Synthesis, Conformation, and Binding Properties of Cyclodextrin Homo- and Heterodimers Connected through Their Secondary Sides

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Abstract: The synthesis of homo- and heterocyclodextrin (CD) dimers, containing two CD moieties that are linked through their secondary sides by aliphatic or 2,2′-bipyridyl spacers is described. In these dimers, the glucose units to which the spacers are linked have been transformed into altrose units. The dimers with an octamethylene spacer show self-complexation of the spacer in one of the CD moieties in aqueous solution, as revealed by ^{1}H and ^{13}C NMR spectroscopy. Using high-resolution (600 and 800 MHz) NMR spectroscopy and a variety of 2D NMR techniques, an assignment of nearly all of the ^{1}H NMR signals of two of the CD dimers was made, affording detailed information about the structure of these compounds in water. The self-inclusion of the spacers leads to lower binding affinities for ditopic guest molecules like *p*-toluidino-6-naphthalene sulfonate (TNS) derivatives and porphyrins. When a rigid 2,2′-bipyridyl group is used to connect the two CD moieties, self-inclusion of the spacer is not possible. This results in the formation of different complexes with ditopic guest molecules, for example, a 2:2 complex with a porphyrin.
The CD heterodimers described in this paper contain an α-CD and a β-CD moiety. These dimers display site-specific binding of guest molecules.

Keywords: cyclodextrins · fluorescence spectroscopy · inclusion compounds · NMR spectroscopy · site-specific binding

Introduction

There is currently great interest in cyclodextrins (CDs) that are covalently linked by flexible or rigid spacer molecules.[1] Because of favorable cooperative binding effects, such dimers are found to display high affinities for organic guest molecules. For instance, by using CD dimers connected through their primary sides, Breslow and Chung[1g] were able to achieve binding constants as high as $10^{10}\,\text{M}^{-1}$ for certain types of ditopic guests. This association is nearly as strong as that between antigens and antibodies. CD dimers offer interesting possibilities in the field of catalysis, because they can immobilize a substrate in a well defined geometry with respect to a catalytically active center.[1h, 1k] Also for developing selective sensor systems CD dimers are of great potential value.[1l, 1m]

The synthesis and properties of CD dimers that are linked through their primary sides are well documented. Few reports, however, have appeared on CD dimers that are connected by their secondary sides. The synthesis of these compounds is more complicated, because selective modification is more difficult to achieve at the secondary side of a CD than at the primary side and, in addition, their purification is more troublesome. A way to overcome this problem is to protect the primary side of CDs by reversible silylation,[2] because the protected compounds can be readily purified by flash chromatography. We recently reported the syntheses of both homo-[3] (**1**, **2**, and **5**) and hetero-CD dimers[4] (**3**, **4**) in pure form, starting from silylated mono-functionalized CD derivatives. In the dimers, the CDs are connected at their secondary faces by flexible aliphatic spacers or by a rigid 2,2′-bipyridyl spacer. In this paper we give a detailed account of the synthesis and characterization of these dimers, including nearly complete assignments of the 600 and 800 MHz ^{1}H NMR spectrum of two of them, and the interpretation of the spectrum in terms of the conformational preference of the particular dimer. In addition, we report on the complexation properties of the dimers as studied by fluorescence spectroscopy.

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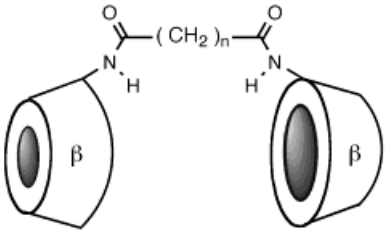

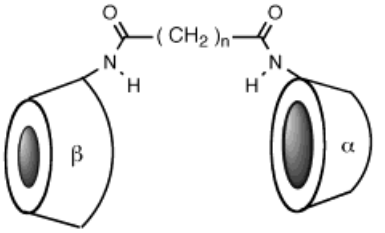

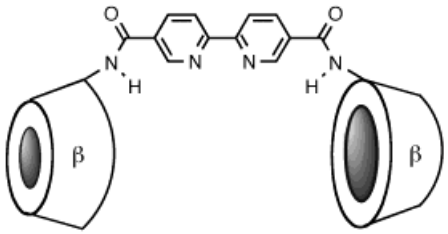

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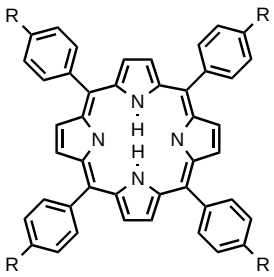
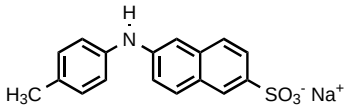
Results and Discussion

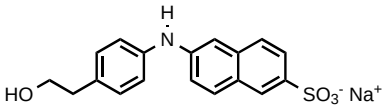
Synthesis and characterization: The syntheses of the homo-CD dimers **1**, **2**, and **5**, and those of the hetero-CD dimers **3** and **4** have been outlined in preliminary communications.[3, 4] The synthetic routes are summarized in Scheme 1 and Scheme 2 (for synthetic details see the Experimental Section). It should be noted that mono-functionalization as described in these schemes results in the presence of one altrose unit per CD moiety.[5] We found that the use of the dimethylthexylsilyl group for the synthesis of **18** does not have any advantages over the use of the *tert*-butyldimethylsilyl group. We therefore used **18** only for the synthesis of **1**.

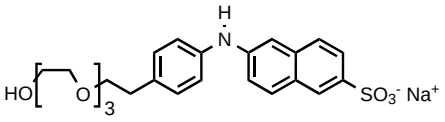
As guest molecules for the binding studies, we used tetrakis(4-benzoic acid)porphyrin (TcPP), tetrakis(4-sulfonatophenyl)porphyrin (TsPP), and *p*-toluidino-6-naphthalene sulfonate (TNS). We also synthesized the guests: 2-(*p*-(2′-hydroxyethyl)anilino)-6-naphthalene sulfonate (**6**) and 2-(*p*-(3′,6′,9′-trioxa-11′-hydroxyundecane)anilino)-6-naphthalene sulfonate (**7**), for which we propose the abbreviations ENS and TENS, respectively .

The fluorescence probe ENS was prepared by a Bucherer reaction[6] from 6-amino-2-naphthalene sulfonic acid and 2-(4′-aminophenyl)ethyl alcohol (Scheme 3). The synthesis of TENS involved four reaction steps (Scheme 3). Monotosylation of triethyleneglycol using NaH as a base gave **34**,[7] which was protected with a triphenylmethyl (Trt) group. The protected compound **35**[7] was allowed to react with the alkoxy anion of 2-(4′-aminophenyl)ethyl alcohol to give **36**, which was deprotected and treated with 6-amino-2-naphthalene sulfonic acid under Bucherer conditions to provide TENS.









NMR studies: The one-dimensional ^{13}C and ^{1}H NMR spectra of compounds **2** and **4** have been described in a preliminary communication.[4] The full assignment of the high-resolution proton spectrum (600 MHz) of **2** was published by us recently.[8] In order to allow a proper discussion of the present high-resolution (800 MHz) 2D NMR study of dimer **4**, the most important results are summarized here. Mono-functionalization of cyclodextrins breaks up the C_7 symmetry, thus making the NMR spectra extremely complicated.[9] The behavior of dimer **2** is illustrated by the ^{13}C NMR spectra in [D_6]DMSO and in D_2O (Figure 1a and b).

When dissolved in D_2O, this compound shows eight signals for the octamethylene spacer in the region of $\delta = 20-40$, while a priori only four signals are expected for these carbon atoms as a result of the symmetry in the molecule (Figure 2a). Also the CD carbon atom, which resonates at $\delta = 52$ (C-3′, next to the amide bond), and the carbonyl atom of the spacer ($\delta = 177$, not shown) appear as two signals instead of one. The proton spectrum of **2** in D_2O also displays twice as many signals as expected for the spacer group (Figure 1d).

We propose that this doubling of signals is the result of the presence of two conformations in solution, in which the alkyl chain is complexed by either one of the cavities as is shown in Figure 2b and c. The complexation of alkyl chains by cyclodextrins is known to be an energetically favorable process.[10]

In an attempt to break down this self-inclusion complex, we increased the temperature of the aqueous solution. Also an equal volume of [D_6]DMSO was added to the D_2O solution to break any possible hydrogen bonds present. Neither of these experiments resulted in a substantial change in the proton spectrum. The interpretation could be that the two conformers do not exchange on the NMR timescale, but since the conformers of **2** are identical it is difficult to determine

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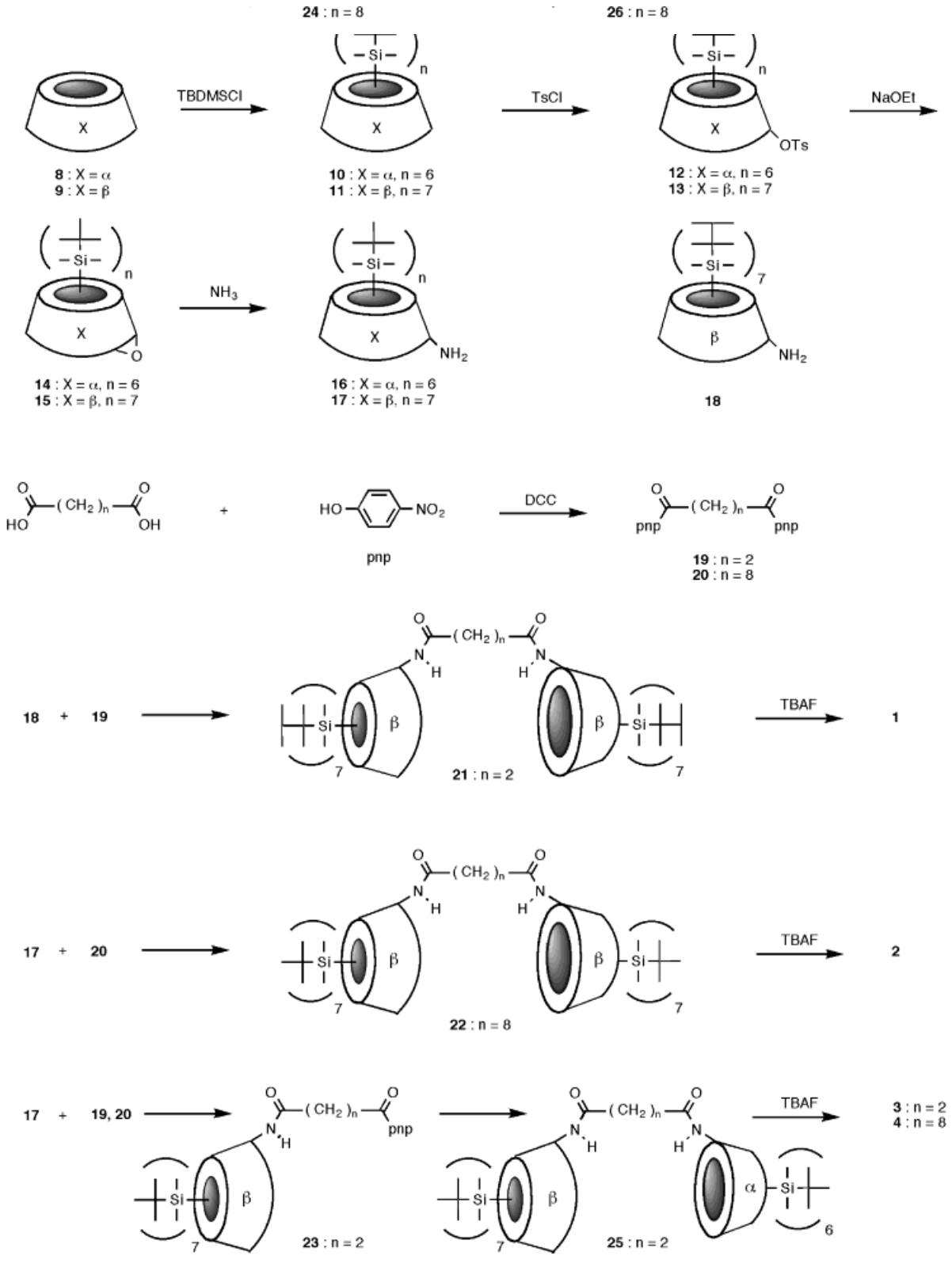
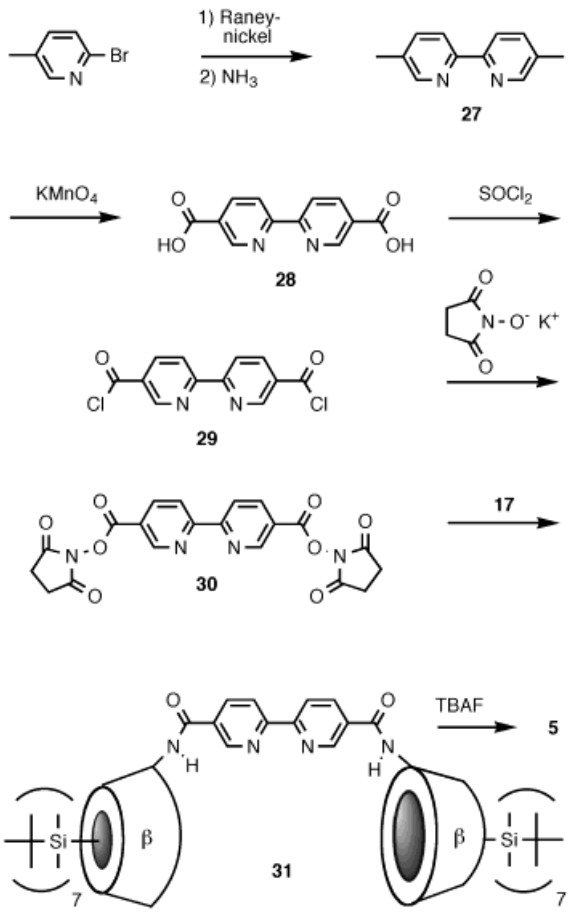
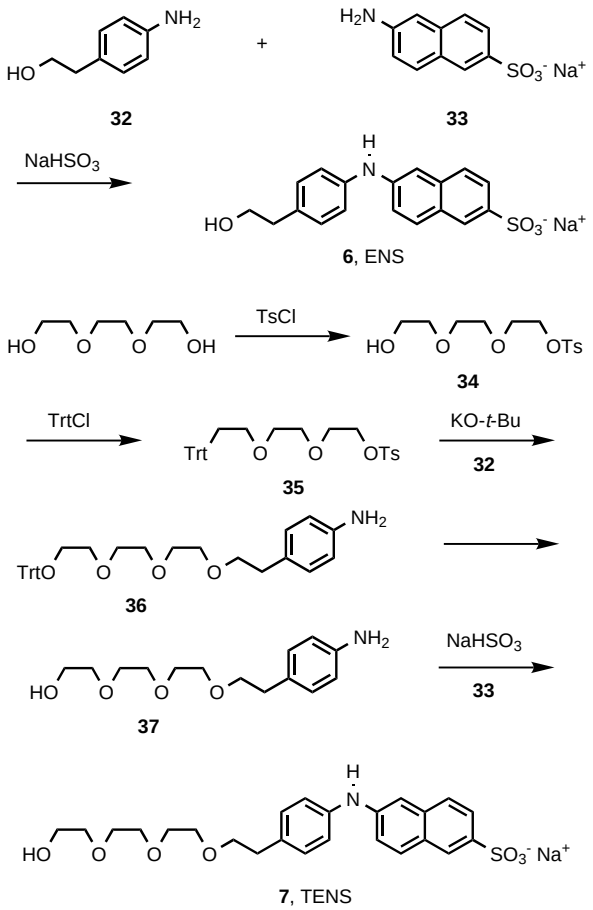


