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THE X-RAY CRYSTAL STRUCTURE OF 2,5-ANHYDRO-D-MANNITOL*

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ABSTRACT

The crystal and molecular structure of 2,5-anhydro-D-mannitol, a model for β-D-fructofuranoses, has been determined by X-ray diffraction and statistical-phasing procedures. The crystals are orthorhombic, space group $P2_12_12_1$, $a = 7.877(3)$, $b = 8.553(1)$, $c = 11.446(2)$ Å, with four molecules per cell. In the crystal, the molecule does not have the expected C_2 symmetry: the ring C–O bonds are unequal in length, and the conformation deviates slightly from the ideal $^4T_3$ structure by a pseudorotation angle of $-11.7°$ (amplitude 39.9°). In contrast, the ^{1}H-n.m.r. spectrum indicated, on average, the $^4T_3$ conformation in solution. A strong, intermolecular, donor–acceptor, hydrogen-bonding network exists between hydroxyl groups on C-1, C-3, and C-4. The C-6 hydroxyl group participates in a much weaker, donor hydrogen-bond with a ring-oxygen atom.

INTRODUCTION

2,5-Anhydro-D-mannitol (**1**) has been utilized in studying the tautomeric and anomeric specificity of a number of glycolytic enzymes acting on β-D-fructofuranose and its phosphates[1–8]. It is also a model for the β-D-furanose form of a number of D-fructosides of biological origin[9,10]. The compound itself is of interest[11] owing to its historical use as a characteristic product isolated from the deamination–reduction of 2-amino-2-deoxy-D-glucose, which is a major monomeric unit in many animal polysaccharides. Furthermore, 2,5-anhydro-D-mannitol appears to have significant, pharmacological properties[12].

Bera *et al.*[13] first prepared 2,5-anhydro-D-mannitol through Raney nickel reduction of deaminated 2-amino-2-deoxy-D-glucose. The material used in the present study was obtained through reduction of deaminated 2-amino-2-deoxy-D-

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glucose with sodium borohydride[1]. A similar procedure was reported by Horton and Philips[14], who also used reduction with sodium borohydride.

Structurally, 2,5-anhydro-D-mannitol has a rotational axis of symmetry (C_2). For the compound and its substituted derivatives in solution, this property has been demonstrated by classic methods[13] and, more recently[1,15–18], by using ^{1}H-, ^{13}C-, and ^{31}P-n.m.r. spectroscopy. These n.m.r. techniques usually show the average conformation of the molecule. The present work utilized X-ray diffraction in order to elucidate the conformation of 2,5-anhydro-D-mannitol in the crystalline state.

EXPERIMENTAL

The sample of 2,5-anhydro-D-mannitol (**1**) was prepared by the method previously reported[1] from this laboraory, and was repeatedly recrystallized from absolute ethanol.

A well-formed, colorless crystal was mounted on an Enraf–Nonius CAD4 diffractometer equipped with a graphite monochromator, and initial investigations indicated that the crystal belongs to orthorhombic space-group $P2_12_12_1$. Least-squares refinement of 25 well-centered reflections ($27° \leq 2\theta \leq 30°$) yielded the lattice constants shown in Table I. All reflections in one octant of reciprocal space, with $1° \leq 2\theta \leq 25°$, were measured with the $\omega/2\theta$ scan technique described elsewhere[19]. Standard reflections were periodically measured during data collection, and one strong reflection near $\chi = 90°$ was measured after data collection using in-

TABLE I

CRYSTALLOGRAPHIC DATA

Formula	$C_6H_{12}O_5$
Mol. wt.	164.26
Cell constants	
a	7.877(3) Å
b	8.553(1) Å
c	11.446(2) Å
Volume	771.14(4) Å^3
Z	4
Density (calc.)	1.412 g/cm^3
Space group	$P2_12_12_1$
Crystal size	0.36 × 0.30 × 0.20 mm^3
λ (MoKα)	0.71073 Å
μ (MoKα)	1.33 cm^{-1}
Minimum rel. transmission	92.9%
Linear decay factors (min/max)	0.78/1.18
Reflections measured ($\omega/2\theta$ scan)	768
Reflections with $I > 3\sigma(I)$	714
Weights (w^{-1})	$\sigma^2(\lvert F_o\rvert) + 0.02\lvert F_o\rvert^2$
Final residual factors	
$R = \Sigma\lvert\lvert F_o\rvert - \lvert F_c\rvert\rvert/\Sigma\lvert F_o\rvert$	0.0379
$R' = (\Sigma w(\lvert F_o\rvert - \lvert F_c\rvert)^2/\Sigma w\lvert F_o\rvert^2)^{1/2}$	0.0381

TABLE II

FRACTIONAL POSITIONAL PARAMETERS AND EQUIVALENT ISOTROPIC TEMPERATURE-FACTORS[22] OF ALL ATOMS IN 2,5-ANHYDRO-D-MANNITOL (e.s.d. IN PARENTHESES). VALUES $\times 10^4$ (10^3 FOR HYDROGEN ATOMS)

