COMPLEX FORMATION BETWEEN SUGARS AND METAL IONS

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ABSTRACT

Cyclitols and sugars containing an axial-equatorial-axial sequence of three hydroxyl groups in a six-membered ring, or a *cis cis* sequence in a five-membered ring, form 1:1 complexes with metal cations in hydroxylic solvents. At least one of the hydroxyl groups can be replaced by a methoxy group without substantially affecting complex formation. Lanthanum(III) forms the strongest complexes (K about 10 mol^{-1} l in water), followed by calcium and strontium. Complex formation causes downfield shifts of the signals in the p.m.r. spectrum, that of the hydrogen atom vicinal to the oxygen atom central in the *ax-eq-ax* sequence being the largest.

Complex formation will change the conformational equilibrium of methyl β-D-ribopyranoside and β-D-lyxopyranose; it will change the anomeric equilibrium of allose, gulose, ribose, and lyxose. It will also alter the equilibrium in methanol between the methyl glycosides of the above-mentioned sugars; in the presence of calcium or strontium chlorides, methyl glycosides can be synthesized which normally are only minor products of methanolysis. Complex formation makes possible the separation of some sugars by electrophoresis and on ion-exchange columns.

INTRODUCTION

The field of sugar metal complexes is still largely unexplored. Yet it is not a small field: the chemical literature records[1] at least 70 crystalline complexes which contain a sugar (or a sugar derivative) and an inorganic salt in stoichiometric proportion (usually 1:1). Without detailed investigation of these complexes it is not possible to determine whether they are specific coordination compounds of one molecule of sugar with one cation—which would remain associated in solution—or arrangements held together in the crystal lattice by intermolecular forces. x-Ray crystallographic analyses would be desirable but have been carried out only in two cases so far. One is that of sucrose sodium bromide dihydrate[2] in which both the cation and the anion were found to be coordinated to more than one sucrose molecule. The other one, D-mannose calcium chloride tetrahydrate, will be discussed later.

The coordination complexes discussed in this lecture are formed by displacement of water molecules in the solvation sphere of cations by

hydroxyl groups of a polyol. Since water solvates ions much better than does a monohydric alcohol, the latter will not displace water to any considerable extent. If two or more hydroxyl groups in a compound are in a sterically favourable arrangement they may displace two or more molecules, respectively, of water from the solvation sphere. There are no cases known, however, of diols complexing strongly with cations in aqueous solution; it appears that at least three hydroxyl groups in favourable steric arrangement are required for complex formation. What constitutes a 'favourable steric arrangement' is a question discussed in this lecture. Only complexes formed in neutral solution are being considered; in alkaline solution hydroxyl groups can, after losing a proton, form much stronger complexes with which, however, we are not here concerned.

Complex formation between sugars and cations in solution has been studied by a variety of methods, such as determination of changes in solubility, vapour pressure, and optical rotation[1]. These studies have produced evidence for complex formation between some sugars and some cations; they have not, however, allowed the determination of stability constants, nor given information on the steric arrangement required for complex formation.

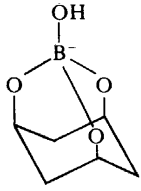
There are two methods which are particularly suitable for the study of these complexes in solution: paper electrophoresis[3] and nuclear magnetic resonance. The former method allows rapid determination of whether a complex is formed or not; if it is, the sugar migrates towards the cathode. It allows rapid comparison of various sugars and various cations in respect of their complexing ability. It is not suitable, however, for determination of stability constants because the electrophoretic mobility depends not only on the extent to which the sugar has been converted into its complex but also on the ionic mobility of the complex ion. This varies considerably and is not readily determined.

The application of proton magnetic resonance spectroscopy to the study of sugar–metal complexes is the subject of this lecture.

COMPLEXING WITH CYCLITOLS

The first suggestions about the geometrical requirements for complex formation with cations are contained in a paper by Mills[4] who found that on electrophoresis in slightly acid solutions of many salts (particularly those of calcium, strontium, and barium) *cis*-inositol migrates rapidly towards the cathode, and *epi*-inositol, D-talose, L-iditol, and some other polyols have good, though lesser, mobility. The behaviour of the cyclitols is reminiscent of their electrophoresis in sodium borate solution in which they show strong mobility towards the anode[5]. It has been established that tridentate borate ester anions (I) are formed by participation of three axial oxygen atoms; *cis*-inositol, which has three axial hydroxyl groups on the same side of the molecule in either of its two chair conformations, moves much more rapidly than *epi*-inositol and 1,2,3,4,5/0-cyclohexanepentol which have to 'flip' to their less stable chair form first. Mills suggested that participation of the three axial oxygen atoms is also responsible for complexing of these cyclitols with cations. This hypothesis can be put to test by the use of n.m.r. spectroscopy. On complex formation with borate anions the n.m.r. spectrum of

epi-inositol (II) changes[6] and the coupling constants show that this change is due to the chair–chair interconversion to the triaxial complex (III). Should the same change be observed on complexing with metal cations, the extent of complexing, and hence the stability constants of the complexes, could be determined.



