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Two halodeoxy sucrose analogues

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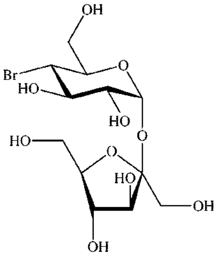
At 160 K, the structure of 4-bromo-4-deoxysucrose, $C_{12}H_{21}BrO_{10}$, is very similar to that of sucrose, particularly with respect to the conformation of the glycosidic linkage. As in sucrose, an intramolecular hydrogen bond exists between the glucopyranosyl and the fructofuranosyl rings. Conversely, the structure of 1′,6′-dibromo-4-fluoro-4,1′,6′-trideoxysucrose monohydrate, $C_{12}H_{19}Br_2FO_8{\cdot}H_2O$, shows large conformational differences when compared with the structures of both sucrose and sucralose. This compound does not exhibit any intramolecular hydrogen bonds. In each compound, a complex series of intermolecular hydrogen bonds link the molecules into an infinite three-dimensional framework. The absolute configuration of each molecule has been determined.

Comment

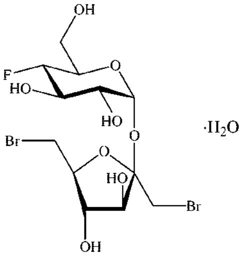
The introduction of halogens at certain sites of the sucrose molecule has a profound effect on the sweetness of the disaccharide (Hough & Phadnis, 1967; Lee, 1982, 1983, 1987*a*). Many of these analogues have been reported to have sweetness intensities which are several thousand times that of the parent sugar. Currently, the most widely accepted explanation for sweetness is the Shallenberger and Acree–Kier AH,B,γ tripartite hypothesis (Shallenberger & Acree, 1967; Kier, 1972). The location of the AH,B,γ glucophore in many classes of high intensity sweeteners, particularly the halogenated sucrose analogues, is still being debated intensely. Furthermore, it is fairly widely recognized that the high sweetness intensity of the halodeoxy sucrose analogues is a direct effect of one or more of the halogen substituents, and for this reason we are interested in the synthesis and structure of these analogues. As part of this programme, the crystal structures of 4-bromo-4-deoxysucrose, (I), and 1′,6′-dibromo-4-fluoro-4,1′,6′-trideoxysucrose monohydrate, (II), have been determined.

The absolute configurations of (I) and (II) have been confidently determined by refinement of the absolute structure parameter and are shown in Figs. 1 and 2, respectively. The bond lengths and angles exhibit normal values and generally agree with those of sucrose (Brown & Levy, 1963, 1973; Hanson *et al.*, 1973) and sucralose (Kanters *et al.*, 1988).

The disposition of the two sugar rings with respect to the C—O bond of the glycosidic linkage of (I) (Table 1) is similar to that of sucrose, since, like sucrose, O12—H is intramolecularly hydrogen bonded to O2. Such an intramolecular hydrogen bond is not observed in (II) because the hydroxy group at C12 has been substituted by bromine. This probably explains the large conformational differences between the corresponding bond angles and torsion angles involving the anomeric O1 atom of (II) and those of sucrose (Table 1). The conformation of the glycosidic linkage in (II) is also very different from that in sucralose (Table 1), where a rotation about the glycosidic linkage allows the formation of an intramolecular O2—H$\cdots$O8 hydrogen bond [labelled as O2—H$\cdots$O13 in Kanters *et al.* (1988)]. This interaction is not present in (II). The O11—H$\cdots$O5 intramolecular hydrogen bond that is present in sucrose [labelled as O′6—H$\cdots$O5 in Brown & Levy (1973)] is also not present in sucralose or (II) because the hydroxy group at C11 has been replaced by a halogen atom. However, even though this hydroxy group is present in (I), the equivalent intramolecular hydrogen bond is absent.



