Structural studies at the Salt-Cocrystal Interface

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WOLFSON CENTRE FOR MATERIALS PROCESSING

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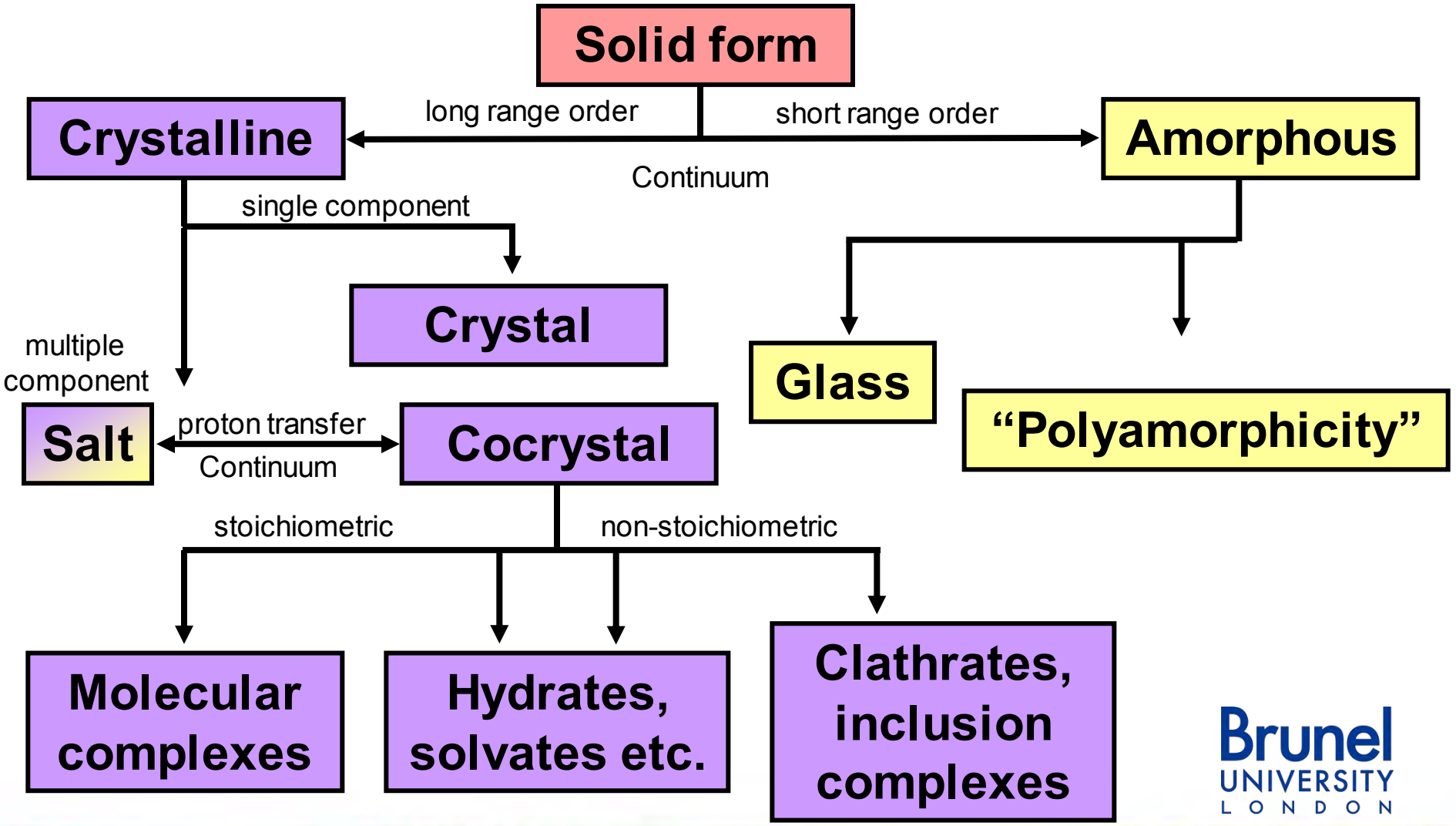
Organic Solid Form



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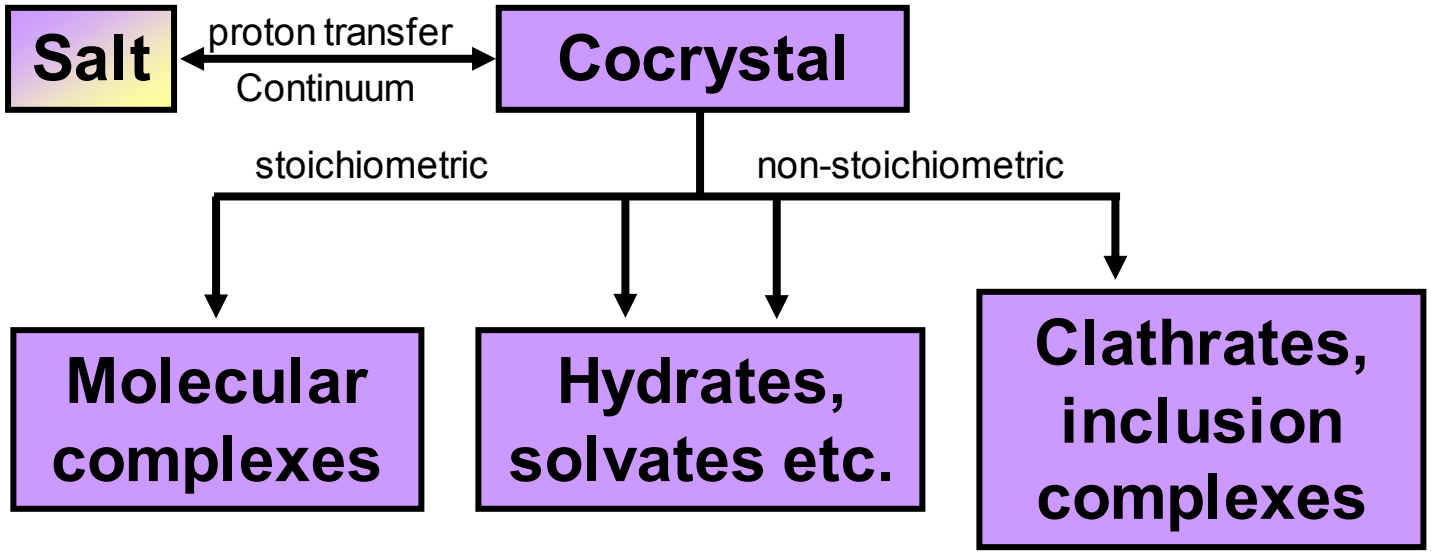
Organic Solid Form



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Adopted cocrystal definition

A + B ⟷ **A-B or A B**

Literature definitions of a cocrystal:

- **"a crystal containing two or more components together"** – ***Dunitz, J. D.***
- "compounds constructed from neutral molecular species…".." ..that are solid at ambient conditions.."..".."..present in definite stoichiometric amounts.." ***Aakeröy, C. B., et al.***.
- Pharmaceutical cocrystal – A multiple component crystal in at least one component is molecular and a solid at room temperature (the cocrystal former) and forms a supramolecular synthon with a molecular or ionic API – ***Zaworotko, M. J.***,
- "Placing two molecules in a crystalline lattice *via* a clearly distinguishable synthon" – ***Jones, W. J., et al***.

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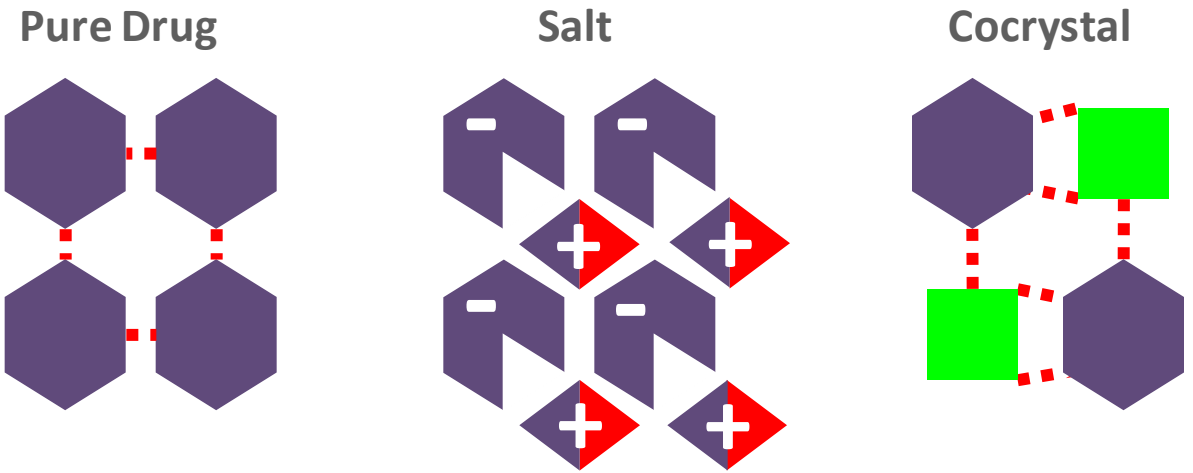
What is a Pharmaceutical Cocrystal?

"A drug and approved excipient crystallised together"



	Pure Drug	Salt	Cocrystal
New IP	✗	✗	✓
Advantageous Properties	✗	✓	✓
API Regulatory Sameness	✓	✗	✓

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Strong validity of pharmaceutical cocrystal IP

- **API cocrystals are eligible for new 'Substance Of Matter' patents**
  - Novelty + Utility + Non-obvious: ***Can't predict their formation, properties or applications (Wouters 2011)***

- **Cocrystal patents have been granted globally (Almarsson 2012)**
  - US PTO >20 SOM patents granted since the first in 1999 (Eli Lilly)
  - EPO >10 SOM patents since 2003
  - Other PO's following suit (e.g. Astellas US8097592, Vertex US8039475)

- **Opportunity to retrospectively secure IP for molecules of interest**
  - 'API IP' creation advantage *vs* technology platform IP
  - ***20 years SOM protection for every new API cocrystal generated***

***Trask: 'An overview of pharmaceutical cocrystals as IP' 2007**

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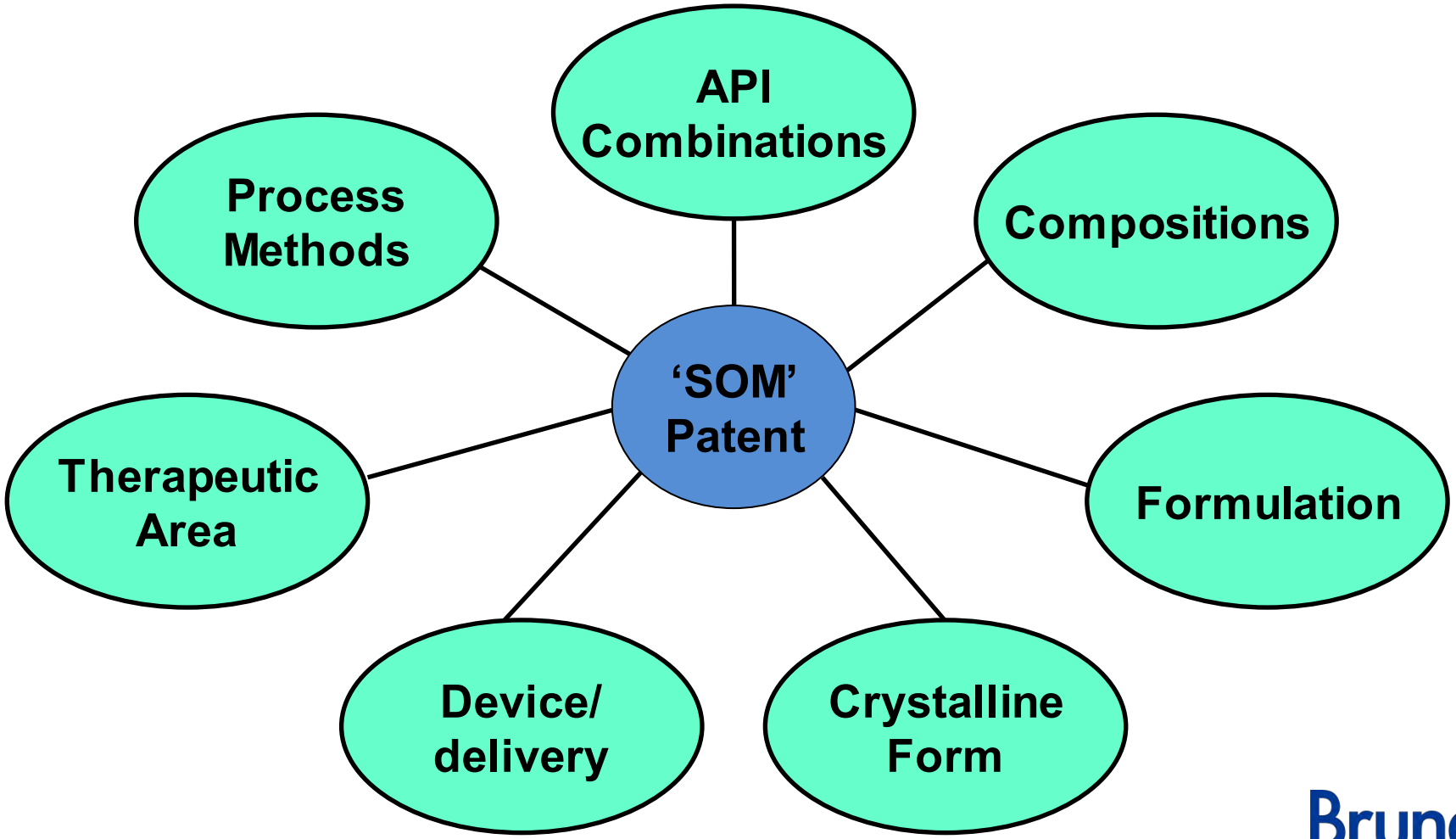
Cocrystal claim strategy can mirror NCE



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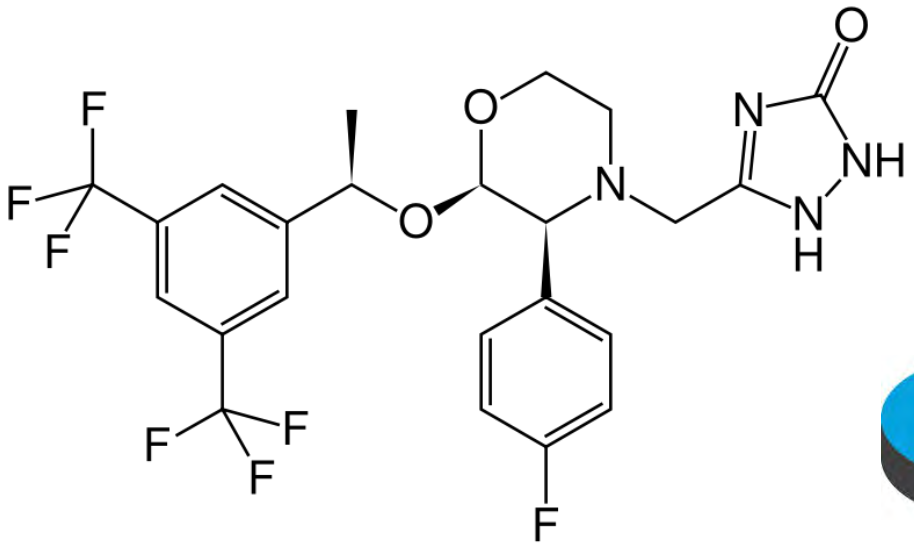
Example: Aprepitant, (Emend™)



nuformix

- Poor dissolution profile requiring licensed nanotechnology to formulate
- Screened against large number of coformers
- One positive hit against *L*-Proline
- First isolated example mono-methanolate solvate
- Methanol subsequently exchanged for water as stable monohydrate

