Carbohydrate Research, 254 (1994) 281–287
Elsevier Science B.V., Amsterdam

Note

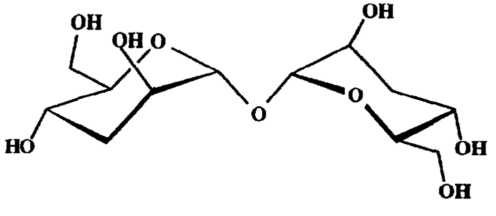
Crystal structure and taste of 3,3′-dideoxy-*α*,*α*-*arabino*-trehalose monohydrate *

C.-Kuan Lee † and Lip Lan I. Koh

Department of Chemistry, National University of Singapore, Kent Ridge 0511 (Singapore)

(Received March 27th, 1993, accepted in revised form August 20th, 1993)

The Shallenberger AH,B theory of sweetness[2] suggests that the fundamental unit of sweetness of a compound is an AH,B system, where A and B are each electronegative atoms in suitable geometric proximity. This unit can hydrogen bond with a complementary AH,B system in the receptor protein of the taste bud so that the resulting doubly hydrogen-bonded complex gives rise to the sweet stimulus. The Kier[3] extension to the AH,B system is that a third hydrophobic (γ) site is required to determine the intensity of the response. In sugars, the AH,B system can be a glycol group and the ideal sugar for taste studies is probably α,α-trehalose. From the comparative taste of a series of deoxy derivatives of α,α-trehalose and methyl α-D-glucopyranoside, it was found[4] that there is a marked decrease in sweetness of the 3-deoxy derivatives, although a potential hydrophobic centre has been created. This accounts for our interest in the molecular and X-ray structure of 3,3′-dideoxy-*α*,*α*-*arabino*-trehalose (**1**).



1 3,3′-Dideoxy-α,α-*arabino*-trehalose

The molecular structure of 3,3′-dideoxy-*α*,*α*-*arabino*-trehalose monohydrate, with the atomic numbering and molecular packing in the crystal, are shown Figs. 1

---

* Crystal Structure of Trehalose Derivatives. Part 2. For Part 1, see ref 1.

† Corresponding author.

SSDI 0008-6215(93)E0309-O

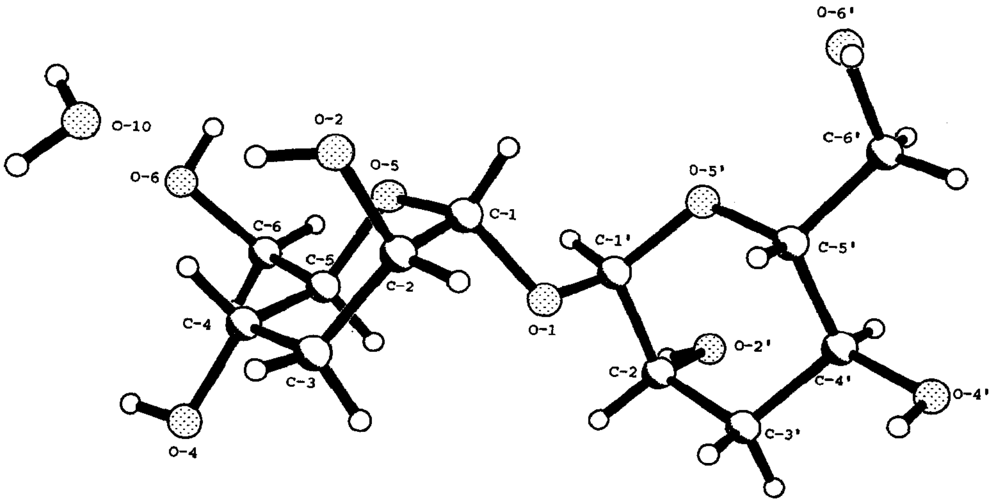


Fig. 1. XP plot[6] of 3,3′-dideoxy-*α*,*α*-*arabino*-trehalose giving the numbering scheme.

and 2. The atomic coordinates and equivalent isotropic coefficients are given in Table I, and the molecular dimensions in Table II. These agree with previously reported values[5]. The average C–C and C–O bond lengths are 1.520 and 1.427 Å, respectively. The C–O bond lengths associated with the anomeric carbon atoms and the ring oxygen atoms (Table II) show systemic trends similar to those observed in *α*,*α*-trehalose[6] and in other *α*-pyranose sugars[7].

