Tetrahedron. Vol. 29, pp. 833 to 844. Pergamon Press 1973. Printed in Great Britain

CONFORMATIONAL STUDIES ON PERTRIMETHYLSILYL DERIVATIVES OF SOME MONO- AND DISACCHARIDES BY 220 MHz PMR SPECTROSCOPY

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(*Received in the UK* 22 *August* 1972; *Accepted for publication* 25 *September* 1972)

Abstract—The complete interpretation of 220 MHz PMR spectra and the accurate chemical shifts and coupling constants, obtained after computer simulation of the spectra, of a number of TMS-mono and -disaccharides are given. By means of an adapted Karplus equation the conformation of the derivatives has been studied in detail. All pyranose rings are found to occur in the Cl(D) chair conformation. As a consequence of their greater steric requirement, the OTMS groups deform the chair conformation more than the OAc groups. The preferred conformation of the C-5–CH_2OTMS group is determined and found to be dependent on the configuration at C-4.

INTRODUCTION

This study was aimed at the elucidation of the conformation of pertrimethylsilyl- (TMS-)derivatives of some mono and disaccharides in solution by means of accurate proton spin–spin coupling data. For several free saccharides and their derivatives, the conformational analysis has been carried out with the aid of NMR data (see review ref. 1). However, for TMS-derivatives only the assignments of the anomeric protons are published.[2–7] In this case the signals of the non-anomeric protons are spread over only 1–1·5 ppm, giving rise to complex spectra, which were made amenable to interpretation by using 220 MHz spectroscopy. Afterwards, refinement of the spectral parameters was obtained by computer simulation of the spectra. Calculation of vicinal coupling constants showed that all pyranose rings, which were investigated in this work, occur in the Cl(D) chair conformation. This result is important for the determination of the configuration of the glycosidic link in TMS-oligosaccharides. This determination is possible from the coupling constants $J_{1,2}$,[5,7] assuming a Cl(D) conformation for the aldohexopyranose ring. The ring deformations in the TMS-aldohexopyranoses with respect to those in Ac-derivatives are discussed in terms of steric and polar interactions between the substituents. Furthermore, the rotamers of the C-5–C-6 fragment are considered in detail on the basis of the vicinal and geminal coupling constants $J_{5,6}$, $J_{5,6'}$ and $J_{6,6'}$.

RESULTS AND DISCUSSION

Interpretation of the spectra. The 220 MHz PMR spectra of pentakis-OTMS-α-D-glucopyranose **1**, -β-D-glucopyranose **2**, -α-D-mannopyranose **3**, -β-D-mannopyranose **4**, -α-D-galactopyranose **5**, -β-D-galactopyranose **6** and of octakis-OTMS-α,α-trehalose **7**, -β,β-trehalose **8**, -α-lactose **9**, -β-lactose **10**, and -β-cellobiose **11** were recorded. In the spectra three groups of signals can be recognized. The OTMS signals appear as strong sharp singlets between δ = 0·1 and 0·3 ppm (Table 3). As a consequence of the strong deshielding effect of the ring oxygen, the doublets of the anomeric protons (H-1) are found between δ = 4·3 and 5·7 ppm. The non-anomeric protons H-2 up to and including H-6 and H-6′ resonate between δ = 2·9 and 4·3 ppm.[7]

The PMR parameters for the compounds **1–6** were largely obtained from a simple first-order subspectral analysis of the spectra. Except for the protons H-6, H-6′ and H-5, which give rise to ABX subspectra, all other subspectra were treated as AM or AMX spectra. The complete elucidation of the spectrum of **1** is shown in Fig 1c. To check the interpretations and to obtain more accurate PMR data, theoretical spectra were calculated from the initial parameters in an interactive iterative procedure with the spin simulation program SIMEQ.[8] In these calculations the proton system is treated as a seven spin system XABCDEF (H-1 up to and including H-6′ respectively). All vicinal coupling constants were taken positive, but the geminal coupling constant $J_{6,6'}$ was assumed to be negative in analogy to the data on geminal coupling constants in other saturated carbohydrates.[9] After several refinements of the initial parameters a good agreement was obtained between the observed and the theoretical spectra. The theoretical spectrum of the non-anomeric protons of **1** is shown in Fig 1d. The refined PMR data of the compounds **1–6** are given in the Tables 1 and 2. The spectra of the trehalose derivatives **7** and **8** resemble those of the glucose derivatives **1** and **2** respectively, i.e. the

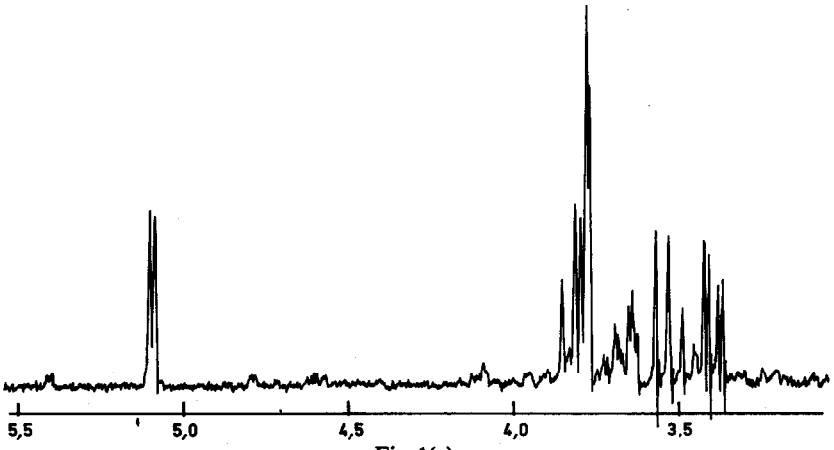

Fig 1(a).

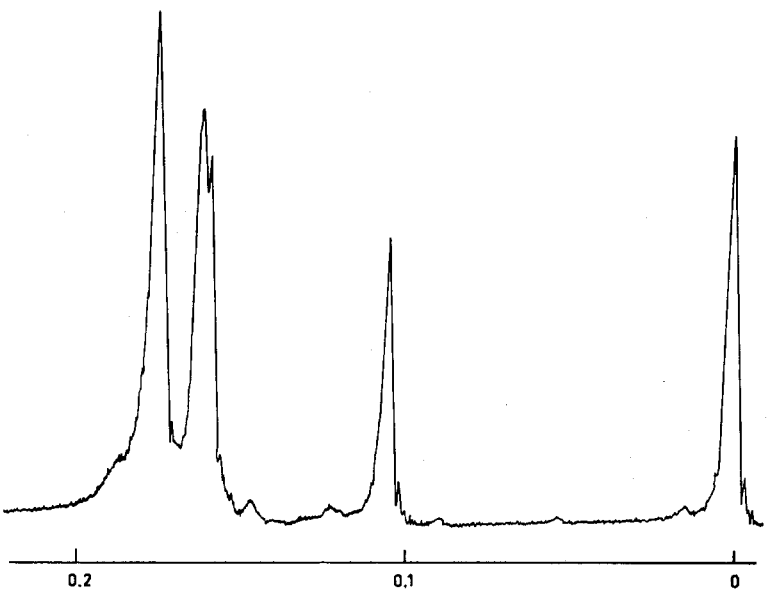

Fig 1(b).

protons of the carbon skeleton give rise to a [XABCDEF]$_2$-type of spectrum and only four OTMS signals can be discerned. As a consequence, the molecules of **7** and **8** must have a mirror plane of symmetry perpendicular to the C-1–C'-1 axis. The spectra were analyzed as described for the monosaccharides and the results are given in Tables 1 and 2.