(I)



(II)

Aside from the intramolecular hydrogen bond in (I), each of the other hydroxy groups in each compound is a donor in an intermolecular hydrogen bond with another hydroxy O atom

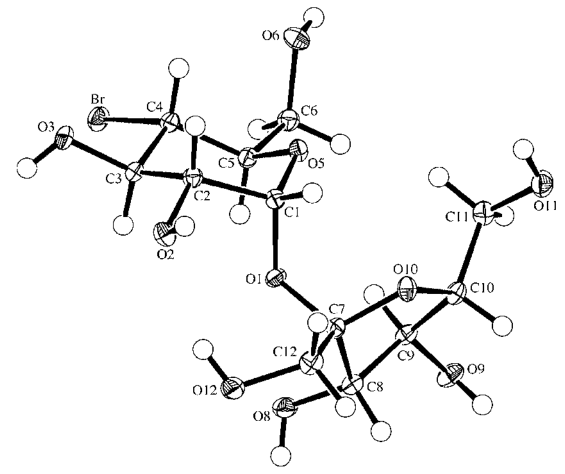


Figure 1
View of the molecule of (I) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of arbitrary size.

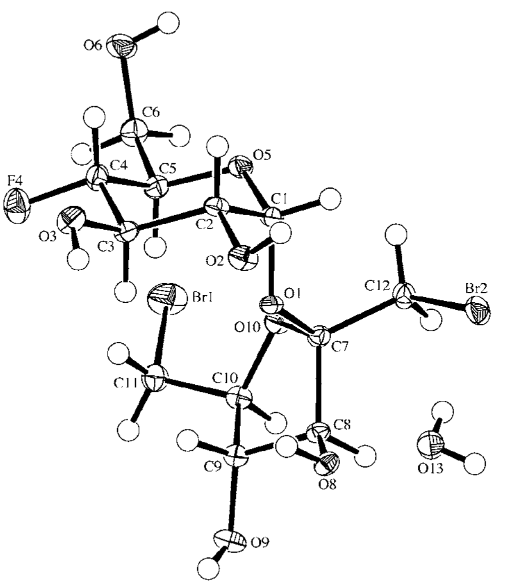


Figure 2

View of the molecule of (II) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of arbitrary size.

of a neighbouring sugar molecule, or with the water molecule in the case of compound (II) (Tables 2 and 3). In (I), atom O2 is an acceptor of both an intramolecular and an intermolecular interaction, while O11 does not accept any hydrogen bonds. In all, six different sugar molecules are hydrogen bonded to a central molecule and these interactions link the molecules into an infinite three-dimensional framework. In (II), the water molecule also donates two hydrogen bonds to neighbouring sugar molecules and the O8 hydroxy group is an acceptor of two hydrogen bonds, one being from a water molecule and the other from an adjacent sugar molecule. In all, four different molecules are hydrogen bonded to a central sugar molecule and these interactions also link the molecules into an infinite three-dimensional framework.

The hydroxymethyl group of the glucopyranosyl ring of both (I) and (II) has the familiar *gauche–gauche* conformation (Table 1), which is also observed for sucrose. In galactopyranosides, such as sucralose (Kanters *et al.*, 1988), 3-*O*-acetyl-1,4,6-trichloro-1,4,6-trideoxy-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-chloro-4-deoxy-α-D-galactopyranoside (Lee, 1987*b*) and 3-*O*-acetyl-1,4,6-trichloro-1,4,6-trideoxy-β-D-tagatofuranosyl 2,3,6-tri-*O*-acetyl-4-chloro-4-deoxy-α-D-galactopyranoside (Lee *et al.*, 1999), this hydroxymethyl substituent has a *gauche–trans* conformation, which is preferred over the *trans–gauche* conformation (Kanters *et al.*, 1978).

The glucopyranosyl rings in compounds (I) and (II) adopt slightly distorted $^4C_1$ chair conformations. The puckering parameters (Cremer & Pople, 1975) are: Q = 0.599 (1) Å, q_2 = 0.116 (1) Å, q_3 = 0.588 (1) Å, φ_2 = 296.1 (6)° and θ = 11.2 (1)° for (I), and Q = 0.586 (2) Å, q_2 = 0.031 (2) Å, q_3 = 0.585 (2) Å, φ_2 = 153 (4)° and θ = 2.2 (2)° for (II). The magnitude of distortion, θ, in compound (I) is much greater than that in sucrose (θ = 5.2°; Cremer & Pople, 1975), while that in compound (II) is significantly smaller than that in sucrose, yet similar to that in sucralose (θ = 1.9°; Kanters *et al.*, 1988). For the fructofuranosyl ring of compound (I), φ_2 = 258.32 (19)°, which is close to a value (252°) that is appropriate for the E_3 conformation. The envelope flap is formed by C8, which lies 0.621 (2) Å from the plane defined by atoms C7, C9, C10 and O10. For compound (II), this ring has the $^4T_3$ twist conformation [φ_2 = 274.4 (3)°], which is very similar to that in sucrose (Rohrer, 1972). The twist is on C8 and C9, with these atoms being −0.256 (5) and 0.431 (5) Å, respectively, from the plane defined by atoms C7, C10 and O10.