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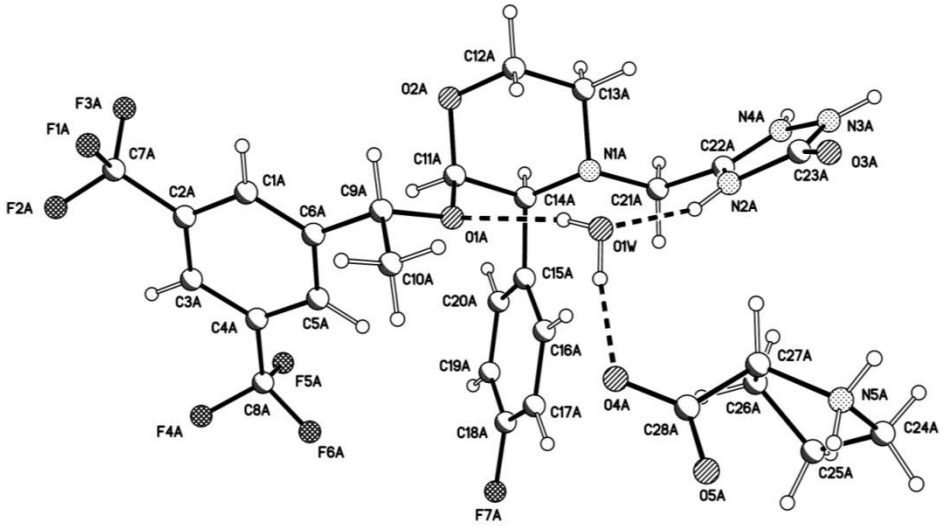
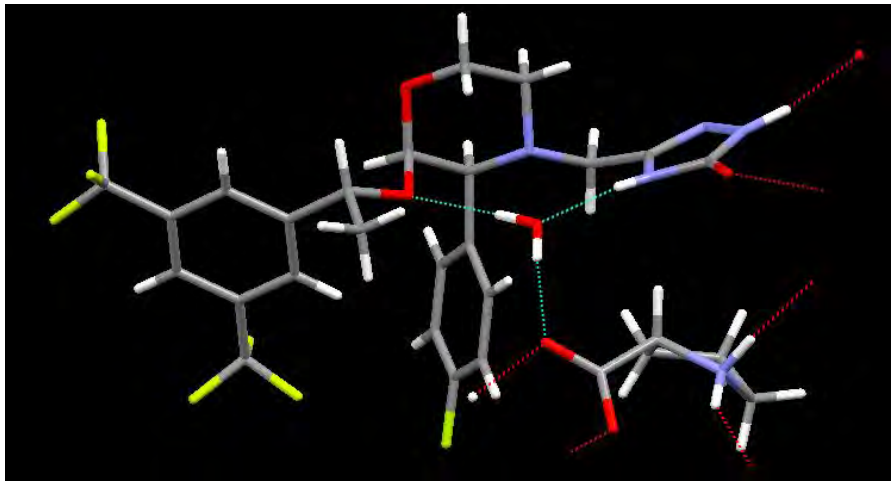
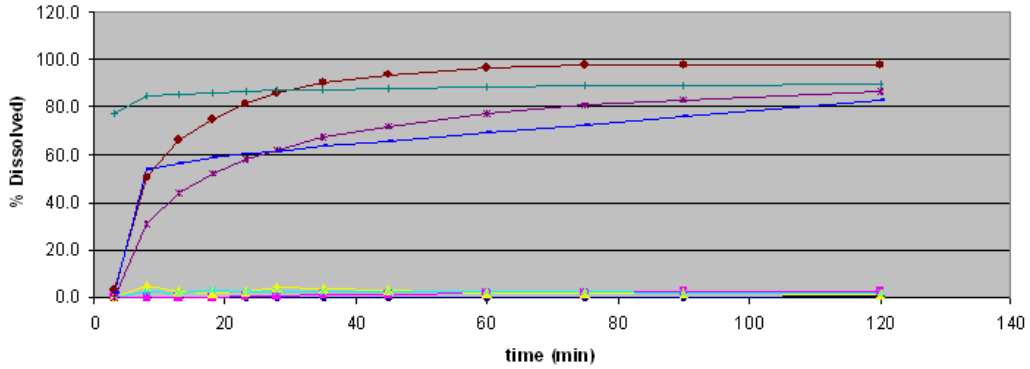
Aprepitant *L*-Proline monohydrate







Aprepitant *L*-Proline Composition and Cocrystal
Christopher Frampton, Joanne Holland, Alan Chorlton and Daniel Gooding.
WO2012038937 29-03-2012

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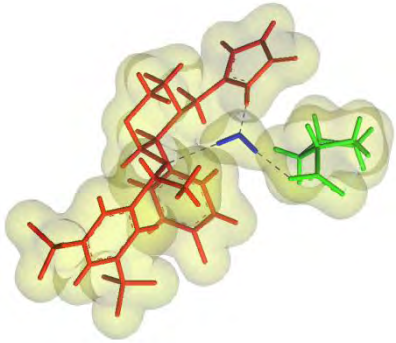
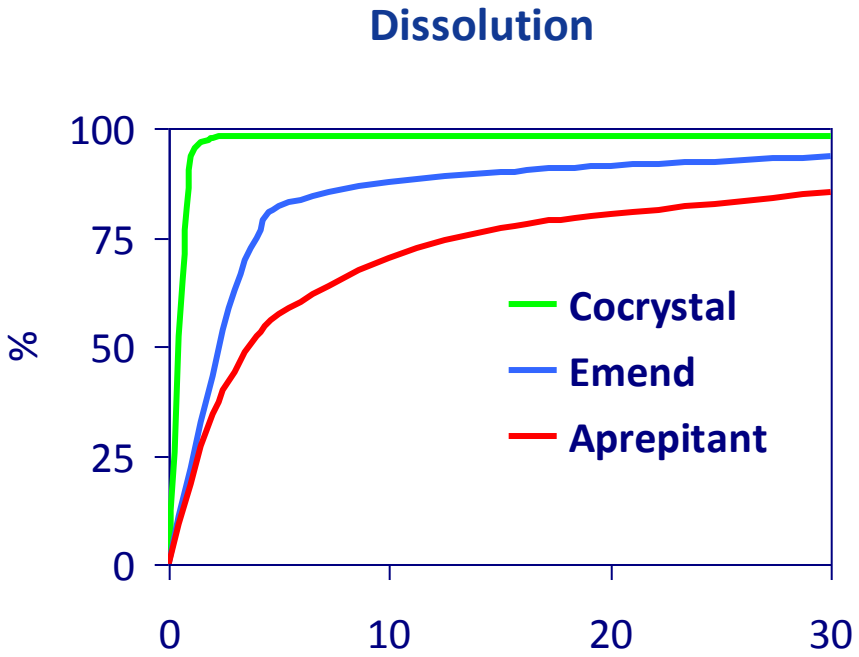
Cocrystal offers important product advantages





- **Aprepitant: Initial formulation failed Phase IIa due to poor absorption**
- **Emend™: 9-step dissolution enhancement gave consistent absorption**
- **Cocrystal: 1-step process gives differentiated cocrystal with potential**

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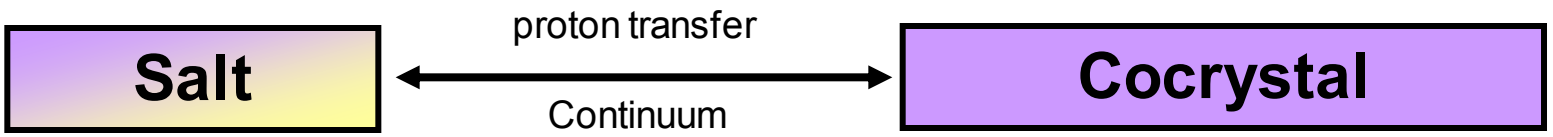
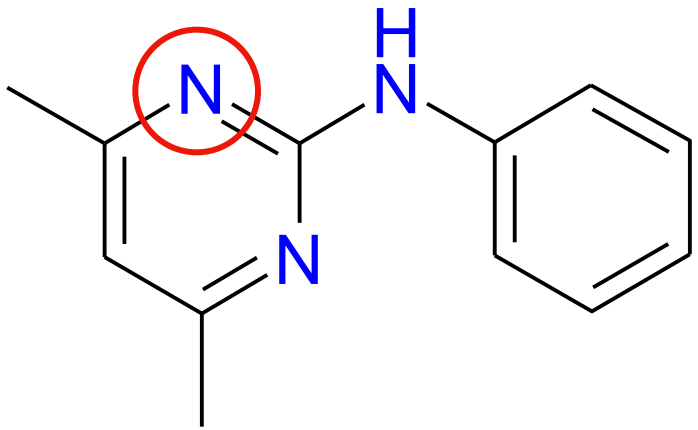
Example Pyrimethanil





Weakly basic nitrogen

Measured *p*Ka 4.05

Pyrimethanil: Weakly basic agrochemical antifungal active

Structural motif includes weakly basic nitrogen

Forms two polymorphs, Forms I and II.

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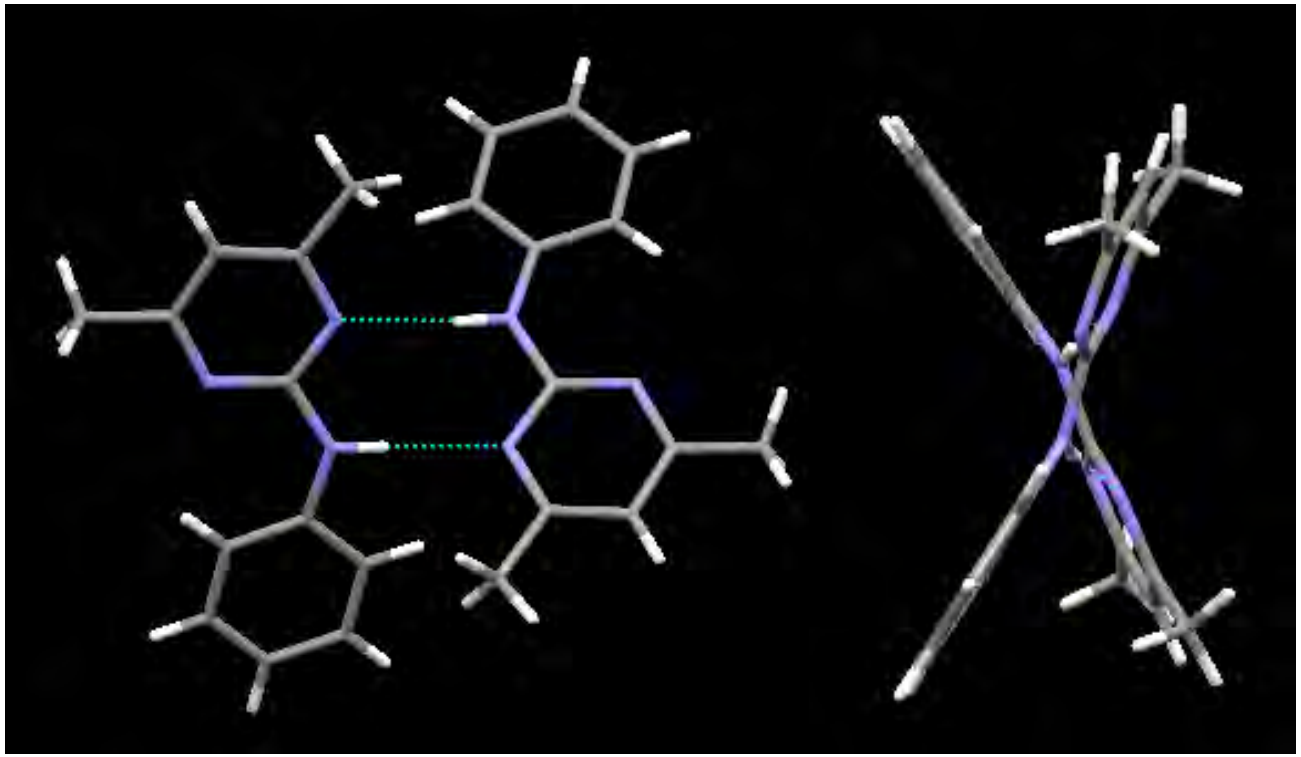
Pyrimethanil, Form I



a = 7.3947(6) Å

b = 11.6287(9) Å

c = 14.4750(13) Å

α = 67.784(8) °

β = 86.940(7) °

γ = 71.684(7) °

Triclinic

P-1,

R_1= 5.05%

Z' = 2, Z = 4

ρ = 1.210

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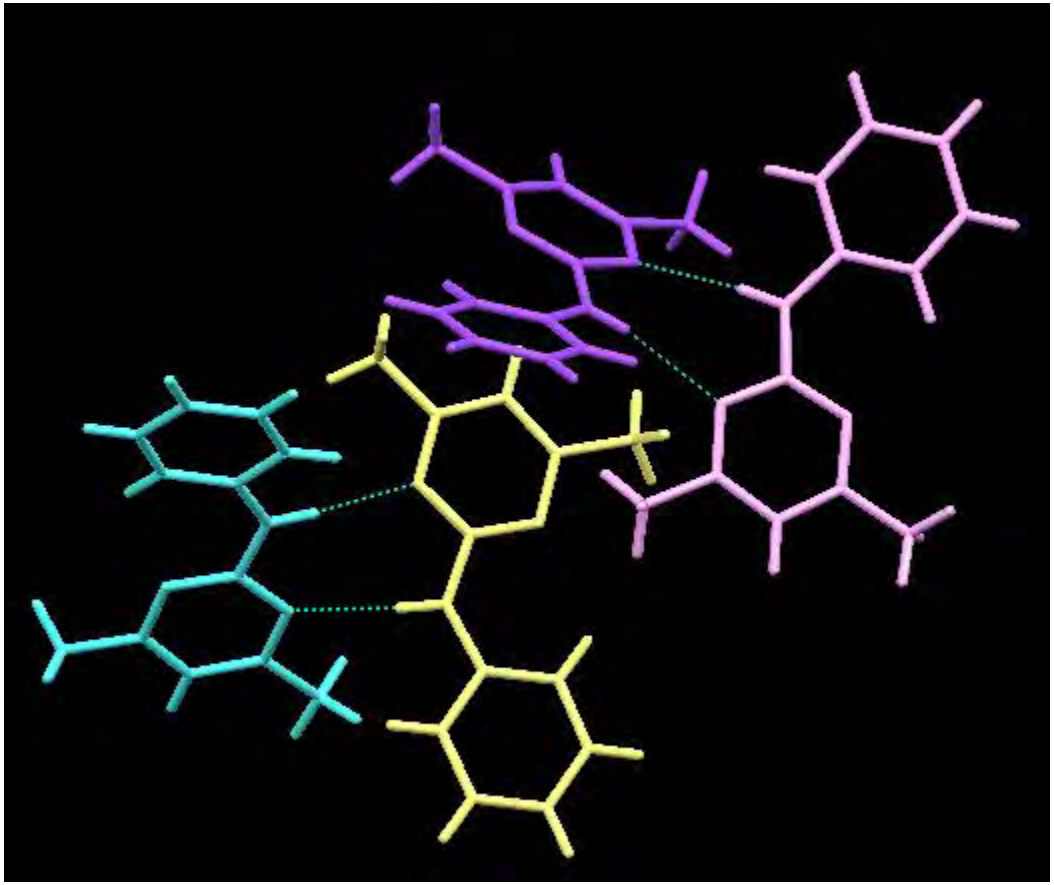
Pyrimethanil, Form II



