Complexes of Carbohydrates with Metal Cations. VII* Lanthanide-Induced Shifts in the P.M.R. Spectra of Cyclitols

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Abstract

Addition of lanthanide ions to *epi*-inositol and related compounds in aqueous solution causes shifts in their p.m.r. spectra which are interpreted as being due to diamagnetic, pseudocontact, and contact interactions. The contact interactions show stereospecificity: they are greatest when the bonds connecting the protons to the cation form a planar zig-zag arrangement.

In Part IV of this series¹ we have shown that cyclitols which have a sequence of an axial, an equatorial and an axial hydroxyl group form complexes with metal cations in aqueous solution. Of all the cations investigated, lanthanum(III) forms the most stable complexes.² Since other lanthanides have chemical properties similar to, and ionic radii only slightly smaller than, those of lanthanum itself, it was expected that all the lanthanide ions would readily form complexes with suitable cyclitols. The point of interest lies in the fact that all the lanthanide(III) ions (other than lanthanum itself) are paramagnetic and will have a perturbing effect³ on the n.m.r. spectra of cyclitols with which they form complexes.

Complexes of lanthanides with diketones are now widely used in organic solvents as 'shift reagents'. Lanthanide salts (nitrates or perchlorates) in water or in polar organic solvents have had only limited use^{4-10} and it was found that in carboxylate

* Part VI, Carbohydr. Res., 1975, 45, 73.

¹ Angyal, S. J., and Hickman, R. J., Aust. J. Chem., 1975, 28, 1279.

² Angyal, S. J., Aust. J. Chem., 1972, 25, 1957.

³ Phillips, W. D., Looney, C. E., and Ikeda, C. K., J. Chem. Phys., 1975, 27, 1435.

⁴ Reyes-Zamora, C., and Tsai, C. S., *Chem. Commun.*, 1971, 1047; Grasdalen, H., Anthonsen, T., Larsen, B., and Smidsrød, O., *Acta Chem. Scand.*, Ser. B, 1975, **29**, 17, 99.

⁵ Angyal, S. J., Greeves, D., and Mills, J. A., Aust. J. Chem., 1974, 27, 1447; Kieboom, A. P. G., Spoormaker, T., Sinnema, A., Toorn, J. M. van der, and Bekkum, H. van, Recl Trav. Chim. Pays-Bas, 1975, 94, 53.

⁶ Sanders, J. K. M., and Williams, D. H., *Tetrahedron Lett.*, 1971, 2813; Hart, F. A., Moss, G. P., and Staniforth, M. L., *Tetrahedron Lett.*, 1971, 3389; Sherry, A. D., Yoshida, C., Birnbaum, E. R., and Darnall, D. W., *J. Am. Chem. Soc.*, 1973, **95**, 3011; Bayer, E., and Beyer, K., *Tetrahedron Lett.*, 1973, 1209; Anteunis, M., and Gelan, J., *J. Am. Chem. Soc.*, 1973, **95**, 6502; Gorin, P. A. J., and Mazurek, M., *Can. J. Chem.*, 1974, **52**, 3070.

⁷ Angyal, S. J., Carbohydr. Res., 1973, 26, 271.

⁸ Angyal, S. J., Greeves, D., and Pickles, V. A., Carbohydr. Res., 1974, 35, 165.

⁹ Barry, C. D., North, A. C. T., Glasel, J. A., Williams, R. J. P., and Xavier, A. V., Nature, 1971, 232, 236.

¹⁰ Levine, B. A., Thornton, J. M., and Williams, R. J. P., J. Chem. Soc., Chem. Commun., 1974, 669.

and phosphate anions they cause shifts in a direction opposite to that caused by the 'shift reagents'.⁶ The possible reasons for this change in direction have been discussed¹¹ but are not fully understood.

Addition of europium or praseodymium salts to aqueous (D_2O) solutions of a complexing carbohydrate causes substantial shifts of the signals in the p.m.r. spectrum. In all cases some of the induced shifts are upfield and some downfield; they appeared to show no recognizable regularity although they proved useful in some cases for the analysis of n.m.r. spectra.^{5,7} In order to understand the nature of the shifts the effect of every lanthanide ion on the spectrum of a model compound was determined.



epi-Inositol (1) was chosen as the model compound because it is readily synthesized,¹² complexes well,¹ and each of its four ring proton signals is recognizable by its size and shape no matter where it is shifted to.¹ The results¹³ are shown in Table 1.

