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Note

Crystal structure of methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate

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Dedicated to Professor Derek Horton on the occasion of his 70th birthday

Abstract

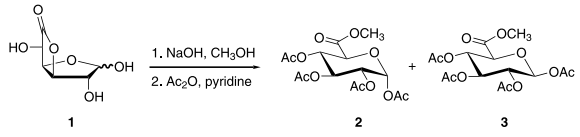
The identity of the crystalline product formed by the acetylation of a mixture of methyl α- and β-D-glucopyranuronates has been confirmed as being methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate (**3**), which agrees with the assignment from ^{1}H NMR. The absolute configuration of compound **3** was assigned to agree with the known chirality of the precursor sugar, D-glucono-6,3-lactone.

Keywords: Uronate; *O*-Glycoside; Anomeric configuration; X-Ray analysis; Single-crystal

Acetate esters of carbohydrates serve as useful derivatives for the study of structure and conformation, as well as being versatile intermediates in the synthesis of carbohydrates modified at C-1, the anomeric carbon. When anomeric mixtures of sugars, either in the furanose or pyranose forms, are acetylated under acidic or basic conditions, a mixture of axial (α) and equatorial (β) products is often produced. ^{1}H NMR coupling constants may be used to determine the configuration at C-1 in common pyranose acetates (apart, for example, in the mannopyranose series); however, similar analysis of furanose acetates is difficult.[1] Determining the configuration at C-1 is essential to ensure the stereochemical integrity of the compound in question, and the application of X-ray diffraction in determining relative (and when possible absolute) stereochemistry is very useful.

As part of a synthesis of glycomimetic compounds related to bacterial amino sugars, we repeated the preparation of glucopyranuronate tetraacetates **2** and **3** (Scheme 1) as previously reported.[2] Treatment of D-glucurono-6,3-lactone (**1**) with NaOH in methanol produces a mixture of methyl D-glucopyranuronates, which are then reacted with acetic anhydride in pyridine to yield two anomeric acetates, namely methyl 1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranuronate (**2**) and methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate (**3**).[2] The anomeric acetates are separated by crystallization of the β anomer **3** from hot 2-propanol to afford compound **3** as needles with melting point 178–180 °C. The two anomers may be distinguished from coupling constants in their ^{1}H NMR spectra. For syrupy **2**, J_{H1-H2} for the H-1 signal is found to be 3.66 Hz, indicating a gauche relationship between H-1 and H-2, whereas for crystalline **3**, J_{H1-H2} is 7.7 Hz, which usually infers a diaxial relationship. The crystal structure determination of **3** now confirms the assignment.

The single-crystal X-ray crystal structure of **3** (Fig. 1) confirms the expected $^4C_1$ conformation of the pyranose ring and the fact that the pyranoses are the thermodynamic products from the opening of lactone **1** with



Scheme 1.

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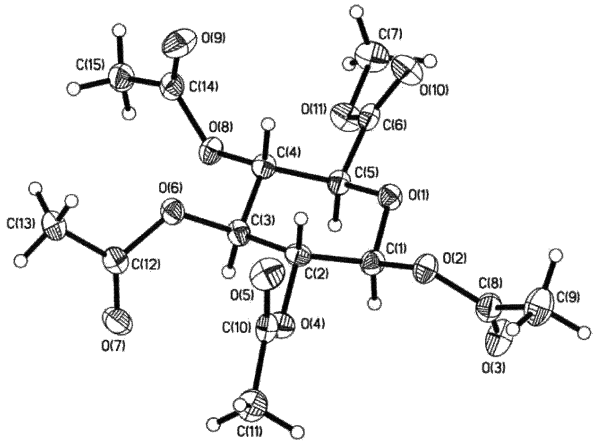

Fig. 1. Molecular structure of **3**, with displacement ellipsoids at the 50% probability level. Hydrogen atoms drawn as circles with an arbitrary radius.

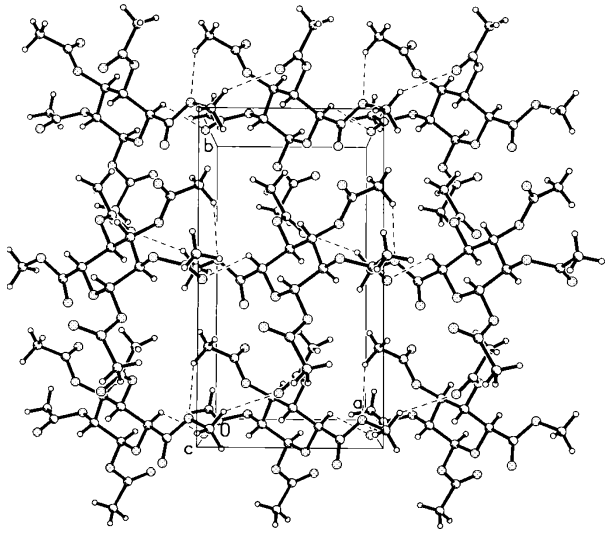

Fig. 2. Packing diagram for **3**, projected along the c-axis. Dotted circles O, shaded circles C. Dashed lines represent intermolecular hydrogen bonds.

