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POLYMORPHISM OF BENZYLTHIOURACIL, AN ACTIVE PHARMACEUTICAL INGREDIENT AGAINST HYPERTHYROIDISM

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20 ABSTRACT

21 The crystal structures of dimorphic benzylthiouracil, a drug against hyperthyroidism, have been redetermined
22 and the atom coordinates of the two independent molecules of form I have been obtained for the first time.
23 The dimorphism convincingly demonstrates the conformational versatility of the benzylthiouracil molecule. It
24 has been established through calorimetric studies that the low-temperature form II transforms
25 endothermically ($\Delta_{II \rightarrow I}H = 5.6(1.5) \text{ J g}^{-1}$) into form I at 405.4(1.0) K. The high-temperature form I melts at
26 496.8(1.0) K ($\Delta_{I \rightarrow L}H = 152.6(4.0) \text{ J g}^{-1}$). Crystallographic and thermal expansion studies show that form I is
27 denser than form II, leading to the conclusion that the slope of the II-I equilibrium curve in the pressure-
28 temperature phase diagram is negative. It follows that this dimorphism corresponds to a case of overall
29 enantiotropic behaviour, which implies that both solid phases possess their own stable phase region
30 irrespective of the pressure. Moreover, form II is clearly the stable polymorph under ambient conditions.

31

32 **Keywords**

33 Benzylthiouracil; Dimorphism; Crystallographic properties; Thermodynamic properties; Pressure-temperature
34 phase diagram; physical stability

35 1 INTRODUCTION

36 Benzylthiouracil (BTU), of which the molecular formula is shown in **Figure 1**, is an active pharmaceutical
37 ingredient (API) for drugs against hyperthyroidism (also Graves-Basedow disease) through the inhibition of
38 thyroid hormone production. A first report of its crystal structure was published in 1986 by Delage et al.
39 (Delage et al., 1986) in which some hydrogen atom coordinates are missing. The CIF is available under the
40 reference FICBEY in the Cambridge Structural Database (CSD) (See Supplementary Information, **Table S1**). A
41 different dataset (space group and lattice parameters) was presented in a conference by Halder one year later
42 (Halder, 1987) leading to the conclusion that BTU is at least dimorphic. However, while reporting that the unit-
43 cell contains two independent molecules, the author did not publish the complete crystal structure. Available
44 crystallographic information in the literature has been compiled in **Table 1**. Very little other solid-state
45 information can be found in the literature on BTU. In the current paper, the structure found by Delage will be
46 called form II and the one found by Halder will be called form I.

47 The information on the solid state of BTU is incomplete, while formulations with the API exist on the market.
48 In fact, after examination and recrystallization of commercial batches of BTU, two crystalline forms were
49 found. Besides a lack in information concerning the crystal structures, it is not clear which of the two forms is
50 more stable at room temperature and which of them would therefore be the most appropriate choice to use
51 in a drug formulation. Therefore, both crystal structures have been solved once again to complete the
52 structural data. Furthermore, the thermal expansion of the two polymorphs has been determined so that their
53 specific volumes can be calculated as a function of the temperature.

54 To determine which of the two forms is stable at room temperature, calorimetric measurements have been
55 carried out. This system is a prime example of a solid-solid transition temperature that changes as a function
56 of the DSC heating rate and therefore the transition cannot easily be related to the equilibrium temperature
57 between the two solid forms (Barrio et al., 2012; Li et al., 2020; Toscani et al., 2016). In the case of benfluorex-
58 HCl, it was possible to use the heating rate of the DSC to find a transition temperature that is consistent with
59 the pressure-temperature phase diagram (Barrio et al., 2012). However, in other cases, such as pyrazinamide
60 and piracetam, this was less evident (Li et al., 2020; Toscani et al., 2016).

61 Finally, a pressure-temperature phase diagram has been constructed, which considerably facilitates the
62 necessary evaluations that are carried out in drug development to determine whether the compound may be
63 sensitive to transformation during processing by grinding (heating of the sample) or by tableting (pressure
64 increase) for example. The phase diagram constructed in this paper is a so-called topological pressure-
65 temperature phase diagram, which can be calculated with the specific volumes of the known polymorphs as a
66 function of the temperature (thermal expansion) and a sufficient number of equilibrium temperatures and
67 transition enthalpies for the involved phases. If the topological phase diagram leads to doubts in relation to
68 possible transformations of the API during processing or storage, further tests can be carried out on the drug
69 molecule. If on the other hand, the phase equilibria are not in the proximity of any processing conditions, a
70 topological phase diagram can be a quick way to rule out the immediate need for more technically demanding
71 experiments.

72 2 MATERIALS AND METHODS

73 2.1 BENZYLTHIOURACIL SAMPLES

74 Benzylthiouracil of medicinal grade (purity > 99.0 %) was kindly provided by Bouchara-Recordati Laboratories,
75 France, and used as such.