Table 1	. Lant	hanide-ind	duced	chem	ical s	shifts	(ppm) i	in the	p.m.r.		
spectrum of <i>epi</i> -inositol (1)											
Positive	values	indicate	down	field	shifts	· r.	crystal	ionic	radius		

1 00101.0				-1, •1,50001 10	
Cation	r_{i} (Å)	H 1,5	H 2,4	H3	H6
La ^{3 +}	1.016	0.17	0.27	0.55	0.07
Ce ³⁺	1.034	-0.4	-0.7	0.8	-1.05
Pr ³⁺	1.013	-1.05	-2.05	2.05	-3.5
Nd ³⁺	0.995	0.3	$-1 \cdot 10$	6.1	-1.65
Sm ^{3 +}	0.964	-0.05	0.15	0.3	-0.3
Eu ³⁺	0.950	-0.35	1.6	-7.2	1.65
Tb ³⁺	0.923	18	- 19	-35	-19
Dy ³⁺	0.908	-21	-21	-24	-26
Ho ³⁺	0.894	8	-5	12	-15
Er ^{3 +}	0.881	0.5	$2 \cdot 1$	$-3 \cdot 4$	3.7
Tm ³⁺	0.87	-4.5	-10	-16	5.7
Yb ³⁺	0.858	-0.25	-2.05	$-4 \cdot 8$	4.45
Lu ^{3 +}	0.85	0.16	0.23	0.50	0.06

¹¹ Sanders, J. K. M., Hanson, S. W., and Williams, D. H., J. Am. Chem. Soc., 1972, 94, 5325. ¹² Posternak, T., Helv. Chim. Acta, 1936, 19, 1333.

¹³ Preliminary communication: Angyal, S. J., Greeves, D., and Pickles, V. A., J. Chem. Soc., Chem. Commun., 1974, 589.

Increasing amounts of lanthanide salts (chloride or nitrate) were added to 0.3-0.5 M solutions of *epi*-inositol in deuterium oxide and the induced shifts were determined. The conditions of the experiment varied widely from metal to metal. Smooth plots of shift against equivalents were obtained for Eu, Pr and Yb; however, these curves do not allow satisfactory extrapolation to complete complexing. These metals were used in concentrations up to 0.4 M. The other lanthanide ions cause broadening which limits their useful concentration: Ce, Nd and Sm were used up to 0.04 M, Er and Tm up to 0.02 M but the other ions only up to 0.002 M. Gadolinium, which is used as a broadening probe,⁹ broadened the signals so severely even at 0.0003 M concentration that it was not possible to observe whether it caused any induced shift.

In order to express the shifts induced by the various lanthanides in a comparable way, the limiting shifts (i.e., those at complete complexing) were calculated on the assumption that 1:1 complexes were formed with a stability constant of 10 mol^{-1} l. This is the approximate value for lanthanum(III) complexed to an ax-eq-ax sequence of hydroxyl groups;² but this value is probably too large for some of the lanthanide ions. The stability constant generally decreases as the ionic radius becomes smaller; lutetium(III) has $K \approx 2 \text{ mol}^{-1}$ l.* It is most likely that the K values decrease from cerium(III) to ytterbium(III) but the value of 10 was used in all the calculations for lack of accurate data. Hence the values of induced shifts in the lower half of Table 1 are probably too small; the relative shifts of the protons in each complex are significant but the absolute values are subject to uncertainty.

