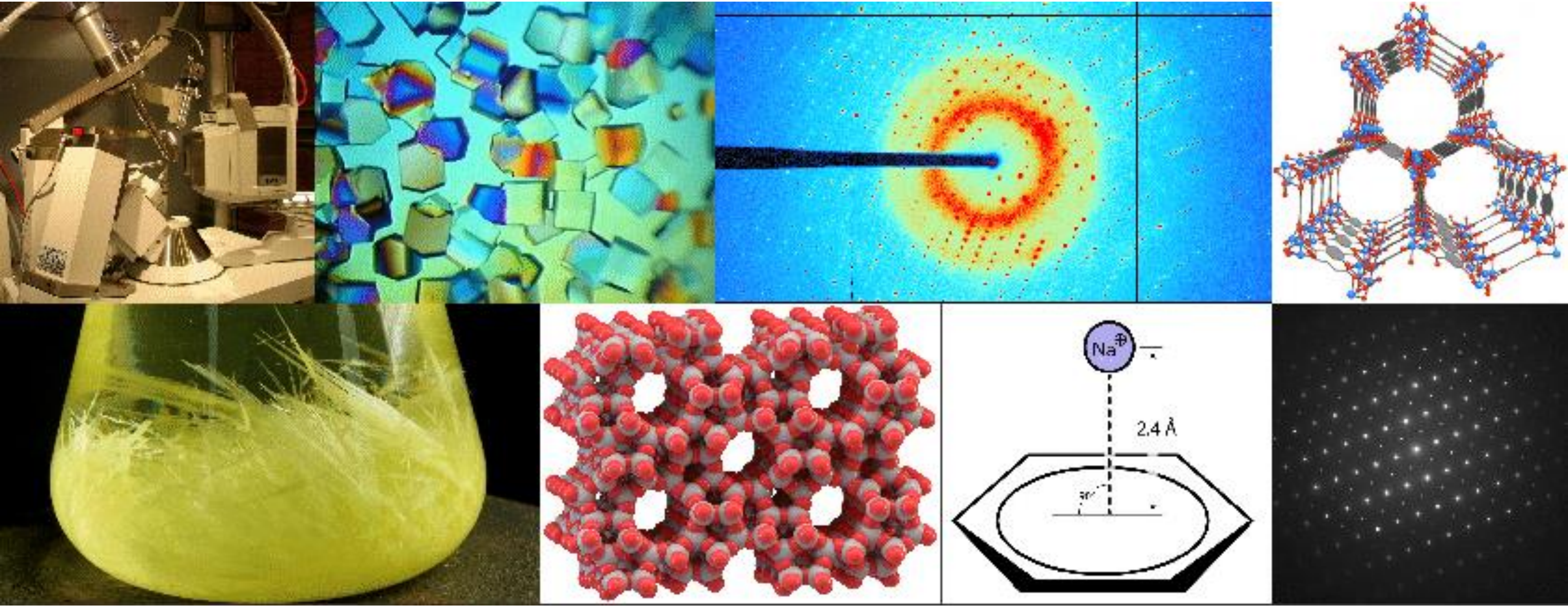
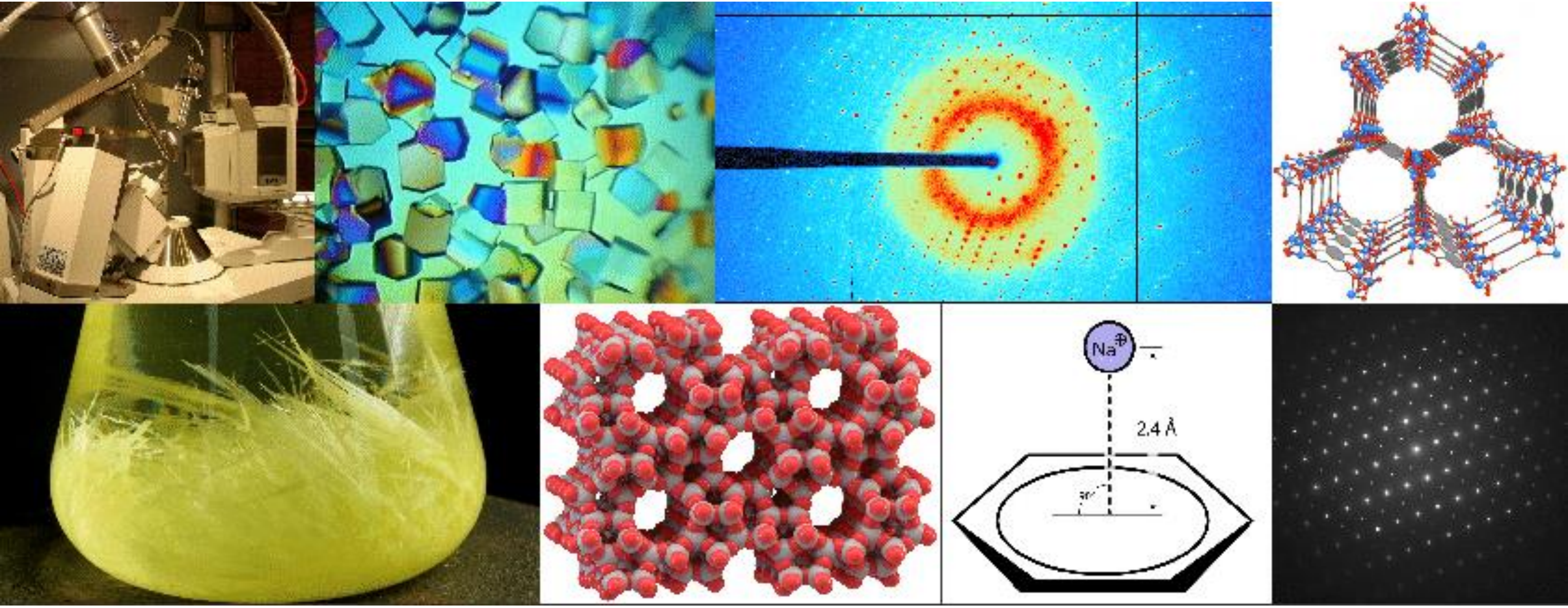


Programa de Actualización| ANUAL| 2018

CARACTERIZACIÓN ESTRUCTURAL Y ANÁLISIS DE PROPIEDADES DE SÓLIDOS CRISTALINOS: POLIMORFOS, SOLVATOS, COCRISTALES Y SALES

Florencia Di Salvo | Sebastián Suárez

Departamento de Química Inorgánica, Analítica y Química Física, FCEN, UBA



Programa de Actualización| Marzo - Abril| 2018

Módulo 1: Estructura molecular. Tipos de sólidos. Interacciones intermoleculares. Redes cristalinas, elementos y operaciones de simetría en sólidos cristalinos.

Florencia Di Salvo | Sebastián Suárez

Departamento de Química Inorgánica, Analítica y Química Física, FCEN, UBA

■ MOTIVATION

- **To understand the concepts related to the process of crystallization and crystal growth and its practical application.**
- **To learn about crystallization strategies for obtaining crystalline material, especially single crystals.**

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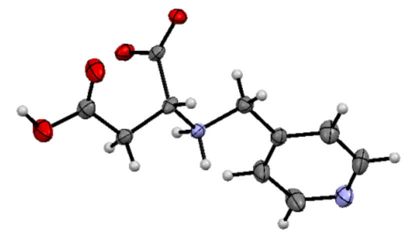
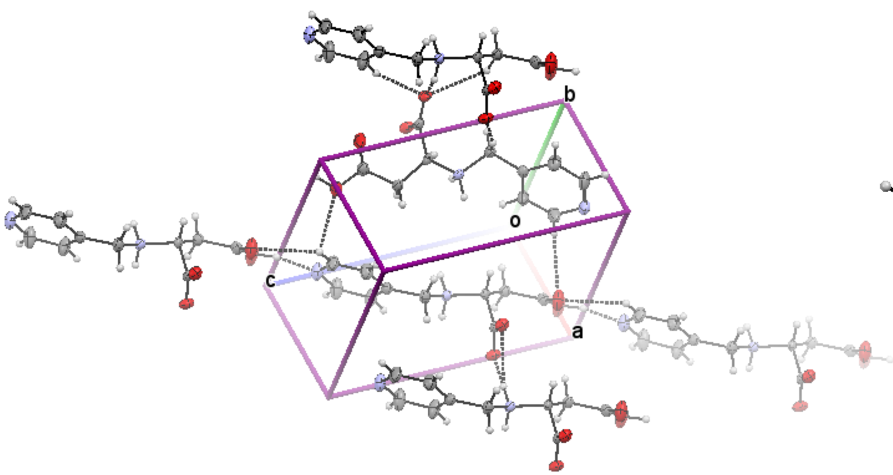
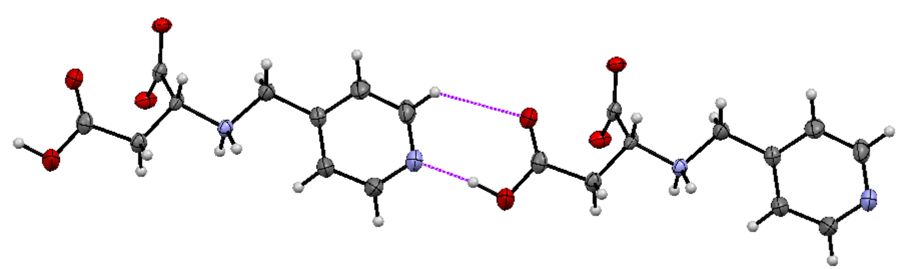
Single-crystal X-ray Diffraction is a methodology which provides detailed information about the internal lattice of crystalline substances, including unit cell dimensions, bond-lengths, bond-angles, and details of site-ordering and connectivity of the atoms thus, it gives the possibility to know unequivocally the molecular and supramolecular structure of our molecule.







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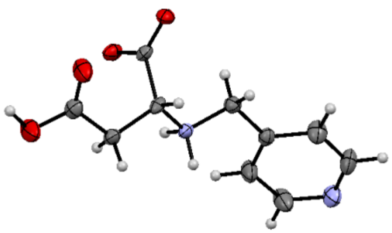
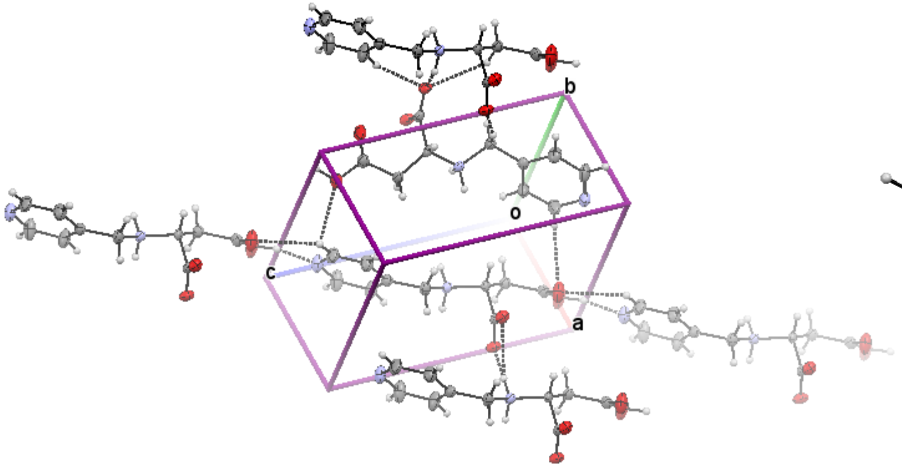
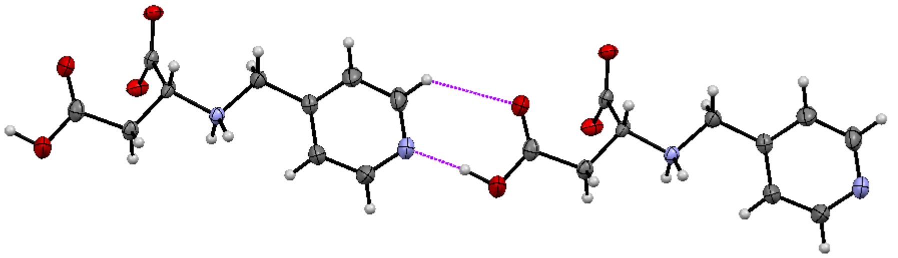


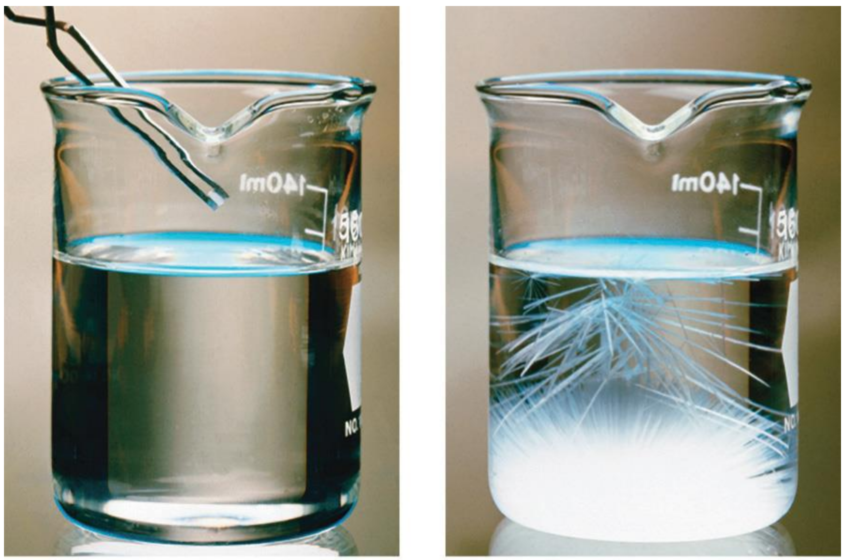




So, far it is the technique that gives you the "PICTURE" of your molecule

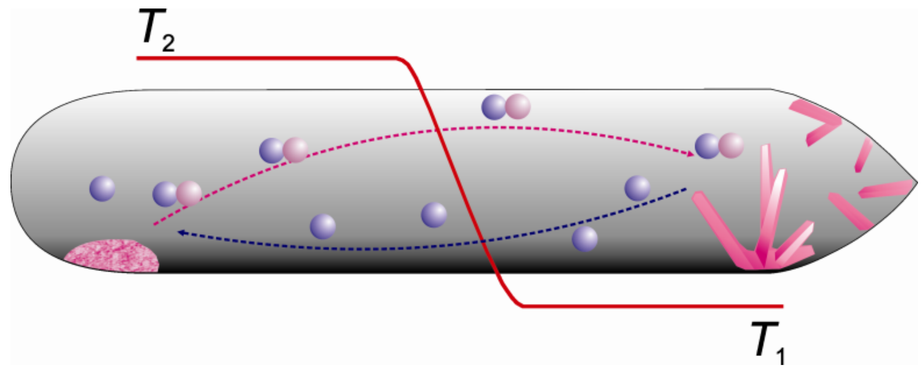
How can we get a crystal?

FROM SOLUTION

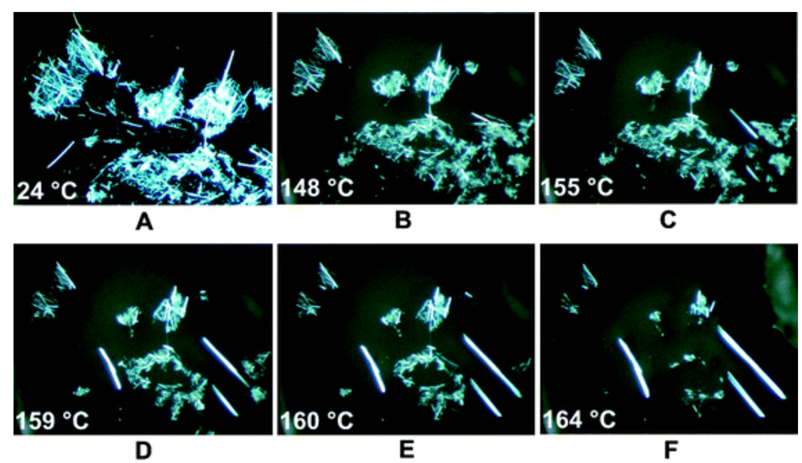


(a) (b)

FROM VAPOR



FROM MELT

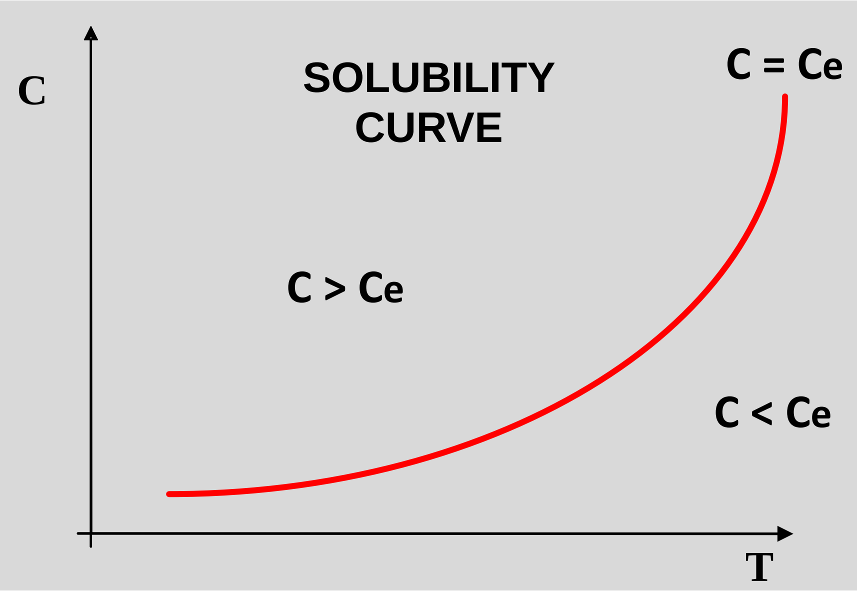


■ SOME BASIC DEFINITIONS

SOLUTION. Homogeneous liquid phase containing the solute dissolved in the solvent

SOLUBILITY. It is the property of a solid, liquid, or gaseous substance called solute, to dissolve in a solid, liquid, or gaseous solvent. The solubility depends on the physical and chemical properties of the solute and solvent as well as, on temperature, pressure and the pH of the solution.

SATURATION CONCENTRATION or EQUILIBRIUM CONCENTRATION (Ce).
The extent of the solubility of a substance in a specific solvent is measured as the saturation concentration, where adding more solute does not increase the concentration of the solution and begins to precipitate the excess amount of solute (maximum amount of solute that can be dissolved in certain solvent at a given T & p)



CONDITION FOR CRYSTAL GROWTH:

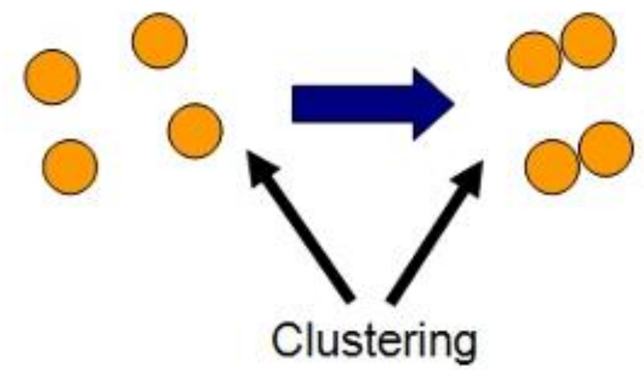
C > Ce => "SUPERSATURATION CONDITION"

CRYSTALLIZATION PROCESS

1. Supersaturation

2. Nucleation

3. Crystal Growth



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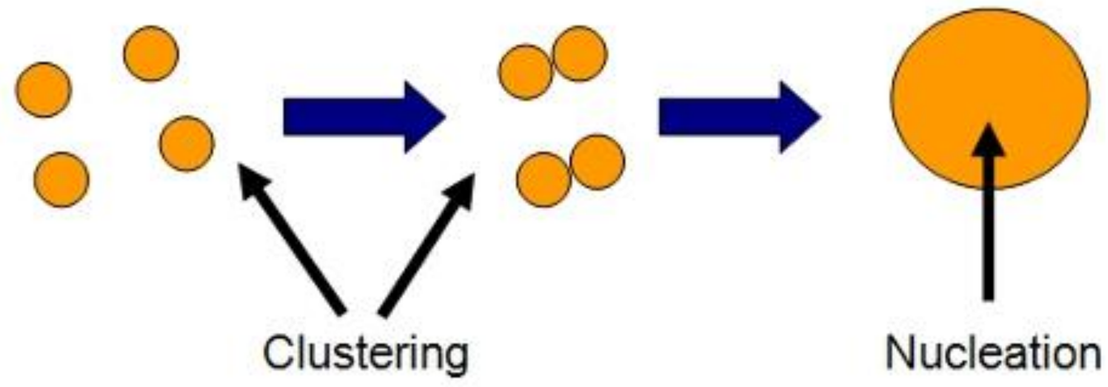


CRYSTALLIZATION PROCESS

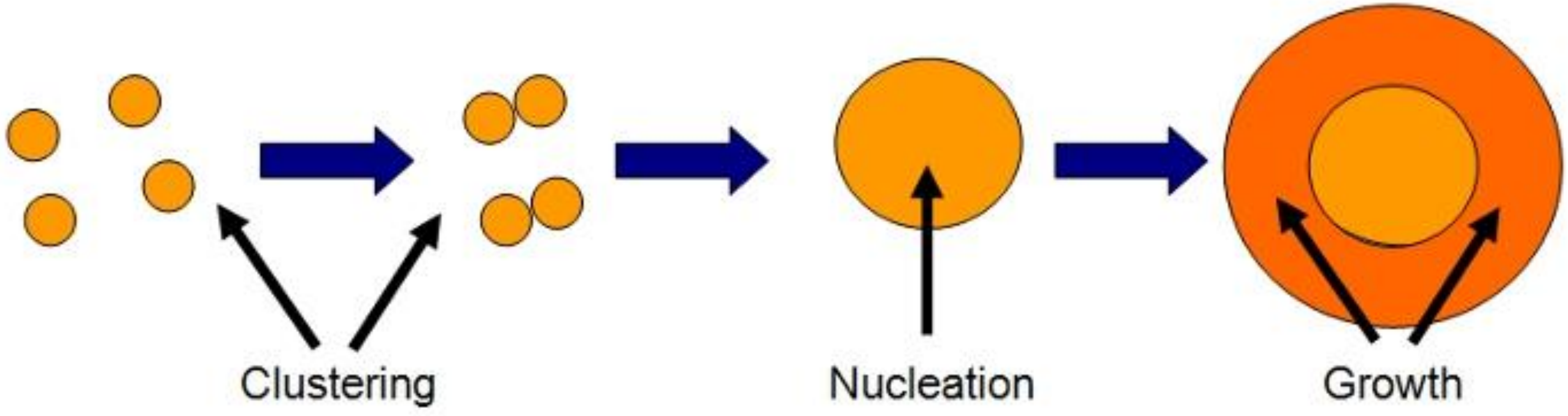
1. Supersaturation

2. Nucleation

3. Crystal Growth

SUMMARY

Supersaturation is critical because it is the driving force for crystal nucleation and growth.
Nucleation is the birth of new crystal nuclei.
Crystal growth is the increase in size of crystals as solute is deposited from solution.



