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Crystal structures of (±)-1,4-di-*O*-benzoyl-2,3-*O*-isopropylidene-*myo*-inositol and (±)-1,4-di-*O*-benzoyl-5,6-*O*-isopropylidene-*myo*-inositol: a conformational analysis

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Abstract

(±)-1,4-Di-*O*-benzoyl-2,3-*O*-isopropylidene-*myo*-inositol (**1**) crystallises in the triclinic space group, $P\bar{1}$ with unit-cell dimensions $a = 10.432(2)$, $b = 11.595(4)$, $c = 12.654(2)$ Å, $\alpha = 67.72(3)$, $\beta = 11.595(4)$, $\gamma = 12.654(2)$ degrees. (±)-1,4-*O*-Dibenzoyl-5,6-*O*-isopropylidene-*myo*-inositol (**2**) crystallises in the monoclinic space group, $P2_1/n$ with unit-cell dimensions $a = 9.101(2)$, $b = 10.4900(9)$, $c = 22.806(4)$ Å, $\alpha = 90$, $\beta = 95.452(10)$, $\gamma = 90$ degrees. The inositol ring of *cis*-acetal **1** is flattened, whereas that of *trans*-acetal **2** is more puckered compared to *myo*-inositol. The acyl migration rates are discussed in terms of the crystalline conformations of **1** and **2**.

Keywords: Inositol; Conformational analysis; Crystallography; Acyl migration rate; Cyclic acetal

1. Introduction

The reactivity of hydroxyl groups in *myo*-inositol is strongly dependent on the stereochemistry and conformation of the molecule. In general, equatorial and axial

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hydroxyl groups exhibit different chemical behaviour, and even equatorial hydroxyl groups in *myo*-inositol are not equivalent. Whereas differences between axial and equatorial hydroxyl groups are reasonably well understood in terms of conformation and steric hindrance, the non-equivalence of the equatorial hydroxyl groups requires further study. We have recently investigated the regioselective functionalisation [1] and benzoyl migration [2] of (±)-1,4-di-*O*-benzoyl-2,3-*O*-isopropylidene-*myo*-inositol (**1**) and (±)-1,4-di-*O*-benzoyl-5,6-*O*-isopropylidene-*myo*-inositol (**2**). According to previous results [3] and our own work on the acyl migration, the *cis*-migration rate is generally faster than the *trans*-migration rate. In addition, our results have shown that the presence of a cyclic acetal enhances the *cis*-/*trans*-migration ratio [2]. In our attempts to understand the origin of the migration rate differences, it has been reasoned that the conformations of these compounds are probably associated with their kinetic behaviour. Thus, in order to make this correlation, the X-ray crystal structures of these two compounds were determined.

2. Results and discussion

The procedures for the synthesis of **1** and **2** were previously reported by us [4]. It was found that good-quality single crystals of **1** could be obtained by slow recrystallisation from tetrahydrofuran–hexane. Single crystals of **2** were grown by slow evaporation of an acetone solution. The relevant crystallographic data of **1** and **2** are given in Table 1. The structures were solved by direct methods using SHELXS-86 [5]. All the non-hydrogen atoms were refined anisotropically. Hydrogen atoms in free OH groups were located from a difference Fourier map and refined isotropically [6]. Hydrogen atoms bonded to carbon were positioned according to idealised geometry (C–H distance 0.95 Å). For **1**, a molar equivalent of tetrahydrofuran co-crystallised to fill the large vacancy in the crystal lattice. The final refinement on F^2 converged to the R indices given in Table 1. The final coordinates of C and O atoms for **1** and **2** are listed in Table 2. Selected bond angles and torsional angles, as key conformational parameters, for **1** and **2** are given in Table 3. ORTEP [7] drawings of **1** and **2** with the atom numbering schemes are shown in Figs. 1 and 2, respectively. [1] In the undistorted chair form of *myo*-inositol, the distance between the *trans*-related vicinal equatorial hydroxyl groups is the same as that between the *cis*-related vicinal axial and equatorial hydroxyl groups. However, the formation of a cyclic acetal induces a flattening effect in the five-membered ring, and as a consequence the cyclohexane moiety is distorted in such a way that the two vicinal hydroxyl groups involved in the acetal become more coplanar. Therefore, the chair conformation of the cyclohexane ring now exhibits two different types of distortion upon the induction of the flattening caused by the cyclic acetalation, depending on the *cis* or *trans* relationship of the two hydroxyl groups involved in acetalation. It was previously suggested that the formation of a *cis*-cyclic acetal flattened the inositol ring and increased the endocyclic