The complete interpretation of the spectrum of **9** was not possible. Only the full set of PMR parameters of the galactopyranose unit could be obtained. In the glucopyranose unit the protons H-3, H-4, H-5 and H-6 give rise to a complex multiplet, which could not be analyzed further. The first-order parameters of H-1, H-2 and H-6' were determined for the glucopyranose unit (Tables 1 and 2).

In the spectrum of **10** the assignment of the signals to the protons of the individual units was possible (Fig 2c). This first-order analysis was checked by separate simulation of the spectra of both units (Figs 2d and 2e). The combination of the two simulations fits with the observed spectrum of **10**. The interpretation of the spectrum of **11** was performed similarly and the results for **10** and **11** are also summarized in Tables 1 and 2.

Adaptation of the Karplus equation. For the conformational analysis of carbohydrates in solution, frequent use has been made of the Karplus equation:[10]

$$J_{HH'} = A + B\cos\phi + C\cos 2\phi. \qquad (1)$$

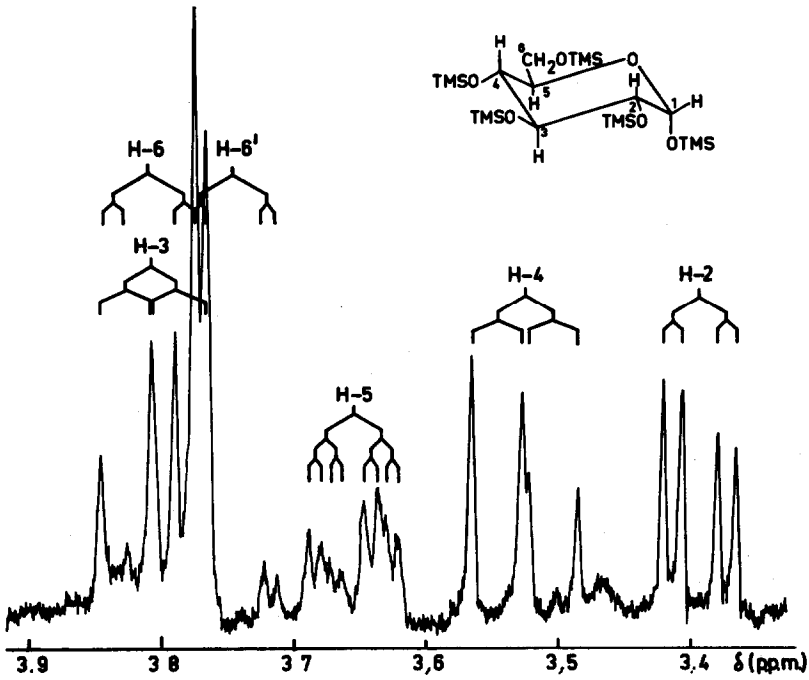

Fig 1(c).

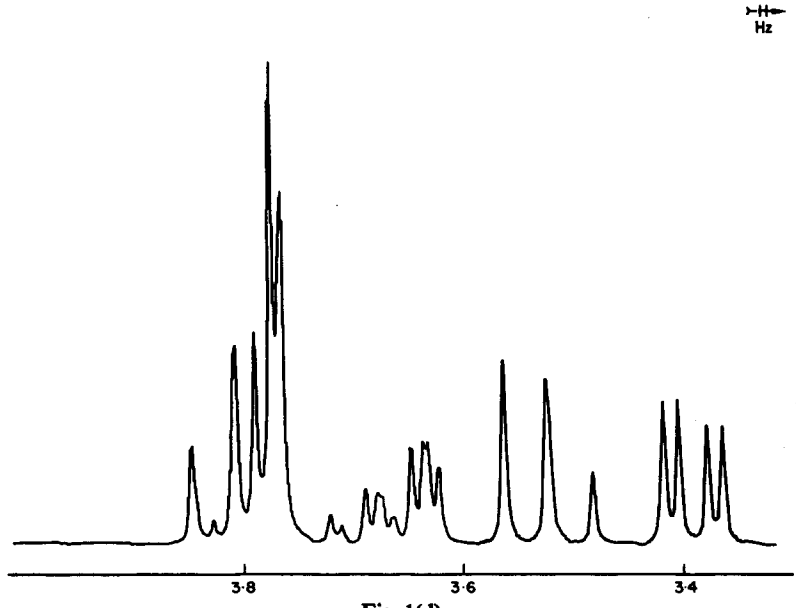

Fig 1(d).

Fig 1. 220 MHz spectrum of pentakis-OTMS-α-D-glucopyranose 1 in acetone-d_6: (a) the signals of the protons of the carbon skeleton, (b) the OTMS signals, (c) observed spectrum of the non-anomeric protons, (d) theoretical spectrum of the non-anomeric protons.

This equation gives the dependence of the vicinal coupling constant $J_{HH'}$ on the dihedral angle ϕ between H and H'. However, vicinal proton couplings are also dependent on the electronegativity of the four substituents, bond lengths and bond angles in a H—C—C'—H' fragment.[11,12]

Recently, in a study dealing with aldopentopyranosyl derivatives, Durette and Horton[13] de-

Table 1. Chemical shifts in ppm of methine and methylene protons of TMS-mono- and -disaccharides in acetone-d_6[a]

Compd.	Configuration	H-1	H-2	H-3	H-4	H-5	H-6	H-6'
1	α-D-Gp	5·06	3·38	3·78	3·51	3·63	3·77	3·74
2	β-D-Gp	4·55	3·18	3·45	3·48	3·27	3·70	3·81
3	α-D-Manp	4·97	3·73	3·85	3·93	3·51	3·78	3·73
4	β-D-Manp	4·83	3·79	3·59	3·82	3·15	3·72	3·80
5	α-D-Galp	5·01	3·83	3·88	3·95	3·87	3·53	3·63
6	β-D-Galp	4·51	3·58	3·64	3·91	3·55	3·54	3·60
7	α-D-Gp-	4·93	3·45	3·95	3·53	3·83	3·77	3·77
	(1 → 1)-α-D-Gp	4·93	3·45	3·95	3·53	3·83	3·77	3·77
8	β-D-Gp-	4·70	3·35	3·45	3·49	3·19	3·73	3·83
	(1 → 1)-β-D-Gp	4·70	3·35	3·45	4·49	3·19	3·73	3·83
9	β-D-Galp-	4·40	3·72	3·51	3·94	3·41	3·65	3·70
	(1 → 4)-α-D-Gp	5·01[c]	3·36[c]	—3·66—		—3·83—	[b]	4·07[c]
10	β-D-Galp-	4·44	3·70	3·50	3·93	3·41	3·66	3·71
	(1 → 4)-β-D-Gp	4·55	3·16	3·44	3·64	3·35	4·01	3·87
11	β-D-Gp-	4·56	3·28	3·39	3·36	3·18	3·67	3·88
	(1 → 4)-β-D-Gp	4·54	3·18	3·49	3·78	3·38	3·98	3·89

[a]Data obtained after refining the initial chemical shifts by simulation of the 220 MHz spectra, unless otherwise noted.
[b]Complex multiplet.
[c]First-order approximation.