The effect of lanthanide ions on the n.m.r. spectrum of 2-C-methyl-epi-inositol¹⁴ (2) is shown in Table 2. The shifts of the ring protons are similar to those of epi-inositol; the signal of the methyl group provides additional information on the mechanism of the lanthanide-induced shift changes.

or z-c-methyl-ept-mositor (z)									
Cation	H1	Н5	H4	Н3	H6	Me			
La ³⁺	0.23	0.18	0.29	0.58	0.12	0.16			
Pr ³⁺	-1.00	-0.8	-1.10	2.8	-3.7	-0.5			
Eu ^{3 +}	-0.5	-0.5	1.45	-9.2	2.3	0.3			

Table 2.	Lanthanide-induced	chemical	shifts	(ppm)	in	the	p.m.r.	spectrum
	of 2-0	C-methyl-e	<i>pi</i> -inos	itol (2)				

The Mechanism of Shift Changes

It appears unlikely that any single mechanism could explain the variety in magnitude and sign of the shifts caused by the various lanthanides in the spectra of polyols. The conventional complex shift reagents, used in organic solvents, are believed to act mainly by pseudocontact interactions.¹¹ There is, however, evidence of contact interactions at the nuclei closest (along bonds) to the complexing site,¹⁵ particularly in ¹³C

* This value was determined for the complexing of α -D-allopyranose with lutetium chloride by the method described in ref. 2. Attempts to determine the *K* values of some lanthanides by this method were unsuccessful. To obtain significant values of the α : β ratio of the allopyranoses, a high concentration of cations is required; at such concentrations the paramagnetic cations cause so much shift and broadening of the signals that the error in the determination of the α : β ratio becomes large.

¹⁴ Angyal, S. J., Klavins, J. E., and Mills, J. A., Aust. J. Chem., 1974, 27, 1075.

¹⁵ Hawkes, G. E., Leibfritz, D., Roberts, D. W., and Roberts, J. D., *J. Am. Chem. Soc.*, 1973, **95**, 1659; Hawkes, G. E., Marzin, C., Johns, S. R., and Roberts, J. D., *J. Am. Chem. Soc.*, 1973, **95**, 1661; ApSimon, J. W., Beierbeck, H., and Saunders, J. K., *Can. J. Chem.*, 1973, **51**, 3874.

spectra. The pseudocontact shifts are downfield with europium and upfield with praseodymium shift reagents, with the exception of rare cases in which the proton lanthanide vector subtends a large angle with the principal magnetic axis.¹¹ In pseudo-contact interactions the ratio of the induced shifts within a molecule is independent of the nature of the lanthanide.¹⁶ The shifts observed in the spectra of *epi*-inositol are clearly not explainable by pseudocontact interactions alone.

It is now proposed that the observed shifts are due to three different mechanisms: through diamagnetic, pseudocontact and contact interactions. Investigations on complexes of some sugar derivatives, reported in the following paper,¹⁷ support this proposal.

(i) The diamagnetic effect, always downfield, is caused by the positive charge of the cation.¹ Its magnitude should be independent of the nature of the cation (provided that the charge is the same); indeed, lanthanum(III) and lutetium(III) cause similar shifts. It can therefore be assumed that these values represent the diamagnetic component of the shifts induced by all the lanthanides; to obtain the paramagnetic effects, these values should be subtracted from the observed data.¹⁸

(ii) The pseudocontact or dipolar interaction operates through space, whereas the contact interaction is transmitted through bonds. In the molecule of *epi*-inositol, H6 is connected through the largest number of bonds to the cation but is not far away through space. Inspection of Table 1 shows that the induced shifts of H6 with different metals are of the same sign and relative magnitude as those observed in other cases attributed to pseudocontact interaction.¹⁶ The signal of the methyl hydrogen atoms in the spectrum of 2-*C*-methyl-*epi*-inositol also shifts in the same direction. Hence it is assumed that in the spectrum of *epi*-inositol the induced shifts of H6 are caused predominantly by pseudocontact interaction.

	-				
Cation	H 1,5	Н 2,4	H 3	H6	OMe
Pr ³⁺	-0.45	-0.7	1.35	-1.3	-0.25
Eu ^{3 +}	-0.55	0.65	-5.8	1.3	0.2
Yb ³⁺	-0.4	-1.5	-3.0	2.05	0.4

Table 3.	Lanthanide-induced	chemical	shifts	(ppm)	in	the	p.m.r.
	spectrum of 6-	O-methyl	- <i>epi</i> -inc	ositol			

To confirm this conclusion, 6-O-methyl-*epi*-inositol was synthesized and its spectrum investigated. In this compound the methyl group is so many bonds away from the coordinating site that any contact interaction seems most unlikely. The induced shifts (Table 3) produced by several lanthanide ions—chosen so as to represent some which give large and some which give small contact shifts—show that the signals of the methyl group shift in the same direction as those of H 6, the proportion being approximately constant. This observation confirms that the shifts of both H 6 and the methyl group are of pseudocontact origin.

