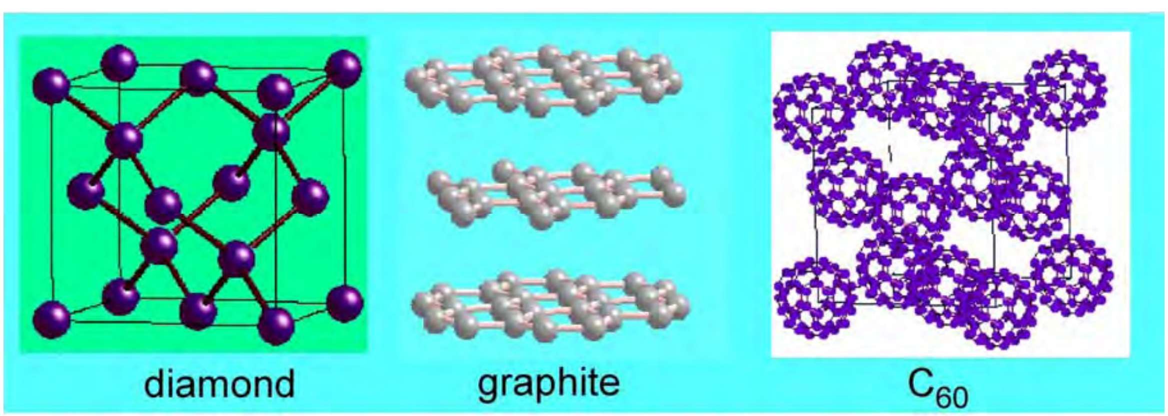
Crystallization in polymorphic systems

Lian Yu
University of Wisconsin – Madison,
School of Pharmacy and
Department of Chemistry

With thanks to
PRF, NSF

Polymorphs of Carbon



Hard	Soft	Soft
Electrical insulator	Semi-metal	Conductive

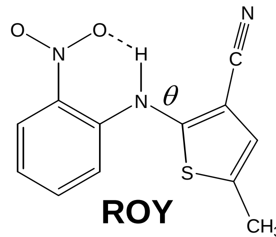
Polymorphs serve two goals of chemical research:

- Finding new materials
- Learning structure-property relations

Polymorphs of ROY

(1) **R** P-1
mp 106.2 ºC
θ = 21.7°

(2) **ON** $P2_1/c$
mp 114.8ºC
θ = 52.6°



ROY

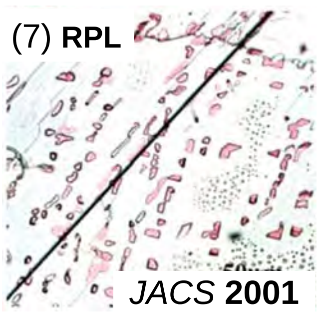
(3) **Y** $P2_1/c$
mp 109.8 ºC
θ = 104.7°

(4) **OP** $P2_1/c$
mp 112.7 ºC
θ = 46.1°

(5) **YN** P-1, mp 99 ºC
θ = 104.1°

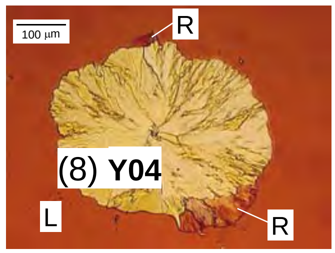
(6) **ORP** Pbca
mp 97 ºC, θ = 39.4°

J. Am. Chem. Soc. **2000**, *122*, 585



(7) **RPL**

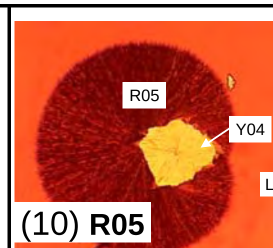
JACS **2001**



(8) **Y04**

JACS **2005a**

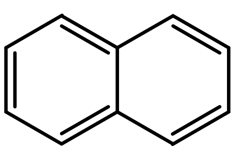
(9) **YT04** $P2_1/c$
mp 106.9ºC
θ = 112.8°



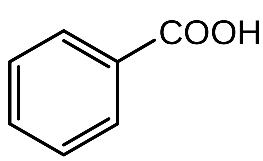
(10) **R05**

JACS **2005b**

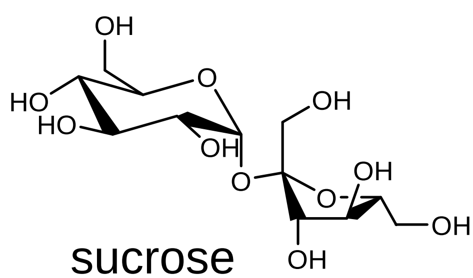
"Non-polymorphic" systems



naphthalene



benzoic acid



sucrose

Polymorphs of drugs have different bioavailability

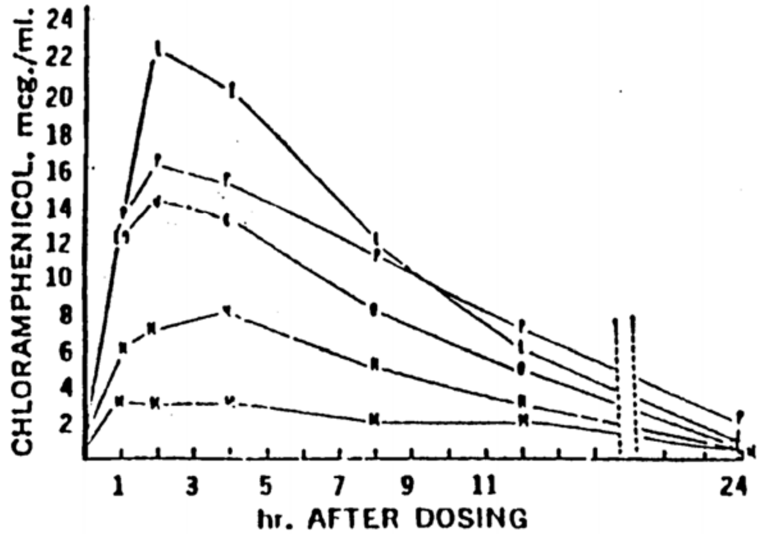


Figure 2—*Comparison of mean blood serum levels obtained with chloramphenicol palmitate suspensions containing varying ratios of* **A** *and* **B** *polymorphs, following single oral dose equivalent to 1.5 g. chloramphenicol. (Percent polymorph* **B** *in the suspension: M, 0%; N, 25%; O, 50%; P, 75%; L, 100%.)*

Polymorphs have been used to test the third law of thermodynamics

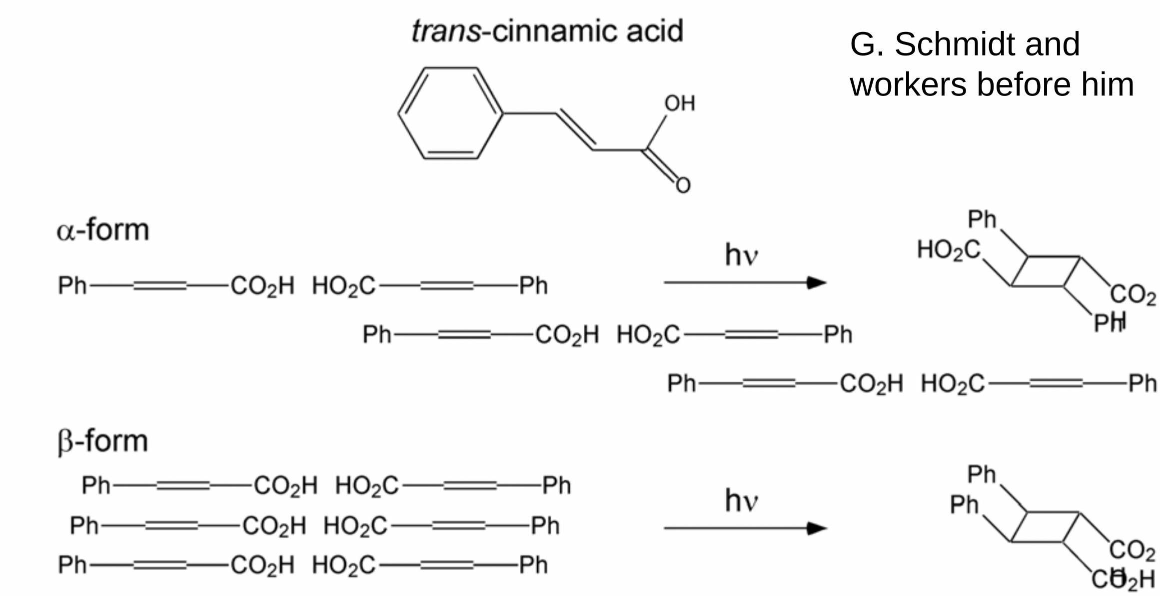
THIRD LAW ENTROPY FOR *n*-PROPYLBENZENE (752)