methoxide. Interestingly in $CDCl_3$ solution the observed ^1H NMR J_{H1-H2} of 7.7 Hz for **3** is less than for the same protons in the related 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (8.4 Hz) suggesting that replacing the CH_2OAc group in that compound with the CO_2CH_3 group in **3** alters the conformation of the pyranose ring in the latter. The crystal structure of the pentaacetate determined by Jones et. al.[3] shows the pyranose ring to be close to a perfect chair, whereas the structure of **3** in Fig. 1 clearly shows distortion away from a perfect chair around the ring, which is compatible with the smaller J_{H1-H2} observed in the ^1H NMR spectrum of **3**. When comparing the acetal C–O bond lengths around the anomeric carbon in the two peracetates the exocyclic C-1–O-2 bond is longer in uronate **3** than in the pentaacetate (1.414 Å versus 1.408 Å), whereas the endocyclic C-1–O-1 bond is shorter in **3** (1.416 Å versus 1.426 Å). The molecular structure and numbering scheme for the atoms are shown in Fig. 1. Fig. 2 shows the packing of the molecules of **3** in the unit cell, projected along the *c*-axis. The adjacent layers of molecules shown along the *b*-axis are related by the respective 2-fold screw axis. Intermolecular hydrogen bonds extend from H(C-5) to O-5, H(C-7) to O-9 and H(C-13) to O-11 at distances of 2.408, 2.567, and 2.556 Å, respectively.

1. Experimental

General methods.—The melting point was determined on a Mel-Temp apparatus and is uncorrected. The ^1H NMR spectrum of **3** was recorded on a Varian Gemini 2000 instrument at 400 MHz as a solution in $CDCl_3$ with Me_4Si as the internal standard.

Compound **3** was prepared by treating D-glucurono-6,3-lactone (**1**) with a methanolic solution of NaOH and acetylation of the resulting crude product mixture with acetic anhydride in pyridine as described previously.[2] The β anomer **3** was crystallized from 2-propanol, and the sample for X-ray analysis was obtained by recrystallizing the solid twice more from the same solvent. ^1H NMR: δ 2.02 (s, 3H, $COCH_3$), 2.03 (s, 6H, $2 \times COCH_3$), 2.10 (s, 3H, $COCH_3$), 3.73 (s, 3H, OCH_3), 4.15 (d, *J* 9.5 Hz, 1H, H-5), 5.11 (dd, *J* 7.8, 9.0 Hz, 1H, H-2), 5.20 (dd, *J* 9.0, 9.5 Hz, 1H, H-4), 5.25 (dd, *J* 9.0, 9.0 Hz, 1H, H-3), 5.74 (d, *J* 7.7 Hz, 1H, H-1). Evaporation of the mother liquors gave a syrup that was mainly the α-anomer **2** as seen by ^1H NMR spectroscopy.

Single-crystal X-ray structure of **3**.—X-Ray data were collected at 100 K on a Bruker SMART APEX 4k CCD Single-Crystal Diffractometer equipped with a normal focus, 2.4 kW sealed tube X-ray source (graphite monochromatized MoK_α radiation, $\lambda =$ 0.71073 Å) operating at 50 kV and 40 mA. The diffraction data was obtained by collection of 606 frames at each of three φ settings, 0, 120, and 240°, using a scan width of 0.3° in ω. At the end of the data collection, 50 initial frames were recollected to monitor crystal decay. The exposure time was 20 s/frame.

The initial unit cell parameters were determined using 469 reflections harvested from 900 frames using Bruker's SMART program.[4] These parameters were then used to integrate all the data in Bruker's SAINT program,[4] where global refinement of the unit cell parameters was also performed to give the final values utilized in the subsequent structural analysis. Prior to structure solution and refinement, the data files written by SAINT were processed through SADABS[5] for correction of errors due to absorption by the glass capillary, crystal decay, and other effects.

