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Variable-Temperature Powder X-ray Diffraction of Aromatic Carboxylic Acid and Carboxamide Cocrystals

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Abstract: The effect of temperature on the cocrystallization of benzoic acid (BA), pentafluorobenzoic acid (FBA), benzamide (BAm), and pentafluorobenzamide (FBAm) is examined in the solid state. BA and FBA formed a 1:1 complex **1** at ambient temperature by grinding with a mortar and pestle. Grinding FBA and BAm together resulted in partial conversion into the 1:1 adduct **2** at 28 °C and complete transformation into the product cocrystal at 78 °C. Further heating (80–100 °C) and then cooling to room temperature gave a different powder pattern from that of **2**. BAm and FBAm hardly reacted at ambient temperature, but they afforded the 1:1 cocrystal **3** by melt cocrystallization at 110–115 °C. Both BA+FBAm (**4**) and BA+BAm (**5**) reacted to give new crystalline phases upon heating, but the structures of these products could not be determined owing to a lack of diffraction-quality single crystals. The stronger COOH and $CONH_2$ hydrogen-bonding groups of FBA and FBAm yielded the equimolar cocrystal **6** at room temperature, and heating of these solids to 90–100 °C gave a new crystalline phase. The X-ray crystal structures of **1**, **2**, **3**, and **6** are sustained by the acid–acid/amide–amide homosynthons or acid–amide heterosynthon, with additional stabilization from phenyl–perfluorophenyl stacking in **1** and **3**. The temperature required for complete transformation into the cocrystal was monitored by in situ variable-temperature powder X-ray diffraction (VT-PXRD), and formation of the cocrystal was confirmed by matching the experimental peak profile with the simulated diffraction pattern. The reactivity of H-bonding groups and the temperature for cocrystallization are in good agreement with the donor and acceptor strengths of the COOH and $CONH_2$ groups. It was necessary to determine the exact temperature range for quantitative cocrystallization in each case because excessive heating caused undesirable phase transitions.

Keywords: carboxamides · carboxylic acids · cocrystals · grinding · hydrogen bonds

Introduction

Molecular complexes and molecular compounds have been studied by chemical crystallographers for over a century.[1] There is a resurgence of interest in multicomponent solid-state assemblies[2] under the banner of a new name, cocrystals. A cocrystal may be defined as the crystalline adduct between two neutral molecules held together by hydrogen bonds.[3] The definition of a cocrystal is flexible: it not only accommodates solvent (liquid) or gas as the second component, but the structure may be assembled through intermolecular interactions other than H bonds, for example, halogen bonds,[4] π–π stacking,[5] and ionic salts.[6] Broadly speaking, a cocrystal is a multicomponent solid-state assembly of two or more molecules mediated by any type or combination of intermolecular interactions. The most common method for obtaining cocrystals is to dissolve the components in a suitable solvent system for single crystals of the binary phase to appear after slow evaporation of the solvent(s). Gentle warming is necessary to dissolve the components, and an antisolvent is added to accelerate the crystallization. This empirical, trial-and-error method, referred to as solution crystallization, is repeated with several solvents until there is evidence of a new crystalline entity. Precipitation of the individual components instead of the desired co-

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crystal and formation of undesired solvates/hydrates are common difficulties in the solution-based approach. The classical method of preparing cocrystals is by solid-state grinding.[7] Despite its simplicity, a major drawback of the grinding method is that the product solid is usually too small in particle size to be amenable for routine structure determination by X-ray diffraction. Recently, the addition of a few drops of solvent, popularly known as solvent-drop grinding or kneading,[8] is demonstrated as a green-chemistry approach to crystal synthesis. Cocrystals represent a new paradigm in crystal engineering:[3a,8c] they are important in pharmaceutical formulation for developing improved medicines,[9] and attempted cocrystallization has led to the discovery of aspirin and maleic acid polymorphs.[10] The development of solvent-free crystallization methods is industrially advantageous because evaporation of the solvent(s) in bulk quantity is difficult and environmentally toxic.

In some of our ongoing cocrystallization studies,[11] we observed cases of partial conversion into the product along with unreacted starting material based on powder X-ray diffraction (PXRD), IR spectroscopy, and differential scanning calorimetry (DSC) analysis. As a rule of thumb, there is a twofold increase in the reaction rate for every 10 °C increase in temperature in molecular collisions with a typical activation energy of 10–20 $\mathrm{kcal\,mol^{-1}}$.[12] As the energy of strong H bonds is in the same energy range, and cocrystallization is nothing but the breaking of H bonds in the starting components (A···A, B···B) to form new, stronger H bonds in the adduct (A···B), we surmised that heating the unreacted solids or the mixture of starting components and product cocrystal should result in complete conversion into the binary adduct.

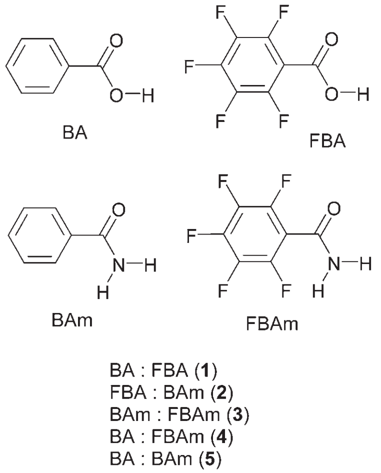
Trask and Jones[8c] provided a historical overview and surveyed the current status of the solid-state grinding approach. Heating is known to promote the reaction between solids that are sluggish or inert at room temperature,[13] but a proper understanding of the factors that influence successful grinding is still lacking. For example, adenine and thiamine formed a cocrystal after 20 min of grinding, but guanine and cytosine showed no product after grinding and heating for up to 7 days, despite the extra number of hydrogen bonds in the latter cocrystal. Whereas cocrystallization was activated by heating in a few cases,[8c] the role of temperature in accelerating cocrystallization has to our knowledge not been systematically studied by in situ powder X-ray diffraction. The molecules selected for this study were benzoic acid (BA), pentafluorobenzoic acid (FBA), benzamide (BAm), and pentafluorobenzamide (FBAm). The reactivity of H-bonding functional groups is significantly altered by the C_6H_5 and C_6F_5 groups; moreover, the prototype acid–acid and amide–amide homosynthons and acid–amide heterosynthon are well-known H-bonding motifs.[14] The temperature for complete cocrystallization was monitored by variable-temperature powder X-ray diffraction (VT-PXRD), and the solids were characterized by single-crystal X-ray diffraction, PXRD pattern match, and melting points (DSC).

