

Two polymorphs of 5-cyclohexyl-5-ethylbarbituric acid and their packing relationships with other barbiturates

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Supporting information

S1. Hydrogen-bonded structures

Table S1 Overview of solid forms of barbiturates (unique entries of the CSD and from recent literature) containing hydrogen-bonded structures (HBSs) of the types C-1 and C-2 and L-4 (as defined in Gelbrich *et al.*, 2011).

| R ¹ | R ² | Common name | Form | HBS | CSD refcode | Reference |
|----------------|------------------------|-----------------------------|-------------------------|----------|-------------|------------------------------------------|
| methyl | methyl | | | C-1 | NUXTAC | (Roux <i>et al.</i> , 2010) |
| ethyl | isopropyl | ipral | I | C-1 | FUFTAC | (Zencirci <i>et al.</i> , 2009) |
| ethyl | butyl | soneryl, butobarbital | RT-Form | C-1 | ETBBAR | (Bideau, 1971) |
| ethyl | butyl | soneryl, butobarbital | LT-Form | C-1 | ETBBAR01 | (Nichol & Clegg, 2005) |
| ethyl | butyl | soneryl, butobarbital | | C-1 | ETBBAR02 | (Nichol & Clegg, 2007) |
| allyl | isobutyl | sandoptal | | C-1 | FUFTIK | (Zencirci <i>et al.</i> , 2009) |
| ethyl | 1-methylbutyl | pentobarbital, nembutal | I | C-1 | FUFTEG01 | (Rossi <i>et al.</i> , 2012) |
| ethyl | 1-methylbutyl | pentobarbital, nembutal | II | C-1 | FUFTEG04 | (Rossi <i>et al.</i> , 2012) |
| ethyl | 1-methylbutyl / phenyl | | co-crystal | C-1 | LATMEA | (Rossi <i>et al.</i> , 2012) |
| ethyl | n-pentyl | | | C-1 | ENPBAR | (Bideau & Marsau, 1974) |
| ethyl | isoamyl | amobarbital | I ^a | C-1 | AMYTAL11 | (Craven & Vizzini, 1969) |
| ethyl | isoamyl | amobarbital | II ^a | C-1 | AMYTAL10 | (Craven & Vizzini, 1969) |
| ethyl | but-2-enyl | | | C-1 | BEBWUA | (Jones & Andrews, 1981a) |
| ethyl | 3-methylbut-2-enyl | | | C-1 | BECLIE | (Jones & Andrews, 1981b) |
| ethyl | 1,3-dimethylbut-1-enyl | | | C-1 | BEBWOU | (Andrews & Jones, 1981) |
| ethyl | 1,3-dimethylbut-2-enyl | | | C-1 | JIFRIZ | (Jones & Horn, 1986) |
| ethyl | 1,3-dimethylbutyl | α -methylamobarbital | | C-1 | MAOBAR | (Smit & Kanters, 1974) |
| ethyl | phenyl | phenobarbital | ACN solv. ^b | C-1 | | (Zencirci <i>et al.</i> , 2014) |
| ethyl | phenyl | phenobarbital | NiMe solv. ^c | C-1 | | (Zencirci <i>et al.</i> , 2014) |
| ethyl | 1-cyclohexen-1-yl | phanodorm, cyclobarbital | | C-1 | ETCYBA01 | (Zencirci <i>et al.</i> , 2009) |
| ethyl | cyclohexyl | | II | C-1 | (Ib) | <i>this work</i> |
| allyl | allyl | dial | | C-1 | DALLBA | (Escobar, 1975) |
| allyl | isopropyl | aprobarbital | I | C-1 | AIPBAR | (Rae, 1975) |
| F | phenyl | | | C-2 | HEKTOG | (DesMarteau <i>et al.</i> , 1994) |
| ethyl | ethyl | barbital | II | C-2 | DETBA02 | (Craven <i>et al.</i> , 1969) |
| ethyl | pentan-2-yl | pentobarbital | III | C-2 | FUFTEG02 | (Rossi <i>et al.</i> , 2012) |
| ethyl | phenyl | phenobarbital | III | C-2 | PHBARB09 | (Zencirci <i>et al.</i> , 2010) |
| ethyl | phenyl | phenobarbital | DCM solv. ^d | C-2 | | (Zencirci <i>et al.</i> , 2014) |
| ethyl | 6-oxocyclohexenyl | 6-oxocyclobarbital | | C-2 | OXCBAR | (Chentli-Benchikha <i>et al.</i> , 1977) |
| ethyl | phenyl | phenobarbital | I | C-2, L-3 | PHBARB07 | (Zencirci <i>et al.</i> , 2010) |
| ethyl | phenyl | phenobarbital | II | C-2, L-3 | PHBARB08 | (Zencirci <i>et al.</i> , 2010) |
| ethyl | cyclohexyl | | I | L-4 | (Ia) | <i>this work</i> |
| isopropyl | 2-bromoallyl | noctal | II | L-4 | UXIYIK | (Gelbrich <i>et al.</i> , 2011) |

