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Mechanisms of Mechanochemistry

Laboratory Real-Time and In Situ Monitoring of Mechanochemical Milling Reactions by Raman Spectroscopy**

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Abstract: *Mechanistic understanding of mechanochemical reactions is sparse and has been acquired mostly by stepwise ex situ analysis. We describe herein an unprecedented laboratory technique to monitor the course of mechanochemical transformations at the molecular level in situ and in real time by using Raman spectroscopy. The technique, in which translucent milling vessels are used that enable the collection of a Raman scattering signal from the sample as it is being milled, was validated on mechanochemical reactions to form coordination polymers and organic cocrystals. The technique enabled the assessment of the reaction dynamics and course under different reaction conditions as well as, for the first time, direct insight into the behavior of liquid additives during liquid-assisted grinding.*

Mechanochemical reactions[1] are traditionally used for the processing of inorganic materials,[2] but have also been recognised as a powerful approach for transformations of organic,[3] pharmaceutical,[4] and metal–organic materials[5] in a selective, energy- and atom-efficient, and clean manner.[6] However, understanding of mechanisms of mechanochemical reactions remains poor, primarily because such reactions are conducted in sealed, rapidly moving reaction chambers (milling jars) and involve rapid and violent motion of the milling media (milling balls), thus severely hindering attempts to directly monitor the reaction course. For example, while the accelerating and templating effect of liquid and ionic additives is well-documented,[1a,c,d,6a] little is known about the underlying mechanisms of such liquid-assisted grinding (LAG)[7] and ion- and liquid-assisted grinding (ILAG) processes.[8] Usually, mechanistic studies of mechanochemical reactions are performed in a stepwise manner,[9] whereby milling is interrupted at designated time intervals and the milling vessel opened for a sample of the reaction mixture to be taken for ex situ analysis. This procedure unavoidably disturbs the reaction conditions and involves an inherent delay before analysis. Thus, such analysis is not suited to a number of mechanochemical processes, such as self-sustained reactions,[10] reactions in which the reaction mixture contains volatile components, and processes involving rapidly transforming crystalline or amorphous[11] intermediates. Recently, a method was presented for the real-time in situ monitoring of milling reactions by the diffraction of high-energy synchrotron X-rays.[12] This method proved powerful for the detection of bulk crystalline materials, their transformations, and the evolution of the reaction-mixture composition without the need to interrupt the milling process.[13,14]

However, besides requiring access to a synchrotron radiation source, X-ray diffraction is not a straightforward method for characterizing reaction mechanisms at a molecular level, or for characterizing amorphous phases which may occur during milling.[11,14] Herein we describe a laboratory real-time and in situ monitoring technique in which translucent milling jars made from poly(methyl methacrylate) (PMMA, also known as Perspex or Plexiglas)[12] are used to obtain a time-resolved Raman scattering signal from a milled sample without the need to interrupt the milling process. In contrast to X-ray diffraction, which is largely limited to crystalline materials, Raman spectroscopy will provide information on immediate molecular surroundings within a sample regardless of whether it is in a rigid crystalline, amorphous, or liquid phase. Indeed, Raman spectroscopy has often been used to obtain in situ spectroscopic information[15] in a wide range of systems and became particularly attractive with the introduction of portable Raman spectrometers.[16,9c] Recently, James and co-workers demonstrated the use of Raman spectroscopy to quantitatively monitor the mechanochemical formation of a metal–organic framework.[9b] However, since a conventional steel milling assembly was used in their study, the authors had to resort to stepwise ex situ analysis and a low-vapor-pressure liquid in the form of *N*,*N*-dimethylformamide.

