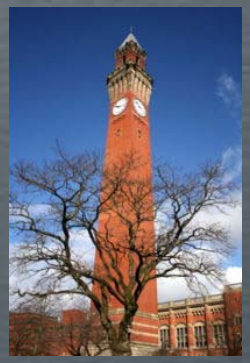
Molecular Cocrystals and Salts: 'Full' Structural Characterisation from PXRD data



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This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

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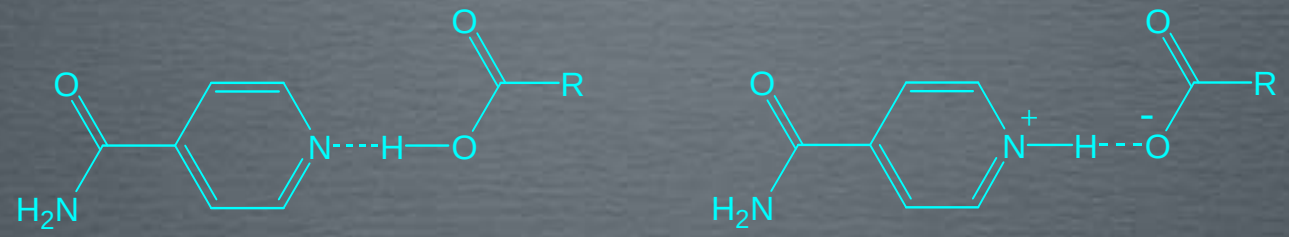
PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

Molecular Cocrystals & Salts

- Crystalline solids containing 2 or more building blocks (solids at rt) in stoichiometric amounts



- Materials that retain the chemical properties of components but display new physical properties

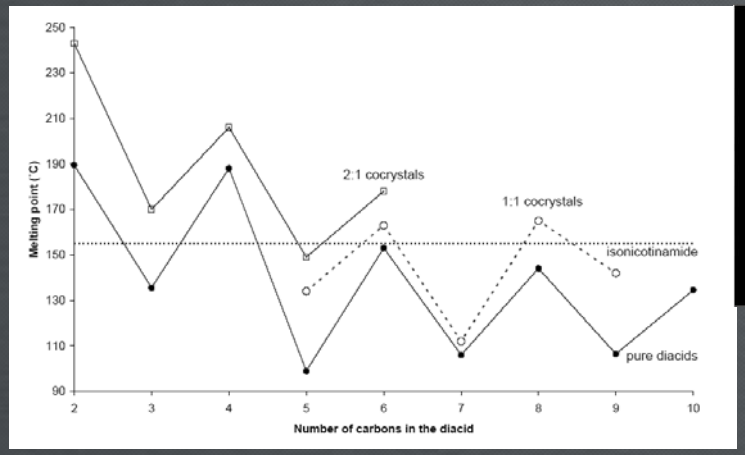
melting point *stability*
solubility *dissolution*
bioavailability *morphology*

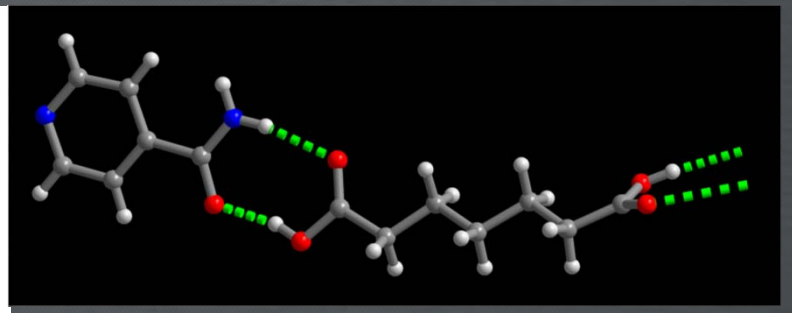
Schultheiss & Newman., *Cryst.Growth & Des.* (2009), 9, 2950

Almarsson & Zaworotko., *Chem. Comm.* (2004), 1889

… melting point …

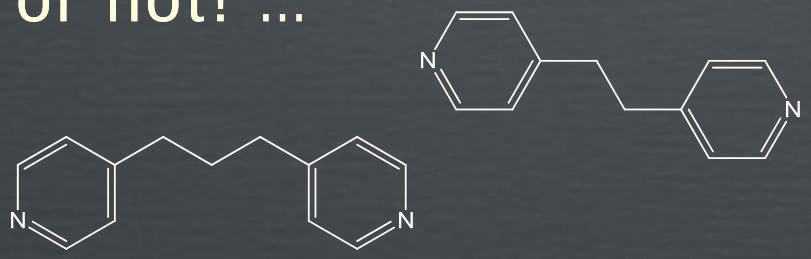
- Used to mimic physical property trends such as alternation of melting point



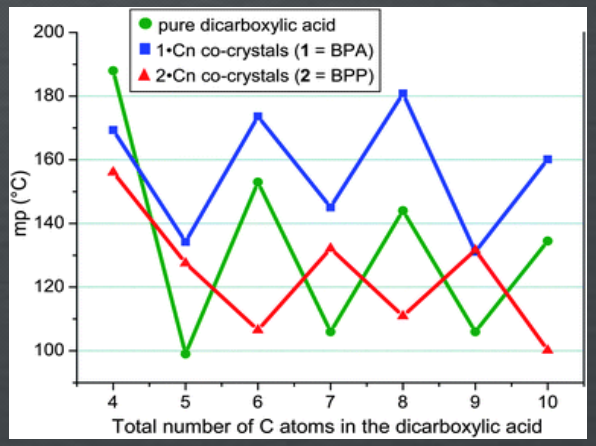


Thompson, Voguri, Male & Tremayne, *CrystEngComm,* (2011), 13, 4188

… or not! …

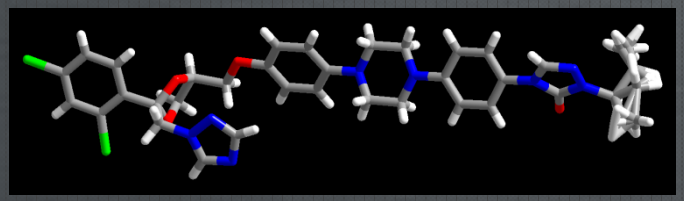


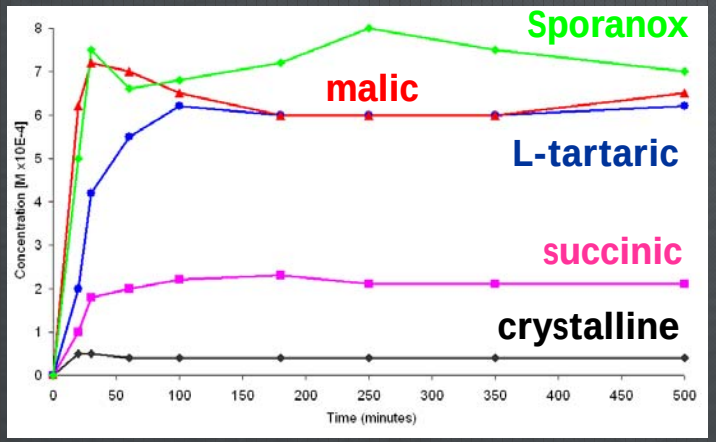
Braga et al., *CrystEngComm.* (2010), 12, 3534



… solubility …

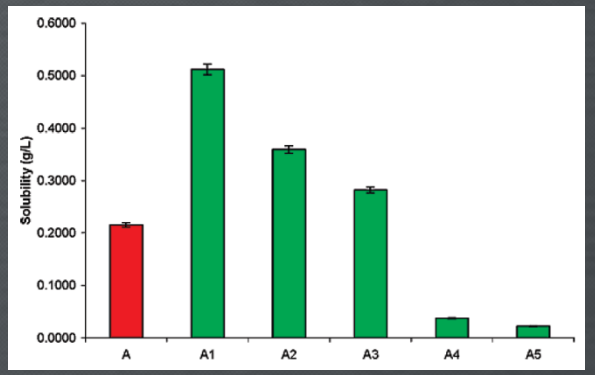
- Crystalline solubility tuned to level of commercial material

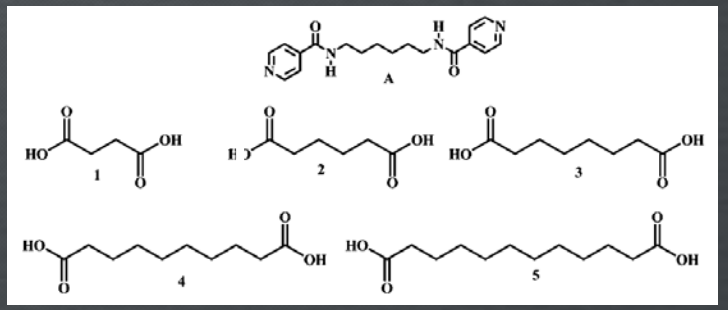




Remenar et al., *JACS.* (2003), 125, 8456

- Property rationalised by diacid solubility

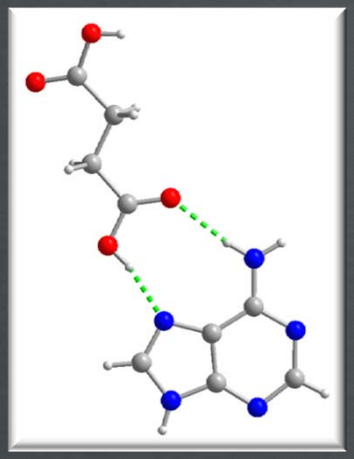




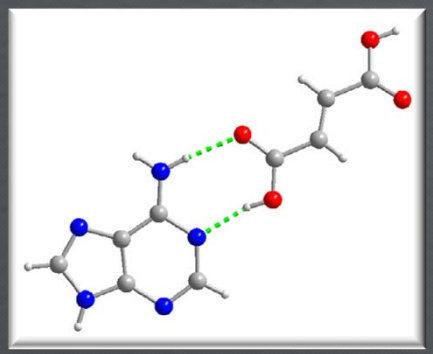
Aakeroy, Forbes & Desper, *JACS.* (2009), 131, 17048

Adenine:cocrystals/salts/solvates/tautomers

- Adenine has an extensive hydrogen bonded network, but forms a variety of forms with diacids with reduced melting point

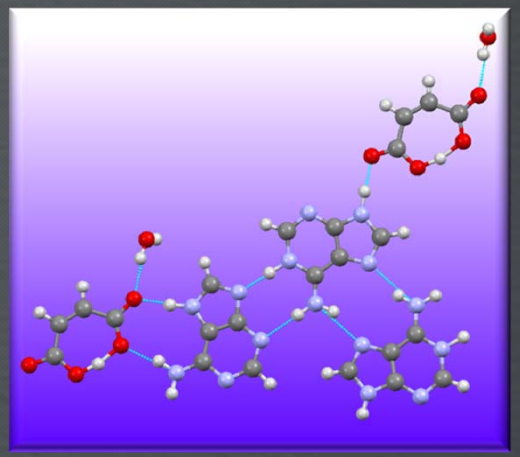


9H cocrystals



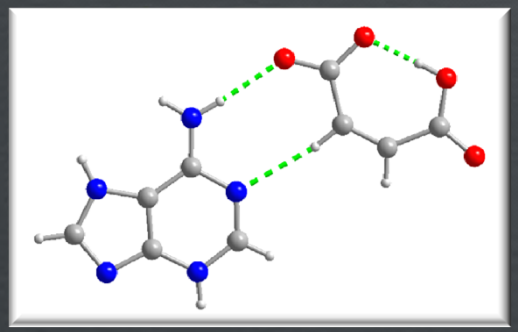
1H,9H salt & 7H neutral

McHugh & Erxleben, *Cryst.Growth & Des.* (2011), 11, 5096

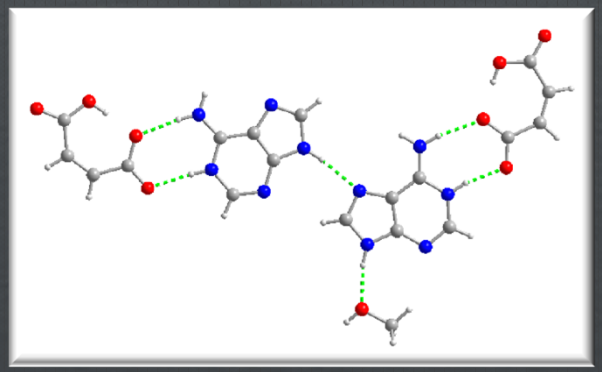


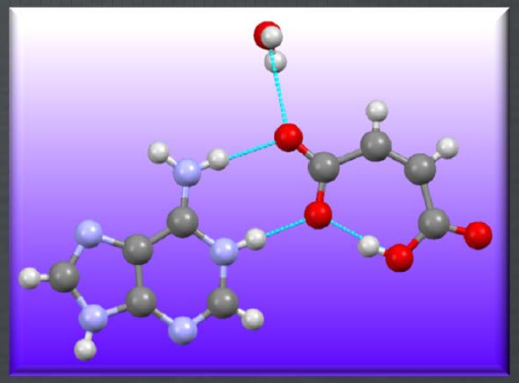
Thompson, Elias, Male & Tremayne, *submitted*

3H,7H salt



1H,9H salts





Sridhar & Ravikumar, *Acta Cryst.* (2007), C63, o415

Why Powder Diffraction?