[1] Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Center. These tables may be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

Table 1
Crystallographic data for **1** and **2** [a]

	1	**2**
Formula	$C_{23}H_{24}O_8 \cdot C_4H_8O$	$C_{23}H_{24}O_8$
Mol wt	500.53	428.42
Space group	triclinic, $P1$	monoclinic, $P2_1/n$
a (Å)	10.432(2)	9.101(2)
b (Å)	11.595(4)	10.4900(9)
c (Å)	12.654(2)	22.806(4)
α (degrees)	67.72(3)	90
β (degrees)	86.31(1)	95.452(10)
γ (degrees)	70.45(2)	90
Volume (Å^3)	1331.3(6)	2167.4(6)
Z	2	4
Temp (°C)	25	25
Density (calcd)(g/cm^3)	1.249	1.313
λ(Mo K_α)(Å)	0.71073	0.71073
Monochromator	graphite	graphite
Linear abs. coeff. (cm^{-1})	0.877	0.928
Crystal size (mm)	0.40×0.35×0.20	0.40×0.35×0.20
Scan mode	$\omega/2\theta$	ω
ω-scan width (degrees)	0.75+0.35 tan θ	0.75+0.35 tan θ
2θ limit (degrees)	50	47
No. of data collected	4919	3666
No. of unique data	4641	3215
No. of unique data with $I > 2\sigma(I)$	2494	2165
No. of variables	331	286
$R(F)$ ($I > 2\sigma(I)$)	0.071	0.071
$wR(F^2)$ (whole data set)	0.269 [b]	0.254 [c]
Largest ΔF peak (hole) (eÅ^{-3})	0.32 (−0.19)	0.19 (−0.21)
Diffractometer	Enraf–Nonius CAD4	

[a] Standard deviations in parentheses.
[b] $w = 1/[2\sigma(F_o^2)+(0.0969P)^2+4.0482P]$ where $P=(F_o^2+2F_c^2)/3$.
[c] $w = 1/[2\sigma(F_o^2)+(0.0195P)^2+2.3090P]$ where $P=(F_o^2+2F_c^2)/3$.

bond angles, whereas the *trans*-ring formation caused shortening of the interatomic distance between the two hydroxyl groups involved in acetalation, thus distorting the chair conformation at the expense of a large amount of energy [8]. This explanation was supported by indirect pieces of evidence provided by examination of hydrogen bonding [9], but the conclusive X-ray data had not been available.

In the reported X-ray conformation of *myo*-inositol, the average bond angle was 110.7° and the torsional angle 56.8° [10]. Results from ab initio calculation showed a reasonable agreement with experimental X-ray data (111.2° and 55.3°, respectively) [11]. Our X-ray data show that both molecules **1** and **2** have chair conformations in their crystalline phases, and the average bond angle and torsional angle in *cis*-acetal **1** are 112.8° and 49.60°, which clearly indicates that the inositol ring is flattened. In the case of *trans*-acetal **2**, the corresponding angles are 110.0° and 58.50°, which again indicates

Table 2
Fractional positional parameters of C and O atoms for **1** and **2** [a] ($\times 10^4$)

