CONFORMATION AND INTRAMOLECULAR HYDROGEN-BONDING IN THE CRYSTAL STRUCTURE OF POTASSIUM D-GLUCONATE MONOHYDRATE

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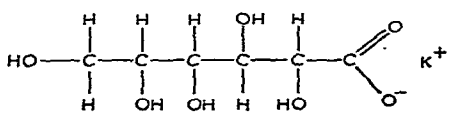
ABSTRACT

The D-gluconate ion is found to have the planar, extended carbon-chain conformation in the crystal structure of potassium D-gluconate monohydrate, with an intramolecular hydrogen-bond between O-2 and O-4. The D-gluconate ions and water molecules are linked in puckered sheets by a series of intermolecular hydrogen-bonds that involve the water molecules, the carboxylate groups, and pairs of hydroxyl groups. One hydroxyl group in the ion does not form a hydrogen bond. The potassium ions lie between the puckered sheets, with an eight-fold coordination of six D-gluconate groups and two water oxygen atoms. The crystal structure was determined from three-dimensional, CuKα, X-ray diffraction data taken on an automatic diffractometer.

INTRODUCTION

The crystal structure of potassium gluconate, $C_6H_{11}KO_7$ (**1**) was determined by Littleton[1] in 1953. Recently, her results became interesting in relation to a series of conformational studies of acyclic sugar derivatives, because it appeared to



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be the only known exception to a rule relating conformation to configuration in polyhydroxyalkyl chains. The rule states that, in polyhydroxyalkyl chains or their acetylated derivatives, the carbon chain is extended and planar, except when the configuration at alternate carbon centers is the same, in which case it is bent (sickle-shaped[2]). This rule has been found to hold for molecules of pentitols and hexitols

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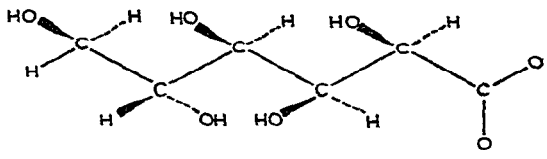

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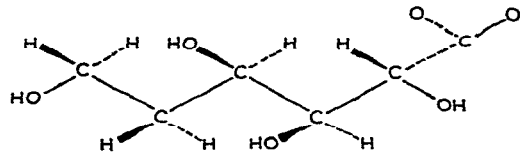

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in the crystalline state in eleven structures[3] and for the D-ribitol chain in[4] vitamin B_2. The same relationship has, by n.m.r. techniques, been found to apply to the rotamers of a variety of acetylated, acyclic sugar derivatives in solution[2,5–7].

When applied to the configuration of the D-gluconate ion **1**, the prediction is that the planar conformer **2**, observed by Littleton[1] in potassium D-gluconate, should be unstable with respect to a bent-chain alternative, such as **3**. The basis of

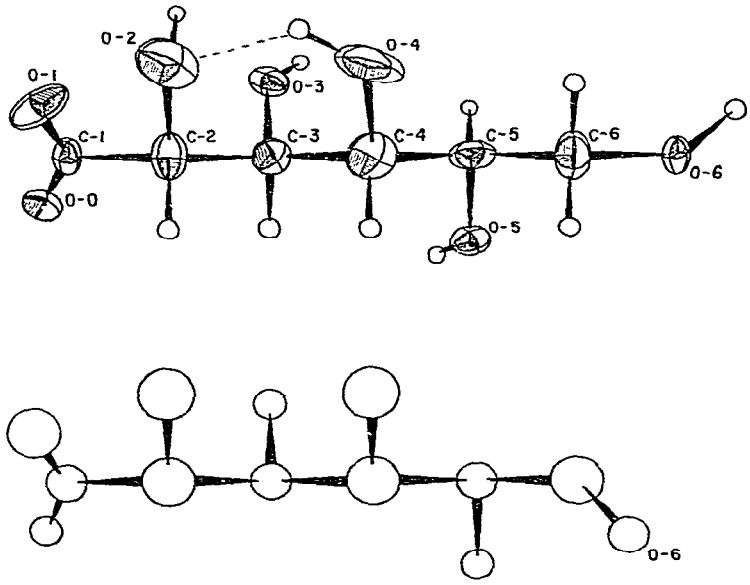

Fig. 1. *Top.* D-Gluconate ion in potassium D-gluconate monohydrate. The ellipsoids represent the thermal motion at the 50 percent probability level. The hydrogen atoms are represented by the small circles. *Bottom.* D-Gluconate ion in potassium gluconate, as determined by Littleton[1]. Atoms are represented by circles; with the hydrogen atoms omitted as they were not directly observed.