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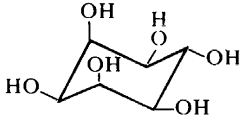

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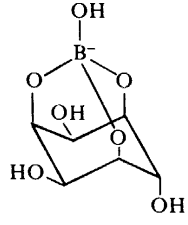


(III)

When calcium chloride was added to a solution of *epi*-inositol (II) in deuterium oxide a significant change occurred in the n.m.r. spectrum[7] (*Figure 1*). There was no change, however, in the splitting of the signals, indicating that there is no alteration in the conformation of the cyclitol. The chemical shifts changed, however, all signals moving to lower field; one signal in particular—readily identified by its coupling constants as that of H-3—moved more than the others, its position amongst the others being dependent on the concentration of calcium ions.

Whilst this work was in progress, McGavin, Natusch, and Young reported[8] that complexing with cations causes a downfield shift of the signals of some protons in the p.m.r. spectra of several glycosides. This complexing was weak (K *ca* 0.1 mol^{-1} l) and was attributed to coordination with two adjacent oxygen atoms of the glycosides.

These downfield shifts are reminiscent of those caused by paramagnetic shift reagents, though they are much smaller. In this case they are due to the dipole formed by the cation and the three oxygen atoms. Since the shielding change of a hydrogen atom bonded to a carbon atom is greatest when the electrostatic field is in the direction of the H–C bond, it was assumed that the metal ion in the *epi*-inositol–calcium ion complex is located approximately in the direction of the bond from H-3 to C-3. Hence the cation seems to be coordinated to O-2, O-3, and O-4, that is, to three oxygen atoms in an *ax–eq–ax* sequence (as shown in (IV)). Similar shifts are observed in the spectra of 1,2,3,4,5/0-cyclohexanepentol (V) and 1,2,3,4/5-cyclohexanepentol (VI), the hydrogen atom (shown in the formulae) whose signal is shifted most,

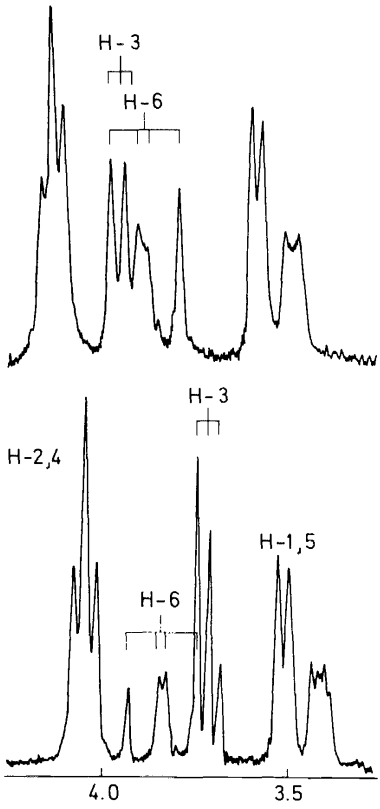
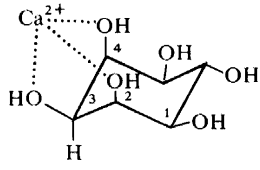


Figure 1. The 100 MHz n.m.r. spectrum of *epi*-inositol in deuterium oxide (lower curve) and in a 1.12M solution of calcium chloride in deuterium oxide (upper curve).

being the one attached to the carbon atom bearing the central oxygen atom of the *ax–eq–ax* sequence. *allo*-Inositol (VII), which also has an *ax–eq–ax* sequence, also complexes well; the other cyclitols form only weak complexes with calcium ions[7]. 3-*O*-Methyl-*epi*-inositol shows downfield shifts in its n.m.r. spectrum, and an electrophoretic mobility, which are only slightly smaller than those of *epi*-inositol; the substitution of a methoxy group for one of the hydroxyl groups in the *ax–eq–ax* sequence therefore does not destroy the ability to form complexes but reduces it somewhat.

