Synthon evolution and unit cell evolution during crystallisation. A study of symmetry-independent molecules ($Z' > 1$) in crystals of some hydroxy compounds†

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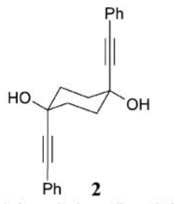
A kinetically favoured crystal, with many molecules in the asymmetric unit, may be a fossil relic of the crystal nucleus of a more stable polymorph.

The structural landscape[1] that is encountered during the crystallisation of a molecular solid from solvent could be considered to begin with solvated molecules, which associate *via* supramolecular synthons[2] to give growth units,[3] followed by nucleation and finally the appearance of metastable (kinetic) crystals that yield eventually to more stable (thermodynamic) polymorphs.[4] Many aspects of this process are still in the realm of conjecture, although there have been some attempts to monitor directly the early stages of crystallisation.[5] From the crystallographic viewpoint the very occasional appearance of large unit cells, possibly with solvent incorporated in the structure and the presence of multiple molecules in the asymmetric unit ($Z' > 1$) is reflective of 'frozen' or interrupted crystallisation.[6] Accordingly, the intermediate stages of crystallisation may be imaged directly with X-ray methods, because of the fortuitous appearance of crystals which are essentially metastable and represent high energy minima in the supramolecular reaction coordinate. In this communication, we report the polymorphism of pentafluorophenol, **1**, and *trans*-1,4-bis(phenylethynyl)cyclohexane-1,4-diol, **2**. In each case, one of the polymorphs has a high value of Z', the number of molecules in the asymmetric unit ($Z' = 3$ for **1** and $Z' = 8$ for **2**).

The appearance of high Z' crystal structures has been noted and discussed regularly.[7] The most recent account in this respect is by Steed,[8] who has made valuable comments on several aspects of the phenomenon. In particular Steed notes that "crystals form under non-equilibrium conditions and the observed structure may be readily viewed as a fossil relic of the fastest growing crystal nucleus rather than a thermodynamic minimum structure". Nangia and co-workers in a study of polymorphism of 4,4-diphenyl-2,5-cyclohexadienone have noted that "the two triclinic crystals present snapshot pictures at different stages of crystallization, from an evolving array of ordered molecules in many conformations (form C, $Z' = 12$) to a more compact lattice (form B, $Z' = 4$)".[9] The occurrence of high Z' structures among alcohols and phenols has been rationalised by Brock and Duncan;[10] we note that both our examples **1** and **2**, are hydroxy compounds. High Z' structures are often pseudosymmetric with the multiple molecules in the asymmetric unit being sometimes related to each other by local symmetry elements. The suggestion is that such crystals represent stages in a pathway towards more stable crystals where the symmetry is more neatly expressed.

1
Pentafluorophenol



2
trans-1,4-bis(Phenylethynyl)cyclohexane-1,4-diol

Liquid pentafluorophenol, **1**, (mp 307–309 K) was subjected to cryocrystallisation using equipment and techniques previously described.[11] The crystal structure (space group $P2_1/c$) is shown in Fig. 1 and has $Z' = 1$.‡ The structure (**1-L**) has an infinite O–H···O–H···O–H hydrogen bonded chain and is reminiscent of several other mono and dihydric phenols.[12] The packing closely follows the guidelines established by Brock and Duncan for these compounds.[10] The high Z' polymorph (**1-H**) was obtained during cryocrystallisation of a 1 : 1 mixture of **1** and pentafluoroaniline and is more curious; it has space group *Cc* and $Z' = 3$.‡ Very unusually, the three symmetry independent molecules are O–H···O hydrogen bonded in an isolated, discrete arrangement (Fig. 2). While closed O–H···O trimer synthons and helical O–H···O patterns around real and pseudo-3 and 3_1 axes are common in phenols,[13] we know of few other discrete O–H···O oligomers of the type seen in **1-H**.[14] The arrangement is terminated

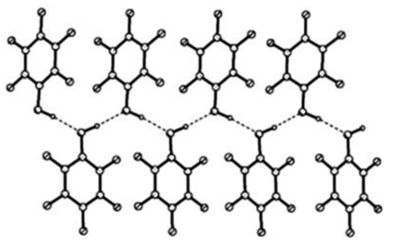


Fig. 1 Form **1-L** ($Z' = 1$) of pentafluorophenol. Note the infinite ···O–H···O–H···O–H··· pattern.

