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Ethyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate

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The crystal structure, at 120 K, and solution ^{1}H and ^{13}C NMR spectra of ethyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate, (**8**) have been determined. Compound **8** crystallizes in the triclinic space group, $P1(Z = 1)$ with $a = 6.0209(3)$ Å, $b = 8.9698(5)$ Å, $c = 9.9818(8)$ Å, $\alpha = 104.965(2)^\circ$, $\beta = 98.522(3)^\circ$, $\gamma = 106.790(5)^\circ$. The Cremer and Pople puckering parameters [$Q = 0.602(4)$ Å, $\theta = 7.1(4)^\circ$, $\phi = 325(3)^\circ$] for the pyranose ring in the solid state indicate a near ideal $^4C_1$ chair conformation with a slight distortion in the direction towards $^0H_5$. A number of weak, soft intermolecular C—H · · · O hydrogen bonds set up a 3D array. NMR spectra and FAB and EIMS data have been obtained. Solution NMR parameters suggest that the solid state conformation is maintained in solution in chloroform.

KEY WORDS: Glucopyranuronic derivatives; conformation; NMR; MS.

Introduction

D-Glucopyranuronic acid (**1**), its mono- and polysaccharide derivatives are widely distributed in plants and animals.[1] This and their numerous medicinal and industrial applications make them important compounds.

The structures of various monosaccharide α- and β-D-glucopyranuronic acid derivatives are listed in the Cambridge Structural Data Base,[2] at the Chemical Database Service of the EPSRC at Daresbury.[3] These include hydrated metal β-D-glucopyranuronates, e.g., hydrates of **2**,[4–6] α-D-glucopyranuronamide[7] **3** and its mono hydrate [**3**: H_2O][8], and polyesterified glycoside derivatives, **4**,[9] **5**,[9] **6**,[10] and **7**.[11] Compounds containing amido and/or free hydroxyl groups, such as **2–4**, take part in classic and strong H-bonding, e.g., O—H · · · O and N—H · · · O interactions, which connect the molecules into supramolecular assemblies in the solid state and in solution. In recent times, weak or soft H-bonds, such as C—H · · · O, have increasingly been recognised as also being of considerable importance in the organization of molecular assemblies in the solid state.[12]

As part of our studies on soft H-bonds,[13] we have determined the crystal structure of the peresterified D-glucopyranuronic acid derivative, ethyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate (**8**). In **8**, as all OH groups are fully derivatised as ester groups, the only H-bonds present would be of the soft C—H · · · O variety.

Relatively few targeted formations of **8** have been indicated in the literature. Reaction of ethyl D-glucopyranuronate with AcONa and Ac_2O produced an ethyl 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronate product, mp 143°C, assumed to be the β-anomer, **8**, from its $[\alpha]_D$ value.[14] A mixture of **8** and its anomer, ethyl 1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranuronate (**9**), was

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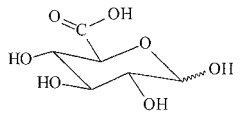

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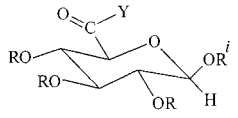
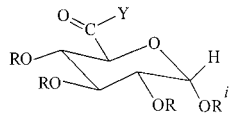




β-isomers

α-isomers

2: R = R′ = H; Y = OM: M = Na, K, Rb or CaBr
5: R = Ac; R′ = $CH_2CH{=}CH_2$; Y = OMe
6: R = Ac; R′ = CH_2CH_3; Y = OMe
7: R = Ac; R′ = CH(OMe)Pr; Y = OMe
8: R = R′ = Ac; Y = OEt
10: R = R′ = Ac; Y = OH

3: R = R′ = H; Y = NH_2
4: R = Ac; R′ = H; Y = OMe
9: R = R′ = Ac; Y = OEt

obtained from the reaction of diazoethane and a mixture of 1,2,3,4-tetra-*O*-acetyl-α- and β-D-glucopyranuronic acid:[15] while the ^{1}H and^{13}C NMR spectra of the mixture was reported, no data for separated compounds were provided. The melting point of our sample, determined both via a Kofler hotstage and by DSC, was somewhat lower at 133–134°C. In order to obtain reliable data for **8**, a directed synthesis using well characterised 1,2,3,4-tetra-acetyl-*O*-β-D-glucuronic acid (**10**) has been employed. The ^{1}H and^{13}C NMR spectra are reported along with the crystal structure of **8**.