a = 10.5237(4) Å

b = 19.1569(6) Å

c = 22.0806(8) Å

β = 102.811(4) °

Monoclinic

$P2_1/n$

R_1 = 4.95%

Z' = 4, Z = 16

ρ = 1.220

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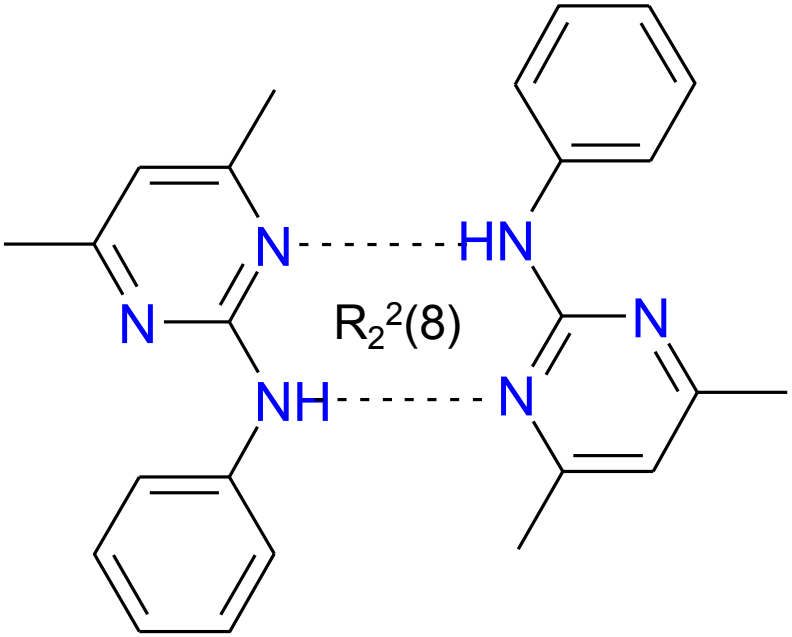
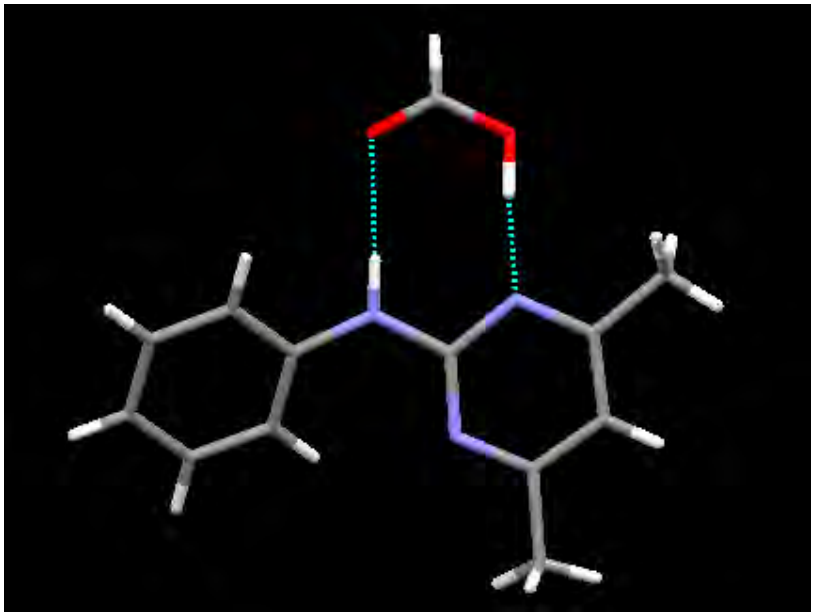
Structural motif





Both polymorphs form an $R_2^2(8)$ dimer structure and therefore carboxylic acids are a good starting place to for cocrystals

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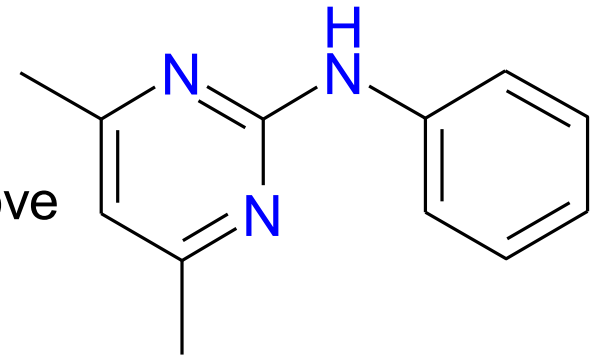
Control of species formation

Measured *p*ka = 4.05

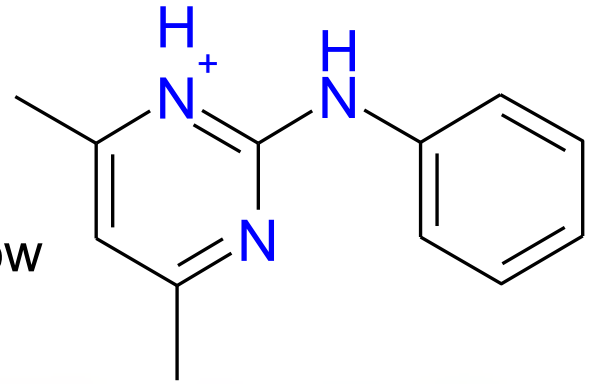
Would expect.....

Cocrystal *p*ka 4.00 or above



proton transfer

Salt *p*ka 2.00 or below



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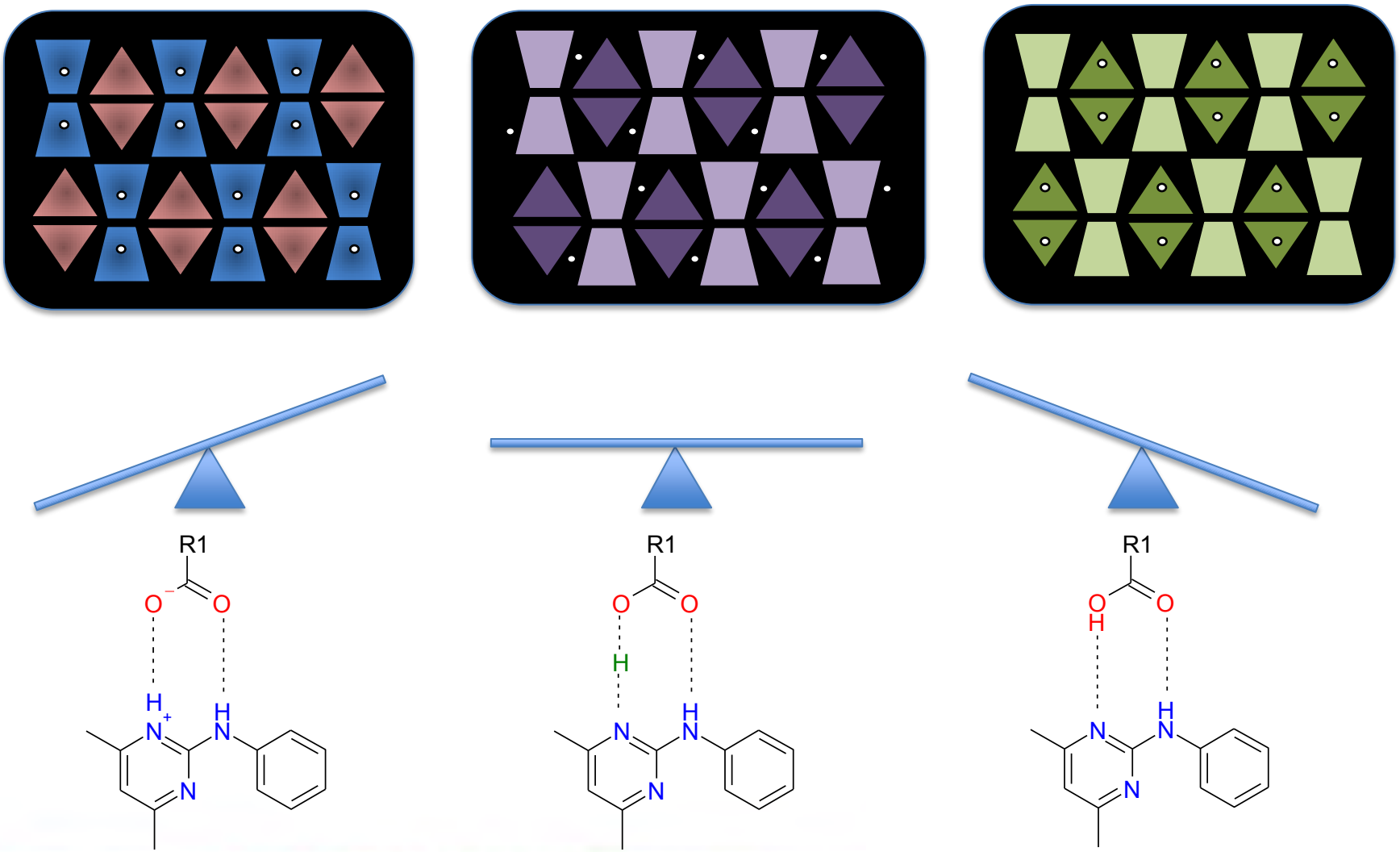
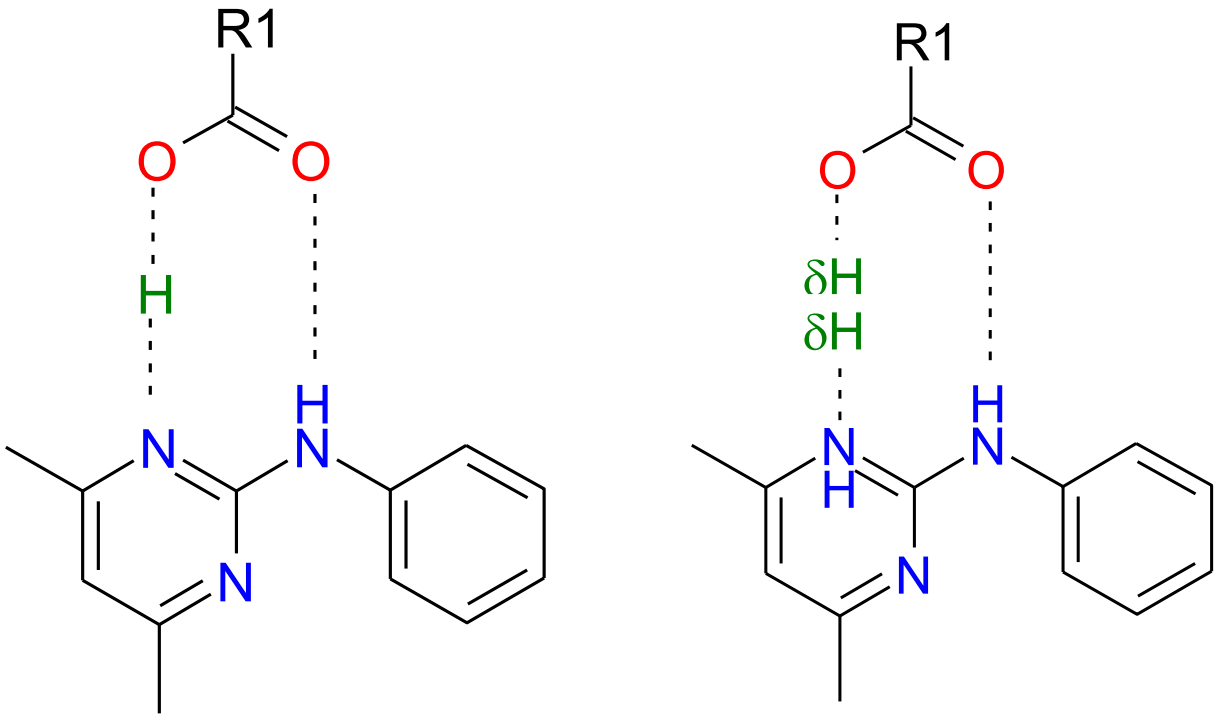
Increasing *p*Ka



Possible structures:
Dependant on *p*ka of coformer



Intermediate complexes, order and disorder models

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Comment	Coformer	Ratio	Product	Solvent	pKa
$P2_1/n$	Pyrimethanil, Form 1		Freebase	IPA	4.06
P-1	Pyrimethanil, Form 2		Freebase	IPA	4.06
	Oxalic acid	4:3	Salt	IPA	1.27
	Maleic acid	1:1	Salt	IPA	1.92
	2-Nitrobenzoic acid	1:1	Salt	IPA	2.16
Twin	2-Bromobenzoic acid	1:1	Salt	DMSO	2.85
	2-Chlorobenzoic acid	1:1	Cocrystal	IPA	2.97
$P2_1/c$	Pyrazinecarboxylic acid, Form 1	1:1	Cocrystal	DMSO	2.91
P-1	Pyrazinecarboxylic acid, Form 2	1:1	Cocrystal	DMSO	2.91
	DL-Tartaric acid:IPA	2:1:0.5	Salt/Cocrystal	IPA	2.96/4.24
	2,5 dihydroxybenzoic acid:DMSO	1:1:1	Salt/Solvate	DMSO	3.01
	2-Fluorobenzoic acid	1:1	Cocrystal	IPA	3.27
	2,4 dihydroxybenzoic acid	1:1	Salt	IPA	3.32
Iso with R	R/S-Mandelic acid	1:1	Salt	EtOAc	3.41
Iso with R/S	R-Mandelic acid	1:1	Salt/Cocrystal	EtOAc	3.41
	4-(Methylsulfonyl)benzoic acid	1:1	Intermediate	IPA	3.42
	4-Nitrobenzoic acid	1:1	Intermediate	DMSO	3.44
$P2_1/n$	3-Nitrobenzoic acid, Form 1	1:1	?	IPA	3.45
P-1	3-Nitrobenzoic acid, Form 2	1:1	Salt	IPA	3.45
	Thiazole-4-carboxylic acid	1:1	Salt	DMSO	3.57
	1-Naphthoic acid	1:1	Cocrystal	IPA	3.69
	Formic acid	1:1	Cocrystal	Neat	3.77
	3-Chlorobenzoic acid	1:1	Cocrystal	DMSO	3.83
	Diphenylacetic acid	1:1	Cocrystal	IPA	3.94
	4-Chlorobenzoic acid	1:1	Cocrystal	DMSO	3.97
	4-Iodobenzoic acid	1:1	Cocrystal	IPA	4.02
C2/c	Benzoic acid, Form 1	1:1	Cocrystal	IPA	4.20
$P2_1/n$	Benzoic acid, Form 2	1:1	Cocrystal	DMSO	4.20
	Succinic acid	2:1	Cocrystal	DMSO	4.20
	6-Methoxy-2-naphthoic acid	1:1	Cocrystal	DMSO	4.30
	2-Methoxybenzoic acid	1:1	Cocrystal	DMSO	4.09
	Biphenyl carboxylic acid	1:1	Cocrystal	IPA	4.19
	Adipic acid	2:1	Cocrystal	IPA	4.43/5.41
	4-Methoxybenzoic acid	1:1	Cocrystal	DMSO	4.47
	4-Aminobenzoic acid	1:1	Cocrystal	IPA	4.65
	Sorbic acid	1:1	Cocrystal	IPA	4.75
	1-adamantane carboxylic acid	1:1	Cocrystal	IPA	4.80
	1,4 Benzene dicarboxylic acid	2:1	Cocrystal	DMSO	4.82
	2-Amino-4-fluorobenzoic acid	1:1	Cocrystal	IPA	4.88
	Cyclohexane carboxylic acid	1:1	Cocrystal	IPA	4.90
	Stearic acid	1:1	Cocrystal	IPA	4.90

