A Homologous Series of Persubstituted Cyclodextrin Amino Acids: The Quest for Tubular Self-Assembly

Tomáš Kraus,*[a] Miloš Buděšínský,[a] Ivana Císařová,[b] and Jiří Závada[a]

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The synthesis, conformation and diverse self-assembling patterns of the homologous series of chemically uniform per(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-substituted α-, β- and γ-cyclodextrins **6a**–**6c** are reported. Helical self-assembly of the lowest homologue **6a** gave rise to a three-dimensional system of separate collinear channels. For the higher homologues **6b**–**6c**, such a unique architecture is prohibited by unfavorable geometrical factors. A comparison has been made with the corresponding series of native and permethylated cyclodextrins, and the role played by hydrogen bonds in promoting tubular architectures has been assessed.

Introduction

Inspired by the shapes of channels, tubes and pipes, and their important functions in the industrial environment, as well as in living systems, chemists are attempting to construct tubular structures on a molecular level.[1] Numerous approaches have been employed, giving rise to nanotubes endowed with various properties and functions. Besides the widely explored preparation of covalently bonded carbon nanotubes, the supramolecular self-assembly of complementary building units represents an alternative "bottom-up" approach. As a prominent example, tubular assemblies have been designed from six- or eight-membered cyclic D,L-peptides.[2] It has been shown that these assemblies can be incorporated into lipid membranes[3,4] and can enhance transport of small molecules and ions.[5–7] Presumably due to these properties, they also exhibit significant antibacterial effects.[8]

In addition to cyclopeptides, cyclic oligosaccharides are also interesting materials for tubular self-assembly. Artificial oligosaccharides composed of eight and ten alternating D- and L-rhamnopyranose units display tubular architecture in the solid state, supported by hydrogen bonds between hydroxylic groups of stacked units.[9,10] Native cycloglucopyranoses (cyclodextrins), on the other hand, do not tend to form spontaneously tubular structures in the solid state unless appropriate guest molecules are present.[11–14]

However, it has been shown that cyclodextrins modified with suitable binding sites on one rim of the cavity self-assemble into dimeric species. Thus, cyclodextrins bearing carboxylic acid groups appended onto the primary rim form stable dimers in non-polar media.[15] Upon their treatment with complementary derivatives persubstituted with amino groups, head-to-head couples are formed, even in aqueous solutions.[16–19]

Consequently, it is interesting to speculate that hermaphroditic cyclodextrins, persubstituted with complementary donor and acceptor functional groups at the opposite rims of the cavity, could self-assemble into infinite head-to-tail nanotubes. Such assemblies, based on pairing of carboxylic acid and amino groups, might also provide a route – via amide coupling – to the corresponding covalently-linked nanotubes.

We have designed the series of per(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-cyclodextrins **6a**–**6c** (Scheme 1) as suitable models for such investigation. In a preliminary note,[20] we outlined the behavior of the lowest homologue **6a**; herein we report the synthesis, conformation and diverse self-assembling patterns found in the full homologous series.

Results and Discussion

Syntheses

Cyclodextrins persubstituted with amino groups at the primary face and with carboxymethyl groups at the secondary face are elusive synthetic targets. Due to the adverse combination of steric hindrance and low selectivity factors, inseparable mixtures containing a wide array of incompletely substituted as well as oversubstituted by-products have previously been obtained.[21] Aiming at the chemically uniform per(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-substituted cyclodextrins, which are indispensable

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[a] Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic
Flemingovo nám. 2, 16610 Praha 6, Czech Republic
Fax: +420-220183560
E-mail: kraus@uochb.cas.cz
[b] Department of Inorganic Chemistry, Charles University
Hlavova 2030, 12840 Praha 2, Czech Republic

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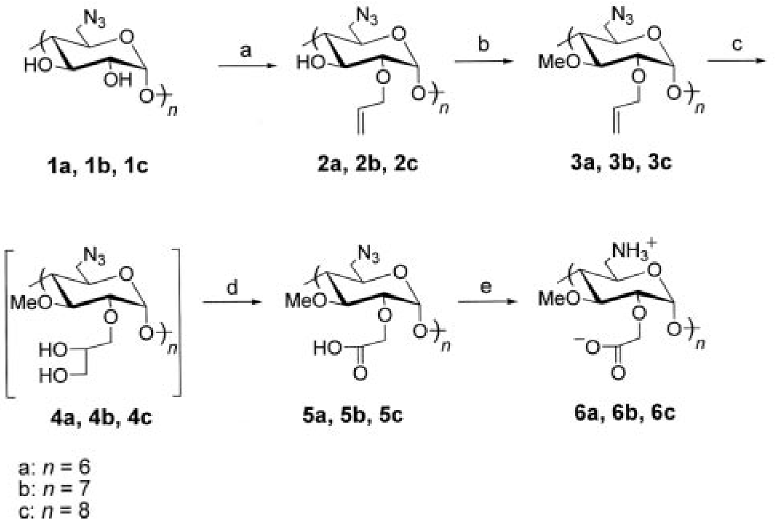

Scheme 1. a) for **1a**: allyl bromide, $Ba(OH)_2{\cdot}H_2O$, BaO, DMF, 25 °C, 24 h, 52%; for **1b** and **1c**: allyl bromide, LiOH. H_2O, DMF, 25 °C, 8 h, 32% and 20%, respectively; b) MeI, NaH, DMF, 25 °C, 3.5 h, 95−99%; c) OsO_4, 4-methylmorpholine *N*-oxide, acetone/water, 25 °C, 24 h, 71−75%; d) i. $NaIO_4$, H_2O, 25 °C, 2.5 h, ii. TEMPO, NaBr, NaClO, 25 °C, 2.5 h, 86−91%; e) H_2S, pyridine/water, 25 °C, 72 h, 89−90%.

for X-ray diffraction analysis, we developed a novel procedure[22] for the facially-selective percarboxymethylation of cyclodextrins. In the first step (Scheme 1), all the secondary hydroxyls at the C2 positions were selectively allylated. The reaction of **1a** with two equivalents of allyl bromide, in the presence of two equivalents of $Ba(OH)_2$ and one equivalent of BaO, gave a mixture of products, from which the pure hexaallyl derivative **2a** was isolated in 52% yield by preparative chromatography. Allylation of the higher homologues **1b** and **1c** under the same reaction conditions gave the desired products **2b** and **2c** in only 19% and 10% yields, respectively. Monitoring of the reactions indicated that over-substituted (at O3) by-products formed faster in these reactions than in the case of the allylation of **1a**. In order to optimize the reaction conditions, we tested alternative bases (LiH, NaH, LiOH and NaOH). We found that the amount of undesired by-products could be minimized when 1.5 equivalents of both lithium hydroxide and allyl bromide were used; the desired products **2b** and **2c** were isolated in 32% and 20% yields, respectively.

To avoid oxidation of C3 in the ensuing oxidative cleavage of the allyl groups, all hydroxylic groups at the C3 positions were methylated; treatment of **2a**, **2b** and **2c** with an excess of methyl iodide and sodium hydride in DMF furnished the permethylated compounds **3a**, **3b** and **3c**, respectively, in quantitative yields. The allylic groups of **3a**, **3b** and **3c** were then catalytically dihydroxylated with osmium tetroxide, using 4-methylmorpholine 4-oxide as the auxiliary oxidant, and the resulting diastereoisomeric mixtures of **4a**, **4b** and **4c**, respectively, were isolated by reversed-phase chromatography in yields over 70%. The diol groups were cleaved with sodium periodate, and, in one pot, the intermediate polyaldehydes were oxidized with TEMPO/NaClO/KBr to give the carboxymethyl derivatives **5a**, **5b** and **5c**, respectively, in overall yields ranging from 85 to 91%. In the final step of the synthesis, attempted reduction of the azido groups at C6 with triphenylphosphane and aqueous ammonia failed. Although these reagents had previously proved valuable for the reduction of a wide range of cyclodextrin azido derivatives, for the reduction of **5a**, only a poorly soluble mixture of incompletely reacted products was obtained. Fortunately, an excellent alternative was found using hydrogen sulfide in a mixture of pyridine and water,[23] which allowed the isolation of the pure amino acid **6a** in nearly quantitative yield. The same method was also successfully employed for the reduction of the homologues **5b** and **5c**.

The structures of compounds **2a**, **2b**, **2c** − **5a**, **5b**, **5c** were proved by ESI-MS, and ^{1}H and ^{13}C NMR spectral analysis. Free amino acids **6a**, **6b**, **6c** were characterized by of ^{1}H NMR, ESI-MS and X-ray analysis.

Crystallographic Analysis

Single crystals of **6a** suitable for X-ray analysis were obtained by slow evaporation of its solution in aqueous ammonia over partially hydrated P_2O_5 in a desiccator. The more soluble homologues **6b** and **6c** were crystallized from hot water.

