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Synthesis and Self-Inclusion of Bipyridine-Spaced Cyclodextrin Dimers

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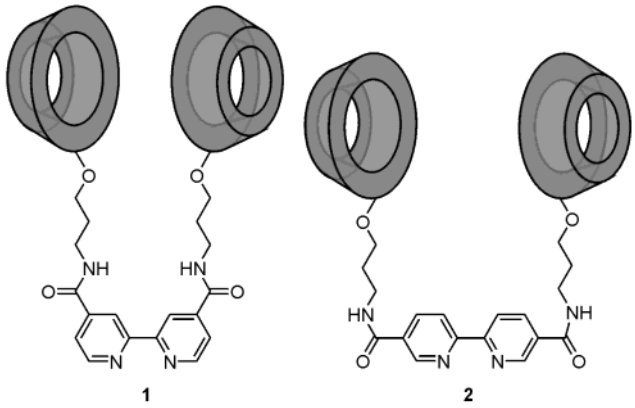
Received February 27, 2002

The synthesis and conformational behavior of two cyclodextrin dimers containing aromatic bipyridine spacers is presented. The proton NMR spectra of these dimers in aqueous solution show a doubling of signals in the aromatic region due to complete or partial self-inclusion of the spacer. The degree and the strength of self-inclusion is dependent on the substitution pattern of the bipyridine unit. This unexpected difference in the self-inclusion behavior is revealed by 2D NOESY and circular dichroism spectra.

Introduction

Cyclodextrins (CDs) are cyclic oligomers of 6, 7, or 8 α-D-glucose units, named α-, *β*-, and *γ*-cyclodextrin, respectively. Over the years CDs have proven to be very efficient host molecules for the binding of a large number of organic guest molecules in aqueous solution.[1] This makes them very interesting candidates for use as receptor molecules in, for instance, sensor devices.[2] Selectivity is an important issue for this application, however, and monomeric cyclodextrin hosts are usually not very selective in their choice of guest molecules.[3] Connecting two cyclodextrins via a spacer results in dimers, which have the advantage of possessing two binding sites in one molecule. As a result, cooperative interactions between the two cavities may occur, leading to significantly higher binding constants compared to the monomeric species.[4] The binding of ditopic guests, i.e. molecules which possess two moieties each of which can be bound by a cyclodextrin, can be expected to be favored over the binding of monotopic ones. This provides a tool to increase the selectivity of a potential sensor for ditopic guest molecules. Recently, it was reported that a cyclodextrin dimer with an appending fluorophore in the spacer indeed shows markedly enhanced binding of ditopic steroids compared to a monomeric analogue.[5] To make the binding of cyclodextrin dimers even more selective one can think of introducing additional recognition sites in the spacer. Inoue and co-workers have synthesized oligoethyleneamine tethered *β*-CD dimers which show an enhanced binding of guests upon coordination of Cu^{2+} ions.[6] A similar effect was described by the same group for selenium-bridged dimers which bind platinum ions in their spacer.[7]

CHART 1



Attractive building blocks in this respect are bipyridines which can coordinate to a variety of metal ions, and in fact this property has been used to mimic the action of esterases.[8] Recently, Liu et al. have studied the recognition behavior of bipyridine-spaced cyclodextrins connected through their primary sides and they have shown that the introduction of metal ions has a marked effect on the binding properties of these dimers.[9,10] We have previously reported on the synthesis and binding behavior of cyclodextrin dimers connected at their secondary rims through alkyl and bipyridine (bpy) spacers.[11−14] Complexation of guest molecules usually takes place via

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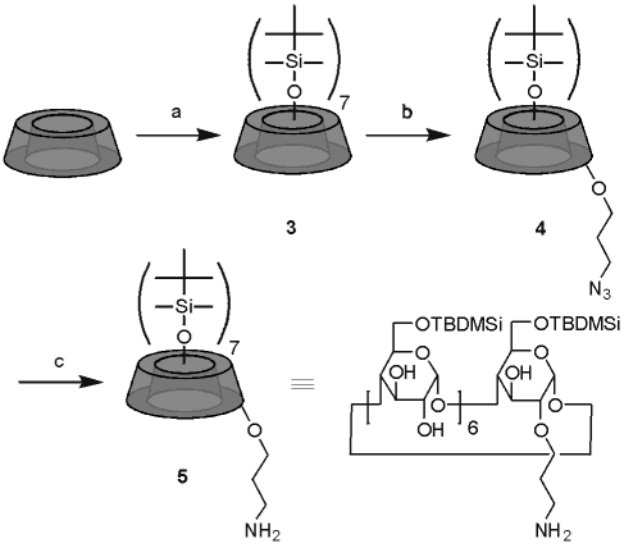
10.1021/jo0256641 CCC: $22.00
Published on Web 07/20/2002

SCHEME 1[a]



