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Structure and taste of 3,6:3',6'-dianhydro-α,α-trehalose monohydrate†

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The X-ray diffraction structure of 3,6:3',6'-dianhydro-α,α-trehalose (3,6-anhydro-α-D-glucopyranosyl 3,6-anhydro-α-D-glucopyranoside) monohydrate is described. The molecule has exact two-fold symmetry through the anomeric oxygen atom. The pyranosyl ring has a slightly distorted $^1C_4$ chair conformation and the *cis*-fused five-membered anhydro ring has a near perfect ^4E envelope conformation. X-ray crystal data show an absence of a sweet AH,B glucophore, which would explain the absence of sweetness. Evidence indicating the importance of hydrophobic character to bitterness is presented.

INTRODUCTION

The Shallenberger & Acree theory (1967) of sweetness proposes that the basic requirement for a compound to be sweet is an AH,B moiety. The intensity of sweetness (Kier, 1972; Shallenberger & Lindley, 1977) requires a third hydrophobic γ site (Deutsch & Hansch, 1966). In hexopyranoses in the favoured $^4C_1$ conformation, O(3) acts as B with either O(4), normally, and less commonly O(2) acting as AH (Birch & Lee, 1974). The $^1C_4$ conformation is not normally found for most common sugars in the free state. A notable exception is β-D-fructopyranose. The AH,B glucophore in such sugars is not generally defined. It may be different from that of $^4C_1$ sugars, as seen in β-D-fructopyranose (Shallenberger & Acree, 1967). Anhydro derivatives of D-sugars also exist in the $^1C_4$ conformation, but unlike hexopyranoses in the $^4C_1$ conformation O-3 (in 3,6-anhydro sugars) or O-6 (in 1,6-anhydro sugars) is now part of a ring system. Furthermore, in 1,6- and 3,6-anhydroglucopyranoid structures, O-3 has *trans*-diaxial relationships with both O-2 and O-4, so that it may not be able to function with either of these hydroxyl groups as a sweet AH,B glucophore. We are, therefore, interested in the X-ray structure of 3,6:3',6'-dianhydro-α,α-trehalose.

MATERIALS AND METHODS

3,6:3',6'-Dianhydro-α,α-trehalose (**1**) was prepared by the method of Birch *et al.* (1971). Colourless prisms of **1** were grown in ethanol solution at room temperature. The crystal data and intensity-measurement data were obtained using a Siemens R3m/V diffractometer with Mo K_α radiation (γ = 0·71073 Å) (graphite monochromator) and are given in Table 1 together with the refinement data.

The structure was solved by the direct method and refined by full matrix least-squares refinement on F using SHELXTL PLUS (Sheldrick, 1990) on a Micro Vax 2000. The carbon and oxygen atoms were refined anisotropically; CH hydrogen atoms were at calculated positions, and H atoms were assigned U values, which are about 1·3 times that of U_{eq} of the carbon atoms to which the atoms are attached. They were included with isotropic temperature factors in the final R calculation, but their positions were not refined. All the hydrogen atoms of hydroxyl groups could not be located from the difference map because intensity data were rather poor. Lists of final atomic parameters, anisotropic thermal parameters and hydrogen positions are available from the authors.

RESULTS AND DISCUSSION

The atomic notation and thermal ellipsoids of **1** are shown in Fig. 1. The molecular packing in the crystal showing the hydrogen bonding interactions is given in Fig. 2. These figures also depict the correct absolute configuration of the molecule as established by its synthesis. The atomic coordinates of nonhydrogen atoms are given in Table 2. Bond lengths, bond angles and selected torsion angles are given in Table 3.

In the structure of **1**, unlike in α,α-trehalose (Brown *et al.*, 1972; Taga *et al.*, 1972; Jeffrey & Nanni, 1985) and 2,2'-di-*O*-acetyl-3,6:3',6'-dianhydro-4,4'-dideoxy-α,α-trehalose (Lee & Koh, 1994), the molecule has perfect

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†Part 6 in the series 'Structure of Trehalose Derivatives'. For Part 5, see Lee, C. K. & Linden, A. (1995).

