*Carbohydrate Research*, 180 (1988)175–182
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

# THE CRYSTAL AND MOLECULAR STRUCTURE OF AN INTENSELY SWEET CHLORODEOXYSUCROSE; 4,1′,6′-TRICHLORO-4,1′,6′-TRIDEOXY-*galacto*-SUCROSE

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(Received September 10th, 1987; accepted for publication, December 23rd, 1987)

## ABSTRACT

The crystal and the molecular structure of 4,1′,6′-trichloro-4,1′,6′-trideoxy-*galacto*-sucrose (TGS) was determined by X-ray analysis at 294 K. Crystals of TGS are orthorhombic, space group $P2_12_12_1$, with $a$ = 7.318(3), $b$ = 12.027(4), $c$ = 18.136(5) Å, $V$ = 1596(1) Å$^3$, $Z$ = 4; $D_x$ = 1.655 g.cm$^{-3}$, $\lambda(\mathrm{Mo}K_\alpha)$ = 0.71073 Å, $\mu(\mathrm{Mo}K_\alpha)$ = 5.44 cm$^{-1}$, $F(000)$ = 816. The X-ray intensities of 2649 reflections with $I \geqslant 2.5\sigma(I)$ were measured with Zr-filtered Mo$K_\alpha$-radiation. The structure was solved by the Patterson procedure and refined by full-matrix least-squares to a final $R$-value of 0.0298. Large conformational differences between TGS and sucrose were observed, particularly in the conformation of the glycosidic linkage. These differences originate from chlorine substitution, which affects intramolecular hydrogen bonding and sweet-taste glucophores.

## INTRODUCTION

TGS (4,1′,6′-trichloro-4,1′,6′-trideoxy-*galacto*-sucrose), one of a series of chlorodeoxy derivatives of sucrose synthesised by Hough and his colleagues[1–3], was found to be more sweet than saccharin without an unpleasant after-taste. Structure, conformation, and flexibility are associated with the sweetness of carbohydrates, which requires the formation of a pair of hydrogen bonds AH–B with the receptor site[4] and the presence of a hydrophobic center ($\gamma$) in the molecule[5]. Different tripartite glucophores have been proposed[2] to explain the effect of multiple chlorination on the sweetness, but it was assumed that the conformation of the chlorinated molecules remained identical to that of sucrose.

The sweet-taste mechanism involves an aqueous solution, so that solute–sol-

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0008-6215/88/$ 03.50

vent interactions should be taken into account. Differences in solution properties were observed between sucrose and TGS, and a glucophore system based on an F.t.-i.r. study was proposed[6] to account for the enhanced sweetness of TGS. In order to study the effect of chloro substitution on the H-bond system, a precise determination of the molecular structure is needed.

The structure of sucrose, determined by X-ray diffraction[7], has been refined by neutron diffraction[8,9] and by further X-ray studies[10]. Two intramolecular H-bonds were found which restrict rotation around the glycosidic linkage. However, it is likely that the intramolecular hydrogen bonding in sucrose in dilute aqueous solution is ruptured[11,12], which allows some rotation around the glycosidic bond.

We now present the crystal structure results for TGS and show that the essential structural differences between sucrose and TGS reside in intramolecular hydrogen bonding and in the conformation of the glycosidic linkage.

