CrystEngComm

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/crystengcomm

CrystEngComm RSCPublishing

ARTICLE

Evaluation of the formation pathways of cocrystal polymorphs in liquid-assisted syntheses

Cite this: DOI: 10.1039/x0xx00000x

Franziska Fischer,[a,b] Gudrun Scholz,[b] Sigrid Benemann,[a] Klaus Rademann[b] and Franziska Emmerling[a,*]

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

The synthesis of the polymorphic cocrystal caffeine:anthranilic acid was investigated to obtain a better understanding of the processes leading to the formation of different polymorphic forms. In case of these cocrystal polymorphs synthesized by liquid-assisted grinding a distinct influence of the dipole moment of the solvent was found. A pre-coordination between the solvent molecules and the caffeine:anthranilic acid could be identified in the formation of form II. In case of form II the solvent can be regarded as a catalyst. The formation pathway of both polymorphs was evaluated using synchrotron X-ray diffraction.

Introduction

A key challenge in pharmacy is to evoke the best therapeutic effect of a drug and to improve its physicochemical properties especially the water solubility and the bioavailability. Polymorphs, cocrystals, and polymorphs of cocrystals of a given active pharmaceutical ingredient (API) exhibit different structures leading to different, often enhanced physicochemical properties.[1-3] The term "cocrystal" is still under debate. Here we define cocrystals as a two- or more component crystalline phase consisting of uncharged organic compounds, which interact via intermolecular forces. A pharmaceutical cocrystal consists of at least one API and a coformer, typically a small organic molecule.[4-8] Since forming a cocrystal can change the physicochemical properties of an API, the crystallization processes, synthesis pathways and properties of these crystalline forms are of high interest in chemistry and pharmacy. Among the numerous studies in the field of cocrystals only a few examples of polymorphs of cocrystals are known.[9-14] Examples for this phenomenon are caffeine cocrystals. Caffeine is used in the pharmacy treating of migraine and primary apnea and even more it is a drug for all seasons.[15] It represents an ideal model API for cocrystal formation.[16-19] Due to the weakly basic nature of caffeine, its tendency for cocrystallization is higher than forming a salt. Two polymorphic forms and one hydrate form of caffeine were characterized.[20-24]

Trask prepared one of the first caffeine containing cocrystals with glutaric acid as coformer using the so called liquid-assisted grinding (LAG) method.[14] In these milling reactions small amounts of solvent are applied to the solid reactants to enhance the reaction rate. Many more investigations followed using other dicarboxylic acids including maleic acid, malonic acid and oxalic acid as coformers.[25] Several caffeine cocrystals and cocrystal solvates with diverse coformers were described.[26-32] The interest in the formation of caffeine cocrystals increased intensively and synthesis methods were developed in a targeted manner. Recently, Eddleston introduced the cocrystalization by freeze-drying and a new form of a caffeine:theophylline cocrystal could be identified.[12] Bučar pushed forward the application of the heteronuclear seeding and described the 1:1 cocrystal caffeine:benzoic acid. The cocrystal could not be obtained by common synthesis techniques as grinding or from solution.[27]

Despite the numerous known cocrystals of caffeine, there are only a few cocrystals showing the phenomenon of polymorphism. Trask reported that by changing the polarity of the solvent in solvent-drop grinding synthesis the polymorphic form of the cocrystal of caffeine with glutaric acid can be controlled.[14] Moreover, Ghosh and Trask described that the caffeine cocrystals with 4-chloro-3-nitrobenzoic acid and trifluoroacetic acid are able to crystalize in two different forms.[11, 33] Two polymorphic forms were also found by Schultheiss during the cocrystallization of caffeine with pterostilbene as a cocrystal former.[34]

Very recently, Jones published a caffeine:anthranilic acid (cf:ana) cocrystal revealing a high diversity of crystal forms: two polymorphs, two hydrates, and seven solvates. The polymorphic forms were prepared by LAG. A mechanistic explanation for the formation of the polymorphs I and in particular II still remains challenging.[9] Because of its structural diversity, the equimolar cocrystal cf:ana is an ideal model system for investigations of the formation processes. In this study, we show that the polymorphic forms of the cocrystal can be synthesized by LAG in a controlled way. X-Ray diffraction investigations unambiguously allow distinguishing the formation of the different polymorphs, while Raman and solid-state-NMR (ssNMR) give detailed insight into the hydrogen bond network.

To understand the influence of the solvent in the formation of a distinct polymorph in a LAG process, different solvents were added during the milling process. Based on these experiments, the important role of the solvent could be clarified.

