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MOLECULAR GEOMETRIES OF FURANOID b(1®3)- AND b(1®6)-LINKED CYCLOGALACTINS[1]

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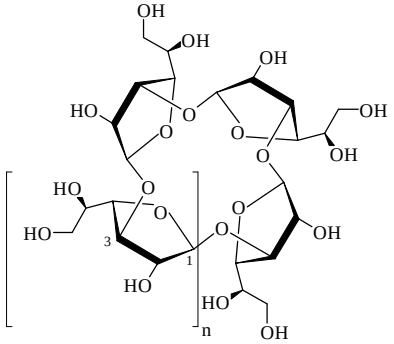
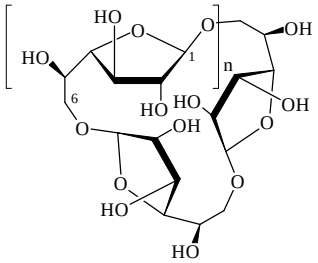
Abstract. The conformational properties of small cyclogalactins composed of β(1→3)- and β(1→6)-linked galactofuranose units, i.e *cyclo*[D-Gal*f* β(1→3)]$_n$, n = 4, 5 (**1** and **2**), and *cyclo*[D-Gal*f* β(1→6)]$_n$, n = 3, 4 (**3** and **4**), were investigated by means of adapted Monte-Carlo simulations. The flexibility of the macrocyclic backbone favors bend and asymmetrical conformations over round geometries. Visualization of the molecular surfaces of the global energy-minimum structures reveal the disk-type shapes of **1** - **4** without central cavities, but featuring distinct indentations close to the 2/3-O-groups, respectively. Molecular lipophilicity patterns prove these surface dents to be hydrophobic for **1** and **2**, whereas **3** and **4** display an inverse situation with a hydrophobic outer core structure.

1. Introduction

In analogy to cyclodextrins[2], cyclomannins[3], and cycloaltrins[4], the generic name *cyclogalactin* was proposed for cyclooligosaccharides composed of galactose units[3]. Although 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-Gal*p* β(1→4)]$_6$ (i.e. α-cyclogalactin), that these compounds may be considered as "*inverso*"-cyclodextrins due to distinctly hydrophobic surface areas on the outside and hydrophilic central cavities[3]. Although the synthesis of pyranoid cyclogalactins has not been accomplished yet, cycloglycosylation of tritylated 1,2-*O*-(1-cyano)ethylidene-derivates of D-galactofuranose led to a number of their furanoid analogs[5], 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**).



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**

Due to the rather modest yields in their preparation, the capabilities of these compounds to form inclusion complexes could not be investigated. Their potential properties to function as hosts and their relationship to the cyclofructins which are equally composed of furanoid building blocks[6], induced us to perform a molecular modeling study on the β(1→3)- and β(1→6)-linked forms, whereby – due to the expected high conformational flexibility – we restricted our analysis to the tetra- and pentamer of *cyclo*[D-Gal*f* β(1→3)]$_n$ (**1** and **2**), as well as to the trimer (**3**) and tetramer (**4**) of the β(1→6)-type cyclooligosaccharides.

2. Methods

All calculations were carried out using the PIMM91 force-field[7] program with external conformational search algorithms[8]. 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[9]. An adapted corner-flapping procedure[10] 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. Proper sampling of the conformational space was ensured by converging minimum energy structures and molecular parameters[11]. For the global energy-minimum structures the molecular contact surfaces[12], cross-section cuts[8], and lipophilicity patterns (MLPs) were computed; color-coded representations were generated using the MOLCAD[13-15] program.

