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Mechanochemically Induced Conversion of Crystalline Benzamide Polymorphs by Seeding

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Abstract: *Benzamide has been known for its polymorphism for almost 200 years. Three polymorphic forms are described. To date, it was only possible to crystallize a metastable form in a mixture together with the thermodynamically most stable form I. A complete transformation of form I into the metastable form III by mechanochemical treatment has been achieved. Catalytic amounts of nicotinamide seeds were used to activate the conversion by mechanochemical seeding. NMR experiments indicated that the nicotinamide molecules were incorporated statistically in the crystal lattice of benzamide form III during the conversion. The transformation pathway was evaluated using in situ powder X-ray diffraction.*

Almost 200 years ago, the polymorphism of a chemical compound was first described for benzamide by Wöhler and Liebig.[1] A second polymorph was characterized based on extensive experimental and theoretical work.[2] It was only 175 years after the discovery by Wöhler and Liebig, that the structure of a third polymorphic form was solved by reproducing the original experiments.[3] A fourth polymorph was proposed by Benoit, based on a molecular simulation study, suggesting a high-pressure synthesis route for this compound.[4] Until now, this benzamide polymorph has not been found experimentally.

Ostwald proposed that distinct experimental parameters have to be found for the formation of a distinct metastable form from solution or melt. These parameters should suppress the secondary nucleation of the thermodynamically favored form and support the initial nucleation of the desired polymorph. When secondary nucleation occurs, dissolution of the nucleated metastable form and reprecipitation lead to the stable polymorph.[5] For benzamide, polymorph control is difficult. Despite intensive investigations on this polymorphic compound, it has not been possible to crystallize one of the metastable forms (form II and form III) exclusively. Either a mixture of form I and form III or a trimorphic system was obtained. The crystallization of form III is particularly challenging, since specific cooling rates and secondary nucleation must be considered.[3,6] For the crystallization of a specific polymorph of benzamide, approaches starting from melt or solution and applying sublimation were performed.[3] Recently, Altheimer et al. investigated the mechanochemical conversion of crystalline polymorphs of a capped amino acid by changing the milling conditions, suggesting that such an approach might be suitable to obtain form II and III exclusively and robustly.[7] For the convenience of readers, Table 1 provides crystallographic data pertaining to the polymorphs under discussion.

Herein, we introduce mechanochemical seeding as an alternative to obtain form III of benzamide quantitatively. When benzamide (form I) is milled in the presence of nicotinamide (form I) and ethanol, a complete transformation of benzamide into form III is observed independently of the benzamide:nicotinamide ratio (Figure 1; Supporting Information, Figure S1). The milling syntheses were performed by liquid-assisted grinding of benzamide and nicotinamide in a ball mill (MM400, Retsch, Germany) at 30 Hz for 25 min. A 10 mL steel vessel with two steel balls (10 mm diameter, 4 g) was used for a total load of 1 g of the compounds and 250 μL of added ethanol. Grinding experiments, during which pure benzamide or nicotinamide were ground together with ethanol, did not lead to any change in their crystalline structure.

Table 1: Crystallographic data of the polymorphs of benzamide (ba) and nicotinamide (na).[6,8]

Compound	ba form I	ba form II	ba form III	na form I	na form II
Formula	C_7H_7NO	C_7H_7NO	C_7H_7NO	$C_6H_6N_2O$	$C_6H_6N_2O$
Molar Mass [g mol^{-1}]	121.14	121.14	121.14	122.12	122.12
Crystal System	monoclinic	orthorhombic	monoclinic	monoclinic	monoclinic
Space Group	$P2_1/c$	Pba2	$P2_1/c$	$P2_1/c$	$P2/n$
a	5.607(2)	17.43216	5.05506(12)	3.975(5)	15.0634(5)
b	5.046(2)	14.19371	5.51404(14)	15.632(8)	10.6976(4)
c	22.053(8)	4.97731	22.95644(91)	9.422(4)	15.2067(5)
β	90.66(3)	90	101.2914(20)	99.03(7)	102.188(2)
V [Å^3]	623.902	1231.52	627.498	578.201	2395.21