Abstract in Hindi:

घन अवस्था मे बेंज़ोइक एसीड (BA) और पेंटाफलौरो बेंज़ोइक एसीड के सहस्फ़टीकीकरण पर तापमान के असर का अध्ययन कीया गया। BA और FBA को सामान्य तापमान पर खल्दस्ते से पीसने के बाद 1:1 सहस्फ़टीक बना। FBA ओर BAM को साथ मे पीसने से 1:1 सहस्फ़टीक (**2**) मे 28 °C पे आंशकि परीवर्तन ओर 78 °C मे संपूरण परीवर्तन हुआ, जीसे और गरम कर के सामान्य तापमान पे ठंडा करने से **2** से अलग PXRD मीली। BAm और FBAm सामान्य तापमान पे मुश्कील से प्रकरि्या करते है लेकनि 110-115 °C पर गलन सहस्फ़टीकीकरण द्वारा 1:1 सह स्फ़टीक बनाते है। BA + FBAm (**4**) और BA + BAm (**5**) दोनो ही गरम करने पर प्रकरि्या करके नया स्फ़टीकी रूप बनाते है लेकिन वीवर्तन के अनुरूप स्फ़टीक नही मीलने से उसका बंधारण तय नही कीया जा सका। FBA और FBAm के मज़बूत हायड्रोजन बंधक समूह COOH और $CONH_2$ के कारण वह सामान्य तापमान पे ही 1:1 सहस्फ़टीक (**6**) बनाते है जीसको 90-100 °C पर गरम करने से वह नये स्फ़टीकी रूप मे परीवर्तीत होता है। क्ष-कीरण स्फ़टीक बंधारण 1, **2**, **3** और **6** एसीड-एसीड/ एमाइड-एमाइड होमोसीनथोन या एसीड-एमाइड हेटेरोसीनथोन द्वारा जकड़े हुए हैं एवं 1 और **3** फ़ीनायल-परफ्लोरोफ़ीनायल स्टेकींग द्वारा अतरिक्ति स्थीरता पाते हैं। सहस्फ़टीक मे संपूरण रूपांतर के लीये ज़रूरी तापमान का चलित-तापमान पावडर क्ष-कीरण वीवर्तन (VT-PXRD) द्वारा कीया गया और सहस्फ़टीक का गठन प्रायोगीक PXRD और अनुमानित PXRD के साथ तुलना करके प्रमाणीत कीया गया। हायड्रोजन बंधक समूह की तीव्रता और सहस्फ़टीकीकरण के तापमान का COOH एवं $CONH_2$ समूह की दाता और स्वीकार्य शक्ती के साथ अच्छा तालमेल देखा गया। हर सहसफ़टीकीकरण प्रयोग मे ठीक तापमान नीरधारीत करना आवश्यक है क्योकी अत्याधीक गर्मी से रूप परीवर्तन होता है।

Results

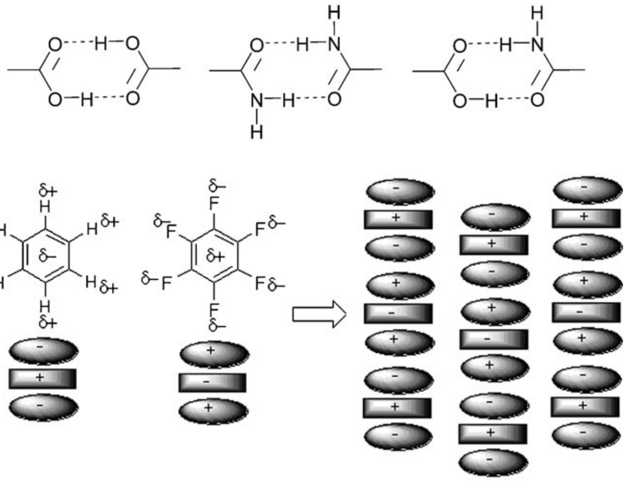
The four starting components can produce up to six molecular adducts of equimolar stoichiometry (Scheme 1), excluding solvates, hydrates, cocrystals of different stoichiometry,



BA : FBA (**1**)
FBA : BAm (**2**)
BAm : FBAm (**3**)
BA : FBAm (**4**)
BA : BAm (**5**)
FBA : FBAm (**6**)

Scheme 1. Six cocrystals of the starting components. The stoichiometry is 1:1 for **1**, **2**, **3**, and **6**.

and polymorphs. These molecules were selected to optimize hydrogen bonding through homo- and heterosynthons as well as phenyl–perfluorophenyl (Ph^F) stacking interactions. The Ph−Ph^F synthon, stabilized by quadrupole–quadrupole interactions,[15] has an energy of 4–5 kcal mol^{-1} at an inter-ring separation of 3.6–3.7 Å (Scheme 2).[16] The acid–acid/amide–amide homosynthon and acid–amide heterosynthon



Scheme 2. The acid–acid, amide–amide, acid–amide, and phenyl–perfluorophenyl stacking synthons.

have bond strengths of 12–15 kcal mol^{-1} for the dimer motif.[17] The C_6F_5 group not only promotes aromatic stacking with the C_6H_5 ring but also increases the H-bond-donor strength of COOH and $CONH_2$ groups owing to its electron-withdrawing nature. We analyzed X-ray crystal structures of the 1:1 cocrystals, BA·FBA (**1**), FBA·BAm (**2**), and BAm·FBAm (**3**), in a preliminary study.[18] The main supramolecular interactions in these crystal structures are the phenyl–perfluorophenyl stacking and O−H···O and N−H···O hydrogen bonds. Figure 1 shows salient H-bonding and stacking interactions in crystal structures **1**–**3**. Single crystals of BA·FBAm (**4**), BA·BAm (**5**), and FBA·FBAm (**6**) could not be obtained at that time. The X-ray crystal structure of the perfluorinated cocrystal **6** is reported herein. These single crystals were obtained by the solution-crystallization method. We have now prepared the above cocrystals by solid-state grinding and determined the temperature for cocrystal formation by in situ VT-PXRD. We show herein that it is necessary to know the correct temperature for optimal cocrystallization within a 5–10 °C range because excessive heating can cause transformation into amorphous or polymorphic phases.