CRYSTALLIZATION PROCESS

1. Supersaturation

Definition: **is a state of a solution that contains more of the dissolved material (solute) than could be dissolved by the solvent under normal circumstances.**

It is considered the "Driving Force" for Crystal Nucleation & Growth

⇒ **It is a very important variable**

⇒ **The quality of the crystals depends on the supersaturation**

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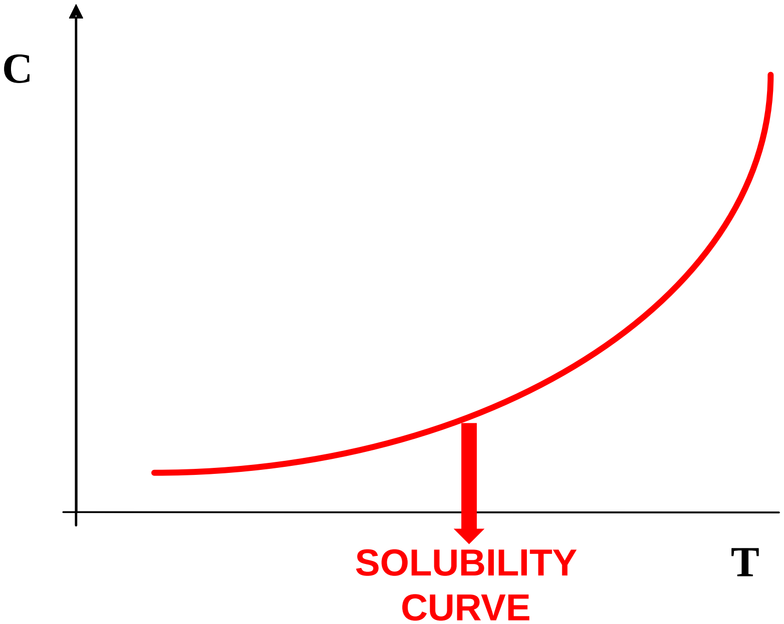

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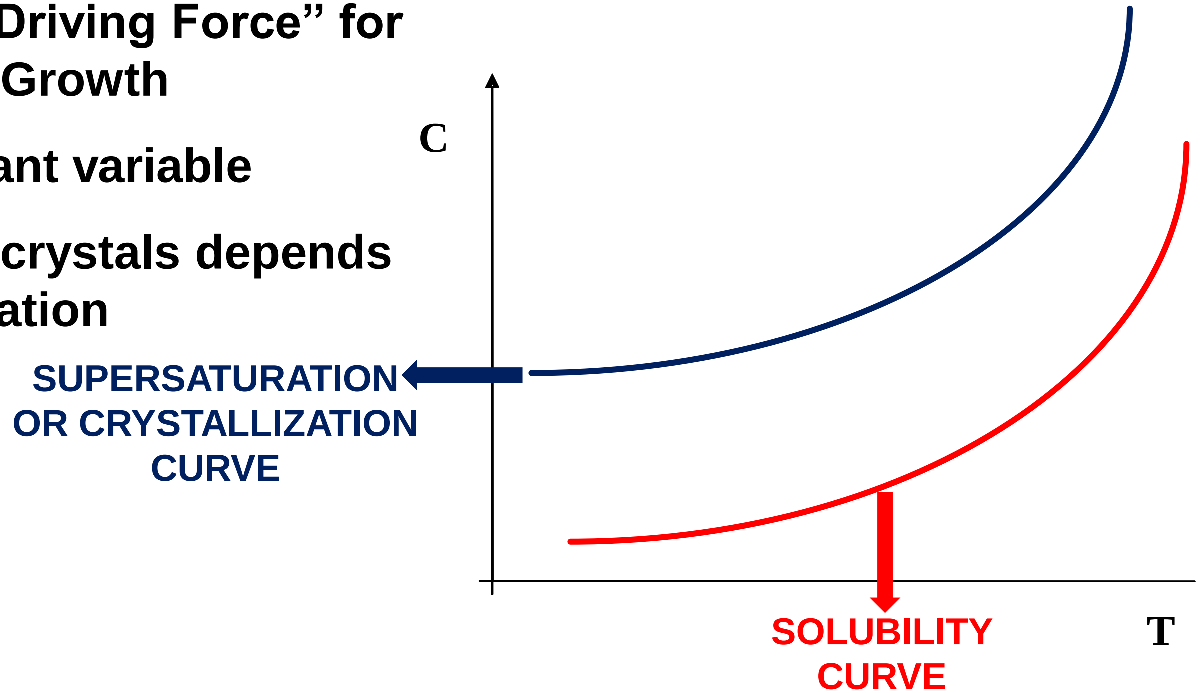

CRYSTALLIZATION PROCESS

GOAL: to obtain single crystals

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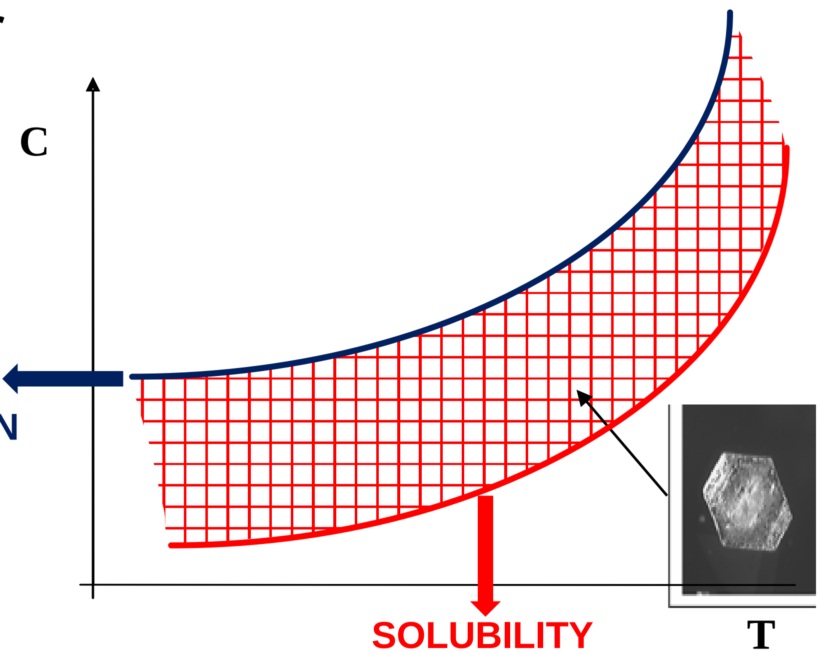

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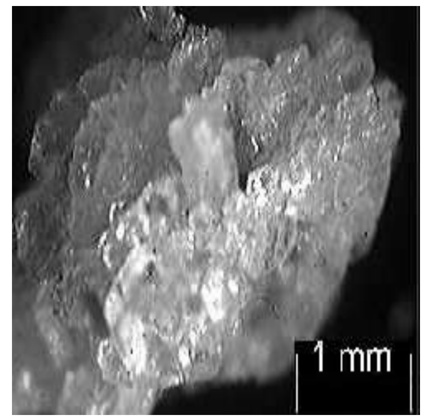
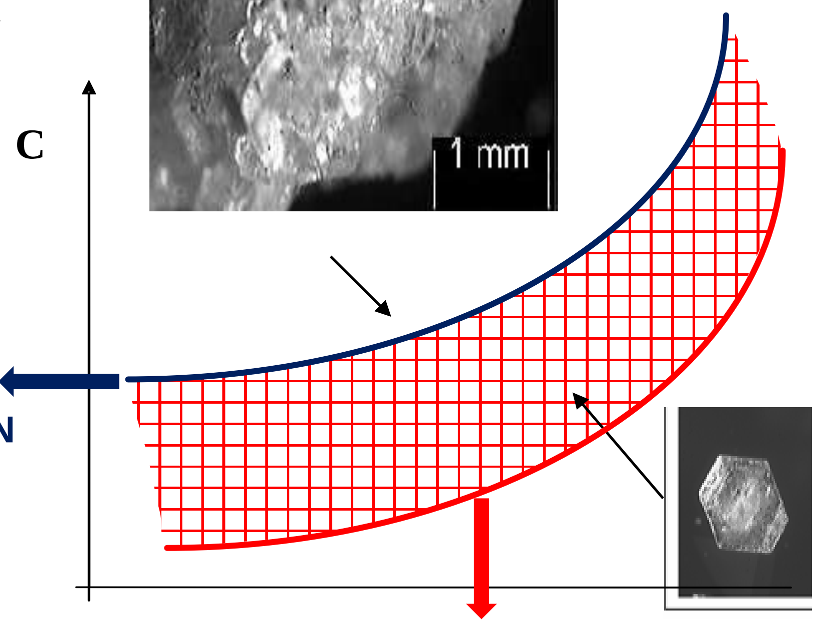
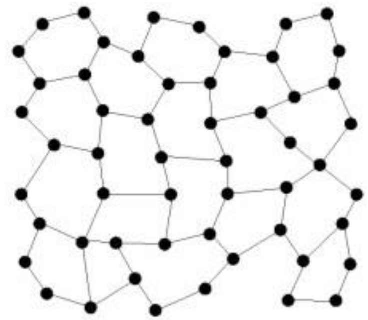


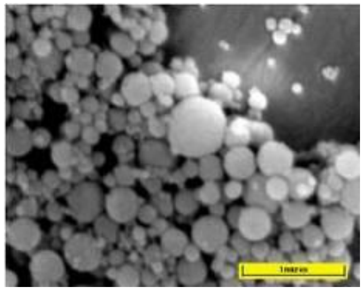
⇒ Avoid this area



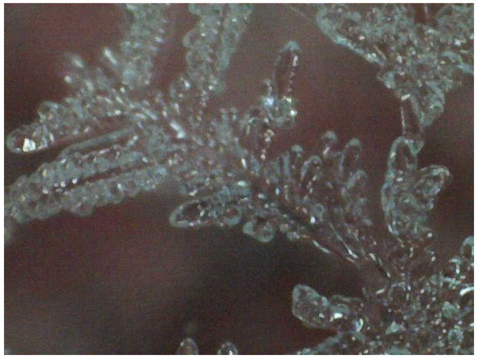
Effect of the degree of supersaturation on the crystal quality/form

- **Very high supersaturation**
  AMORPHOUS MATERIAL

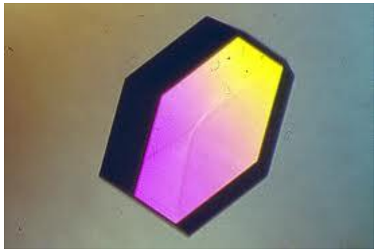




- **High supersaturation**
  DENDITRIC CRYSTALS
  Aggregates of small crystals



- **Low or intermediate supersaturation**
  SINGLE CRYSTALS



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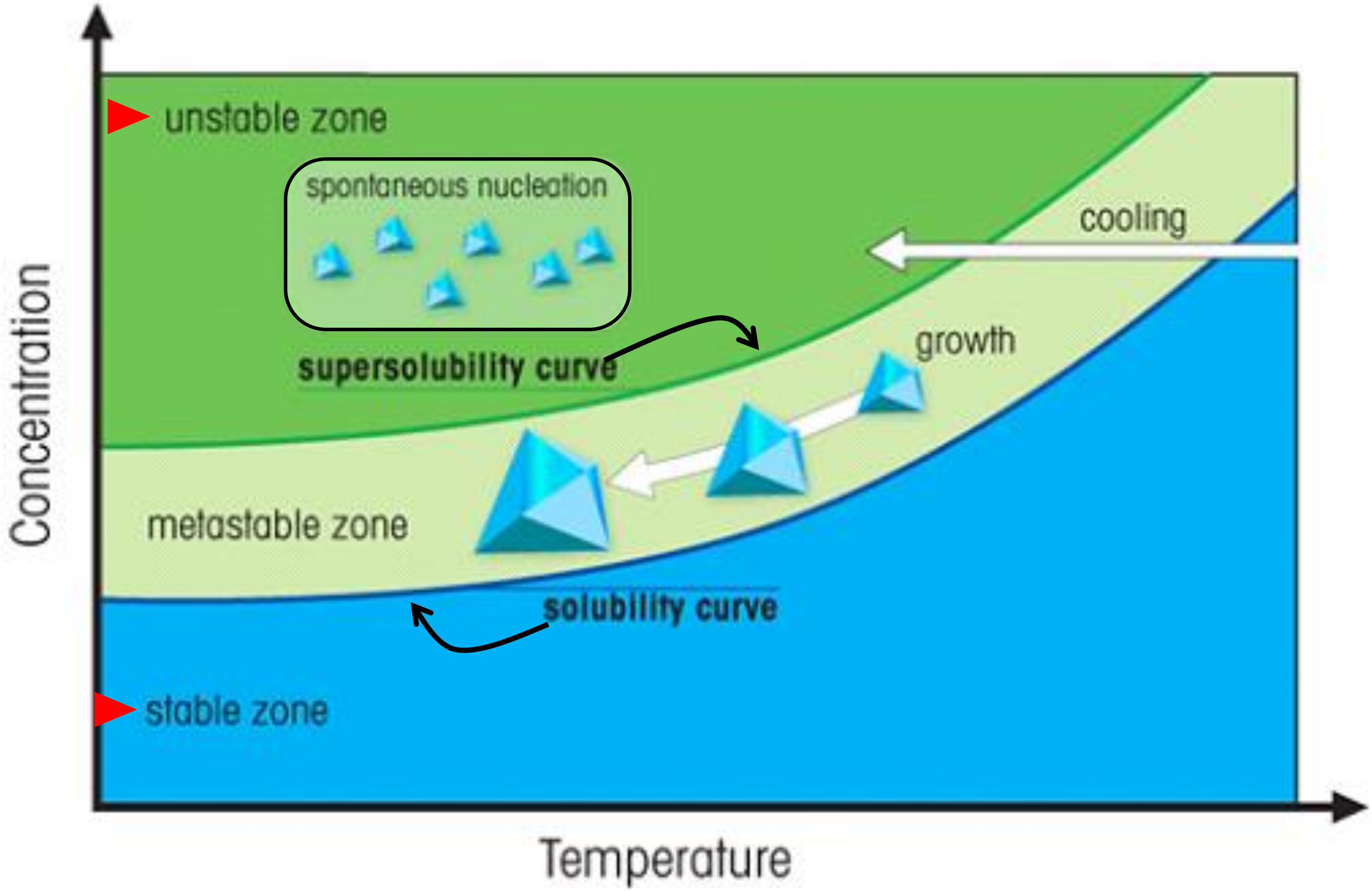
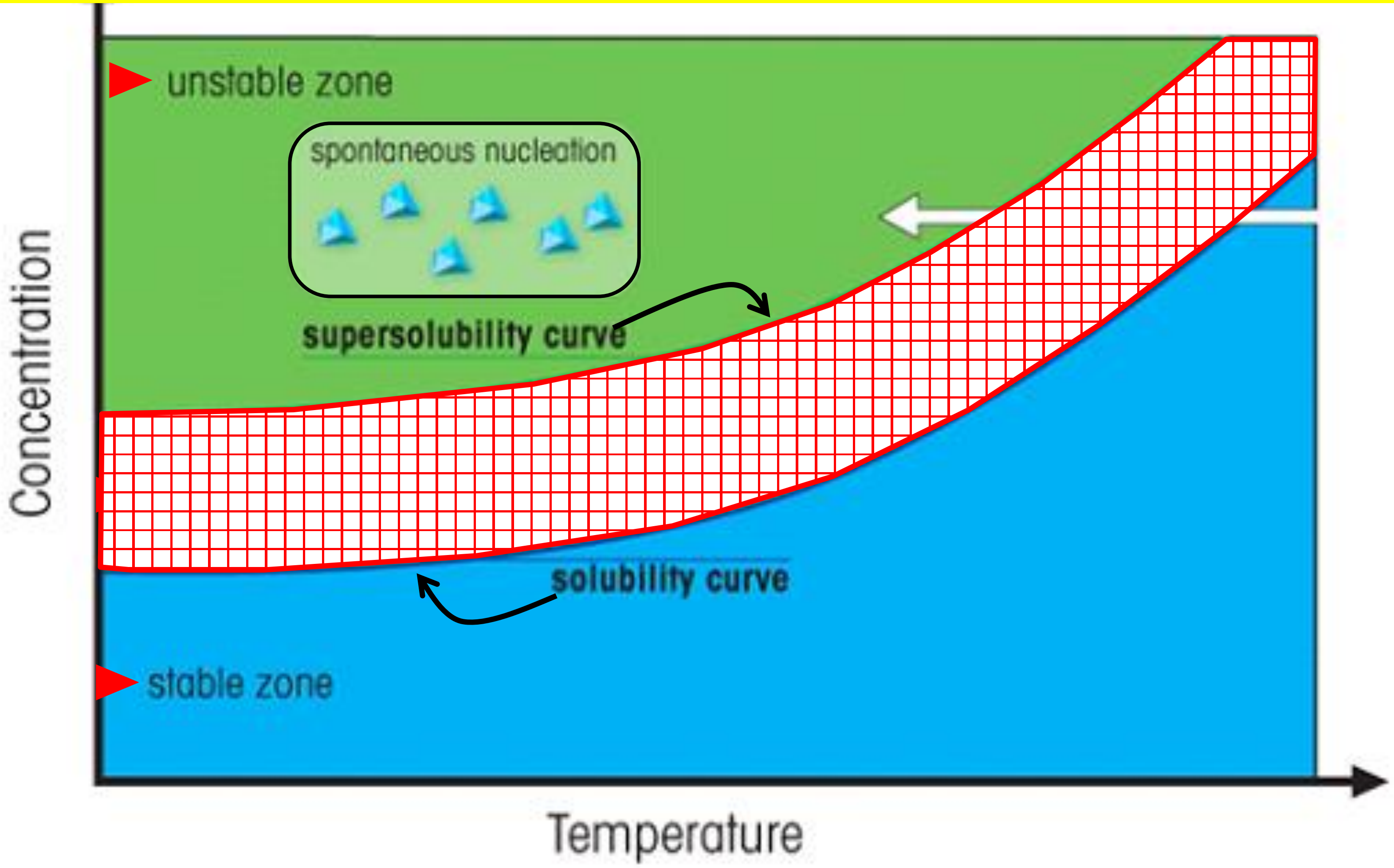


Effect of the degree of supersaturation on the crystal quality/form

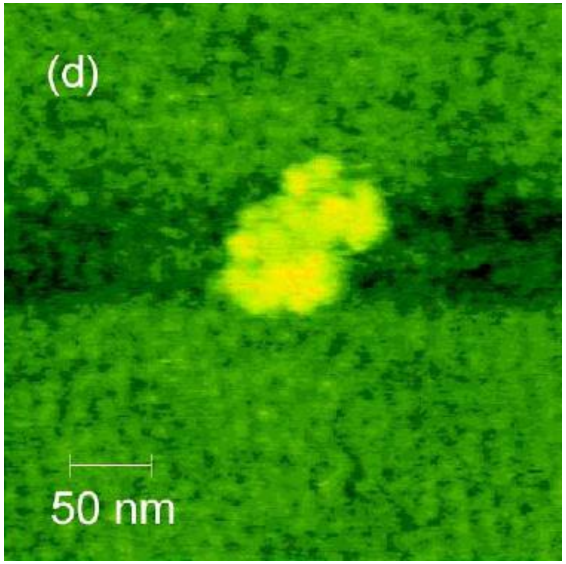
CONCLUSION: Stay in the area between the solubility curve and crystallization curve in order to get a **GOOD SINGLE CRYSTAL**



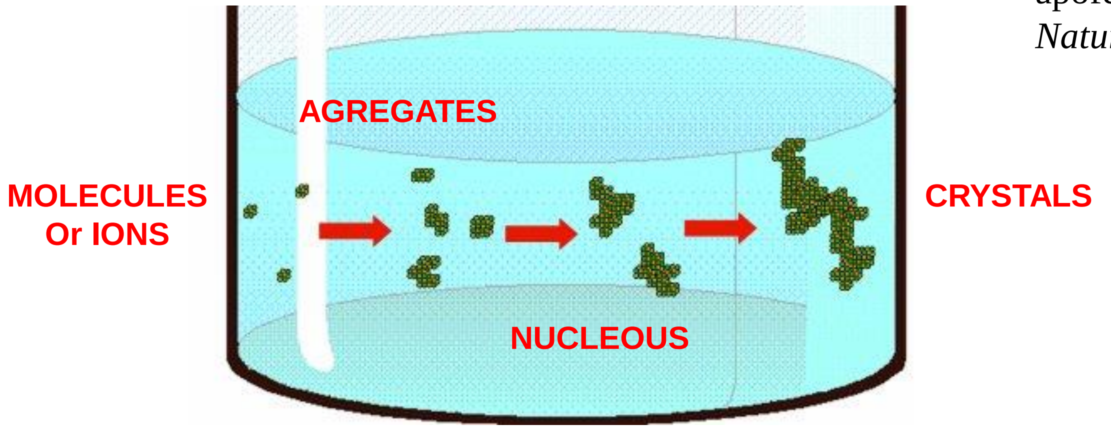
CRYSTALLIZATION PROCESS

2. Nucleation

Definition. Nucleation is the first step in the formation of either a new thermodynamic phase via self-assembly or self-organization. The previous phase is metastable, and thus nucleation is the initial step of this new stable phase. Nucleation is the then, the first step in the formation of a crystal.



Cluster of about 20 molecules of apoferrin (Yauand Vekilov, *Nature*, **2000**).



CRYSTALLIZATION PROCESS

2. Nucleation

PRIMARY

The nuclei is generated spontaneously from solution

HOMOGENEOUS

Spontaneous. It takes place in the absence of foreign particles or crystals

Relative higher supersaturation

HETEROGENEOUS

Induced. It takes place in the presence of foreign particles

Relative lower supersaturation

SECONDARY

The nuclei is generated in the presence of crystals of the same substance

CRYSTALLIZATION PROCESS

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The nuclei is generated spontaneously from solution

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Induced. It takes place in the presence of foreign particles

SECONDARY

The nuclei is generated in the presence of crystals of the same substance

VERY IMPORTANT FOR INDUSTRIAL CRYSTAL GROWTH (e.g. Pharmaceutical companies)

The addition of germs, surfaces, interfaces intentionally, etc. allows:

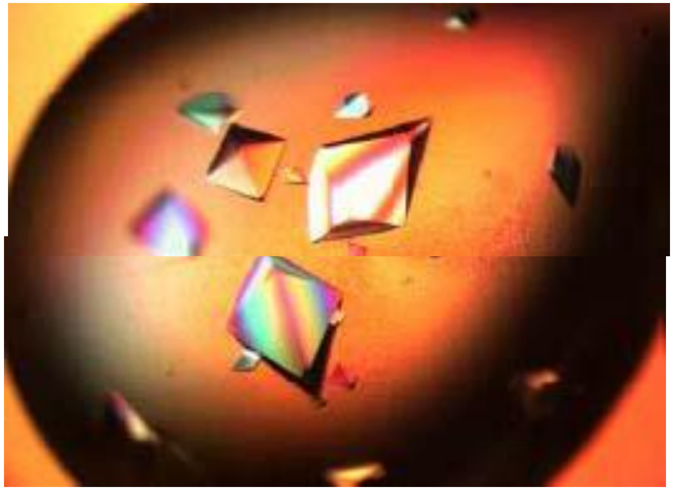
- The growth and isolation of a specific crystal form/phase
- Phase conversion control
- Avoid heterogeneous nucleation due to unknown contaminates, particles & impurities
- Larger crystals

CRYSTALLIZATION PROCESS

3. Crystal Growth

Definition. Crystal growth is the increase in size of crystals as solute is deposited from solution.

It depends on the interaction between the solute and solvent and other factors related with the processes developed in the "growing crystal".



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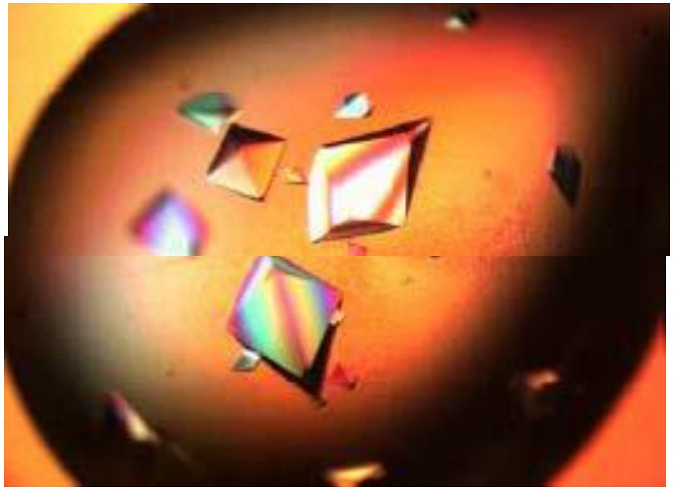
It depends on the interaction between the solute and solvent and other factors related with the processes developed in the "growing crystal".

