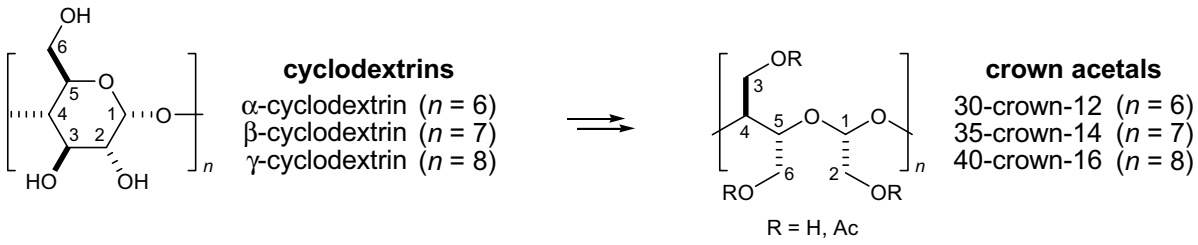
Chapter 6

Cyclodextrin-derived Crown Acetals



Synthesis and Molecular Geometry of an Achiral 30-Crown-12 Polyacetal from α-Cyclodextrin

S. Immel, T. Nakagawa, H. J. Lindner, and F. W. Lichtenthaler,
Chem. Eur. J. **2000**, *6*, 3366-3371.

Hydroxymethyl-substituted Crown Acetals with 35-C-14 and 40-C-16 Skeletal Backbones: Synthesis and Molecular Geometries

S. Immel, F. W. Lichtenthaler, H. J. Lindner, and T. Nakagawa,
Tetrahedron: Asymmetry **2001**, *12*, 2767-2774.

Large-ring Crown Acetals from Cyclodextrins

T. Nakagawa, S. Immel, H. J. Lindner, and F. W. Lichtenthaler,
Proc. 10th Int. Symp. Cyclodextrins (Ed.: J. Szejtli), Mia Digital Publ., Ann Arbor, Michigan, **2000**, pp. 18-23.

Flexible Non-glucose Cyclooligosaccharides

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FULL PAPER

Molecular Modeling of Saccharides, Part 27[±]

Synthesis and Molecular Geometry of an Achiral 30-Crown-12 Polyacetal from α-Cyclodextrin

Stefan Immel, Toshio Nakagawa, Hans J. Lindner, and Frieder W. Lichtenthaler*[a]

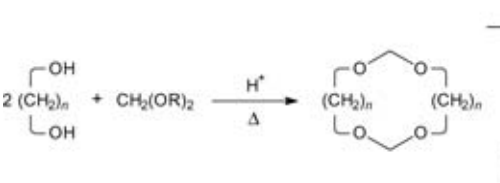
Abstract: Periodate oxidation of α-cyclodextrin followed by borohydride reduction readily provided an octadecahydroxymethyl-substituted 30-crown-12 polyacetal **1**, its 30-membered macrocycle being composed of six *meso*-butanetetrol/glycolaldehyde acetal units, which is, consequently, optically inactive. Its solid-state molecular geometry emerged from the X-ray structural analysis of the well-crystallizing octadecaacetate **2**, which revealed the undulated macrocycle to be molded into three loops with a unique order of succession of the -CHR-CHR-O-CHR-O- units: alternating *gauche*- and *anti*-conformations of the *meso*-butanetetrol portions and consecutive disposition of the glycolaldehyde-acetoxymethyl groups above and below the mean-plane of the macrocycle. In solution, however, as evidenced by ^{1}H- and ^{13}C-NMR spectra, the macrocycle is highly flexible at ambient and higher temperatures, its mobility becoming distinctly restricted only below −20 °C.

Keywords: cyclodextrins · crown acetals · macrocyclic polyacetals · oligosaccharides

Introduction

Unlike crown ethers that have played a pivotal role in the development of supramolecular chemistry,[1] macrocycles with acetalic oxygen atoms have received comparatively little attention, conceivably because their cation complexation properties—as compared to the more basic ether oxygens—are less propitious. Thus, Pedersen[2] noted already thirty years ago "that -O-CH_2-O- is a less favorable linkage than -O-CH_2CH_2-O- for complexation", based on crown ether acetals of the type 18-C-6, 20-C-7, and 22-C-8, namely cyclic polyethers with one or two acetal groupings in their skeletal backbone. Various other investigators have since amply corroborated the drastic decrease in cation binding ability by introducing acetal groupings into crown ethers even when bearing the same number of oxygen atoms.[3–6]

Macrocycles exclusively containing acetal-oxygen atoms, and, hence, deserving the designation *crown acetal*,[7, 8] are rare, the presently known examples being limited to systems with two formaldehyde/alkanediol acetal units, that is containing only four oxygens in the ring (Figure 1).



n	acronym	ref.
2	10-C-4	[9]
3	12-C-4	[10]
4	14-C-4	[11]
5	16-C-4	[12]
6	18-C-4	[13]
9	24-C-4	[13]
10	26-C-4	[13]
14	34-C-4	[13]

Figure 1. Crown acetals[7] composed of two alkanediol/formaldehyde units. Of these, only the geometries of 10-C-4[9] and 14-C-4[11] have been verified by X-ray structural analysis.

Cycloacetals with a higher number of oxygens in the ring are, as of now, utter curiosities: The products formed on BF_3-induced oligomerization of 1,3-dioxolane in yields of 1–2% were deemed to be the 10-crown-4, 15-crown-6, 20-crown-8, and 25-crown-10 polyacetals,[3a] despite of insufficient characterization, and the polyaldehydes generated by periodate oxidation of α-, β-, and γ-cyclodextrin,[14] which de facto constitute polyacetals with a 30-crown-12, 35-crown-14, and 40-crown-16 skeletal backbone; they have similarly eluded

[a] Prof. Dr. F. W. Lichtenthaler, Dr. S. Immel, Prof. Dr. T. Nakagawa, Prof. Dr. H. J. Lindner
Institut für Organische Chemie, Technische Universität Darmstadt
Petersenstrasse 22, 64287 Darmstadt (Germany)
Fax: (+49) 6151-166674
E-mail: fwlicht@sugar.oc.chemie.tu-darmstadt.de

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Supporting information for this article is available on the WWW under http://caramel.oc.chemie.tu-darmstadt.de/immel/3Dstructures.html (3D structures of Figure 2) and http://caramel.oc.chemie.tu-darmstadt.de/immel/molcad/gallery.html (MOLCAD graphics).

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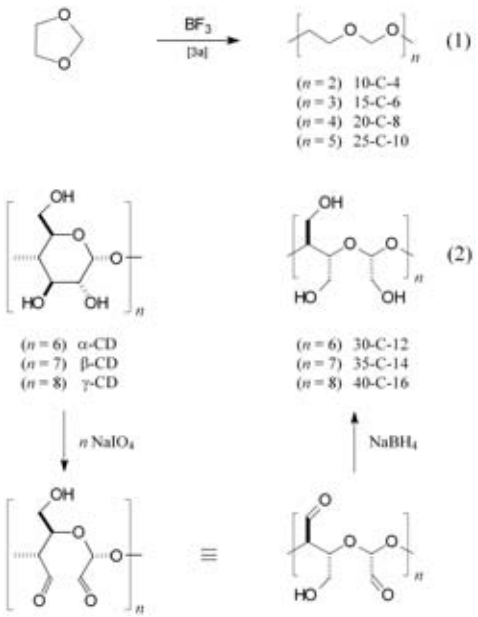
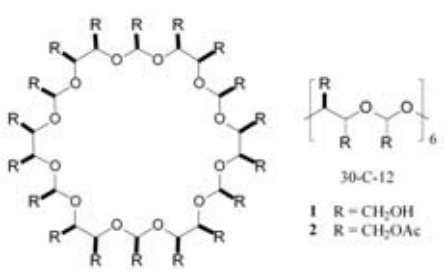
unequivocal structural characterization—not surprising in view of the manifold possibilities of elaborating cyclic acetal and hemiacetal structures. Of the products ensuing from these "CD-polyaldehydes" upon chlorite oxidation[15] and borohydride reduction,[16] only the per-hydroxymethylated 30-crown-12 and 35-crown-14 polyacetals—prepared from α- and β-CD in modest yields—have been unequivocally characterized as such and as their per-*O*-acetates,[16a] yet the sparse NMR data provided gave no clues as to their molecular geometries.



Scheme 1. Synthetic access to large ring crown acetals with repetitive C-C-O-C-O-fragments in their skeletal backbones. *Top*: Systems with two to five ethyleneglycol/formaldehyde units[3a] [Eq. (1)]. *Lower part*: cyclodextrin-derived substituted analogues composed of six, seven, and eight consecutive D-erythrose/glyoxal[14] or—upon hydride reduction—*meso*-butanetetrol/glycolaldehyde segments [Eq. (2)].

Our past interest in the generation of flexible cyclooligosaccharide hosts[17] to mimic the induced-fit mode[18] rather than the rigid lock-and-key principle[19] has led presently to the preparatively satisfactory, high-yield preparation of the α-cyclodextrin-derived 30-crown-12 polyacetal **1** composed of six consecutive *meso*-butanetetrol/glycolaldehyde acetal units, and to the unravelment of its molecular geometry through an X-ray structural analysis of its octadeca-acetate **2**.



Results and Discussion

Of the three native cyclodextrins readily accessible, α-cyclodextrin (α-CD), with six α-(1 → 4)-linked glucose units the smallest, undergoes periodate oxidation of its diol functionalities slowest,[14] yet when reacted with a 3.0 molar excess of oxidant for 11 d at $\approx 0\,^{\circ}C$, the conversion was complete. The resulting polyaldehyde, due to its manifold possibilities of forming hemiacetals and/or hemialdal hydrates, was only characterized as a chromatographically uniform powder, and then subjected to reduction with sodium borohydride in methanol to provide the octadeca-hydroxymethyl 30-crown-12 polyacetal **1**. Its characterization in pure form is best accomplished by in situ acetylation to yield its well-crystallizing, octadeca-acetate **2** (92% based on α-CD) and subsequent Zemplén deacetylation. Neither **1** nor **2** showed any rotational value—expectedly, since the six butanetetrol units generated from α-CD by the periodation–reduction sequence have *erythro*-configuration and erythritol is a *meso*-compound.

Invited by the high crystallinity of the 30-crown-12 polyacetal **2**, an X-ray structural analysis could be performed (Figure 2), which revealed the unique conformational intricacies of the 30-membered macrocycle: The ring adopts a three-loop shape, which is not planar but assumes a distinct undulating form. The ring symmetry is reduced from C_{6v} to approximately C_3, with the six acetoxymethyl groups of the glycolaldehyde acetal units pointing alternatingly above and below the mean-plane of the macrocyclic backbone. In addition, each of the six pairs of vicinal acetoxymethyl groups of the *meso*-butanetetrol units features one OAc group pointing towards the front, and the next directed to the rear relative to the ring periphery. As is lucidly borne out by the color representations of Figure 2 and particularly by the side-view ribbon model therein, a total of nine acetoxymethyl groups point away from either side of the macrocyclic backbone in an alternating fashion. This entails for the crown acetal **2** a compact, nearly cylindrical overall shape. Albeit **2** was crystallized from EtOH, the crystals do not contain any residual solvent since the molecular packing is very tight and the center of the molecule seems to be inaccessible for any guest. As detailed in Figure 2 (bottom plots), the three-looped structure is caused by a characteristic alternating *gauche*- and *anti*-arrangement for the O-C-C-O-torsion angles of the six *meso*-butanetetrol units, a conformational feature that was translated into a conventional formula drawing in Figure 3.

As **2** itself is an achiral compound with an achiral space group (monoclinic, *P*n), each unit cell contains two symmetry related formula units of **2**, one being the exact mirror geometry of the other. Thus, the *meso*-butanetetrol units in the solid-state geometry of **2** adopt either successive (+)-*gauche*/*anti*- or (−)-*gauche*/*anti*-conformations, of which only the former are shown in Figure 2. The ring torsion angles Θ_1–Θ_5 for each *meso*-butanetetrol/glycolaldehyde unit A–F of the 30-membered macroring are listed in Table 1: Of these values, Θ_3 reflects directly the alternating *gauche*/*anti*-arrangements described above, whilst the other torsion angles display less pronounced fluctuations only.

Although the 30-crown-12 macrocycle is anticipated to be quite flexible in solution, both temperature dependent ^{1}H-

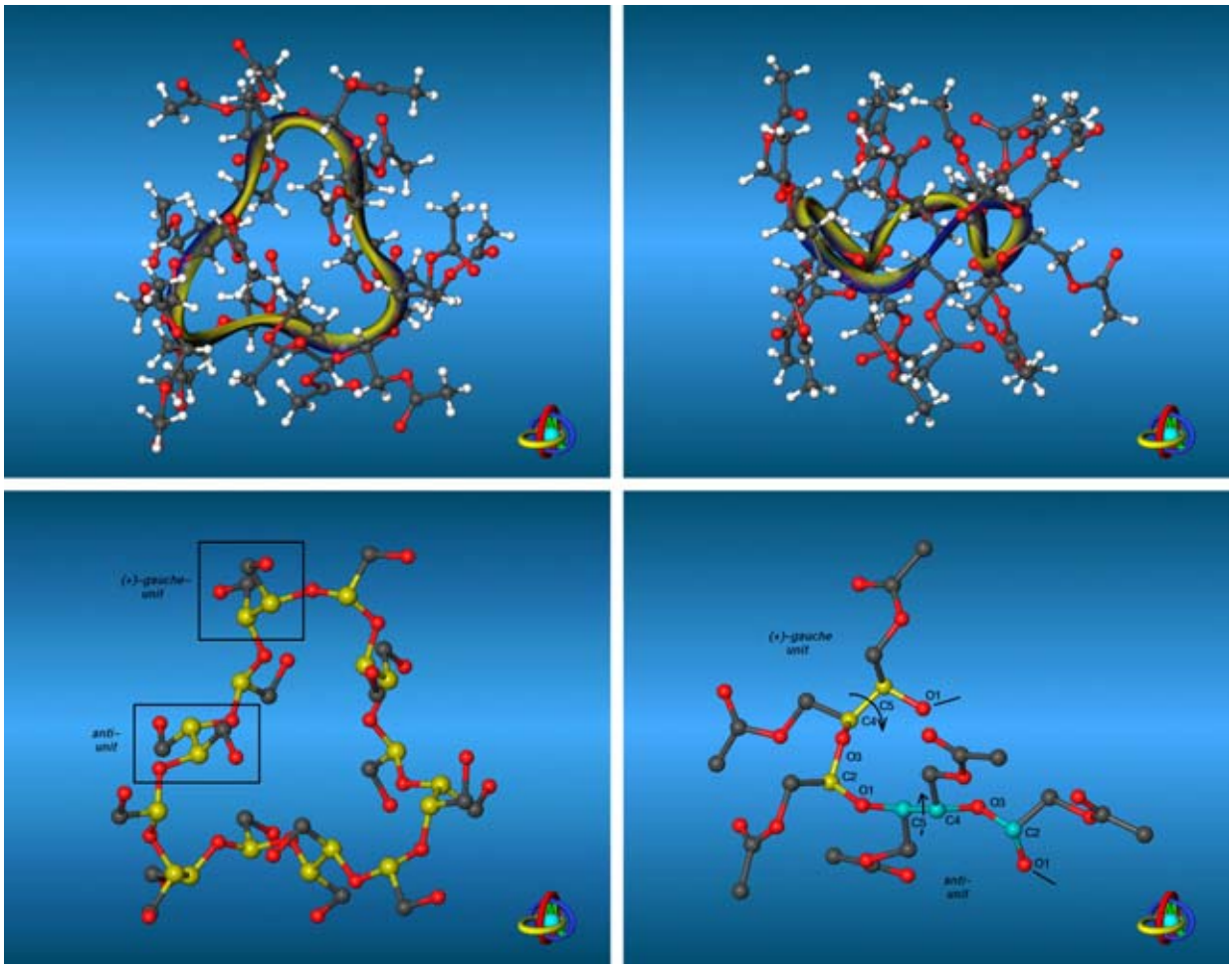
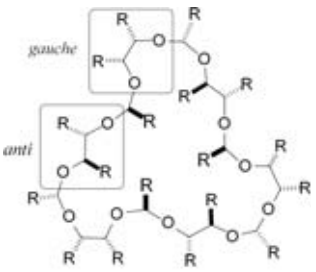


Figure 2. Solid-state topography for the asymmetric unit of the octadeca-(acetoxymethyl)-30-crown-12 polyacetal **2** in ball-and-stick type representations. *Top*: Ribbon models of the macrocyclic core, amply illustrating its three-looped shape, which, as shown in the side view (left), is not planar but adopts an undulatory form with the yellow-blue coloring of the braid; this indicates the twist of the backbone. In the crystal lattice, two formula units of achiral **2**—the geometry shown here and its symmetry related mirror image—occupy each unit cell. *Bottom*: Accentuation of the skeletal backbone of the 30-membered macrocycle (left) with acetyl groups and hydrogens omitted for clarity and all ring carbon atoms marked yellow; the molecular orientation corresponds to the top left plot. The *meso*-butanetetrol units are successively in *gauche*- and *anti*-arrangements (as labeled), whereas the acetoxymethyl groups of the six glycolaldehyde units are alternatingly directed towards both sides of the macrocycle. On the right, a single-loop segment of the macrocycle is enlarged, with one (+)-*gauche meso*-butanetetrol/glycolaldehyde unit colored yellow and atoms labeled; in the following -OCCOCO- repeating unit, of which the carbon atoms are in green color, the butanetetrol unit is in *anti*-arrangement.



