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Interactions of Calcium Ions with Carbohydrates: Crystal Structure of Calcium D-Glucarate Tetrahydrate

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The crystal structure of calcium D-glucarate tetrahydrate has been determined from three dimensional X-ray data, and refined by the least squares method including an anisotropic temperature factor. The crystals are orthorhombic, space group $P2_12_12_1$ with $a=16.09$, $b=11.36$ and $c=6.68$Å. The calcium ion is bound to two glucarate molecules and three water molecules. The eight oxygen atoms form the calcium coordination shell of a distorted square-antiprism geometry. The carboxyl group including C(1) of D-glucarate has an eclipsed conformation relative to C(2) and O(2), and is coordinated with one calcium ion through the carboxyl oxygen O(1) and the α-hydroxyl oxygen O(2), and with the other calcium ion through the carboxyl oxygen O′(1) and the hydroxyl oxygens O(3) and O(4). The other carboxyl group including C(6) has an unusual staggered conformation relative to C(5) and O(5), and is not coordinated with calcium ions. However the oxygen atoms of the latter carboxyl group are attached by hydrogen bonds to a number of hydroxyl groups and water molecules, all of which are coordinated with calcium ions.

Studies on the binding of calcium ions to carboxylic sugars are important in relation to various biological systems which depend on the presence of calcium ions.[1–4] As part of a program of investigation of the structural characteristics of calcium binding, in this paper we describe the crystal structure of calcium D-glucarate tetrahydrate, $CaC_6H_8O_8 \cdot 4H_2O$. D-Glucaric acid or D-saccharic acid, which is a dicarboxylic sugar acid derived from the oxidation of D-glyconic acid, is known to have a high affinity for calcium ions in alkaline solutions, and was expected to have structural characteristics typical of chelating agents.[5] In investigating the structure of calcium D-glucarate tetrahydrate we are interested therefore in interaction between calcium ions and the carboxyl groups and in particular the relationship between each carboxyl–calcium interaction and structural features which result from the conformation of the molecule as a whole.

Experimental

The crystals of strip shape were grown by slow evaporation from a dilute hydrochloride solution at room temperature. A preliminary examination showed that the crystals are orthorhombic, space group $P2_12_12_1$ as indicated by the systematic absences of $h00$, $0k0$ and $00l$ for h, k and l odd. $Z=4$, $D_x=1.74$ g/cm³, $D_m=1.77$ g/cm³ at 20 °C. The cell dimensions are $a=16.09(9)$, $b=11.36(7)$ and $c=6.68(5)$ Å. The reflection data were collected by visual estimations of the intensities from equi-inclination Weissenberg photographs obtained by rotating the crystal (0.1×0.15×0.15 mm) about the a- and c-axes, using Cu$K\alpha$ radiation. The reflection data were converted to structure amplitudes without absorption correction and the structure was solved by the direct method using the program MULTAN.[6] Three cycles of the full matrix least squares refinement using 913 reflections gave an R-value of 0.12. A further seven cycles of the block diagonal least squares refinement which included anisotropic thermal parameters reduced the R-value to 0.093. The weighting scheme used was $W^{-1}=(1+|F_o|+0.013|F_o|^2)$.[7] Scattering factors for all atoms were obtained from the International Table for X-ray Crystallography IV.[8] The positions of the hydrogen atoms were determined from the difference Fourier maps and included in the final cycle of the structure factor calculation.

Results and Discussion

The configuration and atomic numbering of the D-glucarate molecule are given in Fig. 1. The final heavy-atom parameters and their estimated standard deviations are listed in Table 1. Observed and calculated structure factors are listed in Table 2.[9] The bond distances and angles calculated from these parameters are given in Table 3. The C–C bond distances range from 1.52 to 1.58 Å with a mean value of 1.54 Å. The C–OH bond distances range from 1.42 to 1.47 Å with a mean value of 1.44 Å. The mean value for the C–C–C bond angle is 110.5° and the mean value for the C–C–OH bond angle is 110.1°. Each carboxyl group is symmetrical within the limits of experimental error. The four C–O bond distances range from 1.24 to 1.28 Å and the C–C–O angles range from 116° to 118°. The C–C–O bond angles are 126° and 128°. The carbon chain of D-glucarate has a bend conformation although the section C(2)–C(6) approximates to an extended planar zigzag. The C(1) atom is in a + synclinal position relative to C(4). (see Table 4) This conformation is unfavorable because of the repul-