^aThis nomenclature according to Brandstätter-Kuhnert & Aepkers (1963) and Zencirci *et al.* (2009) differs from that of Craven & Vizzini (1969) and the corresponding CSD entries.

^bAcetonitrile solvate.

^cNitromethane solvate.

^dDichloromethane solvate.

S2. Comparison of crystal structures

Table S2 Corresponding lattice directions in the isostructural crystal structures of (Ia) and form II of noctal (UXIYIK).

| CSD refcode | <i>t</i> 1 | | <i>t</i> 2 | | <i>t</i> 3 | | $\angle t2,t3$ | $\angle t1,t3$ | $\angle t1,t2$ |
|-------------|-------------|--------|------------|--------|-------------|--------|----------------|----------------|----------------|
| (Ia) | $\bar{1}00$ | 17.932 | 010 | 10.496 | $00\bar{1}$ | 13.219 | 90 | 95.9 | 90 |
| UXIYIK | 200 | 16.183 | 010 | 11.347 | 001 | 13.267 | 90 | 105.8 | 90 |

Table S3 Corresponding lattice directions in (Ib) and four isostructural crystal forms.

| CSD refcode | <i>t</i> 1 | | <i>t</i> 2 | | <i>t</i> 3 | | $\angle t2,t3$ | $\angle t1,t3$ | $\angle t1,t2$ |
|-------------|-------------|--------|-------------------|--------|-------------|--------|----------------|----------------|----------------|
| (Ib) | 001 | 10.331 | 101 | 12.078 | 010 | 21.074 | 90 | 90 | 67.3 |
| FUFTAC | $00\bar{1}$ | 10.278 | $\bar{1}0\bar{1}$ | 11.815 | $0\bar{1}0$ | 17.373 | 90 | 90 | 69.4 |
| LATMEA | $00\bar{1}$ | 10.253 | $\bar{1}0\bar{1}$ | 11.918 | $0\bar{1}0$ | 20.689 | 90 | 90 | 69.3 |
| AMYTAL11 | $\bar{1}00$ | 10.281 | 001 | 11.679 | $0\bar{1}0$ | 22.601 | 90 | 90 | 70.9 |
| BECLIE | $00\bar{1}$ | 10.195 | 100 | 11.590 | $0\bar{1}0$ | 22.188 | 90 | 90 | 71.0 |

