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Capturing a metastable chiral polymorph of an achiral molecule—hexa-*O*-benzoyl-*myo*-inositol†

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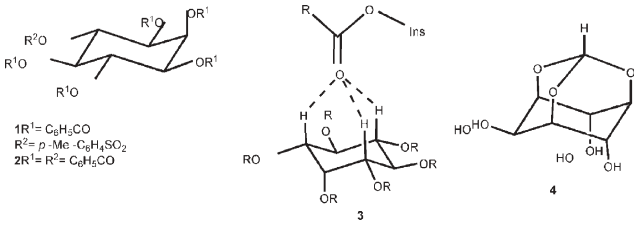
***myo*-Inositol hexabenzoate having *meso* configuration produces chiral polymorph (form I) when crystallized rapidly but yields achiral polymorph (form II) when allowed to crystallize slowly; in the mother liquor form I slowly but completely disappears to give form II.**

Polymorphism is a vigorously pursued research topic of recent times because of the tremendous basic and commercial research interest in pharmaceutical solids.[1] Intrigued by the pseudopolymorphic behavior of the racemic *myo*-inositol derivative **1** (Scheme 1),[2] we investigated the polymorphic behavior of the *meso*-hexabenzoate **2**.[3] In this communication, we report the X-ray structures of two polymorphs and one pseudopolymorph of **2** which provide some insight into the patterns of weak intermolecular interactions that are responsible for the polymorphism exhibited by **2**.



Scheme 1

Crystallization of **2** from supersaturated solutions of ethyl acetate yielded long needle like crystals (form I, Fig. 1a) belonging to a chiral space group $P6_1$.‡ These crystals upon standing in the mother liquor gradually disappeared with the simultaneous appearance of small plate like crystals (Fig. 1b) belonging to the achiral space group $P\bar{1}$ (form II). These crystals could also be obtained from a number of other solvents such as ethyl acetate, pyridine, nitromethane and benzene by slow evaporation ($\sim$2 days, Fig. 1c). However, only the chiral form I could be reproducibly obtained from these solvents when nucleation was achieved very rapidly ($\sim$30–60 min.). Seeding the chiral crystals in mother liquor also produced more of form I crystals initially but not exclusively.

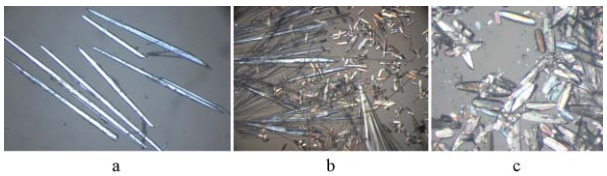


Fig. 1 Photomicrographs of crystals of forms I and II (see text for details).

† Electronic supplementary information (ESI) available: ORTEP diagrams, details of intra- and intermolecular interactions in forms I, II and III, DSC and TGA/DTA data for forms I and II. See http://www.rsc.org/suppdata/cc/b4/b410051d/

These results suggest that the formation of metastable chiral crystals is favoured under 'kinetic' conditions while formation of form II is favoured under 'thermodynamic' conditions.§[1,4] The hexabenzoate **2** also produced pseudopolymorphs containing dihalomethanes. Very large but unstable crystals (form III) could be grown by slow evaporation of dihalomethane (halogen = Cl, Br) solutions.

Closely interacting pairs of molecules in forms I and II¶ are shown in Fig. 2. In the chiral form I, the neighbouring molecules make C–H···O interactions in such a way that the 'helicity' is spontaneously generated at the nucleation of this basic unit. The two C–H groups, C4–H4 and C6–H6, of molecule 1 make a bifurcated C–H···O interaction with O9 of molecule 2; in turn oxygen O12 of molecule 1 accepts protons from C3–H3 and C5–H5 belonging to molecule 2 (Fig. 2a).‖ In continuing this pattern, each successive molecule gets a twist of 60°, which coincides with the crystallographic six-fold screw axis.

