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Co-crystal synthesis: Fact, fancy, and great expectations

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From discrete and dispersed to condensed and organized, directed assembly provides a link between molecular structure and macroscopic properties. If we are able to combine several different molecular entities within the same crystalline lattice and make co-crystals, then we can also access a wider chemical space whilst circumventing the need for complex covalent synthesis. Co-crystal technology can offer versatile avenues for the design and preparation of new solid forms that have tunable physical properties. All of this, however, requires an improved understanding of intermolecular interactions—over the full range of molecular size and structure. In this Perspective, we highlight some strategies and protocols that have been developed in order to synthesize co-crystals with predetermined and desirable structural features.

Introduction

The idea of making crystalline solids by design or with a purpose, as reflected in the term "crystal engineering", has been around for over sixty years,[1] but as a focused and readily identifiable research area, it began to flourish only in the 1990s.[2]

With its shared language and close links to concepts and principles developed in supramolecular chemistry, crystal engineering can be appropriately viewed as "supramolecular synthesis in the solid state". This is a truly interdisciplinary field which spans from theories of new and exotic intermolecular interactions to engineering and manufacturing of products and devices based on multi-functional and tunable materials. A primary driver behind research in this area is the realization that the precise three-dimensional orientation and organization of molecules, as controlled by symmetry and long-range order, ultimately determines many fundamental physical properties of that particular substance such as density, mechanical and thermal behavior, and optical and magnetic properties, to name but a few. Consequently, if we can successfully translate principles of molecular recognition into solid-state assembly and can change and control the metrics and topologies of the crystalline environment of a material by carefully exploiting the directionality and selectivity of non-covalent interactions, then we can build a foundation for bottom-up design and engineering of new materials with properties that can be dialed-in with unprecedented precision and efficiency.

The synthesis of co-crystals (*i.e.* multicomponent molecular crystals) has become a real focal point in crystal engineering.[3] The actual history of co-crystals has its origin in Wöhler's work in the 1850's on quinhydrone (which is a 1:1 co-crystal of quinone and hydroquinone, Figure 1),[4] but the modern interpretation of the term "co-crystal" has been around only for about 30 years. It owes a considerable debt of gratitude to both Desiraju's seminal book on crystal engineering[5] and to Etter's groundbreaking work on co-crystals.[6]

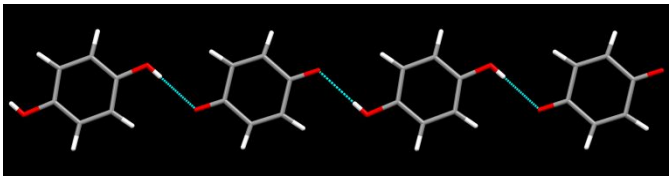

Figure 1: Primary hydrogen bonds in the structure of quinone/hydroquinone (1:1) co-crystal.

Now, what would be the point of spending a lot of effort on developing, testing, and refining synthetic protocols for the explicit purpose of simply making new co-crystals? Well, in short, co-crystals can not only enhance our fundamental understanding of various supramolecular interactions and molecular recognition, nucleation and crystal growth events but also pave the way to new solid forms of specialty chemicals with improved performance (such as active pharmaceutical ingredients, energetic materials, agrochemicals, *etc.*).[7] However, the chances of accidentally making a co-crystal, that is, bringing together different molecular species within one periodic crystalline lattice, are very small without effective synthetic protocols.[8] So how do we go about developing practical, reliable, and versatile synthetic methods for the deliberate and directed assembly of co-crystals? That's the topic for this contribution.

Covalent *versus* non-covalent synthesis

Co-crystal synthesis is clearly a feature of chemical synthesis, broadly defined, and it is therefore both appropriate and helpful to draw analogues between key aspects of covalent/molecular and non-covalent/supramolecular

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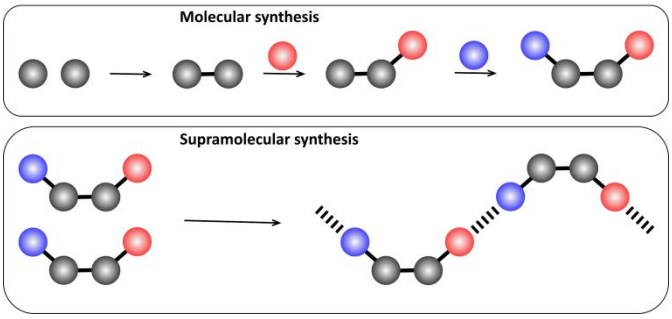
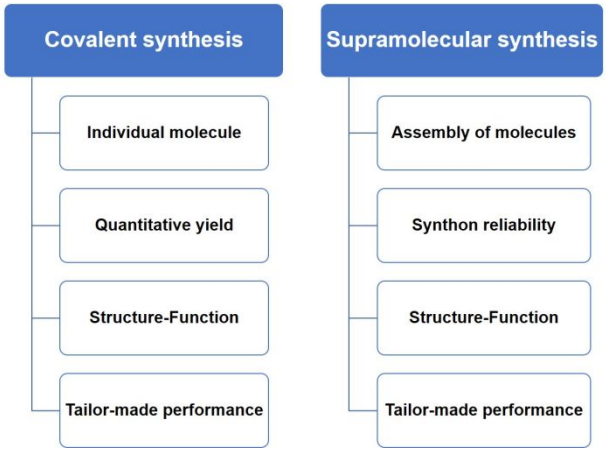
synthesis. Conventional chemical synthesis normally refers to the construction of new molecular species by bringing together two discrete entities, accompanied by the breaking and making of covalent bonds. The goals of such activities tend to be specific molecules with well-defined shape and stereochemistry, decorated with a number of different functional groups. Organic synthesis has a long and illustrious history and today we are capable of making molecules that can approach those that are found in living systems in terms of chemical complexity and structural intricacy. A retrosynthetic analysis of the target molecule allows the synthetic chemist to devise a step-wise protocol wherein she can reverse-engineer the goal through a sequence of transformations of simpler precursors. The chemical modifications are accomplished with the aid of an extensive library of named reactions that have been discovered and developed for almost two centuries. Although several chemical synthetic procedures are robust and versatile, many more will only work on a narrow range of substrates and they often require very specific reaction conditions or custom-designed catalysts. In some cases, a synthetic procedure will, despite considerable efforts to refine and optimize the reaction conditions, only deliver the desired product in but small quantities. Nevertheless, if the reaction ultimately yields the desired molecule, it is generally considered to be an example of a successful chemical synthesis.

The main challenge facing the supramolecular synthetic chemist is that she can no longer rely on the strength and stability of the covalent bond. The fact that all co-crystal synthesis has to rely on intermolecular interactions adds the inevitable element of reversibility which, in practice, essentially restricts all co-crystal synthesis to one-pot reactions (Scheme 1). For the preparation of co-crystals, we do not have the luxury of being able to sequester intermediates, nor can we employ conventional protecting groups and other “tricks of the trade” that are regularly deployed in order to realize a particular target molecule *via* covalent synthesis. Since a supramolecular intermediate can rarely be prepared, isolated and then added to another reactant in order to perform sequential, assembly-line type synthesis, we are faced with a particular challenge. How can we devise sophisticated and reliable synthetic pathways towards heteromeric supramolecular structures if we are limited to one-step reactions? A possible solution to the problem of making one-pot synthesis “sequential” may be to devise modular assembly processes that operate through a hierarchy of intermolecular interactions.



Scheme 1: Covalent *versus* supramolecular synthesis.[9]

The success of a “conventional” covalent reaction is often measured in terms of its selectivity, versatility, and yield. A similar approach can be used to judge the quality of a strategy or a protocol for co-crystal synthesis. First, "selectivity" translates to an ability to construct supermolecules with predictable connectivity based upon principles of molecular recognition. Second, "versatility" means that the assembly process should be able to operate effectively under different reaction conditions (*e.g.* change in solvents). Third, "yield", in a supramolecular sense, translates to frequency of occurrence of a specific molecular-recognition/binding event in the presence of other potentially disruptive intermolecular interactions. When evaluating the relative success of a supramolecular synthetic protocol, it is not unreasonable to point out that many molecular targets fail to be prepared in high yields through covalent synthesis. Finally, whether we are dealing with covalent or supramolecular synthesis, some of their goals are essentially the same (Scheme 2).



