Carbohydrate Research, 124 (1983) 324–332
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Geometrical features of calcium–carbohydrate interactions

MARIE L. DHEU-ANDRIES AND SERGE PÉREZ
Centre de Recherche sur les Macromolécules Végétales, BP 68, 38042, Saint-Martin d'Hères (France)*

(Received July 12th, 1983; accepted for publication, August 10th, 1983)

Complex-formation between carbohydrates and cations could have important biological implications. Carbohydrates chelate calcium ions in aqueous solution and in the solid state; these kinds of interactions have been implicated in such processes as calcium storage[1], calcification[2,3], and calcium-dependent cell–cell adhesion[4–6]. Complexing is more likely to occur on the surface of polysaccharides. This is found for a large number of substrates, either for such ionized polysaccharides as glycosaminoglycans[7], heparin[8], alginate[9], and pectates[10], or for such neutral polysaccharides as highly branched D-glucans having α-(1→6) and α-(1→3) linkages[11]. It has been suggested that the interactions are nonspecific, or are governed by simple Coulombic binding of the calcium cation to the anionic carboxyl groups[12]. Contrary to this view, there is evidence that calcium interactions display considerable stereospecificity[13], suggesting that the polysaccharides probably bind calcium through chelation sites composed of several ligands that act in concert.

Solution studies show that simple carbohydrates strongly bind calcium ions only if they can provide sites with three or more hydroxyl groups in a geometrical arrangement that is suitable for calcium coordinations[14]. The Ca^{2+} ion is outstanding for its variation of oxygen coordination[15]. A five-coordinated, distorted trigonal bipyramidal environment of oxygen atoms for calcium, up to a ten-coordinated calcium position in the structure of β-calcium nitrate dihydrate[16], had been reported. A 12-fold coordination of Ca^{2+} is found in the structure of perovskite, $CaTiO_3$. Information about the overall geometry of the chelation between hydroxyl groups and calcium ion is provided by crystal structures of calcium salts of sugar acids, and also by the crystal structures of adducts formed by cocrystallization of neutral sugars with calcium halides. The aim of this communication is to use the information available from single crystals, in the hope that geometrical features of a general nature could be identified that would aid in the understanding of the structural chemistry of calcium interacting with polysaccharides. This work is intended to complement a previous report on the structures of calcium–carbohydrate complexes[17].

---

*Laboratoire Propre du C.N.R.S., associé à l'Université Scientifique et Médicale de Grenoble, France.

0008-6215/83/$ 03.00

TABLE I

REPORTS OF CRYSTAL STRUCTURES FROM WHICH CALCIUM–CARBOHYDRATE EXAMPLES ARE DRAWN

Compounds	*References*	*Coordination*	
α,α-Trehalose · $CaBr_2$ · H_2O	21	7	3 O 3 O 1 W
α-D-Xylose · $CaCl_2$ · 3 H_2O	22	7	2 O 2 O 3 W
β-D-Fructopyranose · $CaCl_2$ · 2 H_2O	23	7	2 O 2 O 1 O 2 W
α-L-Fucose · $CaBr_2$ · 3 H_2O	24	7	2 O 2 O 3 W
α-Lactose · $CaBr_2$ · 7 H_2O	25	8	2 O 2 O 4 W
α-D-Galactose · $CaBr_2$ · 3 H_2O	26	8	2 O 2 O 1 O 3 W
Ca D-glucarate · 4 H_2O	27	8	3 O 2 O 3 W
α-L-Arabinose · $CaCl_2$ · 4 H_2O	28	8	2 O 2 O 4 W
myo-Inositol · $CaBr_2$ · 5 H_2O	29	8	2 O 2 O 4 W
CaBr lactobionate · 4 H_2O	30	8	3 O 2 O 3 W
CaBr D-glucuronate · 3 H_2O	31	8	2 O 2 O 2 O 2 W
Lactose · $CaCl_2$ · 7 H_2O	32	8	2 O 2 O 4 W
Ca [3-deoxy-2-*C*-(hydroxymethyl)-D-*erythro*-pentonate]$_2$ ("α"-D-glucoisosaccharinate)	33	8	4 O 4 O
Ca L-ascorbate · 2 H_2O	34	8	3 O 2 O 1 O 1 W
Methyl D-*glycero*-α-D-*gulo*-heptopyranoside · $CaCl_2$ · H_2O	35	8	3 O 3 O 1 Cl 1 W