As the first model system, we investigated the previously reported neat-grinding (NG) and LAG reactions of cadmium chloride ($CdCl_2$) and cyanoguanidine (cnge).[17] Depending on the ratio of $CdCl_2$ and cnge, two coordination polymers are known to form: the three-dimensional (3D) material $Cd(cnge)Cl_2$ (**1**) and one-dimensional (1D) $Cd(cnge)_2Cl_2$ (**2**; Scheme 1). Ex situ powder X-ray diffraction (PXRD) showed that the 3D polymer **1** was formed by brief neat grinding (up

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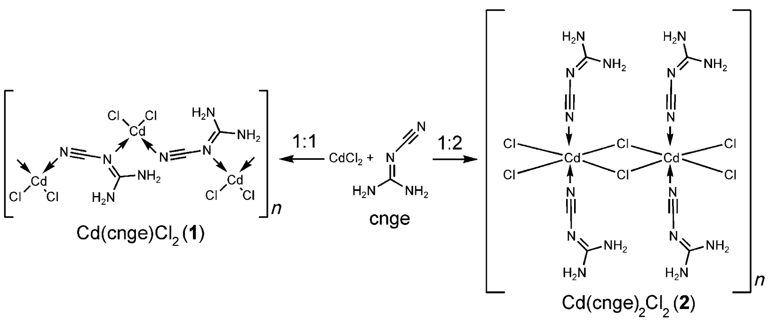

Scheme 1. Mechanochemical reactions between $CdCl_2$ and cnge.

to 10 min) with either two small balls (1.3 g each) or one heavier ball (4.0 g), regardless of whether the initial ratio of the reactants $CdCl_2$ and cnge was 1:1 or 1:2. The 1D polymer **2** was more difficult to obtain and required longer milling with a 4 g ball.

Surprisingly, in situ monitoring of the neat grinding of $CdCl_2$ with either 1 or 2 equivalents of cnge and two small balls revealed no changes in the Raman spectrum even after milling for 40 min (Figure 1 b,c). However, ex situ analysis of the reaction mixtures 3 days later (by Raman spectroscopy and PXRD) revealed pure **1** resulting from the 1:1 starting mixture and a mixture of **1** and cnge resulting from the 1:2 starting mixture. Thus, it is likely that **1** was previously formed not by milling of the reaction mixture, but upon its subsequent aging. To test whether the observed difference in behavior from the previous study may have been caused by the difference in the milling-jar material, we repeated the reactions in a steel milling assembly. After milling for 25 min, the steel vessels were opened, and the reaction mixtures rapidly (within seconds) analyzed by Raman spectroscopy, which revealed only a mixture of reactants. However, subsequent aging of these mixtures resulted in the formation of **1** (see Figures S9 and S10 in the Supporting Information). We found that the aging time required for the formation of **1** greatly varied from sample to sample, ranging from minutes to days, and is probably influenced by humidity.

Switching to a heavier ball (4.0 g) resulted in the formation of **1** from a 1:1 mixture of reactants (Figure 1 d). Evidence for the reaction progress is clearest in the spectral region below 300 cm^{-1}, where the stretching vibrations involving cadmium are positioned, and in the region from 2100 to 2250 cm^{-1}, where the nitrile-group vibrations lie. Approximately 10 min into the milling process, the band at 228 cm^{-1} increased in intensity and gradually shifted towards 240 cm^{-1} to give the three characteristic low-wave-number bands of **1**. This change was accompanied by a gradual decrease in the cnge band at 2158 cm^{-1} and the emergence of bands at 2169 and 2208 cm^{-1} as cnge coordinated to cadmium to form **1**. The reaction was complete after approximately 30 min.

From the 1:2 mixture of $CdCl_2$ and cnge, polymer **2** was previously obtained by neat grinding only when a 4 g ball was used. Furthermore, attempts to investigate the formation of **2** by ex situ analysis were unsuccessful, as the division of the milling process into 5 min periods led to the persistent formation of **1**. This observation led to a proposal that **1** is an intermediate in the synthesis of **2**. In contrast, in situ monitoring by Raman spectroscopy revealed that **2** can form directly from the reactants after milling for 35 min, and that its formation is complete after 60 min (Figure 1 e). The formation of **2** was accompanied by the emergence of a band at 253 cm^{-1}. The nitrile-group vibrations in **2** are similar to those in pure cnge but shifted by about 6 cm^{-1} to higher wave numbers. Remarkably, when a ball with a weight of 2.9 g was used, the time-resolved spectra revealed the formation of **1** after 27 min; this material then reacted with the remaining cnge to yield pure **2** after milling for about 40 min (see Figures S14–S17).

