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CONFORMATIONAL POLYMORPHISM IN RACEMIC 2,4-DI-*O*-BENZOYL-6-*O*-TOSYL *MYO*-INOSITOL 1,3,5-ORTHOACETATE

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The title compound, $C_{29}H_{26}O_{10}S$, yields two conformational polymorphs concomitantly from dichloromethane-methanol mixture; the major polymorph grows as plates (Form I, monoclinic, $P2_1/n$) and the minor polymorph grows as needles (Form II, triclinic, P-1). The two forms differ mainly in orientation of the tosyl group. In Form I, sulfonyl oxygen of the tosyl group makes intermolecular C—H···O interactions, whereas the same group in Form II is involved in an intramolecular short dipolar S=O···C=O (sulfonyl-carbonyl) contact. The molecular organization and the influence of various weak non-covalent interactions that stabilize these conformers in the crystal lattices are discussed.

K e y w o r d s: conformation, crystal structure, dipolar interactions, inositol, non-covalent interactions, polymorphism, sulfonyl-carbonyl contact.

INTRODUCTION

Polymorphism has a strong relevance to pharmaceutical solids, dyes, pigments and explosives because of the required consistency in physical and chemical properties, which can be achieved by restricting the formation of undesired polymorphs [1—4]. Different orientations adopted by a flexible molecule can often exhibit conformational polymorphism [5, 6]. Competition between various energetically similar weak non-covalent interactions during molecular aggregation leads to the formation of polymorphs [7, 8]. Structural studies of racemic 2,4-di-*O*-benzoyl-6-*O*-tosyl *myo*-inositol 1,3,5-orthoaceate (Chart 1) were explored for its possible molecular association *via* dipolar S=O···C=O short contacts [9—11]. *O*-Sulfonated *myo*-inositol orthoesters are important intermediates [12] for the synthesis of biologically relevant phosphoinositols and other cyclitols [13].

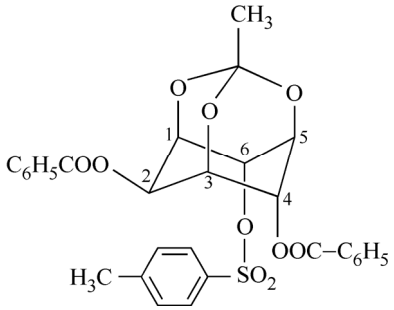

Chart 1. Schematic chemical structure with inositol ring atom numbering

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EXPERIMENTAL SECTION

Preparation of racemic 2,4-di-*O*-benzoyl-6-*O*-tosyl-*myo*-inositol 1,3,5-orthoacetate. Racemic 2,4-di-*O*-benzoyl *myo*-inositol orthoacetate [14] (0.412 g, 1 mmol) and tosyl chloride (0.570 g, 3 mmol) were dissolved in pyridine (8 mL) and the mixture stirred at 80 °C for 60 h. Solvents were evaporated from the reaction mixture under reduced pressure and the residue obtained was dissolved in ethyl acetate. The resulting solution was washed with dilute HCl, saturated $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The crude product obtained on evaporation of the solvent was finally purified by flash column chromatography (silica gel) using ethyl acetate-light petroleum ether mixture as eluent. Yield: 0.269 g, 47 %; mp: 184—186 °C.

Calc. for $C_{29}H_{26}O_{10}S$, 566.56 (%): C 61.48; H 4.63; Found (%): C 61.27; H 4.36.

IR ($CHCl_3$, cm^{-1}): 1726 (C=O).

^1H NMR ($CDCl_3$, 200 MHz): δ 1.53 (s, 3H, O_3CMe), 2.40 (s, 3H, ArMe), 4.44—4.52 (m, 2H, Ins H), 4.56—5.63 (m, 1H, Ins H), 5.22—5.29 (m, 1H, Ins H), 5.50 (t, 1H, J = 1.6 Hz, Ins H), 5.72—5.78 (m, 1H, Ins H), 7.20—7.72 (m, 10H, ArH), 8.02—8.16 (m, 4H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.6, 23.9, 62.2, 67.1, 67.2, 69.7, 70.1, 72.2, 109.2, 127.9, 128.4, 128.5, 128.6, 129.3, 129.9, 130.0, 130.1, 132.2, 133.5, 133.5, 145.6, 165.0, 165.8 ppm.

