Particle Formation by Crystallization

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Acknowledgement
Joop ter Horst I use some of his slides

TU Delft
Delft University of Technology

Crystallization

A. Crystallization: Phenomena, Process & Product Properties

- Introduction Crystallization
- Crystals as Product:
  - Crystal purity, Crystal Size Distribution, Crystal shape and crystal solid form
- Crystallization kinetics
  - Nucleation, Crystal Growth, Attrition
- Crystallization process
  - thermodynamics
  - process design
  - equipment

B. Advanced crystallization topics

- Polymorphism
- Chiral crystallization

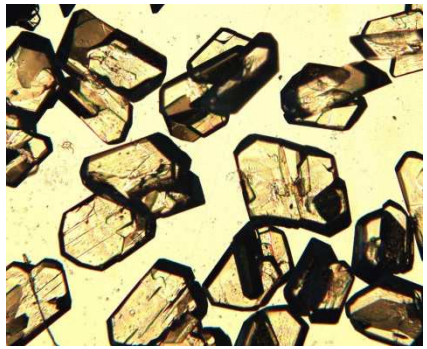
Literature

Basic references

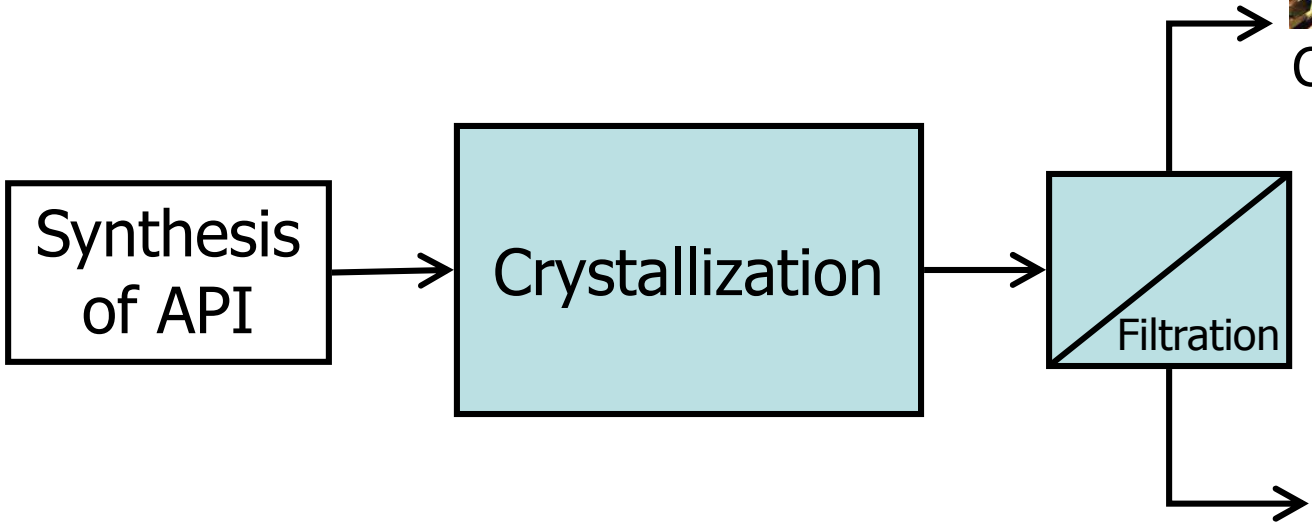
- Industrial Crystallization, fundamentals and application, A. Lewis, M.S. Seckler, H.J.M. Kramer and G.M van Rosmalen, Cambrridge University press, will appear in 2015
- Handbook of Industrial Crystallization, A.S Myerson, 2002, Butterworth- Heinemann
- Crystallization, J.W. Mullin, 2001,Butterworth & Heinemann
- Crystallization, H.J.M. Kramer, G.M. van Rosmalen, In: *Encyclopedia of Separation Science*, Ed. I.D. Wilson, 2000, Vol. 1, page 64-84.

Crystallization

A separation unit operation



Crystalline product
99.99% pure



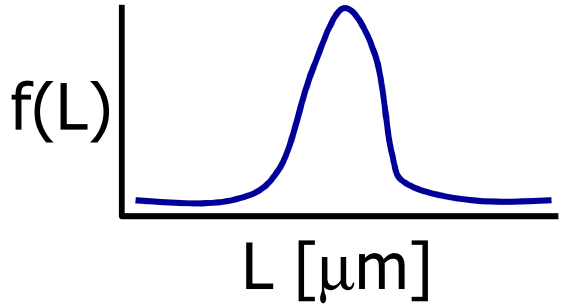
Solution containing impurities and dissolved synthesis product

- ✓ High selectivity
- ✓ Mild conditions
- ✓ Low energy demand
- ✓ Particular product
- ✓ Slow process

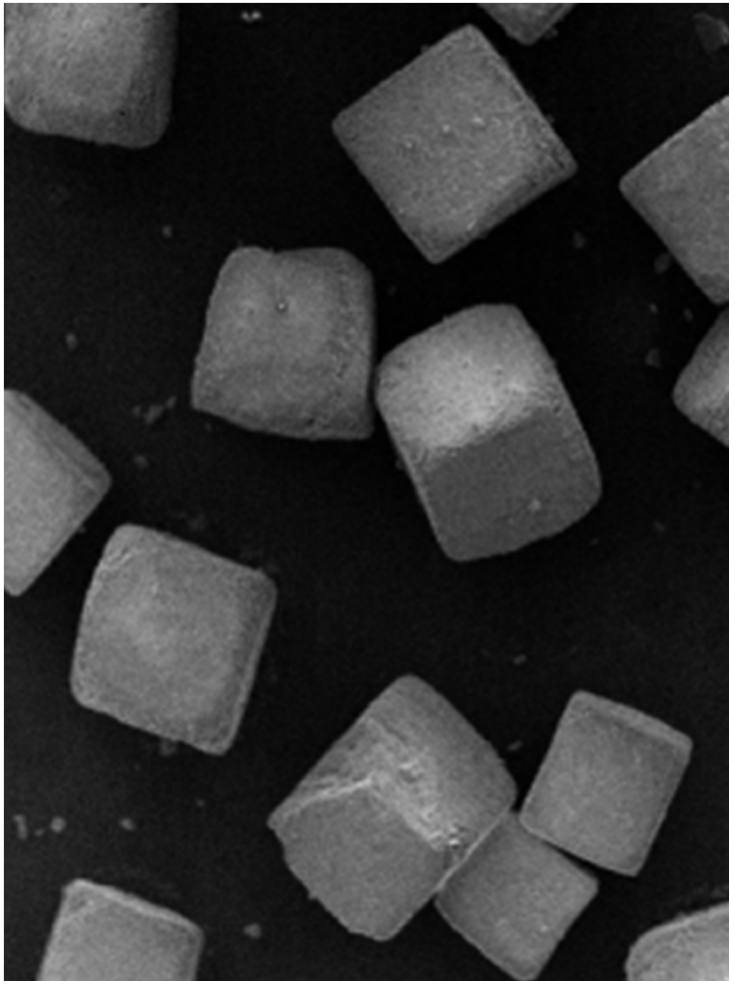
The Crystalline Product

Table salt

- Crystal purity >99.9%
- Crystal size distribution



- Crystal shape: cubic
- Crystal form: anhydrate



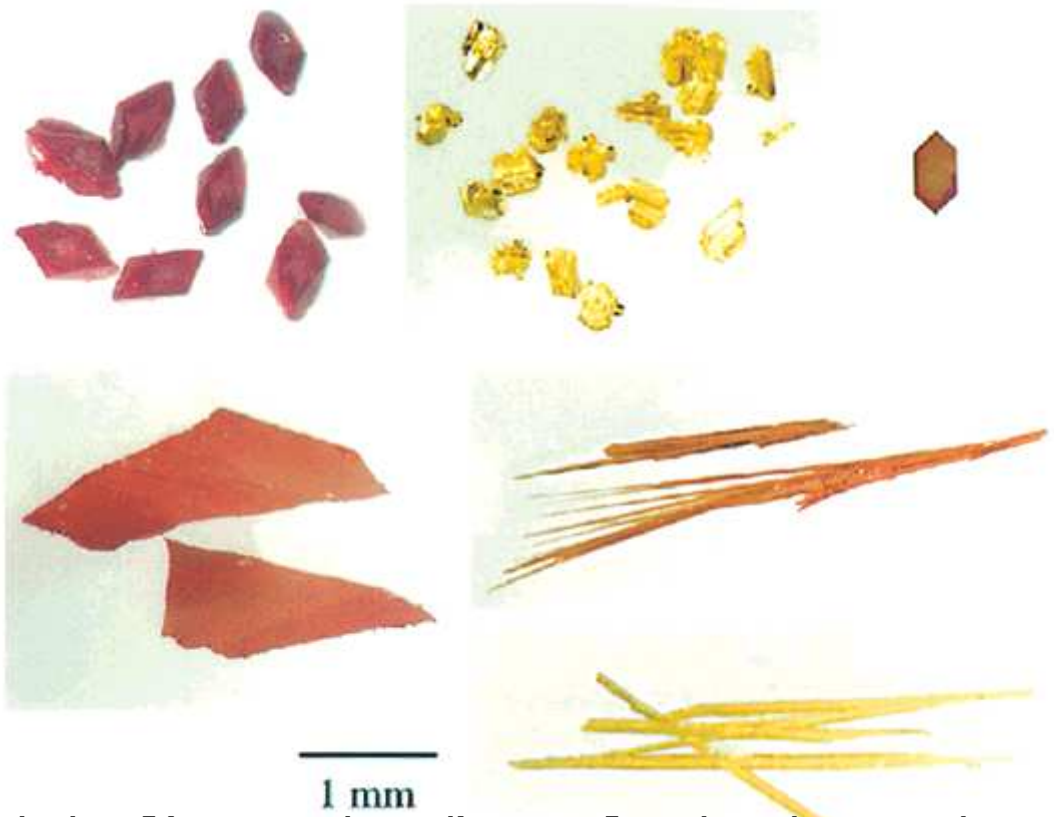
Other properties of crystal products

Type of polymorph

- Shape
- Color
- Solubility
- Stability

Chirality

- Bio activity



5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile
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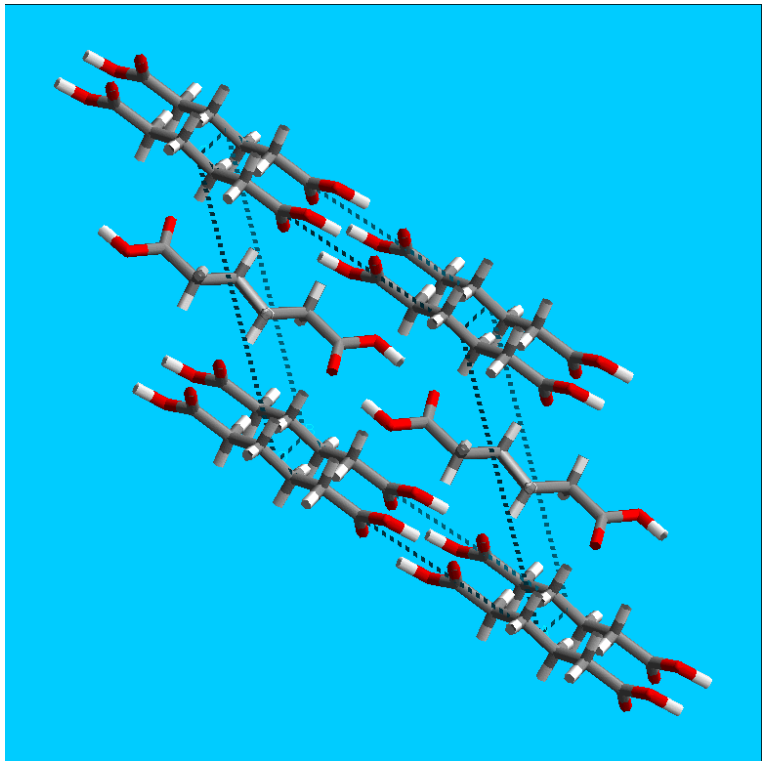
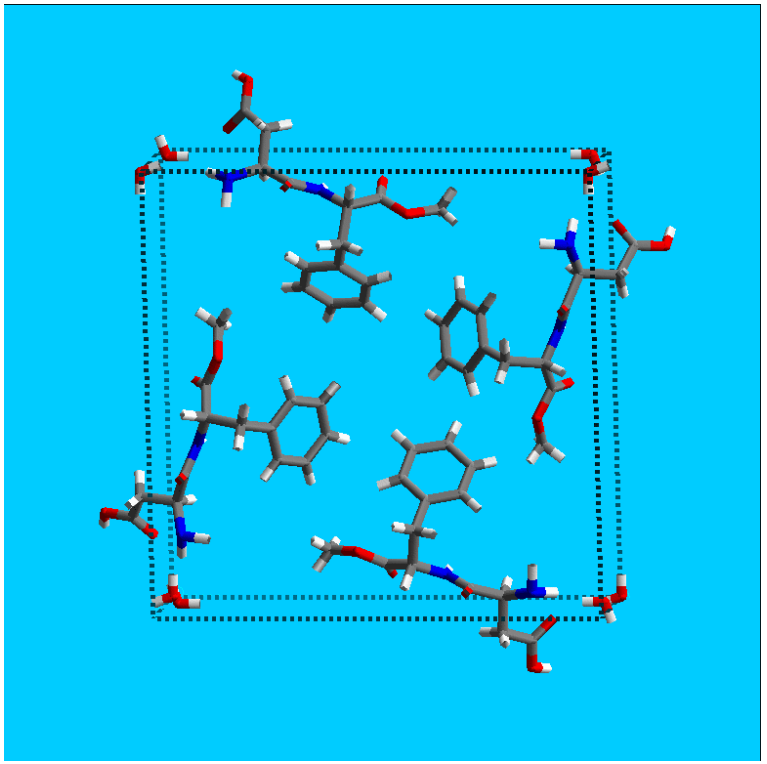
Molecular structure: the crystal unit cell



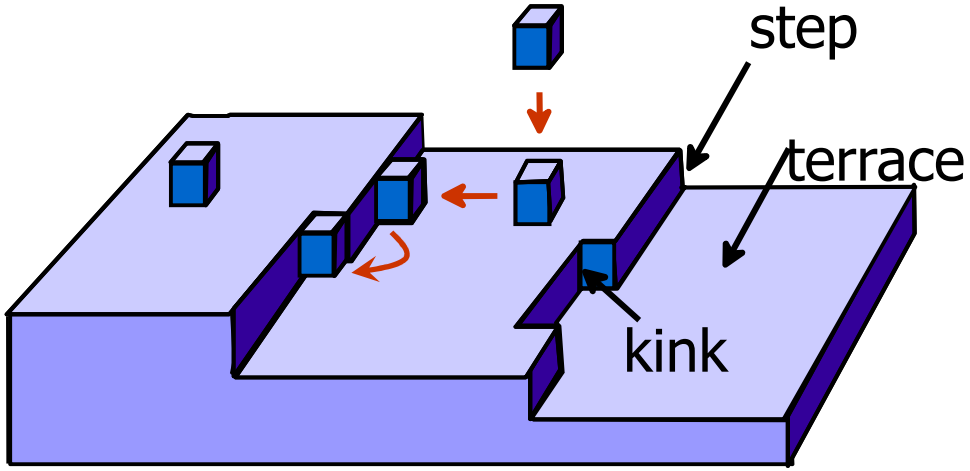
Adipic acid
Monoclinic (P21/c)
$a \neq b \neq c$, $\alpha = \beta = 90° \neq \gamma$



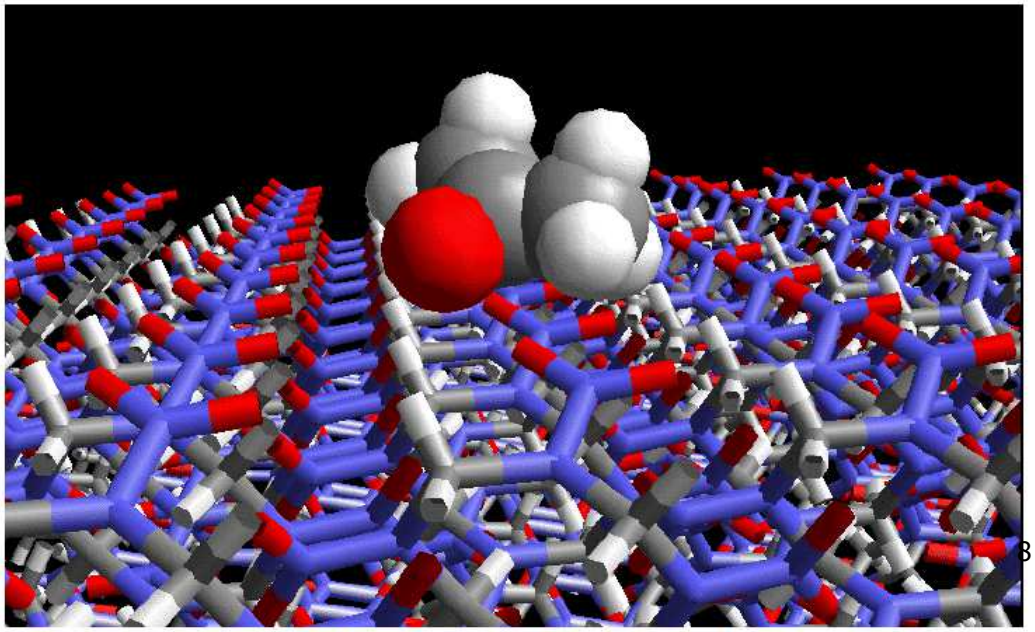
Aspartame
Tetragonal (P41)
$a = b \neq c$, $\alpha = \beta = \gamma = 90°$

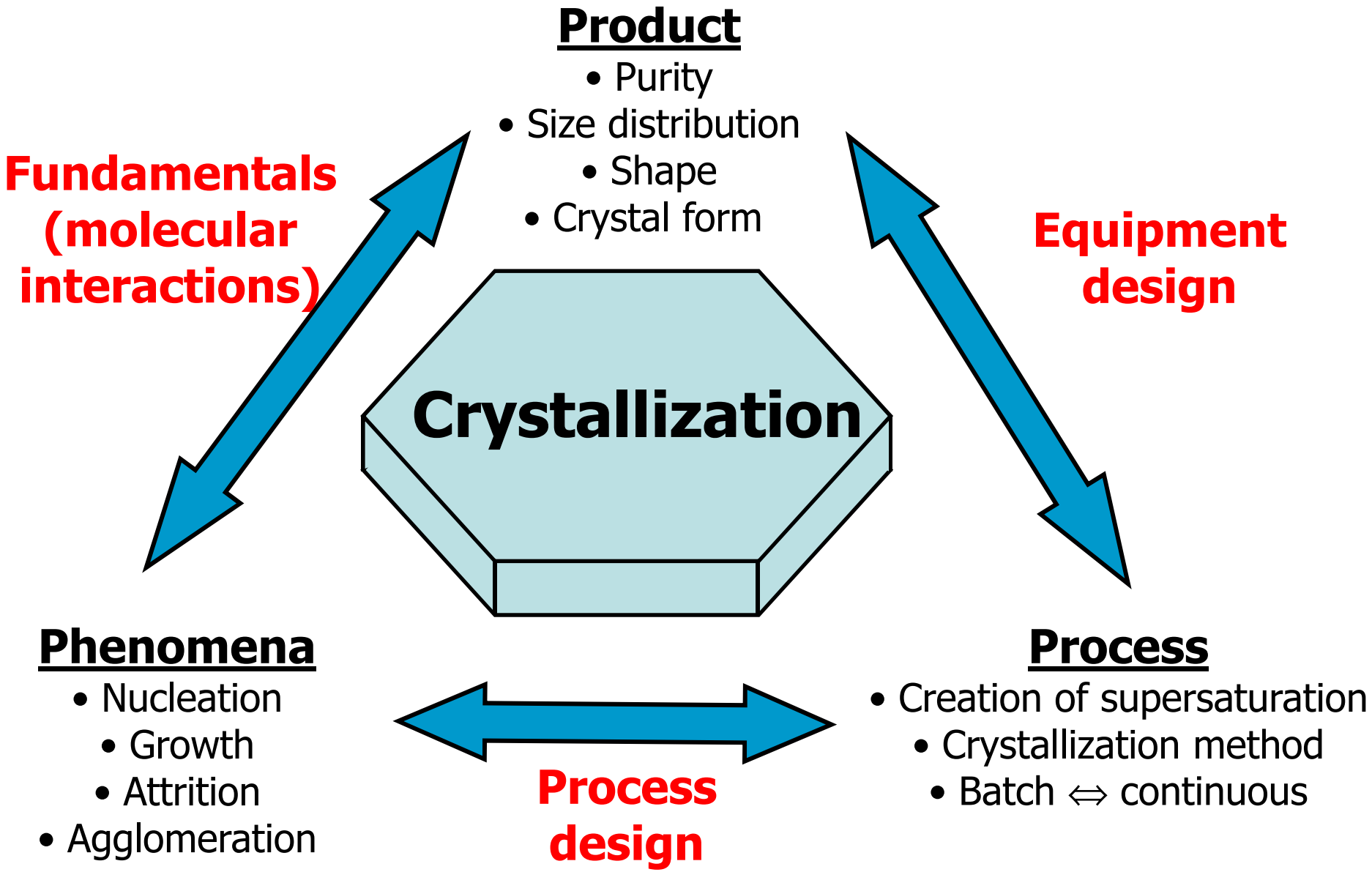
Crystallization occurs at molecular level

Incorporation of single molecules into the crystal lattice

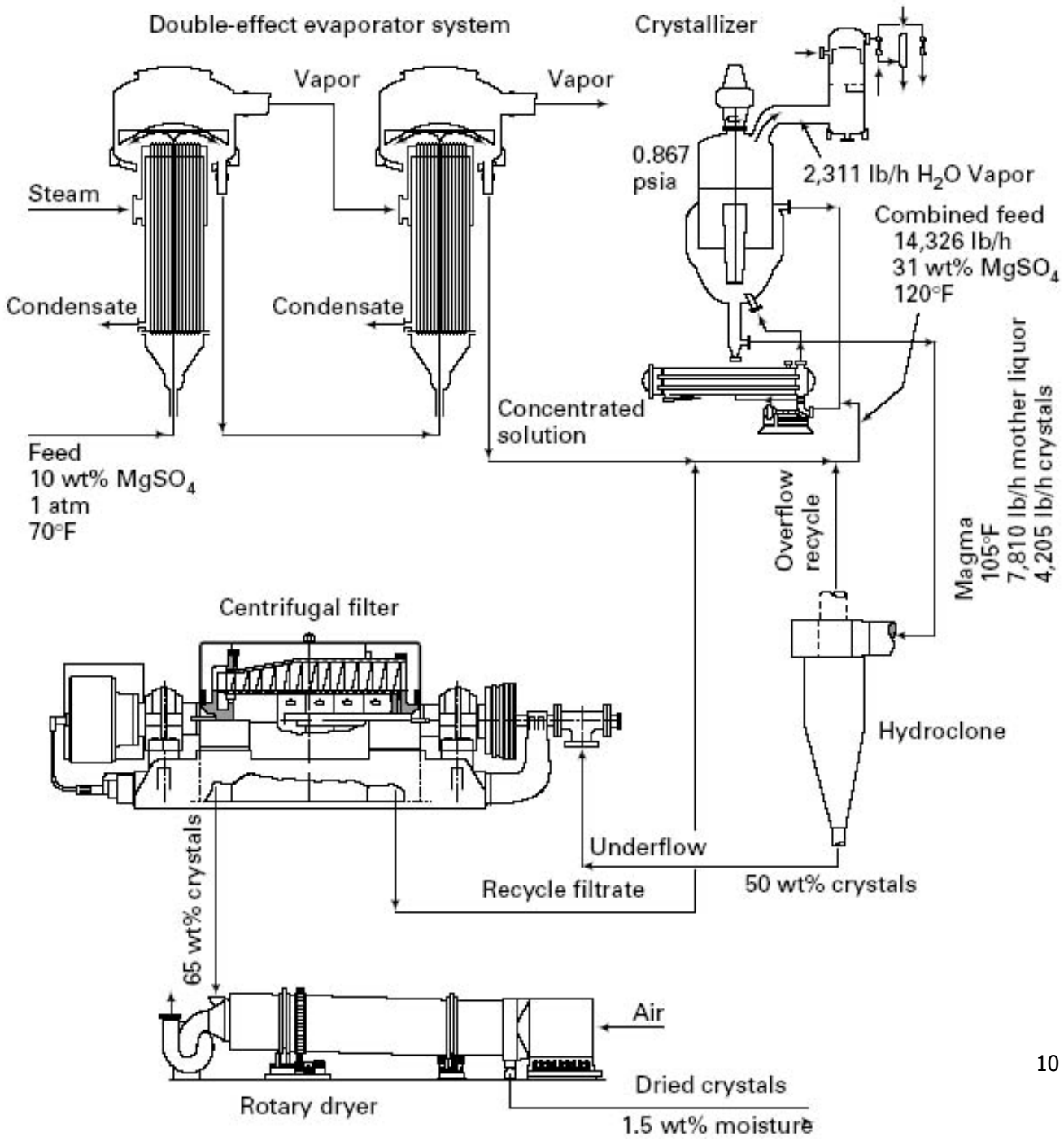


Arrangement of millions of molecules into crystal lattice
Interaction at surface with solvent and impurities

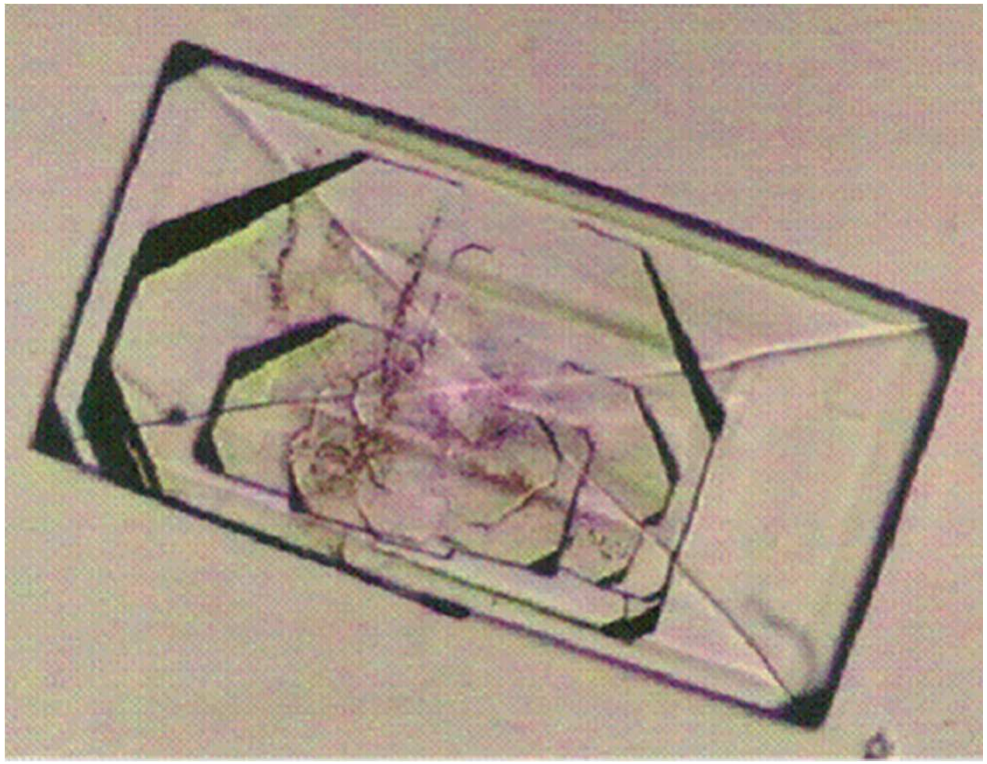



Product
• Purity
• Size distribution
• Shape
• Crystal form
Fundamentals (molecular interactions)
Equipment design
Crystallization
Phenomena
• Nucleation
• Growth
• Attrition
• Agglomeration
Process design
Process
• Creation of supersaturation
• Crystallization method
• Batch ⇔ continuous

$MgSO_4$ Crystallisation plant

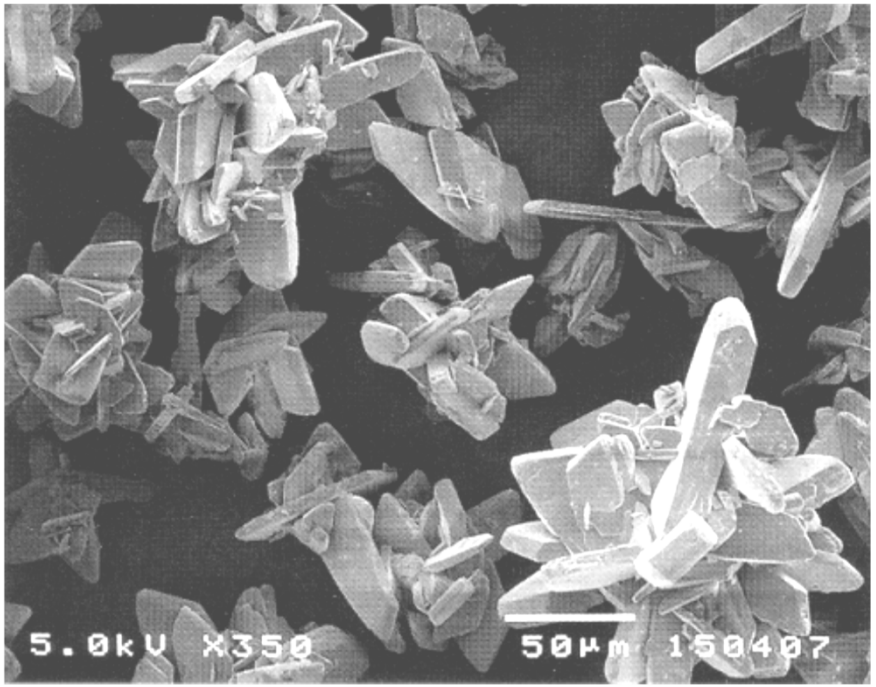


Product ⇔ phenomena



Impurity effect on product quality

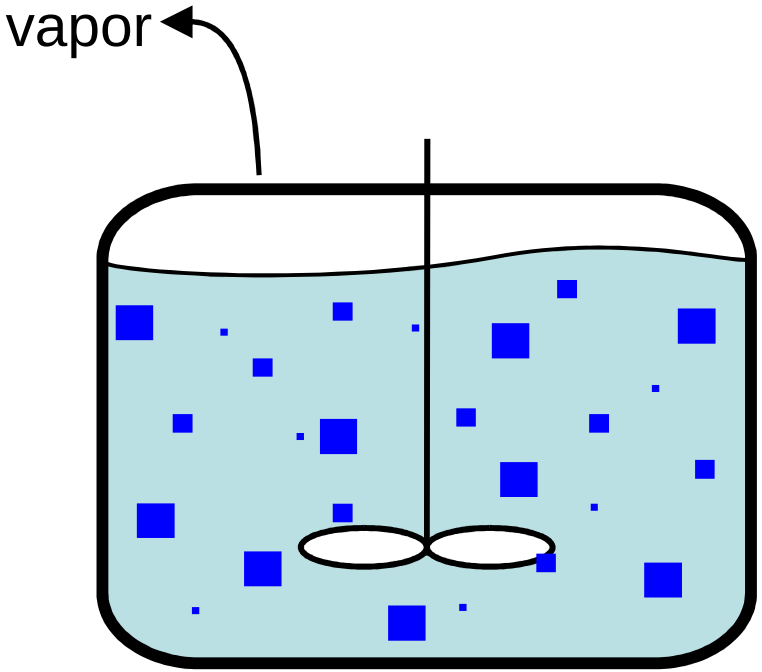
Product ⇔ process



Stimulate agglomeration during process to enhance filterability

Gypsum - $CaSO_4.2H_2O$

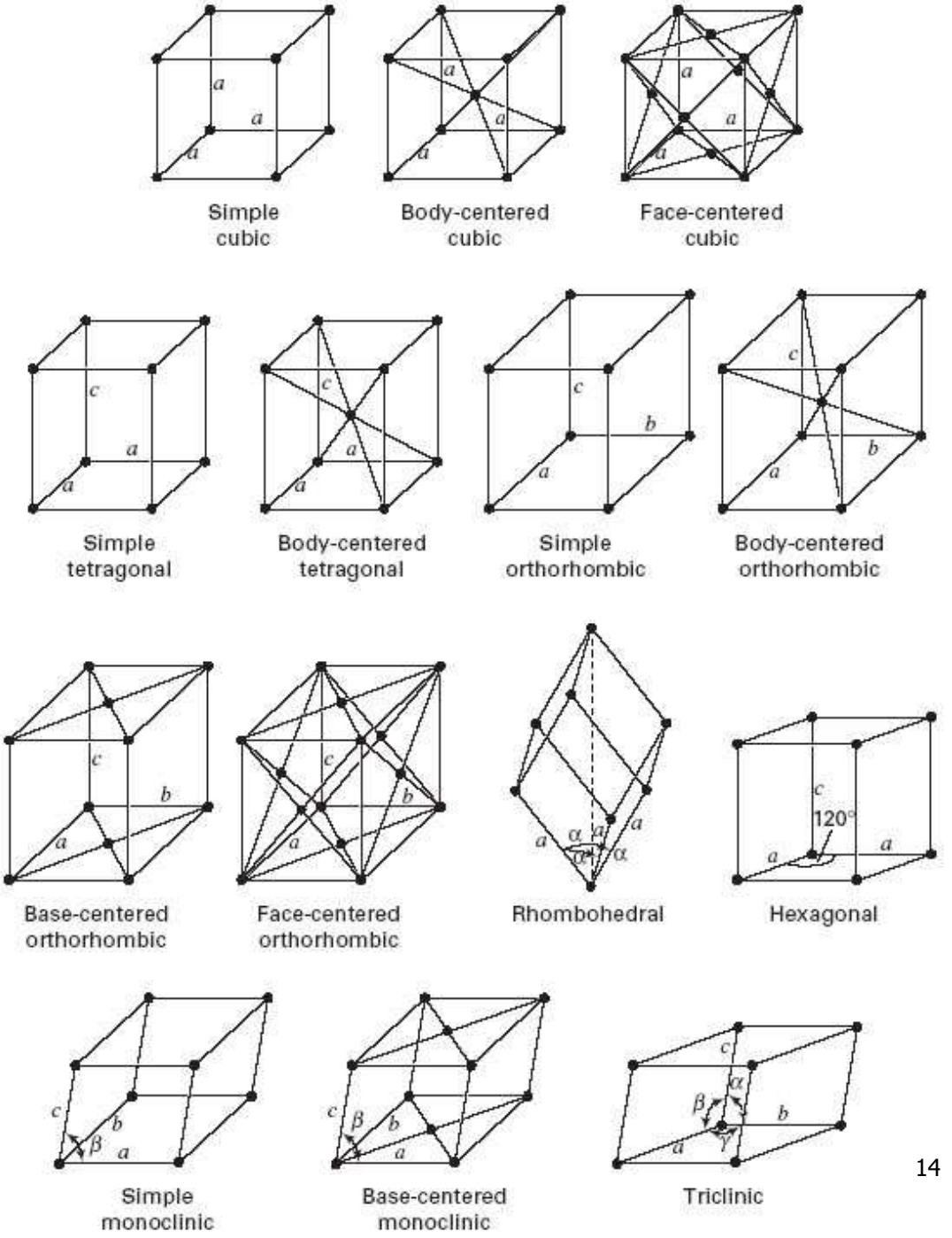
Process ⇔ phenomena



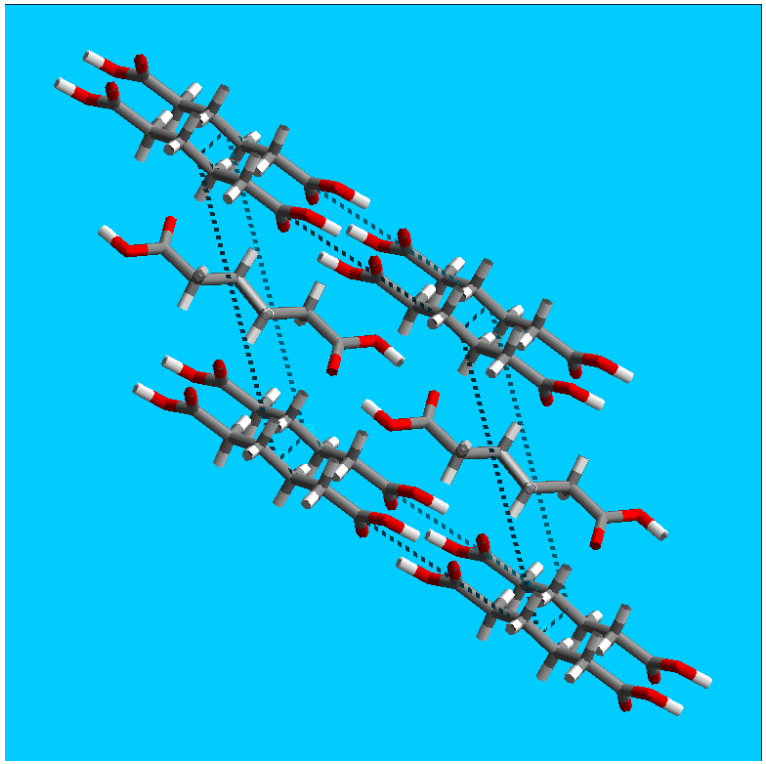
- Primary nucleation or seeding
- Primary nucleation and growth
- Secondary nucleation
- Growth
- Agglomeration

What is a crystal?