Pyrimethanil *vs* 36 Carboxyilic Acids, *p*Ka range 1.27- 5.41

Interesting range 2.97 – 3.57 ~ 0.6

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Twin	2-Bromobenzoic acid	1:1	Salt	DMSO	2.85
	2-Chlorobenzoic acid	1:1	Cocrystal	IPA	2.97
$P2_1/c$	Pyrazinecarboxylic acid, Form 1	1:1	Cocrystal	DMSO	2.91
P-1	Pyrazinecarboxylic acid, Form 2	1:1	Cocrystal	DMSO	2.91
	DL-Tartaric acid:IPA	2:1:0.5	Salt/Cocrystal	IPA	2.96/4.24
	2,5 dihydroxybenzoic acid:DMSO	1:1:1	Salt/Solvate	DMSO	3.01
	2-Fluorobenzoic acid	1:1	Cocrystal	IPA	3.27
	2,4 dihydroxybenzoic acid	1:1	Salt	IPA	3.32
Iso with R	R/S-Mandelic acid	1:1	Salt	EtOAc	3.41
Iso with R/S	R-Mandelic acid	1:1	Salt/Cocrystal	EtOAc	3.41
	4-(Methylsulfonyl)benzoic acid	1:1	Intermediate	IPA	3.42
	4-Nitrobenzoic acid	1:1	Intermediate	DMSO	3.44
$P2_1/n$	3-Nitrobenzoic acid, Form 1	1:1	?	IPA	3.45
P-1	3-Nitrobenzoic acid, Form 2	1:1	Salt	IPA	3.45
	Thiazole-4-carboxylic acid	1:1	Salt	DMSO	3.57
	1-Naphthoic acid	1:1	Cocrystal	IPA	3.69

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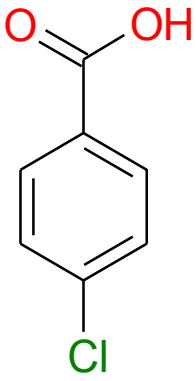
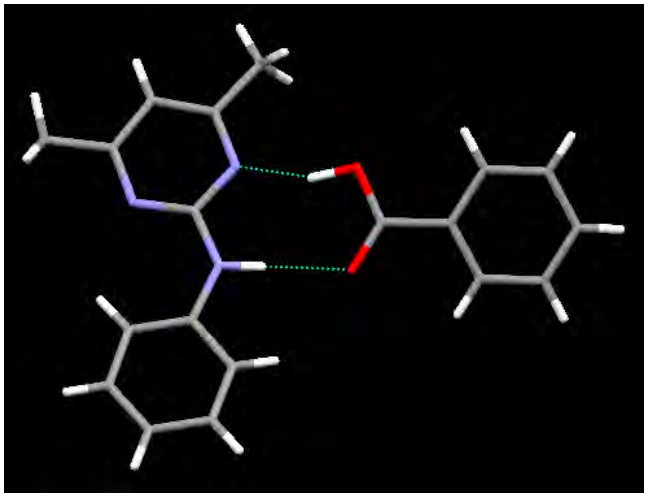
Cocrystal formation

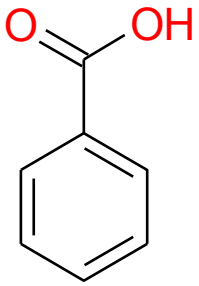
4-Cl Benzoic acid



*p*ka = 3.97



Benzoic acid



*p*ka = 4.21

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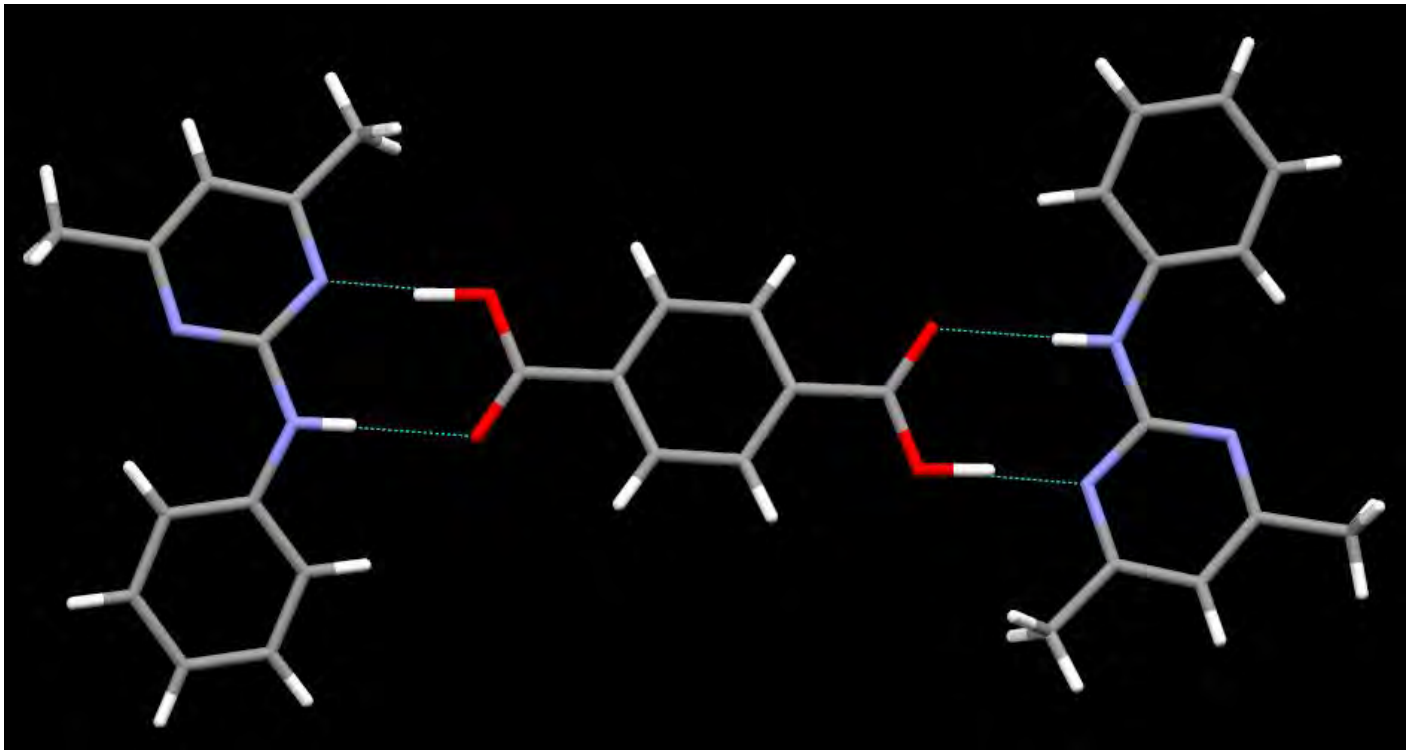
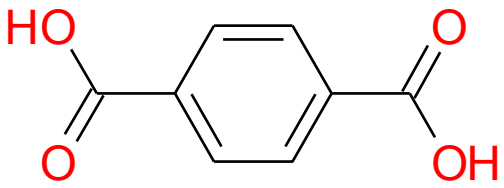
Cocrystal formation: 2:1 complexes





1,4-benzene dicarboxylic acid acid, *p*Ka = 4.82

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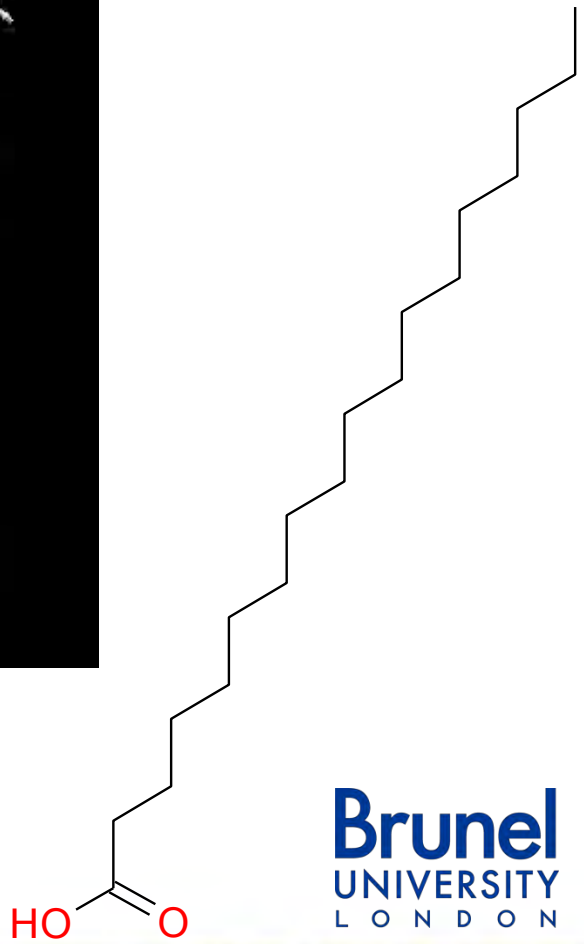
Cocrystal formation

Stearic acid

*p*ka = 4.90



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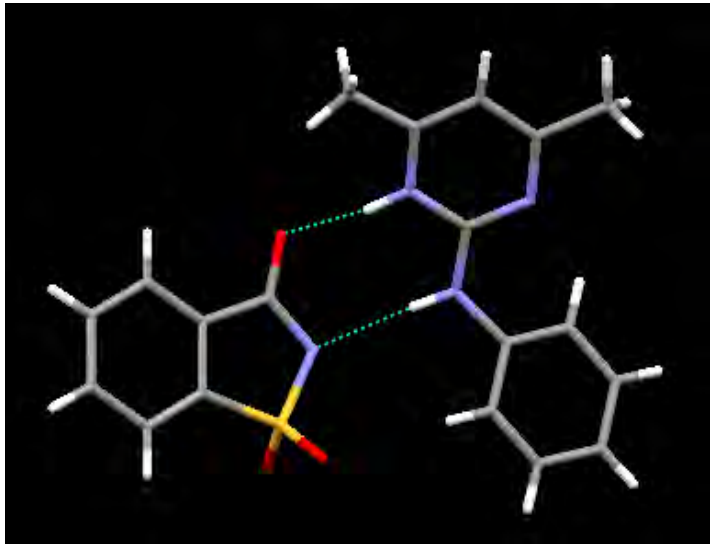
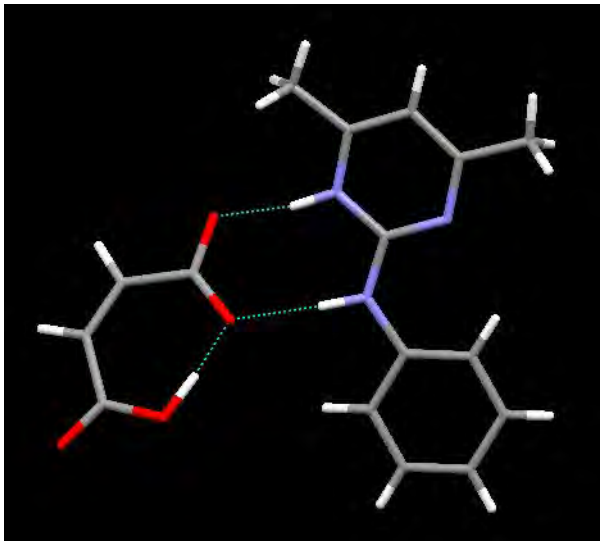
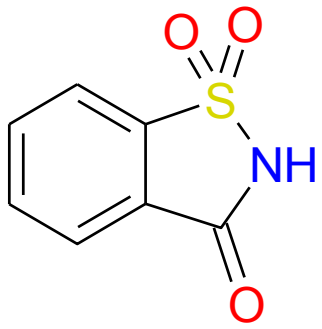
Salt formation



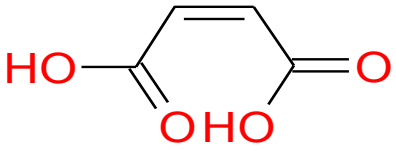
Saccharin



Maleic acid



*p*ka = 2.10



*p*ka = 1.92

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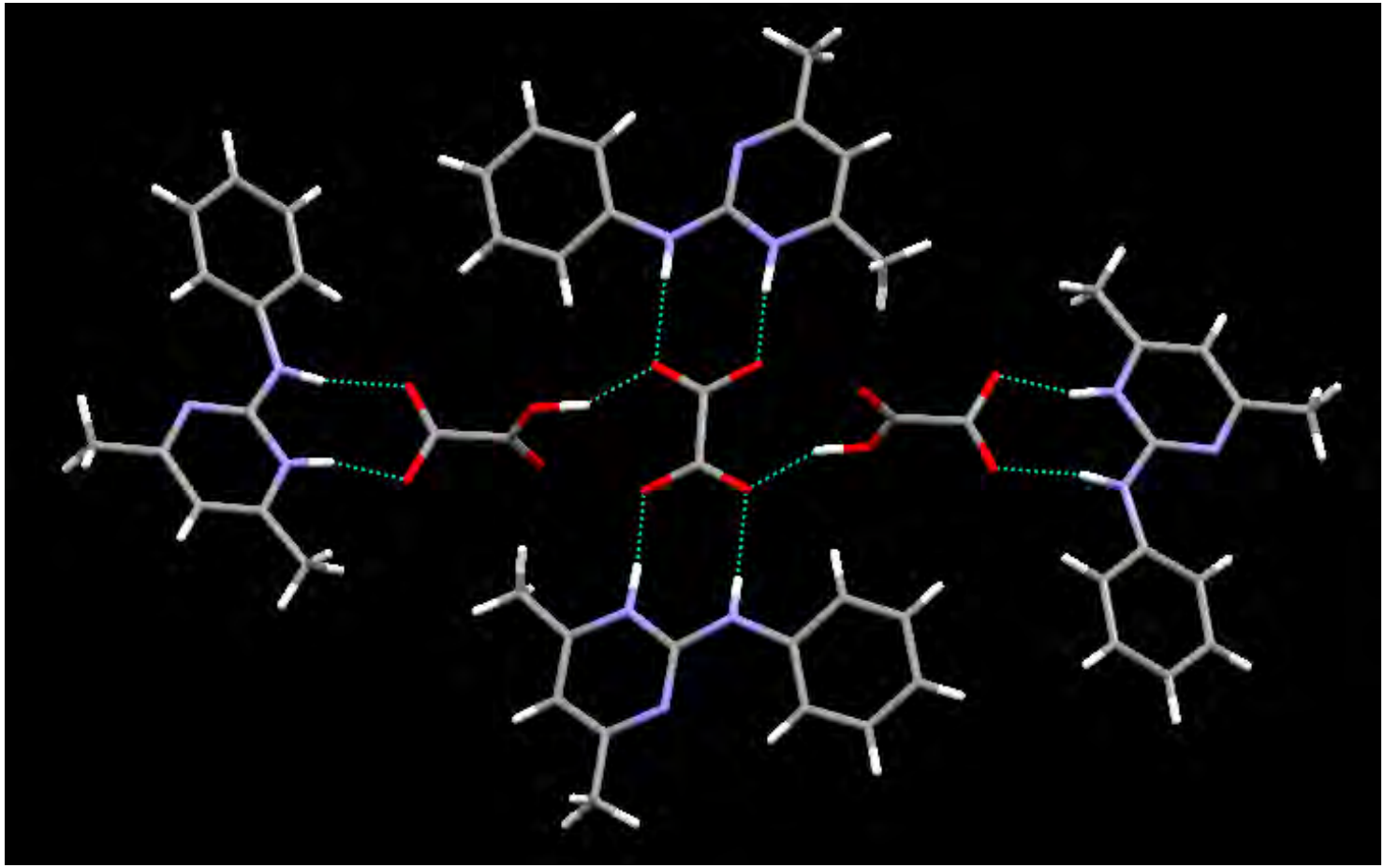
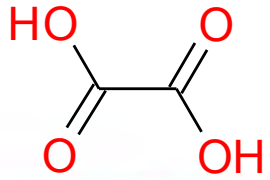
Salt formation