Table 2. Coupling constants in Hz of TMS-mono- and -disaccharides in acetone-d_6[a]

Compd.	Configuration	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
1	α-D-Gp	3·0	8·9	8·6	9·3	3·8	1·7	−11·5
2	β-D-Gp	7·3	8·3	8·4	8·7	4·9	2·0	−11·0
3	α-D-Manp	2·2	2·5	9·2	9·1	4·4	1·9	−11·7
4	β-D-Manp	0·9	2·7	8·9	9·2	5·0	1·7	−11·2
5	α-D-Galp	3·1	9·4	2·6	1·3	6·2	7·4	−9·5
6	β-D-Galp	7·2	7·4	1·8	1·0	5·0	7·5	−9·5
7	α-D-Gp-	3·2	9·3	8·8	9·5	2·9	2·9	[b]
	(1 → 1)-α-D-Gp	3·2	9·3	8·8	9·5	2·9	2·9	[b]
8	β-D-Gp-	8·1	8·3	8·9	8·7	4·6	2·0	−11·5
	(1 → 1)-β-D-Gp	8·1	8·3	8·9	8·7	4·6	2·0	−11·5
9	β-D-Galp.	7·4	9·1	2·5	0·5	5·0	7·7	−9·6
	(1 → 4)-α-D-Gp	3·4[d]	8·4[d]	—[c]	—[c]	—[c]	2·7[d]	−11·1[d]
10	β-D-Galp-	7·7	9·0	2·6	0·7	4·9	8·2	−9·6
	(1 → 4)-β-D-Gp	7·3	8·5	8·8	9·6	3·3	1·7	−10·8
11	β-D-Gp-	7·5	8·6	8·4	8·7	6·1	1·9	−11·1
	(1 → 4)-β-D-Gp	7·6	9·2	9·2	9·0	3·1	1·6	−11·1

[a]Data obtained after refining the initial coupling constants by simulation of the 220 MHz spectra, unless otherwise noted.
[b]No $J_{6,6'}$ observed.
[c]Complex multiplet.
[d]First-order approximation.

scribed a modified Karplus equation, which takes into account the electronegativity X of the substituents:

$$J_{HH'} = (7{\cdot}8 - 1{\cdot}0\cos\phi + 5{\cdot}6\cos 2\phi)(1 - 0{\cdot}1\Delta X) \quad (2)$$

*A value of 3·5 for X_{OTMS} was used; this value was calculated by the method of Cavanaugh and Dailey[14] from PMR data of $CH_3—CH_2—OSi(CH_3)_3$.[15] The other electronegativities used, are[13] $X_H = 2{\cdot}1$, $X_{O_r} = 3{\cdot}3$, $X_{-C-O-} = 2{\cdot}5$, $X_{OCH_3} = 3{\cdot}3$, $X_{OAc} = 3{\cdot}7$ and $X_{Br} = 3{\cdot}0$.

where $\Delta X = X - X_H$, representing the difference in electronegativity between a substituent and hydrogen. For X the values determined by Cavanaugh and Dailey[14] were used. However for various substituted aldohexopyranoses like pertrimethylsilyl-* and peracetyl-derivatives (see for instance refs. 16, 17, 18 and 19) it was found with equation 2 that $(J^{max}_{HH'})_{observed} > (J^{max}_{HH'})_{calculated}$ or $(J^{min}_{HH'})_{observed} < (J^{min}_{HH'})_{calculated}$. Therefore the equation was modified by changing the constant 7·8 into 6·6 to lower the minimum value of $J_{HH'}$ and further by taking

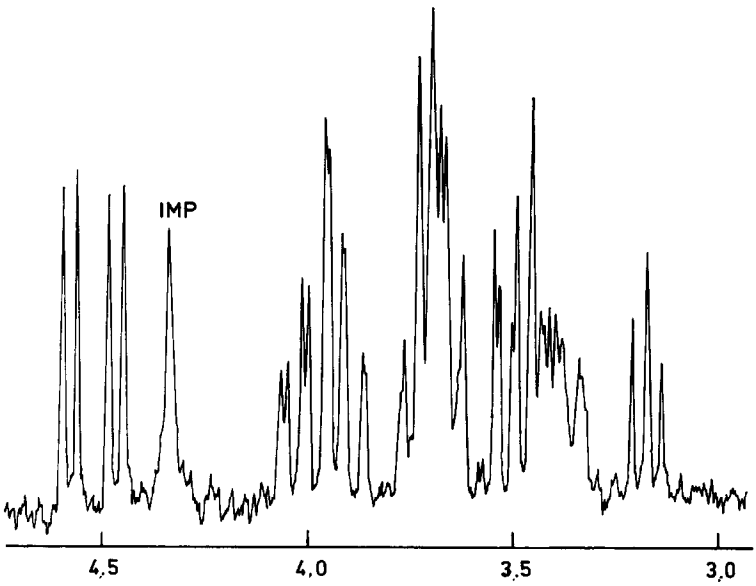

Fig 2(a).