When europium (III) chloride was added to a solution of *epi*-inositol similar, but much larger, shifts of the proton signals were observed. The signals were sharp, with no broadening, and their splittings were unchanged. This experiment shows that paramagnetic metal ions can be used to expand the spectra of unsubstituted polyols if coordination occurs at a specific site. These large, readily measured, spectral changes supply information on the geometry of the molecule and will provide a new method for studying the structure of metal–polyol complexes and the conformation of polyols in solution.

It appears from these experiments that the *ax–eq–ax* sequence of three oxygen atoms on a six-membered ring forms a good site for complex formation with cations. Extensive electrophoretic experiments[9,10] have since shown that every sugar which has such an arrangement in its pyranose form (or can achieve it without undue expenditure of free energy) forms complexes with calcium ions; for example, talose and ribose. Sugars and sugar derivatives lacking this arrangement show low mobility on electrophoresis.



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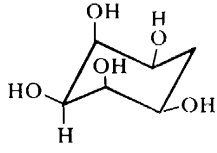

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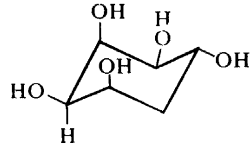

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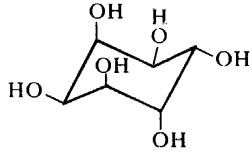
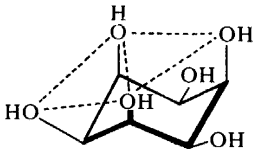


(VII)

Jeffrey and Kimm[11] have shown that in the crystals of *epi*-inositol the two axial oxygen atoms are separated by 2.95 Å, owing to their mutual repulsion. The distance between an axial and a vicinal equatorial oxygen atom is about the same; the three oxygen atoms in the *ax–eq–ax* sequence therefore form an approximately equilateral triangle. This triangle appears to constitute a good complexing site for cations.

cis-Inositol is a unique compound. Recent x-ray crystallographic analysis[12] has shown that each axial oxygen atom is equidistant from four other (2 axial, 2 equatorial) oxygen atoms. There are three *ax–eq–ax* sequences and, in addition, a similar triangle formed by the three axial oxygen atoms, offering thereby four sites for complexing (VIII). It is not surprising therefore that its complexes are much more stable than those of any other polyol so far studied. By potentiometric measurements[10] of the calcium ion concentration the stability constant of the *cis*-inositol–calcium complex was found to be 21 mol^{-1} l, that of the *epi*-inositol complex 3.2 mol^{-1} l. These measurements also showed that at higher concentrations some 2:1 complex is present in equilibrium in addition to the 1:1 complex.

Because the binding site in *epi*-inositol for complexing with a cation is different from the one used for forming a borate ester—and in a different conformation of the ring—it was of interest to look at the ester ion formed with periodate. Barker, who described[13] the existence of such triesters of periodate ion, suggested that the iodine atom is attached to an *ax–eq–ax* sequence of oxygen atoms. The n.m.r. spectrum confirmed this suggested structure (IX). It also showed that the ester is surprisingly stable; the spectrum was still clearly recognizable after the aqueous solution of the ester stood for a day. It appears that the borate anion requires the triaxial site for bonding because this alone allows tetrahedral angles on the boron atom and short boron–oxygen distances. Considerable free energy is required, however, to 'flip' *epi*-inositol into the chair form with three axial oxygen atoms. In the periodate ester and in the complexes with cations the bond angles are not tetrahedral and the interatomic distances are much longer than the boron–oxygen bond; hence the *ax–eq–ax* site is used, without the need for 'flipping'.



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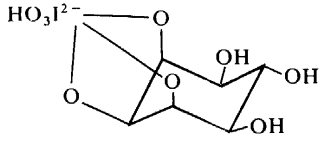

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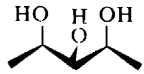


(X)

It is interesting to mention that formation of the complexes with cations is fast on the n.m.r. time-scale; hence, at room temperature, the spectra of the complexed and uncomplexed molecules are not seen separately, but an average spectrum is observed. By contrast, formation of the periodate ester ion is slower; when less than one equivalent of periodate is added to *epi*-inositol the superimposed spectra of the inositol and its complex are observed.

Alditols which have three consecutive *threo* hydroxyl groups also show good mobility on electrophoresis and this becomes greater when there are four or five such groups (D-iditol, *meso-glycero-ido*-heptitol)[9]. In the planar zigzag conformation these compounds have three (or more) oxygen atoms in the same geometrical arrangement (X) as in the *ax–eq–ax* sequence on a six-membered ring in the chair form.

