

Crystal structure of anhydrous δ -*D*-mannitol

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The crystal structure of anhydrous δ -*D*-mannitol ($C_6H_{14}O_6$) was solved from high-resolution synchrotron X-ray powder diffraction data collected on a mixture containing 20% and 80% w/w of β - and δ -*D*-mannitol, respectively. The direct space simulated annealing program PSSP, and Rietveld analysis employing GSAS were used to determine and refine the structure. The polymorph has monoclinic symmetry, space group $P2_1$ with $a = 5.08941(5)$ Å, $b = 18.2504(2)$ Å, $c = 4.91702(5)$ Å, and $\beta = 118.303(2)^\circ$. There is one molecule in the irreducible volume of the unit cell. The pattern of hydrogen bonding is significantly different than the previously known α and β forms. © 2003 International Centre for Diffraction Data. [DOI: 10.1154/1.1582460]

I. INTRODUCTION

D-mannitol is an acyclic sugar alcohol (polyol) that, unlike its optical isomer, *L*-mannitol, is naturally produced by several plants and animals. The lower caloric value of polyols (compared to regular sugars), and their ability to be metabolized without an appreciable increase in the blood sugar concentration, make them attractive to the food industry, especially for use in diabetic diet products. *D*-mannitol is also used as an osmotic diuretic to reduce cerebral edema and to treat acute renal failure. Widespread use of *D*-mannitol occurs in the pharmaceutical industry as an excipient in products prepared by freeze-drying, given that *D*-mannitol distinguishes itself from other polyols by a strong tendency to crystallize from frozen aqueous solutions.

It is well known that the crystallization of *D*-mannitol may lead to the formation of different solid forms, depending on the processing conditions such as the solvent type and concentration, the temperature, or the rate of crystallization. Although research on the polymorphic modifications of *D*-mannitol precedes the discovery of X-rays, there remain substantial uncertainties. This is pointed out in a recent review (Burger *et al.*, 2000) where it is suggested that, in spite of numerous reports of anhydrous mannitol modifications, there are only three pure *D*-mannitol polymorphs: α - and β -, whose existence were reported by Groth in 1910, and δ -*D*-mannitol, observed by Walter-Levi in 1968. (In this work, we are using the labels α , β , and δ , in agreement with the usage in the Powder Diffraction File; Burger *et al.* have assigned these the names form II, form I, and form III, respectively.) The structures of the β and α forms of *D*-mannitol were solved from single crystal X-ray diffraction data, by Berman *et al.* (1968) and Kim *et al.* (1968), respectively; the authors of the latter paper called their material K, but it clearly has the same powder diffraction pattern as the currently accepted α . Until now, the structure of the δ modification remains unknown. According to Burger *et al.* (2000), several other reported *D*-mannitol modifications appear to be different mixtures of the pure forms α , β , and δ . Furthermore, a crystalline mannitol hydrate forms during freeze-

drying, though the hydrate stoichiometry and structure have not yet been solved (Yu *et al.*, 1999).

Structure determination methods based on high-resolution powder diffraction data are a powerful tool in the study of polymorphism for at least two reasons. First, the determination of a crystal structure allows a precise, direct and unequivocal identification of a given polymorph. Second, modern powder diffraction data analysis techniques allow the study of diffraction patterns from multiple-phase systems and, consequently, a mixture of different polymorphs can be identified, the contributions from each individual component can be isolated and subsequently used for structure determination.

Here we report the structure determination of the δ modification of *D*-mannitol from powder diffraction data collected on a mixture containing 20% and 80% w/w of β - and δ -*D*-mannitol, respectively. We obtained the integrated intensities of the δ phase from a Le Bail (1988) profile fit performed simultaneously with a Rietveld refinement of the β component. The intensities were then input into a locally developed simulated annealing program, PSSP (Pagola *et al.*, 2000), and the structure determined by PSSP was subsequently refined using GSAS (Larson and Von Dreele, 1987).