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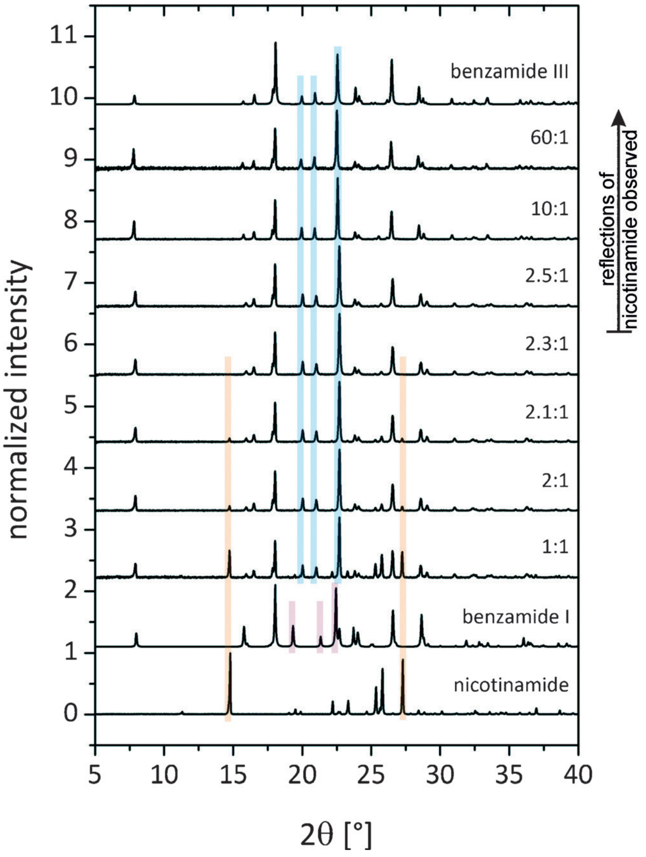

Figure 1. Powder patterns of milling products obtained from mixtures of benzamide and nicotinamide in different ratios (benzamide:nicotinamide) with ethanol. Colored bars indicate the most prominent reflections of nicotinamide (orange), benzamide form I (purple), and form III (blue).

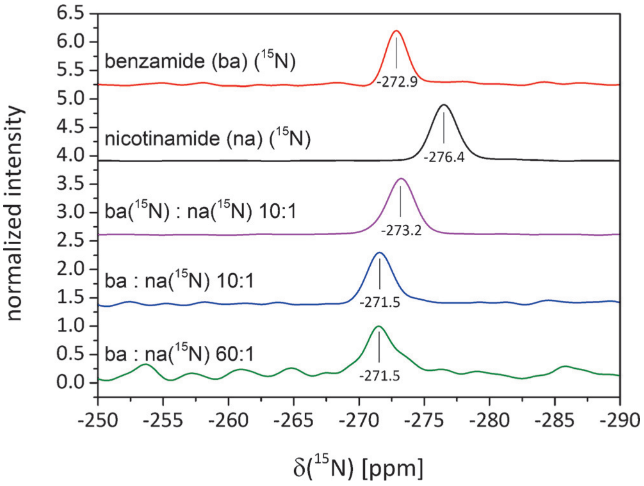

Figure 2. Solid-state NMR spectra of the milling products of benzamide and nicotinamide in different ratios with ^{15}N-doped amide groups and the pure doped reactants.

After the reaction, the powders were dried in air for four hours. The high-resolution powder diffraction patterns of the products reveal a complete transformation of benzamide into the metastable form III. Based on these powder patterns a cocrystal formation with nicotinamide can be excluded, since no new reflections are observable. With a 2.5-fold molar excess of benzamide in the milling reaction no nicotinamide reflections can be detected in the milling product. On the other hand in a physical mixture of benzamide and nicotinamide with a molar ratio of 20:1 the reflections of nicotinamide are still detectable. An amorphization of nicotinamide can be excluded, since milling of pure nicotinamide does not lead to an increase of the background of the powder pattern. This leads to the hypothesis that the nicotinamide molecules are incorporated in the crystal lattice of benzamide. To confirm this hypothesis, solid-state NMR experiments were conducted. For milling products with different ratios of benzamide and nicotinamide, two types of experiments were conducted where either one or both reactants were enriched to 98 atom% ^{15}N at the amide group. Pure ^{15}N-labeled benzamide exhibits a ^{1}H-^{15}N CPMAS NMR signal at −272.9 ppm (Figure 2, red), and pure labeled nicotinamide at −276.4 ppm (black). Milling ^{15}N-labeled benzamide with ^{15}N-labeled nicotinamide in a ratio of 10:1 leads to a chemical shift at −273.2 ppm (pink). The experiment was repeated with non-labeled benzamide to monitor only the chemical shift of the labeled nicotinamide. In this case the signal occurs at −271.5 ppm (blue). The transformation also occurs in a 60-fold excess of benzamide, compared to nicotinamide. In this case, the product also exhibits a signal at −271.5 ppm (green), indicating that in this product the nicotinamide molecules encounter a different chemical environment as compared to pure nicotinamide. The data validate the assumption, that the nicotinamide molecules are integrated in the crystal lattice of benzamide during the milling process. Based on this embedding behavior, nicotinamide can be regarded as a heterogeneous seed in the milling system. As a consequence of the incorporation, the melting behavior of the compounds also changes slightly (as summarized in the Supporting Information, Figures S2–S4).

