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Note

X-ray diffraction and high-resolution NMR spectroscopy of methyl 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enopyranuronate

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Abstract—Single-crystal X-ray diffraction and high-resolution ^{1}H and ^{13}C NMR spectral data for methyl 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enopyranuronate are reported. The $^{5}H_4$ conformation was found to be the preferred form for this glycal, both in the crystal lattice and in solution. The factors determining the $^{4}H_5 \rightleftarrows {}^{5}H_4$ conformational equilibrium for acetylated glycals are discussed.

Keywords: Methyl 3,4-di-*O*-acetyl-D-glucuronal; X-ray diffraction; Single crystal; Torsion angle; $^{5}H_4$ Conformation

1,5-Anhydro-2-deoxy-1-enitols—trivial name glycals—are monosaccharides with a double bond between carbon atoms C-1 and C-2 of the pyranose ring. Since the double bond in glycals is adjacent to an anomeric carbon atom, these sugars are very useful as glycosylating agents.[1–5]

Conformational studies of the pyranose ring are important and have been meticulously investigated: detailed knowledge of the conformations of sugars is essential for understanding their physical, chemical, and biological properties.[6,7] The conformations of glycals undoubtedly play a significant role in the stereochemistry of the reactions in which they participate.[8–10]

This paper reports on single-crystal X-ray diffraction and high-resolution NMR spectral data for methyl 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enopyranuronate (**4**), a versatile intermediate in the synthesis of glucopyranuronates modified at the anomeric carbon,[11–13] and discusses the conformation of the glucuronic acid methyl ester glycal **4** in the crystal lattice and in solution.

Methyl 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enopyranuronate (**4**)—commercial name methyl 3,4-di-*O*-acetyl-D-glucuronal—was synthesized from D-glucurono-6,3-lactone (**1**) according to a well-known procedure (Scheme 1).[11] This involves the base-catalyzed transesterification of **1**, followed by acetylation; then, the reaction of **2** with hydrobromic acid in acetic acid, followed by the reduction of α-bromide **3** with zinc dust in aq acetic acid.

In the crystal, **4** adopts the $^{5}H_4$ half-chair conformation (Fig. 1) with ring-puckering parameters[14,15] $Q = 0.447(4)$ Å, $\Theta = 127.4(5)°$ and $\Phi = 90.9(6)°$. The $^{5}H_4$ form of **4** is illustrated by the torsion angles listed in Table 3. For example, the O-6–C-1–C-2–C-3 torsion angle 3.6° indicates an almost planar orientation of the respective atoms. Next, the O-11–C-4–C-5–C-15 torsion angle of 176.1° is in agreement with an antiperiplanar orientation of the 4-OAc and 5-COOMe groups, and the O-7–C-3–C-4–O-11 torsion angle −162.5° confirms the quasi-antiperiplanar orientation of the 3-OAc and 4-OAc groups. The C-1–C-2–C-3–C-4 (10.6°) and C-2–C-1–O-6–C-5 (13.6°) torsion angles show that the deflections of carbon atoms C-4 and C-5 from the double-bond plane are similar and rather small.

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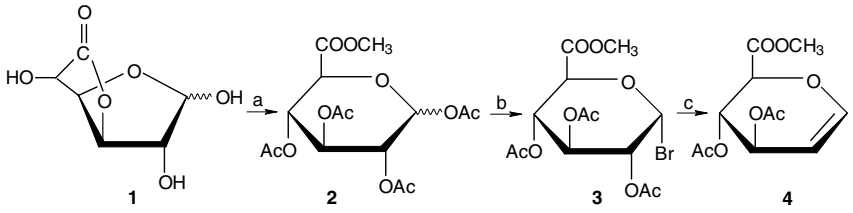

Scheme 1. Reagents: (a) (1) NaOH/CH_3OH; (2) Ac_2O/pyridine; (b) HBr/AcOH; (c) Zn/AcOH.

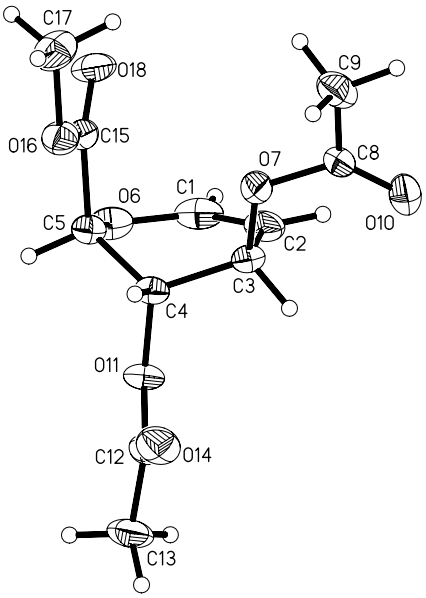

Figure 1. Structure of **4** showing 25% probability displacements for ellipsoids.

