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Note

Crystal structure of 1L-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol; A comparison of its conformation in solid and solution states

Kana M. Sureshan,* Tomomi Miyasou and Yutaka Watanabe*

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790-8577, Japan

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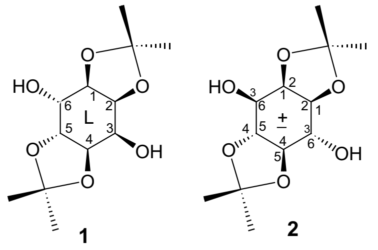
Abstract—The X-ray crystal structure of 1L-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol, is described. The inositol ring deviate slightly from the ideal chair conformation to a flattened chair. A comparison of its conformation in solution with that in solid was made by the use of ^{1}H NMR. This conformational analysis revealed that the title compound adopts similar conformations in solid state and in solution in low polar solvents like benzene and $CHCl_3$ while in high polar solvents such as Me_2SO, the solid state conformation is not retained.

Keywords: Inositol; *allo*-Inositol; Conformation; Cyclitol; Crystal structure

myo-Inositol derivatives have been the subject of intense research in the recent past due to the established biological roles of their phosphorylated derivatives in cellular signal transduction[1] and other cellular processes.[2] Many of these phosphoinositols are known to undergo site selective phosphorylation or dephosphorylation by the action of different and specific enzymes (kinases and phosphatases). Since each of these phosphorylation–dephosphorylation processes have specific biological implications, the design and syntheses of effectors or inhibitors of the enzymes involved in these processes are necessary to unravel the finer details of cellular events. The judicious design and screening of different structurally modified natural substrates of different enzymes has thus become a major focus of inositol chemistry. Although derivatives of the nine isomeric inositols are strong candidates for these studies, the facts that only six isomeric inositols are naturally occurring and the paucity of naturally occurring ones are major impediments to such an investigation. As a consequence, there has been a greater deal of interest to synthesize these inositols from different starting materials. During our efforts to synthesize isomers of inositols we have made 1L-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol, **1** (Scheme 1).[3] We herein report the crystal structure of **1**. Also a qualitative comparison of its conformation in solid and solution states is made based on NMR spectroscopy. Also a comparison of solid state conformation is made with its isomer 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol, **2**, the crystal structure of which is known.[4]



Scheme 1. The outer numbering for **2** is *myo*-inositol numbering and the inner numbering is similar to that in *allo*-diketal **1** for brevity and consistency in comparison.

Crystal structure analysis of **1** revealed that the inositol ring deviated from an ideal chair to a flattened

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* Corresponding authors. Tel./fax: +81-899-279-944; e-mail addresses: sureshankm@yahoo.co.in; wyutaka@dpc.ehime-u.ac.jp

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Table 1. A comparison of ring (CCC) angles of **1** and **2**

Ring angle	**1** (°)	**2**[a] (°)
C-1–C-2–C-3	117.5	115.9
C-2–C-3–C-4	105.4	106.8
C-3–C-4–C-5	111.0	111.0
C-4–C-5–C-6	111.4	110.5
C-5–C-6–C-1	107.9	107.0
C-6–C-1–C-2	118.9	117.9

[a] The ring angle values of **2** were taken from Ref. 4.