It is now strongly believed that the AH,B unit of the Shallenberger and Acree–Kier AH,B,γ glucophore (Shallenberger & Acree, 1967; Kier, 1972) spans the two sugar rings of sucrose (Mathlouthi *et al.*, 1993). Using molecular mechanics and dynamics studies, Hooft *et al.* (1993) proposed that the 'sweet conformation' of halogenated sucrose analogues should have values for the torsion angles defined by Φ(C1—O1—C7—O10) and Ψ(C7—O1—C1—O5) of 75 and 95°, respectively. However, both (I) and (II) have corresponding torsion angles that are very different from these theoretical values (Table 1), although those for (I) are quite similar to those of sucrose. Similarly, sucralose, which has a sweetness that is 650 times that of sucrose, has a completely different set of values for these torsion angles.

Experimental

The synthesis of compound (I) has been described by Muhammad Sofian & Lee (2001*a*). Suitable crystals were obtained by slow evaporation of a methanol solution [m.p. 422–423 K, $[\alpha]_D$ 34.7° (*c* 0.49, H_2O)]. For the synthesis of compound (II), trifluoromethane sulfonic anhydride (0.30 ml, 1.78 mmol) was added to a solution of 3,4-di-*O*-acetyl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α-D-glucopyranoside (0.27 g, 0.49 mmol) (Muhammad Sofian & Lee, 2001*b*) in dry CH_2Cl_2/pyridine (15:1, 16 ml) at 195 K. The mixture was stirred at 195 K for 15 min and then at 273 K for 2 h. The mixture was diluted with dichloromethane and the organic solution was washed successively with aqueous $KHSO_4$ (10%), saturated $NaHCO_3$ and water, then dried (Na_2SO_4) and concentrated. The crude product was stirred with LiBr (0.40 g) in dry acetone (15 ml) overnight at room temperature. The reaction mixture was concentrated and the residue was taken up in dichloromethane, washed thoroughly with water, dried (Na_2SO_4), filtered and again concentrated to give, after flash chromatography (ethyl acetate/hexane, 1:3), 3,4-di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α-D-glucopyranoside (0.21 g, 63%) as a colourless syrup. Spectroscopic analysis: $[\alpha]_D$ 22.2° (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$, δ, p.p.m.): 2.03, 2.05, 2.06, 2.11 (*s*, 15H, 5 × CH_3), 3.40–3.56 (*m*, 4H, H1′*a*,*b*, H6′*a*,*b*), 4.13–4.50 (*m*, 5H, H4, H5, H5′, H6*a*,*b*), 4.78 (*ddd*, 1H, $J_{1,2}$ = 3.8, $J_{2,3}$ = 10.4, $J_{2,\mathrm{F}}$ = 0.7 Hz, H2), 5.30 (*t*, 1H, $J_{3',4'}$ = $J_{4',5'}$ = 6.0 Hz, H4′), 5.44–5.55 (*m*, 2H, H1, H3), 5.65 (*d*, 1H, H3′); ^{13}C NMR: δ 170.4, 170.0, 169.7, 169.6, 169.5 (*C*OCH$_3$), 103.8 (C2′), 90.0 (C1), 86.7 ($J_{4,\mathrm{F}}$ = 187.6 Hz, C4), 81.0 (C5′), 76.8, 76.7 (C3′, C4′), 69.6 ($J_{2,\mathrm{F}}$ = 7.6 Hz, C2), 69.3 ($J_{3,\mathrm{F}}$ = 20.0 Hz, C3), 68.2 ($J_{5,\mathrm{F}}$ = 23.5 Hz, C5), 62.0 (C6), 32.5, 32.1 (C1′, C6′), 20.7, 20.6, 20.4 (CO*C*H$_3$); ^{19}F NMR: δ −122.3 (*dd*, $J_{\mathrm{F,H3}}$ = 15.3, $J_{\mathrm{F,H4}}$ = 53.4 Hz); HRMS–ESI (positive mode): calculated for $[M + \mathrm{Na}]^+$ 700.9857:-702.9837:704.9817; found: 700.9869:702.9866:704.9800 (1:2:1). De-acetylation of the above 1′,6′-dibromo-4-fluoro derivative (0.12 g, 0.17 mmol) by treatment with NaOMe (pH ∼ 8.5) and recrystallization from methanol afforded compound (II) (0.0612 g, 75%, m.p. 367–368 K). Spectroscopic analysis: $[\alpha]_D$ 27.2° (*c* 1.35, H_2O); ^{1}H NMR (D_2O, δ, p.p.m., the assignments employ the crystallographic atom numbering used in Fig. 2): 4.12 (*dd*, 1H, $J_{1,2} = 3.8$, $J_{2,3} = 10.4$ Hz, H2), 4.16–4.38 (*m*, 6H, H3, H9, H11*a*,*b*, H12*a*,*b*), 4.50–4.65 (*m*, 4H, H5, H6*a*,*b*, H10), 4.86 (*dt*, 1H, $J_{3,4} = J_{4,5} = 9.4$, $J_{4,\rm F} = 50.5$ Hz, H4), 4.98 (*d*, 1H, $J_{8,9} = 8.4$ Hz, H8), 5.93 (*m*, 1H, H1); ^{13}C NMR: (D_2O, δ, p.p.m.) 103.5 (C7), 93.0 (C1), 89.6 ($J_{4,\rm F} = 179.9$ Hz, C4), 81.6 (C10), 77.6, 77.0 (C8, C9), 71.3 ($J_{3,\rm F} = 17.6$ Hz, C3), 71.1 ($J_{2,\rm F} = 8.2$ Hz, C2), 70.7 ($J_{5,\rm F} = 24.1$ Hz, C5), 60.4 (C6), 33.3, 32.3 (C11, C12); ^{19}F NMR: δ −122.6 (*dd*, $J_{\rm F,H3} = 15.3$, $J_{\rm F,H4} = 53.4$ Hz); HRMS–ESI (positive mode): calculated for $[M + \rm Na]^+$ 490.9330:492.9308:494.9288; found 490.9327:492.9295:494.9275 (1:2:1).