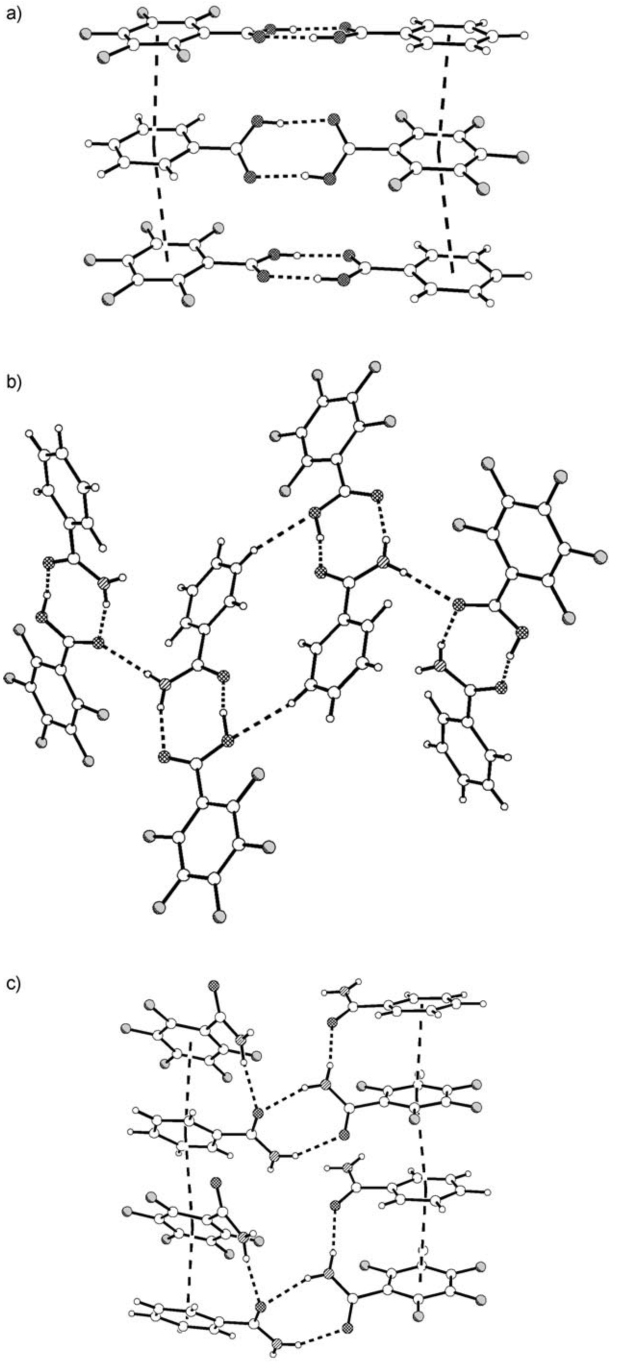


Figure 1. Crystal structures of **1**–**3**. a) Acid–acid homosynthon of O−H···O hydrogen bonds in **1** (1.63–1.68 Å) and π–π stacking (3.81, 3.84, 3.95, 3.97 Å) between Ph and Ph^F rings. There are two molecules of each component in the asymmetric unit. b) Acid–amide heterosynthon in **2** (N−H···O 2.02 Å, O−H···O 1.51 Å). Ph−Ph^F stacking is not so significant. c) Amide–amide homosynthon of N−H···O hydrogen bonds (1.94–2.16 Å) and Ph−Ph^F stacking (3.66, 3.71 Å) in **3**. H atoms are shown as small circles and F as large gray circles. Ph−Ph^F stacking columns are present in structures **1** and **3**.

BA·FBA (1)

Benzoic acid and pentafluorobenzoic acid (1:1) were ground together for 10 min with a mortar and pestle. PXRD showed that cocrystallization between BA and FBA was complete: there are no peaks corresponding to the individual components and there is evidence of a new phase (Figure 2a). There are peaks corresponding to cocrystal **1** but none for the pure components, for example, the diagnostic

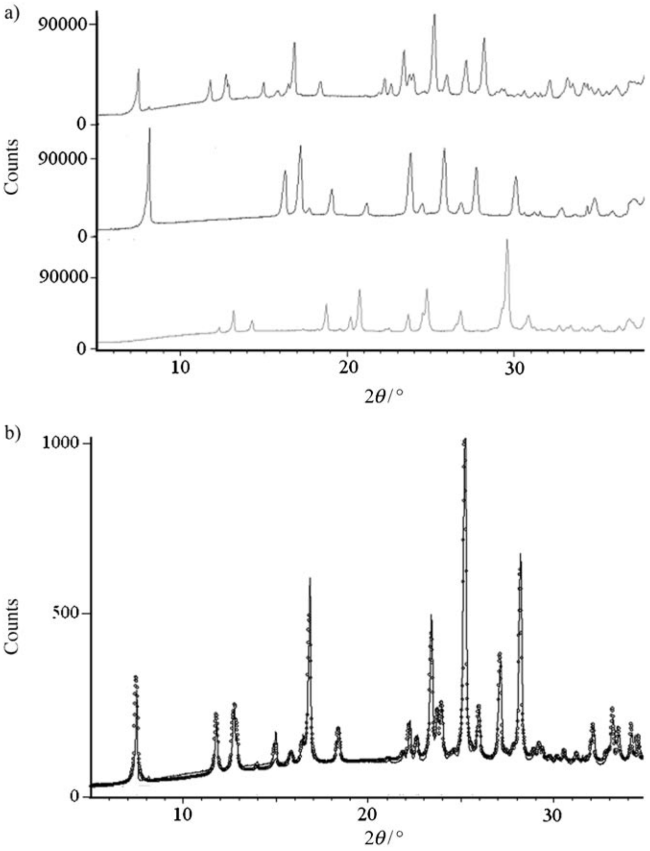


Figure 2. a) Experimental powder-diffraction pattern of the starting materials, BA (middle) and FBA (bottom), and the product **1** (top). b) Excellent powder-profile match for cocrystal **1** between simulated (circles) and experimental (line) data.

