# Supporting Information

# The Crystal Polymorphs of Barbital: News about a Classic Polymorphic System†

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# 1. Solvent crystallization scheme

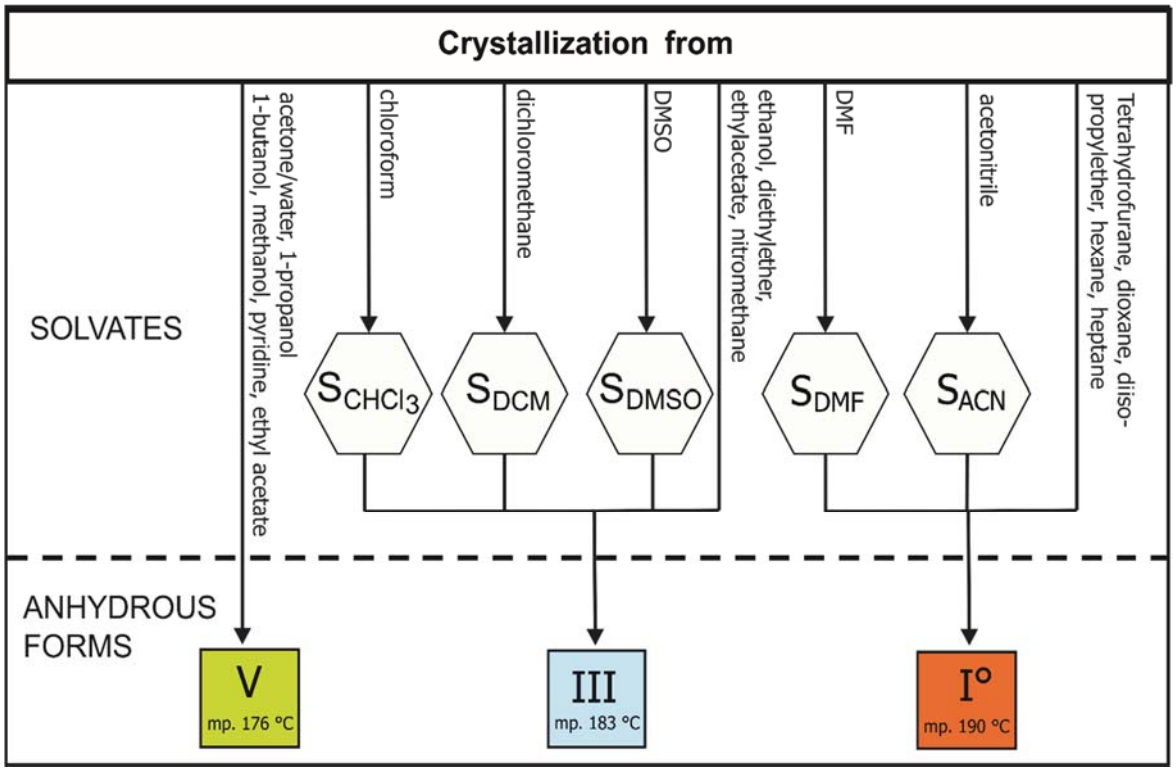



**Figure S1**. Solvent crystallization scheme demonstrating the production of the three polymorphs and the solvates of Btl. From most solvents more than one form was obtained. In the scheme mainly those solvents are stated which give a corresponding form in higher yields.

# 2. Solid forms of barbital (Veronal)

**Table S1**. Assignment of Btl forms in the literature.

| **Form**<br>m.p. (°C) | | **I°**<br>190 | **II**<br>183.5 | **III**<br>183 | **IV**<br>181 | **V**<br>176 | **VI**<br>159 |
|---|---|---|---|---|---|---|---|
| Author | Ref. | | | | | | |
| Fischer & Kofler (1932) | 1 | I | – | II | III | – | – |
| Lindpaintner (1939) | 2 | I | – | II | III | IV | – |
| Brandstätter (1942) | 3 | I | – | II | III | – | – |
| Kofler (1947, 1954) | 4 | I | – | II | III | IV | – |
| Huang (1951) | 5 | I | – | II | III | IV | – |
| Huang (1953) | 6 | I | – | II | III | IV | – |
| Cleverley & Williams (1959) | 7 | I | – | II | – | IV | – |
| Brandstätter-Kuhnert & Aepkers (1962, 1963) | 8 | I | II | III | IV | V | VI |
| Nogami (1969) | 9 | I | – | II | – | III | – |
| Craven et al. (1969, 1971) | 10 | I | – | II = III‡ | – | IV | – |
| Sekiguchi et al. (1975) | 11 | I | – | II | – | IV | – |
| Grabowska et al. (1976)* | 12 | I | – | II | – | IV(?) | – |
| McMullan et al. (1978) | 13 | – | – | II | – | – | – |
| Hollenbach et al. (1979-82) | 14 | B | – | A | – | – | – |
| Burger & Ramberger (1979) | 15 | I | II | III | IV | V | VI |
| Caillet & Claverie (1980) | 16 | I | – | II | – | IV | – |
| Craven et al. (1982) | 17 | – | – | II | – | – | – |
| Chauvet et al. (1986) | 18 | I | – | II | III | IV | – |
| Fournival et al. (1987) | 19 | I | – | II | X(?) | IV | – |

*A form III is mentioned but cannot be assigned to any form of Btl; ‡ assumed that Btl-III and Btl-IV are identical; (?) = doubtful assignment.

