Two Acute Problems Among Molecular Crystals: (1) Structural Purity (2) Fluid Inclusions

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Agenda

Strutural purity?.....(definition, problems, ….)

Fluid Inclusions

Discussions and no conclusion!…

Introduction to structural purity

Literature can simply be quoted to highlight the importance of the 'structural purity' :

'The question of structural purity is, in many areas of chemistry, as important as that of chemical purity'

S.C.B. Aakeröy & K.R. Seddon, Chem. Soc. Rev. 1993, p 404

Is there a clear definition which received consensus ?....

Proposition of a definition for the so-called ‘structural purity’ :

In addition to the pre-supposed chemical purity, a solid is ‘structurally pure’ when it exhibits the same 3D arrangement for every particle.

Coquerel, G., The 'structural purity' of molecular solids-An elusive concept? *Chem. Eng. Process* 2006, 45, 857-862.

1) All types of defaults and disorders are homogeneously distributed among the particles. i.e. : nature , distribution and concentration of defaults…….(pb with the surface!…)

2) The thermodynamic state of the sample is not explicitly mentioned . The sample can be stable, metastable or even out of equilibrium.

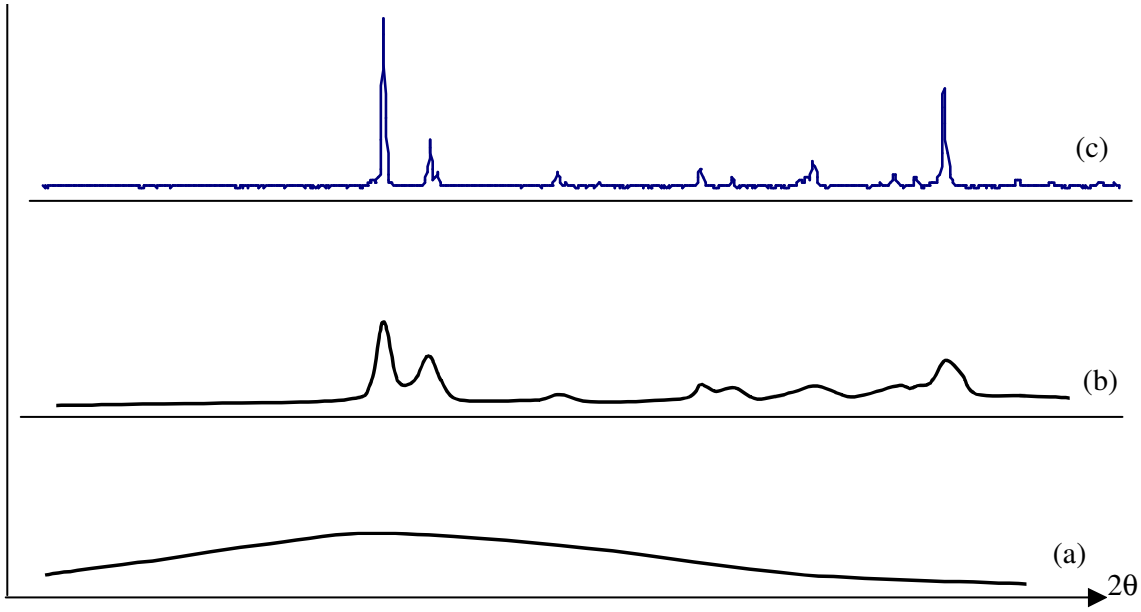
3) A glass can be made of structurally disorganized individual molecules but it can be constituted of randomly distributed dimers as well. Each of these pure two glasses is considered as a structurally pure substance (different Tg might be observed): polyamorphates (ss-nmr).

4) Polytypism (see : Polymorphic-polytypic transition induced in crystals by interaction of spiral and 2D growth mechanism. D. aquilano, S. Veesler, J-P. astier & L. Pastero, J. Cryst. Growth, 2003, 247, 541-550).

See also 'one- pot polymorphism of nonlinear optical materials. First example of organic polytypes' , T.V. Timofeeva et al. Crystal Engineering, 3, (2000), 263-288

5) Incommensurable phases (4D, 5D, 6D structure), SiC , Sulphur, …….

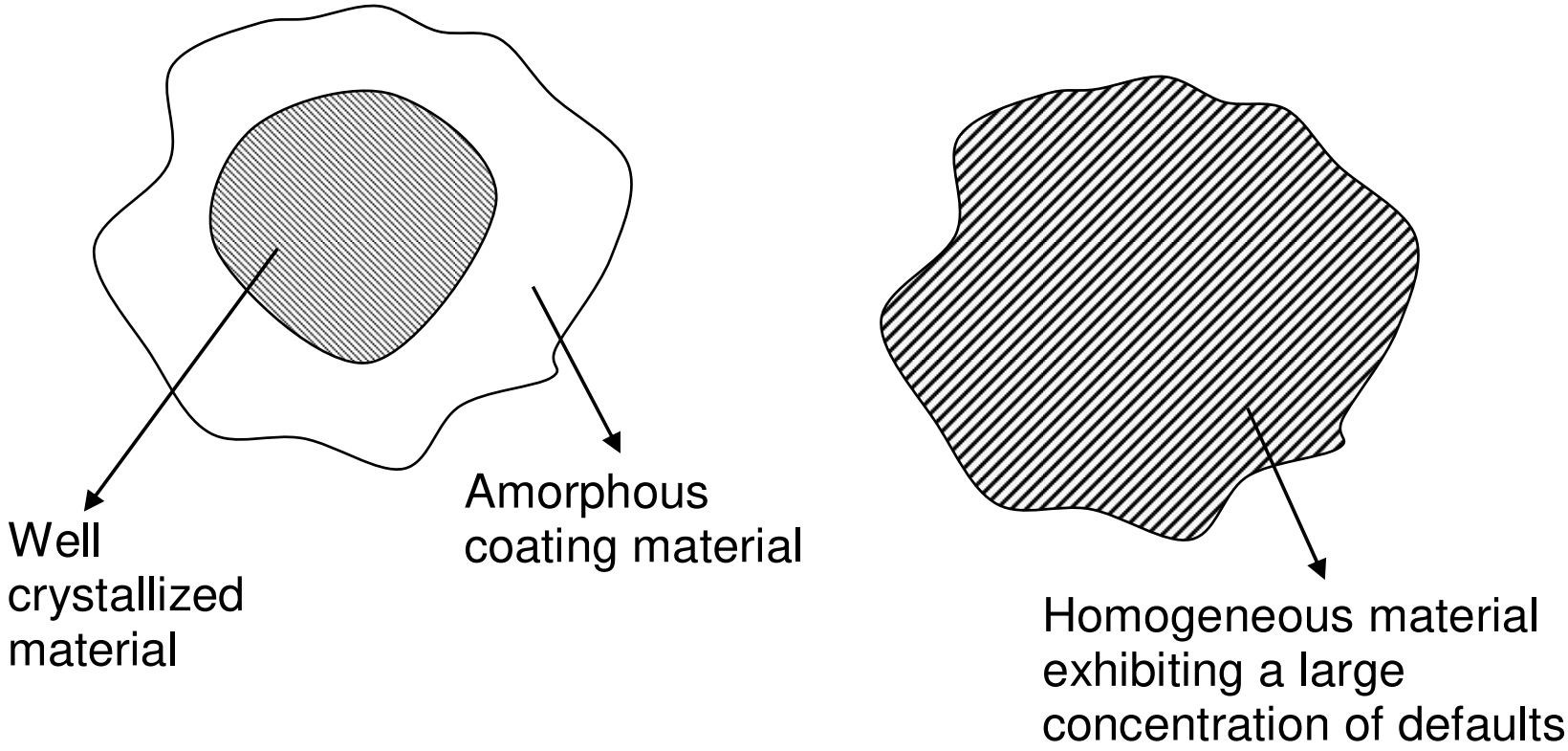
Schematic representations of various XRPD patterns of a supposed chemically pure substance; particle size ≈ 50 µm



From the definition, if a chemically pure compound is made up with x % of amorphous material and (100- x) % of crystallized material, it is not structurally pure.

i.e. (a) plus (c) is different from (b) .

Homogeneity and heterogeneity of the LRO



The superficial layers of the particles undergo more stress than the core: i.e. on ageing the stuctural purity can deteriorate.

Practical limitations of the concept of ‘structural purity’

The evaluation of the ‘structural purity’ relies on the detection, characterization and ultimately quantification of the phases and the distribution of defects in the solid state.

When the crystal structure is resolved with a good reliability factor (c.a. < 5%), the corresponding XRPD pattern can be calculated.

Extra peaks without possible hkl assignment reveal the presence of (at least) another crystallized phase. If the chemical purity is not questionable, one (several) structural impurity(ies) has (have) to be considered.

Unfortunately, the access to the single crystal for every polymorphic form and/or solvate is rather exceptional.

In many cases several polymorphic forms (and/or) solvates can only be identified by their XRPD patterns.

The problem becomes more acute when the crystallinity of the phases is poor.

Practical limitations of structure determination via single crystal X-ray diffraction