peaks at $2\theta = 7.51$, 16.83, 23.41, 25.21, and 28.22°. Least-squares refinement in Powder Cell 2.3[19] of the simulated peaks from the X-ray crystal structure with the experimental powder-diffraction profile gave an excellent match (Figure 2b). There is rapid and quantitative complex formation of **1** by manual grinding at room temperature. VT-PXRD shows peaks corresponding to the sample holder only (alumina) at 90 °C after melting (see Supporting Information, Figure S1), with no indication of polymorphism at high temperature. The unit-cell parameters of the X-ray crystal structure were corrected for the temperature of the experimental powder pattern to calculate the simulated powder profile for comparison. There are small differences in the intensity of the simulated and experimental peaks due to the preferred orientation of microcrystalline particles. All PXRD data were recorded in the 2θ range 5–50° but plotted from 5–35° because there were no significant diagnostic peaks in the high-angle range.

FBA·BAm (2)

The PXRD patterns of pentafluorobenzoic acid, benzamide, and the ground mixture showed new peaks corresponding to cocrystal **2** (Figure 3a) at $2\theta = 10.11$, 15.00, 17.26, and 27.08°. However, cocrystal formation was judged to be incomplete at 28 °C owing to the presence of peaks corresponding to the starting material (marked with arrows in Figure 3b). The H-bonded cocrystal was completely formed at 78 °C based on the PXRD match (Figure 3c). Further heating to 83–99 °C resulted in an amorphous phase upon melting, and cooling to ambient temperature afforded a different solid (see Supporting Information, Figure S2 for VT-

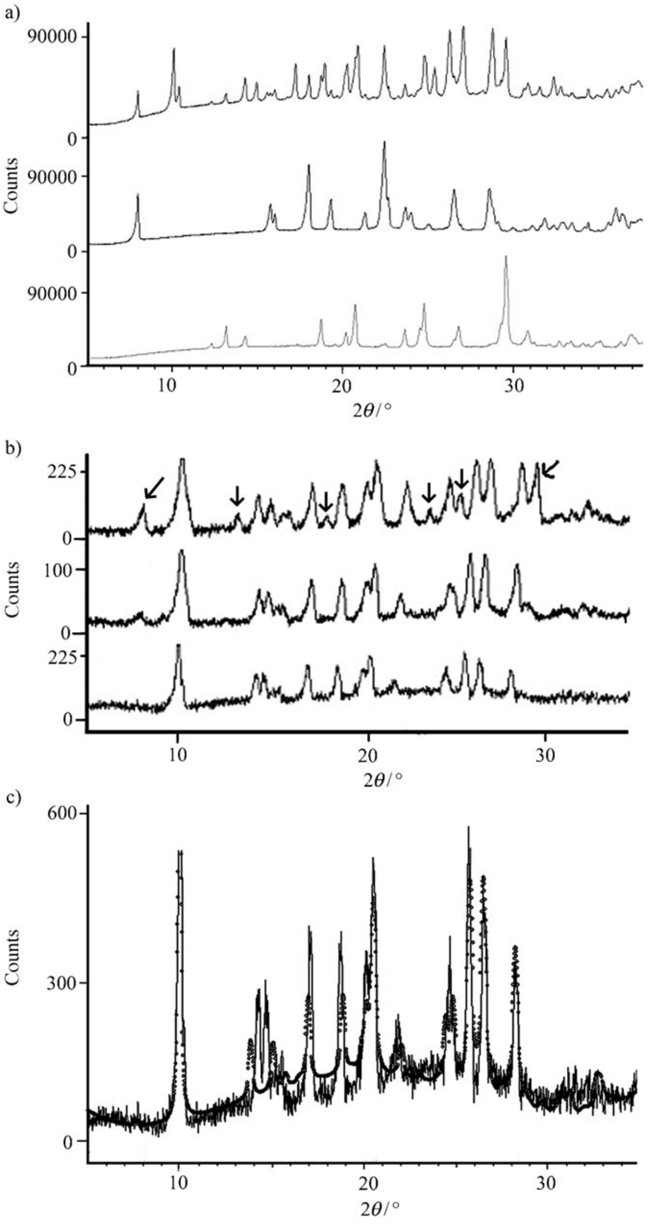


Figure 3. a) Comparison of the experimental powder pattern for FBA (bottom), BAm (middle), and cocrystal **2** (top). b) VT-PXRD pattern of **2** at 28 (top), 70 (middle), and 78 °C (bottom). Arrows indicate peaks corresponding to the starting materials. The powder profile changes towards that of the product as the temperature is raised to 78 °C. c) Refinement of the simulated profile (circles) with the observed diffraction pattern (line) at 78 °C shows quantitative conversion into **2**. There is a new phase upon further heating to 100 °C and cooling to room temperature (see Supporting Information, Figure S2).

PXRD plot) to the 1:1 cocrystal **2** or the 1:2 FBA·BAm cocrystal[20] by PXRD match. The ideal temperature range for this cocrystal synthesis is 75–80 °C.

