Structure and conformation of tri-*O*-acetyl-D-glucal dimer in solid state and in solution

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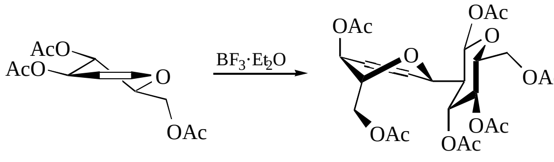
X-Ray crystallography and ^{1}H NMR spectroscopy indicate that the conformations of both rings A and B and the relative orientation of the rings in the C-linked disaccharide 1,3,4,6-tetra-*O*-acetyl-2-*C*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2-deoxy-β-D-glucopyranose in solution are virtually identical to the crystalline structure.

Due to increasing importance of *C*-disaccharides as mimics of natural *O*-disaccharides, we became interested in the chemistry of compounds with only one C–C bond between monosaccharide units.[1] The first example of this type, reported by R. J. Ferrier and N. Prasad,[2] was crystalline dimerisation product 1,3,4,6-tetra-*O*-acetyl-2-*C*-[4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl]-2-deoxy-β-D-glucopyranose **2**, obtained in 10% yield upon the treatment of 3,4,6-tri-*O*-acetyl-D-glucal **1** with boron trifluoride in benzene (Scheme 1).[†]



1 **2**

Scheme 1

The structural assignment of **2** was based[2] upon ^{1}H NMR (100 MHz) coupling constants from cyclohexene systems[3] and 2,3-dideoxy-2-eno-D-pyranoses[4,5] with $_5H^0$ conformation. Those spectra are now not state of the art because of non-first-order effects, poor resolution and overlap of signals. The reliability of chemical reasoning and deriving of the structure from optical rotation data[2] is also questionable.[6]

Through the TOCSY and ROESY ^{1}H NMR investigation of a saturated *C*-disaccharide prepared by hydrogenation of **2**, Wessel and Englert[6] have indirectly confirmed the original structural assignment for **2**.[2] Steel *et al.*[7] reported the NOE confirmation of a structure for a major product obtained in $AcClO_4$-induced dimerisation of **1**. However they postulated a different anomeric form with an axial acetoxy group at C(1).[7] In order to obtain a direct proof for the structure of **2** and to verify the NMR criteria for *C*-disaccharides of this type,[1] we have performed an X-ray crystal structure analysis and ^{1}H NMR measurements for compound **2**.

The conformational assignment for saturated ring A in **2** (Figure 1) is rather straightforward. The large spin–spin coupling constants $H(1)^A$–$H(2)^A$, $H(2)^A$–$H(3)^A$, $H(3)^A$–$H(4)^A$ and $H(4)^A$–$H(5)^A$ (Table 1) point to the *trans*-diaxial orientation of these pairs of protons, and, consequently, to the equatorial position of all substituents. The anomeric configuration is, therefore, β-D-gluco. For the conformational assignment of unsaturated ring B, Ferrier and Prasad[2] used the three-bond vicinal and four-bond allylic–vinylic coupling constants in cyclohexene and dihydropyran systems:[2,3–5] the vicinal coupling ^3J ~ 2 Hz and the allylic coupling ^4J –2.5 Hz for the quasi-axial allylic proton, and the vicinal coupling ^3J ~ 5 Hz and the allylic coupling ^4J –0.3 Hz for the quasi-equatorial proton. The values for conformationally biased 4-*tert*-butyl-5,6-dihydro-4*H*-pyran (2.2 Hz for vicinal and 2.0 Hz for allylic coupling of quasi-axial proton) obtained later[8] are consistent with these estimations. The coupling constants were believed to be appreciably smaller for $H(1)^B$ due to the electronegativity of the endocyclic oxygen.[2] Therefore, $H(1)^B$, showing splittings of 1.2 and 2.0 Hz, was concluded to be quasi-axial, and $H(4)^B$ with splittings of 0.3 and 5.2 Hz, quasi-equatorial.[2] The small coupling constant between $H(4)^B$ and $H(5)^B$ of 1.7 Hz supports a *gauche* orientation of these protons and, consequently, a *trans*-diaxial position of the 4^B-acetoxy and 5^B-acetoxymethyl groups.[2] Thus, the NMR data are in accordance with the structure of **2** (Figure 1).