S3. FT-IR spectroscopy

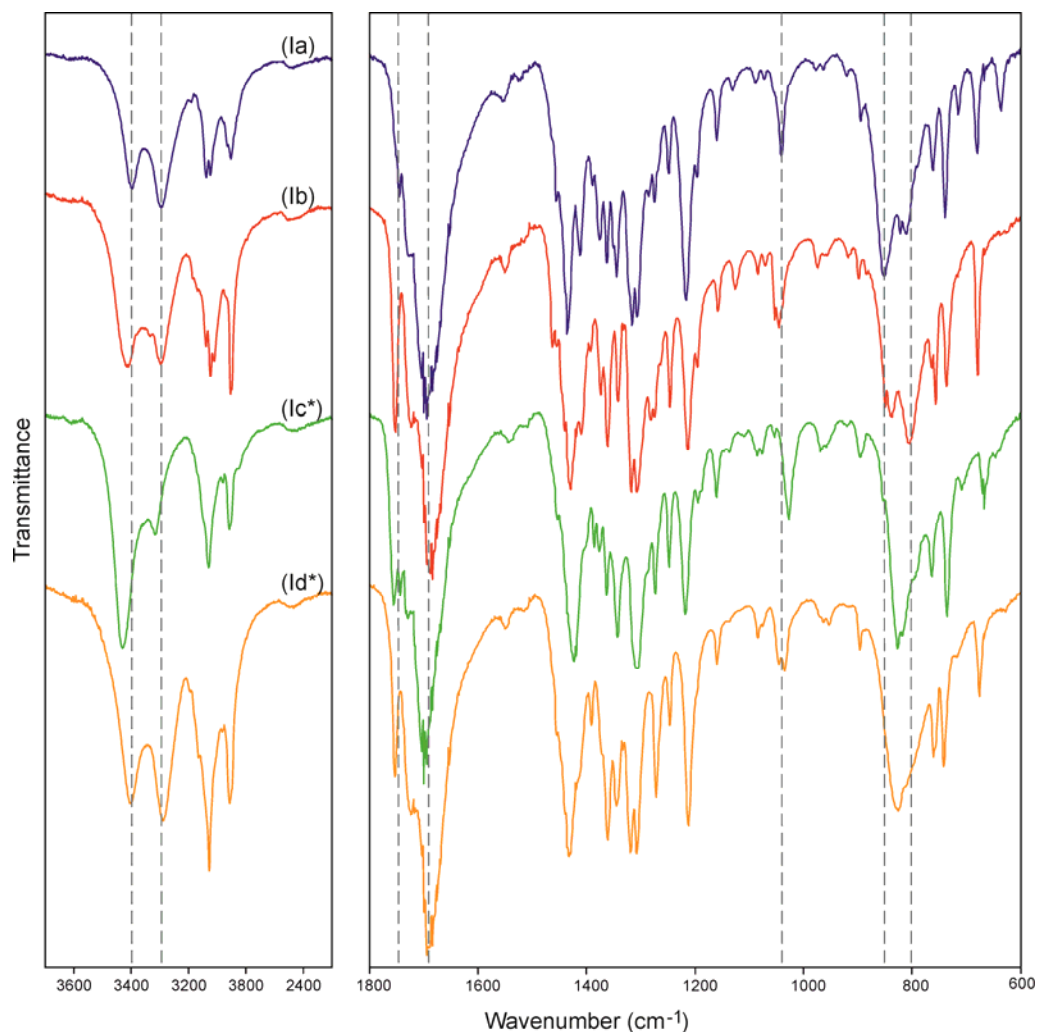


Figure S1 FT-IR spectra for four polymorphs of (I), with selected distinctive regions indicated by broken lines. The patterns labelled (Ic*) and (Id*) were recorded for different aggregates contained in a melt preparation from a hot-bench experiment which correspond morphologically with the phases (Ic) and (Id) obtained in hot-stage microscopy experiments and described in section 2.2. The spectra were recorded in the range from 4000 to 450 cm^{-1} , using a PERKIN-ELMER Spectrum Two IR spectrometer equipped with an ATR attachment.

Table S4 Selected IR bands (cm^{-1}) for four polymorphs of (I).

| Polymorph | ν (N–H) | ν (C=O) | ν (N–H out-of-plane) |
|-----------|-------------|-------------------------|--------------------------|
| (Ia) | 3196, 3096 | 1745, 1725, 1695 | 851 , 822, 811 |
| (Ib) | 3208, 3096 | 1751, 1723, 1688 | 823, 805 |
| (Ic*) | 3230, 3116 | 1755, 1700 | 827 |
| (Id*) | 3203, 3089 | 1754, 1724, 1696 | 827 |