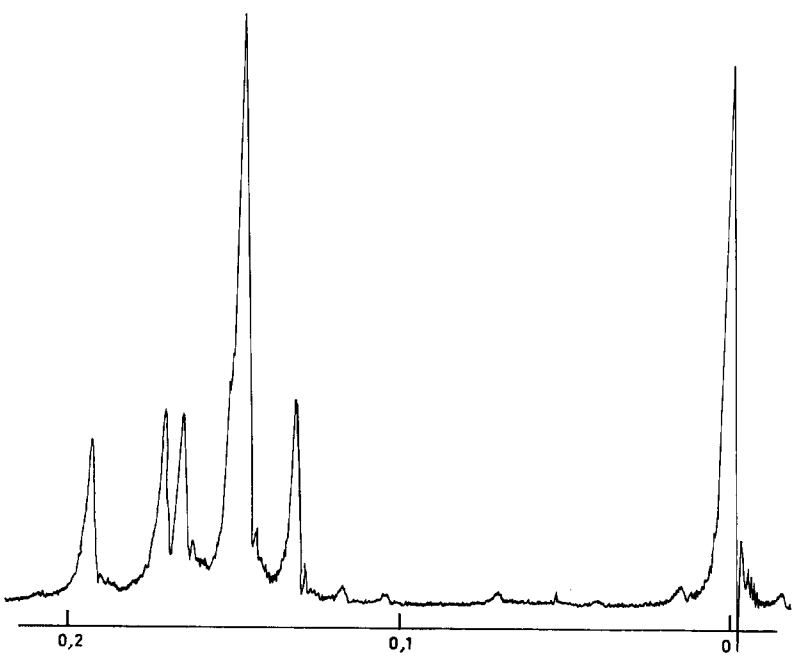

Fig 2(b).

into account the angular dependence of the electronegativity effects on vicinal coupling.[20,21] An electronegative group R has its maximum effect when R is transcoplanar to H in the system R—C—C—H ($\theta = 180°$, Fig 3a), while a smaller maximum is present when $\theta = 0°$ (Fig 3b); if $\theta = 60°$ the effect is nearly absent[22] (Fig 3c).

For these reasons the electronegativity factor f (0·1 in Eq. 2) was taken 0·05 for θ smaller than 90° and 0·15 for θ larger than 90°; the following

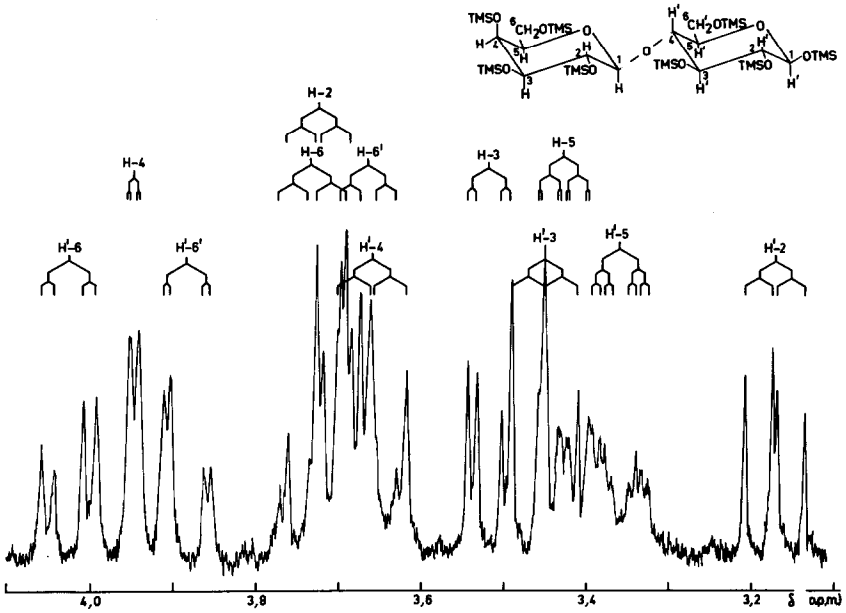

Fig 2(c).

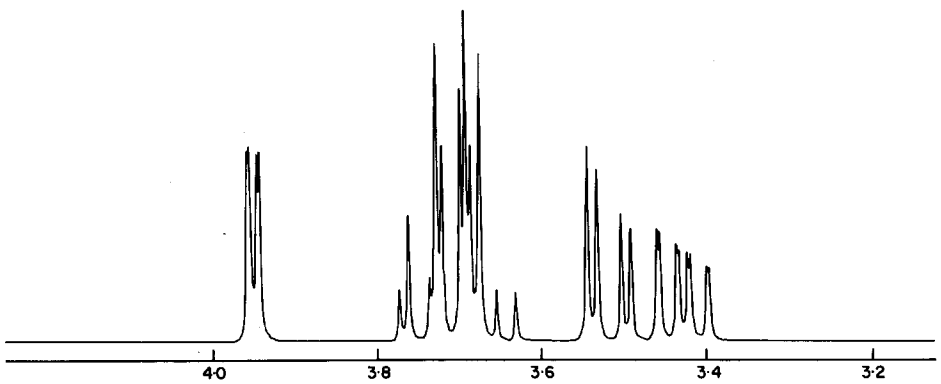

Fig 2(d).

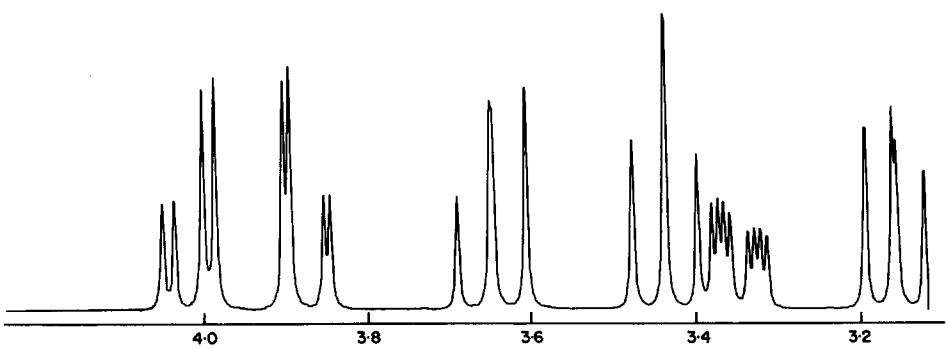

Fig 2(e).

Fig 2. 220 MHz spectrum of octakis-OTMS-β-D-lactose **10** in acetone-d_6: (a) the signals of the protons of the carbon skeleton, (b) the OTMS signals, (c) observed spectrum of the non-anomeric protons, (d) theoretical spectrum of the non-anomeric protons of the β-D-galactopyranose unit, (e) theoretical spectrum of the non-anomeric protons of the β-D-glucopyranose unit.

Table 3. Chemical shifts in ppm of OTMS methyl protons of TMS-mono- and disaccharides in acetone-d_6

Compd.	TMS-der. of	Chemical shifts (integral, protons)				
1	α-D-Gp	0·105 (9)	0·158 (9)	0·161 (9)	0·175 (18)	
2	β-D-Gp	0·122 (9)	0·158 (9)	0·169 (9)	0·172 (9)	0·182 (9)
3	α-D-Manp	0·116 (9)	0·137 (9)	0·147 (9)	0·163 (9)	0·173 (9)
4	β-D-Manp	0·127 (18)	0·139 (9)	0·158 (9)	0·169 (9)	
5	α-D-Galp	0·106 (9)	0·143 (18)	0·155 (9)	0·169 (9)	
6	β-D-Galp	0·109 (9)	0·128 (9)	0·149 (9)	0·154 (9)	0·180 (9)
7	α,α-trehalose	0·113 (18)	0·162 (18)	0·177 (18)	0·184 (18)	
8	β,β-trehalose	0·146 (18)	0·183 (36)	0·219 (18)		
9	α-D-lactose	0·131 (9)	0·144 (9)	0·147 (9)	0·150 (18)	0·159 (9)
		0·161 (9)	0·195 (9)			
10	β-D-lactose	0·134 (9)	0·147 (27)	0·150 (9)	0·166 (9)	0·171 (9)
		0·193 (9)				
11	β-D-cellobiose	0·149 (9)	0·160 (9)	0·164 (9)	0·177 (9)	0·182 (18)
		0·187 (9)	0·190 (9)			

