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P.M.R. STUDIES ON FULLY METHYLATED ALDOHEXOPYRANOSIDES AND THEIR 6-DEOXY ANALOGUES USING LANTHANIDE SHIFT REAGENTS*

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ABSTRACT

The complexes of lanthanide shift reagents (LSR) with permethylated aldohexopyranosides and their 6-deoxy analogues having the *gluco*, *galacto*, and *manno* configurations have been studied. On the basis of shift data from $Eu(fod)_3$ and $Pr(fod)_3$, and broadening data from $Gd(fod)_3$, it was found that the LSR bind preferentially to two neighbouring MeO-oxygens having the axial–equatorial relationship. Because of its steric requirements, the C-5 substituent hinders the binding increasingly in the following order: O-2(ax)–O-3(eq) < O-1(ax)–O-2(eq) < O-4(ax)–O-3(eq). Equatorial groups bind the LSR only weakly. Strong binding to O-6 was found when MeO-6 is predominantly "axially" oriented; when this group has the "equatorial" position, O-6 is not favoured over any other equatorial oxygen. In view of the preference of the LSR to bind to an O(ax)–O(eq) site, it is proposed that O-5 is involved in the binding to the axial O-6. $Eu(fod)_3$ seems to have less tendency to bind to the O-6(ax)–O-5 site than the other two LSR.

INTRODUCTION

The methoxyl signals in the p.m.r. spectra of fully methylated (PM) sugars form a characteristic pattern and are therefore useful in the identification of these compounds. Even for small quantities of PM-sugars, encountered for example in the methylation analysis of polysaccharides and many glycosides, these 3-proton singlets can readily be observed, the remaining signals being still hidden in the background noise of the spectrum. Two of the difficulties in using the MeO signals as a means of identification are (*a*) the narrow range in which they appear (normally within 0.3 p.p.m.) and (*b*) the assignment of the signals. As far as the second problem is concerned, the assignments can, in principle, be made by comparing the spectrum of the PM-sugar with spectra of partially deuteriomethylated analogues. In this way, the assignments have been made for several PM-aldohexopyranosides[1,2]. It was found that the MeO groups, as a consequence of differences in steric and electronic environ-

*Dedicated to the memory of Professor Edward J. Bourne.

ment, resonate in different regions of the spectrum. However, these regions overlap and, for assignment purposes, a modified approach, using lanthanide shift reagents (LSR), was explored.

Few such experiments have been carried out with compounds containing several functional groups of equal, intrinsic coordination capacity[3–7]. In a previous paper[8], however, experiments involving chemical shift measurements on PM-α-D- and -β-D-galactopyranoside complexed with EuIII and PrIII tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) [$Eu(fod)_3$ and $Pr(fod)_3$, respectively] were described and large differences in the complexing properties of these two sugar derivatives were found. In order to establish the factors which influence the binding of the LSR, we have studied the LSR complexes of a series of PM-aldohexopyranosides and their 6-deoxy analogues. If it were found that the binding of LSR to these compounds, in spite of their large number of functional groups, is still specific, it could be anticipated that such LSR experiments would be an aid in MeO-assignments of other PM-mono-, as well as higher, saccharides, and would yield information about the structure of these compounds in solution.

EXPERIMENTAL

Materials. — The monosaccharides used are commercially available. The lanthanide shift reagents $Eu(fod)_3$ and $Pr(fod)_3$ (both Merck), and $Gd(fod)_3$ (Nuclear Magnetic Resonance Ltd.), were stored over P_2O_5 before use. Chloroform-*d* (Merck) was dried over Linde Molecular Sieve type 3A.

Preparation of the methylated derivatives. — Permethylation was performed by the method of Kuhn *et al.*[9]. Purification and separation of the anomers was achieved by t.l.c. on silica gel plates (Merck) using benzene–methanol (96:4) for glucosides, quinovosides, mannosides, and rhamnosides, and hexane–acetone (3:2) for galactosides and fucosides. After spraying of the plates with 1% methanolic quercitin, the sugars were revealed under u.v. light. Extraction from the silica gel was performed with chloroform.

For the identification of the OMe-signals in the p.m.r. spectra of the permethylated (PM) sugars, partially deuteriomethylated analogues were prepared by perdeuteriomethylation (Kuhn method, with CD_3I) of partially methylated derivatives, which in turn were synthesised by methods described in the literature[1,10].

P.m.r. spectroscopy. — All the glassware used in the p.m.r. experiments was heated at 100° for at least 5 h, except for the p.m.r. tubes and syringes which were dried overnight in a vacuum oven at 50°. Samples of the sugar derivatives were dried by co-evaporation of moisture with benzene (three times) and subsequent storage of the compounds over P_2O_5. Filling of the p.m.r. tubes and the addition of LSR were carried out in a dry box containing dry nitrogen. Spectra of 0.1M solutions of the PM-sugars in $CDCl_3$ were recorded on a Varian XL-100 n.m.r. spectrometer, operating in the frequency-sweep mode, at a probe temperature of 35°. Chemical shifts are given relative to Me_4Si on the δ-scale, with an accuracy of 0.01 p.p.m.

