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Note

Comparative structural analysis of 5,6,7,9-tetra-*O*-acetyl-4,8-anhydro-1,3-dideoxy-D-*glycero*-L-*gluco*-nonulose and its 1-*O*-acetylated analog, 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose using X-ray crystallography☆

Rishi Kumar, Pallavi Tiwari, Prakas R. Maulik and Anup Kumar Misra*

Medicinal and Process Chemistry Division and Molecular and Structural Biology Division, Central Drug Research Institute, Chattar Manzil Palace, Lucknow 226001, UP, India

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Abstract—Comparative X-ray diffraction analysis of 5,6,7,9-tetra-*O*-acetyl-4,8-anhydro-1,3-dideoxy-D-*glycero*-L-*gluco*-nonulose (**1**) and a structurally related analog, 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (**2**), are reported. Both crystals have one molecule in the unit cell and the pyranose rings in both exist in the $^4C_1$ conformation.

Keywords: *C*-Glycoside; *O*-Glycoside; Conformation; X-ray crystallography; Glycosyl acetate

C-Glycosides are close analogs of oligosaccharides whose intersaccharide oxygen bridges (glycosidic bonds) have been replaced by a methylene moiety. In recent years, *C*-glycosides have gained considerable interest because of their significance as chiral synthons for natural products syntheses. In addition, *C*-glycosides are resistant to hydrolytic enzymes and as such have been of interest as pharmaceutical agents.[1–6] Therefore, *C*-glycosides have been of interest to scientists working in the areas of carbohydrate, enzymatic, and metabolic chemistry as well as in organic synthesis.[7–11] Because biological activity and enzymatic recognition are closely related to molecular structure, structural comparisons of *C*-glycosides with their *O*-glycoside analogs could be useful in designing novel carbohydrate derived therapeutics. It is important to evaluate whether replacing the glycosidic oxygen with a methylene group (which eradicates the *exo*- as well as *endo*-anomeric effect and the capability of hydrogen bonding with the glycosidic oxygen) modifies the conformational properties of the molecule, resulting in enhanced or impaired biological activity.

As a part of our program[12] on the synthesis of *C*-glycosides, 5,6,7,9-tetra-*O*-acetyl-4,8-anhydro-1,3-dideoxy-D-*glycero*-L-*gluco*-nonulose (**1**, Fig. 1), a *C*-glycoside analog of 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (**2**) has been prepared following the elegant synthetic methodology reported by Lubineau and co-workers.[13] Although its structure was been established by NMR spectroscopy, it was desirable to further ensure the stereochemical integrity at C-1. For this purpose, we undertook an X-ray crystallography study of **1** and **2**. This comparative study allowed us to determine differences in the conformation of **1** and **2** in the solid state.

Following an earlier report,[13] compound **1** was prepared by the reaction of D-galactose with pentane-2,4-dione in the presence sodium bicarbonate in water. Using another literature procedure,[14] compound **2** was prepared by heating a mixture of D-galactose, acetic anhydride, and anhydrous sodium acetate at reflux. Compounds **1** and **2** were initially characterized by ^{1}H and ^{13}C NMR spectroscopy. From the ^{1}H NMR

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* Corresponding author. E-mail: akmisra69@rediffmail.com

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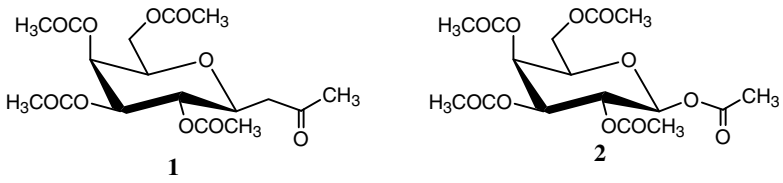

Figure 1. Structures of 5,6,7,9-tetra-*O*-acetyl-4,8-anhydro-1,3-dideoxy-D-*glycero*-L-*gluco*-nonulose (**1**) and 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (**2**).

spectrum in $CDCl_3$ solution it was found that anomeric proton (H-1) of **1** appears as a multiplet as a result of multiple couplings between H-2 and H-1′ whereas H-1 of **2** appears as a doublet ($J_{1,2} = 8.2$ Hz), which infers a diaxial relationship between H-1 and H-2. The X-ray crystal structures of **1** and **2** were obtained to compare their absolute stereochemistry and solid-state conformations. The atom numbering of **1** and **2** are shown in Figures 2 and 3, respectively; crystal data and structural refinements of **1** and **2** are listed in Table 1. Selected bond lengths, bond angles, and torsion angles are presented in Tables 2 and 3.

