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Crystal structure, solid state and solution conformation of 1D-1,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol

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

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 7908577, Japan

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Abstract—The X-ray crystal structure of 1D-1,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol is described. Both inositol ring and OAM (*O*-acetylmandeloyl) moiety deviate from their respective ideal conformations. Inositol ring adopts a flattened chair conformation while OAM adopts an *ap* (antiperiplanar) conformation. A comparison of its conformation in solution with that in solid was made by the use of NOESY and anisotropic shielding effect in ^{1}H NMR. This conformational study revealed that the title compound adopts similar conformations in both the states.

Keywords: Inositol; Resolution; Conformation; *O*-Acetylmandeloyl; Mosher's ester

1. Introduction

In the recent past, there has been a leaping advance in the chemistry and biology of *myo*-inositol and its derivatives due to their important biological roles.[1] The realization that phosphatidylinositol phospholipase C (PIPLC) mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate [PI(4,5)P_2] to the second messengers D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] and diacylglycerol (DAG), augmented the pace of research in this field. Many phosphoinositols are involved in the *myo*-inositol cycle, through which Ins(1,4,5)P_3 recycles back to the lipid PI(4,5)P_2. In addition, recently many other phosphatidylinositol phosphates (PIP$_n$s) have been found in living cells. But a clear understanding of the biological significance of these phosphoinositols is lacking mainly due to difficulties to isolate these derivatives from natural resources. As the isolation of these phosphorylated derivatives from natural sources is impracticable, biological studies rely on the efficient synthesis of these phosphoinositol derivatives. As *myo*-inositol is a *meso* cyclohexane hexol, efficient protection–deprotection strategies[2] and resolution methods are of utmost importance in the synthesis.

The most commonly used starting materials for the syntheses of phosphoinositols are the diketal derivatives **1** and **2** because of the possible discriminations between two ketals (*cis* and *trans*) and hydroxyls (cis and trans orientation with adjacent oxygen). For instance, the relative reactivity of hydroxyl groups in 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol, **1**, has been studied extensively.[3] It is reported that phosphorylation,[4] acylation,[3,5]silylation,[3,6] alkylation,[3,7] etc. occur selectively at the O-3 position. Also it is documented in literature[7a,8] that the *trans*-isopropylidene can be cleaved in the presence of the *cis*-isopropylidene.

During our ongoing programme to provide easy access to many inositol phosphates and their lipid analogues, we have resolved[9] the diketal **1** via sequential crystallizations of its di-(*S*)-*O*-acetylmandeloyl derivatives **3** and **4**. We herein report the crystal structure of

* 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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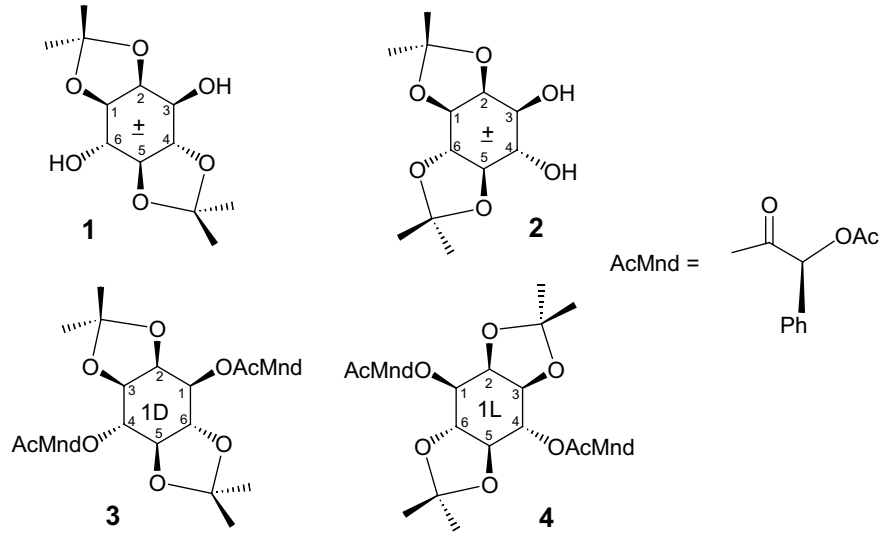

1D-1,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol, **3**. Also a qualitative comparison of its conformation in solid and solution states is made based on NMR spectroscopy.