BAm·FBAm (3)

The powder-profile match of benzamide, pentafluorobenzamide, and the ground mixture at room temperature (Figure 4 a) showed that there are peaks corresponding to the product **3** at $2\theta = 11.92$, 13.29, 18.70, 22.43, 24.59, and 28.75°. However, the transformation into **3** was only about 20 % complete at 25–30 °C (Figure 4 b) and about 40 % at 95–100 °C according to powder-profile matching of the peak intensities.[19] The unreacted BAm and FBAm were consumed only in the melt phase at 110–115 °C to give **3** in a near-quantitative yield of about 95 % (Figure 4 c). Similar results were obtained in the kneading experiment (see next section). These observations suggest that the fluid state, either in the melt phase or by the drop of solvent added, activates and accelerates the reaction. The solid-state composition was determined by least-squares refinement of the peak intensities of the starting materials and the cocrystal in the experimental powder-diffraction profile with the calculated pattern.

BA·FBAm (4) and BA·BAm (5)

Benzoic acid and pentafluorobenzamide did not react at room temperature, but there was complex formation at 90–100 °C. The product was stable to a cool–heat cycle as the PXRD pattern is unchanged (see Supporting Information, Figure S3). It is difficult to say whether this new phase is the 1:1 cocrystal **4** because single crystals could not be obtained so far by solution crystallization. Heating a 1:1 molar ratio of powdered benzoic acid and benzamide to 80–90 °C gave a melt phase, which upon cooling to room temperature showed new PXRD peaks (see Supporting Information, Figure S4). Once again, we were unable to ascertain the structure of this product for lack of suitable crystals. DSC indicated a single melting endotherm at a temperature different from that of the starting components in each case (Table 1).

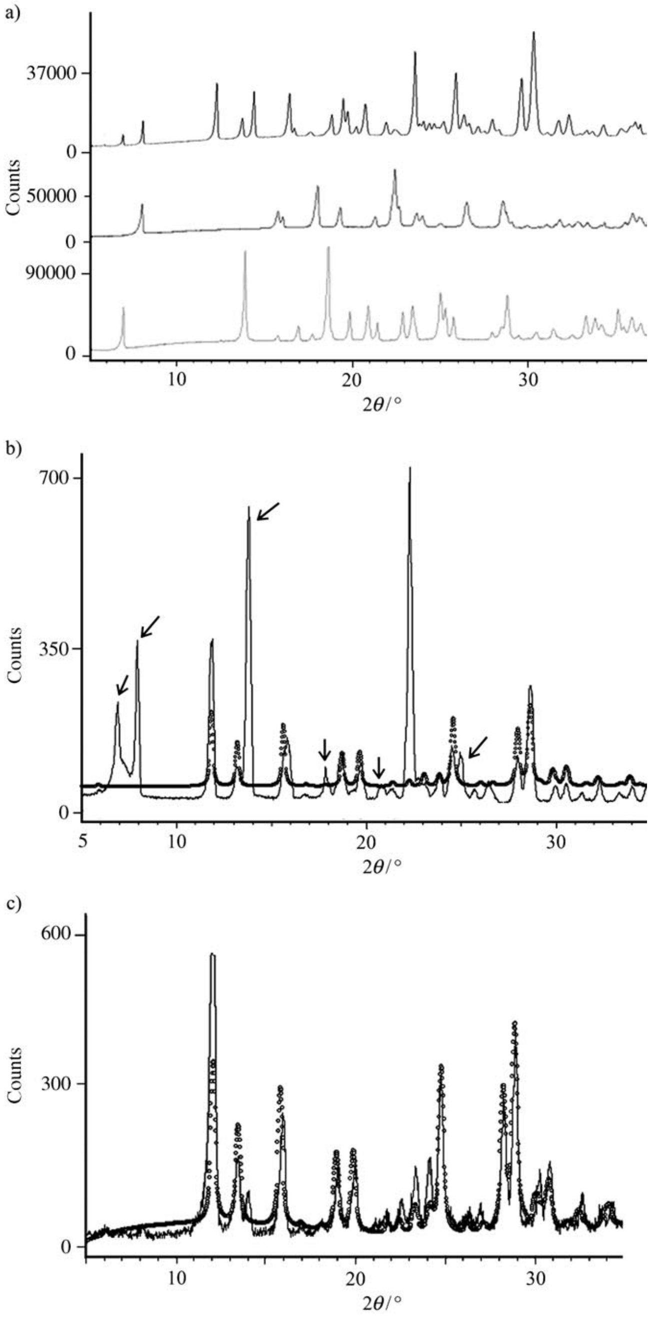


Figure 4. a) Experimental powder-diffraction pattern of BAm (middle), FBAm (bottom), and product cocrystal **3** (top). b) Simulated and experimental powder profile of **3** showing that the reaction was incomplete (≈20 % product) at room temperature (arrows indicate peaks corresponding to the starting materials). c) Near-quantitative transformation (≈95 %) was effected through cocrystallization via the melt phase at 110–115 °C. The peak at 14.04° is due to residual FBAm.

FBA·FBAm (6)

Comparison of the experimental powder pattern of pentafluorobenzoic acid, pentafluorobenzamide, and their 1:1 ground mixture showed that peaks corresponding to the product are different from those of the components (Figure 5 a). For example, the peaks at $2\theta = 5.40$, 19.22, 20.56, 26.26, and 30.15° are diagnostic of a new phase, indicating the formation of cocrystal **6**. Cocrystallization of FBA and FBAm in a 1:1 molar ratio by slow evaporation of a solution in dioxane at room temperature afforded suitable single crystals. The crystal structure of **6** is stabilized by the acid–amide heterosynthon (Figure 6) of O−H···O (1.65 Å, 167.0°) and N−H···O (1.90 Å, 166.0°; 1.93 Å, 164.9°) H bonds. The C_6F_5 groups are twisted with respect to the COOH and $CONH_2$ groups (24.8°, 44.4°, respectively) because of steric/electronic repulsion from the *ortho*-F atoms. Despite the presence of several fluorine atoms, there is no evidence for short F···F contacts. The simulated PXRD pattern of cocrystal **6** matched perfectly with the experimental powder pattern at room temperature (Figure 5 c). VT-PXRD (Fig-

Table 1. Melting points, intramolecular F···O contacts (<3.0 Å), and O−H···O/N−H···O hydrogen bonds between COOH and $CONH_2$ groups of starting materials and cocrystals.