Products showing poor crystal growth resulting from:

solvent-mediated crystallisation or sonic slurry

Products from solid state synthesis:

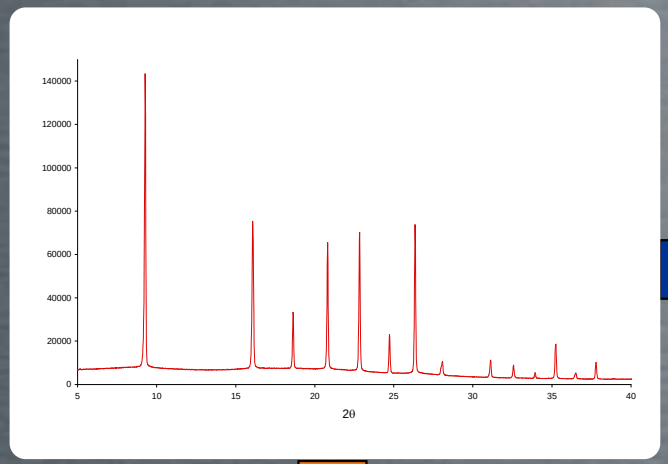
liquid assisted or dry grinding

alternative stoichiometry
incompatable solubilities
solvent-free form
or *atypical structural behaviour*

Shan et al., *Chem. Comm.* (2002), 2372

Fricic et al., *Faraday. Dis.* (2007), 136, 167

Direct Space Methods for SDPD



Intensities

Structure solution

Predict trial structure

Compare simulated & exp data, R_{wp}

Global optimisation locates best structure

Optimum structure solution

Positions

Indexing

Unit cell

Rietveld refinement

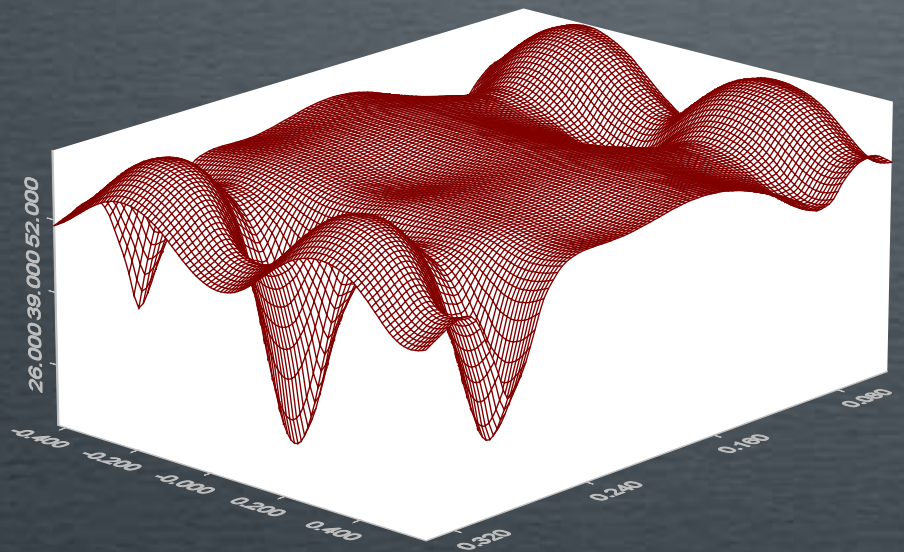
Final crystal structure

Global Optimisation

- Multi-dimensional search problem:

  Individual set of parameters
  $(x,y,z;\ \theta,\phi,\gamma\ ;\ \tau_1 \ldots \tau_n)$ *per molecule or unit*

- Objective – best fit to experimental data:
  e.g: *global minimum in* R_{wp} *or* χ^2



Monte Carlo

Grid Search

Simulated Annealing

Parallel Tempering

Evolutionary Algorithms

- Evolutionary algorithms:
  - → population of trial structures
  - → mating, mutation & natural selection until global minimum is found
- Each member of the population defined by genetic code $(x,y,z)[0\text{-}1](\theta,\phi,\gamma,\tau_1.....\tau_n)[0\text{-}360]$
  - → genetic algorithms
  - → differential evolution

Differential Evolution (DE)

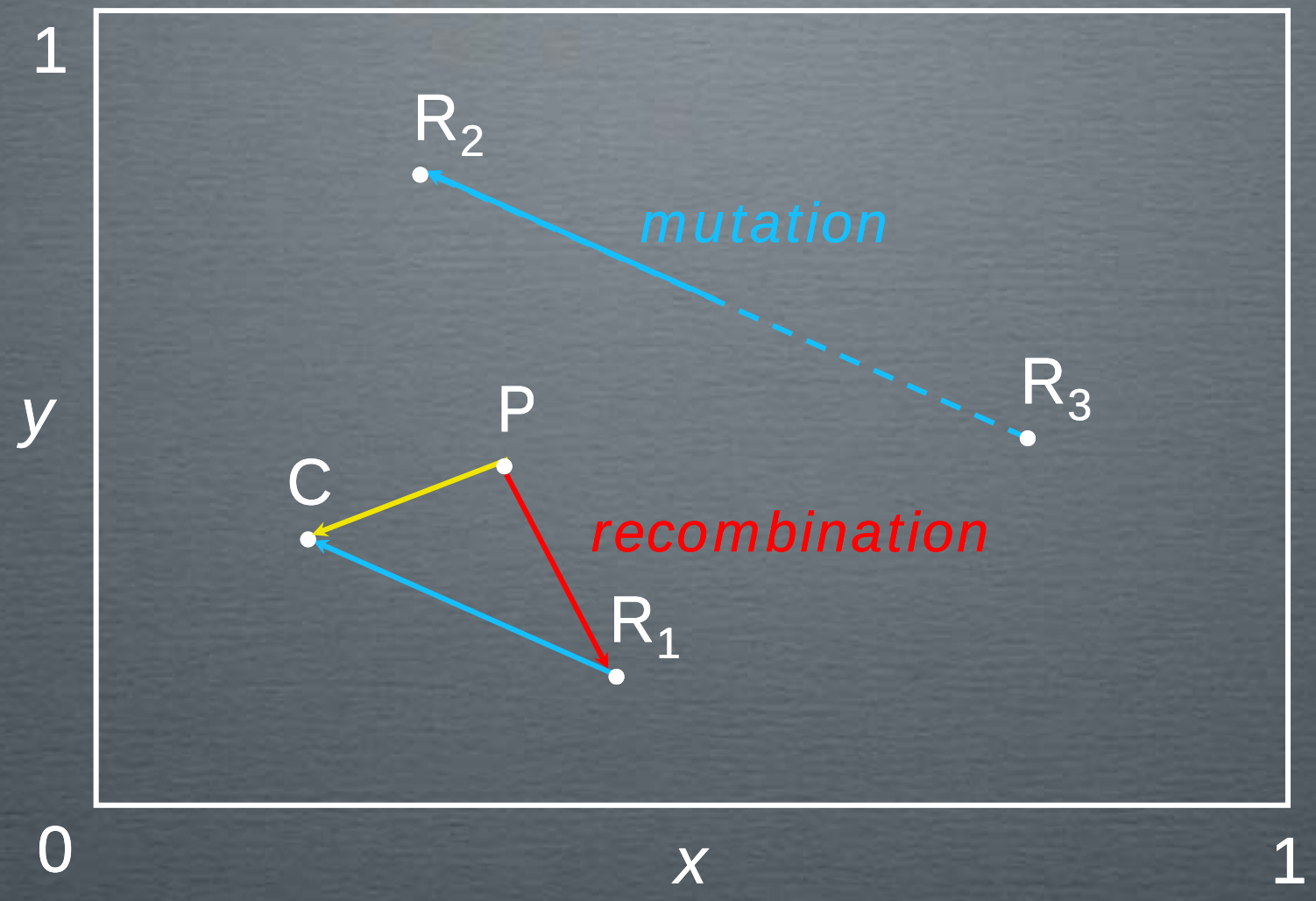
- Mating and mutation in one step:

$$\text{Trial} = \text{Parent} + K(\text{Random}_1 - \text{Parent}) + F(\text{Random}_2 - \text{Random}_3)$$

- *3 control parameters:* N_p, K & F
- No mutants needed
- Best of child/parent added to population; deterministic selection – fast convergence
- New members used within the generation

Price, *New Ideas in Optimization*, McGraw-Hill, London, UK, 77, (1999)

Trial = Parent + K(Random$_1$ - Parent)
+ F(Random$_2$ - Random$_3$)



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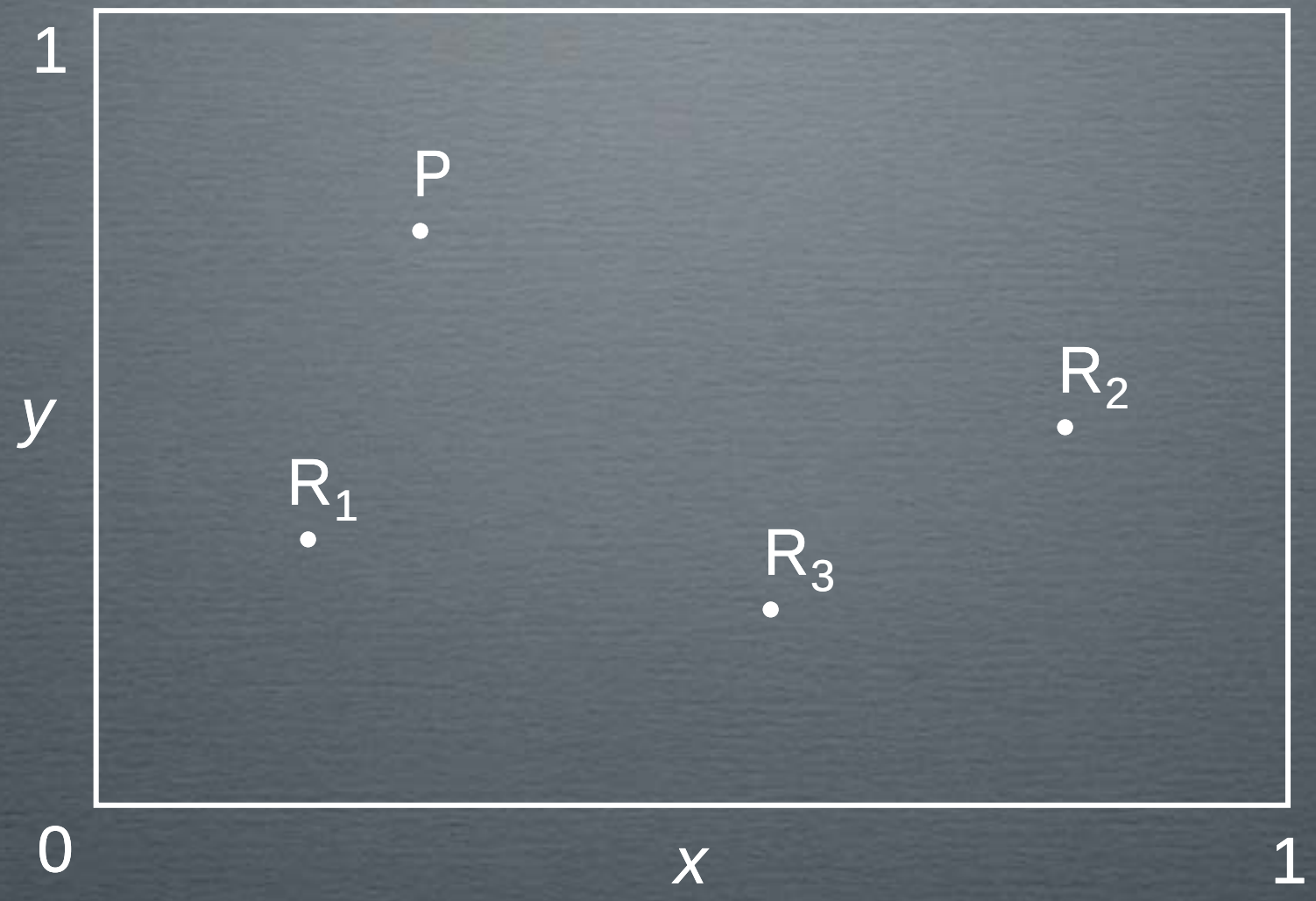
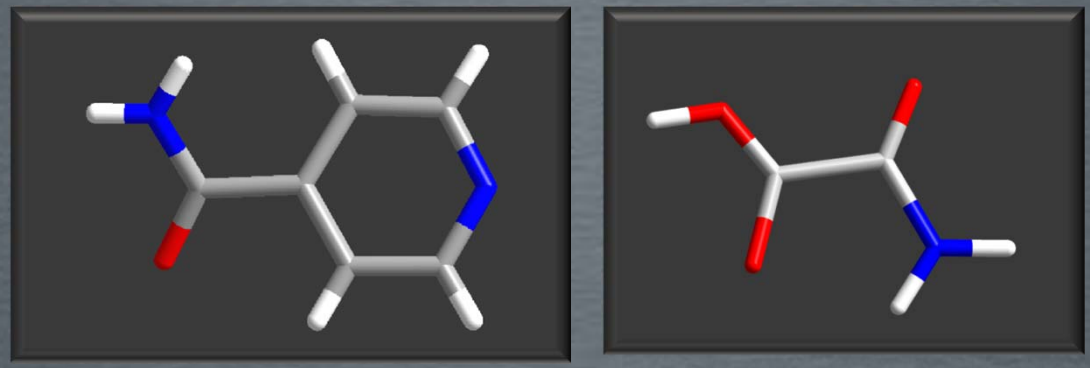


Isonicotinamide : Oxamic Acid



Crystallisation from MeOH, 1:1 ratio

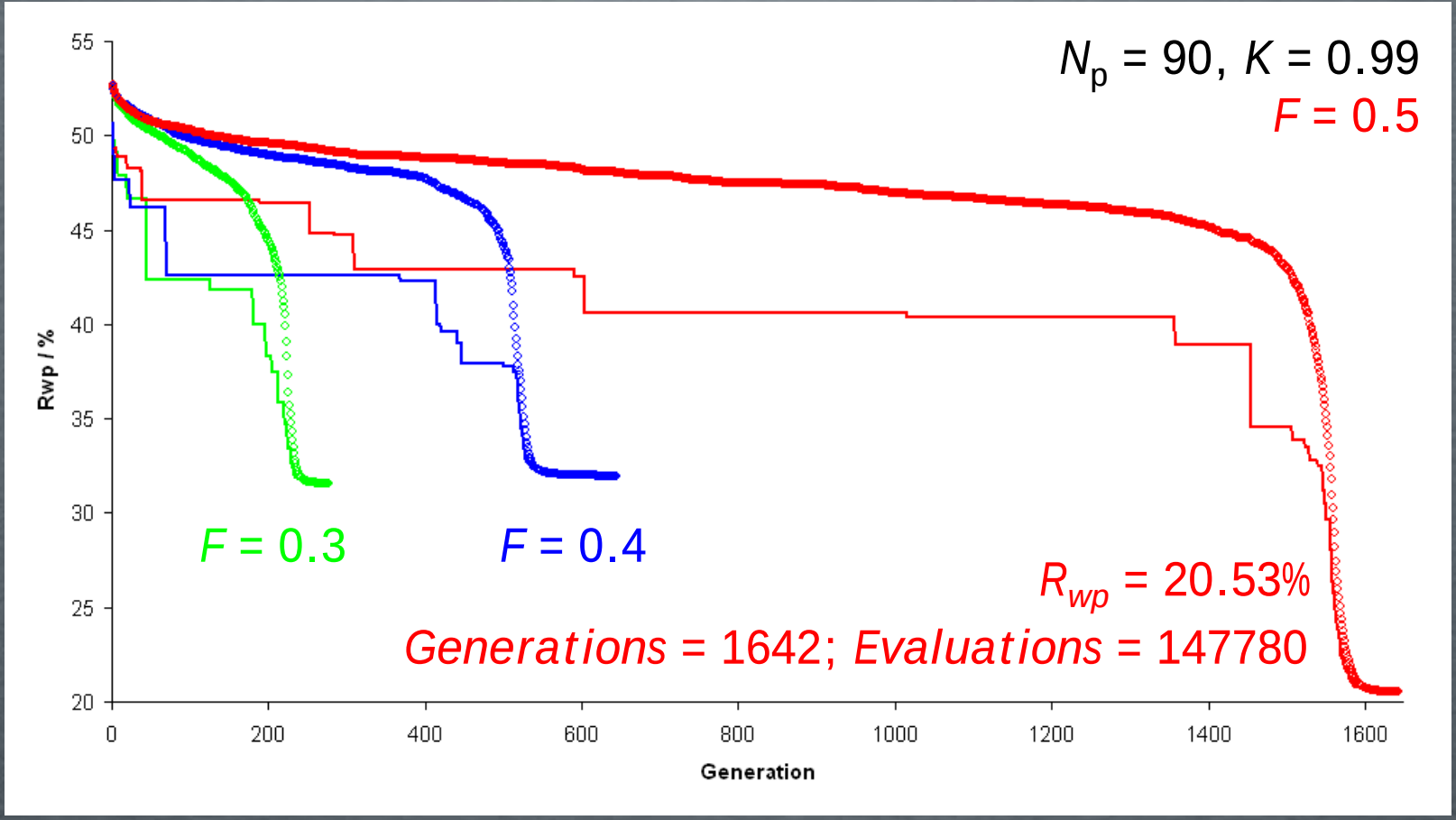
Solid state IR – salt

GC & EA & NMR – 1:1 stoichiometry

Structure determination from lab PXRD (DE)

