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THE CRYSTAL STRUCTURE OF D-GLUCARO-1,4-LACTONE MONOHYDRATE*

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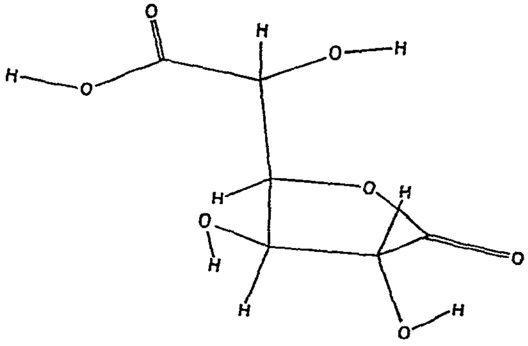
ABSTRACT

In the crystal structure of D-glucaro-1,4-lactone monohydrate, $C_6H_8O_7 \cdot H_2O$, the molecules have the E_3 lactone-ring conformation, with a small distortion of the ring to $_3T^2$. The α-hydroxycarboxylic acid side-chain is axial, with the HO–C–C=O torsion angle within 6° of *cis*-planar. The orientation of the side-chain is such that the hydroxyl group lies over the lactone ring, which is the same conformation as is reported to preponderate in solution. Calculations of non-bonding repulsion energy show that this conformation corresponds to an energy minimum, although comparable minima can also be obtained with the ring in the alternative ^3E conformation. The lactone and water molecules are hydrogen-bonded to form layers two molecules wide, separated by Van der Waals interactions. One of the water hydrogen atoms is involved in a weak, bifurcated hydrogen-bond.

INTRODUCTION

D-Glucaro-1,4-lactone (**1**) is of considerable biochemical interest as it is a highly specific inhibitor of β-D-glucosiduronase[1] and is used in cancer chemotherapy[2]. This study was undertaken to provide structural information relating to the molecule



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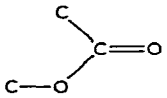
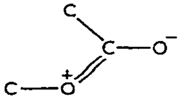
in the crystalline state for comparison with the conformational studies in solution by Walaszek[3] and by Horton and Walaszek[4].

DESCRIPTION OF THE STRUCTURE

The D-glucaro-1,4-lactone molecule, as observed in the crystal structure of the monohydrate, is shown in Figs. 1 and 2, with the values of the bond-torsion angles and bond lengths and angles. The lactone group is close to planar, but not exactly so, as shown by the torsion angles of −3.7° and 176.4° between the bonds adjacent to C-1–O-4. The C-1–O-4 length is shorter and O-4–C-4 is longer than the normal C–O single-bond length of 1.425 Å. These differences, which have been observed in other 1,4-lactones (see Table I), are consistent with the valence-bond resonance representations (I) and (II).



(I)



(II)

With a planar lactone group, the lactone ring is necessarily an envelope, ^{3}E or E_3. In this structure it is close to E_3, with the side-chain axial and the two hydroxyl-groups equatorial. The small deviation from exact planarity of the lactone group corresponds to a distortion from the ideal envelope in the direction of the $_{3}T^{2}$ (twist) conformation. The major and minor displacements of C-3 and C-2 are 0.42 Å and 0.09 Å, respectively, out of the C-4, O-4, C-1 plane. In terms of the pseudo-rotation diagram of Altona and Sundaralingam[8], this distortion corresponds to a shift in the pseudorotational phase-angle to $P = 192°$, from the ideal value of 198° for E_3. The corresponding puckering parameters as defined by Cremer and Pople[9] are $q_2 = 0.317$ Å and $\varphi_2 = 101.8°$, where q_2 is the amplitude of displacement about a mean plane and the phase-angle φ_2 for E_3 is 108° (the reference point for $\varphi_2 = 0$ is $^{\circ}E$, and $\varphi_2 = P - 90°$).

As shown in Table I, of the four crystal structures of 1,4-lactones that have been studied, distortions of similar magnitude are observed in all but that of the gulonolactone. They do not appear to be related to the configurational differences and may be caused by the intermolecular packing-forces in the crystal. There is no evidence that the equilibrium conformation would be other than the ideal E_3 envelope in either the free molecules or in solution.

