CRYSTAL GROWTH & DESIGN

Perspective

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Engineering Molecular Crystals: Backbreaking, yet Gratifying

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As a recently appointed Topic Editor of *Crystal Growth & Design*, I am delighted to take the opportunity offered by this *Perspective* article to introduce myself to the journal's readers. Rather than subjecting you to a potted history of our career milestones and achievements, my fellow Topic Editors and myself will be using these articles to express our individual views on subjects that lie at the heart of *Crystal Growth & Design*, while describing some of the research being pursued in our laboratories. With this in mind, it will be sufficient for now to introduce myself as an organic solid-state chemist with a passion for molecular crystals and a keen interest in crystal engineering. I am privileged to lead a growing research group at University College London, where we study (among other things) supramolecular structures in molecular crystals, how such crystals form, and how they can be put to good use.

This *Perspective* article was inspired in part by the many discussions I have had with colleagues regarding our ability to design molecular crystals for bespoke applications. The field of pharmaceutical solid-state chemistry is particularly successful in demonstrating how crystal engineering and cocrystallization can help to tackle the myriad challenges associated with retaining promising molecules in drug discovery pipelines.[1] This success can be easily credited to the tremendous improvements (over the last 20 years) in our understanding of molecular self-assembly in the solid state[2−7] and of how supramolecular interactions, such as hydrogen and halogen bonds, steer such processes,[8−14] as well as to the development of sophisticated and reliable screening methods for polymorph, salt, and cocrystal screening.[15−17] These developments have been accompanied by commensurate advances in analytical tools for the characterization of molecular solids and dynamic processes occurring therein (both *in situ* and *ex situ*).[18] But despite this great expansion in knowledge and expertise, organic solids still baffle us more often than we would like, with sudden unpredictable alterations that confound efforts to regulate the crystal form of a particular compound. The cases of ranitidine hydrochloride, ritonavir, rotigotine, and other pharmaceuticals have clearly demonstrated that there is much to learn before we can claim full control over the organic solid state.[19] As the title of this article suggests, I believe that there are still substantial hurdles to overcome before we can *easily and precisely* practice the three main aspects of crystal engineering, namely, *designing*, *building*, and *using* crystal structures.[20]

In the following sections, I will describe some of the hurdles encountered by our research group when studying each of the aforementioned aspects of crystal engineering. These examples from our research should illustrate the "backbreaking" nature of the crystal engineering endeavor, as well as the limitations of our *current* abilities to understand, engineer, and maintain molecular crystals; I leave it to the reader to imagine the gratification to be gained by overcoming these limitations in the future.

DESIGNING CRYSTALS

My first example concerns a recent study of cocrystal design, involving cocrystals of theophylline (thp) and each of 19 different fluorobenzoic acids (FBA) (Figure 1a).[21] The aim of the study was to predict the formation of supramolecular synthons in each of the 19 cocrystals. There were several reasons to expect that the cocrystallization would proceed in a straightforward manner: thp and benzoic acid (BA) are well studied in the context of pharmaceutical cocrystals, while FBAs are similar to BA in size, shape, and their capacity to engage in hydrogen bonding. FBAs are also small, rigid molecules, displaying a very limited number of potential hydrogen-bonding functional groups. In addition, we could easily access numerous well-established computational methods (e.g., predictions of molecular complementarity,[22] ΔpK_a calculations,[23] and calculations of molecular electrostatic potential surfaces[24−27]) and statistical tools (e.g., knowledge-based hydrogen-bond propensity calculations[28,29]) to predict the outcome of the proposed cocrystallizations.