GOAL: to obtain single crystals

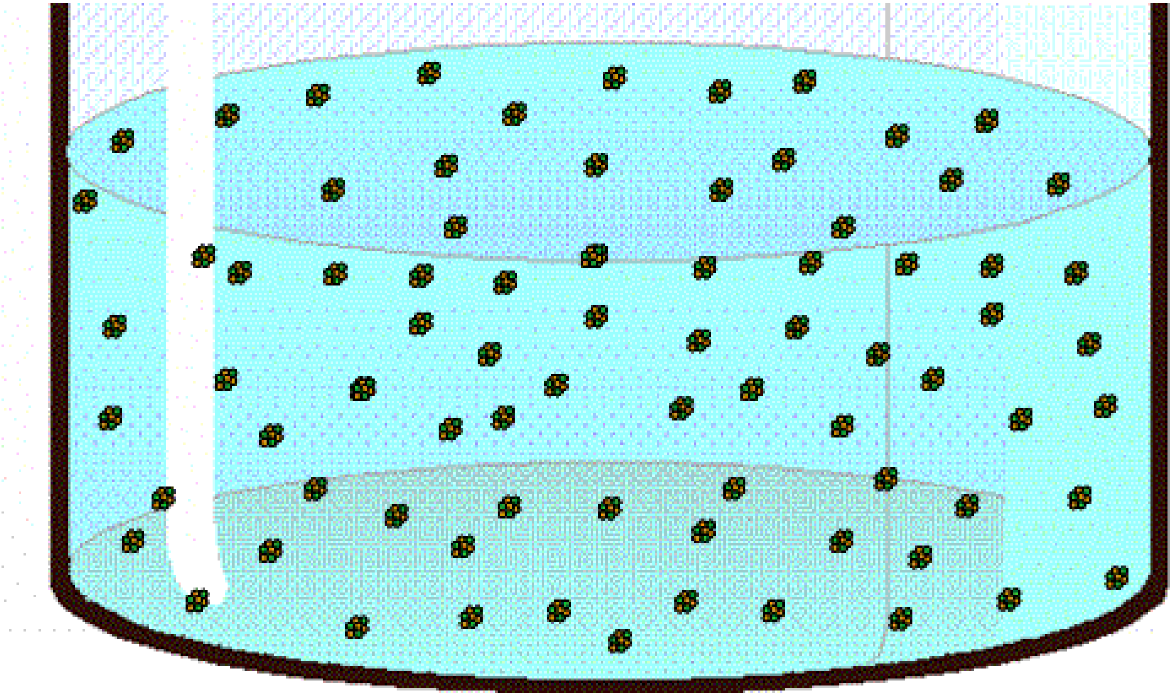
So, take in mind the idea of a ordered crystal with certain periodicity to analyze the steps related with the crystal growth



CRYSTALLIZATION PROCESS

3. Crystal Growth

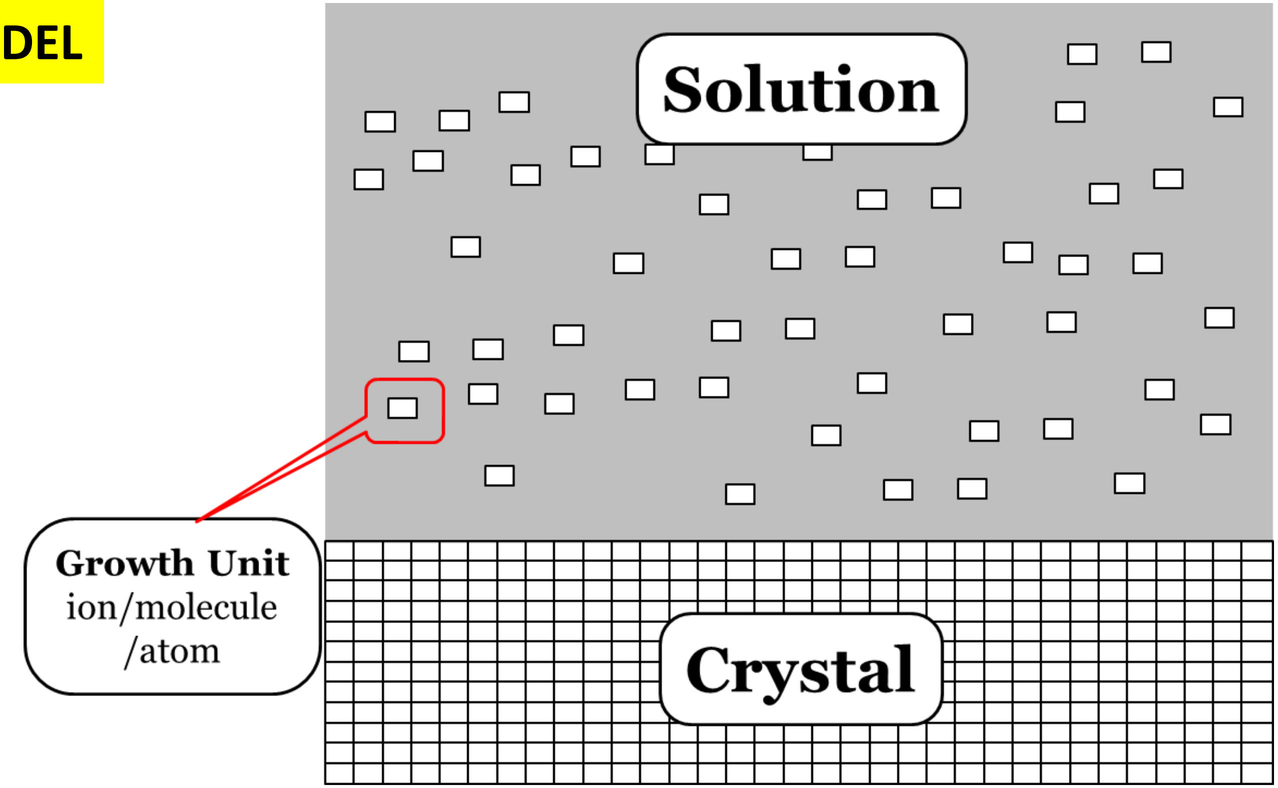
(Animación)



CRYSTALLIZATION PROCESS

3. Crystal Growth: *How does the crystal growth?*

MODEL

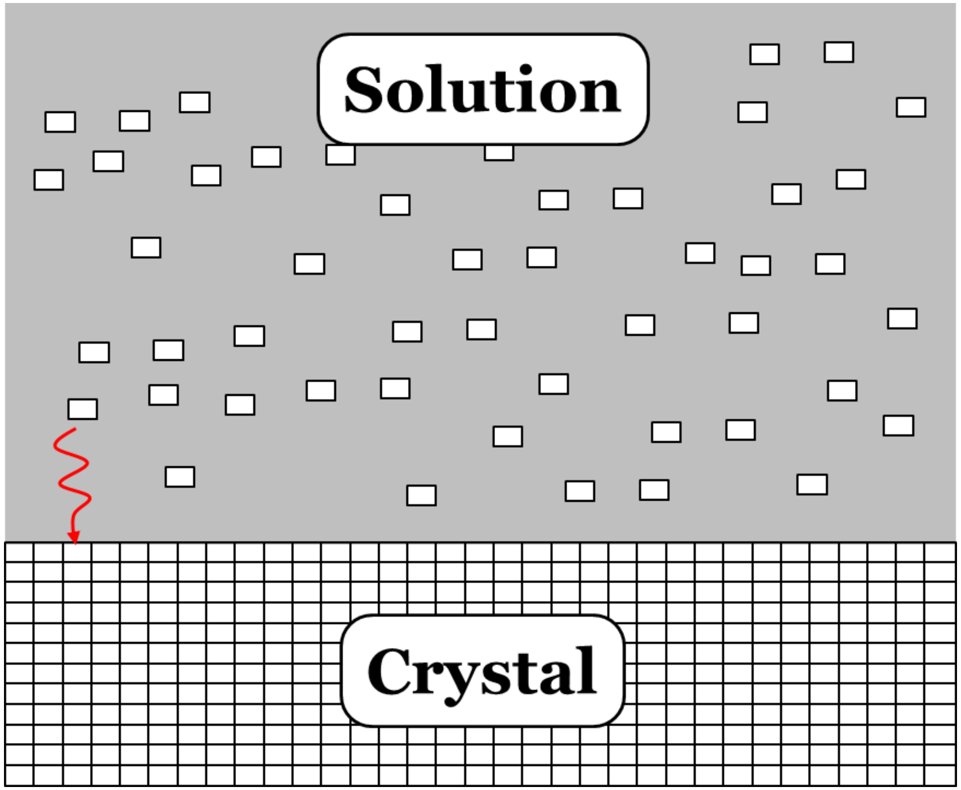


CRYSTALLIZATION PROCESS

3. Crystal Growth: *How does the crystal growth?*

MODEL

Process that involves several steps that can be reduced to two main ones:

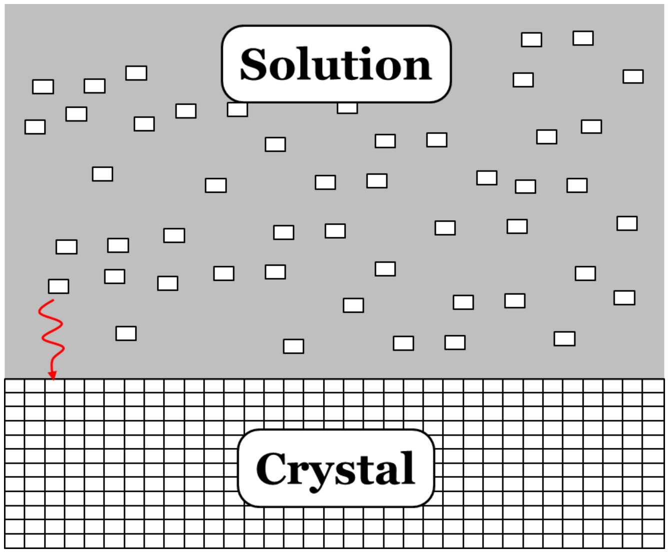


1. The transport of growth units from the bulk solution towards the crystal face;
2. The interactions taking place at the crystal interface until the growth units move themselves into a lattice position minimizing the reticular energy and contributing to forming a perfect crystal.

CRYSTALLIZATION PROCESS

3. Crystal Growth: *How does the crystal growth?*

MODEL

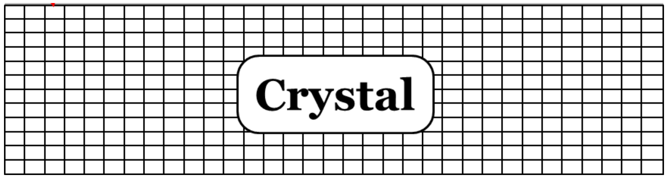


N : number of growth units

J : rate (number of growth units per unit time)

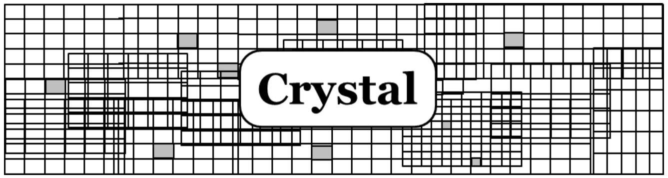
Possible scenarios

A) Small value for *J*



Perfectly ordered crystal (single crystal)

B) Higher value for *J*



Crystal with a clear degree of disorder (presence Vacancies, dislocations, and boundary grains will appear)

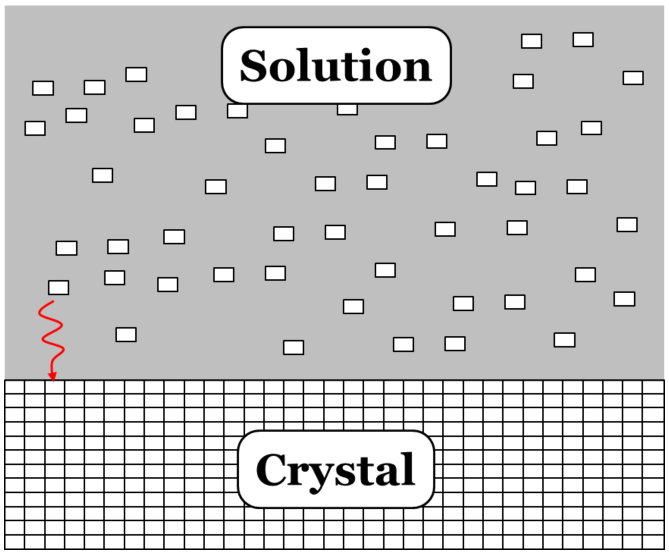
C) Very large value of *J*

Amorphous material

CRYSTALLIZATION PROCESS

3. Crystal Growth: *How does the crystal growth?*

MODEL



Comment

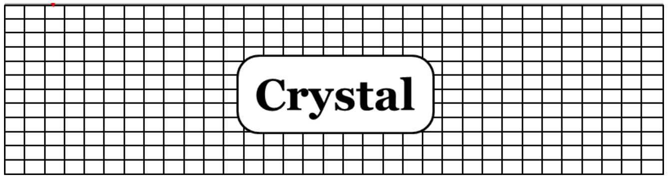
Material in **B)** might be divided into a number of regions, ***M***, made up of growth units that are perfectly arranged as regards the pattern, but slightly disoriented with respect to the neighboring regions. This number ***M*** is related to the term mosaicity and increases with ***J***

N : number of growth units

J : rate (number of growth units per unit time)

Possible scenarios

A) Small value for *J*



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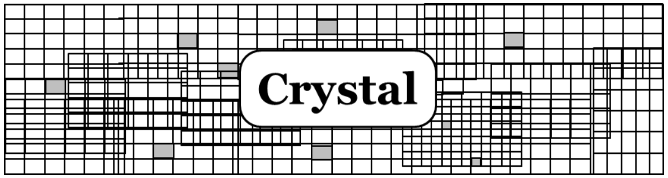

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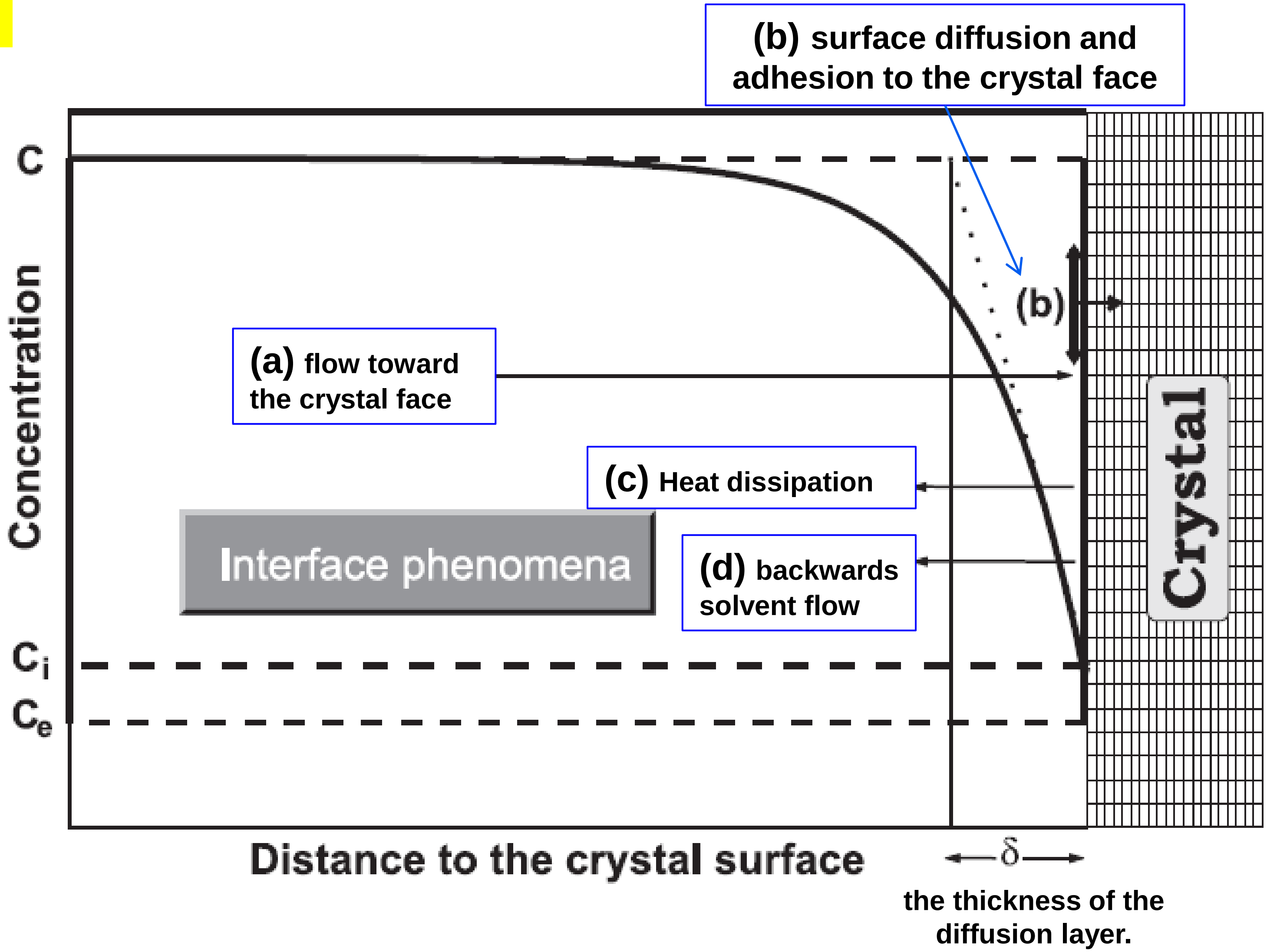
3. Crystal Growth

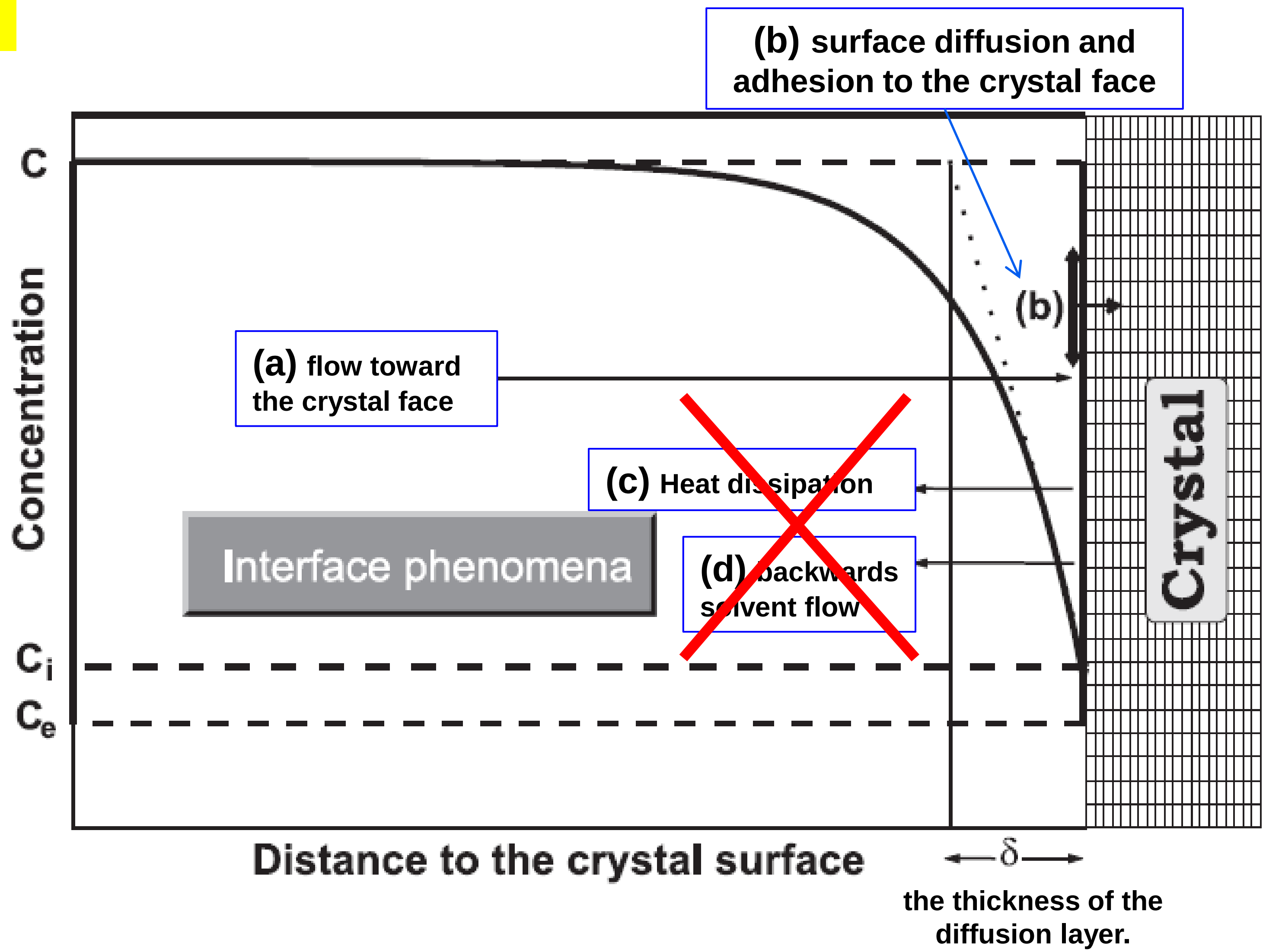
STEP 1



Juan Manuel García-Ruiz *J. Chem. Ed. 76*. **1999**, 499-501

3. Crystal Growth

STEP 1



Juan Manuel García-Ruiz *J. Chem. Ed. 76*. **1999**, 499-501

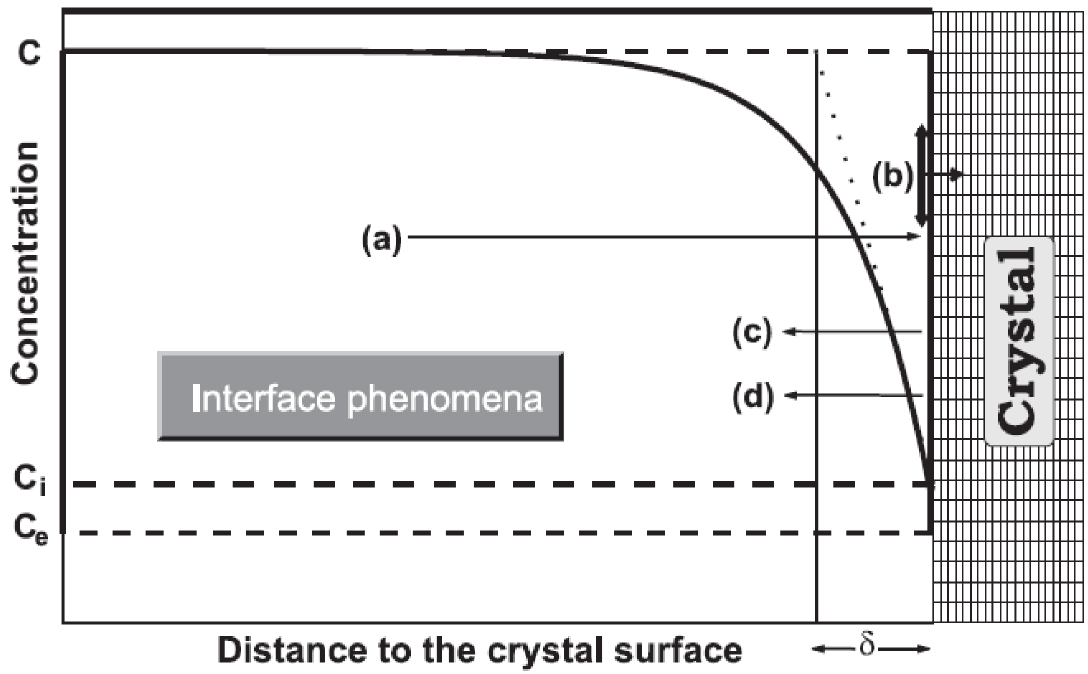
3. Crystal Growth

STEP 1

Analysis

- C = C at the bulk
- Volume of the crystal ↑
- C at the neighboring ↓(= C_i)
- => a C difference is formed ($\Delta C = C - C_i$) and thus, a C gradient ($\Delta C/\Delta x$)
- Flow of the particles follows Fick's first law of diffusion:

$$J_D = -D\frac{\Delta C}{\Delta x}$$



D = diffusion constant (for small molecules ~ 10^{-5} cm^{2}s^{-1}, macromolecules ~ 10^{-7} cm^{2}s^{-1})

J_D = flow of the particules ("rate")