COMPLEXING WITH D-ALLOSE

In order to compare the complexing ability of various cations with the *ax–eq–ax* sequence of oxygen atoms, and to determine stability constants, a

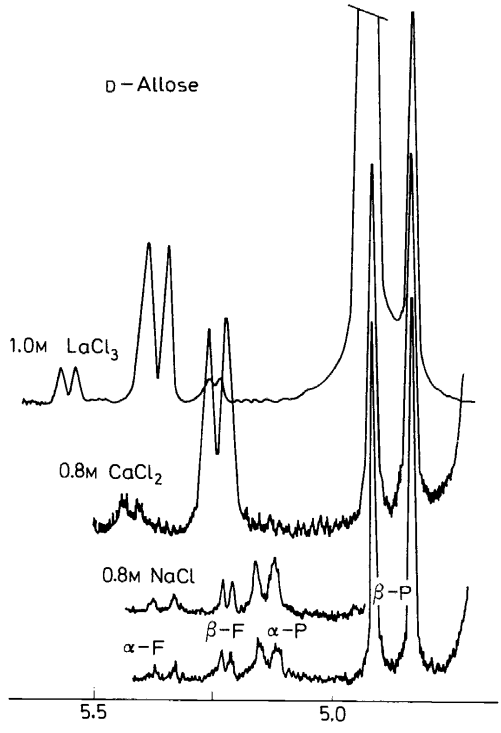
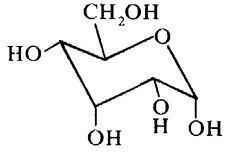


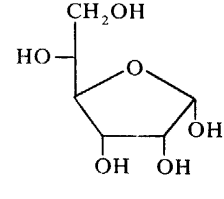
Figure 2. The anomeric region of the 100 MHz n.m.r. spectrum of D-allose in deuterium oxide (lower curve) and in 0.8M sodium chloride, 0.8M calcium chloride, and 1.0M lanthanum chloride (successive curves), all in deuterium oxide.

tautomeric system was sought in which one component of the equilibrium has, and the other has not, the required steric arrangement. Such a system was found[14] in the anomeric equilibrium of D-allose.

α-D-Allopyranose, in its more stable *C1* conformation (XI), contains *ax–eq–ax* sequence of hydroxyl groups but the β-anomer does not. Hence addition of a complexing cation should increase the proportion of the α-anomer in equilibrium. The proportion of the pyranose and furanose anomers in aqueous solution can readily be determined from the n.m.r. spectrum (*Figure 2*); the signals of the anomeric protons of the four tautomeric



(XI)



(XII)

forms are well separated from each other. Addition of complexing salts to the solution of D-allose in deuterium oxide causes two changes in the n.m.r. spectrum: the signal of the α-pyranose increases in intensity and shifts downfield (*Figure 2*). The effect of sodium ion is small: it complexes weakly. Calcium ion causes a substantial increase in the proportion of the α-pyranose form; its anomeric signal shifted downfield so as to overlap with that of the β-furanose form. The effect of lanthanum ion is even greater; of all the cations investigated it forms the most stable complexes and causes the greatest downfield shifts in the n.m.r. spectrum.

If it is assumed that the proportion of the uncomplexed tautomers is not affected by the presence of ions, the amount of uncomplexed α-pyranose can be calculated. The excess over this figure is regarded as being complexed to the cation. The stability constant can then be calculated.

Table 1. The effect of salts on solutions of D-allose in deuterium oxide: composition, stability constants of complexes formed with α-D-allopyranose, and downfield shift of the anomeric signal of α-D-allopyranose

Salt	M	α-F %	β-F %	α-P %	β-P %	K mol^{-1} l	$\Delta\delta$ ppm
		3.5	5.0	14.0	77.5		
NaCl	1.6	3.0	4.4	16.1	76.5	0.12	0.02
$MgCl_2$	1.1	3	5	16.5	75.5	0.19	0.02
$CaCl_2$	0.7	6.7	44.2		49.1	6.2	0.10
$Y(NO_3)_3$	0.7	4.2	30.8		65	1.9	0.14
$LaCl_3$	0.9	10.4	2.6	49.4	37.6	10.4	0.22

By this method the complexing ability of various cations with D-allose was compared; some of the results are shown in *Table 1*. The monovalent metals form only weak complexes, that of sodium being comparatively the most stable. Amongst the alkaline earth metals, calcium forms the strongest complexes, followed by strontium and barium; magnesium complexes weakly, beryllium has no observable effect. Lead(II) forms comparatively strong complexes; cadmium and tin(II) weaker ones; the effect of zinc is barely noticeable, and mercury(II) forms no complex. Although lanthanum forms the strongest complexes, the element above lanthanum in the periodic table, yttrium, complexes weakly (K 1.9 mol^{-1} l).

