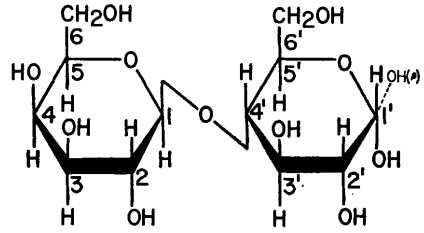
Calcium Ion Binding to Uncharged Sugars: Crystal Structures of Calcium Bromide Complexes of Lactose, Galactose, and Inositol

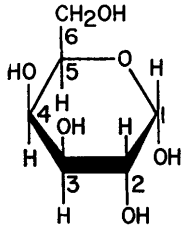
By CHARLES E. BUGG* and WILLIAM J. COOK
(*Institute of Dental Research, University of Alabama in Birmingham, 1919 Seventh Avenue, South, Birmingham, Alabama* 35233)

Summary Interactions of calcium ions with uncharged sugars lead to complexes in which the calcium ions are surrounded by square-antiprism co-ordination shells composed of water molecules and sugar hydroxyl groups.

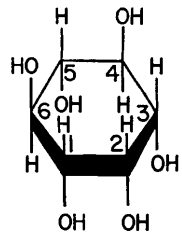
IT has been demonstrated that calcium ions complex with uncharged sugars in aqueous solutions,[1–4] and it is likely that interactions of this type are of importance in biological calcium transport processes[2] and in the binding of calcium ions to carbohydrates of cell surfaces.[5–6] However little is known about the factors involved in sugar–calcium interactions, or about the stereochemistry of the resultant complexes. We report the stereochemistry and calcium interactions in the crystal structures of hydrated calcium bromide complexes of lactose (I), α-galactose (II), and *myo*-inositol (III).



(I) $CaBr_2 \cdot 7\,H_2O$



(II) $CaBr_2 \cdot 3H_2O$



(III) $CaBr_2 \cdot 5H_2O$

Crystals of the complexes were obtained by evaporating aqueous solutions that contained approximately equimolar mixtures of calcium bromide and the respective sugars. Crystal data are listed in the Table. X-ray intensity data were collected with a diffractometer by use of copper radiation. Intensity measurements were made for all unique reflections with $2\theta < 128°$. Trial structures were obtained by the heavy atom method and refined by least-squares. All hydrogen atoms, except those bonded to one of the water molecules in the lactose complex, were located. Difference Fourier maps showed that the lactose complex contains a mixture of alpha and beta anomers; refinement of population parameters for the two O(1′) positions indicates that 87 ± 2% of the lactose molecules are in the alpha form. The final R index is 0·043 for the lactose complex, 0·048 for the galactose complex, and 0·039 for the inositol complex.

TABLE. *Crystal data*

	Lactose–$CaBr_2,7H_2O$	Galactose–$CaBr_2,3H_2O$	Inositol–$CaBr_2,5H_2O$
a	21·952(3) Å	19·388(3) Å	7·513(3) Å
b	13·705(3)	8·746(2)	8·280(3)
c	8·792(4)	8·672(1)	15·035(3)
α	90°	90°	70·43(3)°
β	90	90	82·06(3)
γ	90	90	68·08(4)
Space Group	$P2_12_12_1$	$P2_12_12_1$	$P\bar{1}$
Z	4	4	2

An outstanding feature of these complexes is the interaction of hydroxyl groups with calcium ions. The Figure shows the environments of the calcium ions in the three crystal structures. In the lactose complex, Figure (a), the calcium ion binds two lactose molecules and four water molecules. One of the lactose molecules is co-ordinated to the calcium ion through O(3) and O(4) of its galactose moiety, and the second is co-ordinated through O(2′) and O(3′) of its glucose moiety. In the galactose complex, Figure (b), the calcium ion is co-ordinated to three carbohydrate molecules, one that binds through hydroxyl groups O(1) and O(2), one that binds through hydroxyl groups O(3) and O(4), and a third that binds through its O(6) hydroxyl group; the calcium shell is completed by three water molecules. In the inositol complex, Figure (c), the calcium ion is co-ordinated to two inositol molecules and four water molecules. One inositol molecule binds through its O(2) and O(3) hydroxyl groups and the second binds through its O(5) and O(6) hydroxyl groups. Thus the three structures display calcium shells that are composed of eight oxygen atoms, of which four or five are from hydroxyl groups, and the others are from water molecules.