A **crystal** is
a solid
in which its building units
(molecules, atoms, ions)
are packed in
regularly ordered,
repeated patterns
extending in all 3 dimensions



Crystal unit cell



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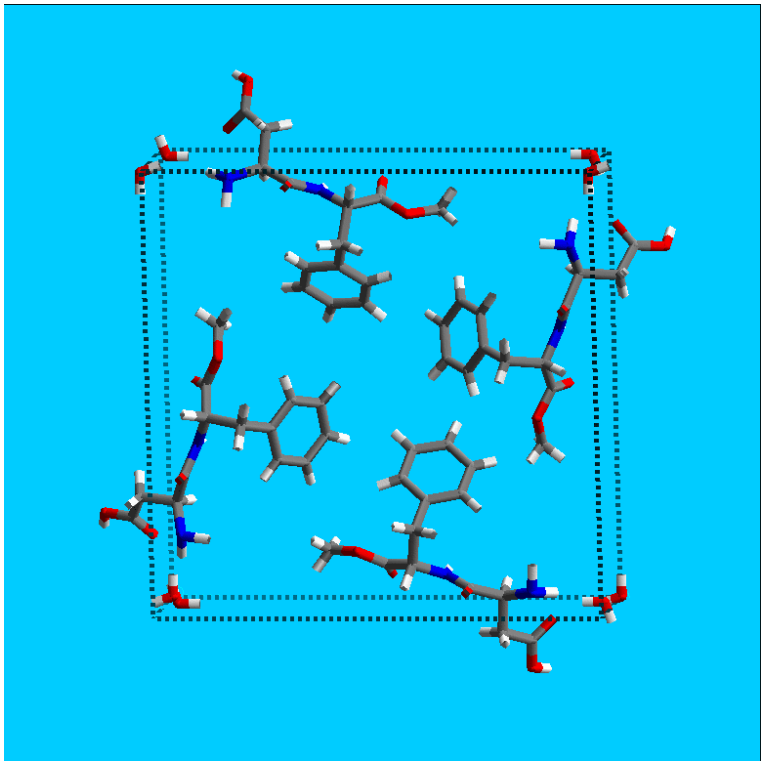

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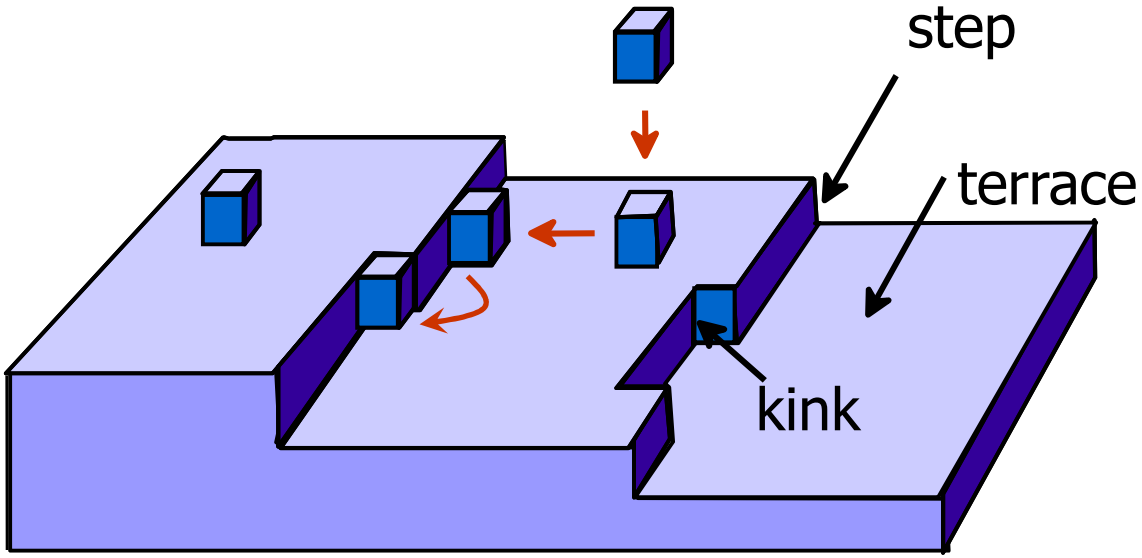
Crystallization is a molecular level process

the growth mechanism

A directed spontaneous self-assembly of
a 3-dimensional array of atoms, molecules or ions.



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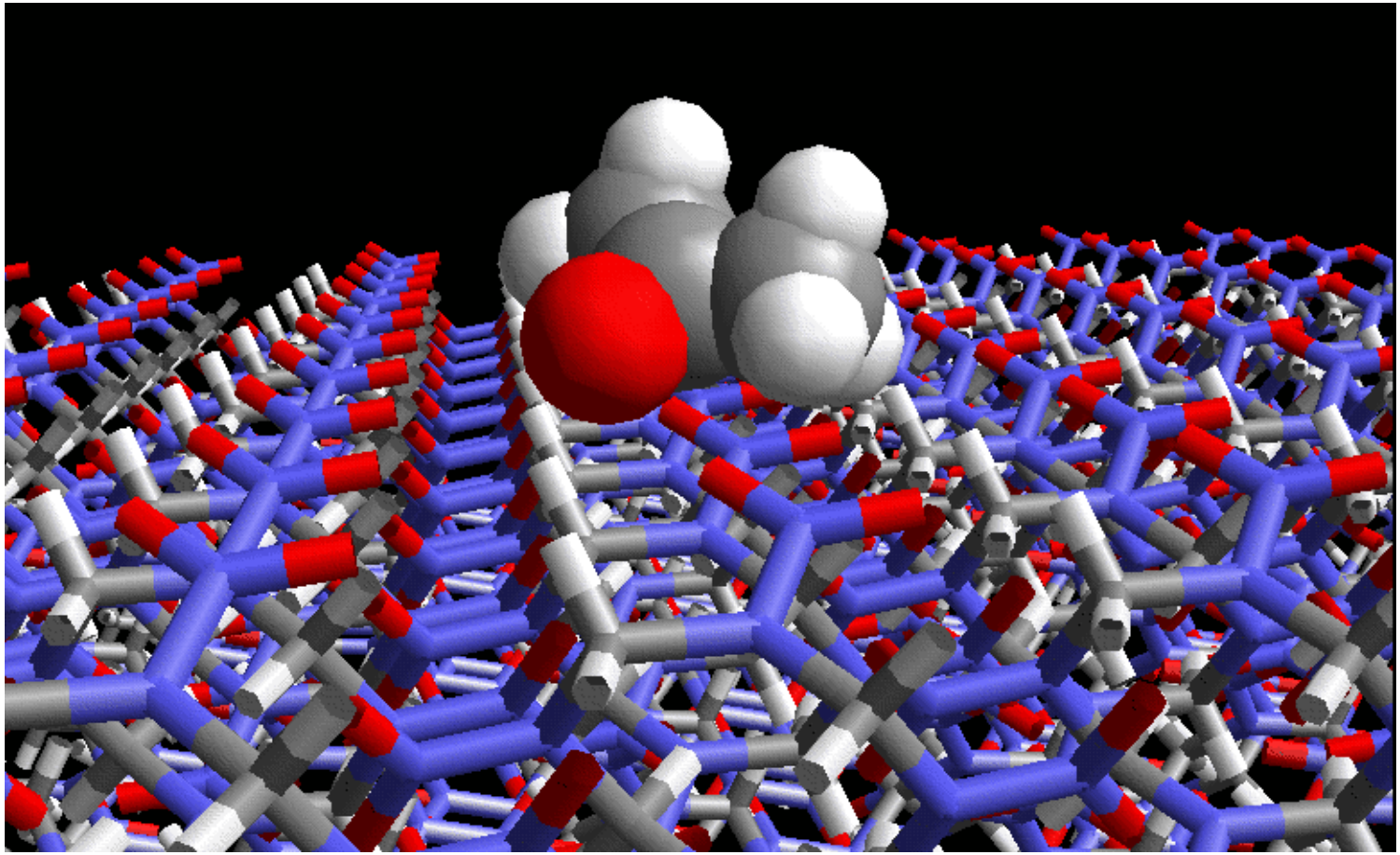


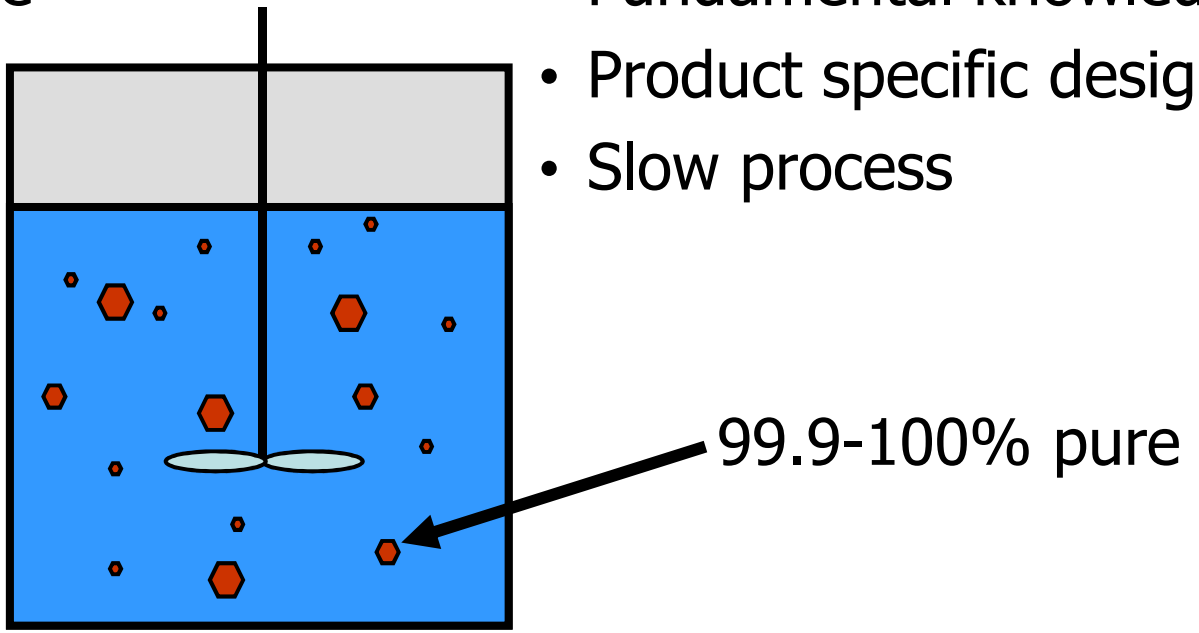
Crystallization is highly selective

One step crystallizations can result in 99.9% pure products

Pro's & Con's of Crystallization

- **Highly selective**
- Energy efficient
- Mild conditions
- No auxiliary phase
- Solid particulate product

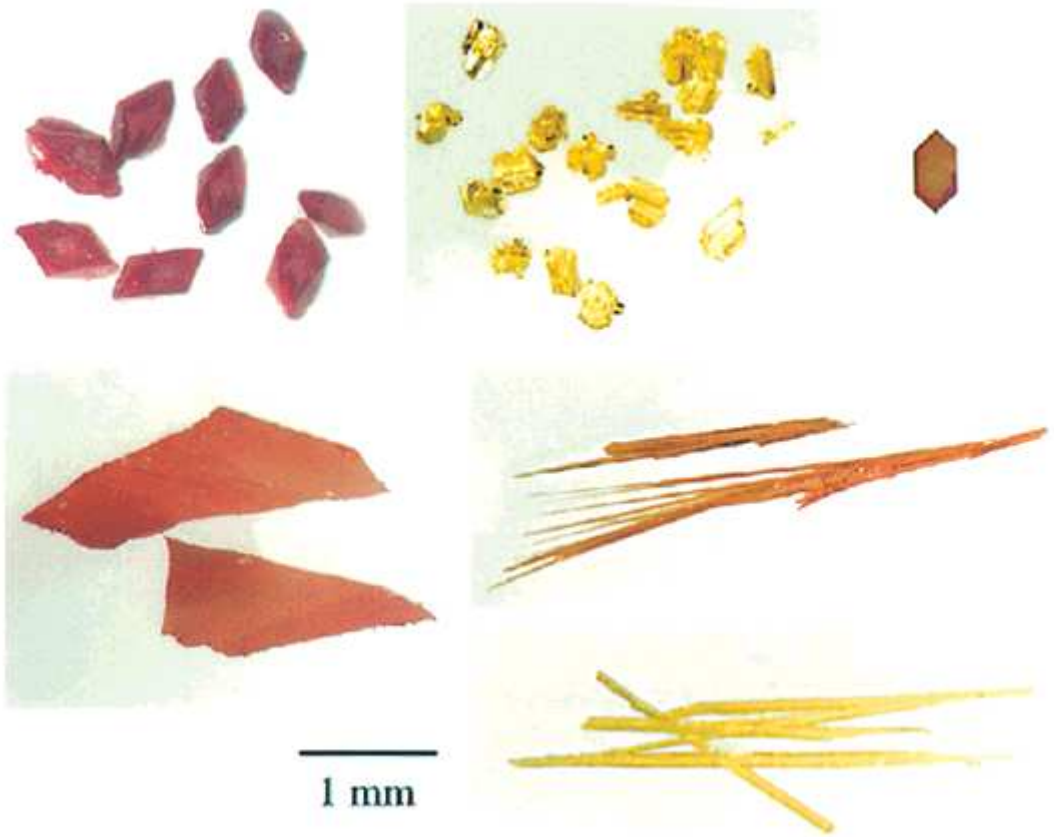
- **Slurry handling**
- Solid/liquid separation
- Complex control
- Fundamental knowledge
- Product specific designs
- Slow process



Crystallization as a molecular affinity separation

- A directed spontaneous self-assembly of a 3-dimensional array of atoms, molecules or ions
- Crystallization is more than a separation technique: integration of separation and product formation
- Product quality aspects
  - Purity, CSD, shape, crystal form
- Crystallization requires sold/liquid separation steps

Main product quality characteristics



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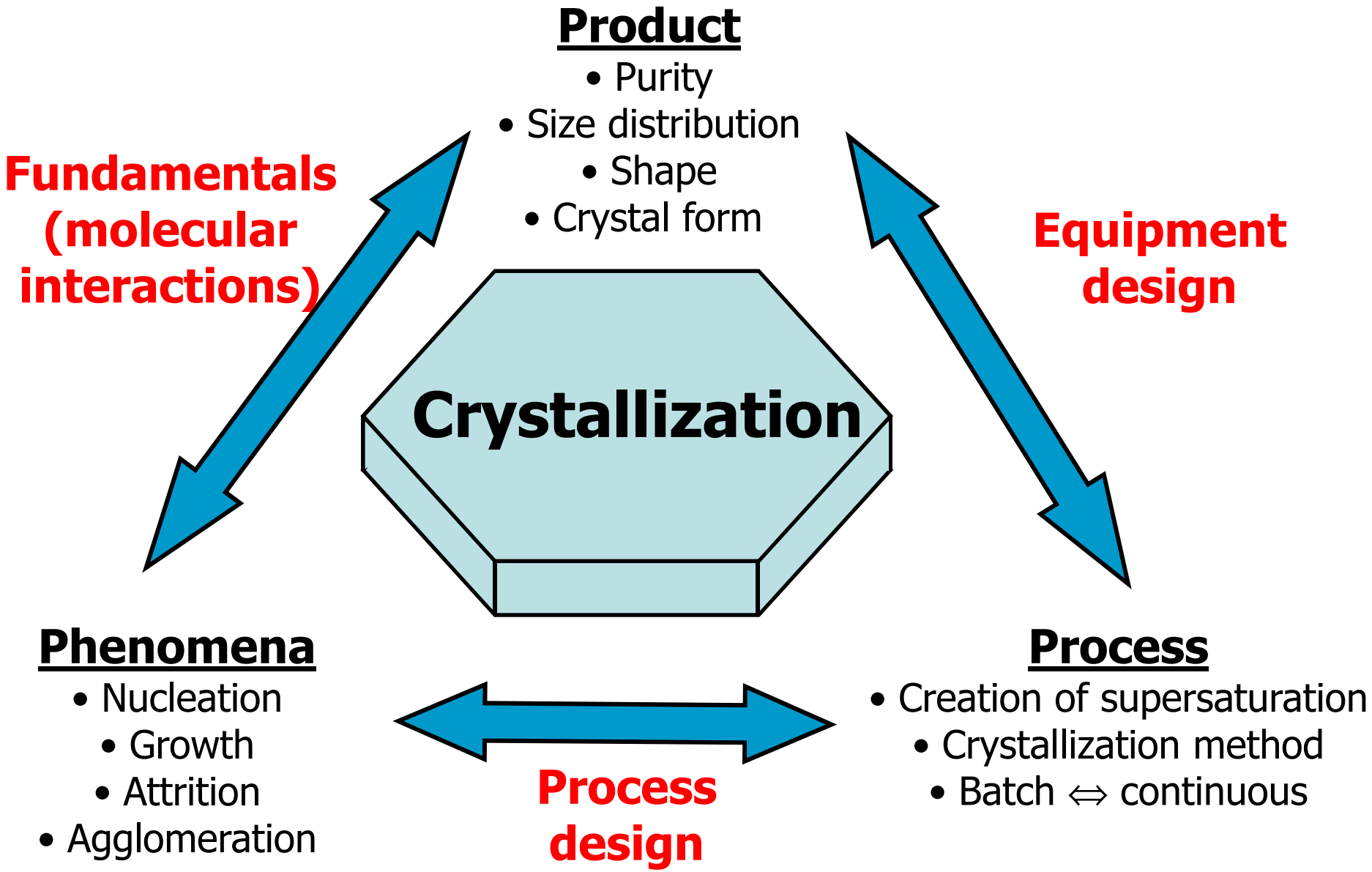
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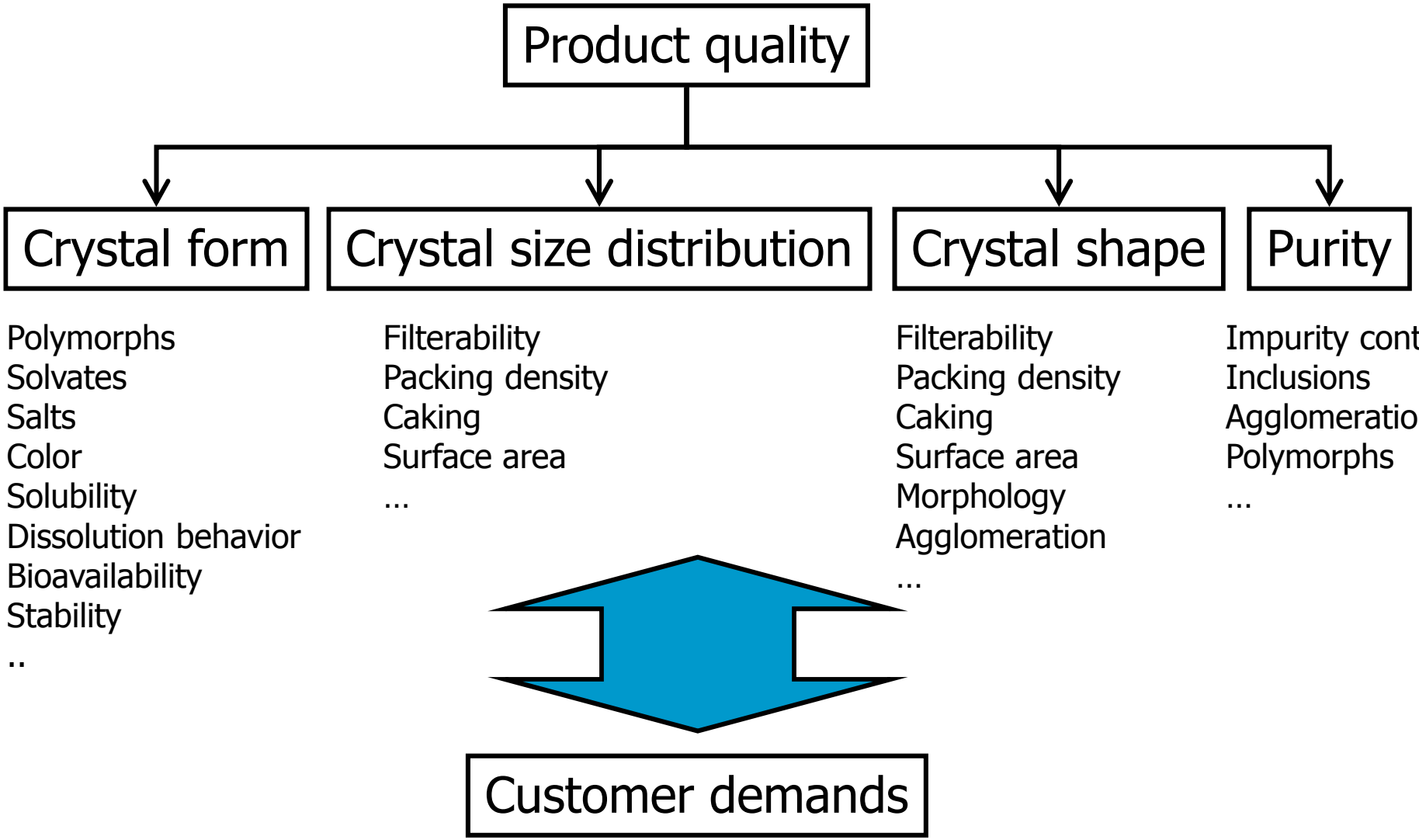
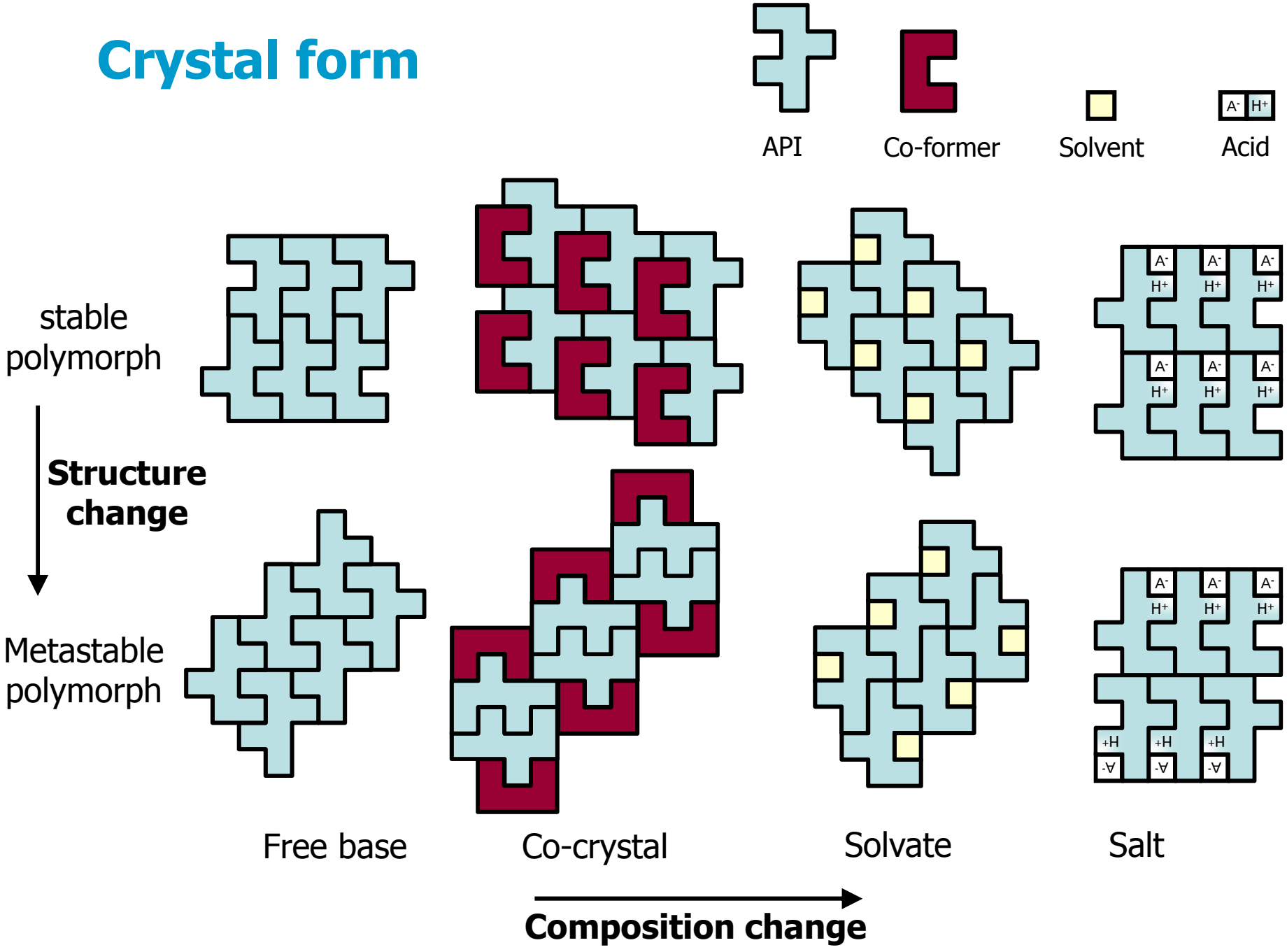
Main product quality characteristics

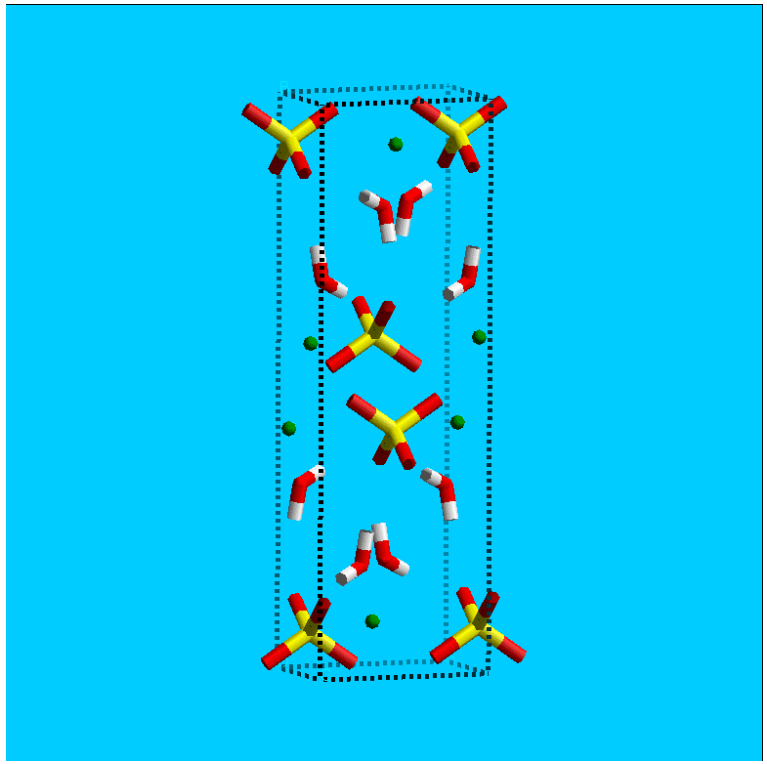


Crystal form

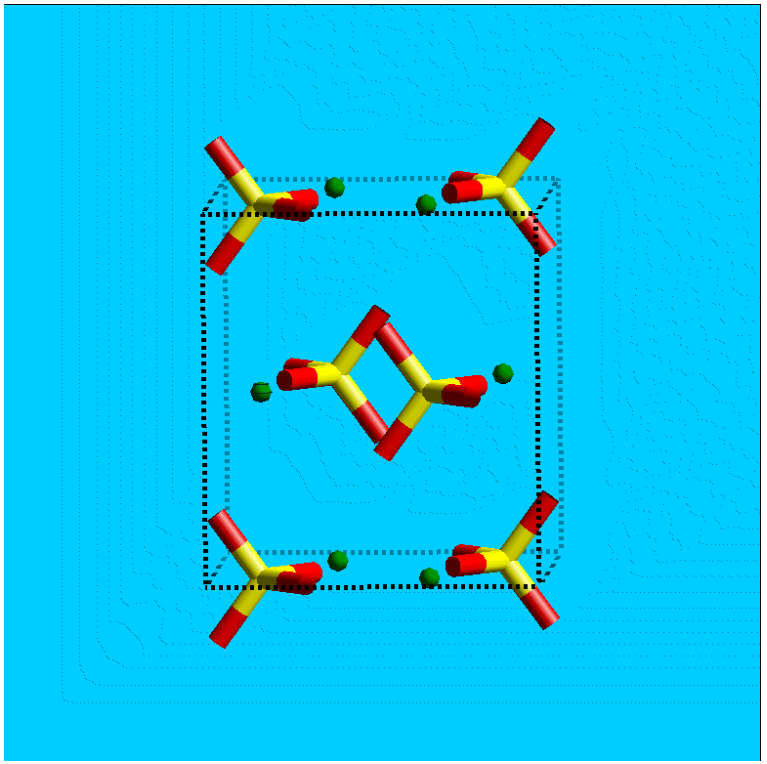
Crystal form



Crystal form: Hydrates and solvates



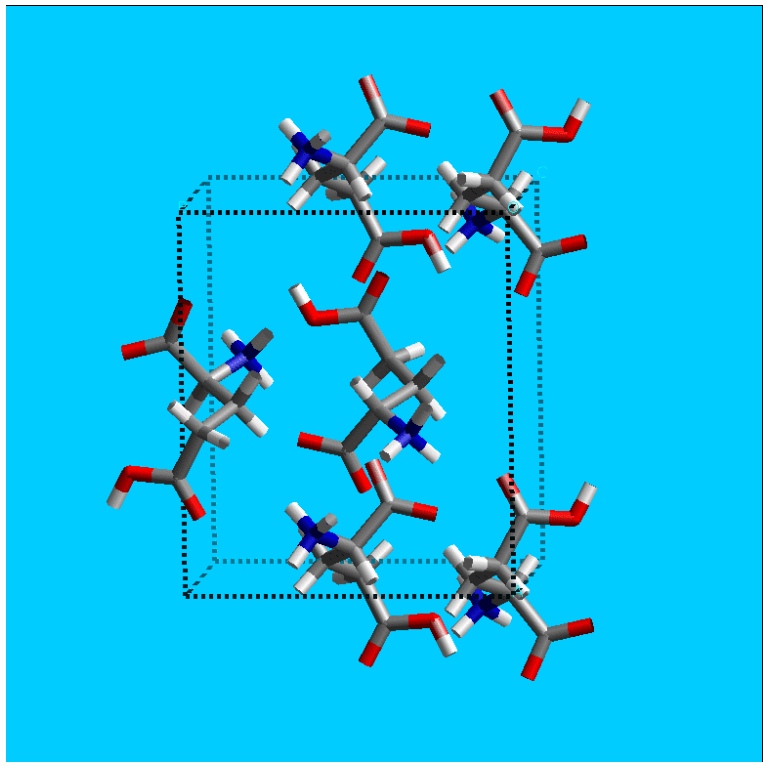
Gypsum ($CaSO_4.2H_2O$)



