Self-Assembled Monolayers as Nucleating Surfaces to Study Early Formation Pathways of Crystal Polymorphs

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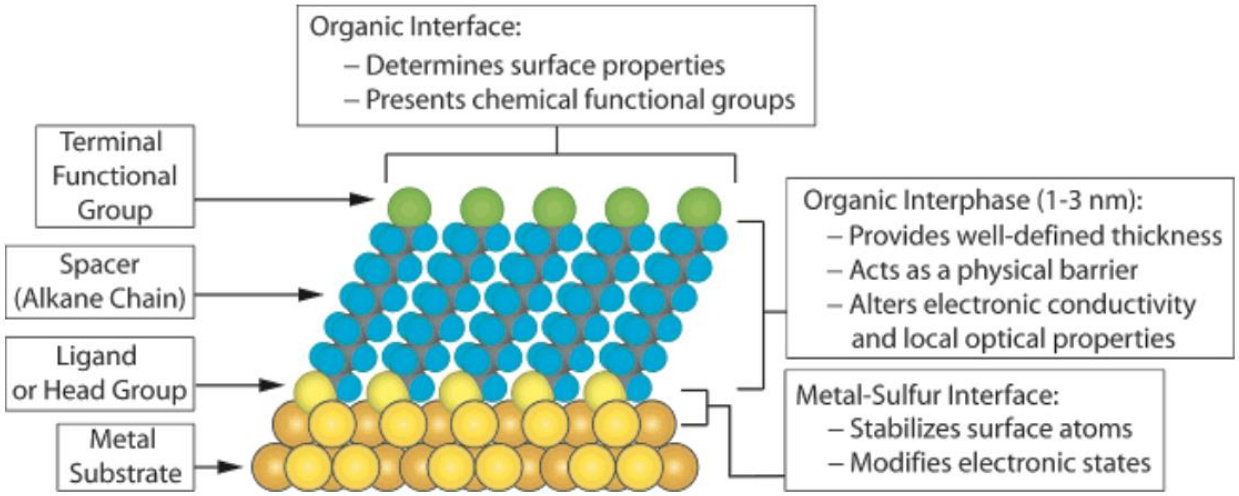
Research Project Brief

- Fund project to understand and control crystallinity, polymorphism, and particle morphology in the *early formation stages*.
- Use advanced techniques like cryo-TEM, synchrotron derived pair-correlations, solid-state C^{13} NMR, and in-situ AFM, to visualize these stages.
- High level objectives of this project:
  - *identify appropriate model system(s)* to study, adapt and apply characterization techniques to describe early particle formation stages;
  - collect data that is relevant for the development of molecular dynamic simulation or other computational physics models.

Proposed Approach

- Use self-assembled monolayers (SAMs) to study the relationship between nucleation and polymorph selection.

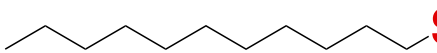
- Advantages: (i) Enables establishment of scientific correlations between chemistry of nucleation surface and observed polymorph and (ii) may provide access to polymorphs not accessible via solution methods.

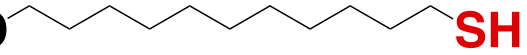


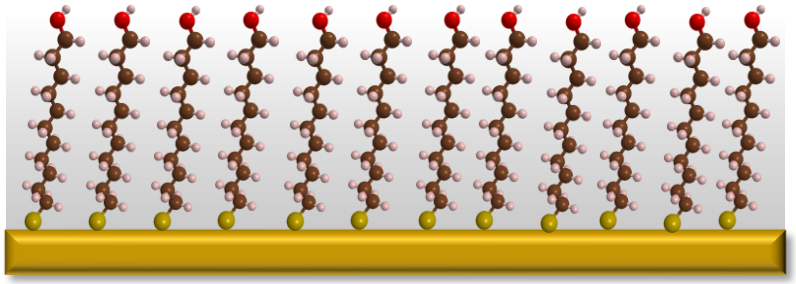
J.C. Love et al., *Chem. Rev.* **2005**, 105, 1103−1169.

Two substrate chemistries: Au and SiO_2

Thiol-gold chemistry

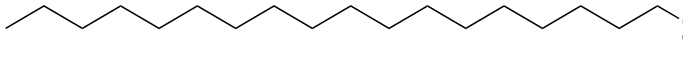
UDT: 

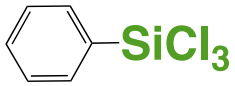
MUOH: 

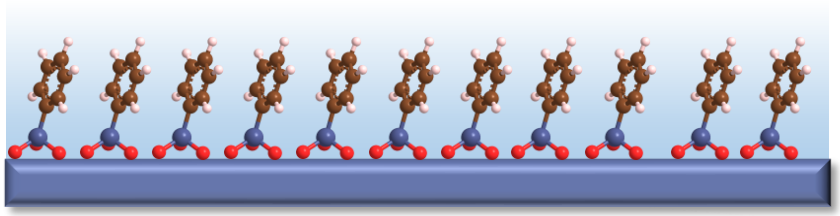


- Highly ordered SAMs
- Poor solution stability
- More expensive

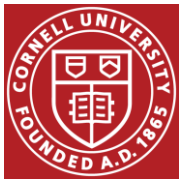
Silane-SiO_2 chemistry

OTS: 

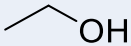
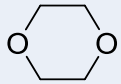
PTS: 



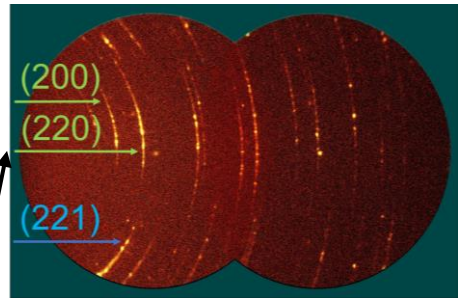
- Less ordered than Au SAMs
- Very good solution stability
- Works on Si-wafers and glass