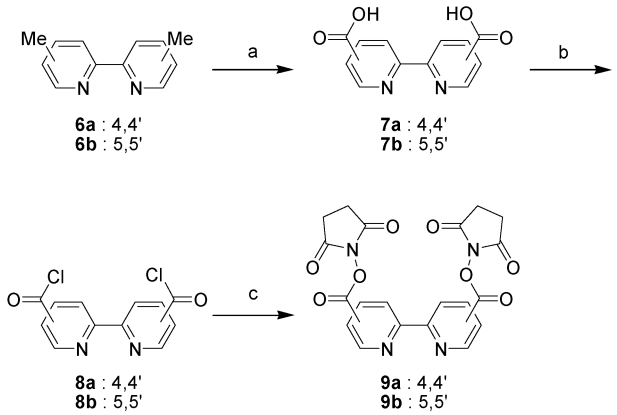
[a] Conditions: (a) TBDMSiCl, pyridine. (b) *i*, NaH, THF; *ii*, 3-azidopropyl tosylate, THF. (c) H_2, $Pd(OH)_2$, MeOH.

the broader secondary side and it has been shown that dimers connected via this side display higher binding affinities.[15,16] It offers advantages, therefore, to connect the cyclodextrins of a dimer through this side, even though this is synthetically more difficult. These dimers display self-inclusion of their spacer into one of the cyclodextrin cavities in aqueous solution and this affects the binding behavior, since one binding site is partly blocked. In this paper we describe the synthesis of two related bpy-bridged dimers, **1** and **2**, and present evidence for the self-inclusion of the spacer in these dimers on the basis of NMR and circular dichroism spectra. One of the dimers (**1**) has previously been used for the construction of a sensor with switch-on signaling behavior for steroids.[17]

Results and Discussion

The synthesis of dimer **1** has already been briefly described in a previous paper.[17] Dimer **2** was synthesized following the same strategy as reported by us before for a related bpy-spaced dimer,[14,17] but with slightly different conditions. The synthetic route toward **2** requires the preparation of a monofunctionalized cyclodextrin, containing a propylamine group on one of its C2-OH groups (Scheme 1). This can be achieved by using the well-known route via a cyclodextrin intermediate that has *tert*-butyldimethylsilyl (TBDMSi) protecting groups on its primary C6-OH functions.[18]

SCHEME 2[a]



[a] Conditions: (a) $KMnO_4$, H_2O, Δ; (b) $SOCl_2$; (c) NHS, Et_3N, CH_3CN.

β-Cyclodextrin was converted into **3** by reaction with TBDMSiCl in pyridine (yield 79%). In the next step the C2-OH groups of this compound, which are more acidic than the C3-OH groups, were selectively deprotonated with NaH and reacted with 1-azido-3-tosyloxypropane.[19] This reaction gives a statistical mixture of nonreacted and singly and doubly reacted species, which was separated by column chromatography (yield 20%). The resulting azide (**4**) was reduced to the corresponding amine by catalytic hydrogenation (yield 100%).

Synthesis of the spacer groups started with the oxidation of 4,4′- and 5,5′-dimethyl-2,2′-bipyridine to their corresponding diacids **7a**,**b** (yield 75% in both cases, Scheme 2). These compounds were converted to the diacid chlorides **8a**,**b**, which were not isolated but directly reacted with *N*-hydroxysuccinimide (NHS) in acetonitrile to yield the diactive esters **9a**,**b** (yield 54 and 56%, respectively). This procedure gives increased yields compared to the route with the potassium salt of NHS and dichloromethane as the solvent, described by us previously.[14]

Coupling of the monofunctionalized cyclodextrin **5** with the diactivated esters resulted in the protected cyclodextrin dimers **10a**,**b** (yield 63 and 48%, respectively, Scheme 3). Deprotection of the silyl groups with tetrabutylammonium fluoride (TBAF) led to the desired water-soluble dimers **1** and **2** in yields of 57 and 41%, respectively.

The self-inclusion of the spacers in compounds **1** and **2** was studied by 500-MHz proton NMR. The inclusion process was particularly evident in the aromatic region of the spectra. The bipyridine unit is C_2 symmetric and therefore only three signals are expected. The spectra of compounds **1** and **2** in DMSO-d_6 indeed showed these three peaks, with the correct multiplicity (Figure 1). Additional signals were observed for the amide protons at 9.02 and 8.84 ppm, respectively. In the anomeric region (4.8−5.2 ppm, not shown) two peaks were observed

