Persistent Needle Challenges:
a class of compounds preventing crystallization routes to modulate bulk powder properties

Patrick McArdle
Scoil na Ceimice
Ollscoil na hEireann, Gaillimh

Factors Controlling Persistent Needle Crystal Growth: The Importance of Dominant One-Dimensional Secondary Bonding, Stacked Structures, and van der Waals Contact

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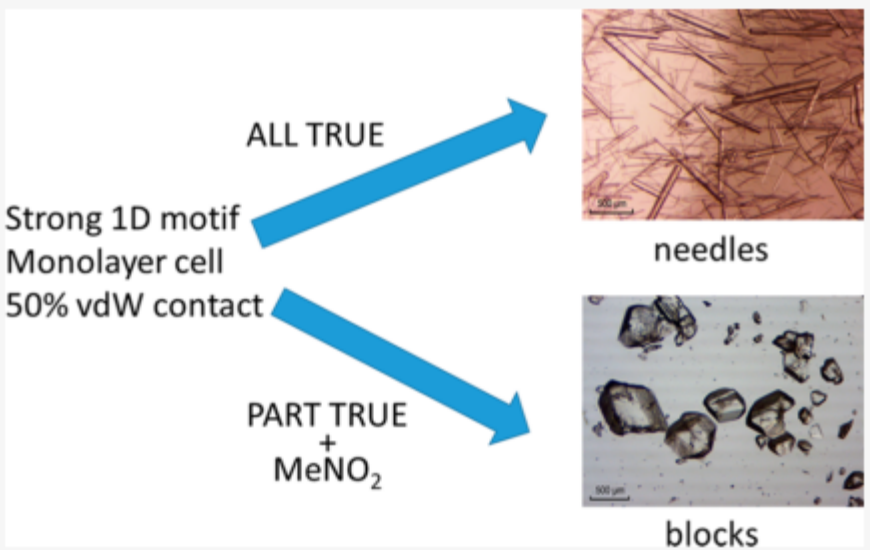
ABSTRACT: Needle crystals can cause filtering and handling problems in industrial settings, and the factors leading to a needle crystal morphology have been investigated. The crystal growth of the amide and methyl, ethyl, isopropyl, and t-butyl esters of diflunisal have been examined, and needle growth has been observed for all except the t-butyl ester. Their crystal structures show that the t-butyl ester is the only structure that does not contain molecular stacking. A second polymorph of a persistent needle forming phenylsulfonamide with a block like habit has been isolated. The structure analysis has been extended to known needle forming systems from the literature. The intermolecular interactions in needle forming structures have been analyzed using the PIXEL program, and the properties driving needle crystal growth were found to include a 1D motif with interaction energy greater than −30 kJ/mol, at least 50% vdW contact between the motif neighbors, and a filled unit cell which is a monolayer. Crystal structures are classified into persistent and controllable needle formers. Needle growth in the latter class can be controlled by choice of solvent. The factors shown here to be drivers of needle growth will help in the design of processes for the production of less problematic crystal products.



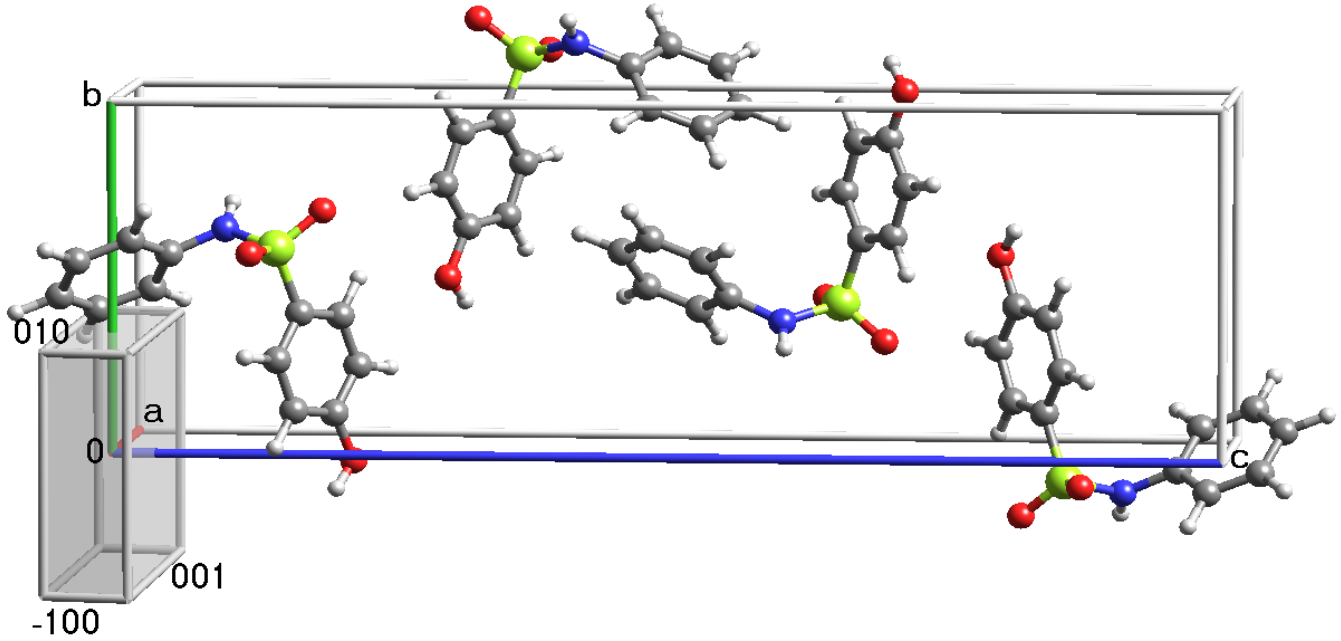
Crystal shape can have an important influence on the ease of processing crystalline solids.

- In general block shaped crystals will have the least problems.
- Plate like crystals may have problems associated with consistent powder density
- Needle like crystals are the most difficult to handle.
  They may form a gel, be difficult to filter and break easily to give fines.
- Needle forming compounds can be persistent or controllable needle formers
- Controllable needle formers can be controlled by solvent choice
- Thus persistent needle crystals present the greatest problems*

*Civati, F., et al. (2021). "Factors Controlling Persistent Needle Crystal Growth:
The Importance of Dominant One-Dimensional Secondary Bonding, Stacked Structures, and van der Waals Contact.
Crystal Growth & Design **21**(6): 3449-3460

