Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 339 (2004) 1803–1807
Carbohydrate RESEARCH

Note

Solid and solution state conformation of 1L-1-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-*chiro*-inositol

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

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama, Japan

Received 16 April 2004; accepted 10 May 2004

Abstract—The X-ray crystal structure of 1L-1-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-*chiro*-inositol is described. The inositol ring deviates considerably 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 states irrespective of solvent polarity.

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

1. Introduction

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-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-*chiro*-inositol (**1**) *via* nucleophilic substitution of 1D-3-*O*-trifluoromethylsulfonyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol.[3] We herein report the crystal structure of **1**. A qualitative comparison of its conformation in solid and solution states is made based on ^{1}H NMR spectroscopy. Also comparisons of solid state conformation of **1** with that of its parent L-*chiro*-inositol (**2**)[4] and structurally related 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**3**)[5] and 1L-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol (**4**)[6] were made (Chart 1).

2. Results and discussion

Compound **1** crystallizes in orthorhombic crystal system with $P2_12_12_1$ space group. Each unit cell contains four molecules. The inositol ring deviated considerably from an ideal chair to a flattened chair conformation. The ring C–C bond lengths (1.490–1.544 Å) and C–O bond lengths (1.410–1.441 Å) are in the normal range. The

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

0008-6215/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2004.05.005

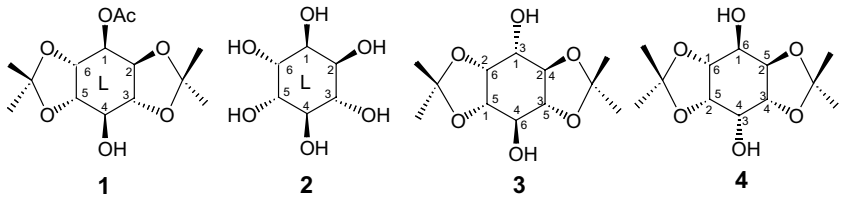


Chart 1. The outer numbering for **3** and **4** are *myo*-inositol numbering and *allo*-inositol numbering, respectively, and the inner numbering is similar to that in *chiro*-diketal **1** for brevity and consistency in comparison.

ring valence angles (106.6–118.9°) deviate from that of a perfect chair. Similarly the CCO angles vary from 100.9 to 114.8. The valence angles C-4–C-5–C-6 (117.4°) and C-5–C-6–C-1 (118.9°) deviate considerably from the ideal tetrahedral angle. The ring angles in **1** are similar to those in structurally related *myo*-inositol derivative **3** and *allo*-inositol derivative **4** but different from its parent L-*chiro*-inositol.[4] Various ring angles of **1**–**4** are tabulated in Table 1. A comparison of ring angles of **1**–**4** reveals that structurally similar **1**, **3** and **4** adopt similar conformations in the crystalline state. Figure 1 shows an ORTEP diagram of **1**.

Torsion angles in the carbocyclic skeleton also deviate much from that of a perfect chair or of the parent L-*chiro*-inositol. While the torsion angle C-1–C-2–C-3–C-4 expanded to 71.5°, the torsion angles C-3–C-4–C-5–C-6 (39.1°), C-4–C-5–C-6–C-1 (−33.0°) and C-5–C-6–C-1–C-2 (39.0°) experienced compression. The torsion angles in **1** are similar to the respective torsion angles (Table 2) in the structurally similar derivatives **3** and **4**, which are known[5,6] to adopt flattened chair conformations in their crystals. Also the torsion angles between vicinal oxygen atoms of **1** deviate from that of a perfect chair. The torsion angles between different vicinal oxygens are also comparable with that of derivatives **3** and **4** (Table 2). Thus the comparison of torsion angles and valence angles unequivocally establishes that compounds **1**, **3** and **4** have similar conformations in the solid state. Similar conformations of structurally similar derivatives **1**, **3** and **4** demonstrate that their conformations in the solid state are decided by two isopropylidene (one cis and one trans) conformational locks. Also this study establishes that the relative configuration at the other two carbon atoms (which are not connected to isopropylidene) have negligible contribution towards the conformational preference in the solid state. Comparison of conformations of a class of structurally related derivatives will help to elicit the structural features controlling the particular orientation or conformation. Such knowledge is inevitable for successful crystal engineering.

Table 1. A comparison of ring (CCC) angles of **1**–**4**

Ring angle	**1** (°)	**2**[a] (°)	**3**[a] (°)	**4**[a] (°)
C-1–C-2–C-3	112.0	113.1	110.5	111.4
C-2–C-3–C-4	111.4	110.6	111.0	111.0
C-3–C-4–C-5	107.3	112.6	106.8	105.4
C-4–C-5–C-6	117.4	111.3	115.9	117.5
C-5–C-6–C-1	118.9	109.7	117.9	118.9
C-6–C-1–C-2	106.6	110.0	107.0	107.9

[a]The ring angle values of **2**, **3** and **4** were taken from Refs. 4, 5 and 6, respectively.