2 R = CH_2OAc

Figure 3. Conventional formula drawing of the crown acetal **2** in the same orientation as given in the left plots of Figure 2 to visualize the successive *gauche*/*anti*-arrangements of the *meso*-butanetetrol units.

and ^{13}C-NMR patterns in CD_2Cl_2 and $C_2D_2Cl_4$, point towards the overall shape of the solid-state conformation being largely retained in these solvents. At ambient temperature (24 °C) the individual ring protons, that is the acetalic hydrogen H-2, the secondary hydrogens of the butanetetrol units (cf. ^{1}H NMR in Figure 4), and the ring carbons C-2, C-4, and C-5 (^{13}C NMR) are largely unresolved and display unusually broad signals. At elevated temperatures (up to +100 °C), the NMR spectra (in $C_2D_2Cl_4$) exhibit one set of signals consistent with a time-averaged C_{6v} symmetrical structure of **2**: a single low-field triplet for H-2, chemically equivalent resonances for H-4, H-5, and 4,5-CH_2, and the 2-CH_2 signals (although 4,5-H^A and 4,5-H^B are magnetically nonequivalent and thus, largely separated). The acetyl resonances are resolved into two peaks with an integral ratio of 12:6 for the *meso*-butanetetrol and glycolaldehyde units (^{1}H NMR in Figure 4, the ^{13}C-NMR spectra display analogous characteristics). At lower temperatures (−90 to 0 °C in CD_2Cl_2), all signals are significantly broadened or split; most notably the H-2 protons are clearly separated at −60 °C into two triplets (cf. Figure 4), and the acetyl groups split into four peaks with a ratio of 6:6:3:3. Below −60 °C the C-4 and C-5 signals are separated into a total of four peaks. All of these data are consistent with the

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Table 1. Succession of 30 ring torsion angles in the solid-state geometry of the 30-crown-12 acetal **2** with estimated standard deviations in parenthesis.[a]

Torsion angles [°]	Θ_1 O1-C2-O3-C4	Θ_2 C2-O3-C4-C5	Θ_3 O3-C4-C5-O1′	Θ_4 C4-C5-O1′-C2′	Θ_5 C5-O1′-C2′-O3′
A	119.3(7)	−148.7(6)	71.6(8)	161.8(7)	−115.7(7)
B	98.9(7)	−147.3(6)	−170.0(5)	135.6(6)	−80.7(7)
C	136.3(6)	−136.8(6)	65.9(7)	148.6(6)	−127.4(7)
D	82.2(7)	−145.1(6)	−173.0(6)	160.5(6)	−64.7(8)
E	116.2(7)	−142.9(7)	70.1(7)	150.7(7)	−99.0(8)
F	109.5(7)	−144.4(7)	−171.6(6)	146.9(7)	−65.4(9)

[a] Torsions are listed in row-column order, equivalent torsions for **2** are listed in columns; the atom numbering Scheme corresponds to Figure 4 (i.e., $[\text{-O1-C2-O3-C4-C5-}]_6$ with units labeled *A*–*F* for the 30-membered macroring), primed atom designators refer to the neighboring unit. The torsion angles Θ_1 and Θ_5, as well as Θ_2 and Θ_4 are chemically equivalent (clockwise and anti-clockwise ring numbering, symmetry C_{6v}); the alternating *gauche*–*trans* sequence of units in **2** is manifested through the O-C-C-O-torsion angle of the *meso*-butanetetrol units (Θ_3). All torsion angles are listed for one molecule of **2** contained in the unit cell only, the second molecule being the exact mirror image of the former with all torsion angles of opposite sign, respectively.

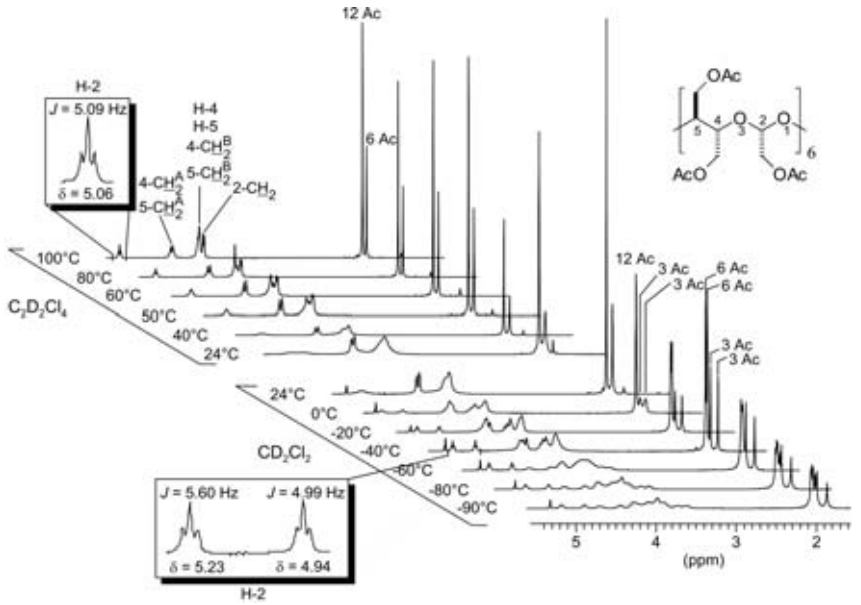

Figure 4. ^{1}H NMR (300 MHz) spectral patterns of **2** at different temperatures recorded in CD_2Cl_2 ($T = -90$ – $+24$ °C) and $C_2D_2Cl_4$ ($T = +24$ – $+100$ °C). At -60 °C the H-2 resonances of the glycolaldehyde acetal protons are separated into two triplets with equal populations, whereas at 100 °C both signals collapse into a single triplet (see box insertions and enlarged spectra); coalescence is observed at about room temperature. The very broad low-temperature (-90 °C) signals between $\delta = 3.5$–4.7 evolve into sharply resolved single peaks at above 50 °C, as the acetyl group resonances start to form separate singulets with an integral ratio of 12:6 (i.e., twelve equivalent OAc groups at C-4 and C-5 versus six glycolaldehyde OAc residues).

notion that the solid-state geometry of **2** is largely retained in solution as the succession of *anti*- and (±)-*gauche*-*meso*-butanetetrol units reduces the ring symmetry and accounts for the NMR patterns observed.

At higher temperatures the *gauche* ↔ *anti* transitions are sufficiently fast and display the time-averaged patterns, whereas at lower temperatures **2** starts to freeze into its solid-state geometry. The coalescence temperature T_C for the H-2 and C-2 resonances is observed at about room temperature, although the solvent had to be changed at around 24 °C. From the low-temperature separation of the signals, and dynamic NMR line shape analysis,[20] the rough estimate $T_C \approx 290 \pm 25$ K yields an activation barrier of approximately $\Delta G^{\ddagger} \approx 60 \pm 5$ kJ mol^{-1} for the *gauche* ↔ *anti* transitions of the butanetetrol segments within the macroring. The strait-jacket of the macrocycle obviously favors low-symmetry conformations energetically over all-*gauche* or all-*anti* arrangements, with the conformational transitions occuring in a cooperative fashion. Hence, the solid-state geometry of **2** can be considered a realistic snapshot over the state in solution.

Conclusion

The solid-state structure of the per-acetoxymethyl-substituted 30-C-12 crown acetal **2** detailed herein provides the second X-ray diffraction study of a 30-membered crown compound, the first being the simple aliphatic 30-C-10 crown ether.[21] A comparison of their molecular geometries is interesting in such as they are distinctly different—not unexpected as $\text{-OCH}_2\text{CH}_2\text{O-}$ units in crown ethers and the respective $\text{-OCH}_2\text{CH}_2\text{OCH}_2\text{O-}$ units in the crown acetal are apt to follow different crystal engineering patterns. Thus, whilst the 30-membered ring in crown acetal **2** adopts an undulating three-loop shape (Figure 2), the 30-C-10 crown ether macrocycle organizes itself in a planar, rectangular form, characterized by the bridging of two parallel sets of three $\text{-OCH}_2\text{CH}_2\text{-}$ units in *anti*-arrangement with two *gauche*-oriented ethylenedioxy units on either end in a handle-like fashion (Figure 5).[21] In solution, however, both macrocycles are highly flexible and thus capable of elaborating variously sized cavities, which in their size can adapt to the size of the potential guest molecules or cations to be incorporated. In the case of 30-C-10 this has been already evidenced by the X-ray structure of its tetrahydrate, which has the four water molecules located inside the substantially widened macrocycle.

Attempts to induce the 30-C-12 crown acetals **1** and **2** to form inclusion compounds, as of now, have not been successful. More favorable in this respect are the β-CD- and γ-CD-derived 35-C-14 and 40-C-16 crown acetal analogues of **1** and **2**. The prospects for their acquisition in a form suitable for X-ray structural investigations appear to be favorable, as

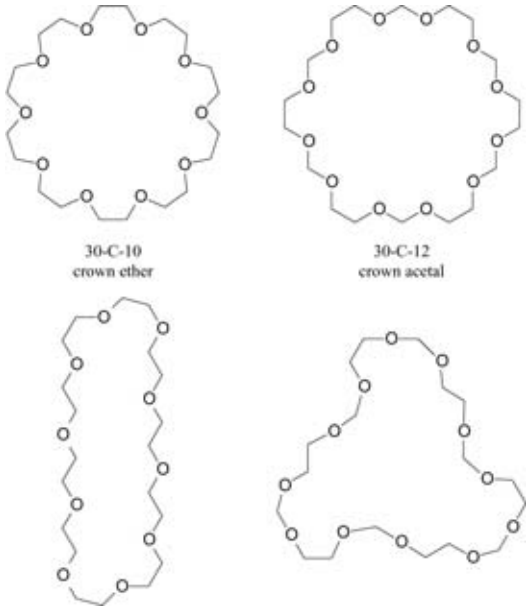

Figure 5. Solid-state molecular geometries of the 30-membered macrocycles in a 30-C-10 crown ether[21] and in the 30-C-12 crown acetal detailed herein, that is a planar rectangular shape versus an undulated three-looped structure.

the β-CD- and γ-CD derived analogue of **2**, that is the peracetoxymethyl-substituted 35-crown-14 and 40-crown-16 polyacetals with seven and eight CCOCO-units in the macrocyclic core, have already been crystallized (m.p. 109–111 and 143.5–145 °C). The solid-state molecular geometry of the crown acetal with the "uneven" (seven) *meso*-butanetetrol/glycolaldehyde acetal units may be predicted to resemble that of **2**, with the "uneven" unit inserted in *gauche*-orientation into the alternating *gauche*/*anti*-arrangements, inasmuch as two successive *anti*-disposed glycol fragments would inflict considerable strain into the macrocycle. For the γ-CD-derived 40-C-16 crown acetal analogues of **1** and **2**, however, we envisage an undulated four-loop structure, not unlike the shape of a four-leaf clover. We hope to be in a position to report on these issues in the near future.

Experimental Section

Octadeca-(acetoxymethyl)-30-crown-12 polyacetal (2):[22] α-Cyclodextrin (1.95 g, 2.00 mmol) was added to a stirred and cooled (0–5 °C) aqueous solution of $NaIO_4$ (3.85 g, 18.0 mmol, in 90 mL) and the clear solution was kept at 0 °C in a dark ice-box for 11 d, whereafter TLC revealed a single spot ($R_f = 0.64$, 2:2:1 *n*BuOH/MeOH/water) of the dodeca-aldehyde (in one of the various hemiacetal and/or hemialdal hydrate forms possible). Then, 1,2-ethanediol (0.34 mL, 6.1 mmol) was added while stirring to decompose excess $NaIO_4$, the mixture was kept in a dark ice-box overnight, and an aqueous $BaCl_2$ solution (1.90 g, 9.12 mmol, in 10 mL) was added to the mixture. The solution as allowed to stand for a few hours at ambient temperature, and the resulting precipitate was filtered off, followed by evaporation of the filtrate to dryness in vacuo. The residue was suspended in dry MeOH (20 mL), kept in a refrigerator overnight, the solids were filtered off upon addition of charcoal, and the filtrate was evaporated to dryness in vacuo at ≈35 °C. This procedure was repeated twice to give a white powder (2.33 g), which was dissolved in MeOH/water (40 mL, 3:1). Upon cooling (0 °C) $NaBH_4$ (600 mg) was added while stirring and the mixture was kept at room temperature overnight. Addition of acetone (3 mL) to remove excess reagent, neutralization with cation-exchange resin (IR 120, H^+ form), evaporation to dryness, and several co-evaporations of the residue from dry MeOH left the polyol **1** as a colorless solid. Polyol **1** was dissolved in a mixture of Ac_2O (15 mL) and pyridine (30 mL), and stirred overnight at room temperature. Subsequent evaporation to dryness in vacuo at 40 °C, followed by co-evaporation with toluene (3 × 25 mL) afforded a syrup which was dissolved in hot EtOAc, treated with charcoal, filtered, and evaporated to dryness. The residue was crystallized by trituration with EtOAc/EtOH, affording **2** (3.20 g, 92 %) as colorless plates of m.p. 171–173 °C. Lit.:[16a] m.p. 162–164 °C; yield 0.6 %. $[\alpha]_D^{22} = 0.00$ (c = 2, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): $\delta = 5.06$ (t, 6H, J = 5.1 Hz, 2-H), 4.40 (dd, 12H, J = 8.6, 4.0 Hz, 4-CH_2^A, 5-CH_2^A), 4.15–4.03 (br m, 24H, 4-H, 4-CH_2^B, 5-H, 5-CH_2^B), 4.01 (d, J = 5.1 Hz, 12H, 2-CH_2), 2.03 (s, 36H, 12 AcCH_3), 1.98 (s, 18H, six 2-AcCH_3); ^{13}C NMR (75 MHz, $C_2D_2Cl_4$, 100 °C): $\delta = 170.4$, 170.3 (Ac*C*O), 101.4 (C-2), 77.1 (4-*C*H$_2$, 5-*C*H$_2$), 65.0 (2-*C*H$_2$), 64.2 (C-4, C-5); for other temperatures, see Figure 4; ESI-MS: m/z: 1763.5 $[M+Na]^+$; $C_{72}H_{108}O_{48}$ (1741.6): calcd C 49.65, H 6.25; found C 49.29, H 6.18.