Using the crystallographic data obtained for **6a**, **6b** and **6c**, we inspected the geometry of the individual glucose rings (via the torsion angle ν5,[24] Table 1) as well as that of the whole cyclodextrin macrocycle (via the torsion angles φ and ψ about the glucosidic bonds,[24] Table 1) and compared the pertinent data with those observed for the native cyclodextrins (Table 2). The overall schemes of hydrogen bonding and supramolecular packing were determined.

Hexakis(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-α-cyclodextrin (6a)

Of the three cyclodextrin amino acids **6a**−**6c**, the geometry of the macrocycle of **6a** (Figure 1, a) is the least

Table 1. Torsion angles (°) of amino acids **6a**−**6b**

	6a			**6b**			**6c**		
$G(n)$[a]	φ	ψ	ν_5	φ	ψ	ν_5	φ	ψ	ν_5
1	105.9	140.0	55.4	98.9	133.2	58.5	87.6	−62.8	60.9
2	91.1	128.1	63.6	116.0	73.0	−53.5	59.9	77.2	52.0
3				92.2	−178.4	68.1	104.2	153.7	55.3
4				107.8	137.4	56.5	81.5	48.6	58.1
5				80.6	80.2	58.9			
6				122.9	152.2	61.4			
7				106.7	135.7	55.4			

[a] Number of glucose residues $G(n)$ in asymmetric unit.

Table 2. Torsion angles (°) of native α-, β- and γ-cyclodextrins

	α			β			γ		
	φ	ψ	ν_5	φ	ψ	ν_5	φ	ψ	ν_5
average[a]	105.6	130.7	59.3	109.8	128.1	59.6	108.8	128.4	61.3
min.	87.7	111.4	52.4	101.43	111.1	53.0	103.6	111.9	54.2
max	121.2	170.5	64.1	120.1	142.0	64.7	123.2	138.3	66.4

[a] Values based on data obtained from Cambridge Structural Database (ref. [27]).

distorted. The cavity displays C_3 symmetry. Positive "gauche" values of the ν5 torsion angle (Table 1) reveal the usual $^4C_1$ chair conformation of the glucose rings.

By analyzing the crystal packing of **6a**, we have identified a highly symmetrical arrangement distinguished by the *R*3 space group, unique in the family of cyclodextrins. The individual cyclodextrin tectons recline on helical (staircase) trajectories (Figure 2) along the crystallographic *c* axis so that the i^{th} and $(i + 3)^{\text{th}}$ tectons occupy eclipsed positions. This results in an infinite array of parallel columns in which each column is shifted by one third (±1/3) of the cell parameter *c* with respect to its neighbors.

Closer analysis reveals that the intriguing helical framework is held together by hydrogen bonds. A complete proton transfer from carboxyl to amino groups has occurred in the crystal, giving rise to a complex hydrogen-bonding pattern (Figure 3). Each cyclodextrin unit is bound to its neighbors by 30 hydrogen bonds, with each pair of the neighboring cyclodextrins being bonded by three intermolecular single hydrogen bonds; thus, for example, in the segment ABC, two bonds link ammonium cations of A and carboxylate anions of B, whereas the third one points from an ammonium group of A to methoxy group of B. In ad-

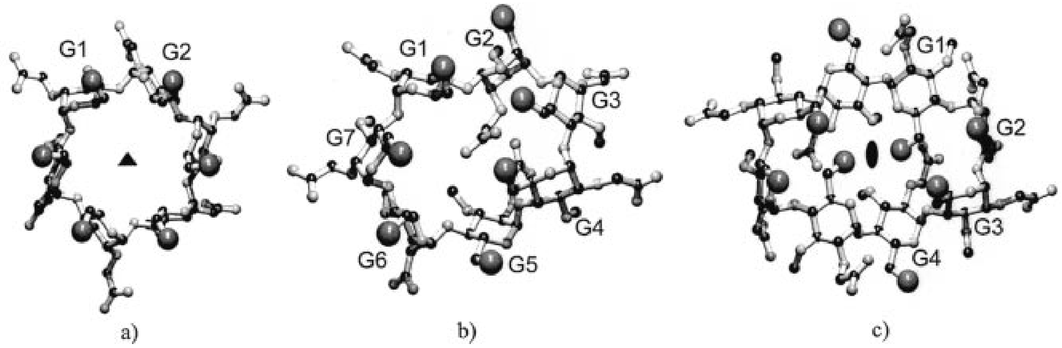

Figure 1. Ball and stick representations of the crystal structures of amino acids **6a**−**6c**. Water molecules and hydrogen atoms are omitted for clarity. Black spheres: carbon atoms, light-gray spheres: oxygen atoms, dark-gray spheres with expanded diameter: nitrogen atoms. a) **6a** with indicated threefold axis, b) **6b**, c) **6c** with indicated twofold axis.

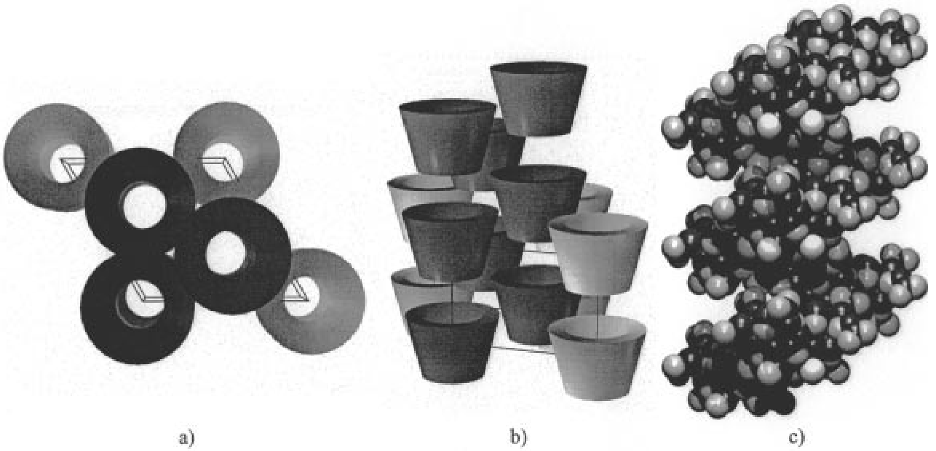

Figure 2. Perspective view of the packing of **6a** in the unit cell; schematic representation viewed along the *c* axis (Figure 2, a) and along the *b* axis (Figure 2, b) of the unit cell. The darker units show the helical arrangement expanded along the *c* axis. CPK representation (Figure 2, c) of the same helix.

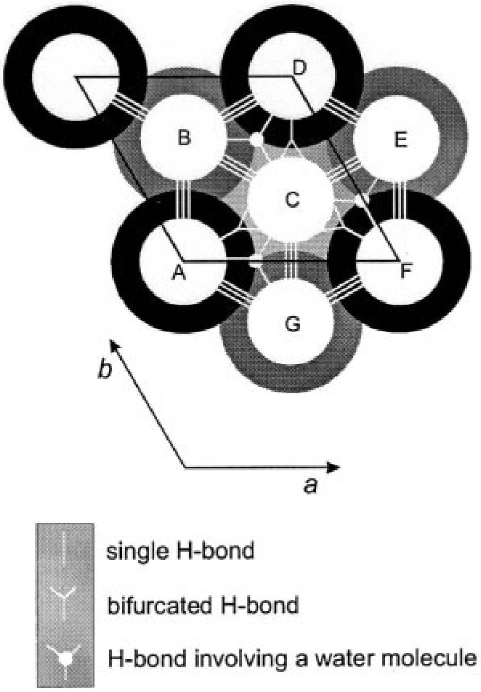

Figure 3. Schematic representation of the hydrogen bonding found in the structure of **6a**; view along the *c* axis with hydrogen bonds depicted as white lines (tectons E and G are added to the unit cell to describe the complete bonding pattern). Fifteen hydrogen bonds (a bifurcated hydrogen bond counted as one) are depicted for the tecton C; the remaining fifteen bonds are "hidden" below the tecton C. The intensity of shading reflects the relative distance of cyclodextrin units from the observer (the black color represents the nearest macrocycles).

dition, a bifurcated hydrogen bond connects an ammonium group of molecule A and a carboxylate moiety of another proximate cyclodextrin C. Moreover, one of the five fully occupied water molecules contributes to the overall stability of the helix by accepting two hydrogens from ammonium cations, one from macrocycle A and the second from macrocycle G; at the same time, it acts as a donor of two hydrogen bonds to the oxygen of one carboxyl group of C and a neighboring water molecule.

