discussions and suggestions, Mrs Marlene C. Morris for aid in obtaining the cell dimensions, and Miss Ellen J. Bailey for measuring the intensities, assisting in processing the data and performing various computations.

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The Crystal Structure of Dipotassium Glucose-1-phosphate Dihydrate

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(*Received* 24 *March* 1964)

A complete structure determination has been made of dipotassium glucose-1-phosphate dihydrate. The crystal is monoclinic, belonging to the space-group $P2_1$ and has the following cell dimensions:

$$a = 10{\cdot}44,\ b = 9{\cdot}025,\ c = 7{\cdot}518\ \text{Å};\ \beta = 110°24'.$$

The observed density of 1·85 g.cm^{-3} agrees with that calculated for two units of $K_2.C_6H_{11}O_5.O.PO_3.2H_2O$ per unit cell.

The structure was determined primarily by vector methods, partly using the isomorphous diammonium glucose-1-phosphate dihydrate, and refined both by difference maps and by the method of least-squares. The α-configuration on carbon (1) has been confirmed, and the angles and dimensions of the esterified phosphate group found to agree generally with those of other sugar phosphates. The crystal is bound together both by electrostatic and by hydrogen bonds.

Introduction

Glucose-1-phosphate, the Cori ester, is found widely in both plants and animals. In plants it is the immediate precursor of starch, and in animals of glycogen, being also the first product in the breakdown and utilization of these substances. Though not classified as one of the high-energy phosphates, its heat of hydrolysis ($\sim$ 4800 cal.mole^{-1}) is appreciably higher than that of glucose-6-phosphate and the other low energy phosphates ($\sim$ 2500 cal.mole^{-1}). Kalckar (1941) considers this to be the energy which, loosely speaking, 'drives' the synthesis of these polysaccharides. In the presence of the appropriate enzyme and substrate the Cori ester also enters into the syntheses of a number of disaccharides, *e.g.* with fructose and in the presence of sucrose phosphorylase, sucrose is produced (Bonner, 1950). This enzyme, however, appears to be specific to glucose-1-phosphate only, as other disaccharides, some quite unknown in nature, can be produced by changing the sugar in the substrate.

The configuration of the molecule has been studied chemically both by Cori, Colowick & Cori (1937) and by Wolfrom & Pletcher (1941) who concluded from comparisons with a synthetic product, and from the high dextrorotation, that the natural ester was α-glucose-1-phosphate, which is confirmed by the present study.

Experimental

The potassium salt of glucose-1-phosphate can be obtained commercially in a very pure state. Crystals of this derivative, which is a dihydrate, are easily grown by slow cooling of a hot saturated aqueous solution, forming prisms with a length:breadth ratio of about 2:1.

Zero-layer Weissenberg photographs were taken about the three axes, and the crystal was found to be monoclinic, the unique axis being parallel to the long axis of the prism. The cell dimensions were:

$$a = 10\cdot44 \pm 0\cdot005,\ b = 9\cdot025 \pm 0\cdot005,$$
$$c = 7\cdot518 \pm 0\cdot005\ \text{Å};\ \beta = 110°\ 24' \pm 6'.$$

Volume 665 Å^3. Observed density 1·85 g.cm^{-3}.

The linear absorption coefficient (calculated) μ = 80 cm^{-1}.

The only systematic extinctions were in the $0k0$ intensities with $k = 2n+1$. The space group was therefore $P2_1$, the alternative of $P2_1/m$ with a cell of twice the volume being discounted because of the optical activity of this substance in solution, and a positive response of the crystalline form to the Giebe–Scheibe test for piezoelectricity.

Normal beam zero- and upper-layer photographs were taken about the a, b and c axes and about the shorter ac diagonal. In measuring the intensities, the triple-film overlay method, with one Ilford Industrial G and two Industrial B, was used. Some 1350 intensities were estimated by visual comparison with a set of standard reflexions from the same crystal, and converted to F^2's. No absorption correction was applied. A sharpened, three-dimensional Patterson function and three projections down the main axes were computed.

