Crystal Solubility:
Importance, Measurement and More

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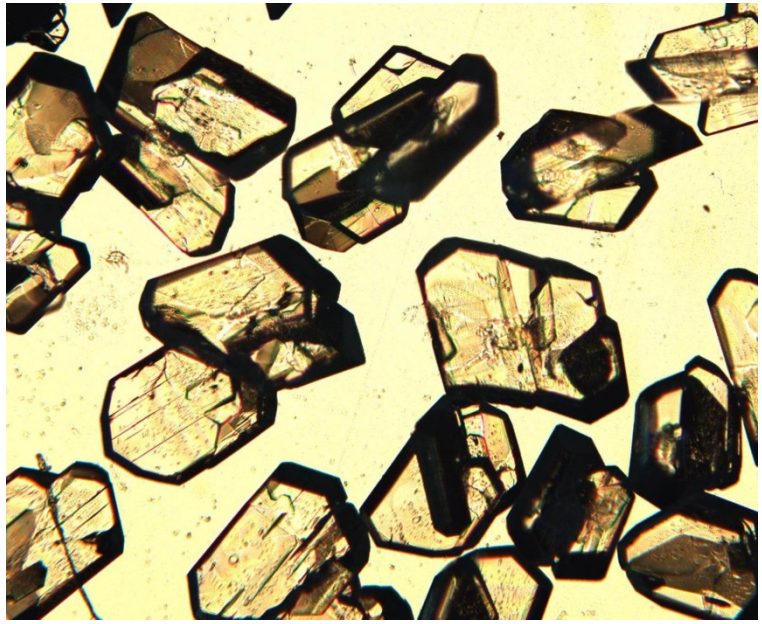

EPSRC
Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

CMAC

Industry Demand Led Research

Accelerate the adoption of continuous processing in pharmaceutical manufacturing

- **Improve particulate based product supply via continuous processes**
- **Develop understanding of complex interactions between process, materials and quality**
- **Implement flexible continuous process technologies that deliver benefits:**

Robustness | **Consistency** | **Manufacturability** | **Performance**

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CMAC

Product

- Complex multicomponent systems

Crystal Nucleation

Chiral resolution

Crystallization

Phenomena

- New level of understanding for prediction and control

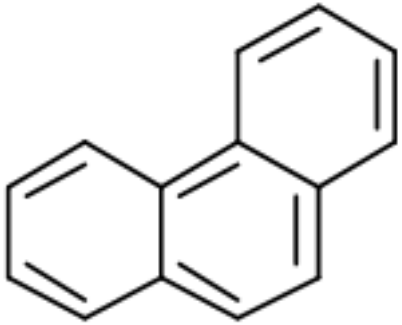
Process

- **Flexible** and **sustainable** production facilities

Pharmaceutical & Protein Crystallisation

Crystal Solubility

Binary Systems

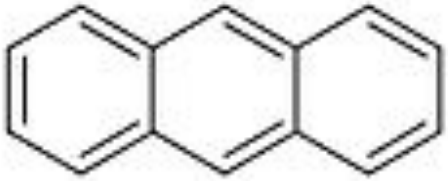


Phenanthrene

in

Benzene

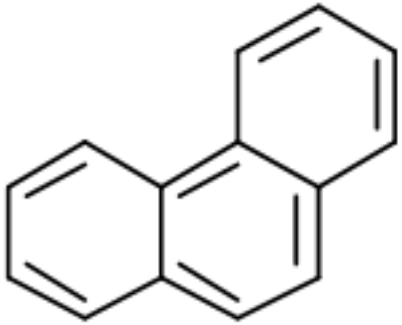
Intermolecular interactions between solute and benzene are essentially **identical**



Anthracene

Crystal Solubility

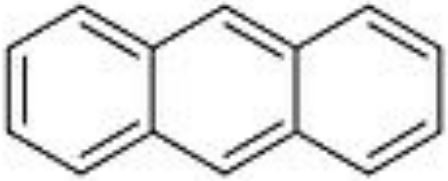
Binary Systems



Phenanthrene

in

Benzene



Anthracene

x^*=20.7 mol%

T_m=100°C

Intermolecular interactions in **Anthracene** crystal are much larger than in **Phenanthrene** crystal:

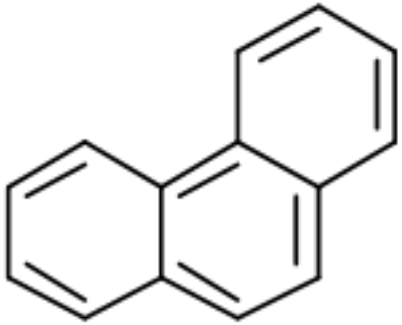
Anthracene prefers the solid phase

x^*=0.81 mol%

T_m=217°C

Crystal Solubility

Binary Systems

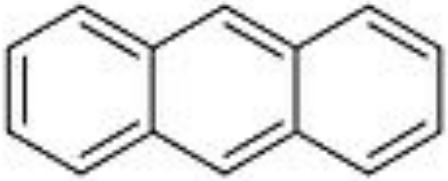


Phenanthrene

in

Benzene

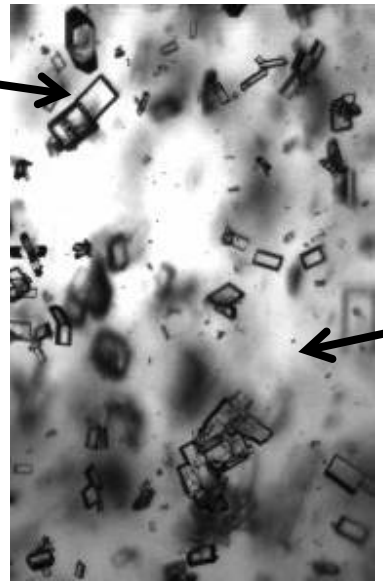
Solubility is determined by intermolecular interactions in both **solution** and **solid**



Anthracene

Crystal Solubility

Binary Systems



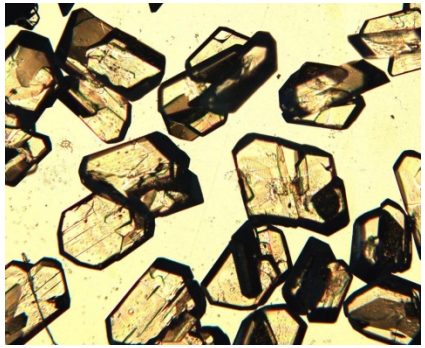
Crystal solubility *C:**

The solution concentration that is in equilibrium with the crystalline solid at a specific temperature *T* and pressure *P*.

Crystal Solubility

- Crystallization
- Solubility Measurements
- Solubility Analysis
- Solubility Measurements in Complex Multicomponent Systems
- Solubility in Complex Multicomponent Systems
- Crystallization Kinetics

Crystallization from Solution

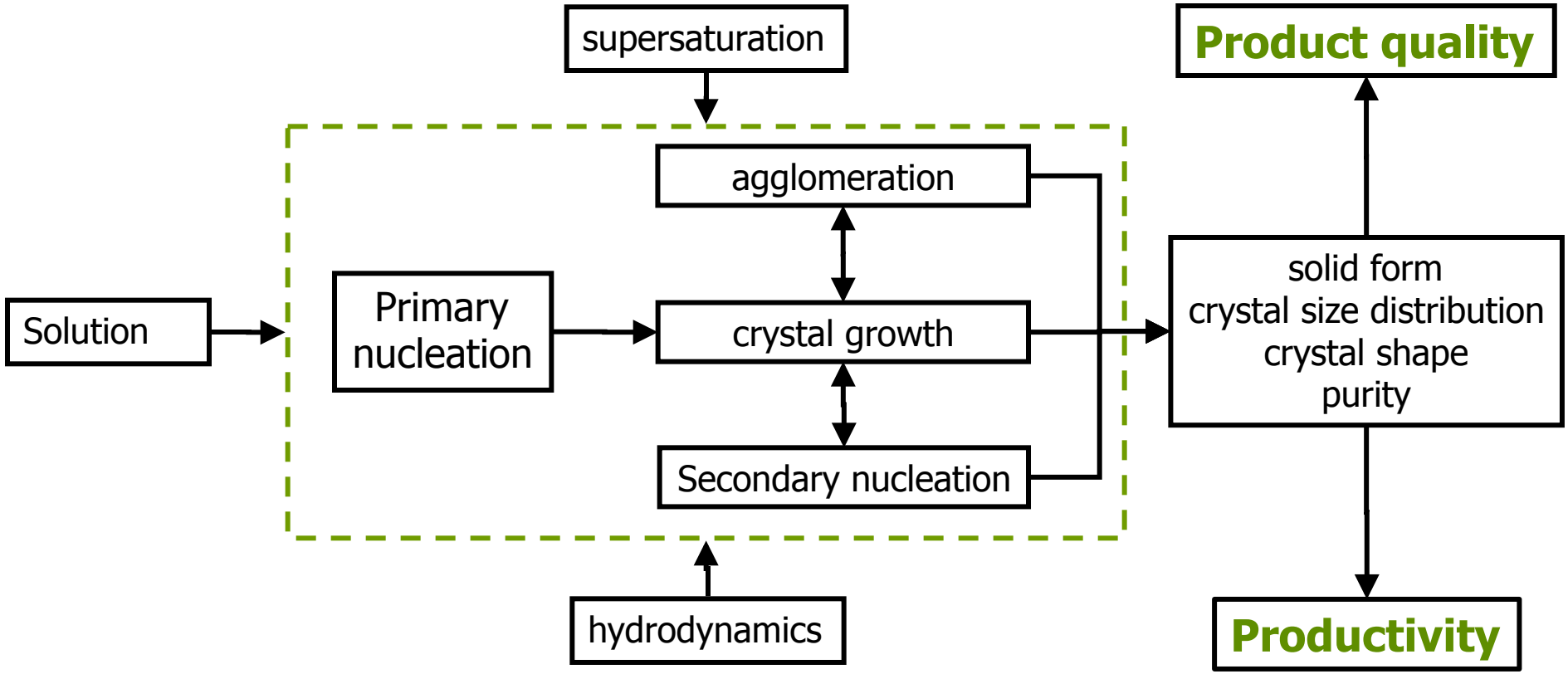


Crystalline product
99.99% pure

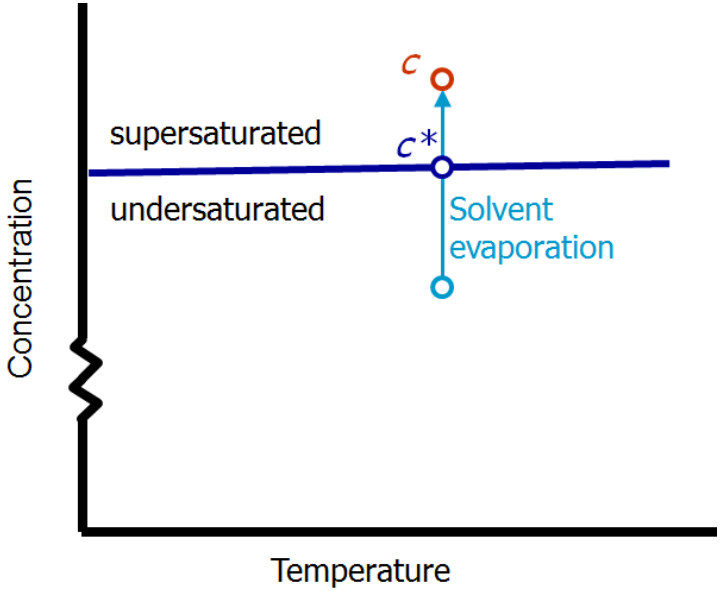
Synthesis of API → **Single stage Crystallization** → Filtration

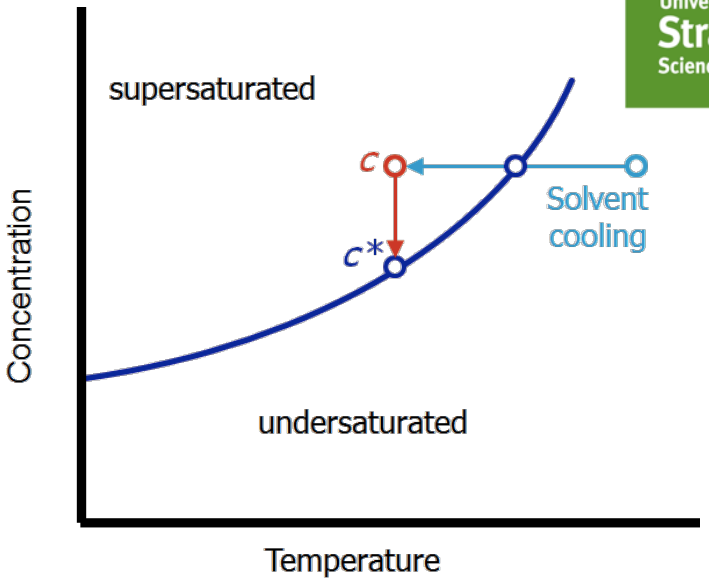
Filtration → Solution containing impurities and dissolved synthesis product