Scheme 1. Synthesis of the homodimers **1** and **2** and the heterodimers **3** and **4**.

whether exchange indeed takes place. No line broadening was observed even at high temperatures, suggesting that exchange, if any, is slow on the NMR timescale. When compound **2** was dissolved in pure [D_6]DMSO, both the ^{13}C and the ^{1}H NMR spectra were simplified (Figure 1). Apparently, the spacer is released in pure DMSO and as a result the symmetric structure (Figure 2a) is obtained. Since the spacer is not released upon heating the samples in D_2O, we can conclude that the conformations in which the alkyl chains are bound in the CD cavities are very stable.



Scheme 2. Synthesis of the 2,2′-bipyridyl dimer **5**.



Scheme 3. Synthesis of ENS and TENS.

The ^{13}C NMR spectrum of the CD heterodimer **4** in D_2O solution shows sixteen signals for the octamethylene spacer in the $\delta = 20-40$ region (spectra shown in ref. [4]). In addition, four signals are observed for the carbon atoms at C-3′ of the altrose units, which contain the spacer and four signals for the carbonyl carbon atoms in the spacer. This multitude of signals can be explained by assuming that the spacer is bound either in an α-CD or in a β-CD cavity, which results in two conformations (Figure 2b and c). These exchange slowly on the NMR timescale. In contrast to dimer **2**, dimer **4** is dissymmetric, and the two conformations are not equivalent, resulting in an extra doubling of the signals observed for compound **4** when compared to **2**. The ^{13}C NMR spectrum of **4** in [D_6]DMSO was recorded and was again in accordance with a structure in which the spacer is released (see structure shown in Figure 2a). Two separate signals remained for both carbon atoms at C-3′ and for the two carbonyl carbon atoms of the spacer group, which are the result of the inherent dissymmetry in the structure of the heterodimer.

The ^{13}C NMR spectrum of **4** in D_2O at 310 K showed another interesting feature, since all signals for corresponding carbon atoms appeared in the same ratio, that is 2:1, supporting the presence of the two proposed conformers. The fact that this ratio was observed for all pairs of carbon atoms indicated that relaxation effects could be ignored. The two carbonyl carbon signals with the highest intensity in the

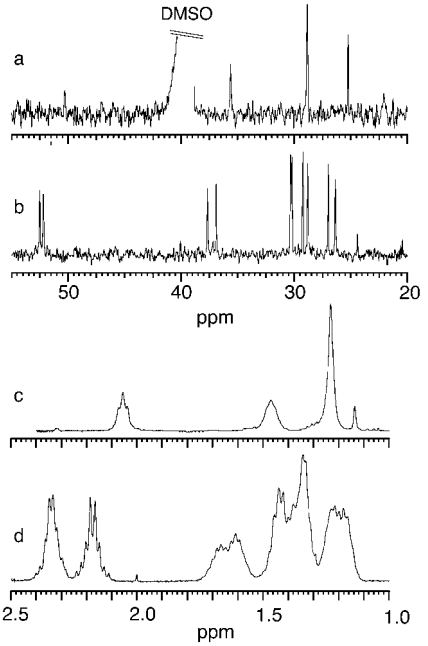


Figure 1. 100 MHz ^{13}C NMR spectrum of **2** in [D_6]DMSO a) and D_2O b) and 400 MHz ^{1}H NMR spectrum of **2** in [D_6]DMSO c) and D_2O d).

^{13}C spectrum of **4** in D_2O, that is those at $\delta = 176.9$ and 177.8, resonated at the same frequency as the carbonyl signals of compound **2** in D_2O ($\delta = 177$). We therefore ascribe these two signals to the conformation in which the alkyl chain is bound

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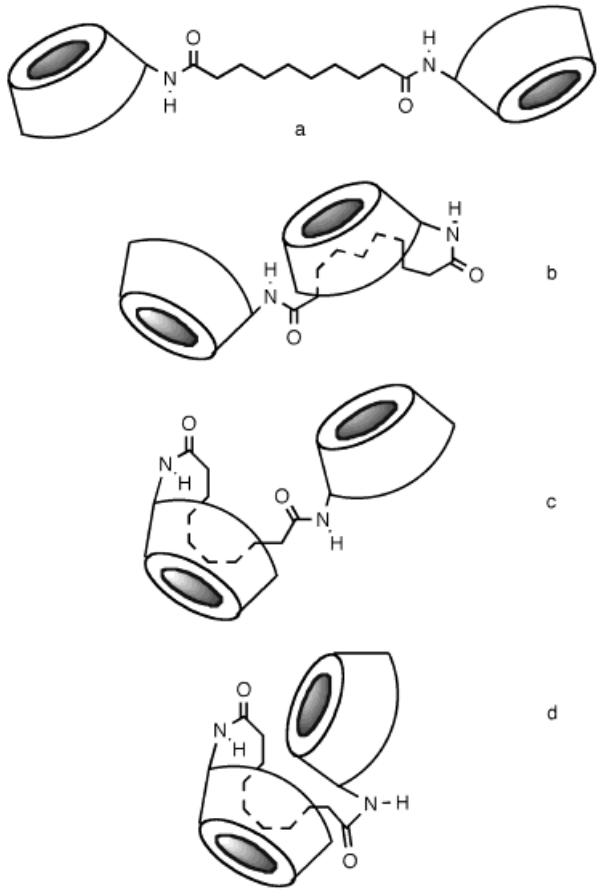


Figure 2. Possible conformations of the cyclodextrin dimers in solution.

in the β-CD unit. Given this assignment, we may conclude that the spacer of compound **4** is included in the β-CD unit for approximately ⅔ of the time and in the α-CD unit for ⅓ of the time.

Since the two conformers of **4** are not identical, in contrast to **2**, the exchange equilibrium between them can be studied by variable-temperature NMR spectroscopy. When the temperature was raised, the exchange equilibrium was found to shift to the β-CD complexed form. This shift could be quantified by integrating the H-2 signals of the altrose units belonging to the α and β-CDs that contain the spacer group. The temperature variation of these ratios was used to construct an Arrhenius plot, from which the thermodynamic parameters of the exchange reaction were calculated: $\Delta H^\circ = 2.7 \pm 0.1$ kcal mol^{-1} and $\Delta S^\circ = 10.1 \pm 0.4$ cal mol^{-1} K^{-1}. The sign of both parameters suggests that the complexation in the β-CD cavity is mainly entropy driven.

The conformation in which the alkyl spacer is included in the CD cavity appeared to be extremely stable in water (vide supra). To exclude other possibilities that could explain the NMR results (like hindered rotation around the amide bonds or chair–chair interconversions of the two altrose residues in the CD units), we decided to assign all proton signals in the ^{1}H NMR spectra of compound **2** in D_2O using high-frequency NMR spectroscopy (600 MHz) and 2D techniques. The complete assignment and the chemical shifts of the protons of **2** were presented by us recently[8] and are summarized in Table 1.

The most interesting results were the variations in the chemical shifts found for the H-3 protons. If the values for the

Table 1. Chemical shifts of protons in the 600 MHz spectrum of compound **2** in D_2O.

Pyranoside unit [a]	H-1	H-2	H-3	H-4	H-5	H-6,6′	N-H
a	4.961	3.785	4.203	3.909	4.273	3.812	8.063
b	4.981	3.664	4.002	3.606	3.939	–	
c	5.149	3.687	3.956	3.598	–	–	
d	5.151	3.703	3.937	3.588	–	–	
e	5.076	3.653	3.977	3.621	–	–	
f	5.047	3.630	3.994	3.597	3.898	-	
g	5.069	3.634	3.934	3.710	3.698	–	
h	4.999	4.146	4.552	4.124	3.952	3.791	7.503
i	5.079	3.516	3.666	3.595	–	3.892	
j	5.070	3.643	3.860	3.600	–	–	
k	5.093	3.666	3.861	3.614	3.700	–	
l	5.095	3.672	3.852	3.626	3.701	3.896	
m	5.085	3.674	3.853	3.662	3.706	3.910	
n	5.104	3.625	3.766	3.688	3.759	3.924	

[a] For the labeling of the pyranoside units of **2**, seen from their primary sides, see Figure 3.

units **a** and **h** (Figure 3) were not considered, the chemical shifts of the H-3 protons of β-CD I were all between $\delta = 4.002$ and 3.934, whereas those of β-CD II were shifted upfield, giving δ values lying between 3.860 and 3.666. This suggests that the C_8 spacer is included in the cavity of β-CD II, and this

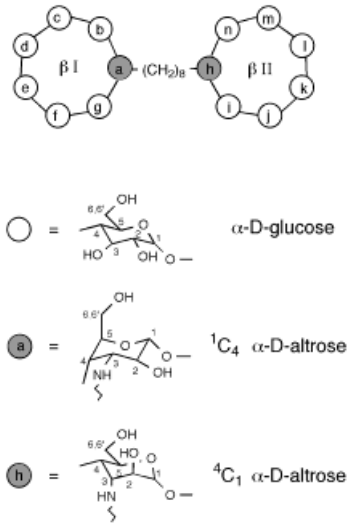


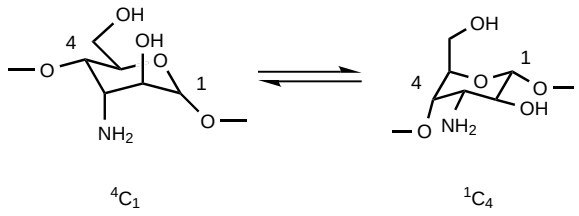
Figure 3. Labeling of the pyranoside units of **2**, seen from the primary side.

was confirmed by off-resonance ROESY experiments, which showed through-space interactions between protons of the spacer group and some H-3 signals of β-CD unit II.

