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The conformation of tetrafluorinated methyl galactoside anomers: crystallographic and NMR studies

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ABSTRACT

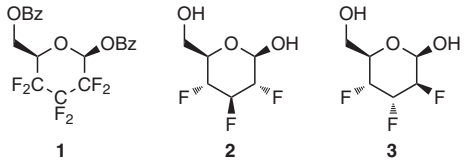
The first single-crystal X-ray diffraction study of tetrafluorinated monosaccharide derivatives is presented. Both α- and β-methyl 2,3-dideoxy-2,2,3,3-tetrafluoro-D-galactopyranoside anomers adopt the $^4C_1$ conformation. The values for the C1–O1 and C1–O5 bond lengths and the O5–C1–O1–CH_3 dihedral angles are in line with what can be expected from the anomeric and *exo*-anomeric effects. The chair conformations are slightly distorted, presumably due to repulsion between 1,3-diaxial C–O and C–F bonds. The asymmetric unit of both compounds contains up to three independent molecules, which differ in the conformation of the hydroxymethyl group (including in one case a 'forbidden' *gg* rotamer). The molecular packing of the β-anomer shows a clear segregation between fluorinated and hydrophilic domains, while for the α-anomer the regions of fluorine segregation are broken by interleafing of OMe groups. There is one close OH···F contact, which is likely to arise from the crystal packing. NMR studies show that the two anomers also adopt a $^4C_1$ conformation in solution (D_2O, $CDCl_3$).

1. Introduction

The selective substitution of hydroxyl groups by fluorine atoms to obtain deoxofluorosugars is a common modification in carbohydrate chemistry.[1] The systematic replacement of hydroxyl groups across a sugar ring has been employed to probe the importance of these hydroxyl groups in protein–carbohydrate interactions.[2] The incorporation of fluorine has an impact on many physical and chemical properties.[3] For example, the strong electron withdrawing effect of fluorine changes the hydrogen bond donating/accepting capacities of adjacent alcohol groups, especially upon replacing a CHOH by a CF_2 group. The same effect is responsible for a change in anomeric reactivity, which can be dramatic when C2 is difluorinated, and results in a deceleration of both S_N1 and S_N2 type reactions. This effect has been exploited for the study of glycosyl transfer enzymes,[4] and for the synthesis of hydrolysis-resistant antigens.[5]

Polyfluorinated carbohydrates[6] have become a topic of interest in relation to the 'polar hydrophobicity' effect proposed by DiMagno,[6a,b] in which a hydrophobic domain is created by replacement of ring CHOH groups by CF_2 groups (as in **1**, Fig. 1). However, the polar C–F bond is still expected to engage in stabilizing electrostatic interactions with 'fluorophilic' protein residues, examples of which have been described by Diederich[7] and further illustrated by Vincent on a (mono)fluoro sugar derivative.[8] Our group has been involved in developing synthetic methodology towards tetrafluorinated sugars for subsequent use as carbohydrate mimetics and probes to explore the polar hydrophobicity effect.[6c–e]

The shape of carbohydrates is of great importance for their biological activity.[9] The conformation of the carbohydrate ligand recognized by the protein is likely to be one of the most common conformations present in solution,[10] although binding of high-energy conformers does occur.[11] Hence, it is of interest to investigate the shape of modified carbohydrates. There are few crystal structures of heavily fluorinated carbohydrates available. The 2,3,4-trideoxy-2,2,3,3,4,4-hexafluoropyranoside derivative **1** (Fig. 1), synthesized by DiMagno,[6a] as well as of 2,3,4-trideoxy-2,3,4-trifluoro-D-glucose **2** and –altrose **3**, both synthesized by O'Hagan,[6f] show that these polyfluorinated sugars exist in the $^4C_1$ conformation. Withers has shown that the vicinal difluorinated 2-fluoro-2-deoxy-β-D-mannopyranosyl fluoride also adopts the $^4C_1$ conformation both in the solid and in solution phase.[12]



1 2 3

Figure 1. Heavily fluorinated carbohydrates.