76 2.2 SCANNING ELECTRON MICROSCOPY

77 Electron microscopy images have been obtained using a Hitachi TM-1000 (Japan) tabletop scanning electron
78 microscope with a scanning voltage of 15 kV. To improve the quality of the sample images, the samples were
79 coated with a thin layer of gold.

80 2.3 HIGH RESOLUTION X-RAY POWDER DIFFRACTION

81 Powder X-ray diffraction (PXRD) was carried out on a transmission mode diffractometer using the
82 Debye-Scherrer geometry equipped with cylindrical position sensitive detectors (CPS120) from INEL (France)
83 containing 4096 channels (0.029° 2 θ angular step) with monochromatic Cu K α_1 ($\lambda = 1.5406 \text{ \AA}$) radiation.
84 Specimens were introduced into a 0.5 mm diameter Lindemann capillary, which during the measurements was

85 rotating perpendicularly to the X-ray beam to improve the average over the crystallite orientations. External
86 calibration using the $\text{Na}_2\text{Ca}_2\text{Al}_2\text{F}_{14}$ cubic phase mixed with silver behenate was performed by means of cubic
87 spline fittings.

88 2.4 SINGLE CRYSTAL X-RAY DIFFRACTION

89 Single-crystal X-ray diffraction (SC-XRD) data were recorded on a Bruker Smart Apex single crystal
90 diffractometer. A molybdenum μS microfocus X-ray source was used, running at 50 kV and 0.6 mA, emitting
91 $\text{Mo-K}\alpha$ radiation ($\lambda = 0.710731 \text{ \AA}$). A charge-coupled device (CCD chip 4K, 62mm) area detector was positioned
92 at 6.0 cm.

93 For both crystalline forms, the orientation matrices and unit cells were established using the APEX2 (v2014.11-
94 0) program suite (Sheldrick, 2014). The 3D reflection profile and the integration of all reflections were
95 processed with SAINT (v8.34A) (Sheldrick, 2014). SADABS (v2014/5)(Sheldrick, 2014) was used to correct for
96 Lorentz and polarization effects and for absorption due to the sample. The SHELXTL (v2014/7) program suite
97 (Sheldrick, 2014) was used to solve the structure by the intrinsic phasing method and to refine the solution by
98 full-matrix least-squares calculations on F^2 (Sheldrick, 2014). All hydrogen atoms were located using a Fourier
99 difference map and subsequently included in the refinement with one overall isotropic thermal parameter.

100 An Oxford Cryosystems nitrogen cryostat (Cryostream Plus) was used to control the temperature during single
101 crystal X-ray diffraction experiments at various temperatures ranging from 80 K up to 400 K.

102 2.5 DIFFERENTIAL SCANNING CALORIMETRY

103 Differential scanning calorimetry (DSC) was used to obtain the peak onset temperature and heat of transition.
104 A Q100 thermal analyser from TA Instruments was used and various heating rates were applied. The analyser
105 was calibrated using the melting point of indium ($T_{\text{fus}} = 429.75 \text{ K}$ and $\Delta_{\text{fus}}H = 28.45 \text{ J g}^{-1}$). The specimens were
106 weighed using a microbalance sensitive to 0.01 mg and sealed in aluminium pans.

107

108

109 2.6 THERMOGRAVIMETRY

110 Thermogravimetric (TG) measurements were performed by means of a Q50 system from TA Instruments (USA)
111 under nitrogen flux from room temperature to 550 K. Heating rates of 10 K·min⁻¹ and sample masses of ca. 5
112 mg were used.

113 2.7 OPTICAL MICROSCOPY PHOTOGRAPHS AS A FUNCTION OF THE TEMPERATURE

114 Photographs of a single crystal of form II were taken with a Leica DMRB microscope while heating at a rate of
115 10 K min⁻¹ using a Linkam TMS94 system as a temperature controller.

116 3 RESULTS

117 3.1 PREPARATION OF THE POLYMORPHS

118 Powder X-ray diffraction at room temperature was used to examine a number of BTU specimens. Some of the
119 diffraction patterns matched the calculated pattern ascribed to form II, using the structure from the CIF FICBEY
120 (CSD) of which the atom coordinates have been compiled in **Table S1**. Other specimens exhibited a different
121 pattern, which was ascribed to form I after the full crystal structure had been determined from single-crystal
122 X-ray diffraction (see below). A third group of specimens was found to be a mixture of forms I and II in varying
123 ratios. In fact, a systematic observation of commercial batches by optical microscope allowed the selection of
124 single crystals of both polymorphs that were suitable for single-crystal structure determination (see **Figure 2a**
125 and **Figure S1** in the supplementary materials). In addition, by slow evaporation of a solution of BTU in acetone
126 at 277 K, large crystals of form II were obtained in the bottom of the beaker, while on the walls of the beaker,
127 a few small crystals of form I were observed too (**Figure 2b**). Moreover, the crystalline powders of pure form II
128 were observed to transform into form I upon standing for months with an excess of either water or ethanol at
129 room temperature.