TABLE I

CHEMICAL SHIFTS (δ, IN P.P.M.) OF THE MeO AND Me-5 GROUPS OF COMPOUNDS **1–12** IN $CDCl_3$

Per-O-methyl derivative of		*MeO-1*	*MeO-2*	*MeO-3*	*MeO-4*	*MeO-6*	*Me-5*
α-D-Glc*p*	**1**	3.43	3.52	3.64	3.55	3.43	—
α-D-Qui*p*	**2**	3.40	3.51	3.62	3.56	—	1.26
β-D-Glc*p*	**3**	3.54	3.58	3.64	3.54	3.42	—
β-D-Qui*p*	**4**	3.52	3.57	3.62	3.56	—	1.30
α-D-Gal*p*	**5**	3.41	3.51	3.51	3.57	3.40	—
α-L-Fuc*p*	**6**	3.41	3.53	3.53	3.61	—	1.28
β-D-Gal*p*	**7**	3.52	3.59	3.53	3.57	3.41	—
β-L-Fuc*p*	**8**	3.53	3.60	3.53	3.60	—	1.32
α-D-Man*p*	**9**	3.39	3.50	3.49	3.53	3.43	—
α-L-Rha*p*	**10**	3.37	3.50	3.50	3.56	—	1.30
β-D-Man*p*	**11**	3.50	3.63	3.53	3.53	3.42	—
β-L-Rha*p*	**12**	3.51	3.65	3.52	3.57	—	1.36

Table I lists the chemical shifts of all of the methyl groups in the compounds **1–12**. For the PM-aldohexopyranosides, assignments were made by comparing the spectra of the fully methylated compounds with those of partially deuteriomethylated analogues. Assignments for the 6-deoxyaldohexopyranosides were made by comparison with the corresponding PM-aldohexopyranosides; replacement of MeO by H at C-6 has practically no influence on the chemical shifts of the remaining MeO groups[2].

LSR experiments. — Known quantities of either $Eu(fod)_3$ or $Pr(fod)_3$ were added to 0.1M solutions of the PM-monosaccharides in $CDCl_3$ and the chemical shifts of MeO groups were recorded after each addition. Up to a molar ratio $X = 0.1$ (X = [LSR]/[sugar]), the LSR was added from a stock solution in $CDCl_3$ using a syringe. Beyond $X = 0.1$ (up to $X = 1$), the LSR was added as a solid powder.

For each compound, the chemical shifts of the MeO groups, and of Me-5 in the 6-deoxy analogues, were plotted against X. To make certain of the assignments, the experiments were, whenever necessary, repeated with partially deuteriomethylated analogues. As an example, the graphs obtained for compounds **1** and **11** are given in Fig. 1. With few exceptions, the MeO signals shift to lower fields with increasing amounts of $Eu(fod)_3$, whereas the opposite holds for $Pr(fod)_3$. Table II gives the shift gradients G (in p.p.m. for $X = 1$) as derived from the initial slopes of the curves relating chemical shifts to X. Broadening of the MeO signals was followed on adding the relaxation reagent $Gd(fod)_3$. Because of overlap of the MeO signals not only with each other, but also with the signals of the remaining protons, the broadenings could not be measured accurately and are given qualitatively in Table II. For comparison, the broadenings due to $Eu(fod)_3$ and $Pr(fod)_3$ were followed as well, at low concentration of LSR ($X < 0.1$). Because $Gd(fod)_3$ broadens the signals typically much more

TABLE II

SHIFT GRADIENTS G (IN P.P.M., FOR $X=1$) AND RELATIVE BROADENING[a] (BETWEEN PARENTHESES), INDUCED BY LSR, OF THE MeO AND C-5–CH_3 GROUPS OF THE COMPOUNDS **1–12**

Per-O-methyl derivative of	*LSR*	G-*values (in p.p.m.) and relative broadening* (+) *of:*					
		MeO-1	*MeO-2*	*MeO-3*	*MeO-4*	*MeO-6*	*Me-5*
α-D-Glc*p* (1)	$Eu(fod)_3$	4.2 (+++)	2.4 (++)	1.1	2.9 (+)	0.3	—
	$Pr(fod)_3$	−17.9 (+++)[b]	−12.1 (+++)	−0.8	−5.2	−15.8 (+++)[b]	—
	$Gd(fod)_3$	(+++)[b]	(+++)			(+++)[b]	—
α-D-Qui*p* (2)	$Eu(fod)_3$	15.1 (+++)	13.8 (+++)	0.2 (+)	4.3	—	8.4
	$Pr(fod)_3$	−41.0 (++++)	−40.0 (++++)	1.5	−3.6	—	−10.5
	$Gd(fod)_3$	(+++)	(+++)	(+)		—	
β-D-Glc*p* (3)	$Eu(fod)_3$	7.1 (+)	3.9	2.4	2.6	5.9 (+)	—
	$Pr(fod)_3$	−16.2 (+)	−6.2	−4.3	−5.1	−20.6 (++)	—
	$Gd(fod)_3$	(+)[b]				(++)	—
β-D-Qui*p* (4)	$Eu(fod)_3$	5.5	5.8	4.3	3.1	—	3.6
	$Pr(fod)_3$	−16.0 (+)	−15.4 (+)	−13.6 (+)	−8.7	—	−10.8
	$Gd(fod)_3$	(+)	(+)[b]	(+)		—	
α-D-Gal*p* (5)	$Eu(fod)_3$	8.6 (+++)	7.7 (+++)	0.5	3.3	1.8	—
	$Pr(fod)_3$	−20.7 (+++)	−10.5 (+++)	0.6	−3.3	−3.7	—
	$Gd(fod)_3$	(++)[b]	(++)[b]				—
α-L-Fuc*p* (6)	$Eu(fod)_3$	16.2 (+++)	14.4 (+++)	0.4	5.6 (+)	—	7.6 (+)
	$Pr(fod)_3$	−65.0 (++++)	−57.5 (++++)	7.0	−13.5 (+)	—	−17.5 (+)
	$Gd(fod)_3$	(+++)	(+++)[b]		(+)	—	(+)