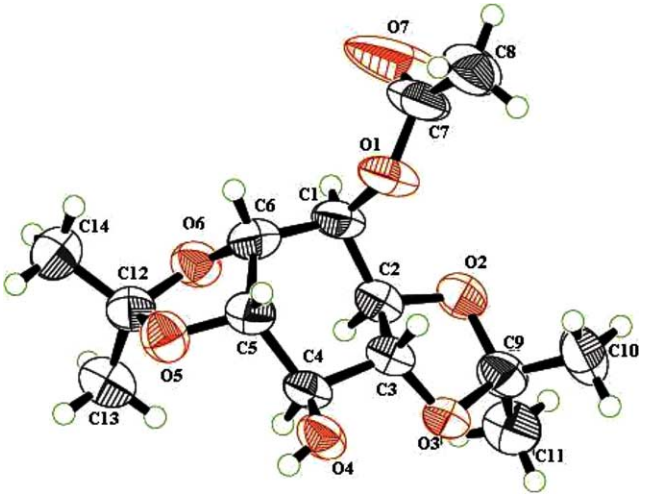


Figure 1. ORTEP diagram of **1**.

Table 2. Comparison of selected torsion angles of **1**–**4**

Torsion	**1** (°) *chiro*	**2**[a] (°)	**3**[a] (°) *myo*	**4**[a] (°) *allo*
O-1–C-1–C-2–O-2	−60.2(8)	−60.6(2)	[b]	−52.3(5)
O-2–C-2–C-3–O-3	−42.5(6)	−62.2(2)	−42.5(1)	−40.4(4)
O-3–C-3–C-4–O-4	68.7(7)	67.4(2)	65.1(2)	[b]
O-4–C-4–C-5–O-5	−85.4(7)	−60.9(2)	−83.5(2)	[b]
O-5–C-5–C-6–O-6	−35.4(7)	−57.0(2)	−36.5(1)	−34.5(4)
O-6–C-6–C-1–O-1	166.8(5)	173.6(2)	[b]	159.4(3)
C-1–C-2–C-3–C-4	71.5(6)	51.6(2)	72.6(2)	73.0(4)
C-2–C-3–C-4–C-5	−57.4(7)	−52.1(2)	−60.1(2)	−61.1(4)
C-3–C-4–C-5–C-6	39.1(7)	56.2(2)	42.8(2)	41.9(5)
C-4–C-5–C-6–C-1	−33.0(9)	−57.7(2)	−36.9(2)	−32.4(5)
C-5–C-6–C-1–C-2	39.0(8)	56.7(2)	42.3(2)	36.2(5)
C-6–C-1–C-2–C-3	−57.0(7)	−54.8(2)	−58.4(2)	−54.7(5)

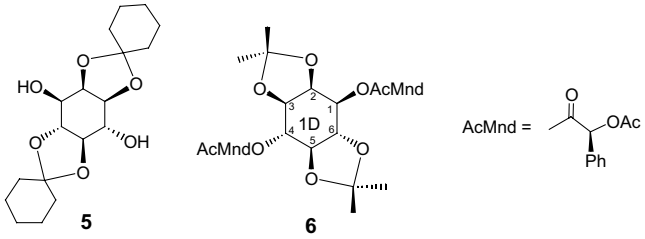
The number in parenthesis is the standard deviation.
[a]The torsion values of **2**, **3** and **4** were taken from Refs. 4, 5 and 6, respectively.
[b]Since O-1 in **3** and O-4 in **4** are inverted these values were not compared.

Table 3. Comparison of calculated and observed vicinal coupling constants ($^3J_{HH}$ in Hz) of **1** in solvents of different polarity

H–H	Me_2CO-d_6	CD_3OD	$CDCl_3$	Me_2SO-d_6	HH (ϕ°) torsion	J_{calcd}
H-1–H-2	1.80	1.80	2.40	1.80	−58.66	2.34
H-2–H-3	[a]	[a]	[a]	[a]	−170.93	8.92
H-3–H-4	[a]	[a]	[a]	[a]	−175.91	8.23
H-4–H-5	5.40	5.70	6.40	5.90	155.42	5.93
H-5–H-6	5.40	5.60	5.60	5.70	−34.76	4.83
H-6–H-1	1.80	1.82	2.40	1.80	−73.03	2.32

[a]These values could not be measured due to the overlapping of signals.

