

Cyclitols. Part XXXIV.¹ X-Ray Crystal and Molecular Structure of 1,2:5,6-Di-*O*-isopropylidene-3,4-di-*O*-tosyl-*L*-chiro-inositol, and its Conformation in Solution by Nuclear Magnetic Resonance

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The crystal structure of the title compound was determined from X-ray diffractometer data by direct methods and refined by least-squares techniques to R 0.047 for 1317 observed reflections. Crystals are tetragonal, space group $P4_12_12$, $a = 9.304 \pm 0.005$, $c = 32.008 \pm 0.017$ Å, $Z = 4$. The cyclohexane ring was found to be in a flattened skew conformation, with four substituents in axial orientation. By contrast, n.m.r. spectroscopy indicates that in solution the title compound adopts predominantly a distorted chair conformation. The conformations of six-membered rings fused to five-membered rings are discussed.

THE stable conformation of six-membered saturated rings is the chair form. However, when a five-membered ring is fused to such a ring, it cannot retain its undistorted chair form; it must be either distorted or changed into another conformation. Particularly important examples of such arrangement are the cyclic acetals formed from *cis*-1,2-dihydroxy-derivatives of cyclohexane; in this case the five-membered ring is a 1,3-dioxolan. At a time when accurate data on conformations were not yet available it was believed that five-membered rings were flat, and that therefore fusion of a five-membered to a six-membered ring would require a torsion angle of 0° at the bridgehead.² Consequently the six-membered ring was believed to be forced into a boat or half-chair conformation.

When n.m.r. data became available it was found that the torsion angle at the bridgehead of such compounds was much larger than 0° . Coupling constants of *ca.* 5 Hz were observed³⁻⁸ between the two hydrogen atoms located at the bridgehead and these were interpreted by the use of the Karplus equation⁹ as indicating torsion angles of $35-45^\circ$. The 1,3-dioxolan ring is highly flexible and its shape depends on the nature and location of its substituents.¹⁰ When the dioxolan ring is not fused to another ring, vicinal *cis*-coupling constants between H-4 and H-5 range from 5.4 to 7.5 Hz, corresponding to torsion angles of $30-45^\circ$. Such an angle can be accommodated between two *cis* oxygen atoms on adjacent carbon atoms of a six-membered ring in a chair form, with some distortion.

Analysis of n.m.r. spectra proved that the six-membered ring is in a distorted, somewhat flattened, chair form in the following compounds: bis(ethylsulphonyl)(4-*O*-acetyl-2,3-*O*-isopropylidene- α -D-lyxo-

pyranosyl)methane,¹¹ alkyl 1,2-orthoesters of α -D-glucopyranose,³ several 1,2-*O*-alkylidene-3,4,6-tri-*O*-acetyl- α -D-glucopyranoses,^{4,5} methyl 2,3-*O*-isopropylidene- α -L-rhamnopyranoside,⁶ and 1,2:4,5-di-*O*-isopropylidene- β -D-fructopyranose. Initially the n.m.r. spectra of 1,2-*O*-alkylidene- α -D-glucopyranose derivatives were interpreted⁸ as being in accord with a skew conformation for these compounds. However, an X-ray crystallographic analysis¹² of 1,2-*O*-(2-amino-1-methylethylidene)- α -D-glucopyranose hydriodide showed the pyranose ring to be in a distorted, flattened chair form, and it was suggested that the n.m.r. data are not incompatible with such a conformation.

The torsion angle at the bridgehead was shown by the X-ray analysis¹² to be only 12° , much less than indicated by the n.m.r. spectra. The conformation of the pyranose ring in the crystal is therefore much closer to the half-chair than to the chair form.

When there are two five-membered rings *cis*-fused to a six-membered ring, the conformation is different: the distortions required by the two attached rings appear to be sufficient to change the chair into a skew form. It was suggested,¹³ from a study of the intramolecular hydrogen bonds in solutions of di-*O*-isopropylidene-inositols, that these compounds are predominantly in skew forms. Whereas the chair form provides only one torsional angle (54.4°), the ideal skew form consists¹⁴ of carbon atoms with a sequence of torsion angles as follows: -30.1 , -30.1 , 62.8 , -30.1 , -30.1 , and 62.8° . At the smaller angles two fused five-membered rings can be accommodated without distortion. It was predicted¹⁵ that 1,2:3,4-diacetals of pyranoses would also be found in skew conformations; subsequently

¹ Part XXXIII, S. J. Angyal and R. J. Hickman, *Carbohydrate Res.*, 1971, **20**, 97.

² H. G. Derx, *Rec. Trav. chim.*, 1922, **41**, 318; W. Hüchel and H. Friedrich, *Annalen*, 1926, **451**, 132.

³ R. U. Lemieux and A. R. Morgan, *Canad. J. Chem.*, 1965, **43**, 2199.

⁴ R. G. Rees, A. R. Tatchell, and R. D. Wells, *J. Chem. Soc. (C)*, 1967, 1768.

⁵ R. U. Lemieux and D. H. Detert, *Canad. J. Chem.*, 1968, **46**, 1039.