TABLE II (*continued*)

Per-O-methyl derivative of	*LSR*	G-*values (in p.p.m.) and relative broadening* (+) *of:*					
		MeO-1	*MeO-2*	*MeO-3*	*MeO-4*	*MeO-6*	*Me-5*
β-D-Gal*p* (7)	$Eu(fod)_3$	2.7 (+)	5.0 (+)	3.8 (+)	1.3	2.8 (+)	—
	$Pr(fod)_3$	−9.0 (+)	−8.9 (+)	−7.5 (+)	−3.4	−9.0 (+)	—
	$Gd(fod)_3$	(+)	(+)	(+)		(+)	—
β-L-Fuc*p* (8)	$Eu(fod)_3$	8.3	10.5	3.8	2.5	—	3.6
	$Pr(fod)_3$	−21.0	−21.0	−10.5	−8.5	—	−7.5
	$Gd(fod)_3$					—	
α-D-Man*p* (9)	$Eu(fod)_3$	4.6 (+)	8.9 (+++)	6.3 (+++)	1.1	−0.5	—
	$Pr(fod)_3$	−4.6	−27.4 (+++)	−14.9 (+++)	−4.4	0.2	—
	$Gd(fod)_3$		(+++)[b]	(+++)[b]		(+)	—
α-L-Rha*p* (10)	$Eu(fod)_3$	5.7 (+)	13.3 (+++)[c]	11.0 (+++)[c]	0.6	—	5.3
	$Pr(fod)_3$	−6.3	−31.5 (+++)[c]	−28.3 (+++)[c]	1.8	—	−3.4
	$Gd(fod)_3$		(+++)[b]	(+++)[b]	(+)	—	
β-D-Man*p* (11)	$Eu(fod)_3$	−3.2 (++)	−9.4 (+++)	−3.4 (++)	4.2 (+)	1.9	—
	$Pr(fod)_3$	4.4 (++)	11.3 (+++)	4.0 (++)	−6.6 (+)	−2.5	—
	$Gd(fod)_3$	(++)	(+++)	(++)[b]	(+)[b]		—
β-L-Rha*p* (12)	$Eu(fod)_3$	−1.9 (+)[c]	−4.5 (++)	−2.8 (+)[c]	3.0 (+)	—	5.9 (++)
	$Pr(fod)_3$	4.8 (++)[b,c]	7.8 (+++)	5.3 (++)[b,c]	−6.0 (+)	—	−10.9 (+++)
	$Gd(fod)_3$	(+)	(++)	(+)		—	(++)

[a]Broadenings are given qualitatively: ++++, very strong; +++, strong; ++, moderate; and +, weak broadening; the remaining signals show no broadening at all. [b]Extent of broadening less certain, because of overlap of signals. [c]Assignments might be reversed.

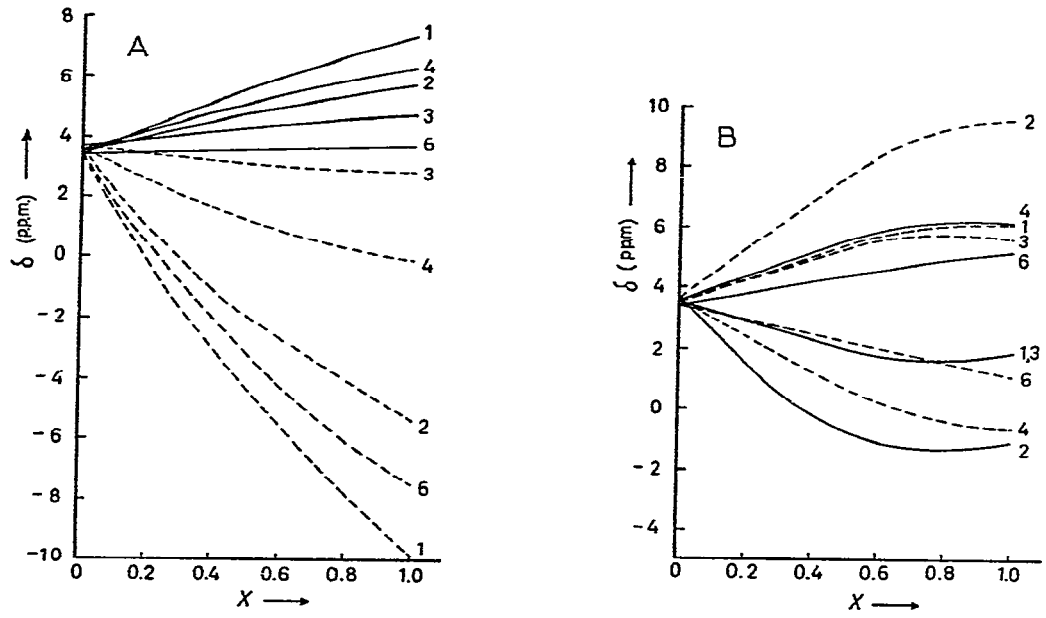

Fig. 1. Shifts of MeO-1,2,3,4,6 of PM-α-D-glucopyranoside **1** (*A*) and PM-β-D-mannopyranoside **11** (*B*), induced by Eu(fod)$_3$ (————) and Pr(fod)$_3$ (– – – –) (solvent $CDCl_3$, X = [LSR]/[sugar]).

than Pr(fod)$_3$, and Pr(fod)$_3$ more than Eu(fod)$_3$, the data were normalised, so as to be able to make comparisons between the LSR.