Scheme 2: Comparison of goals of covalent and supramolecular synthesis.[10]

The hydrogen bond (HB), for reasons of strength and directionality, has been at the center of most protocols for co-crystal synthesis reported to date, and many hundred examples of successful applications of HB-driven synthesis of multi-component solid-state architectures have been described. However, in order to design co-crystals of higher complexity, structurally as well as compositionally, we need to look beyond

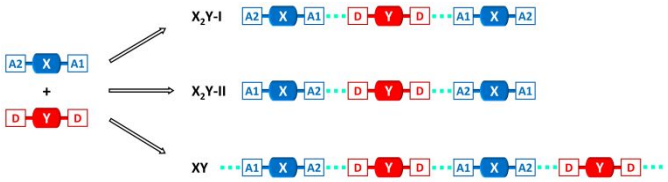
the exclusive use of hydrogen bonds. A suitable complement to a HB-based strategy may be provided by halogen bonds (XBs),[11] but more complex supermolecules and higher-order co-crystals can likely be synthesized using logical strategies derived from an improved awareness of the balance and competition between many other intermolecular interactions.

Dealing with synthon competition

Any "co-crystal engineering" project can be divided into three phases; design, construction (*via* a bottom-up approach) and utilization. As described before, such syntheses need to be carried out in one-pot manner and are mediated by inherently dynamic supramolecular forces. Hence, the success (indicated by the target having desired connectivity, composition and properties) heavily depends on the quality of the design step, which becomes harder due to competition among "supramolecular synthons",[12] especially when the number of reactants and their structural intricacy are high.

Supramolecular competition can arise whenever there is a shortage of complementary binding sites, typically as a result of a mismatch in acceptor/donor ratio, or when multiple interactions/synthons strive for dominance over one another. This will often lead to the downfall of the intended synthetic strategy and, as a result, the outcome of the co-crystallizations becomes less predictable, frequently with unwanted connectivities, stoichiometries and properties.

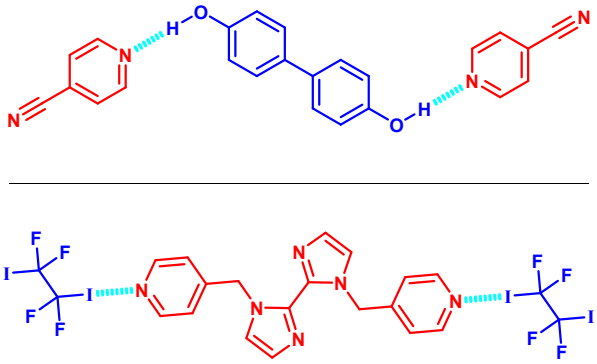
Even though synthon competition is an inescapable part of co-crystal synthesis, there are methods for minimizing such events in order to render structural insulation and guarantee the exclusive appearance of a certain synthon (or a set of synthons), while masking the undesired ones. Let's consider a simple, hypothetical co-crystallization experiment involving a heteroditopic acceptor, **X**, and a homoditopic donor, **Y**. As shown in Scheme 3, one can readily envisage at least three different compositional/structural outcomes from their association. If the desired product is a **X_2Y-I** trimer comprised of A1···D interactions, other synthon crossover events (in this case, the formation of A2···D interactions) need to be avoided. This can be achieved by establishing a hierarchy, that is, designing **X** in such a way that the A1 site is significantly stronger (or "better") than A2. If not, undesired synthons may not be completely suppressed so that the desired product will be contaminated with "by-products" such as **X_2Y-II** and **XY**. Such events not only reduce the supramolecular reliability but also pose difficulties in obtaining phase-pure material. In a worst-case scenario, the synthesis may become completely ineffective/counterproductive.



Scheme 3: Synthon competition and crossover which can lead to multiple products.

For the purpose of monitoring competition and selectivity of diverse supramolecular synthons, as well as of devising strategies to minimize synthon crossover possibilities, several groups have carried out systematic co-crystallization experiments with custom-designed multifunctional probe molecules. Co-crystals are ideal for such studies because their formation (*i.e.* heteromeric association) itself usually indicates selectivity and fidelity across a spectrum of recognition processes. Moreover, as functional groups are spread over multiple molecules, laborious syntheses can be avoided and influences from steric hindrance can be minimized.

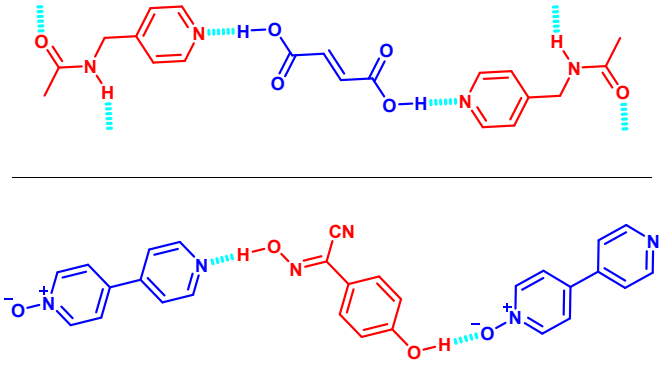
The hydroxy···pyridyl and hydroxy···cyano O–H···N interactions are two commonly encountered synthons that typically dominate over homomeric hydroxy···hydroxy interactions. What would be the outcome when all three functional groups exist together? Co-crystallizations with pyridyl, cyano and hydroxy moieties dispersed among pairs of co-formers (*e.g.* cyanophenols and pyridines, cyanopyridines and phenols) suggest that O–H···N(pyridine) interactions are favored over competing O–H···N(cyano) interactions (Scheme 4, top).[13] This means that the pyridyl/cyano competition for hydroxy group is a zero-sum game where the pyridyl acceptor prevails. In a similar study, we used isomeric *N,N'*-bis(pyridylmethyl)-2,2'-biimidazoles with the intention of mapping out their solid-state binding preferences with various HB and XB donors.[14] Again, even though they hold two different acceptor sites, imidazole-N and pyridine-N, the primary structure-directing interactions always involve the latter functionality (Scheme 4, bottom).



Scheme 4: Reactant combinations that lead to zero-sum synthon competition.

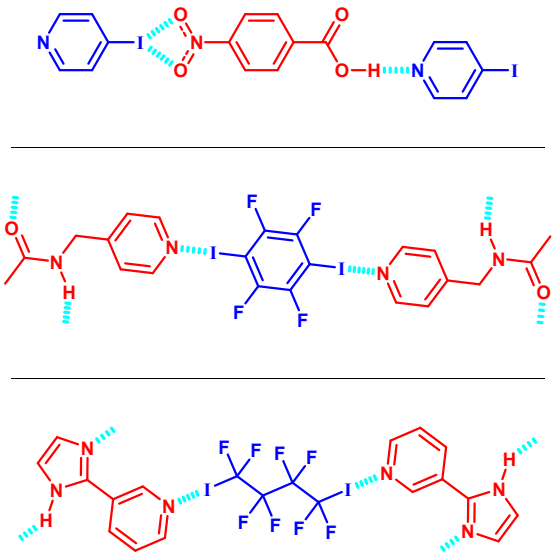
Occasionally, the competition between synthons can lead to a win-win or co-operative situation, but maintaining an appropriate and adequate hierarchy is still often essential in order to drive the assembly process in the desired direction. Acetamido- or acetamidomethyl-substituted pyridines co-crystallize with diacids in a 2:1 ratio.[15] While the heteromeric O–H(acid)···N(pyridine) hydrogen bond acts as the primary driving force for the formation of those co-crystals, the resulting binary aggregates are further organized through catemeric amide···amide (N–H···O) interactions (Scheme 5, top). From the

point of view of hydrogen bonding efficiency, hydroxyl and cyanoxime donors behave quite similarly (single-point donors),[16] and can be even more effective than carboxylic acids.[17,18] A structural study of (*Z*)-*N*,4-dihydroxybenzimidoyl cyanide, which contains both these functional groups, and asymmetric ditopic acceptors demonstrated that the hydroxy group is more competitive for the best available acceptor site (Scheme 5, bottom).[19]



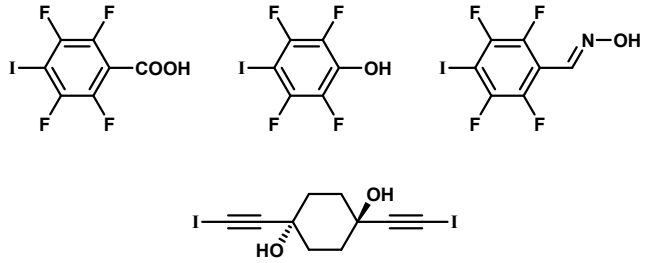
Scheme 5: Reactant combinations that lead to win-win synthon competition.