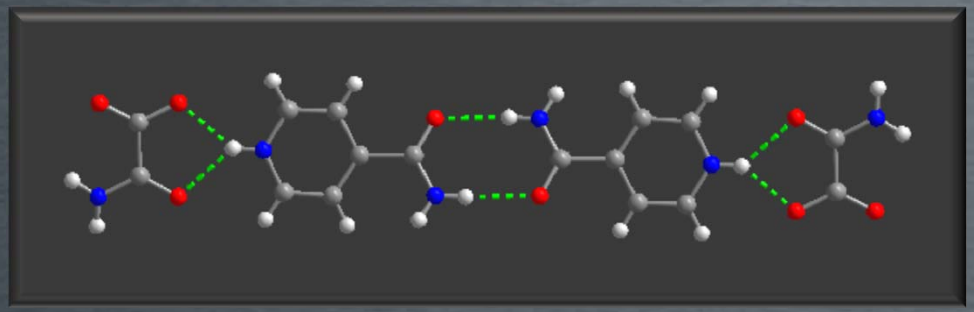
2 independent molecules, 14 parameters

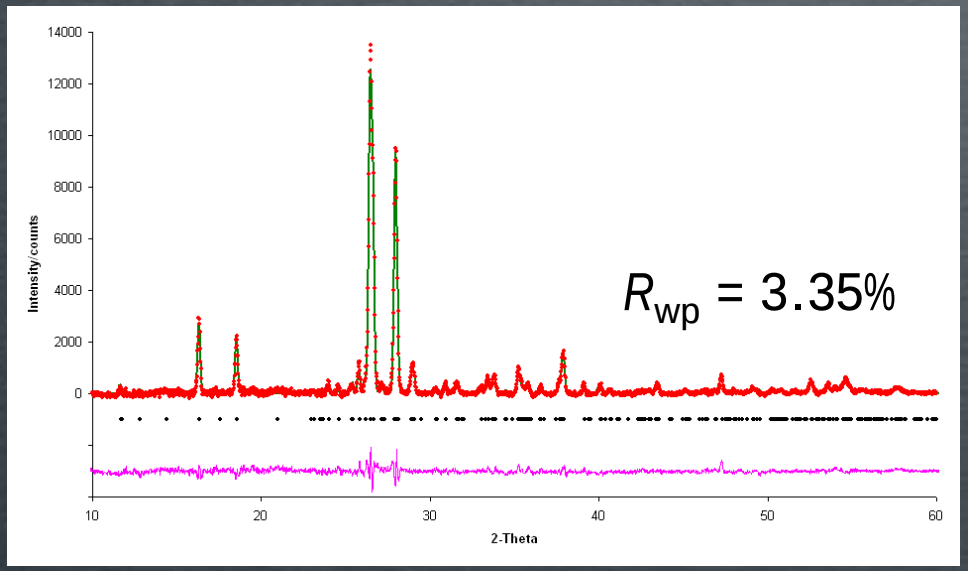
Effect of Mutation Rate *F*

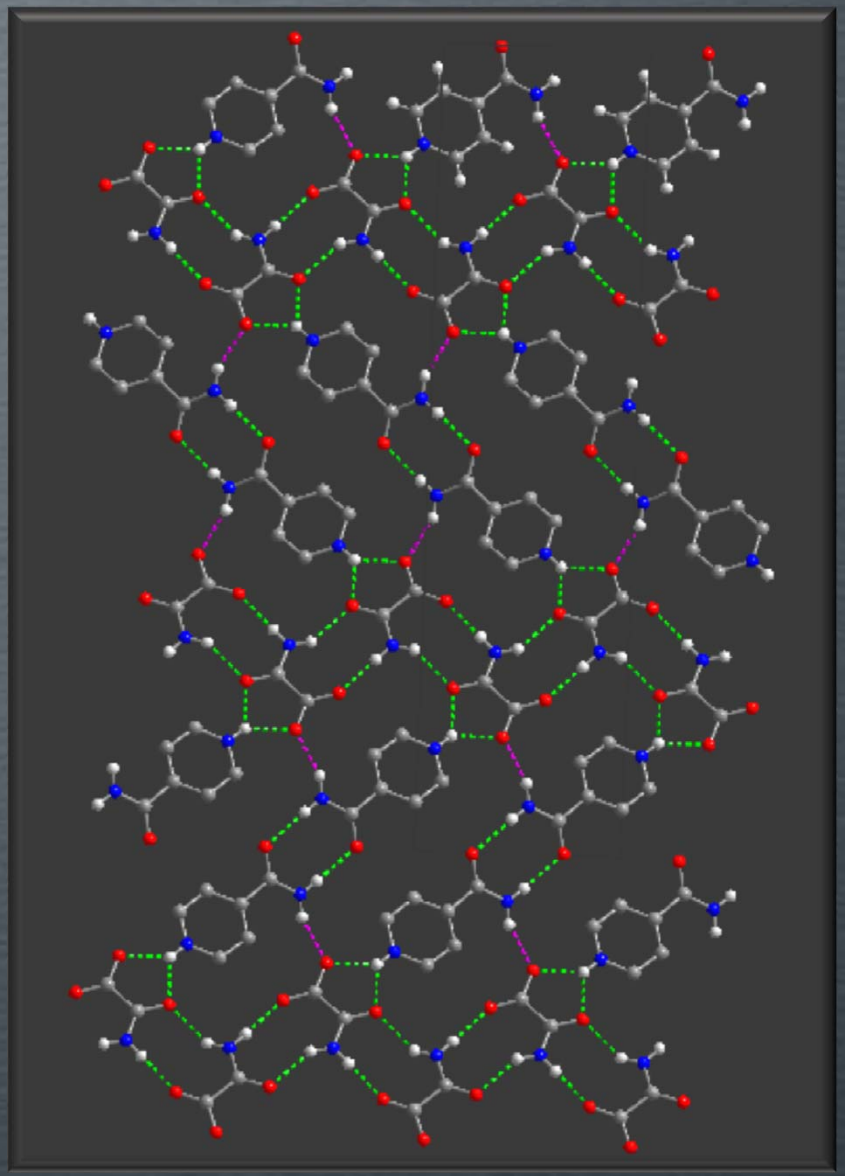


Isonicotinamide : Oxamate

- (1/1 salt); Bifurcated link
- Amide dimer
- Oxamate acid-amide motif

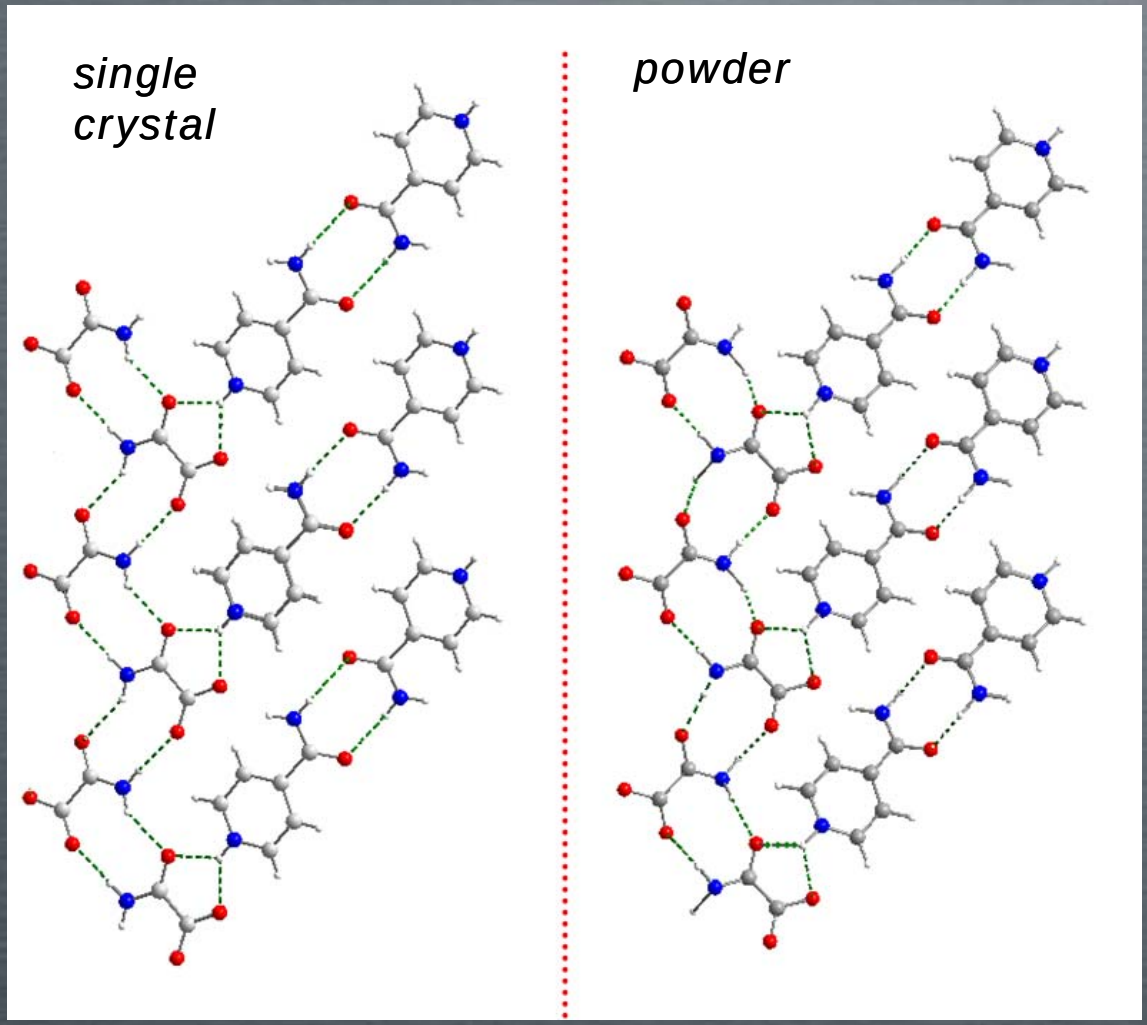


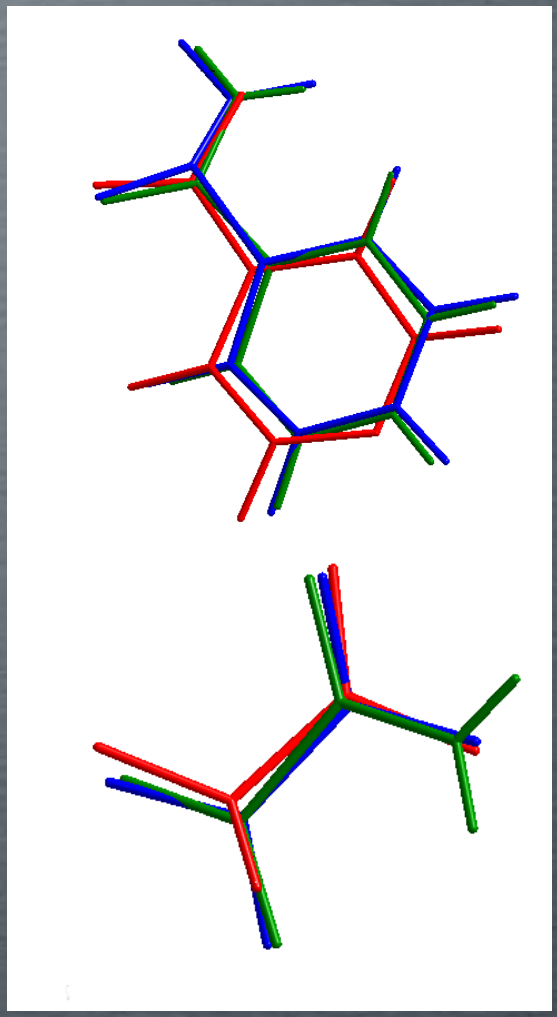




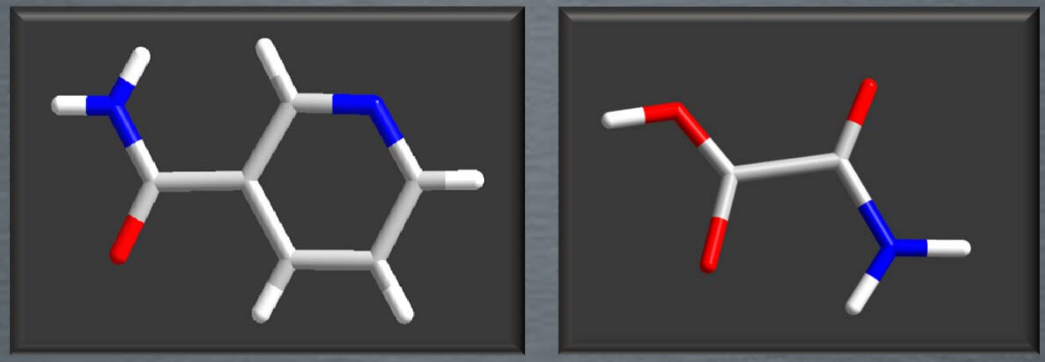
Isonicotinamide : Oxamate

Structure & conformation confirmed by single crystal





Nicotinamide : Oxamic Acid



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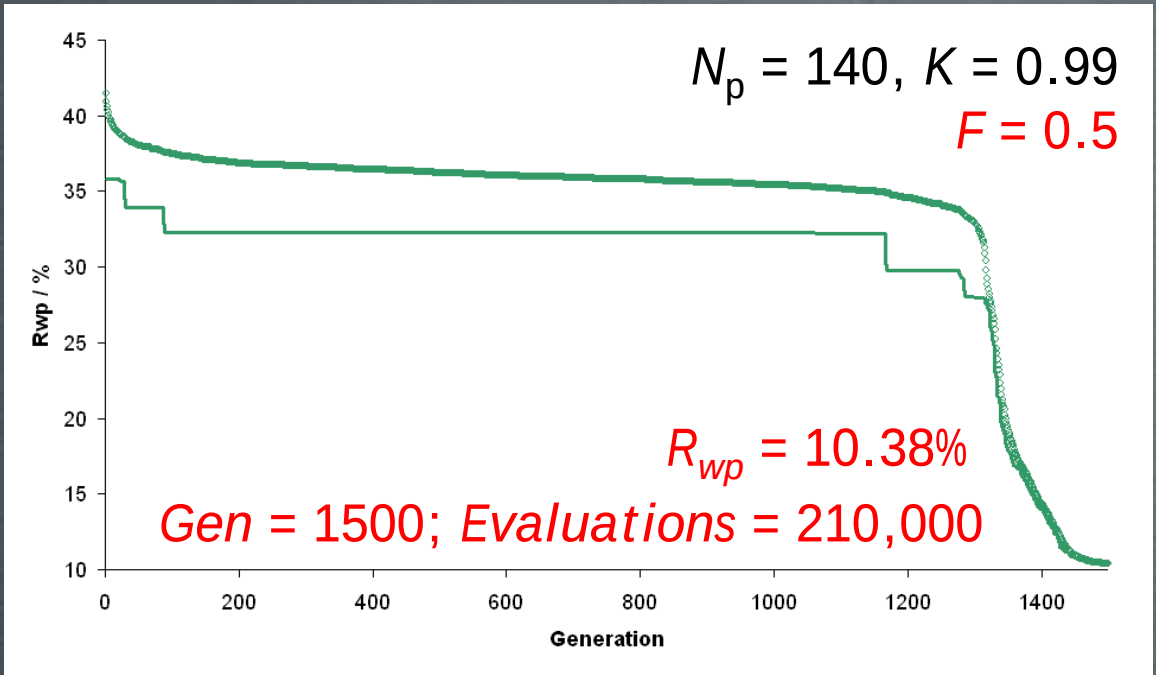
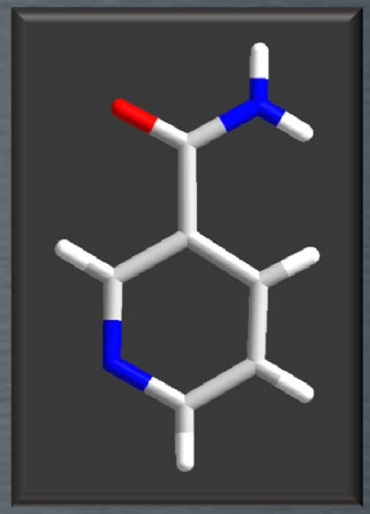
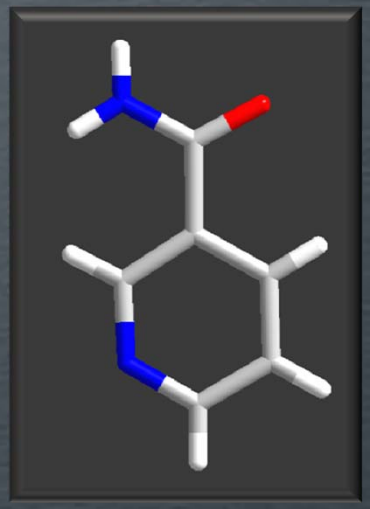




anti R_{wp}=10.38%



