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Temperature resolved second harmonic generation to probe the structural purity of *m*-hydroxybenzoic acid

S. Clevers · F. Simon · V. Dupray · G. Coquerel

Phase-Equilibria Special Chapter
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Abstract We report the use of second harmonic generation (SHG) and temperature resolved second harmonic generation (TR-SHG) for in situ probing and monitoring the structural purification of *m*-hydroxybenzoic acid (MHBA). Pure and mixtures of the two polymorphic forms of MHBA (metastable Pna2₁ and stable P2₁/c) and commercial MHBA were analysed by: DSC, XRPD and SHG. Results obtained with these three techniques are compared and demonstrate for that particular component, the high sensitivity and accuracy of SHG in assessing the polymorphic purity of MHBA. The SHG detection threshold for the metastable polymorph is circa 2 ppm and is several orders of magnitude better than the sensitivity of XRPD (1 wt%) and DSC (only 17 wt%). The proportion of the metastable phase in the commercial MHBA was evaluated to 1 wt% by SHG. Results of TR-SHG measurements performed on commercial MHBA at 5 K min^{−1} heating rate show that TR-SHG is a good technique for an in situ monitoring of the structural purity. The present study clearly demonstrates that SHG and TR-SHG are relevant and accurate techniques for probing the structural purity and for the monitoring of solid–solid phase transitions provided one of the two varieties crystallizes in a non-centrosymmetric space group.

Keywords Polymorphism · Second harmonic generation · Structural impurity · Phase transition · Monotropy · Hydroxybenzoic acid

Introduction

The detection, identification and quantification of impurities are of fundamental importance in material science and most of all for compounds involved in the production of active pharmaceutical ingredients (APIs). Impurities can originate from starting materials, by-products, intermediates, reagents, degradation products, ligands, catalysts, etc. Pharmaceutical compounds are often administered in the form of crystalline powders and impurities can, for example, be present as liquid inclusions inside the solid phase [1–3]. Pharmaceutical compounds can also exist in various solid phases including: polymorphs, hydrates, solvates, co-crystals, host–guest associations, salts and hybrids of all sorts of these phases. As polymorphs have different physicochemical and physical characteristics (solubility, hardness, compressibility, density, melting point, etc.) not only chemical but also structural impurities have to be considered in the impurity profile [4]. Notably, if the marketed form of a compound is not the most stable form, storage conditions (temperature, hygrometry...) can induce phase transitions. Then, the structural purity assessment of products all along their formation processes (from the production to the formulation) is nowadays a necessity.

A standard value of 0.1 % has been fixed by regulatory authorities as the threshold, above which impurities have to be properly identified [5]. Several analytical methods are commonly used to probe the purity of products. Concerning chemical impurities, HPLC with UV detection and LC–MS are the most common analytical methodologies used to monitor impurities at very low levels. Structural impurities are often more difficult to identify and to quantify as they are constituted of the same molecules as the original compound. Spectroscopic techniques such as Infrared or Raman spectroscopy are frequently used to characterise

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contaminated samples with reported limits of detection in the range of 3–5 wt% [6]. XRPD certainly constitutes the most direct way to identify the presence of a polymorph but suffers limitations as long as the mass fraction remains below 5 % in the physical mixture. Differential scanning calorimetry and differential thermal analysis are also widely used to reveal phase transitions in solids with a usual reported detection threshold of 1 wt% [7]. Consequently, the detection of a structural impurity at a threshold below 1 wt% seems to constitute the actual limit for usual analytical methods. Nonlinear optics and second harmonic generation (SHG) can be precisely a way to overcome this limit.

SHG is a nonlinear optical effect occurring in crystal with non-centrosymmetric space groups. Two photons at the fundamental angular frequency ω can interact in a noncentric crystal structure to give a new photon at twice of the fundamental frequency (therefore, SHG signal at 2ω). Interfaces between inhomogeneous media (air/crystal for example) can also generate SHG because of an obvious lack of centrosymmetry. But, the surface-related SHG signal is usually very weak compared to the SHG generated from the bulk and can be neglected. In the crystal, a slight deviation from centrosymmetry can induce strong changes in the SHG response of a sample. Thus, SHG was formerly proposed as a rapid, reliable and very sensitive test of non-centrosymmetry for crystalline compounds [8] with applications to structure assignments. Recently, it was proposed as an efficient technique for pre-screening of conglomerate forming compounds [9].