Establishing a synthon hierarchy and would obviously be easier if two (or more) different types of non-covalent interactions that are unlikely to interfere with each other (*i.e.* orthogonal interactions) are accommodated simultaneously in the synthetic protocol. In this context, hydrogen bonding and halogen bonding are known to provide a useful partnership (Scheme 6).[20-22] Even though less commonly explored, other σ-hole interactions (chalcogen,[23] pnictogen[24] and tetrel[25] bonding) may also potentially be used to good effect.[26]



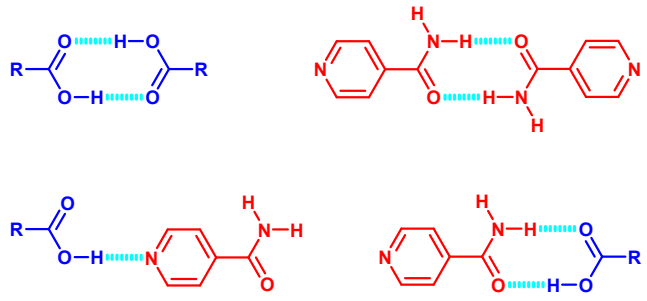
Scheme 6: Reactant combinations that lead to co-existent hydrogen- and halogen-bonding interactions.

A major concern when trying to combine hydrogen- and halogen-bonds within the same one-pot synthesis is that a given Lewis base can act as a perfectly capable acceptor for either interaction, and this may eventually hamper effective co-crystal synthesis. For example, selectivity has been difficult to achieve with when molecules featuring HB and XB donors of comparable strength are combined with N- or O-based, symmetric ditopic acceptors (Scheme 7).[27,28] Such situations may still be manageable by using either asymmetric or weakly basic acceptors; the former tends to choose hydrogen bonding,[27,29] whereas weak Lewis bases such as 1,4-dithiane are known to be partial to halogen bonding.[30]



Scheme 7: Molecules bearing strong HB and XB donor sites.

Another strategy for structurally insulating desirable molecular recognition event(s) may be built by employing electrostatic and geometric complementarities in such a way as to allow multipoint molecular recognition. Multipoint interactions typically benefit from both kinetic (supramolecular chelating effect) and thermodynamic contributions. Isonicotinamide, for instance, easily affords discrete tetramers and infinite chains with mono- and di-carboxylic acids, respectively.[31] In both cases, the two-point N–H···O interaction forming head-to-head amide dimer and the single-point O–H···N interaction between acid and pyridine remain very consistent, despite the fact that pyridyl, carbamoyl and carboxy groups can form a wide variety of synthons (Scheme 8). When, in place of pyridine, a heteroaryl moiety with sufficiently low HB accepting ability is used, the acid, which also possesses a good electrostatic and geometric fit for binding to the amide, abandons the N-heterocycle in favor of the acid···amide heterodimer.[32]



Scheme 8: Possible synthons between isonicotinamide and carboxylic acids.

It is worth mentioning that, when acting alone, geometrical biases can be somewhat fickle. In the isonicotinamide/carboxylic acid reactions discussed above, the acid may disrupt the formation of the amide···amide homosynthon.[33] A similar, more pronounced ambiguity was observed with carboxylic acids and 2-aminopyridine-functionalized supramolecular reagents such as 2-aminopyrazines, again due to the interplay between two-point (both homomeric and heteromeric) and single-point HB interactions.[34] However, incorporating a strictly single-point interaction (*e.g.* halogen bonding) can grant an additional level of control in these circumstances by facilitating the "survival" of the intended homodimer (Figure 2).[20,35]

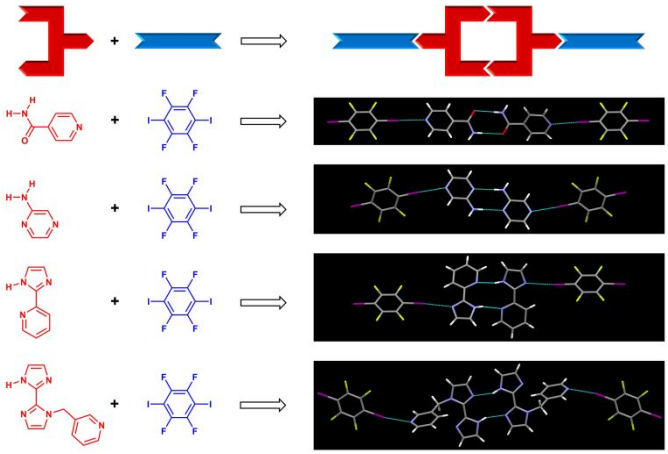


Figure 2: Co-crystallizations driven by two-point homomeric hydrogen bonds and single-point halogen bonds.

Alternatively, as 2-aminopyridines/pyrimidines associate strongly with carboxylic acids and sometimes easily surpass pyridine acceptors,[36] the homodimer formation can be turned off by grafting the XB donor with a carboxylic acid moiety (Figure 3).[37]

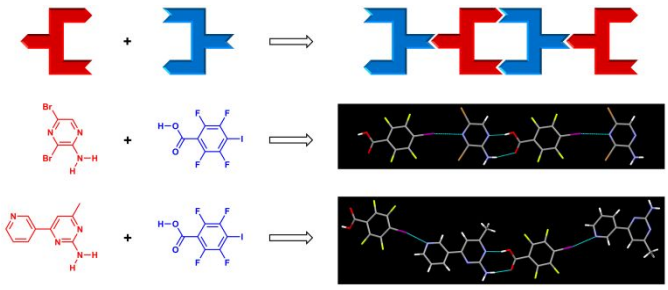
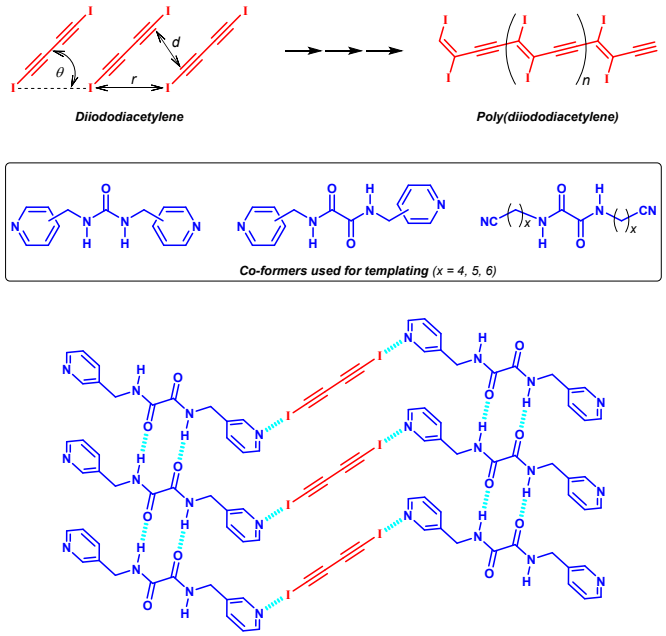


Figure 3: Co-crystallizations driven by two-point heteromeric hydrogen bonds and single-point halogen bonds.

A nice illustration of how practical applications of simple and reliable molecular recognition events can be envisioned was offered by Goroff and co-workers who devised an effective co-crystal-based pathway for preparing poly(diiododiacetylene).[38]

The polymerization of diiododiacetylene requires selective 1,4-addition that can only be achieved in the solid state *via* adequate topochemical control. By co-crystallizing diiododiacetylene with carefully selected host molecules (*e.g.* bis(pyridylmethyl)ureas, bis(pyridylmethyl)oxalamides, bis(cyanoalkyl)oxalamides), the mutual arrangement of the diacetylene monomers could be finely tuned within the crystalline solid so as to impose that essential regioselectivity over the course of polymerization (Scheme 9). Here, the urea and oxalamide derivatives can, predictably and persistently, assemble into one-dimensional chains *via* self-complementary hydrogen bonds, leaving terminal N-donor sites available for halogen bonding with monomeric units. Interestingly, in some monomer/template combinations, polymerization took place even in a topotactic manner without any phase change (Figure 4).



Scheme 9: Engineering of the relative orientation and spacing of the diacetylene monomers by means of urea- and oxalamide-based templates, where inter-template hydrogen bonds work in concert with monomer-template halogen bonds.