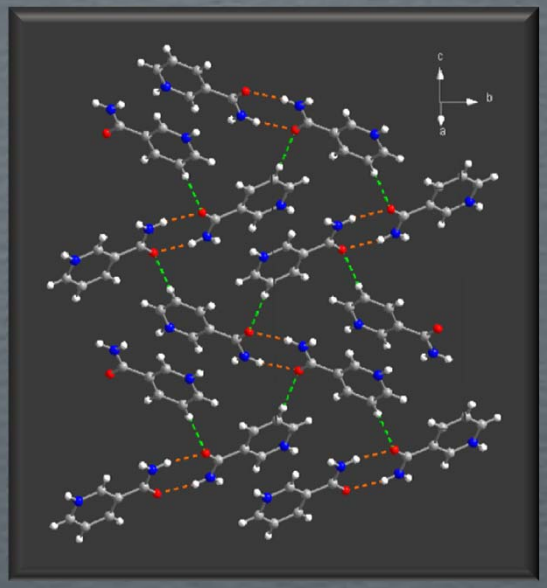
syn R_{wp}=11.21%

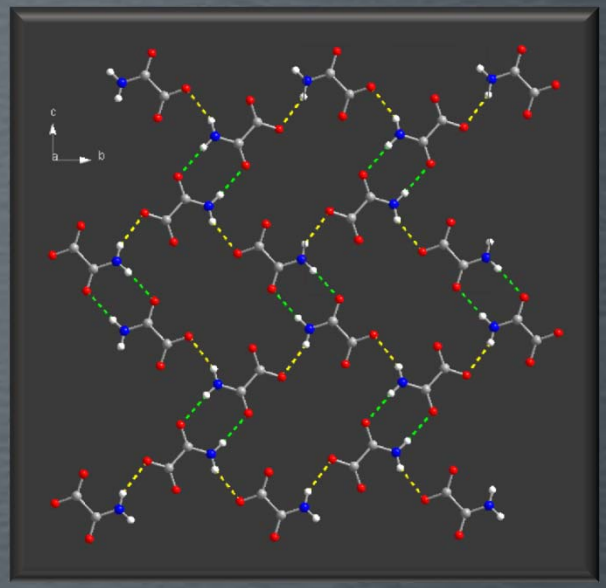
Amide 'flip' indicated by *restrained Rietveld refinement*

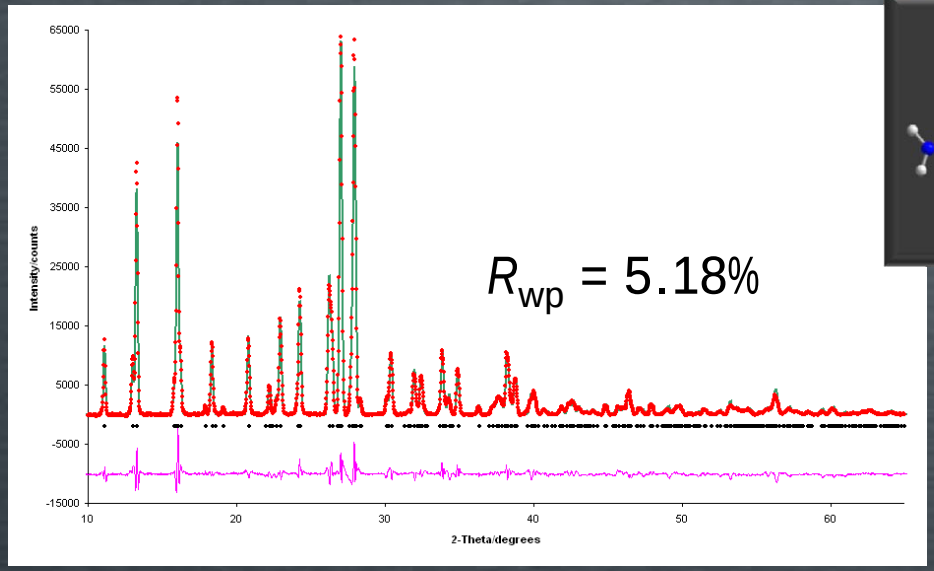
Amide group *not* correct from DE – but R_{wp} minimum *correctly* located

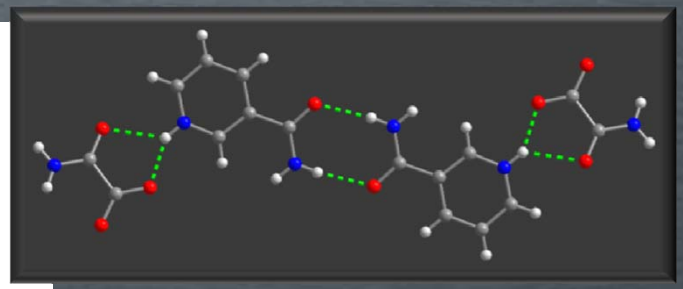
Nicotinamide : Oxamate

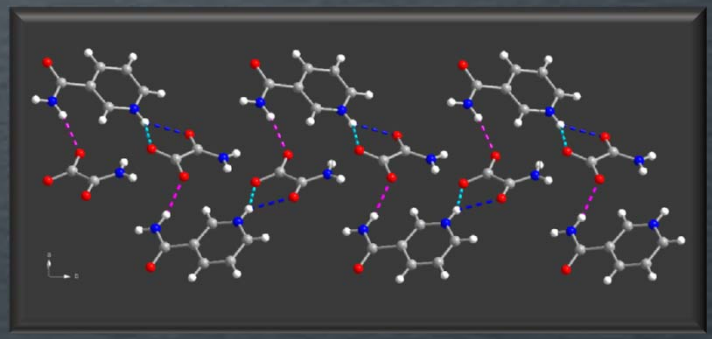
- Distinct layers of components
- (1/1 salt); Bifurcated link
- Amide dimer
- Oxamate amide-amide motif





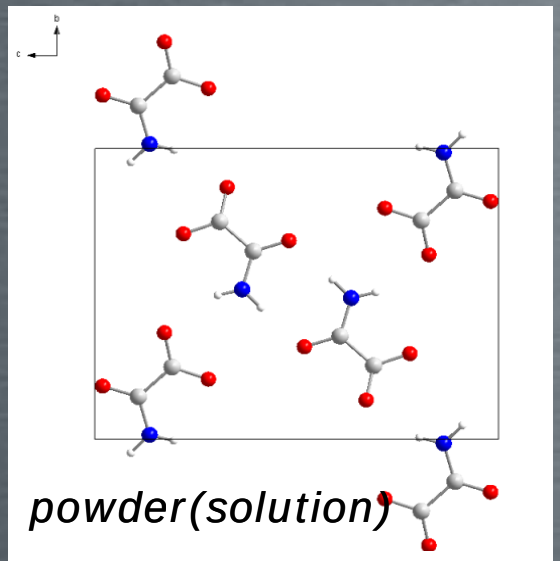




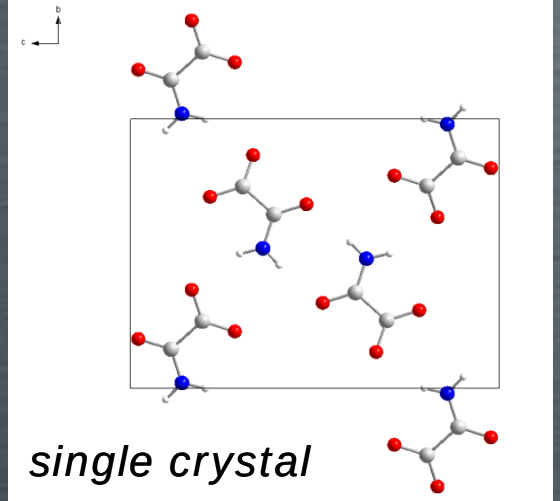


Nicotinamide : Oxamate

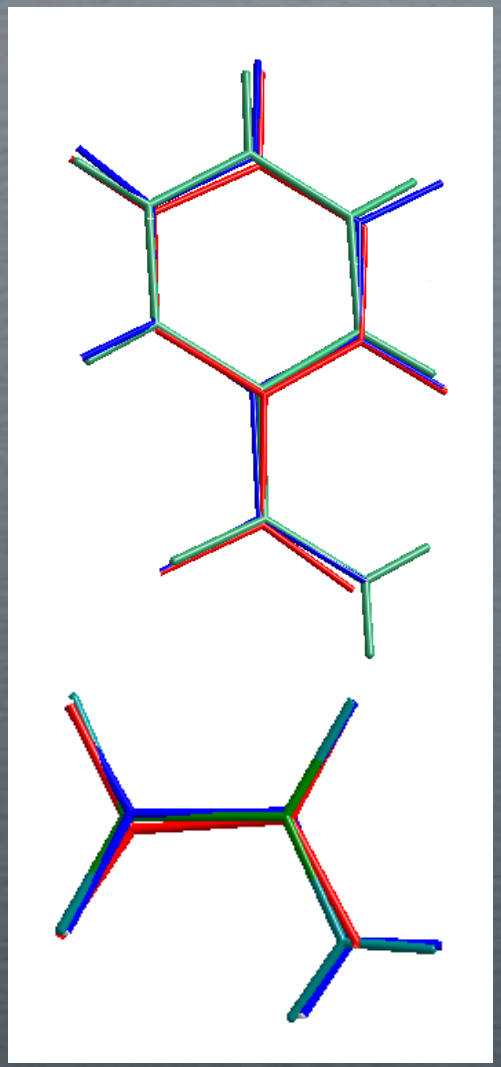
Structure & syn-conformation confirmed by single crystal

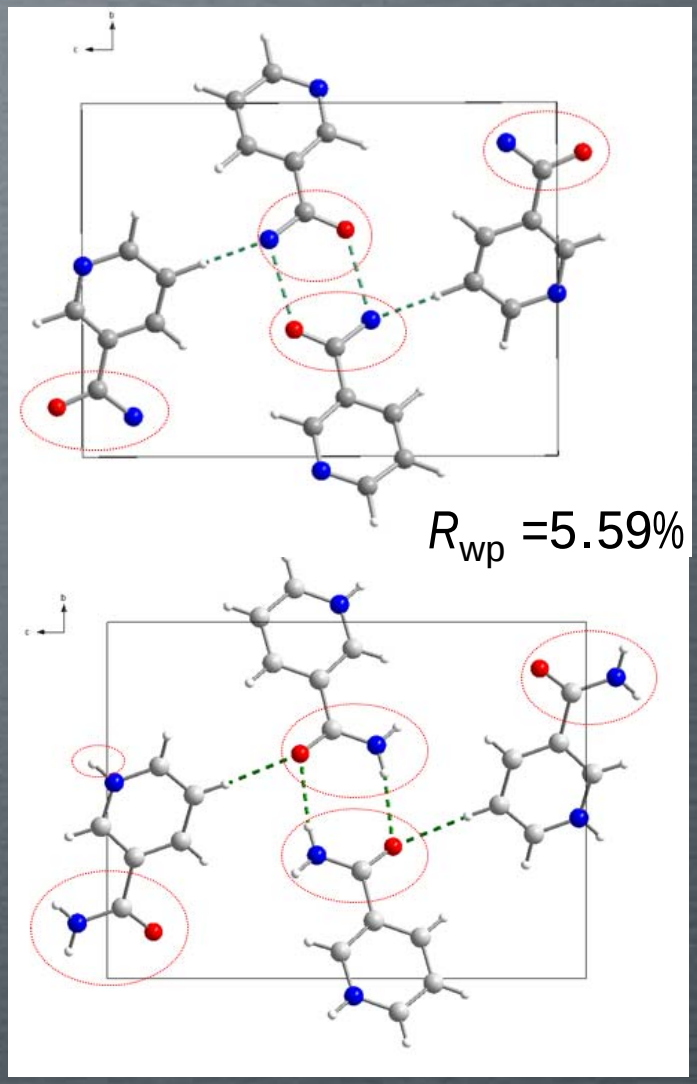


powder(solution)