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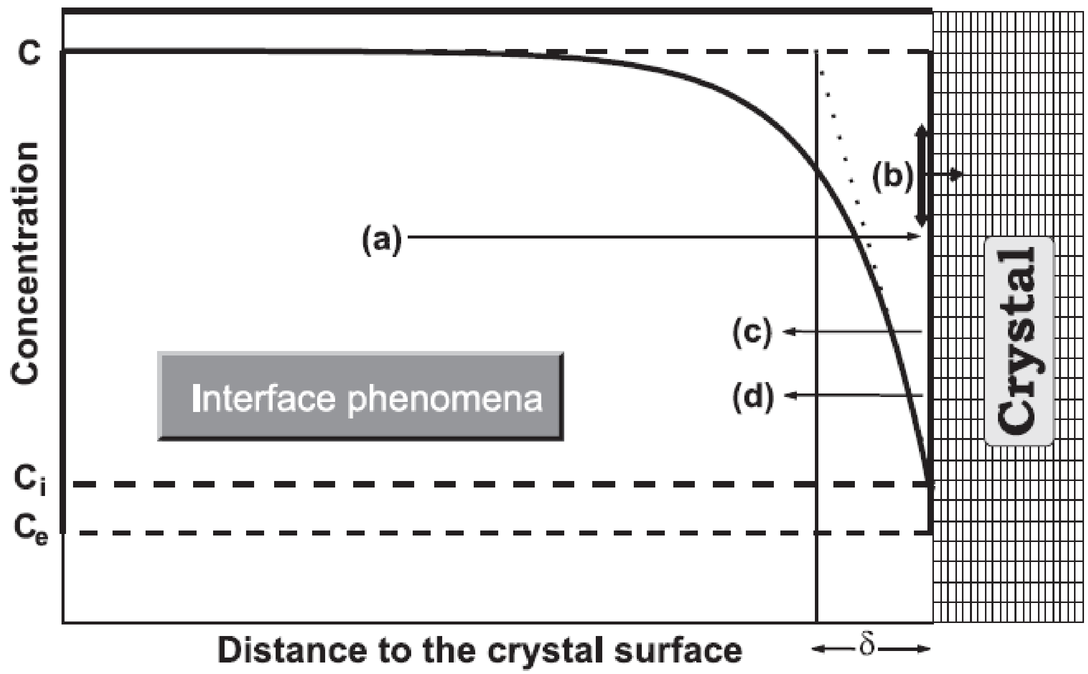


OBJECTIVE: J small enough to have good crystals

⇒ To ensure that diffusion takes control of the mass transport, other mechanisms such as, convection must be prevented

⇒ **IN THE LAB:** porous media, high viscosity fluids, thin capillary volumes, low gravity, crystal growth in gels…(We will see crystal growing methods in a few slides)

3. Crystal Growth

STEP 1

Analysis

- Flow of the particles follows Fick's first law of diffusion:

$$J_D = -D\frac{\Delta C}{\Delta x}$$

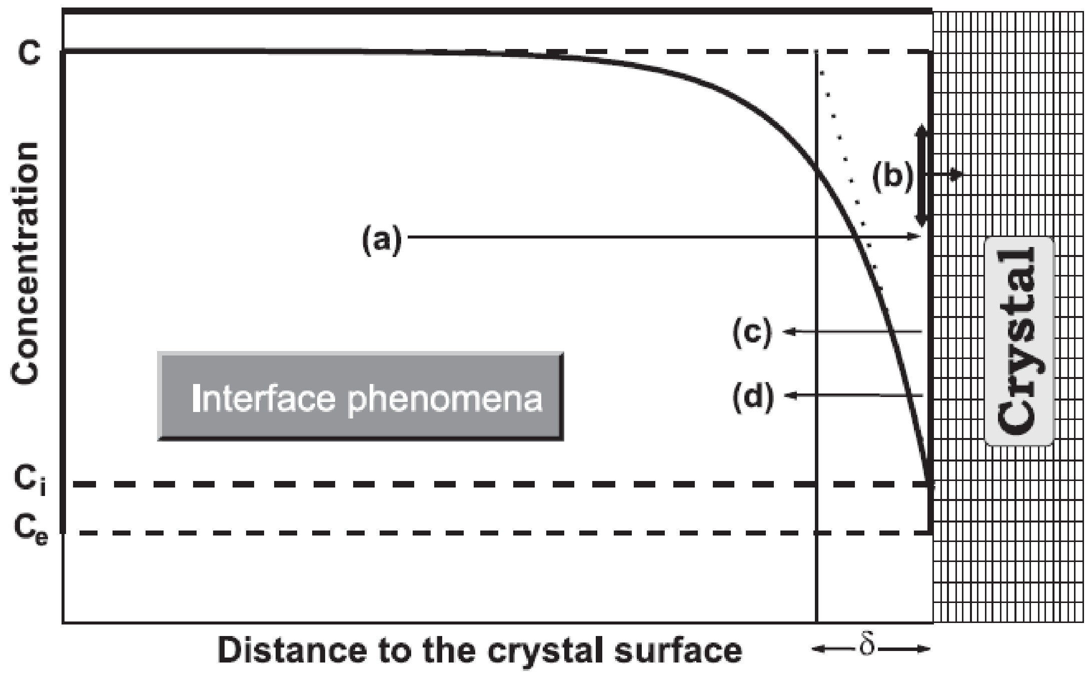
D = diffusion constant

J_D = flow of the particules ("rate")

- Approximation of the mass transfer rate dm/dt form the bulk (at C_i) to the crystal surface (at C_i):

$$\frac{dm}{dt} = k_D(C - C_i)^d$$

$k_D = D/\delta$ d = kinetic order



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3. Crystal Growth

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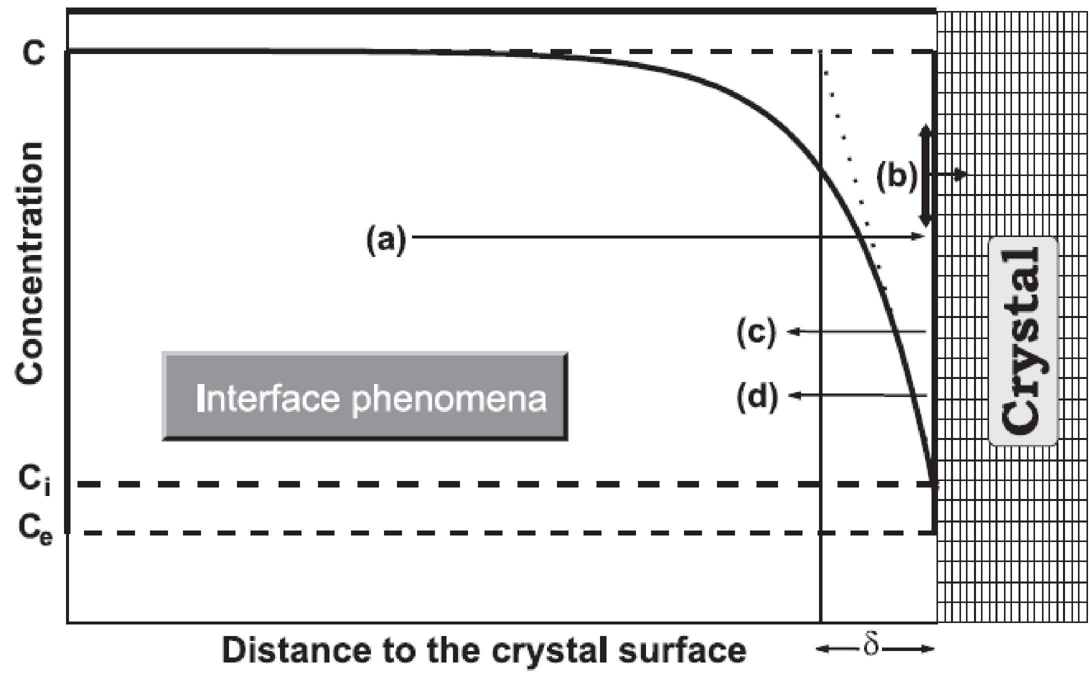


QUESTIONS

how slow should the mass transfer be in order to grow a perfect crystal?

What happen when the growth units arrives the surface?

Does the crystal growth depends on the growth unit identity?

Juan Manuel García-Ruiz *J. Chem. Ed. 76*. **1999**, 499-501

3. Crystal Growth

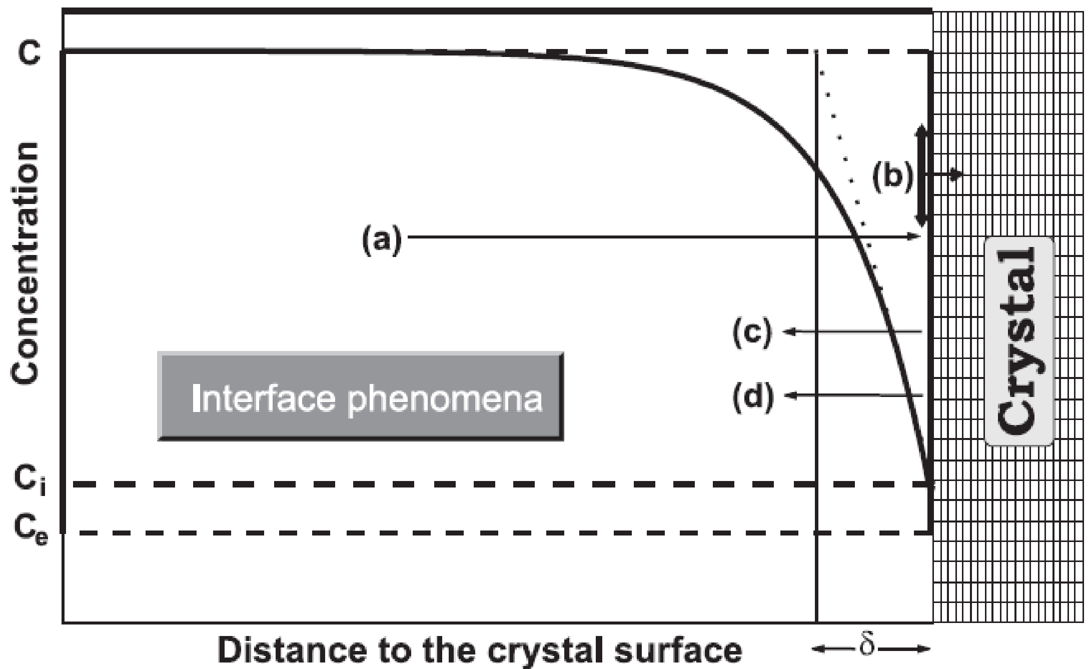
STEP 1

Analysis

- Approximation of the mass transfer rate dm/dt form the bulk to the crystal surface :

$$\frac{dm}{dt} = k_D(C - C_i)^d$$

k_D = D/δ d = kinetic order



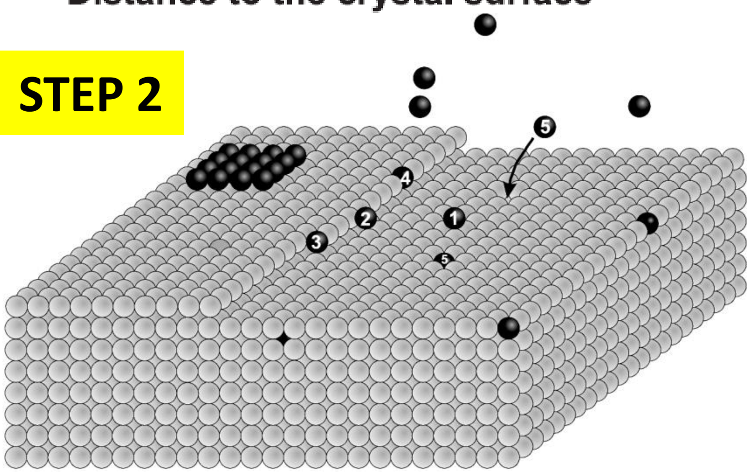
STEP 2

- The rate of transport of the growth units onto the crystal surfaces depends on considerations of energetics. The mass deposition is controlled by:

$$\frac{dm}{dt} = k_r(C_i - C_e)^r$$

k_r = kinetic coef. That depensd on the surface roughness r = kinetic order C_e = equilibrium C

STEP 2



Juan Manuel García-Ruiz *J. Chem. Ed. 76*. **1999**, 499-501

3. Crystal Growth

STEP 1

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CONCLUSION 1

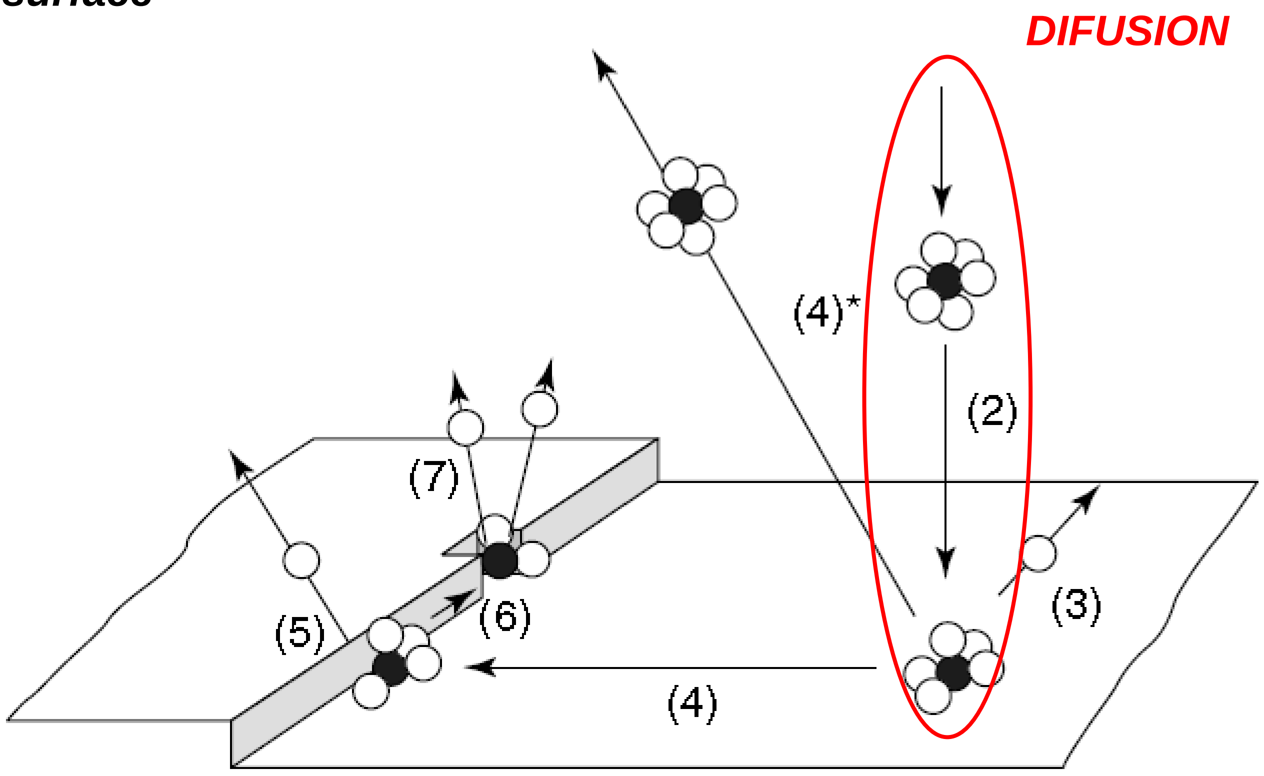
The compromise between the kinetics of the **processes taking place on the crystal surface** and those of the **transport of growth units toward this surface** determines the quality of the growing crystal. Thus, **crystals growing at a <u>rate controlled by mass diffusion</u> will contain a low density of defects, have reduced mosaicity, and presumably will diffract X-rays with better resolution.**

To ensure that **<u>diffusion takes control of the mass transport</u>**, other mechanisms such as, convection must be prevented.

3. Crystal Growth

All the involved mechanisms at glance

***DIFUSION* of the growing unit to the crystal surface**

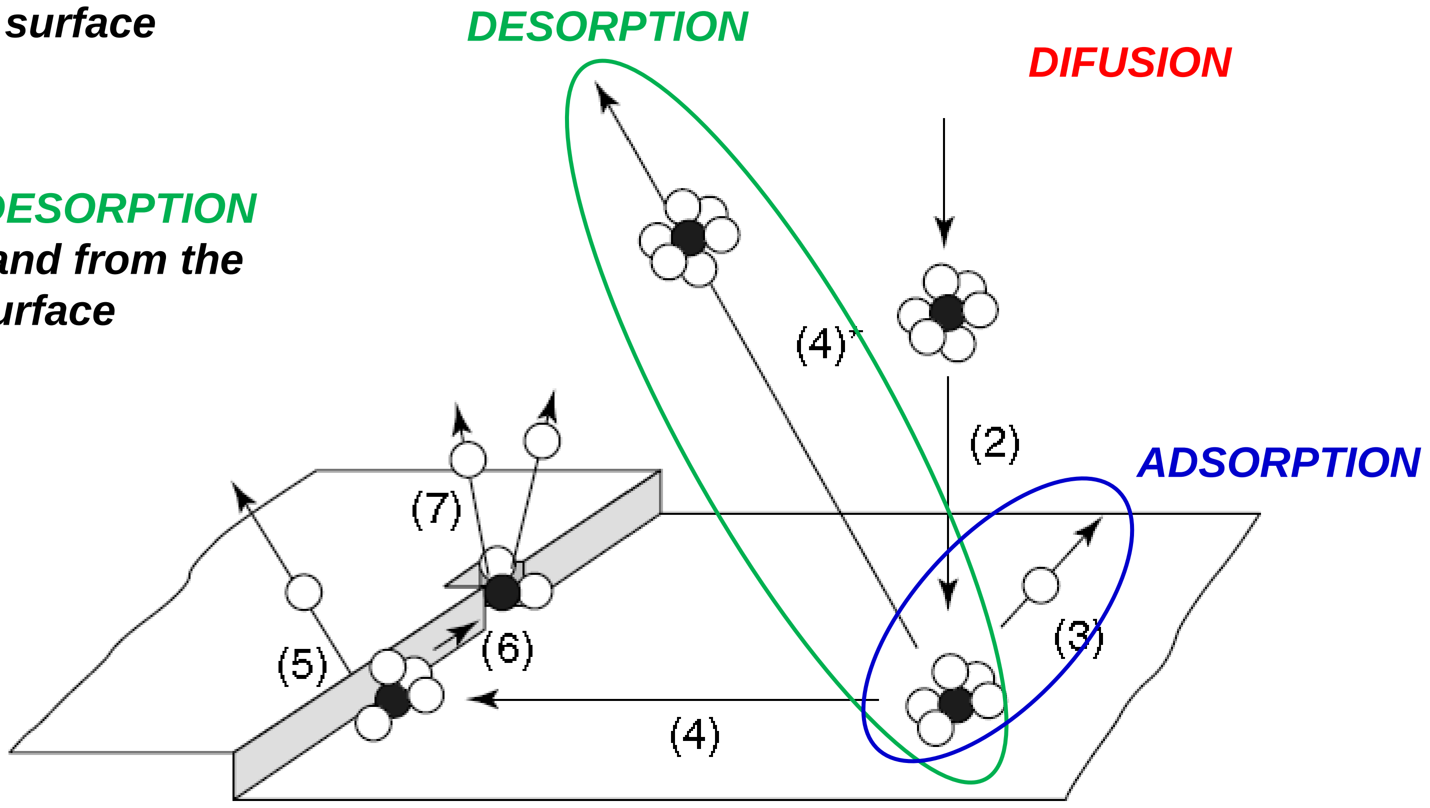


3. Crystal Growth

All the involved mechanisms at glance

***DIFUSION* of the growing unit to the crystal surface**

***ADSORPTION* & *DESORPTION* of the species to and from the crystal growing surface**



3. Crystal Growth

All the involved mechanisms at glance

***DIFUSION** of the growing unit to the crystal surface*

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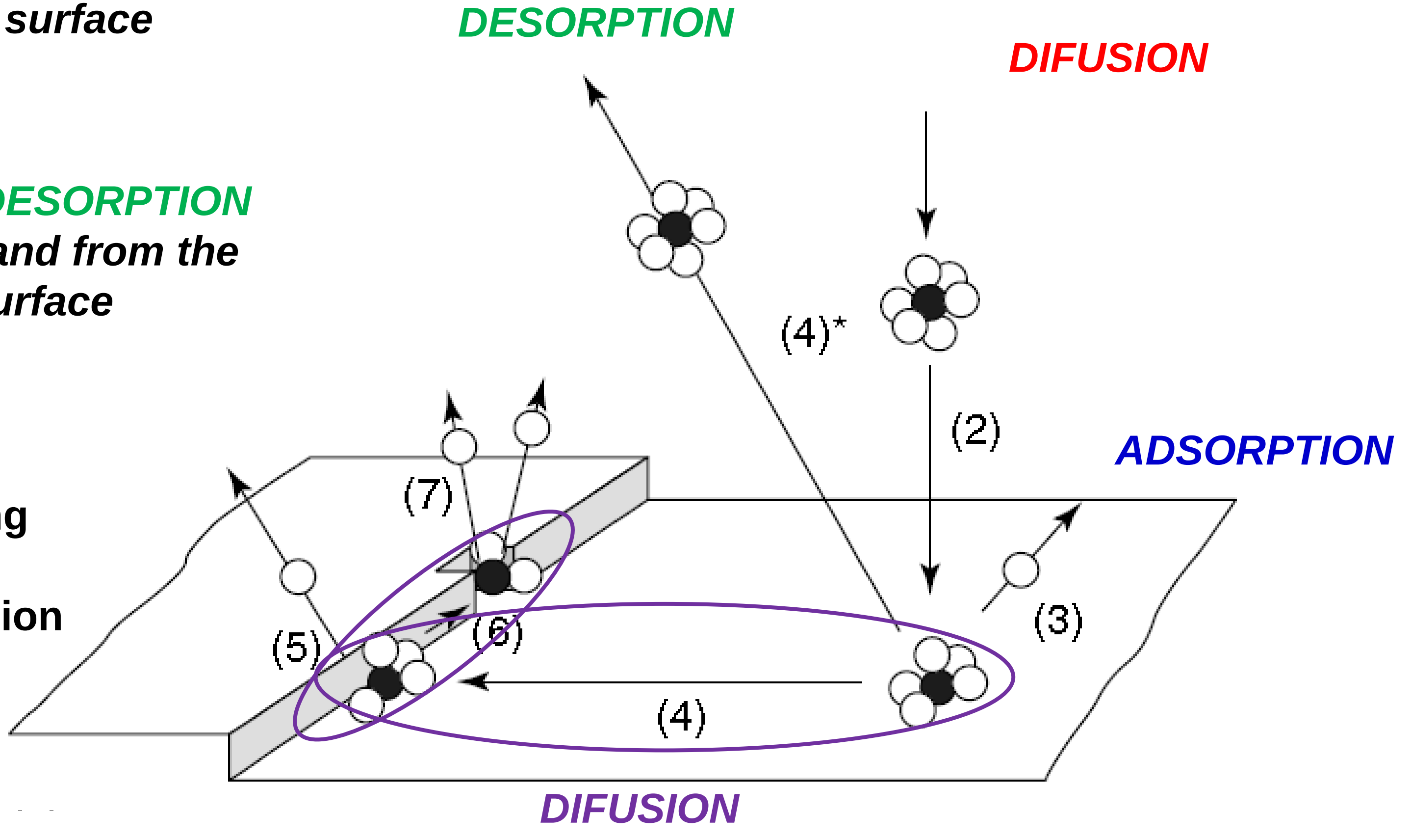
DIFUSION IN THE SURFASE: growing due to the irreversible inclusion of the specie



