Synthesis, Structure, and Conformational Features of α-Cycloaltrin: A Cyclooligosaccharide with Alternating \(^4C_1/1C_4\) Pyranoid Chairs**

Yasuyoshi Nogami, Kyoko Nasu, Toshitaka Koga, Kazuko Ohta, Kahee Fujita,* Stefan Immel, Hans J. Lindner, Guido E. Schmitt, and Frieder W. Lichtenthaler*

The wealth of knowledge that has accumulated on the starch-derived cyclodextrins and their unique ability to form inclusion complexes\(^{[1]}\) is contrasted by a peculiar paucity of data on cyclooligosaccharides composed of sugars other than glucose.\(^{[2]}\) Except for certain cyclofructans, obtainable by bacterial action on the polysaccharide inulin,\(^{[3]}\) all of the non-glucose cyclooligosaccharides presently known have been acquired synthetically and require laborious multistep procedures to assemble the linear oligosaccharide from its monosaccharide units in a form suitable for cycloglycosylation. In this way, \(\alpha(1 \rightarrow 4)\)-linked cyclooligosaccharides composed of D-mannose (\(\alpha-, \beta-, \gamma\)-cyclomannin), of L-rhamnose (\(\alpha\)-cyclorhamnin), and of alternating D-mannose/L-rhamnose units\(^{[4]}\) have been prepared, yet in such minute amounts as to preclude investigations into their inclusion complex behavior. Molecular modeling studies on \(\alpha\)-cyclomannin\(^{[1]}\) and its 6-deoxy \(\beta\)-analogue \(\alpha\)-cyclorhamnin\(^{[5]}\) showed that their axially disposed 2-OH points away from the cavity; thus they fairly closely resemble \(\alpha\)-cyclodextrin in backbone structure, cavity dimensions, and lipophilicity patterns. The same, in fact, is to be expected for the cyclohexasaccharide with alternating D-mannose and L-rhamnose units. For a cyclogalactin composed of six \(\beta(1 \rightarrow 4)\)-linked galactopyranose residues, molecular modeling revealed a \(\alpha\)-CD-like geometry, yet a distinctly different lipophilicity distribution such that hydrophobic surface regions at the primary hydroxyl face are substantially enlarged.\(^{[6]}\)

More profound changes in shape, cavity dimensions, and guest binding properties are to be anticipated for cyclooligosaccharides with axially disposed 3-OH groups in the pyranoid rings—\(\alpha\)-cycloalillin for example—as these would be directed towards the interior of the cavity, resulting in considerable steric congestion, which is likely to be released by deformation of the \(4C_1\) chairs. Topologically even more interesting appears to be \(\alpha\)-cycloaltrin, as the \(4C_1\) and \(1C_4\) conformations of \(\alpha\)-altropyranoid chains are very similar in stability\(^{[7]}\) and, hence, in a macrocyclic array several conformations could be formed, such as the all-\(\alpha\)-\(2C_1\) (1a) or all-\(\beta\)-\(4C_4\) forms (1b), or even more likely in solution, an equilibrium between the two, that passes through the skew \(S_5\) geometries (1c) of the pyranoid rings (Scheme 1).

In context with our studies on non-glucose cyclooligosaccharides,\(^{[2]}\) we report on a straightforward synthesis of \(\alpha\)-cycloaltrin

\[\text{α-cycloaltrin} \xrightarrow{\text{90% } \text{BuMeSiCl}} \text{α-cycloaltrin 1} \quad \text{H}_2\text{O \ reflux} \]

\[\text{1) NaH/DMF} \quad \text{2) } \text{C}_6\text{H}_5\text{SO}_3\text{Cl} \quad 64\% \]

Scheme 2. Synthesis of 1 from \(\alpha\)-cycloaltrin.
4 (92%), which simply by refluxing in water was converted into 1 and isolated by reversed-phase chromatography (68%). The overall yield for the four-step sequence is a satisfactory 36%, but is lower than the conversion of β-cyclodextrin into its all-altro analogue (52%\cite{10}), obviously reflecting the lesser steric strain, and hence cleaner reactions, in the cycloheptamer.

Cycloaltrin 1 crystallized with 21 water molecules and is thus embedded in a water matrix in the solid state. Its X-ray structural analysis\cite{12} not only gave evidence of the water molecules built into the crystal lattice (Figure 1), but revealed the unique conformational features of the altropyranoid rings: neither the all\(^{4}C_{1}\) form 1a nor the all\(^{1}C_{4}\) form 1b is adopted, nor one of the various nonchair conformations conceivable (for instance, 1c); instead, the altrose units display alternate \(^{4}C_{1}\) and \(^{1}C_{4}\) altropyranoid chair conformations (Figure 1, top), entailing the macrocycle to be made up of three banana-shaped disaccharide portions. The molecules are disk-shaped, devoid of a cavity, and stacked in transposed layers (Figure 1, bottom), the space in between being occupied by water molecules.