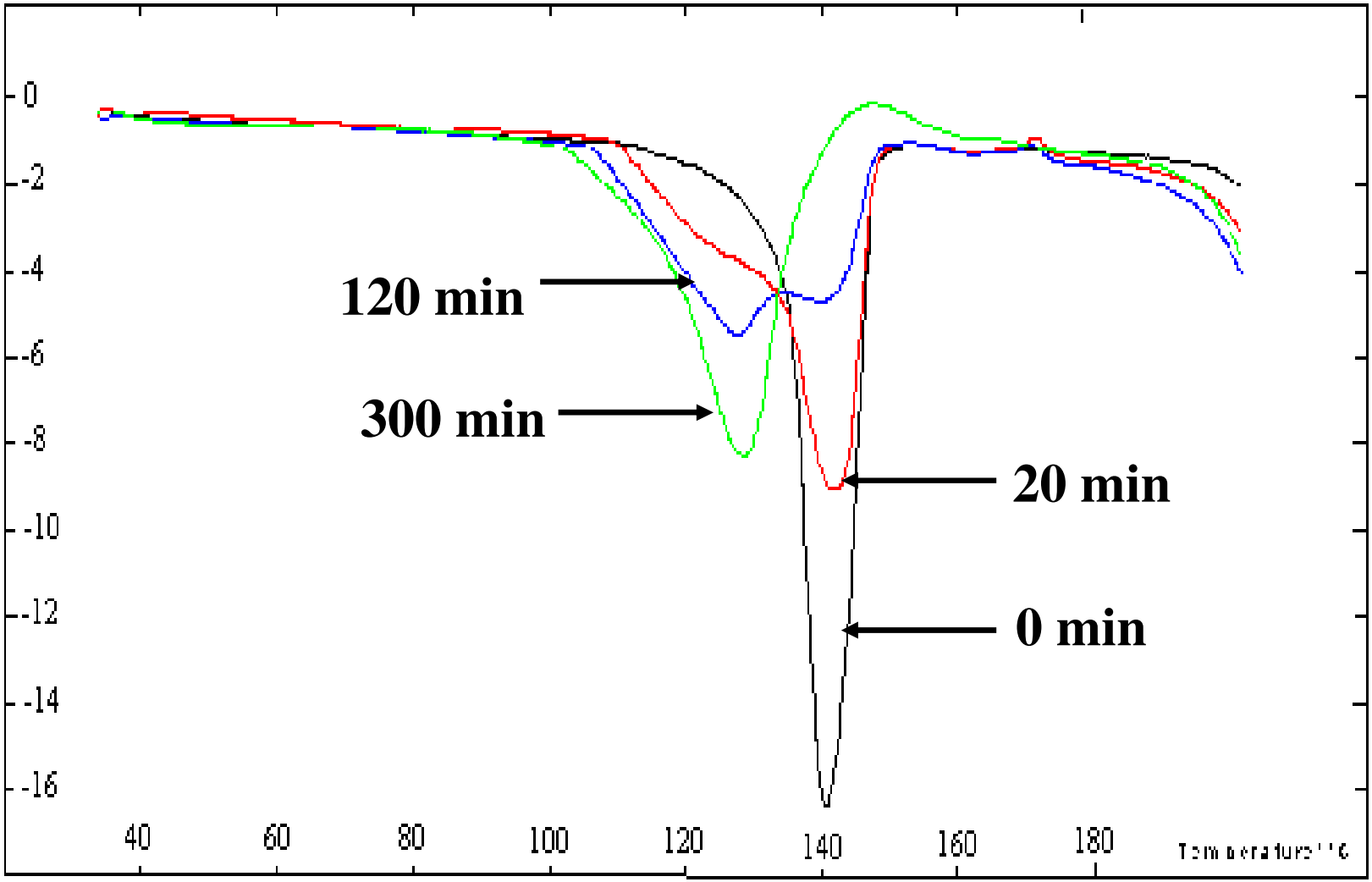
X-ray diffraction on single crystal gives only an average ideal structure regardless defaults

e.g. Elena Cariati et al. New J. Chem. 2002, 26, 13-15

Trans-stilbazole is well resolved in P $2_1/c$ space group but exhibits a significant SHG effect !!!…..

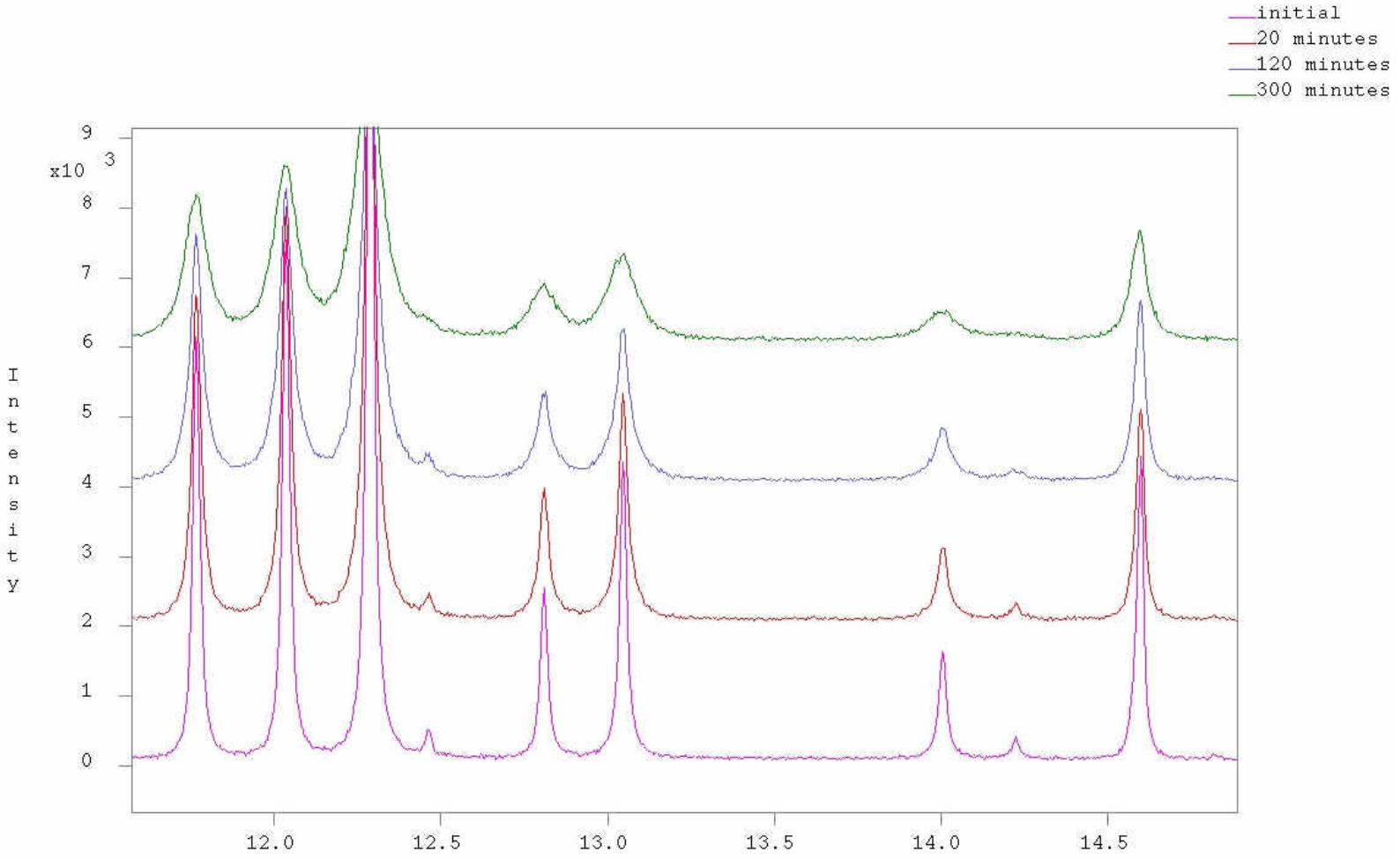
Average crystal structure allows sequence errors. Crystals are twinned with a disordered central part that gradually transforms into two ordered Pc domains of opposite polarity on the two side of the needles.

Thermal behaviour of α-Lactose under the influence of 'soft' grinding



Int. J. Pharm. 2008, 361, 131-140.

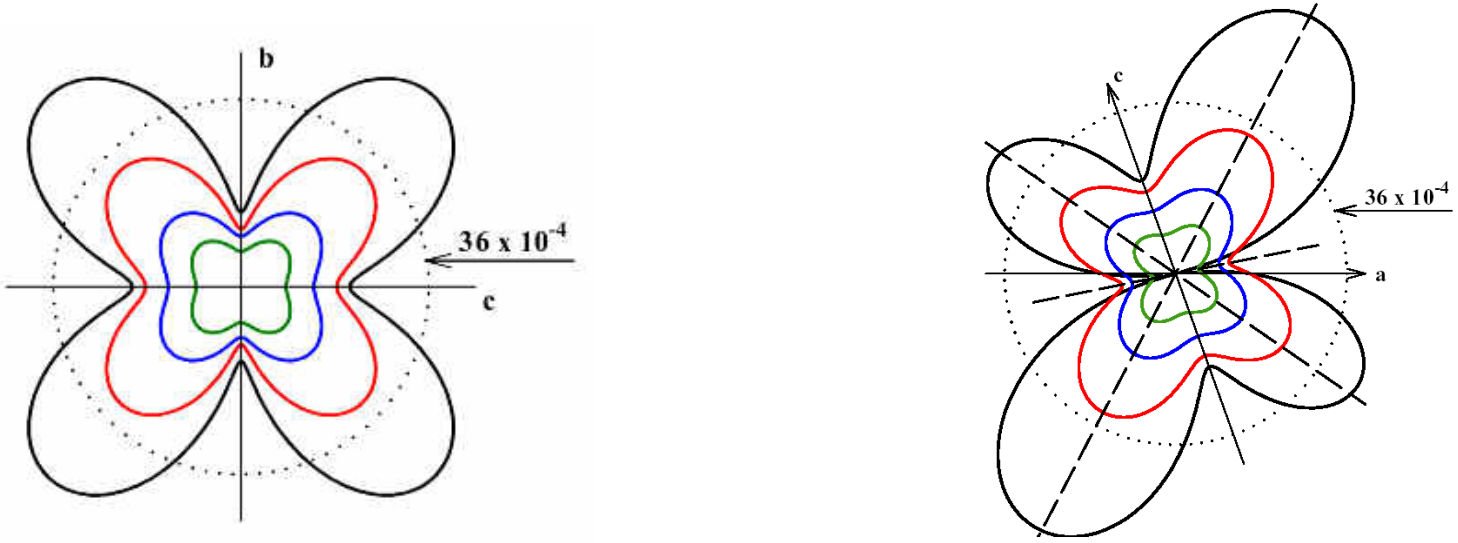
Example of difficulty to check if the structural purity is preserved after a mechanical treatment.



Close examination with a zoom in

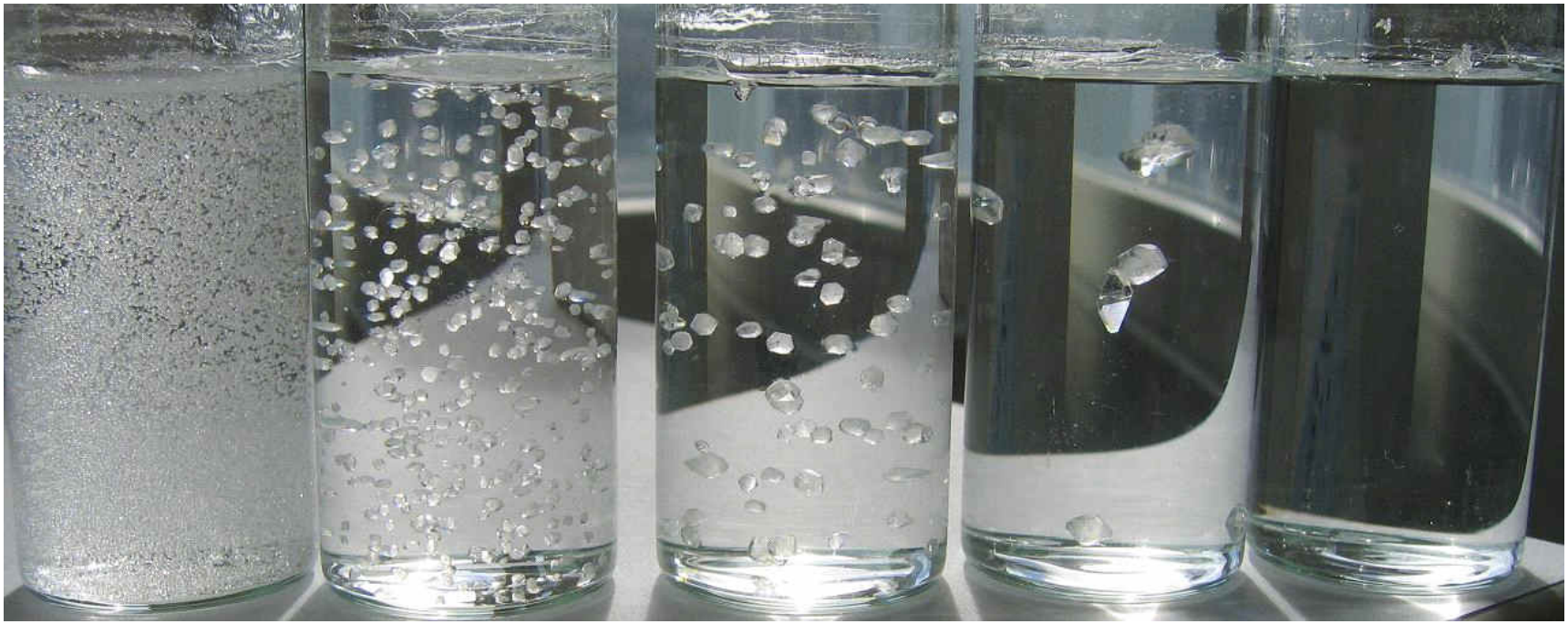
Anisotropic strains after ‘soft’ grinding (at 20°C)