Each of the three glucose pairs of the α-cyclodextrin macrocycle acts as a donor and acceptor of hydrogen bonds in two helices differing in the sense of twist. Thus, each cyclodextrin unit represents a nodal point of six intersecting helices with alternating handedness (for example, ABC vs. DBC, DEC vs. FEC, FGC vs. AGC, as depicted for the central macrocycle C in Figure 3). In this way, a strong hydrogen-bonded network is formed, cross-linking the parallel columns, the surprising feature being a complete absence of hydrogen bonds between the proximate heads and tails of the eclipsed tectons constituting the individual columns. This contrasts with the customary channel architecture of the native cyclodextrin inclusion complexes, which consists of hydrogen-bonded pillars of tectons (vide infra).

Although the van der Waals distance between the faces of the eclipsed cyclodextrin units is about 4 Å in the crystal of **6a**, the staircase arrangement of cyclodextrin units in the neighbouring columns effectively shields these "holes", giving rise to a system of separate collinear channels.

Heptakis(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-β-cyclodextrin (6b)

The geometry of the cavity of **6b** (Figure 1, b) significantly departs from the ideal C_7 symmetry; the molecule is C_1-symmetrical and has a quasi-elliptical shape. Evidence for this distortion comes from a wide range of φ (80.6°−122.9°) and ψ (−178.4° to 152.2°) torsion angles (Table 1). Analysis of the ν5 torsion angles reveals that in addition to six glucose residues (G1 and G3-G7) that have the usual $^4C_1$ conformation, one glucose ring (G2) is inverted into the $^1C_4$ chair conformation. The carboxymethyl groups belonging to residues G1 and G3−G7 are directed outside the cavity, whereas in glucose unit G2, the carboxy group points into the cavity and forms intramolecular hydrogen bonds with two proximal inward-orientated ammonium groups. Each molecule participates in 18 intermolecular and 2 intramolecular hydrogen bonds of the $NH_4^+\cdots COO^-$ type. There are 30 molecules of water per cyclodextrin unit, and these are distributed over 36 sites, of which only one is located inside the cavity; the others occupy the intermolecular space.

This irregular arrangement is reflected in the overall molecular packing. The whole molecule **6b** constitutes an asymmetric unit that adopts four mutually different positions in the unit cell (Figure 4), related by symmetry operations of the $P2_12_12_1$ space group. As a consequence, no elements of tubular architecture are apparent in the crystal structure of the β-cyclodextrin derivative, in contrast to the lower homologue **6a**.

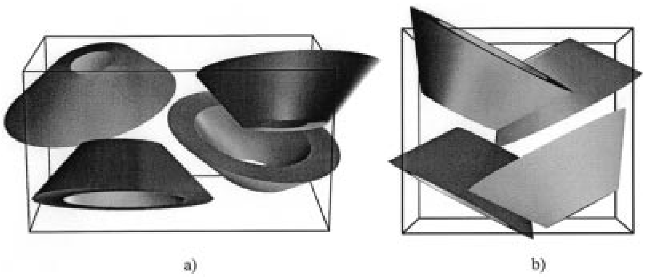

Figure 4. Perspective schematic representation of the packing of **6b** in the unit cell; a) view along the *a* axis; b) view along the *c* axis.

Octakis(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-γ-cyclodextrin (6c)

Similarly to **6b**, the shape of **6c** is somewhat elliptical (Figure 1, c) and bowl-shaped. The molecule is C_2-symmetrical, with the twofold axis perpendicular to the mean plane delineated by the O4 atoms. The torsion angles ν5 reveal a (+)gauche orientation, consistent with the common $^4C_1$ conformation. The φ and ψ torsion angles indicate an even larger degree of distortion of the macrocycle than in **6b**. Indeed, the two G4 glucose units (related by the C_2 axis) are completely submerged below the O4 mean plane, and the adjacent carboxyl groups protrude over the cyclodextrin cavity, thus closing it from one side. The two G1 glucose units are lifted above the plane, and their two ammonium groups point inside the cavity and form intramolecular hydrogen bonds with the two aforementioned proximal carboxyl groups.[25]

The remaining six ammonium and six carboxylate groups are orientated outwards and form a three-dimensional network of intermolecular hydrogen bonds. Altogether, there are 12 intermolecular and 2 intramolecular hydrogen bonds between ammonium and carboxylic groups. There are 27.25 molecules of water per cyclodextrin molecule, distributed over 38 sites. Molecules of **6c** crystallize in the $P4_32_12$ space group. The asymmetric unit consists of half of the molecule **6c**, and adopts four different symmetry-related positions in the unit cell (Figure 5). A view along the unique *c* axis (Figure 5, b) reveals a "parquet-like" pattern,[9] and thus falls into the category of cage-type structures.

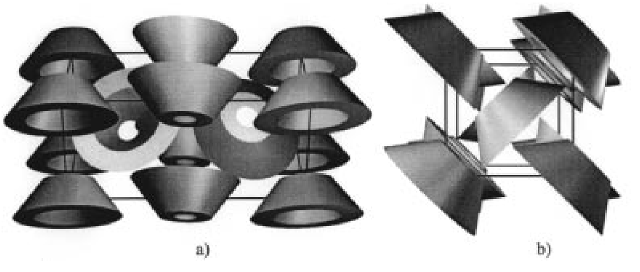

Figure 5. Perspective schematic representation of the packing of **6c** in the unit cell; a) view along the *a* axis; b) view along the *c* axis.

The geometry of the macrocycles and their orientation in the crystal lattice do not allow tubular packing, as observed for **6a**; yet there are very narrow straight channels in the crystal packing of **6c**. They are located, however, exclusively in the intermolecular (extra-annular) space along the fourfold axis (*c* axis direction), and they are filled with water molecules.

Corroborative Evidence from NMR Studies

In order to gain additional insight on the structure of the free amino acids **6a**−**6c** in the aqueous environment, ^{1}H NMR spectra of their dilute D_2O solutions were investigated at room as well as elevated temperatures. Interestingly, in the spectrum of **6c**, four signals, in a 1:1:1:1 ratio, appeared at 5.3−5.7 ppm (Figure 6), and were assigned to the four distinguishable H1 protons. With increasing temperature, the four signals coalesced into a broad singlet. This observation suggests that at room temperature, the free amino acid **6c** is C_2-symmetrical in aqueous solution, in agreement with the C_2 symmetry of **6c** found in the solid state. Such a phenomenon − presumably due to the abovementioned intramolecular hydrogen bonds − is absent in well-resolved ^{1}H NMR spectra of the lower homologues **6a**, **6b**, and neither is it observed for native or other persubstituted cyclodextrins.[26]

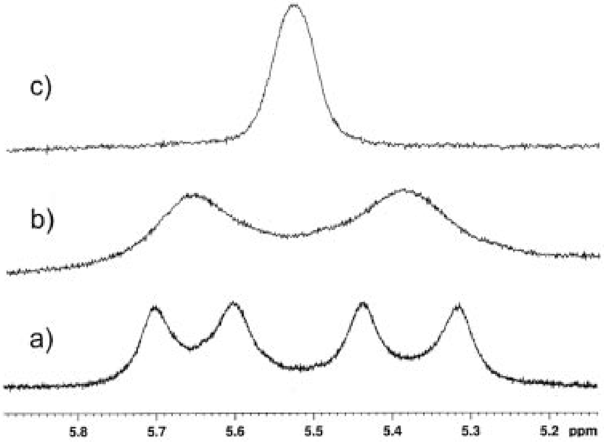

Figure 6. Expanded ^{1}H NMR spectra of the H-1 protons of **6c** in D_2O at a) 25 °C, b) 50 °C, c) 80 °C.

Comparison with the Parent and Permethylated Cyclodextrins

A prominent structural feature distinguishing the parent α-, β- and γ-cyclodextrins is a ring of intramolecular hydrogen bonds occurring between the O2−H and O3−H hydroxyl groups of adjacent glucose units. The cyclic arrangement of the intramolecular hydrogen bonds, which becomes increasingly strong on going from the α- to the γ-homologue, stabilizes the orientation of one glucose unit relative to its adjacent neighbors, as well as the macrocyclic conformation. As pointed out by Saenger,[12] this organization limits the conformational space of the torsion angles φ and ψ, which describe rotation about the glucosyl C1(n) − O4(n-1) and O4(n-1) − C4(n-1) bonds. Accordingly, a gradual leveling out of the individual values of the torsion angles on going along the homologous series **6a**−**6c** may be observed (Table 2).[27]

Such a structure-forming factor is absent in the cyclodextrin amino acids **6a**−**6c** now under study, and this may account for their less ordered arrangement, particularly in the cases of the larger β- and γ-homologues (Table 1). Notably, but not entirely surprisingly, a closely related conformational situation to that of the cyclodextrin amino acids has been observed[31] for the per(2,3,6-*O*-methylated) α-, β-cyclodextrins, which are completely devoid of the capability for the intramolecular hydrogen bonding.

