“Impact of Low-Level Hydrogen-Bonding Impurities on Nucleation Rates”

Crystallization Workshop: Nucleation, Applications and Process Optimization

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October 04, 2023

Personal Introduction – Carlos Pons Siepermann

- B.S.E Chemical Engineering – University of Michigan (2013)

- M.S. Chemical Engineering Practice – MIT (2016)
- PhD. Chemical Engineering – MIT (2018)
  - Allan S Myerson research group
- Senior Scientist - Bristol Myers Squibb (2018-2021)
  - Chemical Process Development
- Associate Principal Scientist – Merck (2021-Present)
  - Chemical Engineering Research & Development – X-labs

Control in Crystallization

- Batch/process conditions regulate product characteristics
- Solution chemistry impacts all aspects of crystallization: kinetics, yield, purity, form
- Solution complexation should be thought of as a parameter that regulates crystallization
  - Purification enhancement
  - Nucleation rate control

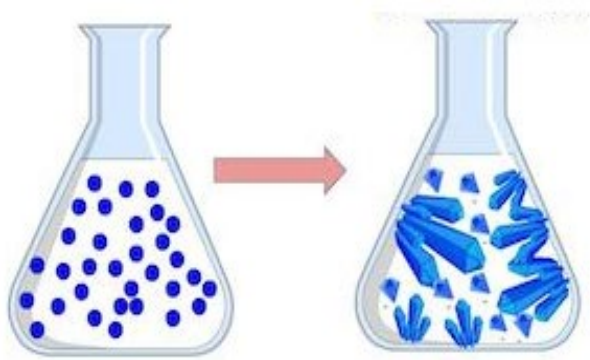
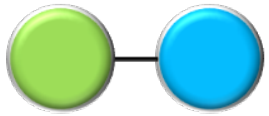
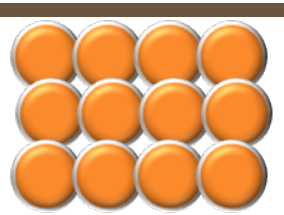


Image adapted from: study.com/academy/lesson/how-to-prepare-a-supersaturated-solution.html

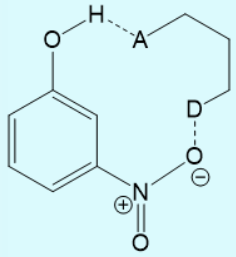
PhD Thesis Work Distribution



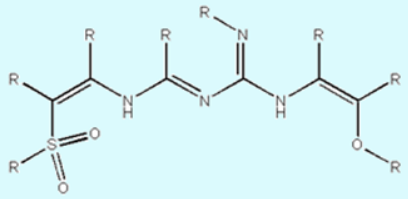
Solution Complexation + Crystallization



Purification

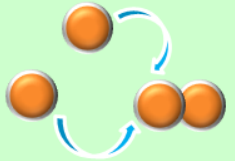


Isomer Separation

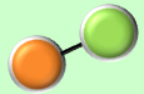


Complex API

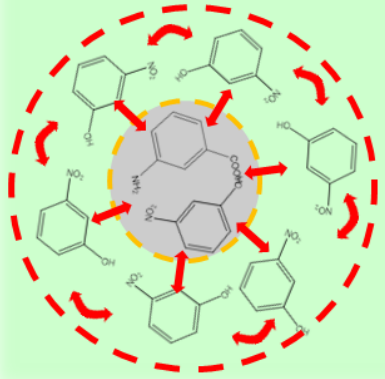
Inhibition



Vs.



Demonstration

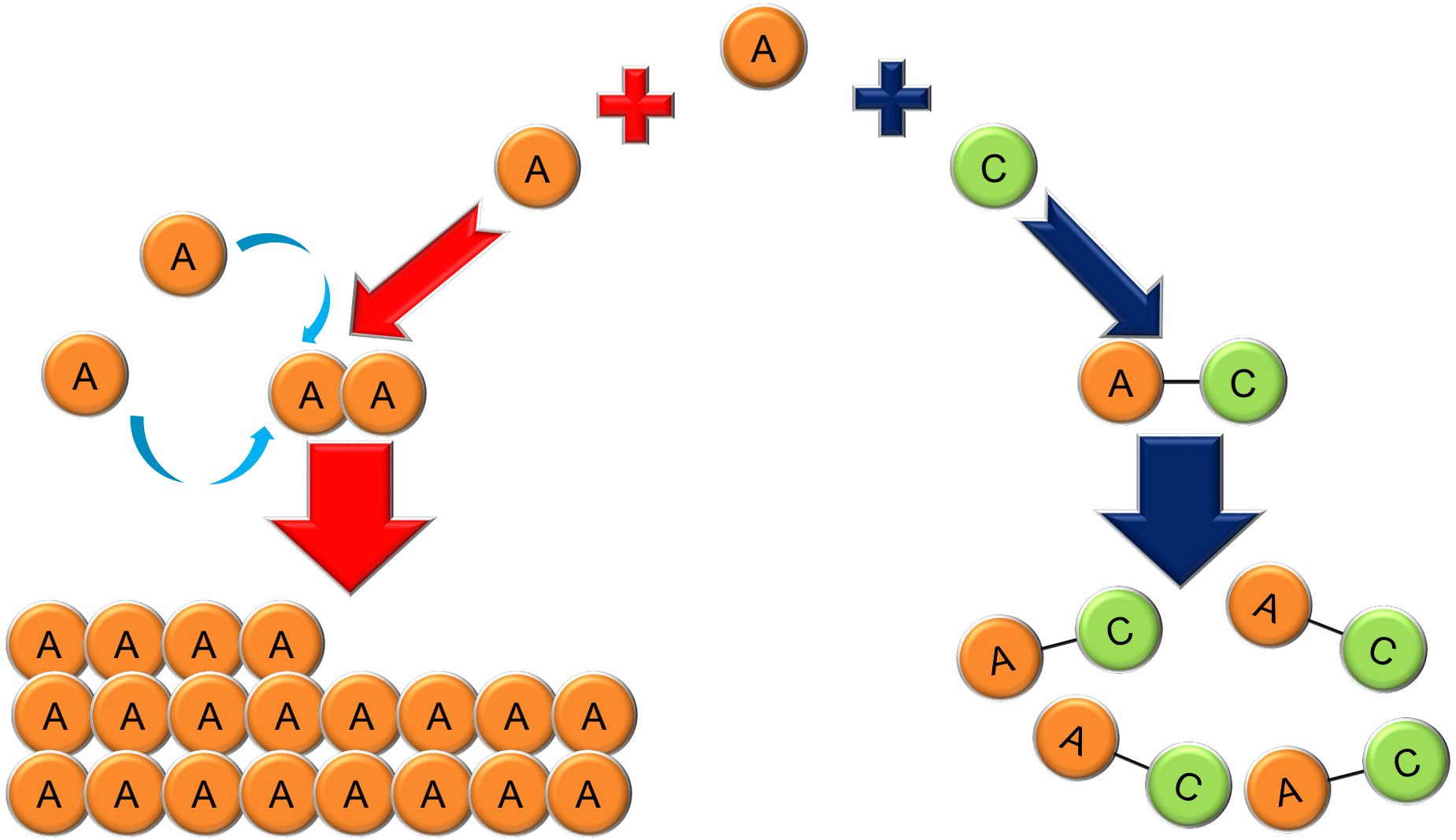


Mechanism (?)

Today's talk

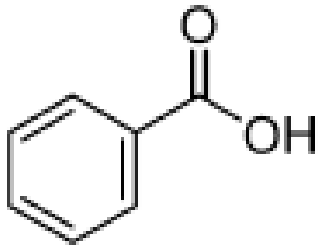
Adapted from: Pons-Siepermann, Carlos; *"Effects of Solution Complexation on Crystallization Processes"*, Graduate Thesis, **2018**, https://dspace.mit.edu/handle/1721.1/121897

Review of Nucleation Inhibition using Complexation

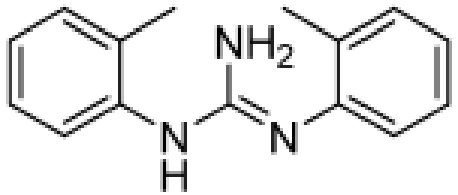


Part 1: Nucleation Inhibition of Benzoic Acid

- Systematically evaluate nucleation rates for a molecule in the presence of a well-known complexing additive
- Crystallization of benzoic acid (BA)
- Complexing agent: 1,3-di-*o*-tolylguanidine (DOTG)
- System is well-studied and proven to complex effectively[a]



BA



DOTG

[a] Weber, C, G Wood, A Kunov-Kruse, D Nmagy, B Trout, and A Myerson. 2014. *Crystal Growth and Design* 14: 3649-3657.

Nucleation Theory

$$P_m = \frac{N^m}{m!}\exp(-N)$$

$$P_0 = \exp(-N)$$

$$P_{>1} = P^* = 1 - \exp(-N)$$

$$N = JVt$$

$$P^* = 1 - \exp(-JVt)$$

$$\mathbf{\ln(1 - P^*) = -JVt}$$

Jiang, S.; Horst, J. *Crystal Growth & Design.* **11**, 2011, PP. 256-261

Legend:

P_m = probability of m crystals to have formed after time t

P_0 = probability of 0 crystals to have formed after time t

P^*= probability of any crystals to have formed after time t

N = average number of crystals expected to form after time t

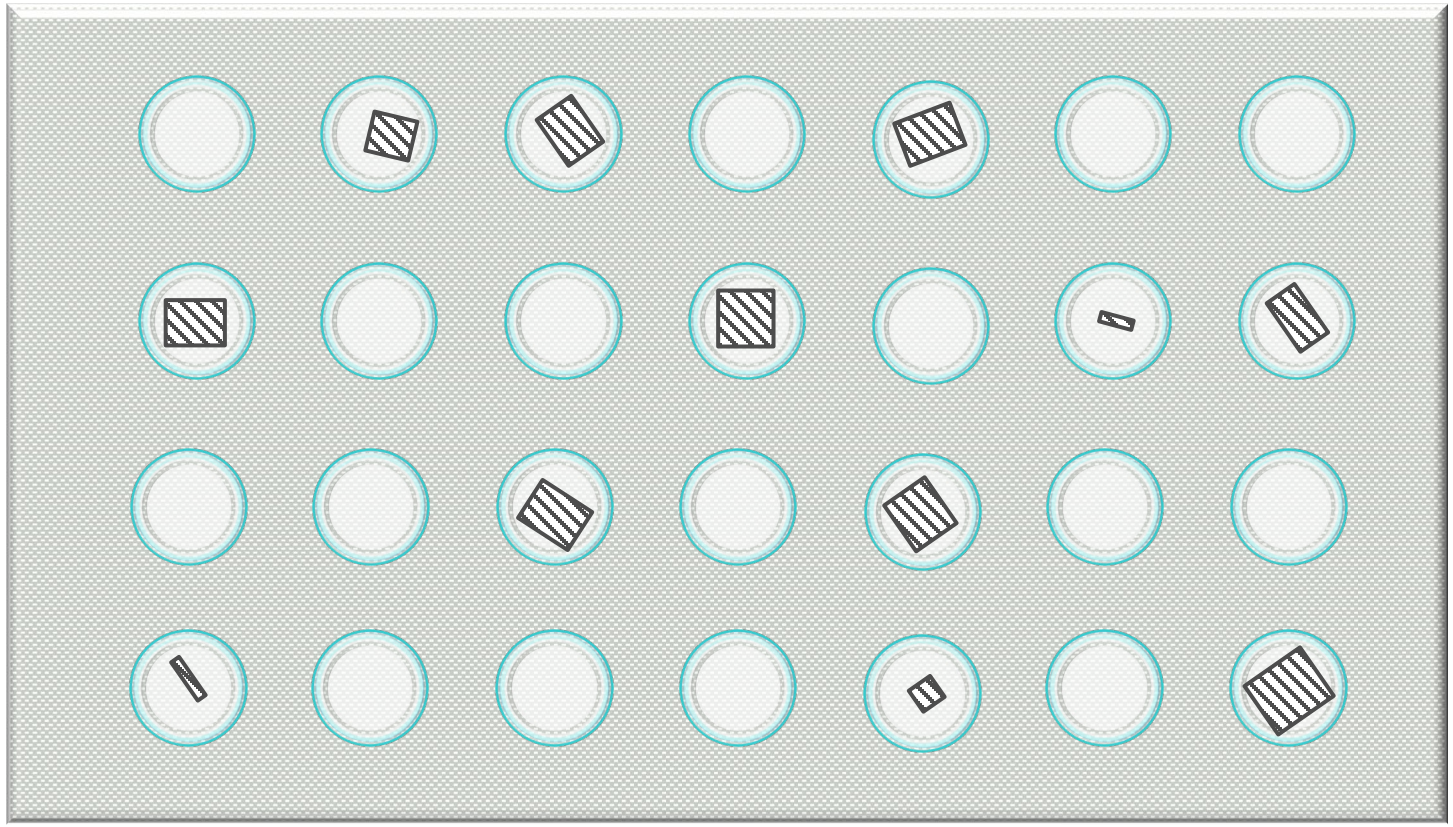
J = average nucleation rate

V = vessel volume

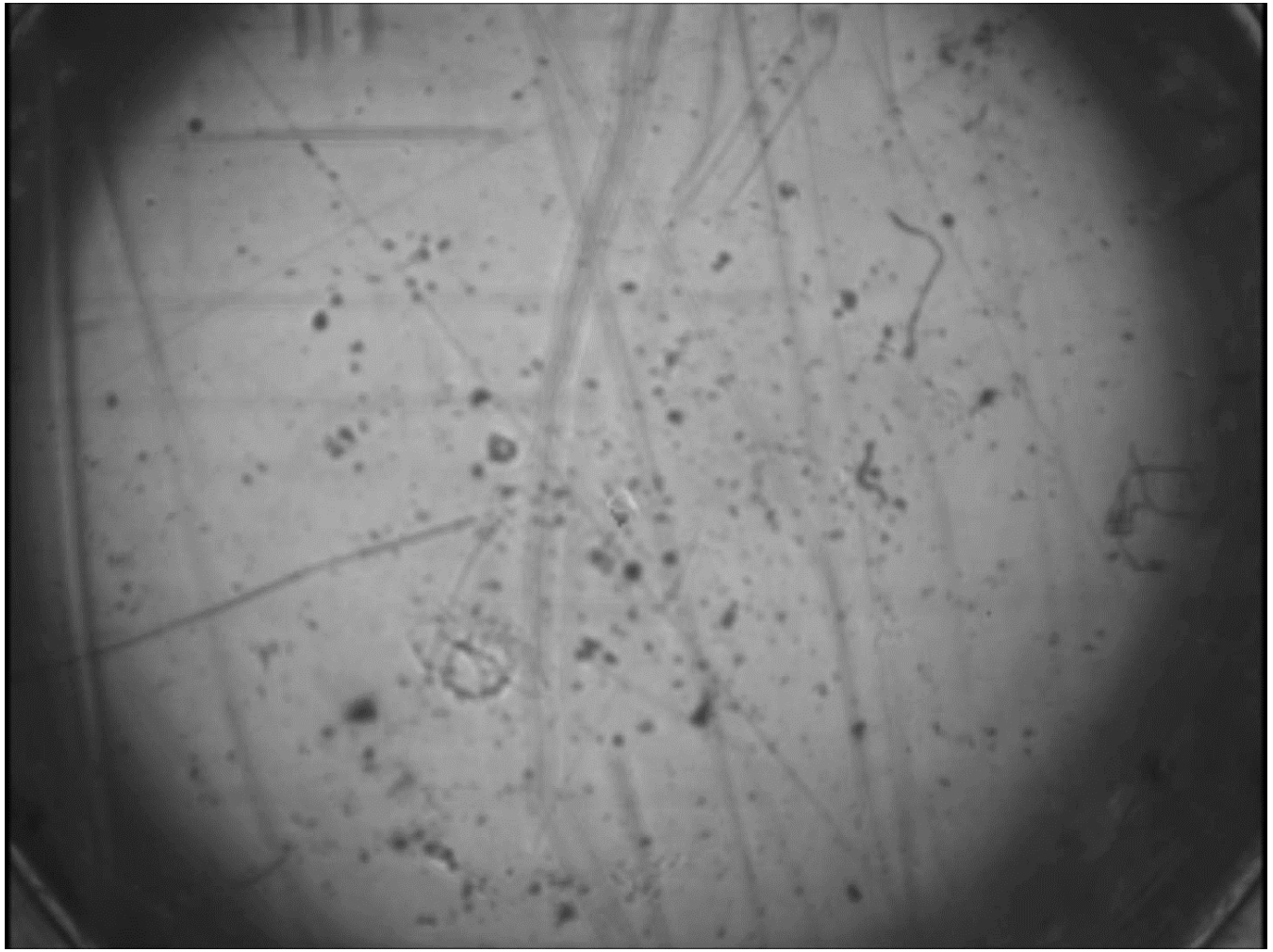
t = time

Experimental Setup

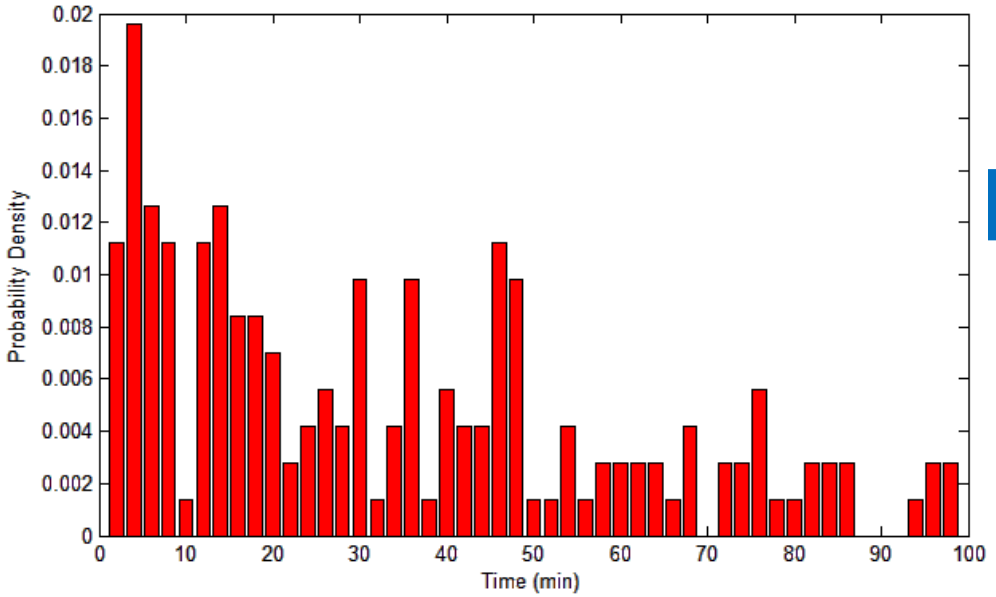
- Custom microscope with custom rotating stage with underside automated camera imaging
- Parallel imaging of 80 experiments at a time
- Enabled use of smooth, high quality glass vials (impact on heterogeneous nucleation rates)
- Expensive/complex but powerful alternative to cycling approaches for induction time measurements



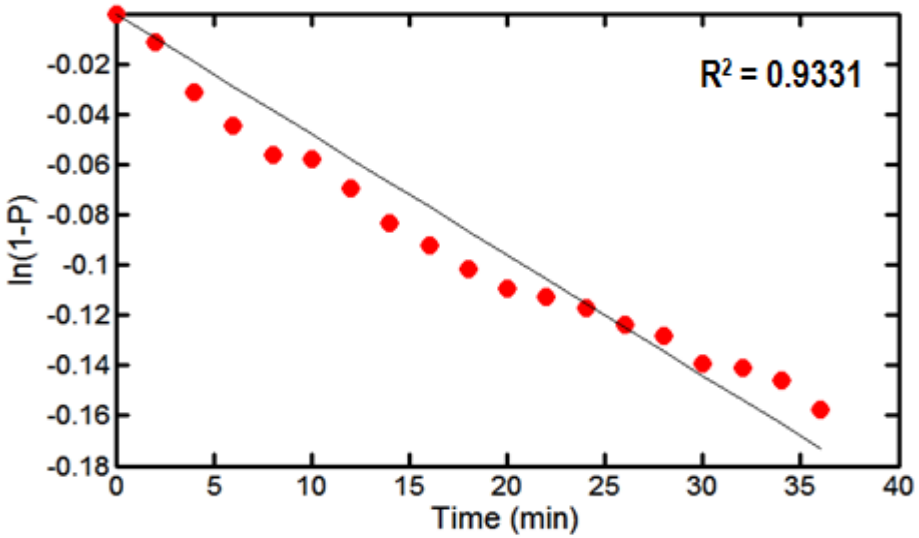
Crystal Growth in Microscope



Data Processing form Microscope Experiments



$$P^* = 1 - \exp(-JVt)$$

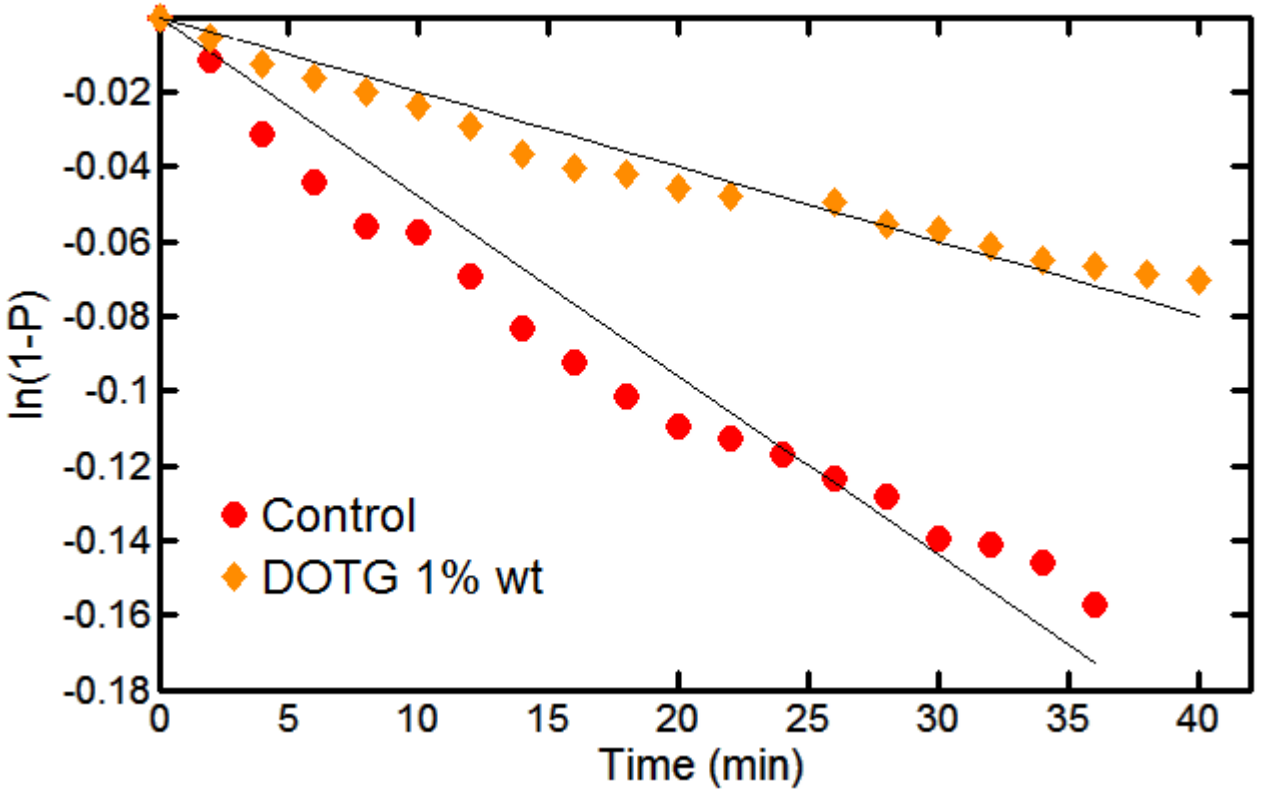


$$\ln(1 - P) \approx -0.0048t$$

$$\tau = \frac{1}{|-0.0048|} = 208\ min$$

Images from: C. A Pons Siepermann; S. Huang; A. S. Myerson;, **Cryst. Growth. Des.**, 2017, 17 (5), 2646-2653

Complexation Effect

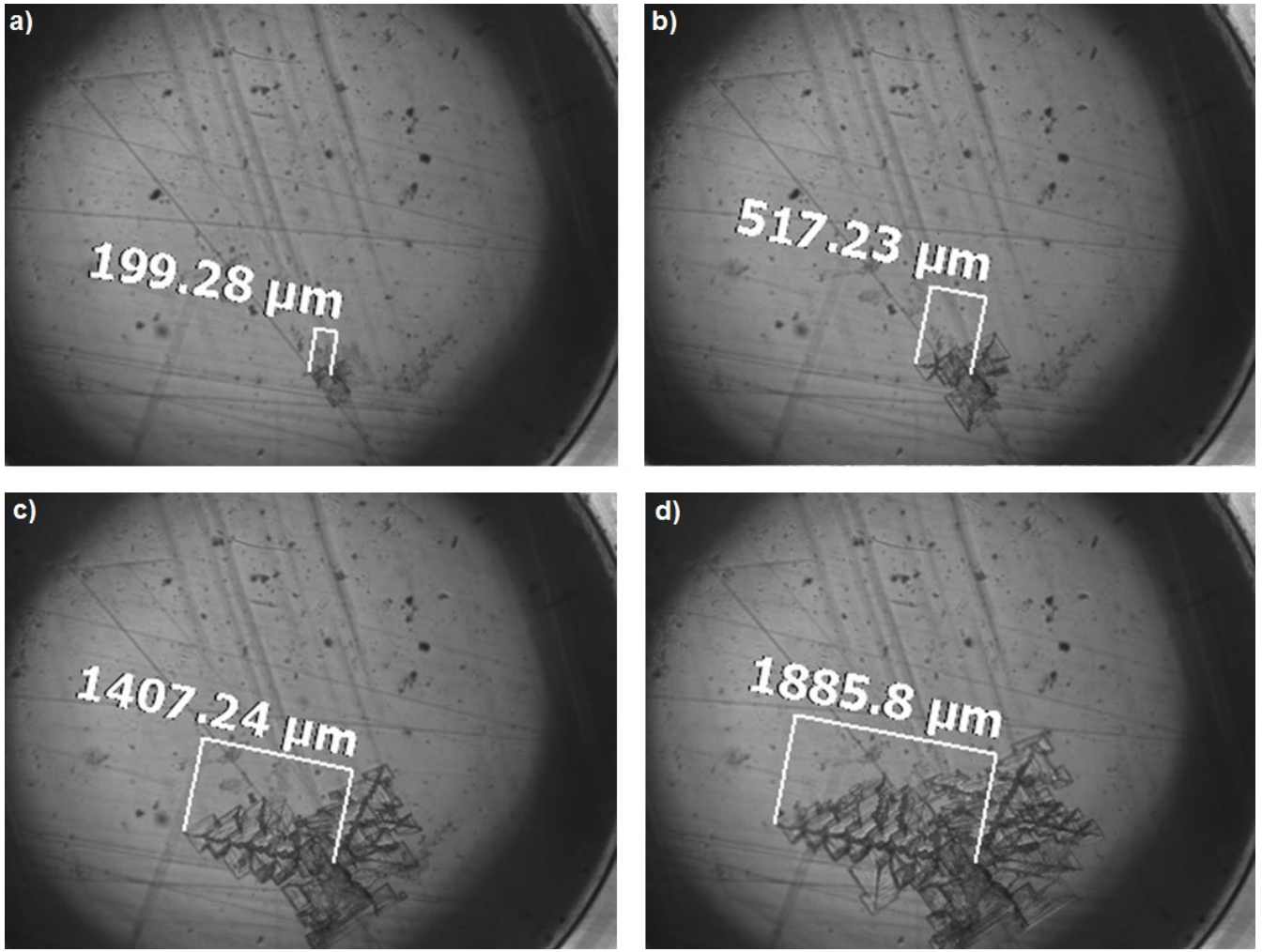


Control: 208 min

DOTG 1 %wt: 500 min

Image from: C. A Pons Siepermann; S. Huang; A. S. Myerson;, **Cryst. Growth. Des.**, 2017, 17 (5), 2646-2653