# 3. Characteristic crystal morphologies

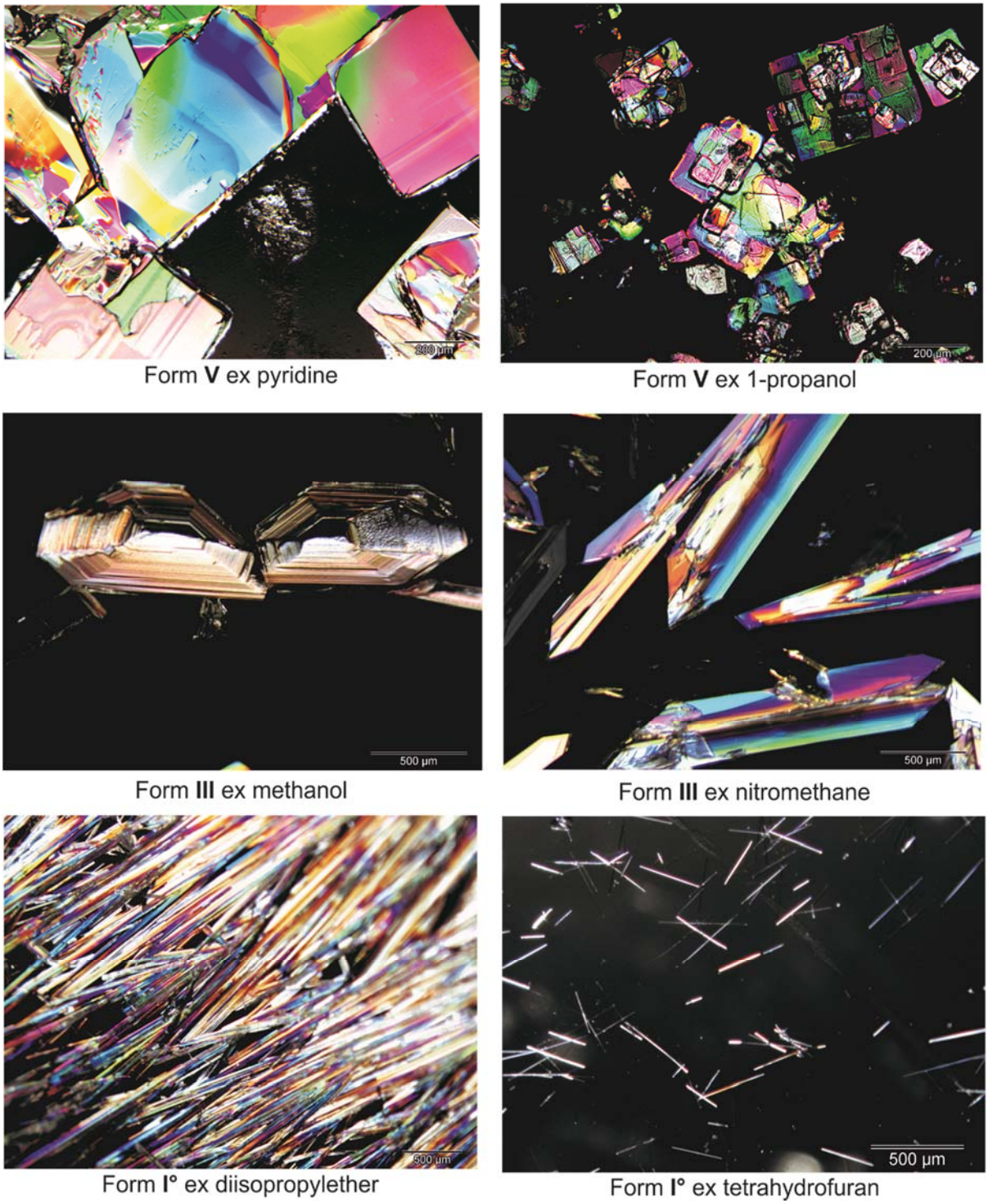



**Figure S2.** Photomicrographs (polarized light) of the Btl forms **I**, **III** and **V** (crystallized from solvents), showing their characteristic morphologies.