We do not know yet how to calculate the pseudocontact shifts in complexes of polyols. The direction of the principal magnetic axis is not known and it is not certain that the McConnell-Robertson equation¹⁹ is applicable to this tridentate system (it

¹⁶ Horrocks, W. D., Jr, and Sipe, J. P., III, J. Am. Chem. Soc., 1971, 93, 6800, and references therein. ¹⁷ Angyal, S. J., Greeves, D., Littlemore, L., and Pickles, V. A., Aust. J. Chem., 1976, 29, 1231.

¹⁸ Bleaney, B., Dobson, C. M., Levine, B. A., Martin, R. B., Williams, R. J. P., and Xavier, A. V., J. Chem. Soc., Chem. Commun., 1972, 791.

¹⁹ McConnell, H. M., and Robertson, R. E., J. Chem. Phys., 1958, 29, 1361.

was found inapplicable to bidentate aromatic complexes²⁰ but was used successfully for bidentate carboxylate¹⁰ and phosphate⁹ complexes).

(iii) It is assumed that contact shifts are operative on those protons whose shift is considerably less than, or in the opposite direction to, that of H 6. With all cations the strongest contact effect is seen to be on H 3. Only terbium, dysprosium and holmium cause shifts of all proton signals in the same direction; theoretical calculations²¹ and experimental data²² indicate that with these metals the contact and pseudocontact shifts are in the same direction (namely, upfield).

The induced shifts of H 3 are regarded as being representative of contact interactions. There is, of course, also pseudocontact interaction there (probably of a magnitude similar to that at H 6) but the contact effect, which is in opposite direction, predominates. The ratio of the induced shifts of H 3 and H 6 can be regarded as a measure of the relative magnitude of the contact and pseudocontact interaction. It is seen that this ratio is large for europium and neodymium, and small for praseodymium and ytterbium, in accordance with theoretical considerations²³ and other experimental findings.²⁴

Presumably the strong contact interactions caused by lanthanide ions in aqueous solution are due to their being strong Lewis acids. It has been reported²⁴ that $Eu(fod)_3$ causes greater contact shifts than $Eu(dpm)_3$ and this has been attributed to the former being the stronger Lewis acid.

The contact effects show, to a surprising extent, the stereospecificity first observed by Morishima et al.²⁵ in the ¹³C spectra of complexes of amines with nickel(II) acetylacetonate (there is also substantial theoretical evidence for this stereospecificity²⁶). Contact interaction occurs most strongly through saturated bonds when the resonating nucleus, the lanthanide cation, and the intervening bonds are in a plane (that is, the bonds form an antiparallel zig-zag). In epi-inositol H2 and H3 are both connected through three bonds to the cation and are about equidistant from it but H 3 lies in the plane formed by C3, O3, and the ion, and H2 does not. Hence the contact effect is strong on H3, weak on H2. Along the planar zig-zag the contact effect can be conveyed through further bonds: the bond-path from the ion to H1 is close to planar and the contact effect is clearly discernible. It is interesting that with the highest members of the lanthanide series (Tm, Yb) the contact effect becomes strong on H2. This is probably caused by the decreasing size of the higher lanthanides (see Table 1) which affects the geometry of the complex. If the oxygen-metal distances are 2.6 Å, the angles subtended by the H2-C2 and the C1-C2 bonds with the metal-O2-C2 plane are approximately 40° and 80°, respectively; if the distances are only $2 \cdot 2$ Å,

²⁰ Bhacca, N. S., Selbin, J., and Wander, J. D., J. Am. Chem. Soc., 1972, 94, 8719.

²¹ Golding, R. M., and Halton, M. P., Aust. J. Chem., 1972, 25, 2577.

²² Lewis, W. B., Jackson, J. A., Lemons, J. F., and Taube, H., J. Chem. Phys., 1962, 36, 694.

²³ Reuben, J., in 'Progress in N.M.R. Spectroscopy' (Eds J. W. Emsley, J. Feeney and L. H. Sutcliffe) Part 1, Vol. 9, p. 16 (Pergamon: Oxford 1973).