single crystal

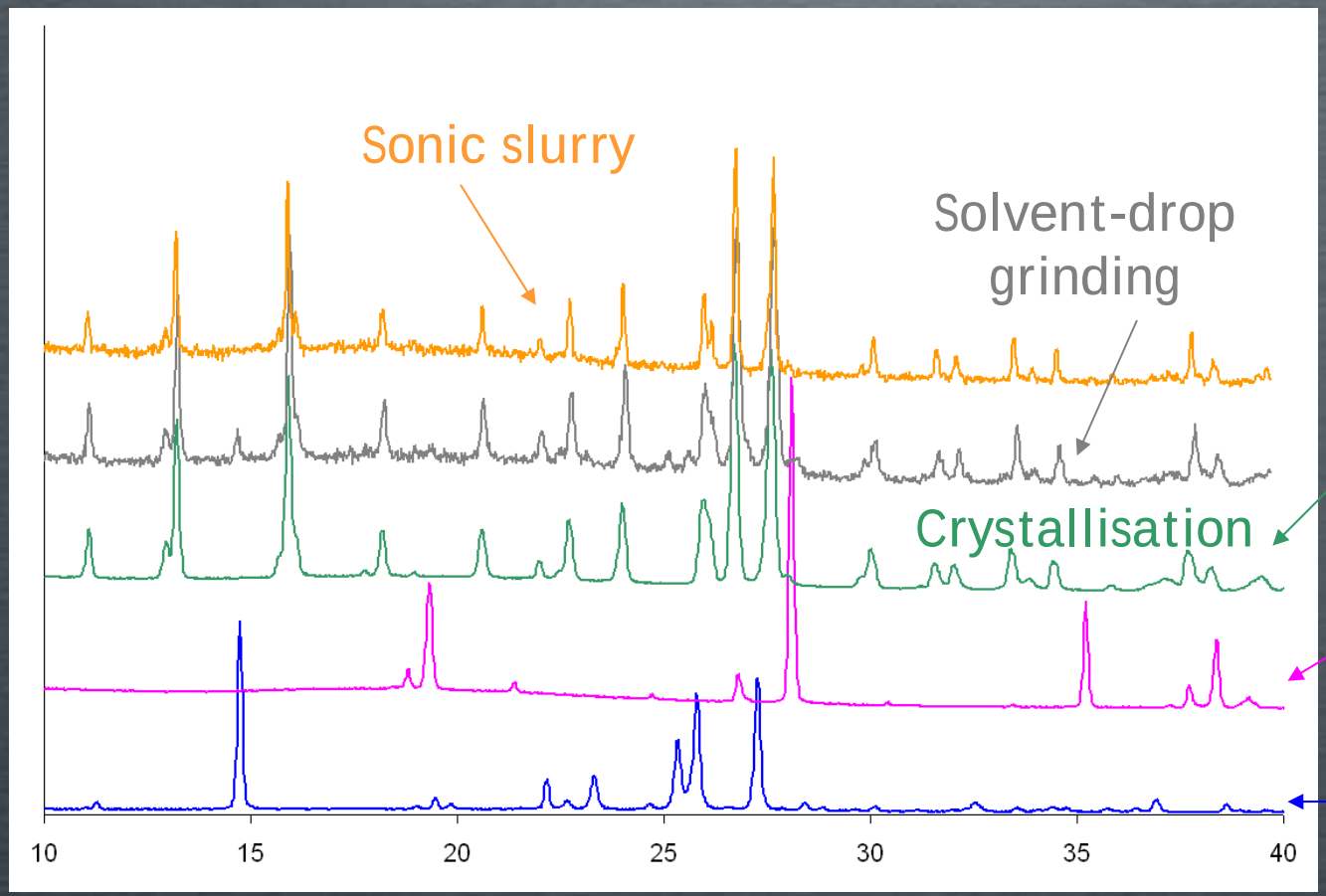


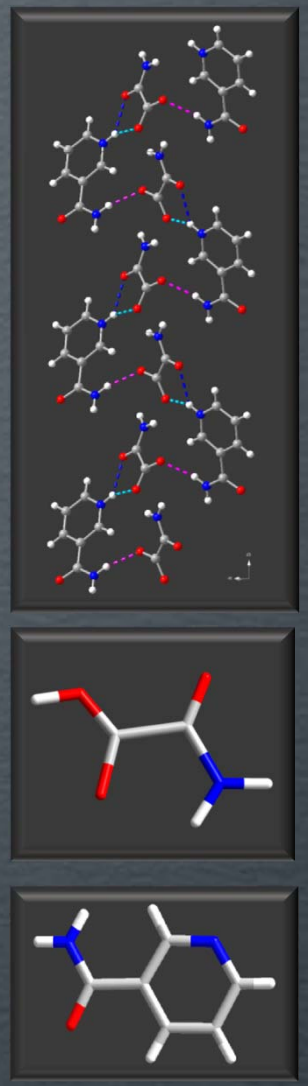


R_{wp} =5.59%

Synthesis – but multi-phase …

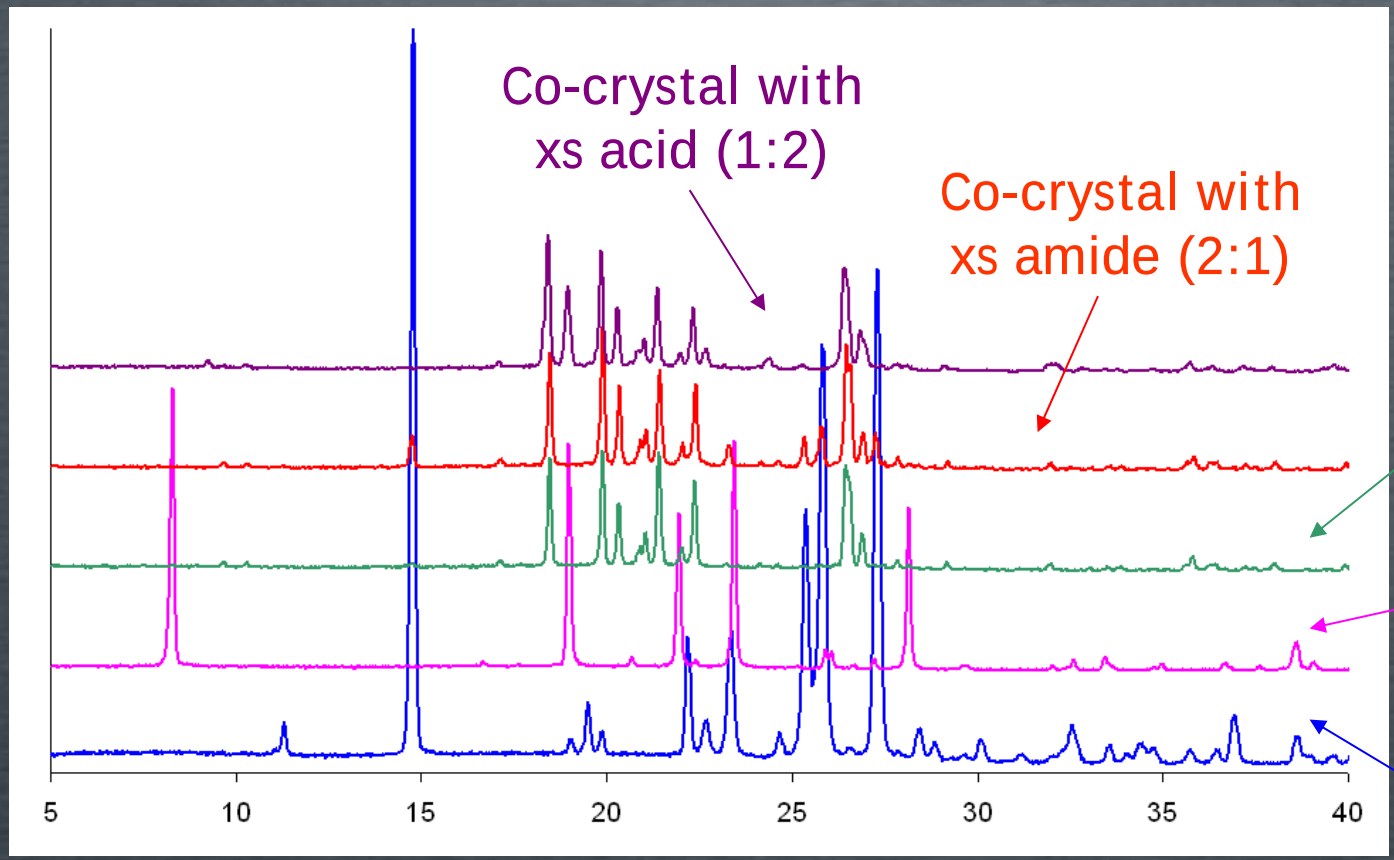
- Crystallisation/SD grinding/sonic slurry

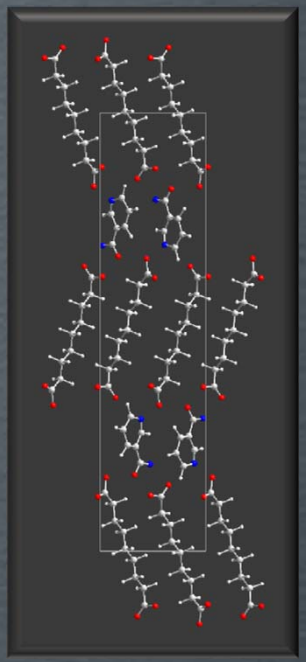


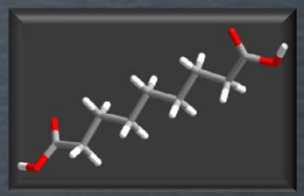


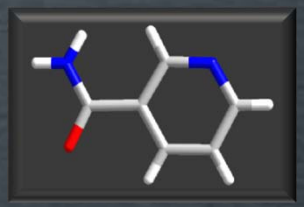
Synthesis – but multi-phase …

- Crystallisation from xs starting ratios

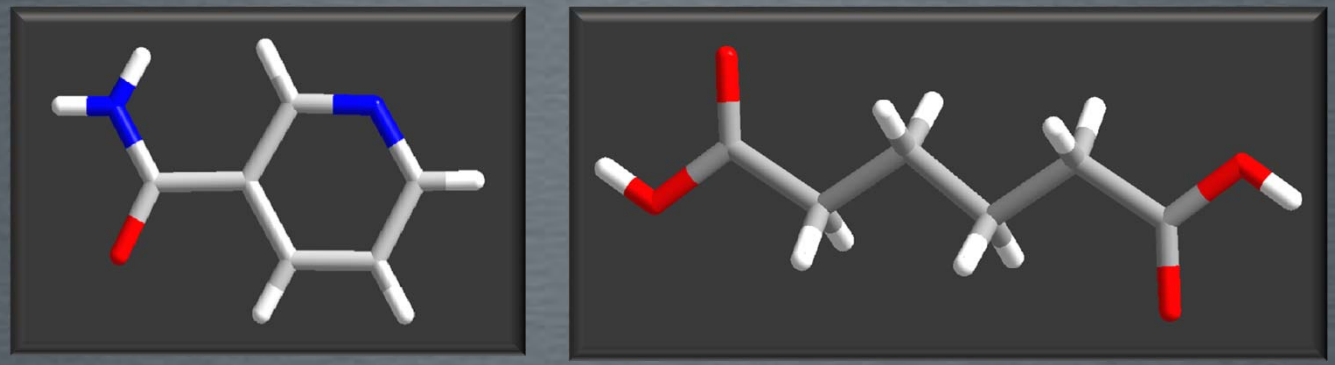


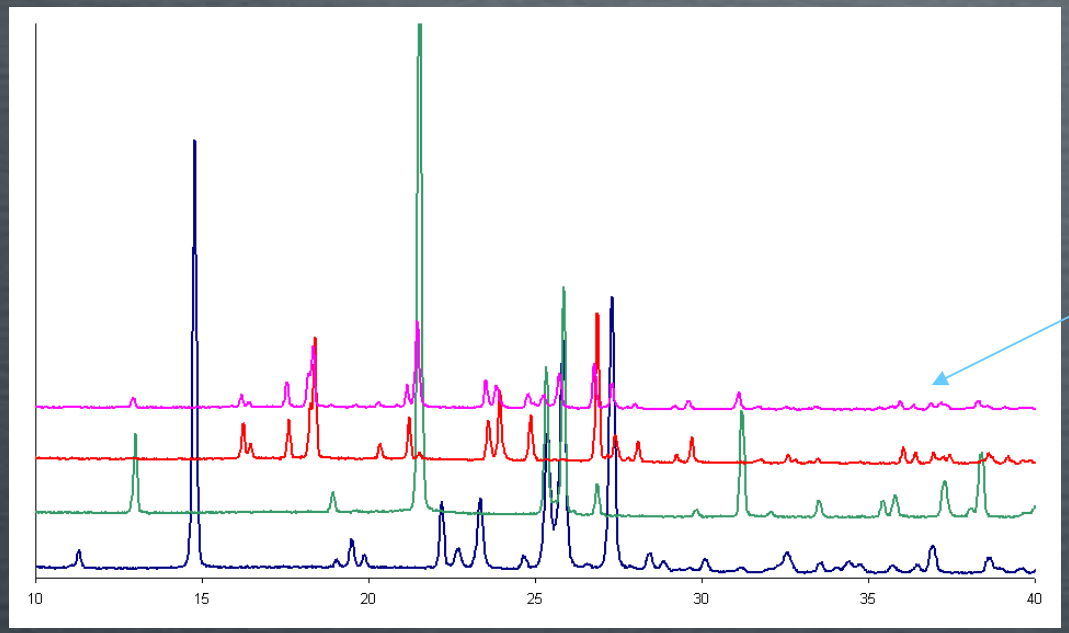






Nicotinamide : Adipic Acid





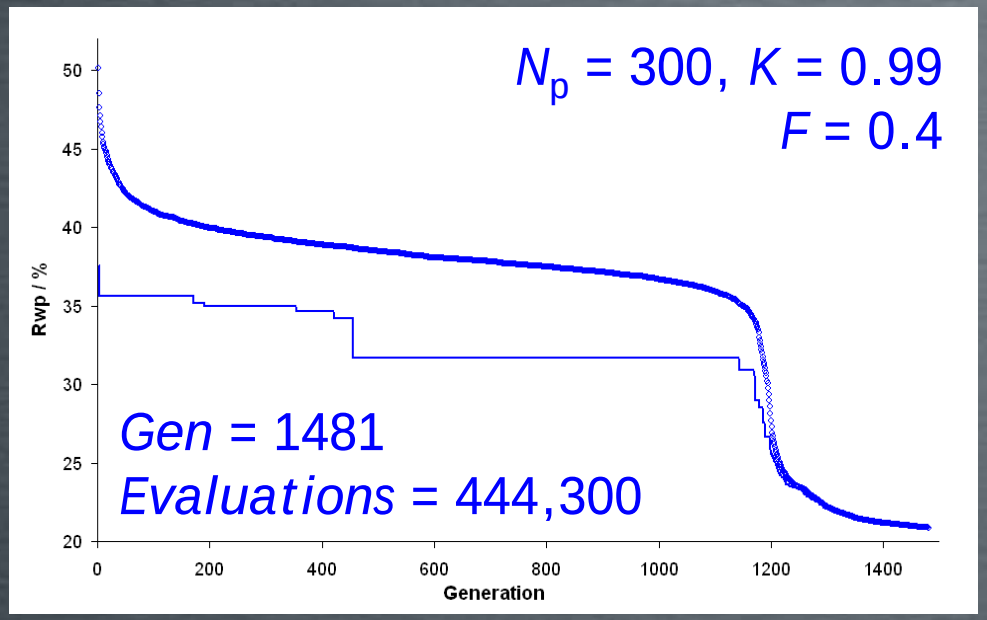
Crystallisation from 1:2 ratio

1:1 cocrystal with xs adipic acid

- Structure from *multi-phase lab PXRD* (using DE)