Crystals suitable for X-ray analysis were obtained by slow crystallization of **2** from EtOH containing a small amount of EtOAc. A colorless crystal of dimensions 0.55 × 0.20 × 0.18 mm was analyzed on a Enraf-Nonius CAD-4 diffractometer using graphite-monochromated $Mo_{K\alpha}$ ($\lambda = 0.71093$ Å) radiation. Crystal data of **2**: $C_{72}H_{108}O_{48}$, $M_r = 1741.59$ g mol^{-1}, monoclinic, space group *P*n, $a = 15.729(2)$, $b = 12.757(1)$, $c = 22.333(5)$ Å, $\beta = 96.04(2)$, V = 4456.3(12) Å^3, $Z = 2$, $\rho = 1.298$ g cm^{-1}, $\mu(Mo_{K\alpha}) = 0.103$ mm^{-1}, T = 298(2)1 K. Of 7333 reflections collected, 7333 are independent (R_{int} = 0.0000). The structure was solved by direct methods (SHELXS-86)[23] and successive synthesis. Refinement (on F^2) was performed by full-matrix least squares method with SHELXL-97.[23] $R(F) = 0.0608$ for reflections with $I \geq 2\alpha I$, $\omega R(F^2) = 0.2022$ for all 7333 reflections ($\omega = 1/[\sigma^2(F_0^2) + (0.1293P)^2 + 2.3009P]$; where $P = (F_0^2 + 2F_c^2)/3$); goodness-of-fit on F^2: $S = 1.045$. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were considered in calculated positions with the 1.2 U_{eq} value of the corresponding bound atom. Graphics of Figure 2 were generated using the MolArch$^+$ program.[24]

Crystallographic data (excluding structure factors) for the structure **2** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-143715. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Octadeca-(hydroxymethyl)-30-crown-12 polyacetal (1):[22] A few drops of 2N methanolic sodium methoxide were added to a solution of octadeca-acetate **2** (2.75 g, 1.58 mmol) in dry MeOH (50 mL) and the mixture was stirred at room temperature overnight. After neutralization with IR-120 (H^+ form) the solution was evaporated to dryness in vacuo, and the residue was crystallized from 1-propanol as colorless plates (1.30 g, 84 %); m.p. 200–203 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 4.92$ (t, 6H, J = 5.6 Hz, 2-OH), 4.88 (t, 6H, J = 4.9 Hz, 2-H), 4.65 (t, 12H, J = 5.4 Hz, 4-OH, 5-OH), 3.84 (br s, 12H, 4-H, 5-H), 3.65–3.45 (m, 24 H, 4-CH_2, 5-CH_2), 3.45–3.37 (br t, J = 5.0 Hz, 2-CH_2); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 103.2$ (C-2), 78.3 (4-*C*H$_2$, 5-*C*H$_2$), 63.1 (2-*C*H$_2$), 60.9 (C-4, C-5); ESI-MS: m/z: 1007.6 $[M+Na]^+$; $C_{36}H_{72}O_{30} \cdot 1.5\,H_2O$ (1012.0): calcd C 42.73, H 7.47; found: C 42.69; H 7.52.

Acknowledgement

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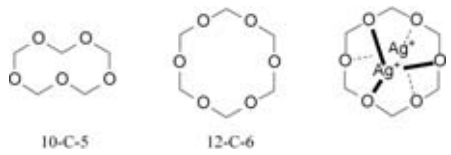
[7] *Nomenclature*: Although macrocyclic polyacetals, such as **1** or its peracetate **2**, do not adopt a crown-like molecular geometry—the terminology for macrocyclic ethers was derived from their crown-like shape—it appears not only logical but practical to extend this well-introduced notational mode to the acetal analogues of crown ethers, resulting in the term *crown acetals* for macrocycles with acetal oxygens only; similarly adapting the description established for ring size and number of oxygens, **2** is the octadeca-(hydroxymethyl) derivative of a 30-crown-12 polyacetal, the β-CD- and γ-CD-derived analogues are macrocycles with a 35-crown-14 and 40-crown-16 skeletal backbone.

[8] a) The cyclic pentamer and hexamer of formaldehyde—abbreviated in correspondence to crown ether terminology as 10-C-5 and 12-C-6, respectively—are neither crown ethers nor crown acetals, but de facto *crown aldals*,[8b] as they originate from the reaction between two aldehydes rather than between two diols or between an aldehyde and a diol.



Whilst the X-ray-confirmed molecular geometries of 10-C-5[8c] and 12-C-6[8d] show close analogies to those of the crown acetals of the same ring size, their cation binding capabilities are apt to be different, as evidenced, for example, by the unique di-silver ion complex of 12-C-6.[8e] b) The terms aldal, hemialdal, and hemialdal hydrate are commonly used in carbohydrate chemistry to denote the various forms adopted by sugar-derived dialdehydes: R. D. Guthrie, *Adv. Carbohydr. Chem.* **1970**, *16*, 118–140; c) Y. Chatani, K. Kitahama, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2300–2305; d) Y. Chatani, T. Ohno, T. Yamauchi, Y. Miyake, *J. Polym. Sci. Polym. Phys.* **1973**, *11*, 369–373; e) H. W. Roesky, E. Peymann, J. Schimkowiak, M. Noltemeyer. W. Pinkert, G. M. Sheldrick, *J. Chem. Soc. Chem. Commun.* **1983**, 981–982.

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TETRAHEDRON: *ASYMMETRY*

Hydroxymethyl-substituted crown acetals with 35-C-14 and 40-C-16 skeletal backbones: synthesis and molecular geometries†

Stefan Immel,* Frieder W. Lichtenthaler, Hans J. Lindner and Toshio Nakagawa

Institut für Organische Chemie, Technische Universität Darmstadt, D-64287 Darmstadt, Germany

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Abstract—An oxidation/reduction sequence readily converts β- and γ-cyclodextrin into hydroxymethyl-substituted crown acetals with 35-C-14 and 40-C-16 skeletal cores. X-Ray analysis of their well crystallizing peracetates reveals the 40-membered ring of the γ-CD derived octaacetal to mould into an undulated four-loop structure with alternating *gauche* and *anti*-conformations of the eight *meso*-butanetetrol units, the overall shape resembling a four-leaf clover. In the β-CD derived, 35-membered crown heptaacetal, six of the seven glycolaldehyde/butanetetrol segments are lined up in alternating *gauche*/*anti* arrangements with the seventh, uneven unit inserted in *gauche* orientation. In solution, however, the macrocycles are highly flexible as evidenced by their ^{1}H and ^{13}C NMR spectra, which at 300 K show only one set of signals for the respective -CHR-CHR-O-CHR-O- units (R = CH_2OH or CH_2OAc).

1. Introduction

Macrocycles exclusively containing acetal oxygens, and hence, deserving the designation *crown acetal*,[2] are rare, the presently known examples being limited to systems with one[3] or two[4] formaldehyde/alkanediol acetal units, i.e. containing only two or four oxygens in the ring.[5] Cycloacetals with a higher number of ring oxygen atoms, albeit never considered as such, happen to be the products generated by periodate oxidation of cyclic oligosaccharides. The polyaldehydes derived from α-, β-, and γ-cyclodextrin[6] de facto constitute macrocycles with 30-crown-12, 35-crown-14, and 40-crown-16 skeletal backbones, yet have eluded unequivocal structural characterization due to their manifold possibilities of elaborating cyclic acetals, hemiacetals and hemialdals. Of the products ensuing from borohydride reduction, the α- and β-cyclodextrin-derived polyhydroxymethyl-30-C-12 and 35-C-14 crown acetals **1** and **3** have been prepared,[7,8] yet only the 30-membered ring of the well-crystallizing peracetate of **1**, i.e. **2**, has yielded to an X-ray analysis, unveiling the macrocycle to be molded into an undulated three-loop core with a unique order of succession of the -CHR-CHR-O-CHR-O- units: alternating *gauche* and *anti*-conformations of the *meso*-butanetetrol portions and consecutive disposition of the glycolaldehyde–acetoxymethyl groups above and below the mean-plane of the backbone.[8] In solution, however, the macrocycle is highly flexible,[8] providing a suitable host for mimicking the induced-fit mode of molecular recognition[9]—rather than the rigid lock-and-key-type mechanism[10]—as the host can sterically adapt to a guest to be bound and incorporated. In continuation of our studies towards the generation of flexible hosts[11] to probe the induced-fit mode of guest inclusion, we here wish to report on the equally unique molecular geometries for the β- and γ-CD-derived crown acetals **4** and **6**.

2. Results and discussion

Periodate oxidation of β- and γ-CD was performed on a preparative scale (5–10 g) by keeping their aqueous solutions with a three molar excess of oxidant at 0–4°C for 5–7 days. The resulting CD–polyaldehydes obtained as chromatographically uniform powders, were subjected directly to reduction with $NaBH_4$ in methanol, yet the polyhydroxymethyl-substituted crown acetals **3** and **5** are preferably isolated the well-crystallizing peracetates **4** and **6**, respectively, obtainable with yields in the 80–90% range based on β- and γ-CD. Subsequent

* Corresponding author. Tel.: +49-6151-16 5277; fax: +49-6151-16 6674; e-mail: lemmi@sugar.oc.chemie.tu-darmstadt.de

† Part 29 of the series Molecular Modeling of Saccharides. For Part 28, see Ref. 1.

Zemplén deacetylation (NaOMe/MeOH) then smoothly afforded the respective polyols, i.e. the heneicosa-(hydroxymethyl)-35-crown-14 heptaacetal **3**, and its homolog, the tetraicosa-(hydroxymethyl)-40-crown-16 octaacetal **5**, both in crystalline form. None of the crown acetals prepared showed any rotational value, which was to be expected, as the butanetetrol units generated from the CDs by the periodation–reduction sequence have *erythro* configuration and erythritol is a *meso* compound (Scheme 1).

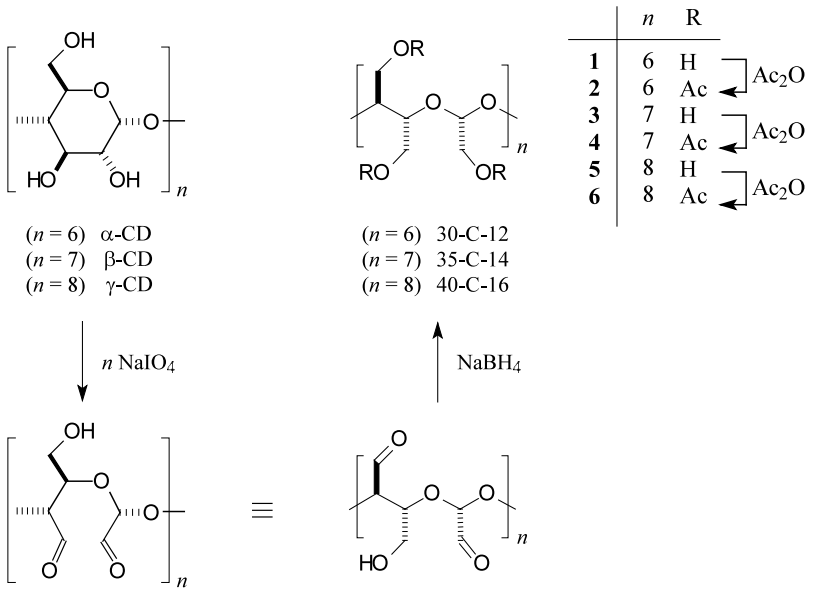
Unlike the hydroxymethyl-substituted crown acetals **3** and **5**, which as of now, only gave crystals unsuitable for X-ray analysis, their peracetates **4** and **6** did, straightforwardly unravelling their molecular geometries (cf. Fig. 1).

In the γ-CD-derived 40-C-16 octaacetal **6**, the 40-membered macrocycle is molded into four loops with the eight acetoxymethyl groups of the glycolaldehyde acetal units pointing alternatingly above and below the undulated mean-plane of the macrocyclic backbone. Similarly, the eight *meso*-butanetetrol units adopt alternating *gauche*- and *anti*-arrangements of their two acetoxymethyl groups (Fig. 1, top right). In this, the molecular arrangement is reminiscent of the folding of the α-CD-derived 30-C-12 analog **2**, in which the 30-membered ring is organized into three loops (Fig. 1, top left). Insertion of two further -CHR-CHR-O-CHR-O- groupings (with $R = CH_2OAc$) into the three looped 30-membered ring of **2** simply results in the elaboration of a fourth loop.

In the case of the β-CD-derived crown heptaacetal **4**, having seven, i.e. an uneven number of butanetetrol/glycolaldehyde segments, six of these units are lined up in alternating *gauche*/*anti* arrangements with the seventh residue being inserted into the macrocycle in *gauche* conformation (Fig. 1, top center); obviously incorporation of the 'uneven' butanetetrol unit in an *anti*-geometry would result in two successive *anti*-disposed glycol fragments inflicting considerable strain into the macrocycle.

The center row of Fig. 1 displays a single unit cell for the solid-state structures of **2**, **4**, and **6** with a colored representation of the Hirshfeld surfaces[12] of each molecule. These surfaces are roughly equivalent to the solvent accessible surfaces[13] for each molecule, yet for crystal lattices they are obtained as non-overlapping molecular surfaces arising from partitioning of the crystal space according to the volume occupied by each molecule. The front opened forms with ball-and-stick models inserted display the unit cell of **2** (Fig. 1, center left) to contain two molecules of the 30-C-12 hexaacetal, both molecules being symmetry-related with each other ($Z = 2$, space group P_n) through a sliding mirror plane. Obviously, the achiral compound **2** adopts two mirror image conformations with alternating (+)-*gauche*/*anti* (yellow Hirshfeld surface) and (−)-*gauche*/*anti* (orange) arrangements, respectively. Similar conditions are observed in the structures of **4** and **6** (space groups $\bar{P}$ and $C2/c$) in which four molecules per unit cell were established: in the case of **4**, two symmetry independent molecules are correlated with their mirror image conformers through symmetry operations (Fig. 1, center), whilst for **6** (Fig. 1, center right) all four molecules are symmetry related in the crystal lattice (pair wise mirror image conformers). In particular, the ribbon models of Fig. 1 (bottom row) display the mode of stacking of the individual macrorings in the solid-state structures.

Unlike the 30-C-12 crown acetal **2**, which crystallized from 95% ethanol as such, both the 35-C-14 and 40-C-16 homolog obtained in crystalline form from the same



Scheme 1. Synthetic access to large ring crown acetals with repetitive C-C-O-C-O- fragments in their skeletal backbones: α-, β-, and γ-cyclodextrin-derived hydroxymethyl substituted analogs composed of six, seven, and eight consecutive D-erythrose/glyoxal or—upon hydride reduction—*meso*-butanetetrol/glycolaldehyde segments.