Both **1** and **2** crystallize in the $P2_12_12_1$ space group. It was found that both crystals have one molecule in the crystal unit cell and that the pyranose rings both adopt $^4C_1$ conformations; however, due to crystal packing forces, they are slightly distorted. The Cremer–Pople puckering parameters[15] for the each pyranose ring are as follows. For **1**, $Q = 0.58$ Å, $\Theta = 4.23°$, and $\varphi = 270.0°$ and for compound **2**, $Q = 0.585$ Å, $\Theta = 1.49°$, and $\varphi = 270.97°$. A comparison of the C–O bond lengths at the anomeric center showed that in **1** the endocyclic C1–O1 bond (1.438(4) Å) is longer than C1–O1 bond (1.406(4) Å) in compound **2** (Table 2).

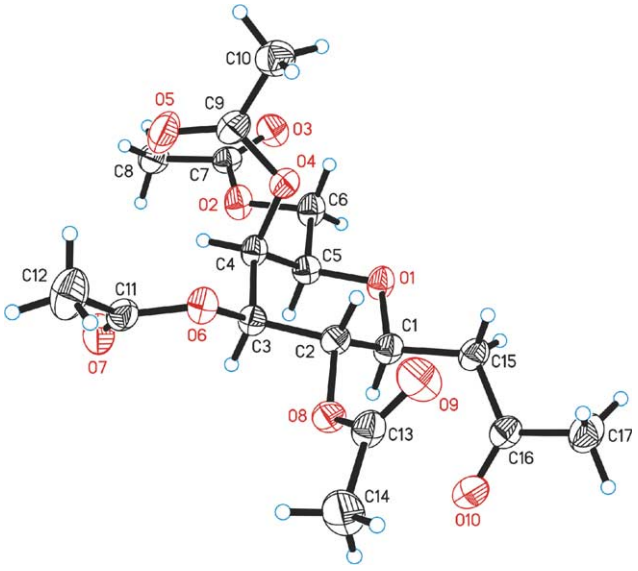

Figure 2. ORTEP diagram of **1** (at 30% probability level) with atomic labeling.

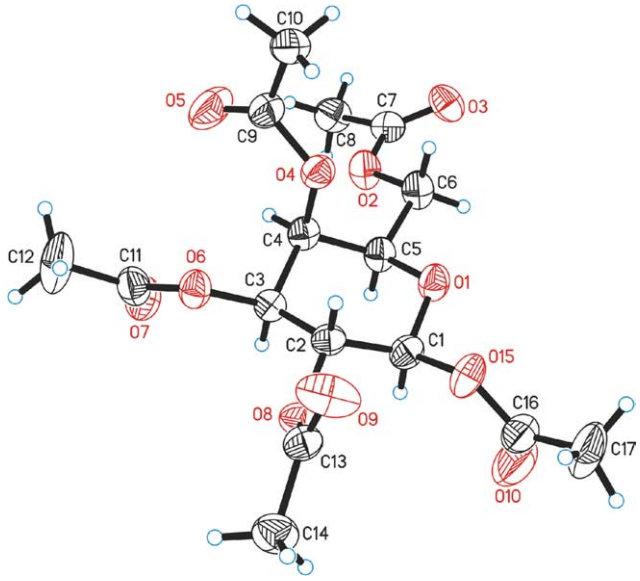

Figure 3. ORTEP diagram of **2** (at 30% probability level) with atomic labeling.

The shortening of endocyclic C1–O1 bond in **2** in comparison with **1** may be explained by considering the electronegativity of the atoms linked to the anomeric center. In **1**, the anomeric carbon is linked to one endocyclic oxygen atom (electronegativity 3.5, Pauling scale) and one exocyclic carbon atom (electronegativity 2.5, Pauling scale), whereas in compound **2**, two oxygen atoms (endocyclic and exocyclic) are linked to the anomeric carbon, which is also consistent with the earlier literature reports.[16–18] The most interesting structural difference between the solid-state structures of **1** and **2** is the difference in torsion angles about the glycosidic bond. The O1–C1–C15–C16 dihedral angle of **1** is −161.8°(3), whereas O1–C1–O15–C16 dihedral angle of **2** is −101.0(4) (Table 3). This difference in the torsion angles suggests a greater flexibility around the glycosidic bond in **1** compared to **2**, which is also a strong indication of the stereoelectronic basis for the *exo*-anomeric effect, as mentioned in earlier, on the conformational studies of *C*-glycosides.[19–22] As compounds **1** and **2** do not possess hydrogen bond donors (OH or NH), no strong intermolecular hydrogen bonds were observed in the crystal packing. However, both **1** and **2** appear to possess weak intermolecular hydrogen bonds mainly