Concerning the pattern of crystal packing, no simple correlation with the cyclodextrin substitution and/or conformation can be found. Examination of the literature[11,12,27] reveals that the series of homologous parent cyclodextrins prefers, in the absence of guest compounds other than water, cage-type crystal packing over channel-type.[13] In the presence of appropriate guests, the parent α-, β- and γ-cyclodextrins yield crystalline channel-type complexes in which the host molecules are stacked on top of each other like coins in a tube, such that the linearly aligned cavities frame "infinite" channels in which the guest molecules are embedded. The stacks of cyclodextrins are stabilized by intermolecular hydrogen bonds, either between the secondary (O2−H/O3−H) and primary (O6−H) sides, producing head-to-tail patterns, or between secondary and secondary on one side, and primary and primary on the other side, leading to head-to-head arrangements. This might suggest that the intra- and intermolecular hydrogen bonds co-operate in the organization of the channels, with the ring-system of the former (intramolecular O2−H/O3−H) bonds providing the optimal donor-acceptor platform for "docking" of the neighbor tectons, this being controlled by the latter (intermolecular) hydrogen bonds.

This notwithstanding, the unique hydrogen bonding capability of native cyclodextrins appears neither to be the sole nor even the main prerequisite for their columnar stacking. Such a possibility can be refuted by the striking resemblance with the inclusion complexes of the corresponding per(2,3,6-*O*-methylated) cyclodextrins, which also exclusively exhibit columnar (head-to-tail) stacking, in the absence of hydrogen bonding. This strongly suggests that the structure of guest molecules, rather than the hydrogen-bonding ability of the hosts, provides the main driving force for the channel-type packing of the native as well as modified cyclodextrins. In this way, the helical self-assembly of the tubular architecture encountered in the free cyclodextrin amino acid **6a** appears to be a remarkable anomaly originating from a combination of favorable geometrical, conformational and hydrogen-bonding factors.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were measured on a Varian UNITY-500 (^{1}H at 500 MHz; ^{13}C at 125.7 MHz) FT NMR spectrometer. Chemical shifts are referenced to the signals of solvents. 2D-COSY spectra were used for the structural assignment of protons. Carbon signals were assigned using heteronuclear ^{1}H-^{13}C 2D-HMQC spectra. Mass spectra (Finnigan, ESI ionization) were recorded in a full-scan mode with m/z = 50−2500 Dalton range of analyzed ions. The capillary was heated to 275 °C, spray voltage was set to 4.5 kV, 38 V on capillary. Optical rotations were recorded on AUTOPOL IV (Rudolph Research Analytical). Preparative reversed-phase chromatography (RP) was carried out on medium pressure columns containing 200 g or 40 g of C-18 modified silica (Tessek, 30 µm and 15 µm resp.). Thin-layer (TLC) and reversed-phase thin-layer chromatography (RPTLC) were performed with precoated Silica Gel 60F and RP-18 F plates (E. Merck) resp., which were developed by spraying with 5% H_2SO_4 in EtOH and heating. All chemicals used were commercially available. Compounds **1a**, **1b**, **1c** were prepared according to described procedures.[32,33] Low solubilities of compounds **6a**−**6c** precluded measurements of their ^{13}C spectra and optical rotations. Samples were dried in a desiccator over P_2O_5 for 24 hours under reduced pressure. However, satisfactory elemental analysis could not be obtained for compounds **5a**−**5c** and **6a**−**6c** unless variable numbers of water molecules are taken into account. Thus, calculations based on weights of these compounds (molarity, yield, optical rotation) are related to the hydrated molecules.

Hexakis(2-*O*-allyl-6-azido-6-deoxy)-α-cyclodextrin (2a): Compound **1a** (1.123 g, 1.00 mmol) was dissolved in dry DMF (50 mL). $Ba(OH)_2{\cdot}H_2O$ (2.27 g, 12 mmol) and BaO (0.919 g, 6 mmol) were added to the reaction mixture, followed by allyl bromide (1.04 mL, 12 mmol). The mixture was stirred for 24 hours and then the reaction was quenched by addition of aqueous ammonia (25% solution, 0.45 mL). After 30 minutes, the mixture was filtered through a Celite layer on a glass frit, and the filtrate was evaporated to dryness under reduced pressure at 40 °C. The residue was partitioned between HCl (0.5 N, 200 mL) and ether (250 mL) by stirring the mixture until no insoluble material remained in either of the phases. The organic layer was separated and washed with HCl (0.2 N, 2 × 100 mL), followed with water (2 × 100 mL) and $NaHCO_3$ (5% aqueous solution, 100 mL), after which it was dried with $MgSO_4$ and the solvents evaporated to dryness to give a yellow foam (1.285 g). The analysis of this crude product on TLC plates ($CHCl_3$/MeOH, 98:2) revealed four spots; the most abundant product **2a** at R_f = 0.15 was isolated by flash chromatography (silica gel, 100 g, gradient elution from $CHCl_3$ to $CHCl_3$/MeOH, 98:2) as a colorless oil (705 mg, 52%); R_f = 0.15 ($CHCl_3$/MeOH, 98:2). $[\alpha]_D^{25}$ = +98 (c = 0.3 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 5.92 (dddd, J = 17.2, 10.3, 7.0, 5.4 Hz, 1 H, −CH=, 2-*O*-allyl); 5.32 (dm, J = 17.2, 1.5, 1.3, 1.1 Hz, 1 H, =C*H*aHb, 2-*O*-allyl), 5.26 (dm, J = 10.3, 1.3, 1.2, 1.1 Hz, 1 H, =CHa*H*b; 2-*O*-allyl), 4.90 [d, J(1,2) = 3.5 Hz, 1 H, H-1), 4.63 [d, J(OH,3) = 1.1 Hz, 1 H, OH), 4.45 (m, J = 12.5, 5.4, 1.5, 1.2 Hz, 1 H, O-C*H*aHb-; 2-*O*-allyl), 4.23 (ddt, J = 12.5, 7.0, 1.1, 1.1 Hz, 1 H, O-CHa*H*b-; 2-*O*-allyl), 4.08 (ddd, J(3,2) = 9.7, J(3,4) = 8.4 and J(3,OH) = 1.1 Hz, 1 H, H-3), 3.82 (ddd, J(5,4) = 9.8, J(5,6a) = 2.2 and J(5,6b) = 6.1 Hz, 1 H, H-5), 3.70 [dd, J(6a,6b) = 13.2 and J(6a,5) = 2.2 Hz, 1 H, H-6a), 3.55 [dd, J(6b,6a) = 13.2 and J(6b5) = 6.1 Hz, 1 H, H-6b), 3.45 [dd, J(2,3) = 9.7 and J(2,1) = 3.5 Hz, 1 H, H-2), 3.38 [dd, J(4,5) = 9.8 and J(4,3) = 8.4 Hz, 1 H, H-4). ^{13}C NMR (125.7 MHz, $CDCl_3$, 20 °C): δ = 133.86 (=CH-), 119.02 (=CH_2), 101.38 (C-1), 84.78 (C-4), 78.26 (C-2), 73.39 (O-CH$_2$-), 73.31 (C-3), 70.50 (C-5), 51.66 (C-6). ESI-MS: m/z = 1385.4 for $[M + Na]^+$; elemental analysis calcd. (%) for $C_{54}H_{78}N_{18}O_{24}$ (1363.3): calcd. C 47.57, H 5.77, N 18.49; found C 47.19, H 6.02, N 18.24.

