

# Hydrogen bond polarization overcomes unfavourable packing in the most stable high Z' polymorph of Pterostilbene

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## Electronic Supplementary Information

### Table of contents:

1. Experimental methods.....	2
Table S1.....	2
Table S2.....	3
Table S3.....	4
2. Characterization of the solids.....	5
Table S4.....	18
3. References.....	19

## 1. Experimental methods

### 1.1. Materials and measurements.

Pterostilbene was purchased from Dynveo and purified, since Pterostilbene capsules contain pterostilbene (form I) and two excipients: calcium hydrogen phosphite and magnesium stearate. Pure pterostilbene was obtained according to the following method: the material from the capsules ( $\approx 12 - 18$  g) was suspended in dichloromethane (200 mL) at 25 °C into a round-bottomed flask provided with magnetic stirring and it was stirred overnight. Then, the solution was first filtered using a paper filter. A turbid solution was obtained and it was filtered again through a 0.45  $\mu\text{m}$  filter. Then, the solvent was removed under reduced pressure and the solid was suspended in heptane (100 mL). The suspension was stirred for 3 days at 25 °C and it was filtered, dried and analyzed by PXRD. The PXRD analysis confirms that pterostilbene form II was obtained with a suitable purity.

A polymorph screening has been carried out (Table S1) and as a result, the three forms have been isolated and characterized.

**Table S1. Screening of pterostilbene (form II)**

Methodology	Solvent	Form obtained (according to PXRD)
Slow evaporation at 25 °C	ACN, Methyl isobutyl ketone, DMF, Et <sub>2</sub> O and THF	Form I
	Butanol, Formic acid, Pentane, Heptane, AcOEt, Dimethyl ether, Isopropyl ether, Dioxane, Dichloromethane, Chloroform and Acetic acid	Form II
	Methanol	Form III

Pterostilbene form I has been obtained by slow evaporation at 25 °C in ACN after 6 days. Pterostilbene form II has been obtained by slow evaporation at 25 °C in butanol after 9 days. Pterostilbene form III has been obtained by slow evaporation at 25 °C in methanol after 2 days.

The polymorphic stability of pterostilbene was studied through slurry interconversion experiments in heptane. Form I appears to be thermodynamically favored compared to Form II-III at 25 °C.

**Table S2. Polymorphic stability of Pterostilbene**

Forms	XRPD Result	Time (days)
Form I-II	Form I	5
Form I-III	Form I	4
Form II-III	Form II	4

## 1.2. X-ray crystallographic analysis.

Powder X-ray diffraction patterns of polymorph screening were obtained on a PANalytical X'Pert PRO MPD diffractometer in transmission configuration using Cu K $\alpha$ 1+2 radiation ( $\lambda = 1.5406 \text{ \AA}$ ) with a focalizing elliptic mirror and a PIXcel detector working at a maximum detector's active length of  $3.347^\circ$ . Configuration of convergent beam with a focalizing mirror and a transmission geometry with flat samples sandwiched between low absorbing films measuring from  $1$  or  $2$  to  $40$  or  $75^\circ$  in  $2\theta$ , with a step size of  $0.026^\circ$  and a total measuring time of two or four hours. The powder diffractograms of form I, II and III were indexed and the lattice parameters were refined by means of LeBail fits by means of Dicvol04,<sup>1</sup> and the space groups were determined from the systematic absences. The crystal structure was determined by direct space methodologies starting from a molecular model optimized with the commercial software SPARTAN<sup>2</sup> by means of the program FOX with the parallel tempering algorithm. Some constraints were introduced to FOX, considering aromatic rings as rigid groups. Several trials of 20 million runs were performed. The refinement of the structure has been performed by the Rietveld method using FullProf,<sup>3</sup> figures S4, S8 and S12 depicts the final Rietveld plot, respectively.

**Table S3. Crystallographic data of pterostilbene forms**

Structure	Form I	Form II	Form III
Empirical formula	C <sub>16</sub> H <sub>16</sub> O <sub>3</sub>	C <sub>16</sub> H <sub>16</sub> O <sub>3</sub>	C <sub>16</sub> H <sub>16</sub> O <sub>3</sub>
Formula Weight	256.3	256.3	256.3
Temperature (K)	298	298	298
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	P2 <sub>1</sub> /c	P2 <sub>1</sub> /n	P2 <sub>1</sub> /c
a, b, c (Å)	15.4310(9) 5.7893(3) 30.8114(19)	9.5466(3) 4.11726(9) 33.6694(13)	15.7225(8) 11.0550(5) 7.6201(3)
β (°)	93.277(2)	93.162(2)	94.025(2)
Volume (Å <sup>3</sup> )	2748.0(3)	1321.39(7)	1321.20(10)
Z, Density (calc.) (Mg/m <sup>3</sup> )	8, 1.250	4, 1.288	4, 1.288
θ range for data collection (°)	1.0 to 40 step 0.026 (2θ)	2.0 to 75 step 0.026 (2θ)	2.0 to 65 step 0.026 (2θ)
Refinement method	Rietveld	Rietveld	Rietveld
Final R indices [I > 2σ(I)]	R <sub>wp</sub> = 10.4 Chi <sup>2</sup> = 60.7	R <sub>wp</sub> = 10.6 Chi <sup>2</sup> = 105	R <sub>wp</sub> = 9.08 Chi <sup>2</sup> = 31.2
CCDC	1896241	1896242	1896244

**1.3 Differential Scanning Calorimetry (DSC).** Differential scanning calorimetry analysis were carried out by means of a Mettler-Toledo DSC-822e calorimeter. Experimental conditions: aluminium crucibles of 40 μL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10 °C/min. The calorimeter was calibrated with indium of 99.99% purity (m.p.: 156.8 °C; ΔH: 28.47 J/g).

**1.4 Thermogravimetric Analysis (TGA).** Thermogravimetric analyses were performed on a Mettler-Toledo TGA-851e thermobalance. Experimental conditions: alumina crucibles of 70 μL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10 °C/min.