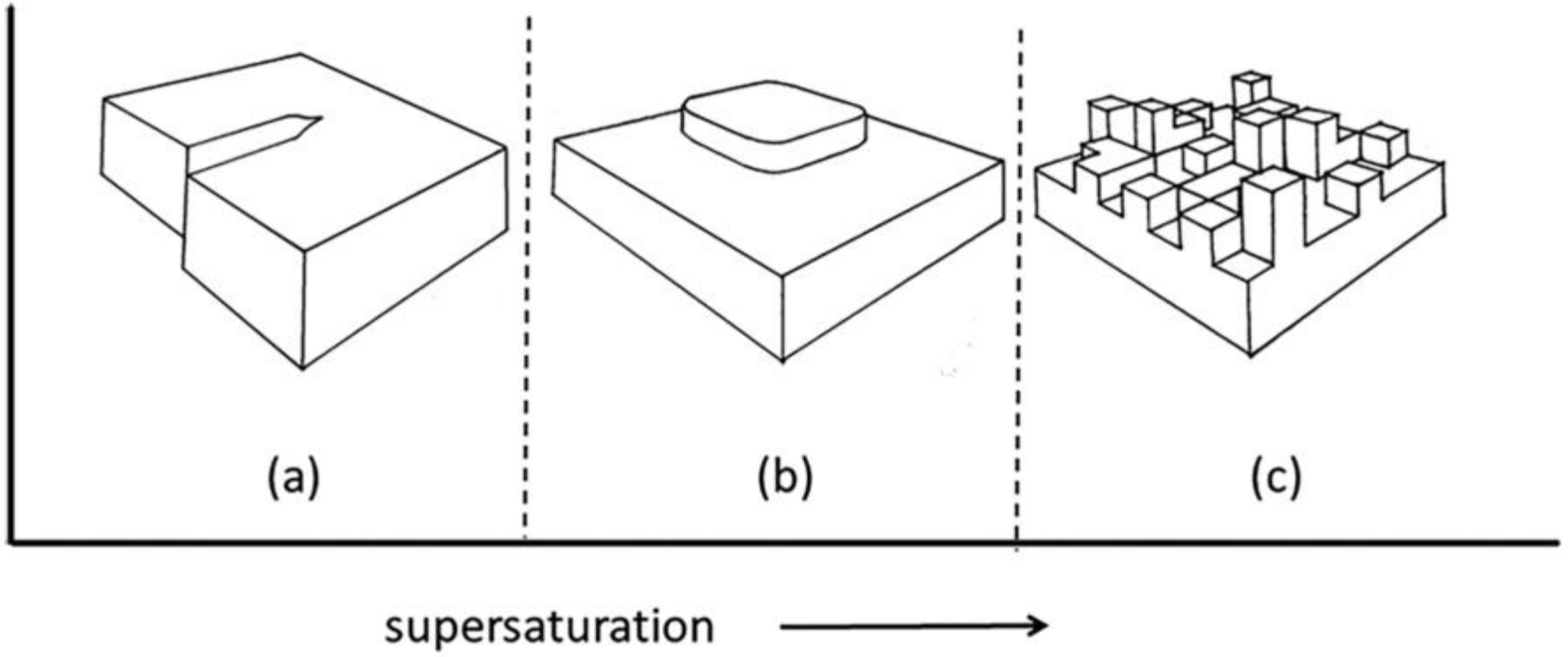
Crystal Shape from the BFDH rule*

- BFDH 495,000 hits on Google
- *“the morphological importance of a crystal face is inversely proportional to its reticular area”*
- The rate of growth of a crystal face is directly proportional to its area
- The BFDH shape is often the inverse of the unit cell
- The BFDH rule ignores the unit cell contents and it kind of works because things often tend to average out
- BFDH will never predict needle growth as unit cells are not often needle shaped.
- Using slice attachment energies leads to only modest changes in shape.



*Donnay, J. D. and D. Harker (1937). "A new law of crystal morphology extending the law of Bravais." Amer. Mineral. **22**: 446-447

Crystal growth mechanisms

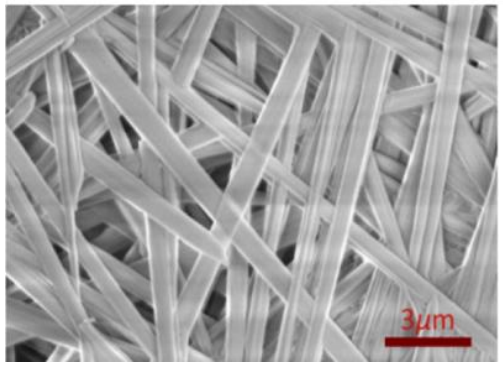


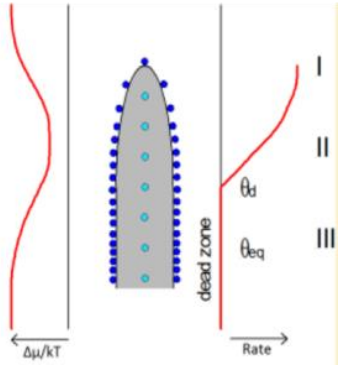
(a) Screw dislocation providing a constant nucleation source for spiral growth at low supersaturation, (b) 2D nucleation at moderate supersaturation, and (c) rough growth at high supersaturation.

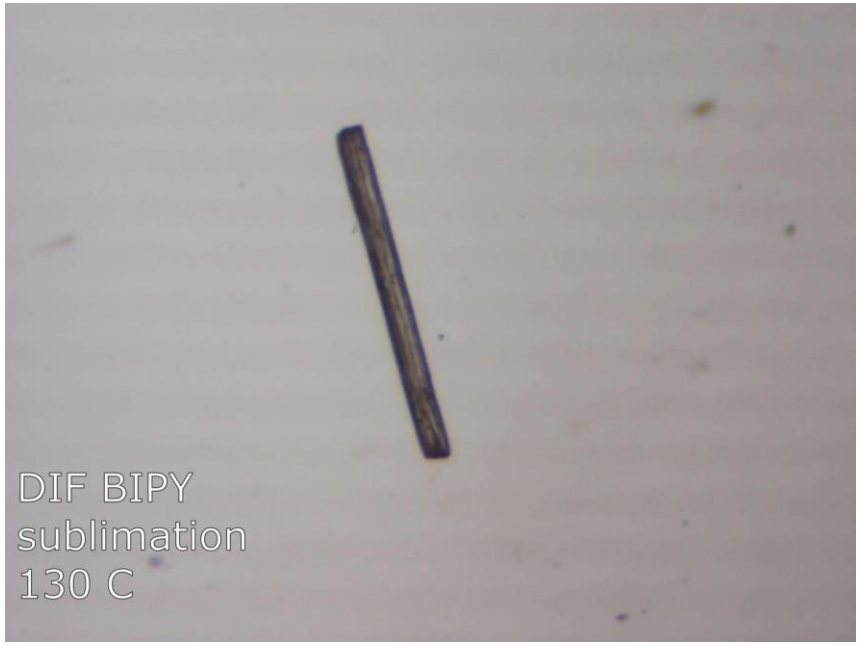
We wish to thank Breandán Ó Laochdha for drawing the Figure

Needle crystal growth

- Needle crystals have smooth growth at the needle side faces and rough pointed growth at the needle tip
- This has been observed for a wide range of organic compounds including β-phthalocyanine, aspartame and urea.
- It has also been observed for NaCl*
- Needle dissolution/sublimation reverses this process





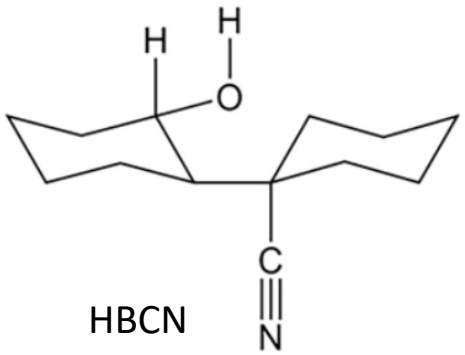


*Townsend, E. R., et al. (2018). Additive Induced Formation of Ultrathin Sodium Chloride Needle Crystals.“ Crystal Growth & Design **18**(2): 755-762

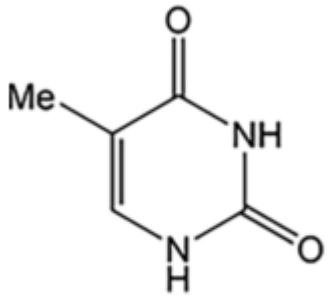
What is the driving force behind needle growth?