Crystallization. Crystallization of the title compound from a saturated solution of organic solvents such as dichloromethane, chloroform, acetonitrile, ethyl acetate containing light petroleum (used as precipitant) produced solvent-free crystals (Form I). However, slow evaporation from dichloromethane-methanol (9:1) mixture at room temperature yielded concomitant dimorphs with different morphologies; the majority of crystals were plates (Form I) and traces of thin needles (Form II). In all the crystallization attempts we failed to obtain good quality crystals of Form II, as they were always encountered as traces of fragile thin needles.

Crystallographic details. X-ray intensity data for Form I and II crystals were collected on a Bruker SMART APEX CCD diffractometer in ω—ϕ scan mode, λ(MoK_α) = 0.71073 Å at room temperature. All the intensities were corrected for Lorentzian, polarization and absorption effects using Bruker′s SAINT and SADABS programs [15]. All the crystal structures were solved by direct methods using the SHELXS-97 program; the full-matrix least squares refinements on F^2 were carried out by using SHELXL-97 [16]. The ORTEP-3 [17] and MERCURY CSD 2.1 [18] programs were used to prepare the molecular graphics. All the hydrogen atoms were placed in idealized positions (C—H = = 0.98 Å for inositol ring H atoms, C—H = 0.93 Å for phenyl H atoms and C—H = 0.96 Å for methyl H atoms) and constrained to ride on their parent atoms, with U_{iso}(H) = 1.2U_{eq}(C). Table 1 summarizes the crystal data for the dimorphs. The Form II crystal was thin and did not diffract to higher angle and therefore diffraction data were not adequate for anisotropic refinement for all the atoms. The final R-index was also high (R1 = 0.1315) due to poor quality of the data.

Crystallographic data for the dimorphs reported in this paper have been deposited with the Cambridge Crystallographic Data Centre; CCDC numbers: 664583 and 664584 (see Table 1). These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Director, The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2, 1EZ, UK; fax: +44(0) 1223-336033.

Statistical analysis of tosyl orientation. The Cambridge Crystallographic Structural Database, CSD version 5.29, was used for the statistical analysis of torsion angle (X—X—S—C, X = any element) in the crystal structures of organic compounds containing tosyl group. All the searches were carried out with error free structures with 3D co-ordinates and restricting entries with disorder, ionic and polymeric structures, and structures elucidated from X-ray powder diffraction data. There were 1610 entries of organic compounds with tosyl groups found in the CSD; out of these 950 (60 %) were included with a torsion angle range of 70 to 90°.

RESULTS AND DISCUSSION

The title compound yielded dimorphs; Form I crystallizes in the monoclinic $P2_1/n$ space group whereas Form II crystallizes in the triclinic P-1 space group. Structures of Form I and II crystals reveal

T a b l e 1

Summary of crystallographic data for the dimorphs studied

Crystal data	Form I	Form II
CCDC number	664583	664584
Chemical formula	$C_{29}H_{26}O_{10}S$	$C_{29}H_{26}O_{10}S$
Formula weight	566.56	566.56
Colour	Colorless	Colorless
Crystal size, mm	0.48 × 0.37 × 0.04	0.42 × 0.06 × 0.02
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	P-1
a, b, c, Å	15.3915(19), 10.6781(13), 16.722(2)	7.107(3), 13.831(7), 15.272(7)
α, β, γ, deg.	90, 95.776(2), 90	65.826(8), 77.644(8), 76.627(10)
Volume, Å^3	2734.4(6)	1320.3(11)
Z	4	2
D_{calc}, g·cm^{-3}	1.376	1.425
μ, mm^{-1}	0.177	0.183
T_{min}, T_{max}	0.920, 0.992	0.927, 0.996
θ range for data collection, deg.	1.17—25.0	1.47—25.0
Index ranges	$-18 \le h \le 18$, $-12 \le l \le 12$, $-19 \le k \le 17$	$-8 \le h \le 8$, $-16 \le l \le 16$, $-18 \le k \le 18$
No. of reflections collected	18018	12755
No. of unique reflections	4800	4654
No. of observed reflections	3277	2595
No. of parameters	363	363
R_{int}	0.033	0.080
Goodness of fit on F^2	1.01	1.18
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0458$, $wR2 = 0.1037$	$R1 = 0.1315$, $wR2 = 0.2258$
R indices (all data)	$R1 = 0.0739$, $wR2 = 0.1175$	$R1 = 0.2163$, $wR2 = 0.2597$
Residual max, min (e·Å^{-3})	0.26, –0.21	0.34, –0.32

that the flexible tosyl group adopts two different orientations due to rotation around O6—S1 bond (Figs. 1, *a*, *b*); C6—O6—S1—C23 torsion angles were found to be 91.2 and 165.5° respectively. It is