LSR-competition experiments. — Increasing amounts of Eu(fod)$_3$ were added to a mixture of equal amounts of PM-α-D-Glc*p* (**1**) and -β-D-Glc*p* (**3**) in $CDCl_3$ (total concentration of sugar derivatives, $[S]_{tot} = 0.2$M). The shift gradients of the MeO groups of **1** and **3** in the mixture (G_{mix}) were determined from the initial slopes of the graphs of the shifts versus the molar ratio X ($X = [Eu(fod)_3]/[S]_{tot}$). The experiment was repeated with Pr(fod)$_3$.

DISCUSSION

The structures of the sugar–LSR complexes

For the interpretation of the results of the LSR experiments in terms of structure of the sugar–LSR complexes, it must be kept in mind that the five MeO-oxygens and the ring-oxygen are all donor sites and that complexing can occur at more than one site. The observed LSR-induced shifts (LIS) are then the time-averaged sum of the contributions from complexing at different sites. Because the method[11] of separating such contributions is only applicable when the binding sites are far apart (which condition is not fulfilled in **1**–**12**), no attempt has been made to calculate the exact position(s) of the bound LSR on the basis of shift data. Furthermore, because of uncertainties about the position of the magnetic axis of the complex, qualitative use

only will be made of the McConnell–Robertson equation[12], $LIS = K(3\cos^2\theta - 1)/r^3$, where r is the distance between the lanthanide atom and the observed proton, and θ is the angle between the vector, along which r is measured, and the magnetic axis of the complex.

Caution is needed in applying the r^{-6} relationship[13] of the LSR-broadening data to obtain structural information; although this has been done[14] to locate the bound LSR, it has been shown recently[15] that such calculations are not rigidly valid. Only the relaxation reagents containing gadolinium give reliable results[15]; for this reason, $Gd(fod)_3$ was included in this series of experiments.

The information in Table II allows the following description of the complexes to be made.

LSR complexes with PM-D-glucopyranosides (**1** *and* **3**) *and PM-D-quinovopyranosides* (**2** *and* **4**)

The large shift-gradients (*G*-values), taken into consideration with the broadenings of MeO-1 and MeO-2 in PM-α-D-Glc*p* (**1**) and -α-D-Qui*p* (**2**), point to a preferred, bidentate* binding of the three LSR to O-1 and O-2 in these compounds. There is good overlap between the O-1 and O-2 lone-pairs and the lanthanide atom when the latter is located below the plane of the ring (Fig. 2). This conclusion is supported by the effects observed for MeO-3 in **1** and **2**. The small *G*-values of MeO-3 can be explained on the basis of values close to 55° for the angle θ in the McConnell–Robertson equation. For MeO-3 in **2**, a downfield shift is observed even with $Pr(fod)_3$ ($\theta > 55°$). Molecular models show that θ can reach these values when the lanthanide atom is in the position indicated (assuming that the magnetic axis of the complex points between O-1 and O-2).

A difference in effects of the three LSR on MeO-6 in **1** is observed. Whereas $Eu(fod)_3$ has practically no influence on the MeO-6 signal, $Pr(fod)_3$ causes a strong shift and both $Pr(fod)_3$ and $Gd(fod)_3$ give a considerable broadening of the signal. It seems that, in contrast to $Eu(fod)_3$, the other LSR bind strongly to O-6. In order to elucidate the mode of binding of the LSR to this site, it is necessary to consider the preferred conformation of the C-5–CH_2OMe groups in the different PM-aldohexopyranosides in detail.

The mole fractions n of the three staggered rotamers *a*, *b*, and *c* of the C-5–CH_2OMe group (Fig. 3) were calculated[16] (Table III) on the basis of the published[2] coupling constants $J_{5,6}$ and $J_{5,6'}$. Unfortunately, the data for PM-β-D-Gal*p* (**7**) are not known, but after comparison with the per-*O*-trimethylsilyl derivatives (Table IIIB), it can safely be assumed that the C-5 substituents in the α- and the β-D-galactose derivatives have the same conformational preferences. From Table IIIA, it can be inferred that the configuration at C-4 is the determining factor in the conformational preferences of the C-5–CH_2OMe group. For compounds (**1**, **3**, **9**, and **11**) having an

*It is not known whether the binding is truly bidentate or monodentate with rapid exchange between the two oxygens; this remark holds for all cases in which the term "bidentate" is used.