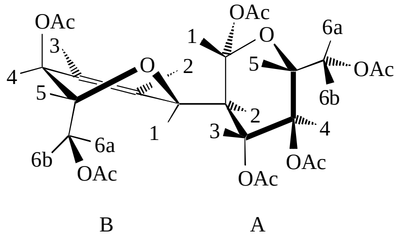


Figure 1 Structural assignment of compound **2** based upon ^{1}H NMR data (Table 1).

Our measurements of signal splitting in ^{1}H NMR spectra gave similar values for three- and four-bond couplings (Table 1), that support the suggested structure, provided the structural NMR criteria are valid for dihydropyran rings. The $CDCl_3$ solution data are consistent with those previously published.[3]

The average position of the two ring planes in **2** may be considered nearly perpendicular based upon the small coupling constant between $H(2)^A$ and $H(1)^B$. The value $^3J_{H(2)^A,H(1)^B}$ 1.2–1.8 Hz points to a torsion angle of approximately 52–56° or 111–114° according to the Altona–Haasnoot equation[9] (for a review of different versions of the Karplus equation see ref. 10).

Interestingly, the conformational equilibrium for both rings appears to be strongly biased. The absence of a solvent dependence for intracyclic coupling constants (Table 1) also supports this idea. It is reasonable to assume that alternative conformations of the rings do not contribute to any detectable extent to the measured coupling constants.[‡]

An NOE between $H(2)^A$ and $H(2)^B$, but no NOE at $H(2)^B$ when $H(1)^A$ was irradiated (the mixing time 300 ms), supports the overall conformation of **2** (Figure 1).

[†] Compound **2** was synthesised according to a procedure proposed by Ferrier and Prasad[2] and modified by us[1] (Scheme 1) and separated from the mixture of products by flash chromatography on silica gel (ethyl acetate–hexane). The assignment of signals was made based upon COSY, NOESY and HETCOR experiments (Varian Mercury spectrometer, 300 MHz).

[‡] In case of the anomeric dimer[7] the alternative conformation of ring B with a quasi-axial ring A, and a *trans*-diequatorial position of the 4^B-acetoxy and 5^B-acetoxymethyl groups was suggested based on the NOE data.

Table 1 Coupling constants and chemical shifts for **2** in various solvents (Varian Mercury spectrometer, 300 MHz).

