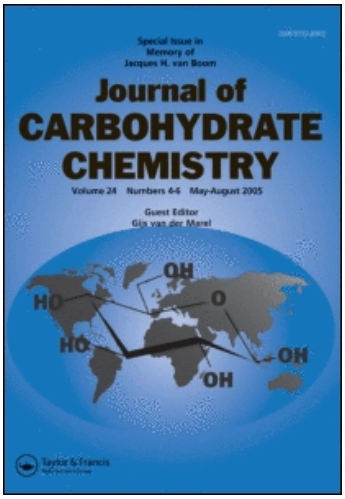


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis, Structure and Sweetness Of 4-Chloro-4-Deoxy-α-D-Galactopyranosyl 1,4,6-Trichloro-1,4,6-Trideoxy-β-D-Tagatofuranoside

C. Kuan Lee; H. Chuan Kang; Anthony Linden

To cite this Article Lee, C. Kuan , Kang, H. Chuan and Linden, Anthony(1999) 'Synthesis, Structure and Sweetness Of 4-Chloro-4-Deoxy-α-D-Galactopyranosyl 1,4,6-Trichloro-1,4,6-Trideoxy-β-D-Tagatofuranoside', Journal of Carbohydrate Chemistry, 18: 2, 241 — 253
To link to this Article: DOI: 10.1080/07328309908543993
URL: http://dx.doi.org/10.1080/07328309908543993

J. CARBOHYDRATE CHEMISTRY, 18(2), 241–253 (1999)

SYNTHESIS, STRUCTURE AND SWEETNESS OF 4-CHLORO-4-DEOXY-α-D-GALACTOPYRANOSYL 1,4,6-TRICHLORO-1,4,6-TRIDEOXY-β-D-TAGATOFURANOSIDE

C. Kuan Lee,[a]* H. Chuan Kang[a] and Anthony Linden[b]

[a]Department of Chemistry, National University of Singapore, Kent Ridge, Singapore 0511

[b]Organisch-Chemisches Institut, Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

Received July 28, 1998 - Final Form December 10, 1998

ABSTRACT

The reaction of 6-*O*-acetylsucrose with sulfuryl chloride was reexamined. The major product, after dechlorosulfation and acetylation, was determined by X-ray diffraction to be 2,3,6-tri-*O*-acetyl-4-chloro-4-deoxy-α-D-galactopyranosyl 3-*O*-acetyl-1,4,6-trichloro-1,4,6-trideoxy-β-D-tagatofuranoside and not the corresponding sorbofuranoside, as reported earlier. The mechanism of chlorination at C-4' is discussed. The intensity of sweetness of the free 4'-chlorodeoxy *tagato* isomer is determined to be only about one-tenth the sweetness of the corresponding chlorodeoxy *fructo* isomer, which strongly suggests that the hydrophobic γ-site is located at C-4'.

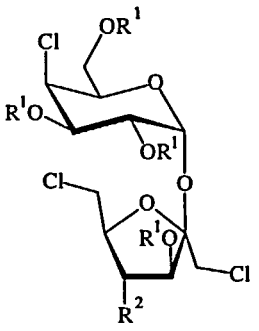
INTRODUCTION

Substances that are sweet come in all shapes and sizes, and are found in many inorganic and organic classes of compounds, yet a small stereochemical change or substitution of one atom for another in a given molecule may change the taste drastically.

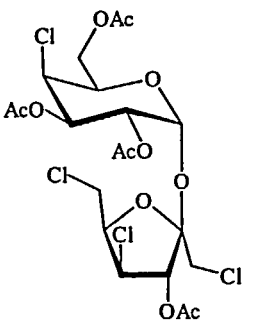
Thus, stereoisomers can have very different sweetness; D-galactose and D-mannose are both less than half as sweet as D-glucose[1] and galactosucrose has very low sweetness compared with sucrose.[2] Tetrahalodeoxy derivatives of sucrose, especially those with a halodeoxy substituent at C-4 of the fructofuranosyl moiety, exhibit substantially enhanced sweetness, and many of these compounds are several thousand times sweeter than sucrose.[3] Since all these sucrose analogues have a 4-deoxy-4-halo substituent in the fructofuranosyl ring, we are interested in the structure-taste relationship of other 4-deoxy-4-halo hexulofuranosyl analogues, particularly, 4-deoxy-4-halo-β-D-sorbo- and tagatofuranosyl analogues. In the course of our study, when the reaction of 6-*O*-acetylsucrose and sulfuryl chloride[4] was reexamined, it was found, based on the X-ray crystallographic evidence, that the major product of the reaction, after dechorosulfation and acetylation, was 2,3,6-tri-*O*-acetyl-4-chloro-4-deoxy-α-D-galactopyranosyl 3-*O*-acetyl-1,4,6-trichloro-1,4,6-trideoxy-β-D-tagatofuranoside, and not the 1,4,6-trichlorosorbofuranoside.