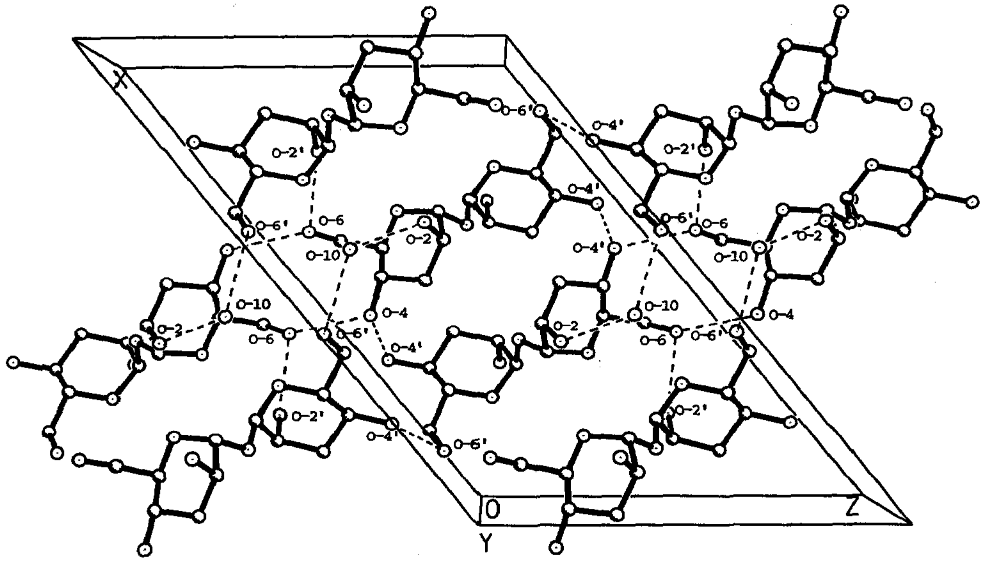


Fig. 2. Molecular packing of the crystal of 3,3′-dideoxy-*α*,*α*-*arabino*-trehalose.

TABLE I

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($Å \times 10^3$) with standard deviations in parentheses

Atom	*x*	*y*	*z*	U_{eq} [a]
C-1	3384(1)	1205	4873(2)	33(1)
C-2	4051(2)	2555(4)	5346(2)	35(1)
C-3	4966(2)	2125(4)	6671(2)	34(1)
C-4	4885(1)	1462(4)	7732(2)	28(1)
C-5	4204(1)	114(4)	7127(2)	28(1)
C-6	4022(2)	−524(4)	8077(2)	36(1)
C-1′	3053(1)	−1319(4)	3780(2)	31(1)
C-2′	3576(1)	−2705(4)	3793(2)	33(1)
C-3′	3808(1)	−2374(4)	2837(2)	35(1)
C-4′	2955(2)	−1972(4)	1409(2)	32(1)
C-5′	2461(1)	−594(4)	1478(2)	30(1)
C-6′	1551(2)	−303(4)	118(2)	41(1)
O-1	3664(1)	−24(3)	4419(1)	32(1)
O-2	3664(1)	3948(4)	5444(2)	54(1)
O-4	5759(1)	902(3)	8867(1)	34(1)
O-5	3348(1)	666(3)	5920(1)	33(1)
O-6	3825(1)	688(4)	8651(1)	43(1)
O-2′	3025(1)	−4086(3)	3323(1)	39(1)
O-4′	3150(1)	−1604(3)	486(2)	42(1)
O-5′	2286(1)	−936(3)	2437(1)	32(1)
O-6′	1106(1)	1069(3)	117(2)	46(1)
O-10	4276(1)	5429(4)	7795(2)	58(1)

[a] Equivalent isotropic *U* defined as one third of the trace of the orthogonalised U_{ij} tensor. Hydrogen atoms were assigned *U* values which are ~1.3 times that of U_{eq} of the C atoms to which the H atoms were attached.