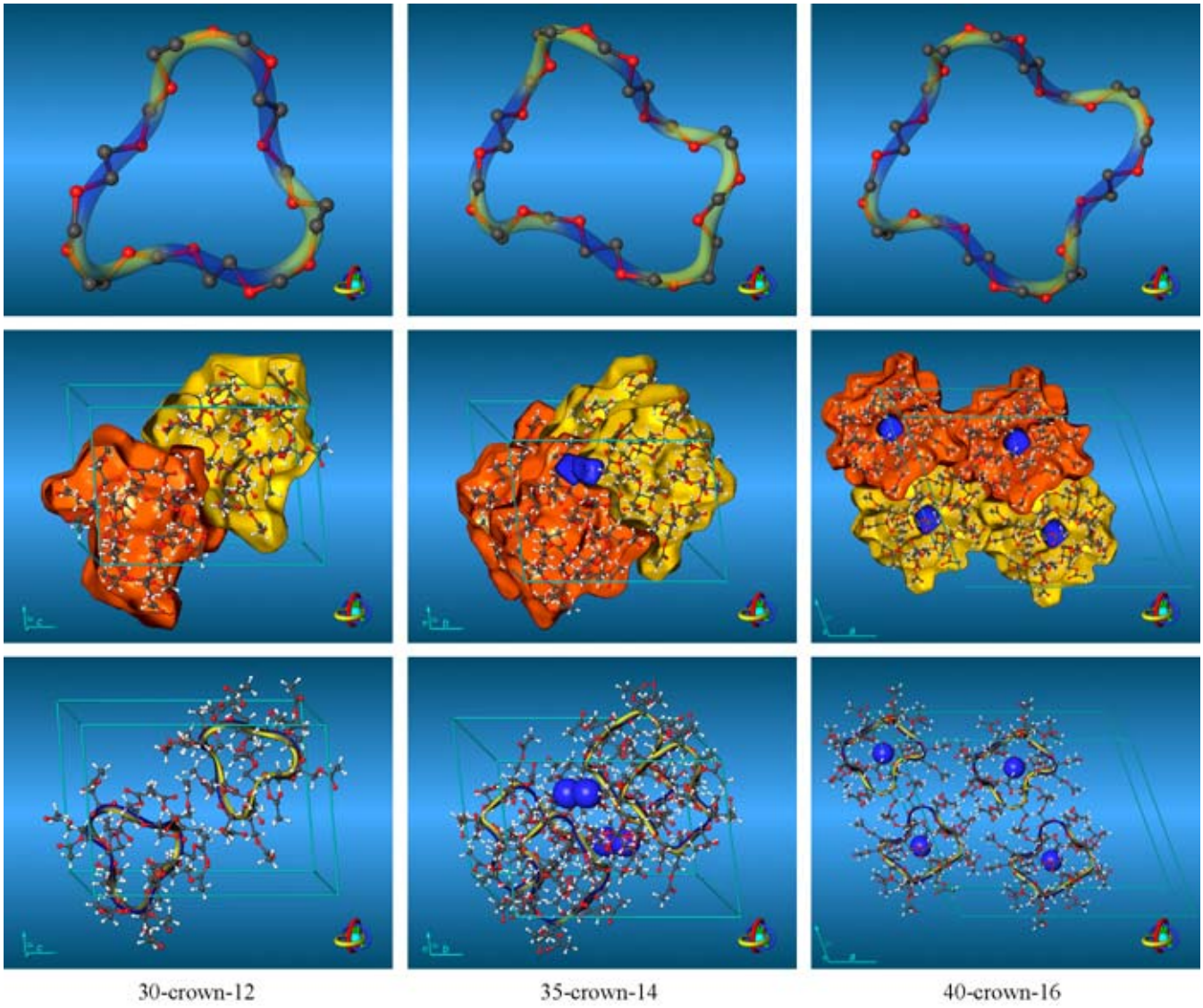


Figure 1. Solid-state structures of the 30-C-12 (**2**, left), 35-C-14 (**4**·H_2O, center), and 40-C-16 (**6**·H_2O, right) polyacetal peracetates. In the top row, all -CH_2OAc ring substituents and hydrogen atoms have been removed for visualization, the semi-transparent ribbon models are colored according to the alternating (+)-*gauche* (yellow) and *anti* (blue) conformations of the constituting *meso*-butanetetrol residues. The center entries display a single unit cell for each structure with the non-overlapping Hirshfeld surfaces indicating the crystal volumes occupied by each molecule. Symmetry related mirror image conformations of the achiral compounds with alternating (+)-*gauche*/*anti* and (−)-*gauche*/*anti meso*-butanetetrol units are labelled by yellow and red surface colors, respectively. The bottom row ribbon models show the mode with which water molecules (blue spheres) are incorporated into the crystal lattice of **4** and **6**: whilst in **4** the water occupies interstitial positions between the macrocycles (center row), in **6** each water molecule is fully included into a 40-C-16 octaacetal host (right row).

solvent, incorporated one water molecule per macrocycle (rather than ethanol) into the crystal lattice. Whilst in **4** the four water molecules per unit cell (blue surfaces and blue spheres in Fig. 1) occupy interstitial places between the macrocycles (in Fig. 1, center, only two of the four water molecules are visible, the others being covered by the surfaces of front crown-acetals), the water of crystallization is fully immersed into the macrocyclic hosts of **6**, occupying almost the center of geometry of the 40-C-16 octaacetals in an inclusion complex type fashion, de facto filling their entire inner space.

A detailed plot of the ring geometries of **4** and **6** is provided by Fig. 2, in which selected *meso*-butanetetrol residues have been labelled according to their conformation about the central C–C bond. Whilst the 'even' membered 40-C-16 octaacetal **6** allows for an fully alternating gauche/anti succession of the repeating unit within the ring, the 'uneven' 35-C-14 heptaacetal features two neighboring gauche residues in the macrocycle.

2.1. Solution geometries

The quite elaborate, well-organized structures found for the solid-state do not survive on dissolution in water in the case of the hydroxymethyl substituted crown acetals **3** and **5**, or in organic solvents such as chloroform for the peracetates **4** and **6**. As clearly evidenced by their ^1H

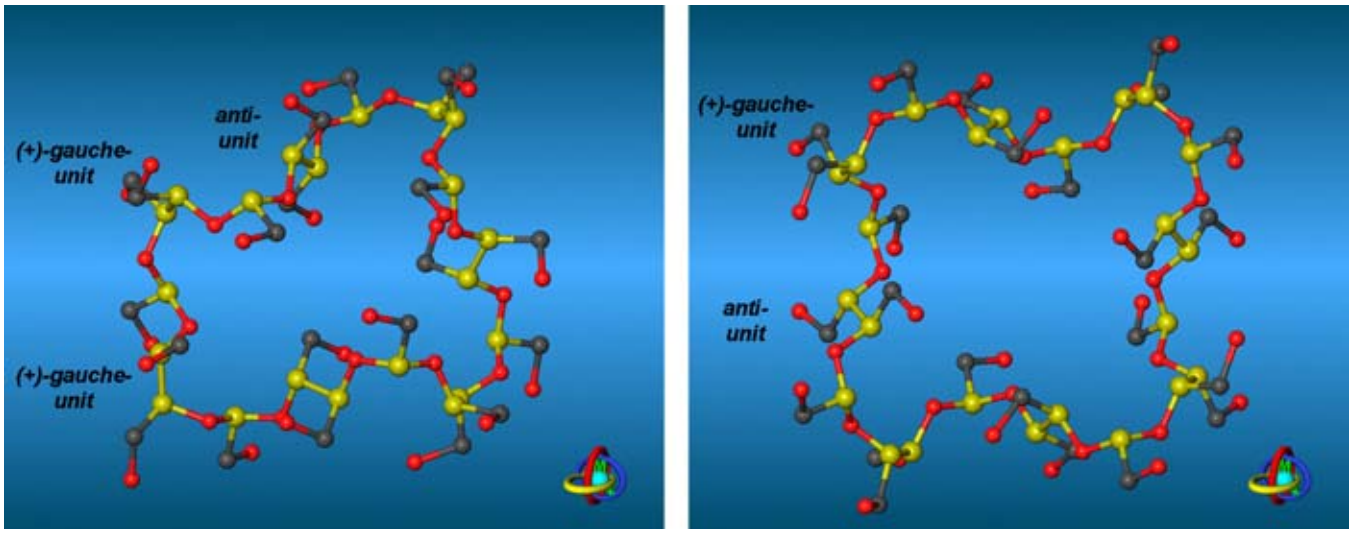


Figure 2. Comparison and ball-and-stick models of the solid-state ring conformations of the 35-C-14 heptaacetal and 40-C-16 octaacetal peracetates **4** and **6**. For visualization of the macrorings all ring carbon atoms are colored yellow, all hydrogen atoms and the acetyl groups of the substituents were left off for clarity. Representative *meso*-butanetetrol units are labeled according to their conformation (+)-*gauche* and *anti*; note the two consecutive (+)-*gauche*-oriented residues in the structure of the 'uneven' 35-membered ring of **2** on the left.

and ^{13}C NMR spectra, as of now measured only at 27°C (300 K), the macrocyclic crown acetals are highly flexible. Thus, for each, i.e. **3** and **5** in D_2O, **4** and **6** in $CDCl_3$), only one averaged set of signals is observed for the seven resp. eight -CHR-CHR-O-CHR-O- units: 5 Hz triplets for H-2 and doublets for the CH_2-protons of the glycolaldehyde acetal groups, 9–9.5 Hz triplets for H-4/H-5, and, invariably, the butanetetrol-4- and 5-CH_2OH protons as the AB part of an ABX system, with X being H-4 and H-5; the same holds for the ^{13}C NMR signals, showing three distinct resonances for the core carbons of the macrocycles, which could be unequivocally assigned on the basis of CH-decouplings. By consequence, in solution the 35-C-14 and 40-C-16 crown acetals are highly flexible macrocycles in which the seven resp. eight monomeric -CHR-CHR-O-CHR-O- units (with $R = CH_2OAc$), strung together to 35- and 40-membered cycles, are fully equilibrated and, hence, identical when observed in NMR time scale.

In turn, this high flexibility predisposes the crown acetals to adapt their conformation to guests for incorporation in a guest–host relationship and thus meet our aims for acquiring flexible hosts to study the induced-fit mode of molecular recognition. The peracetylated crown acetals **4** and **6**, as evidenced by Fig. 1 (mid-center and center right), display a distinct affinity to water, incorporating one molecule per macrocycle even when crystallized from 95% ethanol. The inclusion behavior of the crown acetals **3** and **5**, featuring 21 resp. 24 highly hydrophilic hydroxymethyl groups around the macrocycle, is different. The 35-C-14 heptaacetal **3** exhibits a distinct predilection for alcohols forming, on the basis of ^1H and ^{13}C NMR evidence, 1:1 complexes with ethanol or *n*-propanol when crystallized from these solvents. Fig. 3, depicting the surprisingly simple ^1H NMR spectrum of **3**·*n*-PrOH in D_2O gives ample proof of 1:1 complex. The type of binding though, i.e. whether the guest sits inside or outside the cavity—in D_2O it may be even in solution—must await X-ray analysis of the crystals, which as of now have not been obtained in a suitable form.

By contrast, the 40-crown-16 octaacetal **6** has no tendency at all to incorporate low molecular weight alcohols when crystallized therefrom, conceivably because its cavity can entertain only larger, possibly more hydrophobic guests. Investigations along this vein are presently being performed.

3. Experimental

3.1. General methods

Melting points were determined on a Bock Monoskop apparatus and are uncorrected. High-resolution mass spectra (ESI-MS) were recorded on Varian MAT 311 and MAT 212 spectrometers. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 instrument at 500 and 125 MHz at 300 K, respectively; ^{13}C NMR were proton decoupled. Chemical shifts are given in ppm relative to tetramethylsilane ($CDCl_3$) and sodium 2,2,3,3-tetradeutera-3-trimethylsilylpropionate (D_2O) as internal standards. Elemental analysis were determined on a Perkin–Elmer 240 elemental analyzer. Analytical thin-layer chromatography (TLC) was performed on precoated Merck plastic sheets (0.2 mm silica gel 60 F_{254}) with detection by UV (254 nm) and/or spraying with H_2SO_4 (50%) and heating.

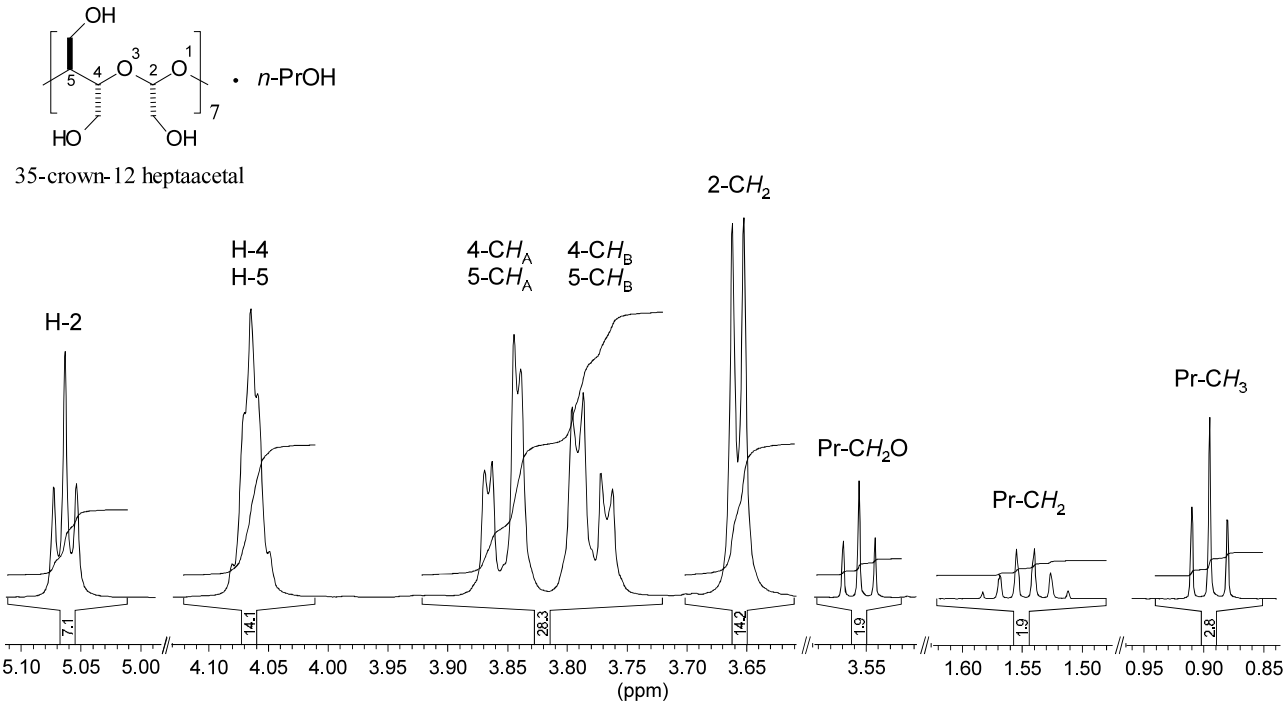


Figure 3. ^{1}H NMR spectrum (500 MHz in D_2O) of the 35-C-14 heptaacetal **3** obtained after dissolution of a sample of **3** previously crystallized from *n*-propanol. Besides a single time-averaged set of signals observed for the seven repeating units of **3**, the *n*-propanol resonances show the formation of a 1:1 inclusion complex.

