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Methyl 4-*O*-β-D-galactopyranosyl α-D-glucopyranoside (methyl α-lactoside)

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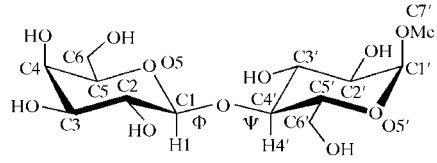
Methyl α-lactoside, $C_{13}H_{24}O_{11}$, (I), is described by glycosidic torsion angles φ ($O5_{gal}-C1_{gal}-O1_{gal}-C4_{glc}$) and ψ ($C1_{gal}-O1_{gal}-C4_{glc}-C5_{glc}$), which have values of −93.52 (13) and −144.83 (11)°, respectively, where the ring atom numbering conforms to the convention in which C1 is the anomeric C atom and C6 is the exocyclic hydroxymethyl ($-CH_2OH$) C atom in both residues. The linkage geometry is similar to that observed in methyl β-lactoside methanol solvate, (II), in which φ is −88.4 (4)° and ψ is −161.3 (4)°. As in (II), an intermolecular $O3_{glc}-H\cdots O5_{gal}$ hydrogen bond is observed in (I). The hydroxymethyl group conformation in both residues is *gauche–trans*, with torsion angles ω_{gal} ($O5_{gal}-C5_{gal}-C6_{gal}-O6_{gal}$) and ω_{glc} ($O5_{glc}-C5_{glc}-C6_{glc}-O6_{glc}$) of 69.15 (13) and 72.55 (14)°, respectively. The latter torsion angle differs substantially from that found for (II) [−54.6 (2)°; *gauche–gauche*]. Cocrystallization of methanol, which is hydrogen bonded to $O6_{glc}$ in the crystal structure of (II), presumably affects the hydroxymethyl conformation in the Glc residue in (II).

Comment

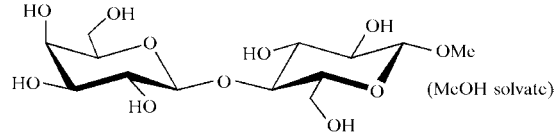
The global structures of biologically important oligosaccharides are largely determined by the conformations of their constituent glycosidic linkages and of their exocyclic substituents, commonly hydroxymethyl and *N*-acetyl groups. Systematic structural comparisons within this series of biomolecules are hampered currently by the limited number of reported crystal structures containing biologically relevant glycosidic linkages in different structural contexts. Additional complications arise from the presence of either free or protected reducing ends, often in the latter case with diverse functionality.

The crystal structure of methyl α-lactoside, (I), has not been reported, but that of methyl β-lactoside methanol solvate, (II), has been published (Stenutz *et al.*, 1999). Given the interest in deciphering the role of anomeric configuration in determining preferred linkage geometry, (I) was synthesized and crystallized from methanol. Unlike (II), (I) crystallizes without the inclusion of a methanol solvent molecule.

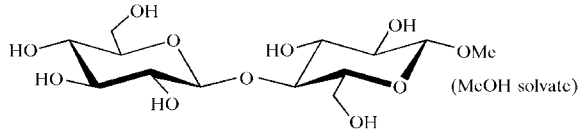
The structural parameters in (I) (Fig. 1) are compared with those in (II) and methyl β-cellobioside methanol solvate, (III) (Ham & Williams, 1970) (Table 2). The C1′—O1′ bond in (I) is considerably longer than those in (II) and (III) (by ∼0.02 Å), consistent with its change from an equatorial to an axial



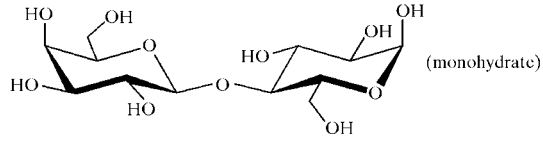
(I) (methyl α-lactoside)



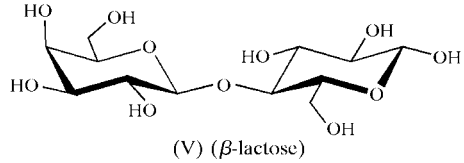
(II) (methyl β-lactoside)



(III) (methyl β-cellobioside)



(IV) (α-lactose)



(V) (β-lactose)

orientation. Likewise, the C4—O4 bonds in (I) and (II) are longer than that in (III) (by ∼0.01 Å), again as a result of the axial orientation in the former structures. The C1′—O5′ and C2′—O2′ bond lengths also vary considerably in (I)–(III), with

