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4,1',6'-Trichloro-4,1',6'-trideoxysucrose monohydrate

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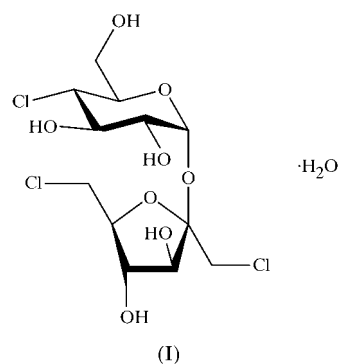
At 160 K, the glucopyranosyl ring in 1,6-dichloro-1,6-dideoxy- β -D-fructofuranosyl 4-chloro-4-deoxy- α -D-glucopyranoside monohydrate, $C_{12}H_{19}Cl_3O_8 \cdot H_2O$, has a near ideal 4C_1 chair conformation, while the fructofuranosyl ring has a 4T_3 conformation. The conformation of the sugar molecule is quite different to that of sucralose, particularly in the conformation about the glycosidic linkage, which affects the observed pattern of intramolecular hydrogen bonds. A complex series of intermolecular hydrogen bonds links the sugar and water molecules into an infinite three-dimensional framework.

Comment

Halogenated analogues of sucrose generally have intense sweetness, with many being several times sweeter than sucrose. This is rather puzzling, since halogenated analogues of all other sugars are either much less sweet than their parent sugar and/or very bitter. It is still not very clear why this is so, nor is it well understood which structural features of a molecule are responsible for producing a sweet taste. The most accepted explanation for sweetness is that a sweet molecule requires the formation of a pair of hydrogen bonds, $AH \cdots B$, with the receptor site (Shallenberger & Acree, 1967), as well as the presence of a hydrophobic centre, γ (Kier, 1972). The location of the AH, B, γ tripartite glucophore in sucrose and its sweet analogues is still far from certain. As a continuation of our research programme on the structure–sweetness relationship of sugars, we now report the crystal structure of 1,6-dichloro-1,6-dideoxy- β -D-fructofuranosyl 4-chloro-4-deoxy- α -D-glucopyranoside monohydrate or 4,1',6'-trichloro-4,1',6'-trideoxysucrose monohydrate, (I).

The absolute configuration of (I) has been determined confidently by refinement of the absolute structure parameter (Flack, 1983) and is shown in Fig. 1. Compound (I) is

isostructural with 1',6'-dibromo-4-fluoro-4,1',6'-trideoxysucrose monohydrate (Linden *et al.*, 2001), including the pattern of hydrogen bonds. The bond lengths and angles in (I) also generally agree with those of sucralose, which is the C4 epimer of (I) (Kanters *et al.*, 1988). However, the conformation about the glycosidic C—O bond of (I) is quite different from that found for sucralose. This is mainly a result of rotation about the C7—O1 bond, as shown by a comparison of the torsion angles for these two compounds (Table 1). The epimerization at C4 apparently alters the most stable packing arrangement, which leads to the molecule twisting into the most economical conformation that allows this packing. As a result, there is a difference in the intramolecular hydrogen bonds formed by each compound. In sucralose, the two sugar rings are linked by an intramolecular O2—H \cdots O8 hydrogen bond [labelled as O2—H \cdots O13 by Kanters *et al.* (1988)], whereas in (I), O2—H is involved in an intermolecular hydrogen bond and, instead, O8—H forms a very weak intramolecular hydrogen bond with the glycosidic O1 atom (Table 2).