130 3.2 STRUCTURE DETERMINATIONS FROM SINGLE-CRYSTAL X-RAY DIFFRACTION

131 The crystal structures of forms I and II have been determined using single crystals similar to those shown in
132 **Figure 2a** and **b**. Concerning form I, the structure is the same as the one reported by Halder (Halder, 1987);

133 however, it has been refined using the standard space group $P2_1/c$ instead of the non-standard setting $P2_1/a$
134 by switching parameters a and c . Crystal and experimental data have been compiled in **Table 2**. The fractional
135 atom coordinates and isotropic displacement parameters for BTU form I at 296 K (space group $P2_1/c$) have
136 been compiled in **Table S2**. The fractional atom coordinates and isotropic displacement parameters for form II
137 at 297 K (space group $P2_1/c$) have been compiled in **Table S3**. X-ray crystallographic information files (CIFs) can
138 be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC), deposit numbers
139 2045868 (form I) and 2045660 (form II) via www.ccdc.cam.ac.uk/data_request/cif. The geometrical features
140 (bond lengths and bond angles) of the molecules in the two structures can be found in these files. Atom labels
141 for the two independent molecules of form I can be found in **Figure S2** in the supplementary materials.

142 3.3 THERMODYNAMIC ANALYSIS WITH RESULTS FROM THERMOGRAVIMETRY, DIFFERENTIAL 143 SCANNING CALORIMETRY, AND HOT STAGE MICROSCOPY

144 DSC curves demonstrate that the II \rightarrow I transition is endothermic (**Figure 3a**); however, the onset temperature
145 of the transition depends on the heating-rate (see **Figure S3** in the supplementary materials for hot-stage
146 microscopy photographs). After the solid-solid transition, fusion of form I is observed (**Figure 3a**). TG analysis
147 demonstrates that no weight loss occurs on heating below 510 K (**Figure 3b**). The latter finding is independent
148 of the polymorph.

149 On heating forms I or II at rates below or equal to $10 \text{ K}\cdot\text{min}^{-1}$, the mean melting temperature of form I was
150 found to be $T_{I\rightarrow L} = 496.8 \pm 1.0 \text{ K}$ (**Figure 4**). By extrapolating the heating rate to $0 \text{ K}\cdot\text{min}^{-1}$ in **Figure 4**, the
151 equilibrium temperature between form II and form I is expected to be $T_{II\rightarrow I} = 405.4 \pm 1.0 \text{ K}$. In addition, the
152 mean value of the heat of fusion of form I was found to be $152.6 \pm 4 \text{ J}\cdot\text{g}^{-1}$ and the mean value of the heat of the
153 II \rightarrow I transition was found to be $5.6 \pm 1.5 \text{ J}\cdot\text{g}^{-1}$ (see the values in **Tables S4a and S4b** in the supplementary
154 materials).

155 3.4 THERMAL EXPANSION OF BENZYLTHIOURACIL FORMS I AND II

156 Unit-cell metrics and symmetry have been determined isothermally at temperatures ranging from 80 K to 400
157 K for form I and 80 K to 296 K for form II with the same single crystals as used for the structure resolutions. The
158 specific volumes of the two forms, shown in **Figure 5**, have been calculated with the lattice parameters

159 compiled in **Tables S5a and S5b** in the supplementary materials. These results were fitted to the following
160 quadratic functions with v in $\text{cm}^3\cdot\text{g}^{-1}$ and T in K:

$$161 \quad v_{\text{I}} = 0.7167(7) + 4.36(60) \times 10^{-5} T + 1.2(1) \times 10^{-7} T^2 \quad (r^2 = 0.9994) \quad (1)$$

$$162 \quad v_{\text{II}} = 0.7201(7) + 4.47(90) \times 10^{-5} T + 1.2(2) \times 10^{-7} T^2 \quad (r^2 = 0.9995) \quad (2)$$

163 4 DISCUSSION

164 4.1 CRYSTAL STRUCTURES

165 In contrast to the structure of form II, form I contains two independent molecules in its asymmetric unit ($Z' =$
166 2), as previously mentioned by Halder (Halder, 1987). These two molecules (A and B in **Figure S2** in the
167 supplementary materials) possess two different conformations (**Figure 6**) caused by the different orientations
168 of the heterocycle with respect to the aromatic ring. In molecule A, the torsion angles N2A-C4A-C5A-C6A and
169 C4A-C5A-C6A-C7A are equal to 176.41° and 97.80° , respectively, while angles N1B-C4B-C5B-C6B and C4B-C5B-
170 C6B-C7B are -77.71° and -50.53° , respectively, in molecule B (see atom labels in **Figure S2**).

