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Per(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-α-cyclodextrin: Helical Self-Assembly of a Polyionic Amino Acid into Nanotubes**

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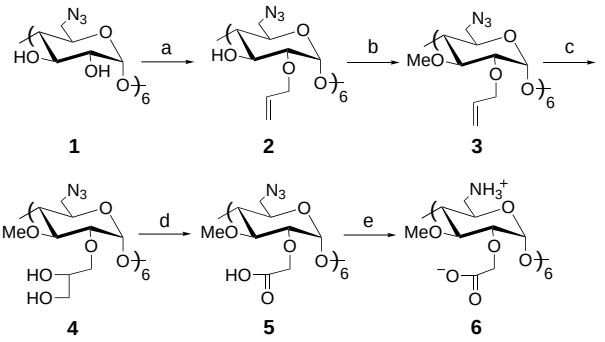
Designed macrocyclic oligopeptides[1] and oligosaccharides[2] serve as versatile building units (tectons) for supramolecular self-assembly of nanotubes.[3] In this respect, cyclodextrin derivatives possessing a hollow, chiral, truncated-cone interior with a variable diameter deserve particular interest. The two rims of cyclodextrin, respectively bearing primary and secondary hydroxy groups, can be selectively modified to create complementary binding sites. Cyclodextrins monofacially persubstituted at the primary rim with carboxy groups were already shown[4] to self-assemble in nonpolar solvents into dimeric head-to-head hydrogen-bonded aggregates. Analogous amino-persubstituted cyclodextrins associate, on treatment with the corresponding monofacially carboxymethyl-persubstituted derivatives, by means of ionic hydrogen bonds into head-to-head heterodimers, which persist even in aqueous solutions.[5, 6] This strongly suggests that hermaphroditic cyclodextrins bearing complementary donor and acceptor groups on the opposite rims might self-assemble into infinite head-to-tail chiral nanotubes. We designed hexakis(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-α-cyclodextrin (**6**) as a model for such investigation. Here we report on its synthesis and its unique architecture in the solid state.

The persubstituted amino acid **6** is an elusive target because of the array of incompletely substituted derivatives that can arise and persist in the course of synthesis.[7] To obtain a chemically uniform persubstituted product, which is indispensable for X-ray diffraction analysis, we employed a novel procedure[8] for the facial percarboxymethylation of cyclodextrins. Starting from the easily accessible[9] hexakis(6-azido-6-deoxy)-α-cyclodextrin (**1**; Scheme 1), all secondary hydroxy groups at C2 were selectively allylated, and the pure hexaallyl derivative **2** was isolated by chromatography in 52 % yield. Subsequent methylation of the free hydroxy groups at C3 furnished the peralkylated compound **3** in a quantitative yield. The allylic groups of **3** were catalytically dihydroxylated with osmium tetroxide and 4-methylmorpholine *N*-oxide as auxiliary oxidant, and the resulting mixture of diastereoisomers **4** was isolated by reversed-phase chromatography in 71 % yield. The diol groups were cleaved with sodium periodate and, in the same pot, the intermediate polyaldehyde was oxidized to the carboxymethyl derivative **5** with TEMPO/NaClO/KBr in an overall yield of 91 %. Customary reduction of per-6-azidocyclodextrins with triphenylphosphane surprisingly failed. However, an excellent alternative for the reduction



Scheme 1. a) Allyl bromide, $Ba(OH)_2 \cdot H_2O$, BaO, DMF, 25 °C, 24 h, 52 %; b) MeI, NaH, DMF, 25 °C, 3.5 h, 99 %; c) OsO_4, 4-methylmorpholine *N*-oxide, acetone/water, 25 °C, 24 h, 71 %; d) 1. $NaIO_4$, H_2O, 25 °C, 2.5 h; 2. TEMPO, NaBr, NaClO, 25 °C, 2.5 h, 91 %; e) H_2S, pyridine/water, 25 °C, 72 h, 90 %. TEMPO = 2,2,6,6-tetramethyl-1-piperidineoxyl.

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of **5** was devised by using hydrogen sulfide[10] in pyridine/water, which allowed isolation of the pure amino acid **6** in nearly quantitative yield.