To investigate the formation pathway of this mechanochemical polymorph transformation in detail, the milling syntheses were followed using in situ X-ray diffraction (XRD). A self-constructed 10 mL Perspex jar, which was transparent to synchrotron radiation, was used as reaction vessel. The setup allowed the investigation of the transformation under real conditions. The milling syntheses were conducted in a manner similar to those performed in the laboratory using a mixer mill (Pulverisette 23, Fritsch, Germany) at 50 Hz with two steel balls (10 mm diameter, 4 g). The XRD data were recorded every 30 s during the milling process. Molar ratios of the reactants between 1:1 and 20:1 were investigated. The data indicate that the transformation of benzamide into the metastable form III proceeds from the start of the grinding process for all ratios. The reflections of form III can be monitored in each reaction in the first powder pattern during grinding (Figure 3; Supporting Information, Figures S5 and S6). The excess of benzamide determines the transformation rate.

Starting from an equimolar ratio of benzamide I and nicotinamide (Figure 3a), the transformation of benzamide into the metastable form III is completed within the first 30 s of milling. No reflections of benzamide I are observable in the

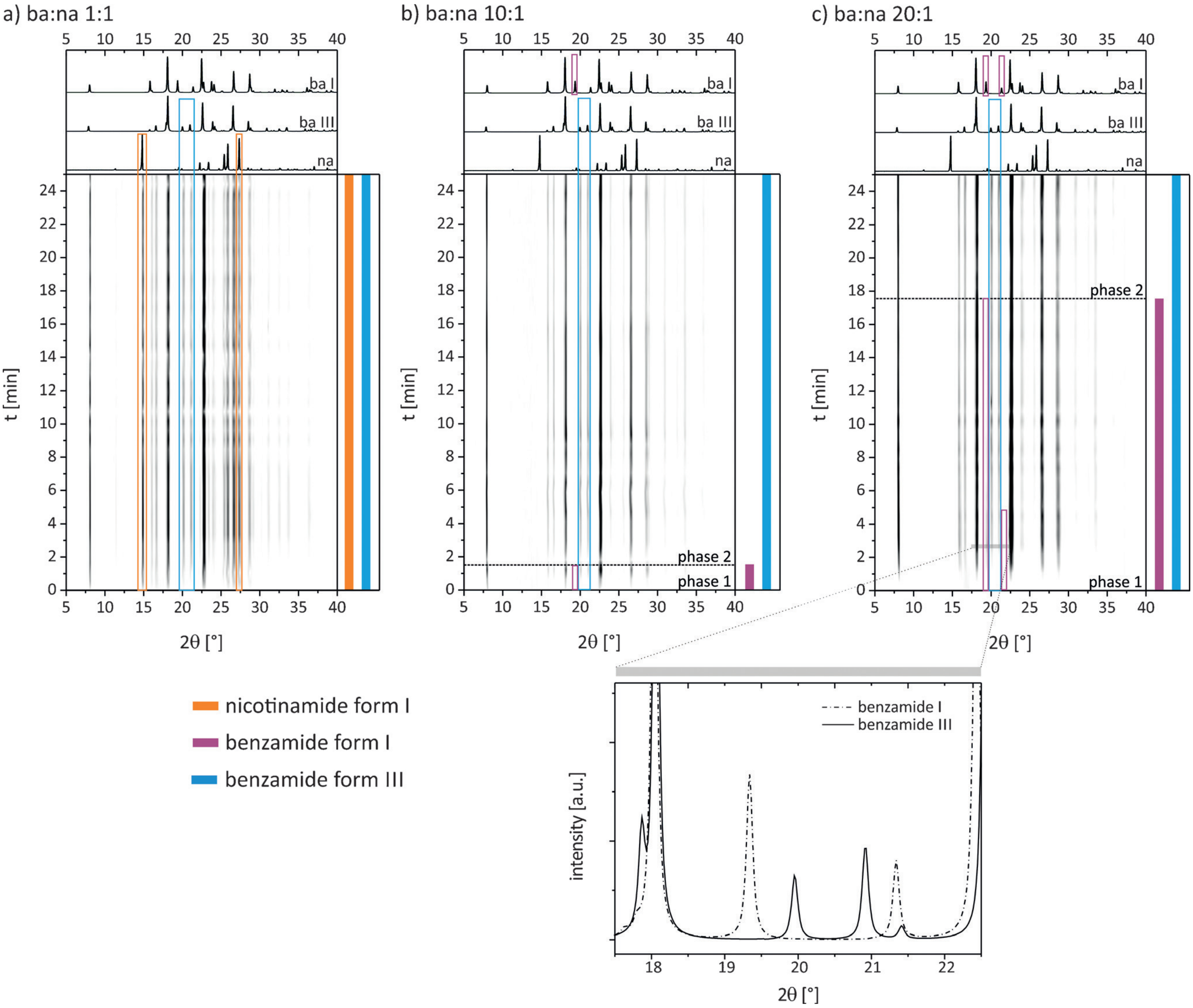

Figure 3. Time-resolved pathway of the powder patterns during grinding of benzamide (ba) and nicotinamide (na) in different molar ratios a) 1:1, b) 10:1, and c) 20:1, with ethanol. Characteristic reflections of nicotinamide form I (orange), benzamide form I (blue), and form III (purple).