It appears that the optimum ionic radius for complex formation with the *ax–eq–ax* sequence of hydroxyl groups is about 1.0 Å (Na^+ 0.97, Ca^{2+} 0.99, La^{3+} 1.02 Å). For the same ionic radius, higher charge of the cation gives stronger complexes (and also causes greater downfield shift of the n.m.r. signals). The nature of the anion does not appear to have any substantial effect.

The n.m.r. spectra of D-allose and the data in *Table 1* also show that the signal of the anomeric proton of the α-furanose form (XII) also increases and moves downfield on the addition of metal ions. 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 hydroxyl groups on a five-membered ring also constitutes an arrangement suitable for the formation of complexes with metal ions. Since the proportion of furanoses in the equilibrium solution of D-allose is small, the changes in their proportion cannot be accurately measured. Hence the equilibrium of 5-*O*-methyl-D-ribose was studied; the n.m.r. spectrum showed that there is 33 per cent of α-furanose and 67 per cent of β-furanose at equilibrium in aqueous solution; on addition of calcium chloride to make the solution 1.6M the composition changes to 70 per cent α and 30 per cent β. The stability constant therefore is 3 mol^{-1} l, somewhat smaller than that of the α-pyranose form. The α-furanose can easily take up a conformation in which O-1, O-2, and O-3 are quasi-axial, quasi-equatorial, and quasi-axial, respectively; this arrangement does not differ greatly from the favoured *ax eq ax* arrangement in six-membered rings.

Striking confirmation of this assumption is provided by the recent x-ray crystallographic analysis[15] of β-D-mannofuranose calcium chloride tetrahydrate. In this compound the calcium ion was found to be coordinated to O-1, O-2, and O-3 of mannose which are in a geometrical arrangement close to that of an *ax–eq–ax* sequence in a six-membered ring. (The ion is also coordinated to O-4 and O-5 of another mannose molecule.)

The conclusion that α-D-allopyranose and α-D-allofuranose complex with cations, but the β-anomers do not, is also confirmed by paper electrophoresis of the corresponding methyl glycosides: the α-pyranoside and the α-furanoside migrate (the former somewhat faster), the β-anomers do not[10]. This experiment again shows that the presence of a methyl group on one of the oxygen atoms of the *ax–eq ax* sequence does not prevent complex formation.

COMPLEXING WITH OTHER SUGARS

D-Gulose and D-*glycero*-D-*gulo*-heptose, sugars which have an *ax–eq–ax* sequence of O-1, O-2, and O-3 in the α-pyranose forms, behave like D-allose on addition of cations to their solutions: the proportion of the α-pyranose form increases and its signal shifts downfield. The extent of complexing is similar to that of D-allose; with lanthanum chloride K is calculated to be 11.5 mol^{-1} l. The proportion of the furanose forms in these sugars is very small[16], however, and the furanose signals are not observed.

More than 40 years ago Isbell[17] had already observed complex formation between D-gulose and calcium ions. He found that an equilibrated solution of D-gulose, $CaCl_2$ underwent further mutarotation on dilution with water. He correctly interpreted the phenomenon by postulating that α-D-gulopyranose, but not β-D-gulopyranose, forms a complex with calcium ions, and that this complex dissociates on dilution. Isbell had no means, however, for determining the steric requirements for formation of the complex.

No substantial changes in the equilibrium composition or in the n.m.r. spectra of D-glucose, D-mannose, and D-arabinose were observed on the addition of calcium chloride. These sugars lack the required *ax–eq–ax* sequence of hydroxyl groups.

Complexing of D-ribose with metal ions presents an interesting case[14]. The α-pyranose and the α-furanose signals in the n.m.r. spectrum (*Figure 3*)

