Is Second Harmonic Generation a reliable tool for studying solid-solid phase transition and structural purity?

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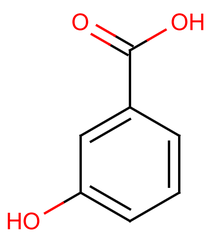
Introduction

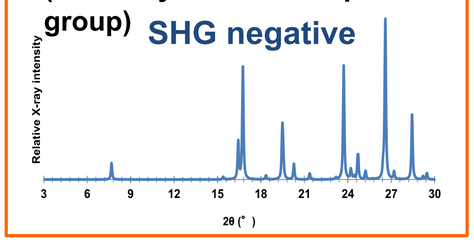
Second Harmonic Generation (SHG):

SHG is an optical process which can be used to detect the non-centrosymmetry of crystalline compounds[1,2] (powder form). In order to study phase transitions, a device has been developed to perform SHG measurements versus temperature. The case of 3-hydroxybenzoic acid is considered.

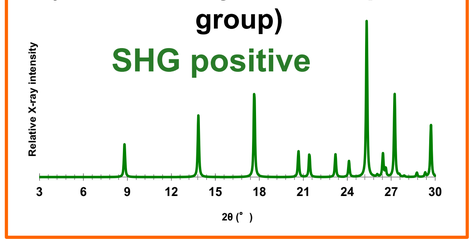
3-Hydroxybenzoic acid (MHBA) exhibits two polymorphic forms :



A stable form $P2_1/c$ (Centrosymmetric space group) **SHG negative**



A metastable form $Pna2_1$ (Non centrosymmetric space group) **SHG positive**



A known irreversible phase transition from the non-centrosymmetric metastable form (SHG Positive) to the centrosymmetric stable form (SHG negative) occurs at circa 160° C[3] .

⇩

The SHG device can be used to track this phase transition.

Aim of this study : To evaluate the potential of SHG signal measurements to detect the phase transitions by comparison with other usual techniques such as Differential Scanning Calorimetry (DSC), X-Ray Powder Diffraction (XRPD). Two samples are studied : a commercial MHBA (normally constituted of the stable form) and a pure metastable product obtained by recrystallization in acetone.

Thermo-SHG

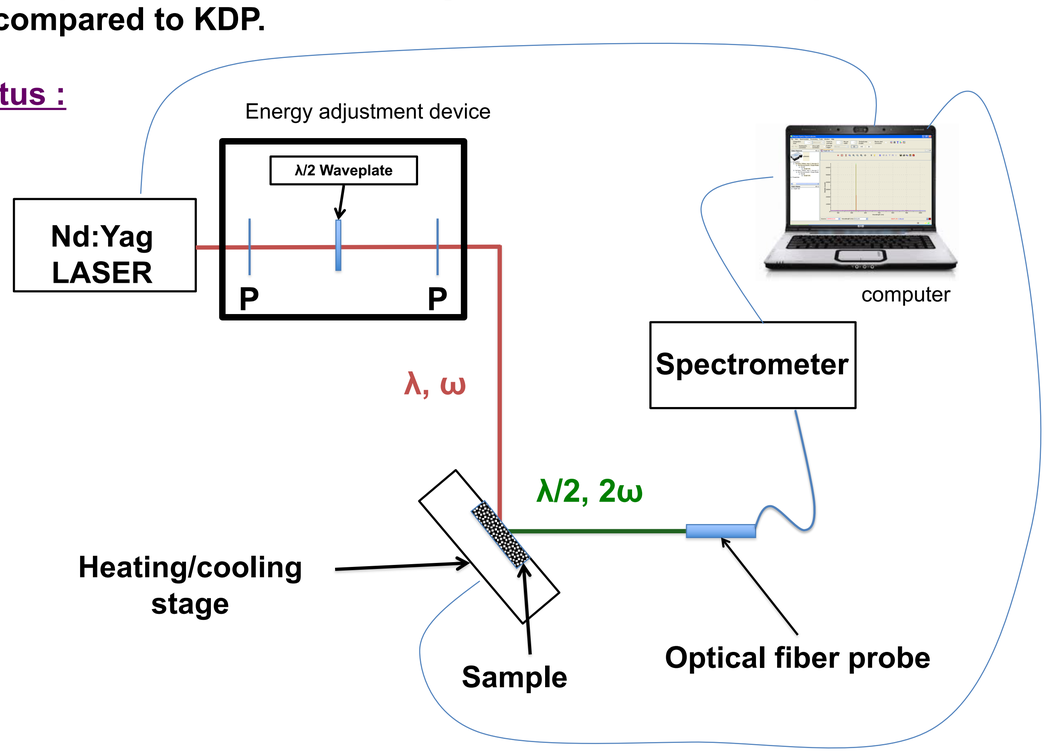
Principle of SHG:

A laser beam is sent on the sample at the fundamental frequency ω

⇨If the sample is non centrosymmetric a SHG signal is detected at twice the fundamental frequency.

⇨According to the Kurtz and Perry method[1] the signal is compared to a reference signal. In our case, samples were compared to KDP.

Apparatus :

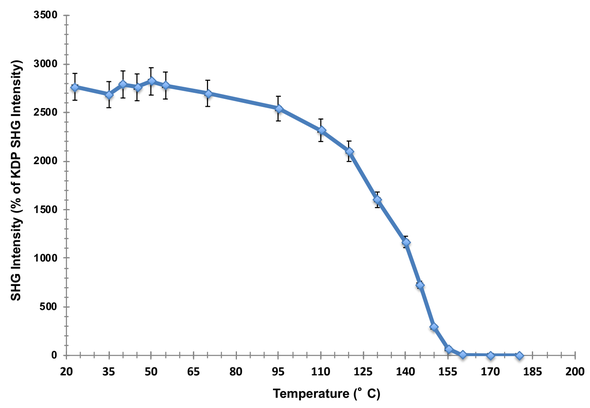


⇨The powder sample is placed in an heating/cooling stage (computer controlled).

⇨The SHG signal is measured versus temperature using a spectrometer.

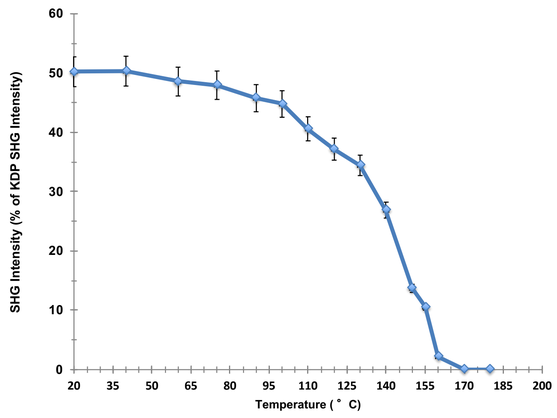
Results:

Recrystallized MHBA



- Exhibits SHG signal
- SHG intensity decreases progressively with the temperature
- 90% of the signal is lost between 100° C and 160° C.
- The SHG signal disappears completely at 170° C. (mean heating rate 2K/min)

Commercial MHBA



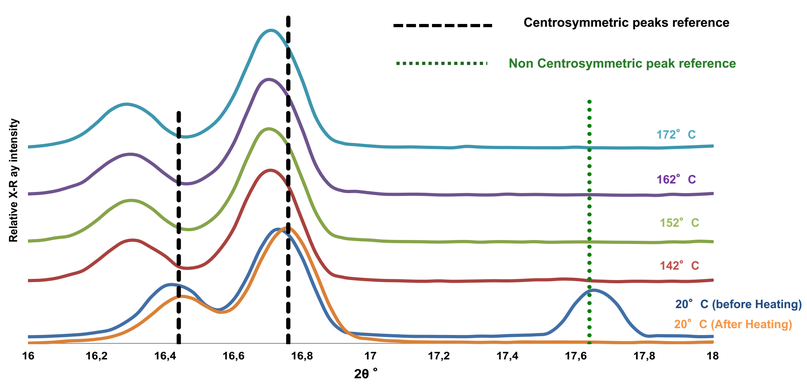
- Results similar to the recrystallized product results: Inconsistent with the centrosymmetric space group assignment.
- The commercial compound exhibits a low SHG signal (55 times less intense than the recrystallized product).