first recorded powder pattern during the milling process. The subsequent powder patterns reveal no changes in the milling product of benzamide III and nicotinamide. When benzamide is used in a 2.5-fold excess, as depicted in Figure S5b (Supporting Information), the reflections of nicotinamide vanish after a milling period of 1.00 min. Moreover, in this case, as well as with a 5-fold excess of benzamide, the transformation proceeds within the first 30 s. As shown in Figure S5c (Supporting Information), with a benzamide:nicotinamide molar ratio of 5:1 no nicotinamide reflections are observable during the transformation pathways.

Reflections of the thermodynamically stable form I were recorded during the transformation pathway only when benzamide is added in a 10-fold excess compared to nicotinamide, whereas the formation of the metastable form of benzamide is still fast. The formation proceeds within 1.5 min, as shown in Figure 3b. The reaction rate decreases significantly when the ratio of reactants is further increased; the transformation needs 12.5 min in the case of a molar ratio of 15:1 (Supporting Information, Figure S6), and a further 5.00 min at a molar ratio of 20:1 (Figure 3c).The reaction times increase with a decreasing amount of nicotinamide seeds. The more nicotinamide seeds available in the reaction mixture, the more benzamide particles are triggered to convert into form III simultaneously, which once again serve as seeds for further transformations. In the presence of only a few nicotinamide seeds, the conversion of benzamide into form III proceeds rather consecutively.

Figure 4 summarizes the transformation times of benzamide form I into form III by mechanochemical seeding. Starting from a molar ratio of 2.5:1 (benzamide:nicotinamide) the nicotinamide molecules are completely incorporated in the crystal lattice of benzamide. Based on the XRD data, it can be assumed that the nicotinamide molecules are statistically distributed in the benzamide lattice. This interpretation is also in agreement with the NMR results.