Temperature range		ΔS values, cal deg^{-1} mole^{-1}
Crystal I		
ΔS(0–10°K)	Debye extrapolation	0.187
ΔS(10–173.60°K)	$\int (C/T)\mathrm{d}T$, crystal I	30.784
ΔS(173.60°K)	$\Delta Hm/T$, fusion	12.758
ΔS(173.60–298.15°K)	$\int (C/T)\mathrm{d}T$, liquid	25.048
	$S_{298.15} - S°_0 =$	68.777
Crystal II		
ΔS(0–10°K)	Debye extrapolation	0.219
ΔS(10–171.67°K)	$\int (C/T)/\mathrm{d}T$, crystal II	31.181
ΔS(171.67°K)	$\Delta Hm/T$, fusion	11.830
ΔS(171.67–298.15°K)	$\int (C/T)\mathrm{d}T$, liquid	25.535
	$S_{298.15} - S°_0 =$	68.765
	$S°_0(\mathrm{I}) - S°_0(\mathrm{II}) =$	-0.012

Westrum & McCullough (1963)

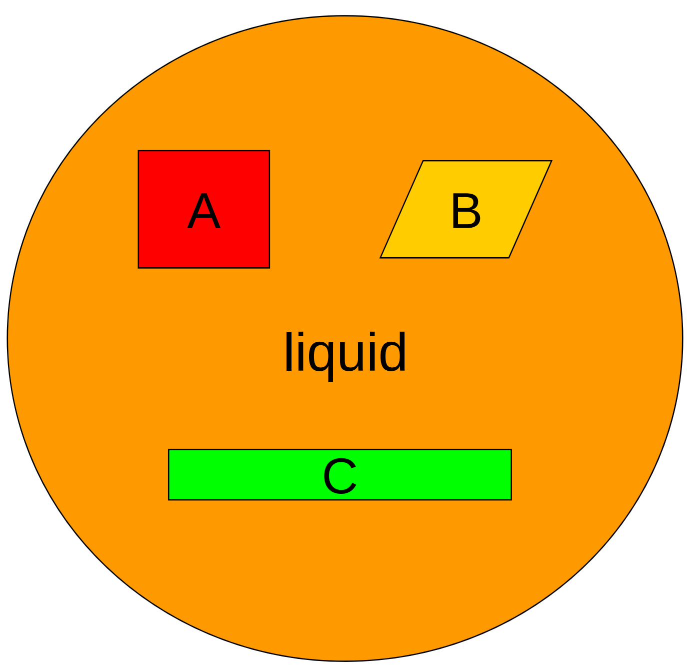
… and other structure-property relations

G. Schmidt and workers before him



Solution or melt $\xrightarrow{h\nu}$ no reaction

The problem of controlling polymorphism: Crystallizing from the same liquid, which polymorph "wins"?



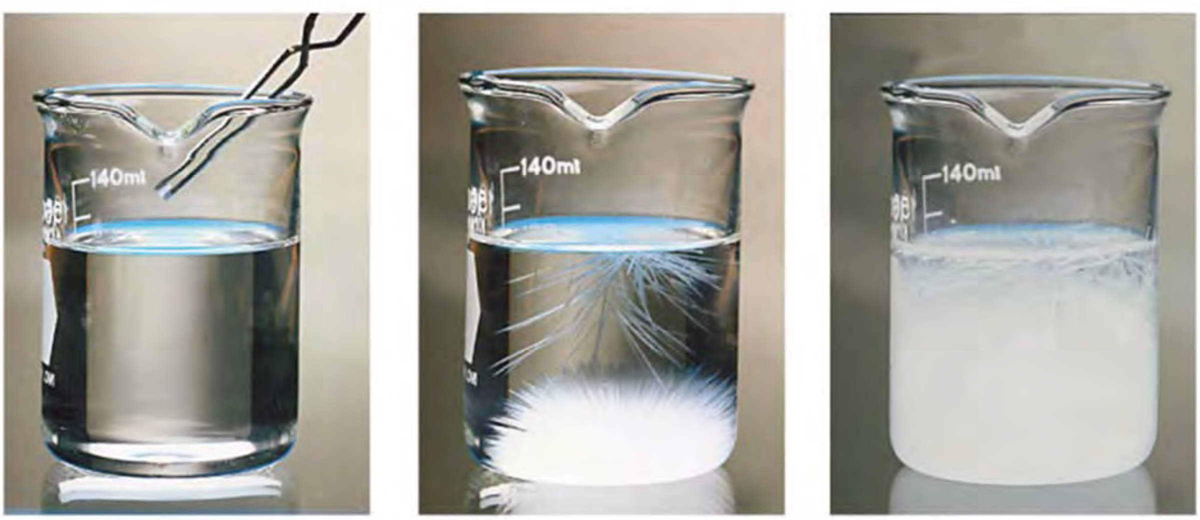
This talk
Crystallization in polymorphic systems

(1) A new mechanism: Nucleation of one polymorph by another

(2) Hidden polymorph discovered by cross-nucleation

(3) Survival of the fittest polymorph: Fast nucleater vs. fast grower

Crystallization = nucleation + growth

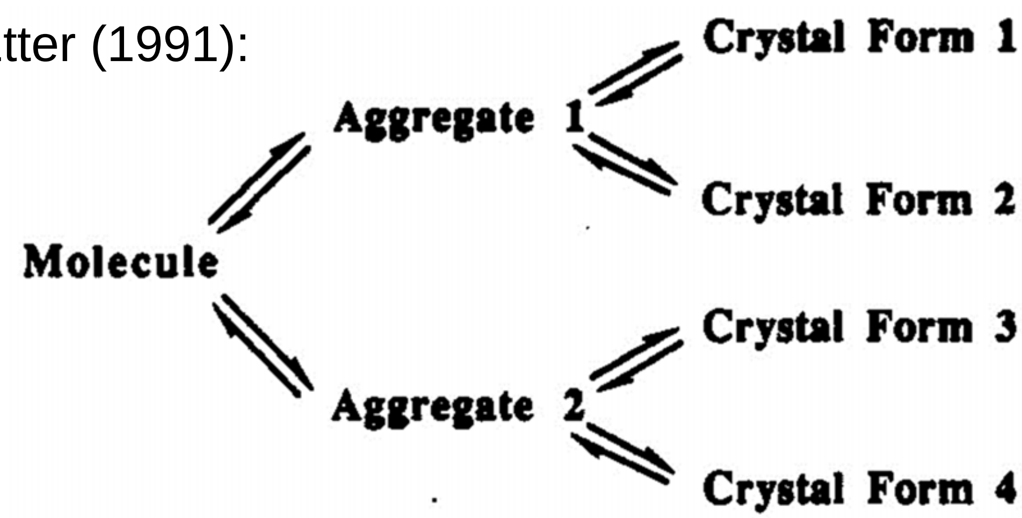


Crystallization in polymorphic systems

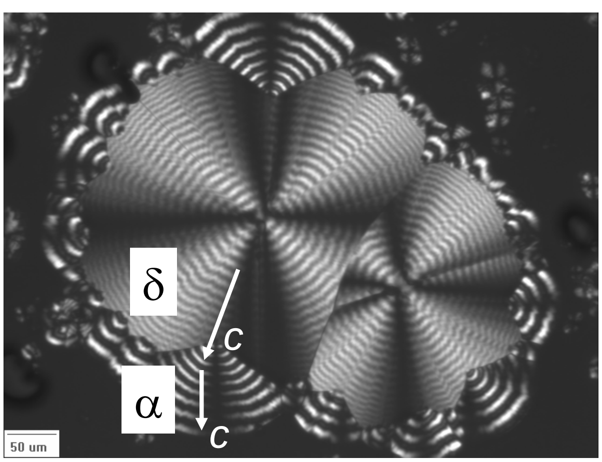
Ostwald (1897):

liquid → least stable → 2nd least stable → ···· → most stable

Etter (1991):



