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COMPLEXING OF POLYOLS WITH CATIONS

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Abstract—Polyols containing three O atoms in a suitable steric arrangement form complexes with cations in aqueous solution. Suitable steric arrangements are (i) three *syn*-axial oxygen atoms on a 6-membered ring, and (ii) three O atoms on three consecutive C atoms constituting a clockwise and an anti-clockwise *gauche* arrangement. Complex formation is detected by paper electrophoresis and by NMR spectroscopy. Complex formation with diamagnetic cations causes small downfield shifts in the NMR spectra. Paramagnetic cations cause large shifts which are interpreted as being due to diamagnetic, pseudocontact, and contact interactions. The contact effect appears to be stereospecific: it requires planarity of the resonating nucleus, the metal, and the intervening bonds.

INTRODUCTION

Innumerable co-ordination compounds are known in which metal atoms are co-ordinated to O atoms of the ligands; in the great majority of these compounds, however, the O atoms form part of an anion (carboxylate or enolate). Metals co-ordinated to neutral O atoms are found in the newly developed crown compounds[1] and cryptates;[2] these are tailor-made compounds in which six or more O atoms surround the metal cation.[3]

It is not generally realized, however, that as few as three neutral O atoms in a molecule suffice to form well-defined and reasonably stable complexes with metal cations, even in aqueous solution, provided that the three O atoms are in a suitable steric arrangement.[4] The interest in such complexes stems from the fact that polyols (sugars, cyclitols, alditols) and metal cations coexist in aqueous solution in biological fluids where complex formation could take place.

Surprisingly, the steric requirements for complex formation between polyols and cations are rather rigid; so far only two steric arrangements have been found[5] which give rise to reasonably strong complexes. The size of the cation is also important. The two steric arrangements and their properties will briefly be described now; detailed justification of the statements will be given subsequently in this review.

One of the steric arrangements suitable for complexing with cations is a group of three *syn*-axial O atoms on a cyclohexane ring. This arrangement is uncommon and its only well-studied example is that in *cis*-inositol (1). There are, of course, many cyclohexane derivatives containing three equatorial OH groups in position 1, 3, and 5, but complexing with cations does not usually provide sufficient energy for the chair–chair inversion; *cis*-1,3,5-cyclohexanetriol does not form a complex with cations.[5] (An exception has been discussed in Ref 5.)

The other steric arrangement suitable for complex formation with cations is that of three O atoms on three consecutive C atoms in such a conformation that the first and second are *gauche* clockwise and the second and third *gauche* anti-clockwise or *vice versa* (see formula 2). In accordance with the terminology of Cahn, Ingold, and Prelog,[6] who use the symbols *M* and *P* to designate the two different *gauche* relationships, it is proposed to refer to this steric arrangement as the "*M,P* arrangement".[7] Its most common occurrence is a sequence of an axial, an equatorial and an axial OH group on a 6-membered ring in its chair form (3); most studies of complex formation with cations have been carried out with this system.[8] Acyclic polyols can, by rotation around C–C bonds, acquire an *M,P* arrangement, as discussed in Section 6.

The triaxial and the *M,P* arrangements have similar geometry: they both consist of three O atoms, at a distance of approximately 2·95 Å from each other, forming an equilateral triangle. They differ, however, in two respects: the relative directions of the orbitals containing free electron pairs, and their resistance towards bringing the O atoms closer together. These differences account for their different reactivity towards some anions; for example, borate ion forms complexes only at the triaxial site whereas the periodate dianion complexes only at the *ax-eq-ax* site.[5] *cis*-Inositol (1) forms a tridentate borate at O1,O3,O5 but a tridentate periodate at O1,O2,O3. The *ax-eq-ax* site is more selective towards cations; it complexes only with cations with ionic radii larger than *ca* 0·8 Å (the optimum being about 1·0 Å), whereas the triaxial site coordinates with cations with ionic radii larger than *ca* 0·6 Å.

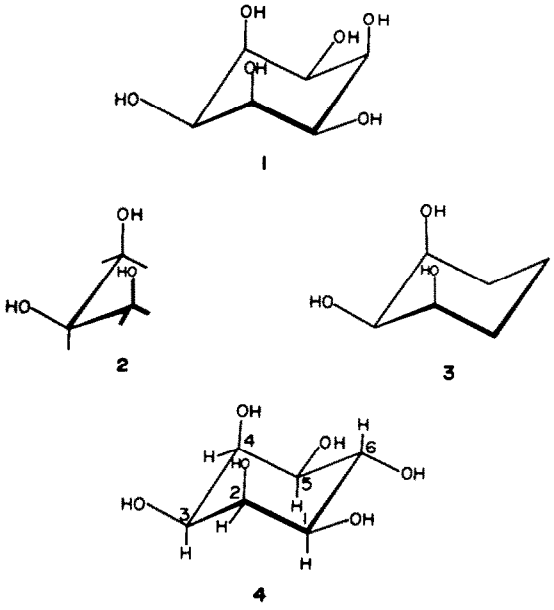
No unequivocal evidence has yet been produced to show that complex formation between cations and polyols involves an *M,P* arrangement; however, of the many cyclitols and sugars so far investigated all that have such an arrangement com-