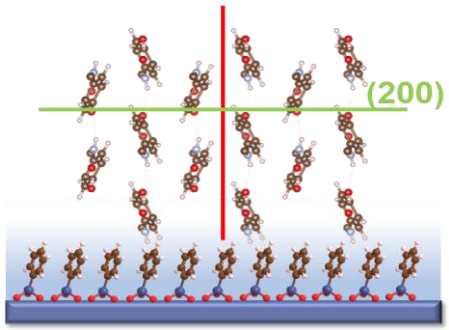


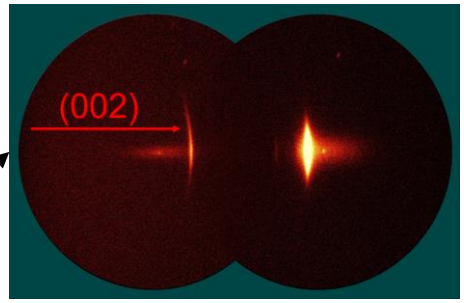
Past experiences on Acetaminophen:
Both solvent and substrate work together to control crystal polymorph

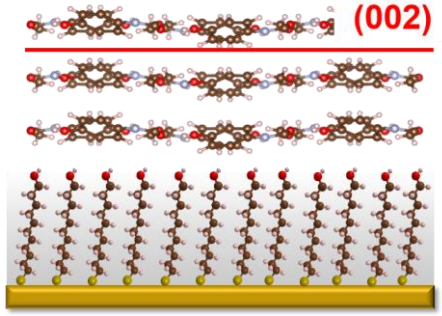
Solvent	*SAMs*	*n*	*Form I*	*Form II*
Ethanol 	UDT	20	**80%**	20%
	OTS	18	**94%**	6%
	PTS	14	**93%**	7%
	MUOH	11	9%	**91%**
DI water	UDT	9	**93%**	7%
	OTS	18	**89%**	11%
	PTS	10	**90%**	10%
	MUOH	17	**100%**	0%
1,4-dioxane 	UDT	12	**100%**	0
	OTS	10	**90%**	10%
	PTS	10	**70%**	30%
	MUOH	10	20%	**80%**
DI water/ dioxane 20:80	UDT	11	9%	**91%**
	OTS	11	0	**100%**
	PTS	9	0	**100%**
	MUOH	10	0	**100%**

- Solvent and surface chemistry must be considered in concert for polymorph selection
- Substrate can dictate crystallographic orientation: Form II
- General area X-ray diffraction (GADDS) results & proposed molecular interpretation