Table I (continued)

Ca (D-arabinonate)$_2$ · 5 H_2O	36	8	3 O 3 O 2 W
Bis(β-D-fructopyranose) · $CaCl_2$ · 3 H_2O	37	8	3 O 3 O 2 W
Ca (D-*xylo*-5-hexulosonate)$_2$ ("5-keto-D-gluconate") · 2 H_2O	38	8	3 O 3 O 2 W
Ca β-D-*arabino*-hexulosonate · 3 H_2O	39	9	2 O 3 O 3 O 1 W
CaNa (α-D-galacturonate)$_3$ · 6 H_2O	40	9	2 O 2 O 2 O 2 W
α-D-Allopyranosyl α-D-allopyranoside · $CaCl_2$ · 5 H_2O	41	9	5 O 4 W

Coordination features

In Table I are listed the 21 different crystal-structure reports from which calcium–carbohydrate examples are drawn. In the same Table, the coordination of calcium is indicated, along with composition in terms of the number of oxygen atoms, belonging to the same molecule, that participate in the chelation scheme. Three kinds of coordination geometry are found: a seven-fold coordination (in 4 examples), a fairly common eight-fold coordination (in 14 cases), and a nine-fold coordination (in 3 instances); they occur in a way that seems to be independent of the neutral or acidic nature of the sugar. In the adduct with neutral sugars, there is only one example (methyl D-*glycero*-α-D-*gulo*-heptopyranoside · $CaCl_2$ · H_2O) in which the halide is not excluded from the coordination sphere against Coulombic attraction. In 20 cases, the crystalline structures are hydrated, and from 1 to 4 water molecules are incorporated within the calcium coordination shell. With the exception of α-D-allopyranosyl α-D-allopyranoside · $CaCl_2$ · pentahydrate, it is consistently found that the calcium ions are coordinated to two or more carbohydrate molecules, and usually to water molecules, thus forming hydrated carbohydrate–calcium–carbohydrate bridges.

Fig. 1 shows a histogram that depicts the distribution of the distances (Ca–O) between Ca ions and the oxygen atoms of the hydroxyl groups. Fig. 2 is the same, except for the distribution of the distances (Ca-W) between the Ca ions and the oxygen atoms of the water (W) molecules. The majority of the Ca–O distances lie between 2.30 and 2.65 Å, and the average distance is 2.48 Å. Quite a significant average distance is found for the Ca–W kind of interactions, as the mean value is 2.41 Å and the distribution from 2.30 to 2.60 Å. This value agrees with the tabulated mean Ca–W distance of 2.42 Å, derived from a survey of 150 examples of calcium–

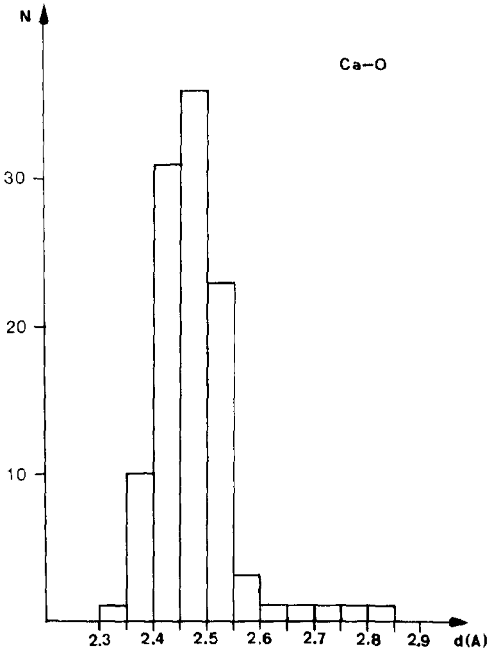

Fig. 1. Histogram showing numbers of examples as a function of d(A), the Ca–O distance.