Oxalic acid, *p*Ka = 1.27

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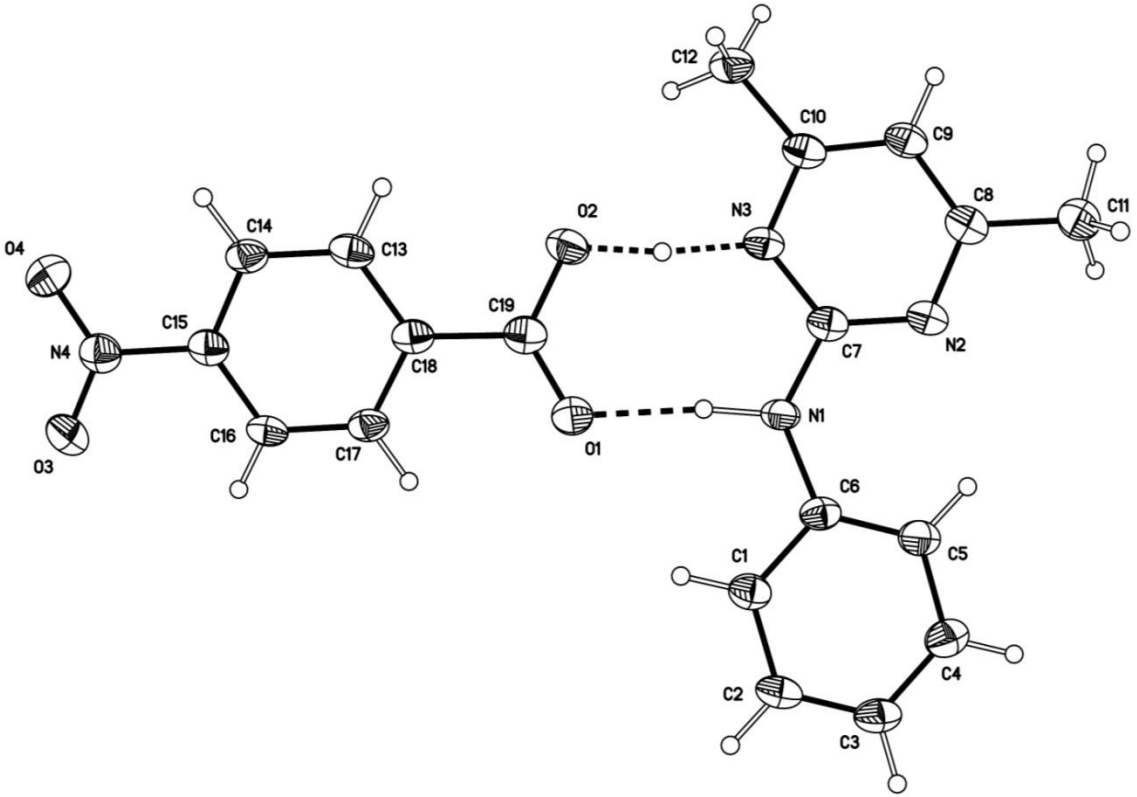
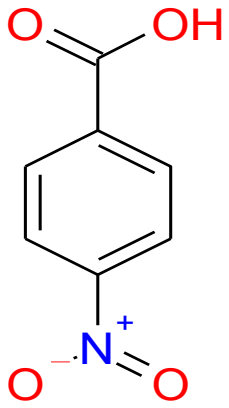
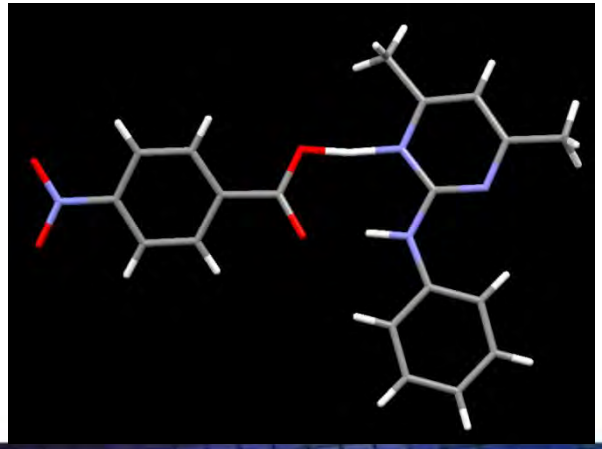
Control of salt formation: Intermediate