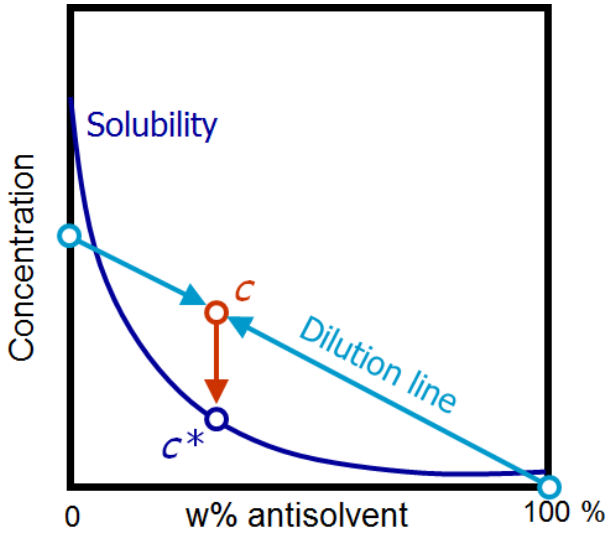
Crystallization from Solution

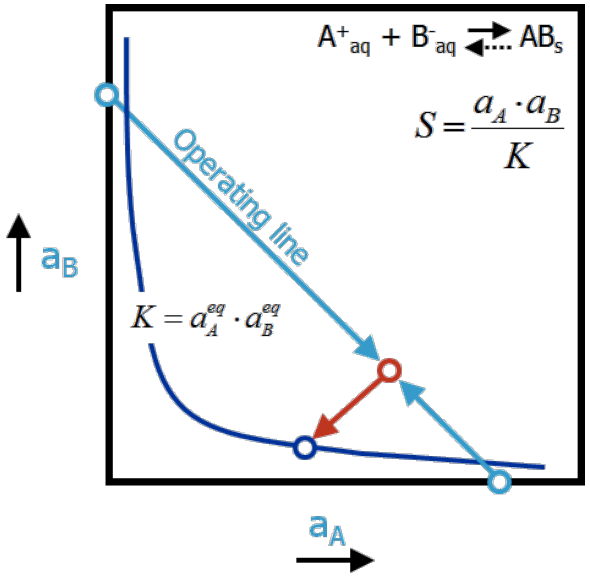


Crystallization from Solution



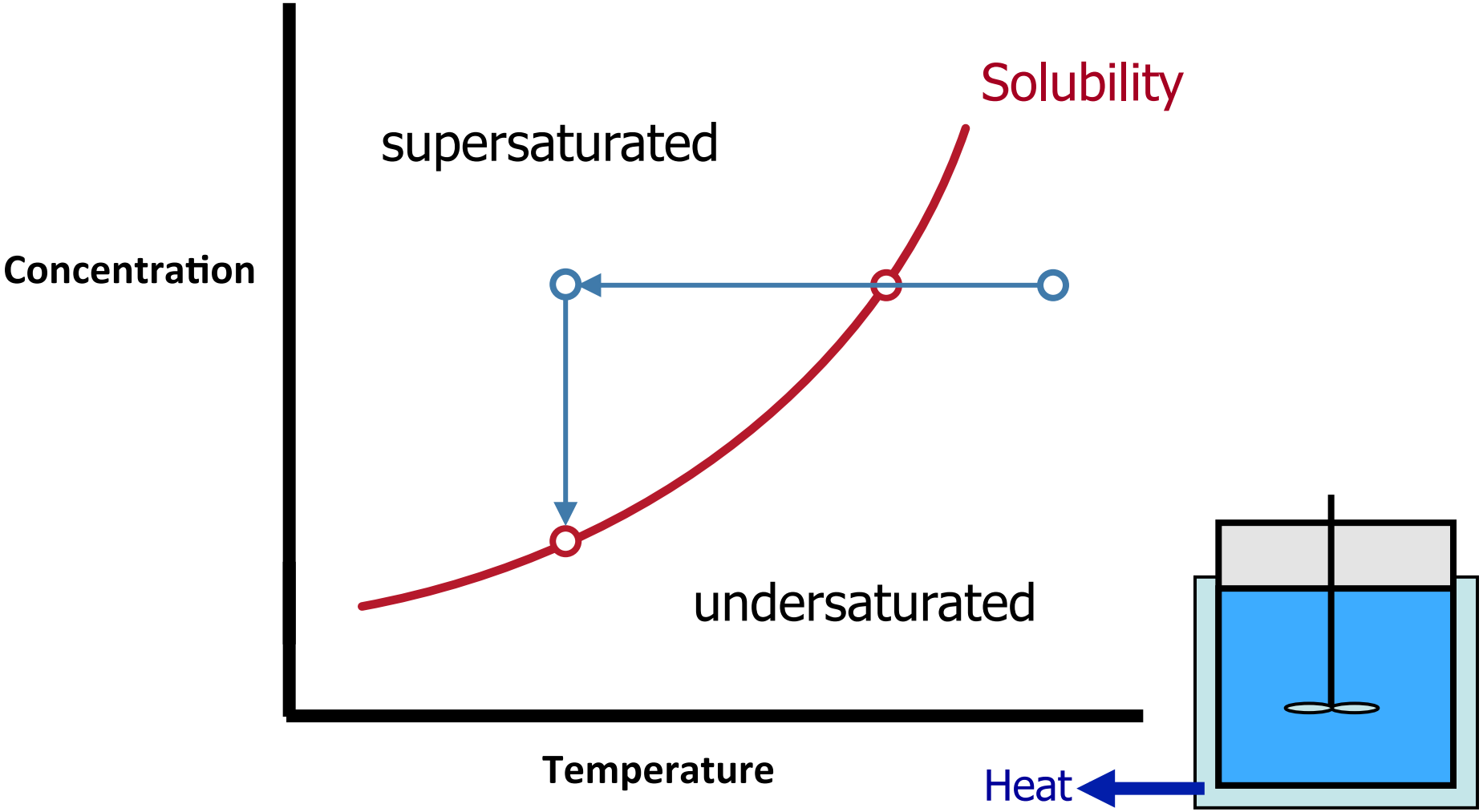






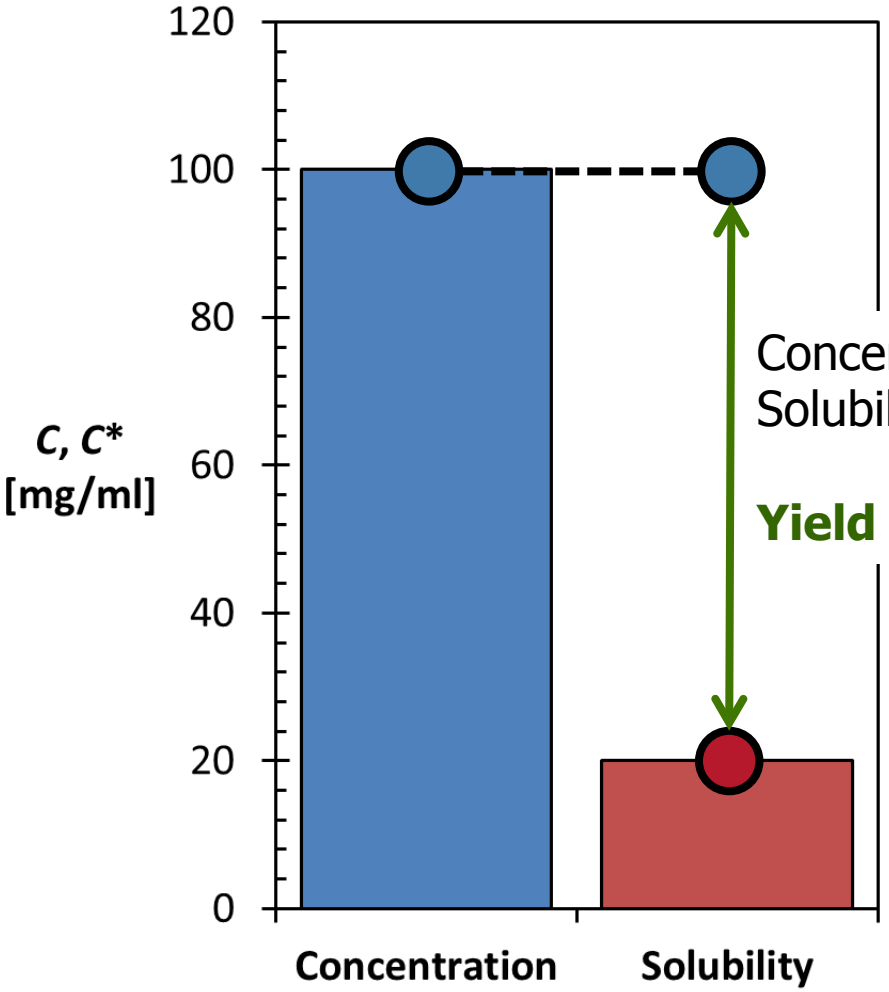
Crystallization from Solution

Binary Systems



Crystallization from Solution

Binary System at constant P,T



Concentration C = 100 mg/ml solvent

Solubility C^* = 20 mg/ml solvent

Yield C-C^* = 80 mg crystals/ml solvent

80% is crystallized,
20% remains in solution

The solubility curve is the first step towards a crystallization process design

Crystal Solubility

- Crystallization
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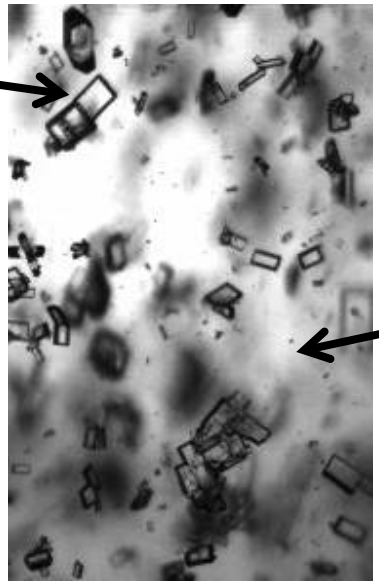
Crystal Solubility Measurement

100% pure
Crystalline phase



Solution with
Concentration *C**
At temperature T,
Pressure T

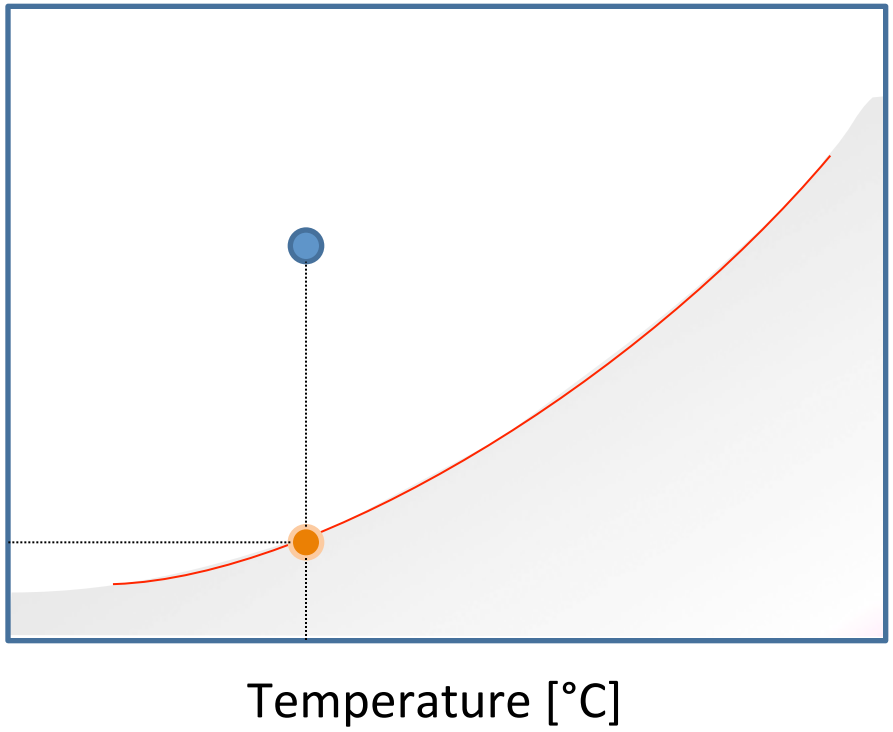
Crystal solubility *C**:
The solution concentration that is in equilibrium with the crystalline solid at a specific temperature *T* and pressure *P*.

Equilibrium Method

- Equilibrate suspension at constant temperature, pressure
- Sample solution & analyze concentration
  - HPLC
  - Gravimetric
  - Etc.

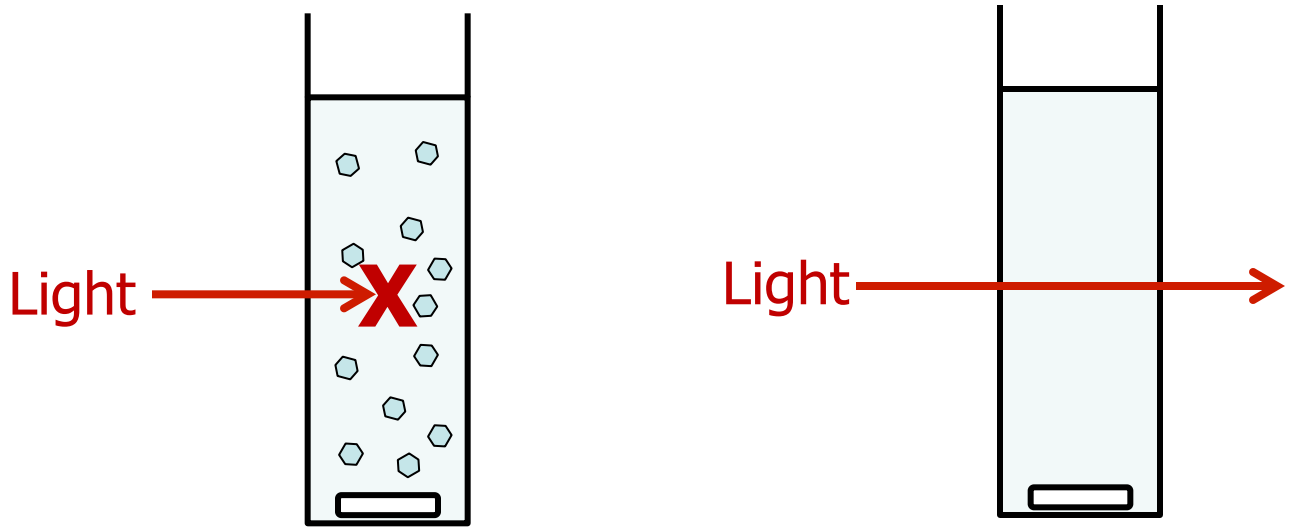
- **Accurate**

- **Time consuming**



Temperature Variation Method

Clear point temperature



Suspension
(Low T)

Clear solution
(high T)