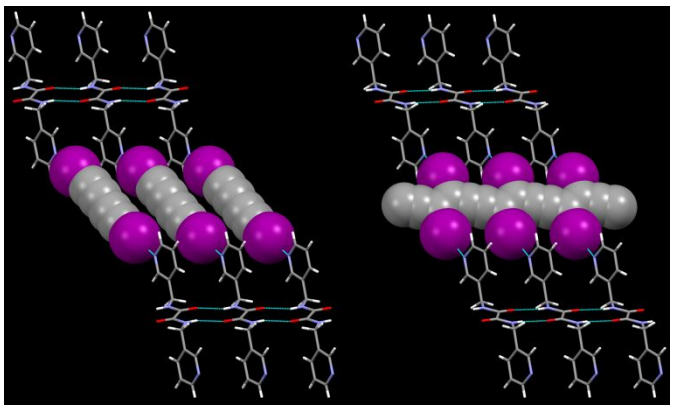


Figure 4: Topochemical polymerization of diiododiacetylene, templated by *N,N'*-bis(3-pyridylmethyl)oxalamide. Monomers and the resulting polymer chain are shown in space-filling CPK mode.

In contrast to diiodoacetylene and its congeners, iodoethynylarenes tend to be stable enough for trouble-free handling.[39,40] Moreover, the presence of an aromatic ring provides room for further modifications; various substituents can be introduced to modulate the donor strength and/or to bring about additional, non-disruptive interactions to the assembly process. Two examples of co-crystals made up of such iodoethynyl derivatives are shown in Figure 5.[41,42]

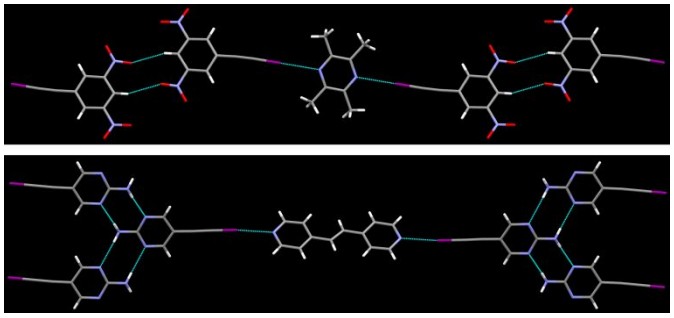


Figure 5: Structures of a) 1-(iodoethynyl)-3,5-dinitrobenzene/2,3,5,6-tetramethylpyrazine (2:1) and b) 5-(iodoethynyl)pyrimidin-2-amine/1,2-bis(4-pyridyl)ethylene (2:1) co-crystals.

From the HB- and XB-based co-crystals presented thus far, it is clear that pyridine-containing acceptors have been very popular in co-crystal synthesis. However, it is also worth pointing out that pyridine-*N*-oxides, which are readily available from pyridines *via* direct oxidation represent another important family of building-blocks for co-crystal synthesis. Owing to the charge separation of the N–O bond and the anionic nature of the acceptor site, pyridine-*N*-oxides are markedly stronger than corresponding pyridines; they make robust synthons with amines, alcohols, carboxamides, sulfonamides, *etc*.[43] Another significant structural characteristic is their ability to partake in bifurcated interactions, again thanks to the *O*-donor.[44] Further, monoxides derived from symmetric ditopic molecules such as pyrazine and 4,4'-bipyridine are effective in selective binding (see Scheme 5).[19,42,45] As a result of these beneficial features, heteroaromatic *N*-oxides have a great potential in strategic co-crystal construction—but still remain relatively underdeveloped in the realm of crystal engineering.

One can also expect that π···π stacking interactions,[46] since they have much different origins compared to hydrogen- and halogen-bonds, can deliver structural orthogonality which again, should minimize synthon crossover. Especially, when packing in the solid state, electron-rich and electron-deficient arenes tend to arrange on top of each other (thanks largely to favorable quadrupole-quadrupole interactions) so as to enable the formation of aromatic charge-transfer (CT) or electron donor-acceptor (EDA) complexes.[47] These face-centered parallel stacking motifs usually extend into infinite columnar architectures that can easily be coupled with other directional non-covalent interactions.[48] The structure of the benzoic acid/perfluorobenzoic acid (1:1) CT complex is illustrative of the cooperative interplay between phenyl-perfluorophenyl interaction,[49] arguably the most versatile aromatic stacking in crystal engineering, and hydrogen bonding (Figure 6).[50]

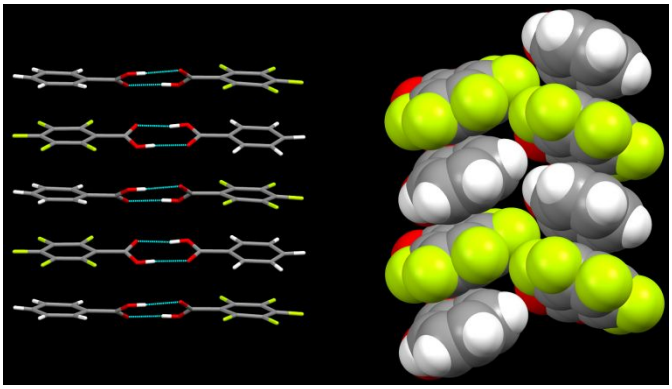


Figure 6: Structure of the benzoic acid/perfluorobenzoic acid (1:1) complex. (a) hydrogen-bonded heterodimers stacked in a head-to-tail fashion; (b) space-filling representation showing π-stacks of alternating phenyl and perfluorophenyl residues.

So far, we have discussed detrimental effects of synthon competition and crossover, as well as some proven strategies for circumventing them in order to accomplish reliable co-crystal synthesis. However, are there ever any benefits of synthon competition and crossover events? Let's go back to Scheme 3 and have a closer look at the by-product, **X_2Y-II**. In fact, it is a supramolecular isomer, and can be described as a synthon polymorph (same chemical composition, different synthons) of **X_2Y-I**. Since polymorphs exhibit dissimilar physicochemical properties, synthon crossover can provide opportunities for accessing more than one solid form from the same starting materials.

An early observation of synthon polymorphism in a co-crystal was made in 4-hydroxybenzoic acid/2,3,5,6-tetramethylpyrazine (Figure 7),[51] and 4-hydroxybenzoic acid/4,4'-bipyridine[52] and 3-hydroxybenzoic acid/acridine[53] were also found to behave in an analogous way. The use of hydroxybenzoic acid, which has two highly competitive donor sites, is undoubtedly the origin of synthon polymorphism in all

three systems,[17,45] and different combinations of the synthons depicted in Scheme 10 are responsible for the formation of those polymorphs. Other molecular dyads that exhibit synthon polymorphism include carbamazepine/saccharin,[54] urea/barbituric acid,[55] 2-ethoxybenzamide/3,5-dinitrobenzoic acid,[56] 2,4-dihydroxybenzoic acid/nicotinamide[53] and 1-iodo-3,5-dinitrobenzene/1,4-diazabicyclo[2.2.2]octane.[57] The increasing number of polymorphic co-crystals in the literature (the excellent review by Aitipamula and Tan[58] presents more data) helps to dispel the notion that co-crystallization can shut down polymorphism of molecules known to be polymorphic in their unimolecular states; it may, however, limit the frequency of occurrence.

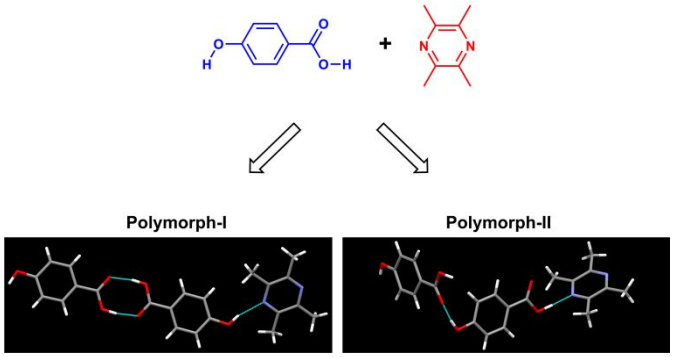
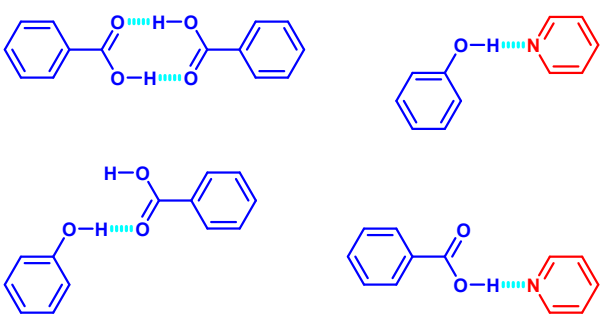


Figure 7: Synthon polymorphism in 4-hydroxybenzoic acid/2,3,5,6-tetramethylpyrazine.