Like α,α-trehalose[6], the two pyranosyl rings has approximate C_2 symmetry. The torsion angles about C-1–O-1 differ significantly from those about C-1′–O-1 (Table II). The orientations of the primary hydroxyl group in the two pyranose rings also show a significant difference, the conformation is *gauche–gauche* in one ring [O-5–C-5–C-6–O-6, −70.9°, C-4–C-5–C-6–O-6, 49.8°] and *gauche–trans* (64.9 and −174.8°, respectively) in the other. This has also been observed in α,α-trehalose[6]. Departure of the molecule from C_2 symmetry is also found in the conformations of the C-2 and 2′, and C-4 and 4′ hydroxyl groups (Fig. 1, Table II).

Both pyranose rings have the expected $^4C_1$(D) conformation, with torsion angles showing normal variations commonly observed in other pyranose systems[8]. The chair conformations of both rings are only slightly distorted, with $Q = 0.543$ (0.550) Å, $\theta = 5.2°$ (3.6°), $\phi = 308.9°$ (16.5°), $q_2 = 0.049$ (0.034) Å, and $q_3 = 0.541$ (0.549) Å, where values[9] in parentheses are those for the primed ring. As with anhydrous trehalose[6], there is a large difference in the ϕ value of the two rings.

The molecules of the sugar and water are held together by an extensive network of hydrogen bonds, whose distances and angles are given in Table III. One of the hydrogen bonds involving the water molecule, O-10B–H ··· O-6′ [4,001], is only

TABLE II

Bond lengths (Å), bond angles (°) and selected torsion angles (°) with standard deviations in parentheses