RESULTS AND DISCUSSION

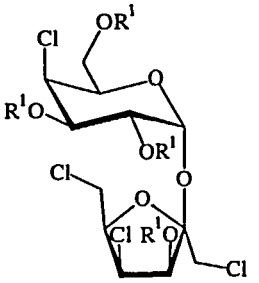
It was reported[4] that treatment of 6-*O*-acetylsucrose with sulfuryl chloride in chloroform-pyridine gave, after dechlorosulfation and acetylation, 2,3,6-tri-*O*-acetyl-4-chloro-4-deoxy-α-D-galactopyranosyl 3,4-di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-β-D-fructofuranoside (**1**, 11.3%), 2,3,6-tri-*O*-acetyl-4-chloro-4-deoxy-α-D-galactopyranosyl 3-*O*-acetyl-1,4,6-trichloro-1,4,6-trideoxy-β-D-fructo- (**2**, 13.6%) and sorbofuranoside (**3**, 32%). Chlorination at C-4' was proposed[4] to proceed via ring opening of intermediate C-3',4' epoxides by chloride ions. If this were the case, the 4'-chloro-4'-deoxy *fructo* isomer **2** rather than the *sorbo* isomer **3**, would be expected to be formed as the major product, since studies[5] have shown that base treatment of sucrose 3',4'-disulfonates produced 3',4'-*lyxo* and *ribo*-epoxides in 76 and 12%, respectively. Subsequent nucleophilic ring opening of the former gave the fructofuranosyl isomer, while the latter gave the sorbofuranosyl isomer. When we repeated the reaction of 6-*O*-acetylsucrose with sulfuryl chloride, we also obtained, after dechlorosulfation and acetylation, a mixture of one trichloro and two tetrachloro derivatives. The trichloro (**1**) and one of the tetrachloro derivatives (**2**) were identical to those reported.[4] The second tetrachloro derivative, when recrystallised from dimethyl sulfoxide, had a significantly different mp from that previously reported.[4] This



1. R^1 = Ac, R^2 = OAc
2. R^1 = Ac, R^2 = Cl
5. R^1 = H, R^2 = OH
6. R^1 = H, R^2 = Cl



3



4. R^1 = Ac
7. R^1 = H

tetrachloro derivative was reported to crystallise as twinned crystals in ether-light petroleum, and the compound was characterised based on its NMR data. The crystals from dimethyl sulfoxide were found to be single crystals, and an X-ray crystallographic analysis of this tetrachloride showed the compound to be 2,3,6-tri-*O*-acetyl-4-chloro-4-deoxy-α-D-galactopyranosyl 3-*O*-acetyl-1,4,6-trichloro-1,4,6-trideoxy-β-D-tagatofuranoside (**4**) and not the sorbofuranoside **3**.

With the establishment of the chiralities of C-3' and C-4' of the tetrachlorides **2** and **4**, the mechanism of sulfuryl chloride chlorination at C-4' of sucrose is now clear. The initially formed tetrachlorosulfated fructofuranosyl moiety first undergoes displacement at the primary positions. The resulting 1',6'-dichloro-3',4'-bis(chlorosulfate) then reacts in two ways: (i) it undergoes direct displacement of the 4'-chlorosulfate group to give the 1',4',6'-trichloro-*tagato* isomer, (ii) it also undergoes epoxide formation. Since base treatment of sucrose 3',4'-disulfonates preferentially gives the 3',4'-*lyxo*-epoxide, it is likely that only the 1',6'-dichloro-3',4'-*lyxo*-epoxide is formed. Ring opening of this epoxide by chloride ions then gives the 4-chlorodeoxyfructofuranosyl derivative **2** after dechlorosulfation and acetylation. In view of this finding, it is likely that the 3',4'-epoxides reported by Lee[4] and Ballard *et al.*[6] had been incorrectly assigned as *ribo*-epoxides.

The molecular structure of **4** in the crystal and the atom numbering system is shown in Fig. 1. The figure depicts the correct absolute configuration of the molecule, which was

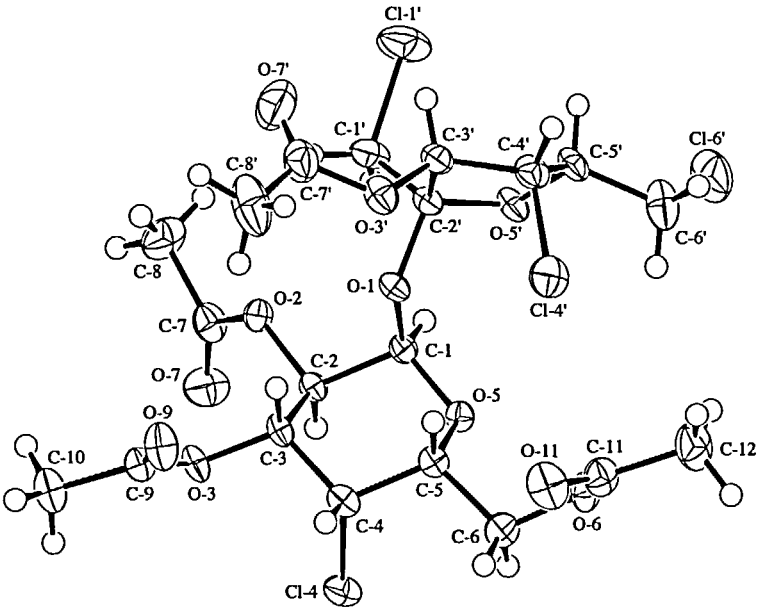


Fig. 1. ORTEP drawing of **4**

assigned to agree with that of its known precursor. This was further confirmed independently by the X-ray analysis. The atomic coordinates of the non-H atoms are given in Table 1.