The glucopyranoside ring in (I) adopts a slightly distorted 4C_1 chair conformation, with puckering parameters (Cremer & Pople, 1975) $Q = 0.5914$ (15) Å, $q_2 = 0.0365$ (14) Å, $q_3 = 0.5903$ (15) Å, $\theta = 3.48$ (14)° and $\varphi_2 = 152$ (2)°. This distortion is slightly larger than that in sucralose ($\theta = 1.9$ °; Kanters *et al.*, 1988). The fructofuranosyl residue has a twisted 9T_8 conformation [*i.e.* 4T_3 with conventional furanosyl ring numbering; $q_2 = 0.4081$ (15) Å and $\varphi_2 = 272.5$ (2)°], with atoms C8 and C9 -0.287 (4) and 0.384 (4) Å, respectively, from the plane defined by atoms O10, C7 and C10. As in sucrose (Brown & Levy, 1963, 1973), the hydroxymethyl group of the glucopyranosyl ring has the familiar *gauche-gauche* conformation. In sucralose, the *gauche-trans* conformation is preferred over *gauche-gauche*, as this avoids an unfavourable 1,3-*peri* interaction. The C7 and C10 chloromethyl substituents of (I) are both *gauche-trans*. In sucralose, the former substituent has a *gauche-gauche* conformation, while the latter, as in (I), is *gauche-trans*.

Unlike sucralose, the structure of which is anhydrous, the asymmetric unit of (I) contains one sugar molecule and one water molecule. The sugar and water molecules are linked into an infinite three-dimensional framework by a complex series of intermolecular hydrogen bonds (Table 2), which involves all available hydrogen-bond donors in these molecules. Atom O8, which is the donor in the weak intramolecular hydrogen bond

described above, also acts as a donor for a much stronger intermolecular interaction and as an acceptor of two intermolecular interactions. When considered individually, the intermolecular hydrogen bonds involving donor atoms O3, O6, O8 and O9 link the molecules into infinite one-dimensional chains, which have unitary graph-set motifs (Bernstein *et al.*, 1995) of $C(9)$, $C(7)$, $C(5)$ and $C(9)$, respectively. The chain involving atom O6 as the donor runs parallel to the x axis, while all the other chains run parallel to the y axis. Atom O2 acts as a hydrogen-bond donor to atom O13 of the water molecule which, in turn, donates hydrogen bonds to two other sugar molecules. Considering the path through each of the H atoms of the water molecule separately, each of these patterns forms an infinite one-dimensional sugar–water–sugar–water–chain, which has a binary graph-set motif of $C_2^2(12)$. One of these chains runs parallel to the x axis, while the other runs parallel to the y axis. The intramolecular hydrogen bond involving the $O8 \cdots O1$ interaction creates a five-membered loop with a graph-set motif of $S(5)$.

Currently, the most accepted explanation for sweetness is the Shallenberger & Acree–Kier AH,B, γ model mentioned above (Shallenberger & Acree, 1967; Kier, 1972). For sugars, the distance parameters are $A \cdots B \simeq 2.8$, $A \cdots \gamma \simeq 3.5$ and $\gamma \cdots B \simeq 5.5$ Å. The location of the AH,B, γ glucophore in sucrose and the intensely sweet halogenated sucrose analogues is still being debated (Shallenberger & Lindley, 1977; Hough & Khan, 1978, 1993; van der Heijden *et al.*, 1985; Mathlouthi & Seuvre, 1988; Hough, 1989; van der Heijden, 1993; Hoof *et al.*, 1993; Lichtenhaler & Immel, 1993; Mathlouthi *et al.*, 1993; Tsuami *et al.*, 1994). However, work by Tsuami *et al.* (1994) strongly suggests that, in sucrose derivatives, $O8-H,O2$ (*i.e.* $O3'-H,O2$ in the normal numbering convention) acts as the AH,B grouping. Since all galactosucrose C4–Cl derivatives are intensely sweet compared with the corresponding sucrose C4–Cl epimers [sucralose is 650

times sweeter than sucrose (Hough & Khan, 1978; Jenner, 1981; Lee, 1982, 1983, 1987)], it is very likely that the halogen at C4 functions as a γ -site.