The above-described comparison of in situ studies with results of earlier ex situ investigations clearly shows that grinding reactions are highly sensitive to the reaction conditions and sample manipulation. As a result, ex situ analysis may lead to misleading results, thus highlighting the benefit of the laboratory method presented herein to assess the reaction course without interrupting the milling process.

Next, LAG reactions of $CdCl_2$ and cnge were performed with two small balls (1.3 g each) and methanol (MeOH) as the grinding liquid. Raman spectroscopy enabled, for the first time, direct investigation of the behavior of the added liquid during milling. The vibration bands of MeOH (C–O stretch at 1034 cm^{-1} and C–H stretch at 2841 cm^{-1}) did not change significantly from those of pure methanol. The MeOH bands were clearly visible in the spectra when the mixture became homogenous (ca. 30 s into milling) and did not change their position and intensity during milling (see Figures S18 and S20), thus indicating that MeOH does not actively participate in the mechanochemical reaction. However, MeOH significantly enhanced reactivity (Figure 1 f,g) and enabled the synthesis of pure **1** from a 1:1 mixture of $CdCl_2$ and cnge after only 4 min. Such a rapid transformation could not readily be monitored by using the earlier ex situ PXRD technique.[17] Similarly, LAG of the 1:2 mixture of $CdCl_2$ and cnge almost immediately yielded **1** as an intermediate. The formation of **1** in a mixture with residual cnge was indicated by the two bands due to the nitrile group, the intensity of which became similar, as well as by the emergence of a band at 240 cm^{-1}. Subsequent milling yielded **2**, as evidenced by the emergence of bands at 250 and 1578 cm^{-1}, and by the change in the relative intensity of the two nitrile vibration bands.

Next, we investigated the use of in situ Raman spectroscopy to monitor the course of the formation of a model pharmaceutical cocrystal of nicotinamide (na) and suberic acid (sub). Depending on the reactant ratio, two cocrystals may be formed: the 1:1 cocrystal (na)(sub) (**3**) and the 2:1 cocrystal $(na)_2(sub)$ (**4**; Figure 2 a).[14,18] Previous in situ monitoring by synchrotron X-ray diffraction revealed the direct formation of **3** from a 1:1 mixture of na and sub, as well as the stepwise formation of **4**, via the intermediate **3**, from a 2:1 mixture of na and sub.[14] The results of monitoring by in situ Raman spectroscopy were challenging to analyze, since the reactants and the two cocrystals have very similar Raman