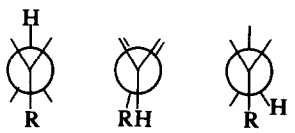

Fig 3.

equation was obtained:

$$J_{HH'} = (6{\cdot}6 - 1{\cdot}0\cos\phi + 5{\cdot}6\cos 2\phi)\left(1 - \sum_{i=1}^{4} f_i \Delta X_i\right) \quad (3)$$

Although no reasonable corrections could be made for changes in bond lengths and bond angles, it is still likely that the introduction of factors, about which information is available will improve the reliability of the results. Because of the cos 2ϕ term in the equation, calculation of angles from observed coupling constants is more accurate for angles of about 60° or 120° than for angles of about 0°, 90° or 180°. By studying the conformational changes due to different substituents in a series of closely related compounds, most of the uncertainties in the constants in the Karplus equation and in the other factors (e.g. bond lengths, bond angles), influencing the vicinal coupling constants, are largely eliminated.[12]

Other modifications of the Karplus equation are possible, which upon the whole lead to the same conclusions; however Eq. 3 gives the best fit to the experimental data. In the following Eq. 3 is used to determine the ring conformation of the TMS-saccharides and for a detailed study of the structure of these derivatives.

Determination of the type of ring conformation. The type of ring conformation of TMS-aldohexopyranose units was inferred from comparison of the experimental coupling constants with those obtained by calculation for 14 possible ideal conformations[23] (Table 4). The theoretical coupling constants were calculated from the dihedral angles estimated from Dreiding molecular models by using Eq. 3. In Table 4 details are given for pentakis-OTMS-α-D-galactopyranose 5: in the Cl(D) chair conformation all calculated constants have a good fit with the experimental ones, while for the other conformations at least one coupling constant deviates more than 2·5 Hz. The last column in Table 4 shows that the sum of the differences between the calculated and observed values is small for the Cl(D) conformation compared to the other conformations. The situation is analogous for the other TMS-derivatives: only the Cl(D) conformation gives a reasonably good fit for all the corresponding calculated and observed vicinal coupling constants (Tables 4 and 5); so, there is no evidence

Table 4. Calculated $^3J_{HH}$ couplings in pentakis-OTMS-α-D-galactopyranose 5 in different conformations

Conformation[a]	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$\sum_{i=1}^{4} \lvert J_i^{calc} - J_i^{obs} \rvert$
Chair C1 $^4C_1$	2·0	10·8	2·1	1·9	3·6
Chair 1C $^1C_4$	1·7	2·4	2·1	2·5	10·1
Boat $^{1,4}B$	1·7	3·2	2·1	1·9	8·7
Boat $^{2,5}B$	2·0	10·8	5·2	2·5	6·3
Boat $^{3,0}B$	3·8	2·4	2·1	5·5	12·4
Boat $B_{1,4}$	2·0	3·2	2·1	2·5	9·0
Boat $B_{2,5}$	1·7	2·4	5·2	1·9	11·6
Boat $B_{3,0}$	3·8	10·8	2·1	5·5	6·8
Skew Boat $^1S_5$	1·0	0·7	5·2	1·1	13·6
Skew Boat $^0S_2$	4·2	3·8	5·2	4·6	12·6
Skew Boat $^3S_1$	4·9	0·7	1·2	6·1	16·7
Skew Boat $^5S_1$	1·1	8·9	5·2	1·4	5·2
Skew Boat $^2S_0$	4·2	9·5	5·2	4·6	7·1
Skew Boat $^1S_3$	4·2	8·0	1·2	4·6	7·2
$^3J_{HH'}$ observed[b]	3·1	9·4	2·6	1·3	

[a] For nomenclature of conformations see ref. 24.
[b] See Table 2.

Table 5. Observed and calculated $^3J_{HH}$ couplings, assuming ideal Cl(D) chair conformation

Compd.	TMS-der. of	Observed values				Calculated values			
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
1	α-D-Gp	3·0	8·9	8·6	9·3	2·0	10·8	10·8	11·0
2	β-D-Gp	7·3	8·3	8·4	8·7	10·3	10·8	10·8	11·0
3	α-D-Manp	2·2	2·5	9·2	9·1	2·0	2·1	10·8	11·0
4	β-D-Manp	0·9	2·7	8·9	9·2	1·7	2·1	10·8	11·0
5	α-D-Galp	3·1	9·4	2·6	1·3	2·0	10·8	2·1	1·9
6	β-D-Galp	7·2	7·4	1·8	1·0	10·3	10·8	2·1	1·9
7	α,α-trehalose	3·2	9·3	8·8	9·5	2·1	10·8	10·8	11·0
8	β,β-trehalose	8·1	8·3	8·9	8·7	10·4	10·8	10·8	11·0
9	β-D-Galp-(1 → 4)-α-D-Gp	7·4	9·1	2·5	0·5	10·4	10·8	2·1	1·9
		3·4[a]	8·4[a]	—[b]	—[b]	2·0	10·8	11·0	11·1
10	β-D-Galp-(1 → 4)-β-D-Gp	7·7	9·0	2·6	0·7	10·4	10·8	2·1	1·9
		7·3	8·5	8·8	9·6	10·3	10·8	11·0	11·1
11	β-D-Gp-(1 → 4)-β-D-Gp	7·5	8·6	8·4	8·7	10·6	10·8	10·8	11·0
		7·6	9·2	9·2	9·0	10·3	10·8	11·0	11·1

[a]First-order approximation.
[b]No data available.

for these compounds to exist in another conformation.

The structure of the chair conformation. To study the structure of the rings more in detail, the dihedral angles (Table 6a) were calculated from the coupling constants $J_{1,2}$, $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ of the compounds **1–6** (Table 2).

The literature presents evidence that the ring in tetrahydropyran[25] and in polysubstituted derivatives (compare ref. 13) is flattened with respect to the ideal chair conformation. X-ray data show a flattening of the ring in saccharide-derivatives, e.g. the conformational angles (dihedral angles in C–C–C–C fragments) in β-DL-arabinopyranose vary between 55° and 60°,[26] while those in tri-OAc-β-D-arabinopyranosyl bromide vary between 53° and 56°, indicating an even more pronounced flattening of the ring.[27] Inspection of the calculated dihedral angles (Table 6a) shows that a similar trend is present in the TMS-derivatives.

