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Crystallization from the Gas Phase: Morphology Control, Co-Crystal and Salt Formation

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Abstract

Multicomponent crystallisation is a widely studied technique in pharmaceutical chemistry to enhance physical properties of API's such as solubility, stability and bioavailability without chemically modifying the drug moiety itself. Methods to produce multicomponent crystals are varied with solution crystallisation being the predominant method. Crystal morphologies also influence an API's properties with needle shaped crystals dissolving slower and possess poor flow properties compared to a more equant block shape.

In this study, we develop a method for the production of multicomponent crystals via cosublimation. Samples are sublimed on a laboratory scale from both ends of standard 15 x 160 mm test tubes sealed under vacuum with two heaters were used to equalize the sublimation rates of the components. We have shown that a range of multicomponent pharmaceutical crystals can be prepared and that for the first time, tailor made additives can be used to obtain unprecedented morphology control of gas phase crystal growth. Salt formation was observed to occur during gas phase crystallisations in accordance with the pKa rule of 3 and modelling studies were carried out to understand the nature of proton transfer in these crystals in the absence of a solvent. In addition, we have shown that in addition to binary systems, ternary crystals can also be obtained via this technique

Gas Phase Crystal Growth

- Solvent crystallisation is the predominant method for crystal growth but sublimation can provide a green alternative. Previously in our group the growth of single component crystals have been studied and control of sublimation rates and polymorph selectivity have been achieved.^{1,2}
- Co-Crystal production from the gas phase has been previously reported for a limited number of examples in the literature using various methods.
- Growth of co-crystals is difficult as components can have widely different sublimation rates, therefore a system is needed to achieve similar rates.

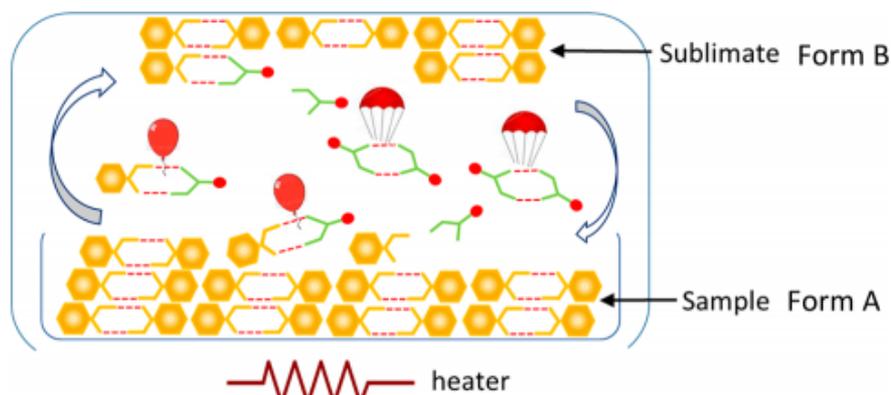


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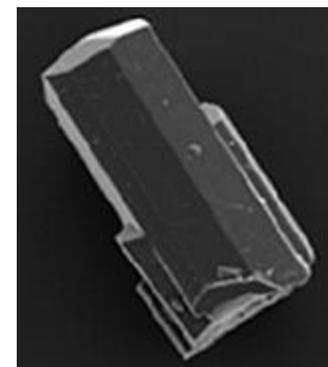
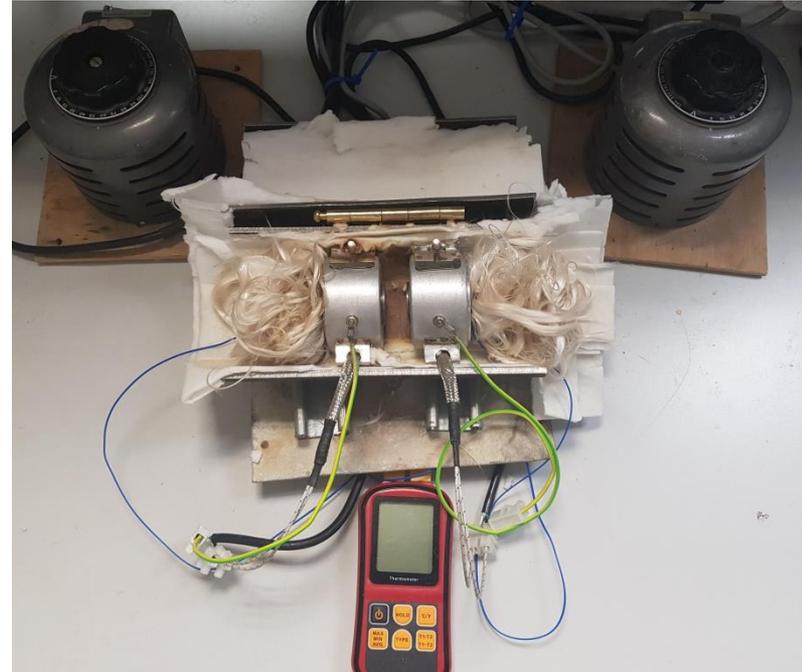


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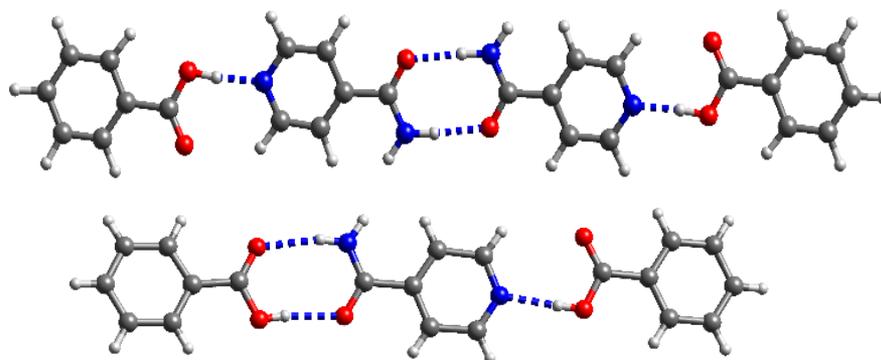
Gas Phase Crystal Growth