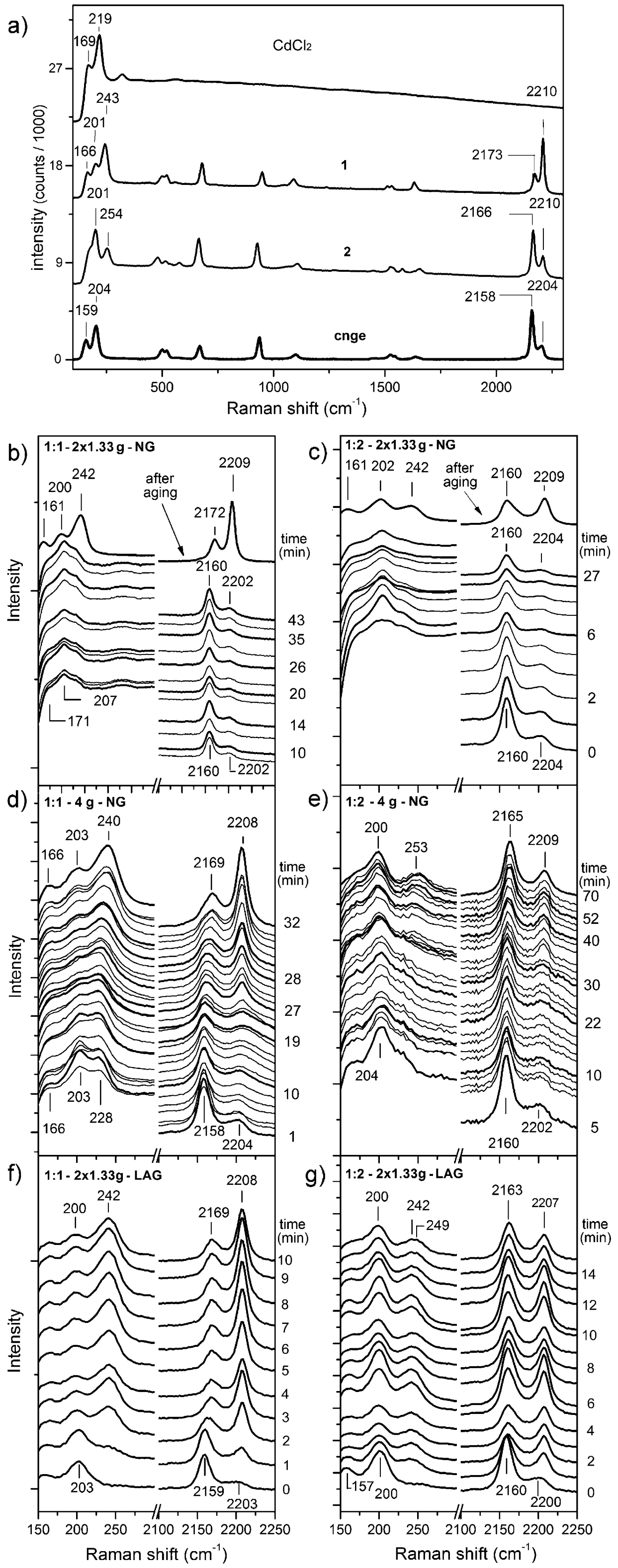

Figure 1. a) Raman spectra of the pure reactants and two products. b–e) Time-resolved Raman spectra recorded during NG of 1:1 and 1:2 reactant mixtures with two small balls (b and c, respectively), during NG of 1:1 and 1:2 reactant mixtures with one heavier ball (d and e, respectively), and during LAG of 1:1 and 1:2 reactant mixtures with two small balls (f and g, respectively). Wave numbers of characteristic bands are indicated on the spectra.