The α-hydroxycarboxylic acid group, with the exception of the hydrogen atoms, is close to planar, with an O–C–C=O torsion-angle of 5.6°. This is a characteristic conformational feature of the many α-hydroxycarboxylic acids and carboxylates that have been studied by crystal-structure analysis. It is observed in glycolic acid[10], and generally in the tartaric and citric acids and in the tartrates, gluconates, and citrates.

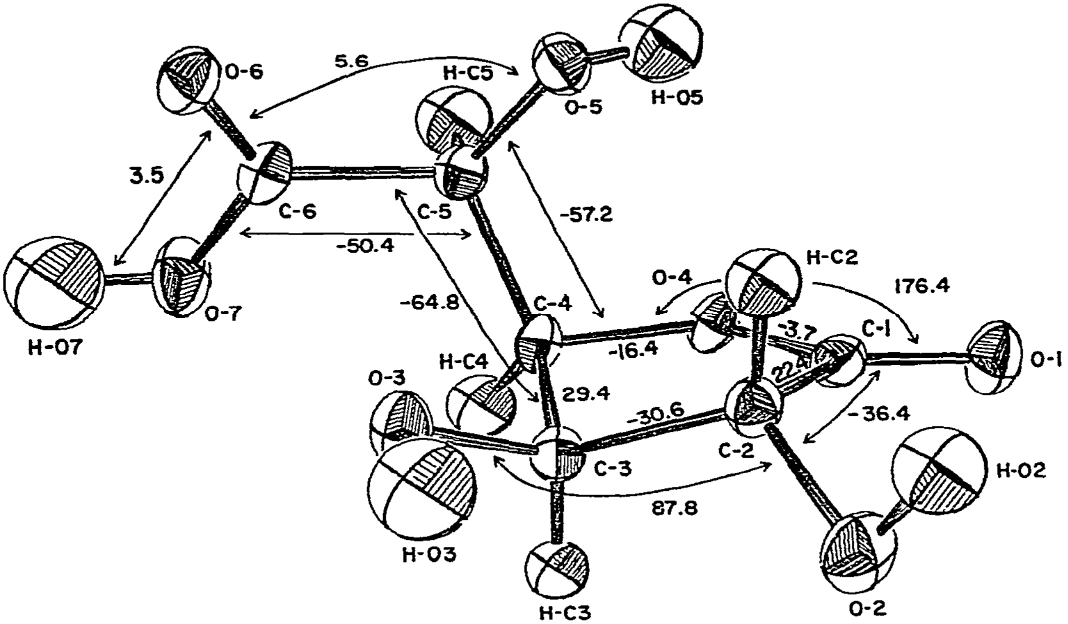


Fig. 1. The molecule of D-glucaro-1,4-lactone, with the thermal ellipsoids at 50% probability (Johnson[14]). The numerical values are the bond-torsion angles as indicated. H–O2 is shown at the position that refined with half-occupancy.