- Samples sublimed in 15 x 160mm test tubes sealed under vacuum
- 2 circular heaters controlled by variable voltage transformers
- Gun barrel pipe lined with calcium magnesium silicate insulation and glass wool
- 3 thermocouple digital thermometers measure temperature
- 2 compounds sublimed concurrently with equalised sublimation rates
- Diffraction quality pharmaceutical co-crystals can be obtained



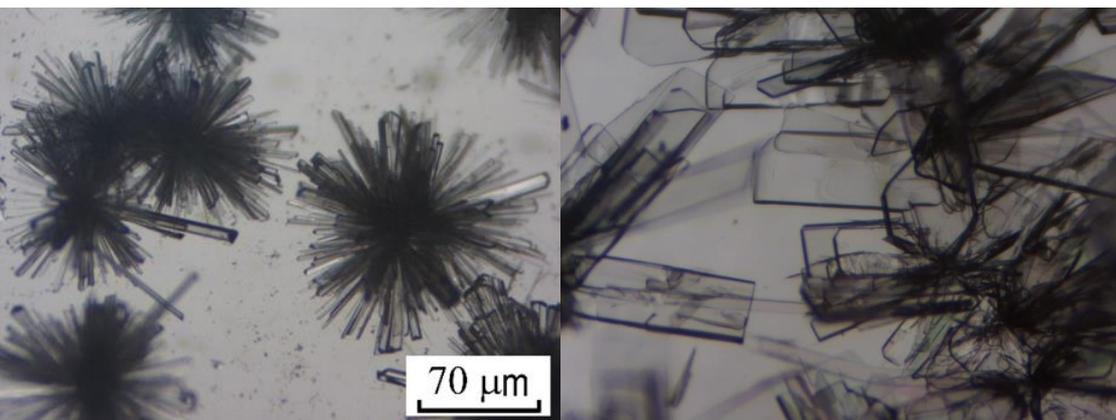
Benzoic acid and Isonicotinamide

- 1:1 and 2:1 cocrystals known to exist
- Structural characterisation only achieved for 1:1 system
- Previous 2:1 crystals reported were poorly diffracting/ twinned with no structural data available
- Successful growth of 1:1 (needles) and 2:1 (plates) cocrystals using co-sublimation



Molecular synthons in 1:1 structure (top) and 2:1 structure (bottom)

Experiment	Result	Temperatures(C)	Time (hrs)
Isonicotinamide/ Benzoic acid (1:1)	1:1 crystal (needles)	Ben – 116.7 INA- 151.5 Middle- 141	2
Isonicotinamide/ Benzoic acid (1:1) w/ 1% Benzamide	1:1 crystal (Blocks)	Ben- 116 INA- 161 Middle - 150	2
Isonicotinamide/Benzoic acid (2:1)	2:1 crystal	Ben – 100 INA- 165	2

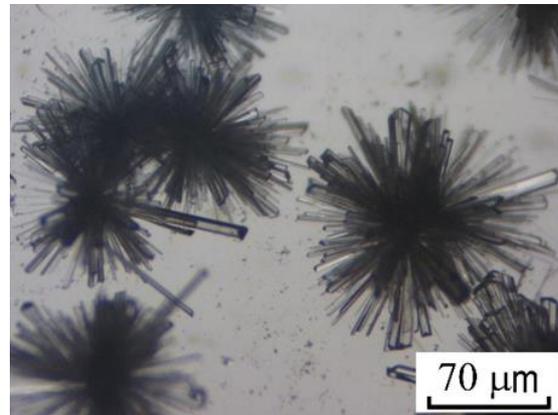


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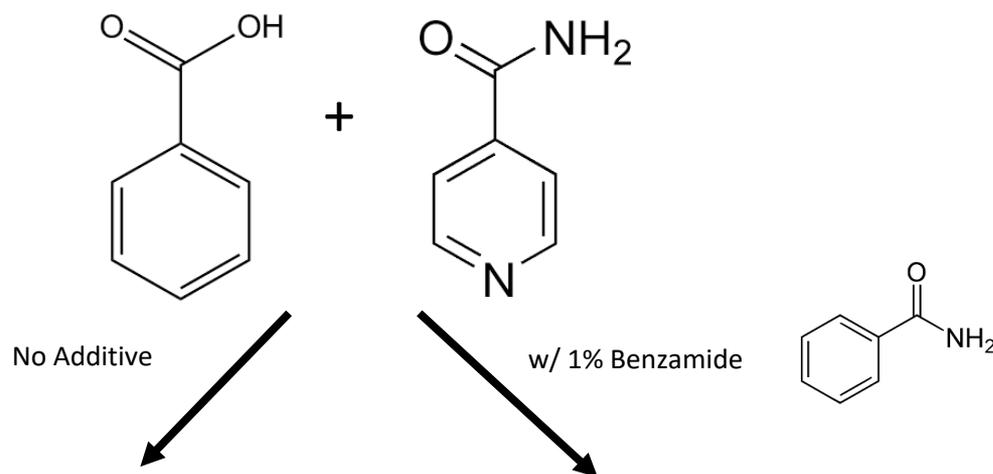
1) C.O'Malley, A.Erxleben, S.Kellehan, P. McArdle. *Chem. Commun.*, 2020, 56, 5657