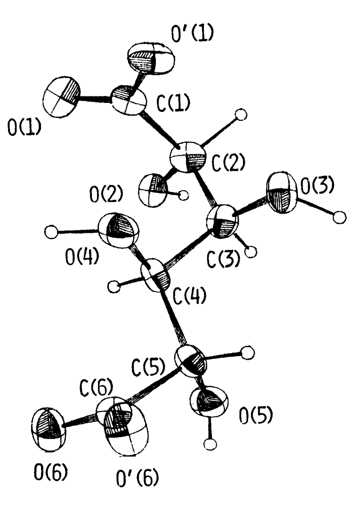

Fig. 1. The configuration and atomic numbering of the D-glucarate molecule.

TABLE 1. HEAVY-ATOM PARAMETERS AND THEIR ESTIMATED STANDARD DEVIATIONS
The values have been multiplied by 10^4. Temperature factors are in the form
$T^{-1}=\exp(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Ca	3100(1)	2259(2)	8596(4)	26(1)	39(1)	108(7)	−2(1)	−3(2)	−3(3)
C(1)	2714(6)	2528(9)	3565(21)	20(3)	48(9)	80(35)	5(4)	3(10)	31(14)
C(2)	3273(6)	3605(11)	3251(23)	24(4)	53(9)	127(43)	−2(5)	4(11)	30(16)
C(3)	4003(7)	3615(9)	4742(24)	27(4)	22(7)	191(45)	−6(4)	4(12)	17(14)
C(4)	4520(7)	2498(9)	4664(22)	24(3)	37(8)	105(44)	7(4)	11(10)	−16(13)
C(5)	5366(7)	2675(10)	5638(21)	21(3)	39(7)	105(33)	4(4)	12(9)	0(14)
C(6)	5760(7)	1405(10)	5884(24)	19(3)	50(9)	164(47)	1(5)	−2(10)	−10(15)
O(1)	2598(6)	1869(8)	2041(16)	40(4)	52(7)	120(27)	−9(4)	−13(9)	30(11)
O′(1)	2415(5)	2377(9)	5251(15)	19(2)	92(9)	82(27)	3(5)	15(7)	20(12)
O(2)	3557(5)	3652(7)	1161(15)	34(3)	41(6)	122(26)	−2(4)	−3(9)	16(11)
O(3)	3765(5)	3822(7)	6778(14)	36(3)	43(6)	78(26)	−3(4)	17(8)	−6(10)
O(4)	4076(5)	1622(7)	5749(16)	23(3)	39(6)	224(34)	3(3)	10(7)	14(11)
O(5)	5869(5)	3413(7)	4347(18)	23(3)	45(6)	251(36)	1(4)	5(8)	11(11)
O(6)	5945(6)	889(7)	4316(16)	38(4)	37(6)	181(32)	12(4)	−14(9)	−5(11)
O′(6)	5813(6)	1024(8)	7681(17)	46(4)	59(8)	133(31)	12(5)	−13(10)	2(12)
O(W1)	2467(8)	355(9)	8395(24)	54(5)	69(9)	361(49)	−4(6)	24(16)	−16(17)
O(W2)	4247(6)	1034(9)	9981(20)	37(4)	89(9)	205(35)	13(5)	6(10)	17(16)
O(W3)	1795(6)	3235(12)	8942(19)	37(4)	128(12)	195(38)	32(6)	−10(10)	−6(18)
O(W4)	5738(9)	4276(11)	335(27)	80(8)	83(11)	373(54)	9(8)	−15(18)	2(21)