II. EXPERIMENTAL DETAILS

To prepare the sample, aqueous mannitol solutions (10% w/v) were cooled in a tray freeze-dryer from 25 to -50°C at $1^\circ\text{C}/\text{min}$, and held isothermally for 12 h. The frozen solutions were subsequently heated at $1^\circ\text{C}/\text{min}$ to the primary drying temperature of -15°C and dried for 60 h at a pressure of 50 mTorr. High-resolution powder diffraction data were collected on the SUNY X3B1 beamline at the National Synchrotron Light Source, Brookhaven National Laboratory. The sample was sealed in a 1-mm-diam glass capillary, mounted on a custom-designed spinner and aligned along the central axis of the diffractometer, perpendicular to the direction of the incident beam. The direct synchrotron beam was monochromated by a double Si(111) crystal monochromator which selects X-rays of wavelength $0.70224(1)$ Å, as determined from seven well-defined reflections of an Al_2O_3 flat plate standard (NIST 1976a). Before reaching the sample, the

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TABLE I. Crystallographic data and details of the Rietveld refinement for the δ - + β -*D*-mannitol mixture.

	Crystallographic data	
	β - <i>D</i> -mannitol	δ - <i>D</i> -mannitol
Space group	$P 2_1 2_1 2_1$	$P 2_1$
a (Å)	8.679 0(1)	5.089 41(5)
b (Å)	16.896 2(2)	18.250 4(2)
c (Å)	5.549 72(7)	4.917 02(5)
α (deg)	90	90
β (deg)	90	118.303(2)
γ (deg)	90	90
V (Å ³)	813.826	402.103
ρ (g cm ⁻³)	1.394	1.377
Weight fractions (%)	20	80
No. of reflections	229	179
No. of refined parameters	44	43
No. of nonhydrogen atoms	12	12
R_B	0.068	0.052 4
U_{iso}	0.029 83(7)	0.034 96(13)
Rietveld refinement details		
λ (Å)	0.702 24(1)	
$(\sin \theta/\lambda)_{max}$ (Å ⁻¹)	0.3686	
Step length (deg)	0.003	
R_p	0.0534	
R_{wp}	0.0600	
χ^2	3.01	

2×8 mm incident beam was monitored by an ion chamber and the diffracted signal was normalized for the decay of the primary beam. The diffracted beam was reflected by a Ge(111) analyzer crystal before being detected by a NaI scintillation counter. Diffraction data were collected at room temperature by counting for 2 s at each 2θ , in steps of 0.003° from 4° to 30° . The low angle peaks, which exhibited a pronounced asymmetry due to axial divergence, had an intrinsic full width at half maximum of 0.015° (measured in 2θ).

III. STRUCTURE DETERMINATION AND DISCUSSION

Initial inspection of the measured diffraction pattern revealed a mixture of two *D*-mannitol polymorphs: β -*D*-mannitol, the three-dimensional structure of which is available from single crystal data (Berman *et al.*, 1968), and δ -*D*-mannitol. The presence of the δ polymorph was identified by comparison to published diffraction patterns, e.g., International Centre for Diffraction Data, Powder Diffraction File entry 22-1794. (Our refined lattice parameters, listed in Table I, are in substantial agreement with the parameters, $a = 5.095$ Å, $b = 18.254$ Å, $c = 4.919$ Å, $\beta = 118.36^\circ$, space-group $P2_1$, given in the Powder Diffraction File.) Next, we performed a profile (Le Bail *et al.*, 1988) fit to the δ phase, simultaneously with a Rietveld refinement of the β phase using the program FULLPROF (Rodriguez-Carvajal, 1990). We extracted 179 integrated intensities for the δ phase, and input them, together with the crystallographic unit cell information, into the simulated annealing program PSSP.

PSSP measures agreement of a model structure with the observed diffraction pattern through a parameter S , which is similar to the usual weighted profile R factor (Pagola *et al.*,

2000). S permits very efficient comparison with extracted intensities even in the case of substantial overlap of diffraction peaks, similar to the technique described by David *et al.* (1998) based on Pawley extraction. The simulated annealing method treats S as being analogous to the energy of a physical system, and attempts to find the structure that minimizes S by Monte Carlo searches of parameter space at progressively lower values of a control parameter T (analogous to the temperature). Each trial configuration is generated using a set of parameters that necessarily include the center of mass coordinates and Euler angles that determine the position of the rigid molecule in the unit cell. Molecular flexibility can be taken into account by considering additional parameters such as the torsion angles of a given molecular fragment around a particular interatomic axis.

