Note

The conformation of methyl 4,6-0-(S)-benzylidene-2-chloro-2-deoxy- α -D-idopyranoside in the crystalline state and in chloroform solution

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The crystal structure of methyl 4,6-O-(S)-benzylidene-2-chloro-2-deoxy- α -Didopyranoside (2) was determined from Weissenberg photographs. It crystallises in space group P2₁ with a = 11.83, b = 12.70, c = 4.62 Å, and $\beta = 91.8^{\circ}$. Refinement led to an R-value of 0.081. The pyranoside ring is in a ${}^{O}S_{2}$ skew conformation (2c), possibly stabilised by hydrogen bonding between the pyranoid-ring oxygen and HO-3 of the neighbouring molecule. ¹H-N.m.r. spectroscopy shows that the pyranoside ring of 2 in chloroform solution exists in the ${}^{4}C_{1}$ conformation (2a), stabilised by hydrogen bonding of HO-3 to the glycosidic oxygen.

INTRODUCTION

Methyl 2-chloro-2-deoxy- α -D-idopyranoside¹ (1) reacts with benzaldehyde and zinc chloride to give a 4,6-O-benzylidene derivative 2. Since 2 contains a *cis*-fused ring system, analogous to *cis*-decalin²⁻⁴, two chair-chair conformations, 2a and 2b, are possible, in which the phenyl group is in the more-stable equatorial orientation to be expected from benzylidenation performed under equilibrating conditions. Mills² has designated these conformations as "O-inside" and "H-inside", respectively, and has argued that an "O-inside" conformer would, in general, be preferred. The configuration of the benzylidene group is S in 2a and R in 2b.

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In 1954, it was expected¹ that the benzylidene group in 2 might have the R configuration (as in 2b), because of the belief⁴ that methyl α -D-idopyranoside (3) had the ${}^{1}C_{\pm}$ conformation. However, it was established that 2 was the S diastereoisomer (as in 2a), as follows. When treated with base, 2 affords¹ the known⁵ methyl 2,3-anhydro-4,6-O-benzylidene- α -D-gulopyranoside (4), which is derived from the galactoside 5 by a sequence unlikely to affect the configuration of the benzylidene group. Foster and his colleagues established⁶, by ¹H-n.m.r. spectroscopy, that 5 has the "O-inside" conformation 5a, so that the benzylidene carbon atom is therefore S in configuration. It follows that 2 must also be the S diastereoisomer. Since the chair-chair conformation 2a, in which the benzylidene carbon has the S configuration, contains some unfavourable, non-bonded interactions, it was of interest to study 2 by X-ray crystallography and by ¹H-n.m.r. spectroscopy to study the benzylidene derivatives (6a and 6b) of methyl α -D-idopyranoside (3), and Brimacombe and his colleagues

have published¹⁰ X-ray structures of the unstable 4,6-O-benzylidene derivatives of methyl 2,3-di-O-methyl- α -D-gluco- and - β -D-galacto-pyranoside which are formed under conditions of kinetic control.

EXPERIMENTAL

Methyl 4,6-O-(S)-*benzylidene-2-chloro-2-deoxy*- α -D-*idopyranoside*¹ (2). — N.m.r. data at 100 MHz (in chloroform-d): δ 3.41 (s, 3 H, OMe), 4.00 (dd, 1 H, $J_{5,6}$ 2.1, $J_{6,6}$, 12.6 Hz, H-6), 4.29 (dd, 1 H, $J_{5,6}$, 1.6, $J_{6,6}$, 12.6 Hz, H-6'), 4.98 (s, 1 H, $J_{1,2} < 1$ Hz, H-1). and 5.44 (s, 1 H, CHPh).