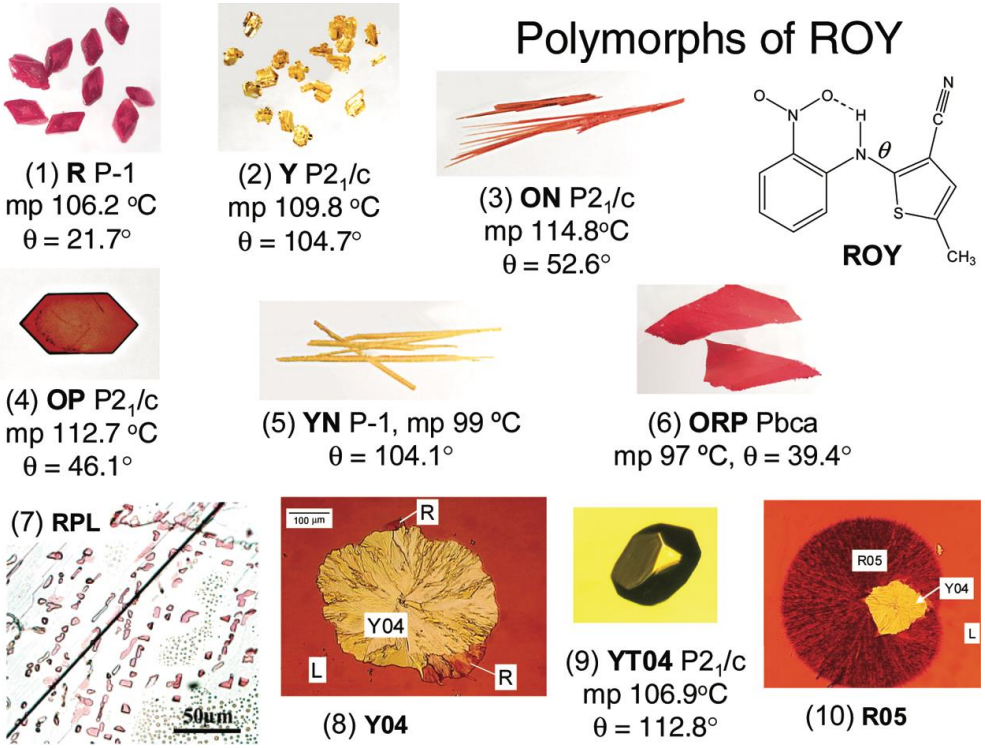


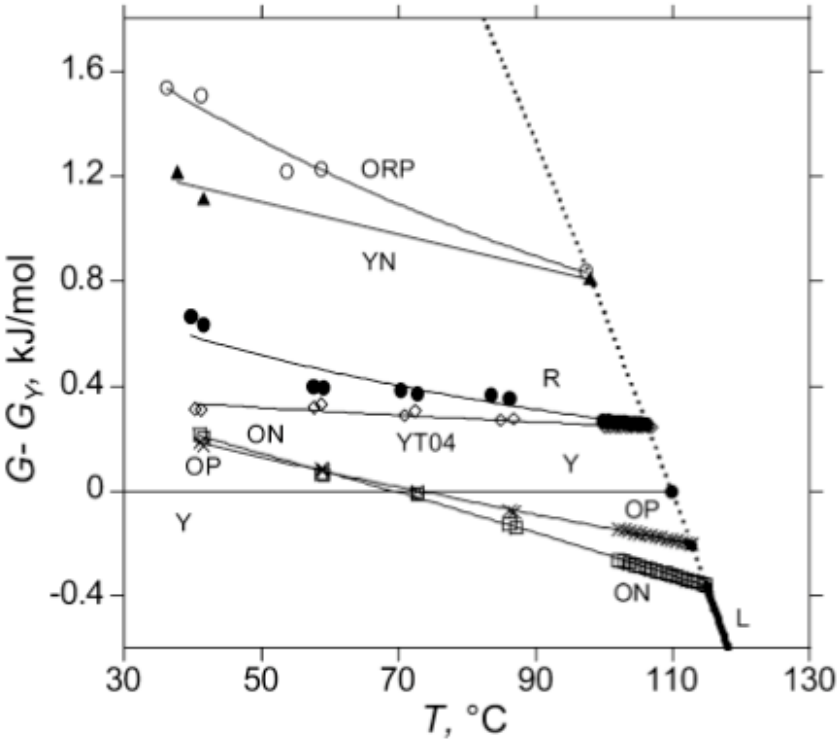
*Unpublished data

Conclusions

- *In-situ* synchrotron studies of crystal nucleation and growth of model compound acetaminophen (ACM) from solution on self-assembled monolayers (SAMs) provided first insights into early formation stages that could be important for polymorph selection.
- Two independent studies of seeded ACM Form II on PTS in dioxane/water revealed crystals growing upwards from the SAM substrate-solution interface with preferred (002) plane orientation perpendicular to substrate supporting SAMs as nucleation sites.
- Two independent studies of spontaneous nucleation & growth of Form 1 on PTS in water revealed unusual peak shifts at the earliest time points in similar q ranges. While details of the observed shift differed, both of these observations were suggestive of structural transformations (versus simple rotations) at early stages of ACM crystal formation.
- Deeper understanding of these early structural transformations likely require molecular dynamics simulations or other computational physics models.

After discussions with several IFPRI members: New model system: 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY)





Up to now, ROY has 11 known polymorphs, 9 of which have a fully elucidated crystal structure.

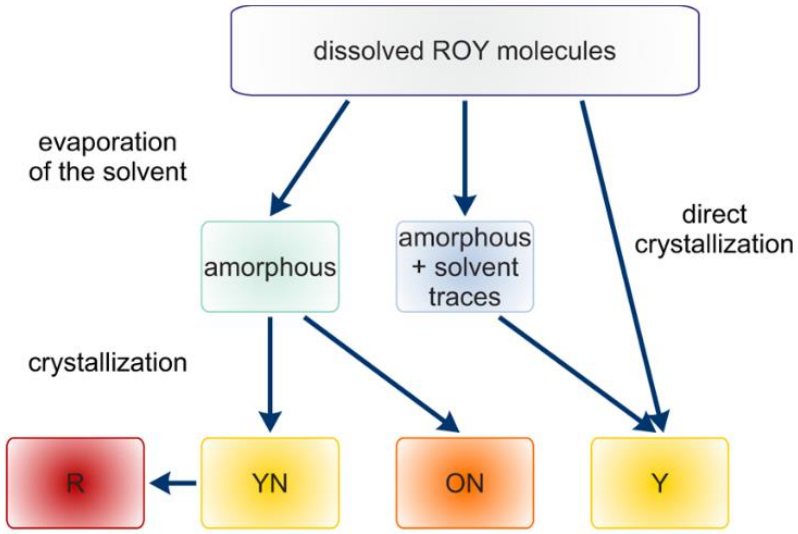
Y is the most stable polymorph below 70 ℃

Yu, L.. *Acc. Chem. Res.* **2010**, *43*, 1257−1266.

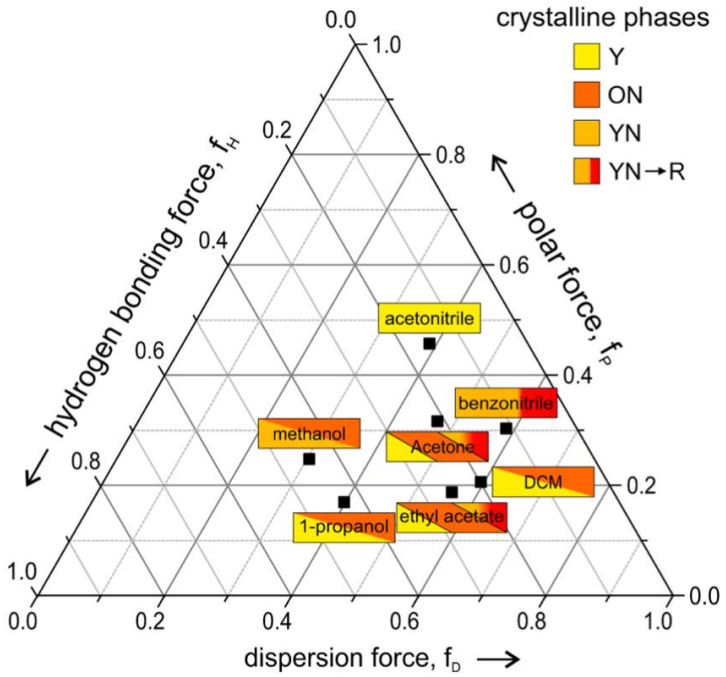
Yu, L. et al. *J. Am. Chem. Soc.*, **2000**, *122*, 585– 591