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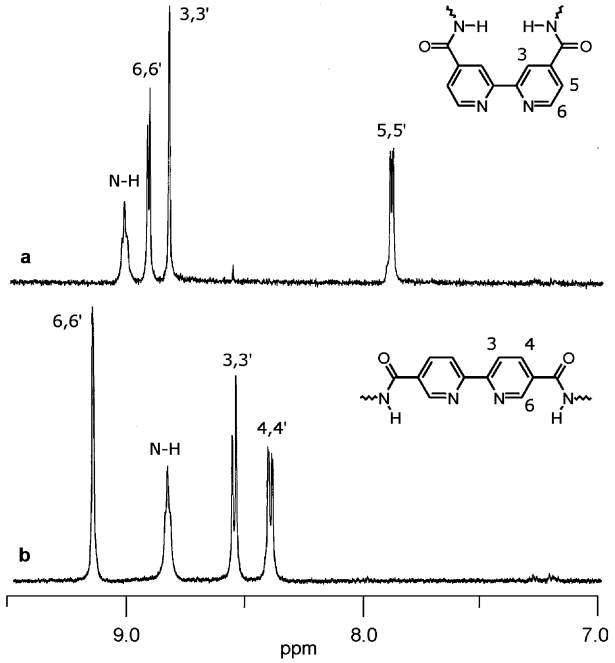
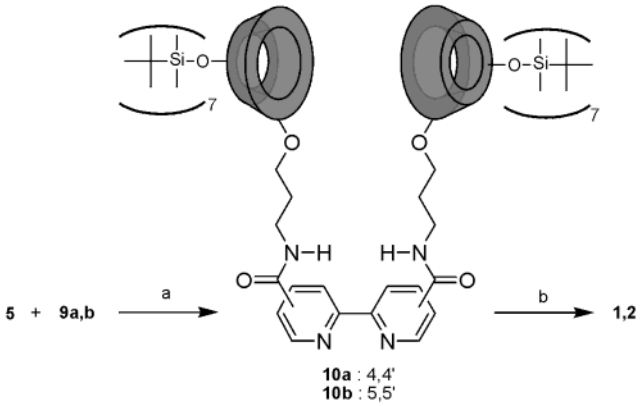


FIGURE 1. Aromatic region of the 500-MHz proton spectra of dimers **1** (a) and **2** (b) recorded in DMSO-d_6 at 25 °C.

SCHEME 3[a]



[a] Conditions: (a) Et_3N, THF. (b) TBAF, THF.

in the ratio 2:12, reflecting the monofunctionalization of the cyclodextrins at their secondary sides, which gives rise to a downfield shift of the anomeric protons of the modified glucopyranose units.[18]

The spectra of compounds **1** and **2** in D_2O showed a different picture (Figure 2). In the aromatic region of **1** six signals were observed, instead of the expected three, all with the same intensity. The number of peaks in the anomeric region had also increased, viz. from 2, to a total of 5 separated peaks in the ratio 1:1:1:1:10. Apparently, the dimer had lost its C_2 symmetry in aqueous solution, which can be explained by assuming that part of the aromatic spacer is self-included into the cyclodextrin cavities.[20] In D_2O solution hydrophobic effects provide a driving force for this process. In DMSO-d_6, however, this force is absent and the symmetric structure is adopted.

(20) Intermolecular inclusion of the bipyridine moiety of one dimer into the cavity of another dimer might also explain this behavior. However, CPK models indicate that this is not possible.

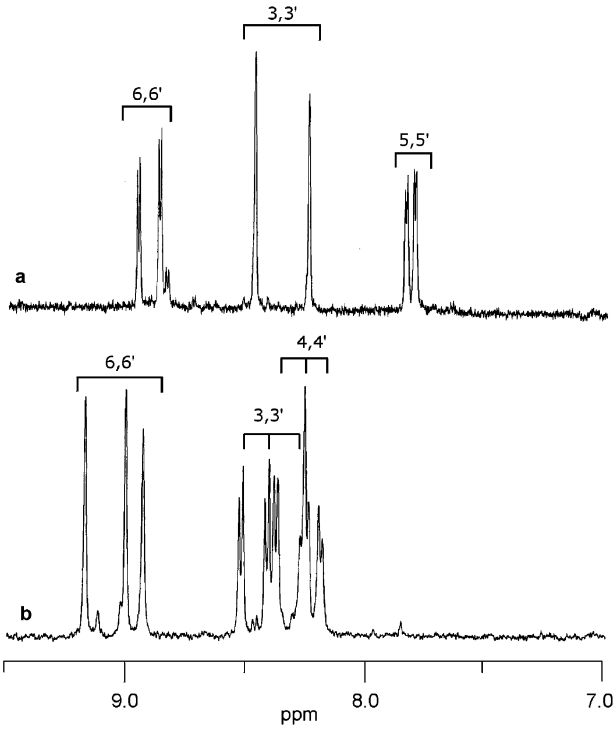


FIGURE 2. Aromatic region of the 500-MHz proton spectra of dimers **1** (a) and **2** (b) recorded in D_2O at 25 °C (for numbering see Figure 1).

The phenomenon of self-inclusion has been observed before by us,[14] viz. in the case of cyclodextrin dimers with alkyl spacers, and this appears to be a general feature for this type of compounds. Inspection of CPK models for **1** and **2** revealed that the propyl spacers are long and flexible enough to allow self-inclusion of the aromatic groups, despite the rigidity of the bpy moiety and the transoid configuration of the amide bonds.[21]

In the case of the previously reported alkyl-bridged cyclodextrin dimers, the self-inclusion complexes appeared to be extremely stable. Heating up to 90 °C in D_2O or addition of 50% DMSO-d_6 did not break up the structure. Dimer **1**, however, adopts almost completely the C_2-symmetric structure in a DMSO-d_6/D_2O mixture (1:1 v/v), proving that the self-inclusion in this case is much weaker.