## EXPERIMENTAL

Crystals {m.p. 103–104°, $[\alpha]_D$ +68.2° (chloroform)} of 4,1′,6′-trichloro-4,1′,6′-trideoxy-*galacto*-sucrose (TGS) were grown at room temperature by slow concentration of a solution in ethanol. A needle-shaped crystal (1.33 × 0.25 × 0.18 mm) was mounted on an Enraf–Nonius CAD-4 diffractometer equipped with Zr-filtered Mo$K_\alpha$-radiation ($\lambda$ = 0.71073 Å). Lattice parameters were obtained from least-squares fitting of the alternative setting angles of eight symmetry-related reflections (4 6 10, $\bar{4}$ 6 10, *etc.*) according to the "set 4" method of de Boer and Duisenberg[13]. 2791 unique intensity data were collected for $0 \leqslant h \leqslant 10$, $0 \leqslant k \leqslant 16$, and $0 \leqslant l \leqslant 25$ by the $\omega$–$2\theta$ scan technique [$\omega = (0.55 + 0.35\tan\theta)°$, $\theta_{\max} = 30°$] of which 2649 having $I \geqslant 2.5\sigma(I)$ were considered to be observed. Systematic absences $h00$, $0k0$, and $00l$ with $h,k,l = 2n + 1$ indicate space group $P2_12_12_1$. The intensity variation of the two control reflections 200 and 024 in the period of data collection amounted to 2.0 and 2.5%, respectively. After instability and Lorentz-polarisation corrections, the structure was solved by the Patterson procedure PATT and the SHELXS-86[14] program, which gave all non H-atoms. After anisotropic refinement, the H-atoms were found on difference maps and included in the refinement with isotropic thermal parameters. The hydroxyl-group H-atoms, found on difference maps and included in the refinement with isotropic thermal parameters, were kept at a fixed distance of 0.95 Å. The full-matrix refinement on $F$ was performed with SHELX-76[15] minimising $\Sigma w\Delta^2$, where $\Delta = [|F_o| - |F_c|]$ and $w = 1/\sigma^2(F)$ based on counting statistics, which converged at $R = 0.0298$ and $R_w = 0.0277$. There were no shifts in any of the parameters greater than $0.092\sigma$.

The absolute configuration was ascertained by refining the inverted model, which resulted in a significantly higher $R$ value of 0.0314 and $R_w = 0.0309$.

Scattering factors of Cl, C, and O atoms were taken from Cromer and Mann[16], for H from Stewart *et al.*[17], and anomalous dispersion corrections from Cromer and Liberman[18].

Final atomic co-ordinates and anisotropic thermal parameters of the non-H atoms, atomic co-ordinates and isotropic thermal paameters of H-atoms, and a complete description of the internal geometry have been deposited*.

## DISCUSSION

Bond distances, bond angles, and torsion angles are given in Table I. The bond lengths are normal and generally agree with the corresponding distances in sucrose[10]. However, there are large differences between the corresponding bond and torsion angles of TGS and sucrose involving the anomeric oxygen (Table II). A perspective view of the molecules of TGS and sucrose together with atom numbering is shown in Fig. 1.

The disposition of the rings with respect to the C–O bonds of the glycosidic link of TGS is quite different from that of sucrose and is caused mainly by rotation about C-12–O-1 and, to a lesser extent, C-1–O-1, as follows from the torsion angles in Table II.

The large conformational differences must be attributed to the formation of an intramolecular H-bond O-2–H · · · O-13 in TGS. This bond replaces the intramolecular O-11–H · · · O-2 bond of sucrose, which cannot be formed in TGS because of chlorine substitution at C-11. The same holds for the O-16–H · · · O-5 intramolecular H-bond, which cannot occur because of the chlorine substitution at C-16. The same conformation about the glycosidic link occurs in 1′-chloro-1′-deoxysucrose, as was established by n.m.r. spectroscopy[19].

The galactopyranoside ring in TGS adopts an ideal chair conformation, as follows from the puckering parameter $\theta$ of Cremer and Pople[20], which amounts to 1.9°. In sucrose, the glucoside ring is more distorted ($\theta$ = 5.1°). The fructose rings in TGS and sucrose each adopt a half-chair conformation, namely, in TGS $14\beta/15\alpha$ ($\Delta C_2$ = 0.8°) and in sucrose $13\alpha/14\beta$ ($\Delta C_2$ = 5.0°). The conformation of the hydroxymethyl group of the galactoside ring is gt which has preference over the tg conformation[21], whereas this group in the glucoside ring of sucrose has the familiar gg conformation.

Apart from the intramolecular hydrogen bond O-2–H · · · O-13, there are four intermolecular hydrogen bonds (Table III, Fig. 2) which form a three-dimensional network.

Shallenberger and Acree[4] indicated that all sweet-tasting compounds contain an A–H · · · B moiety, and a hydrophobic binding-site "$\gamma$" in the molecule[22,23], if present, amplifies the sweet-taste sensation[5] (Fig. 3).

In considering the sweetness in TGS, the distances A · · · B, A · · · $\gamma$, and B · · · $\gamma$ have been taken between the wide limits of 2–3.5, 3–5.5, and 5–7.5 Å,

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*These data have been deposited with, and may be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/397/*Carbohydr. Res.*, 180 (1988) 175–182.