Known dependencies of ROY polymorph selection

Nucleation pathway dependence of polymorph selection via solvent evaporation



Solvent dependence of polymorph selection due to intermolecular forces



Gnutzmann, T. et al. *Cryst. Growth Des*. **2014**, 14, 6445-6450

Effects on polymorph selection

This time - involve the effect of supersaturation

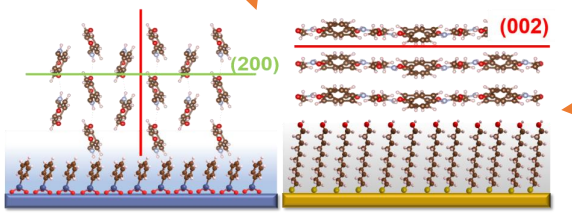
SAM surface chemistry

Solvent

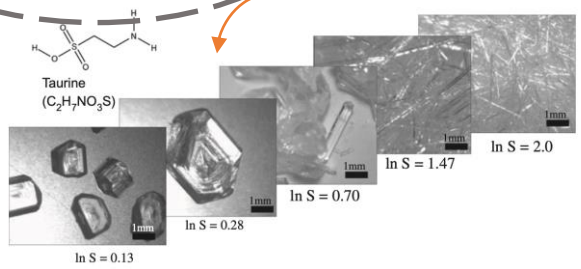
Supersaturation

Energy Barrier

Polymorphism & Morphology

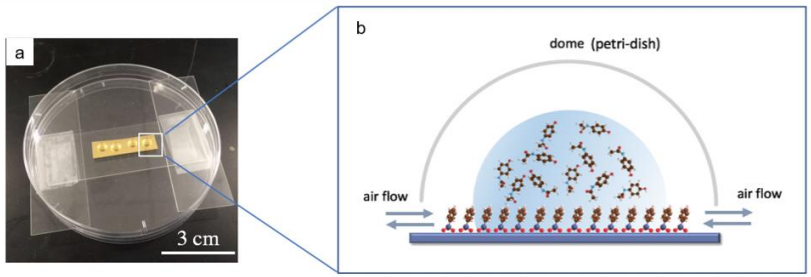


SAMs + solvent effect was studied by ACM



Past experimental setup – no control over degree of supersaturation

Solvent evaporation crystallization



Convenient way to screen conditions

Hard to track solution concentration vs time of nucleation

Direct solution crystallization by cooling

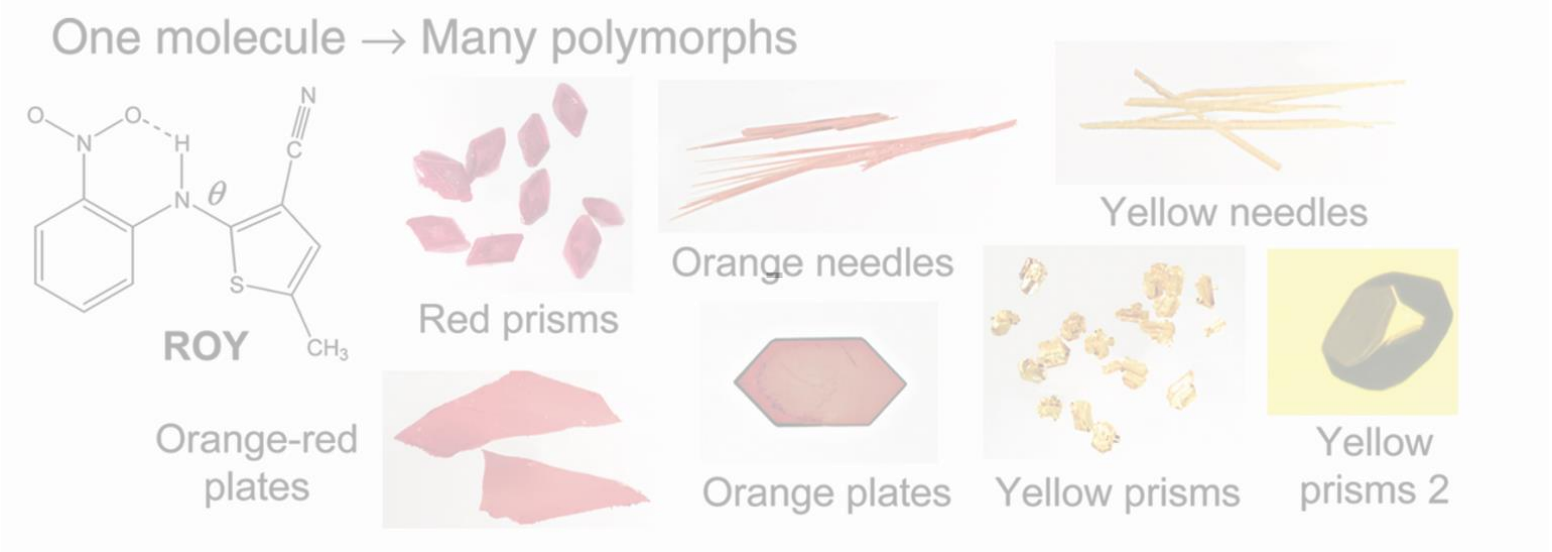
- Concentration is related to **solubility curve**
- Able to know concentration by tracking solution temperature profile

For solution crystallization, solvent needs to have a high boiling point and high ROY solubility.

Possible solvent: **DMSO, Benzyl Alcohol, Toluene…**

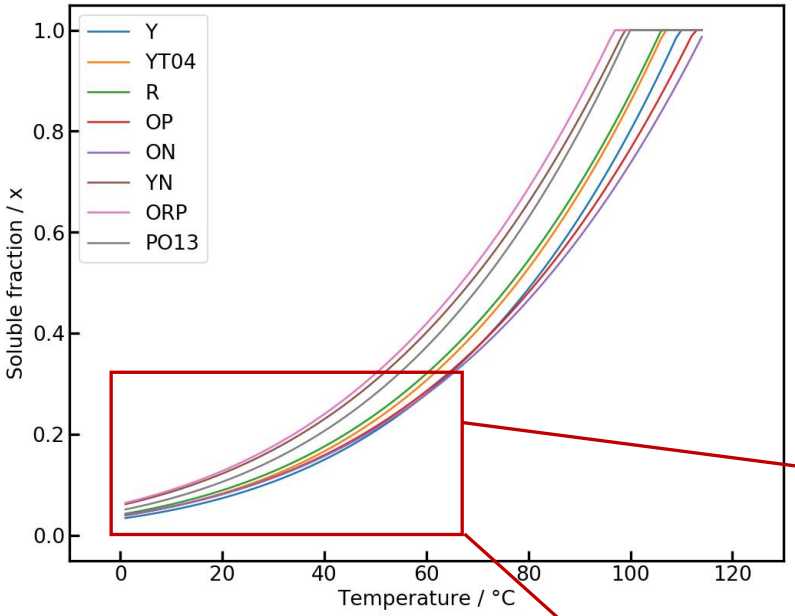
Takiyama, H. *Adv. Powder Technol*. **2012**, *23*, 273-278

Results of solubility tests & preliminary direct solution crystallization experiments



Yu, L.. *Acc. Chem. Res.* **2010**, *43*, 1257−1266.