²⁴ Gansow, O. A., Loeffler, P. A., Davis, R. E., Willcott, M. R., III, and Lenkinski, R. E., *J. Am. Chem. Soc.*, 1973, **95**, 3389; Johnson, B. F. G., Lewis, J., McArdle, P., and Norton, J. R., *J. Chem. Soc., Chem. Commun.*, 1972, 535.

²⁵ Yonezawa, T., Morishima, I., and Ohmori, Y., J. Am. Chem. Soc., 1970, **92**, 1267; Morishima, I., Okada, K., Ohashi, M., and Yonezawa, T., Chem. Commun., 1971, 33; Ohashi, M., Morishima, I., Okada, K., Yonezawa, T., and Nishida, T., Chem. Commun., 1971, 34.

²⁶ Roberts, J. D., Hawkes, G. E., Husar, J., Roberts, A. W., and Roberts, D. W., *Tetrahedron*, 1974, **30**, 1833.

the angles are nearly equal (55 and 65°), and the contact effect is conveyed nearly equally. Grenthe²⁷ observed that the metal–oxygen distance in complexes of lanthanides decreases approximately to the same extent as the ionic radius of the cation decreases.

The operation of contact shift requires at least a partial overlap of the orbitals on the metal and on the oxygen atom; this is more easily achieved when the oxygen atom is bonded to a carbon and a hydrogen atom, rather than to two carbon atoms. In the study of the complexes of glycosides it has been noticed that the anomeric hydrogen atom shows no contact shift.¹⁷ Hence 3-O-methyl-epi-inositol was investigated (Table 4) and it was found that there was now little indication of contact interaction on H3; this proton now shows nearly 'normal' shifts, thereby providing further evidence that in *epi*-inositol it is subject to contact interaction. The other contact interactions of 3-O-methyl-epi-inositol are also weaker, though they are noticeable on H1 with the larger, and on H2 with the smaller ions. The position of the cation in the complex seems to be the same as in the complex formed with *epi*-inositol because the diamagnetic shifts caused by La are practically the same. The paramagnetic shifts of the methyl group correspond in sign and relative magnitude to the usual pseudocontact shifts; they are about as large as those of H3 and it appears therefore that the principal magnetic axis is directed towards the oxygen atom bearing the methyl group. This may be the explanation of the very small shifts of H6 with Eu and Pr (in contrast to those in *epi*-inositol): this hydrogen atom lies close to the critical angle of 54° . With the higher (and therefore smaller) lanthanides, however, H 6 shows large shifts; the structure of the complex appears to be different. This is borne out by the diamagnetic shifts caused by the smaller Lu cation which are rather different from those caused by La. The cation now appears to be more distant from O3; maybe it is bonded only to O2 and O4; the electron distribution or the direction of the principal magnetic axis have changed. In the following paper¹⁷ other examples are given of the change in the structure of complexes with decreasing size of the complexing cations.

oi 3-O-metnyl-epi-mositol							
Cation	H1,5	H2,4	H 3	H6	OMe		
La ³⁺	0.19	0.22	0.43	0.08	0.18		
₽r ³ +	-0.65	-1.7	-1.7	0.05	-1.45		
Eu ³⁺	-0.05	0.55	0.15	-0.2	0.45		
Tm ^{3 +}	c. 1·35	-0.05	1 · 1	1.25	1.4		
Yb ³⁺	0.6	0.40	c. 0·6	1.6	0.5		
Lu ^{3 +}	0.15	0.11	0.16	0.07	0.05		

 Table 4.
 Lanthanide-induced chemical shifts (ppm) in the spectrum of 3-O-methyl-epi-inositol

In the hope of eliminating all contact interactions, hexa-O-methyl-epi-inositol was synthesized by methylation of epi-inositol. However, this compound did not form a complex with lanthanide cations; addition of europium chloride to its solution caused no change in its n.m.r. spectrum. It has already been pointed out² that the methyl of an axial methoxyl group is sterically hindered when the neighbouring oxygen atoms are both equatorial, so that weak complexing with cations results.

²⁷ Grenthe, I., Acta Chem. Scand., 1972, 26, 1479.

