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The concomitant crystallization of two polymorphs of 1-deoxy-α-D-tagatose

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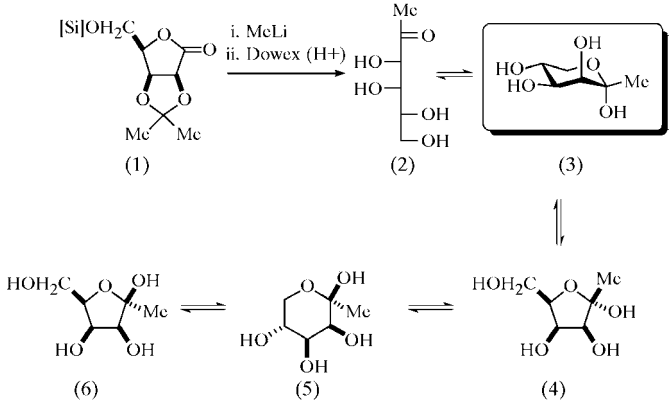
The crystalline form of 1-deoxy-D-tagatose, $C_6H_{12}O_5$, is shown to be 1-deoxy-α-D-tagatopyranose; the absolute configuration is determined by use of D-lyxono-1,4-lactone as the starting material. The title compound crystallized as concomitant polymorphs from a mixture of ethyl actate and methanol. Although the melting points of the materials differ by 7 K, the molecular conformations are almost identical and, in both polymorphs, each molecule is subject to four O—H···O hydrogen bonds.

Comment

The properties of 1-deoxy ketohexose sugars have been little studied. The crystal structure of 1-deoxy-D-sorbose has recently been published (Jones *et al.*, 2006) and as part of a project to extend the range of simple monosaccharide derivatives, 1-deoxy-D-tagatose, (2), was synthesized. 1-Deoxy-D-tagatose has previously been synthesized (Wolfrom & Bennett, 1965; Dills & Covey, 1981; Cubero & Poza, 1985), but no crystal structure has been reported.



The demand for the large-scale production of rare sugars by biotechnological (Izumori, 2002, 2006; Granstrom *et al.*, 2004) and chemical (Beadle *et al.*, 1992) methods is driven by the demand for alternative foodstuffs (Skytte, 2002) and D-tagatose itself is used as a low-calorie sweetener (Levin, 2002; Howling & Callagan, 2000; Bertelsen *et al.* 1999). Rare monosaccharides themselves, however, have been found to demonstrate interesting pharmaceutical properties; for example, D-psicose (Takata *et al.*, 2005; Menavuvu *et al.*, 2006) and D-allose (Sui *et al.*, 2005; Hossain *et al.*, 2006) have significant chemotherapeutic properties and D-tagatose has been found to be an antihyperglycemic agent (Zehner *et al.*, 1994; Donner *et al.*, 1999) and therefore potentially useful in the treatment of diabetes.

1-Deoxy-D-tagatose, (2), was synthesized from protected D-lyxono-1,4-lactone, (1), by methylation using methyl lithium and subsequent deprotection with dowex resin (H+) (Jones *et al.*, 2007). The deoxy sugar was readily crystallized and the present paper firmly establishes that, as for 1-deoxy-D-sorbose (Jones *et al.*, 2006), 1-deoxy-D-tagatose exists in the crystalline state as the α-anomer of the pyranose ring form (3), in a chair conformation. Two polymorphic forms were observed to crystallize from the same mother liquor but at different rates. The two forms were needles and hexagonal plates. The hexagonal plates were found to crystallize out after 16 h, whereas the needles were only observed after 72 h. In both polymorphic forms, the title compound was in the α-pyranose

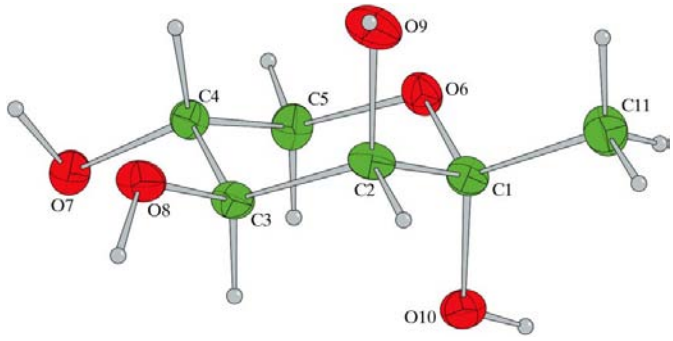


Figure 1
The title compound from the needle crystals, with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radii.