3.1.1. X-Ray structures. Suitable crystals of cycloacetals **4** and **6** were analyzed on a Siemens CCD three-circle diffractometer with graphite-monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation. The structures were solved by direct methods (SHELXL-97) and successive Fourier synthesis. Refinement (on F^2) was performed by the full-matrix least-squares method with SHELXL-97.[14] All non-hydrogen atoms were refined anisotropically; hydrogen atoms were considered in calculated positions with the 1.2 U_{eq} value of the corresponding bound atom. Experimental details of the structure determinations are summarized in Table 1.

Crystallographic data (excluding structure factors) for **4** and **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-143712 and CCDC-143713. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: (+44) 1223 336-033, or e-mail: deposit@ccdc.cam.ac.uk.

3.1.2. Computational details. Calculation of the molecular Hirshfeld surfaces[12] and generation of molecular graphics was performed using the MolArch$^+$ program.[15]

3.2. Heneicosa-(acetoxymethyl)-35-crown-14 heptaacetal 4[16,17]

β-Cyclodextrin (7.39 g, 6.5 mmol) was added with stirring to a cooled (0–5°C), aqueous solution of $NaIO_4$ (13.9 g, 65 mmol, in 400 mL) and the clear solution was kept at 0°C in a dark ice-box for 7 days, whereafter TLC revealed a single spot ($R_f = 0.75$ in 2:2:1 *n*BuOH/MeOH/H_2O) of the respective tetradeca-aldehyde in one of the various hemiacetal and/or hemialdal hydrate forms possible. Then 1,2-ethanediol (1.09 mL, 19.5 mmol) was added with stirring to decompose excess $NaIO_4$ and the mixture was kept at 0°C overnight. An aqueous $BaCl_2$ solution (6.86 g, 32.9 mmol, in 30 mL) was then stirred into the mixture resulting in a precipitate, followed by evaporation of the filtrate to dryness in vacuo. The residue was suspended in dry MeOH (60 mL), kept in a refrigerator overnight, the solids were filtered off upon addition of charcoal, and the filtrate was evaporated to dryness in vacuo at ≈35°C. This procedure was repeated twice to give a white powder (8.4 g), which was dissolved in MeOH/water (100 mL, 3:1). Upon cooling (~0°C), $NaBH_4$ (2.0 g) was added with stirring and the mixture was kept at rt overnight. Addition of acetone (20 mL) to destroy the excess reagent, neutralization with cation exchange resin (IR-120, H^+ form), evaporation to dryness, and several co-evaporations of the residue with absolute MeOH left polyol **4** as a colorless solid which was dissolved in a mixture of pyridine (100 mL) and Ac_2O (50 mL), and kept overnight at rt. Subsequent evaporation to dryness in vacuo at 40°C, followed by co-evaporation with toluene (3×50 mL) afforded a syrup which was dissolved in hot EtOAc, treated with charcoal, filtered, and evaporated to dryness. The residue crystallized on dissolution in 95% EtOH and addition of small amounts of EtOAc to afford 11.62 g (88%) of **4** as colorless plates of mp 109–111°C; $[\alpha]_D^{22}$ 0.0 (*c* 2, $CHCl_3$); lit.:[7a] mp 106–107°C, 11% yield. ESI-MS: *m*/*z* 2053.2 ($M+Na^+$). ^{1}H NMR ($CDCl_3$): δ 5.14 (t, 7H, $J = 5.1$ Hz, 2-H), 4.47 (d, 14H, $J = 9.5$ Hz, 4-H, 5-H), 4.12 (broad 28H-m, AB part of an ABX system, 4-CH_2, 5-CH_2),

4.03 (d, 14H, $J=5.1$ Hz, 2-CH_2), 2.09 (s, 42H, 14AcCH_3), 2.05 (s, 21H, 7AcCH_3). ^{13}C NMR ($CDCl_3$): δ 169.5 (Ac*C*O), 99.5 (C-2), 74.7 (C-4, C-5), 63.5 (2-*C*H$_2$), 62.7 (4-*C*H$_2$, 5-*C*H$_2$), 19.6 and 19.7 (Ac*C*H$_3$). Anal. calcd for $C_{84}H_{126}O_{56}\cdot H_2O$[17] (2049.9): C, 49.22; H, 6.29. Found: C, 49.34; H, 6.21.

Crystals suitable for X-ray analysis were obtained by slow crystallization of **4** from 95% EtOH containing a small amount of EtOAc; crystal data are summarized in Table 1.

Table 1. Crystal data and structure refinement for the crown acetal per-*O*-acetates **4** and **6**

Compound	**4**·H_2O	**6**·H_2O
Empirical formula	$C_{84}H_{126}O_{56}\cdot H_2O$	$C_{96}H_{144}O_{64}\cdot H_2O$
Formula weight	2049.87	2340.13
Temperature (K)	173(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Triclinic	Monoclinic
Space group	$\bar{P}$	$C2/c$
Unit cell dimensions		
a (Å)	17.140(2)	36.654(3)
b (Å)	23.284(3)	12.219(1)
c (Å)	26.374(3)	30.577(3)
α (°)	97.50(1)	90
β (°)	97.28(1)	116.41(2)
γ (°)	97.41(1)	90
Volume (Å^3)	10237(2)	12265.4(19)
Z	4	4
D_{calcd} (g cm^{-1})	1.330	1.267
Absorption coefficient (mm^{-1})	0.106	0.101
$F(000)$	4344	4959
Crystal size (mm)	$0.33\times0.22\times0.10$	$0.55\times0.40\times0.35$
Θ Range (°)	0.79–27.53	1.24–27.30
Limiting indices	$-21\le h\le21$; $-29\le k\le30$; $-33\le l\le32$	$-46\le h\le46$; $-15\le k\le15$; $-39\le l\le39$
Reflections collected	92760	77665
Independent reflections	39750 ($R_{int}=0.0942$)	12680 ($R_{int}=0.0493$)
Absorption correction	Empirical	Empirical
Max. and min. transmission	0.9927 and 0.9767	0.9761 and 0.9628
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	39750/66/2671	12680/14/756
Goodness-of-fit on F^2	1.071	1.384
Final R indices $[I>2\sigma(I)]$[a]	$R_1=0.1305$; $wR_2=0.2569$	$R_1=0.1463$; $wR_2=0.4019$
R indices (all data)	$R_1=0.2578$; $wR_2=0.3170$	$R_1=0.2436$; $wR_2=0.4648$
Largest difference peak and hole (e Å^{-3})	0.916 and −0.392	0.859 and −0.281

[a] For **4**: $w=1/[\sigma^2(F_o^2)+(0.1165P)^2+15.8740P$; for **6**: $w=1/[\sigma^2(F_o^2)+0.2000P)^2+0.0000P$, where $P=(F_o^2+2F_c^2)/3$.

3.3. Heneicosa-(hydroxymethyl)-35-crown-14 heptaacetal 3[16]

3.3.1. 1:1 Complex with 1-propanol (3·*n*-C_3H_7OH). To a solution of **4** (5.00 g, 2.46 mmol) in absolute MeOH (125 mL) were added a few drops of 2N methanolic NaOMe and the mixture was stirred at rt overnight. After neutralization with IR-120 (H^+ form) the solution was evaporated to dryness in vacuo, and the residue was crystallized from 1-PrOH: 2.54 g (86%) of colorless plates of mp 145–157°C. ESI-MS: m/z 1172.1 (M+Na$^+$). ^{1}H NMR (D_2O): δ 5.06 (t, 7H, $J=4.9$ Hz, 2-H), 4.06 (m. 14H, X-part of an ABX-system, 4-H, 5-H), 3.86 (dd, 14H, $J=3.0$ and 12.2 Hz, 4-CH_2^A, 5-CH_2^A), 3.78 (dd, 14H, $J=4.8$ and 12.2 Hz, 4-CH_2^B, 5-CH_2^B), 3.66 (d, 14H, $J=4.9$ Hz, 2-CH_2), 3.56 (t, 2H, $J=7.4$ Hz, EtCH_2O), 1.55 (sext., 2H, $J=7.4$ Hz, MeCH_2CH$_2$O), 0.89 (t, 3H, $J=7.4$ Hz, PrCH_3). ^{13}C NMR (D_2O): δ 101.6 (C-2), 77.4 (C-4, C-5), 62.7 (Et*C*H$_2$O), 62.2 (2-*C*H$_2$), 59.7 (4-*C*H$_2$, 5-*C*H$_2$), 23.7 (Me*C*H$_2$CH$_2$O), 8.7 (Pr*C*H$_3$). Anal. calcd for $C_{42}H_{84}O_{35}\cdot C_3H_7OH$ (1209.2): C, 44.70; H 7.67. Found: C, 44.65; H, 7.78.

3.3.2. 1:1 Complex with ethanol (3·EtOH). An aqueous solution of **3**·PrOH (0.85 g in 20 mL) was evaporated to dryness at 50°C in vacuo and the residue was subjected to another two evaporations from water. The resulting powder was crystallized from ethanol to yield 0.74 g (87%) of colorless plates exhibiting an unusually wide melting range of 125–157°C without decomposition, undoubtedly due to release of ethanol on melting; lit.[7b] mp 125–132°C for a sample believed to be **3**, but obtained by crystallization from ethanol. ^{1}H NMR (D_2O): δ 5.07 (t, 7H, $J=4.8$ Hz, 2-H), 4.6 (m, 14H, X-part of an ABX system, 4-H, 5-H), 3.86 and 3.77 (two dd for the AB part of an ABX system, 14H each, 4-CH_2 and 5-CH_2), 3.67 (d, 14H, 2-CH_2), 3.64 (q, 2H, EtCH_2), 1.19 (t, 3H, EtCH_3). ^{13}C NMR (D_2O): δ 105.4 (C-2), 80.8 (C-4, C-5), 65.9 (2-*C*H$_2$), 63.4 (4-*C*H$_2$, 5-*C*H$_2$). Anal. calcd for $C_{42}H_{84}O_{35}\cdot C_2H_5OH$ (1195.2): C, 44.22; H, 7.59. Found: C, 44.98; H, 7.50.

3.4. Tetraicosa-(acetoxymethyl)-40-crown-16 octaacetal 6[16]

To a stirred and cooled (0–5°C) aqueous solution of $NaIO_4$ (12.95 g, 60.5 mmol, in 400 mL) γ-cyclodextrin (7.14 g, 5.5 mmol) was added and the clear solution was kept at 0°C in a dark ice-box for 5 days whereafter TLC revealed a single spot ($R_f=0.75$ in 2:2:1 *n*BuOH/MeOH/H_2O). Then, 1,2-ethanediol (0.92 mL, 16.5 mmol) was added with stirring to decompose excess $NaIO_4$ and the reaction was worked up in a manner analogous to that described above for the periodation of β-CD. The respective polyaldehyde was obtained as white powder (8.32 g). Subsequent reduction with $NaBH_4$ (2.0 g) and acetylation with pyridine/Ac_2O (2:1, 150 mL) as described for the acquisition of **4** from β-CD gave a syrup that gradually crystallized on titration with EtOH/EtOAc and was isolated on standing overnight at ambient temperature: 10.6 g (82%) as colorless plates of mp 143.5–145°C; $[\alpha]_D^{22}$ 0.0 (c 2, $CHCl_3$). ESI-MS: m/z 2345.1 (M+Na$^+$). ^{1}H NMR ($CDCl_3$): δ 5.16 (t, 8H, $J=4.9$ Hz, 2-H), 4.49 (dd, 16H,

$J=9.4$ and 1.3 Hz, 4-H, 5-H, X-part), 4.13 and 4.09 (16H, dd and 16H-m, 4-CH_2 and 5-CH_2 as an ABX system), 4.00 (d, 16H, $J=5.0$, 2-CH_2), 2.08 (s, 48H, 4-AcCH_3, 5-AcCH_3), 2.05 (s, 24H, 2-AcCH_3). ^{13}C NMR ($CDCl_3$): δ 170.4 and 170.3 (Ac*C*O), 101.0 (C-2), 76.3 (C-4, C-5), 64.7 (2-*C*H_2), 63.9 (4-*C*H_2, 5-*C*H_2), 20.7 and 20.6 (Ac*C*H_3). Anal. calcd for $C_{96}H_{144}O_{64}\cdot H_2O$[17] (2340.1): C, 49.27; H, 6.29. Found: C, 49.29; H, 6.26.

Crystals for X-ray analysis were obtained by slow crystallization of **6** from 95% EtOH containing a small amount of EtOAc; crystal data are summarized in Table 1.

3.5. Tetraicosa-(hydroxymethyl)-40-crown-16 octaacetal 5[16]

Zemplén deacetylation of **6** (2.00 g, 0.85 mmol) was carried out in a similar manner described above for (**4**→**3**). Crystallization from 1-PrOH afforded colorless needles (1.00 g, 89%) of mp 163–165°C. ESI-MS: *m*/*z* 1335.3 (M+Na$^+$). ^{1}H NMR (D_2O): δ 5.07 (t, 8H, $J=4.5$ Hz, 2-H), 4.07 (broad m, 16H, X-part of an ABX-system, 4-H and 5-H), 3.83 and 3.78 (two dd of an AB system, 16H each, 4-CH_2 and 5-CH_2), 3.67 (d, 16H, 2-CH_2). ^{13}C NMR (D_2O): δ 105.7 (C-2), 81.1 (C-4, C-5), 65.7 (2-*C*H_2), 63.1 (4-*C*H_2, 5-*C*H_2). Anal. calcd for $C_{48}H_{96}O_{40}$ (1313.3): C, 43.90; H, 7.36. Found: C, 43.65; H, 7.44.

Acknowledgements

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17. That the crown acetal peracetates **4** and **6** crystallize with one molecule of water each—crystallization was effected from 95% EtOH/EtOAc—emerged from the X-ray data (cf. Fig. 1) and not from their microanalysis, as differentiation on that basis between anhydrous compound and monohydrate is not possible.

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LARGE-RING CROWN ACETALS FROM CYCLODEXTRINS

T. NAKAGAWA, S. IMMEL, H. J. LINDNER, F. W. LICHTENTHALER

Institute of Organic Chemistry, Darmstadt University of Technology, D-64287 Darmstadt, Germany

ABSTRACT

Periodate oxidation followed by borohydride reduction readily converts α-, β-, and γ-cyclodextrin into crown acetals with 30-C-12, 35-C-14, and 40-C-14 skeletal backbones and a hydroxymethyl group at each of the carbon atoms. Isolated as their crystalline peracetate (**1** -**3**) or as such (**4** - **6**) in yields of 82-92 %, X-ray structures revealed their unique molecular geometries: the 30-membered ring in α-CD-derived **1** adopts a three-looped, undulated shape with alternating *gauche* and *anti* conformations of the six *meso*-butanetetrol units, and above / below positioning of the six glycolaldehyde acetoxymethyl groups. Key structural features of the γ-CD-derived 40-membered macrocycle with 16 ring oxygens are a four-looped, clover-leaf type shape in similarly undulated form. In solution though, the macrocycle **1** is highly flexible showing one set of NMR signals (^{1}H and ^{13}C) at high temperature (~80 °C), and distinct broadening at ambient temperature, whilst the signals fall into two sets at -60 °C, indicating a "freezing out" of the solid state molecular geometry.

