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# Growing single crystals of small molecules by thermal recrystallization, a viable option even for minute amounts of material?†

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The growth of single crystals of small molecules by thermal recrystallization of only a few milligrams of material has been studied for carbamazepine, *para*-aminobenzoic acid and vitamin $B_{12}$. High quality single crystals could be grown for carbamazepine and *para*-aminobenzoic acid within just six hours. Various solvents and concentrations were tested for their influence upon the growth of crystals.

## 1. Introduction

In contrast to inorganic polymeric materials, for which single crystals are frequently grown by thermal recrystallization,[1,2] thermal recrystallization of small molecules is described in most introductions into single crystal growth,[3] however the method is rarely used in research laboratories.[4–8] There is an exceptional report about the extremely slow cooling of an ethanol solution (0.5 °C per day) to achieve growth of a single crystal of an organic compound.[9] Another report described a single crystal grown by cooling a 150 °C hot solution at a rate of −1.25 °C per hour.[10] In many cases, it is essential that the employed crystallization methods only use few milligrams of material, as the supply of the compound of interest is limited.[11]

In this publication, we describe our results from attempts to grow single crystals of 3 different molecular compounds (carbamazepine, *para*-aminobenzoic acid and vitamin $B_{12}$) by thermal recrystallization using a small volume of only 0.1 ml with the help of the CrystalBreeder. The single crystals had to have sufficient quality and size in order to allow X-ray analysis on a source diffractometer equipped with a CCD detector and Microfocus Mo and Cu X-ray tubes respectively. This publication is meant to be an extension of our previous tutorial about the growth of single crystals of small molecules, which focused on isothermal methods.[11]

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† Electronic supplementary information (ESI) available: X-ray powder diffraction of commercial **CBZ** and ***p*ABA**. Diffraction image obtained during the initial unit cell determination of a twinned vitamin $B_{12}$ crystal. UPLC-ESI-MS chromatograms of vitamin $B_{12}$ before and after the thermal treatment. CCDC 1494536–1494538. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ce02222g

## 2. Experimental section

Carbamazepine (**CBZ**, 97%, *P*-monoclinic form III,[12] see ESI;† we employ the nomenclature of ref. 13) was purchased from ABCR GmbH & Co. KG. *Para*-Aminobenzoic acid (***p*ABA**, ≥99%, α-form, see ESI†[14]), 1-propanol (≥99%), 2-propanol (≥99.5%), 2-butanol (≥99%), tetrahydrofuran (THF, ≥99.9%), cyclohexane (≥99.5%), acetonitrile (≥99.9%) and ethyl acetate (≥99.9%) were purchased from Sigma Aldrich. All chemicals were used without further purification.

The crystallization experiments were performed with help of the CrystalBreeder (CB), a multi-reactor crystallization platform for medium-throughput solid state research. The CB shows real time turbidity information for 32 parallel vials with a working volume of only 0.1 ml. The vials are arranged in 8 blocks, which can be temperature controlled independently within a range of −15 °C to 145 °C.

UPLC-ESI-MS spectra were recorded on an Acquity Waters system equipped with a PDA detector and an autosampler using an ACQUITY UPLC BEH C18 Gravity 1.7 μm (2.1 mm × 50 mm) reverse phase column. The UPLC system was connected to a Bruker Daltonics HCT ESI-MS spectrometer. A total volume of 1 μL of a sample solution was analysed. A gradient (0 to 0.5 min 5% B, 0.5 to 2 min 30% B, 2 to 4 min 100% B, 4 to 5 min 100% B) of acetontitrile (solvent B) *versus* Millipore water containing 0.1% formic acid (solvent A) was applied using a flow rate of 0.3 ml $min^{-1}$. All solvents used were of LCMS grade.

### 2.1 Thermal crystallization of carbamazepine

The carbamazepine single crystals were grown by thermal crystallization in various solvents and with various concentrations always with 0.1 ml of solvent (Table 1).