To determine the structure of δ -*D*-mannitol, we first considered a rigid *D*-mannitol molecule whose atom coordinates with respect to its center of mass were determined from the known β -*D*-mannitol structure. The molecule was randomly placed in the unit cell, a large starting value of the temperature control parameter ($T = 500$) was input, and PSSP was run to perform Monte Carlo searches in the six-dimensional parameter configuration space. The temperature was then reduced by 20% and the process was repeated until T reached 0.01. In all cases, 68 extracted intensities were used, for $d > 1.88$ Å. The number of structures generated at each temperature was 5×10^4 . Several such cycles were run, but all yielded large values of $S (> 1)$, which indicate rather poor candidate solutions. This suggested that our initial rigid molecule assumption was not accurate. Next, we allowed free variation of the five internal torsions that define the zig-zagged backbone of the *D*-mannitol molecule, which resulted in a substantial reduction of S to usable values in the neighborhood of 0.1.

The best structure solution of δ -*D*-mannitol furnished by PSSP ($S = 0.102$) was then refined by the Rietveld method using the program package GSAS. Figure 1 shows the best Rietveld refinement for the β - + δ -*D*-mannitol mixture. For each phase we refined the nonhydrogen atom coordinates and isotropic thermal parameters, the profile parameters, unit-cell parameters, and weight fractions. To describe the individual peak profiles we used a pseudo-Voigt function (Thompson *et al.*, 1987) convoluted with an asymmetry function (Finger *et al.*, 1994) that accounts for the asymmetry due to axial divergence. Soft restraints were attached to the bond distances and bond angles. Following refinement to overall figures of merit $R_{wp} = 6.54\%$ and $\chi^2 = 3.57$, we searched the Fourier difference map for evidence of hydrogen atoms. The eight hydrogens bonded to carbon atoms showed up clearly, and so we added them to the model, but we were not able to obtain a stable refinement of their positions. There is no such clear diffraction evidence for the location of the six atoms that are expected to participate in hydrogen bonds. We did not consider the hydrogen atoms in the β phase. Subsequent refinement of the heavy atoms reduced R_{wp} and χ^2 to 6.00% and 3.01, respectively. Other details of the Rietveld refinement and the resulting crystallographic data are shown in Table I.

The fractional coordinates of the carbon, oxygen, and eight of the hydrogen atoms of δ -*D*-mannitol are presented in Table II, and the corresponding three-dimensional struc-

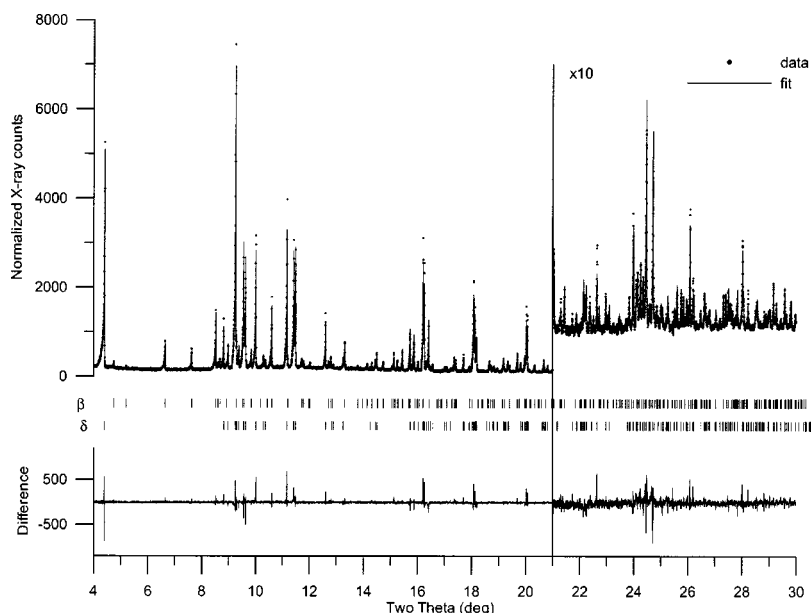


Figure 1. Two-phase best Rietveld fit for the δ - + β -*D*-mannitol mixture. The closed squares show the scattered intensity as a function of the diffraction angle 2θ , while the solid line represents the calculated pattern. The lower trace is the difference between the observed and the calculated patterns and the vertical bars are the reflection markers for the two phases. Note the vertical scale factor increases at high angles.