	^3J	$CDCl_3$		[$^2H_6$]acetone		[$^2H_5$]pyridine		[$^2H_6$]DMSO	
		δ/ppm	^3J/Hz	δ/ppm	^3J/Hz	δ/ppm	^3J/Hz	δ/ppm	^3J/Hz
H(1)^A	1^A–2^A	5.85	9.0	5.73	9.0	6.32	9.0	5.82	9.0
H(2)^A	2^A–1^A	2.14	9.0	2.09	9.6	2.45	9.0	2.30	9.6
	2^A–3^A		11.1		11.1		10.5		10.5
	2^A–1^B		1.8		1.8		1.2		0.9
H(3)^A	3^A–2^A	5.38	11.1	5.26	11.4	5.83	10.8	5.30	11.1
	3^A–4^A		9.3		9.0		9.0		9.3
H(4)^A	4^A–3^A	4.93	9.9	4.77	9.3	5.37	9.6	4.81	9.9
	4^A–5^A		9.9		9.3		9.6		9.9
H(5)^A	5^A–4^A	3.74	10.2	~3.9	–[a]	4.11	10.2	–[a]	–[a]
	5^A–6^A		3.6		–[a]		4.2		–[a]
	5^A–$6b^A$		2.1		1.5		2.1		–[a]
H(6a)^A	$6a^A$–5^A	4.28	4.2	4.13	6.0	4.56	4.2	–[a]	–[a]
	$6a^A$–$6b^A$		12.3		13.0		12.3		–[a]
H(6b)^A	$6b^A$–5^A	3.99	1.8	3.84	2.1	4.31	2.4	–[a]	–[a]
	$6b^A$–$6a^A$		12.6		12.0		12.3		–[a]
H(1)^B	1^B–2^B	4.25	<1	4.23	1.8	~4.4	–[a]	–[a]	–[a]
	1^B–3^B		<1		<1		–[a]		–[a]
	1^B–2^A		2.1		1.8		1.2		–[a]
H(2)^B	2^B–1^B	5.95	<1	6.00	1.8	6.07	1.2	–[a]	–[a]
	2^B–3^B		10.5		10.5		10.5		–[a]
	2^B–4^B		1.5		<1		<1		–[a]
H(3)^B	3^B–1^B	~5.8	–[a]	5.76	2.4	5.93	2.4	–[a]	–[a]
	3^B–2^B		–[a]		9.9		10.5		–[a]
	3^B–4^B		4.8		5.4		5.7		–[a]
H(4)^B	4^B–2^B	4.71	<1	4.66	1.2	4.98	<1	–[a]	–[a]
	4^B–3^B		5.4		6.0		5.4		–[a]
	4^B–5^B		<1		1.2		0.9		–[a]
H(5)^B	5^B–4^B	4.14	<1	3.99	1.8	–[a]	–[a]	–[a]	–[a]
	5^B–$6a^B$		9.9		10.5		–[a]		–[a]
	5^B–$6b^B$		3.6		3.9		–[a]		–[a]
H(6a)^B	$6a^B$–5^B	4.43	9.6	4.30	9.6	4.66	9.9	4.31	9.9
	$6a^B$–$6b^B$		12.0		12.0		12.0		12.3
H(6b)^B	$6b^B$–5^B	3.72	3.6	3.75	3.6	3.98	3.6	3.89	3.6
	$6b^B$–$6a^B$		12.0		12.0		12.3		12.3

[a] Overlapped.

Note that the reference values used for coupling constants in 2,3-dideoxy-2-eno-D-pyranoses[4,5] are actually valid for a $_5H^0$-conformation. For compound **2**, however, a $_5H^0$-conformation, as discussed above, could possess significantly different NMR coupling constants. Hence, an additional proof of this structure is still needed, which can be obtained by X-ray crystal structure analysis.

In this work, the molecular structure of compound **2** has been established unambiguously by X-ray crystallographic data[§] (Figure 2).

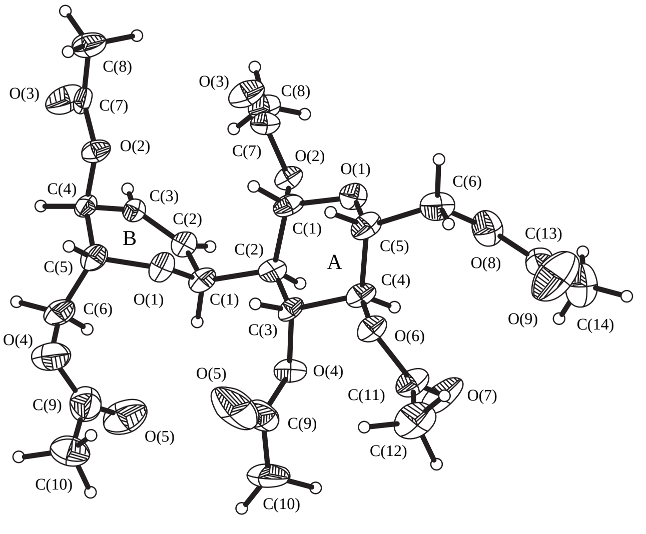
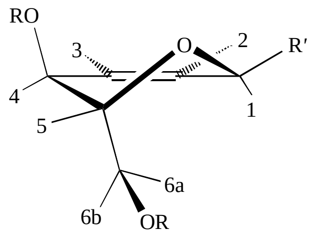


Figure 2 Molecular structure of compound **2**. Selected torsion angles (°): O(1)^B–C(1)^B–C(2)^A–C(1)^A –66.6(6), O(1)^B–C(1)^B–C(2)^A–C(3)^A 55.8(6), C(2)^B–C(1)^B–C(2)^A–C(1)^A 56.8(6), C(2)^B–C(1)^B–C(2)^A–C(3)^A 179.2(4).