Growth Rate Measurement



Solubility Adjustment

- BA equilibrium solubility measured with HPLC at varying concentrations of DOTG

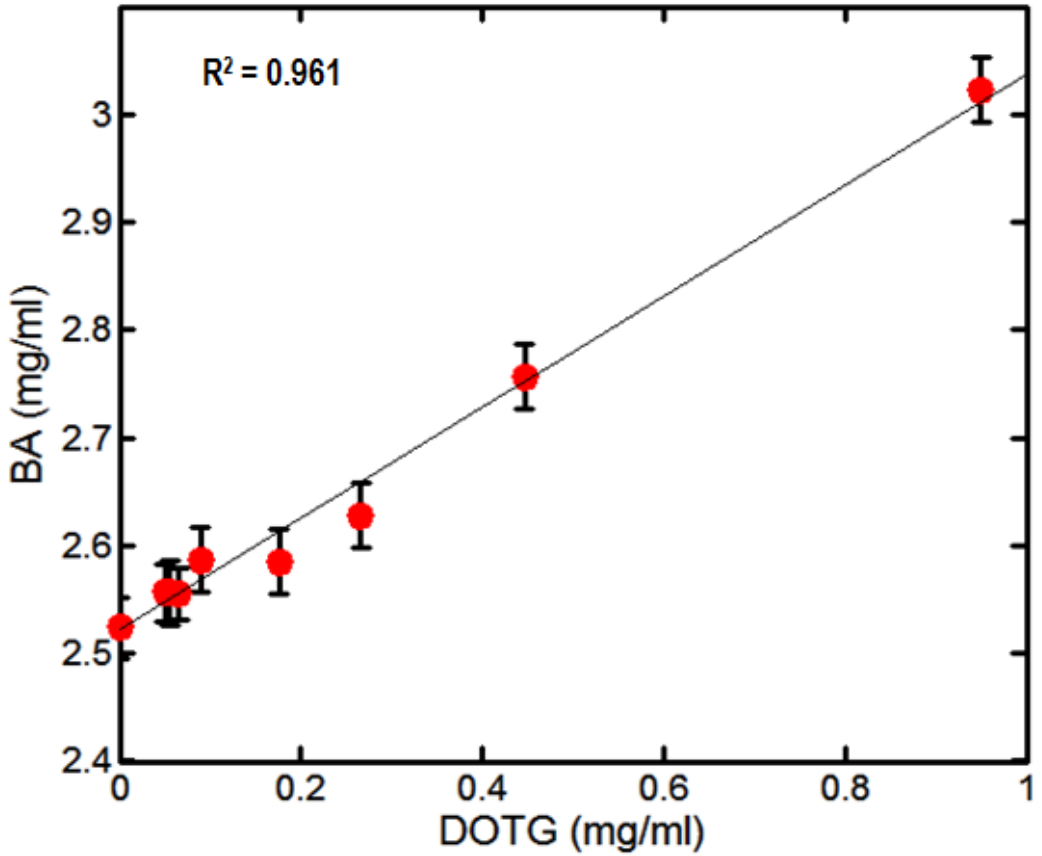


Image from: C. A Pons Siepermann; S. Huang; A. S. Myerson;, **Cryst. Growth. Des.**, 2017, 17 (5), 2646-2653

Effect of Varying DOTG Amount at Constant S

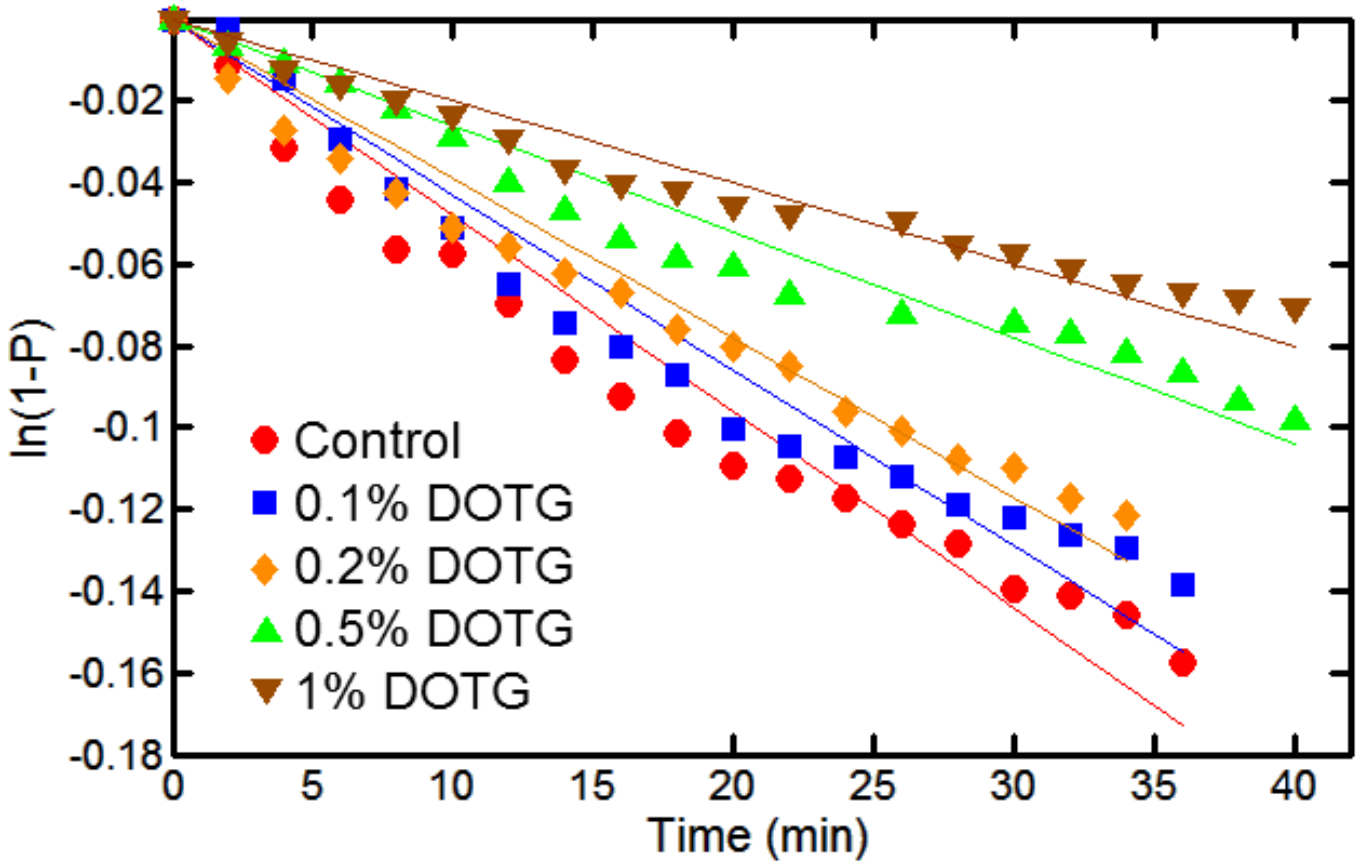
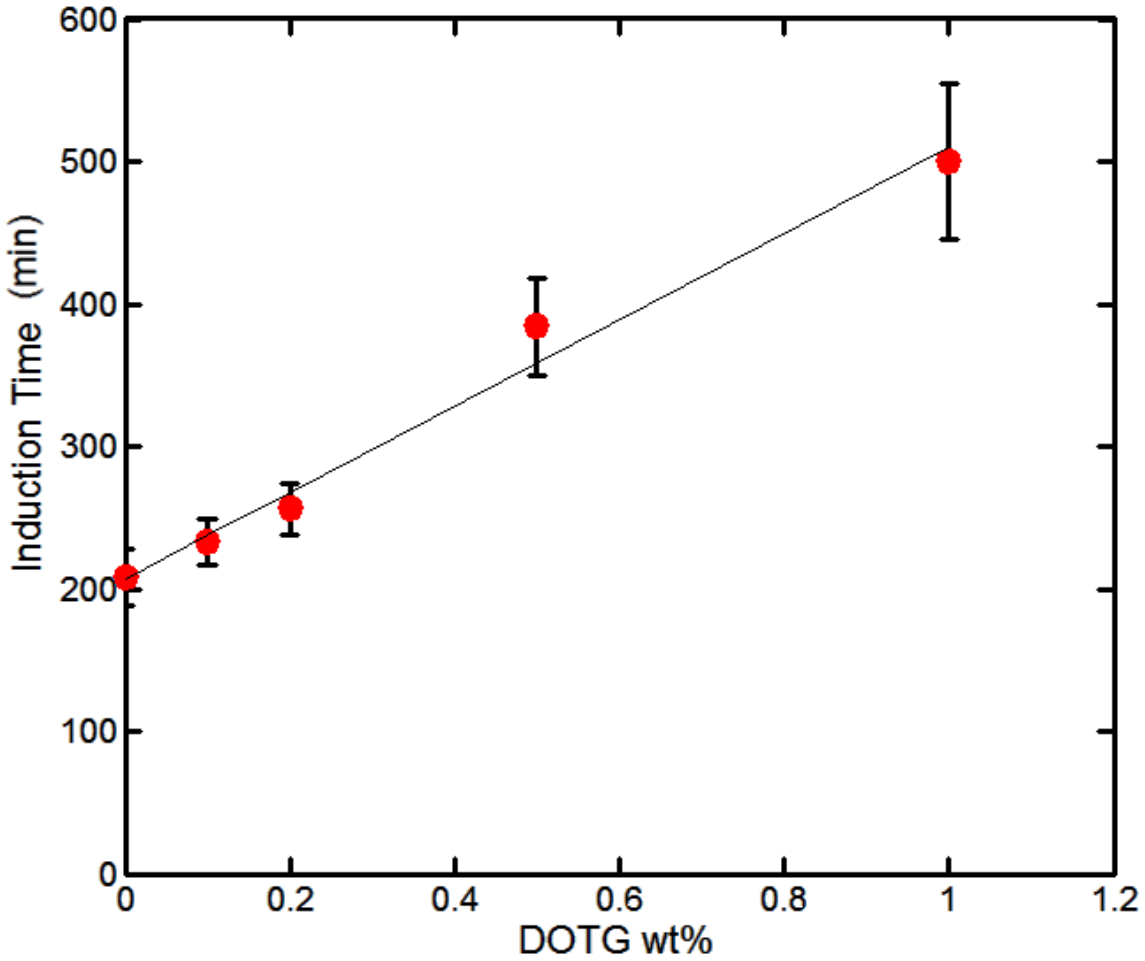


Image from: C. A Pons Siepermann; S. Huang; A. S. Myerson;, **Cryst. Growth. Des.**, 2017, 17 (5), 2646-2653

Effect of Varying DOTG Amount



Control: 208 min

DOTG 0.1%: 233 min

DOTG 0.2%: 256 min

DOTG 0.5%: 384 min

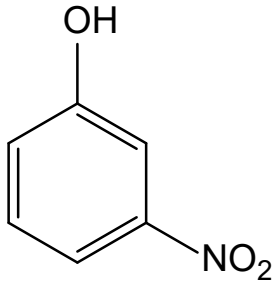
DOTG 1%: 500 min

Image from: C. A Pons Siepermann; S. Huang; A. S. Myerson;, **Cryst. Growth. Des.**, 2017, 17 (5), 2646-2653