⇨The commercial sample contains a SHG positive compound = small amount of metastable noncentrosymmetric form

⇨ -SHG allow the monitoring of the polymorphic transition of MHBA from its metastable to its stable form
- SHG can probe the stuctural purity of the sample and track the conversion of a small amount of metastable form.

Comparison with X-Ray Powder Diffraction

Commercial MHBA

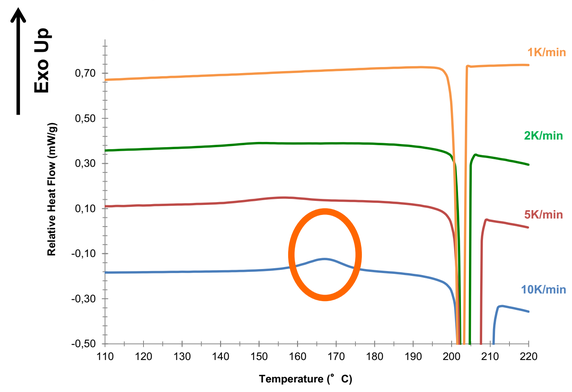


- XRPD confirms that :
  - the 2 polymorphic forms are present in commercial MHBA.
  - the structural impurity highlighted by SHG corresponds to the metastable form.
- Non centrosymmetric peak reference disappears between 142° C and 152° C

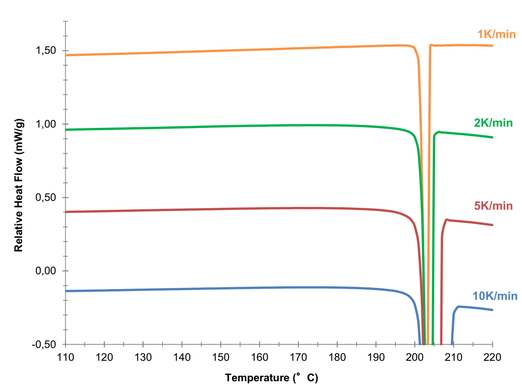
⇨ SHG and XRPD are complementary techniques

Comparison with Differential Scanning Calorimetry

Recrystallized MHBA



Commercial MHBA



- In two cases : Average onset fusion peak ≈ 201.7° C
- Recrystallized MHBA DSC scans exhibit a weak exothermic event around 167° C (at 10K/min) attributed to the crystallization of the metastable ($Pna2_1$) form into the stable form ($P2_1/c$).
- DSC curves of commercial MHBA exhibit no heat exchange corresponding to a phase transition. In the case of commercial product, this technique can not detect the phase transition.

⇨ DSC is unable to detect the phase transition in the case of the commercial product

Conclusion

⇨Possibility to follow a phase transition by SHG measurements.

⇨High sensitivity of SHG compared to DSC.

⇨In favorable cases SHG is a very sensitive probe to assess the structural purity.

Further Work

Understanding the possible relationship between the lattice thermal expansion (highlighted by a peak shift in TR-XRPD) and the SHG signal and determine more accurately the temperature of the solid-solid phase transition.

(1) J.P. Dougherty and S.K. Kurtz, *J.Appl Crystallogr*, vol. 9, no. 2, pp. 145–158, (1976).

(2) A. Galland, V.Dupray, B.Berton, S.Morin-Grognet, M.Sanselme, H.Atmani and G.Coquerel, *Cryst Growth & Des*, vol. 9, no. 6, pp. 2713–2718, (2009).

(3) F. L. Nordström and Å.C. Rasmuson, *European J.Pharm Sci*, vol. 28, no. 5, pp. 377–384, (2006).