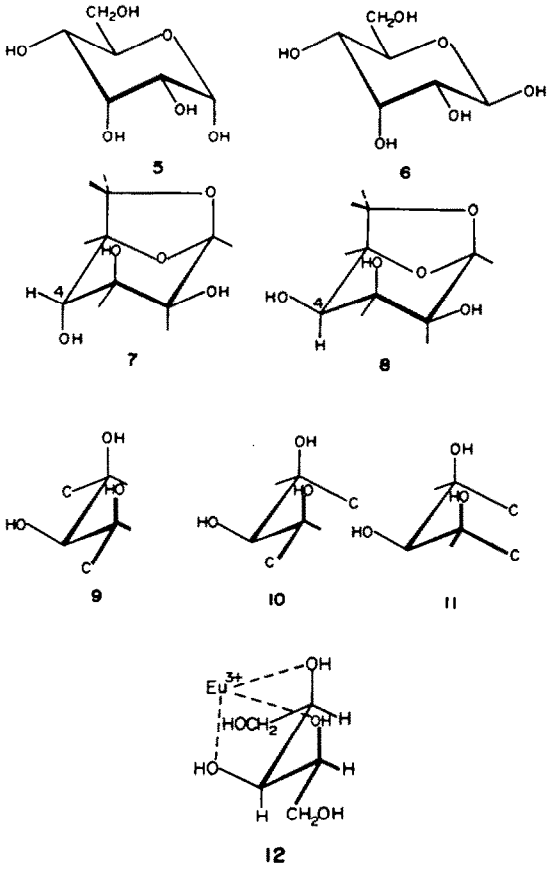
plex well, and all that have not complex weakly, if at all. (Other possible complexing arrangements have been discussed in Ref 5) For strong complexing, the *M,P* arrangement has to be present in the *predominant* conformation. Complexing of polyols with cations yields very little free energy. If the conformational change which provides an *M,P* arrangement requires little energy (1–2 kcal/mol) complexing will occur but weakly; if it requires much energy, complexing will be negligible.

Complex formation between sugars and metal ions has been extensively studied by a variety of methods,[9] none of which yielded much information on the structure or the stability of the complexes. Although many crystalline complexes between sugars and cations are known,[9] X-ray crystallography has been of little help so far because, invariably, the cation is found[10] to be coordinated in the crystal to one or two hydroxyl groups of two or three sugar molecules, an arrangement which would have little stability in solution. Only in one case[10a] (β-D-mannofuranose, $CaCl_2$, $4H_2O$) was the cation found to be attached to three oxygen atoms of one polyol and these are, indeed, in an *M,P* arrangement. Recently, however, two methods have yielded[8] considerable information: electrophoresis and NMR spectroscopy.

Electrophoresis

J. A. Mills has first shown that many polyols move towards the cathode on paper electrophoresis in supporting electrolytes containing acetates of various metals.[11] The results were interpreted as a partial, reversible combination of the polyols with metal cations in solution, the extent of the combination depending on the configuration of the polyol and the ionic radius and preferred co-ordination geometry of the cation.





Amongst the polyols tested, *cis*-inositol (**1**) showed the greatest mobility in solutions of all metal acetates tested, moving rapidly in solutions containing Ca^{2+}, Sr^{2+}, and Ba^{2+} ions. This is not now surprising since *cis*-inositol contains four complexing sites: the triaxial group and three *ax-eq-ax* groups of oxygen atoms. The mobility of *epi*-inositol (**4**) under these conditions is about one-third that of *cis*-inositol; other compounds having an *ax-eq-ax* arrangement of oxygen atoms in their most stable conformation show similar mobility; cyclitols and sugars which lack such an arrangement show very little movement.[12]

Amongst compounds of similar structures one can assume that their complexes with a given cation will have similar ionic mobilities, and that the mobility will decrease with increasing molecular weight and with the presence of bulky substituents, such as methyl groups. When allowance is made for the molecular weight and for substituents, the relative mobilities will show the extent to which the individual compounds are present in solution as complexes with the cation. This argument is only valid when the extent of complexing is moderate;

when it is nearly complete, differences in mobilities are no longer observable. In a 0·2 M solution of calcium acetate, if K is *ca* 20 for *cis*-inositol (Section 4), about 66% of the cyclitol is present as the complex; hence the above condition is fulfilled. Some typical values of ionophoretic mobility compared to that of *cis*-inositol, M_i, in 0·2 M calcium acetate are: *epi*-inositol 0·42, *allo*-inositol 0·44, D-talose 0·27, L-iditol 0·24, allitol 0·09, *myo*-inositol 0·02.