The anomeric region of dimer **1** in D_2O was relatively well-resolved and could be used as a starting point for the assignment of all signals of the dimer by 2D NMR techniques.[14,22] Upon monofunctionalization the cyclodextrin itself loses its C_7 symmetry and the nonanomeric region of the spectrum (3.4−4.6 ppm) becomes extremely complex. In our dimers the situation is even more complicated, since due to the self-inclusion the two cyclodextrin units are no longer equivalent. Spectral overlap in the 1D proton and the 2D COSY spectra only

(21) It is of interest to compare our results with those for a cyclodextrin dimer with an *o*-phenantroline spacer linked by ethylene chains where it was concluded that the spacer is sandwiched between the two cyclodextrins. The difference with our present results is likely to be due to the larger size of the aromatic moiety, combined with the shorter alkyl tails. See: Sallas, F.; Marsura, A.; Petot, V.; Pinter, I.; Kovacs, J.; Jicsinszky, L. *Helv. Chim. Acta* **1998**, *81*, 632.

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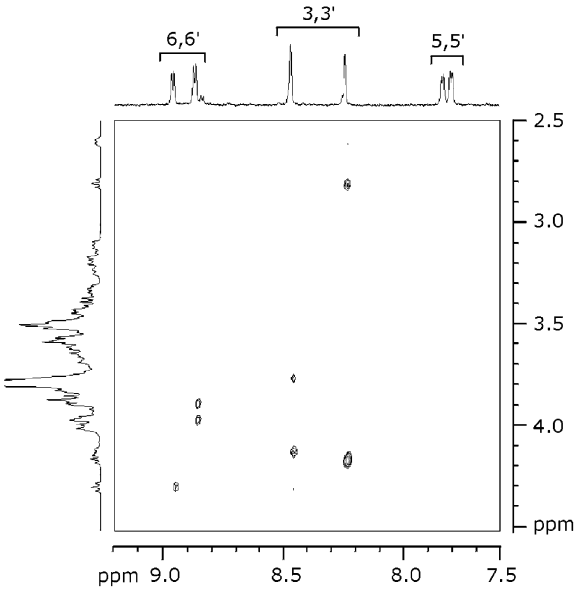

FIGURE 3. Part of the 500-MHz 2D NOESY spectrum of dimer **1** in D_2O at 25 °C (for numbering see Figure 1).

allowed the assignment of H1, H2, and H3 of the glucose moieties that had a resolved H1 signal. The H3 protons are very interesting in this case since they are located at the inside of the cavity and act as spectator protons for the inclusion of guests. [23] They were identified at 4.17, 4.00, 3.98, 3.79, and 2.82 ppm.

In the 2D NOESY spectrum of dimer **1** in D_2O 7 cross-peaks were found between the aromatic protons and the nonanomeric cyclodextrin protons (Figure 3). Further analysis indicated that 5 out of 7 of these cross-peaks were related to H3 cyclodextrin protons, which were identified with the help of COSY experiments (vide supra) which unambiguously show the inclusion of the spacer into the cyclodextrin cavity. Since β-cyclodextrin has seven glucose moieties, the two remaining cross-peaks must be assigned to H3 signals of the other two glucose moieties whose anomeric signals could not be identified due to spectral overlap. Since the H3 protons are located at the secondary side of the cavity, we may conclude that the bipyridine unit enters the cyclodextrin via this side. One of the H3 signals showed a large upfield shift, up to 2.82 ppm. This is probably related to the proximity of the carbonyl moiety of the amide, which is likely to reside in the cavity as well given the fact that the 3,3′-bpy protons also give dipolar interactions with the cyclodextrin protons.

It is interesting to note that no cross-peaks were visible between the 5,5′-protons of the bipyridine unit of **1** and the cyclodextrin protons. Apparently, this bipyridine unit is included with its long axis parallel to the cyclodextrin C_7 axis, rendering the 5,5′-protons in the center of the cavity and too far away to experience dipolar interactions with the cavity protons (conformation I, Figure 4). Another interesting observation is that the aromatic protons show cross-peaks only to one or two neighboring H3 protons, rather than all seven. This implicates a fixed position of the included bpy moiety with no rotational flexibility.

Dimer **2** displayed similar behavior in aqueous solution as **1** (Figure 2b). The aromatic region of the spectrum in

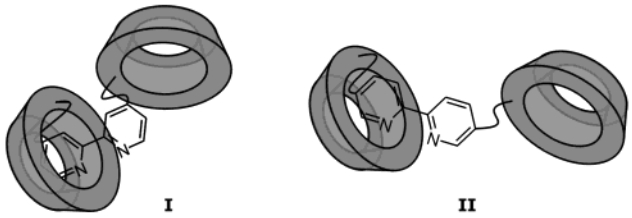

FIGURE 4. Schematic drawings of the proposed structures of the self-inclusion conformer of dimer **1** (I) and dimer **2** (II).