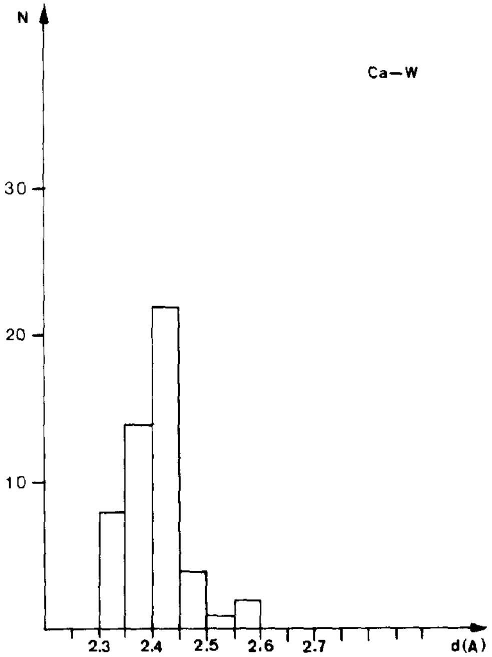

Fig. 2. Histogram showing numbers of examples as a function of d(A), the Ca–W distance.

water interactions in crystalline hydrates[18]. The difference between the mean Ca–O and the mean Ca–W distances can be accounted for in terms of simple electrostatic factors, which involve one attractive interaction between the Ca ion and the oxygen atom of the polar water molecules, coupled with repulsive interaction between the Ca cation and the water hydrogen atoms[18]. In the present work, there are insufficient experimental data available to permit the conclusion that the average distances, either Ca–O or Ca–W, vary directly with the calcium coordination number.

In most cases, the calcium coordination shell results in a number of short (<2.85 Å) oxygen–oxygen contacts (O–O mean 2.92 Å, from 2.55 to 3.48 Å; O–W mean 3.10 Å, from 2.71 to 3.45 Å; W–W mean 3.12 Å, from 2.60 to 3.40 Å). However, there is, so far, only one experimental example for the formation of a hydrogen bond within the calcium coordination shell. As for hydroxylic oxygen atoms belonging to the same carbohydrate unit, it has been found that decrease of 0.1 to 0.2 Å in the interatomic spacing produces changes in both torsion angle (4–10°) and bond angle.

As derived from Table I, the usual calcium coordination is eight-fold, and it can be described as a square-antiprism geometry. Although such an arrangement is always distorted in the carbohydrate structures, the number of examples available is sufficient to permit performing a statistical analysis, in order to define an

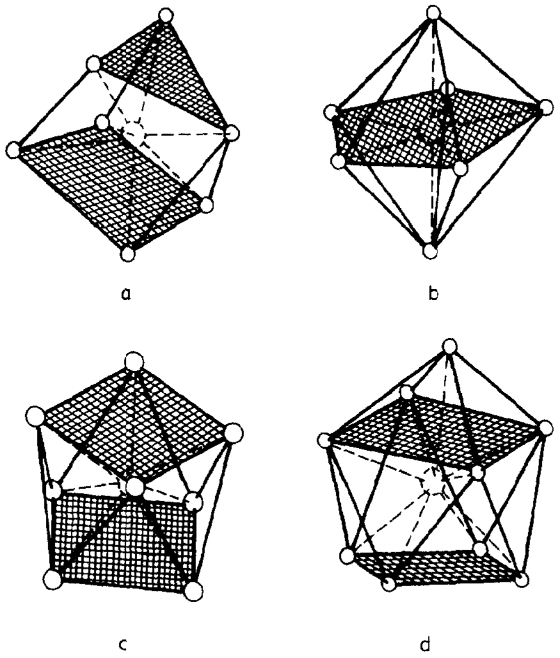

Fig. 3. Computer drawings of (a) a seven-fold coordination of Ca^{2+}, (b) a seven-fold coordination described as a pentagonal bipyramid, (c) an idealized coordination geometry found in the eight-fold coordination of Ca^{2+}, and (d) a nine-fold coordination of Ca^{2+}.

