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QUANTITATIVE TREATMENT OF LANTHANIDE-INDUCED SHIFTS FOR SOME CARBOHYDRATE SYSTEMS WHERE CHELATION IS OBSERVED

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ABSTRACT

An approximate model (D) for the calculation of lanthanide-induced shifts for some *trans*-fused benzylidene acetals which chelate to shift reagents is described. Shifts calculated for the model system 4,5-dimethylveratrole using model D were in good agreement with the reported data. With the aid of model D, rotamer conformations of the methoxyl group on C-1 of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside, methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside, and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside were investigated.

INTRODUCTION

In general, the interpretation of lanthanide-induced n.m.r. shifts (LIS) for systems with one dominant donor site is straightforward, and good agreement with predictions based on the simple form of the McConnell–Robertson relationship have been found for a wide range of substrate molecules[1-5]. Suitable carbohydrate-systems are no exception, and quantitative treatments have been given with the hydroxyl as the unique donor-group[1,6]. However, some *trans*-fused benzylidene acetals that were thought initially to possess a single, dominant donor-site gave shift data that could not be fitted to the simple, single-site model. We now report that chelate effects are important and describe an approximate method for their treatment.

RESULTS AND DISCUSSION

^{1}H-N.m.r. shifts induced in the spectrum of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside[7] (2) are given in Table I. Attempts to fit these data to a simple model (A) were not successful. The models used in this work are described below.

Model A, with the magnetic axis coincident with the europium–oxygen bond and with axial symmetry in the Eu(fod)$_3$–substrate adduct, gave a best fit which placed the Eu atom at the unrealistic distance of 5.03 Å from the co-ordinating oxygen (Table II).

TABLE I

OBSERVED, ^{1}H, RELATIVE SHIFT-GRADIENTS[a] (G) FOR COMPOUNDS 2–8

Proton	**2**	**2'**	**3**	**4**	**5**	**6**	**7**	**8**
H-1	10 08	9 47	6 46	6 36	10 54	2 47	17 76	15 39
H-2	24 28	21 95	16 11	16 64	—	5 44	—	—
H-3	17 88	17 10	11 75	11 95	—	10 17	—	—
H-4	20 28	17 21	13 98	15 44	—	9 06	—	—
H-6*a*	3 06	2 14	1 75	2 72	2 56	2 86	—	4 28
H-6*e*	3 64	2 44	2 33	2 86	3 01	1 90	3 80	5 00
H-7	—	—	—	—	−1 47	4 06	2 80	2 14
MeO-1	4 06	3 64	2 55	2 44	3 60	0 76	8 06	6 67[b]
MeO-2	—	—	—	—	5 74	—	6 10	—
MeO-3	12 08	6 46	—	—	12 16	—	−0 08	12 50[b]
PhCH$_2$	—	—	10 11	—	—	2 42	—	—

[a] P p m per mol of Eu(fod)$_3$ per mol of substrate, except for **2'**, where the shift reagent was Eu(dpm)$_3$ (**2'** shift gradients scaled to **2** values for comparison) [b] May be interchanged

It is well established[8 9] that methyl glycosides and cyclitols which contain three vicinal *cis*-hydroxyl groups exhibit tridentate chelation to a variety of aqua-metal cations including lanthanides Bidentate chelation, involving conventional shift-reagents, *e g* , Eu(fod)$_3$, by methoxyl and hydroxyl groups in substituted cyclohexanols[10], by carbonyl and methoxyl groups in 3-methoxycycloalkanones[11], and by methoxyl groups in di- and tri-substituted benzenes has been reported[12 13] Some of the latter, however, gave data more typical of a contact interaction than a dipolar one. Recently, it has been reported that fully methylated aldohexopyranosides gave unexpectedly large shifts for their methoxyl resonances only when either two or three vicinal *cis*-methoxyl groups were present[14] Although few of these reports involved a quantitative interpretation of LIS data, it must be concluded that **2** is a likely candidate for chelation, since it contains vicinal, *cis* hydroxyl and methoxyl groups