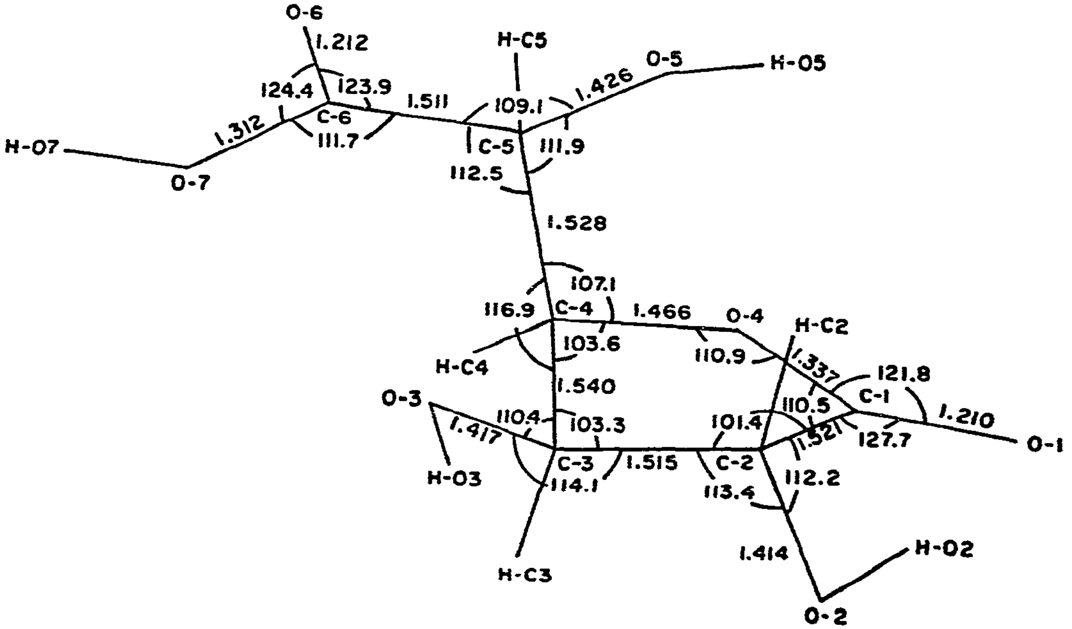


Fig. 2. The bond lengths and valence angles in D-glucaro-1,4-lactone.

TABLE I

RING GEOMETRY OF 1,4-LACTONES IN CRYSTAL STRUCTURES[a]

Aldono-1,4-lactone	φ	*C-1–O-4*	*O-4–C-4*	*P (degrees)*	*Conformation*	*Reference*
D-Glucaro-	−3.7	1.337(4)	1.466(4)	192	$_3T^2$	This work
D-Galactono-	4.9	1.358(5)	1.464(5)	205	$_3T^4$	5
D-Gulono-	−0.4	1.346(3)	1.472(3)	198	$_3E$	6
2,3,6-Tri-*O*-methylgalactono-	−2.3	1.350(5)	1.455(6)	195	$_4T^2$	7

[a] φ is the C-2–C-1–O-4–C-4 torsion angle; the deviation from zero is a measure of the departure from planarity of the lactone group. *P* is the pseudorotational phase-angle of the five-membered lactone ring, as defined by Altona and Sundaralingam[8].

The conformation of the linkage bond (C-4–C-5) between the ring and the side-chain is staggered, with an O–C–C–O torsion-angle of 57°, bringing the hydroxyl group (OH-5) over the center of the lactone ring.

All of the hydrogen atoms except H-O2 were located with no difficulty at reasonable C–H and O–H distances and angles. The nearest neighbors to O-2 are O-5 on an adjacent molecule at 2.98 Å and the carbonyl oxygen atom (O-1) on the same molecule, which is closer at 2.90 Å. A small peak of about 0.3 e/Å^3 was found about 1 Å from O-2 in the direction of O-5 at a reasonable angle, but this could only be refined by least squares by assuming half-occupancy. While suggesting that H-O2 is disordered between the two weak hydrogen-bonding interactions, this is uncertain because the other half-occupied position could not be located.

THE MOLECULAR CONFORMATION

The conformation of the molecule in solution has been studied by u.v., i.r., o.r.d., and n.m.r. spectroscopy[3,4]. The n.m.r. results indicate an $^3E \rightleftharpoons E_3$ equilibrium favoring the same conformation as observed in the crystal, with the side-chain hydroxyl group over the lactone ring. The coupling constants $J_{2,3} = 8.8$, $J_{3,4} = 7.8$, and $J_{4,5} = 2.8$ Hz from n.m.r. studies[4] in methanol-d$_4$ and D$_2$O solution are con-

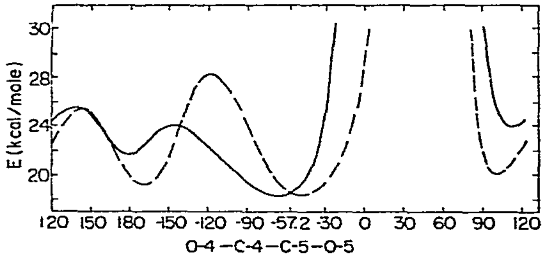


Fig. 3. Conformational energy versus the torsion angle O-4–C-4–C-5–O-5. The full line is for the E_3 conformer observed in the crystal structure. The dotted line is for a hypothetical ^3E conformer having the same bond lengths and valence angles. The conformation angle in the crystal structure is −57.2°.

sistent with the vicinal torsion-angles observed in the crystal structure (H-2–C–C–H-3 −165°, H-3–C–C–H-4 25°, H-4–C–C–H-5 −53°). The reason for this favored conformation in both the crystal and in solution is not obvious, as the ${}^3E$ lactone-ring, which has the side-chain more equatorial, should permit a wider range of conformers because of fewer steric interactions. This view is supported by the potential-energy plots given in Fig. 3. The relative non-bonding repulsion energies were calculated by using a Buckingham-type potential versus φ, the C–C–C–O torsion angle across C-4–C-5. It was assumed that both the lactone group and the α-hydroxylcarboxylic acid side-chain retain their nearly planar conformation, so that only rotation about the linkage bond (C-4–C-5) need be considered.