⁶ S. J. Angyal, V. A. Pickles, and R. Ahluwalia, *Carbohydrate Res.*, 1967, **3**, 300.

⁷ T. Maeda, K. Tori, S. Satoh, and K. Tokoyama, *Bull. Chem. Soc. Japan*, 1969, **42**, 2635.

⁸ B. Coxon and L. D. Hall, *Tetrahedron*, 1964, **20**, 1685.

⁹ M. Karplus, *J. Chem. Phys.*, 1959, **11**, 30.

¹⁰ W. E. Willy, G. Binsch, and E. L. Eliel, *J. Amer. Chem. Soc.*, 1970, **92**, 5394.

¹¹ L. D. Hall, L. Hough, K. A. McLauchlan, and K. G. R. Pachler, *Chem. and Ind.*, 1962, 1465.

¹² J. Trotter and J. K. Fawcett, *Acta Cryst.*, 1966, **21**, 366.

¹³ S. J. Angyal and R. M. Hoskinson, *J. Chem. Soc.*, 1962, 2991.

¹⁴ J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1967, **89**, 7036.

¹⁵ E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965, p. 361.

n.m.r. measurements on 1,2:3,4-di-*O*-isopropylidene- β -L-arabinopyranose,¹⁶ 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose,¹⁶ 2,3:4,5-di-*O*-isopropylidene- β -D-fructopyranose,*¹⁷ and 1,2:5,6-di-*O*-isopropylidene-3,4-dithio-L-*neo*-inositol¹⁸ were interpreted in terms of skew conformations.

Cone and Hough have noted¹⁶ that in these diacetals the coupling constants between bridgehead hydrogen atoms are larger than the usual values for fused 1,3-dioxolan rings. For example, $J_{3,4}$ in the arabinose and galactose derivatives is *ca.* 8 Hz, indicating that the bridgehead hydrogen atoms must have smaller torsion angles than in other fused 1,3-dioxolan rings previously studied by n.m.r. spectroscopy.

Since the coupling constants give only approximate values for the torsion angles we wished to obtain accurate data on a diacetal which is likely to be in a skew form.

1,2:5,6-Di-*O*-isopropylidene-3,4-di-*O*-tosyl-L-*chiro*-inositol¹⁹ was chosen and was submitted to X-ray crystallographic analysis. A fully *O*-substituted derivative was chosen in order to avoid the possibility of the conformation being controlled by hydrogen bonds.

Part (A). X-Ray Crystallographic Analysis

Clear, well-formed dipyramidal prismatic crystals, m.p 146–147 °C, were obtained by slow evaporation of an ethyl alcohol solution. Unit-cell parameters were obtained from diffractometer measurements.

Crystal Data.— $C_{26}H_{32}O_{10}S_2$, $M = 568.377$. Tetragonal, $a = 9.304 \pm 0.005$, $c = 32.008 \pm 0.017$ Å, $U = 2770$ Å³, $D_m = 1.40$ (by flotation), $Z = 4$, $D_c = 1.35$. Space group $P4_12_12$ or $P4_32_12$ from systematic absences, the former chosen arbitrarily. $Cu-K\alpha$ radiation, $\lambda = 1.5418$ Å; $\mu(Cu-K\alpha) = 22.7$ cm⁻¹.

Data were collected for a spherical crystal of radius 0.019 \pm 0.001 cm on a Siemens automatic single-crystal diffractometer by use of the 'five-value'²⁰ method. 1617 Independent reflections were measured, and corrected for absorption, Lorentz factor, and polarization. Of these, 300 were unobserved. Reflections 440, 441, 442, 443 were inadvertently omitted during the collection process, but examination of Weissenberg films showed them to be all of low intensity.

Since $Z = 4$, with eight equivalent general positions, it was obvious that the molecule must possess a two-fold axis of symmetry which in the crystal coincides with the diad axes of the type $[1\bar{1}0]$. This means that 19 non-hydrogen atoms and 16 hydrogen atoms had to be located.

The Fourier synthesis program used in this investigation employed only tests for parity, so the space-group $P4_12_12$ was degraded to $P2_12_12_1$, with an origin shift to $(\frac{1}{2}, 0, \frac{3}{8})$. In effect, this degrades a four-fold axis to a diad

* Glazkov *et al.*¹⁷ recorded the same coupling constants for this compound but concluded, erroneously, that it was in the 1C conformation.

¹⁶ C. Cone and L. Hough, *Carbohydrate Res.*, 1965, **1**, 1.

¹⁷ V. I. Glazkov, E. M. Malakhaev, and B. N. Stepanenko, *Doklady Akad. Nauk S.S.S.R.*, 1968, **182**, 1322.

¹⁸ G. E. McCasland, S. Furuta, A. Furst, L. F. Johnson, and J. N. Shooley, *J. Org. Chem.*, 1963, **28**, 456.

¹⁹ S. J. Angyal and N. K. Matheson, *J. Amer. Chem. Soc.*, 1955, **77**, 4343.

