

Pharmaceutical cocrystals: synthesis and screening through mechanochemistry

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Outline

- 1. Cocrystals... why?**
- 2. Synthesis of cocrystals: solid-state vs. solution**
- 3. Pharmaceutical relevance and early results**
- 4. Exploring non-covalent interactions through grinding & cocrystals**
- 5. Mechanism of mechanochemistry**



Outline

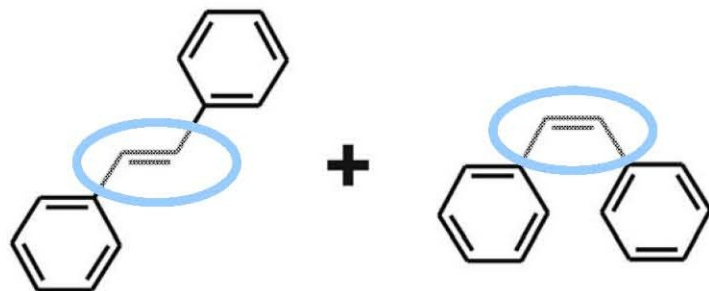
1. Cocrystals... why?
2. Synthesis of cocrystals: solid-state vs. solution
3. Pharmaceutical relevance and early results
4. Exploring non-covalent interactions through grinding & cocrystals
5. Mechanism of mechanochemistry

Acknowledgments: William Jones, Shyam Karki, [László Fábián \(CCDC\)](#), Graeme Day, Andrew Trask, [Sam Motherwell \(CCDC\)](#), [Dave Reid and Melinda Duer \(SS NMR\)](#), [Jonathan Burley \(Nottingham\)](#), Ed Parrott, Axel Zeitler, Lynn Gladden, Lien Nguyen (Cavendish), [Nick Blagden \(Bradford\)](#)

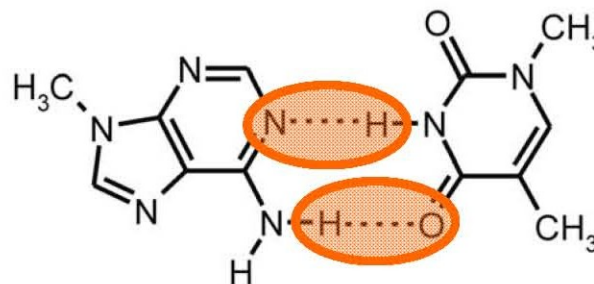
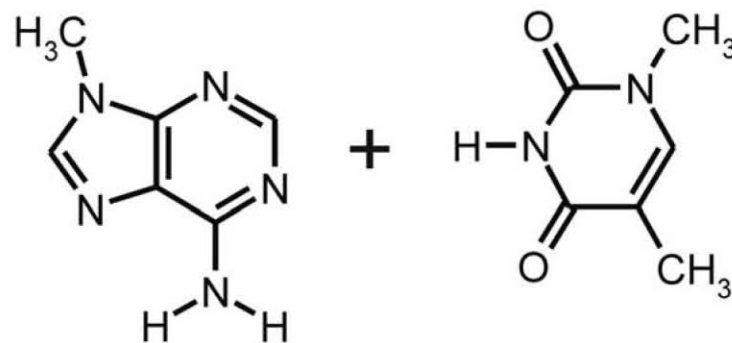


Why Cococrystals?

The cococrystal exemplifies supramolecular synthesis: its formation is ultimately dependent on our understanding of supramolecular forces



Covalent (molecular) synthesis



Non-covalent (supramolecular) synthesis

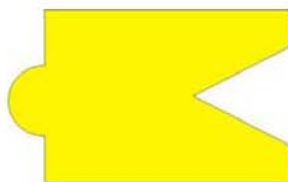


The potential of cocrystals

Different environment: different physicochemical properties



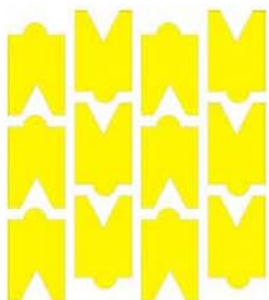
molecule 1



molecule 2



molecule 3



polymorph 1



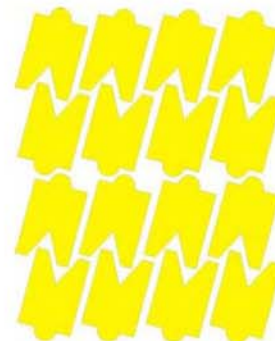
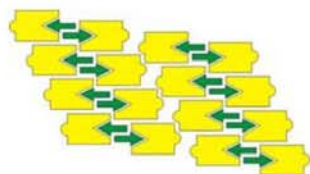
cocrystal 1 (binary)



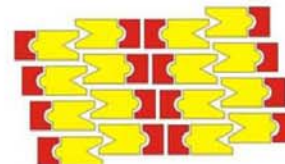
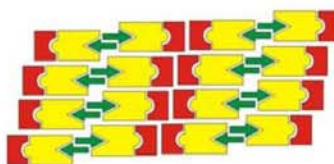
cocrystal 3 (ternary)



cocrystal 2 (binary)



polymorph 2



cocrystals provide a virtually infinite number of solid forms



Pharmaceutical cocrystals

Current Options in the Management of Apnea of Prematurity

Jatinder Bhatia, MD

Summary: Apnea of prematurity (AOP) is a common problem that affects premature infants and, to a lesser degree, term infants. Apnea of prematurity appears to be due to immaturity of the infant's neurologic and respiratory systems. Apnea of prematurity is a diagnosis of exclusion that can be made only when other possible infectious, cardiologic, physiologic, and metabolic causes of apnea have been ruled out. The fundamental principles for managing apnea of prematurity include monitoring the infant closely while instituting supportive care measures such as tactile stimulation, continuous positive airway pressure, or mechanical ventilation. When necessary, pharmacologic therapy may be used to stimulate breathing. The first-line agents of choice for the management of AOP are the methylxanthines. And, for second-line therapy, a switch to a different class of agent, such as the respiratory stimulant doxapram, is an option. Of the methylxanthines, theophylline is the most extensively used. However, a review of the literature suggests that caffeine citrate may be the agent of choice for AOP. Comparative clinical studies have demonstrated that caffeine is at least as effective as theophylline, has a longer half-life, is associated with fewer adverse events, and, in addition, has a greater ease of administration. Caffeine stimulates the respiratory and central nervous systems more effectively and penetrates into the cerebrospinal fluid more readily than theophylline. In addition, because of stable plasma levels, caffeine has a wide therapeutic margin and few side effects. In contrast, theophylline plasma levels may fluctuate widely, which necessitates frequent monitoring, and has a higher incidence of adverse events than caffeine. Before the FDA approval of caffeine citrate (Cafcit®) for administration either intravenously and/or orally, caffeine preparations were "homemade." A few studies suggest that use of pharmacotherapy to treat AOP is not generally associated with long-term sequelae, although more data are needed before this can be definitively concluded. *Clin Pediatr.* 2000;39:327-336

Introduction

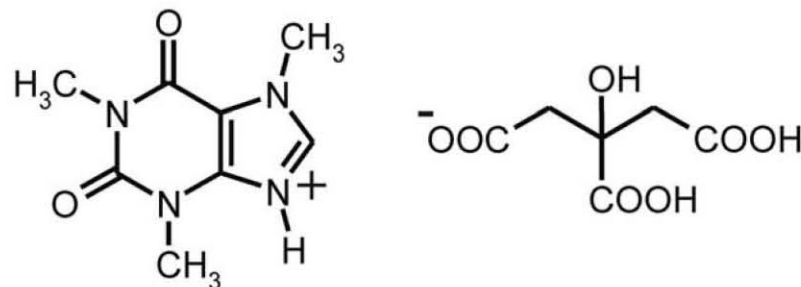
Section of Neonatology, Medical College of Georgia, Augusta, GA.

An educational grant from Roxane Laboratories was provided for manuscript development and editorial assistance; however, Roxane had no input into the content of this article.

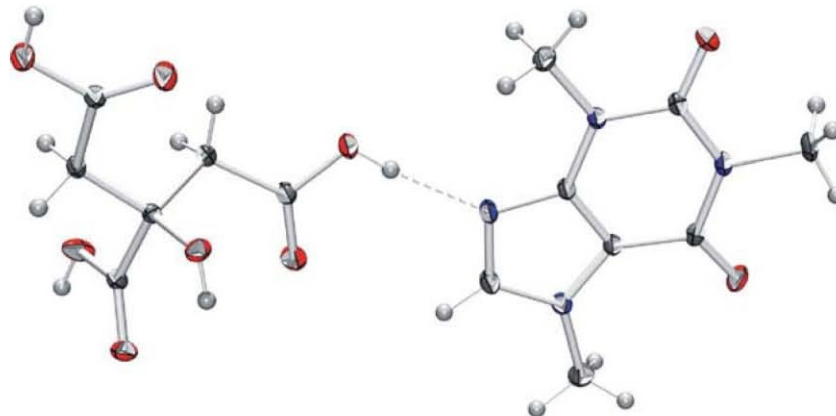
Reprint requests and correspondence to: Jatinder Bhatia, MD, Professor and Chief, Section of Neonatology, Medical College of Georgia, 1120 15th Street, Room B1W6033, Augusta, Georgia 30612.

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Apnea is the most important disorder in the control of breathing in the neonate and is one of the most common problems in the neonatal intensive care unit.¹ Apnea of prematurity (AOP) is defined as the cessation of breathing for periods from 10 to 20 seconds, with



Unusual conductivity properties?



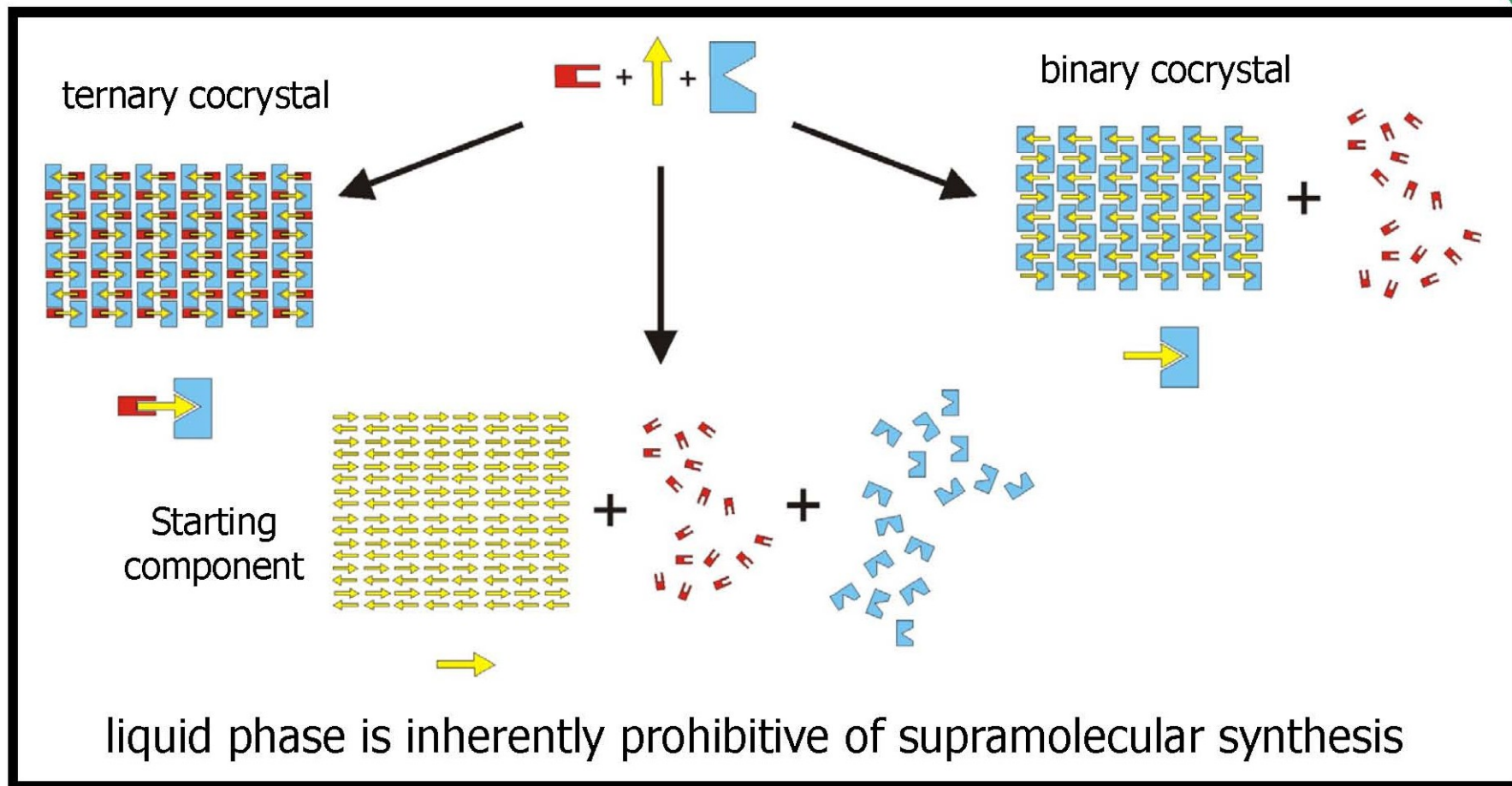
JUNE 2000

CLINICAL PEDIATRICS 327

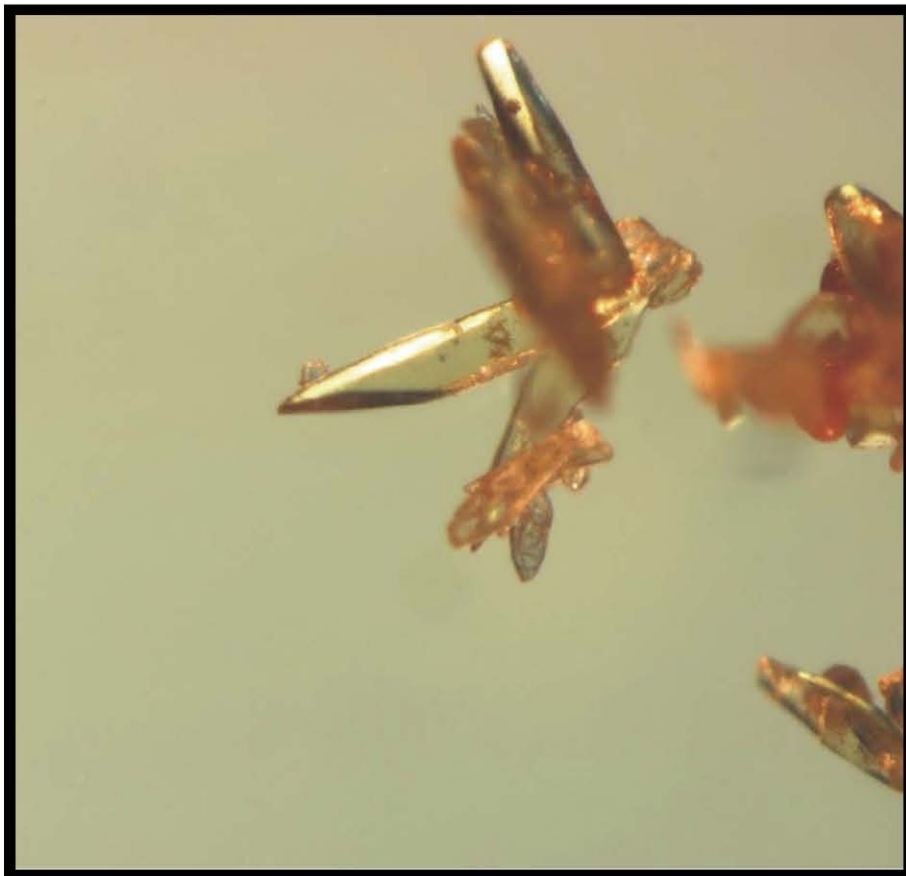
Karki, Friscic, Motherwell, Jones *Mol. Pharm.* **2007**, *4*, 347-354.



Why mechanochemical synthesis (grinding)?



A purely practical reason



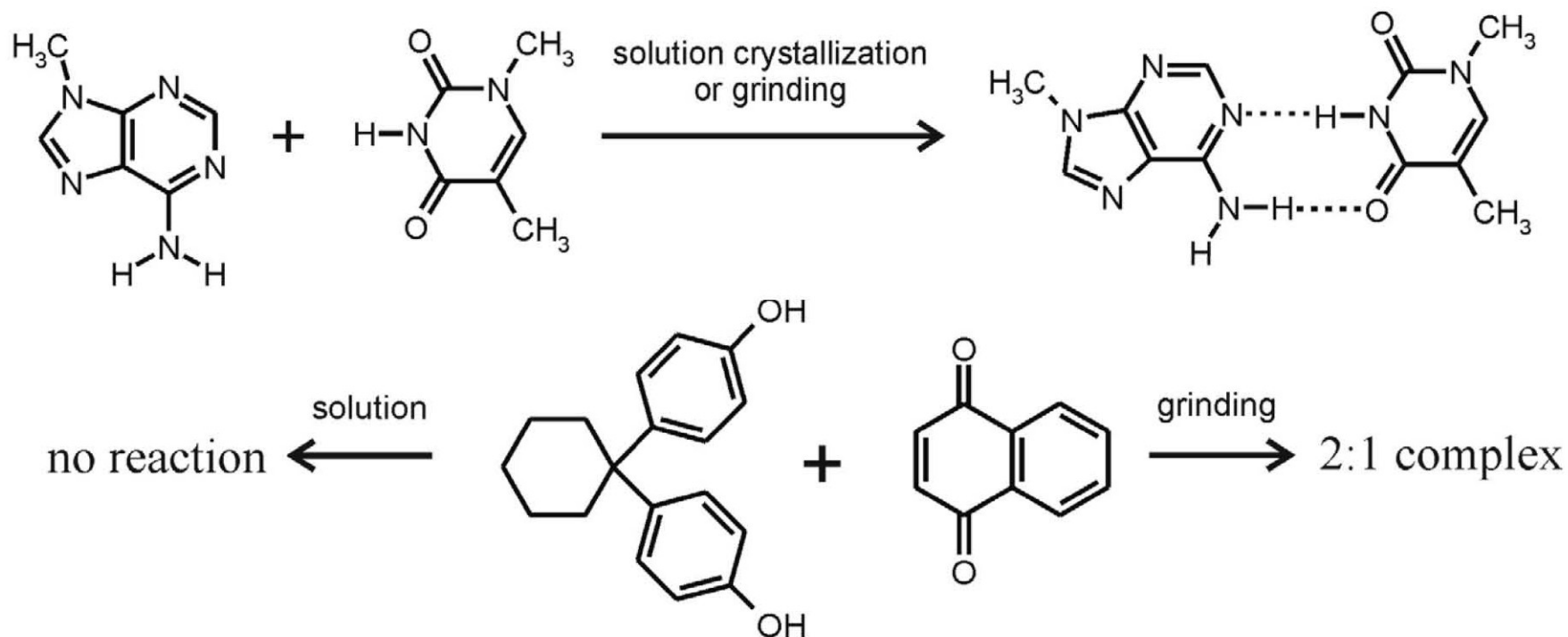
Exposure to solvents can lead to contamination

We need a better medium to gauge our ability to conduct supramolecular synthesis!