The E_3 plot shows one minimum of lower energy, within which lies the value for $\varphi = -57.2°$, observed in the crystal structure. This orientation places OH-5 over the lactone ring and is the favored conformation for the molecules in solution from the n.m.r. data[4]. The secondary minimum at $\varphi = 180°$ places the hydrogen atom on C-5 over the ring and brings HO-5 closer to HO-3. This is 3.5 kcal.mol^{-1} higher in energy, but the O···O separation is such that it could be stabilized by intramolecular hydrogen-bond formation between the two hydroxyl groups, in a non-aqueous solvent for example[3]. The ${}^3E$ plot shows three minima within 2 kcal.mol^{-1} of that of the observed E_3 conformer. They correspond to the three staggered orientations about C-4–C-5, none of which incur close, non-bonded steric interactions. As these calculations were made with the molecular geometry based on that observed in the crystal structure, these three ${}^3E$ conformers could have energies as low as that of the observed structure.

In seeking alternative reasons why the E_3 conformer might be more stable, it should be noted that, in all four 1,4-lactones hitherto studied by crystal-structure analysis, a common conformational feature is the E_3 ring with the substituent on C-2 in the equatorial position (see Table I). When the substituent is a hydroxyl group, a weak, intramolecular hydrogen-bond can be formed to the adjacent carbonyl oxygen atom, and this bond could stabilize this conformer. The "partial disappearance" of H–O2 in this structure analysis may be due to disorder, or large thermal motion, arising from the competition between this interaction and the weak, intermolecular bond. In addition, the common occurrence of the *cis*-planar HO–C–C=O conformation, even without hydrogen bonding, as in the side chain of this molecule, suggests that the equatorial orientation of C–OH-2 may be more stable than the axial, because of an internal bond-rotation potential that would tend to make the O-1–C-1–C-2–O-2 torsion-angle as small as possible.

MOLECULAR PACKING

The molecular packing and hydrogen-bonding is shown in Figs. 4 and 5. The distances and angles of the hydrogen bonds are given in Table II. The hydrogen bonding is unusual for a carbohydrate in that it connects the molecules into layers ather than into a three-dimensional net. These layers, which are two molecules wide,