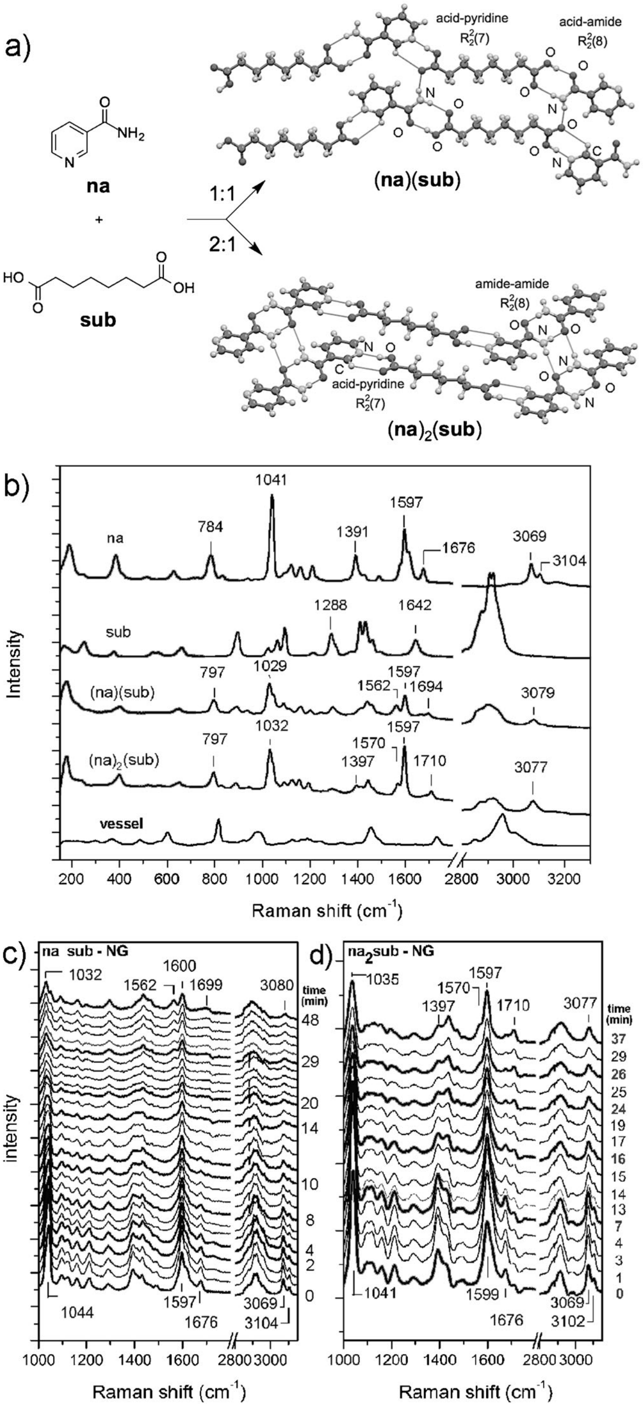

Figure 2. a) Cocrystal formation from nicotinamide and suberic acid. Two cocrystals of different stoichiometries may be formed. b) Raman spectra of the pure reaction participants. c, d) Time-resolved Raman spectra of neat-grinding reactions with a 1:1 (c) and 2:1 (d) na/sub reactant ratio.

spectra (Figure 2b). Nevertheless, we were able to monitor the consumption of reactants and clearly establish the formation of pure **3** from the 1:1 na/sub mixture from the spectrum obtained after neat milling for about 40 min. The consumption of na could also be followed on the basis of the gradual disappearance of the two bands due to C–H stretching vibrations at 3069 and 3102 cm^{-1}, as well as of the carbonyl stretching band at 1676 cm^{-1} (Figure 2c).

The analysis is further complicated when both **3** and **4** may occur simultaneously. The supramolecular architectures of **3** and **4** are comprised of similar supramolecular units (Figure 2a), thus resulting in almost identical Raman spectra. The most pronounced differences in the spectra of the two cocrystals can be found in ring vibrations bands around 1600 cm^{-1}, where the relative intensities of the bands of **3** and **4** differ (Figure 2b). Neat milling of a 2:1 mixture of na and sub resulted in the formation of **4** after about 30 min, as indicated by the band at 1710 cm^{-1} (stretching vibration of the amide carbonyl group), but, unlike by X-ray diffraction, the intermediate **3** could not be clearly identified (Figure 2d).

The LAG cocrystallization was performed by using acetonitrile as the liquid additive. The transformation of the 2:1 mixture of na and sub was rapid and led to the complete formation of **4** after 10 min, which corresponds to fourfold acceleration as compared to neat grinding. The nitrile stretching vibration is sensitive to its surroundings; hydrogen bonding with proton donors results in broadening of the C≡N band and its shift to higher wave numbers, for example, by up to about 10 cm^{-1} in mixtures with water or methanol, and even up to 30 cm^{-1} with very strong hydrogen-bond donors, such as HF.[19]

In our time-resolved LAG experiment (Figure 3), the nitrile band (2253 cm^{-1}) was significantly broadened but remained at almost the same position as in liquid acetonitrile (2252 cm^{-1}; see Figure S30). It also did not change its position and intensity during the whole milling process. Thus, band broadening indicates acetonitrile participation in the LAG reaction mechanism, but its extensive involvement in hydrogen bonding seems to be absent.

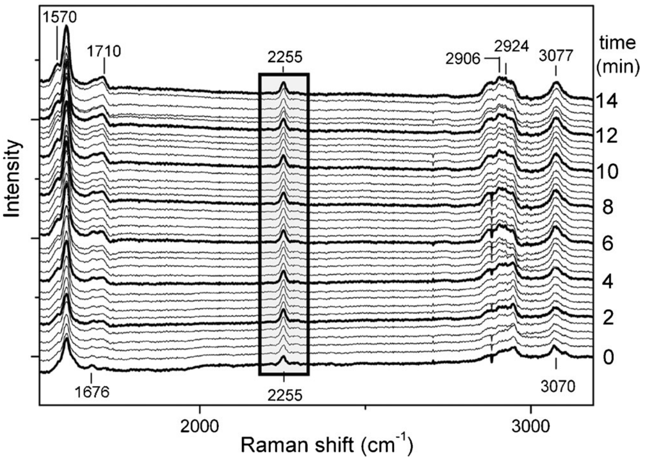

Figure 3. Time-resolved Raman spectra of the LAG formation of the $(na)_2(sub)$ cocrystal. The liquid-acetonitrile band at 2253 cm^{-1} is highlighted by the rectangle.