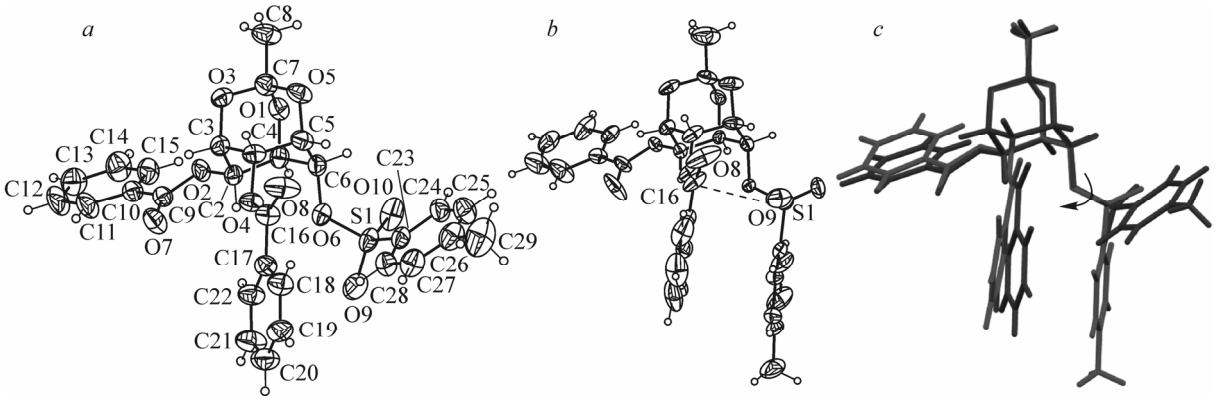

Fig. 1. ORTEP view of (*a*) Form I with atom numbering scheme and (*b*) Form II [blue dashed lines indicate dipolar S=O···C=O contact] with 30 % probability displacement ellipsoids. (*c*) Molecular overlap plot of Form I (black) and II (grey)

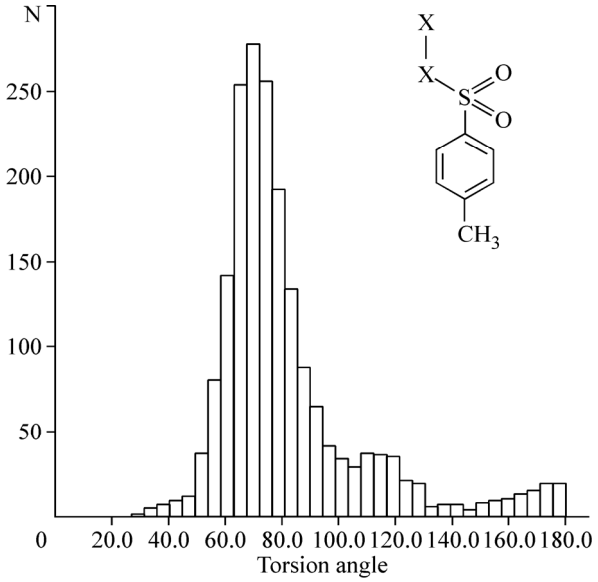

Fig. 2. Histogram of torsion angle of tosyl group (X—X—S—C, X = any element) in the CSD

noteworthy that such a significant difference in orientation of the tosyl group (Fig. 1, *c*) was observed for dimorphs under identical crystallization conditions.

We carried out a statistical analysis to find the orientational preference of the tosyl group using Cambridge Crystallographic Structural Database, which showed preference to the orientation similar to that observed in Form I crystals (Fig. 2). Interestingly, the least preferred conformation of the tosyl group was that observed for Form II crystals, which makes intramolecular S=O···C=O (sulfonyl-carbonyl) short contacts (Fig. 1, *b*). The geometry (S1=O10···C16=O8 = 3.157(8) Å, O10···C16=O8 = 94° and S1=O10···C16 = 116°) observed here is of interaction motif Type III *i.e.* sheared parallel motif [19, 20]. It is interesting to note that in Form II crystals, tosyl oxygen atoms (O9 and O10) do not take part in any significant intermolecular interaction except for the intramolecular dipolar S=O···C=O contact. Therefore, the tosyl group is packed more closely to the axial benzoyl group in Form II crystals resulting in denser crystal packing (1.425 $g \cdot cm^{-3}$) compared to Form I crystals (1.376 $g \cdot cm^{-3}$). The literature survey showed that the metastable form of benzoyl methyl phenyl sulfone fungicide having intramolecular short S=O···C=O and C=O···S=O dipolar contacts in their crystals transformed to a more stable form devoid of such contacts [21].