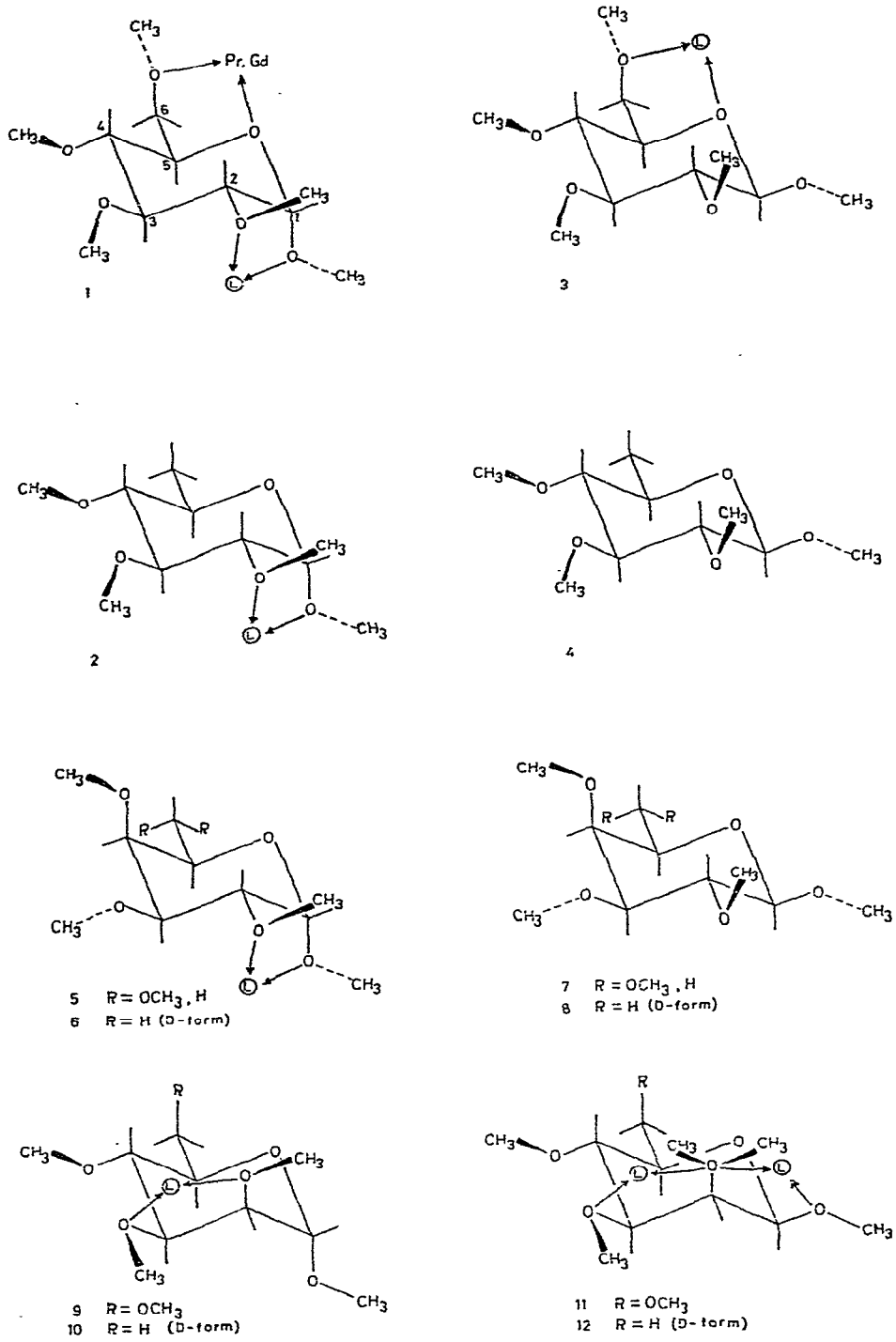

Fig. 2. Preferred binding-sites for the LSR (L) in compounds **1–12**; for explanation, see text. For **6, 8, 10,** and **12,** the D forms of the sugars are drawn-out for convenience. For **5** and **7,** *both* favoured rotamers of the C-5–CH_2OMe group, and for **11** and **12,** *both* favoured rotamers of MeO-2, are shown.

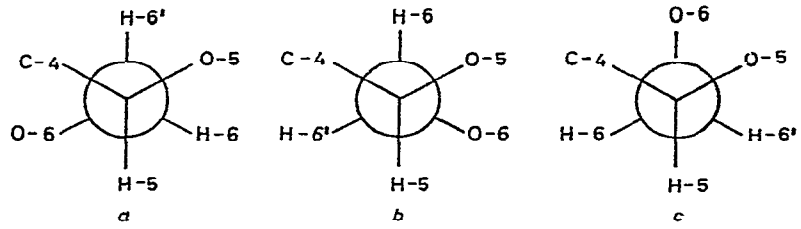

Fig. 3. The three staggered rotamers *a*, *b*, and *c* of the C-5–CH_2OMe group.

TABLE III

OBSERVED COUPLING CONSTANTS $J_{5,6}$ AND $J_{5,6'}$ OF PM-ALDOHEXOPYRANOSIDES[a] AND OF PER-*O*-TRIMETHYLSILYL-GALACTOPYRANOSIDES[b], AND CALCULATED[c] MOLE FRACTIONS (*n*) OF THE ROTAMERS *a*, *b*, AND *c* OF THE C-5-SUBSTITUENT