3. Crystal Growth

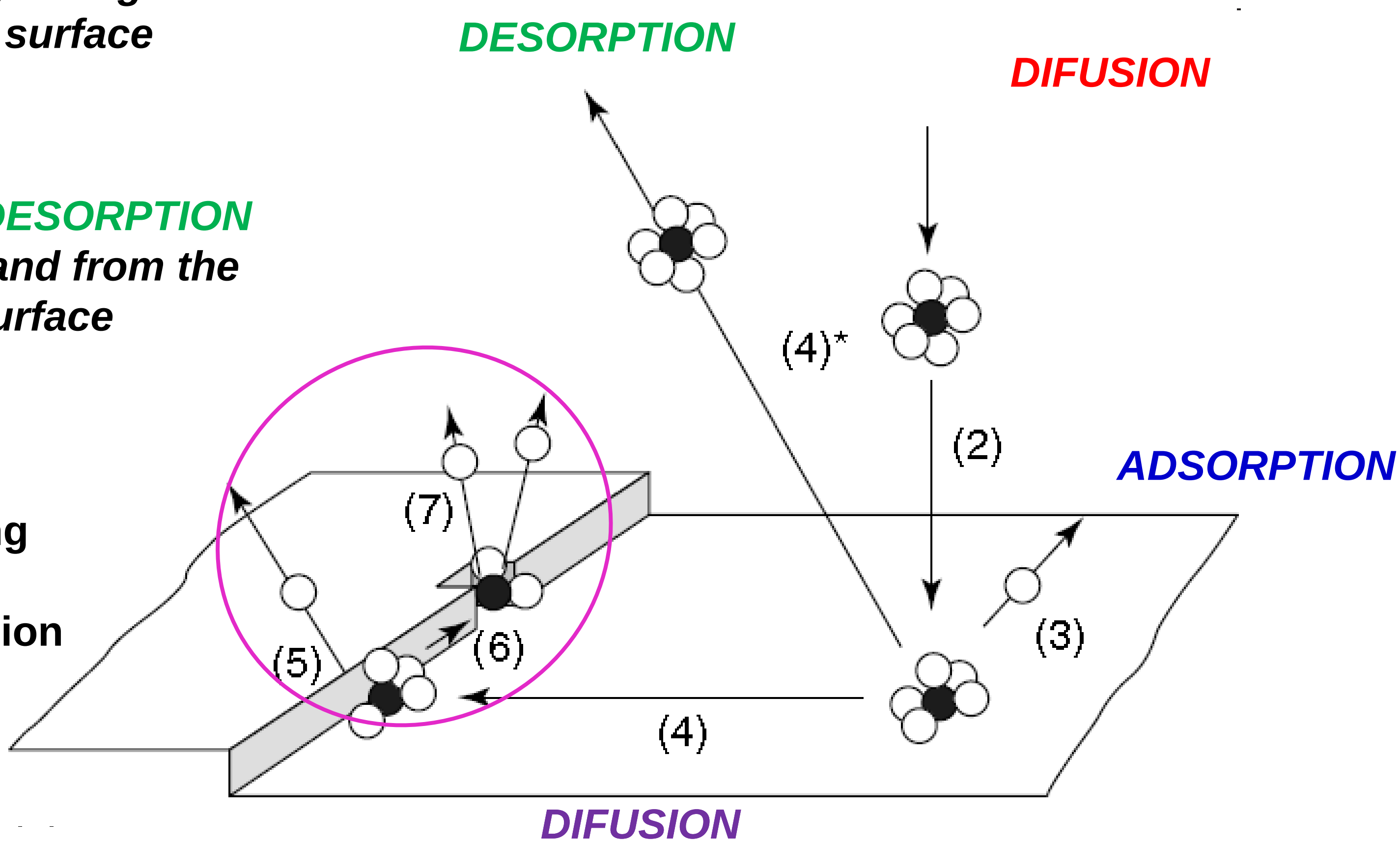
All the involved mechanisms at glance

***DIFUSION* of the growing unit to the crystal surface**

***ADSORPTION* & *DESORPTION* of the species to and from the crystal growing surface**

DIFUSION IN THE SURFASE: growing due to the irreversible inclusion of the specie

INCLUSION TO A VACANCY OR STEP

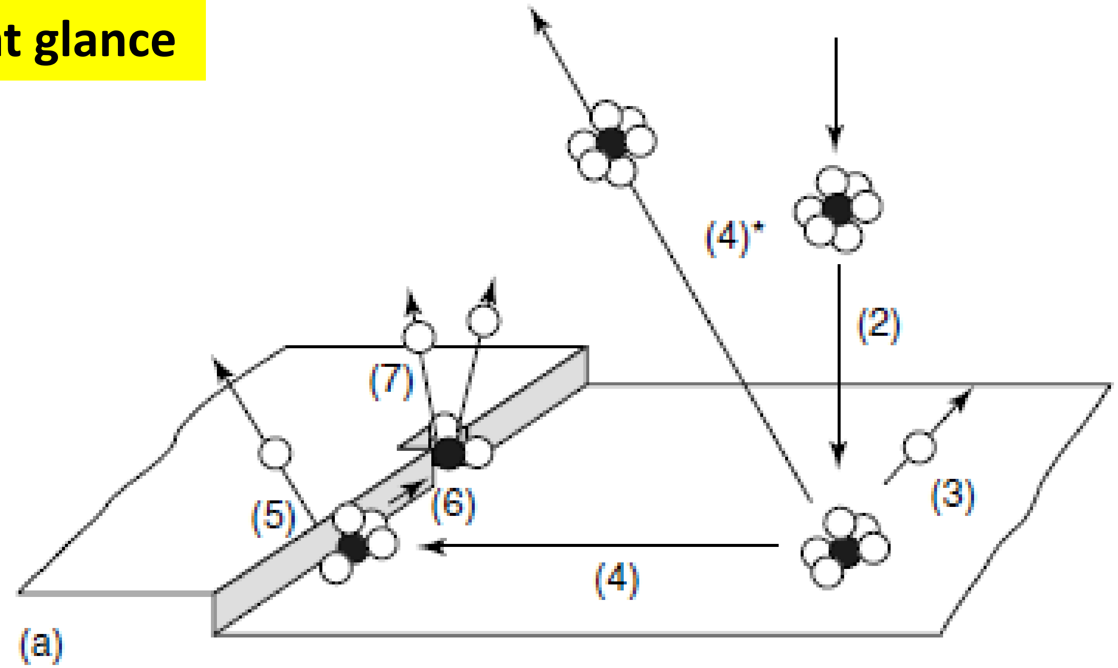


3. Crystal Growth

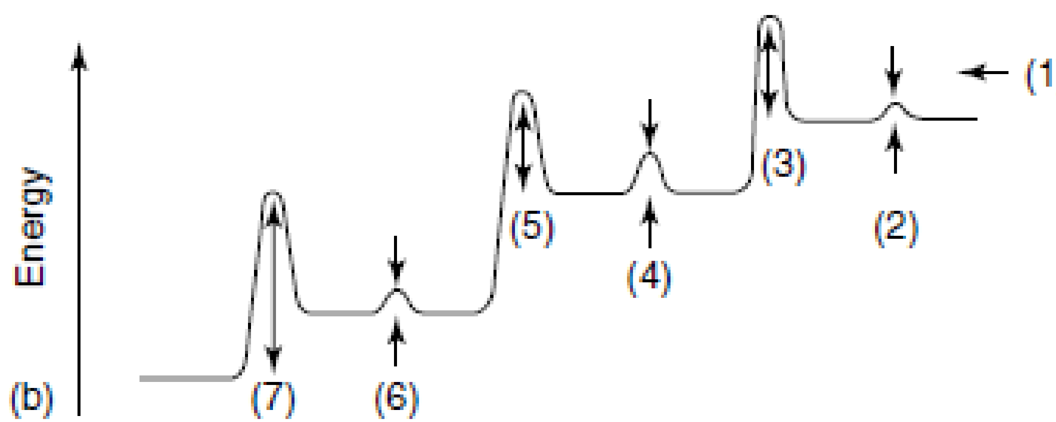
All the involved mechanisms at glance

Processes involved in the crystal growth:

(1) Transport of solute to a position near the crystal surface; (2) diffusion through boundary layer; (3) adsorption onto crystal surface; (4) diffusion over the surface; (4*) desorption from the surface; (5) attachment to a step or edge; (6) diffusion along the step or edge; (7) Incorporation into kink site or step vacancy



Associated energy changes for the processes depicted above



Zeolites and Catalysis, Synthesis, Reactions and Applications. Vol. 1. Edited by J. Cejka, A. Corma, and S. Zones. **2010** WILEY-VCH. **CAP. 1**, pp. 1-56

3. Crystal Growth

CONCLUSION 1. The importance of the diffusion control

The compromise between the kinetics of the **processes taking place on the crystal surface** and those of the **transport of growth units toward this surface** determines the quality of the growing crystal. Thus, **crystals growing at a rate controlled by mass diffusion will contain a low density of defects, have reduced mosaicity, and presumably will diffract X-rays with better resolution.**

To ensure that **diffusion takes control of the mass transport**, other mechanisms such as, convection must be prevented.

CONCLUSION 2. The relationship between SUPERSATURATION, NUCLEATION AND CRYSTAL GROWTH

Supersaturation is critical because it is the **driving force for crystal nucleation and growth**. **Nucleation** is the birth of new crystal nuclei – either spontaneously from solution (primary nucleation) or in the presence of existing crystals (secondary nucleation). **Crystal growth is the increase in size** of crystals as solute is deposited from solution. **These often competing mechanisms ultimately determine the final crystal size distribution and quality.**

3. Crystal Growth

CONCLUSION 2. The relationship between SUPERSATURATION, NUCLEATION AND CRYSTAL GROWTH

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- Simple kinetic equations to represent the nucleation (not considered before) and the crystal growth (already analyzed). Both equations depends on the concentration, thus on the degree of supersaturation.

$$v_n = k_n \Delta C^n$$

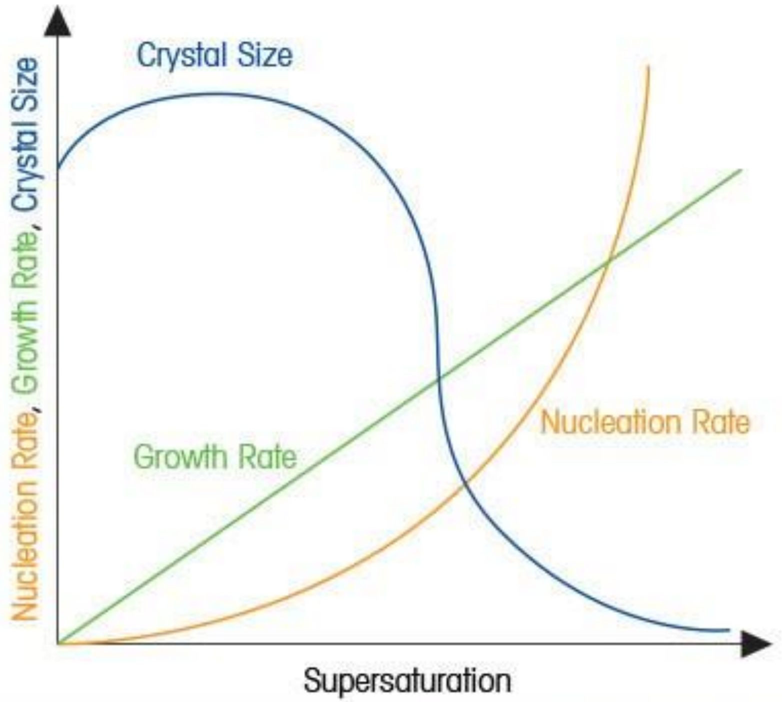
v_n = nucleation rate k_n = growth constant

n = nucleation order ΔC = supersaturation

$$v_g = k_g \Delta C^g$$

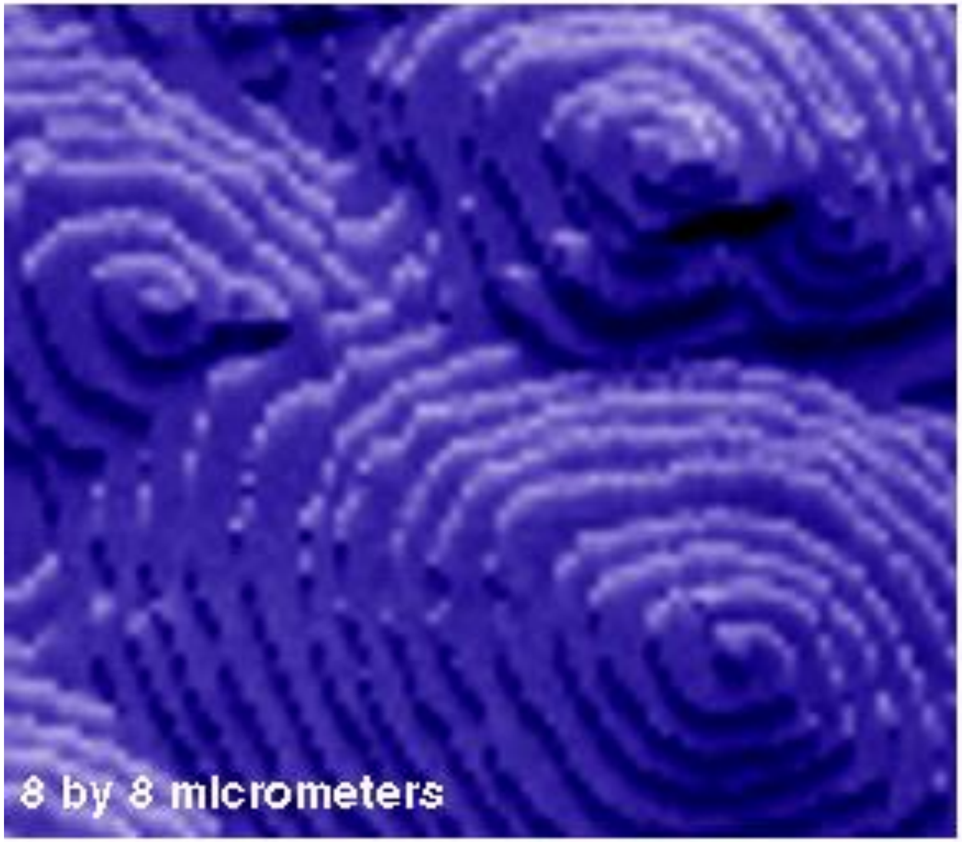
v_g = growth rate k_g = growth constant

g = growth order ΔC = supersaturation

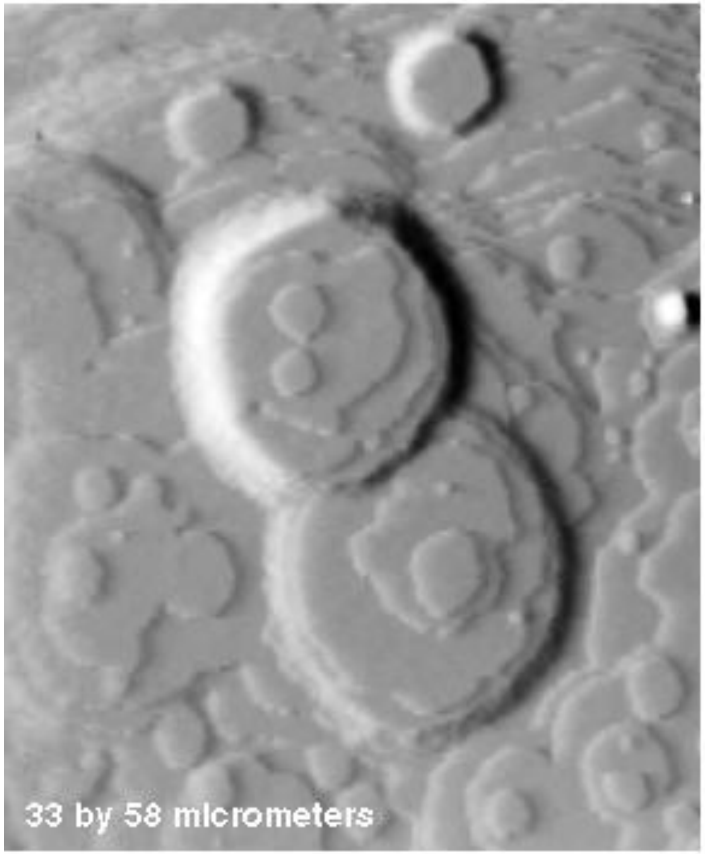


3. Crystal Growth

Examples of crystal growing analyzed by AFM microscopy



LOW SUPERSATURATION

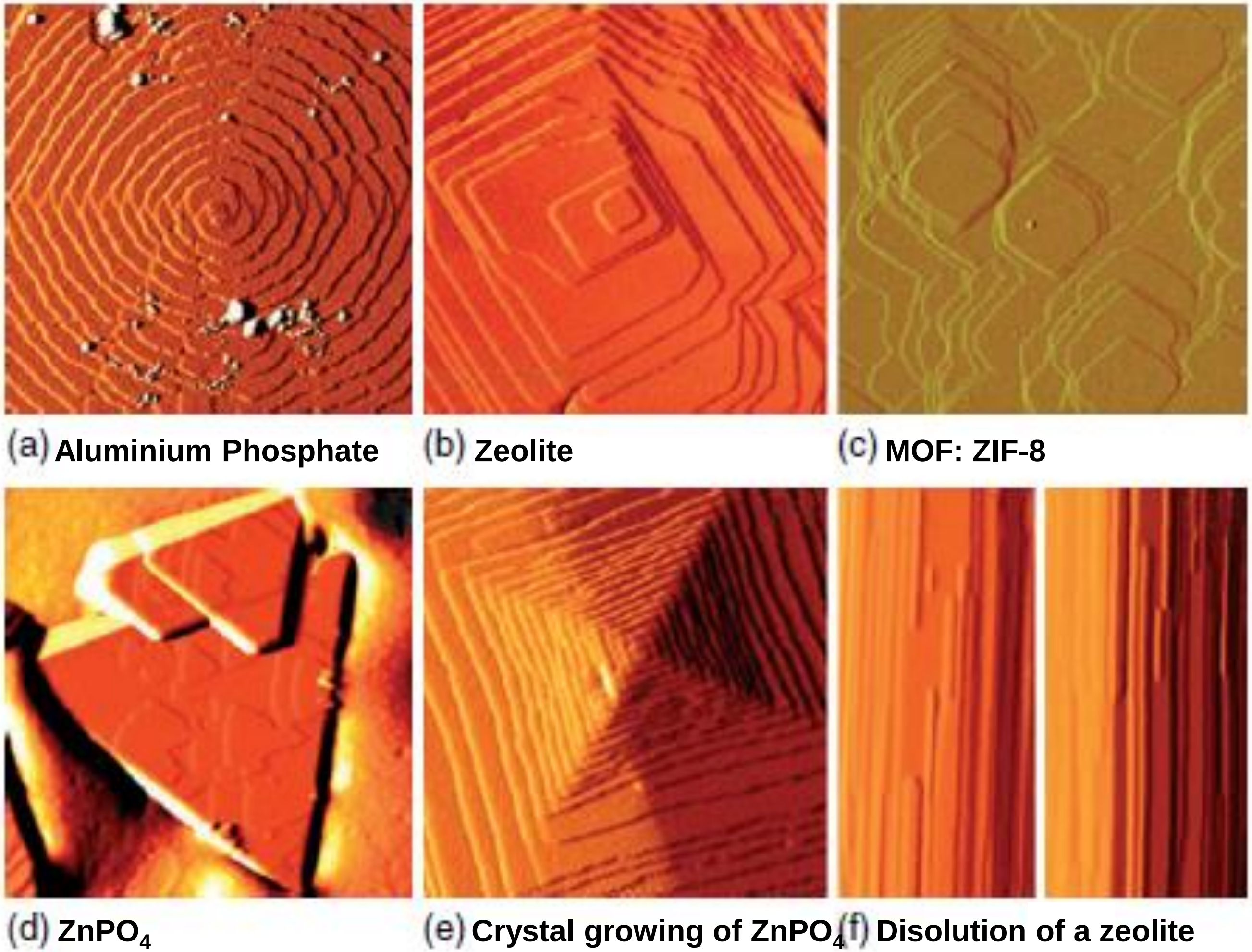


MIDIUM-HIGH SUPERSATURATION

Zeolites and Catalysis, Synthesis, Reactions and Applications. Vol. 1. Edited by J. Cejka, A. Corma, and S. Zones. **2010** WILEY-VCH. **CAP. 1**, pp. 1-56

3. Crystal Growth

Examples of crystal growing analyzed by AFM microscopy



STUDY OF THE CRYSTALLIZATION PROCESS

Summary of the variables to take into account

- **Growing unit = compound** (identity of the specie: size, M, king of posible intermolecular interactions…)
- **Solvent**
- **Supersaturation (& its relationship with nucleation and growing rates)**
- **Diffusional control**
- **Convection**
- **Thermal instability**
- **Temperature**
- **Presence of impurities**
- **Time**

STUDY OF THE CRYSTALLIZATION PROCESS

VARIABLE: compound (“crystal unit”)

1. **Combine knowledge of solubility profile with crystal growing techniques**
2. **Purify your compound** (using conventional crystallization and/or other purification steps)
3. **Consider the empirically established physical properties of your compound – sensitivities, thermal stability, etc.**
4. **Develop a solubility profile of your compound**
5. **Impure samples do not recrystallize as well as pure samples**
6. **Recrystallization minimizes the presence of foreign insoluble material which increases the number of nucleating sites**
7. **Successive crystallizations purify the compound**
8. **Always use recrystallized material when setting up a crystal growing attempt**

STUDY OF THE CRYSTALLIZATION PROCESS

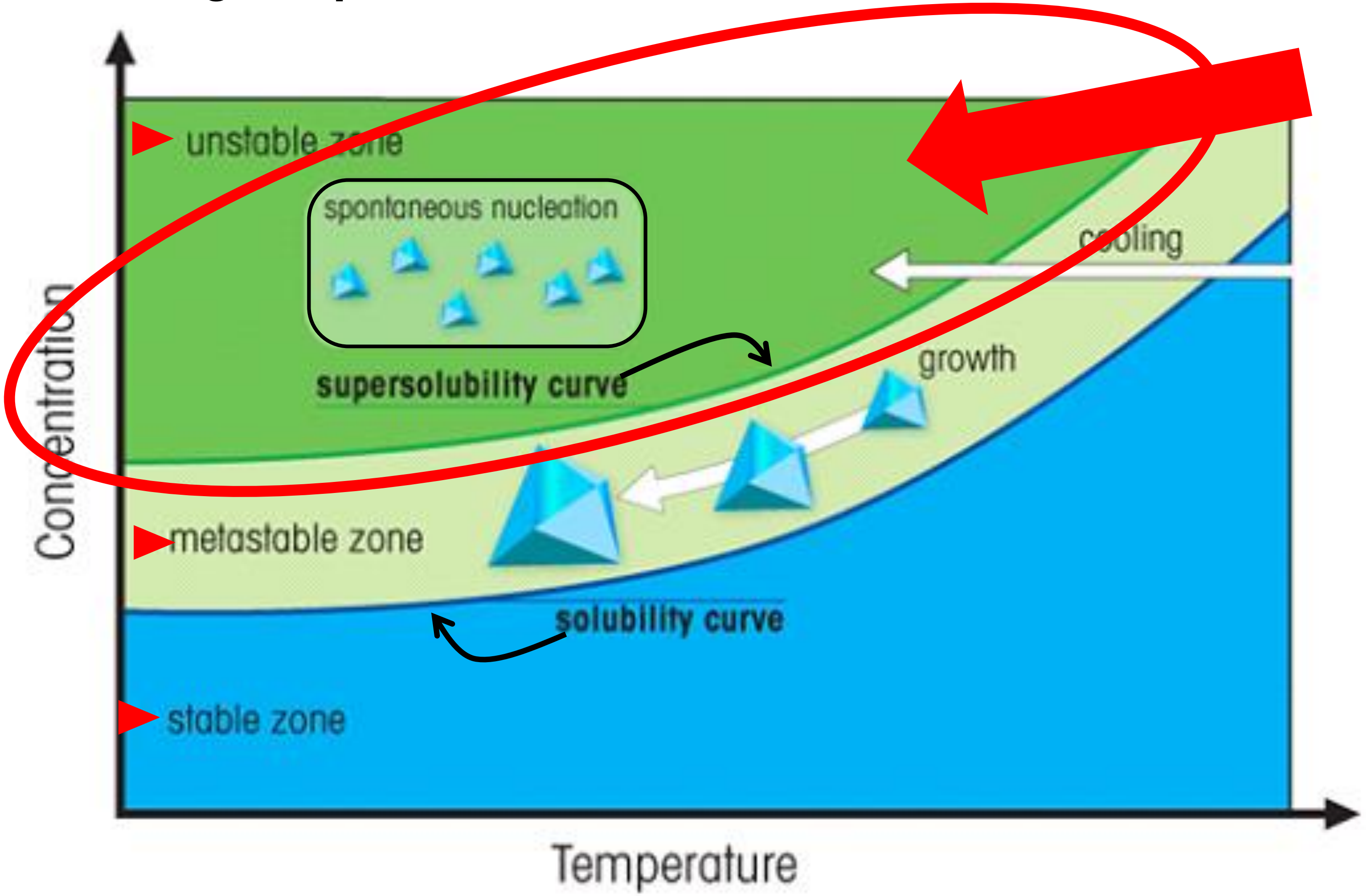
VARIABLE: Solvent

1. **Solvent influences in the crystal growth**
2. **It can be incorporated into the crystalline network**
3. **Useful rule: use the least amount of solvent in the experiments**
4. **Golden Rule: “similar dissolves similar"**
5. **Explore several solvents and mixtures**
6. **Moderate solubility is best (avoid supersaturation)**
7. **Hydrogen bonding can help or hinder crystallization.**
8. **Avoid highly volatile solvents**
9. **Avoid long chain alkyl solvents, they can be significantly disordered in crystals. Choose solvents with “rigid geometries” (e.g. toluene)**