this prediction is the assumption of an unfavorable, nonbonding, repulsive interaction between O-2 and O-4, which is present in **2** and absent from **3**. It is reasonable to assume that the exception represented by potassium D-gluconate arises either from a misinterpretation in the earlier work, which was based on two-dimensional, X-ray film diffraction data, or a particular structural feature of the D-gluconate ion which stabilizes the planar conformation. In the course of re-investigating this problem, we obtained crystals of the monohydrate of potassium D-gluconate and have determined its structure, in order to obtain a second observation of the D-gluconate ion in a crystal-field environment different from that of the anhydrous salt.

RESULTS AND DISCUSSION

This crystal-structure determination showed that the D-gluconate ion in the monohydrate has the same planar conformation of the carbon chain as was reported by Littleton[1] for the anhydrous salt. The conformation of the ion, as revealed in both analyses, is shown in Fig. 1. The only conformational difference is in the terminal oxygen atom, O-6, which is *anti* in the hydrate and *synclinal* in the anhydrous salt.

The parallel C-2–O-2, C-4–O-4 bonds, which are the basis of conformational instability in other polyhydroxyalkyl systems, lead to the formation of an intramolecular hydrogen-bond in the D-gluconate ion. The detailed geometry of this

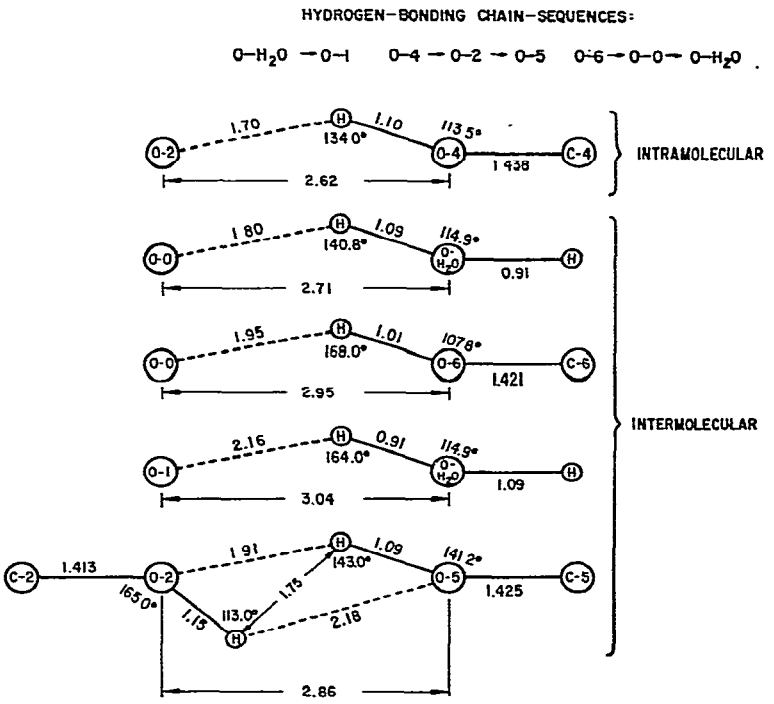

Fig. 2. Hydrogen-bonding distances and angles in the crystal structure of potassium D-gluconate monohydrate.

hydrogen-bond is shown in Fig. 2. Although the O-4–H···O-2 angle is more acute for the intramolecular bond than are the comparable angles of the intermolecular hydrogen-bonds, the O-4···O-2 and O-4-H···O-2 distances of 2.62 and 1.70 Å are shorter. This geometry shows conclusively that there is strong, secondary bonding-

TABLE I

BOND DISTANCES AND ANGLES IN POTASSIUM D-GLUCONATE MONOHYDRATE[a]