Water molecules are located between (020) planes in channels parallel to c axis . The grinding may have a shearing effect, creating shortcut pathways.



FullProf [Rodriguez-Carvajal, 2001] interfaced by WinPLOTR graphic software [Roisnel and al, 2001]

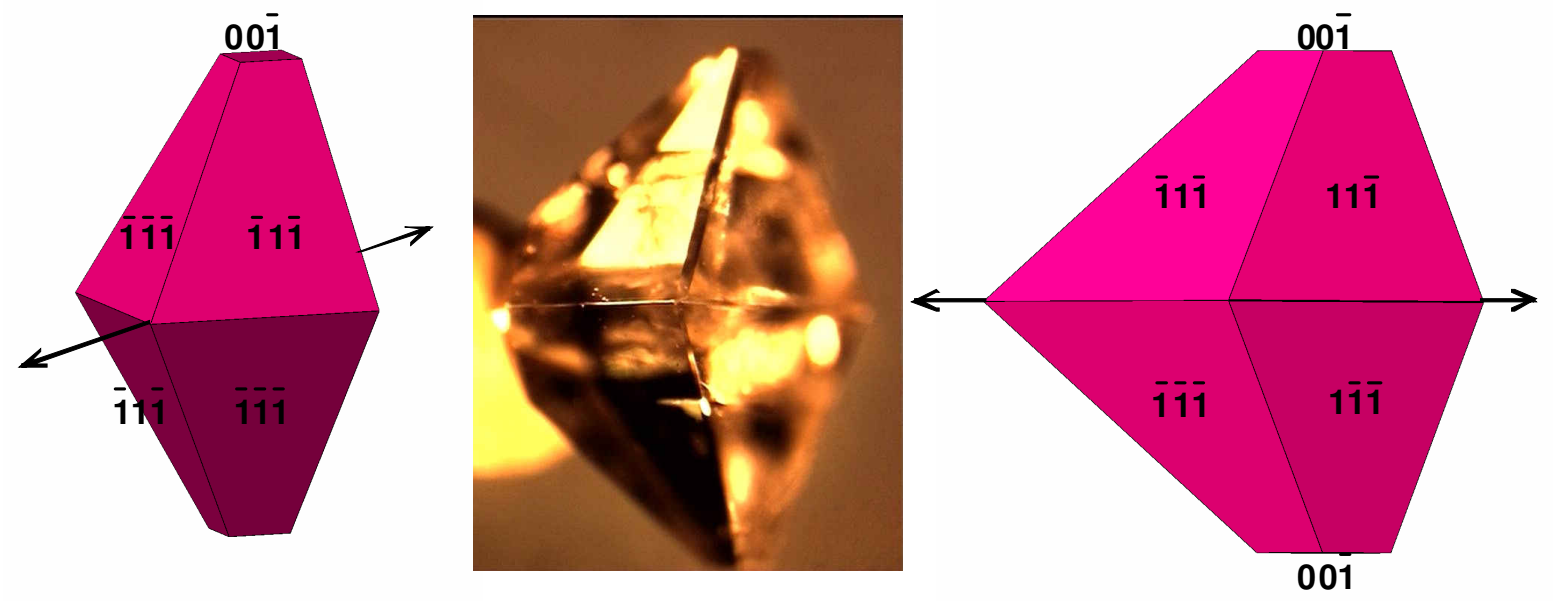
Crystal growth in gel versus concentration
Rac Modafinil



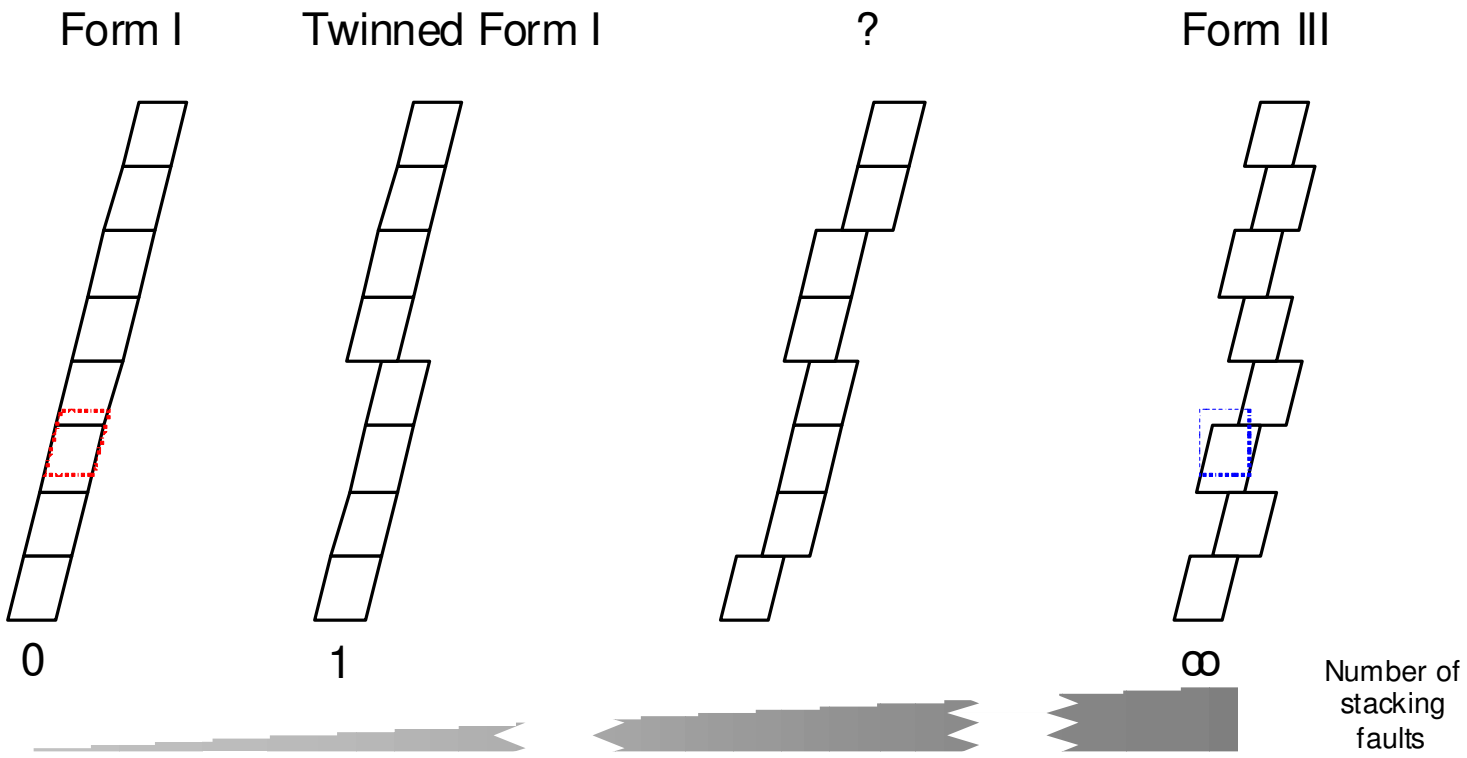
Gel = TMOS

Crystal Growth & Design **2004, 4, (6), 1143-1151.**
Crystal Growth & Design **2007, 7, (9), 1612-1614.**

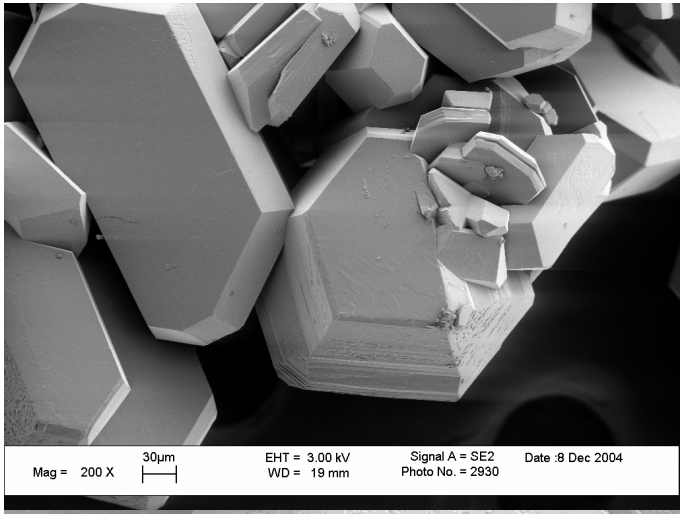
Twinned Form I = 2D form III

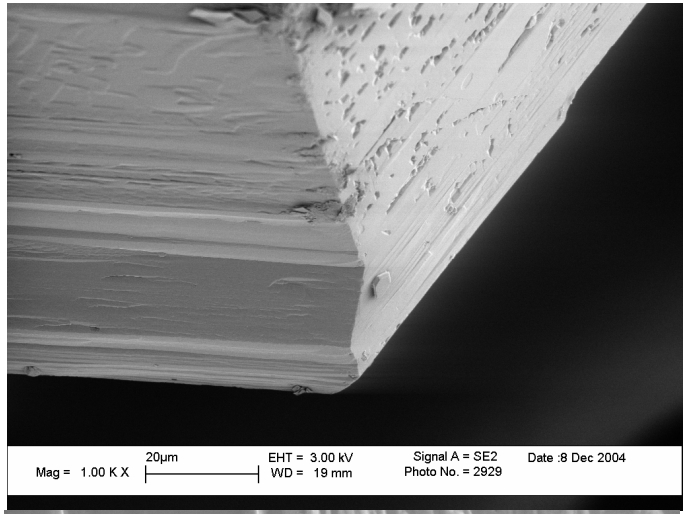


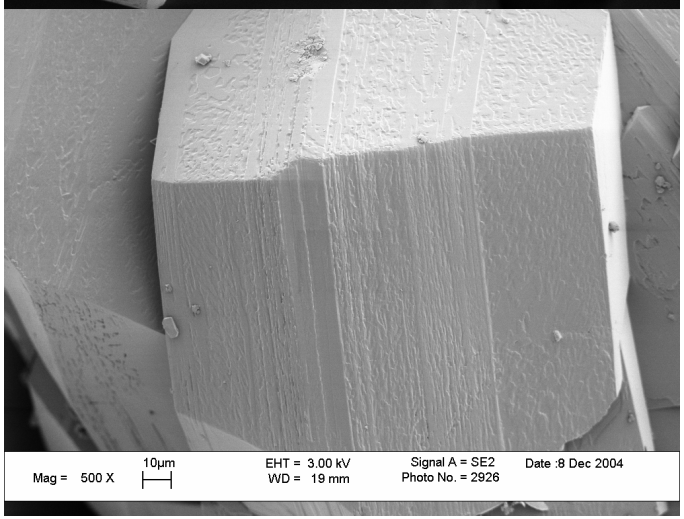
Error on the one side of the packing is the rule on the other (and vice versa !)