At neutral pH, the zwitterionic **6** is insoluble in both protic (water, methanol, ethanol) and dipolar aprotic solvents (dimethyl sulfoxide) at ambient temperature and at the boiling point. However, it dissolves readily in water on addition of an acid (HCl) or a base (NaOH, NH_4OH). Structural identity and homogeneity of the product were proved by ^1H and ^{13}C NMR spectra of the water-soluble hydrochloride salt of **6** which confirmed the expected symmetry of the molecule. Single crystals of the free amino acid **6** could be obtained by slow evaporation of a solution in aqueous ammonia.

Cyclodextrins and their derivatives and inclusion complexes crystallize in three arrangements:[11] cage, channel, and layer types. In the crystal structure of **6** we have identified[12] a highly symmetrical arrangement (space group *R*3) unique in the family of cyclodextrins. Individual cyclodextrin tectons recline on helical (staircase) trajectories (Figures 1 and 2) along the crystallographic *c* axis so that the *i*th and $(i+3)$th tectons always occupy eclipsed positions (e.g., units A and D in Figure 1a). An infinite array of parallel columns thus results in which each column is shifted by $\pm 1/3$ of the cell parameter *c* with respect to its neighbors.

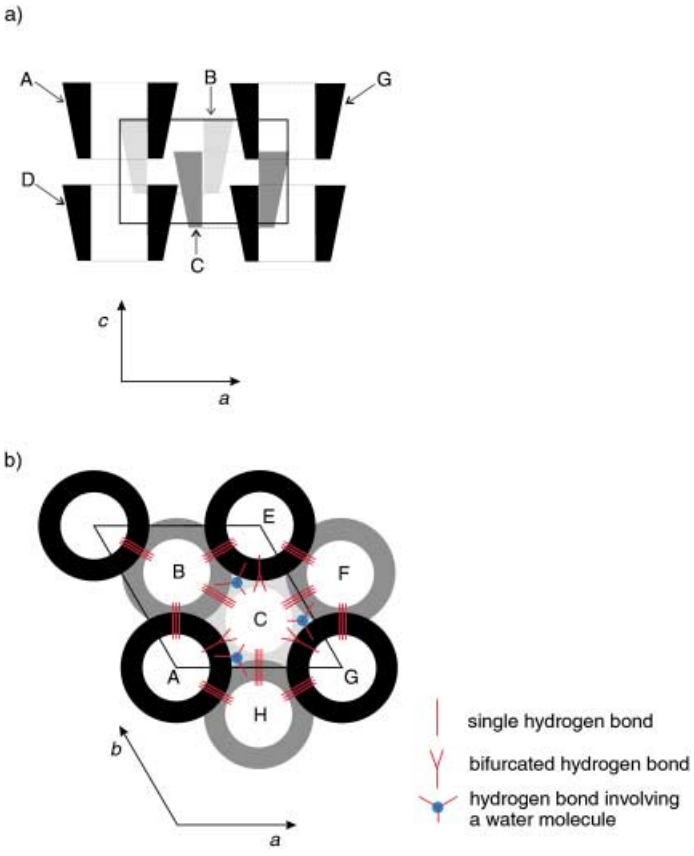

Figure 1. Schematic representation of packing of **6** in the unit cell; a) view along the *b* axis; b) view along the *c* axis with hydrogen bonds depicted as red lines (tectons F and H are added to the unit cell to describe the complete bonding pattern). The degree of shading reflects the relative distance of CD units from the observer (black represents the nearest macrocycles).