Bond	*Bond distance (Å)*	*Bonds*	*Bond angle (degrees)*
C-1–C-2	1.527 (6)	O-0–C-1–O-1	125.7
	[1.55]		[123]
C-2–C-3	1.533 (4)	O-0–C-1–C-2	117.9
	[1.54]		[121]
C-3–C-4	1.538 (4)	O-1–C-1–C-2	116.3
	[1.57]		[116]
C-4–C-5	1.520 (4)	C-1–C-2–C-3	112.1
	[1.55]		[109]
C-5–C-6	1.533 (6)	C-1–C-2–O-2	109.9
	[1.53]		[109]
C-1–O-0	1.237 (4)	O-2–C-2–C-3	111.9
	[1.23]		[109]
C-1–O-1	1.254 (4)	C-2–C-3–C-4	112.0
	[1.28]		[114]
C-2–O-2	1.431 (5)	C-2–C-3–O-3	109.0
	[1.44]		[112]
C-3–O-3	1.437 (3)	O-3–C-3–C-4	108.6
	[1.40]		[119]
C-4–O-4	1.438 (3)	C-3–C-4–C-5	115.7
	[1.48]		[106]
C-5–O-5	1.425 (4)	C-3–C-4–O-4	111.2
	[1.43]		[101]
C-6–O-6	1.421 (5)	O-4–C-4–C-5	104.3
	[1.43]		[101]
C-2–H	1.1	C-4–C-5–C-6	109.0
			[103]
C-3–H	1.0	C-4–C-5–O-5	113.1
C-4–H	1.0		[109]
C-5–H	0.9	O-5–C-5–C-6	106.2
			[105]
C-6–H	1.1	C-5–C-6–O-6	112.9
			[115]
C-6–H′	1.2		
O-2–H	1.1		
O-3–H	1.0		
O-4–H	1.1		
O-5–H	1.1		
O-6–H	1.0		

[a]Numbers in parentheses are estimated standard deviations. Numbers in square brackets are corresponding values in the anhydrous salt, as determined by Littleton[1]. All C–H and O–H distances have estimated standard deviations of 0.1 Å. All angles have estimated standard deviations of 0.5°.

interaction between the two hydroxyl groups. It is probable that the same type of hydrogen-bond stabilizes the planar D-gluconate conformation in the anhydrous salt, but this will have to be confirmed by updating the experimental diffraction data for that compound, as the earlier measurements were not sufficiently accurate or extensive to permit location of the hydrogen atoms.

Although similar stereochemical opportunities for intramolecular hydrogen-bonds between hydroxyl groups on alternate carbons, *i.e.*, O-(n)–H, O-(n+2), are fairly common in the carbohydrates, there are no other examples reported for the acyclic series. The only known examples in the crystalline, cyclic monosaccharides are in two thioribopyranosides[8], where the configuration is such that either 1,3 or 2,4 axial interactions occur in the two possible chair conformations. Where intramolecular, O-H···O hydrogen-bonds are observed in the disaccharides, it is between hydroxyl groups on different monosaccharide units (*e.g.*, in sucrose[9] and methyl β-maltopyranoside[10]).