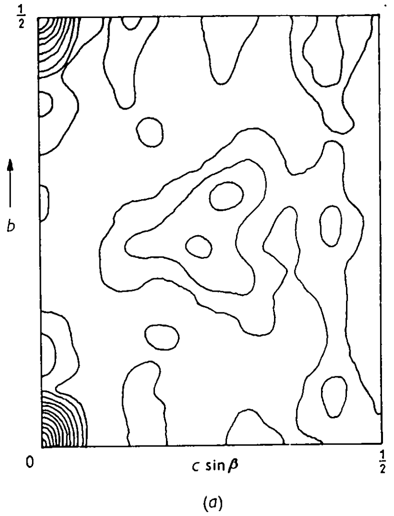
Interpretation

The most striking features of the vector maps were first the heavy peaks lying along the a axis both at $y = 0$ and $y = \frac{1}{2}b$, and the overall 'layer' arrangement of the vectors which were situated mainly at the levels of $y = 0$, $y = \frac{1}{4}b$ and $y = \frac{1}{2}b$. Peaks at $y = \frac{1}{2}b$ are, of course, to be expected, since this is the Harker section, but there did appear to be a special concentration in this region. This was interpreted as being caused by numbers of atoms possessing the same y coordinate.

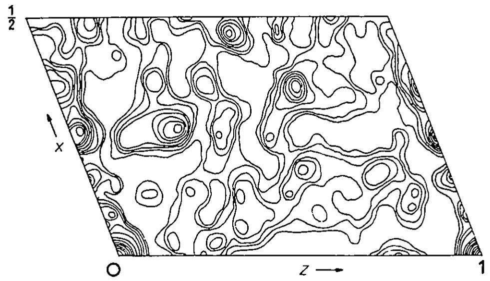
An examination of the peaks around the origin (Beevers & Ehrlich, 1959) indicated that the pyranose ring of the glucose residue was lying perpendicular to the screw axis, one of the sides of the hexagon being parallel to the a axis. From the foregoing evidence, it was deduced that the general picture of the structure consisted of the phosphorus atom and the cations lying in one plane, perpendicular to the screw axis, with the pyranose ring lying in another plane, parallel to the first and separated from it by about $\frac{1}{4}b$. The water molecules were not considered at this stage. It now remained to find the x and z coordinates of the various components of the structure.

The general plan was to find an arrangement of the phosphorus and potassium atoms which led to a set of vectors corresponding to the larger vectors in the Patterson map. In effect, these atoms were treated in isolation from the rest of the structure. The sugar residue could be found either by a superposition method (from the positions of the heavier atoms) or, quite independently, by making use of the partial centrosymmetry of the pyranose ring, since two centrosymmetric groups related by a centre of symmetry will give rise to a multiple vector equal to the separation of their centres. With the space group $P2_1$, only the b-axis projection is centrosymmetric and the 'centre–centre' peak will therefore occur only on this projection. The orientation of the ring, however, was such that in three dimensions this multiple peak would occur as a diffuse streak, stretched in the y direction by about 0·5–0·6 Å on each side of the Harker section. Correct identification of the centre–centre vector is sufficient to locate the ring centre and hence, ring orientation being known, the atom positions.

From the a-axis projection (Fig. 1(a)) it was postulated that the potassium and phosphorus atoms were collinear, lying almost exactly along the a axis. From the vectors lying on the y axis at about 1·0 Å above and below both the origin and the Harker plane it was further presumed that the tetrahedral



(a)



(b)

Fig. 1. Dipotassium salt. (a) Patterson projection down the a axis. (b) Patterson projection down the b axis.

phosphate (PO_4) group was orientated with one of its $\bar{4}$ axes parallel to the *b* axis, two oxygen atoms lying along the *a* axis and above the phosphorus, and two lying exactly across this axis, below the phosphorus. Finally, a diffuse peak extended over the Harker section was chosen as a likely centre–centre vector, and the sugar ring allocated a *z* coordinate from this. The concentration of peaks on the *b*-axis projection (Fig. 1(*b*)) had made the identification of a centre–centre peak impossible.