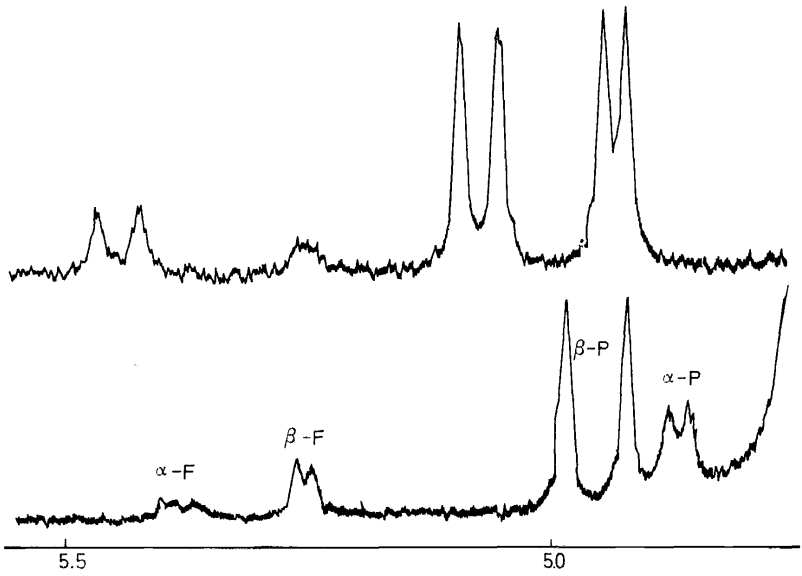


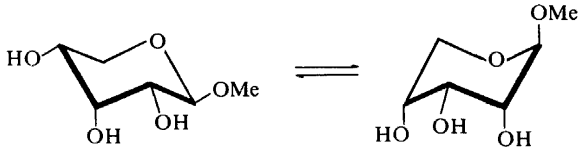
Figure 3. The anomeric proton signals in the n.m.r. spectrum of D-ribose at 100 MHz in deuterium oxide (lower curve) and 1.27M calcium chloride solution in deuterium oxide (upper curve).

have shifted downfield on addition of calcium chloride, as expected since they have the required arrangement of three hydroxyl groups. However, the signal of the β-pyranose form has also shifted, and, in this case, there is also a change in its splitting (from 6.4 to 4.2 Hz). In aqueous solution β-D-ribopyranose is a conformational mixture of approximately 3 parts of the *C1* and 1 part of the *1C* forms[16]; the latter contains an *ax–eq–ax* sequence of O-2, O-3, and O-4 which can form a complex. Hence complex formation will change the conformational equilibrium, and the change in chemical shift and in the splitting both reflect the increasingly equatorial character of the anomeric hydrogen atom. In 1.27M calcium chloride solution, as calculated from the splitting, over 60 per cent of the β-pyranose is in the *1C* conformation.

Table 2. The effect of added calcium chloride on the conformation of methyl β-D-ribopyranoside in deuterium oxide

$CaCl_2$ (M)	—	0.7	1.4	2.1
$J_{1,2}$ (Hz)	5.4	3.6	2.95	2.5
C1 form (%)	57	29	19	12

To confirm this interpretation of the behaviour of β-D-ribopyranose, the complexing of methyl β-D-ribopyranoside was investigated. On successive additions of calcium chloride to its aqueous solution the *C1* form (XIII) is gradually converted to the *1C* form (XIV) as shown by the data in *Table 2*.



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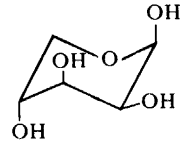

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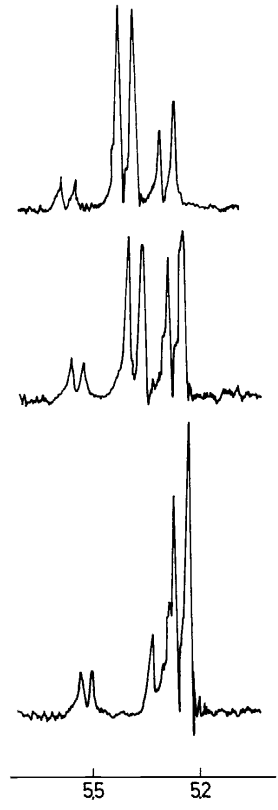
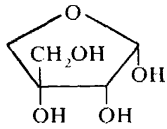


Figure 4. The anomeric proton signals in the n.m.r. spectrum of D-apiose at 100 MHz in deuterium oxide (lower curve) and in 0.81 and 1.46M calcium chloride solution in deuterium oxide (successive curves).

Conformational change is also involved in the complex formation of D-lyxose. The α-pyranose form lacks the required *ax–eq–ax* sequence but the β-pyranose form contains it in its *1C* conformation (XV). This conformation, with three axial hydroxyl groups, is not normally observed. The n.m.r. spectrum[18] of D-lyxose in 2.15M calcium chloride solution shows that the β-anomer is strongly complexed: its proportion is about 50 per cent (compared to 28 per cent in the absence of cations) and its signal appears at lower field than that of the α-anomer (in contrast to that of uncomplexed β-D-lyxopyranose). The splitting of the anomeric proton signal is greater (2.6 Hz) than that found (1.5 Hz) for the *C1* form; all this indicates considerable 'flipping' to the *1C* form.