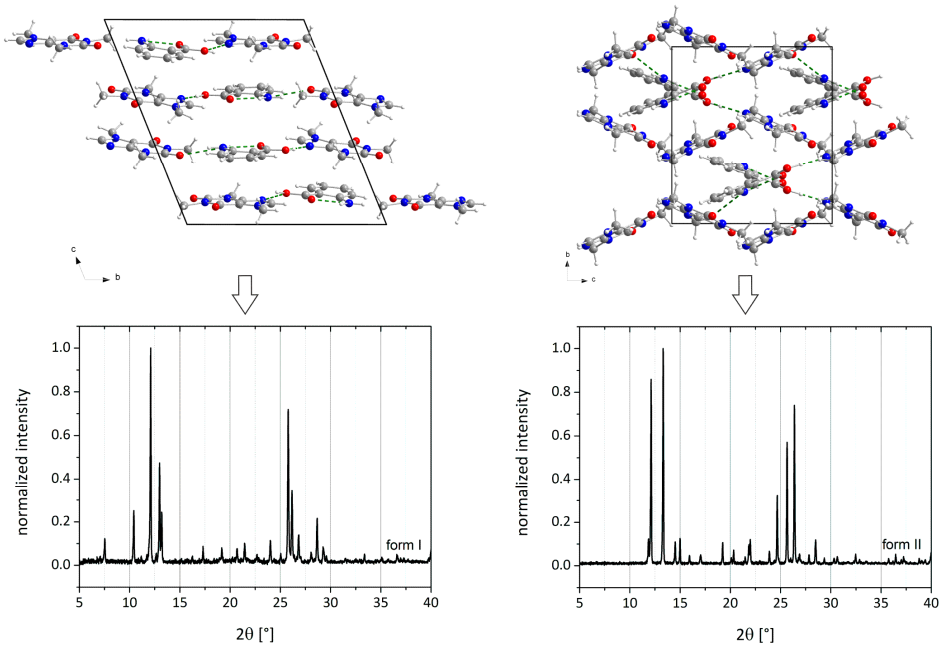

Fig. 1 Crystal structures and PXRD patterns of cf:ana form I (left) and form II (right).[9]

Results and discussion

Prior to the interpretation of liquid-assisted grinding experiments the possible salt formation has to be excluded. Therefore, Raman and ssNMR spectra of the reactants and the cocrystals were collected.

Raman spectra of both polymorphic cocrystal forms and the reactants were recorded. Since the hydrogen-bonding arrangements of form I and form II are equivalent, the chemical environment of the molecules in the cocrystal polymorphs is identical, and the Raman spectra are very similar as shown in Figure 2.

The Raman bands of caffeine at 1654 cm^{-1} and 1698 cm^{-1} (stretching vibration of carbonyl groups) and of anthranilic acid (ana) at 1245 cm^{-1} (deformation vibration of amino group) and 1373 cm^{-1} (stretching vibration of carboxylate group) were analyzed to decide if there is a complete shift of the acidic proton of ana towards caffeine.[35, 36] The carbonyl band of the caffeine molecule at 1654 cm^{-1} shifts by 12 cm^{-1} (form I) and 2 cm^{-1} (form II) to higher wavenumbers, whereas the second carbonyl band appears at 1665 cm^{-1} in form I and 1658 cm^{-1} in form II. These small Raman shifts reveal that the caffeine molecules are not highly affected in the conformation of the cocrystal. The amino group of ana is also not influenced, because the Raman deformation vibration band at 1245 cm^{-1} underlies only a small shift by 5 cm^{-1} (form I) and 4 cm^{-1} (form II). A strong shift of the symmetrical stretching band of the carboxylate group can be observed. In ana the band appears at 1373 cm^{-1}, while in both polymorphic forms of the cocrystal the band is located at 1333 cm^{-1}. This strong shift can be assigned to the change of the chemical environment concerning the acid group of ana. In pure ana a homosynthon between the carboxylic acid groups is formed,[37] and the protons of both carboxylic acids are delocalized. On the contrary, in the cocrystal the proton of the acidic group of ana is involved in the hydrogen bond to a carbonyl oxygen atom of caffeine and is not bridged in such a strong manner. It is connected to the oxygen atom of ana and the cocrystal consists only of neutral molecules.

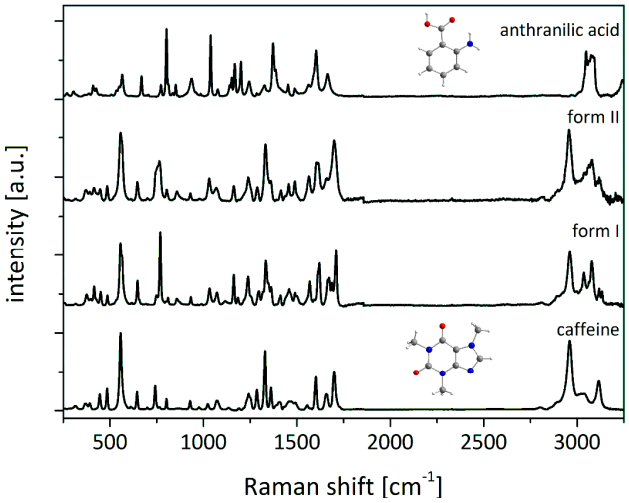

Fig. 2 Raman spectra of ana, the cf:ana cocrystal polymorphs, and caffeine.