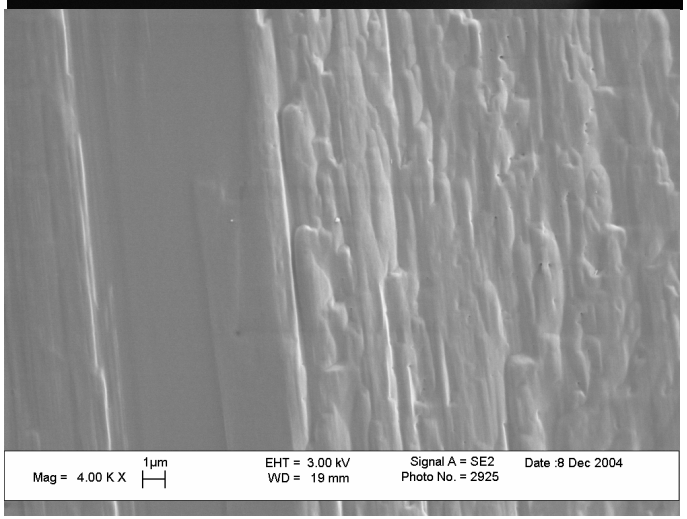


Visual evidence !….

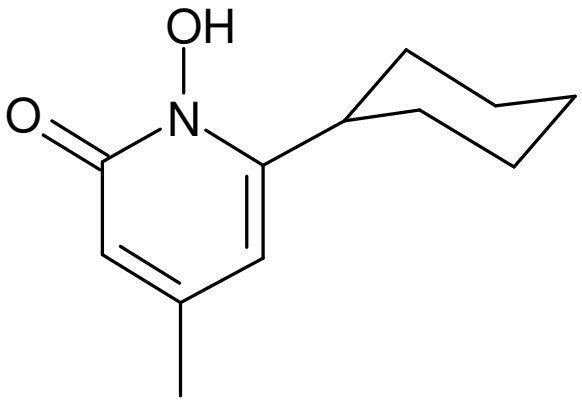


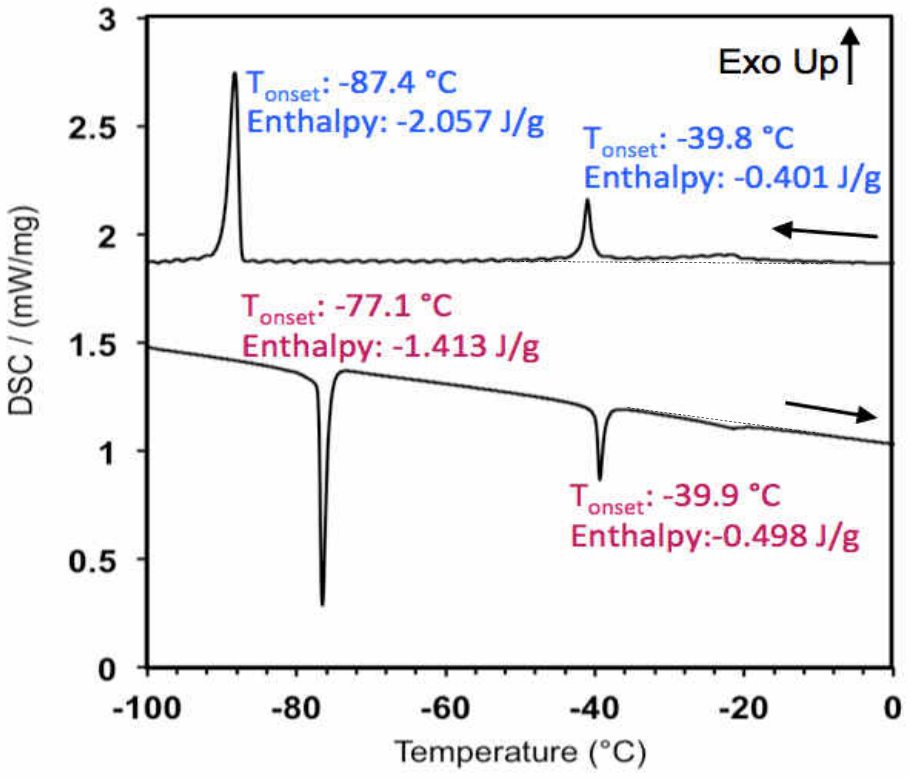






Ciclopirox: saga at low temperature…..

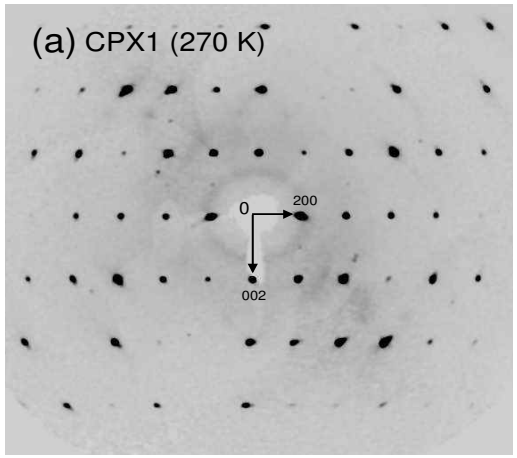


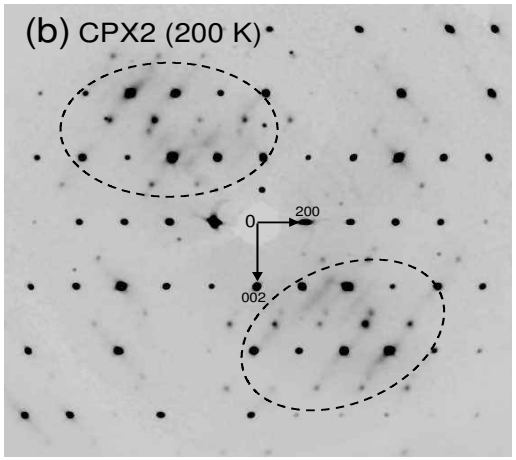


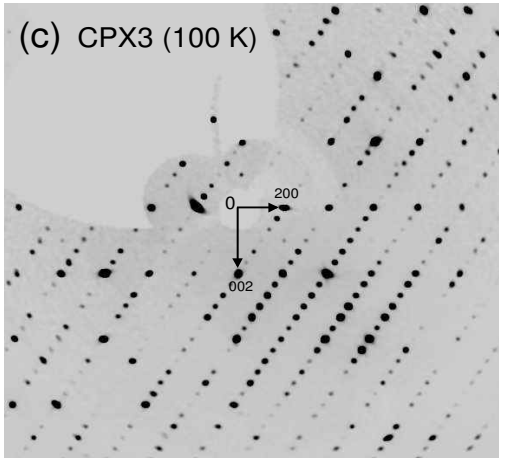
Chemistry of Materials, 2015, 27, (18), 6360-6073

Ciclopirox : X-ray on single particles of forms I, II and III

Visual inspection of the reciprocal lattice (h*0*l*)

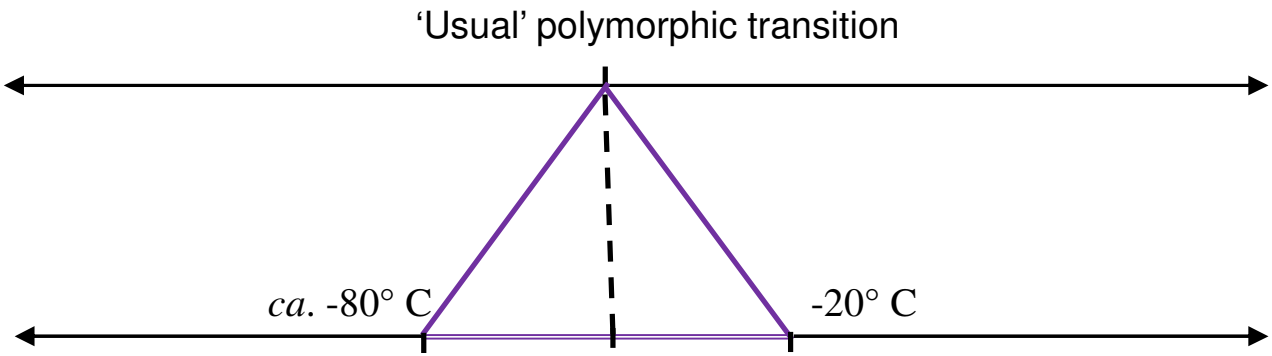






Streakings persist even after long annealing

Deconvolution of a polymorphic transition ?

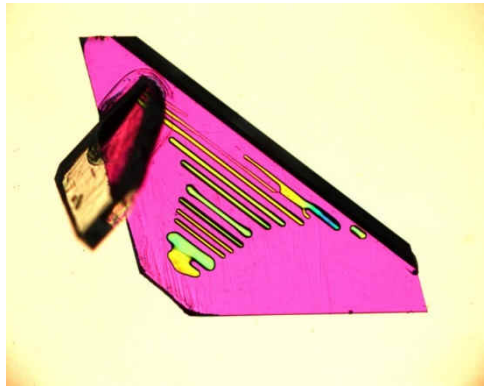


CPX3	$CPX2_{LT}$ $CPX2_{HT}$	CPX1
Z'= 12	Z' = 20 or 40	Z'= 1
$P2_1/c$	P1 or P-1	C2/c
LROrder	LRDisorder	LROrder
Mol Order	Mol. Order	Mol. Disorder

Structural purity here?