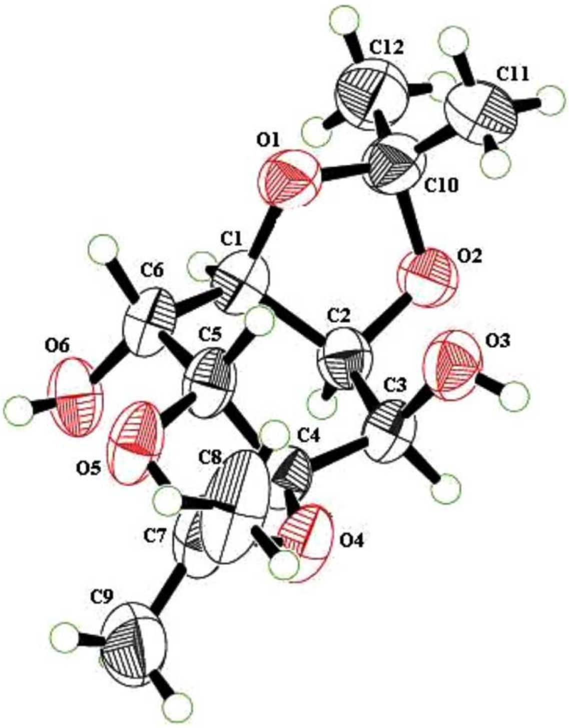


Figure 1. ORTEP diagram of **1**.

chair conformation. The ring C–C bond lengths (1.499–1.555 Å) and C–O bond lengths (1.413–1.430 Å) are in the normal range. The CH bond lengths of the isotropically refined H atoms are in the range 0.92–1.07 Å. The ring angles (105.4–118.9°) deviate from that of a perfect chair. Similarly the CCO angles vary from 101.4° to 115.6°. Bond angles C-1–C-2–C-3 (117.5°), C-2–C-3–C-4 (105.4°) and C-6–C-1–C-2 (118.9°) deviate considerably from the ideal tetrahedral angle. The ring angles in **1** are similar to those in its *myo*-isomer **2**.[4] Various ring angles of **1** and **2** are tabulated in Table 1. A comparison of ring angles of **1** and **2** reveal that they adopt similar conformation in the crystalline state. Figure 1 shows an ORTEP diagram of **1**.

Also torsion angles in the carbocyclic skeleton deviate much from that for a perfect chair and are comparable to that of its *myo*-isomer **2**, which is reported[4] to adopt a flattened chair conformation in its crystals. A comparison of torsion angles (Table 2) of **1** and **2** further substantiates the similarity in their conformations. The torsion angle C-3–C-4–C-5–C-6 expanded to 73.0° while C-6–C-1–C-2–C-3 experienced compression to −32.4°. The respective torsion in *myo*-inositol derivative **2** is 72.6° and −36.9°, respectively. Also the torsion angles between vicinal oxygen atoms of **1** deviate from that of a perfect chair. The torsion between axial-equatorial (O-1–C-1–C-2–O-2) and di-equatorial (O-4–C-4–C-5–O-5) vicinal oxygens are comparable with that of *myo*-isomer **2** (Table 2). These similar conformations of **1** and **2** demonstrate that inversion of free hydroxyl groups at 3- and 6- position of **2** did not affect the conformational preference in crystalline state.

Crystal packing is in such a way that each unit cell contains four molecules of **1** held together by various intermolecular hydrogen bondings. Each C-3–OH (donor) is intermolecularly hydrogen bonded (162.1°, 2.07 Å) with C-6–OH (acceptor) of a neighbouring molecule. Additionally each C-6–OH (donor) is in intramolecular H-bonding (173°, 1.96 Å) with O-5 (acceptor) of a third molecule. Thus each C-3–OH is in intermolecular H-bonding with one neighbouring molecule while each C-6–OH is in intermolecular H-bonding with two neighbouring molecules. There are other short contacts too, which may help in reinforcing the crystal packing. For instance, two of the hydrogens on C-8 of each molecule are in CH···O contact with O-2 of two neighbouring molecules. Thus O-2 of each molecule is in CH···O contact (148.6°, 2.59 Å; 131.6°, 2.67 Å) with one of the Hs of C-8 of two different molecules.

