Showcasing research from the laboratories of Professor Friščić, Department of Chemistry, McGill University, Québec, Canada and Professor Baltrusaitis, Lehigh University, U.S.A.

In situ monitoring of mechanochemical synthesis of calcium urea phosphate fertilizer cocrystal reveals highly effective water-based autocatalysis

Real-time and in situ monitoring of the mechanosynthesis of the calcium urea phosphate fertilizer cocrystal by Raman spectroscopy and synchrotron X-ray powder diffraction enabled the first quantitative observation of chemical autocatalysis in a milling reaction. Minute quantities of reaction by-product water, orders of magnitude smaller than those typical for liquid-assisted mechanochemistry, accelerate the neutralisation and cocrystallisation reactions through positive feedback kinetics. This indicates that acceleration of mechanochemistry by a liquid can sometimes be described through concepts based in catalysis. The authors thank Raphael Rychetsky on Unsplash for the background image.
In situ monitoring of mechanochemical synthesis of calcium urea phosphate fertilizer cocrystal reveals highly effective water-based autocatalysis†

Patrick A. Julien, Luzia S. Germann, Hatem M. Titi, Martin Etter, Robert E. Dinnebier, Lohit Sharma, Jonas Baltrusaitis and Tomislav Frisic†

Using the mechanochemistry of the calcium urea phosphate fertilizer cocrystal as a model, we provide a quantitative investigation of chemical autocatalysis in a mechanochemical reaction. The application of in situ Raman spectroscopy and synchrotron X-ray powder diffraction to monitor the reaction of urea phosphate and either calcium hydroxide or carbonate enabled the first quantitative and in situ study of a mechanochemical system in which one of the products of a chemical reaction (water) mediates the rate of transformation and underpins positive feedback kinetics. The herein observed autocatalysis by water generated in the reaction enables reaction acceleration at amounts that are up to 3 orders of magnitude smaller than in a typical liquid-assisted mechanochemical reaction.

The need for more sustainable agriculture and agrochemicals has driven the search for novel and efficient fertilizers, which minimize the negative environmental impacts of runoff and eutrophication.1–3 Recently, co-crystallization has emerged as a powerful approach to develop new solid forms of fertilizers, which could maximize absorption by crops while minimizing runoff, which negatively impacts the environment and human health via eutrophication.4–5 Urea phosphate is one of the most prevalent fertilizer components for the delivery of critical plant nutrients nitrogen and phosphorus, with the added benefit of reducing ammonia losses by enzymatic degradation.6 The loss of ammonia from urea fertilizers is further reduced by the presence of calcium, another key nutrient for plants, leading to improved formulations for simultaneous delivery of nitrogen, phosphorus and calcium.7–9 An example is calcium urea phosphate Ca[CO(NH₂)₂]₄(H₂PO₄)₂ (1), an example of an agrochemical ionic cocrystal.10–11 The cocrystal 1 is highly desirable as a fertilizer due to its stability, reduction in ammonia loss, while providing three critical nutrients and good moisture stability. Mechanochemical reactions, conducted by milling, grinding or extrusion, have emerged as an efficient and rapid route to synthesize a wide range of molecules and materials, from pharmaceutical cocrystals to metal–organic frameworks.12 Mechanochemistry has been shown to enable synthesis independent of the relative solubilities of reactants, providing an excellent opportunity to form agrochemical cocrystals that are typically based on inexpensive but poorly soluble ionic starting materials.13 Mechnochemistry enables rapid reactions, such as the green synthesis of calcium urea phosphate, from very poorly soluble inorganic precursors, such as calcium carbonate or calcium hydroxide, producing innocuous by-products of water and CO₂ (Fig. 1).

Here, we investigate and compare the mechanisms of mechanochemical formation of the agrochemical cocrystal 1 by a neutralization reaction from either Ca(OH)₂ or CaCO₃, using the recently developed techniques for monitoring mechanochemical reactions in real time using Raman spectroscopy and

Fig. 1 Mechanochemical synthesis of the agrochemical cocrystal 1 from urea, urea phosphate and either calcium hydroxide or carbonate. Calcium ions are shown in green, and hydrogen bonding interactions are displayed in light blue for 1 (CSD code URECAP10).
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further consistent with the sigmoidal behaviour being a result of water-based autocatalysis (see ESI†). The observed high sensitivity of mechanochemical reaction kinetics to deliberate additions of minute amounts of water is consistent with the proposed self-acceleration of reaction progress due to released water. This was further validated by probing the kinetics of reactions in which a fraction of the CaCO₃ reactant was replaced by an equivalent amount of Ca(OH)₂. Real-time monitoring by Raman spectroscopy of mechanochemical reactions with 5, 10, 13, and 17 mol% of CaCO₃ replaced by Ca(OH)₂ reveals immediate and significant improvement in reaction rate and shortening of the induction period (Fig. 4a). The Ca(OH)₂ reactant is expected to generate twice the amount of water by-product compared to CaCO₃, effectively acting as solid source of catalytic amounts of water. Real-time monitoring of the reactions permitted us to plot the time required for 50% conversion with respect to water added as a liquid, or in the form of Ca(OH)₂, revealing a non-linear relationship consistent with autocatalysis (Fig. 5a).