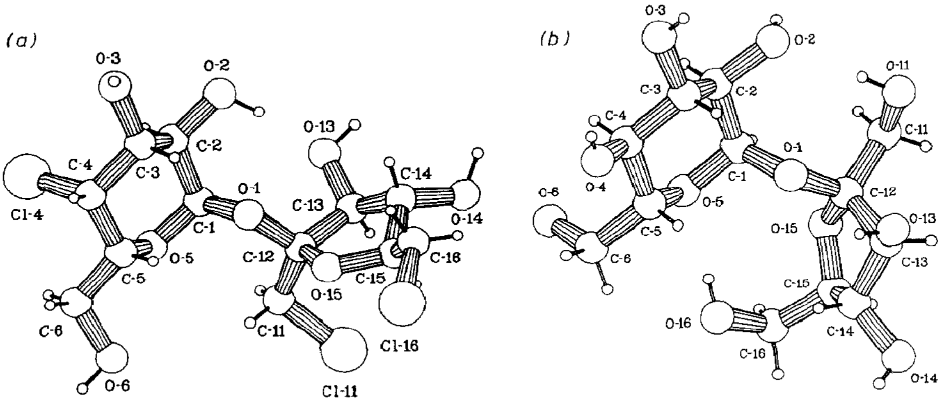

Fig. 1. Perspective view of (*a*) TGS and (*b*) sucrose with atom numbering.

TABLE I

BOND LENGTHS (Å), BOND ANGLES (°), AND TORSION ANGLES (°) WITH E.S.D.'S IN PARENTHESES

| | | | |
|---|---|---|---|
| Cl-4–C-4 | 1.801(2) | O-15–C-12 | 1.422(3) |
| Cl-11–C-11 | 1.786(3) | O-15–C-15 | 1.448(3) |
| Cl-16–C-11 | 1.789(2) | C-1–C-2 | 1.527(3) |
| O-1–C-1 | 1.429(3) | C-2–C-3 | 1.512(3) |
| O-1–C-12 | 1.413(3) | C-3–C-4 | 1.524(3) |
| O-2–C-2 | 1.414(3) | C-4–C-5 | 1.520(3) |
| O-3–C-3 | 1.420(3) | C-5–C-6 | 1.504(3) |
| O-5–C-1 | 1.410(3) | C-11–C-12 | 1.530(3) |
| O-5–C-5 | 1.433(3) | C-12–C-13 | 1.554(3) |
| O-6–C-6 | 1.431(3) | C-13–C-14 | 1.521(3) |
| O-13–C-13 | 1.413(3) | C-14–C-15 | 1.515(3) |
| O-14–C-14 | 1.412(3) | C-15–C-16 | 1.498(3) |
| C-1–O-1–C-12 | 119.2(2) | O-6–C-6–C-5 | 109.0(2) |
| C-1–O-5–C-5 | 114.3(2) | Cl-11–C-11–C-12 | 110.7(2) |
| C-12–O-15–C-15 | 110.4(2) | O-1–C-12–O-15 | 102.7(2) |
| O-1–C-1–C-2 | 106.3(2) | O-1–C-12–C-11 | 110.1(2) |
| O-5–C-1–C-2 | 111.0(2) | O-1–C-12–C-13 | 112.5(2) |
| O-1–C-1–O-5 | 110.8(2) | O-15–C-12–C-11 | 109.2(2) |
| O-2–C-2–C-3 | 110.4(2) | O-15–C-12–C-13 | 106.6(2) |
| C-1–C-2–C-3 | 110.8(2) | C-11–C-12–C-13 | 115.1(2) |
| O-2–C-2–C-1 | 112.1(2) | O-13–C-13–C-12 | 109.5(2) |
| O-3–C-3–C-4 | 113.2(2) | C-12–C-13–C-14 | 104.0(2) |
| C-2–C-3–C-4 | 110.2(2) | O-13–C-13–C-14 | 114.3(2) |
| O-3–C-3–C-2 | 108.9(2) | C-13–C-14–C-15 | 103.6(2) |
| Cl-4–C-4–C-3 | 110.9(1) | O-14–C-14–C-13 | 114.2(2) |
| Cl-4–C-4–C-5 | 110.2(2) | O-14–C-14–C-15 | 110.2(2) |
| C-3–C-4–C-5 | 109.4(2) | O-15–C-15–C-14 | 104.6(2) |
| O-5–C-5–C-4 | 111.1(2) | O-15–C-15–C-16 | 110.1(2) |
| O-5–C-5–C-6 | 106.7(2) | C-14–C-15–C-16 | 111.9(2) |
| C-4–C-5–C-6 | 114.4(2) | Cl-16–C-16–C-15 | 113.0(2) |