The metal ions fall into three groups;[13] (i) Those, e.g., Ca^{2+}, Sr^{2+}, Ba^{2+}, La^{3+} which, when used as electrolytes, produce good mobilities of *cis*- and *epi*-inositols; these ions have ionic radii larger than 0·8 Å. (ii) There are many cations (Mn^{2+}, Fe^{3+}, Ni^{2+}, Co^{2+}, Cu^{2+}, Zn^{2+}, Mg^{2+}) in whose solutions only *cis*-inositol shows substantial mobility while other polyols hardly move at all. It is assumed that these cations complex with the triaxial but not with the *ax-eq-ax* site; their ionic radii are between 0·6 and 0·8 Å. (iii) No mobility is observed in solutions of Be^{2+} and Al^{3+}; these ions have radii smaller than 0·6 Å. Li^{+}, although somewhat larger, also belongs to this group.

NMR Spectra

Diamagnetic cations. Much information is obtained on polyol-cation complexes by the study of their NMR spectra. When, for example, calcium chloride is added to a solution of *epi*-inositol (**4**) in deuterium oxide, a significant change occurs in the NMR spectrum.[4] All signals move to lower field, that of H3 moving the most. Similar downfield shifts occur in the spectra of related compounds (e.g., 1,2,3,4,5/0- and 1,2,3,4/5-cyclohexanepentols) on complex formation. There is no change, however, in the coupling constants, indicating that the conformation of these molecules does not alter on complex formation. In their stable conformations, the only three oxygen atoms sufficiently close to each other for coordinating with a cation are those in the *ax-eq-ax* sequence; hence it is assumed that this is the site of complex formation. The NMR spectra of cyclitols which lack this sequence, e.g., *myo*- and *neo*-inositol, are not changed on addition of calcium chloride. The behaviour of *cis*-inositol will be discussed later (section 5).

These downfield shifts, denoted as "diamagnetic shifts", are caused by the charge of the cation. Lanthanum ion causes larger, sodium ion much smaller shifts than calcium ion. On the assumption that the cation is equidistant from the three O atoms of the *ax-eq-ax* sequence, the expected shifts can be approximately calculated by the formula[14]

$$\Delta\sigma = -2\times10^{-12}E_z - 10^{-18}E^2,$$

where $\Delta\sigma$ is the proton screening constant of an X–H bond when it is subjected to an electric field E, and E_z is the component of E in the bond direction. For *epi*-inositol and lanthanum ions the calculated values are: H1, 0·28; H2, 0·43; H3, 0·59; H6, −0·18 ppm; the observed values are 0·20, 0·25, 0·55, and 0·05 ppm, respectively.[12]

Establishment of the equilibrium between polyols and cations is fast on the NMR time-scale, hence separate spectra for the polyol and its complex are not observed, only average spectra. Addition of further amounts of a complexing cation causes further shifts of the protons; complete conversion to the complex is, however, not achieved at concentrations which allow the running of NMR spectra. Hence the limiting shift cannot be directly determined; moreover, at high concentrations, weaker complexing with other hydroxyl groups causes some additional small shifts.

The three complexing O atoms need not be present as OH groups; at least one of them can be in an ether or acetal grouping. In the spectrum of 3-O-methyl-*epi*-inositol, calcium ions cause downfield shifts similar to, and only slightly less than, those in the spectrum of *epi*-inositol.[12] Methyl glycosides in which the glycosidic group is part of an *ax-eq-ax* sequence, e.g., methyl α-D-allopyranoside, also form complexes.

Stability constants

Attempts to determine the stability constants of the polyol-cation complexes have not been fully successful, although several methods have been used.[15] The activities of the ions cannot be neglected at the high concentrations required for complex formation; but the activities of the complex cations are not known and therefore concentrations, rather than activities, have been used in calculating the "stability constants". There is also some uncertainty regarding the stoichiometry of the complexes. Potentiometric determination of free metal cations in the solution of complexes has shown[12] the presence of some 1:2 complex in addition to the 1:1 complex, particularly in the case of *cis*-inositol. Nevertheless, approximate stability constants, calculated for 1:1 complexes, are useful because they allow a comparison of the complexing ability of various cations and of various polyols, and they enable the calculation of the approximate extent of complex formation under given conditions.

A practical method[15] for determining the extent of complex formation at an *ax-eq-ax* site makes use of a chemically mobile system in which the position of equilibrium can be altered by complex formation, and then measured. Such a system was found in the anomeric equilibrium of D-allose.