Supramolecular Mechanochemical Synthesis

Hydrogen-bonds can be constructed through grinding



Etter, M.C. *et al.* *J. Am. Chem. Soc.* **1993**, 115, 4411; Toda, F. *et al.* *Chem. Commun.* **1987**, 279.

Braga, D *et al.* *Dalton Trans.* **2006**, 1249



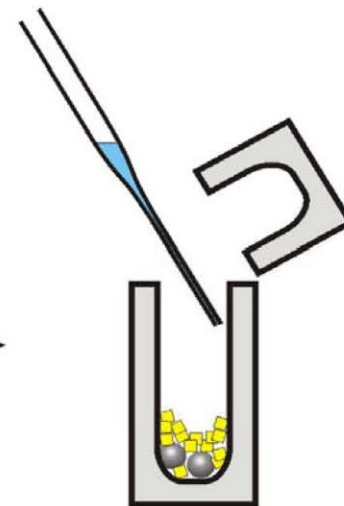
Evolution of mechanochemical synthesis



**manual
grinding**



**neat
grinding**
simple, easily
delineated grinding
conditions



**liquid-assisted
grinding**
fast, improved
crystallinity,
liquid-controlled
formation of product

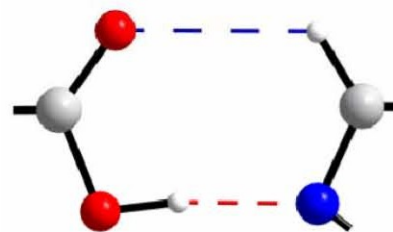
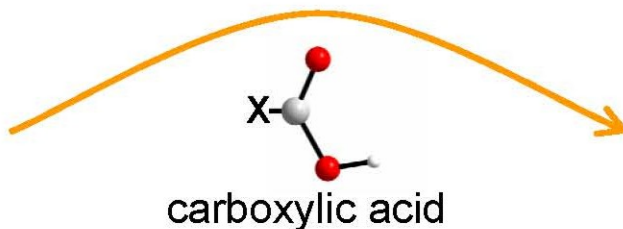
Shan, Toda & Jones. *Chem. Commun.*, **2002**, 2372-2373.



A synthon based design: addressing hydration stability

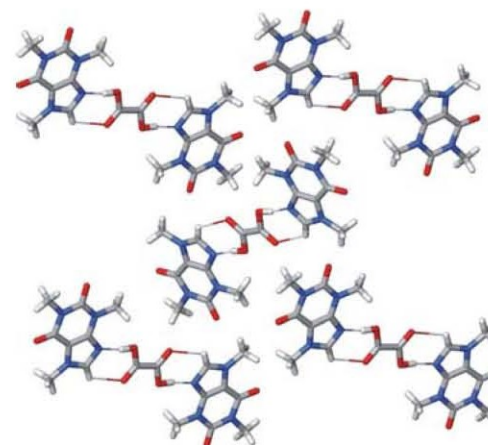
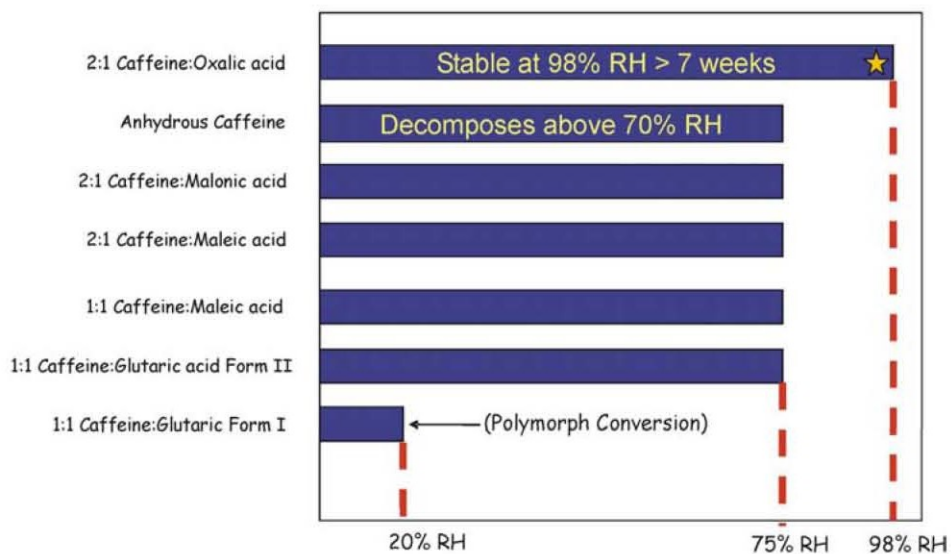


caffeine = forms a hydrate
in moist air



a supramolecular
synthon

Effect of storage for 7 weeks



caffeine:oxalic acid

Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Cryst. Gr. Des.* **2005**, *5*, 1013.



Solution growth vs. Solid-state Grinding



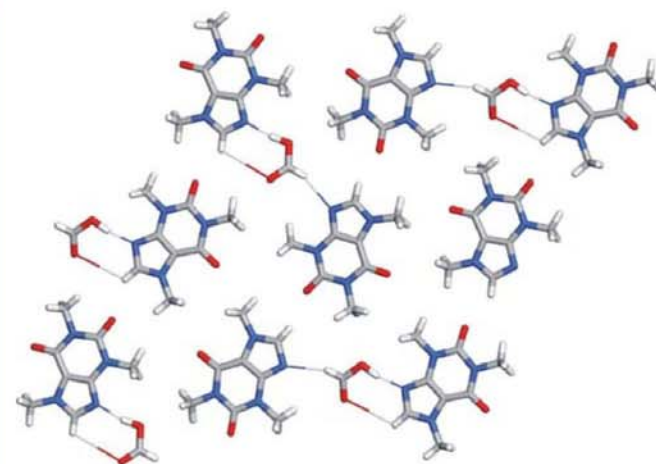
caffeine

Solution Growth



formic acid

Solid-state Grinding

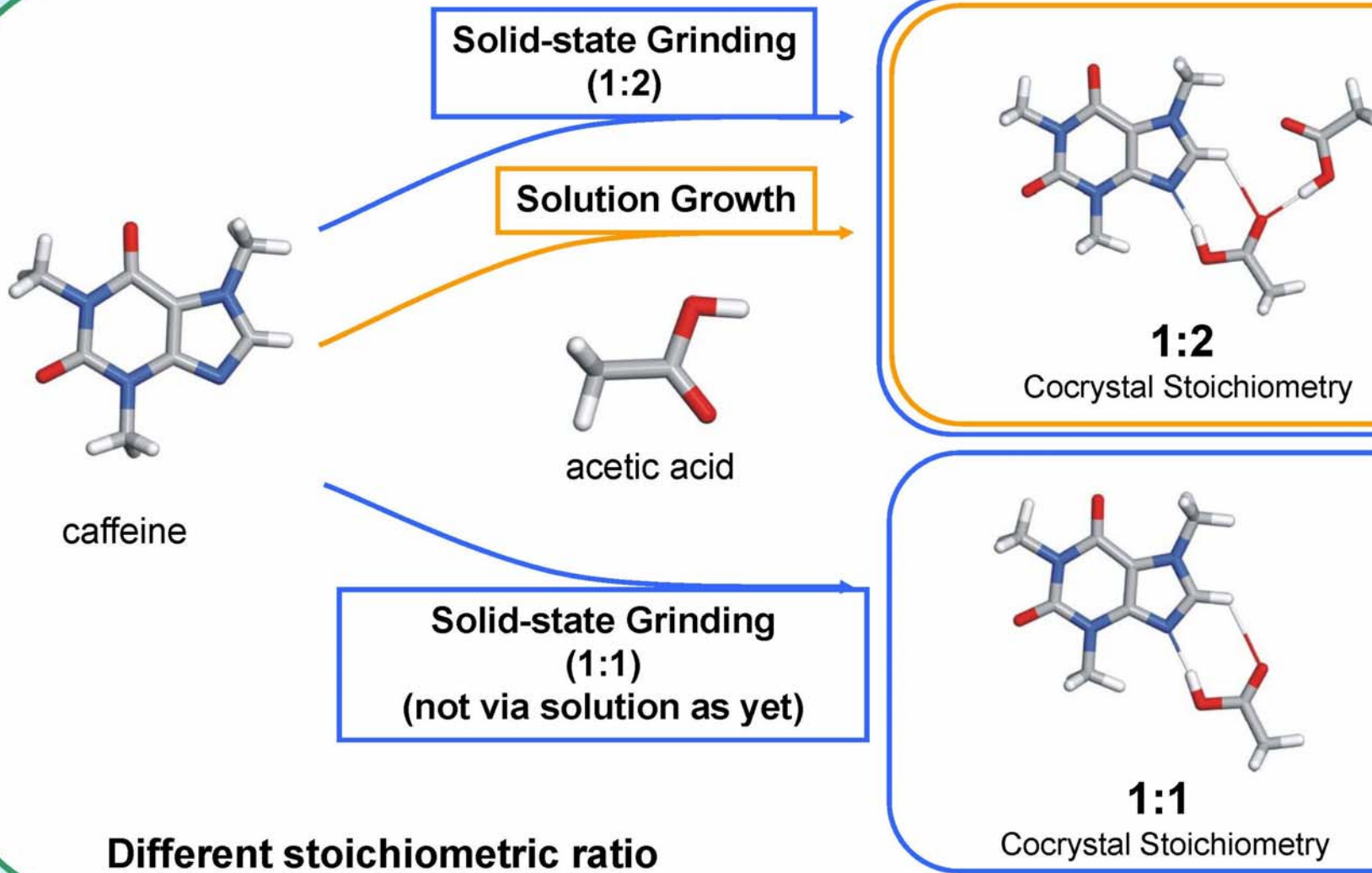


2:1 Caffeine:Formic Acid Cocrystal

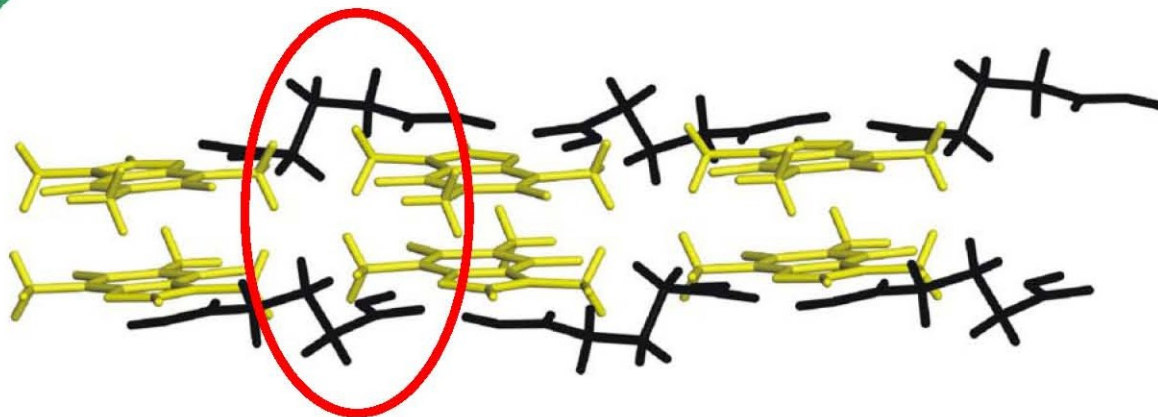
Same cocrystal product



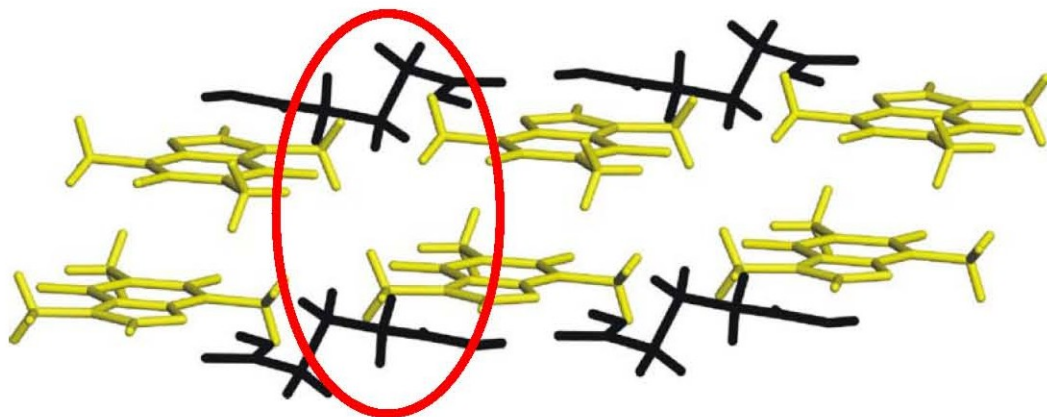
A new cocrystal stoichiometry is revealed by grinding



Selective polymorph formation via liquid-assisted grinding



Caffeine:Glutaric acid 1:1 **form I**
(Obtained using cyclohexane)



Caffeine:Glutaric acid 1:1 **form II**
(Obtained using chloroform)

Trask, A. V.; Motherwell, W. D. S.; Jones, W.
Chem. Commun. **2004**, 890.

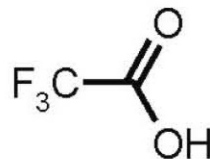
Cocrystallization from solution results in the formation of both polymorphs



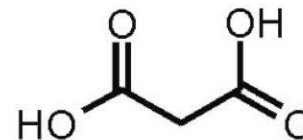
Activating a 'bad molecule' via liquid-assisted grinding



theobromine

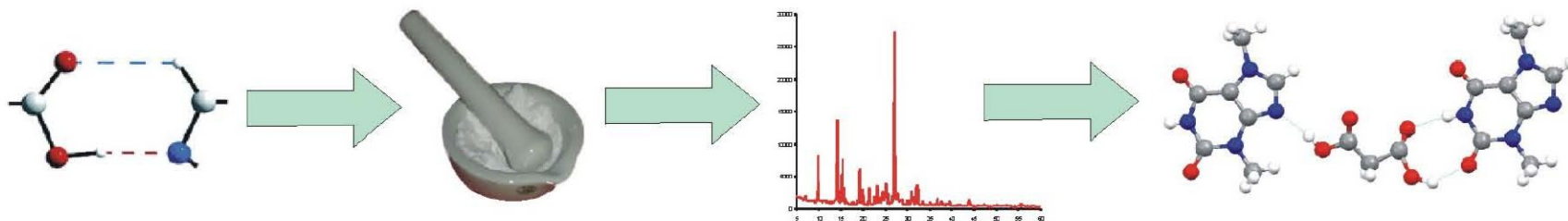


trifluoroacetic acid



malonic acid

Solution cocrystallisation attempts yielded only theobromine precipitates



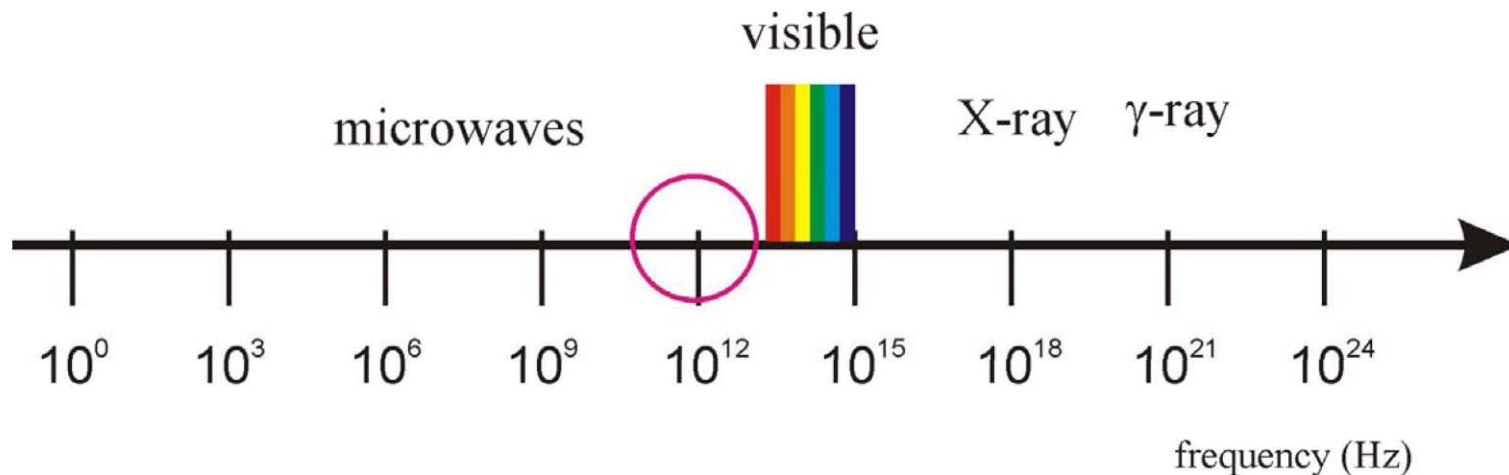
From reactants to products in less than a day

Karki; Fábíán; Frišćić; Jones *Org. Letters.* **2007**, *9*, 3133-3136.



