Concomitant dimorphs of tri-*O*-[*p*-halobenzoyl]-*myo*-inositol 1,3,5-orthoformates with different halogen bonding contacts: first order crystal-to-crystal thermal phase transition of kinetic form to the thermodynamic form†

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Crystallization of tri-*O*-[*p*-halobenzoyl]-*myo*-inositol 1,3,5-orthoformates from ethyl acetate–petroleum ether solution produced concomitant dimorphs that have different halogen bonding contacts; the kinetic form with C–Br···O–C contacts upon heating to 185 °C, converts completely to the thermodynamic form with C–Br···O=C contacts *via* crystal-to-crystal first order phase transition.

Polymorphism and crystal growth are among the most intensively researched areas of present times because of the tremendous basic and commercial interest in pharmaceutical solids.[1] The primary process of crystallization governed predominantly by intermolecular interactions remains intractable even for small organic molecules because of the complexity with which molecules interact with each other.[2] The polymorphic behavior exhibited by small organic molecules with no possibility of forming conventional H-bonding interactions, offers a unique opportunity to study the interplay of weak intermolecular interactions[3] that takes place in the nucleation event leading to growth of different crystal forms. In this communication, we report for the first time structures of concomitant polymorphs of **1** that primarily utilize different 'halogen bonding' contacts[4] C–Br···O–C (ether oxygen, Form I) and C–Br···O=C (carbonyl oxygen, Form II) during their crystal growth. Remarkably, crystals of Form I exhibit first order crystal-to-crystal phase transition to Form II crystals when heated to 185 °C, although large molecular movements are invoked in the phase change.

Tri-*O*-[*p*-halobenzoyl]-*myo*-inositol 1,3,5-orthoformates‡ **1** and **2** gave concomitant dimorphs (Fig. 1) – thin long needles (Form I) and octahedral blocks (Form II), when crystallized from ethyl acetate–petroleum ether mixture (~ 1 : 4, v/v). Needles appeared from solution within the first few hours; while the blocks were obtained after two days from the same flask (by slow evaporation). Needles of Form I could also be obtained by achieving rapid nucleation by cooling a saturated solution of **1** or **2** (in chloroform, dichloromethane or acetone). This indicated Form I and Form II to be kinetic and thermodynamic crystals respectively.[1,3a,5]

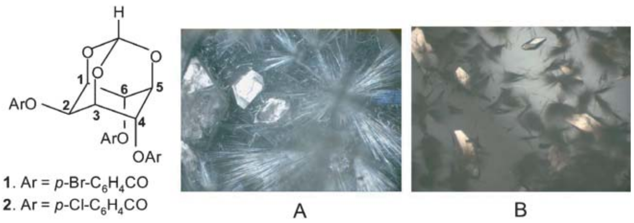

Fig. 1 Photomicrographs of concomitant polymorphs of **1** (A) and **2** (B).

The DSC of Form I crystals of **1** (Fig. 2A) showed two sharp endotherms, the first one at 188 °C suggesting a first order phase transition[6] and the second one at 198 °C corresponding to the melting of the crystal. Interestingly, a repeat of the DSC for the

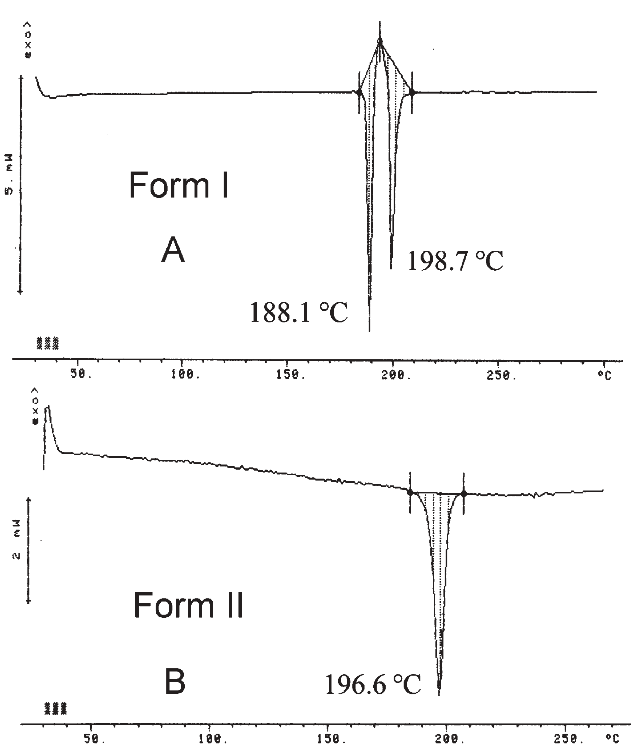

Fig. 2 DSC (A) of Form I showing a sharp peak corresponding to phase transition just before the melting endotherm and (B) of Form II.