DE solution phase 1: nicotinamide:adipic acid

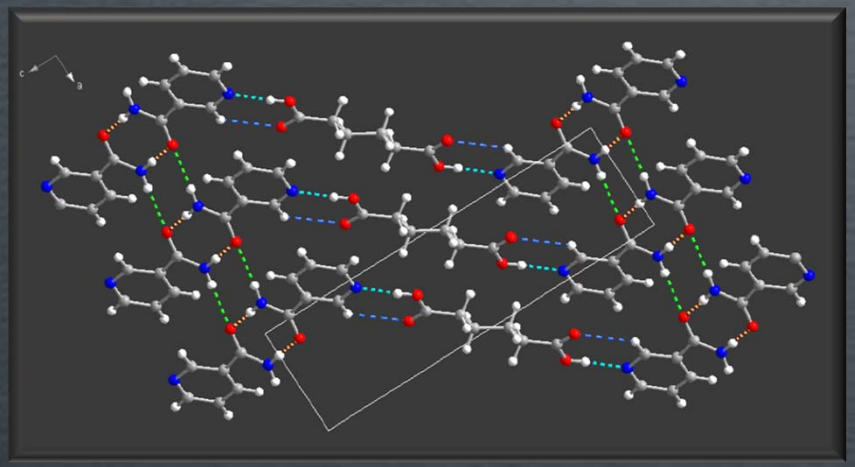
2 independent molecules, 18 parameters

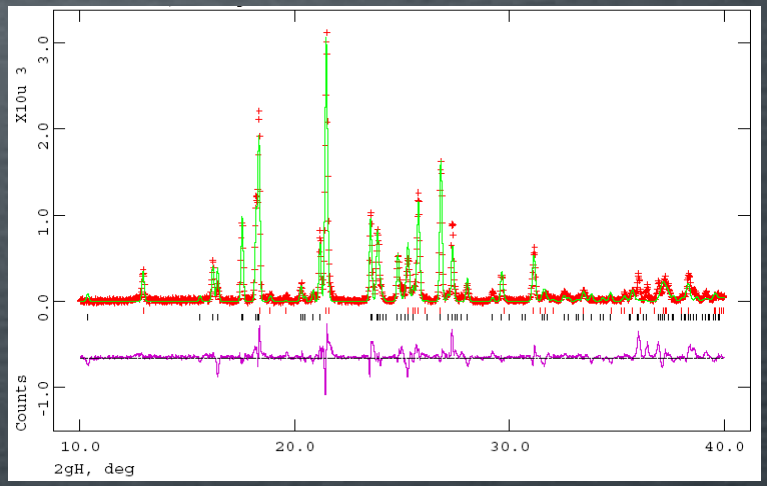


Fixed phase 2

xs adipic acid

Refinement of phase fraction





Nicotinamide with … Succinic Acid

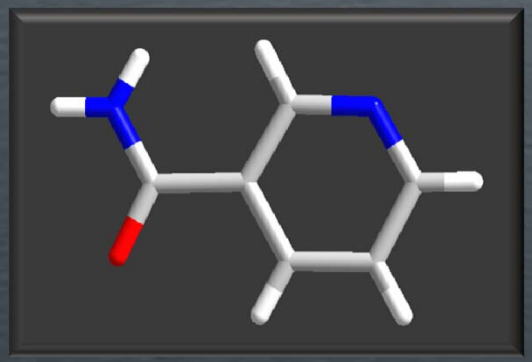
- Nicotinamide is a prolific coformer with dicarboxylic acids in stoichiometric variations

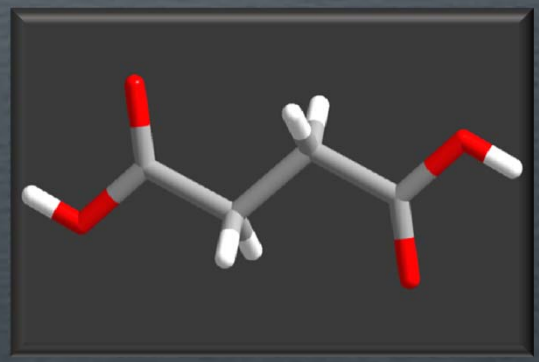
Karki et al., *CrystEngComm,* (2009), 11, 470

oxalic	malonic	succinic	glutaric	adipic	pimelic	suberic	azelaic	sebacic	fumaric
1:1			1:1	1:1	1:1	1:1	1:1	(1:1)	1:1
(2:1)	2:1	(2:1)		2:1	(2:1)	2:1		2:1	2:1

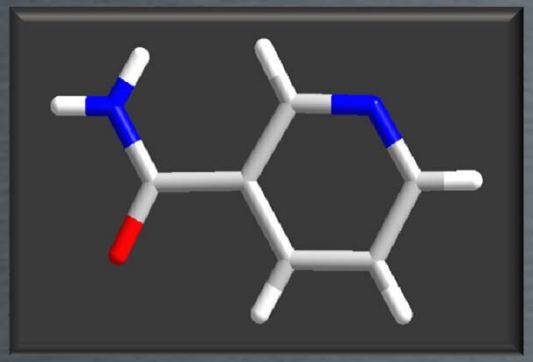
Amide:Acid Stoichiometry

Athimoolan et al., *Acta Cryst.,* (2007), 63, o263 Orola et al., *CrystEngComm,* (2009), 11, 415

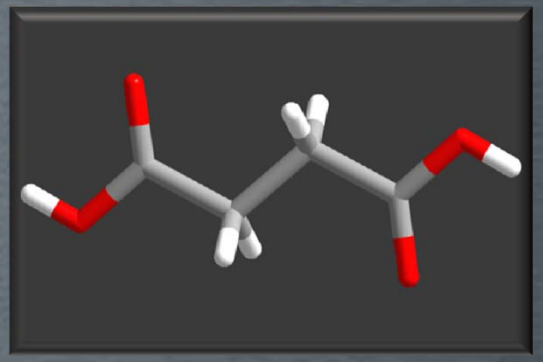




Nicotinamide : Succinic Acid 2:1

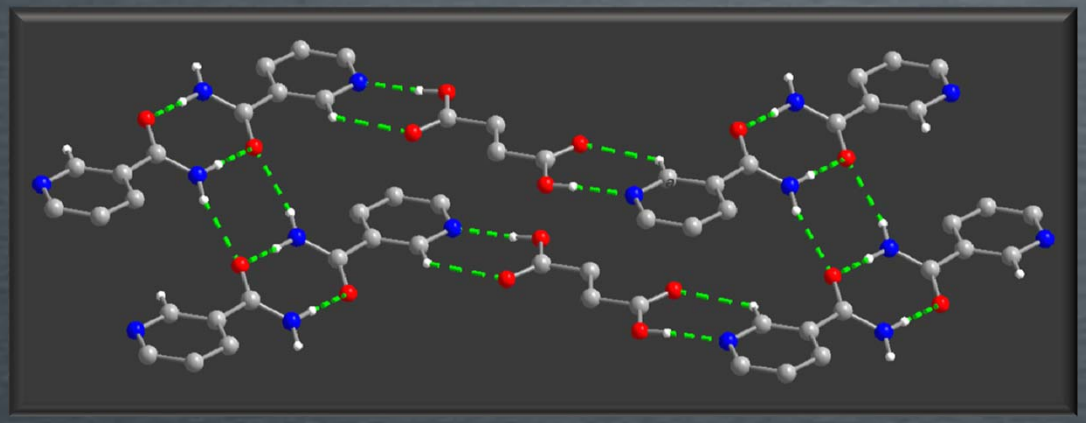


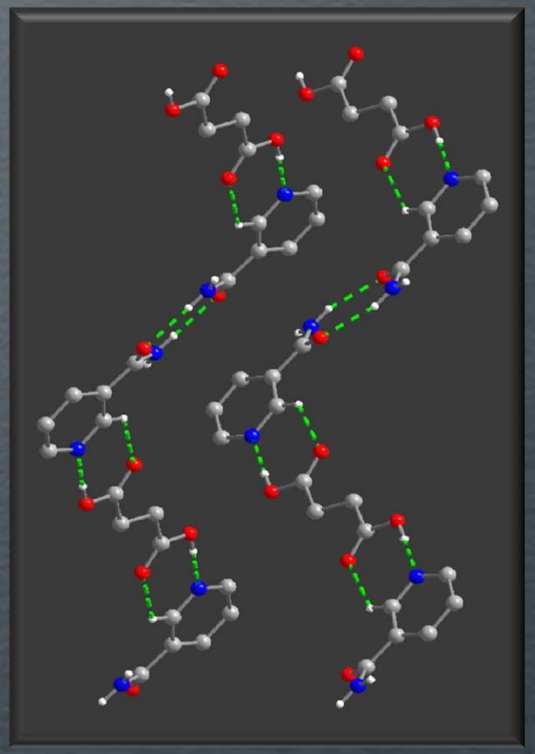
Crystallisation
from MeOH
1:1 ratio



2:1 cocrystal

Single crystal determination



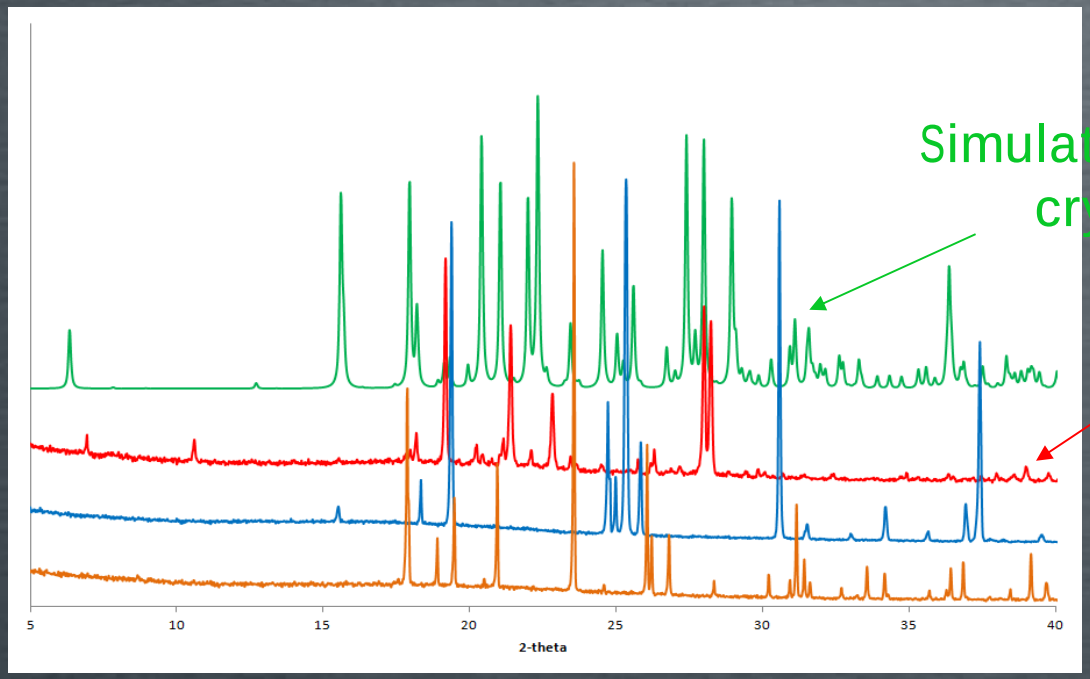


- Acid-pyridine & amide-amide motifs
- *Anti* & *syn* nicotinamide conformations

Thompson, Voguri, Cowell, Male & Tremayne, *Acta Cryst,* (2010), C66, o421

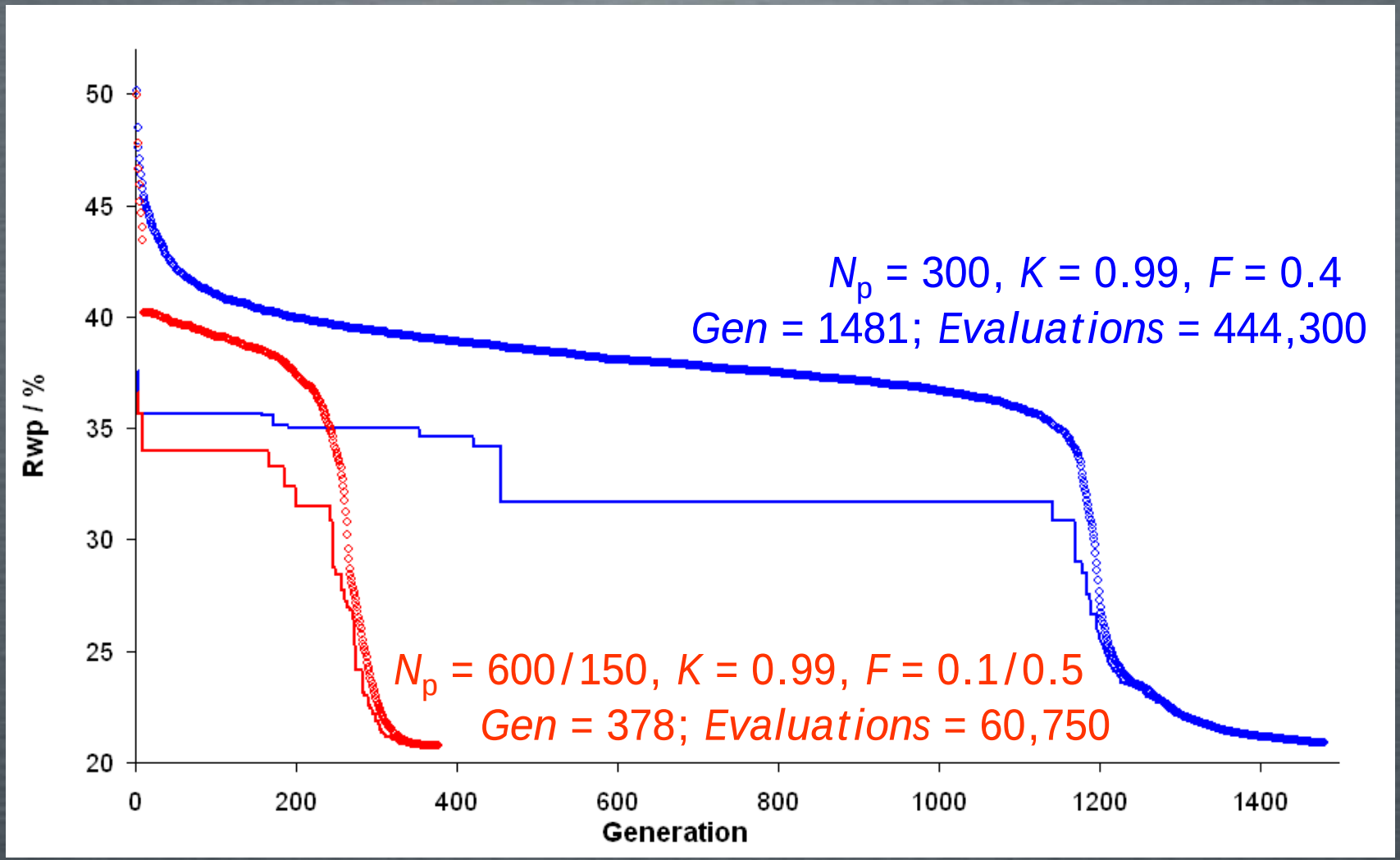
Nicotinamide : Succinic Acid 1:1

Crystallisation from MeOH, 1:1, 'controlled conditions'
Solid state IR – inconclusive
GC & EA & NMR – 1:1 stoichiometry