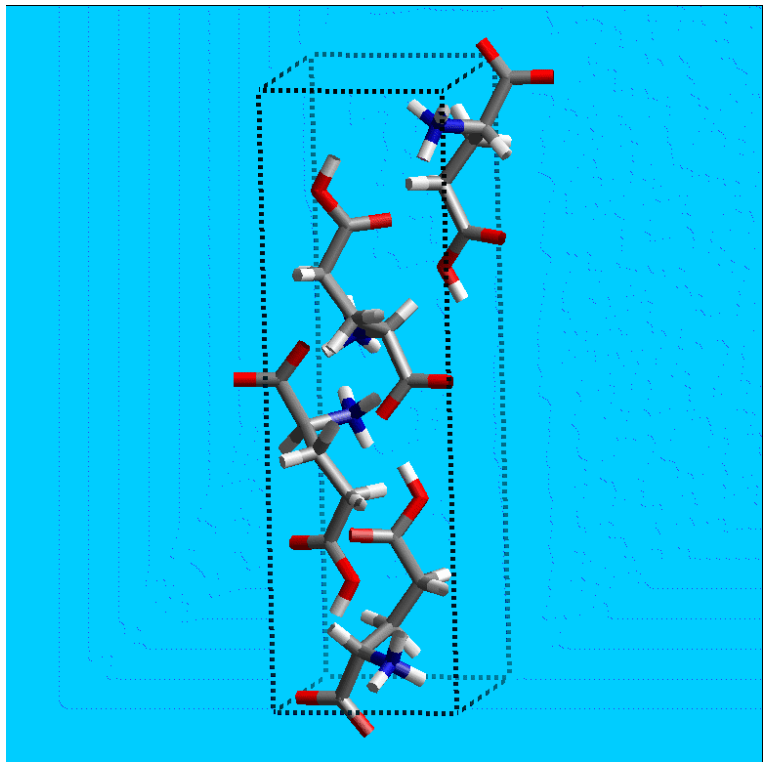
Anhydrite ($CaSO_4$)

Crystal form: Polymorphism

L-Glutamic acid

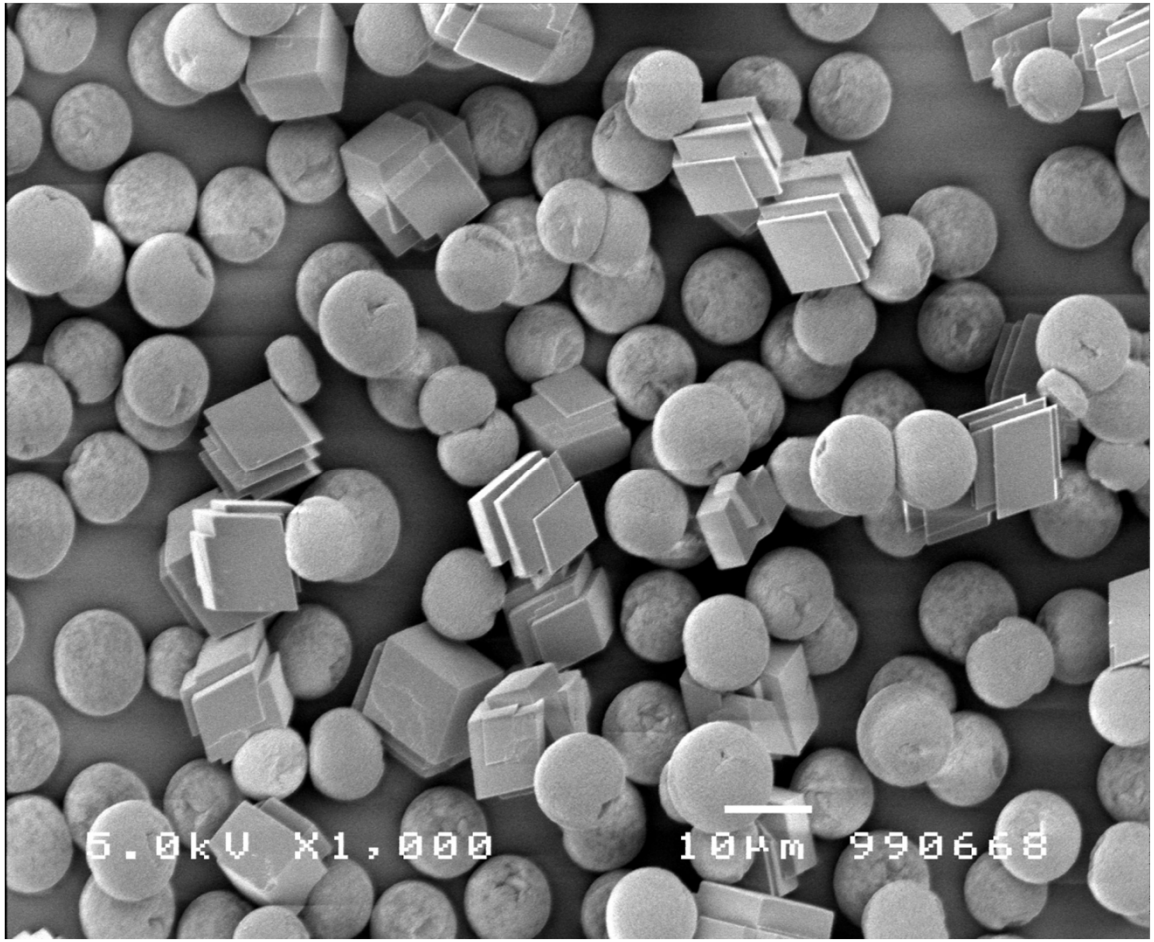


α-form



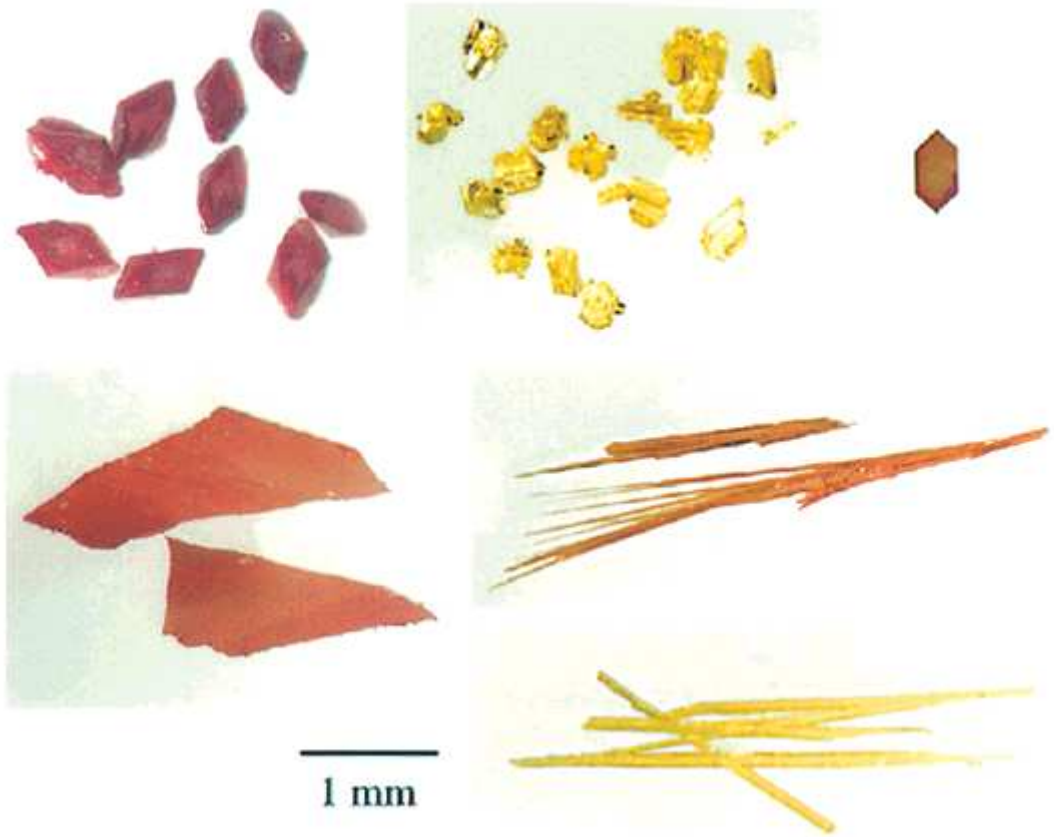
β-form

Crystal form: Polymorphism



$CaCO_3$ - Calcite (lozenges) and vaterite (spheres)

Crystal form: Polymorphism



6 polymorphs!

5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile
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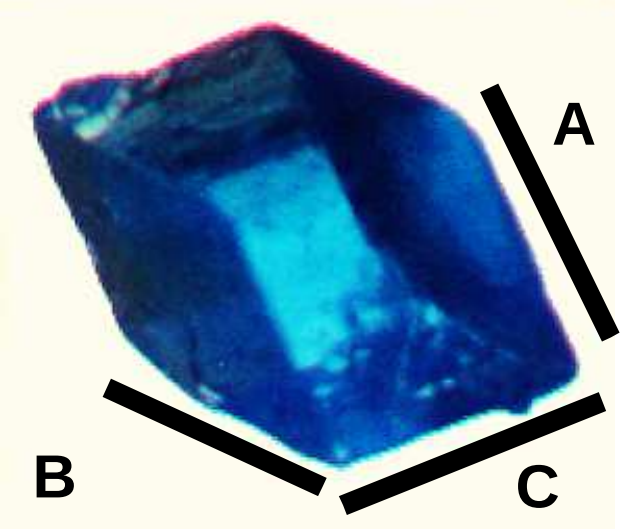
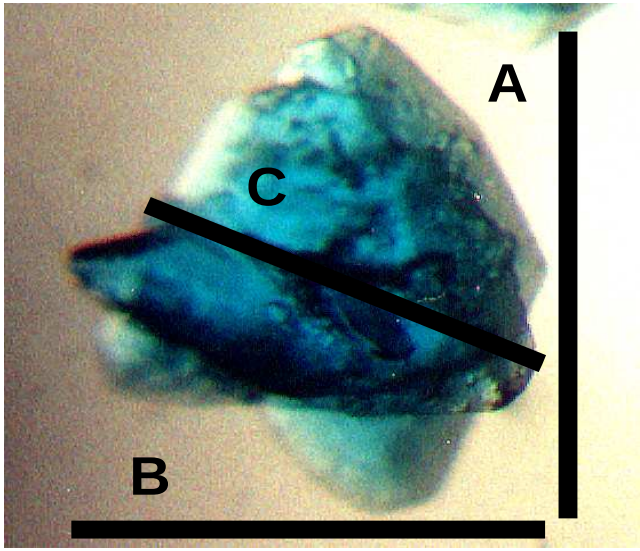
Crystal Size Distribution

Crystal size versus particle size





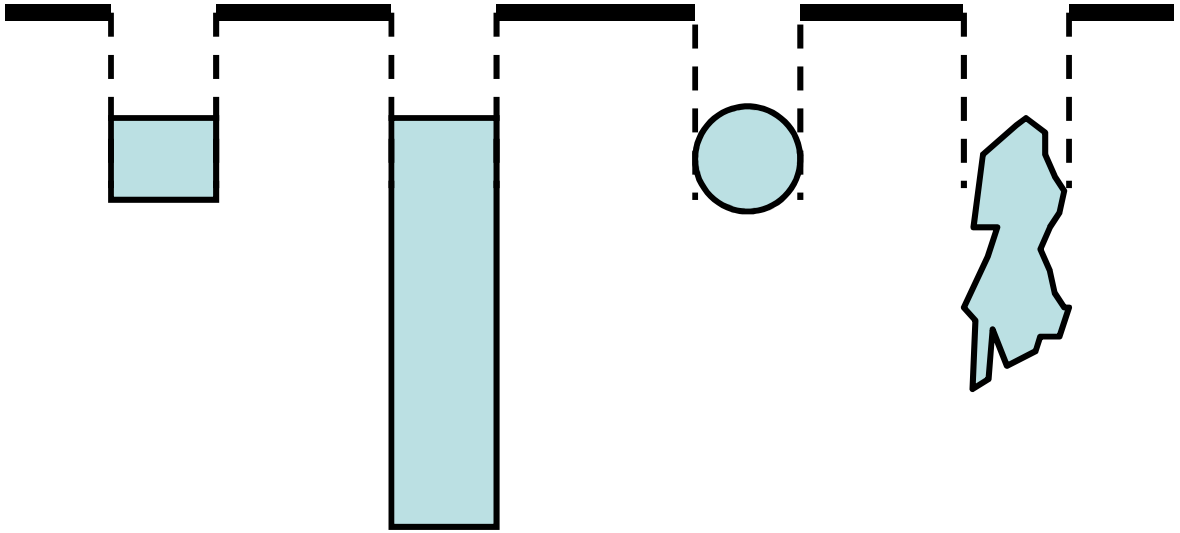
Particle size is a broader term

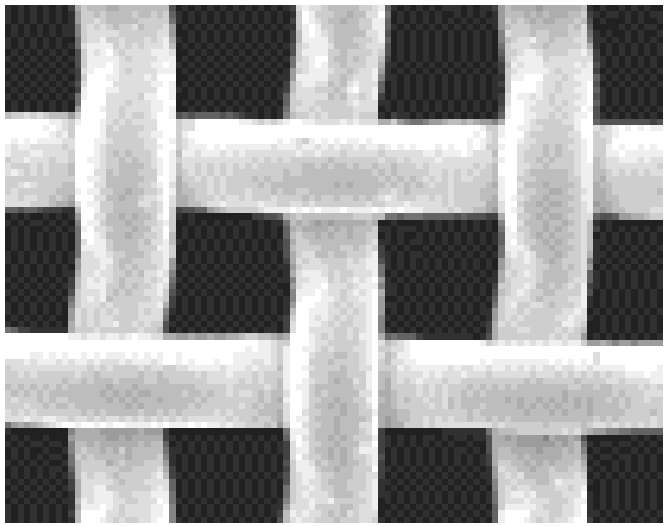
Particle size definitions

name	*definition*
length	maximal length
sieve diameter	width of the minimum square aperture through which the particle will pass
volume diameter	diameter of a sphere having the same volume as the crystal
surface diameter	diameter of a sphere having the same surface area as the crystal
projected area diameter	diameter of a sphere having the same projected area as the crystal viewed from a fixed direction

- Each method for size measurement captures a specific feature of particle size
- Do not compare sizes measured by distinct methods **!**

Particle size: Sieving

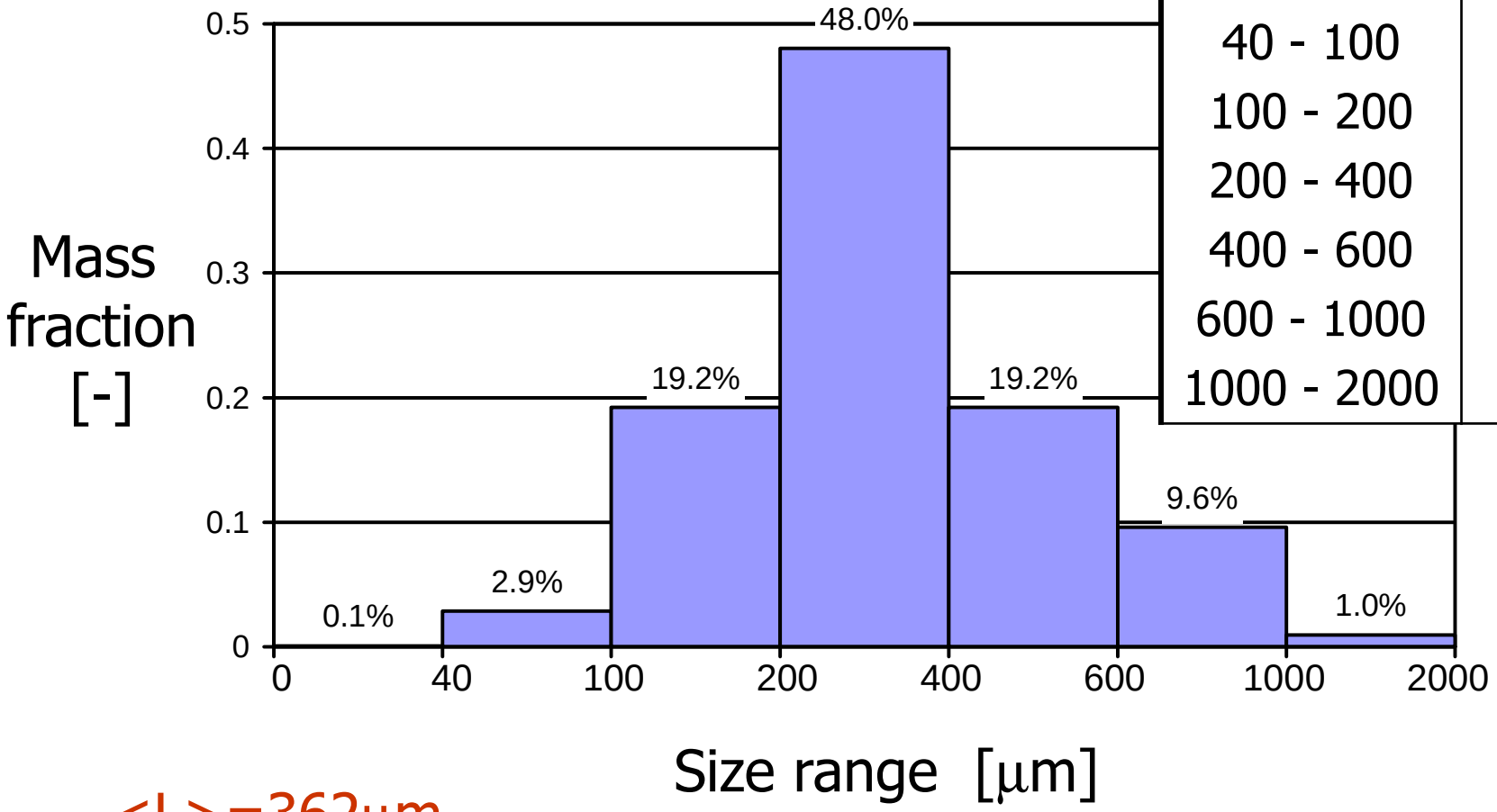




Aperture

Particle size distributions

Mass density distribution

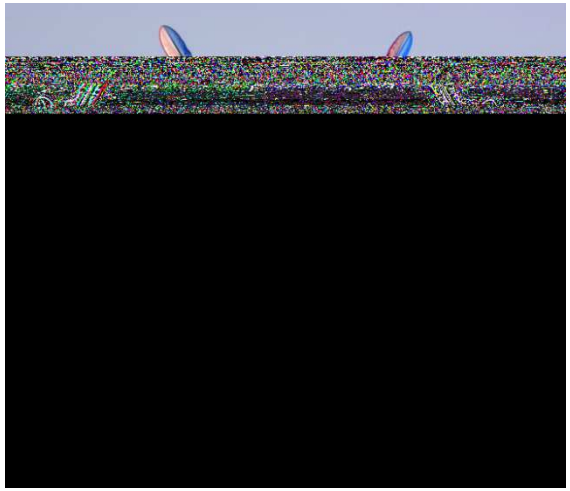


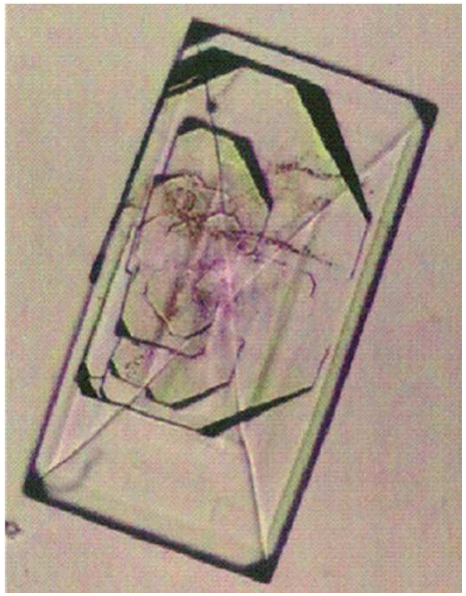
Size range [μm]	Mass [g]
0 - 40	0.1
40 - 100	2.9
100 - 200	19.2
200 - 400	48.0
400 - 600	19.2
600 - 1000	9.6
1000 - 2000	1.0

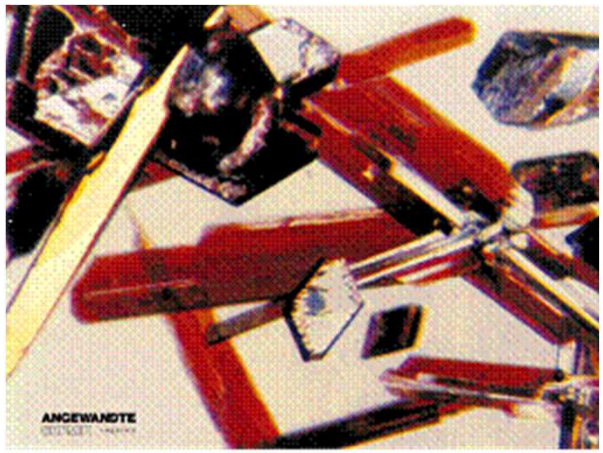
<L>=362μm

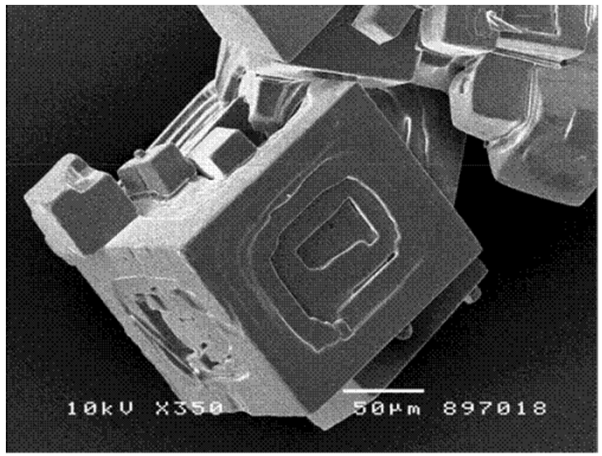
Crystal Shape

Crystal shape

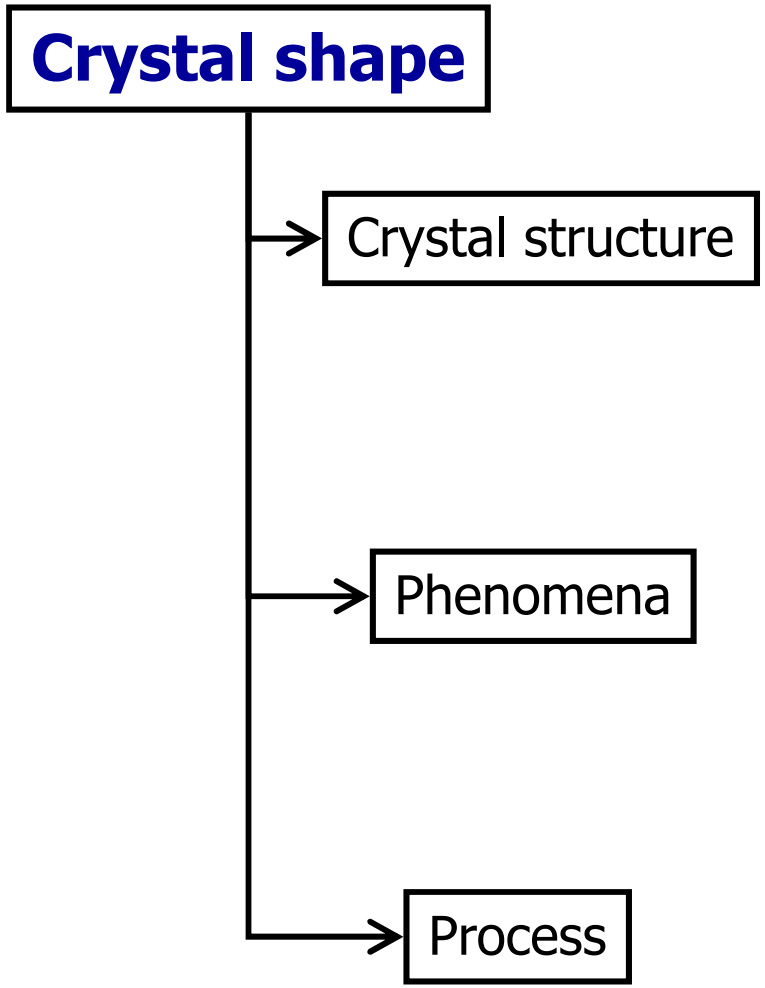








Crystal shape



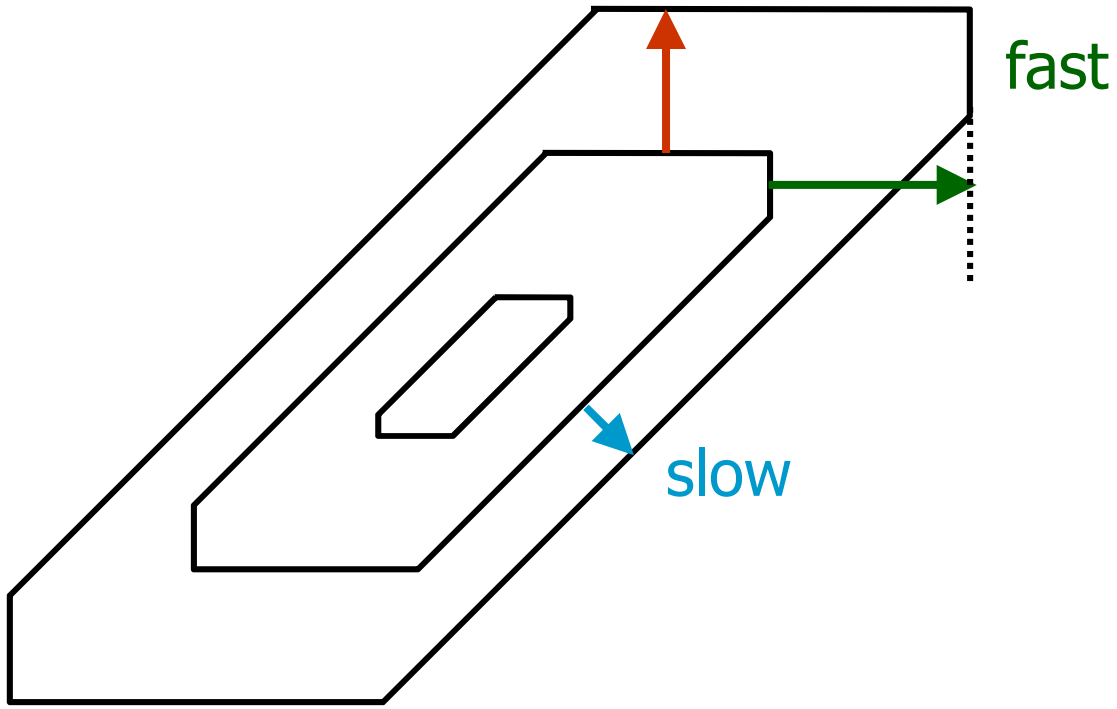
crystal form (equilibrium shape)

nucleation
growth
agglomeration

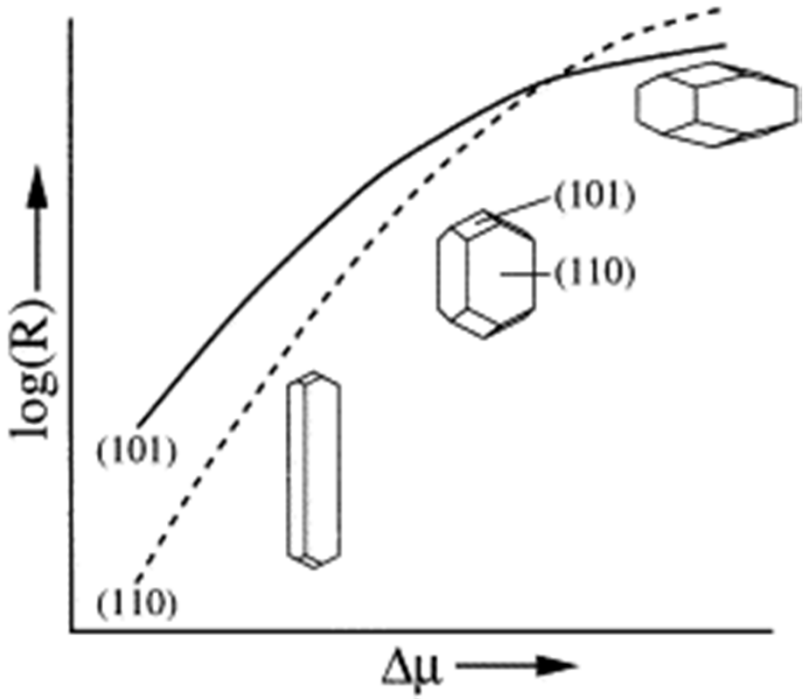
supersaturation
impurities
solvent
temperature

Crystal morphology

- Morphology is determined by the slowest growing faces



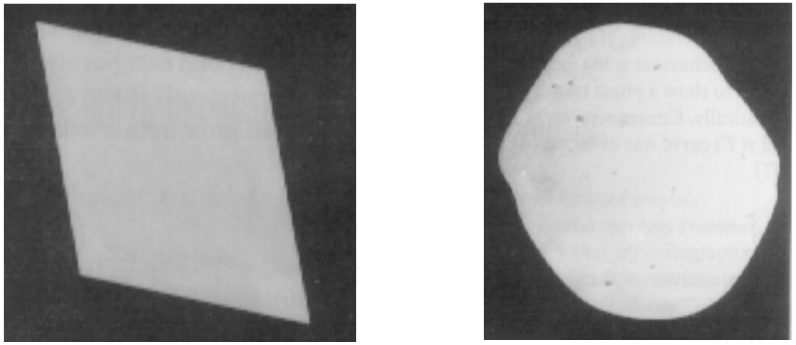
Crystal shape: supersaturation effect



Lysozyme

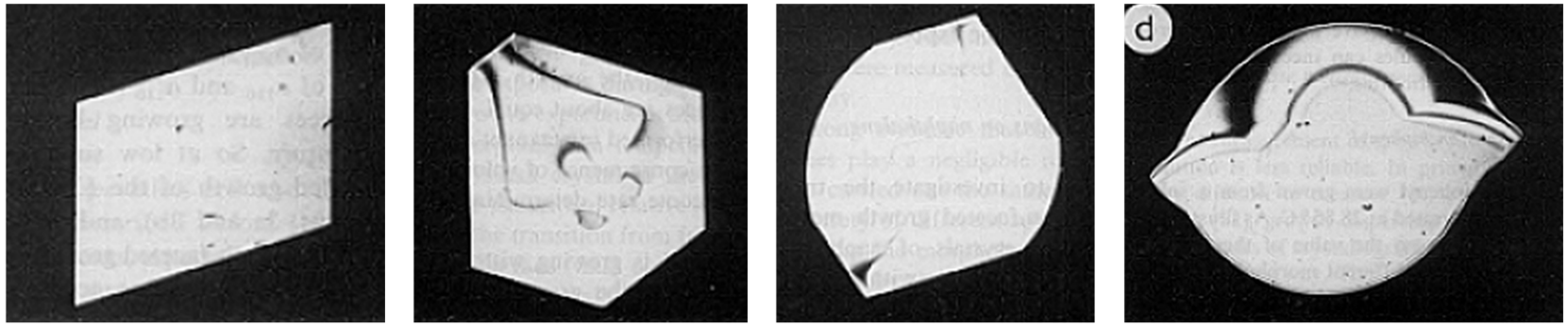
Crystal shape

Thermal roughening



Temperature (S=1)

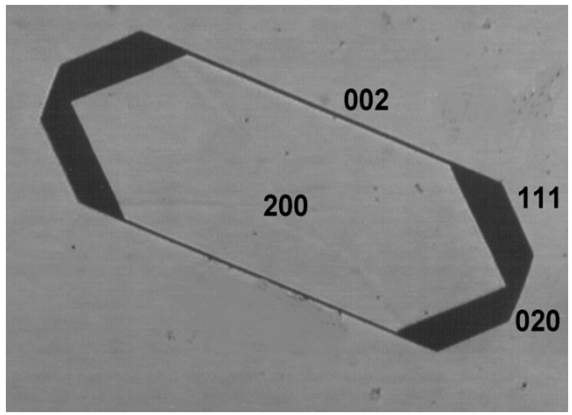
Kinetic roughening

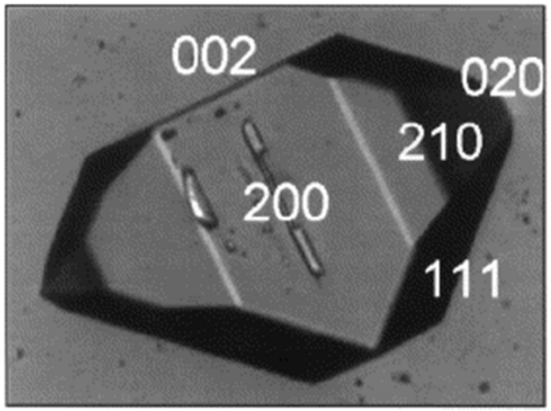


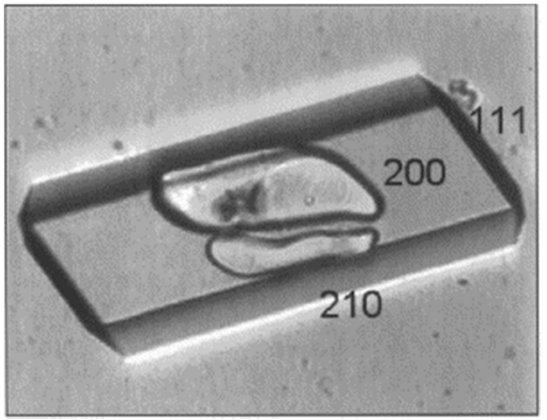
Supersaturation (constant T)