The resulting structure was very plausible, since the separation required from the phosphorus atom to the plane of the sugar ring was correct for α-glucose-1-phosphate in its most extended form, one of the oxygen atoms straddling the *a* axis being the link with C(1), on the glucose residue. Structure factors were calculated for the proposed structure, and some measure of agreement between calculated and observed values was obtained. Refinement by means of difference syntheses was carried out, and presumed water molecules were inserted after three cycles. During the refinement, the whole sugar molecule moved slightly, indicating that the originally chosen 'centre–centre' vector was incorrect. The *R* index could not be reduced below the high value of 30%, and difference maps did not give any clear indication of the reason.

This difficulty was resolved when the ammonium salt of glucose-1-phosphate was prepared by B.D.H. Ltd., and proved to be isomorphous with the potassium salt. General intensity data up to $l=3$ were obtained, some 700 reflexions being measured. The sharpening function $(1+8\sin^3\theta)$ which had been found, quite empirically, to be suitable for sharpening the potassium salt vector map to the 'atoms at rest' case was applied twice over to these data, *i.e.* the Patterson function was sharpened by $(1+8\sin^3\theta)^2$. This is quite a high degree of sharpening, but had no detrimental effects, despite the limited number of terms and abrupt cut-off. Comparison of the resulting vector map with that of the potassium salt showed that the medium-weight atoms, which included the replaceable cations, could not be collinear, one of these being displaced from the two atoms which were on the *a* axis by about $\frac{1}{2}c$. The deductions concerning the rest of the structure were confirmed, the tetrahedral P–O vectors of the PO_4 group, and the centre–centre vector showing up well (Fig. 2). Examination of the correct centre–centre peak on the potassium salt vector map showed it to be much more diffuse than anticipated. The re-positioning of the potassium atom and location of the sugar ring were effected and *h*0*l* structure factors for $\sin\theta \leq 0{\cdot}85$ calculated. A difference map showed the positions of the water molecules and O(6). Their *y* coordinates were determined approximately by building a model of the structure as far as it was known and estimating the *y* coordinates on steric considerations.

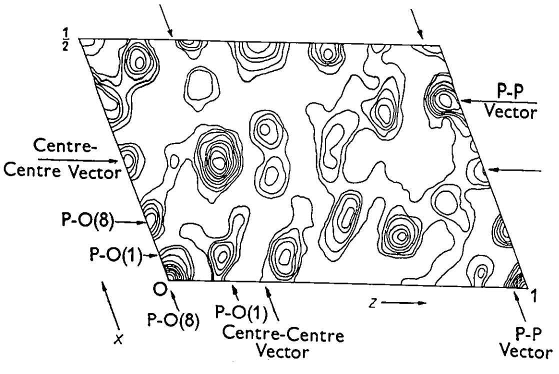


Fig. 2. Diammonium salt. Patterson projection down the *b* axis.

Refinement

Refinement was carried out initially by difference maps of the projections down each axis. The amount of overlap in projection was considerable, and refinement was therefore continued in three dimensions, at first by difference maps and finally by least squares on the DEUCE computer of the University of Glasgow, using the programs of Rollett (1961). The *R* index for the 1350 reflexions uncorrected for absorption levelled out after a number of cycles at some 20·5%. Further refinement was carried out on 970 reflexions which had been obtained from an approximately cylindrical crystal and corrected for absorption by assuming a perfect cylinder. The residual after two further cycles was 17·2% after scaling F_o against F_c in ranges of $\sin^2\theta$. The parameters finally obtained are shown in Table 1. The approximate probable errors in atomic positions for each atomic type were calculated from the equation derived by Cruickshank (1960) as:

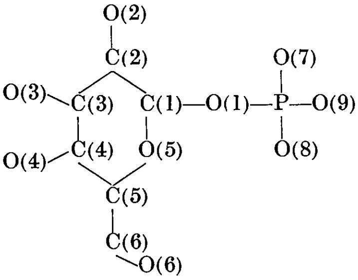
K^+	±0·008 Å	O	±0·024 Å
P	±0·009	C	±0·034

Table 1. *Atomic parameters*

Atom	*x/a*	*y/b*	*z/c*	(thousandths)
K(1)	948	454	439	
K(2)	421	2	986	
P	203	510	984	
C(1)	266	271	193	
C(2)	223	193	353	
C(3)	323	252	544	
C(4)	471	209	572	
C(5)	502	281	405	
C(6)	656	248	438	
O(1)	238	419	177	
OH(2)	87	225	337	
OH(3)	284	195	694	
OH(4)	551	298	735	
O(5)	406	227	221	
OH(6)	684	302	275	
O(7)	84	609	980	
O(8)	332	599	3	
O(9)	161	405	823	
W(1)	956	204	692	
W(2)	852	430	23	