²⁰ W. Hoppe, *Angew Chem.*, 1965, **77**, 484.

axis, so that orthorhombic data had to be used in the Fourier synthesis, *i.e.* hkl data as well as hkl data were included. Similarly, structure factors suitable for an orthorhombic Fourier input were obtained by using eight symmetry positions, corresponding to the new origin: x, y, z ; $\frac{1}{2} - x, y, \frac{1}{2} + z$; $\bar{x}, \frac{1}{2} + y, \frac{1}{2} - z$; $\frac{1}{2} + x, \frac{1}{2} - y, z$; $\frac{3}{2} + y, \frac{1}{2} + x, \frac{1}{2} - z$; $\frac{3}{2} - y, \frac{3}{2} - x, \frac{3}{2} - z$; $\frac{1}{2} - y, \frac{3}{2} + x, \frac{1}{2} + z$; and $\frac{1}{2} + y, \frac{1}{2} - x, \frac{3}{2} + z$.

For the least-squares refinement, tetragonal data were used.

Solution of the Structure.—The structure was solved by direct methods by use of local programs.²¹ For convenience in calculating E -maps, the orthorhombic space group $P2_12_12_1$ was used. However as the structure is truly tetragonal, only two reflections were necessary to specify the origin. The specification of the phase of any reflection h, k, l implied the phase of \bar{h}, \bar{k}, l which was calculated and included in the starting set. Reflections with $E \geq 1.25$ were used, involving 589 reflections, equivalent to 316 independent reflections on the tetragonal set.

$\Sigma 1$ Relationships²² gave probable phases for 10 (orthorhombic) reflections, and symbolic addition²³ suggested an additional 54 phases. A tangent refinement based on these starting phases accepted 586 out of the 589 phases, with $\sigma 20^\circ$. 97 Of these with variance < 0.2 were excluded from the input to the E -map Fourier series. From the resulting E -map, most non-hydrogen atoms were readily identified, and the remainder obtained from a difference-Fourier synthesis.

Refinement.—Refinement was carried out by use of the least-squares program ORFLS,²⁴ using weights inversely proportional to the standard deviation, which was determined from counting statistics. With isotropic thermal parameters, refinement terminated at *ca.* $R 0.13$ with several strong reflections showing marked evidence of extinction. Anisotropic temperature parameters produced only a small improvement ($R 0.105$) due to the non-inclusion of hydrogen atoms. These were located from a difference-Fourier synthesis, based on atomic parameters from a high-angle ($\sin \theta > 0.3$) refinement cycle.

The hydrogen atoms of the aromatic methyl group occupy unequivocal positions. Of three other tosylates studied recently two^{25,26} have shown a bistable configuration in regard to the terminal methyl hydrogens, with each set occupied with equal probability. These findings were confirmed by neutron diffraction analyses. The third tosylate²⁷ showed unequivocal positions (confirmed by neutron diffraction analysis) for the hydrogen atoms as in this present case.

Six reflections badly affected by extinction (marked by S in the structure factor tables) were removed from the refinement which then continued smoothly to $R 0.047$. Atomic positional and thermal parameters together with their estimated standard deviations are shown in Table 1.

²¹ C. T. Grainger, unpublished data.

²² H. Hauptman and J. Karle, *Amer. Chem. Association Monograph No. 3*, 1953.

²³ J. Karle and I. L. Karle, *Acta Cryst.*, 1966, **21**, 849.

²⁴ W. R. Busing, K. O. Martin, and A. A. Levy, *ORNL-TM-305*, 1962.

²⁵ V. J. James and J. F. McConnell, *Tetrahedron*, 1971, **27**, 5475.

²⁶ P. L. Johnson, C. J. Cheer, J. P. Schaeffer, V. J. James, and F. H. Moore, *Tetrahedron*, 1972, **28**, 2893.

²⁷ P. L. Johnson, J. P. Schaeffer, V. J. James, and J. F. McConnell, *Tetrahedron*, 1972, **28**, 2901.

TABLE 1

Atomic (fractional co-ordinates) and anisotropic thermal parameters * ($\times 10^6$) with standard deviations in parentheses