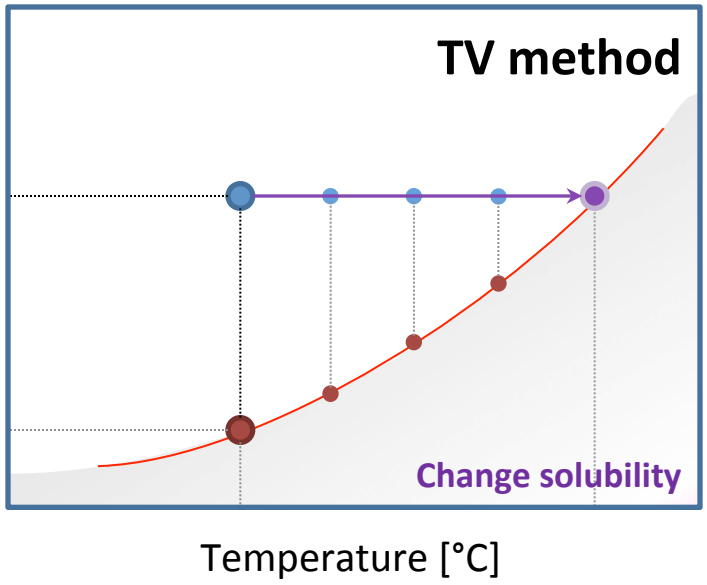
Clear point temperature:
The temperature at which a suspension becomes a clear solution during heating with a certain rate

Temperature Variation Method

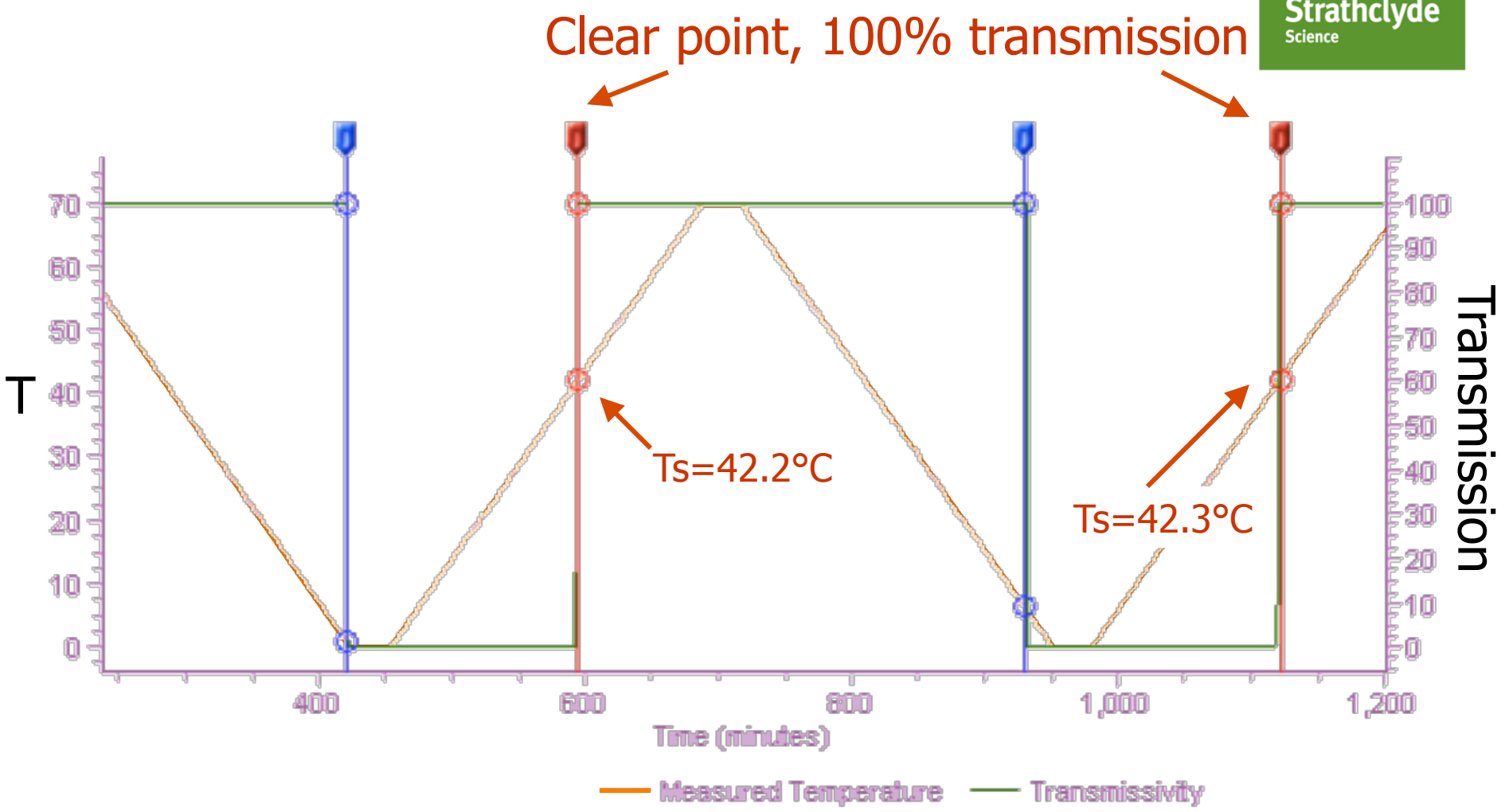
Clear point temperature

- Increase solubility until suspension turns into a clear solution

- Reproducing results fairly quick
- Also metastable zone width



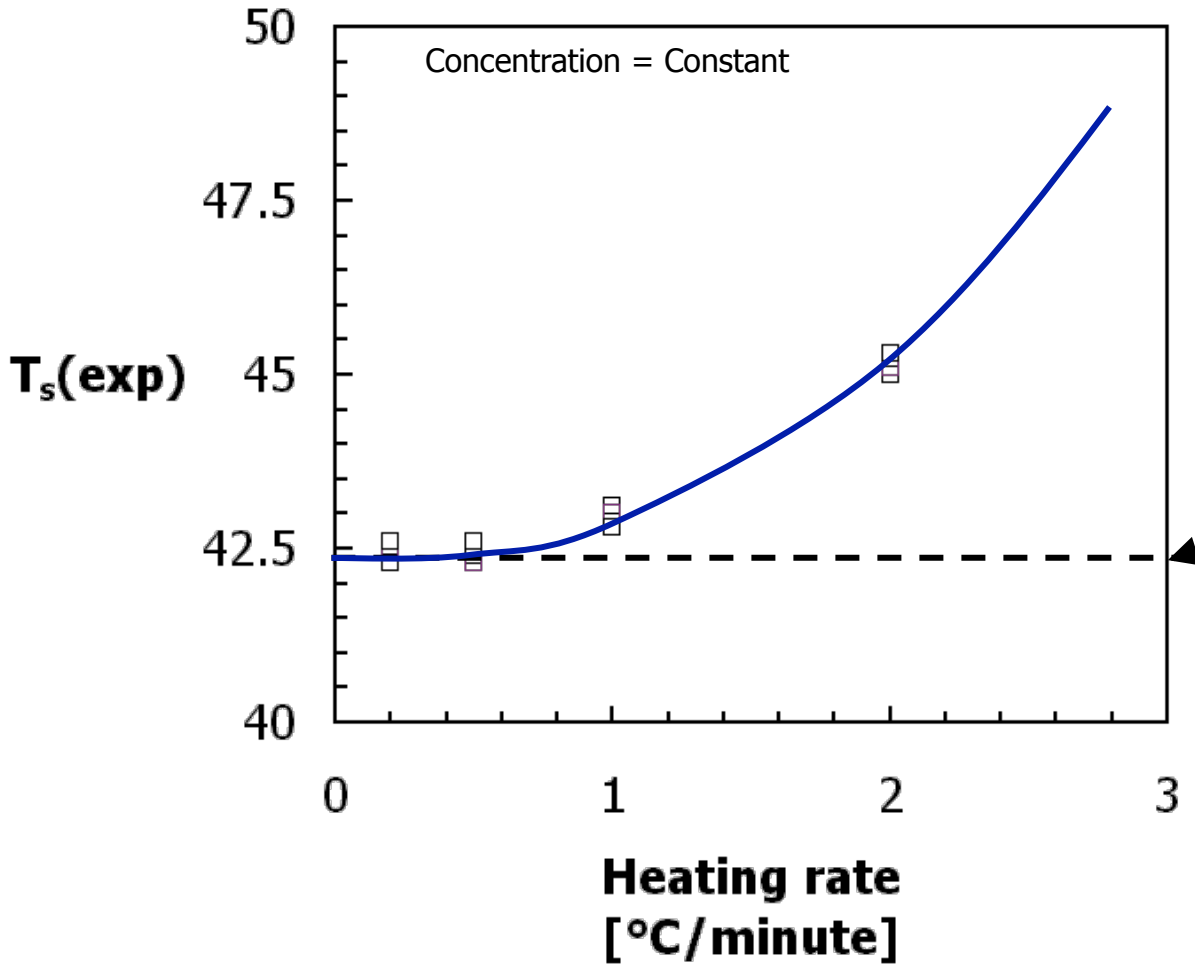
Clear & Cloud Point Measurements



Heating rate = 0.3°C/min

1440 min = 1 day

Clear Point & Solubility



Thermodynamic
Saturation temperature

If:

- Crystal detection limit is low
- Dissolution is fast
- No fouling
- No crowning
- …

Look at the vials!

Often, a heating rate of 0.3°C/min gives sufficiently accurate data

Crystal Solubility

- Crystallization
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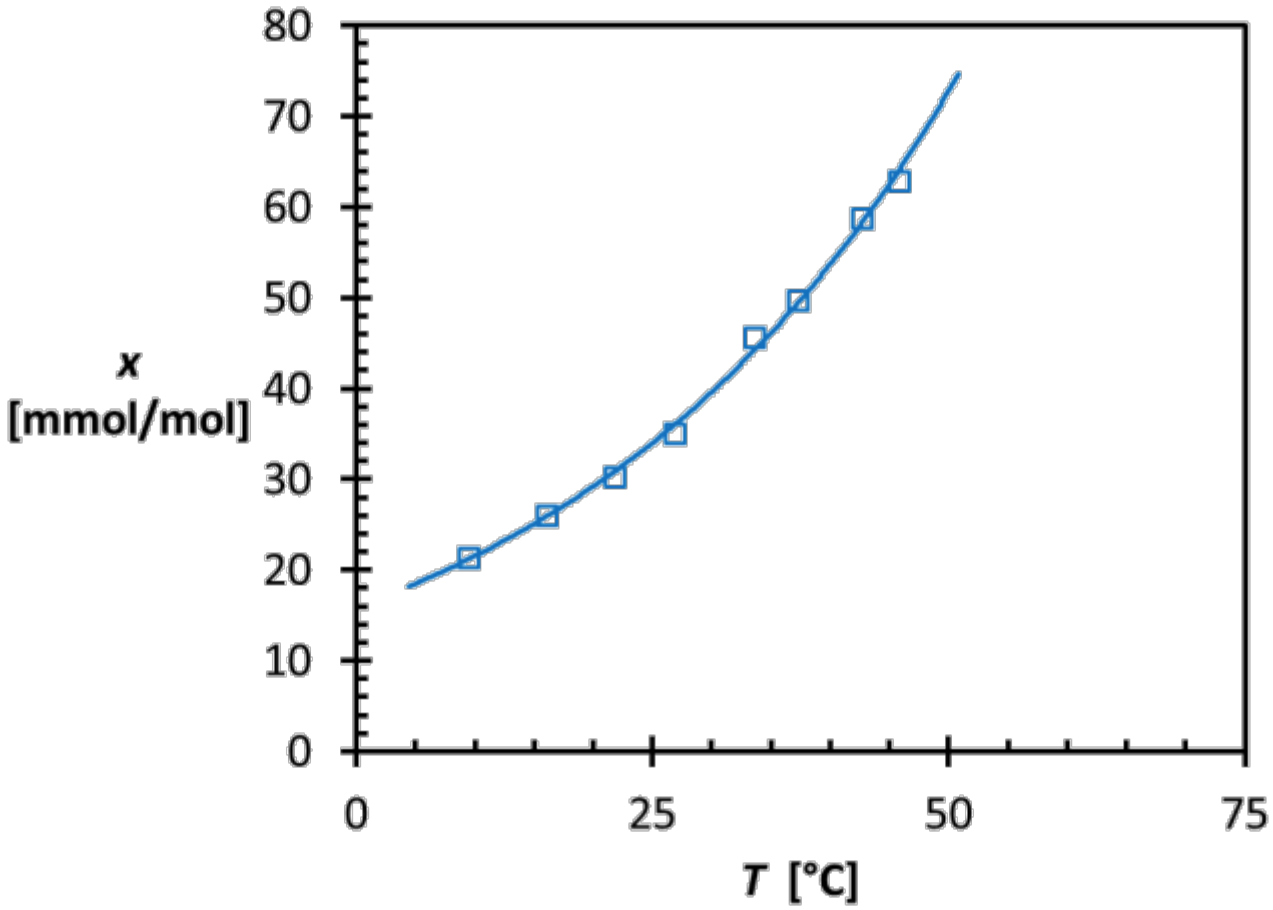
- Crystallization Kinetics

Solubility Diagram

Of isonicotinamide (**INA**) in Ethanol



Solubility

University of Strathclyde Science

Solubility <u>ideal</u> system:

Enthalpy of fusion of pure A

$$x^* = \exp\left(-\frac{\Delta H}{R}\left(\frac{1}{T}-\frac{1}{T_m}\right)\right) = \exp\left(\frac{A}{T}+B\right)$$

solubility

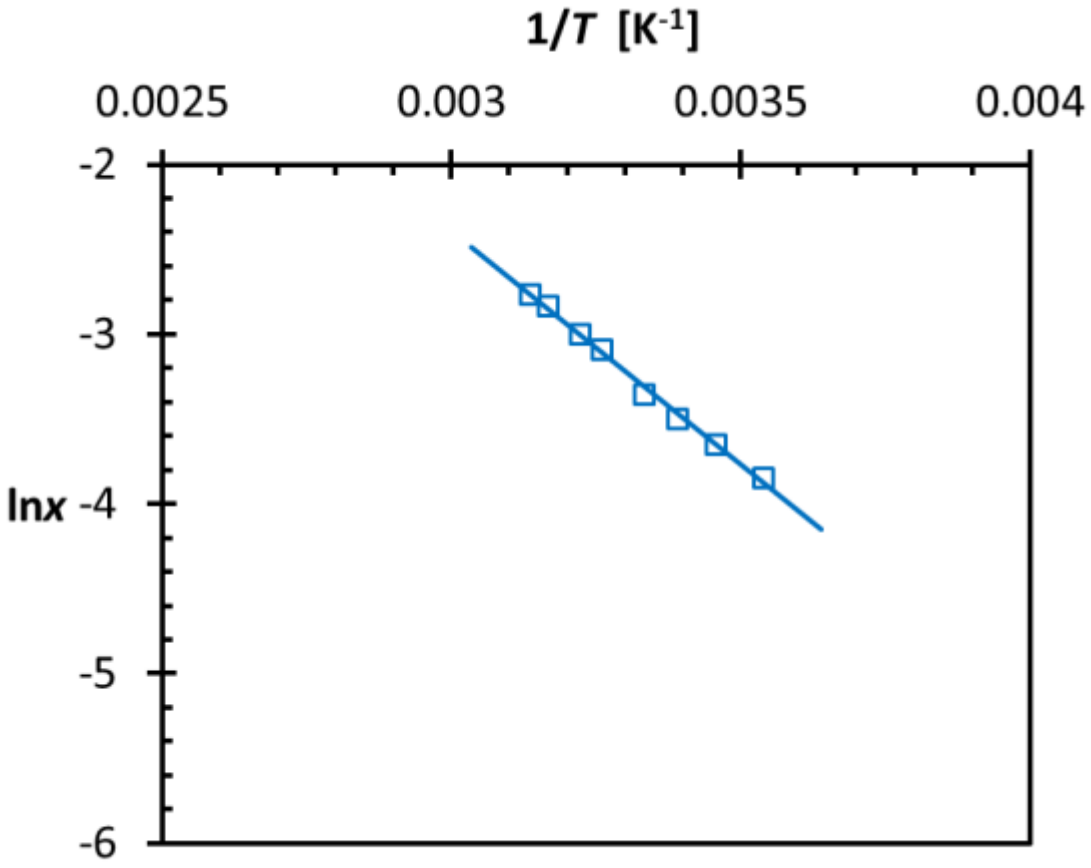
Melting temperature of pure A

Fitting the solubility data of a real system:

$$\ln x^* = \frac{A}{T} + B$$

Van 't Hoff-plot

Of isonicotinamide (**INA**) in Ethanol



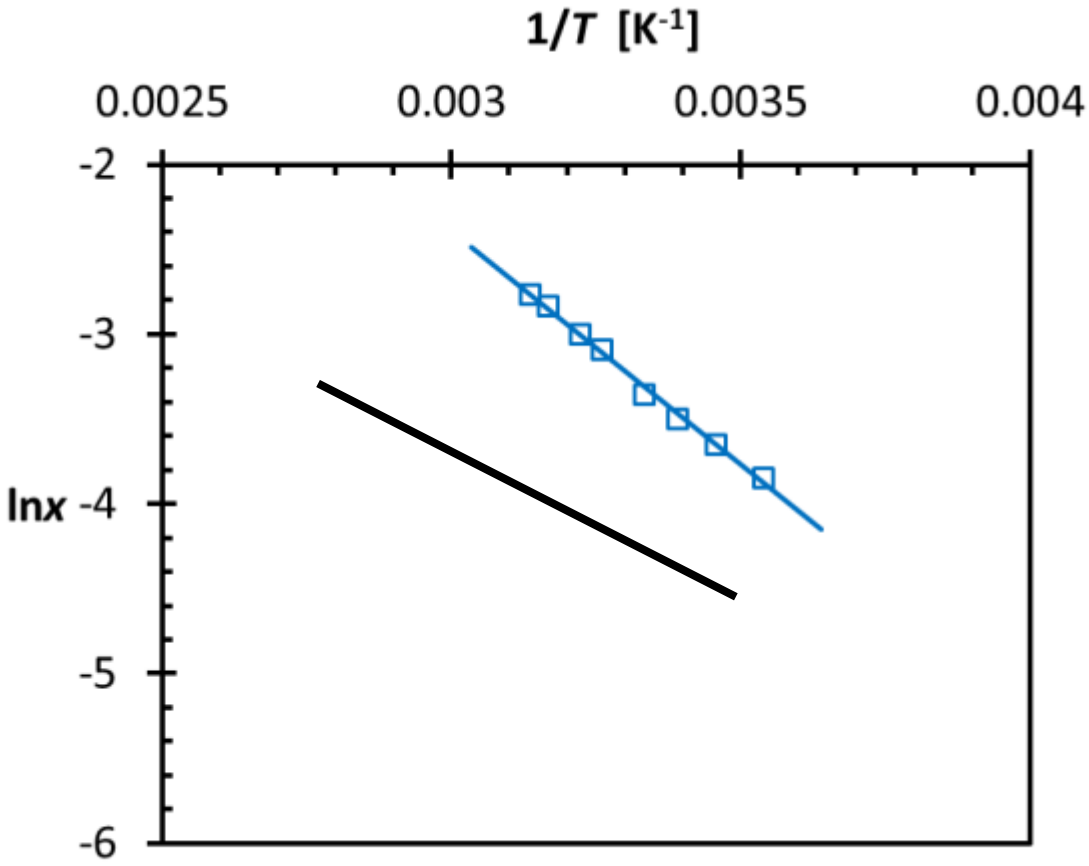
Fitting equation:

$$\ln x^* = \frac{A}{T} + B$$

Convenient and accurate to extrapolate

Van 't Hoff-plot

Of isonicotinamide (**INA**) in Ethanol



Fitting equation:

$$\ln x^* = \frac{A}{T} + B$$

Ideal solubility:

$$\ln x^* = -\frac{\Delta H}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right)$$

Why is there a difference between ideal and real solubility?

Chemical Potential

University of Strathclyde Science

Ideal system

$$\mu_L^{eq} = \mu_L^{eq} * + kT \ln x_{eq}$$

Real system

$$\mu_L^{eq} = \mu_L^{eq} * + kT \ln a_{eq}$$

The **activity coefficient *γ*** describes non-ideality

$$a = \gamma x$$

Crystal Solubility

- Crystallization
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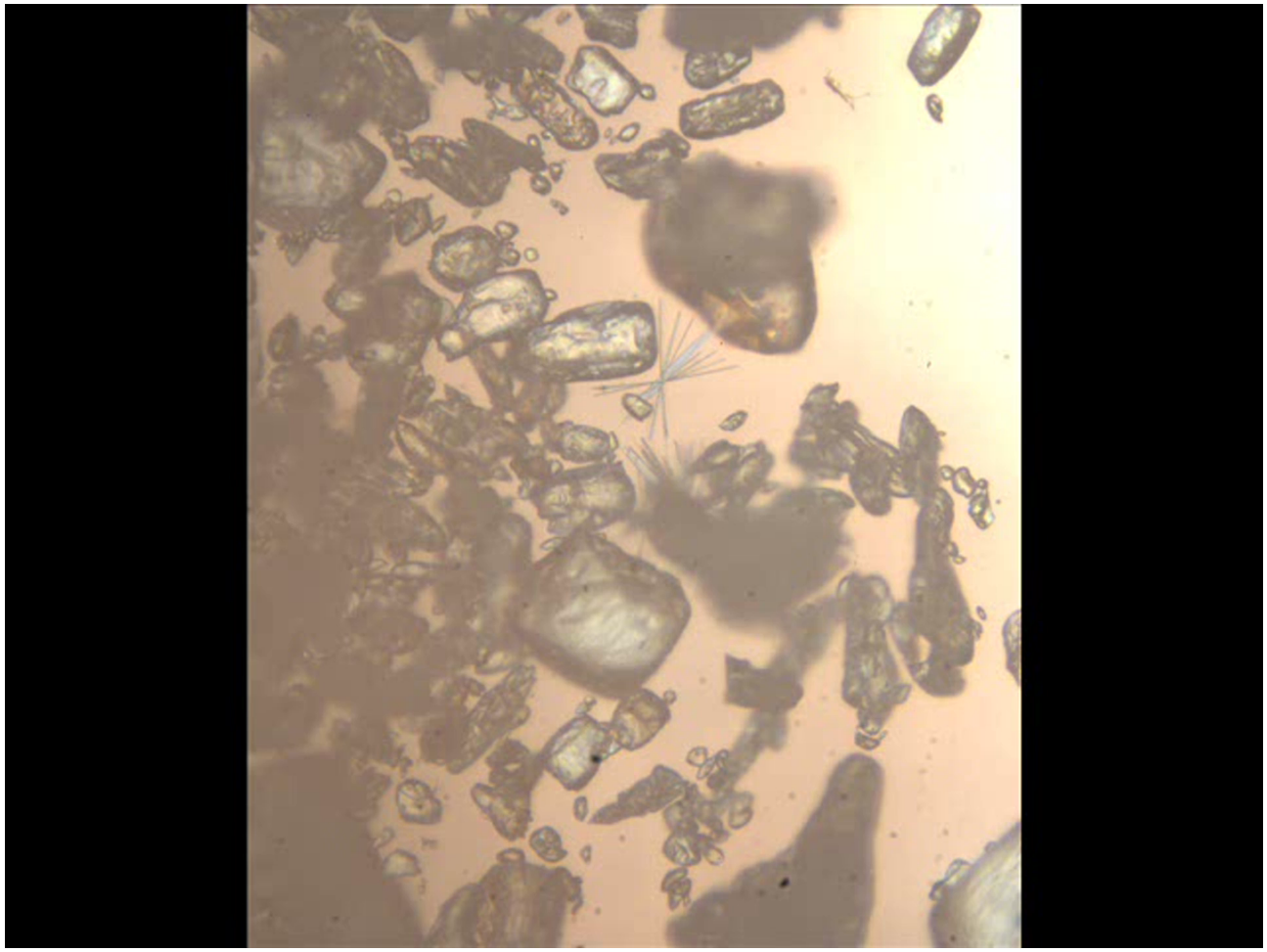
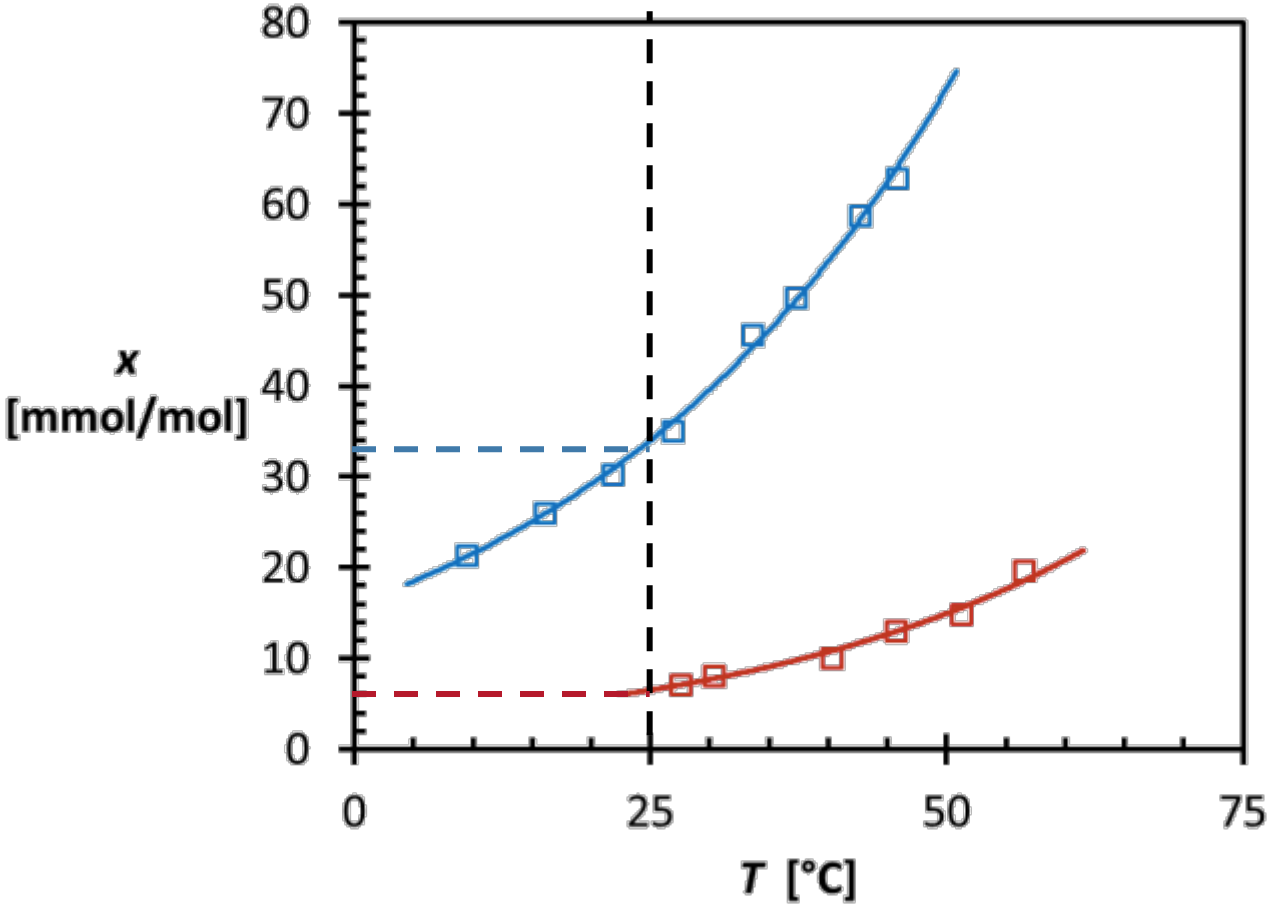
Co-crystallization