Benzoic acid and Isonicotinamide – Morphology Control

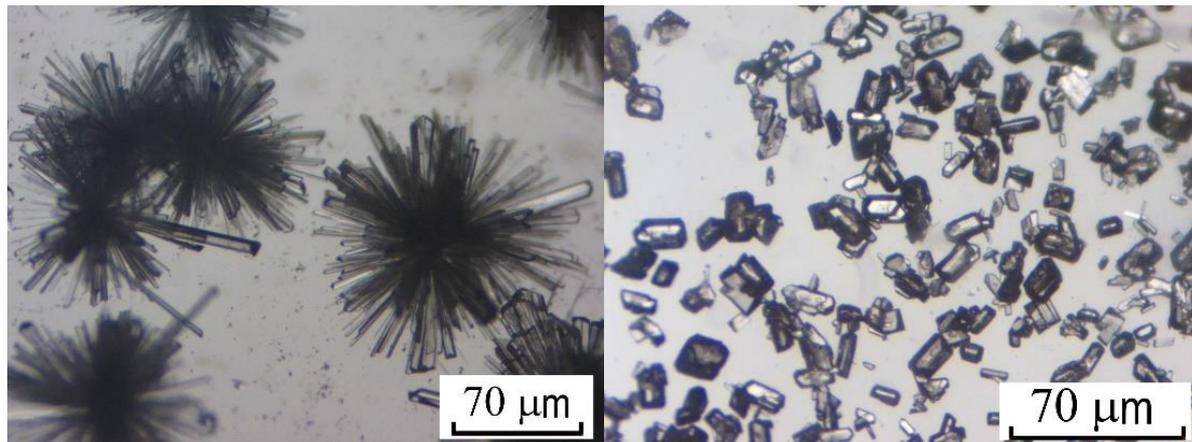
- Growth of 1:1 BZA/INA by sublimation produces needles growing in a sea urchin fashion.
- Can tailor made additives be used to control crystal growth to obtain morphology control?
- Theorised that additives with a similar size and shape to one of the cofomers but with a lower H-bonding capacity will introduce faults in stacked structures
- If stacking interactions dominate crystal growth this will alter morphology
- Such additives can have modest effects in solution crystallisation.



Benzoic acid and Isonicotinamide – Morphology Control

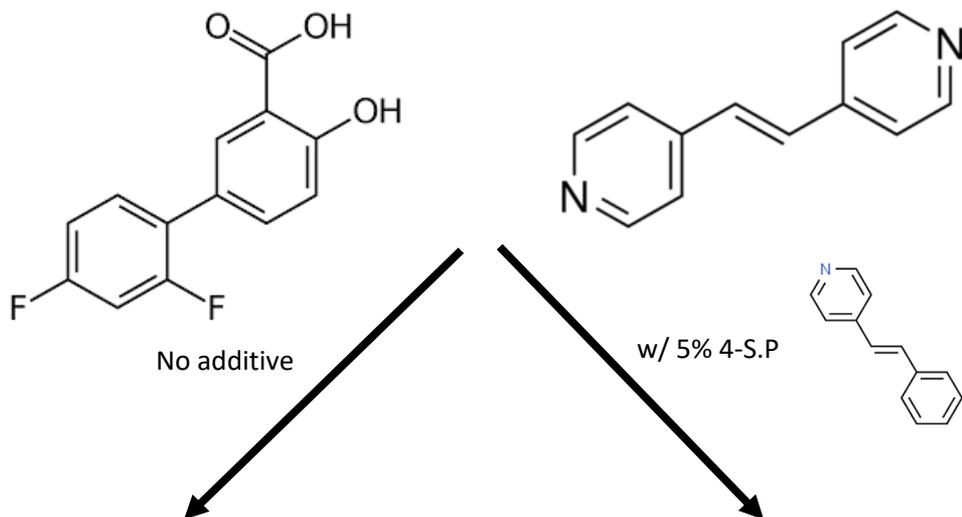


- Addition of 1% benzamide (BEN) during sublimation provided growth as block crystals
- Dramatic morphology change from the gas phase



Cocrystals of 1:1 BZA-INA grown by sublimation (Left) without additive and (Right) with 1% BEN. Figure reproduced with permission from ref. 1

Diffunisal and EBIPY- A Closer Look at Morphology Control



- Fine plates by sublimation
- Difficult to collect structural data for
- With the addition of 4-styrylpyridine the morphology was able to be converted to needles
- Needles showed much stronger diffraction than the plates

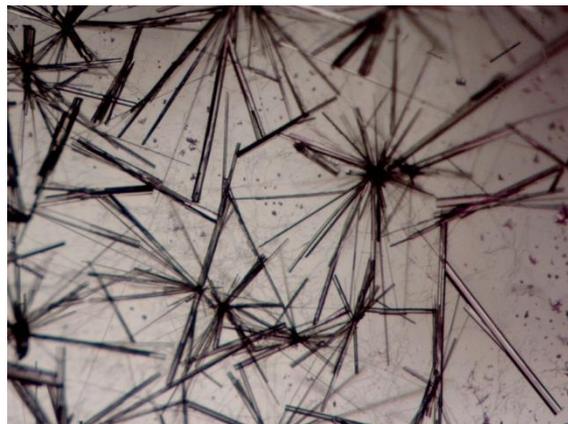
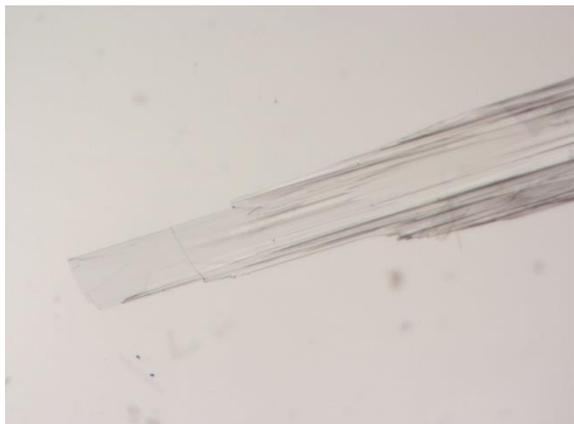


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Diffunional and EBIPY- How We Control Morphology