Another mechanism: Nucleation of one polymorph by another

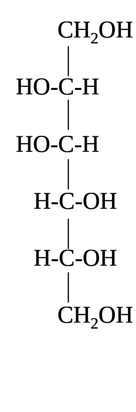


D-mannitol

(1) δ crystallizes first

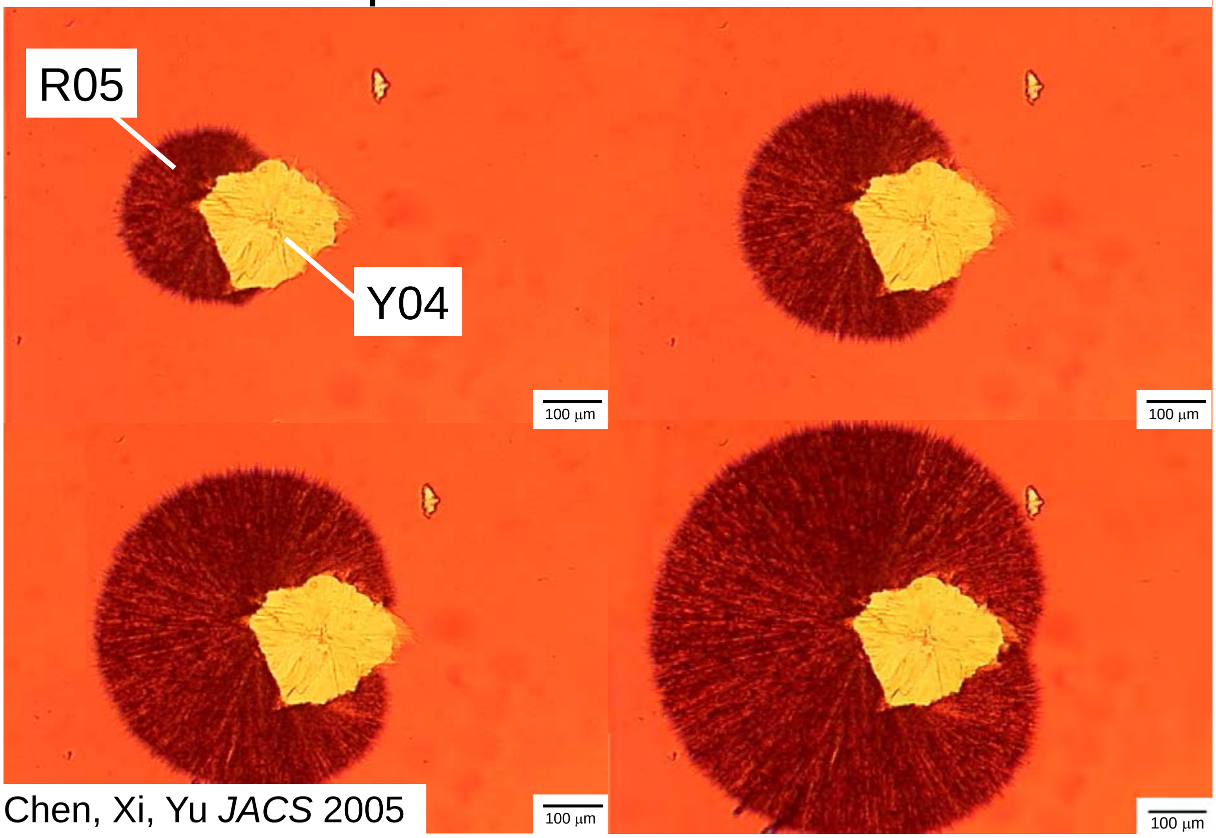
(2) α nucleates on δ *while δ continues to grow*

(3) α grows faster



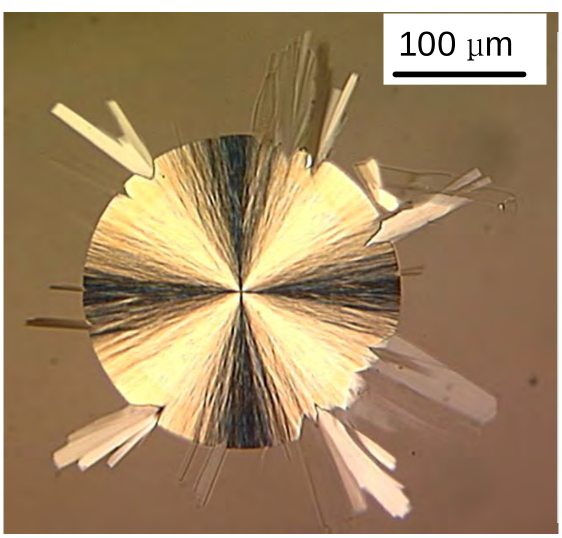
Yu, L. *J. Am. Chem. Soc.* **2003**, *125*, 6380

Other examples of cross-nucleation: ROY

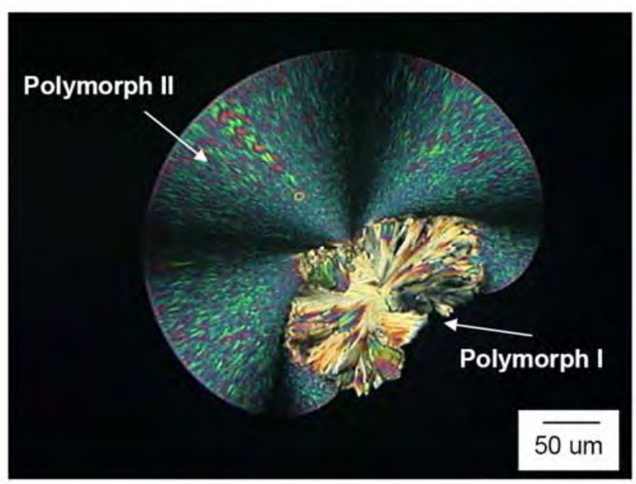


Chen, Xi, Yu *JACS* 2005

Other examples: Phenobarbital and carbamazepine/nicotinamide

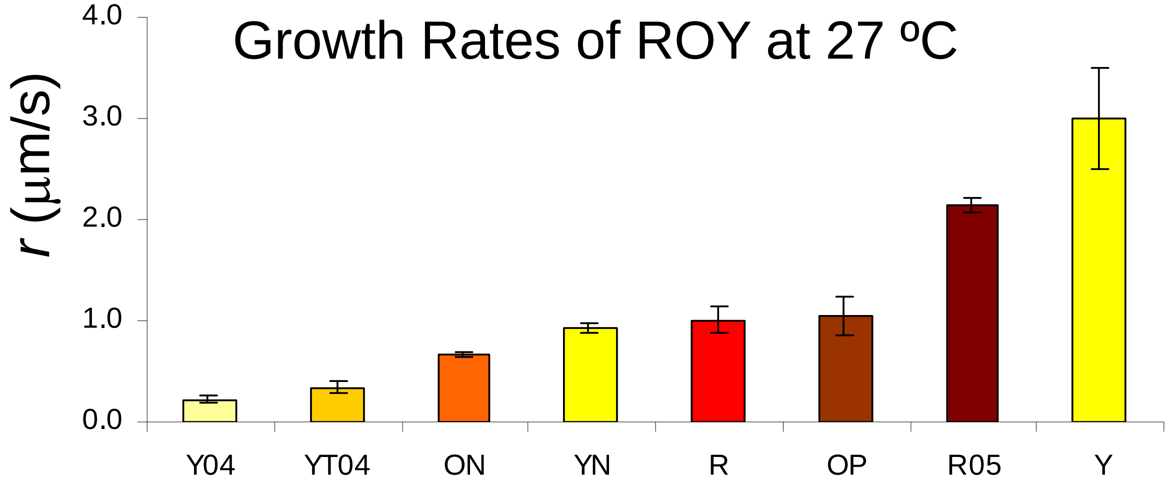


Phenobarbital



Carbamazepine/Nicotinamide

The new polymorph must grow faster than or as fast as the initial polymorph



Direction of cross nucleation:

Y04 → R, R05; R → YN

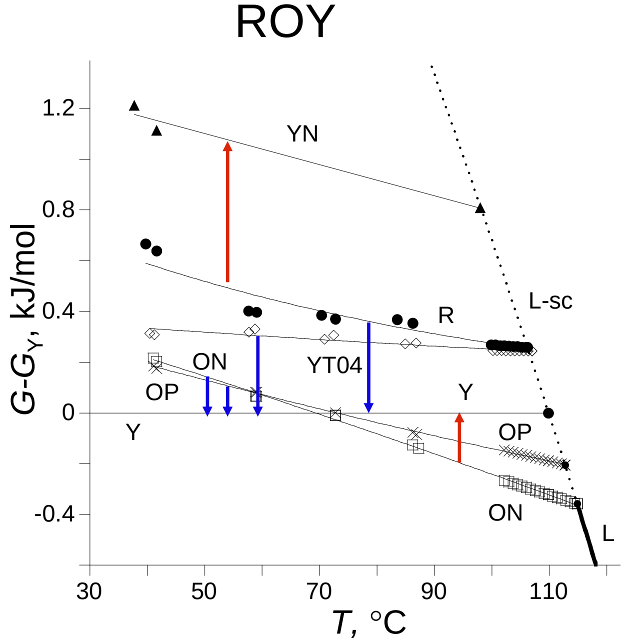
ON, OP, YT04 → Y

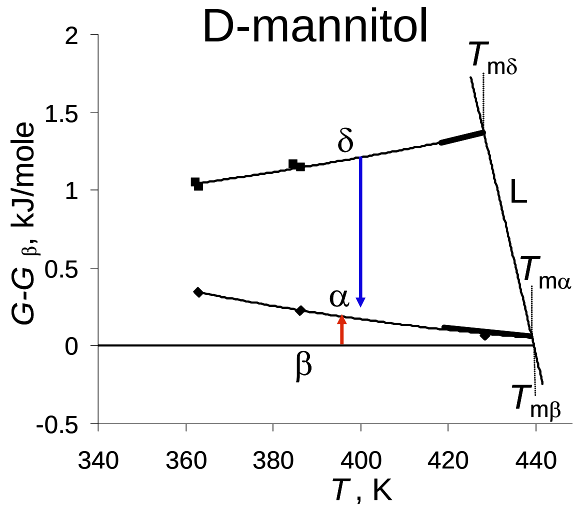
Crystallographic Data of ROY

Form	YT04	Y	ON	OP	R	YN	ORP
crystal sys.	monoclinic	monoclinic	monoclinic	monoclinic	triclinic	triclinic	orthorhombic
space group	$P2_1/n$	$P2_1/n$	$P2_1/c$	$P2_1/n$	*P-1*	*P-1*	*Pbca*
description	yellow prism	yellow prism	orange needle	orange plate	red prism	yellow needle	orange-red plate
a, Å	8.2324	8.5001	3.9453	7.9760	7.4918	4.5918	13.177
b, Å	11.8173	16.413	18.685	13.319	7.7902	11.249	8.0209
c, Å	12.3121	8.5371	16.3948	11.676	11.9110	12.315	22.801
α,°	90	90	90	90	75.494	71.194	90
β,°	102.505	91.767	93.830	104.683	77.806	89.852	90
γ,°	90	90	90	90	63.617	88.174	90
volume, Å^3	1169.36	1190.5	1205.9	1199.9	598.88	601.85	2409.8
Z	4	4	4	4	2	2	8
D_{cal}, gcm^{-3}	1.473	1.447	1.428	1.435	1.438	1.431	1.429

No apparent lattice matching exists between cross-nucleating structures

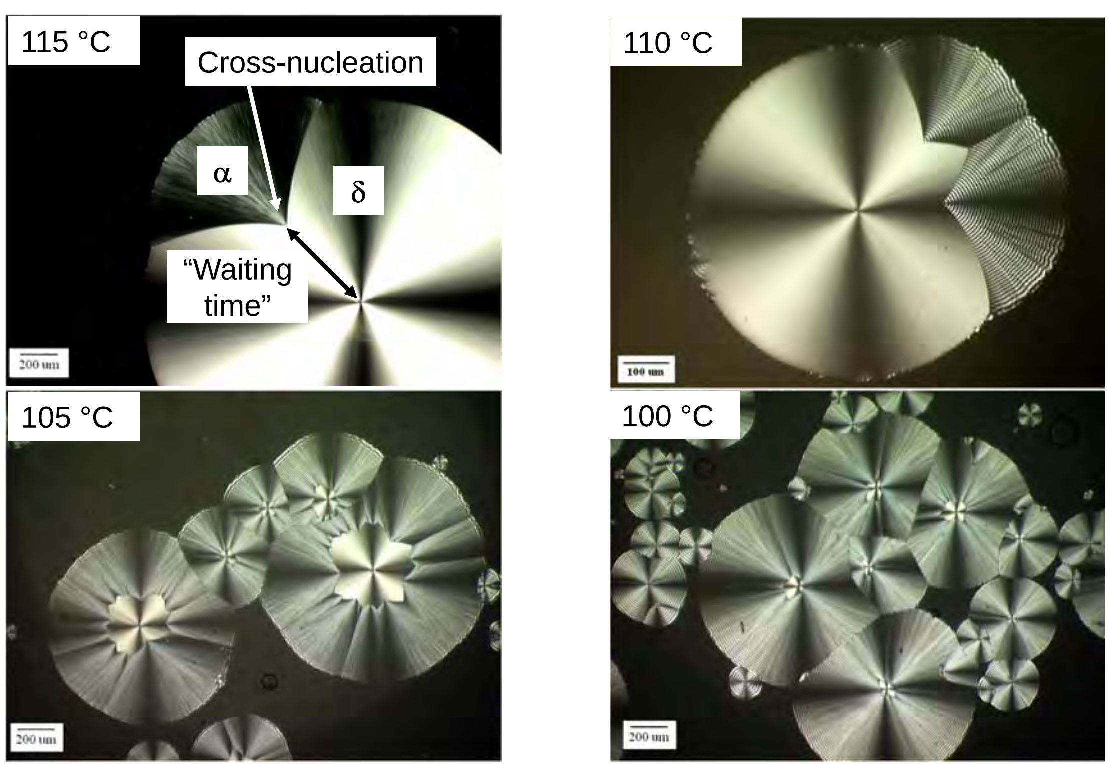
The less stable polymorph can nucleate the more stable (↓) and vice versa (↑).



