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Three polymorphs (*α*, *β*, and *δ*) of D-mannitol at 100 K

Frank R. Fronczek,[a]* Haidy Nasr Kamel[b] and Marc Slattery[b]

[a]Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803-1804, USA, and [b]Department of Pharmacognosy, University of Mississippi, University, MS 38677-1848, USA
Correspondence e-mail: ffroncz@lsu.edu

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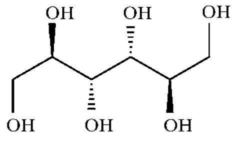
In the monoclinic δ polymorph of D-mannitol, $C_6H_{14}O_6$, both the molecule and the packing have approximate twofold rotational symmetry. The $P2_1$ structure thus approximates space group $C222_1$, and the α' polymorph, previously reported in that space group, is almost certainly identical to the δ polymorph. However, torsion angles along the main backbone of the molecule deviate from twofold symmetry by as much as 7.4 (3)° and the hydrogen-bonding pattern does not conform to the higher symmetry. The α polymorph reported here is identical to the previously reported κ polymorph, and the low-temperature structure of the β polymorph agrees well with previously reported room-temperature determinations. The range of C—O bond lengths over the three polymorphs is 1.428 (2)–1.437 (4) Å, and the range of C—C distances is 1.515 (4)–1.5406 (19) Å. The δ polymorph has the highest density of the three, both at room temperature and at 100 K.

Comment

The acyclic sugar alcohol D-mannitol, (I), is a natural product produced by various plants, algae and fungi, and is one of the classic examples of a compound which crystallizes in several polymorphs, often simultaneously (Bernstein, 2002; Berman *et al.*, 1968). This polymorphism was reported at least 115 years ago (Zepharovich, 1888). Understanding of the various forms is of importance to the pharmaceutical industry, because mannitol is used as an excipient in the formulation of tablets and granulated powders (Burger *et al.*, 2000), and the polymorphs differ somewhat in their physical properties.

Approximately eight polymorphs of D-mannitol have been claimed over the years, leading to much confusion in the literature. Burger *et al.* (2000) have summarized and correlated the various claims, and have concluded that only three, *viz.* α, β, and δ, are proven to exist. Walter-Levy (1968) has reported the cell dimensions of the three, which are also designated modifications II, I, and III, respectively, by some authors. Two of the polymorphs have previously been fully characterized by crystal structure determinations at room temperature. A full structure determination of the thermodynamically most stable polymorph, β (modification I), was reported in space group $P2_12_12_1$ by Berman *et al.* (1968), and was further refined by Kaminsky & Glazer (1997), including determination of the absolute configuration. Kim *et al.* (1968) reported the structure of a form which they designated κ, also in $P2_12_12_1$. The cell dimensions of this κ form correspond to those of the polymorph historically designated as α (Groth, 1910; Rye & Sörum, 1952), or modification II.



(I)

Walter-Levy (1968) reported the cell dimensions and space group of a monoclinic $P2_1$ form, designated the δ form or modification III. Walter-Levy & Strauss (1972) also reported the X-ray powder diffraction pattern of the δ form. Burger *et al.* (2000) have studied the thermodynamic properties and compression behavior of the mannitol polymorphs. They have concluded that, although the δ polymorph is not the thermodynamically stable form, it has considerable kinetic stability and exhibits the best consolidation behavior for pharmaceutial use. The structure of the important δ form has not been reported to date, probably because high-quality single crystals are difficult to prepare. Berman *et al.* (1968) also reported an 'α' form', and determined its structure in projection from film data in $C222_1$. However, they report that 'the crystals of the α' form were small and bladelike, and gave very elongated spots'. Based on ^{13}C NMR data and X-ray powder patterns, Grindley *et al.* (1990) concluded that the α' and δ forms are identical. We have isolated D-mannitol from the brown alga *Dictyota dichotoma* by accelerated solvent extraction (Richter *et al.*, 1996), and single crystals of the δ form were obtained directly from the extract. Their visual appearance was poor, but they yielded reasonably clean diffraction patterns and were suitable for structure determination. The structure of the δ form is reported for the first time herein. We have also prepared crystals of the α and β polymorphs from a commercial sample and have determined their structures at 100 K, that of the α form to confirm its identity with the κ form of Kim *et al.* (1968), and that of the β form for completeness.