Atom	*X*	*Y*	*Z*	*U*
C-1	−4897(4)	−3431(4)	−8382(3)	382(9)
C-2	−6444(4)	−4159(3)	−8921(2)	315(8)
C-3	−8103(4)	−3664(3)	−8360(2)	302(8)
C-4	−9247(4)	−5013(4)	−8668(2)	307(8)
C-5	−8076(4)	−6419(3)	−8554(3)	326(9)
C-6	−8461(5)	−7772(4)	−9364(3)	393(9)
O-1	−3367(3)	−3853(3)	−8970(2)	440(7)
O-3	−8675(3)	−2203(2)	−8802(2)	383(6)
O-4	−10686(3)	−5186(3)	−7930(2)	395(6)
O-5	−6383(3)	−5825(2)	−8776(2)	400(7)
O-6	−8554(4)	−7255(3)	−10540(2)	494(8)
H-11	−483(4)	−383(4)	−749(3)	56(2)
H-12	−495(4)	−239(4)	−839(3)	39(2)
H-2	−644(4)	−396(3)	−967(3)	35(2)
H-3	−797(4)	−363(4)	−752(3)	33(2)
H-4	−958(4)	−492(4)	−942(2)	34(2)
H-5	−811(4)	−680(4)	−772(2)	25(2)
H-61	−758(4)	−862(4)	−927(3)	56(2)
H-62	−965(4)	−824(4)	−913(2)	54(2)
H-O1	−344(4)	−360(3)	−977(1)	74(2)
H-O3	−895(4)	−149(3)	−819(2)	57(2)
H-O4	−1168(2)	−478(3)	−827(2)	73(2)
H-O6	−928(3)	−793(3)	−1096(2)	50(2)

cremental values of 10°. Thus, both a linear-decay correction and an empirical, absorption correction could be applied to the data, in addition to the standard Lp correction.

Direct-methods procedures (MULTAN[20]) revealed the positions of all eleven non-hydrogen atoms; hydrogen atoms were located from difference-electron-density, Fourier syntheses. The final model, refined by weighted, full-matrix least-squares, contained 149 variables and incorporated the following features: anisotropic thermal parameters for all non-hydrogen atoms, isotropic parameters for hydrogen atoms, independent refinement of hydrogen-atom positions, an isotropic, extinction parameter (0.0258), and a parameter which adjusts the weights for high-intensity effects (0.02). The atomic-scattering factors were those of Cromer and Mann[21]. Atomic coordinates are listed in Table II. The anisotropic thermal parameters, the observed and calculated structure-amplitudes, and the complete set of torsion angles are listed in Tables III, IV, and V*.

*Tables III, IV, and V are deposited with, and can be obtained from, Elsevier Scientific Publishing Company, BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/257/*Carbohydr. Res.*, 119 (1983) 49–55.

TABLE VI

HYDROGEN BONDS

Hydrogen bonds	*O---H*	*H-O*	*O-----O*	*OHO*
O-1-----H-O-4(I)[a]	1.74(2)	0.94(2)	2.679(3)	173(2)
O-4-----H-O-3(II)	1.73(2)	0.95(2)	2.676(3)	176(3)
O-3-----H-O-1(III)	1.79(2)	0.94(1)	2.716(3)	170(3)
O-5-----H-O-6(IV)	1.99(3)	0.94(2)	2.877(3)	156(3)

[a]Hydroxyl groups in symmetry-related molecules in the crystalline lattice, as follows: (I) x + 1, y, z; (II) -x-2, y-1/2, -z-3/2; (III) x-1/2, -y-1/2, -z-2; and (IV) x + 1/2, -x-3/2, -z-2.

RESULTS AND DISCUSSION

Bond lengths and angles are shown in Fig. 1, and selected torsion-angles, in Fig. 2. The absolute configuration is assumed to be D, based on the synthetic route and the specific optical rotation of the starting material. All calculations related to the diffraction experiment conform to this assignment. A stereoscopic view of the molecule is shown in Fig. 3. The conformation is $^4T_3$, with a pseudorotation[23] amplitude (τ_m) of 39.9° and a phase angle (P) of −11.7°. The molecules pack in the crystal in such a way as to form a network of intermolecular hydrogen-bonds (see Table VI).

As reported previously[15,16], the ^{13}C-n.m.r. spectrum of **1** in solution contains only three resonances, consistent with the D-*manno* stereochemistry. The ^{1}H-n.m.r. spectrum showed a high degree of symmetry, and the coupling constants indicated $^4T_3$ as the average conformation in solution[18].