However, initial database searches, quantum-chemical calculations, and statistical analyses were not too helpful, as two supramolecular interactions (labeled as A and B in Figure 1) were found to have a very similar propensity to occur in the two-component cocrystal. Furthermore, neither a (thp)·(BA) cocrystal nor cocrystals based on thp and a BA derivative lacking additional hydrogen-bonding functional groups were known at that time. This meant that we did not have sufficient information to attempt reverse crystal engineering, i.e., the extraction of design principles from similar/related crystal structures (the latter process is often imprecisely described simply as "engineering"). We were thus only able to hypothesize that all di-, all tri-, and all tetra-substituted FBAs might display identical synthons. It was also possible that mono- and disubstituted FBAs would behave in a similar manner, while tetra- and penta-substituted FBAs would act similarly, though in another way.

The naivety of our hypotheses was exposed by the results of the ensuing synthesis. All cocrystals were prepared under identical mechanochemical conditions, but subsequent structural analysis showed that some FBAs formed a cocrystal, while others did not. It was also interesting to note that crystallization attempts carried out at two different locations yielded consistently different synthon polymorphs[30] (Figure 1b). In addition, cocrystals containing FBAs with the same number of fluorine atoms exhibited different compositions and supramolecular interactions. For example, thp and 25diFBA formed a 1:2 cocrystal, while 34diFBA and 35diFBA formed a 1:1 thp

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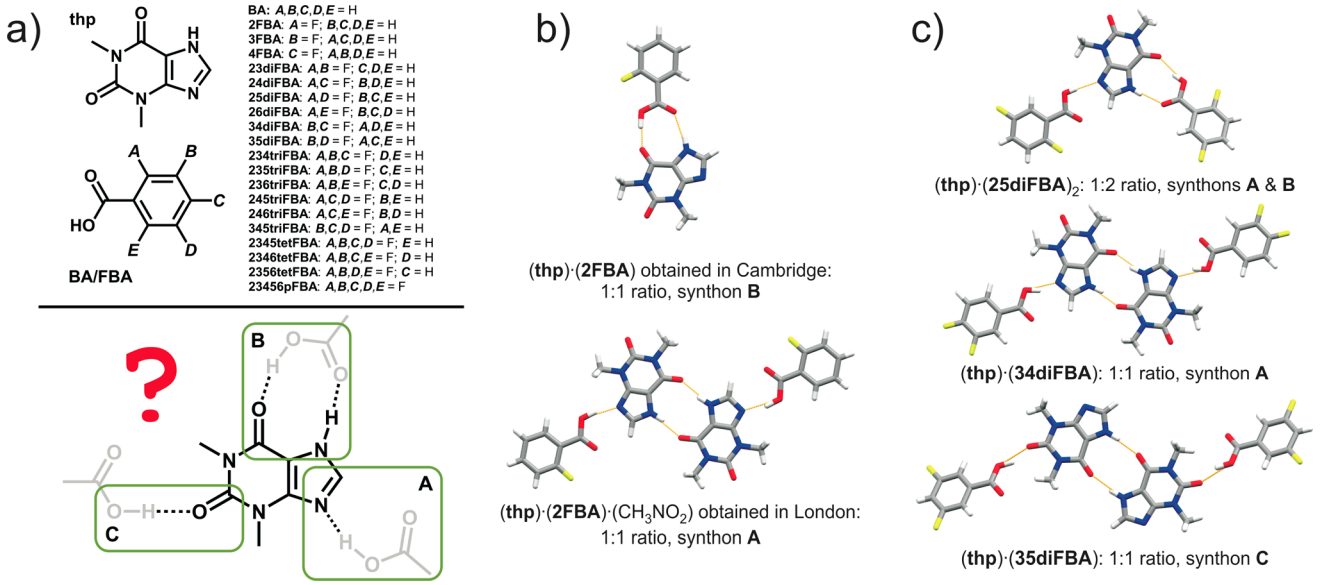

Figure 1. (a) Molecular structures of thp and FBA cocrystal formers; (b) (thp)·(2FBA) and (thp)·(2FBA)·(CH_3NO_2) cocrystals obtained in different laboratories under identical mechanochemical reaction conditions; (c) supramolecular assemblies in thp cocrystals of difluorobenzoic acids based on different compositions and hydrogen-bonding patterns.