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† Electronic supplementary information (ESI) available: Ortep diagrams and other structures, crystallisation of polymorphs, thermal analysis of compound 2, hot stage microscopy for compound 2, thermal analysis for compound 1, table of lattice energies, table of cell parameters before and after minimization. See DOI: 10.1039/b514076e

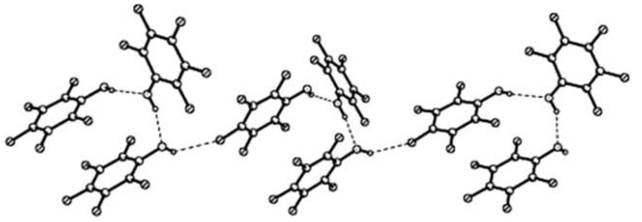

Fig. 2 Form **1-H** ($Z' = 3$) of pentafluorophenol with discrete O–H···O–H···O–H trimers. Note the weak O–H···F–C bridges.

with a co-operative O–H···F–C bridge but the stability conferred by this weak interaction is expected to be marginal.

Energy calculations (Cerius^2, Compass force field) for **1-L** (-85.4 kJ mol^{-1}) and **1-H** (-76.6 kJ mol^{-1}) show the high Z' structure to be the less stable. Energy differences of this magnitude are not uncommon in polymorphic systems.[15] From the structural viewpoint, the stability of **1-L** might have been expected because the advantage conferred by cooperativity in an infinite $(\text{O–H}\cdots\text{O–H}\cdots\text{O–H}\cdots)_n$ arrangement would be greater than in the isolated O–H···O–H···O–H···F–C arrangement in **1-H**.

The close structural relationship between forms **1-H** and **1-L** is seen in Fig. 3, which gives a possible mechanism of conversion of **1-H** to **1-L**. The figure shows discrete trimers along [100]. Translation along [100] of entire rows of trimers would connect the trimers with O–H···O bonds to give an infinite O–H···O chain of the type seen in **1-L**. While we have no experimental evidence for such a transformation of **1-H** to **1-L**,§ the packing similarities between the polymorphs, and their relative energies suggest that the infinite O–H···O synthon in **1-L** evolves through the discrete open O–H···O trimers as seen in **1-H**. The crystal structure of the less stable **1-H** is therefore a reasonable precursor of the more stable **1-L**. To use Steed's terminology,[8] **1-H** is a fossil relic of the crystal nucleus of **1-L**.

Diol **2**, was examined as part of a more extended study of *gem*-alkynols.[16] Two polymorphs **2-L** ($P\bar{1}$, $Z' = 2$) and **2-H** ($P\bar{1}$, $Z' = 8$) were obtained concomitantly from acetone. The packing of **2-L** is shown in Fig. 4.‡ One of the symmetry independent molecules occupies a general position while two half-molecules occupy distinct inversion centres making $Z' = 2$ overall. O–H···O hydrogen bonds are again dominant and the tetramer $(\text{O–H}\cdots\text{O})_4$ synthons are connected by cyclohexyl connectors to give a 4.8^2 net. The packing in **2-H** is virtually the same as observed for **2-L**† but instead of one molecule on a general position, there are six, and instead of two half-molecules on special positions there are four making $Z' = 8$ overall.‡ Essentially, there are small conformational and translational variations among the molecules† but the unit cell volume is effectively increased fourfold.

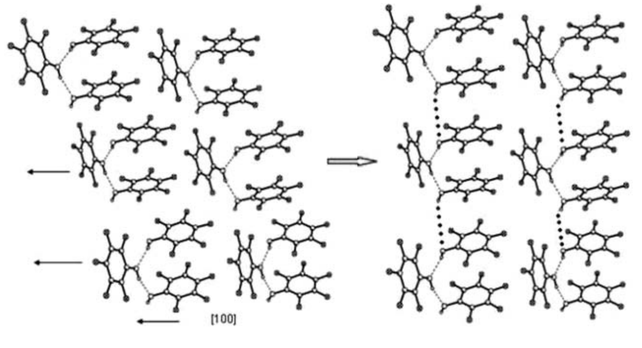

Fig. 3 A mechanism for synthon evolution, **1-H** → **1-L**. Shearing of trimers along [100] would form the putative O–H···O bonds shown in bold, completing the infinite $(\text{O–H}\cdots\text{O–H}\cdots)_n$ chain which is characteristic of **1-L**.

