Rational crystal design: supramolecular chemistry and molecular recognition in molecular solids

In particular the formation of cocrystals

How does a molecule become a material?

Supramolecular chemistry
- studies the way in which the molecules join, interact and assemble to form larger assemblies... which eventually become objects in our everyday life

Nanotechnology
- studies and creates objects composed of ca. 1-1,000 molecules

Crystal engineering
- deals with systematic construction of crystal structures, using molecules as 'bricks'

Impact on drug delivery and tablets

Why are the tablets so big? Why big litigation over patents?

Lipitor: Annual sales >$13 million per annum

Why are the numbers so large?
What do we know/understand about the process of crystallization?

“One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition.”

“...there are many mysteries of nature that we have not solved. Hurricanes, for example, continue to occur and often cause massive devastation. Meteorologists cannot predict months in advance when and with what velocity a hurricane will strike a specific community. Polymorphism is a parallel phenomenon. We know that it will probably happen. But not why or when. Unfortunately, there is nothing that we can do to prevent a hurricane from striking any community or polymorphism from striking any drug.”
Dr. Eugene Sun
Abbott Laboratories, 1998
(re: Ritonavir)

Main point, therefore, is: understanding molecular solids

Solids are (in our case) built up of molecules. Molecular properties are largely determined by functional groups, e.g.:

Solid state properties will depend, however, on the nature of the solid that is formed.

- the molecular structure
- the structure of the molecular assembly
- solid-state properties of a material
What do we mean by crystal form?

There are two general uses of the words “crystal form”. One looks at the external shape of the crystal while the other relates to the internal arrangement of the molecule in the solid.

A molecular view
differences in the internal architecture of the crystal:

paracetamol form I paracetamol form II

A macroscopic view
differences in crystal habit or shape:

Level 1: Is there order within the crystal?
The first step in understanding molecular solids is in elucidating the organisation of the molecular assembly.

molecule

low order high order

amorphous - “random” arrangement

The solid state is “DYNAMIC” in that interconversion is possible between structures

crystalline - 3-dimensional periodicity
For a particular building block (molecule) there are many potential ways of solid-state ordering (polymorphs):

- crystalline form
- polymorph 1
- polymorph 2
- polymorph 3
- polytypes

Typically, only one polymorph is stable. The rest are metastable and may convert to the stable one.

Level 2: Variations of the order

New crystalline forms are also achieved through formation of multicomponent systems e.g. salts, cocrystals, hydrates, solvates, solid solutions, mixed crystals

Level 3: More than one type of species in the crystal

Supramolecular chemistry

Supramolecular chemistry is the chemistry of the "intermolecular bond" based on the underlying theme of "mutual recognition".

1987 Nobel prize for Supramolecular Chemistry:
Jean-Marie Lehn, Donald J. Cram and Charles J. Pedersen


What are intermolecular bonds in a crystal?
“Intermolecular bonds”
Typical strength = 10-15 kcal mol⁻¹. A certain degree of directionality is required.

- **Example 1:**
  Hydrogen bonds (H-bonds)
  ![Diagram of hydrogen bonds](image1)

- **Example 2:**
  Halogen bonds (X-bonds)
  ![Diagram of halogen bonds](image2)

Molecular assembly via intermolecular bonds
Molecules within the crystal join through these non-covalent interactions to form molecular assemblies: supermolecules.
Lehn: “Supermolecules are to molecules and the intermolecular bond as molecules are to atoms and the covalent bond.”

- **Polyethylene:** a covalent polymer
- **Benzamide:** crystallizes from water as hydrogen-bonded “non-covalent” polymeric chains

The entire benzamide crystal is in a sense a giant supermolecule!

A crystal as a product of supramolecular synthesis
During crystallization of an organic solid, patterns of intermolecular interactions are established. A type of “synthesis strategy”. Indeed we will use the description “synthons.”
Analysis of crystal structures reveals that some patterns are frequently encountered:

- ![Diagram of synthons](image3)

These robust patterns of interactions are “supramolecular synthons.”
So we can say: supramolecular synthesis through cocrystallisation?
Supramolecular synthons can be utilised to design a supramolecular synthesis, like traditional synthons of organic chemistry.