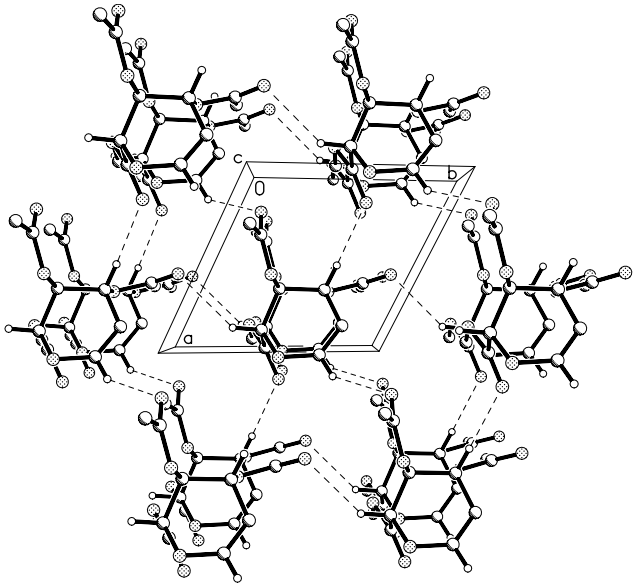

Figure 2. Molecular packing of **4** (view along *c*-axis). The hydrogen atoms not involved in C–H···O interactions have been omitted.

In solution, glycals exist in equilibrium between the $^4H_5$ and $^5H_4$ half-chair conformations (Fig. 3). The following factors influence the conformational equilibrium of peracetylated glycals. The first, known as the allylic effect, favors the quasi-axial orientation of the allylic acetoxy group at the C-3 carbon atom[8] and in this way stabilizes the $^5H_4$ form of glycals with the D-*arabino* (**4** and **5**) or D-*lyxo* (**6** and **7**) structures (Fig. 3). The second factor displays no preference for the quasi-axial orientation of the 3-OAc group when the group bound to the C-5 carbon atom is oriented axially owing to the unfavorable 1,3-diaxial interactions occurring between these two groups. In this way the second factor competes with the first one and destabilizes the $^5H_4$ form of glycals **4**–**7**. In our opinion, there is also a third factor affecting the conformational equilibrium of peracetylated glycals. This factor prefers the 4-OAc group to be oriented axially when the 3-OAc group is oriented quasi-equatorially. Two equatorially oriented groups

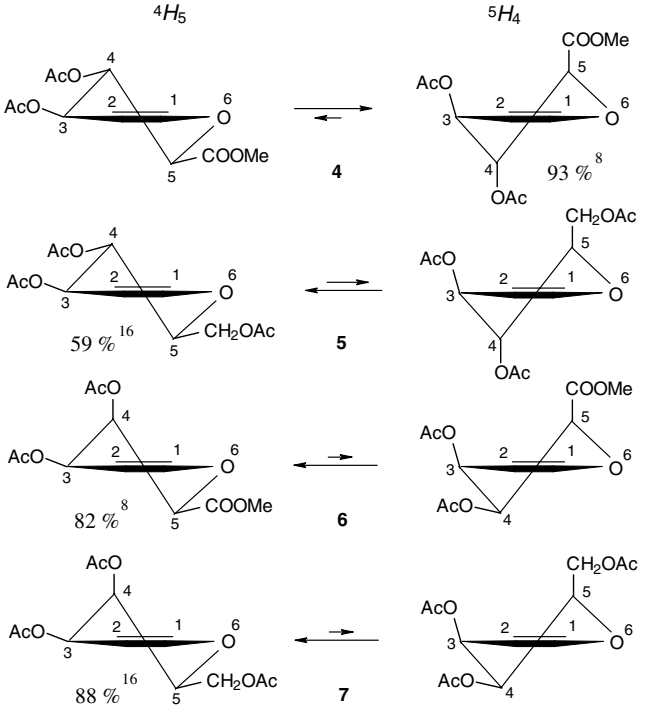

Figure 3. The $^4H_5 \rightleftarrows {}^5H_4$ conformational equilibrium for glycals **4**–**7** in solution.

