Crystallography

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Polymorphism in Benzamide**

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One of the major challenges of solid-state chemistry in the early 21st century is, without doubt, the understanding of the structural, thermodynamic, and kinetic factors associated with the crystallization of molecular compounds. Our limited ability to predict and control the appearance of desirable crystal phases of molecular materials has a major and lasting impact on both technological and commercial progress in the fields of pharmaceuticals, health care, specialty chemicals, and optoelectronics. Although there have been major advances in the field over recent years (in terms of strategies for structure prediction and nucleation control), apparently simple systems such as benzamide sometimes present seemingly intractable problems. In their seminal paper of 1832, Wöhler and Liebig[1] described how slow cooling of a "boiling hot" aqueous solution of benzamide resulted in solidification of the liquid in a white mass of silky needles (Figure 1 a). They noted that the transformation of this mass gave a few well-formed rhombic crystals (Figure 1 b,c) and identified this process as a phase transformation. This stable, rhombic form of benzamide has been widely studied over the years and its monoclinic crystal structure was first determined in 1959 by using single-crystal X-ray diffraction.[2–4] In contrast, the very existence of a metastable form appears to have been largely forgotten. In 1904, Mohr [5] performed some microscopic studies and Penfold and White[2] made a fleeting reference to it in 1959 but otherwise, probably as a result of its highly metastable nature,[6] it has not received any serious attention. The "plaitlike" fibrous intertwining of the birefringent, metastable crystals shown in Figure 1 a, suggests a high degree of strain and structural disorder at the molecular level. Figure 1 d reveals the possibility of a direct solid-state transformation between the two forms and gives an initial indication that the needle axis is related to the monoclinic *b* axis of the known stable structure.

With the availability of third-generation synchrotron sources, it is now possible to record diffraction data sufficiently quickly to determine the structures of transient species through powder-diffraction analysis, even in the presence of solvents and other crystalline phases. To this end, we performed a series of X-ray powder diffraction (XRPD) experiments on beamline ID31 at the European Synchrotron Radiation Facility in Grenoble, France. A hot aqueous solution of benzamide (0.347 M) was loaded into a glass capillary (1.5 mm), which was flame-sealed at both ends. The capillary was first warmed to ensure complete dissolution of the solid, cooled to 20 °C, and mounted on the goniometer of the diffractometer. The capillary was then rotated at 2 kHz to minimize the effects of the preferred orientation, and an incident wavelength of 0.8 Å was applied. Although the resulting XRPD pattern was dominated by the known monoclinic form, a small quantity of a new form was also observed. Through the use of a more-dilute aqueous solution of benzamide (0.173 M), cooled in situ on the diffractometer to 2 °C and then flash cooled through brief contact with a cotton bud soaked in liquid nitrogen, a substantial increase in the relative proportion of the new form was obtained; it was not possible to eliminate the known monoclinic form completely. This new form persisted for over 60 min, and the XRPD patterns collected during this period allowed the identification of just twelve diffraction peak positions that are attributable to the new form. These were indexed by using the program DICVOL91[7] to give an orthorhombic unit cell ($a = 17.4322$, $b = 14.1937$, $c = 4.9773$ Å) with excellent figures