For every solvent, a minimum of four different concentrations were chosen. Each sample was heated at 1 °C $min^{-1}$ starting from room temperature until five degrees below the

Table 1 Properties of solvents tested for the thermal recrystallization of **CBZ**

| Solvent | Solubility of **CBZ** in that solvent | Melting point | Boiling point | Mass (in mg) of **CBZ** for 0.1 ml of a saturated solution |
|---|---|---|---|---|
| 1-Propanol | 18.1 g $l^{-1}$ (25 °C)[15] | −126 °C | 97 °C | 1.8 |
| 2-Propanol | 9.11 g $l^{-1}$ (25 °C)[15] | −88 °C | 82 °C | 0.91 |
| 2-Butanol | ~8 g $l^{-1}$ (25 °C)[a] | −115 °C | 99 °C | 0.8 |
| THF | 45.2 g $l^{-1}$ (22.4 °C)[16] | −108 °C | 66 °C | 4.5 |
| Cyclohexane | 0.055 g $l^{-1}$ (25 °C)[15] | 6.7 °C | 81 °C | 0.005 |

[a] Estimated from the solubility in 2-propanol.

boiling point of the solvent, held at this temperature for 15 minutes, cooled at −0.5 °C $min^{-1}$ until −15 °C (for cyclohexane only until 0 °C because its melting point is at 7 °C and the solution should not be frozen) and held at the lowest temperature for 15 minutes (Table 2). All samples were stirred with a paddle while heating to ensure that all solids had dissolved. The stirrers were turned off during the cooling.

### 2.2 Thermal crystallization of *p*-aminobenzoic acid (*p*ABA)

Crystals of *para*-aminobenzoic acid were grown by the same method used for **CBZ** (Tables 3 and 4).

### 2.3 Thermal crystallization of vitamin $B_{12}$

Crystals of vitamin $B_{12}$ were grown by the same method used for **CBZ**. The reported solubility of vitamin $B_{12}$ in water is 10.2 g $l^{-1}$,[18] however we employed higher concentrations of 4 to 8 mg of vitamin $B_{12}$ in 0.1 ml of water. We obtained crystals by cooling down from 95 °C to −5 °C with cooling rates of either −0.1 or −0.05 °C $min^{-1}$. Unfortunately, in both cases, the obtained crystal quality was not good enough for an X-ray analysis, since the crystals were clearly not single (see Fig. S1 in the ESI†). Using smaller crystals did not help, as it is our repeated experience with crystals derived from $B_{12}$ that they need a much bigger size to diffract decently compared with "normal" small molecules.[19–26] Furthermore, we have previously made the experience that vitamin $B_{12}$ and its derivates are rather delicate molecules to crystallize, that only appreciate very few crystallization conditions. Using a concentration of 20 g $l^{-1}$ (twice the reported concentration of saturation) did not yield any $B_{12}$ crystals. We checked by UPLC-ESI-MS whether any degradation like hydrolysis of the amide group or removal of the cyanide of the $B_{12}$ was observed during the extended thermal treatment in an aqueous solution. As can be seen in Fig. S2 in the ESI,† no deterioration of the $B_{12}$ could be observed, when compared with $B_{12}$ that did not undergo any thermal treatment, based upon peak purity, retention time and isotopic distribution of the mass spectra.

### 2.4 X-ray measurement

Crystallographic data were collected at 183(2) K on an Agilent SuperNova, dual source, single X-ray diffractometer equipped with an Atlas CCD detector with either Mo Kα radiation (λ = 0.7107 Å) for the monoclinic form of **CBZ** and ***p*ABA** or with Cu Kα radiation (λ = 1.54184 Å) for the rhombohedral form of **CBZ**. Suitable crystals were covered with oil (Infineum V8512, formerly known as Paratone N), placed on a nylon loop that is mounted on a CrystalCap Magnetic™ (Hampton Research) and immediately transferred to the diffractometer. Data were corrected for Lorentz and polarisation effects as well as for absorption. The program suite CrysAlisPro was used for data collection, multi-scan absorption correction (additionally a numerical absorption correction was done for ***p*ABA**) and data reduction.[27] Structures were solved with direct methods using SIR97 (ref. 28) and were refined by full-matrix least-squares methods on $F^2$ with SHELXL-2014.[29] CCDC-1494536–1494538 contain the supplementary crystallographic data for this paper.