The molecular structure of the α polymorph is shown in Fig. 1. While crystals were prepared from 70% ethanol, the standard method for obtaining α, it is clear that they are identical to the 'κ polymorph' of Kim *et al.* (1968), obtained from a water–methanol solution containing boric acid. We have chosen the now-conventional $c > b > a$ setting, rather than the previously used $b > a > c$ setting. Refinement using low-temperature CCD data has led to only a slight improvement in precision compared with the room-temperature data from 35 years ago. The OH groups at both ends of the mol-

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ecule form C—C—C—O torsion angles of nearly 60° (Table 1), rather than being extended with the carbon chain, and the molecule has nearly C_2 symmetry, with the exception of the conformations of the OH groups. The hydrogen bonding has been described fully by Kim *et al.* (1968).

The structure of the β polymorph is shown in Fig. 1. The torsion angles in Table 1 indicate that the conformation of the main backbone is essentially the same as that of the α form. The OH groups have different conformations and conform to a different hydrogen-bonding scheme, as has been discussed by Berman *et al.* (1968). Our results are in excellent agreement with the room-temperature structure of Kaminsky & Glazer (1997), with a maximum difference in any bond distance of 0.008 (3) Å (for C4—O4) and an r.m.s. difference of 0.004 Å.

The full structure of the monoclinic δ polymorph is reported here for the first time, and its structure is shown in Fig. 1. The conformation of its main backbone is very similar to those of the other two polymorphs, as can be seen from the torsion angles in Table 1. However, this conformation deviates more from local C_2 molecular symmetry than do those of the α and β forms. The torsion angle about C1—C2 differs from that about C5—C6 by 7.4 (3)°, and the one about C2—C3 differs from that about C4—C5 by 6.9 (3)°. The hydrogen-bonding pattern is described in Table 4 and illustrated in Fig. 2. Prominent features of the pattern are chains in the *b* direction formed by single hydrogen bonds with atom O1 as donor, and triply bonded chains in the *a* direction in which OH groups O2, O4, and O6 on the same molecule all serve as donors. A portion of the triply bridged chain is shown in Fig. 3. This motif is also seen in DL-mannitol (Kanters *et al.*, 1977). Similar triply bonded chains exist in the *a* direction of both the α and β polymorphs of D-mannitol, but in those cases, the three donors are not all on the same molecule. The two-dimensional net formed by the single and triple chains in the δ form are crosslinked by hydrogen bonds donated by atoms O3 and O5, forming a three-dimensional network.

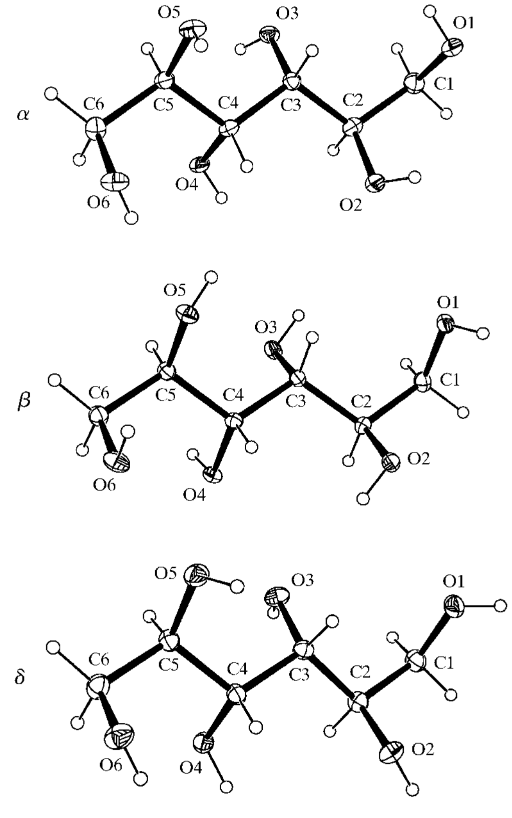

Figure 1
Molecular views of the three polymorphs of (I), with the atom-numbering schemes. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