Crystal structures have been used to explain the reactivities in solid[5] and solution[6] states of inositol derivatives. Chung et al. extrapolated the crystal structure conformations of *myo*-inositol derivatives to solutions to compare the rate of acyl migrations[7] between *cis* and *trans* vicinal oxygens in solution. The increased reactivity of C-3–OH of 1,2:4,5-di-*O*-isopropylidene-

Table 2. Selected torsion angles of **1** and **2**

O–C–C–O	**1** (°) *allo*	**2**[a] (°) *myo*	C–C–C–C	**1** (°) *allo*	**2**[a] (°) *myo*
O-1–C-1–C-2–O-2	−34.5(4)	−36.5(1)	C-1–C-2–C-3–C-4	41.9(5)	42.8(2)
O-2–C-2–C-3–O-3	39.0(4)	[b]	C-2–C-3–C-4–C-5	−61.1(4)	−60.1(2)
O-3–C-3–C-4–O-4	−56.0(5)	[b]	C-3–C-4–C-5–C-6	73.0(4)	72.6(2)
O-4–C-4–C-5–O-5	−40.4(4)	−42.5(1)	C-4–C-5–C-6–C-1	−54.7(5)	−58.4(2)
O-5–C-5–C-6–O-6	−52.3(5)	[b]	C-5–C-6–C-1–C-2	36.2(5)	42.3(2)
O-6–C-6–C-1–O-1	159.4(3)	[b]	C-6–C-1–C-2–C-3	−32.4(5)	−36.9(2)

[a] The torsion values of **2** were taken from Ref. 4.

[b] Since O-3 and O-6 are inverted in **2** these values are not compared.

Table 3. Comparison of calculated and observed vicinal coupling constants (in Hz) of **1** in solvents of different polarity

Vicinal protons	$^3J_{HH}$ in C_6D_6	$^3J_{HH}$ in $CDCl_3$	$^3J_{HH}$ in Me_2SO-d_6	HH torsion (ϕ°) in crystal	J_{calcd} from ϕ
H-1–H-2	5.9	6.0	4.4	−28.69	5.4
H-2–H-3	4.4	4.4	3.4	45.35	3.8
H-3–H-4	2.4	2.4	1.5	−57.82	2.4
H-4–H-5	9.8	10.0	9.8	−168.35	9.0
H-5–H-6	3.4	3.2	4.4	−54.52	2.8
H-6–H-1	1.5	1.6	0.5	−75.89	2.0

myo-inositol and 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol towards various electrophiles[8] was also explained by extrapolating their crystal structure conformation to solution.[6] For such a comparison of conformations, solution state conformation has been studied by using ^{1}H NMR spectrum. Chung and Ryu[6] reported the retention of conformation of 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol in solid and solution states. Later Spiers et al. found similar retention of conformation of 1,2;4,5-di-*O*-cyclohexylidene-*myo*-inositol[9] in solid and solution states. We have recently reported[10] the consistency in conformation in solution and solid state of 1D-1,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]2,3:5,6-di-*O*-isopropylidene-*myo*-inositol. It is reasonable to think that the presence of two ketal rings (one *cis* and one *trans*) in these derivatives could be responsible for their conformational freezing. Since **1** also possesses structural similarity with these derivatives (presence of *cis* and *trans* ketals), we anticipated a retention of its solid state (crystal) conformation in solution.

As the ring protons are well resolved (in $CDCl_3$) in the ^{1}H NMR spectrum, it is very easy to get an idea about its conformation based on vicinal coupling constants. The observed coupling constants (in $CDCl_3$) are in agreement with the calculated coupling constants (Table 3) based on torsion angle (ϕ) in the crystal structure by using the Altona's equation.[11] The magnitude of calculated J values for all but H-1–H-6 vicinal hydrogens are slightly smaller than the experimental J values. This small variation of the calculated and observed coupling constants could be due to the limitation of the Karplus equation. As J values depends on a constant, C in addition to the variable $\cos\phi$ according to Karplus type equations, this small difference can be compensated (to more matching values) by adding a constant term 0.2 or 0.3 to the calculated values. It is well known[11,12] that the coupling constant between vicinal protons depends on electronegativity, orientation, etc. of the other substituents on carbon bearing the Hs. It is apparent to think that the origin of the small difference between the observed and calculated coupling constants could be due to these orientation effects. Similar difference between calculated (with other forms of Karplus equation) and observed coupling constants of *myo*-inositol derivatives had been reported previously.[6,9]