Compound	M.p. [°C][a]	C_{PhF}−C_{Ph}−C=O [°]	F···O [Å]	O···O/N···O [Å]	Ph···Ph^F stacking [Å]
BA[b]	122	–	–	2.62	–
FBA[b]	101	28.8	2.65, 2.70	2.66	–
BAm[b]	129	–	–	2.94, 2.92	–
FBAm[c]	149	41.0	2.79	2.90, 2.91	–
BA·FBA (**1**)[c]	87–89	11.3, 32.7	2.58, 2.57, 2.68, 2.70	2.60, 2.62, 2.64, 2.65	3.81, 3.84, 3.95, 3.97
BAm·FBA (**2**)[c]	89–90	22.5	2.60, 2.67	2.49, 3.00, 2.98	3.97
BAm·FBAm (**3**)[c]	112–114	42.8	2.80	2.94, 3.00, 3.12, 3.09	3.66, 3.71
BA·FBAm (**4**)[d]	99–100	–	–	–	–
BA·BAm (**5**)[d]	86–87	–	–	–	–
FBA·FBAm (**6**)[e]	91–92	24.7, 44.4	2.61, 2.67, 2.82	2.62, 2.89, 2.91	–

[a] Determined from DSC endotherm peak (see Supporting Information, Figure S6). [b] Data from the Cambridge Structural Database. [c] Data from reference [18]. [d] Cocrystal data obtained by PXRD. [e] Data from this paper.

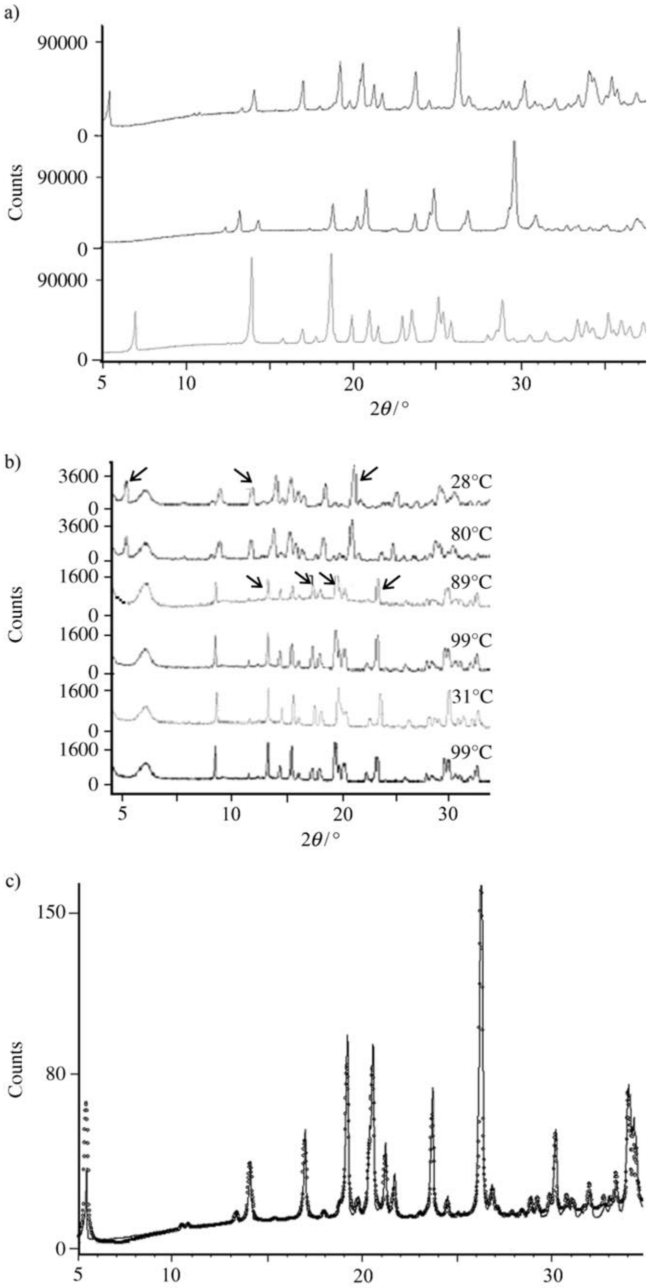


Figure 5. a) Experimental powder pattern of FBA (middle), FBAm (bottom), and cocrystal **6** (top) at 28 °C. b) VT-PXTD pattern of **6** showing that it is stable up to 80 °C but transforms into a new phase at 80–90 °C. Arrows indicate the diagnostic diffraction peaks. c) Excellent match in the simulated (circles) and experimental (line) powder diffraction peaks at 28 °C.

ure 5b) of **6** showed the emergence of new peaks at high temperature. The IR spectrum of the solid **6** at ambient temperature is different from that of the high-temperature phase (see Supporting Information, Figure S5), indicating the formation of a new phase. The presence of doublet bands at 3100–3400 cm^{-1} and the C=O stretching bands at 1640 and 1710 cm^{-1} mean that both $CONH_2$ and COOH groups are present, implying that this new solid is a mixture of FBA and FBAm (conglomerate crystal) rather than a polymorph of one of the components.

The appearance of new X-ray diffraction peaks in a mixture of two components after grinding may be interpreted as follows: 1) the expected 1:1 cocrystal is formed, 2) a cocrystal of different stoichiometry (conglomerate phase) is formed, or 3) there is no cocrystallization, but a polymorph of one of the components resulted. In the absence of confirmation with single-crystal XRD, we can only speculate on these options. The solution of the structures of **4**, **5**, and **6** may be attempted by Rietveld refinement of high-resolution PXRD data. The generic algorithm approach to crystal-structure solution is no doubt a powerful method,[21] but direct space-structure determination from the PXRD data is nontrivial and difficult to carry out routinely. We were not able to grow single crystals by seeding the solution.

