β(1→3)- and β(1→6)-linked Cyclogalactofuranosides: Conformations and Molecular Shapes

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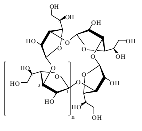
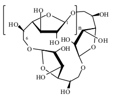
Introduction

In analogy to cyclodextrins[1], cyclomannins[2], and cycloaltrins[3], the generic name cyclogalactin was proposed for cyclooligosaccharides composed of galactose units[2]. Altough the former are all made up of α(1→4)-linkages, pyranoid (1→4)-galactose units in such a cyclic arrangement require β-type intersaccharidic bonds, and it was noted in an earlier molecular modeling study on *cyclo*[D-Galp β(1→4)]$_6$ (i.e. α-cyclogalactin) that these compounds may be considered as "*inverso*"-cyclodextrins with a unique distribution of hydrophobic surface areas on the outside, and distinctly hydrophilic central cavities[2]. Although the synthesis of pyranoid cyclogalactins has not been accomplished yet, a number of their furanoid analogs have been prepared by cycloglycosylation of tritylated 1,2-*O*-(1-cyano)ethylidene-derivates of D-galactofuranose[4], i.e. cyclogalactooligosaccharides with β(1→3)- (e.g. **1** and **2**), β(1→5)-, and β(1→6)-linked galactofuranose units (e.g. **3** and **4**).

Due to the rather modest yields in these preparations, the capabilities of these compounds to form inclusion complexes were not investigated. Therefore, the potential properties of these compounds to function as hosts, and their relationship to the cyclofructins[5] equally composed of furanoid building blocks, induced us to perform a molecular modeling study on the β(1→3)- and β(1→6)-linked forms.



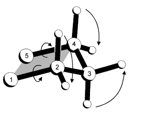
cyclo[D-Gal*f* β(1→3)]$_4$ **1**
cyclo[D-Gal*f* β(1→3)]$_5$ **2**



cyclo[D-Gal*f* β(1→6)]$_3$ **3**
cyclo[D-Gal*f* β(1→6)]$_4$ **4**

Methods

All calculations were carried out using the PIMM91 force-field[6] program with external conformational search algorithms[7]. A pre-optimized galactofuranose unit was assembled to various symmetrical and asymmetrical starting structures of the cyclogalactofuranosides **1** - **4**, which were subjected to conformational analysis using "*Monte-Carlo*" and "*random-walk*" techniques[8]. An adapted corner-flapping procedure[9] was used to effectively vary the ring geometries of the furanose units as well as of the macrocyclic backbone without breaking bonds in the different rings.



Analysis of β-D-Galactofuranose Conformations

The conformational properties of the galactofuranose units are characterized by opposite tendencies of the anomeric substituent and the C5-C6-side-chain to adopt pseudo-axial and pseudo-equatorial arrangements, respectively. The adiabatic (PIMM91) energy potential surface of β-D-galactofuranose reveals a single, broad energy-minimum in the $^4T_3 \leftrightarrows {}^4E \leftrightarrows {}^4T_O \leftrightarrows E_O$ region for the furanose rings. Although the closely related $^1T_O \leftrightarrows {}^1E$ conformations seem to be preferred in the few solid-state structures of galactofuranose derivatives reported in the CCDF data file[10], an analysis of ^{1}H NMR $^3J_{H\text{-}H}$ coupling constants of various galactofuranosides[11] reveals preferred solution geometries in the $^4E \leftrightarrows {}^4T_O \leftrightarrows E_O \leftrightarrows {}^1T_O$ range. In general, conformations along these overlapping regions (i.e. the western part of the pseudorotational itinerary within 10 kJ/mol above the global energyminimum) characterize β-D-galactofuranosides, and for the cyclogalactins ^{1}E (**1** and **2**) and $^4T_3$ (**3** and **4**) geometries are realized in the energy-minimum structures[12].

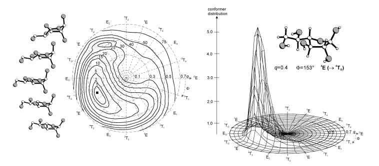


Figure 1. Adiabatic energy map of β-D-galactofuranose as function of the Cremer-Pople-parameters[13] *q* and ϕ (PIMM91 force field[6], energy levels are indicated in kJ/mol). The filled square marks the position of the energy-minimum, which correlates with the structure shown on the right. The 3-D contour plot displays the Boltzmann-distribution of conformers calculated from the energy map for *T* = 300 K.

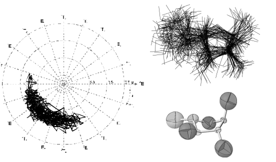
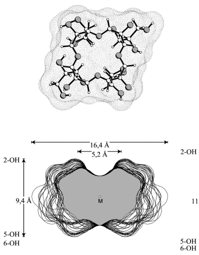


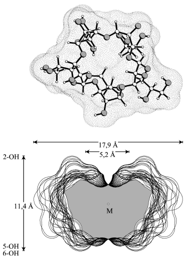
Figure 2. On the left, the molecular conformations of β-D-galactofuranose obtained from a 100 ps *in vacuo*-MD-simulation are projected onto the polar-coordinate-type grid of the *q* and ϕ Cremer-Pople parameters. Superimposition of 50 galactofuranose snapshot geometries taken from the trajectory (upper right), as well as the MD-derived anisotropic probability ellipsoids (lower right, hydrogen atoms and the C-6-substituent are omitted for clarity) display the flexibility of the furanose rings.

