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CRYSTAL STRUCTURE OF METHYL 2,6-DICHLORO-2,6-DIDEOXY-3,4-*O*-ISOPROPYLIDENE-α-D-ALTROPYRANOSIDE. A PYRANOSIDE SYSTEM CLOSE TO A SKEW-BOAT CONFORMATION

George Hung-Yin Lin*, M. Sundaralingam† and J. Jackobs‡
Department of Biochemistry, College of Agriculture and Life Sciences, University of Wisconsin Madison, Wisconsin 53706 (U. S. A.)

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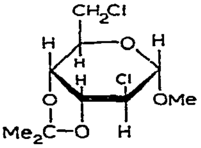
ABSTRACT

The crystal structure of methyl 2,6-dichloro-2,6-dideoxy-3,4-*O*-isopropylidene-α-D-altropyranoside (1) has been determined by X-ray diffraction. The compound crystallizes in the orthorhombic system, space group $P2_12_12_1$, with unit-cell dimensions $a = 7.932$, $b = 8.133$, and $c = 20.447$ Å. The structure was solved by the heavy-atom method and refined by the least-squares technique to an R value of 0.047 by using 736 intensities measured on a diffractometer. The pyranoside ring is close to a skew-boat conformation, with C-2 and C-5 being maximally displaced from the least-squares plane through the remaining four atoms. The H-1–H-2 dihedral angle of −158° is in agreement with the $J_{1,2}$ value of 4.5 Hz. Thus the solid-state conformation appears to correspond with the conformation in solution. The dioxolane ring is in a twist form, with O-4 and C-8 puckered on opposite sides of the plane of the other ring atoms. The pyranose-ring substituents are in equatorial and pseudo-equatorial orientations. The hydrogen atoms at C-3 and C-4 are in a *cis* arrangement. The orientations of both the methoxyl group and the chloromethyl group with respect to the ring are *gauche–trans*. The exocyclic anomeric C-1–O-1 bond-distance (1.39 Å) is the shortest C–O bond in the structure. The intracyclic C–O bonds are significantly different, C-1–O-5 being less than C-5–O-5.

INTRODUCTION

Methyl 2,6-dichloro-2,6-dideoxy-3,4-*O*-isopropylidene-α-D-altropyranoside ($C_{10}H_{10}Cl_2O_4$) (1) has been synthesized as one of the products from the reaction of



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*Present address: Department of Chemistry, University of California, Riverside, California.
†To whom correspondence should be addressed.
‡Present address: Department of Chemistry, Heidelberg College, Tiffin, Ohio.

carbohydrates with (halomethylene)dimethyliminium halides[1]. At the time when this crystal-structure analysis was begun, the molecular structure of the compound was not fully established. In the meantime, the correct chemical structure was deduced to be **1** from nuclear magnetic resonance and chemical investigations[1]. The present X-ray structure investigation not only confirms the chemical structure but also shows that the pyranoside ring adopts an unusual skew-boat conformation.

EXPERIMENTAL

Crystals of **1** were kindly supplied by Dr. S. Hanessian of the University of Montreal, Canada. A sample of dimensions $0.05 \times 0.1 \times 0.3$ mm^3 was used for the X-ray study. The long axis of the crystal was parallel to the b axis. Oscillation, Weissenberg, and precession photographs indicated that the crystal belonged to the space group $P2_12_12_1$. The cell constants measured on a diffractometer are $a = 7.932(2)$, $b = 8.133(2)$, $c = 20.447(4)$ Å. The density of the crystal (1.362 g.cm^{-3}) was measured by flotation in a mixture of carbon tetrachloride and n-heptane; the value is in good agreement with that (1.365 g.cm^{-3}) calculated for four molecules of $C_{10}H_{16}Cl_2O_4$ in the unit cell.