Experimental

Melting points were determined using a Kofler hotstage. Solution NMR were obtained on Bruker 250 MHz and Varian 400 MHz instruments, IR spectra on Philips Analytical PU 9800 FTIR and Nicolet 205 FTIR instruments, DSC on a Mettler Toledo DSC 821^e instrument. X-ray data were collected by the EPSRC National Crystallography Service, at the University of Southampton on an Enraf Nonius Kappa CCD diffractometer (graphite-monochromatised Mo Kα radiation, $\lambda = 0.71073$ Å), and MS data were obtained by the EPSRC National Mass Spectrometry Service Centre, at the University of Wales, Swansea.

D-Glucopyranuronic acid was a commercial sample.

*1,2,3,4-Tetra-O-acetyl-β-D-glucopyranuronic acid (**10**)*

D-Glucopyranururonic acid (**1**) (5.0 g, 26 mmol) was added with stirring to acetic anhydride (25 mL), containing concentrated sulfuric acid (3 drops). The temperature was allowed to rise to 60°C. After complete dissolution, a further quantity (5.0 g) of **1** was added. The solution was cooled to room temperature and water added (75 mL). The precipitate of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronic acid: monohydrate (**10**:H_2O) was collected, mp 92–93°C, 9.8 g, 50%.

^{1}H NMR (250 MHz, $CDCl_3$): δ 2.01, 2.03, 2.06, 2.10 (4s, $4 \times CH_3CO$), 2.81 (s, $H_2O + CO_2H$), 4.61 (d, 1H, $J = 9.2$ Hz, H-5), 5.13 (dd, 1H, $J = 6.7$, 8.2 Hz, H-2), 5.27 (t, 1H, $J =$ ca 9.0 Hz, H-4), 5.44 (br t, 1H, $J =$ ca. 9.0 Hz, H-3), 5.85 (d, 1H, $J = 6.7$ Hz, H-1).

*Synthesis of **8***

Compound (**10**:H_2O) was dehydrated azeotropically with toluene. To a solution of **10** (2.0 g, 5.5 mmol), *p*-(dimethylamino)pyridine (6 mg) and EtOH (1 mL, 22 mmol) in acetonitrile (5 mL) was added 1,3-dicyclohexylcarbodiimide (DCC) (1.3 g, 6.1 mmol) with stirring. The reaction mixture was stirred for 3 h, filtered and the filtrate rotary evaporated. The oily residue was crystallised from ethanol to give **8**: yield 1.0 g, 46%; mp 134–135°C (Kofler hotstage), 132–133°C (DSC): lit value[11] mp 143°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, $J =$ 7.2 Hz, 3H, CH_3CH_2), 1.98 (s, 3H, CH_3CO), 1.99 (s, 6H, $2 \times CH_3CO$), 2.07 (s, 3H, CH_3CO), 4.12 (d, 1H, $J = 9.2$ Hz, H-5), 4.14 (dt, 1H, $J = 7.2$, 12.6 Hz, CH_2) 4.18 (dt, 1H, $J = 7.2$, 12.6 Hz, CH_2), 5.12 (br t, 1H, $J = 7.9$, 8.8 Hz, H2), 5.21 (t, 1H, $J = 9.2$ Hz, H-4), 5.26 (t, 1H, $J =$ ca. 9 Hz, H-3), 5.72 (d, $J = 7.9$ Hz, 1H, H-1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3CH_2), 20.4$_7$[CH_3CO], 20.4$_9$[CH_3CO],

20.5_2[CH_3CO], 20.7[CH_3CO], 62.3[C6], 68.9[C4], 70.2[C2], 71.9[C5], 73.21[C3], 91.3[C1], 166.3[C=O at C6], 168.8[C=O], 169.1_6[C=O], 169.2_2[C=O], 169.9[C=O].

IR (KBr) ν: 1761, 1371, 1225, 1215, 1088, 1063, 1039 cm^{-1}.

MS (FAB^+): 413.3 $(M + Na)^+$, 331.2 (M − AcO), 169.0.