171 The molecules form infinite linear chains parallel to the a axis (see **Figure S4** in the supplementary materials).
172 Molecules A and B participate in hydrogen-bonded 'dimers' through pseudo-cycles alternatingly made of pairs
173 of N—H \cdots O and N—H \cdots S bonds, as shown in **Figure 7**. The distances and angles of these hydrogen bonds are
174 listed in **Table S6** in the supplementary information in which those for form II are listed for comparison.

175 In contrast to form I, only one independent molecule is present in the asymmetric unit of the structure of form
176 II, as previously found by Delage et al. (Delage et al., 1986). In **Figure 8**, one can see how centro-symmetric
177 hydrogen-bonded dimers are formed through N-H \cdots O hydrogen bonds (see **Table S6**). A 3D network exists
178 with bifurcated hydrogen bonds linking the dimers to each other.

179 4.2 THE PRESSURE-TEMPERATURE PHASE DIAGRAM

180 It has been established that the monovariant, two-phase equilibrium lines in a pressure-temperature state
181 diagram are straight lines over a considerable range of temperatures and pressures, in particular within the

182 ranges applicable to APIs (Ceolin et al., 2017). Therefore, using the Clapeyron equation to determine the
183 slopes in a pressure-temperature phase diagram (dP/dT), these equilibria can be extrapolated as straight,
184 monotonically rising lines. These curves are the projections on the pressure-temperature plane of the
185 monotonic Gibbs-energy surface intersections reflecting the absolute stability of the phases in a one-
186 component system.

187 The Clapeyron equation, in the form $dP/dT = \Delta H/T\Delta V$, requires the enthalpy change and the change in specific
188 volume, ΔH and ΔV , determined at the temperature T at which the two-phase equilibrium is located for a
189 given pressure P , most often ordinary pressure. In the case of BTU, the following quantities have been
190 obtained from the measurements and results discussed above:

191 $T_{II \rightarrow I} = 405.4(1.0)$ K, $\Delta_{II \rightarrow I}H = 5.6(1.5)$ J·g⁻¹, $T_{I \rightarrow L} = 496.8(1.0)$ K, and $\Delta_{I \rightarrow L}H = 152.6(4.0)$ J·g⁻¹.

192 Other transition data such as for the melting of form II, $T_{II \rightarrow L}$ and $\Delta_{II \rightarrow L}H$, and the volume changes such as $\Delta_{II \rightarrow L}V$
193 can be obtained by calculation. The enthalpy of fusion of form II is found to be $\Delta_{II \rightarrow L}H = 158.2 \pm 4.2$ J·g⁻¹ using
194 Hess's law by adding $\Delta_{II \rightarrow I}H$ to $\Delta_{I \rightarrow L}H$ and neglecting the difference in specific heat between the two
195 polymorphs. The temperature of fusion of form II can be found using a modification of the relationship
196 proposed by Yu (Yu, 1995) to provide the temperature of fusion of one of the polymorphs (Gana et al., 2013):

197
$$T_{II \rightarrow L} = \frac{\Delta_{I \rightarrow L}H + \Delta_{II \rightarrow I}H}{\frac{\Delta_{I \rightarrow L}H}{T_{I \rightarrow L}} + \frac{\Delta_{II \rightarrow I}H}{T_{II \rightarrow I}}} \quad (3)$$

198 This leads to a melting temperature for form II of 492.9 ± 1.4 K.

199 The volume change associated with the II→I transition is negative: $\Delta_{II \rightarrow I}V = v_I - v_{II} = -0.0036$ cm³·g⁻¹ at $T_{II \rightarrow I}$
200 from eqs. 1 and 2. The volume change on melting of form I cannot be calculated directly, because the specific
201 volume of the liquid is not known. Liquid volumes of APIs are often difficult to determine due to degradation in
202 the liquid state or at high temperatures even in the solid state. Nonetheless, with statistical information about
203 the volume change on melting of small organic molecules including APIs, it has been found that the mean ratio
204 $v_{\text{liquid}}/v_{\text{solid}}$ between the specific volume of the liquid and that of the highest melting polymorph at its
205 temperature of fusion equals 1.11 (Barrio et al., 2019; Ceolin and Rietveld, 2017; Céolin and Rietveld, 2015;
206 Goodman et al., 2004; Rietveld and Céolin, 2015).

207 Using eq. 1, the specific volume of form I at fusion (496.8 K) can be calculated leading to $0.7684 \text{ cm}^3 \cdot \text{g}^{-1}$. For
208 the liquid, this leads to $v_{\text{liquid}} = 0.8529 \text{ cm}^3 \cdot \text{g}^{-1}$ at $T_{\text{I} \rightarrow \text{L}}$ and a volume change on melting of $\Delta_{\text{I} \rightarrow \text{L}} v = 0.0845 \text{ cm}^3 \cdot \text{g}^{-1}$.