In summary, we have described the first real-time in situ laboratory technique for monitoring the course of mechanochemical milling reactions by using Raman spectroscopy. In contrast to the recently described in situ X-ray diffraction method,[13] in situ Raman scattering enables direct insight into the mechanochemical transformations at the molecular level and is thus sensitive for crystalline, amorphous, and liquid reaction participants. The results presented herein highlight the complexity of mechanochemical reactions and demonstrate the sensitivity of the reaction course on slight variations in reaction conditions. The technique was validated in the neat and liquid-assisted mechanochemical formation of a coordination polymer and a model pharmaceutical cocrystal. Our findings strongly emphasize the need for in situ measurements to understand mechanistic aspects of milling reactions, since ex situ analysis may sometimes not accurately reflect the mechanism of mechanochemical reactions, as demonstrated herein for the assembly of cadmium-based coordination polymers. This in situ method, to the best of our knowledge, offers unique opportunities for studying the role of volatile liquid additives in milling reactions and should also be relevant for reactions in which eutectic mixtures are formed and thus partial or complete melting occurs. The presented method is straightforward to implement in a standard research laboratory, and we expect it to gain widespread use in mechanistic investigations and the optimization of milling reactions.

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[1] a) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed, D. C. Waddell, *Chem. Soc. Rev.* **2012**, *41*, 413; b) A. Stolle, T. Szuppa, S. E. S. Leonhardt, B. Ondruschka, *Chem. Soc. Rev.* **2011**, *40*, 2317; c) E. Boldyreva, *Chem. Soc. Rev.* **2013**, *42*, 7719; d) T. Friščić, W. Jones, *Cryst. Growth Des.* **2009**, *9*, 1621.

[2] a) V. Šepelák, A. Düvel, M. Wilkening, K.-D. Becker, P. Heitjans, *Chem. Soc. Rev.* **2013**, *42*, 7507; b) V. V. Boldyrev, *Russ. Chem. Rev.* **2006**, *75*, 177.

[3] G. W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668.

[4] a) D. Braga, L. Maini, F. Grepioni, *Chem. Soc. Rev.* **2013**, *42*, 7638; b) V. André, A. Hardeman, I. Halasz, R. S. Stein, G. J. Jackson, D. G. Reid, M. J. Duer, C. Curfs, M. T. Duarte, T. Friščić, *Angew. Chem.* **2011**, *123*, 8004; *Angew. Chem. Int. Ed.* **2011**, *50*, 7858; c) R. Hüttenrauch, S. Fricke, P. Zielke, *Pharm. Res.* **1985**, *2*, 253; d) T. P. Shakhtshneider, *Solid State Ionics* **1997**, *101–103*, 851; e) V. V. Boldyrev, *J. Mater. Sci.* **2004**, *39*, 5117; f) S. Karki, T. Friščić, W. Jones, W. D. Motherwell, *Mol. Pharm.* **2007**, *4*, 347.

[5] a) T. Friščić, I. Halasz, V. Štrukil, M. Eckert-Maksić, R. E. Dinnebier, *Croat. Chem. Acta* **2012**, *85*, 367; b) W. Yuan, T. Friščić, D. Apperley, S. L. James, *Angew. Chem.* **2010**, *122*, 4008; *Angew. Chem. Int. Ed.* **2010**, *49*, 3916; c) A. Pichon, S. L. James, *CrystEngComm* **2008**, *10*, 1839; d) D. Braga, S. L. Giaffreda, F. Grepioni, A. Pettersen, L. Maini, M. Curzi, M. Polito, *Dalton Trans.* **2006**, 1249.

[6] a) K. Užarević, I. Halasz, I. Đilović, N. Bregović, M. Rubčić, D. Matković-Čalogović, V. Tomišić, *Angew. Chem.* **2013**, *125*, 5614;

Angew. Chem. Int. Ed. **2013**, *52*, 5504; b) M. Pascu, A. Ruggi, R. Scopelliti, K. Severin, *Chem. Commun.* **2013**, *49*, 45.