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† Electronic supplementary information (ESI) available: molecular overlap of Form I and Form II, seven figures showing other weak interactions, two scatter plots for CSD survey, one Table each for intermolecular interactions and CSD survey. See DOI: 10.1039/b511754b

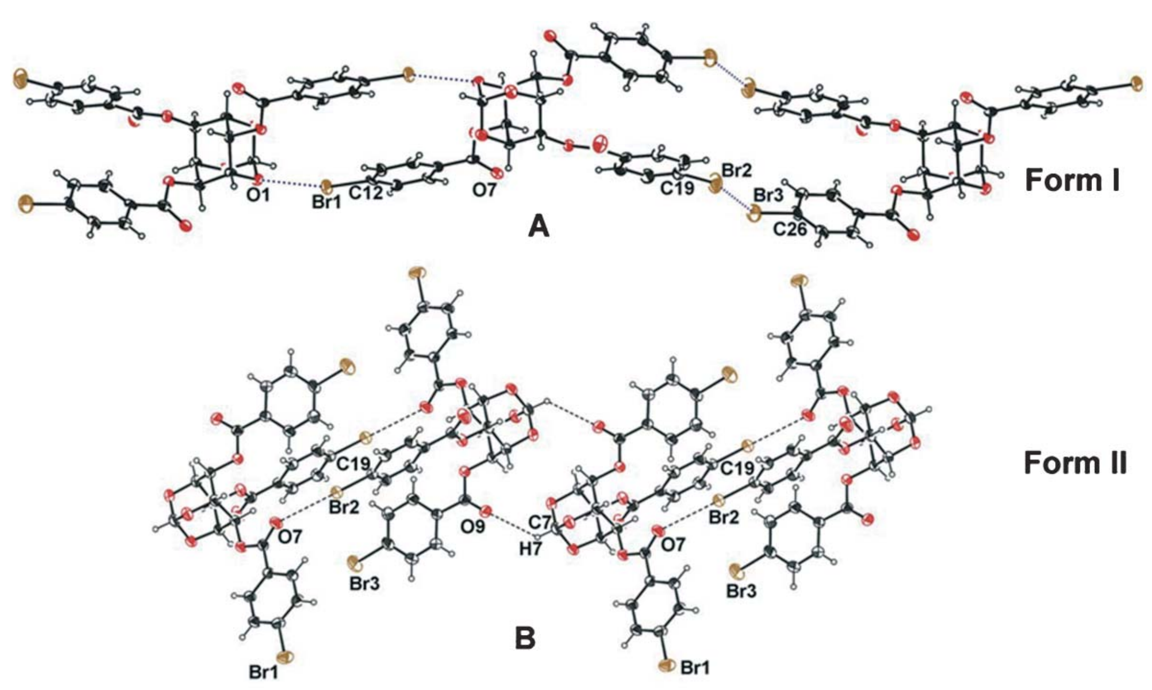

Fig. 3 ORTEP views depicting differences in the halogen bonding contacts. (A) Dimers making C12–Br1···O1(–C) contacts linked by Br2···Br3 interactions in Form I; (B) centrosymmetric association linked *via* C19–Br2···O7(=C) bridged by C7–H7···O9 bonds in Form II.

Form I crystals of **1** (cooled after heating up to the transition temperature 188 °C) contained only a melting endotherm at 198 °C, suggesting an irreversible phase transition of Form I. The DSC of Form II crystals of **1** showed a single peak representing melting of the crystal (Fig. 2B).