- Highly anisotropic crystal growth is most likely due to kinetic rather than thermodynamic factors
- The growth mechanism in one direction must be different from any other direction
- A 1D motif in the crystal structure is a likely possibility
- Could a 1D H-bonding motif be responsible for needle growth?

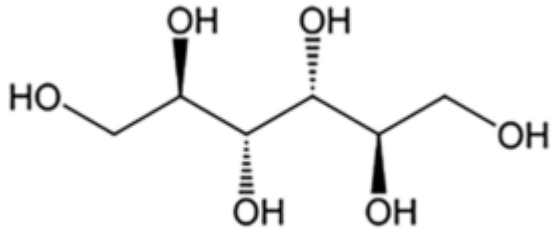
1D H-bond motifs in action



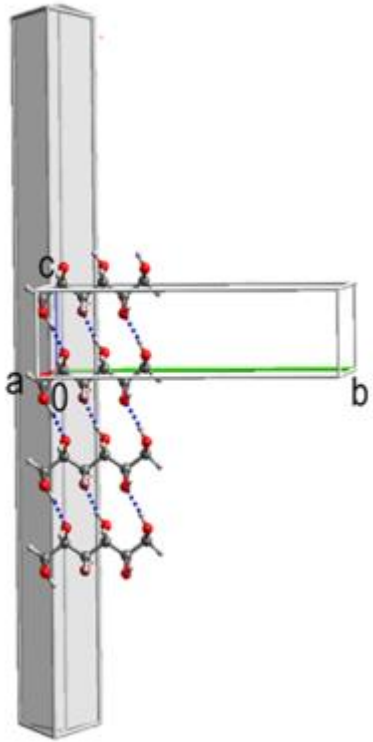
HBCN



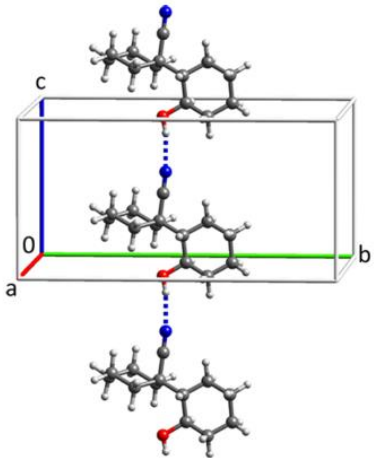
thymine



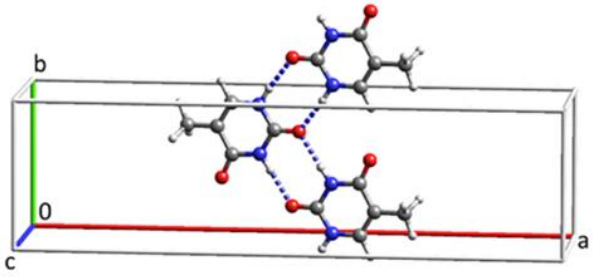
D-mannitol



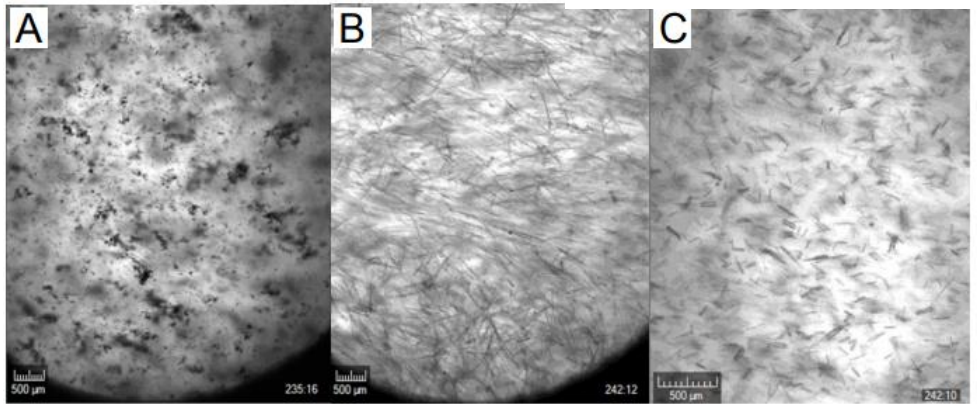
Persistent needles*



Needles from CH_2Cl_2
Blocks from MeOH

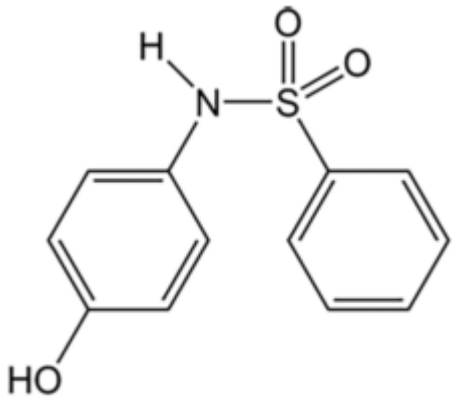


Prismatic crystals from ethanol

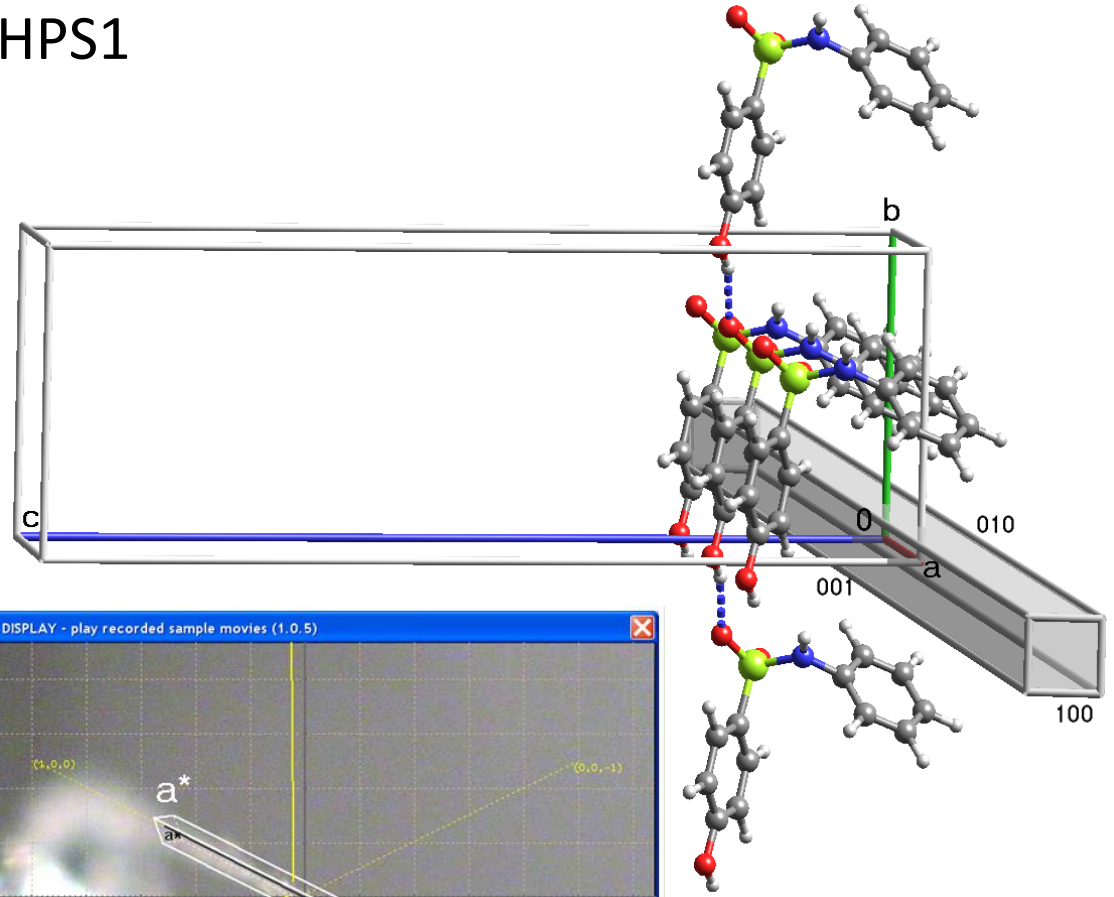


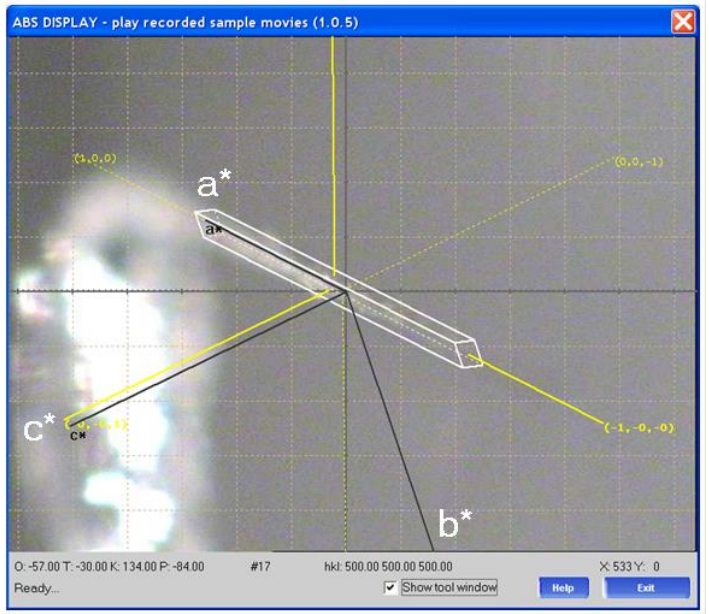
*Penha, F. M., et al. (2021). "Selective Crystallization of d-Mannitol Polymorphs Using Surfactant Self-Assembly." Crystal Growth & Design **21**(7): 3928-3935

4-Hydroxy-N-phenylbenzenesulfonamide, HPS1 is a persistent needle former



HPS





- Its crystals are like cotton wool from most solvents and its needles were too thin for SCXRD
- After many attempts crystals suitable for SCXRD were obtained by careful sublimation
- The structure has a 1D H-bond motif
- However, something other than 1D H-bonding is causing the persistent needles as needle growth is normal to the 1D H-bond motif

Pixel analysis of intermolecular interactions

- Angelo Gavezzotti's Pixel program can calculate the interaction energy between molecules
- The energy is partitioned into Coulombic, polarization, dispersion and repulsion
- H-bonding is mainly Coulombic
- vdW contact interactions are mainly dispersive
- HPS1 H-bond is -45.5 and its vdW contact stack is -39.1 kJ/mol
- Simple Indicative Lattice Analysis can detect vdW stacks.