TABLE I

ATOMIC CO-ORDINATLS

Cl-I		-0.0023(0)	-0.0650(06)
0-1	-0 1798(5)	-0.2398(5)	-0.3429(13)
0-2	0.0258(6)	0.0755(5)	-0.2460(15)
0-3	-0.0033(5)	-0.2443(5)	-0.1300(13)
0-4	0.1999(4)	-0.0978(5)	-0.0902(13)
0-5	0.2520(5)	-0.2682(5)	-0.1933(13)
C-1	-0.1095(7)	-0.1924(7)	-0.1340(19)
C-2	-0.0981(7)	-0.0775(7)	0.2327(19)
C-3	0.0152(7)	-0.0306(6)	-0.1436(19)
C-4	0.1086(7)	-0.0963(7)	-0.2914(20)
C-5	0.0709(7)	-0.2065(7)	-0.3663(18)
C-6	0.1682(7)	-0.2821(9)	0.4071(20)
C-7	0.2877(7)	-0.1633(8)	-0.1884(21)
C-8	0.3848(7)	-0.1546(8)	0.0113(18)
C-9	0.4252(8)	0.0554(9)	0.0832(23)
C-10	0.5168(9)	-0.0423(11)	0.2625(24)
C-11	0.5623(9)	-0.1317(11)	0.3900(25)
C-12	0.5238(9)	-0.2318(11)	0.3199(25)
C-13	0.4332(8)	-0.2439(10)	0.1410(22)
C-14	-0.2259(9)		-0.2509(28)
H-1 ,	0.1232	0.0669	-0.4289
H-2	-0.1605	-0.1935	0.0475
H-3	0.0436	-0.0439	0.0596
H-4	0.1453	0.0567	-0.4591
H-5	0.0340	0.2001	-0.5577
H-6	0.2006	-0.2507	-0.5761
H-7	0.1349	-0.3543	-0.3823
H-8	0.3211	0.1448	-0.3588
H-9	0.3805	0.0106	-0.0102
H-10	0.5522	0.0329	0.3207
H-11	0.6567	-0.1230	0.5208
H-12	0.5605	-0.3106	0.4109
H-13	0.3907	-0.3208	0.0935
H-14	-0.3000	0.3400	-0.1300
H-15	-0.2600	0.3600	-0.4000
H-16	-0.1750	~-0.4000	-0.1300
H-17	0.0200	0.1400	-0.1200



Fig. 1. Bond lengths and angles. The estimated standard deviations are 0.015Å and 1°, respectively.

(a) Crystal data. $C_{14}H_{17}ClO_5$, M = 300.8, monoclinic, needles along |c|, 0.1 × 0.1 × 1.0 mm, grown from mixtures of acetone and light petroleum (b.p. 60-80°). Space group P2₁, $a = 11.83 \pm 0.06$, $b = 12.70 \pm 0.05$, $c = 4.62 \pm 0.01$ Å, $\beta = 91.8^{\circ}$: U = 693 Å³, $D_m = 1.417 \pm 0.003$ g.cm⁻³ (by flotation), Z = 2, $D_c = 1.441$ g.cm⁻³; F(000) = 316, $\mu(CuK\alpha) = 26.3$ cm⁻¹.

(b) Data collection. (hk0) To (hk4) equi-inclination, Weissenberg photographs with four-film packs were used. Intensities were estimated visually, and the layers were correlated by double-slit photographs¹¹. Only 1200 out of 1750 reflections were measurable. Absorption was not corrected for.

(c) Determination of the structure. The approximate positions of the chlorine atoms and of the benzene ring were deduced from Patterson sections. These allowed the calculation of enough phases to yield a reasonable Fourier kh0-projection. Least-squares refinement gave a residual of 12.7%.

This projection down the short c-axis did not, however, fully define the molecular shape. The chlorine atom did not predominate sufficiently to calculate phases for the three-dimensional structure-factors, and the Patterson map was insufficiently resolved to give information on z parameters. A three-dimensional Patterson using data sharpened by the application of a function¹² $M(s) = 1/f_c^2 \cosh(as) \exp(-\pi^2 s^2/p)$, with a = 4 and p = 3, led to a three-dimensional trial structure which, on leastsquares refinement, attained a residual for all observed reflections of 8.45%. Hydrogen atoms were included in their calculated positions with isotropic temperature factors, and were not refined.

A Table showing the agreement between observed and calculated structure factors is available from the authors. The final parameters, with their standard deviations (in brackets), are listed in Table I. Bond lengths and bond angles are shown in Fig. 1. Their estimated, standard deviations are ~ 0.015 Å and 1°, respectively.

DISCUSSION

Most previous structure determinations of sugars show the pyranoid ring in the chair conformation. However, the idopyranoside described in this paper has an ideal skew conformation, ${}^{O}S_2$ (2c), halfway between $B_{5,2}$ and $B^{3,0}$. This conformation allows all the non-H substituents to lie in equatorial positions, generally regarded as the most stable. In addition, the dioxane ring has a chair conformation with the phenyl group equatorial. Fig. 2 shows the structure projected down the c axis. Starting with the C-1-C-2 bond, the six endocyclic torsion-angles are -32, +61, -24, -36, +71, and -34° : the four exocyclic torsion-angles of the non-H substituents of the pyranoid ring, all of which lie within 0.6 Å of the mean plane through the sugar part of the molecule, are +91, -63, +95, and -42° for the successive pairs from O-1, C-1, O-2, O-4, and C-6.