The self-inclusion of the spacer also affected the NH amide signals of the altrose units **a** and **h**, which appeared as two doublets. Since the shifts of amide protons in peptides as a function of temperature can be used as a measure of the degree of exposure of the amide group to the water phase, we decided to determine these temperature coefficients for compound **2** in a mixture of H_2O and D_2O (95:5, v/v). The values were quite different and amounted to -10.1 and -3.4 ppb per K, for NH_a and NH_h, respectively. These numbers indicate that the amide group of β-CD II is either

protected from the solvent or forms a strong intramolecular hydrogen bond. Both explanations are in agreement with the self-inclusion of the spacer in the cavity of β-CD II.

Another interesting observation was the difference in coupling constants found for the altrose units **a** and **h**. For unit **a** the ^3J coupling constants were $J_{12} = 7.2$ Hz, $J_{23} = 10.7$ Hz, $J_{34} = 3.8$ Hz, and $J_{NH,H3=}8.8$ Hz, whereas for unit **h** the values were: $J_{12} = 1.7$ Hz, $J_{23} = 3.2$ Hz, $J_{34} = 4.3$ Hz, $J_{45} = 10.4$ Hz, and $J_{NH,H3} = 9.0$ Hz. The measured coupling constants are in agreement with the following conformations (Figure 4):



$^4C_1$ $^1C_4$

Figure 4. $^4C_1$ and $^1C_4$ conformation of the altrose units.

altrose unit **a** in a $^1C_4$ conformation, and altrose unit **h** in a $^4C_1$ conformation. The coupling constants for the other glucopyranose units were $J_{12} \approx 3.6$ Hz and $J_{23} = 9.7$ Hz, which indicate that these units are in the most stable $^4C_1$ conformation.

In aqueous solution, the conformational free energies of the $^4C_1$ and the $^1C_4$ conformation of α-D-altrose are nearly identical.[11] The observation that the altrose unit **h** in **2** prefers the $^4C_1$ conformation can be explained by inspection of CPK models. The axial position of the spacer substituent in the $^4C_1$ conformation directs the spacer towards the cavity, and thus favors inclusion. This interaction slows down the conformational equilibrium (Figure 4) for altrose unit **h** and shifts it to the $^4C_1$ conformation. The $^1C_4$ conformation of altrose unit **a** might be stabilized by a hydrogen bond between the hydroxyl group at C-2 of the altrose unit and the OH group at C-3 of the adjacent glucose unit.[12] However, there is no experimental evidence to support such a hydrogen bond. An extra indication that the $^4C_1$ conformation of **h** in water is stabilized by the self-inclusion of the spacer is obtained from the coupling constant of the H-1 protons of units **a** and **h** (for both units $J_{12} = 7.1$ Hz) of compound **2** dissolved in [D_6]DMSO. These values show that in this solvent both units **a** and **h** prefer the $^1C_4$ conformation.

Since the self-inclusion of the spacer in compound **2** could be very well studied by high-resolution 2D NMR spectroscopy, we were interested in performing the same type of experiments with the heterodimer **4**. Because of the inherent dissymmetry present in dimer **4,** the 600 MHz proton spectra were even more complicated than those of **2**, and were not very revealing. To obtain better resolved spectra, a 800 MHz NMR spectroscopy study was carried out. Some results are presented in Figure 5.

For the assignment of the proton signals of **4**, the same strategy was used as for **2**.[8] Figure 5a shows the remarkable increase in resolution observed in the indirect dimension of a semi-soft COSY experiment. Homonuclear decoupling during the t_1 evolution decay further improved the resolution of the spectra, as is shown in Figures 5b – d.

The chemical shifts of the protons of **4** in D_2O can be divided into two groups, corresponding to the two conformers present in solution (Figure 2b and c). The chemical shifts of the protons of the conformer with the spacer in the β-CD cavity are collected in Table 2, while Table 3 contains the proton chemical shifts of the conformer with the spacer in the α-CD cavity. If the altrose units (**A**, **H**, **N**, and **U**, Figure 6) are not considered, comparison of the two tables reveals that the

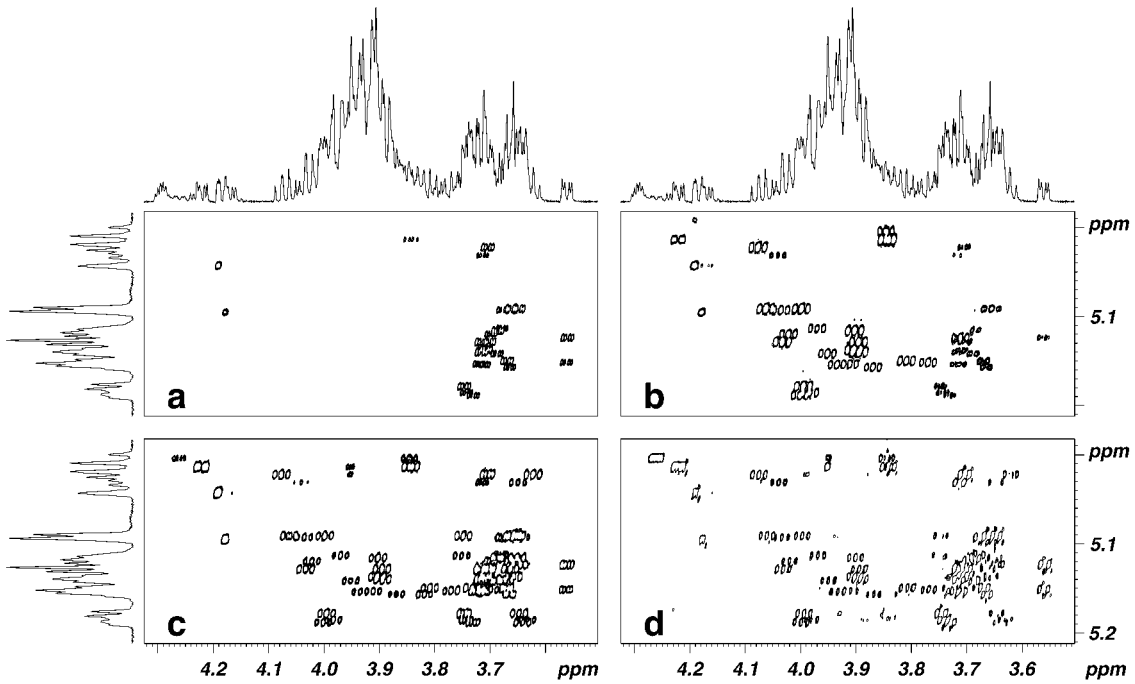


Figure 5. 800 MHz 2D semi-soft ^{1}H NMR spectra of **2** in D_2O with homonuclear decoupling in the indirect dimension; a) COSY spectrum; b) single RELAY; c) double RELAY; d) phase-sensitive TOCSY (MLEV17 composite sequence for mixing, mixing time 70 ms).

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Table 2. Chemical shifts of protons in the 800 MHz spectrum of compound **4** in D_2O. Conformer with the spacer included in the β-CD cavity.

Pyranoside unit [a]	H-1	H-2	H-3	H-4	H-5
A	5.043	4.190	4.592	4.169	–
B	5.124	3.560	3.711	3.640	–
C	5.116	3.686	3.902	3.650	–
D	5.137	3.707	3.903	3.657	–
E	5.142	3.687	3.951	3.670	–
F	5.129	3.701	3.895	3.712	–
G	5.150	3.669	3.808	3.732	–
H	5.014	3.843	4.220	3.952	–
I	5.024	3.704	4.076	3.622	3.988
J	5.179	3.746	3.994	3.647	3.930
K	5.129	3.716	4.033	3.663	–
L	5.092	3.661	3.997	3.657	–
M	5.091	3.648	4.062	3.748	–

[a] For the labeling of the pyranoside units see Figure 6.

Table 3. Chemical shifts of protons in the 800 MHz spectrum of compound **4** in D_2O. Conformer with the spacer included in the α-CD cavity.

Pyranoside unit [a]	H-1	H-2	H-3	H-4	H-5
N	5.004	3.844	4.262	3.951	–
O	5.033	3.713	4.041	3.649	3.968
P	5.186	3.742	3.983	3.632	–
Q	5.189	3.730	4.000	3.641	3.884
R	5.093	3.677	4.035	3.640	–
S	5.120	3.699	4.021	3.658	–
T	5.114	3.677	3.970	3.751	–
U	5.095	4.178	4.623	4.232	–
V	5.152	3.562	3.769	3.711	–
W	5.140	3.716	3.894	3.672	–
X	5.154	3.708	3.934	3.718	–
Y	5.154	3.721	3.911	3.770	–
Z	5.157	3.664	3.869	3.818	–

[a] For the labeling of the pyranoside units see Figure 6.

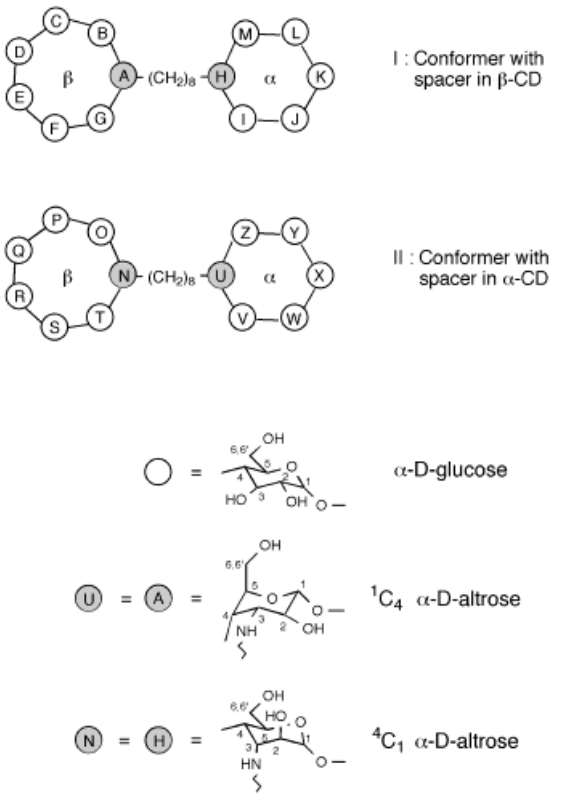

Figure 6. Labeling of the pyranoside units of **4**, seen from the primary side.

chemical shifts of the H-3 signals of the CD units containing the spacer (**B**–**G** and **V**–**Z**) are all below 3.951, whereas those of the empty CDs (**I**–**M** and **O**–**T**) display values higher than $\delta = 3.970$. This upfield shift is attributed to the shielding effect of the included spacer, just as was observed for **2**. The assignment of the filled cavities was supported by recording a ROESY spectrum, which revealed that only H-3 protons of occupied cavities, that is those whose signal is below $\delta = 3.951$, give rise to cross peaks with the aliphatic spacer protons (Figure 7).