STUDY OF THE CRYSTALLIZATION PROCESS

VARIABLE: supersaturation

EXAMPLE: High supersaturation => Unstable Zone



STUDY OF THE CRYSTALLIZATION PROCESS

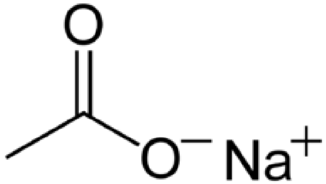
VARIABLE: supersaturation

EXAMPLE: High supersaturation => Unstable Zone

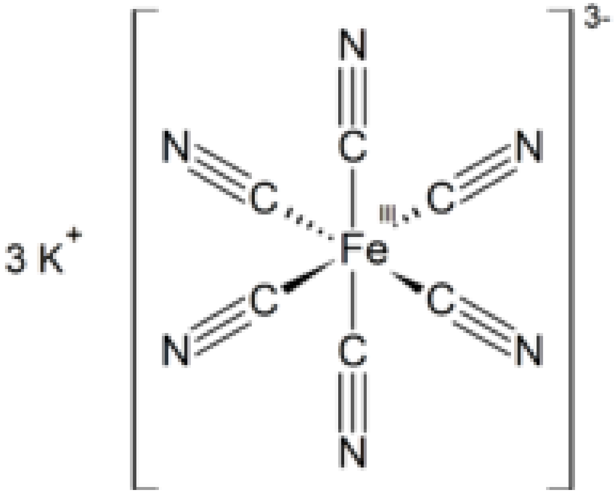
Characteristic of the crystals: Dendrites (aggregates)

- ***Sodium Acetate***

VIDEO 1



- ***Potassium Ferricyanide***

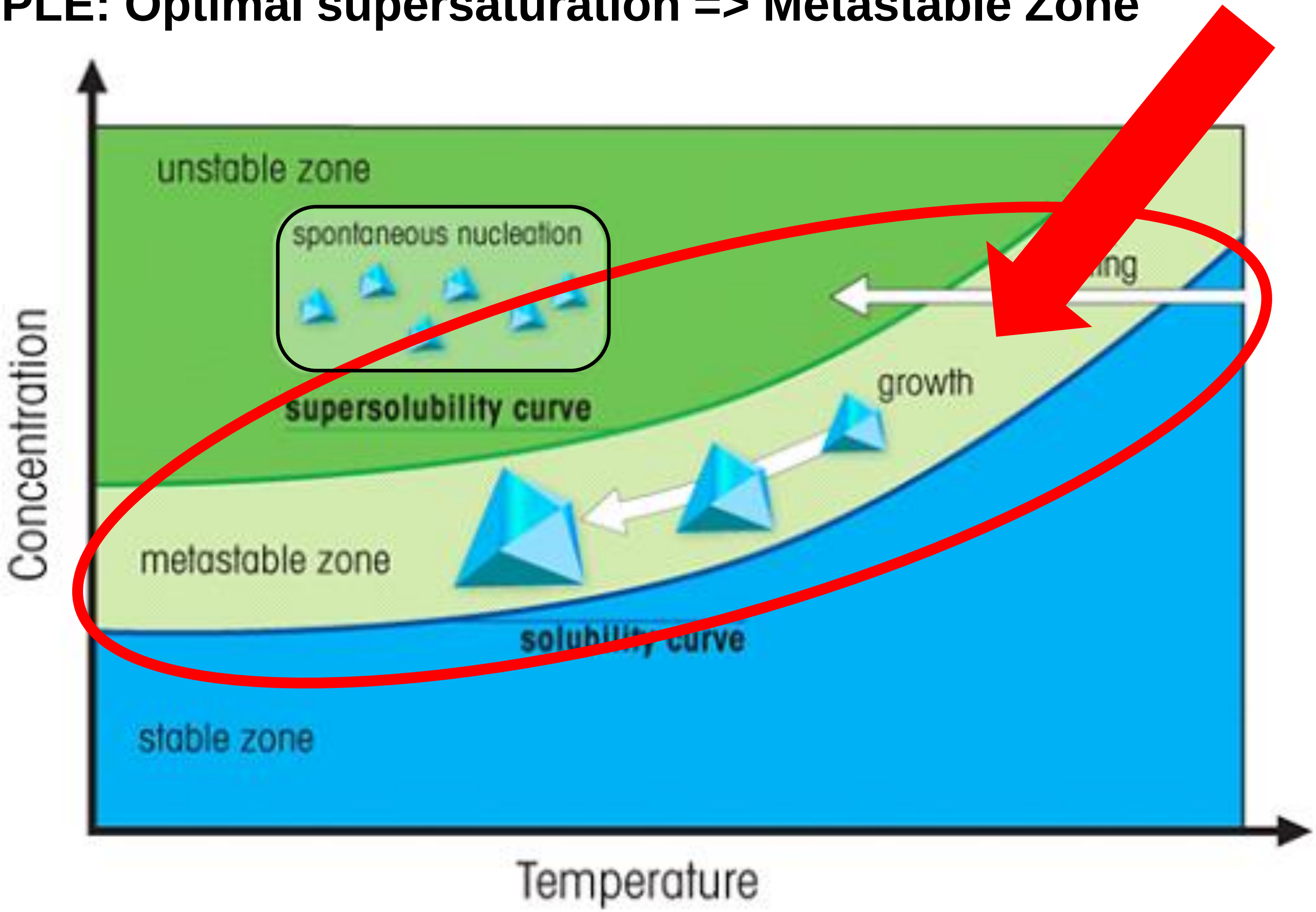


VIDEO 2

■ STUDY OF THE CRYSTALLIZATION PROCESS

VARIABLE: supersaturation

EXAMPLE: Optimal supersaturation => Metastable Zone



STUDY OF THE CRYSTALLIZATION PROCESS

VARIABLE: supersaturation

EXAMPLE: Optimal supersaturation => Metastable Zone

Characteristic of the crystals: Single crystals (superficial or bidimensional growing)

Nucleación **Cristal** crecimiento

Líquido

- ***Protein*** VIDEO 3

- ***Perovskites*** *(hybrid organic-inorganic material)* $[CH_3NH_4][PbI_3]$ and $[CH_3NH_4][PbBr_3]$

http://www.nature.com/ncomms/2015/150706/ncomms8586/full/ncomms8586.html

VIDEO 4

■ STUDY OF THE CRYSTALLIZATION PROCESS

VARIABLE: diffusional control / convection

1. **Do not perturb the system** (keep crystal growth vessels away from sources of mechanical agitation)
2. **Avoid areas with vibrations , mechanical disturbances are bad** (Set-up away from vacuum pumps, rotovaps, hoods, doors, drawers, and so on)
3. **Use small diameter vials and tubes**
4. **Explore gel crystallization** (see next slides)

VARIABLE: temperature

1. **Take into account that usually solubility is highly influenced by T. So, the stent of supersaturation (and thus the nucleation and growing rate) is influenced by T**
2. **Study the thermal stability of your system before study the crystallization process. Take into account your system could exhibit different crystalline phases.**

▪ STUDY OF THE CRYSTALLIZATION PROCESS

VARIABLE: impurities

1. Unless desired, avoid the presence of impurities. They will favor nucleation
2. Avoid ambient dust, filter paper fibers, hair, broken off pipette tips all provide opportunities for nucleation – take steps to remove them.
3. Use CLEAN glassware as crystal growing vessels
4. Before setting up a crystal growing attempt think about how the crystals will be handled
5. Crystals will need to extracted from the vessel without damage
6. Therefore, pick a suitable crystal growing vessel

VARIABLE: time

1. Quality crystals grow best over time in near equilibrium conditions
2. The longer the time, the better the crystals
3. Larger crystals tend to grow at the expense of smaller crystals
4. Patience, patience, patience!!

CRYSTAL GROWING TECHNIQUES

1. Crystal growing in solution

- Slow evaporation
- Slow cooling
- Vapor diffusion
- Solvent diffusion
- convection
- Addition of additives, pH
- Solvothermal/hydrothermal (p, T, sv)
- Chemical modification

2. Crystal growing without solvent

- From melt
- Sublimation

3. Seeding

4. Gel Crystallization

5. Chemical Modification (change of counterion, formation of salt)

■ CRYSTAL GROWING TECHNIQUES

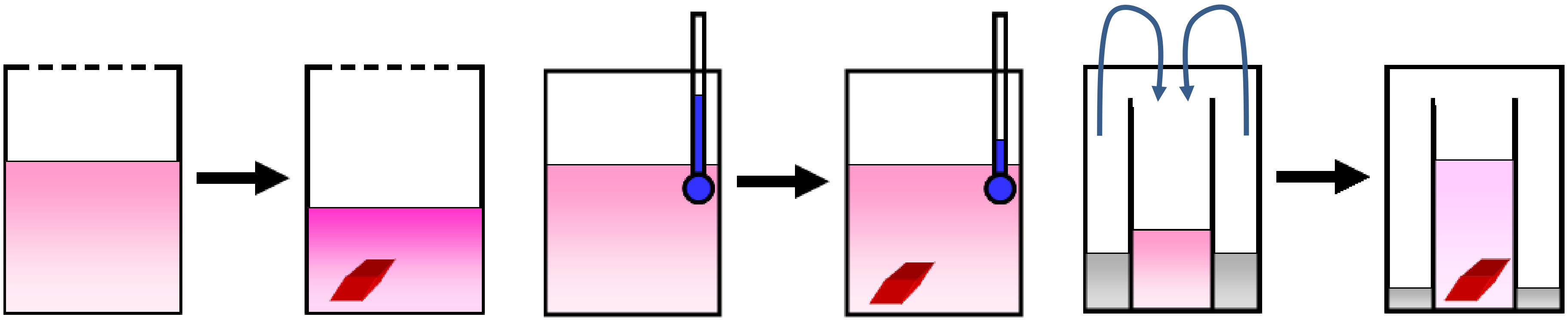
1. Crystal growing in solution

☑ **Solvent**

Pure, mixtures, polarity, volatility

☑ **Techniques**

- **Slow evaporation**
- **Slow cooling**
- **Vapor diffusion**



http://web.mit.edu/x-ray/cystallize.html

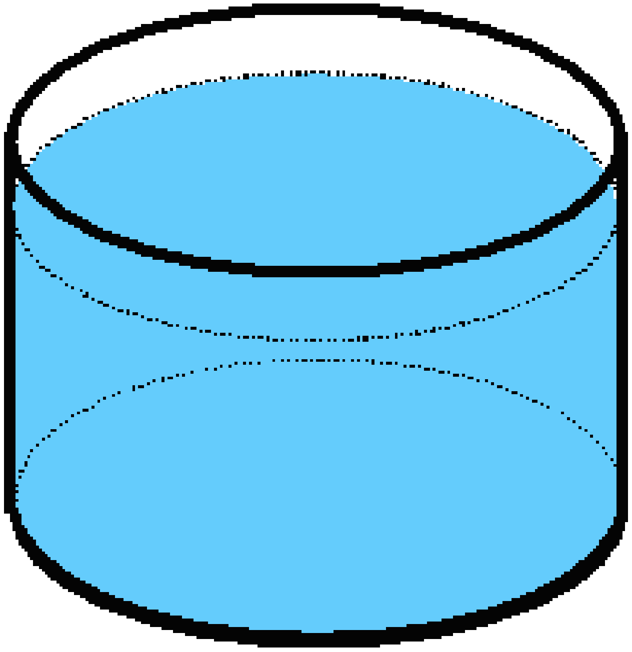
■ CRYSTAL GROWING TECHNIQUES

1. Crystal growing in solution

☑ **Techniques**

- **Slow evaporation**

(animación)



www.parakeets4peace.com/crystals/

CRYSTAL GROWING TECHNIQUES

1. Crystal growing in solution

- Slow evaporation systems

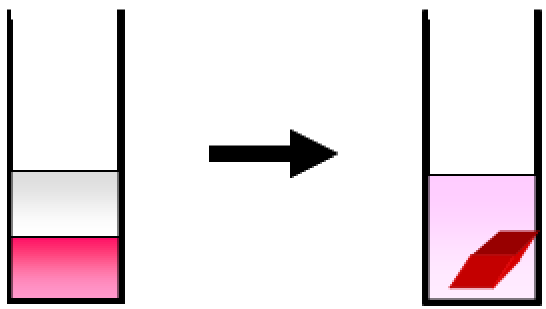
- Vapor diffusion

■ CRYSTAL GROWING TECHNIQUES

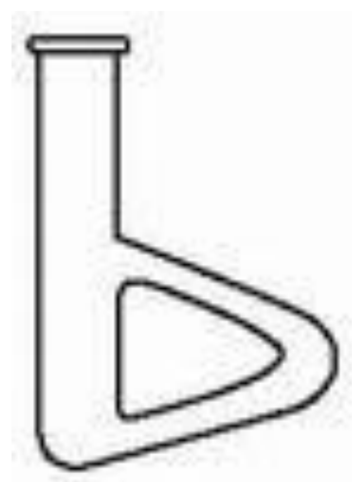
1. Crystal growing in solution

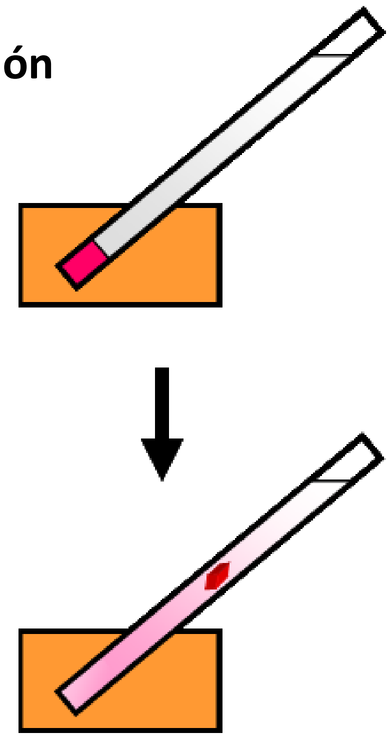
☑ **Techniques**

- **Solvent diffusion**



- **Termal convección**





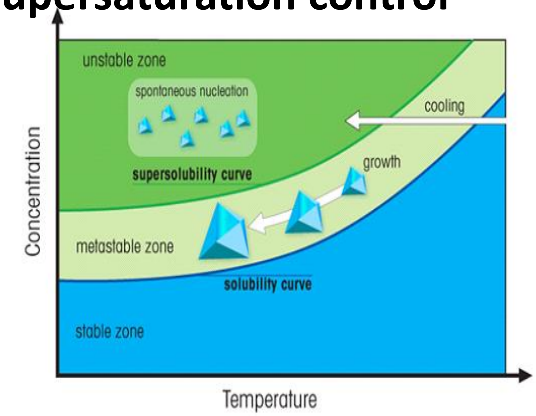
http://web.mit.edu/x-ray/cystallize.html

CRYSTAL GROWING TECHNIQUES

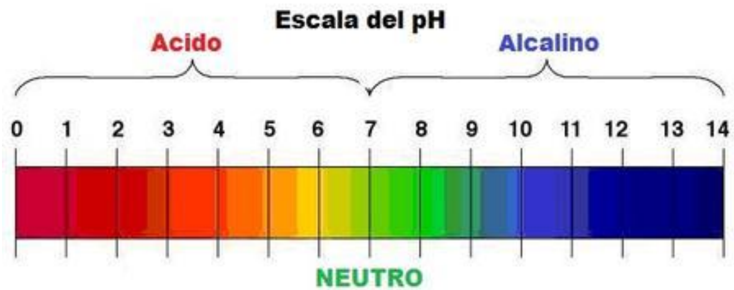
1. Crystal growing in solution

Other methods and strategies

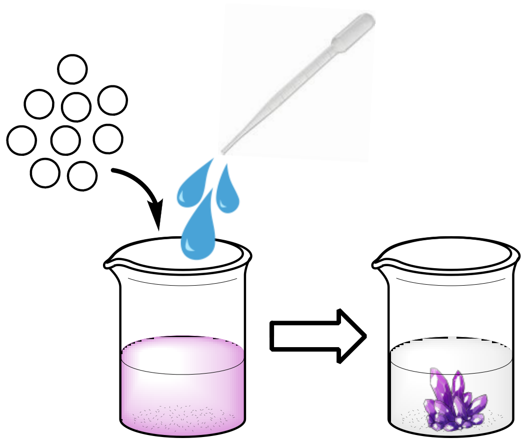
- Supersaturation control



- pH variation



- Addition of anti-solvent / additives ("salting out")

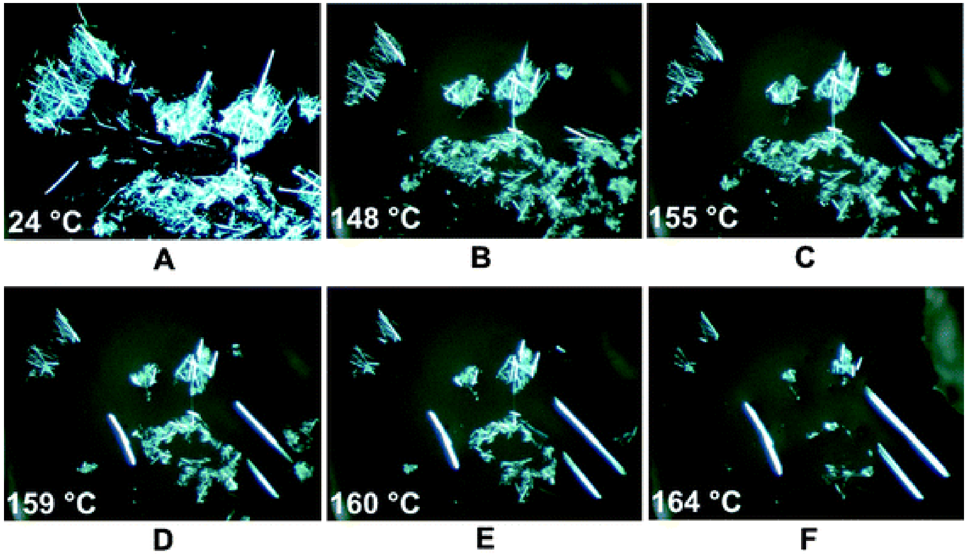


- Hydrothermal/solvothermal

CRYSTAL GROWING TECHNIQUES

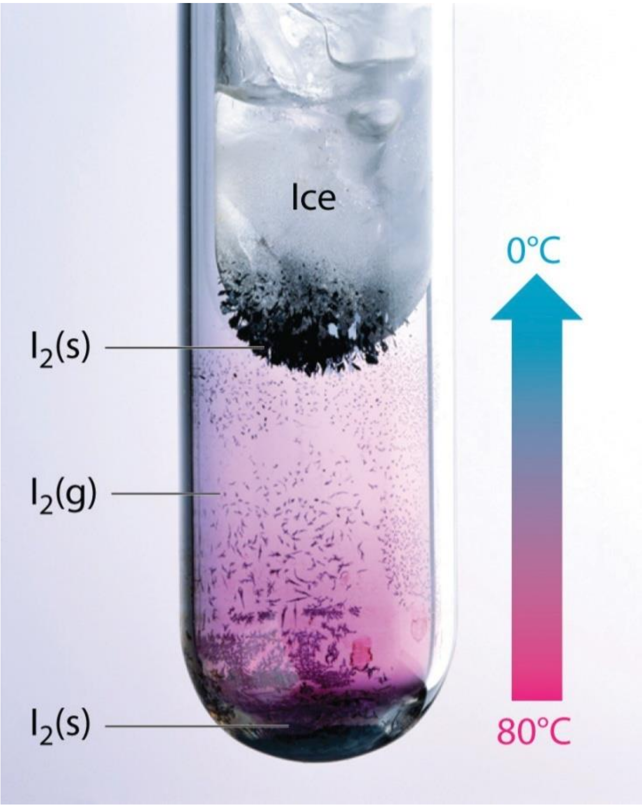
2. Crystal growing without solvent

- **From melt**



- **Sublimation**

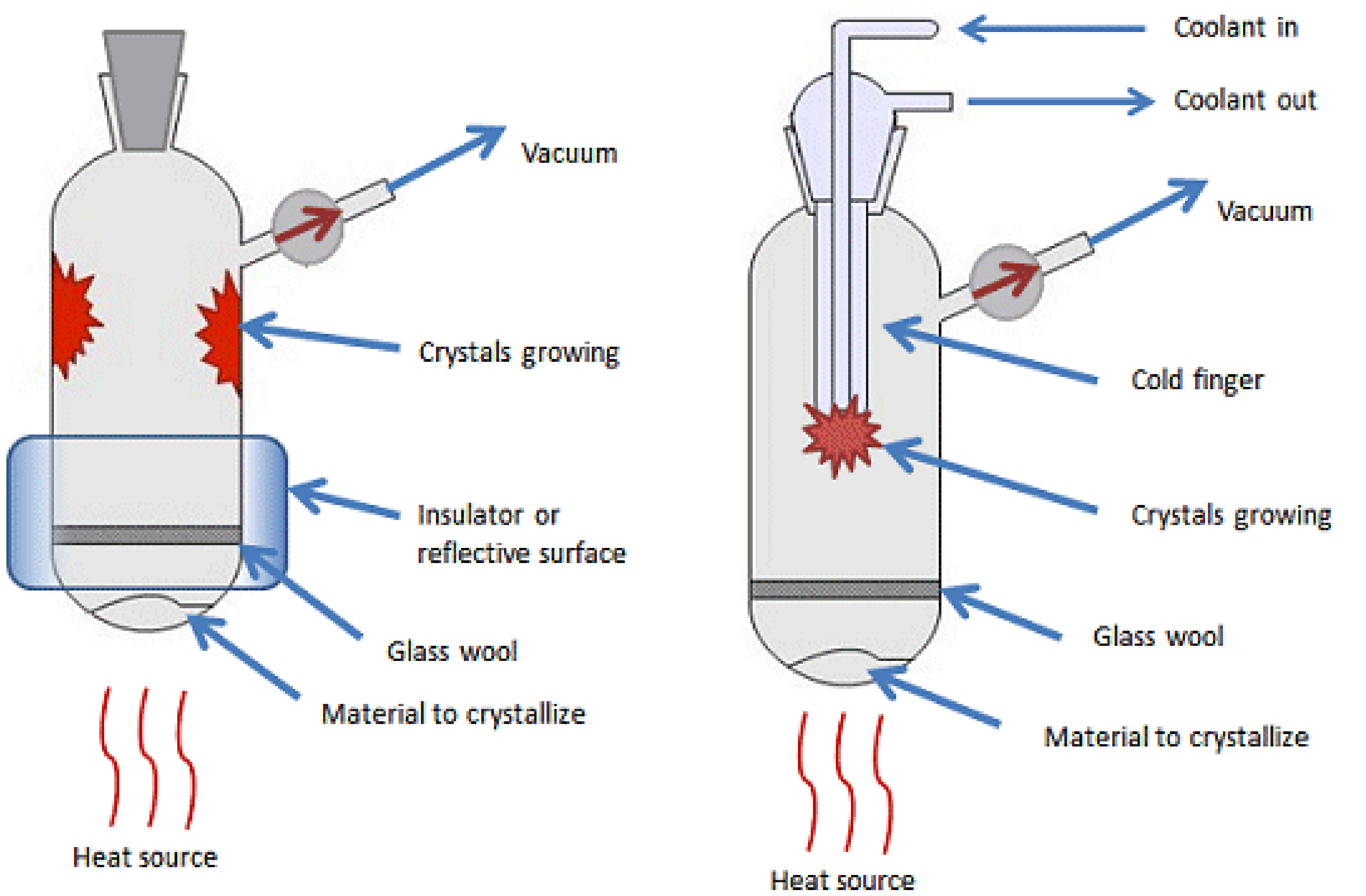
Ej. caffeine, Sulphur, iodine, salicylic acid