Having studied the conformation of **1** in the solid state, we became interested to analyze its conformational preference in various solutions. There are instances where different regioselectivities are observed in different solvents. Such a dependence of regioselectivities on the solvent is attributable in part to the different conformational preferences. In such a scenario, the study of solution state conformation is important since regioselectivity is one of the major concerns in inositol or sugar chemistry in general. The increased reactivity of C-3–OH of 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol and 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol towards various electrophiles[7] has been explained by extrapolating their crystal structure conformation to solution.[8] Also the rate of acyl migrations[9] between cis and trans vicinal oxygens in *myo*-inositol derivatives have been explained based on their crystal structures. During such studies, Chung and Ryu[8] reported similar conformation of 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**3**) in solid and solution states. Later, structurally related 1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (**5**) was also reported[10] to show similar conformations in solid and solution states. We have reported 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 (**6**)[11] and 1L-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol (**4**).[6] 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.



The ^{1}H NMR spectra of **1** in various solvents showed similar pattern where H-1, H-5 and H-6 signals are well resolved and separated from the overlapped H-2, H-3 and H-4 signals. The vicinal coupling constants of the resolved protons were compared to get an idea about the conformation of **1** in these solvents. Comparison of conformation in solid and solution states were also made by comparing the observed coupling constant and the calculated coupling constants (Table 3) based on torsion angle (ϕ) in the crystal structure by using Altona's equation.[†12] The similar observed coupling constants in all the solvents tested demonstrate that the conformation of **1** in all these solvents is the same. In addition, the observed coupling constants are in agreement with the calculated ones suggesting that the solid-state conformation is retained in solution too.

In conclusion, we have presented the single crystal structure of a synthetically useful and important optically active *chiro*-inositol derivative for the syntheses of isomeric phosphoinositol derivatives. Considerable 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 both the states. Attempts have been made, in the past, to explain the solid state[13] and solution state[8] 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 comparison and correlation (in both states) of a library of structurally related molecules will dramatically change the pace of research in this direction and hopefully will pave the way to effective 'solution engineering'.

3. Experimental

3.1. General

Compound **1** was prepared as reported.[3] Crystal data collection was done on a Rigaku AFC7S Diffractometer with graphite monochromated Cu-Kα radiation. ^{1}H NMR spectra were recorded on a Bruker-DPX-400

[†] The equation $13.86\cos^2\phi - 0.81\cos\phi + \Sigma\Delta\chi_i\{0.56 - 2.32\cos^2(\xi i\phi + 17.9°|\Delta\chi_i|)\}$ in Ref. 12 was used.

Table 4. Crystallographic data

Formula	$C_{14}H_{22}O_7$
Formula weight	302.32
Crystal dimensions:	0.12×0.12×0.48 mm
Crystal system:	Orthorhombic
Space group	$P2_12_12_1$ (#19)
Lattice parameters	$a = 16.266(5)$ Å
	$b = 17.294(8)$ Å
	$c = 5.529(6)$ Å
	$V = 1555(1)$ Å^3
Z	4
D_{calc}	1.291 g/cm^3
μ(CuKα)	8.77 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	$(1.26 + 0.30 \tan\theta)°$
2θ max	119.9°
No. of reflections measured	Total: 1396
	Unique: 1374 ($R_{int} = 0.000$)
Structure solution	Direct methods (SIR92)
Refinement	Full matrix least-squares (SHELXL-97)
Function minimized	$\Sigma w(Fo^2 - Fc^2)^2$
Least squares weights	$w = 1/[\sigma 2(Fo^2) + (0.1503.P)^2 + 0.0000 \cdot P]$
	where $P = (\mathrm{Max}(Fo^2, 0) + 2Fc^2)/3$
No. variables	191
Residuals: $R1$; R_w	0.067; 0.106
Goodness of fit Indicator	1.039
Maximum peak in final diff. map	0.25 e-/Å^3
Minimum peak in final diff. map	−0.24 e-/Å^3

(400 MHz) instrument. Chemical shifts (δ_H values relative to tetramethylsilane) and coupling constants (J values) are given in ppm and Hz, respectively.

3.2. X-ray data

Good crystals of **1** were obtained by slow evaporation of its EtOAc soln. 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. The co-ordinates of all nonhydrogen atoms are deposited.[‡]

[‡] Crystallographic data are deposited as CCDC 236206. 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).

3.3. ^{1}H NMR data

3.3.1. ^{1}H NMR (Me_2SO-d_6). 1.24 (s, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 2.05 (s, 3H), 3.58 (m, H-4), 3.64–3.68 (overlapped, H-2 and H-3), 3.96 (dd, 5.9 Hz, 5.7 Hz, H-5), 4.22 (dd, 5.7 Hz, 1.8 Hz, H-6), 5.38 (t, 1.8 Hz, H-1), 5.62 (d, 5.5 Hz, OH).