Looking deeper: Terahertz spectroscopy

Terahertz spectroscopy is gaining importance for identification and quantification of pharmaceutical ingredient solid forms

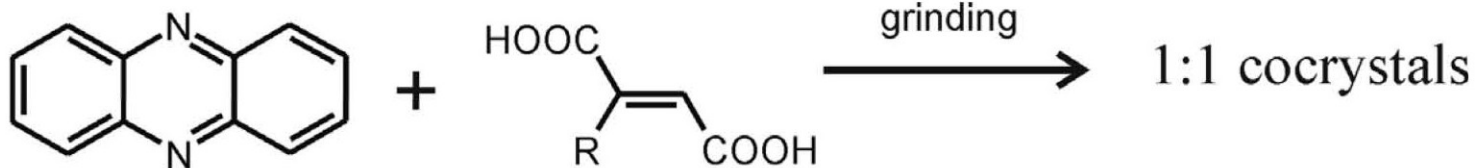


Terahertz spectroscopy allows the observation of lattice vibration modes



Exploring mechanisms: phenazine and mesaconic acid

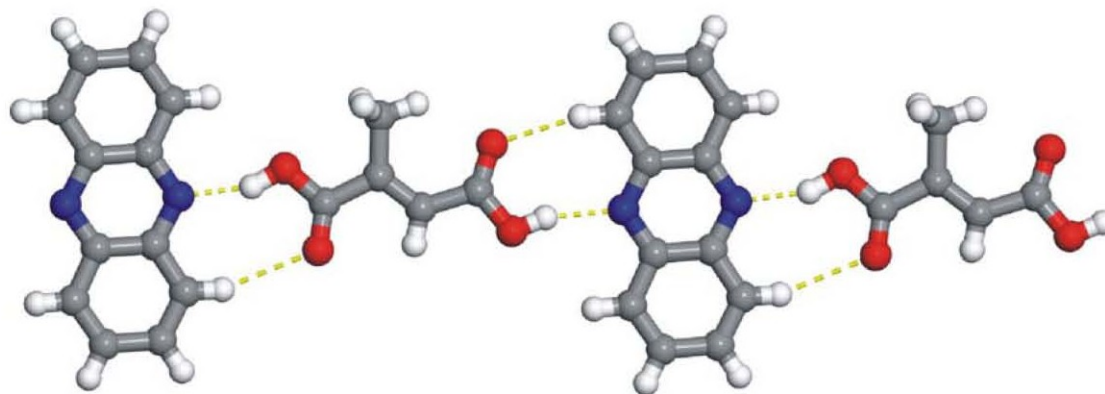
Cocrystals of phenazine and dicarboxylic acids can readily be prepared by grinding together the two components:



R = H, CH₃

Typical neat grinding times: 40-90 minutes for 1 mmol samples

Cocrystal of phenazine and mesaconic acid:

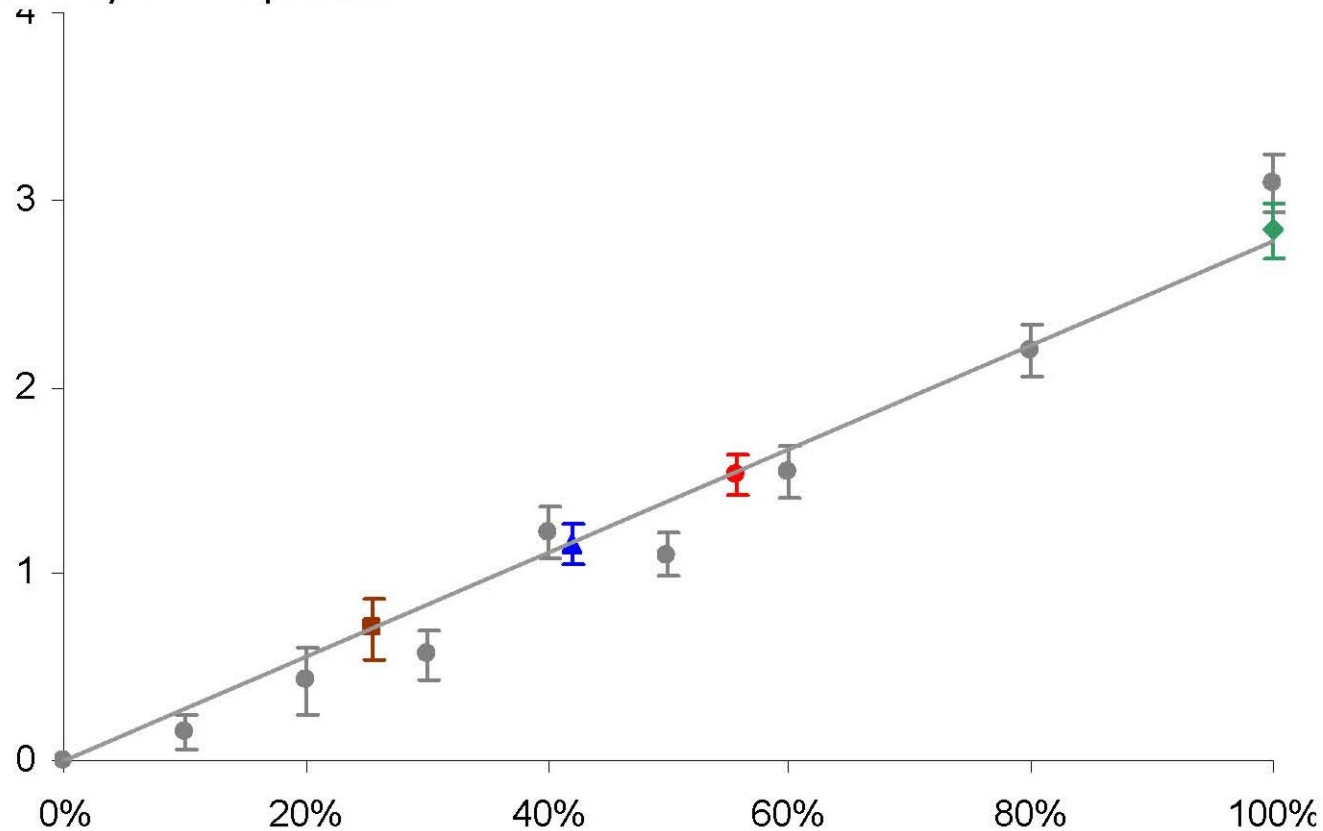


Batchelor, E.; Klinowski, J.; Jones, W. *J. Mat. Chem.* **2000**, *10*, 839.



THz monitoring of (liquid-assisted) grinding cocrystallization

The presence of a liquid phase reduces the grinding time and increases the crystallinity of the product:

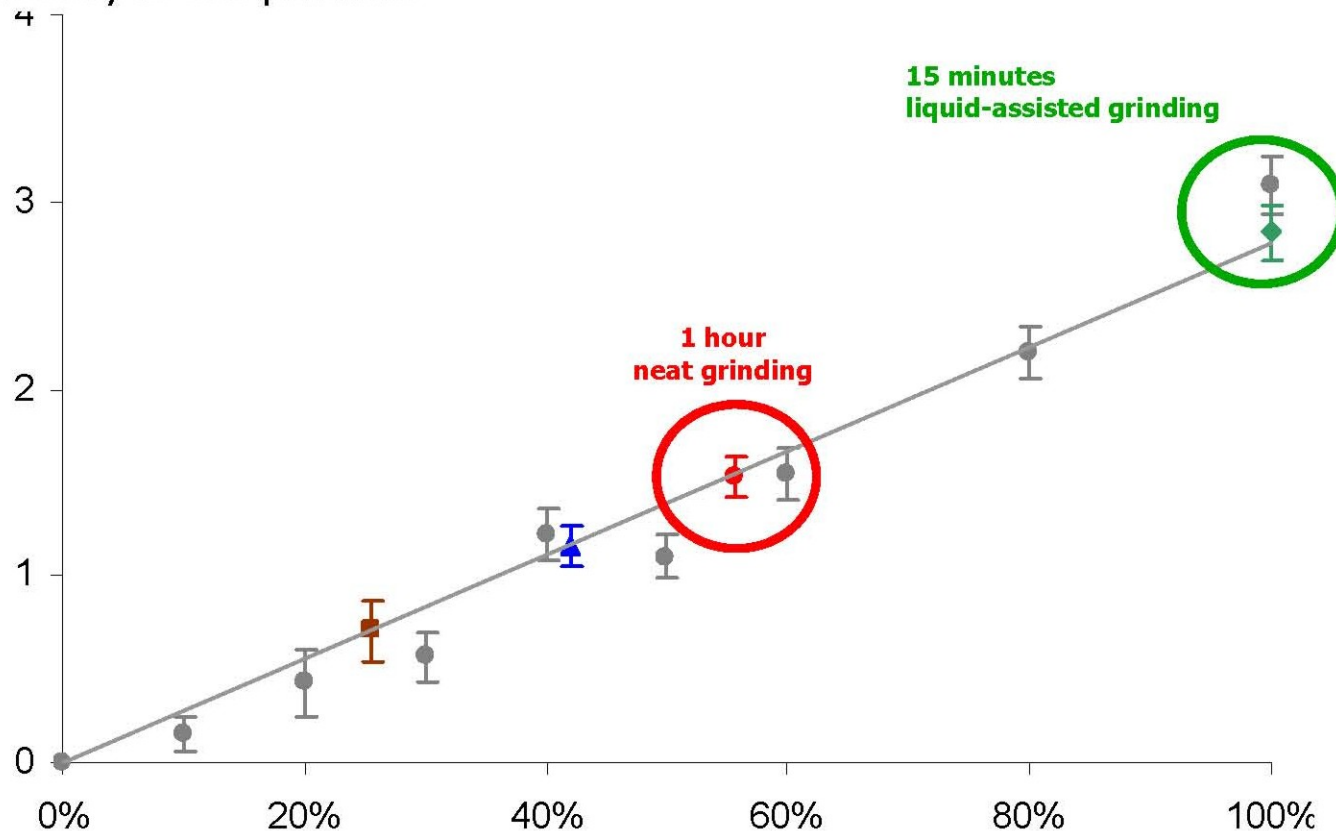


Nguyen, K. L.; Friscic, T.; Day, G. M.; Gladden, L. F.; Jones, W. *Nature Materials*, **2007**, *6*, 206-209.



THz monitoring of (liquid-assisted) grinding cocrystallization

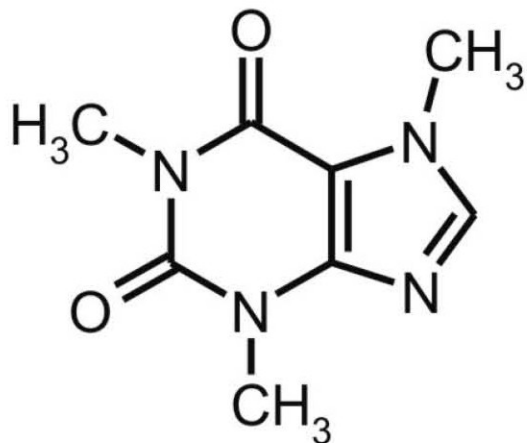
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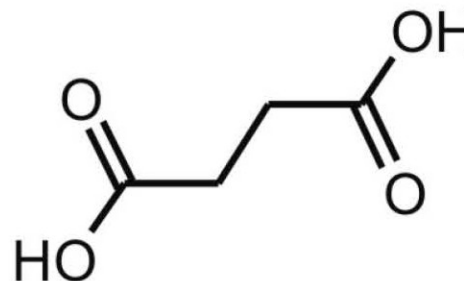
Nguyen, K. L.; Friscic, T.; Day, G. M.; Gladden, L. F.; Jones, W. *Nature Materials*, **2007**, *6*, 206-209.



Failure of the synthon-based approach?



caffeine

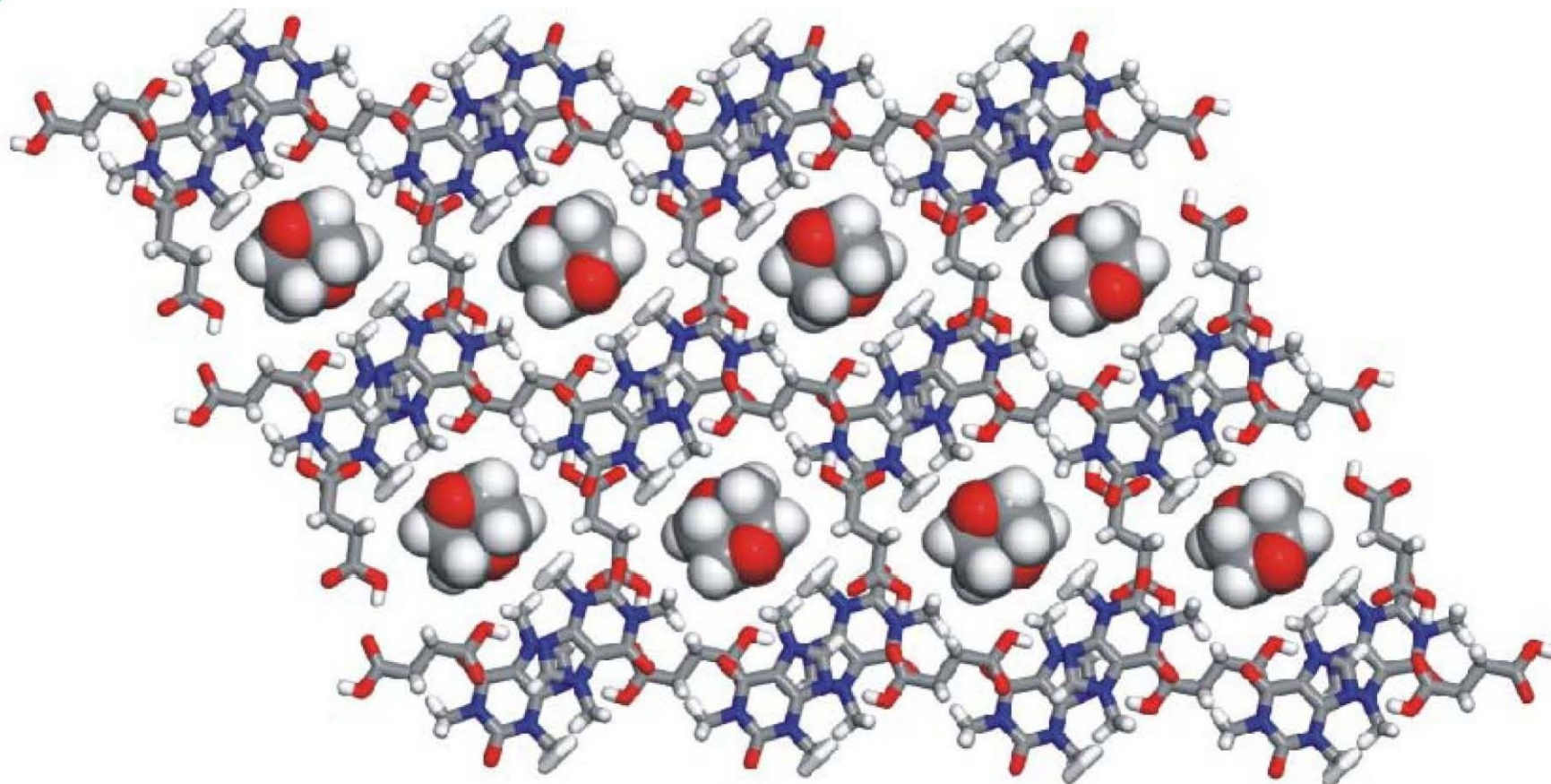


succinic acid

No reaction on neat grinding or by growth from "conventional" solvents



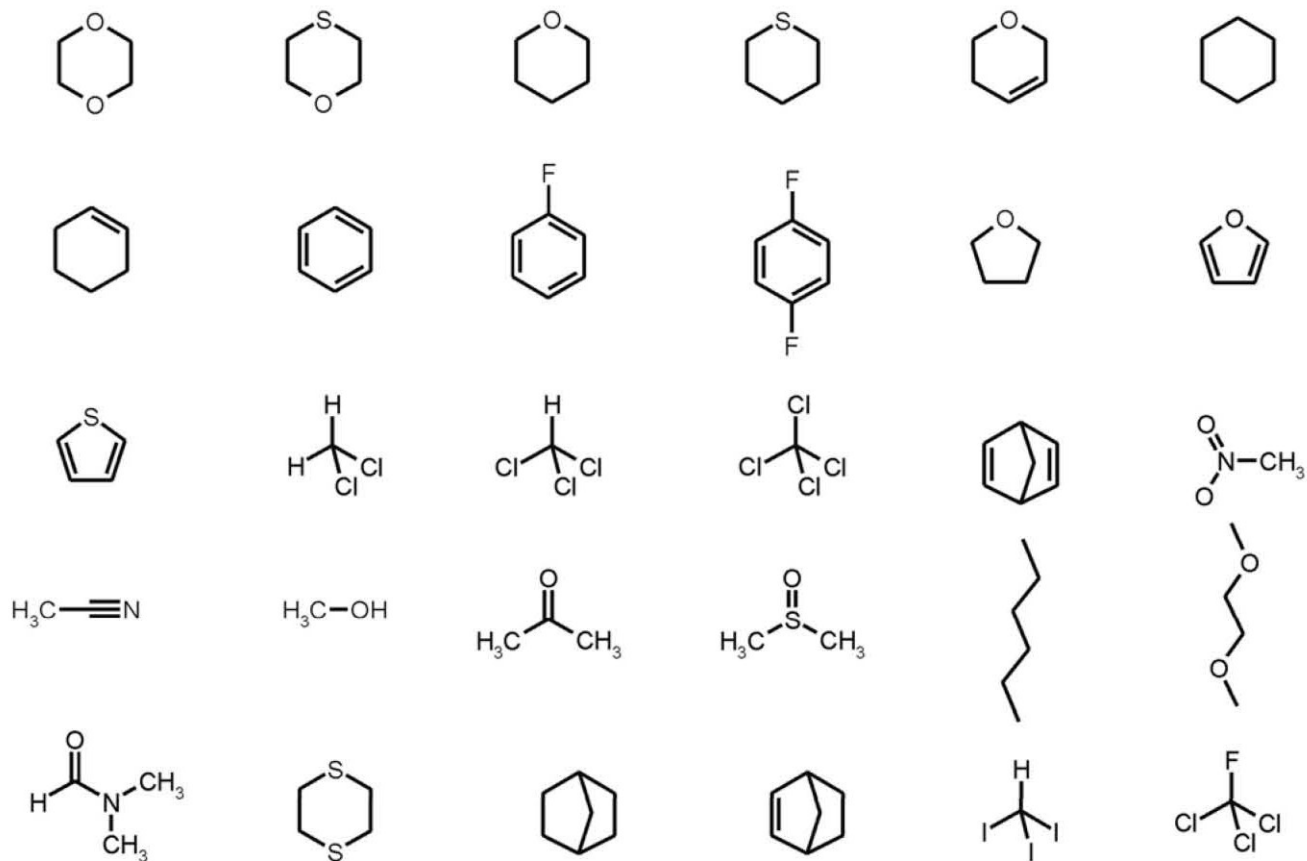
But dioxane yields a three-component solid: *synthon did not fail*



Friscic; Trask; Jones; Motherwell *Angew. Chem., Int. Ed.* **2006**, *45*, 7546-7550.