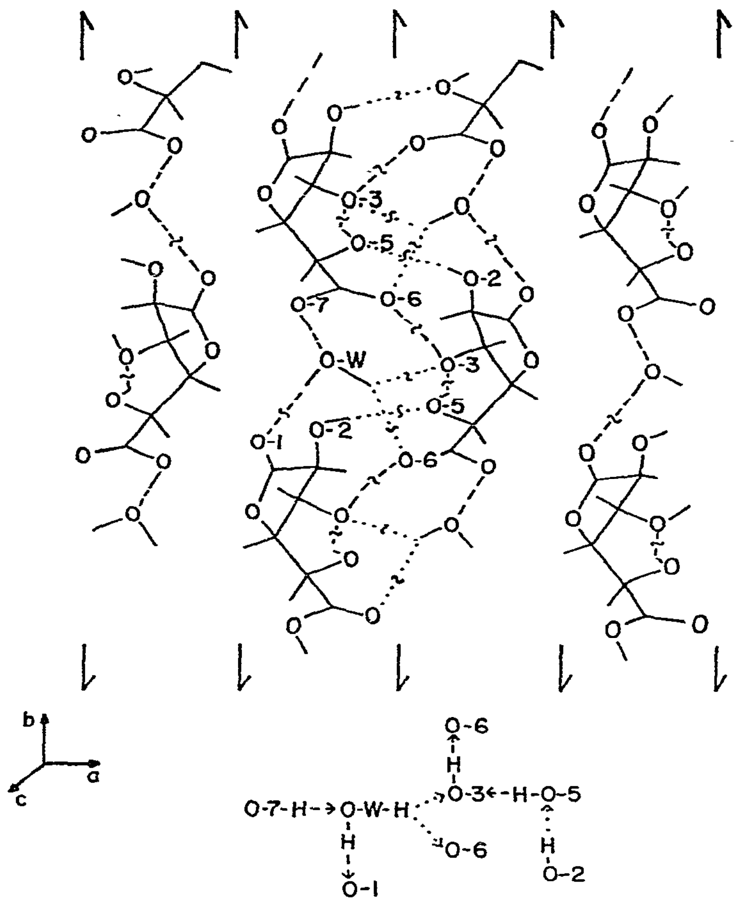


Fig. 4. The molecular packing and hydrogen-bonding in D-glucaro-1,4-lactone monohydrate, showing the layer structure. The bifurcated bonds and that involving H–O2 are dotted, as in Table II.

TABLE II

HYDROGEN-BOND DISTANCES IN Å AND ANGLES

Bond		*O–H*	*H···O*	*O···O*	*O–$\hat{H}$···O*
O-7–H ·······O-W		1.0	1.6	2.59	175°
O-3–H ·······O-6[a]		0.8	1.9	2.71	169°
O-5–H ·······O-3[b]		0.9	2.0	2.84	153°
O-W–H-1······O-1[c]		0.9	2.0	2.87	173°
O-W–H-2	O-3[d]	1.0	2.3	3.06	131°
	O-6[d]	1.0	2.5	3.30	142°
O-2–H[f] ······O-5[e]		1.1	1.9	2.93	166°

Symmetry relationships: [a]$2-x$, $\frac{1}{2}+y$, $1-z$; [b]x, y, $1+z$; [c]x, $y-1$, $z-1$; [d]$2-x$, $-\frac{1}{2}+y$, $1-z$; [e]$2-x$, $\frac{1}{2}+y$, $2-z$; [f]half-occupancy.

are separated by Van der Waals interactions, as shown in Fig. 4. The layers contain chains of lactone and water molecules, which are linked in the [011] direction by the hydrogen-bonds O-7–H···O-W and O-1···H–1OW. These chains are cross-linked to form layers by the O-5–H···O-3 bonds in the [c] direction and by O-3–H···O-6 and the weak interactions involving H–2OW and O-2 across the two-fold screw axes at $x = 0$, as shown in Fig. 5.

Both carbonyl oxygen atoms accept hydrogen bonds; that of the carboxylic acid group (O-6) is involved in a normal hydrogen-bond with H–O-3 and the weaker of a bifurcated interaction with the water molecule. The water molecule accepts one hydrogen bond, forming a pyramidal rather than planar coordination with the two O–H bonds. The hydrogen atoms of the water molecule have large thermal parameters and their positions were the least well-defined of those observed, except for H–O2. Again this is associated with their relatively weak hydrogen-bonding environment, especially for H–2OW. The H···O and O···O distances span an unusually wide range, from those of a strong hydrogen bond to a very weak bifurcated interaction, namely 1.6 to 2.5 Å and 2.59 to 3.30 Å, respectively. The oxygen atom of the lactone ring is not hydrogen bonded; its nearest intermolecular neighbor is H–O7 at 2.70 Å.

EXPERIMENTAL

Crystals of D-glucaro-1,4-lactone monohydrate were provided by Professor D. Horton, The Ohio State University. The crystal data and those relating to the structure determination are given in Table III. The final atomic parameters are given in Table IV. The table of structure factors is deposited with and can be obtained from: Elsevier Scientific Publishing Company, BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/044/*Carbohydr. Res.*, 50 (1976).

TABLE III

CRYSTAL AND EXPERIMENTAL DATA FOR D-GLUCARO-1,4-LACTONE MONOHYDRATE

$C_6H_8O_7 \cdot H_2O$, mol. wt. 210.14, m.p. 91–92°
Monoclinic, space group $P2_1$, $Z = 2$
Cell dimensions: $a = 8.2973(4)$ Å, $b = 9.1337(5)$ Å, $c = 5.6039(5)$ Å, $\beta = 104.887(7)°$ at 17°
$D_x = 1.701$ g·cm^{-3}; $D_m = 1.692$ g·cm^{-3} (flotation)
Enraf–Nonius CAD-4 diffractometer
Ni-filtered CuK_α radiation, $\lambda = 1.5418$ Å
Size of crystal, $0.19 \times 0.20 \times 0.33$ mm^3
Intensity data: Two equivalent quadrants averaged to give 827 $|F|$s of which 805 had $|F| > 3\sigma$
$\mu_{CuK_\alpha} = 14.6$ cm^{-1}, no absorption corrections applied