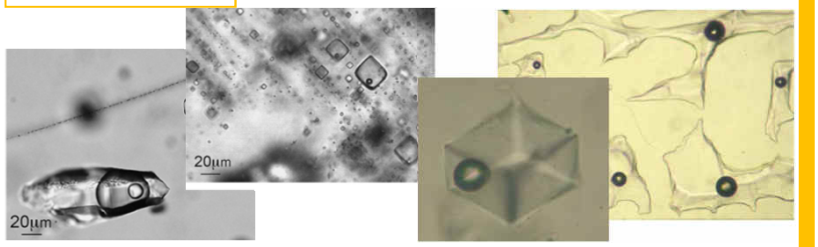
Motivation for studies on formation of vacuoles in crystals

- Detrimental properties of crystals with inclusions (i.e. 3D defects):
  - Chemical purity (pharmaceutical industries)
  - Residual solvents (pharmaceutical industries)
  - Choc sensitivity (energetic materials)
  - Possible caking and other adverse phenomena on ageing
  - Possible modification of the polymorph on ageing
  - Modifications of the optical and mechanical properties
  - Etc.



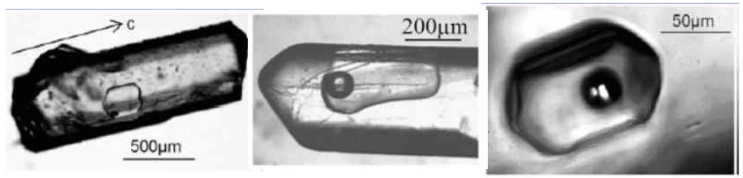
Examples of Fluid inclusions in Literature

Minerals



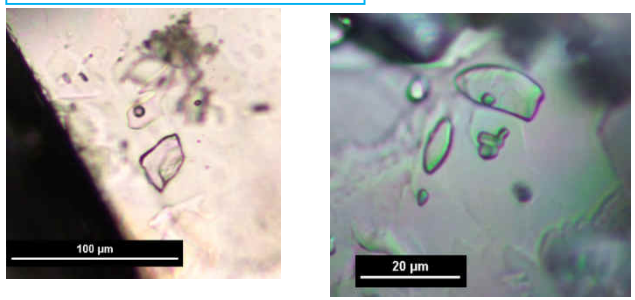
J. Geochem. Explo. 2012, 112, 1-20.
Encyclopedie of Geology 2005, Elsevier, UK.

Crystal drugs

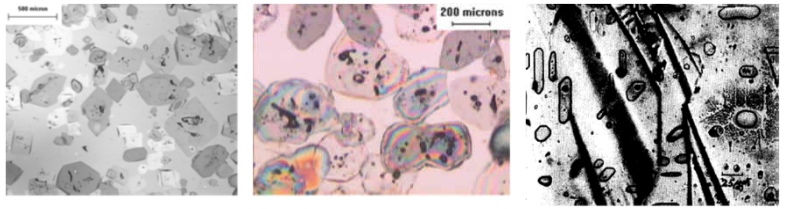


Cryst. Growth Des. 2011, 11, 2580-2587.
J. Cryst. Growth 2012, 342, 72-79.

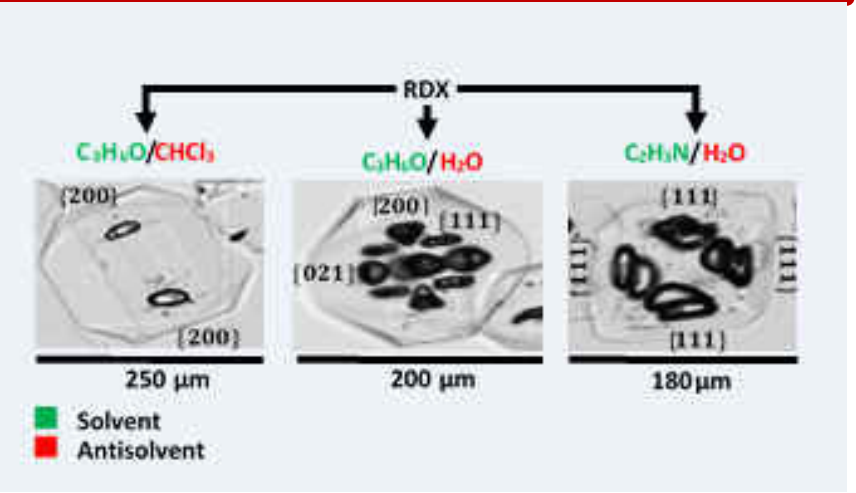
Daddy® Sugar



RDX Crystals

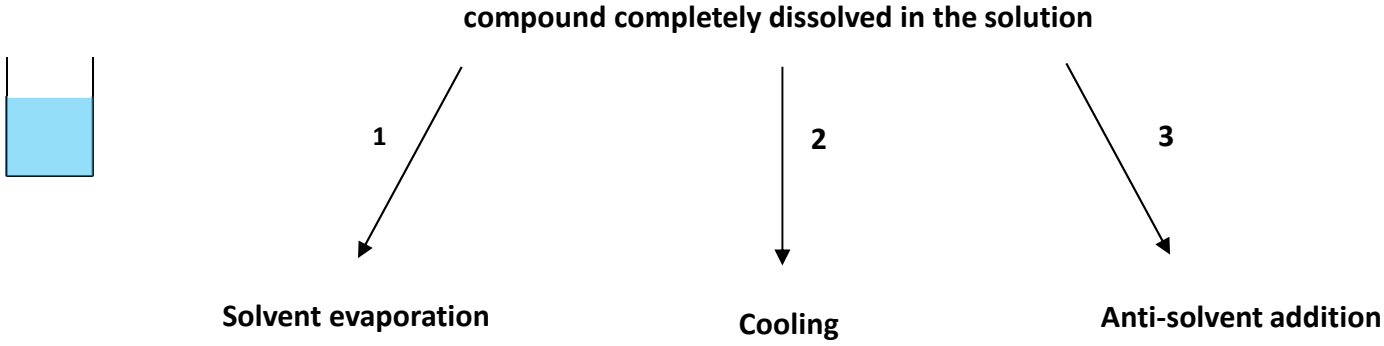


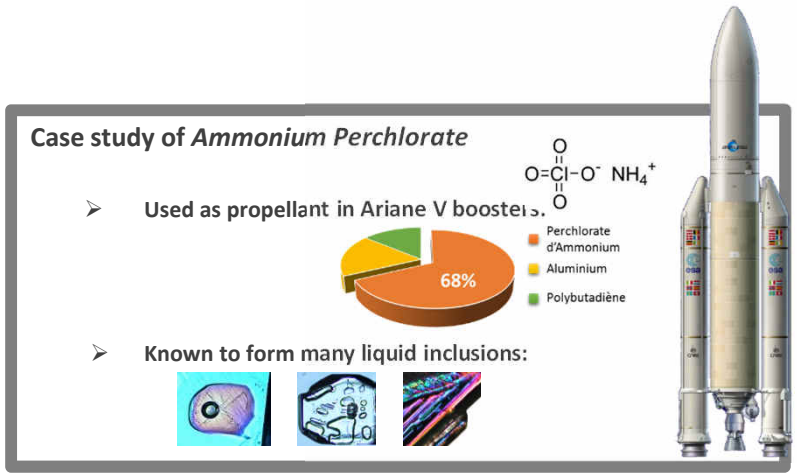
Org. Process Res. Dev., 15, 602-609, 2011
Cryst. Growth Des., 9, 6, 2009
J. Cryst. Growth, 6, 210-212, 1970

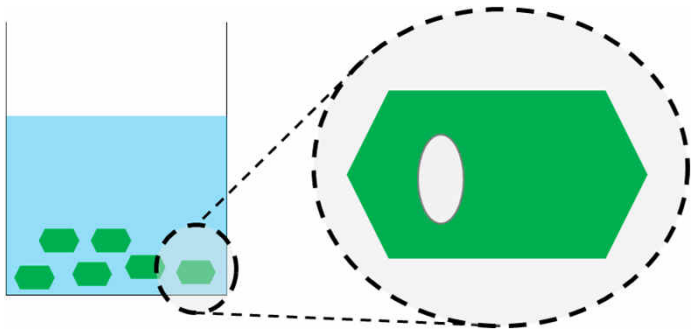


Cryst. Growth Des. 2020, 20, 7120–7128

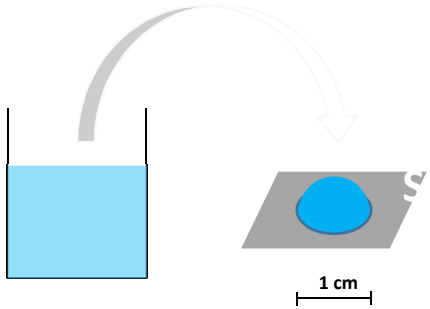
Crystallization from Solution





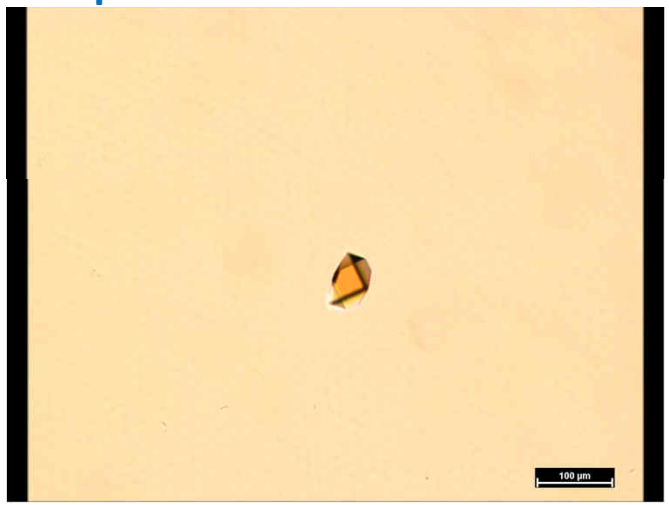


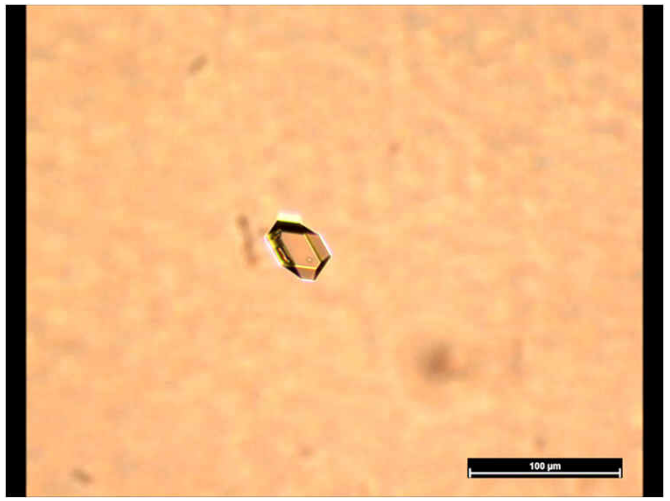
Monitoring of crystal growth under stagnant conditions



