedures similar to those described above. 1H NMR (500 MHz, D2O, TMS): δ = 3.42–3.46 (m, 7H), 3.49–3.51 (m, 7H), 3.64–3.69 (m, 21H), 3.77–3.81 (m, 7H), 4.10–4.15 (m, 7H), 7.20–7.21 (d, 2H), 7.50–7.52 (d, 2H), 7.63–7.66 (m, 2H), 8.19–8.30 ppm (d, 2H); MS (HR-MALDI): calcd for C18H24O6N4Ss, m/z = 355.2981, found m/z = 354.3353 [M+].

Preparation and Data Collection of Crystals 1-6: A powdered sample of the complex was dissolved in hot H2O to make a saturated solution, which was then cooled to room temperature. After removing any precipitate by filtration, a small amount of H2O was added to the filtrate. The resultant solution was kept at room temperature for several days. Crystals were collected for X-ray crystallographic analyses. The crystal data, experimental and refinement parameters for the complexes 1-6 are shown in Table 2. Because of the occurrence of many disordered H2O molecules in the crystals, some of the oxygen atoms in these disordered H2O molecules did not give reasonable O-H bond lengths. For the β-CD and guests, all non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed at idealized positions in a riding model. CCDC 610479 for 1, CCDC 629367 for 2, CCDC 629365 for 3, CCDC 610480 for 4, CCDC 629365 for 5, CCDC 629364 for 6, and CCDC 629366 for 4,4′-vinyleneDipyridine contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

General Methods
Job Plots: Typically, the total concentrations of guest and β-CD were maintained at 1.0 × 10−3 mol dm−3 in D2O, while the molar ratios of guest and β-CD were varied from 1:0 to 0:1 in steps of 0.1. The 1H NMR spectra of the samples were recorded at 25°C. The Job plots were drawn based on the induced chemical shifts of the observed protons in the guest and β-CD, respectively.

1H NMR Titration Experiments: Typically, a sample of guest (host) was dissolved in D2O (generally concentrations of about 0.5–1.0 × 10−3 mol dm−3 were used). A portion of this solution was used as guest (host) NMR sample, and the remainder was used to dissolve a sample of the host (guest), so that the guest (host) concentration remained constant throughout the titration. Successive aliquots of the host (guest) solution (about 0–2.0 × 10−3 mol dm−3) were added to the guest (host) NMR sample, and 1H NMR spectra were recorded after each addition at 25°C.

Microcalorimetric Titration: The microcalorimetric titrations were performed using an isothermal titration microcalorimeter at atmospheric pressure and 25°C in aqueous phosphate buffer solution (pH 7.0). In each run, a buffer solution of the β-CD host in a 0.250 mL syringe was sequentially injected with stirring at 300 rpm into a buffer solution of the guest in the sample cell (1.4 mL volume). Each titration experiment was comprised of 30 successive injections. A control experiment was performed to determine the heat of dilution by injecting a host buffer solution into a pure buffer solution, containing no guest. The dilution enthalpy was subtracted from the apparent enthalpy obtained in each titration run, and the net reaction enthalpy was analyzed by using the “one-set-of-binding-sites” model. The Origin software (Microcal) was used to determine simultaneously the complex formation constant (Kc) and reaction entropy (ΔS) with the standard derivation on the basis of the scatter of data points from a single titration experiment. Two independent titration experiments were performed to afford self-consistent parameters and give the averaged values.

Acknowledgements
We thank Dr. Ru-Qiang Zou at Los Alamos National Laboratory for his kind help in refining the crystal structures. This work was supported by the Microelectronics Advanced Research Corporation (MARCO) and its Focus Center Research Program (FCRP), the Center on Functional Nanotechnology (FENA), as well as the Center for Nanoscale Innovation for Defense (CNID).


[44] Crystal data for 4,4'-vinylendi(pyridine): C12H10N2·H2O; m = 200.24; orthorhombic; space group: Pna21; unit cell dimensions: a = 9.1735 (8), b = 14.7709 (14), c = 7.6115 (7) Å; V = 1031.36 (16) Å3; α = 90, β = 90, γ = 90; Z = 4; R = 0.0793; λ (MoKα) = 0.084 mm–1; R = (I > 2σ(I)) = 0.0288; wR2 (all data) = 0.0793.