Two of the basic methods which have been used to treat chelating systems[13] are briefly described as models B and C For model B, an axially symmetric, susceptibility tensor is assumed, and the magnetic axis adopts an averaged position (in systems with symmetry $\geqslant C_{2v}$, the effective magnetic axis will lie along the symmetry axis) For model C, a non-axial susceptibility tensor is assumed (Eq *1*), and the orientation of the tensor components is determined either by symmetry or by experiment The induced pseudo-contact or dipolar shift, Δ_i, is given by Eq. *1*

$$\Delta_i = k\left[(X_{zz} - \bar{X})\frac{(3\cos^2\theta_i - 1)}{r_i^3} + (X_{xx} - X_{yy})\frac{(\sin^2\theta_i\cos 2\phi_i)}{r_i^3}\right] \qquad (1)$$

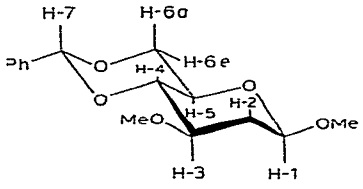
Model B involves only the first part of Eq *1*, whereas model C involves the full equation

TABLE II

CALCULATED, ^{1}H RELATIVE SHIFT-GRADIENTS FOR MODELS A, B, AND D FOR COMPOUNDS 2–4,6

Model		*Proton*	2	2′	3	4	6
A		H-1	9 54	8 14	6 27		3 03
		H-2	24 45	22 32	16 21		5 69
		H-3	17 83	16 83	11 57		10 12
		H-4	20 26	17 54	14 05		8 86
		H-6*a*	4 21	3 19	2 49		2 30
		H-6*e*	2 77	1 94	1 55		1 64
		H-7	—	—	—		4 26
	rLn O-2 (Å)		5 03	4 85	4 84		—
	rLn O-3 (Å)		—	—	—		4 9
	R		4 08	5 42	4 39		5 8
B		H-1	9 45	8 18	6 59	6 24	2 47
		H-2	24 46	22 95	16 20	17 20	5 44
		H-3	17 88	17 10	11 75	11 95	10 17
		H-4	20 27	16 95	13 88	15 37	9 06
		H-6*a*	3 30	2 82	1 70	3 45	2 81
		H-6*e*	3 36	3 01	2 28	2 88	1 95
		H-7	—	—	—	—	4 06
	rLn O-2 (Å)		4 96	4 59	3 90	3 61	5 87
	rLn O-3 (Å)		5 41	4 70	3 29	4 00	3 77
	R		1 98	5 48	0 79	3 48	0 45
D		H-1	9 70	8 86	6 54	6 77	2 98
		H-2	24 42	22 16	16 08	16 52	5 71
		H-3	17 97	16 76	11 87	13 34	10 40
		H-4	20 26	17 64	13 90	15 11	8 39
		H-6*a*	3 13	2 04	1 80	2 83	2 49
		H-6*e*	3 37	2 71	2 11	2 64	1 72
		H-7	—	—	—	—	4 50
	rLn O-2 (Å)		2 96	2 92	3 05	3 39	7 60
	rLn O-3 (Å)		3 17	3 05	3 26	3 36	4 90
	rLn O-4 (Å)		4 69	4 51	4 69	5 01	—
	R		1 32	2 61	1 11	2 66	6 93