sion between the parallel C(1)–C(2) and C(4)–O(4) bonds. (Jeffrey and Kim10) have pointed out that parallel C-n-O [or C-n-C] and C-(n+2)-O [or C-(n+2)-C] bonds give rise to conformational instability in the carbohydrate chain.) The unfavorable C(1)–O(4) proximity in the +synclinal conformation is relaxed by a rotation of O(4) about the C(3)–C(4) bond. As a result of this rotation, O(3) and O(4) approach each other quite closely (2.64 Å). The carboxyl group at each end of the chain has a different conformation. The carboxyl group including C(1) is co-planar with the C(1)C(2)O(2) plane. The carboxyl oxygen O(1) is in an eclipsed position relative to C(2) and O(2), and is close to O(2) (2.61 Å). While the plane of the carboxyl group including C(6) is approximately perpendicular to the C(4)C(5)O(5) plane. The carboxyl oxygen O(6) is in a staggered position relative to C(4) and O(5) with the C(4)–C(5)–C(6)–O(6) torsional angle=67°. The latter staggered conformation is favorable with respect to the nonbonding interactions between the carboxyl oxygens and the atoms attached to C(5). However the former eclipsed conformation appears to be a feature of a number of carboxylic compounds. The stability of such an eclipsed form has been investigated by several workers without reaching any definite conclusion.11–13)

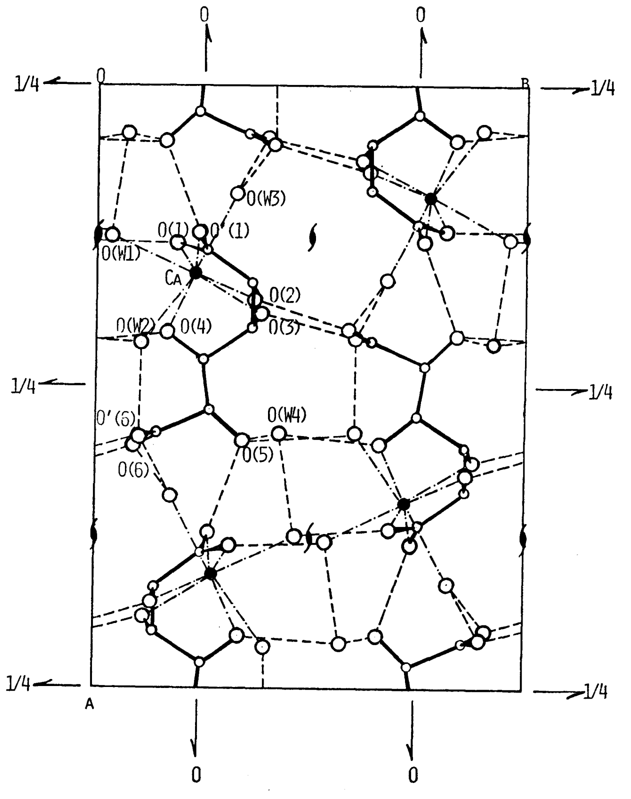

Fig. 2. The projection of the structure along the c-axis. The broken lines are hydrogen bonds.

The crystal packing and the coordination of calcium ions with glucarates and water molecules are shown in Figs. 2, 3, and 4. The calcium ion lies between three water molecules and two glucarate molecules which are related by translation along the c-axis, and is surrounded by eight oxygen atoms in a distorted square-antiprism arrangement. The Ca–O distances vary from 2.39 to 2.50 Å with a mean value of 2.46 Å. One glucarate molecule is coordinated with a calcium ion through an O(1) carboxyl oxygen and an O(2) α-hydroxyl oxygen. The second glucarate is coordinated through the O′(1) carboxyl oxygen and the O(3) and O(4) hydroxyl oxygens arranged in a triangular form. The O–O distances in this formation are 2.64 Å for O(3)–O(4), 2.83 Å for O′(1)–O(3) and 2.91 Å for O′(1)–

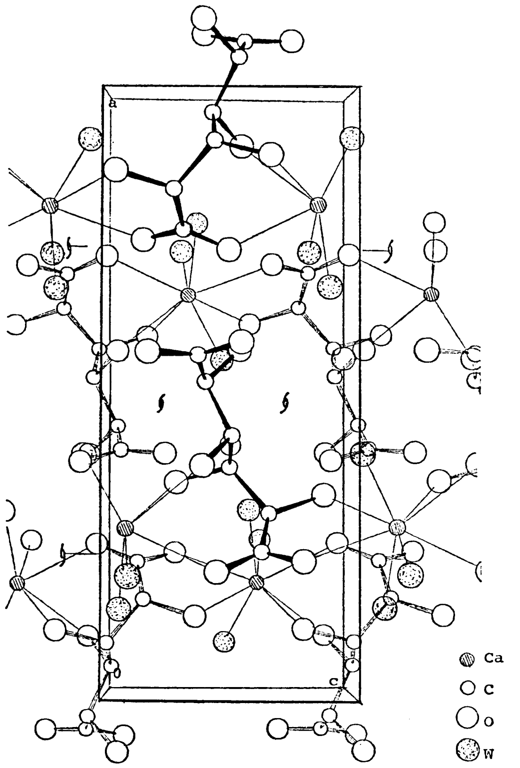

Fig. 3. A perspective view of the structure along the b-axis.