Compound (I)

Crystal data

$C_{12}H_{21}BrO_{10}$
$M_r = 405.19$
Oryhorhombic, $P2_12_12_1$
$a = 10.4516$ (1) Å
$b = 11.3466$ (1) Å
$c = 12.5599$ (1) Å
$V = 1489.48$ (2) Å^3
$Z = 4$
$D_x = 1.807$ Mg m^{-3}

Mo *Kα* radiation
Cell parameters from 39 393 reflections
$\theta = 1.0$–30.0°
$\mu = 2.81$ mm^{-1}
$T = 160$ (1) K
Prism, colourless
0.20 × 0.20 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans with κ offsets
Absorption correction: numerical (Coppens *et al.*, 1965)
$T_{\rm min} = 0.556$, $T_{\rm max} = 0.693$
58 745 measured reflections
4340 independent reflections

4246 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.045$
$\theta_{\rm max} = 30.0°$
$h = -14 \rightarrow 14$
$k = -15 \rightarrow 15$
$l = -17 \rightarrow 17$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.017$
$wR(F^2) = 0.042$
$S = 1.05$
4340 reflections
216 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0194P)^2 + 0.5248P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\rm max} = 0.004$
$\Delta\rho_{\rm max} = 0.32$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.26$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0045 (4)
Absolute structure: Flack (1983)
Flack parameter = −0.005 (4)

Table 1
Comparison of selected geometric parameters (Å, °) for (I) and (II) with those of sucrose and sucralose.

	(I)	(II)	Sucrose[a]	Sucralose[b]
C1—O1—C7	118.63 (10)	120.56 (16)	114.30 (8)	119.2 (2)
O1—C1—O5	109.67 (10)	113.37 (17)	110.49 (8)	110.8 (2)
O1—C1—C2	109.27 (10)	105.86 (16)	110.33 (8)	106.3 (2)
O1—C7—O10	113.00 (10)	110.85 (16)	111.00 (8)	102.7 (2)
O1—C7—C8	105.08 (10)	105.89 (16)	108.43 (7)	112.5 (2)
O1—C7—C12	109.03 (10)	115.37 (18)	109.93 (8)	110.1 (2)
C1—O1—C7—C8	−146.31 (10)	168.62 (17)	−159.81 (8)	83.7 (2)
C1—O1—C7—O10	−32.23 (15)	−78.9 (2)	−44.75 (11)	−162.2 (2)
C1—O1—C7—C12	86.54 (13)	38.1 (2)	73.70 (10)	−46.1 (2)
C7—O1—C1—C2	−131.92 (11)	−177.93 (16)	−129.25 (9)	−147.9 (2)
C7—O1—C1—O5	107.31 (11)	61.5 (2)	107.82 (10)	91.4 (2)
O5—C5—C6—O6	−65.69 (13)	−71.7 (2)	−56.42 (13)	66.9 (2)
C4—C5—C6—O6	53.23 (15)	50.8 (3)	64.39 (13)	−169.8 (2)

