# Complexing of Sugars with Metal Ions

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*Summary* Sugars containing an *ax-eq-ax* sequence of three hydroxy-groups in a six-membered ring, or a *cis-cis* sequence in a five-membered ring, form complexes with metal ions, and particularly with alkaline-earth metal ions, in aqueous solution.

COMPLEXES formed between sugars and inorganic salts are known and there is much evidence to show that in aqueous solution these complexes are formed reversibly.[1-3] However, little is known about the structures of these complexes as they exist in solution or their stability constants.

Recently McGavin, Natusch, and Young[4] studied the [1]H n.m.r. spectra of some sugars in aqueous ($D_2O$) solution and found that addition of metal ions causes small downfield shifts of the signals of some hydrogen atoms. Assuming the formation of 1:1 complexes, they calculated stability constants to be low (*ca.* $0.1M^{-1}$).

In order to obtain more information on complex formation, *epi*-inositol was investigated since this compound is known[3] to complex strongly with metal ions and in its n.m.r. spectrum every proton is readily distinguishable. Addition of calcium chloride to its solution in $D_2O$ causes a strong downfield shift ($0.32$ p.p.m. in $2M$-$CaCl_2$ solution) of one proton, recognized by its coupling constants ($J_{2,3} = J_{3,4}$ $3.25$ Hz) as H-(3); the other protons also shift but to a lesser extent. There is no change in the coupling constants. 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,[5] it was assumed that the metal ion in the complex is located approximately in the direction of the bond from H-(3) to C-(3); it would then be co-ordinated to O-(2), O-(3), and O-(4) (I). It appears that an *ax-eq-ax* sequence of three oxygen atoms is favourable for complex formation; the other cyclitols (*allo*- and *cis*-inositols and *cis*-quercitol) which are known to complex strongly[3] have such an arrangement, but *myo*-inositol, which has not, shows neither strong complexing, nor pronounced changes in chemical shifts. An approximate calculation, from the chemical shifts, of the stability constant of the *epi*-inositol–calcium ion complex gave a value of $3M^{-1}$.

In order to confirm our hypothesis, and obtain more accurate values of the stability constants, the equilibrium of D-allose in aqueous solution was investigated.

α-D-Allopyranose has the required arrangement of hydroxy-groups but the β-anomer has not. Hence addition of an inorganic salt should increase the proportion of the α-form in equilibrium; this was found to be the case. Since the position of the equilibrium is readily obtained from the n.m.r. spectra,[6] different metal ions can be compared and stability constants calculated. Calcium and strontium ions give the strongest complexes ($K$ *ca.* $4M^{-1}$) while magnesium complexes weakly. Of the alkali metals, sodium complexes weakly ($K$ *ca.* $0.1M^{-1}$), while no complex formation was observed with lithium, caesium, and rubidium.

In a $0.85M$-solution of $CaCl_2$ the equilibrium composition of D-allose is $4.5\%$ α-furanose, $3.8\%$ β-furanose, $37.2\%$ α-pyranose, and $54.5\%$ β-pyranose, compared with $3.4:5.3$

: $13.8 : 77.5$ in the absence of salts at $30°$. Hence *ca.* $75\%$ of α-D-allopyranose is in the form of a complex. At higher calcium concentrations there is more α- than β-pyranose in the equilibrium solution. Methylation in the 3-position (to 3-*O*-methyl-D-allose) reduces the extent of complex formation of the α-pyranose, but not of the α-furanose, form. D-Gulose behaves similarly; Isbell[7] concluded, from his studies of optical rotation, that the α-pyranose form complexes with calcium ions.

The n.m.r. spectra show that not only the α-pyranose but also the α-furanose signal increases on addition of calcium chloride to a solution of D-allose; both signals shift downfield. To study the furanose forms better, 5-*O*-methyl-D-ribofuranose was investigated. Addition of calcium chloride to its solution changed the α : β ratio from $33:67$ in $D_2O$ to $70:30$ in $1.57M$-calcium chloride solution; $K$ is then *ca.* $3 M^{-1}$, that is, somewhat smaller than for the pyranose forms. It is assumed that complexing occurs at O-(1), O-(2) and O-(3), which are *cis* in the α-form; the signal of H-(1) of the α-furanose shifts downfield on complex formation, but the signals of H-(2) and H-(3) are not discernible in the spectrum.



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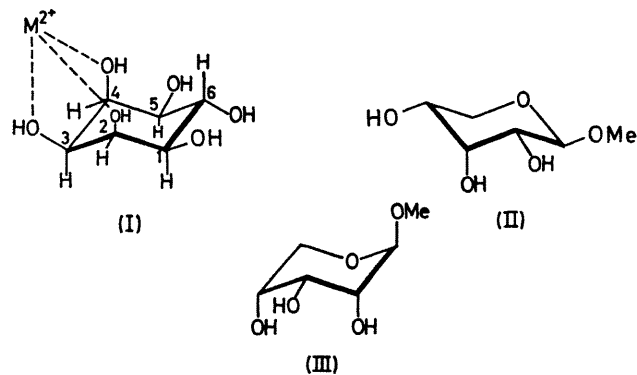
No substantial changes in the equilibrium composition or in the n.m.r. spectra of D-glucose, D-mannose, and D-arabinose were observed on the addition of calcium chloride. These sugars lack the required *ax-eq-ax* sequence of hydroxy-groups.

α-D-Lyxopyranose does not contain the required *ax-eq-ax* sequence but the β-anomer does in its less stable 1C(D) conformation (which is not normally observed).[8] Addition of calcium chloride to a solution of D-lyxose causes an increase in the proportion of the β-form and a shift of its anomeric signal downfield until, at high calcium concentration, that of the β-anomer appears at lower field than that of the α-anomer; at the same time $J_{1,2}$ of the β-form increases from $1.5$ Hz to *ca.* $2.8$ Hz, indicating that its conformation has been changing into the 1C(D) form.

As another instance of a conformational change caused by complex formation, methyl β-D-ribopyranoside was studied. In aqueous solution this compound is in equilibrium between the C1(D) (II) and the 1C(D) (III) forms, the former predominating ($J_{1,2}$ $5.4$ Hz). On addition of

calcium chloride to its solution, the H-(1) signal moves downfield and $J_{1,2}$ decreases; in 2·08M-solution $J_{1,2}$ is 2·5 Hz, corresponding to 88% of the 1C(D) form. The calculated stability constant of the complex between the 1C(D) form and calcium chloride is *ca.* 5 M$^{-1}$.

All tautomeric forms of D-ribose, except the $\beta$-furanose, have an arrangement suitable for complexing with metal ions, the $\beta$-pyranose only in its 1C(D) form. On addition of calcium chloride to a solution of D-ribose the proportion of the $\alpha$-pyranose and the $\alpha$-furanose forms increases and $J_{1,2}$ of the $\beta$-pyranose form decreases.

On heating D-allose with methanolic hydrogen chloride the main product is methyl $\beta$-D-allopyranoside.[9] When the reaction is carried out in the presence of calcium chloride, the $\alpha$-furanoside or the $\alpha$-pyranoside become the main product, depending on the period of heating. Complexing with metal ions can therefore be used in some cases to control the outcome of reactions of sugars.

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