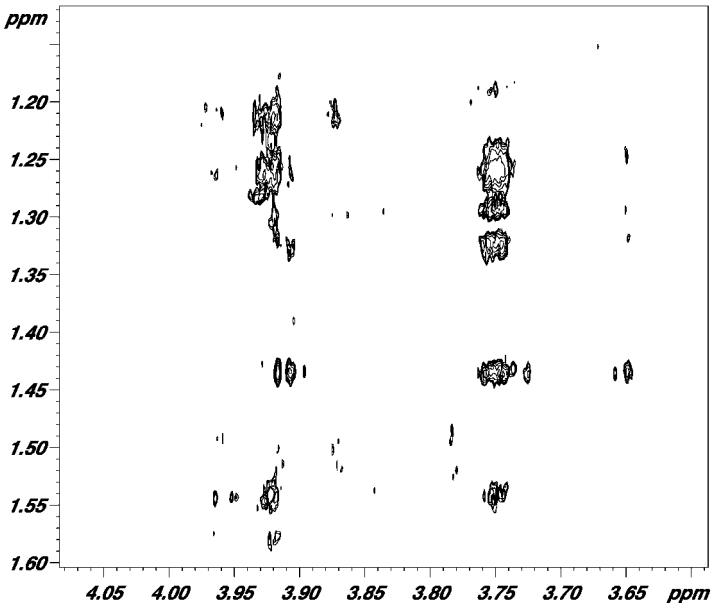

Figure 7. Contour plot of a 800 MHz semi-soft ROESY experiment of **4** in D_2O, showing through-space interactions between the aliphatic protons and the protons of the cyclodextrins. Aliphatic protons were excited by a 270° gaussian pulse for 3.5 ms (their evolution thus created the indirect dimension). Mean spin-lock angle 54.7°, mixing time 100 ms.

A study of the coupling constants of the altrose units showed that units **A** and **U** are in the $^4C_1$ conformation ($J_{12} \pm 1.5$ Hz), whereas units **H** and **N** are in the $^1C_4$ conformation ($J_{12} \pm 6.9$ Hz). This again is in accordance with the observation made for dimer **2**: altrose units of filled CDs are forced into a $^4C_1$ conformation by the inclusion of the spacer.

In the ROESY spectrum, we could also identify cross peaks between spacer protons and the H-4 protons of units **M** and **T**, which belong to empty CD units. Since the H-4 protons are situated at the outside of the cyclodextrin wall, this means that the empty CD is located very close to the spacer group. We, therefore, tentatively propose a structure as depicted in Figure 2d, in which the empty CD forms a cap over the filled CD unit.

Binding studies with fluorescent guests: The binding properties of the homodimers **1** and **2** and the heterodimers **3** and **4** were investigated with the help of the fluorescent guests TNS, ENS, and TENS. Titrations in which the fluorescence intensities were monitored as a function of the concentration of the host molecule, at a fixed concentration of the guest molecule, afforded the binding constants K_b. These constants are summarized in Table 4 together with the observed

Table 4. Binding constants of complexes between fluorescent guests and hosts.[a]

Host	Binding constant [M^{-1}] TNS	ENS	TENS
α-CD	25 ± 10 (453)	25 ± 10 (442)	30 ± 10 (440)
β-CD (1:1)	2100 (459)	2400 (453)	2500 (451)
(2:1)	200 ± 100 (446)	–[b]	–[b]
1	10500 (440)	8000 (434)	6000 (433)
2	6700 (436)	4100 (430)	3800 (430)
3	2800 (453)	3000 (450)	4000 (447)
4	600 (453)	1000 (450)	1400 (448)

[a] Maximum emission wavelength in parentheses. The estimated error in the binding constants is 5% unless indicated otherwise. Excitation wavelengths are 322, 318, and 319 nm for TNS, ENS and TENS, respectively; [guest] $= 1 \times 10^{-5}$ M, [CD] $= 1 \times 10^{-3}$ M, [CD dimer] $= 1 \times 10^{-4}$ M. [b] Not determined.

maximum emission wavelengths λ_{max}. For comparison the K_b values for α-CD and β-CD were also determined.

All guests are bound more tightly by the symmetrical β-CD dimers **1** and **2**, than by monomeric β-CD, which indicates a cooperative binding process in the former CDs. On going from TNS to ENS and then to TENS, the binding constants decrease for CD dimers **1** and **2**. This can be explained by inspecting CPK models of the dimers and the guests. The hydrophobic aromatic regions of the guests are approximately 14 Å long, whereas the length of the hydrophobic region of the CD dimers is larger than 16 Å (value for two CD rings in close proximity). This means that TNS cannot completely fill the cavities of the CD dimer, while ENS and TENS will use their relatively hydrophilic hydroxyethyl and ethylene glycol chains for binding. The result of this will be that the energy gain upon complexation, due to hydrophobic interactions, will be smaller for ENS and TENS than for TNS, which leads to the observed binding profile. For the heterodimers **3** and **4**, the opposite effect is observed: despite the fact that the guests become more hydrophilic on going from TNS to ENS and then to TENS, the binding constants increase in this direction. This may be due to the larger length of the side chains in ENS and TENS as compared to TNS. The first two guests, in contrast to TNS, can form a more stable complex with the α-CD part of the dimer, because their side chains fit in more tightly. This more favorable fit compensates for the negative effect of binding a hydrophilic chain in an apolar cavity. The binding profiles observed for heterodimers **3** and **4** in combination with the binding profiles of the symmetrical dimers **1** and **2** are indicative of a site-specific guest binding in the former set of host molecules.

Table 2 reveals that the CD dimers with short linkers (**1** and **3**) display higher binding constants than the dimers with long spacers (**2** and **4**). This would be consistent with the observations of Petter et al,[13] who proposed that the longer the linking spacer between two CDs is, the more entropy must be quenched to form a highly ordered inclusion complex. Our NMR spectroscopy studies on the CD dimers, however, suggest a more likely explanation of the results (vide supra). Before the substrate can be bound in the CD dimers, it is necessary to remove the spacers from the CD cavities. This process is energetically unfavorable, which is reflected in the lower binding constants.[14]

The positions of the emission maxima (λ_{max}) in the fluorescence spectra of the complexes of the anilinonaphthalene sulfonates with the CD derivatives provide information on the extent of shielding of the guests from the aqueous solution.[15] The values found for the complexes between TNS and the monomeric CDs, and for the complexes between this guest and the dimers **1** and **2** (Table 2) indicate that TNS is encapsulated by both CD cavities of the dimers. This also indicates that the shielding effect of a dimer is more efficient (lower value of λ_{max}) than the shielding of two noncovalently linked CD molecules. The same holds for ENS and TENS. With dimer **2** a more efficient shielding of the guests is achieved than with **1**. This is probably caused by an additional shielding effect of the larger apolar spacer in the former CD dimer. In the case of the heterodimers, the λ_{max} values are close to those measured for the 1:1 complexes of β-CD. Table 4 shows that the encapsulation of a guest by a free α-CD results in a lower value of λ_{max} than encapsulation by a free β-CD. This decrease is not clearly observed in the case of the complexes with the heterodimers, suggesting that the shielding contribution of α-CD in the heterodimers is different from the shielding by free α-CD. A possible explanation for this result may be that the λ_{max} value depends on the binding geometry of the guest-α-CD complex.[16] In the free α-CD, the encapsulation of the aniline part of the guest will occur through the primary side. This may result in a more efficient shielding (a lower value of λ_{max}) than is possible for a complex, in which the aniline part is encapsulated through the secondary side. In the complexes with **3** and **4**, the guest can only enter through the secondary side of the α-CD ring, which may cause the observed effect.

Binding studies with porphyrins: As part of our studies on the supramolecular chemistry of porphyrins,[17] we were interested in binding porphyrin derivatives in the cavities of the CD dimers. For these studies compounds **1**, **2**, and **5** were chosen as the hosts, and the porphyrins TcPP and TsPP as the guests. Fluorescence spectroscopy was again used as the technique to follow the binding process. We first investigated the aggregation behavior of TcPP and TsPP in water by making use of the fact that aggregation leads to quenching of the fluorescence of these molecules.[18] These experiments showed that the host–guest titrations had to be performed below 0.5 μM of porphyrin to prevent aggregation from occurring.

The binding of porphyrins in the cavities of the CD dimers **1** and **2** resulted in a decrease of the fluorescence intensities, yielding titration curves corresponding to the formation of 1:1 (porphyrin:CD dimer) complexes. The binding constants (K_bs) of these complexes, calculated from curve fitting of the data points, are summarized in Table 5.[19] For comparison, the binding constants of complexes between the unsubstituted β-CD monomer and the two porphyrins are also given in Table 5.

The very high binding constants found for our CD dimers, as compared to those observed for β-CD itself, indicate a strong chelate effect.[20] Since encapsulation of a porphyrin in dimer **2** requires the self-included octamethylene spacer to be removed first, this dimer shows a lower binding constant when compared to dimer **1**.

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Table 5. Binding constants of complexes between porphyrins and CD dimers.[a]

Host	Binding constant [M^{-1}] TsPP	TcPP
β-CD	1400	1700
1	0.8×10^6	1.9×10^6
2	0.4×10^6	0.9×10^6
5	$> 5 \times 10^7$[b]	–

[a] At $25.0 \pm 0.1\,^{\circ}C$; phosphate buffer 0.1M, pH 7.0, $\lambda_{exc} = 415$ nm, $\lambda_{em} = 635$ nm. The estimated error in the binding constants is smaller than 10%. [b] Estimated value.

In order to study the binding geometries (*syn* or *anti*,[21] Figure 8a), of the CD dimer–porphyrin complexes, ^{1}H NMR spectra of the complexes between TsPP and dimers **1** and **2** were recorded in CD_3OD/D_2O (1:3, v/v) at $-10\,^{\circ}C$.[19] The observed patterns indicated that the **1**–TsPP complex has a *syn* structure, and the complex between **2**–TsPP a mixed *syn*/*anti* structure.[19] From the intensity of the signals the ratio of the *syn*/*anti* conformers could be calculated to be 2:1. The geometry of the *anti* complex could also be deduced from the δ values of the methylene spacer protons, which showed an upfield shift (broad signals at $\delta = 1 - -2$) due to the shielding effect of the porphyrin core.

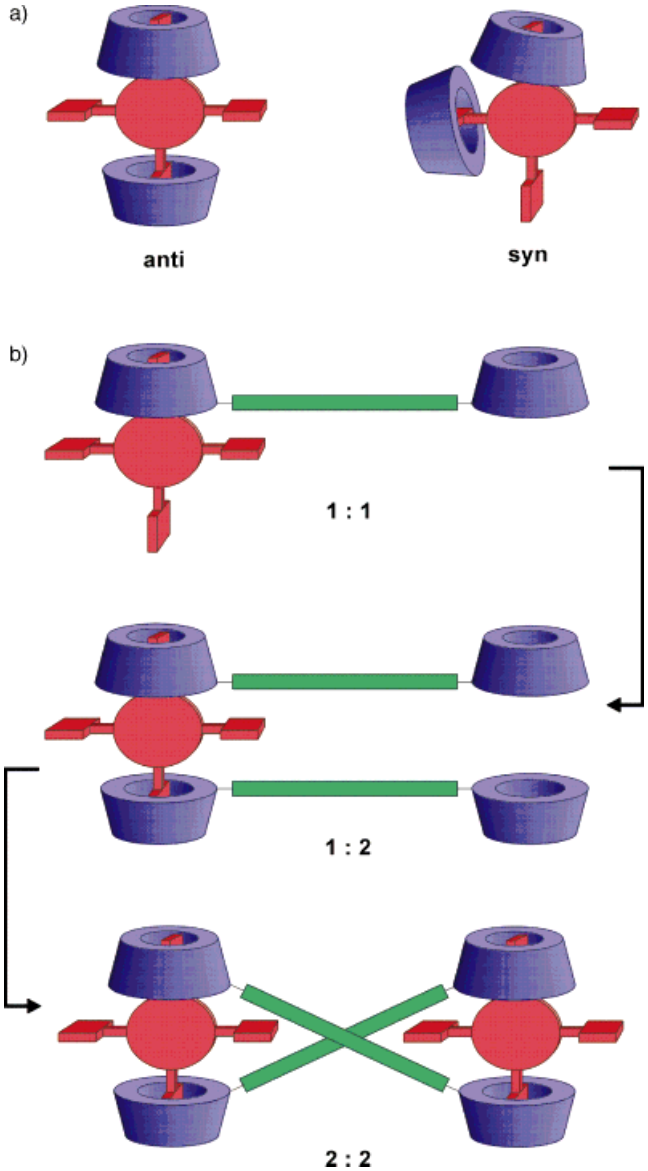

Figure 8. a) *Syn* and *anti* binding geometries of CD dimer porphyrin complexes; b) proposed mechanism for the subsequent formation of 1:1, 1:2, and 2:2 CD dimer porphyrin complexes from the CD dimer **5** and TsPP.