Kanters *et al.* (1988) proposed that a possible AH,B, γ system in sucralose is $O8-H,O2,Cl4$, where $O2 \cdots O8 = 2.80$, $O2 \cdots Cl4 = 4.46$ and $O8 \cdots Cl4 = 6.45$ Å. These dimensions correspond quite well with the Shallenberger & Acree–Kier AH,B, γ model. In contrast, the corresponding geometric pattern in (I) [$O2 \cdots O8 = 4.2108$ (14), $O2 \cdots Cl4 = 5.1119$ (12) and $O8 \cdots Cl4 = 6.7555$ (11) Å] does not correlate well with this tripartite model. This could possibly explain why (I), which is 100 times sweeter than sucrose (Hough & Khan, 1993), has only a fraction of the sweetness of sucralose. All of the other C4-halodeoxy sucrose analogues that have been tested also have very much lower sweetness than the corresponding galacto epimer (Muhammad Sofian & Lee, 2002). In addition, 4,6,1',6'-tetrachloro-4,6,1',6'-tetra-deoxysucrose is only half as sweet as the corresponding galacto epimer (Lee, 1987). This offers strong support to our earlier prediction (Lee *et al.*, 1999) that not only is the halogen substituent at C4 (as well as that at C8) important in determining the sweetness of halodeoxy sucrose analogues, but the stereochemical disposition of these halogen atoms is critical as well.

Experimental

Carbon tetrachloride (1.5 ml, 9.74 mmol) was added dropwise to a stirred solution of 3,4-di-*O*-acetyl- β -D-fructofuranosyl 2,3,6-tri-*O*-acetyl- α -D-galactopyranoside (0.67 g, 1.21 mmol) in pyridine (10 ml) and triphenylphosphine (1.90 g, 7.25 mmol) at 273 K under an argon atmosphere. The reaction mixture was stirred at 273 K for 30 min and at room temperature for another 30 min, and then heated at ~ 358 K until all the starting material had reacted (thin-layer chromatography, ethyl acetate–hexane, 1:2). Work-up in the usual manner and flash column chromatography (ethyl acetate–hexane, 1:2) gave 3,4-di-*O*-acetyl-1,6-dichloro-1,6-dideoxy- β -D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-chloro-4-deoxy- α -D-glucopyranoside (0.66 g, 89%) as a colourless syrup. Spectroscopic analysis: $[\alpha]_D +23.2^\circ$ (c 2.26, $CHCl_3$); 1H NMR (300.13 MHz, $CDCl_3$, δ , p.p.m.): 2.01, 2.03, 2.04, 2.06, 2.12 ($5 \times s$, 15H, $5 \times CH_3$), 3.49–3.72 (m , 4H, $H1'a,b$, $H6'a,b$), 3.82 (t , 1H, $J_{3,4} = J_{4,5} = 10.1$ Hz, H4), 4.15–4.46 (m , 4H, H5, H5', H6a,b), 4.77 (dd , 1H, $J_{1,2} = 3.5$, $J_{2,3} = 10.1$ Hz, H2), 5.31 (t , 1H, $J_{3',4'} = J_{4',5'} = 5.9$ Hz, H4'), 5.41 (t , 1H, $J_{2,3} = J_{3,4} = 10.1$ Hz, H3), 5.57 (d , 1H, $J_{1,2} = 3.5$ Hz, H1), 5.60 (d , 1H, $J_{3',4'} = 5.9$ Hz, H3'); ^{13}C NMR (75.47 MHz, $CDCl_3$, δ , p.p.m.): 170.2, 169.9, 169.6, 169.4, 169.4 ($COCH_3$), 104.3 ($C2'$), 90.1 ($C1$), 81.2 ($C5'$), 76.0, 75.9 ($C3'$, $C4'$), 70.9 ($C3$), 70.7 ($C5$), 70.5 ($C2$), 62.5 ($C6$), 54.9 ($C4$), 44.7, 43.7 ($C1'$, $C6'$), and 20.5, 20.5, 20.4, 20.4, 20.3 ($COCH_3$); HRMS–ESI (positive mode), calculated for $[M + Na]^+$: 629.0331:631.0302:633.0512; found: 629.0583:631.0560:633.0527.