SHG is all the more interesting than further data can be obtained by performing SHG measurement versus temperature. Temperature resolved SHG (TR-SHG) has already been employed to monitor solid–solid phase transitions (including order–disorder phase transitions) in inorganic compounds and seldom in organic materials and organic–inorganic hybrids [10–12]. SHG was also used to follow in situ the crystallization of a non-centrosymmetric phase from a supersaturated solution [13–15], to quantify crystalline phases arising from amorphous materials [16] or to study the relaxation of polymers or glasses above glass transitions [17, 18]. However, to our knowledge, TR-SHG has never been used to probe the structural purity and to tackle the structural purification of organic products.

In this study, a thermal-induced structural purification of *m*-hydroxybenzoic acid (hereafter MHBA) was monitored with SHG. MHBA is an intermediate in the production of pharmaceuticals, plasticizer, germicides and preservatives. Its sodium salt is claimed to promote the discharge of bile [19]. Two polymorphic forms of MHBA are reported in the literature and referenced in the Cambridge Structural Database (CSD) as BIDLOP for the centrosymmetric $P2_1/c$ form and BIDLOP01 for the non-centrosymmetric $Pna2_1$

form [20]. This non-centrosymmetric form is metastable at all temperature investigated and as a consequence, the polymorphic system is of monotropic character under usual pressure. Under normal pressure, a known irreversible solid–solid phase transition from the metastable form to the stable form occurs associated to an exothermic event [21].

The present paper shows how SHG and TR-SHG can be used to detect and quantify structural impurities in commercial *m*-hydroxybenzoic acid and above all to monitor the structural purification of this product. The sensitivity of SHG is also compared with other usual techniques such as X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

Experimental

Materials and sample preparation

M-hydroxybenzoic acid (MHBA) was purchased from Acros Organic (Cas registry number 99-06-9) with a chemical purity better than 99 %. Different samples were prepared:

- (1) StabMHBA: Stable MHBA (Commercial MHBA annealed at 145 °C during 1 h)
- (2) MetMHBA: Metastable MHBA (recrystallization in acetone by evaporation under normal pressure and room temperature)
- (3) ComMHBA: Commercial MHBA without further purification

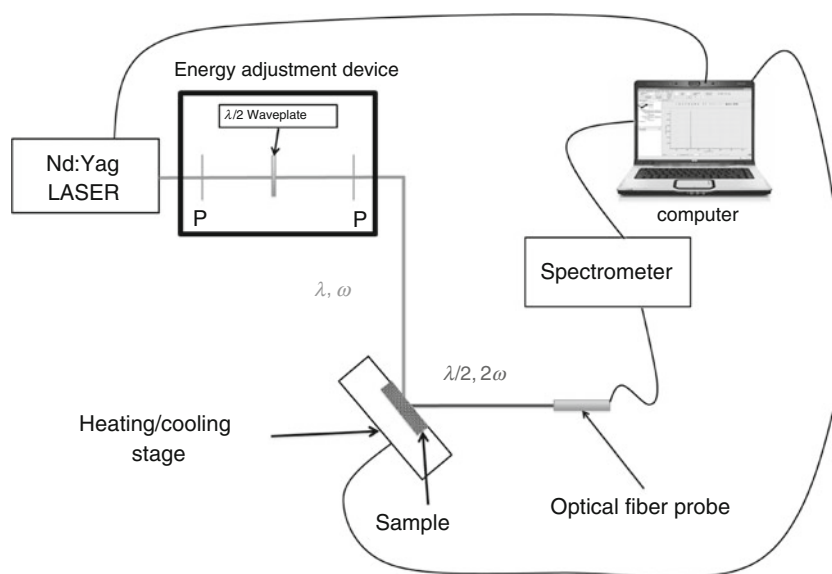
Analytical methods

Temperature resolved second harmonic generation (TR-SHG)