S4. Preparation of crystal forms and hot-stage microscopy

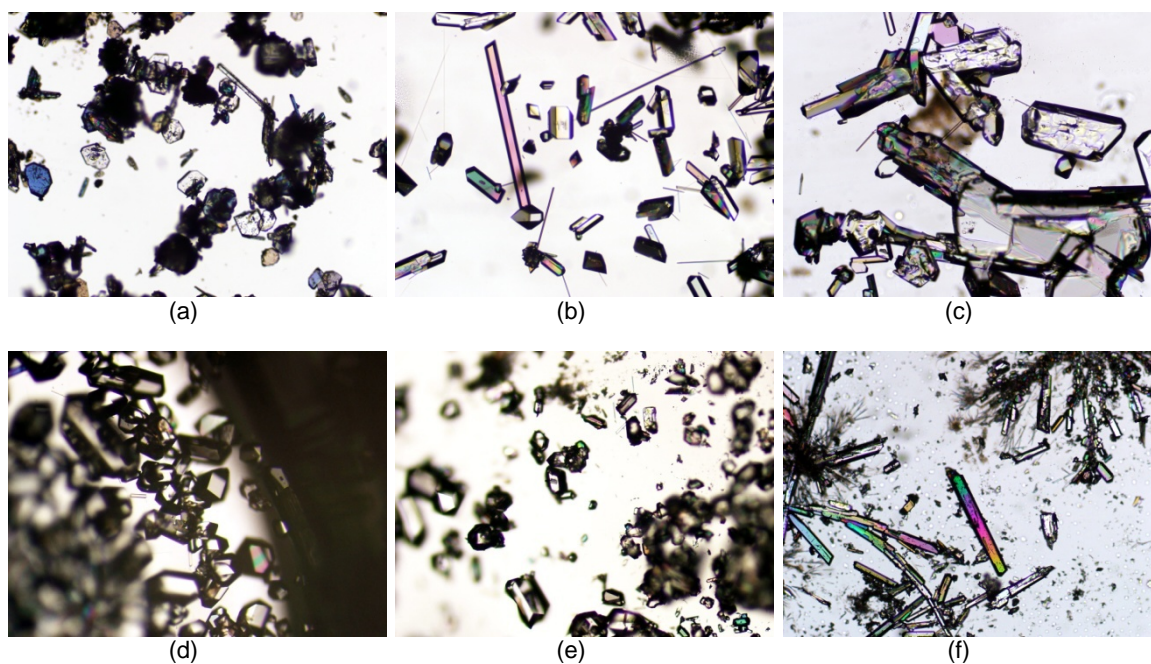


Figure S2 Light microscopy images of samples of (I) (magnification 100 \times); a) original sample consisting of hexagonal plates of (Ia) and oblong prisms of (Ib); (b) crystals of (Ib) on a cover slip of a hot-stage microscopy preparation at 188°C, crystallised from the sublimate; (c) crystals of (Ia) grown from a melt containing residual seeds; d) and e) isometric crystals of (Ia) obtained by sublimation; f) crystals of (Ib) obtained by sublimation.

S5. PXRD pattern of the original sample

Experimental. The powder X-ray diffraction pattern was recorded using an X'Pert PRO diffractometer (PANalytical, Almelo, The Netherlands) equipped with a θ/θ coupled goniometer in transmission geometry, programmable XYZ stage with well plate holder, Cu- $K_{\alpha 1,2}$ radiation source with a focussing mirror, a 0.5° divergence slit and a 0.02° Soller slit collimator on the incident beam side, a 2 mm antiscattering slit and a 0.02° Soller slit collimator on the diffracted beam side and a solid state PIXcel detector. The pattern was recorded at a tube voltage of 40 kV, tube current of 40 mA, applying a step size of $2\theta = 0.013^\circ$ with 80 s per step in the 2θ range between 2° and 40° .