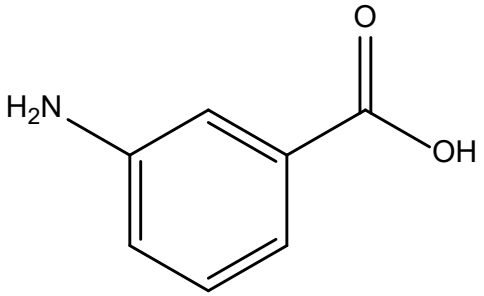
Part 2 – Nucleation Inhibition of 3-Nitrophenol

- Expand the findings for the BA inhibition project
  - New complexation motif, not reliant on ion exchange
  - Weaker interaction between molecules
- Further elucidate the mechanisms of inhibition

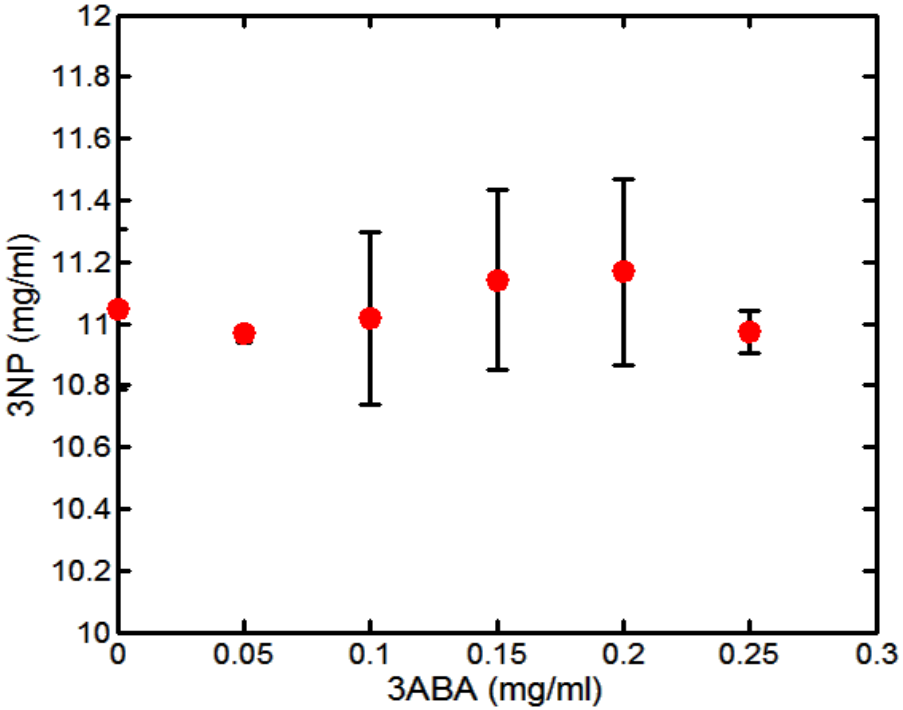
Temp. (K)	K	ΔG (kJ/mol)	ΔH (kJ/mol)	ΔS (kJ*mol^{-1}*K^{-1})
278	13.4 ± 0.7	-6.00 ± 0.1	-198 ± 5	-0.69 ± 0.02
298	6 ± 2	-4.3 ± 0.8	-224 ± 24	-0.74 ± 0.08



3-Nitrophenol



3-Aminobenzoic acid



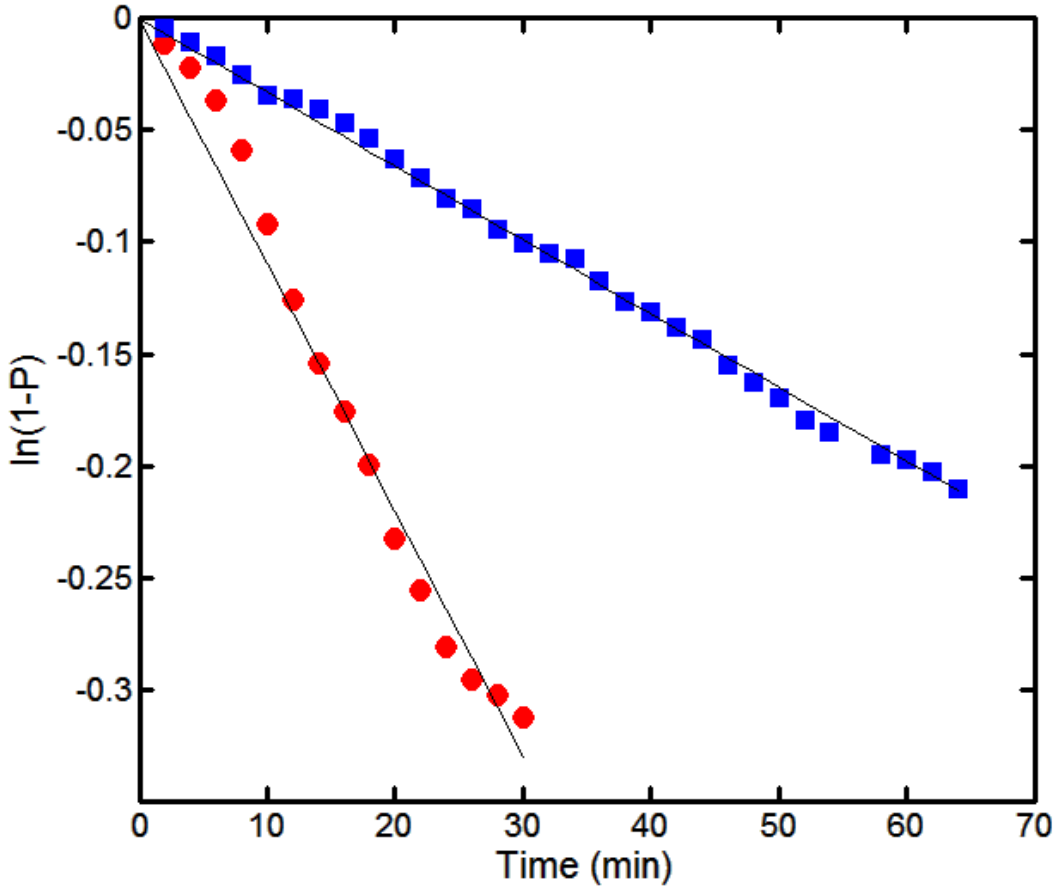
Images from: C. A Pons Siepermann; A. S. Myerson;, **Cryst. Growth. Des.**, 2018, 18 (6), 3584–3595

Induction Results for Control Groups

Sample	S	C_{3NP} (mg/ml)	J (# sec^{-1} m^{-3})	τ (min)	n
Control	1.810	20.00	367 ± 15	91 ± 4	559
0.05 mg/ml 3ABA	1.810	20.00	110 ± 1	303 ± 3	480

Control

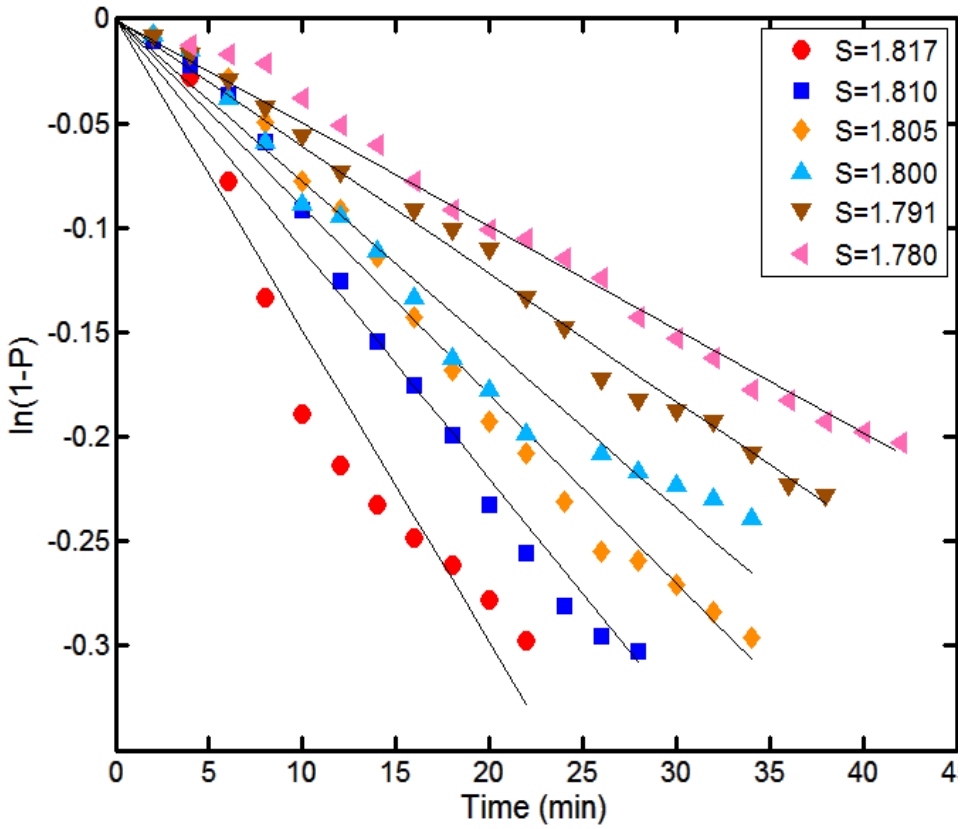
3ABA 0.25 % wt



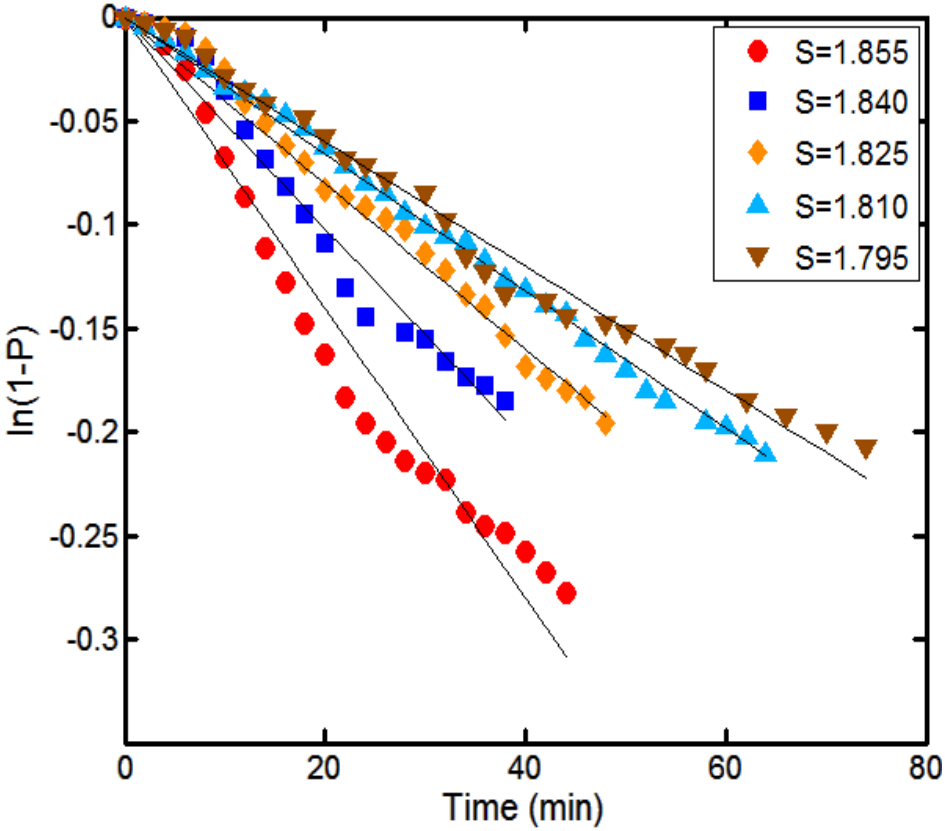
Images from: C. A Pons Siepermann; A. S. Myerson;, **Cryst. Growth. Des.**, 2018, 18 (6), 3584–3595

Effect of Changing Supersaturation on *J*

Pure 3NP



3ABA 0.25 % wt



Images from: C. A Pons Siepermann; A. S. Myerson;, **Cryst. Growth. Des.**, 2018, 18 (6), 3584–3595