Three-dimensional intensity data up to $(\sin\theta/\lambda) = 0.5$ were collected on a Picker automated diffractometer with Ni-filtered CuKα radiation ($\lambda = 1.5418$ Å), by using the $2\theta - \theta$ scan technique. The crystal was mounted in a capillary tube with the b axis parallel to the ϕ axis of the goniostat. Both the crystal alignment and crystal decay were monitored by recording a few standard reflections at frequent intervals during the period of intensity measurement. At the end of data collection, the standard showed a decrease in intensity of 9% from its initial value. Reflections having $I > 1.5\sigma(I)$ (where $\sigma(I) = \sqrt{N}$, and N = total counts) were considered as observed. There were 736 observed reflections out of the 832 reflections scanned. The data were corrected both for the variations in the standard and the usual Lorentz and polarization effects.

DETERMINATION AND REFINEMENT OF THE STRUCTURE

The structure was solved by the heavy-atom method. A sharpened three-dimensional Patterson map was computed and the positions of the two chlorine atoms were derived from the Harker sections. Based on these positions, a three-dimensional electron-density map was computed and all of the non-hydrogen atoms were found in the map.

The structure was refined by the method of full-matrix least-squares, with the ORFLS program[2]. Two cycles of refinement with isotropic temperature factors for the atoms, followed by two cycles of refinement with anisotropic temperature factors, decreased the reliability index R to 0.080, where $R = \Sigma||F_0| - |F_c||/\Sigma|F_0|$, and F_0 and F_c are the observed and calculated structure-factors, respectively. The weighting scheme used was essentially that of Hughes[3], where $\sigma_F = 1\sqrt{w} = 1.33$ for $|F_0| < 17.27$, and $\sigma_F = 1\sqrt{w} = 0.0916\,|F_0| - 0.28$ for $|F_0| \geq 17.27$. The latter scheme was based on a plot of $|\Delta F|$ versus $|F_0|$. A difference Fourier-map was calculated and the positions of all of the hydrogen atoms were found. The hydrogen atoms were included, but not refined, in the subsequent refinement of the nonhydrogen atoms. The final R factor was 0.047 and the ratios of shift/σ were less than 0.25 for all of the positional and thermal parameters.

The scattering factors for Cl, O, and C atoms were those of Cromer and Waber[4] and that for H from Stewart, Davidson, and Simpson[5].

RESULTS

The observed and calculated structure-amplitudes have been deposited with the American Documentary Institute. The final positional and thermal parameters for non-hydrogen atoms are given in Table I, and the observed positional parameters for hydrogen atoms are given in Table II. A stereoscopic ORTEP drawing of the molecule is shown in Fig. 1. The bond distances and bond angles involving non-hydrogen atoms, together with the atomic numbering in **1**, are shown in Fig. 2. The estimated standard-deviations in bond distances are C–Cl = 0.007 Å, C–C = C–O = 0.010 Å, and in bond angles they are about 0.5°.

DESCRIPTION OF THE STRUCTURE

Dimensions of the pyranoid ring. — The C–C bond distances in the pyranoid ring have a mean value of 1.531 Å, which is close to that reported for other carbo-