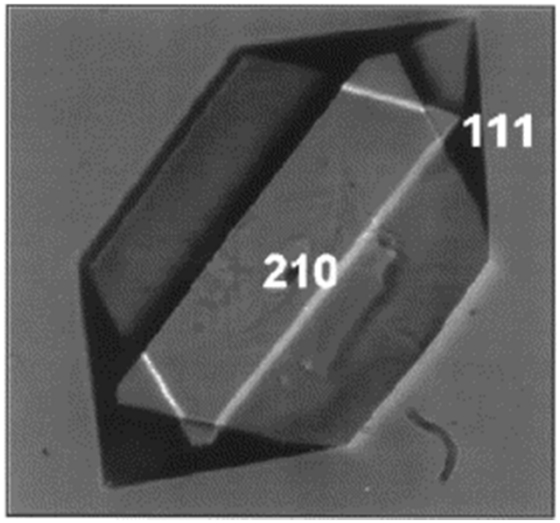
Crystal shape: solvent effect

RDX crystal morphology from different solvents









Solvent can have a distinct effect on the crystal shape

Crystal shape: impurity effect

NaCl crystals

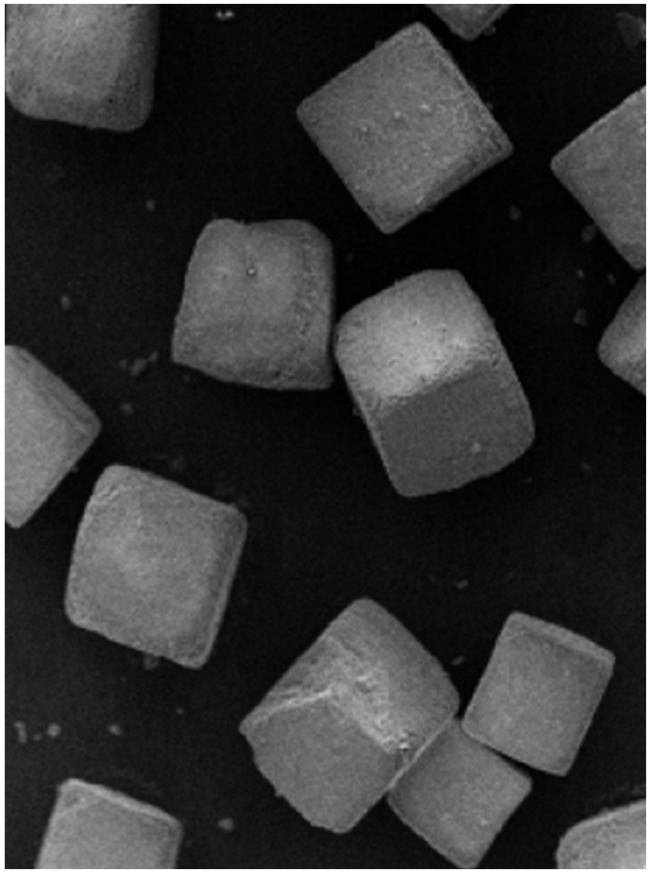
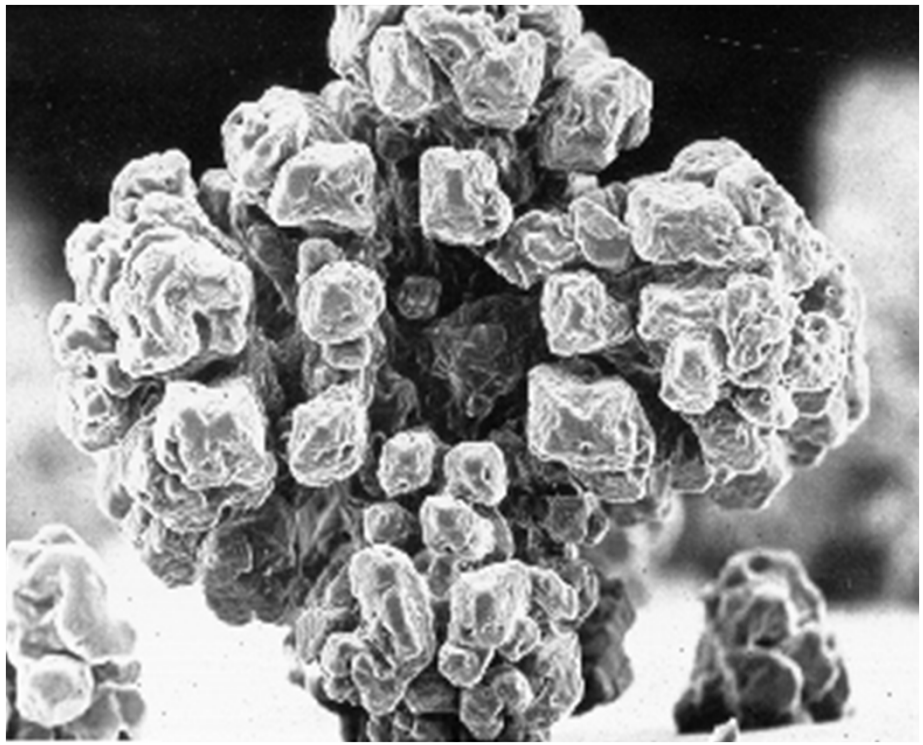
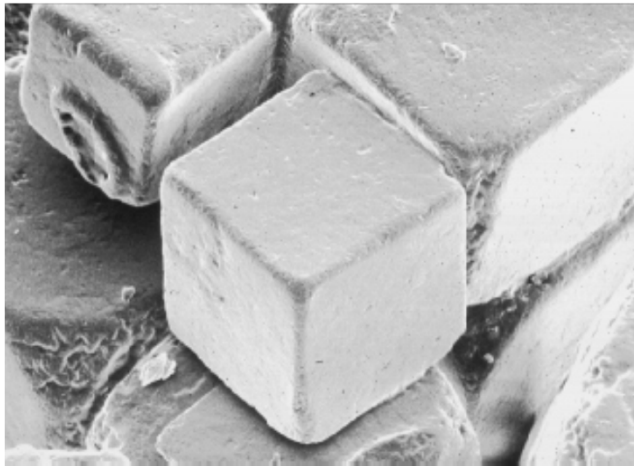


Table salt

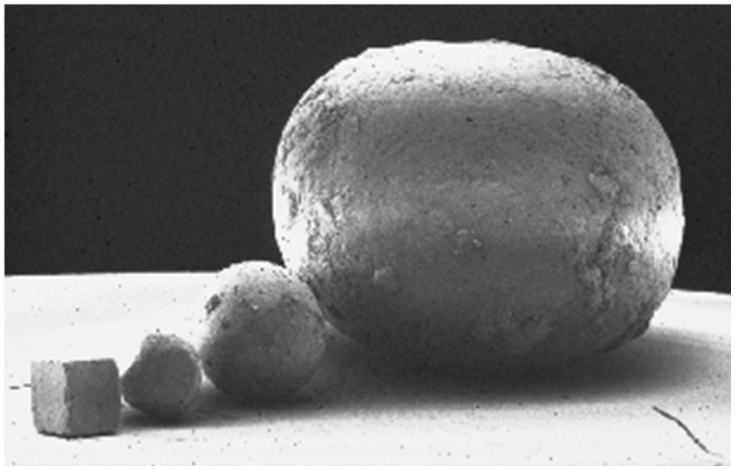


grown in the presence of $Fe(CN)^{4-}_6$

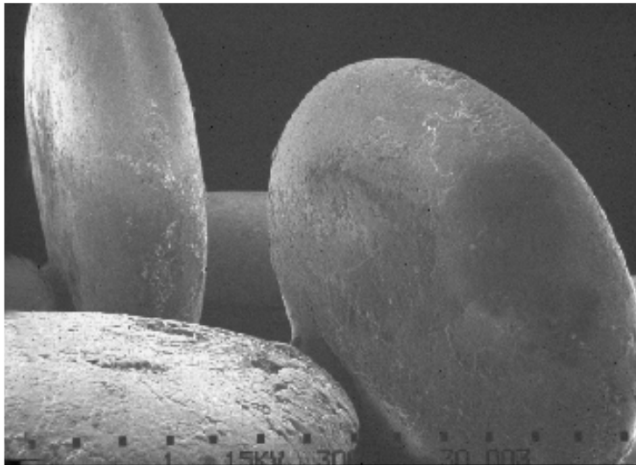
Crystal shape: crystallizer



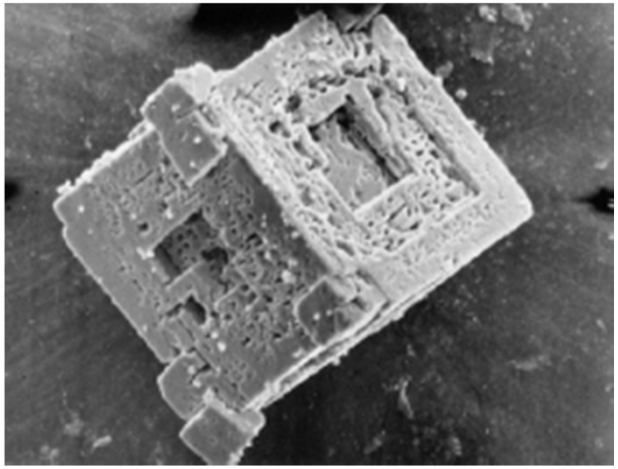
NaCl from a fluid bed crystallizer



NaCl from an Oslo crystallizer



NaCl grown in a rotating flow

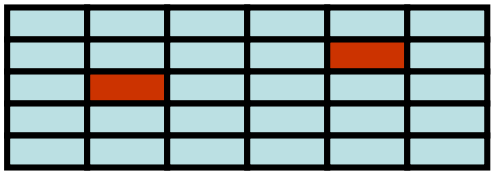


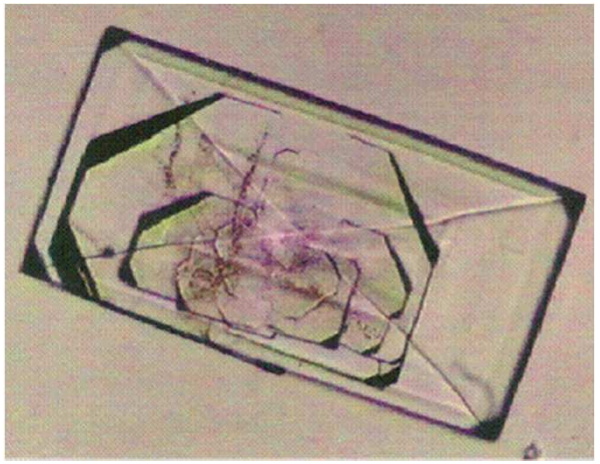
NaCl grown under high supersation

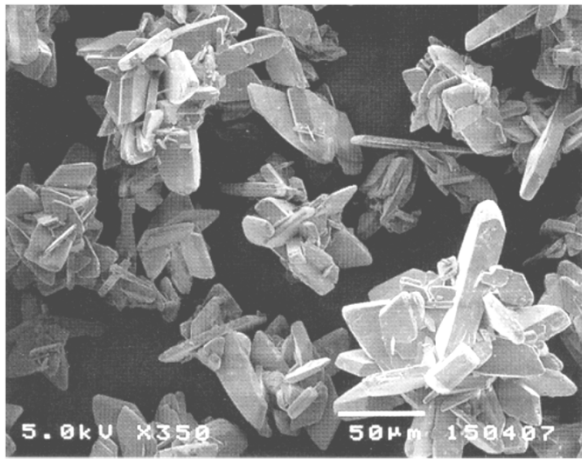
Crystal Purity

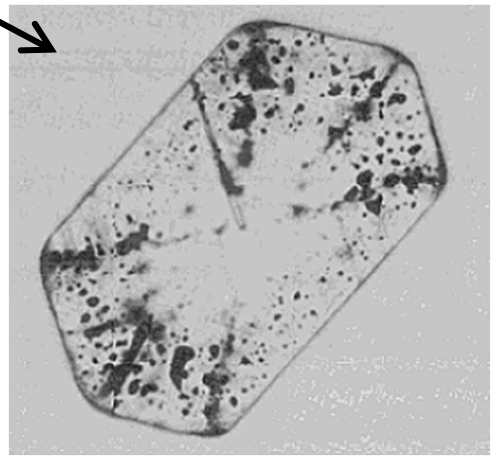
Product purity

- Impurity incorporation in crystal lattice
- Inclusion of mother liquor
  - due to impurity and growth
  - due to attrition / secondary nucleation
- Impure product due to agglomeration
- Adhering mother liquor







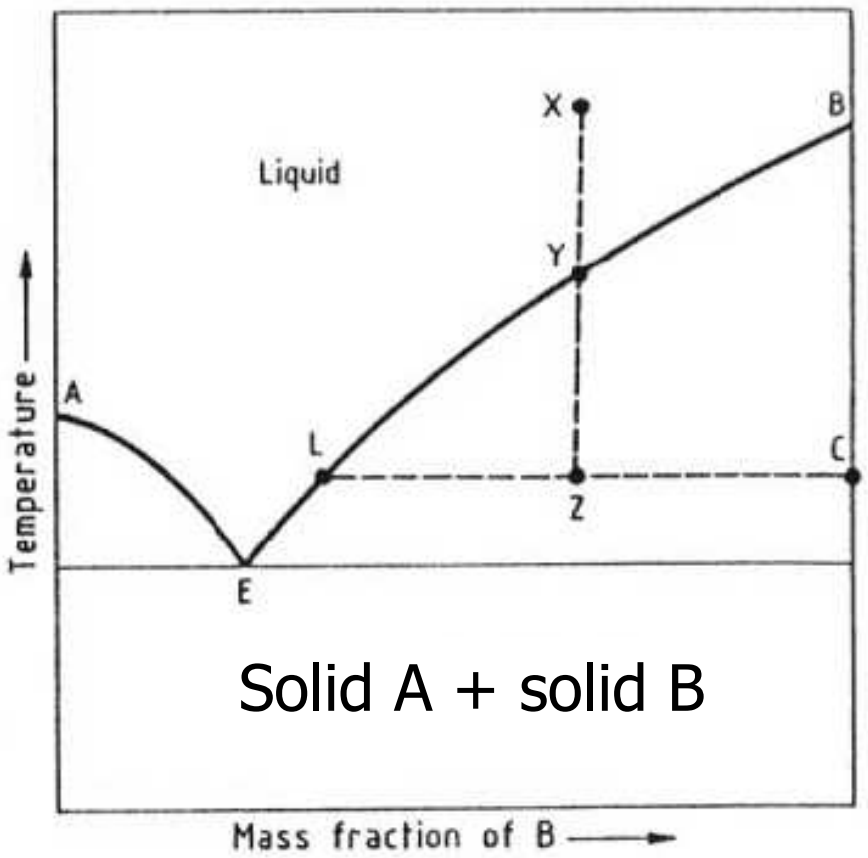


Crystallization phenomena

- **Nucleation** (formation of a new crystalline phase)
  - Primary nucleation
  - Secondary nucleation
- **Crystal growth** (mass deposition on existing crystals)
  - Mass transfer
  - Integration of solute molecules in crystal lattice
- **Agglomeration**
  - Collision
  - Cementation
  - Rupture

Phase Behavior (binary systems)

Eutectic system, constant P



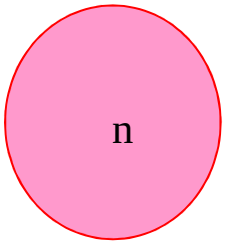
Lever-rule:

$$\text{Suspension density} = \frac{LZ}{LC}$$

crystallization kinetics

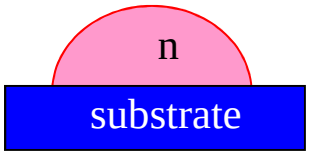
Primary Nucleation

Homogeneous Nucleation (HON)



spherical cluster in solution

Heterogeneous Nucleation (HEN)



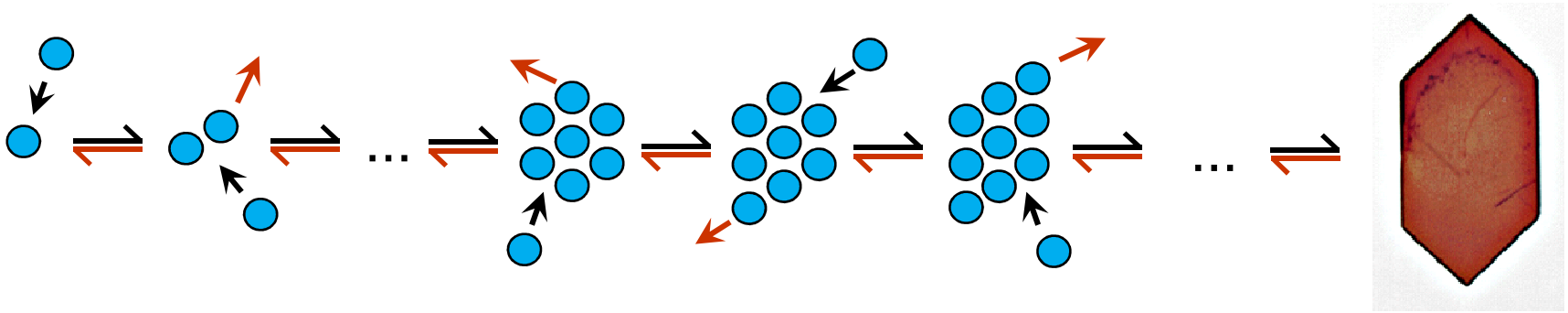
cap-shaped cluster on a substrate

Primary nucleation is the process of random generation of nanoscopically small formations of a new phase that have the ability for irreversible growth to macroscopically large sizes.

Primary nucleation

Nucleation model of Szilard: nucleation is a series of bimolecular "reactions" between molecules (monomers) and clusters.

$$1 \rightleftharpoons 2 \rightleftharpoons 3 \rightleftharpoons \ldots \rightleftharpoons n^*-1 \underset{g_n}{\overset{f_{n-1}}{\rightleftharpoons}} n^* \underset{g_{n+1}}{\overset{f_n}{\rightleftharpoons}} n^*+1 \rightleftharpoons \ldots$$



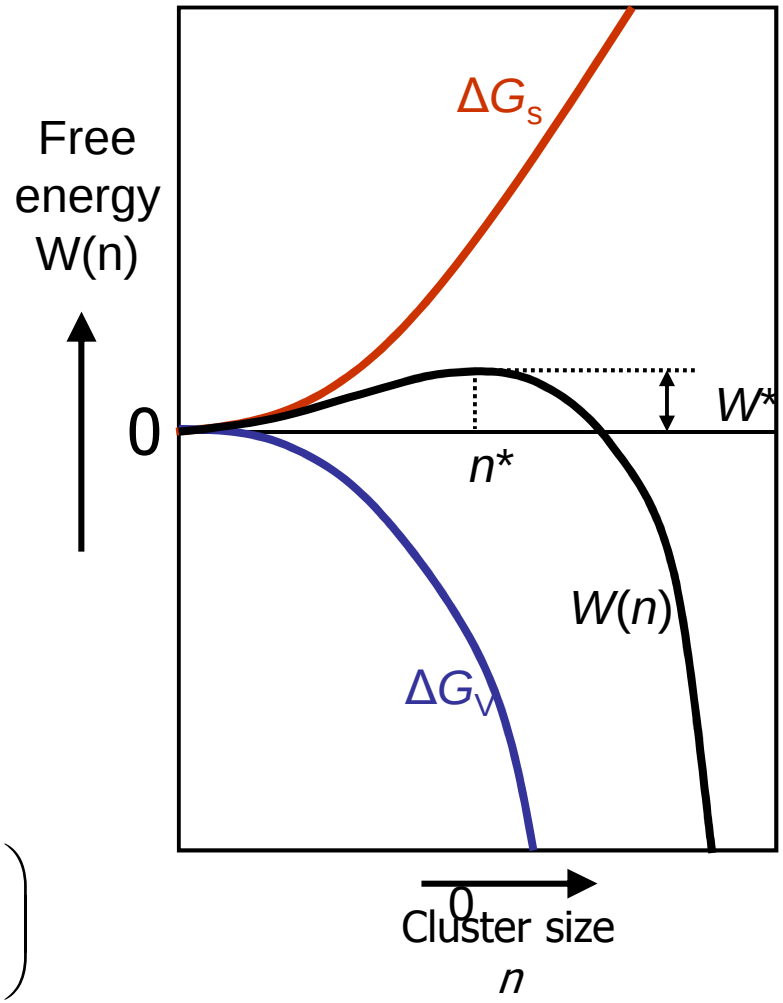
f_n – attachment frequency of monomers to n-sized cluster
g_n – detachment frequency of monomers to n-sized cluster

Nucleation work for HON

For spherical particles:

$$W^* = \frac{16\pi\, v^2}{3k^2T^2}\,\frac{\gamma^3}{\ln^2 S}$$

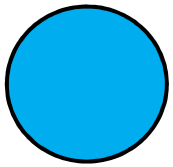
Interfacial energy γ
and
supersaturation ratio S



$$J = A\exp\left(-\frac{W^*}{kT}\right) = A\exp\left(-\frac{16\pi\, v^2\gamma^3}{3k^3T^3\ln^2 S}\right)$$

Homogeneous and heterogeneous nucleation

There are always heterogeneous particles (dust particles, impurities, …) present in solutions



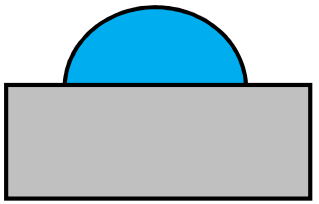
Homogeneous

$A_{HON} = 10^{30}\text{-}10^{35}$

γ

$A_{HON} > A_{HEN}$

$\gamma > \gamma_{ef}$



Heterogeneous

$A_{HEN} = 10^{15}\text{-}10^{25}$

$\gamma_{ef} = \Psi\gamma$

with $0<\Psi<1$

At high S
Homogeneous nucleation dominant

At lower S
Heterogeneous nucleation dominant

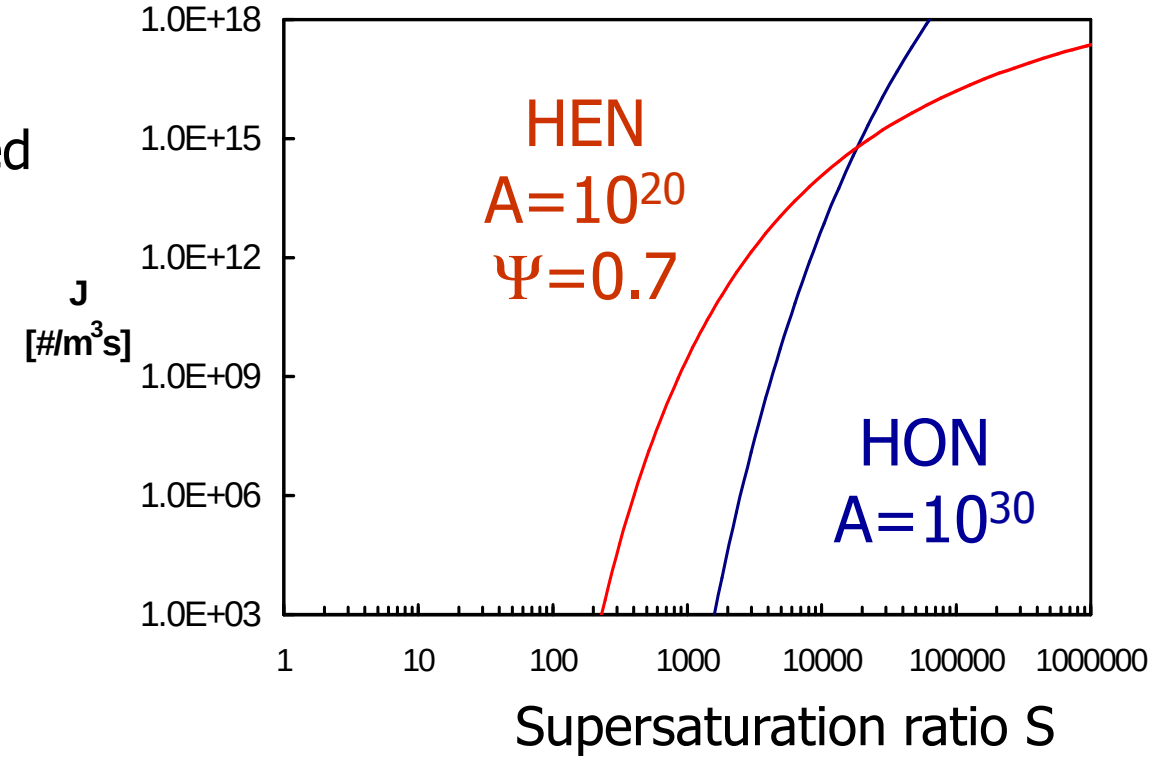
Primary nucleation rate

The number of crystals created per unit of volume and time

J in units [$m^{-3}s^{-1}$]

Arrhenius type reaction

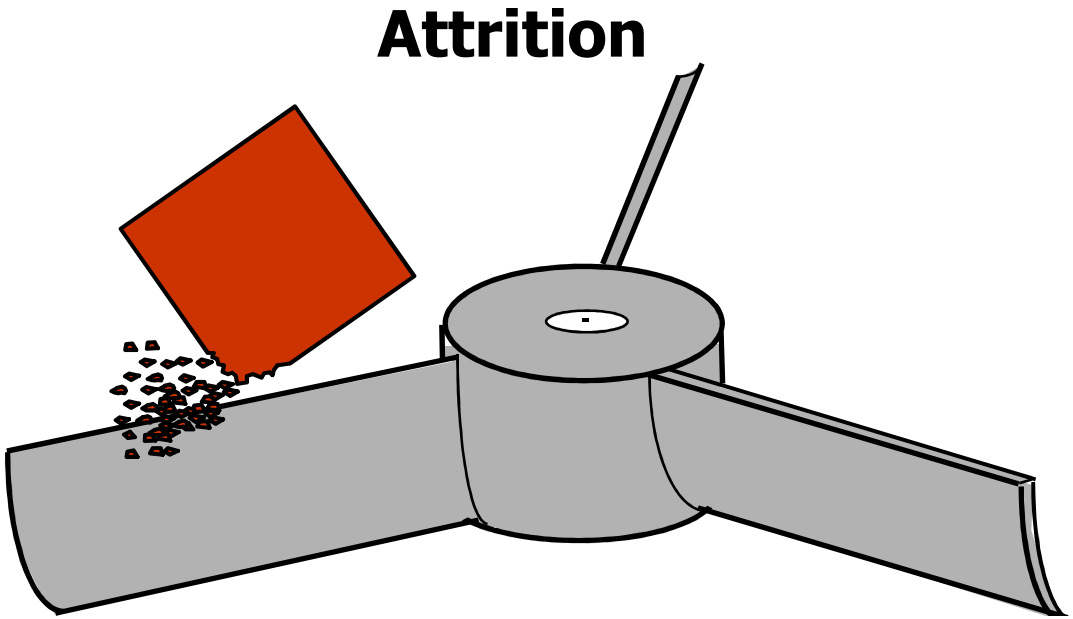
with energy barrier W^*



$$J = A\exp\left(-\frac{W^*}{kT}\right) = A\exp\left(-\frac{16\pi v^2\gamma^3}{3k^3T^3\ln^2 S}\right)$$

Highly non-linear behavior towards S and γ

Secondary nucleation



- Takes place in the presence of larger crystals (parent crystals)
  - Stages:
    - generation of attrition fragments
    - removal of fragments from parent crystal
    - survival and growth of the fragments

Secondary nucleation rate: power law

$$B_0 = k_N G_L^i N^h M_T^j$$

or

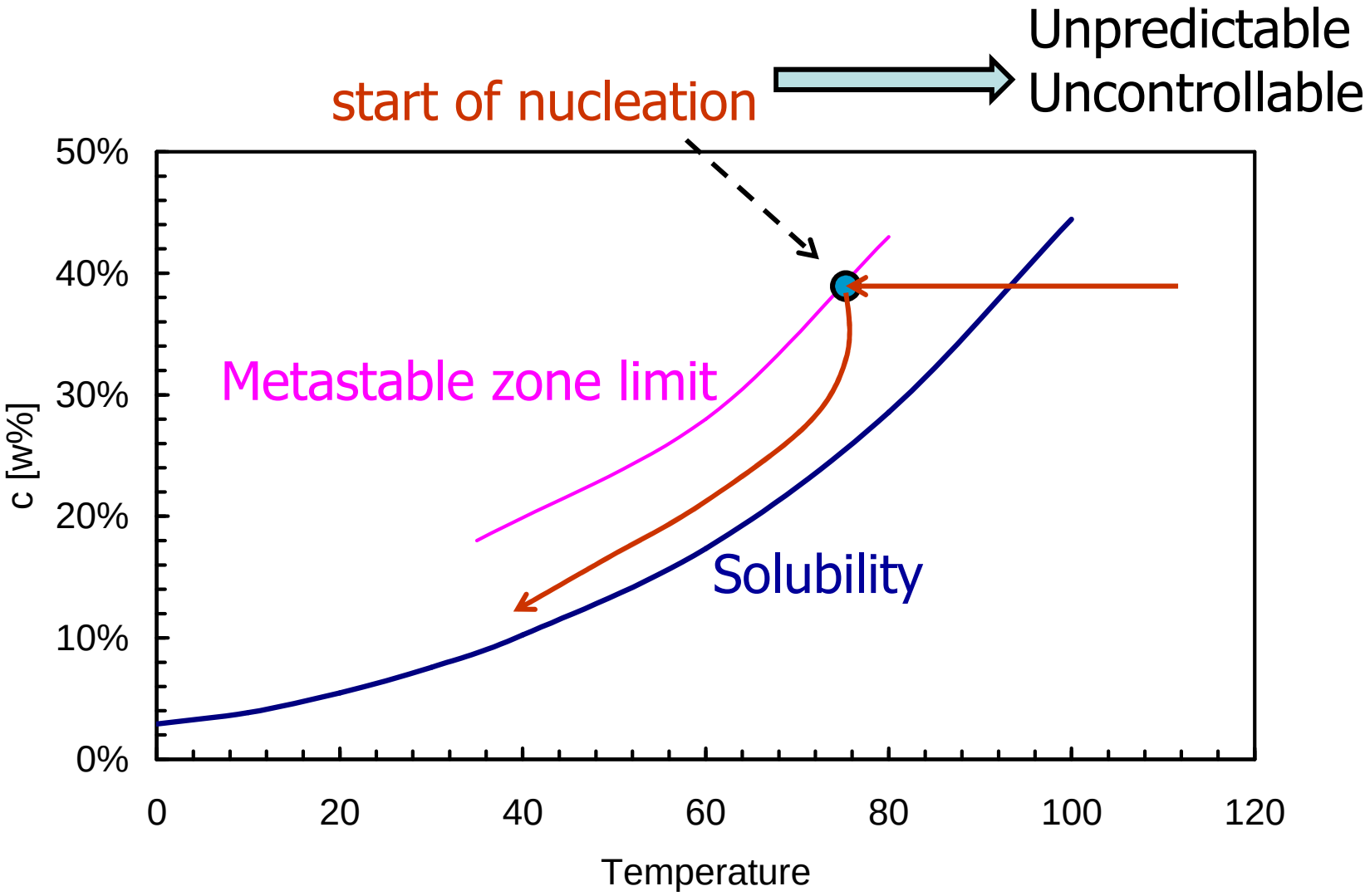
$$B_0 = k_N^1 \sigma^b \overline{P}_{sp}^{\ k} M_T^j$$

B_0	=	Secondary nucleation rate [# m^{-3} s^{-1}]
G_L	=	Crystal growth rate (m/s), $G_L = k_g \sigma^b$
N	=	Impeller rotational speed [rpm]
M_T	=	Total mass of crystals per unit volume
σ	=	relative supersaturation σ (-)
P_{sp}	=	specific power input $P_{sp} \sim N^3$

k_N and k_N^1 are constants related to crystallizer geometry (impeller type, number of blades, scale of operation)

$1 < b < 3$; $0.6 < k < 0.7$; $j = 1$ or 2

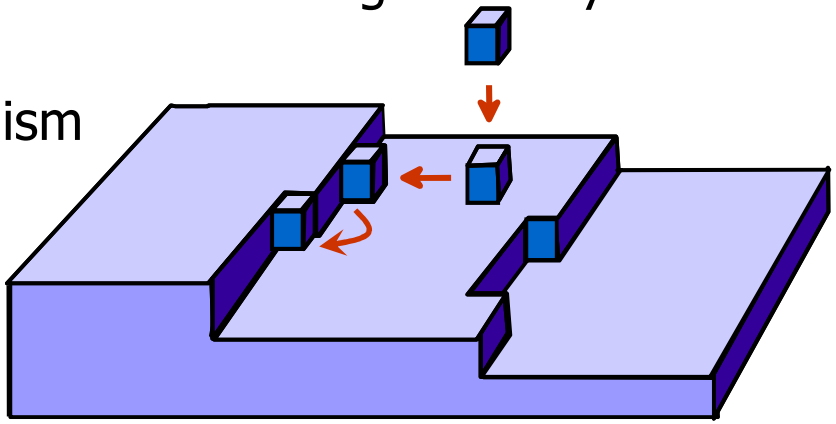
Nucleation & growth in a batch process



Crystal growth: Smooth or rough surface

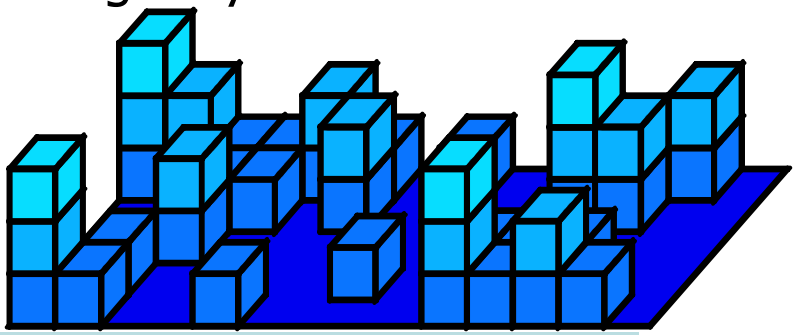
Smooth or layer growth

- growth units attach to kinks sites in the steps
- steps propagate along the crystal surface and form growth layers
- two step sources generate steps:
  - Birth and Spread growth mechanism
  - Spiral growth mechanism



Rough growth

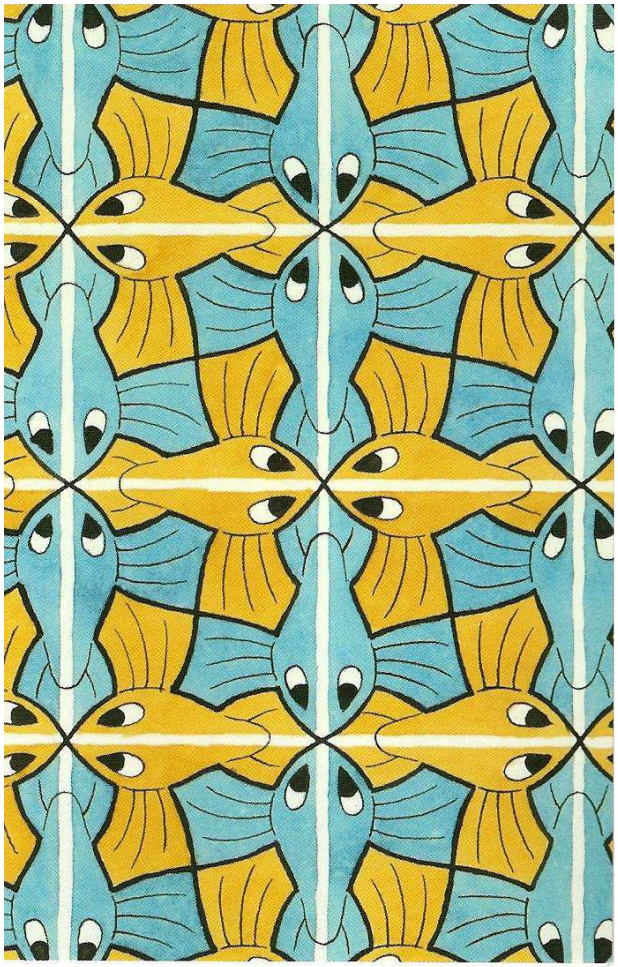
- growth units attach anywhere to the rough crystal surface
  - Rough growth mechanism