(XVI)

Complex formation was also used to study the equilibrium present in the solution of D-apiose. This branched-chain sugar can exist in four furanose forms (two α, two β); nothing is known about their proportion in equilibrium. The n.m.r. spectrum of D-apiose in deuterium oxide shows three anomeric signals (*Figure 4*). On addition of calcium chloride the middle signal shifts downfield and becomes the major component. It is assumed that this is the signal of the anomeric proton of α-D-apio-D-furanose (XVI) which has three *cis* hydroxyl groups on C-1, C-2, and C-3.

APPLICATIONS

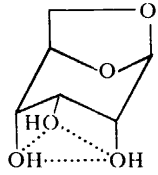
Complex formation between sugars and cations can be of manifold practical use; some examples are given below.

(i) Sugars which do not crystallize can sometimes be obtained, and purified, as crystalline complexes with salts, e.g. α-D-gulopyranose, $CaCl_2$ and methyl β-D-mannofuranoside, $CaCl_2$. One would now try to crystallize particularly those sugars which have the *ax–eq–ax* or the *cis–cis* sequence of three hydroxyl groups, with various calcium and strontium salts. It appears likely, for example, that D-apiose could be obtained crystalline in this way.

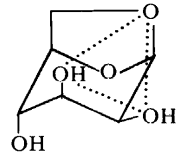
(ii) Polyols and sugars with a suitable configuration can sometimes be purified through their metal complexes. For example, *epi*-inositol often contains *myo*-inositol which is not readily separated from it by crystallization. However, crystallization in the presence of calcium chloride gives a complex of *epi*-inositol while the *myo* isomer remains in the mother liquors.

(iii) Qualitative separation of many sugars and polyols can be achieved by paper electrophoresis in salt solutions; an understanding of the geometry of the complexing site now allows prediction of the expected separation. The 1,6-anhydrohexopyranoses provide a good example[10]. 1,6-Anhydro-β-D-allopyranose (XVII), having an *ax–eq–ax* sequence of three hydroxyl

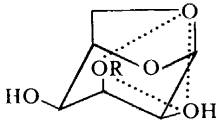
groups, migrates rapidly (mobility relative to *cis*-inositol, 0.58); the *manno* (XVIII) and *talo* (XIX) isomers move less rapidly (0.25 and 0.33, respectively) because here one of the axial oxygen atoms is involved in a ring. 1,6-Anhydro-β-D-glucopyranose (XX) migrates slowly (0.07); complex formation here utilizes the two axial and the ring oxygen atoms, a less favourable site. The other 1,6-anhydrohexopyranoses do not migrate.



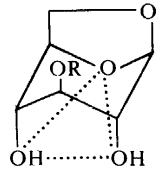
(XVII)



(XVIII)



(XIX)



(XX)

(iv) Preparative separation of some sugars can be achieved by chromatography on an anion-exchange resin containing a metal ion. For example, Jones and Wall[19] separated the products formed by the action of alkali on D-galactose, namely, D-galactose, D-tagatose, and D-talose, by chromatography on a column of Dowex 50 W in the barium form. The order of emergence of these compounds from the column is now understood, and could be predicted: D-talose contains an *ax–eq–ax* sequence in either of its pyranose forms, D-tagatose only in the (less stable) β-pyranose form, and D-galactose not at all. Recently Sowa[20] described a remarkable synthesis of D-altrose from D-allose; the two sugars were ultimately separated by preparative paper chromatography, a method unsuitable for large-scale use. Undoubtedly they could now be separated on a column in the calcium or strontium form, D-altrose being the first to be eluted.

(v) In some cases analysis of the n.m.r. spectrum of a polyol is facilitated by the downfield shift of signals on complex formation. An example is shown in *Figure 5*: the signals of the methylene group in the spectrum of 1,2,3,4,5/0-cyclohexanepentol overlap and cannot be readily analysed. In 2.25M calcium chloride solution, owing to the downfield shift of the signal of the axial hydrogen atom, first-order analysis becomes possible. Europium(III) as a complexing cation would presumably be more effective but has not yet been tried.