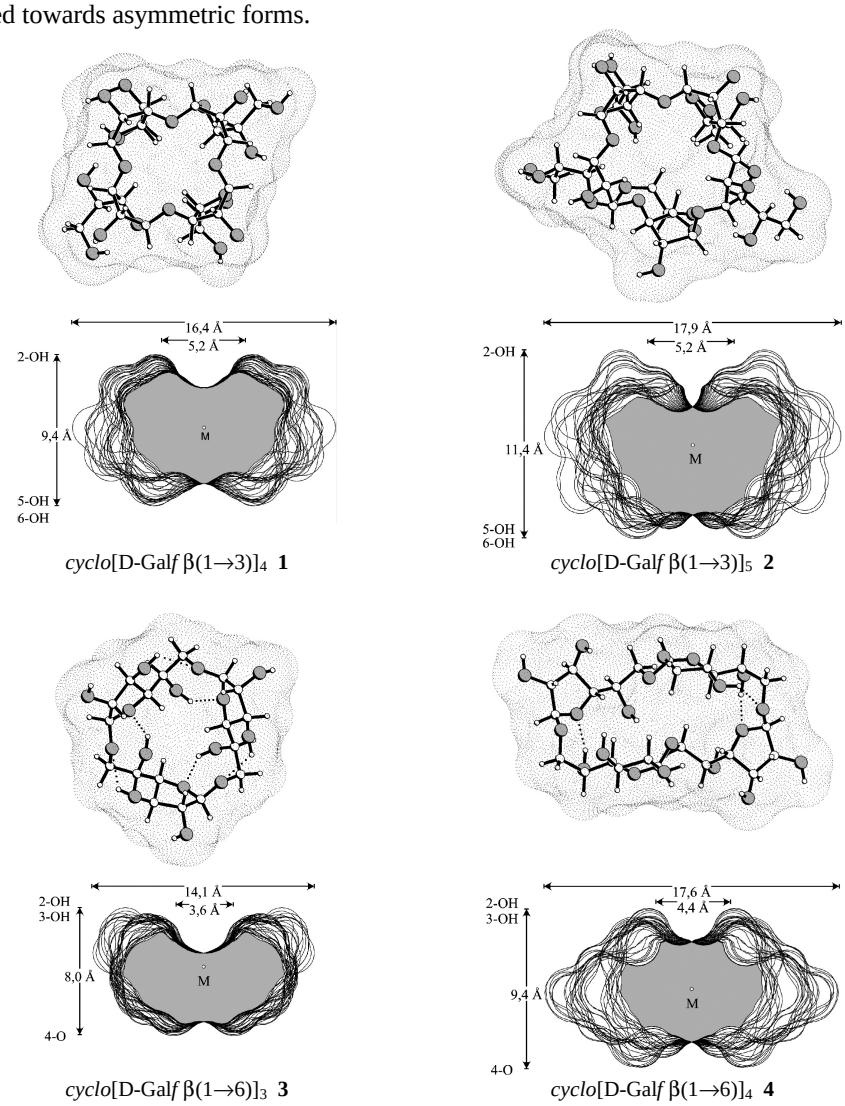
3. Results and Discussion

*Molecular Geometries of **1 - 4**.* — 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 $^4T_3 \rightleftharpoons {}^4E \rightleftharpoons {}^4T_O \rightleftharpoons E_O$ region for the furanose rings. Although the closely related $^1T_O \rightleftharpoons {}^1E$ conformations seem to be preferred in the few solid-state structures of β-galactofuranose derivatives reported in the CCDF data file[16], an analysis of ^{1}H NMR $^3J_{H\text{-}H}$ coupling constants of various galactofuranosides[17] reveals preferred solution geometries in the $^4E \rightleftharpoons {}^4T_O \rightleftharpoons E_O \rightleftharpoons {}^1T_O$ range. In general, conformations along these overlapping regions (i.e. the western part of the pseudorotational itinerary within 10 kJ/mol above the global energy-minimum) 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[11].

In contrast to the almost perfectly round-shaped, symmetrical cyclogalactins composed of β(1→4)-linked galactopyranoses[3], the high flexibility of the furanoid rings in **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. The energy-minimum geometries of **1 - 4** displayed in Fig. 1[11] show that 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, conceivable conformational equilibria are likely to be shifted towards asymmetric 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**

Figure 1. Global energy-minimum structures of the cyclogalactofuranosides **1** - **4** including their dotted contact surfaces; intramolecular hydrogen bonding interactions are shown by bold dots. All structures are displayed perpendicular to the macrocycles with the O-2 / O-3 sides facing the viewer. In addition, surface cross-section plots perpendicular to the mean macro-ring planes are shown, with approximate molecular dimensions in Å.