1. INTRODUCTION

Macrocycles exclusively containing acetal oxygens, and, hence, deserving the designation crown acetal,[1] are rare, the presently known examples being limited to systems with two formaldehyde/alkanediol acetal units, i. e. containing four oxygens in the ring.[2] Cycloacetals with a higher number of ring oxygen atoms, albeit never considered as such, happen to be the products generated by periodate oxidation of cyclic oligosaccharides. The polyaldehydes derived from α-, β-, and γ-cyclodextrin[3] constitute macrocycles with 30-crown-12, 35-crown-14, and 40-crown-16 skeletal backbones, yet have eluded unequivocal structural characterization, conceivably due to the manifold possibilities of elaborating cyclic acetals, hemiacetals and hemialdals. Of the products ensuing from borohydride reduction and subsequent acetylation,[4] only the per-acetoxy methyl 30-C-12 crown acetal **1** and its 35-C-4 analog **2** have been prepared – in yields of 0.6 and 11 %[4a] for the three steps from α- and β-CD, respectively – and fairly well characterized, yet the sparse NMR data given provided no indications as to their molecular geometries.

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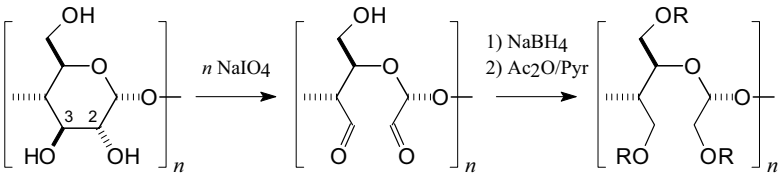
Our past interest in the generation of flexible cyclooligosaccharide hosts[5] to mimic the induced-fit mode of enzyme action[6] rather than Emil Fischer's classical static lock-and-key concept[7] has now led us to preparatively satisfactory syntheses for the α-, β- and γ-CD-derived crown acetals **1**-**6** in crystalline form each, their unequivocal characterization and an exploitation of their conformational features via X-ray and NMR.



α-CD (n = 6)
β-CD (n = 7)
γ-CD (n = 8)

	n	R	macrocycle[1]
1	6	Ac	30-C-12
2	7	Ac	35-C-14
3	8	Ac	40-C-16
4	6	H	30-C-12
5	7	H	35-C-14
6	8	H	40-C-16

2. MATERIALS AND METHODS

Preparation. Periodate oxidation of α-, β-, and γ-CD was performed on a preparative scale (5-10 g) by keeping their aqueous solutions with a 3 molar excess of oxidant at 0-4 °C for 5-11 d. The resulting CD-polyaldehydes obtained as chromatographically uniform powders, were directly subjected to reduction with $NaBH_4$ in aqueous methanol, yet the polyhydroxymethyl-substituted crown acetals **4**, **5** and **6** are preferably not isolated at this stage, because peracetylation with acetic anhydride/pyridine provides the well-crystallizing peracetates **1**-**3**, isolable in yields in the 80-90 % range based on the CDs. Subsequent Zemplén deacetylation (NaOMe/MeOH) then smoothly affords the respective polyols, i. e. the octadecakis(hydroxymethyl)-30-crown-12 hexaacetal **4**,[8] and its 35-crown-14 and 40-crown-16 analogs **5** and **6**.[8] Selected data for **1** - **6**:

1: mp 171-173 °C, 92 % yield over 3 steps from α-CD (lit.[4a] mp 162-164 °C, 0.6 %), ESI- MS 1763.5 ($M + Na^+$).

2: mp 109-111 °C, 88 % from β-CD, ESI-MS 2053.6 ($M + Na^+$).

3: mp 143.5-145.5 °C, 82 % from γ-CD, ESI-MS 2343.2 ($M + Na^+$).

4: mp 200-203 °C, 84 % from **1**, ESI-MS 1007.6 ($M + Na^+$).

5: mp 145-157 °C (cryst. from n-PrOH), 80 % from **2**, ESI-MS 1171.4 ($M + Na^+$).

6: mp 163-165 °C, 85 % from **3**, ESI-MS 1335.6 ($M + Na^+$).

X-Ray Structures. Details on the X-ray analysis of the α-CD-derived **1** are published elsewhere[9]; see also CCDC 143 715. – Crystallographic data for **3**: $C_{96}H_{144}O_{64} \bullet H_2O$, M_r = 2340.18 g mol^{-1}, monoclinic, space group $C2/c$, a = 36.654(3), b = 12.219(1), c = 30.577(3) Å, β = 116.41(2), V = 12265.4(19) Å^3, Z = 4, ρ = 1.266 g cm^{-1}, $\mu(Mo_{K\alpha})$ = 0.101 mm^{-1}, crystal dimensions 0.55 x 0.40 x 0.35 mm, T = 293(2). Of

77665 reflections collected on a Siemens CCD diffractometer, graphite-monochromated $Mo_{K\alpha}$ ($\lambda = 0.71073$ Å) radiation, 12680 are independent ($R_{int} = 0.0493$). The structure was solved by direct methods (SHELXS-97[10]) and successive Fourier synthesis. Refinement (on F^2) was performed by full-matrix least squares method with SHELXL-97.[10] $R(F) = 0.1463$ for reflections with $I \geq 2\sigma I$, $\omega R(F^2) = 0.4648$ for all 12680 reflections ($\omega = 1/[\sigma^2(F_o^2)+(0.2000P)^2+0.0000P]$; where $P = (F_o^2+2F_c^2)/3$). All non-hydrogen atoms were refined anisotropically; hydrogen atoms where considered in calculated positions with the $1.2\,U_{eq}$ value of the corresponding bound atom. Crystallographic data (excluding structure factors) for **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-143 713.

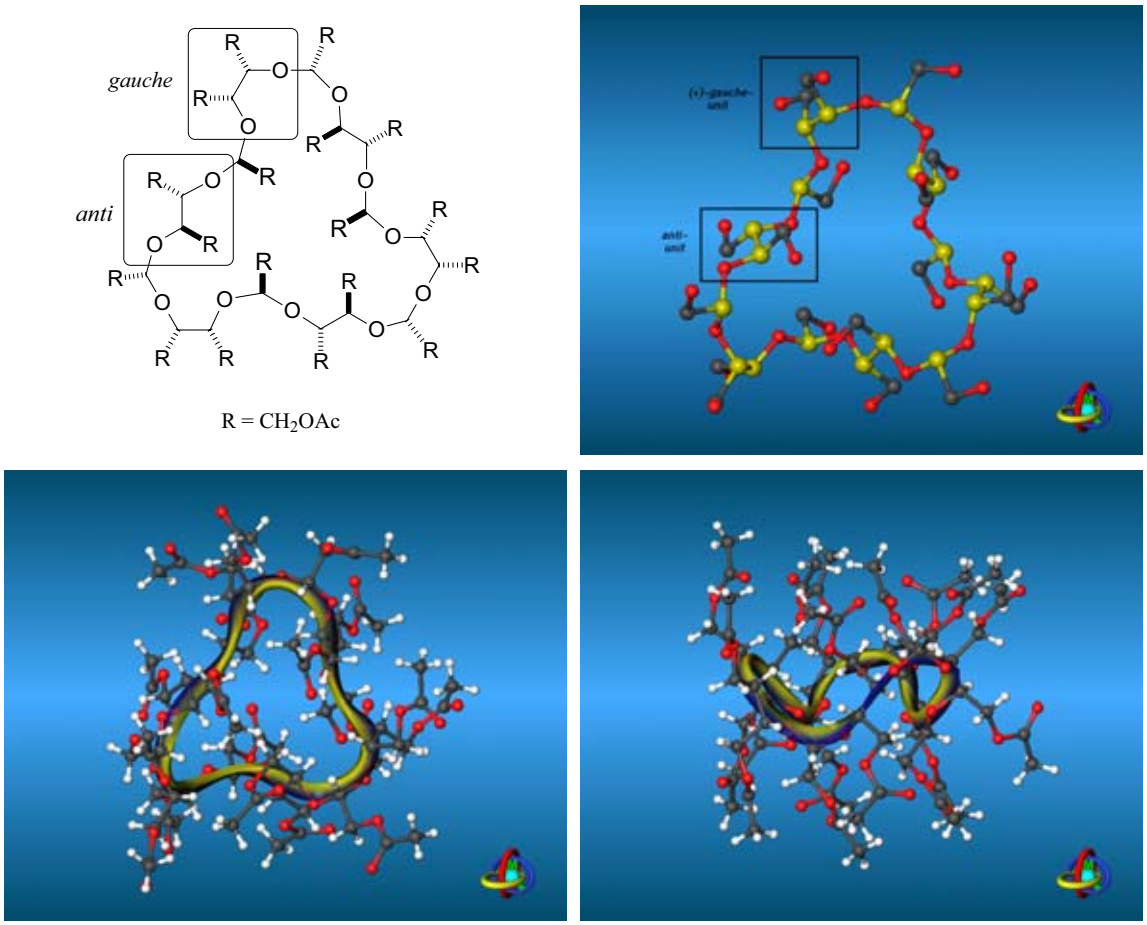


Figure 1. Solid-state topography of the octadecakis(acetoxymethyl)-30-crown-12 hexaacetal **1** in conventional formula drawing (upper left) and in ball-and-stick representation with the hydrogen atoms and 18 acetyl residues omitted for clarity (upper right): The *meso*-butanetetrol units alternating in *gauche* and *anti*-conformation versus above / below succession of glycolaldehyde acetal groups. The ribbon models (bottom entries) amply illustrate the three-looped shape (bottom left) and its undulatory form (bottom right) with the yellow/blue-coloring of the braid signifying the twist of the backbone. [11]

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3. RESULTS AND DISCUSSION

None of the crown acetals prepared showed any rotational value, which was to be expected, as the butanetetrol units generated from the CDs by the periodation-reduction sequence have *erythro*-configuration and erythritol is a *meso*-compound. An X-ray analysis of the α-CD-derived 30-crown-12 hexaacetal **1**[9] revealed the 30-membered macrocycle to be molded into three loops with six acetoxymethyl groups of the glycolaldehyde acetal units pointing alternatingly above and below the mean-plane of the macrocyclic backbone; the six *meso*-butanetetrol units are similarly alternating between *gauche*- and *anti*-arrangements for the two acetoxymethyl groups and, hence, O–C–C–O–torsion angles (Figure 1). Although the 30-crown-12 macrocycle of **1** is anticipated to be quite flexible in solution, both temperature dependent ^{1}H[9] and ^{13}C NMR patterns in CD_2Cl_2 and $C_2D_2Cl_4$, respectively (cf. Figure 2), point towards the over-all shape of the solid-state conformation being largely retained in these solvents.

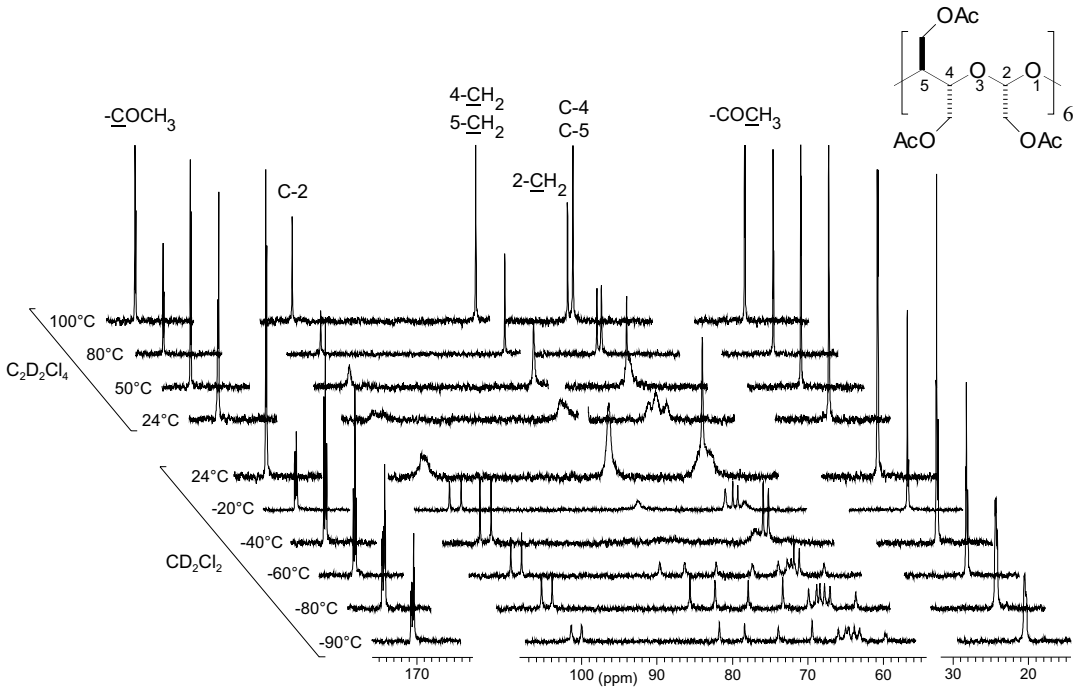

Figure 2. ^{13}C NMR spectral patterns of **1** in dependence of temperature, recorded in CD_2Cl_2 (T = +24 to -90 °C) and $C_2D_2Cl_4$ (24 - 100 °C). At 100 °C there is only one set of carbon atoms indicating full flexibility of the macrocyclic core with fast interconversions of any individual conformations; coalescence is observed at about room temperature whilst at -90 °C each of the signals is doubled, consistent with the notion that the solid-state geometry of **1** with its alternating *gauche* / *anti* arrangements of the six butanetetrol units and the above / below positioning of the glycolaldehyde acetoxymethyl groups has been "frozen out".

Preliminary X-ray structural data on the γ-CD-derived tetracosakis(acetoxymethyl)-40-crown-12 octaacetal **3** showed the 40-membered ring to have an undulated four-loop structure (cf. Figure 3), not unlike the shape of a four-leaf clover. For the 35-C-14 analog **2**, comprising seven *meso*-butanetetrol / glycolaldehyde acetal units, we envisage its conformational features to resemble that of **1** with the "uneven" unit inserted in *gauche*-orientation into the alternating *gauche* / *anti*-arrangements, because two successive *anti*-disposed glycol fragments would enter considerable strain into the macrocycle.

Unequivocal evidence for inclusion compounds of the crown acetals **1** - **6**, as of now, is not available, yet the unusually broad melting range of the β-CD-derived **5**, when crystallized from *n*-propanol (145-157 °C), and the ^{1}H NMR in D_6-DMSO, which reveals the presence of one equivalent of *n*-propanol, is strongly indicative of the product being a 1:1 complex **5** · n-PrOH. Whether the guest though sits inside the 35-C-14-macrocycles cavity or is only associated to hydroxymethyl substituents remains to be established.