2. Results and discussions

Good crystals of **3** were obtained by slow evaporation of its chloroform solution. The crystallographic data are given in Table 1. The structure was solved by direct methods using SIR92[10] and all calculations were performed using TEXSAN.[11] All non-hydrogen atoms were refined anisotropically. The co-ordinates of all non-hydrogen atoms are deposited.[†] The inositol ring deviated from an ideal chair to a flattened chair conformation. The angle between backrest (planes C-1, C-2, C-3) and seat (planes C-1, C-3, C-4, C-6) increased such that backrest (C-1, C-2, C-3) and tip of footrest (C-5) shared a common plane. The ring C–C bond lengths (1.493–1.554 Å) and C–O (1.403–1.461 Å) bond lengths deviated slightly from that of *myo*-inositol (C–C 1.521 ± 0.007 and C–O 1.429 ± 0.006).[12] C–O bond lengths for C-1–O-1 and C-4–O-4 are slightly higher than other four ring carbon–oxygen bonds (1.417 Å) probably due to the attachment of ester groups. All CH bond lengths are in the normal range 0.94–0.96 Å.

The ring angles (107.2°–118.7°) deviate from that of either inositol (mean $110.7° \pm 1.2°$) or a perfect chair (111°). Bond angles C-1–C-2–C-3 (118.7°) and C-2–C-3–C-4 (115.1°) deviate considerably from the ideal tetrahedral angle. Similarly the CCO angles vary from 101.0° to 116.0°. Figure 1 shows an ORTEP diagram of **3**.

Table 1. Crystallographic data

Formula	$C_{32}H_{36}O_{12}$
Formula weight	612.63
Crystal dimensions	$0.50 \times 0.45 \times 0.30$ mm
Crystal system	Triclinic
Space group	*P*1 (#1)
Lattice parameters	$a = 6.379(1)$ Å
	$b = 9.871(3)$ Å
	$c = 13.195(2)$ Å
	$\alpha = 99.55(2)°$
	$\beta = 96.54(1)°$
	$\gamma = 96.38(2)°$
	$V = 806.8(3)$ Å^3
Z	1
D_{calcd}	1.261 g/cm^3
μ(MoKα)	0.97 cm^{-1}
Diffractometer	Rigaku AFC5R (rotating anode)
Radiation	MoKα $\lambda = 0.71069$ Å (graphite monochromated)
Temperature	25.0 °C
Collimator size	1.0 mm
Take-off angle	6.0°
Scan type	ω–2θ
Scan width	$(1.52 + 0.30 \tan\theta)°$
$2\theta_{max}$	55.0°
No. of reflections measured	Total: 3913
	Unique: 3699 ($R_{int} = 0.023$)
Function minimized	$\sum w(F_o^2 - F_c^2)^2$
Least squares weights	$w = 1/\sigma^2(F_o^2)$
p-factor	0.0500
No. of variables	399
Residuals: R; R_w	0.061; 0.122
Residuals: R_1	0.046
Goodness of fit	
Indicator	1.20
Maximum peak in final diff. map	0.14 e/Å^3
Minimum peak in final diff. map	−0.14 e/Å^3

[†] Crystallographic data are deposited as CCDC 215964. 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).

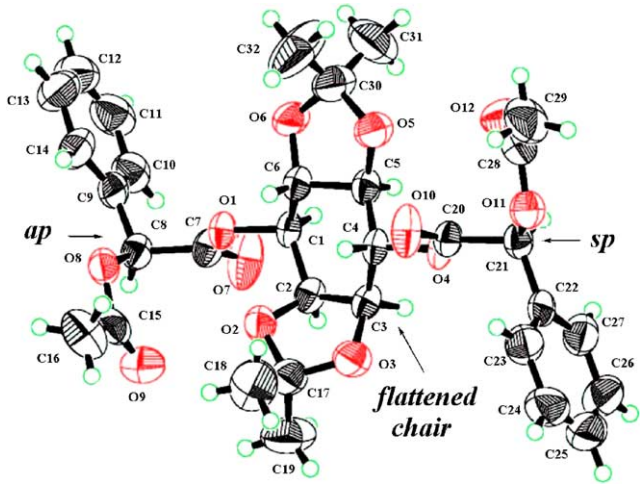

Figure 1. ORTEP diagram of **3**.