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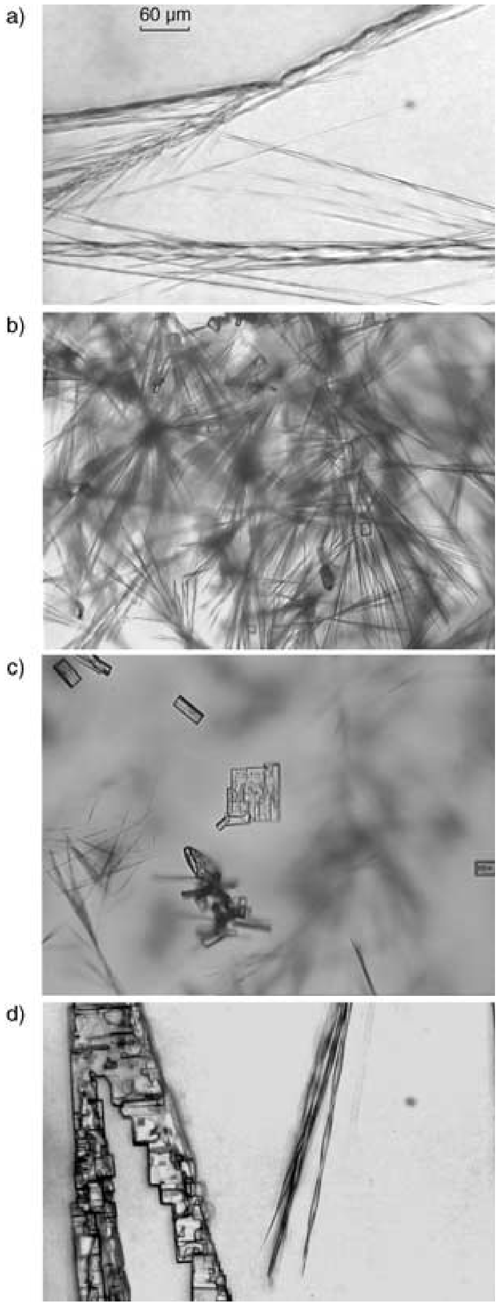

Figure 1. a) Needlelike plaits of the metastable form of benzamide in aqueous solution at room temperature. b) An aqueous suspension of needles taken 30 s after crystallization, and c) the same sample 60 s after crystallization shows the solution-mediated transformation of the needles to the stable form. d) An aggregate of stable monoclinic crystals (left) and a plait of needles (right). The individual crystals of the monoclinic aggregate are all aligned with their *b* axes along its length.[11] As this aggregate originated from the solid-state transformation of a metastable needle, it is reasonable to deduce that the directions of elongation in both forms share a common structural motif. In all photos the scale can be judged from the diameter of a needle, which (as seen from the 60-μm scale bar in a)) is about 30-μm in all cases.

of merit,[8] $M(12) = 63.6$ and $F(12) = 156.3$. The unit cell volume was 1231.52 Å^3, which is slightly less than double that of the monoclinic form (624.25 Å^3) and suggests, unusually, that the metastable form is denser than the stable form. A probabilistic analysis of the extracted reflection intensities, obtained by using the program DASH,[9] identified the most likely extinction symbol to be *Pba-* (the log-likelihood gain of *Pba-* over *P---* was 7.4), which corresponds to space group *Pba*2 or *Pbam*. The centrosymmetric space group *Pbam* was initially chosen as the most likely candidate for the crystal structure as it results in the presence of only one molecule in the asymmetric unit. Structure determination was performed by global-optimization methods by using DASH, and the molecular geometry of the benzamide molecule (excluding the torsion-angle value for the single rotation of the amide group relative to the benzene ring) was taken from the known crystal structure. However, no satisfactory solutions were found in this space group, either from the point of view of profile fitting or crystal packing. Indeed, the best Rietveld χ^2 value in *Pbam* was 254.0, which is very poor when compared with the Pawley χ^2 value of 4.0. Accordingly, structure determination was then performed in the noncentrosymmetric space group *Pba*2, which requires the use of two crystallographically independent benzamide molecules in the asymmetric unit. Ten independent global-optimization runs were conducted, and in eight of the ten attempts, the same excellent fit to the data was obtained with a Rietveld χ^2 value of 6.30, which is very close to the Pawley χ^2 value. Promisingly, the crystal structure that corresponds to these runs exhibited good packing and formation of favorable hydrogen bonds. To obtain reliable structural coordinates from the multiphase XRPD pattern, restrained refinement of the structure of the orthorhombic form was performed simultaneously with refinement of the structure of the known monoclinic form and the solvent background structure. The final Rietveld refinement of the crystal structure was performed with the program TOPAS[10] (refinement details are given in Table 1). The two independent benzamide molecules, which form a dimer in the structure, were modeled by using a constrained Z-matrix description for each molecule. Bond-length and planarity restraints were employed to maintain the dimer

Table 1: Rietveld refinement details for the XRPD data obtained at room temperature.