A better insight into the influence of OTMS groups on the structure of the ring can be obtained by comparing the calculated dihedral angles of TMS- and Ac-derivatives. The dihedral angles in Ac-derivatives were calculated from literature data (Table 6b). The changes in angles can be interpreted in terms of deformations resulting from changes in substitution. These distortions arise from the polar and steric interactions between the substituents. Since no 1, 3-diaxial interactions are present in the compounds studied, only the gauche interactions between substituents have to be considered. Because of the adjacent polar bonds present, the "gauche effect" (the tendency to adopt that structure which has the maximum number of gauche interactions between polar bonds[29]) plays an important role in the distortions of the rings. The electronegativity of the group R is generally taken as an indication for the polarity of the C—R bond.[30]

Table 6. Calculated dihedral angles $\phi_{HH'}$ for differently substituted aldohexopyranoses

Compound	$\phi_{1,2}$	$\phi_{2,3}$	$\phi_{3,4}$	$\phi_{4,5}$
a TMS-derivatives				
Pentakis-OTMS-α-D-Gp (1)	50	154	151	156
Pentakis-OTMS-β-D-Gp (2)	145	149	150	151
Pentakis-OTMS-α-D-Manp (3)	59	56	156	154
Pentakis-OTMS-β-D-Manp (4)	73	54	154	155
Pentakis-OTMS-α-D-Galp (5)	49	158	55	67
Pentakis-OTMS-β-D-Galp (6)	144	143	63	72
b Ac-derivatives				
Me-tetrakis-OAc-α-D-Gp[a]	47	166	166	163
Tetrakis-OAc-α-D-Gp bromide[b]	46	166	161	158
Me-tetrakis-OAc-β-D-Gp[c]	150	152	156	154
Pentakis-OAc-β-D-Gp[c]	151	156	156	154
Tetrakis-OAc-α-D-Manp bromide[b]	67	50	166	158
Me-tetrakis-OAc-β-D-Manp[d]	66	50	166	156
Pentakis-OAc-β-D-Manp[d]	67	50	161	154
Tetrakis-OAc-α-D-Galp bromide[b]	49	166	49	47

[a]Ref. 16.
[b]Ref. 17.
[c]Ref. 28.
[d]Ref. 19.

Since the electronegativity of OTMS groups (3·5) is slightly less than that of OAc groups (3·7), the attractive electronic forces between the former are somewhat smaller. On the other hand, the steric requirement of OTMS groups is much larger than of OAc groups. Hence, it is reasonable to assume that the differences in the distortions of the chair conformation between TMS-aldohexopyranoses and Ac-derivatives are mainly due to steric repulsion forces. Because only small differences are observed in the $\phi_{1,2}$ angles when the substituent at C-1 is changed from OAc into OMe or Br (e.g. $\phi_{1,2}$ in the three D-mannopyranose derivatives in Table 6b: 67°, 66° and 67°) it seems that the previous con-

clusion also holds for the Ac-derivatives with OMe or Br at C-1. For a discussion of the ring deformations the C—C ring fragments may be considered independently as can be inferred from the calculated angles, e.g. in compound **5**, the angles $\phi_{1,2}$, $\phi_{3,4}$ and $\phi_{4,5}$ (all 60° in the ideal chair conformation) are found to be 49°, 55° and 67° respectively (Table 6a). The deviations that can be expected in terms of the dihedral angles ϕ between the H atoms, if the steric requirement of the substituents increases, are shown in Fig 4. The conclusions in

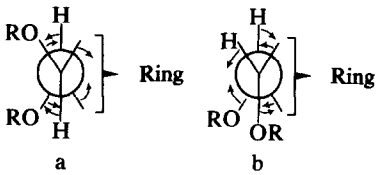

Fig 4. Deformations of the ring-fragments when R becomes larger: (a) Two equatorial oriented substituents: the orientation will become less equatorial which results in a flattening of this ring-fragment and a decrease of ϕ. (b) One equatorial and one axial substituent: a less pronounced flattening in this ring-fragment will occur which results in an increase of ϕ.

the subscriptions of Fig 4 are confirmed by the observed values for ϕ (Table 6a and b). Situation a: all angles larger than 120° are smaller in the TMS-derivatives than in corresponding Ac-derivatives, e.g. $\phi_{2,3}$ in compound **2** (149°) and $\phi_{2,3}$ in other β-D-glucopyranose-derivatives (152° and 156°). The average distortion is −7°. Situation b: the dihedral angle in TMS-derivatives is larger than in corresponding Ac-derivatives, e.g. $\phi_{1,2}$ in β-D-manno or α-D-glucopyranose derivatives. The average distortion is +6°. In α-D-mannopyranose derivatives two axial groups on adjacent C atoms are present in the C-1–C-2 fragment. When the equatorial group at C-3 becomes larger, the group at C-2 will become more axial (compare situation b). Although the axial group at C-1 has only the ring oxygen at the adjacent place, it is still likely that the overall effect is a less pronounced flattening of this ring fragment (Fig 5) and a decreasing of ϕ. This is confirmed by the angles found: $\phi_{1,2}$ in **3** (59°) is smaller than in tetrakis-OAc-α-D-mannopyranosyl bromide (67°). The observed trends in deformation can satisfactorily be explained in

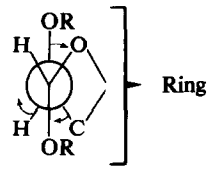

Fig 5. Deformation of the C-1–C-2 fragment in α-D-mann opyranoses, when R becomes larger.

terms of greater steric interaction between the OTMS groups. Molecular models show that OTMS groups in fact hinder each other much more than OAc groups. Unfortunately no crystallographic data are available for TMS-saccharides to corroborate these conclusions. Similar calculations of dihedral angles in the TMS-disaccharides are carried out (Table 7). However, for the disaccharides **7–11** no comparisons could be made with differently substituted ones. The angles ϕ found for the monosaccharide units in the TMS-disaccharides are similar to those in the corresponding TMS-monosaccharides. Therefore, the Cl(D) chair conformation of these units are deformed nearly to the same extent as that of the corresponding monosaccharides.

The conformation of the C-5–CH_2OTMS *group.* The C-5–CH_2OTMS group can adopt various conformations by rotation around the C-5–C-6 bond. The three staggered rotamers 1, 2 and 3 (Fig 6) can be considered as the most important ones. Each of these rotamers contributes to the time-averaged spectrum.[31,32]

Table 7. Calculated dihedral angles $\phi_{HH'}$ for TMS-disaccharides

Compound		$\phi_{1,2}$	$\phi_{2,3}$	$\phi_{3,4}$	$\phi_{4,5}$
Octakis-OTMS-α-D-Gp-		49	156	153	157
(1 → 1)-α-D-Gp	**7**	49	156	153	157
Octakis-OTMS-β-D-Gp-		150	149	154	151
(1 → 1)-β-D-Gp	**8**	150	149	154	151
Octakis-OTMS-β-D-Galp-		145	155	56	90
(1 → 4)-α-D-Gp	**9**	46[a]	150[a]	—[b]	—[b]
Octakis-OTMS-β-D-Galp-		147	154	55	79
(1 → 4)-β-D-Gp	**10**	145	151	152	157
Octakis-OTMS-β-D-Gp-		145	151	150	151
(1 → 4)-β-D-Gp	**11**	147	156	155	153

[a]Calculated from first-order coupling constants.
[b]No data available.