α-D-Allopyranose, in its more stable C1 conformation (**5**), contains an *ax-eq-ax* sequence of OH groups (at C1,C2,C3), but the β-anomer (**6**) does not. Addition of a complexing cation therefore increases the proportion of the α-anomer in the

equilibrium (which is spontaneously established at ambient temperature in a short time). The proportion of the pyranose (and also of the furanose) anomers in aqueous solution can be determined from the PMR spectrum; the signals of H1 of the four tautomeric forms are well separated from each other (Fig 1). At 30° the equilibrium composition is 13·8% α-pyranose, 77·5% β-pyranose, 3·4% α-furanose, and 5·3% β-furanose. In a 0·85 M solution of calcium chloride the composition is 37·2:54·5:4·5:3·8 (Fig 1). On the assumption that a 1:1 complex is formed and that the proportion of the *uncomplexed* tautomers is not affected by the presence of salts, the stability constant of α-D-allopyranose-$CaCl_2$ was calculated to be *ca* 6 mol^{-1} l.

By using salts of other metals, the complexing ability of various cations with an *ax-eq-ax* sequence of OH groups can be determined by this method.[15] Lanthanum(III) was found to form the strongest complexes (*K ca* 10 mol^{-1} l), followed by calcium (*ca* 6), strontium (*ca* 5), barium (*ca* 3); magnesium and sodium (*ca* 0·1 mol^{-1}l) form much weaker complexes.* Apparently higher charge of the cation favours complex formation; amongst those with the same charge, an ionic radius of *ca* 1·0 Å seems to be most favourable for complex formation (Na^+, Ca^{2+}, La^{3+}, respectively). The downfield shift of the signal of H1 also increases with increasing charge of the cation.

The PMR spectra of D-allose (Fig 1) disclose that the signal of HI of the α-furanose form also increases and shifts downfield on addition of metal cations. The spectrum of the β-furanose form, like that of the β-pyranose form, is not affected. It appears that a *cis–cis* sequence of three O atoms on a 5-membered ring also constitutes a good complexing site for cations. With only little expenditure of energy, the three O atoms can form an *M,P* arrangement by becoming quasi-axial, quasi-equatorial and quasi-axial, respectively. This is, indeed, the steric disposition found[10a] in the crystals of β-D-mannofuranose, $CaCl_2$, $4H_2O$. The conclusion that α-D-allopyranose and α-D-allofuranose form complexes with cations, while the β-anomers do not, is confirmed by paper electrophoresis of the corresponding methyl glycosides: only the α-anomers migrate towards the cathode.[12] The complexing ability of the *cis–cis* arrangement on a 5-membered ring is only slightly less than that of the *ax-eq-ax* arrangement on a six-membered ring.

The method using D-allose is not suitable for measuring the stability constants of complexes with paramagnetic cations. In order to produce substantial changes in the α:β ratio of the allopyranoses, a high concentration of cations is required; at such concentrations the paramagnetic cations cause so much scattering and broadening of the signals that the α:β ratio cannot be determined accurately.

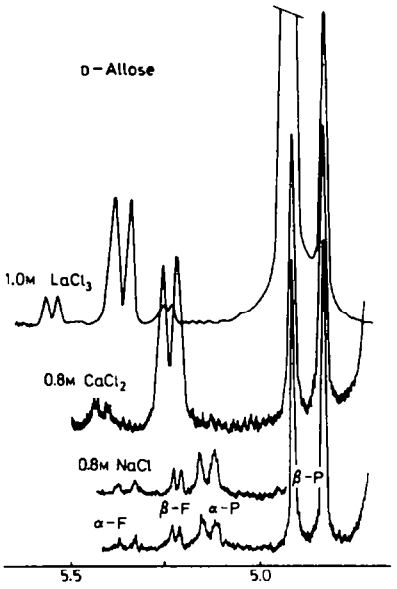


Fig 1. Partial PMR spectrum (H1 only) at 100 MHz of D-allose in deuterium oxide (lower curve) and in 0·8M sodium chloride, 0·8M calcium chloride, and 1·0M lanthanum chloride (successive curves), all at 31°.*

NMR spectra

Paramagnetic cations. When a salt of a paramagnetic cation (e.g., europium nitrate, praseodymium chloride) is added to an aqueous solution of a complexing polyol, large and rather bewildering shifts of the proton signals occur (e.g. Fig 2), thereby providing a very sensitive method for the detection of complex formation; the spectra of polyols which lack the required triaxial or *M,P* arrangement are not affected by lanthanide ions.

epi-Inositol is a convenient substance for studying these shifts because any proton signal in its spectrum is readily recognised wherever it is shifted to. Some examples of the shifts caused by various lanthanide ions are shown in Table 1. In most cases some of the signals are shifted to higher and some to lower field. (One should note that, since the shifts are given in δ values, positive figures indicate downfield, negative figures upfield, shifts). The shifts are obviously not accounted for by pseudocontact interactions only because then the shift ratios of the protons would be independent of the nature of the metal ion[16]—which is not even approximately true.