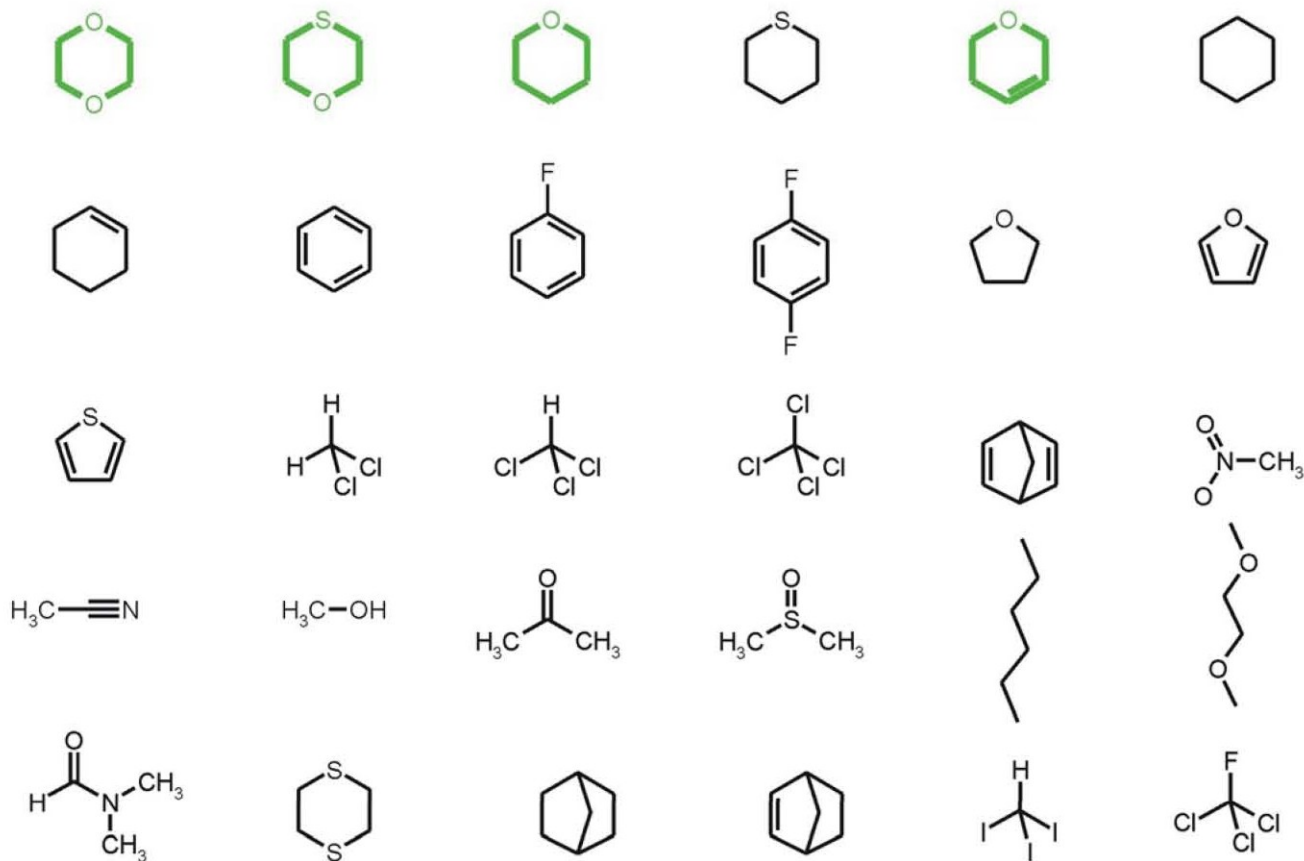


A three-component crystal is formed with numerous guests: gauging the efficiency of cocrystallisation methods



Frisic; Trask; Jones; Motherwell *Angew. Chem., Int. Ed.* **2006**, *45*, 7546-7550.

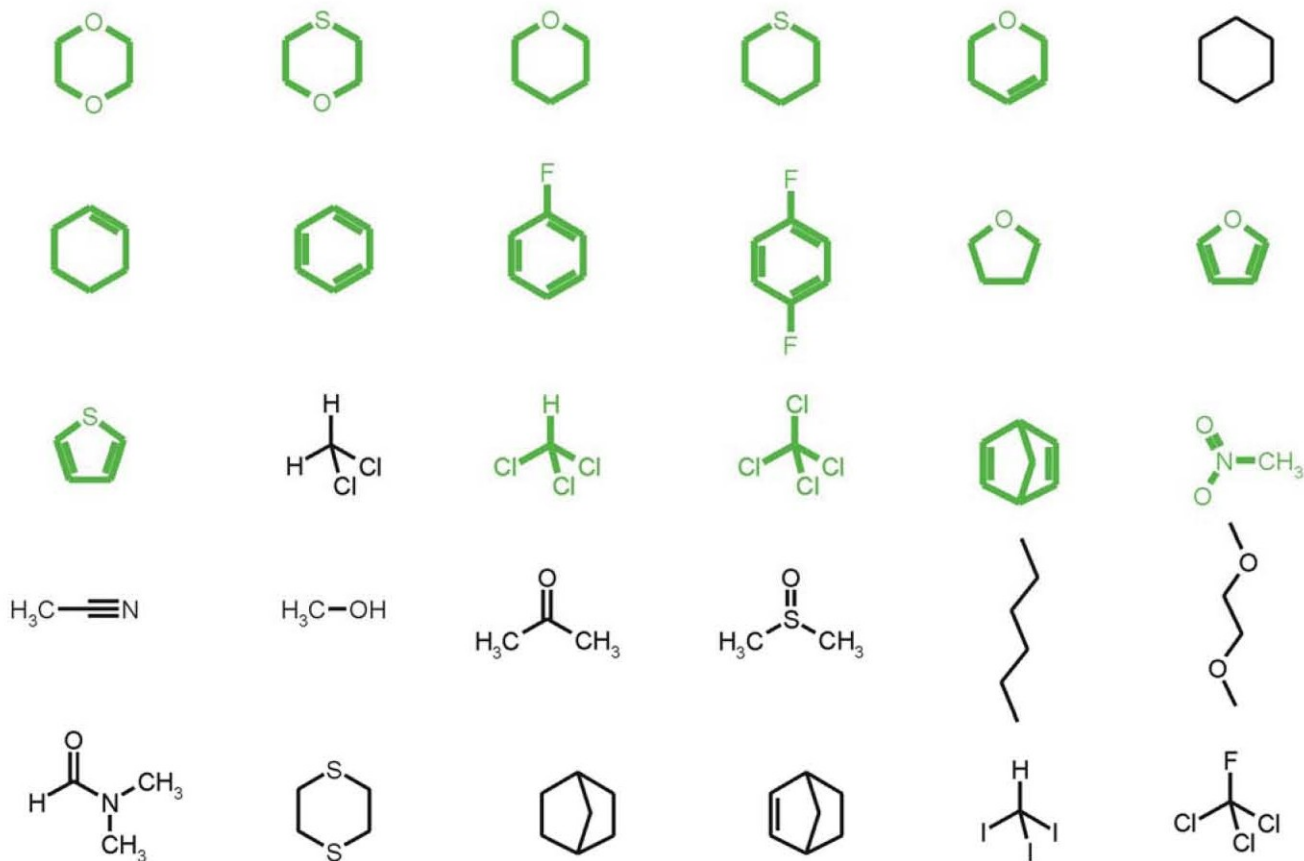
A three-component crystal is formed with numerous guests: gauging the efficiency of cocrystallisation methods



4 hits out of 30 *via* solution crystallization



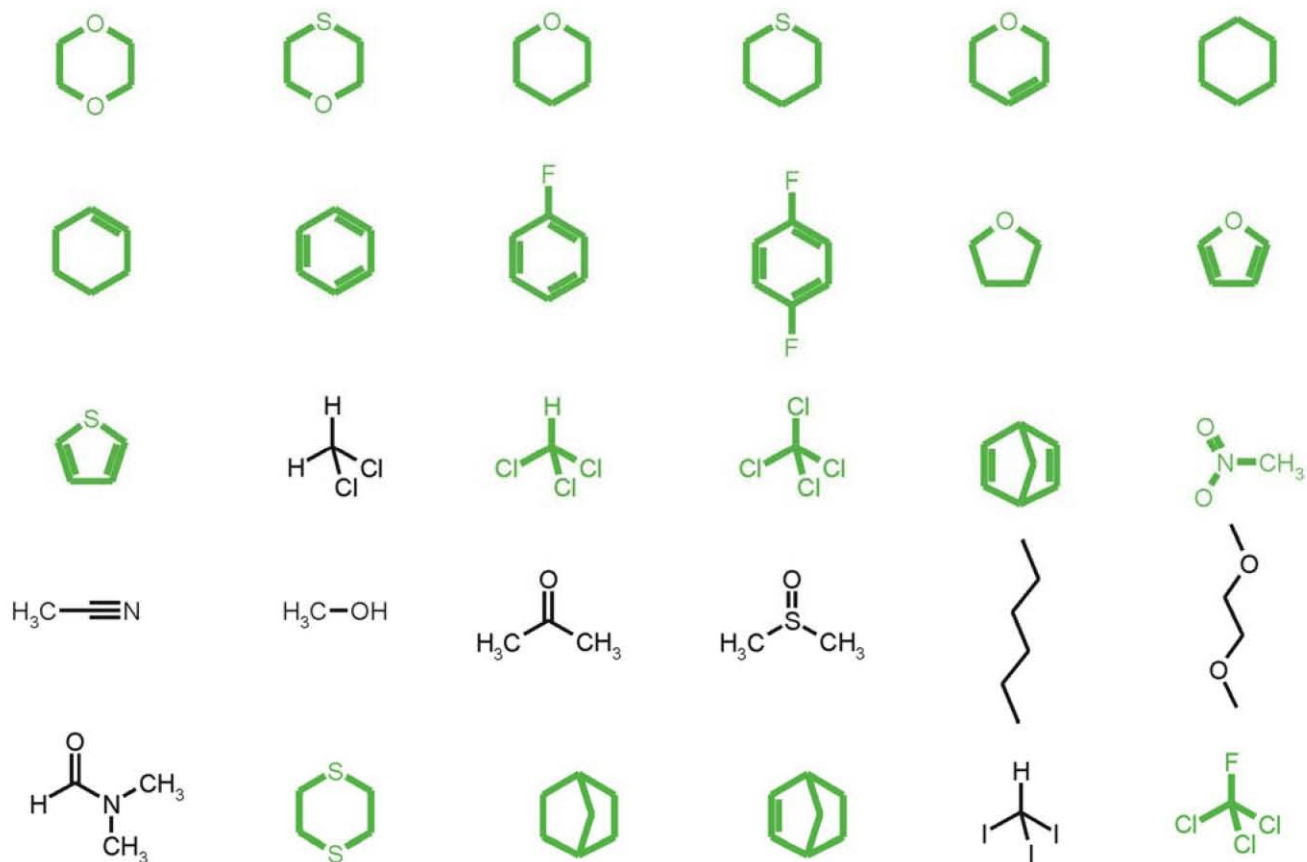
A three-component crystal is formed with numerous guests: gauging the efficiency of cocrystallisation methods



16 hits out of 30 *via* neat grinding



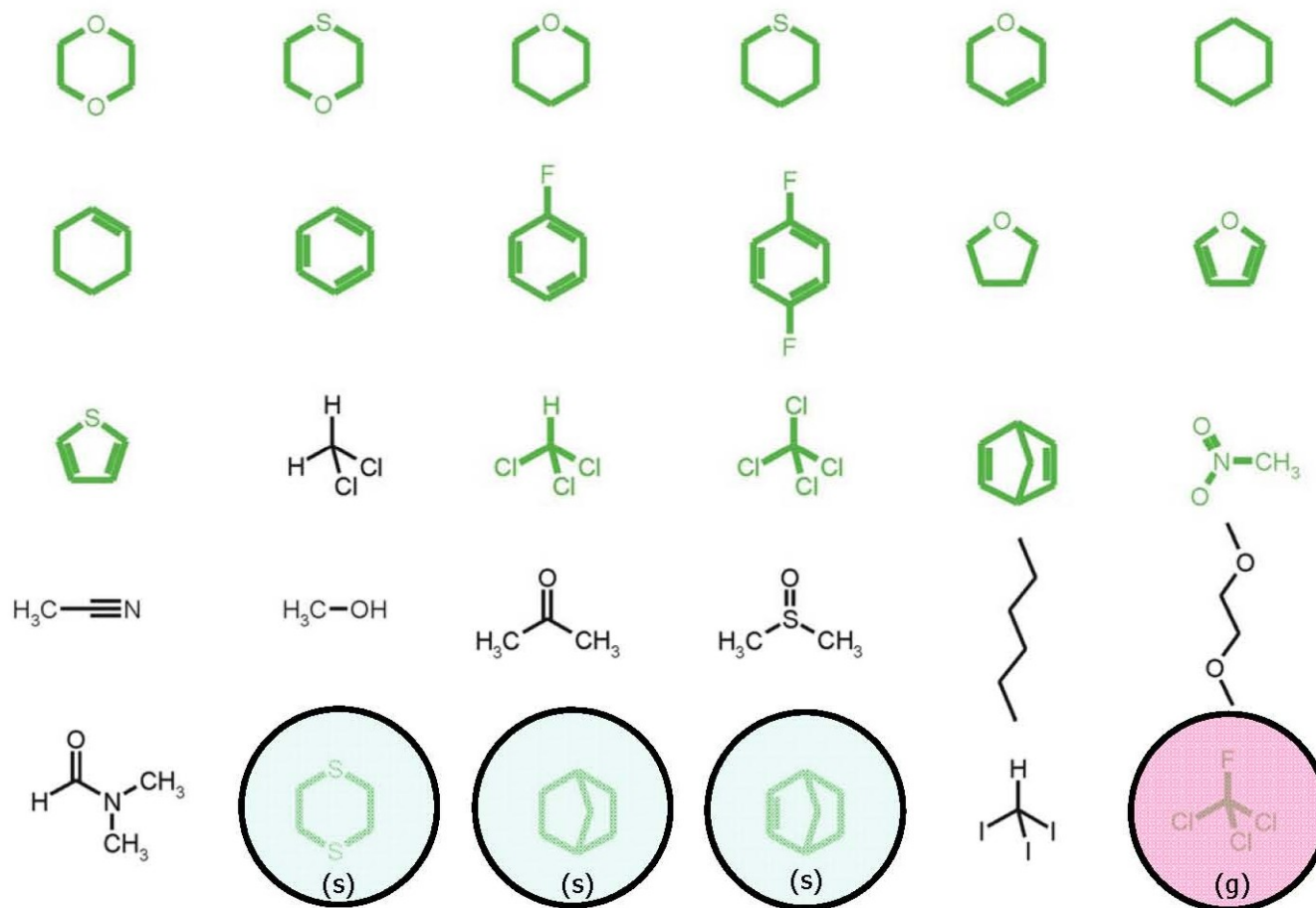
A three-component crystal is formed with numerous guests: gauging the efficiency of cocrystallisation methods



21 hits out of 30 *via* liquid-assisted grinding

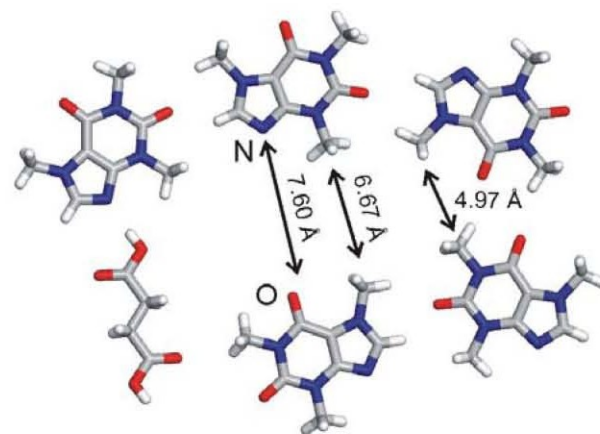
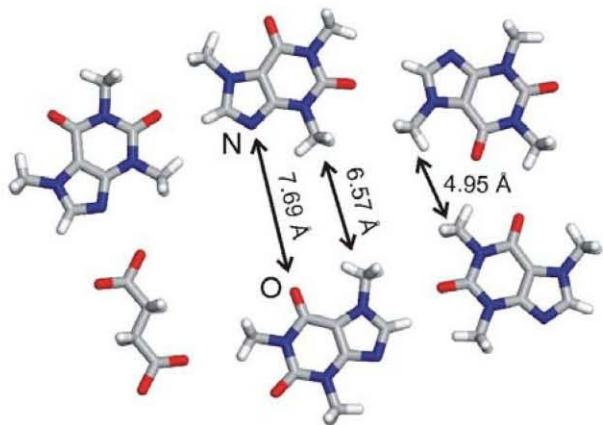
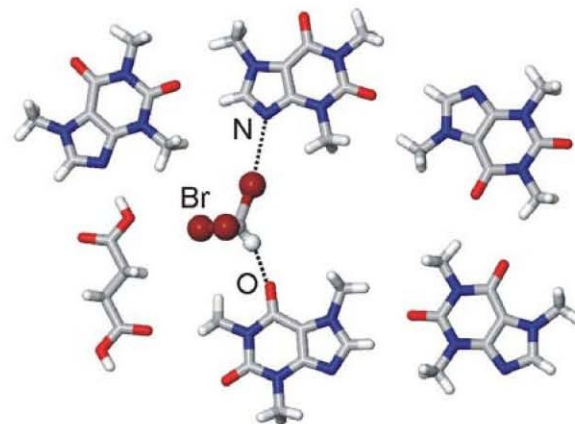
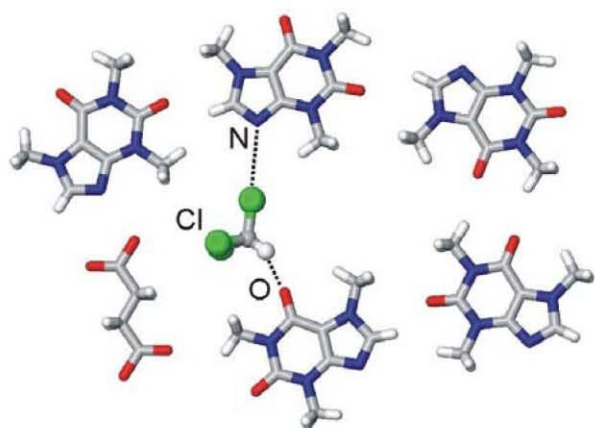


A three-component crystal is formed with numerous guests: gauging the efficiency of cocrystallisation methods



Ability to contain solids, liquids and gases!