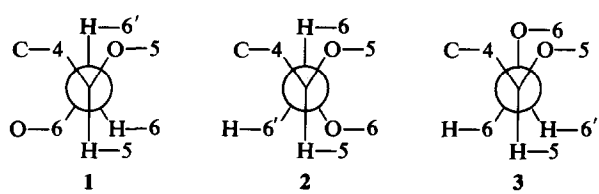

Fig 6. The three staggered rotamers 1, 2 and 3 of the C-5–CH_2OTMS group in TMS-aldohexopyranoses.

The vicinal coupling constants $J_{5,6}$ and $J_{5,6'}$ can be expressed in the mole fractions n_1, n_2 and n_3 of the three rotamers, leading to the following equations:

$$J_{5,6} = n_1(J_{5,6})_1 + n_2(J_{5,6})_2 + n_3(J_{5,6})_3 \quad (4)$$
$$J_{5,6'} = n_1(J_{5,6'})_1 + n_2(J_{5,6'})_2 + n_3(J_{5,6'})_3 \quad (5)$$
$$n_1 + n_2 + n_3 = 1. \quad (6)$$

For the calculation of the $J_{5,6}$ and $J_{5,6'}$ values in the rotamers Eq. 3 was applied (the equilibrium dihedral angles were assumed to be 65° and 185°[33]): $(J_{5,6})_1 = 2{\cdot}1$ Hz, $(J_{5,6})_2 = 11{\cdot}1$ Hz, $(J_{5,6})_3 = 1{\cdot}5$ Hz, $(J_{5,6'})_1 = 11{\cdot}1$ Hz, $(J_{5,6'})_2 = 1{\cdot}9$ Hz and $(J_{5,6'})_3 = 1{\cdot}7$ Hz. In view of the simplifications, which underlie this model, a further approximation has been made, by taking an intermediate value for $(J_{5,6})_1$ and $(J_{5,6'})_2$: 2·0 Hz and for $(J_{5,6})_3$ and $(J_{5,6'})_3$: 1·6 Hz. By using these parameters the different mole fractions were calculated for the compounds **1–11** (Table 8). H-6 and H-6′ are interchangeable, so two alternatives are obtained (Table 8, columns a and b), in which n_1 and n_2 have changed places.

To make a choice between the two possibilities, the steric interactions between large substituents are considered. In the D-gluco- and D-mannopyranose units in **1–4**, **7**, **8**, **10** and **11**, rotamer 1 is strongly disfavoured because of the parallel 1,3-interaction between the OTMS groups at C-4 and C-6. Therefore column a in Table 8 represents the most probable mole fractions for these compounds. An indication, that the parallel 1,3-interaction is a very important factor in disfavouring a rotamer, is given by the negligible amounts of rotamer 3 in the D-galactopyranose units of **5**, **6**, **9** and **10** ($n_3 \sim 0$, columns a and b). In rotamer 3 such an interaction exists between the OTMS groups at C-4 and C-6.

For the D-galactopyranose derivatives a choice between the two possibilities of n_1 and n_2 can be made on the basis of the geminal coupling constants $J_{6,6'}$. MO theory has shown that these couplings increase algebraically with an increase in amount of that rotamer in which the C—C—O plane bisects the axis between the geminal protons in a —CH_2—CHO— fragment.[34] In rotamer 1 (Fig 6) this situation is present; in the rotamers 2 and 3, this is not the case. Therefore an algebraic increase of $J_{6,6'}$ reflects an increase in amount of rotamer 1. In the compounds with a D-gluco- or D-manno-configuration the amount of rotamer 1 is negligible, therefore the minimum value for $J_{6,6'}$ in TMS-derivatives lies in the range from −10·8 to −11·7 Hz (Table 8, last column). The maximum value for $J_{6,6'}$ is not known but for peracetyl aldopentopyranose derivatives, it was found that the difference in $J_{6,6'}$ values between conformational extremes is about 3 Hz[13] and it is reasonable to suggest that the same trend is present in TMS-aldohexopyranoses. The $J_{6,6'}$ values in the D-galactopyranose units are −9·5 or −9·6 Hz. The relatively large difference between these values and the minimum value, makes it likely that the situation in these compounds is represented by the highest values for n_1 (Table 8, column a). This conclusion is confirmed by calculations on analogous Ac-derivatives, as will be shown in the next paragraph. The favoured conformations of the C-5–CH_2O-TMS groups of the aldohexopyranose units in TMS-mono- and -disaccharides are visualized in Fig 7. On the basis of the ratios of the rotamers 1 and 2 in the different saccharides, assignments of the protons H-6 and H-6′ can be made (rotamer 3 gives the same contribution to $J_{5,6}$ and $J_{5,6'}$). Starting from the sequence of H-6, H-6′ and OTMS at C-6 as indicated in Fig 6 (looking along the C-5–C-6 axis: counterclockwise), $J_{5,6}$ must be larger

Table 8. Calculated mole fractions of the rotamers 1, 2 and 3 of the C-5–C-6 fragment in TMS-mono- and disaccharides[a]

Compd.	TMS-derivative of	a			b			
		n_1	n_2	n_3	n_1	n_2	n_3	$J_{6,6'}$
1	α-D-Gp	0·00	0·23	0·77	0·23	0·00	0·77	−11·5
2	β-D-Gp	0·03	0·34	0·63	0·34	0·03	0·63	−11·0
3	α-D-Manp	0·02	0·29	0·69	0·29	0·02	0·69	−11·7
4	β-D-Manp	0·00	0·36	0·64	0·36	0·00	0·64	−11·2
5	α-D-Galp	0·55	0·45	0·00	0·45	0·55	0·00	−9·5
6	β-D-Galp	0·61	0·34	0·05	0·34	0·61	0·05	−9·5
7	α,α-trehalose	0·13	0·13	0·74	0·13	0·13	0·74	— [b]
8	β,β-trehalose	0·03	0·31	0·66	0·31	0·03	0·66	−11·5
9	β-D-Galp-	0·63	0·33	0·04	0·33	0·63	0·04	−9·6
	(1 → 4)-α-D-Gp	—	—	—[b]	—	—	—[b]	−11·1
10	β-D-Galp-	0·68	0·32	0·00	0·32	0·68	0·00	−9·6
	(1 → 4)-β-D-Gp	0·00	0·18	0·82	0·18	0·00	0·82	−10·8
11	β-D-Gp-	0·01	0·47	0·52	0·47	0·01	0·52	−11·1
	(1 → 4)-β-D-Gp	0·00	0·16	0·84	0·16	0·00	0·84	−11·1

[a] In column a the most probable mole fractions are given.
[b] No data available.