hps1xxxx								
eco	polo	edo	ero	polen	toto	Orca	MP2	
-78.7	-37.7	-141.8	92.4	0	-165.7			
typ.	no.	no.	dist.	Coul.	pol.	disp.	rep.	Pixel
AA	1	15	8.631	-40.7	-16.3	-15.5	27	-45.5
AA	1	16	8.631	-40.7	-16.3	-15.5	27	-45.5
AA	1	12	5.229	-13.7	-7.5	-38.7	20.8	-39.1
AA	1	19	5.229	-13.7	-7.5	-38.7	20.8	-39.1

hps1xxxx ** Indicative Lattice Analysis **

H-bond Rozenberg et al.Phys.Chem.Chem.Phys.,2000,2,2699-2702
values > than -10. kJ/mol not important
vdW disp. energy empirical estimate (e.a.) Walshe et al.Cryst.Growth Des.2015,15,3235-3248

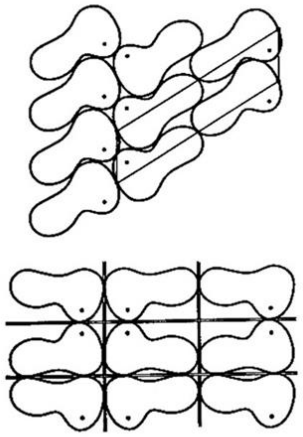
From Resid. 1 to Resid. 65501 1 Cn.dist 5.229
H-bond H1N1 O1 0.156 <vdWsum -8.51 kJ/mol
** Mean% vdW contact 51.79% e.a. -36.2 kJ/mol

From Resid. 1 to Resid. 56501 1 Cn.dist 8.631
** H-bond O2 H1O3 0.832 <vdWsum -21.65 kJ/mol
Mean% vdW contact 16.07% e.a. -22.5 kJ/mol

Gavezzotti, A. (2005). "Calculation of lattice energies of organic crystals: the PIXEL integration method in comparison with more traditional methods." Zeitschrift für Kristallographie-Crystalline Materials **220**(5/6): 499-510.

McArdle, P. (2021). "Pixel calculations using Orca or GAUSSIAN for electron density automated within the Oscail package." Journal of Applied Crystallography **54**(5)

Packing organic molecules was first considered by Kitaigorodsky



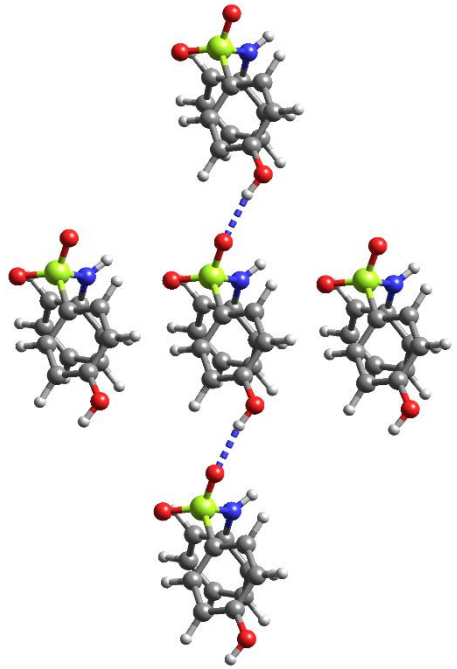
- Left: “Complementary Kitaigorodsky” by Istvan Orosz *
- Right two examples of packing arrangements of an arbitrary shape in the plane after Kitaigorodsky and a single stack of bowls fitted into each other.
- **Titus Lucretius Carus** c 99 – 55 BC *De rerum natura (on the nature of things)*

  “Things whose fabrics show opposites that match,
  one concave where the other is convex,
  and *vice versa* will form the closest union.”