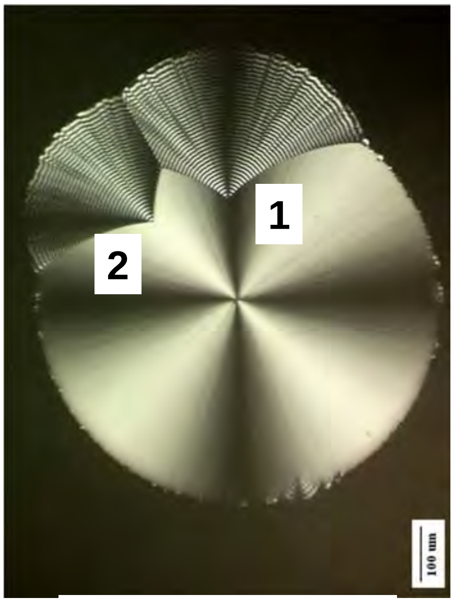


Cross-nucleation rate depends on temperature

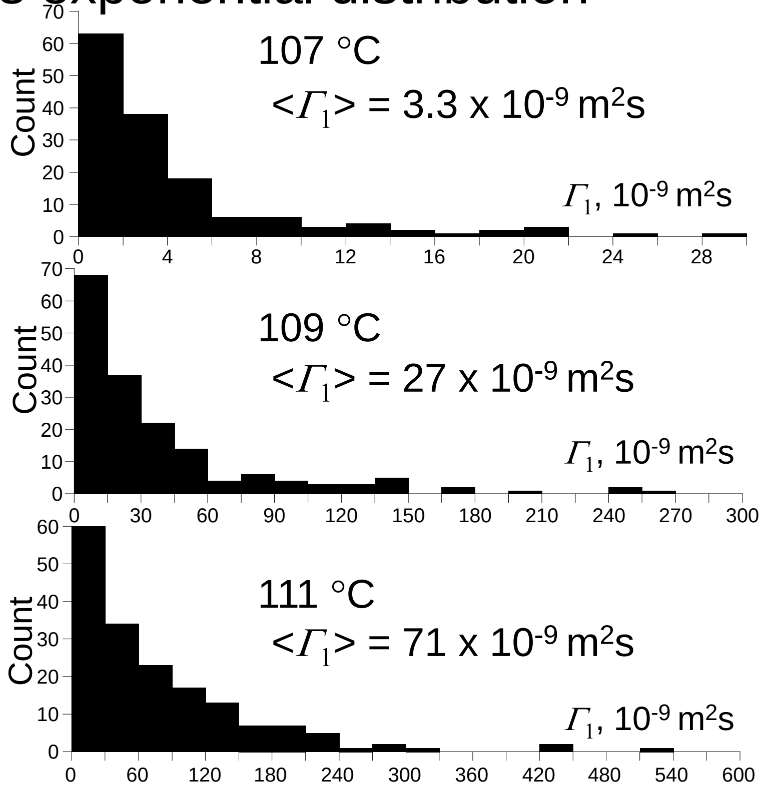
D-mannitol/PVP



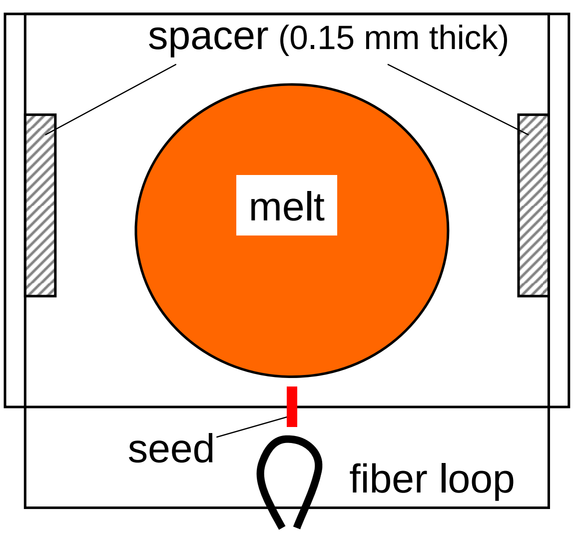
A Poisson process: “Waiting time” to the first success has exponential distribution



1: 1st success
2: 2nd success

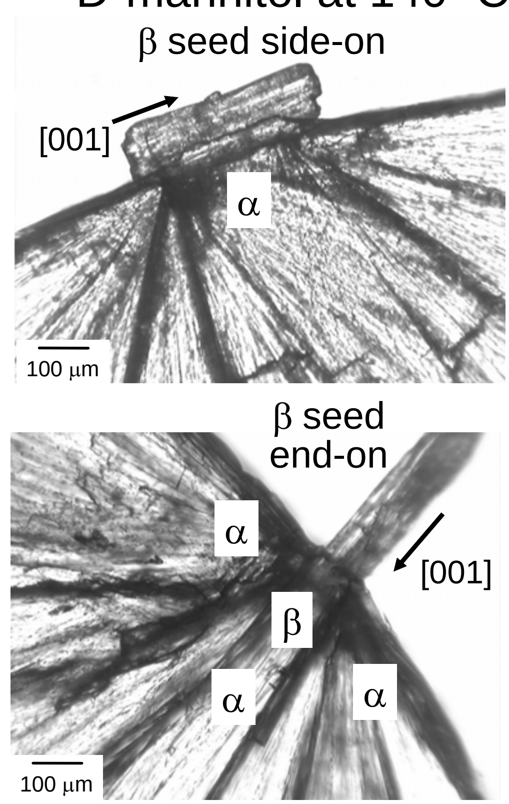


Cross-nucleation in seeded crystallization



Polymorphs identified by Raman microscopy, XRD

D-mannitol at 140 ºC



Tao, J.; Yu, L. *Cryst. Growth Des.* **2007**, *7*, 2410

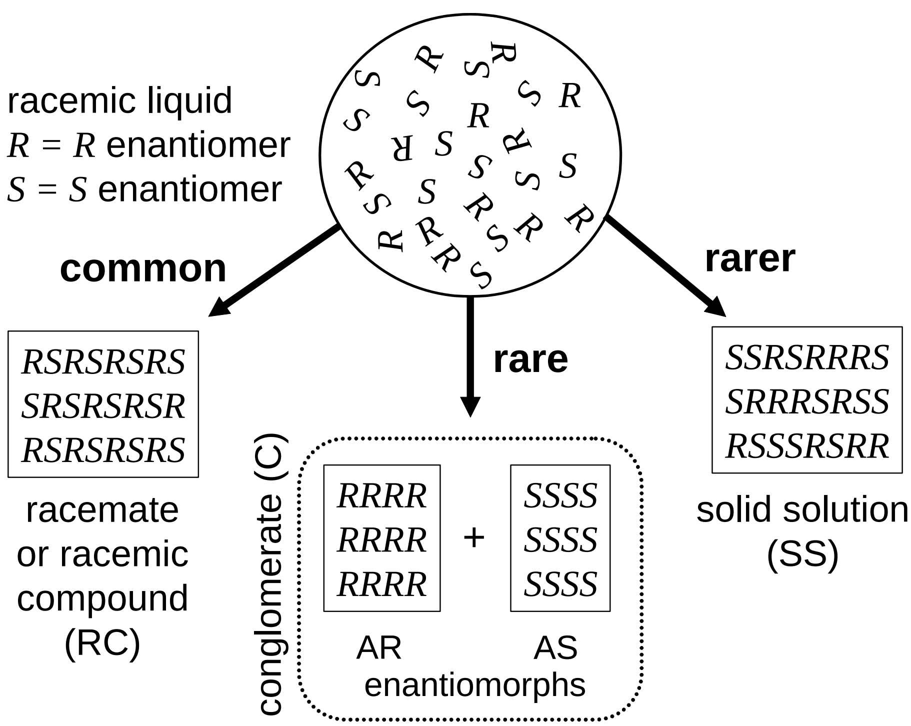
This talk
Crystallization in polymorphic systems