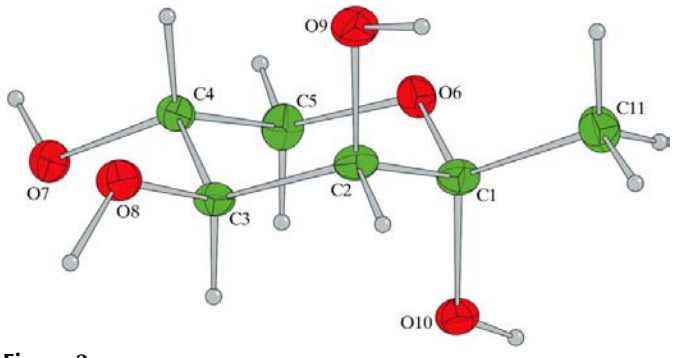


Figure 2
The title compound from the hexagonal plate crystals, with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radii.

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form (3). In contrast, in aqueous solution it exists as an equilibrium mixture of the open chain, (2), α-pyranose, (3), α-furanose, (4), β-pyranose, (5), and β-furanose, (6), forms.

Crystals of two distinctly different habits, *viz*. needles and plates, were observed in approximately equal quantities in the mother liquor. Cell parameters were determined for both forms and found to be different. Full data collections and structure solutions were performed on a sample of each habit. With the exception of the hydroxyl H atoms, the molecules were essentially identical (Figs. 1 and 2), with an r.m.s. displacement between equivalent atoms of 0.05 Å after superimposing one molecule on the other.

The formation of two different polymorphs of a material simultaneously in the same environment is termed 'concomitant polymorphism' (Bernstein *et al.*, 1995). There seems to be some uncertainly about the frequency of occurrence of this phenomenon. Bernstein *et al.* (1995) remark that it is rarely reported in the recent literature, but that it had been widely observed (von Groth *et al.*, 1906) before the advent of X-ray crystallography. Perhaps this is because the thrust of many structure determinations has been focused on the molecular structure rather than the crystal structure, so that the work was performed on the first good quality crystal obtained rather than on a survey of a whole batch of material. Bowes *et al.* (2003) support this: 'our identification, essentially by chance, of four such examples within a rather short space of time suggests to us that the phenomenon of concomitant polymorphism may, in fact, be a rather common one, certainly far more common than the current literature tends to suggest, but one which goes largely unnoticed.' In recent years, the current authors have analysed almost 100 saccharide derivatives and this is the first one where polymorphism was clearly evident.

The different polymorphs arise from differences in the hydrogen-bonding network (Figs. 3 and 4, and Tables 1 and 2). The most densely packed molecules occur in the plate-like crystals. As is usual in $P2_12_12_1$, the molecules are linked into hydrogen-bonded helices around the twofold screw axes. The relationship between the two polymorphs is most easily visualized by concentrating on the helices containing atoms O7 and O10. In the more dense polymorph, this is a helix involving four molecules. One turn consists of the sequence O7—H7···O10—H10···O7—H7···O10—H10···O7. In projection along the *a* axis, the four O atoms form an approximate square (Fig. 4). In the less dense polymorph, the helix is expanded to contain contributions from six molecules. Atom O10 still donates to atom O7, but atom O7 is now linked *via* atoms O8 and O9 back to an equivalent molecule that uses atom O10. One turn of this extended sequence contains O10—H10···O7—H7···O8···H9—O9 and the same pattern repeated by symmetry (Fig. 3). In the plate-like crystal, molecules 1 and 2 lie more or less side by side. In the needle-shaped crystals they are displaced with respect to each other so that the cross-section of the helix becomes oval. Other O—H···O hydrogen bonds crosslink these helices. There are no unusually short intermolecular contacts.