It is now well established that the shifts caused by NMR shift reagents[17] in organic solvents are mainly due to pseudocontact effects.[18,19] There is, however, evidence of contact interactions at the

*To illustrate what the stability constants mean: in a 1 M solution of a cation, if *K* is 10 mol^{-1}l, 91% of the polyol is present as a complex; if *K* is 1 mol^{-1}l, 50%; if *K* is 0·1 mol^{-1}l, 9%.

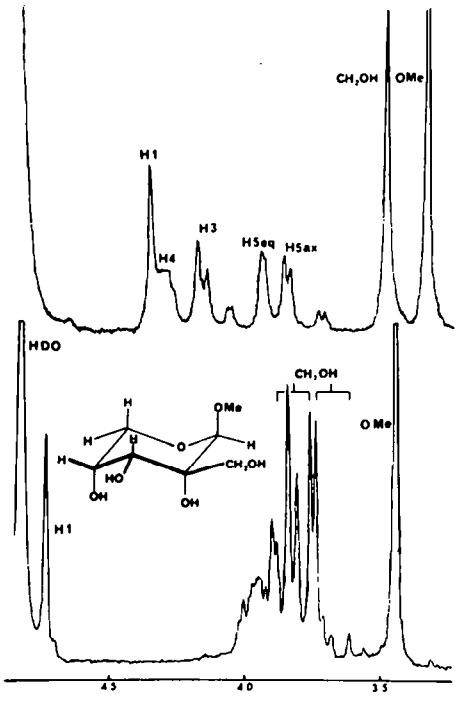


Fig 2. The 100 MHz PMR spectrum of methyl β-D-hamamelopyranoside in deuterium oxide at 30°. The upper curve shows the spectrum after the addition of 0·22 equivs of praseodymium chloride.[29]

Table 1. Lanthanide ion-induced shifts (ppm) in *epi*-inositol in aqueous solution[23]

Cation	H1,5	H2,4	H3	H6
La^{3+}	0·20	0·25	0·55	0·05
Pr^{3+}	−1·05	−2·05	2·05	−3·5
Nd^{3+}	0·30	−1·10	6·1	−1·65
Eu^{3+}	−0·35	1·60	−7·2	1·65
Dy^{3+}	−21	−21	−24	−26
Yb^{3+}	−0·20	−2·1	−4·9	4·5

nuclei closest (along bonds) to the complexing site;[19,20] the contact shift is more evident with the fod than with the dpm shift reagents because the former are stronger Lewis acids;[21] and more evident with europium and neodymium than with praseodymium and ytterbium.[22] In the tridentate complexes of *epi*-inositol most of the hydrogen atoms are only a few bonds away from the tripositive cation which is a much stronger Lewis acid than the NMR shift reagents; hence the occurrence of contact shifts is not unexpected.

It is now believed[23] that the shifts observed in the polyol-lanthanide complexes are due to three different interactions: diamagnetic, pseudocontact, and contact. (i) The diamagnetic effect, always downfield, is caused by the charge of the cation; its value should be independent of the nature of the lanthanide ion (except for the slight effect of the decrease in ionic radius with increasing atomic number). The shifts caused by lanthanum(III) can therefore be taken as representing the diamagnetic component of the shifts induced by all lanthanides.

(ii) The shift of the signal of H6 in the spectrum of *epi*-inositol (Table 1) induced by various lanthanide ions has the sign and the relative magnitude typical of pseudocontact shifts.[18] Hence it is assumed that in the spectrum of *epi*-inositol only this signal represents the pseudocontact effect. It is that of the only hydrogen atom connected to the cation through more than four bonds. Typically, the shift is downfield in the europium and ytterbium, upfield in the praseodymium and neodymium complexes. At present the magnitude of the pseudocontact shift cannot be calculated; the direction of the principal magnetic axis is not known, nor is it known whether the McConnell–Robertson equation[24] is applicable to this tridentate system.

(iii) It is assumed that contact shift is operative at those nuclei whose shift is considerably less than, or in the opposite direction to, that of H6. With all metals the strongest contact effect is seen at H3. For most lanthanides the contact and pseudocontact shifts are in opposite directions;[25] the exceptions are terbium, dysprosium, and holmium, and these are the metals which cause all signals in the spectrum of *epi*-inositol to shift in the same direction, namely upfield. The ratio of contact to pseudocontact shift is known to be larger for europium and neodymium than for ytterbium and praseodymium;[22] and this is seen to be true in the present instance if one looks at the ratio of the shifts of H3 and H6. It is useful, in fact, that the two lanthanide metals most commonly used (because they cause the least broadening of the signals) are europium and praseodymium, which give the most and the least contact shift, respectively.

