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Mechanochemical carbon–carbon bond formation that proceeds *via* a cocrystal intermediate†

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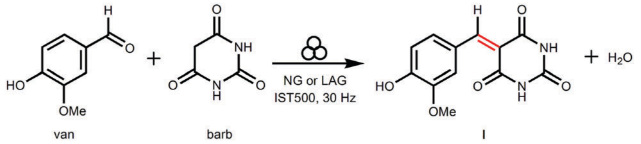
We report the first cocrystal as an intermediate in a solid-state organic reaction wherein molecules of barbituric acid and vanillin assume a favorable orientation for the subsequent Knoevenagel condensation.

The Knoevenagel condensation is an important carbon–carbon bond forming reaction. More than a hundred years after the original report by Knoevenagel,[1] Suzuki[2] and Kaupp[3] demonstrated an efficient and quantitative Knoevenagel condensation in the solid state achieved by milling. Other studies of solvent-free Knoevenagel condensation reactions soon followed.[4–10] The reaction of barbituric acid (barb) and vanillin (van) was even used as a model mechanochemical organic reaction for assessing energetics of milling,[11,12] to test twin-screw extrusion for solid-state organic synthesis,[13] and latest, to reveal a peculiar deviation of solid-state reaction kinetics from the one observed in solution, stemming from changes in the rheology of the milled sample.[14] However, studies of barb–van Knoevenagel condensation were thus far limited to *ex situ* reaction monitoring by, *e.g.*, solution UV-Vis[11] or NMR spectroscopies.[14]

In this work, we employ real-time *in situ* Raman spectroscopy monitoring[15,16] to reveal that the solid-state Knoevenagel condensation (Scheme 1) of barb and van proceeds through a cocrystal intermediate. In the cocrystal, packing of barb and van is such that molecules of barb are suitably positioned for the nucleophilic attack to the carbonyl C-atom of van, which is the first step of the Knoevenagel condensation. Furthermore, solid-state *ab initio* calculations offer a plausible reaction path for the C═C bond to form within the cocrystal. Liquid-assisted grinding (LAG) with ethanol considerably accelerated the reaction in comparison to LAG with non-protic liquids or neat grinding. On the other hand, LAG with a strong non-nucleophilic base provided a reaction pathway that circumvented the cocrystal intermediate.



Scheme 1 Solid-state Knoevenagel condensation of van and barb under mechanochemical milling conditions. The new C═C bond is shown in red.

As far as we are aware, the Knoevenagel condensation of barb and van studied here is the first mechanochemical organic reaction where a cocrystal of reactants is formed *in situ* during milling before the targeted reaction and the formation of a new covalent bond occurred. Nevertheless, cocrystals as multicomponent solids have been recognised as a promising medium to conduct solid-state reactions efficiently and selectively.[17–19] As such, they have been used at length in crystal engineering to design and construct solids to enable specific and usually photochemical reactivity.[20–23] Targeted use of cocrystals to achieve thermal solid-state reactions has also been explored, albeit to a lesser extent.[24–29]

Milling of 1 mmol of barb and 1 mmol of van was performed using a vibratory IST500 ball mill operating at 30 Hz, and equipped with 2 stainless steel balls of 7 mm (each weighing 1.4 g) in diameter as the milling media. *In situ* monitoring of neat grinding revealed only mixing of reactants during the first 70 minutes of milling after which a new intermediate phase started to emerge, and it was followed by a slow formation of the product **I** over a period of several hours (Fig. 1). According to solution NMR, **I** was the expected Knoevenagel condensation product and was amorphous as evidenced by PXRD (Fig. S2, ESI†). In a repeated experiment, we used *in situ* monitoring to isolate the intermediate by stopping the reaction at an appropriate

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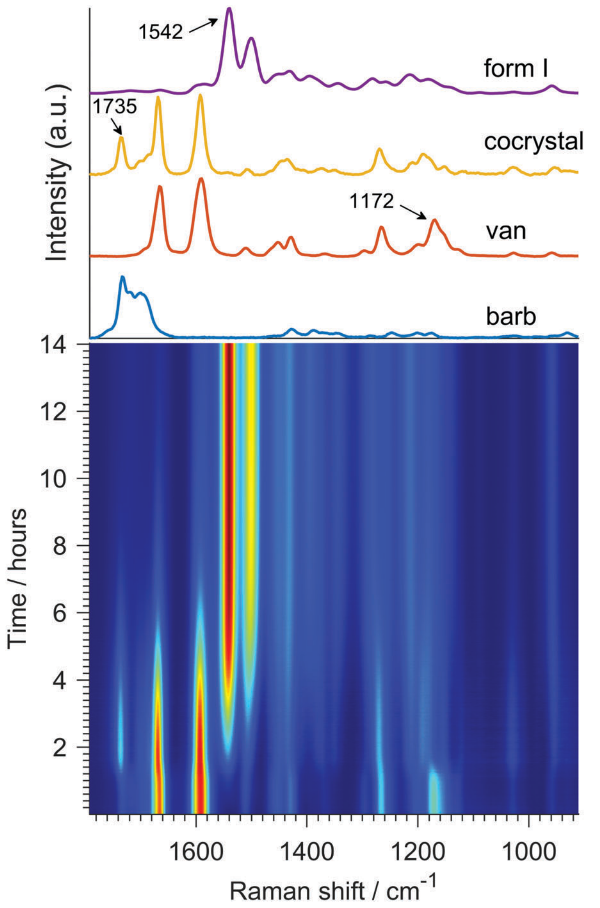