Table 1. Crystal structure and refinement data for 3,6:3'6'-dianhydro-α,α-trehalose monohydrate

Crystal data
$C_{12}H_{18}O_9.H_2O$; M_r 324·2; m.p. 199–206°C; C_2; $Z = 2$
Cell dimensions at 298 K: $a = 11{\cdot}105(2)$, $b = 7{\cdot}352(2)$, $c = 9{\cdot}570(2)$ Å, $\beta = 115{\cdot}730(10)°$
$V = 703{\cdot}9(3)$ Å^3, D_{calc} 1·501 g cm^{-3}; $\mu = 0{\cdot}134$ mm^{-1}
Crystal dimensions: 0·3 mm × 0·3 mm × 0·2 mm, colourless plate
Radiation: Mo $K\alpha$ ($\lambda = 0{\cdot}71073$) graphite monochromator
Cell dimensions based on 20 reflections in the range $6{\cdot}9° < 2\theta < 22{\cdot}2°$
Data collection
Siemens R3m/V diffractometer
Absorption correction: no absorption correction
722 reflections were measured by ω scan technique and a maximum 2θ value of 50°, of which 682 were unique R_{int} = 0·0505) and 558 were observed, $F > 4.0\sigma(F)$; 101 variable parameters refined
Scanning rate: variable; scan range = 1.20°
Standard reflections: three measured every 97 reflections
Refinement
Function minimised, $\Sigma w(|F_0| - |F_c|)^2$, using SHELXTL PLUS (Sheldrick, 1990) where $w^{-1} = \sigma^2(F) + 0{\cdot}0000F^2$ based on counting statistics
Extinction correction: $\chi = 0.075(12)$ where $F^* = F[1 + 0{\cdot}002\chi F^2/\sin(2\theta)]^{-1/4}$
Final agreement factors: $R = 0{\cdot}0784$, $wR = 0{\cdot}0785$; goodness-of-fit = 0·98
Atomic scattering factors from *International Tables for X-ray Crystallography*, Vol. IV, Kynoch Press, UK (1974).

C_2 symmetry. Bond lengths and angles are normal and generally agree with related compounds. The C–O bond lengths associated with the anomeric carbon atoms and ring oxygen atoms also show similar systematic trends (Berman *et al.*, 1967). The strain introduced by the *cis*-fused five-membered anhydro ring causes a narrowing of the C-3—C-4—C-5 angle (98·6(6)°). This is also observed in other 3,6-anhydro-α-D-hexopyranosyl derivatives (Lindberg *et al.*, 1972; Campbell & Harding, 1972; Isaac & Kennard, 1972). The distance between C-3 and C-5 is also shortened (*c.* 2·3 Å) significantly (*c.* 0·2 Å) compared to those found for an unbridged pyranose ring. Consequently, the O-2 ··· O-4 distance is shortened to *c.* 2·6 Å, which is *c.* 0·2 Å shorter than that in the corresponding methyl α-D-glucopyranoside.

The fused-ring conformation of **1** is very similar to that of 2,2'-di-*O*-acetyl- 3,6:3',6'-dianhydro-4,4'-dideoxy-α,α-trehalose (Lee & Koh, 1994), as shown in the puckering parameters (Cremer & Pople, 1975) ($Q = 0{\cdot}661$, $\phi_2 = 62{\cdot}2°$, $\theta = 162°$, $q_2 = 0{\cdot}204$, $q_3 = 0{\cdot}629$). The five-membered anhydro ring has a near pure envelope (4E) conformation ($\phi_2 = 3{\cdot}0°$, $Q = q_2 = 0{\cdot}487$ Å) with C-4 lying 0·742 Å above the least squares plane through C-3, O-3, C-5, C-6. The slight distortion is expressed by the small torsion angle C-5—C-6—O-3—C-3 (–1·6(7)°).