TABLE I

FINAL POSITIONAL AND ANISOTROPIC THERMAL PARAMETERS FOR NON-HYDROGEN ATOMS[a,b]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C-1	2529(10)	3902(10)	2203(3)	197(17)	175(15)	17(2)	9(13)	2(5)	8(5)
C-2	2542(9)	4714(11)	1529(4)	93(11)	200(15)	29(2)	15(12)	2(4)	7(5)
C-3	1213(8)	3999(9)	1076(3)	134(13)	203(16)	20(2)	6(12)	8(5)	0(5)
C-4	−545(9)	4103(9)	1402(3)	164(15)	186(16)	17(2)	−1(12)	2(4)	−6(4)
C-5	−398(8)	4507(10)	2128(3)	144(13)	171(13)	15(2)	−7(14)	−1(4)	−1(5)
C-6	−2046(10)	4064(10)	2473(3)	170(14)	242(18)	16(2)	5(14)	−1(5)	6(5)
C-7	3372(10)	4384(15)	3292(4)	224(18)	443(27)	28(3)	−23(22)	−21(6)	43(8)
C-8	−650(9)	5453(13)	420(3)	164(15)	301(20)	15(2)	7(17)	−4(4)	8(6)
C-9	−666(12)	7121(14)	167(4)	180(18)	386(26)	29(3)	8(18)	0(6)	44(7)
C-10	−1552(12)	4225(13)	−9(4)	228(18)	366(24)	22(2)	−23(20)	−6(6)	−3(6)
O-1	3185(7)	5043(7)	2643(2)	205(10)	250(12)	20(1)	−22(10)	−19(3)	7(3)
O-3	1087(6)	4948(8)	503(2)	143(9)	317(15)	18(1)	27(10)	0(3)	18(4)
O-4	−1317(5)	5434(7)	1065(2)	137(8)	268(11)	15(1)	26(9)	−4(3)	1(3)
O-5	878(6)	3408(7)	2376(2)	133(9)	204(11)	20(1)	7(9)	1(3)	11(3)
Cl-2	4615(2)	4511(4)	1182(1)	127(3)	400(6)	30(1)	8(4)	5(1)	24(2)
Cl-6	−1874(3)	4483(3)	3335(1)	254(4)	282(5)	16(1)	−3(5)	10(1)	0(1)

[a] All parameters and their estimated standard deviations (in parentheses) have been multiplied by 10^4.
[b] Anisotropic thermal parameters are of the form $\exp[-(\beta_{11}h^2 + \ldots + 2\beta_{12}hk + \ldots)]$.

TABLE II

OBSERVED POSITIONAL PARAMETERS FOR HYDROGEN ATOMS[a]

Atom	x	y	z
H-1	0.332	0.284	0.221
H-2	0.221	0.583	0.158
H-3	0.175	0.300	0.088
H-4	−0.108	0.304	0.129
H-5	−0.008	0.558	0.225
H-6,1	−0.288	0.483	0.229
H-6,2	−0.238	0.279	0.246
H-7,1	0.413	0.362	0.329
H-7,2	0.250	0.413	0.346
H-7,3	0.417	0.542	0.354
H-9,1	−0.025	0.729	−0.017
H-9,2	−0.175	0.743	0.017
H-9,3	−0.017	0.813	0.046
H-10,1	−0.129	0.325	0.017
H-10,2	−0.258	0.446	−0.004
H-10,3	−0.121	0.438	−0.046

[a] The isotropic thermal parameter B for all hydrogen atoms was set[2] at 4.5 Å.

hydrates[6–8]. The exocyclic (axial) anomeric C-1–O-1 bond (1.394 Å) is significantly shorter than the normal C–O bond distance (1.425 Å) but is close to the average value found in the glycosides having O-1 axial[7]. The inequality in the intracyclic C–O bonds, namely, C-1–O-5 (1.415 Å)<C-5–O-5 (1.442 Å)[9] also follows the same trend as that found in the glycosides having O-1 axial[7].

The largest and smallest intracyclic valence-angles are at O-5 and C-5, which are adjacent to each other. The significant decrease in the angle at C-5 (105.2°) is related to the large puckering exhibited by C-5 (see later). In general, the angles at the odd-numbered carbon atoms of the pyranoside ring are smaller than the angles at the even-numbered ones. The exocyclic angles at each ring atom differ significantly; this is probably a universal feature of the pyranosides[8].