## 2.- Characterization of the solids

Figure S1: DSC of Form I

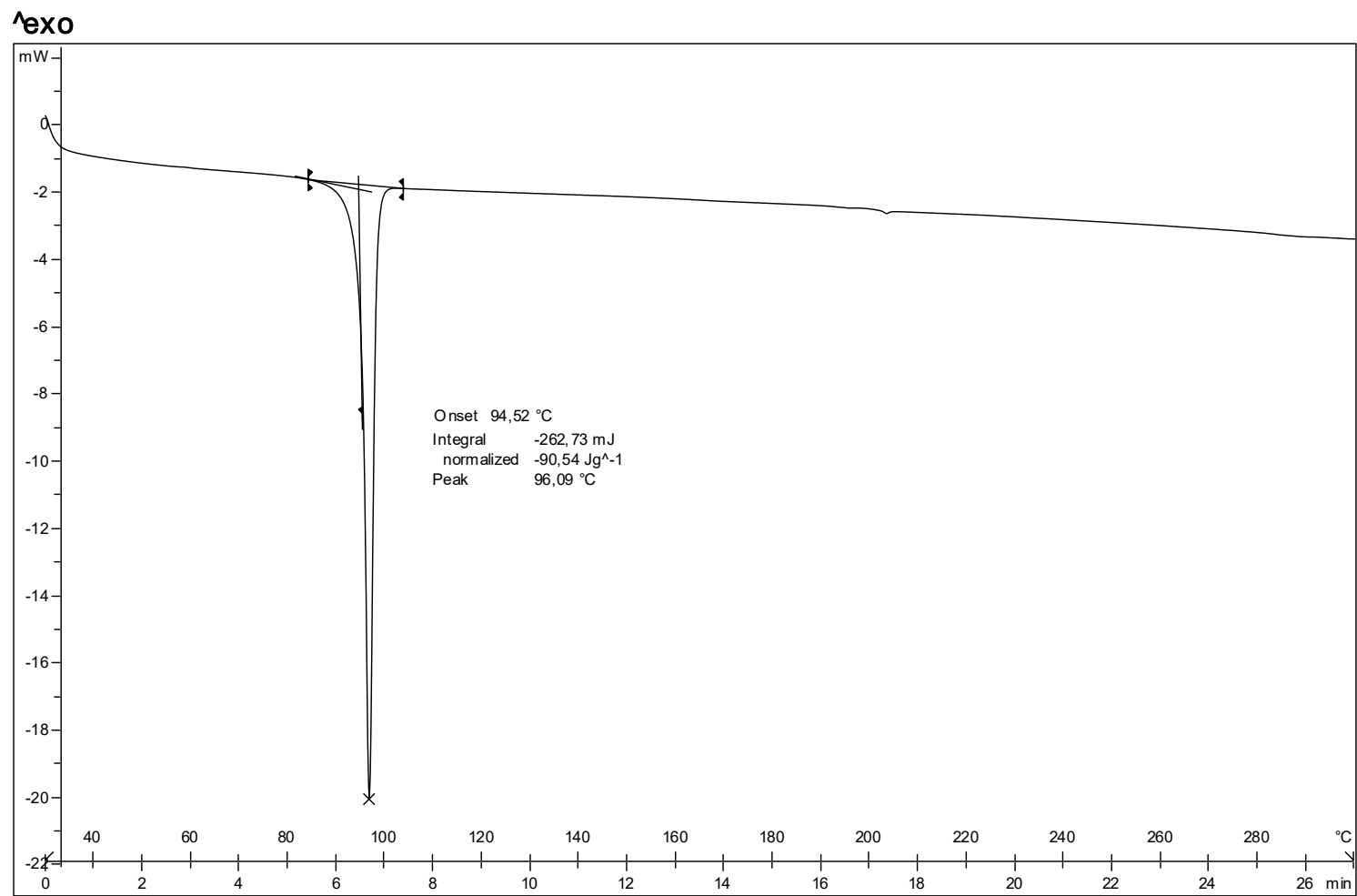


Figure S2: TGA Form I

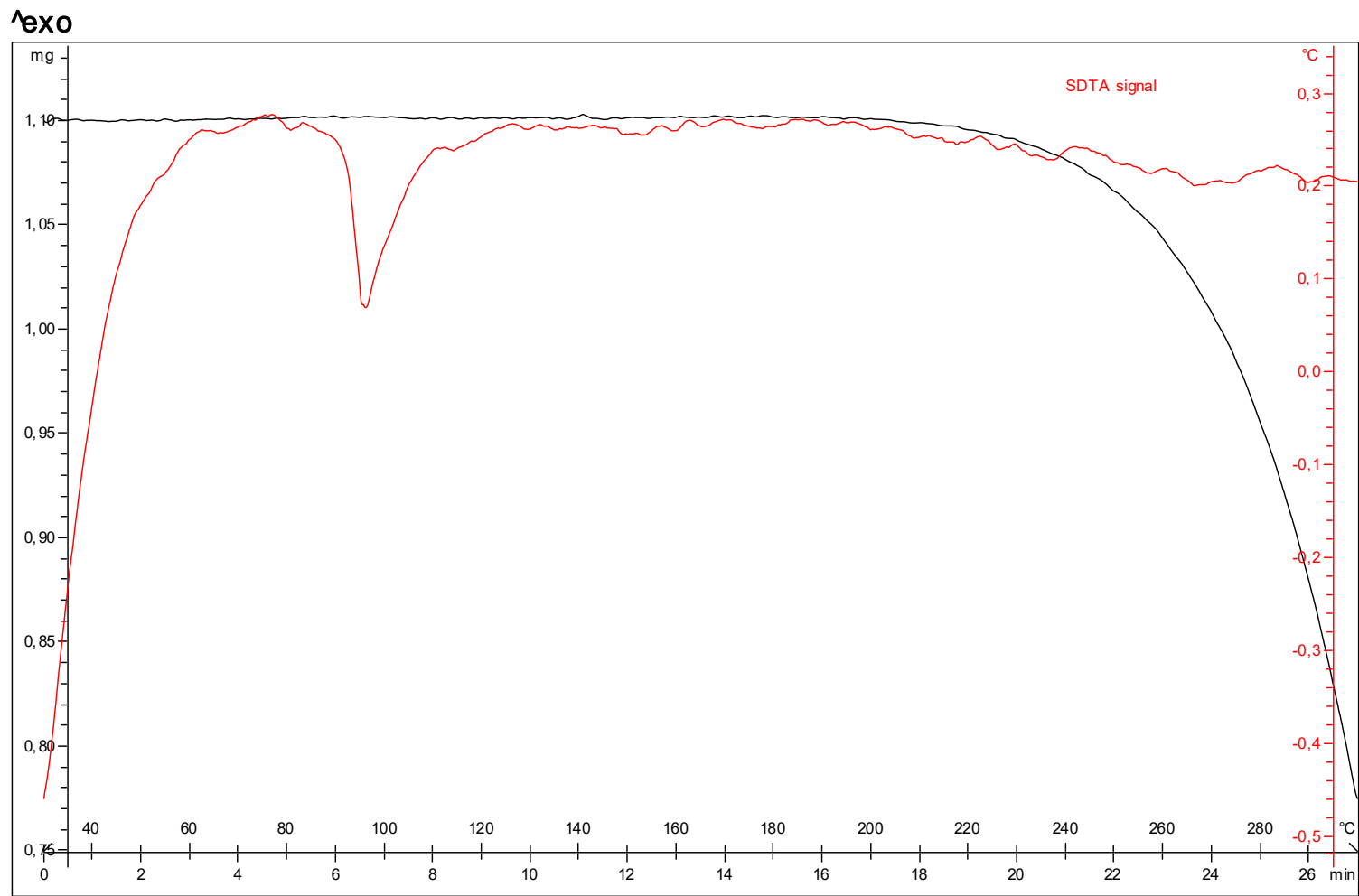


Figure S3: PXRD of Form I

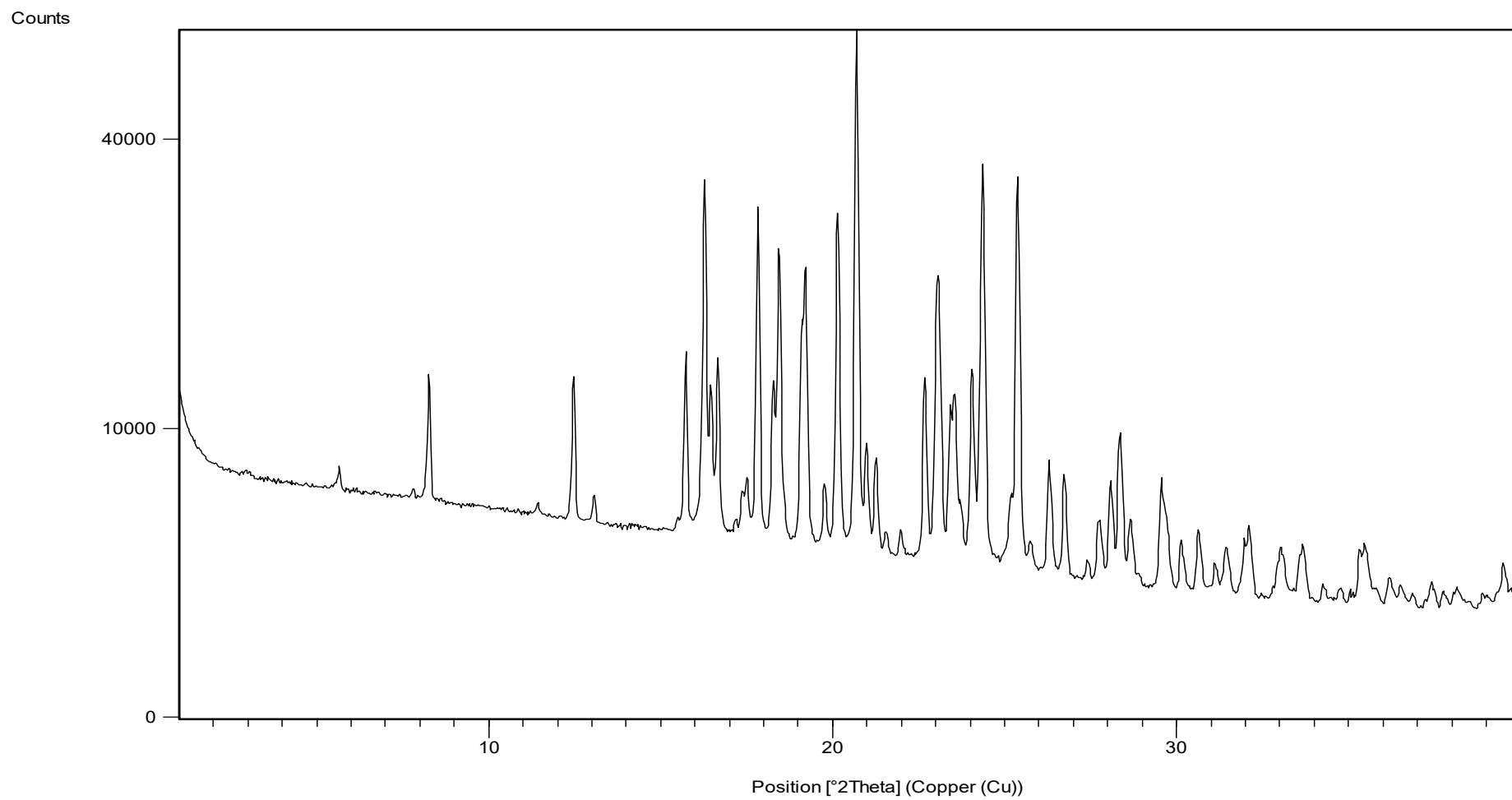


Figure S4: The XRPD of Form I has been indexed with the following proposed monoclinic cell:  $a=15.4310(9)$  Å,  $b=5.7893(3)$  Å,  $c=30.8114(19)$  Å,  $\beta=93.277(2)^\circ$ ,  $V=2748(3)$  Å<sup>3</sup> ( $R_{wp}=10.4$ ), a  $P2_1/c$  space group is compatible with the cell.