## 3. Results and discussion

For every solvent at least four different concentrations were chosen. The lowest concentration was at about 75% of the solubility at room temperature and the other three concentrations were from 100 to 150/200% of the RT solubility. Each sample was heated until five degrees below the boiling point of the solvent. Despite the small starting volume, no solvent loss from tube could be observed. However, in case of viscous solvents (like water), up to 18% of the solvent ended up in

Table 2 Chosen amounts of **CBZ** and thermal recrystallization cycle

| Solvent | Vial 1 (mg) | Vial 2 (mg) | Vial 3 (mg) | Vial 4 (mg) | Heating rate (°C $min^{-1}$) | Max temp. (°C) | Cooling rate (°C $min^{-1}$) | Lowest temp. (°C) |
|---|---|---|---|---|---|---|---|---|
| 1-Propanol | 1.5 | 2 | 2.5 | 3 | 1 | 92 | 0.5 | −15 |
| 2-Propanol | 0.5 | 1 | 1.5 | 2 | 1 | 77 | 0.5 | −15 |
| 2-Butanol | 0.5 | 1 | 1.5 | 2 | 1 | 94 | 0.5 | −15 |
| THF low conc. | 4.5 | 5 | 5.5 | 6 | 1 | 60 | 0.5 | −15 |
| THF high conc. | 6 | 6.5 | 7 | 7.5 | 1 | 60 | 0.5 | −15 |
| Cyclohexane | 0.005 | 0.01 | 0.02 | 0.05 | 1 | 76 | 0.5 | 0 |

Table 3 Properties of solvents tested for the thermal recrystallization of *p*ABA

| Solvent | Solubility of *p*ABA at 20 °C | Melting point | Boiling point | Mass (in mg) of *p*ABA for 0.1 ml solvent |
|---|---|---|---|---|
| 2-Propanol | 48 g $l^{-1}$ (ref. 17) | −88 °C | 82 °C | 4.8 |
| Ethyl acetate | 68 g $l^{-1}$ (ref. 17) | −83 °C | 77 °C | 6.8 |
| Acetonitrile | 47 g $l^{-1}$ (ref. 17) | −45 °C | 82 °C | 4.7 |

Table 4 Chosen amounts of *p*ABA and thermal recrystallization cycle

| Solvent | Vial 1 (mg) | Vial 2 (mg) | Vial 3 (mg) | Vial 4 (mg) | Max. temp. (°C) | Heating rate (°C $min^{-1}$) | Lowest temp. (°C) | Cooling rate (°C $min^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| 2-Propanol | 4.5 | 5 | 5.5 | 6 | 77 | 1 | −15 | 0.5 |
| Ethyl acetate | 6.5 | 7 | 7.5 | 8 | 72 | 1 | −15 | 0.5 |
| Acetonitrile | 4.5 | 5 | 5.5 | 6 | 77 | 1 | −15 | 0.5 |

separated drops above the original solution between the outer wall and the paddle.