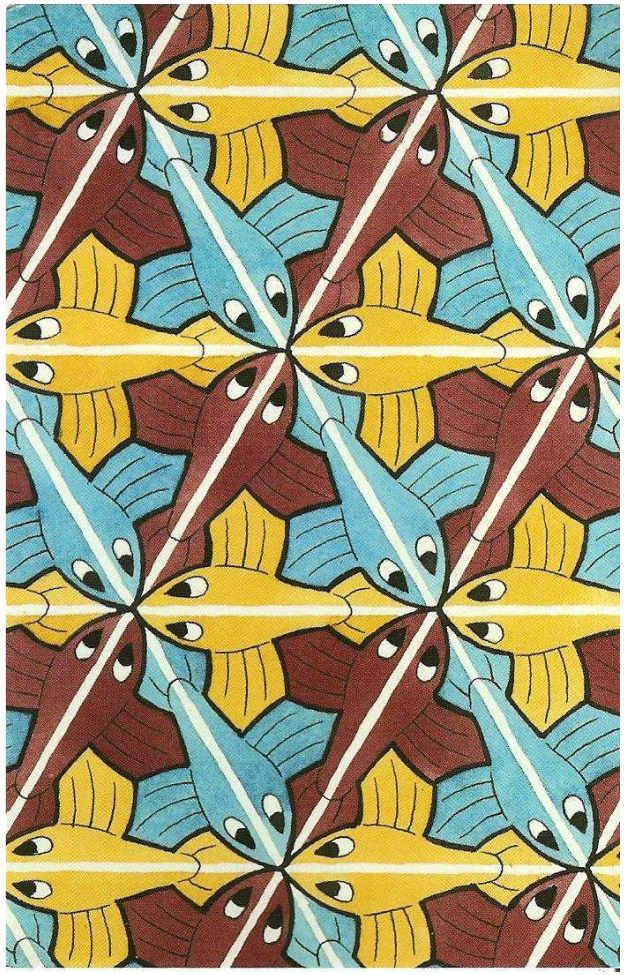
The growth units are incorporated in an existing crystal lattice

Polymorphism

Dutch painter **Escher**

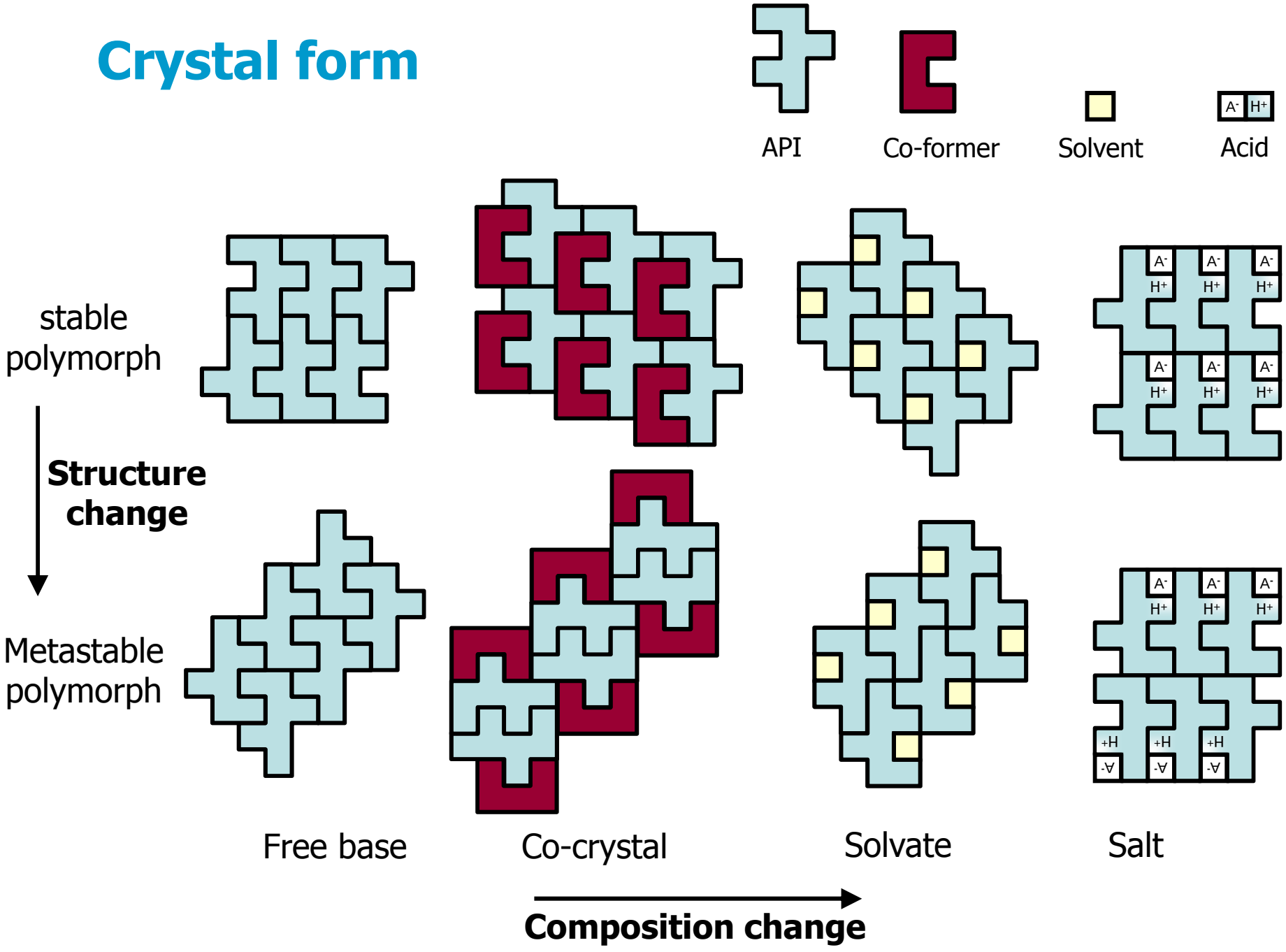


Fish form I



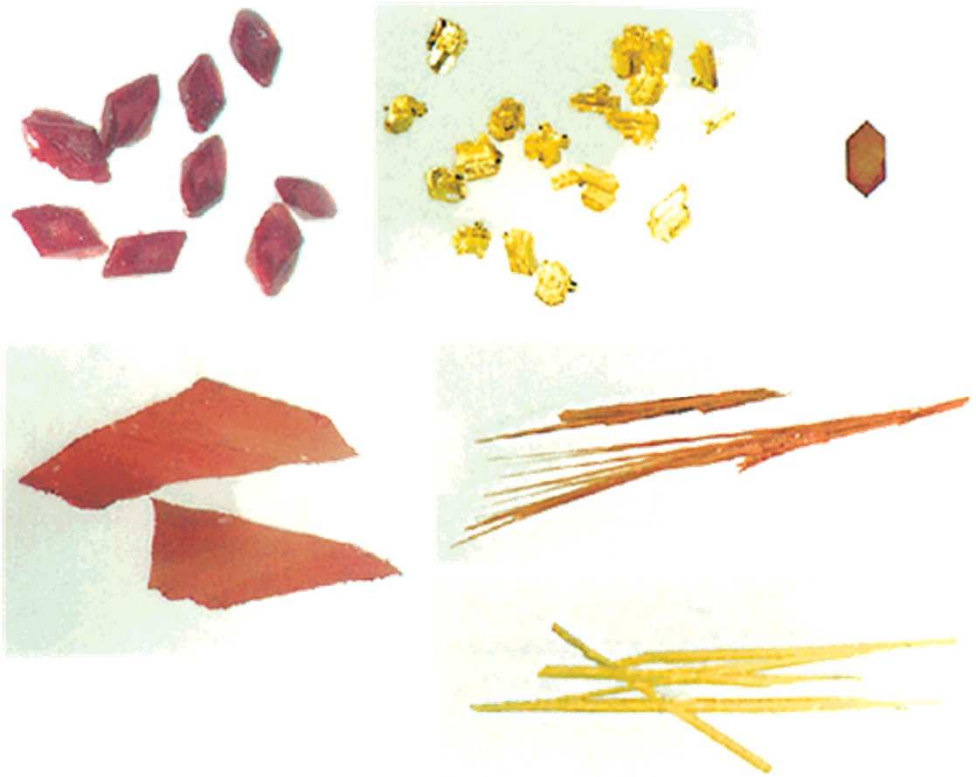
Fish form II

Crystal form



Polymorphism: product quality

The ability of a chemical compound to crystallize into different crystalline compounds



Polymorphism

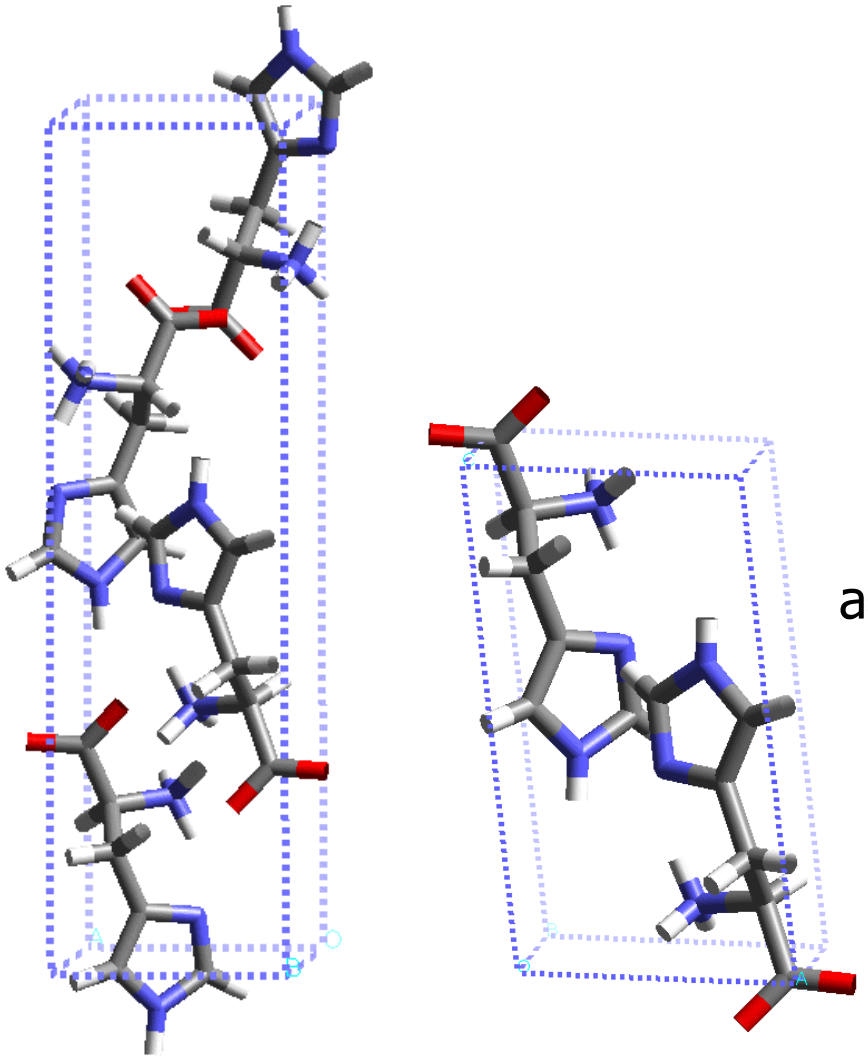
- The number of forms known for a given compound is proportional to the time and money spent in research on that compound (McCrone, 1965)
  - Currently not true anymore – although now and then a new polymorph pops up
  - Succesfull research strategies have been developed to search for polymorphs

Record: 17 polymorphs

J.A. Pesti, R.A. Chorvat, G.F. Huhn, Chem. Innovations 2002, Oct. 28

Polymorphism: L-histidine

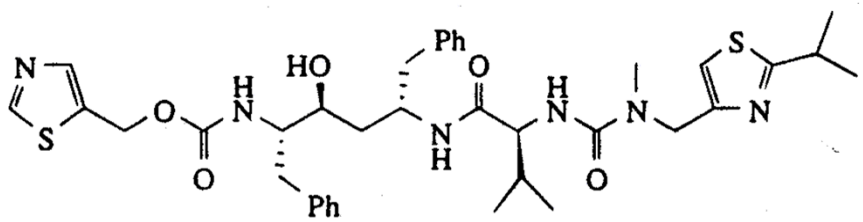
α-form
Orthorhombic
(P21 21 21)
a≠b≠c, α=β=γ=90°



β-form
monoclinic
(P21)
a≠b≠c, α=β=90°≠γ

Polymorphism: Ritonavir

- The HIV-1 and HIV-2 protease inhibitor Ritonavir



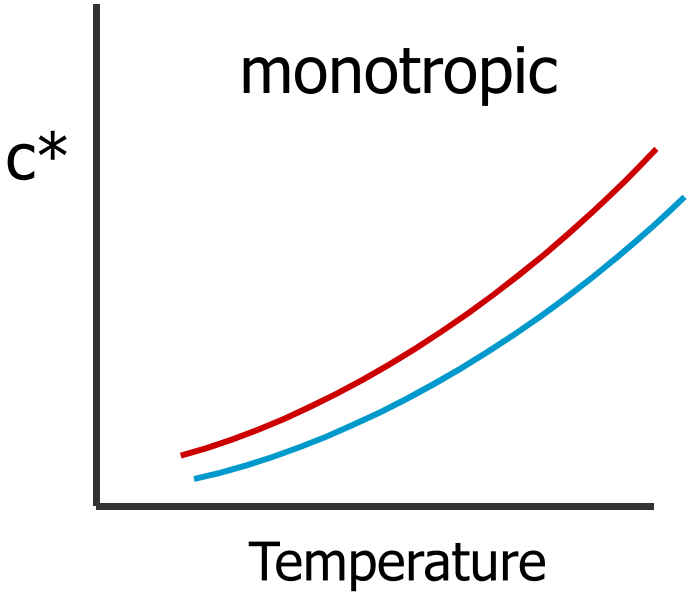
- In 1996 Ritonavir was introduced on the market

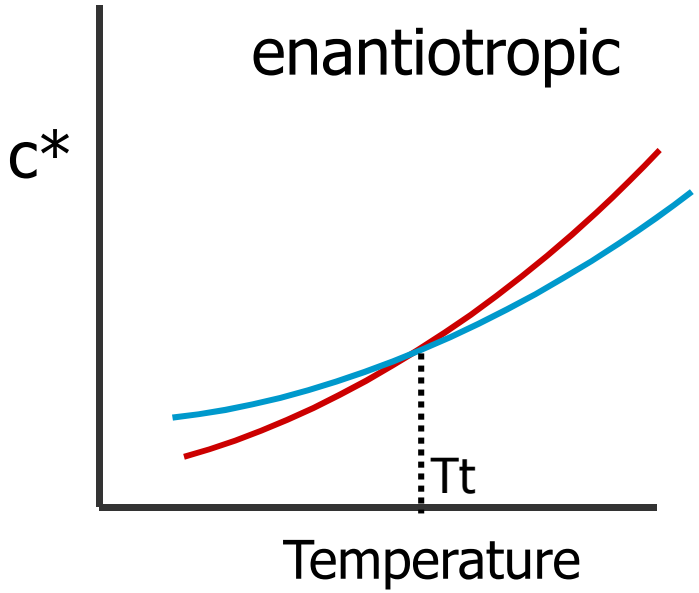
- In 1998 a **new, more stable form** appeared
- The new polymorph had a 4 times **lower solubility**
- This affected the **bioavailability** of the pharmaceutical
- The company Abbott withdrew Ritonavir from the market

- 1 year of research effort enabled the production of the old less stable polymorph again.

- **Costs**: 100 of millions of dollars

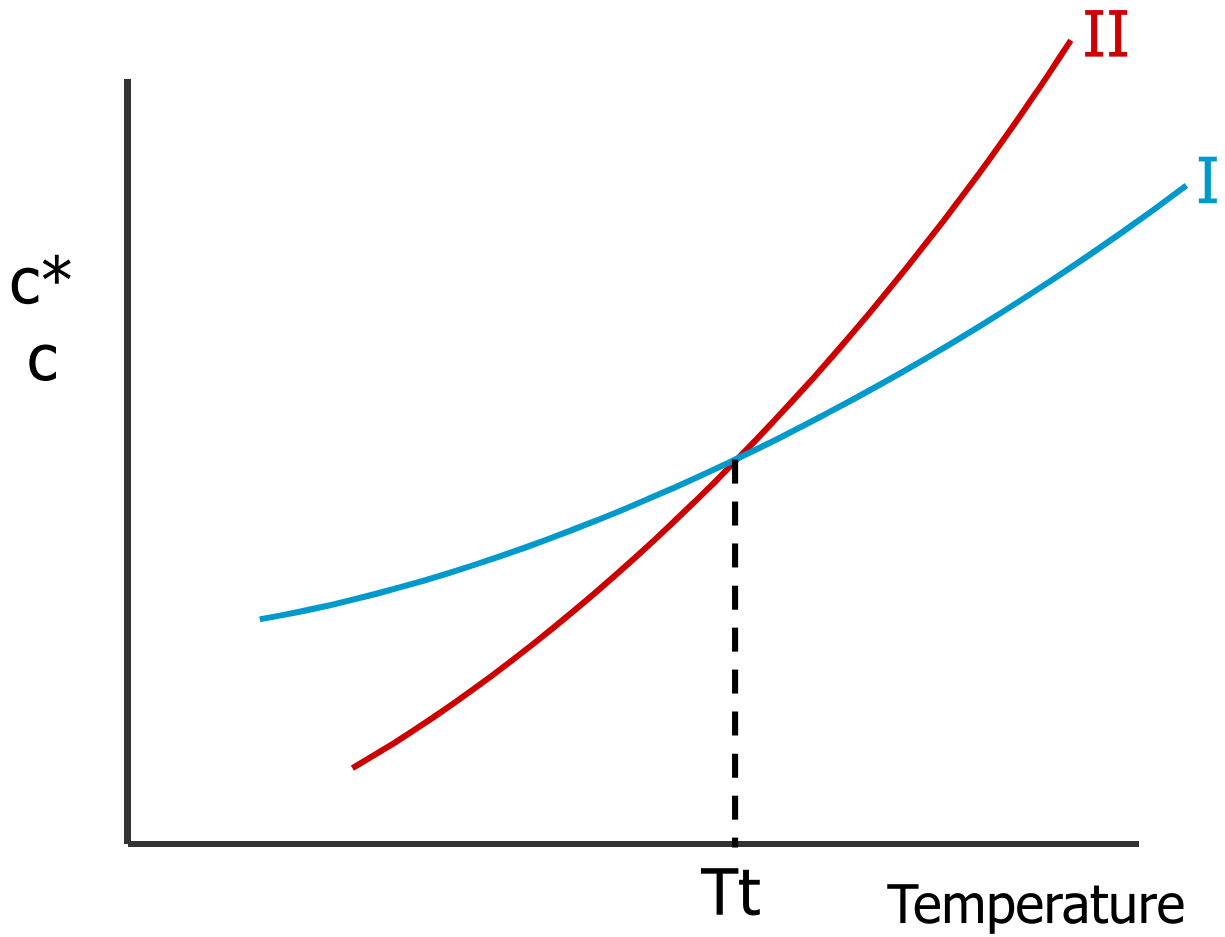
Thermodynamic stability: solubility





The transition temperature is independent from the solvent

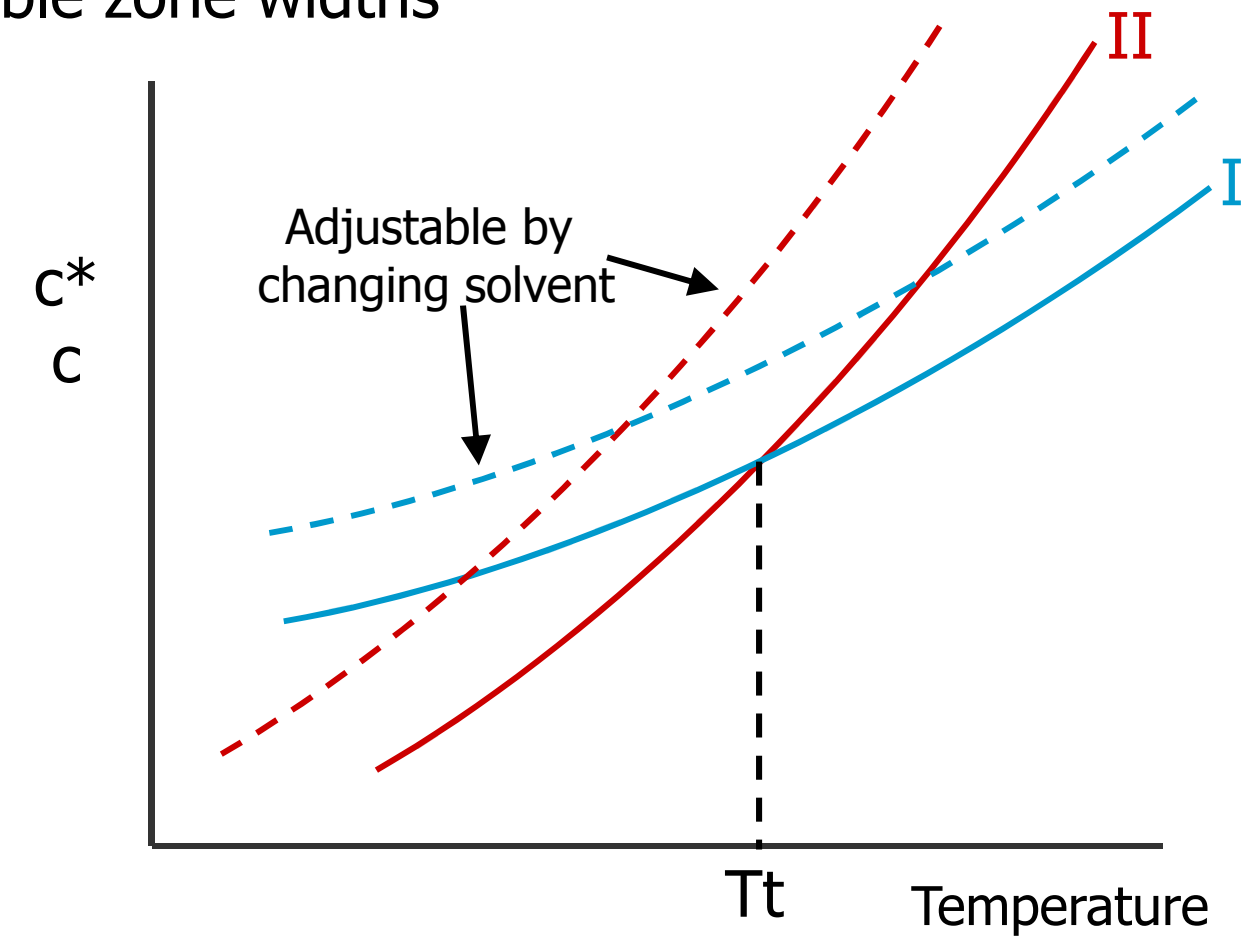
Kinetics in cooling crystallization



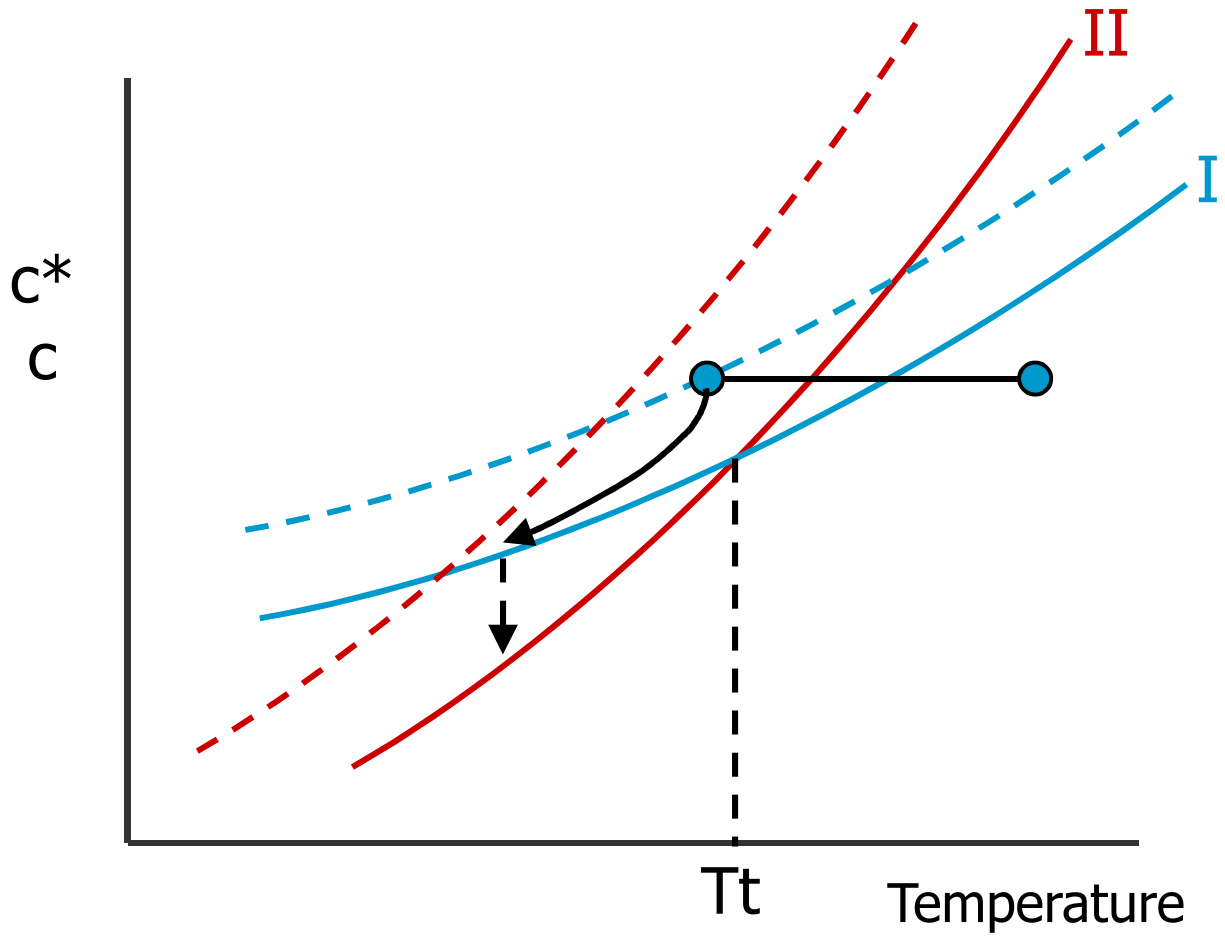
Thermodynamics: Above Tt **I** is obtained, below Tt **II** is obtained, **but** …

Kinetics in cooling crystallization

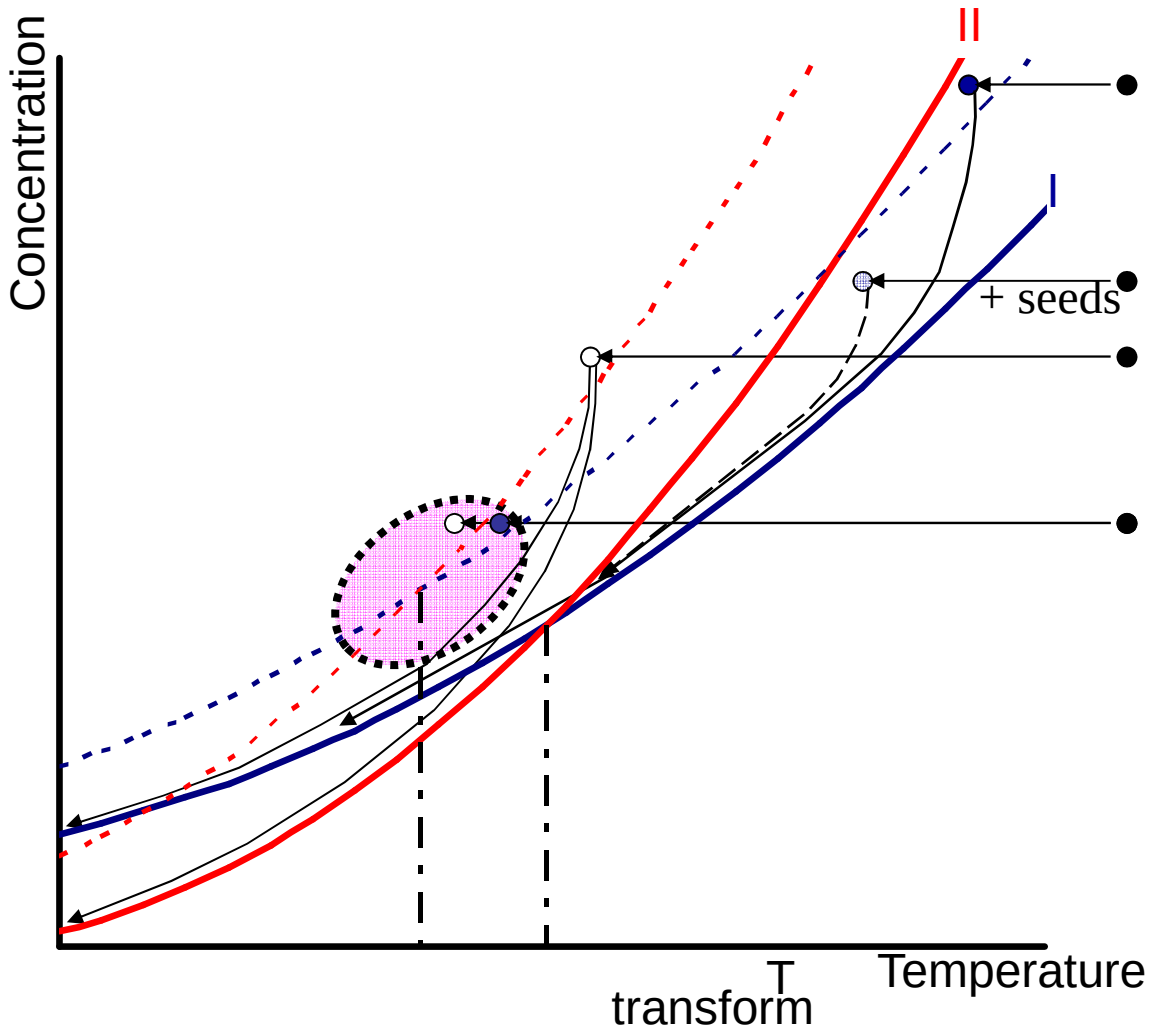
Metastable zone widths



Kinetics in cooling crystallization

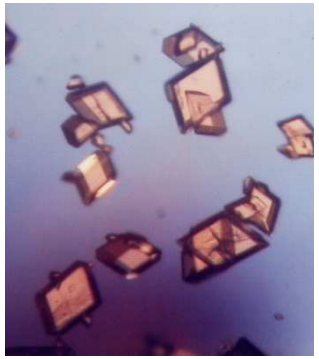


Kinetics in cooling crystallisation



Solvent mediated polymorph transformation: L-glutamic acid

Supersaturation



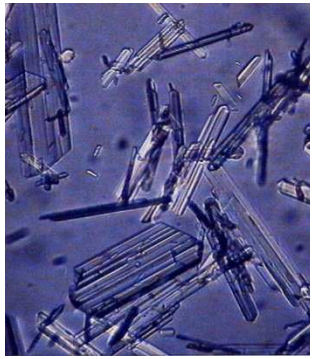
Nucleation

&

crystal growth

Unstable Polymorph α

Supersaturation



Nucleation

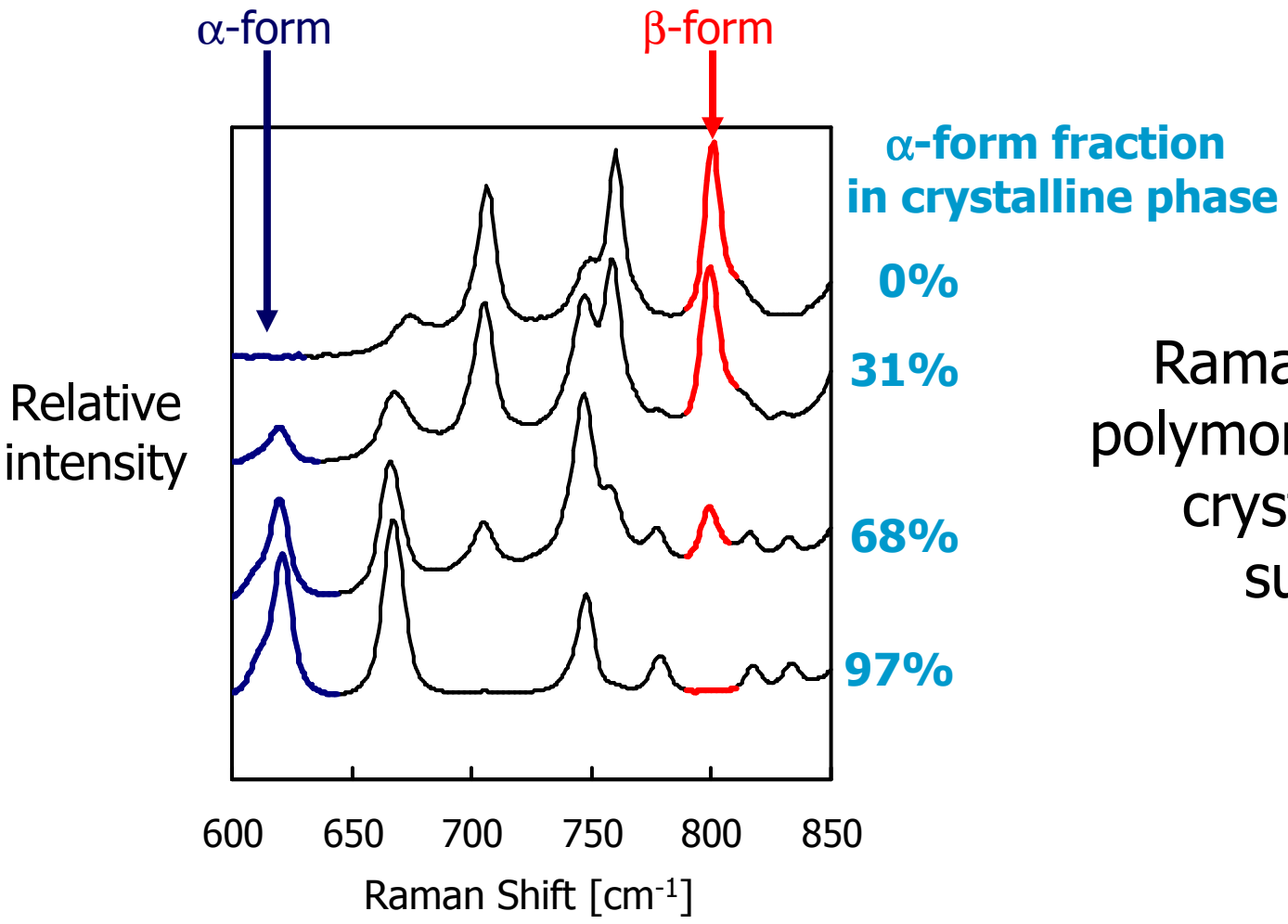
&

crystal growth

Stable Polymorph β

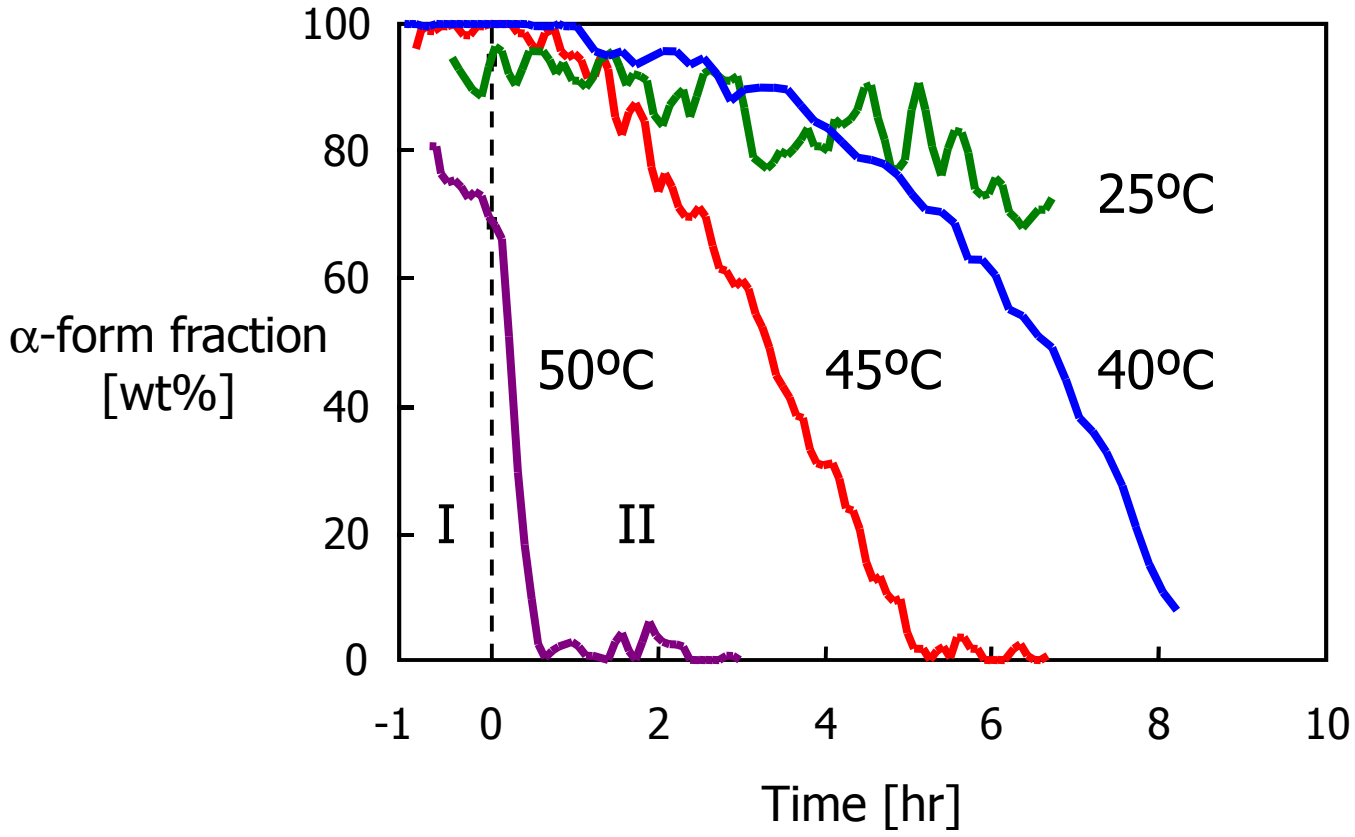
Solvent mediated polymorph **transformation**