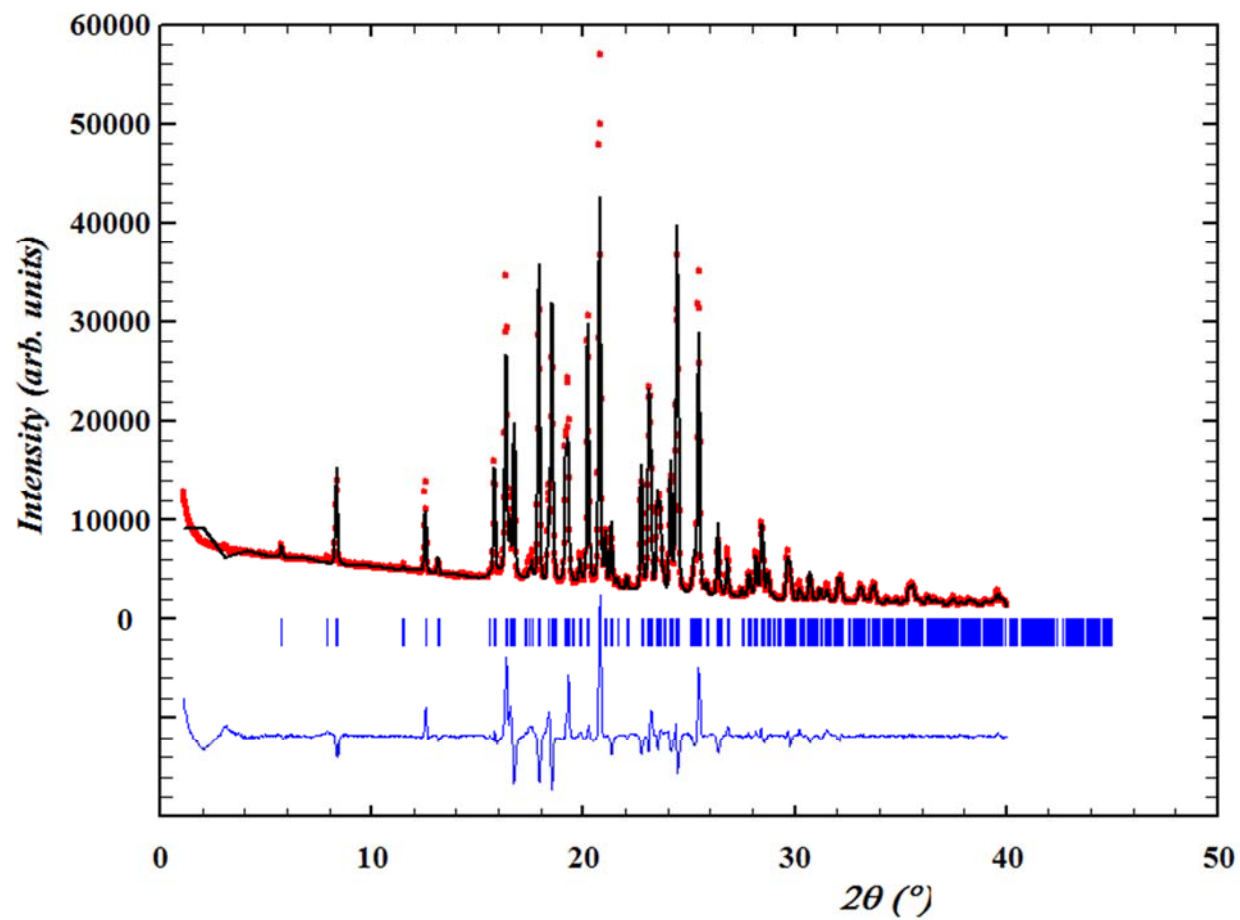




Figure S5: DSC of Form II

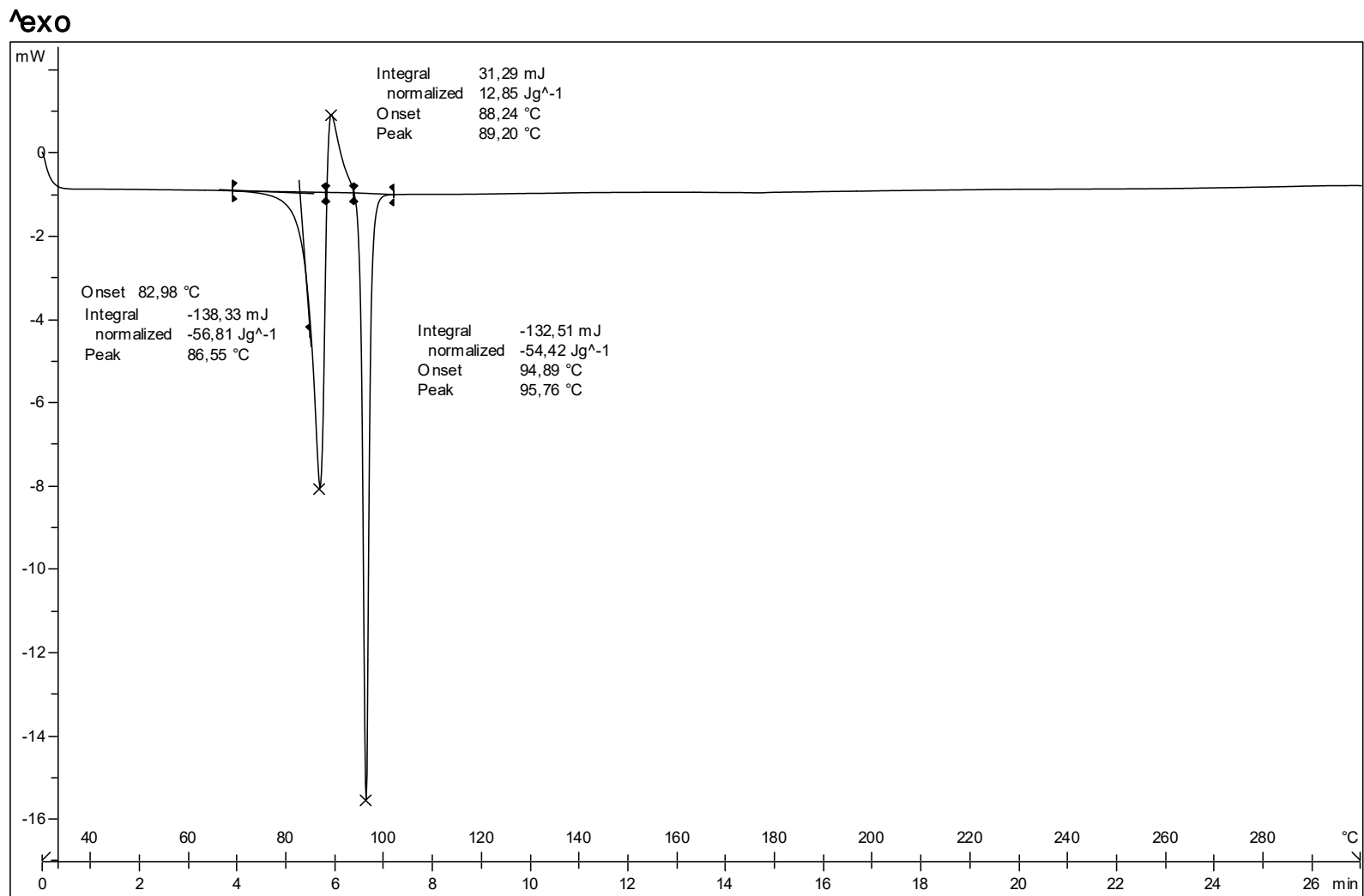


Figure S6: TGA Form II

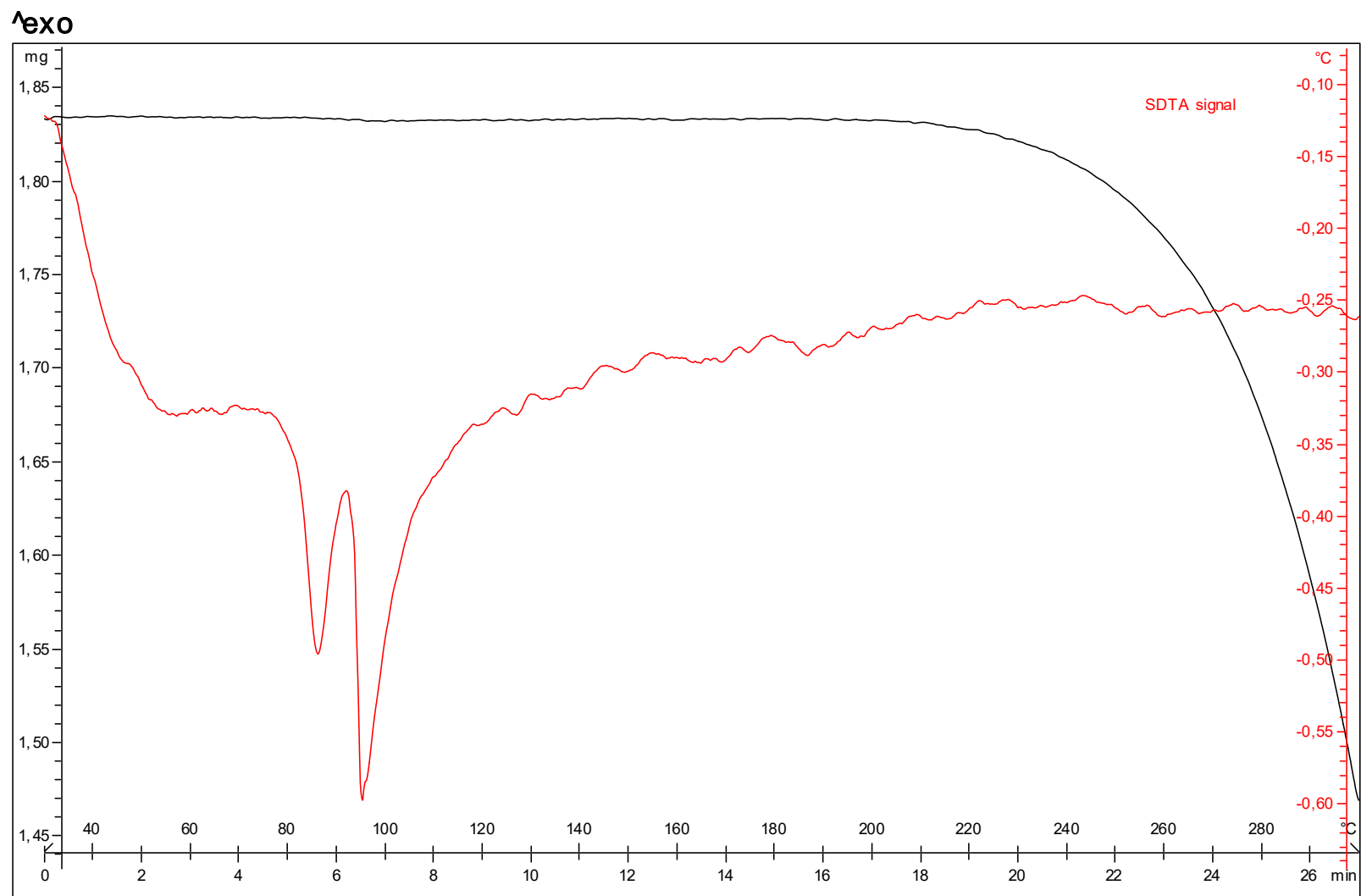


Figure S7: PXRD of Form II

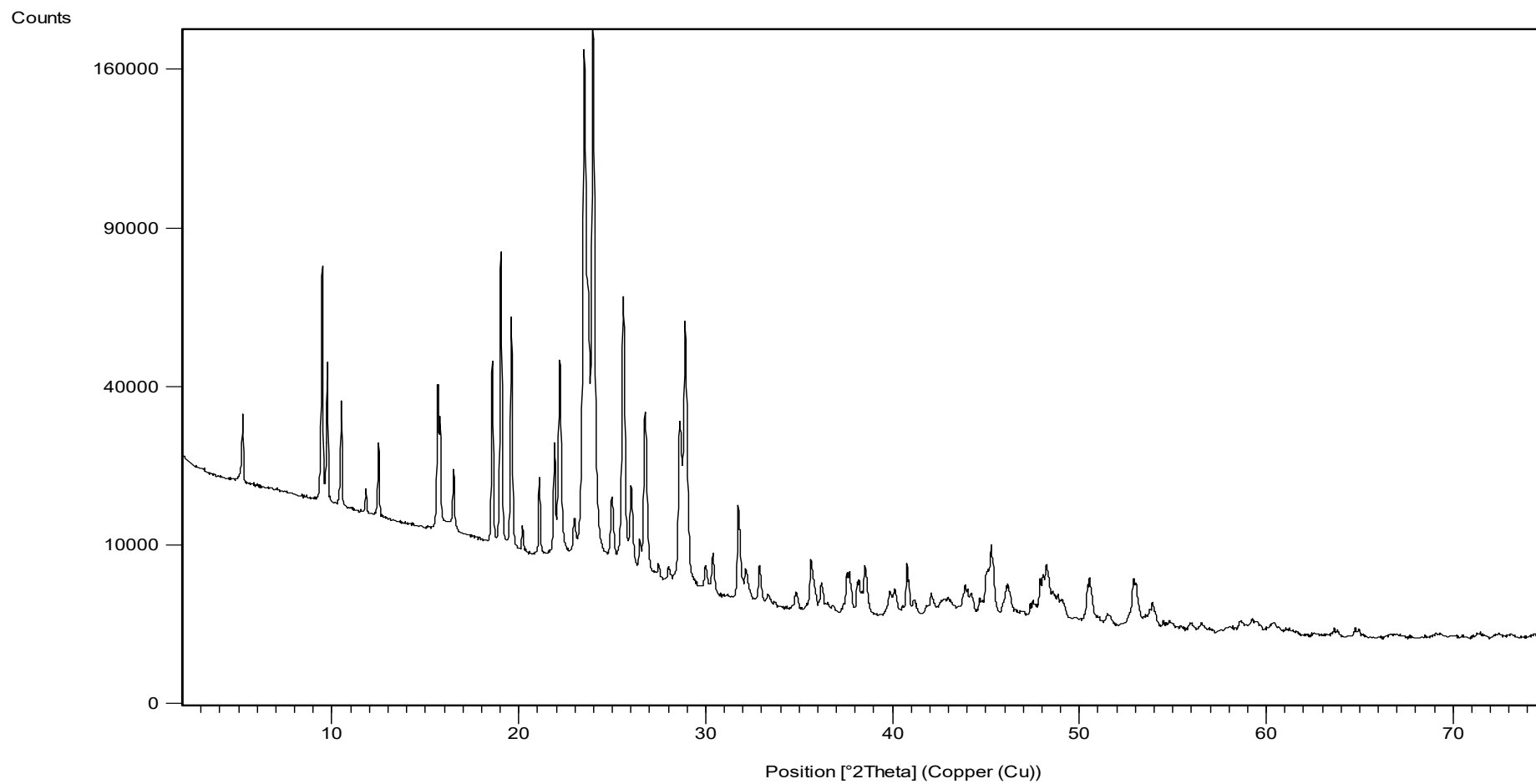


Figure S8: The XRPD of Form II has been indexed with the following proposed monoclinic cell:  $a=33.6698(13)$  Å,  $b=4.11759(9)$  Å,  $c=9.54694(3)$  Å,  $\beta=93.1620(2)^\circ$ ,  $V=1321(7)$  Å<sup>3</sup> ( $R_{wp}=10.6$ ), a  $P2_1/n$  space group is compatible with the cell