Fig. 1 *In situ* Raman monitoring of neat grinding of barb and van. Raman spectra of barb, van, the cocrystal, and **I** are given above the 2D plot. Formation of the cocrystal can be monitored by the Raman band at 1735 cm^{-1} that corresponds to the C═O stretching of barb molecules in the cocrystal. The Raman band of the newly formed C═C bond at 1542 cm^{-1} indicates the formation of **I**. Intensity colour code: blue – low, red – high.

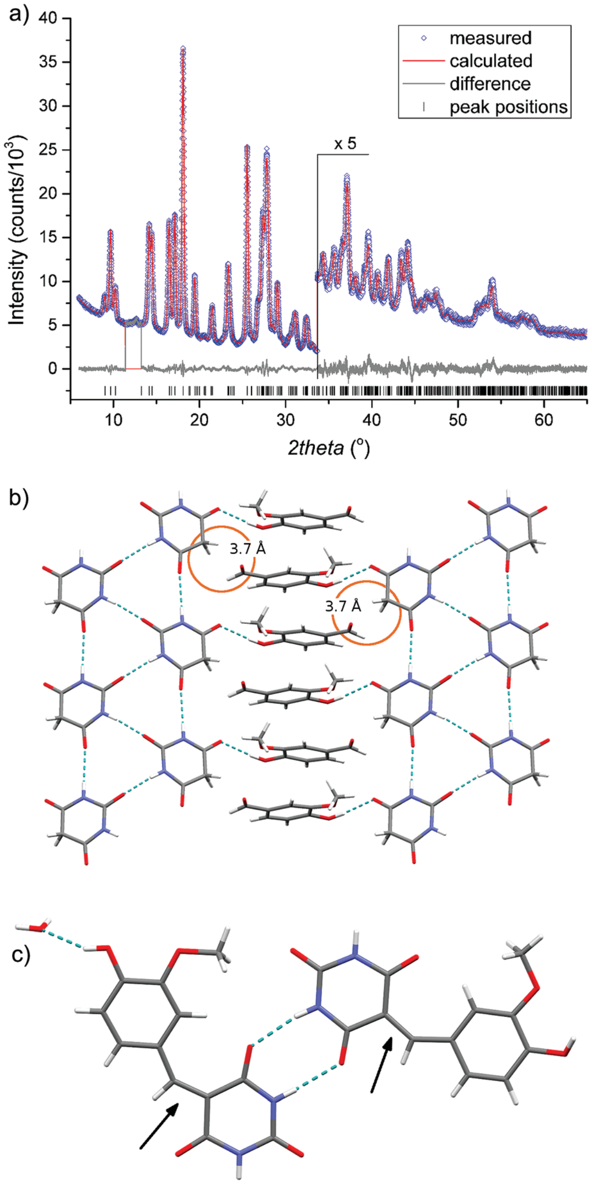

Fig. 2 (a) Rietveld plot for the 1 : 1 barb:van cocrystal structure determined from powder diffraction data collected using CuKα X-rays. A high-angle region is enlarged to reveal more details. Refinement parameters: R_p = 2.3%, R_{wp} = 3.1%, R_{Bragg} = 1.0%, and gof = 1.91. (b) Ribbons of barb and stacks of van molecules in the cocrystal. Orange circles highlight the closest distance between the barb methylene group and the van carbonyl group. The 3.7 Å is the distance between the corresponding carbon atoms. Dashed bonds represent hydrogen bonds. (c) Two Knoevenagel condensation product molecules and one water molecule in the asymmetric unit of **II**. Arrows point to newly formed C═C bonds.

time and solved its crystal structure from laboratory PXRD data (Fig. 2a), revealing it to be a 1 : 1 cocrystal of barb and van.