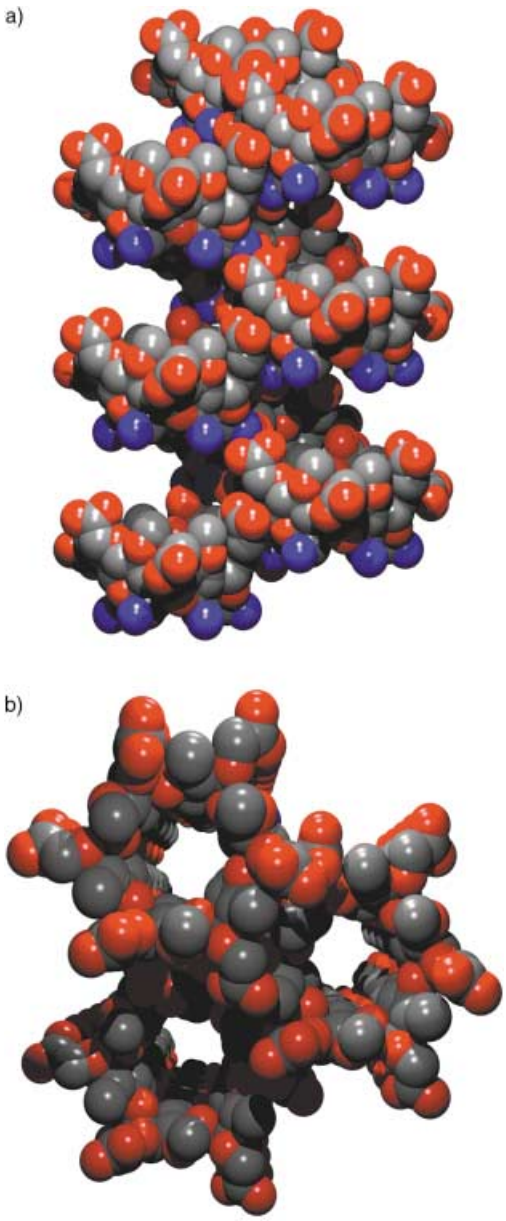

Figure 2. Space-filling representation of the crystal structure of **6**; a) helical arrangement viewed along the *b* axis and b) open channels viewed along the *c* axis. Hydrogen atoms and water molecules are omitted for clarity.

A closer analysis reveals that the helical framework is held together by hydrogen bonds (red lines in Figure 1b). A complete proton transfer from carboxy to amino groups occurs in the crystal. The overall hydrogen-bonding pattern is nonetheless complex; each cyclodextrin unit is anchored to its neighbors by 30 hydrogen bonds. Each pair of neighboring cyclodextrins is bonded by three intermolecular hydrogen bonds; two bonds are formed between ammonium cations of A and carboxylate anions of B, while the third involves an ammonium group of A and a methoxy group of B. In addition, a bifurcated hydrogen bond connects an ammonium group of molecule A and a carboxylate moiety of another proximate cyclodextrin C. One of the five water molecules (in fully occupied positions[13]) contributes to the overall stability of the helix by accepting two free hydrogen atoms from

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ammonium cations, one from macrocycle A and the other from macrocycle H; at the same time, it acts as a donor for two hydrogen bonds to the oxygen atom of one carboxy group of C and a neighboring water molecule (for the detailed description of hydrogen bonds and an ORTEP plot, see Supporting Information).

Each of the three glucose pairs of the cyclodextrin macrocycle respectively acts as a donor and acceptor of hydrogen bonds in two helices that differ in the sense of twist. Thus, each cyclodextrin unit represents a nodal point of six intersecting helices with alternating handedness (e.g., ABC, EBC, EFC, GFC, GHC, and AHC, as depicted for the central macrocycle C in Figure 1b).[14] In this way, a strong hydrogen-bonded network is formed that cross-links the parallel columns, but the surprising feature is the complete absence of hydrogen bonds between the proximate heads and tails of the eclipsed tectons in the individual columns. This differs from the customary[11] cyclodextrin channel architecture, in which hydrogen-bonding interactions bind together the tectons stacked in the individual columns, whereas weak van der Waals interactions govern the packing along the remaining directions.

Although the distance between the faces of the eclipsed cyclodextrin units is 4 Å in the crystal of **6**, the staircase arrangement of cyclodextrin units in the neighboring columns effectively shields these "holes" and gives rise to a system of separate straight channels. Thus, the helical self-assembly of the C_3-symmetrical α-cyclodextrin tectons **6** gives rise to a highly cross-linked, densely packed nanotubular material; the higher (β- and γ-) homologues, which are now on our agenda, are envisaged to open access to other chiral tubular superstructures, with different porosity and other physicochemical properties (e.g., solubility).

Experimental Section

^{1}H and ^{13}C spectra were assigned by using 2D COSY and ^{1}H-^{13}C 2D-HMQC experiments; hard copies of the spectra of the hexahydrochloride of **6** can be found in the Supporting Information.