D_2O, however, showed a total of nine signals instead of six. The COSY spectrum (Figure 5a) revealed that these can be divided into two sets, one of 3 signals (8.91, 8.21, and 8.18 ppm) and an other set of 6 signals (9.15, 8.97, 8.53, 8.41, 8.34, and 8.25 ppm). The first set was assigned to the C_2-symmetric, nonincluded structure and the second to the self-included conformer. This assignment could be easily verified with the help of a NOESY spectrum (Figure 5b) that only showed cross-peaks between the cyclodextrin protons and the aromatic protons of the self-included structure. Contrary to **1**, the aromatic protons of compound **2** showed dipolar couplings with more than two H3 cyclodextrin protons, indicating a higher degree of rotational flexibility of the included bipyridine spacer.

Since separate signals were observed, the exchange between the nonincluded and self-included structure must be slow on the NMR time scale, implying that a high kinetic barrier needs to be overcome for the spacer to be released from the cavity. This is surprising, since most reported examples of inclusion of guests in cyclodextrins appear to involve fast processes.[23] From the integrals the ratio of the nonincluded conformer (peak at 8.91 ppm, Figure 2b, representing two protons) and the self-included conformer (peaks at 9.15 and 8.97 ppm, Figure 2b, each representing one proton) was determined to be 1:2. This ratio appeared to decrease, leading to a predominance of the nonincluded conformer at higher temperature (up to 85 °C). This variation was used to determine the thermodynamic parameters for the self-inclusion process: $\Delta H° = -9.0 \pm 0.3$ kcal mol^{-1} and $\Delta S° = -25.8 \pm 0.6$ cal mol^{-1} K^{-1}. The process has a very unfavorable entropy, suggesting the formation of either a rather rigid structure or a structure with many organized water molecules. In view of the dynamic flexibility that is apparent from the multitude of NOE contacts with various CD cavity protons, a structure with organized water appears to be more likely. The dynamic inclusion of the spacer and the presence of organized water apparently do not prevent favorable van der Waals contacts from occurring, as such contacts are the most likely explanation for the favorable enthalpy of inclusion.

The observation that in the case of dimer **2** both conformers are present in solution, whereas in the case of **1** only the self-included species is observed, indicates that the inclusion of the spacer in **1** is stronger than that in **2**. This is probably a steric effect; the connection of the spacer at the 5,5′-positions in **2** is more likely to hinder the entrance of the bipyridine unit in the cyclodextrin cavity than at the 4,4′-positions. Dimer **2** there-

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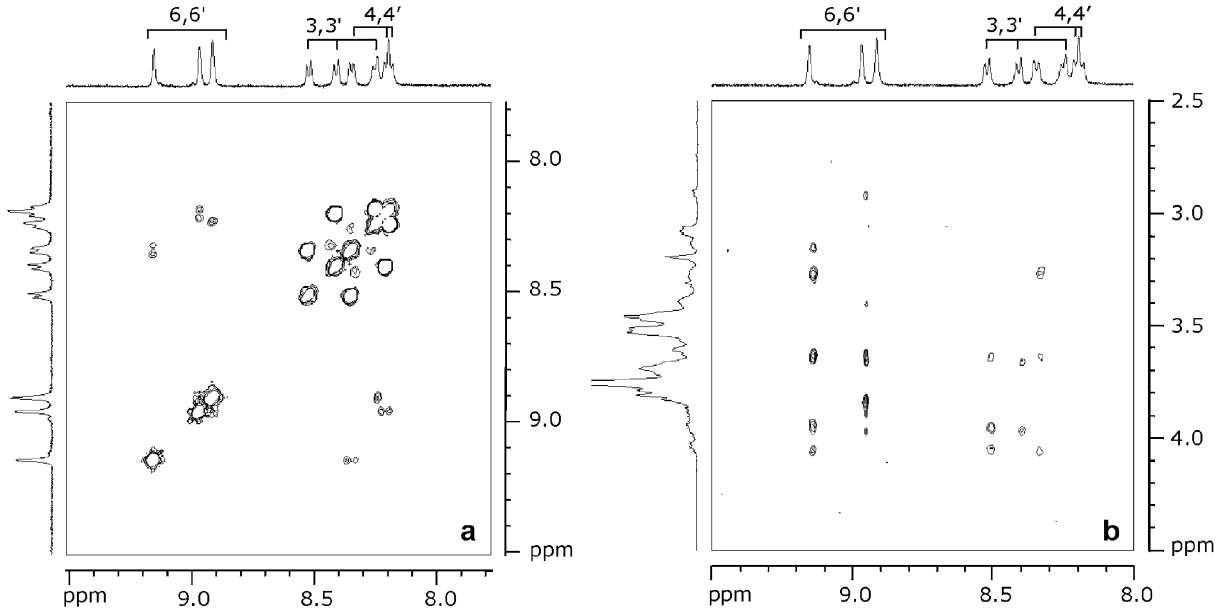

FIGURE 5. Part of the 500-MHz 2D COSY (a) and NOESY (b) spectrum of dimer **2** in D_2O at 25 °C (for numbering see Figure 1).