In summary, 1-deoxy-D-tagatose, (2), exists in the crystalline state as 1-deoxy-α-D-tagatopyranose, (3); the absolute configuration is determined by the use of D-lyxono-1,4-lactone as the starting material. The X-ray crystal structure determined the stereochemistry at the anomeric position as being α, with the hydroxyl group in the axial position. As well as the potential biological properties of 1-deoxy ketoses, they are likely to provide a new set of building blocks for the synthesis of a wide variety of complex biomolecules.

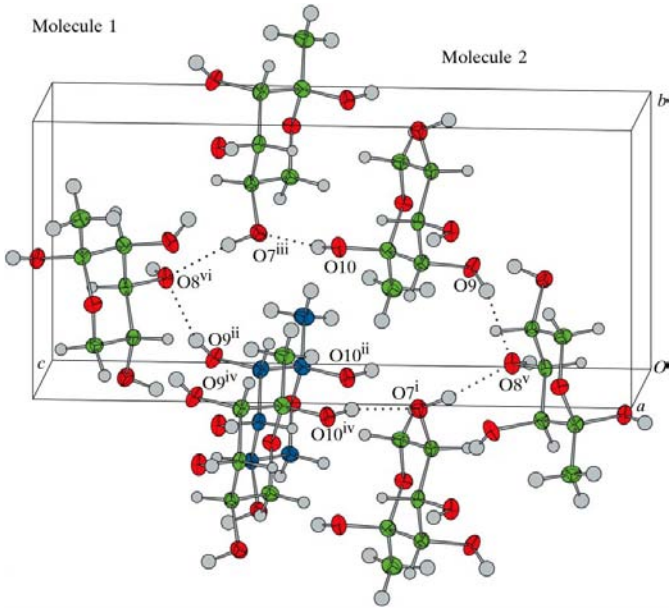

Figure 3
Part of the three-dimensional hydrogen-bonding network in the needle crystals, viewed approximately parallel to *a* and showing one turn of the helix (starting from the molecule with symmetry code ii). Molecules labelled 1 and 2 are described in the *Comment*. [Symmetry codes: (i) x, $y-1$, z; (ii) $x-\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (iii) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (iv) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (v) $-x+2, y-\frac{1}{2}, -z+\frac{1}{2}$; (vi) $-x+\frac{3}{2}, -y+1, z+\frac{1}{2}$.]

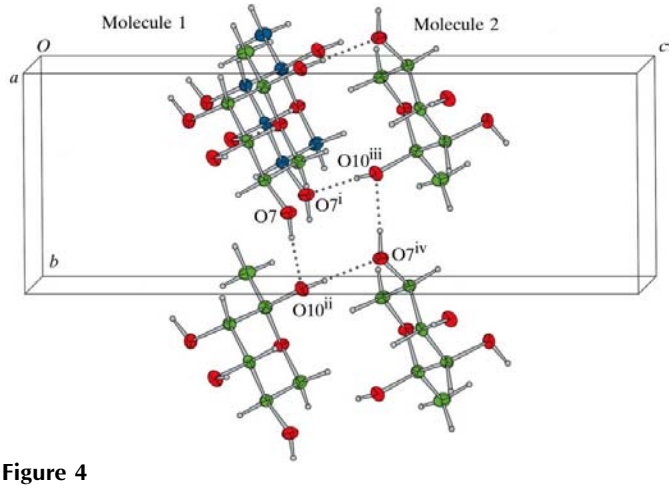

Figure 4
The equivalent part of the three-dimensional hydrogen-bonding network in the plate crystals, viewed approximately parallel to *a* and showing one turn of the helix (starting from the molecule with symmetry code i). In strict *a*-axis projection, the sides of the helix form an almost square lozenge. Molecules labelled 1 and 2 are described in the *Comment*. [Symmetry codes: (i) $x-1, y, z$; (ii) $x, y+1, z$; (iii) $x-\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (iv) (iv) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$.]