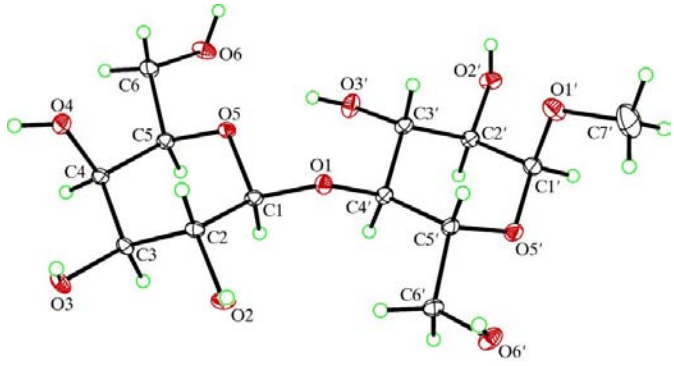


Figure 1
The structure and atomic numbering of methyl α-lactoside, (I). Displacement ellipsoids are shown at the 50% probability level for the C and O atoms. H atoms are shown as spheres of arbitrary radii.

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both bonds longer in (III) than in (I) and (II). Interestingly, these bond lengths differ in (II) and (III), despite their similar C1′ configurations. Endocyclic C—C bond lengths in (I)–(III) involving non-anomeric C atoms appear on average to be slightly longer than the exocyclic C5—C6 bonds. This behavior may explain in part the generally larger $^1J_{C5,C6}$ values observed in aldohexopyranosyl rings compared with the $^1J_{CC}$ values involving the ring C atoms (Wu *et al.*, 1992).

The glycosidic C—O—C bond angles are larger for the internal linkages of (I)–(III) (∼116°) than for terminal methyl aglycones (∼113°) (Table 2), presumably owing to the greater steric demands of the reducing residue compared with the methyl group. Imaginary O3′—H···O5 bond angles vary from 134 to 150°, which is notably smaller than the value of 180° considered optimal for hydrogen bonding. Related bond angles for the methanol solvate hydrogen bonding in (II) and (III) are somewhat larger (∼164°).

The internal pyranosyl ring torsion angles differ considerably from the idealized values of 60° (Table 2). Torsion angles solely involving C atoms appear more deformable than those involving the ring O atom, assuming values of between ∼44 and 58°. In contrast, torsion angles involving the ring O atom are nearly ideal (∼64°), although the values range from ∼57 to 70°.

The internal glycosidic torsion angles in (II) more closely resemble those in (III) than those in (I). For example, using the heavy atoms as references, φ ($O5_{gal}$—$C1_{gal}$—$O1_{gal}$—$C4_{glc}$) and ψ ($C1_{gal}$—$O1_{gal}$—$C4_{glc}$—$C5_{glc}$) differ by ∼2° in (II) and (III), whereas the corresponding values in (I) differ by ∼4 (φ) and ∼15° (ψ). In contrast, the absolute values of φ for the terminal glycosidic linkages differ by less than 4° in (I)–(III). Overall, however, glycosidic linkage conformations in (I)–(III) are highly conserved. Interestingly, recent NMR investigations of (I) and (II) in aqueous solution suggest highly similar conformations about their internal glycosidic linkages, implying that anomeric configuration at the reducing end of the disaccharide does not influence internal linkage conformation significantly.

The presence of methanol in the crystalline lattice influences the hydroxymethyl conformation significantly. In the solvates (II) and (III), methanol is hydrogen bonded to O6′, leading to values of ω' ($O5_{glc}$—$C5_{glc}$—$C6_{glc}$—$O6_{glc}$) of ∼−55° (*gauche–gauche* rotamer), whereas in (I), ω' assumes a value of 72.55 (14)° (*gauche–trans* rotamer). The values of ω ($O5_{gal}$—$C5_{gal}$—$C6_{gal}$—$O6_{gal}$) are similar in (I)–(III) (*gauche–trans* rotamer), regardless of the configuration at atom C4. In contrast, recent NMR studies showed a roughly equal distribution of *gauche–gauche* and *gauche–trans* rotamers in Glc monomers and a highly preferred *gauche–trans* rotamer (∼70%) in Gal monomers in aqueous solution (Thibaudeau *et al.*, 2004).

Intramolecular hydrogen bonding between atoms O3′ and O5 is observed in (I)–(III), with internuclear distances between the heavy atoms of ∼2.8 Å (Table 2). This distance is comparable to that observed between the methanol O atom and atom O6′ in (II) and (III), which averages 2.7 Å.