Molecular Geometries of the Cyclogalactofuranosides

β(1→3)-Cyclogalactofuranosides



cyclo[D-Gal*f* β(1→3)]$_4$ **1**



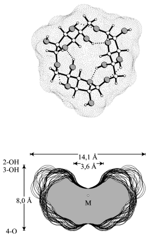
cyclo[D-Gal*f* β(1→3)]$_5$ **2**

In contrast to the almost perfectly round-shaped, symmetrical pyranoid cyclogalactins[2], the high flexibility of the furanoid rings within **1** - **4**, and the β(1→6)-linkage in **3** and **4** with four torsion angles involved, leads to structures of lower symmetry to be favored with increasing ring size of the macrocycles. On the left and right, the energy-minimum geometries of **1** - **4** are displayed together with their solvent-accessible surfaces in dotted form. The small ring homologs **1** and **3** retain symmetry as much as possible (C_4 and C_3, resp.), but **2** and **4** prefer C_1 (asymmetric) and C_2-type structures.

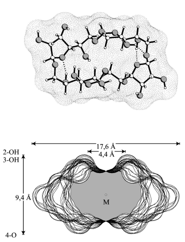
In the case of **3**, and to a lesser extent in **4**, the conformational symmetry is only retained through favorable intramolecular hydrogen bonding interactions of the 3-OH ··· O-6 and 5-OH ··· O-4'-type. In aqueous solution these effects are expected to become less important, hence, conformational equilibria are likely to be shifted towards more asymmetric forms.

The molecular contact surfaces computed for **1** - **4** as well as the corresponding surface cross-section cuts display the effective steric extensions of these macrocycles, and provide evidence for their disk-type shapes. All compounds feature side-on indentations only, and lack central cavities to form inclusion complexes.

β(1→6)-Cyclogalactofuranosides



cyclo[D-Gal*f* β(1→6)]$_3$ **3**



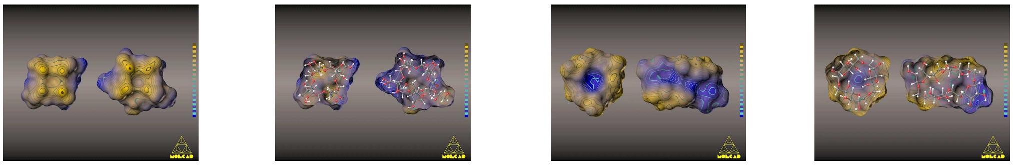
cyclo[D-Gal*f* β(1→6)]$_4$ **4**

Molecular Lipophilicity Patterns

Beside the steric demands of **1** - **4**, their hydrophobic characteristics are of major interest to evaluate their properties. In the pictures below the corresponding molecular lipophilicity patterns (MLPs) were computed and mapped in color-coded form onto the contact surfaces. Most remarkably, these graphics reveal a fundamental difference of the distribution of hydrophilic and hydrophobic surface areas for both classes of the β(1→3)- and β(1→6)-linked cyclogalactins. In the case of **1** and **2** the surface is significantly indented in the center, although both structures lack "through-going" central cavities.

Due to their association with the O1-C2(H)-C3(H) fragments of the galactofuranose moieties, these surface dents are remarkably hydrophobic, whereas O4 and the side chain 5-OH and 6-OH groups render the opposite molecular sides much more hydrophilic. Most notably, the outer rim of the disk-shaped molecules carrying the 2-OH hydroxyls is predominantly hydrophilic.

A different situation prevails for the β(1→6)-cyclogalactins **3** and **4**: the type of intersaccharidic linkages, their increased flexibility, and the altered orientation of the furanoid rings in relation to the macrocycle cause an inverse alignment of hydrophilic and hydrophobic surface regions. The 5-OH groups pointing towards the central surface dents provide a hydrophilic environment that is augmented by the 3-OH groups, whereas on the back the close alignment of the O-4 ring atoms contributes to slightly less hydrophilic regions. The most hydrophobic surface areas on **3** and **4** are situated on the outer edge of the macrocycles, and are made up by the C1(H), C3(H), and C5(H)-C6(H2) fragments.



cyclo[D-Gal*f* β(1→3)]$_4$ **1** *cyclo*[D-Gal*f* β(1→3)]$_5$ **2** *cyclo*[D-Gal*f* β(1→3)]$_4$ **1** *cyclo*[D-Gal*f* β(1→3)]$_5$ **2** *cyclo*[D-Gal*f* β(1→6)]$_3$ **3** *cyclo*[D-Gal*f* β(1→6)]$_4$ **4** *cyclo*[D-Gal*f* β(1→6)]$_3$ **3** *cyclo*[D-Gal*f* β(1→6)]$_4$ **4**

Figure 3. MOLCAD-program[14-16] generated molecular lipophilicity patterns (MLPs) projected onto the contact surfaces of the β(1→3)- (**1**, **2**) and β(1→6)-cyclogalactofuranosides (**3**, **4**). The color-code was adapted to the range of relative hydrophobicity calculated for each molecule, ranging from dark blue for the most hydrophilic areas to full yellow corresponding to the most hydrophobic surface regions. The orientation of all models is such that the O-2/O-3 atoms face the viewer, whereas the O-4 atoms are directed to the back; the halfopened models on the right visualize the molecular orientation as well as the surface properties of the back.

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