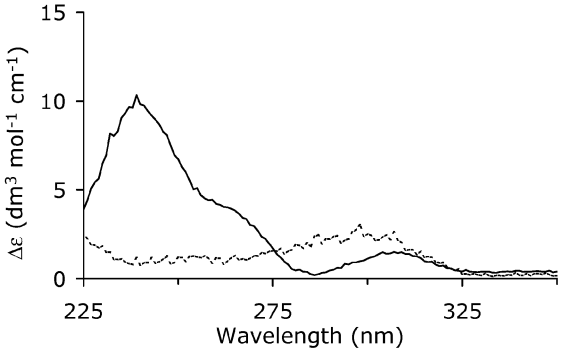

FIGURE 6. Circular dichroism spectra of dimers **1** (full line) and **2** (dashed line) in D_2O at 25 °C, [dimer] = 1×10^{-4} M.

fore presumably adopts a structure similar to conformation II in Figure 4.

Information about the self-inclusion process can also be obtained from circular dichroism studies since the proximity of an achiral chromophoric guest to the cyclodextrin cavity can give rise to induced circular dichroism (ICD).[24] The sign of this ICD signal depends on the orientation of the transition dipole moment of the chromophore with respect to the dipole moment of the cyclodextrin; the latter is directed along the C_7 axis. The generally accepted sector rule[25,26] predicts that electronic transitions parallel to the cyclodextrin axis give a positive ICD signal, whereas perpendicular transitions give a negative signal. For a guest located just outside the cavity this situation is reversed. Parallel transitions give a negative sign, perpendicular transition a positive one.

The ICD spectra of cyclodextrin dimers **1** and **2** in D_2O are presented in Figure 6. As can be seen from this figure, both dimers only give positive Cotton effects. This could either mean that the bipyridine units are self-included with their long axis parallel to the cyclodextrin axis or that they are lying flat on the surface of the cyclodextrin. Since our NOESY experiments indicated self-inclusion we can conclude that the former explanation is the most likely one.

Figure 6 also shows that the ICD signal of **1** is much stronger than that of **2**. Theory predicts[26] that the ICD signal will be at a maximum in the center of the cavity, so a deep self-inclusion will give a stronger signal. The data in Figure 6 support our conclusion from the NMR data that the aromatic spacer of dimer **2** is only shallowly self-included, while that of dimer **1** is much stronger included.

Conclusion

We have demonstrated by a combination of NMR and circular dichroism studies that the spacers of dimers **1** and **2** are included in one of the two cyclodextrin cavities of these molecules. This self-inclusion takes away part of the advantage of having two binding sites in close proximity to each other. If one of the cavities is blocked by the spacer the energy required to remove it will be reflected in a lower binding constant for ditopic guests. This, however, can also be seen in a positive sense, viz. as a tool to introduce selectivity, since only ditopic guests with a sufficiently high binding constant will be able to remove the spacer and take advantage of the second binding site. Others with low binding constants will only show a marginal benefit from the presence of two cavities. As we have shown, a subtle change of the substitution pattern of the bipyridine unit changes the strength of the self-inclusion and this will have a marked effect on the binding affinities toward the guest.

Experimental Section

General. The synthesis of compound **7b** has been reported previously.[14] The compounds 4,4′- and 5,5′-dimethyl-2,2′-bipyridine were purchased from Aldrich. THF was distilled

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from sodium and benzophenone. Ethyl acetate was distilled in vacuo and acetonitrile was distilled from sodium hydride. All other solvents were used as received. Flash column chromatography of cyclodextrin derivatives was performed on silica gel (particle size <0.063 mm). The eluent was a mixture of ethyl acetate, ethanol, and water, 50:2:1 (v/v). Addition of 0.4% toluene to this eluent gave a much better separation, presumably because of inclusion of the toluene, which expels the appended moiety from the cavity, making the difference between a functionalized and nonfunctionalized cyclodextrin larger. TLC's were taken on precoated silica gel 60 F_{254} on glass plates (Merck). Compounds containing cyclodextrins were detected by spraying with a 10% H_2SO_4 solution in ethanol followed by heating. Circular dichroism spectra were taken at 25 °C in a standard quartz cuvette (2 × 10 × 45 mm). The cyclodextrin-containing products showed no melting points, but degraded at approximately 300 °C.