A. *Per*-O-*methyl derivative of*		$J_{5,6}$	$J_{5,6'}$	n_a	n_b	n_c
α-D-Glc*p*	1	3.4	3.4	0.17	0.17	0.66
β-D-Glc*p*	3	4.9	2.1	0.04	0.33	0.63
α-D-Gal*p*	5	6.0	6.7	0.52	0.43	0.05
β-D-Gal*p*	7	—[d]	—[d]	—	—	—
α-D-Man*p*	9	3.8	2.4	0.08	0.21	0.71
β-D-Man*p*	11	4.6	1.5	0.00	0.28	0.71
B. *Per*-O-*trimethylsilyl derivative of*						
α-D-Gal*p*		6.2	7.4	0.55	0.45	0.00
β-D-Gal*p*		5.0	7.5	0.61	0.34	0.05

[a] *J* values taken from Ref. 2; solvent, acetonitrile-d_3. [b] Values taken from Ref. 16; solvent, acetone-d_6. [c] See Ref. 16. [d] Values not known; H-5,6,6' form a complex multiplet.

equatorial MeO-4, the rotamer *c* is favoured, whereas both rotamers *a* and *b* are favoured* for those having an axial MeO-4 (**5** and **7**).

The binding of the $Pr(fod)_3$ and $Gd(fod)_3$ to the O-6 site in **1** is probably bidentate to O-6 and O-5, because, in the preferred conformation (Table IIIA), O-6 and O-5 have a gauche relationship similar to the axial–equatorial relationship between O-1 and O-2. The results for the galactosides **5** and **7** (see later) support such bidentate binding to O-6(ax)–O-5 in **1**.

For the preferred binding site(s) in PM-β-D-Glc*p* (**3**), three possibilities follow from Table II: O-1, O-6, or both O-1 and O-6. By inspection of the results for the 6-deoxy analogue **4**, it can be seen that the equatorial O-1 is not preferred over other equatorial methoxyl oxygens. MeO-1, -2, and -3 in **4** show about equal LIS and the

*For convenience, the position of O-6 will be denoted as "axial" when O-6 is anti to H-5 (rotamer *c*, Fig. 3) and as "equatorial" when O-6 is anti to O-5 or to C-4 (rotamers *a* and *b*, respectively).

same broadenings, which means that they have approximately equal affinities towards the LSR. (The disfavouring of MeO-4 is probably due to the steric hindrance of C-5–CH_3). Hence, O-6 is the preferred binding site in **3**, probably again in combination with O-5 (as in **1**), because in **3** the same orientation of MeO-6 is favoured (*cf.* Table III). The strong effects on MeO-1 are then caused by the proximity of the LSR bound to the O-6–O-5 site (Fig. 2).

Thus, the results for compounds **1–4** show that bidentate binding to two oxygens that have an axial–equatorial relationship, or its equivalent, is preferred over binding to equatorially oriented oxygens. Furthermore, it seems that $Eu(fod)_3$ binds more strongly to O-1(ax)–O-2(eq) than to O-6(ax)–O-5, whereas $Pr(fod)_3$ and $Gd(fod)_3$ have equal affinities towards these pairs of sites. More evidence for this can be found by means of a competition experiment[6] because, if this conclusion is valid, the difference between the equilibrium constants for PM-α-D-Glc*p* (**1**) and PM-β-D-Glc*p* (**3**) will be smaller for $Pr(fod)_3$ [and $Gd(fod)_3$] than for $Eu(fod)_3$. In Table IV, the results of the competition experiments are given. For $Eu(fod)_3$, it was found that the shift gradients for the five MeO groups of **1**, when mixed with equal amounts of **3** (G_{mix}-values in Table IV), are, on average, a factor of 2.0 larger than the values for **1** alone (G); for **3**, the G_{mix}-values are a factor 0.10 smaller than the G-values. Taking

TABLE IV

SHIFT GRADIENTS G (IN P.P.M., FOR $X = 1$) FOR MeO-1,2,3,4,6 OF **1** AND **3** IN COMPETITION EXPERIMENTS WITH $Eu(fod)_3$ (A) AND WITH $Pr(fod)_3$ (B). G_{mix} ARE THE VALUES WHEN LSR IS ADDED TO A MIXTURE OF EQUAL AMOUNTS OF **1** AND **3**, G ARE THE VALUES FOR **1** AND **3** SEPARATELY

A. *Eu(fod)*$_3$	*MeO-1*	*MeO-2*	*MeO-3*	*MeO-4*	*MeO-6*	
PM-α-D-Glc*p* (**1**)						
G_{mix}	8.3	4.8	2.3	5.9	0.6	
G^a	4.2	2.4	1.1	2.9	0.3	
G_{mix}/G	2.0	2.0	2.1	2.0	2.0	av. 2.0
PM-β-D-Glc*p* (**3**)						
G_{mix}	0.85	0.35	0.20	0.25	0.65	
G^a	7.1	3.9	2.4	2.6	5.9	
G_{mix}/G	0.12	0.09	0.08	0.10	0.11	av. 0.10
B. *Pr(fod)*$_3$						
PM-α-D-Glc*p* (**1**)						
G_{mix}	−28.1	−21.0	−1.3	−8.8	−23.1	
G^a	−17.9	−12.1	−0.8	−5.2	−15.8	
G_{mix}/G	1.6	1.7	1.6	1.7	1.5	av. 1.6
PM-β-D-Glc*p* (**3**)						
G_{mix}	−4.9	−1.9	−1.3	−1.4	−5.6	
G^a	−16.2	−6.2	−4.3	−5.1	−20.6	
G_{mix}/G	0.30	0.31	0.30	0.28	0.27	av. 0.29

[a]Values taken from Table II.

the ratio of these factors as an approximation to the ratio of the equilibrium constants[7], $K_{1,Eu(fod)_3}/K_{3,Eu(fod)_3} = 20$. Repeating the experiment with $Pr(fod)_3$ gives $K_{1,Pr(fod)_3}/K_{3,Pr(fod)_3} = 6$.