Nucleation Kinetics

Condition	Average *A* (# sec^{-1} m^{-3})	Range *A* (# sec^{-1} m^{-3})	*B*
No Additive	$4.79*10^{8}$	$1.06*10^{7} – 2.18*10^{10}$	5.1 ± 1.3
3ABA 0.25 % wt	$1.26*10^{5}$	$7.67*10^{3} – 2.07*10^{6}$	2.7 ± 1.0

$$J = ASexp\left(-\frac{B}{\ln^2 S}\right)$$

$$S = \frac{C}{C^*}$$

■ Pure 3NP

● 3ABA 0.25 % wt

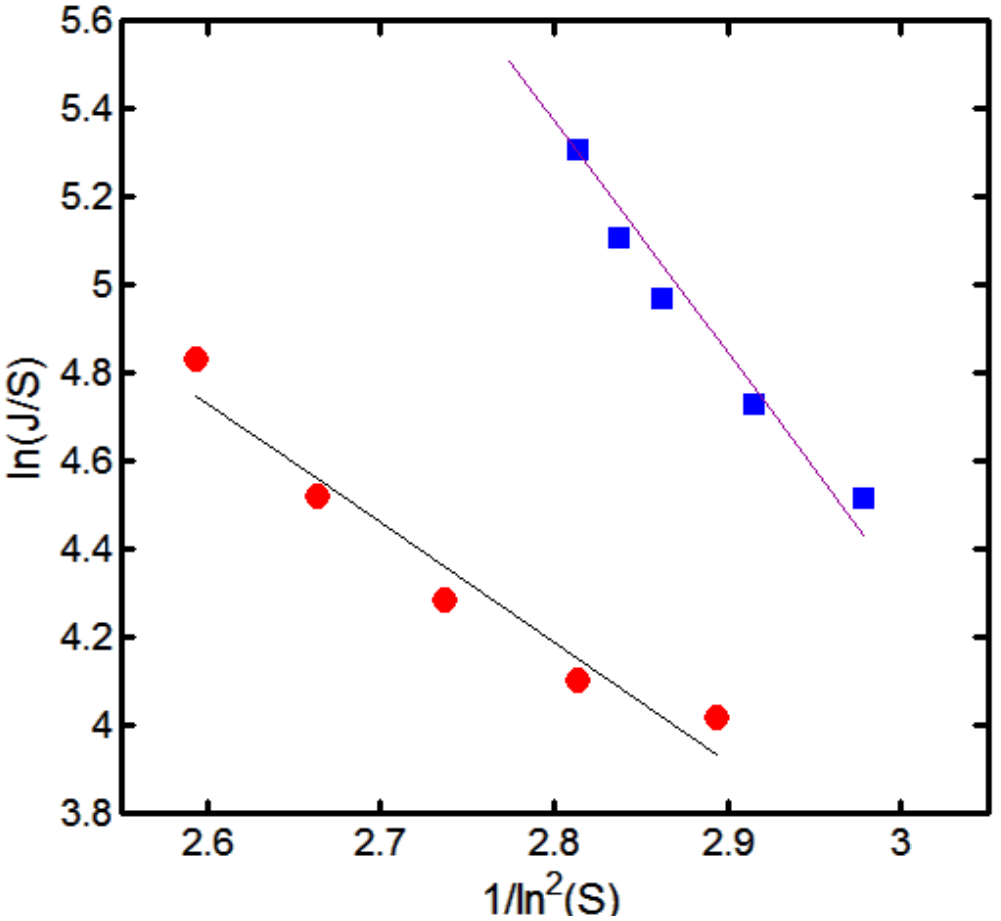


Image from: C. A Pons Siepermann; A. S. Myerson;, **Cryst. Growth. Des.**, 2018, *Published online*

Nucleation Mechanisms

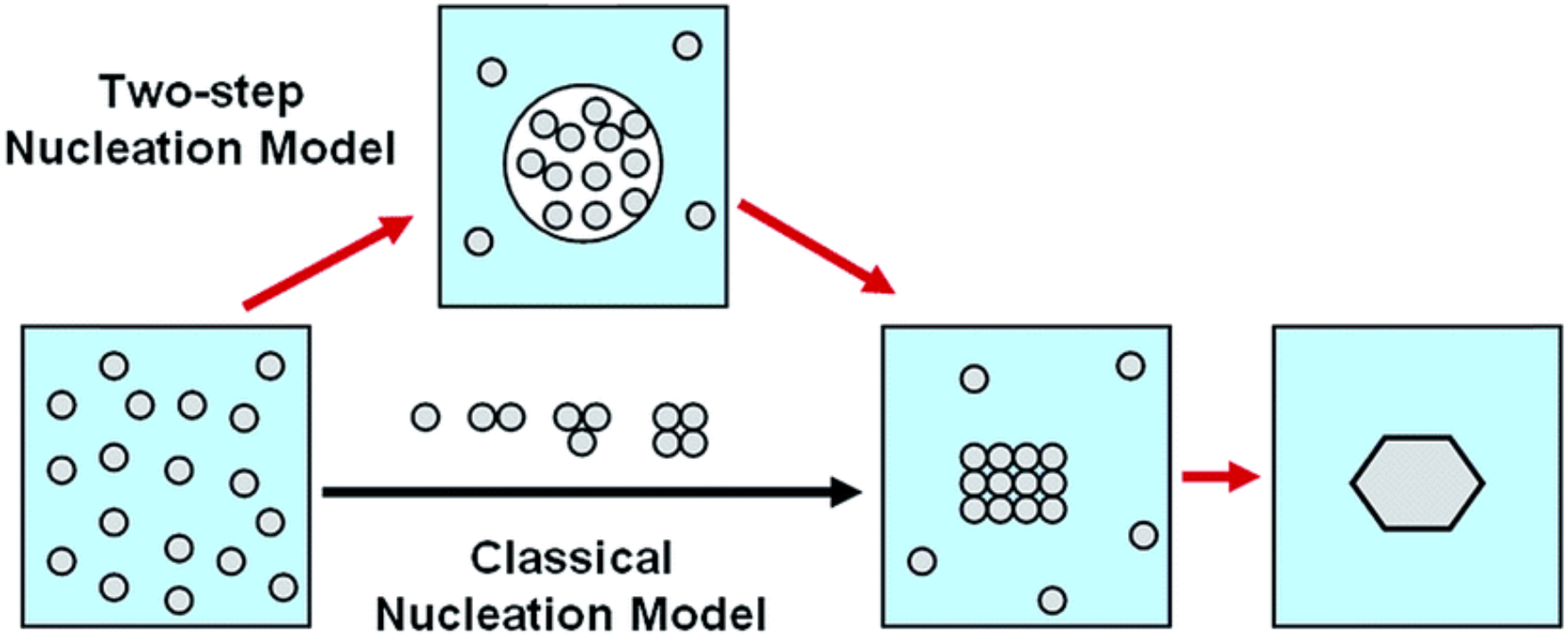


Image from: Myerson, A. S.; *Faraday Discuss.*, **2015**, *179,* 543-547

Theoretical Analysis

$$J = AS \exp\left(-\frac{B}{\ln^2 S}\right)$$

Classical Nucleation[a]:

$$A = \left(\frac{4\pi}{3v_0}\right)^{\frac{1}{3}} \left(\frac{\gamma_e}{kT}\right)^{\frac{1}{2}} DC^* \qquad B = \frac{16\pi v_0^2 \gamma^3}{3\,(k_B T)^3}$$

[a] Kashchiev, D.; Rosmalen, G.; *Cryst. Res. Technol.* **2003**, *38*, 555-574

Vekilov's Two-Step Model[b]:

$$J = \frac{k_2 C_1 T exp\left(-\frac{\Delta G_2^*}{k_b T}\right)}{\eta_1(C_1, T)\left[1 + \frac{U_1}{U_0}\exp\left(\frac{\Delta G_C^0}{k_B T}\right)\right]} \Leftrightarrow J = \frac{\phi k_2 C_1 T}{\eta}\exp\left(-\frac{\Delta G_2^*}{k_b T}\right)$$

[b] Vekilov, P.; *Nanoscale*, **2010**, *2,* 2346-2357

Two-Step Model Analysis

$$J = \frac{\phi k_2 C_1 T}{\eta} \exp\left(-\frac{\Delta G_2^*}{k_b T}\right)$$

$$\frac{\phi k_2 C_1 T}{\eta} \approx AS \qquad \left(\frac{\partial J}{\partial S}\right)_T \qquad -\frac{\Delta G_2^*}{k_b T} = -\frac{B}{\ln^2 S}$$

$$J = AS \exp\left(-\frac{B}{\ln^2 S}\right)$$

Two-Step Model – Activation Energy

$$J = \frac{Sk_2C_1T}{A''\eta}\exp\left(-\frac{\Delta G_2^*}{k_bT}\right)$$

$$\Delta G_2^* = \frac{16v_0^2\gamma^3}{3\Delta\mu^2} \longleftarrow \Delta\mu = k_BT\ln S$$

$$\Delta G_2^* = \frac{16v_0^2\gamma^3}{3(k_BT)^3\ln^2 S} \longleftrightarrow \text{Constants}$$

$$J = \frac{\phi k_2C_1T}{\eta}\exp\left(-\frac{B}{\ln^2 S}\right)$$

Two-Step Model Analysis – Pre Exponential

$$J = \frac{\phi k_2 C_1 T}{\eta} \exp\left(-\frac{B}{\ln^2 S}\right)$$

$$\frac{1}{\phi} = 1 + \frac{U_1}{U_0} \exp\left(\frac{\Delta G_C^0}{k_B T}\right) \quad \Leftarrow \quad \Delta G_C^0 > 0$$

$$\frac{1}{\phi} \approx \frac{U_1}{U_0} \exp\left(\frac{\Delta G_C^0}{k_B T}\right) \quad \Leftarrow \quad U_0 = \alpha C$$

$$\frac{1}{\phi} \approx \frac{U_1}{\alpha S C^*} \exp\left(\frac{\Delta G_C^0}{k_B T}\right) \approx \frac{A''}{S} \quad \Leftarrow \quad S = \frac{C}{C^*}$$

Two-Step Model Analysis – Pre Exponential

$$J = \frac{\phi k_2 C_1 T}{\eta} \exp\left(-\frac{B}{\ln^2 S}\right) \quad \Longleftrightarrow \quad \frac{1}{\phi} \approx \frac{U_1}{\alpha S C^*} \exp\left(\frac{\Delta G_C^0}{k_B T}\right) \approx \frac{A''}{S}$$

$$J = \frac{S k_2 C_1 T}{A''} \exp\left(-\frac{\Delta G_2^*}{k_b T}\right)$$

Define: $A = \frac{k_2 C_1 T}{A''}$

$$J = AS \exp\left(-\frac{B}{\ln^2 S}\right)$$

Functional Form Equivalence

- S was changed at constant temperature for all experiments and data discussed
- Solid product purity and crystal form was unaffected by additives

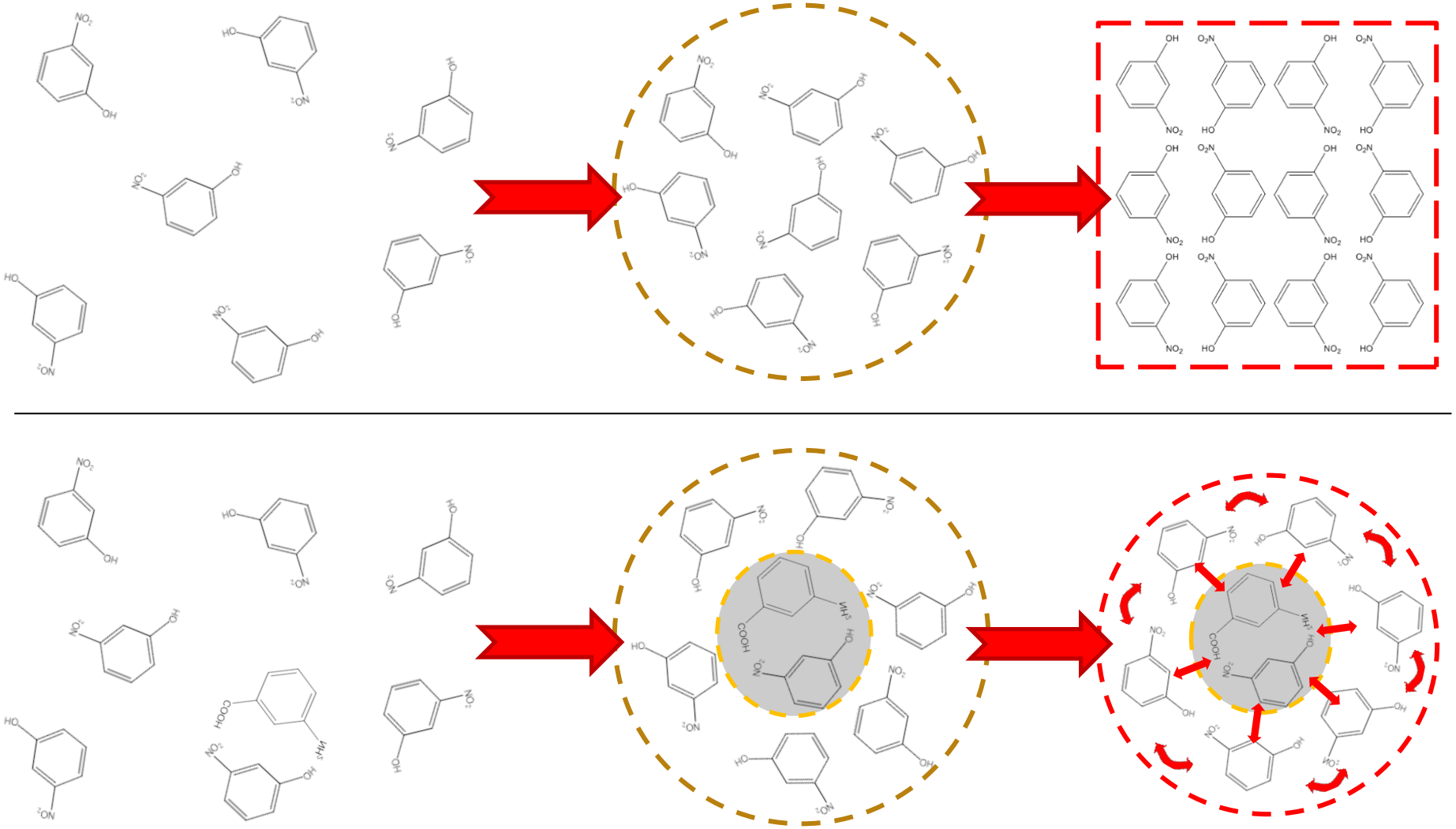
$$J = AS \exp\left(-\frac{B}{\ln^2 S}\right)$$