Solvent mediated polymorph transformation: L-glutamic acid & Raman spectroscopy



Raman can detect polymorphic fraction in crystal phase of suspension

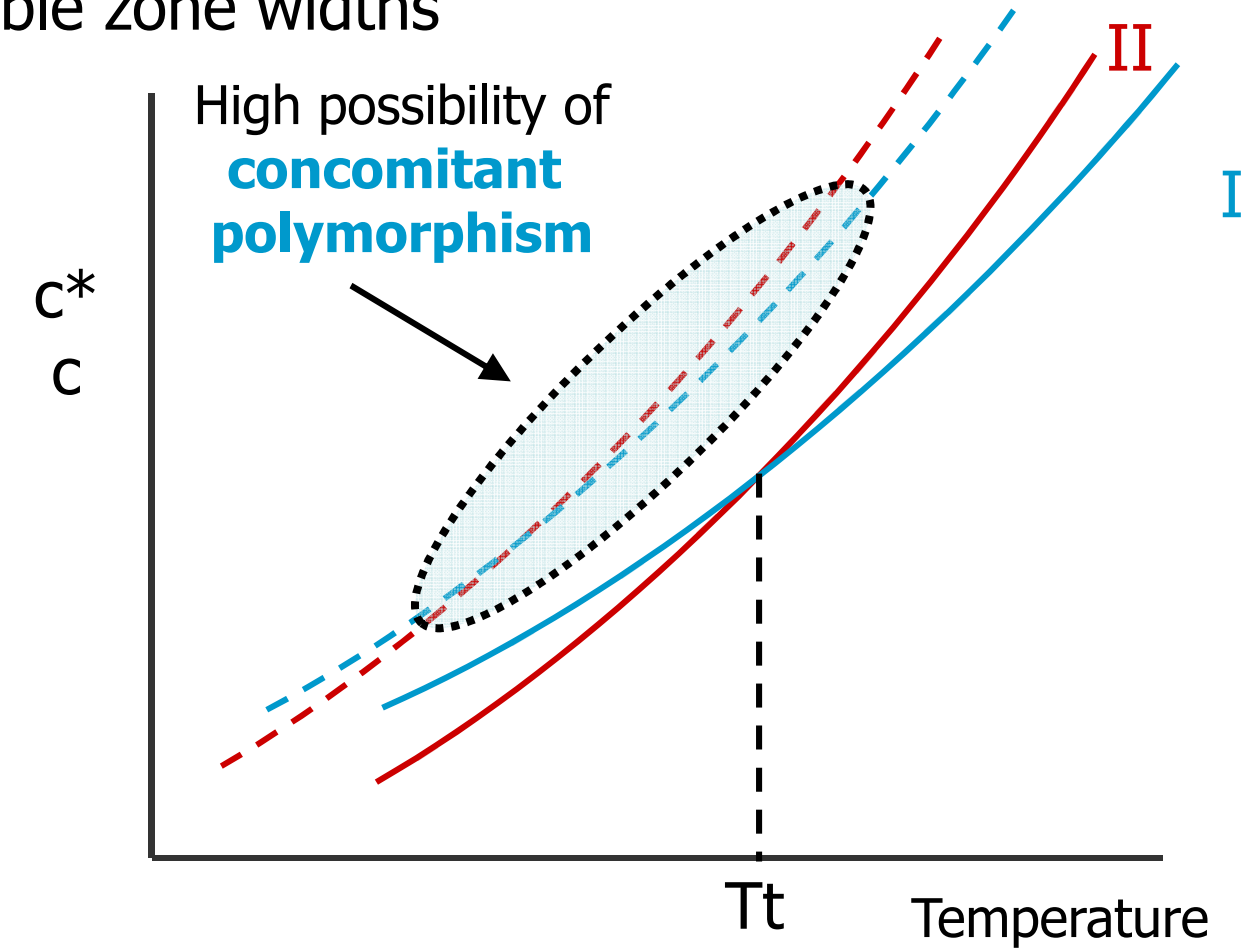
Control & optimization of polymorph crystallization



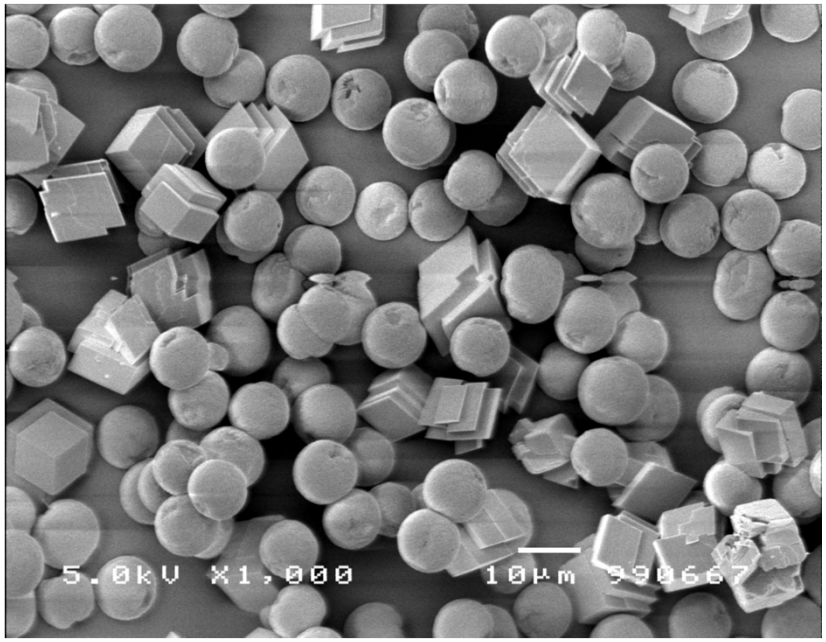
Large effect of temperature on transformation process

Kinetics in cooling crystallization

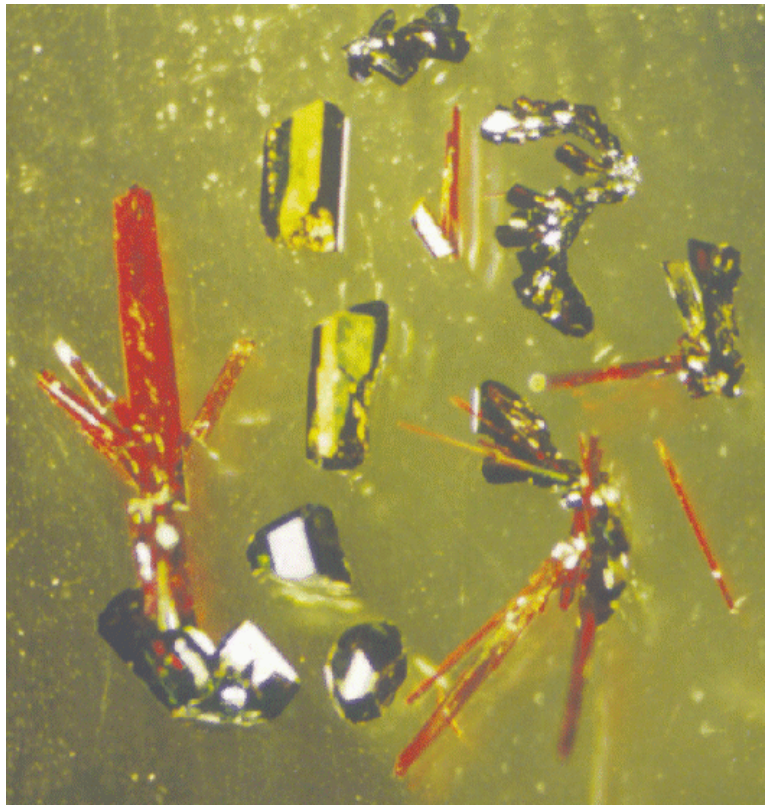
Metastable zone widths



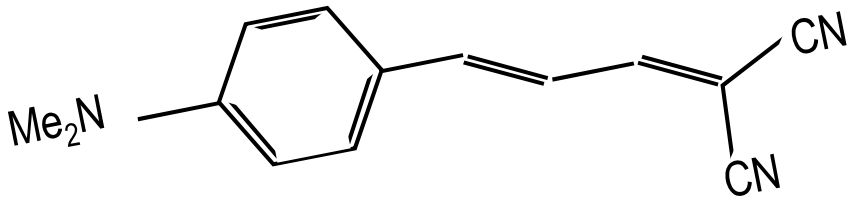
Concomitant polymorphism



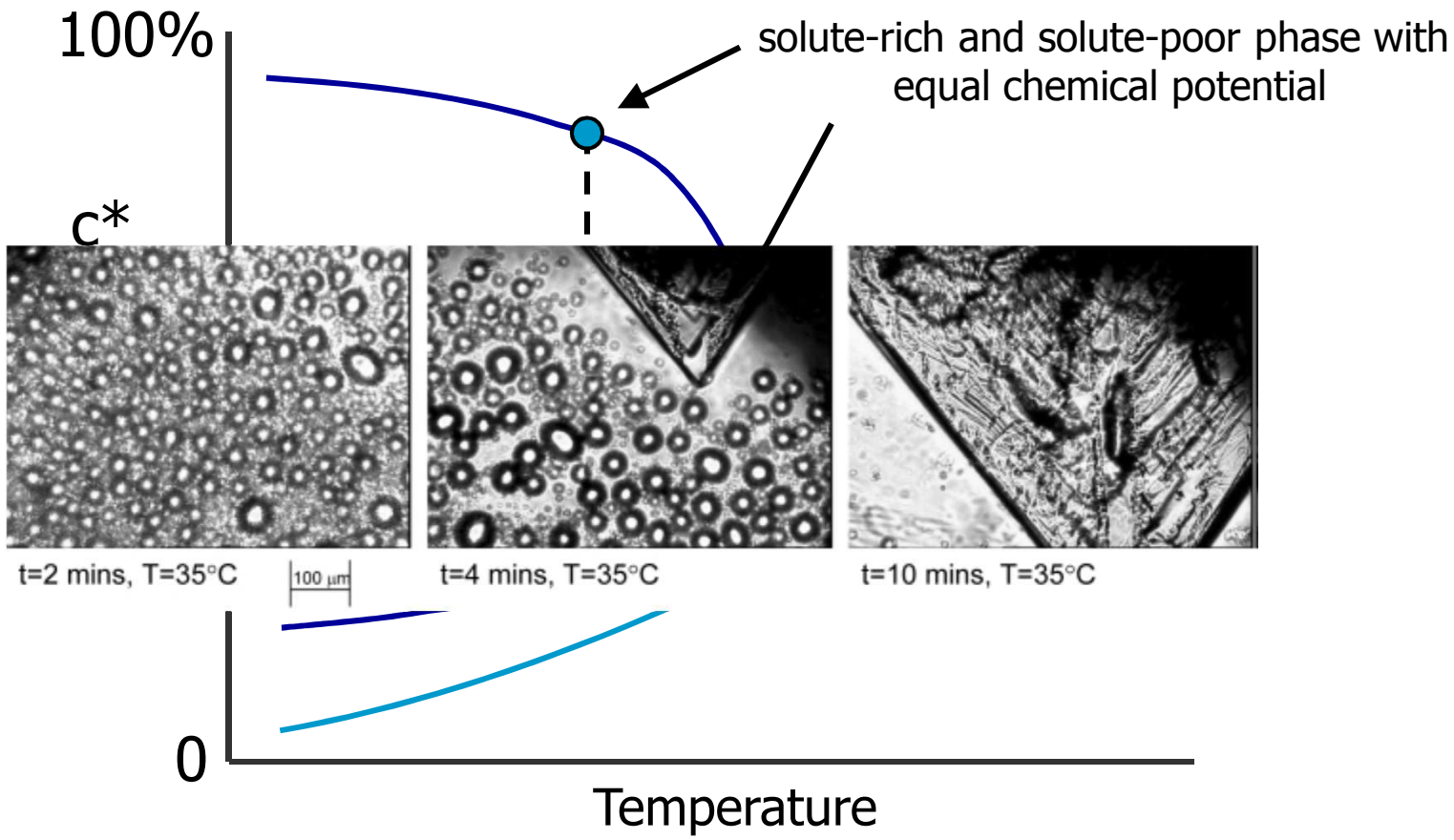
Calcite and vaterite ($CaCO_3$)



1,1-dicyano-4-(4-dimethylaminophenyl)-1,3-butadiene



Kinetics in cooling crystallization: oiling out

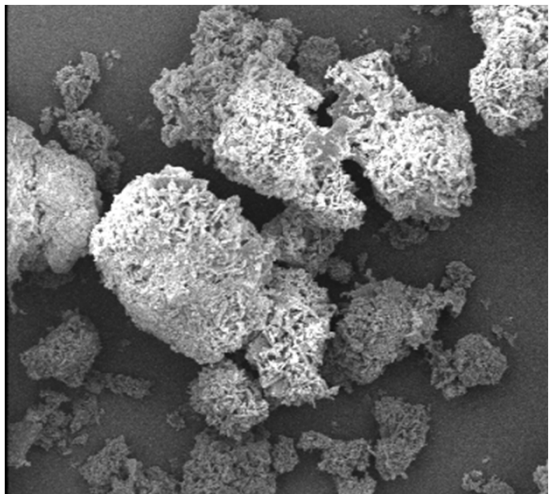


crystallization usually starts in the solute rich phase

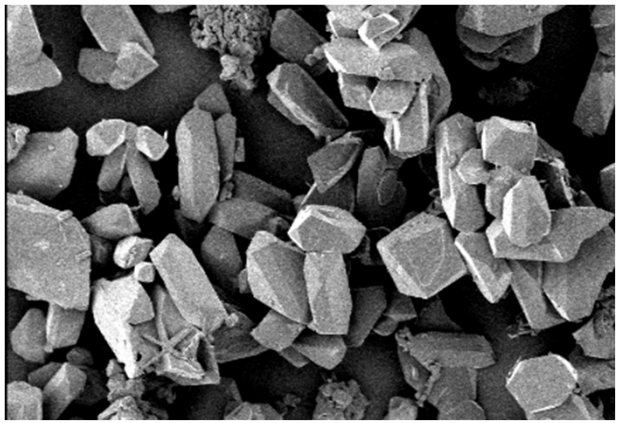
Roger Davey, Chem. Comm. 2003

Anti-solvent crystallization

- Why?
  - Thermally instable API
  - Removal from remaining solution after cooling crystallization
- Solubility is variable
- Be aware of local conditions
- Many process configurations
- Wide variety of particle size distributions and polymorphs

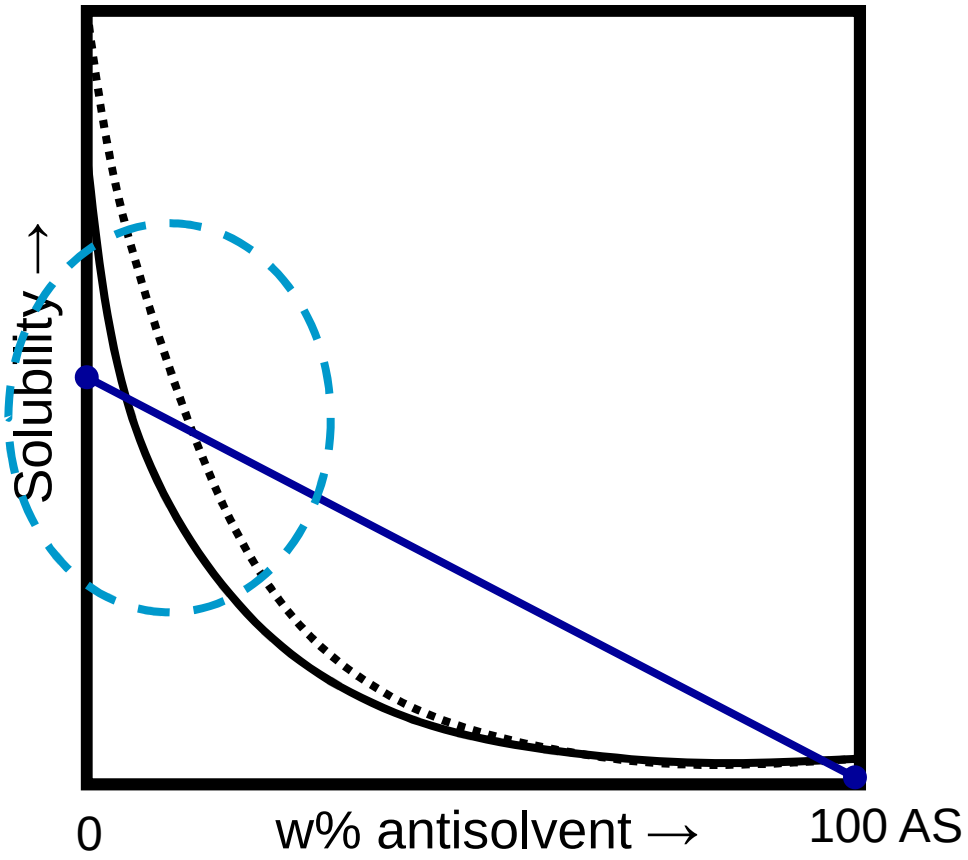


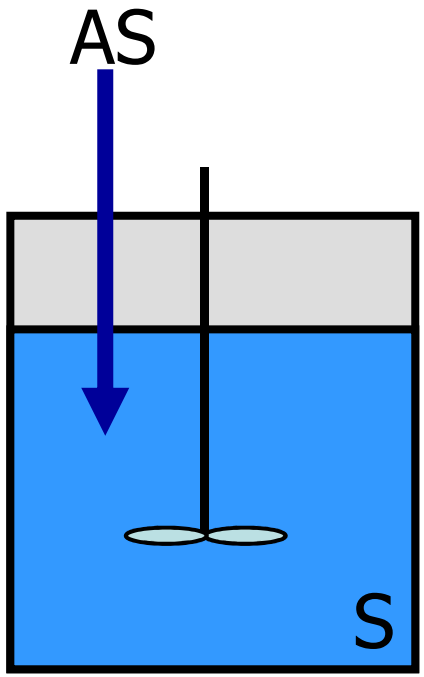
Ascorbic acid from EtOH/CO_2



Acetaminophen from EtOH/CO_2

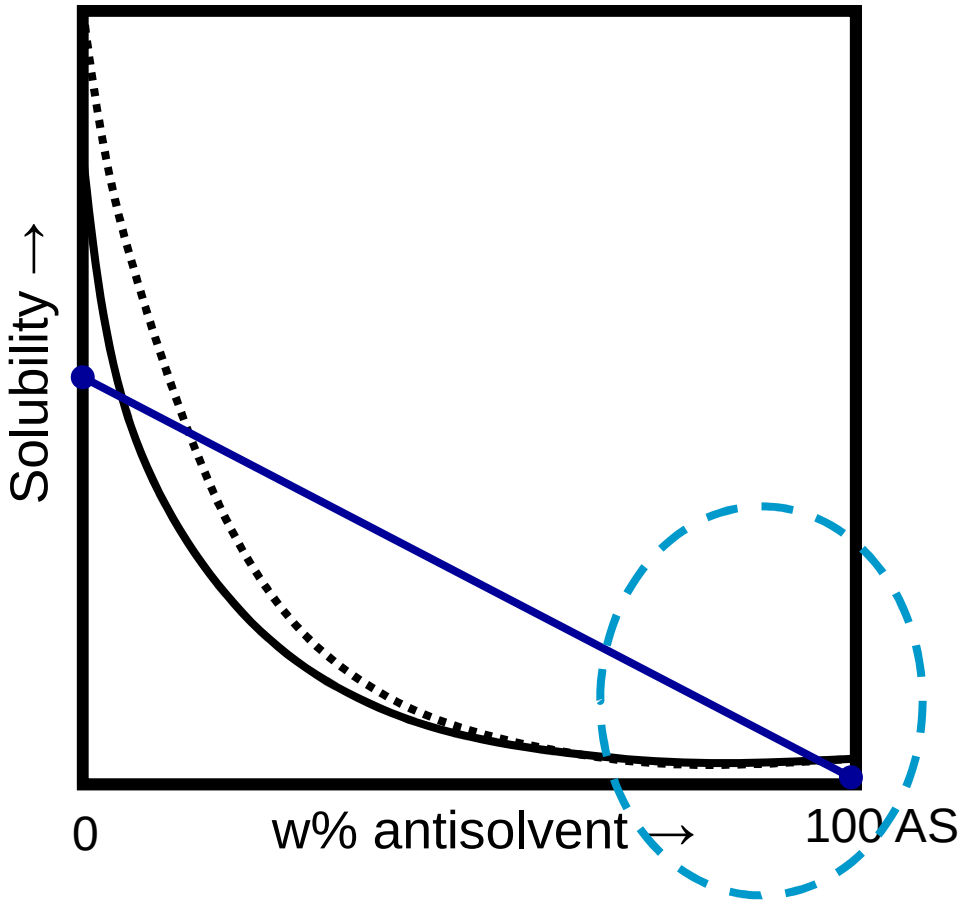
Kinetics in antisolvent crystallization

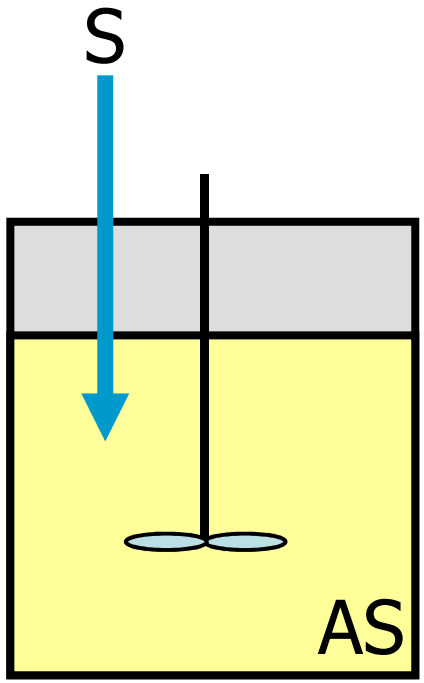




- Slow addition
- mild conditions
- less chance for unwanted polymorph

Kinetics in antisolvent crystallization

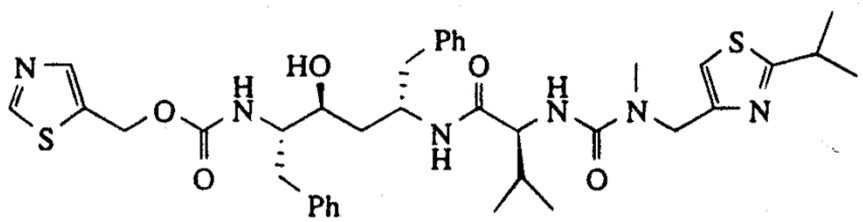




- Extreme supersaturations
- Concomitant polymorphism

Polymorphism: Ritonavir

- The HIV-1 and HIV-2 protease inhibitor Ritonavir



- In 1996 Ritonavir was introduced on the market

- In 1998 a **new, more stable form** appeared
- The new polymorph had a 4 times **lower solubility**
- This affected the **bioavailability** of the pharmaceutical
- The company Abbott withdrew Ritonavir from the market

- 1 year of research effort enabled the production of the old less stable polymorph again.

- **Costs**: 100 of millions of dollars

Kinetics in antisolvent crystallization

How to obtain the metastable form I of Ritonavir?

1. **Crystallize** form I
   a. suspension form I seeds in anti-solvent
   b. fed-batch addition of solution to anti-solvent

2. **Inhibition of transition** I => II
   Choice of solvent mixture inhibits transition

   Ethyl-acetate/Heptane **2:1** >90% polymorph **II**
   Ethyl-acetate/Heptane **1:2** mostly polymorph **I**

Conclusions

- Polymorphism is the ability of a chemical compound to form different crystalline lattices
- polymorphs differ in their physical properties and is therefore an important issue in pharmaceutical industry
- The crystallization of polymorphs is a process of nucleation and growth of both polymorphs and the possible solvent mediated transition from a metastable form to a more stable form.
- Crystallization of polymorphs is a balance between thermodynamics and kinetics

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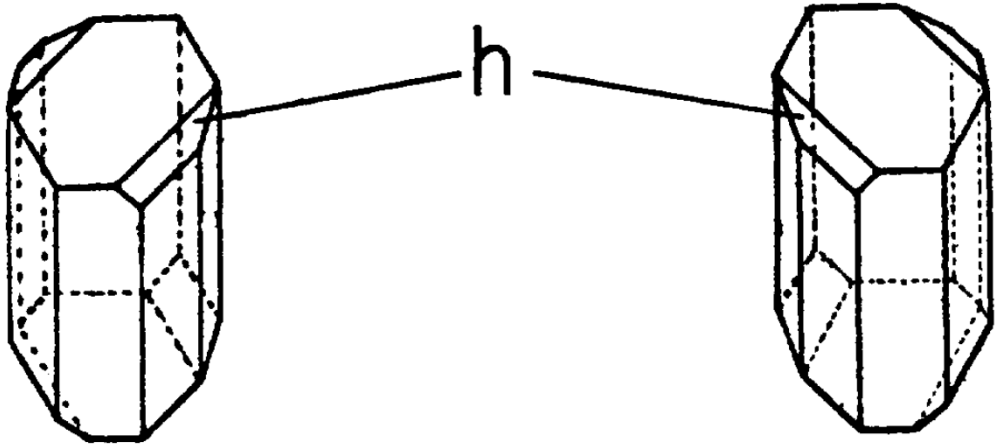
Chiral separation



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Chirality

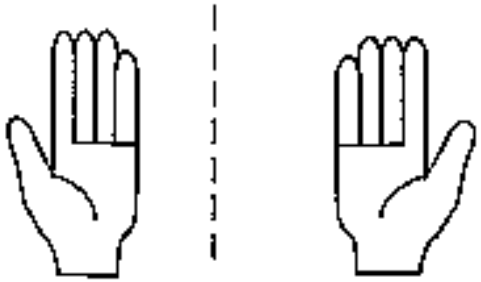
"I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realised, cannot be brought to coincide with itself."

Lord Kelvin.

Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light, 1904.

Enantiomers

Enantiomers are stereoisomer pairs in a mirror-image relationship.



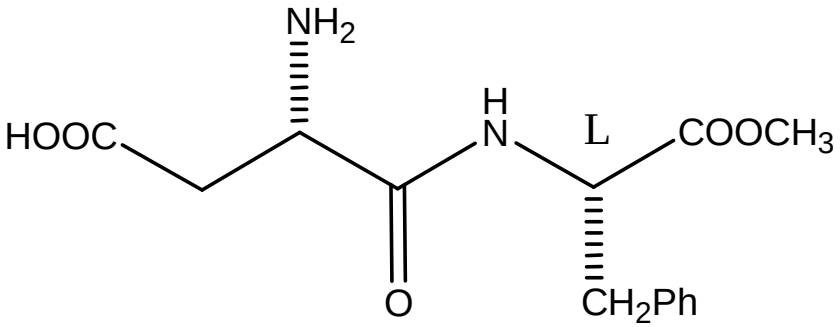
Enantiomer pairs possess *identical physical properties*, but their *biological activities* and *effects can be markedly different*.

Amino acids

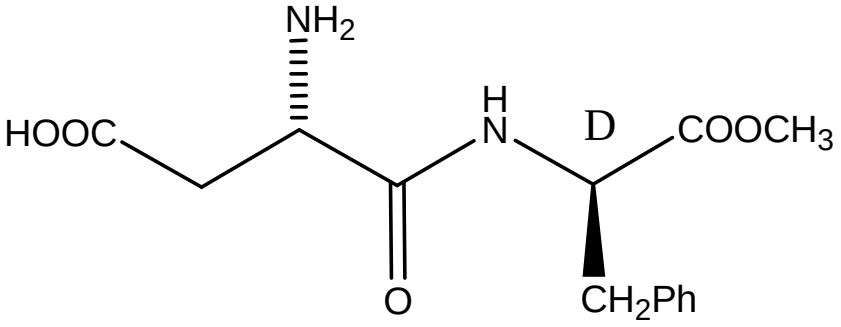
L-leucine
L-phenylalanine
L-tyrosine
L-tryptophan
All taste *bitter*.

D-leucine
D-phenylalanine
D-tyrosine
D-tryptophan
All taste *sweet*.