The crystallographic interest in these materials arises from the concomitant polymorphism, few cases of which are reported in the literature, but which may eventually be of use for the fine-tuning of structure prediction programs.

Experimental

The title compound was recrystallized from a mixture of ethyl acetate and methanol to give colourless crystals; $[\alpha]_D^{22}$ −13 (*c* 2.0, H_2O). The melting points of the two crystalline forms were found to be different, *viz*. 409–411 K for the needles and 416–418 K for the hexagonal plates.

Polymorph (I)

Crystal data

$C_6H_{12}O_5$
M_r = 164.16
Orthorhombic, $P2_12_12_1$
a = 6.0243 (2) Å
b = 7.5022 (3) Å
c = 15.9717 (8) Å
V = 721.85 (5) Å^3
Z = 4
D_x = 1.510 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.13 mm^{-1}
T = 190 K
Needle, colourless
0.40 × 0.10 × 0.10 mm

Data collection

Nonius KappaCCD diffractometer
ω scans
Absorption correction: multi-scan (*DENZO*/*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.829, T_{max} = 0.987
5125 measured reflections
975 independent reflections
879 reflections with $I > 2\sigma(I)$
R_{int} = 0.057
θ_{max} = 27.5°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.069
S = 1.00
975 reflections
100 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F^2) + (0.03P)^2 + 0.18P]$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O7—H7···O8^{vii}	0.87	1.93	2.788 (2)	170
O8—H8···O6^{viii}	0.85	1.88	2.698 (2)	164
O10—H10···O7^{iii}	0.83	2.05	2.865 (2)	165
O9—H9···O8^{v}	0.84	2.10	2.913 (2)	162

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

Polymorph (II)

Crystal data

$C_6H_{12}O_5$
M_r = 164.16
Orthorhombic, $P2_12_12_1$
a = 6.0177 (2) Å
b = 6.4672 (2) Å
c = 18.0218 (7) Å
V = 701.37 (4) Å^3
Z = 4
D_x = 1.555 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.14 mm^{-1}
T = 190 K
Hexagonal plate, colourless
0.20 × 0.20 × 0.10 mm

Data collection

Nonius KappaCCD diffractometer
ω scans
Absorption correction: multi-scan (*DENZO*/*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.865, T_{max} = 0.986
3322 measured reflections
949 independent reflections
883 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 27.5°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.027
$wR(F^2)$ = 0.066
S = 1.03
949 reflections
100 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F^2) + (0.02P)^2 + 0.2P]$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 2
Hydrogen-bond geometry (Å, °) for polymorph (II).

D—H···A	D—H	H···A	D···A	D—H···A
O10—H10···O7^{iii}	0.99	1.80	2.778 (2)	170
O7—H7···O10^{ii}	0.90	1.90	2.791 (2)	172
O9—H9···O8^{v}	0.91	1.88	2.786 (2)	174
O8—H8···O6^{vi}	0.95	1.87	2.803 (2)	165

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

In the absence of significant anomalous scattering, Friedel pairs were merged and the absolute configuration assigned from the starting materials. The relatively large ratio of minimum to maximum corrections applied in the multi-scan process (1:1.19 and 1:1.14) include factors in addition to absorption, which were taken into account (Görbitz, 1999) by the multi-scan inter-frame scaling (*DENZO*/*SCALEPACK*; Otwinowski & Minor, 1997). H atoms were all located in a difference map, but those attached to C atoms were repositioned geometrically. H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H = 0.93–0.98 Å and O—H = 0.82 Å) and U_{iso}(H) values (in the range 1.2–1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints.

For both compounds, data collection: *COLLECT* (Nonius, 2001); cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3070). Services for accessing these data are described at the back of the journal.

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