# 4. DSC curve of a recrystallized melt preparation

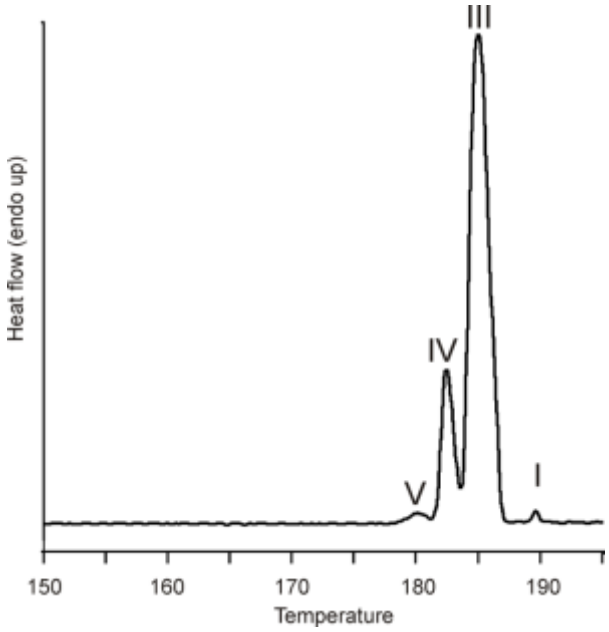
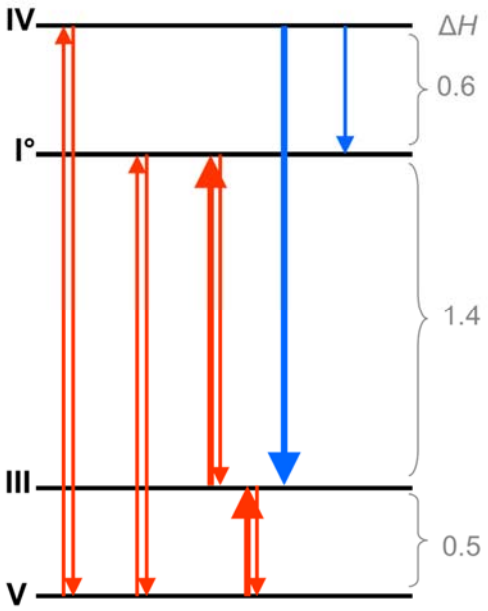



**Figure S3.** DSC curve of a recrystallized melt preparation showing melting endotherms of forms **I°**, **III**, **IV** and **V** (heating rate 5 K $min^{-1}$).

# 5. Energy data for phase transitions




| Pair | Rela-tion | $\Delta_{trs}H$ (meas.) | $\Delta_{trs}H$ (calc.) |
|---|---|---|---|
| V/III | E | +0.5 | |
| V/I° | E | | +1.9 |
| III/I° | E | +1.4 | |
| V/IV | E | | +2.5 |
| IV/III | M | -2.0 | |
| IV/I° | M | | -0.6 |

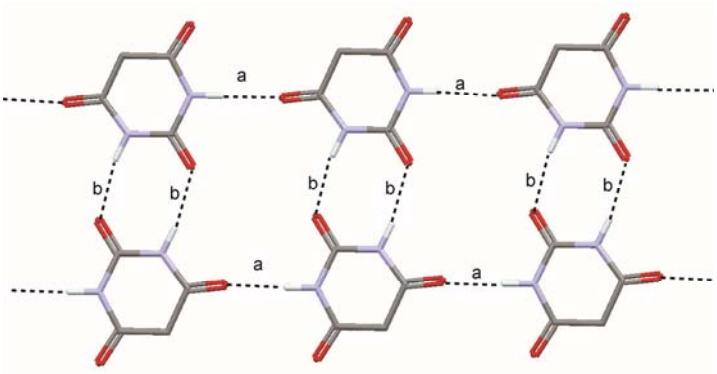
**Figure S4.** Schematic demonstration of the energy transformation data for the Btl polymorphs and the heat of transition values ($\Delta_{trs}H$, kJ mol$^{-1}$) for individual polymorphic pairs (from experimental DSC data). The pairs of red arrows represent enantiotropic (E) and the blue arrows monotropic (M) transitions. Experimentally measured (meas.) enthalpy changes are indicated by bold arrows (calc. = calculated).