	Mixed-phase refinement	
	Orthorhombic component	Monoclinic component
a [Å]	17.4317(2)	5.607
b [Å]	14.1944(3)	5.0394
c [Å]	4.977(1)	22.0930
β [°]	–	90.626
V [Å^3]	1231.4(3)	624.25
space group	*Pba*2	*P*2$_1$/*c*
Z	8	4
Z′	2	1
reflections	187	151
phase fraction	17.3(2)	82.7(2)
data range 2*θ* [°]	2–27.97	
number of data points	8657	
R_e (background subtracted)	8.43	
R_{wp} (background subtracted)	13.24	
zero point	−0.0039	

geometry. Separate isotropic temperature factors for each molecule were required to obtain an adequate structural refinement. The final fit between the observed and calculated diffraction patterns is shown in Figure 2, and the figures of merit ($R_{exp} = 8.4\,\%$ and $R_{wp} = 13.2\,\%$, background subtracted) confirm the excellent fit obtained. The sample was found to be comprised of approximately 20 % monoclinic form and 80 % orthorhombic form. A (001) projection of the resultant metastable orthorhombic crystal structure is shown in Figure 3 a, with the corresponding (010) projection of the stable monoclinic form shown for comparison (Figure 3 b). The intermolecular interactions perpendicular to the plane are essentially identical in both structures and confirm the evidence from optical microscopy for a common major-growth direction for both forms (Figure 1 d); the needle axis of the metastable form is, therefore, along the short [001] direction, which was anticipated from basic crystal morphology arguments.[11] Anisotropic broadening of the Bragg peaks in the powder diffraction pattern also indicates that the needle axis of the metastable structure is along the c axis. This is indicated in Figure 4, where it can be seen that the (001) reflection is substantially broader than the other peaks at similar 2θ values. Interestingly, the 2θ dependence of the anisotropic broadening refinement indicates that the origin of the broadening is dominated not by size but rather by strain effects—the plaitlike habit is caused by strain effects that are predominantly associated with the needle direction in which the root-mean-square strain $\Delta d/d$, measured from the anomalous peak width, is approximately 0.004. Furthermore, the constrained refinement of the crystal structure revealed that the isotropic temperature factor for one of the molecules was anomalously large ($B = 12.4(3)$ Å^2, the other value being 4.3(3) Å^2), which is consistent with substantial structural disorder. Thus, the plaitlike morphology appears to be associated with the static disorder of only one of the molecules in the asymmetric unit. The XRPD data are of insufficient quality to allow a more-detailed characterization of the disorder beyond that of the initial observations.

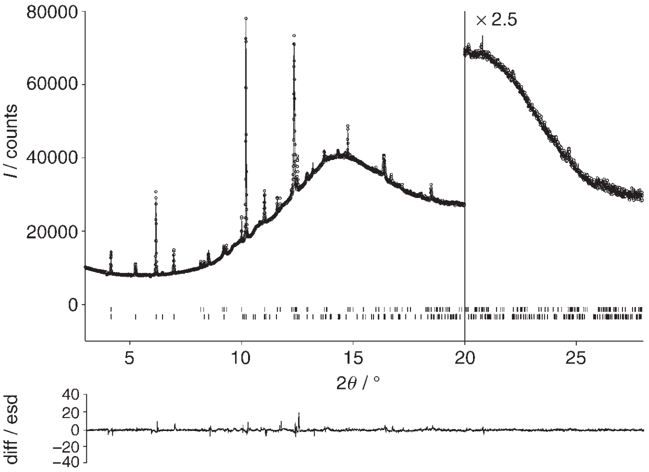

Figure 2. The powder X-ray diffraction pattern shows the excellent fit between the observed and calculated data based upon a two-phase refinement. The upper and lower tick marks indicate the positions of the Bragg reflections in the monoclinic and orthorhombic forms, respectively. The large background is a result of the water that surrounds the benzamide crystallites in the capillary. The y axis for the region beyond $2\theta = 20°$ is expanded by a factor of 2.5 for clarity. A difference over estimated standard deviation (esd) plot for the fit to the data is also shown.