Selected bond lengths, bond angles and torsion angles are given in Table 2. The bond lengths and angles are normal and generally agree with the corresponding values in other sugars. The bond angles about the anomeric centres are very similar to those of the *fructo* isomer **2**[7] (Table 3) but there are some differences in the conformation about the C–O bonds associated with the anomeric carbons. This is caused by rotation about C-2'–O-1 and C-1–O-1 in **2**, as shown by the torsion angles (Table 2). Interestingly, the conformation about the glycosidic C–O bonds of **4** is very similar to that of sucrose (Table 3); in sucrose this conformation is the consequence of two intramolecular hydrogen bonds, OH-6'···O-5, and OH-1'···O-2.

The hydroxymethyl group at C-5 and chloromethyl groups at C-2' and C-5' in **4** have interesting conformational features. The C-5 and C-5' substituents have the *gauche-trans* conformations and that at C-2' is *gauche-gauche* (Table 2). These groups in **2**[3] and **5**[7] also have the same conformations. In sucrose, however, both the C-5 and C-5'

Table 1. Fractional atomic coordinates and equivalent isotropic temperature factors (A^2) of **4** with standard uncertainties in parentheses.

*U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor. Origin defined by fixing the *x*, *y*, *z* coordinates of Cl-4.

ATOM	*x*	*y*	*z*	U_{eq}*
Cl-4	0.40238	0.37601	0.37536	0.0313(3)
Cl-1'	0.7116(1)	1.0356(1)	1.1552(1)	0.0545(5)
Cl-4'	0.5072(1)	0.9959(1)	0.4442(1)	0.0378(4)
Cl-6'	0.1409(1)	1.3435(1)	0.8433(2)	0.0584(5)
O-1	0.6068(2)	0.7657(2)	0.7024(2)	0.0208(8)
O-2	0.7006(2)	0.5393(2)	0.8719(2)	0.0240(8)
O-3	0.7483(2)	0.2914(2)	0.5787(2)	0.0251(8)
O-5	0.3709(2)	0.7280(2)	0.5504(2)	0.0207(8)
O-6	0.2197(2)	0.8287(2)	0.2322(2)	0.0297(9)
O-7	0.6252(3)	0.3927(3)	0.9550(3)	0.044(1)
O-9	0.9290(3)	0.2560(2)	0.4298(3)	0.036(1)
O-3'	0.8162(2)	0.8368(2)	0.6451(3)	0.0301(9)
O-5'	0.4544(2)	1.0246(2)	0.8246(2)	0.0263(8)
O-7'	1.0133(3)	0.7794(3)	0.8738(4)	0.068(1)
O-11	0.3970(3)	0.7747(2)	0.0689(3)	0.040(1)
C-1	0.4891(3)	0.7161(3)	0.7040(3)	0.020(1)
C-2	0.5785(3)	0.5462(3)	0.7167(3)	0.021(1)
C-3	0.6617(3)	0.4504(3)	0.5614(3)	0.022(1)
C-4	0.5349(3)	0.4678(3)	0.3949(3)	0.024(1)
C-5	0.4380(3)	0.6402(3)	0.3946(3)	0.022(1)
C-6	0.2970(3)	0.6678(3)	0.2447(3)	0.028(1)
C-7	0.7068(4)	0.4627(3)	0.9841(4)	0.031(1)
C-8	0.8278(4)	0.4839(4)	1.1447(4)	0.044(2)
C-9	0.8868(3)	0.2081(3)	0.5117(4)	0.026(1)
C-10	0.9762(4)	0.0521(3)	0.5551(4)	0.037(1)
C-1'	0.6857(4)	0.8698(3)	1.0023(4)	0.032(1)
C-2'	0.6120(3)	0.9039(3)	0.8240(3)	0.023(1)
C-3'	0.7074(3)	0.9587(3)	0.7568(3)	0.026(1)
C-4'	0.5754(3)	1.0814(3)	0.6627(4)	0.029(1)
C-5'	0.4465(3)	1.1528(3)	0.7741(4)	0.029(1)
C-6'	0.2753(4)	1.2381(4)	0.6897(5)	0.045(2)
C-7'	0.9688(4)	0.7555(3)	0.7214(5)	0.041(2)
C-8'	1.0670(4)	0.6340(4)	0.5879(5)	0.060(2)
C-11	0.2787(4)	0.8637(3)	0.1317(4)	0.032(1)
C-12	0.1779(4)	1.0288(4)	0.1123(4)	0.047(2)

Table 2. Selected bond lengths (Å), bond angles (°) and torsion angles (°) of **4** with standard uncertainties in parentheses.