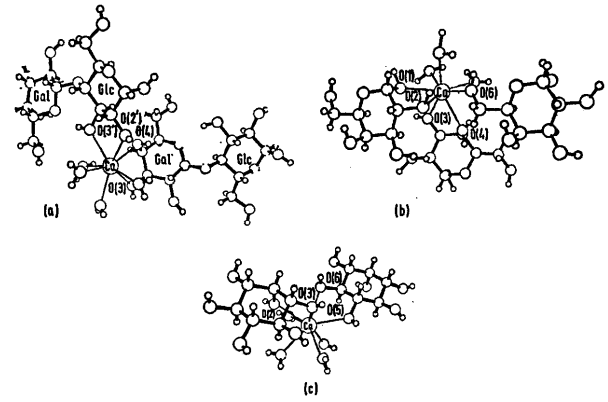


FIGURE. *The calcium-ion co-ordination shells in (a) the lactose complex, (b) the galactose complex, and (c) the inositol complex. Only the alpha anomer of lactose is shown;* ca. 13% *of the lactose sites are occupied by the beta anomer. The program ORTEP*[7] *was used in making these drawings.*

The eight oxygen atoms of the calcium shells form distorted square-antiprisms. The calcium–oxygen distances range from 2·35—2·55 Å. There is no hydrogen bonding between oxygen atoms within the co-ordination shells, but the calcium–oxygen interactions result in a number of short (<2·85 Å) oxygen–oxygen contacts. It is noteworthy that there are no direct contacts between the calcium cations and the bromide anions. The closest calcium–bromide contact is 4·5 Å, a distance 1·5 Å longer than the sum of the bromide and calcium ionic radii.

It appears that the calcium interactions produce conformational changes at the calcium binding sites. In all cases, calcium binding to adjacent hydroxyl groups results in a decrease of about 0·2 Å in the intramolecular spacing between the hydroxyl oxygen atoms. For example, comparison of the lactose conformation with that found in the crystal structure of lactose monohydrate[8] indicates that calcium binding to the glucose moiety produces a decrease of 7° in the magnitude of the O(2′)–C(2′)–C(3′)–O(3′) torsion angle, and a decrease of 5° in the C(3′)–C(2′)–O(2) bond angle, resulting in a 0·2 Å decrease in the spacing

between O(2′) and O(3′). Concomitantly, calcium binding to the galactose moiety of lactose causes a decrease of 9° in the magnitude of the O(3)–C(3)–C(4)–O(4) torsion angle, a decrease of 5° in the C(4)–C(3)–O(3) bond angle, and a corresponding decrease of 0·2 Å in the O(3)–O(4) spacing. The conformation about the C(3)–C(4) bond in the galactose–$CaBr_2$ complex is the same as that found for the galactose moiety in the lactose–$CaBr_2$ complex. Similar conformational changes are also seen in the inositol complex. Comparison with the conformations found in the crystal structures of *myo*-inositol[9] and *myo*-inositol dihydrate[10] indicates that the calcium–inositol interactions result in decreases of 13—14° in the magnitudes of the O(2)–C(2)–C(3)–O(3) and O(4)–C(4)–C(5)–O(5) torsion angles, with decreases of 0·2 Å in the O(2)–O(3) and O(4)–O(5) spacings.

This work was supported by U.S.P.H.S. Research Grants.

(*Received, 5th April* 1972; *Com.* 561.)

[1] J. A. Rendleman, jun., *Adv. Carbohydrate Chem.*, 1966, **21**, 209.
[2] P. Charley and R. Saltmann, *Science*, 1963, **139**, 1205.
[3] J. A. Mills, *Biochem. Biophys. Res. Comm.*, 1961/62, **6**, 418.
[4] S. J. Angyal and K. P. Davies, *Chem. Comm.*, 1971, 500.
[5] R. M. Hays, B. Singer, and S. Malamed, *J. Cell Biol.*, 1965, **25**, 195.
[6] J. F. Manery, *Fed. Proc.*, 1966, **25**, 1804.
[7] C. K. Johnson, ORTEP, A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1965.
[8] D. C. Fries, S. T. Rao, and M. Sundaralingam, *Acta Cryst.*, 1971, B**27**, 994.
[9] I. N. Rabinowitz and J. Kraut, *Acta Cryst.*, 1964, **17**, 159.
[10] T. R. Lomer, A. Miller, and C. A. Beevers, *Acta Cryst.*, 1963, **16**, 264.