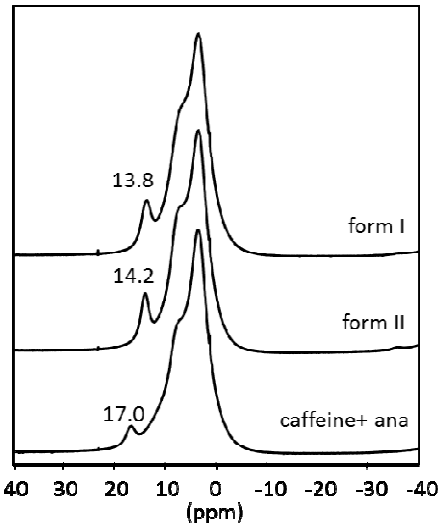

Fig. 3 ^{1}H magic angle spinning (MAS) NMR spectrum of the cf:ana cocrystal form I (above), the form II (middle) and the superimposed spectra of the reactants (below) without the spinning sidebands.

For further characterization the polymorphs of the cocrystal were investigated via ssNMR. Figure 3 shows the spectra of both polymorphs along with the sum of spectra of the two reactants, measured under identical conditions. The methyl groups and the tertiary carbon of caffeine have resonance absorptions at 3.5 ppm and 7.8 ppm, respectively. These signals superimpose with the ssNMR signal of ana at 6.9 ppm, which covers the aromatic protons and the amino groups of ana. The proton of the carboxylic group leads to a signal at 17.0 ppm. This distinct shift reveals that the acidic proton of ana is bridged in a strong manner because of the crystal packing in pure ana as expected from the Raman results.

The spectra of the cocrystal polymorphs resemble on a first view the sum of the single spectra of the reactants, but are not identical. Especially the strongly bridged acidic proton of ana is highly influenced, since its resonance position shifts ca. 3 ppm in both cocrystal forms. The other protons seem not to be highly affected in the cocrystal. Based on these results, it can be concluded that the acidic proton of ana is not as strongly bridged in the cocrystal as in pure ana.

To investigate the morphology of the cocrystal forms, SEM micrographs were taken. As shown in Figure 4, both forms exhibit rod-shaped crystals, which are arranged locally in a parallel manner. This similarity can be traced back to the resembling crystal structures of the polymorphs and similar crystallization conditions. The main difference resides in the length of the crystals. In form I only short crystals can be obtained. In the case of form II, the crystals are elongated slightly. Despite this intensive characterization using SEM, Raman and ssNMR spectroscopy an unambiguous differentiation between the polymorphs is only possible on the basis of XRD data.

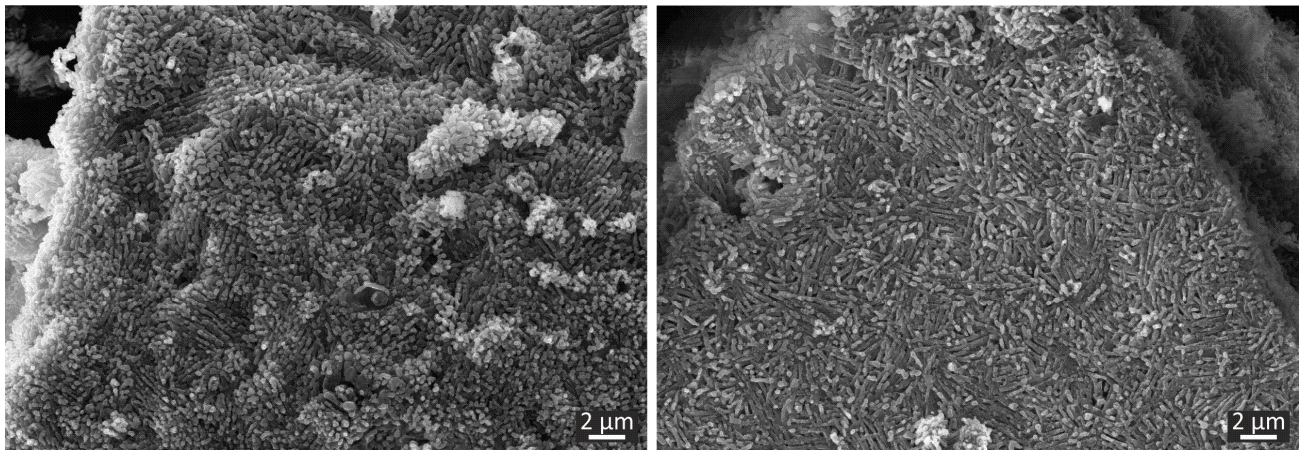

Fig. 4 SEM micrographs of the cf:ana cocrystal material form I (left) and form II (right).