Grinding and Kneading

There is now an advancement in the almost-century-old technique of solid-state grinding in an agate mortar, namely, the addition of a few drops of solvent to accelerate the reaction.[8] As cocrystals **2** and **3** reacted only at high temperature, the requisite components, FBA+BAm and BAm+FBAm, were ground with a small amount of EtOAc added. In both cases, the expected cocrystal was obtained at room temperature after 30–45 min of manual grinding. There was incomplete reaction in the absence of added solvent. Attempts to coax the reaction of BA with FBAm or BAm, which occur at about 90 °C by grinding, did not afford any new solids by the solvent-drop-grinding method. Solvent-drop grinding activates the reaction through the small

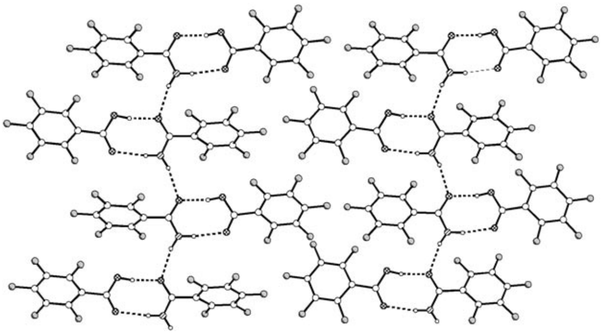


Figure 6. Acid–amide heterodimer and N−H_{anti}···O hydrogen bonds in cocrystal **6**. There is an F···F contact of 2.89 Å.

amount of liquid that acts like a lubricant and facilitates molecular diffusion from one point of the mixture to another until cocrystallization is complete.

Besides manual grinding, the components were ground in a ball mill for about 5 min at 20 Hz. These automated experiments validate the results for manual grinding. Cocrystals **1**, **2**, **3**, and **6** were readily formed but there was no indication of product formation for **4** and **5**. The product cocrystal was matched with simulated PXRD data of the crystal structure and the components to assess the progress of the reaction.

Discussion and Conclusions

Crystallization is like a supramolecular reaction in the solid state.[22] Supramolecular assembly may be directed to produce a single-crystalline product or at times lead to more than one crystal structure, namely polymorphism.[23] The grammar and rules for the directed assembly of cocrystals are yet to be fully understood. Even as the strongest-donor to strongest-acceptor hydrogen-bond-hierarchy model is able to predict the expected synthons in the crystal structure,[24] important issues such as the cocrystal stoichiometry (1:1 or 1:2),[2g] the correct temperature[13a] and preferred method of cocrystallization,[8a] hydration,[11b] and polymorphism[2b,8d] are answered only after exhaustive experimentation. Our VT-PXRD experiments on cocrystallization show good correlation of the strength of H-bonding groups with their supramolecular reactivity: stronger substrates react upon manual grinding at 25–30 °C to give cocrystals **1** and **6**, and weaker ones produce cocrystals **2** (75–80 °C) and **3** (110–115 °C) at higher temperature. There is a new crystalline entity of **2** and **6** or a different stoichiometry cocrystal thereof when the mixture of components was heated too much, to 85–100 and 90–100 °C, respectively. Cocrystallization of BA with FBAm and BAm (to new products **4** and **5**) proceeds on heating to 80–100 °C in the melt phase. Similarly, ball-mill grinding gave pure products **1**, **2**, **3**, and **6** but not **4** and **5**. The take-home lesson from the above results on aromatic carboxylic acid and amide cocrystals is that it is important to know the exact temperature for quantitative cocrystallization in the solid state because excessive heating beyond the optimal temperature or during melt crystallization can lead to phase transitions, products of different stoichiometry, or polymorphs. Such complications are likely in common organic solids that have melting points in the typical range of 70–200 °C. Heating to 80–100 °C surely accelerates the reaction, but it also causes physical changes such vaporization and/or melting of one (or both) of the components. Different reaction products are known to result in the solution, vapor, or fluid phase than with solid-solid grinding.[25] There are several crystallization possibilities, given the variable stoichiometry of cocrystals and polymorphism, and many organic solids would begin to effuse vapor or melt at about (100 ± 20) °C, at least for part of the material if not all. Analysis of the solid-state product(s) as the temperature is increased will provide the optimal activation conditions for a given cocrystallization reaction. In this respect, VT-PXRD is an accurate and rapid technique for studying phase changes and polymorphism in situ.[26] We recently discovered two polymorphs of an organic host compound by carrying out sublimation and melt crystallization at slightly different temperatures, 150–175 and 180–190 °C, respectively.[27]

A puzzling observation in this study is that the melting point of the cocrystal is lower than that of the individual components (Table 1). Generally, the melting point of the cocrystal is higher than those of the starting materials because of stronger hydrogen-bonding and intermolecular interactions in the product. Whereas it is relatively easy to correlate melting-point alternation with molecular packing and hydrogen bonding in a series of homologous cocrystals,[17b,28] the present set of diverse crystal structures, in terms of different substituent groups, molecular conformations, multiple molecules, hydrogen bonding, and stacking interactions, makes it difficult to establish crystal-packing and crystal-density relationships with the cocrystal melting point. Moreover, lowering of the melting point could be because of lower enthalpy or higher entropy or both ($T_m = \Delta H/\Delta S$). Notably, the molecular conformation of the C_6F_5 group varies considerably in FBA and FBAm in the pure and cocrystal structures, which in turn means severe or less F···O repulsion depending on the distance and the torsion angle (Table 1). Secondly, both the H-bonding and the Ph−Ph^F stacking distances vary considerably in these structures. Continuous stacks of alternating C_6H_5 and C_6F_5 rings stabilize both crystal structures **1** and **3** (Figure 1). However, given that the melting point of the 1:1 complex of benzene and hexafluorobenzene is 19 °C higher than that of either of the component liquids,[5a] the lower melting point of the above cocrystals is quite enigmatic.

It is necessary to know the exact temperature range for effecting cocrystallization by solid-state grinding because excessive heating results in accidental phase transition, conglomerate crystallization, or polymorphism. The optimal temperature range for the reaction to proceed to completion in relatively short times (< 1 h) and without by-product(s) is best derived by in situ diffraction experiments. It is estimated that carboxylic acids and amides constitute about 18% and 15% of compounds, respectively, in crystal-former libraries, the highest among common organic functional groups.[29] These and other functional groups (e.g., pyridine, amines, esters, etc.) are commonly found in active pharmaceutical ingredients for cocrystal engineering and drug formulation. Our VT-PXRD analysis on the cocrystallization of carboxylic acids and amides should be useful in planning cocrystal synthesis by solid-state grinding and heating in newer systems.