CRYSTAL GROWING TECHNIQUES

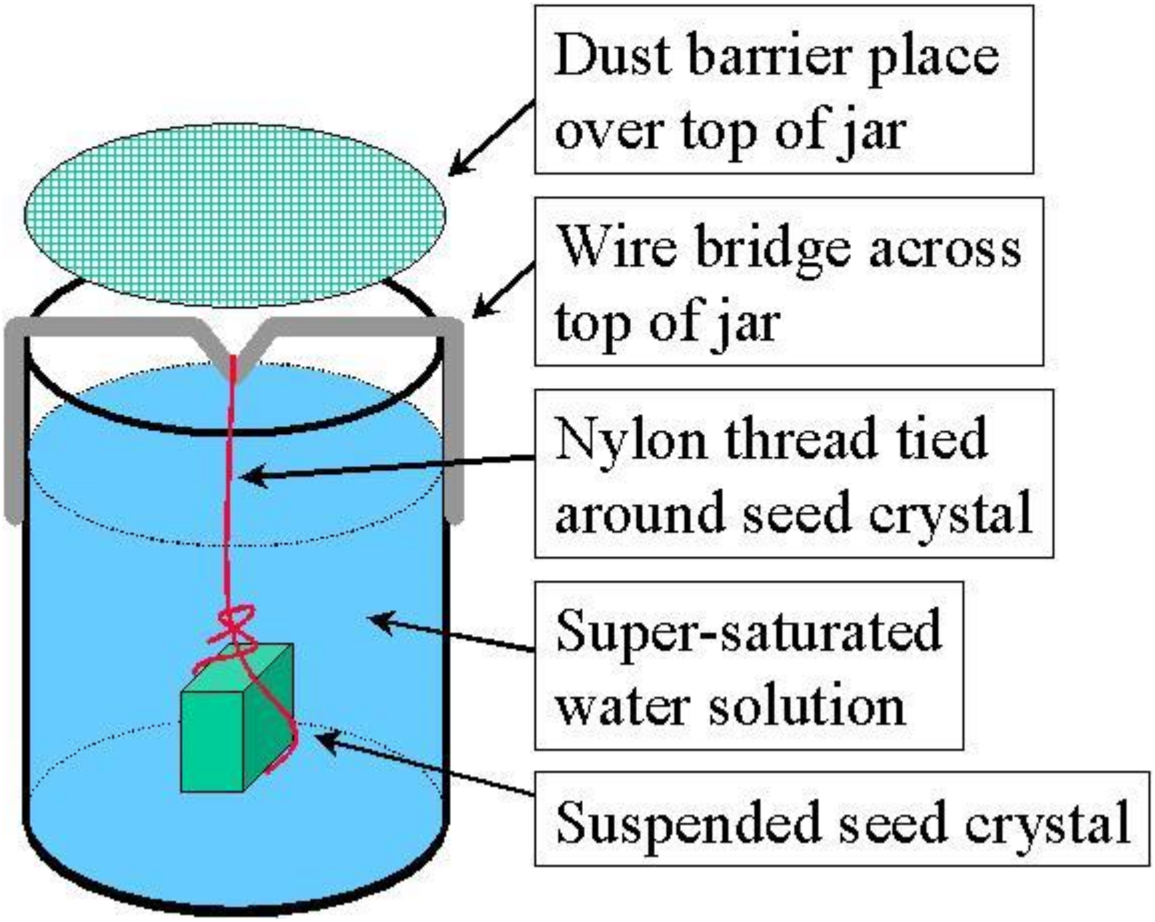
2. Crystal growing without solvent

- **Laboratory sublimation system**



CRYSTAL GROWING TECHNIQUES

3. Seeding



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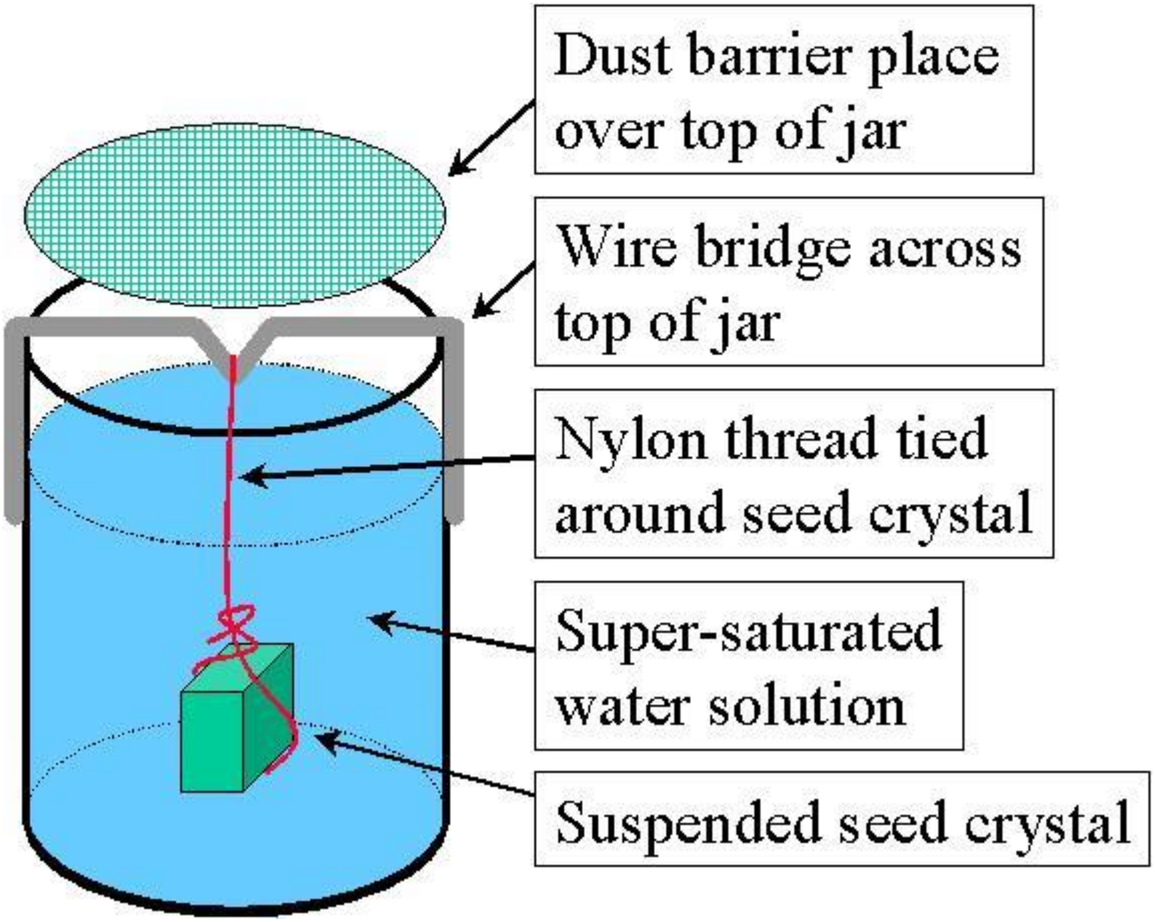
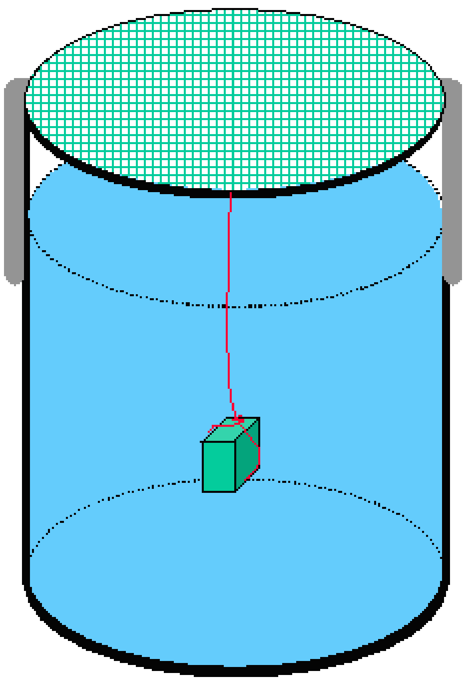
CRYSTAL GROWING TECHNIQUES

3. Seeding



animación



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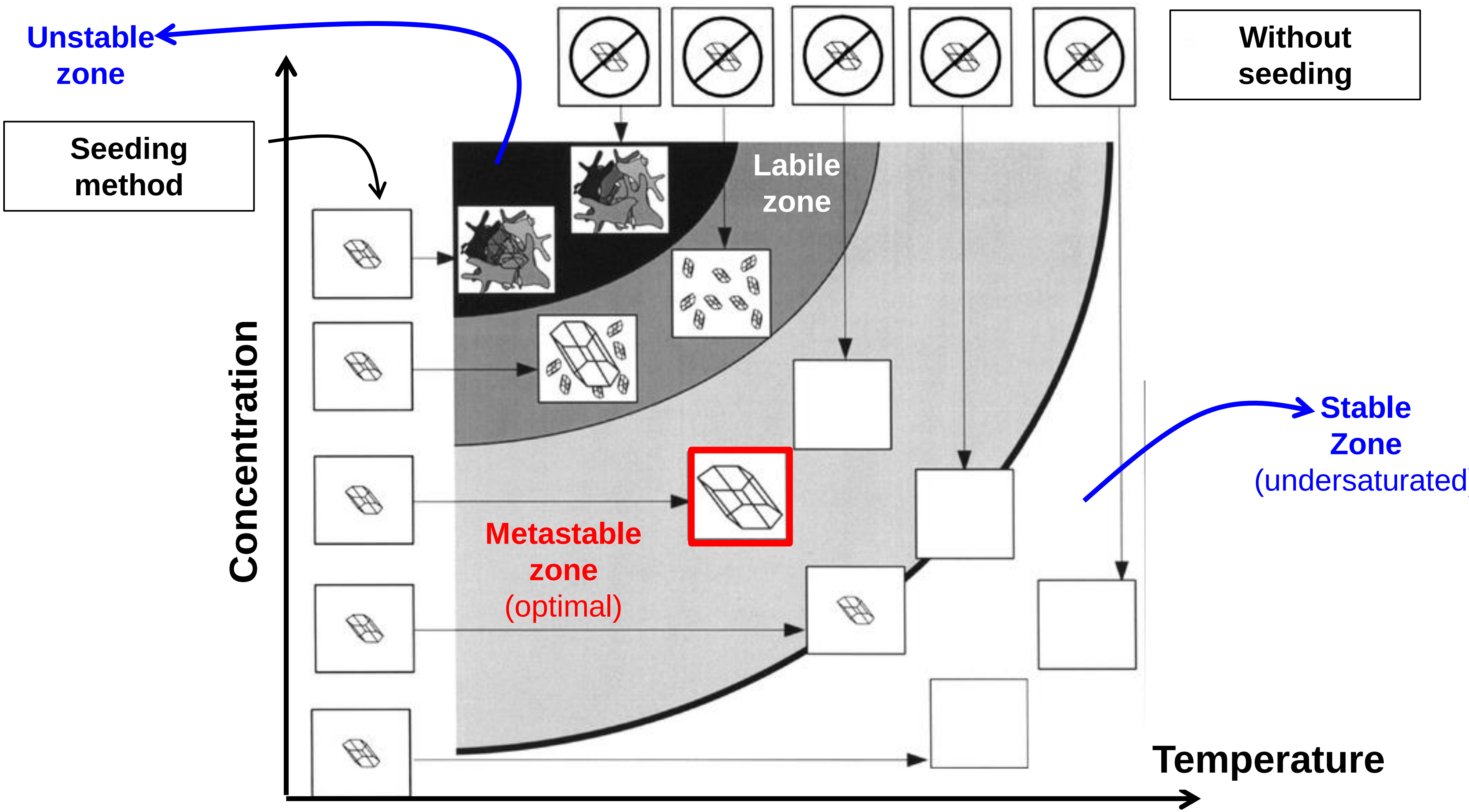
CRYSTAL GROWING TECHNIQUES

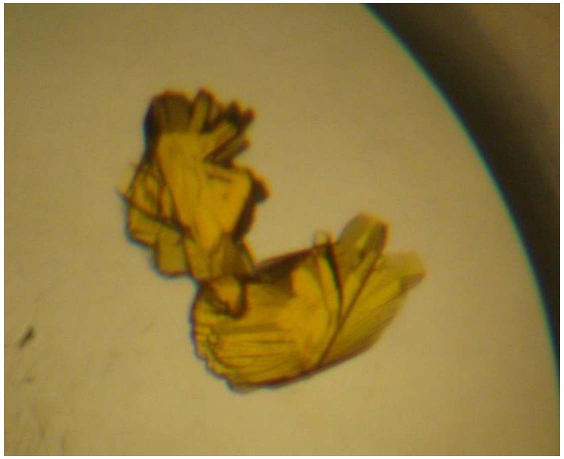
3. Seeding

- Solubility and crystallization curves to analyze the optimal conditions



CRYSTAL GROWING TECHNIQUES

3. Streak Seeding

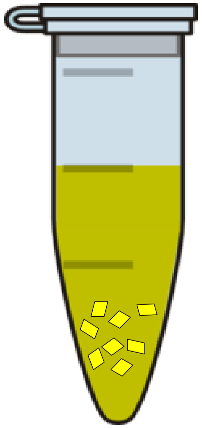


Cristal tipo macla de Riboflavina sintasa

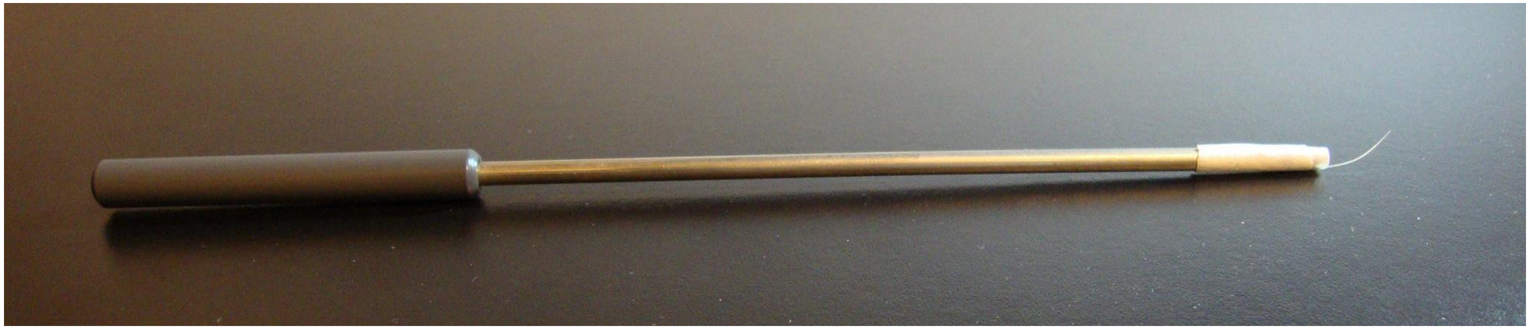
+

Aguja de acupuntura

→



Stock de semillas



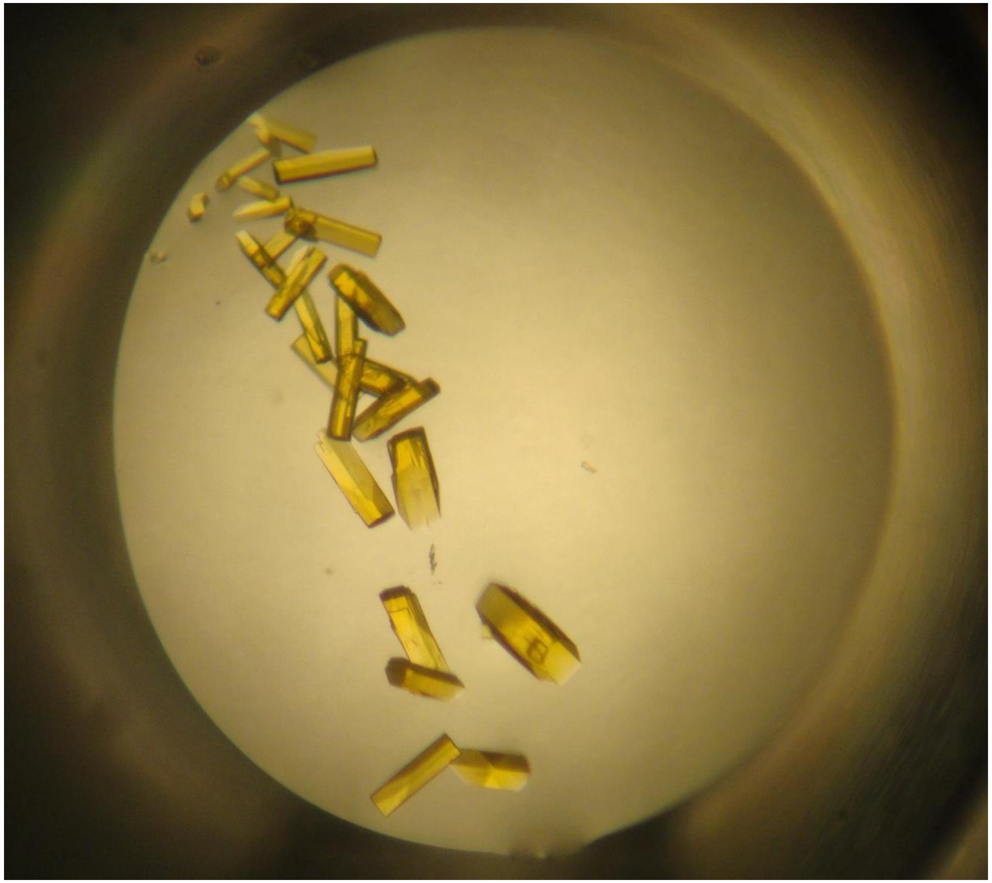
"Seeding tool" casera con pelo de pony

Cortesía: Dr. Sebastián Klinke, Instituto Leloir-CONICET, Buenos Aires Argentina

CRYSTAL GROWING TECHNIQUES

3. Streak Seeding

- **Streak seeding de Riboflavina sintasa**



Menor tiempo

Mejor forma

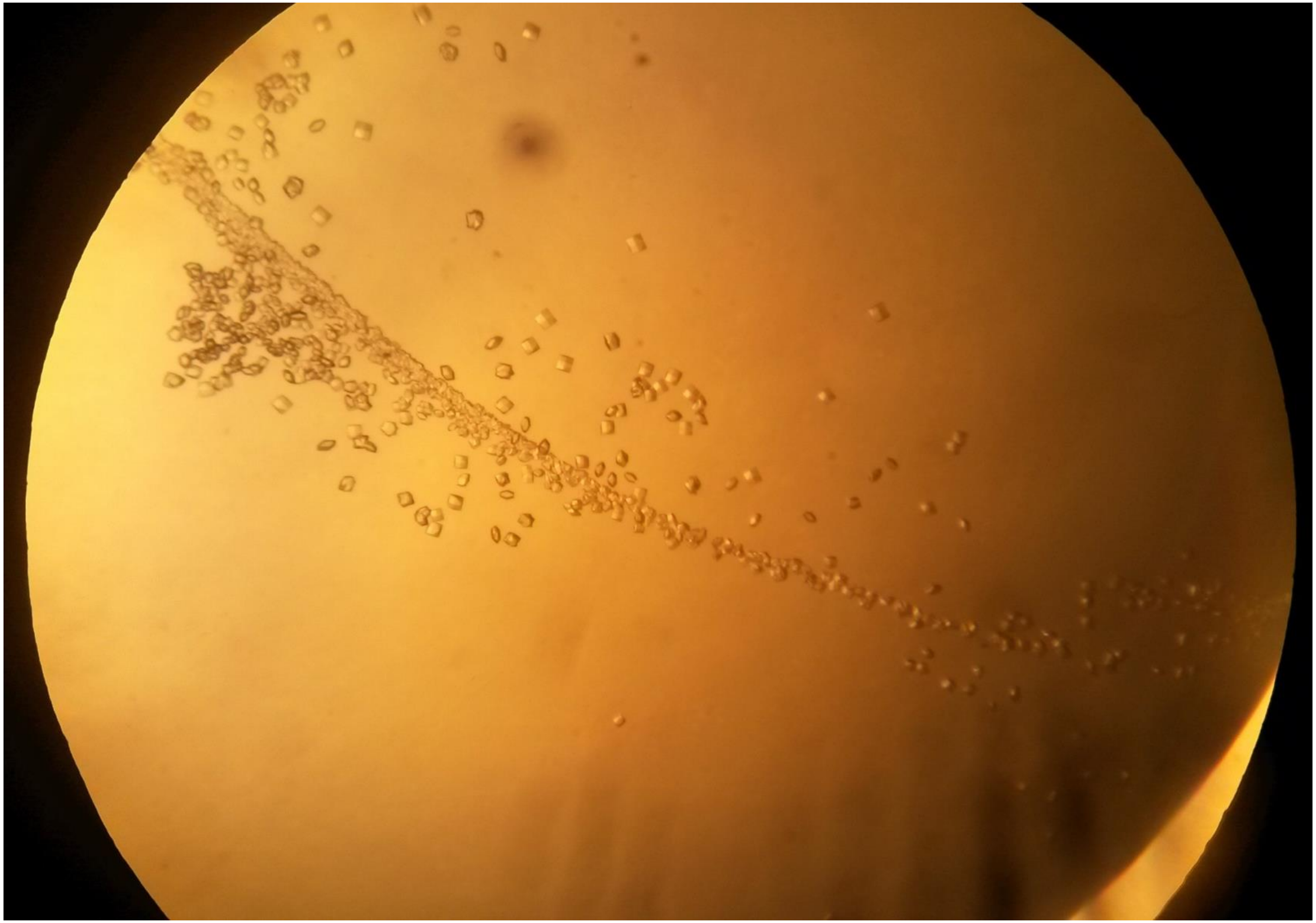
Mayor tamaño

Crecimiento a lo largo de la línea de siembra

Cortesía: Dr. Sebastián Klinke, Instituto Leloir-CONICET, Buenos Aires Argentina

CRYSTAL GROWING TECHNIQUES

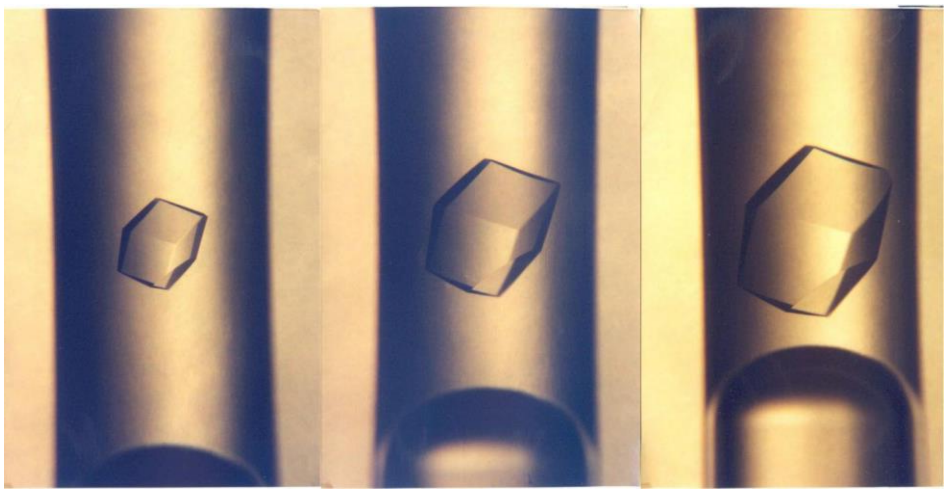
3. Streak Seeding



Cortesía: Dr. Sebastián Klinke, Instituto Leloir-CONICET, Buenos Aires Argentina

CRYSTAL GROWING TECHNIQUES

4. Crystallization in Gel



☑ **Characteristics of the compound to crystallize**

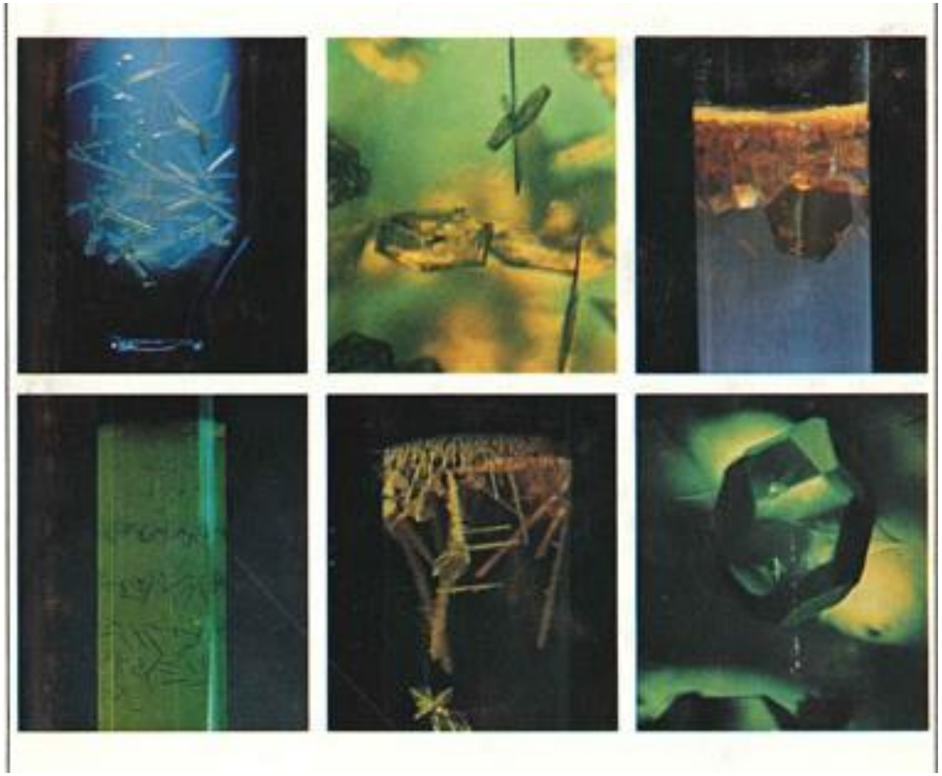
- **Low solubility**
- **Solubility highly dependent with T**
- **Soluble in water but very insoluble in other solvents**