Table 1 Solubility of caffeine and ana in water and ethanol at room temperature and solvents added in the LAG syntheses and the resulting polymorph of the cocrystal.[38-40]

Compound	Solubility in water [mg·ml^{-1}]	Solubility in EtOH [mg·ml^{-1}]	Compound	Solubility in water [mg·ml^{-1}]	Solubility in EtOH [mg·ml^{-1}]
Anthranilic acid	5	200	**Caffeine**	16	15
Solvent	**Dipole moment [·10^{-30} C·m]**	**Polymorphic Form**	**Solvent**	**Dipole moment [·10^{-30} C·m]**	**Polymorphic Form**
1,4-Dioxane	1.3	Form I	**Methanol**	5.5	Form I
2-Butanone	9.2	Form I	**n-Heptan**	0.0	Form I
Acetophenone	9.7	Form I	**n-Hexan**	0.0	Form I
Chloroform	3.7	Form I	**n-Pentane**	0.0	Form I
Cyclohexane	0.0	Form I	**Nitromethane**	10.3	Form I[9]
Dichloromethane	6.0	Form I	**Tetrahydrofuran**	5.7	Form I
Diethyl ether	4.2	Form I			
Ethanol	5.7	Form I	**Acetone**	10.0	Form II
Ethyl acetate	6.2	Form I	**Acetonitrile**	11.7	Form II
Ethylene glycol	6.7	Form I	**Dimethylformamide**	12.7	Form II

In order to investigate the formation of the polymorphic forms of the cf:ana cocrystal different solvents were added to the reactants caffeine and ana during the milling synthesis. In a typical experiment 1 g of the cocrystal reactants were milled together with 250 µL of the solvent at 30 Hz for 25 min. The results of the syntheses are summarized in Table 1. Mostly, polymorph I is formed. In each experiment a pure cocrystal form is obtained and no crystalline phase mixtures were found. It can be supposed that the crystallization of form I proceeds without any interaction or pre-coordination between the solvent and the reactants. This polymorph is also formed by neat grinding or by adding non-polar solvents, which cannot create any intermolecular bonds with the reactants. Both polymorphic forms show a comparable thermodynamic stability, since the melting points differ only by 2 K (Figure S2). This assumption is supported by temperature dependent PXRD measurements. These measurements show that the polymorphs do not convert into each other below the melting points (Figure S3). Slurry experiments reveal that in an 1:1 slurry of form I and form II in heptane only form I can be obtained after seven days. Therefore, form I can be considered slightly more stable than form II.[9] Due to the results of the temperature dependent PXRD experiments a preferred formation of a distinct polymorph based on its thermodynamic stability can be excluded.

The formation of the polymorphs of the cf:ana cocrystal form I or II depends decisively on the solvent which is added in the LAG synthesis. Only three of the 18 solvents lead to form II. The screening reveals that two facts play an important role for the formation of form II: the dipole moment, and the kind of functional group. Only if the solvent molecule has a high dipole moment, more precisely higher than $10 \cdot 10^{-30}$ C·m, form II can be formed. This includes the solvents acetone, acetonitrile, dimethylformamide and nitromethane. Nitromethane seems to be an exception. Despite the high dipole moment, nitromethane generates form I.[9] In comparison to other solvents, only nitromethane has a nitro-group as a functional group. This implies that next to the high dipole moment also a carbonyl or nitrile group is necessary for the cocrystal formation of form II. These observations suggest that the formation of form II is triggered by a pre-coordination with the solvent molecule.

Both polymorphic forms exhibit the same synthon. Each caffeine molecule is connected to two ana molecules via hydrogen bonds. One hydrogen bond is formed between the imidazolic nitrogen atom from a caffeine molecule and the carboxyl oxygen atom from an ana molecule. An additional hydrogen bond is formed between the amino group of an ana molecule and the carbonyl group of a caffeine molecule, leading to a chain structure. The main difference between the polymorphic forms is the environment around the latter hydrogen bond. In the form I, all molecules of the chains are in plane leading to a planar layered structure, whereas in the form II the caffeine molecule is twisted at the amino-carbonyl hydrogen bond resulting in zigzag-type chains. Based on this difference, it can be assumed that the described torsion results from the pre-coordination with the solvent molecules, which takes place at the amino group of ana. Since the solvent molecule occupies too much space, the caffeine molecule cannot bind in the same planar layer and is twisted approximately 30° as shown in Figure 5.