| | | | |
|---|---|---|---|
| C-12–O-1–C-1–C-2 | −147.9(2) | Cl-4–C-4–C-5–O-5 | 66.5(2) |
| C-12–O-1–C-1–O-5 | 91.4(2) | Cl-4–C-4–C-5–C-6 | −54.4(2) |
| C-1–O-1–C-12–O-15 | −162.2(2) | C-3–C-4–C-5–O-5 | −55.7(2) |
| C-1–O-1–C-12–C-11 | −46.1(2) | C-3–C-4–C-5–C-6 | −176.6(2) |
| C-1–O-1–C-12–C-13 | 83.7(2) | O-5–C-5–C-6–O-6 | 66.9(2) |
| C-5–O-5–C-1–C-2 | −57.2(2) | C-4–C-5–C-6–O-6 | −169.8(2) |
| C-5–O-5–C-1–O-1 | 60.6(2) | Cl-11–C-11–C-12–O-1 | −171.1(1) |
| C-1–O-5–C-5–C-4 | 58.7(2) | Cl-11–C-11–C-12–O-15 | −59.2(2) |
| C-1–O-5–C-5–C-6 | −176.0(2) | Cl-11–C-11–C-12–C-13 | 60.6(2) |
| C-15–O-15–C-12–O-1 | −128.8(2) | O-1–C-12–C-13–O-13 | −21.7(2) |
| C-15–O-15–C-12–C-11 | 114.4(2) | O-1–C-12–C-13–C-14 | 100.9(2) |
| C-15–O-15–C-12–C-13 | −10.5(2) | O-15–C-12–C-13–O-13 | −133.4(2) |
| C-12–O-15–C-15–C-14 | 27.7(2) | O-15–C-12–C-13–C-14 | −10.8(2) |
| C-12–O-15–C-15–C-16 | 148.1(2) | C-11–C-12–C-13–O-13 | 105.4(2) |
| O-1–C-1–C-2–C-3 | −66.3(2) | C-11–C-12–C-13–C-14 | −132.0(2) |
| O-1–C-1–C-2–O-2 | 57.5(2) | C-12–C-13–C-14–C-15 | 26.6(2) |
| O-5–C-1–C-2–C-3 | 54.3(2) | C-12–C-13–C-14–O-14 | 146.5(2) |
| O-5–C-1–C-2–O-2 | 178.1(2) | O-13–C-13–C-14–C-15 | 146.0(2) |
| O-2–C-2–C-3–C-4 | −178.6(2) | O-13–C-13–C-14–O-14 | −94.2(2) |
| O-2–C-2–C-3–O-3 | 56.6(2) | C-13–C-14–C-15–O-15 | −33.3(2) |
| C-1–C-2–C-3–C-4 | −53.8(2) | C-13–C-14–C-15–C-16 | −152.5(2) |
| C-1–C-2–C-3–O-3 | −178.6(2) | O-14–C-14–C-15–O-15 | −155.8(2) |
| O-3–C-3–C-4–Cl-4 | 54.9(2) | O-14–C-14–C-15–C-16 | 85.0(2) |
| O-3–C-3–C-4–C-5 | 176.7(2) | O-15–C-15–C-16–Cl-16 | 61.3(2) |
| C-2–C-3–C-4–Cl-4 | −67.4(2) | C-14–C-15–C-16–Cl-16 | 177.2(2) |
| C-2–C-3–C-4–C-5 | 54.4(2) | | |