A solution of this 4,1',6'-trichloro derivative (0.12 g, 0.197 mmol) in methanol was treated with methanolic NaOMe at pH ~ 9 for 1 h at room temperature, after which thin-layer chromatography (methanol– $CHCl_3$, 3:17) showed only one slower moving product. The mixture was neutralized using Amberlite IR120 (H^+) ion-exchange resin, filtered and concentrated to give the title compound, (I) (0.071 g, 90%); m.p. 382–383 K (methanol). Spectroscopic analysis: $[\alpha]_D +44.8^\circ$ (c 1.36, methanol); 1H NMR (300.13 MHz, D_2O , δ , p.p.m.): the assignments employ the crystallographic atom numbering used in Fig. 1): 4.14 (dd , 1H, $J_{1,2} = 3.8$, $J_{2,3} = 9.7$ Hz, H2), 4.30–4.68 (m , 11H,

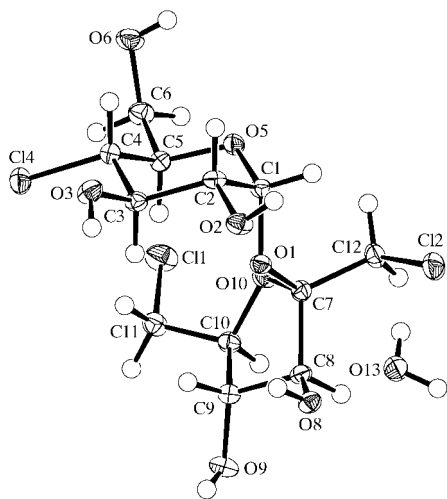


Figure 1

A view of the asymmetric unit of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by spheres of arbitrary size.

H3, H4, H5, H6a,b, H9, H10, H11a,b, H12a,b), 4.93 (*d*, 1H, $J_{8,9}$ = 8.0 Hz, H8), 6.01 (*d*, 1H, $J_{1,2}$ = 3.8 Hz, H1); ^{13}C NMR (75.47 MHz, D_2O , δ , p.p.m.): 104.1 (C7), 93.4 (C1), 81.7 (C10), 76.9, 75.9 (C8, C9), 73.5 (C3), 73.1, (C5), 72.0 (C2), 61.0 (C6), 58.5 (C4), and 45.4, 44.0 (C11, C12); HRMS-ESI (positive mode), calculated for $[\text{M} + \text{Na}]^+$: 396.0145:398.0116:400.0086; found: 396.0139:398.0110:400.0083. Suitable crystals were obtained by slow evaporation of a solution of (I) in methanol.

Crystal data

$\text{C}_{12}\text{H}_{19}\text{Cl}_3\text{O}_8 \cdot \text{H}_2\text{O}$	Mo $K\alpha$ radiation
$M_r = 415.65$	Cell parameters from 41 833 reflections
Orthorhombic, $P2_12_12_1$	$\theta = 2.0\text{--}30.0^\circ$
$a = 7.5571$ (1) Å	$\mu = 0.59 \text{ mm}^{-1}$
$b = 9.4931$ (1) Å	$T = 160$ (1) K
$c = 23.4455$ (2) Å	Prism, colourless
$V = 1681.99$ (3) Å ³	$0.25 \times 0.15 \times 0.10 \text{ mm}$
$Z = 4$	
$D_x = 1.641 \text{ Mg m}^{-3}$	

Data collection

Nonius KappaCCD area-detector diffractometer	4903 independent reflections
φ and ω scans with κ offsets	4460 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (Blessing, 1995)	$R_{\text{int}} = 0.056$
$T_{\text{min}} = 0.819$, $T_{\text{max}} = 0.947$	$\theta_{\text{max}} = 30^\circ$
51 545 measured reflections	$h = -10 \rightarrow 10$
	$k = -13 \rightarrow 13$
	$l = -32 \rightarrow 32$