Cl-4–C-4	1.813(3)	O-5–C-1	1.415(3)	C-3–C-4	1.530(4)
Cl-1'–C-1'	1.790(3)	O-5–C-5	1.444(3)	C-4–C-5	1.530(3)
Cl-4'–C-4'	1.794(3)	O-6–C-6	1.451(3)	C-5–C-6	1.509(4)
Cl-6'–C-6'	1.792(3)	O-3'–C-3'	1.436(3)	C-1'–C-2'	1.518(4)
O-1–C-1	1.418(3)	O-5'–C-2'	1.410(3)	C-2'–C-3'	1.553(3)
O-1–C-2'	1.426(3)	O-5'–C-5'	1.446(3)	C-3'–C-4'	1.515(4)
O-2–C-2	1.442(3)	C-1–C-2	1.530(3)	C-4'–C-5'	1.514(4)
O-3–C-3	1.445(3)	C-2–C-3	1.518(3)	C-5'–C-6'	1.499(4)

C-1–O-1–C-2'	117.9(2)	C-1'–C-2'–C-3'	115.1(2)
C-1–O-5–C-5	114.0(2)	C-2'–C-3'–C-4'	104.2(2)
C-1–C-2–C-3	108.9(2)	C-2'–O-5'–C-5'	110.1(2)
C-2–C-3–C-4	109.8(2)	C-3'–C-4'–C-5'	100.3(2)
C-3–C-4–C-5	109.3(2)	C-4'–C-5'–C-6'	115.9(2)
C-4–C-5–C-6	112.4(2)	O-5'–C-2'–C-1'	110.0(2)
O-1–C-1–C-2	107.7(2)	O-5'–C-2'–C-3'	105.4(2)
O-1–C-1–O-5	110.6(2)	O-5'–C-5'–C-4'	105.4(2)
O-1–C-2'–C-1'	108.8(2)	O-5'–C-5'–C-6'	109.3(2)
O-1–C-2'–C-3'	106.5(2)	Cl-4–C-4–C-5	111.5(2)
O-1–C-2'–O-5'	111.0(2)	Cl-1'–C-1'–C-2'	110.1(2)
O-5–C-1–C-2	109.3(2)	Cl-4'–C-4'–C-5'	112.7(2)
O-5–C-5–C-6	107.0(2)	Cl-6'–C-6'–C-5'	111.4(2)

Within the hexopyranose ring		Within the hexulofuranose ring	
C-1–C-2–C-3–C-4	-58.4(2)	C-2'–C-3'–C-4'–C-5'	34.6(2)
C-1–O-5–C-5–C-4	57.6(3)	C-2'–O-5'–C-5'–C-4'	26.3(3)
C-2–C-3–C-4–C-5	54.6(3)	C-3'–C-2' –O-5'–C-5'	-3.4(3)
C-2–C-1–O-5–C-5	-60.5(2)	O-5'–C-2'–C-3'–C-4'	-20.5(2)
O-5–C-1–C-2–C-3	60.2(2)	O-5'–C-5'–C-4'–C-3'	-37.4(2)
O-5–C-5–C-4–C-3	-52.8(3)		

Outside the hexopyranose ring		Outside the hexulofuranose ring	
C-1–O-1–C-2'–C-1'	73.2(3)	C-1'–C-2'–C-3'–C-4'	-141.9(2)
C-1–O-1–C-2'–C-3'	-162.1(2)	C-1'–C-2'–O-5'–C-5'	121.2(2)
C-1–O-5–C-5–C-6	-179.1(2)	C-3'–C-4'–C-5'–C-6'	-158.3(2)
C-2–C-1–O-1–C-2'	-127.6(2)	O-1–C-2'–C-3'–C-4'	97.4(2)
C-3–C-4–C-5–C-6	-173 .0(2)	Cl-1'–C-1'–C-2'–O-1	174.7(2)
O-1–C-1–O-5–C-5	57.8(2)	Cl-1'–C-1'–C-2'–O-5'	-63.5(2)
O-5–C-1–O-1–C-2'	113.1(2)	Cl-1'–C-1'–C-2'–C-3'	55.3(3)
O-5–C-5–C-6–O-6	65.0(2)	Cl-4'–C-4'–C-3'–C-2'	-84.9(2)
Cl-4–C-4–C-3–C-2	-68.2(2)	Cl-4'–C-4'–C-5'–C-6'	-39.9(3)
Cl-4–C-4–C-3–O-3	51.9(2)	Cl-4'–C-4'–C-3'–O-'3	38.3(3)
Cl-4–C-4–C-5–O-5	69.2(2)	Cl-4'–C-4'–C-5'–O-5'	81.1(2)
Cl-4–C-4–C-5–C-6	-51.0(2)	Cl-6'–C-6'–C-5'–C-4'	-170.4(2)
		Cl-6'–C-6'–C-5'–O-5'	70.8(3)

Table 3. Comparison of bond angles (°) involving the anomeric oxygen O-1, and selected torsion angles (°) of chlorinated sucrose analogues **2**, **4**, **5**, and sucrose