The most detailed studies of chelating systems involve rigid substrates having C_{2v} symmetry For example, De Boer *et al*[13] examined 4,5-dimethylveratrole (DMV) (Fig 1) and concluded that only the full, non-axial model C gave reasonable results Attempts to fit shift data for **2** to model B were not successful The best R-value was obtained with unreasonably long lanthanide–oxygen distances and with magnetic-axis orientation that did not even intersect the substrate molecule It is interesting that similar results with long lanthanide–oxygen distances were obtained by De Boer when model B was used for DMV To test our use of model B, the previously published data[6] for methyl 4,6-*O*-benzylidene-3-*O*-methyl-*β*-D-glucopyranoside (**1**) were repeated by using model B instead of A An almost identical lanthanide position was obtained using model B, and the magnetic axis deviated from the lanthanide–oxygen bond by less than 2°. In going from model A to model C, the number of unknown parameters increases from four to eight. On the basis of ^{1}H data alone, it would not be possible to use model C in the systems studied here as, in general, there are less than seven hydrogen atoms for which shift data can be obtained Inclusion of ^{13}C LIS-data might solve this problem, but large amounts of sample would be required, and a method for the extraction of contact contributions to the LIS would probably be necessary[13] It would, therefore, be useful if some approximate method for treating chelating systems could be devised which would require fewer unknown parameters These considerations led to model D



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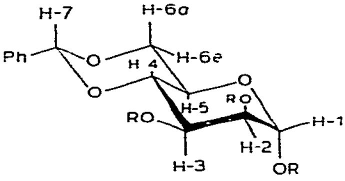
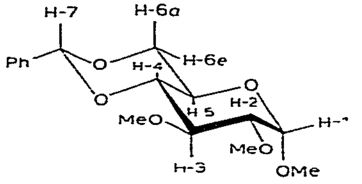


2 R = R″ = Me R = H
3 R = Bzl R = Me R = H
4 R = R = H R″ = Me
5 R = R = R″ = Me
6 R = H R′ = Bzl R = Me



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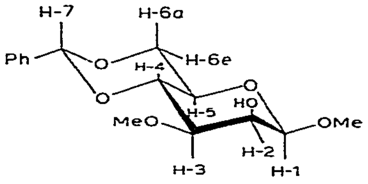

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Model D involves alternate co-ordination and magnetic-axis generation by each of the ligating atoms, axial symmetry about each lanthanide–oxygen bond, and only four unknown parameters When model D was applied to the shift data for **2**, the reasonable fit described in Table II resulted Shift data obtained using Eu(dpm)$_3$ could be used to define an almost identical position for the lanthanide The close correspondence of Eu(fod)$_3$ and Eu(dpm)$_3$ data suggests that the observed ^{1}H-shifts do not contain large contact contributions[15]. Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[7] (**3**) and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[16] (**4**) also gave very reasonable results with model D The apparent position of the lanthanide was predicted to be approximately the same for **2**–**4** In an effort to confirm this prediction, line-broadening studies of lanthanide location using Gd(fod)$_3$ were carried out[4,17] It was possible to measure only approximate line-broadening data for **2** This was as follows MeO-3 $\gg$ H-7 $\sim$ H-1 $\gg$ MeO-1 Calculated line-broadening