Refinement

Refinement on F^2	$(\Delta/\sigma)_{\text{max}} = 0.001$
$R[F^2 > 2\sigma(F^2)] = 0.028$	$\Delta\rho_{\text{max}} = 0.25 \text{ e \AA}^{-3}$
$wR(F^2) = 0.068$	$\Delta\rho_{\text{min}} = -0.29 \text{ e \AA}^{-3}$
$S = 1.05$	Extinction correction: <i>SHELXL97</i> (Sheldrick, 1997)
4900 reflections	Extinction coefficient: 0.0078 (11)
247 parameters	Absolute structure: Flack (1983), with 2099 Friedel pairs
H atoms treated by a mixture of independent and constrained refinement	Flack parameter = 0.02 (4)
$w = 1/[\sigma^2(F_o^2) + (0.0355P)^2 + 0.3153P]$	
where $P = (F_o^2 + 2F_c^2)/3$	

Table 1

Comparison of selected geometric parameters ($^\circ$) for (I) and sucralose†.

	(I)	Sucralose†
C1–O1–C7	120.48 (11)	119.2 (2)
O1–C1–O5	113.47 (11)	110.8 (2)
O1–C1–C2	106.28 (11)	106.3 (2)
O1–C7–O10	110.92 (11)	102.7 (2)
O1–C7–C8	105.96 (11)	112.5 (2)
O1–C7–C12	115.25 (12)	110.1 (2)
C1–O1–C7–C8	168.45 (11)	83.7 (2)
C1–O1–C7–O10	−78.79 (14)	−162.2 (2)
C1–O1–C7–C12	38.64 (17)	−46.1 (2)
C7–O1–C1–C2	−178.27 (11)	−147.9 (2)
C7–O1–C1–O5	61.02 (16)	91.4 (2)
O5–C5–C6–O6	−72.85 (16)	66.9 (2)
C4–C5–C6–O6	49.59 (18)	−169.8 (2)
C8–C7–C12–C12	−65.09 (15)	60.6 (2)
O10–C7–C12–C12	−178.97 (9)	−59.2 (2)
C9–C10–C11–C11	175.17 (10)	177.2 (2)
O10–C10–C11–C11	58.21 (14)	61.3 (2)

† Kanters *et al.* (1988).

Table 2

Hydrogen-bonding geometry (Å, $^\circ$).

$D\text{--}H\cdots A$	$D\text{--}H$	$H\cdots A$	$D\cdots A$	$D\text{--}H\cdots A$
O2–H2···O13 ⁱ	0.90 (2)	1.80 (2)	2.6964 (17)	170 (2)
O3–H3···O8 ⁱⁱ	0.81 (2)	2.07 (2)	2.8722 (15)	171 (2)
O6–H6···O3 ⁱⁱⁱ	0.80 (2)	2.16 (2)	2.8384 (17)	143 (2)
O8–H8···O1	0.81 (2)	2.450 (19)	2.7280 (13)	101.4 (15)
O8–H8···O9 ⁱⁱ	0.81 (2)	1.99 (2)	2.7870 (16)	169 (2)
O9–H9···O2 ^{iv}	0.80 (3)	1.85 (3)	2.6410 (16)	175 (3)
O13–H131···O6 ^v	0.82 (2)	1.91 (2)	2.7364 (16)	176 (2)
O13–H132···O8 ^{vi}	0.86 (3)	2.09 (3)	2.9340 (16)	167 (2)

Symmetry codes: (i) $x, 1+y, z$; (ii) $2-x, \frac{1}{2}+y, \frac{1}{2}-z$; (iii) $x-\frac{1}{2}, \frac{5}{2}-y, 1-z$; (iv) $2-x, y-\frac{1}{2}, \frac{1}{2}-z$; (v) $x-\frac{1}{2}, \frac{3}{2}-y, 1-z$; (vi) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$.

The asymmetric unit of (I) contains one molecule of the title sugar and one molecule of water. The hydroxy and water H atoms were located in a difference Fourier map and their positions were refined freely along with individual isotropic displacement parameters. All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with C–H distances in the range 0.99–1.00 Å and $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$. The determined absolute configuration agreed with that expected for a natural sucrose derivative. Three low-angle reflections were omitted from the final cycles of refinement because their observed intensities were much lower than the calculated values, as a result of being partially obscured by the beam stop.

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2002).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1596). Services for accessing these data are described at the back of the journal.

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