The operation of contact shift requires at least a partial covalent character of the bond between the metal and the O atom;[26] this is more easily established when the O atom is bonded to a hydrogen atom, rather than to two C atoms. In further support of the assumption that a strong contact shift is operative, it is found that replacement of a complexing OH group by a methoxyl group removes or considerably reduces the contact shift. Whereas H3 in *epi*-inositol shows a very large upfield shift on addition of europium nitrate, it shifts only slightly, and downfield, in 3-O-methyl-*epi*-inositol.

A similar picture emerges[23] from the NMR spectra of two anhydro-sugars, 1,6-anhydro-β-D-mannopyranose (7) and 1,6-anhydro-β-D-talopyranose (8). In each case there are seven proton signals, five of which shift downfield with europium and upfield with praseodymium (Table 2), that is, predominantly by the pseudocontact

Table 2. Lanthanide ion-induced shifts (ppm) in 1,6-anhydro-β-D-manno- (7) and -talo-pyranoses (8)[23]

Compound	Cation	H1	H2	H3	H4	H5	$H6_{exo}$	$H6_{endo}$
manno	Eu^{3+}	1·25	−2·4	−0·85	0·70	0·70	1·4	3·0
	Pr^{3+}	−3·05	1·8	1·9	−1·5	−1·9	−3·9	−7·6
talo	Eu^{3+}	2·25	−3·5	−1·6	0·18	1·15	2·7	5·35
	Yb^{3+}	1·45	0·32	−0·45	0·55	1·1	1·8	3·7

mechanism. Complexing occurs at O1,O2,O3, as shown by comparison with diastereomers which have different configurations of these atoms.[12] The hydrogen atom closest to the cation, through space but not through bonds, is $H6_{endo}$ and this shows the greatest pseudocontact shift, as expected. The signals shifting upfield with europium are those of H2 and H3, the hydrogen atoms connected through only three bonds to the cation; H1, a similar number of bonds away, is not linked through a OH group and therefore shows little contact effect.

While all these considerations do not definitely prove that contact interactions are operating in this system, the assumption of their presence provides a self-consistent picture of the induced shifts. If this assumption is correct, the induced shifts display a stereospecificity of the contact interaction which has already been observed by Morishima *et al*[27] in the spectra of complexes of amines with nickel(II) acetylacetonate. In *epi*-inositol both H2 and H3 are connected through three bonds to the cation and are about equidistant from it; yet the contact interaction is very strong at H3, weak at H2. It appears (and there is substantial theoretical evidence for it[17,27]) that contact interaction is maximal when the bonds intervening between the resonating nucleus and the cation form a planar zig-zag arrangement; the more the bonds depart from planarity, the weaker will be the interaction. In *epi*-inositol H3 is exactly in the plane, H2 is not. Along a planar zig-zag the interaction may be conveyed through further bonds; H1 in *epi*-inositol, although one bond further away, shows more contact interaction than H2 because it lies in a planar zig-zag. A good example is presented by the two anhydrosugars which differ only in the configuration of H4. In the talose derivative (8) this hydrogen atom lies in a planar zig-zag and is subject to considerable contact effect; in the mannose derivative (7) it is out of the zig-zag plane and does not appear to be subject to contact effect. In the xylitol-europium complex (Section 6) H2 and H4 are close to a zig-zag plane and shift upfield, though not as strongly as H3 which is exactly in such a plane.

There are also indications of stereospecific contact interactions in the ^{13}C spectra of cyclic amines coordinated to $Ni(acac)_2$,[27] of borneol and related compounds with $Eu(fod)_3$,[17,19] and of anhydrosugars in the presence of lanthanide ions.[28]

At this point, let us have another look at the complexes of *cis*-inositol (1). Because each OH group in this molecule has to pass between two other OH groups during ring inversion, this inversion is slow on the NMR time-scale and the coalescence temperature of the signals is above ambient temperature. Hence, although the two chair forms of *cis*-inositol are equivalent, the signals of the equatorial H atoms (δ 4·03) and of the axial H atoms (δ 3·66) are separately observed.[5] Europium salts shifts both signals upfield, praseodymium salts, downfield; in each case that of the equatorial H atom shifts to a greater extent. Complexing at the *ax-eq-ax* sites would produce a strong contact effect on the axial H atoms; triaxial complexing would similarly affect the equatorial H atoms which would be in a planar zig-zag arrangement. Complexing therefore occurs at both types of site; and since there are three *ax-eq-ax* sites for one triaxial site, the conclusion probably is that the latter forms the stronger complex.

Like the NMR shift reagents in organic solvents, lanthanide cations can be used in aqueous solution for the expansion of intractable spectra[29] provided, of course, that the compounds form complexes with cations in aqueous solution. An example is shown in Fig 2. The NMR shift reagents can do more than this: information on the spatial arrangement can be obtained from the shifts on the assumption that they are of pseudocontact origin.[19] As we have seen, for polyols this assumption is not valid, but here the contact shifts can give spatial information. The signal of the hydrogen atom attached to the central C atom of the *M,P* arrangement always shifts strongly upfield with europium; those on the outer carbon atoms shift upfield if they are *anti* to the central oxygen atom, and downfield if they are *gauche* to it. Since europium gives the largest contact shifts, it is the metal of choice for this purpose. An application of this method to alditols is discussed in the next Section.