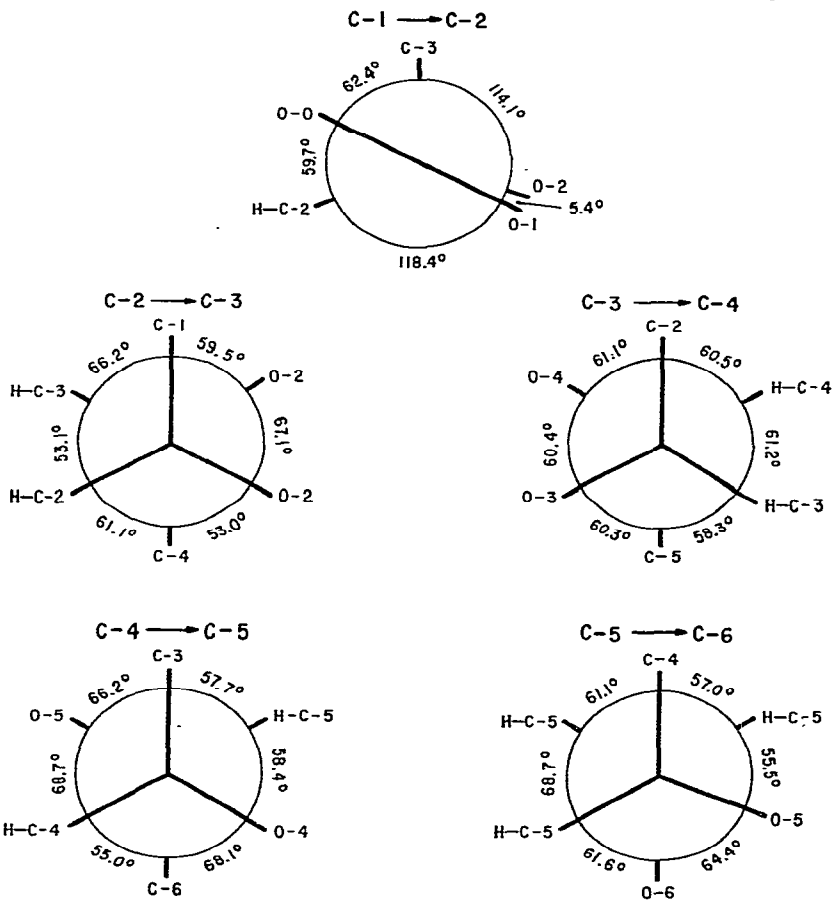

Fig. 3. Dihedral angles about C–C bonds in the D-gluconate ion (viewed in Böeseken projections).

The interatomic distances and valence angles in potassium D-gluconate monohydrate are given in Table I. The C–C bond-lengths range from 1.520 to 1.538 Å, and the differences from the mean of 1.530 Å are not significant. The C–OH bonds range from 1.413 to 1.438Å, and the differences from the mean are not significant. These results are in good agreement with those of the crystal structures in the alditol series[3]. The same is true of the valence angles; the mean value for the C–C–C angles is 112°, *versus* 110° for that of the C–C–O angles. The carboxylate group is symmetrical within experimental error, with an angle of 125.7° between the two C–O bonds. The dihedral angles about the C–C bonds are shown in Fig. 3. The plane of the carboxylate ions makes an angle of 62° with that of the carbon chain. The terminal oxygen atom (O-6) is in the *anti* situation. The extended-chain carbon atoms (C-1 to C-6) and O-6 lie, within 0.09 Å, in one plane. The carboxylate group, O-1, O-0, C-1, and C-2 lie, within 0.012 Å, in one plane. With the exception of the planar-chain conformation and the intramolecular bond, the geometry of the D-gluconate ion is unremarkable, and is as would be anticipated from previous studies of related molecules and ions.

The D-gluconate ions and water molecules are so hydrogen-bonded in the crystal structure as to form puckered sheets that extend parallel to the (100) plane, as shown in Figs. 4 and 5. The potassium ions are so situated between these puckered sheets that they have eight "nearest-neighbor" oxygen atoms in a distorted, anti-

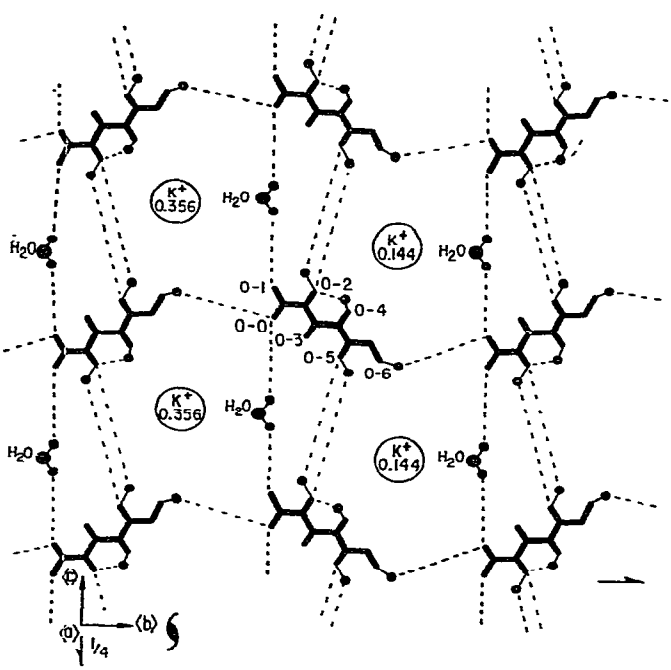

Fig. 4. Schematic diagram of the puckered, hydrogen-bonded sheets of D-gluconate ions and water molecules in projection. The center of the D-gluconate ions is at approximately $x = 0$; the x coordinates of the K^+ ions are shown.