Of isonicotinamide (**INA**) and Carbamazepine (**CBZ**) in Ethanol



Pure Component Solubility

Of isonicotinamide (**INA**) and Carbamazepine (**CBZ**) in Ethanol



T = 25°C

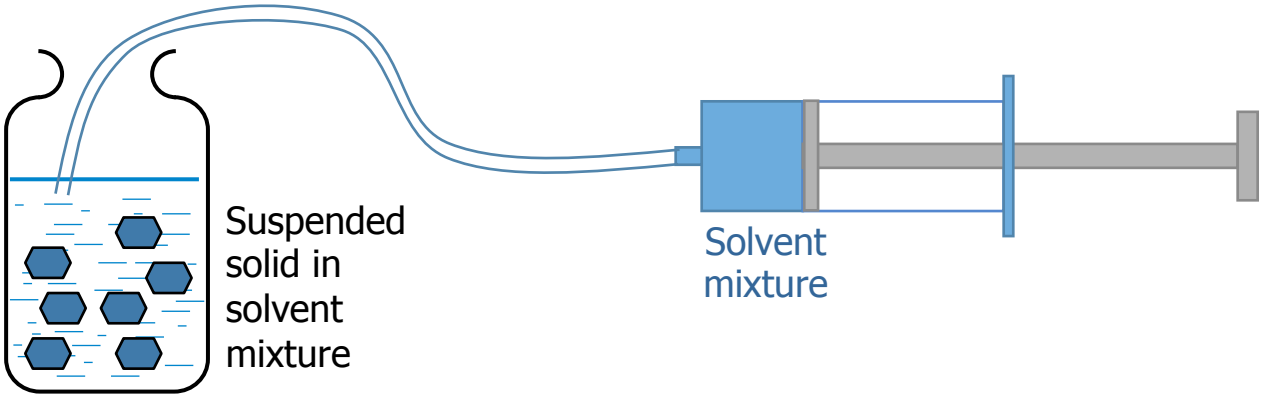
INA
x* = 33.3 mmol/mol
(c* = 72 mg/ml)

CBZ
x* = 5.7 mmol/mol
(c* = 24 mg/ml)

Solubility of **INA** is 6 times higher than that of **CBZ**

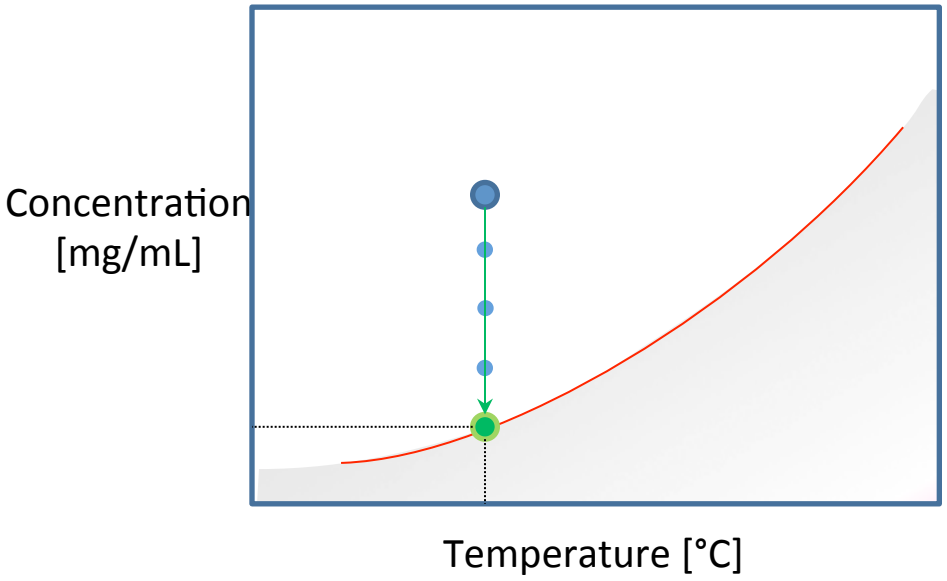
Solvent Addition Method

Clear point concentration

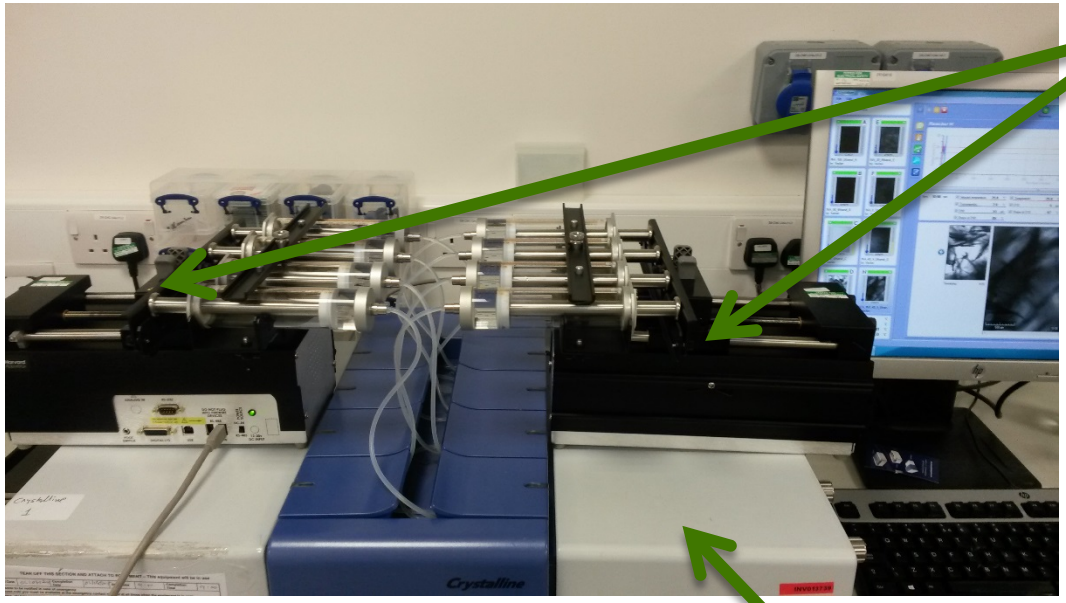


- Change the composition until clear point concentration **at constant temperature**

- Faster than Equilibrium Method
- Suitable for multicomponent systems
- No limitation # components in sample and added solution



Solvent Addition Method



2x4 Syringe Pumps:
Each syringe can hold a different solvent composition.
Two different flow rates can be tested in one go.

Crystalline:
8 Reactors with independent temperature control and PVM

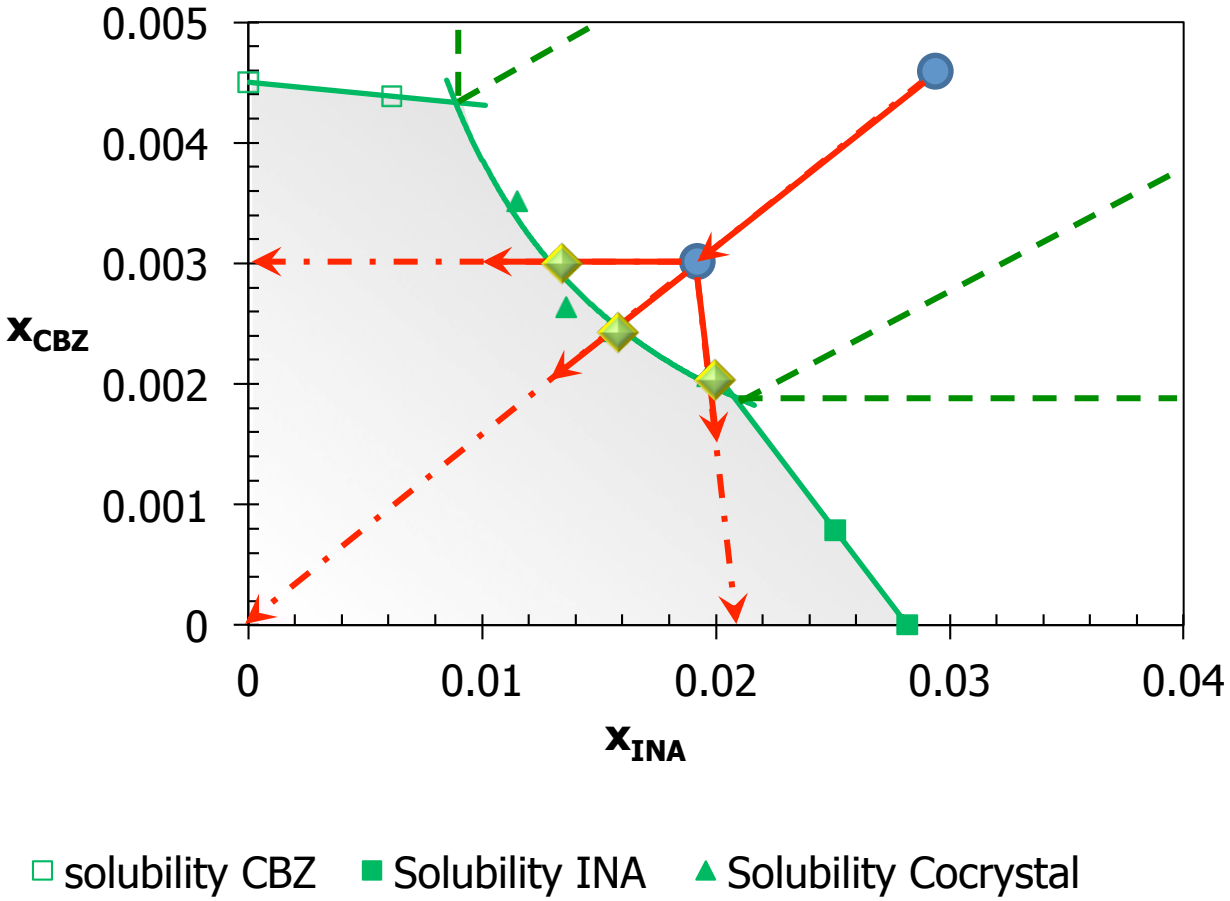
Co-crystal Phase diagram

Carbamazepine (CBZ)

Isonicotinamide (INA)

Ethanol

T = 20°C



Crystal Solubility

- Crystallization
- Solubility Measurements
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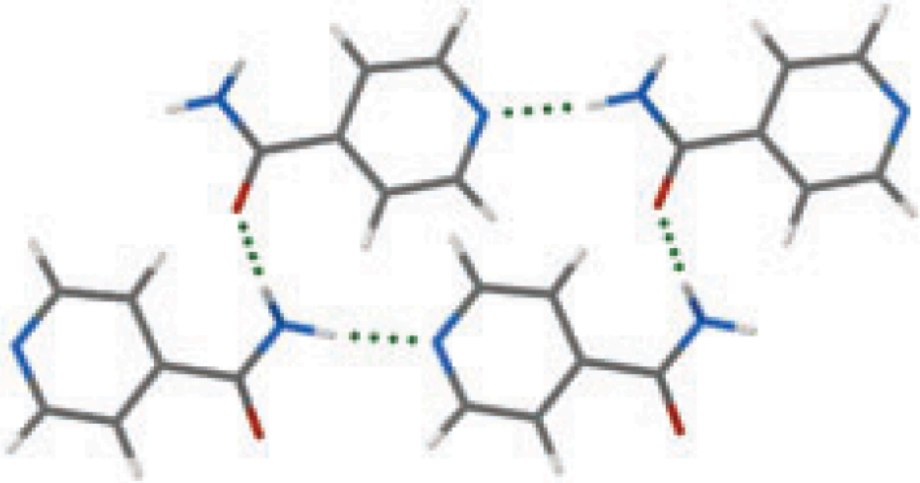
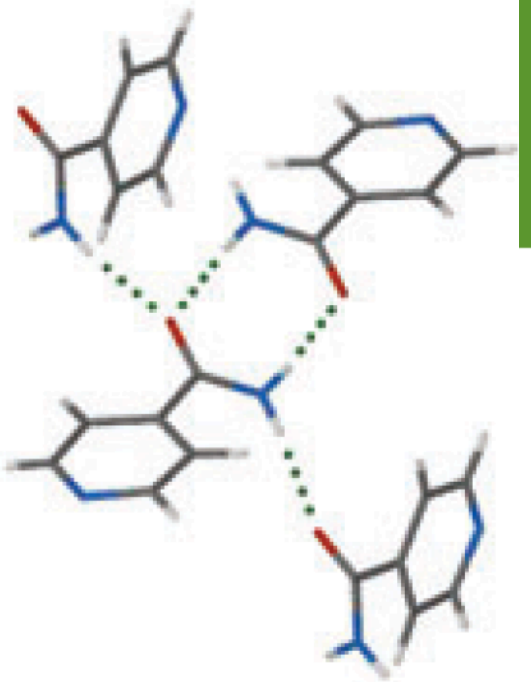
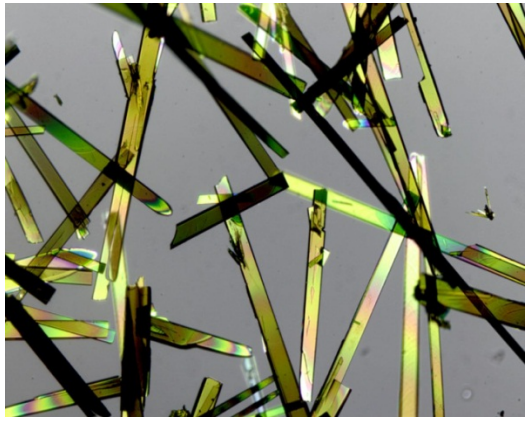
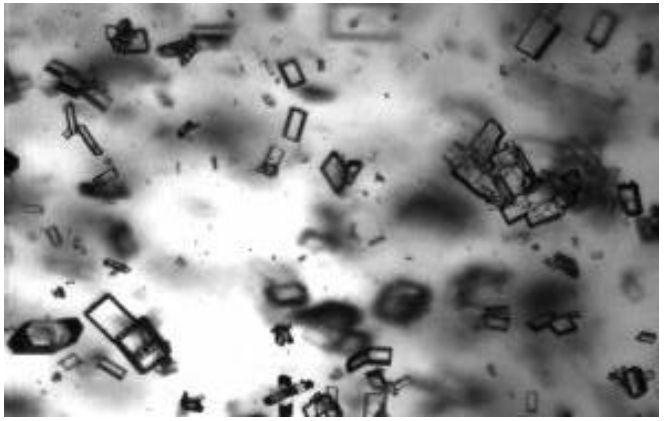
Crystal Form