	4	**2**	**7**[6]	sucrose[7]
C-1–O-1–C-2'	117.9(2)	116.6(3)	119.2(2)	114.30(8)
O-1–C-1–C-2	107.7(2)	109.4(4)	106.3(2)	110.33(8)
O-1–C-1–O-5	110.6(2)	111.0(3)	110.8(2)	110.49(8)
O-1–C-2'–C-1'	108.8(2)	106.6(4)	110.1(2)	109.93(8)
O-1–C-2'–C-3'	106.5(2)	107.8(4)	112.5(2)	108.43(7)
O-1–C-2'–O-5'	111.0(2)	111.7(3)	102.7(2)	111.00(8)
C-1 –O-1–C-2'–C-1'	73.2(3)	93.4(4)	-46.1(2)	73.70(10)
C-1–O-1–C-2'–C-3'	-162.1(2)	-140.1(4)	83.7(2)	-159.81(8)
C-1–O-1–C-2'–O-5'	-48.0(3)	-25.1(5)	-162.2(2)	-44.75(11)
C-2–C-1–O-1–C-2'	-127.6(2)	-140.7(4)	-147.9(2)	-129.25(9)
O-5–C-1–O-1–C-2'	113.1(2)	99.5(4)	91.4(2)	107.82(10)
O-5–C-5–C-6–O-6	65.0(2)	77.1(5)	66.9(2)	-56.42(13)
O-6–C-6–C-5–C-4	-172.2(2)	-158.9(4)	-169.8(2)	64.39(13)
Cl-4–C-4–C-5–O-5	69.2(2)	67.9(4)	66.5(2)	
Cl-4–C-4–C-5–C-6	-51.0(2)	-53.7(5)	-54.4(2)	
Cl-1'–C-1'–C-2'–C-3'	55.3(3)	58.3(5)	60.6(2)	
Cl-1'–C-1'–C-2'–O-5'	-63.5(2)	-60.5(5)	-59.2(2)	
Cl-6'–C-6'–C-5'–C-4'	-170.4(2)	172.8(3)	177.2(2)	
Cl-6'–C-6'–C-5'–O-5'	70.8(3)	56.9(5)	61.3(2)	

hydroxymethyl groups are *gauche-gauche*, while that at C-2' is *trans-gauche*.[8] These conformational differences in sucrose are probably due to the two intramolecular H-bonds. The *gauche-trans* conformations in **4** for both O-6 and Cl-6' about the C-5–C-6 and C-5'–C-6' bonds, respectively, are favourable arrangements, as these will avoid any 1,3-*peri* interaction with Cl-4 and Cl-4'. For Cl-1', the *gauche-gauche* conformation positions Cl-1' under the furanose ring, avoiding both possible *peri* interactions with O-5' and O-3', and also a repulsive dipole-dipole interaction between the chloro substituent and the anomeric oxygen atom.

The galactopyranosyl ring in **4** adopts the $^4C_1$ chair conformation. The puckering parameters[9] (Table 4) describe a slightly distorted chair conformation; a similar distorted conformation was also observed for **2**. The distortion ($\theta = 5.0°$ for **4** and $\theta = 4.7°$ for **2**) is comparable with that in sucrose ($\theta = 5.2°$),[9] but it is much greater than that ($\theta = 1.9°$)[7] in 4-chloro-4-deoxy-α-D-galactopyranosyl 1,6-dichloro-1,6-dideoxy-β-D-fructofuranoside (**5**). The furanoid ring in **4** has an envelope conformation with C-4' as the envelope flap, i.e., ^4E

Table 4. Puckering parameters for the pyranose and furanose rings in **2** and **4**

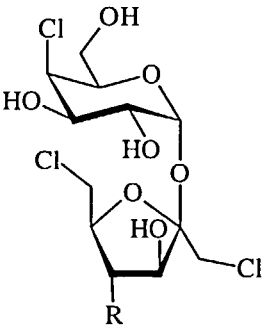
	pyranose ring		furanose ring	
	2	**4**	**2**	**4**
Q [Å]	0.546(5)	0.579(3)		
q_2 [Å]	0.046(5)	0.049(3)	0.414(5)	0.372(3)
q_3 [Å]	0.544(5)	0.577(3)		
φ_2 [°]	347(6)	117(3)	268.1(6)	291.3(4)
θ [°]	4.7(5)	5.0(3)		

(θ = 291.3°). The same conformation is also observed in **5**.[7] In **2**, this ring has a $^4T_3$ twist conformation (θ = 268.1°) which is the same as in sucrose and also in planteose.[10]

Evaluation of the sweetness intensity of 4-chloro-4-deoxy-α-D-galactopyranosyl 1,4,6-trichloro-1,4,6-trideoxy-β-D-tagatofuranoside (**7**) shows the compound to be about 205 times as sweet as sucrose (5% solution). The sweetness of 4-chloro-4-deoxy-α-D-galactopyranosyl 1,4,6-trichloro-1,4,6-trideoxy-β-D-fructofuranoside (**6**) is confirmed to be 2,200 × sucrose (5% solution).