Aspartames



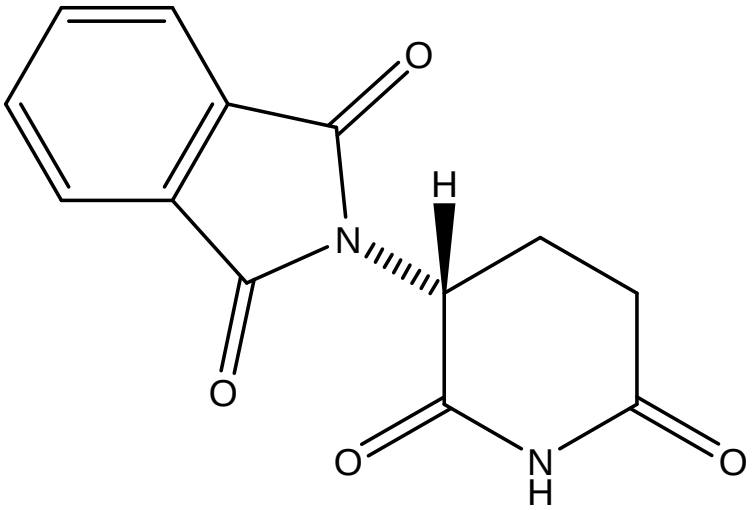
sweet



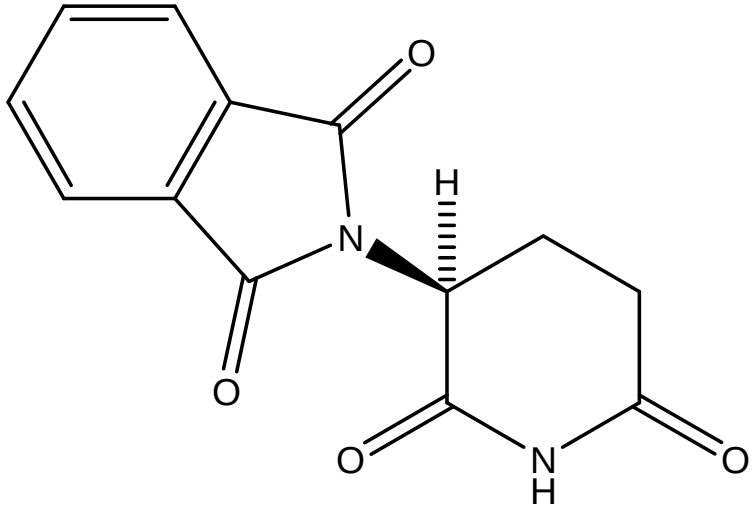
bitter

Thalidomide

In the 1960s, thalidomide was administered as a mixture of two enantiomeric forms:-



R-thalidomide
mild sedative

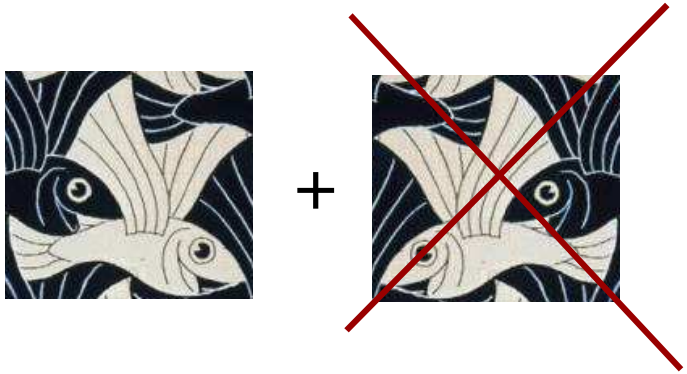


S-thalidomide
Causes birth defects

Chiral compounds

Racemic compound

enantiopure compound



Escher

Crystallization from a racemic mixture

Racemic compound

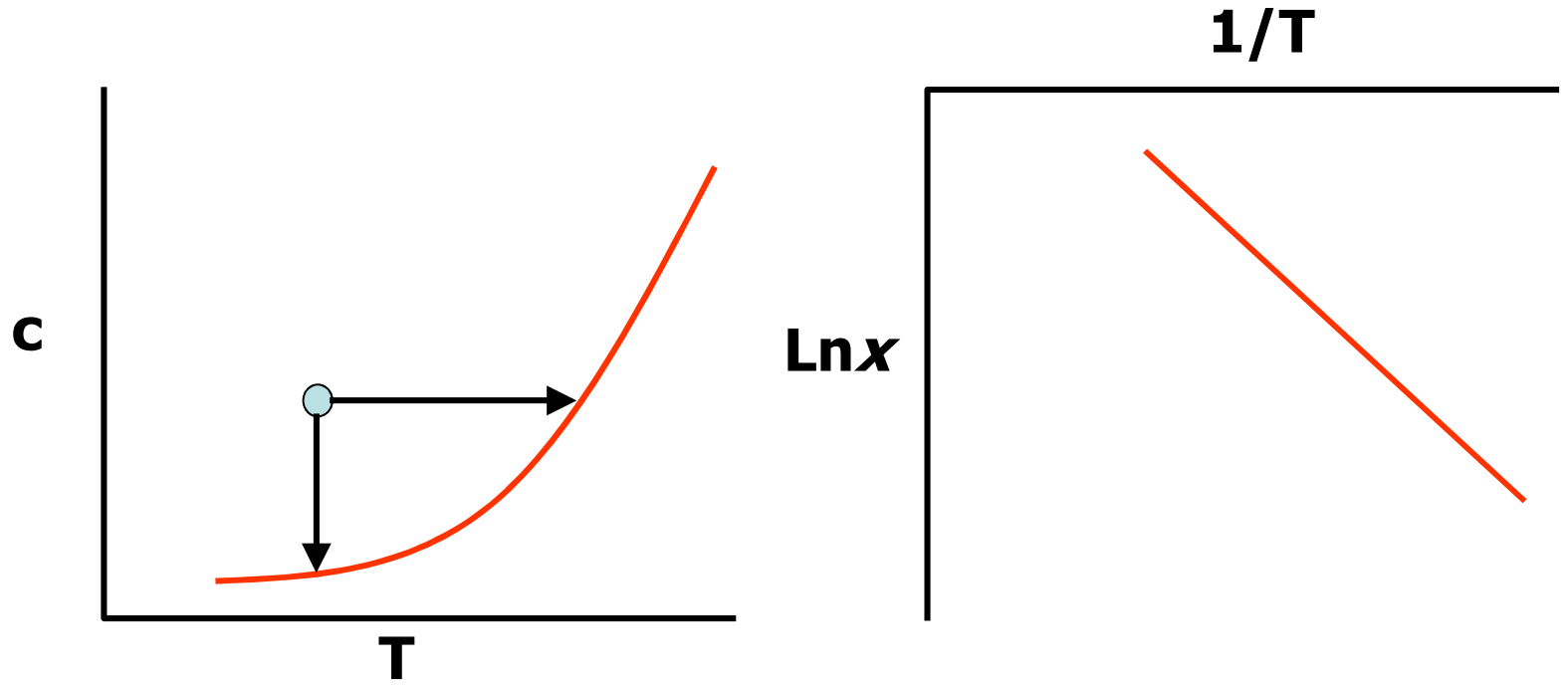
conglomerate

Escher

Crystallization from a racemic mixture

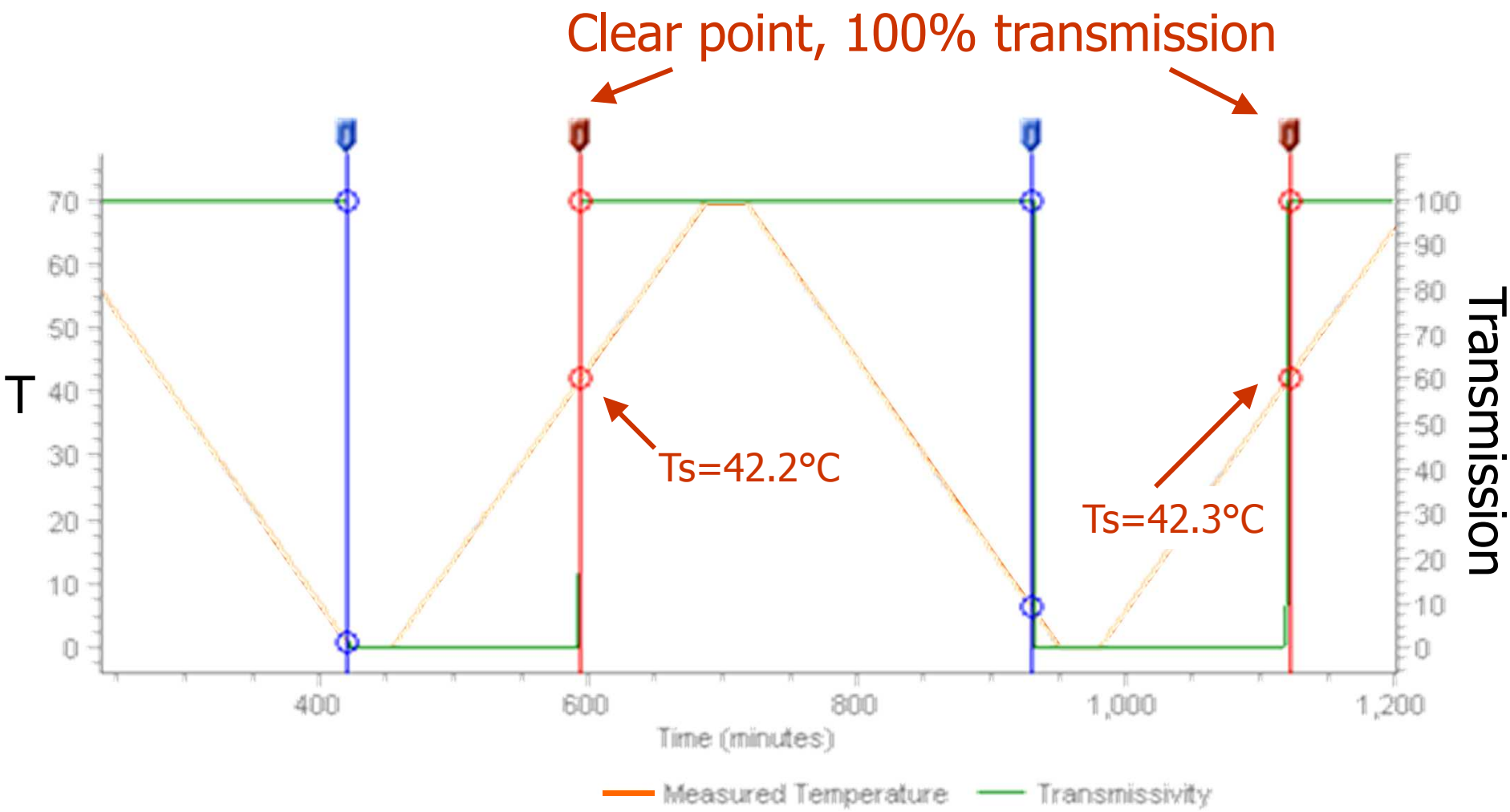
- **Racemic crystals** (92%).
  - Enantiomer pairs incorporated stoichiometrically into the unit cell.
  - Resolvable only by chemical intervention.
- **Conglomerates** (8%).
  - Mechanical mixtures of homochiral crystals of the two enantiomer forms.
  - Resolvable physically by crystallization methods.
- **Pseudoracemates** (very few).
  - Crystallize as solid solutions.
  - Require chemical intervention for resolution.

Solubility

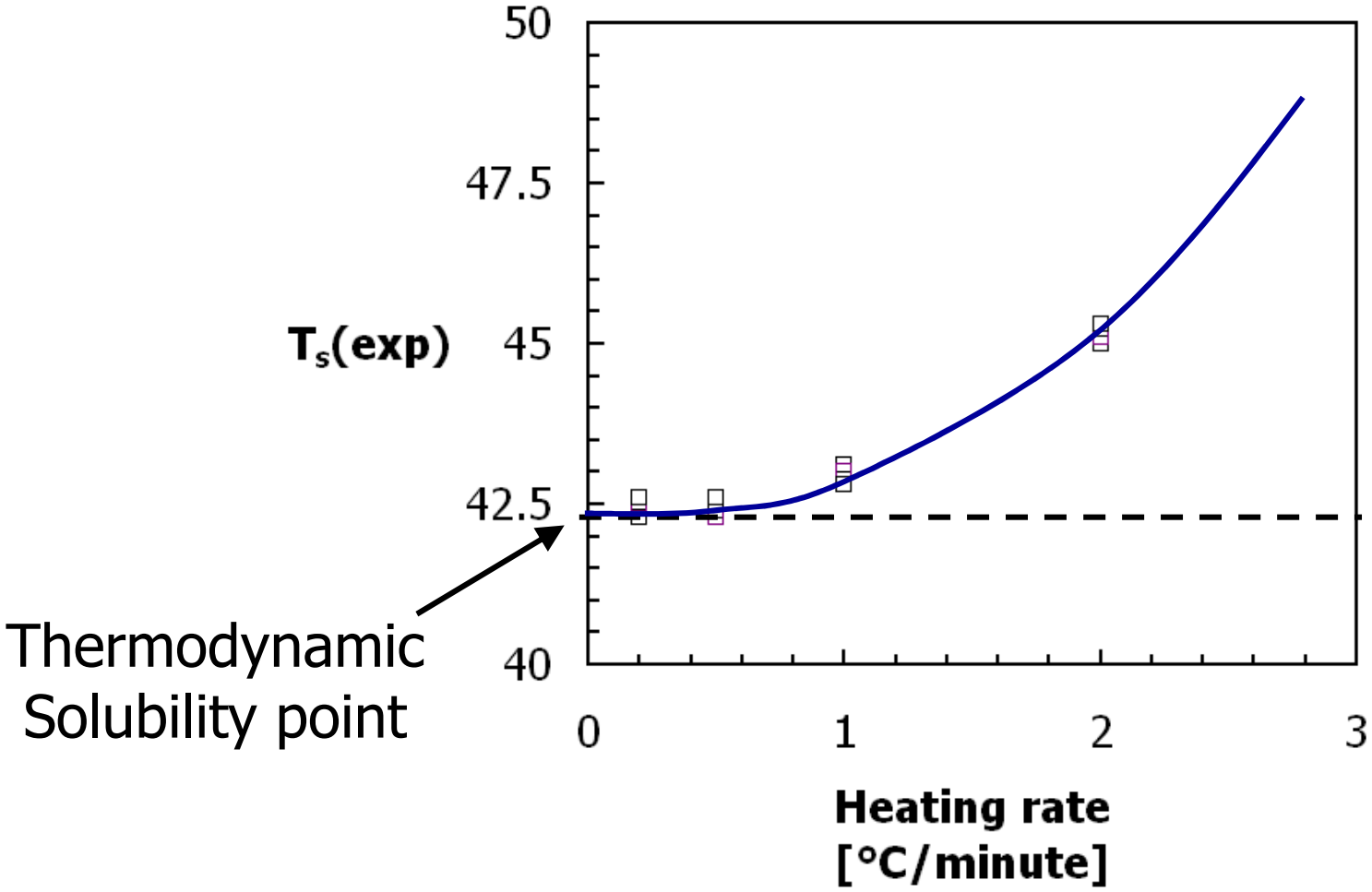


If the solubility is low, the saturation temperature is high

Clear & Cloud Point Measurements

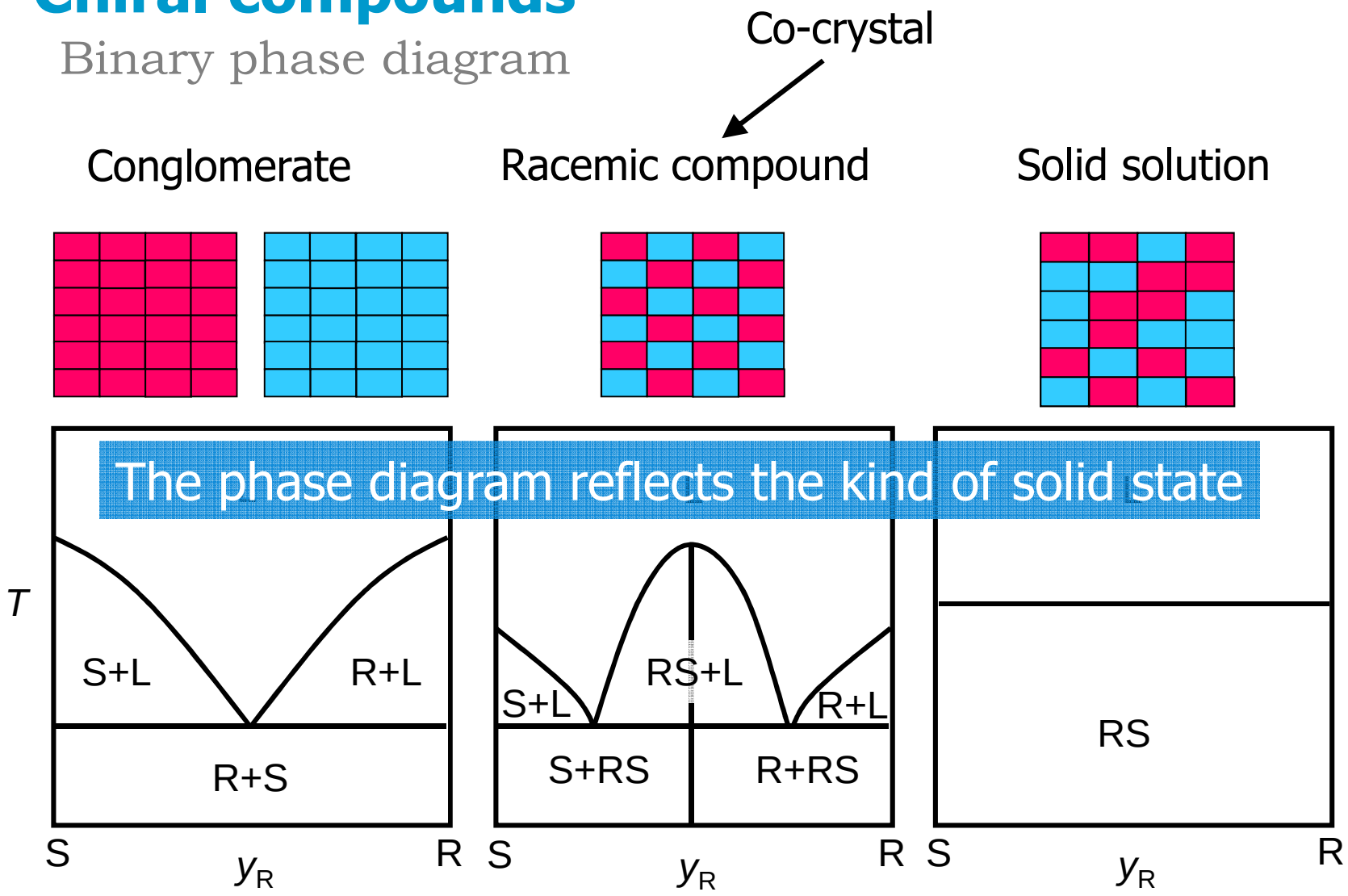


Clear Point & Solubility



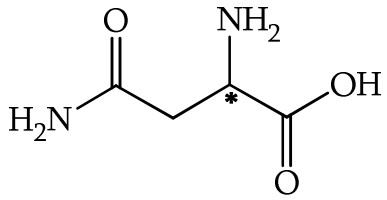
Chiral compounds

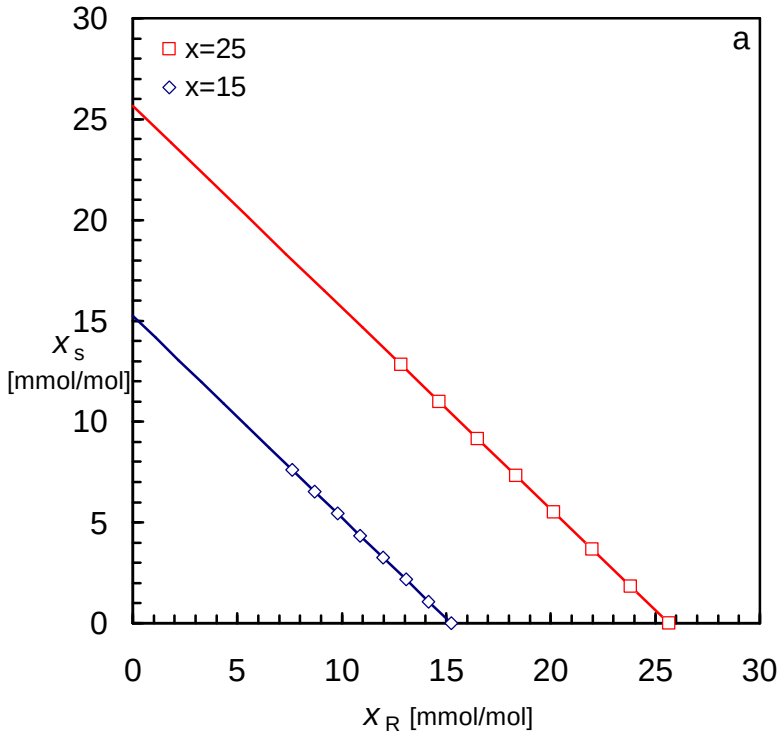
Binary phase diagram

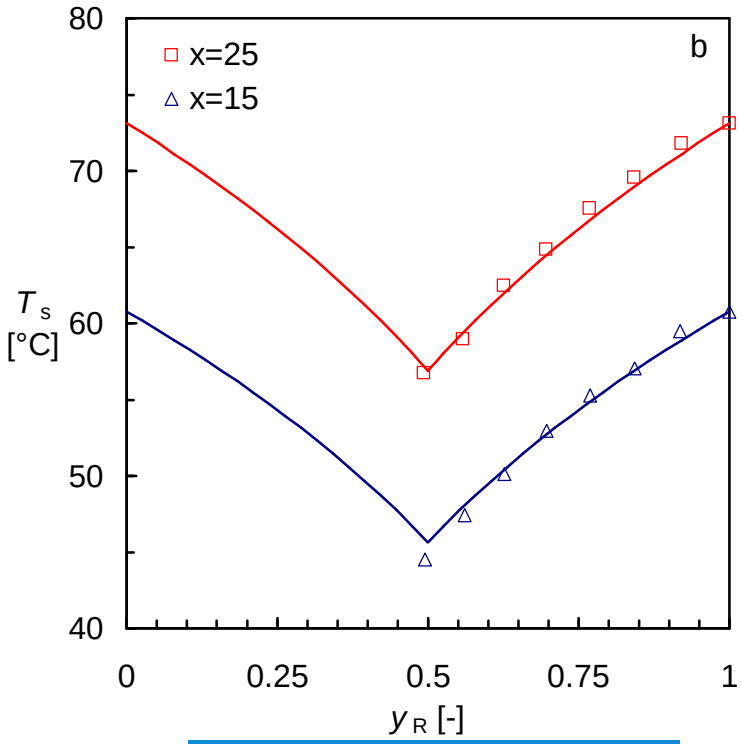


Chiral Compounds: Asparagine in Water

Ternary phase diagram screening



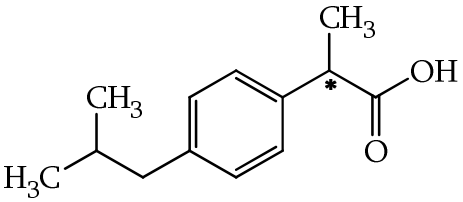


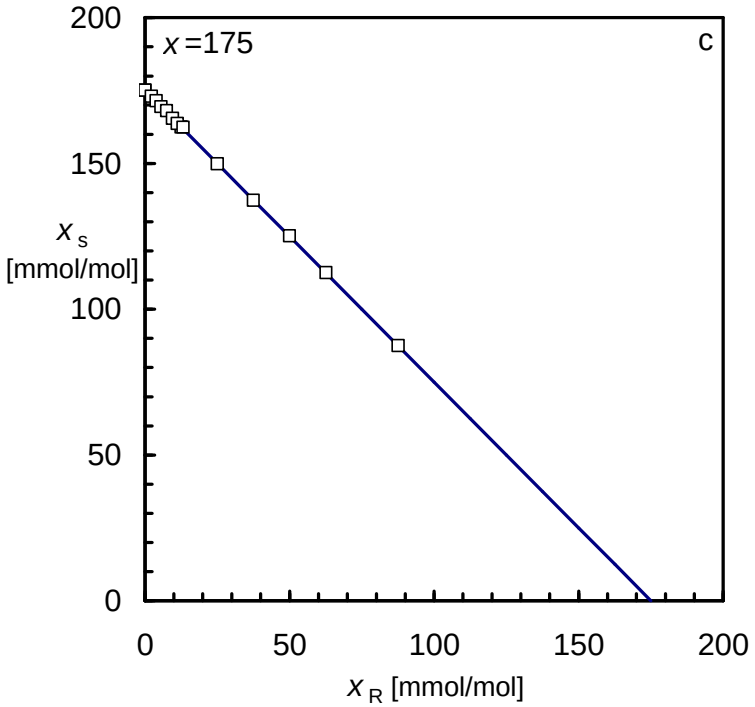


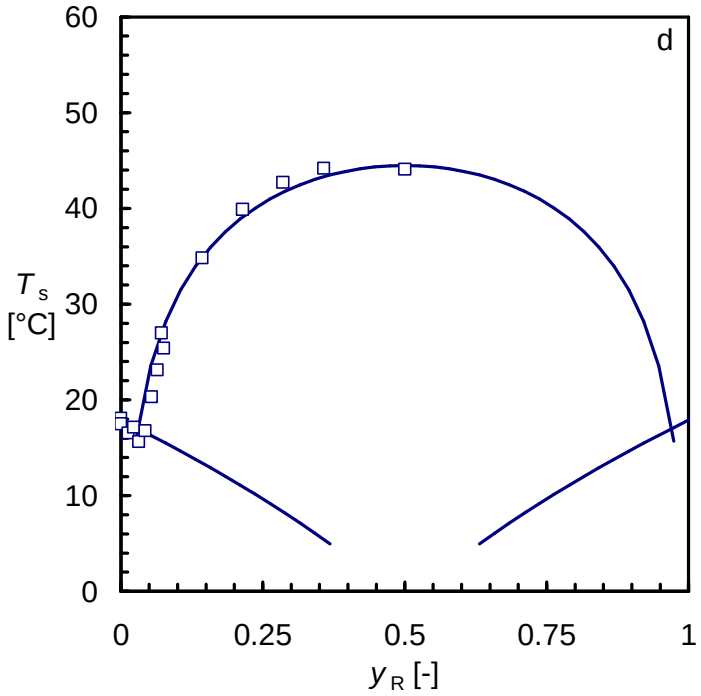
Conglomerate

Chiral Compounds: Ibuprofen in Hexane

Ternary phase diagram screening



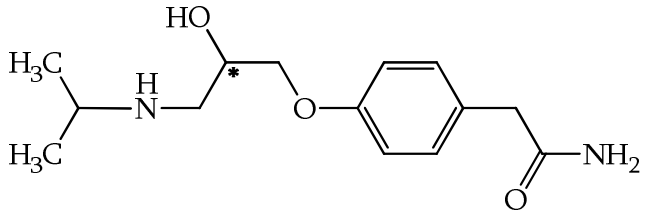


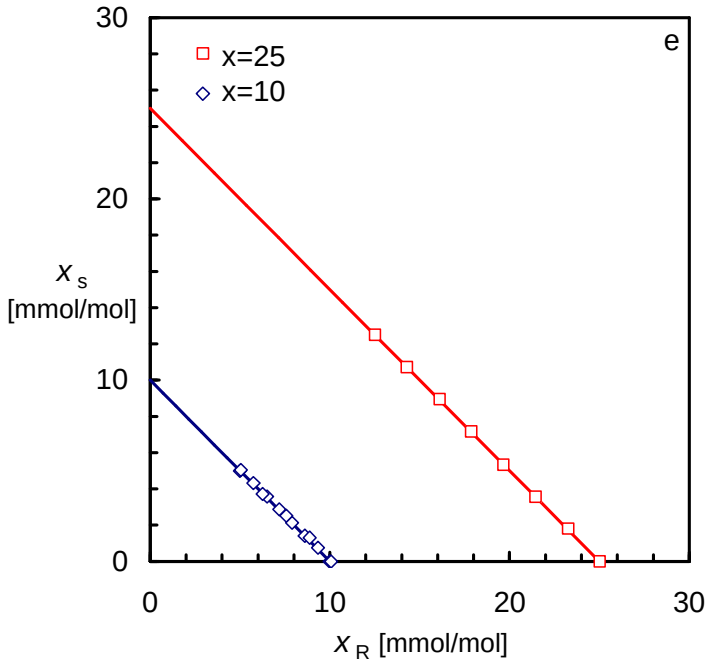


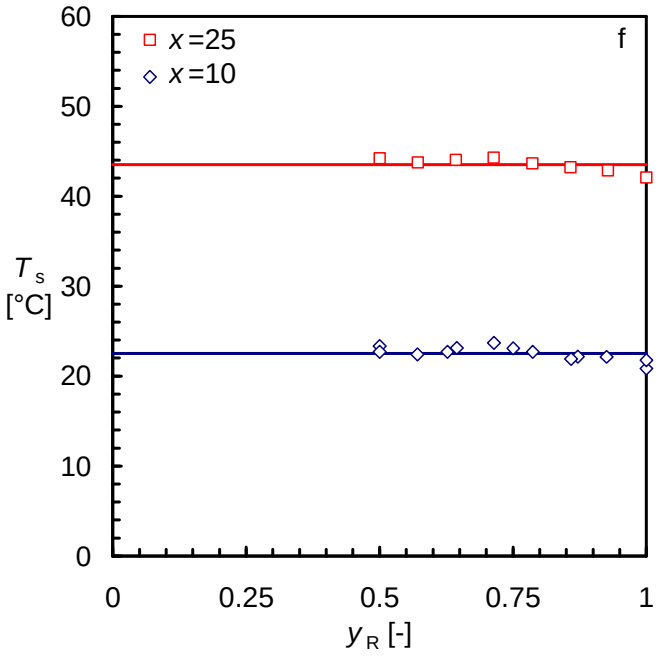
Racemic compound

Chiral Compounds: Atenolol in Ethanol

Ternary phase diagram screening







Solid solution

Chiral Compounds

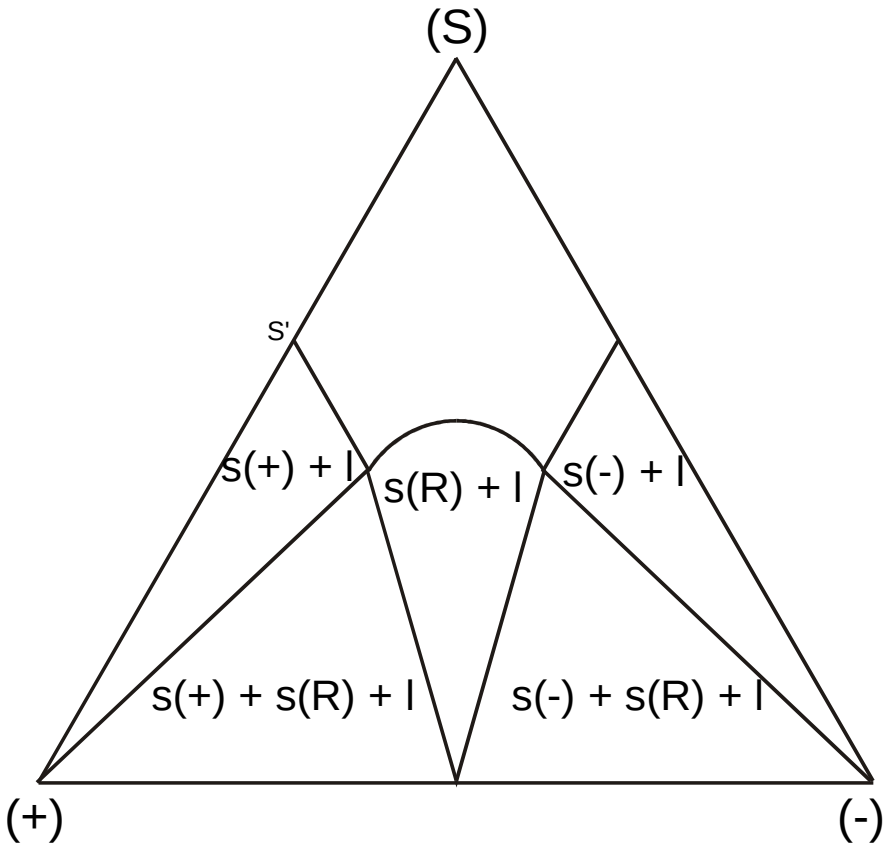
Ternary phase diagram screening

Racemic Compound, Conglomerate or Solid Solution?

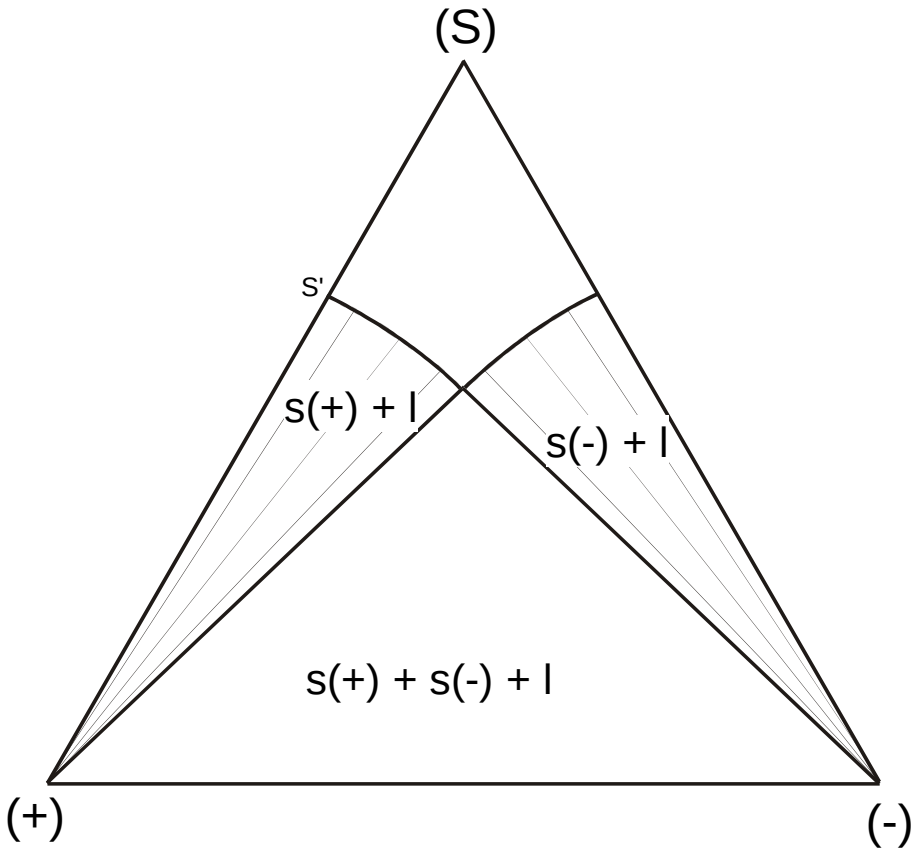
- Saturation temperature measurements can be used to identify the kind of solid state of a chiral pharmaceutical at solution crystallization conditions
- The ternary phase diagram is obtained as a bonus

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.