Figure 1 shows the experimental setup used for the TR-SHG measurements. A Nd:YAG Q-switched laser (Quintel) operating at 1.06 μm was used to deliver 360 mJ pulses of 5 ns duration with a repetition rate of 10 Hz. An energy adjustment device made up of two polarizers (P) and a half-wave plate ($\lambda/2$) allowed to vary the incident energy from 0 to ca. 200 mJ per pulse. A RG1000 filter was used after the energy adjustment device to remove light from laser flash lamps. The samples (few mg of powder in a crucible) were placed in a computer controlled heating–cooling stage (Linkam THMS-600) and were irradiated with a beam (diameter of 4 mm).

The signal generated by the sample (diffused light) was collected into an optical fibre (500 μm of core diameter) and directed onto the entrance slit of a spectrometer (Ocean Optics). A boxcar integrator allowed an average spectrum (spectral range 490–590 nm) with a resolution of 0.1 nm to

Fig. 1 Experimental setup second harmonic generation apparatus constituted of Nd:YAG Q-switched laser operating at 1,064 nm



be recorded over 2 s (20 pulses). To avoid problems related to the sublimation of the samples, the heating-stage was opened but only during the SHG measurements so it had no significant influence on the temperature regulation.

According to Kurtz and Perry [8] SHG powder method, SHG signal intensities were compared to the signal of a reference compound (quartz—45 μm average size).

Temperature resolved X-ray powder diffraction (TR-XRPD)

Crystalline solid phases were analysed at room temperature by means of X-ray powder diffraction (XRPD) on a Bruker–Siemens D5005 apparatus (θ – θ) set, with Cu $K_{\alpha 2}$ radiation (1.54056 Å) (Kb filter) under 40 kV and 30 mA and collected on a scintillation detector. The θ angle calibrations were carried out using Siemens slits and a quartz sample (secondary standard). Temperature was controlled and monitored using an Anton Paar TTK450. The intensity was measured with a 2θ step of 0.04° during 4 s.

Differential scanning calorimetry

Thermal analyses of the solids were conducted on DSC 204 F1 Netzsch equipped with an Intracooler. Solid samples (mass of c.a. 15 mg with maximum deviation of 0.05 mg) were placed in a 25 μL close aluminium crucible. The atmosphere of the analyses was regulated by helium flux (40 mL min^{-1}), and heat runs were conducted at different constant heating rate. The data treatment was performed with the Netzsch–TA Proteus[®] Software v 4.8.4.

Results and discussion

In order to evaluate the potential of the SHG technique for probing, the structural purity of MHBA, samples of StabMHBA, MetMHBA and ComMHBA were first characterised by XRPD, DSC and SHG.

Characterisation

XRPD analyses were performed on StabMHBA, MetMHBA and ComMHBA samples in the 2θ range from 3° to 30° (Fig. 2) at room temperature. The diffractogram of StabMHBA matches with the diffractogram of the centrosymmetric polymorph obtained from the CSD database ($P2_1/c$ BIDLOP [20]). The diffractogram of MetMHBA fits with the diffractogram of the non-centrosymmetric polymorph ($Pna2_1$) (BIDLOP01 [20]). The diffractogram of ComMHBA exhibits 3 supplementary peaks by comparison to the diffractogram of the centric phase. These three peaks are also present on the diffractogram of MetMHBA. Two peaks (8.79° – 17.66°) correspond to a same lattice plane set ($h00$) with $h = 2n$ and $n = 1, 2$ and the latter peak (29.70°) corresponds to the (410) lattice interspace.

Consequently, XRPD results show that the commercial product (mainly centrosymmetric) is not structurally pure and contains a detectable amount of metastable $Pna2_1$ phase (with preferred orientation).