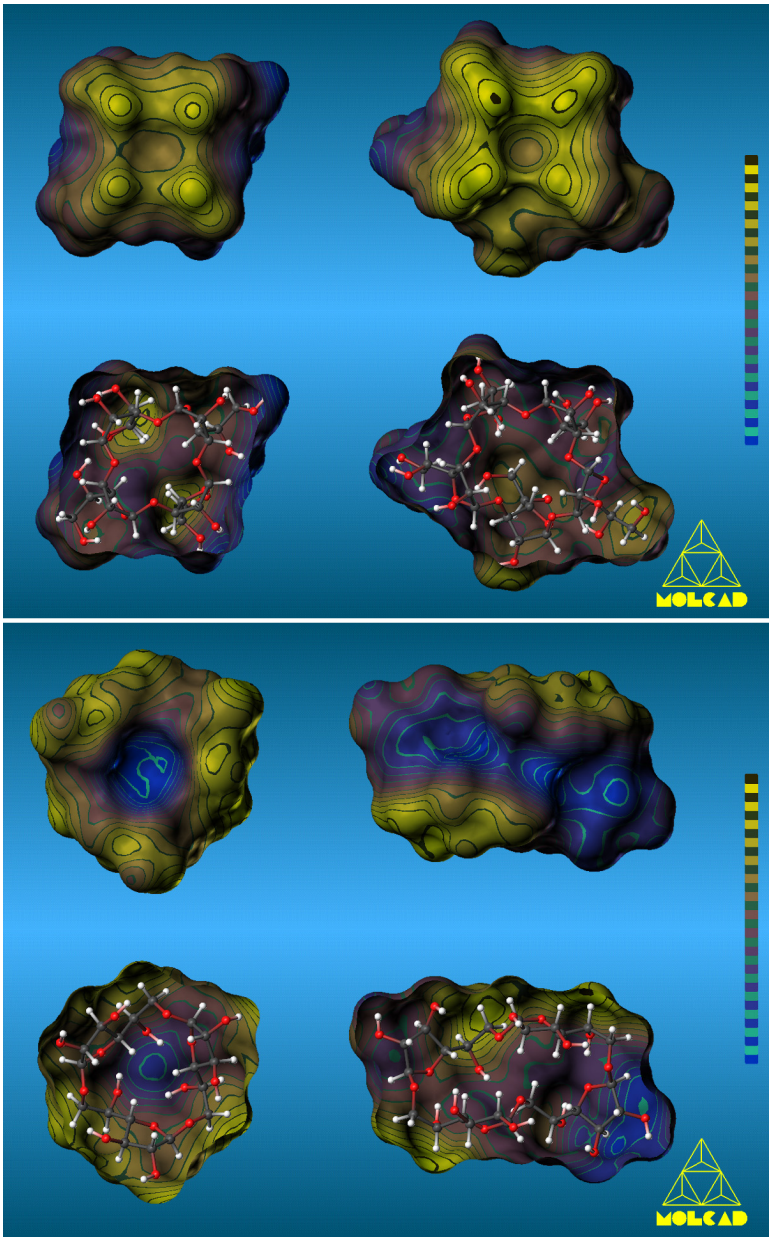


Figure 2. MOLCAD program generated molecular lipophilicity patterns (MLPs) projected onto the contact surfaces of the β(1→3)- (top: **1** and **2**) and β(1→6)-linked cyclogalactofuranosides (bottom: **3** and **4**). The color-code was adapted to the range of relative hydrophobicity calculated for each 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 half-opened models on the bottom each visualize the molecular orientation as well as the surface properties of the back.

The molecular contact surfaces computed for **1 - 4** (cf. Fig. 1) as well as the corresponding surface cross-section cuts provide evidence for the disk-type shapes of these macrocycles, with small puckering amplitudes of less than 0.5 Å along their backbones. The surface models not only display the effective steric extensions of these molecules and their lack of central cavities to form inclusion complexes, but also allow to map their lipophilicity patterns in color-coded form, as has already been proved useful in earlier studies to assess the properties of cyclodextrins[2] and related compounds[3].

Molecular Lipophilicity Patterns (MLPs). — Beside the steric demands of **1 - 4**, their hydrophobic characteristics are of major interest to evaluate their properties. In Fig. 2, the corresponding MLPs were computed and mapped in color-coded form onto the contact surfaces of Fig. 1. 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** (Fig. 2, top), the surface is significantly indented in the center without elaborating "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 O-4 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** (Fig. 2, bottom): the type of intersaccharidic linkage, 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 of **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(H_2) fragments.

In summation, this molecular modeling study of the furanoid cyclogalactins **1 - 4** provides reliable insights into their molecular architecture such, that they not only lack round-shaped geometries, but also central cavities with which to form inclusion complexes similar to those formed by cyclodextrins[18]. In contrast to the pyranoid cyclogalactohexaoside (α-cyclogalactin)[3], the intersaccharidic connectivity of **1 - 4**, the arrangement of their sugar units on the ring, as well as their molecular lipophilicity patterns may at most allow the formation of loose sandwich-type adducts.

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