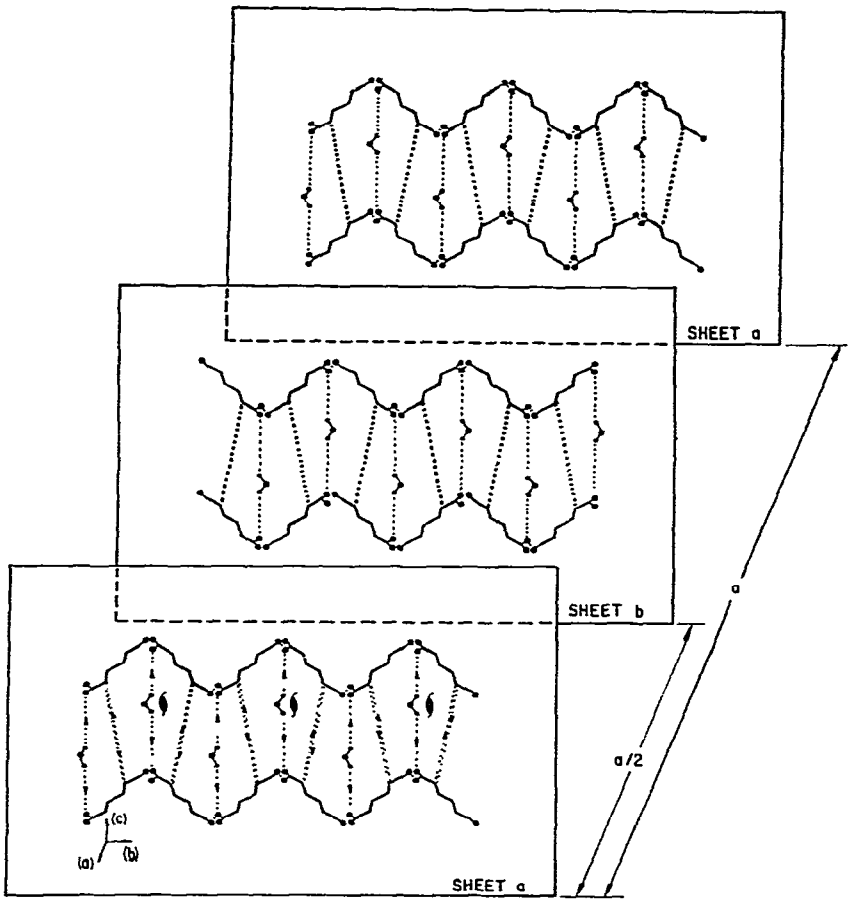

Fig. 5. Schematic diagram, showing the puckering of the hydrogen-bonded sheets. K^+ ions lie between sheets.

prism arrangement. The potassium-ion coordination is shown in Fig. 6. (Similar, eight-fold coordination is found round the cations in calcium and strontium D-*gluco*-isosaccharate[11,12].) Surprisingly, the carboxylate oxygen atoms, O-0 and O-1, are not part of the first coordination sphere of the potassium ion.

The hydrogen bonding in the crystal structure consists of three finite chains that link the oxygen atoms as follows, O-W–O-1, O-4–O-2–O-5, O-6–O-0–O-W, where W = water. The structural details of these bonds are shown in Figs. 2 and 4. The water molecules link the carboxylate groups through finite chains of hydrogen bonds extending in the direction of the *c* axis. There is a parallel series of intermolecular bonds, from O-5–H to O-2, between the D-gluconate ions. The cross-linking in the direction of the *b* axis is by a hydrogen bond from O-6 to O-0. Of the five hydroxyl groups on the D-gluconate ion, O-4–H and O-6–H each donates, but does not accept, a hydrogen bond; O-2–H and O-5–H both donate and accept bonds; and

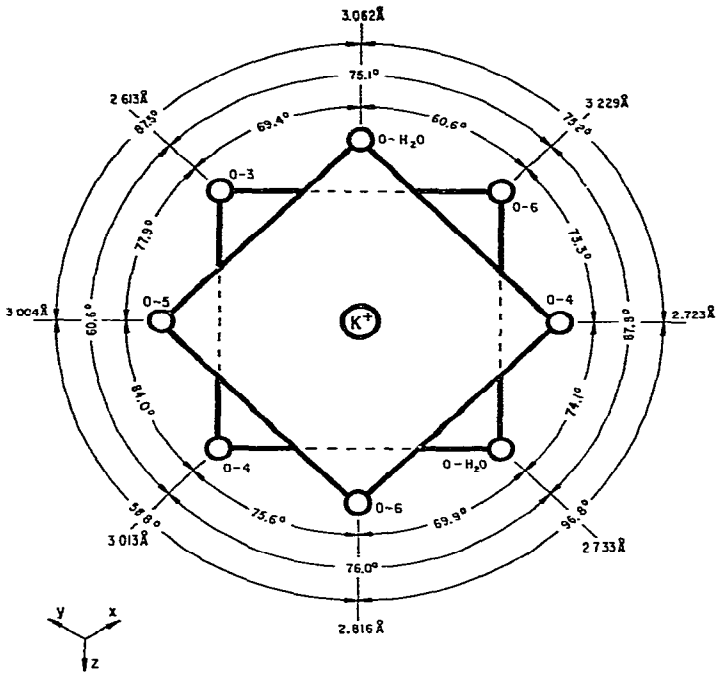

Fig. 6. Schematic diagram of environment of K^+ ion, showing square, anti-prism coordination.