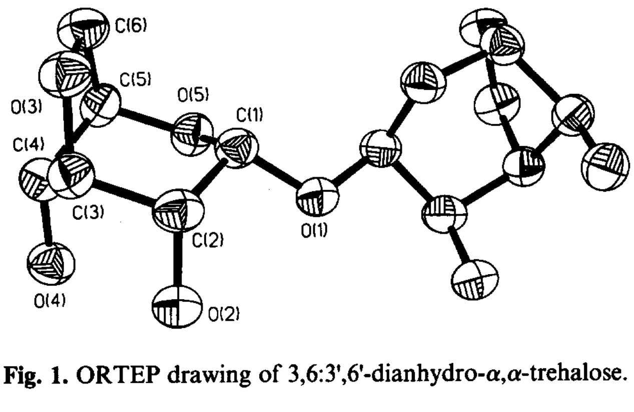

Fig. 1. ORTEP drawing of 3,6:3',6'-dianhydro-α,α-trehalose.

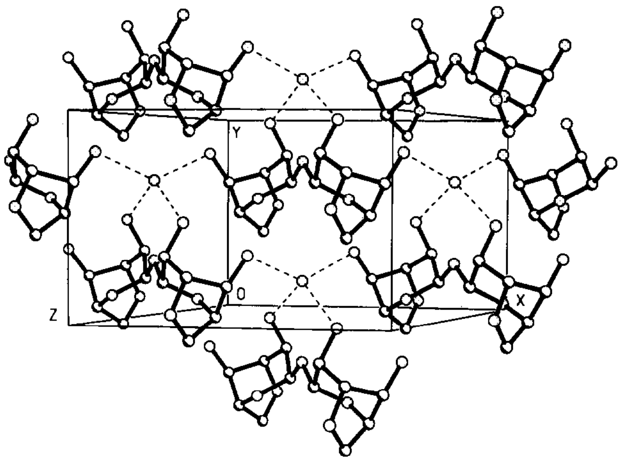

Fig. 2. Molecular packing of 3,6:3',6'-dianhydro-α,α-trehalose monohydrate, showing the hydrogen bonding interactions.

The crystal is packed through a very neat system of hydrogen bonding between water and the sugar molecules (Fig. 2; Table 4). However, the hydrogen-bonded hydrogen atoms could not be located by difference electron density maps because of rather poor intensity data. It is, therefore, not possible to be certain whether the hydroxyl groups are serving as a donor or acceptor, but hydrogen bonding in either direction is equally possible.

The water molecule forms four hydrogen bonds to three sugar molecules. Two of these bonds are to O^{I}-2 and O^{II}-2' (both 2·709 Å)† of the same sugar molecule, while the other two bonds are to O^{III}-4 and O^{IV}-4 (both 2·686 Å)† of two other sugar molecules. Like in the corresponding glucopyranoside derivative (Lindberg *et al.*,

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†Symmetry operators: (I) x, y, z; (II) $x + ½, y - ½, z$; (III) $x - ½, y - ½, -z$, (IV) $-x, y, -z$.

Table 2. Atomic coordinates (×10^4) and equivalent isotopic displacement coefficients (Å × 10^3) (with esds in parentheses)

Atom	x	y	z	U_{eq}^{a}
O–1	0	2738	5000	69(3)
O–2	2034(5)	4704(11)	7001(6)	79(2)
O–3	2786(5)	475(11)	9180(5)	81(2)
O–4	4135(5)	3147(12)	7004(6)	80(2)
O–5	1805(5)	878(10)	5635(5)	73(2)
C–1	963(6)	1718(14)	6238(8)	65(3)
C–2	1710(7)	3068(13)	7532(g)	73(3)
C–3	3031(7)	2189(13)	8685(8)	69(3)
C–4	3868(7)	1687(14)	7813(8)	71(3)
C–5	3019(7)	135(12)	6845(7)	70(3)
C–6	2789(9)	–897(14)	8086(10)	82(4)
O–21	5000	1777(12)	5000	80(3)

^{a}Equivalent isotropic U defined as one-third of the trace of the orthogonalised U_{ij} tensor.