Conformation of the pyranoid ring. — The most interesting aspect of the structure is the conformation of the pyranoid ring. Unlike the most stable *C1*(D) chair conformation found in the majority of the pyranosides, the shape of the pyranoid ring found here is close to a boat form. In fact, the conformation is between the ideal boat and ideal skew-boat[10], resembling the former more closely. The torsional angles for the ring bonds found in the present compound are compared in Table III with those for the idealized conformations. The conformation of the pyranoid ring may also be described in terms of the calculated four-atom least-squares planes. (The four atoms comprise the pair of bonds on opposite sides of the pyranoid ring). It is found that the best four-atom least-squares plane comprises the atoms O-5, C-1, C-3, and C-4 (Table IV). The puckered atoms C-2 (0.560 Å) and C-5 (0.695 Å) are displaced on the same side of this plane. As indicated earlier, C-5

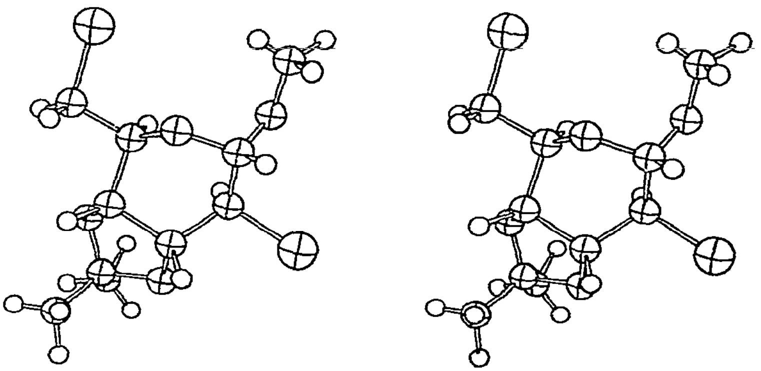


Fig. 1. A stereoscopic view of the molecule of **1**, showing its configuration and conformation.

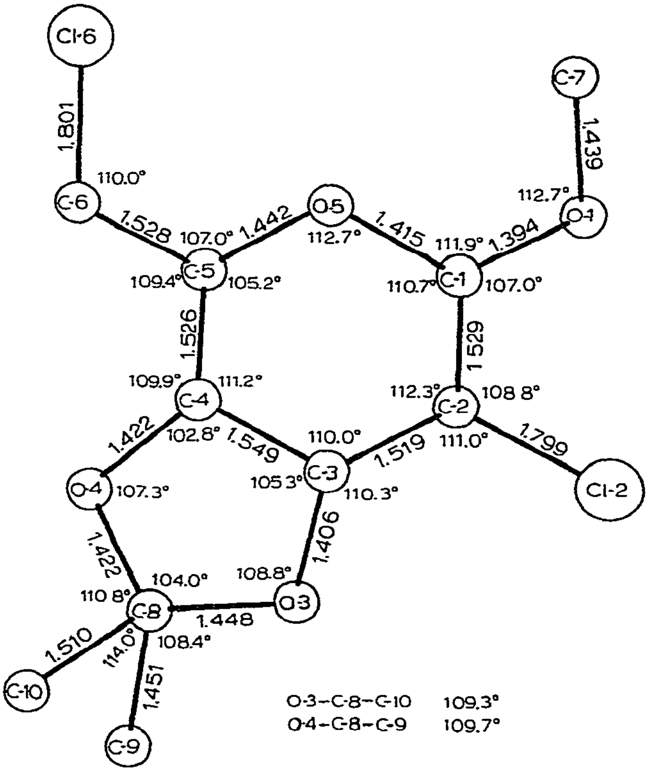


Fig. 2. Atomic numbering and bond distances and bond angles involving non-hydrogen atoms. Average standard-deviations are 0.010 Å for C–C, C–O bonds; 0.007 Å for C–Cl bonds, and 0.5° for all angles involving nonhydrogen atoms.

shows the maximal puckering. The least-squares planes through the adjacent four-atom planes C-5–O-5–C-1–C-2 and C-2–C-3–C-4–C-5 are also given in Table IV. The dihedral angle between these planes is 125.3°.