ture is shown in Figure 2, in a similar view to the previously known structures of α - and β -. Refined fractional coordinates for β -*D*-mannitol are given in Table III. Table IV contains the values of the bond distances, bond angles, and torsion angles in β - and δ -*D*-mannitol, as they result from the best Rietveld fit in Figure 1. In all cases, the estimated standard deviations (ESDs) from the Rietveld refinement are listed. It should be emphasized that these are statistical estimates, which are valid under the assumption that the only difference between the derived model and physical reality is in the experimental counting statistics. There have been numerous attempts to derive confidence intervals by “corrections” to the

statistical ESDs, but they are intrinsically questionable because the differences between the refined profile and the raw data are generally systematic rather than statistical.

For β -*D*-mannitol, we present a comparison between the refined values and previous single-crystal determinations by Berman *et al.* (1968); we note that the differences (column 3 in Table IV) are generally small, showing that the above-described two-phase Rietveld refinement preserves the previously known structure of β -*D*-mannitol. Since the agreement is generally within the ESD values, it is plausible that the ESD values of the parameters for δ -*D* mannitol provide suitable confidence limits.

TABLE II. Fractional atomic coordinates in δ -*D*-mannitol. Numbers in parentheses are statistical estimated standard deviations from the Rietveld fit.

	<i>X</i>	<i>Y</i>	<i>Z</i>	<i>U</i> _{iso}
Fractional coordinates (δ -mannitol)				
C1	0.3487(17)	0.9800(19)	0.6092(17)	0.034 96(13)
C2	0.3339(17)	0.9072(19)	0.7845(17)	0.034 96(13)
C3	0.3299(13)	0.8394(19)	0.5813(13)	0.034 96(13)
C4	0.3435(13)	0.7701(19)	0.7601(14)	0.034 96(13)
C5	0.3590(18)	0.7017(19)	0.5692(17)	0.034 96(13)
C6	0.3511(17)	0.6276(19)	0.7475(17)	0.034 96(13)
O1	0.1036(12)	0.9848(17)	0.3118(12)	0.034 96(13)
O2	0.0813(10)	0.9076(17)	0.8284(10)	0.034 96(13)
O3	0.5582(9)	0.8451(18)	0.4924(10)	0.034 96(13)
O4	0.6008(9)	0.7685(17)	1.0521(8)	0.034 96(13)
O5	0.1233(11)	0.7010(17)	0.2613(11)	0.034 96(13)
O6	0.1063(12)	0.6232(17)	0.7827(11)	0.034 96(13)
C-bonded hydrogens (δ -mannitol)				
H1	0.324	1.015	0.767	0.034 96(13)
H2	0.552	0.970	0.517	0.034 96(13)
H3	0.583	0.906	1.000	0.034 96(13)
H4	0.179	0.843	0.335	0.034 96(13)
H5	0.125	0.776	0.833	0.034 96(13)
H6	0.594	0.694	0.607	0.034 96(13)
H7	0.542	0.635	1.042	0.034 96(13)
H8	0.317	0.590	0.499	0.034 96(13)

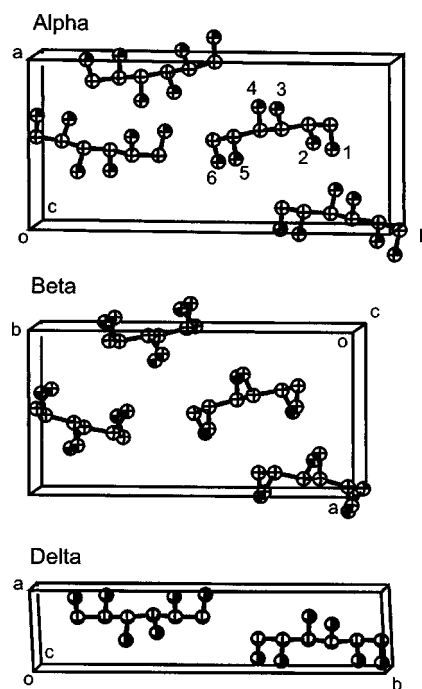


Figure 2. Comparison of the structures of α -, β -, and δ -*D*-mannitol, all viewed along their respective *c* axes. The former two structures are taken from Kim *et al.* (1968) and Berman *et al.* (1968), respectively.

TABLE III. Fractional atomic coordinates in β -*D*-mannitol. Numbers in parentheses are statistical estimated standard deviations from the Rietveld fit.

	Fractional coordinates (β -mannitol)			
	X	Y	Z	U_{iso}
C1	-0.0014(17)	0.5084(8)	0.4382(30)	0.029 83(7)
C2	0.0303(13)	0.5432(7)	0.1855(29)	0.029 83(7)
C3	0.0723(13)	0.6318(7)	0.2066(29)	0.029 83(7)
C4	0.0902(16)	0.6711(7)	-0.0372(26)	0.029 83(7)
C5	0.1254(17)	0.7632(7)	-0.0115(25)	0.029 83(7)
C6	0.1391(18)	0.8026(9)	-0.2631(29)	0.029 83(7)
O1	-0.1198(19)	0.5478(8)	0.5662(20)	0.029 83(7)
O2	-0.1097(18)	0.5347(8)	0.0476(19)	0.029 83(7)
O3	0.2108(15)	0.6377(8)	0.3312(24)	0.029 83(7)
O4	0.2132(16)	0.6356(8)	-0.1719(24)	0.029 83(7)
O5	-0.0043(15)	0.7985(8)	0.1088(22)	0.029 83(7)
O6	-0.0003(15)	0.7895(8)	-0.3950(22)	0.029 83(7)

TABLE IV. Bond lengths, bond angles, and torsion angles in δ - and β -*D*-mannitol molecules. For β , a comparison between the results from single-crystal by Berman *et al.* (1968) and powder data (present work) is presented. Numbers in parentheses are statistical ESD values derived from the Rietveld refinement.

	β single crystal	β powder	Difference	δ powder
Bond distances (Å)				
C1–C2	1.505(10)	1.545(17)	-0.040(27)	1.605(10)
C2–C3	1.522(10)	1.546(15)	-0.024(25)	1.585(9)
C3–C4	1.513(10)	1.515(16)	-0.002(26)	1.524(10)
C4–C5	1.537(10)	1.592(14)	-0.055(24)	1.585(10)
C5–C6	1.503(10)	1.552(16)	-0.049(26)	1.624(10)
C1–O1	1.425(9)	1.416(17)	0.009(26)	1.404(8)
C2–O2	1.440(9)	1.443(16)	-0.003(25)	1.401(8)
C3–O3	1.433(9)	1.390(17)	0.043(26)	1.426(6)
C4–O4	1.448(9)	1.434(15)	0.014(24)	1.412(7)
C5–O5	1.444(9)	1.439(16)	0.005(25)	1.417(8)
C6–O6	1.436(9)	1.431(18)	0.005(27)	1.339(7)
Bond angles (deg)				
C1–C2–C3	111.6(6)	110.0(8)	1.6(14)	107.3(5)
C2–C3–C4	112.8(6)	112.4(7)	0.4(13)	107.5(5)
C3–C4–C5	113.3(6)	111.6(7)	1.7(13)	108.2(5)
C4–C5–C6	113.2(6)	110.7(8)	2.5(14)	108.4(6)
O1–C1–C2	112.9(6)	113.9(8)	-1.0(14)	111.4(6)
O2–C2–C1	107.7(6)	107.1(8)	0.6(14)	111.0(7)
O2–C2–C3	109.8(6)	109.6(8)	0.2(14)	111.3(7)
O3–C3–C2	109.3(6)	108.2(8)	1.1(14)	111.6(7)
O3–C3–C4	108.7(6)	108.9(8)	-0.2(14)	114.6(8)
O4–C4–C3	109.9(6)	111.0(8)	-1.1(14)	111.7(8)
O4–C4–C5	108.7(6)	108.2(8)	0.5(14)	107.7(7)
O5–C5–C4	109.5(6)	107.3(8)	2.2(14)	112.7(7)
O5–C5–C6	106.5(6)	107.4(8)	-0.9(14)	110.1(6)
O6–C6–C5	111.8(6)	109.2(8)	2.6(14)	112.5(6)
Torsion angles (deg)				
O1–C1–C2–O2	-64.5	-61.47	-3.03	-62.72
O2–C2–C3–O3	-176.93	-177.49	0.56	170.25
O3–C3–C4–O4	59.01	57.82	1.19	66.34
O4–C4–C5–O5	176.47	175.98	0.49	-175.09
O5–C5–C6–O6	-64.89	-59.39	-5.5	-65.3

TABLE V. Hydrogen bonds in the three polymorphs of *D*-mannitol.

Phase	Atom 1	Atom 2	Distance		
			(Å)	Symm 2 ^a	Cell 2
Alpha ^b	O1	O2	2.76	1	0 0 -1
	O2	O1	2.80	4	1 0 0
	O3	O4	2.74	1	0 0 -1
	O4	O5	2.72	2	-1 0 0
	O5	O6	2.74	1	0 0 -1
	O6	O3	2.84	2	0 0 0
Beta	O1	O2	2.68	1	0 0 1
	O2	O1	2.73	4	-1 -1 0
	O3	O4	2.76	1	0 0 1
	O4	O5	2.72	2	0 -1 0
	O5	O6	2.76	1	0 0 1
	O6	O3	2.82	2	-1 -1 0
Delta	O1	O2	2.72	1	0 0 -1
	O2	O3	2.64	1	-1 0 0
	O3	O4	2.67	1	0 0 -1
	O4	O5	2.66	1	1 0 1
	O5	O6	2.71	1	0 0 -1
	O6	O1	2.70	2	0 -1 1

^aFor α and β , the symmetry operations are: (1) x, y, z ; (2) $\frac{1}{2}+x, \frac{1}{2}-y, -z$; (3) $-x, \frac{1}{2}+y, \frac{1}{2}-z$; (4) $\frac{1}{2}-x, -y, \frac{1}{2}+z$. For δ , the symmetry operations are: (1) x, y, z ; (2) $-x, \frac{1}{2}+y, -z$.

^bData taken from Kim *et al.* (1968).

The individual molecule in δ -*D*-mannitol differs little from its β -counterpart. The same (quasi-)planar zigzagged carbon chain is present. Bond distances and angles are not significantly different from either the single crystal or the powder refinement of β -. The main distinction between the two molecules occurs in the O2–C2–C3–O3 and O4–C4–C5–O5 torsion angles. For example, the opposite-sign deviations from a perfect alignment of the (O2,C2,C3) and (C2,C3,O3) planes, indicate that O3 is slightly off plane in both cases, but on one side of (O2,C2,C3) for δ , and on the opposite side for β . The backbone is slightly arched out of the plane, toward O3 and O4 in α - and β -, while it arches in the opposite direction in δ -*D*-Mannitol. In all three structures, the molecule has nearly a twofold axis. In δ , that axis is inclined about 1.5° from c^* . Rotation of the molecule by 180° about that axis, switching C1 and C6, O1 and O6, etc., places each atom within a rms distance of 0.11 Å of its partner. This symmetry is even better obeyed in the other two forms: 0.02 Å for α and 0.06 Å for β .

In contrast to the structure of the molecule *per se*, the hydrogen bonding pattern of δ -*D*-mannitol is significantly different from the other two polymorphs. Table V lists the hydrogen bonds in all three forms. δ -*D*-mannitol has a single chain of hydrogen bonds which advances one unit along the c axis in two repeats -O1–O2–O3–O4–O5–O6-. Each chain revisits a single molecule once, at O2 and O5. In α - and β -, there are two families of hydrogen bonds. Both have a closed rectangle O3–O4–O5–O6 connecting four different molecules. Both also have an infinite chain O1–O2–O1–O2 which advances one unit along the c axis in four bonds; in the case of β -, the pattern is essentially planar whereas in α -, there is a distinct spiral.

Note added in proof: Since the original submission of this manuscript, we became aware of an unpublished single

crystal structure determination of this material by J-O. Henck and J. Benet-Buchholz. Their results seem to be in substantial agreement with ours.

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