### 3.1 Carbamazepine crystals

Carbamazepine is known to form five polymorphs and many solvates.[13,30] While there are many publications about the influence of cooling rates, concentrations, solvents, seeds and stirring rates upon the (co)formation of one of these polymorphs,[5,13,15,16,30–36] the focus of this work is exclusively on the formation of single crystals suitable for X-ray analysis. We have tested five different solvents at 4–8 concentrations for the growth of carbemazepine single crystals upon cooling back to the originally (super)saturated solutions at room temperature. No crystals or even any precipitate could be obtained from 1-propanol. In the case of 2-propanol, colourless, thin needles and prismatic single crystals appeared on the bottom of the vials with 1.5 mg and 2 mg of material (Fig. 1), respectively. Only one small crystal grew on the pedal stirrer in the vial with 1 mg of **CBZ**. By single-crystal analysis, we could show that the needles are the **CBZ** *P*-monoclinic form III and that the thick, prismatic, 3-dimensional crystals are **CBZ** with one sixth occupied water molecule as a solvate crystallizing in the space group $R\bar{3}$ (Fig. 3 left and Table 5). It must be noted that in several publications, an identical rhombohedral cell has been reported, however once the single crystal data were refined without any solvate molecules and named trigonal form II.[37] In two other publications with a very similar cell, one partially occupied THF[38] or a partially occupied water[35] were found in the structure. As in 2-propanol, needle-shaped crystals of **CBZ** grew from 2-butanol on the bottom of the vial and on the stirrer. However, no prismatic single crystals appeared. From THF, **CBZ** crystallized not only as needles but also as prismatic single crystals (Fig. 2). At a concentration of 50 mg $ml^{-1}$, needle-like crystals appeared on the bottom of the vial and on the stirrer (Fig. 2 left). Increasing the concentration to 55 mg $ml^{-1}$ yielded crystalline needles in the vial and one small prismatic crystal on the edge of the vial (Fig. 2 middle). Finally, just one large single crystal can be seen in the vial with a concentration of 60 mg $ml^{-1}$ (Fig. 2 right). Only a few small, crystalline needles grew on the stirrer from cyclohexane, as was expected due to the low solubility of **CBZ** in cyclohexane.

Matzger and co-workers obtained the *P*-monoclinic form III by slow evaporation from ethanol and the metastable trigonal form II by cooling a hot ethanol solution.[13] Both forms were characterized by X-ray powder diffraction. Sefcik observed a temporary formation of form II in ethanol followed by appearance of form III.[34] They noted the influence of stirring and of an unknown impurity upon the crystallization pathway.


Fig. 1 Crystals of **CBZ** grown from 2-propanol in the shape of needles and prisms. The picture shows the vial together with the paddle.

### 3.2 *p*-Aminobenzoic acid crystals

***p*ABA** did not form any crystals in 2-propanol for all concentrations used in the experiments. In ethyl acetate, plate-like crystals of ***p*ABA** formed (Fig. 4). In acetonitrile, the same result was obtained as in ethyl acetate: some needle crystals were formed on the bottom of the vial. Single crystals of excellent quality were obtained from ethyl acetate at concentration of 80 mg $ml^{-1}$ (Fig. 3, right, Table 5). The exceptional quality of obtained dataset is indicated by the final difference electron density maps, where the largest peaks of residual density lie between bonded atoms and represent the bonding electrons, which are not accounted for by classical spherical atom refinement models. Sullivan obtained single crystals of

 