To learn more about contact interactions, the effect of Co^{2+} and Ni^{2+} on *epi*inositol was explored. There were, however, no substantial changes in the spectrum, indicating that these ions are too small to form stable complexes.⁸

Other Cyclitols

Cyclitols which do not contain an axial-equatorial-axial sequence of three hydroxyl groups in their predominant conformation show no changes in their n.m.r. spectra (except a small general shift, presumably caused by weak complexing involving pairs of hydroxyl groups). Thus *myo*-inositol, *neo*-inositol and cyclohexane-1,2,3,5/4-pentol form no complexes; the alternative chair form of each of these compounds contains complexing sites but the free energy of complex formation is apparently not sufficient to cause ring inversion. Similarly, cyclohexane-*cis*-1,3,5-triol forms no complex. The case of 2-deoxy-2-*C*-methyl-*epi*-inositol, which readily forms a complex by ring inversion, has been discussed elsewhere.⁸ *cis*-Inositol, which contains a triaxial site in addition to three ax-eq-ax sites, complexes strongly with lanthanide cations.⁸

 Table 5.
 Lanthanide-induced chemical shifts (ppm) in the p.m.r. spectra of cyclohexane-1,2,3,4,5/0and -1,2,3,4/5-pentols

Compound	Cation	H 1	H 2	H 3	H 4	Н5	H 6ax	H 6eq
1,2,3,4,5/0	Eu^{3+}	-1.3	0.8	-8.2	0.8	-1.3	$1 \cdot 2$	0.3
1,2,3,4/5	Eu^{3+}	$\begin{array}{c} c. = 0.7 \\ 0.4 \end{array}$	$c_{1} - 10.0$	-0.7	-1.83 -0.6	2 0.7 1.1	-2.8	0.4
	Pr ³⁺	-2.7	3 · 1	1.9	-1.2	-3.1	0.22	-0.27

Two quercitols have the required ax-eq-ax arrangement and form complexes with lanthanide ions (Table 5). Cyclohexane-1,2,3,4,5/0-pentol (3) differs from *epi*-inositol only in the absence of a hydroxyl group on C6; the lanthanide-induced shifts are similar to those in *epi*-inositol, and the additional H 6eq shifts in the same direction but to a lesser extent than H 6ax, as expected from pseudocontact interaction. In cyclohexane-1,2,3,4/5-pentol (4) the complexing site is at O 1, O 2, O 3 and, accordingly, the strongest contact shift is that of H2. However, H1 and H3 shift in opposite directions; this behaviour is explained by the fact that the quercitol is a conformational mixture in solution. The calculated free energy difference²⁸ between the two chair forms, (4) and (4a), is only $2 \cdot 3$ kJ mol⁻¹, and the axial-axial coupling constants $(J_{4,5} 8 \cdot 2 \text{ Hz}, J_{5,6ax} 9 \cdot 3 \text{ Hz})$ and the equatorial-equatorial coupling constant, $J_{1,6eq} 5 \cdot 8$ Hz, show that nearly a quarter of the molecules are in the alternative chair form (4a). This conformation has a complexing site at O 2, O 3, O 4, giving strong contact interaction at H 3. The observed lanthanide-induced shifts are the weighted average values of those of the two chair forms.

Cyclohexane-1,2,3,4/5-pentol is another example of the stereospecificity of the contact interaction: H 6ax, but not H 6eq, shows substantial contact effect. Only the former lies in a planar zig-zag with the cation.

Experimental

The n.m.r. spectra were recorded on a Varian A-60 spectrometer, operating at a probe temperature of 44° , and on a JEOL JNM-4H-100S spectrometer, operating at 25° , in deuterium oxide solution.

²⁸ Angyal, S. J., and McHugh, D. J., Chem. Ind. (London), 1956, 1147.

standard. It was ascertained, by comparison with the signal ($\delta 3.19$) of tetramethylammonium iodide,¹¹ that lanthanide ions have no substantial effect on the chemical shift of this standard.

epi-Inositol,¹² 3-O-methyl-epi-inositol,¹ DL-2-C-methyl-epi-inositol¹⁴ and cyclohexane-1,2,3,4,5/0pentol²⁹ were prepared as previously described; DL-cyclohexane-1,2,3,4/5-pentol³⁰ was a gift of Dr G. E. McCasland. The p.m.r. spectra of these cyclitols have been described.^{1,14} The lanthanide salts were commercial samples; the chloride hexahydrates were used, except for europium which was added in most cases as the nitrate hexahydrate. The nature of the anion does not affect the proportion of the lanthanide-induced shifts, although europium nitrate gives somewhat larger shifts than does europium chloride.