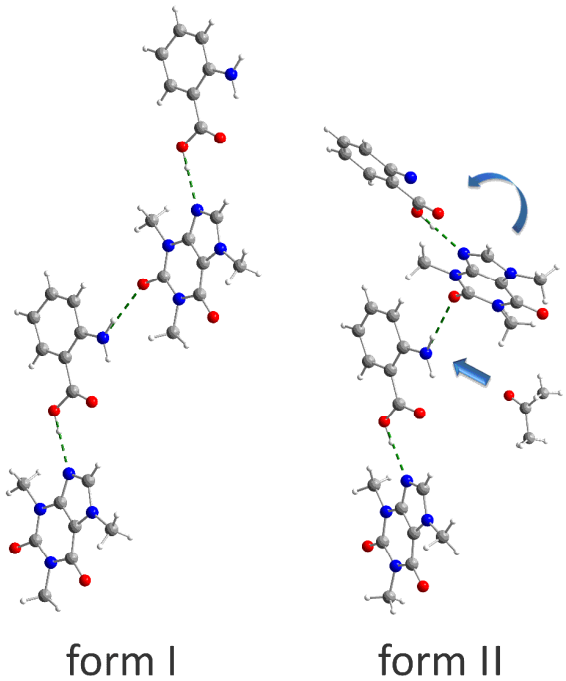

Fig. 5 Bonding arrangement of the cf:ana form I (left) and form II (right).

Systematic investigations with different volumes of acetonitrile added to the reactant mixture during the milling process were performed. Here, it can be observed that already after the addition of 5 µL acetonitrile to a total load of 1 g cocrystal material, the form II crystallizes spontaneously (Figure 6). This observation indicates that the coordination of the reactants with only a few solvent molecules already leads to a sufficient amount of the cocrystal form II as seeds for further crystallization. Because the solvent is not embedded in the crystal system, it can be thought of as a catalyst. Comparing the powder patterns of the cocrystals of form II synthesized with different amounts of acetonitrile. Figure 6 compares the powder patterns of the cocrystals synthesized using different amount of acetonitrile. The intensity of the reflections decreases with smaller amount of solvent used during the grinding. The amount of solvent accelerates the product formation.

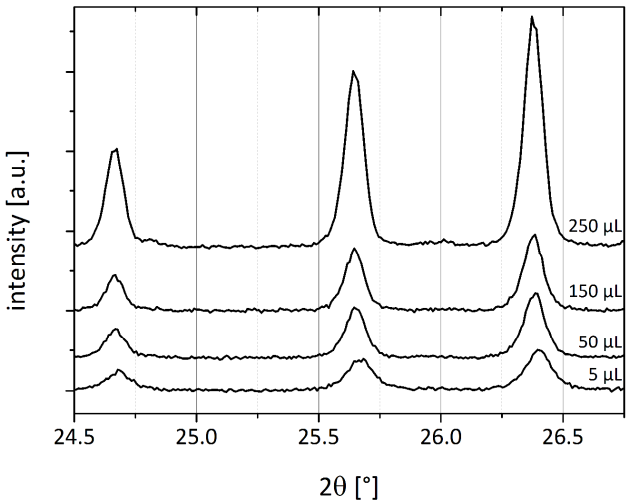

Fig. 6 PXRD patterns of cf:ana form II with different amounts of acetonitrile (5 µL-250 µL) added to 1 g of the reactant mixture.

To exclude a similar pre-coordination for form I, milling experiments were conducted adding different mixture ratios of ethanol and acetonitrile to the LAG synthesis. If both polymorphic forms were induced by pre-coordination with the solvent molecules, a transition of one form to another would appear with the corresponding increasing solvent. Figure 7 illustrates that already at a volume mixing ratio of 49:1 (ethanol:acetonitrile) the exclusive formation of polymorph II is triggered by the presence of acetonitrile. Consequently, a pre-coordination with the solvents leading to form I can be ruled out.

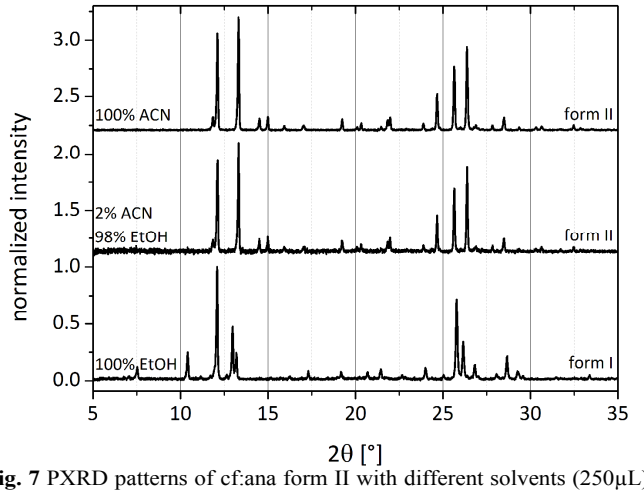

Fig. 7 PXRD patterns of cf:ana form II with different solvents (250µL) added to 1 g of the reactant mixture: acetonitrile (ACN), ethanol an acetonitrile (49:1, corresponding to the volumes of the solvents) and ethanol.