# 6. Second-level graph-set representations of N–H···O=C-bonded structures

## 6.1. C-4 type: form I

**Table S2.** Graph-set representation[28] for polymorph **I°** (type **C-4**; CSD: DETBAA01;[12] a: O4/6, b: O2).

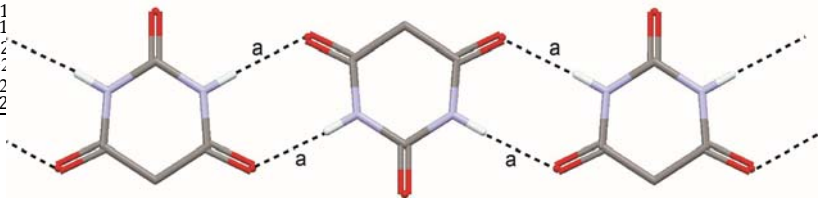
| | |
|---|---|
| $C_1^1(6)$ | a |
| $R_2^2(8)$ | >b>b |
| $R_4^4(16)$ | >a>b>a>b |
| $C_4^4(18)$ | >a>b<a<b |
| $R_4^4(18)$ | >a>b>a<b |
| $R_4^4(20)$ | >a<b>a<b |
| $R_6^6(28)$ | >a>a>b>a>a>b |
| $R_6^6(30)$ | >a>a>b>a>a<b |
| $R_6^6(32)$ | >a>a<b>a>a<b |




## 6.2. C-2 type: form III

**Table S3.** Graph-set representation[28] for polymorph **III** (type **C-2**;[29] CSD: DETBAA02;[12] a: O4/6).

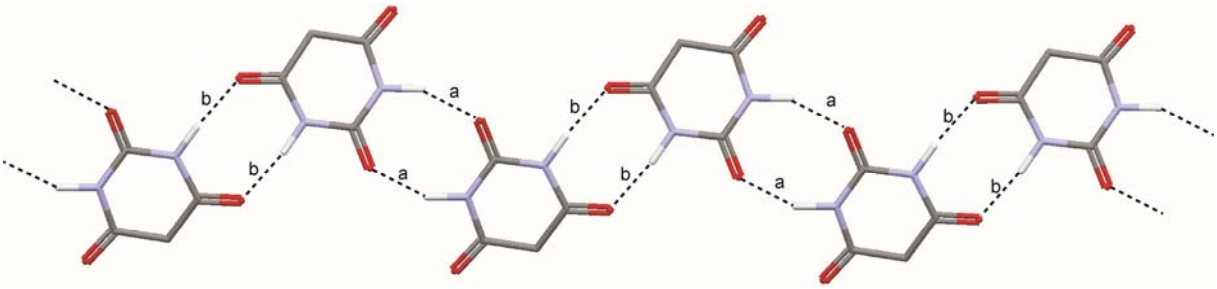
| | |
|---|---|
| $C_1^1$ | |
| $R_2^2$ | |
| $C_2^2$ | |




## 6.3. C-1 type: form IV

**Table S4.** Graph-set representation[28] for polymorph **IV** (type **C-1**;[29] a: O2, b: O4/6).

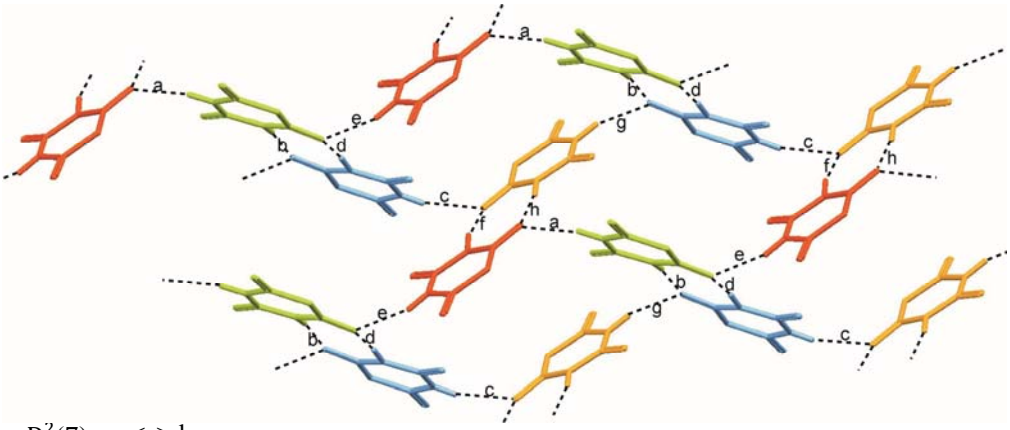
| | |
|---|---|
| $R_2^2(8)$ | >a>a |
| $R_2^2(8)$ | >b>b |
| $C_2^2(10)$ | >a<b |
| $C_2^2(10)$ | >a>b |
| $C_4^4(20)$ | >a>b<a<b |



