Conformational Analysis of Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-6-phenylsulfinyl-α-D-glucoside

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Conformational analysis of methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-(*R*)-phenylsulfinyl-α-D-glucopyranoside (1), methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-(*S*)-phenylsulfinyl-α-D-glucopyranoside (2) and methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-phenylsulfonyl-α-D-glucopyranoside (3) in solution ($CDCl_3$) and the crystalline state was carried out using ^{1}H-NMR spectra and X-ray crystallographic data. The conformational preference of the C6–S bond in the above mentioned compounds was found to be GT (GT is short for *gauche-trans*), and as a 1 : 1 mixture of rotamers for the (*S*)-S-oxide (2) and sulfone (3) but not in the (*R*)-S-oxide (1) in the solid state.

Key words conformation of D-hexose; thiosugar S-oxide; ^{1}H-NMR; X-ray analysis

Generally the conformation of the C5–C6 linkage along with the chirality at the anomeric center determines the overall shape of oligosaccharides with a glycosidic linkage to O6. To date, many reports on the conformation around the C5–C6 bond have appeared.[1)] It is also noteworthy that oligosaccharides, in general, and D-hexoses, in particular, may be quite versatile starting materials both for the chemical industry and for chemical synthesis; preparation of α,β,γ-dextrin and chiral synthesis from D-glucose are known. Among others, we have been concerned with the chemistry of thiosugars including S-oxides. Particularly, we have been interested in the Pummerer and Cope reactions of 6-arylthio derivatives. We[2)] and Gonzales and Baer[3)] have succeeded in obtaining L-sugars starting from 6-deoxy-6-phenylthio-D-hexoses *via* the S-oxide using the Pummerer rearrangement. In both cases, a mixture of the (*R*) and (*S*) epimers with respect to the S-oxides was used. As there are few reports on the conformation of thiosugars around the C5–C6 bond, herein we report the preparation of pure samples of the (*R*)-S-oxide (**1**), (*S*)-S-oxide (**2**) and sulfone (**3**), and the structural conformation related to the stereochemistry of the monothiosaccharides by NMR and X-ray analysis.

Results and Discussion

We earlier carried out a novel series of reactions including the Pummerer rearrangement as a key reaction starting with 6-deoxy-6-phenylthio-D-hexoses. In the current work, treatment of 6-deoxy-6-phenylthio-D-hexoses with *m*-chloroperbenzoic acid (*m*-CPBA) at −65 °C provided the sulfoxide as a mixture of diastereomers in quantitative yield, but reaction with an excess of *m*-CPBA yielded the sulfone as a by-product.

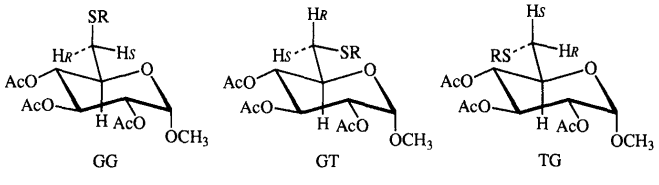

Fig. 1. The Three Possible Rotamers about the C5–C6 Bond

A mixture of diastereomers of the sulfoxide was separated into the (*R*)-form (**1**) and (*S*)-form (**2**). We elucidated the stereochemistry of **1** and **2** and also the sulfone (**3**) using X-ray crystallographic analysis and ^{1}H-NMR spectra.

In hexopyranosides, the conformation around C5–C6–O falls into three types, as shown in Fig. 1.

X-Ray crystallographic analysis of **1**, **2** and **3** was performed. Crystal data from the X-ray analysis of **1**, **2** and **3** are shown in Table 1.

ORTEP drawings of compounds **1**, **2** and **3** are shown in Fig. 2.

Rotational isomers were apparent in **2** (**2A**, **2B**) and **3** (**3A**, **3B**) but not in **1** in the crystalline state (Fig. 2). Selected torsional angles are summarized in Table 2.