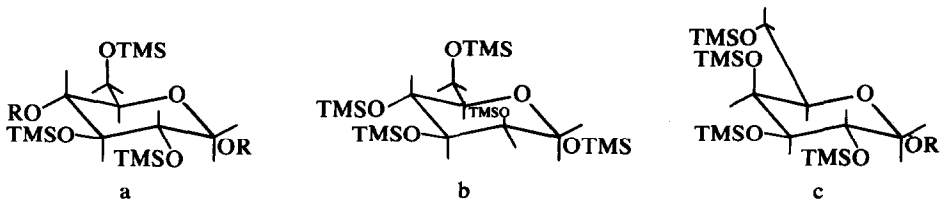

Fig 7. Favoured conformations of the C-5–CH_2OTMS groups in (a) D-glucopyranose, (b) D-mannopyranose, and (c) D-galactopyranose units in TMS-mono- and -disaccharides (R is glycose or TMS group).

than $J_{5,6'}$ in the D-gluco- and D-mannopyranose units (rotamer 2 favoured), while $J_{5,6}$ must be smaller than $J_{5,6'}$ in the D-galactopyranose units (rotamer 1 favoured). In the Tables 1 and 2 the assignments of the protons H-6 and H-6′ are given according to this reasoning.

We also calculated mole fractions for a number of Ac-derivatives (Table 9). The choice between the two alternatives of n_1 and n_2 in the D-gluco- and D-mannopyranose derivatives was made on the basis of the same considerations as for the TMS-analogues, leading to the mole fractions as indicated in Table 9. Comparison of the Tables 8 and 9 show, that in these compounds rotamer 3 is somewhat less favoured with regard to the TMS-derivatives. In the Ac-derivatives of D-mannopyranose rotamer 1 is not so strongly disfavoured. Probably, this is a result of the smaller steric hindrance between OAc groups. For the compound 1-thio-pentakis-OAc-β-D-galactopyranose the following mole fractions were found $n_1 = 0{\cdot}09$, $n_2 = 0{\cdot}91$ and $n_3 = 0{\cdot}00$, in which n_1 and n_2 can be interchanged. Comparison of the $J_{6,6'}$ value (−11·0 Hz) with that of the D-gluco-analogue (−12·4 Hz) (Table 9) show that n_1 must be 0·91, because in the last compound rotamers 2 and 3 (as already mentioned, both giving rise to a small geminal coupling constant) are both favoured: $n_2 + n_3 = 1{\cdot}00$. If n_2 in the D-galacto-analogue was 0·91, about the same value for $J_{6,6'}$ had to be expected. This result reinforces the conclusions about the TMS-D-galactopyranoses, because it is likely to assume that the TMS- and Ac-derivatives of D-galactopyranose do not differ greatly with respect to the conformational preferences of the C-5–C-6 fragment. Literature data concerning these conformational preferences are very sparse (Table 9, last column). Comparison with our results show that agreement exists to a certain extent. Especially for the last compound in Table 9, in which Holland *et al.*[18] presumed a preference for rotamer 2, a disagreement is found.

EXPERIMENTAL

Carbohydrates. α-D(+)-glucopyranose, α-D(+)-galactopyranose, α-D(+)-mannopyranose, α,α-trehalose dihydrate and α-D-lactose monohydrate were obtained from J. T. Baker Chemicals N.V.; β-D(+)-glucopyranose and β-D-lactose from Calbiochem, β-D(+)-mannopyranose from Hoffman-La Roche and β-D-cellobiose from Fluka A.G. β,β-trehalose was kindly supplied by Dr. G. G. Birch.

Preparation of pertrimethylsilyl derivatives. 20 mg of a mono- or disaccharide was converted into its pertrimethylsilyl derivative with hexamethyldisilazane (E.G.A. Chemie) and chlorotrimethylsilane (Schuchardt) in dry pyridine as described.[7] The isolation of pentakis-OTMS-β-D-galactopyranose from the anomeric mixture was carried out on a Pye Model 105 automatic preparative gaschromatograph, provided with a flame ionisation detector, on a glass column (2 m × 9·6 mm O.D.) containing 10% XF 1150[3] on Chromosorb W/NAW 30–60 mesh at 135°. For the purification of octakis-OTMS-β-cellobiose a glass column packed with 10% OV 17 on Chromosorb W/NAW 30–60 mesh was used and the oven temperature was 270°. The TMS-derivatives were dissolved in 0·5 ml of acetone-d_6.

Table 9. Calculated mole fractions of the rotamers 1, 2 and 3 of the C-5–C-6 fragment in Ac-aldohexopyranoses

Compound	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	n_1	n_2	n_3	Reference data
Pentakis-OAc-β-D-Gp[a]	4·7	1·9	−12·4	0·02	0·33	0·65	$n_1 \ll n_2$ or n_3[a]
1-Thio-pentakis-OAc-β-D-Gp[b]	5·6	1·7	−12·4	0·00	0·43	0·57	$n_1 \sim 0\ n_2 > n_3$[b]
Pentakis-OAc-α-D-Manp[c]	5·0	2·3	−12·5	0·05	0·36	0·59	
Me-tetrakis-OAc-α-D-Manp[c]	5·0	2·5	−12·5	0·07	0·36	0·57	
Pentakis-OAc-β-D-Manp[c]	5·0	2·6	−12·1	0·09	0·36	0·55	
Me-tetrakis-OAc-β-D-Manp[c]	5·0	3·0	−12·0	0·14	0·36	0·50	
1-Thio-pentakis-OAc-β-D-Galp[b]	10·2	2·8	−11·0	0·91	0·09	0·00	$n_1 < n_2 n_3 \sim 0$[b]

[a]Ref. 31.
[b]Ref. 18.
[c]Ref. 19.

PMR spectroscopy. The spectra were recorded at 220 MHz with a Varian HR-220 spectrometer (TNO Central Laboratories, Delft, The Netherlands), operating in the field-sweep mode at a probe temp of 25°. Spectrum simulations were run on a 16 k Varian 620 i computer coupled with the XL-100 spectrometer using a slightly modified SIMEQ spin simulation program.[8] Chemical shifts are given relative to TMS (indirect to acetone-d_6; $\delta = 2{\cdot}05$ ppm) with an accuracy of about 0·005 ppm. The accuracy of the coupling constants is about 0·1 Hz. In the case of first-order analysis these accuracies are about 0·01 ppm and 0·2 Hz respectively.

Acknowledgements—Thanks are due to Dr. E. Talman and Mr. J. L. Hoogendoorn (TNO Central Laboratories, Delft, The Netherlands) for recording the 220 MHz spectra. This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

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