Hexakis(6-amino-2-*O*-carboxymethyl-6-deoxy-3-*O*-methyl)-α-cyclodextrin hexahydrochloride: Compound **6** (20 mg, 12.6 μmol) was dispersed in water (1 mL), and aqueous hydrochloric acid (0.10 N, 0.130 mL, 13 μmol) was added. The solution was lyophilized to give a white foam (22.4 mg, 99 %, calculated for nonahydrate). ^{1}H NMR (D_2O, 500 MHz, 50 °C): δ = 3.69 (dd, $J(6',6)$ = 13.8, $J(6',5)$ = 5.4 Hz, 6H, H-6′), 3.79 (dd, $J(6,6')$ = 13.8, $J(6,5)$ = 3.8 Hz, 6H, H-6), 3.90 (dd, $J(2,1)$ = 3.3, $J(2,3)$ = 9.8 Hz, 6H, H-2), 3.97 (s, 18H, OCH_3), 4.04 (dd, $J(4,3)$ = 8.1, $J(4,5)$ = 9.2 Hz, 6H, H-4), 4.20 (dd, $J(3,2)$ = 9.8, $J(3,4)$ = 8.1 Hz, 6H, H-3), 4.57 (m, $J(5,4)$ = 9.2, $J(5,6)$ = 3.8, $J(5,6')$ = 5.4 Hz, 6H, H-5), 4.72 (s, 12H, OCH_2COO), 5.64 (d, $J(1,2)$ = 3.3 Hz, 6H, H-1); ^{13}C NMR (D_2O, 125.7 MHz, 50 °C): δ = 43.42 (C-6), 63.89 (OCH_3), 71.24 (C-5), 71.25 (OCH_2COOH), 82.16 (C-2), 83.68 (C-4), 83.71 (C-3), 102.15 (C-1), 177.15 (OCH_2COOH); ESI-MS: *m*/*z*: 1399.4 (30 %) $[M+H]^+$, 700.4 (100 %) $[M+2H]^{2+}$; elemental analysis (%) calcd for $C_{54}H_{96}Cl_6N_6O_{36}\cdot 9H_2O$: C 36.43, H 6.45, N 4.72; found: C 36.44, H 6.25, N 4.55.

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[12] Crystallographic data for **6**: Prismatic crystals were grown from a solution of **6** in aqueous ammonia; $C_{54}H_{126}N_6O_{54}$, M_r = 1723.61, ρ_{calcd} = 1.279 g cm^{-3}, crystal dimensions 0.3 × 0.25 × 0.1 mm, trigonal, space group *R*3 (No. 146), a = 23.2901(4), c = 14.2681(3) Å, Z = 3. Data collection: Nonius Kappa CCD diffractometer, $Mo_{K\alpha}$ radiation (λ = 0.71073 Å, graphite monochromator) at 150(2) K. A total of 36549 reflections were collected, 6747 were unique (R_{int} = 0.040), and 6091 observed ($I > 2\sigma(I)$). The structure was solved by direct methods (SIR 97[15a]) and refined by full-matrix least-squares technique on F^2 (SHELXL97[15b]). The hydrogen atoms were located on the difference Fourier map, except those on partially occupied water molecules; however, some of them behaved erroneously during refinement, and therefore all hydrogen atoms of the cyclodextrin moiety were recalculated in idealized positions (riding model) and assigned temperature factors $H_{iso}(H) = 1.2\,U_{eq}$ (pivot atom), multiplied by 1.5 for the methyl group. Final *R* factors: R_1 = 0.049 (observed data) and 0.057 (all data); wR_2 = 0.134, S = 1.057, 365 parameters. Residual peaks on final difference map were $\Delta\rho_{max}$ = 0.760 and −0.296 e Å^{-3}. CCDC 171795 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[13] Aside from the five molecules of water (per asymmetric unit, i.e., one glucose pair of the cyclodextrin macrocycle) fully occupying positions in the intercolumnar space, there are disordered water molecules that partially occupy two distinguishable positions; one is located above the secondary rim of the cavity, while the other is situated in the mean plane defined by the methoxy groups, so that the space inside the cyclodextrin cavity is essentially left empty (see Supporting Information).

[14] All cyclodextrin units in the crystal lattice are equivalent; the arbitrary denotations A–H are only used to describe the bonding pattern.

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