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The Crystal Structure of γ-D-Gulonolactone

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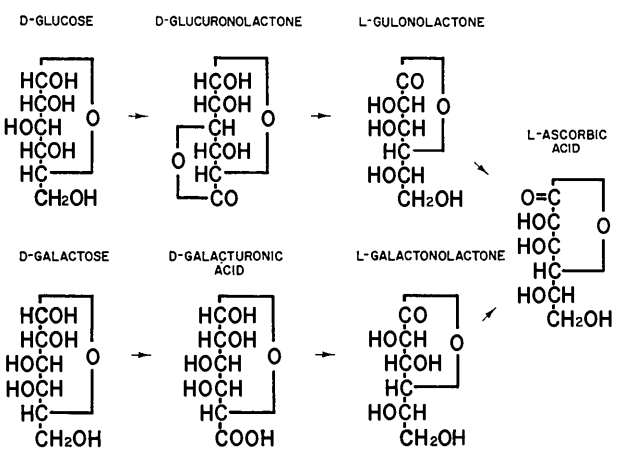
The crystal structure of γ-D-gulonolactone, a precursor of ascorbic acid, has been solved using a tangent refinement procedure and refined with full-matrix least-squares to an R value of 0·039. There are four formula units of $C_6H_{10}O_6$ in a unit cell of dimensions $a=11{\cdot}489$ (5), $b=9{\cdot}478$ (5) and $c=6{\cdot}576$ (2) Å in space group $P2_12_12_1$. Gulonolactone greatly resembles galactonolactone, an alternative precursor of ascorbic acid, both in its bond distances and the planarity of its lactone group. Even though the only difference between the two lactones is the configuration at C(3), the change in the relative positions of the O(3)H and O(5)H hydroxyl groups considerably affects the conformation of the side chain. All of the molecules in the unit cell are connected by a single hydrogen-bonding chain involving O(2)H and O(5)H.

Introduction

There are two metabolic pathways (I) which lead to the production of ascorbic acid. Both of these involve the stepwise oxidation of a hexose to produce a five-membered lactone ring with substituent hydroxyls and a hydroxyl-bearing side chain.



(I)

Significant conformational changes would be expected to accompany the configurational changes which occur in these pathways. The crystal structures of glucuronolactone (Kim, Jeffrey, Rosenstein & Corfield, 1967), galactonolactone (Jeffrey, Rosenstein & Vlasse, 1967), ascorbic acid (Hvoslef, 1968) and now gulonolactone, form a basis for discussion of these changes.

Experimental

Single crystals of γ-D-gulonolactone grown by evaporating an aqueous solution were ground into spheres using a Bond sphere grinder. One sphere with a diameter of 0·49 mm was used to collect diffractometer data using Ni-filtered Cu $K\alpha$ radiation and θ–2θ scans of 2°. Ten-second background counts were taken at both sides of the peak. The 800 independent reflections were reduced to structure amplitudes using a program written by Craven & Chu (1967). The Bond (1959) corrections for absorption by a sphere were applied.

Crystal data

γ-D-Gulonolactone, $C_6H_{10}O_6$
Space group $P2_12_12_1$, $Z=4$

$a=11{\cdot}489(5)$ Å $\mu_{Cu\,K\alpha}=11{\cdot}82$ cm^{-1}
$b=9{\cdot}478(5)$ $D_m=1{\cdot}652$ g.cm^3
$c=6{\cdot}576(2)$ $D_x=1{\cdot}656$ g.cm^3

Structure solution and refinement

The structure was determined using the tangent refinement procedure. Three origin phases and one enantiomorph phase were chosen in such a way that they combined to yield highly interacting general phases. These four phases alone were used as input to the tangent refinement and extension program written by Hall (1967). The E syntheses based on the ninety-two phases with E's greater than 1·5 yielded the structure, with an R value of 0·24. Full-matrix anisotropic refinement (Shiono, 1966) using a Hughes (1941) weighting scheme reduced this to 0·075 at which time a difference synthesis was calculated. The ten hydrogen atoms were among the eleven highest peaks on the map. Subsequent refinement of the temperature and positional parameters of the heavier atoms and the positional parameters of the hydrogen atoms to which were assigned isotropic temperature factors gave a final R value of 0·039. The structure factors are given in Table 1; the positional and temperature parameters are in Table 2.