Structure solution by MULTAN[13] and E-map based on 200 $|F|$s with $E > 1.2$
Structure refinement by full-matrix, least squares on $\Sigma\omega_i(|F_0| - |F_c|)^2$ where $\omega = 1/\sigma^2(F_0)$.
Anisotropic temperature factors for C, O, isotropic for H
Final agreement $R = 0.041$, $\omega R = 0.053$

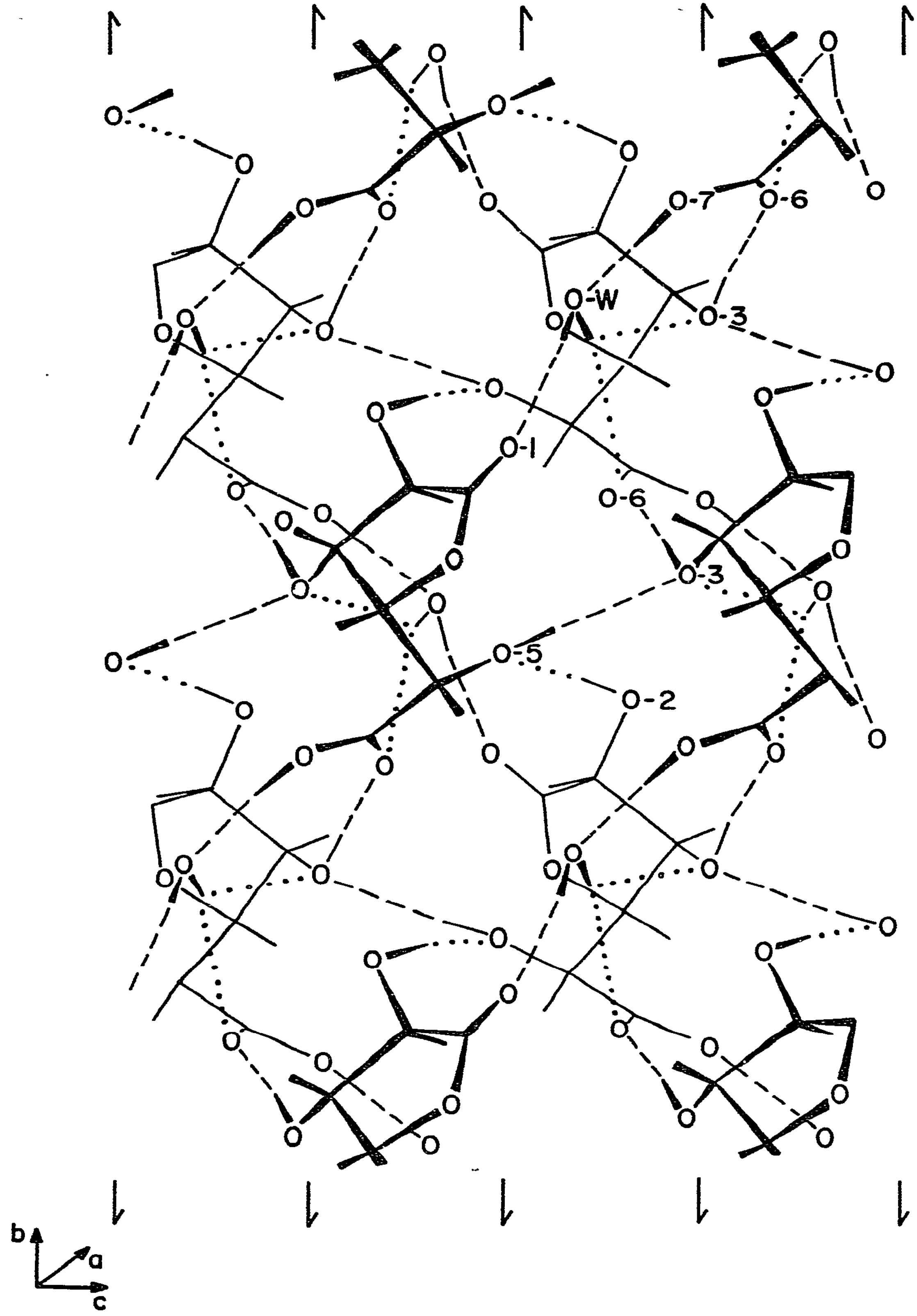

O-7
O-6
O-W
O-3
O-1
O-6
O-3
O-5
O-2
b
a
c

TABLE IV

FINAL FRACTIONAL COORDINATES AND THERMAL PARAMETERS FOR D-GLUCARO-1,4-LACTONE MONOHYDRATE[a]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C-1	6428(4)	6677(5)	9111(6)	64(5)	42(4)	148(11)	8(4)	25(6)	3(5)
C-2	7715(4)	6853(5)	7627(7)	79(5)	39(4)	146(11)	−7(4)	38(6)	−6(5)
C-3	7142(4)	5707(5)	5636(6)	65(5)	42(4)	124(11)	1(4)	27(6)	−4(5)
C-4	6352(4)	4522(5)	6928(6)	51(4)	41(4)	155(11)	4(3)	35(5)	−13(5)
C-5	7512(4)	3333(6)	8331(6)	63(5)	42(4)	145(11)	−2(4)	26(6)	−5(5)
C-6	8233(4)	2388(6)	6646(7)	71(5)	40(4)	176(12)	5(4)	37(6)	−8(5)
O-1	6032(3)	7566(5)	10458(5)	110(4)	57(3)	224(10)	10(3)	73(5)	−22(5)
O-2	7732(4)	8288(5)	6687(6)	154(6)	44(3)	253(11)	−23(3)	83(6)	2(5)
O-3	8439(3)	5123(5)	4700(5)	90(4)	53(3)	205(9)	−7(3)	83(5)	−10(4)
O-4	5733(3)	5347(5)	8755(4)	60(3)	42(3)	200(9)	5(3)	61(4)	−2(4)
O-5	8842(3)	3933(5)	10215(5)	63(3)	74(4)	151(8)	10(3)	11(4)	−29(4)
O-6	9704(3)	2110(5)	7009(5)	78(4)	86(4)	212(10)	31(3)	29(5)	−26(5)
O-7	7068(3)	1895(5)	4767(6)	80(4)	87(4)	270(11)	1(3)	7(5)	−83(6)
O-W	8056(3)	139(5)	1791(6)	86(4)	72(4)	298(11)	−3(4)	53(5)	−42(5)
H-C2	884(6)	659(6)	893(9)	22(9)					
H-C3	629(5)	611(6)	428(8)	18(8)					
H-C4	536(6)	414(6)	572(9)	26(9)					
H-C5	699(7)	261(6)	909(10)	32(11)					
H-O2	887(20)	862(21)	798(29)	75(42)					
H-O3	893(7)	583(8)	422(11)	42(14)					