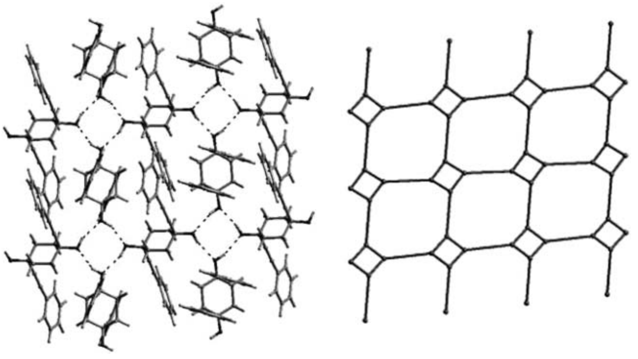

Fig. 4 Form **2-L** ($Z' = 2$) of *trans*-1,4-bis(phenylethynyl)cyclohexane-1,4-diol. Notice the $(\text{O–H}\cdots\text{O})_4$ square synthon and the 4.8^2 network.

A key concept in this study is that the higher Z' structure in a pair of polymorphs represents a high energy metastable intermediate en route to the crystallisation of the lower Z' structure. This was demonstrated experimentally for **2-L** and **2-H**. Crystals of **2-L** were grown routinely by crystallisation from acetone. When these were heated, DSC showed that melting occurs normally at 456 K with no other event (Fig. 5). When the melt was cooled, a crystallisation exotherm was observed at 389 K. When the cooled melt was reheated, a solid state phase transformation was observed at 389 K. A single crystal from the cooled melt was studied on the diffractometer and shown to be the high Z' polymorph **2-H**.¶ Accordingly, we conclude that cooling of the melt produces **2-H** which reconverts back to **2-L** upon heating. This behaviour was also monitored on the hot stage microscope wherein the solid state transformation **2-H**→**2-L** could be clearly observed (Fig. 6). These observations are very typical of dimorphic systems in that the higher energy metastable dimorph (here, **2-H**) is obtained by what is essentially rapid cooling of the melt of the stable dimorph (here, **2-L**).[17]

Accordingly, one might consider these dimorphs as defining the reaction coordinate in the crystallisation process, and say further that a larger unit cell in the initial stages of the process evolves to the smaller, final cell as crystallisation is completed with a decrease in the variation amongst the molecular conformations.

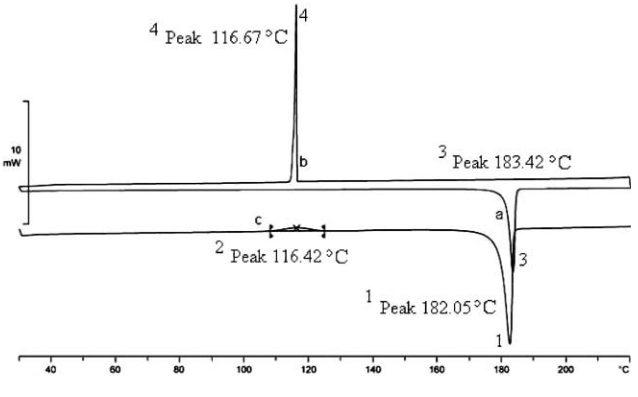

Fig. 5 DSC traces to show (a) the melting endotherm of **2-L** at 456 K; (b) crystallisation exotherm of **2-H** from the melt at 389 K; (c) solid state phase transformation of **2-H**→**2-L** at 389 K.

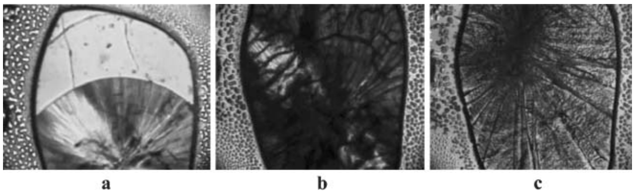

Fig. 6 (a) Crystallisation of the high Z' polymorph **2-H** from the melt obtained by heating the low Z' polymorph **2-L** of compound **2** to its melting temperature of 456 K. Crystallisation occurs at 369 K; (b) Solid state transformation **2-H**→**2-L** at 392 K. The **2-L** material obtained is amorphous (dark regions); (c) Solid state crystallisation of crystalline **2-L** from amorphous **2-L** at 407 K.[‖]

We searched the CSD (version 5.26, May 2005) for occurrences of high Z' values among substances known to be polymorphic. Sets of polymorphs were selected so that at least one structure has $Z' \geqslant 3$; 60 such sets were obtained. In seven of these sets, the space group had been mis-assigned for at least one compound.[18] The 53 surviving sets were examined for their synthon content and 18 sets were selected wherein the synthons and/or the one-dimensional structural patterns in the crystal structures of the polymorphs are similar. For these 18 sets of polymorphs, energy calculations were carried out with the Dreiding 2.21 force field. To assess the quality of the force field in these calculations, only those compounds were further considered in which the experimental and calculated unit cell dimensions differed by less than 5%. In this way, one set of refcodes was eliminated leaving 17 sets. The results are given in the Supplementary Information[†] and show that in eleven cases, the lower Z' structure has the lower energy. In two cases, the polymorphs are equi-energetic while in four cases, the lower Z' structure has the higher energy. These numbers are suggestive of a scenario wherein the higher Z' structure corresponds to a less stable, kinetically formed structure while the lower Z' structure is closer to the thermodynamic form.