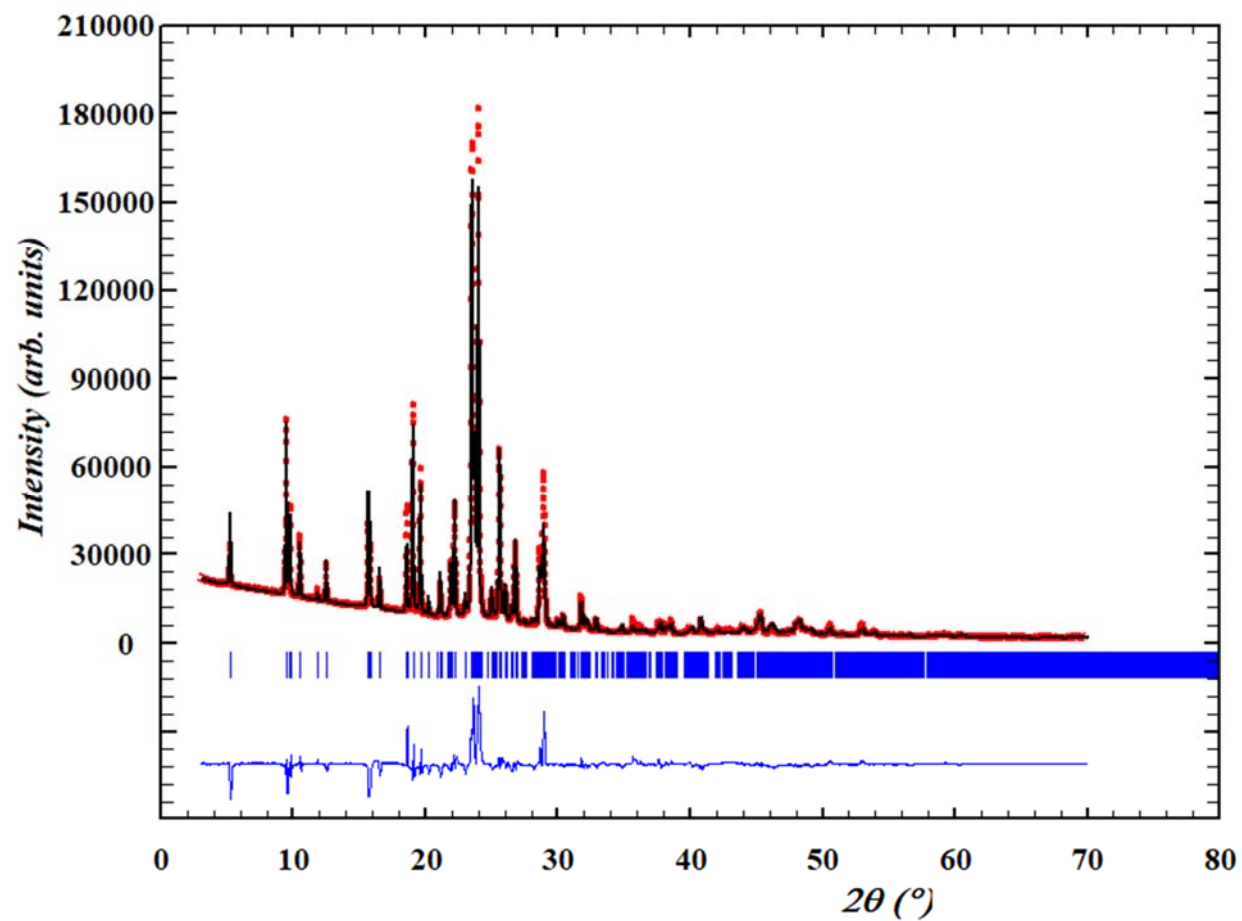


Figure S9: DSC Form III

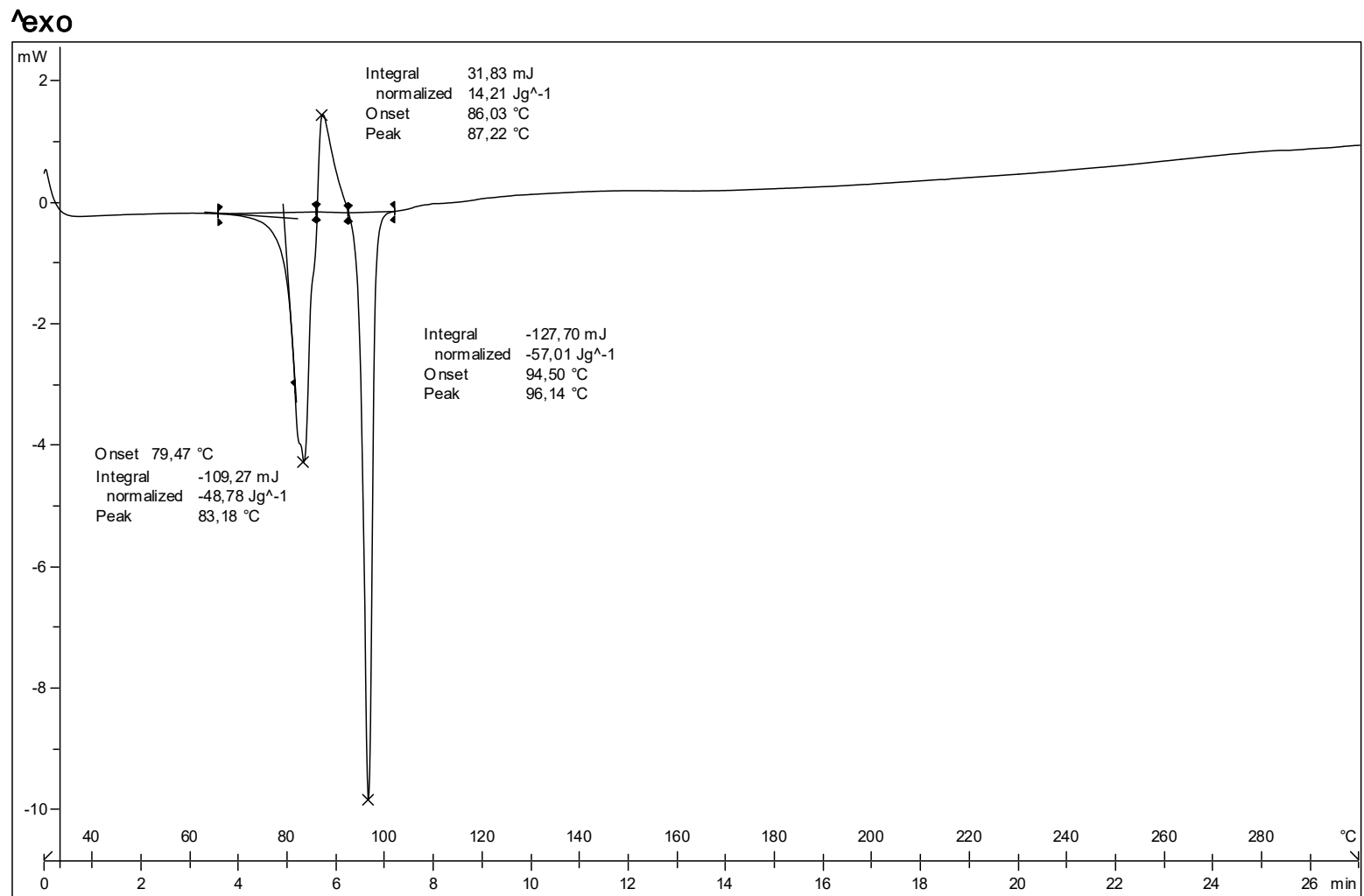


Figure S10: TGA Form III

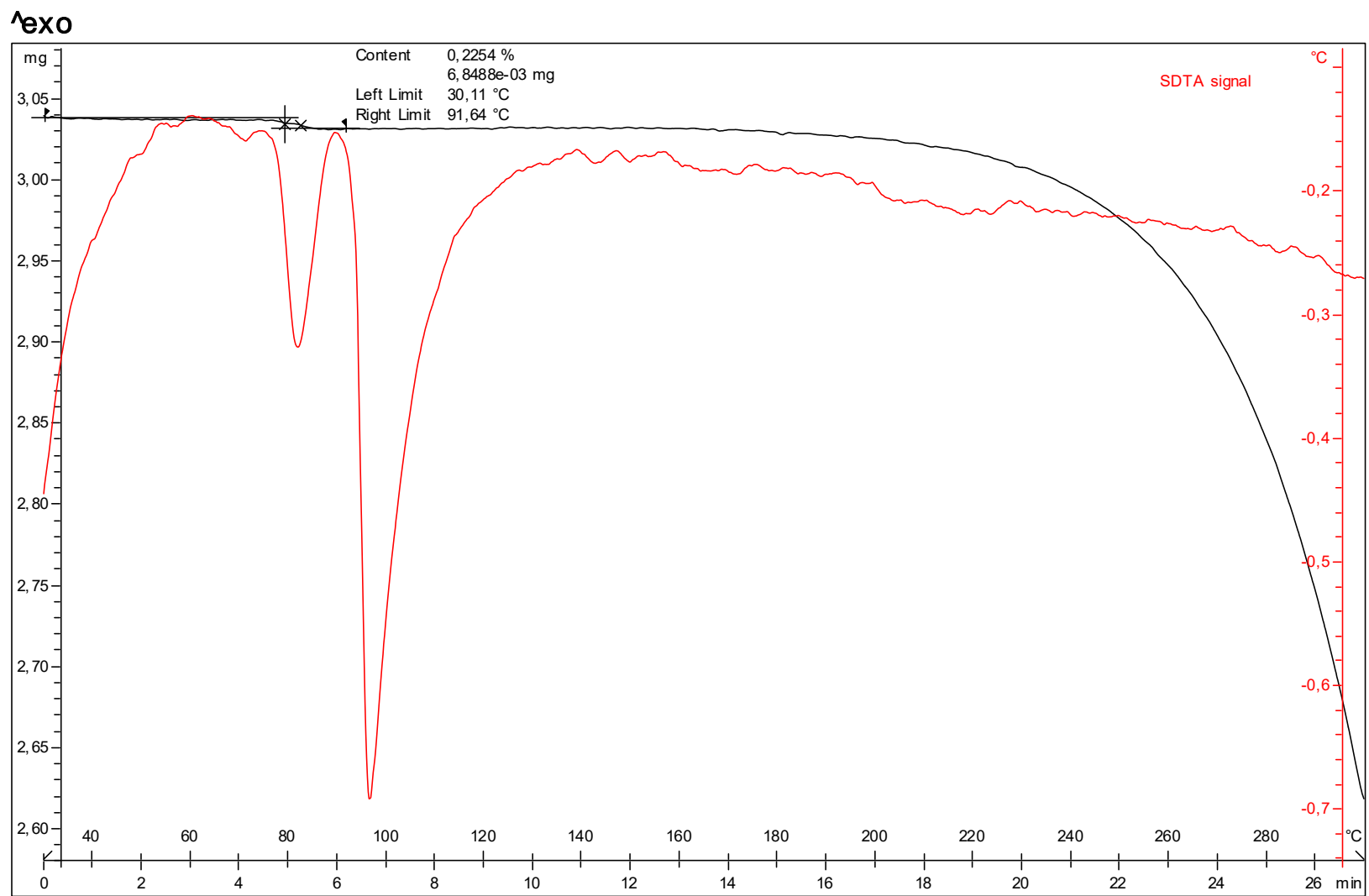


Figure S11: PXRD of Form III

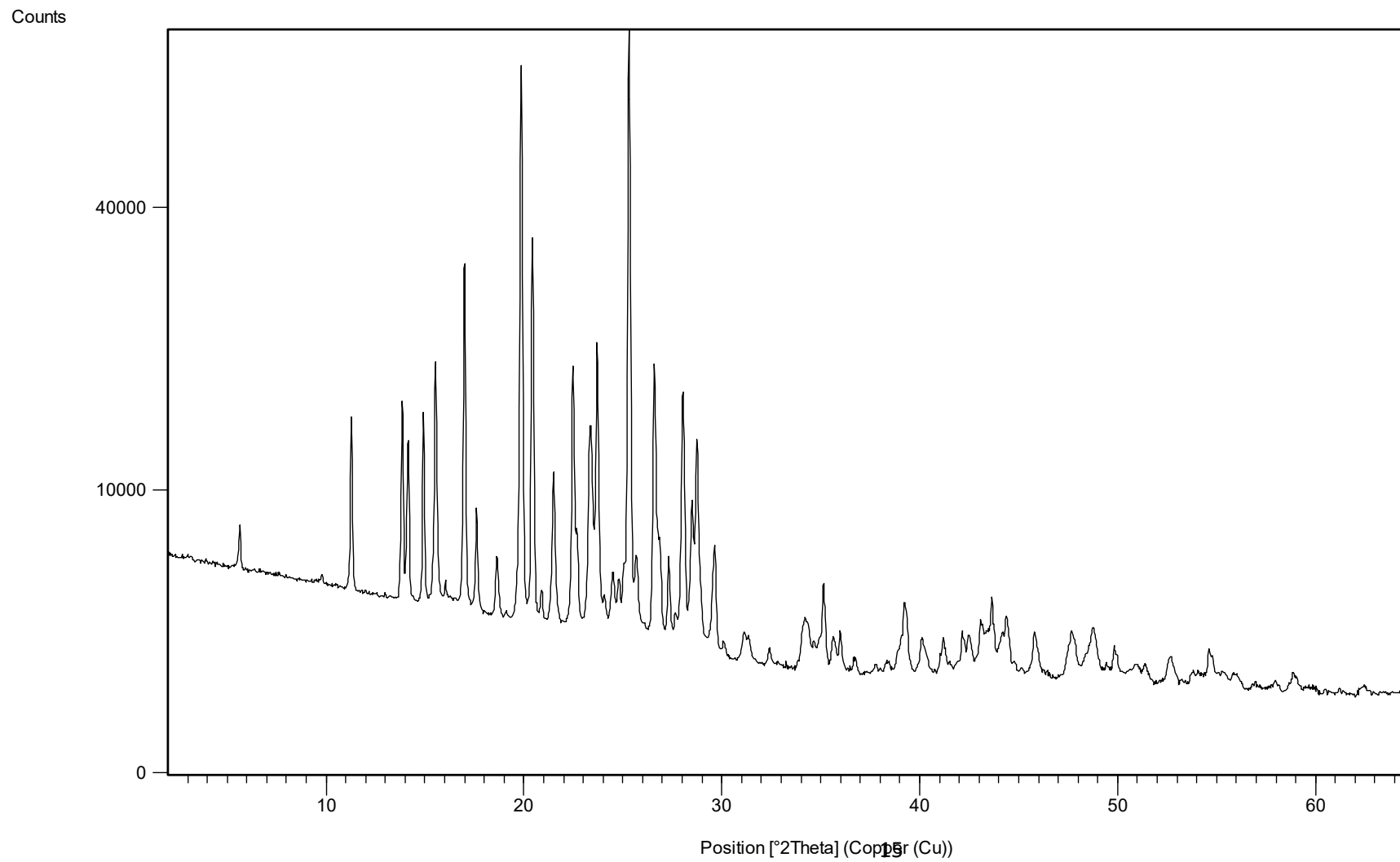


Figure S12: The XRPD of Form III has been indexed with the following proposed monoclinic cell:  $a=15.7225(8)$  Å,  $b=11.0550(5)$  Å,  $c=7.6201(3)$  Å,  $\beta=94.025(2)^\circ$ ,  $V=1321.20(10)$  Å<sup>3</sup> ( $R_{wp}=9.07$ ), a  $P2_1/c$  space group is compatible with the cell