As shown in Fig. 3, molecules **1**, **2A**, **2B**, **3A** and **3B** have the same GT conformation in the crystalline state. The torsional angles for the O(1)–C(1)–C(6)–S(1) of these compounds were 76.5 (7)°, 89.8 (7)°, 77 (1)°, 83 (1)° and 61

Table 1. Crystal Data for **1**, **2** and **3**

Compd.	1	2	3
Formula	$C_{19}H_{24}O_9S$	$C_{19}H_{24}O_9S$	$C_{19}H_{24}O_{10}S$
Formula weight	428.45	428.45	444.45
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	$P\,2_12_12_1$	$P\,2_1$	$P\,2_1$
Size (mm)	0.1 × 0.2 × 0.2	0.1 × 0.2 × 0.2	0.2 × 0.3 × 0.5
Lattice parameters			
a (Å)	8.6 (2)	14.241 (3)	14.237 (2)
b (Å)	44.9 (2)	9.043 (3)	8.916 (3)
c (Å)	5.5 (1)	17.700 (2)	18.002 (2)
β (°)		107.71 (1)	107.03 (1)
z value	4	4	4
V (Å^3)	2134 (5)	2171.4 (9)	2184.8 (7)
F (000)	904	904	936
λ (Å)	1.54179	1.54179	1.54179
μ (cm^{-1})	17.21	16.91	17.34
D_x (g/cm^3)	1.334	1.31	1.351
No. observations	1303	2035	3094
Crystal color	colorless	colorless	colorless
Diffractometer	AFC-5R	AFC-5R	AFC-5R
$R(R_w)$	0.062 (0.061)	0.074 (0.052)	0.051 (0.063)

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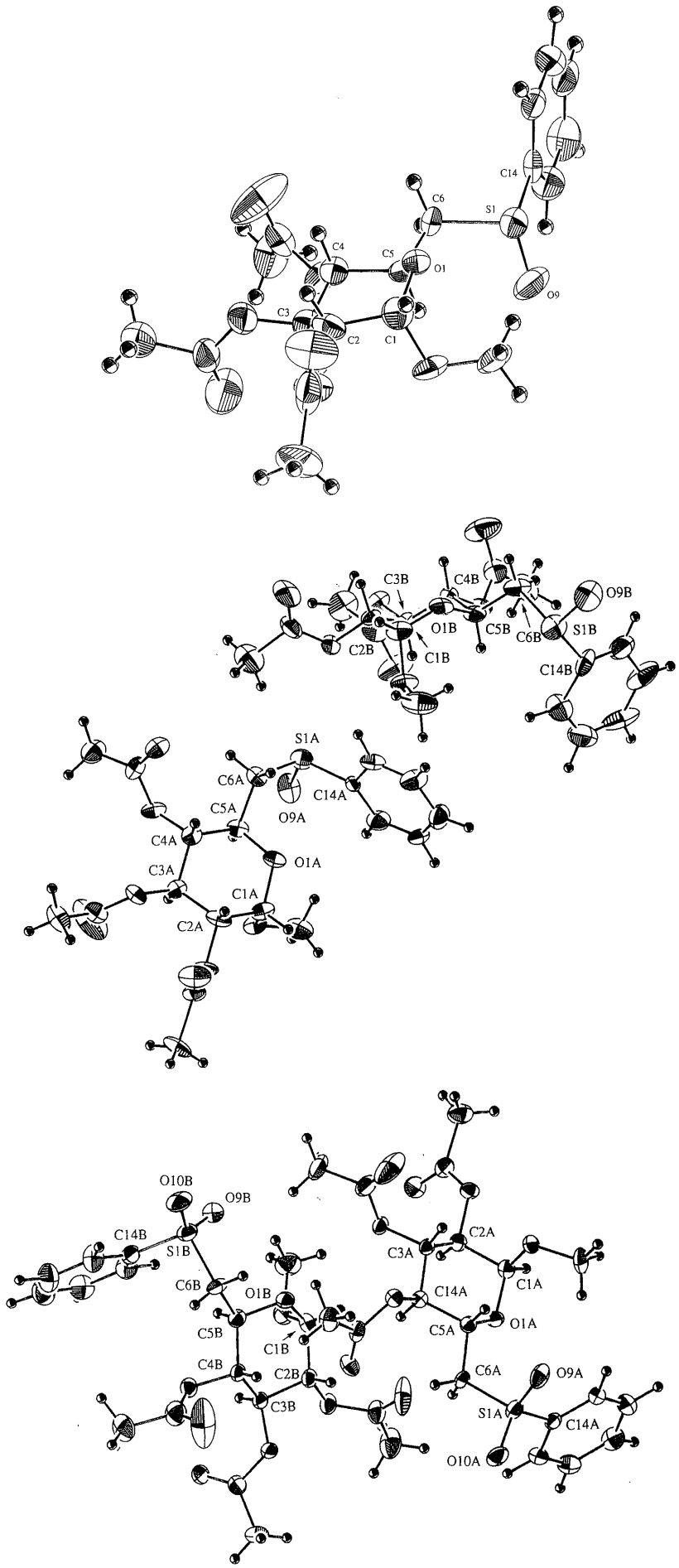