(1) A new mechanism: Nucleation of one polymorph by another

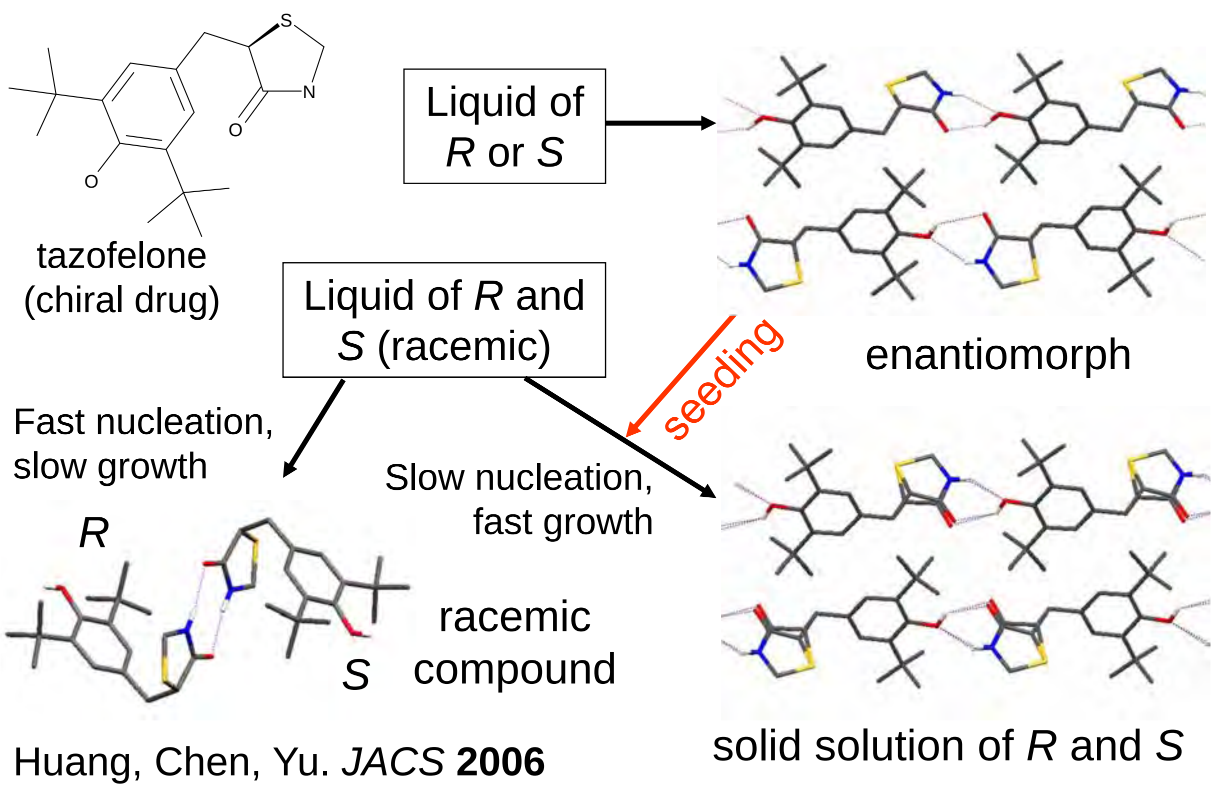
(2) Hidden polymorph discovered by cross-nucleation

(3) Survival of the fittest polymorph: Fast nucleater vs. fast grower

Crystals of resolvable chiral molecules: a special case of polymorphs



A hidden polymorph discovered by seeding

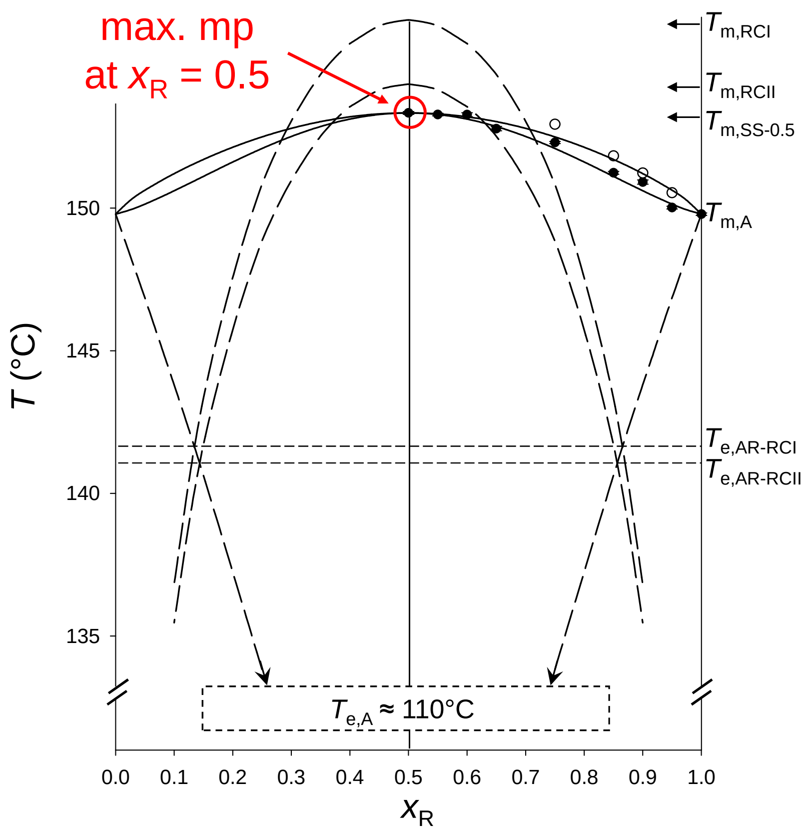


Huang, Chen, Yu. *JACS* **2006**

Crystallographic data of the racemic solid solution of R and S tazofelone

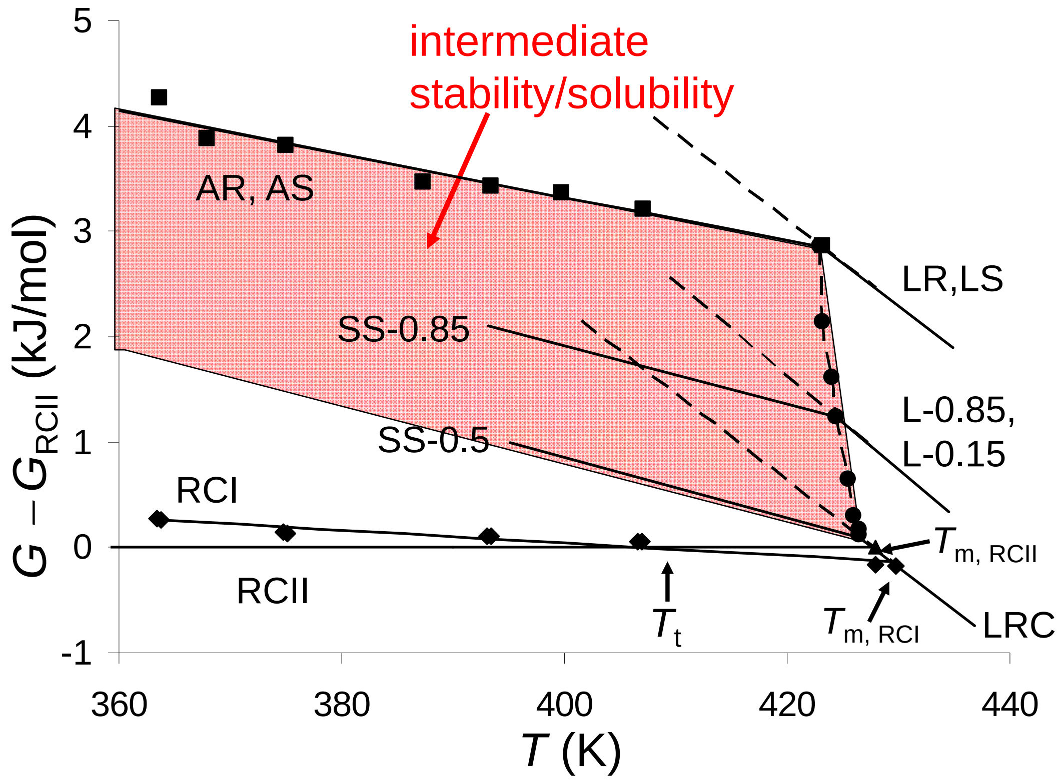
	SS-0.5	**SS-0.5**	**AS**	**RCI**	**RCII**
T/K	100	296	293	293	295
Space group (No.)	$P2_1/n$ (14)	$P2_1/n$ (14)	$P2_1$ (4)	$P2_1/c$ (14)	*Pbca* (61)
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
a/Å	9.1969(9)	9.3882(14)	9.392	11.313	17.204
b/Å	10.9212(11)	10.9503(16)	10.962	17.082	11.287
c/Å	17.6758(17)	17.855(3)	17.823	19.324	18.860
β/°	93.1731(18)	93.766(3)	94.29	101.11	90
V/Å^3	1772.7(3)	1831.6(5)	1829.8	3665	3662.2
Z	4	4	4	8	8
ρ_{calc}/g cm^{-3}	1.205	1.166	1.167	1.165	1.166