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
S	0.25703(28)	0.68478(24)	0.48717(7)	1757(39)	1357(33)	153(3)	-5(30)	42(9)	133(8)
O(1)	0.25473(65)	0.51532(50)	0.48216(14)	1630(90)	1197(74)	138(6)	-217(77)	-117(22)	109(18)
O(2)	0.23844(74)	0.72069(58)	0.53001(16)	2603(114)	1661(96)	158(7)	118(106)	232(25)	35(22)
O(3)	0.15619(62)	0.73184(70)	0.45663(19)	1684(91)	2078(117)	235(9)	102(90)	-81(26)	350(30)
O(4)	0.28612(62)	0.31560(54)	0.57807(13)	2513(120)	1216(76)	89(5)	-513(83)	-53(20)	32(17)
O(5)	0.23750(68)	0.10222(49)	0.54824(14)	2229(106)	1109(73)	92(5)	-278(83)	-41(23)	28(17)
C(1)	0.42998(84)	0.73579(89)	0.47128(22)	1479(124)	1116(117)	110(8)	-37(111)	22(27)	83(29)
C(2)	0.50710(106)	0.82840(96)	0.49576(27)	1834(162)	1233(124)	140(10)	10(119)	11(36)	-23(34)
C(3)	0.63696(111)	0.87544(100)	0.48116(31)	1870(181)	1405(146)	172(14)	-126(112)	-133(40)	10(37)
C(4)	0.69209(108)	0.83521(112)	0.44333(32)	1698(162)	1623(159)	165(13)	-36(134)	-40(39)	153(38)
C(5)	0.83484(151)	0.88968(176)	0.42882(44)	1577(198)	3671(357)	290(25)	197(204)	66(59)	452(72)
C(6)	0.61277(130)	0.74051(134)	0.41943(29)	2611(204)	2163(196)	132(11)	-134(179)	175(44)	73(46)
C(7)	0.48006(118)	0.69148(108)	0.43301(26)	2508(202)	1937(179)	117(10)	-699(149)	33(37)	-45(35)
C(8)	0.33167(86)	0.42817(79)	0.51316(21)	1630(135)	1161(113)	101(9)	-277(104)	-114(28)	85(26)
C(9)	0.21903(97)	0.35081(82)	0.53962(21)	1642(159)	1116(117)	93(8)	-226(96)	-7(30)	18(24)
C(10)	0.16772(92)	0.20381(92)	0.52245(22)	1494(122)	1389(121)	93(8)	-392(108)	5(28)	11(26)
C(11)	0.25418(117)	0.16870(90)	0.58770(22)	2299(164)	1220(121)	100(8)	-408(131)	-2(37)	68(27)
C(12)	0.11916(136)	0.15913(131)	0.61378(30)	2391(235)	2217(210)	113(11)	-750(177)	88(43)	60(43)
C(13)	0.38466(167)	0.10556(132)	0.60839(45)	3634(288)	1554(187)	163(15)	44(210)	-288(56)	58(44)
H(1)	0.4580(97)	0.8569(85)	0.5240(21)	1852	1219	141	-1	6	-22
H(2)	0.7089(93)	0.9361(86)	0.4951(26)	1855	1387	177	-137	-138	20
H(3)	0.6356(111)	0.7074(107)	0.3957(24)	2547	2081	136	-152	172	80
H(4)	0.4266(98)	0.6157(95)	0.4178(22)	2522	1926	115	-667	33	-47
H(5)	0.3854(82)	0.4962(78)	0.5333(19)	1625	1177	100	-283	-116	90
H(6)	0.1303(88)	0.4235(82)	0.5432(20)	1677	1118	92	-248	-2	20
H(7)	0.0670(88)	0.1881(93)	0.5266(20)	1485	1362	92	-411	6	9
H(8)	0.4025(144)	0.0258(153)	0.5950(28)	2937	1762	179	-212	-233	160
H(9)	0.3715(147)	0.0266(156)	0.6177(36)	2937	1762	179	-212	-233	160
H(10)	0.4165(124)	0.1523(111)	0.6331(29)	2937	1762	179	-212	-233	160
H(11)	0.1296(104)	0.2034(108)	0.6403(25)	2871	2201	117	-778	92	77
H(12)	0.0359(106)	0.1995(111)	0.5974(24)	2871	2201	117	-778	92	77
H(13)	0.0923(103)	0.0495(113)	0.6168(24)	2871	2201	117	-778	92	77
H(14)	0.8248(127)	0.9396(135)	0.4078(35)	1569	3166	282	-174	97	382
H(15)	0.8798(128)	0.8126(134)	0.4135(37)	1569	3166	282	-174	97	382
H(16)	0.9065(106)	0.8704(131)	0.4487(34)	1569	3166	282	-174	97	382

* As coefficients in the expression $T_i = \exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)]$. Hydrogen thermal parameters were not refined.

Observed and calculated structure factors ($10 \times$ absolute) are listed in Supplementary Publication No. SUP 20450 (5 pp., 1 microfiche).^{*} Hydrogen thermal parameters were not refined, but were given the same values as the carbon atom to which they are attached, taken finally from a cycle when R was *ca.* 0.05.

Bond distances and angles between all non-hydrogen atoms are shown in Figure 1. The mean C-H distances were 0.97 Å, with a maximum deviation of 0.18 Å which is $< 2\sigma$.

Figure 2 is a stereographic pair of diagrams (produced by ORTEP²⁸) which show clearly the conformation of the cyclohexane and dioxolan rings. The ellipsoids represent the root-mean-square value of atomic displacement due to thermal motion.

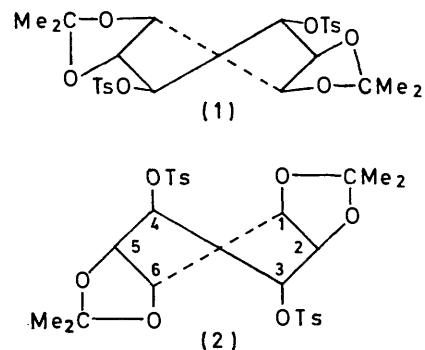
Figure 3 shows the packing arrangement of the molecules in the unit cell.