DSC analyses were performed on StabMHBA, MetMHBA and ComMHBA samples for a heating rate of 16 K min^{-1} (Fig. 3). This heating rate was chosen as the optimal rate for the detection of the exothermic event in the case of the solid–solid phase transition of MHBA. As expected, StabMHBA curve (a) exhibits a single thermic

Fig. 2 XRPD patterns in the 2θ range from 3° to 30° for StabMHBA (a), MetMHBA (b) and ComMHBA (c). The star labelled peaks are attributed to the metastable form. Dash-line diffractograms correspond to the diffractograms calculated from CSD data

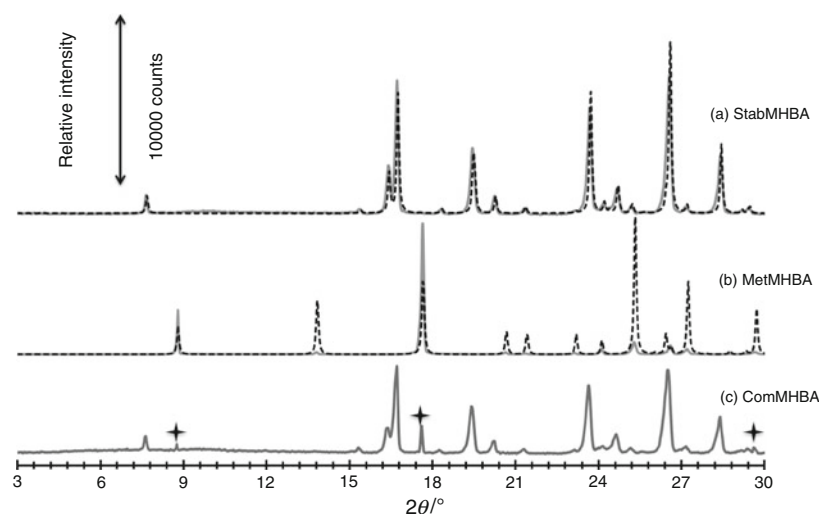
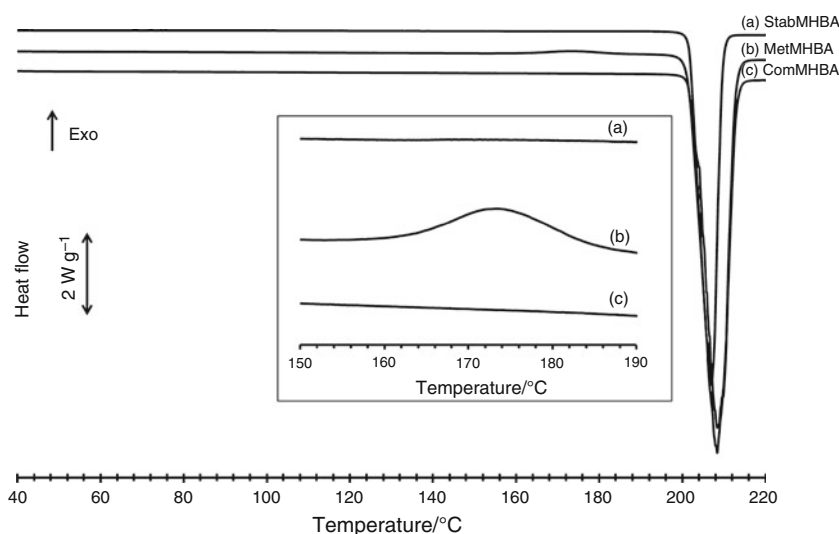


Fig. 3 DSC curves from 40 to 220 °C and magnification between 150 and 190 °C for StabMHBA (a), MetMHBA (b) and ComMHBA (c) (heating rate: 16 K min⁻¹). The masses used to obtain curves were 15.00, 14.98 and 15.05 mg, respectively. The exothermic event (conversion of the metastable form into the stable form) is visible only for MetMHBA



event (endothermic) corresponding to the melting. The melting enthalpy of StabMHBA derived from the DSC curves is 32.7 kJ mol⁻¹. This value is in fairly good agreement with the enthalpy reported by Nordstöm (35.9 kJ mol⁻¹) [21]. However, a lower value of 26.2 kJ mol⁻¹ has also been reported [22]. MetMHBA curve (b) exhibits a weak exothermic event at circa 175 °C in addition to the fusion peak already observed for StabMHBA (see magnification of the DSC traces on Fig. 3). This exothermic event corresponds to the irreversible conversion of the metastable (Pna2₁) form into the stable form (monoclinic P2₁/c). Note that the solid–solid phase transition was also confirmed by polarized thermomicroscopy (results not shown). ComMHBA curve (c) does not exhibit any detectable exothermic event and is superimposable to the StabMHBA curve.