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Description of the structure

The D-gulonolactone molecule is shown in Fig. 1. The thermal ellipsoids enclose a probability density of 0·50 for the nonhydrogen atoms. Fig. 2 shows L-gulonolactone, L-galactonolactone and L-ascorbic acid and their projections along the C(4)–C(5) bonds. Gulonolactone and galactonolactone are stereoisomers with respect to the hydroxyl groups attached to C(2) and C(3). These hydroxyl groups are both brought into the plane of the ring by an enzymatic oxidation which introduces a double bond between C(2) and C(3), thus forming ascorbic acid from either precursor. The conformation of the side chain is directly influenced by the configuration of the ring. The conformation of the side chain of galactonolactone is similar to ascorbic acid except for the orientation of O(6)H. If gulonolactone had this conformation, however, there would be a close non-bonded contact between O(5)H and O(3)H. Therefore O(5)H would be expected to lie in one of the two other staggered orientations. The alternative actually found was predicted by applying what we have been referring to privately as the zigzag principle. That is, in gulonolactone the sequence O(1)–C(1)–O(4)–C(4)–C(5)–C(6)–O(6) forms a slightly twisted extended zigzag chain, analogous to the sequence O(2)–C(2)–C(3)–C(4)–C(5)–C(6)–O(6) in galactonolactone and galactitol. Both of these zigzag conformations are of course available to ascorbic acid but we feel that the planar carbon backbone is more likely than the planar heterochain partly because of attraction between the groups on alternate atoms.

In the precursor to gulonolactone, glucuronolactone, the side chain cyclizes to form a fused ring system. The conformation of C(4)–C(5) is thus constrained, but interestingly enough, O(5) is oriented in the same general direction with respect to O(4) as in gulonolactone.

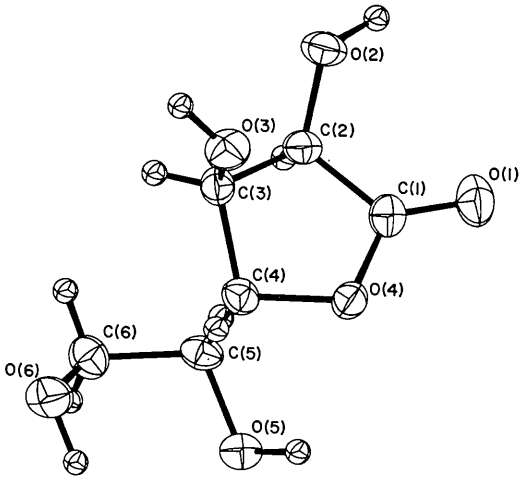
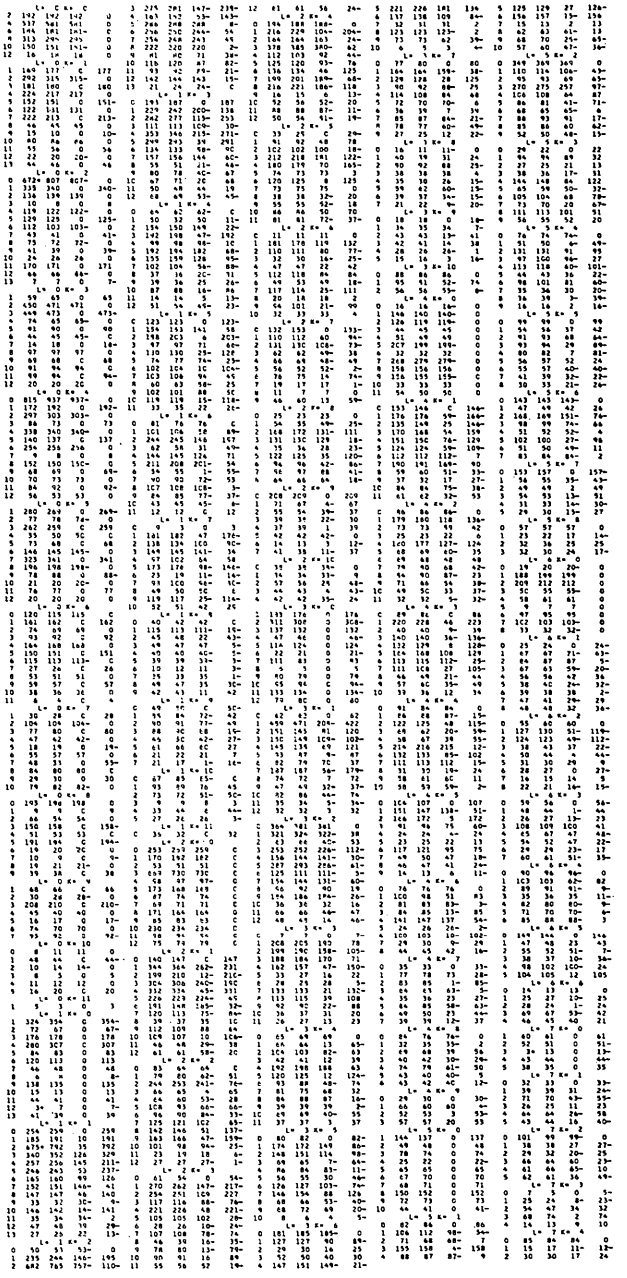