Currently, the most plausible and widely accepted explanation for sweetness is the Shallenberger and Acree-Kier[11a,b] AH,B,γ concept. Shallenberger and Acree[11a] proposed that the initial chemistry of the sweet taste response is due to intermolecular hydrogen bonding between an AH,B moiety of a compound and a complementary system at the receptor site. A hydrophobic (γ) binding-site,[12] if present at an appropriate distance from the AH,B moiety, will enhance sweetness potency.[11b] The location of the AH,B,γ glucophore in sucrose and the intensely sweet 4-deoxy-4-halo sucrose analogues is still being intensely debated.[11-19] The high sweetness of these chlorodeoxy analogues clearly suggests that the intense sweetness of these compounds is a direct effect of the hydrophobicity of the halogen substituent(s). The location of the γ-site of tetrahalodeoxy sucrose analogues has been assigned to be the C-4,[15,18] C-4,[14,16,17] C-1',[14,16,19] and C-6',[14,15,18] halogen atoms. The 10-fold difference in the sweetness of 4-chloro-4-deoxy-α-D-galactopyranosyl 1,4,6-trichloro-1,4,6-trideoxy-β-D-fructofuranoside (**6**) and 4-chloro-4-deoxy-α-D-galactopyranosyl 1,4,6-trichloro-1,4,6-trideoxy-β-D-tagatofuranoside (**7**) clearly suggests that the halogen substituent at C-4' and its stereochemistry play a very important role in the sweetness of these compounds, since the two compounds differ only

Table 5. Sweetness intensity of 4,1',4',6'-tetrahalo-4,1',4',6'-tetradeoxygalactosucrose analogues (sucrose = 1)



	Relative Sweetness
R = F	1000
R = Cl	2200
R = Br	3000
R = I	3500 (5000)[13]

in the configuration at C-4'. If, indeed the halogen atoms in these compounds function as the γ-site,[19] then Cl-4' is most probably a major if not the specific γ-site. This is further strongly supported by the systematic increase in the relative sweetness of 4-chloro-4-deoxy-α-D-galactopyranosyl 1,6-dichloro-4-halo-1,4,6-trideoxy-β-D-fructofuranoside when going from the C-4' fluoro to the chloro, bromo and iodo derivatives (Table 5), that is, with increasing hydrophobicity of the halogen substituent. The structure-sweetness intensity relationship of 4'-deoxy-4'-halo sucrose analogues should give further insight into the importance of the C-'4 substituent, and we are currently studying the taste of a series of 4-halodeoxysorbofuranosyl and tagatofuranosyl derivatives.

Recent work by Tsuami *et al.*[16] appears to support this proposal. In their study using computer graphics, they showed that the (*S*)-C-4' chlorine substituent of 4-chloro-4-deoxy-α-D-galactopyranosyl 1,6-dichloro-4-halo-1,4,6-trideoxy-β-D-fructofuranoside is in a position to form a dispersion bond with the side chain of the 4th amino acid residue of a hypothetical proteinaceous receptor model, this interaction being assisted by weak hydrogen bonding between OH-6 and Cl-6'.

It is generally thought that the conformation of a sweet compound in its crystal structure is probably not the main sweet conformation.[19,20] In our preliminary investigation of the 'sweet' conformations of tetrachloro analogues of sucrose using quantum mechanical simulations, optimised molecular structures are found using density functional methods in the local density approximation (LDA).[21] From molecular mechanics and dynamics studies, Hooft *et al.*[19] proposed that the sweet conformation of these chlorinated analogues have

Table 6. AH,B,γ distances (Å) of the computer modelled conformations of **6** and **7**

AH,B,γ distances	6a	6b	7a	7b
O-2···O-3	2.85	2.89	2.87	2.78
O-2···Cl-4'	6.87	5.55	6.36	6.27
O-3···Cl-4'	8.29	3.00	7.35	8.61
O-3'···O-2	4.84	3.04	4.67	3.30
O-3'···Cl-4'	3.78	2.95	2.94	3.67
OH-2···O-3	2.94	3.39	3.21	2.24
OH-2···Cl-4'	6.20	5.05	5.41	7.06
OH-3'···O-2	3.96	2.80	4.06	2.31
OH-3'···Cl-4'	4.32	2.77	2.90	4.37

$\Phi_{C\text{-}1\text{-}O\text{-}1\text{-}C\text{-}2'\text{-}O\text{-}5'}$ = 75° and $\Psi_{C\text{-}2'\text{-}O\text{-}1\text{-}C\text{-}1\text{-}O\text{-}5}$ = 95°. We obtained the optimised low-energy structures **6a** and **7a** while constraining Φ and Ψ at these values; conformation **6a** is slightly more stable (0.8 Kcal) than **7a**. In both these structures, the conformation of the C-6 hydroxy group is *gauche-trans*, and both primary chloro groups on the hexulofuranose ring have the *gauche-gauche* conformations. Adopting the two AH,B pairs (a) OH-2,O-3, proposed by Hooft *et al.*[19] and Lichthenthaler and Immel,[13] and (b) OH-3',O-2, proposed by Mathlouthi and Seuvre[17], and Tsuami *et al.*,[16] the two sets of AH-B-γ distances are shown in Table 6.