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In this contribution, we report and discuss the first crystal structures of tetrafluorinated carbohydrates, the two anomers of methyl-2,3-dideoxy-2,2,3,3-tetrafluoro-D-galactoside (**4** and **5**, Fig. 2). While crystallization of the parent unprotected sugar has so far proven to be elusive, methylation of the anomeric hydroxyl group has allowed us to obtain both anomers in crystalline form, enabling a side-by-side analysis of bond lengths and angles. To the best of our knowledge, such a structural comparison has not yet been reported for fluorosugar anomers. In addition, NMR studies are presented, both in $CDCl_3$ and in D_2O as solvent.

2. Results and discussion

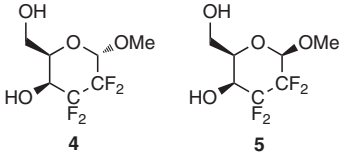
2.1. Synthesis

The synthesis of both methyl 2,3-dideoxy-2,2,3,3-tetrafluoro-D-galactopyranoside anomers is shown in Scheme 1. The 4,6-di-*O*-benzyl ethers **6** and **7** were prepared as reported via anomeric alkylation of the corresponding pyranose.[6d] The anomers **6** and **7** could be separated by preparative HPLC, and were each subjected to hydrogenolysis with Pearlman's catalyst. Removal of the catalyst by filtration was followed by crystallization in Et_2O.

2.2. Crystallographic data for 4 and 5

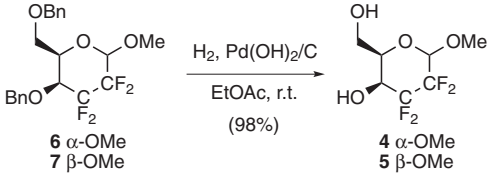
The crystallographic data and structural refinement details for the crystal structures are given in Table 1. Compound **4** crystallized as monoclinic, with space group $P2_1$, whereas **5** crystallized as tetragonal, with space group $P4_32_12$. No disorder was observed, but interestingly, the asymmetric unit for **4** contained three crystallographically independent molecules, each being a different C5–C6 rotamer including the 'forbidden'[13] *gg* rotamer. The asymmetric unit for **5** contained only two different C5–C6 rotamers; in this case the *gg* rotamer was not present. The corresponding *ORTEP* diagrams and the atom labeling for the different conformers of **4** and **5** are shown in Figures 3 and 4. All structures are present in the $^4C_1$ chair conformation. The significant bond distances, bond angles and torsion angles are listed in Tables 2–4, together with relevant data from the crystal structure of the corresponding nonfluorinated methyl α- and β-galactopyranoside **8** and **9** (each of which crystallized as the *gt* rotamer).[14]

The C–C bond lengths within the pyranose rings are between 1.515 and 1.534 Å (both **4**, **5**, all rotamers; Table 2, entries 1–4), which is very similar to that seen for the nonfluorinated analogues **8** and **9** (1.523–1.530 Å).



4 **5**

Figure 2. Structure of α- and β-methyl 2,3-dideoxy-2,2,3,3-tetrafluoro-D-galactopyranoside.



6 α-OMe
7 β-OMe

4 α-OMe
5 β-OMe

Scheme 1. Synthesis of the tetrafluorinated methyl galactoside anomers.