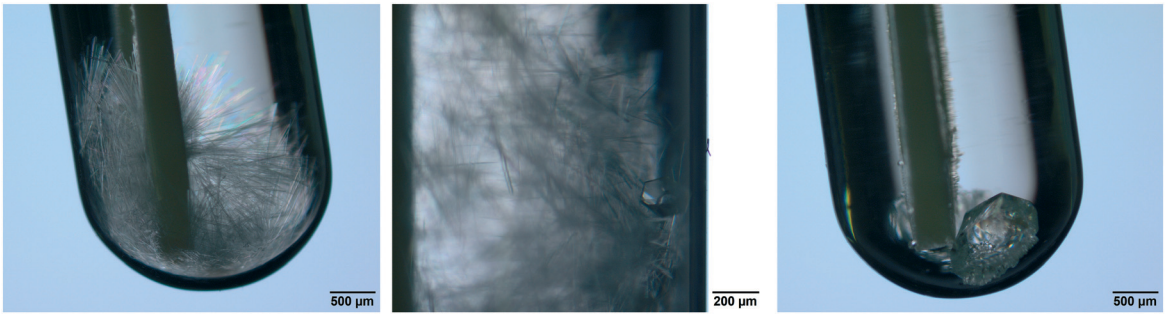


**Fig. 2** Crystals of **CBZ** grown from THF at a concentration of 50 mg ml$^{-1}$ (left), of 55 mg ml$^{-1}$ (middle) and of 60 mg ml$^{-1}$ (right).

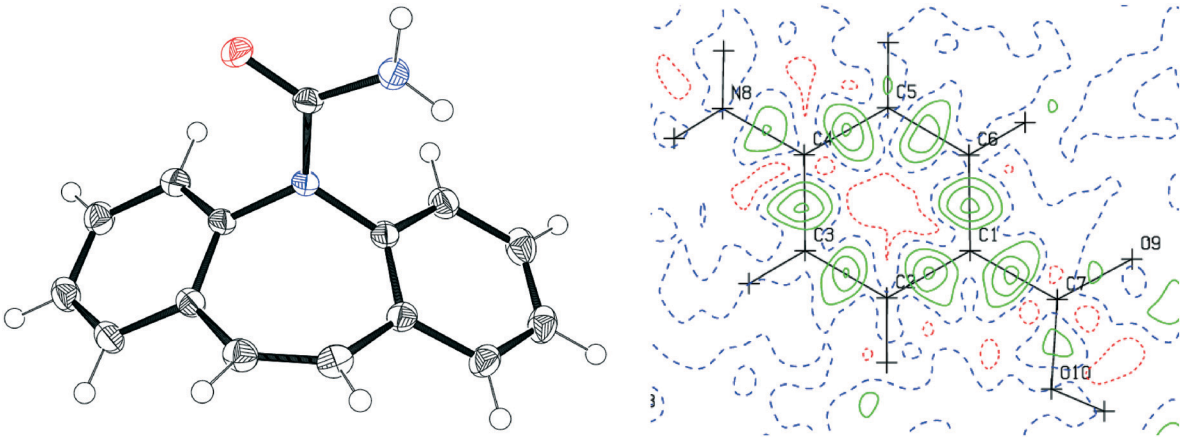


**Fig. 3** Left: ORTEP representation of the *P*-monoclinic form of **CBZ** at 50% probability; right: residual electron density map for the ***p*ABA** structure.

**Table 5** Crystallographic data of the measured single crystals of **CBZ** and ***p*ABA**

| Compound | **CBZ** | **CBZ·1/6($H_2O$)** | ***p*ABA** |
|---|---|---|---|
| Grown from[a] | 2-Propanol at a concentration of 15 g l$^{-1}$ | 2-Propanol at a concentration of 15 g l$^{-1}$ | Ethyl acetate at a concentration of 80 g l$^{-1}$ |
| Space group | $P2_1/n$ | $R\bar{3}$ [b] | $P2_1/n$ |
| Form | *P*-Monoclinic form III[12] | | α-form[39] |
| *a* [Å] | 7.49441(10) | 35.2832(9) | 18.5413(3) |
| *b* [Å] | 11.06430(14) | 35.2832(9) | 3.77083(7) |
| *c* [Å] | 13.80360(15) | 5.20165(13) | 18.5858(3) |
| $\alpha$ [°] | 90 | 90 | 90 |
| $\beta$ [°] | 92.9142(11) | 90 | 93.6727(17) |
| $\gamma$ [°] | 90 | 120 | 90 |
| Volume [Å$^3$] | 1143.12(2) | 5608.0(3) | 1296.78(4) |
| Crystal size [mm$^3$] | 0.37 × 0.33 × 0.17 | 0.17 × 0.05 × 0.05 | 0.34 × 0.09 × 0.07 |
| X-ray wavelength [Å] | 0.71073 | 1.54184 | 0.71073 |
| Independent reflections | 5891 [$R$(int) = 0.0244] | 2482 [$R$(int) = 0.0086] | 4512 [$R$(int) = 0.0201] |
| Reflections observed [$I > 2\sigma(I)$] | 4768 | 2277 | 3791 |
| Completeness to resolution | 99.9% to 0.60 Å | 99.9% to 0.84 Å | 99.9% to 0.70 Å |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1$ = 0.0426, w$R_2$ = 0.1200 | $R_1$ = 0.0474, w$R_2$ = 0.1566 | $R_1$ = 0.0505, w$R_2$ = 0.1313 |
| Largest diff. peak and hole [e Å$^{-3}$] | 0.459 and −0.219 | 0.635 and −0.233 | 0.368 and −0.190 |