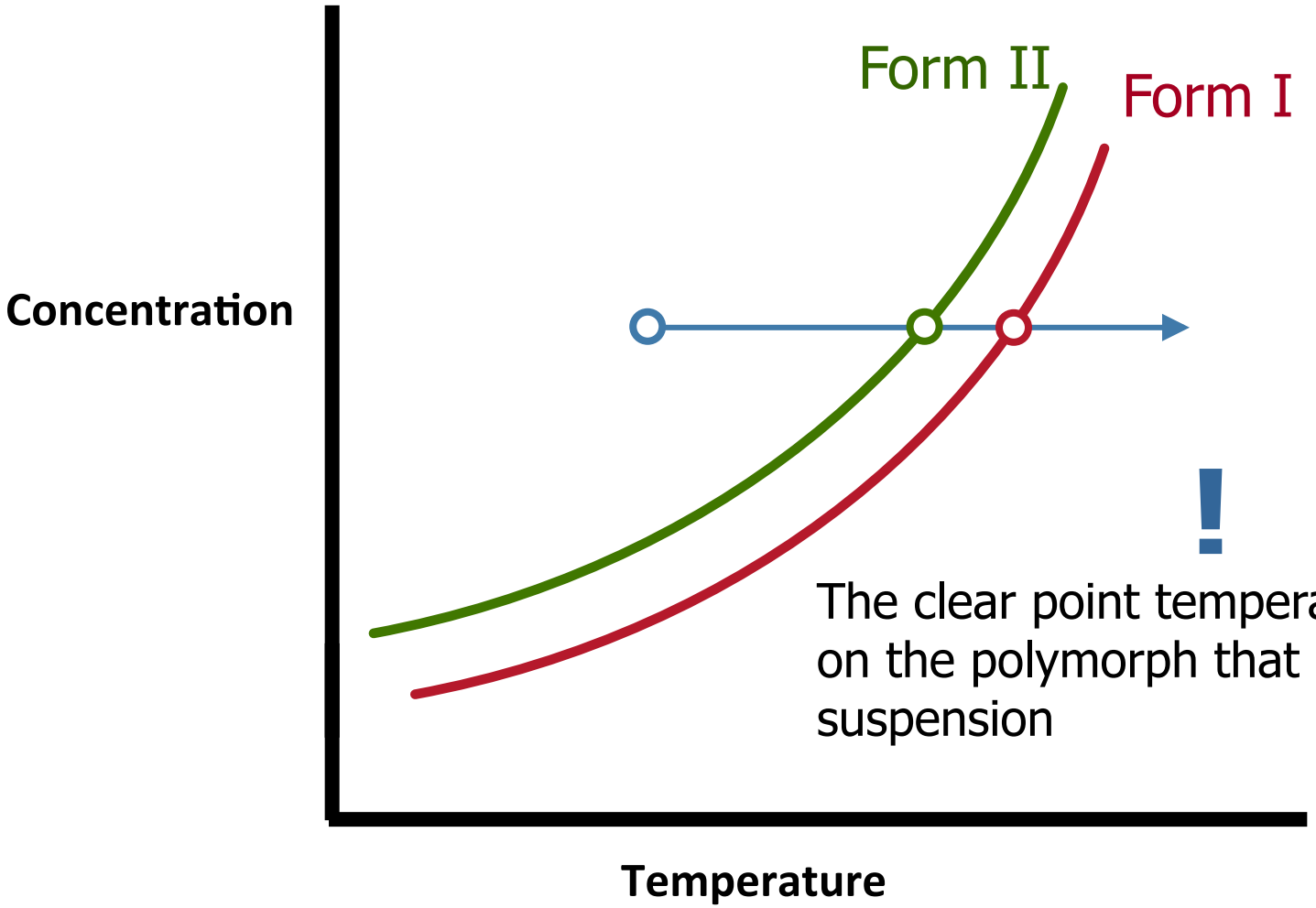
Form I



Form II

Polymorphism: The ability of a chemical compound to form 2 or more crystal structures

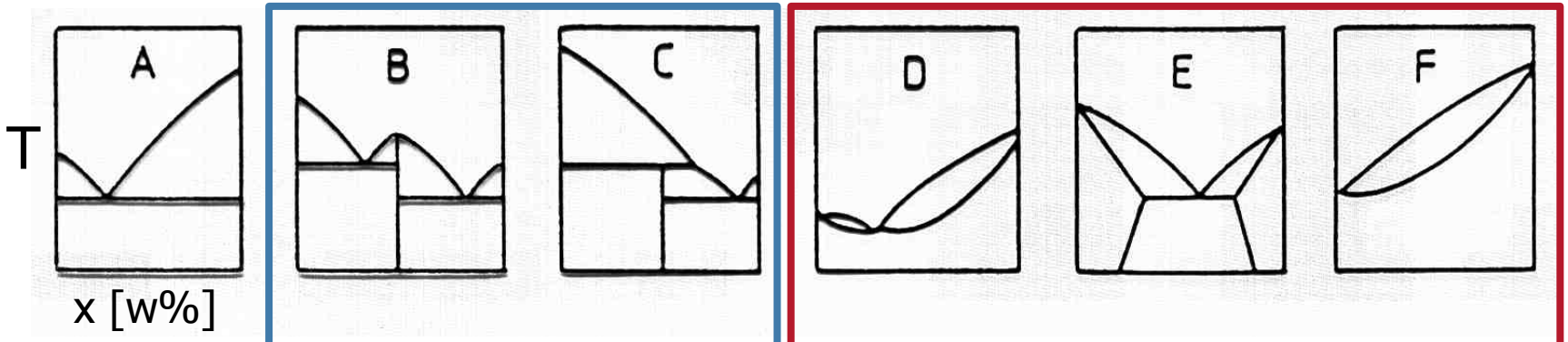
Crystal Form



!

The clear point temperature depends on the polymorph that is present in the suspension

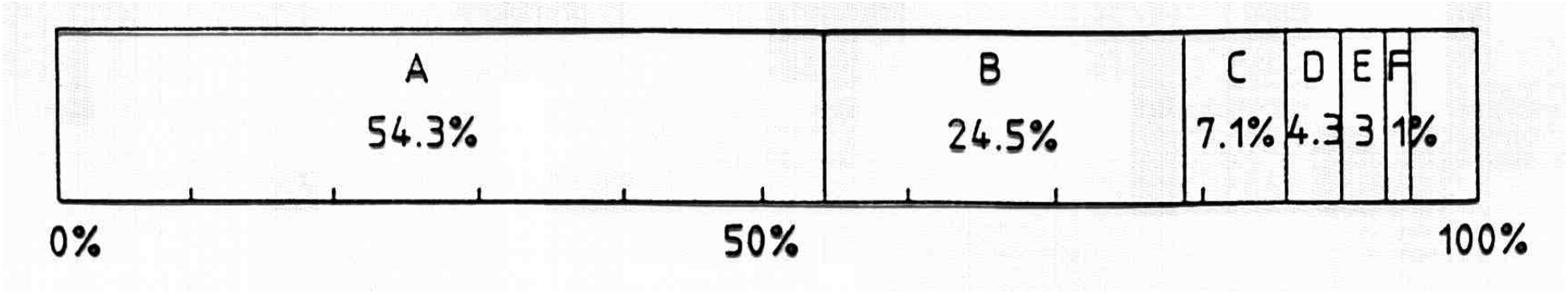
Complex Phase Behavior



(Normal)

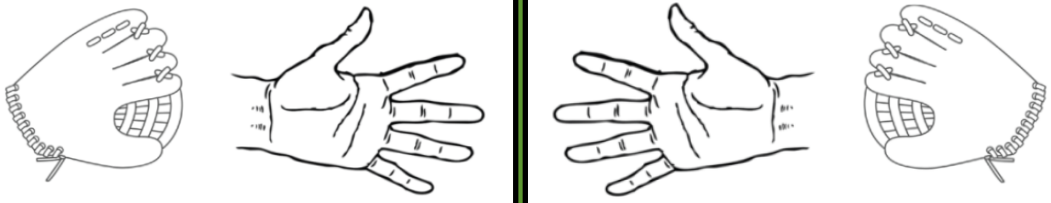
Salt, Co-crystal, solvate: The crystal phase might contain more components in specific ratios

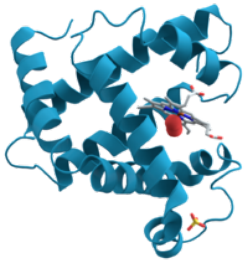
Solid Solution: The crystal phase might contain more components in varying ratios

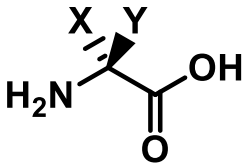


M. Matsuoka,1978

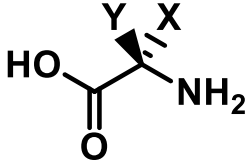
Chirality





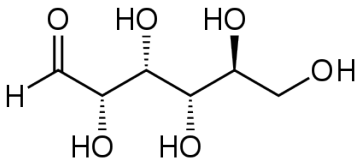


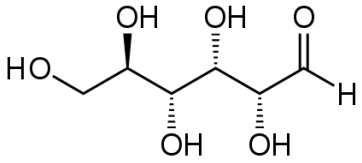
(*S*)

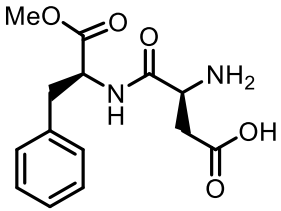


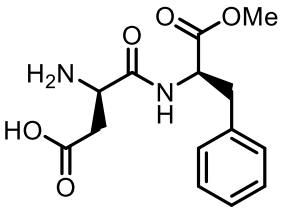
(*R*)