Hexakis(2-*O*-allyl-6-azido-6-deoxy-3-*O*-methyl)-α-cyclodextrin (3a): Compound **2a** (681 mg, 0.50 mmol) was dissolved in dry DMF (20 mL). Sodium hydride (240 mg of a 60% dispersion in oil, 6.0 mmol) was washed with petroleum ether and added to the stirred solution under argon. Methyl iodide (0.467 mL, 7.5 mmol) was added dropwise, and the stirring mixture was allowed to react for 5 hours at room temperature. The excess of sodium hydride was decomposed by dropwise addition of MeOH (2 mL) with cooling, and the solvents were evaporated under reduced pressure at 40 °C. The residue was partitioned between H_2O (100 mL) and petroleum ether (250 mL). The organic layer was washed with 10% aqueous solution of sodium thiosulfate (50 mL), followed with H_2O (2 × 100 mL) and dried over magnesium sulfate. Evaporation of the solvent furnished the crude product (0.745 g) as a white foam. TLC analysis ($CHCl_3$/MeOH, 99:1) showed only one significant spot at R_f = 0.5. The crude product was purified by flash chromatography (silica gel, 50 g, gradient elution from neat CH_2Cl_2 to CH_2Cl_2/MeOH, 99:1) to give **3a** (715 mg, 99%) as a white foam; R_f = 0.5 ($CHCl_3$/MeOH, 99:1). $[\alpha]_D^{25}$ = +135 (c = 0.2 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 5.96 (dddd, J = 17.3, 10.4, 5.8, 5.2 Hz, 1 H, −CH=, 2-*O*-allyl); 5.33 (dm, J = 17.3, 1.8, 1.7, 1.6 Hz, 1 H, =C*H*aHb, 2-*O*-allyl), 5.19 (dm, J = 10.4, 1.8, 1.5, 1.3 Hz, 1 H, =CHa*H*b; 2-*O*-allyl), 4.95 [d, J(1,2) = 3.5 Hz, 1 H, H-1), 4.26 (m, J = 13.0, 5.8, 1.6, 1.3 Hz, 1 H, O-C*H*aHb-; 2-*O*-allyl), 4.12 (m, J = 13.0, 5.2, 1.7, 1.5 Hz, 1 H, O-CHa*H*b-; 2-*O*-allyl), 3.80 (ddd, J(5,4) = 9.4, J(5,6b) = 5.6 and J(5,6a) = 2.1 Hz, 1 H, H-5), 3.77 [dd, *J*(6a,6b) = 13.2 and *J*(6a,5) = 2.1 Hz, 1 H, H-6a), 3.62 (s, 3 H, OCH_3), 3.61 [dd, *J*(6b,6a) = 13.2 and *J*(6b,5) = 5.6 Hz, 1 H, H-6b), 3.54 [dd, *J*(3,2) = 9.9 and *J*(3,4) = 8.6 Hz, 1 H, H-3), 3.45 [dd, *J*(4,5) = 9.4 and *J*(4,3) = 8.6 Hz, 1 H, H-4), 3.30 [dd, *J*(2,3) = 9.9 and *J*(2,1) = 3.5 Hz, 1 H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$, 20 °C): δ = 135.14 (=CH-), 116.86 (=CH_2), 100.32 (C-1), 83.15 (C-4), 81.19 (C-3), 79.47 (C-2), 71.76 (O-*C*H_2), 71.07 (C-5), 62.05 (OCH_3), 51.97 (C-6). ESI-MS: *m*/*z* = 1469.5 for [M + Na]$^+$; elemental analysis calcd. (%) for $C_{60}H_{90}N_{18}O_{24}$ (1447.5): calcd. C 49.79, H 6.27, N 17.42; found C 49.52, H 6.43, N 17.21.

Diastereomeric Mixture of Hexakis[6-azido-6-deoxy-2-*O*-(2,3-dihydroxypropyl)-3-*O*-methyl]-α-cyclodextrin (4a): Compound **3a** (675 mg, 0.466 mmol) was dissolved in acetone (8 mL), and 4-methylmorpholine 4-oxide monohydrate (567 mg, 4.19 mmol) was added, followed by H_2O (4 mL). Osmium tetroxide (0.175 mL of 2.5 wt.% solution in *tert*-butyl alcohol, 31.7 μmol) was added to the stirred cloudy mixture. The reaction mixture was kept for 24 h at room temperature under argon with moderate stirring and occasional shaking. TLC analysis (RP TLC, H_2O/MeOH, 30:70) of the reaction mixture revealed a minor spot at R_f = 0.4 and one intensive spot of **4a** at R_f = 0.18. Thus, the solvents were evaporated, and the residue was dissolved in MeOH/H_2O, 50:50 and charged onto an RP column. Subsequent reversed-phase chromatography (gradient elution from H_2O/MeOH, 50:50 to 20:80) yielded **4a** as a white amorphous solid (548 mg, 71%); R_f = 0.18 (RP TLC, H_2O/MeOH, 30:70). ESI MS: *m*/*z* = 1673.5 for [M + Na]$^+$; elemental analysis calcd. (%) for $C_{60}H_{102}N_{18}O_{36}$ (1651.6): calcd. C 43.63, H 6.23, N 15.27; found C 43.25, H 6.38, N 15.14.

Hexakis(6-azido-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-α-cyclodextrin (5a): A diastereomeric mixture of **4a** was dissolved in CH_3CN/H_2O, 3:7 (30 mL), and $NaIO_4$ (642 mg, 3 mmol) was added. The solution was allowed to react for 2.5 hours at room temperature. Then it was cooled down to 0−5 °C, and TEMPO (270 mg, 2 mmol) and $NaHCO_3$ (168 mg, 2 mmol) were added, followed by an aqueous solution of NaBr (1 M, 2 mL, 2 mmol) and a pre-cooled aqueous solution of NaOCl (0.7 M, 11.4 mL, 8 mmol). The pH of the mixture was adjusted to 10.0 by addition of NaOH (0.5 M) and maintained for 2.5 hours. Then the reaction was quenched with MeOH (the color of the solution turned from red to yellow). After 10 minutes, TEMPO was extracted with diethyl ether (5 × 20 mL), and the alkaline aqueous mixture was filtered. The filtrate was acidified with HCl (2N) to pH 1.5 whilst stirring, and the resulting white precipitate was collected and washed with water. Then it was dissolved in a mixture of CH_3CN/H_2O, 1:1, and subjected to an RP chromatography (gradient elution from CH_3CN/H_2O/TFA, 10:89.9:0.1 to 50:49.9:0.1). Evaporation of the solvents gave **5a** as a white crystalline material (491 mg, 91%, calcd. for tetrahydrate); m.p. 125−135 °C (dec.); R_f = 0.10 (RP TLC, H_2O/CH_3CN/TFA 60:39.9:0.1). $[\alpha]_D^{25}$ = +119 (*c* = 0.3 in DMSO). ^1H NMR (500 MHz, DMSO, 50 °C): δ = 12.40 (b, 1 H, COOH), 5.15 [d, *J*(1,2) = 3.4 Hz, 1 H, H-1), 4.26 (d, *J* = 16.4 Hz, 1 H, O-*CH*aHb-COOH), 4.15 (d, *J* = 16.4 Hz, 1 H, O-CHa*H*b-COOH), 3.82 [m, *J*(5,4) = 9.1, *J*(5,6b) = 6.6 and *J*(5,6a) = 2.5 Hz, 1 H, H-5), 3.82 [dd, *J*(6a,6b) = 13.8 and *J*(6a,5) = 2.5 Hz, 1 H, H-6a), 3.60 [dd, *J*(6b,6a) = 13.8 and *J*(6b,5) = 6.6 Hz, 1 H, H-6b), 3.52 (s, 3 H, OCH_3), 3.51 [dd, *J*(4,5) = 9.1 and *J*(4,3) = 8.5 Hz, 1 H, H-4), 3.45 [dd, *J*(3,2) = 9.8 and *J*(3,4) = 8.5 Hz, 1 H, H-3), 3.35 [dd, *J*(2,3) = 9.8 and *J*(2,1) = 3.4 Hz, 1 H, H-2). ^{13}C NMR (125.7 MHz, DMSO, 50 °C): δ = 171.32 (COOH), 99.24 (C-1), 82.01 (C-4), 81.12 (C-3), 79.45 (C-2), 70.39 (C-5), 67.22 (O-*C*H_2-COOH), 60.78 (OCH_3), 51.63 (C-6). ESI-MS: *m*/*z* = 1577.4 for [M + Na]$^+$; elemental analysis calcd. (%) for $C_{54}H_{78}N_{18}O_{36}$·$4H_2O$ (1627.4): calcd. C 39.85, H 5.33, N 15.49; found C 39.77, H 5.13, N 15.26.

Hexakis(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-α-cyclodextrin (6a): Compound **5a** (200 mg, 0.123 mmol) was dissolved in mixture of pyridine (5 mL) and water (5 mL). The stirred mixture was bubbled with argon. Hydrogen sulfide was slowly introduced through a septum with a slight overpressure. After about 2 hours, the solution turned orange. The reaction mixture was allowed to react for 72 hours with occasional introduction of hydrogen sulfide, so that the color of the mixture was kept orange (a yellow color indicates an insufficient concentration of H_2S) over the course of the reaction. The solvents were then evaporated to dryness, and the residue was dispersed in water and the mixture was acidified with aqueous solution of HCl (1 M) to pH ≈ 2. The material dissolved and the solution was allowed to stand for 1 hour. Then the mixture was charged onto a column containing Dowex 50 H^+ (20 mL), and the column was washed with water (approximately 50 mL) until the eluate became neutral. Then the column was eluted with 1 N NH_4OH (50 mL), and fractions containing alkaline eluate were collected. Slow evaporation of this solution on a rotary evaporator under reduced pressure yielded crystalline material (181 mg) which was further purified by crystallization; the material was dispersed in water (5 mL) and aqueous ammonia (1N) was added dropwise with simultaneous stirring until all material dissolved. The solution was filtered through a fine-sintered glass and the flask with the solution was placed into an desiccator over small amount of partially hydrolyzed P_2O_5. Colorless crystals of **6a**, some of which were submitted for X-ray analysis, formed within 5 days. The overall yield of **6a** after drying in vacuo over P_2O_5 at 40 °C for 10 hours was 167 mg (90%, calcd. for hexahydrate); no melting point up to 300 °C. ^1H NMR (500 MHz, D_2O, 80 °C): δ = 5.38 [d, *J*(1,2) = 3.0 Hz, 1 H, H-1), 4.20−4.05 (m, 3 H, H5 and O−C*H*$_2$-COOH), 3.83 [dd, *J*(3,2) = 9.8 and *J*(3,4) = 8.0 Hz, 1 H, H-3), 3.74 [dd, *J*(4,5) = 9.2 and *J*(4,3) = 8.0 Hz, 1 H, H-4), 3.67 (s, 3 H, OCH_3), 3.51 [dd, *J*(2,3) = 9.8 and *J*(2,1) = 3.0 Hz, 1 H, H-2), 3.24 (b, 2 H, H-6a and H-6b). ESI-MS: *m*/*z* = 1399.4 (30%) for [M + H]$^+$, 700.4 (100%) for [M +2H]$^{2+}$; elemental analysis calcd. (%) for $C_{54}H_{90}N_6O_{36}$·6 H_2O (1507.4): calcd. C 43.03, H 6.82, N 5.58; found C 43.27, H 6.88, N 5.47.