It is reasonable to speculate that chances for synthon polymorphism increase when two (or more) competing interactions are energetically equally favorable. However, this is not always the case as crystallization of metastable polymorphs takes place under kinetic rather than thermodynamic control. Moreover, they often emerge from the same reaction mixture under same conditions (concomitant polymorphism) as minor polymorphic impurities and hence can be elusive. Such reactions may, however, be influenced by means of external factors (crystallization conditions such as solvents used, temperature, initial concentrations and molar ratios of reactants, method of co-crystallization, *etc.*) to deliberately and selectively synthesize each polymorphic form in high yields.[59]



Scheme 10: Primary synthons between hydroxybenzoic acid and pyridine derivatives.

Empirical knowledge and our experience about the behavior of various supramolecular synthons are the essentials in rational co-crystal design. The success we witness today in the field can therefore be credited to huge improvements in our understanding of various supramolecular synthons (their robustness, reproducibility, transferability and relative strengths), gained through extensive co-crystal screening and structural landscape studies. Unfortunately, such studies are often tedious and costly in terms of time, effort and resources (unless you have access to high-throughput, automated screening methods coupled with fast preparative and analytical tools).

The Cambridge Structural Database (CSD),[60] which currently contains approximately a million entries of experimentally determined crystal structures, contribute substantially to the evolution of the field. With the help of its associated software components such as Mercury, ConQuest, IsoStar and Mogul that enable easy search, retrieval, visualization and analysis of structural information, we can extract design principles and/or make informed predictions about the structural outcome of a targeted co-crystallization reaction by exploring the supramolecular behavior of similar systems available in the CSD. A recent addition to knowledge-based predictive methods is the hydrogen-bond propensity (HBP) tool, which statistically analyze related structures in the CSD and calculates the probability of occurrence of each possible HB interaction among the functional groups of interest.[61] Analogous methodologies for other kinds of supramolecular forces are yet to come. Since the CSD is continually growing, the accuracy of these knowledge-based predictive methods can be expected to improve gradually.

As in many other disciplines, computational methods can provide a great backup when developing practical co-crystal synthetic strategies. Especially, electrostatic potentials calculated on molecular surfaces (molecular electrostatic potentials, MEPs) appear to be highly promising; studies demonstrate that they can be used as a simple tool for ranking different HB/XB acceptors and donors.[62] In most of our HB- and XB-based work, we have used MEPs, along with Etters's empirical rules, to successfully predict primary supramolecular interactions in the solid state. We have also explored whether there is a threshold potential difference (ΔMEP) required for two competing binding sites in order to impart selectivity.[63] MEPs do not directly correspond to actual quantitative measures of interaction energies, but correlate well with them. Hunter *et al* put forward a set of guidelines for quantifying HB interactions by using calculated MEP values of donor and acceptor sites.[64]

Since occasional failures and exceptions are inevitable, it is always helpful to rely on several different complementary methods. In our recent work with thiazole amides and carboxylic acids where multiple, competing HB interactions are possible, both MEP- and HBP-based approaches accurately predicted the experimentally observed interactions.[65] These emerging theoretical and data-driven techniques can narrow down (or at least prioritize) the co-forming candidates for a

given experimental screening process and would ultimately open the doors to high-throughput, virtual screening and landscape mapping.

Binary-to-ternary progression

The performance and functionality of co-crystals can be enhanced by adding structural and compositional complexity, and the most obvious way of doing so is to increase the number of molecular components in their make-up. At the same time, this task represents one of the biggest challenges to the crystal engineer who deals with inherently dynamic non-covalent interactions and one-pot reactions to realize such assemblies. Failures are commonplace when attempting to prepare multi-component molecular solids, even with well-thought-out synthetic strategies. Such difficulties are magnified further as we try to advance to higher-order (ternary, quaternary, *etc.*) systems. This is also underscored by the fact that higher-level co-crystals are not as abundant as binary co-crystals. Most of the literature examples of higher-order solids contain solvents and/or charged species as their constituents,[66] or have been prepared from statistical methods and are therefore non-stoichiometric (organic alloys, solid solutions or mixed crystals).[67] In some cases, the desired product is accompanied by several side-products, so its isolation requires careful and tedious sorting.[68] Finally, there is a substantial number of fortuitous preparations of higher co-crystals reported in the literature.[69]

Higher-component co-crystal synthesis necessitates the presence of a range of chemical functionalities in the participating molecular entities which unfortunately may open the door to diverse binding events and multiple structural outcomes. To keep control over the reaction and to realize high yield of the target product, such syntheses should rely on hierarchical supramolecular synthons that are sufficiently insulated from each other. However, we also need to appreciate that, if a particular synthon is distinctly stronger than others, it tends to terminate the process at initial stages, thereby yielding lower-level co-crystals. Hence, to avoid such synthetic dead ends, incorporating moderately strong, but subtly discriminated/balanced supramolecular interactions is the key in these endeavors.

In 2001, we explored a purely synthon-based strategy for making ternary co-crystals,[70] counting on the hierarchical nature of hydrogen-bonded synthons. The success of our effort can be ascribed partly to the selection of isonicotinamide as one of the ingredients. This bifunctional molecule, despite its simplicity, is itself polymorphic and exhibits considerable synthon flexibility.[71] As a consequence, it has the capability to readily co-crystallize with a vast variety of reagents. Notably, as mentioned earlier, isonicotinamide and carboxylic acids represent one of the best "couples" in the arena and can produce well-defined supermolecules in very high yields.[31] They can engage in two robust, but markedly different, heterosynthons, namely acid···pyridine and acid···amide HB interactions (see Scheme 8). Even though the latter is relatively weak, it can effectively break acid···acid and amide···amide homosynthons, thereby favoring the heteromeric assembly of components. The 1:1 and 1:2 co-crystals of isonicotinamide and benzoic acid nicely reveal all these features (Figure 8a and 8b).[70,72] At this point, it is quite easy to visualize the structural outcome when two different monoacids with varying strengths are allowed to react with isonicotinamide; the stronger acid (best donor) would preferentially go for the pyridyl site whereas the weaker acid (second best donor) would bind to the amide site. This is the logical basis that we employed in order to prepare ternary co-crystals with pre-determined structures and compositions in high yields (Figure 8c).[70,71,73]

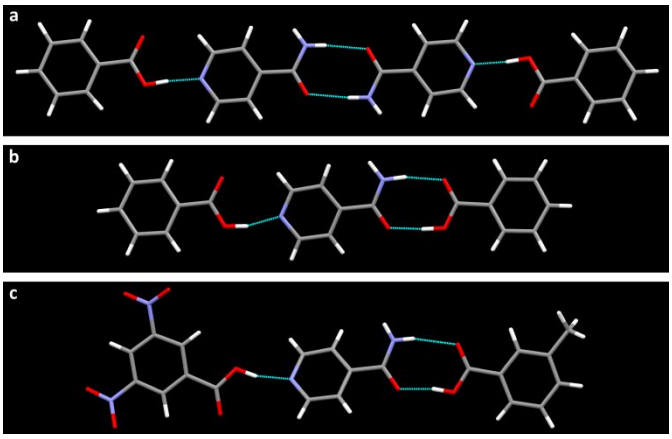


Figure 8: Structures of a) isonicotinamide/benzoic acid (1:1), b) isonicotinamide/benzoic acid (1:2) and c) 3,5-dinitrobenzoic acid/isonicotinamide/3-methylbenzoic acid (1:1:1) co-crystals.

The strategy of using a central linker molecule (which has two inequivalent binding sites) and two different peripheral molecules to fabricate triheteromolecular adducts was quite simple yet offered high fidelity. These results also inspired us to seek out other potential bifunctional supramolecular reagents for making ternary co-crystals. This led us to a new set of "ternaries" prepared from a family of picolyl-substituted benzimidazoles as the central components.[18,74] In these tailor-made ditopic HB acceptors, benzimidazole-N and pyridyl-N represent the best acceptor and second-best acceptor, respectively (as ranked by a simple electrostatic view of long-range hydrogen-bond interactions). Unlike isonicotinamide, the strengths of the two binding sites could be tuned independently, thereby allowing us to widen the synthon scope and to accommodate other functional groups such as cyanoxime (Figure 9).