O-3–H is not involved in hydrogen bonding, either as a donor or an acceptor. Thus, the hydrogen bonding of the D-gluconate ion consists of six bonds, of which one is intramolecular. This is in marked contrast to most carbohydrates, where the hydrogen bonding is generally very extensive and involves all of the hydroxyl hydrogen atoms, each oxygen atom functioning as both a donor and an acceptor. In the pentitols and hexitols, for example, each molecule has a crystal field of ten and twelve hydrogen-bonds, respectively[13]. Clearly, in the D-gluconate salt, it is the ionic forces from the K^+ and the carboxylate–water hydrogen-bonds that control the packing of the D-gluconate ions, and the most stable arrangement is that which best satisfies these two primary considerations. As a consequence, the hydrogen atom on O-3 is not in a position to engage in hydrogen bonding; it lies in a void in the structure, and its closest intermolecular neighbors are, in fact, other hydrogen atoms. The nearest non-bonded neighbors to H-O-3 are two hydrogen atoms at 1.95 Å and 2.86 Å, and the K^+ ion at 2.35 Å. The position of H-O-2 is also anomalous. The *double-stranded* linkage between O-2–H and O-5–H, shown in Figs. 2 and 4, is very unusual, and, in fact, has not been observed previously. The H-O-2 to O-5 distance of 2.18 Å, combined with the O–H–O angle of 113°, indicates a very weak bond (*cf.*, H-H_2O to O-1 of 2.16 Å and 164°). The stereochemistry also incurs a H···H separation of 1.75 Å, which is the inner limit of a normal Van der Waals separation for two hydrogen atoms. It could, indeed, be argued that H-O-2 is a second free hydroxyl hydrogen

atom not involved in hydrogen bonding. The most reasonable position for this hydrogen atom is towards O-1, forming a second intramolecular bond, because the separation between O-2 and O-1 is 2.60 Å. However, the electron-density distribution observed in the region 1 Å from O-2 definitely favors the position shown in Figs. 1, 2, and 4 for the hydrogen atom. Further confirmation, by neutron diffraction, is desirable.

The shape of the carboxylate group is also not that which might be expected for the minimizing of nonbonding interactions between the atoms O-0,O-1, and O-2, C-3,H-C-2. As shown in the projection down C-1→C-2 in Fig. 3, O-1 and O-2 are almost eclipsed, whereas the favored orientation expected would be with O-1 in the staggered position relative to C-3 and O-2. This planar, or almost planar, orientation of atoms C-1, O-1, O-0, and O-2 is a common structural characteristic of α-hydroxy carboxylic ions and acids[14], and is observed in the citric[15] and tartaric[16] acids and their salts[15,17]. In all cases, as in this structure, there is a close approach of the carboxylate and α-hydroxyl oxygen atoms, without the formation of an intramolecular hydrogen-bond. An extended Hückel calculation has given some semi-empirical, quantum-mechanical justification for the stability of this planar α-hydroxy carboxylate system[11].

Turning now to the question as to why the planar carbon chain conformation is stabilized by intramolecular bonding in the D-gluconate ion, but not in such molecules as D-glucitol, ribitol, and xylitol[18], we presume that the answer lies in the difference in the crystal-field forces, rather than in any differences in electronic distribution of the polyhydroxyalkyl ions *versus* that of the molecules. In crystal structures of polyhydroxy molecules, hydrogen bonding is the strongest cohesive force, and, generally, it would appear that intermolecular bonding always takes precedence over intramolecular bonding[19]. A particularly striking example is *epi*-inositol[20], where there is the same *axial* orientation of alternating hydroxyl groups, but no intramolecular hydrogen-bonding. The inositol molecules are so arranged in the crystal structure as to permit an extensive system of intermolecular hydrogen-bonds (twelve around each molecule), which take precedence over intramolecular bond-formation. Instead, the inositol ring is distorted because of the repulsion between the axial hydroxyl groups (O-2–H, O-6–H). The O-2–O-6 separation becomes 2.96 Å, as against 2.62 Å for O-2–O-4 in the D-gluconate ion. In the alditols, also, it would seem that intermolecular bonding takes precedence, so that, in such crystal structures as those of D-glucitol, etc., the bent-chain conformer having two intermolecular bonds per hydroxyl group is more stable than a straight-chain conformer having one or more intramolecular bonds. The reason that intermolecular hydrogen-bonds contribute more to the crystal energy than intramolecular bonds having comparable, or even shorter, O-H···O separations is probably that there are less-favorable, hydrogen-bond valence-angles*, *cf.*, the O-H···O angles in Fig. 2.