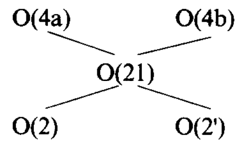
Table 3. Bond lengths (Å), bond angles (°) and selected torsion angles (°) (with esds in parentheses)

Bond lengths (Å)			
O(1) - C(1)	1·418(7)	C(1) - C(2)	1·522(12)
O(2) - C(2)	1·412(12)	C(2) - C(3)	1·543(10)
O(3) - C(3)	1·414(12)	C(3) - C(4)	1·539(13)
O(3) - C(6)	1·455(12)	C(4) - C(5)	1·514(11)
O(4) - C(4)	1·427(12)	C(5) - C(6)	1·522(14)
O(5) - C(l)	1·434(11)	O(5) - C(1)	1·434(11)
Bond angles (°)			
C(1) - O(1) - C(1')	116·1(7)	O(3) - C(3) - C(4)	102·6(7)
C(1) - O(5) - C(5)	112·6(5)	C(2) - C(3) - C(4)	108·9(6)
O(1) - C(1) - O(5)	106·1 (5)	O(4) - C(4) - C(3)	115·4(8)
O(5) - C(1) - C(2)	112·8(6)	O(4) - C(4) - C(5)	117·2(6)
O(2) - C(2) - C(1)	113·4(7)	C(3) - C(4) - C(5)	98·6(6)
O(2) - C(2) - C(3)	107·6(6)	O(5) - C(5) - C(4)	108·7(7)
C(1) - C(2) - C(3)	108·8(7)	O(5) - C(5) - C(6)	113·5(7)
O(3) - C(3) - C(2)	110·6(6)	C(4) - C(5) - C(6)	99·8(6)
Torsion angles (°)			
Within the pyranose ring		*Outside the pyranose ring*	
O(5) - C(1) - C(2) - C(3)	-46·5(1·0)	O(1) - C(1) - C(2) - C(3)	-162·5(0·6)
C(1) - C(2) - C(3) - C(4)	59·3(0·9)	O(1) - C(1) - C(2) - O(2)	-42·8(0·9)
C(1) - C(2) - C(3) - O(3)	-52·6(0·9)	O(1) - C(1) - C(5) - C(5)	166·5(0·6)
C(2) - C(3) - C(4) - C(5)	-70·2(0·8)	O(2) - C(2) - C(3) - C(4)	-63·9(0·9)
C(2) - C(3) - O(3) - C(6)	87·7(0·8)	O(2) - C(2) - C(3) - O(3)	-175·8(0·7)
C(3) - C(4) - C(5) - C(6)	-46·2(0·7)	O(5) - C(1) - O(1) - C(1')	67·7(0·5)
C(3) - C(4) - C(5) - O(5)	72·8(0·7)	C(2) - C(1) - O(1) - C(1')	-170·0(0·7)
C(4) - C(5) - C(6) - O(3)	31·0(0·8)		
C(4) - C(5) - O(5) - C(1)	-66·3(0·9)		
C(5) - O(5) - C(1) - C(2)	50·4(1·0)		
C(5) - C(6) - O(3) - C(3)	-1·6(0·7)		

1972), there is a fairly strong intramolecular hydrogen bond between O-2 and O-4 (2·597 Å).

Taste studies on anhydro sugars (Lee & Birch, 1975) have shown that 3,6-anhydro-α-D-glucopyranosides, including **1**, are tasteless. In contrast, the 1,6-anhydro-β-D-hexopyranoses, including those with *cis*-diaxial C-2,4 substituents, are bitter/sweet. In these derivatives at least one of the C-2,3,4 hydroxyl oxygen atoms is located at a distance of 2·9–3·6 Å from another hydroxyl oxygen or the ring oxygen atom. Thus, one of these hydroxyl groups could function with either of the other two or the ring oxygen atom as a sweet AH,B glucophore. However, since O-2, O-3 and O-4 are located at very similar distances from the ring oxygen (O-5) in both the 1,6- and 3,6-anhydro derivatives, it is apparent that O-5 is not involved in sweetness. Therefore, like sugars in the $^4C_1$ conformation a pair of the C-2,3,4 hydroxyl groups constitute the sweet AH,B glucophore.