Table 1
Structural data of the tetrafluorinated galactose derivatives

Compound reference	**4**	**5**
Chemical formula	$C_7H_{10}F_4O_4$	$C_7H_{10}F_4O_4$
Formula mass	234.15	234.15
Crystal system	Monoclinic	Tetragonal
Space group	$P2_1$	$P4_32_12$
No. of formula units per unit cell, Z	6 (Z' = 3)	16 (Z' = 2)
a (Å)	12.2256(5)	8.8756(6)
b (Å)	8.2904(2)	8.8756(6)
c (Å)	13.8049(5)	46.642(5)
β (°)	96.087(1)	
Unit cell volume (Å^3)	1391.31(8)	3674.3(5)
Density (g/cm^3)	1.677	1.693
Crystal size (mm)	0.4 × 0.1 × 0.04	0.4 × 0.3 × 0.02
Absorption coefficient, μ (mm^{-1})	0.182	0.184
T_{min}, T_{max}	0.9306, 0.9927	0.9300, 0.9963
No. of reflections measured	19,386	19,634
No. of unique reflections	3399	2295
No. of independent reflections, R_{int}	0.0607	0.0899
θ min, max (°)	2.97, 27.48	3.17, 26.37
h min, max	−15, 15	−10, 10
k min, max	−10, 10	−6, 11
l min, max	−17, 17	−58, 28
Final R_1 values ($I > 2\sigma(I)$)	0.0383	0.0518
Final wR_2 values ($I > 2\sigma(I)$)	0.0885	0.1164
Final R_1 values (all data)	0.0548	0.1013
Final wR_2 values (all data)	0.0979	0.1343
Goodness of fit on F^2	1.019	1.046
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e A^{-3})	0.234, −0.256	0.255, −0.282

The C1–O5 and C1–O1 bond lengths (L2, L3, entries 7 and 8) show the expected trends due to the anomeric effect.[13,15,16] For the α-anomer, the exocyclic C1–O1 distance (entry 8) is somewhat shorter compared to that for the endocyclic C1–O5 bond (entry 7), with both values close to the corresponding bond lengths of the nonfluorinated methyl α-galactoside **8**. Curiously, the C1–O1 bond length of the *gg* rotamer is significantly shorter. For the β-anomer **5**, the exocyclic C1–O1 distance (entry 8) is considerably shorter compared to that for the endocyclic C1–O5 bond (entry 7) due to the *exo*-anomeric effect. While the shortening of the endocyclic C1–O5 bond is again very similar to that of the nonfluorinated counterpart (**9**), the exocyclic C1–O1 bond distance of **5** is significantly more reduced compared to **9**. The L2,L3 bond shortening leads to a lengthening of the L1,L4 bonds (entries 6 and 9), with a notable extra increase of the O1–C7 bonds compared to the nonfluorinated methyl galactosides.

DiMagno has suggested that a CF_2 group is a good isostere for CHOH, with a similar size but different angular orientation.[6b] From the crystal data, it can be seen that the equatorial C–F bonds are shorter than the corresponding C–O bonds of **8** and **9** (entries 10 and 11), and that the axial C–F bonds in **4**, **5** are significantly longer than the corresponding C–H bonds in **8**, **9** (entries 12 and 13). There is no obvious trend in bond length difference between axial and equatorial C–F bonds. Despite the variation in bond length, for a given C–F bond, between the different rotamers of **4** or **5**, the average bond length of the axial and equatorial C–F bonds of all structures is actually very similar (about 1.359 Å), and is shorter than the C–F bond length of monofluorinated sugars (e.g., 1.402 Å in 4-deoxy-4-fluoro-β-D-glucopyranose).[17]

The ring C–CF_2–C bond angles (Table 3, entries 1 and 2) are consistently larger compared to the equivalent C1–C2–C3 and C2–C3–C4 bond angles of **8** and **9**. This presumably follows from the known change in geometry/hybridization at carbon when difluorinated, which results in a C–CF_2–C bond angle widening (e.g., 116.8° for 2,2-difluoropropane).[3] This is accompanied by a slightly smaller F–C–F angle for **4** and **5** (entries 10 and 15) compared to the H–C–O angle in **8** and **9**.

Regarding the angles A1–A3 involving the anomeric substituent (entries 5, 7 and 9), only minimal differences from the nonfluori-