■ CRYSTAL GROWING TECHNIQUES

4. Crystallization in Gel

☑ **Function of the gel**

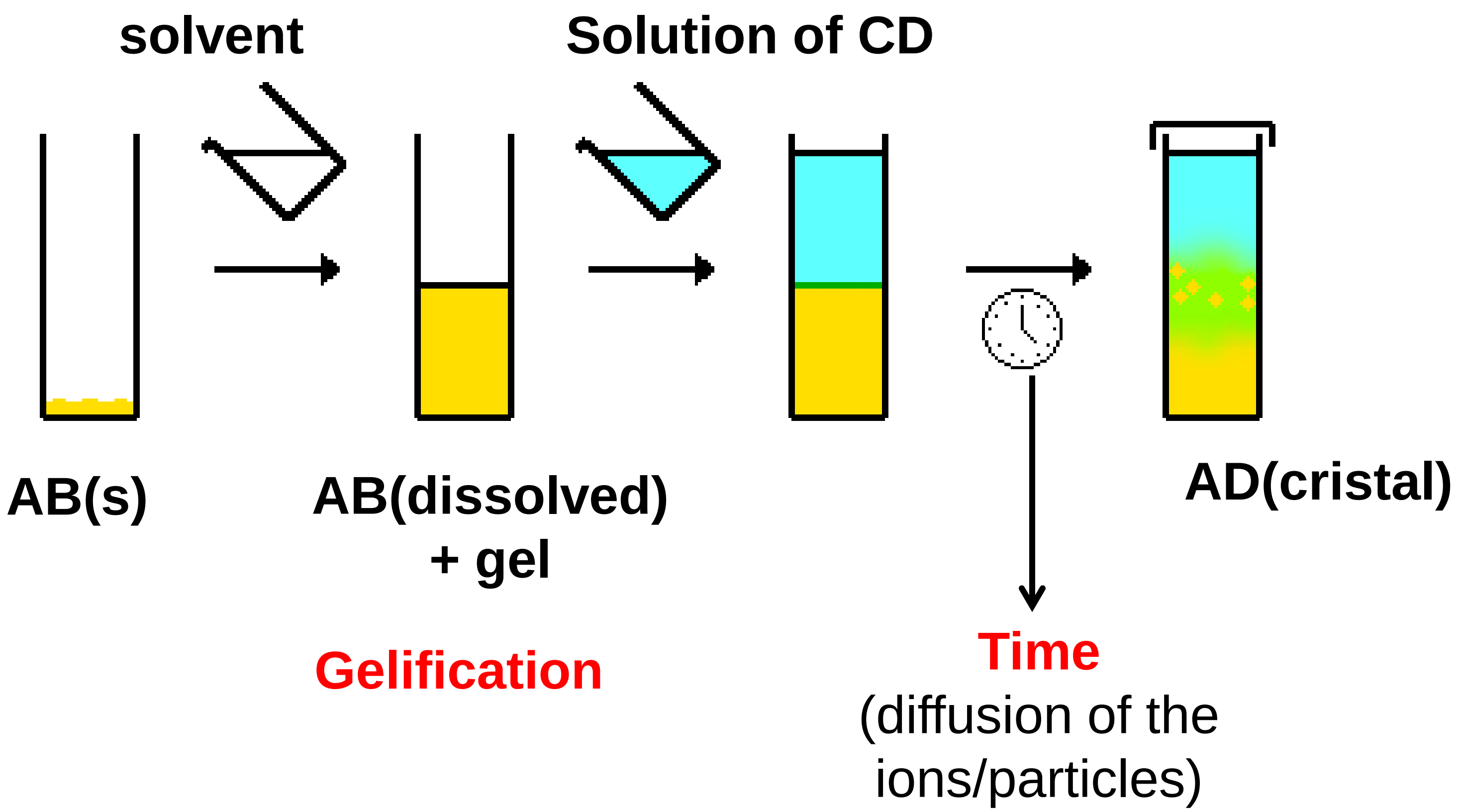
- **Inert media**
- **Diffusion control**
- **Avoid convection (T and mechanical)**
- **Homogeneous supersaturation**
- **Control over nucleation, crystal growth and quality of the crystal**



CRYSTAL GROWING TECHNIQUES

4. Crystallization in Gel

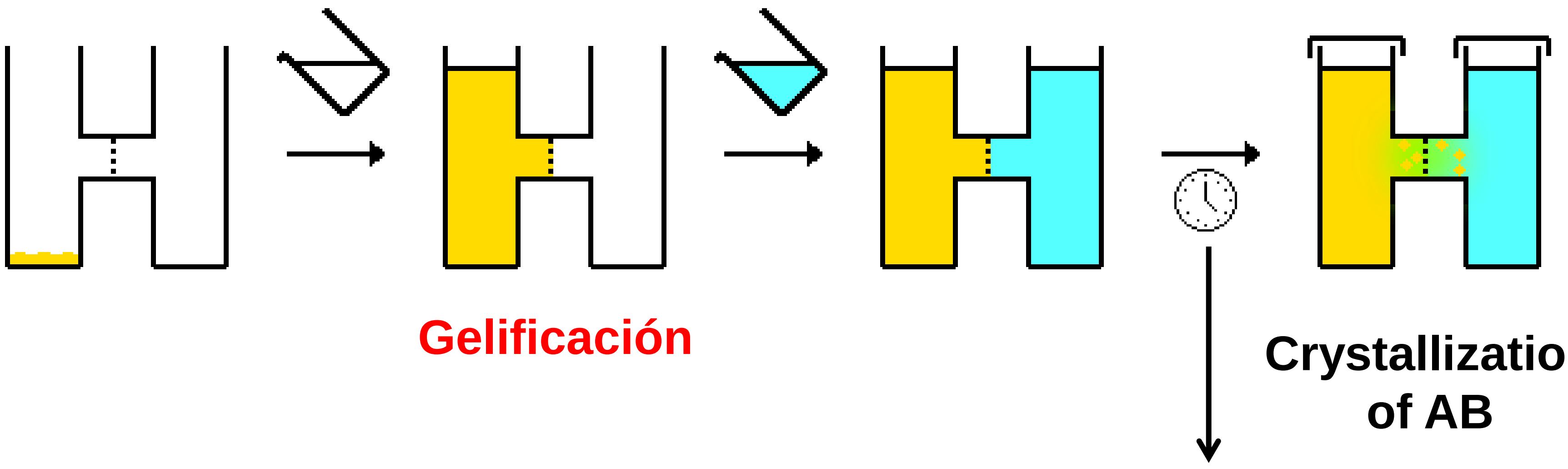
- **Example**



CRYSTAL GROWING TECHNIQUES

4. Crystallization in Gel

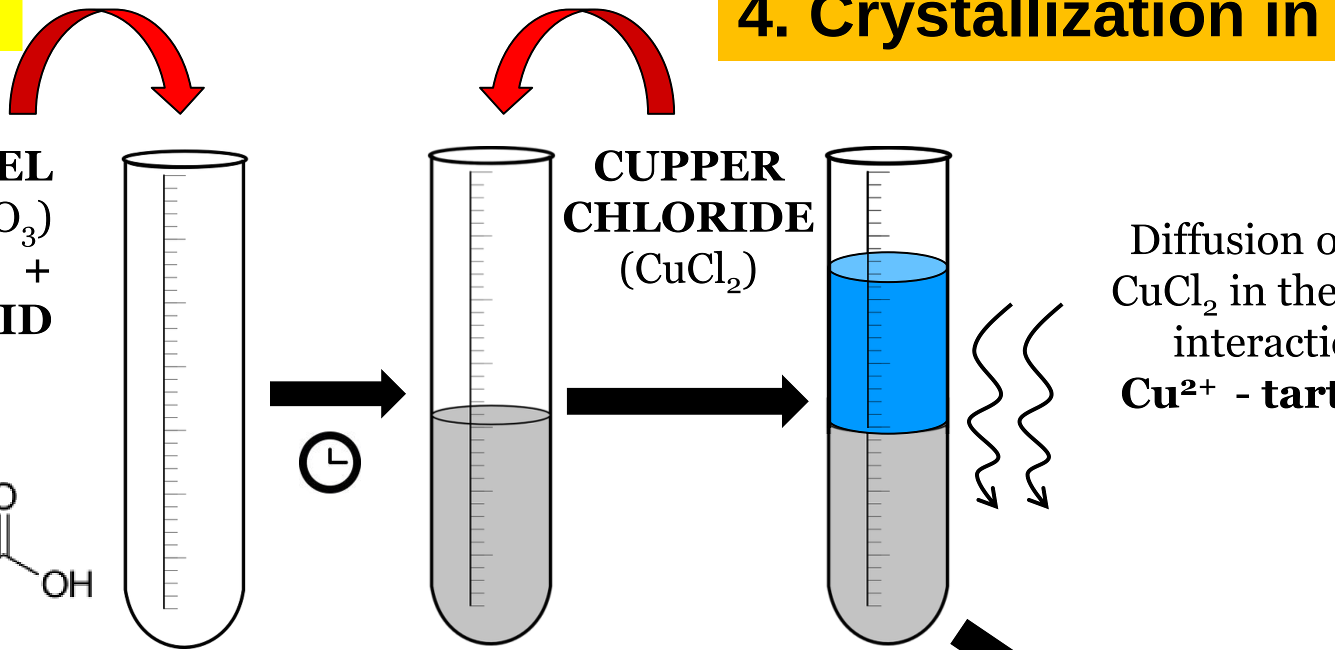
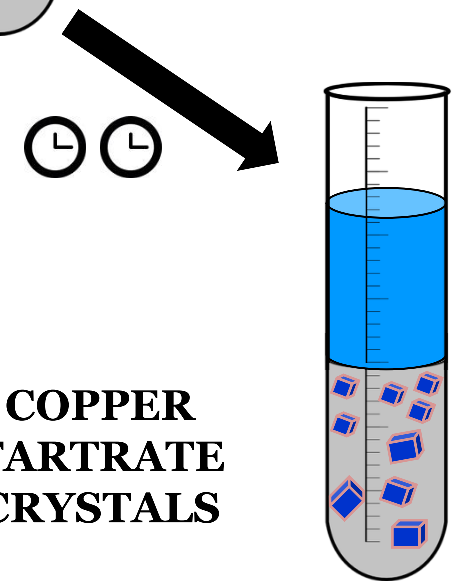
- **Example**

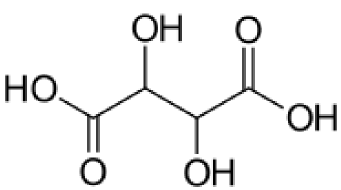


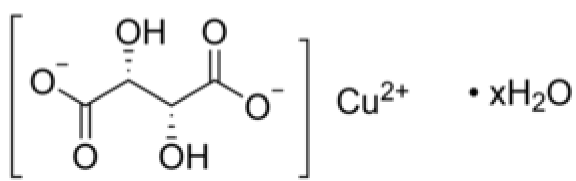
CRYSTAL GROWING TECHNIQUES

- **Example**

4. Crystallization in Gel





■ CRYSTAL GROWING TECHNIQUES

5. Chemical Modification

☑ **Strategy for inorganic compounds tipically**

- **Change of the counterion in order to change solubility and crystallinity.**

- **Counterions of similar volumen/size, usually give place to better crystals.**

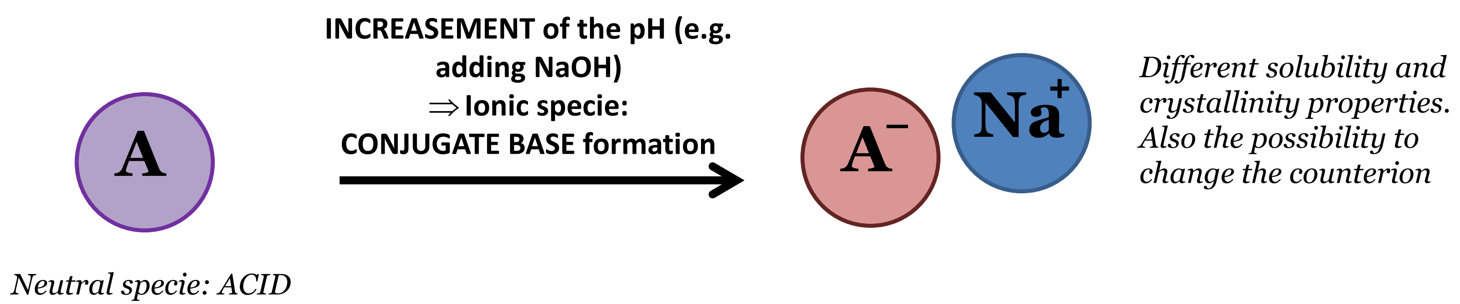
- **Tip: use counterions of rigid geometries such as, triflate, BPh_4^-, Me_4N^+, $(Ph_3P)_2N^+$, Ph_4P^+**
- **Be sure that the counterions do not react with the sample.**

CRYSTAL GROWING TECHNIQUES

5. Chemical Modification

☑ **Strategy neutral compounds that are ionizable**

- **The onic specie could have better supramolecular properties than the neutral, e.g. stronger intermolecular interactions**



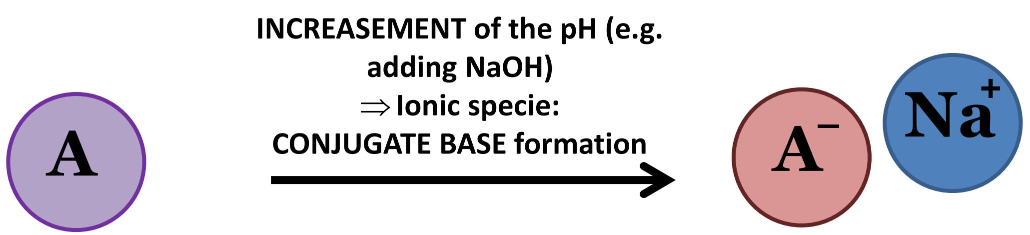
- **Although the resultant system is not the same as the starting material, it could be the only way to get a crystal**
- **Once you have the ionic specie, it is possible to change the counterion as it was illustrated in the previous slide.**

CRYSTAL GROWING TECHNIQUES

5. Chemical Modification

☑ **Strategy neutral compounds that are ionizable**

- **The onic specie could have better supramolecular properties than the neutral, e.g. stronger intermolecular interactions**



Different solubility and crystallinity properties. Also the possibility to change the counterion

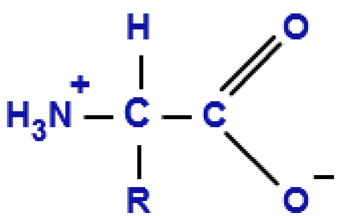
Neutral specie: ACID

- **Although the resultant system is not the same as the starting material, it could be the only way to get a crystal**
- **Once you have the ionic specie, it is possible to change the counterion as it was illustrated in the previous slide.**

CRYSTAL GROWING TECHNIQUES

5. Chemical Modification

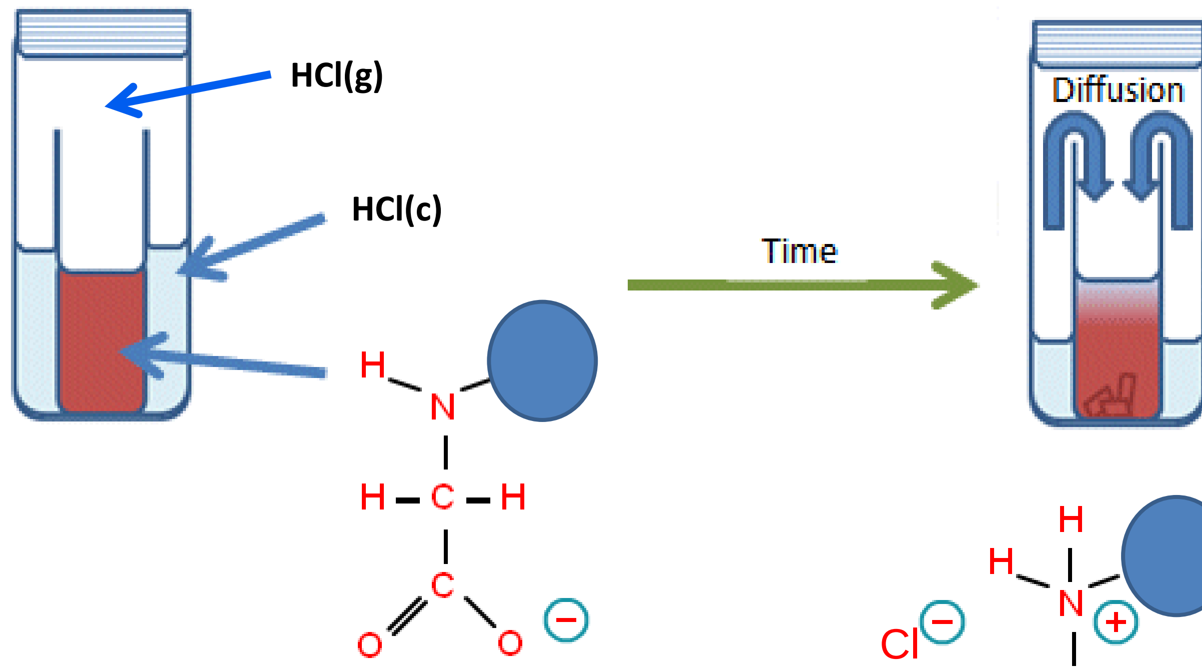
- **Example:**



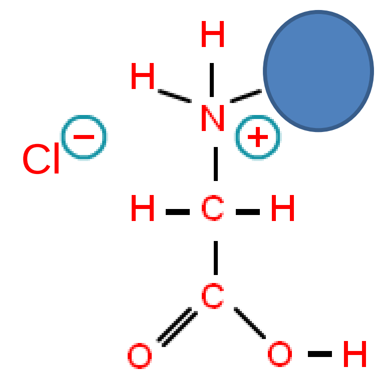
Zwitterion

SOLID FORM
AMINO ACID / AMINO ACID DERIVATIVE
as zwitterion

A-B properties



AMINO ACID DERIVATIVE Dissolved in basic solution H_2O/NaOH

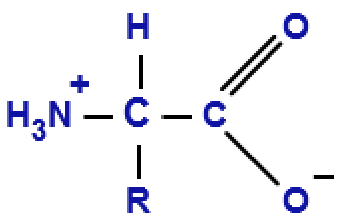


CRYSTALS

CRYSTAL GROWING TECHNIQUES

5. Chemical Modification

- **Example:**

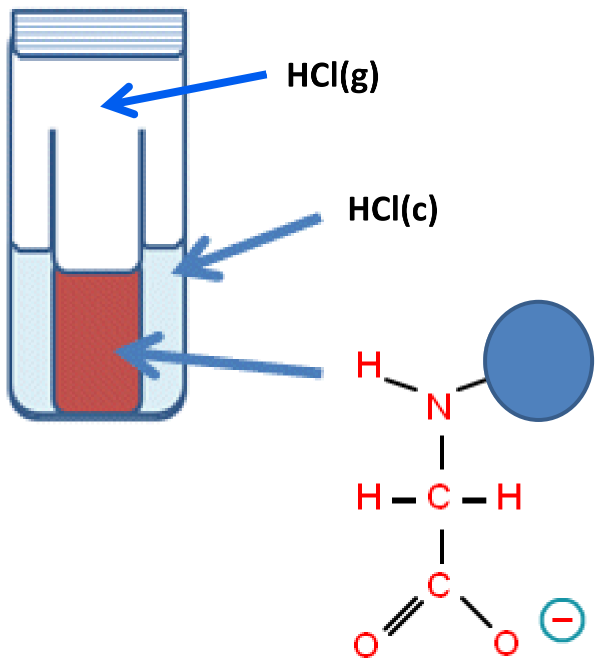


Zwitterion

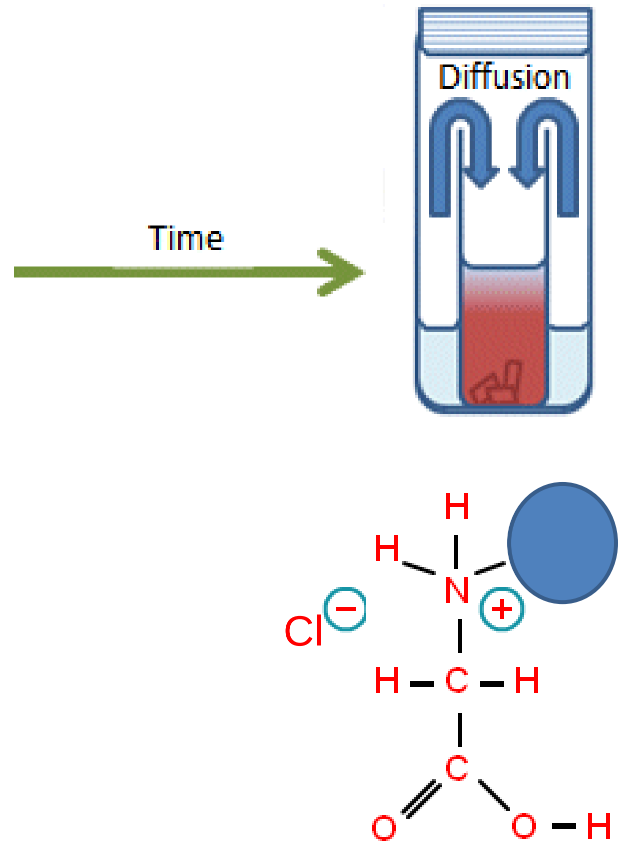
SOLID FORM

AMINO ACID / AMINO ACID DERIVATIVE as zwitterion

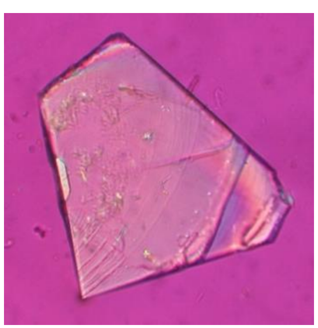
A-B properties

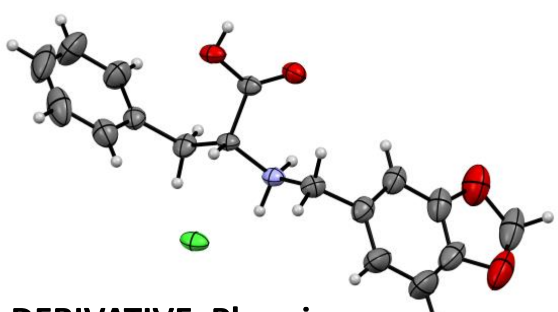


AMINO ACID DERIVATIVE Dissolved in basic solution H_2O/NaOH



CRYSTALS





DERIVATIVE: Phe-pip

CONCLUSIONS AND COMMENTS

●● REGARDING THE COMPOUND TO BE CRYSTALLIZED ●●

- **Purify the compound to be crystallized before the crystallization EXPERIMENT.**
- **Know the physical properties such as, thermal stability and solubility.**
- **Develop a solubility profile of the compound of interest.**
- **Use clean material**
- **Test different crystallization conditions in parallel.**
- **Use enough material (do not use low mass)**

■ CONCLUSIONS AND COMMENTS

●● REGARDING YOUR ACTTITUD ●●

- **Crystals growth of is a difficult art, unpredictable, takes a long time and without guarantee of success.**
- **The best crystallization conditions are not known in advance. Therefore, it is important to try different techniques and variables.**
- **The quality and precision of the results obtained from the crystals (crystal structure) depends directly on the quality of the crystals. Therefore, consider crystal growth strategies as research projects themselves.**
- **To be successful you need time, effort and a lot lot of patience!**

REFERENCES

http://xray.chem.uwo.ca/Guides.html

http://web.mit.edu/x-ray/cystallize.html

http://www.iucr.org/education/teaching-resources/crystal-growing

https://www.iucr.org/education/pamphlets/20/full-text-english

https://www2.chemistry.msu.edu/Facilities/Crystallography/xtalgrow.pdf

http://blog.autochem.mt.com/2011/03/supersaturation-driving-force-for-crystal-nucleation-growth/

Juan Manuel García-Ruiz *J. Chem. Ed*. *76*. **1999**, 499-501

Journal of Crystal Growth, Volumes 3–4, 1968, Pages 377-383)

Advanced readings

https://str.llnl.gov/str/DeYoreo.html

Zeolites and Catalysis, Synthesis, Reactions and Applications. Vol. 1.

Edited edited by Jiri Cejka, Avelino Corma, Stacey Zones. 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Cap5. Nucleation

Protein crystal growth

Dessau M.A., Modis Y. (2011). Protein Crystallization for X-ray Crystallography., JoVE. 47. http://www.jove.com/details.php?id=2285, doi: 10.3791/2285