Bond lengths (Å)			
C-1–C-2	1.519(4)	C-1′–C-2′	1.520(5)
C-2–C-3	1.518(3)	C-2′–C-3′	1.518(5)
C-3–C-4	1.518(4)	C-3′–C-4′	1.524(3)
C-4–C-5	1.521(4)	C-4′–C-5′	1.522(5)
C-5–C-6	1.510(5)	C-5′–C-6′	1.508(2)
O-1–C-1	1.425(3)	O-1–C-1′	1.421(4)
O-2–C-2	1.426(5)	O-2′–C-2′	1.424(4)
O-4–C-4	1.433(2)	O-4′–C-4′	1.431(4)
O-5–C-5	1.442(4)	O-5′–C-5′	1.443(4)
O-6–C-6	1.420(4)	O-6′–C-6′	1.428(4)
Bond angles (°)			
C-1–O-1–C-1′	114.4(2)		
C-1–O-5–C-5	113.8(2)	C-1′–C-5′–C-5′	115.5(2)
C-1–C-2–O-2	108.1(2)	C-1′–C-2′–O-2′	109.0(2)
C-1–C-2–C-3	110.7(2)	C-1′–C-2′–C-3′	110.0(3)
C-2–C-3–C-4	112.0(2)	C-2′–C-3′–C-4′	110.1(2)
C-3–C-4–C-5	110.6(2)	C-3′–C-4′–C-5′	110.3(2)
C-3–C-4–O-4	107.9(2)	C-3′–C-4′–O-4′	111.8(2)
C-4–C-5–C-6	114.1(2)	C-4′–C-5′–C-6′	111.9(2)
C-4–C-5–O-5	109.3(2)	C-4′–C-5′–O-5′	110.3(3)
C-5–C-6–O-6	112.7(3)	C-5′–C-6′–O-6′	113.2(2)
O-1–C-1–C-2	106.4(3)	O-1–C-1′–C-2′	107.0(2)
O-1–C-1–O-5	111.3(2)	O-1–C-1′–O-5′	111.6(3)
O-2–C-2–C-3	113.7(2)	O-2′–C-2′–C-3′	108.4(2)
O-4–C-4–C-5	110.1(2)	O-4′–C-4′–C-5′	110.0(3)
O-5–C-1–C-2	112.4(2)	O-5′–C-1′–C-2′	111.9(2)
O-5–C-5–C-6	106.4(2)	O-5′–C-5′–C-6′	106.0(2)
Selected torsion angles (°)			
Within the pyranose rings			
C-1–C-2–C-3–C-4	−48.8(0.4)	C-1′–C-2′–C-3′–C-4′	−54.4(0.3)
C-2–C-3–C-4–C-5	52.1(0.3)	C-2′–C-3′–C-4′–C-5′	55.5(0.4)
C-2–C-1–O-5–C-5	−58.7(0.3)	C-2′–C-1′–O-5′–C-5′	−55.9(0.4)
C-3–C-4–C-5–O-5	−56.1(0.3)	C-3′–C-4′–C-5′–O-5′	−54.5(0.3)
C-4–C-5–O-5–C-1	60.6(0.3)	C-4′–C-5′–O-5′–C-1′	56.0(0.3)
O-5–C-1–C-2–C-3	51.2(0.3)	O-5′–C-1′–C-2′–C-3′	54.0(0.3)
Outside the pyranose rings			
C-2–C-1–O-1–C-1′	−172.7(0.2)	C-2′–C-1′–O-1–C-1	−161.7(0.2)
C-3–C-4–C-5–C-6	−175.1(0.2)	C-3′–C-4′–C-5′–C-6′	−172.3(0.3)
C-4–C-5–C-6–O-6	49.8(0.3)	C-4′–C-5′–C-6′–O-6′	−174.8(0.3)
O-4–C-4–C-5–C-6	65.8(0.3)	O-4′–C-4′–C-5′–C-6′	63.9(0.3)
O-5–C-1–O-1–C-1′	64.6(0.2)	O-5′–C-1′–O-1–C-1	75.5(0.3)
O-5–C-5–C-6–O-6	−70.9(0.3)	O-5′–C-5′–C-6′–O-6′	64.9(0.3)

very weak, the oxygen–oxygen distance being 3.125 Å (Table III). All of the hydroxyl groups of the sugar molecule take part in hydrogen bonding and act as both proton donors and acceptors. Neither the ring-oxygen atoms nor O-1 are

TABLE III

Hydrogen-bonding distances (Å) and angles (°) in the crystal structure of 3,3′-dideoxy-*α-α-arabino*-trehalose

Hydrogen bond	Symmetry operations [a]	Distances (Å)			Angle (°) O–H···O
		O–H	O···O	H···O	
O(2)–H···O(10)	[1,000]	0.832	2.690	1.881	164
O(2′)–H···O(2)	[1,010]	0.826	2.686	1.879	165
O(4)–H···O(6)	[2,102]	0.825	2.670	1.858	168
O(4′)–H···O(4)	[2,101]	0.831	2.701	1.905	160
O(6)–H···O(2′)	[4,001]	0.826	2.760	1.946	168
O(6′)–H···O(4′)	[4,000]	0.830	2.766	1.943	171
O(10A)–H···O(6′)	[3,001]	0.831	2.864	2.039	172
O(10B)–H···O(6′)	[4,001]	0.826	3.125	2.413	145

[a] Symmetry operations: (1) x, y, z; (2) $-x, y, -z$; (3) $1/2+x, 1/2+y, z$; (4) $1/2-x, 1/2+y, z$. Each O of H_2O and sugar OH form two hydrogen bonds (a donor and an acceptor)

involved in hydrogen bonding. And like α,α-[6] and β,β-trehalose[1], there are no direct intramolecular hydrogen-bonds.