Consequently, DSC, contrary to XRPD, does not detect the presence of the metastable phase in the commercial product.

SHG analyses were performed on StabMHBA, MetMHBA and ComMHBA samples at room temperature. StabMHBA did not show any measurable SHG signal (as expected for this centrosymmetric structure). Thus, the surface related SHG signal can be neglected. Contrary to StabMHBA, MetMHBA exhibited a high SHG value (3,000 % of quartz). ComMHBA exhibited a weak SHG signal (28 % of quartz), indicating the presence of a non-centrosymmetric impurity (here the metastable polymorph of MHBA).

Finally, SHG and XRPD detected the presence of the metastable form (structural impurity) into the commercial product whereas DSC did not.

Detection threshold

In order to compare the sensitivity of the three techniques, their detection thresholds were assessed. The detection

threshold is defined here as the minimum mass fraction of metastable MHBA (in a physical mixture of MetMHBA and StabMHBA) measurable by the experimental device.

Several calibration standards containing mass fraction of metastable MHBA comprised between 2 ppm and 50 % were then prepared and submitted to XRPD, DSC and SHG analyses.

XRPD exhibits a good detection threshold with 1 wt% of metastable form detected. This value is significantly better than the commonly accepted value of 5 %. It is probably due to a relatively high intensity of the diffraction peak of the metastable form. It is known that parameters such as preferential orientation, crystal size, crystallinity or low absorption coefficient can positively affect the response of the sample. It is also worth noting that some detection thresholds lower than 1 wt% have already been reported in favourable cases [23].

By comparison, DSC presents a poor detection threshold of 17 wt% (on Fig. 4, the exothermic event is no more visible for compositions below this value). This low sensitivity is mainly due to the weakness of the thermodynamic exothermic event associated with the irreversible transformation from the Pna2₁ form (SHG positive) to the P2₁/c form (SHG negative).

Most interesting is the 2 ppm threshold exhibited by the SHG technique which underlines the high sensitivity of SHG for the detection of very small quantities of structural impurities. However, this threshold value can not be considered as a universal detection threshold for SHG as it highly depends on the sample studied. Indeed, the intensity of the SHG signal is related to various parameters such as the susceptibility tensor $\chi^{(2)}$, the shape and the size of the particles, the crystallinity, etc. It is also worth mentioning that SHG can only originate from non-centrosymmetric crystals, which limits the technique to non-centrosymmetric

polymorphic phases or non-centrosymmetric impurities. From this point of view, *m*-hydroxybenzoic acid constitutes a favourable case as the structural impurity (here the metastable MHBA) crystallizes in a non-centrosymmetric structure and exhibits a high nonlinear response (the intensity of the SHG signal of the pure metastable phase is 30 times that of the alpha quartz).

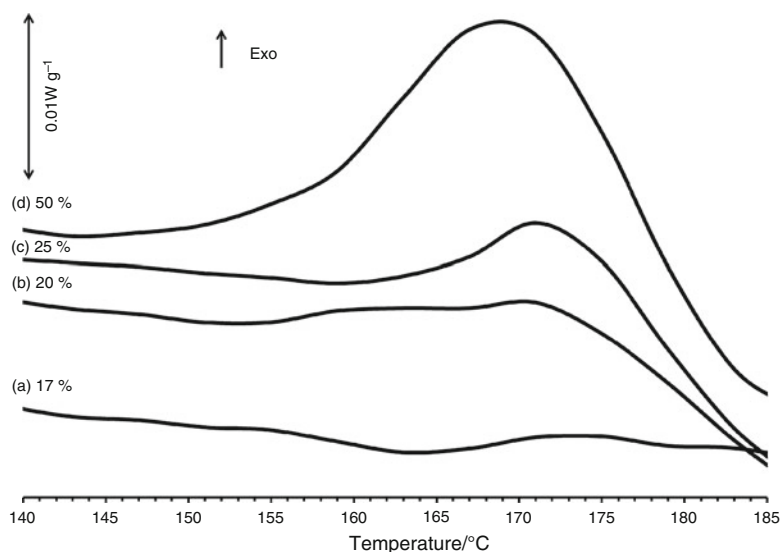
Nevertheless, provided a sufficient SHG activity of the impurity, SHG can be used to probe the structural purity of a sample at the level of few ppm.