enantiomers



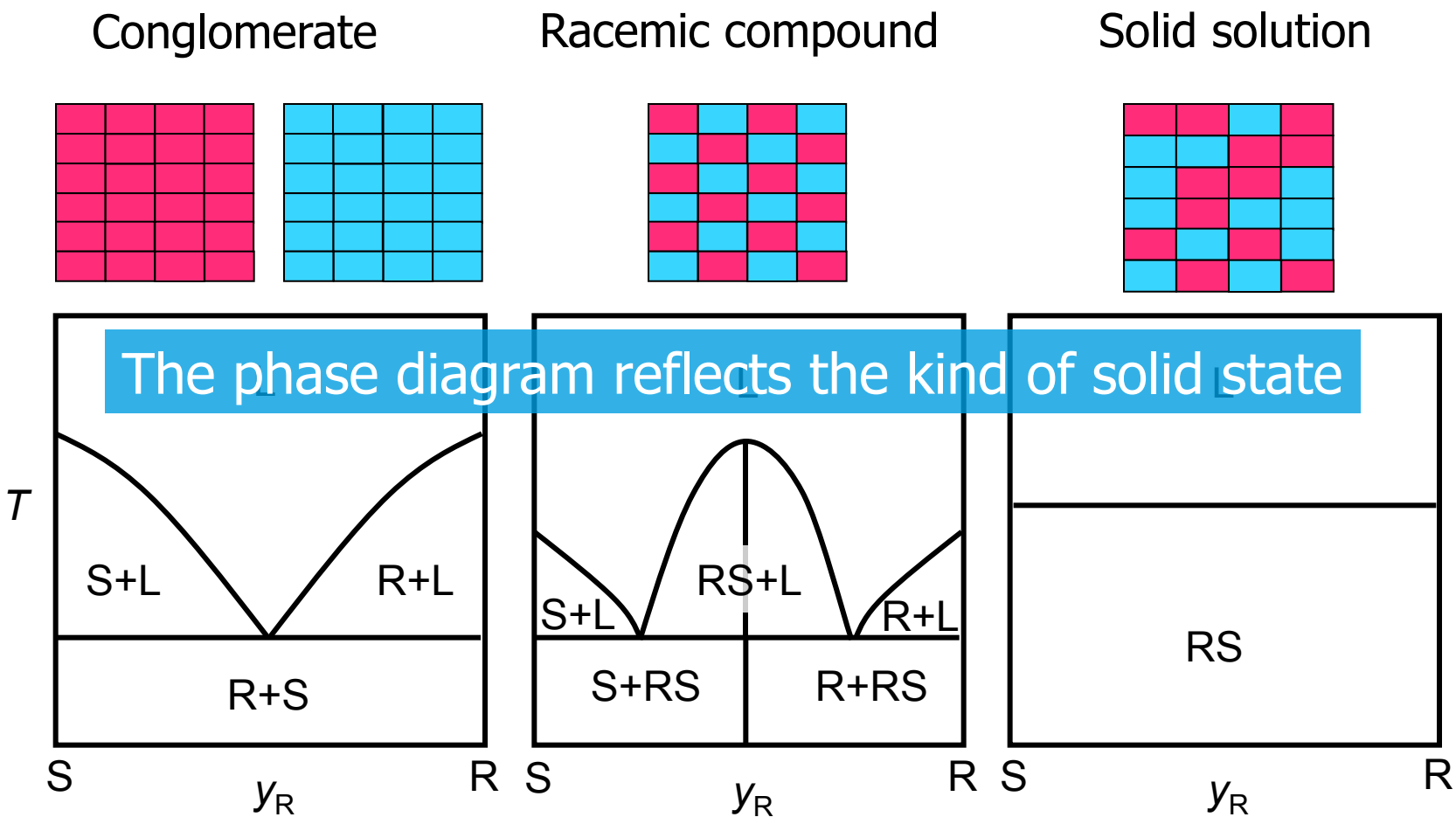






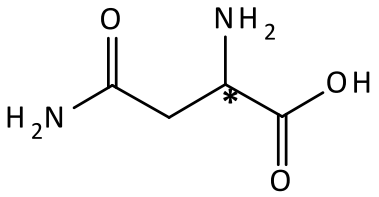
Chiral compounds

Binary phase diagram



Chiral Compound Solubility
Asparagine in Water

Ternary phase diagram screening



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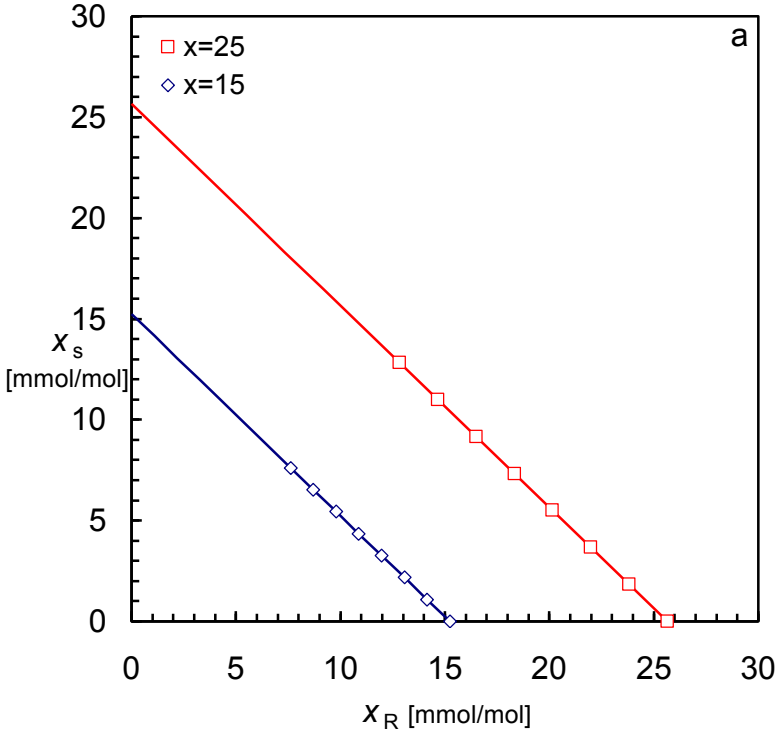
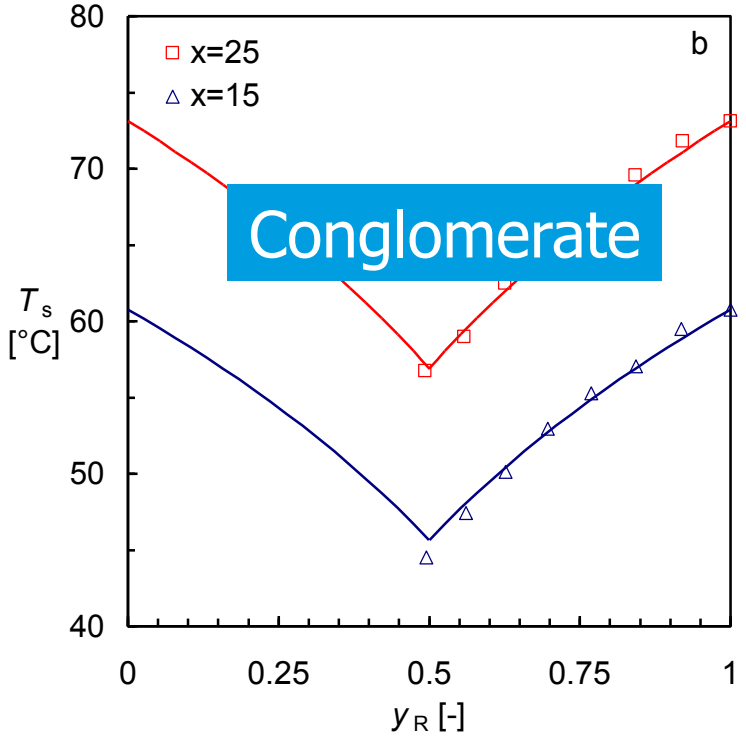
Sample composition



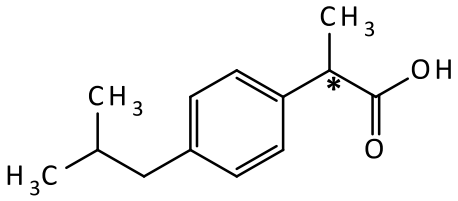
Clear point temperatures

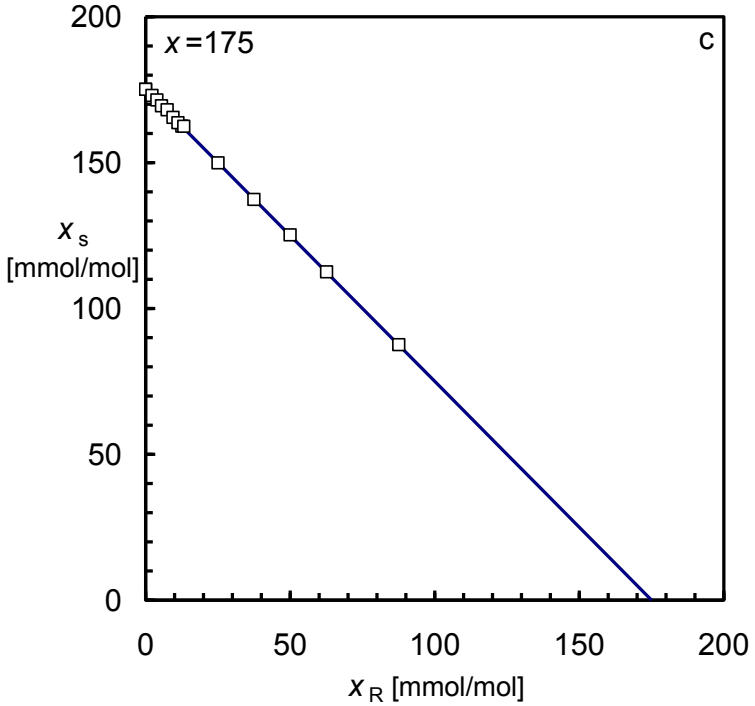


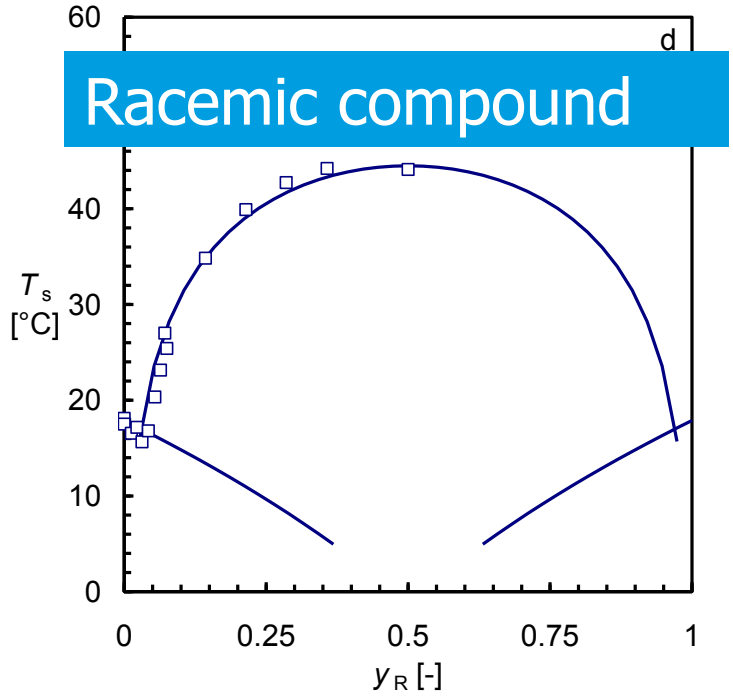
$$y_R = x_R/(x_R+x_S)$$

Chiral Compound Solubility: Ibuprofen in Hexane

Ternary phase diagram screening



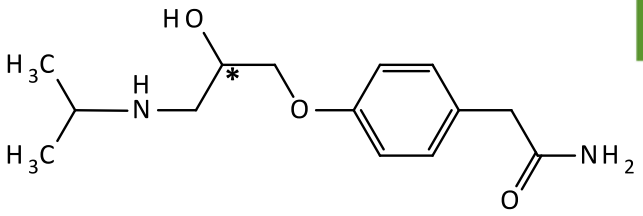


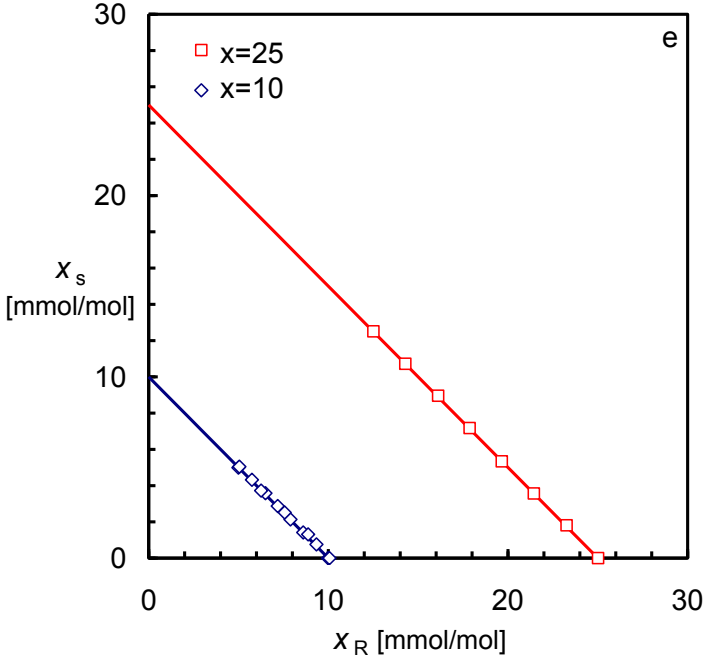


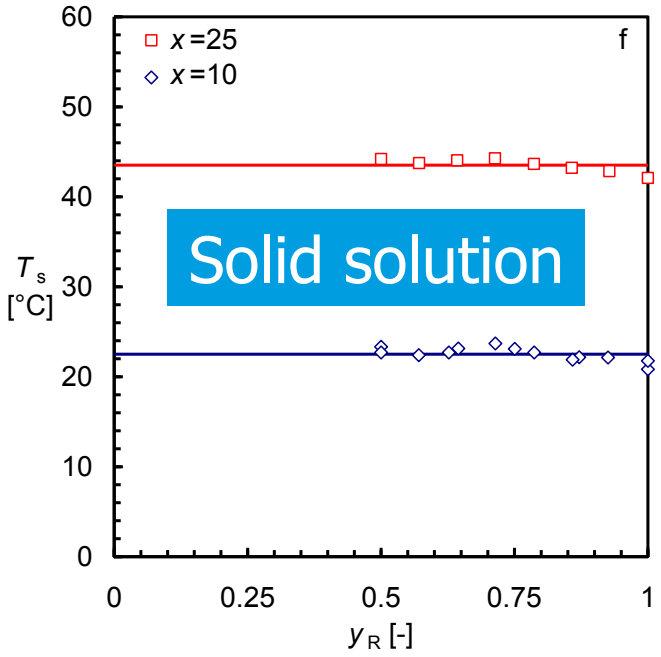
$$y_R = x_R/(x_R+x_S)$$

Chiral Compound solubility: Atenolol in Ethanol

Ternary phase diagram screening





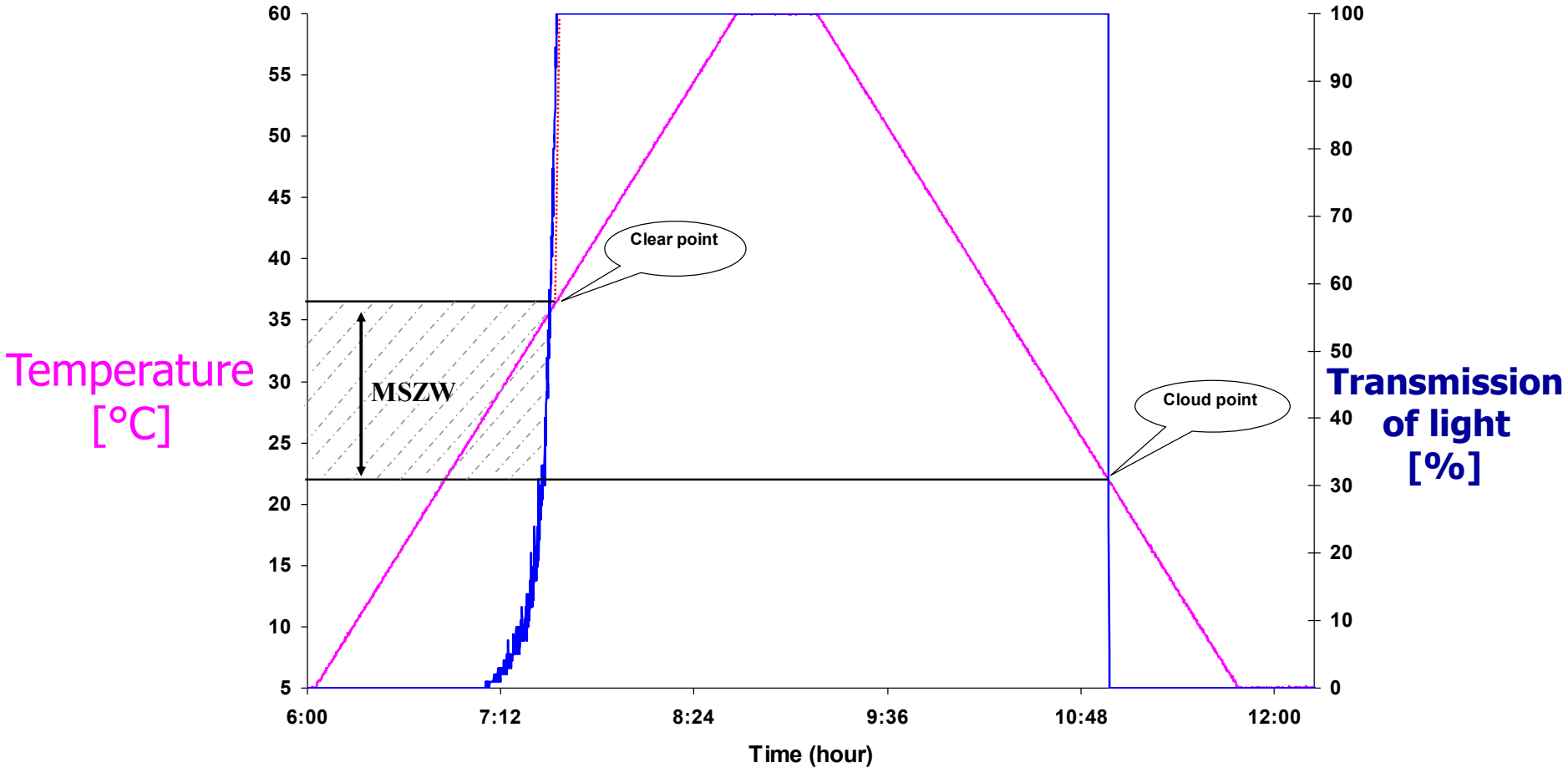


S. Sukanya, J.H. ter Horst, Racemic Compound, Conglomerate, or Solid Solution: Phase Diagram Screening of Chiral Compounds, *Crystal Growth Design* 10(4) (2010) 1808-1812.