When **6** was optimised with no constraints on Φ and Ψ, we obtained a structure **6b** which has the torsion angles, Φ = 82.5° and Ψ = 13.8°. Like **6a**, the conformation of the C-6 hydroxyl is *gauche-trans*, and both chloro groups on the hexulofuranose ring are *gauche-gauche*. Conformation **6b** is slightly more stable than **6a** (by 1.2 Kcal). We have also obtained the optimised structures of **7** with torsion angles Φ/Ψ constrained to 75°/95° (**7a**) and 82.5°/13.8° (**7b**); the conformations **7a** and **7b** are less stable than **6** by ~0.5 Kcal and ~1.9 Kcal, respectively.

The calculated values in Table 6 show that the O-2···O-3···Cl-4' distances in **6a** and **7a** (Φ/Ψ = 75°/95°) do not fit well with the receptor description (A···B = ~3.0 Å, A···γ = ~3.5 Å, B···γ = ~7.4 Å) proposed by Shallenberger-Acree/Kier.[11] The O-3'···O-2···Cl-4' distances corresponded better, but the A···B distances (4.84 and 4.06 Å, respectively) are too far apart. However, both conformations **6b** and **7b** (Φ/Ψ = 82.5°/13.8°) produce O-3'···O-2···Cl-4' distances which agree reasonably well with the Shallenberger-Acree/Kier

distance. To obtain a more conclusive definition of these distances, we are determining other low energy structures for these compounds and the other halogenated analogues.

EXPERIMENTAL

Molecular structure optimization. In this preliminary study, we use quantum mechanical methods to perform (a) single-point calculations of the energy of model structures, and (b) geometry optimisations, which find local energy minima for a specific starting structure. Optimised structures are found using the density functional method within the local density approximation. The exchange-correlation energy is calculated using the SVWN functional.[22] Calculations were performed with Slater type orbitals and double-zeta basis sets using the ADF package[23]

Crystal structure determination for compound 4. Crystal data: $C_{20}H_{26}Cl_4O_{11}$, M_r = 584.23, triclinic, space group $P1$, a = 9.433(2), b = 10.018(2), c = 8.365(2) Å, α = 109.77(2), β = 108.01(2), γ = 62.05(2)°, V = 646.3(3) Å^3, Z = 1, D_c = 1.501 g cm^{-3}, $F(000)$ = 302 e, crystal dimensions: 0.25 × 0.37 × 0.43 mm, T = -100 °C, Rigaku AFC5R diffractometer, Mo-Kα radiation, λ = 0.71069 Å, μ = 0.512 mm^{-1}, $\omega/2\theta$ scans, $2\theta_{max}$ = 55°. The unit cell parameters were refined from the setting angles of 25 carefully centered reflections in the range 24° < 2θ < 26°. The data collection included the measurement of the Friedel opposites of all reflections with 2θ < 40°. Friedel pairs were not averaged, so that all 4577 measured reflections were considered unique. Three standard reflections measured after every 150 reflections showed negligible variation in intensity. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. The structure was solved by direct methods using *SHELXS86*[24] and refined on F by full-matrix least-squares methods which minimized the function $\Sigma w(|F_o| - |F_c|)^2$, where $1/w = [\sigma^2(F_o) + (0.005F_o)^2]$. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were located in a difference electron density map, but their positions were subsequently geometrically idealised [d(C-H) = 0.95 Å] and held fixed. Each H-atom was assigned a fixed isotropic temperature factor with a value equal to $1.2U_{eq}$ of the parent C-atom. The refinement of 314 parameters using 4474 observed reflections with $I > 2\sigma(I)$ gave R = 0.0295, wR = 0.0330, S = 2.684 and $\Delta\rho_{max}$ = 0.50 e Å^{-3}. The absolute structure parameter refined to -0.02(4), thereby confirming that the absolute configuration of the molecule

corresponded with that of its known precursor. All calculations were performed using the *TEXSAN* crystallographic software package.[25] Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition number CCDC-102056.[26]

Reaction of 6-*O*-acetylsucrose[27] with sulfuryl chloride. A solution of 6-*O*-acetylsucrose[27] (5.0 g) in pyridine (10 mL) and dry chloroform (10 mL) at -60 °C was treated with surfuryl chloride (13.8 mL, 14 mol) according to the method of Lee[4] without modification. The products obtained were (i) **1** [11.1%, mp 91-94 °C, $[\alpha]_D$ +65.9° ($CHCl_3$); lit.[28] mp 92-94 °C, $[\alpha]_D$ +66.8° ($CHCl_3$)], (ii) **2** [35.3%, mp 103-105 °C, $[\alpha]_D$ +78° ($CHCl_3$); lit.[4] mp 103-104 °C, $[\alpha]_D$ +75° (MeOH)], and (iii) **4** [12.2%, mp 111-112 °C (methyl sulfoxide), $[\alpha]_D$ +78.0° (*c* 1.0, $CHCl_3$); lit.[4] mp 169-169 °C, $[\alpha]_D$ +86.5°.

Anal. Calcd for $C_{20}H_{26}Cl_4O_{11}$ (408.20): C, 41.12, H, 4.49, Cl, 24.27; Found: C, 41.37; H, 4.50; Cl, 24.35].

ACKNOWLEDGEMENTS

We thank the National University of Singapore for financial support under a grant (RP960671) awarded to C.K.L.

REFERENCES

1. R. S. Shallenberger, *J. Food Sci.*, **28**, 584 (1963).
2. M. G. Lindley, G. G. Birch and R. Khan, *J. Sci. Food Agric.*, **27**, 140 (1976).
3. C. K. Lee, *Eur. Pat Appl.* EP 50.952 (1982); *US Pat.* 4.405.654 (1983); *Adv. Carbohydr. Chem.*, **45**, 199 (1987).
4. C. K. Lee, *Carbohydr. Res.*, **162**, 53 (1987).
5. H. Lindseth, *PhD Thesis*, University of Reading, 1980; R. Khan, In *Sugar: Science and Technology*, G. G. Birch and K. J. Parker, Eds., Applied Science: London, (1978) p 181; M. R. Jenner. In *Developments in Food Carbohydrates. 2.* C. K. Lee, Ed. Applied Science: London, (1980) pp. 91-143.
6. J. M. Ballard, L. Hough, A. C. Richardson and P. H. Fairclough, *J. Chem. Soc. Perkin Trans. 1,* 1524 (1973).
7. J. A. Kanters, R. L. Scherrenberg, B. R. Leeflang and J. Kroon, and M. Mathlouthi, *Carbohydr. Res.*, **180**, 175, (1988).
8. G. M. Brown and H. A. Levy, *Acta Crystallogr.*, **B29**, 790 (1973).
9. D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, **97**, 1354 (1975).
10. D. C. Rohrer, *Acta Crystallogr.*, **B28**, 425 (1972).
11. (a) R. S. Shallenberger and T. E. Acree, *Nature (London)*, **216**, 480 (1967); (b) L. B. Kier, *J. Pharm. Sci.*, **61**, 1394 (1972);

12. R. S. Shallenberger and M. G. Lindley, *Food Chem.*, **2**, 145 (1977); E. W. Deutsch and C. Hansch, *Nature (London)*, **216**, 75 (1966)
13. F. W. Lichtenthaler and S. Immel, In *Sweet-taste Chemoreception*, M. Mathlouthi, J. A. Kanters and G. G. Birch, Eds., Elsevier Applied Science: London, (1993), p 21.
14. A. van der Heijden, H. van der Wel and H. G. Peer, Chemical Senses, **10**, 73 (1985); A. van der Heijden, In *Sweet-taste Chemoreception*, M. Mathlouthi, J. A. Kanters and G. G. Birch, Eds., Elsevier Applied Science: London, (1993), p 103.
15. L. Hough. *Int. Sugar J.*, **91**, 26 (1989); L. Hough and R. Khan, In *Sweet-taste Chemoreception*, M. Mathlouthi, J. A. Kanters and G. G. Birch, Eds., Elsevier Applied Science: London, (1993), p 91.
16. T. Suami, L. Hough, M. Tsuboi, T. Machinami, *J. Carbohydr. Chem.*, 13, 1079 (1994).
17. M. Mathlouthi, C. Bressan, M. O. Potmann and S. Serghat, In *Sweet-taste Chemoreception*, M. Mathlouthi, J. A. Kanters and G. G. Birch, Eds., Elsevier Applied Science: London, (1993), p 141; M. Mathlouthi and A. M. Seuvre, *J. Chem Soc. Faraday Trans.* **84**, 2641 (1988).
18. L. Hough and R. Khan, *Trends Biochem. Sci.*, **3**, 23 (1978).
19. R. W. W. Hooft, J. A. Kanters and J. Kroon, In *Sweet-taste Chemoreception*, M. Mathlouthi, J. A. Kanters and G. G. Birch, Eds., Elsevier Applied Science:London, (1993) p 11
20. C. Meyer, S. Pérez, C. H. du Penboat and V. Michon, *J. Am. Chem. Soc.*, **115**, 10300 (1993).
21. W. Kohn and L. J. Sham, *Phys. Rev.*, **140**, 1133 (1965).
22. S.H. Vosko, L. Wilkes and M. Nusair, *Can. J. Phys.*, **58**, 1200 (1980).
23. E. J. Baerends, D. E. Elis and P. Ros, *Chem. Phys.*, **2**, 41 (1973); P. M. Boerrigter, G. te Velde and E. J. Baerends, *Int. J. Quant. Chem.*, **33**, 87 (1988); G. te. Velde and E. J. Baerends, *J. Comput. Phys.*, **99**, 84 (1994).
24. Sheldrick, G. M. *SHELXS-86. Acta Crystallogr.*, **A46**, 467 (1990).
25. *TEXSAN.* Single Crystal Structure Analysis Package, Version 5.0. Molecular Structure Corporation, The Woodlands, Texas (1989).
26. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033: e-mail: deposit @chemcrys.cam.ac.uk)
27. W. M. Macindoe, A. Williams and R. Khan, *Carbohydr. Res.*, **283**,17 (1966).
28. P. H. Fairclough, L. Hough and A.C. Richardson, *Carbohydr. Res.*, **40**, 285 (1975).