Autocatalytic behaviour was validated by analysing in situ data using an autocatalysis model for solid–state reactions, with respect to mol fraction of generated water (α):²⁹

\[
\frac{d\alpha}{dt} = k\alpha(1 - \alpha)
\]

While the amount of water in the reaction is not readily measured by Raman spectroscopy, in the reaction of CaCO₃ it should be equivalent to the amount of product formed. In the α range from 0.2 to 0.8, when the molar fraction of the product in the reaction is between 20% and 80%, eqn (1) yields a linear plot (Fig. 5b), consistent with water-mediated autocatalysis. The inability to obtain a linear fit during early and late phases of the reaction might be due to poor diffusion or mixing issues when the amount of product or reactants is low. It is remarkable that autocatalytic behavior can be observed at α = 0.2, which would correspond to ca. 1.2 μL of water generated in the reaction, and an approximate η of 0.007 μL mg⁻¹. Such η value is nearly three orders of magnitude lower than in a typical LAG reaction and, considering that the water is generated directly in the reaction, indicates that the observed reaction enhancement is an example of chemical autocatalysis rather than liquid-assisted₂⁶–₂⁸ mechanochemistry.

The herein presented autocatalytic behaviour is central for the ability to rapidly synthesize 1 without large amounts of water. The ability to accelerate synthesis by using water amounts that are minuscule even for LAG mechanochemistry is particularly important due to the high aqueous solubility of this material, which is beneficial for fertilizer use but hinders its preparation from solution. Once mechanochemically made, 1 exhibits properties highly desirable in a fertilizer. Thermal analysis reveals a high thermal stability for 1, which releases urea at 124 °C, a higher temperature compared to urea phosphate which decomposes at 116 °C (see ESI†). Moisture stability of 1 was compared to that of urea by dynamic vapour sorption.

Fig. 3 Real-time XRPD monitoring of the formation of 1: (a) time-resolved XRPD patterns of the reaction using CaCO₃ with corresponding calculated patterns for reactants and product shown above the plot and the reaction profile obtained by sequential Rietveld refinement of the in situ XRPD data shown below; (b) time-resolved XRPD patterns of the reaction using Ca(OH)₂ with corresponding calculated patterns for reactants and product shown above the plot and the reaction profile obtained by sequential Rietveld refinement of the in situ XRPD data shown below.
(DVS) across the relative humidity (RH) range from 0–95%, at 25 °C. The measurements confirm the ability of 1 to interact with water more strongly, while maintaining a more modest water absorption profile compared to urea (Fig. 6). For urea, increasing RH led to negligible water uptake until the deliquescence point at 74% RH, with further increases in humidity leading to continuous hygroscopic growth of the aqueous droplet. On decreasing RH, the droplet decreased in size, below 74% RH became supersaturated with respect to urea, and below 50% RH formed an effloresced particle. Cocrystal 1 exhibited a deliquescence phase transition at 65% RH, but no distinct efflorescence point, as evidenced by a continuous hysteresis down to low humidity values (<20% RH) values. The hysteresis and presence of absorbed water in 1 over a wide range of RH values suggests a continuous transition of the bound-to-free water, potentially due to strong hydrogen bonding to hydrophilic, polar groups of 1. While such behaviour is beneficial for fertilizer use, it also clearly illustrates the synthetic benefit of the herein demonstrated autocatalytic effect, as it enables access to 1 as a well-defined and dry (by TGA) solid, using only traces of water.

In conclusion, we used in situ X-ray diffraction and spectroscopy to provide direct and quantitative evidence of chemical autocatalysis in a mechanochemical reaction. The presented results further our understanding of fundamental principles and mechanisms of mechanochemistry, an area that has recently attracted significant interest. While chemical autocatalysis is not the only potential reason for appearance of sigmoidal kinetics in a mechanochemical reaction, this study provides direct evidence that such a model is relevant for mechanochemical reactions and, in principle, may be broadly applicable to water-forming acid–base milling reactions. The enhancement of mechanochemical reactions in liquid-assisted grinding can sometimes be explained by a purely physical effects of dissolution and having a liquid phase present.

Fig. 4 (a) Monitoring the relative rates of formation of 1 from CaCO3 (blue) and Ca(OH)2 (grey), as well as various mixtures. (b) The addition of small volumes of water to the synthesis of 1 from CaCO3, results in a significant increase in reaction rate as observed by in situ Raman spectroscopy. In each case the total weight of solid reactants was approximately 180 mg.

Fig. 5 (a) The reaction rate measured as the time required to reach 50% conversion as a function of the total equivalents (relative to calcium) of water present and/or generated in the system. (b) Reaction rate (dα/dt)/α vs. α, where α is the mol fraction of 1 as determined by in situ Raman spectroscopy for the synthesis using CaCO3 reactant. Linear behaviour is observed between α = 0.2 and 0.8, consistent with autocatalysis due to a reaction product. Fitting parameters are reported in the ESI.

Fig. 6 Adsorption/desorption branches of RH on urea and 1.
valuable material whose synthesis in solution is made
izer cocrystal material using only minuscule amounts of water,
value, as it enables the synthesis of a highly hygroscopic fertil-

The efficient autocatalysis observed herein is also of practical 
value, as it enables the synthesis of a highly hygroscopic fertil-
izer cocrystal material using only minuscule amounts of water,
even for standards of liquid-assisted mechanochemistry. This
demonstrates how water-based autocatalysis can be used to
greatly simplify the preparation of ionic cocrysalts and other
valuable material whose synthesis in solution is made

Conflicts of interest

T. F. is a co-founder of the company Form-Tech Scientific, Inc.
that manufactures some of the equipment used in this study.

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Notes and references

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Notes and references

† Sigmoidal profile of product formation for solvent-free (including mechano-
chemical) reactions can be also caused by kinetics related to product nucleation
and crystal growth, and such phenomena (for example polymorph transformation
or nucleation of metal-organic frameworks) have been observed in situ by both
synchronous X-ray diffraction, as well as by Raman spectroscopy, see: (a) G.
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