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Conformations of methyl 2,5-di-*O*-acetyl-β-D-glucofuranosidurono-6,3-lactone and 1,2,5-tri-*O*-acetyl-β-D-glucofuranurono-6,3-lactone in the crystal structure and in solution

Beata Liberek,[a,*] Dorota Tuwalska,[a] Iwona do Santos-Zounon,[a] Antoni Konitz,[a,b] Artur Sikorski[a] and Zygfryd Smiatacz[a]

[a]*Faculty of Chemistry, University of Gdańsk, Sobieskiego 18, PL-80-952 Gdańsk, Poland*
[b]*Department of Inorganic Chemistry, Gdańsk University of Technology, Narutowicza 11/12, PL-80-952 Gdańsk, Poland*

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Abstract—The single-crystal X-ray diffraction and high-resolution ^{1}H and ^{13}C NMR spectral data for methyl 2,5-di-*O*-acetyl-β-D-glucofuranosidurono-6,3-lactone and 1,2,5-tri-*O*-acetyl-β-D-glucofuranurono-6,3-lactone are reported. The lactones were synthesized as byproducts of reactions carried out to obtain methyl 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronate. The conformations of these lactones in the crystal structure and in solution are discussed. A $^{1}T_{2}$-like conformation was found to be the preferred form for these lactones in both the crystal lattice and in solution.

Keywords: β-D-Glucofuranurono-6,3-lactone; X-ray diffraction; Single-crystal; Coupling constant; Torsion angle; $^{1}T_{2}$ Conformation; Anomeric effect

1. Introduction

Despite their ubiquity in biological structures, furanosides have received much less attention than pyranosides with regards to conformational analysis. This is because different conformations of five-membered rings have quite similar energies,[1] whereas six-membered rings are normally present in a single, low-energy chair conformation. Therefore, conformations of pyranosides in solution are easily identified, for example, by NMR techniques, which is not the case with furanosides.

Furanose rings exist as mixtures of ideal envelope (*E*) conformations with four atoms in a plane or twist (*T*) forms with three atoms in a plane (Fig. 1). Since such a description may be inadequate for intermediate conformations, a particular furanose ring conformer is usually described by two parameters: the amplitude of pseudorotation τ_{m},[2,3] defined as an upper limit for the endocyclic torsion angle (maximum torsion angle θ_{m}[4]) and the pseudorotational phase angle (*P*).[2–4] The pseudorotation phase angle *P* is calculated from the endocyclic torsion angles, θ_0, θ_1, θ_2, θ_3, and θ_4, according to Eq. 1:[4]

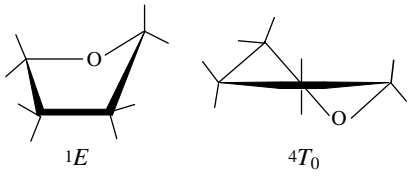

Figure 1. Examples of furanose ring conformations: *left*, envelope; *right*, twist.

$$\tan P = [(\theta_4 + \theta_1) - (\theta_3 + \theta_0)]/[2\theta_2(\sin 36^\circ + \sin 72^\circ)] \quad (1)$$

The phase angle *P* is defined to be 0° when θ_2 is maximally positive, which corresponds to the $^{3}T_{2}$ conformation and returns to the same point at $P = 360^\circ$ (Fig. 2).

* Corresponding author. Tel.: +48 58 3450344; fax: +48 58 3410357; e-mail: beatal@chem.univ.gda.pl

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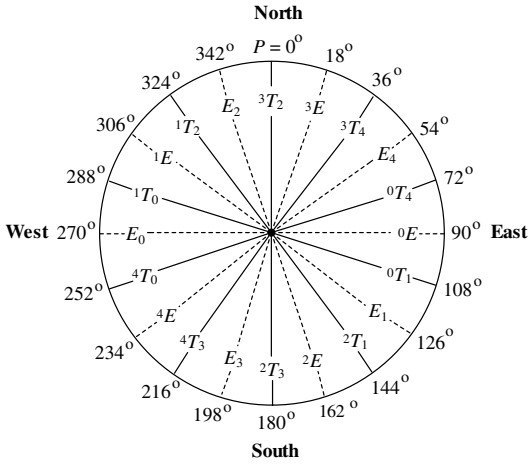

Figure 2. Pseudorotational itinerary for a D-aldofuranose ring.