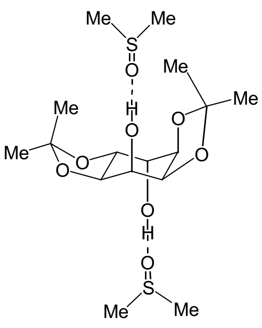
A comparison (Table 3) of the coupling constants in solvents of different polarity (benzene-d_6, $CDCl_3$ and Me_2SO-d_6) revealed that the conformation deviate slightly depending on the solvent polarity. As low polar solvents (C_6D_6 and $CDCl_3$) showed similar coupling constants as calculated ones, it is apparent that the solid state (crystal structure) conformation is retained in low polar solvents. But the variation in the magnitude of coupling constants in Me_2SO from either that in low polar solvents or from the calculated value suggests that the conformation of **1** deviate in high polar solvents. In other words the conformation of **1** in solution changes with solvent polarity.[†] Except for the H-4–H-5 coupling constant, all other H–H coupling constants in Me_2SO-d_6 deviated from that in low polar solvents (benzene and $CDCl_3$). The same coupling constants for H-4–H-5 in all the solvents is as expected, as the rotational mobility around C-4–C-5 bond is restricted due to the *trans* isopropylidene conformational lock. The $^3J_{HH}$ values in Me_2SO suggest that the magnitude of torsion angle for H1–H2, H2–H3, H3–H4 and H6–H1 increased (expansion), while that of H5–H6 decreased (compression) compared to that in the low polar solvents and in crystal. This is interesting since different conformations can often give rise to different regioselectivities in various reactions. This also suggests that care must be taken while extrapolating the crystal structure conformations to solutions to explain or predict the reactivities.

Interestingly **2**, the *myo*-isomer, is reported[6] to adopt similar conformations in both low polar ($CDCl_3$) and high polar solvents (Me_2SO). In **1**, both the hydroxyl groups are in axial disposition where as in **2** they are in equatorial disposition. Thus, it is rational to think that the disposition of the free hydroxyl groups has a major role in deciding the conformation in high polar solvents. Strong hydrogen bond is possible between hydroxyl group and Me_2SO. Thus the solvated (via hydrogen bonding with Me_2 SO) hydroxyl groups become bulky. Sterically unfavourable axial disposition of such a bulky species in **1** could be the reason for the conformational change in Me_2SO.[‡] The nondeviated conformation of **2**

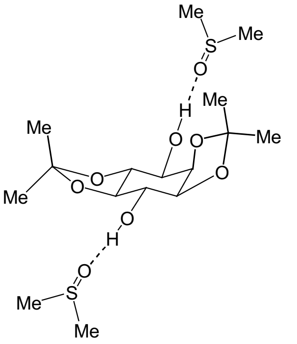
[†] The NMR spectra in acetone-d_6 and CD_3OD were not well resolved to assign the peak and to calculate J values.

[‡] Conformation of monosaccharides is sometimes very different in Me_2SO when compared to that in aqueous solution. This is presumably due to the bulkiness of hydroxyl groups when hydrogen-bonded to Me_2SO. See Ref. 13.

in Me_2SO can be rationalized based on the equatorial disposition of such bulky moieties in **2**.



1.Me$_2$SO



2.Me$_2$SO

In conclusion, we have presented the single crystal structure of a synthetically flexible and important optically active *allo*-inositol derivative for the syntheses of isomeric phosphoinositol derivatives. To the best of our knowledge this is the first report on the crystal structure of an *allo*-inositol derivative. Very slight conformational deviation from a chair to a flattened chair was observed for the inositol ring. A comparison of its conformation in solid and solution states using NMR revealed that the molecule adopts similar conformation in low polar solvents while a conformational change is observed in high polar solvents. Attempts have been made, in the recent past, to explain the solution state reactivities of inositol derivatives based on their crystal structure conformations. Although such an extrapolation of solid state structures to solution state to predict the reactivity is in its infancy, structural correlation (in both states) of a library of structurally related molecules will dramatically change the pace of research in this direction.