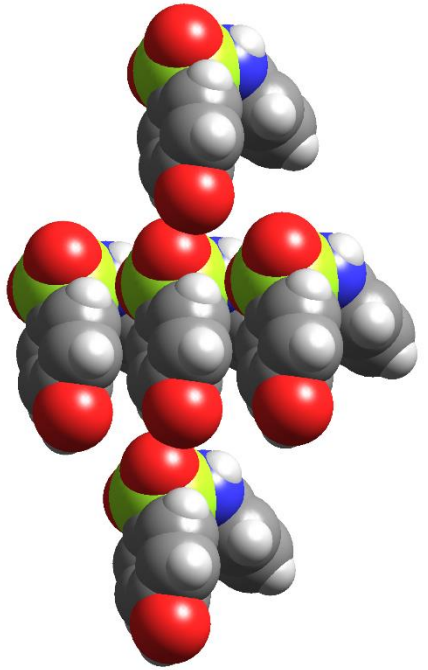
https://www.iucr.org/news/newsletter/volume-29/number-2/from-lucretius-to-kitaigorodsky

* I. Hargittai & M. Hargittai (2000). *In Our Own Image: Personal Symmetry in Discovery.* New York: Kluwer/Plenum, Chapter 6: “Aleksandr Kitaigorodskii,” pp. 112–142.

HPS1 H-bonding and vdW stacking



A molecule and its 2
strongest interactions

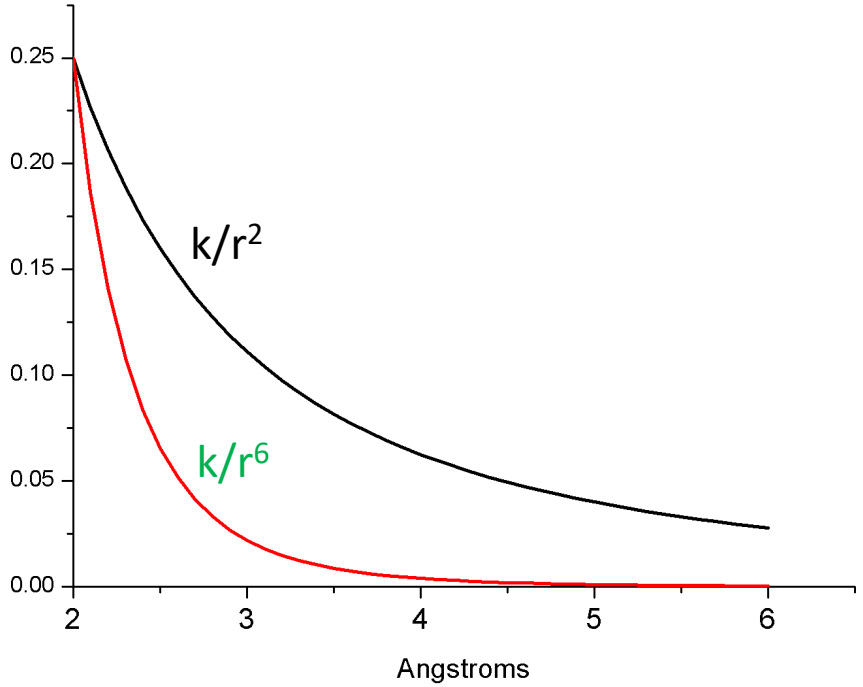


vdW stack
52% atoms
in contact

H-bond
1D motif
16% atoms
in contact

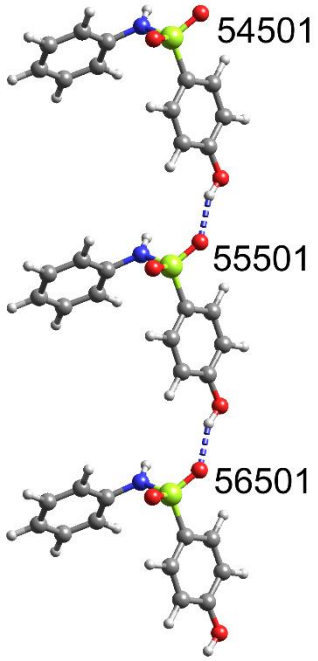
Why does vdW contact stacking outperform H-bonding in HPS1 crystal growth?

- H-bonding is Coulombic and it obeys a k/r^2
- vdW contact dispersion obeys a k/r^6 law
- The Coulombic attraction will attract molecules from longer distances
- If a molecule has H-bond donors and acceptors at two places it may be attracted to the growth site in the wrong orientation and that may block further growth
- Because vdW operates over short distances the incoming molecule has to be in the correct orientation before any attraction is operating