To elucidate the catalytic influence of the solvents forming form II, the synthesis of both cocrystal polymorphs was investigated via pseudo-*in situ* monitoring. The grinding synthesis was stopped after different periods of time and small amounts of the material were immediately investigated using synchrotron X-ray diffraction. Figure 8 illustrates exemplarily the formation pathway of form II, which was obtained by adding 250 µL acetonitrile. While the reflections of ana are not observable in the powder pattern after 20 s, the first reflections of the cocrystal appear at that time. The reflections of caffeine disappear after 100 s of the LAG synthesis, and the cocrystal formation can be regarded as completed. The monitoring of the cocrystal synthesis also reveals that the formation pathway leads directly to the form II without any transitional stages.

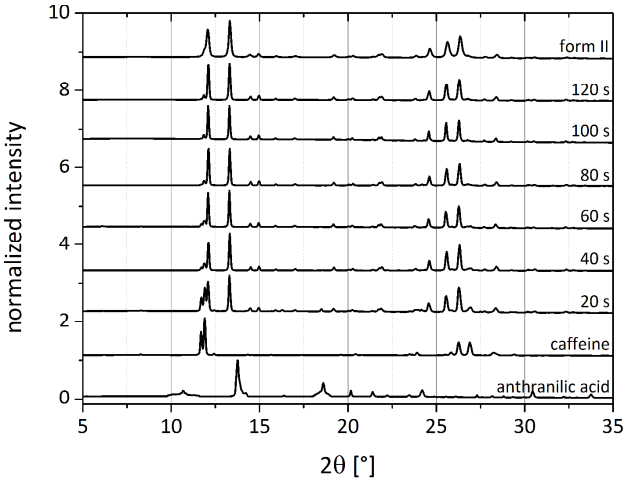

Fig. 8 PXRD patterns of the cf:ana cocrystal form II after different milling time intervals.

In a similar experiment the formation of form I (Figure S 4) was also observed by pseudo-*in situ* monitoring using 250 µL dioxane. Here, the reflections of ana disappear also after 10 s. The formation of form I is much slower, and caffeine reflections disappear after 6 min. It can be postulated that the pre-coordination prior to the formation of form II causes also an acceleration of the reaction rate.

Experimental

Materials

Caffeine, $C_8H_{10}N_4O_2$, (ReagentPlus®, Sigma Aldrich, Germany), anthranilic acid, $C_7H_7NO_2$, (≥ 98%, Acros Organics, USA), and all solvents were used without further purification.

Milling synthesis

The synthesis of the two polymorphs was conducted by neat or liquid-assisted grinding (LAG) in a ball mill (MM400, Retsch, Germany) at 30 Hz for 25 min. A 10 mL steel vessel with two steel balls (10 mm) was used for a total load of 1 g reactants. In case of LAG 250 µL solvent were added.

XRD

The gained product was measured by PXRD. All X-ray diffraction experiments were carried out using a D8 diffractometer (Bruker AXS, Karlsruhe, Germany) in transmission geometry (Cu-Kα_1 radiation, λ = 1.54056 Å).

Synchrotron

Pseudo-*in situ* measurements were performed at the micro-focus beamline µSpot (BESSY II, Helmholtz Centre Berlin for Materials and Energy, Germany) in transmission geometry. The powder patterns were collected with a wavelength of 1.0039 Å using a Si (111) double-crystal monochromator and were recorded with a two-dimensional MarMosaic CCD X-ray detector with 3072x3072 pixels. In a typical experiment, XRD patterns were collected for 30 s. The obtained scattering images were processed and converted into diagrams of scattered intensities versus scattering vector q ($q=4\pi/\lambda\sin\theta$) employing an algorithm from the FIT2D software.[41] For the graphical representations, q-values were transformed to the diffraction angle 2θ (Cu) to provide a direct comparison to results obtained by XRD with Cu radiation.

Raman

Raman measurements were performed on a Raman RXN1™ Analyzer (Kaiser Optical Systems, France). The spectra were collected using a laser with a wavelength of λ = 785 nm and a contactless probe head (working distance 1.5 cm, spot size 1.0 mm). Raman spectra were recorded with an acquisition time of 5 s and 5 accumulations. NIR excitation radiation at λ = 785 nm and an irradiation of 6.6 W/cm² were performed.

ssNMR

^{1}H MAS NMR spectra were recorded on a Bruker AVANCE 400 spectrometer using a 2.5 mm double-bearing MAS probe (Bruker Biospin) and applying a spinning speed of 20 kHz. The ^{1}H MAS NMR spectra were recorded with a $\pi/2$ pulse lengths of 3.7 µs, a recycle delay of 5 s and an accumulation number of 256. Existent background signals were suppressed with a phase-cycled depth pulse sequence according to Cory and Ritchey.[42]