Quantification of structural impurity

Another challenging issue is to evaluate the proportion of structural impurity with a good accuracy. To find out if the mass fraction of metastable MHBA in the commercial product can be determined precisely by SHG, the SHG signal of mixtures of known compositions (prepared from the same batches of MetMHBA and StabMHBA) was measured, and the SHG intensity was plotted versus the mass fraction of metastable MHBA. Results of Fig. 5 show that the SHG intensity can be considered as linear with the mass fraction (determination coefficient of the regression line equal to 0.997). At first glance, this result could seem surprising because the *SHG signal is theoretically quadratic with the number of molecules within a crystal*. Nevertheless, signals arising from different crystals are not correlated so the SHG signal scales linearly with the number of non-centrosymmetric crystals in powders [24]. As a consequence, for powders SHG measurements, the dependence of the SHG signal with the mass fraction has often been reported to be linear or between linear or quadratic depending on the sample [12, 25].

Consequently, from the slope of the regression line and the SHG intensity measured for the commercial product,

Fig. 4 DSC curves for physical mixture of 17, 20, 25 and 50 wt% of Metastable MHBA. The weak exothermic event attributed to the solid–solid phase transition is no more visible for fraction of metastable MHBA below 17 wt%



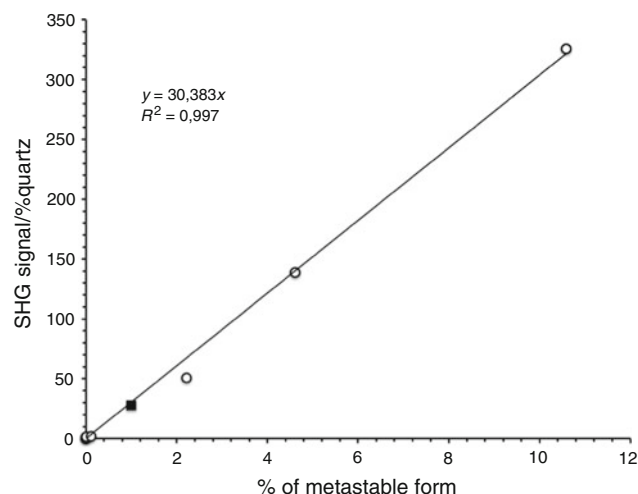


Fig. 5 SHG signal (%quartz SHG signal) versus fraction of metastable form inside the mixture (*open circle*). The fraction of metastable form in the commercial product estimated from the curve is 1 % (*filled square*)

the mass fraction of metastable MHBA in the commercial product can be evaluated to circa 1 wt%.

However, the accuracy of this result is difficult to evaluate. Indeed, the intensity of the SHG signal depends on the particle size. So, samples with different crystal size distribution but same mass fraction of impurity will not exhibit exactly the same SHG response. As a consequence, a certain variability of the results can be observed if non-calibrated samples are analysed. Nonetheless, when the crystal size, exceeds the coherence length, the SHG signal is independent of the crystal size for phase matchable materials. According to Ref. [8], phase matchable materials of average size greater than 100 μm are not likely to exhibit a dependence of the SHG intensity with the crystal size. MetMHBA is phase matchable and the average crystal size of the crystals has been measured to circa 150 μm . Then, the SHG signal should not be strongly affected if samples from different batches have to be analysed. Finally, if SHG can detect structural impurity at a very low level, it is not the preferred option in terms of precise quantification of impurity. Nevertheless, we show in the following, that due to its exceptional sensitivity, SHG coupled with a temperature control (TR-SHG) can be used with a significant relevancy to follow in situ the structural purification of “contaminated” products.