Table 4. Hydrogen bonding in 3,6:3',6'-dianhydro-α,α-trehalose



Hydrogen bond (or O ··· O contact)	Symmetry operators^a	Distances (Å) O ··· O	Angle (°) O ··· O ··· O
Intramolecular			
O(4) ⟷ O(2)	[1000]	2·597	
Intermolecular			
O(21) ⟷ O(2)	[2000]	2·709	
O(21) ⟷ O(2')	[3001]	2·709	
O(21) ⟷ O(4a)	[1000]	2·686	
O(21) ⟷ O(4b)	[4101]	2·686	
O(4) ··· O(21) ··· O(4b)			136
O(4a) ··· O(21) ··· O(2)			98·8
O(4b) ··· O(21) ··· O(2)			105·6
O(2) ··· O(21) ··· O(2')			111·4

^{a}Symmetry operators: (1) x, y, z; (2) $x + ½, y - ½, z$; (3) $x - ½, y - ½, -z$, (4) $-x, y, -z$.

In the *gluco*-configuration, the C-2 and C-4 hydroxyl groups in 1,6- and 3,6-anhydro derivatives are *cis*-diaxial. The interorbital O···O distance is, however, very different. The strain resulting from the formation of the 1,6-anhydro ring forces these hydroxyl groups apart so that the O···O distance widens to 3·3 Å (Park *et al.*, 1971). The strain caused in the formation of the 3,6-anhydro ring, on the other hand, causes the distance to shorten to *c.* 2·6 Å. In the former, therefore, the C-2,4 hydroxyl groups is suitably positioned to function as a sweet AH,B glucophore. In the latter, as predicted on the basis of molecular models (Lee & Birch, 1975), there is a strong intramolecular hydrogen bonding between these hydroxyl groups. There is, therefore, no AH,B glucophore in 3,6-anhydroglucopyranoid structures, and consequently they are not sweet.

Studies of conformationally defined sugars and organic molecules have shown that the sweet and bitter responses are intimately associated. Chemical modification often alters the taste of sweet compounds to produce bitter–sweet or bitter products. Thus, the 4,4'-dideoxy and 4,4'-dichloro-4,4'-dideoxy derivatives of **I** (Birch *et al.*, 1974) and of methyl-3,6-anhydro-α-D-hexopyranoside (Lee, 1973) are not only devoid of sweetness, they often have strong bitter tastes (Lee & Birch, 1975). Although a hydrophobic γ site, if present in a sweet-tasting compound, amplifies the sweet-taste sensation, studies on amino acids and peptides (Wieser & Belitz, 1975, 1976; Belitz *et al.*, 1979, 1981; Gardner, 1979; Ney, 1979) and sugars (Lee, 1973, 1987; Birch & Lee, 1974; Lee & Linden, 1995) suggest that, increasing the hydrophobic character of a compound, for example, by removal of hydroxyl groups, generally causes increased bitterness (Birch & Lee, 1974), even when a AH,B glucophore is present. Thus, 2-, 3-, 4- and 6-deoxy- and *O*-methylhexopyranosyl derivatives are sweet, but with some bitterness, whereas the corresponding 2,6-, 3,6- and 4,6-dideoxy and di-*O*-methyl derivatives are all bitter, and devoid of sweetness (Birch & Lee, 1974; Birch *et al.*, 1975; Lindley & Birch, 1975). Similarly, quercitols and inositols are all distinctly sweet and free from bitterness while cyclohexane derivatives, having less than four hydroxyl groups, are always bitter and never sweet (Birch & Lindley, 1973). The increased hydrophobic character of the compound, probably causes the molecule to align itself on the receptor site differently from that of the parent sugar or to bind to a 'bitter site'. However, we are still not clear whether the two basic tastes are each a feature of a single compound or whether the compound interacts with two different sets of receptor sites, representing sweet and bitter taste modalities.

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