Torsion angles between vicinal oxygen atoms deviate from that of a perfect chair (56°). Torsion angles in the carbocyclic skeleton also deviate much from its parent diketal **1**, which is reported[13] to adopt a chair conformation in its crystals. A comparison of torsion angles (Table 2) of **1** and **3** clearly indicates the deviation of **3** from the chair conformation. The torsion angle C-4–C-5–C-6–C-1 expanded to −75.7° while C-1–C-2–C-3–C-4 experienced compression to 29.1°. Other ring torsion angles also vary considerably (Table 2).

Another important point to note is the conformation of *O*-acetylmandeloyl ester groups in crystals of **3**. OAM is a frequently used chiral anisotropy reagent for the determination of absolute configuration of chiral alcohols.[14] The assignment of the absolute configuration is based on a conformational model, similar to MPA (methoxy phenylacetic acid) ester, where *O*-acetyl (*O*-methyl in the case of MPA ester) and carbonyl group of the mandelate group are assumed to take *syn*-periplanar (*sp*) orientation in the esters. Analysis of the crystal structure of **3** reveals that one of the OAM (OAM attached to C-4–O) is in ideal *sp* conformation whereas the other OAM (OAM attached to C-1–O) is in anti-periplanar (*ap*) orientation. The torsion O=C–C–OAc for the OAM at C-4 is −20.8° (syn) while that for the OAM at C-1 is 151.3° (anti). This deviation could be a result of conformational compromise between the inositol ring part and OAM part due to steric crowding. Since the inositol ring is conformationally locked with two five-membered ketal rings, it is reasonable to think that the comparatively flexible OAM part compromised its ideal conformation. This remarkable conformational difference is of much significance in the light of frequent use of OAM as a CAR. This is the first case where an OAM ester adopts an *ap* conformation while all other reported crystal structures of OAM esters have shown the ideal *sp* conformation.[15]

These notable conformational deviations of both inositol ring (from chair to a flattened chair) and OAM ester (from *sp* to *ap*) in crystals of **3** made us eager to investigate its conformation in solution also. As the ring protons are well resolved 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 are in agreement with the calculated coupling constants (Table 3) based on torsion angle (ϕ) in the crystal structure by using the Altona's version[16] of Karplus equation.[17] The small variation of the calculated and observed coupling constants could be due to the limitation of the equation.

It is well known[16,18] that the coupling constant between vicinal protons depend on electronegativity, orientation, etc. of the other substituents on carbon bearing the Hs. It is apparent to think that the origin of

Table 2. Selected torsion angles of **3** and **1**[a]

O–C–C–O	**3** (°)	**1** (°)	C–C–C–C	**3** (°)	**1** (°)
O-1–C-1–C-2–O-2	−39.0(3)	49.3(2)	C-1–C-2–C-3–C-4	29.1(4)	36.9(2)
O-2–C-2–C-3–O-3	31.5(3)	36.5(1)	C-2–C-3–C-4–C-5	−42.9(4)	−42.8(2)
O-3–C-3–C-4–O-4	82.5(3)	83.5(2)	C-3–C-4–C-5–C-6	66.4(3)	60.1(2)
O-4–C-4–C-5–O-5	−61.8(4)	−65.1(2)	C-4–C-5–C-6–C-1	−75.7(3)	−72.6(2)
O-5–C-5–C-6–O-6	39.7(3)	42.5(1)	C-5–C-6–C-1–C-2	55.6(4)	58.4(2)
O-6–C-6–C-1–O-1	−71.7(3)	−66.2(2)	C-6–C-1–C-2–C-3	−34.7(4)	−42.3(2)

[a]The torsion angles for the compound **1** (columns 3 and 6) are derived from Ref. 13 and the value given are for the L-1,2;4,5-di-*O*-isopropylidene-*myo*-inositol.