In the crystal structure of (I) (Fig. 2), intermolecular hydrogen bonds can be divided into two groups, *viz.* an infinite chain with hydrogen bonds alternating between atoms O6 and O3, and a six-membered chain starting at atom HO4, passing through HO3′ and ending at atom O5. For (II) and (III), a similar infinite chain is observed, but the finite chain contains seven members, including a link through a methanol molecule. This seven-membered chain starts at atom HO4 and ends at atom O5.

All hydroxy H atoms in (I) are involved in intermolecular hydrogen bonding as donors, while the O atoms serve as acceptors to a maximum of one hydrogen bond (Table 1). In this way, a two-dimensional hydrogen-bonded network in the (001) plane is developed. Atoms O1′, O5′, O1 and O4 are not involved in intermolecular hydrogen bonding, and atom O5 experiences intramolecular hydrogen bonding to O3′ (see above). Similar behavior is observed in (II) and (III).

Solution structures of α-lactose have been reported as a monohydrate, (IV) (Fries *et al.*, 1971), and as calcium complexes (Cook & Bugg, 1973; Bugg, 1973). The values of φ and ω in (IV) are very similar to those observed in (I) (Table 3). The pyranosyl ring distortions observed in (I) are also observed in (IV), and *gauche–trans* hydroxymethyl rotamers are found in (IV) as in (I) [the water molecule in the crystal structure of (IV) is not bonded to O6′]. Interestingly, the C1—O1—C4′ bond angle is considerably larger in (IV) (117°) than in (I) [115.26 (10)°]. The C1′—O1′ bond is shorter in (IV) (1.387 Å) than in (I) [1.4012 (19) Å], whereas the C1′—O5′ bond is longer in (IV) than in (I). These bond-length differences are attributed in part to the changes in O1′ substitution. Some of these trends are maintained when

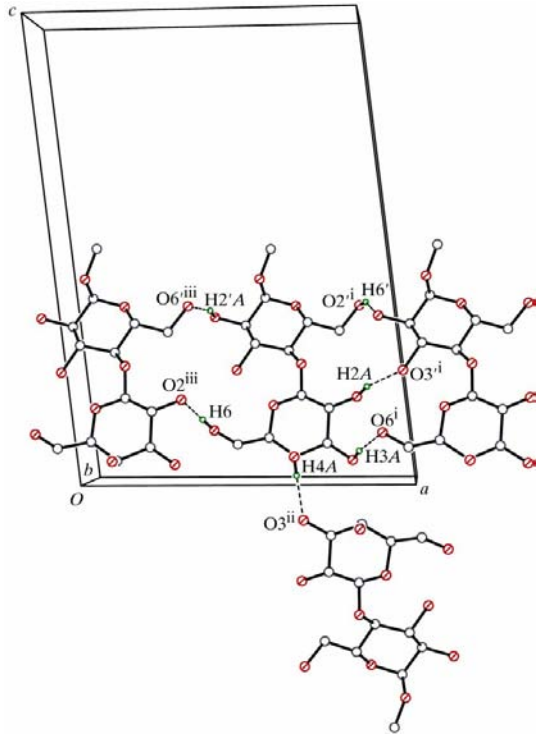

Figure 2
The hydrogen-bonding network in methyl α-lactoside. [Symmetry codes: (i) $x+\frac{1}{2}, y-\frac{1}{2}, z$; (ii) $-x+\frac{3}{2}, y-\frac{1}{2}, -z$; (iii) $x-\frac{1}{2}, y-\frac{1}{2}, z$.]

comparing (II) to β-lactose, (V) (Hirotsu & Shimada, 1974) (Table 3). In this case, the C1—O1—C4′ bond angles and C1′—O1′ bond lengths are very similar, but the C1′—O5′ bond is shorter in the glycoside. These results suggest that the effects of O1′ substitution on proximal bond lengths and angles depend on anomeric configuration. The hydroxymethyl conformation in the Glc residue of (V) is *gauche–trans*, in contrast to the *gauche–gauche* form observed in (II).

A comparison of the packing structure of the methanol solvates (II) and (III) with that of (I) is informative. In (II) and (III), the methyl aglycones are aligned along a well defined, relatively hydrophobic, channel that includes the methanol solvent molecule. This alignment appears critical to crystal formation in the methyl glycosides, as evidenced by the fact that a similar alignment is observed in (I), although apparently the structural requirements (*i.e.* hydrogen bonding) are met in this case without the need for co-crystallization of solvent methanol. Structures either lacking the methyl aglycone [*e.g.* (V)] or co-crystallizing with water [*e.g.* (IV)] do not appear to crystallize with similar channels.