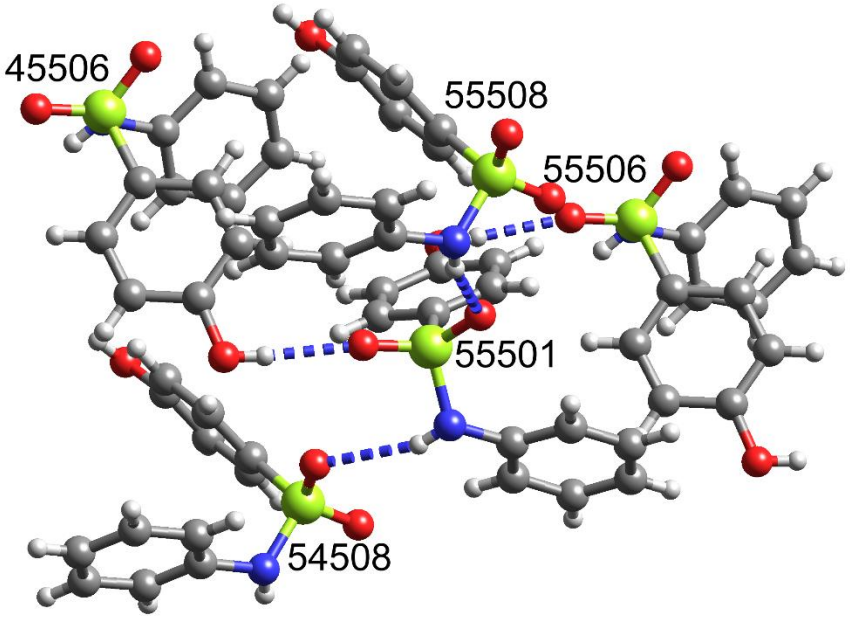


H-bonding in the polymorphs of HPS

HPS1

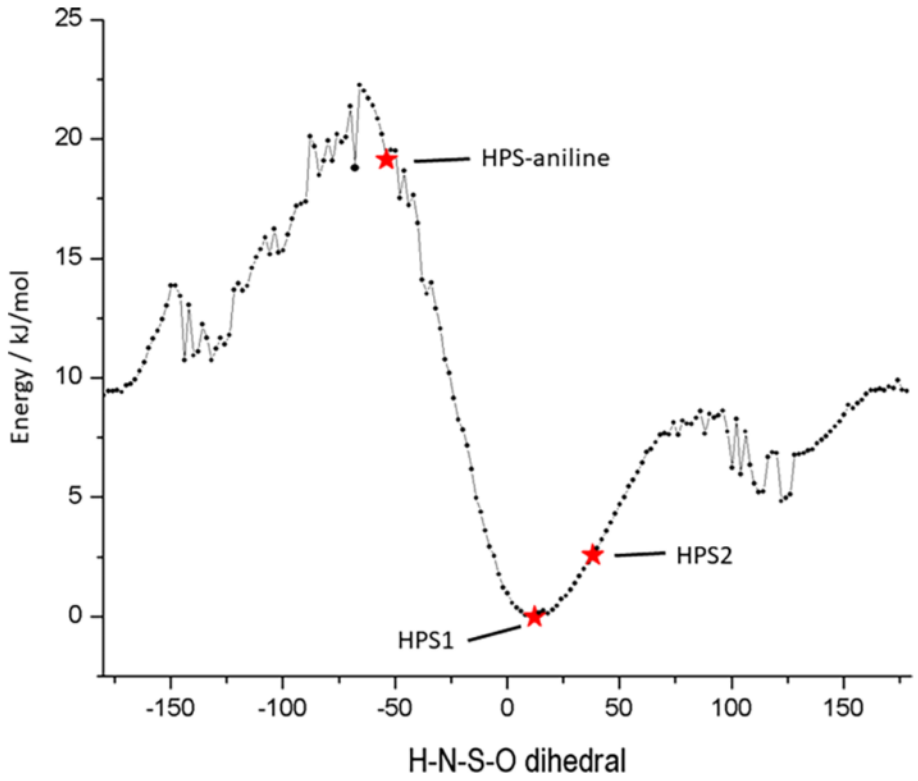


HPS2



- HPS2 was obtained by crash cooling a solution of HPS in EtOH
- It is a kinetic product which maximizes H-bonding

The H-N-S-O dihedral is an important property of the sulphonamides*



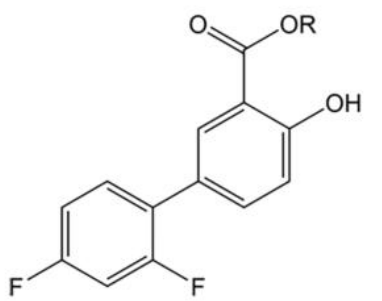
*Perlovich, G. L., et al. (2013). "Sulfonamide Molecular Crystals: Structure, Sublimation Thermodynamic Characteristics, Molecular Packing, Hydrogen Bonds Networks + sulfamethoxazole." Crystal Growth & Design **13**(9): 4002-4016**.**

Properties required for persistent needle formation

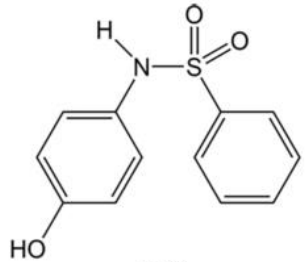
- vdW contact stacking with < -30 kJ/mol interaction energy
- At least 50% of the atoms in a molecule in vdW contact with its stack neighbours
- A filled unit cell should be a monolayer – this means that the symmetry relationship between a molecule and its stack neighbours is a unit translation.
- Molecular stacks must be aligned to the unit cell axes not along a cell diagonal
- Molecular flatness should be low (less than 0.75)

Flatness = height / length
height = max dist.above lsq.plane + max dist.below lsq.plane
length = largest interatomic distance
0.0 = flat
1.0 = sphere HPS1 0.75

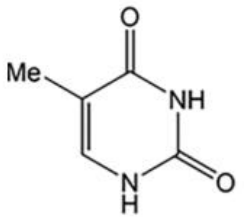
Some compounds which give needle crystals