Due to orientational changes in the tosyl group in Forms I and II, sulfonyl oxygen atoms are differently associated to other molecules in their dimorphic modifications. In Form I, the sulfonyl group is involved in the intermolecular C—H···O interactions; whereas in Form II, it does not make any significant contacts, except for the intramolecular dipolar S=O···C=O contacts mentioned earlier. As a result, in Form I crystals dimeric association of molecules is between tosyl oxygen O9 and benzoyl proton H13 (Fig. 3, *a*, Table 2), whereas in Form II crystals it is *via* orthoester oxygen O3 and benzoyl proton H13 (Fig. 3, *b*, Table 3). Additionally in Form II crystals, C2 benzoyl groups are engaged in making aromatic π···π stacking interactions (Cg1···Cg1^{i} = 3.743 Å, dihedral angle = 0°, symmetry

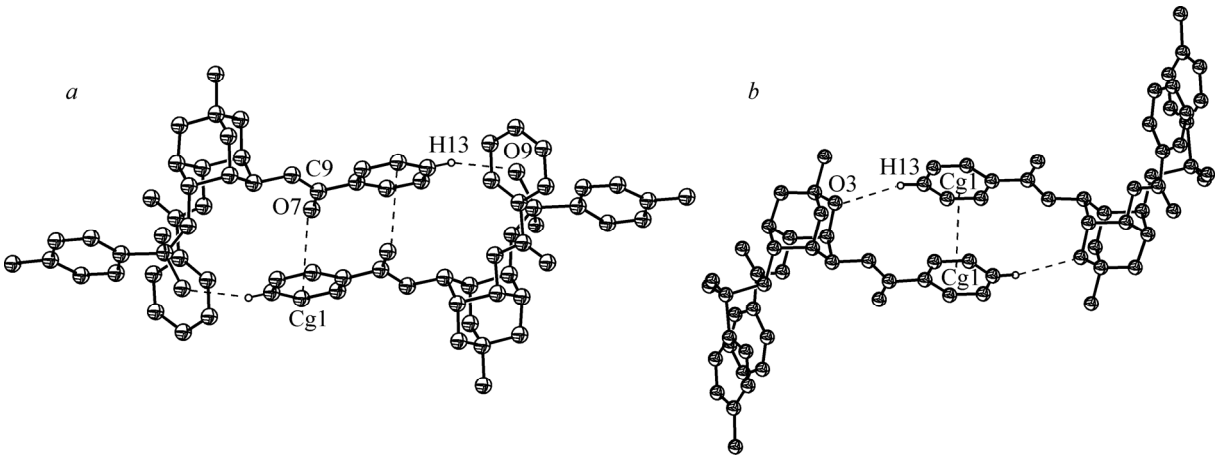

Fig. 3. Centrosymmetric dimer formation *via* C—H···O interactions in (*a*) Form I and (*b*) Form II crystals

Table 2

Intermolecular hydrogen bond geometry for Form I *crystals* (Å, deg.)

D—H···A	*d*(D—H)	*d*(H···A)	*d*(D···A)	∠(D—H···A)	Symmetry code
C1—H1···O10	0.98	2.50	3.328(3)	142	–*x*, –*y*, –*z*
C3—H3···O5	0.98	2.36	3.231(3)	148	1/2–*x*, 1/2+*y*, 1/2–*z*
C13—H13···O9	0.93	2.51	3.259(4)	138	–*x*, 1–*y*, –*z*
C18—H18···O8	0.93	2.65	3.284(3)	126	–*x*, –*y*, 1–*z*

Table 3

Intermolecular hydrogen bond geometry for Form II *crystals* (Å, deg.)