Analysis of the data shows that there is virtually no difference between the solution and crystal conformations of both rings in compound **2**. The proton coupling constants correspond satisfactorily to the endocyclic torsion angles in the crystal structure (*cf.* Figures 1 and 2). Also, the relative orientation of the rings does not change dramatically in solution. We determined the H(1)^B–C(1)^B–C(2)^A–H(2)^A torsion angle to be +58° in the solid state (MM2 estimation[12] based on X-ray data). It agrees well with our torsion angle of approximately +52–56° obtained by the Altona–Haasnoot equation.

Moreover, the orientation of the 5^B-acetoxymethyl group with respect to ring B in solution corresponds perfectly to the solid state geometry. The value $^3J_{H(5)^B,H(6a)^B}$ 9.9–10.5 Hz points to the predominantly antiperiplanar orientation of these protons (*cf.* Figures 1 and 2). The solid state conformation of the 5^A-acetoxymethyl group (Figure 2) is also preferred in $CDCl_3$

[§] *X-ray diffraction analysis*. Crystals of compound **2** as thin long colourless needles were grown from methanol. Crystal data for **2** were collected at 173 K with MoKα-radiation on a Siemens SMART Platform CCD diffractometer: $C_{24}H_{32}O_{14}$, $M = 544.50$, orthorhombic crystals, space group $P2_12_12_1$, $a = 5.6647(4)$, $b = 13.4269(9)$, $c = 34.744(2)$ Å with $\alpha = \beta = \gamma = 90°$, $V = 2642.6(3)$ Å^3, $Z = 4$, $D_{calc} = 1.369$ g cm^{-3}. The space group $P2_12_12_1$ was determined based upon systematic absence of reflections and intensity statistics.[11] The structure of compound **2** was solved by a direct method. All non-hydrogen atoms were refined with anisotropic displacement parameters; the hydrogen atom coordinates were refined isotropically. Based upon the starting material, the absolute configuration of **2** is D. $R = 0.0812$ for 2613 independent observed reflections [$I > 2\sigma(I)$], $wR_2 = 0.1598$. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 1999. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/41.



$^3J_{\mathrm{H1,H2}}$	0–2 Hz
$^4J_{\mathrm{H1,H3}}$	0–2.5 Hz
$^3J_{\mathrm{H4,H3}}$	4.8–5.7 Hz
$^4J_{\mathrm{H4,H2}}$	0–1.5 Hz

Figure 3 Refined coupling constants for $_5H^0$-conformation of 2,3-dideoxy-2-enopyranose system.

and pyridine. The small coupling constants $^3J_{\mathrm{H(5)^A,H(6a)^A}} \cong 4$ Hz and $^3J_{\mathrm{H(5)^A,H(6b)^A}} \cong 2$ Hz (Table 1) are indicative of the C(5)^A–H(5)^A bond bisecting the H(6a)^A–C(6)^A–H(6b)^A angle (Figure 1).

The data of X-ray crystal structure analysis and NMR measurements confirm the structure of compound **2** as found by Ferrier *et al*.[2] The conformation was determined to be fairly rigid. The all-equatorial conformation of ring A is totally predominant for obvious reasons. The A moiety of molecule **2**, as a very bulky substituent, strongly prefers the quasi-equatorial position, and forces 4^B-acetoxy and 5^B-acetoxymethyl groups to adopt an unusual diaxial conformation. Our conclusion was also supported by molecular mechanics calculations (MM2[12]). The conformation under consideration is also fixed by multiple intramolecular dipole–dipole and van der Waals attractions (note the parallel orientation of the substituents in Figure 2, which has been reproduced by molecular mechanics). Intermolecular interactions of the same character probably contribute to the stabilisation of this conformation in the crystal state: all molecules are arranged in pairs by an attraction between the anti-parallel chains C(8)–C(10) (Figure 2).

The results of this work also allow us to suggest a set of approximate 'standard' coupling constants for use in the structural analysis of 2,3-dideoxy-2-enopyranose systems with the α-*erythro* configuration in the unusual $_5H^0$-conformation (Figure 3).

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