MS (ES^+): 803.2 $(2M + Na)^+$, 413.2 $(M + Na)^+$.

MS (ES^-): 361.3 $(M - Et)^+$.

Crystal structure determination

The sample used in the structure determination was recrystallised from MeOH. The structure of **8** was solved by direct methods with SHELXS-97[16] and refined by least squares methods using SHELXL-97.[17] Refinement proceeded smoothly to the values given and all H-atoms were placed geometrically and refined using a riding model. The absolute configuration was not determined by anomalous dispersion effects in the diffraction measurements, and thus the enantiomer was assigned by reference to an unchanging chiral centre in the synthetic procedure.

Table 1. Crystal Data and Structure Refinement for **8**

CCDC deposit no.	175193
Color	Colorless
Chemical formula	$C_{16}H_{22}O_{11}$
Formula weight	390.34
Temperature (K)	120(2)
Crystal system	Triclinic
Space group	$P1$
Cell dimensions	
a (Å)	6.0209(3)
b (Å)	8.8698(5)
c (Å)	9.9818(8)
α (°)	104.965(2)
β (°)	98.522(3)
γ (°)	106.790(5)
Volume ($Å^3$)	483.91(5)
Z	1
Density (calculated density) (Mg/m^3)	1.339
Absorption coefficient (mm^{-1})	0.115
Diffractometer/scan	Enraf Nonius Kappa CCD area detector
θ range for data collection (°)	3.64–27.48
Reflections measured	6289
Independent/observed reflections	06289 [$R_{int} = 0.0938$]/2106 [$I > 2\sigma(I)$]
Data/restraints/parameters	2106/3/249
Goodness of fit on F^2	1.033
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0578$, $wR_2 = 0.1356$
R indices (all data)	$R_1 = 0.0844$, $wR_2 = 0.1515$

Table 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters (Å $\times 10^3$) for **8**

Atom	x	y	z	U_{eq}[a]
C1	4400(7)	1276(5)	2072(4)	21(1)
C2	3712(7)	922(5)	3385(4)	23(1)
C3	5309(7)	105(5)	4002(4)	23(1)
C4	5359(7)	−1385(5)	2861(3)	22(1)
C5	6081(7)	−805(5)	1612(4)	22(1)
C6	6141(7)	−2213(5)	400(4)	23(1)
C7	3441(9)	2812(5)	627(5)	33(1)
C8	1415(10)	3234(7)	−27(6)	44(1)
C9	2291(7)	2974(5)	4655(4)	27(1)
C10	2993(9)	4434(7)	5971(5)	47(1)
C11	5811(11)	169(8)	6421(6)	55(2)
C12	4446(13)	−288(8)	7492(6)	63(2)
C13	6518(5)	−3448(5)	3547(5)	30(1)
C14	8632(9)	−3896(6)	4027(6)	40(1)
C15	8698(10)	−3570(6)	−508(5)	42(1)
C16	9218(11)	−2954(7)	−1721(6)	49(1)
O1	2677(5)	1795(3)	1402(3)	26(1)
O2	4141(5)	2431(3)	4494(3)	27(1)
O3	4353(5)	−426(4)	5106(3)	30(1)
O4	7193(5)	−1924(3)	3443(3)	26(1)
O5	4317(5)	−210(3)	1060(3)	24(1)
O6	8311(5)	−2325(4)	605(3)	33(1)
O7	5460(6)	3254(5)	504(4)	48(1)
O8	333(5)	2346(4)	3868(3)	33(1)
O9	7851(9)	1000(9)	6680(5)	119(3)
O10	4464(6)	−4325(4)	3265(5)	55(1)
O11	4475(5)	−3079(4)	−584(3)	33(1)

[a] U_{eq} is defined as one third of the orthogonalized U_{ij} tensor.