Alditols

All the alditols form complexes with cations but the extent of complex formation varies considerably, the electrophoretic mobility of the hexitols in calcium acetate ranging from 0·24 for iditol to 0·09 for allitol.[7] By rotation around C–C bonds any alditol can acquire an *M,P* arrangement of OH

groups but the energy required will depend on its configuration. When three consecutive C atoms have the *threo-threo* configuration, the *M,P* arrangement (**9**) has no unfavourable interaction other than those inherent in the *M,P* arrangement; the configuration is favourable for complex formation. An *erythro-threo* configuration produces an *M,P* arrangement (**10**) in which there is a *gauche* interaction between two segments of the carbon chain; this is somewhat less favourable. An *erythro-erythro* sequence produces an *M,P* arrangement (**11**) in which there is a 1,3-parallel interaction between two segments of the carbon chain; this is an unfavourable arrangement, and *erythro-erythro* configurations do not give rise to stable metal complexes. Somewhat similar considerations apply to the terminal OH group when it is involved in complex formation (for a full discussion, see Ref 7).

The sites of complexing in alditols and their conformations in aqueous solution have been determined by the use of NMR spectroscopy. The spectra of the alditols give little information since most of the signals overlap; however, on addition of europium nitrate first-order analysis of all or part of the spectrum becomes feasible. The spectrum of xylitol is shown in Fig 3. The upfield shifts of H2 and H4, and the stronger upfield shift of H3, identify the site of complexing as O2,O3,O4: the conformation of the complex (**12**) is thereby defined. However, the spectrum also contains information on the conformation of the uncomplexed alditol. Under the conditions used in this experiment only about 10% of xylitol is present as a metal complex; since the spectrum observed is the weighted average of those of the complexed and uncomplexed molecules, the coupling constants are essentially those of uncomplexed xylitol. They are incompatible with the planar zig-zag conformation of the carbon chain which occurs in the complex, and show that the alditol is bent, by rotation around the C2–C3 (or the C3–C4) bond to avoid the interaction of O2 and O4. This is the conformation which has been observed for various derivatives of alditols in organic solvents.[30] Similar conclusions have been reached for the other alditols.[7]

The interesting feature of this method is that the lanthanide-induced shifts (since they occur only in the complex) give information on the conformation of the complex, whereas the coupling constants give information on the conformation of the uncomplexed molecule. This instance also serves as a reminder that one should not automatically assume that complex formation will leave the conformation unaltered.

Applications

Besides assisting the interpretation of NMR spectra, complex formation between polyols and cations can have other practical uses. It can assist

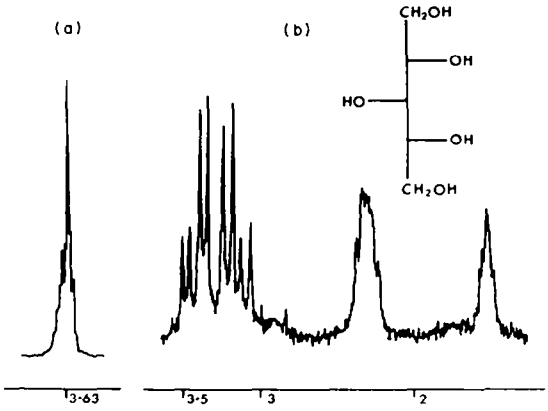


Fig 3. The 100 MHz PMR spectrum of (a) xylitol and (b) 0·3M xylitol and 0·16M europium nitrate in deuterium oxide at 25°.[7]

in the crystallization and purification of polyols; for example, D-gulose has only been obtained crystalline as the complex, α-D-gulopyranose, $CaCl_2$, H_2O, in which complexing presumably occurs at O1,O2,O3. Polyols can be characterized by their electrophoretic mobility in solutions of salts, and can be separated on a preparative scale on columns of cation-exchange resins containing calcium or strontium ions.[8] Finally, the outcome of chemical reactions which lead to equilibria can be altered by addition of a cation which forms a complex with one of the products. The potential of this method is greatly increased by the fact that complexing of polyols with metal ions is much stronger in alcoholic than in aqueous solutions.[9] When D-allose is heated with methanolic hydrogen chloride, the predominant product at equilibrium is methyl β-D-allopyranoside. When the reaction is carried out in the presence of strontium chloride, the α-pyranoside becomes the main product at equilibrium, the α-furanoside after a short reaction period. Methods have been worked out for the synthesis of any of the four methyl allosides in good yield by methanolysis in the presence or absence of strontium chloride.[31] Syntheses have also been worked out, by this method, for some other, not readily available, glycosides.[32]