Systematic studies[4] on the taste of a series of deoxy derivatives of methyl α-D-glucopyranoside and α,α-trehalose indicated the unique importance of the 3-OH group in eliciting the sweet-taste response. A marked decrease in sweetness was observed when this hydroxyl group was removed. In contrast, there is little or no reduction in the sweetness when the other hydroxyl groups were individually removed or protected[10], indicating that O-3 acts as B in Shallenberger's AH,B system, with either the 4-OH, normally, and less commonly, the 2-OH group acting as AH, as for example in 2-deoxy hexopyranosides. It would be expected that the sterically reactive primary 6-OH group should be able to function with the 4-OH group as an AH,B system. The X-ray data, however, show that the interatomic distances between O-4 and OH-6, and OH-4 and O-6 in both halves of 3,3-dideoxy-*α,α-arabino*-trehalose are > 4.2 Å, clearly significantly greater than the optimum AH to B distance[2] of 3.0 Å. Furthermore, the hydrogen atoms of these hydroxyl groups are oriented away from the neighbouring oxygen atoms, particularly in the ring with the primed atoms, because of hydrogen bonding. Since the sweet-taste mechanism involves an aqueous solution, the dynamic interplay of hydrogen bonds in aqueous solution probably governs a molecule's taste-eliciting capacity. The crystal structure of a compound may not necessarily be that in solution. However, the X-ray data at least provide some evidence that there is no AH,B system in the 3-deoxy hexopyranoside, thus explaining the lack of sweet taste. The crystal structure of 4,4-dideoxy-*α,α-xylo*-trehalose, which is nearly as sweet as trehalose[4], is being investigated.

The γ-function is viewed as a function that facilitates the approach of a taste molecule to taste receptors and may be important for sweetness intensity. Although its role in sugar molecules is generally agreed to be minimal, it is of structural interest to modify the γ-effect. The removal of the 3-OH group makes

TABLE IV

Crystal structure and refinement data for 3,3′-dideoxy-*α*,*α*-*arabino*-trehalose

Crystal Data
$C_{12}H_{24}O_{10}$; M_r 328.3; mp 120–122°C; C2; Z = 4
Cell dimensions at 298 K: $a = 18.756(3)$, $b = 8.444(2)$, $c = 12.377(2)$ Å, $\beta = 127.95(2)$
$V = 1546.5(5)$ Å^3; $D_x = 1.410$ mg m^{-3}; $\mu = 0.124$ mm^{-1}
Crystal dimensions: 0.4 × 0.3 × 0.25 mm, colourless prisms
Radiation: Mo*Kα* ($\lambda = 0.71073$ Å) graphite monochromator
Cell dimensions based on 17 reflections with $4.4 \leq \theta \leq 11.0°$

Data collection
Siemens R3m/V diffractometer
Absorption correction: none
1518 reflections were measured by $\omega/2\theta$ scan, of which 1469 were independent and 1361 were observed, $F > 4.0\sigma(F)$
Scanning rate: 2.49–29.30° per min.; $3.5° \leq 2\theta \leq 50°$; $0 \leq h \leq 22$, $0 \leq k \leq 10$, $-14 \leq l \leq 10$
Standard reflections: 3 measured every 97 reflections

Refinement
Function minimised, $R = \Sigma w(|F_o| - |F_c|)$, using SHELXTL PLUS (ref 12) where $w^{-1} = \sigma^2(F) + 0.0003F^2$ based on counting statistics
Final agreement factors: $R = 0.0258$, w$R = 0.0326$; goodness-of-fit = 1.27.
Extinction coefficient: $\chi = 0.0012$ (2) where $F^* = F[1 + 0.02\chi F^2/\sin 2\theta]^{-1/4}$
Atomic scattering factors from Atomic scattering factors from International
Tables for X-ray Crystallography (ref. 13)

this position a likely γ-site, but with the absence of an AH,B system, this is mere speculation.