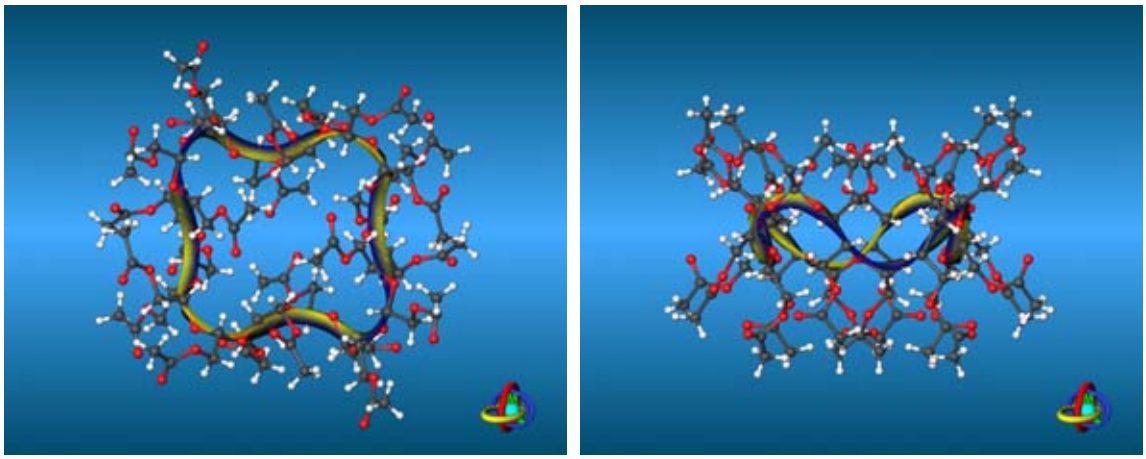

Figure 3. X-ray-derived molecular geometry of the γ-CD-derived tetracosakis(acetoxymethyl)-40-crown-16 octaacetal **3** in ball-and-stick representation, illustrating the four-looped clover-leaf type structure and its distinctly waved form.[11]

ACKNOWLEDGMENTS

Appreciation is expressed to the Fonds der Chemischen Industrie, Frankfurt, and the Südzucker AG, Mannheim / Ochsenfurt, for financial support, to Mrs. S. Foro for collecting the X-ray data of **1** and **3**, and to Wacker-Chemie, Burghausen, for generous gifts of the cyclodextrins.

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NOTES AND REFERENCES

[1] *Nomenclature:* Although macrocyclic polyacetals such as **1** - **6** are improbable to adopt a crown-like molecular geometry – the terminology for macrocyclic ethers was derived from their crown-like shape – it appears logical as well as practical to extend this well-introduced notational mode to the acetal analogs of crown ethers, resulting in the term *crown acetals* for macrocycles with acetal oxygens only. Likewise, it appears most appropriate to adopt for crown acetals the crown ether-type description for ring size and number of oxygens; accordingly, **4** is the octadecakis(hydroxymethyl) derivative of a 30-crown-12 hexaacetal, whereas the respective β-CD- and γ-CD-derived analogs **5** and **6** are macrocycles with a 35-crown-14 and 40-crown-16 backbone.

[2] *Crown acetal skeletal backbones: (a)* 10-C-4: Bassi, I. W., Scordamaglia, R., Fiori, L., *J. Chem. Soc., Perkin Trans. 2* **1975**, 1129-1132. –*(b)* Substituted 10-C-4-systems: Terzis, A., Grindley, T. B., *Can. J. Chem.* **1979**, *57*, 2154-2157. – Stoddart, J. F., Szarek, W. A., *Can. J. Chem.* **1968**, *46*, 3061-3069. – *(c)* 12-C-4: Borgen, G., Dale, J., *J. Chem. Soc., Chem. Commun.* **1974**, 484-485; Dale, J., *Tetrahedron* **1974**, *30*, 1683-1694. – *(d)* 14-C-4: Bassi, I. W., Scordamaglia, R., Fiori, L., *J. Chem. Soc., Perkin Trans. 2* **1972**, 1726-1729. – *(e)* 16-C-4: Dale, J., Ekeland, T., *Acta Chem. Scand., Ser. A* **1973**, *27*, 1519-1525. – Groth, P., *ibid.* **1975**, *29*, 642-643. – *(f)* 18-C-4, 24-C-4, 26-C-4, and 34-C-4: Hill, J. W., Carothers, W. H., *J. Am. Chem. Soc.* **1935**, *57*, 925-928.

[3] *(a)* French, D., McIntyre, R. J., *J. Am. Chem. Soc.* **1950**, *72*, 5148-5150. – *(b)* Hisamatsu, M., Yamada, Y., Nakashima, K., Tobata, K., *Starch/Stärke* **1992**, *44*, 188-191.

[4] *(a)* Stoddart, J. F., Szarek, W. A., Jones, J. K. N., *Can. J. Chem.* **1969**, *47*, 3213-3215. – *(b)* Kandra, L., Lipták, A., Jodál, I., Nánási, P., Szejtli, J., *J. Inclusion Phenom.* **1984**, *2*, 869-875.

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[6] Koshland, D. E., *Angew. Chem.* **1994**, *106*, 2368-2372; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2375-2378.

[7] Fischer, E., *Ber. Dtsch. Chem. Ges.* **1884**, *27*, 2985-2993. – Lichtenthaler, F. W., *Angew. Chem.* **1994**, *106*, 2456-2467; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2364-2374.

[8] Systematic name for **4**: 2,4,5,7,9,10,12,14,15,17,19,20,22,24,25,27,29,30-octadecakis(hydroxymethyl)-1,3,6,8,11,13,16, 18,21,23,26,28-dodecaoxacyclotriacontane; the hexaacetal **1** is the octadeca-acetate thereof. Correspondingly, **5** is a derivative of tetradecaoxacyclopentatriacontane; **6** one of a hexadecaoxacyclotetracontane.

[9] Immel, S., Nakagawa, T., Lindner, H. J., Lichtenthaler, F. W., *Chem. Eur. J.* **2000**, *6*, in press (October issue).

[10] Sheldrick, G. M., *SHELXS-97* and *SHELXL-97 – Programs for Crystal Structure Solution and Refinement*, University of Göttingen, Germany, **1990** and **1997**.

[11] Graphics of Figures 1 and 3 were generated using the MolArch$^+$ program: Immel, S. *MolArch$^+$ MOLecular ARCHitecture Modeling Program*. Darmstadt University of Technology, Germany, **1999**.

Proc. 10th Int. Symp. Cyclodextrins (Ed.: J. Szejtli), Mia Digital Publ., Ann Arbor, Michigan, **2000**, pp. 24-31.

FLEXIBLE NON-GLUCOSE CYCLOOLIGOSACCHARIDES

S. IMMEL

Institute of Organic Chemistry, Darmstadt University of Technology, D-64287 Darmstadt, Germany

ABSTRACT

Despite lack of torus stabilization through interresidue hydrogen bonds, per-2,3-anhydro-α-cyclomannin adopts almost C_6 symmetrical conformations in the solid-state structures of its ethanol and 1-propanol inclusion complexes. Thoroughly flexible cyclooligosaccharides are obtained from incorporation of α-D-altropyranose residues into the macroring: mono-*altro* β-cyclodextrin displays an "*induced-fit*" type complexation of adamantane 1-carboxylate, and α-cycloaltrin (α-CA) is characterized by an alternating sequence $^4C_1$ / $^1C_4$ altrose geometries. Analysis of the conformational properties of α-CA reveals a mechanism of global pseudorotational motions in the macrocycle. Similar effects are observed in highly substituted cyclodextrin derivatives, as well as in cyclofructins, and CD-derived large ring crown acetals.

1. INTRODUCTION

The rather static "*lock-and-key*"[1] type formation of inclusion complexes by cyclodextrins (CDs) is caused by their rigid, truncated-cone type structures, which — at least for α-, β-, and γ-CD — generally undergo only minor structural changes upon incorporation of guest molecules.[2] To mimic biological "*induced-fit*"[3] type mechanisms of inclusion, the strait-jacket of the macrocycles has to be released, and some flexibility needs to be introduced into the host molecules. Of the various possibilities to affect such modifications, substitution of OH-groups on both the secondary and/or primary face of the CDs increases their flexibility through steric hindrance and repulsion between neighboring substituents, often also implying a lowered torus stabilization through disruption of the ring of interresidue 2-O ··· O-3' hydrogen bonds.[4] Thoroughly flexible cyclooligosaccharides are also generated from exchange of the rather stiff α-D-glucose residues against more flexible pyranose units such as α-D-altrose,[5,6] or by per-iodate oxidation of the C-2 - C-3 bonds as demonstrated by the CD-derived large ring crown acetals.[7,8] This account describes some conformational properties of various flexible non-glucose cyclooligosaccharides.

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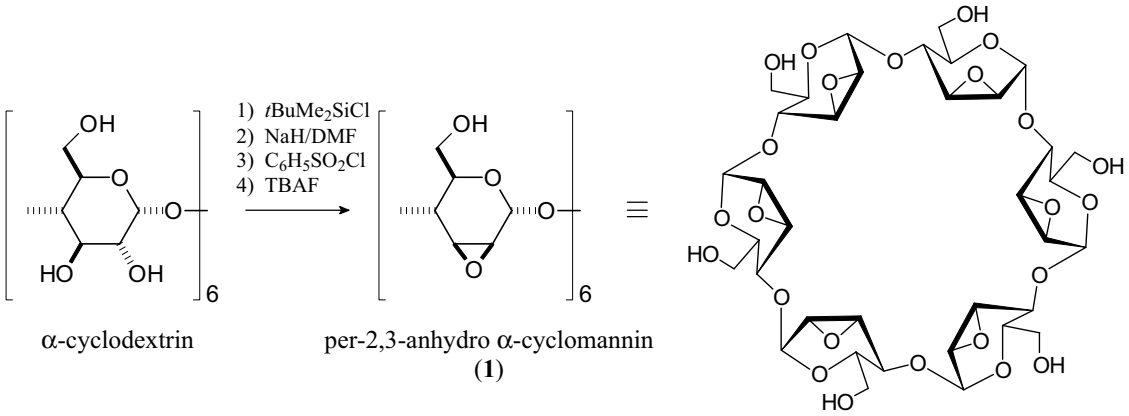
2. RESULTS AND DISCUSSION

2.1 Per-2,3-anhydro-α-cyclomannin (1)

Per-2,3-anhydro-α-cyclomannin **1**[5,9] is readily available from α-CD in a straight-forward four-step sequence of reactions, implying protection of the primary 6-OH groups and base-induced activation of the 2-OH groups, followed by epoxide ring formation and deprotection.[5]



When crystallized from aqueous ethanol or 1-propanol, **1** accumulates as the ethanol[10] or 1-propanol[11] 1 : 1 inclusion complex, respectively, with varying amounts of co-crystallized water. X-Ray solid-state structural analysis reveals both crystal structures to be isomorphic (both trigonal, space group $P3_212$, $Z = 6$); Figure 1 displays segments of the structures. In both complexes, the cyclomannin hosts are stacked in an alternating head-to-head and tail-to-tail like fashion along the *c*-axis, forming layers of complex dimers through the epoxide ring carrying faces of the macrocycles. These dimeric units are embedded between layers of water molecules, which in turn form a hydrogen bonding network with the primary 6-OH groups.[10,11]

Ethanol and 1-propanol are included with opposite regioselectivities: the two ethanol molecules entrapped in the cavity of a dimeric unit of the complex form a hydrogen bond between their hydroxyl groups.[10] In the 1-propanol complex, the hydroxyl groups of the guest molecules form hydrogen bonds towards water molecule in the layer around the 6-OH groups, and the two propyl side chains face each other.[11] Obviously, ethanol is not large enough to fully occupy the cavity of **1** while forming ethanol - water hydrogen bonds, thus leading to the elaboration of a guest-guest hydrogen bond rather than leaving a hydrophobic void in the cavity. The 1-propanol guest fills the cavity more effectively, and allows for hydrophobic contacts between the alkyl chains in the cavity.

Without introducing steric hindrance, the six epoxide rings in **1** block the formation of 2-O ··· O-3' interresidue hydrogen bonds, leaving the torus less stabilized than in the CDs. However, the two inclusion complexes of **1** display very little variations in the almost C_6 symmetrical macrocyclic ring conformations of the host molecules. This may be — at least in part — attributed to the still rather rigid conformations of the 2,3-anhydro mannoside residues, which invariably adopt $^{O}H_5$ pyranose ring geometries.

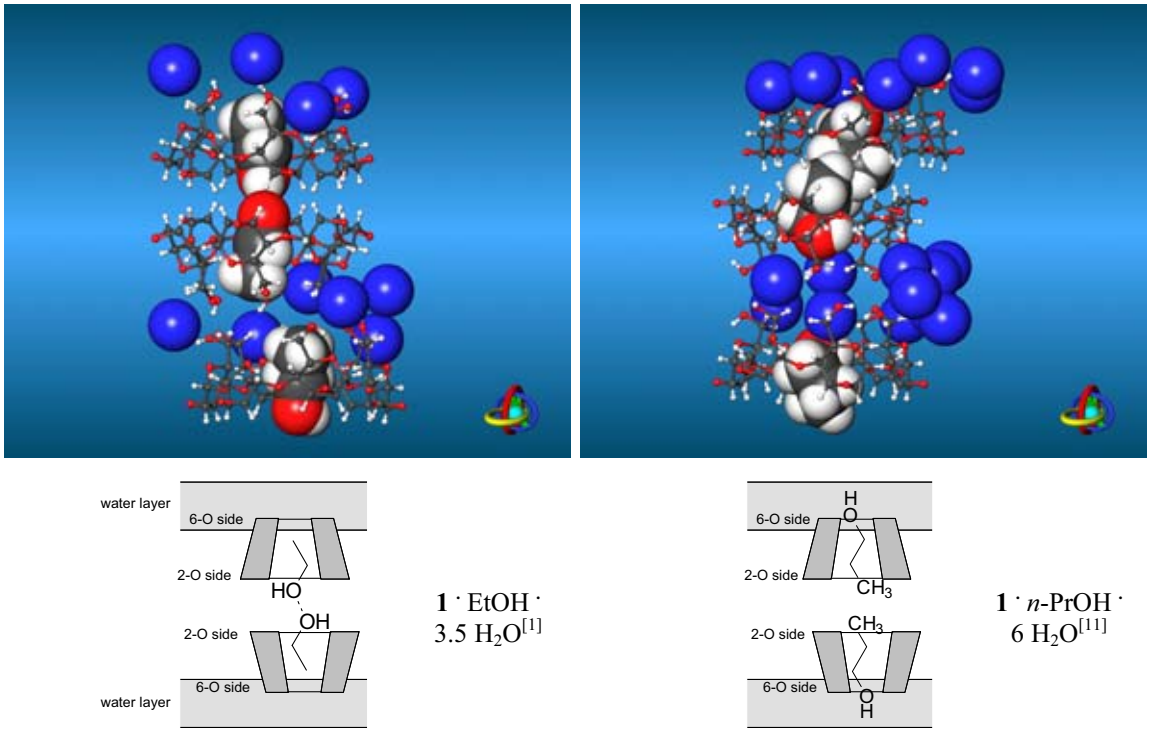


Figure 1. Segments of the crystal structures of the per-2,3-anhydro-α-cyclomannin (**1**) ethanol[10] (left) and 1-propanol[11] inclusion complex (right). Both isomorphic structures feature stacks of head-to-head oriented hosts, separated through layers of water molecules (blue spheres). The two guest molecules entrapped in the cavity of a complex dimer are displayed as CPK-type models; the opposite mode of inclusion of ethanol and 1-propanol is indicated by the schematic plots.