The closeness of the chair conformations to the ideal is remarkable: nearly perfect geometry in the \(^{4}C_{1}\)-portions with \(\phi_{4}\) and \(\psi_{4}\) in a fairly antiparallel disposition (167.5°) and with the six pyranoid ring torsion angles in the 52–58° range. The \(^{4}C_{1}\) chairs, by contrast, are less ideal, as the \(\phi_{4}\) and \(\psi_{4}\) torsion angle (–45.7°) reveals some flattening at C-2 and C-3, whilst \(\phi_{1}\), \(\phi_{2}\), and \(\phi_{3}\) are still in a fairly antiparallel disposition (C-1–C-2–C-3 166.2°, C-2–C-3–C-4 166.5°). Another salient feature of the structure is the different orientations of the 6-OH groups relative to the pyranoid rings: \text{gauche–trans} disposition (\(\phi = 55.7°\)) in the three \(^{1}C_{4}\) forms in which the CH\(_{2}\)OH groups are directed towards the outside of the macrocycle versus a \text{gauche–gauche} arrangement (\(\phi = -66.8°\)) in the three \(^{4}C_{1}\) forms in which their equatorially disposed CH\(_{2}\)OH groups point towards the center of the macrocycle, thereby closing it (Figure 2). Accordingly, the disk-shaped molecule has a shallow indentation on one side, and a pronounced hole-like depression on the other. Provided that this disk-shaped, solid-state structure of 1, already embedded in a water matrix, is retained in aqueous solution, not only separate sets of NMR signals should be observed for the \(^{4}C_{1}\) and the \(^{1}C_{4}\) portions, but also distinctly different coupling patterns for the respective pyranoid ring protons as revealed by the calculated J values (Table 1).

The high resolution \(^{1}H\) and \(^{13}C\) NMR spectra of 1 in D\(_{2}\)O\cite{14} however, unambiguously provide only one set of signals for both the altropyranoid hydrogen atoms and the carbon atoms, and the \(^{1}H\) coupling constants are an average of those calculated for the \(^{4}C_{1}\) and \(^{1}C_{4}\) conformations (Table 1); moreover, the observed J-values correlate surprisingly well with those calculated for the all-skiw (twist-boat) \(^{3}S_{2}\) geometry of 1c, which, in
Table 1. Dihedral angles as well as the $^1$H--$^1$H coupling constants measured in D$_2$O (800 MHz[14], 30°C) and those calculated for the altropyranoid ring in $^1\text{C}_1$, $^1\text{C}_4$, and all-$^9\text{S}_2$ (skew) forms of 1.

<table>
<thead>
<tr>
<th>Dihedral angle[a]</th>
<th>$^1\text{C}_1$[a]</th>
<th>$^1\text{C}_4$[a]</th>
<th>$^9\text{S}_2$[b]</th>
<th>found</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1-C1-C2-H3</td>
<td>-69.4</td>
<td>-178.0</td>
<td>138.3</td>
<td></td>
</tr>
<tr>
<td>H2-C2-C3-H3</td>
<td>70.4</td>
<td>-176.0</td>
<td>176.2</td>
<td></td>
</tr>
<tr>
<td>H3-C3-C4-H4</td>
<td>-61.5</td>
<td>51.8</td>
<td>44.7</td>
<td></td>
</tr>
<tr>
<td>H4-C4-C5-H5</td>
<td>-71.3</td>
<td>179.8</td>
<td>-141.9</td>
<td></td>
</tr>
</tbody>
</table>

Coupling constant[Hz][c]

| J(1,2)            |  2.2             |   8.0           |   4.0           |  4.73 |
| J(2,3)            |  2.7             |  10.2           |   2.4           |  5.32 |
| J(3,4)            |  3.4             |   2.4           |   4.5           |  3.71 |
| J(4,5)            |  9.7             |   1.4           |   6.4           |  5.32 |

[a] Angles from the solid-state structure of 1. [b] Data calculated for the global energy minimum (all-skew form) from HTA simulations. [c] Calculation based on the Karplus-type dependence of H-C-C-H torsion angles on coupling constants, including the electronegativity effect of the substitution pattern by use of the generalized Haasnoot equation [15].

fact, emerges from extensive HTA calculations[163] as the global energy minimum structure. Favored over the $^1\text{C}_1$/ $^1\text{C}_4$ solid-state geometry by as much as 36 kJ mol$^{-1}$—a major portion of this energy gain undoubtedly stems from hydrogen bonding between the 2-OH of one altrose moiety to the 0-3 of the next—this all-skew form features a cavity that pierces the disk (Figure 3) and a pyranose tilt inverse to that of the cycloextrinsics.