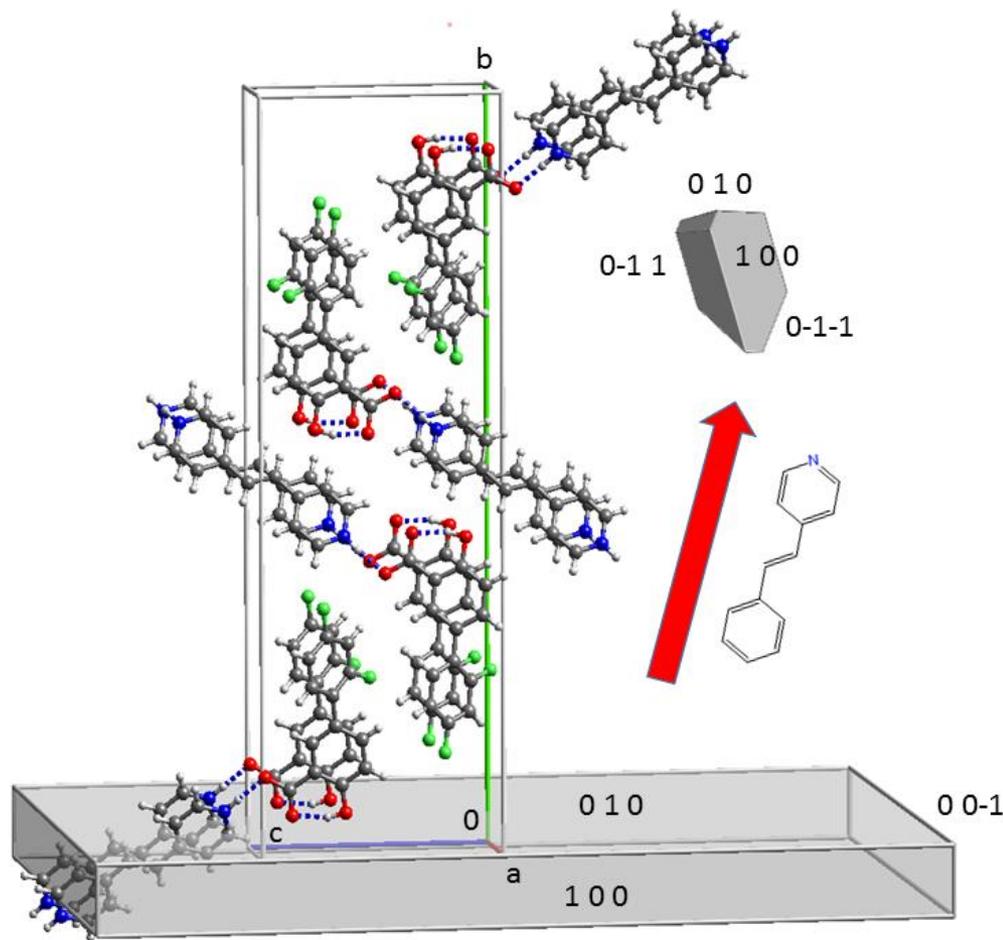


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- In the plate we see the predominant growth direction is along the c-axis with extended growth along a-axis and negligible growth along the b-axis.
- With the addition of 4-SP as an additive growth is halted along the c-axis with the predominant growth direction now becoming the a-axis.
- Along the c-axis Ebipy is orientated to provide hydrogen bond driven growth sites. Poisoning of these sites with 4-SP prevents further growth in this direction due to the lack of a hydrogen bond acceptor.
- The predominant growth face then becomes the a-axis, the molecular stacking direction.

Diflunisal and Isonicotinamide – An Extreme Case

- A 2:1 co-crystal of diflunisal and isonicotinamide has been well studied in the literature.
- Efforts to achieve a single crystal structure have been unsuccessful due to “cotton candy” like crystallisation behaviour.
- Sublimed in the presence of 10% benzamide, single crystals were able to be grown of sufficient quality for structure determination.
- Simulated XRPD pattern matches previously reported cocrystal.
- Additive was shown to suppress needle growth sufficiently to obtain single crystal structure in extreme cases.