EXPERIMENTAL

3,3′-Dideoxy-*α*,*α*-*arabino*-trehalose (1) was prepared by the method of Hough and coworkers[11]. Colourless prisms were grown as the monohydrate by slow evaporation of an ethanolic solution containing traces of water. The crystal data and intensity-measurement data were obtained using a Siemens R3m/v diffractometer with Mo*Kα* radiation ($\lambda = 0.71073$ Å) (graphite monochromator) and are given in Table IV * together with the refinement data.

The structure was solved by the direct method and refined by a full matrix least-squares refinement on F using SHELXTL PLUS[12] on a Micro VAX 2000. The carbon and oxygen atoms were refined anisotropically. The CH hydrogen atoms were at calculated positions. Hydrogen atoms were assigned U values which are ~ 1.3 times that of U_{eq} of the carbon atoms to which the atoms are attached. The OH hydrogen atoms were located from a difference map. The hydrogen atoms

---

* Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

were included with isotropic temperature factors in the final R calculation, but their positions were not refined. The final refinement gave $R = 0.0258$, w$R = 0.0326$, max $\Delta/\sigma = 0.002$ with a goodness-of-fit = 1.27; largest difference peak = 0.13 eA^{-3}. The weighting scheme was $\mathrm{w}^{-1} = \sigma^2(F) + 0.0003F^2$.

ACKNOWLEDGMENTS

We thank the National University of Singapore for financial support, and Miss G.K. Tan for technical assistance.

REFERENCES

1 C.K. Lee and L.L. Koh, *Acta Crystallogr., Sect. C*, 49 (1993) 621–624.
2 R.S. Shallenberger and T.E. Acree, *Nature*, 216 (1967) 480; R.S. Shallenberger and Acree, in L.M. Beidler (Ed.), *Handbook of Sensory Physiology. IV. Chemical Senses*, 2, Springer-Verlag, Berlin, (1971) 221–277.
3 L.B. Kier, *J. Pharm. Sci.*, 61 (1972) 1394–1397.
4 G.G. Birch and C.K. Lee, *J. Food Sci.*, 39 (1974) 947–949.
5 G. Strahs, *Ad. Carbohydr. Chem. Biochem.*, 25 (1970) 53–107; D.C. Fries, S.T. Rao, and M. Sundaralingam, *Acta Crystallogr., Sect. B*, 27 (1971) 994–1005; D. Lamba, C. Burden, W. Mackie, and B. Sheldrick, *Carbohydr. Res.*, 153 (1985) 262–267
6 G.M. Brown, D.C. Rohrer, B. Berking, C.A. Beevers, R.O. Gould, and R. Simpson, *Acta Crystallogr., Sect. B*, 28 (1972) 3145–3158; T. Taka, M. Senma, and K. Osaki, *ibid.*, 28 (1972) 3258–3263; G.A. Jeffrey and R. Nanni, *Carbohydr. Res.*, 137 (1985) 21–30.
7 H.M. Berman, S.C. Chu, and G.A. Jeffrey, *Science*, 157 (1967) 1576–1577.
8 G.M. Brown and H.A. Levy, *Science*, 141 (1963) 921-923; S.C. Chu and G.A. Jeffrey, *Acta Crystallogr., Sect. B*, 24 (1968) 830–838; G.A. Jeffrey and S. Tagaki, ibid., 33 (1977) 738–742.
9 G. Cremer and J.A. Pople, *J. Am. Chem. Soc.*, 99 (1975) 1354–1358.
10 G.G. Birch and M.G. Lindley, *J. Sci. Food Agric.*, 26 (1975) 117–124.
11 L. Hough, A.C. Richardson, and E. Tarelli, *J. Chem. Soc., C*, (1971) 2122–2127.
12 G.M. Sheldrick, SHELXTL Plus Release 4.0, Siemens R3m/V Crystallographic Research System, Siemens Analytical X-ray Instruments, Madison, WI, USA, 1990.
13 International Tables for X-ray Crystallography, Vol. 1V, Kynoch Press, Birmingham, UK, 1974.