## 6.4. L-1 type: form V (Z' = 4) and vinbarbital (Z' = 1)

**Table S5.** Graph-set representation[28] for polymorph **V** (type **L-1**;[29] CSD: DETBAA02;[13] *Z*' = 4).

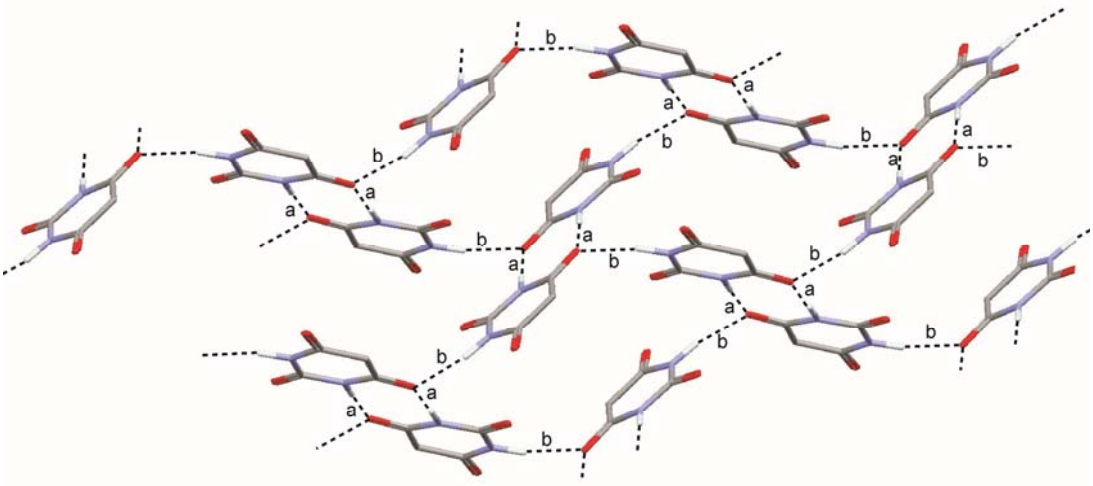
| | |
|---|---|
| $D_1^1(2)$ | a |
| $D_1^1(2)$ | b |
| $D_1^1(2)$ | c |
| $D_1^1(2)$ | d |
| $D_1^1(2)$ | e |
| $D_1^1(2)$ | f |




| | |
|---|---|
| $D_2^2(7)$ | <c>d |
| $D_2^2(7)$ | <e>f |
| $D_2^2(7)$ | <g>h |
| $D_2^2(8)$ | >b>c |
| $D_2^2(8)$ | >d>a |
| $D_2^2(8)$ | >f>g |
| $D_2^2(8)$ | >h>e |
| $R_2^2(8)$ | >b>d |
| $R_2^2(8)$ | >f>h |
| $C_2^2(12)$ | >a>e |
| $C_2^2(12)$ | >c>g |

**Table S6.** Graph-set representation[28] for vinbarbital (type **L-1**;[29] CSD: VINBAR;[32] *Z*' = 1; a, b: O4/6).

| | |
|---|---|
| $C_1^1(6)$ | b |
| $R_2^2(8)$ | >a>a |
| $C_2^1(6)$ | >a<b |
| $C_2^2(10)$ | >a>b |
| $C_4^3(16)$ | >a>b<a<b |
| $R_6^4(24)$ | >a<b<b>a<b<b |
| $R_6^5(28)$ | >a>b>b<a>b>b |
| $R_6^6(32)$ | >a>b>b>a>b>b |