Images recorded with optical microscope connected to a camera, to analyze the crystal growth

Saturated aqueous solution of AP





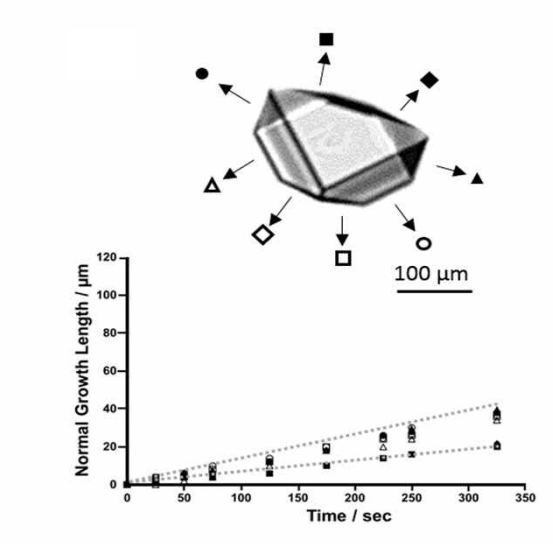
Normal growth rate measurements

Crystal free of inclusions

Smaller

Isometric Shape

Homothetic growth around the center of gravity



VS

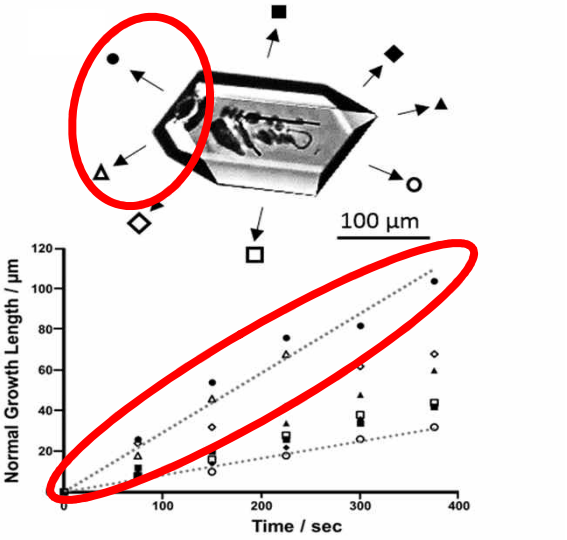
Crystal forming inclusions

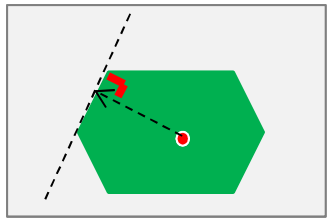
Bigger

Elongated shape towards liquid inclusions

Non-homothetic growth

Displacement of the center of gravity





Correlation between:

High growth rate and Formation of inclusions

&

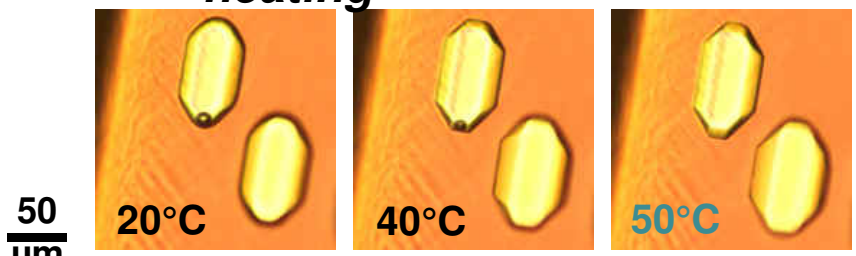
Localized on a specific face

Chem Eng Technol 2015, 38.

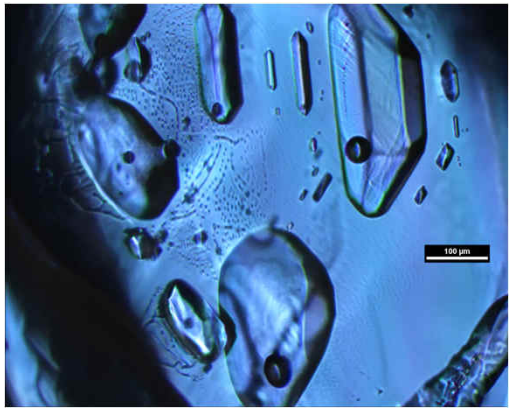
Two kinds of gas bubbles

Shrinkage Bubbles or retreat Bubbles:

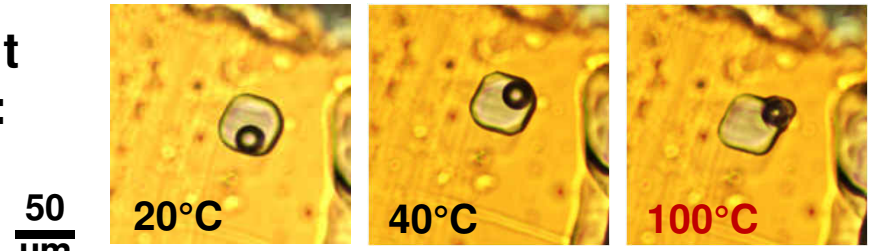
Different behaviors upon heating

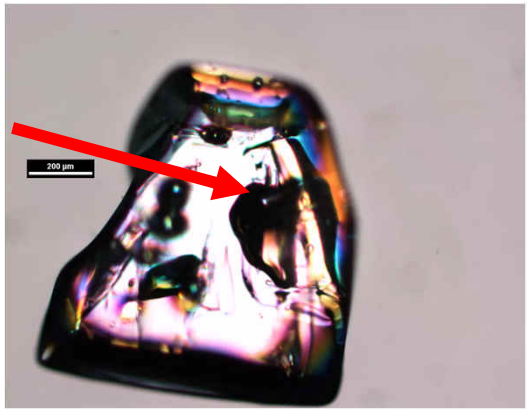


Different behaviors during crystal dissolution



Persistent Bubbles:

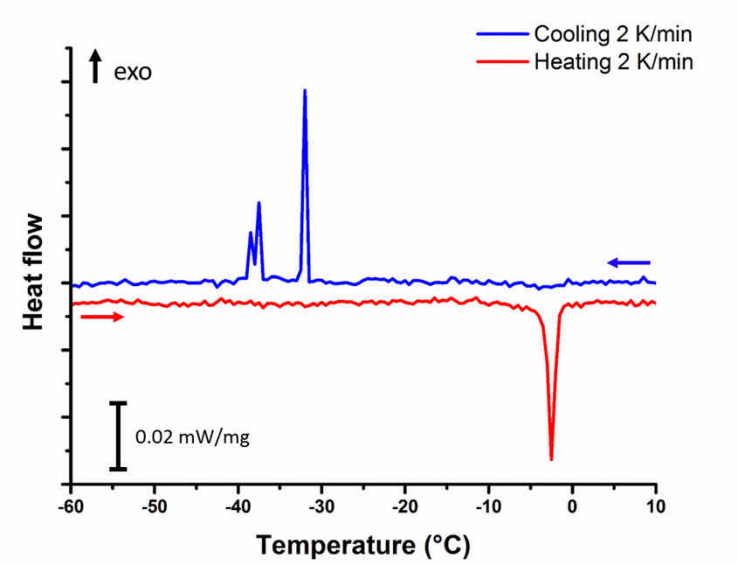


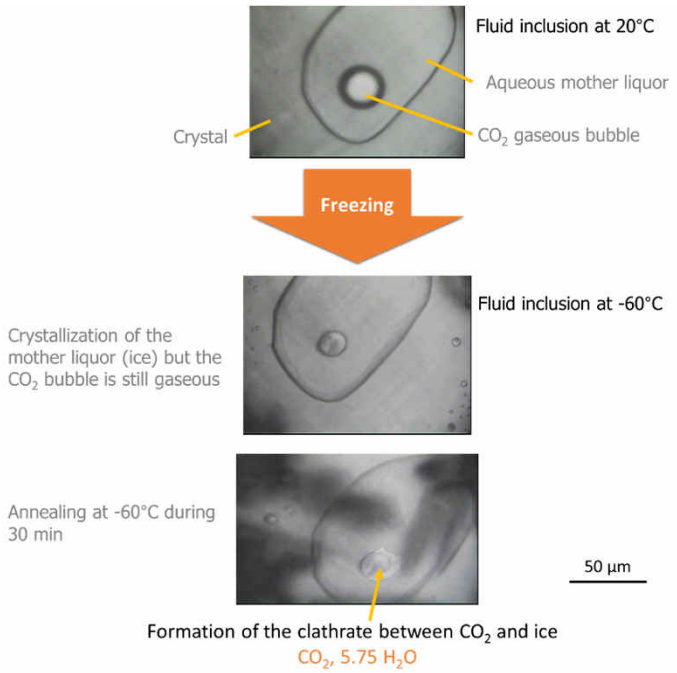


Cryst Eng Comm 2016, 18, 5287–5295

Freezing of aqueous inclusions

DSC data from the fluid inclusions

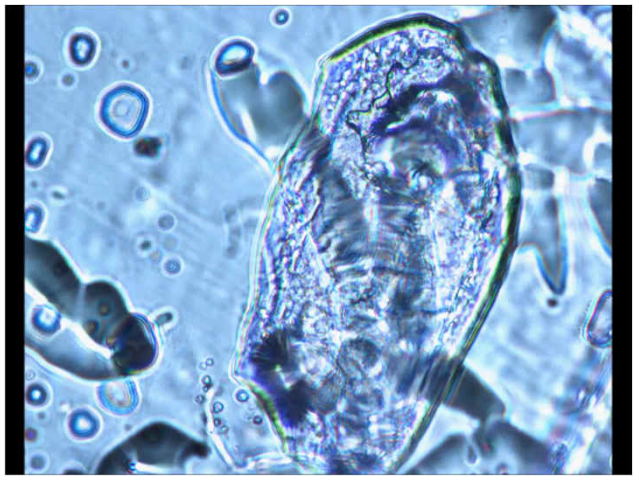




Monitoring of the melting of the mixture: Clathrate + Ice

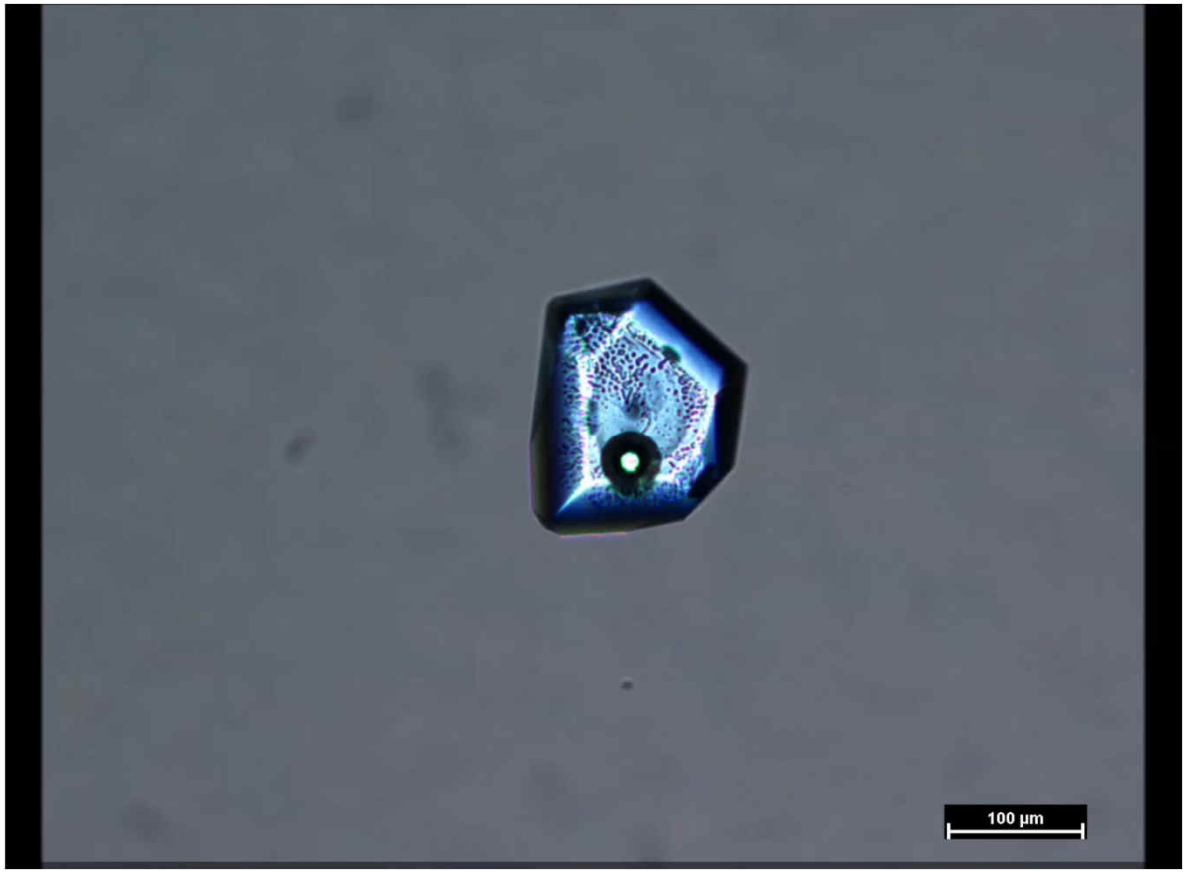
Heating 5 K/min (x32)

From -45°C up to 0°C



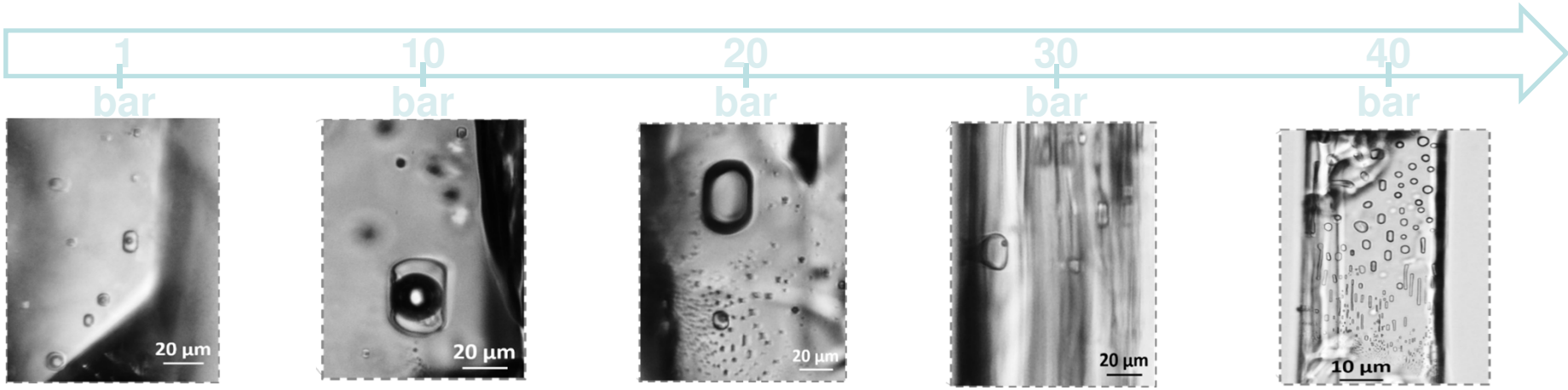
Melting at ca. -2°C

Air bubble trapped by Ammonium Perchlorate single crystal



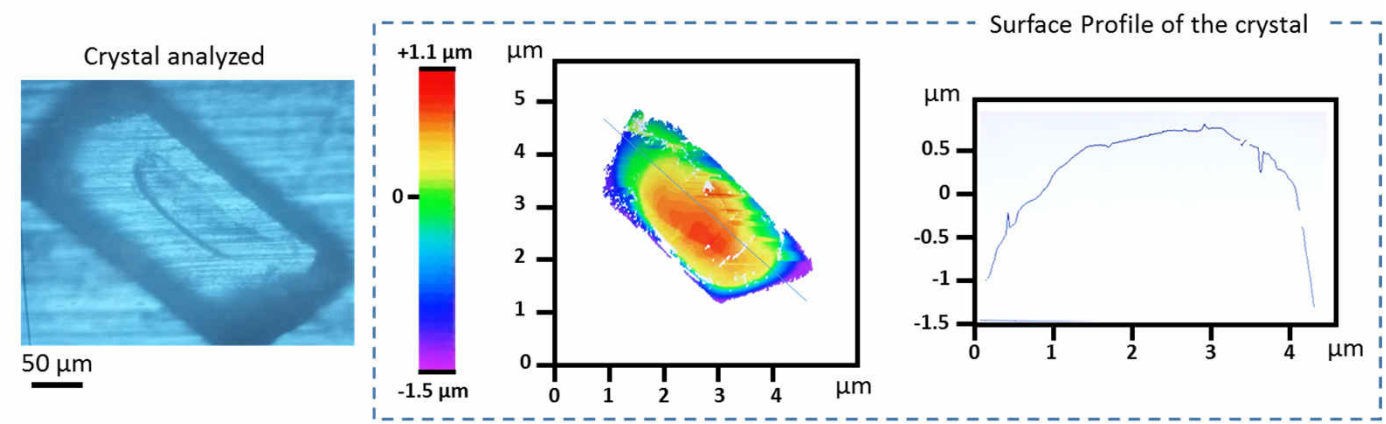
Case study of NMU crystallized in IPA

- ↗ **Pressure of CO_2**
- ↗ **Crystal size**
- ↗ **Amount of inclusions**



Impact on the crystal surface

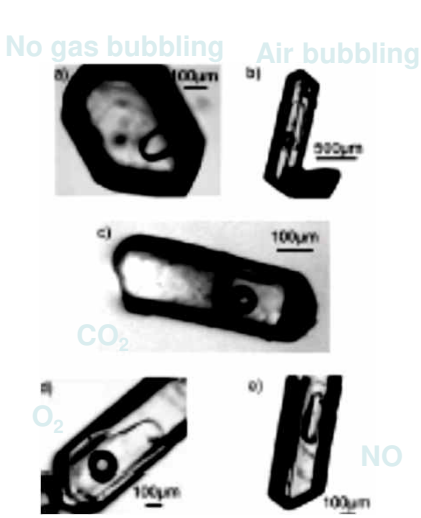
Interferometry data on Ammonium Perchlorate single crystal



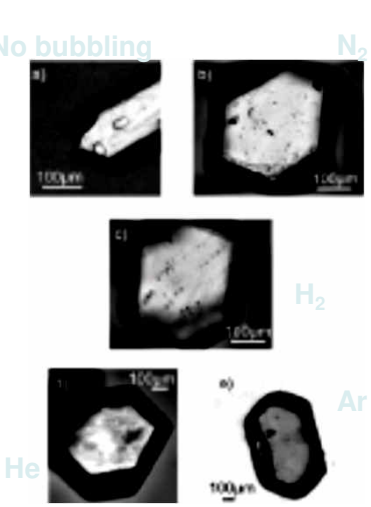
Deformation of the crystal lattice in the vicinity of the vacuole when its is not far from the surface

Influence of dissolved gases: Case study of Ciclopirox

Gases containing oxygen atom

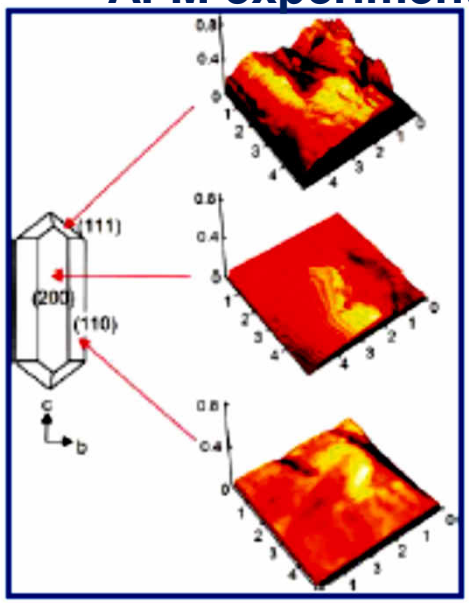


Gases not containing oxygen atom

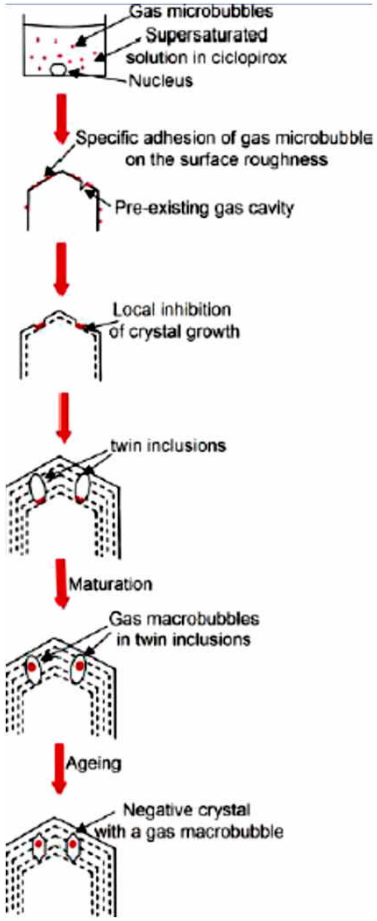


Large fluid inclu Smaller inclusions

AFM experiments



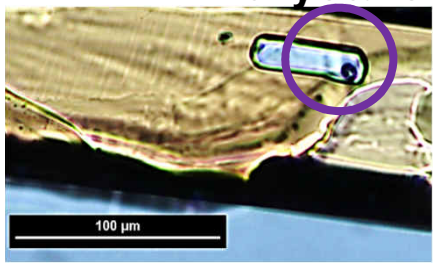
Better adherence of gas bubbles on rough surfaces.