In the D-gluconate salt, the major component to the lattice energy comes from

*In the absence of two-dimensional, potential-energy functions that would permit correlation of hydrogen-bonding energy both with O-H···distances and angles, this is a reasonable hypothesis.

the ionic forces, and this determines the packing, which is such that one or, possibly, two of the hydroxyl groups cannot form intermolecular bonds. With this competition removed, the intramolecular bond can be formed, and this gives the crystal structure containing the straight-chain conformer an energy advantage over the bent-chain alternatives.

An important corollary to these solid-state results is the realization that the rule described in the introduction must be applied with reservation in situations where the molecular or ionic environment is such that intermolecular hydrogen-bonding is suppressed. Without competition from intermolecular hydrogen-bonding, intramolecular bonding can reverse the premise upon which the rule is based. Most of the conformational studies in solution have thus far been made on acetylated derivatives in which intramolecular bonding cannot occur. Similarly, in aqueous or polar solvents, the transitory hydrogen-bonding to solvent molecules should preempt the formation of intramolecular bonds. It is probably only in strongly ionic environments that we can expect to find exceptions to the rule, as in this particular case.

EXPERIMENTAL

Crystal data and diffraction measurements. — The crystal data for potassium D-gluconate monohydrate are as follows:

Dehydration temperature, 112–116°; m.p. 176–180°

Orthorbombic, space group $P2_12_12_1$, from the absent spectra:

$h00$, $0k0$, and $00l$ for h, k, or l odd.

$a = 8.220 \pm 0.004$, $b = 17.840 \pm 0.008$, $c = 6.717 \pm 0.003$Å

($\lambda_{CuK\alpha} = 1.5418$ Å)

$V = 985 \pm 2$ Å^3

$Z = 4$

$D_x = 1.701 \pm 0.007$ g. cm^{-3}; $D_m = 1.743 \pm 0.007$ g. cm^{-3}

Well-formed, prismatic crystals suitable for X-ray diffraction measurements were obtained by slow evaporation at room temperature of a saturated solution in distilled water. (The anhydrous form crystallizes from alcohol–water[1].) The unit-cell parameters and intensity data were measured on a crystal $0.5 \times 0.5 \times 0.25$ mm, mounted about the c axis, by using an Enraf–Nonius CAD 3 diffractometer with Ni-filtered CuKα radiation. A multicycle, $\theta - 2\theta$ scan-mode was used that rescanned the reflection until either a preset, integrated count of 40,000 was accumulated, or a preset number of 7 scan-cycles was reached. The intensities of three reference reflections (4,0,0), (0,14,0), and (0,0,4) were monitored at 50 reflection-intervals during the data collection, and the small, but significant, changes observed were used to correct the data for X-ray instability. Of the 1677 reflections recorded, which contained three unique hkl sets, 45 had integrated intensities less than two standard deviations, estimated from counting statistics, and these were considered to be unobserved. The intensities were transformed to structure amplitudes, without absorption corrections, by using an IBM 1130 program.

TABLE II

FRACTIONAL, ATOMIC COORDINATES AND ANISOTROPIC, TEMPERATURE FACTORS OF POTASSIUM D-GLUCONATE HYDRATE[a]