Heptakis(2-*O*-allyl-6-azido-6-deoxy)-β-cyclodextrin (2b): Compound **1b** (3.160 g, 2.41 mmol) was dissolved in dry DMF (70 mL). Freshly powdered LiOH·H_2O (1.063 g, 25.3 mmol) was added to the reaction mixture. Then allyl bromide (2.19 mL, 25.33 mmol) was added dropwise to the stirring mixture over 2 hours. The mixture was stirred for a further 6 hours and then the reaction was quenched by addition of aqueous ammonia (25% aq. solution, 1.0 mL). After 30 minutes, the solvents were taken up under reduced pressure at 40 °C. The residue was partitioned between water (200 mL) and ether (250 mL). The organic layer was separated and washed with water (2 × 200 mL) and brine (200 mL). Afterwards, it was dried with $MgSO_4$ and the solvents evaporated to dryness to give a white foam (3.620 g). Analysis of this crude product on TLC plates (toluene/acetone, 5:1) revealed three spots; the most abundant product **2b** at R_f = 0.3 was isolated by flash chromatography (silica gel, 300 g, gradient elution from toluene to toluene/acetone, 9:1) as a colorless foam (1.240 g, 32%); R_f = 0.3 (toluene/acetone, 5:1). $[\alpha]_D^{25}$ = 101 (*c* = 0.1 in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 5.93 (dddd, *J* = 17.2, 10.3, 7.1, 5.4 Hz, 1 H, −CH=, 2-*O*-allyl), 5.32 (dm, *J* = 17.2, 1.7, 1.5, 1.0 Hz, 1 H, =C*H*aHb, 2-*O*-allyl), 5.25 (dm, *J* = 10.3, 1.7, 1.2, 1.2 Hz, 1 H, =CHa*H*b; 2-*O*-allyl), 4.90 (s, 1 H, OH), 4.88 [d, *J*(1,2) = 3.7 Hz, 1 H, H-1), 4.48

(m, J = 12.4, 5.4, 1.5, 1.2 Hz, 1 H, O-C*H*aHb-; 2-*O*-allyl), 4.24 (ddt, J = 12.4, 7.1, 1.2, 1.0 Hz, 1 H, O-CHa*H*b-; 2-*O*-allyl), 3.90 [dd, $J(3,2)$ = 9.6 and $J(3,4)$ = 8.8 Hz, 1 H, H-3), 3.71 (ddd, $J(5,4)$ = 9.4, $J(5,6b)$ = 6.5 and $J(5,6a)$ 2.2 Hz, 1 H, H-5), 3.72 [dd, $J(6a,6b)$ = 13.5 and $J(6a,5)$ = 2.2 Hz, 1 H, H-6a), 3.55 [dd, $J(6b,6a)$ = 13.5 and $J(6b,5)$ = 6.5 Hz, 1 H, H-6b), 3.44 [dd, $J(2,3)$ = 9.6 and $J(2,1)$ = 3.7 Hz, 1 H, H-2), 3.30 [dd, $J(4,5)$ = 9.4 and $J(4,3)$ = 8.8 Hz, 1 H, H-4). ^{13}C NMR (125.7 MHz, $CDCl_3$, 20 °C): δ = 133.79 (=CH-), 119.09 (=CH_2), 101.81 (C-1), 84.72 (C-4), 78.66 (C-2), 73.57 (O-*C*H_2-), 73.01 (C-3), 70.20 (C-5), 51.50 (C-6). ESI-MS: m/z = 1612.5 for $[M + Na]^+$; elemental analysis calcd. (%) for $C_{63}H_{91}N_{21}O_{28}$ (1590.5): calcd. C 47.57, H 5.77, N 18.49; found C 47.62, H 5.96, N 18.22.

Heptakis(2-*O*-allyl-6-azido-6-deoxy-3-*O*-methyl)-β-cyclodextrin (3b): Compound **3b** was prepared from **2b** (1.200 g, 0.755 mmol) analogously to **3a**. The product was isolated as a colorless foam (1.420 g, 97%); R_f = 0.4 (toluene/acetone, 10:1). $[\alpha]_D^{25}$ = 107 (c = 0.1 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 5.95 (dddd, J = 17.3, 10.2, 5.8, 5.4 Hz, 1 H, −CH=, 2-*O*-allyl); 5.32 (dm, J = 17.3, 1.7, 1.6, 1.5 Hz, 1 H, =C*H*aHb, 2-*O*-allyl), 5.28 (dm, J = 10.2, 1.7, 1.4, 1.4 Hz, 1 H, =CHa*H*b; 2-*O*-allyl), 5.06 [d, $J(1,2)$ = 3.7 Hz, 1 H, H-1), 4.23 (m, J = 12.8, 5.8, 1.5, 1.4 Hz, 1 H, O-C*H*aHb-; 2-*O*-allyl), 4.18 (m, J = 12.8, 5.4, 1.6, 1.4 Hz, 1 H, O-CHa*H*b-; 2-*O*-allyl), 3.81 (ddd, $J(5,4)$ = 9.1, $J(5,6b)$ = 5.4 and $J(5,6a)$ = 2.2 Hz, 1 H, H-5), 3.73 [dd, $J(6a,6b)$ = 13.2 and $J(6a,5)$ = 2.2 Hz, 1 H, H-6a), 3.63 (s, 3 H, OCH_3), 3.59 [dd, $J(6b,6a)$ = 13.3 and $J(6b,5)$ = 5.4 Hz, 1 H, H-6b), 3.54 (m, 1 H, H-4), 3.52 (m, 1 H, H-3), 3.34 [dd, $J(2,3)$ = 9.6 and $J(2,1)$ = 3.7 Hz, 1 H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$, 20 °C): δ = 134.98 (=CH-), 116.98 (=CH_2), 98.94 (C-1), 81.68 (C-3), 80.59 (C-4), 79.03 (C-2), 72.05 (O-*C*H_2-), 70.92 (C-5), 61.61 (OCH_3), 51.83 (C-6). ESI-MS: m/z = 1710.6 for $[M + Na]^+$; elemental analysis calcd. (%) for $C_{70}H_{105}N_{21}O_{28}$ (1688.7): calcd. C 49.79, H 6.27, N 17.42; found C 49.89, H 6.19, N 17.25.

Diastereomeric Mixture of Heptakis[6-azido-6-deoxy-2-*O*-(2,3-dihydroxypropyl)-3-*O*-methyl]-β-cyclodextrin (4b): Compound **4b** was prepared from **3b** (1.100 g, 0.651 mmol) analogously to **4a**. The product was isolated as a colorless foam (0.941 g, 75%); R_f = 0.38 (MeOH − H_2O, 70:30). ESI-MS: m/z = 1948.6 for $[M + Na]^+$; elemental analysis calcd. (%) for $C_{70}H_{119}N_{21}O_{42}$ (1926.8): calcd. C 43.63, H 6.23, N 15.27; found C 43.25, H 6.38, N 14.94.