Structure determination from *PXRD (using DE)*
2 independent molecules, 16 parameters

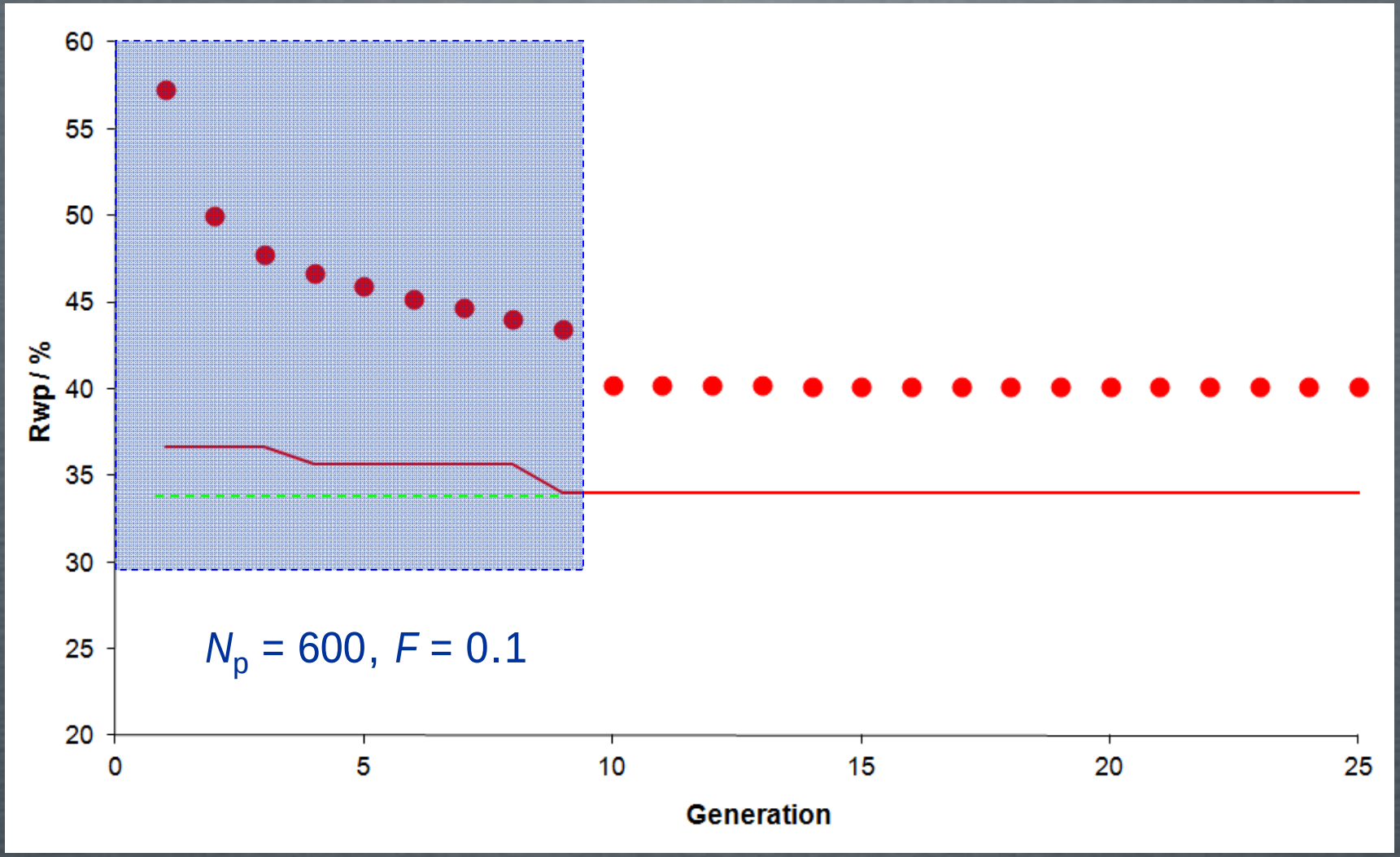
Making the DE more efficient .....



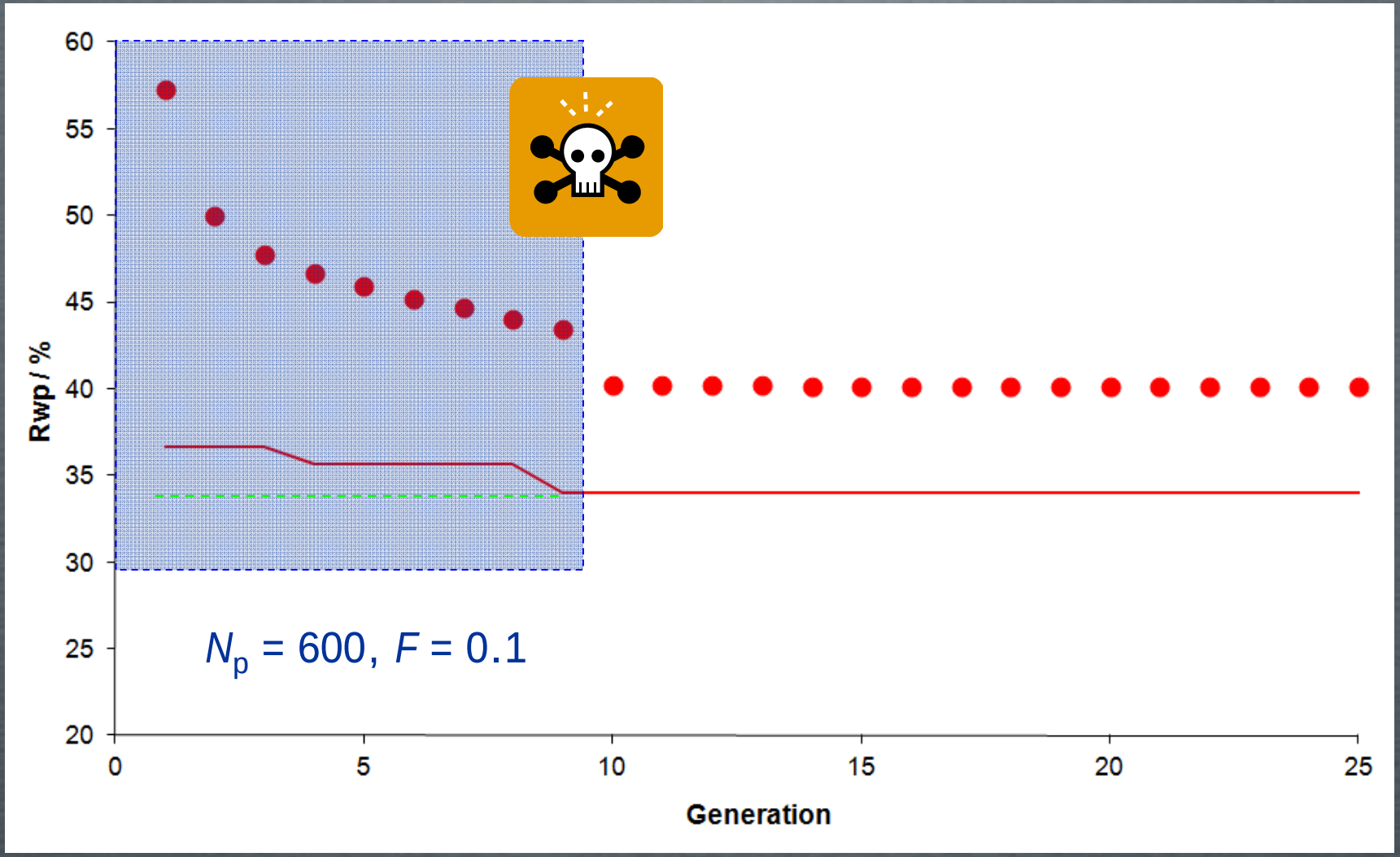
Making the DE more efficient .....

1. Very large initial population – maximize diversity of the search
2. Exterminate ¾ of the population after a few generations to improve genetic fitness of the population
3. Invoke process when ¼ of population are better than the *initial best solution*
4. Increase *F* after cull to prevent premature convergence

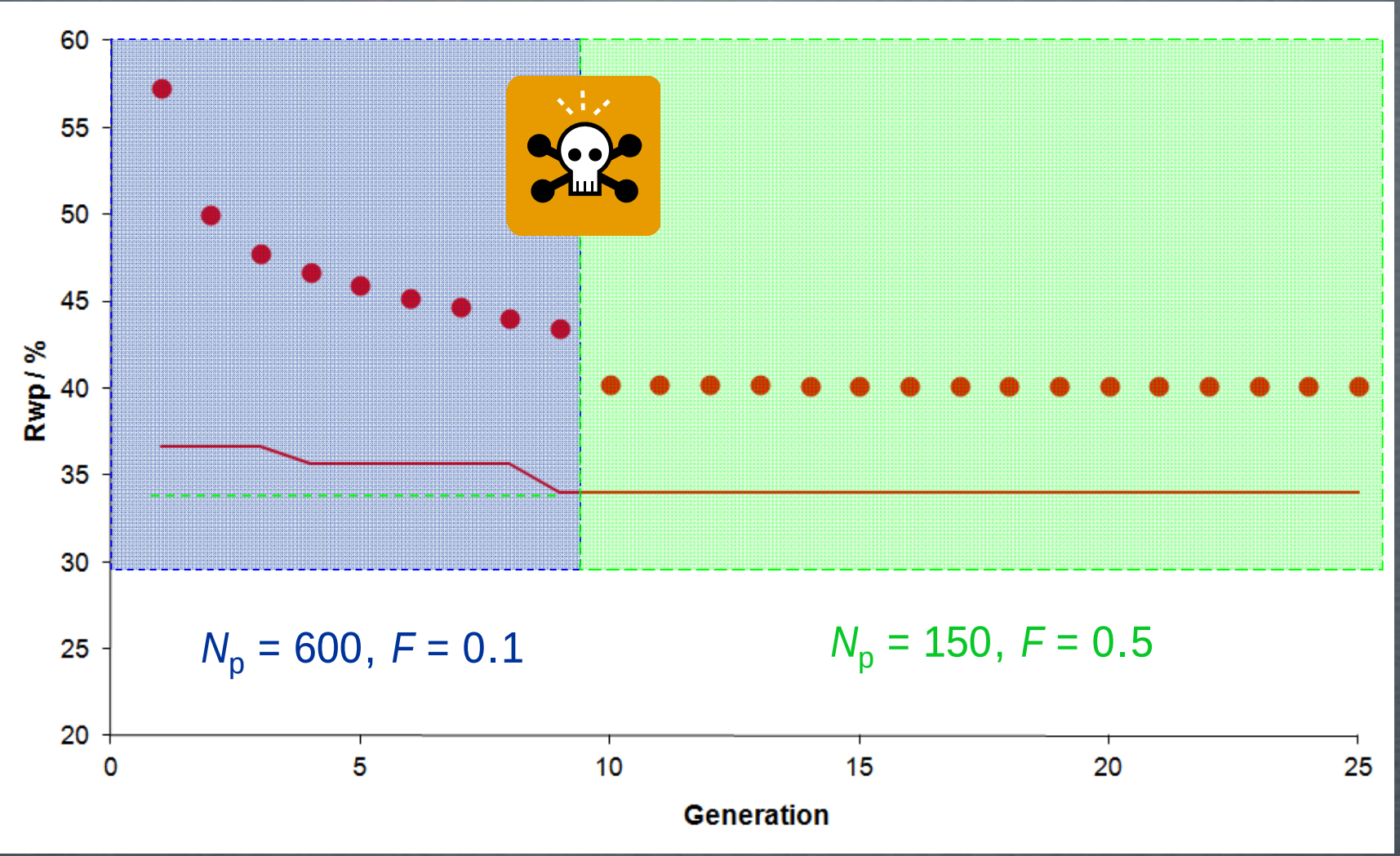
Making the DE more efficient .....



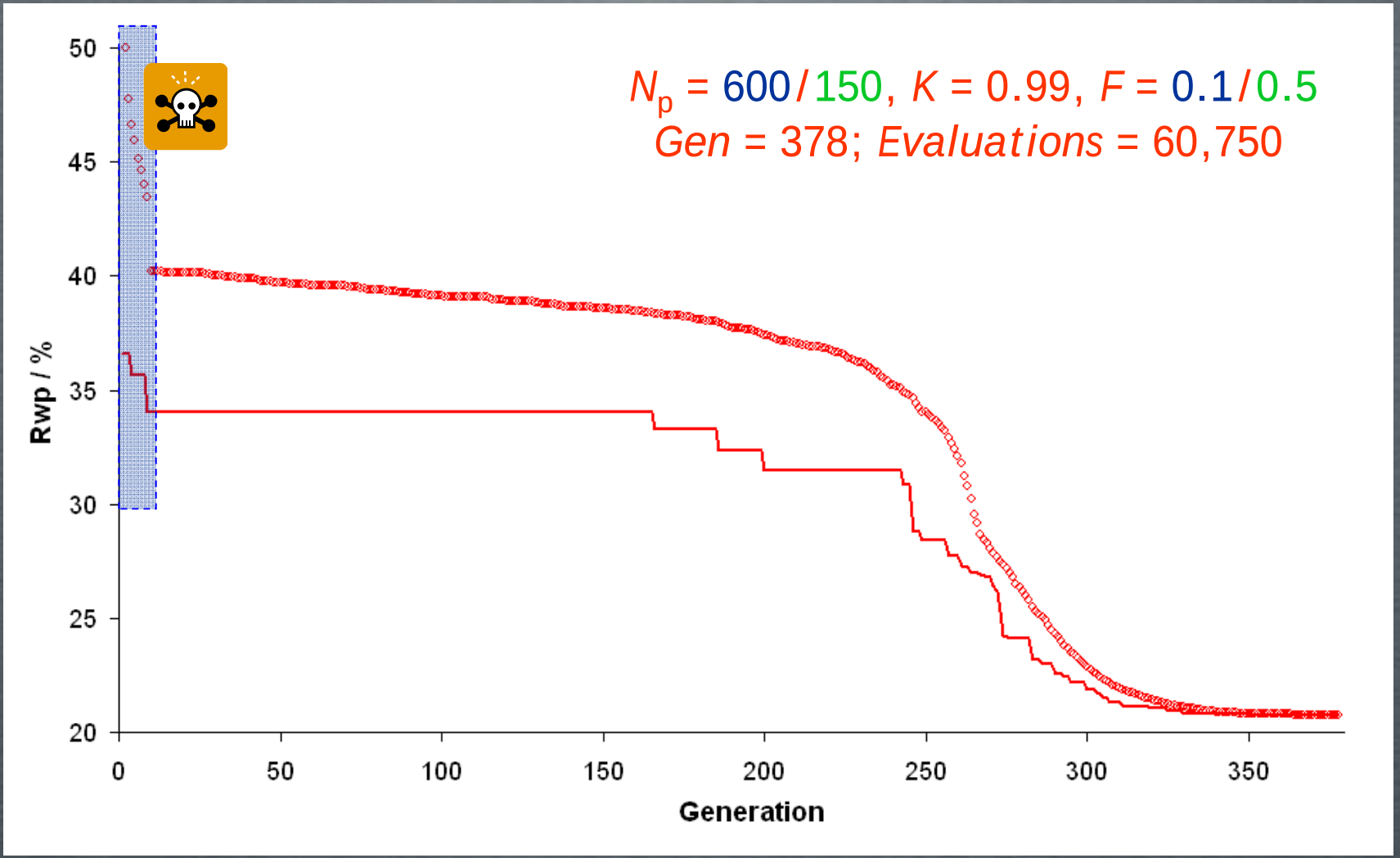
Making the DE more efficient .....