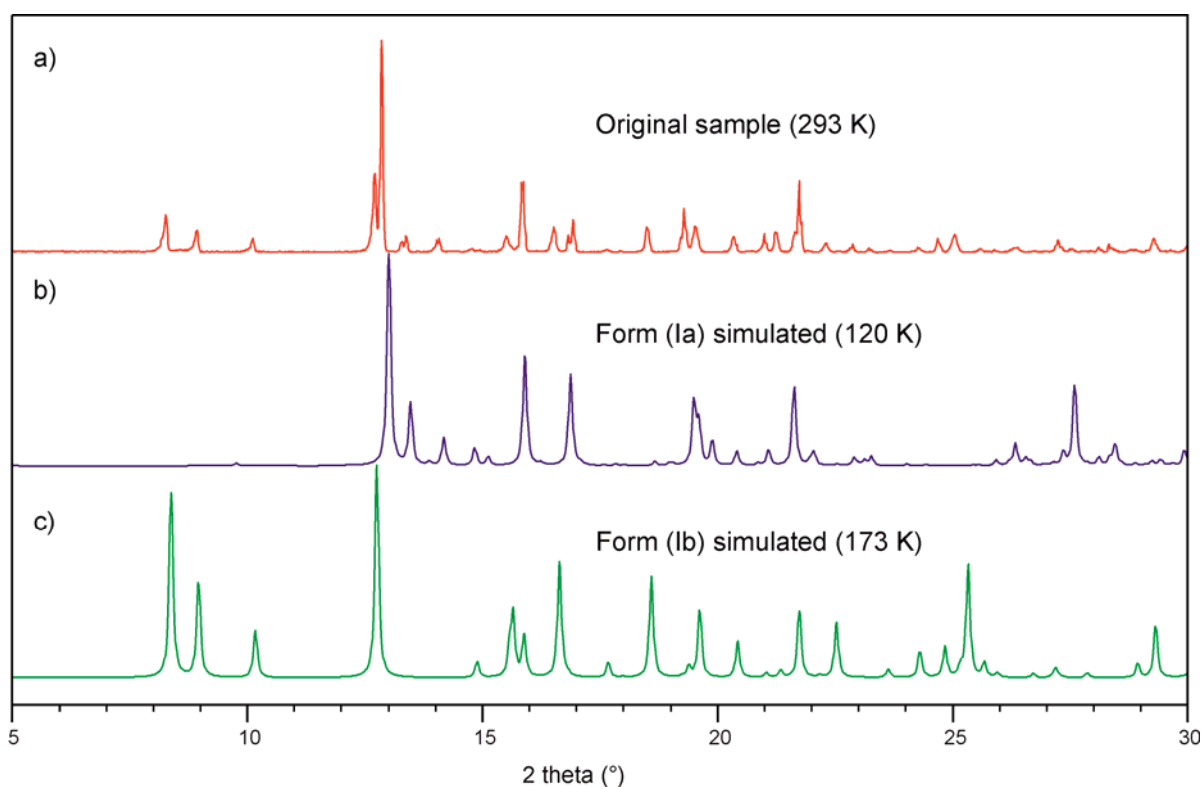


Figure S3 a) PXRD pattern of the original sample ($\lambda = 1.5418 \text{ \AA}$), which consists of polymorphs (Ia; main component) and (Ib); b) and c) simulated PXRD patterns based on the structure models for polymorphs (Ia) and (Ib).

S6. Differential scanning calorimetry

Experimental. The DSC thermogram was recorded on a DSC 7 instrument (Perkin-Elmer Norwalk, Ct., USA) controlled by the Pyris 7.0 software. Using a UM3 ultramicrobalance (Mettler, Greifensee, Switzerland), approximately 4 mg of sample was weighed into a sealed aluminium pan. The applied heating rate was $10\text{ }^{\circ}\text{C min}^{-1}$ and dry nitrogen was used as purge gas (purge: 20 ml min^{-1}). The instrument was calibrated for temperature with pure benzophenone (mp $48.0\text{ }^{\circ}\text{C}$) and caffeine ($236.2\text{ }^{\circ}\text{C}$), and the energy calibration was performed with indium (mp $156.6\text{ }^{\circ}\text{C}$, heat of fusion 28.45 Jg^{-1}).

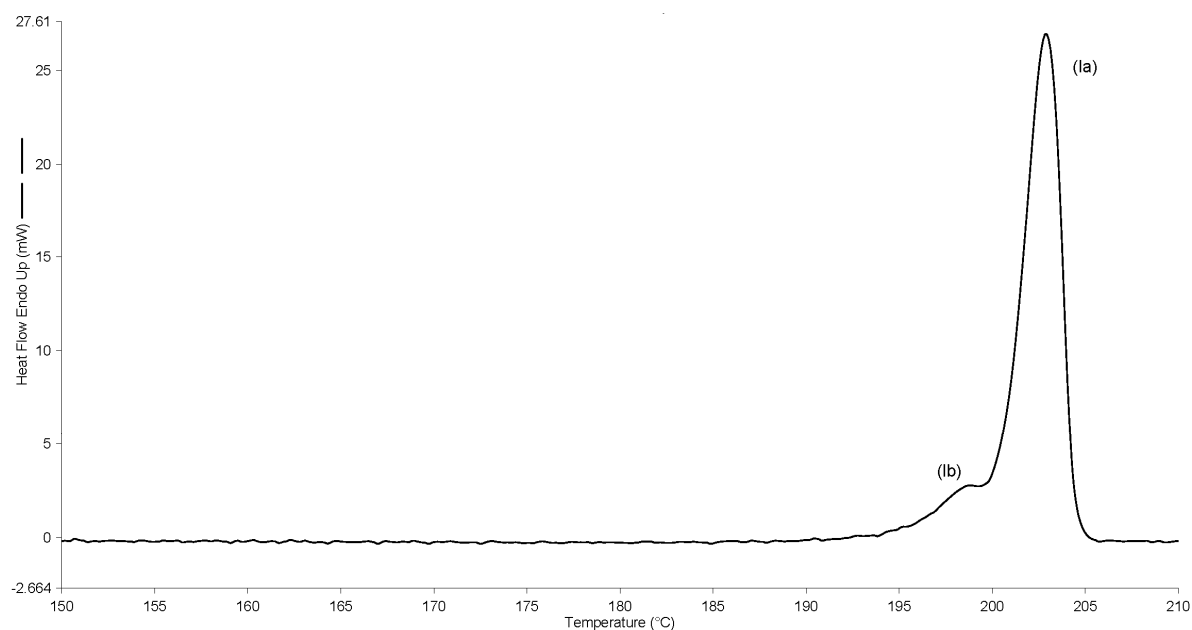


Figure S4 DSC curve of the original samples showing the overlapping melting endotherms of (Ib) and (Ia). Heating rate: 10 K min^{-1} .