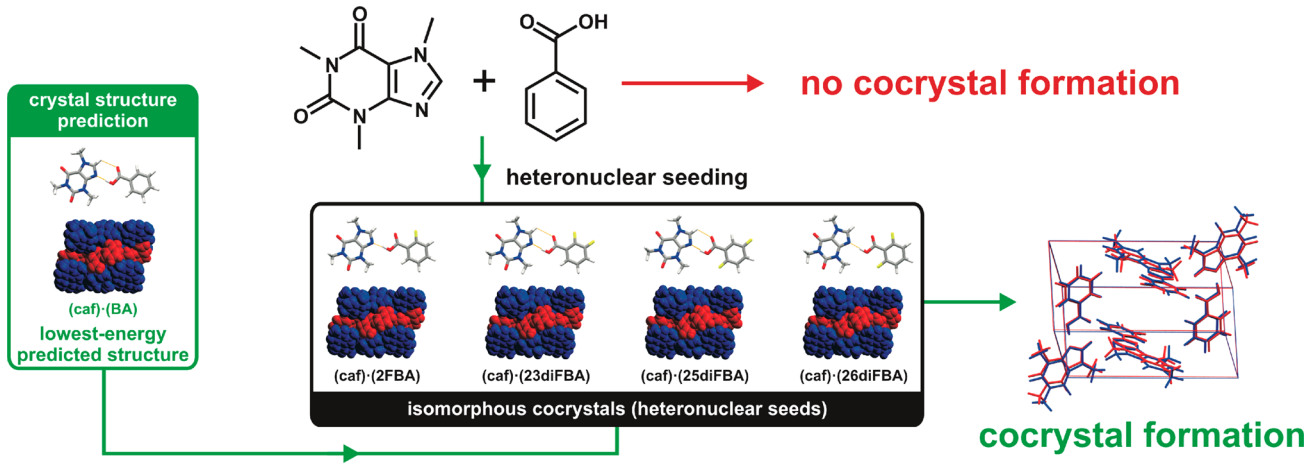

Figure 2. Synthesis of the elusive (caf)·(BA) cocrystal through heteronuclear seeding. Several (caf)·(FBA) cocrystals (highlighted in black) were selected as heteronuclear seeds due to their structural similarity with the lowest-energy predicted (caf)·(BA) structure (highlighted in green). Powder X-ray diffraction studies showed that the obtained (caf)·(BA) is indeed identical to the lowest-energy predicted cocrystal structure, as evidenced by the overlay on the bottom right (red: predicted structure, blue: observed structure).

cocrystal, but the 34diFBA and 35diFBA cocrystals displayed distinct supramolecular synthons (Figure 1c). The matter was further complicated by the propensity of the (thp)·(FBA) cocrystals to form polymorphs—many of which were synthon polymorphs. A very limited polymorph screen showed that synthetic conditions clearly dictate the formation of supramolecular synthons.

Given these observations, it would be complacent on our part to be satisfied with our current ability to accurately predict and understand the empirical outcomes of cocrystallization experiments, even when small and rigid molecules are involved (and despite our ambitions being limited to the prediction of hydrogen-bonding patterns, rather than the entire crystal structure).

BUILDING CRYSTALS

My second example demonstrates that building a thermodynamically stable cocrystal structure can be anything but straightforward, even if sophisticated cocrystallization methods are employed. This example also highlights how gaps in our knowledge of the nucleation process and crystal growth of multicomponent crystals can constrain cocrystallization efforts.