When porphyrin TsPP was titrated with CD dimer **5**, the titration curve was clearly different from the titration curve of dimers **1** and **2**.[19] This curve had a sigmoidal shape and could not be fitted assuming simple 1:1 (CD dimer:porphyrin) complex formation. The sigmoidal shape, however, can be explained if such a 1:1 complex is formed first, followed by formation of a 2:1 (CD dimer:porphyrin) complex. In a subsequent step, the two remaining empty CD units then encapsulate a second porphyrin to form a 2:2 complex (Figure 8b). The formation of such a complex was confirmed by gel chromatography experiments.[19] The **5**–TsPP complex was eluted faster than the complexes **1**–TsPP and **2**–TsPP, which suggests that the former complex has a higher molecular weight, supporting the idea of the formation of a 2:2 complex.

Since the bipyridine spacer of CD dimer **5** is capable of binding metal ions, we also performed the titration of TsPP in the presence of 0.5 equivalent of Zn^{II} ions.[19] The formation of the 2:2 complex was facilitated, probably because the metal ion coordinates the bipyridine units of two molecules of **5** in a tetrahedral fashion (Figure 9). This 2:2 cross dimer structure was supported by ^{1}H NMR spectroscopy studies.[18] The binding constants for both the **5**–TsPP complex and the **5**–TsPP–Zn^{2+} complex are very high: the estimated values amounted to $K_b \gg 5 \times 10^7\,M - 1$.

Conclusion

The studies presented here reveal that CD dimers linked by a long aliphatic spacer undergo self-complexation in aqueous solution. This self-inclusion leads to more signals in the ^{1}H and ^{13}C NMR spectra than are expected on the basis of the symmetric structures of the CD dimers. Using soft-pulse 2D NMR spectroscopy techniques, we were able to assign nearly all of the ^{1}H NMR signals of CD dimers **2** and **4**. This allowed us to get detailed information on the conformations of the dimers, in particular on those of the altrose moieties to which the aliphatic spacers are attached. The altrose unit belonging to the CD which includes the spacer has the $^4C_1$ and the other the $^1C_4$ conformation. Although the conformational free energies of the $^4C_1$ and the $^1C_4$ conformations of α-D-altrose itself are rather similar, the inclusion of the spacers in **2** and **4** stabilizes the $^4C_1$ conformation of one of the altrose units, probably because in this conformation the spacer is more favorably directed towards the cavity.

The self-inclusion of the spacer affects the affinities of the CD dimers for ditopic guests like TNS and TNS analogues, and porphyrins, as was demonstrated by host–guest binding studies. When the CD rings are connected by a rigid 2,2′-bipyridyl spacer, the self-inclusion process of this spacer is not possible, leading to a higher affinity for porphyrin guests. The results obtained with the TNS analogues show that site-specific binding in CD dimers is possible if host and guest are well tuned to one another.

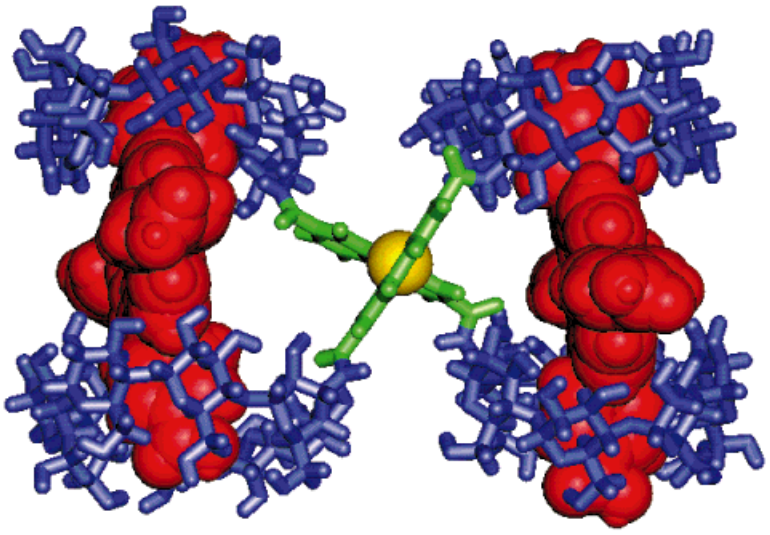

Figure 9. Computer-generated model of the **5**-TsPP-Zn^{2+} complex.

Experimental Section

General methods: THF and toluene were distilled from sodium and benzophenone. Ethanol was dried by refluxing for at least 8 h over magnesium (activated by a little iodine) followed by distillation. Pyridine and acetonitrile were dried by refluxing for at least 8 h over CaH_2 (5 g L^{-1}) followed by distillation. DMF was dried by stirring overnight on CaH_2 followed by distillation under reduced pressure (1 mm Hg). All dry solvents were kept over molecular sieves (3 Å). Ethyl acetate was distilled in vacuo. All other solvents were used as received. Flash column chromatography of cyclodextrin derivatives was performed on silica gel (Merck, particle size <0.063 mm). Other compounds were purified on silica 60 (Merck). The TLC plates used were precoated silica gel 60 F_{254} on glass plates (Merck). Compounds containing a cyclodextrin unit were detected by spraying with a 10% solution of H_2SO_4 in ethanol followed by heating with a heat gun. Eluents used in chromatography were mixtures (v/v) of ethyl acetate, ethanol, and water (A: (100:4:2); B: (100:8:4); C: (100:14:8); D: (100:30:16); E: (100:2:1)) and a mixture (v/v) of *n*-propanol:ethyl acetate:water:ammonia (F: (5:3:3:1)). Tosyl chloride was recrystallized from hexane before use. 2-Bromo-5-methylpyridine was prepared from commercially available 2-amino-5-methylpyridine in 92% yield using a procedure described by Adams et al.[22] for 2-bromo-3-methylpyridine. The Raney nickel was dried before use as follows: water was removed and the solid was repeatedly washed with ethanol under argon, twice with ethanol, technical grade, and twice with ethanol, analytical grade. The last traces of ethanol were removed in vacuo. The potassium salt of *N*-hydroxysuccinimide was prepared as described before.[23] All other reagents were used as received.

NMR spectra were recorded on Bruker WH-90, Bruker AC-100, or Bruker AM-400 instruments. Chemical shifts (δ) are reported in ppm downfield from internal $(CH_3)_4Si$ (TMS). In order to facilitate the interpretation of the ^{13}C NMR spectra of the cyclodextrin derivatives, ^{13}C 135-DEPT spectra were recorded, which enabled the assignment of the CH_2 and the quarternary carbon atoms. FAB mass spectra were recorded on a VG 7070E instrument or a Finnigan MAT 90 spectrometer. The matrix for these measurements was *m*-nitrobenzylalcohol (NBA) for the silylated cyclodextrin derivatives and glycerol for the desilylated cyclodextrins. Melting points were determined on a Reichert Thermopan microscope and are uncorrected. IR spectra were measured on a Perkin Elmer 298 spectrophotometer. Elemental analyses were carried out on a Carlo Erba EA 1108 instrument.

2D NMR experiments: 600 MHz ^1H NMR spectra were acquired on a Bruker AMX-600 spectrometer, upgraded with a multichannel interface and a cooling unit. Sample concentrations were 5 mM and the temperature was set at 298 K. For soft pulses, typically a 7 ms Gaussian 270° pulse and a 18.5 ms G3 Gaussian Cascade pulse were used for the selective excitation and refocusing of the anomeric proton signals. All spectra except RELAYs were acquired in the phase sensitive mode using the TPPI method. The 800 MHz spectra were recorded on a Bruker DRX-800 spectrometer, equipped with a 15N/13C/1H 5 mm inverse probehead. Thanks to digital filtering the non-anomeric CD protons could be detected separately.

Fluorescence measurements: Fluorescence measurements were performed on a Perkin Elmer LS50B luminescence spectrometer. A 1.00 cm quartz cuvette (4 mL) was used, which was placed in a thermostated (25.0 ± 0.1 °C) cuvette holder. All measurements were carried out using a 0.1 M buffer (pH 7.0) of KH_2PO_4 in distilled or demineralized water. The concentration of the fluorophore was kept constant in every experiment by using stock solutions of known concentrations. Typical concentrations were 1×10^{-5} M for the TNS derivatives and 2×10^{-7} M for the porphyrins. A known amount of CD (dimer) was added to a portion of these stock solutions, yielding a solution with known concentrations of CD and fluorophore. The concentration of CD (dimer) that was used, depended on the binding constant of the complex and was chosen in such a way that the titration yielded at least 10 data points in the region where 20–80% of complex is formed. This region allows the most accurate determination of binding constants.[24] The excitation wavelengths that were used, are (nm): TNS, 322; ENS, 318; TENS, 319; TsPP, 413; and TcPP, 415. The excitation slits were 2.5 nm and the emission slits were between 2.5–10 nm depending on the fluorescence intensity of the probe under investigation. No oxygen quenching of the fluorescence was observed for TNS derivatives. Significant photodecomposition of the porphyrins occurred if the excitation slits were >2.5 nm, and if the scan speeds were <60 nm min^{-1}. A scanning speed of 120 nm min^{-1} over a region of only 20 nm therefore was used in the case of the porphyrins studied. The titrations were carried out by starting with a solution of the probe compound (2000 µL) and adding small portions of the CD stock solution (5–1000 µL). After every addition a spectrum was recorded, which was stored in a computer. By substracting the first from the last spectrum, a difference spectrum was obtained, which revealed at what wavelength the maximum change in the fluorescence intensity had occurred. Subsequently, the fluorescence intensity at this wavelength was determined in the stored spectra. Intensities were plotted as a function of the CD (dimer) concentration, and data were fitted assuming a 1:1 complex.[7]

Gel chromatography of porphyrin dimer complexes: Gel chromatography was performed using standard procedures for column packing. A column (length 30 cm, bed volume 200 mL) was filled with Fractogel (TSK HW-40 (F), Merck). The flow rate was 13.2 mL h^{-1}. The exclusion limit of the column for carbohydrates was M_r 7000 as quoted by the manufacturer. Compounds were detected with a UV detector (LKB Uvicord S 2138) at 278 nm. The fractions that gave a signal on the detector were checked after lyophilization for the presence of CD derivatives and porphyrins by ^1H NMR spectroscopy (90 MHz).

NMR spectra of porphyrin dimer complexes: ^1H NMR spectra (400 MHz) were recorded in a mixture of D_2O and CD_3OD (75:25, v/v). [porphyrin] = 1.5×10^{-3} M, [cyclodextrin dimer] = $3-4.5 \times 10^{-3}$ M. Before acquisition, the sample was presaturated to reduce the HDO signal.

***N,N′*-Bis[mono(3-deoxy)-*β*-CD]-butan-1,4-diamide (1)**: To a solution of dimer **21** (0.77 g, dried at 40 °C, 2 h, 0.05 mm Hg) in THF (25 mL) was added a solution of TBAF (3.20 mL, 1.0 M) in THF. After 18 h refluxing, water (25 mL) was added, and the reaction mixture was concentrated in vacuo. The resulting residue was dissolved in a minimum amount of water and precipitated in ethanol (100 mL, analytical grade). The precipitate was collected by centrifugation. The precipitation was repeated two times to remove all tetrabutylammonium salts. Yield: 0.39 g (95%). M.p.: 265–268 °C; R_f(E) = 0.1; ^1H NMR (400 MHz, D_2O): $\delta = 5.09$ (d, 1H; H-1), 5.03–4.96 (m, 12H; H-1), 4.90 (d, 1H; H-1), 4.21–4.15 (m, 4H), 3.96–3.75, and 3.66–3.52 (2 × m, ca. 84H; H-2, H-3, H-4, H-5, H-6), 2.57 (m, 4H; CH_2 spacer); ^{13}C NMR (100 MHz, D_2O): $\delta = 176.12$ (*C*=O), 105.06–102.41 (C-1), 82.32–81.21, 74.41–71.11, 61.58 (C-2, C-3, C-4, C-5), 60.97 (C-6), 59.38, and 52.20 (C–NH), 32.28 (CH_2); IR (KBr): $\tilde{\nu} = 1680-1610$, 1560–1550 cm^{-1} (amide I and II); MS (FAB): *m/z*: 2349.9 [*M*+1]; $C_{88}H_{144}N_2O_{70} \cdot 15H_2O$: calcd C 40.34, H 6.69, N 1.07; found C 39.92, H 6.52, N 1.07.