The shortest, non-bonded, intramolecular distances involving C or O atoms are separations of 2.28 Å between O-1 and O-3 and between C-6 and C-7. Most other next-nearest neighbours are 2.3-2.5 Å apart. The only short intermolecular distance (2.88 Å) is that between the pyranoid-ring oxygen and HO-3, which indicates hydrogen bonds roughly along the *b* axis of the crystal, and this may, in fact, stabilise the ${}^{O}S_{2}$ conformation in the solid.

By contrast, the ¹H-n.m.r. spectrum of 2 in solution in CDCl₃ shows that 2 exists as the chair-chair conformation 2a and not in the conformation 2c. Thus, the coupling constant $J_{1,2}$ is very small, showing that H-1 and H-2 have a di-equatorial relationship. The other discernible feature, that $J_{5,6}$ and $J_{5,6'}$ are both small, confirms that 2 has an "O-inside" conformation in which H-5 is symmetrically located with



Fig. 2. Projection of the structure down the c axis (a horizontal, b vertical). Hydrogen bonds are drawn as thin lines.

respect to H-6 and H-6'. These results agree with studies^{7–9} of methyl 4,6-O-benzylidene- α -D-idopyranoside (6) and some derivatives. The configuration of the benzylidene carbon atom in 6 is known to be S, both by its method of preparation⁵ from 4, of known⁶ S-chirality, and by correlation¹³ with 4 through periodate oxidation. The pyranoid ring of 6 in solution in CDCl₃ has a chair conformation (6a), but a skewboat conformation, probably 6c (${}^{O}S_{2}$), in aqueous dimethyl sulphoxide^{8,9}. It is believed^{8,9,14} that intramolecular hydrogen-bonding of HO-3 with MeO-1 and of HO-2 with O-4 is responsible for the stability of the chair from 6a, whereas hydration of the hydroxyl groups in aqueous dimethyl sulphoxide leads to the stability of the skew-boat, as in 6c, containing equatorial hydroxyl groups. It is likely that intramolecular hydrogen-bonding between HO-3 and MeO-1 is responsible for the stability of 2a in chloroform solution.

Originally¹, it had been expected that some of the R diastereoisomer (in conformation 2b) would be produced when the chlorodeoxyidoside 1 reacted with benzaldehyde, but only the S isomer was detected. Similarly, methyl α -D-idopyranoside (3) yields^{8.15} only the known (S)-benzylidene acetal 6a and 6c (or its enantiomer in the L series¹⁶).

Recently, Angyal and Kondo⁸ described the benzylidenation of methyl α -Didopyranoside 2,3-carbonate (7). with the intention of preparing the R isomer of 8 and subsequently of 6. Even though the *trans*-carbonate ring precludes the ${}^{4}C_{1}$ conformation of the pyranoid ring, the S isomer of 8 was still the major product (88%). The R isomer, isolated in 10% yield, was converted by alkaline hydrolysis into the (R)-diol, whose conformation in CDCl₃ was shown by ¹H-n.m.r. spectroscopy to be ${}^{4}C_{1}$ (6d), having an axial phenyl group, rather than 6b. In aqueous dimethyl sulphoxide, however, the conformation was mainly ${}^{1}C_{4}$ (6b); the effect of hydrogen bonding in chloroform solution is again apparent.

Mills' prediction² that "O-inside" structures are more stable has now been proved in many cases^{2.3.10}. Mills considered that the difference in interactions of oxygen lone-pairs and of axial hydrogens was the major influence, but Angyal¹⁷ has pointed out that the main instability of the "H-inside" conformation lies in the *sym*axial interactions of methylene or methine groups, as in the *cis*-decalins. In the thermodynamically unstable *R*-isomer of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl- β -Dgalactopyranoside⁶, the "O-inside" conformation is preferred in the crystal¹⁰ and, as in the idose compound **6d**, the phenyl group is axial on a chair ring.

The confusion regarding the possibility of isomerism in the 4,6-O-benzylidene derivative (5) of methyl α -D-galactopyranoside was finally resolved by Bell and Greville¹⁸, who concluded that acid-catalysed benzylidenation afforded only one isomer, later confirmed⁶ by ¹H-n.m.r. spectroscopy.

Similarly, there was some indication¹⁹ from periodate oxidation that methyl α -D-gulopyranoside might form a 4,6-O-benzylidene derivative of opposite (*i.e.*, R) stereochemistry. Later work¹³, also using periodate oxidation, did not confirm this result and it would now be surprising, in the light of more-recent work⁸, if gulopyranosides differed from the *galacto* and *ido* series.

NOTE

We have not made any further attempts to synthesise the R isomer of the chlorodeoxyidoside 2.

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