Whether, however, the all-skew form 1c is adopted in aqueous solution—in HTA simulations molecules are in vacuum rather than surrounded by a solvation shell—remains open. If prevalent in aqueous solution, its cavity is conceivably filled with water. Thus not only the six primary, but also the 12 secondary hydroxyl groups are likely to satisfy their hydrogen bonding requirements towards the solvent rather than intramolecularly. This results in a tightly associated first water shell around 1, which will have to follow any geometry changes within the macrocycle. This hydration sphere could readily be character-

or flip over of the pyranoid chairs or skew forms to alternate topologies takes place within a 600 ps time frame; that is, profound conformational changes like the flipping from $^4\text{C}_1$ to $^1\text{C}_4$ within the macrocycle are comparatively slow, and require the 10$^6$ times longer, millisecond time frame of NMR spectroscopy to become observable.

The temperature-dependent $^1$H and $^{13}$C NMR studies proved to be more meaningful in determining the nature of the conformational changes occurring in aqueous solutions of 1,[14] the coupling constant $J_{2,3}$ of 8.2 Hz at 30°C in D$_2$O decreases to 7.6 and 7.1 Hz at 20 and 4°C, respectively, thereby narrowing the well-separated signal for 3-H; more profound effects are observed for the C-4 and C-5 signals, which, like all other carbon atoms, give rise to sharp singlets at 30°C but show substantial broadening at 4°C, which indicates the onset of “freezing out” certain conformations the $^1\text{C}_1$-$^1\text{C}_4$ equilibrium. Consequently, in water, $\alpha$-cycloaltrin does not adopt a fixed geometry, such as the all-$^9\text{S}_2$-form; rather, the d-altropyranoid rings, tied up in a macrocyclic “straitjacket”, adopt a variety of conformations within the $^4\text{C}_1$-$^9\text{S}_2$-$^1\text{C}_4$ pseudorotational “turntable” (Scheme 3), and this necessarily in a coordinated way: flexure of one altropyranoid chair into the intermediate skew $^9\text{S}_2$-form via half-chair transition states forces the two adjoining altrose chairs to follow suit, thereby eliciting a consecutive “rolling around” in the probably elliptically distorted macrocycle. NMR data provide an averaged picture thereof and give evidence through the comparatively large $J_{2,3}$ and, particularly, $J_{3,4}$ couplings that the position of the equilibrium in water at 30°C lies pronouncedly on the $^1\text{C}_4$-$^9\text{S}_2$ side.

**Experimental Section**

3: To a solution of NaN$_3$ (0.40 g, 10.8 mmol) in anhydrous DMF (60 mL) was added 2 (1.0 g, 0.6 mmol) [9], and the mixture was kept under N$_2$ at 60°C for 2 h. After cooling, benzene sulfonyl chloride (568 µL, 4.32 mmol) in anhydrous DMF (10 mL) was injected followed by stirring at room temperature for 30 min. Filtration and flash chromatography on a silica gel column (4 x 15 cm) with benzene/THF (4/1, 250 mL) afforded 600 mg (64%) of 3, m.p. 203°C (decomp.); $[\alpha]_D^20 = +70.1$ (c = 0.36 in THF). $^1$H NMR (500 MHz, CDCl$_3$, relevant data): $\delta = 3.11$ (d, 1 H, 2-H), 3.32 (d, 1 H, 3-H), 3.56 and 4.24 (two d, 1 H, 6-H$_2$), 3.64 (d, 1 H, 4-H), 3.93
Pyridine): 6

4: A 1m solution of Bu4NF in THF (4.6 mL) was added to a solution of silylepoxide 3 (1.0 g 0.65 mmol) in an anhydrous THF (50 mL) under N2, and the mixture was stirred at 40°C for 4 h. Concentration in vacuo, addition of methanol (10 mL), and stirring at 40°C for 4 h yielded 4. 105.53 (C-1), 71.98 (C-6), 63.05 (C-6), 79.65 (C-4), 105.53 (C-1). FAB-MS: m/z 365 [M+].

5: A solution of epoxide 4 (1.0 g 1.14 mmol) in distilled water (250 mL) was heated at reflux for 5 days. Concentration of the mixture in vacuo and chromatography on a reversed-phase column (Merck Lobar, size C) with water yielded 1 (765 mg 68%); m.p. 215°C (decomp.). δ: 4.01 (s, 1 H, 1-H), 4.30 (m, 2 H, 2-H, 6-H), 4.47 (d, 1 H, 4-H), 5.57 (s, 1 H, 1-H), 7.12 (d, 1 H, 2-H) ppm. 1H NMR (300 MHz) ppm.

6: The (800 MHz) and 13C (200 MHz) NMR spectra were recorded at the "Large Scale Facility for Biomolecular NMR" in Frankfurt. We are grateful to Prof. Dr. G. Moeckel, Dr. H. Schwalke, Institut für Organische Chemie, Universität Frankfurt am Main, for support.

Keywords: z-cycloaldrin · cyclodextrins · macrocycles · molecular modeling

References:


