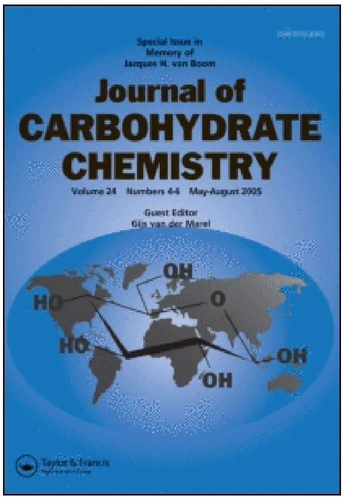

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Structure and Taste of 3,3',4,4'-tetra-*O*-benzoyl-2,2'6,6'-tetradeoxy-α, α-ribotrehalose[1]

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To cite this Article Lee, C. Kuan and Linden, Anthony(1995) 'Structure and Taste of 3,3',4,4'-tetra-*O*-benzoyl-2,2'6,6'-tetradeoxy-α, α-ribotrehalose[1]', Journal of Carbohydrate Chemistry, 14: 1, 9 — 16
To link to this Article: DOI: 10.1080/07328309508006433
URL: http://dx.doi.org/10.1080/07328309508006433

J. CARBOHYDRATE CHEMISTRY, 14(1), 9-16 (1995)

STRUCTURE AND TASTE OF 3,3',4,4'-TETRA-*O*-BENZOYL-2,2',6,6'-TETRADEOXY-α,α-RIBOTREHALOSE[1]

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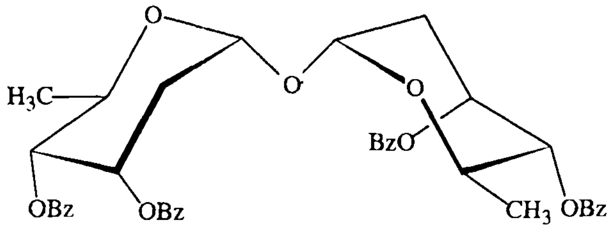
Received March 31, 1994 - Final Form August 2, 1994

ABSTRACT

The X-ray crystal structure of 3,3',4,4'-tetra-*O*-benzoyl-2,2',6,6'-tetradeoxy-α,α-ribotrehalose (**1**) (3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-ribohexopyranosyl 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-ribohexopyranoside) is reported. The molecule possesses crystallographic C_2 symmetry. The hexopyranosyl residues have a distorted $^4C_1$ conformation. The X-ray data show that O(3) and O(4) are optimally positioned to function as the Shallenberger AH,B glucophore in the free sugar, yet the free sugar is devoid of sweetness, and is, instead strongly bitter. A stereochemical basis of the biter taste of this compound has been proposed.

INTRODUCTION

Our primary interest in the deoxy derivatives of trehalose has been to study the chemical basis of sweetness and bitterness.[2] α,α-Trehalose offers an ideal model for such a study, since its derivatives are sweet and/or bitter, non-reducing and conformationally stable. The molecule is symmetrical about the central bridging O-atom, so that the two pyranose residues are physically and chemically equivalent. The synthesis[3] of the titled compound (**1**) and the taste of its 3,3',4,4'-tetrahydroxy analogue[2] have already been reported. We now report the X-ray crystal structure of **1**.



3,3',4,4'-Tetra-*O*-benzoyl-2,2',6,6'-tetradeoxy-α,α-ribotrehalose (**1**)

RESULTS AND DISCUSSION

The atomic coordinates of the non-H atoms are given in Table 1. Bond lengths and bond angles, and selected torsion angles are given in Tables 2 and 3, respectively. A view of **1**, showing the thermal ellipsoids and the atomic numbering scheme, is presented in Fig. 1, which also depicts the correct absolute configuration of the molecule as established by the synthesis of the compound.

There are no unusual geometrical features in the structure of **1**. The bond lengths and bond angles all lie within the expected ranges. However, unlike α,α-trehalose,[4] and most of its derivatives[5] the molecules of **1** possess perfect crystallographic C_2 symmetry about the bridging atom, O(1).

The hexopyranosyl ring adopts a slightly distorted $^4C_1$ conformation, with the torsion angles around the six-membered ring ranging from 48° to 59° (Table 3). The distortion is towards the $^4E/^4H_5$ conformation (φ_2 being between 240° and 270°) as shown by its puckering parameters:[6] $Q = 0.546$ Å, $\theta = 8.96$ °, $\varphi_2 = 253.2°$, $q_2 = 0.085$ Å, $q_3 = 0.540$ Å. This flattening of the ring-O atom and C(3) allows the ring angles C(1)–O(5)–C(5) and C(1)–C(2)–C(3) to widen to 116.5(2)° and 112.8(2)°, respectively.

The molecular packing of the crystal of **1** is shown in Fig. 2. The plane of the phenyl ring, C(8)–C(13) lies approximately 3.65 Å from the plane of the one related to it by the molecular 2-fold axis, although the rings are tilted slightly towards one another by ~5°. The closest contact, C(8)···C(13'), is 3.472(4) Å. Since the centroid of the ring lies at virtually 1/2, 3/4, z, the inter- and intra-molecular separations of the rings are almost identical. The intermolecular distance between neighbouring ring planes is also approximately 3.65 Å and the closest contact, C(10)···C(11"), is 3.476(4) Å . Thus the rings are evenly spaced along the crystal *b*-axis and the alignment is presumably due to packing efficiency. The distances are probably too large to suggest any interactions between their π systems.

The Shallenberger and Acree AH,B theory of sweetness[7] proposes that all sweet-tasting compounds contain an AH,B moiety (A and B being electronegative atoms with an internuclear distance of approximately 3 Å). A third hydrophobic γ binding site,[8] if present, determines the intensity of sweetness.[9] In sugars, it is generally agreed that the γ-function plays little or no part in sweetness[10] because of its extreme hydrophilic character. However,

TABLE 1. Fractional atomic coordinates and equivalent isotropic temperature factors (Å^2) for **1** (with e.s.d.s in parentheses).

Atom	x	y	z	Ueq*	Atom	x	y	z	Ueq*
O(1)	0.5	1.0	0.4566(2)	0.0260(6)	C(8)	0.45516(9)	0.8090(3)	0.8432(2)	0.0232(6)
O(3)	0.41828(6)	0.9114(2)	0.6483(1)	0.0242(4)	C(9)	0.4520(1)	0.8024(3)	0.9761(2)	0.0277(7)
O(4)	0.33079(6)	0.6726(2)	0.5672(1)	0.0245(4)	C(10)	0.5002(1)	0.7421(4)	1.0458(2)	0.0342(7)
O(5)	0.42792(6)	0.8672(2)	0.3238(1)	0.0273(5)	C(11)	0.5518(1)	0.6847(4)	0.9842(3)	0.0364(8)
O(7)	0.35372(6)	0.9056(2)	0.8142(1)	0.0328(5)	C(12)	0.5550(1)	0.6896(4)	0.8523(3)	0.0360(8)
O(14)	0.24350(6)	0.8233(2)	0.5800(2)	0.0363(5)	C(13)	0.5067(1)	0.7519(3)	0.7821(2)	0.0292(6)
C(1)	0.44741(9)	1.0269(3)	0.3826(2)	0.0257(6)	C(14)	0.27501(8)	0.7028(3)	0.6151(2)	0.0253(6)
C(2)	0.39988(9)	1.1061(3)	0.4702(2)	0.0263(6)	C(15)	0.25840(8)	0.5727(3)	0.7158(2)	0.0241(6)
C(3)	0.37257(9)	0.9697(3)	0.5594(2)	0.0240(6)	C(16)	0.21399(9)	0.6239(3)	0.8020(2)	0.0277(7)
C(4)	0.35275(8)	0.8087(3)	0.4822(2)	0.0230(6)	C(17)	0.1971(1)	0.5096(4)	0.8986(2)	0.0321(7)
C(5)	0.40522(9)	0.7307(3)	0.4075(2)	0.0239(6)	C(18)	0.2234(1)	0.3431(4)	0.9085(2)	0.0361(8)
C(6)	0.3874(1)	0.5763(4)	0.3230(3)	0.0359(8)	C(19)	0.2672(1)	0.2903(4)	0.8219(2)	0.0354(8)
C(7)	0.40279(9)	0.8796(3)	0.7706(2)	0.0239(6)	C(20)	0.28498(9)	0.4062(4)	0.7264(2)	0.0289(7)

* $U_{eq}$is defined as one third of the trace of the orthogonalized U_{ij} tensor

increasing the hydrophobic character of a sweet compound, for example by removing the hydroxyl groups in sugars, while maintaining the integrity of the AH,B,γ glucophore, will eventually lead to a maximum level of bitterness.[11] The X-ray data of **1** reveals that the O(3)···O(4) distance is ~2.8 Å, which is approximately the optimum A-to-B distance for sweetness.[12] This should also be the approximate O(3)···O(4) distance in 2,2',6,6'-tetradeoxy-α,α-ribotrehalose, but this compound is devoid of sweetness, and is, instead, strongly bitter.[2] Temussi et al.[13] recently suggested that, since simple D-amino acids and peptides are sweet, the difference between the sweet and bitter tastes can possibly be accounted for by assuming that the AH,B entities of the twin receptors for sweet and bitter tastes are related through inversion *via* a binary operation. In essence, the tripartite glucophore for bitterness is the mirror image of that for sweetness. Based on this proposal, the AH,B,γ glucophore in **1** [AH = 4(OH), B = 3(O), γ = C(6) or C(2)] has the conformation that allows it to be superimposed upon the tripartite unit for bitter, thus accounting for the bitterness (Fig. 3). Although the molecule is able to bind to the sweet receptor, the increase in the hydrophobicity of **1** due to the removal of the hydroxyl groups at C(2) and C(6) probably exerts a strong enough influence for the molecule to fit only the mirror-image bitter active site, as has been proposed[13] for 5,6-benzo-saccharin. A similar mechanism has also been reported for 4,4',6,6'-tetrachloro-4,4',6,6'-tetradeoxy-α,α-galactotrehalose.[14] We are presently studying other similar systems to determine the dimension of the A···B···γ triangle.

EXPERIMENTAL

3,3',4,4'-Tetra-*o*-benzoyl-2,2',6,6'-tetradeoxy-α,α-ribotrehalose (**1**) was prepared by the method of Hough, Richardson and Tarelli.[3] Suitable crystals were obtained from an ethanol solution.

TABLE 2. Bond lengths (Å) and bond angles (°) for **1** (with e.s.d.s in parentheses).

Bond lengths (Å)		Bond angles (°)	
O(1)–C(1)	1.423(2)	C(1)–O(1)–C(1')	113.8(2)
O(3)–C(3)	1.451(2)	C(3)–O(3)–C(7)	119.0(2)
O(3)–C(7)	1.350(2)	C(4)–O(4)–C(14)	114.8(2)
O(4)–C(4)	1.444(3)	C(1)–O(5)–C(5)	116.5(2)
O(4)–C(14)	1.363(2)	O(1)–C(1)–O(5)	111.7(2)
O(5)–C(1)	1.419(3)	O(1)–C(1)–C(2)	107.5(2)
O(5)–C(5)	1.444(2)	O(5)–C(1)–C(2)	112.3(2)
O(7)–C(7)	1.204(2)	C(1)–C(2)–C(3)	112.8(2)
O(14)–C(14)	1.206(3)	O(3)–C(3)–C(2)	108.6(2)
C(1)–C(2)	1.526(3)	O(3)–C(3)–C(4)	107.8(2)
C(2)–C(3)	1.517(3)	C(2)–C(3)–C(4)	109.1(2)
C(3)–C(4)	1.523(3)	O(4)–C(4)–C(3)	109.5(2)
C(4)–C(5)	1.527(3)	O(4)–C(4)–C(5)	107.8(2)
C(5)–C(6)	1.515(3)	C(3)–C(4)–C(5)	110.8(2)
C(7)–C(8)	1.494(3)	O(5)–C(5)–C(4)	108.0(2)
C(8)–C(9)	1.397(3)	O(5)–C(5)–C(6)	106.4(2)
C(8)–C(13)	1.387(3)	C(4)–C(5)–C(6)	113.2(2)
C(9)–C(10)	1.380(3)	O(3)–C(7)–O(7)	124.5(2)
C(10)–C(11)	1.390(4)	O(3)–C(7)–C(8)	110.3(2)
C(11)–C(12)	1.386(3)	O(7)–C(7)–C(8)	125.2(2)
C(12)–C(13)	1.387(3)	C(7)–C(8)–C(9)	118.8(2)
C(14)–C(15)	1.488(3)	C(7)–C(8)–C(13)	121.6(2)
C(15)–C(16)	1.396(3)	C(9)–C(8)–C(13)	119.5(2)
C(15)–C(20)	1.391(3)	C(8)–C(9)–C(10)	120.1(2)
C(16)–C(17)	1.382(3)	C(9)–C(10)–C(11)	120.2(2)
C(17)–C(18)	1.388(4)	C(10)–C(11)–C(12)	119.9(2)
C(18)–C(19)	1.393(3)	C(11)–C(12)–C(13)	120.0(2)
C(19)–C(20)	1.387(3)	C(8)–C(13)–C(12)	120.3(2)
		O(4)–C(14)–O(14)	123.1(2)
		O(4)–C(14)–C(15)	112.4(2)
		O(14)–C(14)–C(15)	124.5(2)
		C(14)–C(15)–C(16)	117.1(2)
		C(14)–C(15)–C(20)	122.9(2)
		C(16)–C(15)–C(20)	120.0(2)
		C(15)–C(16)–C(17)	119.8(2)
		C(16)–C(17)–C(18)	120.1(2)
		C(17)–C(18)–C(19)	120.4(2)
		C(18)–C(19)–C(20)	119.6(2)
		C(15)–C(20)–C(19)	120.1(2)

Primed atoms have been transformed about the 2-fold axis by the symmetry operator: $1-x$, $2-y$, z

TABLE 3. Torsion angles (°) for **1** (with e.s.d.s in parentheses).

Within the pyranose rings		Outside the pyranose rings	
C(1)–C(2)–C(3)–C(4)	-50.4(2)	O(1)–C(1)–C(2)–C(3)	-75.7(2)
C(2)–C(1)–O(5)–C(5)	-52.7(2)	O(1)–C(1)–O(5)–C(5)	68.2(2)
O(5)–C(1)–C(2)–C(3)	47.6(2)	O(3)–C(3)–C(2)–C(1)	66.9(2)
C(1)–O(5)–C(5)–C(4)	58.0(2)	O(3)–C(3)–C(4)–C(5)	-60.8(2)
C(2)–C(3)–C(4–C(5)	57.0(2)	O(3)–C(3)–C(4)–O(4)	58.0(2)
O(5)–C(5)–C(4)–C(3)	-59.3(2)	O(3)–C(7)–C(8)–C(9)	167.0(2)
		O(4)–C(4)–C(3)–C(2)	175.7(2)
		O(4)–C(4)–C(5)–O(5)	-179.1(1)
		O(4)–C(4)–C(5)–C(6)	63.4(2)
		O(4–C(14)–C(15)–C(16)	157.6(2)
		O(5)–C(1)–O(1)–C(1')	72.6(2)
		C(1)–O(1)–C(1')–C(2')	-163.8(2)
		C(1)–O(5)–C(5)–C(6)	179.8(2)
		C(2)–C(3)–O(3)–C(7)	142.2(2)
		C(3)–O(3)–C(7)–C(8)	176.0(2)
		C(3)–C(4)–O(4)–C(14)	76.2(2)
		C(3)–C(4)–C(5)–C(6)	-176.8(2)
		C(4)–O(4)–C(14)–C(15)	-171.7(2)

Primed atoms have been transformed about the 2-fold axis by the symmetry operator: 1-*x*, 2-*y*, *z*

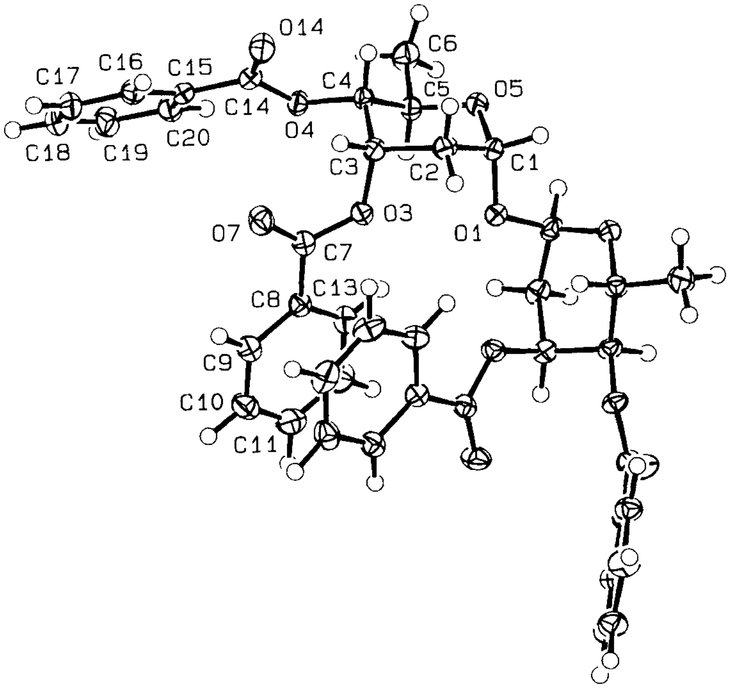


Fig. 1. ORTEP drawing of **1**

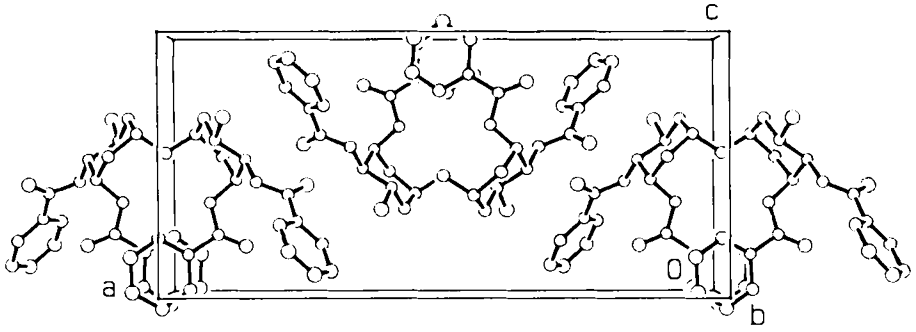
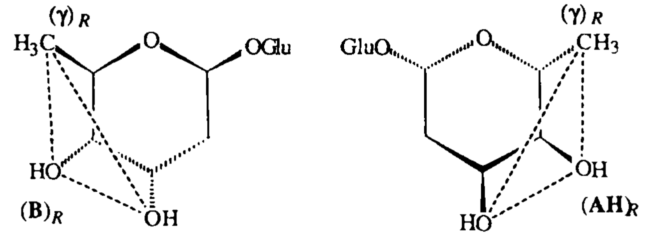


Fig. 2. Molecular packing of the crystal of **1** viewed down the *b* axis



(AH,B,γ)$_R$ system for sweetness (AH,B,γ)$_R$ system for bitterness

Fig. 3. Tripartite superpositioning of 2,2',6,6'-tetradeoxy-α,α-ribotrehalose upon the receptor (AH,B,γ)$_R$ systems for sweet and bitter tastes.

Crystal structure determination. Crystal data for $C_{40}H_{38}O_{11}$, M_r = 694.73, orthorhombic $P2_12_12$ (#18), a = 22.338(2), b = 7.525(4), c = 10.496(2) Å, V = 1764(1) Å^3, Z = 2, D_{calc} = 1.308 g cm^{-3}, $\lambda(MoK_\alpha)$ = 0.71069 Å, $\mu(MoK_\alpha)$ = 0.089 mm^{-1}, F(000) = 732, T = -100 °C. The diffraction data were obtained from a single crystal of approximate dimensions 0.23 x 0.28 x 0.35 mm mounted on a glass fiber using a *Rigaku* AFC5R diffractometer with graphite-monochromated MoK_α radiation. The unit cell parameters were refined from the setting angles of 22 carefully centered reflections in the range $37° < 2\theta < 40°$. Intensities were collected using ω-2θ scans with a fixed scanning rate of 16° min^{-1} (up to 4 scans/reflection). The intensities of three reflections which were measured every 150 reflections remained stable throughout the data collection. Of the 3649 reflections which were collected with $2\theta \leq 60°$, 3481 were unique (R_{int} = 0.018) and 2669 with intensities $I > 3\sigma(I)$ were used for structure analysis.

The structure was solved by direct methods[15] and refined by full-matrix least-squares methods based on F. An absorption correction was not applied. The non-hydrogen atoms were refined with anisotropic thermal parameters and all of the hydrogen atoms, located in a difference electron density map, were refined with individual isotropic temperature factors. The weighting scheme used in the final refinement was $w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$. The refinement converged to give $R = 0.0368$, $R_w = 0.0323$ and $S = 1.536$. All calculations were performed using the *TEXSAN*[16] crystallographic package. Supplementary material, including experimental details, atomic coordinates and equivalent isotropic temperature factors, non-hydrogen atoms anisotropic temperature factors, additional interatomic distances, bond angles, torsion angles and observed and calculated structure factors for this structure are available from the second author.

ACKNOWLEDGEMENTS

One of us (CKL) wishes to thank the National University of Singapore for financial support, and we thank Miss I. Klingenfuss for technical assistance.

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