Calculated solubility of ROY

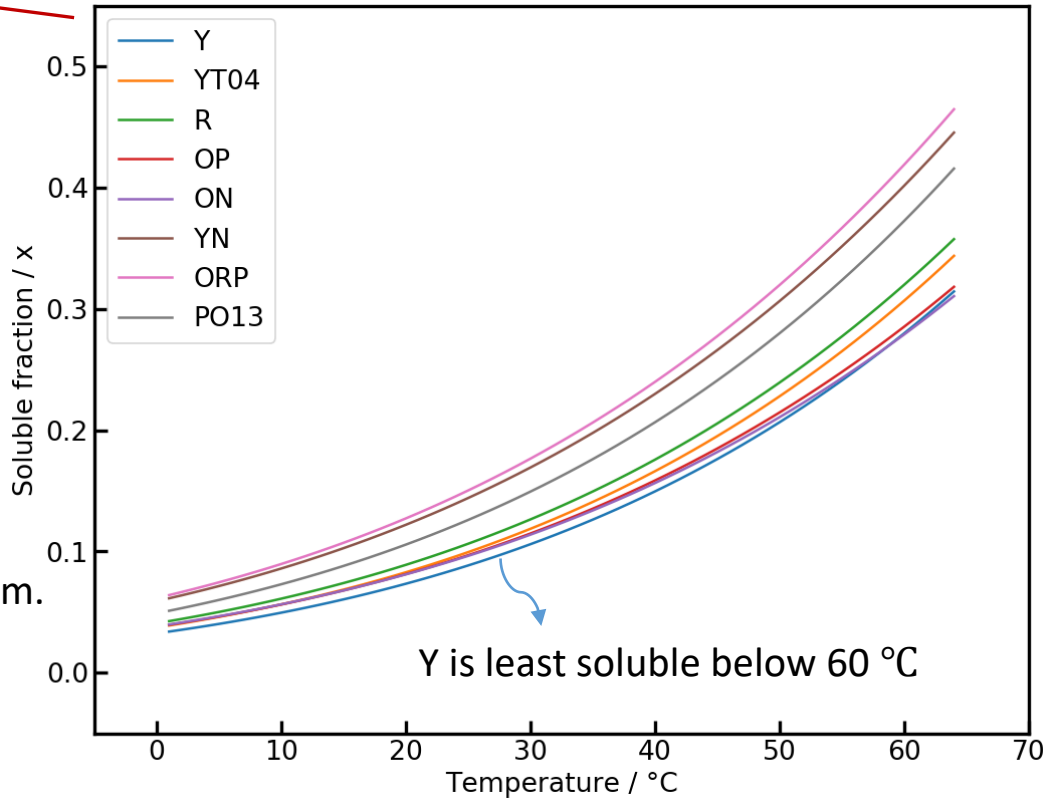


The van't hoff equation:

$$\ln x = \frac{\Delta H_f}{R}\left[\frac{1}{T_f} - \frac{1}{T}\right] = -\frac{\Delta H_f}{RT} + \frac{\Delta S_f}{R}$$

ΔH_f : enthalpy of fusion

ΔS_f : entropy of fusion



Y is also the most stable polymorph below 70℃.
Therefore, the measured solubility is ROY in Y form.

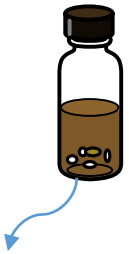
Yu, L.. *Acc. Chem. Res.* **2010**, *43*, 1257−1266.

Solubility test:

Gravimetric method

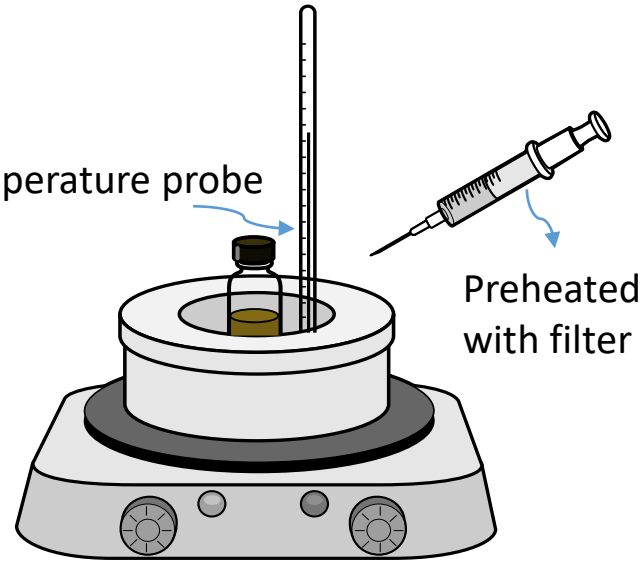
Thanks for support by John Hone (Syngenta)

Step 1:



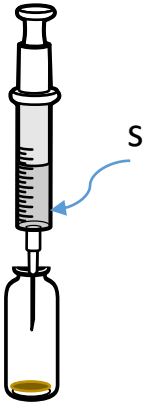
Excess ROY in preheated solvent (supersaturated)

Step 2:

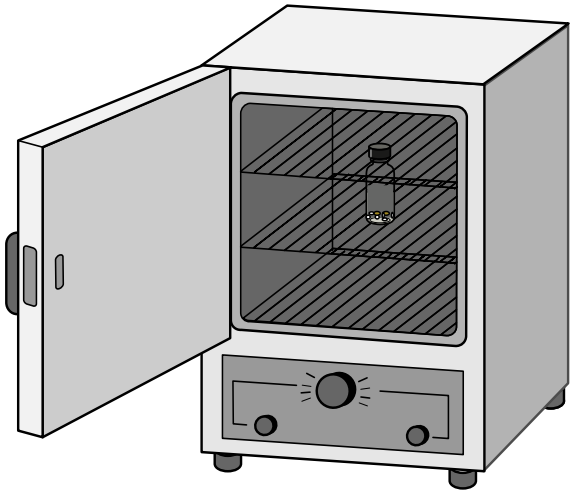


Oil bath

Step 3:



Step 4:

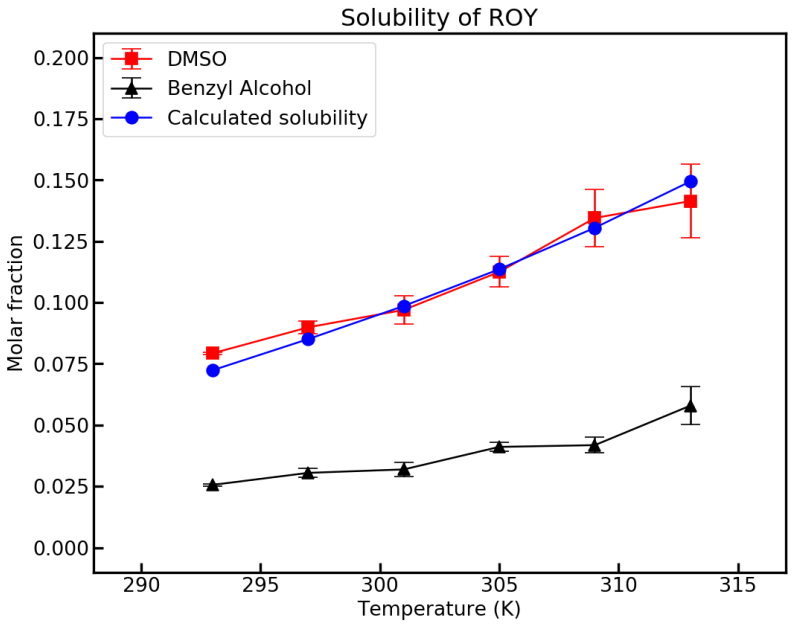


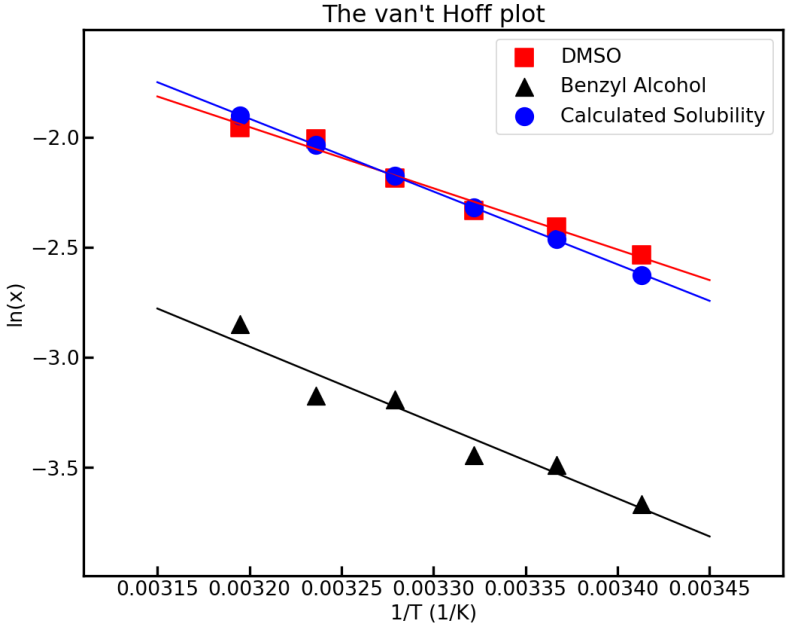
Vacuum dry for more than 8 hrs

Solubility (g/g) = $\frac{m_{dried\ sample} - m_{empty\ vial}}{m_{sample} - m_{dried\ sample}}$

Experimental Results:

Solubility of ROY in DMSO and Benzyl Alcohol





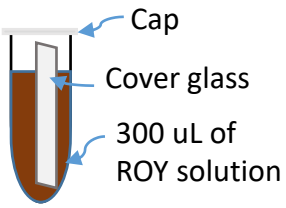
Including solvent effects:

$$\ln x = -\frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R}$$

ΔH_d : enthalpy of dissolution
ΔS_d: entropy of dissolution

Solvent	ΔH_d (kJ/mol)	ΔS_d (J/molK)
Ideal	27.52	72.14
DMSO	23.11	57.74
Benzyl Alcohol	28.69	67.28

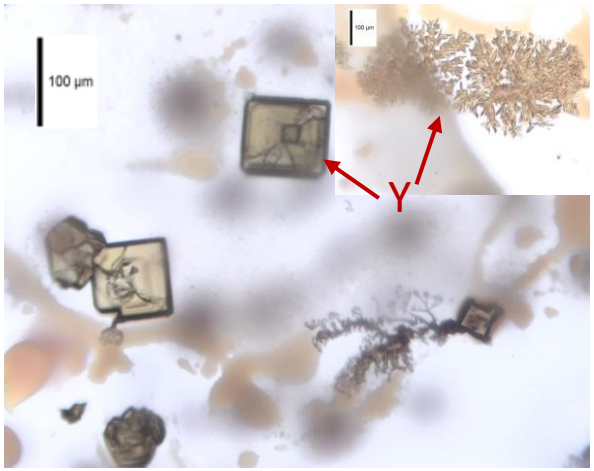
ROY Nucleation on cover glass as a func. of supersaturation



- **Supersaturation: 1.5, 2, 2.5**
- Nucleation surface: cover glass
- Temperature change: 60 ℃ to 20 ℃ natural cooling
- Solvent: Benzyl Alcohol

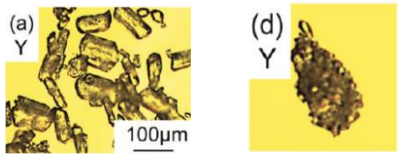
$$\text{Supersaturation (S)} = \frac{\textit{initial solution concentration}}{\textit{solubility at the crystallization temperature}}$$