Structural purification of MHBA

The SHG signals emitted by MetMHBA and ComMHBA were measured versus temperature during heating at a rate of 5 K min^{-1} . The evolution of the mass fraction x of metastable MHBA converted to stable MHBA versus temperature is plotted on Fig. 6 for each sample. A

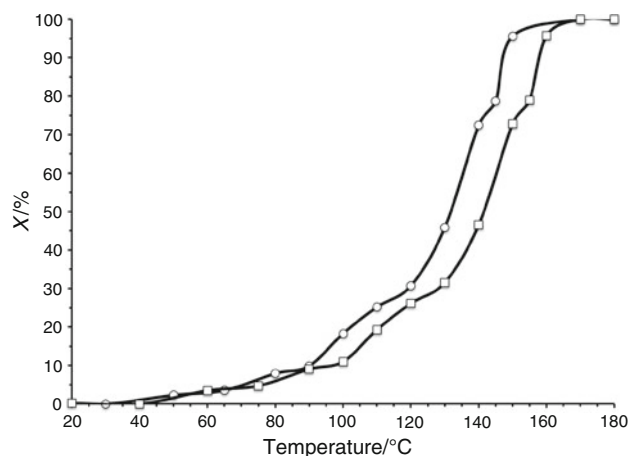


Fig. 6 Evolution of the converted mass fraction x during heating at 5 K min^{-1} for (*open circle*) ComMHBA and (*open square*) MetMHBA

converted mass fraction x equal to 0 % corresponds to the maximum SHG signal measured and a value of x equal to 100 % is obtained when the SHG signal has totally vanished. So, x can be considered as the degree of completion of the solid–solid phase transition (i.e. of the structural purification process).

Results for MetMHBA show that the structural purity of the sample starts to increase at 40 °C but the phenomenon becomes really significant after circa 100 °C. Above 160 °C, the purification is completed (i.e. the material is constituted of the stable form (P2₁/c) only).

Results for ComMHBA show that despite the low mass fraction of metastable polymorph in the commercial product (previously evaluated at circa 1 wt%), TR-SHG measurements allow to monitor with a high accuracy the solid–solid phase transition, and thus, the structural purification of the sample. Moreover, the conversion starts and is completed at slightly lower temperatures compared to MetMHBA which underlines the promoting effect of stable MHBA in the solid–solid phase transition.

In both cases, the curves are not perfectly smooth as some cut-off segments can be observed. This could be due to the crystal size distribution of the sample. Indeed, the solid–solid phase transition between MetMHBA and StabMHBA is monotropic. Thus, the solid–solid phase transition can occur at any temperature once the energy barrier is overcome. The elevation in temperature enhances the molecular motion and helps to overcome this energy barrier. The crystal size acts as a kinetic barrier. As a consequence, in a polydisperse sample with a homogeneous distribution of crystal defects, most of the crystals of equivalent size will experience the transition simultaneously. In other terms, once the activation energy corresponding to a given crystal size class is reached, the transformation starts and the SHG signal decreases

(x increases) until the transformation is completed. Afterwards, the SHG intensity remains stable awaiting the energy barrier for a larger size class to be reached. This behaviour seems consistent with a mechanism of nucleation and growth.

Conclusions

The structural purity of commercial MHBA has been investigated by second harmonic generation. The following conclusions can be drawn:

- (1) SHG can be used to detect the presence of structural impurities provided that the contaminant exhibits a non-centrosymmetric structure in a centrosymmetric matrix.
- (2) SHG can show in favourable cases a detection threshold of few ppm. Such sensitivity cannot be reached by XRPD or DSC techniques.
- (3) SHG can be used to measure the fraction of structural impurity in a contaminated sample. However, quantification with SHG has to be considered with care when non-calibrated samples are used since the SHG intensity can vary upon the particle size distribution.
- (4) TR-SHG can be used to monitor, in situ, the purification of a contaminated sample even if the fraction of impurity in the starting product is far below 1 wt%.
- (5) SHG and TR-SHG can be used at various stage of the process to control the structural purity with a particular relevance when polymorphs are in a monotropic relationship.

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