Classical Nucleation	Vekilov's Two-Step Model
$A = \left(\frac{4\pi}{3v_0}\right)^{\frac{1}{3}} \left(\frac{\gamma_e}{k_B T}\right)^{\frac{1}{2}} D C^*$	$A = \frac{k_2 \alpha C_1 T}{U_1 C^* \eta_1 \exp\left(\frac{\Delta G_C^0}{k_B T}\right)}$

Constants: T, C^*, k_B, U_1, ΔG_C^0, α, C_1, v_0

Variables: γ_e, D, η_1, k_2

Kinetic Inhibition Hypothesis



Images from: C. A Pons Siepermann; A. S. Myerson;, **Cryst. Growth. Des.**, 2018, 18 (6), 3584–3595

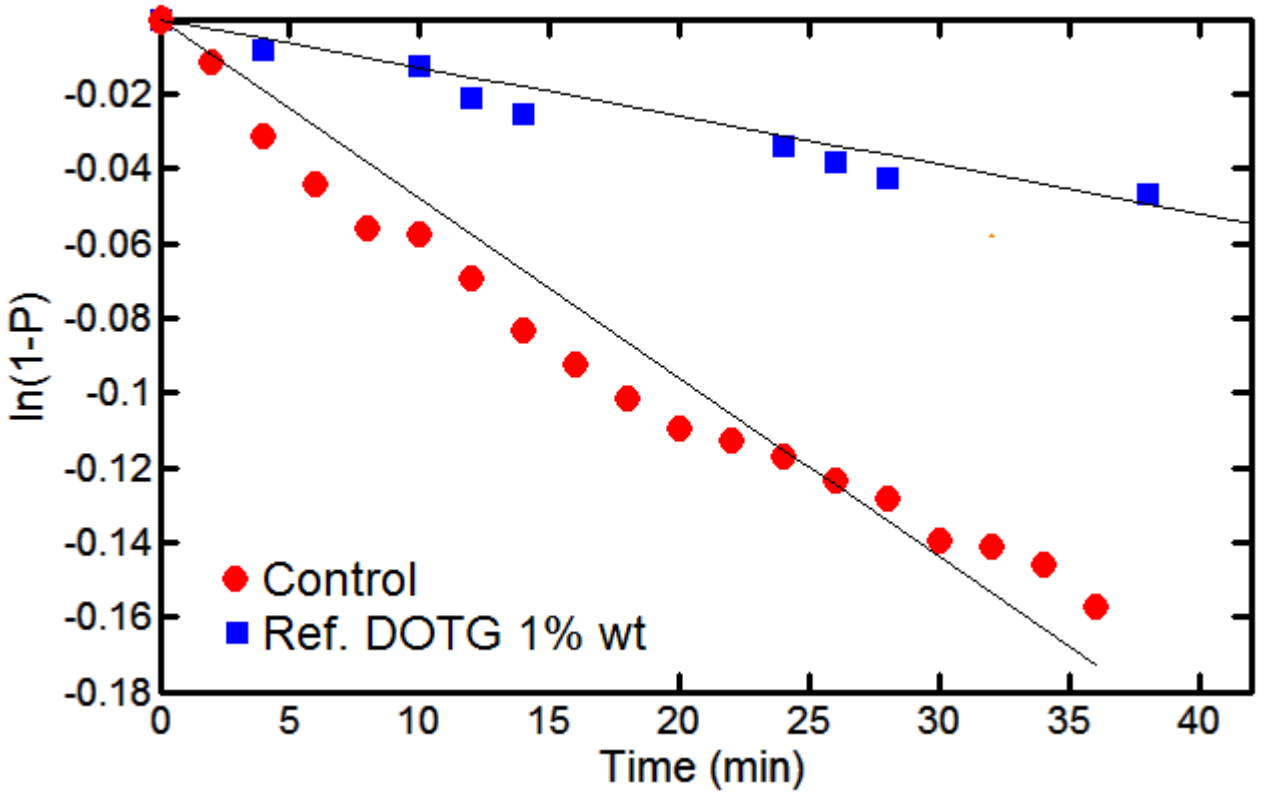
Acknowledgements

- Allan Myerson research group
- Merck CERD/X-Lab
- Gerard Capellades
- Fernando Ferreira

Thank You for Your Time

Questions

“Complete Picture” of Complexation Effect

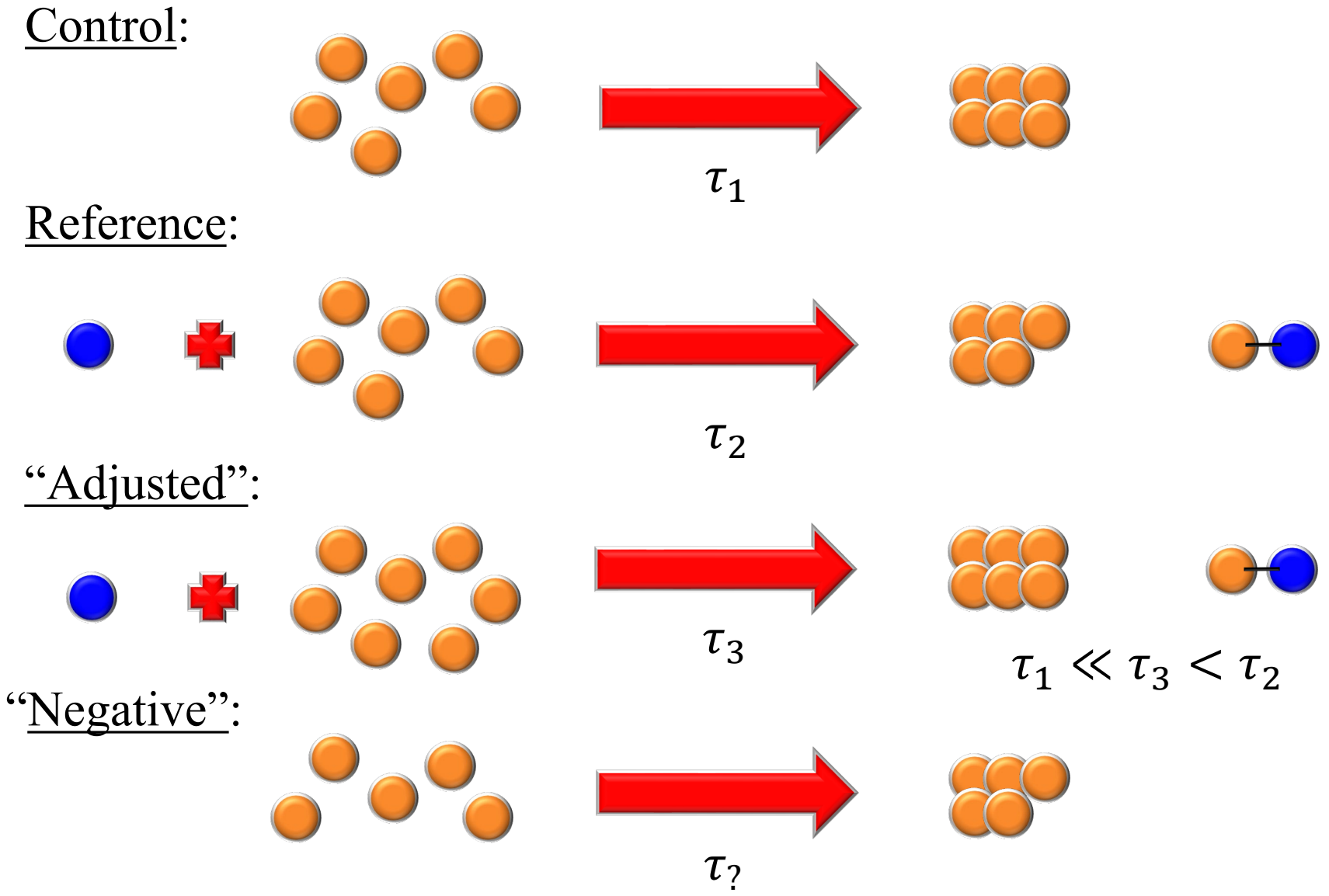


Control: 208 min

Reference: 769 min

Image modified from: C. A Pons Siepermann; S. Huang; A. S. Myerson;, **Cryst. Growth. Des.**, 2017, 17 (5), 2646-2653

Speciation Theory of Inhibition



“Negatives” to Test Magnitude of Inhibition

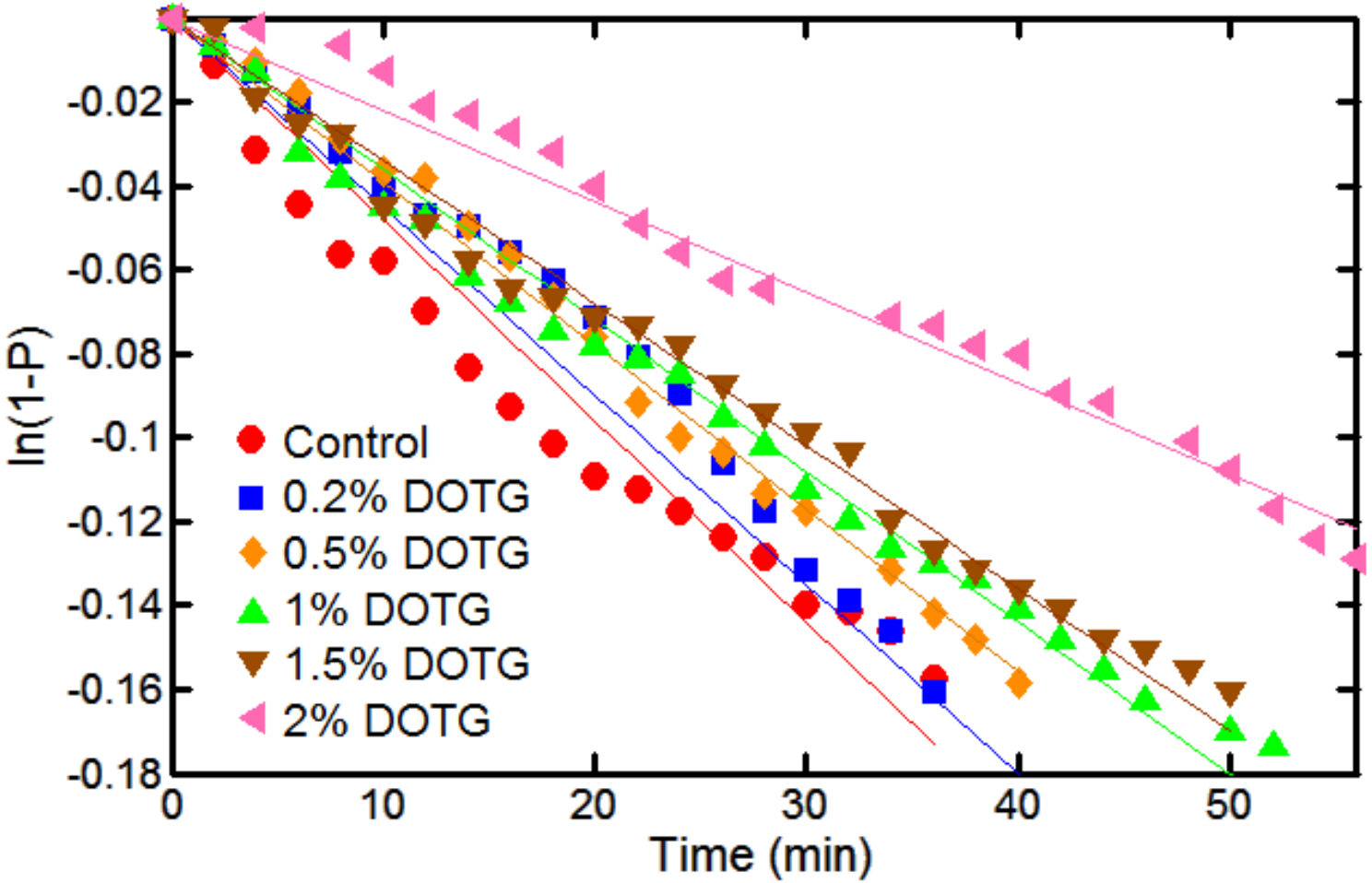
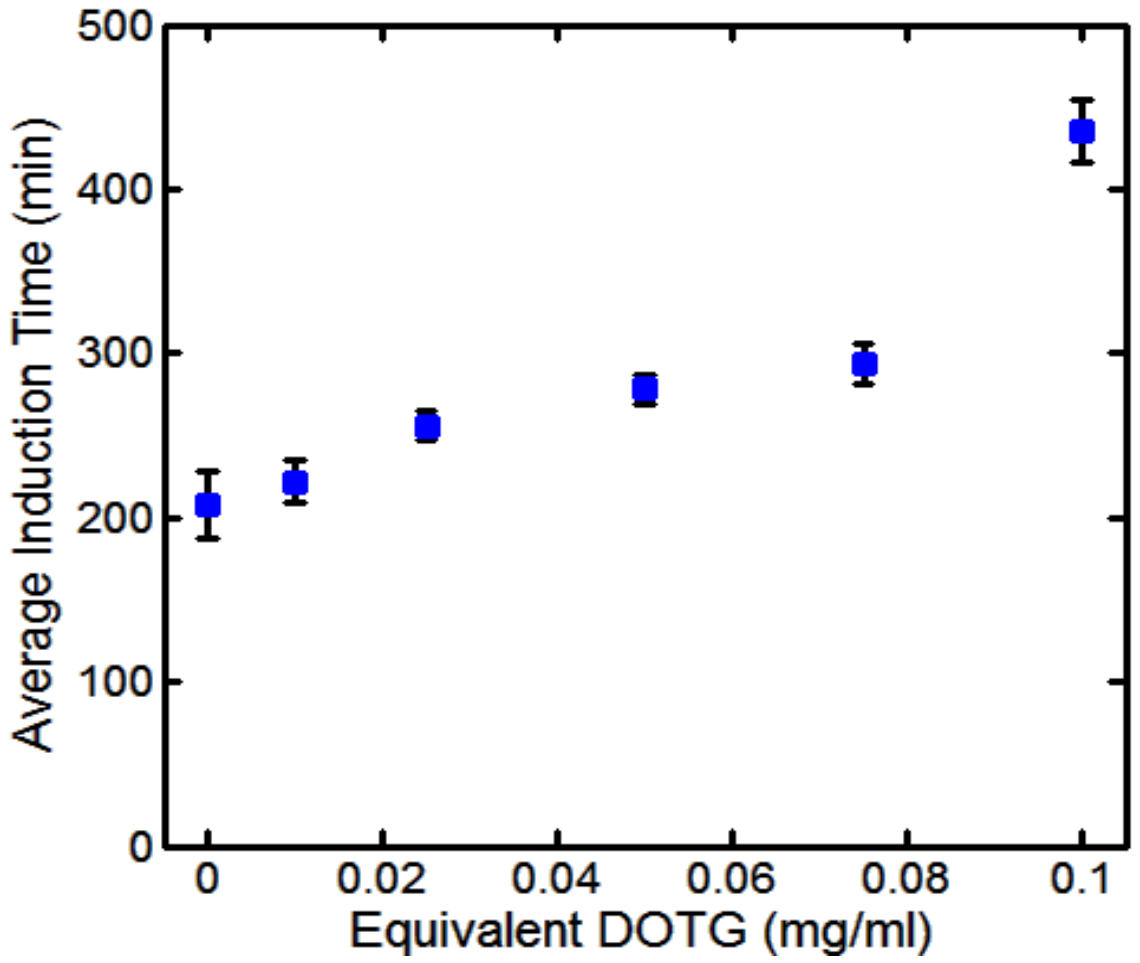