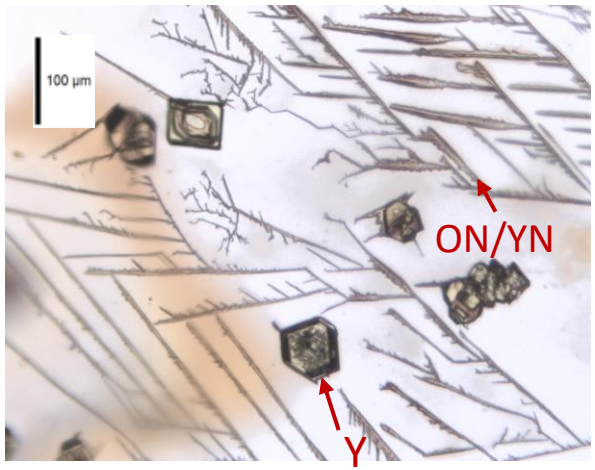
Based on literature, Y, R, & ON could be crystallized from benzyl alcohol solutions



S=1.5

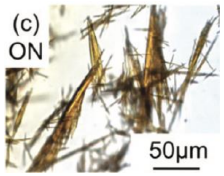
- Only prism shape crystals appear
- Possible polymorph: Y





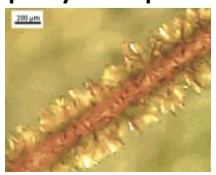
S=2

- Both prism and needle shape crystals appear
- Possible polymorph: Y+ON/YN



S=2.5

- No trace of prism crystals; some needles grown on the large needle crystal
- Possible polymorph: ON



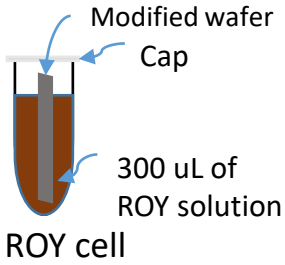
At different supersaturation levels, the dominant polymorph changes.

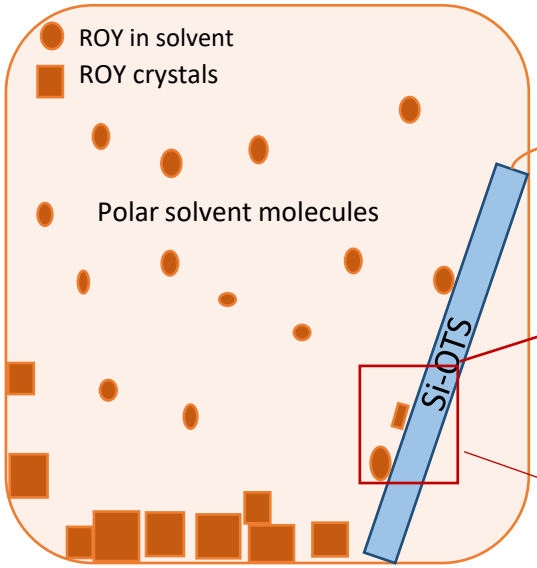
Diao, Y. et al. *J. Am. Chem. Soc.* **2012**, *134*, 673-684
Chen, S. et al. *J. Am. Chem.* Soc. **2005**, *127*, 17439-17444

ROY Nucleation on SAM as a function of supersaturation

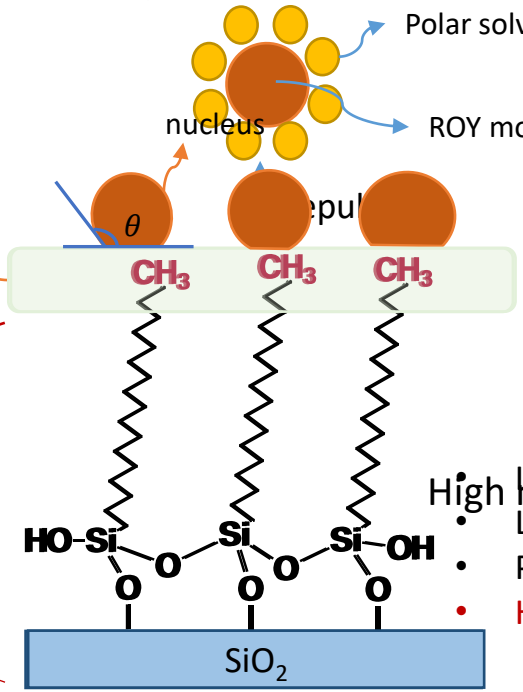
- **Supersaturation: 1.5, 2, 2.5**
- Nucleation surface: Si-OTS
- Temperature change: 60 ℃ to 20 ℃ natural cooling
- Solvent: Benzyl Alcohol/DMSO

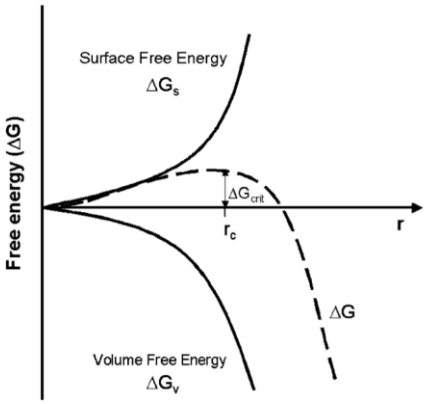
Alternative Explanation





Hydrophobic surface





- Large contact angle θ
- Low interfacial free energy
- Poor wetting on the substrate
- High nucleation energy barrier

High nucleation energy barrier

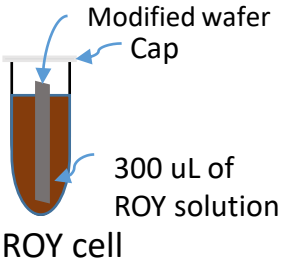
- Little crystallization on SAM surface occurred during 2 days (for all supersaturation levels)
- Crystal clusters appeared at the bottom of the vial
  → Either preference for homogeneous nucleation in solution or heterogeneous nucleation on container wall

Hydrophobic surface + polar solvent does not favor heterogenous nucleation

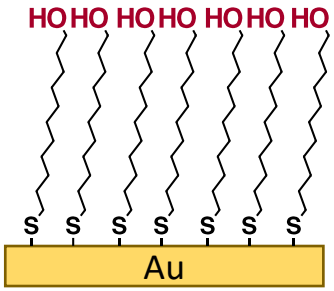
Alternative systems:

- Hydrophilic surface (Au-MUOH) + polar solvent (Benzyl Alcohol)
- Hydrophobic surface (Si-OTS) + nonpolar solvent (Toluene)