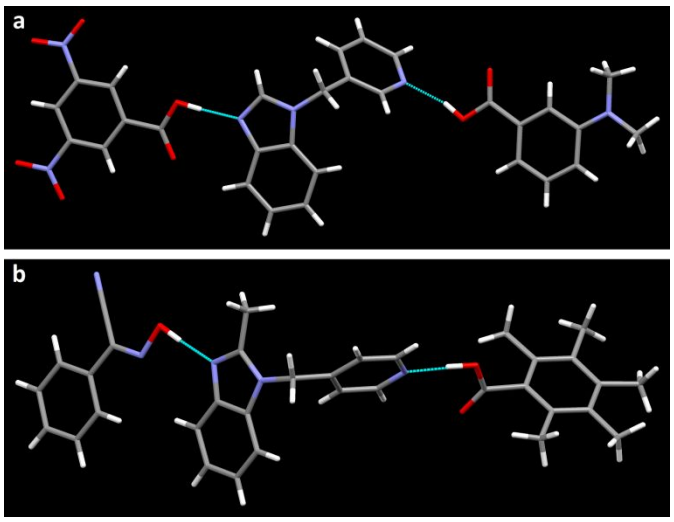
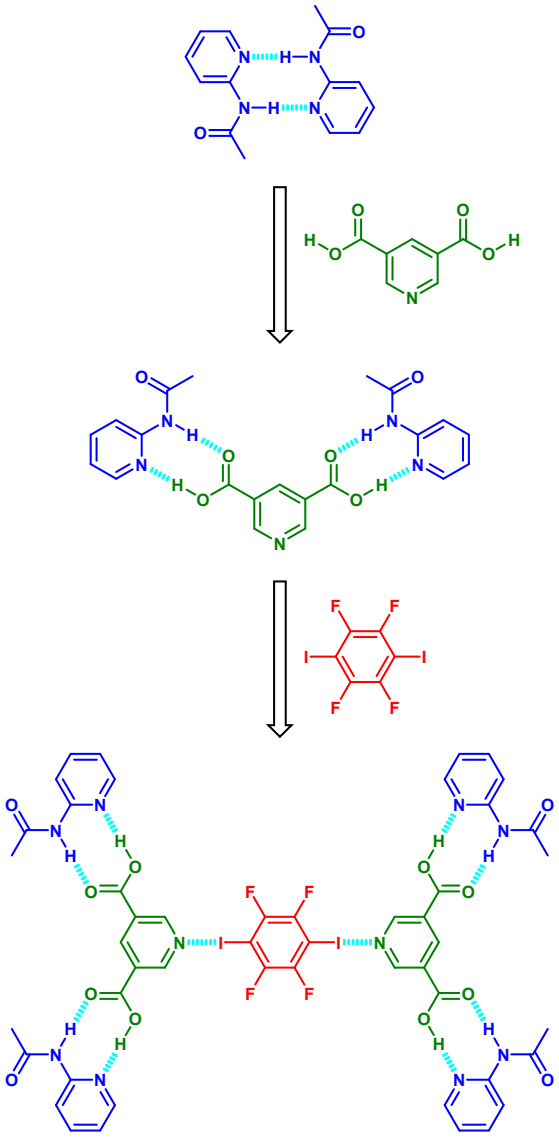


Figure 9: Structures of a) 3,5-dinitrobenzoic acid/1-(pyridin-3-ylmethyl)benzimidazole/3-(dimethylamino)benzoic acid (1:1:1) and b) phenylcyanoxime/2-methyl-1-(pyridin-4-ylmethyl)benzimidazole/pentamethylbenzoic acid (1:1:1) co-crystals.

We then wanted to attain synthon hierarchy/orthogonality and selectivity with the use of two fundamentally different supramolecular linkages. To that end, we set out to use 1,4-diiodotetrafluorobenzene, one of the most effectual halogen-bond donors, along with pyridine-3,5-dicarboxylic acid and *N*-(pyridin-2-yl)acetamide in an effort to introduce halogen bonding into ternary assemblies.[22] The rationale behind the selection of these three components is quite straightforward. *N*-(pyridin-2-yl)acetamide, which has an ideal binding pocket for a carboxylic acid functionality,[75] would react with pyridine-3,5-dicarboxylic acid to afford discrete trimers. Since each trimer still possesses an open pyridyl site that can further interact with ditopic 1,4-diiodotetrafluorobenzene, discrete heptamers made up in a 1:2:4 stoichiometric ratio was our expectation (Scheme 11).



Scheme 11: Anticipated 1,4-diiodotetrafluorobenzene/pyridine-3,5-dicarboxylic acid/*N*-(pyridin-2-yl)acetamide (1:2:4) ternary system.

First of all, the resulting solid did, indeed, contain all three components. In other words, we succeeded in the simultaneous use of hydrogen- and halogen-bonds in making a ternary system. Acetamidopyridine and the dicarboxylic acid had combined in the intended fashion through O–H···N/N–H···O interactions, forming trimeric units but, to our "partial" disappointment, the way those trimers engaged in halogen bonding with diiodotetrafluorobenzene was quite unusual and hence unpredictable, and we ended up with an extended architecture with an altered composition (Figure 10).

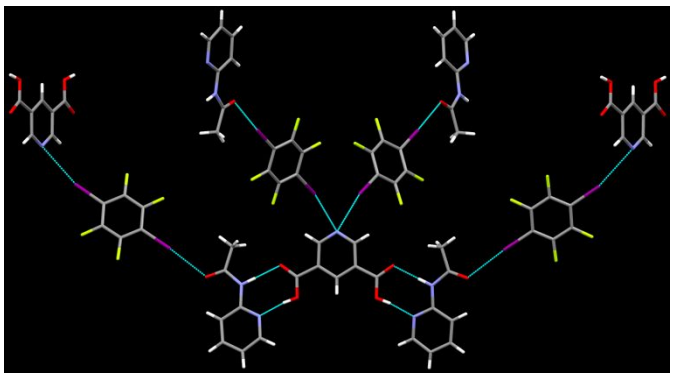
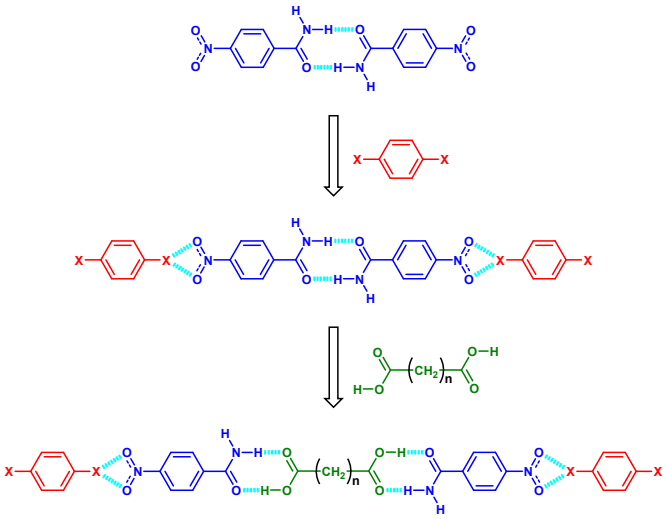


Figure 10: Structure of 1,4-diiodotetrafluorobenzene/pyridine-3,5-dicarboxylic acid/*N*-(pyridin-2-yl)acetamide (2:1:2) co-crystal.

Another strategy for the synthesis of higher-order co-crystals is based upon supramolecular homologation (*i.e.* extension through molecular lodging), in which a new molecular entity is inserted into a homomeric adduct, thereby increasing the number of components in the system by one unit. For example, the trimer formation step between pyridine-3,5-dicarboxylic acid and *N*-(pyridin-2-yl)acetamide (see Scheme 11 and Figure 10) can be viewed as a homologation reaction where the diacid is inserted into the acetylaminopyridine dimer.[76] Similarly, the 2:1:1 ternary co-crystals of 4-hydroxybenzamide, a dicarboxylic acid (*e.g.* fumaric acid, succinic acid) and a ditopic base (*e.g.* pyrazine, phenazine) can be considered as being derived from two independent events; insertion of a diacid between the amide···amide homodimer and insertion of a ditopic base in between the phenolic catemer motif (*i.e.* the infinite O–H···O–H··· synthon).[77,78]