D—H···A	*d*(D—H)	*d*(H···A)	*d*(D···A)	∠(D—H···A)	Symmetry code
C1—H1···O8	0.98	2.44	3.134(10)	127	1+*x*, *y*, *z*
C2—H2···O8	0.98	2.69	3.089(9)	105	1+*x*, *y*, *z*
C5—H5···O5	0.98	2.64	3.170(9)	114	1–*x*, 1–*y*, 1–*z*
C6—H6···O1	0.98	2.55	3.391(9)	144	2–*x*, 1–*y*, 1–*z*
C13—H13···O3	0.93	2.64	3.546(10)	165	2–*x*, 2–*y*, 1–*z*
C19—H19···O7	0.93	2.37	3.173(15)	145	1–*x*, 2–*y*, –*z*

code: (i) –*x*, –*y*, 1–*z*], while in Form I crystals, they are weakly associated *via* off-centered π···π contacts [(C9=)O7···Cg1^{ii} = 3.825 Å, C9=O7···Cg1= 80.0°, symmetry code: (ii) –*x*, 1–*y*, –*z*].

In Form I crystals, the neighboring 2_1 screw axis related dimers are associated *via* C3—H3···O5 interactions along *b*-axis forming a helical arrangement and are linked to adjacent similar chains *via* centrosymmetric C18—H18···O8 interactions viewing down *c*-axis (Fig. 4, *a*, Table 2). In case of Form II crystals, the dimers are unit translated along *b*-axis *via* centrosymmetric C5—H5···O5 interactions and these are weaved to form 2-dimensional layer along *c*-axis *via* C19—H19···O7 interactions (Fig. 4, *b*, Table 3).

In the third dimension, molecules of Form I crystals are associated *via* centrosymmetric C—H···O interactions between the phenyl proton H18 and C4-benzoyl oxygen O8 (Table 2). But in

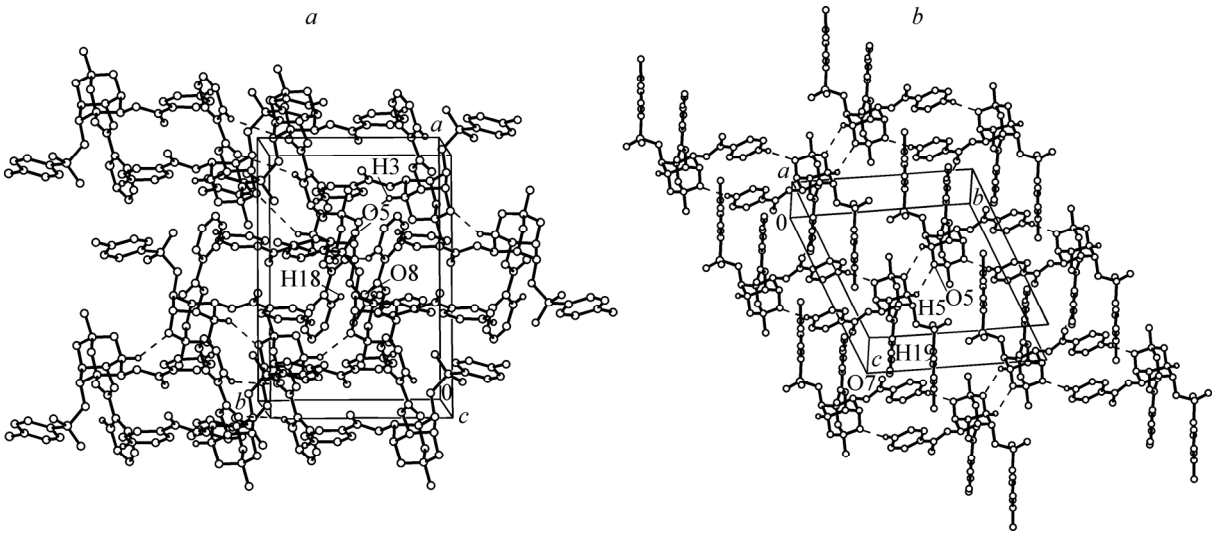

Fig. 4. Molecular layer formation *via* C—H···O interactions in Form I (*a*) and Form II (*b*) crystals

Form-II crystals, the molecules are weaved very closely *via* centrosymmetric C6—H6···O1 contacts and bifurcated C—H···O interactions between the C4-benzoyl oxygen O8 and inositol ring protons H1 and H2 (Table 3).

CONCLUSIONS

The title compound crystallizes with different conformations of the tosyl group in the two crystal structures studied due to the free rotation possible around S—O bond resulting in different patterns of weak intra- as well as intermolecular interactions. It is noteworthy that the interplay of different intra- and intermolecular weak interactions could significantly alter the conformation of flexible molecules leading to the formation of polymorphs. The conformational polymorphism observed in the present study is often exhibited by sulfa drugs [22] having a significant effect on their bioavailability and subsequently on their formulation.

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