The noughties witnessed a surge in interest in pharmaceutical cocrystals that led to the development of numerous rapid, efficient experimental screening methods.[15,17,31−33] The success of these new methods has been attributed to the fact that the applied cocrystallization conditions maximize the potential for cocrystal formation, supposing a thermodynamically feasible cocrystal phase exists.[31,34] One must keep in mind, though, that a negative outcome of a cocrystal screen does not necessarily mean that the target cannot materialize under the studied condition due to thermodynamic constraints. Considering the

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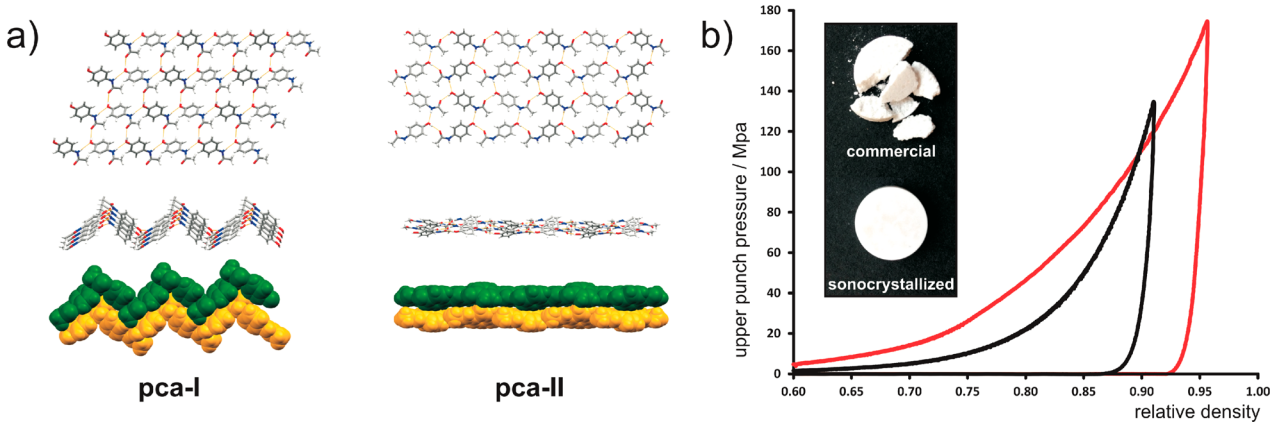

Figure 3. (a) Crystal structure of pca-I and pca-II (viewed along the *c* and *a* crystallographic axes, respectively), (b) comparison of stress–density curves for commercial pca-I (black) and sonocrystallized pca-I (red). The relative density (*x*-axis) refers to the powder density relative to the density of the pca-I crystal structure (ρ = 1.263 g cm^{-3}). Inset: tablets composed of commercial and sonocrystallized pca-I after compaction).

established effectiveness of contemporary cocrystallization methods,[35] however, it is not surprising that one is often tempted to (injudiciously) ascribe a failed cocrystallization attempt to the inability of the cocrystal formers to form stable supramolecular structures and/or crystal lattices.

This was the case with the cocrystal based on caffeine (caf) and benzoic acid (BA) with a 1:1 caf/BA ratio, a latent material whose elusiveness was explained by the inability of its components to form supramolecular structures capable of packing into a thermodynamically stable crystal lattice.[36] The synthesis of the (caf)·(BA) cocrystal was unsuccessfully attempted on numerous occasions in the last 60 years.[36−38] After a series of unsuccessful attempts to prepare this cocrystal in our laboratories, we turned to computational crystal structure prediction and global lattice energy minimization calculations to assess the possible existence of the target material. Comparing the calculated energies of the pure cocrystal components with the energy of the most stable predicted cocrystal clearly indicated that the formation of (caf)·(BA) is thermodynamically feasible. This result suggested that the negative cocrystal screens might be due to unsuccessful nucleation of the solid and that, perhaps, a high kinetic barrier hinders the nucleation and growth of the thermodynamically stable target cocrystal.