Crystal data and structure refinement details are listed in Table 1. The entire process of data collection, cell refinement, and data reduction was accomplished by means of the programs DENZO[18] and COLLECT:[19] correction for absorption was by means of SORTAV.[20] Other software packages used were ORTEP-3 for Windows,[21] PLATON, [22] and OSCAIL.[23] Final atom coordinates and equivalent isotropic displacement parameters are listed in Table 2. Atomic coordinates, bond angles and lengths, torsional angles, and thermal parameters

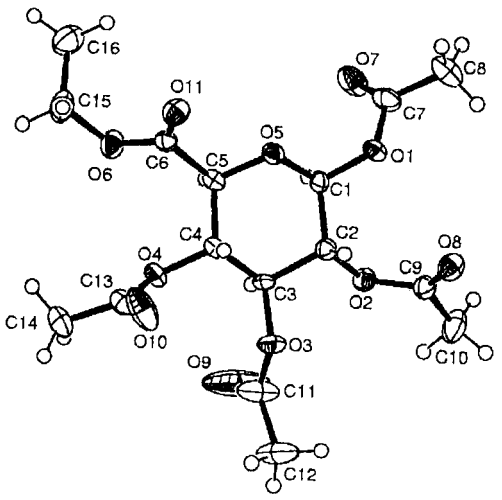


Fig. 1. Atom arrangements and numbering system for **8**.

have been deposited at the Cambridge Crystallographic Data Centre: deposition no: 175193.

Results and discussion

A standard procedure was used to obtain **8** from a well-characterised sample of **10** and EtOH, using *p*-(dimethylamino)pyridine and DCC as promoters. The composition of the α-, β-mixture of 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronic acids obtained on reaction of **1** and acetic anhydride depended greatly on the reaction conditions. The α:β ratios were readily determined from the different δ^1H1 signals [α: 6.29 (d, $J = 3.7$ Hz) and β: 5.85(d, $J = 6.7$ Hz)] in the NMR spectra: δ^1H1 for the α-:β-forms, respectively. Using the procedure outlined in the experimental section, only the β-form was isolated; lower reaction temperatures generally led to a higher proportion of the α-form. Full characterisation of **8** was achieved by X-ray crystallography and also by NMR and IR spectroscopy, and by FAB and ES mass spectrometry. Complete assignment of the 400 MHz ^{1}H NMR spectrum was aided by a 1D-TOCSY experiment. The CH_2 protons in the ethyl ester group at C6 are diastereotopic. The NMR spectra, especially the J(H,H) values for ring H atoms, indicate a chair conformation for the pyranose ring.

Table 3. Selected Bond Lengths (Å) and Angles (°) for **8** at 120(2) K

C5—O5	1.422(5)	C1—O1	1.406(5)
O5—C1	1.432(4)	C2—O2	1.436(5)
C1—C2	1.513(6)	C3—O3	1.440(5)
C2—C3	1.518(6)	C4—O4	1.445(5)
C3—C4	1.515(6)	C5—C6	1.520(6)
C4—C5	1.535(5)		
C5—O5—C1	110.6(3)	O5—C1—C2	109.6(3)
C1—C2—C3	110.1(3)	C2—C3—C4	110.9(3)
C3—C4—C5	108.4(3)	C4—C5—O5	107.7(3)
O5—C1—O1	106.0(3)	C2—C1—O1	108.8(3)
C1—C2—O2	110.2(3)	C3—C2—O2	105.2(3)
C2—C3—O3	107.7(3)	C4—C3—O3	109.4(3)
C3—C4—O4	108.4(3)	C5—C4—O4	107.4(3)
C4—C5—C6	112.1(3)	O5—C5—C6	107.2(3)

Crystal structure

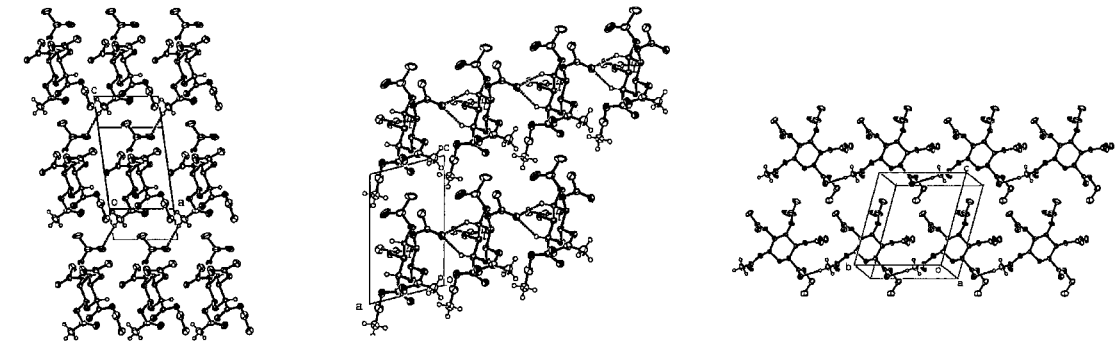
Crystals of **8**, suitable for X-ray determination, were obtained from methanol solution. The atom numbering system is shown in Fig. 1. Selected bond angles and lengths are given in Table 3.