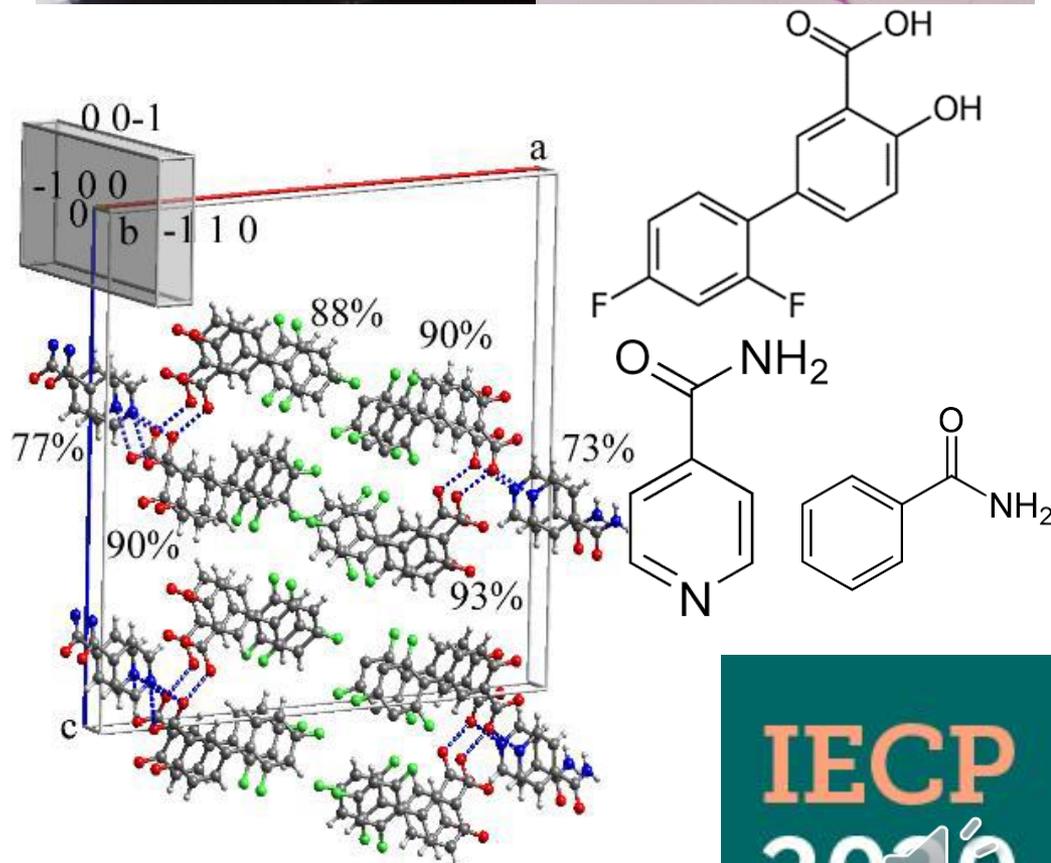
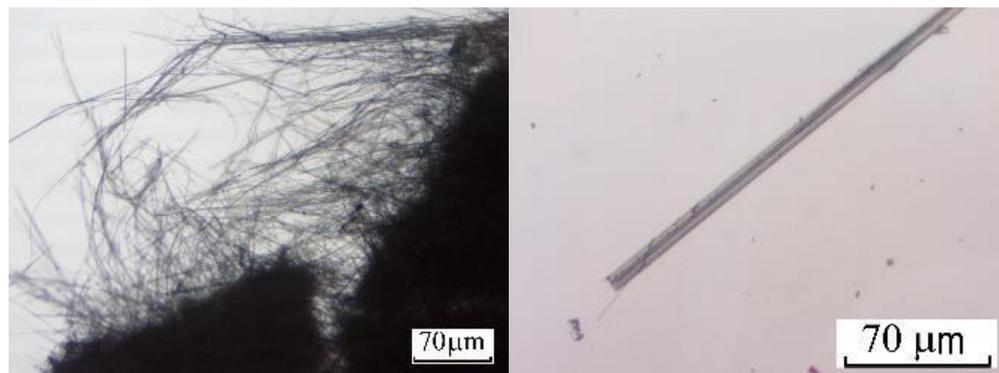


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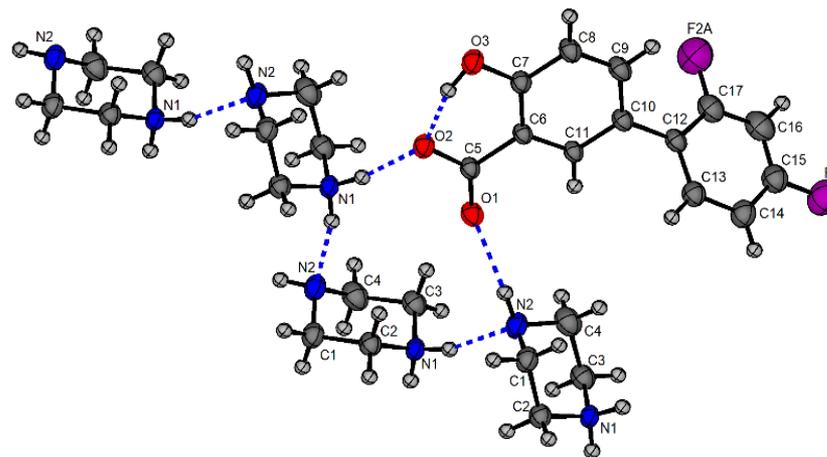
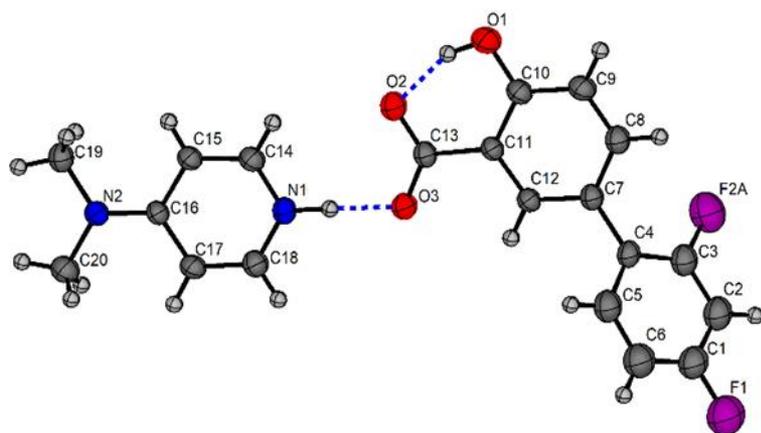
1) C.O'Malley, A.Erxleben, S.Kellehan, P. McArdle. *Chem. Commun.*, 2020, 56, 5657

Diflunisal Cocrystals and Organic Salts

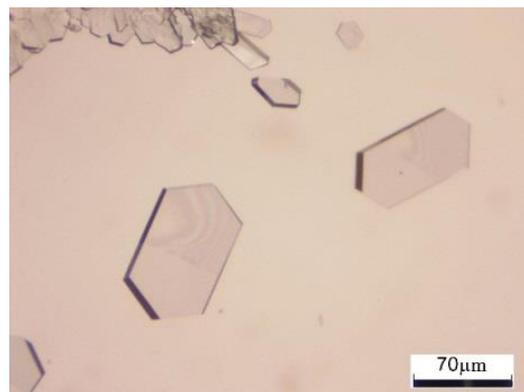
- Non-Steroidal Anti-Inflammatory
- BCS Class 2- low solubility
- Co-crystals of Diflunisal desired to address problems with bioavailability
- Previously the crystallisation behaviour of DIF with bipyridine derivatives has been studied from solution
- We were able to determine structures where previously no structures (Bipy) or solvates (Ebipy) were found.
- Proton transfer was observed.
- Salts are known to occur with a pK_a difference between cofomers >3 .
- This rule was developed from crystals grown from solution.
- We can show that the pK_a rule of 3 holds for multicomponent crystals grown from the gas phase as well.
- This raises the question, how does proton transfer take place in the absence of solvent?