Crystal Solubility

- Crystallization
- Solubility Measurements
- Solubility Analysis
- Solubility Measurements in Complex Multicomponent Systems
- Solubility in Complex Multicomponent Systems
- Crystallization Kinetics

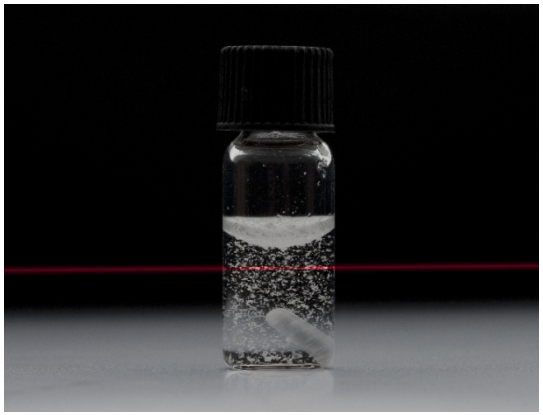
Metastable Zone Width



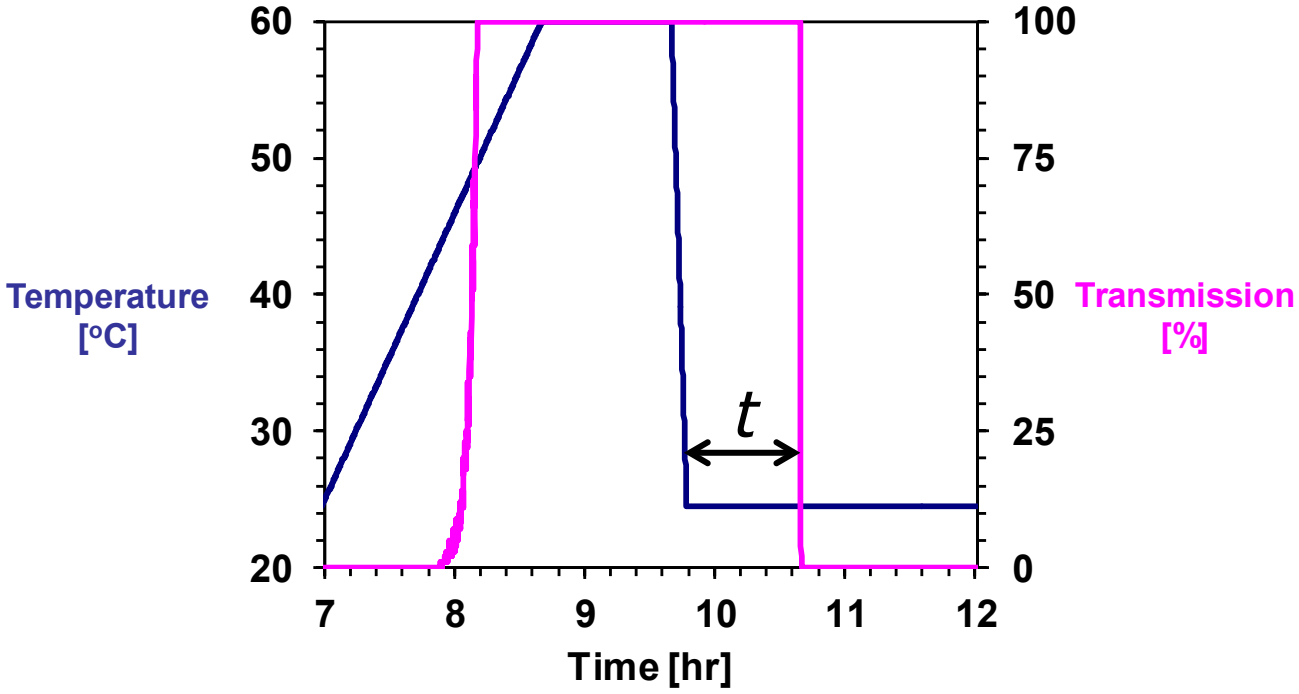
Measuring Induction Times

The time until detection of crystals at a constant supersaturation

- Accurate temperature control

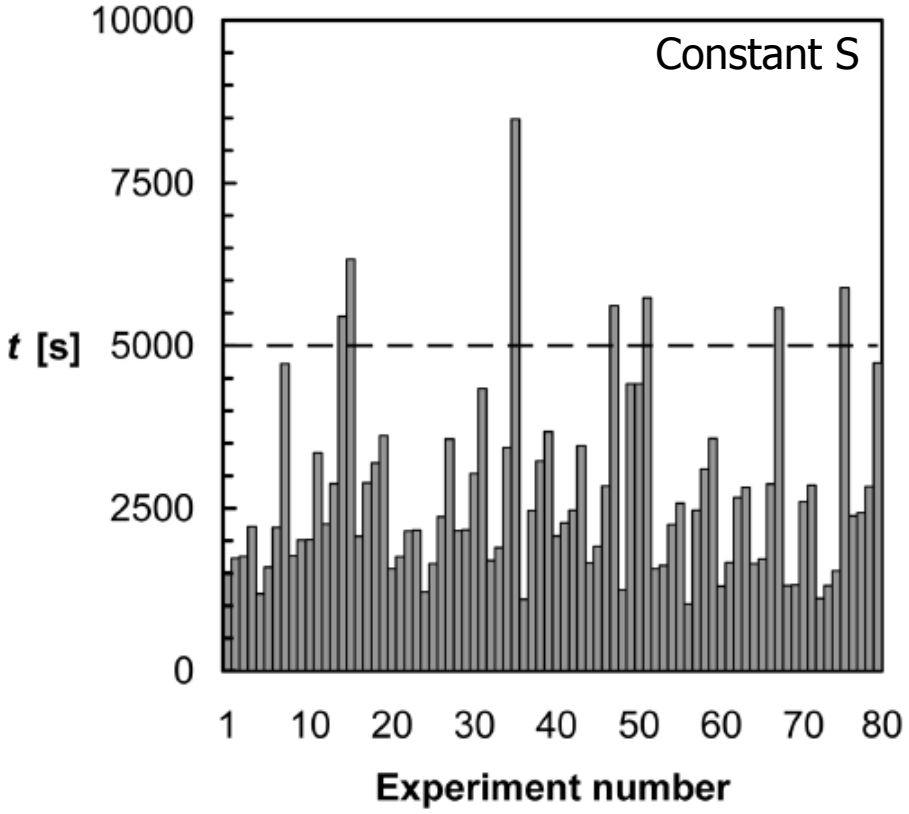


1 ml

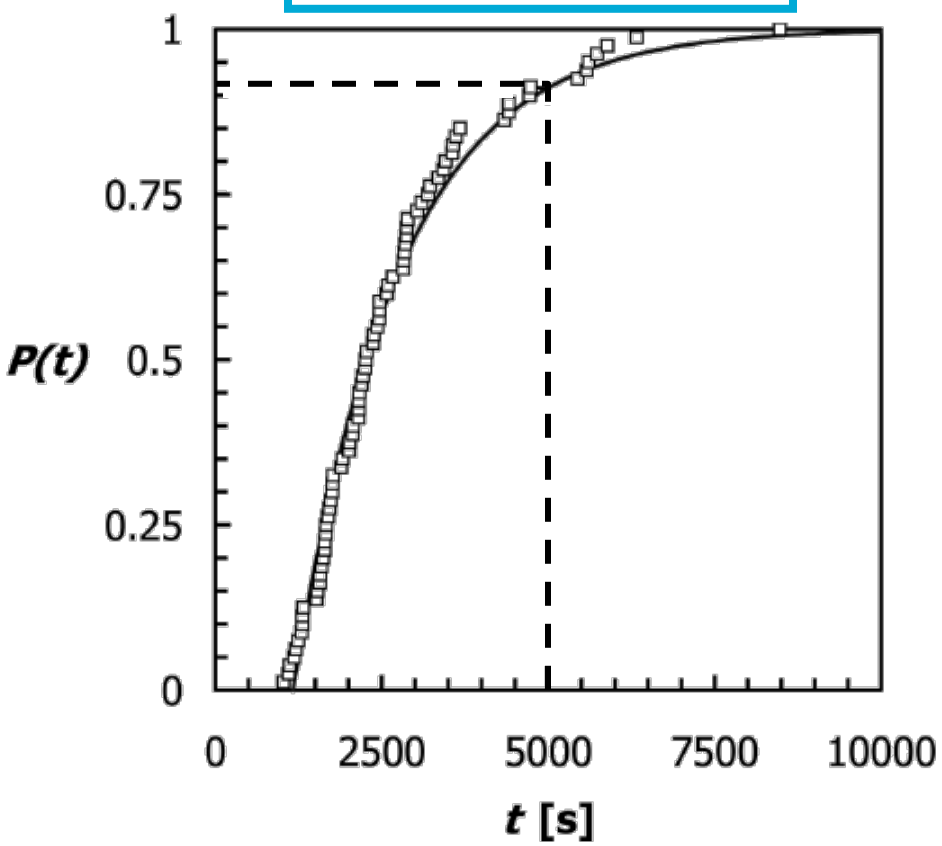


Measuring Induction Times

- Create constant supersaturation
- Measure induction time
- Do this a large number of times, say *M* times



$$P(t) = M^{+}(t_i)/M$$

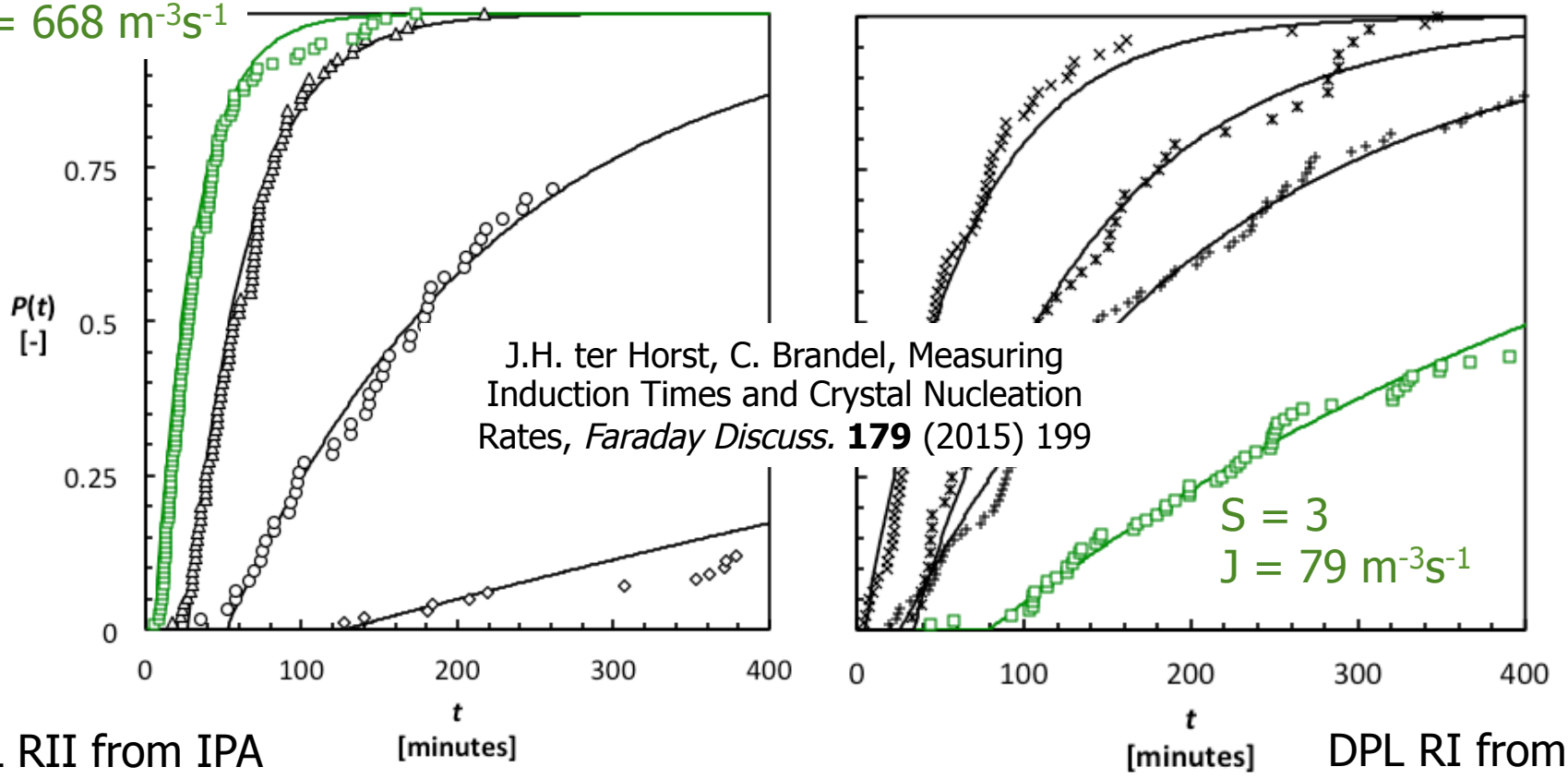


S. Jiang, J.H. ter Horst, *Crystal Growth Design* **11** (2011) 256-261

Induction Time Distributions

	DPL RII from IPA		DPL RI from DMF	
S [-]	J [$m^{-3}s^{-1}$]	t_g [min]	J [$m^{-3}s^{-1}$]	t_g [min]
1.5	11.6	128		
1.7	97.0	52		
2.0	429	27		
3.0	668	5.9	35.7	79
3.5			88.7	26
4.0			157	34
4.2			275	4.7

S = 3
J = 668 $m^{-3}s^{-1}$



J.H. ter Horst, C. Brandel, Measuring Induction Times and Crystal Nucleation Rates, *Faraday Discuss.* **179** (2015) 199

DPL RII from IPA

DPL RI from DMF

Crystal Solubility

- Crystallization
- Solubility Measurements
- Solubility Analysis
- Solubility Measurements in Complex Multicomponent Systems
- Solubility in Complex Multicomponent Systems
- Crystallization Kinetics

Crystal Solubility

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- All crystalline compounds behave differently
- The temperature dependent solubility of a compound in a solvent is the first step towards a crystallization process design
- Temperature measurement methods
  - Gravimetric, temperature variation, solvent addition
- Metastable zone width, induction times and crystal nucleation rates

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Google Scholar: http://scholar.google.nl/citations?user=tEOvZXEAAAAJ&hl=en
ResearchGate: http://www.researchgate.net/profile/JH_Ter_Horst2

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