209 Using the inequalities and temperatures that have been obtained experimentally or by calculation, $dP/dT_{\text{II} \rightarrow \text{I}}$
210 and $dP/dT_{\text{I} \rightarrow \text{L}}$ can now be calculated leading respectively to $-3.82 \text{ MPa} \cdot \text{K}^{-1}$ and $3.63 \text{ MPa} \cdot \text{K}^{-1}$.

211 Taking the vapor pressure as 0 MPa for the II→I transition and for the fusion of form I, the calculated slopes
212 can be used to extrapolate the equilibrium lines from the respective transition temperatures obtained by DSC.

213 The equations for the two equilibrium curves, I-II and the fusion of form I, become:

$$214 \quad P_{\text{II} \rightarrow \text{I}} / \text{MPa} = -3.82 T / \text{K} + 1548 \quad (4)$$

$$215 \quad P_{\text{I} \rightarrow \text{L}} / \text{MPa} = 3.63 T / \text{K} - 1806 \quad (5).$$

216 Calculating the intersection of these two equations, leads to the coordinates of the I-II-liquid triple point with
217 the triple point temperature equal to 450 K and the pressure equal to -170 MPa .

218 The equilibrium curve of the fusion of form II will pass through the triple point II-liquid-vapor obtained by
219 calculation above. The temperature is equal to 492.9 K and once again taking the pressure at this point equal
220 to 0 MPa, which can be done because of the steepness of the slope associated with this equilibrium, the
221 equation of the equilibrium curve of the fusion of form II can be calculated using the coordinates of the I-II-L
222 triple point. This leads to the following expression:

$$223 \quad P_{\text{II} \rightarrow \text{L}} / \text{MPa} = 3.97 T / \text{K} - 1956 \quad (6).$$

224 With the equations 4, 5, and 6, a preliminary pressure-temperature phase diagram has been drawn (**Figure 9a**)
225 containing the stable phase regions for the condensed phases. It demonstrates that forms I and II exhibit their
226 own stability domains: form II at lower temperature and form I at higher temperature. It can also be observed
227 that the stable phase region of form I expands towards lower temperatures as the pressure increases, in
228 accordance with the Le Chatelier principle (transition II→I is shifted right on heating since it is endothermic
229 and favoured by a pressure increase, since form I is denser than form II). The phase relationship between the
230 two forms is therefore enantiotropic.

231 Taking into account the vapor phase, the topological P-T phase diagram in **Figure 9b** has been drawn, while
232 making sure that the two-phase equilibrium curves obey the stability alternation rule around each triple point.
233 One can see that two of the four triple points are stable (I-II-vapor and I-liquid-vapor), and two others are
234 metastable (II-liquid-vapor and I-II-liquid) corresponding to a case of overall enantiotropic behaviour,
235 previously described by Bakhuis-Roozeboom as case 2 among the four possible cases of pressure-temperature
236 phase diagrams describing dimorphism (Bakhuis Roozeboom, 1901; Ceolin and Rietveld, 2016; Ceolin et al.,
237 2008).

238 5 CONCLUDING REMARKS.

239 The crystal structures of the two known forms of benzylthiouracil have been redetermined and in the case of
240 form I, a full crystallographic description has been provided with atom coordinates. As far as the high-
241 temperature form I is concerned, the crystal structure was found to be the same as solved by Halder, which
242 remained unpublished up to now (Halder, 1987).

243 These two structures illustrate the conformational versatility of the benzylthiouracil molecule, which can
244 adopt at least three conformations, two found in form I and another in form II. They are shown in **Figure 10**
245 with the benzene ring of each molecule superimposed to demonstrate the relative position of the heterocycle.
246 This dimorphism is once again another case of conformational polymorphism (Bernstein and Hagler, 1978;
247 Négrier et al., 2013).

248 Concerning the thermodynamic aspect of this case of dimorphism, it has been shown that the reconstructive
249 transition from form II to form I occurs on heating at a heating-rate dependent onset temperature. The fusion
250 of form I is observed at a relatively high temperature of 496.8 K, as a result of strong hydrogen-bonding. It is
251 accompanied with a high melting enthalpy of $152.6 \text{ J}\cdot\text{g}^{-1}$ ($33.31 \text{ kJ}\cdot\text{mol}^{-1}$) with respect to a generally observed
252 melting enthalpy of about $100 \text{ J}\cdot\text{g}^{-1}$ for small molecular compounds, although the similarly aromatic
253 pyrazinamide also possesses a high melting enthalpy of $241 \text{ J}\cdot\text{g}^{-1}$ ($29.67 \text{ kJ}\cdot\text{mol}^{-1}$), while its melting temperature
254 is lower with 462 K (Li et al., 2020).