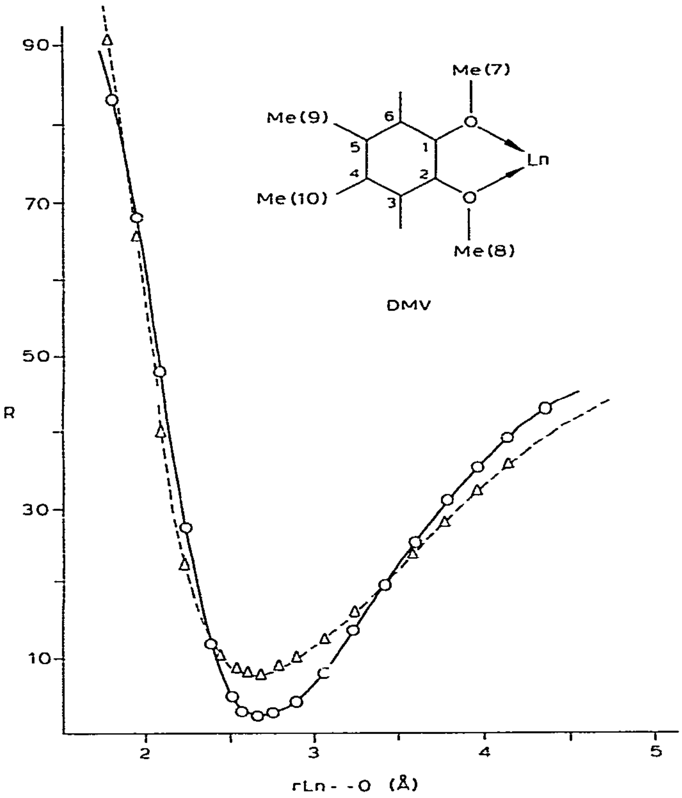

Fig 1 Plot of R *vs* the lanthanide-oxygen distance for DMV and model D —○— ^1H data —△—, ^1H and ^{13}C data

ratios were 10 0 1 0 0 9 0 012, and are in good agreement with experimental data. A common feature of these glycosides is the presence of an axial hydroxyl group at C-2 Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[18] (**6**), which has HO-3 *cis* to BzlO-2, gave poor results for models A, B, and D (Table II) The observed shift gradients for **6** are lower than those for **2**–**4**, whereas the H-7 shift is much larger, suggesting either a different position for the lanthanide or a different mode of binding in the **6**–Eu(fod)$_3$ adduct For the fully substituted methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-mannopyranoside[19] (**5**) and methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside[20] (**7**), which, on the basis of closely related results[14], would be expected to chelate to Eu(fod)$_3$, very severe line-broadening was observed and only limited shift-data could be obtained (Table I) Similar line-broadening problems were also encountered using Pr(fod)$_3$ The origin of this unexpectedly severe line-broadening is not clear and insufficient shift data were available for lanthanide location The limited shift-data for **5** are comparable to those obtained for **2** and suggest that similar chelation is occurring Qualitative results for line broadening (MeO-3 $\sim$ MeO-2 $\gg$ H-7 $\sim$ H-1 $\gg$ MeO-1) with Gd(fod)$_3$ also support this position

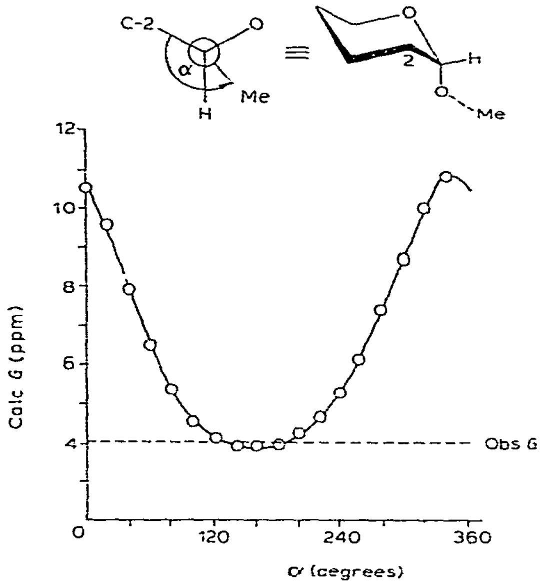

Fig 2 Plot of MeO-1 conformation vs calculated shift-gradients for compound 2

for Eu The shift data for compound **7** and line-broadening results [Gd(fod)$_3$ MeO-1 ~ MeO-2 > H-1 ~ H-2 > MeO-3] are as expected for chelation of the shift reagent by MeO-1 and MeO-2 Unfortunately, satisfactory shift-data could not be obtained for methyl 4.6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside[21] (**8**), which has two chelating-sites Most of the protons in this molecule appear to have similar shift-gradients, since they were not resolved on addition of Eu(fod)$_3$

In exploring the usefulness of model D, attempts were made to define the conformation of the methoxyl group on C-1 of **2**–**4** For each compound, the twist angle (α) of the OMe bond relative to a reference plane was used to define a set of possible positions for the methyl group A plot of calculated shift-gradients against α gave U-shaped curves with well-defined minima (Fig 2) In each case, the experimentally observed shift-gradient was close to the minimum point in the curve (α +160°) This conformation with the methyl group *gauche* to both the ring oxygen and H-1 is reasonable, and agrees with that expected on the basis of steric considerations, the *exo*-anomeric effect, and crystal-structure data for related systems[22].