TABLE III

COMPARISON OF THE PYRANOSIDE-RING CONFORMATION OF **1** WITH THE IDEAL SKEW-BOAT AND BOAT CONFORMATIONS OF CYCLOHEXANE

	Skew boat[a]	**1**	*Boat*[b]	*Torsional angles (degrees) about the dioxolane-ring bonds*	
C-1–O-5	−33	−33.8	0	C-3–C-4	−14.5
O-5–C-5	+70	+76.2	+60	C-4–O-4	30.7
C-5–C-4	−33	−47.3	−60	O-4–C-8	−35.4
C-4–C-3	−33	−13.2	0	C-8–O-3	25.4
C-3–C-2	+70	54.9	+60	O-3–C-3	−6.6
C-2–C-1	−33	−32.1	−60		

[a,b]These torsional angles (degrees) are Hendrickson's values[10] for the corresponding ideal conformations in cyclohexane.

TABLE IV

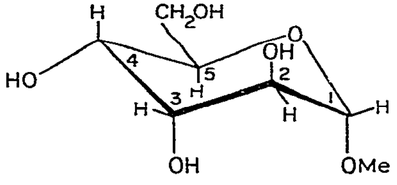
DEVIATIONS (IN Å) FROM LEAST-SQUARES PLANES[a,b] THROUGH THE PYRANOID RING AND THE EXOCYCLIC ISOPROPYLIDENE RING

Atom	*Pyranose*			*Dioxolane*	
	Plane I	*Plane II*	*Plane III*	*Plane IV*	*Plane V*
C-1	−0.136[a]	−0.166[a]	−0.957		
C-2	−0.560	0.085[a]	0.042[a]		
C-3	0.121[a]	1.255	−0.072[a]	0.036[a]	−0.082[a]
C-4	−0.131[a]	1.038	0.072[a]	−0.021[a]	0.080[a]
C-5	−0.695	−0.092[a]	−0.042[a]		
O-5	0.146[a]	0.173[a]	−1.203		
O-3				−0.038[a]	0.056[a]
O-4				−0.465	−0.055[a]
C-8				0.023[a]	0.440
R.m.s. Δ	0.134	0.135	0.059	0.030	0.069
$\sigma_{\text{rms}}\Delta$	0.007	0.007	0.008	0.008	0.006

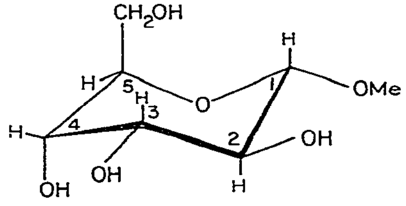
[a]Atom used to calculate the least-squares plane. [b]The equation of the plane is of the form $lx+my+nz=d$, where l, m, n are the direction cosines of the normal to the plane; d is the distance of the plane from the origin in Å; and x, y, z are the coordinates (in Å).

Plane I: $-0.176x+0.946y-0.272z = 2.380$
Plane II: $0.165x+0.806y+0.569z = 5.285$
Plane III: $0.043x-0.986y-0.164z = -3.646$
Plane IV: $0.238x+0.847y+0.476z = 4.065$
Plane V: $0.424x+0.717y+0.554z = 3.875$

The *C1* and *1C* chair conformations for the methyl α-D-altropyranoside are shown in the accompanying formulas. It is seen that 1,3-diaxial interactions may tend to destabilize the *C1* conformation, whereas the interaction of the axial CH_2OH at C-5 with H-1 and H-3 will tend to destabilize the *1C* conformation. It appears then that methyl α-altropyranoside might exist as an equilibrium mixture containing both of these ring forms (and/or possibly some of the skew-boat form). However, the pyranoid ring turns out to be approximately a skew-boat form, probably because of alleviation of the 1,3-interaction. The latter interaction is also expected to favor the skew-boat form for the pyranoid ring in solution. In fact, the n.m.r. data on methyl α-D-altropyranoside gives a $J_{1,2}$ value of 4.5 Hz, intermediate between that expected for an axial-axial (J_{aa}) and an equatorial–equatorial (J_{ee}) orientation of H-1 and H-2, thus suggesting that the compound occurs predominantly in the skew-boat conformation in solution. Also, the value of $J_{1,2}$ agrees reasonably well with the observed torsional angle H-1–C-1–C-2–H-2 (= −158°).