Heptakis(6-azido-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-β-cyclodextrin (5b): Compound **5b** was prepared from **4b** (1.050 g, 0.545 mmol) analogously to **5a**. The product was isolated as a colorless amorphous solid (0.910 g, 87%, calcd. for hexahydrate). $[\alpha]_D^{25}$ = +95 (c = 1.0 in DMSO). ^{1}H NMR (500 MHz, DMSO, 50 °C): δ = 12.21 (b, 1 H, COOH), 5.22 [d, $J(1,2)$ = 3.4 Hz, 1 H, H-1), 4.26 (d, J = 16.5 Hz, 1 H, O-C*H*aHb-COOH), 4.19 (d, J = 16.5 Hz, 1 H, O-CHa*H*b-COOH), 3.80 [dd, $J(6a,6b)$ = 13.7 and $J(6a,5)$ = 2.5 Hz, 1 H, H-6a), 3.79 [m, $J(5,4)$ = 9.3, $J(5,6b)$ = 6.7 and $J(5,6a)$ = 2.5 Hz, 1 H, H-5), 3.59 [dd, $J(6b,6a)$ = 13.7 and $J(6b,5)$ = 6.7 Hz, 1 H, H-6b), 3.54 [dd, $J(4,5)$ = 9.3 and $J(4,3)$ = 8.1 Hz, 1 H, H-4), 3.53 (s, 3 H, OCH_3), 3.42 [dd, $J(3,2)$ = 9.7 and $J(3,4)$ = 8.1 Hz, 1 H, H-3), 3.39 [dd, $J(2,3)$ = 9.7 and $J(2,1)$ = 3.4 Hz, 1 H, H-2). ^{13}C NMR (125.7 MHz, DMSO, 20 °C): δ = 171.45 (COOH), 98.48 (C-1), 81.64 (C-4), 80.15 (C-3), 79.30 (C-2), 70.47 (C-5), 67.70 (O-*C*H_2-COOH), 60.73 (OCH_3), 51.55 (C-6). ESI-MS: m/z = 1836.9 for $[M + Na]^+$; elemental analysis calcd. (%) for $C_{63}H_{91}N_{21}O_{42}\cdot 6H_2O$ (1922.6): calcd. C 39.36, H 5.40, N 15.30; found C 39.49, H 5.23, N 14.98.

Heptakis(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-β-cyclodextrin (6b): Compound **6b** was prepared from **5b** (0.744 g, 0.387 mmol) analogously to **6a**. The product was isolated as a yellowish solid (0.593 g, 89%, calcd. for pentahydrate). An analytical sample was recrystallized from water; colorless needles; no melting point up to 300 °C (dec.). ^{1}H NMR (500 MHz, D_2O, 80 °C): δ = 5.54 [br. d, $J(1,2)$ = 3.2 Hz, 1 H, H-1), 4.15 (m, 3 H, H5 and O−C*H*$_2$-COOH), 3.96 [dd, $J(3,2)$ = 9.5 and $J(3,4)$ = 8.5 Hz, 1 H, H-3), 3.85 [dd, $J(4,5)$ = 8.0 and $J(4,3)$ = 8.5 Hz, 1 H, H-4), 3.63 [dd, $J(2,3)$ = 9.5 and $J(2,1)$ = 3.2 Hz, 1 H, H-2), 3.58 (s, 3 H, OCH_3), 3.46 [dd, $J(6a,6b)$ = 13.3 and $J(6a,5)$ = 3.2 Hz, 1 H, H-6a), 3.23 [dd, $J(6b,6a)$ = 13.3 and $J(6b,5)$ = 7.4 Hz, 1 H, H-6b). ESI-MS: m/z = 1632.7 for $[M + H]^+$; elemental analysis calcd. (%) for $C_{63}H_{105}N_7O_{42}\cdot 5\ H_2O$ (1722.6): calcd. C 43.93, H 6.73, N 5.69; found C 43.70, H 6.77, N 5.59.

Octakis(2-*O*-allyl-6-azido-6-deoxy)-γ-cyclodextrin (2c): Compound **2c** was prepared from **1c** (1.632 g, 1.090 mmol) analogously to **2b**. **2c** was isolated as a colorless foam (0.405 g, 20%). $[\alpha]_D^{25}$ = +121 (c = 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 5.93 (dddd, J = 17.2, 10.3, 7.1, 5.4 Hz, 1 H, −CH=, 2-*O*-allyl); 5.33 (dm, J = 17.2, 1.6, 1.6, 1.2 Hz, 1 H, =C*H*aHb; 2-*O*-allyl), 5.26 (dm, J = 10.3, 1.6, 1.0, 1.0 Hz, 1 H, =CHa*H*b; 2-*O*-allyl), 4.94 [d, $J(OH,3)$ = 1.0 Hz, 1 H, OH), 4.93 [d, $J(1,2)$ = 4.0 Hz, 1 H, H-1), 4.50 (m, J = 12.4, 5.4, 1.6, 1.0 Hz, 1 H, O-C*H*aHb-; 2-*O*-allyl), 4.25 (ddt, J = 12.4, 7.1, 1.2, 1.0 Hz, 1 H, O-CHa*H*b-; 2-*O*-allyl), 3.95 (ddd, $J(3,2)$ = 9.6, $J(3,4)$ = 9.0 and $J(3,OH)$ = 1.0 Hz, 1 H, H-3), 3.79 (ddd, $J(5,4)$ = 9.8, $J(5,6b)$ = 6.0 and $J(5,6a)$ = 2.2 Hz, 1 H, H-5), 3.68 [dd, $J(6a,6b)$ = 13.2 and $J(6a,5)$ = 2.2 Hz, 1 H, H-6a), 3.47 [dd, $J(6b,6a)$ = 13.2 and $J(6b,5)$ = 6.0 Hz, 1 H, H-6b), 3.47 [dd, $J(2,3)$ = 9.6 and $J(2,1)$ = 4.0 Hz, 1 H, H-2), 3.32 [dd, $J(4,5)$ = 9.8 and $J(4,3)$ = 9.0 Hz, 1 H, H-4). ^{13}C NMR (125.7 MHz, $CDCl_3$, 20 °C): δ = 133.78 (=CH-), 119.09 (=CH_2), 101.74 (C-1), 84.22 (C-4), 78.92 (C-2), 73.61 (O-*C*H_2-), 72.94 (C-2), 70.76 (C-5), 51.39 (C-6). ESI-MS: m/z = 1839.3 for $[M + Na]^+$; elemental analysis calcd. (%) for $C_{72}H_{104}N_{24}O_{32}$ (1817.7): calcd. C 47.57, H 5.77, N 18.49; found C 47.43, H 5.79, N 18.12.

Octakis(2-*O*-allyl-6-azido-6-deoxy-3-*O*-methyl)-γ-cyclodextrin (3c): Compound **3c** was prepared from **2c** (0.760 mg, 0.418 mmol) analogously to **3a**. The product was isolated as a colorless foam (0.772 g, 95%). $[\alpha]_D^{25}$ = 133 (c = 0.3 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 5.95 (dddd, J = 17.2, 10.4, 5.8, 5.5 Hz, 1 H, −CH=; 2-*O*-allyl); 5.34 (dq, J = 17.2, 1.6, 1.6, 1.6 Hz, 1 H, =C*H*aHb; 2-*O*-allyl), 5.19 (dm, J = 10.4, 1.6, 1.6, 1.4 Hz, 1 H, =CHa*H*b; 2-*O*-allyl), 5.14 [d, $J(1,2)$ = 3.7 Hz, 1 H, H-1), 4.23 (m, J = 12.8, 5.8, 1.6, 1.4 Hz, 1 H, O-C*H*aHb-; 2-*O*-allyl), 4.19 (m, J = 12.8, 5.5, 1.6, 1.4 Hz, 1 H, O-CHa*H*b-; 2-*O*-allyl), 3.83 (ddd, $J(5,4)$ = 9.4, $J(5,6b)$ = 5.1 and $J(5,6a)$ = 2.2 Hz, 1 H, H-5), 3.71 [dd, $J(6a,6b)$ = 13.3 and $J(6a,5)$ = 2.2 Hz, 1 H, H-6a), 3.63 (s, 3 H, OCH_3), 3.59 [dd, $J(4,5)$ = 9.4 and $J(4,3)$ = 9.0 Hz, 1 H, H-4), 3.56 [dd, $J(6b,6a)$ = 13.3 and $J(6b,5)$ = 5.1 Hz, 1 H, H-6b), 3.56 [dd, $J(3,2)$ = 9.5 and $J(3,4)$ = 9.0 Hz, 1 H, H-3), 3.36 [dd, $J(2,3)$ = 9.5 and $J(2,1)$ = 3.7 Hz, 1 H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$, 20 °C): δ = 134.86 (=CH-), 117.20 (=CH_2), 98.35 (C-1), 81.67 (C-3), 79.13 (C-4), 79.10 (C-2), 72.26 (O-*C*H_2-), 70.80 (C-5), 61.34 (OCH_3), 51.58 (C-6). ESI-MS: m/z = 1951.6 for $[M + Na]^+$; elemental analysis calcd. (%) for $C_{80}H_{120}N_{24}O_{32}$ (1929.9): calcd. C 49.79, H 6.27, N 17.42; found C 49.85, H 6.31, N 17.19.