Experimental Section

Cocrystals were identified by the difference in melting point from the pure components, and the structures were confirmed by X-ray diffraction. Reference melting points are benzoic acid 122 °C, benzamide 129 °C, pentafluorobenzoic acid 101 °C, and pentafluorobenzamide 149 °C. All melting points reported were measured according to the DSC endotherm peak value (see Supporting Information, Figure S6), which are in excellent agreement with those determined on the Fisher–Johns apparatus.

Cocrystallization

Single crystals of **1**, **2**, **3**, and **6** were obtained by the following method. A 1:1 molar mixture of the two components was ground with a mortar and pestle and dissolved in hot EtOAc/hexane (1:1) (for **1**, **2**, and **3**) or dioxane (for **6**). Single crystals appeared after a few days at room temperature.

BA·FBA (**1**): Plate-shaped crystals, m.p. 87–89 °C.

BAm·FBA (**2**): Needle-shaped colorless crystals, m.p. 89–90 °C.

BAm·FBAm (**3**): Needle-shaped colorless crystals, m.p. 112–114 °C.

FBA·FBAm (**6**): Needle-shaped colorless crystals, m.p. 91–92 °C.

Attempted cocrystallization of BA and FBAm under the above conditions did not afford the expected cocrystal **4**. Crystals of benzoic acid precipitated after a few days. In the case of cocrystal **5**, BA and BAm precipitated after complete drying of the solvent.

BA·FBAm (**4**): M.p. 99–100 °C.

BA·BAm (**5**): M.p. 86–87 °C.

Thermal Measurements

DSC and thermal gravimetric analysis (TGA) were performed on Mettler Toledo DSC 822e and Mettler Toledo TGA/SDTA 851e instruments, respectively. Samples were placed in open alumina pans for TGA and in crimped but vented aluminum pans for DSC. The sample size in each case was 5–7 mg. The sample was heated from 30 to 200 °C at 10 °C min^{-1} and purged with dry nitrogen at 150 mL min^{-1} for DSC and 50 mL min^{-1} for TGA.

Single-Crystal X-ray Diffraction

X-ray crystal structures of cocrystals **1**, **2**, and **3** were reported previously.[18] Crystal data of **6**: $C_{14}H_3F_{10}NO_3$, $M=423.17$, orthorhombic, space group *Pbca*, $a=9.8555(12)$, $b=9.3305(12)$, $c=32.741(4)$ Å, $V=3010.8(7)$ Å^3, $Z=8$, $\rho_{\text{calcd}}=1.867$ g cm^{-3}, $T=298(2)$ K, $\mu=0.211$ mm^{-1}, $F(000)=1664$, 8299 reflections measured, 2916 independent, 1892 observed ($I>2\sigma_1$), 265 parameters, $R_1=0.0496$, $wR_2=0.1056$ (all data), $S=1.020$. Data were collected on a Bruker Smart Apex CCD diffractometer with $\text{Mo}_{K\alpha}$ radiation (0.71073 Å). The structure was solved by direct methods with SHELXS-97 and refined by full-matrix least squares on F^2 with anisotropic displacement parameters for non-H atoms in SHELXL-97.[30] CCDC-634435 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (e-mail: deposit@ccdc.cam.ac.uk) at www.ccdc.cam.ac.uk/data_request.cif.

Powder X-ray Diffraction

PXRD data were collected on a PANalytical X'Pert Pro MPD diffractometer with $\text{Cu}_{K\alpha}$ radiation (1.54056 Å). The power of the X-ray generator was set to 40 kV and 40 mA. The sample stage used was an Anton Paar HTK1200N high-temperature chamber. A microcrystalline mixture of the solids was prepared by grinding an equimolar ratio of the precursors with a mortar and pestle for 10–20 min. Vigorous grinding was avoided to minimize potential phase transitions. Samples were ground to particle sizes greater than 20 μm and loaded onto a 10-mm alumina holder. Peak shifts due to variation in sample height were prevented by the use of a parallel X-ray beam from a primary PW3149/63 hybrid monochromator consisting of a combined graded multilayer parabolic X-ray mirror and a two-bounce Ge monochromator. Rapid data collection was achieved by using the fast X'Celerator RTMS detector. In VT-PXRD experiments,[26] reflections were collected at 10 °C intervals from 30 to 100 °C by heating at 1 °C min^{-1}. Diffraction patterns were collected in the 2θ range of 5–50°. Room temperature refers to 25–32 °C, which is the ambient temperature in Johannesburg and Hyderabad. X-ray powder patterns were calculated with Powder Cell 2.3,[19] and X'Pert Plus and X'Pert High Score were used to compare the powder profiles. The unit-cell parameters of the single-crystal structure were corrected for the temperature of the powder-diffraction measurement to calculate the simulated powder pattern. Small differences in the intensity of the experimental peaks relative to the calculated ones are due to the preferred orientation of the microcrystalline solid. The solid-state composition was estimated by least-squares refinement of the experimental powder-diffraction peaks with the simulated powder lines for the starting materials and the product cocrystal.

Solid-State Grinding

The reacting solids (1:1 molar ratio) were ground with a mortar and pestle for varying amounts of time (10–45 min) and checked for cocrystal formation. For solvent-drop grinding, 3–4 drops of EtOAc were added to an equimolar mixture of BAm+FBA and BAm+FBAm, and the solids were ground for 30–45 min. PXRD showed complete conversion into the product cocrystals **2** and **3**. Cocrystallization was incomplete in the absence of added solvent.

For automated ball-mill grinding, a 1:1 mixture of the components was shaken in a Wig-L-Bug-type mixer mill equipped with a 5-mL stainless-steel grinding jar and balls of 4-mm diameter. Grinding was performed for about 5 min at an oscillation rate of 20 Hz.

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