TABLE II

COMPARISON OF BOND AND TORSION ANGLES (DEGREES) INVOLVING THE ANOMERIC OXYGEN O-1 OF TGS AND SUCROSE

| *Angle θ* | $\theta_{TGS}$ | $\theta_{sucrose}$ | $\Delta\theta$ |
|---|---|---|---|
| C-1–O-1–C-12 | 119.2 | 113.8 | 5.4 |
| O-1–C-1–O-5 | 110.8 | 110.1 | 0.7 |
| O-1–C-1–C-2 | 106.3 | 110.2 | −3.9 |
| O-1–C-12–O-15 | 102.7 | 110.9 | −8.2 |
| O-1–C-12–C-13 | 112.5 | 108.2 | 4.3 |
| O-1–C-12–C-11 | 110.1 | 110.2 | −0.1 |
| *Torsion angle φ* | $\phi_{TGS}$ | $\phi_{sucrose}$ | $\Delta\phi$ |
| C-1–O-1–C-12–C-13 | 83.7 | −159.9 | 116.4 |
| C-1–O-1–C-12–O-15 | −162.2 | −45.1 | 117.1 |
| C-1–O-1–C-12–C-11 | −46.1 | 73.4 | 119.5 |
| C-12–O-1–C-1–C-2 | −147.9 | −129.2 | 18.7 |
| C-12–O-1–C-1–O-5 | 91.4 | 108.2 | 16.8 |

TABLE III

SCHEME OF HYDROGEN BONDS IN TGS

| *Hydrogen bond* | *Acceptor* | *O–H(Å)* | *H · · · O(Å)* | *O · · · O(Å)* | *O–H · · · O (°)* |
|---|---|---|---|---|---|
| O-2–H-21 · · · O-13 | $x, y, z$ | 0.94(2) | 1.88(2) | 2.800(3) | 166(2) |
| O-3–H-31 · · · O-6 | $-1+x, y, z$ | 0.94(2) | 1.82(2) | 2.750(3) | 169(2) |
| O-6–H-61 · · · O-15 | $\frac{1}{2}+x, 1\frac{1}{2}-y, 1-z$ | 0.95(2) | 2.06(2) | 3.007(2) | 172(2) |
| O-13–H-131 · · · O-3 | $-x, \frac{1}{2}+y, \frac{1}{2}-z$ | 0.95(2) | 1.79(2) | 2.733(2) | 170(2) |
| O-14–H-141 · · · O-2 | $-x, \frac{1}{2}+y, \frac{1}{2}-z$ | 0.94(2) | 1.81(2) | 2.747(3) | 172(2) |