An alternative framework

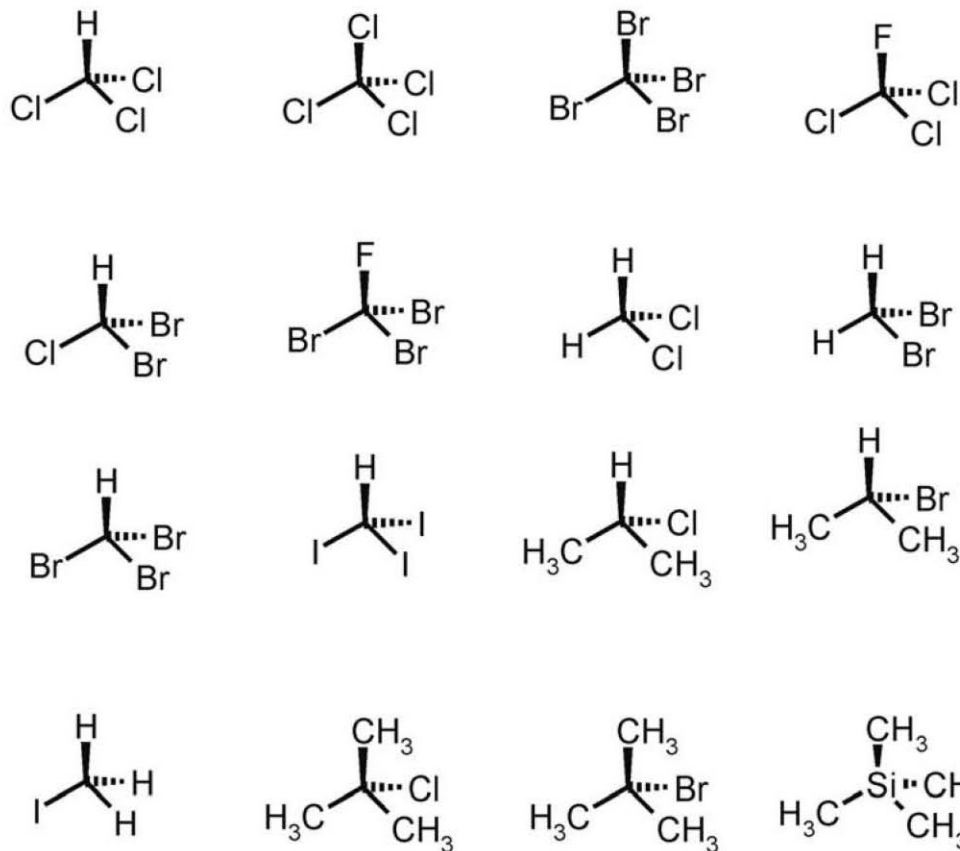


The new caffeine:succinic acid (4:1) framework is supported by halogen and C-H...O bonds



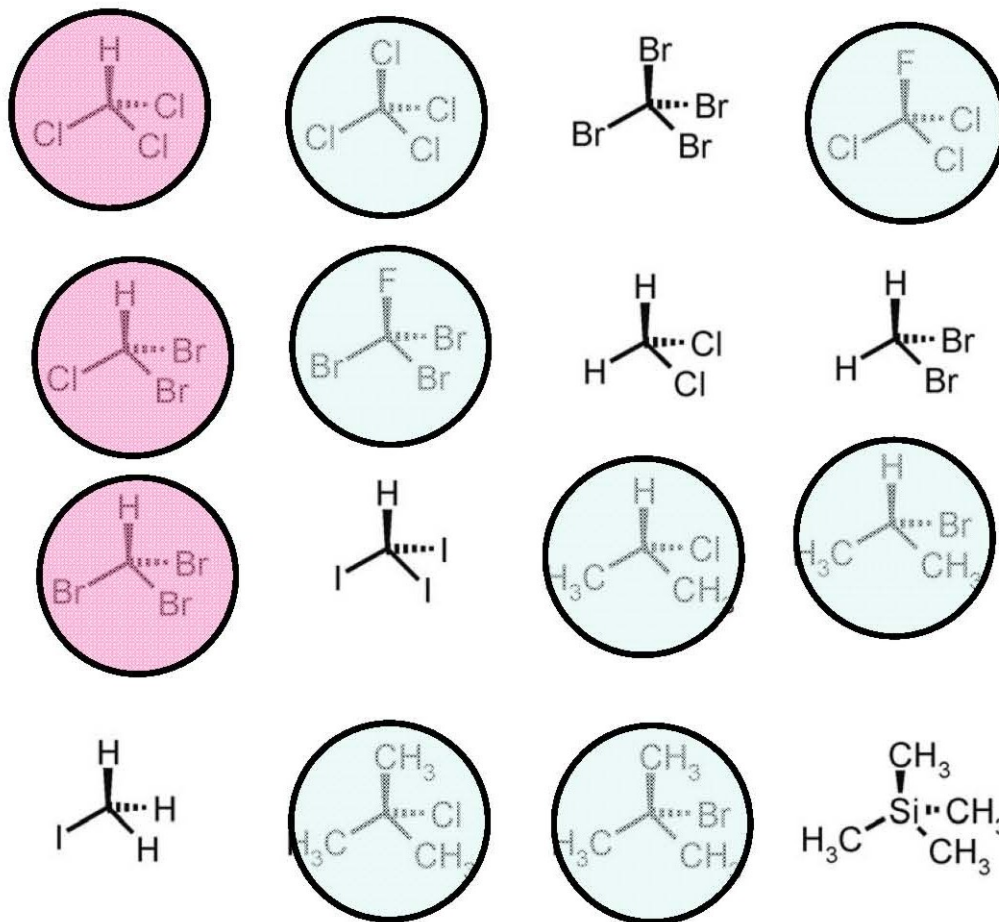
Mechanochemical screening for molecular templates

A library of potential molecular templates to gauge the importance of halogen and C-H...O bonding for constructing the new framework



Mechanochemical screening for molecular templates

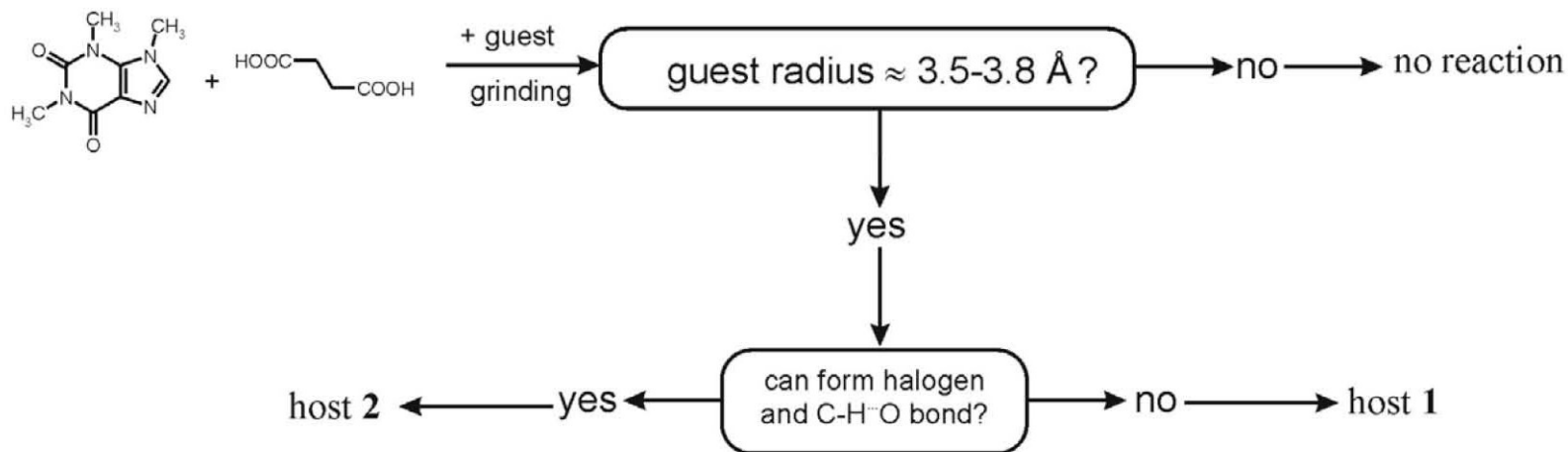
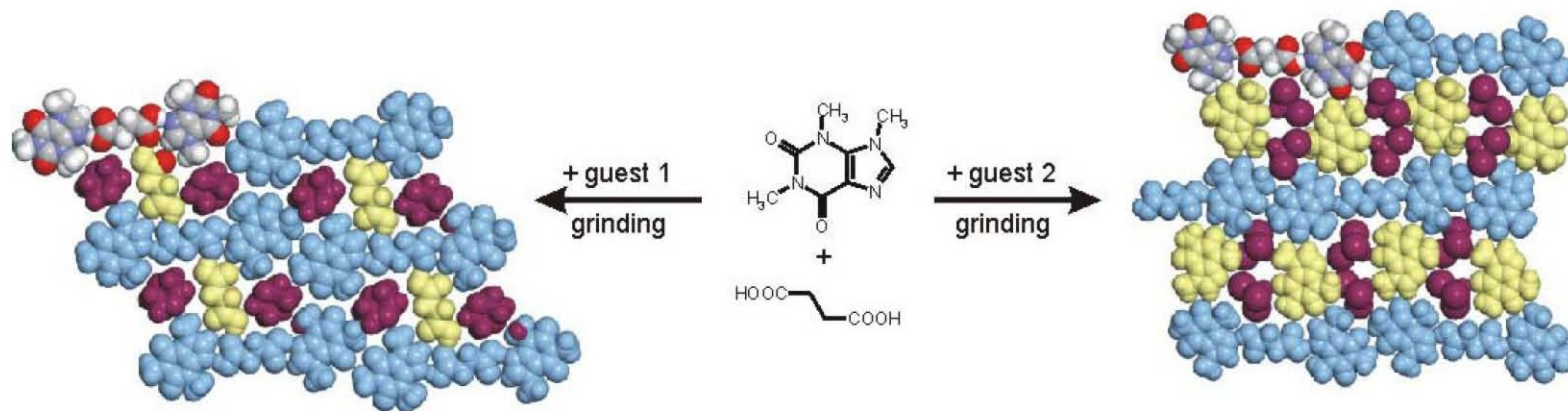
A library of potential molecular templates to gauge the importance of halogen and C-H...O bonding for constructing the new framework



1:1

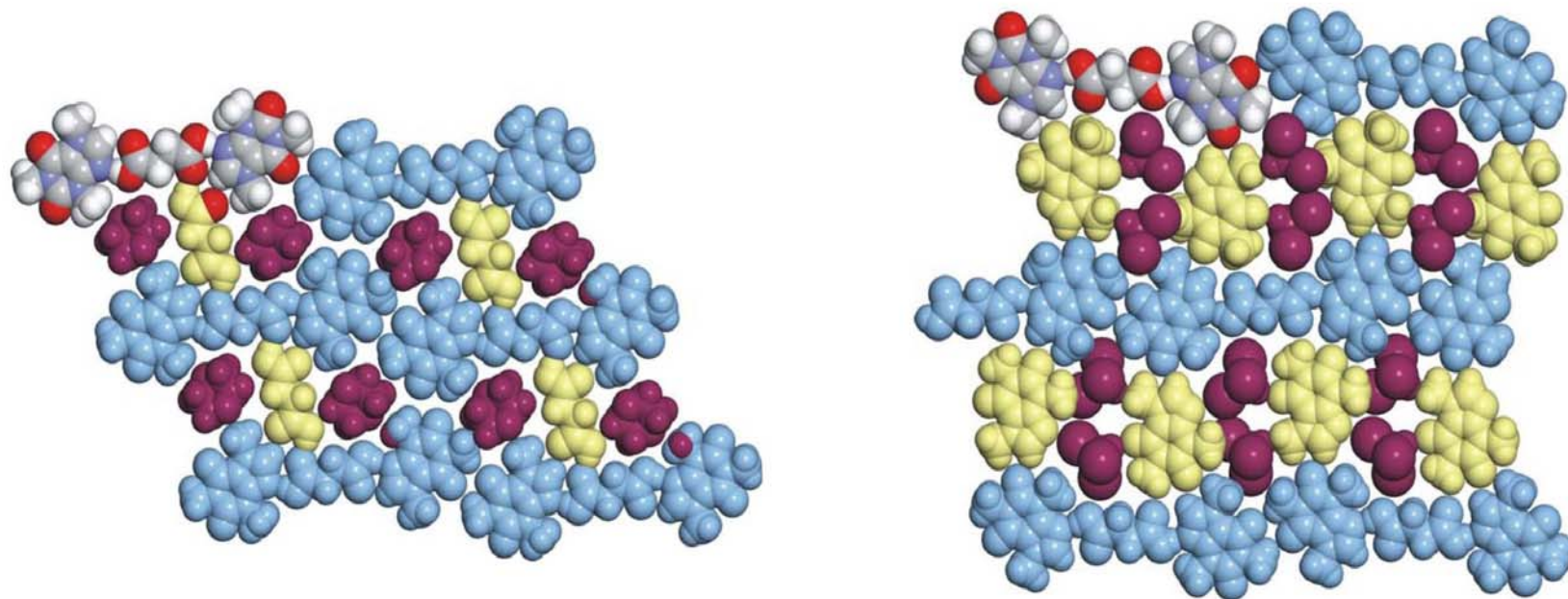
4:1

Guidelines for the synthesis of two frameworks



Friscic, Trask, Motherwell, Jones *Cryst. Growth Des.* **2008**, 1605-1609.

Why is succinic acid a poor cocrystal former in the absence of a third molecule?

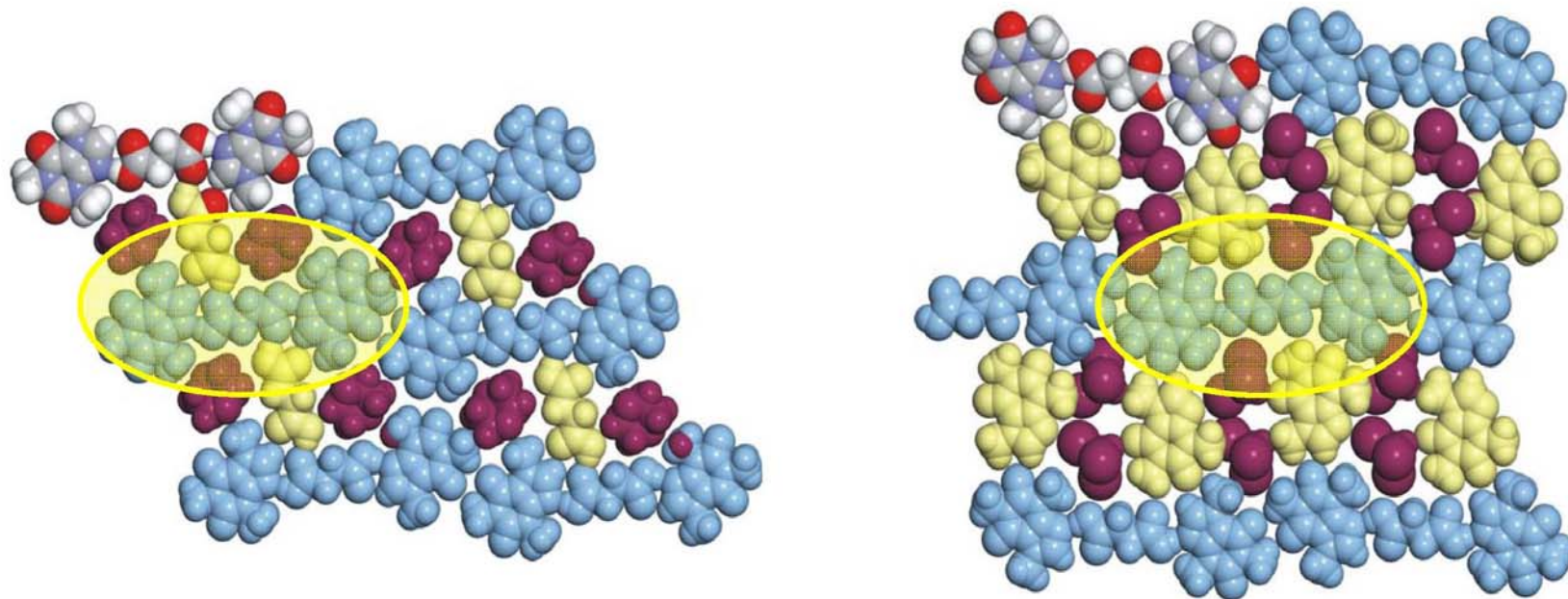


Both inclusion frameworks are made up of “pillared layers” containing the $(\text{caf})_2(\text{succ})$ dumb-bell assemblies

Friscic, Trask, Motherwell, Jones *Cryst. Growth Des.* **2008**, 1605-1609.



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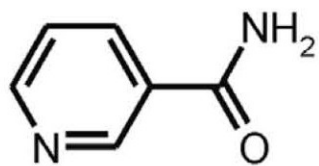


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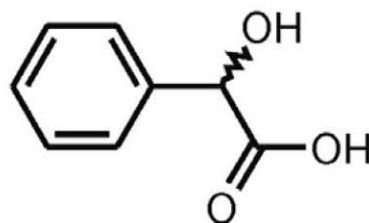
Friscic, Trask, Motherwell, Jones *Cryst. Growth Des.* **2008**, 1605-1609.