Crystals of form II (Fig. 2b) and III consist of centrosymmetric dimers with strikingly similar trifurcated C–H···O interactions. The three axial H-atoms H1, H3 and H5 of the *myo*-inositol ring from

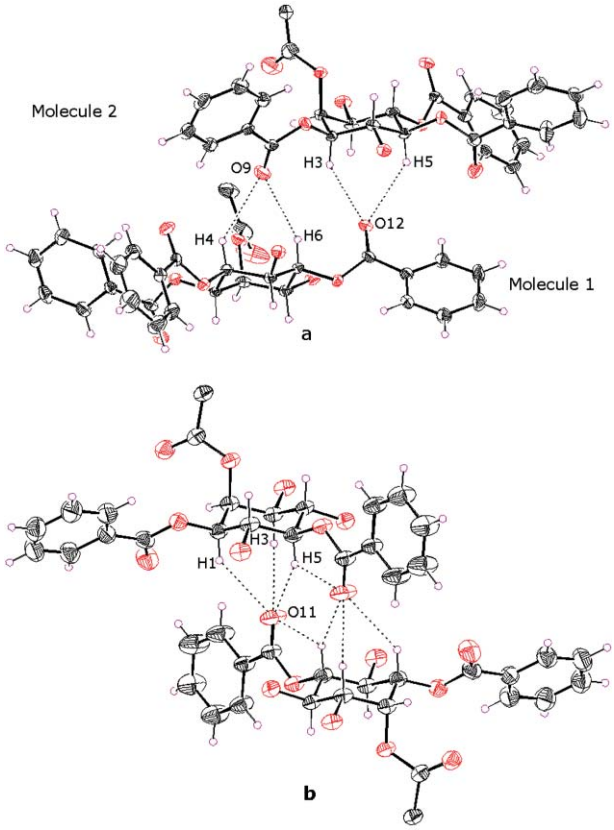


Fig. 2 ORTEP view of form I (a) and form II (b) showing significant C–H···O interactions; some benzoyl groups are omitted for clarity.

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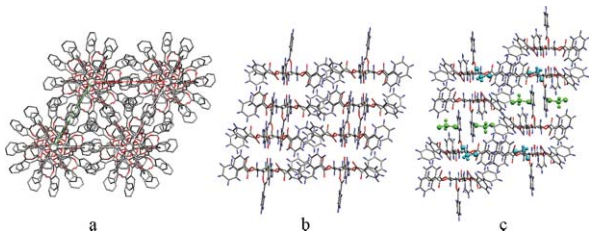

Fig. 3 Molecular packing in the three forms (see text for details).

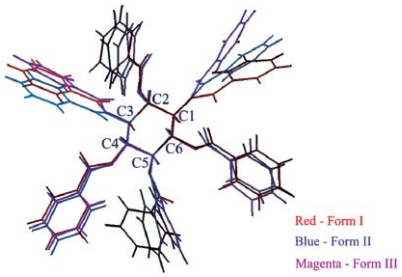

Fig. 4 Overlap of conformations of forms I, II and III.

each molecule make contacts with the carbonyl oxygen O11 of the other molecule. Hydrogen H5 also makes a somewhat compromised intramolecular C–H···O interaction with O11. These two C–H···O interactions doubly bridge the two centrosymmetrically related molecules (Fig. 2b).¶ In the crystallization process, the formation of the 'nuclei' starting from the first interacting pair seems to be critical in deciding the outcome of the polymorph. The centrosymmetric pair produce stable form II crystals, whereas the helically related pair give a metastable chiral form I. The stability of form II could arise due to the adamantane-like geometry formed by the three C–H···O hydrogen bonds (**3**), a robust non-covalent 'supramolecular synthon'[5] also observed in other hexa substituted *myo*-inositol derivatives containing a carbonyl oxygen.[2,6] This resembles the covalently bridged molecular structure of *myo*-inositol orthoformate (Scheme 1, **4**). The centrosymmetric dimers are linked by weak interactions in forms II and III; two weak C–H···O contacts along the *a*-axis link them in II whereas such weak interactions (C–H···Cl and C–H···O) in form III are between the guest and the host.

Helical assembly in form I leaves no possibility for guest accommodation without breaking this symmetry (Fig. 3a). However, form II consisting of weakly bonded layers of dimers (Fig. 3b) has the capacity to expand and accommodate the guest molecules as seen in the pseudopolymorph (form III, Fig. 3c). The polymorphic behaviour of **2** may be attributed to the conformational flexibility that generates different patterns of intermolecular weak interactions, *e.g.* C–H···O in the present case. Overlap of molecular conformations of **2** in three crystal forms (Fig. 4) reveals differences essentially in the benzoate groups attached to C1, C3 and C5 positions. The axial benzoate at C2 exhibits rotational disorder in form I (details included in the deposited crystallographic data**), perhaps due to the non-involvement of these atoms in any significant intermolecular interactions.