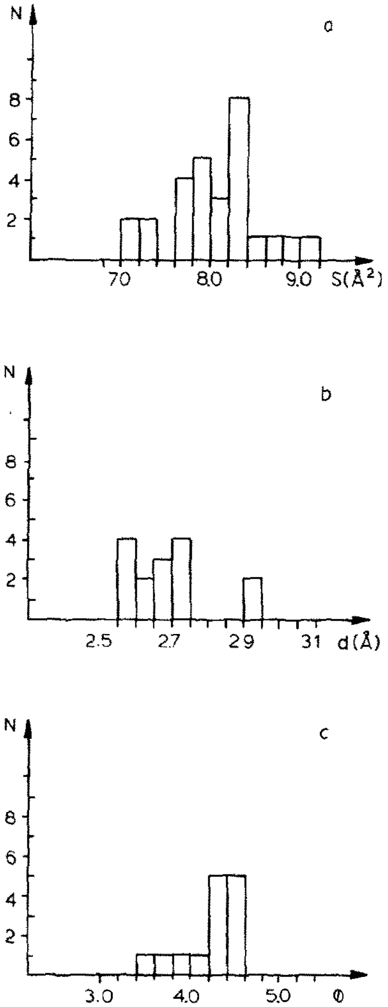

Fig. 4. Histograms describing the distribution of some geometrical parameters associated with the eight-fold coordination of Ca^{2+}. (a) Surface (A^2) of the square base, (b) distance (A) between the center of the square bases, and (c) relative orientation (°) about the center-to-center axis relating one square base to the other one.

idealized polyhedron. Fig. 3c is a computer drawing[19] of an idealized, eight-fold coordination geometry, whereas the histograms that depict the distribution of the pertinent geometrical parameters are shown in Fig. 4. The idealized geometry can be described as resulting from two square-based prisms sharing the calcium ion. Each square results in a planar arrangement of 4 oxygen atoms (either from water molecules or from hydroxyl groups). The average value of the base surface is 8.1 $Å^2$. The centers of the bases are collinear with the calcium ion, the center-to-center average distance being 2.67 Å. The bases run parallel to each other, and there is a 45° rotation about the center-to-center axis that relates one square to the other one. This seems to indicate that, in the case of eight-fold coordination, the square anti-prism is a more satisfactory coordination polyhedron than the cube. As a net result, eight triangular faces having an average surface of 3.88 Å^2 are found.

The seven-fold coordination of Ca^{2+} results from a slight alteration of the square antiprism previously described, in which one square-based prism is now a trigonal prism. Again, the two prisms share the calcium ion (see Fig. 3a). The geometry of the square-based prism is not significantly different from the one found in the eight-fold coordination; the base surface averages 8.27 Å^2, and the distance between the center of the base to the calcium ion is 1.15 Å. As for the trigonal prism, the base surface is 4.00 Å^2, and the distance between the base center to the calcium ion is 1.61 Å. The center of the bases are collinear with the calcium ion, and the relative orientation about the center-to-center axis is such that one of the oxygen atoms of the triangular face lies at 45° to one of the corners of the square plane. This description holds true, except for the coordination of calcium in the case of β-D-fructopyranose · $CaCl_2$, where the seven-fold coordination fits a pentagonal, bipyramidal arrangement almost perfectly (see Fig. 3b).

The nine-fold coordination of Ca^{2+} can also be rationalized as resulting from an alteration of the square anti-prism geometry. Here again, a square-based prism is found (base surface = 7.60 Å^2, center of the base to Ca = 1.62 Å). Opposite to this square-based prism, a second square-based prism exhibiting a significantly larger surface (10.30 Å^2) is also found. In this case, the center of the base to Ca is only 0.90 Å, but the relative orientation of the square is comparable (mean value 42°) to the one found in the square antiprism geometry. This larger surface allows another oxygen atom to interact with the calcium ion, in a direction defined by the center-to-center axis. Fig. 3d depicts a diagram of a typical geometry resulting from the nine-fold coordination.

For the seven- and nine-fold coordinations, the respective pentagonal bipyramid and cube arrangement had already been proposed[20]. The three kinds of coordination schemes observed in the crystal structures have in common the fact that each coordination polyhedron can be built up by assembling two triangular arrangements of oxygen atoms. Addition of single oxygen atoms, essentially from water molecules, would fill up the other sites. Such a type of tridentate-based chelation has been proposed for complexation in solution. As already discussed by Rees[20], the mechanism implied would be favorable in solution, as it enables each set of three coordination positions to be filled for the loss of only three, instead of nine, translational degrees of freedom. Obviously, this is not expected to occur in the solid state, where all translational movement is lost.