H-O5	838(7)	421(7)	1140(11)	32(11)					
H-O7	737(8)	123(8)	363(11)	49(15)					
H-1OW	738(8)	−68(10)	149(13)	60(17)					
H-2OW	913(7)	−40(7)	230(10)	39(12)					

[a] Non-hydrogen positional and anisotropic thermal parameters are $\times 10^4$. Hydrogen atoms have positional coordinates $\times 10^3$ and isotropic temperature factor ($\times 10$). The form of the anisotropic temperature factor is $T = \exp\,[-\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$. Estimated standard-deviations are given in parentheses for the least significant figures.

The non-bonding potential-energy curves in Fig. 3 were calculated from the atomic coordinates in Table IV by using the Buckingham potential $E_r = A \exp(-Br) - Cr^{-6}$, by means of the program WMIN[11] on a CDC 7600 computer. In the absence of reliable values of the empirical constants for intermolecular interactions, a set of values for A, B, and C were used that had been applied successfully to the packing analysis of amino acids[12]. These calculations are believed to give reliable estimates for the positions of the energy minima and their relative values, but have much less physical significance in the higher-energy regions.

The ^3E conformation of the molecule was derived from the bond distances and torsion angles of the observed structure by reversing the sign of the torsion angles in the ring. The atomic coordinates for use in WMIN were then computer-generated by the programs BUILDR and PRJCTN on the CRYSNET system[13].

← Fig. 5. The molecular packing and hydrogen-bonding in D-glucaro-1,4-lactone monohydrate, showing one layer of hydrogen-bonded molecules.

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