Differences in packing structures, and thus hydrogen-bonding patterns, are likely to modulate the crystal structures of saccharides, thus complicating comparisons between apparently similar structures such as (I) and (IV). The presence of inter- and intramolecular hydrogen bonding, and packing forces, is expected to modulate bond lengths, angles and torsion angles in a fashion that is not currently predictable or quantifiable, and conclusions based on structural comparisons within this restricted set of structures must be viewed with this limitation in mind.

Experimental

Compound (I) was prepared by coupling 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate [(VI); 600 mg, 1.21 mmol] with methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside [(VII); 500 mg, 1.08 mmol] in the presence of silver triflate (350 mg, 1.4 mmol) in dichloromethane (20 ml) at ~253 K. When the reaction was complete (~2 h), the product was deprotected at room temperature with 400 mg of 10% Pd/C in EtOAc (20 ml), followed by a 0.1 *M* methanolic solution (15 ml) of $NaOCH_3$. Compound (VI) was prepared by standard methods (Schmidt *et al.*, 1984) and (VII) was prepared by reacting methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (450 mg, 0.97 mmol) in tetrahydrofuran (30 ml) with $NaBH_3CN$ (0.85 g, 13.7 mmol), immediately followed by the addition of 1 *N* HCl in Et_2O (14 ml). Purification of (I) was achieved by chromatography on silica gel using methanol/dichloromethane (1:4 *v*:*v*) as the solvent. Crystals were grown from methanol by slow evaporation at 277 K.

Crystal data

$C_{13}H_{24}O_{11}$
M_r = 356.32
Monoclinic, *C*2
a = 14.6984 (3) Å
b = 5.0061 (1) Å
c = 21.1204 (5) Å
β = 96.5502 (12)°
V = 1543.93 (6) Å^3
Z = 4
D_x = 1.533 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 8868 reflections
θ = 2.8–31.5°
μ = 0.14 mm^{-1}
T = 100 (2) K
Needle, colorless
0.36 × 0.22 × 0.18 mm

Data collection

Bruker SMART APEX CCD diffractometer
φ and ω scans
11448 measured reflections
2845 independent reflections
2758 reflections with $I > 2\sigma(I)$
R_{int} = 0.027
θ_{max} = 31.5°
$h = -21 \rightarrow 19$
$k = -7 \rightarrow 5$
$l = -31 \rightarrow 29$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.032
$wR(F^2)$ = 0.095
S = 1.04
2845 reflections
225 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0697P)^2 + 0.4616P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.043
$\Delta\rho_{max}$ = 0.55 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}
Absolute structure: Flack (1983), 1277 Friedel pairs
Flack parameter: 0.2 (4)

Table 1
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2—H2*A*···O3′^{i}	0.84	2.00	2.8026 (15)	161
O3—H3*A*···O6^{i}	0.84	1.92	2.7469 (14)	169
O4—H4*A*···O3^{ii}	0.84	1.99	2.8243 (14)	178
O6—H6···O2^{iii}	0.84	1.84	2.6619 (14)	167
O2′—H2′*A*···O6′^{iii}	0.84	1.89	2.6962 (14)	159
O6′—H6′···O2′^{i}	0.84	1.94	2.7138 (14)	153

Symmetry codes: (i) $x+\frac{1}{2}, y-\frac{1}{2}, z$; (ii) $-x+\frac{3}{2}, y-\frac{1}{2}, -z$; (iii) $x-\frac{1}{2}, y-\frac{1}{2}, z$.

Table 2
Comparison of geometric parameters (Å, °) in (I)–(III).

gt is *gauche–trans* and *gg* is *gauche–gauche*.