The pyranose ring in **7** has a near ideal $^4C_1$ conformation. The Cremer and Pople puckering parameters,[24] as calculated by the PLATON program[22] are $Q = 0.602(4)$ Å, $\theta = 7.1(4)^\circ$, $\phi = 325(3)^\circ$, which suggests a slight distortion in the direction towards $^oH_5$.[25] Structures of the related compounds, **5**–**7**,[9–11] also have conformations close to $^4C_1$. The anomeric C—O [C1—O1] bond length in **8** at 1.405(5) Å is significantly shorter than all the other ring carbon to oxygen

Table 4. Soft H-Bonds in **8**

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (°)
Intermolecular				
C3—H3···O8^{i}	1.00	2.29	3.155(5)	143.8
C5—H5···O8^{i}	1.00	2.35	3.231(5)	146.2
C8—H8A···O9^{ii}	0.98	2.46	3.383(7)	156.1
C8—H8B···O11^{iii}	0.98	2.55	3.517(6)	167.4
Intramolecular				
C3—H3···O9	1.00	2.21	2.665(6)	105.7
C4—H4···O10	1.00	2.28	2.700(5)	104.0

Note: Symmetry operation: i: $x + 1$, y, z; ii: $x - 1$, y, $z - 1$; iii: x, $y + 1$, z.



a *b* *c*

Fig. 2. H-bonding interactions in **8**: (a) C8─H8A···O9^{ii}, which provides chains in the [$\bar{0}1\bar{1}$] direction; (b) C3─H3···O8^{i} and C5─H5···O8^{i}, which provides chains in the [100] direction; and (c) C8─H8B···O11^{iii}, which provides chains in the [010] direction. Symmetry operations: i: $x + 1, y, z$; ii: $x - 1, y, z - 1$; iii: $x, y + 1, z$.

bond lengths, C(n)─O(n); n = 2–4, which range from 1.437(5) to 1.457(5) Å. This agrees with findings in other similar fully substituted molecules, including **5–7**.[9–11]

There are various soft C─H···O hydrogen bonds in **8**, see Table 4. All four intermolecular H-bonds involve carbonyl oxygens in **8**: the only carbonyl oxygen not involved in intermolecular H-bonding is O7, i.e., that in the ester unit at the anomeric position. A 3D network is set up from the combinations of chains in the [$\bar{0}1\bar{1}$] direction arising from C8─H8A···O9^{ii} interactions, chains in the [100] direction from C3─H3···O8^{i} and C5─H5···O8^{i} interactions, and chains in the [010] direction from C8─H8···O11^{iii}, see Fig. 2.

Compounds **5–7** are also fully derivatised β-D-glucuronic acid derivatives, only differing with **8** in each having alkoxy groups at the anomeric position rather than an ester unit.[9–11] However, there are marked differences in the H-bonding interactions in the four molecules **5–8** in terms of the numbers of H-bonds present, the division between inter- and intramolecular H-bonds, and the acceptor centres used. In **5**, intermolecular H-bonding involves the carbonyl oxygen in the ester group at C2, while the intramolecular H-bond acceptors are the carbonyl oxygens in the C2 and C4 ester groups. The result in **5** is thus to form chains of molecules.[9] In **6**, there are two intermolecular H-bonds, both having carbonyl ester oxygen acceptors (at C2 and C3), which provides a 3D network. The sole intramolecular H-bond in **6** has the carbonyl oxygen at C4 as the acceptor.[10] In contrast, in **7**, the single intermolecular H-bonding involves the ether oxygen at the anomeric position, i.e., at C1: intramolecular H-bonding, however, utilises both carbonyl oxygens (at C2, C3, and C4) and the ring oxygen as the acceptor centres.[11]

It is very clear that intermolecular interactions, and thus supramolecular arrangements, are very difficult to predict.

Acknowledgments

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