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***N,N′*-Bis[mono(3-deoxy)-β-CD]-decane-1,10-diamide** (**2**): Deprotection of **22** was performed as described for compound **1**. Using dried dimer **22** (0.59 g) and a solution of TBAF (2.70 mL, 1.0 M) in THF yielded the pure product after work up. Yield: 0.31 g (88 %). M.p.: 246–248 °C; R_f(E) = 0.1; ^{1}H NMR (600 MHz, D_2O): see Table 1. ^{13}C NMR (100 MHz, D_2O): δ = 177.84 and 176.98 (C=O), 105.02–102.30 (C-1), 82.41–80.05 and 77.86–69.06 (C-2, C-3, C-4, C-5), 61.90–60.71 (C-6), 52.45 and 52.13 (C–NH), 37.62, 36.87, 30.28, 30.16, 29.12, 28.77, 26.95 and 26.32 (8 × CH_2–spacer); IR (KBr): $\tilde{\nu}$ = 1670–1610, 1560–1550 cm^{-1} (amide I and II); MS (FAB): *m/z*: 2430.5 [*M* − 2]; $C_{94}H_{156}N_2O_{70} \cdot 7H_2O$: calcd C 44.10, H 6.69, N 1.09; found C 44.01, H 6.91, N 1.17.

***N*-[Mono(3-deoxy)-β-CD]-*N′*-[mono(3-deoxy)-α-CD]-butane-1,4-diamide** (**3**): To a solution of compound **25** (140 mg) in THF (10 mL) was added TBAF (0.57 mL of a 1.0 M stock solution in THF, 15 equiv). The mixture was refluxed (24 h) until the reaction was completed according to TLC (eluent E). The reaction mixture was concentrated in vacuo, and the residue was dissolved in a minimum amount of water. This solution was poured into acetone yielding a white precipitate. Repeating this procedure twice afforded pure compound **3**. Yield: 42 mg (50 %). M.p.: > 280 °C (decomp); R_f(E) = 0.1; ^{1}H NMR (400 MHz, D_2O): δ = 5.06 (m, 3H; H-1), 5.00 (m, 6H; H-1), 4.95 (m, 2H; H-1), 4.89 (m, 2H; H-1), 4.17–4.13 (m, 4H), 3.93–3.76 and 3.64–3.52 (2 × m, ca. 74H; H-2, H-3, H-4, H-5, H-6), 2.56 (br.s, 4H; CH_2–spacer); ^{13}C NMR (100 MHz, D_2O): δ = 176.07 (C–O), 105.48 and 105.00 (C-1^A and C-1$^{A'}$), 103.16–101.62 (C-1), 82.79–81.21, 79.75, 77.28, 74.37–72.43, 71.36 and 71.06 (C-2, C-3, C-4, C-5), 62.01–60.91 (C-6), 52.19 and 51.98 (C–NH), 32.25 (CH_2--spacer); IR (KBr): $\tilde{\nu}$ = 1680–1610, 1560–1520 cm^{-1} (amide I and II); MS (FAB): *m/z*: 2189 [*M*+1]; $C_{82}H_{134}N_2O_{65} \cdot 5H_2O$: calcd C 43.24, H 6.37, N 1.23; found C 43.08, H 6.30, N 1.30.

***N*-[Mono(3-deoxy)-β-CD]-*N′*-[mono(3-deoxy)-α-CD]-decane-1,10-diamide** (**4**): Deprotection of compound **4** was achieved as described for **3**. Starting with compound **26** (140 mg), a crude product was obtained after removal of the solvent. This was dissolved in a minimum amount of water and poured into ethanol (analytical grade), yielding a white precipitate. Repeating this precipitation afforded compound **4**, which was still contaminated with tetrabutylammonium salts. The latter salts could be removed by running the compound, dissolved in water, over a cation exchange column in the NH_4^+ form. Yield: 60 mg (71 %). M.p.: > 310 °C (decomp); R_f(E) = 0.1; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 4.90–4.57 (5 × m, 13H; H-1), 4.03 (m, 4H), 3.90 (m, 2H), 3.76–3.25 (2 × m, ca. 74H; H-2, H-3, H-4, H-5, H-6), 2.06 (br.t, 4H; CH_2–CO) 1.48 (br.s, 4H; CH_2–spacer), 1.24 (br.s, 8H; CH_2–spacer), see also Table 2 and 3 for 800 MHz spectrum in D_2O; ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 172.21 and 172.03 (2 × C=O), 104.72 and 104.35 (C-1^A and C-1$^{A'}$), 102.49–101.15 (C-1), 82.92, 81.96–80.53, 79.66, 79.47, 76.59, 73.54–71.72, 70.58 (C-2, C-3, C-4, C-5), 59.92–59.45 (C-6), 50.20 and 49.63 (CH_2–CO spacer), 35.65, 28.87 and 25.27 (CH_2–spacer); IR (KBr): $\tilde{\nu}$ = 1670–1600, 1560–1520 cm^{-1} (amide I and II); MS (FAB): – *m/z*: 2271 [*M* − 1]; $C_{88}H_{146}N_2O_{65} \cdot 4H_2O$: calcd C 45.09, H 6.62, N 1.20; found C 45.12, H 6.49, N 1.24.

***N,N′*-Bis[mono(3-deoxy)-β-CD]-5,5′-dicarboxamide-2,2′-bipyridine** (**5**): Compound **31** (640 mg) was dried (1 h, 0.05 mm Hg, 40 °C) and dissolved in THF (15 mL). After addition of a stock solution of TBAF (2.4 mL, 1.0 M) in THF (15.5 equiv), the reaction mixture was refluxed for 24 h. After concentration in vacuo, the crude product was dissolved in a minimum amount of water. This solution was poured into ethanol (analytical grade), and the product was collected by centrifugation. Repeating this procedure twice afforded pure compound **5** as a slightly purple precipitate. Yield: 260 mg (67 %). M.p.: 325–327 °C (decomp); ^{1}H NMR (400 MHz, D_2O): δ = 8.90 (s, 2H; Ar–H), 8.24 (br.s, 2H; Ar–H), 8.13 (br.s, 2H; Ar–H), 5.08–4.98 (m, 14H; H-1), 4.45, 4.21 (2 × br.s, 2 × 2H) and 4.07–3.49 (2 × m, ca. 80H; H-2, H-3, H-4, H-5, H-6); ^{13}C NMR (100 MHz, D_2O): δ = 168.9 (C=O), 157.7 (bipy-C-2), 149.5 (bipy-C-6), 138.5 (bipy-C-4), 131.4 (bipy-C-5), 123.3 (bipy-C-3), 105.0, and 103.2–102.5 (C-1), 82.4, 82.1, 81.9, 81.4, 74.4–72.6, and 71.07 (C-2, C-3, C-4, C-5), 61.5–61.1 (C-6), 53.0 (C–NH); IR (KBr): $\tilde{\nu}$ = 1625, 1510 cm^{-1} (amide I and II, and bipyridine C=C); MS (FAB): *m/z*: 2477 [*M*+1]; $C_{96}H_{146}N_4O_{70} \cdot 10H_2O$: calcd C 43.41, H 6.30, N 2.11; found C 43.49, H 6.31, N 2.09.

2-(*p*-(2′-Hydroxyethyl)anilino)-6-naphthalene sulfonate (**ENS, 6**): The synthesis of this compound was carried out as described by Cory et al.[6] 2-Amino-6-naphthalene sulfonate (1.75 g, 7.88 mmol), NaOH (291 mg, 7.28 mmol), and $NaHSO_3$ (17 g) were dissolved in water (50 mL). After the addition of 2-(4′-aminophenyl)ethyl alcohol (2.0 g, 14.6 mmol), the reaction mixture was refluxed for 72 h. On cooling a precipitate was formed, which was removed by filtration. After recrystallization (twice) from water, the resulting slightly yellow solid was collected and dried in vacuo. Yield: 1.40 g (53 %). M.p.: > 350 °C; ^{1}H NMR (90 MHz, D_2O:[D_6]DMSO, 10:1, v/v): δ = 8.3 (s, 1H; H–Ar), 8.0 (d, 1H; H–Ar), 7.7 (m, 2H; H–Ar), 7.5 (m, 2H; H–Ar), 7.3 (m, 4H; H–Ar), 3.8 (t, 2H, CH_2–OH), 2.8 (t, 2H, CH_2–Ar); MS (FAB): *m/z*: 365 [*M*+1]; $C_{18}H_{16}NSO_4Na$: calcd C 59.17, H 4.41, N 3.83; found C 58.95, H 4.30, N 3.81.

2-(*p*-(3′,6′,9′-Trioxa-11′-hydroxyundecane)anilino)-6-naphthalene sulfonate (**TENS, 7**): 2-Amino-6-naphthalene sulfonate (98 mg, 0.40 mmol) and NaOH (16 mg, 1 equiv) were dissolved in water (5 ml). This solution was added to compound **37** (107 mg, 1 equiv). After addition of sodium bisulphite (2.5 g), the reaction mixture was refluxed for 48 h. Hereafter, water (25 mL) was added and the aqueous solution was extracted with ethyl acetate to remove unconverted **37**. The water layer was concentrated in vacuo, and the resulting residue was extracted by stirring with ethanol (3 ×), and the combined ethanol fractions were concentrated to a small volume. This solution was poured into hexane, and the resulting red precipitate was collected by centrifugation. Yield: 13.9 mg (7 %). M.p.: > 350 °C; ^{1}H NMR (90 MHz, D_2O): δ = 8.1–6.6 (m, 10H; Ar–*H*), 3.8–3.1 (m, 14H; CH_2–O), 2.8 (t, 2H; CH_2–Ar); MS (FAB): *m/z*: 520 [*M*+Na]; $C_{24}H_{28}NSO_7Na \cdot 4H_2O$: calcd C 49.23, H 6.20, N 2.39, S 5.47; found C 49.09, H 6.04, N 2.74, S 5.96.

Hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-CD (**10**): This compound was prepared as compound **11,** except for some modifications: To dried α-cyclodextrin (19.0 g, 100 °C, 0.05 mm Hg, 9 h) in THF (350 mL) was added, at 0 °C over a period of 1 h, *tert*-butyldimethylsilyl chloride (22.6 g, 7.7 equiv) in dry pyridine (50 mL). After stirring for 24 h at room temperature, the reaction mixture was poured into ice/water (1 L) and stirred for 15 min. The white precipitate was filtered over Celite and dissolved in dichloromethane. The solution was washed twice with HCl (1 M), once with a saturated $NaHCO_3$ solution (100 mL), and once with brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield a crude product (40 g). Repeated column chromatography (1.6 kg silica, eluent A) resulted in a TLC-pure compound. Yield: 22.6 g (69 % yield). M.p.: 331 °C (decomp), (ref. [25] 323–326 °C, (decomp); R_f(C) = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.88 (d, 6H; H-1), 4.01 (t, 6H; H-3), 3.91 (dd, 6H; H-6), 3.84 (d, 6H; H-6), 3.75 (d, 6H; H-5), 3.64 (dd, 6H; H-2), 3.59 (t, 6H; H-4), 0.89 (s, 54H; CH_3–C), 0.03 (s, 36H; CH_3–Si); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.39 (C-1), 81.40, 74.45, 73.04, and 72.19 (C-2, C-3, C-4, C-5), 61.95 (C-6), 25.97 (CH_3–C), 18.42 (CH_3–*C*), – 5.19 (CH_3–Si). MS (FAB): *m/z*: 1681 [*M*+1]; $C_{72}H_{144}O_{30}Si_6$: calcd C 52.15, H 8.75; found C 52.39, H 8.53.

Heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD (**11**): Compound **11** was synthesized according to modified literature methods refs. [2, 26]. β-Cyclodextrin was dried (100 °C, 0.05 mm Hg, 10 h) yielding a product (33 g), which was dissolved under vigorous stirring in dry pyridine (500 mL). At 0 °C, *tert*-butyldimethylsilyl chloride (37.28 g, 8.5 equiv) in dry pyridine (100 mL) was added in 1.5 h. After stirring overnight at room temperature, the reaction mixture was poured into ice/water (1 L) and stirred for 15 min. The white precipitate was filtered (over Celite) and dissolved in ethyl acetate (800 mL), washed twice with aqueous HCl (100 mL, 1 M), once with a saturated $NaHCO_3$ solution (100 mL), and once with brine. The resulting organic layer was dried ($MgSO_4$) and concentrated in vacuo yielding 66 g of crude product. Repeated column chromatography (1.4 kg silica, eluent A) resulted in a TLC-pure compound **11** (in our hands, purification as mentioned in refer. [26] did not yield a TLC-pure compound). Yield: 44.4 g (79 % yield). M.p.: 287–289 °C (crystals from MeOH/$CHCl_3$, 95:5, v/v); R_f(C)=0.40; ^{1}H and ^{13}C NMR data were in close agreement with reported literature values.[2] MS (FAB): *m/z*: 1957 [*M*+Na], 2067 [*M*+Cs]; $C_{84}H_{168}O_{35}Si_7 \cdot 2H_2O$: calcd C 51.17; H 8.84; found C 51.07; H 8.85.