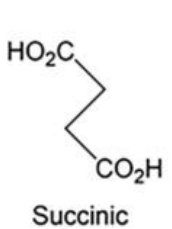
DIF esters R = Me, Et, i-Pr, t-Bu



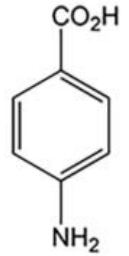
HPS



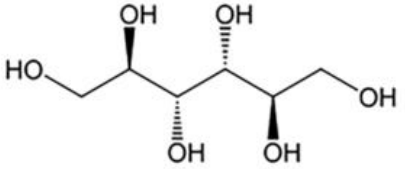
thymine



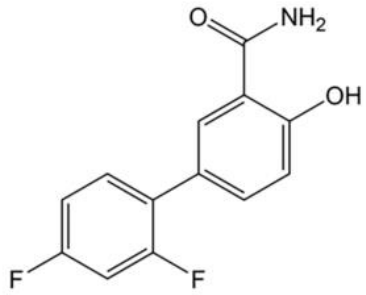
Succinic acid



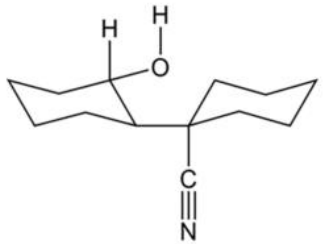
p-aminobenzoic acid



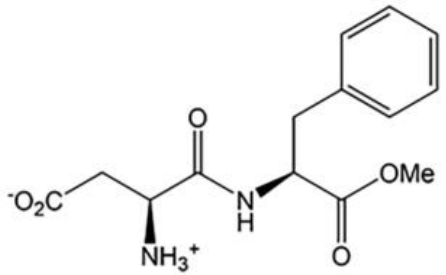
D-mannitol



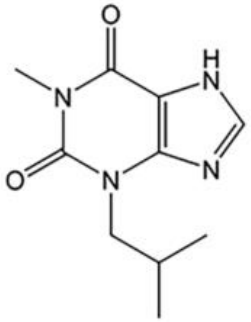
diflunisal amide



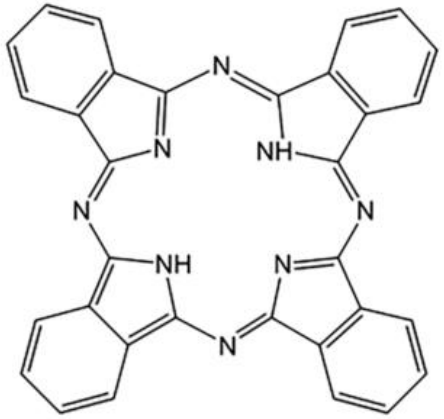
HBCN



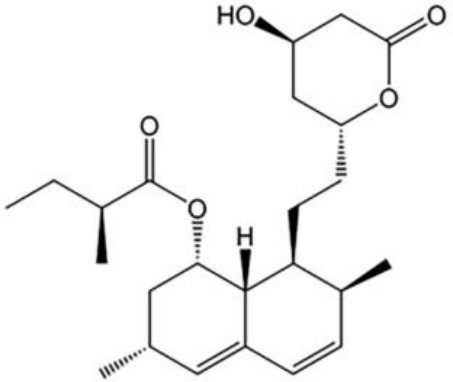
aspartame



3-Isobutyl-1-methylxanthine



βphthalocyanine



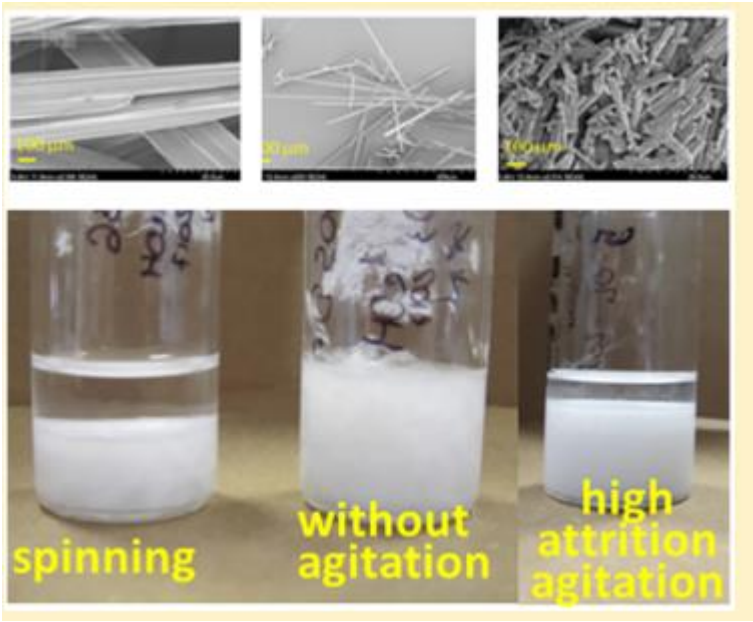
lovastatin

Compound/polymorph	1D motif [a], direction and energy/kJ/mol	% atoms in vdW contact	molecular flatness	cell a monolayer	aligned to unit cell	persistent needle growth	packing index
Diflunisal form III; FAFWIS02	Stack c -30.6	87.5	0.22	yes	yes	yes	72.8
Diflunisal methyl ester	Stack a -33.6	82.76	0.41	yes	yes	yes	71.2
Diflunisal ethyl ester	Stack a -40.7	82.81	0.40	yes	yes	yes	70.0
Diflunisal i-propyl ester	Stack b -45.5	70.0	0.53	no	yes	yes	70.4
Diflunisal t-butyl ester	none	-	0.39	no	-	-	-
Diflunisal amide solvate	Stack b -30.4	83.3	0.48	yes	yes	yes	69.5
HPS1; VUKRAW	Stack a -35.1	51.79	0.75	yes	yes	yes	68.0
HPS2	none		0.83	no	no	no	65.8
HPS aniline solvate	Stack a -48.9, -13.2	55.36, 46.43	0.53, 0.09	yes	yes	yes	70.7
HBCN	s-HB c -32.1	3	0.66	no	yes	no	66.5
Thymine; THYMIN03	d-HB b -74.8	20	0.29	yes	yes	no	72.6
D-mannitol; DMANTL01	t-HB c -99.9	56	0.42	yes	yes	yes	74.2
Succinic acid; SUCACB18	d-HB along [101] -75.2	57 54 55	0.25	no	no	no	76.6
Aspartame hemihydrate; DAWGOX	HB c -136.3, In stack disp -60	57	0.40	yes	yes	yes	67.1
Aspartame; KETXIR	HB b -98 -127 In stack disp -60	52.55	0.69	yes	yes	yes	68.9
3-Isobutyl-1-methylxanthine;	Stack a -32.0	61.67	0.48	yes	yes	yes	70.9
PABA Form I; AMBNAC07	Stack b -14.2	77.94	0.02	yes	yes	no	73.5
PABA Form V; AMBNAC09	Stack b mean -14.3 [b]	79.41	0.03	yes	yes	no	74.0
MNA; MNIANL05	Stack c -10.7	46.9	0.01	yes	yes	no	72.6
NMBA; NMBYAN01	Stack a -21.2	43.3	0.13	yes	yes	no	75.9
β-phthalocyanine; PHTHCY14	Stack b -101.5	70.69	0.01	yes	yes	yes	72.7
Lovastatin; CEKBEZ01	Stack a -54.8, s-HB b -31.6	42.31	0.72	yes	yes	no	69.9

Can anything be done if a compound is a persistent needle former?

- Pushing the system closer to thermodynamic equilibrium has been shown to work – but it is very slow
- We have called the method
  High Shear Ultra Low Attrition Agitation, HSULAA*
- The sample is spun at 8 to 13 rps and the direction of rotation is changed every 3s
- Time required using our setup 3 to 4 weeks

- Put in a t-butyl group
- Use an additive to block growth in the needle direction
- Use an additive with temperature cycling
- It may be easier to get an additive to work for cocrystals

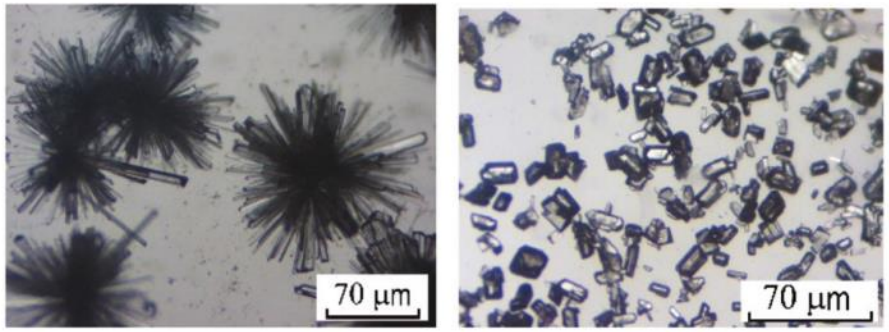


diflunisal in ethanol

*Civati, F., et al. (2019). "Conversion of Gel-Forming Crystal Needles To Easily Processable More Equant Crystals Using High-Shear Ultralow Attrition Agitation: Accelerated Ostwald Ripening without Crystal Attrition." Crystal Growth & Design **19**(3): 1502-1504

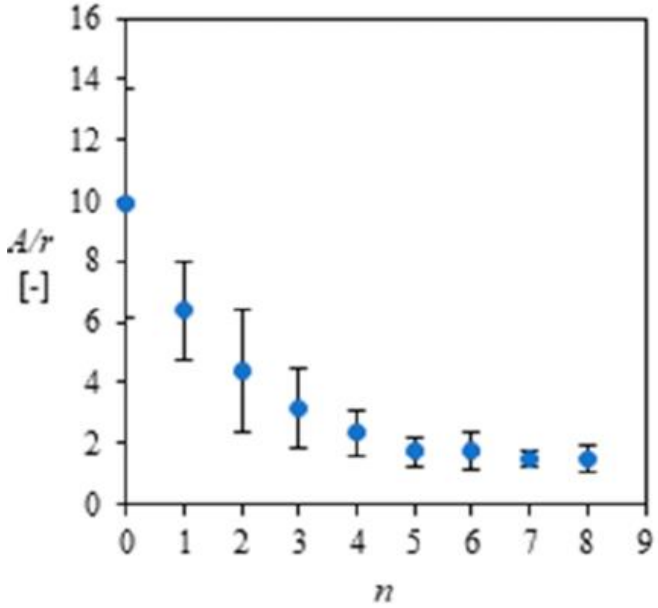
Benzoic acid isonicotinamide cocrystals

Use an additive to block gas phase growth in the needle direction



Sea-urchins are converted to blocks when 1% of benzamide is added to the gas phase*

Using the same additive with temperature cycling is solution



Aspect ratio after each cycle with 0.7% additive**

*O'Malley, C., et al. (2020). "Unprecedented morphology control of gas phase cocrystal growth using multi zone heating and tailor made additives." Chemical Communications (Cambridge, United Kingdom) **56**(42): 5657-5660

Civati, F., et al. (2021). "Manipulating Cocrystal Size and Morphology using a Combination of Temperature Cycling and Additives." Crystal Growth & Design **21(3): 1496-1506.