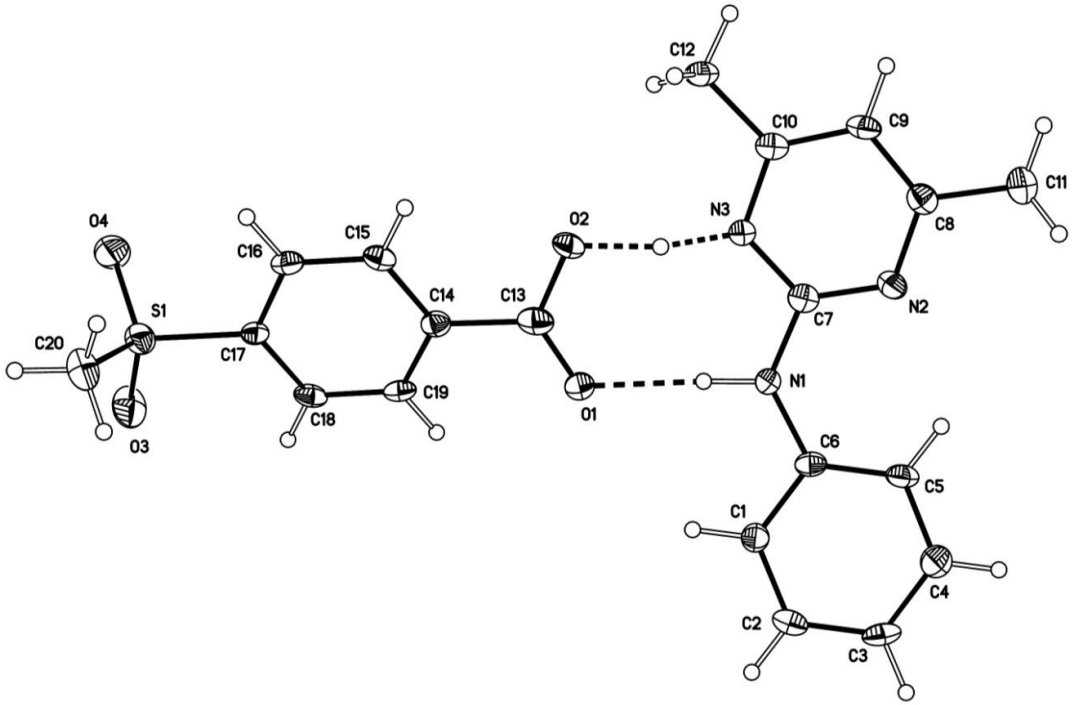
4-NO_2 Benzoic acid



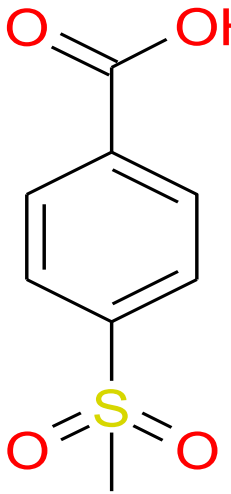
*p*ka = 3.44



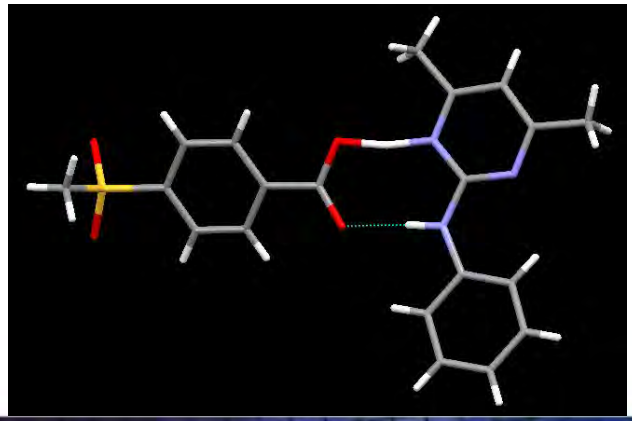
Control of salt formation: Intermediate



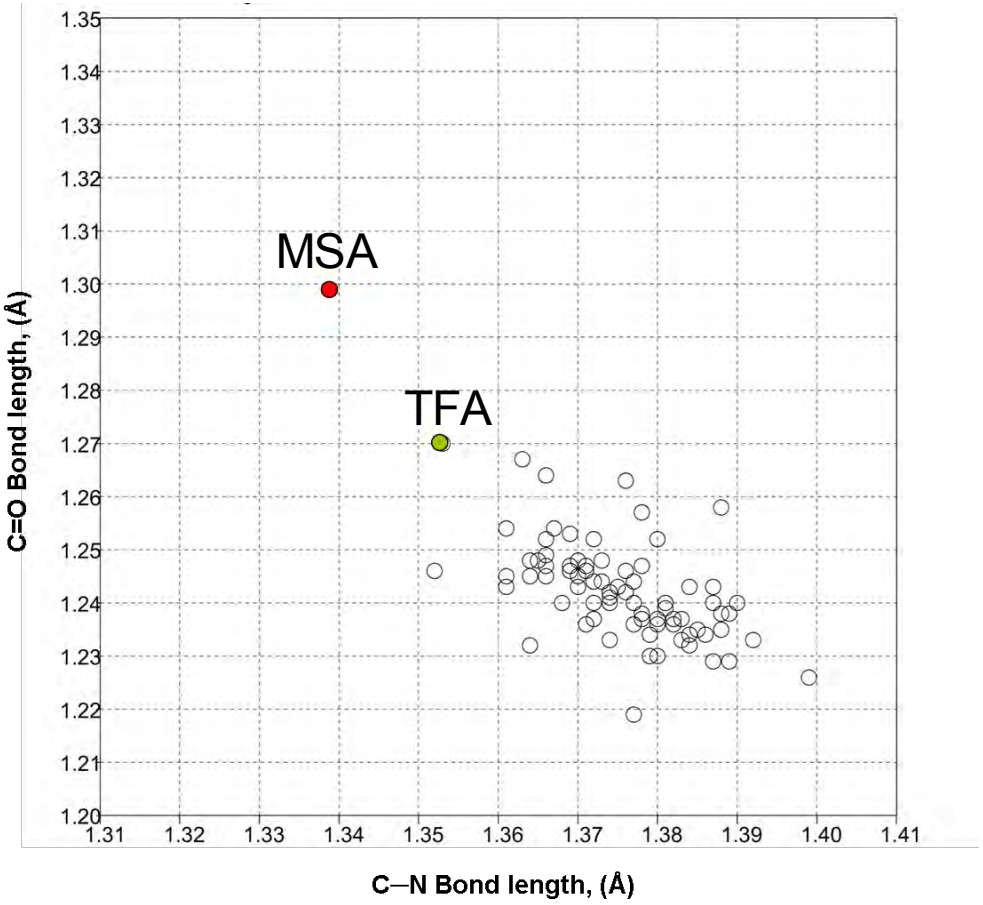
4-$MeSO_2$ Benzoic acid

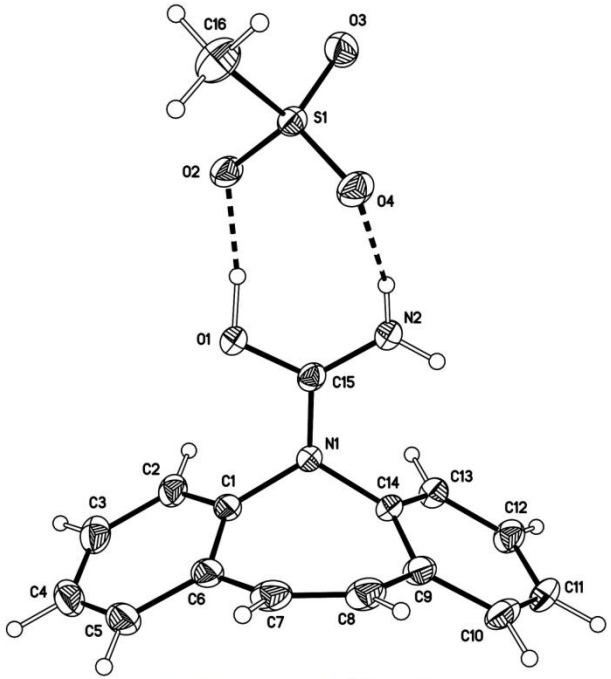


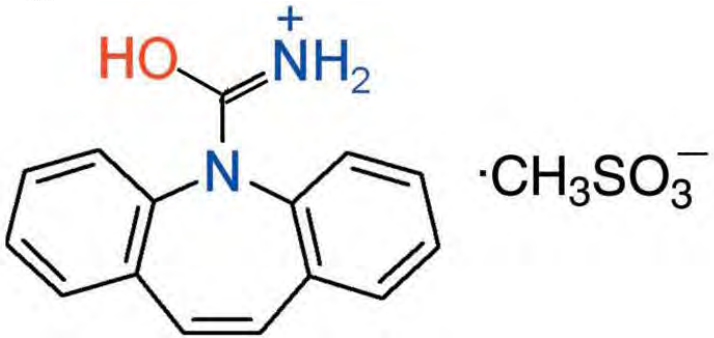
*p*ka = 3.42



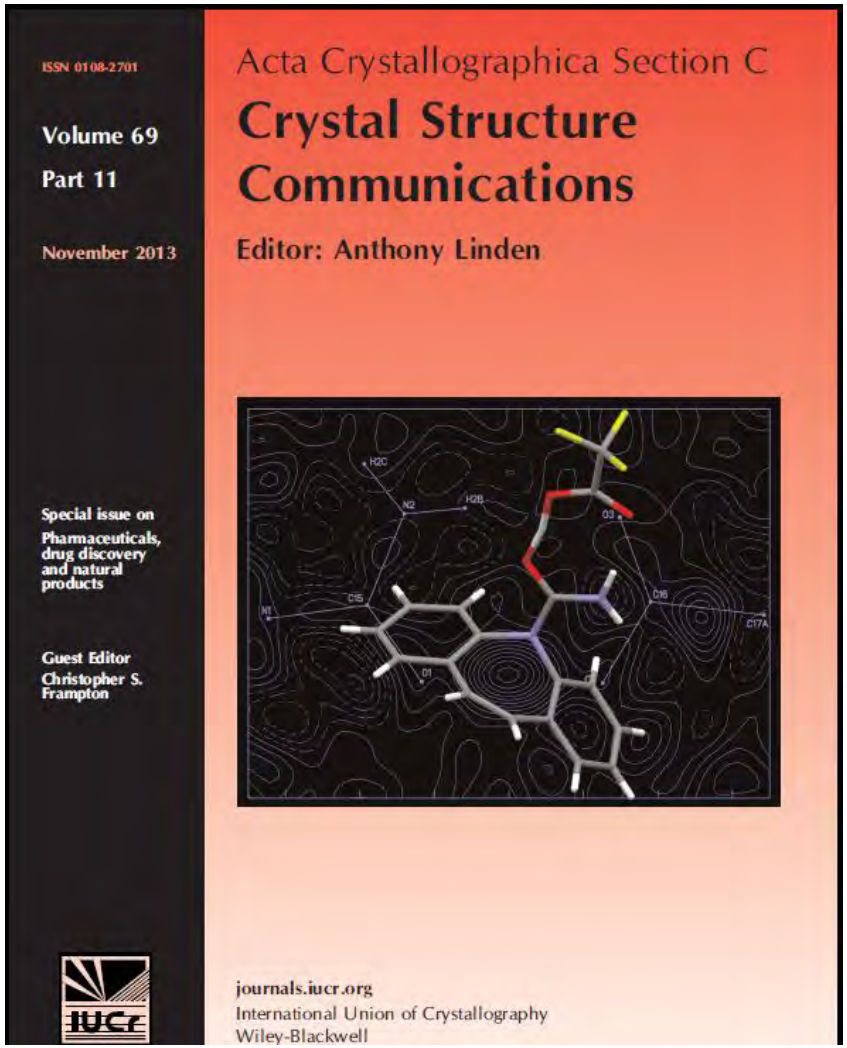
Carbamazepine Complexes with Methanesulfonic acid and trifluoroacetic acid







Carbamazepine and trifluoroacetic acid



pharmaceuticals and natural products

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Methanesulfonic acid salt forms of carbamazepine and 10,11-dihydro-carbamazepine

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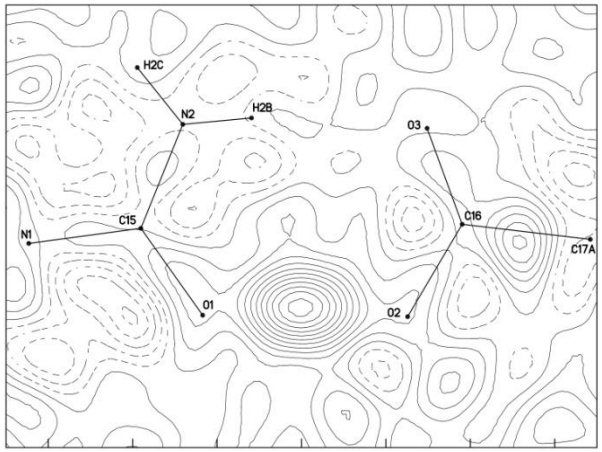

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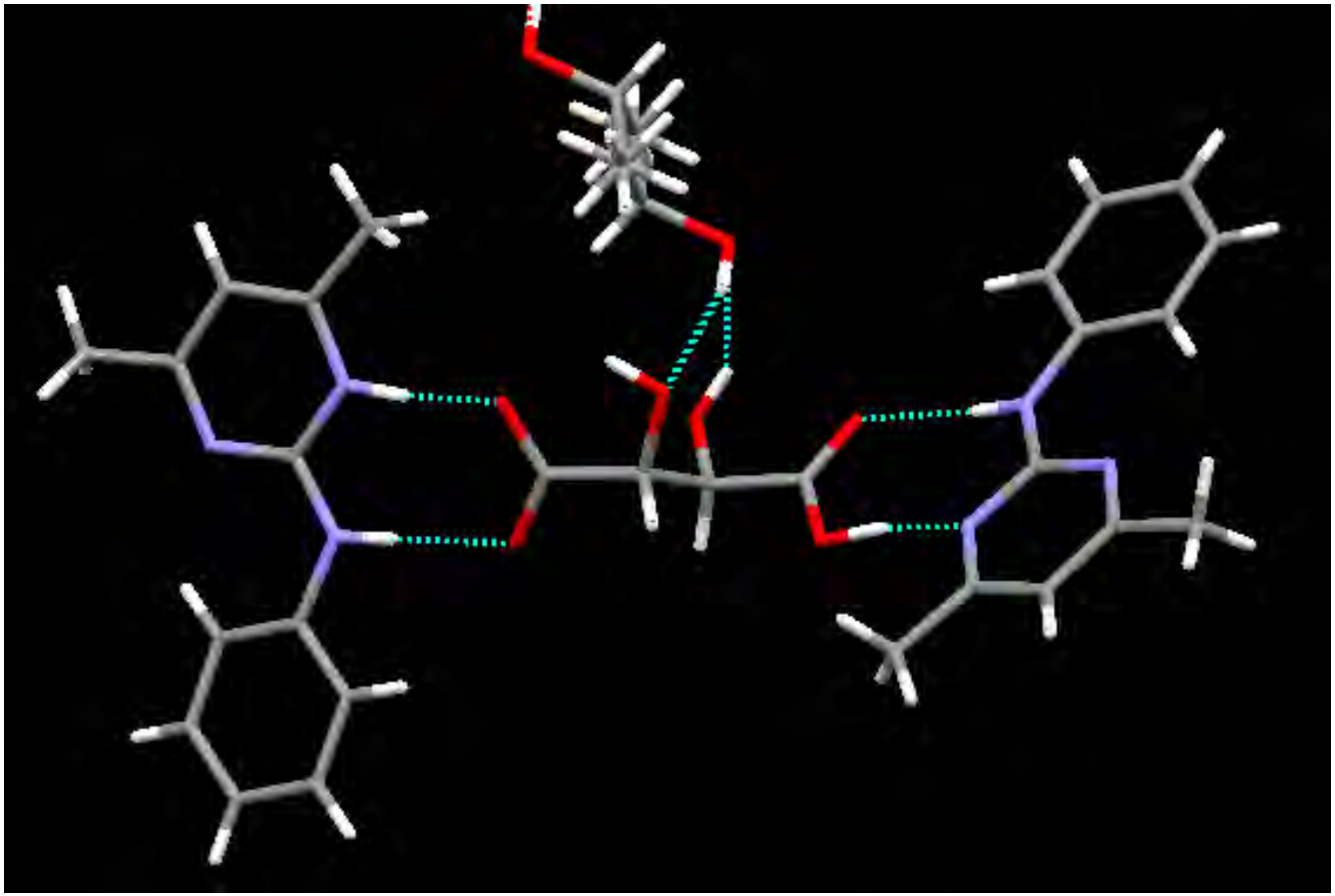
Salt/Cocrystal DL-Tartaric acid, 0.5IPA



*p*Ka = 2.94/4.24

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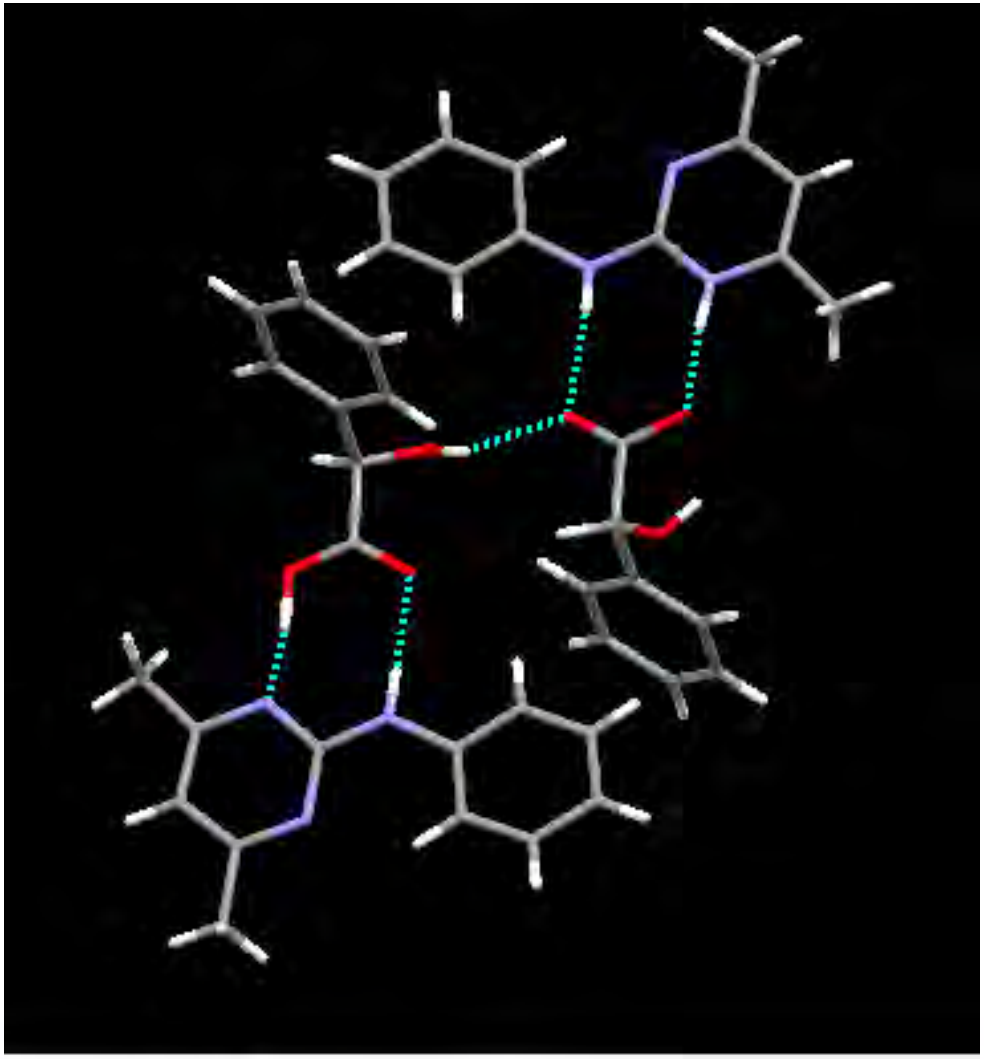
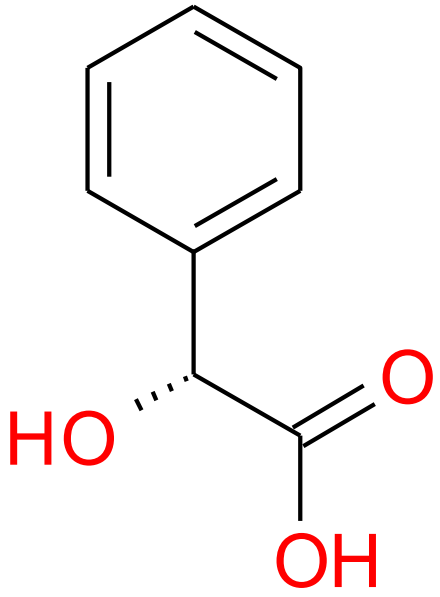
Salt and Cocrystal *R*-Mandelic acid





*p*Ka = 3.41

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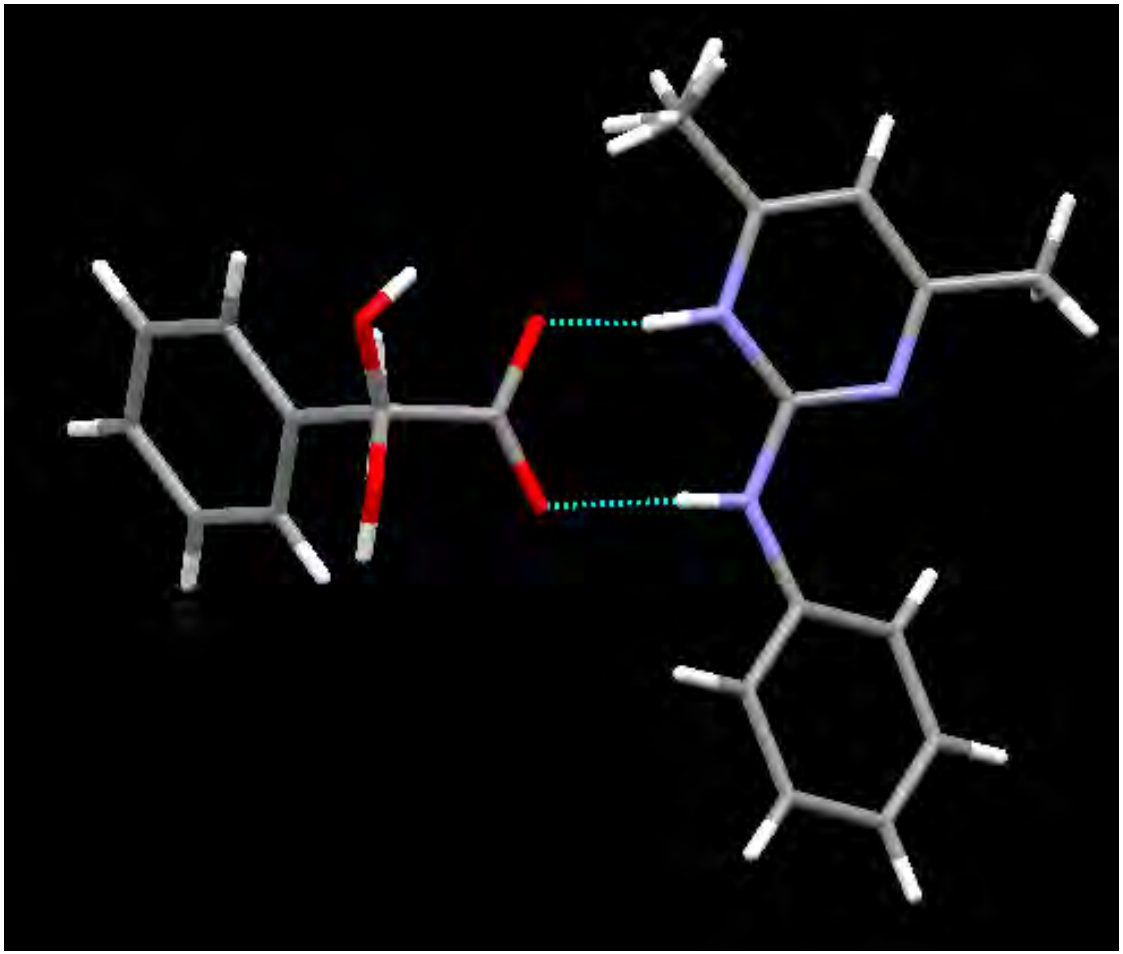
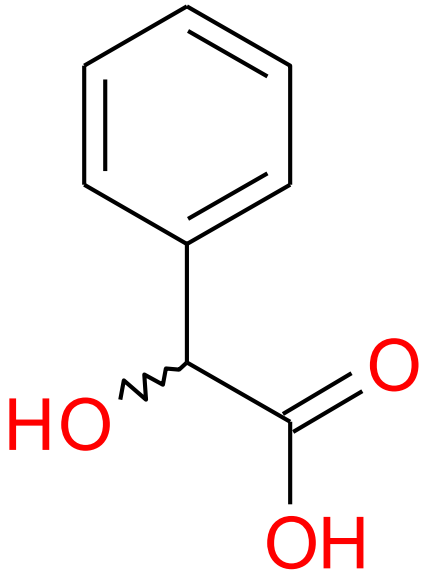
Salt *R,S*-Mandelic acid