The spontaneous generation of chirality is an enigmatic phenomenon[7] which continues to fascinate chemists and biologists. The form I crystals capable of showing optical activity can be compared with a class of crystals where the activity is due to the helical arrangement of the molecules in the entire lattice (*e.g.* quartz) rather than configurational or conformational[8] chirality of individual molecules. Our observation of an achiral organic molecule producing a chiral crystal due to its topology of weak interactions could have relevance in asymmetric synthesis[9] and in designing nonlinear optical materials.[10]

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Notes and references

‡ The assignment of $P6_1$ or $P6_5$ for an organic molecule with no heavy atom scatterer cannot be established with Mo–K_α radiation.
§ Thermograms (DSC and TGA/DTA) recorded for forms I and II are provided in supplementary data.† In form II, the appearance of an endotherm ~235 °C indicates a phase transformation (most likely a new phase) just before the melting endotherm begins.
¶ Trifurcated C–H···O bridging in form III is very similar to form II.
‖ Form I: H4···O9^a = 2.67 Å; C4···O9 = 3.491(5) Å; C4–H4···O9 = 141.1°, H6···O9^a = 2.63 Å; C6···O9 = 3.461(5) Å; C6–H6···O9 = 143.1°, H3···O12^b = 2.40 Å; C3···O12 = 3.259(4) Å; C3–H3···O12 = 145.9°, H5···O12^b = 2.56 Å; C5···O12 = 3.369(4) Å; C5–H5···O12 = 139.3°. Form II: H1···O11^c = 2.48 Å; C1···O11 = 3.340(3) Å; C1–H1···O11 = 146.9 °, H3···O11^c = 2.70 Å; C3···O11 = 3.514(3) Å; C3–H3···O11 = 140.2 °, H5···O11^c = 2.48 Å; C5···O11 = 3.335(3) Å; C5–H5···O11 = 145.4°, H5···O11 = 2.24 Å; C5···O11 = 2.69 Å; C5–H5···O11 = 106.3°. $^a y, -x + y + 1, z$-1/6, $^b x - y + 1, x, z + 1/6$, $^c -x + 1, -y + 1, -z$.
** *Crystal data*: form I: $C_{48}H_{36}O_{12}$, M = 804.77, crystal dimensions 0.74 × 0.08 × 0.06 mm, hexagonal, space group $P6_1$, a = 13.9840(7), c = 36.504(3) Å, V = 6182.1(7) Å^3, Z = 6, D_c = 1.297 g cm^{-3}, μ(Mo–K_α) = 0.094 mm^{-1}, T = 133(2) K, 31322 reflections collected, 7233 unique [$I > 2\sigma(I)$], R = 0.0673, $wR2$ = 0.1265 (all data R = 0.0988, $wR2$ = 0.1363). Form II: $C_{48}H_{36}O_{12}$, M = 804.77, crystal dimensions 0.38 × 0.15 × 0.06 mm, triclinic, space group $P\bar{1}$, a = 11.931(3), b = 14.463(4), c = 14.722(4) Å, α = 64.109(4), β = 71.642(5), γ = 67.851(6)°, V = 2082.2(10) Å^3, Z = 2, D_c = 1.284 g cm^{-3}, μ(Mo–K_α) = 0.093 mm^{-1}, T = 293(2) K, 15011 reflections collected, 7285 unique [$I > 2\sigma(I)$], R = 0.0541, $wR2$ = 0.1211 (all data R = 0.1159, $wR2$ = 0.1474). Form III: $C_{48}H_{36}O_{12}\cdot 1.75CH_2Cl_2\cdot 0.25H_2O$, M = 957.90, crystal dimensions 0.66 × 0.58 × 0.38 mm, triclinic, space group $P\bar{1}$, a = 13.961(2), b = 14.214(2), c = 15.134(2) Å, α = 104.827(2), β = 101.516(2),γ = 117.970(2)°, V = 2377.7(6) Å^3, Z = 2, D_c = 1.338 g cm^{-3}, μ(Mo–K_α) = 0.283 mm^{-1}, T = 133(2) K, 11397 reflections collected, 8203 unique [$I > 2\sigma(I)$], R = 0.0667, $wR2$ = 0.1866 (all data R = 0.0828, $wR2$ = 0.2021). CCDC 244385–244387. See http://www.rsc.org/suppdata/cc/b4/b410051d/ for crystallographic data in .cif or other electronic format.

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