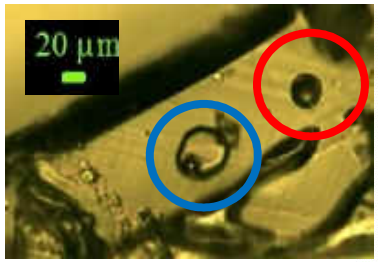


Cryst. Growth Des. 2011, 11, 2463-2470.

Influence of dissolved gases: Traces of O_2

Crystals obtained under O_2:





T_h = 57°C

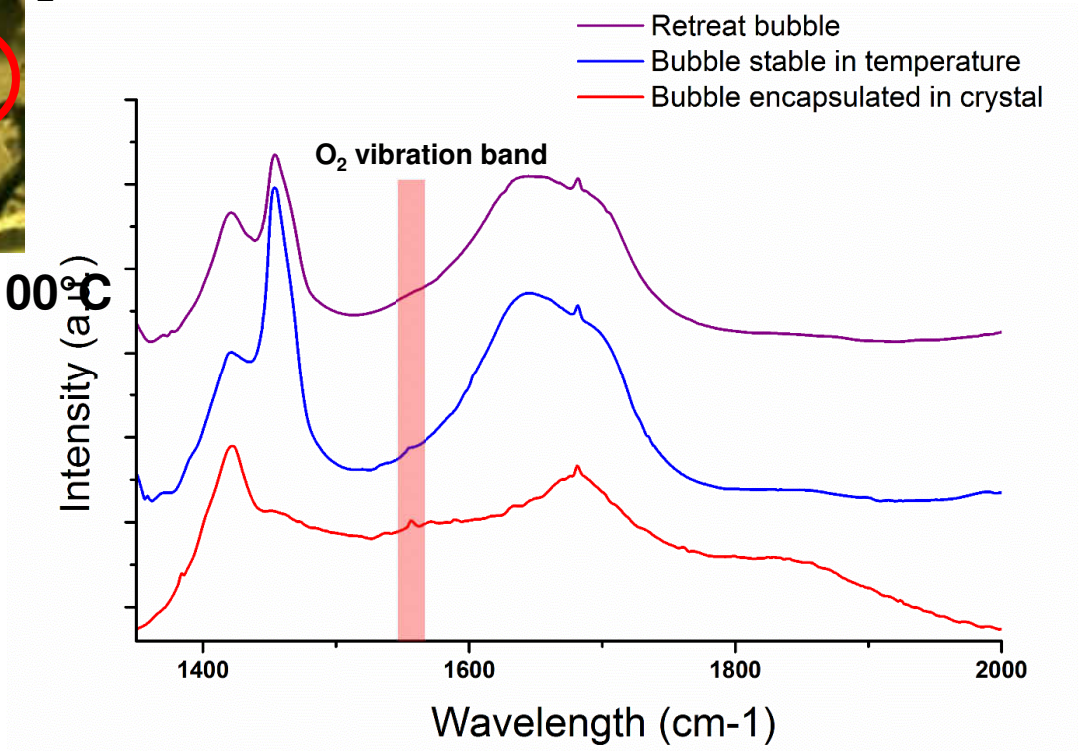
Stable until 100°C

The dioxygen was dissolved in the solution

⇩

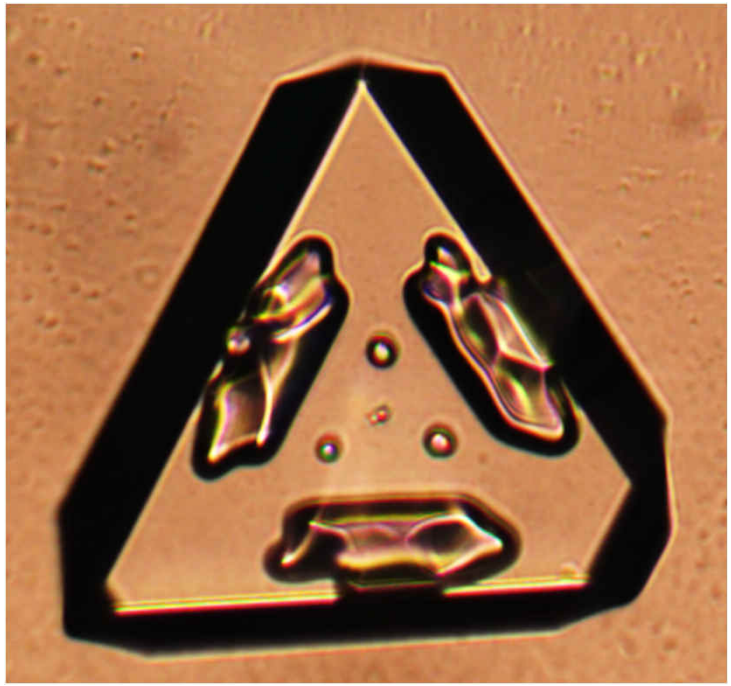
Traces of dioxygen detected in some bubbles by Raman Spectroscopy

RAMAN SPECTROSCOPY



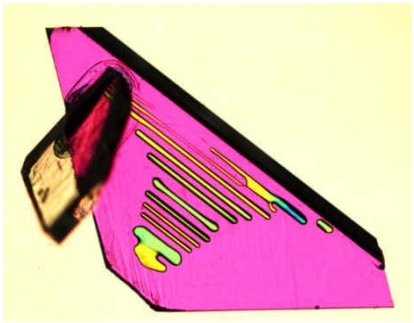
Inclusions reveal some of the symmetries of adamantane : Fm-3m at RT

Single crystal obtained without solvent by sublimation.
These features are not in favor of a strictly stochastic phenomenon.



Take-home messages

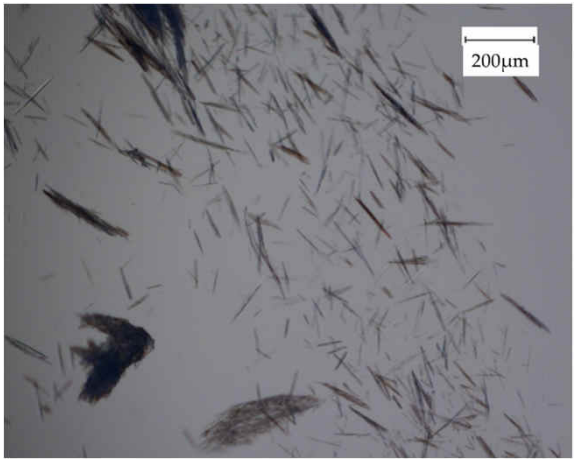
- The experiments conducted under pressure confirm that growth rate dispersion on a single crystal of tens of micron in size. The location of liquid inclusions does not reflect the centrosymmetric space group of the crystal i.e. (hkl) and (-h-k-l) faces do not grow at the same rate.
- The faces that grow exceedingly fast undergo repetitive formation of vacuoles
- Our study confirms that dissolved gases have an impact on the formation of liquid and fluid inclusions.
- There are two types of fluid inclusions
- As a matter of consequence, the locations of inclusions inside the single crystals can be used in the retrospection of the history of the dissymmetric crystal growth (retrogrowth).



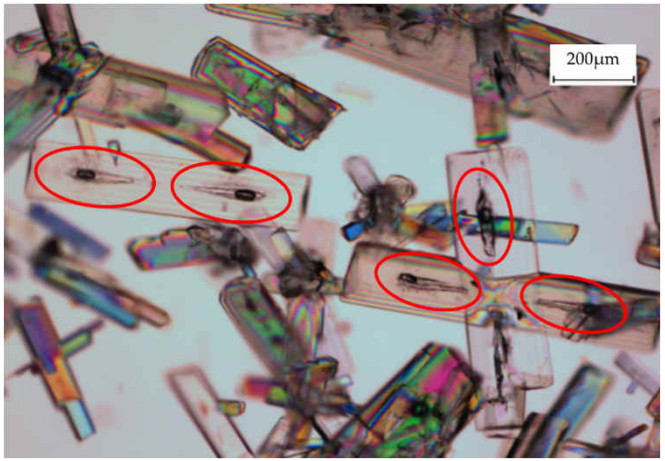
Thank you for your attention !

Influence of solid solution and water information of fibrous crystals and fluid inclusions

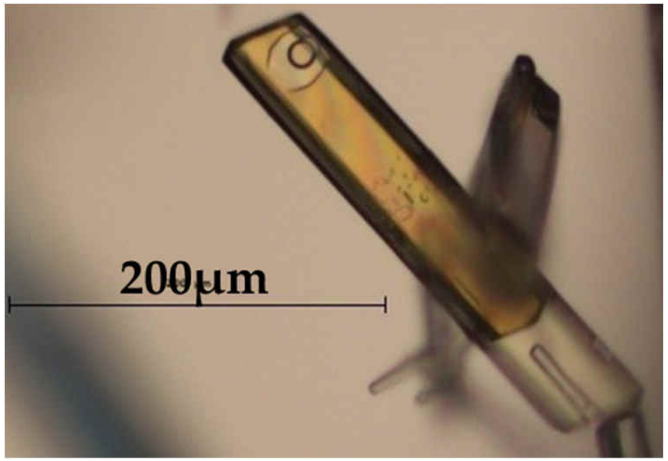
ss-(S)IBU/(S)αMBA
In pure Ethanol

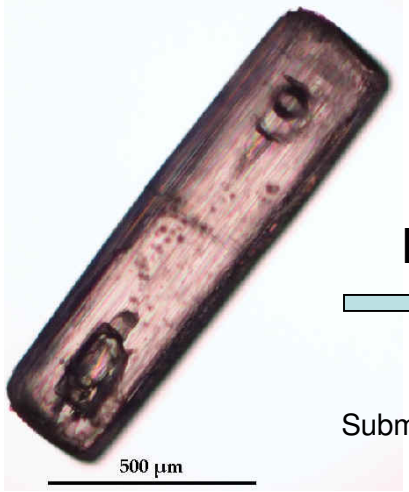


ss-(S)IBU/(S)αMBA
In 80/20 EtOH/H2O



Pure (S)IBU/(S)αMBA
In 80/20 EtOH/H2O





Heating up to 120°C

Submitted to crystals