The five torsion angles are related from the phase angle P by Eq. 2:[4]

$$\theta_j = \theta_m \cos(P + j\delta) \quad (2)$$

where $j = 0$, 1, 2, 3, or 4, $\delta = 720°/5 = 144°$ and θ_m is the maximum torsion angle[4] (the amplitude of pseudorotation τ_m[2,3]), derived by setting $j = 0$, Eq. 3:[4]

$$\theta_m = \theta_0 / \cos P \quad (3)$$

Two opposite conformers of the furanose ring, in which the signs of all torsion angles are reversed (e.g., $^3T_2$ and $^2T_3$ forms), exist in equilibrium in solution. One of these opposite forms is present in the northern hemisphere of the pseudorotational wheel, the other in the southern hemisphere. Interconversion between such conformers occurs via the eastern or western pathway of the pseudorotation itinerary, which depends on the identity and orientation of the substituents on the ring.[2]

Conformational analysis of a furanose ring based on NMR studies is complicated because two furanose conformers are equilibrating rapidly on the NMR scale, and averaging of coupling constants occurs. Thus, using ^{1}H–^{1}H NMR coupling constants, we can usually predict the region of the pseudorotational itinerary in which the favored conformers will be found. For example, the coupling constants of the β-D-galactofuranose derivatives described in the literature, like the majority of their furanoid solution geometries, fall within the $^4E \leftrightharpoons {}^4T_0 \leftrightharpoons E_0 \leftrightharpoons {}^1T_0$ range, that is, in the western part of the pseudorotational itinerary.[5] $^3J_{H,H}$ data, though not indicating any particular conformation, can be successfully used for making conformational comparisons between different furanosides,[6] since they provide information about the axial or equatorial preferences of substituents, for example, an aglycone. Computational investigations of furanoid ring conformations often confirm NMR-derived data, but they also suggest, which region of the pseudorotational itinerary is the most favored one.[5] Combining NMR studies with theoretical calculations seems to be an accurate methodology for determining the preferred conformers of the furanose ring.[2,7] A least-squares minimization program, PSEUROT 6.2,[8] with the use of intracyclic ring $^3J_{H,H}$ data, calculates the N/S ratio and provides P values from which the ring forms can be determined.[2]

Important findings concerning the anomeric effect in a series of *N*-, *C*-, *S*-, and *O*-'furanosides' were obtained when a tetrahydrofuran ring was conformationally restricted by a rigid norbornane skeleton attached at carbons C-3 and C-4.[9] The norbornane skeleton maintains the 'furanoside' ring carbons in one plane, allowing only the ring oxygen to move above or below the plane. Such norbornyl 'furanosides' can exist in two conformations only—^0E and E_0—and the anomeric effect is a major factor influencing the $^0E \leftrightharpoons E_0$ conformational equilibrium.

Investigation of furanosides and their derivatives by X-ray crystallography is a precise way of determining their structures and conformations. However, in the case of the furanoid ring, this analysis is restricted to the crystal structure. Since the energies of furanose ring conformations are similar, the conformation of a furanoside enclosed in a crystal lattice may differ significantly from that adopted in solution.

Methyl 2,5-di-*O*-acetyl-β-D-glucofuranosidurono-6,3-lactone (**1**) and 1,2,5-tri-*O*-acetyl-β-D-glucofuranurono-6,3-lactone (**2**) were obtained as byproducts of two independent procedures, which were examined in order to obtain methyl 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronate, the versatile intermediate in the synthesis of glucopyranuronates modified at the anomeric carbon. We found the conformational studies of these lactones interesting. The present paper reports on their 3D molecular structures as determined by X-ray crystallography, and compares their conformations in the crystal with those in solution as revealed by high-resolution NMR spectroscopy.

2. Results and discussion

The first procedure that we examined to obtain methyl 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronate involved the acid-catalyzed esterification of glucuronic acid with methanol,[10] followed by acetylation of the hydroxyl groups. This yielded five products, among them being methyl 2,5-di-*O*-acetyl-β-D-glucofuranosidurono-6,3-lactone (**1**) (Scheme 1). But since this procedure was not very effective, we tested another one using D-glucurono-6,3-lactone as the starting compound. This was transesterified with methanol in the presence of basic catalysts to produce a mixture of methyl D-glucopyranuronates,[11] which when acetylated, yielded good quantities of methyl 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronates