



Paper

The crystal structure of an unstable polymorph of β -D-allose

P. Arnaud Bonnet,^a Jacco van de Streek,^{*b} Andrew V. Trask,^a
W. D. Samuel Motherwell^b and William Jones^a

^aPfizer Institute for Pharmaceutical Materials Science, Department of Chemistry,
University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW

^bCambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK CB2 1EZ.
E-mail: streek@ccdc.cam.ac.uk

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The crystal structure of a new polymorph, Form II, of β -D-allose has been determined by X-ray powder diffraction. The unit cell is hexagonal, $a = b = 16.598 \text{ \AA}$, $c = 4.856 \text{ \AA}$, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$, space group $P6_2$ with $Z = 6$, $Z' = 1$. The molecule adopts the 4C_1 chair-conformation, with a torsional change of conformation of the O6 side-chain compared to the orthorhombic Form I. The two polymorphs share a common feature of a stacked hydrogen bonded column of molecules in the short axis direction. The structures differ in hydrogen linking of these columns. The more stable Form I has more immediate neighbours linked by hydrogen bonds to a reference molecule, and higher crystal density than Form II.

Introduction

The crystal structure of β -D-allose (Fig. 1) has been reported in the literature,¹ see also the Cambridge Structural Database² (CSD) reference code COKBIN.

Powder X-ray diffraction (PXRD) analysis, differential scanning calorimetry, optical rotation measurements, and ${}^{13}\text{C}$ CP/MAS solid- and ${}^{13}\text{C}$ solution-state NMR spectroscopy of D-allose samples obtained from different suppliers suggested the presence of 2 polymorphs of β -D-allose in one of the batches analysed.

Wolfrom *et al.*³ have reported the melting points and PXRD patterns of two pure polymorphs of β -D-allose, with melting points of 128°C (unstable polymorph, Form II) and 141°C (stable polymorph, Form I), but no structure had been reported. On storage, the unstable polymorph converted to the stable Form I.³

Our attempts to obtain single crystals of β -D-allose from different solvents (water, ethanol, methanol, ethyl acetate) and solvent combinations were unsuccessful. The difficulty in obtaining single crystals of β -D-allose has been highlighted in the literature.¹ Solutions of the sugar were therefore left to evaporate for two weeks at room temperature, and the deposit obtained was lightly ground into a powder and characterised. When a sample of the pure, stable polymorph of β -D-allose was dissolved in water, followed by the addition of ethanol to the point of incipient turbidity, and the solution allowed to evaporate, a white powdery deposit was observed. PXRD analysis of the solid, and comparison with the simulated PXRD pattern for the reported structure of β -D-allose, COKBIN, indicated that the solid deposit was a mixture of 2 phases,

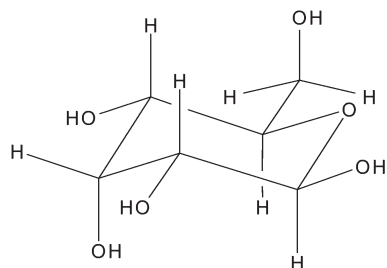


Fig. 1 4C_1 chair-conformation of β -D-allose.

which corresponded to the pattern reported by Wolfrom.³ Elemental analysis of the solid gave 39.93% C, 6.69% H and 53.38% O (expected for pure β -D-allose: 40.00% C, 6.71% H, 53.28% O). Differential scanning calorimetry analyses (with melting point onsets at 128°C and 140°C) suggested that a mixture of polymorphs of allose anhydrate had been obtained. Solution NMR analysis confirmed these observations. It was found that the unstable polymorph was formed as the main component of the mixture of the two polymorphs and the structure of the new polymorph was investigated.

Experimental

PXRD data were recorded at ambient temperature in transmission mode with a spinning borosilicate capillary on a Philips X'Pert diffractometer (Ge-monochromated Cu $K\alpha_1$ radiation; wavelength 1.54056 \AA). A scanning RTMS X'Celerator detector with an active length of 2.127° in 2θ was used with a step size of 0.017° in the 2θ range of $3\text{--}80^\circ$. The data were collected for 26 h.

Structure determination

Comparison of the recorded powder pattern (Fig. 2a) with a powder pattern simulated from the stable polymorph (Fig. 2b) showed that the peak at $2\theta = 20.70^\circ$ should be assigned to the known polymorph (Form I, COKBIN), present as an impurity, and also indicates that this impurity does not have significant diffraction anywhere else in the pattern. A comparison of the recorded powder pattern with the powder pattern reported by Wolfrom *et al.*³ for the unstable polymorph showed good agreement. (The minor hump at $2\theta = 13.79^\circ$ is known to be an artefact of the instrument from other experiments with and without capillary mounting.)

Owing to the excellent crystallinity of the sample and good counting statistics there is significant diffraction out to 1.25 \AA resolution ($2\theta = 76.0^\circ$), and all of the pattern was used in the subsequent steps. The background was subtracted with a Bayesian high-pass filter.⁴ Peak positions for indexing were obtained by fitting with an asymmetry-corrected Voigt function. The background subtraction, peak fitting and indexing algorithms used are as implemented in the DASH program.⁵

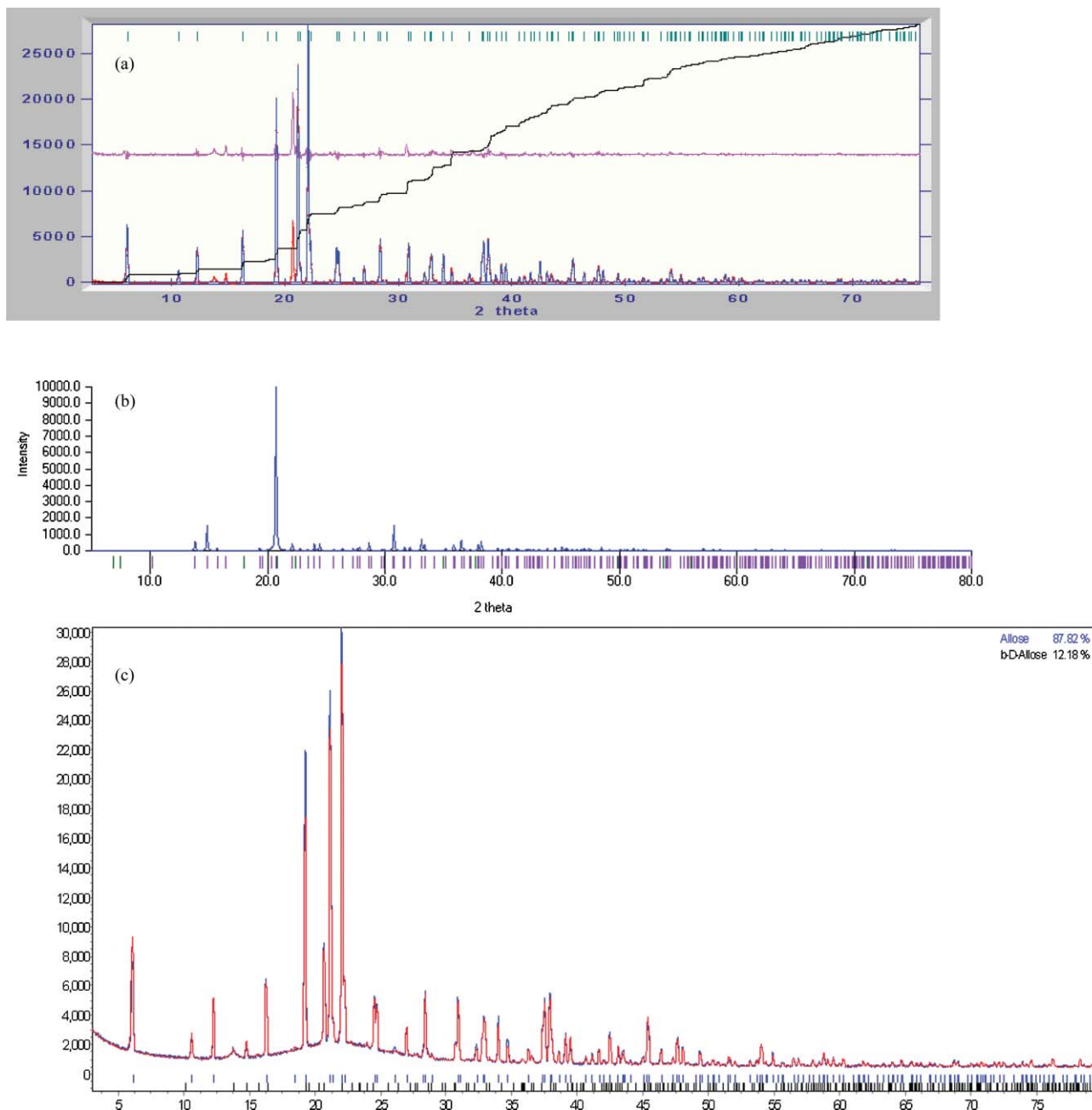


Fig. 2 (a) Calculated (blue), observed (red) and difference (magenta) profile. Tick marks are shown in green, the cumulative χ^2 is shown in black. (b) Simulated powder diffraction pattern of the known polymorph. (c) Result of two-phase Rietveld refinement.

Initial indexing attempts returned several unit cells with $\alpha = \gamma = 90^\circ$ and a unit-cell volume indicating $Z = 3$. α and γ being 90° pointed to at least a monoclinic crystal system, which makes $Z = 3$ highly unlikely due to the lack of molecular point-group symmetry, and it was therefore assumed that Z should be 6, *i.e.* that one of the unit-cell axes should be doubled. $Z = 6$ suggests a hexagonal unit cell, and when the indexing was restricted to the hexagonal crystal system a single unambiguous unit cell $a = b = 16.59825 \text{ \AA}$, $c = 4.85602 \text{ \AA}$, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$ was readily found. Note that the reflection at $2\theta = 20.70^\circ$ associated with a small amount of Form I, does not interfere with any of the peaks calculated from this unit cell. The unit-cell volume, 1159 \AA^3 , agrees very well with $Z = 6$, *i.e.* $193 \text{ \AA}^3 \text{ molecule}^{-1}$ when compared to the crystal structures of similar compounds such as β -D-allose,¹ α -D-galactose, β -D-galactose⁶ and α -D-mannopyranose⁷ with molecular volumes of 188, 185, 189 and $191 \text{ \AA}^3 \text{ molecule}^{-1}$, respectively.

Space-group determination based on statistics of the extracted intensities and their correlations⁸ as implemented in DASH narrowed the choice of space groups down to $P6_1$,

$P6_2$ or $P6_3$. Pawley refinement in all three space groups gave profile- χ^2 values of 17.15, 17.08 and 17.19 for $P6_1$, $P6_2$ and $P6_3$, respectively. Crystal-structure solution by means of a direct-space simulated-annealing algorithm as implemented in DASH was attempted in all three space groups. 10 runs of 15 000 000 moves each were performed for each space group. The starting geometry of the molecule was taken from the single crystal structure of the known polymorph COKBIN, the O6–C6–C5–C4 torsion angle was left as a degree of freedom to be optimised during the simulated annealing.

The simulated annealing in space group $P6_2$ readily yielded 10 identical solutions with a profile χ^2 of 13.5, even lower than the profile χ^2 obtained from the Pawley fit (this is usually not possible but is caused by various approximations applied in order to speed up the calculations). Space groups $P6_1$ and $P6_3$ each yielded 10 identical solutions, none of which had a profile χ^2 lower than 146, ten times higher than $P6_2$. The reproducibility of the solutions is a strong indication that the global minima have been found, and the correct space group is therefore $P6_2$. Full rigid-body Rietveld refinement, including

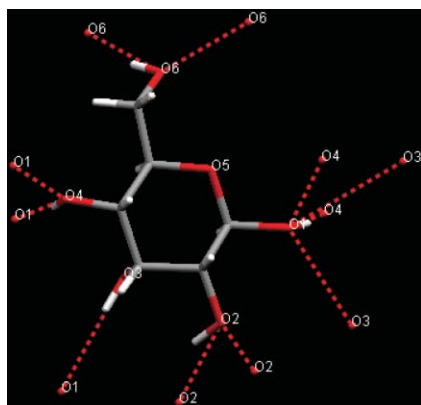


Fig. 3 Form II ($P6_2$) molecular conformation with all non-bonded $O\cdots O$ contacts less than the sum of van der Waals radii + 0.2 Å.

bond angles and bond lengths not involving rings or hydrogen atoms, resulted in little change in position, orientation or geometry of the molecule and gave a final profile χ^2 of 7.24, and intensity χ^2 of 2.56. Fig. 2a shows the excellent final fit. The minor discrepancies at $2\theta = 14.82^\circ$ and 30.70° are both due to the presence of the other polymorph. Hydrogen atoms were placed in chemically reasonable positions. A two-phase Rietveld refinement, including the crystal structure of the known polymorph, showed that all features in the experimental powder pattern are accounted for by the two phases (Fig. 2c).

Discussion

Polymorphism is rarely reported for pyranose monosaccharides; in fact this appears to the first case of a pair of polymorphs with full structure determination. It is therefore of interest to compare the crystal structures in some detail to identify any common features. The molecular conformation and numbering of the Form II, $P6_2$, crystal structure is shown in Fig. 3, including its H-bonded contacts. For comparison we show the molecule of Form I, $P2_12_12_1$, (COKBIN) with its H-bonding contacts in Fig. 4.

Conformation

There is a difference in conformation of the one flexible side-chain, defined by the torsion angle $O5-C5-C6-O6$, (τ Form I $\tau = -75.3^\circ$ and Form II $\tau = 66.8^\circ$). These values are typical of this angle in a survey of the available 17 structures of hexoses in the CSD (version 5.26 Nov 2003). There is some evidence that there is only a small energy difference between the conformations, see the example of α -D-mannopyranose (ADMANN) which has two independent molecules in the asymmetric unit, with $\tau = -63.7$ and 66.7° .

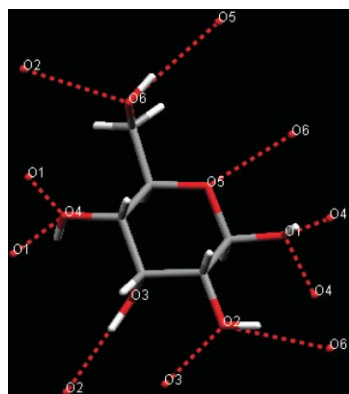


Fig. 4 Form I ($P2_12_12_1$) showing all $O\cdots O$ contacts less than sum of van der Waals radii + 0.2 Å, corresponding to the hydrogen bonds.

Hydrogen bonding

In Form II the contacts to atom O3 are longer than usual, and the ring atom O5 is not involved in H-bonding. All contacts are reasonable given the limited accuracy of the coordinates. In both structures the acyclic oxygens O1, O2, O4, O6 are involved in one donor and one acceptor H-bond, as is normal for sugars. At O3 there is only a donor bond, and no acceptor, and this is a rather weak H-bond at $O\cdots O$ of 3.22 Å. Comparison of the total number of H-bonds per atom shows the same values for all O atoms except that in Form I there is an H-bond to O5, not seen in Form II.

The hydrogen bond networks are very complex, as expected, and a full analysis is not felt to be necessary here. However a common feature is noted that in both structures we have a chain of H-bonds $O4\cdots O1\cdots O4\cdots O1$ in the direction of the short axis. In Form I the $O\cdots O$ distances are 2.728, 2.635 and in Form II 2.500 and 2.986 Å. In Form I we have a strongly linked network $O2\cdots O6$ (2.838 Å) and $O4\cdots O1$ (2.635 Å) where each molecule is doubly H-bonded to its neighbour in the c -direction. In Form II we also have doubly H-bonded molecular links $O2\cdots O2$ (2.468 Å), $O3\cdots O1$ (3.197 Å), and $O1\cdots O4$ (2.986 Å), $O4\cdots O6$ (2.804 Å), contributing to extension in the a -direction.

Packing comparison

The most obvious similarity is the almost identical short-axial lengths, and also the approximately equal axes b and c in Form I, and the exact equality a and b in Form II.

Polymorph	Space group	$a/\text{Å}$	$b/\text{Å}$	$c/\text{Å}$	Z	$V/\text{Å}^3$	$V/Z/\text{Å}^3$	$T_m/^\circ\text{C}$
I stable	$P2_12_12_1$	4.918	11.925	12.805	4	751.0	187.7	141
II unstable	$P6_2$	16.598	16.598	4.856	6	1158.6	193.1	128

We note that Form II is less dense than Form I, and has a lower melting point³ as is expected for the unstable member of a monotropic polymorphic pair.

For comparison of the overall crystal structure of the polymorphs we show the short axis projection of the new Form II in Fig. 5 and the stable Form I in Fig. 6.

It is often found for pairs of polymorphs for hydrogen bonded molecules that some periodic fragment of one polymorph crystal is present in the other polymorph.⁹ Here the common feature is the packing of the molecules in the short axis direction, which are remarkably similar in orientation with respect to the short axis. The chains along the short

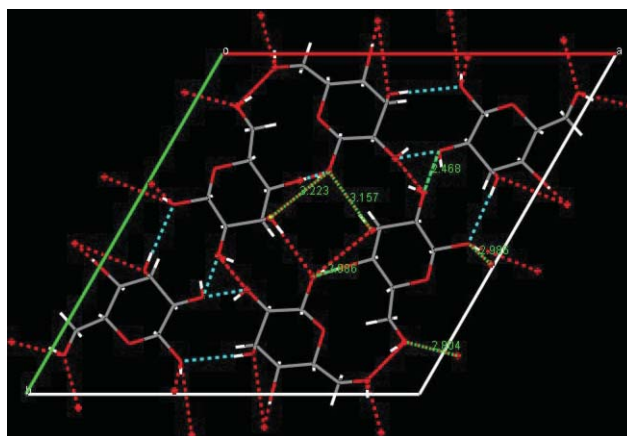


Fig. 5 Crystal structure of Form II ($P6_2$) projected down the c -axis. Hydrogen bonds are shown as dotted lines for all contacts $O\cdots O$ less than sum of van der Waals radii plus 0.2 Å. Red dotted lines mean that there are links extending beyond this section of the crystal. Click here to access a 3-D image of Fig. 5.

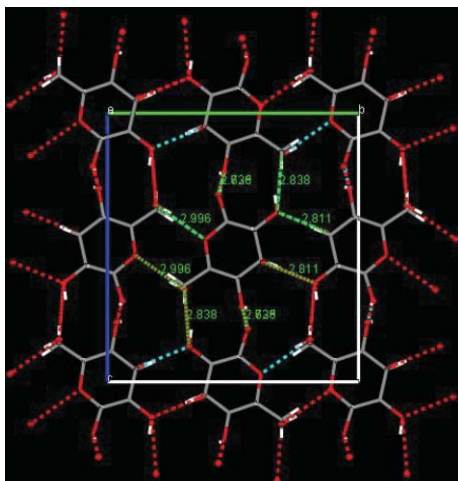


Fig. 6 Crystal structure of Form I ($P2_12_12_1$) projected down the short a -axis. Hydrogen bonds are shown as dotted lines for all contacts $O\cdots O$ less than sum of van der Waals radii.

axis involve $O1\cdots O4\cdots O1$ in both cases, see Fig. 7a,b. So, both structures can be viewed as stacked columns of molecules in the short axis direction, but differently linked to neighbouring columns.

In the hexagonal Form II structure we see a helical 3_1 screw axis chain formed by $O2\cdots O2$ (2.468 Å) at $x = 2/3, y = 1/3$, see Fig. 5. The space group $P6_2$ is quite rare in the CSD, only 25 entries with coordinates, only 9 containing OH, and only one example of a 3_1 $OH\cdots OH$ helix. A survey of space groups $P3_1$ and $P3_2$ show 130 structures with OH present. It was noticed that when this 3_1 chain occurs it is usually associated with a much longer axial direction, e.g., BESRIA 8.05, CARHYD, 7.11, CEMKAG 7.43 Å, the shortest found being BAVLOZ with 5.98 Å. This suggests that the chain observed for Form II is not in a state of optimal geometry for the hydrogen bonds.

There is also an unusually complex 6_1 screw axis arrangement $O6\cdots O6$ (2.804 Å) at $x = 0, y = 0$, which forms a helix of the doubly H-bonded molecules in the short axis direction (Fig. 8).

The question of why form II is unstable is impossible to answer in terms of packing energy, since we do not know the H-atom positions sufficiently accurately. However, the idea of extending the structure by H-bond links, using all links to get

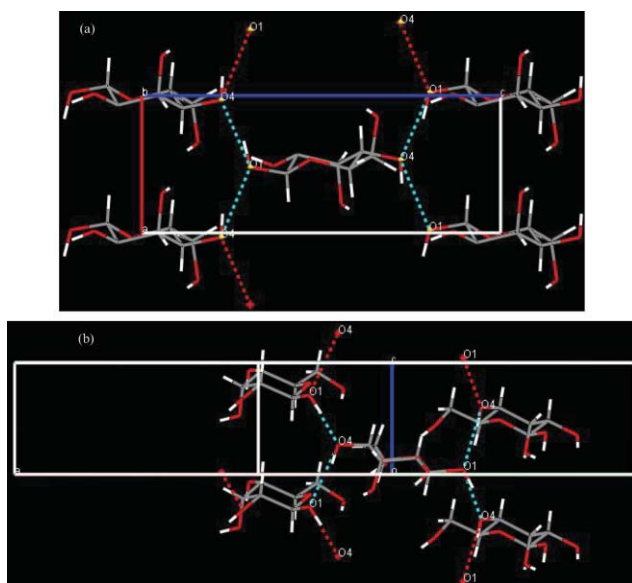


Fig. 7 (a) Form I. Stacked molecules in a -axis direction linked by $O1\cdots O4\cdots O1$ H-bonds of length 2.63, 2.73 Å. (b) Form II. Stacked molecules in c -axis direction linked by $O1\cdots O4\cdots O1$ H-bonds of length 2.50, 2.99 Å.

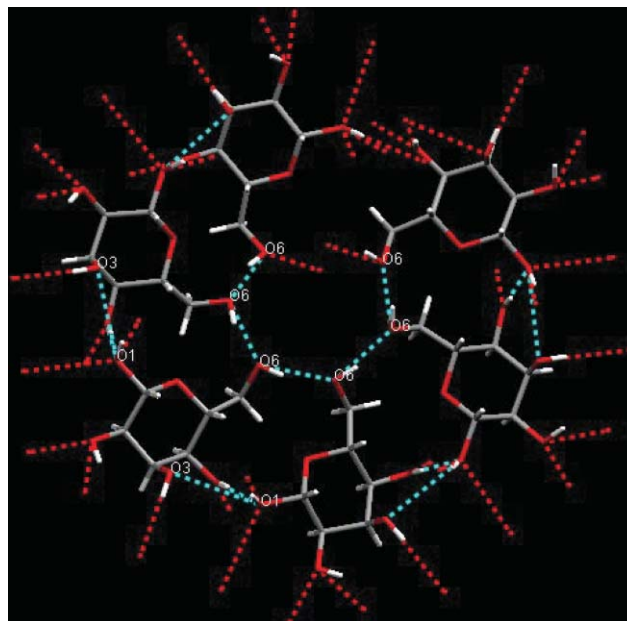


Fig. 8 Form II. Helix structure using a 6_1 operator, formed by $O6\cdots O6$ and $O3\cdots O1$ H-bonds in the short axis direction.

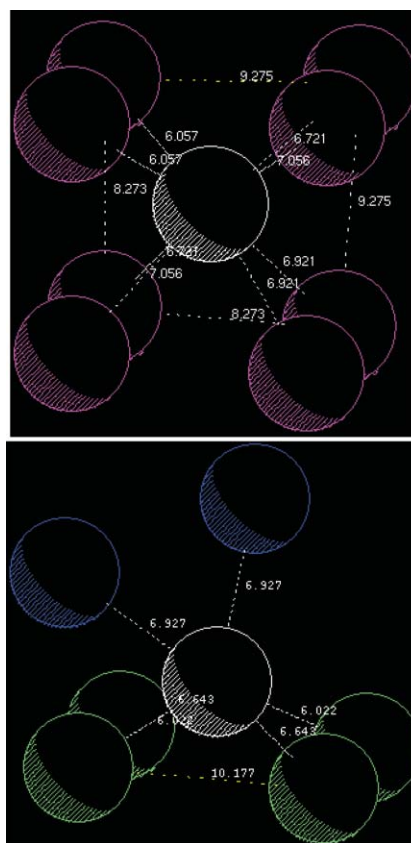


Fig. 9 Comparison of first-neighbour shells of molecules linked by H-bonding to the reference molecule. The Form I shell (top) is rather symmetrical, the purple colour indicating that these neighbour molecules are generated by a 2_1 screw axis. The form II shell (bottom) is less symmetrical, the colour coding indicates that the green molecules are generated by a 6_2 screw axis, and the blue by a 3_1 screw axis. The distances (Å) show some similarity in spacing of the molecular centres.

the first neighbour shell of molecules may be useful. In Form I the shell consists of 8 molecules in an arrangement reminiscent of a cubic close packed array, flattened in the short axis direction. In Form II the shell consists of 6 molecules, and is less symmetrical. This can be seen by a simplified plot where we replace each molecule by a sphere at its molecular centre (Fig. 9).

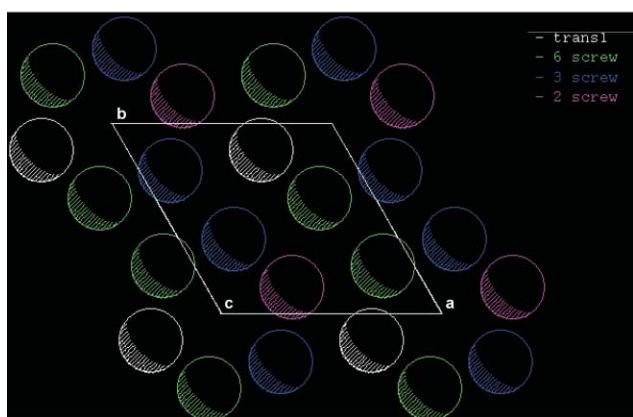
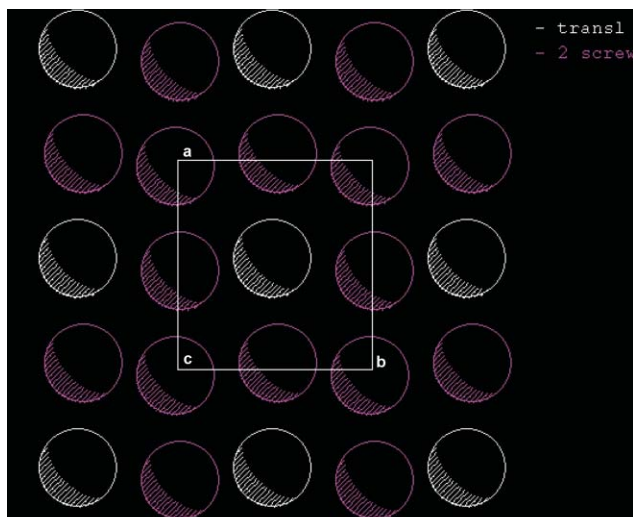


Fig. 10 Simplified view of the packing of allose molecules represented by a sphere of radius 2.4 (Å) at the molecular centre. Both structures are projected down the short axis. Form I (top) shows a pattern reminiscent of body-centred cubic packing, whereas Form II (bottom) shows a more open structure with more apparent void space in the region of (0, 0, z).

A wider view of the total crystal packing in Fig. 10 shows the columns of molecules viewed along the short axis. It can be seen that in this projection the more stable Form I approximates to a

pseudo-cubic arrangement and seems to fill the space more evenly than the less stable Form II.

Conclusions

The methodology of crystal structure solution from PXRD opens up the possibility of obtaining detailed structural studies of less stable polymorphs which are sometimes impossible to obtain in single crystal form. This unusual hexose crystal structure suggests that the more stable Form I is favoured when molecules are linked by the maximum number of H-bonds for available donor/acceptor atoms, and of the best quality (as judged by shorter O...O distances). The higher crystal density of Form I and the more symmetrical, evenly distributed void space may be an important factor. It is perhaps significant that in the more stable Form I each molecule is linked in all three cell directions by H-bonds to 8 neighbours as compared to 6 neighbours in Form II.

CCDC reference number 248562.

See <http://www.rsc.org/suppdata/ce/b4/b412962h/> for crystallographic data in CIF or other electronic format.

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