# 7. Deconvolution of the methyl $^{13}C$ signal for form V

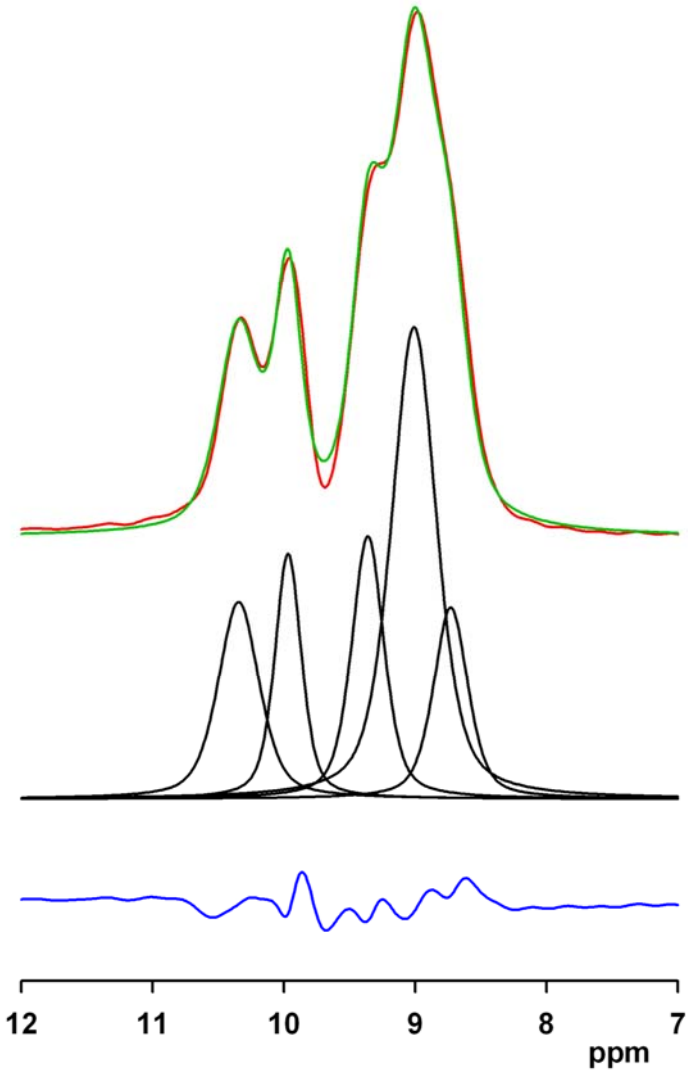



**Figure S5.** Deconvolution of the methyl $^{13}C$ signal for Btl-**V**. The top plot shows the experimental spectrum together with a simulated spectrum from the summation of the five lines shown in the middle spectrum, which are in an approximate ratio 1:1:1:4:1, with chemical shifts 10.3, 10.0, 9.4, 9.0 and 8.7 ppm respectively. The bottom trace is of the difference between the experimental and simulated spectra.