DISCUSSION OF THE STRUCTURE

The structure of 1,2:5,6-di-*O*-isopropylidene-3,4-di-*O*-tosyl-*L*-*chiro*-inositol shows some unusual features. The cyclohexane ring is, as expected, in a skew form but this skew form is considerably flattened. The sequence of torsion angles is -14.5 , -27.5 , 49.6 , -27.5 , -14.5 , and 36.1° instead of the ideal¹⁴ -30.1 , -30.1 , 62.8 , -30.1 , -30.1 , and 62.8° , showing flattening in that part of the ring which is fused to the dioxolan rings. The flattening results in bond angles within the cyclohexane ring which are all larger than tetrahedral.

It is hard to see why this flattening should occur when the 30.1° angle of the ideal skew form would provide the apparently usual angle for the fusion of the rings. In other words, the angle strain in the molecule is greater than appears necessary.

Moreover, the cyclohexane ring is not in the 3S_1 skew form (1) postulated¹³ for the untosylated parent



compound, 1,2:5,6-di-*O*-isopropylidene-*L*-*chiro*-inositol, in solution. This conformation has no axial substituents, whereas in the 1S_3 conformation (2) found in the crystal

^{*} For details see Notice to Authors No. 7 in *J. Chem. Soc. (A)*, 1970, Issue No. 20 (items less than 10 pp. are sent as full size copies).

²⁸ C. K. Johnson, USAEC Report, ORNL-3794, 1965.

structure four oxygen atoms, O(1), O(3), O(4), and O(6) are in axial positions. The two oxygen atoms carrying

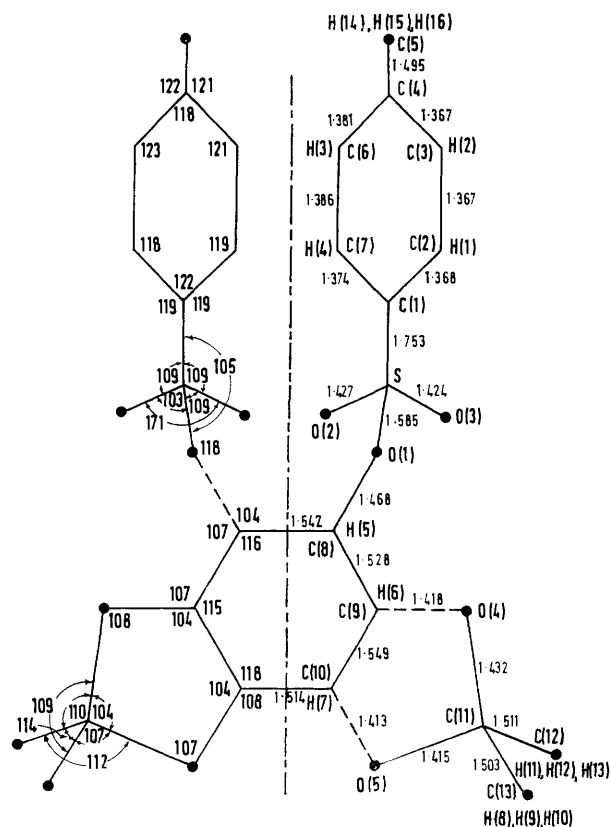


FIGURE 1 Schematic diagram of the molecule showing bond lengths (Å) and bond angles (°). The dashed line represents a diad axis

the tosyl groups, with a torsion angle of 174.6° between them, are very close to true axial positions; the other

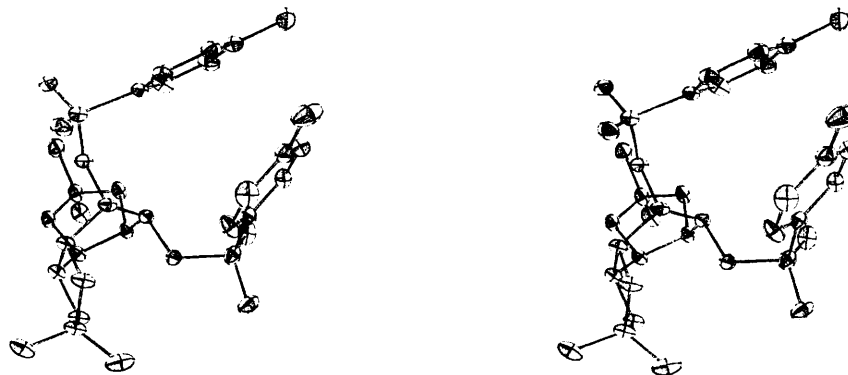


FIGURE 2 Stereographic pair of views (6° apart) of the molecule. The ellipsoids represent relative thermal vibration amplitudes

two, with a torsion angle of 162.1° between them, are slightly displaced outwards from the true axial positions. One would not expect this to be the most stable con-

* N.m.r. spectra were measured with a JNM-4H-100 spectrometer at 100 MHz.