Notes: (*a*) Brown & Levy (1973); (*b*) Kanters *et al.* (1988).

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2—H2···O6$^{\rm i}$	0.84	1.85	2.6708 (14)	166
O3—H3···O12$^{\rm ii}$	0.84	1.92	2.7362 (14)	165
O6—H6···O9$^{\rm iii}$	0.84	1.84	2.6723 (14)	173
O8—H8···O2$^{\rm iv}$	0.84	1.90	2.7287 (14)	171
O9—H9···O3$^{\rm v}$	0.84	2.01	2.8410 (14)	170
O11—H11···O8$^{\rm vi}$	0.84	1.97	2.7692 (15)	160
O12—H12···O2	0.84	2.09	2.8953 (15)	160

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

Compound (II)

Crystal data

$C_{12}H_{19}Br_2FO_8 \cdot H_2O$
$M_r = 488.10$
Orthorhombic, $P2_12_12_1$
$a = 7.6133$ (1) Å
$b = 9.4705$ (1) Å
$c = 23.2227$ (2) Å
$V = 1674.40$ (3) Å^3
$Z = 4$
$D_x = 1.936$ Mg m^{-3}

Mo *Kα* radiation
Cell parameters from 60 953 reflections
$\theta = 1.0$–30.0°
$\mu = 4.90$ mm^{-1}
$T = 160$ (1) K
Prism, colourless
0.23 × 0.22 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans with κ offsets
Absorption correction: numerical (Coppens *et al.*, 1965)
$T_{\rm min} = 0.349$, $T_{\rm max} = 0.583$
58 507 measured reflections
4893 independent reflections

4620 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.057$
$\theta_{\rm max} = 30.0°$
$h = -10 \rightarrow 10$
$k = -13 \rightarrow 13$
$l = -31 \rightarrow 32$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.024$
$wR(F^2) = 0.061$
$S = 1.07$
4891 reflections
231 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0273P)^2 + 1.3147P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} = 0.001$
$\Delta\rho_{\rm max} = 0.47$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.82$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0013 (3)
Absolute structure: Flack (1983)
Flack parameter = −0.002 (6)

Table 3
Hydrogen-bonding geometry (Å, °) for (II).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2—H2···O13$^{\rm i}$	0.84	1.89	2.728 (3)	172
O3—H3···O8$^{\rm ii}$	0.84	2.02	2.851 (2)	168
O6—H6···O3$^{\rm iii}$	0.84	2.05	2.804 (2)	149
O8—H8···O9$^{\rm ii}$	0.84	2.01	2.830 (2)	167
O9—H9···O2$^{\rm iv}$	0.84	1.83	2.663 (2)	172
O13—H131···O8$^{\rm v}$	0.77 (4)	2.23 (4)	2.997 (2)	175 (3)
O13—H132···O6$^{\rm vi}$	0.77 (4)	1.96 (4)	2.712 (2)	166 (4)

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

For each compound, all H atoms were initially located in a difference Fourier map. The hydroxy H atoms were then constrained to an ideal geometry, with O—H distances of 0.84 Å and fixed displacement parameters defined by $U_{\rm iso}(\rm H) = 1.5U_{\rm eq}(\rm O)$, but they were allowed to rotate freely about the C—O bonds. The positions of the H atoms of the water molecule of (II) 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 $U_{iso}(H) = 1.2U_{eq}(C)$. In each case, the determined absolute configuration agreed with that expected for a natural sucrose derivative. For (II), two low-angle reflections, whose intensities were zero, were omitted from the final cycles of refinement.

For both compounds, 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: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97 and *PLATON* (Spek, 2001).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1519). Services for accessing these data are described at the back of the journal.

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