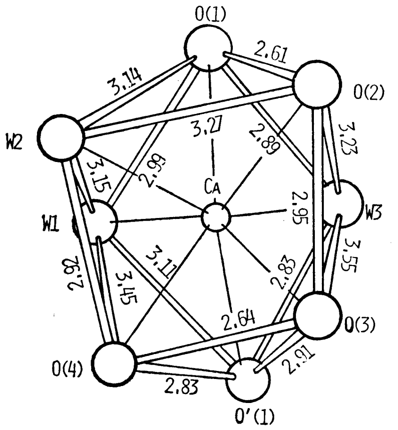

Fig. 4. The calcium coordination shell.

Table 3. Intramolecular bond distances (Å) and angles (°) with their estimated standard deviations

Bond distance		Bond angle	
C(1)-C(2)	1.534(16)	C(1)-C(2)-C(3)	111.4(1.1)
C(2)-C(3)	1.540(19)	C(2)-C(3)-C(4)	112.9(1.1)
C(3)-C(4)	1.519(15)	C(3)-C(4)-C(5)	111.4(1.0)
C(4)-C(5)	1.522(17)	C(4)-C(5)-C(6)	106.3(0.9)
C(5)-C(6)	1.584(16)	C(2)-C(1)-O(1)	116.4(1.2)
C(1)-O(1)	1.277(17)	C(2)-C(1)-O'(1)	117.6(1.1)
C(1)-O'(1)	1.236(17)	C(5)-C(6)-O(6)	116.2(1.2)
C(6)-O(6)	1.237(18)	C(5)-C(6)-O'(6)	115.6(1.2)
C(6)-O'(6)	1.279(19)	C(1)-C(2)-O(2)	110.0(1.0)
C(2)-O(2)	1.469(18)	C(3)-C(2)-O(2)	112.1(1.0)
C(3)-O(3)	1.431(19)	C(2)-C(3)-O(3)	114.3(1.0)
C(4)-O(4)	1.424(15)	C(4)-C(3)-O(3)	108.5(1.1)
C(5)-O(5)	1.449(16)	C(3)-C(4)-O(4)	106.9(1.0)
Ca-O(1)	2.478(11)	C(5)-C(4)-O(4)	108.9(1.1)
Ca-O'(1)	2.495(10)	C(4)-C(5)-O(5)	108.8(1.1)
Ca-O(2)	2.445(10)	C(6)-C(5)-O(5)	111.4(0.9)
Ca-O(3)	2.402(9)	O(1)-C(1)-O'(1)	126.0(1.0)
Ca-O(4)	2.569(10)	O(6)-C(6)-O'(6)	128.1(1.1)
Ca-O(W1)	2.395(11)		
Ca-O(W2)	2.490(11)		
Ca-O(W3)	2.386(11)		

O(4). It has been demonstrated that in aqueous solutions the affinity of calcium ions for carboxylic acids is increased by the presence of an α-oxygen and this affinity is further enhanced by the presence of additional hydroxyl groups in the molecule.[14,15] In all the crystal structures of calcium salts of other carboxylic compounds determined to date,[16-23] the carboxyl oxygen and the α-oxygen are both coordinated with the calcium ion. Therefore the carboxylic oxygen and the α-hydroxyl oxygen in an eclipsed conformation as in O(1) and O(2) are generally coordinated with the calcium ion through the formation of a stable five membered ring $\overline{\mathrm{O{-}C{-}C{-}O{-}Ca}}$. The triangular structure of O'(1), O(3) and O(4) is a previously unobserved type of oxygen arrangement which excludes the α-oxygen atom. (In the structures determined for Ca D-xylo-5-hexalosonate $2H_2O$,[21] CaBr lactobionate $4H_2O$[22] and Ca arabonate $5H_2O$,[23] the α-hydroxyl oxygen is included in the 'oxygen triangle' coordinated with the calcium ion.) The nonbonding distance between O(3) and O(4) is shorter than that between O'(1) and O(3) and between O'(1) and O(4), and a stable five membered chelate ring including a calcium ion is formed through the O(3)–C(3)–C(4)–O(4) linkage.