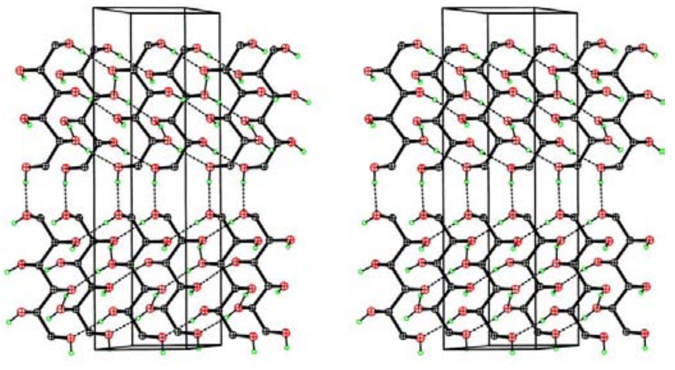

Figure 2
A stereoview of the unit cell of the δ polymorph of D-mannitol, showing the hydrogen bonding. The view is down the approximate twofold rotation direction. The *a* axis is horizontal and the *b* axis is vertical.

Fig. 2 illustrates that, not only does the molecule in the δ form have approximate twofold rotational symmetry, but the packing does also, except for the H atoms. The unit-cell transformation (−100, 102, 010) generates a *C*-centered cell with near-orthorhombic metric, having dimensions a = 4.899 (2), b = 8.873 (3) and c = 18.268 (6) Å, and $\alpha = \beta = 90°$ and γ = 90.67 (2)°. Thus, the structure, minus the hydroxy H atoms, conforms approximately to space group $C222_1$, with the molecule lying on a twofold axis. This suggests that the α' form of Berman *et al.* (1968), described in that space group with similar cell dimensions, is the same as the δ polymorph reported here. They obtained an R value of 0.18 from two-dimensional film data. Transforming our monoclinic data to the *C*-centered setting and averaging under Laue group *mmm* yielded an $R_{\rm int}$ value of 0.135, and refinement of the structure in $C222_1$ reproduced the results of Berman *et al.* (1968). For this refinement, the R value was 0.107, but the H atoms were not visible and the ellipsoids were not reasonable, including that of atom C3 (= C4), which became non-positive definite. A calculated X-ray powder pattern from our $P2_1$ model also matches that reported by Burger *et al.* (2000) for modification III, which Grindley *et al.* (1990) equate to both the α' and δ polymorphs. Thus, it is nearly certain that α' does not exist as an orthorhombic polymorph, but is identical to δ.

We have also measured the intensity data for the δ polymorph at 300 K, and refinement of the structure to an R value of 0.039 confirms that it is the same at room temperature and at 100 K. Cell dimensions at 300 K are a = 4.918 (2), b = 18.263 (6) and c = 5.093 (3) Å, and β = 118.31 (2)°, which yields a density of 1.502 Mg m^{-3}. Thus, the δ form is the most dense of the three established polymorphs at room tempera-

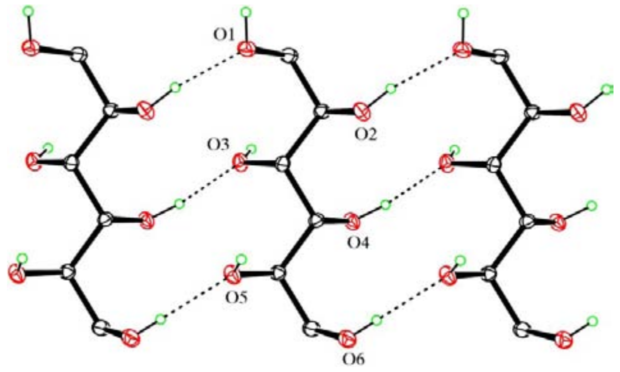

Figure 3
A portion of the triply bridged hydrogen-bonded chain of the δ polymorph of D-mannitol. H atoms on C atoms are not shown.

ture, the density of the α form being 1.471 Mg m^{-3} and that of the β form being 1.487 Mg m^{-3}. The δ polymorph is also the most dense at 100 K, and is more dense than the racemic form (Kanters *et al.*, 1977) at both room and low temperature.

We conclude that there are only three well established polymorphs of D-mannitol, *viz.* α, β, and δ, all having approximate C_2 molecular symmetry and none having crystallographic C_2 symmetry. The α form is identical to the κ form, and the δ form is identical to the α' form.