²⁹ E. Pallister, N. C. Stephenson, and J. D. Stevens, *Chem. Comm.*, 1972, 98.

formation of the molecule, since axial substituents in a skew form destabilize a molecule even more than those in a chair form.¹⁴

The dioxolan rings take up twist conformations: the acetal carbon atom is above, and O(1) below, the plane formed by the other three atoms of the ring. The torsion angle at the bridgehead, -12° , is surprisingly small; however, the high coupling constants found in similar compounds^{7,16} suggest that this may be a common occurrence in six-membered rings in the skew conformation. An even lower torsion angle at the bridgehead has recently been found.²⁹

Part (B). Conformation in Solution

Having found an unusual and unexpected conformation in the crystals of 1,2:5,6-di-*O*-isopropylidene-3,4-di-*O*-tosyl-*L*-*chiro*-inositol we thought it of interest to determine the conformation of this compound in solution by the use of n.m.r. spectroscopy.* Unfortunately the six ring protons give signals close to each other, forming, because of the presence of a two-fold axis of symmetry, an AA'BB'CC' pattern, difficult to analyse.

Initially, therefore, two closely similar compounds were investigated: the 3-*O*-acetyl-4-*O*-tosyl¹⁹ and the 3,4-di-*O*-acetyl³⁰ derivatives of 1,2:5,6-di-*O*-isopropylidene-*L*-*chiro*-inositol. In the former, two one-proton pairs of doublets at δ 5.11 and 4.70 p.p.m. were assigned to H-3 and H-4, respectively, on the basis of the well-known deshielding by an acetoxy-group. First-order analysis of this portion of the spectrum gave $J_{2,3}$ 8.2, $J_{3,4}$ 11.1, and $J_{4,5}$ 7.9 Hz.

The diacetyl derivative has a spectrum (Figure 4) approximating to the AA'KK'XX' type. In [²H₆]acetone solution H-3 and H-4 gave rise to an almost symmetrical (with respect to intensities) six-line multiplet at δ 5.02 p.p.m. and H-1 and H-6 gave a six-line multiplet at δ 4.53 p.p.m. (on five-fold expansion the two inner lines appear as shoulders on the strongest peaks). Both these multiplets were analysed as the AA' portion of an AA'XX'

system³¹ (in which $J_{XX'}$ is zero, thereby simplifying the usual ten-line pattern to six lines).

The values obtained by this analysis (Table 2) were checked by use of the LAOCOON-3 iterative n.m.r. spec-

³⁰ S. J. Angyal and C. G. Macdonald, *J. Chem. Soc.*, 1952, 686.

³¹ J. A. Pople, W. G. Schneider, and H. J. Bernstein, *Canad. J. Chem.*, 1957, **35**, 1060.

trum analysis program,³² treating these multiplets as the AA' portion of an AA'BB' system and allowing all the coupling constants to vary, excepting $J_{BB'}$ which was held at zero. The agreement between the two sets of coupling constants obtained was excellent. A spectrum of the diacetate in [²H]chloroform was not so readily analysed because the two central peaks of the multiplet due to H-1 and H-6 were not resolved from the two high intensity

to that of the diacetate except that the multiplets are closer together. Analysis³¹ of this spectrum was carried out in the same manner as for the diacetate. This analysis was then followed by LAOCOON-3 iterative analysis for the H-2, H-3, H-4, and H-5 portion of the spectrum, which gave coupling constants involving these protons which were only insignificantly different from those obtained by the first analysis. The values of $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ (Table 2)

TABLE 2

N.m.r. data * of derivatives of 1,2:5,6-di- <i>O</i> -isopropylidene- <i>L</i> - <i>chiro</i> -inositol												
Derivative	Solvent	$J_{1,2}, J_{5,6}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{1,6}$	$J_{2,4}, J_{3,5}$	$J_{1,5}, J_{2,6}$	H-1, H-6	H-2, H-5	H-3	H-4
3- <i>O</i> -Acetyl-4- <i>O</i> -tosyl	CDCl ₃		8.2	11.1	7.9				4.52	4.27	5.11	4.70
3,4-Di- <i>O</i> -acetyl	(CD ₃) ₂ CO	6.16	8.35	11.5	8.35	2.35	-0.15	-0.6	4.53	4.32	5.02	
	CDCl ₃	5.75	8.35	11.2	8.35	1.5	-0.15	-0.75	4.53	4.30	5.05	
3,4-Di- <i>O</i> -tosyl	CDCl ₃	6.75	5.9	8.8	5.9	1.8	0.4	-0.95	4.45	4.23	4.59	

* δ Values; coupling constants in Hz.

peaks, resulting in an increase in the uncertainty associated with the determination of $J_{1,6}$. The coupling constants determined from this spectrum are included in Table 2,