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

	C_6D_6	$CDCl_3$	DMSO-d_6	Torsion, ϕ°	J_{calcd} from ϕ
H-1–H-2	4.4	4.4	4.4	−40.42	4.6
H-2–H-3	4.9	4.9	4.9	32.42	5.4
H-3–H-4	6.6	6.6	6.6	−158.6	6.5
H-4–H-5	11.2	10.2	10.5	−175	9.2
H-5–H-6	9.5	9.8	10.0	165.7	9.4
H-6–H-1	10.3	9.6	10.3	174.21	9.8

Table 4. Chemical shift (δ) of ring protons in different solvents

	C_6D_6	$CDCl_3$	Me_2SO-d_6
H-1	5.12	5.08	5.31
H-2	4.22	4.34	4.23
H-3	3.37	3.80	3.93
H-4	5.60	5.22	5.12
H-5	3.20	3.45	3.83
H-6	4.33	4.08	4.00

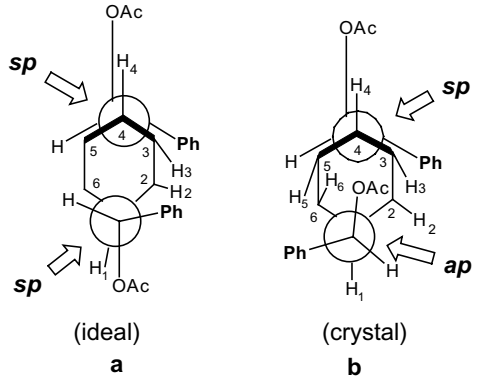

Figure 2. Conformational models.

the small difference between the observed and calculated coupling constants could be due to these orientation effects. Similar difference between calculated and observed coupling constants of *myo*-inositol derivatives had been reported previously.[3,19] 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 solvent polarity has little effect on coupling constants. In other words the conformation is the same in all the solvents tested irrespective of their polarity. This is not unexpected as **3** is conformationally locked with two ketal rings.

Although the vicinal coupling constants in differently polar solvents are the same, it is worthy to note that the relative position of chemical shifts of different ring protons varies from solvent to solvent (Table 4). H-1, H-3 and H-5 shifted downfield with increase of polarity of the solvent whereas H-4 and H-6 showed an upfield shift. But H-2 experienced only a minimal shift with different solvent polarities. The exact reason for these up- and downfield shifts of adjacent protons is not clear.

Since the OAM part deviates from its ideal *sp* conformation in the solid state, we next aimed to elicit the conformational preference of the OAM part in solution. For this we relied on the anisotropic shielding effect. A comparison of the ^1H NMR spectra of **3** and its diastereomer **4** revealed that the OAMs in **3** take a conformation exactly similar to that in the crystal structure.[20] NOESY spectroscopy of **3** showed cross peaks of aromatic protons with H-6 and H-3 (as in Fig. 2b) while no cross peak with H-2 was observed. This suggests that conformations of OAMs in solution is like in Figure 2b (*sp* and *ap*) but not in ideal *sp sp* conformation (Fig. 2a). This further substantiates similar conformational preference of **3** in both crystal and solution states.

In conclusion, we have presented the single crystal structure of an important intermediate for the syntheses of phosphoinositol derivatives. Notable conformational deviations are observed for both the inositol ring and its pendant OAM substituent. A comparison of its conformation in solid and solution states using NMR revealed that the molecule has similar conformation in both the states. This represents an interesting example for the consistence in conformation of not only the *myo*-inositol ring but its pendant substituents also in solid and solution states. Since OAM is a frequently used CAR for the determination of absolute configuration of alcohols, its conformational deviation from *sp* to *ap* is of interest and thought-provoking to a wider cross section of organic chemists as this is the first report of an unusual conformation of OAM.

Examples are there in the literature where crystal structure of inositol derivatives have been used to predict their reactivity in both solid[21] and solution states.[22] In some cases, the correlation between conformation in solid (X-ray) and solution states is studied by using solution ^1H NMR spectroscopy. 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 small molecules will dramatically change the pace of research in this direction.

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