Experimental

Crystals of the α and β polymorphs were obtained by recrystallization of a commercial sample of D-mannitol (Mallinckrodt). Slow cooling of a saturated solution at 323 K in 70% ethanol yielded long flexible needles of the α polymorph after one week. Slow evaporation of an aqueous solution yielded crystals of the β polymorph. A sample of the brown alga *Dictyota dichotoma* collected from Saipan was freeze dried and then extracted in an accelerated solvent extractor (Richter *et al.*, 1996) at 313 K and 1500 p.s.i. (1 p.s.i. = 6894.76 Pa) in a 1:1 methanol–methylene chloride solution. The crystal of the δ polymorph used for data collection formed directly from the extract.

Compound (I), *α* form

Crystal data

$C_6H_{14}O_6$
$M_r = 182.17$
Orthorhombic, $P2_12_12_1$
$a = 4.8653$ (10) Å
$b = 8.873$ (2) Å
$c = 18.739$ (3) Å
$V = 809.0$ (3) Å^3
$Z = 4$
$D_x = 1.496$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1228 reflections
$\theta = 2.5$–29.1°
$\mu = 0.14$ mm^{-1}
$T = 100$ K
Needle fragment, colorless
0.50 × 0.03 × 0.02 mm

Data collection

Nonius KappaCCD area-detector diffractometer (with an Oxford Cryosystems Cryostream cooler)
ω scans with κ offsets
8346 measured reflections
1286 independent reflections
951 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.049$
$\theta_{\rm max} = 29.1°$
$h = -6 \rightarrow 6$
$k = -12 \rightarrow 12$
$l = -25 \rightarrow 25$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.054$
$wR(F^2) = 0.128$
$S = 1.07$
1286 reflections
127 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0685P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.35$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.27$ e Å^{-3}

Table 1
Comparison of geometric parameters (Å, °) in the three polymorphs of (I).

	α polymorph	β polymorph	δ polymorph
C1—O1	1.436 (4)	1.4342 (18)	1.431 (3)
C2—O2	1.437 (4)	1.4298 (18)	1.428 (2)
C3—O3	1.433 (4)	1.4363 (17)	1.423 (2)
C4—O4	1.434 (4)	1.4370 (17)	1.431 (2)
C5—O5	1.431 (4)	1.4292 (18)	1.433 (2)
C6—O6	1.429 (4)	1.4310 (18)	1.432 (3)
C1—C2	1.515 (4)	1.5232 (19)	1.519 (3)
C2—C3	1.541 (4)	1.5386 (18)	1.527 (3)
C3—C4	1.520 (4)	1.5251 (18)	1.536 (3)
C4—C5	1.537 (4)	1.5406 (19)	1.525 (3)
C5—C6	1.530 (4)	1.5218 (19)	1.522 (3)
O1—C1—C2—C3	64.2 (3)	55.43 (16)	50.7 (2)
C1—C2—C3—C4	−174.5 (3)	−176.34 (11)	176.44 (18)
C2—C3—C4—C5	177.0 (3)	174.79 (12)	−171.61 (17)
C3—C4—C5—C6	−177.2 (3)	−178.52 (12)	−176.69 (17)
C4—C5—C6—O6	62.1 (3)	56.06 (16)	58.1 (2)

Table 2
Hydrogen-bonding geometry (Å, °) for the α form of (I).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H10···O2$^{\rm i}$	0.79 (4)	1.95 (4)	2.733 (3)	171 (4)
O2—H20···O1$^{\rm ii}$	0.83 (4)	1.97 (4)	2.774 (3)	162 (4)
O3—H30···O6$^{\rm iii}$	0.80 (4)	2.07 (4)	2.812 (3)	155 (3)
O4—H40···O3$^{\rm iv}$	0.79 (4)	1.95 (4)	2.730 (3)	170 (4)
O5—H50···O4$^{\rm v}$	0.79 (4)	1.92 (4)	2.689 (3)	164 (4)
O6—H60···O5$^{\rm iv}$	0.73 (4)	2.00 (4)	2.719 (3)	174 (5)

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

Compound (I), *β* form

Crystal data

$C_6H_{14}O_6$
$M_r = 182.17$
Orthorhombic, $P2_12_12_1$
$a = 5.5381$ (10) Å
$b = 8.580$ (2) Å
$c = 16.795$ (5) Å
$V = 798.0$ (3) Å^3
$Z = 4$
$D_x = 1.516$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1711 reflections
$\theta = 2.5$–34.3°
$\mu = 0.14$ mm^{-1}
$T = 100$ K
Lath, colorless
0.37 × 0.15 × 0.05 mm