C1



1C

The other torsional angles involving the ring-hydrogen atoms are:

H-2–C-2–C-3–H-3	−159°
H-3–C-3–C-4–H-4	−11°
H-4–C-4–C-5–H-5	−169°

The hydrogen atoms at C-3 and C-4 are in a nearly *cis*-planar arrangement whereas the remaining angles indicate the *anti* arrangement. The *cis* disposition for H-3 and H-4 coupled with the *cis* disposition of the dioxolane oxygen atoms O-3 and O-4 probably account for the increased length of the C-3–C-4 bond (1.549 Å) in comparison with the other C–C bonds.

The substituents are oriented either close to equatorial (Cl-2 and C-6) or pseudo-equatorial (O-1, O-3, and O-4). The torsional angles involving the substituents are given in Table V (see also Fig. 1).

TABLE V

TORSIONAL ANGLES INVOLVING THE RING SUBSTITUENTS

Angle	*Degrees*
Cl-2–C-2–C-3–C-4	176.9
Cl-2–C-2–C-1–O-5	−155.4
O-1–C-1–C-2–C-3	−154.3
O-1–C-1–O-5–C-5	85.5
C-6–C-5–O-5–C-1	−167.5
C-6–C-5–C-4–C-3	−162.0
O-4–C-4–C-5–O-5	−160.5
O-4–C-4–C-3–C-2	104.3
O-3–C-3–C-4–C-5	−132.0
O-3–C-3–C-2–C-1	170.6
Cl-2–C-2–C-3–O-3	−67.0
Cl-2–C-2–C-1–O-1	82.0
C-6–C-5–C-4–O-4	85.0
O-3–C-3–C-4–O-4	−15.0

Dioxolane ring. — The isopropylidene group is commonly used to make derivatives in carbohydrate chemistry, but the molecular geometry and conformation of the dioxolane ring has not been hitherto investigated in detail. In a recent paper[11] from this laboratory, the conformations of dioxolane rings found in some X-ray structures were presented. It was found that this ring system adopts both envelope[12] and twist[13] conformations similar to the furanose rings of nucleic acids[14,15]. In the present structure the dioxolane ring was found to adopt the twist conformation (strictly speaking, between the twist and envelope conformations) as seen by the torsional angles (Table III). The O-4 atom exhibits the largest displacement from the best four-atom least-squares plane through the dioxolane ring. With respect to the plane O-3–C-3–C-4, O-4 and C-8 are displaced on opposite sides.

The C–O bond distances in the dioxolane ring range from 1.406 to 1.448 Å, the average (1.424 Å) being in good agreement with the normal value. The variation in the bond distances of the ring are to some extent interrelated with the intracyclic valence angles and torsional angles about the ring bonds. A similar correlation had been found in furanoside rings[14]. The apparent shortening in the dioxolane C–C bond-distances is attributable to thermal motion of the terminal methyl groups.

Both of the C–Cl bond-distances are within the range of values normally observed for such bonds. There are sixteen C–H bonds in the structure and they vary in length from 0.78 to 1.17 Å, with an average of 0.96 Å, close to the value usually found by X-ray structure determinations.