In contrast to the n.m.r. data, the X-ray data indicate that the conformation of the 2,5-anhydro-D-mannitol molecule in the solid state is distorted from the per-

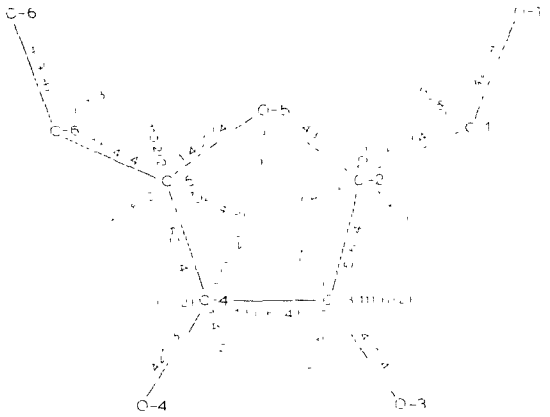

Fig. 1. Bond lengths (in Å, e.s.d. values in parentheses) and valence bond-angles (in degrees, e.s.d. values in parentheses) in 2,5-anhydro-D-mannitol

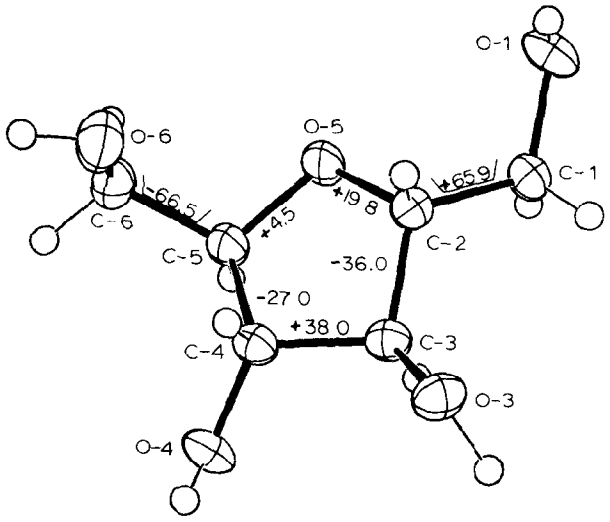

Fig. 2. Selected torsion-angles (in degrees; e.s.d. values are 0.1°) in 2,5-anhydro-D-mannitol.

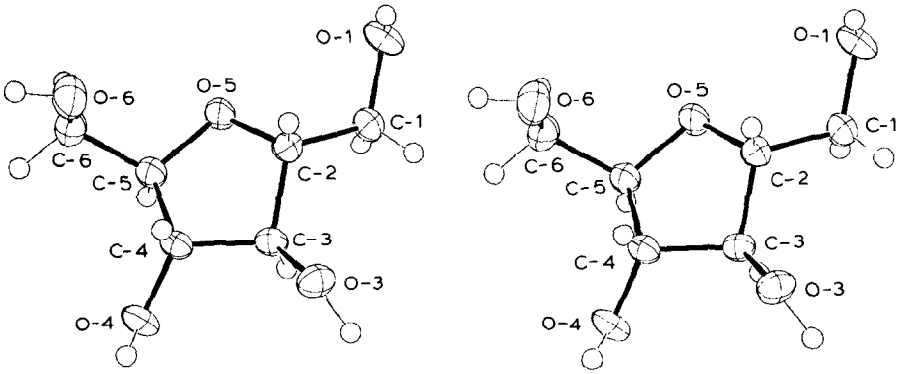

Fig. 3 Stereoscopic view of 2,5-anhydro-D-mannitol.

fect $^4T_3$. Noteworthy is the significantly unequal length of the two ring C–O bonds (1.450 and 1.435 Å). The molecule formed by two further dehydrations of **1**, *i.e.*, 1,4:2,5:3,6-trianhydro-D-mannitol, has the expected, perfect $^4T_3$ symmetry in the solid state[24]. The corresponding C–O bond length is 1.452 Å, and thus is almost the same as the former value. On the other hand, the latter value (1.435 Å) is close to the value for a true anomeric bond of a ketofuranose, *e.g.*, the 1.425 Å reported for 6-deoxy-α-L-sorbofuranose[25].

Strong, intermolecular forces are the apparent cause of the molecular distortion observed. These forces arise from two different types of hydrogen-bonding in-

teraction. In the first type, hydroxyl groups participate both in donor and acceptor roles, as observed for hydroxyl groups on C-1, C-3, and C-4, whereas in the second, the hydroxyl group donates a proton to form only a weaker hydrogen-bond, as observed at C-6.

Swaminathan *et al.*[25] compared various ketofuranoses on a pseudorotation circle. Most of the P values were clustered between −18 and +9°. The value for an exact $^4T_3$ conformation is 0°, and this is the value expected for unperturbed 2,5-anhydro-D-mannitol. However, we observed a value of −11.7°. Apparently, the intermolecular forces in the solid state are sufficient to distort the molecule to the same extent that an anomeric linkage distorts the ring of a ketofuranose.

The present data also reveal that the exocyclic, hydroxymethyl groups attached to C-2 and C-5 adopt +gauche and −gauche dispositions, respectively. This pair of orientations may be compared to those for the β-D-fructofuranose unit of several ketofuranosides[35]. An equivalent $+g$, $-g$ arrangement is present in raffinose, planteose, and 1-kestose (in D-fructose-2). However, the corresponding dispositions in sucrose and 1-kestose (in D-fructose-1) are $-g,t$ and $-g,t$. The difference exhibited by the latter two rings is due to intramolecular bonding and steric interactions.

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