The product of such a supramolecular synthesis is a two- (or more) component crystal: a cocrystal.

The place of supramolecular chemistry

- Understanding supramolecular chemistry is central in controlling crystallisation and the discovery of new solid forms.
- Both areas are important in the practical application of organic solids as functional materials.
- Important applications are in polymorphism and constructing of cocrystals with technologically important properties such as:
  - photo- (or thermo-) switching behaviour
  - reactivity
  - conductivity
- Of particular importance are pharmaceutical solids: the ability to control polymorphism and improve solid forms of an active pharmaceutical ingredient (API) would considerably shorten the manufacture time and reduce costs!

Polymorphism of organic solids
Polymorphs can have very different properties:

**Physico-chemical**: melting point, stability/reactivity, solubility, density, vapour pressure

**Mechanical**: hardness, particle flow, tableting, compactability

**Spectroscopic**: UV/visible (colour), IR and Raman, solid-state NMR

**Pharmaceutically related**: different bioavailability, different formulation properties (e.g. flow, compaction), interactions with excipients in a tablet

Identifying and controlling polymorphic form is a major part of getting drug approval by drug licensing authorities (e.g. FDA in the US), and part of many steps in the development process.

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**Solid Form Selection** – flow diagram of the stages in development of a new drug for the marketplace

1. **Discovery of molecule**
2. **Drug Substance Manufacture**
3. **Drug Product Manufacture**
4. **Preformulation**
5. **Formulation**
6. **Process Development**
7. **Clinical Trials**
8. **Launch**

Rational selection of solid form of drug for development

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**Polymorphism of organic molecular solids**

Polymorphs of organic solids are obtained by rearranging much weaker non-covalent forces: van der Waals interactions or hydrogen bonds.

Molecular crystals are expected to exist in a larger number of polymorphs that are more readily interconvertible.

**Conformational polymorphism**: polymorphism accompanied by changes in molecular conformation.

Example of ROY – Red Orange and Yellow polymorphs found initially.

Conformational polymorphs have different levels of coplanarity between benzene and thiophene rings.

This results in colour differences, due to different extents of delocalisation.
Polymorphism of molecular solids: ROY

Now known polymorphs:
- Red prisms (R)
- Yellow prisms (Y)
- Orange Plates (OP)
- Orange Needles (ON)
- Yellow Needles (YN)
- Orange-Red Plates (ORP)

7th highly unstable form

The energy differences between polymorphs are very small, they can nucleate from the same solution: **concomitant polymorphs**

If the crystallisation and isolation are rapid enough, **concomitant polymorphs** can be separated


Formation of ROY polymorphs

Yellow prisms (Y) is the most stable form of ROY

At high supersaturations, nuclei of other forms in addition to Y can form

Typically, they would dissolve, but high supersaturations enable their growth along with the stable form

![Graph showing the formation of ROY polymorphs](image)

Growth of metastable polymorphs: possible mechanism

Nuclei of less stable polymorphs, that would normally dissolve, can keep growing in high supersaturation regimes

![Diagram showing growth of metastable polymorphs](image)
Polymorphism control

Instead of inducing conditions for the nucleation of new polymorphs, polymer materials can be used as “artificial (insoluble) nuclei” to seed the crystallisation reaction.

This “seeding” strategy allows the control of polymorphism and:
1) avoids unwanted polymorphs and 2) allows the formation of new polymorphs.

Discovery of new polymorphs

Polymorphism control by pseudoseeding (heteromolecular seeding)

Crystals of compounds with molecular shape resembling the target molecule provide potential “blueprints” for new polymorphs.

Polymorphism in this case results in differences in the hydrogen-bonded framework, rather than conformation.
"Jumping crystals" and mechanoluminescence

Oxitropium bromide:
Thermally-induced change in crystal structure results in violent jumps (up to several centimeters)

Two polymorphs of a boron-based cyclic compound have different UV-fluorescence properties and can be transformed by scratching and gentle warming

Compaction and making tablets
Example of paracetamol: 4-(acetylamino)phenol
Two established polymorphs: 1 and 2
Hydrogen-bonding patterns are very similar in both

Form 1 contains corrugated layers, that are not easily compressed as flat layers of form 2.