(3-OAc and 4-OAc) adjacent to the double bond of glycals should destabilize such an almost coplanar structure. This factor has to be taken into account because it is the only one able to explain why tri-*O*-acetyl-D-galactal (**7**) is more stable than tri-*O*-acetyl-D-glucal (**5**) in the $^4H_5$ conformation in solution (molar fractions in the $^4H_5$ form: 88% and 59%, respectively).[16]

High-resolution NMR spectroscopy of **4** (^{1}H, ^{13}C, COSY, HSQC, HMBC), especially the most diagnostic $J_{3,4} = 1{,}95$ Hz and $J_{4,5} = 2{,}44$ Hz coupling constants, call for the equatorial (H-4 and H-5) or quasi-equatorial (H-3) orientation of the respective protons, which is evident for the $^5H_4$ conformation of **4** in chloroform solution, the same as **4** adopts in the crystal lattice. According to the Karplus curve,[17] measured $J_{3,4} = 1{,}95$ Hz and $J_{4,5} = 2{,}44$ Hz coupling constants are in good agreement with the gleaned from the crystallographic data H-3A–C-3–C-4–H-4A torsion angle 76.6° and H-4A–C-4–C-5–H-5A torsion angle −61.9° (Table 3). This additionally confirms the $^5H_4$ conformation of **4** in solution.

Chemical shifts and coupling constants of **4** recorded in chloroform are almost identical with the chemical shifts and coupling constants reported by Thiem and Ossowski, who stated that a 93% molar fraction of **4** adopts the $^5H_4$ conformation in acetone.[8] In order to examine the possible $^4H_5 \rightleftarrows {}^5H_4$ conformational equilibrium the additional ^{1}H NMR spectra of **4** at rt, −20, −50, and −80 °C in acetone were recorded. These spectra, irrespective of the temperature, are the same as spectrum of **4** recorded at rt in acetone by Thiem and Ossowski. In the light of these results, we state that the $^5H_4$ form of **4** is strongly dominant in chloroform and acetone solutions.

In contrast to **4**, structurally very similar compounds, such as 3,4,6-tri-*O*-acetyl-D-glucal (**5**) in both crystal lattice[18] and solution, and methyl 3,4-di-*O*-acetyl-D-galacturonal (**6**), prefer the $^4H_5$ conformation in solution (molar fractions in acetone: 59%[16] and 82%,[8] respectively). A comparison of the conformational preferences of **4**, **5**, and **6** allows us to draw a number of inferences. Firstly, since **4** mostly adopts the $^5H_4$ form whereas **5** prefers the $^4H_5$ form, the unfavorable 1,3-diaxial interactions between the 3-OAc and 5-COOMe groups (**4**) must be weaker than the analogous interactions between 3-OAc and 5-CH_2OAc groups (**5**). These unfavorable interactions in the $^5H_4$ form of **5** force the change of conformation, despite the unfavorable orientation of both 3-OAc and 4-OAc groups in the $^4H_5$ form. In other words, the equatorial orientation of the 5-CH_2OAc group is of greater importance for the stability of glycals than the equatorial orientation of the 5-COOMe group.

Secondly, even though **4** and **6** differ solely in their C-4 carbon atom configurations, they adopt different conformations ($^5H_4$ and $^4H_5$, respectively). This is due to the above-mentioned factor, which prefers the 4-OAc group to be oriented axially when the 3-OAc group is oriented quasi-equatorially, thereby displacing the conformational equilibrium state in the direction of the $^4H_5$ form of **6**.

1. Experimental

1.1. General methods

Melting point was uncorrected. Optical rotation was determined at room temperature with a Hilger–Watt polarimeter in 1-dm tube at the D line of sodium for solution in $CHCl_3$. The IR spectrum was recorded as Nujol mulls with a Bruker IFS 66 spectrophotometer. The NMR spectra were recorded at room temperature on a Unity Plus 500 MHz spectrometer. ^{1}H NMR spectra were measured at 500 MHz and ^{13}C spectra at 125 MHz in $CDCl_3$ or $(CD_3)_2CO$ solutions, using the standard pulse sequence and procedures.