Atoms	**1**			**2**		
	x	*y*	*z*	*x*	*y*	*z*
O-1	8819(3)	8038(3)	1596(2)	1753(3)	8314(3)	5971(1)
O-2	7246(3)	8534(3)	−285(2)	371(4)	6203(3)	5413(2)
O-3	7564(3)	9180(3)	−2202(2)	−974(4)	6352(4)	4262(2)
O-4	10285(3)	7437(3)	−2520(2)	1636(4)	6456(3)	3649(1)
O-5	11500(4)	5370(3)	−353(3)	4376(3)	7020(3)	4429(1)
O-6	11296(4)	6175(3)	1503(3)	4351(3)	8160(3)	5293(1)
O-7	8796(4)	10058(4)	1368(3)	−14(5)	9799(4)	5908(2)
O-8	9263(4)	6139(4)	−2804(3)	1174(4)	4347(3)	3648(1)
C-1	9477(5)	8133(4)	530(3)	1627(5)	8215(4)	5338(2)
C-2	8419(5)	8937(4)	−471(4)	307(5)	7396(4)	5114(2)
C-3	8843(5)	8772(4)	−1589(4)	260(5)	7115(5)	4454(2)
C-4	9684(5)	7354(4)	−1429(3)	1697(5)	6522(5)	4283(2)
C-5	10821(5)	6717(4)	−496(4)	2918(5)	7408(4)	4507(2)
C-6	10236(4)	6726(4)	632(3)	2967(5)	7545(4)	5164(2)
C-7	6534(5)	9054(5)	−1382(4)	5328(5)	7566(5)	4910(2)
C-8	5928(7)	8059(7)	−1440(5)	6180(6)	6498(5)	5230(3)
C-9	5524(6)	10431(7)	−1630(6)	6304(6)	8578(5)	4689(2)
C-10	8540(5)	9071(5)	1917(4)	876(6)	9171(5)	6206(2)
C-11	7881(5)	8840(5)	3020(4)	1096(6)	9194(5)	6856(2)
C-12	7586(6)	7699(6)	3596(4)	2110(7)	8414(7)	7175(3)
C-13	6977(7)	7526(8)	4623(5)	2296(9)	8478(8)	7783(3)
C-14	6684(7)	8495(10)	5064(6)	1464(10)	9301(10)	8073(3)
C-15	6966(7)	9631(9)	4498(6)	451(9)	0087(10)	7765(3)
C-16	7585(6)	9818(7)	3470(5)	271(8)	0022(7)	7156(3)
C-17	9981(5)	6815(4)	−3120(4)	1347(5)	5329(5)	3384(2)
C-18	10633(5)	7059(4)	−4216(3)	1269(5)	5415(5)	2736(2)
C-19	10713(6)	6238(5)	−4803(4)	826(7)	4366(5)	2412(2)
C-20	11267(7)	6466(7)	−5850(5)	752(9)	4412(7)	1802(3)
C-21	11754(6)	7489(7)	−6311(4)	1142(9)	5500(7)	1524(3)
C-22	11683(7)	8309(6)	−5747(5)	1616(9)	6544(7)	1853(3)
C-23	11118(6)	8101(5)	−4703(4)	1674(8)	6506(6)	2454(2)
O-9	6188(8)	5098(8)	1452(8)			
C-24	6094(15)	5864(12)	2047(12)			
C-25	5413(18)	5389(20)	3030(14)			
C-26	4919(18)	4395(19)	2874(17)			
C-27	5466(17)	4299(17)	1883(17)			

[a] Standard deviations in parentheses.

a more puckered conformation for the inositol ring. The newly formed 5-membered ring reveals that the two vicinal hydroxyl groups have indeed become quasi-coplanar in both cases (torsional angles: O-2–O-3 in **1** = 37.20, O-5–O-6 in **2** = 42.47). These data provide the first direct evidence for the suggested effects caused by *cis-/trans*-cyclic acetalation on the inositol conformation.