*p*Ka = 3.41

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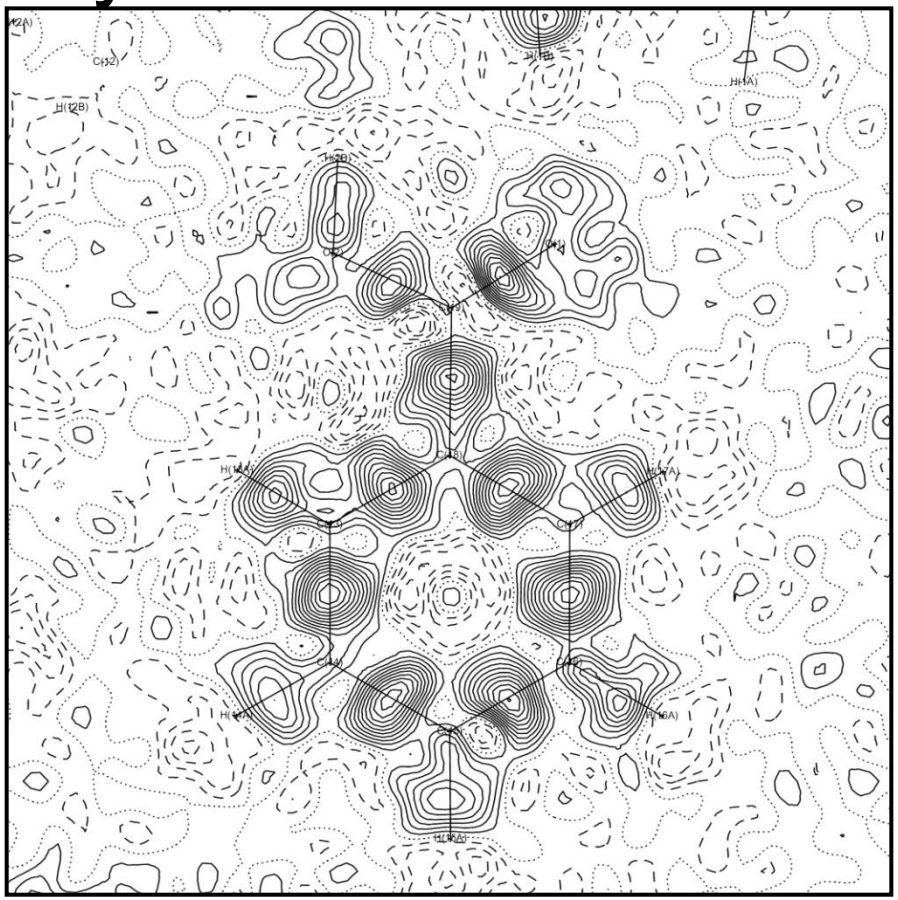
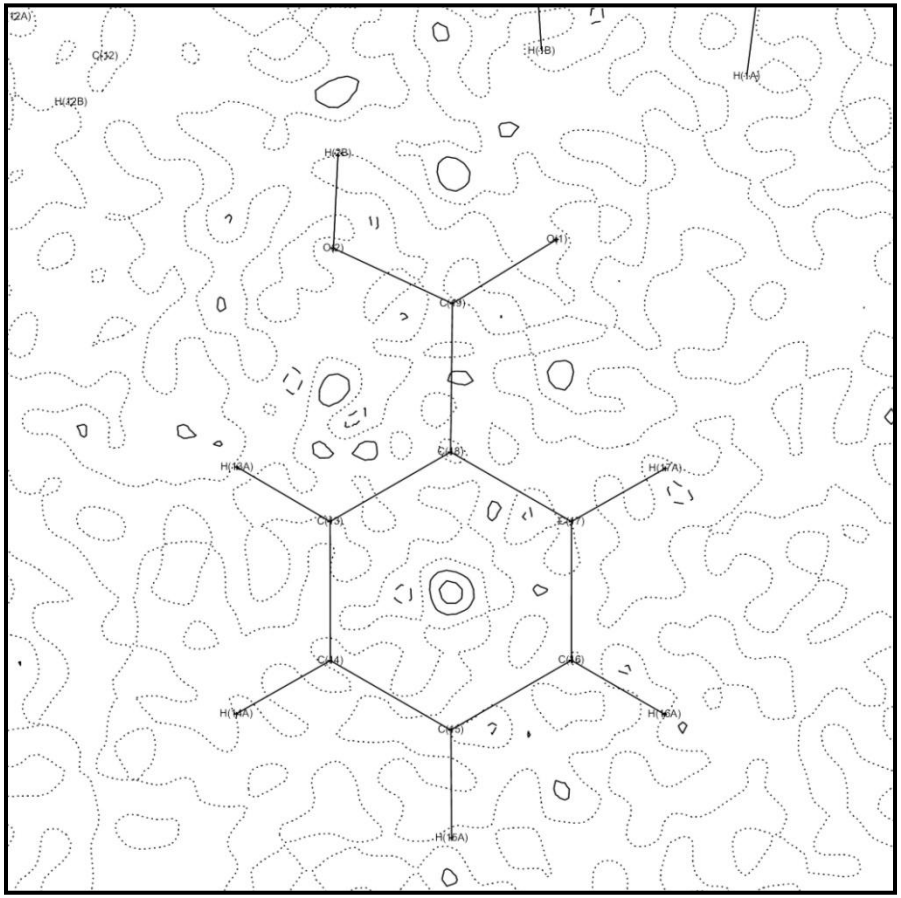
Pyrimethanil Benzoic acid





After spherical atom refinement

After multipole atom refinement

Contour levels 0.05 eÅ^{-3}

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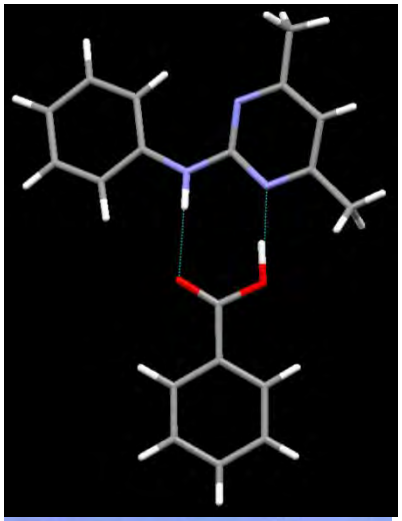
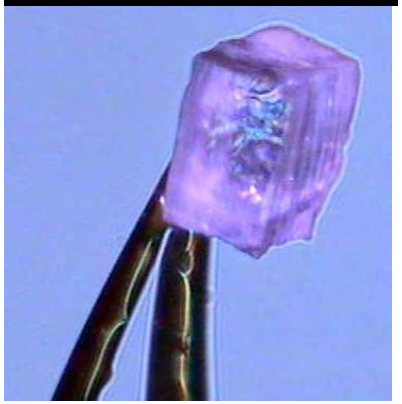
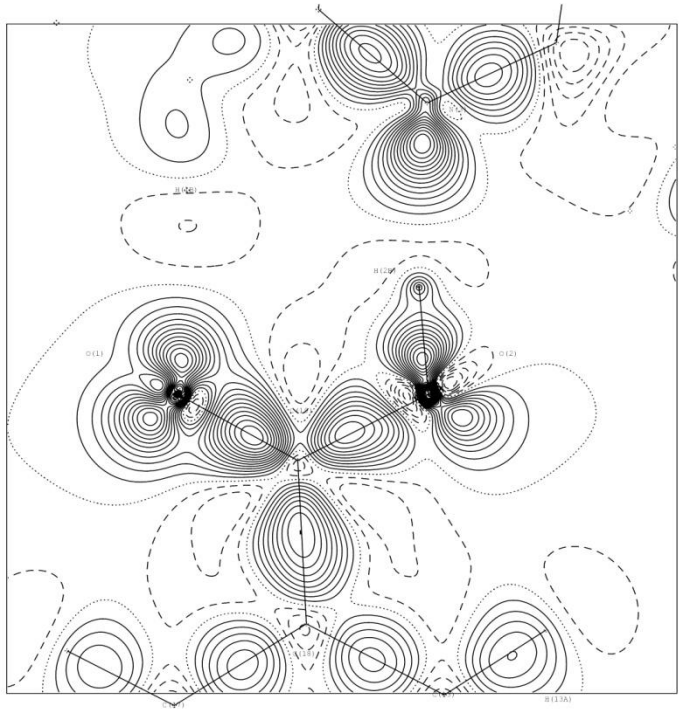
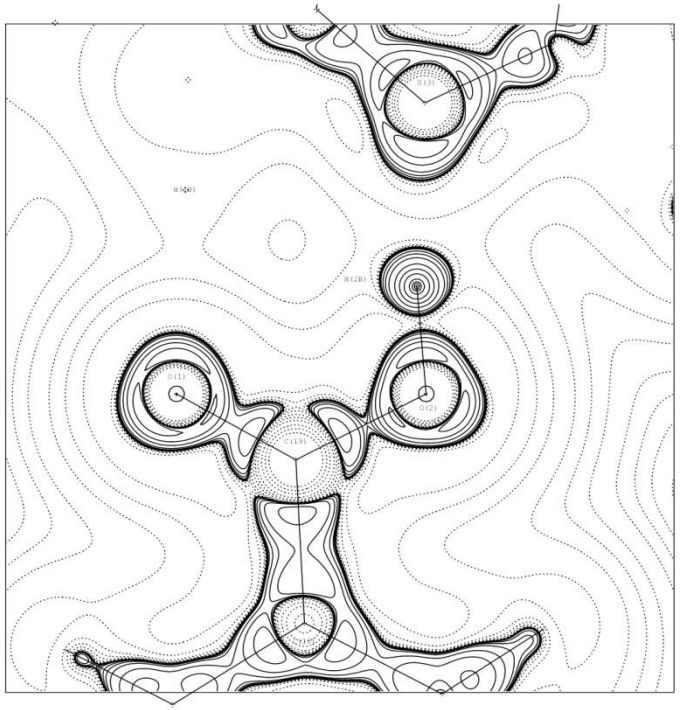
Charge density study

Form II Pyrimethanil:Benzoic acid, $P2_1/n$









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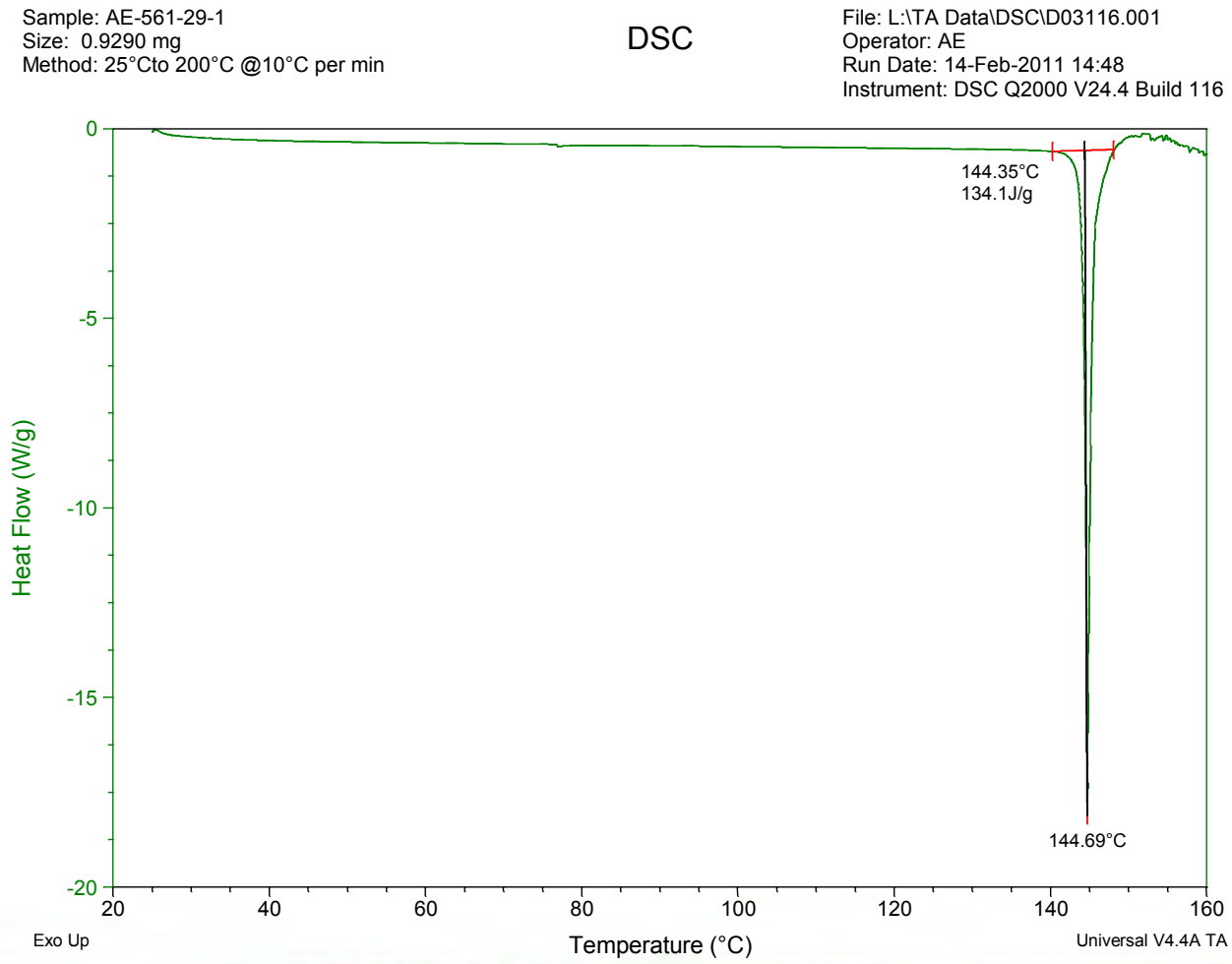
Change in physical properties
Pyrimethanil Maleic acid salt