Unfortunately, form 2 is not stable and commercial product is form 1 with lots of binding material
Drugs of this type are typically used to treat both duodenal and gastric ulcers. At one time Zantac was earning $2 billion per annum. GSK (UK) vs. Novopharm (Canada)

Major legal dispute over patents: not because of pharmacological reasons or the identity of the molecule – but because of the structure of the crystals formed – polymorphic form!

Patenting – not the molecule but the crystal!

Conformational polymorphism

The two forms of Ranitidine HCl are conformational polymorphs

Polymorphism is helped by the flexibility of the molecule - an illustration of the problem that affects most modern high molecular weight drugs! Balance between intra and intermolecular forces.
Bioavailability problem – new polymorph suddenly appeared

Nonvir (Ritonavir) HIV protease inhibitor from Abbott Laboratories

Initial sales of the drug were based on the properties of “Polymorph I”

In 1998: “We have encountered an undesired formation of a crystalline structure “Polymorph II” that effects how the capsule form dissolves”

Sales ceased while new formulation developed and FDA approval obtained.

In pharmaceutical industry, it is becoming crucial to understand how molecules interact with (recognise) each other within the crystal

Most common methods of solid-state characterization

- **Diffraction methods:**
  - X-ray single crystal X-ray diffraction
  - X-ray powder X-ray diffraction (PXRD)

- **Spectroscopic methods:**
  - FT IR, Raman spectroscopy, Terahertz spectroscopy
  - NMR spectroscopy

- **Thermal methods:**
  - Thermogravimetric analysis (TGA)
  - Differential scanning calorimetry (DSC)
  - Differential thermal analysis (DTA)

Typically, diffraction and spectroscopic methods are non-destructive, whereas thermal analysis often leads to the decomposition of the sample

X-ray diffraction on a single crystal

The scattering of X-rays on a crystal can be mathematically described as the reflection of X-ray off different crystallographic planes

The diffracted beams must be in constructive interference, hence “X-ray reflections” are observed only for some values of \( \theta \):

\[
2d \sin \theta = n \lambda \quad \text{(Bragg’s law)}
\]

- \( d \) = spacing between a set of crystallographic planes
- \( \theta \) = diffraction angle
- \( \lambda \) = X-ray wavelength
- \( n \) = integer
Intensity of diffracted radiation

Since there are many planes intersecting the unit cell, X-ray diffraction produces numerous reflections that are distributed in space around the crystal. Each reflection is defined by a characteristic set of Miller indices ($hkl$) of the reflecting plane.

Measuring the positions of reflections allows determining the symmetry and shape of the unit cell.

Structure solution using powder X-ray diffraction

Powder X-ray diffraction (PXRD) relies on the same principle as single crystal diffraction, but the sample is a collection of randomly oriented crystallites.

X-ray diffraction results in rings of diffraction around the sample.

The X-ray detector moves through each ring, providing a diffractogram.

Structure solution using X-ray powder diffraction

The two-dimensional information obtainable using single crystal X-ray diffraction is condensed into one dimension using PXRD.

Significant overlap of peaks makes it difficult to extract structural information – there are two approaches:

1) Extracting individual intensities, followed by structure solution and refinement

2) Building a model structure and fitting the experimental and calculated diffraction patterns
Indexing of the PXRD pattern

The first step in structure determination from PXRD data is always indexing of the powder pattern: each reflection is assigned a Miller index and the unitcell is defined:

\[ \sin^2 \theta = \frac{\lambda}{2(a^2 + b^2 + c^2)} \]

This can readily be accomplished for cubic structures:

The plot of \( \sin^2 \theta \) against \((h^2 + k^2 + l^2)\) gives information on \(a\).

Once all the peaks have been indexed, they can be treated as individual reflections, similar to single crystal reflections, proceeding to structure solution.

Building a model structure

Most structures are too complicated to allow easy indexing of the powder pattern or subsequent extraction of individual intensities.

The alternative approach is to generate random unit cells, taking the most common values of \(a, b, c\) (between 4 and 35 Å) and \(\alpha, \beta, \gamma\) (between 90 and 120 °).