A Type 2 solid solution



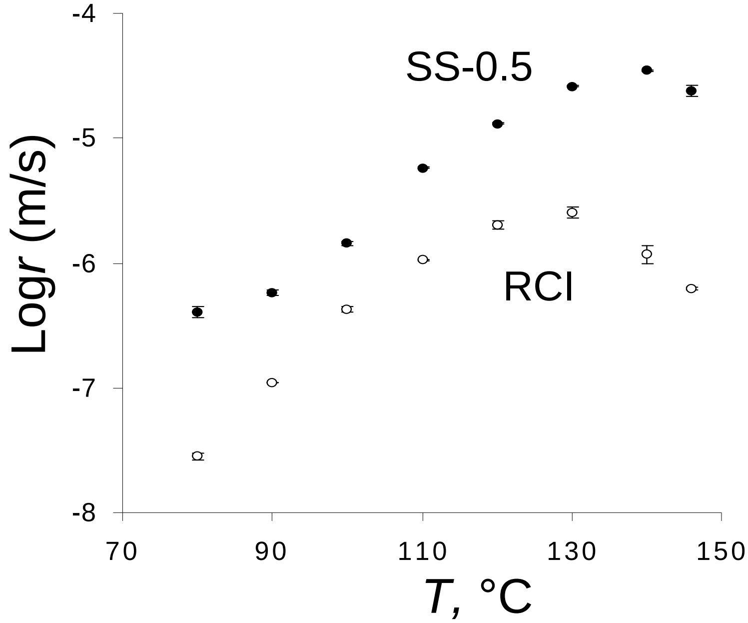
- Solid solutions of enantiomers are rare
- Occurrence in racemate-forming system is unprecedented

Free energies of TZF solid solutions



Yu, L., Huang, J., Jones J. K. *J. Phys. Chem. B* **2005,** *109,* 19915-19922.

The solid solution could be discovered by seeding because it grows faster than the racemic compound, despite its slow nucleation



More hidden polymorphs?

This talk
Crystallization in polymorphic systems

(1) A new mechanism: Nucleation of one polymorph by another

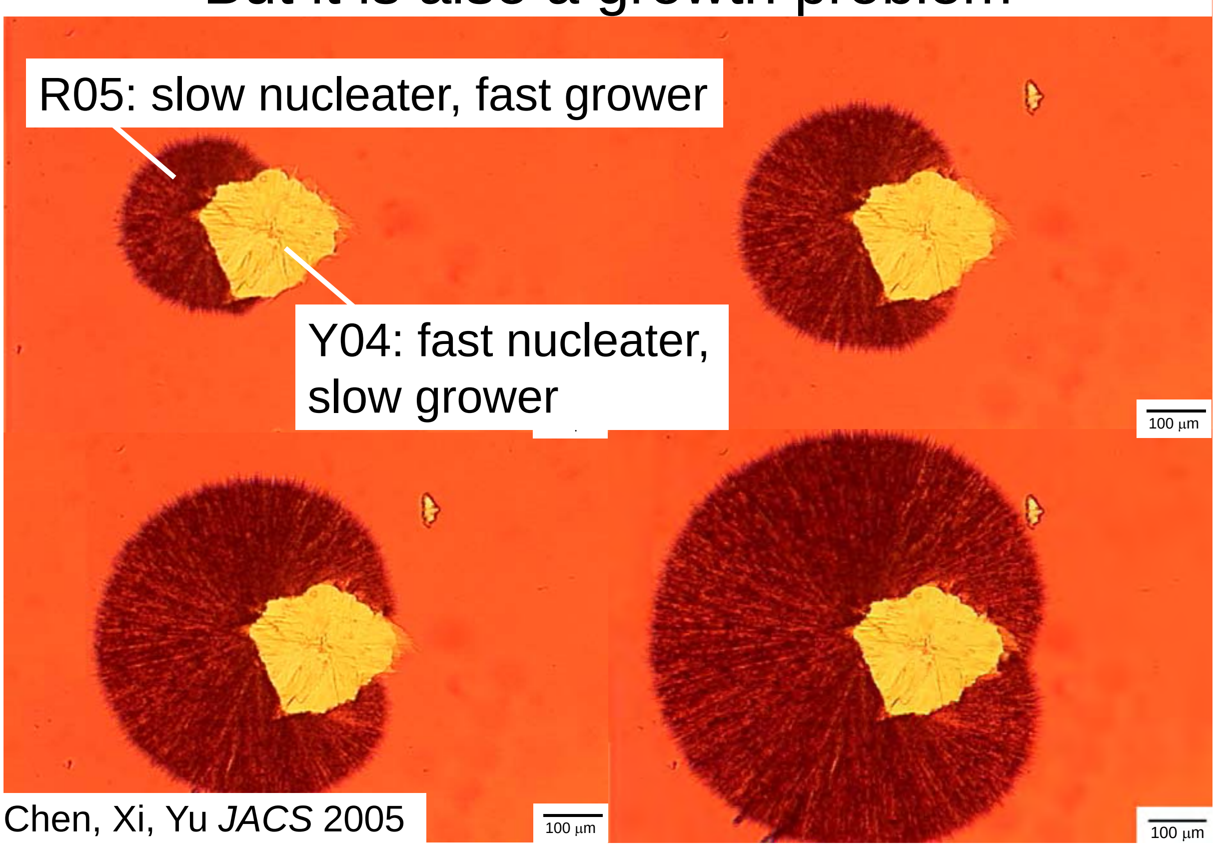
(2) Hidden polymorph discovered by cross-nucleation

(3) Survival of the fittest polymorph: Fast nucleater vs. fast grower

It is common to treat polymorph control as a nucleation problem

- Seeding with a polymorph to grow the same
- The Use of Polymer Heteronuclei for Crystalline Polymorph Selection. Lang, Grzesiak and Matzger* *J. Am. Chem. Soc.* **2002**, *124,* 14834
- Nonphotochemical, Laser-Induced Nucleation of Supersaturated Aqueous Glycine Produces Unexpected γ Polymorph. Zaccaro, Matic, Myerson, and Garetz. *Cryst. Growth & Design* **2001**, *1*, 5

But it is also a growth problem

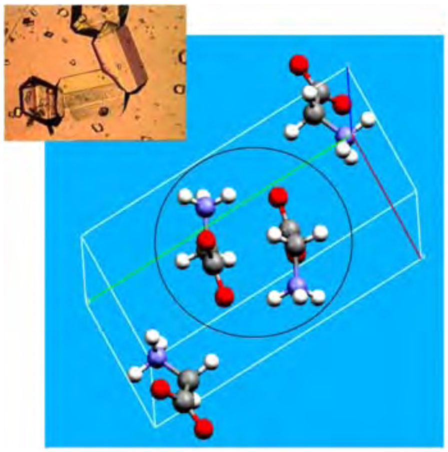


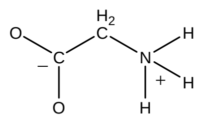
Chen, Xi, Yu *JACS* 2005

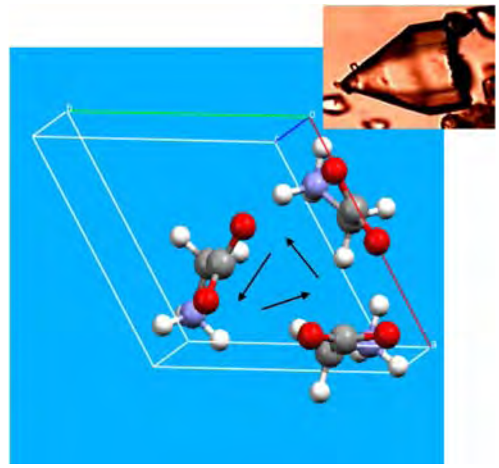
Polymorphs can grow at very different rates

α glycine grows 500 x faster than γ glycine in water at the same supersaturation (10 %)