# 8. Packing diagrams and crystallographic data

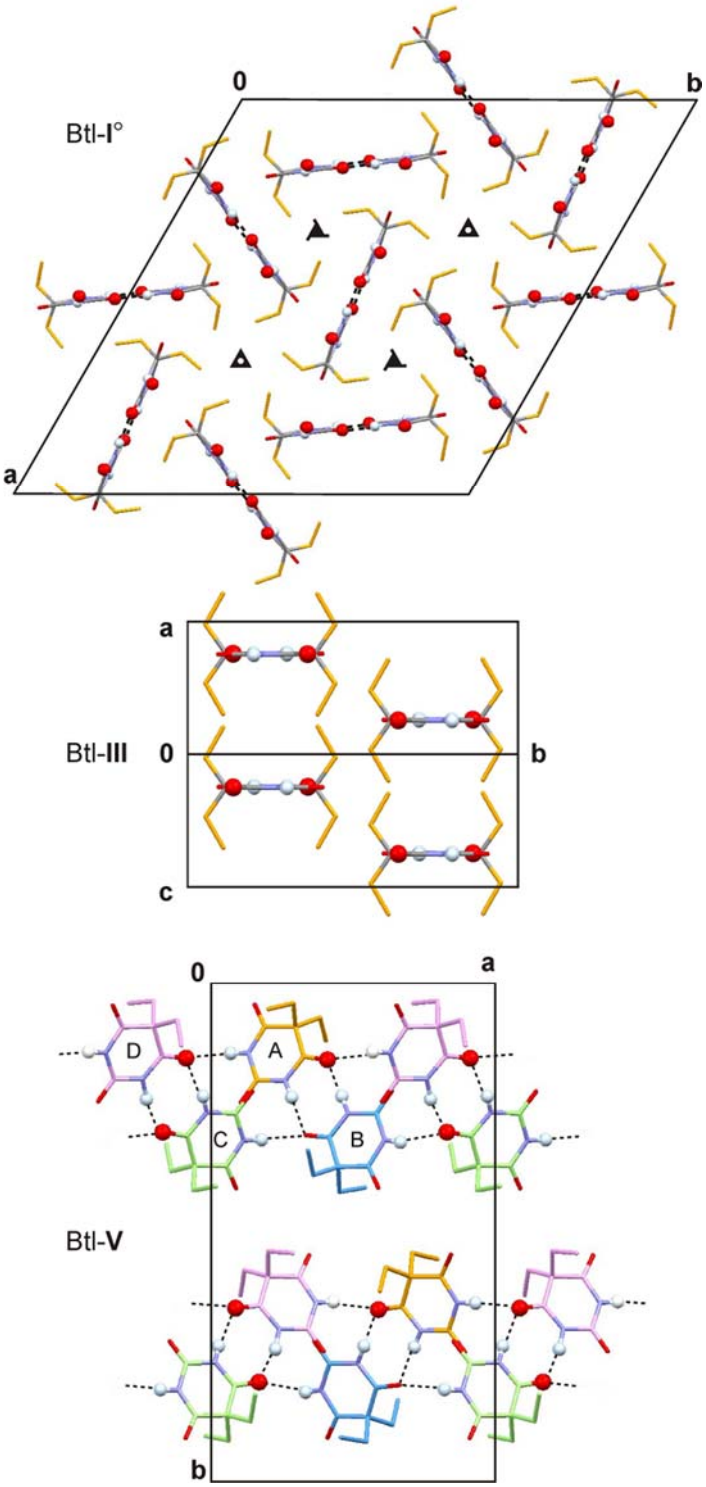



**Figure S6.** Molecular packing in polymorphs of Btl. Top and center: form **I°** (viewed along [001]) and **III** (along [101]; note that in this projection the *ab*- and *bc*-planes are not parallel to the paper plane), but the view is in the plane of the H-bonded chains. Alkyl groups are coloured orange, and O and H atoms involved in hydrogen bonding are represented as balls. All other H atoms are omitted for clarity. In form **I°**, six sets of chains are arranged around a -3 axis and three sets around a $3_1$ axis. Bottom: view of the structure of polymorph **V** (along [001]), showing two 2D H-bonded sheets. The carbon atoms of each of the four crystallographically independent molecules (A-D) are coloured differently.

**Table S7.** Essential crystallographic data for the Btl forms **I°**, **III**, and **V** (at room temperature).

| | **I°** | **III** | **V** |
|---|---|---|---|
| Crystal system | Trigonal | Monoclinic | Monoclinic |
| Space group | *R-3* | *C*2/*c* | $P2_1$ |
| *Z* / *Z'* | 18 / 1 | 4 / 0.5 | 8 / 4 |
| *a* (Å) | 26.921(6) | 7.120(5) | 12.585(8) |
| *b* (Å) | | 14.162(10) | 22.083(10) |
| *c* (Å) | 6.828(9) | 9.810(7) | 6.788 (9) |
| β (°) | | 89.14(3) | 90.55(2) |
| *V* (Å$^3$) | 4285.6 | 989.1 | 1886.2 |
| Ref. | [10a] | [10a] | [10b] |
| CSD nomenclature | i | ii | iv |
| CSD Refcode | DETBAA01 | DETBAA02 | DETBAA03 |

# 9. References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Hollenbach, K.; Pintje-Hodi, K.; Kedvessy, G. Polymorphism of barbiturates in powders and tablets. Part 4: the dissolution of barbital B and Barbital A (modifications I and II) and their release from tablets *Pharmazie* **1980**, *35*, 32-35; (c) Hollenbach, K.; Pintje-Hodi, K.; Kedvessy, G. Polymorphism of barbiturates in powders and tablets. Part 5: Dissolution of recrystallized barbital substances and their release from tablet. *Pharmazie* **1980**, *35*, 95-98; (d) Hollenbach, K.; Pintje-Hodi, K.; Kedvessy, G. Polymorphism of barbiturates in powders and tablets. Part 6: Properties and behavior of a spray-dried barbital preparation *Pharmazie* **1982**, *37*, 562-565; (e) Hollenbach, K.; Pintje-Hodi, K. Polymorphism of barbiturates in powders and tablets. Part 3: Effect of the pressing power on the modification of barbital *Pharmazie* **1979**, *34*, 807-808; (f) Hollenbach, K.; Mezosi, J.; Pintje-Hodi, K.; Kedvessy, G. Polymorphism of barbiturates in powders and tablets. Part 2: Infrared spectroscopy and x-ray diffractometry of barbital *Pharmazie* **1979**, *34*, 240-242.

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# 10. Solvent crystallization table

**Table S8**. Summary of the selective solvent screening program. The identification of the forms was performed with hot stage microscopy and/or infrared microspectroscopy and/or PXRD

| | Evaporation at 20 °C on a watchglass | |
|---|---|---|
| **Solvent** | **Morphology** | **Form** |
| Water | needles, prisms | I°, III |
| Pyridine | platelets, prisms | V, III |
| Aceton/water | platelets, prisms | V, III |
| Methanol | platelets, prisms | V, III |
| Ethanol 70% | platelets, prisms | V, III |
| Ethanol 96% | platelets, prisms | V, III |
| 1-Propanol | platelets, prisms | V, III |
| 2-Propanol | platelets, prisms | V, III |
| 1-Butanol | platelets, prisms | V, III |
| Amylakohol | platelets, prisms | V, III |
| Acetonitril | prisms | solvate |
| DMSO | prisms | solvate |
| DMF | prisms | solvate |
| CHCl3 | prisms/needles | solvate |
| Dichloromethane | needles | solvate |
| Nitromethane | prisms, a few platelets | III, V |
| Aceton | leaflets, prisms | V, III |
| THF | needles, prisms, aggregates | I°, III, V |
| Ethylacetate | prisms, platelets | II,V |
| Dioxane | clusters of small crystals | I°, V |
| Diethylether | prisms | III |
| Diisopropylether | needles | I° |
| n-Heptane | fine needles | I° |
| n-Hexane | fine needles | I° |