***N,N′*-Bis[mono(2-*O*-(3-aminopropyl)-*β*-CD]-4,4′-dicarboxamide-2,2′-bipyridine (1).** The synthesis of this compound has already been briefly described in a previous paper.[17] In 15 mL of THF was dissolved 210 mg (0.05 mmol) of **10a** and 1.0 mL of a 1.0 M solution of tetrabutylammonium fluoride (TBAF) in THF was added. This solution was refluxed for 18 h after which the solvent was evaporated. The residue was dissolved in a minimum amount of water and added dropwise to ethanol (analytical grade). The resulting precipitate was isolated by centrifugation. Repeating this procedure twice afforded the pure dimer. Yield: 78 mg (0.03 mmol, 57%). IR (KBr): ν 1664 and 1540 cm^{-1} (amide I and II). ^1H NMR (500 MHz, DMSO-d_6): δ 9.02 (br t, 2H; N*H*), 8.91 (d, ^3J(H,H) = 4.9 Hz, 2H; bpy-*H*-6,6′), 8.89 (s, 2H; bpy-*H*-3,3′), 7.88 (d, ^3J(H,H) = 4.9 Hz, 2H; bpy-*H*-5,5′), 5.07 (br s, 2H; *H*-1_A), 4.87 (br s, 12H; *H*-1_{B-G}), 3.92−3.19 (m, 92H; *H*-2, *H*-3, *H*-4, *H*-5, *H*-6, C*H*$_2$−NH, C*H*$_2$−O), 1.88 (br quasi qui, 4H; C*H*$_2$−CH$_2$−NH). MS (FAB, glycerol, *m*/*z*): 2592 $[M + 2H]^+$. Anal. Calcd for $C_{102}H_{158}N_4O_{72}$·16H_2O: C 42.51, H 6.65, N 1.95. Found: C 42.25, H 6.19, N 2.06.

***N,N′*-Bis[mono(2-*O*-(3-aminopropyl)-*β*-CD]-5,5′-dicarboxamide-2,2′-bipyridine (2).** This compound was synthesized analogous to **1** from 40 mg of **10b** (9.5 μmol) and 0.15 mL of a 1 M TBAF solution in THF. Yield: 10 mg (3.9 μmol, 41%). ^1H NMR (500 MHz, DMSO-d_6): δ 9.16 (s, 2H; bpy-*H*-6,6′), 8.84 (br t, 2H; N*H*), 8.56 (d, ^3J(H,H) = 8.1 Hz, 2H; bpy-*H*-3,3′), 8.40 (d, ^3J(H,H) = 8.2 Hz, 2H; bpy-*H*-4,4′), 5.06 (br s, 2H; *H*-1_A), 4.87 (br s, 12H; *H*-1_{B-G}), 3.87−3.18 (m, 92H; *H*-2, *H*-3, *H*-4, *H*-5, *H*-6, C*H*$_2$−NH, C*H*$_2$−O), 1.85 (br quasi qui, 4H; C*H*$_2$−CH$_2$−NH). MS (ESI$^+$, H_2O/MeOH, 1:1, v/v, *m*/*z*): 1318 $[M + 2Na]^{2+}$. Anal. Calcd for $C_{102}H_{158}N_4O_{72}$·14H_2O: C 43.05, H 6.54, N 1.97. Found: C 43.28, H 6.24, N 1.86.

Mono(2-*O*-(3-azidopropyl))heptakis(6-*O*-*tert*-butyldimethylsilyl)-*β*-CD (4). A 10-g (5.18 mmol) sample of silylated *β*-cyclodextrin **3** was thoroughly dried in vacuo (0.2 mbar, 80 °C, 5 h) and dissolved in 250 mL of freshly distilled THF in a 500-mL Schlenk tube. After addition of 410 mg (2.1 equiv) of sodium hydride (60% w/w dispersion in mineral oil) the turbid reaction mixture was refluxed for 18 h after which it became homogeneous. To the refluxing solution was added 1.4 g (1.1 equiv) of 3-azidopropyl tosylate and after 4 h the solvent was removed. The residue was taken up in ethyl acetate (250 mL) and washed with water (twice) and brine. The organic layer was dried over $MgSO_4$ and after evaporation of the solvent the crude product was purified by column chromatography (1.5 kg silica). Yield: 2.1 g (1.02 mmol, 20%). In this way also 2 g of pure silylated cyclodextrin **3** could be recovered. IR (KBr): ν 2099 cm^{-1} (N_3). ^1H NMR (500 MHz, $CDCl_3$/CD_3OD, 80:40 v/v): δ 4.86 (d, ^3J(H,H) = 3.3 Hz, 1H; *H*-1), 4.82 (m, 6H; *H*-1), 3.86−3.12 (m, 46H; *H*-2, *H*-3, *H*-4, *H*-5, *H*-6, C*H*$_2$−NH, C*H*$_2$−O), 1.78 (quasi qui, 2H; C*H*$_2$−CH$_2$−NH). MS (FAB, *m*-nitrobenzyl alcohol, *m*/*z*): 2040 [M + Na + H].