Fig. 1. The molecular structure of γ-D-gulonolactone, showing the thermal vibration ellipsoids (Johnson, 1965).

Table 1. *Observed and calculated structure factors*

The columns are F_{obs}, F_{cal}, A_{cal}, B_{cal}.
* Indicates unobserved reflections.



The atoms comprising the lactone group

C(2)–C(1)(=O(1))–O(4)–C(4)

are ±0·01 Å from their mean plane. This group is usually flat (Fridrichsons & Mathieson, 1962) for stereoelectronic reasons, as indeed it is in galactonolactone. Also as in galactonolactone, the five-membered ring is puckered, with C(3) 0·58 Å out of

Table 2. *Fractional atomic coordinates and thermal parameters in γ-D-gulonolactone*

Key to atomic numbering is given in Fig. 2. The temperature factor expression used was

$$\exp -(h^2\beta_{11}+k^2\beta_{22}+l^2\beta_{33}+2hk\beta_{12}+2hl\beta_{13}+2kl\beta_{23}) .$$

Numbers in parentheses refer to standard deviations of the last place.

	x	y	z	β_{11} or B	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	0·0143 (2)	0·1996 (2)	0·0451 (4)	0·0049 (2)	0·0064 (2)	0·0123 (5)	−0·0005 (2)	0·0002 (3)	0·0012 (3)
C(2)	−0·0022	0·3585	0·0248	0·0039	0·0060	0·0129	0·0005	0·0003	0·0001
C(3)	0·0448	0·3858	−0·1895	0·0038	0·0055	0·0122	−0·0005	0·0002	0·0010
C(4)	0·1437	0·2786	−0·1993	0·0033	0·0060	0·0131	−0·0006	−0·0006	0·0004
C(5)	0·1773	0·2300	−0·4105	0·0034	0·0075	0·0118	0·0002	−0·0008	−0·0006
C(6)	0·2347	0·3505	−0·5259	0·0059	0·0080	0·0112	0·0002	0·0012	0·0005
O(1)	−0·0372	0·1190	0·1518	0·0077	0·0087	0·0197	−0·0006	0·0032	0·0030
O(2)	−0·1194	0·3990	0·0443	0·0044	0·0099	0·0160	0·0017	0·0014	0·0016
O(3)	−0·0409	0·3509	−0·3363	0·0043	0·0094	0·0138	0·0007	−0·0021	0·0013
O(4)	0·0983	0·1573	−0·0840	0·0052	0·0057	0·0128	0·0006	0·0007	0·0007
O(5)	0·2580	0·1140	−0·3966	0·0042	0·0065	0·0142	0·0005	0·0001	−0·0005
O(6)	0·2520	0·3159	−0·7342	0·0071	0·0118	0·0111	0·0027	0·0021	0·0013
H(C2)	0·052 (3)	0·414 (3)	0·141 (5)	2·5					
H(C3)	0·072	0·479	−0·207						
H(C4)	0·217	0·314	−0·123						
H(C5)	0·105	0·203	−0·484						
H(C6)	0·312	0·370	−0·465						
H′(C6)	0·177	0·424	−0·540						
H(O2)	−0·154	0·387	0·179						
H(O3)	−0·071	0·424	−0·404						
H(O5)	0·209	0·024	−0·428						
H(O6)	0·305	0·238	−0·726						