Disposition of the side groups. — The orientation of C-7 about the O-1–C-1 bond is *gauche–trans*, and the torsional angles are: C-7–O-1–C-1–O-5 = 63.3°, and C-7–O-1–C-1–C-2 = −175.3°. This arrangement is similar to that found from the crystal-structure analysis of methyl α-D-mannopyranoside[16] methyl α-D-glucopyranoside[17], 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside methiodide[18],

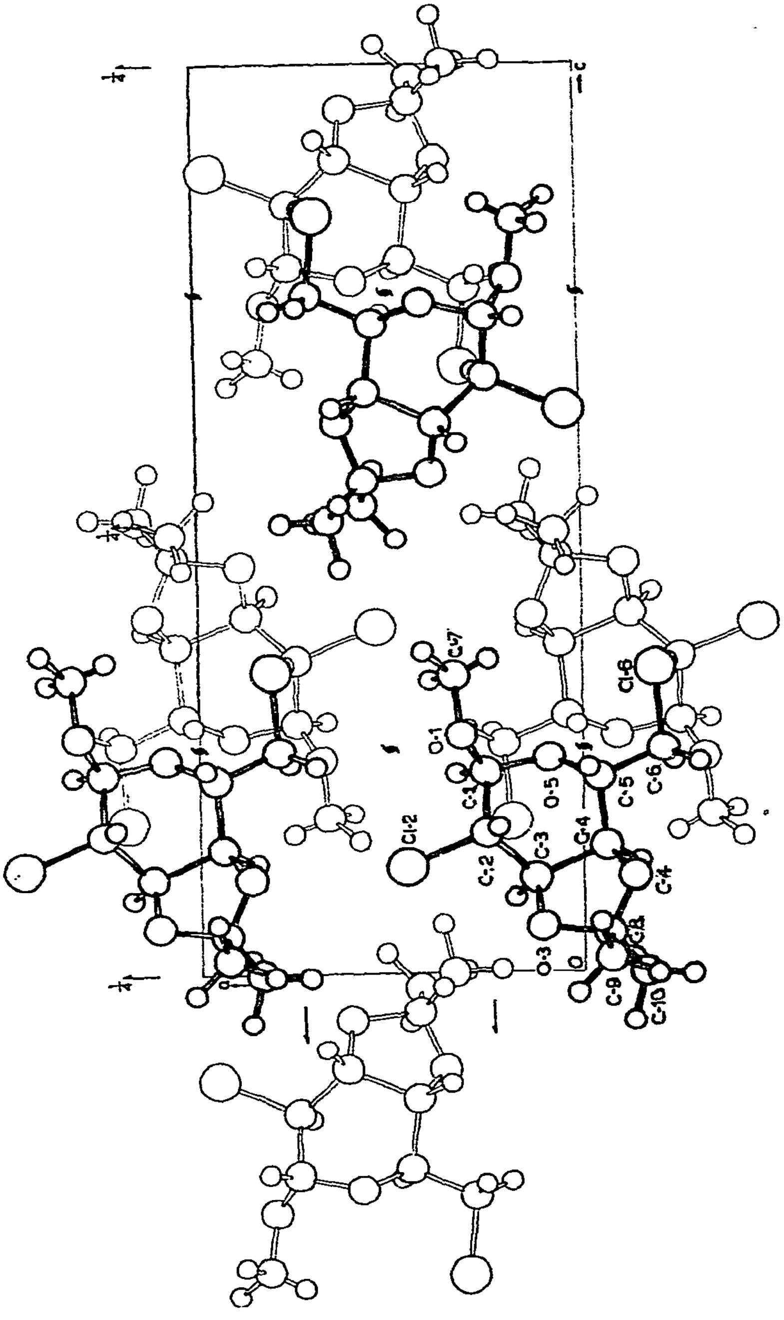


Fig. 3. Projection down the *b* axis showing the molecular packing.

methyl 2-chloro-2-deoxy-α-D-galactopyranoside[19], methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside[20], and methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside[21]. Likewise, the disposition of Cl-6 about the C-6–C-5 bond is *gauche–trans* with reference to the ring bonds C-5–O-5 and C-5–C-4; the torsional angles are Cl-6–C-6–C-5–O-5 = 65.0°, and Cl-6–C-6–C-5–C-4 = 178.5°, respectively. The chloromethyl groups exhibit the alternative staggered conformations in methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside[20] (*trans–gauche*) and in methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside[21] (*gauche–gauche*). Thus, the methoxyl and the chloromethyl groups are disposed within the ranges of orientation observed for the carbohydrates (see also ref. 22).