The crystal system and the internal symmetry of the crystal (space group) can also be explored, trying the most common ones first.

Generating possible structures

After a suitable unit cell has been recognized, it is then filled with molecules. Thousands of trial structures are thus generated.
Refining the structure

Each generated structure is validated by comparing its calculated PXRD pattern with the experimental one. When a suitable structure has been found, it is then fitted to the experimental diffraction pattern using Rietveld refinement.

Identification of solid phases using powder X-ray diffraction

The lack of order in an amorphous phase makes it “invisible” to this method. Note the use of the simulated i.e. theoretically expected pattern.

Terahertz (THz) radiation

It is non-ionising, sensitive to water content and in particular it measures intermolecular vibrations. So unlike IR and Raman it will be very sensitive to crystal packing effects rather than intramolecular vibrations.

$10^{12}$ Hz
Lattice dynamics and THz spectroscopy
(courtesy of Graeme Day, Univ. Cambridge)

Carbamazepine, form I:

Carbamazepine, form III:


Crystal engineering

- We have seen examples of the possibility designing crystal structures to control solid state property.
- This corresponds to the design of materials at the molecular level, if you wish nanotechnology.
- An older term is crystal engineering:
  
  "Understanding of intermolecular interactions in the context of crystal packing and in the utilisation of such understanding in the design of new solid with desired physical and chemical properties."
Some strategies in crystal engineering

Five approaches are:

1) **polymorph control** - it is difficult to achieve and polymorphs have a bad habit of rolling down the energy landscape to form a thermodynamically stable one!

2) **salt formation** - mostly a trial and error technique, heavily used in pharmaceutical industry, as it efficiently increases aqueous solubility of compounds

3) **formation of solid solutions** - forcing a molecule to adopt a lattice site in the crystal of a different compound.

4) **use of steering groups** - specific groups are introduced onto the parent molecule, so as to steer it into a preferred solid state structure. Examples: hydrogen bonding, Cl...Cl and π...π interactions

5) **formation of cocrystals** - most recent and closest to the ultimate goal of crystal engineering, utilises supramolecular synthons to rationally construct supramolecular structures

What is a co-crystal (cocrystal)?

One definition: A multicomponent crystalline solid, composed of more than one type of neutral molecule. Comparison with organic salts.

- Co-crystals have a **stoichiometric composition** - there is specific recognition between molecules that constitute a co-crystal: some identifiable interactions.

Bird and fish are complementary in shape: only in a 1:1 ratio do they fill space fully

Red and white swans have identical shape, they fill space in any ratio (alloy).

Designing cocrystals

As for single component crystals at the simplest level, co-crystals can be obtained by packing molecules to fill space most efficiently

According to Kitaigorodski, molecules will always pack so as to minimise empty space

"Nature abhors a vacuum"

For "badly-shaped" molecules, this can be achieved by adding extra building blocks: forming co-crystals based on shape-fitting
Supramolecular synthons in cocrystal design

Specific interactions between molecules can be achieved by using supramolecular synthons: robust motifs of intermolecular forces, established by database mining.


Directionality of hydrogen bonds - Directionality of supramolecular synthons

Overview of the CSD indicates preference of O-H...O bonds for linearity - especially after the "cone correction".

Robust supramolecular synthons

Supramolecular synthons enable cocrystal synthesis by design because they are robust to changes in molecular size or shape - similar to synthons of organic synthesis.

Generation of finite (or discrete) assemblies

Generation of infinite assemblies

We can also design infinite chains, sheets and cages using the acid dimer synthron:
Amide-amide synthon
Formation of amide chains: a persistent motif in amide crystals. Occurs in both polymorphs of benzamide.

Describing the geometry of supramolecular synthons
Supramolecular synthons are usually described using a "graph-set" notation. Identify the H-bond arrangement, then determine:

\[ \mathcal{G}_{d^a}(n) \]

- \( d \) = the number of hydrogen bond donors
- \( a \) = the number of hydrogen bond acceptors
- \( n \) = the number of atoms in the motif

R \(_2\) (8) R is for "Ring"

Other motifs in graph set analysis
R = Ring
C = Chain
S = Salt
Comparison of homo- and heterosynthons

The examples of carboxylic acid dimers and amide chains are examples of homosynthons: they correspond to self-assembly of identical functionalities.