Diastereomeric Mixture Octakis[6-azido-6-deoxy-2-*O*-(2,3-dihydroxypropyl)-3-*O*-methyl]-γ-cyclodextrin (4c): Compound **4c** was prepared from **3c** (0.524 g, 0.272 mmol) analogously to **4a**. The product was isolated as a colorless foam (0.430 g, 72%). ESI-MS: m/z = 2223.8 for $[M + Na]^+$; elemental analysis calcd. (%) for $C_{80}H_{136}N_{24}O_{48}$ (2202.1): calcd. C 43.63, H 6.23, N 15.27; found C 43.34, H 6.41, N 14.98.

Octakis(6-azido-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-γ-cyclodextrin (5c): Compound **5c** was prepared from **4c** (0.390 g, 0.177 mmol) analogously to **5a**. The product was isolated as a colorless amorphous solid (0.330 g, 86%, calcd. for pentahydrate). $[\alpha]_D^{25} = +107$ ($c = 0.3$ in DMSO). ^{1}H NMR (500 MHz, DMSO, 60 °C): $\delta = 12.57$ (b, 1 H, COOH), 5.29 [d, $J(1,2) = 3.6$ Hz, 1 H, H-1), 4.25 (d, $J = 16.4$ Hz, 1 H, O-C*H*aHb-COOH), 4.21 (d, $J = 16.4$ Hz, 1 H, O-CHa*H*b-COOH), 3.77 [dd, $J(6a,6b) = 13.3$ and $J(6a,5) = 2.2$ Hz, 1 H, H-6a), 3.82 (ddd, $J(5,4) = 9.6$, $J(5,6b) = 6.1$ and $J(5,6a) = 2.2$ Hz, 1 H, H-5), 3.57 [dd, $J(6b,6a) = 13.3$ and $J(6b,5) = 6.1$ Hz, 1 H, H-6b), 3.58 [dd, $J(4,5) = 9.6$ and $J(4,3) = 8.4$ Hz, 1 H, H-4), 3.53 (s, 3 H, OCH_3), 3.49 [dd, $J(3,2) = 9.6$ and $J(3,4) = 8.4$ Hz, 1 H, H-3), 3.40 [dd, $J(2,3) = 9.6$ and $J(2,1) = 3.6$ Hz, 1 H, H-2). ^{13}C NMR (125.7 MHz, DMSO, 20 °C): $\delta = 171.78$ (COOH), 97.81 (C-1), 81.63 (C-3), 79.40 (C-4), 78.50 (C-2), 70.41 (C-5), 67.81 (O-CH_2-COOH), 60.56 (OCH_3), 51.37 (C-6). ESI-MS: $m/z = 2095.5$ for $[M + Na]^+$; elemental analysis calcd. (%) for $C_{72}H_{104}N_{24}O_{48}\cdot 5H_2O$ (2163.8): calcd. C 39.97, H 5.31, N 15.54; found C 40.08, H 5.17, N 15.21.

Octakis(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-γ-cyclodextrin (6c): Compound **6c** was prepared from **5c** (0.300 g, 0.139 mmol) analogously to **6a**. The product was isolated as a yellowish solid (0.246 g, 90%, calcd. for hexahydrate). An analytical sample was recrystallized from water; colorless crystals; no melting point up to 300 °C (dec.). ^{1}H NMR (500 MHz, D_2O, 80 °C): $\delta = 5.57$ (br. s, 1 H, H-1), 4.17−4.10 (um, 3 H, H5 and O−C*H*$_2$-COOH), 3.96 (um, 1 H, H-3), 3.78 (um, 1 H, H-4), 3.60 (um, 1 H, H-2), 3.57 (s, 3 H, OCH_3), 3.41 (br. d, 1 H, H-6a), 3.31 (bdd, 1 H, H-6b). ESI-MS: $m/z = 1866.1$ for $[M + H]^+$; elemental analysis calcd. (%) for $C_{72}H_{120}N_8O_{48}\cdot 6H_2O$ (1973.8): calcd. C 43.81, H 6.74, N 5.68; found C 43.67, H 6.86, N 5.63.

Crystal Data for 6a: Published in a preliminary communication.[20]

Crystal Data for 6b: $C_{63}H_{105}N_7O_{42}\cdot 30H_2O$, $M = 2173.02$, orthorhombic, $P2_12_12_1$ (no. 19), $a = 17.5620(1)$ Å, $b = 19.7130(2)$ Å, $c = 31.1940(3)$ Å, $V = 10799.4(2)$ Å^3, $Z = 4$, $D_x = 1.337$ Mg·m^{-3}. A colorless crystal of dimensions 0.5 × 0.25 × 0.18 mm was mounted into a Lindemann glass capillary and was measured in a Nonius KappaCCD diffractometer using monochromatized Mo-K_α radiation ($\lambda = 0.71073$ Å) at a temperature of 150 K. The absorption was neglected ($\mu = 0.122$ mm^{-1}); a total of 99643 measured reflections in the range $h = -20$ to 20, $k = -23$ to 23, $l = -37$ to 37 ($\theta_{max} = 25°$), from which 18913 were unique (Rint = 0.033) and 16677 observed according to the $I > 2\sigma(I)$ criterion. Cell parameters were determined from 128035 reflections ($\theta = 1-25°$). The structure was solved by direct methods (SIR97)[34a] and refined by full-matrix least-squares based on F^2 (SHELXL).[34b] Assuming complete deprotonation of the carboxyl groups, the hydrogen atoms were fixed into idealized positions (riding model) and assigned temperature factors; either $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom) or $H_{iso}(H) = 1.5\ U_{eq}$(pivot atom) for the methyl moiety. The oxygen atom of one water molecule acquired a large temperature factor during refinement; however, the model with multiple lower occupancy positions did not converge properly. The refinement converged ($\Delta/\sigma_{max} = 0.001$) to $R = 0.065$ for observed reflections and $wR(F^2) = 0.183$, $GOF = 1.069$ for 1327 parameters and all 18913 reflections.

The final difference map displayed peaks: $\Delta\rho_{max.} = 0.843$, $\Delta\rho_{min.} = -0.565$ e·Å^{-3}, the positive one is too close to a carboxyl oxygen and a fully occupied water molecule, and therefore was not assigned to another water molecule. CCDC-229711 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retreiving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EY, UK; fax: +44-1223-336033; or E-mail: deposit@ccdc.cam.ac.uk).

Crystal Data for 6c: $C_{72}H_{120}N_8O_{48}\cdot 27.25\ H_2O$, $M = 2356.7$, tetragonal, $P4_32_12$ (no. 96), $a = 18.4401(2)$ Å, $c = 39.7273(4)$ Å, $V = 13508.8(2)$ Å^3, $Z = 4$, $D_x = 1.159$ Mg·m^{-3}. A colorless crystal of dimensions 0.4 × 0.3 × 0.3 mm was mounted into a Lindemann glass capillary and measured in a Nonius KappaCCD diffractometer using monochromatized Mo-K_α radiation ($\lambda = 0.71073$ Å) at room temperature (lower temperature leads to crystal splitting). The absorption was neglected ($\mu = 0.105$ mm^{-1}); a total of 70816 measured reflections in the range $h = -21$ to 21, $k = -15$ to 15, $l = -47$ to 57 ($\theta_{max} = 25°$), from which 11905 were unique (Rint = 0.028) and 8888 observed according to the $I > 2\sigma(I)$ criterion. Cell parameters were determined from 83933 reflections ($\theta = 1-25°$). The structure was solved by direct methods (SIR97)[34a] and refined by full-matrix least-squares based on F^2 (SHELXL).[34b] Assuming complete deprotonation of the carboxyl groups, the hydrogen atoms were fixed into idealized positions (riding model) and assigned temperature factors; either $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom) or $H_{iso}(H) = 1.5\ U_{eq}$(pivot atom) for the methyl moieties. Some of the methyl groups acquired large temperature factors during refinement due to their disorder; however, a model with disordered and partially occupied water positions positions did not converge properly. The refinement converged ($\Delta/\sigma_{max} = 0.001$) to $R = 0.086$ for observed reflections and $wR(F^2) = 0.260$, $GOF = 1.065$ for 716 parameters and all 11905 reflections.

There are a large number of positions that belong to partially occupied water molecules in the crystal, because the channels along the *c* direction enable their free movement. The exact number of water molecules cannot be determined. However, it cannot differ significantly from the presented model, since the final difference map displayed only peaks: $\Delta\rho_{max} = 0.49$, $\Delta\rho_{min} = -0.298$ e·Å^{-3}, the positive one being too low for another water molecule with reasonable occupation factor.

CCDC-229712 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retreiving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EY, UK; fax: +44-1223-336033; or E-mail: deposit@ccdc.cam.ac.uk).

Acknowledgments

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