Mpt. 144.7 ° C

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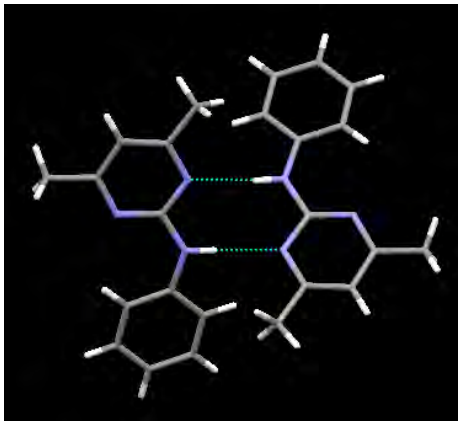
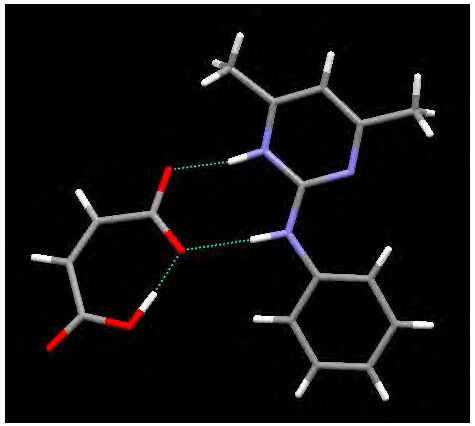
Cocrystal forms…prediction of property
Differing physical properties, melting point

96° C

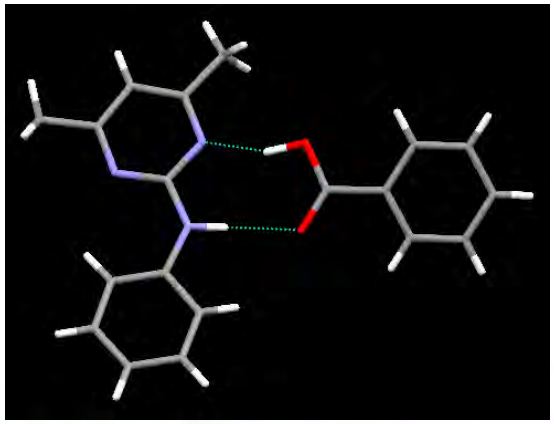


145° C 131° C



55° C 70° C

129° C 122° C



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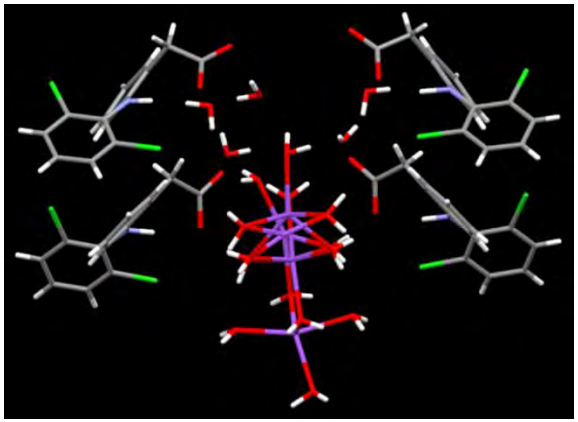
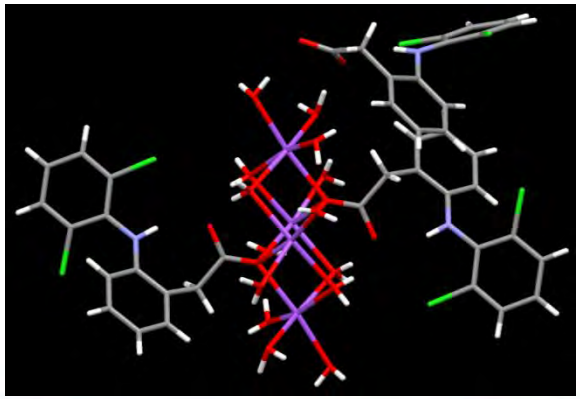
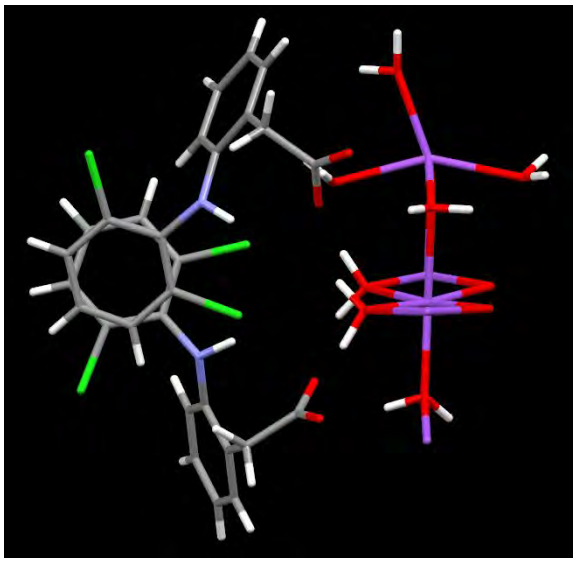
Cocrystals to control hygroscopicity

- Cocrystals have the potential to control problems with hygroscopic sodium/potassium salts by the stepwise replacement of water molecules by poly-alcohols, and glycols
- Na Diclofenac forms 3 badly behaved hydrates, 4.75, 3.50(I) and 3.50(II)







4.75 Structure is based on 4 moles of Na Diclofenac and 19 moles of water in the crystalline asymmetric unit

3.50 Structures are based on 2 moles of Na Diclofenac and 19 moles of water in the crystalline asymmetric unit

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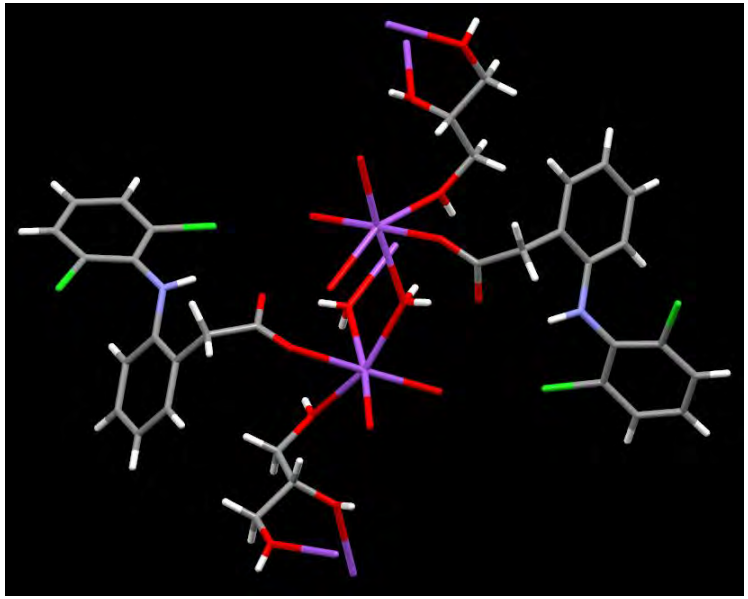
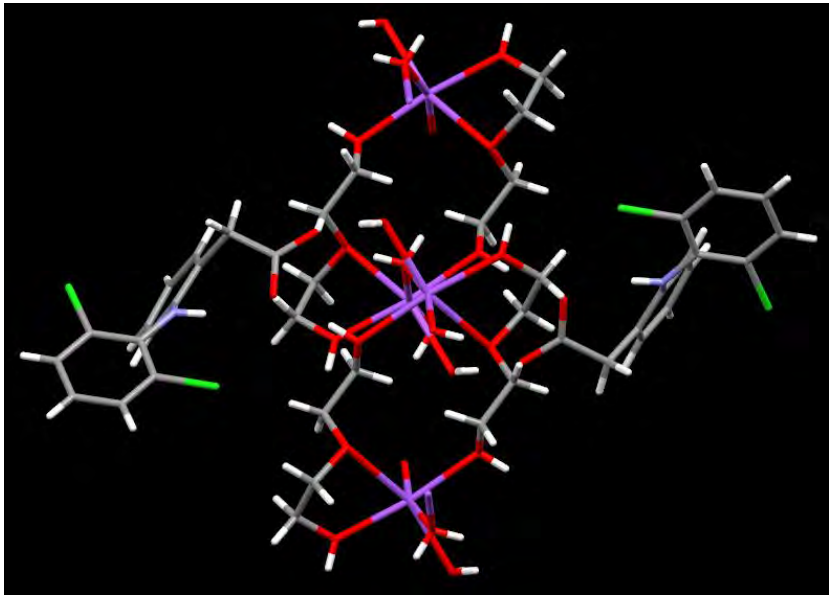
Cocrystals to control hygroscopicity

With the aim of eliminating water totally or at least to obtain a stable hygroscopicity profile



1:1:1 Na Diclofenac Glycerol hydrate



1:1:1.33 Na Diclofenac Diethylene glycol hydrate

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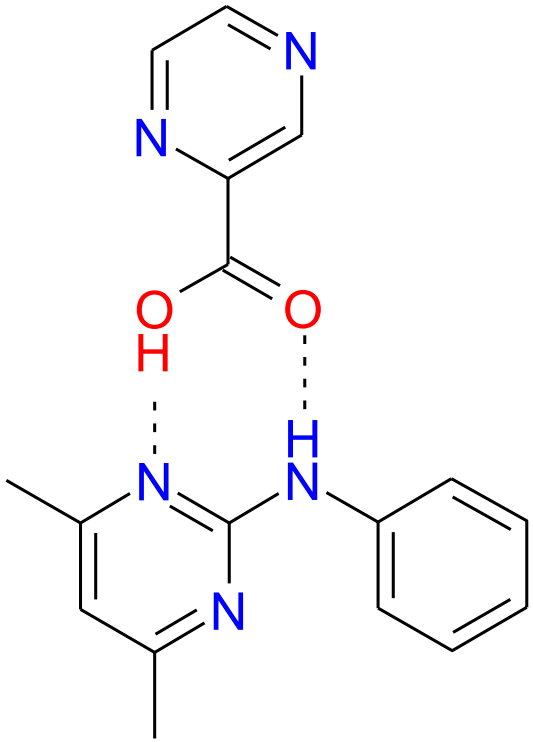
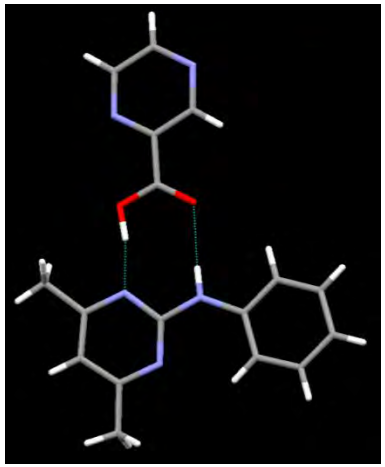
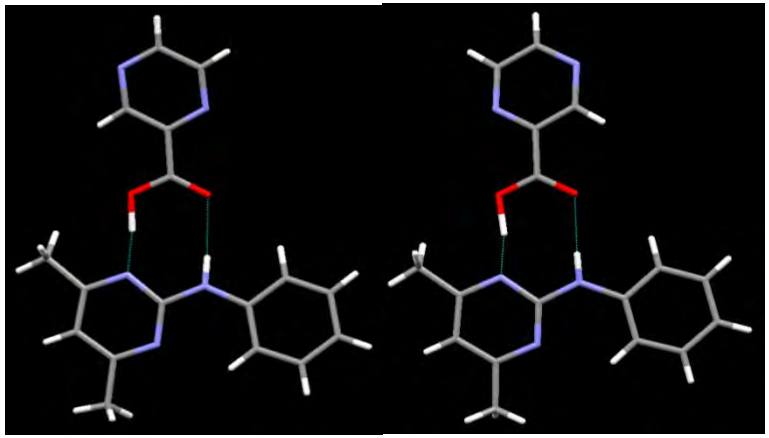
1:1 Pyrimethanil:Pyrazine carboxylic acid Conformational polymorphism





Monoclinic $P2_1/c$, $Z' = 1$

Form 1, $\rho = 1.413 g\ cm^{-3}$



Triclinic $P\text{-}1$, $Z' = 2$

Form 2, $\rho = 1.394 g\ cm^{-3}$

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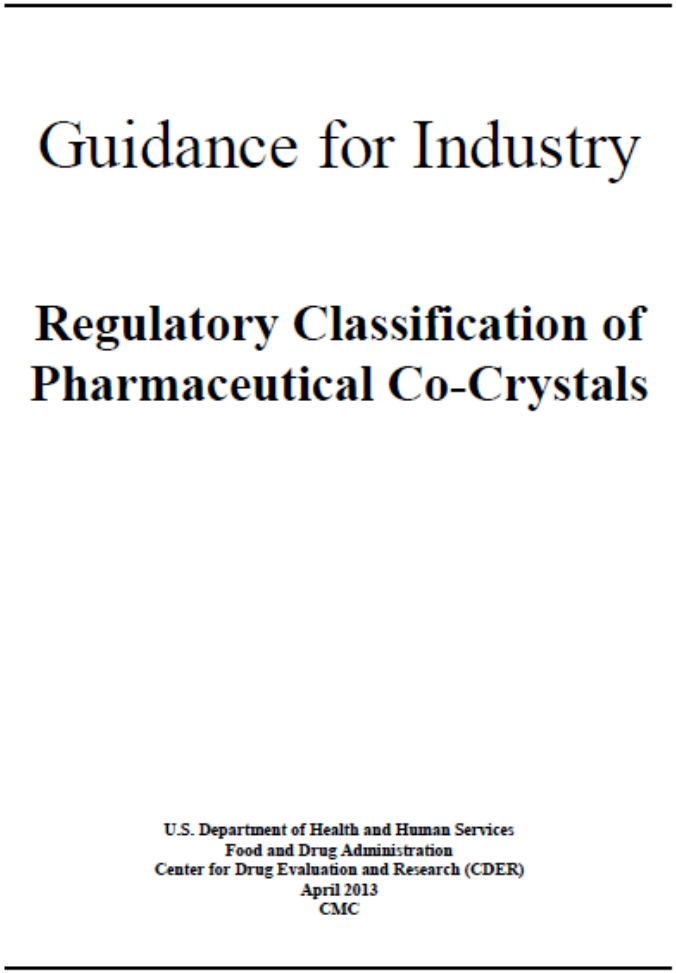
FDA Guidance Released April 2013



Guidance for Industry

Regulatory Classification of Pharmaceutical Co-Crystals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 2013
CMC

Full Guidance for Industry released April 2013

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Key Points from the FDA Guidance

Importance of specification

For NDAs and ANDAs containing or claiming to contain a co-crystal form, you should submit appropriate data that support the following:

- A conclusion that the component API with the excipient compounds in the co-crystal exist in their neutral states and interact via nonionic (versus ionic) interactions. You should consider the following to guide your decision:
    - Generally speaking, if the API and its excipient(s) have a ΔpKa (pKa (base) - pKa (acid)) ≥ 1, there will be substantial proton transfer resulting in ionization and formation of a salt as opposed to a co-crystal. On the other hand, if the API and its excipient(s) have a ΔpKa (pKa (base) - pKa (acid)) < 1, there will be less than substantial proton transfer. If this criterion is met, the active ingredient-excipient complex should be classified as a co-crystal.
    - If, however, you believe that the classification of the pharmaceutical solid as a salt or co-crystal is not predicated on these relative pKa values, then spectroscopic tools using various orthogonal approaches should be used to prove otherwise.
- Assurance that complete dissociation of the API from its excipient occurs prior to reaching the site of action for pharmacological activity.[8]

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- Alan Chorlton

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