For the design of cocrystals much more interesting are heterosynthons: recognition motifs involving different functional groups. These will encourage different molecules to crystallise together. Some of the better known are:

- Adenine-thymine pairs
- Acid-amide synthon

We can also consider synthons involving weak hydrogen bonds

Weak hydrogen bonds can play a supporting role in a supramolecular synthon.

Such weak bonds may have more of a "steering" than bonding role. A good example is the pyridine-carboxylic acid heterosynthon:

- the supporting C-H-O bond forces the pyridine ring to be coplanar with the carboxylic acid moiety.

Variations on the theme

Another example of a supramolecular synthon composed of weak and strong interactions involves cocrystals of molecules like phenazine:

- stronger O-H-N bond
- supporting C-H-O bond
- C-H-O bond again ensures the planarity of the molecular assembly
**Metric engineering of anthracene cocrystals**

Distribution of C-H donors of anthracene and O acceptors of the 3,5-dinitrobenzoic acid could support C-H...O bonding.

Anthracene is missing any strong hydrogen-bonding sites - how about weak C-H donors? Geometric agreement seems likely.

**The outcome of our design**

The molecular recognition is indeed seen between anthracene C-H groups and oxygen atoms of 4-methyl-3,5-dinitrobenzoic acid!

The self-assembly of the acid leads to the formation of a “chicken-wire” framework into which anthracene is incorporated. This self-assembly is achieved by:
1) carboxylic acid dimer synthons
2) C-H...O bonds between nitro and methyl groups

**Another view of the hydrogen bonding in these cocrystals**

Anthracene is incorporated in the framework through weak C-H...O bonds.

If anthracene were a medicinal compound (drug), this could represent a storage or delivery structure from which anthracene could be readily removed!
How important is the methyl group?

The modular nature of the cocrystal allows us to use different components and explore properties and test designs easily, without difficult synthesis!

We can explore a similar molecule:

4-chloro-3,5-dinitrobenzoic acid

Chloro and methyl groups are similar in terms of size, around 20 Å³ each, but the -Cl groups does not form C-H-O bridges!

We can also explore a slightly different molecule:

3,5-dinitrobenzoic acid

The parent compound does not have the ability to form C-H-O linkages via methyl groups.

What is found?

-CH₃ -Cl

Chloro- and methyl groups provide the same structure!

-H

CH₃-O contacts can be replaced by Cl-O contacts (Cl is polarisable)

A strategy to construct isosctructural solids: by duplicating a known structure

what about the case of hydrogen as the substituent?

The space-filling effect

A cocrystal is not formed unless crystallization is done from a benzene solution!

Benzene participates in cocrystal formation, establishing C-H-O contacts to bridge the framework; a three-component cocrystal is formed
What is created is in fact a three-component co-crystal

Extend our definition to pharmaceutical co-crystals.

In this case both components are pharmaceutically active

Cocrystals are modular

Modularity (exchangeable components) allows function:
- increasing bioavailability: dibenzelic acid
Using co-crystals to improve drug bioavailability

**Solubility:** thermodynamic activity (extent of solubilisation)

**Dissolution:** kinetic parameter (rate of solubilisation)

For poorly soluble oral drugs, the rate tends to be the important parameter for absorption.

For example: crystalline itraconazole is poorly absorbed orally and the amorphous form is required for oral bioavailability.

Sporanox® bead concept was introduced to overcome this difficulty, but presented a challenge in formulation development, and had initial problems with residual CH₂Cl₂.

Can cocrystals be used as an alternative to the amorphous form?

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First step: look for potential hydrogen bonding site

The triazole nitrogen atom does not interact with any neighbours in the pure solid itraconazole - suggests carboxylic acids as cocrystal formers.

The cocrystal former (succinic acid) forms a "sandwich" of two itraconazole molecules.

Several of prepared cocrystals exhibited enhanced dissolution rates - comparable to the ones of the amorphous form.