Single crystal X-ray studies were carried out on both the polymorphs of **1** and Form II crystals of **2**. The needles of **2** (Form I) were too thin and their yield too low for single crystal, or even X-ray powder diffraction measurements. Single crystal structure analysis§ revealed that molecules in both the forms of **1** make similar intermolecular interactions like Br···Br, C–H···π, C–H···O *etc.* but make different molecular networks. Relevant to the phase transition are molecules centrosymmetrically associated *via* 'halogen bonding' contacts[4] with a difference in the nature of the acceptor oxygen atom (Fig. 3). In Form I of **1**, the halogen bonding is between the C12–Br1 (of the C2-equatorial benzoyl group) and orthoformate bridge oxygen – O1, whereas in Form II the halogen bonding is between the C19–Br2 (of the C4-axial benzoyl group) and the carbonyl oxygen O7 (of the C2-equatorial benzoyl group). The Br···O distance is slightly shorter in Form I (3.027(3) Å) than in Form II (3.174(3) Å), but the ∠C–Br···O shows more linearity in Form II (173.8(3)°) than in Form I (163.4(5)°). The structure of Form II crystals of **2** is isomorphous to that of **1**, containing C–Cl···O=C contacts (Cl···O = 3.102(2) Å; ∠C–Cl···O = 166.5(3)°). In Form I, the halogen bonded dimeric unit is linked *via* Br2···Br3 short contacts (3.404(1) Å) with the next unit, whereas in Form II these units are linked by C7–H7···O9 contacts (Fig. 3, see supplementary information for detailed intermolecular interactions). Form I crystals of **1** (Fig. 4A) upon heating to ∼ 185–186 °C showed fragmentation transverse to the length of the needle (Fig. 4B), but each of the fragments observed under optical polarizing microscope confirmed its single crystalline nature. Interestingly, the unit cell parameters of one of the fragments mounted on the diffractometer revealed it to be crystals of Form II. Reproducibility of this irreversible crystal-to-crystal transition was confirmed by repeating this experiment on several Form I crystals of **1**. For the conversion of Form I to Form II crystals of **1**, the molecules linked *via* centrosymmetric Br2···Br3 contacts[7] (blue in Fig. 4) in Form I have to rearrange to make C19–Br2···O7 short contacts as in Form II (Fig. 3B). This would

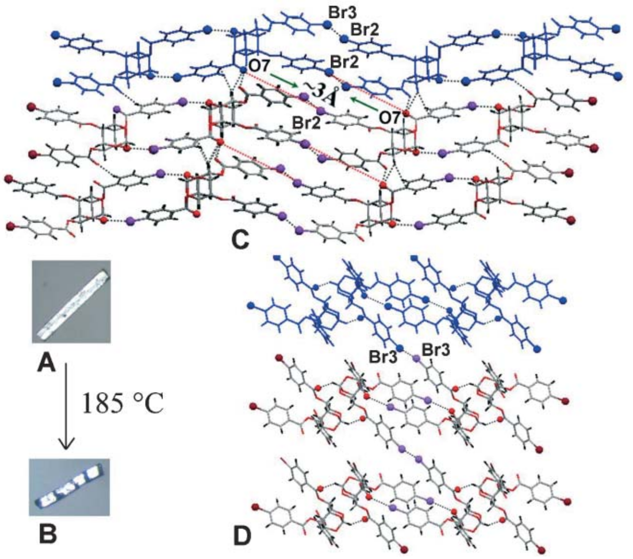

Fig. 4 Photomicrographs of Form I (A) before heating and (B) after heating of the crystal; view of molecular packing in (C) Form I and (D) Form II crystals of **1** down *b*-axis and *c*-axis respectively. The proposed molecular displacement is marked by green arrows in (C), contacts Br2···O7 to be formed are also shown.

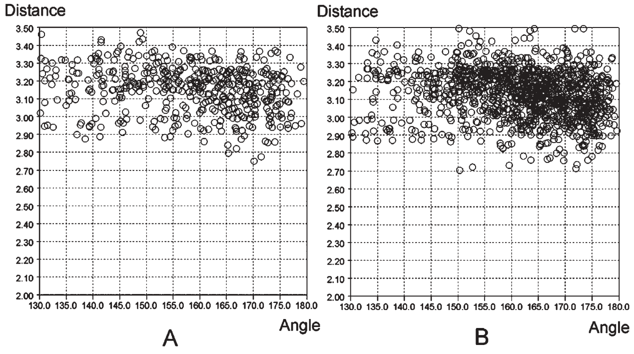

Fig. 5 Scatter plots of distance X···O (Å) *vs.* angle C–X···O (°) for (A) C–X···O–C and (B) C–X···O=C, X = Cl, Br, I.

involve the movement of molecules towards each other by ~ 3 Å (green arrows in Fig. 4C) with the molecule from the next dimeric ribbon with accompanying conformational changes in aromatic rings. The spontaneous fragmentation of the crystal could be the result of these large molecular movements making new interactions (*via* C–Br···O=C) while sacrificing Br2···Br3 and inter ribbon C–H···O interactions (Fig. 4C). It is remarkable that these structural changes occur without loss of single crystalline nature. This is in contrast to molecular movements in reversible phase transformations,[6] which involve minimum molecular movements and hence are restorable. The changes in the present transition are far too large and hence cannot regain the original positions of molecules.