	(I)	(II)	(III)
C1—C2	1.5316 (17)	1.527 (3)	1.526 (6)
C1′—C2′	1.5268 (19)	1.516 (3)	1.513 (6)
C1—O5	1.4295 (16)	1.425 (3)	1.432 (5)
C1′—O5′	1.4156 (15)	1.413 (3)	1.434 (5)
C1—O1	1.3857 (14)	1.387 (3)	1.390 (5)
C1′—O1′	1.4012 (19)	1.384 (3)	1.379 (5)
C4′—O1	1.4467 (17)	1.437 (3)	1.436 (5)
C2—O2	1.4225 (16)	1.414 (3)	1.416 (5)
C4—O4	1.4273 (18)	1.423 (3)	1.410 (5)
C6—O6	1.4333 (17)	1.426 (3)	1.434 (5)
C2′—O2′	1.4185 (15)	1.418 (3)	1.439 (5)
C5—C6	1.5183 (18)	1.511 (3)	1.515 (6)
C5′—C6′	1.5159 (18)	1.508 (3)	1.505 (6)
O3′···O5	2.82	2.76	2.76
O(CH$_3$OH)···O6′	–	2.73	2.70
C1—O1—C4′	115.26 (10)	116.2 (2)	115.8 (3)
C1′—O1′—CH$_3$	112.66 (14)	113.7 (2)	113.1 (3)
O3′—O3′H···O5	150	141	134
O—H(CH$_3$OH)···O6′	–	164	163
C1—C2—C3—C4	−57.6	−54.8	−51.0
C1′—C2′—C3′—C4′	−54.6	−44.2	−45.0
C1—O5—C5—C4	59.6	65.0	67.4
C1′—O5′—C5′—C4′	56.6	67.6	70.1
C2—C1—O1—C4′(φ)	148.1	153.8	152.0
C2′—C1′—O1′—CH$_3$(φ')	−165.5	164.2	166.8
C1—O1—C4′—C3′(ψ)	93.6	78.4	80.3
C1—O1—C4′-C5′(ψ)	−144.8	−161.3	−160.7
O5—C1—O1—C4′(φ)	−93.6	−88.4	−91.1
O5′—C1′—O1′—CH$_3$(φ')	72.6	−77.4	−76.1
H1—C1—O1—C4′(φ)	25.8	31.9	24.3
C1—O1—C4′—H4′(ψ)	−27.5	−43.7	−47.7
O5—C5—C6—O6(ω)	69.2 (*gt*)	57.3 (*gt*)	52.4 (*gt*)
O5′—C5′—C6′—O6′(ω')	72.6 (*gt*)	−54.6 (*gg*)	−55.1 (*gg*)

Table 3
Geometric parameters in (IV) and (V).

gt is *gauche–trans* and *gg* is *gauche–gauche*.

	(IV)	(V)
C1′—C2′	1.531 (5)	1.525 (6)
C1′—O5′	1.443 (4)	1.431 (6)
C1′—O1′	1.387 (4)	1.388 (6)
C2′—O2′	1.429 (3)	1.405 (6)
O3′···O5	2.811 (4)	2.707 (6)
O(H_2O)···O2′	2.981 (4)	
C1—O1—C4′	117.1 (2)	116.5 (4)
C1—C2—C3—C4	−51.4 (3)	−56.4
C1′—C2′—C3′—C4′	−51.2 (3)	−48.8
C1—O5—C5—C4	63.7	60.0
C1′—O5′—C5′—C4′	62.9 (3)	62.5
C2—C1—O1—C4′(φ)	146.2	169.5
C1—O1—C4′—C3′(ψ)	96.0	107.7
C1—O1—C4′—C5′(ψ)	−143.0	−131.5
O5—C1—O1—C4′(φ)	−94.2	−70.9
H1—C1—O1—C4′(φ)	26.4	52.0
C1—O1—C4′—H4′(ψ)	−27.5	−7.6
O5—C5—C6—O6(ω)	59.4 (3) (*gt*)	50.5 (*gt*)
O5′—C5′—C6′—O6′(ω')	63.2 (4) (*gt*)	72.6 (*gt*)

All H atoms were clearly resolved in difference maps and were subsequently allowed for as riding, with C—H distances in the range 0.98–1.00 Å and O—H distances of 0.84 Å. For methyl and hydroxy H atoms, U_{iso}(H) values were set at $1.5U_{eq}$(C,O); for all other C atoms, U_{iso}(H) values were set at $1.2U_{eq}$(C).

Data collection: *APEX2* (Bruker–Nonius, 2004); cell refinement: *APEX2* and *SAINT* (Bruker–Nonius, 2004); data reduction: *SAINT* and *XPREP* (Sheldrick, 2003); program(s) used to solve structure: *XS* (Sheldrick, 2001); program(s) used to refine structure: *XL* (Sheldrick, 2001); molecular graphics: *XP* (Sheldrick, 1998); software used to prepare material for publication: *XCIF* (Sheldrick, 2001) and *enCIFer* (Allen *et al.*, 2004).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1865). Services for accessing these data are described at the back of the journal.

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