255 The dependence of the solid-solid transition temperature between the two polymorphs on the DSC heating
256 rate is a warning not to limit an investigation to a single heating rate as the transition temperature may not

257 reflect the actual equilibrium temperature at all. In the case of BTU, it appears that extrapolating its transition
258 behaviour to zero heating rate leads to a reliable estimate of the equilibrium temperature as the dependency
259 levels off at low heating rates. Nonetheless, such measurements should always be done with care.

260 The topological pressure-temperature phase diagram, constructed with the help of the Clapeyron equation
261 using enthalpy and volume changes measured at ordinary pressure, corresponds to a case of overall
262 enantiotropy. Even if the dP/dT slope of the II-I equilibrium curve is negative, each phase possesses its own
263 stable phase region at pressures relevant for stable organic compounds and APIs. This diagram demonstrates
264 that form II is clearly the stable polymorph under ambient conditions. However, temperatures during
265 processing will need to remain below 400 K and even lower if grinding or tableting is used.

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269 **Declarations of Interest**

270 None

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273 discussions.

274 **Supplementary material**

275 Supplementary data is available online and contains atom coordinates of the original structure published by
276 Delage (Table S1), optical microscopy photographs of crystals in commercial batches (Figure S1), atom
277 coordinates of form I in setting $P2_1/c$ (Table S2), atom labels of benzylthiouracil for form I (Figure S2), atom
278 coordinates in form II (Table S3), optical microscopy photos of the solid-solid transition (Figure S3),
279 calorimetric data on the II-I and I-L transitions (Table S4), lattice parameters as a function of the temperature
280 for forms I and II (Table S5), a figure of the linear hydrogen-bonded chains in form I (Figure S4) and a Table on
281 the hydrogen-bond characteristics (Table S6).

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328

329 **Figure Captions**

330 **Figure 1.** Molecular formula of benzylthiouracil, IUPAC name: 6-Benzyl-2-thioxo-2,3-dihydro-4(1H)-
331 pyrimidinone, C₁₁H₁₀N₂OS, M = 218.28 g mol⁻¹.

332 **Figure 2. (a)** Electron microscopy photographs of single crystals of form I (left-hand side) and form II (right-
333 hand side) selected from commercial batches of benzylthiouracil. **(b)** Optical microscopy photograph of
334 crystals of form II grown by slow evaporation in an acetone solution at 277 K. The white arrows indicate the
335 presence of a few crystals of form I that appeared at the rim.

336 **Figure 3. (a)** Typical differential scanning calorimetry curves (endo up) for benzylthiouracil demonstrating that
337 on heating form II transforms endothermically to form I, which melts subsequently, and **(b)** a corresponding
338 thermogravimetric curve demonstrating that weight loss only occurs once the sample is melting.

339 **Figure 4.** The transition of benzylthiouracil form II into form I (solid circles) and the onset temperatures of the
340 fusion of form I (open diamonds) as a function of the heating rate.

341 **Figure 5.** The specific volumes of benzylthiouracil form I (solid squares) and form II (open circles) as a function
342 of the temperature.

343 **Figure 6.** Molecular conformations in benzylthiouracil form I. Molecule A is blue and molecule B is red with
344 atoms labelled A and B in **Table S2** and **Figure S2**, respectively. The two phenyl rings are superimposed
345 emphasizing the difference in the orientation of the heterocycles.

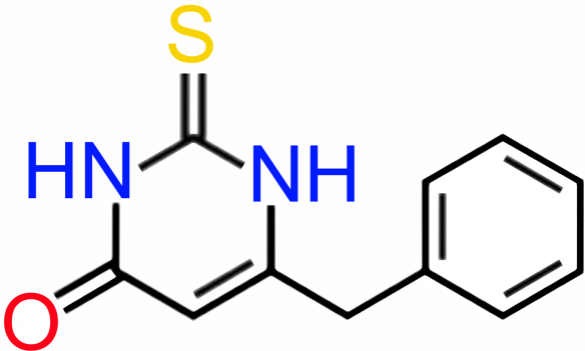
346 **Figure 7.** Hydrogen bonding in the structure of benzylthiouracil form I. Pseudo-cycles of non-centrosymmetric,
347 hydrogen-bonded dimers with non-equivalent molecules A and B. Dimers A...B are formed by N—H...O (left-
348 hand side) and N—H...S (right-hand side) hydrogen bonds (black: C, grey: H, blue: N, red: O, yellow: S).