Phase diagram



Racemic crystals



Conglomerate

S. Srisanga, J.H. ter Horst, *Crystal growth design*, 2010

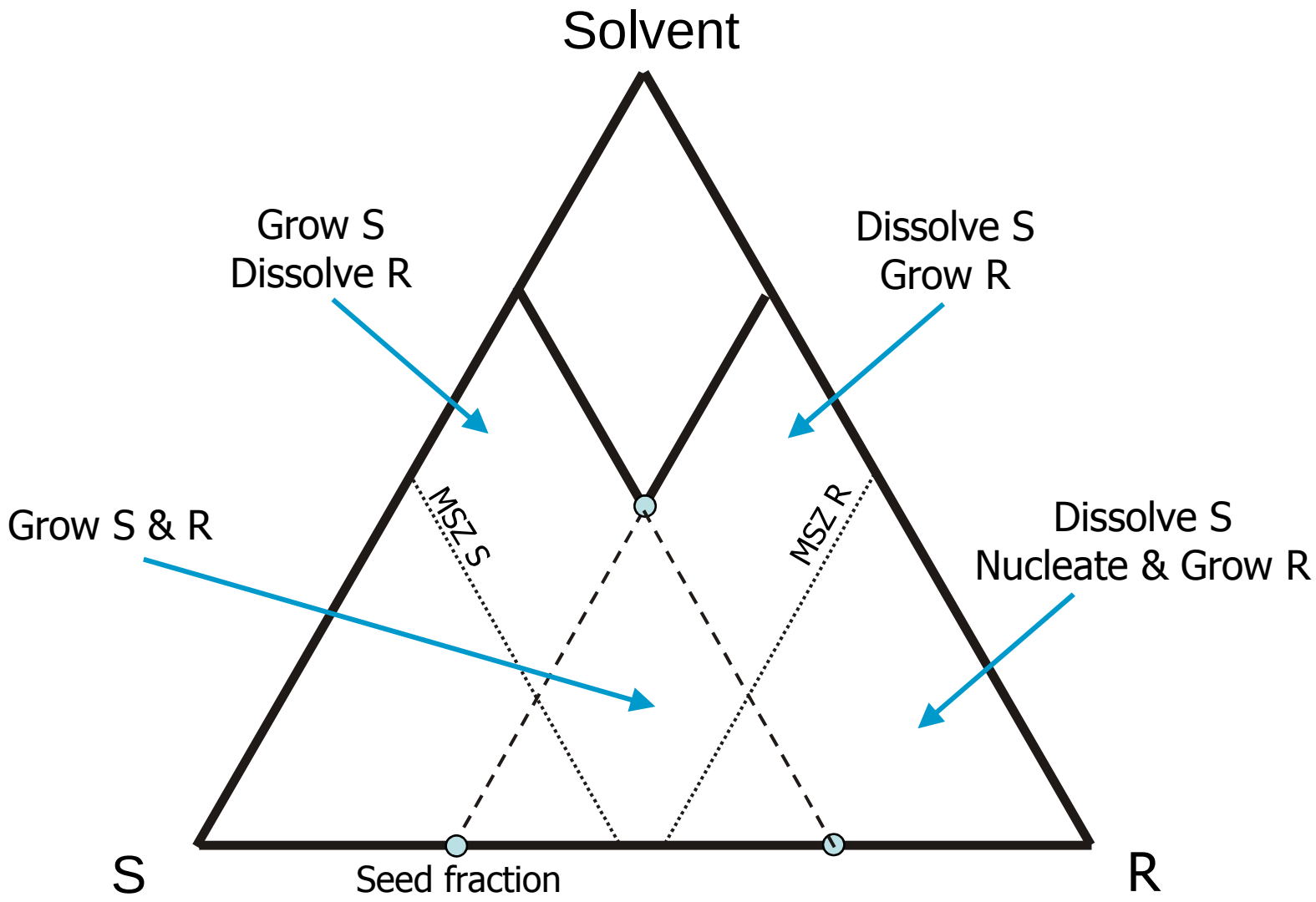
Resolution of Conglomerates - Methods available

1. Preferential crystallization

2. Crystallization of diastereomers

3. The grinding method: Combining a racemization reaction with suspension grinding

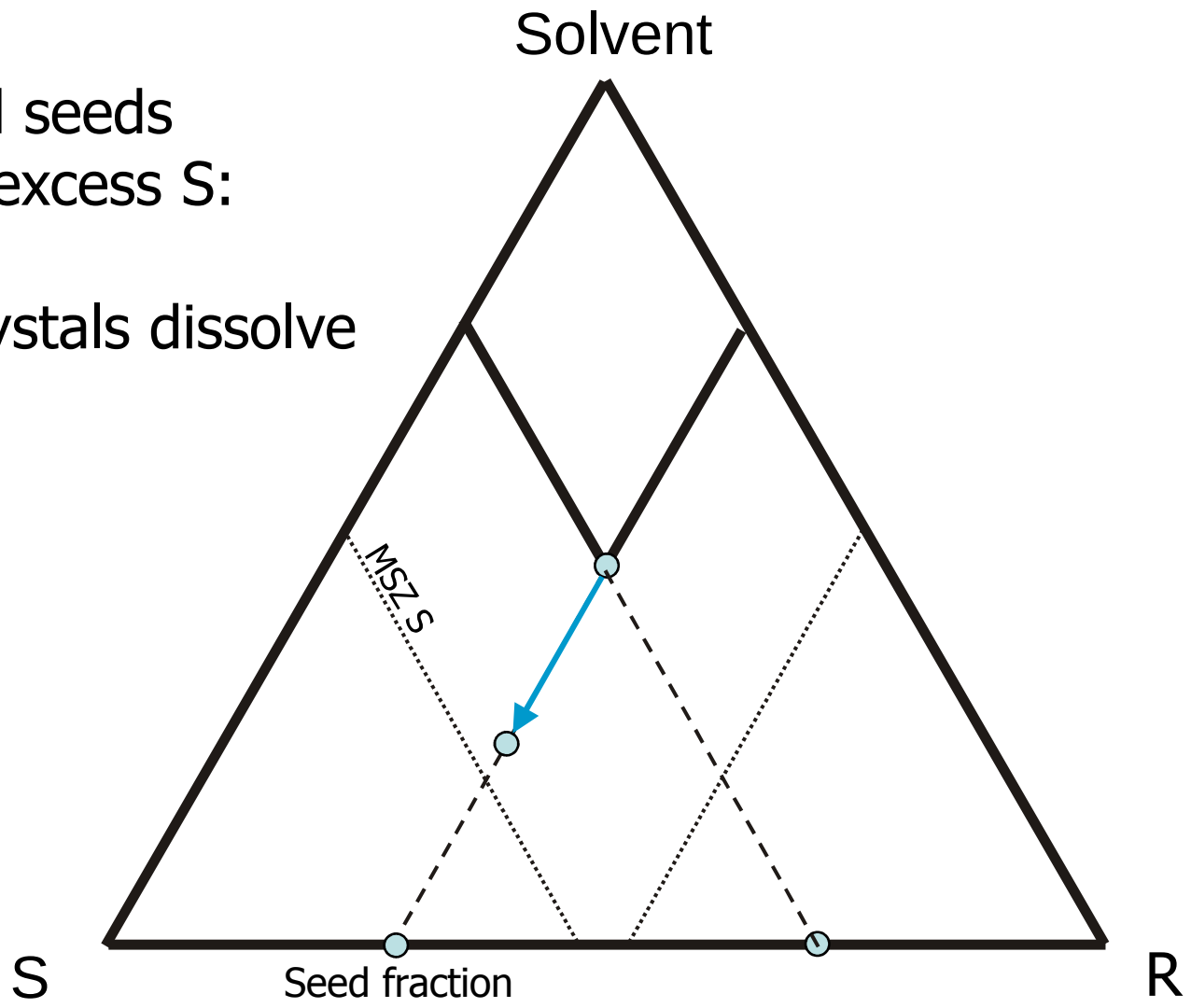
1. Preferential crystallization - principle



1. Preferential crystallization - principle

Add seeds
with excess S:

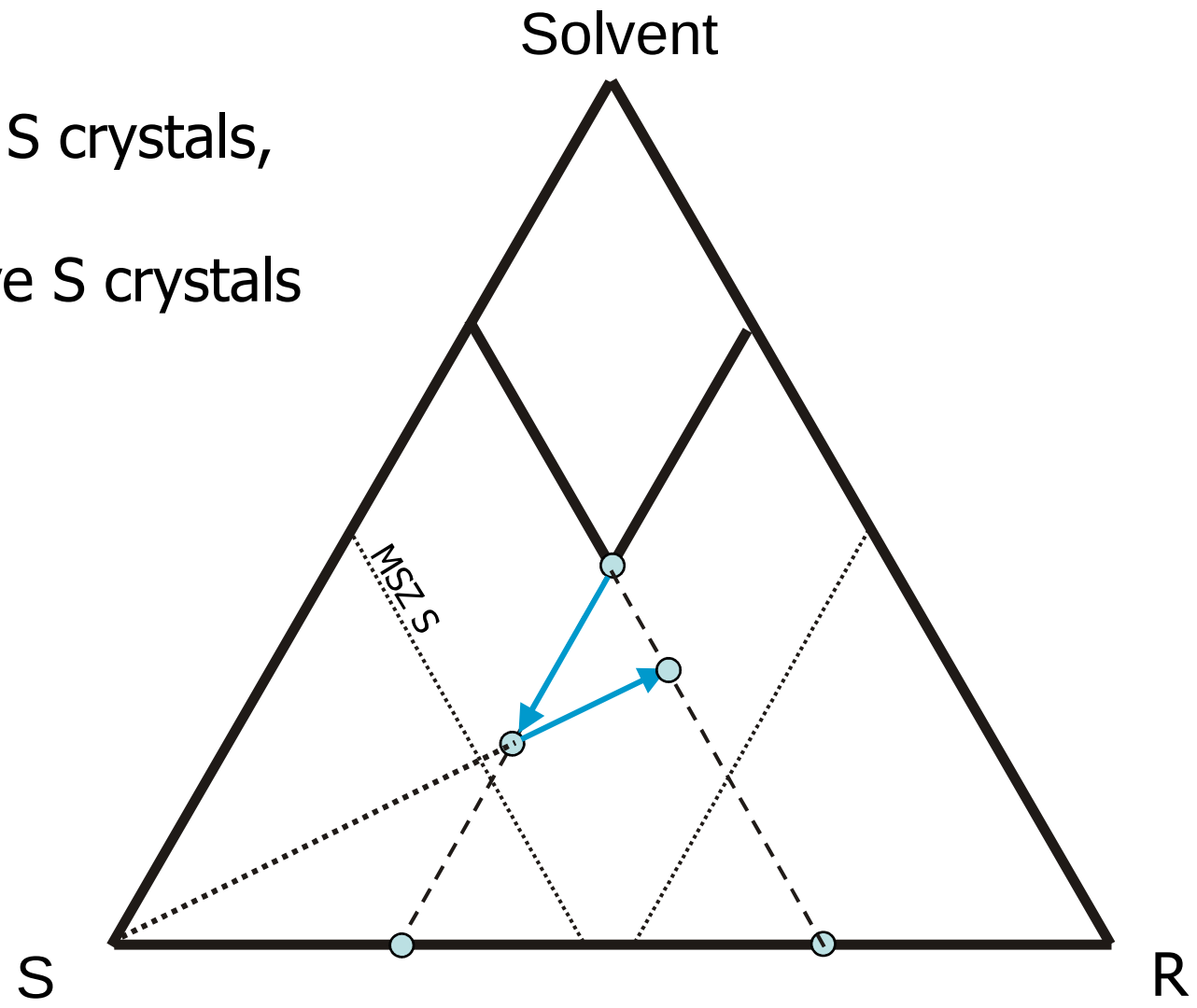
Only R crystals dissolve



1. Preferential crystallization - principle

Grow S crystals,

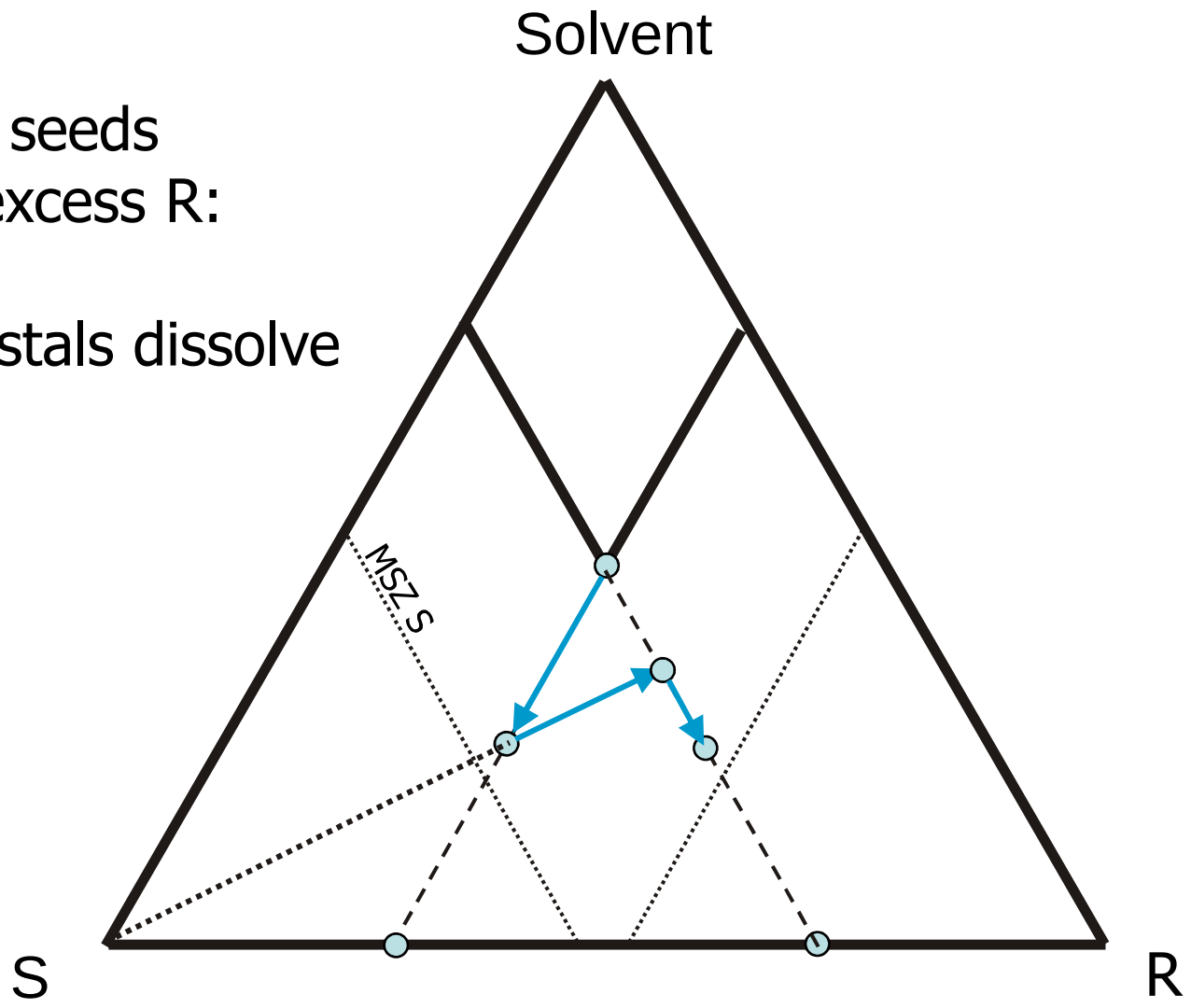
Remove S crystals



1. Preferential crystallization - principle

Add seeds
with excess R:

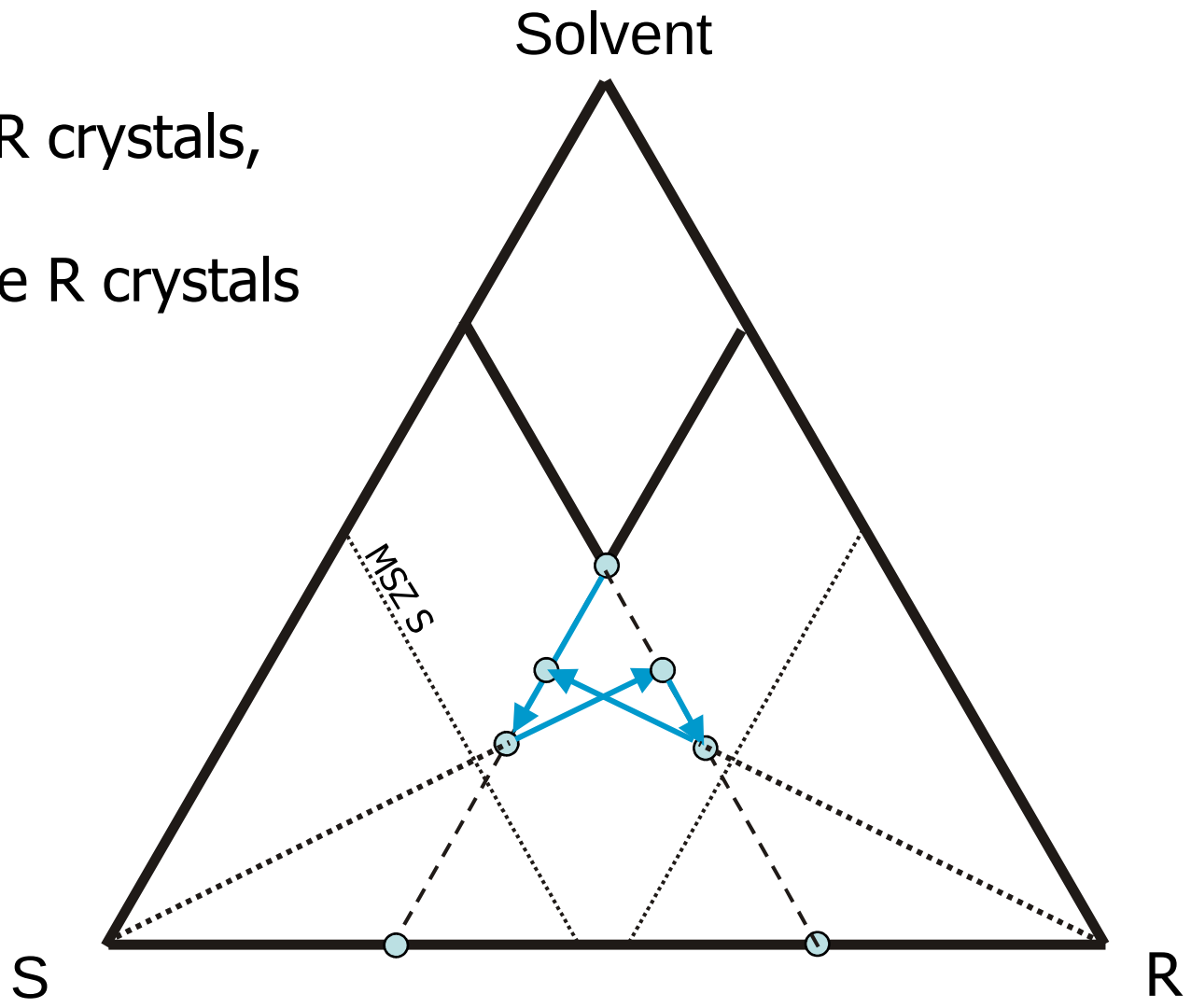
Only S crystals dissolve



1. Preferential crystallization - principle

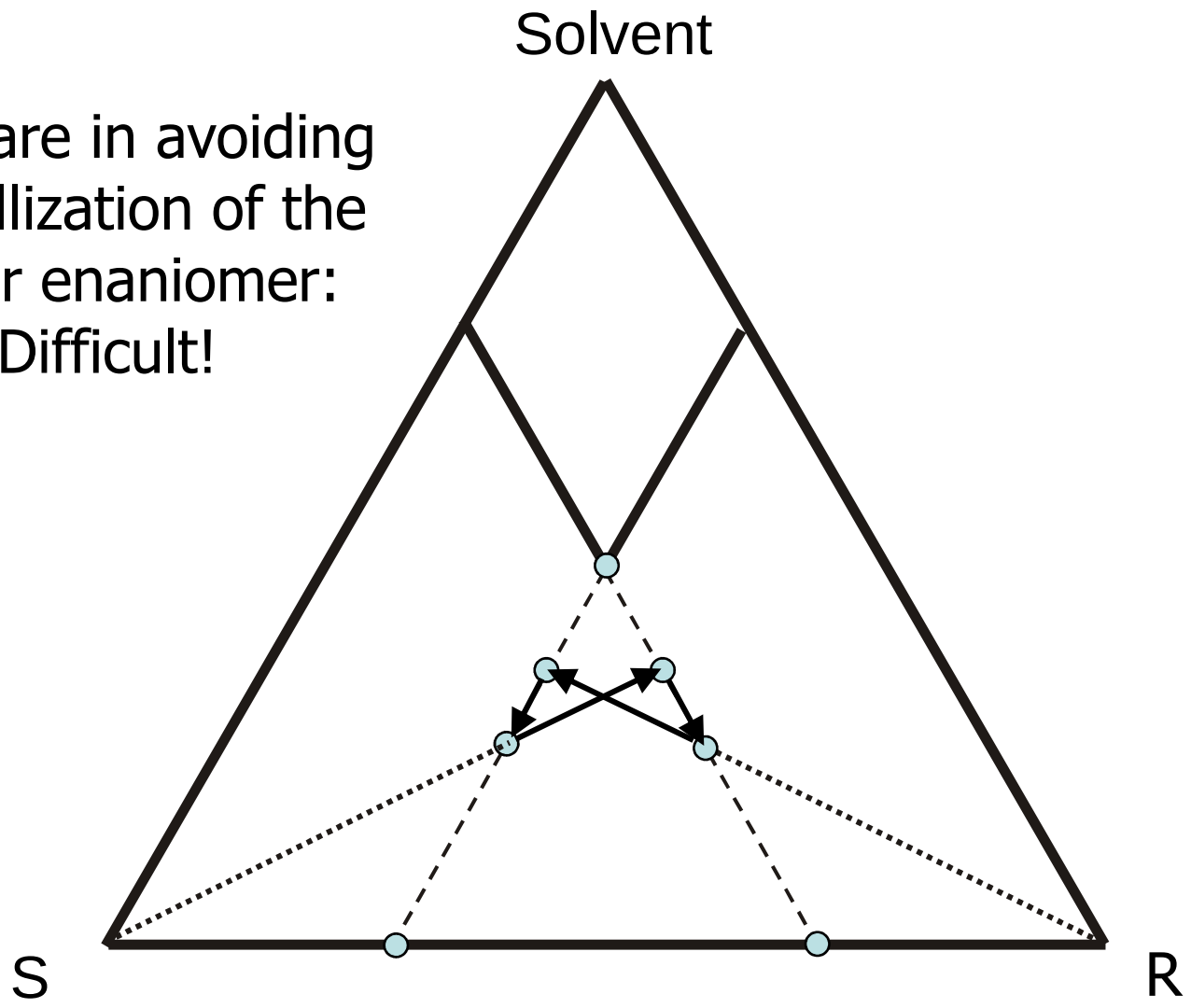
Grow R crystals,

Remove R crystals



1. Preferential crystallization - principle

Take care in avoiding Crystallization of the Other enaniomer: Difficult!



2. Resolution of racemic crystal systems.

A single-enantiomer *resolving agent* can be used to form a pair of products in a *diastereomeric* relationship.

Example: racemic acid **(±)-A^-H^+** and resolving base **(+)-B**:

(±)-A^-H^+ + (+)-B → [(+)-A^-.(+)-BH^+] + [(-)-A^-.(+)-BH^+]

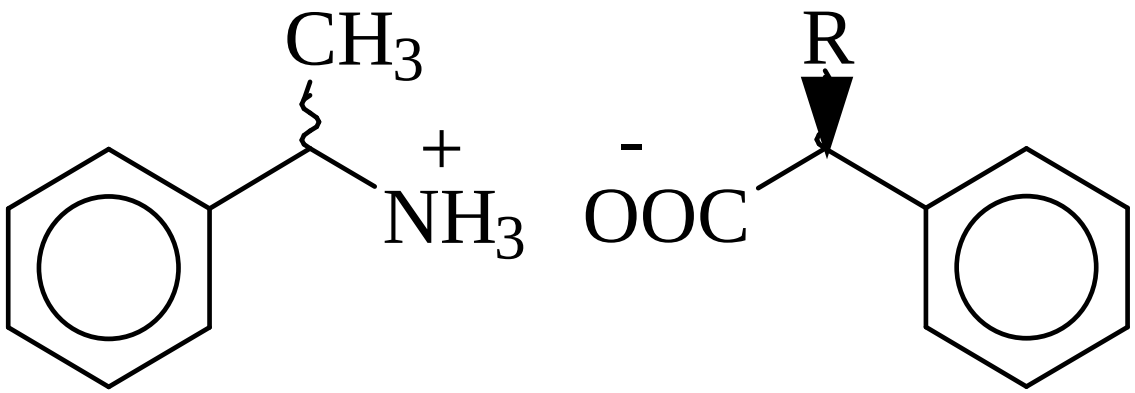
'p'-salt 'n'-salt

Compounds in diastereomeric relationships often exhibit significantly different physical properties, unlike enantiomer pairs.

Selection of resolving agent is a *trial-and-error* exercise.

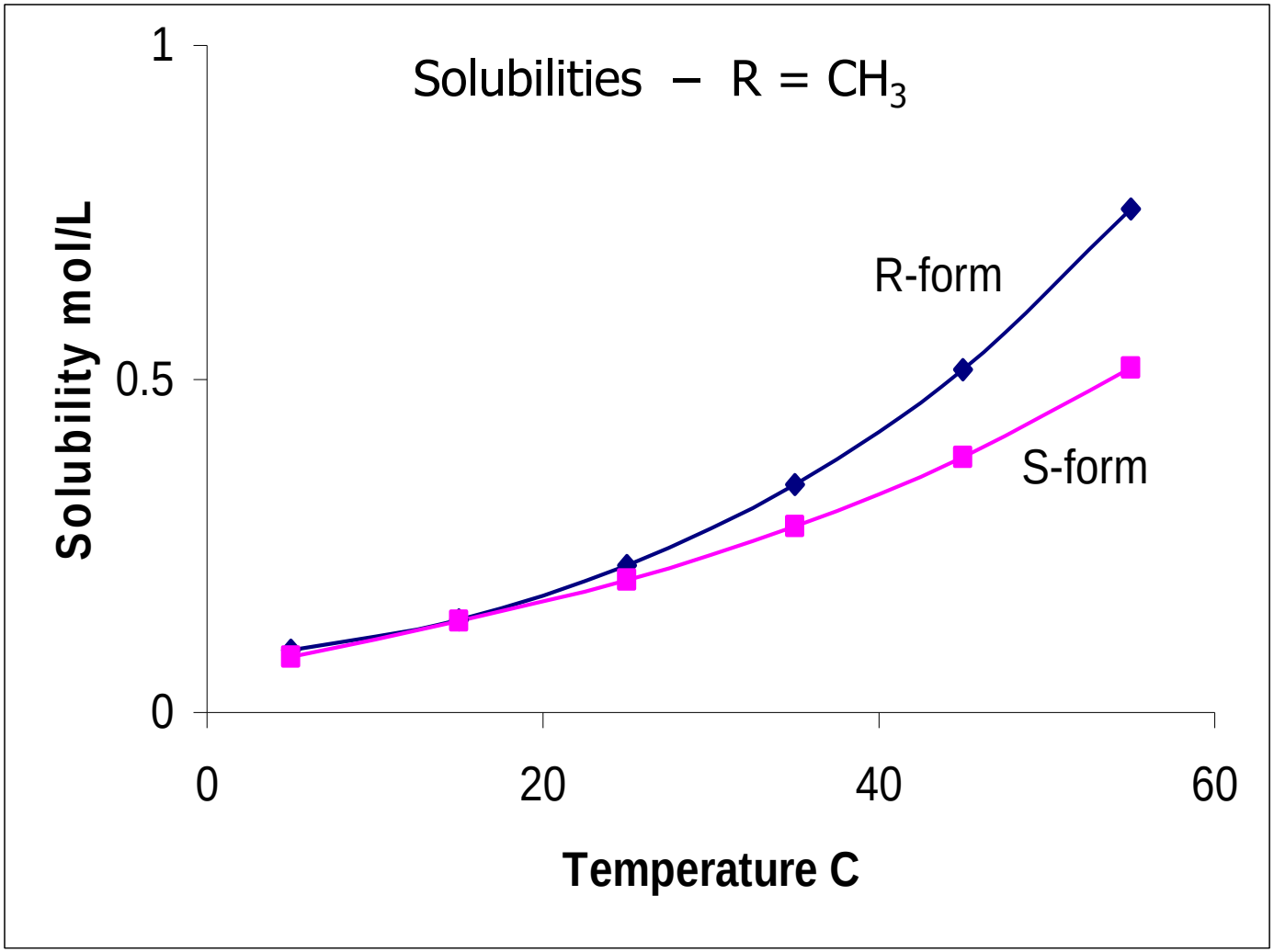
2. Resolution of racemic crystal systems.

Model system

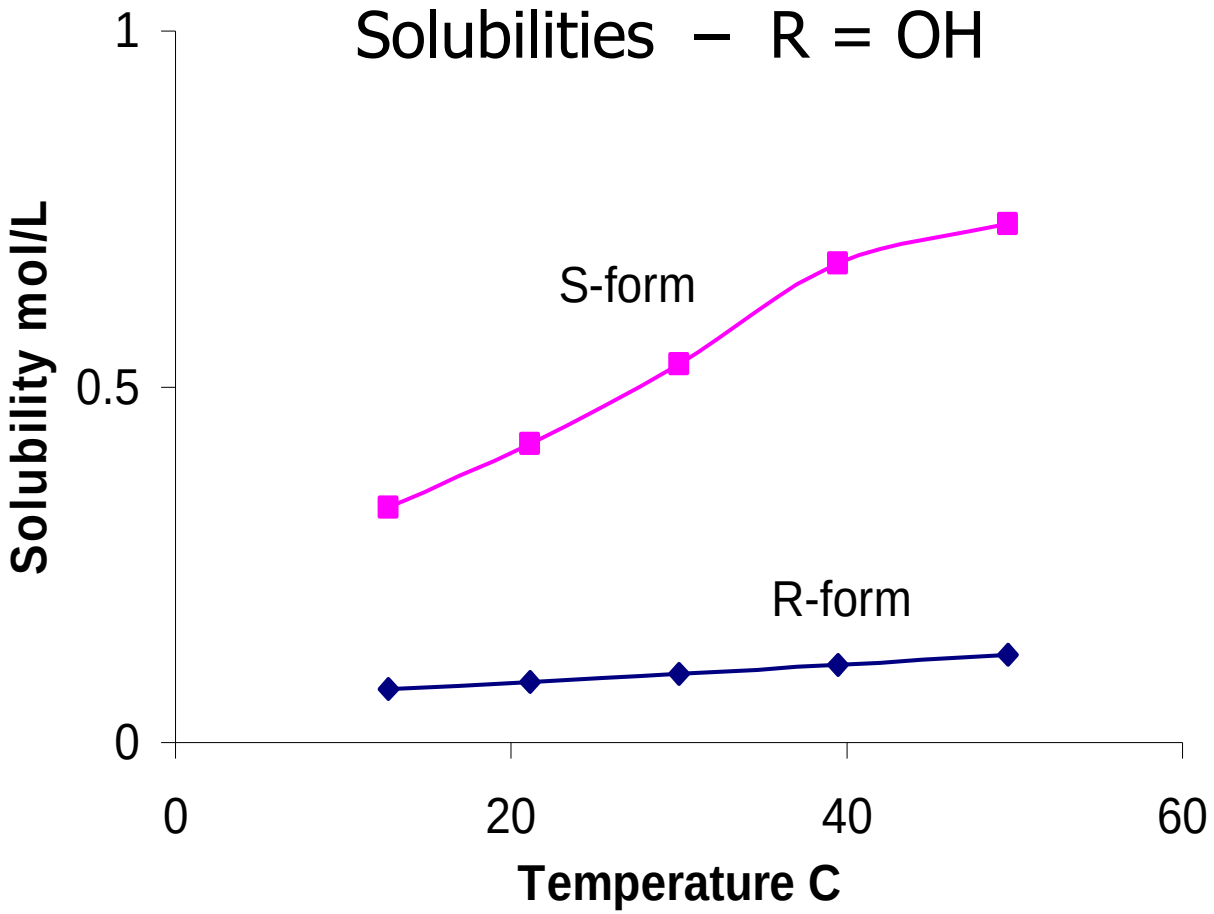


R = CH_3, C_2H_5, OH

2. Resolution of racemic crystal systems

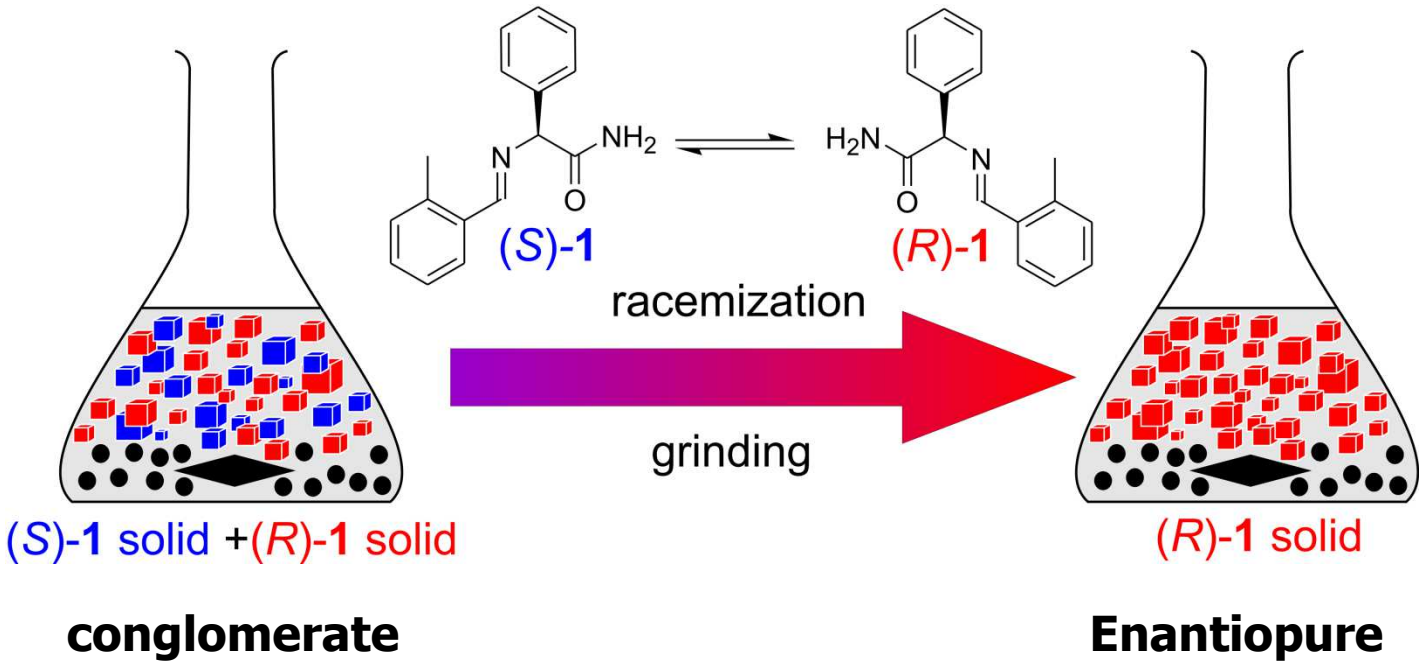


2. Resolution of racemic crystal systems



3. The grinding method

Combining a racemization reaction and suspension grinding



W.L. Noorduin et al., *J. Am. Chem. Soc.* 130 (2008) 1158.

Chiral separation

- A conglomerate system can be separated using preferential crystallization

- A racemic compound can be separated by finding a suited resolving agent forming diastereomeric salts
- This pair of products can have distinct physical properties such as solubilities exploitable for chiral separation through crystallization

- The newly proposed grinding method combines a racemization reaction and grinding