Concerning our original interest in the acyl migration rate, an interesting conclusion may also be drawn from these crystal data. The acyl migration reaction via an orthoacid

Table 3
Selected angles (°) in **1** and **2** [a]

	1	**2**
Bond angles in the inositol ring		
C-2–C-1–C-6	114.6(3)	106.4(4)
C-1–C-2–C-3	115.6(4)	112.7(4)
C-2–C-3–C-4	113.2(4)	112.5(4)
C-5–C-4–C-3	113.4(4)	106.5(4)
C-4–C-5–C-6	109.8(4)	110.5(4)
C-1–C-6–C-5	110.3(3)	111.2(4)
av	112.8	110.0
Torsional angles in the inositol ring		
C-6–C-1–C-2–C-3	−42.1(5)	−54.5(5)
C-1–C-2–C-3–C-4	38.6(5)	54.2(5)
C-2–C-3–C-4–C-5	−47.2(5)	−54.5(5)
C-3–C-4–C-5–C-6	58.2(5)	60.2(5)
C-4–C-5–C-6–C-1	−59.5(5)	−67.0(5)
C-2–C-1–C-6–C-5	52.1(5)	60.6(5)
av	49.6	58.5
Torsional angles between vicinal oxygens		
O-1–C-1–C-2–O-2	−46.4(5)	−52.4(5)
O-2–C-2–C-3–O-3	37.2(4)	58.8(5)
O-3–C-3–C-4–O-4	79.4(4)	62.5(5)
O-4–C-4–C-5–O-5	−66.8(4)	−66.1(5)
O-5–C-5–C-6–O-6	62.6(5)	42.5(4)
O-1–C-1–C-6–O-6	−66.4(4)	−64.1(5)

[a] Standard deviations in parentheses.

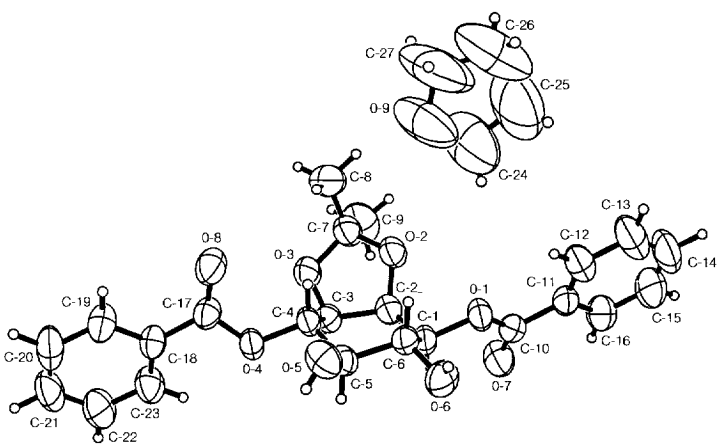

Fig. 1. ORTEP drawing [7] of **1** showing atom numbering.

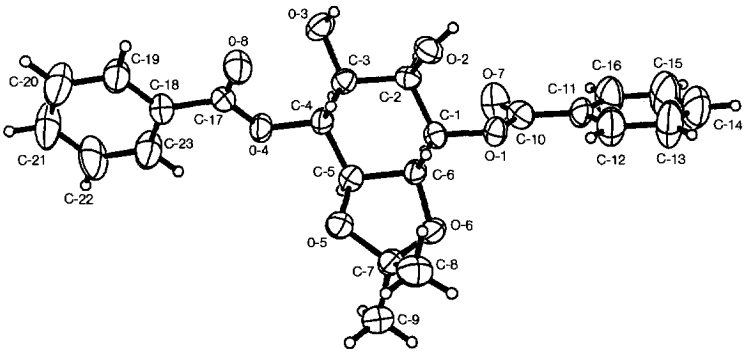

Fig. 2. ORTEP drawing [7] of **2** showing atom numbering.

intermediate requires an approximately coplanar transition state. Therefore, a *cis*-migration is expected to be faster because of the more facile formation of the *cis*-cyclic transition state. Torsional angles between vicinal oxygens of **1** and **2** were examined as an indication of the ease with which the planar cyclic transition state could be formed in the benzoyl migration (Table 3). A remarkably smaller torsional angle between O-1–O-2 (52.36°) compared with that between O-3–O-4 (62.48°) in **2** may account for the faster benzoyl migration observed from O-1 to O-2 over that observed from O-4 to O-3. In accordance with the similar benzoyl migration rates observed in **1**, the two torsional angles of 66.84° for O-4–O-5 and 66.44° for O-1–O-6 are quite similar. Thus it may be concluded that the smaller the torsional angle between the vicinal hydroxyl groups, the faster the migration occurs.

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