In several instances, the case of α-D-allopyranosyl α-D-allopyranoside · $CaCl_2 \cdot 5\,H_2O$ has been referred to as exhibiting peculiar features. In this molecule, the relative orientation of the hydroxyl groups provides a host cavity such that a pentadentate complexation is quite feasible. Within the cavity, the location of Ca^{2+} is such that bridging of another disaccharide molecule is impossible, as it would result in a series of severe intermolecular overlaps. As a net consequence, the remaining sites can only be filled by oxygen atoms of water molecules.

It was of interest to investigate how the calcium interaction may influence the relative orientation of contiguous saccharide units at the glycosidic linkage. This orientation is customarily defined by the glycosidic torsion angles Φ and Ψ. As may be seen from Table I, there is only a limited number of available examples dealing with the complexation of disaccharides with calcium. Nevertheless, comparison between the stable conformation found in uncomplexed disaccharides in the solid state with the one adopted in the complexes shows that there are only small variations (of the order of 10°). Therefore, at least in the case of disaccharide systems in the solid state, complexation with calcium never results in significant conformational changes.

CONCLUSIONS

From the present work, it appears that a calcium–carbohydrate complex must satisfy the overall geometry of the chelation sites, rather than merely assuming a conformation that permits suitable electrostatic contacts between the calcium cations and the carboxyl group (in the case of acid sugars). In most of the crystal structures, the carbohydrate moieties are positioned around the Ca^{2+} in geometrical arrangements that permit the chelating oxygen atoms to form calcium contacts ranging in length from 2.30 to 2.85 Å. The interactions are necessarily subject to some geometrical constraints. It appears that particular coordination geometries may be favored by Ca^{2+}. Only three general types of calcium coordination polyhedra have been found. In most instances, Ca^{2+} is coordinated to eight oxygen atoms, following the geometry dictated by a square-antiprism arrangement. Seven-fold and nine-fold coordination have also been found, the geometry of which can be obtained by slight alterations of the eight-fold coordination. In hydrated, solid-state environments, two hydroxyl groups belonging to the same carbohydrate moiety can serve as an effective, calcium-chelation site. A particularly suitable region for binding calcium ions is provided by the tridentate, chelation site. Obviously, the tetra- and penta-dentate chelation are seldom encountered.

The strongest binding is likely to result from sets of oxygen atoms that possess the proper spacing and geometry for substituting water in the calcium coordination shell. It is therefore reasonable to expect that calcium binding to polysaccharide moieties in biological systems probably occurs preferentially at sites that possess sets of hydroxyl, carboxyl, and sulfate groups, with one among the several geometrical arrangements of oxygen atoms required for calcium coordination. It is therefore possible that calcium–carbohydrate interactions may be sufficiently stereospecific to participate in the control of such processes as gelation, calcification, and calcium-dependent, cell–cell adhesion.