The structure was solved via direct methods using Bruker's SHELXS program,[6] and refined via full-matrix least squares against F^2 on all data using SHELXL.[6] Structure plots that appear in this paper were obtained from the program SHELXP.[6] Positions for all non-hydrogen atoms were refined anisotropically, followed by isotropic refinement of all hydrogen positions. The absolute structure could not be determined reliably due to the absence of significant anomalous scatterers in the sample, although it was taken to be correct based on the NMR data. Refinement data are summarized in Table 1 and atomic coordinates and equivalent isotropic displacement parameters are listed in Table 2.

Table 1
Crystal data summary and refinement results for **3**

Structural formula	$C_{15}H_{20}O_{11}$
Formula weight	376.31
Color	Colorless
Crystal size (mm)	$0.20\times0.06\times0.04$
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (No. 19)
a (Å)	7.5120(18)
b (Å)	13.864(3)
c (Å)	16.918(4)
V (Å^3)	1761.9(7)
Z	4
ρ_{calc} (g/cm^3)	1.419
λ(MoK$_\alpha$) (Å)	0.71073
Temperature (K)	100(2)
μ (mm^{-1})	0.123
θ Range for data collection (°)	1.90–28.37
Limiting indices	$-9\le h\le 9$, $-18\le k\le 18$, $-22\le l\le 21$
No. of reflections collected	16136
No. of independent reflections	4247 ($R_{int}=0.0643$)
No. of parameters	315
Refinement method	Full-matrix least squares on F^2
Hydrogen atom positions	Refined
Final R indices [$I>2\sigma(I)$]	$R_1(F)$ [a] $=0.0431$, $wR_2(F^2)$ [b] $=0.0795$
Final R indices (all data)	$R_1(F)$ [a] $=0.0737$, $wR_2(F^2)$ [b] $=0.0881$
Goodness-of-fit on F^2	0.970
Absolute structure parameter	$-0.1(9)$
Largest diff. peak and hole (e Å^{-3})	0.187 and -0.186

[a] $R_1(F)=\Sigma\|\|F_o|-|F_c\|\|/\Sigma|F_o|$ with $F_o>4.0\sigma(F)$.

[b] $wR_2(F^2)=[\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$ with $F_o>4.0\sigma(F)$, and $w^{-1}=\sigma^2(F_o)^2+(W\cdot P)^2+T\cdot P$, where $P=(\mathrm{Max}(F_o^2,0)+2F_c^2)/3$, $W=0.0345$, and $T=0.00$.

Table 2
Fractional atomic coordinates ($\times10^4$) [a] and equivalent isotropic displacement parameters (A$^2\times10^3$) for **3**

Atom	x	y	z	U(eq) [b]
O(1)	9127(2)	10,549(1)	902(1)	21(1)
O(2)	10,883(2)	11,221(1)	−32(1)	24(1)
O(3)	8566(2)	11,443(1)	−856(1)	35(1)
O(4)	12,609(2)	9436(1)	−265(1)	24(1)
O(5)	15,196(2)	10,057(1)	174(1)	34(1)
O(6)	12,638(2)	8331(1)	1231(1)	22(1)
O(7)	12,762(2)	7230(1)	252(1)	31(1)
O(8)	9180(2)	8229(1)	1915(1)	22(1)
O(9)	10,681(2)	8521(1)	3043(1)	34(1)
O(10)	7332(2)	10,789(1)	2249(1)	30(1)
O(11)	5854(2)	9419(1)	2019(1)	27(1)
C(1)	10,163(3)	10,332(1)	226(1)	21(1)
C(2)	11,722(3)	9705(2)	452(1)	19(1)
C(3)	11,109(3)	8802(2)	887(1)	20(1)
C(4)	9899(3)	9088(2)	1561(1)	20(1)
C(5)	8371(3)	9703(1)	1243(1)	19(1)
C(6)	7147(3)	10,047(2)	1890(1)	21(1)
C(7)	4587(3)	9680(2)	2628(2)	32(1)
C(8)	9929(3)	11,731(2)	−579(1)	27(1)
C(9)	10,851(4)	12,654(2)	−767(2)	39(1)
C(10)	14,372(3)	9668(2)	−340(1)	23(1)
C(11)	15,041(4)	9363(2)	−1126(2)	33(1)
C(12)	13,337(3)	7545(2)	857(1)	22(1)
C(13)	14,853(3)	7165(2)	1328(2)	27(1)
C(14)	9671(3)	8025(2)	2675(1)	22(1)
C(15)	8788(4)	7135(2)	2957(2)	28(1)

[a] E.s.d.'s are given in parentheses.

[b] U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Supplementary data

Complete structural data has been deposited at the Cambridge Crystallographic Data Centre, which may be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 IEZ, UK.

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