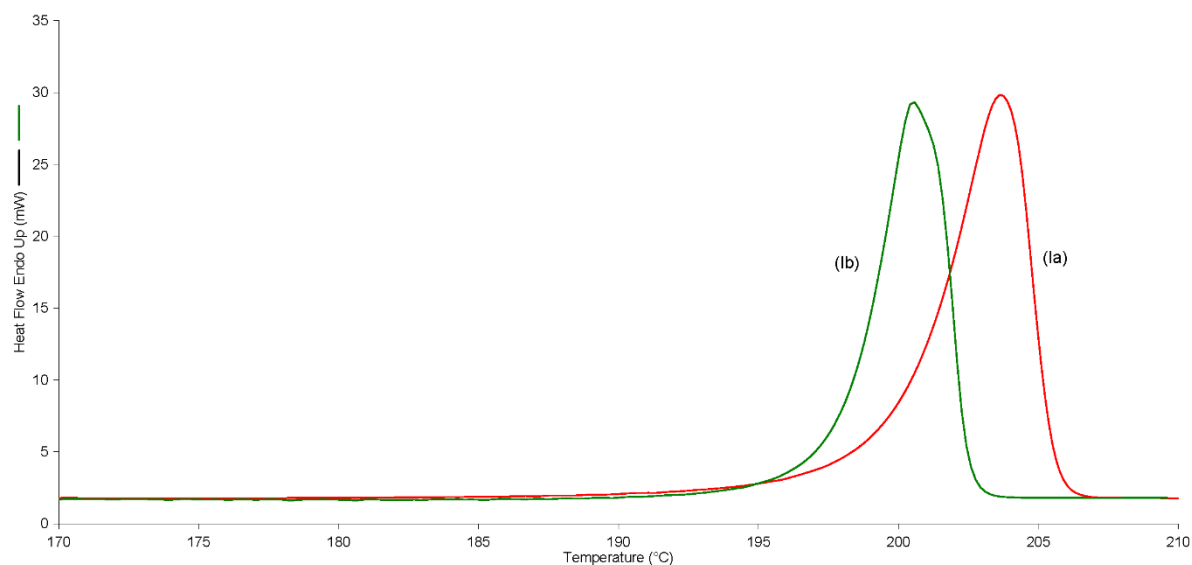


Figure S5 Overlay of the DSC traces (melting endotherms) of the phase pure polymorphs (Ib) and (Ia). Heating rate: 10 K min⁻¹.

The melting process of phase pure (Ib) was obtained in the DSC pan by reheating a completely melted (210 °C) and subsequently cooled sample. On cooling the melt (10 K min⁻¹, 30 °C end temperature) a broad (range ca. 20 K, exothermic) crystallization process is observed between 160 and 100 °C, which results in a mixture of forms (Ib), (Ic) and (Id). In the second heating cycle the portions of (Ic) and (Id) transform to (Ib), which melts as a single phase. Form (Ia) is not formed in this melt crystallization process.

To obtain phase pure form (Ia) the original sample consisting of a mixture of (Ia) and (Ib) was heated to 201.5 °C, subsequently cooled to 160 °C and reheated. At 201.5 °C the portion of (Ib) melts completely leaving (Ia) and the melt of (Ib), which recrystallises to (Ia) on cooling due to seeding effects.

Table S5 Thermochemical data (95 % confidence interval) of (Ia) and (Ib).

| Form | (Ia) | (Ib) |
|------------------------------------------------|-------------|-------------|
| T_{fus} [°C] | 200.6 ± 0.6 | 197.6 ± 0.7 |
| $\Delta_{\text{fus}}H$ [kJ mol ⁻¹] | 28.8 ± 0.6 | 28.0 ± 0.6 |

T_{fus} : melting point; $\Delta_{\text{fus}}H$: enthalpy of fusion

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