SEM

SEM micrographs were obtained using a scanning electron microscope ZEISS Supra 40 equipped with a thermal field emission cathode (Schottky-emitter, ZrO/W-cathode). The acceleration voltage was set to 10 kV and the working distance was at 6.2 mm. The samples were additionally deposed of a thin layer of carbon. The micrographs were acquired with an *In-lens* (SE1) secondary electron detector, a (SE2) secondary electron detector of type Everhart-Thornley and a QBSD back-scatter electron detector.[43]

Conclusions

The formation pathways of two polymorphs of the caffeine:anthranilic acid cocrystal were investigated under mechanochemical conditions. Small amounts of solvents applied during the grinding process lead to different polymorphs depending on the solvent. Solvents with a low dipole moment favour the crystallization of form I. Solvents with high dipole moment lead to the crystallization of form II. In these cases the solvent molecules interact with the amino group of ana molecules. Consequently, the caffeine molecules have to twist for the development of the cocrystal synthon. For solvents with lower dipole moment a pre-coordination is not observed and the caffeine molecules are arranged parallel in the layered structure of form I.

Pseudo-*in situ* monitoring of the synthesis pathway of both polymorphs using synchrotron radiation revealed that the pre-coordination initializes not only the crystallization of the polymorphic form II, but also accelerates the cocrystal formation with respect to the synthesis of form I. Since also only small amounts of the solvents are needed to evoke the crystallization of form II, it can be seen as a catalyst.

These investigations show that in the liquid-assisted grinding synthesis the kind of solvent added during the milling process has an enormous influence and decides about the fate of the cocrystal product.

Acknowledgement

We are grateful to Dr. M. Feist for DTA/TG measurements.

Notes and references

[a] BAM Federal Institute for Materials Research and Testing, Richard-Willstätter-Str. 11, 12489 Berlin, Germany.
E-mail:franziska.emmerling@bam.de.
[b] Department of Chemistry, Humboldt-Universität zu Berlin, Brook-Taylor-Str. 2, 12489 Berlin, Germany.

† Electronic Supplementary Information (ESI) available: ^{1}H MAS NMR spectra of the reactants and the cocrystal. See DOI: 10.1039/b000000x/

References

1. B. Sarma, J. Chen, H. Y. Hsi and A. S. Myerson, *Korean J. Chem. Eng.*, 2011, **28**, 315-322.
2. J. Bauer, S. Spanton, R. Henry, J. Quick, W. Dziki, W. Porter and J. Morris, *Pharmaceutical Research*, 2001, **18**, 859-866.
3. J.-P. Brog, C.-L. Chanez, A. Crochet and K. M. Fromm, *RSC Advances*, 2013, **3**, 16905-16931.
4. S. Aitipamula, R. Banerjee, A. K. Bansal, K. Biradha, M. L. Cheney, A. R. Choudhury, G. R. Desiraju, A. G. Dikundwar, R. Dubey, N.

Duggirala, P. P. Ghogale, S. Ghosh, P. K. Goswami, N. R. Goud, R. R. K. R. Jetti, P. Karpinski, P. Kaushik, D. Kumar, V. Kumar, B. Moulton, A. Mukherjee, G. Mukherjee, A. S. Myerson, V. Puri, A. Ramanan, T. Rajamannar, C. M. Reddy, N. Rodriguez-Hornedo, R. D. Rogers, T. N. G. Row, P. Sanphui, N. Shan, G. Shete, A. Singh, C. C. Sun, J. A. Swift, R. Thaimattam, T. S. Thakur, R. Kumar Thaper, S. P. Thomas, S. Tothadi, V. R. Vangala, N. Variankaval, P. Vishweshwar, D. R. Weyna and M. J. Zaworotko, *Crystal Growth & Design*, 2012, **12**, 2147-2152.