The cocrystal exhibits ribbons of barb molecules while molecules of van pack in stacks (Fig. 2b). Strong N–H···O hydrogen bonds connect molecules of barb within the ribbons, leaving one carbonyl O atom to be an acceptor in a hydrogen bond with the hydroxy group of van. Having both reacting molecules within a crystal brings to mind the topochemical principle which anticipates that the reacting centers should be close.[30] The topochemical principle may hardly be applicable here since the average crystal structure needs not to reflect the changes occurring at the molecular level.[31] However, we do note that the arrangement of molecules in the barb:van cocrystal is such that the barb methylene group and the aldehyde group of van are separated by only *ca.* 3.7 Å and suitably orientated for the addition of the barb nucleophile to the carbonyl C atom of van (Fig. 2b).

We were thus inspired to examine the potential topochemical reaction in the cocrystal by using solid-state *ab initio* calculations. Indeed, we have been able to identify a plausible reaction path for the barb methylene group to attack the aldehyde C atom of van and to create a new C═C bond within the cocrystal. In the process, one water molecule simultaneously leaves, and the calculated energy barrier is below 350 kJ mol^{-1} (Fig. 3). This, however, is an overestimation of the energy barrier resulting from the formation of one product molecule out of the four pairs of barb and van in the cocrystal unit cell. Periodic repetition of the unit cell prevents relaxation of the crystal geometry as it would be the case if only one molecule of the product would form in a bigger crystal. Calculations of a single pair of reactant molecules under vacuum gave an energy barrier of around 130 kJ mol^{-1} (Fig. S1, ESI†).

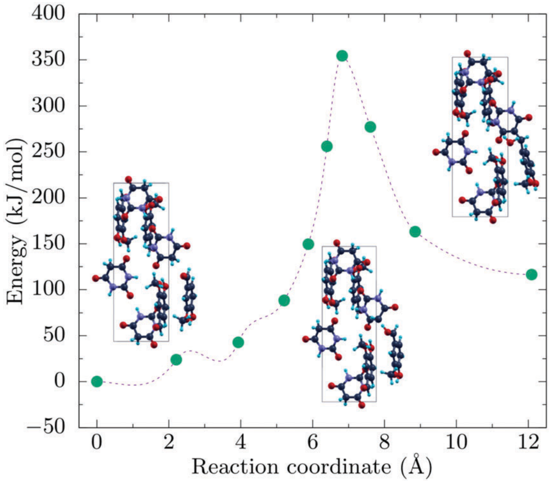

Fig. 3 Minimum energy path for the reaction of one molecule of barb and one molecule of van within the unit cell of the cocrystal. The dashed line is cubic spline interpolation and is a guide to the eye.

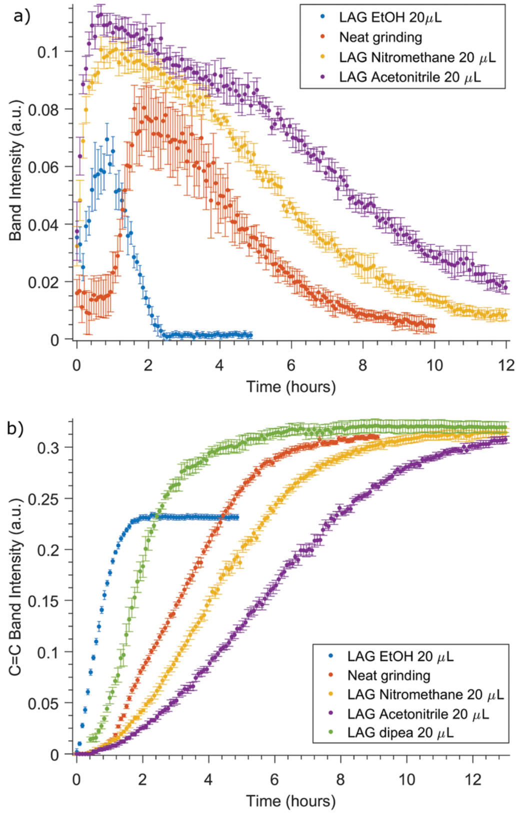

Fig. 4 (a) Formation kinetics and life-span of barb:van cocrystal in neat grinding and LAG reactions, derived from the cocrystal Raman band at 1735 cm^{-1}, and (b) kinetics of C═C bond formation derived from changes in intensities of the band at 1542 cm^{-1}. LAG with EtOH yielded **III** while other liquids yielded **I**. The intensity of the C═C band is lower in **III** than in **I**. Note the different scales in (a) and (b).

Since the neat grinding reaction takes over 14 hours to complete, we tried to accelerate the product formation with the use of liquid-assisted grinding.[18,32,33] Liquid additives are known to accelerate and also selectively direct mechanochemical reactions,[34,35] or even may act as an acid–base catalyst.[16] Here, we have explored LAG with the addition of 20 μL of acetonitrile (MeCN), nitromethane ($MeNO_2$), ethanol (EtOH) and *N*,*N*-diisopropylethylamine (dipea).