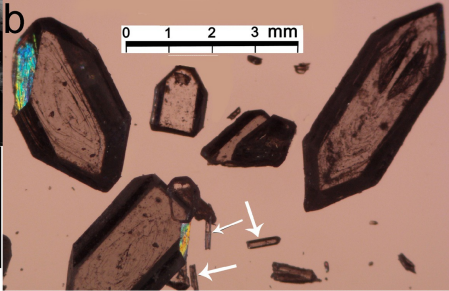
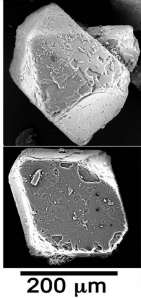
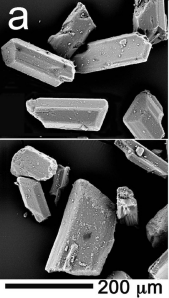
349 **Figure 8.** Hydrogen bonding in benzylthiouracil form II. A centrosymmetric dimer forms through two N1—
350 H5...O1 hydrogen bonds. These dimers are linked by another hydrogen bond (N2—H4...O1) in such a way that
351 atom O1 is linked to atoms N1 and N2 of two different molecules by a bifurcated hydrogen bond (angle N1—
352 O1—N2 = 103.26°). The inversion centre is marked by the solid black point. The atom labels are the same as
353 those in **Table S3** in the supplementary materials.

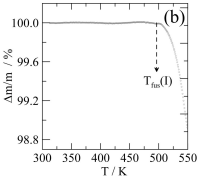
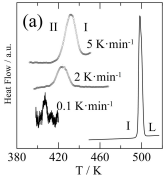
354 **Figure 9. (a)** The benzylthiouracil pressure-temperature phase diagram showing the stable regions of the
355 condensed phases and the equilibrium curves involving forms I and II, and the liquid phase. **(b)** The full
356 topological pressure-temperature phase diagram for the observed dimorphism of benzylthiouracil. Triple
357 points: 1: I-liquid-vapor, 2: II-liquid-vapor, 3: I-II-vapor, and 4: I-II-liquid while solid black circles are stable and
358 half black/half white circles are metastable; two-phase equilibrium lines: a-a: liquid-vapor, b-b: I-liquid, c-c: II-
359 liquid, d-d: I-II, e-e: I-vapor, and f-f: II-vapor while black lines are stable equilibria, dashed lines are metastable,
360 and open lines are super-metastable.

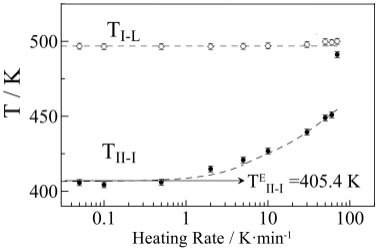
361 **Figure 10.** Conformational versatility of the benzylthiouracil molecule: the red and blue molecules are the
362 conformations encountered in form I (**Figure 6**), whereas the yellow molecule represents the conformation in
363 form II.

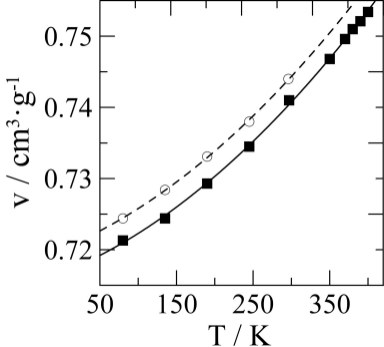
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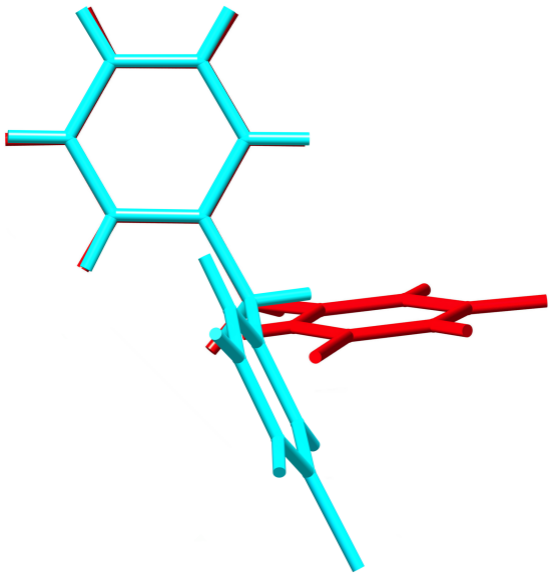


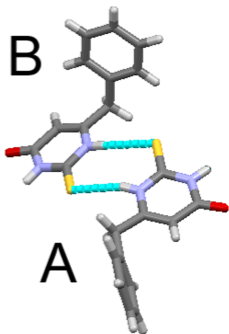
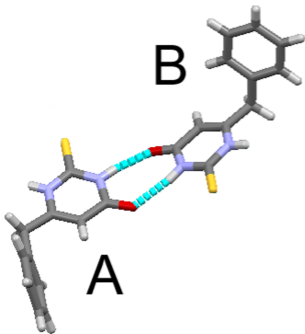