Image from: C. A Pons Siepermann; S. Huang; A. S. Myerson;, **Cryst. Growth. Des.**, 2017, 17 (5), 2646-2653

Effect of “Negatives” on Induction Time



Control: 208 min

DOTG 0.2%: 222 min

DOTG 0.4%: 244 min

DOTG 0.5%: 256 min

DOTG 1%: 278 min

DOTG 1.5%: 294 min

DOTG 2%: 435 min

Image from: C. A Pons Siepermann; S. Huang; A. S. Myerson;, **Cryst. Growth. Des.**, 2017, 17 (5), 2646-2653

Comparison of DOTG and “Negative” Inhibtion

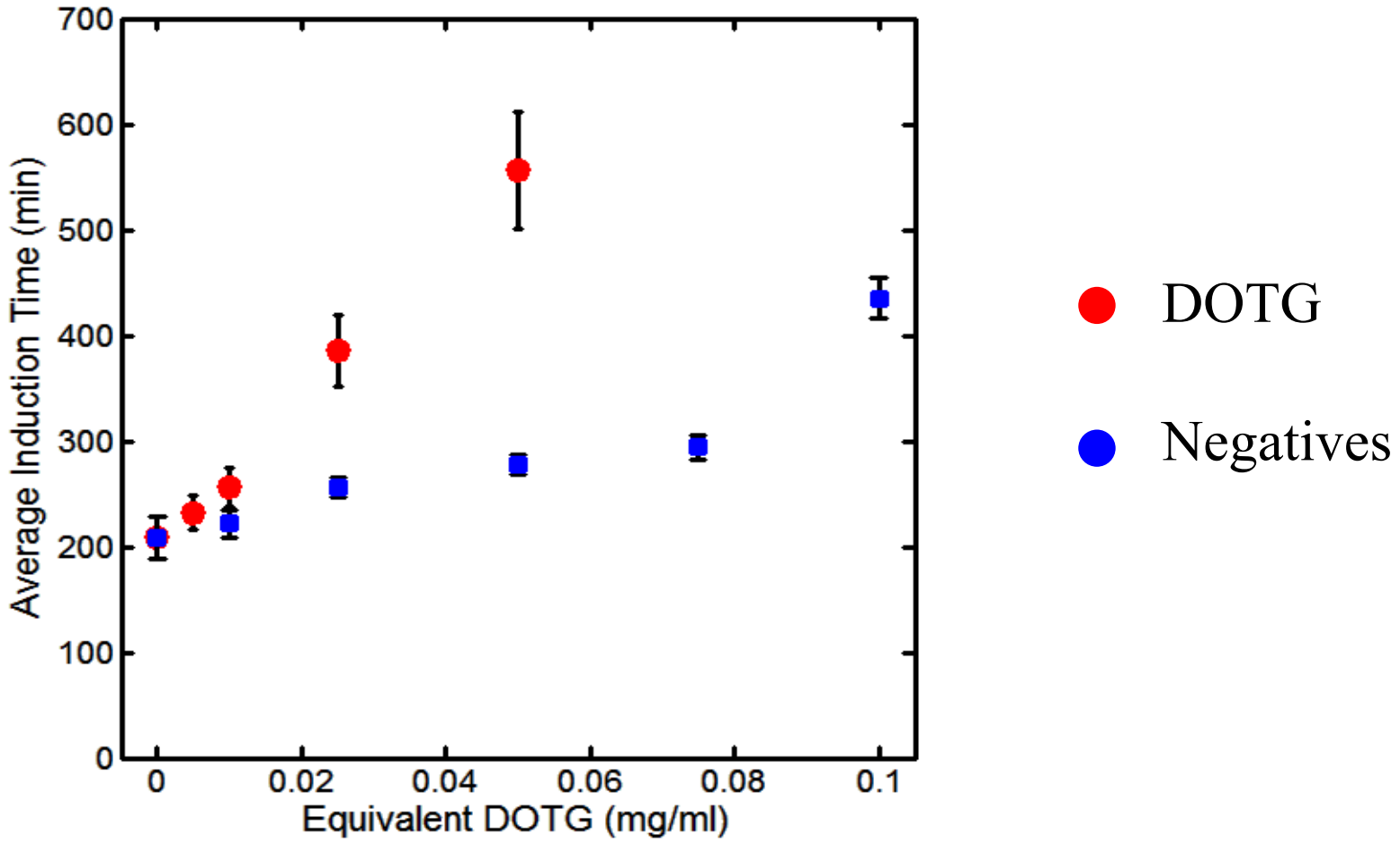


Image from: C. A Pons Siepermann; S. Huang; A. S. Myerson;, **Cryst. Growth. Des.**, 2017, 17 (5), 2646-2653

Summary of Negative Results

Sample	DOTG (min)	Negative (min)	Negative 2X (min)
Control	204	N/A	N/A
DOTG 0.2%	256	222	244
DOTG 0.5%	384	256	278
DOTG 1%	550	278	435

Inhibition effect is greater than a 2:1 stoichiometry of interaction between BA and DOTG

Benzoic Acid Polymorphism

- BA has only one known polymorph
- Data shows that even at largest concentration of additive, no additional or unexpected peaks are observed

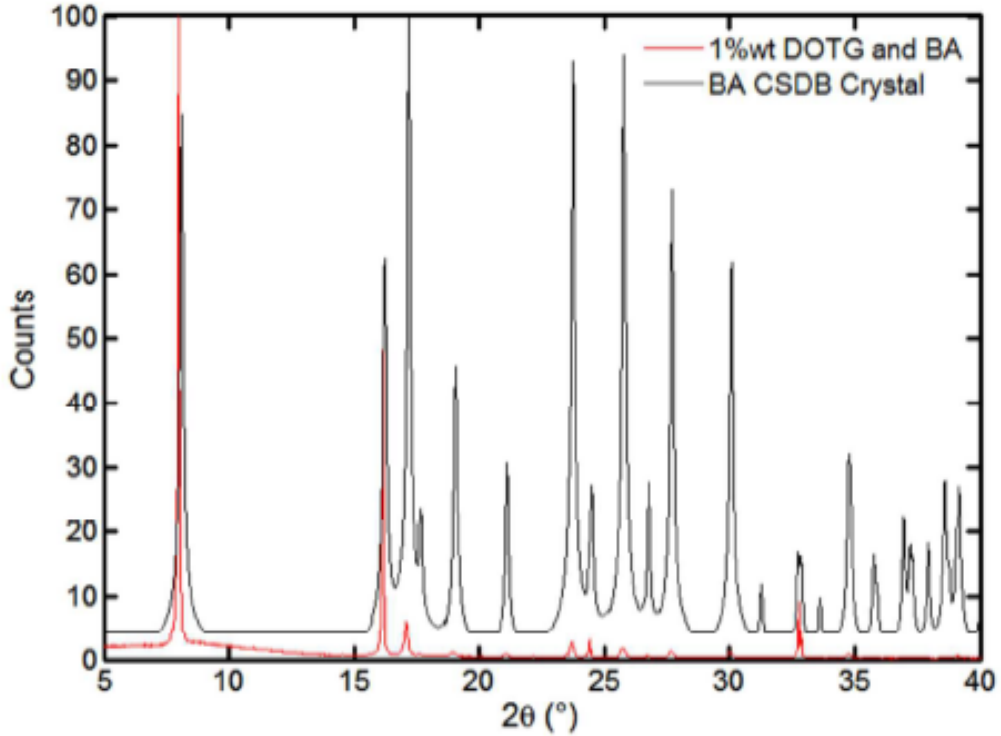
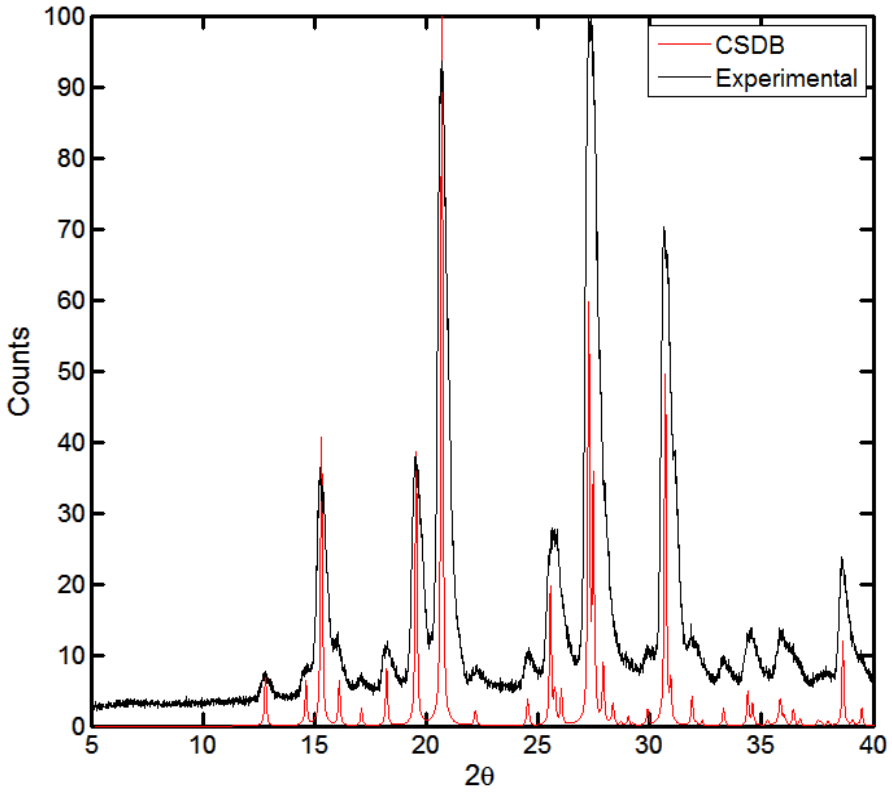
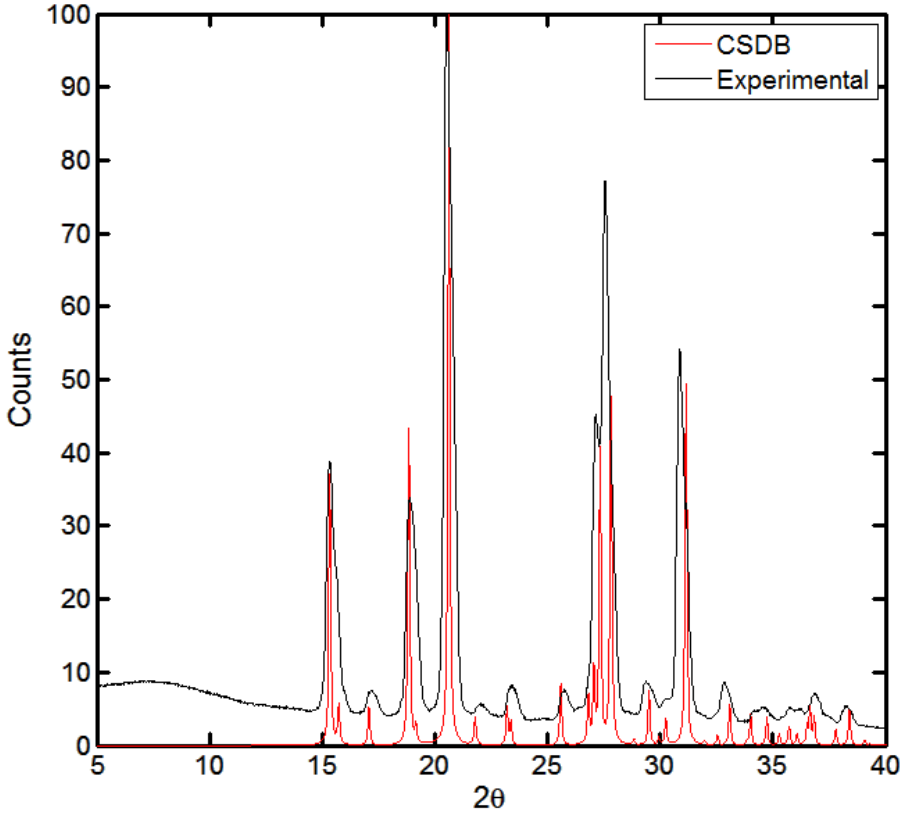