Data collection

Nonius KappaCCD area-detector diffractometer (with an Oxford Cryosystems Cryostream cooler)
ω scans with κ offsets
12 106 measured reflections
1838 independent reflections
1611 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.026$
$\theta_{\rm max} = 34.3°$
$h = -8 \rightarrow 8$
$k = -13 \rightarrow 13$
$l = -26 \rightarrow 26$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.036$
$wR(F^2) = 0.095$
$S = 1.08$
1838 reflections
127 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0488P)^2 + 0.1129P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.38$ e Å^{-3}
$\Delta\rho_{\min} = -0.25$ e Å^{-3}

Table 3
Hydrogen-bonding geometry (Å, °) for the β form of (I).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O···O2$^{\rm i}$	0.82 (2)	1.94 (2)	2.7419 (16)	167 (2)
O2—H2O···O1$^{\rm ii}$	0.83 (2)	1.87 (2)	2.6801 (15)	164 (2)
O3—H3O···O4$^{\rm iii}$	0.86 (2)	1.88 (2)	2.7368 (15)	168 (2)
O4—H4O···O5$^{\rm iv}$	0.82 (2)	2.00 (2)	2.7612 (16)	155 (2)
O5—H5O···O6$^{\rm iii}$	0.85 (2)	1.85 (2)	2.6946 (14)	174 (2)
O6—H6O···O3$^{\rm v}$	0.82 (2)	1.98 (2)	2.7504 (16)	155 (2)

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

Compound (I), δ form

Crystal data

$C_6H_{14}O_6$
$M_r = 182.17$
Monoclinic, $P2_1$
$a = 4.899$ (2) Å
$b = 18.268$ (6) Å
$c = 5.043$ (2) Å
$\beta = 118.39$ (2)°
$V = 397.0$ (3) Å^3
$Z = 2$

$D_x = 1.524$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 901 reflections
$\theta = 2.5$–27.5°
$\mu = 0.14$ mm^{-1}
$T = 100$ K
Lath, colorless
0.42 × 0.12 × 0.01 mm

Data collection

Nonius KappaCCD area-detector diffractometer (with an Oxford Cryosystems Cryostream cooler)
ω scans with κ offsets
5233 measured reflections
940 independent reflections

892 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.021$
$\theta_{\max} = 27.5°$
$h = -6 \rightarrow 6$
$k = -23 \rightarrow 19$
$l = -6 \rightarrow 6$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.031$
$wR(F^2) = 0.079$
$S = 1.07$
940 reflections
127 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0362P)^2 + 0.0992P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.27$ e Å^{-3}
$\Delta\rho_{\min} = -0.23$ e Å^{-3}

Table 4
Hydrogen-bonding geometry (Å, °) for the δ form of (I).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O···O6$^{\rm i}$	0.86 (3)	1.84 (3)	2.697 (2)	172 (3)
O2—H2O···O1$^{\rm ii}$	0.86 (3)	1.85 (3)	2.698 (2)	166 (3)
O3—H3O···O2$^{\rm iii}$	0.82 (3)	1.87 (3)	2.676 (3)	168 (3)
O4—H4O···O3$^{\rm ii}$	0.90 (3)	1.76 (3)	2.650 (2)	171 (3)
O5—H5O···O4$^{\rm iv}$	0.82 (3)	1.90 (3)	2.705 (2)	166 (3)
O6—H6O···O5$^{\rm ii}$	0.80 (3)	1.92 (4)	2.718 (2)	175 (3)

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

H atoms on C atoms were placed in calculated positions, guided by difference maps, with C—H bond distances in the range 0.99–1.00 Å and with $U_{\rm iso}({\rm H}) = 1.2U_{\rm eq}({\rm C})$, and were thereafter treated as riding. The coordinates for the hydroxy H atoms were refined, but the $U_{\rm iso}({\rm H})$ values were fixed at $1.5U_{\rm eq}({\rm O})$. The absolute configuration could not be established from the X-ray data, but was assigned based on the known configuration of the D enantiomer (Kaminsky & Glazer, 1997). Friedel pairs were averaged in all cases.

For all three polymorphs, data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1573). Services for accessing these data are described at the back of the journal.

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