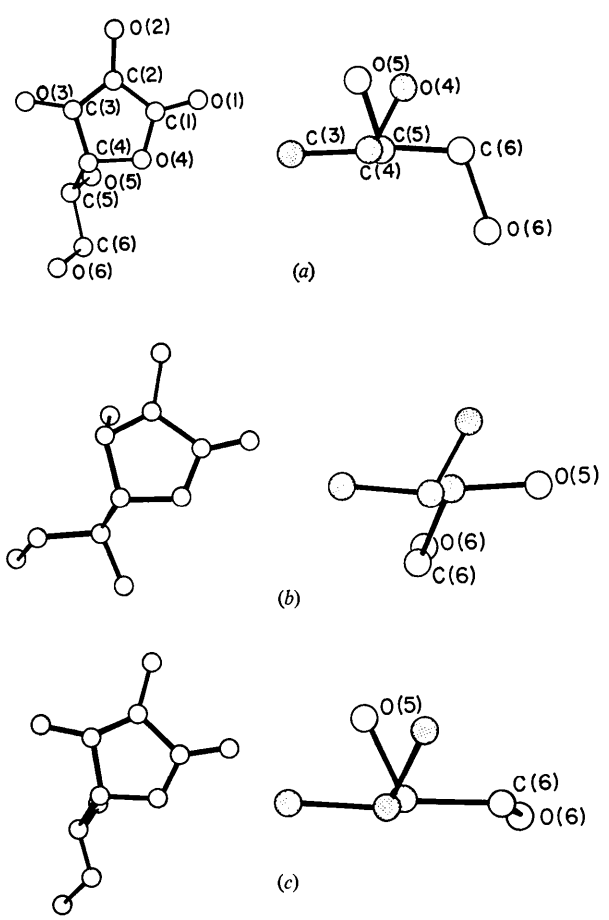


Fig. 2. The projections of (*a*) L-ascorbic acid, (*b*) L-gulonolactone, and (*c*) L-galactonolactone, normal to the ring and down the C(4)–C(5) bond.

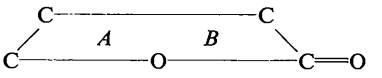
the plane of the lactone group. This distortion results from the non-bonded repulsion between the hydroxyl group and hydrogen atom attached to C(3) and those on C(2), which forces the conformation towards a staggered orientation. In galactonolactone, the hydroxyl groups interact with the hydrogen atoms to twist C(3) 0·64 Å out of the plane. In gulonolactone the interaction on one side of the ring is between hydroxyl groups and on the other side it is between hydrogen atoms.

The same principles apply to glucuronolactone, Fig. 3. (The atoms are renumbered as in gulose.) The undistorted model would have O(2) and O(3) in an eclipsed conformation, with high repulsion. The structure actually found therefore involves a rotation around the C(2)–C(3) bond towards a staggered conformation. This distorts the lactone ring into an envelope form, tilting the carbonyl group C(1)–O(1) *endo*, thus destroying the planarity of the lactone group.

The bond distances found in this structure and other γ-lactones are in Table 3. The ether oxygen is evidently drawn towards the carbonyl carbon by the delocalized electrons from the double bond, which increase the bond order of *A*. As a result there is a net shrinkage in the total length of the two C–O single bonds, *A* and *B*. The angles (Table 4) show no remarkable deviations from those found in related structures.

There are only three independent hydrogen bonds in the crystal structure (see Table 5 and Fig. 4). Both O(2) and O(5) act as donors and acceptors. O(6) is a donor; O(3) is an acceptor. The predominant feature in the hydrogen bonding scheme is an infinite chain connecting all symmetry related molecules O(2) → O(5) → O(2) → O(5) around the *c* screw axis.