Mono(2-*O*-tosyl)hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-CD (**12**): This compound was synthesized from **10** as described for compound **13** from **11**. Starting with a solution of compound **10** (2.87 g, dried at 80 °C, 0.05 mm Hg, 6 h) in THF (150 mL) and a dispersion of NaH (103 mg, 1.5 equiv, 60 %) in mineral oil, and tosyl chloride (495 mg, 1.5 equiv) yielded a crude product (3.0 g), which was subjected twice to column chromatography (first run 800 g silica, eluent A, second run 800 g silica, eluent E). In this way, pure starting material **10** (600 mg, 21 %) was

recovered. Yield 800 mg (25%). M.p.: 218.5°C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD, 10:1, v/v): $\delta = 7.89$ (d, 2H; Ar–H), 7.31 (d, 2H; Ar–H), 5.11, 4.91, 4.86, 4.81, 4.76 (5 × d, total 6H; H-1), 4.13–3.90 and 3.76–3.49 (4 × m, 35H; H-2, H-3, H-4, H-5, H-6), 3.32 (dd, 1H), 2.43 (s, 3H; Ar–CH_3), 0.88 (s, 54H; C–CH_3), 0.04 (s, 36H; Si–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$:CD_3OD, 10:1, v/v): $\delta = 145.42$ and 132.03 (C–Ar), 129.51, 129.05 (CH–Ar), 102.95–101.36 and 99.32 (C-1), 81.62–80.03, 73.46–71.91, 69.32 (C-2, C-3, C-4, C-5), 62.11–61.94 (C-6), 25.96 (CH_3–Ar), 21.71 (CH_3–C), 18.43 and 18.29 (CH_3–C), –5.07 and –5.20 (CH_3–Si); $C_{79}H_{150}O_{32}Si_6S$: calcd C 52.35, H 8.34, S 1.77; found C 52.34, H 8.30, S 1.63.

Mono(2-*O*-tosyl)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD (**13**): To dried compound **11** (15.43 g, 80°C, 0.05 mm Hg, 5 h) dissolved in dry THF (200 mL) was added a dispersion of NaH (335 mg, 1.05 equiv, 60%) in mineral oil. The solution was stirred for at least 17 h at room temperature and 1 h at reflux temperature. To this refluxing solution was added tosyl chloride (1.37 g, 0.9 equiv). After 1 h, TLC (C) showed the formation of two major new products. The reaction mixture was concentrated in vacuo, the product was dissolved in ethyl acetate, and the solution washed with water/brine (50:50, v/v), and dried ($MgSO_4$). After removal of the solvent in vacuo, the resulting crude product (15.5 g) was subjected twice to column chromatography (1.4 kg silica, eluent A). In this way also pure starting material **11** (6.3 g) could be recovered. Yield 4.56 g: (27%, or 46% according to the consumed amount of **11**). M.p.: 204–206°C; R_f(C) = 0.56; ^{1}H and ^{13}C NMR data were in close agreement with reported values.[2] MS (FAB): –*m/z*: 2086 [*M* –], 2239.5 [*M*+NBA – 1]; $C_{91}H_{174}O_{37}Si_7S$: calcd C 52.32, H 8.40, S 1.53; found C 51.92, H 8.40, S 0.99.

Mono(2^A,3^A-anhydro)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD (15): To a solution of compound **13** (500 mg) in dry ethanol (3 mL) was added sodium ethoxide (5 mL, 55 mg of sodium in 50 mL of dry ethanol). After the reaction mixture had been refluxed overnight it was concentrated in vacuo, the residue dissolved in ethyl acetate, and the solution washed with water and brine, dried ($MgSO_4$) and concentrated to dryness. Further purification was achieved by column chromatography (100 g silica, eluent A, (1 L), followed by eluent B). In this way, compound **15** was obtained as a white solid. Yield: 300 mg (65%). M.p.: 258°C; R_f(C) = 0.38; MS (FAB): *m/z*: 1938.5 [*M*+Na]; $C_{84}H_{166}O_{34}Si_7 \cdot H_2O$: calcd C 52.15, H 8.75; found C 52.11, H 8.88.

Mono(3-amino-3-deoxy)hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-CD (**16**): Using the method described for compound **17**, dried compound **12** (700 mg, 100°C, 0.05 mm Hg, 1 h), ethanol (60 mL), and sodium ethoxide (6.0 mL) in ethanol (stock: 81 mg Na in 50 mL ethanol) yielded, after work up, crude product, which was purified by column chromatography (50 g silica, eluent B). Yield: 405 mg (63%). R_f(D) = 0.42; ^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD, 2:1, v/v): $\delta = 4.77$ and 4.73 (2br.s, 5H; H-1), 4.52 (d, ^3J(H,H) = 6 Hz, 1H; H^A-1), 4.05–3.23 and 3.03 (4 × m; H-2, H-3, H-4, H-5, H-6, CD_3OH), 0.75 (s, 54H; C–C*H*$_3$), –0.05 (m, 36H; CH_3 – Si); ^{13}C NMR (100 MHz, $CDCl_3$:CD_3OD, 2:1, v/v): $\delta = 104.98$, 102.70, 102.50, 101.89, and 100.85 (C-1), 81.05–71.61 (C-2, C-3, C-4, C-5) 62.37–61.33 (C-6), 52.09 (C–NH_2), 25.65–25.54 (CH_3–C), 18.02–17.87 (CH_3–*C*), –5.44 – –5.84 (CH_3 – Si); MS (FAB): *m/z*: 1658 [*M*+1], 1789 [*M*+Cs]; $C_{72}H_{145}O_{29}Si_6N \cdot 2H_2O$: calcd C 51.07, H 8.87, N 0.83; found C 51.36, H 8.74, N 0.80.

Mono(3-amino-3-deoxy)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD (**17**): To a refluxing solution of dried compound **13** (2.52 g, 80°C, 0.05 mm Hg, 1 h) in dry ethanol (20 mL) was added a stock solution of sodium ethoxide (14.4 mL, 1.1 equiv) in ethanol (106 mg Na in 50 mL ethanol). After the starting material had been converted into **15** with a yield of more than 90% (6 h, according to TLC, eluent C), the reaction mixture was cooled to 0°C and saturated with ammonia gas. This mixture was transferred into an autoclave and heated at 80°C for 36 h. After removal of the solvent in vacuo, the crude product was dissolved in dichloromethane. The solution was washed with water and brine, dried ($MgSO_4$), and concentrated to dryness. The crude product (2.5 g) was purified by column chromatography (150 g silica, eluent B followed by eluents C and D). Yield: 1.45 mg (62%). M.p.: 245–255°C (decomp); R_f(C) = 0.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.95–4.75 (m; H-1 and HDO), 4.2–3.3 (m, 42H; H-2, H-3, H-4, H-5, H-6), 1.00–0.75 (m, 63H; C–CH_3), 0.2–0.0 (m, 42H; CH_3–Si); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 104.9$, 102.9, 102.6, 102.3, 102.1, 101.8, and 101.3 (C-1), 82.5–71.9 (C-2, C-3, C-4, C-5) 61.9–61.5 (C-6), 52.9 (C–NH_2), 25.9 (CH_3–C), 18.2 (CH_3–*C*), –5.1 (CH_3–Si); MS (FAB): *m/z*: 1934 [*M*+1], 1956 [*M*+Na]; $C_{84}H_{169}O_{34}Si_7N \cdot 3H_2O$: calcd C 50.75, H 8.87, N 0.70; found C 50.70, H 8.80, N 0.67.

Mono(3-amino-3-deoxy)heptakis(6-*O*-dimethylthexylsilyl)-β-CD (**18**): This compound was synthesized following the procedure described for compound **17**. The only difference was the use of dimethylthexylsilyl chloride (11 molar equiv) instead of *tert*-butyldimethylsilyl chloride (8.5 equiv) used for the synthesis of compound **17**. Starting from dried (3.63 g, 5 h, 50°C, 0.05 mm Hg) mono(2-*O*-tosyl)heptakis(6-*O*-dimethylthexylsilyl)-β-CD, pure product **18** (2.81 g, 83% based on the monotosylate) could be obtained. M.p.: 230°C (decomp); R_f(C) = 0.18; MS (FAB): *m/z*: 2130.5 [*M*+1]; $C_{98}H_{197}O_{34}Si_7N$: calcd C 55.26, H 9.32, N 0.66; found C 55.05, H 9.81, N 0.80.

Succinic acid bis(4-nitrophenyl)ester (**19**): Succinic acid (2.04 g), *p*-nitrophenol (6.01 g), and a catalytic amount of 4-dimethylaminopyridine (DMAP) were dissolved in dichloromethane (50 mL). At 0°C, a solution of *N,N'*-dicyclohexylcarbodiimide (7.47 g) in dichloromethane (25 mL) was added. After 25 h at room temperature the reaction mixture was filtered and evaporated to dryness. Purification of the crude product by column chromatography (silica 60, 150 g, CH_2Cl_2) resulted in decomposition of the compound. The product could however be purified by crystallization from chloroform. Yield 2.11 g (34%). M.p.: 184°C; ^{1}H NMR (100 MHz, [D$_6$]DMSO): $\delta = 8.30$ (d, ^3J(H,H) = 9.0 Hz, 4H; Ar–H), 7.39 (d, ^3J(H,H) = 9.0 Hz, 4H; Ar–H), 3.06 (s, 4H; CH_2); MS (CI) *m/z*: 361.2 [*M*+1]; $C_{16}H_{12}O_8N_2$: calcd C 53.34, H 3.36, N 7.78; found C 53.26, H 3.34, N 7.72.

Sebacic acid bis(4-nitrophenyl)ester (**20**): This compound was synthesized as described for **19**. The reaction of sebacic acid (4.85 g), *p*-nitrophenol (10.04 g), a catalytic amount of DMAP, and *N,N'*-dicyclohexylcarbodiimide (11.60 g) yielded pure **20** after work up and purification by repeated crystallizations from acetonitrile. Yield 6.39 g (60%). M.p.: 107°C; ^{1}H NMR (100 MHz, [D$_6$]DMSO): $\delta = 8.13$ (d, ^3J(H,H) = 9.0 Hz, 4H; Ar–H), 7.13 (d, ^3J(H,H) = 9.0 Hz, 4H; Ar–H), 2.5 (t, 4H; CH_2–O), 1.8–1.1 (m, 12H; CH_2); MS (CI) *m/z*: 306 [M-(*p*-nitrophenol)]; $C_{22}H_{24}O_8N_2$: calcd C 59.46, H 5.44, N 6.30; found C 59.82, H 5.41, N 6.58.

***N,N'*-Bis[mono(3-deoxy)heptakis(6-*O*-dimethylhexylsilyl)-β-CD]-butan-1,4-diamide** (**21**): Monoamino-functionalized cyclodextrin **18** was thoroughly dried (40°C, 4 h, 0.05 mm Hg) and the dry compound (1.82 g) was dissolved in THF (25 mL). After addition of compound **19** (0.15 g), the reaction mixture was refluxed until the reaction was completed according to TLC (24 h). The solvent was evaporated, and the residue was dissolved in dichloromethane. This solution was washed with a saturated aqueous solution of $NaHCO_3$ (twice) and with brine (twice), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was subjected to column chromatography (150 g silica, eluent B). Yield: 1.35 g (76%). M.p.: 260°C (decomp); R_f(D) = 0.54; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.56–5.82$ (O*H*), 5.57–4.80 (3 × m; H-1 and OH), 3.92–3.45 (m, ca. 86H; H-2, H-3, H-4, H-5, H-6), 3.28 (t, 2H), 2.96–2.69 (m, 4H; C*H*$_2$–spacer), 2.17–1.98, 1.67–1.56, 1.28–1.24 (m, 3H), 0.98–082 (m, 168H; CH_3–C), 0.12–0.07 (s, 84H; CH_3–Si); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.22$ (C=O), 105.18–101.91 (C-1), 81.66, 81.46, 74.97–67.11 (C-2, C-3, C-4, C-5), 63.17–61.01 (C-6), 52.47 (C–NH), 34.18 (CH–thexyl), 32.73 (*C*H$_2$–spacer), 25.17, 25.05, 23.04, 20.98, 18.47 (C–thexyl), –3.02, –3.30, and –3.44 (CH_3–Si); IR (KBr): $\tilde{\nu} = 1680–1610$, 1570–1550 cm^{-1} (amide I and II); $C_{200}H_{396}O_{76}Si_{14}N_2 \cdot H_2O$: calcd C 55.12, H 9.20, N 0.64; found C 55.12, H 9.92, N 0.73.