LAG with MeCN or $MeNO_2$ resulted in fast cocrystal formation which started 3 min into milling (Fig. 4a and Fig. S4, S5, ESI†). Surprisingly, the subsequent C═C bond formation was slowed down revealing a prolonged life-span of the cocrystal under those reaction conditions (Fig. 4). This can be explained by the stabilisation of the cocrystal with the liquid additives, as was previously observed in related systems.[35,36] However, the amorphous product **I** remained stable after 50 hours of neat grinding (Fig. S3, ESI†), and prolonged milling in LAG reactions resulted in transformation of **I** to new forms of the Knoevenagel condensation product, **II** and **III**, observed after *ca.* 15 and *ca.* 20 hours of continuous milling, respectively (Fig. S4 and S5, ESI†).

The new forms **II** and **III** are crystalline, as opposed to the amorphous form **I** (Fig. S2, ESI†), and each has a distinct Raman spectrum (Fig. S24, ESI†). According to solution NMR, both **II** and **III** are the expected Knoevenagel condensation product (Fig. S2, S12–S14 and S24, ESI†), and thermal analysis suggested that **I** and **II** are hydrates while **III** is likely anhydrous (Fig. S25–S28, ESI†). Formation of a hydrate product was previously suggested[3] and is not surprising since water is a byproduct of Knoevenagel condensation. This is corroborated by the crystal structure of **II**, also confirming the molecular structure of the Knoevenagel condensation product (Fig. 2c). Possible tautomeric variations in **II** and **III** are excluded based on ^{15}N solid-state NMR spectra which exhibited the same chemical shifts for nitrogen atoms (Fig. S20, ESI†).

The reaction using EtOH as a protic liquid additive revealed fast cocrystal formation, but also a significantly increased rate of C═C bond formation, which was complete within *ca.* 2 hours (Fig. 4 and Fig. S6, ESI†). Since other studied reactions were rather slow, we have chosen this reaction for a monitoring experiment using *in situ* synchrotron PXRD,[37–39] in tandem with Raman spectroscopy.[35,40] PXRD showed persistent but diminishing diffraction signals from reactants, and a weak signal coming from the cocrystal. The Knoevenagel product, however, for a limited period of 70 min milling, remained X-ray amorphous, but Raman spectroscopy revealed its formation soon into milling, as evidenced by the emergence of the C═C Raman band at 1542 cm^{-1} (Fig. S31, ESI†).

With dipea, a non-nucleophilic base, the reaction proceeded directly from reactants to **I** (Fig. S7, ESI†) circumventing the cocrystal. Bulky isopropyl and ethyl groups of dipea possibly could not achieve interactions that would stabilise the cocrystal, as was the case with other liquids. As a base, it also likely facilitates proton abstraction from barb and thus the nucleophilic attack on the carbonyl group of van, resulting in a faster reaction rate than in neat grinding.

Being able to isolate the barb:van cocrystal as a pure phase, we were also interested in thermal initiation of Knoevenagel condensation in the cocrystal.[17,24] Heating the cocrystal to 150 °C resulted in complete conversion to the anhydrous product **III** (Fig. S2, ESI†). Interestingly, our attempts to synthesise the cocrystal from solution failed (Fig. S30, ESI†), indicating that it may be accessible only by milling.[34,41]

Finally, we note a striking difference in the observed reactivity of barb and van in our hands and in a recent report by James and coworkers.[14] Namely, our reactions did not change the physical form of the reaction mixture and sticking of the reaction mixture to the milling media. A possible cause for this difference stems from the use of two small milling balls in our case, as compared to the use of one large (13.6 g) ball by James. Two balls, with their mutual collisions, could possibly clean one another, but more importantly, one large milling ball significantly heated the reaction mixture,[14] while two small milling balls cause a minor increase in temperature.[42,43] We believe strong heating in combination with a low melting point of vanillin (*ca.* 82 °C) could have caused eutectic melting of the reaction mixture, which could have readily changed the physical form of the reaction mixture. In addition, lower temperature in our milling setup also explains slower reactions, since even a small or moderate increase in temperature can dramatically influence mechanochemical reaction rates.[42,44]

In summary, we report, as far as we are aware, the first cocrystal as an intermediate in a mechanochemical organic reaction. Remarkably, the cocrystal suitably positioned the reacting centers for the subsequent carbon–carbon bond formation. Coupled with crystal engineering, this observation reveals possibilities for controlled use of cocrystals for targeted reactivity in milling reactions. Moreover, with the choice of liquid additives, we were able to affect cocrystal formation and its stability under milling. We also highlight the value of *in situ* reaction monitoring which enabled identification and isolation of this unique and easily overlooked intermediate. Currently, we are undertaking a detailed *in situ* kinetic study of this model organic reaction with the intention to elucidate the influence of liquid additives.

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Conflicts of interest

There are no conflicts of interest to declare.

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