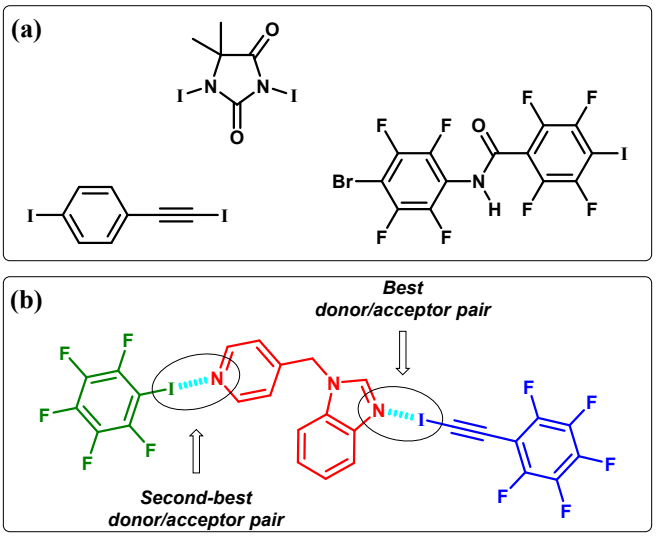
Keeping the same synthetic framework as described above, the functional groups of the three components can be slightly altered to also incorporate halogen-bonded synthons. An example, consisting of 4-nitrobenzamide, 1,4-dihalobenzene and a dicarboxylic acid, is shown in Scheme 12.[79] As expected, the crystallization of a 2:1 mixture of 4-nitrobenzamide and 1,4-diiodobenzene led to a one-dimensional supramolecular chain sustained by amide···amide two-point HB interactions and iodo···nitro bifurcated XB interactions. And the crystallization of a 2:1:1 mixture of 4-nitrobenzamide, 1,4-diiodobenzene and suitable diacids offered ternary co-crystals where the acid was embedded between the amide···amide homosynthon without interfering with the other synthons in the system. Moreover, a complementary route that employed 4-halobenzamide, dicarboxylic acid and 1,4-dinitrobenzene produced analogous results, proving the reliability of those two synthons and the versatility of the overall method.[77]



Scheme 12: Design strategy of 4-nitrobenzamide/1,4-dihalobenzene/dicarboxylic acid (2:1:1) ternary co-crystals.

Thioureas have the ability to engage in concurrent hydrogen- and halogen-bonding interactions.[80] Rissanen and co-workers utilized this inherent feature of thiourea in combination with crown ethers and perfluorocarbon halides to prepare a family of ternary co-crystals, all of which are governed by two orthogonal self-assembly processes; N–H···O(ether) hydrogen bonding and C–X···S(thiourea) halogen bonding.[81]

Even though halogen bonding can be as powerful as hydrogen bonding and is also endowed with greater directionality and tunability, we are not aware of any reports of ternary co-crystals made entirely from halogen bonding. Asymmetric XB donors such as 1-iodo-4-(iodoethynyl)benzene, 1,3-diiodo-5,5-dimethylimidazolidine-2,4-dione and *N*-(4-bromo-2,3,5,6-tetrafluorophenyl)-2,3,5,6-tetrafluoro-4-iodobenzamide (Scheme 13a) are potential candidates for such exercises as each can link to two different monotopic acceptors,[39,82,83] but may suffer from step-wise deactivation of their binding sites.[82,84] Instead, a more promising route may be devised by combining an asymmetric ditopic acceptor and two XB donors of different strengths (Scheme 13b).



Scheme 13: a) Asymmetric XB donors; b) a potential design strategy for XB-based triheteromolecular system.

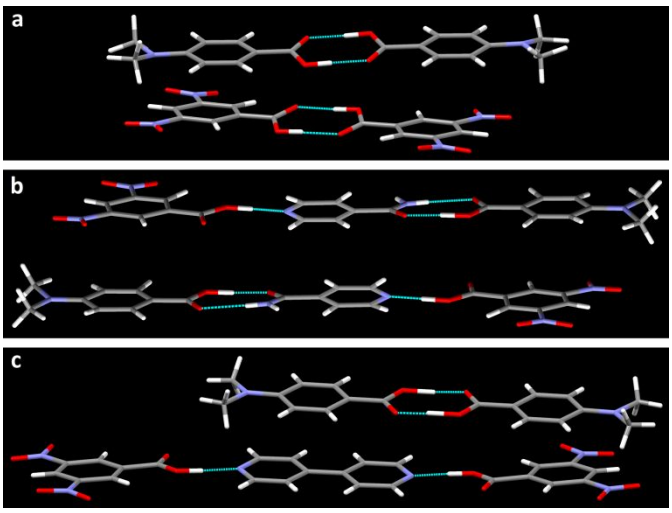
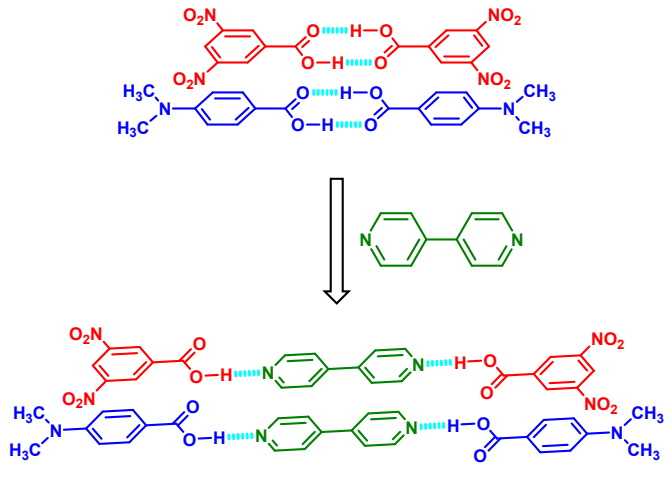


Figure 11: Structures of a) 3,5-dinitrobenzoic acid/4-(dimethylamino)benzoic acid (1:1), b) 3,5-dinitrobenzoic acid/4-(dimethylamino)benzoic acid/isonicotinamide (1:1:1) and c) 3,5-dinitrobenzoic acid/4-(dimethylamino)benzoic acid/4,4′-bipyridine (2:2:1) co-crystals.

As stated before, the eclipsed face-to-face stacking motif in aromatic π-systems that allows charge transfer/electron "hopping" between bipolar aryl species is highly specific and directional,[47] and has therefore found widespread use in crystal engineering. The structure of 3,5-dinitrobenzoic acid/4-(dimethylamino)benzoic acid (1:1) binary co-crystal, for example, consists of alternate donor-acceptor stacks of hydrogen-bonded dimers (Figure 11a).[85] Interestingly, the ternary co-crystal that we obtained with 3,5-dinitrobenzoic acid, 4-(dimethylamino)benzoic acid and isonicotinamide was also able to preserve those polarized π-stacking interactions between the two benzoic acid derivatives (Figure 11b).[70] Later on, Seaton *et al* attempted to use π-stacking in conjunction with hydrogen bonding for synthesizing "ternaries".[86] Their aim was to incorporate 4,4′-bipyridine as the third constituent into binary charge-transfer complexes such as 3,5-dinitrobenzoic acid/4-(dimethylamino)benzoic acid and other similar systems (Scheme 14). It turned out well and resulted in several three-component co-crystals. However, the stoichiometry was inconsistent among the structures and none of them had the predicted 1:1:1 assembly, even though all crystallization experiments were carried out using solutions with equimolar compositions. The 3,5-dinitrobenzoic acid/4-(dimethylamino)benzoic acid/4,4′-bipyridine ternary complex, for instance, showed a 2:2:1 ratio because the base disrupts only the dinitrobenzoic acid homodimer (Figure 11c).

When designing ternary co-crystals, a complete exploration of the structural landscape of binary systems is undeniably very useful in order to identify the preferred synthons and their hierarchies. On some occasions, a careful analysis of structures, especially space-filling features, of known binary co-crystals may provide valuable initial clues as to the possible existence of closely-related ternary systems. They may have voids into which a third component can be added (host-guest design). Simple geometrical arguments (size and shape of the guest molecule, size and shape of the host cavity) may be sufficient for dealing with such situations. Partial replacement, or volume exchange, is another possibility wherein one component in the original co-crystal is exchanged in part with a suitable third component. The presence of a particular constituent in two different environments makes extension/homologation through volume exchange possible, so that the least-privileged type is liable to be swapped. Often, both chemical (supramolecular behavior) and geometrical (size and shape) aspects of the exchanging species need to be considered in this strategy.



Scheme 14: Anticipated 3,5-dinitrobenzoic acid/4-(dimethylamino)benzoic acid/4,4′-bipyridine (1:1:1) ternary system.

The binary 2,2′-dihydroxybiphenyl/phenazine (2:3) co-crystal can be transformed into a 2,2′-dihydroxybiphenyl/phenazine/acridine (2:2:1) ternary system by substituting acridine for one (out of three) phenazine molecule that forms only a single hydrogen bond in the original binary assembly.[87] Binary-to-ternary conversion *via* volume exchange is also realizable with 2-methylresorcinol/4,4′-bipyridine (2:3) and 5-methylresorcinol/4,4′-bipyridine (2:3) co-crystals as they both have bipyridine molecules residing in two distinct crystallographic sites.[88] Only two molecules are involved in O–H···N interactions with methylresorcinol and the remaining one does not form any strong linkages. Consequently, volume equivalents such as acridine, phenazine, anthracene, pyrene, biphenyl and 2,2′-bithiophene readily take up the position of this weakly bound bipyridine molecule, affording ternary co-crystals (Figure 12).