Hexa-O-methyl-epi-inositol (with B. J. Clarke)

A mixture of *epi*-inositol $(1 \cdot 0 \text{ g})$, dimethylformamide (10 ml), freshly distilled), methyl iodide (10 ml) and silver oxide (10 g) was stirred for 24 h.³¹ After dilution with chloroform the mixture was filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in benzene and was chromatographed on a column of silicic acid (Mallinckrodt) with benzene–ethyl acetate (1:1) which removed some by-products. Elution with ethyl acetate then gave a solid which was recrystallized from light petroleum to give *hexa*-O-*methyl*-epi-*inositol* $(1 \cdot 1 \text{ g}, 75\%)$, m.p. $103-104^{\circ}$ (Found: C, 54 · 6; H, 9 · 0. C₁₂H₂₄O₆ requires C, 54 · 5; H, 9 · 1\%). N.m.r. δ (D₂O) 3 · 20, dd, $J_{1,2}$ 3 Hz, $J_{1,6}$ 10 Hz, H 1,5; c. 3 · 28, t, H 3; 3 · 45, Me; 3 · 46, 2Me; 3 · 47, 2Me; 3 · 51, Me; 4 · 11, t, $J_{2,3}$ 3 Hz, H 2,4. The signal of H 6 is hidden under the methyl signals.

6-O-Methyl-epi-inositol (with P. M. Pojer)

The pentaacetate of 6-O-methyl-*epi*-inositol has been described.³² We chose a different route for its synthesis because we had a supply of 5-O-benzoyl-1,2:3,4-di-O-cyclohexylidene-6-O-[(methylthio)-methyl]-*epi*-inositol³³ at hand. This compound (545 mg) and Raney nickel (4 g, wet) in anhydrous ethanol (40 ml) was heated under reflux with stirring for 6 h. After filtration the solvent was evaporated and the residue soon crystallized. Recrystallization from methanol gave 5-O-benzoyl-1,2:3,4*di*-O-cyclohexylidene-6-O-methyl-epi-inositol (450 mg, 90%) as long rectangular needles, m.p. 114–116° (Found: C, 68·8; H, 7·5. C₂₆H₃₄O₇ requires C, 68·1; H, 7·5%). The p.m.r. spectrum in CDCl₃ showed an OMe signal at δ 3·51; none of the other signals was resolved.

The above compound $(1 \cdot 0 \text{ g})$ was heated in methanol (60 ml) with 2 M sodium hydroxide solution (5 ml) for 1 h. The methanol was evaporated under reduced pressure, water (20 ml) was added and the solution extracted with dichloromethane $(3 \times 40 \text{ ml})$. Evaporation of the solvent gave a syrup which was heated at 100° with a mixture of acetic acid (25 ml) and water (25 ml) for 1 h. After evaporation under reduced pressure the residue, which soon solidified, was extracted with ether $(2 \times 20 \text{ ml})$ and recrystallized from propan-2-ol to give 6-O-methyl-epi-inositol in a solvated form, m.p. $51-52^{\circ}$, which after drying melted at 95-96° (340 mg, 80%) (Found: C, 43 \cdot 2; H, 7 \cdot 3. C₇H₁₄O₆ requires C, 43 \cdot 3; H, 7 \cdot 4%). N.m.r. δ (D₂O) $3 \cdot 59$, s, Me; $3 \cdot 68$, t, $J_{2,3}$ 3 Hz, H 3; $4 \cdot 05$, m (owing to virtual coupling), H 2,4; the signals of H 4,5,6 are hidden by the methyl signal. On addition of Eu³⁺ these signals emerge and that of H 2,4 becomes a triplet. A sample of the compound was converted into its pentaacetate which melted at 174° (lit.³² 171–172°), mixed m.p. $173-174^{\circ}$.

Acknowledgment

This research was supported by a grant from the Australian Research Grants Committee.

Manuscript received 8 December 1975

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