1.2. Methyl 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enopyranuronate (4)

Compound **4** was synthesized according to literature data:[11] 82%, mp 84–87 °C, lit.[11] 88–91 °C; $[\alpha]_D^{20}$ −67 (*c* 1.0, $CHCl_3$), lit.[11] −61.3 (*c* 0.87, $CHCl_3$); R_f 0.54 (1:1 *n*-heptane–AcOEt); IR: *v* 1754 and 1731 (C=O), 1646 (C=C), 1218 (CO–O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (d, 1H, $J_{1,2}$ 5.86 Hz, H-1), 5.44 (ddd, 1H, $J_{4,5}$ 2.44 Hz, H-4), 5.04 (td, 1H, $J_{2,3}$ 5.37, $J_{2,4}$ 1.46 Hz, H-2), 5.01 (dt, 1H, $J_{3,4}$ 1.95, $J_{3,5}$ 1.46 Hz, H-3), 4.85 (dd, 1H, H-5), 3.82 (s, 3H, $COOCH_3$), 2.14, 2.01 (2s, 2 × 3H, 2 × OAc); ^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 6.73 (d, 1H, $J_{1,2}$ 6.35 Hz, H-1), 5.43 (td, 1H, $J_{4,5}$ 2.69 Hz, H-4), 4.99 (ddd, 1H, $J_{2,3}$ 5.13, $J_{2,4}$ 1.59 Hz, H-2), 4.95 (dd, 1H, H-5), 4.92 (dddd, 1H, $J_{3,4}$ 2.56, $J_{3,5}$ 1.46, $J_{3,1}$ 0.61 Hz, H-3), 3.80 (s, 3H, $COOCH_3$), 2.10, 1.98 (2s, 2 × 3H, 2 × OAc); ^{13}C NMR (500 MHz, $CDCl_3$): δ 169.73, 169.52 ($C{=}O_{Ac}$), 167.43 ($C{=}O_{ester}$), 146.60 (C-1), 97.47 (C-2), 72.55 (C-5), 67.63 (C-4), 62.83 (C-3), 52.57 (C-6), 21.11, 21.05 (CH_{3Ac}); MALDI-TOFMS: *m*/*z* 281.2 $[M+Na]^+$, 297.2 $[M+K]^+$; Anal. Calcd for $C_{11}H_{14}O_7$: C, 51.17; H, 5.46. Found: C, 51.08; H, 5.48.

1.3. X-ray crystallographic data

Diffraction data were collected at room temperature (298 K) on a KUMA KM-4 four circle diffractometer[19] with Mo Kα radiation ($\lambda = 0.71073$ Å) using the $2\Theta/\omega$ scan mode. Phase angles were initially determined with the SHELXS program.[20] All H atoms were placed geometrically and refined using a riding model with C–H = 0.93–0.98 Å, and $U_{iso}(H) = 1.2U_{eq}(C)$ (C–H = 0.96 Å and $U_{iso}(H) = 1.5U_{eq}(C)$ for the methyl H

Table 1. Crystal data and structure refinement for **4**

Empirical formula	$C_{11}H_{14}O_7$
Formula weight	258.22
Temperature (K)	295(2)
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	
a (Å)	7.195(1)
b (Å)	7.418(1)
c (Å)	7.491(1)
α (°)	106.25(3)
β (°)	113.73(3)
γ (°)	106.07(3)
V (Å^3)	315.0(2)
Z	1
D_{calcd} (Mg m^{-3})	1.361
Absorption coefficient (mm^{-1})	0.115
$F(000)$	136
Crystal size (mm)	$0.4 \times 0.3 \times 0.2$
Θ Range for data collection (°)	3.19–25.24
Limiting indices	$-8 \leqslant h \leqslant 8$, $-8 \leqslant k \leqslant 8$, $-8 \leqslant l \leqslant 5$
Reflections collected/unique	1926/1136 [$R_{int} = 0.0508$]
Completeness $2\Theta = 50.24°$ (%)	97.5
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1111/3/167
Goodness-of-fit on F^2	1.033
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0354$ $wR_2 = 0.0876$
R indices (all data)	$R_1 = 0.0452$ $wR_2 = 0.0936$
Absolute structure parameter	0(1)
Extinction coefficient	0.18(3)
Largest difference in peak and hole (e Å^{-3})	0.153 and −0.160