3.3.2. ^{1}H NMR (CD_3OD). 1.33 (s, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.47 (s, 3H), 2.10 (s, 3H), 3.73–3.81 (overlapped, H-2, H-3 and H-4), 4.06 (dd, 5.7 Hz, 5.6 Hz, H-5), 4.28 (dd, 5.6 Hz, 1.8 Hz, H-6), 5.55 (t, 1.8 Hz, H-1).

3.3.3. ^{1}H NMR (Me_2CO-d_6). 1.28 (s, 3H), 1.32 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 2.08 (s, 3H), 3.74–3.81 (overlapped, H-2, H-3 and H-4), 4.07 (t, 5.4 Hz, H-5), 4.28 (dd, 5.4 Hz, 1.8 Hz, H-6), 4.74 (d, 3.7 Hz, OH), 5.53 (t, 1.8 Hz, H-1).

3.3.4. ^{1}H NMR ($CDCl_3$). 1.34 (s, 3H), 1.40 (s, 3H), 1.46 (s, 3H), 1.49 (s, 3H), 2.11 (s, 3H), 2.73 (br, OH), 3.83–3.90 (overlapped, H-2, H-3 and H-4), 4.13 (dd, 6.4 Hz, 5.6 Hz, H-5), 4.23 (dd, 5.6 Hz, 2.4 Hz, H-6), 5.68 (t, 2.4 Hz, H-1).

Acknowledgements

We thank JSPS for a postdoctoral fellowship (KMS) and Grant-in-aid (No. 02170). We are grateful to Prof. Hidemitsu Uno for the timely help in crystal data collection. Also we thank Venture Business Laboratory and Advanced Instrumentation Center for Chemical Analysis, Ehime University for NMR and elemental analysis, respectively.

References

1. (a) Berridge, M. J. *Nature* **1993**, *361*, 315–325; (b) Hinchliffe, K.; Irvine, R. *Nature* **1997**, *390*, 123–124; (c) Bruzik, K. S., Ed.; *Phosphoinositides: Chemistry, Biochemistry and Biomedical Applications*; ACS symposium Series 718; 1999.
2. Ferguson, M. A. J.; Williams, A. F. *Annu. Rev. Biochem.* **1988**, *57*, 285–320.
3. Sureshan, K. M.; Watanabe, Y. *Synlett* **2004**, 493–496.
4. Jeffrey, G. A.; Yeon, Y. *Carbohydr. Res.* **1987**, *159*, 211–216.
5. Chung, S.-K.; Ryu, Y.; Chang, Y.-T.; Whang, D.; Kim, K. *Carbohydr. Res.* **1994**, *253*, 13–18.
6. Sureshan, K. M.; Miyasou, T.; Watanabe, Y. *Carbohydr. Res.* **2004**, *339*, 1551–1555.
7. (a) Chung, S.-K.; Chang, Y.-T.; Ryu, Y. *Pure. Appl. Chem.* **1996**, *68*, 931–935; (b) Shashidhar, M. S.; Volwerk, J. J.; Griffith, O. H.; Keana, J. F. W. *Chem. Phys. Lipids* **1991**, *60*, 101–110; (c) Ward, J. G.; Young, R. C. *Tetrahedron Lett.* **1988**, *29*, 6013–6016; (d) Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *J. Chem. Soc., Perkin Trans. 1*

1987, 423–429; (e) Liu, C.; Potter, B. V. L. *J. Org. Chem.* **1997**, *62*, 8335–8340.
8. Chung, S.-K.; Ryu, Y. *Carbohydr. Res.* **1994**, *258*, 145–167.
9. Chung, S.-K.; Chang, Y.-T.; Whang, D.; Kim, K. *Carbohydr. Res.* **1996**, *295*, 1–6.
10. Spiers, I. D.; Schwalbe, C. H.; Blake, A. J.; Solomons, K. R. H.; Freeman, S. *Carbohydr. Res.* **1997**, *302*, 43–51.
11. Sureshan, K. M.; Miyasou, T.; Watanabe, Y. *Carbohydr. Res.* **2004**, *339*, 807–811.
12. Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.
13. Praveen, T.; Samanta, U.; Das, T.; Shashidhar, M. S.; Chakrabarti, P. *J. Am. Chem. Soc.* **1998**, *120*, 3842–3845.
14. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Polidori, G. *J. Appl. Cryst.* **1994**, *27*, 435–435.
15. Crystal structure analysis package, Molecular Structure Corporation, 1999.