*LSR complexes with PM-*D*-galactopyranosides* (**5** *and* **7**) *and PM-*L*-fucopyranosides* (**6** *and* **8**)

As in **1** and **2**, the axial O-1 and equatorial O-2 form the preferred, bidentate-binding site for the three LSR in PM-α-D-Gal*p* (**5**)[8] and PM-α-L-Fuc*p* (**6**). For the β-forms **7**[8] and **8**, no such striking differences are found in the effects on MeO-1, -2, and -3; in particular, the lack of broadening shows that these equatorial MeO groups have a low affinity for binding LSR.

Although O-4 and O-3 have the axial–equatorial relationship in compounds **5–8**, O-4–O-3 is not a preferred binding-site. A probable explanation is found by considering the orientation of MeO-4. The O-4–CH_3 bond favours the parallel position with respect to the C-3–O-3 bond, because of the larger 1,3-parallel interaction between Me-4 and the C-5 substitutent ($\Delta G° = 5.5$ kcal/mol)[17] as compared to the 1,3-parallel interaction between Me-4 and O-3 ($\Delta G° = 2.5$ kcal/mole)[18]. (This holds for the PM-aldohexopyranosides as well as their 6-deoxy analogues). In this situation, the O-4 and O-3 lone-pairs cannot give a good overlap with the lanthanide atom.

MeO-6 is hardly influenced in **5** and **7**, indicating that O-6, which is orientated "equatorially" (Table III; rotamers *a* and *b* predominant), is not favoured over any other equatorial MeO group. On the other hand, an "axial" O-6 (as in **1** and **3**) has been shown to bind LSR strongly. These results support the view, expressed above, that O-5 is involved in the binding of the "axial" O-6.

*LSR complexes with PM-*D*-mannopyranosides* (**9** *and* **11**) *and PM-*L*-rhamnopyranosides* (**10** *and* **12**)

Predominantly, bidentate binding occurs at MeO-2 and MeO-3 in PM-α-D-Man*p* (**9**) and PM-α-L-Rha*p* (**10**), again at an axial and an equatorial oxygen. To have good overlap with the O-2 and O-3 lone-pairs, the bound lanthanide atom must be above the plane of the pyranose ring (Fig. 2). This is in agreement with the small *upfield* shift with $Eu(fod)_3$, and the small *downfield* shift with $Pr(fod)_3$, of MeO-6 in **9** (which is mainly "axial"); θ is larger than 55° for this position of the LSR. The broadening of MeO-6 by $Gd(fod)_3$ may be explained by proximity of the LSR bound to MeO-2 and MeO-3; broadening data from $Eu(fod)_3$ and $Pr(fod)_3$ are less reliable.

From the broadening data, which do coincide for the three LSR, it can be inferred that the LSR bind to the β-compounds **11** and **12** in the region MeO-1, -2, and -3. The lanthanide atom is, on the average, closest to MeO-2 and equidistant from the other two. However, these three methoxyl groups show upfield shifts with $Eu(fod)_3$ and downfield shifts with $Pr(fod)_3$. For compounds **1–10**, it has always been found that the MeO groups that are directly involved in the binding show shifts in the normal direction. A possible explanation for the abnormal shifts is that there is a

rapid exchange of the LSR between the two, equally favoured, binding sites: MeO-1(eq)–MeO-2(ax) and MeO-2(ax)–MeO-3(eq). In its average position, the LSR is then closer to the pyranose ring than in the case of binding to only one bidentate site; such a closer approach could produce values larger than 55° for the angles θ towards MeO-1, -2, and -3 and therefore give rise to the abnormal shifts of these methoxyl groups. The greater broadening of the Me-5 signal in **12** relative to **10** is in agreement with this closer approach to the ring.

CONCLUSIONS

The results for compounds **1–12** show that the complexing of LSR to PM-monosaccharides is almost exclusively governed by steric factors: bidentate binding to an axial and an equatorial methoxyl group is preferred over binding to equatorial groups (either mono- or bi-dentate). Differences in binding capacity of axial–equatorial sites are due to steric hindrance from neighbouring groups. In this respect, it is noteworthy that binding to the O-1(ax)–O-2(eq) site is strongly influenced by the presence or absence of MeO-6. The larger *G*-values for MeO-1 and MeO-2 in the 6-deoxy compounds **2** and **6**, compared with the values in **1** and **5**, indicate that the replacement of MeO-6 by H results in a decrease of θ or r, or both; in other words, a different position of the LSR, closer to the ring and/or closer to C-6. The effect is not so apparent for the O-2(ax)–O-3(eq) site because of the larger distance from this site to MeO-6 (*cf.* **9** and **10**).

It appears that no complex formation occurs when, in order to obtain that complex, the methyl groups must be forced into unfavourable interactions with neighbouring groups. The preferred conformations of the MeO groups, in the absence of LSR, can be determined on the basis of the experimental free-energy values[17,18] for gauche and 1,3-parallel interactions between these groups and neighbouring groups. It is found that, for an equatorial MeO group situated between two equatorial MeO groups, the differences in energy between the three staggered rotamers (around the C-OMe bond) are very small. Although the LSR might well be able to force the Me groups of neighbouring, equatorial MeO groups into positions away from the metal atom, no strong complexation is observed at such sites (see, for instance, compound **4**).