5. C. B. Aakeröy, M. E. Fasulo and J. Desper, *Mol. Pharm.*, 2007, **4**, 317-322.
6. M. C. Etter and G. M. Frankenbach, *Chemistry of Materials*, 1989, **1**, 10-12.
7. T. Friščić and W. Jones, *Journal of Pharmacy and Pharmacology*, 2010, **62**, 1547-1559.
8. M. J. Zaworotko, *Crystal Growth & Design*, 2006, **7**, 4-9.
9. N. Madusanka, M. D. Eddleston, M. Arhangelskis and W. Jones, *Acta Crystallographica Section B*, 2014, **70**, 72-80.
10. M. J. Bevill, P. I. Vlahova and J. P. Smit, *Crystal Growth & Design*, 2014.
11. S. Ghosh, A. Mondal, M. S. R. N. Kiran, U. Ramamurty and C. M. Reddy, *Crystal Growth & Design*, 2013, **13**, 4435-4441.
12. M. D. Eddleston, B. Patel, G. M. Day and W. Jones, *Crystal Growth & Design*, 2013, **13**, 4599-4606.
13. N. Schultheiss, M. Roe and S. X. M. Boerrigter, *Crystengcomm*, 2011, **13**, 611-619.
14. A. V. Trask, W. D. S. Motherwell and W. Jones, *Chemical Communications*, 2004, 890-891.
15. B. N. Cronstein, *Journal of Hepatology*, 2010, **53**, 207-208.
16. B. B. Fredholm, K. Battig, J. Holmen, A. Nehlig and E. E. Zvartau, *Pharmacological Reviews*, 1999, **51**, 83-133.
17. R. B. Lipton, W. F. Stewart, R. E. Ryan, J. Saper, S. Silberstein and F. Sheftell, *Arch. Neurol.*, 1998, **55**, 210-217.
18. S. Ghosh and C. M. Reddy, *Crystengcomm*, 2012, **14**, 2444-2453.
19. E. Lu, N. Rodriguez-Hornedo and R. Suryanarayanan, *Crystengcomm*, 2008, **10**, 665-668.
20. S. S. Pinto and H. P. Diogo, *The Journal of Chemical Thermodynamics*, 2006, **38**, 1515-1522.
21. G. D. Enright, V. V. Terskikh, D. H. Brouwer and J. A. Ripmeester, *Crystal Growth & Design*, 2007, **7**, 1406-1410.
22. T. E. Gorelik, A. Sarfraz, U. Kolb, F. Emmerling and K. Rademann, *Crystal Growth & Design*, 2012, **12**, 3239-3242.
23. A. Sarfraz, A. Simo, R. Fenger, W. Christen, K. Rademann, U. Panne and F. Emmerling, *Crystal Growth & Design*, 2012, **12**, 583-588.
24. J. Leiterer, F. Emmerling, U. Panne, W. Christen and K. Rademann, *Langmuir*, 2008, **24**, 7970-7978.
25. A. V. Trask, W. D. S. Motherwell and W. Jones, *Crystal Growth & Design*, 2005, **5**, 1013-1021.
26. S. Aitipamula, P. S. Chow and R. B. H. Tan, *Crystengcomm*, 2012, **14**, 2381-2385.
27. D.-K. Bučar, G. M. Day, I. Halasz, G. G. Z. Zhang, J. R. G. Sander, D. G. Reid, L. R. MacGillivray, M. J. Duer and W. Jones, *Chemical Science*, 2013, **4**, 4417-4425.
28. D.-K. Bučar, R. F. Henry, X. Lou, R. W. Duerst, L. R. MacGillivray and G. G. Z. Zhang, *Crystal Growth & Design*, 2009, **9**, 1932-1943.
29. D. K. Bučar, R. F. Henry, X. C. Lou, T. B. Borchardt and G. G. Z. Zhang, *Chemical Communications*, 2007, 525-527.
30. H. D. Clarke, K. K. Arora, H. Bass, P. Kavuru, T. T. Ong, T. Pujari, L. Wojtas and M. J. Zaworotko, *Crystal Growth & Design*, 2010, **10**, 2152-2167.
31. B. Das and J. B. Baruah, *Crystal Growth & Design*, 2010, **11**, 278-286.
32. T. Friščić, L. Fabian, J. C. Burley, W. Jones and W. D. S. Motherwell, *Chemical Communications*, 2006, **0**, 5009-5011.
33. A. V. Trask, J. van de Streek, W. D. S. Motherwell and W. Jones, *Crystal Growth & Design*, 2005, **5**, 2233-2241.
34. N. Schultheiss, S. Bethune and J. O. Henck, *Crystengcomm*, 2010, **12**, 2436-2442.
35. I. Pavel, A. Szeghalmi, D. Moigno, S. Cîntă and W. Kiefer, *Biopolymers*, 2003, **72**, 25-37.
36. J. S. Suh and M. Moskovits, *Journal of the American Chemical Society*, 1986, **108**, 4711-4718.
37. G. E. Hardy, W. C. Kaska, B. P. Chandra and J. I. Zink, *Journal of the American Chemical Society*, 1981, **103**, 1074-1079.
38. A. L. McClellan, *Tables of experimental dipole moments*, WH Freeman, 1963.
39. A. M. Awwad and A. H. Al-Dujaili, *Journal of Chemical & Engineering Data*, 2001, **46**, 1349-1350.
40. *Merck Index*, 12th edn., 1996.
41. A. P. Hammersley, K. Brown, W. Burmeister, L. Claustre, A. Gonzalez, S. McSweeney, E. Mitchell, J.-P. Moy, S. O. Svensson and A. W. Thompson, *Journal of Synchrotron Radiation*, 1997, **4**, 67-77.
42. D. G. Cory and W. M. Ritchey, *Journal of Magnetic Resonance (1969)*, 1988, **80**, 128-132.
43. A. Guilherme, V. D. Hodoroaba, S. Benemann, J. Coroado and M. L. Carvalho, *J Anal Atom Spectrom*, 2014, **29**, 51-57.

Small but important: The choice of the solvent applied in liquid assisted grinding syntheses of cocrystals triggers the final product and the reaction rate.