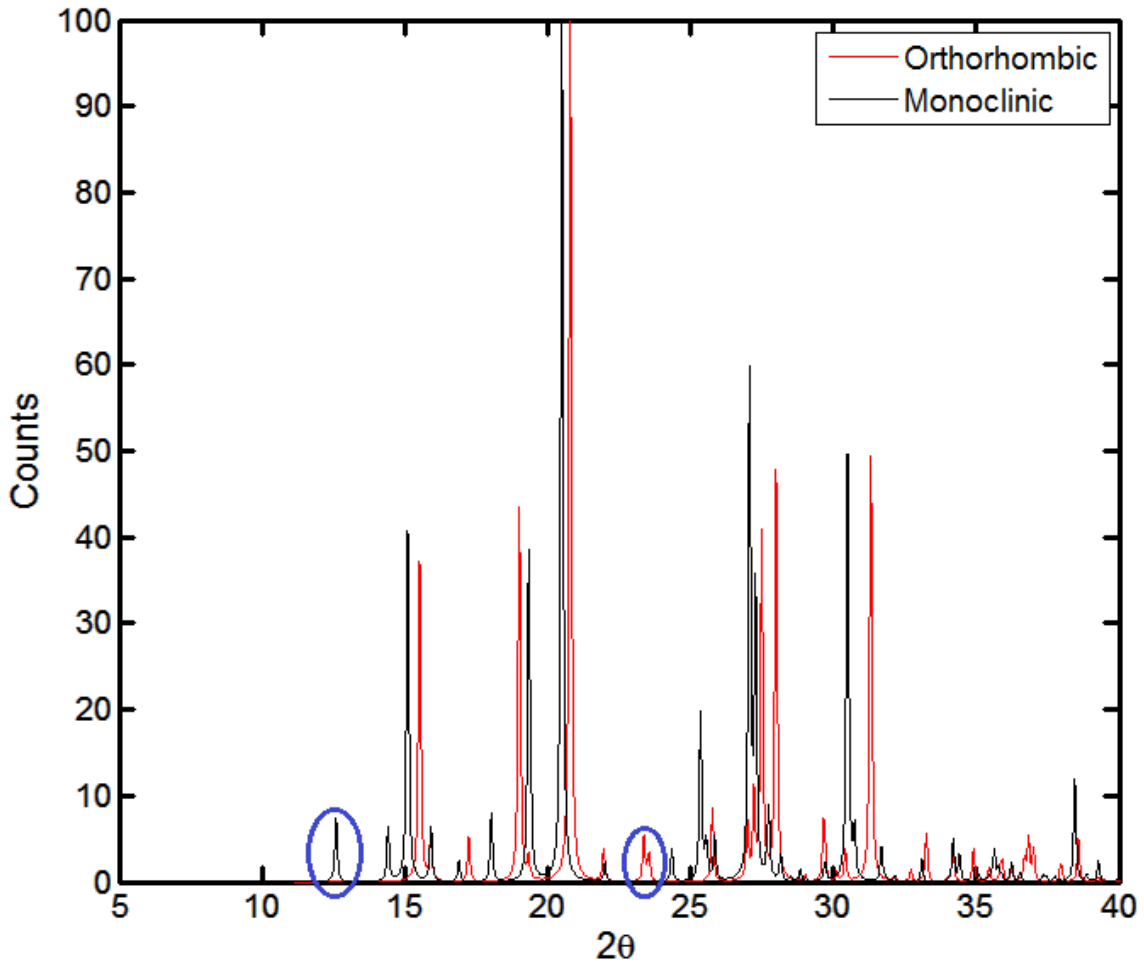
Image from: C. A Pons Siepermann; S. Huang; A. S. Myerson;, **Cryst. Growth. Des.**, 2017, 17 (5), 2646-2653

3NP Polymorphs

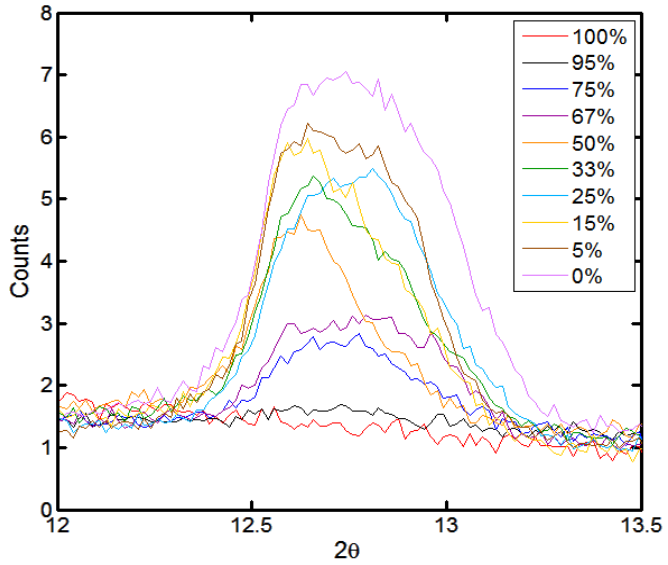


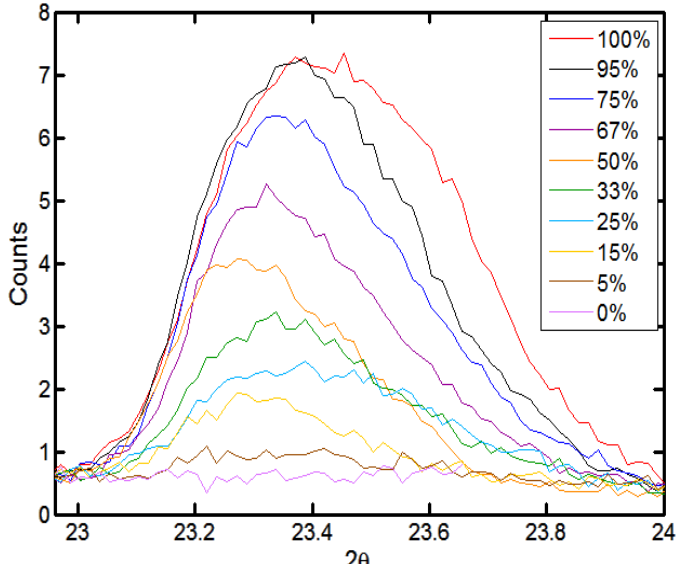


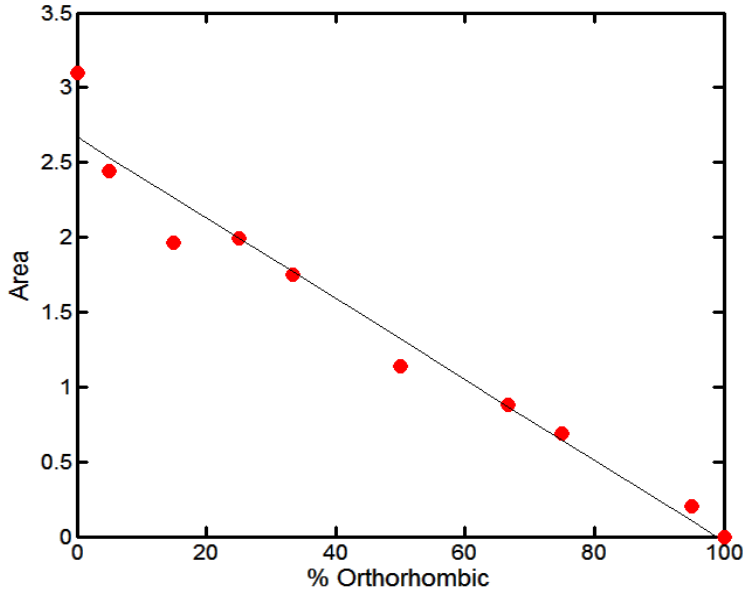
Unique Peaks

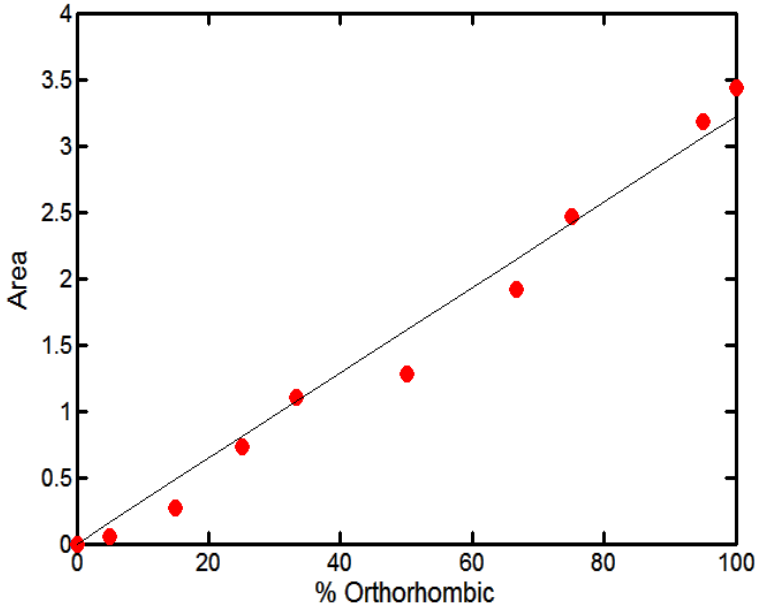


Unique Peak Integration

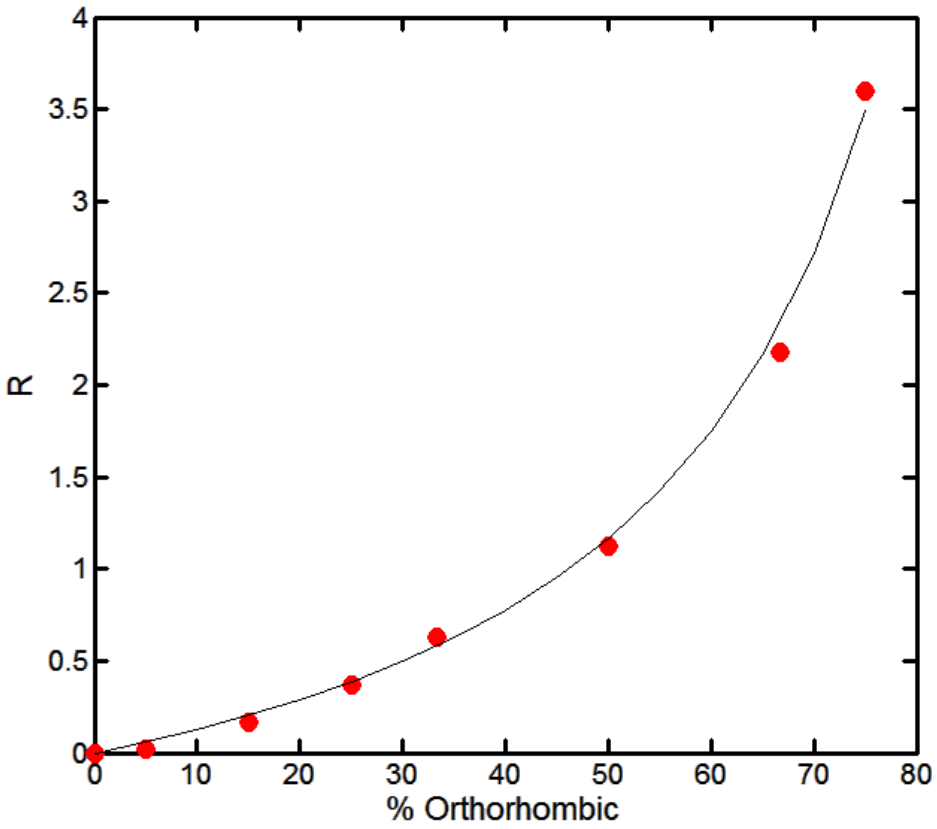








Calibration



$$R = \frac{A_{23\theta}}{A_{12\theta}}$$

$$R = a\frac{O_{\%}}{(100 - O_{\%})}$$

Polymorphism Remained Consistent

Condition	% Orthorhombic
No Additive	17 ± 3
0.05 mg/ml 3ABA	22 ± 5