REFERENCES

1 S. J. Farber, M. Schubert, and N. Schuster, *J. Clin. Invest.*, 36 (1957) 1715–1722.
2 Q. T. Smith and A. Lindenbaum, *Calc. Tissue Res.*, 7 (1971) 290–298.
3 J. M. Bowness, *Clin. Orthop. Rel. Res.*, 59 (1968) 233–247.
4 R. S. Turner and M. M. Burger, *Nature,* 244 (1973) 509.
5 G. Weinbaum and M. M. Burger, *Nature,* 244 (1973) 510.
6 B. Pessac and V. Defendi, *Science,* 175 (1972) 898–900.
7 F. Bettelheim, in A. Veis (Ed.), *Biological Polyelectrolytes,* Marcel Dekker, New York, 1970, pp. 131–209.
8 C. Villiers, C. Braud, and M. Vert, *Carbohydr. Res.*, 66 (1980) 335–349.
9 E. R. Morris, D. A. Rees, D. Thom, and J. Boyd, *Carbohydr. Res.*, 66 (1978) 145–154.
10 R. Kohn and A. Malovikova, *Collect. Czech. Chem. Commun.*, 43 (1978) 1709–1710.
11 L. W. Long and J. R. Edwards, *Carbohydr. Res.*, 24 (1972) 216–217.
12 I. G. F. Gilbert and N. A. Myers, *Biochim. Biophys. Acta,* 42 (1960) 469–475.
13 G. T. Grant, E. R. Morris, D. A. Rees, P. J. C. Smith, and D. Thom, *FEBS Lett.*, 32 (1973) 195–198.
14 S. J. Angyal, *Aust. J. Chem.*, 25 (1972) 1957–1966.
15 *Molecular Structure by Diffraction Methods, Specialist Periodical Reports,* Vol. 2, The Chemical Society, London, 1974.
16 A. Leclaire, *Acta Crystallogr., Sect. B,* 30 (1974) 605–607.
17 W. J. Cook and C. E. Bugg, in B. Pullman and W. Goldblum (Eds.), *Metal-Ligand Interactions in Organic Chemistry and Biochemistry,* Vol. 2, Reidel, Dordrecht, Holland, 1977, pp. 231–256.
18 H. Einspahr and C. E. Bugg, *Acta Crystallogr., Sect. B,* 36 (1980) 264–271.
19 M. L. Dheu and S. Pérez, *PITMOS: Programmes Interactifs de Traceés de Molécules et de Structures,* C.E.R.M.A.V., C.N.R.S., Grenoble, France, 1980.
20 D. A. Rees, *MTP Int. Rev. Sci.*, 5 (1975) 1–42.
21 W. J. Cook and C. E. Bugg, *Carbohydr. Res.*, 31 (1973) 265–275.
22 G. F. Richards, *Carbohydr. Res.*, 26 (1973) 448–449.
23 D. C. Graig, N. C. Stephenson, and J. D. Stevens, *Cryst. Struct. Commun.*, 3 (1974) 277–281.
24 W. J. Cook and C. E. Bugg, *Biochim. Biophys. Acta,* 389 (1975) 428–435.
25 C. E. Bugg, *J. Am. Chem. Soc.*, 95 (1973) 908–913.
26 W. J. Cook and C. E. Bugg, *J. Am. Chem. Soc.*, 95 (1973) 6442–6446.
27 T. Taga and K. Osaki, *Bull. Chem. Soc. Jpn.*, 49 (1976) 1517–1520.
28 A. Terzis, *Cryst. Struct. Commun.*, 7 (1978) 95–99.
29 W. J. Cook and C. E. Bugg, *Acta Crystallogr., Sect. B,* 29 (1973) 2404–2411.
30 W. J. Cook and C. E. Bugg, *Acta Crystallogr., Sect. B,* 29 (1973) 215–222.
31 L. DeLucas, C. E. Bugg, A. Terzis, and R. Rivest, *Acta Crystallogr., Sect. B,* 31 (1975) 19–29.
32 W. J. Cook and C. E. Bugg, *Acta Crystallogr., Sect. B,* 29 (1973) 907–909.
33 R. Norrestam, P. Werner, and M. von Glehn, *Acta Chem. Scand.*, 22 (1968) 1395–1408.
34 R. A. Hearn and C. E. Bugg, *Acta Crystallogr., Sect. B,* 30 (1974) 2705–2716.
35 D. C. Graig and J. D. Stevens, *Cryst. Struct. Commun.*, 8 (1979) 161–166.
36 S. Furberg and S. Melland, *Acta Chem. Scand.*, 16 (1962) 2373–2383.
37 D. C. Graig, N. C. Stephenson, and J. D. Stevens, *Cryst. Struct. Commun.*, 3 (1974) 195–199.
38 A. A. Balchim and C. H. Carlisle, *Acta Crystallogr., Sect. B,* 19 (1965) 103–111.
39 M. A. Mazid, R. A. Palmer, and A. A. Palchim, *Acta Crystallogr., Sect. B,* 32 (1976) 885–890.
40 S. Thanomkul, J. A. Hjortas, and H. Sorum, *Acta Crystallogr., Sect. B,* 32 (1976) 920–922; S. E. B. Gould, R. O. Gould, D. A. Rees, and W. J. Scott, *J. Chem. Soc., Perkin Trans. 2,* (1975) 237–242.
41 J. Ollis, V. J. James, S. J. Angyal, and P. M. Pojer, *Carbohydr. Res.*, 60 (1978) 219–228.