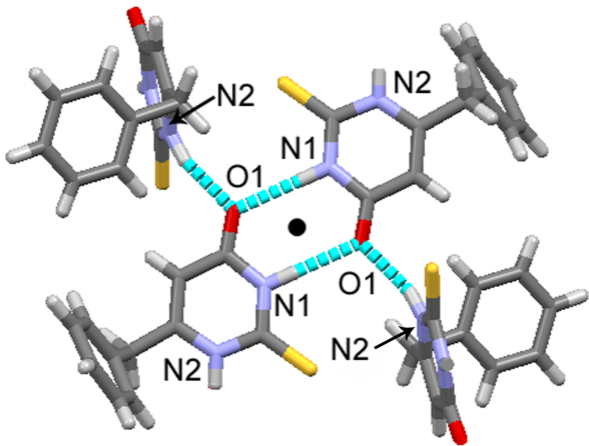












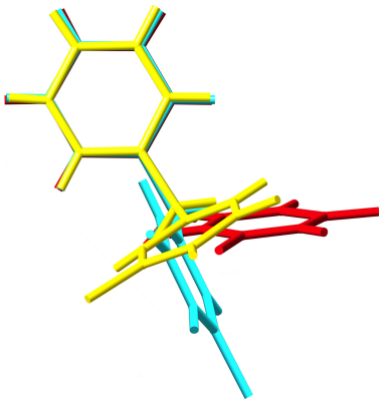


Table 1. Benzylthiouracil crystallographic data at room temperature available in the literature

Reference	(Halder, 1987)	(Delage et al., 1986)
Polymorph identification	Form I	Form II
Crystal system	Monoclinic	Monoclinic
Space group	P2 ₁ /a	P2 ₁ /c
a/Å	10.457(4)	9.735(1)
b/Å	20.131(6)	9.158(1)
c/Å	10.915(10)	12.519(1)
β/°	110.60(4)	106.81(1)
V(cell)/ Å ³	2150.8	1068.42
Z	8	4
Z'	2	1
Density/g cm ⁻³	1.3482	1.3570
Specific volume/cm ³ g ⁻¹	0.74171	0.73690
CSD reference	none	FICBEY

Table 2. Crystal data and structure refinement for Forms I and II of benzylthiouracil^a

	Form I	Form II
Temperature (σ) /K	296(2)	297(2)
Crystal system	monoclinic	monoclinic
Space group	<i>P2₁/c</i>	<i>P2₁/c</i>
<i>a</i> (σ) /Å	10.9378(7)	9.7532(4)
<i>b</i> (σ) /Å	20.1405(13)	9.1767(4)
<i>c</i> (σ) /Å	10.4677(7)	12.5389(5)
β (σ) /°	110.683(1)	106.810(1)
Cell Volume (σ) /Å ³	2157(2)	1074.29(8)
<i>Z</i> / <i>Z'</i>	8 / 2	4 / 1
<i>M</i> /g·mol ⁻¹	218.27	218.27
<i>D</i> _{calc} /g·cm ⁻³	1.344	1.350
<i>V</i> _{calc} /cm ³ ·g ⁻¹	0.74405	0.74074
μ (Mo <i>K</i> α) /mm ⁻¹	0.273	0.274
<i>F</i> (000)	912	456
Crystal shape	rod-like	prism-like
Radiation /Å	Mo <i>K</i> α (λ = 0.71073)	Mo <i>K</i> α (λ = 0.71073)
θ range for data collection /°	1.990 to 28.999	2.794 to 29.075
Reflections collected	15865	10631
Independent reflections	5204 [<i>R</i> _{int} = 0.011, <i>R</i> _{sigma} = 0.010]	2642 [<i>R</i> _{int} = 0.012, <i>R</i> _{sigma} = 0.010]
Reflections with <i>I</i> > 2 σ (<i>I</i>)	4435	2487
No. parameters	351	176
Goodness-of-fit on <i>F</i> ²	1.031	1.040
Final <i>R</i> indexes [<i>I</i> \geq 2 σ (<i>I</i>)]	<i>R</i> ₁ = 0.0468, <i>wR</i> ₂ = 0.1278	<i>R</i> ₁ = 0.0475, <i>wR</i> ₂ = 0.1400
Final <i>R</i> indexes [all data]	<i>R</i> ₁ = 0.0478, <i>wR</i> ₂ = 0.1288	<i>R</i> ₁ = 0.0496, <i>wR</i> ₂ = 0.1423
Largest diff. peak/hole / e·Å ⁻³	0.552/-0.421	0.284/-0.210
CCDC	2045868	2045660

^a estimated standard deviations in parentheses