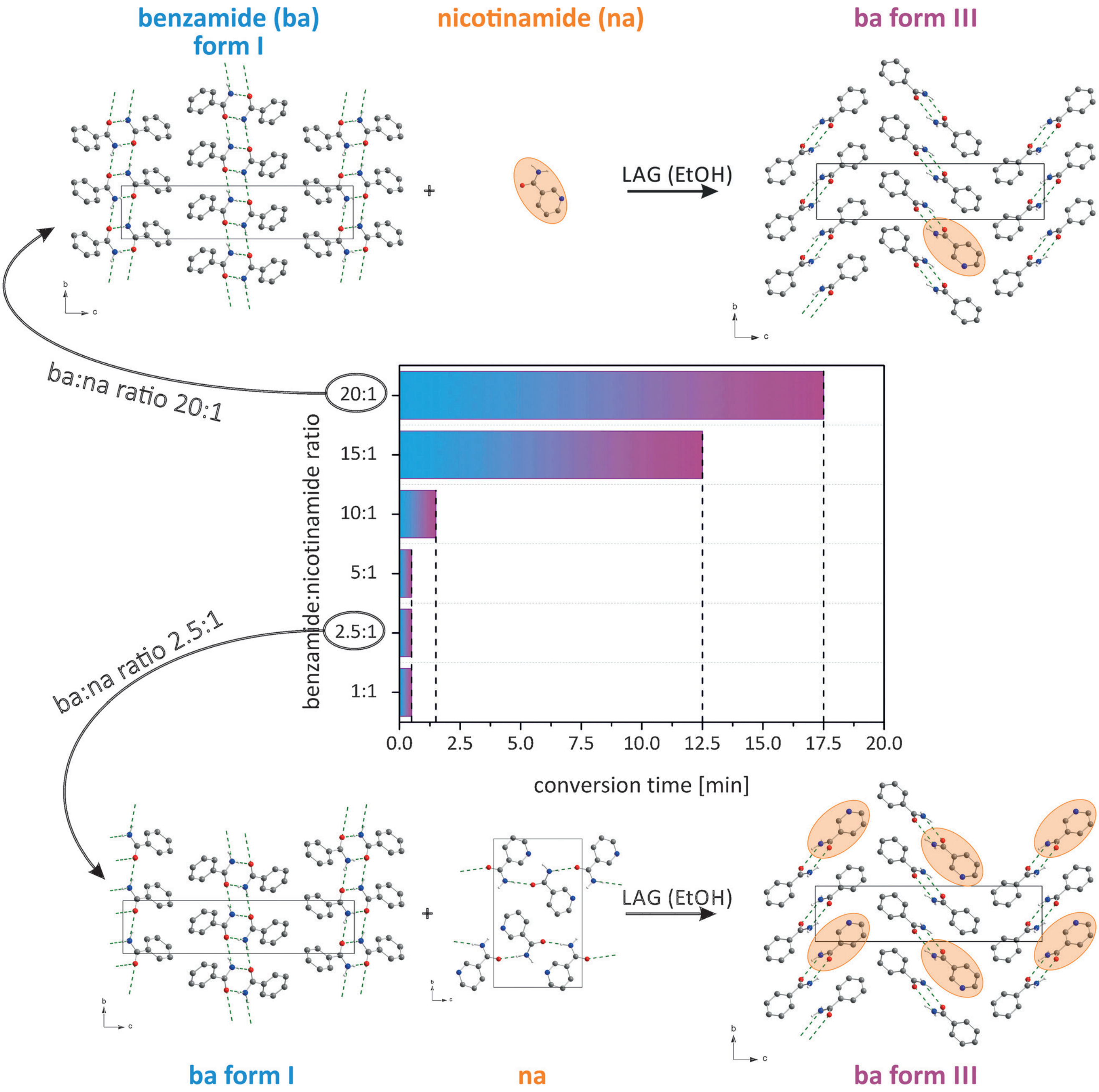

Figure 4. Conversion times required for the transformation of benzamide (ba) form I into form III by liquid-assisted grinding (LAG) with ethanol (EtOH) and nicotinamide (na) seeds.

In summary, we have demonstrated the complete transformation of benzamide I into the metastable form III for the first time. To date, it was only possible to gain a mixture of both forms. Using nicotinamide seeds in a liquid-assisted grinding synthesis with ethanol, a complete formation into the metastable form III of benzamide could be achieved (Figure 4). The reflections of nicotinamide vanished at a molar ratio of 2.5:1 (benzamide:nicotinamide) in the product powder pattern. Therefore, it was assumed that the nicotinamide molecules were included in the crystal system of benzamide, triggering formation of benzamide III. ^{15}N solid-state NMR experiments with doped and non-doped reactants confirmed this assumption. These results reveal the potential of mechanochemistry, and a strategy for obtaining and stabilizing metastable crystal forms. This new strategy opens the way for further academic research.

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Keywords: benzamide · in situ reactions · mechanochemistry · nicotinamide · polymorphs

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