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# Use of Microfluidics for the Study of a Compound Exhibiting Concomitant Polymorphism

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► **To cite this version:**

Hugo Cercel, Clément Brandel, Valerie Dupray. Use of Microfluidics for the Study of a Compound Exhibiting Concomitant Polymorphism. PhD students' day 2024, Jun 2024, Rouen, France. hal-04688173

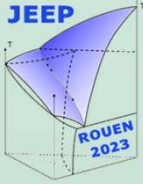
**HAL Id: hal-04688173**

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Submitted on 4 Sep 2024

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## Context

**Polymorphism:** ability of a compound to present different structures at its solid state. For one set of parameters (T, P ...), **only one is stable**, but metastable forms can crystallize first (**Kinetics vs. Thermodynamics**)

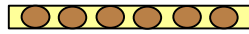
### Second Harmonic Generation (SHG) measurements [2]

- Give information on crystalline phase
- SHG signal is characterized by re-emission of light at half the incident wavelength ( $\lambda/2$ )

One set of parameters  
What crystallizes ?

Stable form      ?      Metastable form

Both forms  
**Concomitant Polymorphism [1]**



### Droplet microfluidics

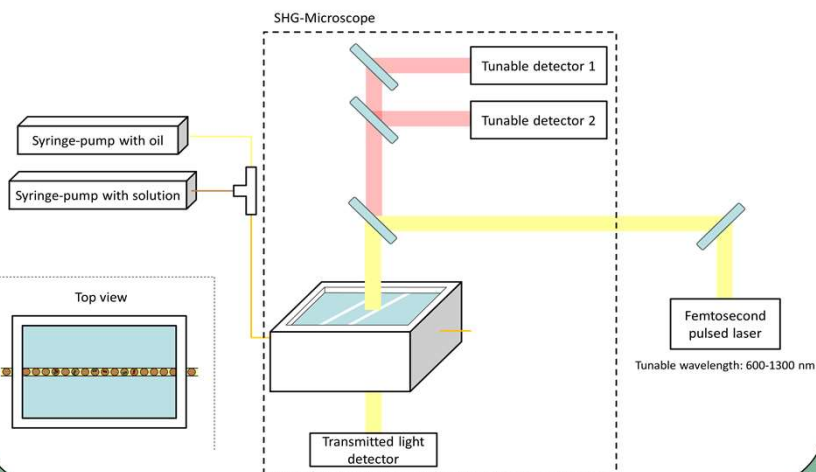
- Identical conditions in each droplet
- Allows fast condition screening with low matter quantity

The coupling between microfluidics and SHG measurement is thus investigated with the aim of studying crystallization for compounds exhibiting concomitant polymorphism

## Experimental setup

The **nonlinear optical Microscope** contains many **spectral detectors** allowing specific characterization

Detector 1 is usually tuned at **half the laser wavelength** to detect SHG signal

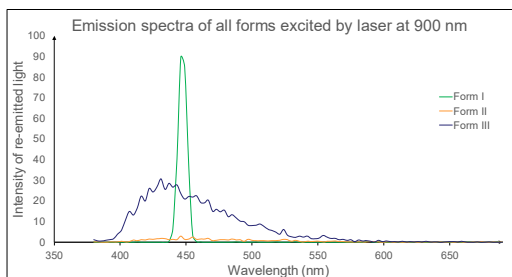


## Polymorph characterization by Nonlinear optical Microscopy

Emission spectra for all forms are obtained

**Sharp and intense peak (at  $\lambda/2$ ) for form I : SHG emission**

**Wide signal for form II and III : Two photons Fluorescence (TPF) emission**



## Conclusion

→ Nonlinear Optical microscopy allows to differentiate Form I from the other forms by detection of SHG signal and Two-Photon fluorescence

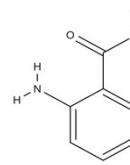
→ **For a given condition, different crystallization phenomena can occur. The use of droplet microfluidics allows the study of many identical crystallization reactors, leading to a better understanding of these phenomena**

→ **Perspectives:** The study of numerous conditions (supersaturation, solvent composition, etc.) can lead to a global understanding of the system. This can lead to the identification of conditions favoring one polymorph over others