We then resorted to heteronuclear seeding experiments using cocrystals composed of caf and FBAs. It was found that several FBA isomers form caf cocrystals that are isomorphous with the lowest energy (caf)·(BA) structure predicted. The synthesis of such heteronuclear seeds and their subsequent use in our cocrystallization experiments resulted in the formation of the target solid. This success came at a cost: once the target solid was obtained, we found that we were no longer able to reproduce the initial negative screening results, which meant that we were unable to explore the nonseeded system in further detail. We then proceeded to repeat the full set of experiments in four different academic and industrial laboratories, with the same outcome in each location: viz. initially, the target cocrystal could not be prepared using well-established cocrystallization methods, but formed immediately once a seed was introduced to the laboratory. In all instances, the failed cocrystallization experiments could not be reproduced for a significant period after the seeding experiments were performed (in some laboratories, for more than two years!).

The inability to reproduce the failed experiments was attributed to residual (and undetectable) crystals of either the synthesized target cocrystal (or the heteronuclear seeds) in the laboratory environment, which were presumably seeding[19] the formation of (caf)·(BA) in experiments that did not involve the deliberate use of seeds. To test this hypothesis, we attempted cocrystal screens using physical mixtures of caf and BA that were isolated in rubber-septa-sealed vessels prior to the introduction of the (caf)·(FBA) cocrystal seed to the laboratory. Once a solution-mediated phase transformation was initiated, the suspension did not convert within more than 3 days (as confirmed by *in situ* Raman spectroscopy), but once the septum was removed, the caf/BA mixture rapidly converted into the cocrystal.

This intriguing instance of an elusive cocrystal process responding in an irreversible fashion to heteronuclear seeding suggests that contemporary screening methods need to be further developed to avoid misleading false negative results, which could easily jeopardize the production of medically and commercially important materials.

■ USING CRYSTALS

My third example—involving a study of the mechanical properties of paracetamol (pca, also knowns as acetaminophen)—not only highlights how very nonobvious properties of organic solids are, but also emphasizes the role of particle features, other than their crystal structure (e.g., size, size distribution),[39] in the shaping of the properties of a material.

Paracetamol is a highly popular analgesic and antipyretic, and is the most prevalent active pharmaceutical ingredient in medicines sold in the U.S., being present in more than 600 prescription medicines or products sold "over the counter".[40] The drug is a textbook example of a poorly tabletable molecule, and the meager compaction properties of pca are generally ascribed to its crystal chemistry. Two out of the three polymorphs of pca are accessible with reasonable ease, the monoclinic form I and the orthorhombic form II. The crystal structure of pca-I exhibits two-dimensional corrugated hydrogen-bonded layers that impede plastic deformations of the pca particles (Figure 3a) and contribute to the poor tabletability of pca-I.[41,42] The structure of pca-II, on the other hand, exhibits flat hydrogen-bonded molecular sheets, that facilitate plastic deformation of the particles and thus better tabletability (Figure 3a).[41,43] Unfortunately, pca-II is less stable than pca-I[44,45] and is

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also less accessible as a phase pure material. The formulation scientist's polymorph of choice is therefore pca-I, which is formulated with a significant amount of excipients to prevent tablet failure in form of lamination, capping, and chipping,[46] resulting in bulky tablets.

Pediatric patients, as well as some adults, generally suffer from dysphagia (i.e., difficulty in swallowing). This means that it is preferable to formulate medicines for this population in the form of liquids, dispersible and chewable tablets.[47] Accordingly, numerous groups have attempted to improve the compaction properties of pca through the development of alternative crystal forms.[48,49] It has also been demonstrated that microparticles of pca-I, obtained using rather demanding crystallization methods, exhibit improved compaction properties.[47] Such material, however, demands the use of compaction pressures that exceed those deemed to be feasible in industrial settings.[47]

We have recently shown that fast and cost-effective sonocrystallization[50] leads to the formation of phase-pure pca-I, comprised of nano- and microcrystals, with significantly enhanced compaction properties.[39] Compaction measurements revealed that tablets of sonocrystallized pca-I exhibit 40% lower porosity than those made from commercial, macrocrystalline pca-I. Additional compaction simulations indicated that the elastic modulus of the sonocrystallized pca-I particles expectedly increased[51] (2.4-fold in comparison to commercial pca-I), which should result in even worse compaction properties. The excellent tabletability of the material, however, was enabled by the improved ability of the solid to plastically deform, and a substantial increase of the cohesion particles in the solid (34-fold in comparison to commercial pca-I). As a result, sonocrystallized pca-I displays compaction behavior that is fairly close to that of microcrystalline cellulose—a pharmaceutical excipient commonly used as binder to maintain the structural integrity of tablets. Moreover, it was demonstrated that sonocrystallized pca-I can be tableted using pressures that are routinely used in industry without the addition of any binders!