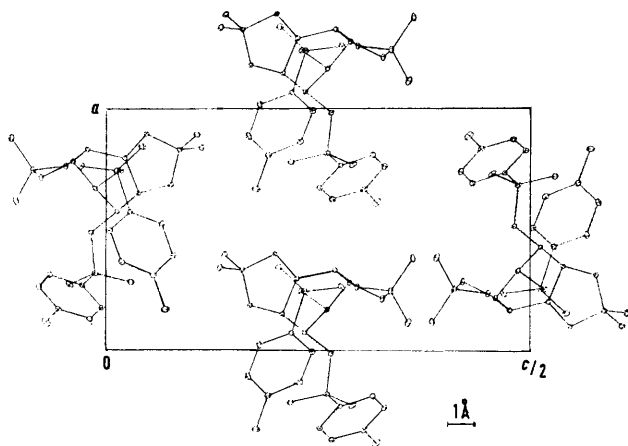


FIGURE 3 Arrangement of the molecules in the unit cell

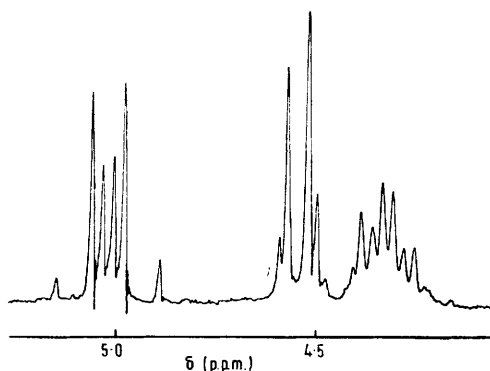


FIGURE 4 Part of the n.m.r. spectrum (100 MHz) of 3,4-di-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-*L*-*chiro*-inositol in [²H₆]-acetone

and it can be seen that the change of solvent has caused small changes in some of these values.

The n.m.r. spectrum of the ditosyl derivative is similar

³² S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, 1964, **41**, 3863.

³³ S. J. Angyal, G. C. Irving, D. Rutherford, and M. E. Tate, *J. Chem. Soc.*, 1965, 6662.

were found to differ considerably from those of the diacetyl and the acetyl tosyl derivatives. The conformation is therefore insensitive to a change of one, but not of both, acetyl groups to tosyl groups. The smaller coupling constants of the ditosyl derivative may have two explanations: significant contribution of another conformation or flattening of the chair form. If the other contributing conformation is the other chair or the ³S₁ skew form, H-1 and H-6 would be axial in some of the molecules and $J_{1,6}$ would become larger. In fact, it is the same as in the diacetate. The smaller values of $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ therefore indicate flattening of the ring, caused, presumably, by interaction of the two bulky tosyl groups.

The spectrum of 3,4-di-*O*-acetyl-1,2:5,6-di-*O*-cyclohexylidene-*L*-*chiro*-inositol (prepared by acetylation of the diacetal³³) was also recorded and was found to be practically indistinguishable in the δ 4–6 p.p.m. region from that of the di-isopropylidene derivative. A variation of the substituents on the dioxolan ring therefore does not change the conformation of the cyclohexane ring.

DISCUSSION

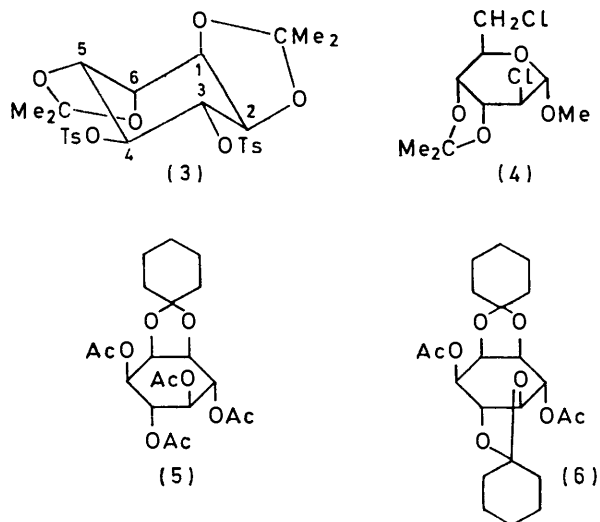
The n.m.r. spectra show that the conformation of 1,2:5,6-di-*O*-isopropylidene-3,4-di-*O*-tosyl-*L*-*chiro*-inositol (and related compounds) in solution is neither the ³S₁ skew form (1) expected from previous results,¹³ nor the ¹S₃ skew form (2) found in the crystalline state, but a distorted chair form (3). The usual values of coupling constants in inositols are 2.75 Hz for coupling between an axial and an equatorial hydrogen atom, and 9.5 Hz for coupling between two axial hydrogen atoms.³⁴ The latter value, which corresponds to a dihedral angle of less than 180°, is in accord with the somewhat flattened nature of the cyclohexane ring in inositols.³⁵ The values (Table 2) of $J_{1,2}$ (5.75–6.75 Hz) and $J_{2,3}$ (5.9–8.35 Hz) indicate to what extent the ring has been partially flattened in the di-isopropylidene derivatives to accommodate the dioxolan rings. The large values (11.1–11.5 Hz) for $J_{3,4}$ of the diacetyl and acetyl tosyl derivatives show puckering in that part of the ring, as a reflex effect of the flattening elsewhere,

³⁴ S. J. Angyal and G. J. H. Melrose, *J. Chem. Soc.*, 1965, 6494.