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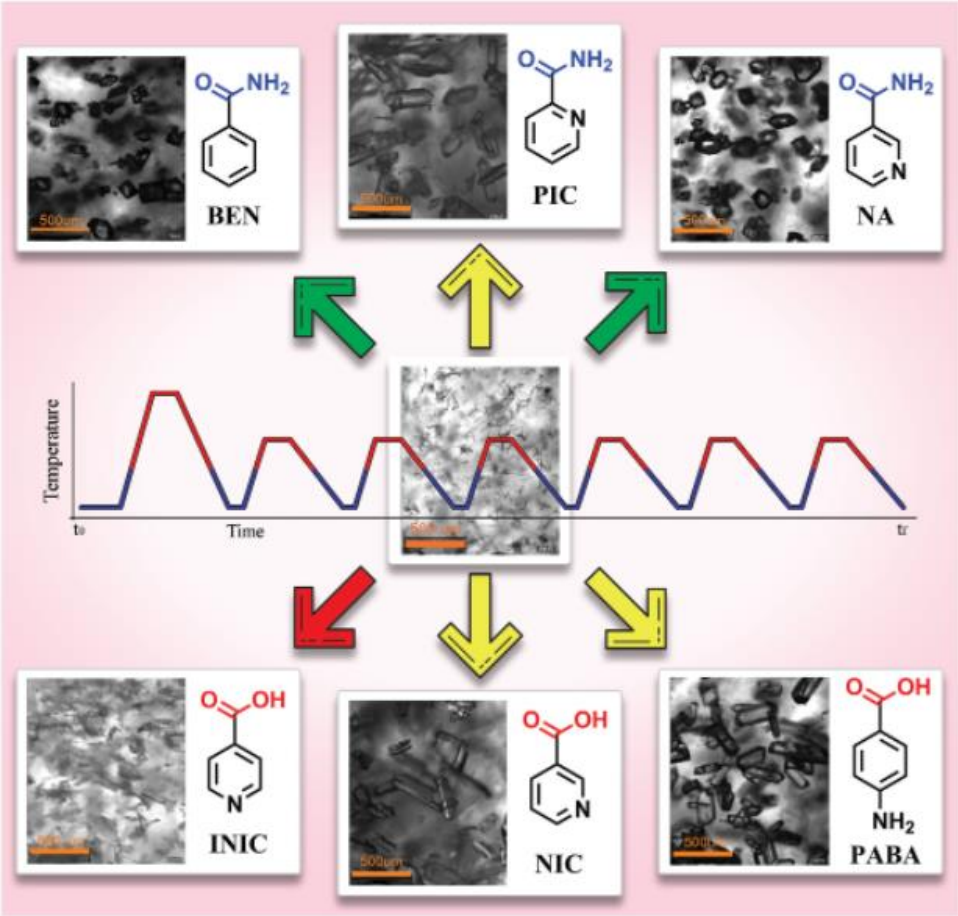
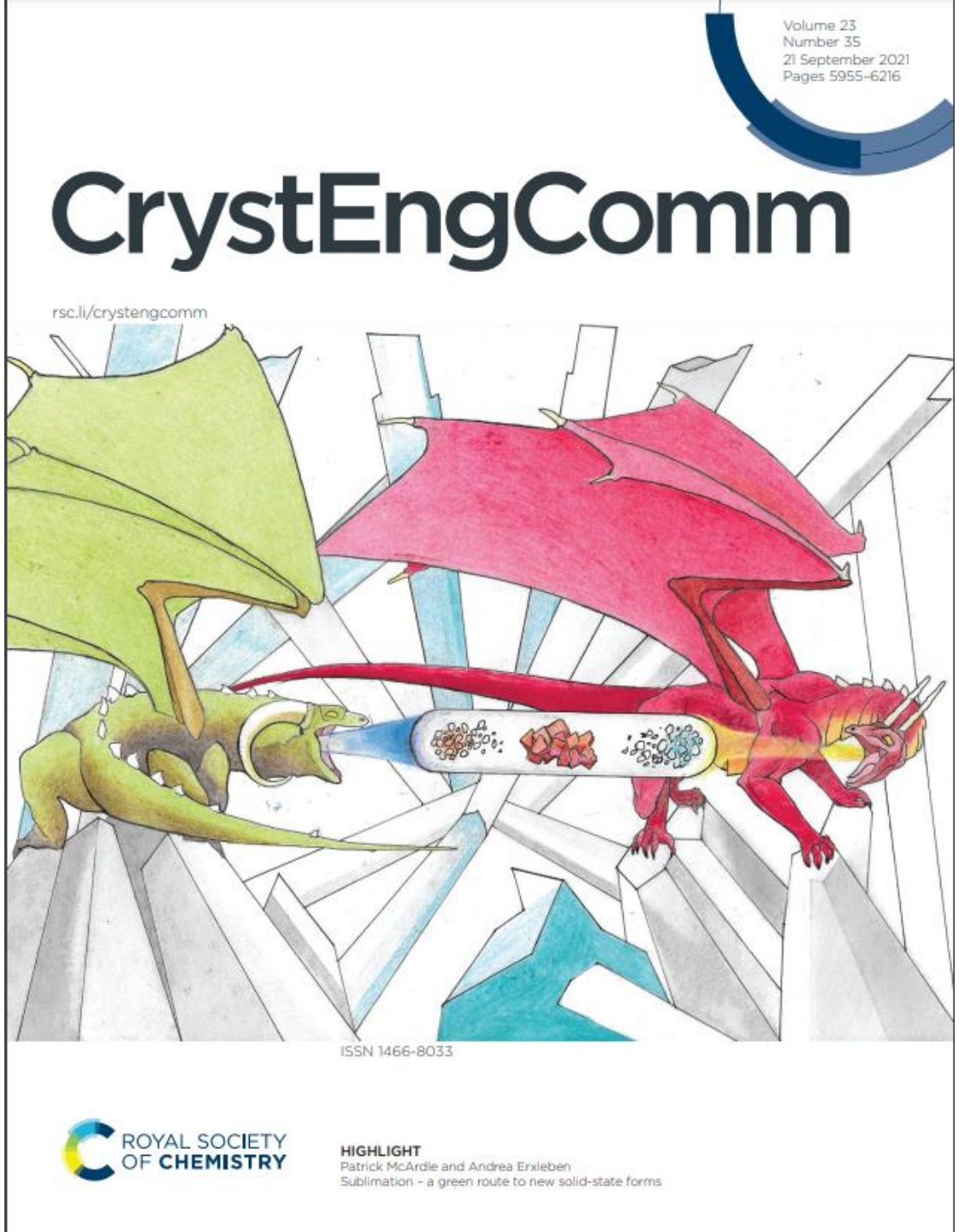
INTEGRATING THE FIELDS OF CRYSTAL ENGINEERING AND CRYSTAL GROWTH FOR THE SYNTHESIS AND APPLICATIONS OF NEW MATERIALS



Civati, F., et al. (2021). "Manipulating Cocrystal Size and Morphology using a Combination of Temperature Cycling and Additives." Crystal Growth & Design **21**(3): 1496-1506.



A Review of Sublimation for the generation of new solid state forms

McArdle, P. and A. Erxleben, "Sublimation – a green route to new solid-state forms." CrystEngComm, 2021, 5965
DOI: 10.1039/d1ce00715g

Conclusions

Persistent needles are formed when compounds/polymorphs have -

- stacked structures with < -30kJ/mol interaction and >50% atoms in vdW contact
- mono layer unit cells
- low molecular flatness factor, < 0.75

Fixing the problem

- Introduce a substituent which will block stacking (1 t-Bu)
- Find an additive which blocks needle growth
- Use temperature cycling + additive and the additive may be catalytic in solution
- Use a cocrystal of the API and it may be easier to find an effective additive

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