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) for **4**

Atom	x	y	z	U_{eq}
C-1	10,183(6)	7300(6)	9706(5)	68(1)
C-2	8573(7)	7693(5)	8525(6)	68(1)
C-3	6562(5)	6059(5)	6389(5)	51(1)
C-4	6483(4)	3919(4)	6062(4)	44(1)
C-5	8828(5)	4040(4)	6914(4)	48(1)
O-6	10,317(4)	5467(4)	9140(3)	62(1)
O-7	6655(3)	6292(3)	4547(3)	55(1)
C-8	6160(5)	7778(5)	4072(6)	59(1)
C-9	6314(7)	7815(6)	2170(6)	72(1)
O-10	5661(7)	8888(5)	5073(6)	97(1)
O-11	5702(3)	3255(3)	7355(3)	52(1)
C-12	3517(5)	1893(4)	6346(5)	52(1)
C-13	2998(7)	1245(7)	7856(8)	82(1)
O-14	2208(4)	1337(4)	4490(4)	74(1)
C-15	9902(5)	4587(4)	5631(5)	48(1)
O-16	8581(4)	3255(3)	3566(3)	58(1)
C-17	9444(8)	3685(8)	2211(6)	78(1)
O-18	11,727(4)	5983(4)	6444(4)	72(1)
H-1A	11,342	8386	11,062	82
H-2A	8694	9041	9041	81
H-3A	5178	6074	6320	61
H-4A	5481	2908	4522	52
H-5A	8688	2649	6781	57
H-9A	7767	7931	2412	108
H-9B	5143	6545	890	108
H-9C	6132	8993	1975	108
H-13A	3722	384	8226	124
H-13B	3548	2465	9154	124
H-13C	1390	464	7166	124
H-17A	9620	5043	2300	117
H-17B	10,885	3653	2706	117
H-17C	8400	2642	729	117

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

atoms). Crystallographic data, data collections, and structure refinements are summarized in Table 1; coordinates of atoms and isotropic temperature factors in Table 2; a selection of crystal's important geometric parameters in Table 3, and short contacts data in Table 4.

The crystal structure of **4** was refined to $R_1 = 0.0452$ (1926 reflections, all unique) and $R_1 = 0.0354$ (1111 reflections with $F_0 > 2\sigma(F_0)$) by the full-matrix least-squares method using the SHELXL-97 program[21] based on 167 parameters. Figure 1 illustrates the compound's structure, showing the conformation and atom numbering system.[22] Figure 2 shows the molecular packing in the crystal, prepared by PLUTO-78.[23] The computational material for publication was prepared using the PLATON program.[14]

Table 3. Selected torsion angles (°) for **4**

Torsion angles	(°)
O-6–C-1–C-2–C-3	3.6(5)
C-1–C-2–C-3–O-7	−104.9(3)
C-1–C-2–C-3–C-4	10.6(4)
O-7–C-3–C-4–O-11	−162.5(2)
C-2–C-3–C-4–O-11	76.5(3)
O-7–C-3–C-4–C-5	82.0(3)
C-2–C-3–C-4–C-5	−39.0(3)
O-11–C-4–C-5–O-6	−59.7(3)
C-3–C-4–C-5–O-6	57.5(3)
O-11–C-4–C-5–C-15	176.1(2)
C-3–C-4–C-5–C–15	−66.7(3)
C-2–C-1–O-6–C-5	13.6(4)
C-4–C-5–O-6–C-1	−43.8(3)
C-15–C-5–O-6–C-1	83.0(3)
H-1A–C-1–C-2–H-2A	3.7
H-2A–C-2–C-3–H-3A	48.2
H-3A–C-3–C-4–H-4A	76.6
H-4A–C-4–C-5–H-5A	−61.9

Supplementary data

Full crystallographic details, excluding structures features, have been deposited (Deposition No. CCDC 626102) with the Cambridge Crystallographic Data Center. These data may be obtained, on request, from The Director, CCDC, 12 Union Road, Cambridge,

Table 4. Hydrogen bonds for **4** with distances (*d*): $d(D\cdots A) < R(D) + R(A) + 0.50$ Å; $d(H\cdots A) < R(H) + R(A) - 0.12$ Å and angle ($\angle$) $\angle D\text{–}H\cdots A > 100.0°$

D–H	A	*d*(D–H)	*d*(H···A)	*d*(D···A)	∠D–H···A
C-1–H-1A	O-14^{i}	0.93	2.57	3.363(4)	144
C-3–H-3A	O-18^{ii}	0.98	2.50	3.481(5)	174
C-5–H-5A	O-10^{iii}	0.98	2.56	3.376(5)	141
C-9–H-9B	O-7^{i}	0.96	2.57	3.343(7)	138

Symmetry codes: (i) $1 + x$, $1 + y$, $1 + z$; (ii) $-1 + x$, y, z; (iii) x, $-1 + y$, z.

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