[a] Used volume: 0.1 ml. [b] See text in chapter 3.1.

the α-form by isothermal evaporation of saturated solutions of 2-propanol, ethanol, methanol, ethyl acetate, acetonitrile, nitromethane and 1 : 1 methanol : toluene at room temperature and the β-form by isothermal evaporation of saturated

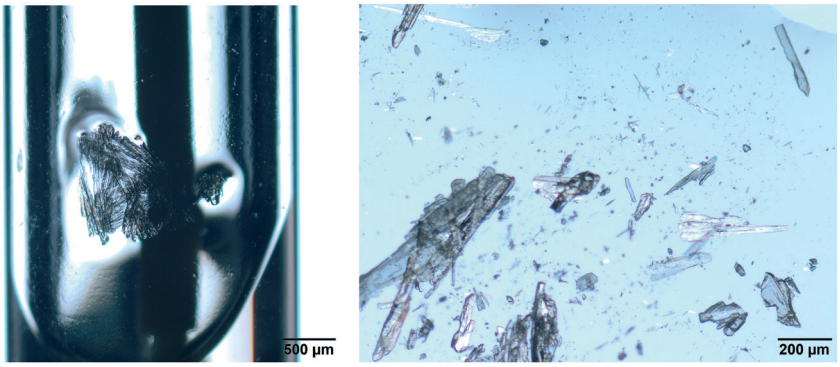


Fig. 4 Left: plate-like crystals of ***p*ABA** grown from ethyl acetate in the vial at a concentration of 80 mg $ml^{-1}$; right: isolated crystals of ***p*ABA** grown from ethyl acetate at a concentration of 80 mg $ml^{-1}$.

solutions of water.[39] They had to wait up to 2 weeks for the completion of the experiments. Extensive concentration of the saturated solution at room temperature was obviously essential for crystal growth at least in the case of 2-propanol, as we could not form any crystals from 2-propanol with our thermal recrystallization method.

## 4. Conclusion

This study was done in order to evaluate the growth of single crystals of small molecules from minute volumes of only 0.1 ml by thermal recrystallization. For this method, it is obviously necessary that the desired molecule must change its solubility with temperature in a steady way and by a significant amount,[40] additionally the molecule must be stable over the chosen temperature range. Since some molecules only slightly change their solubility as a function of temperature, it is extremely helpful to know exactly the solubility in the chosen solvents at the desired temperature (normally around 25 °C), either from the literature or from own experimentation. In order to further minimize the needed amount of material, one could start with one single initial experiment per solvent at an concentration of 150% of the saturated solution. Within only six hours using the CrystalBreeder, we were able to grow excellent quality single crystals of carbamazepine and *p*-aminobenzoic acid from as little as 1.5 mg of material. However, it is clear that this method is not suitable for all molecules, as shown in the case of the vitamin $B_{12}$. Additionally, by comparing our results of ***p*ABA** with the work of Sullivan,[39] it is clear that cooling a slightly supersaturated solution will not yield in all cases crystals, unless evaporation further increases the supersaturation.

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