³⁵ G. A. Jeffrey and H. S. Kim, *Carbohydrate Res.*, 1970, **15**, 310.

which increases the dihedral angle between H-3 and H-4 to about 180° ; in the ditosyl derivative some flattening, rather than puckering, occurs at C-3 and C-4.

After surveying the previously described cases, Angyal³⁶ suggested that fusion of one five-membered



to a six-membered ring left it in the chair conformation but that fusion of two five-membered rings changed it into a skew conformation. The case here reported is the first exception to this generalization. In the previously reported cases the two neighbouring oxygen atoms of the two dioxolane rings are both axial in the skew form; this arrangement may be a particularly stable one. In the present case the chair form has this arrangement and therefore appears to be more stable.

Another exception to the generalization has recently been found: crystal structure analysis of methyl 2,6-dichloro-2,6-dideoxy-3,4-*O*-isopropylidene- α -D-altropyranoside (4) found the six-membered pyranose ring in a skew form,³⁷ although it is fused only to one dioxolane ring. The torsion angle at the bridgehead is very small (14.5°); this seems to be characteristic of a dioxolane ring fused to a six-membered ring in a skew conformation. Both chair forms of α -D-altropyranose have substantial unfavourable steric interactions³⁸ and inversion into a skew form should therefore be com-

paratively easy: in this conformation every substituent is equatorial or pseudo-equatorial.³⁷

The conformations of two other inositol acetals are briefly reported here. In [²H]chloroform solution the n.m.r. spectrum of 1,4,5,6-tetra-*O*-acetyl-2,3-*O*-cyclohexylidene-*myo*-inositol³⁹ (5) clearly shows every ring proton and allows first-order analysis. Signals for two protons appear at higher field, well separated from the others; these must be the protons at the bridgehead but it is not obvious which is that of H-2 and which of H-3. Dr. Laurens Anderson (Wisconsin) provided us with a sample of *myo*-inositol partially deuterated on C-2; this was converted into the tetra-acetyl 2,3-*O*-cyclohexylidene derivative and its n.m.r. spectrum showed that the signal at δ 4.52 p.p.m. was now small; it is that of H-2. By matching the splittings, the spectrum was unravelled: δ 5.51 (H-6), 5.28 (H-4), 5.19 (H-1), 5.02 (H-5), 4.52 (H-2), and 4.22 p.p.m. (H-3), all pairs of doublets; $J_{1,2}$ 3.6, $J_{2,3}$ 5.4, $J_{3,4}$ 6.5, $J_{4,5}$ 8.9, $J_{5,6}$ 8.1, and $J_{6,1}$ 9.7 Hz. The cyclohexane ring is therefore in a chair form, somewhat flattened at C-2 and C-3.

1,4-Di-*O*-acetyl-2,3:5,6-di-*O*-cyclohexylidene-*myo*-inositol³⁹ (6) also gives a well-resolved n.m.r. spectrum in [²H]chloroform.⁴⁰ Two proton signals at low field must be those of H-1 and H-4, and a triplet with small splittings is recognized as that of H-2, the only hydrogen atom with two *cis* hydrogen neighbours. Matching the splittings gave the interpretation of the spectrum: δ 5.26 (H-4), 5.08 (H-1), 4.60 (t, H-2), 4.14 (H-6), 4.13 (H-3), and 3.47 p.p.m. (H-5), all but H-2 pairs of doublets; $J_{1,2}$ 4.4, $J_{2,3}$ 5.0, $J_{3,4}$ 6.7, $J_{4,5}$ 11.2, $J_{5,6}$ 9.5, $J_{6,1}$ 10.5 Hz. This molecule is also in a flattened chair form. It is to be noted that one of the dioxolane rings is *trans*-fused at C-5/C-6; the skew conformation would therefore not be advantageous.

The work described here should serve as a warning: one should not assume that the conformation found in the crystal lattice is also the predominant, or even a significant, conformation in solution. In the present case, the conformation in the crystal lattice seems to be governed by the arrangement of the benzene rings, rather than by the intrinsic stability of the cyclohexane conformations.

[2/444 Received, 28th February, 1972]

³⁶ S. J. Angyal in W. Pigman and D. Horton, 'Carbohydrates—Chemistry and Biochemistry,' Academic Press, New York, 2nd edn., 1972, vol. 1A, p. 211.

³⁷ G. H.-Y. Lin and M. Sundaralingam, *Carbohydrate Res.*, in the press.

³⁸ S. J. Angyal, *Austral. J. Chem.*, 1968, **21**, 2737.

³⁹ S. J. Angyal, M. E. Tate, and S. D. Gero, *J. Chem. Soc.*, 1961, 4116.

⁴⁰ A. F. Russell, Ph.D. Thesis, The University of New South Wales, 1967.