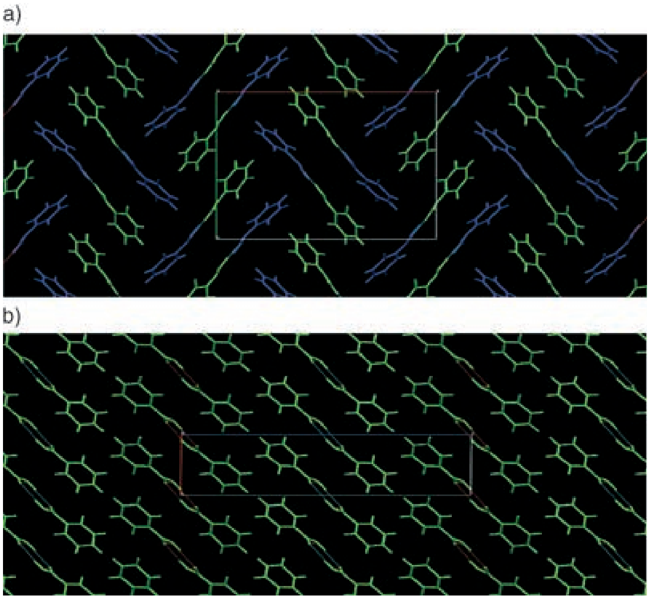

Figure 3. a) A projection of the orthorhombic needle structure looking along [001]. b) A projection of the stable monoclinic structure looking along [010]. In both cases, the views are along hydrogen-bonded ribbons that comprise molecular dimers. The transformation from one form to the other can conserve these ribbon directions and only involve the rearrangement of ribbons in the plane of the pictures. Symmetry-related molecules are shown in identical colors.

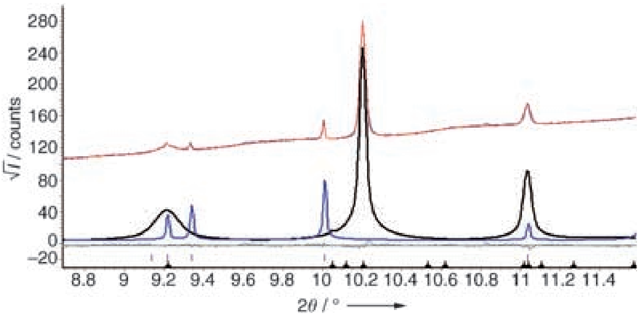

Figure 4. A section of the powder X-ray diffraction pattern that shows the excellent fit between the observed and calculated data based upon a two-phase refinement. The blue line and upper set of tick marks show the contribution of the monoclinic form to this portion of the diffraction pattern; the black line and the lower tick marks show the contribution of the orthorhombic form. The severe anisotropic line broadening in the orthorhombic form is clearly visible in the (001) reflection at just over $2\theta = 9.2°$.

The concomitant appearance of two distinct crystalline polymorphs of benzamide highlights the delicate balance that can exist between kinetics and thermodynamics in the appearance of polymorphic forms. The needlelike habit of the metastable form reflects rapid, uniaxial crystal growth with the molecular disorder possibly driving the formation of fibrous, plaitlike aggregates. At the same time, the complex *ab* plane packing in the metastable form leads to a smaller specific volume than that of the stable monoclinic form, which is more energetically favorable. Furthermore, the entropic factors also favor structural disorder at higher temperatures. From these morphological and thermodynamic arguments, it is not surprising that the metastable structure grows rapidly at first. The subsequent rapid interconversion from metastable to stable polymorph, although clearly facilitated by the preservation of dimer ribbons along the fast-growth axes and their facile rearrangement within the *ab* orthorhombic plane, implies that overall the monoclinic form is significantly more stable than the orthorhombic modification.

Thus, 173 years after the discovery of the first polymorphic molecular crystal, benzamide, by Wöhler and Liebig,[1]the crystal structure of the metastable form has been determined from an in situ synchrotron XRPD experiment. A comparison of the metastable and stable structures provides an explanation not only for the mechanism of transformation but also for the initial rapid crystallization of the metastable structure. The research methods outlined herein are of general applicability to the area of polymorphism and phase transformations, and offer the prospect of the determination of relationships and transformations in numerous polymorphic systems, especially in cases in which metastable states are of a transitory nature.

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