[7] N. Shan, F. Toda, W. Jones, *Chem. Commun.* **2002**, 2372.

[8] T. Friščić, D. G. Reid, I. Halasz, R. S. Stein, R. E. Dinnebier, M. J. Duer, *Angew. Chem.* **2010**, *122*, 724; *Angew. Chem. Int. Ed.* **2010**, *49*, 712.

[9] a) I. A. Tumanov, A. F. Achkasov, E. V. Boldyreva, V. V. Boldyrev, *CrystEngComm* **2011**, *13*, 2213; b) X. Ma, W. Yuan, S. E. J. Bell, S. L. James, *Chem. Commun.* **2014**, *50*, 1585; c) H.-L. Lin, G.-C. Zhang, P.-C. Hsu, S.-Y. Lin, *Microchem. J.* **2013**, *110*, 15; d) A. A. L. Michalchuk, I. A. Tumanov, V. A. Drebushchak, E. Boldyreva, *Faraday Discuss.* **2014**, DOI: 10.1039/C3FD00150D.

[10] a) A. Y. Ibrahim, R. T. Forbes, N. Blagden, *CrystEngComm* **2011**, *13*, 1141; b) L. Takacs, *Prog. Mater. Sci.* **2002**, *47*, 355.

[11] A. Jayasankar, A. Somwangthanaroj, Z. J. Shao, N. Rodríguez-Hornedo, *Pharm. Res.* **2006**, *23*, 2381.

[12] I. Halasz, S. A. J. Kimber, P. J. Beldon, A. M. Belenguer, F. Adams, V. Honkimäki, R. C. Nightingale, R. E. Dinnebier, T. Friščić, *Nat. Protoc.* **2013**, *8*, 1718.

[13] a) T. Friščić, I. Halasz, P. J. Beldon, A. M. Belenguer, F. Adams, S. A. J. Kimber, V. Honkimäki, R. E. Dinnebier, *Nat. Chem.* **2013**, *5*, 66; b) I. Halasz, T. Friščić, S. A. J. Kimber, K. Užarević, A. Puškarić, C. Mottillo, P. Julien, V. Štrukil, V. Honkimäki, R. E. Dinnebier, *Faraday Discuss.* **2014**, DOI: 10.1039/C4FD00013G.

[14] I. Halasz, A. Puškarić, S. A. J. Kimber, P. J. Beldon, A. M. Belenguer, F. Adams, V. Honkimäki, R. E. Dinnebier, B. Patel, W. Jones, V. Štrukil, T. Friščić, *Angew. Chem.* **2013**, *125*, 11752; *Angew. Chem. Int. Ed.* **2013**, *52*, 11538.

[15] a) N. E. Leadbeater, J. R. Schmink, *Nat. Protoc.* **2008**, *3*, 1; b) T. R. M. De Beer, W. R. G. Baeyens, J. Ouyang, C. Vervaet, J. P. Remon, *Analyst* **2006**, *131*, 1137; c) G. Févotte, *Chem. Eng. Res. Des.* **2007**, *85*, 906; d) T. Ono, J. H. ter Horst, P. J. Jansens, *Cryst. Growth Des.* **2004**, *4*, 465.

[16] P. Vandenabeele, H. G. M. Edwards, J. Jehlička, *Chem. Soc. Rev.* **2014**, *43*, 2628.

[17] a) V. Štrukil, L. Fábián, D. G. Reid, M. J. Duer, G. J. Jackson, M. Eckert-Maksići, T. Friščić, *Chem. Commun.* **2010**, *46*, 9191; b) P. Hubberstey, C. P. Falshaw, *J. Chem. Res.* **1982**, *5*, 52.

[18] S. Karki, T. Friščić, W. Jones, *CrystEngComm* **2009**, *11*, 470.

[19] a) M. I. S. Sastry, S. Singh, *Curr. Sci.* **1986**, *55*, 1157; b) J. M. Alía, H. G. M. Edwards, *J. Phys. Chem. A* **2005**, *109*, 7977; c) H. C. Garcia, L. F. C. de Oliveira, B. G. Nicolau, M. C. C. Ribeiro, *J. Raman Spectrosc.* **2010**, *41*, 1720.