Table 1. Comparative crystallographic data and structure refinement for compounds **1** and **2**

	Compound **1**	Compound **2**
Chemical formula	$C_{17}H_{24}O_{10}$	$C_{16}H_{22}O_{11}$
Chemical formula weight (M_r)	388.36	390.34
Cell setting, space group	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$
a (Å)	8.450(1)	8.493(1)
b (Å)	8.949(2)	9.152(1)
c (Å)	26.162(2)	25.604(3)
V (Å^3)	1978.3(5)	1990.1(4)
Z	4	4
D_x (Mg/m^3)	1.304	1.303
μ (mm^{-1})	0.108	0.112
Radiation type; λ (Å)	Mo Kα; 0.71073	Mo Kα; 0.71073
No. of reflection for cell parameters; θ range (°)	56; 4.7–12.3	69; 3.28–12.45
Temperature (K)	293(2)	293(2)
Crystal form, color	Block, transparent	Block, transparent
Crystal size (mm)	$0.2\times0.2\times0.175$	$0.2\times0.225\times0.15$
Diffractometer	Bruker P4	Bruker P4
Data collection method	$\theta/2\theta$-Scan	$\theta/2\theta$-Scan
No. of measured, independent and observed reflections	2701, 2502, and 1552	2705, 2502, and 1650
Criterion for observed reflection	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0236	0.0218
θ_{max} (°)	25	24.99
Range of h, k, l	−1→10, −1→10, −1→31	−10→1, −1→10, −1→30
Absorption correction	None	None
Extinction correction	None	None
Refinement on	F^2	F^2
R, wR, S	0.0455, 0.0989, 0.976	0.0445, 0.1016, 1.004
No. of reflections and parameters used in refinement	2502 and 249	2502 and 250
H-atom treatment	Constrained	Constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^3)	0.180, −0.204	0.229, −0.166

Table 2. Selected bond lengths (Å) and bond angles (°) for **1** and **2** (standard deviations)

Atoms (Å)	Compound		Bond angles (°)	Compound	
	1	**2**		**1**	**2**
O1–C1	1.438(4)	1.406(4)	O1–C1–C2	109.2(3)	112.1 (3)
O1–C5	1.425(4)	1.430(4)	O1–C1–C15	105.4(3)	—
C1–C2	1.542(5)	1.513(5)	O1–C1–O15	—-	105.3(3)
C1–C15	1.508(5)	—	C1–C2–C3	111.1(3)	108.1(3)
C1–O15	—	1.412(4)	C1–C15–C16	117.3(3)	—
C15–C16	1.497(5)	—	C1–O15–C16	—	119.5(3)
O15–C16	—	1.335(5)			

Table 3. Selected torsion angles (°) for **1** and **2** (standard deviations)

Torsion angle	Compound	
	1	**2**
O1–C1–C2–O8	168.1(3)	173.7(3)
O15–C1–C2–O8	—	−70.7(3)
C15–C1–C2–O8	−74.6(4)	—
O1–C1–C2–C3	52.7(4)	57.2(4)
O15–C1–C2–C3	—	172.7(3)
C15–C1–C2–C3	170.0(3)	—
O15–C1–O1–C5	—	−178.5(3)
C15–C1–O1–C5	179.6(3)	—
C2–C1–O1–C5	−57.9(4)	−61.4(4)
C5–C6–O2–C7	−175.1(3)	−168.3(3)
O1–C1–O15–C16	—	−101.0(4)
O1–C1–C15–C16	−161.8(3)	—

due to C–H···O interactions. Although the existence of C–H···O hydrogen bonding is still to be validated with proper experimental support (such as neutron diffraction) as the H···O distances are within the sum of the Van der Waals radii of O and H atoms, these interactions may be present but may not provide significant stabilization to the crystals. However, in light of the earlier literature reports[23–27] dealing with the presence of weak hydrogen bonding (H–A distance ~2.50 Å, D–A distance ~3.27–3.45 Å and ∠D–H–A ~150°), we propose that **1** possesses a weak intermolecular C–H···O hydrogen bond from H3 of molecule B to O3 of molecule A at distance of 2.56 Å. Similarly, **2** also has intermolecular hydrogen bonds due to CH···O interactions extending

from O3 of molecule A to H3 and H5 of molecule B (distances of 2.51 and 2.57 Å, respectively) as well as $H10_A$ of molecule B to O5 of molecule A (distance of 2.52 Å) and $H10_C$ of molecule A to O3 of molecule B (distance of 2.55 Å) (see Figs. S1–S6 and Tables S1–S6 in Supplementary data).