Molecular packing. — The molecular packing as viewed down the *b* axis is shown in Fig. 3. There is no hydrogen bonding in the structure. The molecules related by two-fold screw axes $(0, 0, \frac{1}{4}$ and $\frac{1}{2}, 0, \frac{3}{4})$ are closely packed, with the pyranoid rings so displaced that the axial hydrogen atoms at C-1 and C-5 come closest to the adjacent rings and the chloromethyl group lies over the adjacent pyranoid ring. The shortest Van der Waals contact (3.321 Å) is between Cl-2 and O-4 of an adjacent dioxolane ring. All other intermolecular contacts involving nonhydrogen atoms are greater than 3.4 Å. In general, the molecules are rather loosely packed in the crystal lattice, and thus intermolecular interactions would be expected to be of little importance in influencing the conformation of **1**. It is interesting, as already pointed out, that the conformation observed in the solid state is probably similar to the principal conformation found in solution. It is thus reasonable to state that the intramolecular interactions play the major role in determining the conformation of this compound.

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REFERENCES

1 S. Hanessian and N. Plessas, *J. Org. Chem.*, 34 (1969) 2163.
2 W. R. Busing, K. O. Martin, and H. A. Levy, ORFLS, *A Fortran Crystallographic Least-Squares Program*, ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tennessee.
3 E. W. Hughes, *J. Amer. Chem. Soc.*, 63 (1941) 1737.
4 D. T. Cromer and J. T. Warber, *Acta Crystallogr.*, 18 (1965) 104.
5 R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 42 (1965) 3175.
6 G. A. Jeffrey and R. D. Rosenstein, *Advan, Carbohyd. Chem.*, 19 (1964) 7.
7 H. M. Berman, S. S. C. Chu, and G. A. Jeffrey, *Science*, 157 (1967) 1576.
8 D. C. Fries, S. T. Rao, and M. Sundaralingam, *Acta Crystallogr.*, B27 (1971) 994.
9 M. Sundaralingam, *Abstr. Amer. Crystallogr. Association Meet.*, Suffern, New York, February, 1965.
10 J. Hendrickson, *J. Amer. Chem. Soc.*, 89 (1967) 7047.

11 J. Jackobs, M. Reno, and M. Sundaralingam, *Carbohyd. Res.*, 28 (1973) 75.
12 J. Jackobs and M. Sundaralingam, *Chem. Commun.*, (1970) 175.
13 J. P. Beale, N. C. Stephenson, and J. D. Stephens, *Chem. Commun.*, 484 (1971).
14 M. Sundaralingam, *J. Amer. Chem. Soc.*, 87 (1965) 599.
15 C. Altona and M. Sundaralingam, *J. Amer. Chem. Soc.*, 94 (1972) 8205.
16 B. M. Gatehouse and B. J. Poppleton, *Acta Crystallogr.*, B26 (1970) 1761.
17 H. M. Berman and S. H. Kim, *Acta Crystallogr.*, B24 (1970) 897.
18 R. E. Cook and M. D. Glick, *Acta Crystallogr.*, B26 (1970) 1745.
19 R. Hage and J. Trotter, *J. Chem. Soc. (A)*, (1969) 2170.
20 R. Hage and J. Trotter, *J. Chem. Soc. (A)*, (1969) 2165.
21 R. Hage and J. Trotter, *J. Chem. Soc. (A)*, (1968) 267.
22 M. Sundaralingam, *Biopolymers*, 6 (1968) 189.