The surprising revelation that the tabletability of pca can be improved to such remarkable extent by changing the size of the crystals emphasizes the unpredictable behavior of molecular crystals—even those of highly relevant and extensively studied drug molecules. It also encourages the typical crystal engineer to consider tackling formulation challenges via particle engineering,[52] *viz*. to improve material properties by tuning particle size, size distribution, and morphology of the compound of interest, rather than focusing solely on crystal lattice adjustments.

The three examples described here may appear to offer an unduly critical picture of the current state of the art in the field of crystal engineering; however, that is certainly not my intention. I believe that we are currently witnessing an era of exciting advances in the field,[53] enabled by new and well-developed experimental techniques, sophisticated instrumentation, and ingenious theoretical tools given force by powerful computers. And this progress is, unsurprisingly, underpinned by many studies that report targeted changes to crystal lattices of specialty chemicals leading to their enhanced performance. But in the midst of such sustained success, it is very important to be mindful of the very real issues still facing practitioners.

Several of these issues were encountered in our work with the (caf)·(BA) and (thp)·(FBA) cocrystals, which show that our ability to target and control the formation of particular supramolecular structures in cocrystals, or even to occasionally materialize elusive or "disappearing" crystal forms (briefly discussed below[54−59]), leaves much to be desired. I am not under the illusion that we will be able to fully plan and successfully execute the construction of *any imaginable* crystal lattice any time soon (or perhaps at all?)—particularly not if the field continues to predominantly rely on crystallographic studies, no matter how systematic and carefully conceived they are. But I would prefer we refrain from exhausting ourselves trying to attain such goal. Instead, we would perhaps be better employed trying to master the mapping of crystal structure landscapes, to understand which crystal structures are experimentally obtainable, to reliably produce and maintain them, and, finally, to predict what properties these materials have, even before they were synthesized.[60] Such an undertaking is certainly very ambitious and perhaps too demanding for many chemical crystallographers (which is what most of us in the field trained as). The experimentalists should, therefore, join efforts with theoretical solid-state chemists and physicists whenever possible (a preferred mode of operation in our research group[39,61,62]) and introduce computational methods (e.g., lattice energy calculations,[63] crystal structure prediction[64]), knowledge-based predictive tools,[65,66] and emerging preparative and analytical techniques[67,68] as standard tools into their research programs. Until we do so, we will struggle to uncover obscure (but potentially useful) qualities of existing molecular materials, while continuing to engineer novel molecular crystals with an incomplete understanding of the principles underlying their structure and formation.

I recognize that such a move toward more multidisciplinary and collaborative investigations of fundamental aspects of crystal engineering would require a rather daunting rethink of many research programs in the field. I also realize that such changes can only take place slowly, as it will take a while before the expertise and tools of theoretical solid-state chemists become more accessible to experimentalists, especially since most relevant software is neither commercially available nor facile to use. But I firmly believe that we are already on our way to tackling many of these challenges, and I look forward to seeing the positive impacts of such discipline-wide changes in the near future. I hope that our endeavors to better control and understand the solid state will not only benefit the field of pharmaceutical formulations,[69,70] but will also stimulate solutions[71] to many outstanding chemical problems,[72] such as materials for the storage and distribution of clean energy,[73] and uncovering the processes that enabled the origins of life.[74]

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Notes

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under any circumstances needs to be acknowledged and carefully investigated.
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