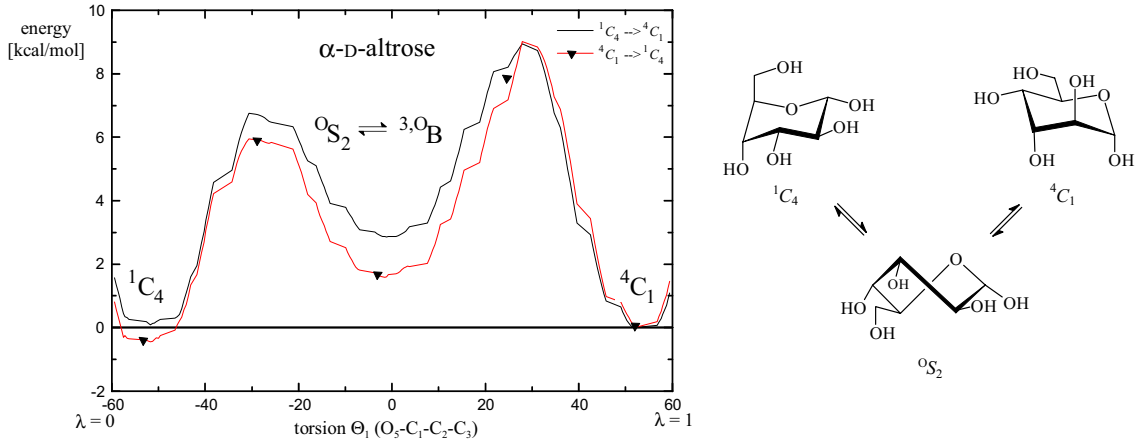


Figure 2. Calculated free energy profile (*"potential of mean force"*, CHARMM) of α-D-altrose in aqueous solution (explicit incorporation of solvent water molecules) as a function of the pyranose ring conformation; energies are given in kcal/mol. Conformations were driven along the reaction coordinate $\lambda = 0.0 \rightarrow 1.0$ through two constrained pyranose ring torsion angles Θ_1 (O_5-C_1-C_2-C_3) and Θ_4 (C_3-C_4-C_5-O_5); the hysteresis in the forward and backward direction of λ indicates the error in energy.

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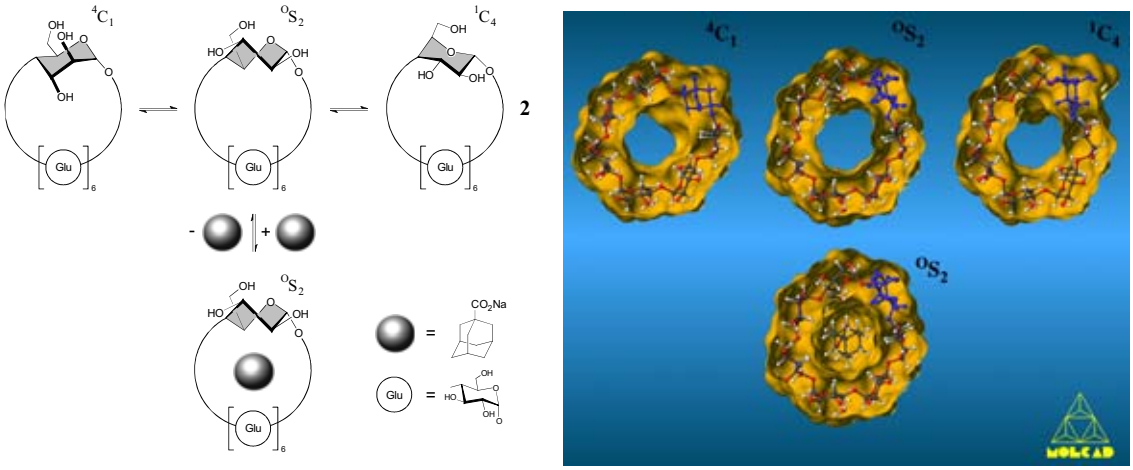


Figure 3. Left: Schematic representation of the "*induced-fit*" type formation of the inclusion complex between mono-*altro*-β-cyclodextrin (**2**) and adamantane-1-carboxylate. The altropyranoid unit is conformational flexible in the free host, although the $^{1}C_{4}$ form is slightly preferred over the $^{4}C_{1}$ and $^{O}S_{2}$ forms. This equilibrium is significantly shifted towards the $^{O}S_{2}$ form upon inclusion of the guest. *Right:* Molecular models of **2** (top row: free host) and its adamantane-1-carboxylate complex (bottom), with the corresponding molecular surfaces superimposed; the altrose units in the macrorings are colored blue, respectively. Of the $^{4}C_{1}$, $^{O}S_{2}$, and $^{1}C_{4}$ forms, only the $^{O}S_{2}$ geometry features an almost symmetrical round cavity which is able in include the ball-shaped adamantane guest without major steric hindrance.

2.2 Mono-altro-β-cyclodextrin (2)

More flexible than glucopyranose rings or the above 2,3-anhydro mannopyranose are altrose residues, which are synthetically accessible via diaxial-opening of the epoxide precursors. It is well established that the $^{4}C_{1}$ and $^{1}C_{4}$ α-D-altropyranose chair and anti-chair conformations are highly flexible.[12] Figure 2 gives the calculated free-energy profile for the $^{4}C_{1} \rightleftharpoons {}^{O}S_{2} / {}^{3,O}B \rightleftharpoons {}^{1}C_{4}$ pathway of α-D-altrose: both chair and anti-chair geometries are almost equal in energy, whilst the intermediate $^{O}S_{2} / {}^{3,O}B$ forms are slightly less stable.[13]

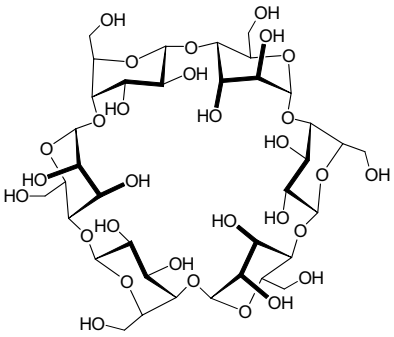
In the case of mono-*altro* β-CD (**2**), NMR titrations yielded all proton-proton coupling constants of the altropyranose rings in the free host, as well as in its adamantane 1-carboxylate inclusion complex.[14] Analysis of these values as a function of the altrose conformations displays a highly characteristic "*induced-fit*" type inclusion complex formation: the slightly preferred $^{1}C_{4}$ altrose ring geometry in free **2** is shifted towards a $^{O}S_{2}$ skew-boat form in the complex.[14] As indicated in Figure 3, only the intermediate skew-boat form features a round-shaped cavity, which is able to accommodate the ball-shaped guest molecule without steric hindrance.

2.3 α-Cycloaltrin (3)

In the solid-state, α-Cycloaltrin (α-CA, **3**)[5] surprisingly adopts a structure comprising an alternating sequence of $^{4}C_{1}$ and $^{1}C_{4}$ pyranoid chair conformations (Figure 4), leaving the molecule of disk-type shape with a central indentation only rather than a through-

going cavity.[5] At ambient temperatures, the ^{1}H (800 MHz) and ^{13}C (200 MHz) NMR spectra in D_2O show one set of signals for the time-averaged, C_6 symmetrical structure of **3** only, yet at 4 °C broadened ^{13}C signals C-4 and C-5 are indicative for dynamic conformational equilibria in α-CA in aqueous solution.[6,15]

^{1}H NMR (500 MHz) data in CD_3OD / D_2O (9 : 1) at -80 °C display a split set of signals, which is consistent with the solid-state structure of **3** as the major form prevailing also in solution.[16] Although standard molecular dynamics (MD) simulations of α-CA (**3**) in aqueous solution proved to be to slow to monitor conformational transitions in the altrose units of the macrocycle, we have used constrained MD techniques to simulate the dynamics of **3** in water.[6] From these calculations, it can be derived that any single conformational transition in the altrose residues induces subsequent conformational changes in neighboring units in the macroring. The geometry variations in the pyranose units induce adjacent residues to follow suit within the strait-jacket of the macrocycle, inducing a "*rolling-around*" of conformational transitions along the macrocycle.[6]



α-cycloaltrin (**3**)

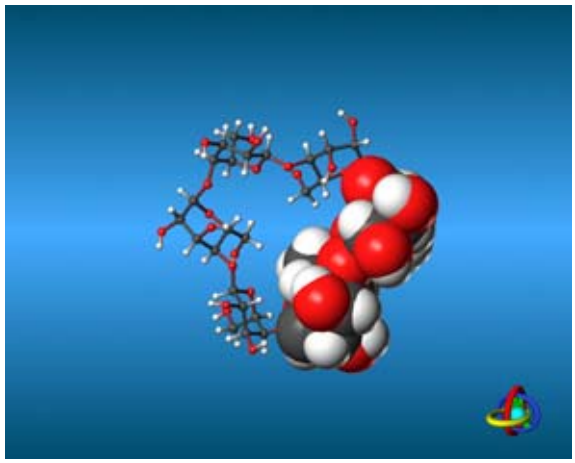


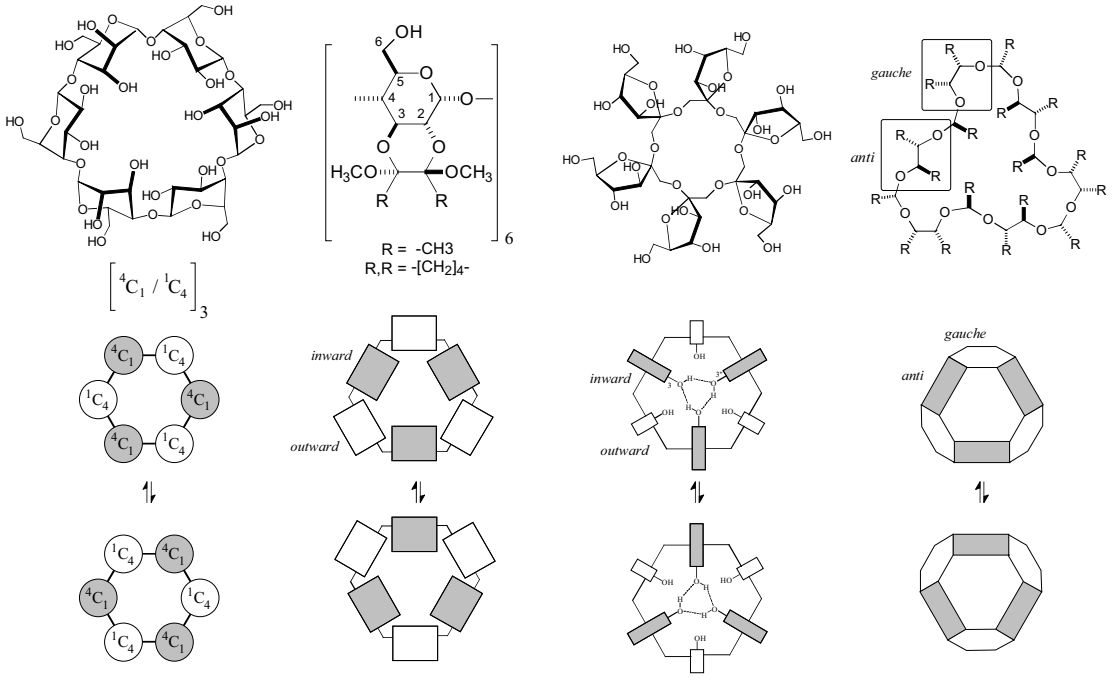
Figure 4. Molecular geometry of α-CA (**3**) in the solid-state:[5] the altropyranose rings adopt $^{4}C_1$ and $^{1}C_4$ conformations in an alternating sequence, rendering the molecule with three-fold rotational symmetry (C_3). On the right, the asymmetric $^{4}C_1$ / $^{1}C_4$ disaccharide unit of **3** is rendered as a CPK-type model.

2.4 Local versus Global Pseudorotation in Cyclooligosaccharides

In solution, the alternating [$^{4}C_1$ / $^{1}C_4$]$_3$ structure of α-CA (**3**) with its symmetry reduced to C_3 represents only a limiting structure in a complex conformation equilibrium.[6] Thermal motions lead to an exchange between [$^{4}C_1$ / $^{1}C_4$]$_3$ and [$^{1}C_4$ / $^{4}C_1$]$_3$ forms in a "*jelly-fish*"-like fashion with an activation barrier of about 8.5 kcal/mol (Figure 5).[16] The transition between both forms cannot occur instantaneously, but must necessarily involve multiple intermediate altropyranose conformations such as $^{O}S_2$ forms, as well as different macrocyclic shapes, such as the *all*-$^{O}S_2$ form of **3**, conceivably. The over-all process is a stereoisomerization of α-CA (**3**) resulting in a structure that appears to have been produced by simple rotation of the entire initial molecule by 60° around its central axis. This mechanism of "*global pseudorotation*" of the entire macrocycle of α-CA is

inseparably correlated with local motions in the altrose residues and their chair / anti-chair transitions ("*local pseudorotation*"). In total, the symmetry of α-CA is lowered from C_6 to C_3, and only time-averaged data accounts for the ^{1}H and ^{13}C NMR spectra of **3** at room temperatures.

The concept of global pseudorotation is not only applicable to α-CA, but is also manifested in a number of structurally diverse flexible cyclooligosaccharides (cf. Figure 5). A force-field based molecular modeling study of the "*extended cavity*" α-CD derivatives of Wenz et al.[17] indicates that these compounds cannot adopt C_6 symmetrical structures due to steric hindrance between neighboring glucose units. Instead, the substituted glucopyranoses are alternatingly tilted "*inward*" and "*outward*" in relation to the central molecular axis (Figure 5), and any exchange must involve successive contra-rotatory movements of neighboring units in the over-all process of "*global pseudorotation*". Similar effects are observed for the corresponding β- and γ-CD derivatives, too.



Fujita, Nogami et al. — α-cycloaltrin

Wenz et al. — "*extended cavity*" cyclodextrins

Uchiyama et el. — α-cyclofructin

Nakagawa et al. — 30-C-12 crown acetal R = -CH_2OH, -CH_2OAc

Figure 5. Schematic representation of the "*global pseudorotation*" observed for various flexible cyclooligosaccharides: none of the compounds listed above adopts fully C_6 symmetrical structures, yet in all cases symmetry is lowered to C_3 by either alternating pyranose ring geometries, alternating "*inward*" and "*outward*" tilting of individual monosaccharide units, or alternating "*anti*" and "*gauche*" disposition of ring torsion angles. Although initiated through different "*local*" molecular motions, in any case above, structures of the $[AB]_3$-type undergo interconversion to $[BA]_3$- geometries through a process of "*global pseudorotation*".

The solid-state structure of α-cyclofructin[18] also displays C_3 symmetry, the β(1→2) *spiro*-type anellation of the fructofuranose residues to the 18-crown-6 backbone is characterized by an alternating "*inward / outward*" inclination of the furanose rings relative to the macrocycle. In each case the 3-OH groups of the three "*inward*" directed units form an homodromic cycle of hydrogen bonds in the center of the molecule (Figure 5). Indeed, a detailed molecular modeling study on cyclofructins composed of six to ten fructofuranose units displayed analogous conformational properties to be maintained throughout the entire series.[19]

The large-ring crown acetals[8] derived from the CDs via periodate oxidation, fit into the same scheme of "*global pseudorotational*" effects: conformational transitions involve interconversions of the alternatingly "*anti*" and "*gauche*" disposed *meso*-butanetetrol units in the macroring.[8]

3. CONCLUSION

Introducing flexibility into macrocyclic compounds seems to simultaneously lower the symmetry of preferred low-energy conformations in the solid-state as well as in solution. For the four compounds listed in Figure 5, symmetry is invariably reduced from C_6 to C_3 through alternating local geometry parameters such as pyranose ring conformations, tilting of monosaccharide residues, and ring torsion angles. The mechanism of "*global pseudorotation*" accounts for the dynamic conformational exchange phenomena observed for these compounds, and their time-averaged symmetrical structures in solution. Presently we are looking forward to study the dynamics of these exchange processes in greater detail.

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