	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{23}	β_{13}	β_{12}
K	0.6436(2)	0.2783(1)	0.0545(2)	88(2)	10(1)	137(3)	4(1)	−10(2)	7(1)
C-1	0.9491(7)	0.4465(3)	0.5494(10)	66(9)	9(2)	136(15)	4(3)	36(11)	5(5)
C-2	0.9327(7)	0.0016(3)	0.0471(10)	56(9)	8(1)	109(13)	1(1)	1(10)	−9(4)
C-3	0.0160(7)	0.0510(3)	0.2037(9)	61(8)	6(1)	91(13)	−2(3)	4(5)	2(4)
C-4	0.8989(7)	0.1096(3)	0.2914(9)	59(9)	7(1)	106(13)	−5(3)	0(9)	0(4)
C-5	0.9704(7)	0.1607(3)	0.4501(10)	73(9)	8(1)	98(13)	2(3)	−12(11)	8(4)
C-6	0.8326(8)	0.2055(3)	0.5475(10)	90(10)	13(2)	121(1)	10(4)	0(13)	−13(5)
O-0	0.8832(6)	0.3982(2)	0.4401(8)	105(8)	11(1)	164(11)	−16(2)	44(9)	−11(3)
O-1	0.9307(6)	0.4522(3)	0.7316(7)	85(7)	31(2)	104(11)	−18(3)	31(8)	8(4)
O-2	0.8548(5)	0.0448(2)	0.8987(7)	64(6)	13(1)	118(10)	8(2)	−21(7)	−10(3)
O-3	0.6506(5)	0.4105(2)	0.8872(6)	37(5)	12(1)	121(1)	6(2)	0(5)	11(3)
O-4	0.8414(6)	0.1602(2)	0.1401(7)	93(7)	8(1)	126(11)	13(2)	−47(8)	−3(3)
O-5	0.5486(6)	0.3794(3)	0.3931(7)	97(7)	16(1)	91(10)	−9(2)	9(7)	9(4)
O-6	0.8901(6)	0.2607(2)	0.6831(7)	151(9)	9(1)	142(12)	8(2)	−39(9)	−15(3)
O-W	0.9852(6)	0.3462(2)	0.0816(8)	146(9)	20(1)	191(15)	13(3)	5(11)	−14(5)
H-C-2	0.859(8)	0.970(4)	0.148(10)						
H-C-3	0.953(8)	0.015(4)	0.319(10)						
H-C-4	0.821(8)	0.075(4)	0.375(10)						
H-C-5	0.976(8)	0.202(4)	0.410(10)						
H-C-6	0.770(8)	0.169(4)	0.659(10)						
H′-C-6	0.749(8)	0.229(4)	0.420(10)						
H-O-2	0.840(8)	0.100(4)	0.800(10)						
H-O-3	0.650(8)	0.410(4)	0.030(10)						
H-O-4	0.820(8)	0.132(4)	0.990(10)						
H-O-5	0.523(8)	0.419(4)	0.275(10)						
H-O-6	0.880(8)	0.311(4)	0.616(10)						
H-W	0.990(8)	0.380(4)	0.980(10)						
H′-W	0.000(8)	0.370(4)	0.230(10)						

[a]Estimated standard deviations are in parentheses. W = water.

Structure determination and refinement. — The phases were generated for 150 normalized, structure amplitudes by using the Long program[21] on an IBM 360-50 computer. The starting phases were $\pi/2$ for 5,13,0 and 0,11,2, and zero for 0,10,3 and 7,6,0. The resulting E-map could not be interpreted, except for one relatively large peak that was assumed to be that for the potassium ion. An E^2-1, Patterson synthesis verified the positions of the potassium ion and indicated the orientation of the D-gluconate ions from the recognition of a vector pattern characteristic of a zigzag chain of bonded atoms. By neglecting (on the E-map) peaks that were inconsistent with this orientation, it was possible to recognize a feasible model consisting of the potassium ion, four of the six carbon atoms, and six of the seven oxygen atoms of the D-gluconate ion. A Fourier synthesis phased on this model revealed the remaining carbon and oxygen atoms, including that of the water molecule, and gave an initial R-index of 0.22, with uniform, isotropic temperature-factors. A full-matrix, least-squares refinement gave $R = 0.095$, at which stage all of the hydrogen atoms were located on difference syntheses. The final refinement-cycles were made by full-matrix, least-squares by using anisotropic, thermal parameters (except for the hydrogen atoms, which were assigned the isotropic factors of the atoms to which they were bonded). The weighting scheme used was $w^{-1} = (1.0 + 0.1|F_o| + 0.001|F_o|^2)$. The anomalous-dispersion corrections were included, and gave a final R of 0.061 for the D configuration and 0.076 for the L. The final parameters are given in Table II, and illustrated by the ORTEP plot[22] with 50 percent probability-limits in Fig. 1. The atomic numbering is the same as that used by Littleton[1]. The observed and calculated structure-factors are given in Table III*.

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*Table III was submitted with the paper for refereeing purposes. Copies are available on request from the Department of Crystallography, University of Pittsburgh, Pittsburgh, Pa. 15213.

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