Compound	pKa	Difference (Base-DIF)	Outcome
Diflunisal	2.94	0	-
BIPY	3.39	0.33	CoCrystal
Isonicotinamide	3.39	0.45	CoCrystal
4-Phenylpyridine	5.08	2.14	CoCrystal
EBipy	5.5	2.56	CoCrystal
PBipy	6.3	3.36	Salt
DMAP	9.7	6.76	Salt
Piperazine	9.83	6.89	Salt
4-Phenylpiperidine	10.2	7.26	Salt

Modelling Proton Transfer in the Gas Phase- DIF/DMAP and DIF/PIP



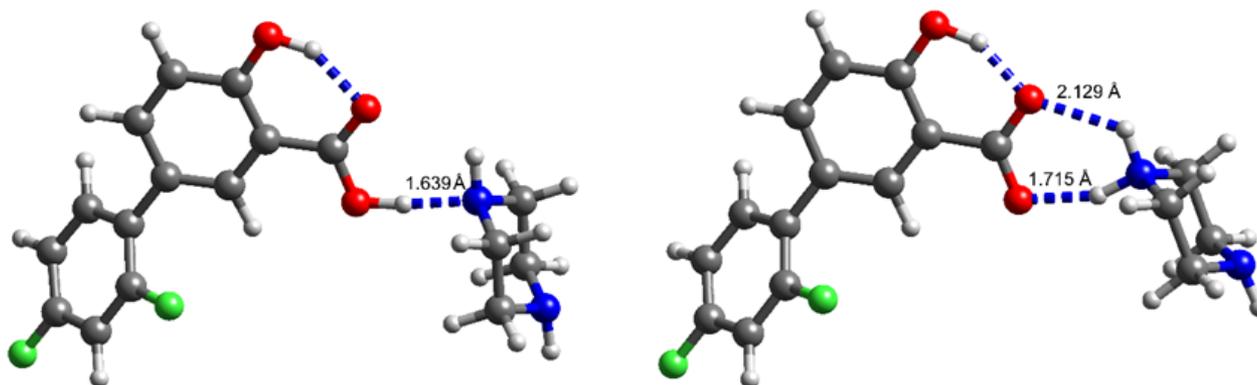
- Modelled 2 systems DIF/DMAP and DIF/PIP
- Both form 1:1 salts via sublimation
- DIF/DMAP only possesses one intramolecular H-bond in the asymmetric unit



Dif/DMAP by
sublimation

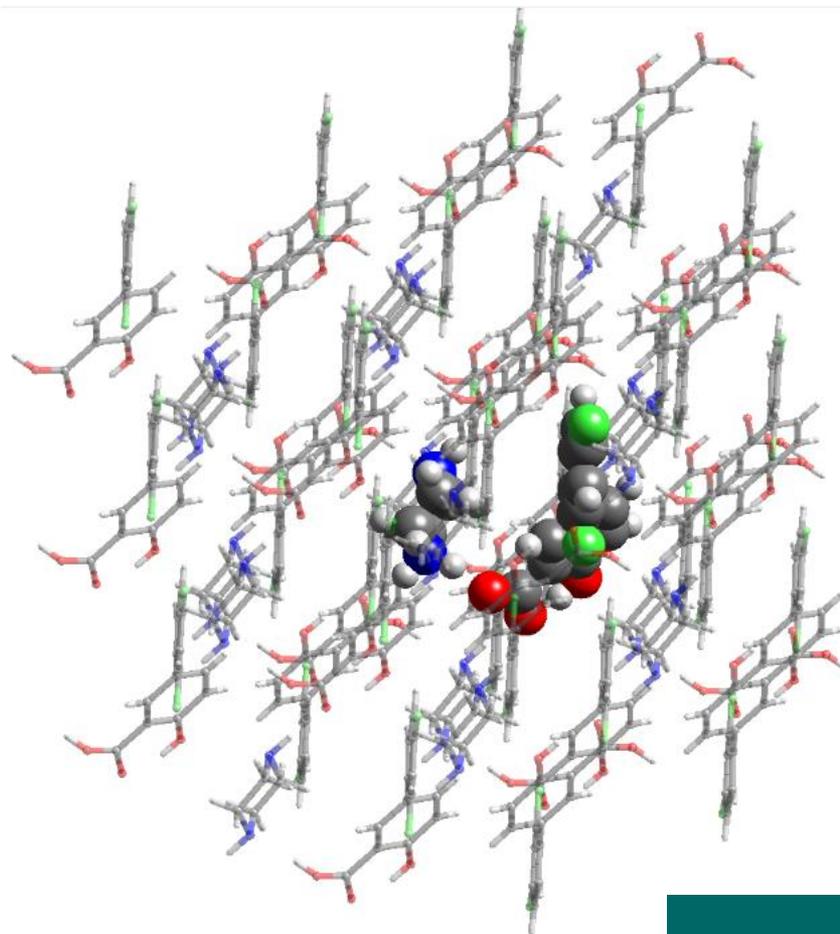
Modelling Proton Transfer in the Gas Phase

- Density functional calculations at WB97XD17 with basis set 6-31G(d,p) using Gaussian16
- Carried out on DIF-PIP and DIF-DMAP adducts
- Determined the energy difference between placing proton on O or N
- In both cases starting with the proton on the N, it moved back to the O
- However when optimizing with a methanol solvent simulation the proton moved onto N, only moving back to O when the simulation was removed