A synthon-based design for melting point enhancement

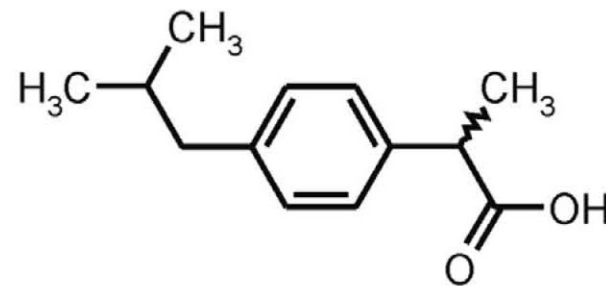


nicotinamide

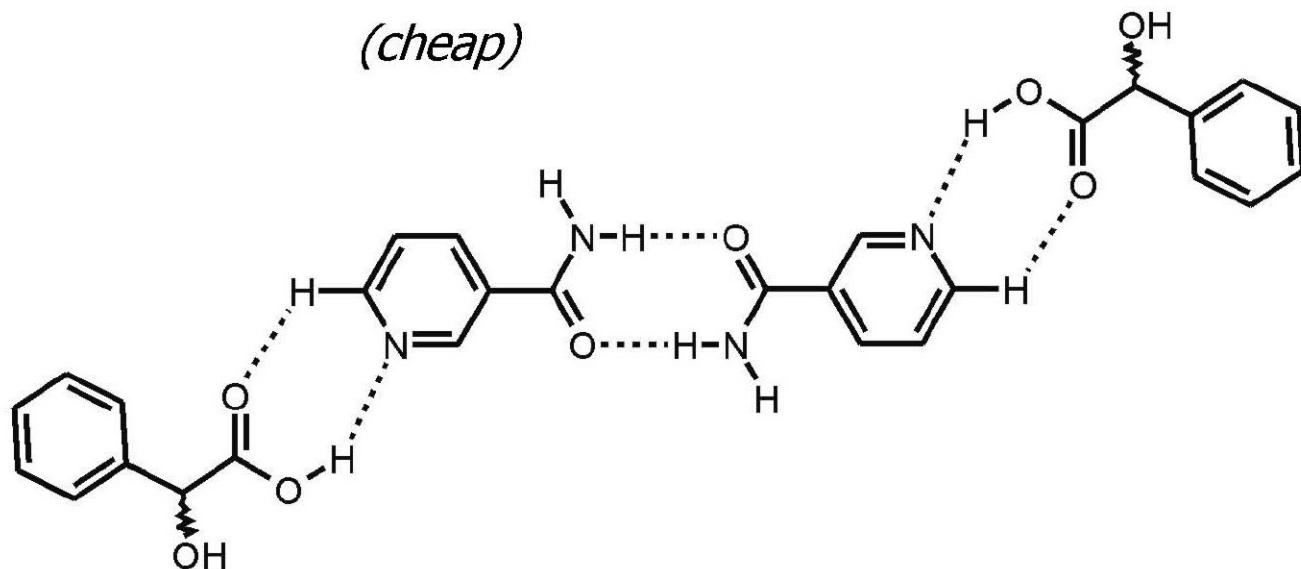


mandelic acid

(cheap)



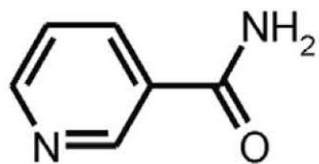
ibuprofen



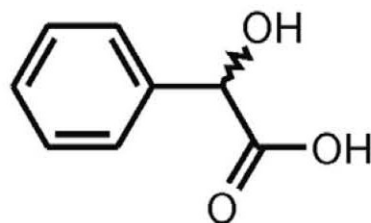
Friscic, T.; Jones, W. *Faraday Discussions* **2007**, *136*, 161-172.



A synthon-based design for melting point enhancement

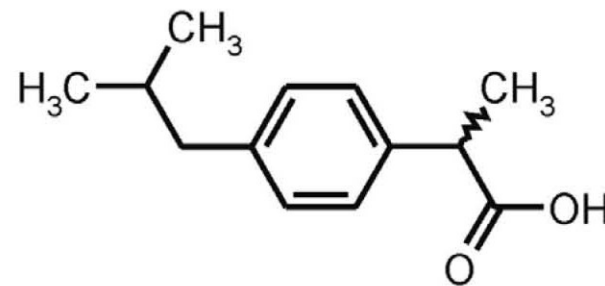


nicotinamide

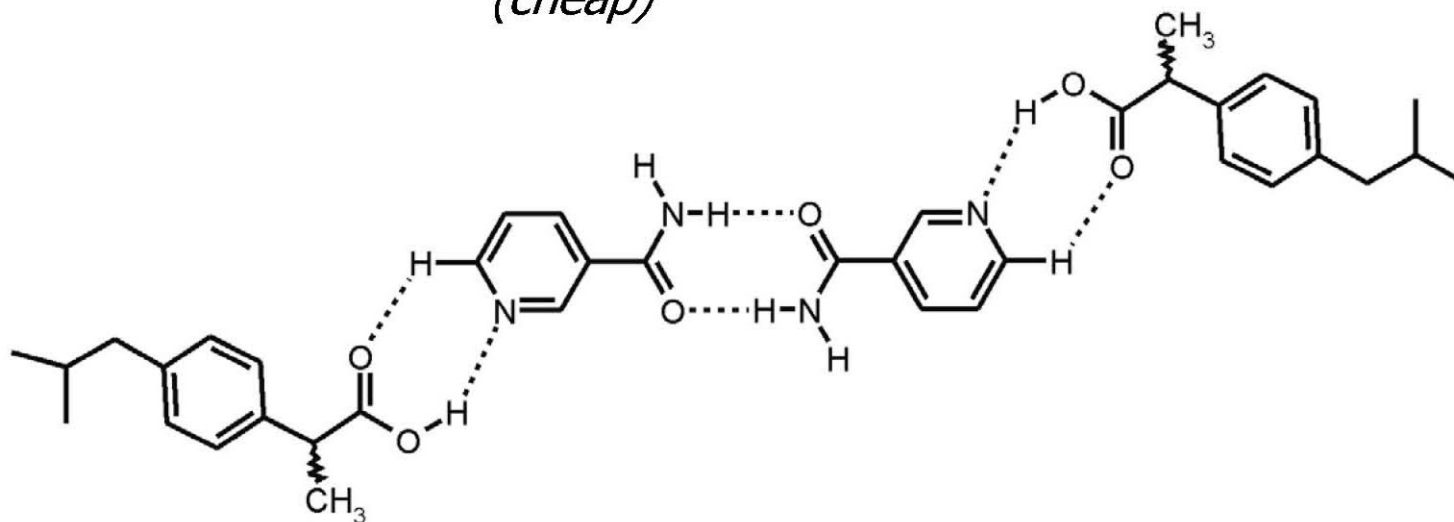


mandelic acid

(cheap)



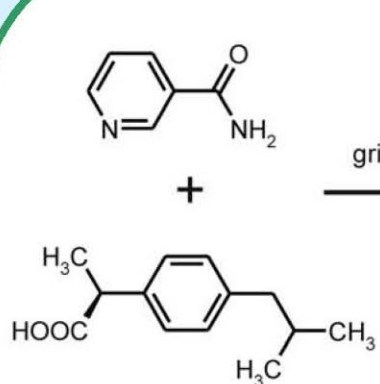
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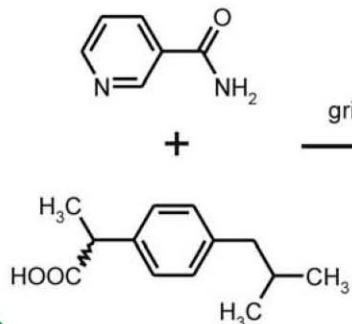
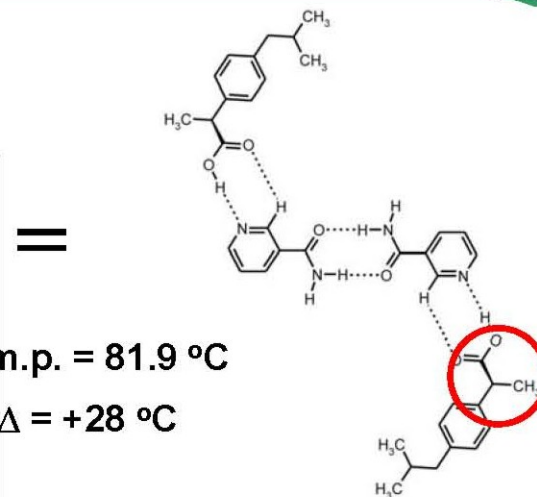
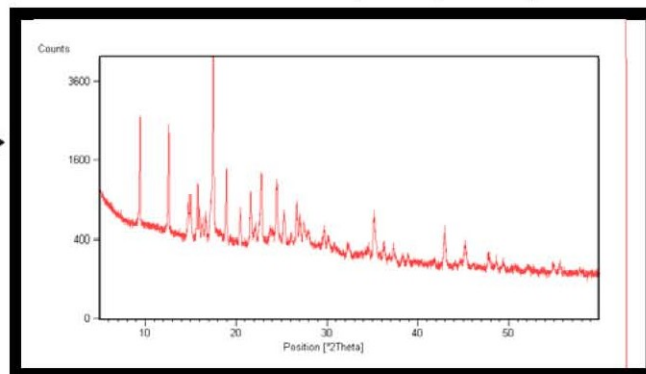
Friscic, T.; Jones, W. *Faraday Discussions* **2007**, *136*, 161-172.



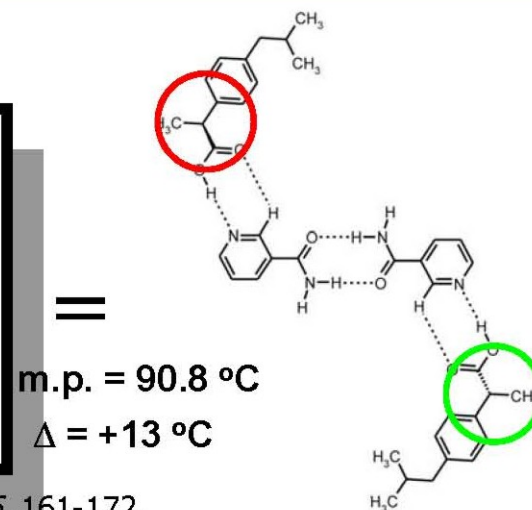
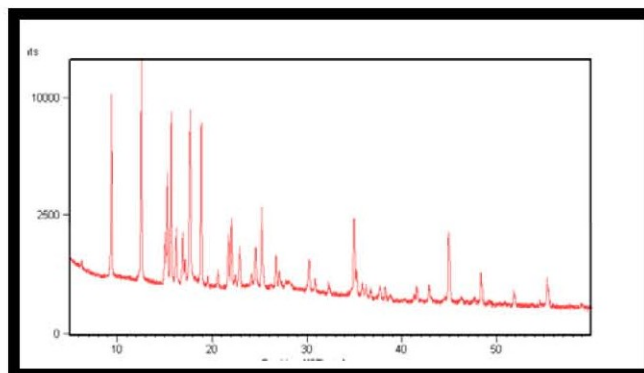
Cocrystals of Ibuprofen



grinding

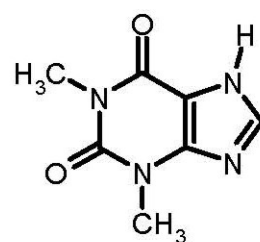
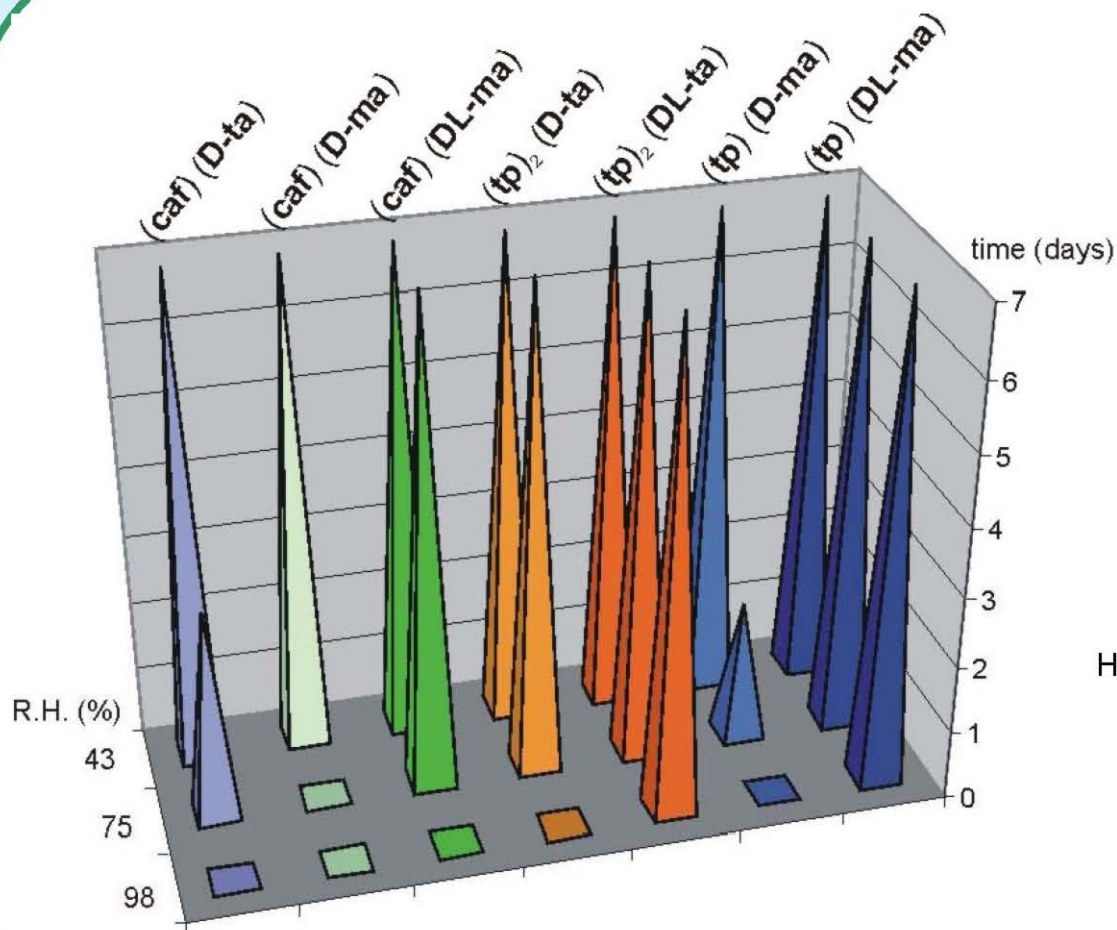


grinding

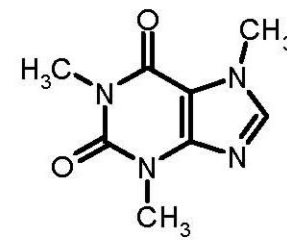


Friscic, T.; Jones, W. *Faraday Discussions* **2007**, *136*, 161-172.

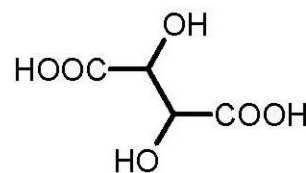
Effect of symmetry on hydration stability



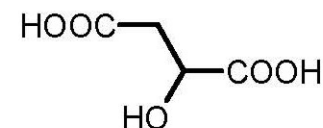
theophylline



caffeine



tartaric acid

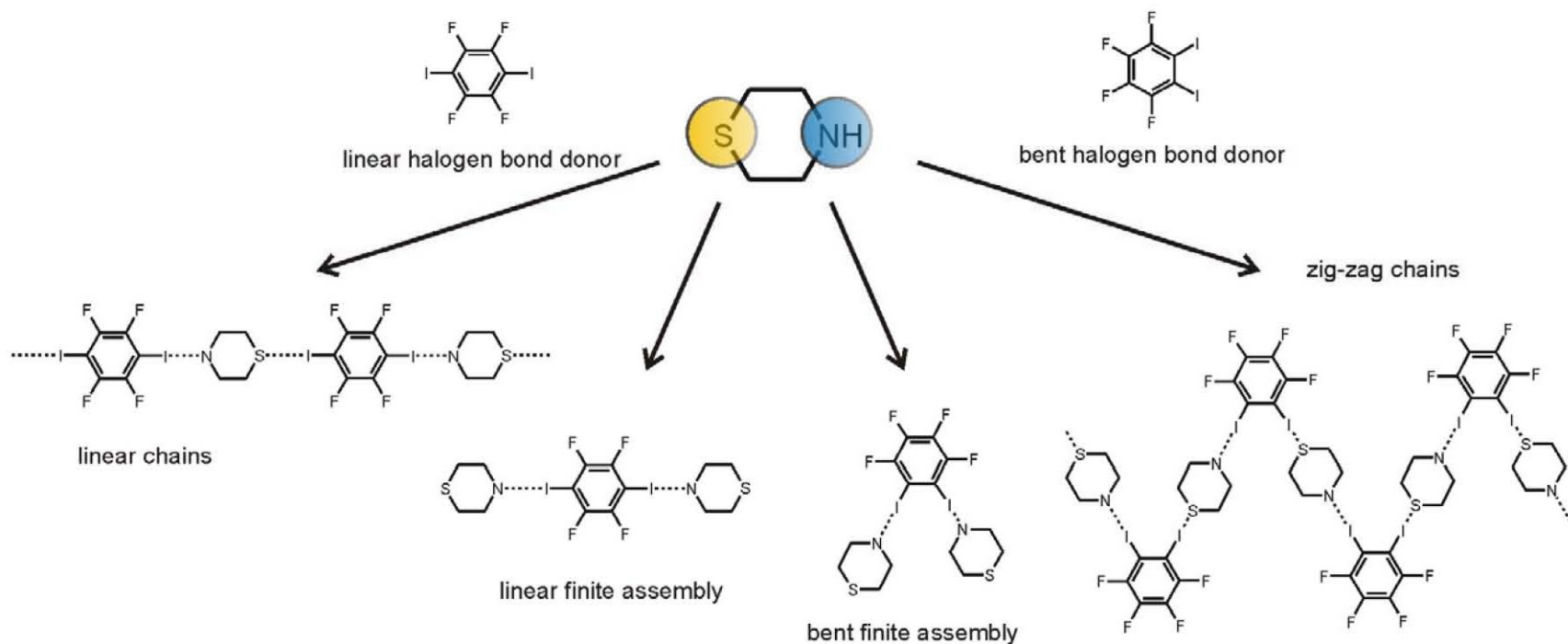


malic acid

Friscic, Fabian, Burley, Reid, Duer, Jones *Chem. Commun.* **2008**, 1644

Constructing halogen-bonds via grinding

A non-symmetrical reactant was used to investigate the interplay of different acceptor groups in halogen-bonded cocrystals:

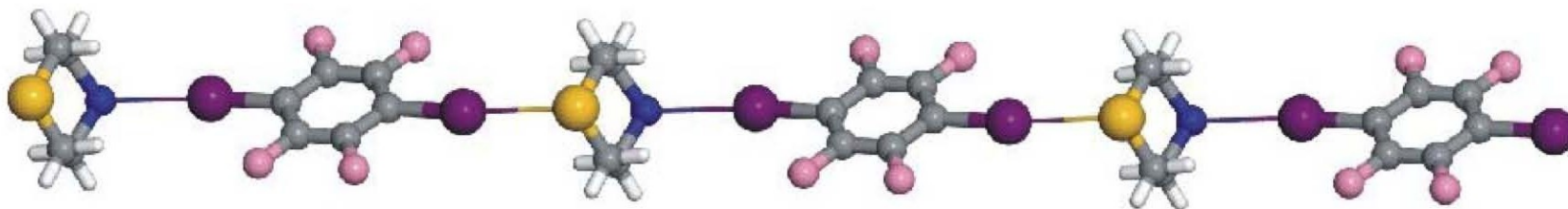


Metrangolo, Neukirch, Pilati, Resnati *Acc. Chem. Res.* **2005**, *38*, 386.