1. Experimental

1.1. General

Compound **1** was prepared as reported.[3] Crystal data collection was done on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation. ^1H NMR spectra were recorded on a Bruker-DPX-400 (400 MHz) instrument. Chemical shifts (δ_H values relative to tetramethylsilane) and coupling constants (J values) are given in ppm and Hz, respectively.

1.2. X-ray data

Good crystals of **1** were obtained by slow evaporation of its dichloromethane solution. The crystallographic data are given in Table 4. The structure was solved by direct methods using SIR92[14] and all calculations were performed using TEXSAN.[15] All nonhydrogen atoms were refined anisotropically. Some hydrogen atoms were refined isotropically and the rest were included in fixed positions. The co-ordinates of all nonhydrogen atoms are deposited.[§]

Table 4. Crystallographic data

Formula	$C_{12}H_{20}O_6$
Formula weight	260.29
Crystal dimensions	0.30×0.30×0.10 mm
Crystal system	Orthorhombic
Space group	$P2_12_12$ (#18)
Lattice parameters	$a = 11.124(2)$ Å $b = 16.1921(9)$ Å $c = 7.572(1)$ Å $V = 1363.9(3)$ Å^3
Z	4
D_{calc}	1.268 g/cm^3
μ(CuKα)	8.58 cm^{-1}
Diffractometer	Rigaku AFC7S (sealed tube)
Radiation	CuKα $\lambda = 1.54178$ Å (graphite monochromated)
Temperature	23.0 °C
Collimator size	1.0 mm
Take-off angle	6.0°
Scan type	ω–2θ
Scan width	$(1.00 + 0.30 \tan\theta)°$
$2\theta_{max}$	120.0°
No of reflections measured	Total: 1217 Unique: 1202 ($R_{int} = 0.000$)
Structure solution	Direct methods (SIR92)
Refinement	Full matrix least-squares (SHELXL-97)
Function minimized	$\sum w(F_o^2 - F_c^2)^2$
Least squares weights	$w = [\sigma^2(F_o^2) + (0.1000P)^2 + 0.000P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
No variables	193
Residuals: $R1$; Rw	0.068; 0.156
Goodness of fit indicator	1.29
Maximum peak in final diff. map	0.26 e/Å^3
Minimum peak in final diff. map	−0.51 e/Å^3

1.3. ^1H NMR data

1.3.1. ^1H NMR (Me_2SO-d_6). 1.26 (s, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 1.44 (s, 3H), 3.80 (dd, 9.8 Hz, 1.5 Hz, H-4), 4.05–4.11 (overlapped, H-3 & H-5), 4.22 (dd, 4.4 Hz, 3.4 Hz, H-2), 4.82 (dd, 4.4 Hz, 0.5 Hz, H-6), 5.30 (dd, 4.4 Hz, 0.5 Hz, H-1).

1.3.2. ^1H NMR (C_6D_6). 1.15 (s, 3H), 1.39 (s, 6H), 1.49 (s, 3H), 3.86–3.90 (overlapped, H-2 & H-4), 4.16 (dd,

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[§] Crystallographic data are deposited as CCDC 228783. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44-1223-336033, e-mail deposit@ccdc.cam.ac.uk).

4.4 Hz, 2.4 Hz, H-3), 4.33 (dd, 5.9 Hz, 1.5 Hz, H-1), 4.53 (dd, 3.4 Hz, 1.5 Hz, H-6), 4.62 (dd, 9.8 Hz, 3.4 Hz, H-5).

1.3.3. ^{1}H NMR ($CDCl_3$). 1.40 (s, 3H), 1.47 (s, 3H), 1.52 (s, 3H), 1.55 (s, 3H), 2.42 (s, OH), 2.47 (s, OH), 3.95 (dd, 10.0 Hz, 2.4 Hz, H-4), 4.29 (dd, 6.0 Hz, 4.4 Hz, H-2), 4.33–4.38 (overlapped, H-3 & H-5), 4.41 (dd, 6.0 Hz, 1.6 Hz, H-1), 4.51 (dd, 3.2 Hz, 1.6 Hz, H-6).

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