(Chew et al. *Cryst. Eng. Comm.* **2007)**



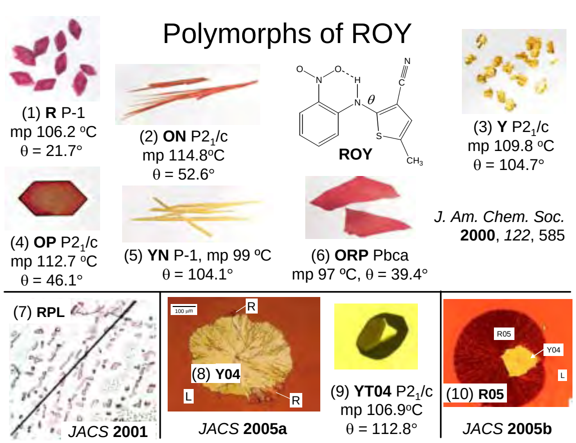


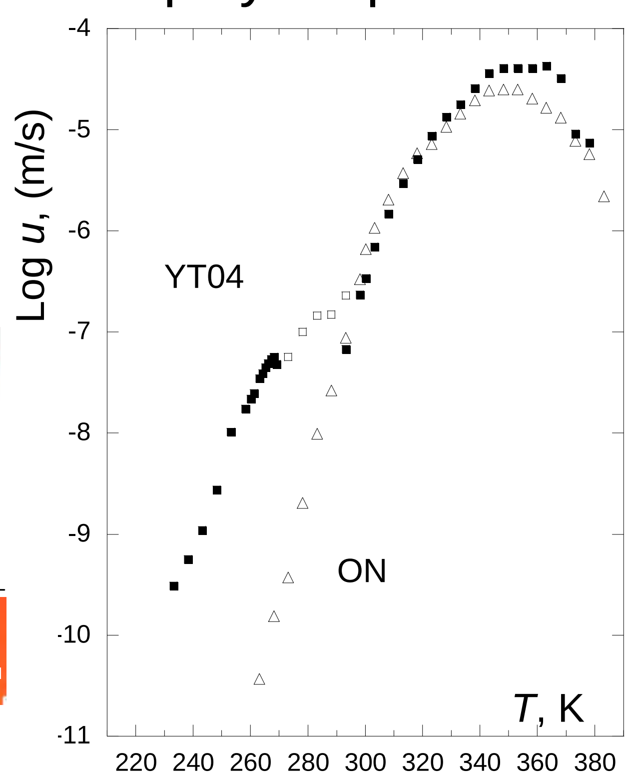


α ($P2_1/n$) – metastable

γ ($P3_1$ or $P3_1$) – stable

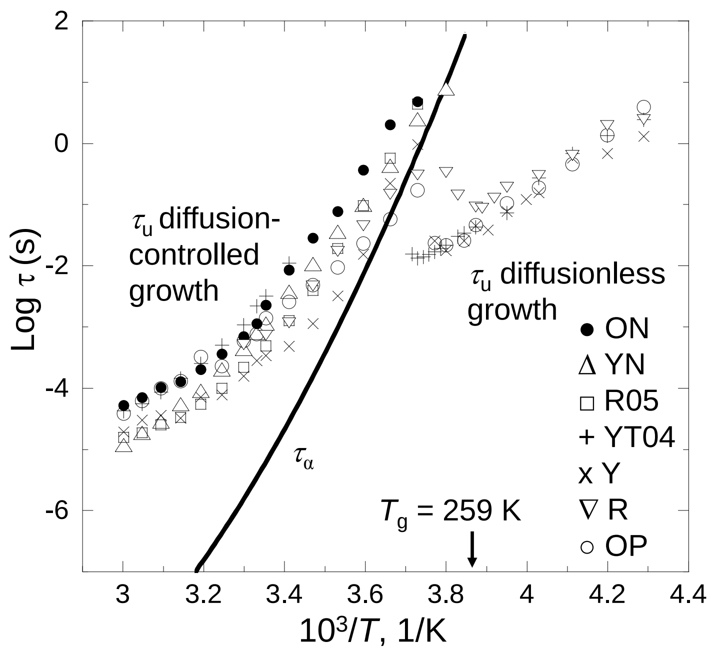
Growth rates between ROY polymorphs can differ by 1000 times and change with temperature





Sun, … *J. Phys. Chem. B* **2008**, *112*, 5594

No good explanations yet…
For ROY, the fast growers can transition from diffusion-controlled to "diffusionless" growth



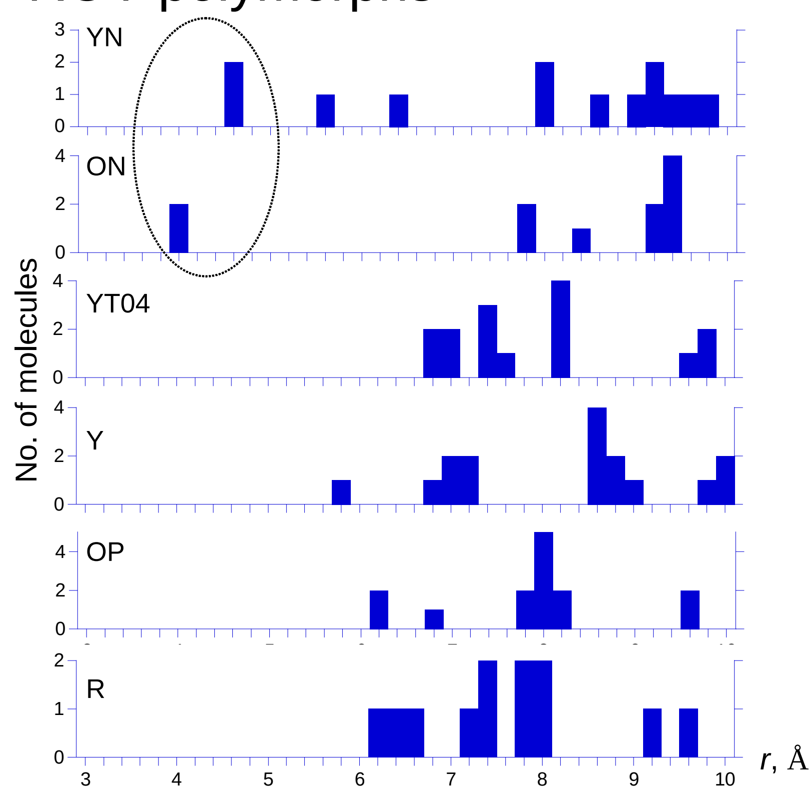
τ_u : time required to add one layer of molecules to the crystal

τ_α : time required for an average molecule in the liquid to reorient or diffuse its diameter

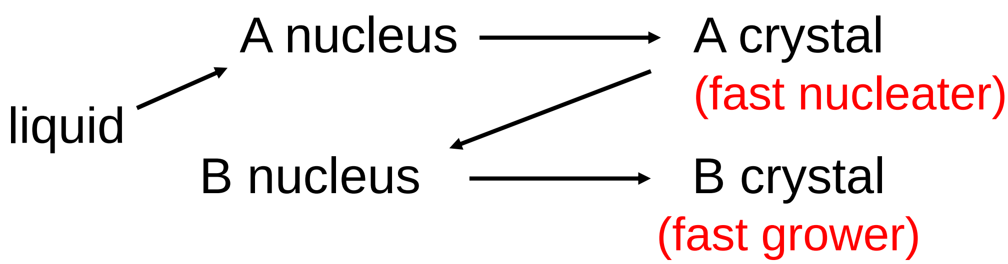
Center-of-mass radial distribution functions of ROY polymorphs

Diffusion-controlled growth

Able to transition to "diffusionless" growth



If the fast grower is not the fast nucleater, it can still “win” by nucleating on an existing polymorph



Summary

- Fast nucleater need not be fast grower
- Through cross-nucleation, a fast-growing polymorph can dominate the product
- Cross-nucleation helps discover a rare solid solution of enantiomers. It is the first example for a racemate-forming system
- The relative growth rates of polymorphs is an important unsolved (likely solvable) problem