Result is increased bioavailability through cocrystals rather than marketing a metastable amorphous form.
Some strategies in crystal engineering

Five approaches are:

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One of the best known solid-state photoreactions:

**[2+2] photodimerization**

Cinnamic acid and derivatives

**Topochemical postulates:**
1) Olefin groups must be parallel
2) d ≤ 4.2 Å

But even cinnamic acid exists as 3 polymorphs - lack of control!

Stereochemistry of the cinnamic acid dimer is controlled by the arrangement of molecules in the reacting crystal:
Using steering groups to "crystal engineer" appropriate alignment

How can we increase the likelihood of β-stacking in such systems?

Cl-Cl interactions are known to bring molecules at a short (4 Å) separation

4-chlorocinnamic acid exists as a single polymorph, with photoactive contacts induced by Cl-Cl interactions.

β-stack

photodimerisation in a β-stack produces only the head-to-head dimer

An alternative approach is to use π–π interactions

Attractive interactions between electron-rich and electron-deficient aromatic moieties can also be utilised to align molecules for a [2+2] photodimerisation:

photodimerisation would produce only the head-to-tail dimer
Imperfection in this steering group design!
Each molecule in a stack has two potential photoreaction partners:

Ideal reaction, 100% yield  reality, yield is limited to ca 70 %

Use a co-crystal approach: template-controlled synthesis
Template-controlled approach focuses on engineering a fragment of the crystal structure, rather than engineering molecular stacks

Through the template-controlled approach photoactivity is isolated from the molecular stack into a discrete molecular assembly

Resorcinol as a hydrogen-bonding template
The role of resorcinol as a template is enabled through the directionality of hydrogen bonds (expected), as well as suitable conformation of resorcinol (hoped for)
Paracyclophane: a target for the supramolecular chemist

The interior of the photoactive assembly can be modified, enabling the control of solid-state reactivity independent of the size of the reacting molecules:

The exterior of the assembly (resorcinol R-group) can also be modified to fine-tune solid-state reactivity.

Template-switching: a combinatorial strategy to avoid the imperfections of the approach

Undesirable photoactive olefin-olefin contacts in cocrystals with 5-OMe resorcinol template disappear upon switching to 4-benzylresorcinol:

Product yield increases from 60 to 100% after removing the parasitic reaction contact

A success of template-controlled synthesis approach: quantitative paracyclophane synthesis

Through template-switching, crystal packing of photoactive assemblies is modified by modifying the template, rather than the reactant.
Further challenges for template-controlled approach

Solid-state photodimerization of conjugated olefins has never been observed in the solid state.

Expected products are unusual strained molecules composed of fused cyclobutane rings: ladderanes

Template-controlled solid-state synthesis of “molecular ladders”

Both strained frameworks are obtained in a 100% yield!

Single-crystal-to-single-crystal transformations

A single-crystal-to-single-crystal (SCSC) is a homogeneous topotactic reaction:

i) The lattice of a solid product shows one or a small number of crystallographically equivalent, definite orientations relative to the lattice of the parent crystal

ii) The reaction proceeds throughout the bulk of the reactant

Technological applications
(holographic memories; crystalline polymers)
In situ study of chemical reactions
(X-ray single crystal diffraction)
SCSC photodimerization

Note similarity to cinnamic acid

SCSC photochromism

Photochromism: reversible, light-induced change in the color of the material
The transformation must be reversible, typically through light or heat
Photochromism of dithienylethylenes is particularly interesting:
1) SCSC
2) Beautiful colors
3) Mechanical effect

Monitoring reaction course through changes in unitcell

large structural changes - the crystal eventually cracks
SCSC reactions in solid solutions

Mechanical effect resulting from small changes in molecular geometry

Direct conversion of light into mechanical motion

[2+2] photodimerization of cinnamic acid

Crystal decomposition is a result of rapid product buildup near the surface of the crystal because of strong and non-uniform absorption.

Mismatch between product and reactant size and shape leads to the "precipitation" of product crystallites: polycrystalline or amorphous material results.
SCSC reactivity obtained by using radiation with weaker absorption: **tail-end irradiation**

Tail-end absorption wavelengths penetrate uniformly in the crystal, enabling a homogeneous reaction.