| | slow cooling | fast cooling |
|---|---|---|
| **Solvent** | **Form** | **Form** |
| Water | I°, III | I°, III,V |
| Aceton/water | III, V, I° | V/III |
| Ethanol 70% | III | |
| Ethanol 96% | III | |
| 1-Propanol | V, III | V, III |
| Nitromethane | III | |
| Aceton | III | |
| THF | I° | |
| Ethylacetate | III | |
| Dioxane | I° | |
| Diethylether | III | |
| Diisopropylether | I° | |
| n-Heptane | I° | |
| n-Hexane | I° | |

## 11. Enlarged plot of Figure 2

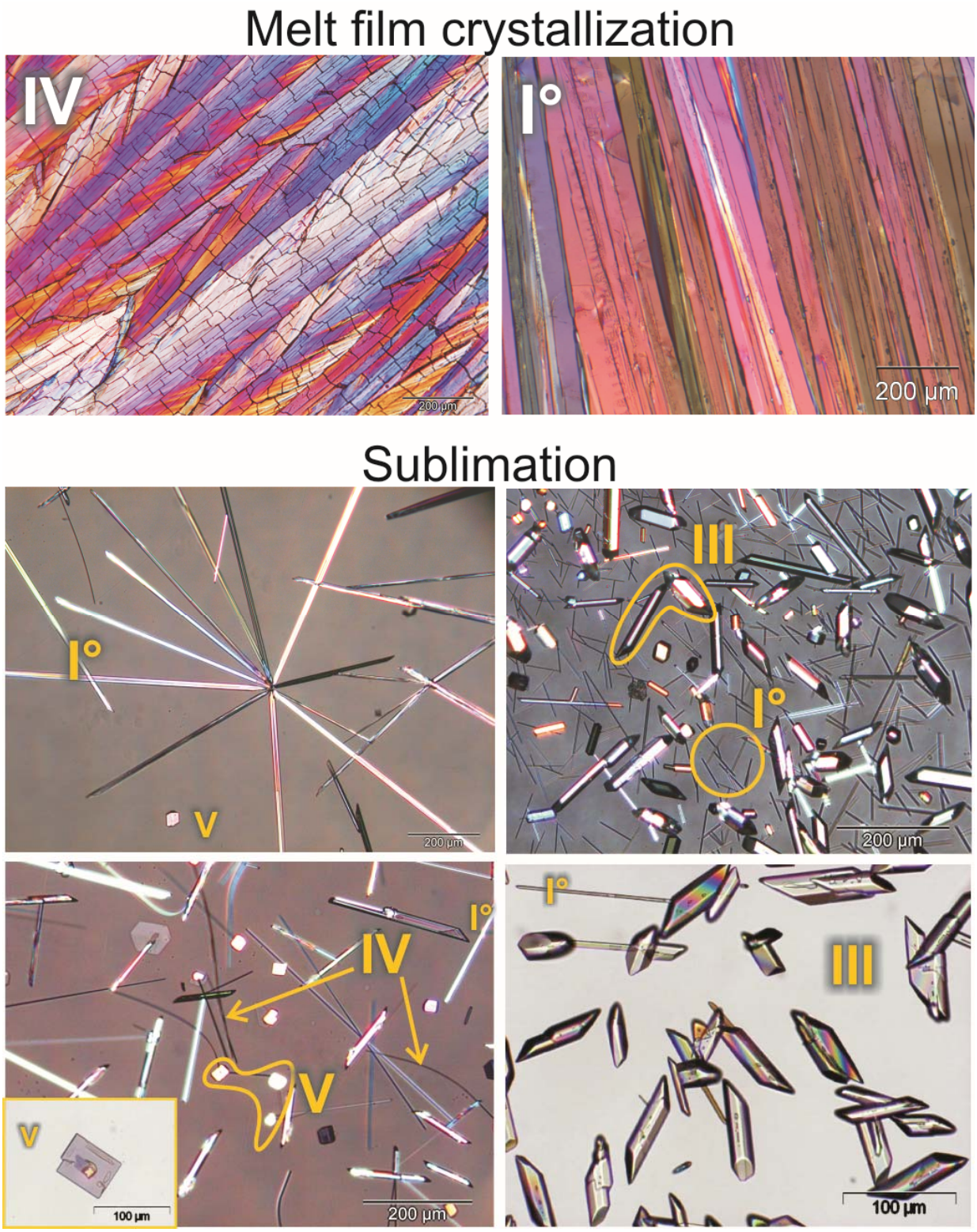


**Figure S7.** Enlarged plot of Figure 2 (main document).