The preference for halogen bonding involving O=C over that of O–C was revealed by a brief survey of the CSD (Fig. 5). The search included organic and organometallic compounds, the halogens selected were F, Cl, Br and I. The number of hits for halogen bonding contacts (all halogens combined) with C–halogen···O=C was much higher (1045) than for C–halogen···O–C contacts (411). In both types, the number of organic compounds is significantly more than the number of organometallic ones. Preferred directionality in halogen bonds C–X···O=C (Fig. 5B) compared to C–X···O–C (Fig. 5A) is evident (see supplementary information for details).¶

Almost competitive with conventional hydrogen bonding, 'halogen bonding' is receiving increasing attention due to its potential applications in designing functional solids.[4] This bonding is comparable in energy to conventional H-bonding interactions[8] and could even dominate them.[9] Its role in molecular aggregation and self assembly is also being increasingly noticed,[4] but its importance in the promotion of crystal growth was first reported by us.[10] We have shown here for the first time that differences in the halogen bonding bridges could lead to polymorphic modifications. The role of halogen bonding interactions in crystal growth is the subject of our further investigations.

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Notes and references

‡ Bromo and chloro derivatives **1** and **2** were prepared by the acylation of *myo*-inositol 1,3,5-orthoformate in pyridine with *p*-bromobenzoyl chloride and *p*-chlorobenzoyl chloride respectively. The triesters **1** (mp 196–197 °C) and **2** (mp 194–195 °C) exhibited spectroscopic (^{1}H and ^{13}C NMR) and microanalytical data consistent with their structures.

§ Crystal Data **1**, Form I: $C_{28}H_{19}O_9Br_3$, M = 739.16, Monoclinic, space group *C2/c*, a = 57.945(13), b = 6.0511(13), c = 15.465(3) Å, β = 103.469(4)°, V = 5273(2) Å^3, Z = 8, D_c = 1.862 g cm^{-3}, μ = 4.646 mm^{-1}, 18012 reflections collected, 4623 unique, 3261 observed [$I > 2\sigma(I)$] reflections, 361 refined parameters, S = 1.010, R value 0.0485, $wR2$ = 0.0973 (all data R = 0.0787, $wR2$ = 0.1074). Crystal Data 1, Form II: $C_{28}H_{19}O_9Br_3$, M = 739.16, Triclinic, space group *P-1*, a = 10.002(2), b = 12.126(2), c = 13.146(3) Å, α = 70.536(3), β = 80.100(3), γ = 68.503(3)°, V = 1396.5(5) Å^3, Z = 2, D_c = 1.758 g cm^{-3}, μ = 4.386 mm^{-1}, 13350 reflections collected, 4893 unique, 4105 observed [$I > 2\sigma(I)$] reflections, 380 refined parameters, S = 1.031, R value 0.0417, $wR2$ = 0.1055 (all data R = 0.0505, $wR2$ = 0.1113). Crystal Data **2**, Form II: $C_{28}H_{19}O_9Cl_3$, M = 605.78, Triclinic, space group *P-1*, a = 10.2740(17), b = 11.2899(18), c = 12.717(2) Å, α = 75.582(3), β = 86.976(3), γ = 68.503(3)°, V = 1328.0(4) Å^3, Z = 2, D_c = 1.515 g cm^{-3}, μ = 0.401 mm^{-1}, 9709 reflections collected, 4648 unique, 3362 observed [$I > 2\sigma(I)$] reflections, 361 refined parameters, S = 1.038, R value 0.0525, $wR2$ = 0.1374 (all data R = 0.0737, $wR2$ = 0.1495). CCDC 281351–281353. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b511754b

¶ The CSD search was carried out with CSD v5.26 (November 2004), constraints applied $R < 0.075$, distances $\leqslant$ sum of van der Waals radii and angles in the range 130–180°.

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