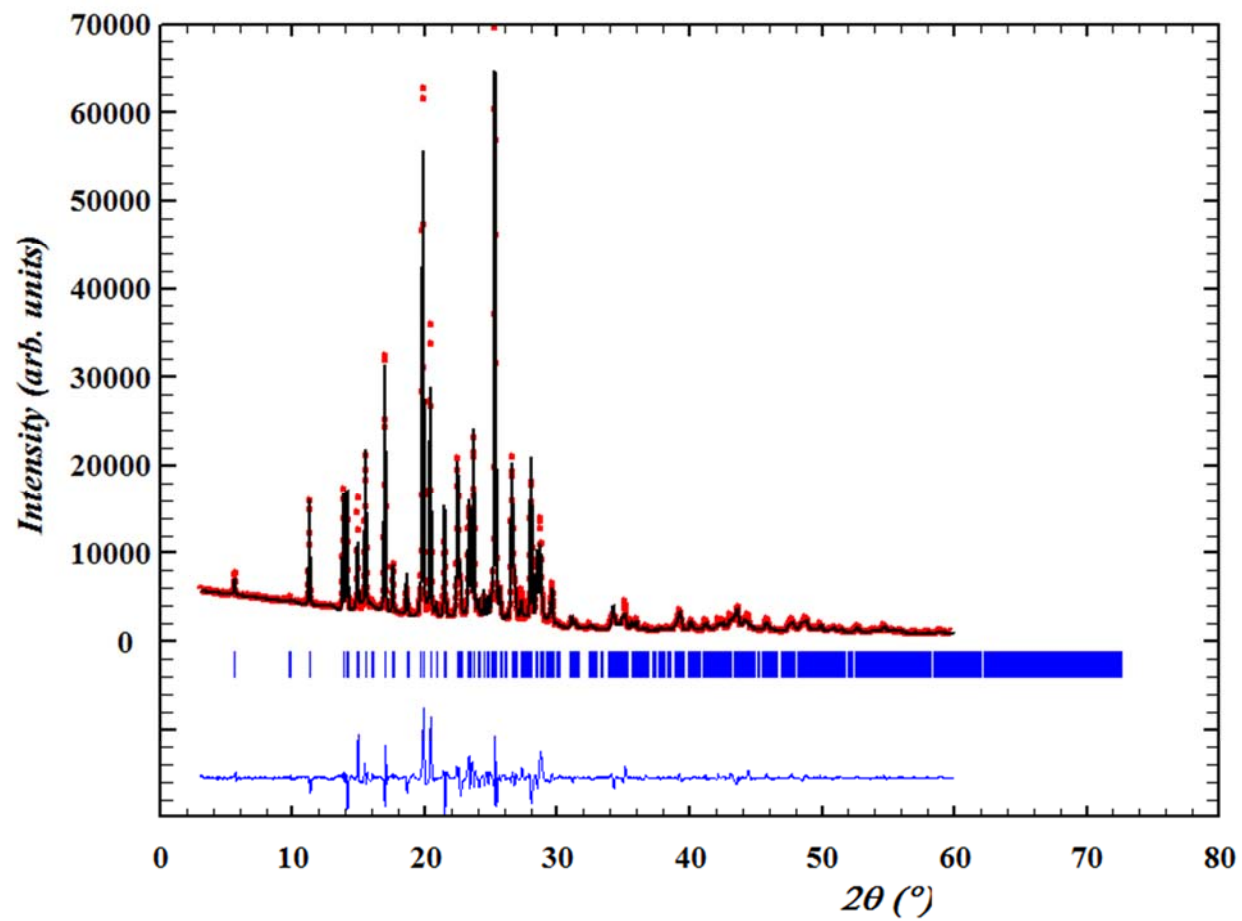
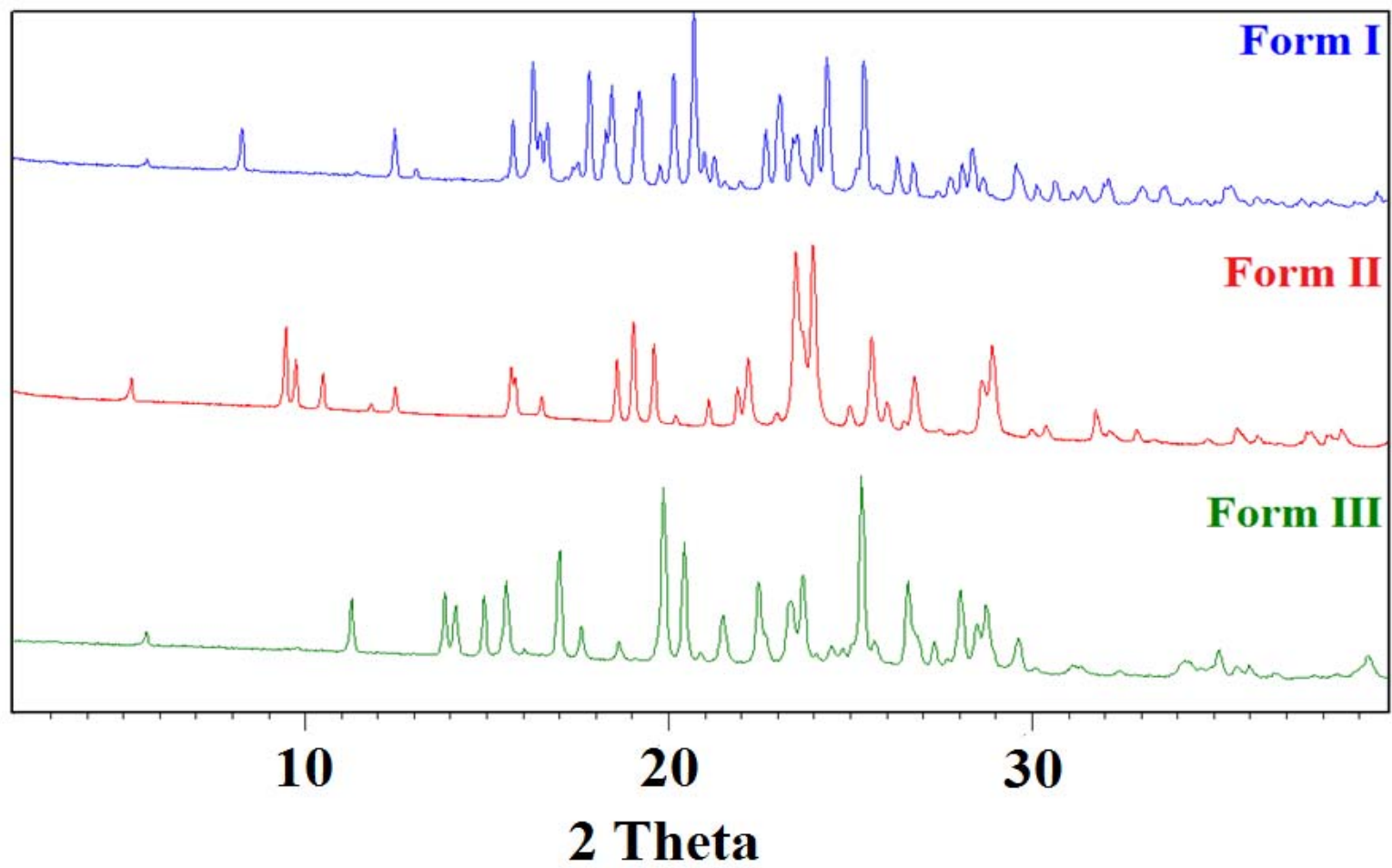




Figure S13: Comparison of the PXRD patterns of Pterostilbene forms: from 2 to 40 (2 $\theta$ )



**Table S4. H-bond parameters of the terminal unit (donor or acceptor) in the aggregates of the three polymorphs of pterostilbene and product of the H-bond parameters ( $\alpha\beta$ ) for the monomer (N=1) to the tetramer (N=4) in the H-bonded aggregates of the three polymorphs of pterostilbene. The  $\alpha$  value corresponds to the phenol hydrogen in all three forms but the  $\beta$  value corresponds to the phenol oxygen in form I but to the methoxy oxygen in forms II and III.**

Form I				Form II				Form III			
N	$\alpha$	$\beta$	$\alpha\beta$	N	$\alpha$	$\beta$	$\alpha\beta$	N	$\alpha$	$\beta$	$\alpha\beta$
1	3,56	4,06	14.4	1	3,50	3,70	12.9	1	3,50	3,93	13.8
2	4,47	6,11	27.3	2	3,00	3,72	11.1	2	3,84	4,48	17.2
3	4,74	6,98	33.1	3	2,93	4,00	11.7	3	4,04	4,71	19.0
4	4,60	7,24	33.3	4	2,84	4,07	11.6	4	4,11	4,87	20.0

### 3.- References

1. A. Boulif and D. Louër, *J. Appl. Crystallogr.* 1991, **24**, 987-993.
2. Spartan'10, version 1.1.0. Wavefunction, Inc. Irvine, CA. 2010.
3. J. Rodriguez-Carvajal, *Physica B.* 1993, **192**, 55-69.