(vi) The outcome of chemical reactions which lead to equilibria can be altered by the 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

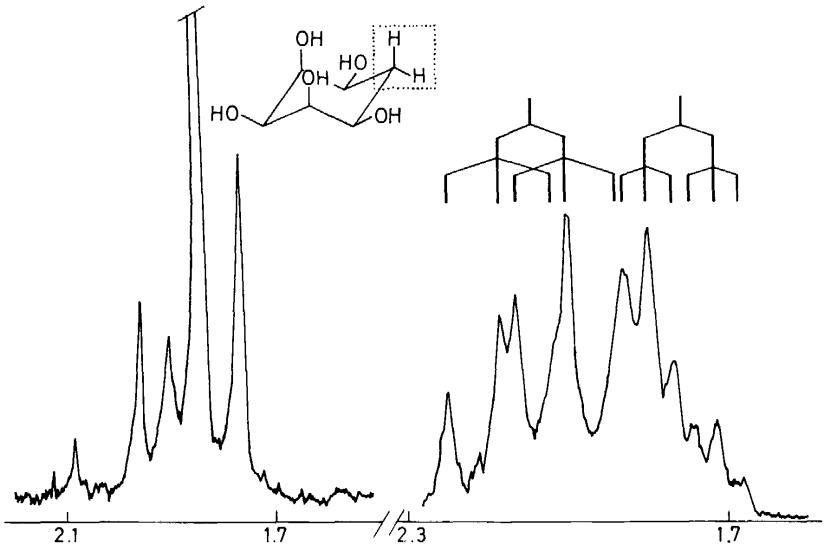


Figure 5. The signals of the methylene group in the n.m.r. spectrum of 1,2,3,4,5/0-cyclohexanepentol in deuterium oxide (left) and in a 2.25M solution of calcium chloride in deuterium oxide (right).

complexing with metal ions is much stronger in alcoholic than in aqueous solutions[1]. When D-allose is heated with methanolic hydrogen chloride, the predominant product 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[21]. Good syntheses have been worked out[22], by this method, for methyl α-D-gulopyranoside, α-D-ribofuranoside, β-D-lyxopyranoside, and β-D-lyxofuranoside. The last compound was unknown until quite recently; in the absence of cations very little of it is formed in the methanolysis of D-lyxose.

ALGINATES

The type of complexing described in this lecture between metal ions and monosaccharides does not appear to be of great biological significance. On the one hand, with the exception of D-ribose, sugars containing an *ax–eq–ax* sequence of hydroxyl groups are uncommon in Nature; on the other, extensive complexing at this site requires concentrations of cations greater than those commonly occurring in biological systems. However, complexing with polysaccharides may be of importance because coordination of the metal ion may occur with more than three oxygen atoms. The calcium salt of alginic acid may be a relevant example.

Alginic acid is a polysaccharide of industrial importance because its calcium salt forms gels useful for the food industry. It consists of two sugar residues, β-D-mannopyranosyluronic acid (in the *C1* form) and α-L-gulopyranosyluronic acid (in the *1C* form) in varying proportion, each of which is linked through C-4. The latter seems to be responsible for the gelling of calcium alginate; the higher the guluronic acid content, the better the gelling properties. Moreover, it was found[23] that polyguluronic acid, alone amongst the polyuronic acids, shows selectivity of complexing: it forms much stronger complexes with strontium and calcium than with magnesium or sodium ions.

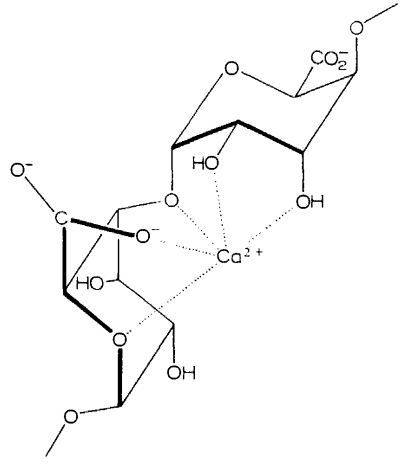


Figure 6. Proposed partial structure of calcium alginate.

Now α-L-gulopyranosyluronic acid has an *ax–eq–ax* sequence of oxygen atoms (O-1, O-2, O-3) and it is tempting to suggest that gelling is due to complex formation at this site. A structure can be built without strain in which a calcium ion is coordinated to the three oxygen atoms of this site and, in addition, to the carboxylate ion and another oxygen atom of an adjacent uronic acid residue (*Figure 6*). Stiffening of the polysaccharide chain by this complex formation may be the cause of gelling. Alternatively, it is possible that a calcium ion coordinated to the *ax–eq–ax* site of one chain and a carboxylate ion of another chain causes packing of the chains, and thereby gelation. Work is at present in progress on the structure of calcium alginate.

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