Another interesting feature of the structure of calcium D-glucarate is that calcium ions are not directly bound to the C(6) carboxyl group. The O(6) carboxyl oxygen in a staggered position is far from the O(5) hydroxyl oxygen. The O(5)–O(6) distance of 2.87 Å is sufficiently great to prevent the formation of a stable chelate ring with a calcium ion. Generally in the carboxyl oxygen in the staggered conformation the electron lone pairs are unshielded by intramolecular atoms, thus the carboxyl oxygens are more capable of forming intermolecular hydrogen bonds than in the case of carboxyl oxygens in the eclipsed form. In fact, the oxygen atoms of the C(1) carboxyl group form only two hydrogen bonds, whereas the oxygen atoms of the C(6) carboxyl group form five hydrogen bonds with the water molecules and the hydroxyl groups of the adjacent molecules. The hydrogen bonding scheme and their distances are given in Fig. 2 and Table 5, respectively. All of the hydroxyl groups and water molecules attached by hydrogen bonds to the C(6) carboxyl group are coordinated with calcium ions. Conversely, the C(6) carboxyl groups link the adjacent calcium centered oxygen polyhedrons.

From the data described here, it is apparent that the calcium-hydroxyl interaction is important in

Table 4. Torsional angles (°) about C–C bonds in D-glucarate molecule

O(1)-C(1)-C(2)-C(3)	−124.2	O′(1)-C(1)-C(2)-C(3)	56.1
O(1)-C(1)-C(2)-O(2)	0.8	O′(1)-C(1)-C(2)-O(2)	−179.0
C(1)-C(2)-C(3)-C(4)	55.7	O(2)-C(2)-C(3)-C(4)	−68.0
C(1)-C(2)-C(3)-O(3)	−68.9	O(2)-C(2)-C(3)-O(3)	167.4
C(2)-C(3)-C(4)-C(5)	162.4	O(3)-C(3)-C(4)-C(5)	−69.9
C(2)-C(3)-C(4)-O(4)	−78.7	O(3)-C(3)-C(4)-O(4)	49.0
C(3)-C(4)-C(5)-C(6)	168.0	O(4)-C(4)-C(5)-C(6)	50.3
C(3)-C(4)-C(5)-O(5)	−71.9	O(4)-C(4)-C(5)-O(5)	170.4
C(4)-C(5)-C(6)-O(6)	67.3	O(5)-C(5)-C(6)-O(6)	−51.1
C(4)-C(5)-C(6)-O′(6)	−109.9	O(5)-C(5)-C(6)-O′(6)	131.7

Table 5. Lengths (Å) of hydrogen bonds with their estimated standard deviations

O(1)···O(W1)	h	2.685(14)
O′(1)···O(5)	b	2.657(11)
O(6)···O(2)	e	2.683(11)
O(6)···O(W3)	c	2.755(16)
O′(6)···O(3)	f	2.617(12)
O′(6)···O(W2)	a	2.950(15)
O′(6)···O(W3)	d	2.879(16)
O(W4)···O(4)	g	2.777(16)
O(W4)···O(5)	a	2.860(21)
O(W4)···O(W1)	c	2.937(20)

Symmetry codes

a :	x,	y,	z
b :	$-1/2+x$,	$1/2-y$,	$1-z$
c :	$1/2+x$,	$1/2-y$,	$1-z$
d :	$1/2+x$,	$1/2-y$,	$2-z$
e :	$1-x$,	$-1/2+y$,	$1/2-z$
f :	$1-x$,	$-1/2+y$,	$3/2-z$
g :	$1-x$,	$1/2+y$,	$1/2-z$
h :	$1/2-x$,	$-y$,	$-1/2+z$

relation to the binding of calcium ions to carboxylic sugars. The intramolecular proximity of the hydroxyl groups and carboxyl oxygens is particularly relevant to the formation of a stable calcium chelate structure possibly accompanied by a conformational change of the ligand molecule to a more favorable arrangement of oxygen atoms. These structural characteristics readily account for the high stability of calcium D-glucarate crystals.

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