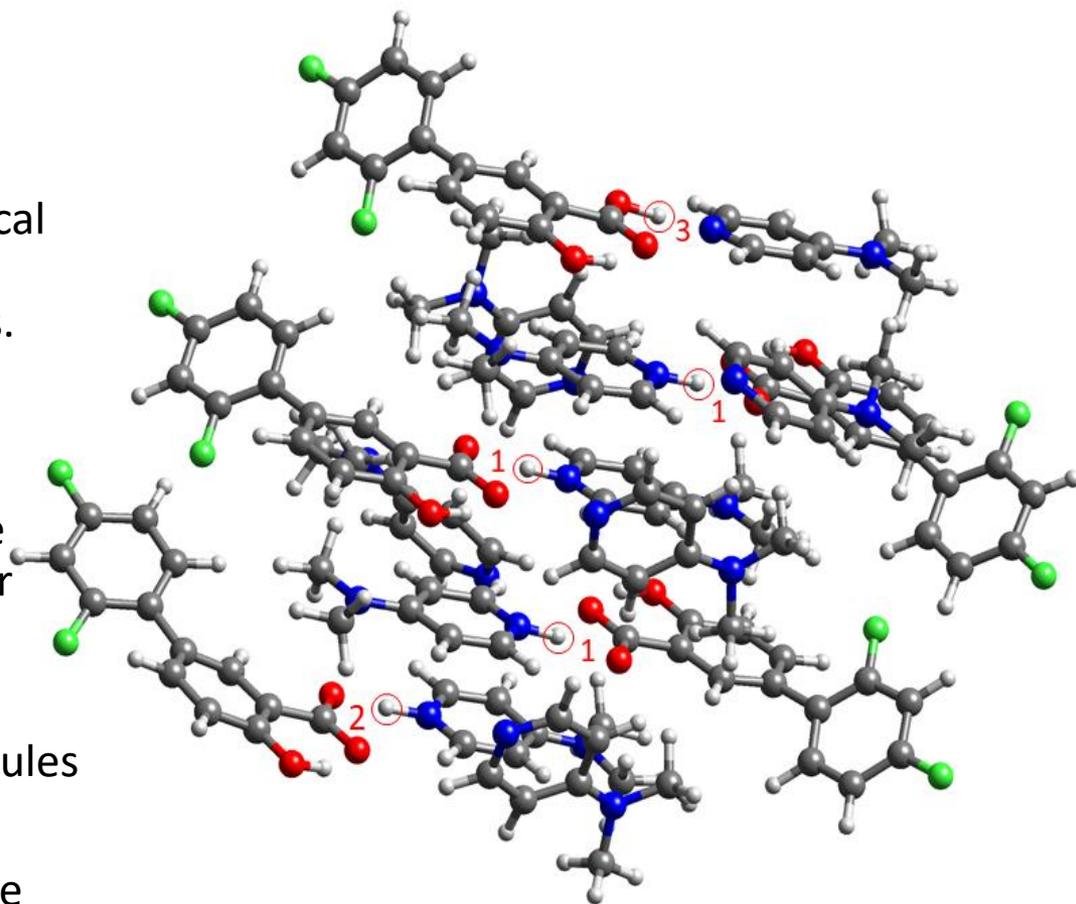
Simulating a Solvent Environment in the Gas Phase

- A molecule cluster was created to simulate a polar solvent environment.
- Cluster of 30 DIF and 20 PIP molecules generated from the P-1 structure of DIF-PIP where the proton had been moved back to the oxygen
- Refine just one specific DIF and adjacent PIP at the center of cluster using NOTATOMS keyword in Gaussian16
- Proton transfers to N
- Regarding proton transfer, the environment around an optimised pair of molecules can emulate MeOH



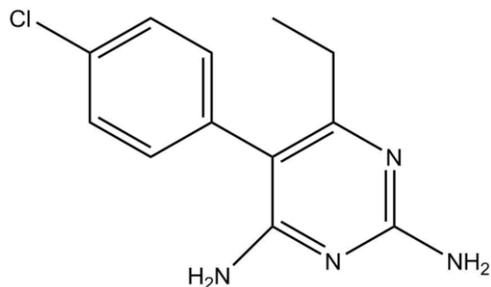
Why Proton Transfer Occurs

- It has been estimated that in a homogenous solution, the critical prenucleation cluster size is between 20 and 100 molecules.
- Sub critical cluster species are reversible.
- Looking at the lower end of the estimated prenucleation cluster size
- Cluster of DIF-DMAP with 5 DIF molecules and 10 DMAP molecules
- 3 DIF protons inside the cluster moving to nitrogen first and one surface DIF moving later

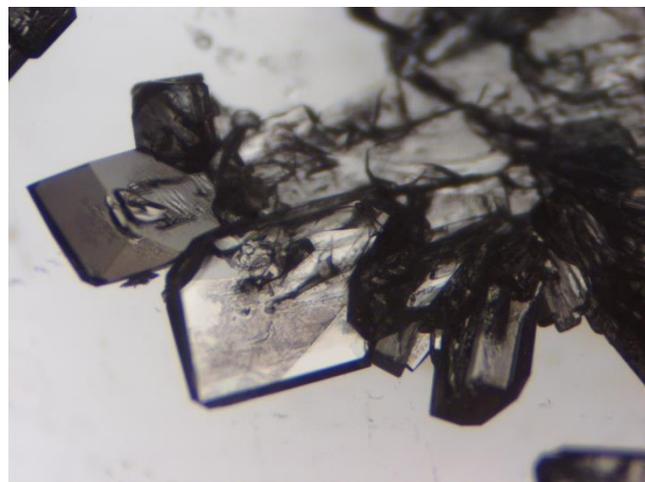


Co-Sublimation with Pyrimethamine

- Solution crystallisation studies have been carried out on pyrimethamine
- Borderline BCS Class III- Low permeability with quite low solubility
- Pyrimethamine is used to treat toxoplasmosis, cystoisoporiasis and parasitic pneumonia in HIV/AIDS
- A range of crystal structures were identified via co-sublimation that were unavailable from solution
 - Saccharin provided a different polymorph than that of solution
 - Nicotinic acid only available as solvate from solution
 - Barbituric acid and glutarimide cocrystal unable to be obtained from solution