Making the DE more efficient .....

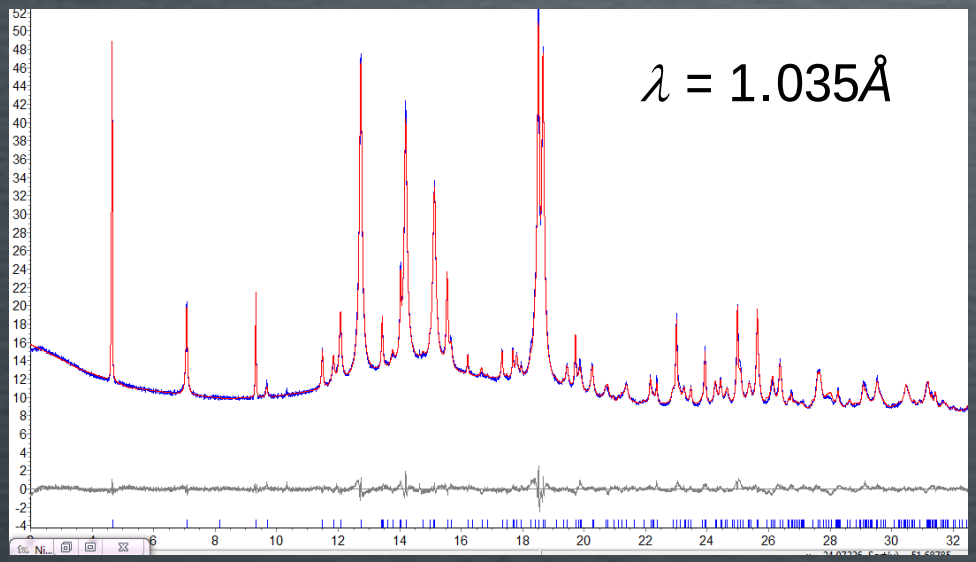


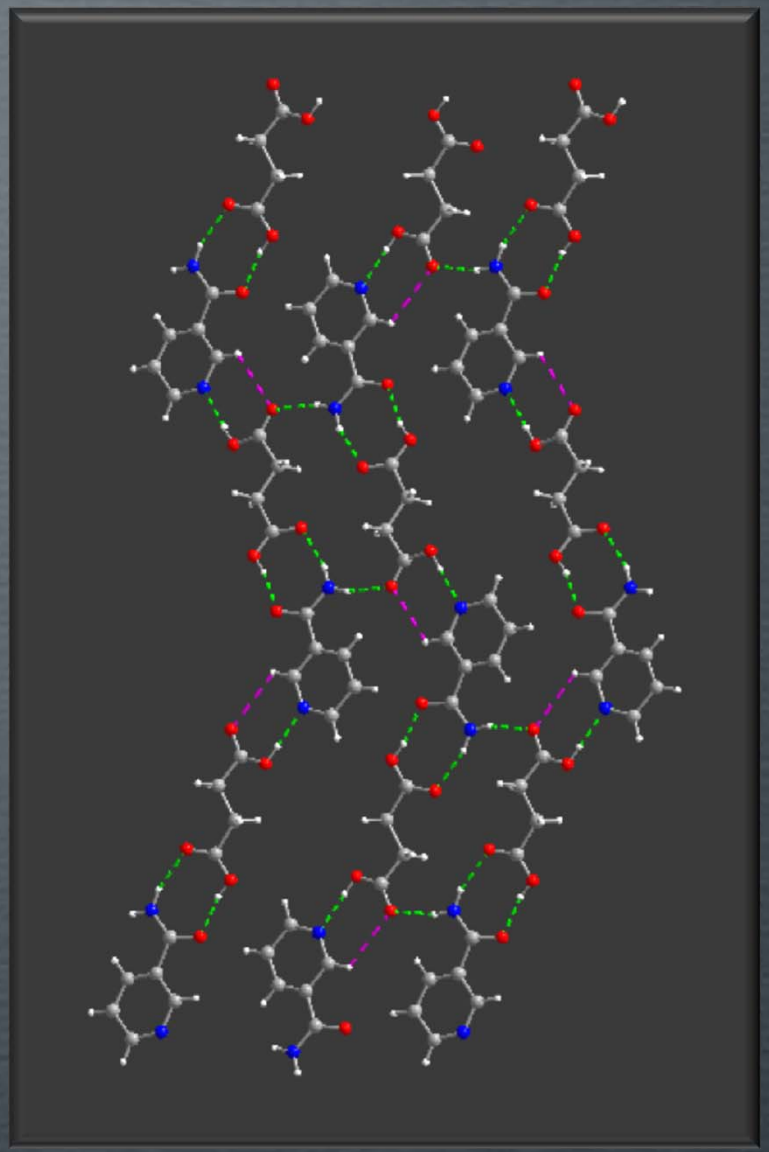
Making the DE more efficient .....



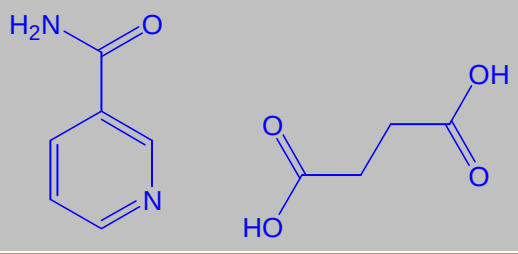
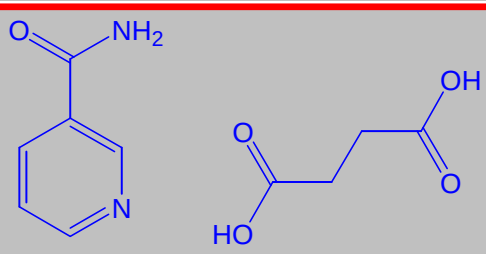
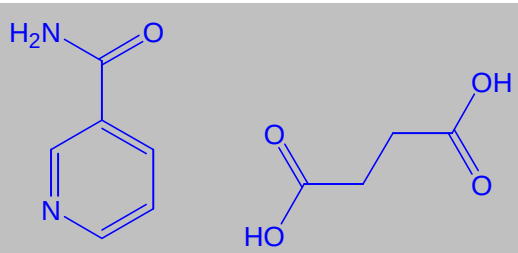
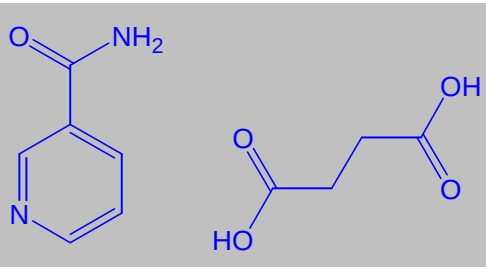
Nicotinamide : Succinic Acid 1:1

- Acid-pyridine & amide-acid motifs
- *Anti* nicotinamide conformation
- Distinctive supramolecular chain motif (1:1)





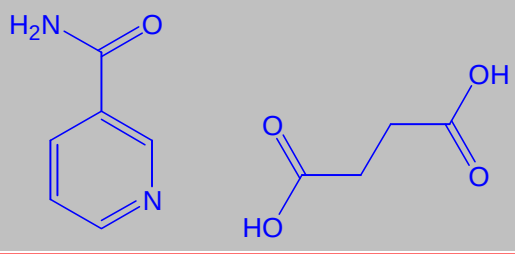
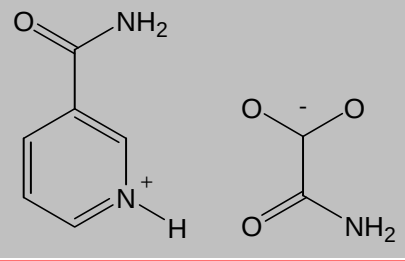
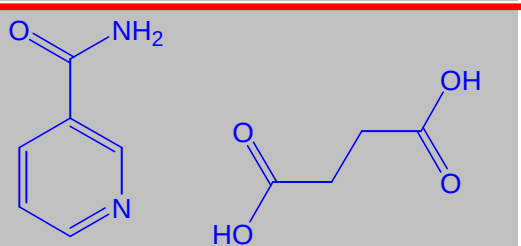
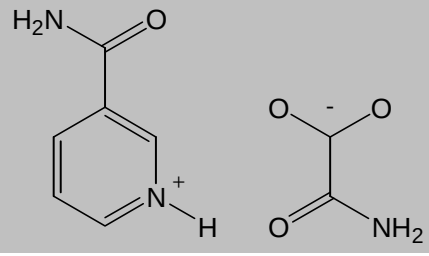
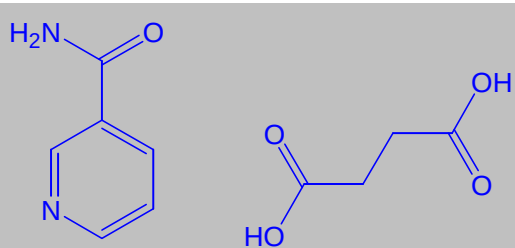
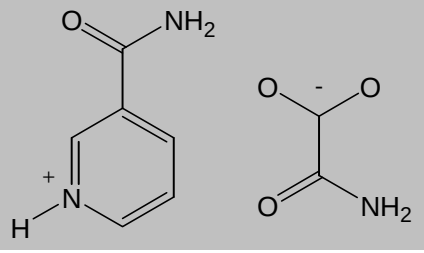
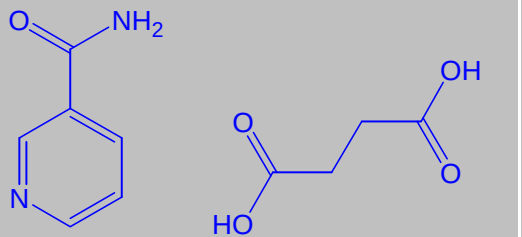
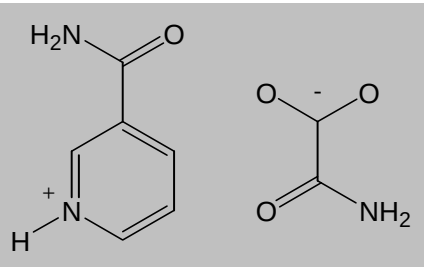
Is the Conformation Correct?

Conformation	R_{wp}(%)
	**3.97** (4.37)
	4.67 (4.61)
	4.58 (4.63)
	5.13 (5.24)

← Synchrotron

← (Lab data)

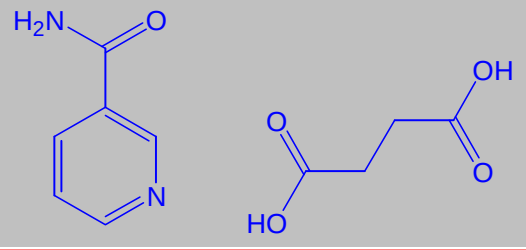
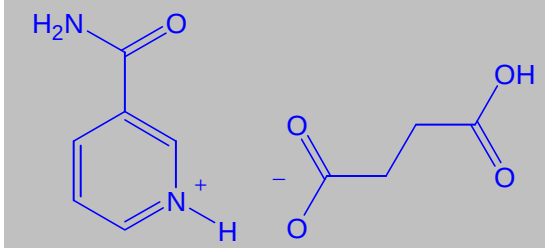
Is the Conformation Correct?

Conformation	R_{wp}(%)	Conformation	R_{wp}(%)
	**3.97** (4.37)		**5.65**
	4.67 (4.61)		6.04
	4.58 (4.63)		6.38
	5.13 (5.24)		6.79

Is it a Cocrystal or a Salt?

Can hydrogen atom positions be reliably determined from synchrotron PXRD?

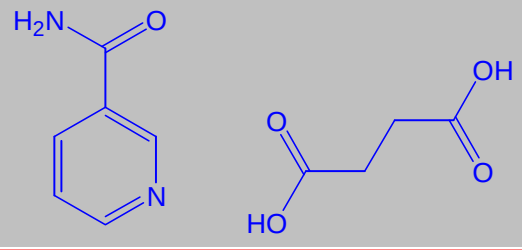
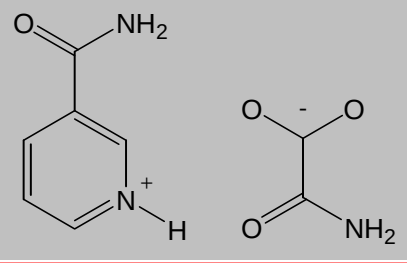
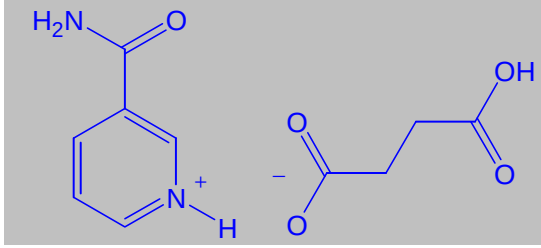
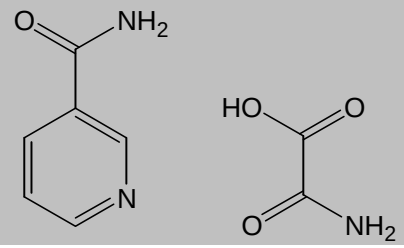
Cernik et al., *J.Appl.Cryst.*, (1991), 24, 222; Noritake et al., *Appl.Phys.Lett.*, (2002), 81, 2008; J-P Soulie et al., *J.Alloys Cmpds.*, (2002), 346, 200.

Conformation	R_{wp}(%)
	**3.97**
	4.09

Is it a Cocrystal or a Salt?

Can hydrogen atom positions be reliably determined from synchrotron PXRD?

Cernik et al., *J.Appl.Cryst.*, (1991), 24, 222; Noritake et al., *Appl.Phys.Lett.*, (2002), 81, 2008; J-P Soulie et al., *J.Alloys Cmpds.*, (2002), 346, 200.

Conformation	R_{wp}(%)	Conformation	R_{wp}(%)
	**3.97**		**5.65**
	4.09		5.76

Conclusions

Structure determination of *multi-component molecular cocrystals* from lab PXRD

↓

variation of stoichiometries from *various* synthetic routes

↓

... *but* ... always be aware of possible alternative conformations

↓

SDPD of cocrystals from *multi-phase data*

High quality PXRD data to confirm form?

Significant optimisation efficiency through a large population using *eugenics*!

Acknowledgements

Adam Cowell

Duncan Bell

Raja Voguri

Laura Thompson

Benson Kariuki

Louise Male

Elizabeth Shotton

UNIVERSITY OF BIRMINGHAM

EPSRC

ICDD