***N,N'*-Bis[mono(3-deoxy)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD]-decan-1,10-diamide** (**22**): Compound **22** was obtained in the same way as described for **21**. Starting from dry compound **17** (1.65 g) and compound **20** (180 mg), a crude product was obtained after work up that was purified by column chromatography (first 150 g silica, eluent B; second 150 g silica, eluent A). Yield: 1.63 g (57%). M.p.: 265–270°C (decomp); R_f(C) = 0.28; IR (KBr): $\tilde{\nu} = 1680–1610$, 1570–1550 cm^{-1} (amide I and II); MS (FAB): *m/z:* 4028.2 [*M* – 3]; $C_{178}H_{352}O_{70}Si_{14}N_2 \cdot H_2O$: calcd C 52.76, H 8.81, N 0.69; found C 52.05, H 8.72, N 0.79.

Coupling product of β-cyclodextrin derivative 17 with compound 19 (**23**): To a solution of dried compound **17** (334 mg, 80°C, 2 h, 0.05 mm Hg) in THF (30 mL) was added compound **19** (500 mg, 8 equiv). The reaction mixture was heated at 40°C for 24 h and subsequently concentrated in vacuo. The crude product was immediately subjected to column chromatography (10 g silica, eluent A). To prevent decomposition during the purification procedure, the column should not be too long and the elution

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rate not be too low. Yield: 188 mg (51%). R_f(C) = 0.53; MS (FAB): *m/z:* 2154 [*M* −], 2014 [*M*-(*p*-nitrophenol)]. Because of its instability, the product was directly converted into compound **25** without further analysis.

Coupling product of β-cyclodextrin derivative 17 with compound 20 (24): Compound **24** was obtained as described for **23**. Starting from dried **17** (280 mg) and compound **20** (760 mg, 12 equiv), a crude product was obtained, which was immediately subjected to column chromatography (75 g silica, eluent A). The decomposition of **24** during purification was less (but not negligible) than observed for compound **23**. Yield: 205 mg (63%). R_f(C) = 0.47; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 8.7 and 7.3 (2 × d, 4H; Ar−H), 4.9 (br.s, 7H; H-1), 4.3–3.5 (br.m, ca. 42H; H-2, H-3, H-4, H-5, H-6), 2.7, 2.5, 1,8, and 1.4 (4 × br.m, ca. 16H; CH_2–spacer), 0.9 (br.s, ca. 63H; CH_3−C), 0.0 (br.s, ca. 42H; CH_3−Si); MS (FAB): *m/z:* 2239.5 [*M*+], 2261 [*M*+Na].

***N*-[Mono(3-deoxy)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD]-*N*′-[mono-(3-deoxy)hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-CD]-butan-1,4-diamide (25)**: To a solution of compound **23** (188 mg) in THF (10 mL) was added compound **16** (150 mg). The reaction mixture was refluxed until the reaction was completed according to TLC (eluent C, 20 h). After concentration in vacuo, the residue was directly subjected to column chromatography (25 g silica, eluent A). Yield: 195 mg (61%). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 4.8 (br. signal; H-1), 4.2–3.4 (br. m; H-2, H-3, H-4, H-5, H-6), 2.5 (br. signal; CH_2–spacer), 0.8 (br. s; CH_3−C), 0.0 (br.s; CH_3−Si); MS (FAB): *m/z:* 3673 [*M*+].

***N*-[Mono(3-deoxy)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD]-*N*′-[mono-(3-deoxy)hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-CD]-decan-1,10-diamide (26)**: This compound was synthesized from compound **24** (135 mg) as described for **25**. The crude product was purified by column chromatography (40 g silica, eluent A). Yield: 180 mg (80%). MS (FAB): *m/z:* 3755 [*M*+].

5,5′-Dimethyl-2,2′-bipyridine (27): The synthesis of compound **27** was performed using a procedure of Breitmaier et al.,[27] which was modified as follows: Under argon, 2-bromo-5-methylpyridine (40.95 g) was dissolved in toluene (150 mL). This solution was added to a suspension of dried Raney nickel (8.0 g) in toluene (50 mL). After refluxing for 3 days, the solution was cooled to room temperature, and the precipitate was collected by filtration. The filtrate was rinsed with toluene to remove unconverted 2-bromo-5-methylpyridine. The green residue was dried in vacuo yielding **27** · $NiBr_2$ (45.5 g, 96%). An amount of this product (25.4 g) was dissolved in aqueous HCl (300 mL, 6M) and an aqueous NH_3 solution (25%) was added until the former solution was basic. Many (approx. 50!) extractions with $CHCl_3$ were necessary to obtain a crude product (10 g). Compound **27** was obtained as white needles, after purification by column chromatography (Silica 60, $CHCl_3$) followed by recrystallization from ethanol. Yield: 8.7 g (74%). M.p.: 114–115 °C (ref. [28]: 114.5–115 °C); ^{1}H NMR (90 MHz, $CDCl_3$): δ = 8.4 (s, 2H; Ar−H-6), 8.3 (d, 2H; Ar−H-3), 7.5 (d, 2H; Ar−H-4), 2.3 (s, 6H; CH_3); $C_{12}H_{12}N_2$: calcd C 78.23, H 6.56, N 15.20; found C 78.14, H 6.82, N 14.98.

[2,2′-Bipyridine]-5,5′-dicarboxylic acid (28): Compound **27** was oxidized with $KMnO_4$ following a procedure described by Case,[29] which was modified as follows: A mixture of $KMnO_4$ (30.8 g) and compound **27** (5.6 g) in water (500 mL) was heated at 70 °C for 24 h. After filtration of the reaction mixture and washing the brown filtrate with aqueous NaOH (1M, 50 mL), the combined water fractions were collected and washed three times with $CHCl_3$ to remove unconverted **27**. The aqueous solution was neutralized with HCl (2M) and concentrated (300 mL). After acidifying to pH 6, the light blue precipitate was collected by centrifugation, washed with ethanol (three times), and dried in vacuo. Yield: 5.25 g (71%). M.p.: > 350 °C; ^{1}H NMR (90 MHz, D_2O, NaOD): δ = 8.9 (s, 2H; Ar−H-6), 8.2 (d, 2H; Ar−H-3), 7.7 (d, 2H; Ar−H-4); IR (KBr): $\tilde{\nu}$ = 1680 (CO), 1590 cm^{-1} (Ar).

[2,2′-Bipyridine]-5,5′-dicarboxylic acid bis(*N*-hydroxysuccinimide) ester (30): Compound **28** (2.17 g) was dissolved in $SOCl_2$ (40 mL) and refluxed for 24 h. After removal of the excess of $SOCl_2$ in vacuo, the resulting diacid chloride was directly dissolved in CH_2Cl_2 and the potassium salt of *N*-hydroxysuccinimide (5.0 g, 3.7 equiv) was added. After 6 h of stirring at room temperature, the reaction was quenched by addition of an aqueous saturated solution of $NaHCO_3$ (200 mL). The aqueous layer was extracted 15 times with CH_2Cl_2 (150 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo yielding a crude product (2.4 g). Removal of unconverted compound **28** was achieved by dissolving the crude product in CH_2Cl_2 (1 L), followed by washings with aqueous NaOH (0.5M), a saturated solution of $NaHCO_3$ and with brine. The resulting compound was recrystallized from acetonitrile to give light yellow crystals. Yield: 1.7 g (43%). M.p.: 300 °C (decomp); ^{1}H NMR (100 MHz, [D_6]DMSO): δ = 9.40 (s, 2H; Ar−H), 8.73 (s, 4H; Ar−H), 2.94 (s, 8H; CH_2); $C_{20}H_{14}N_4O_8$: calcd C 54.80, H 3.22, N 12.78; found C 55.18, H 3.27, N 12.58.

***N*,*N*′-Bis[mono(3-deoxy)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD]-5,5′-dicarboxamide-2,2′-bipyridine (31)**: To a solution of dried (2.45 g, 1 h, 40 °C) monoamino-functionalized cyclodextrin **17** in THF (30 mL) was added compound **30** (277 mg, 1 equiv). After addition of two drops of triethylamine, the reaction mixture was refluxed for 40 h. After removal of the organic solvents in vacuo, the resulting solid was dissolved in ethyl acetate. The solution was washed with NaOH (twice, 1M) and brine (twice), dried over $MgSO_4$, and concentrated in vacuo to yield a crude product (2.5 g). Compound **31** was purified by column chromatography (300 g silica, eluent A) yielding a white solid. Yield: 1.15 g (45%). M.p.: > 350 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.5–7.8 (5 × br. s, ca. 6H; Ar−H), 5.1–4.6 (br. m, 14H; H-1), 4.4–3.2 (br. m; H-2, H-3, H-4, H-5, H-6), 0.9–0.6 (br. s; CH_3−C), 0.2– −0.2) (br. s; CH_3−Si). The peaks in the NMR spectra of this compound were broad, which may be due to the presence of more than one conformer in solution; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168, 156, 149, 147.5, 138, 137.5, 129.5, 124 (Ar−C and CO, more signals than expected probably due to the presence of more conformers), 104.3–100.5 (C-1), 83.1–71.7 (C-2, C-3, C-4, C-5), 62.7–61.4 (C-6), 26.7–25.8 (CH_3−C), 18.3 (CH_3−C), −4.8– −5.5) (CH_3−Si); $C_{180}H_{342}N_4O_{70}Si_{14} \cdot 4H_2O$: calcd C 52.12, H 8.50, N 1.35; found C 52.12, H 8.55, N 1.29.

13-(4′-Aminophenyl)-1,1,1-triphenyl-2,5,8,11-tetraoxatridecane (36): Compound **35** (2.6 g, 4.76 mmol) and 2-(4′-aminophenyl)ethyl alcohol (627 mg, 0.95 equiv) were dissolved in THF (60 mL), and potassium *tert*-butoxide (513 mg, 0.95 equiv) was added in one portion. After 6 h, the reaction mixture was concentrated in vacuo, and the residue dissolved in ethyl acetate. The solution was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (200 g silica 60; eluent 1% MeOH (v/v) in $CHCl_3$). This yielded compound **36** as an orange oil. Yield: 1.7 g (70%). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.5–7.1 (m, 15H; H-Trt), 6.9–6.8 (d, 2H; Ar−H), 6.5–6.4 (d, 2H; Ar−H), 3.8–3.3 (m, 12H; CH_2−O), 3.2 (t, 2H; CH_2−OTrt), 2.8 (t, 2H, CH_2−Ar).

11-(4′-Aminophenyl)-3,6,9-trioxaundecanol (37): Compound **36** (805 mg, 1.37 mmol) was dissolved in acetic acid (150 mL) and kept at 40 °C for 24 h. Subsequently, aqueous HCl (150 mL, 1M) was added, and the reaction mixture was washed with ethyl acetate to remove unconverted starting compound. NaOH was added to the mixture until the pH was 12. The product was extracted with ethyl acetate and the organic layers were dried over $MgSO_4$ and concentrated. After purification by column chromatography (80 g silica 60, eluent 3% MeOH (v/v) in $CHCl_3$) compound **37** was obtained as an orange oil. Yield: 248 mg (59%). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 6.9–6.8 (d, 2H; Ar−H), 6.5–6.4 (d, 2H; Ar−H), 3.8–3.3 (m, 14H; CH_2−O), 2.8 (t, 2H; CH_2−Ar); MS (EI) *m/z:* 269 [*M*+1].

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