When an equatorial MeO group is situated between an axial and an equatorial one, the gauche position towards the axial neighbour is favoured (for instance, Me-2–O-2 in **1** gauche to C-2–H-2 and to C-2–C-1, Fig. 2). Complex formation then depends on the position of the Me-group of the axial MeO group. For instance, in the favoured position of MeO-1 in α compounds, Me is gauche to the ring oxygen (Fig. 2) and strong complexation occurs at the O-1(ax)–O-2(eq) site. This is also the case for the O-2(ax)–O-3(eq) site in **9** and **10**. On the other hand, no complex is formed at the O-4(ax)–O-3(eq) site in the galactosides and fucosides: to obtain this complex, Me-4 must be forced into the unfavourable 1,3-parallel interaction with the C-5 substituent.

In conclusion, the following sequence of preference for binding $Eu(fod)_3$ can be given: O-1(eq)–O-2(ax) ≈ O-2(ax)–O-3(eq) ≈ O-1(ax)–O-2(eq) > O-6(ax)–O-5 > O-1(eq) ≈ O-2(eq) ≈ O-3(eq) ≈ O-6(eq) > O-4 (either ax or eq). For $Pr(fod)_3$ and $Gd(fod)_3$, the sequence is much the same except that O-2(ax)–O-3(eq) > O-1(ax)–O-2(eq) ≈ O-6(ax)–O-5. An explanation for the difference in behaviour of the three LSR with respect to the binding to MeO-6 must await further study. A combination of factors is perhaps responsible for this effect, such as the change of ionic radii and coordination numbers throughout the lanthanide series (see also Ref. 5).

The binding of LSR to PM-sugars is sufficiently specific to give a good dispersion of the spectra. Furthermore, the observed regularities will help the MeO-assignments and structural studies of other PM-sugars, as is shown for PM-disaccharides[19].

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REFERENCES

1 D. GAGNAIRE AND L. ODIER, *Carbohyd. Res.*, 11 (1969) 33–41; E. B. RATHBONE AND A. M. STEPHEN, *Tetrahedron Lett.*, (1970) 1339–1342; E. B. RATHBONE, A. M. STEPHEN, AND K. G. R. PACHLER, *Carbohyd. Res.*, 20 (1971) 141–150.
2 J. HAVERKAMP, M. J. A. DE BIE AND J. F. G. VLIEGENTHART, *Carbohyd. Res.*, 39 (1975) 201–211.
3 B. C. MAYO, *Chem. Soc. Rev.*, 2 (1973) 49–74.
4 S. D. GERO, D. HORTON, A. M. SEPULCHRE, AND J. D. WANDER, *Tetrahedron*, 29 (1973) 2963–2972; G. E. WRIGHT AND T. Y. TANG WEI, *ibid.*, 29 (1973) 3775–3779; H. B. BORÉN, P. J. GAREGG, Å. PILOTTI, AND C.-G. SWAHN, *Acta Chem. Scand.*, 26 (1972) 3261–3268; N. PLATZER, C. LANG, J. J. BASSELIER, AND P. DEMERSEMAN, *Bull. Soc. Chim. Fr.*, (1975) 227–232.
5 I. ARMITAGE AND L. D. HALL, *Can. J. Chem.*, 49 (1971) 2770–2776.
6 H. HART AND G. M. LOVE, *Tetrahedron Lett.*, (1971) 625–628.
7 J. K. M. SANDERS, S. W. HANSON, AND D. H. WILLIAMS, *J. Amer. Chem. Soc.*, 94 (1972) 5325–5335.
8 E. B. RATHBONE AND A. M. STEPHEN, *Carbohyd. Res.*, 39 (1975) 136–140.
9 R. KUHN, H. TRISCHMANN, AND I. LÖW, *Angew. Chem.*, 67 (1955) 32.
10 E. G. GROS, *Carbohyd. Res.*, 2 (1966) 56–62; P. BRIGL AND H. GRÜNER, *Ber.*, 65 (1932) 1428–1434; G. O. ASPINALL AND G. ZWEIFEL, *J. Chem. Soc.*, (1957) 2271–2278.
11 C. C. HINCKLEY, M. R. KLOTZ, AND F. PATIL, *J. Amer. Chem. Soc.*, 93 (1971) 2417–2420.
12 H. M. MCCONNELL AND R. E. ROBERTSON, *J. Chem. Phys.*, 29 (1958) 1361–1365.
13 H. STERNLICHT, *J. Chem. Phys.*, 42 (1965) 2250–2251.
14 J. REUBEN AND J. S. LEIGH, JR., *J. Amer. Chem. Soc.*, 94 (1972) 2789–2793.
15 G. N. LA MAR AND E. A. METZ, *J. Amer. Chem. Soc.*, 96 (1974) 5611–5613.
16 D. G. STREEFKERK, M. J. A. DE BIE, AND J. F. G. VLIEGENTHART, *Tetrahedron*, 29 (1973) 833–844.
17 E. L. ELIEL, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, p. 213 *et seq.*
18 J. F. STODDART, *Stereochemistry of Carbohydrates*, Wiley Interscience, New York, 1971, p. 67 *et seq.*
19 D. G. STREEFKERK AND A. M. STEPHEN, unpublished data.