Fig. 2. ORTEP Drawing of Compounds **1**, **2** and **3**

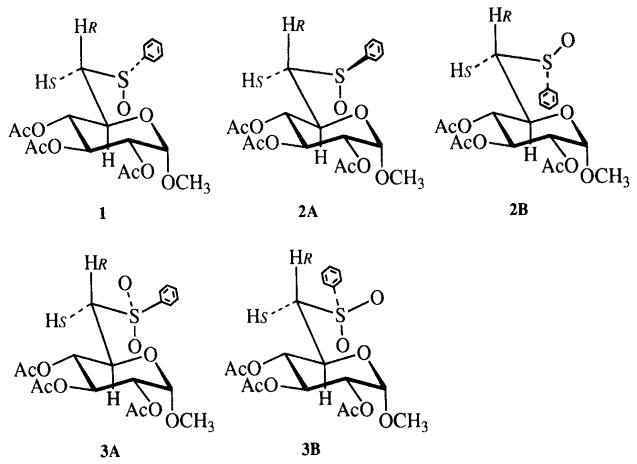

Fig. 3. Conformations of **1**, **2A**, **2B**, **3A** and **3B** Determined by X-Ray Analysis

Table 2. Selected Torsional Angles (°) in **1**, **2** and **3**

	1	2A	2B	3A	3B
C(5)–C(6)–S(1)–O(9)	60 (1)	31 (1)	−166.6 (9)	36.5 (7)	−38.3 (7)
C(5)–C(6)–S(1)–O(10)				164.3 (6)	−168.4 (6)
C(5)–C(6)–S(1)–C(14)	170.4 (8)	−82 (1)	84 (1)	−81.1 (6)	76.6 (7)
O(1)–C(5)–C(6)–S(1)	61 (2)	77 (1)	83 (1)	76.5 (7)	89.8 (7)
O(1)–C(5)–C(6)–H6*S*	−177	−162	−158	−158	−150
O(1)–C(5)–C(6)–H6*R*	−67	− 44	−37	−45	−29
H(5)–C(5)–C(6)–H6*S*	65	80	84	81	94
H(5)–C(5)–C(6)–H6*R*	174	−162	−155	−166	−146

(2)°, respectively.

These values are slightly large compared with those of GT conformations of the primary hydroxymethyl groups of the gluco configuration in aldohexopyranoses.[4)]

The torsion angles H5–C5–C6–H6*S* and H5–C5–C6–H6*R* of **1**, **2A**, **2B**, **3A** and **3B** are 65°, 80°, 84°, 81°, 94° and 174°, −162°, −155°, −166°, −146° respectively. These values indicate that the conformations around C5–C6 are almost the same in all of these molecules. Therefore, the rotamers of **2** and **3** in the crystalline state are derived from rotation around the C6–S(1) bond.

The torsion angles for C5–C6–S–C14 of **2A** and **2B** are −82° and 84°; those of **3A** and **3B** are −81.1° and 76.6°. From these data, rotamers in both compounds originate from the rotation in the opposite direction to the torsion angle C5–C6–S–C14 = 180°. In the case of **1**, the torsion angle C5–C6–S–C14 is 170.4°, which means that the stable conformer is the only one in the crystalline state.

To clarify the conformation of these compounds in solution, ^{1}H-NMR spectra were measured, and the results are as follows. The coupling constants $J_{5,6a}$, $J_{5,6b}$ were 8.5 and 5.0 Hz for **1**, 5 and 6 Hz for **2** and 2 and 9 Hz for **3**, respectively. Because the coupling constant values calculated with the Karplus equation[5)] using the X-ray crystallographic data do not agree with the experimental values, these compounds take different conformations in solution from those in the crystalline state. The coupling constants may reflect the distribution of rotamers such as GT, GG (*gauche-gauche*) and TG (*trans-gauche*).[1)]

Experimental

General Melting points were measured on a Yazawa melting point apparatus BY-1 and are uncorrected. Spectral data were recorded on the following instruments; IR: Jasco A-102 IR spectrophotometer; $[\alpha]_D$: Jasco DIP-150 digital polarimeter; MS: JMS D-100 spectrometer; ^{1}H- and ^{13}C-NMR as well as ^{1}H–^{1}H and ^{1}H–^{13}C shift correlated 2 dimensional (2D)-NMR: Varian VXR-300 (300 MHz), or XL-400 (400 MHz) spectrometers in chloroform-*d* solution unless otherwise noted.

Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-6-(*R*)- and (*S*)-phenylsulfinyl-α-D-glucopyranoside (1) and (2) To a stirred solution of methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-phenylthio-α-D-glucopyranoside (412 mg, 1 mmol) in CH_2Cl_2 (2 ml), a solution of *m*-CPBA (190 mg, 1.1 mmol) in CH_2Cl_2 (2 ml) was added dropwise at −65 °C. The mixture was stirred until the temperature gradually increased to 0 °C during *ca.* 2 h. The mixture was poured into an aq. solution of $NaHCO_3$ (4 ml), and the organic layer was washed with H_2O (3 × 5 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give a syrup, which was purified by elution from a silica gel column with toluene–ethyl acetate (1 : 4), affording 398 mg (92.9%, *R* : *S* = 1 : 1) of **1** and **2** as a colorless syrup. The first syrupy fraction was crystallized from acetone–hexane to give colorless prismatic *R*-epimer (**1**), and the second syrupy fraction was crystallized from $CHCl_3$–hexane to give colorless plates of the *S*-epimer (**2**).

R-Epimer (**1**): $[\alpha]_D^{23}$ +239° (*c* = 0.96, $CHCl_3$); mp 139—141 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.97, 1.99, 2.08 (each 3H, s, –$COCH_3$), 2.79 (1H, dd, H-6a), 2.80 (1H, dd, H-6b), 3.55 (3H, s, –OCH_3), 4.40 (1H, ddd, H-5), 4.90 (1H, dd, H-2),4.91 (1H, dd, H-4), 5.01 (1H, d, H-1), 5.50 (1H, dd, H-3), 7.49—7.64 (aromatic); $J_{1,2}$ = 3.5, $J_{2,3}$ = $J_{3,4}$ = 10.0, $J_{4,5}$ = 10.5, $J_{5,6a}$ = 8.5, $J_{5,6b}$ = 5.0 Hz ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.6, 20.7, 20.7 (3 × –$\underline{C}OCH_3$), 55.9 (–OCH_3), 60.3 (C-6), 63.3 (C-5), 69.9 (C-3), 71.0 (C-2), 71.6 (C-4), 96.7 (C-1), 169.8, 170.0, 170.2 (3 × –$\underline{C}OCH_3$); MS (FAB) *m/z*: 429 [M^+ + H], 451 [M^+ + Na]; HR-MS (FAB) Calcd for $C_{19}H_{25}O_9S$ [M^+ + H] 429.1218. Found: 429.1230.

S-Epimer (**2**): $[\alpha]_D^{23}$ +33.1° (*c* = 1.02, $CHCl_3$); mp 117—119 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.99, 2.03, 2.05 (each 3H, s, –$COCH_3$), 3.00 (1H, dd, H-6a), 3.06 (1H, dd, H-6b), 3.38 (3H, s, –OCH_3), 4.24 (1H, ddd, H-5), 4.82 (1H, dd, H-2), 4.85 (1H, d, H-1), 4.99 (1H, dd, H-4), 5.45 (1H, dd, H-3), 7.48—7.64 (aromatic); $J_{1,2}$ = 3.5, $J_{2,3}$ = 10.0, $J_{3,4}$ = 9.0, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 5.0, $J_{5,6b}$ = 6.0, $J_{6a,6b}$ = 15.5 Hz; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.6, 20.7, 20.7 (3 × –$\underline{C}OCH_3$), 56.0 (–OCH_3), 59.3 (C-6), 64.0 (C-5), 69.6 (C-3), 70.7 (C-2), 72.1 (C-4), 96.8 (C-1); MS (FAB) *m/z*: 429 [M^+ + H], 451 [M^+ + Na]; HR-MS (FAB) Calcd for $C_{19}H_{25}O_9S$ [M^+ + H] 429.1218. Found: 429.1231.

Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-6-phenylsulfonyl-α-D-glucopyranoside (3) To a stirred solution of methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-phenylthio-α-D-glucopyranoside (412 mg, 1 mmol) in CH_2Cl_2 (2 ml), a solution of *m*-CPBA (242 mg, 1.4 mmol) in CH_2Cl_2 (2 ml) was added dropwise and the solution then stirred at 0 °C for 3.5 h. The mixture was poured into an aq. solution of $NaHCO_3$ (4 ml), and the organic layer was washed with H_2O (3 × 5 ml), dried (Na_2SO_4) and evaporated. Silica gel column chromatography (toluene–ethyl acetate 1 : 4) gave 183 mg (41%) of the major fraction (**3**) as a colorless syrup. The minor fraction (146 mg, 34%) was characterized as a mixture of (**1**) and (**2**). Crystallization from acetone–hexane gave colorless plates of (**3**): $[\alpha]_D^{24}$ +112° (*c* = 1.04, $CHCl_3$); mp 152—153 °C; IR (KBr) 1755 (C=O), 1250, 1230 (S=O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.98, 2.01, 2.05 (each 3H, s, –$COCH_3$), 3.23 (1H, dd, H-6a), 3.42 (1H, dd, H-6b), 3.48 (3H, s, –OCH_3), 4.43 (1H, ddd, H-5), 4.74 (1H, dd, H-2), 4.79 (1H, d, H-1), 4.81 (1H, dd, H-4), 5.45 (1H, dd, H-3); $J_{1,2}$ = 3.5, $J_{2,3}$ = 9.0, $J_{3,4}$ = 9.5, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 2.0, $J_{5,6b}$ = 9.0, $J_{6a,6b}$ = 14.0 Hz; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.6, 20.6, 20.6 (3 × –$\underline{C}OCH_3$), 56.2 (–OCH_3), 57.6 (C-6), 64.2 (C-5), 69.5 (C-3), 70.6 (C-2), 71.1 (C-4), 96.7 (C-1), 169.7, 170.0, 170.1 (3 × –$\underline{C}OCH_3$); MS (FAB) *m/z*: 445 [M^+ + H], 467 [M^+ + Na]; HR-MS (FAB) Calcd for $C_{19}H_{24}O_{10}SNa$ [M^+ + Na] 467.0987. Found: 467.1011.

X-Ray Crystallographic Studies of 1, 2 and 3[6)] Compounds **1**, **2** and **3** were crystallized from acetone–hexane, methanol and acetone–hexane, respectively. The X-ray crystallographic analyses were conducted with the crystals thus obtained.

Intensity data for **1**, **2** and **3** were collected on a AFC-5R Rigaku automated four-circle diffractometer using graphite-monochromated CuK_α radiation (λ = 1.54178 Å) at 23 °C. The ω–2θ scan mode with a scan rate of 8°/min was employed in the ω scan range of $(1.57 + 0.30 \tan\theta)°$, $(1.37 + 0.30 \tan\theta)°$ and $(1.68 + 0.30 \tan\theta)°$ with 2θ in the range of $6° < 2\theta < 121.4°$, $6° < 2\theta < 120.5°$ and $6° < 2\theta < 120.2°$ for **1**, **2** and **3**, respectively.

The intensities were corrected for Lorentz, polarization effects and absorption. The structures were solved by the direct method (MULTAN)[7] and were refined by the full-matrix least-squares method. Hydrogen atoms were inserted at their calculated positions and fixed at their positions. At the final stage of refinement, non-hydrogen atoms were refined anisotropically. Unique reflections with $|F_o|>3\sigma(|F_o|)$ were used for refinement. The final R (R_w) values obtained were shown in Table I, where $R=\sum||F_o|-|F_c||/\sum|F_o|$ and $R_w=[(\sum w(|F_o|-|F_c|)^2/\sum wF_o^2)]^{1/2}$ in the weighting scheme $w=4F_o^2/\sigma^2(F_o^2)$. Atomic scattering factors were taken from International Tables for X-Ray Crystallography (1974).[8] Crystal data and details of the refinement are summarized in Table 1.

Calculations for compounds **1**, **2** and **3** were performed using the TEXSAN[9] crystallographic software package of Molecular Structure Corporation.

No peak larger than 0.40 $e\text{Å}^{-3}$ was found in the final difference electron density map for any of the compounds.

References and Notes

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