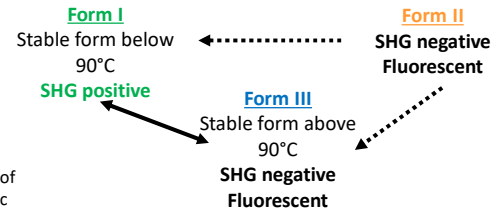
## Ortho-Aminobenzoic Acid

Ortho-aminobenzoic acid (O-ABA) : Precursor for many molecules as tryptophane

**3 different polymorphic forms [3]**



Molecular structure of ortho-aminobenzoic acid



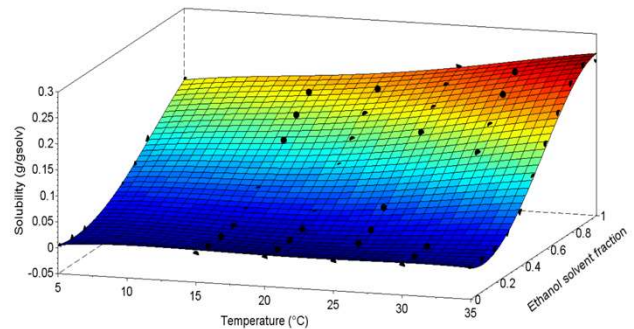
↔ **Enantiotropic relationship**  
 ..... **Monotropic relationship**

**How does it behave in different water-ethanol solvents ?**

## Solubility surface of O-ABA

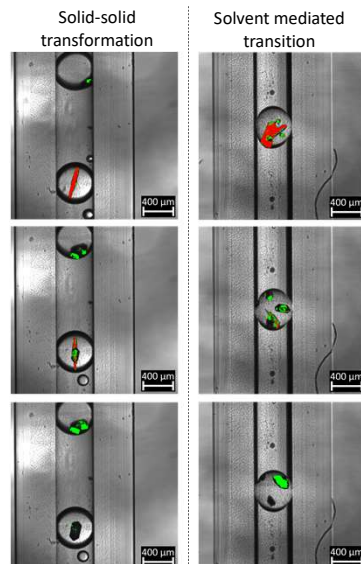
**Solubility surface of O-ABA** in different water-ethanol ratios (determined by gravimetric method) at 20°C (20°C = temperature of crystallization under the SHG-Microscope)

⇒ access to **supersaturation (beta)** values in solutions

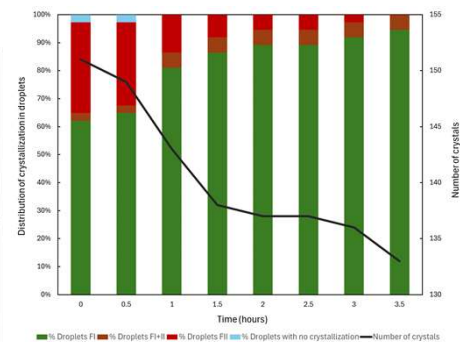


## Characterization of crystallization in microfluidics

Starting from a **50/50 Water/Ethanol fraction** with a supersaturation of **2.2**, crystallization is characterized by non linear optics



Time-based study of crystallization shows multiple phenomena as solid-solid transformation of solvent mediated transition



The nature of crystals in droplets can be easily determined by measuring SHG and TPF signals.

The evolution of number of crystals is then obtained

**For a given condition, multiple phenomena can be identified with non linear optics**

**Time-based analysis enables a better understanding of the stability of polymorphs and can illustrate the phenomenon of Ostwald ripening**

[1] J. Bernstein, R. J. Davey, and J.-O. Henck (1999): **Concomitant Polymorphs**, *Angew. Chem. Int. Ed.*, vol. 38, n° 23, p. 3440-3461

[2] S. K. Kurtz and T. T. Perry (2003): **A Powder Technique for the Evaluation of Nonlinear Optical Materials**, *J. Appl. Phys.*, vol. 39, n° 8, p. 3798-3813

[3] S. Jiang, J. H. ter Horst, and P. J. Jansens (2008): **Concomitant Polymorphism of o-Aminobenzoic Acid in Antisolvant Crystallization**, *Cryst. Growth Des.*, vol. 8, n° 1, p. 37-43