To conclude, data on the two compounds reported by us in this communication allow one to suggest that these high Z' structures represent high energy minima in the crystallisation pathway towards the final thermodynamic crystal, providing valuable insights into the evolution of synthons and unit cells during crystallisation. It is suggested that synthons evolve earlier than unit cells: this indicates the primary role of supramolecular synthons and their related growth units in the crystallisation process.

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Notes and references

[‡] X-ray data of **1-H**, **1-L** were collected on a Siemens SMART CCD area detector at 292(2)K and 269(2)K. *Crystal Data*: **1-H**: (C_6HF_5O), M = 184.07, monoclinic, a = 21.300(4), b = 5.7697(12), c = 16.796(3) Å, β = 114.68(3)°, V = 1875.5(7) Å^3, space group Cc, Z = 12, μ (Mo-K$_\alpha$) = 0.230 mm^{-1}, size 0.30 × 0.30 × 0.30 mm. 3432 total reflections, 1966 independent, 1416 observed. 328 parameters, R_1 [$I > 2\sigma(I)$] = 0.0400; **1-L**: (C_6HF_5O), M = 184.07, monoclinic, a = 13.073(3), b = 4.9295(10), c = 10.163(2) Å, β = 107.31(3)°, V = 625.2(2) Å^3, space group $P2_1/c$, Z = 4, μ (Mo-K$_\alpha$) = 0.230 mm^{-1}, size 0.30 × 0.30 × 0.30 mm. 2012 total reflections, 1199 independent, 777 observed. 109 parameters, R_1 [$I > 2\sigma(I)$] = 0.0388. X-ray data for **2-L** and **2-H** were collected on a Bruker SMART 1K-CCD area detector at 120(2)K. *Crystal Data*: **2-L**: ($C_{22}H_{20}O_2$), M = 316.38, triclinic, a = 9.4940(3), b = 14.0677(5), c = 14.4606(5) Å, α = 95.625(2), β = 106.478(1), γ = 104.627(2)°, V = 1761.79(10) Å^3, space group $P\bar{1}$, Z = 4, μ (Mo-K$_\alpha$) = 0.075 mm^{-1}, size 0.36 × 0.34 × 0.16 mm. 20278 total reflections, 8067 independent, 5523 observed. 444 parameters, R_1 [$I > 2\sigma(I)$] = 0.0634. **2-H**: ($C_{22}H_{20}O_2$), M = 316.38, triclinic, a = 17.6377(8), b = 18.8315(9), c = 23.3591(11) Å, α = 78.402(2), β = 88.367(2), γ = 67.611(2)°, V = 7017.4(6) Å^3, space group $P\bar{1}$, Z = 16, μ (Mo-K$_\alpha$) = 0.075 mm^{-1}, size 0.28 × 0.24 × 0.14 mm. 95843 total reflections, 32149 independent, 16870 observed. 1784 parameters, R_1 [$I > 2\sigma(I)$] = 0.0549. **2-H-neutron** ($C_{22}H_{20}O_2$), M = 316.38, triclinic, a = 17.6377(8), b = 18.8315(9), c = 23.3591(11) Å, α = 78.402(2), β = 88.367(2), γ = 67.611(2)°, V = 7017.4(6) Å^3, space group $P\bar{1}$, Z = 16, T = 20 K, size 1.2 × 0.85 × 0.20 mm. 51904 total reflections, 13238 independent, 6142 observed. 1409 parameters, R_1 (isotropic) [$I > 2\sigma(I)$] = 0.1392. CCDC 283828–283832. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b514076e

[§] It is always possible that a metastable kinetic polymorph dissolves and crystallises as a more stable form. DSC runs between 223 K and 323 K on pentafluorophenol, pentafluoroaniline and a 1 : 1 mixture do not show any evidence of form **1-H**, although there is evidence of another (enantiotropic) polymorph of **1-L**. See Supplementary Information.[†]

[¶] The unit cell obtained was a = 17.637(5), b = 18.828(6), c = 23.392(8) Å, α = 78.36(1), β = 88.36(1), γ = 67.73(1)°, V = 7030.9(6) Å^3 and the refinement of the data collected at 100 K proceeded uneventfully to an R value of 0.082.

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