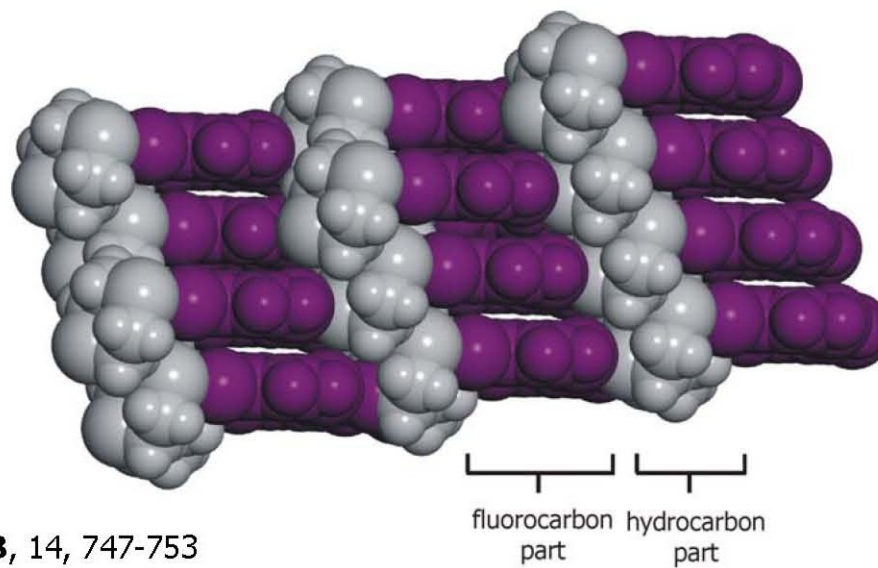


Cocrystals involving a linear bond donor

Cocrystallisation from solution, as well as by grinding, gave the anticipated halogen-bonded chains



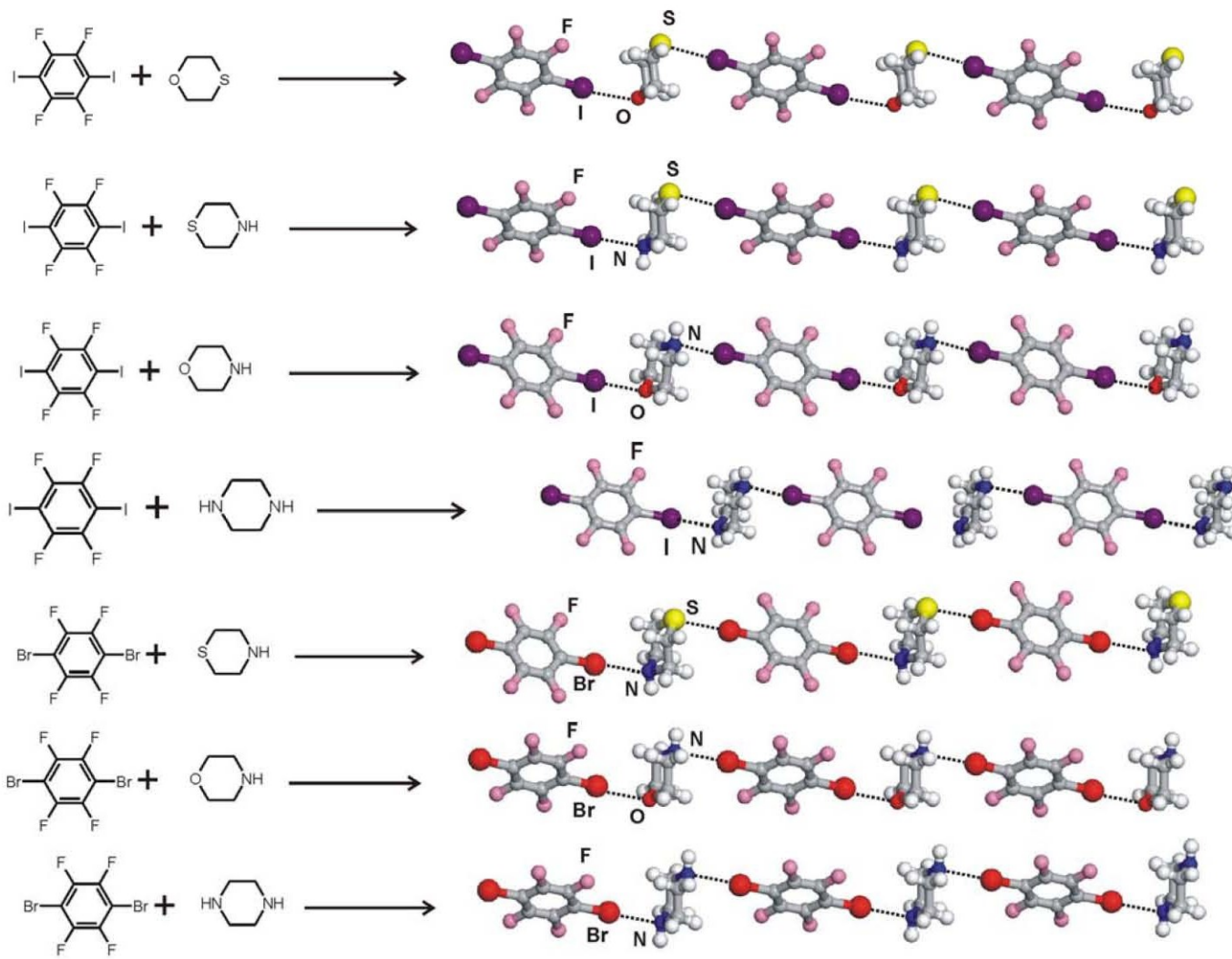
The chains arrange so as to form segregated fluorocarbon and hydrocarbon regions in the cocrystal:



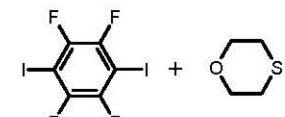
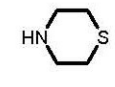
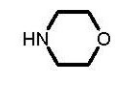
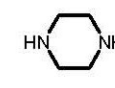
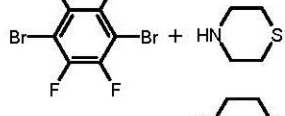
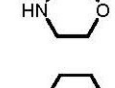
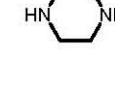
Cincic, Friscic, Jones *Chem. Eur. J.* **2008**, 14, 747-753



Unexpected similarity of crystal structures











Isostructurality!









	$a / \text{\AA}$	$b / \text{\AA}$	$c / \text{\AA}$	$\alpha / ^\circ$	$\beta / ^\circ$	$\gamma / ^\circ$
	5.3461(2)	6.1306(3)	10.7131(5)	90.110(2)	93.987(2)	100.688(2)
	5.3592(1)	6.1210(2)	10.6330(3)	90.470(2)	95.167(2)	100.205(2)
	5.3012(1)	6.0926(2)	10.3171(3)	90.587(2)	97.132(2)	99.809(2)
	5.2777(2)	6.0948(2)	10.3019(3)	90.851(2)	96.934(2)	99.113(1)
	5.2826(3)	5.9859(4)	10.5152(6)	93.304(3)	95.141(3)	100.653(3)
	5.1405(2)	5.8904(2)	10.2902(4)	93.408(2)	95.712(2)	99.554(2)
	5.1235(1)	5.9063(2)	10.2851(4)	93.385(2)	95.970(2)	98.947(2)

Cincic, Friscic, Jones *Chem. Eur. J.* **2008**, 14, 747-753



Isostructural solids with variable properties

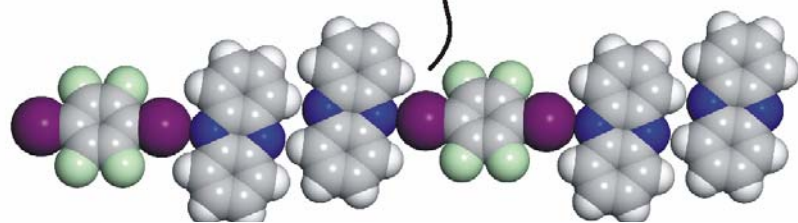
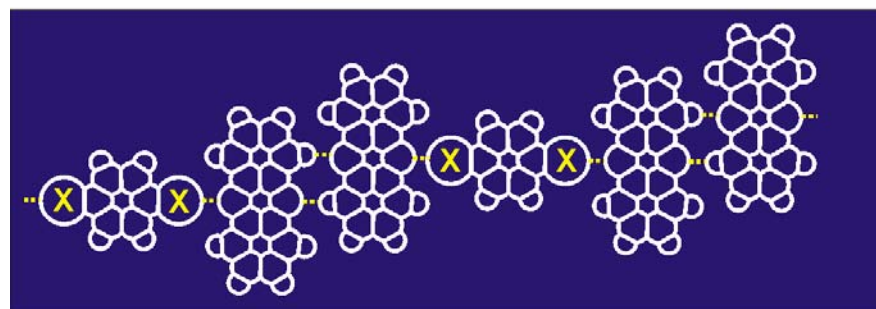
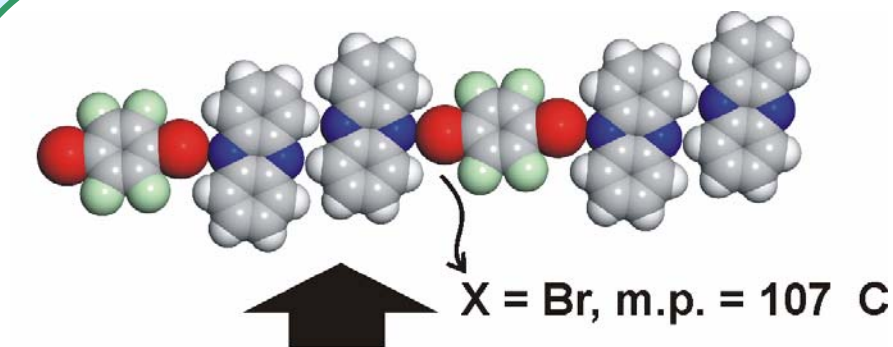
components	cocrystal	melting point / °C
 + 	yes	54
 + 	yes	133
 + 	yes	134
 + 	yes	190

 + 	no	-
 + 	yes	54
 + 	yes	59
 + 	yes	116

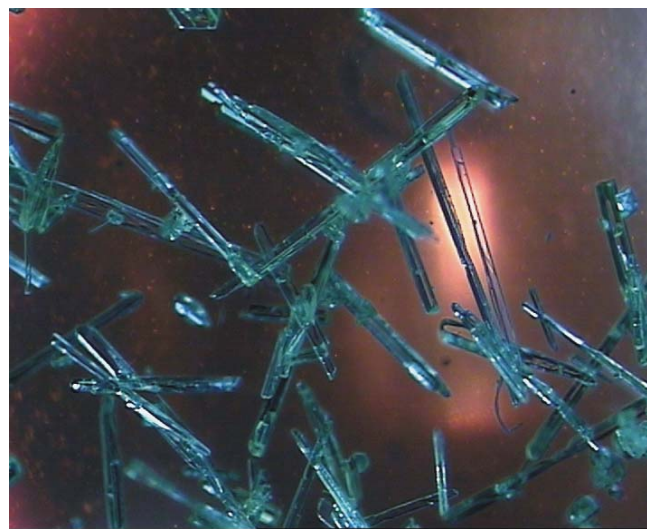
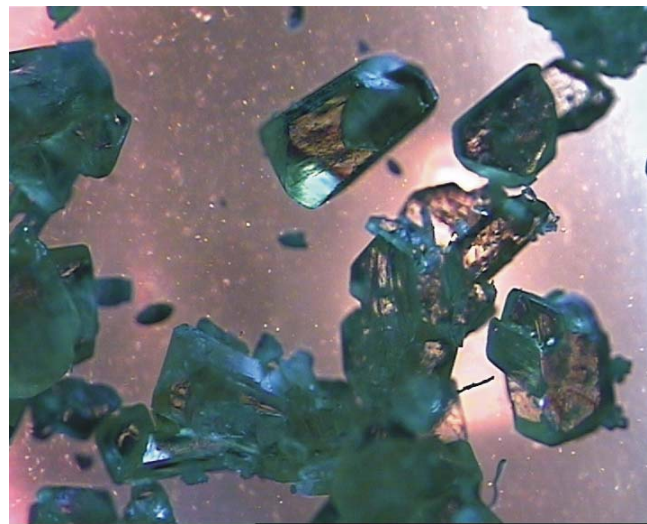
Cincic, Friscic, Jones *Chem. Eur. J.* **2008**, 14, 747-753



Further modifications to physicochemical properties: crystal morphology

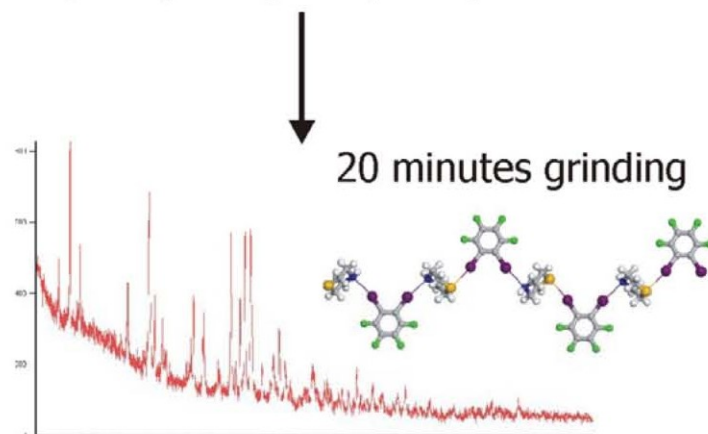
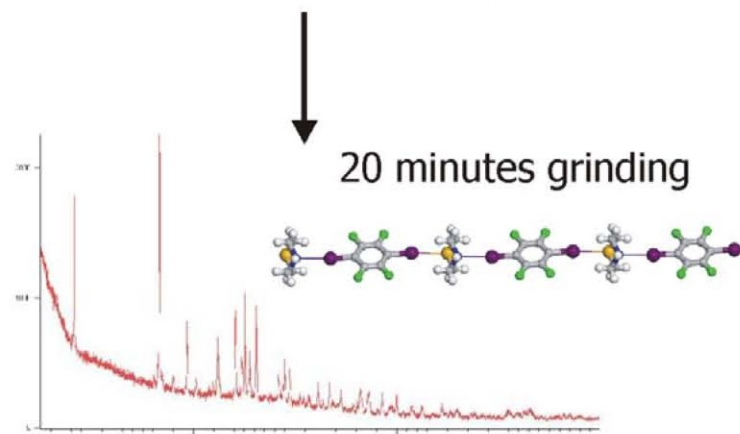
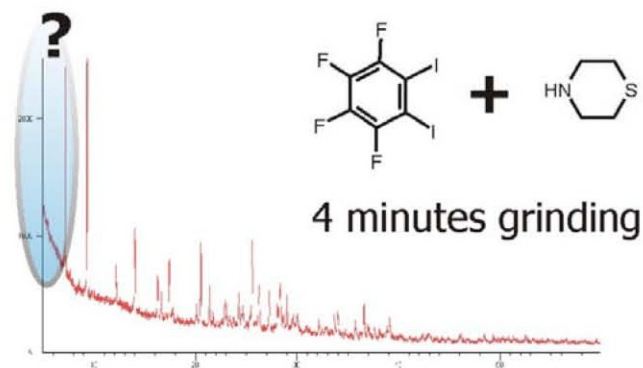
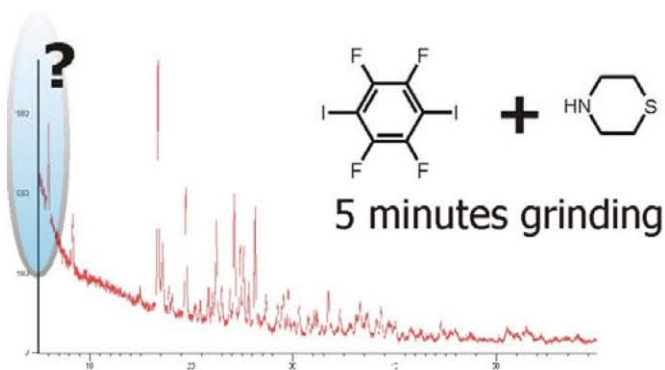


Cincic, Friscic, Jones (submitted to *Chem. Mater.*)