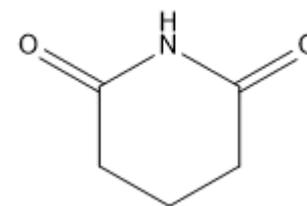
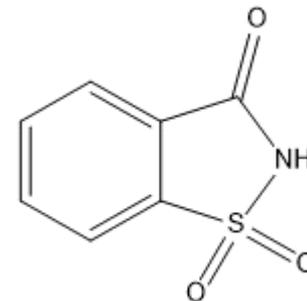
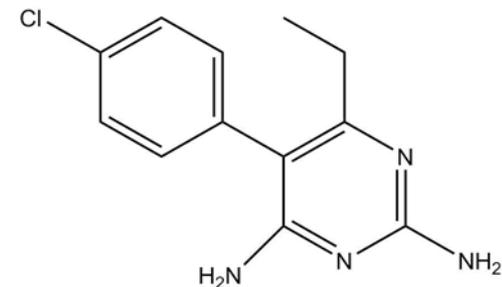
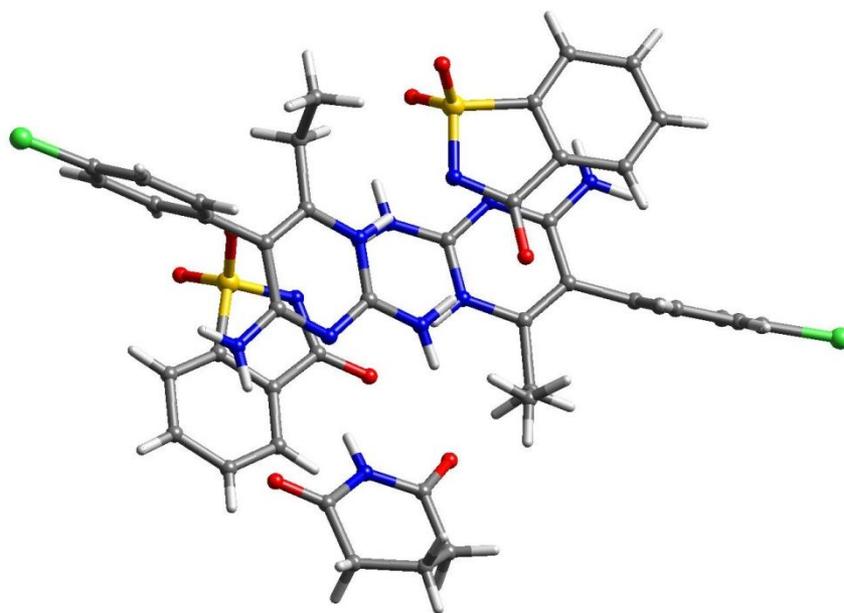
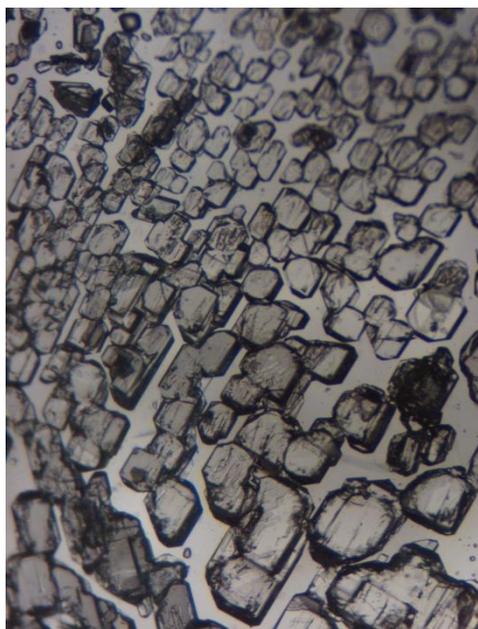
Experiment	Result	Temperatures(C)	Time (hrs)
Pyrimethamine/ Saccharin/ Glutarimide	Ternary Crystal	Pyr/Sac – 225 Glu – 125 Middle - 134	6
Pyrimethamine / Saccharin	1:1 crystal	Pyr/Sac – 212.8 Sor- 127.5 Middle- 128	6
Pyrimethamine/ Nicotinic acid	1:1 crystal	Pyr- 160 Nic – 150 Middle - 137	6
Pyrimethamine / Barbituric acid	2:1 crystal	Pyr – 211.9 Barb – 246.8 Middle - 225	6
Pyrimethamine / Glutarimide	1:1 crystal	Pyr- 175.4 Glu- 125.5 Middle- 142	6



Pyrimethamine and Nicotinic acid

Co-Sublimation with Pyrimethamine – A route to Ternary Crystal Systems

- Ternary crystal system was able to be formed via co-sublimation
- Pyrimethamine-Saccharin-Glutarimide
- This was possible due to similar sublimation rates of pyrimethamine and saccharin at the same temperature
- Can design experiments to create ternary or higher order crystal systems



Conclusions

- Pharmaceutical co-crystals can be grown by sublimation by equalising sublimation rates by multi zone heating
- Tight control of the sublimation rate can suppress nucleation and enhance crystal quality
- Co-crystal structures otherwise unobtainable from solution can be obtained from the gas phase
- Ternary or higher order crystal structures can possibly be obtained by sublimation
- Tailor made additives can be used to provide unprecedented morphology and crystal quality control
- Modelling studies on salt formation show the molecular cluster formed during nucleation from the gas phase provide an ideal environment for spontaneous proton transfer



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