Model D was also applied to the model-system DMV examined by De Boer *et al*[13]. Using reported shift-data the results illustrated in Fig 1 were obtained, the agreement between observed and calculated shift-data was quite good As found by De Boer, it was necessary to use a multipoint model rather than a simple, averaged position for the methoxyl hydrogens to obtain these results The best-fit, apparent distance was not altered when reported ^{13}C-LIS were included The lanthanide–oxygen distance (2 6 Å) is longer than that (2 1 ±0 3 Å) reported for DMV and model C. but is still a reasonable value

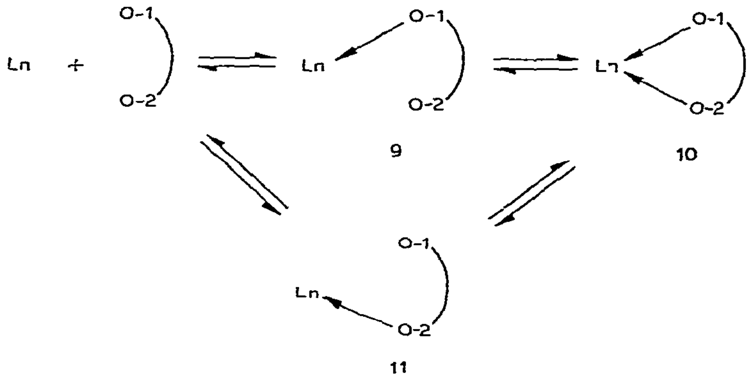

Fig 3 Chelation scheme

CONCLUSION

Thus, trans-fused benzylidene acetals having a cis-arrangement of potential donor groups can chelate to lanthanide shift-reagents, and a simple, approximate model can be used to determine rotamer conformations

It is interesting to consider why model D gives reasonable results The superposition of two, distinct, axial models could give a non-axial, overall effect and perhaps approximate the non-axial model C An alternative, although possibly less-likely, explanation is illustrated in Fig 3 A bidentate chelate (**10**) would form stepwise as illustrated If, for steric reasons, effective, simultaneous binding by both oxygens was not possible, considerable importance would attach to **9** and **11** Rotamer averaging in **9** and **11** could then generate two axially symmetric, magnetic axes whose effect would be additive An approach of this type is normal for a pair of remote binding-sites, where it has been found that contributions to the experimental LIS, due to independent co-ordination of the functional groups, are additive[23-26]

EXPERIMENTAL

Calculations using model A were made by the grid-search procedure[6] Variable magnetic-axis results (model B) were obtained by using LISCA[27] For model D, each point in a grid-search procedure has two calculated-shift contributions (one from each magnetic axis) These were added with equal weights, and scaled to experimental shift-gradients The best fit was that which had the lowest R-factor

$$R = \left[\frac{\sum_{i}(G_{\mathrm{calc}_i} - G_{\mathrm{obs}_i})^2}{\sum_{i}(G_{\mathrm{obs}_i})^2}\right]^{0\,5} \times 100$$

When an extra variable was included to allow for unequal contributions from each magnetic axis, the best fit was that which had equal contributions

^{1}H-N m r spectra (100 MHz) were recorded for solutions in CDCl$_3$ with a JEOL MH-100 spectrometer Appropriate quantities of shift reagent were added to sample solutions, and spectra were recorded after each addition Good straight-line plots of induced shift vs the molar ratio of shift reagent to substrate were obtained for all of the compounds studied

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