Incomplete reaction: proof of a cocystal intermediate

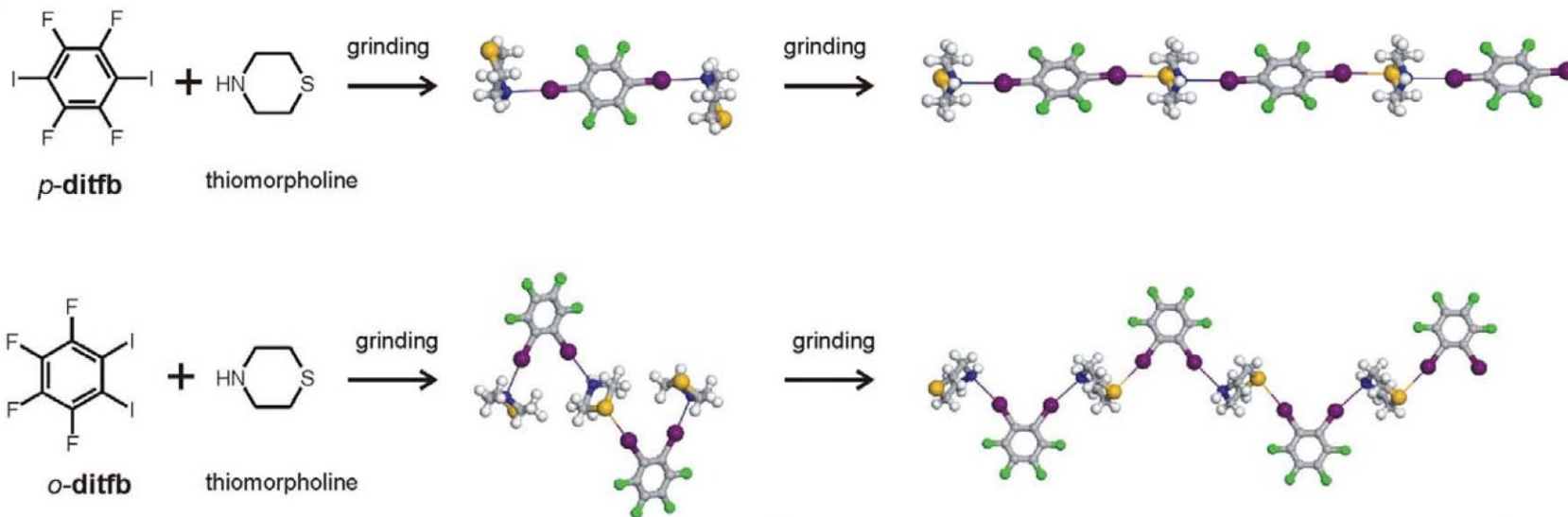
Brief grinding provides evidence of a cocystal intermediate between the pure reactants and the 1:1 cocystal product with either *p*- or *o*-tfib:



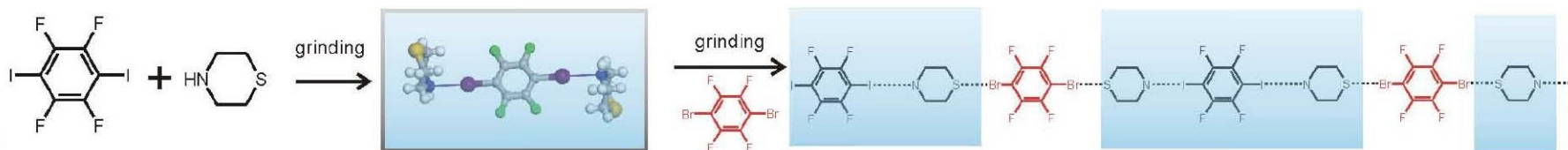
Cinic, Friscic, Jones *J. Am. Chem. Soc.* **2008** (ASAP online article)



Synthesis of halogen-bonded cocrystals via grinding is a two-step process



An opportunity to construct three-component systems:

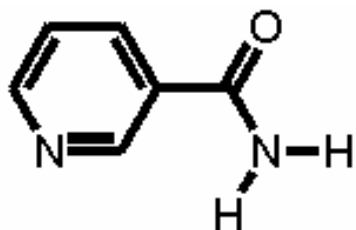


Cinic, Friscic, Jones *J. Am. Chem. Soc.* **2008** (ASAP online article)

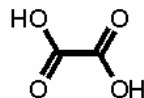


Stepwise formation of hydrogen-bonded cococrystals

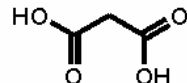
nicotinamide (**na**)



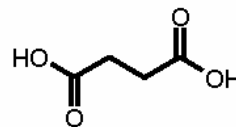
pyridine
group amide
group



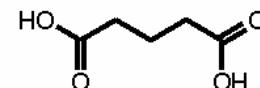
oxalic acid (**oxa**)
2 C atoms



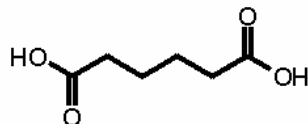
malonic acid (**mal**)
3 C atoms



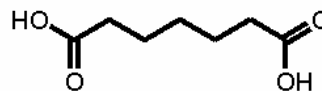
succinic acid (**suc**)
4 C atoms



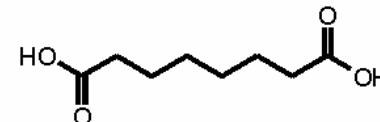
glutaric acid (**glu**)
5 C atoms



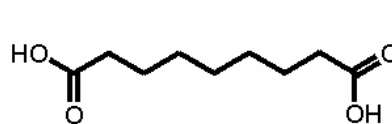
adipic acid (**adi**)
6 C atoms



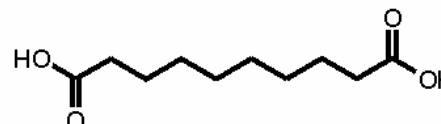
pimelic acid (**pim**)
7 C atoms



suberic acid (**sub**)
8 C atoms



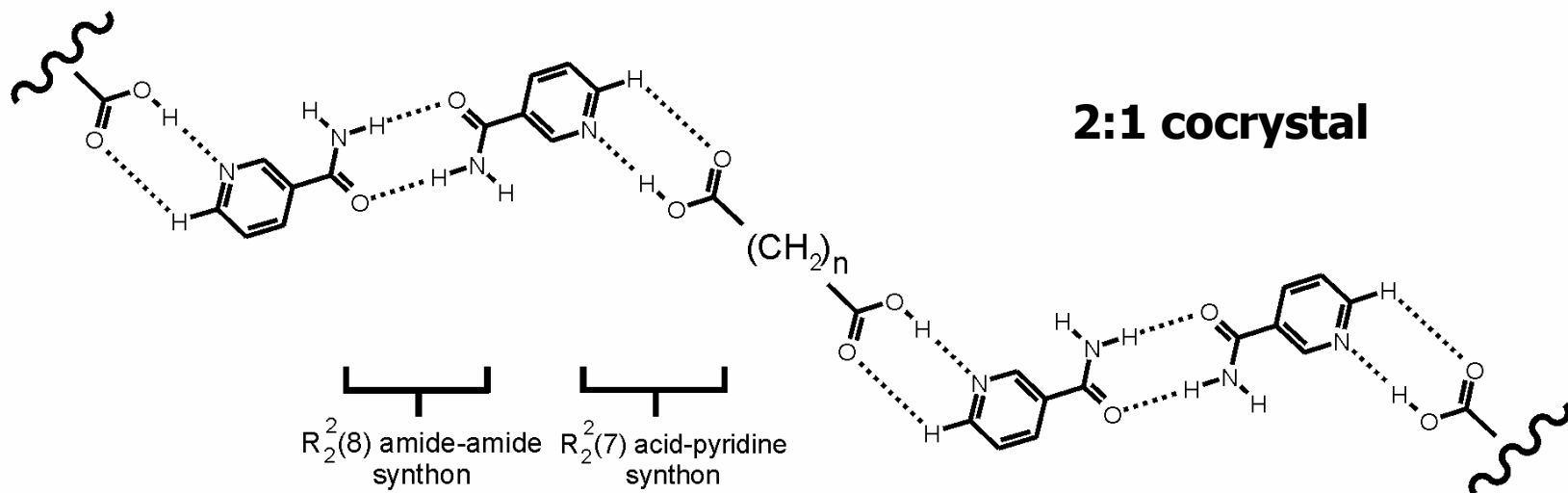
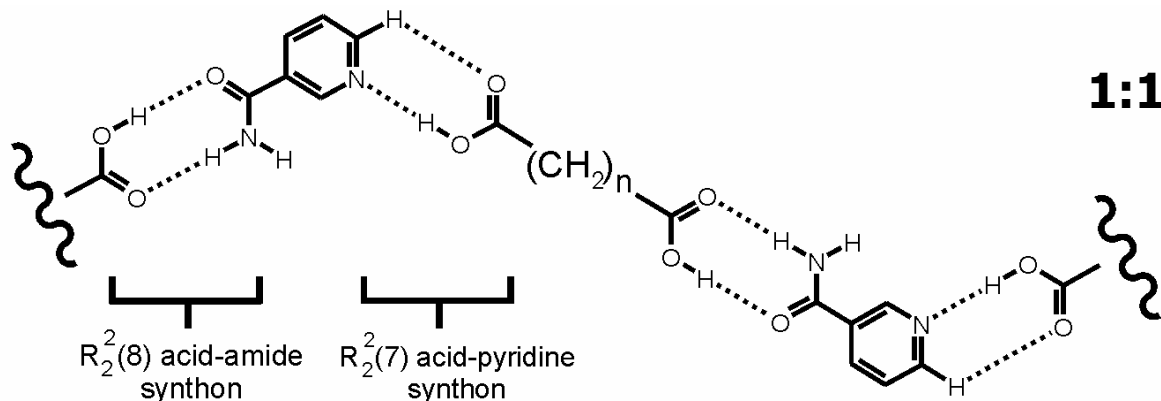
azelaic acid (**aze**)
9 C atoms



sebacic acid (**seb**)
10 C atoms

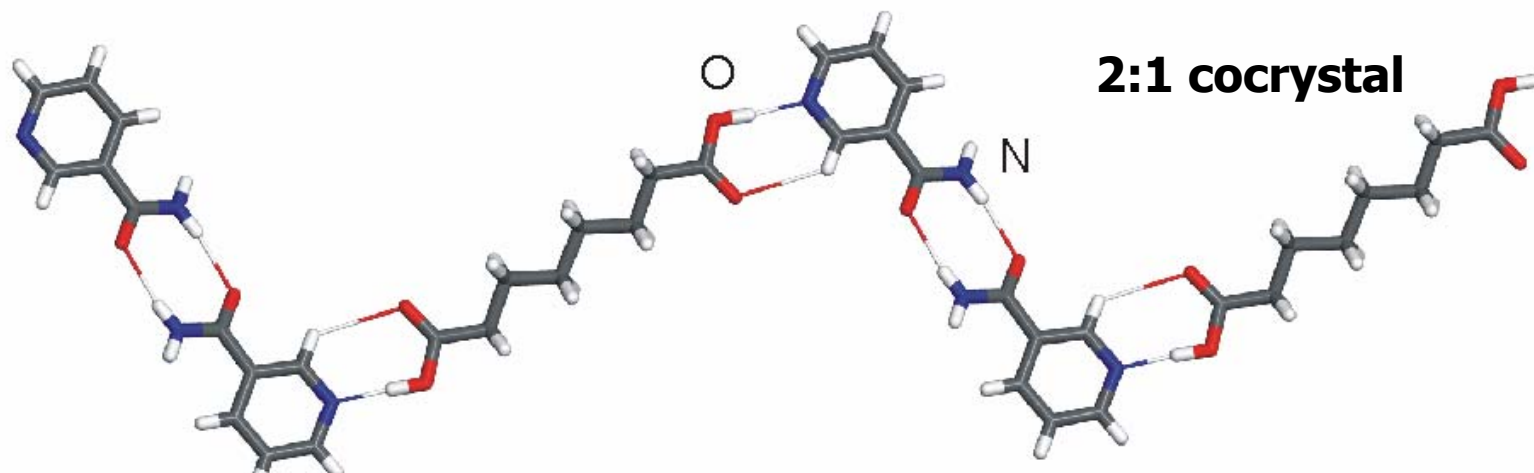
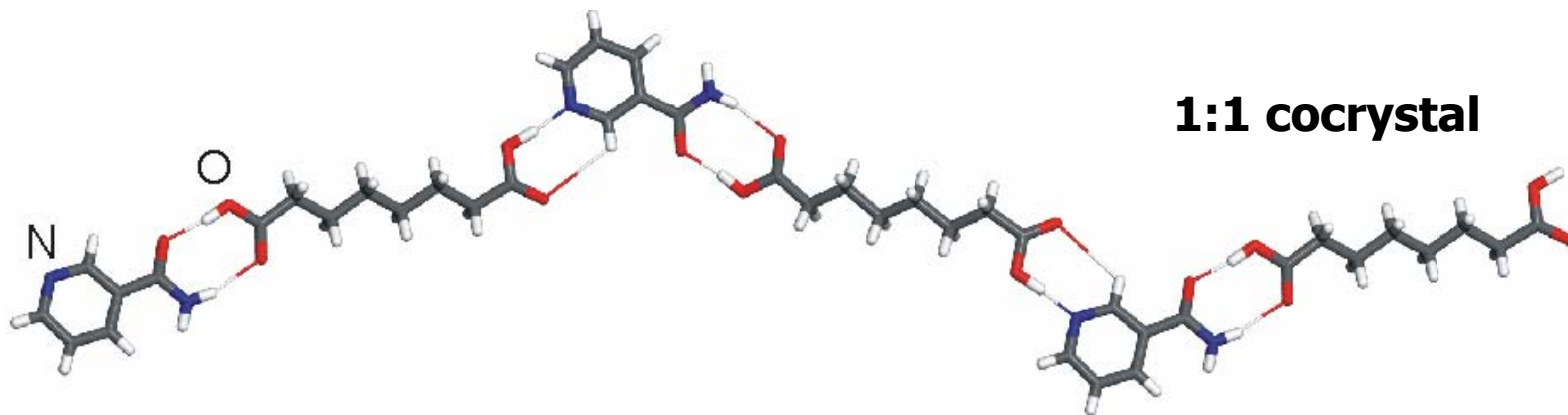


Expected modes of molecular assembly



Stoichiometric variations of the model cocrystal

Model system: cocrystals of nicotinamide with suberic acid

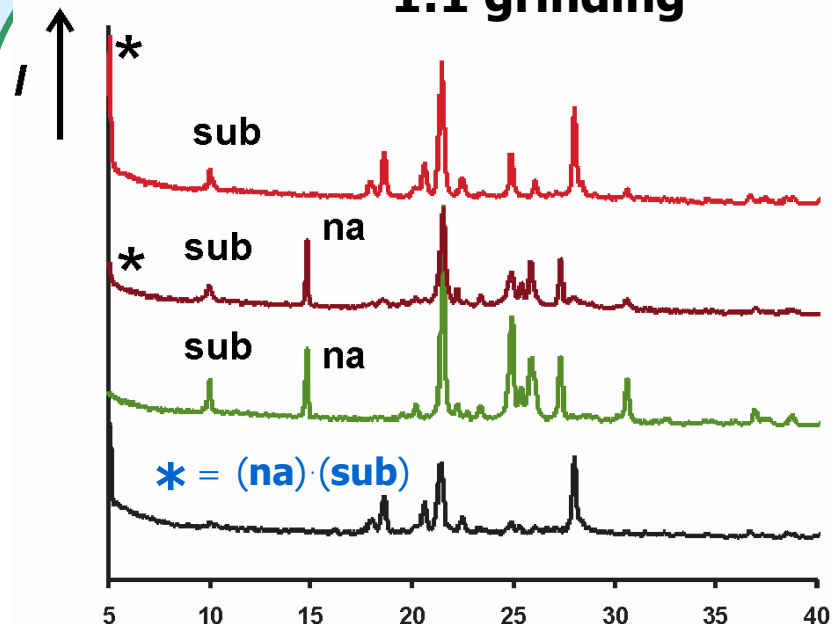


Karki, Friscic, Jones (submitted to *CrystEngComm*)

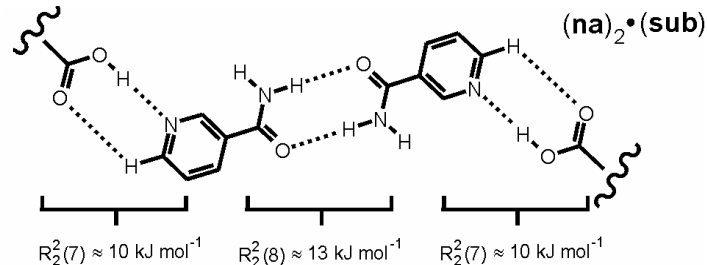
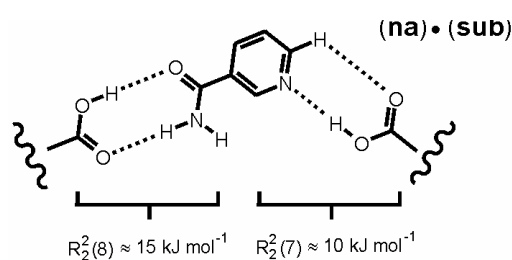
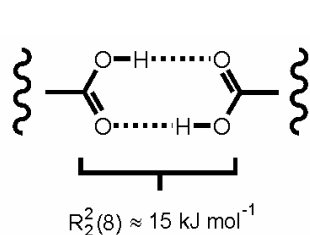
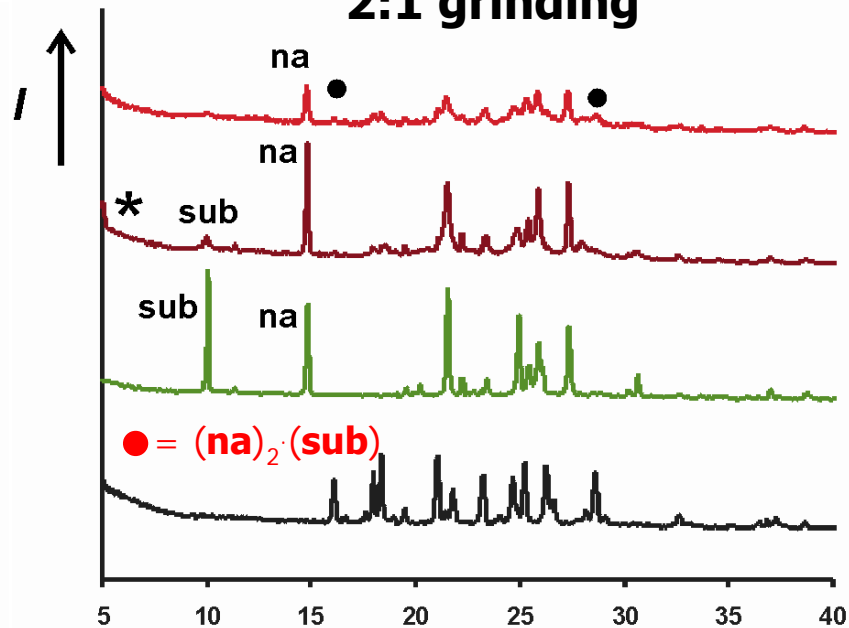


Stepwise formation of the model cococrystal

1:1 grinding



2:1 grinding



Karki, Friscic, Jones (submitted to *CrystEngComm*)



Thank you!