In summary, a comparative structural analysis of 5,6,7,9-tetra-*O*-acetyl-4,8-anhydro-1,3-dideoxy-D-*glycero*-L-*gluco*-nonulose (**1**) and 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (**2**) was carried out by single crystal X-ray crystallography. Both crystals possess one molecule in the independent part of the crystal unit cell and adopt a slightly distorted chair conformation. It has been proposed that *C*-glycoside **1** is more flexible than *O*-glycoside **2** and the implication of the flexibility around the *C*-glycosidic bond is that it may bind to the binding site of the proteins or enzymes without noticeable energy conflicts and thus can be used as a probe to study protein–carbohydrate interactions and could be useful in carbohydrate-based drug design.

1. Experimental

1.1. General methods

Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 300 MHz instrument in $CDCl_3$ using TMS as internal reference. Chemical shift values are expressed in ppm.

1.2. Single-crystal X-ray analysis

Colorless and transparent crystals of **1** and **2** were obtained by slow evaporation from ethyl acetate–hexane solution (2:1 v/v) at room temperature. Diffraction quality crystals were selected after examination under a polarizing microscope and then mounted on a Bruker P4 diffractometer equipped with graphite-monochromated Mo Kα radiation for unit cell measurement and intensity data collection. The data were collected and reduced using XSCANS.[28] Structures were solved by direct methods and refined anisotropically for the non-H atoms by full-matrix-least-squares methods using SHELXTL.[29] All the H-atoms were placed in calculated positions and allowed to ride on their parent atoms during refinements.

The data were deposited at the Cambridge Structural database (deposition numbers 276478 (**1**) and 276479 (**2**)). Copies of this information can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

1.3. 5,6,7,9-Tetra-*O*-acetyl-4,8-anhydro-1,3-dideoxy-D-*glycero*-L-*gluco*-nonulose (1)

This compound was prepared according to the procedure described by Lubineau and co-workers.[13] Yield: 85%; white crystals (EtOAc–hexane), mp 91–92 °C; $[\alpha]_D^{25}$ +5.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.34 (br s, 1H, H-7), 5.01–4.98 (m, 2H, H-5 and H-6), 4.05–3.98 (m, 2H, H-$9_{a,b}$), 3.96–3.85 (m, 2H, H-4 and H-8), 2.81–2.68 (dd, 1H, $J = 16.3$, 8.5 Hz, H-3_a), 2.50–2.40 (dd, 1H, $J = 16.4$, 3.4 Hz, H-3_b), 2.16, 2.15, 2.02, 2.01, 1.96 (5s, 15H, 5 COCH_3); ^{13}C NMR ($CDCl_3$, 75 Hz): δ 204.5, 169.9 (2C), 169.7, 169.6, 74.4, 74.3, 71.9, 69.3, 67.9, 61.6, 45.6, 30.9, 20.7, 20.6 (2C), 20.5; ESI-MS: 411 [M+Na]. Anal. Calcd for $C_{17}H_{24}O_{10}$ (388): C, 52.57; H, 6.23. Found: 52.40; H, 6.50.

1.4. 1,2,3,4,6-Penta-*O*-acetyl-β-D-galactopyranose (2)

This compound was prepared according to the procedure described in the literature.[14] Yield: 92%; white crystals (EtOAc–hexane), mp 140 °C. $[\alpha]_D^{25}$ +19 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.72–5.68 (d, 1H, $J = 8.2$ Hz, H-1), 5.43–5.42 (d, 1H, $J = 3.0$ Hz, H-4), 5.40–5.29 (dd, 1H, $J = 8.5$, 8.5 Hz, H-2), 5.11–5.05 (dd, 1H, $J = 8.6$, 3.3 Hz, H-3), 4.17–4.11 (m, 2H, H-$6_{a,b}$), 4.07–4.04 (m, 1H, H-5), 2.16, 2.12 (2s, 6H, 2COCH_3), 2.04 (s, 6H, 2COCH_3), 1.99 (s, 3H, COCH_3); ^{13}C NMR ($CDCl_3$, 75 Hz): δ 170.0 (2C), 169.7, 169.1, 168.8, 92.3, 71.8, 71.0, 68.2, 67.1, 61.2, 20.9 (2C), 20.8 (2C), 20.7; ESI-MS: 413 [M+Na]. Anal. Calcd for $C_{16}H_{22}O_{11}$ (390): C, 49.23; H, 5.68. Found: C, 49.05; H, 5.85.

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Supplementary data

Supplementary data is available for this paper. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.carres.2005.07.009.

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