Thus, [2+2] photodimerisation of α-cinnamic acid can be accomplished in SCSC manner.

Alternatively reduce the size of the reacting crystals: **SCSC reactivity using nanocrystals**

Reducing crystal size can enable SCSC reactivity. Polymerisation of 1,4-DSP usually occurs with crystal degradation (although small domains of homogeneous reactivity have been observed).

In nanometer-sized crystals the polymerisation is a SCSC process.

SCSC reactivity by enclosing the reaction

By isolating the reacting molecules within a molecular host, changes in molecular shape upon reaction do not affect the overall crystal structure.
Diacetylene 1,4-polymerization: reaction between suitably oriented molecules of a dialkyne:

A different problem than cyclobutane synthesis: how do we template an array of molecules rather than just pairs!

Geometric data for many different derivatives and crystal structures

Use of a self-assembled template

One possible approach is to recognise molecular functionalities that would assemble in the solid state to a similar periodic structure.

The end groups of the self-assembled template need to be able to interact with the end groups of the diacetylene reactant: via hydrogen or halogen bonds.
A pyridine-substituted reactant

The geometry is not ideal and the compound polymerizes slowly.

A carboxylic acid reactant

Using halogen bonds

The product contains only iodine and carbon!
Can we design a new reaction?

Presumably, a 1,6-polymerization of a triacetylene is governed by topochemical rules, similar to the well-established 1,4-polymerisation.

A single-crystal-to-single-crystal polymerization

The 1,6-polymerisation of the triacetylene proceeds in a SCSC manner up to 70% yield to provide a highly conjugated polycarboxylic acid polymer:

How are cocrystals synthesized?

To create intimate homogeneous mixture, we might expect to dissolve in an appropriate solvent and then crystallize, filter, wash and dry.

Laborious and lots of waste solvent

The product can also be contaminated, if reactants are sensitive to solvent!
Other obstacles on the way to cocrystal synthesis

The synthesis of cocrystals is based on the synthesis of supramolecular bonds. These interactions are often susceptible to molecule-solvent interactions when constructing cocrystals from solution.

Different solubilities of the cocrystal components play a significant role in attempts to synthesise cocrystals from solution. To do so would need to determine the phase diagram.

Synthesis of cocrystals by grinding/milling

Hydrogen-bonds can be constructed through grinding

Grinding or mechanochemical synthesis provides a means to reduce the amount of solvent used, avoid solubility and solvent competition effects.

Different approaches to mechanochemical synthesis

The presence of a "catalytic" amount of liquid can greatly enhance the scope of mechanochemical synthesis. Its speed and yield!
The use of mechanochemistry for polymorph conversion

Liquid-assisted grinding can be used to achieve polymorph conversion

Grinding and solution growth provide the same product

Case 1

Solution Growth

2:1 Caffeine/Formic Acid Cocrystal

Same cocrystal product

Solid-state Grinding

A new cocrystal stoichiometry is obtained by grinding

Case 2

Solution Growth

1:2 Cocrystal Stoichiometry

Solid-state Grinding

Different stoichiometric ratio of components in the cocrystal

1:1 Cocrystal Stoichiometry

Solid-state Grinding

1:1 Cocrystal Stoichiometry (not via solution as yet)
Different polymorphs obtained via grinding

Case 3

Solution Growth with Grinding seeds

Solid-state Grinding
(140 mg)

Trifluoracetic acid

Solid-state Grinding
(320 mg)

Form I (orthorhombic)
1:1 Cocrystal Polymorph

Form II (monoclinic)
1:1 Cocrystal Polymorph

Use of seeds for solution growth after discovery by grinding

Solution Growth with Grinding Seeds

Cocystals from solution

Caffeine

Glutaric Acid

CHCl₃ slow evaporation

1:1 Caffeine:Glutaric Acid Cocrystals

Polymorphism

Concomitant polymorphs

Selective polymorph formation via liquid-assisted grinding

Caffeine Glutaric acid 1:1 Form II
(Obtained using cyclohexane)

Results

Caffeine Glutaric acid 1:1 Form III
(Obtained using chloroform)

Cocrystallization from solution results in the formation of both polymorphs