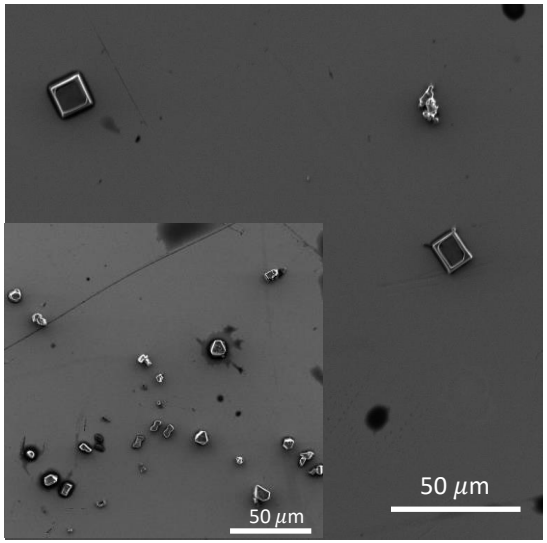
ROY Nucleation from different SAM + solvent combinations

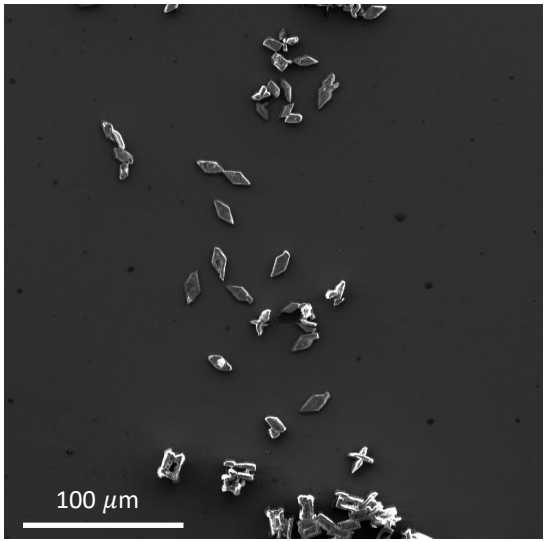


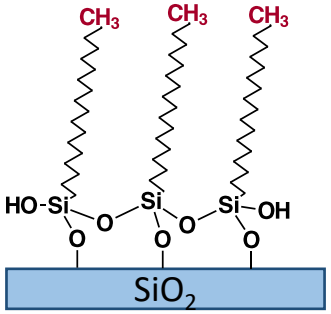
- **Nucleation surface: Au-MUOH (left); Si-PTS (right)**
- **Solvent: Benzyl Alcohol (left); Toluene (right)**
- Supersaturation: 1.5
- Temperature change: 60 °C to 20 °C natural cooling



Solvent: Benzyl Alcohol







Solvent: Toluene

(2) **Y** $P2_1/c$
mp 109.8 °C
θ = 104.7°

(9) **YT04** $P2_1/c$
mp 106.9°C
θ = 112.8°

(1) **R** P-1
mp 106.2 °C
θ = 21.7°

- Hydrophilic head group + polar solvent
- Cubic shape crystals appear
- Possible polymorph: monoclinic Y/YT04

- Hydrophobic head group + nonpolar solvent
- Rhombic shape crystals appear
- Possible polymorph: triclinic R

There is polymorph selectivity when applying different solvent + SAM surface chemistry combinations

Chen, S. et al. *J. Am. Chem. Soc*. **2005**, *127*, 17439-17444

Conclusions

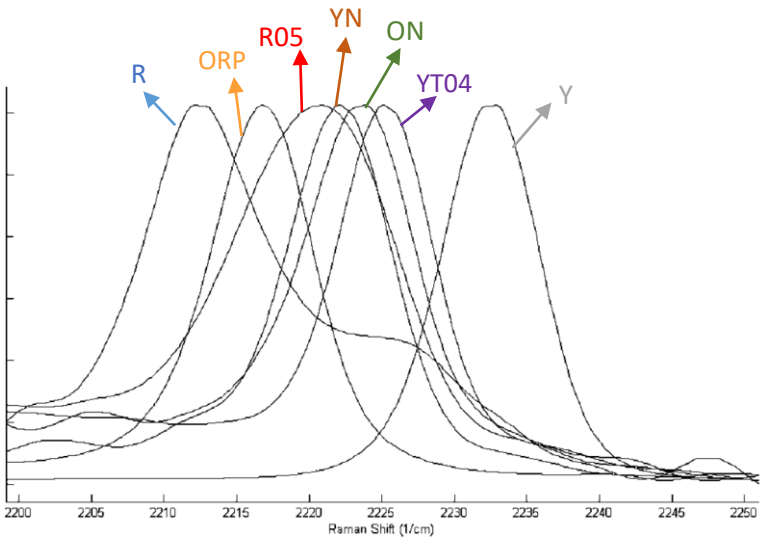
- In the past funding period we successfully switched our studies of polymorph selectivity from Acetaminophen (ACM) to a more complex system, ROY
- In parallel, rather than driven by solvent evaporation, for ROY we established experimental protocols that enable polymorph selection as a function of the degree of supersaturation, which we heard from industry representatives to be the more relevant parameter.
- Solubility curves for ROY in benzyl alcohol and DMSO were successfully determined
- For ROY in benzyl alcohol, in first proof-of-principle experiments we demonstrated polymorph selection as a function of the degree of supersaturation
- Similar to ACM, first experiments suggest that for ROY again solvent and SAM surface chemistry together control polymorph selection

Possible future directions

- Complete sample characterization (*e.g.* XRD) of existing samples to determine the exact ROY crystal polymorphs formed

- Raman Microscopy may be used to distinguish different polymorphs
  - Different nitrile (C-N) stretch for each polymorph (see figure)

- Work on better ways to control, *e.g.* the temperature jump and monitor the appearance of crystals
  - Cooling rate is an essential parameter for temperature and degree of supersaturation tracking



The nitrile stretch (2200-2250 cm^{-1}) of different ROY polymorph

Singh, A. et al. *Cryst. Growth Des*. **2009**, *9*, 1182-1185

Acknowledgement