Table 3. *Bond distances and angles found in γ-lactones*



	Mean bond lengths in the compound				Δ_{C-O}*	
	C–C	C–OH	C=O	3σ	*A*	*B*
Galactono-γ-lactone	1·525 (44)	1·420 (42)	1·198	0·015	+0·044	−0·062
Glucurono-γ-lactone	1·522 (22)	1·421 (37)	1·215	0·015	+0·054	−0·081
Gulono-γ-lactone	1·523 (12)	1·421 (39)	1·194	0·009	+0·050	−0·075

* Δ_{C-O} signifies the deviations of the ring carbon–oxygen bond distances from the average C–OH distances in that compound.

Table 4. *Distances and angles in γ-D-gulonolactone*

i	*j*	*k*	D_{ij}	$\angle_{ijk}$
C(1)	C(2)	C(3)	1·523 Å	101·8°
C(1)	C(2)	O(2)		112·4
C(2)	C(3)	C(4)	1·531	100·9
C(2)	C(3)	O(3)		110·0
C(3)	C(4)	C(5)	1·525	115·6
C(4)	C(5)	C(6)	1·513	109·9
C(4)	O(4)	C(1)		110·2
C(6)	C(5)	O(5)	1·521	109·0
O(1)	C(1)	O(4)	1·194	122·4
O(1)	C(1)	C(2)		128·5
O(2)	C(2)	C(3)	1·406	112·1
O(3)	C(3)	C(4)	1·418	109·5
O(4)	C(4)	C(3)	1·472	103·6
O(4)	C(1)	C(2)	1·346	109·2
O(5)	C(5)	C(4)	1·441	109·8
O(6)	C(6)	C(5)	1·422	111·6

The average estimated standard deviations are 0·003 Å for bond lengths and 0·2° for the angles.

Table 5. *Intermolecular distances and angles*

(*a*) Hydrogen bonds

i	*j*		*k*	D_{jk}	$\angle_{ijk}$
C(5)	O(5)	H	O(2*a*)	2·763 Å	115·0°
C(2)	O(2)	H	O(5*b*)	2·714	124·2
C(6)	O(6)	H	O(3*c*)	2·894	95·0

(*b*) Close contacts (less than 3·5 Å)

i	*j*	D_{ij}
O(3)	O(4*d*)	3·024 Å
O(5)	O(3*c*)	2·920
O(1)	O(3*a*)	3·401

Symmetry operation:

a	$-x, -\frac{1}{2}+y, -\frac{1}{2}-z$
b	$-\frac{1}{2}+x, \frac{1}{2}-y, -z$
c	$\frac{1}{2}+x, \frac{1}{2}-y, -1-z$
d	$-x, \frac{1}{2}+y, -\frac{1}{2}-z$

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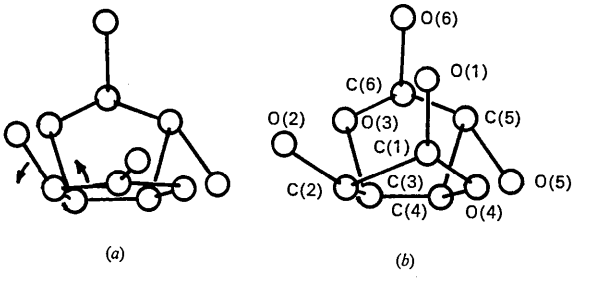

Fig. 3. β-D-Glucuronolactone projected down the C(2)–C(3) bond. (The atoms are numbered as in gulose.) (*a*) A flat lactone ring molecular model. (*b*) The structure as determined.

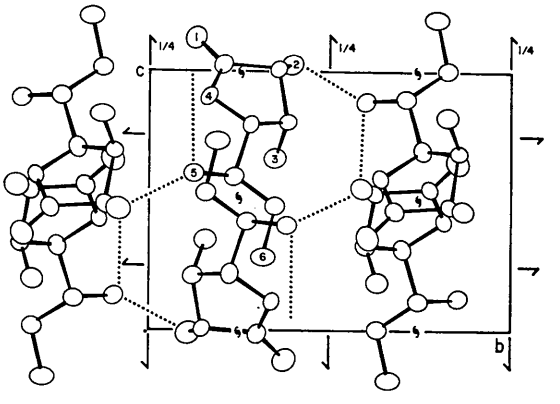

Fig. 4. The crystal structure of γ-D-gulonolactone projected along the *a* axis.

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