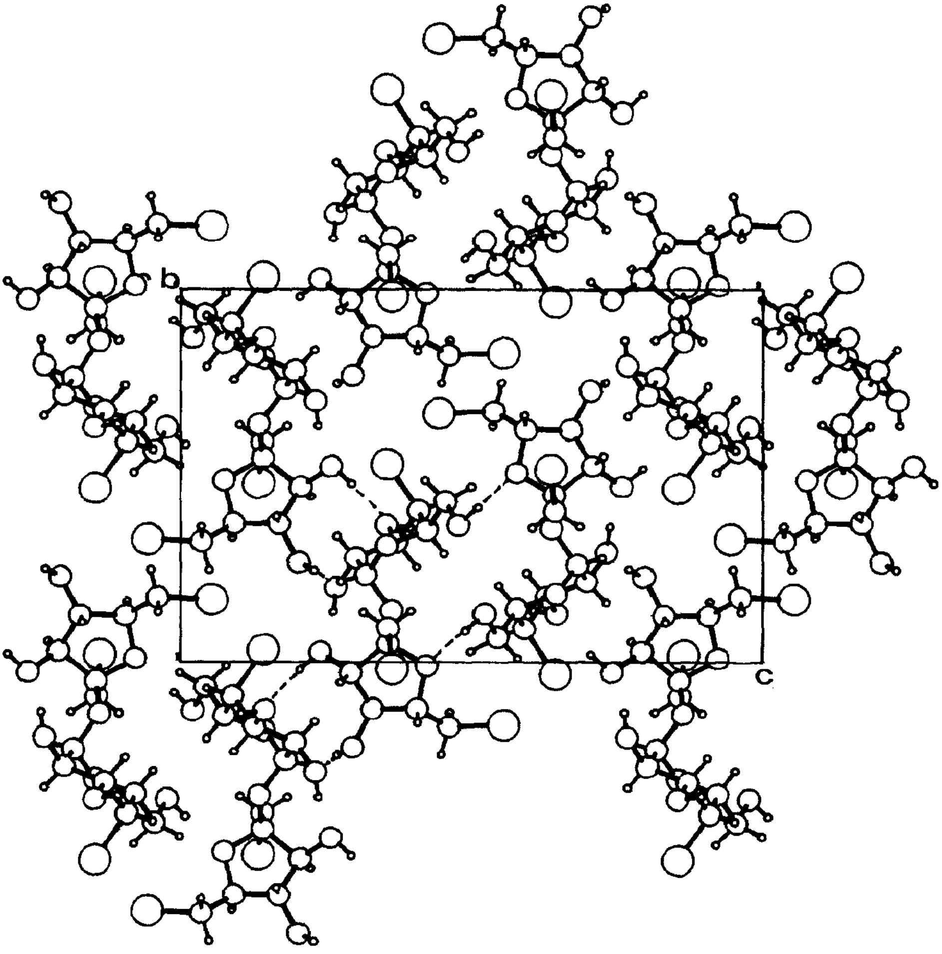

Fig. 2. A view of the crystal structure of TGS down *a*. Hydrogen bonds are represented by dashed lines.

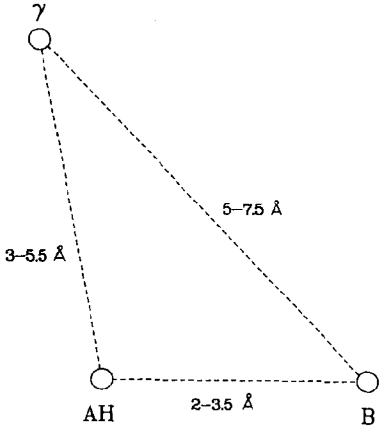

Fig. 3. Schematic illustration of AH–B–γ model.

respectively. Analysis of a homologous series of chloro-*galacto*-sucrose derivatives[24] indicates that all three chlorine substituents, particularly Cl-11, contribute to the sweetness of TGS. The geometric patterns which can be discerned, when all chlorine atoms in TGS are considered as hydrophobic binding sites, are given in Table IV.

In system II, all contributors are in the fructofuranoside fragment. Although fructofuranosides are tasteless because of lack of the required relations between the functional groups[25], 6-chloro-6-deoxy- and 1,6-dichloro-1,6-dideoxy-β-D-fructofuranose[26] are sweet and very sweet, respectively. In system III, the A · · · B contact involves the intramolecular hydrogen bond, which implies that the validity of this system requires the breaking of this bond with preservation of the conformation. This can be brought about by a concomitant rotation of O-2-H about C-2–O-2 and of O-13-H about C-13–O-13. As a consequence, the O-2-H bond takes over the A–H function and a new inter-residue hydrogen bond O-13–H · · · O-2 with a reversed donor–acceptor direction can be formed. This is effected by a counter clockwise rotation of O-13-H about O-13–C-13 of 146°, resulting in a favourable hydrogen-bond geometry with H · · · O 1.90Å and O-H · · · O 157°, which again will stabilise the original conformation.

TABLE IV

POSSIBLE AH–B–γ SYSTEMS IN TGS

| *System* | *A · · · B* | *d(Å)* | *A · · · γ* | *d(Å)* | *B · · · γ* | *d(Å)* |
|---|---|---|---|---|---|---|
| I | O-13 · · · O-2 | 2.80 | O-13 · · · Cl-11 | 4.40 | O-2 · · · Cl-11 | 6.39 |
| II | O-14 · · · O-13 | 3.28 | O-14 · · · Cl-16 | 4.75 | O-13 · · · Cl-16 | 6.18 |
| III | O-2 · · · O-13 | 2.80 | O-2 · · · Cl-4 | 4.46 | O-13 · · · Cl-4 | 6.45 |

Evidence for the reversal of donor–acceptor direction has recently been obtained by $^1$H-n.m.r. spectroscopy of a solution of partially deuterated TGS in $(CD_3)_2SO$, which showed that the main inter-residue link involved O-13-H as donor and O-2 as acceptor. In this proposed mechanism, system I is switched off in favour of system III.

Alternative models for TGS have been proposed by Hough and Khan[2], which differ from those above in that site B was taken as Cl-11. Since these authors constructed a TGS model by progressive chlorination of sucrose, the validity of the model is questionable, as follows from the difference between the structures of sucrose and TGS.

The role of water on the sweet-taste mechanism was shown for simple food carbohydrates[27]. There is a relation between the degree of the hydrophobic effect and the sweetness, and the duration of the sweet sensation depends on the mobility of water around the sweetener. This aspect is under investigation.

## ACKNOWLEDGMENT

We thank Dr. Duisenberg for collecting the X-ray data.

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