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REFERENCES

[1]C. J. Pedersen, *J. Am. Chem. Soc.* **92**, 386, 391 (1970)
[2]J. M. Lehn and J. P. Sauvage, *Chem. Commun.* 440 (1971)
[3]For a review, see C. J. Pedersen and H. K. Frendsdorff, *Angew. Chem.* intern. Ed. **11**, 16 (1972)
[4]S. J. Angyal and K. P. Davies, *Chem. Commun.* 500 (1971)

[5]S. J. Angyal, D. Greeves and V. A. Pickles, *Carbohydrate Research* (1974) in press
[6]R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem.* intern. Ed. **5**, 385 (1966)
[7]S. J. Angyal, D. Greeves and J. A. Mills, *Austral. J. Chem.* **27** (1974) in press
[8]For a more detailed review of earlier work, see S. J. Angyal, *Pure and Appl. Chem.* **35**, 131 (1973)
[9]J. A. Rendleman, Jr., *Advances in Carbohydrate Chem.* **21**, 209 (1966)
[10a]D. C. Craig, N. C. Stephenson and J. D. Stevens, *Carbohydrate Research* **22**, 494 (1972); [b]C. A. Beevers and W. Cochran, *Proc. Roy. Soc. London, Ser. A* **190**, 257 (1947); C. E. Bugg and W. J. Cook, *Chem. Commun.* 1972, 727; W. J. Cook and C. E. Bugg, *J. Am. Chem. Soc.* **95**, 6442 (1973); D. C. Craig, N. C. Stephenson and J. D. Stevens, *Crystal Structure Commun.* (1974) in press; G. F. Richards, *Carbohydrate Research* **26**, 448 (1973)
[11]J. A. Mills, *Biochem. Biophys. Res. Commun.* **6**, 418 (1961)
[12]S. J. Angyal and R. J. Hickman, unpublished results
[13]J. L. Frahn and J. A. Mills, unpublished results
[14]A. D. Buckingham, *Canad. J. Chem.* **38**, 300 (1960)
[15]S. J. Angyal, *Austral. J. Chem.* **25**, 1957 (1972)
[16]D. R. Crump, J. K. Sanders and D. H. Williams, *Tetrahedron Letters* 4419 (1970)
[17]J. D. Roberts, G. E. Hawkes, J. Husar, A. W. Roberts and D. W. Roberts, *Tetrahedron* this issue.
[18]W. D. Horrocks, Jr., and J. P. Sipe, III, *J. Am. Chem. Soc.* **93**, 6800 (1971); *Science* **177**, 994 (1972)
[19]G. E. Hawkes, D. Leibfritz, D. W. Roberts and J. D. Roberts, *J. Am. Chem. Soc.* **95**, 1659 (1973); G. E. Hawkes, C. Marzin, S. R. Johns and J. D. Roberts, *Ibid.* **95**, 1661 (1973)
[20]C. C. Hinckley, M. R. Klotz and F. Patil, *Ibid.* **93**, 2417 (1971)
[21]B. F. G. Johnson, J. Lewis, P. McArdle and J. R. Norton, J.C.S. *Chem. Commun.* 535 (1972)
[22]O. A. Gansow, P. A. Loeffler, R. E. Davis, M. R. Willcott, III, and R. E. Lenkinski, *J. Am. Chem. Soc.* **95**, 3389 (1973)
[23]S. J. Angyal and D. Greeves and V. A. Pickles, *J.C.S. Chem. Commun.* in press.
[24]H. M. McConnell and R. E. Robertson, *J. Chem. Phys.* **29**, 1361 (1958)
[25]W. B. Lewis, J. A. Jackson, J. F. Lemons and H. Taube, *Ibid.* **36**, 694 (1962)
[26]*E. R. Birnbaum and T. Moeller, J. Am. Chem. Soc.* **91**, 7274 (1969)
[27]T. Yonezawa, I. Morishima and Y. Ohmori, *Ibid.* **92**, 1267 (1970); I. Morishima, K. Okada, M. Ohashi and T. Yonezawa, *Chem. Commun.* 33 (1971); I. Morishima, K. Okada, T. Yonezawa and K. Goto, *J. Am. Chem. Soc.* **93**, 3922 (1971).
[28]P. A. J. Gorin, personal communication
[29]S. J. Angyal, *Carbohydrate Research* **26**, 271 (1973)
[30]P. L. Durette and D. Horton, *Advances in Carbohydrate Chemistry and Biochemistry* **26**, 49 (1971)
[31]M. E. Evans and S. J. Angyal, *Carbohydrate Research* **25**, 43 (1972)
[32]S. J. Angyal, C. L. Bodkin and F. W. Parrish, unpublished results