The bond lengths within the glucose phosphate anion are:

P–O(1) = 1·59 Å
P–O(7) = 1·52
P–O(8) = 1·53
P–O(9) = 1·48
C(1)–C(2) = 1·58
C(1)–O(5) = 1·46
C(2)–C(3) = 1·54
C(3)–C(4) = 1·53
C(4)–C(5) = 1·54 Å
C(5)–C(6) = 1·57
C(1)–O(1) = 1·37
C(2)–O(2) = 1·41
C(3)–O(3) = 1·42
C(4)–O(4) = 1·46
C(5)–O(5) = 1·49
C(6)–O(6) = 1·44



The average C–C distance is 1·55 Å, while the average of the two C–O distances within the ring is 1·47 Å and the average C–O involving addenda to the ring is 1·43 Å. The bond-length probable errors are: C–C, ±0·05 Å; C–O, ±0·04 Å; P–O, ±0·03 Å. Bond angles do not deviate greatly from the tetrahedral angle except for the angle P–O(1)–C(1) which is 124°, possibly because of the repulsion between the phosphate group and the glucose ring.

The major source of error probably lies in the observed intensities, partly because of the large absorption coefficient and partly because of the method of intensity measurement. Estimation of intensity by visual comparison is naturally an inaccurate procedure and in retrospect it appeared that there was a tendency to underestimation of the more intense reflexions. Unobserved reflexions were set equal to half the observable minimum.

Description of the structure

The molecule shows the same lengthening of the P–ester-oxygen bond found in analogous structures (Alver & Furberg, 1959; Trueblood, Horn & Luzzati, 1961; Kraut, 1961; Furberg & Mostad, 1962; Kraut & Jensen, 1963) and discussed from a theoretical viewpoint by Cruickshank (1961) before some of these structures were known. The axial C(1)–O(1) bond is shorter than the usual C–O bond length by about 1·5 times the probable error and may be significant. Shortening of the axial C–OH bond on the 1-position was observed by McDonald (1952) in α-D-glucose, though this has been queried by Killean, Ferrier & Young (1962). It was also observed by McGeachin (1957) in α-rhamnose monohydrate. The greater lability of this position on the sugar ring is well known. One of the P–O bonds, P–O(9), is shorter than the average by some 2 × probable error and is probably genuine, suggesting a certain amount of double-bond