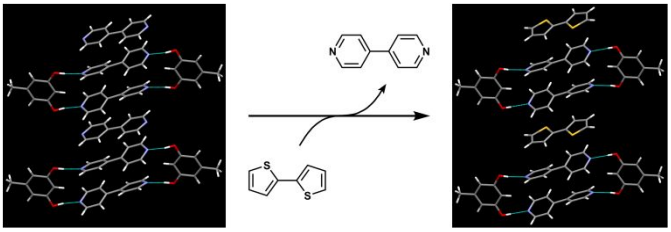


Figure 12: Advancing from 5-methylresorcinol/4,4′-bipyridine (2:3) binary co-crystal to 5-methylresorcinol/4,4′-bipyridine/2,2′-bithiophene (2:2:1) ternary co-crystal.

Sometimes, it is rather difficult to draw clear-cut boundaries between host-guest approach and partial replacement. In the binary 1:2 co-crystal of 1,3,5,7-tetrabromoadamantane and hexamethylenetetramine, one half of the amine molecules are only loosely occupied within the adamantane-like cages of the lattice, and can be replaced by carbon tetrabromide (a size and shape mimic of the amine), to obtain a 1:1:1 ternary solid.[89] Similarly, the 2,4,6-tris(4-bromophenoxy)-1,3,5-triazine/hexamethylbenzene (1:1) inclusion compound can be converted into a ternary dual-guest system by introducing an electron-deficient second guest such as picric acid or 1,3,5-trinitrobenzene; this second aromatic guest undergoes charge-transfer complexation with electron-rich hexamethylbenzene and results in 2:1:1 inclusion compounds.[90]

The success of using structural inequivalence(s) for moving from binary to ternary systems sparked interest in trying to extend a similar approach to the assembly of quaternary co-crystals. In this way, Desiraju and co-workers were able to produce a series of quaternary co-crystals by bringing together various resorcinol and pyridine derivatives (Figure 13).[91] At present, however, except for a handful of quinary and senary solid solutions,[91] there are no known stoichiometric co-crystals containing more than four components. Again, this is not too surprising since, with increasing number of components and functional groups, the number of possible permutations creates a very difficult synthetic challenge.

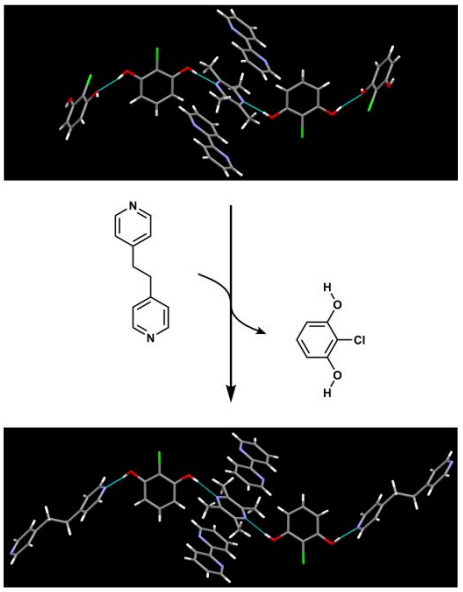


Figure 13: Advancing from 2,3,5,6-tetramethylpyrazine/2,2′-bipyridine/2-chlororesorcinol (1:1:2) ternary co-crystal to 2,3,5,6-tetramethylpyrazine/2,2′-bipyridine/2-chlororesorcinol/1,2-bis(4-pyridyl)ethane (1:1:2:1) quaternary co-crystal.

In any solution-based co-crystallization experiment, apart from a careful selection of synthons, it is also essential to employ a solvent (or solvent system) in which all the starting reagents have comparable solubility to keep them from crashing out as single-component solids. When moving into higher-order co-crystals, the solubilities of possible binary and other low-level phases should also be taken into account, and finding an ideal solvent so as to precisely balance the solubility is very difficult. Moreover, the role of the solvent can be multifaceted and quite complicated, and goes beyond that of a mere medium wherein all the supramolecular reactants are dissolved, so their effects are difficult to rationalize. They can sometimes have an impact on the structural outcome by amplifying certain synthons at the expense of others.[92] Or else, they can actually participate in the reaction and afford unintended solvates.

Mechanochemistry, in the forms of neat and liquid-assisted grinding or milling, can offer an alternative that may avoid some of the issues associated with solvent-dependent synthesis, although this approach clearly is not suitable for delivering crystals for single-crystal X-ray diffraction. Several studies have indicated that a mechanochemical route can be more effective in making ternaries which would otherwise be unattainable *via* conventional solution synthesis.[93]

Binary co-crystals have already found their way into diverse applications. In contrast, most known ternary and quaternary co-crystals are primarily the result of academic curiosities ("can we make them?") and/or esthetic appeal, but they will likely serve as blueprints for more comprehensive and functional materials. With a growing body of research by groups from all around the world, it is just a matter of time before such materials become a reality. It is worth highlighting that high-value compounds such as isoniazid (an antitubercular drug), acetazolamide (a diuretic drug), quercetin (an antioxidant), 1,3,5-trinitrobenzene (a high explosive) have already been obtained as ternary co-crystals.[94] Another compelling case is the ternary dual-drug co-crystal made with two first-line antitubercular drugs, isoniazid and pyrazinamide.[95] These examples clearly point towards what we can expect to achieve with higher-component co-crystals in the near future.

Co-crystals in materials design

When it comes to the many applications that will likely arise from fundamental research on co-crystals, the fact that a family of co-crystals can offer a degree of predictable structural periodicity means that co-crystallization-based technologies offer unique opportunities for deliberate adjustments and dialing-in of bulk properties and performance of new materials. If we are able to make modular changes to the crystalline framework that contains an "active" molecule, we can improve our understanding of how to recognize the connections between molecular descriptors, crystal structure and morphology, and physical properties of organic crystalline solids. In short, by using co-crystallizations to probe the balance and competition between intermolecular interactions in the solid state, we may be in a position to decipher how fundamental laws of physics manifest themselves in structure direction molecular recognition events of critical importance to materials science and biology alike.

Simply making a number of co-crystals without trying to control as many structural degrees of freedom as possible will not bring us any closer to hypothesis-driven bottom-up design of crystalline materials with tailor-made properties. For example, if the non-covalent interactions that drive the co-crystal synthesis essentially produce discrete supramolecular entities, then there are few discernible advantages of heteromeric co-crystals over homomeric molecular solids. In contrast, if the co-crystal contains well-defined and robust supramolecular one- or two-dimensional architectures, the number of possible structural variations in a series of co-crystals becomes much more limited. This, in turn, is a prerequisite for making reliable and transferable correlations between molecular structure (or even properties of the bulk material of the individual homomeric solids), with one or more physical properties of the co-crystal. Consequently, the extent to which co-crystals can provide a useful strategy for effective materials science will increase as the dimensionality of the dominating supramolecular motif increases. If we can fix or restrict the structural framework that contains an "active" molecule, we can simply replace it with a closely related component without any changes to the overall crystal structure and may allow us to deliver a specific property or macroscopic response akin to what can be achieved with alloys in metallurgy and doping in semi-conductors.

A new aspect of materials chemistry is focused on developing self-assembly and crystal engineering into practical avenues for the reliable synthesis of co-crystals and multi-component molecular solids. Central to this task requires us to solve the problem of controlling the balance between a range of reversible, directional, and relatively weak non-covalent interactions. Since functionality in co-crystals often involves hierarchical matter with properties determined across multiple length scales, a focus on modular assembly is critical as this may allow us to "dial-in" a desired structural element without having to re-engineer the whole process from the ground up. The combination of programmable directed assembly for the synthesis of co-crystals, coupled with the diversity of molecular recognition, can subsequently create materials that are both responsive and evolutionary.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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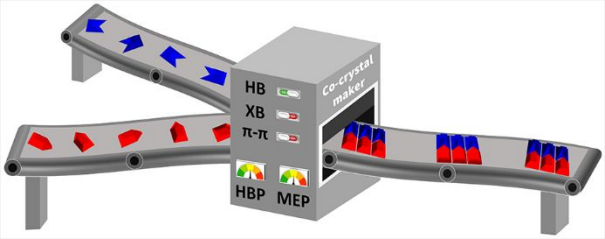

Some strategies for driving co-crystal synthesis using a variety of competing non-covalent interactions are presented.