Mono(2-*O*-(3-aminopropyl))heptakis(6-*O*-*tert*-butyldimethylsilyl)-*β*-CD (5). Cyclodextrin derivative **4** (560 mg, 0.28 mmol) and a catalytic amount of $Pd(OH)_2$/C were slurried in 50 mL of ethanol. A balloon filled with H_2 gas was attached to the 100-mL flask and the reaction mixture was stirred at ambient temperature for 72 h. The solid $Pd(OH)_2$/C was filtered off and the filtrate was evaporated to dryness to yield the white crystalline product. Yield: 557 mg (0.28 mmol, 100%). ^1H NMR (500 MHz, $CDCl_3$/CD_3OD, 80:40 v/v): δ 4.86 (d, ^3J(H,H) = 3.3 Hz, 1H; *H*-1), 4.82 (m, 6H; *H*-1), 3.89−3.15 (m, 46H; *H*-2, *H*-3, *H*-4, *H*-5, *H*-6, C*H*$_2$−NH, C*H*$_2$−O), 1.79 (quasi qui, 2H; C*H*$_2$−CH$_2$−NH). MS (FAB, *m*-nitrobenzyl alcohol, *m*/*z*): 2035 [M + 2Na].

(2,2′-Bipyridine)-4,4′-dicarboxylic Acid (7a). This compound was synthesized from 4,4′-dimethyl-2,2′-bipyridine (1.5 g, 8.4 mmol) and $KMnO_4$ (8.26 g, 6.2 equiv) according to a procedure described by us before for **7b**.[14] Yield: 1.5 g (6.2 mmol, 75%). IR (KBr): ν 1720 cm^{-1} (C=O). ^1H NMR (300 MHz, D_2O/NaOD): δ 8.65 (d, ^3J(H,H) = 5.1 Hz, 2H; bpy-*H*-6,6′), 8.27 (s, 2H; bpy-*H*-3,3′), 7.74 (dd, ^4J(H,H) = 1.4 Hz, ^3J(H,H) = 5.1 Hz, 2H; bpy-*H*-5,5′).

(2,2′-Bipyridine)-4,4′-dicarboxylic Acid Bis(*N*-hydroxysuccinimide) Ester (9a). The diacid **7a** (500 mg, 2.05 mmol) was added to 20 mL of $SOCl_2$ and the resulting mixture was refluxed for 24 h. The excess $SOCl_2$ was removed in vacuo and 20 mL of freshly distilled acetonitrile was added. Then 481 mg (2.04 equiv) of *N*-hydroxysuccinimide was added and after this 625 μL (2.1 equiv) of Et_3N via a syringe. The reaction mixture became turbid and after 6 h an off-white precipitate was isolated which was washed with acetonitrile. Yield: 484 mg (1.11 mmol, 54%). IR (KBr): ν 1737 cm^{-1} (C=O). ^1H NMR (300 MHz, DMSO-d_6): δ 9.13 (d, ^3J(H,H) = 4.8, 2H; bpy-*H*-6,6′), 8.96 (s, 2H; bpy-*H*-3,3′), 8.16 (d, ^3J(H,H) = 4.6 Hz, 2H; bpy-*H*-5,5′), 2.97 (s, 8H; CH_2).

(2,2′-Bipyridine)-5,5′-dicarboxylic Acid Bis(*N*-hydroxysuccinimide) Ester (9b). This compound was synthesized from **7b** (1.0 gr, 4.10 mmol) in the same way as described for **9a** from **7a**. Yield: 1.0 g (2.29 mmol, 56%). IR (KBr): ν 1734 cm^{-1} (C=O). ^1H NMR (300 MHz, DMSO-d_6): δ 9.44 (s, 2H; bpy-*H*-6,6′), 8.78 (d, ^3J(H,H) = 8.2 Hz, 2H; bpy-*H*-4,4′), 8.74 (d, ^3J(H,H) = 8.4 Hz, 2H; bpy-*H*-3,3′), 2.97 (s, 8H; CH_2).

***N,N′*-Bis[mono(2-*O*-(3-aminopropyl)heptakis(6-*O*-*tert*-butyldimethylsilyl)-*β*-CD]-4,4′-dicarboxamide-2,2′-bipyridine (10a).** A 780-mg (0.39 mmol) sample of **5** was dried in vacuo (0.2 mbar, 80 °C, 2 h) and dissolved in 50 mL of THF in a 100-mL Schlenk tube. After addition of 80 mg (0.45 equiv) of diactive ester **9a** the mixture was refluxed for 18 h. The solvent was evaporated and the residue dissolved in ethyl acetate (100 mL). After being washed with aqueous sodium hydroxide (twice) and brine the organic layer was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography (100 g silica, eluent A). Yield: 520 mg (0.12 mmol, 63%). MS (FAB, *m*-nitrobenzyl alcohol, *m*/*z*): 4213 $[M + Na + 2H]^+$.

***N,N′*-Bis[mono(2-*O*-(3-aminopropyl)-*β*-CD]heptakis(6-*O*-*tert*-butyldimethylsilyl)-5,5′-dicarboxamide-2,2′-bipyridine (10b).** This compound was synthesized from **9b** and **5** as described for **10a** from **9a** and **5**.

Acknowledgment. We thank the Dutch Technology Foundation for financially supporting this research.

JO0256641