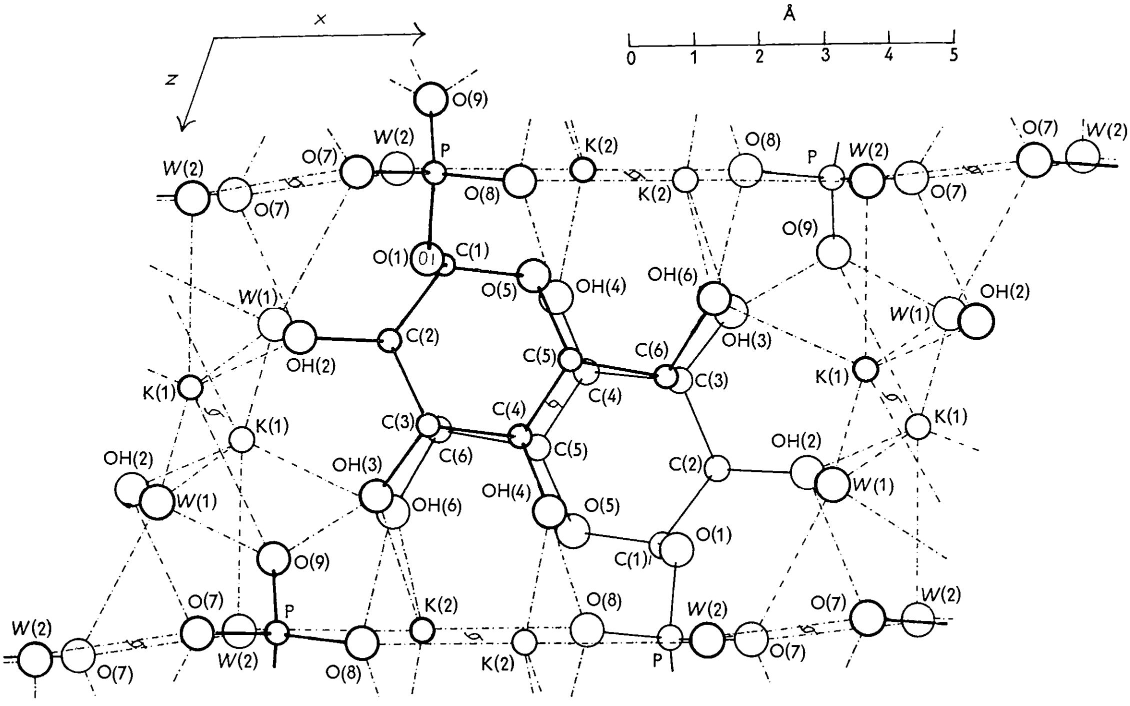


Fig. 3. Projection of the structure down the *b* axis.

character, though the precision of the determination is not high enough to warrant further discussion.

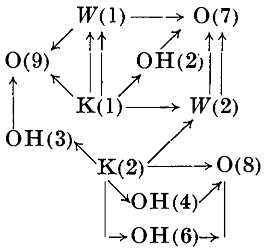
The crystal structure itself is held together by an elaborate system of bonds involving the two potassium ions, the water molecules, the hydroxyl groups and the oxygen atoms O(7), O(8) and O(9) of the PO_4 group. The following distances are involved (see Fig. 3 for the numbering of the atoms):

K(1)–O(9)	2·97 Å	
K(1)–OH(2)	3·05	(long)
K(1)–OH(2′)	2·78	
K(1)–OH(3)	3·14	(long)
K(1)–OH(6)	2·94	
K(1)–*W*(1)	2·93	
K(1)–*W*(1′)	2·78	
K(1)–*W*(2)	2·94	
K(2)–OH(3)	2·77	
K(2)–OH(4)	2·73	
K(2)–OH(6)	2·61	
K(2)–O(8)	2·69	
K(2)–*W*(2)	2·90	
W(1)–O(7)	2·78	
W(1)–O(9)	2·71	
W(2)–O(7)	2·98	
W(2)–O(7′)	3·03	
OH(2)–O(7)	2·60	
OH(3)–O(9)	2·65	
OH(4)–O(8)	2·63	
OH(6)–O(8)	2·75	

There are also distances K(2)–O(5) = 2·70 Å and *W*(1)–O(1) = 2·92 Å, but since these involve oxygen atoms already fully bonded they are to be regarded as very weak bonds.

From this list it will be seen that OH(2) has a bond to K(1) and to O(7) (and also a larger distance to K(1)), OH(3) has bonds to K(2) and O(9), OH(4) has bonds to K(2) and O(8), and OH(6) has bonds to K(2) and O(8) (neglecting the longer OH(6)–K(1) = 2·94 Å). Thus we see that each of the OH groups has one bond to a cation and one to the anion, these eight bonds serving to hold the sugar ring firmly in place.

The water molecules have bonds as follows: *W*(1) to K(1) and K(1′); and to O(7) and O(9). The bonds to K(1), K(1′) and O(7) form an almost planar arrangement, but the complete set of four bonds forms a very distorted tetrahedron. *W*(2) also has four bonds, to K(1) and K(2) and to O(7) and O(7′) with distances as given in the list above. These bonds form another somewhat distorted tetrahedron, but it is of interest that each of the water molecules in the structure has bonds to two cations and to two of the oxygen atoms of the phosphate group. The diagram below gives a convenient summary of these bonds and portrays very clearly the general nature of the bonding as ionic from the K^+ ions to the $[PO_3]^{2-}$ ions, with the OH groups and the water molecules acting as the intermediaries in the bonding.



The full details of the system of bonds are only shown in the structure itself but it is thought that the system is sufficient to link the components together very firmly and to explain the fairly high density and hardness of the crystals.

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