Electronic Supplementary Material (ESI) for Chemical Science.

Supplementary Information for:

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

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1. Experimental Procedures

a. Materials and Methods

Materials: All reagents were used as purchased without further purification. Calcium hydroxide and carbonate were purchased from ACP Chemicals (Montreal, QC) as ACS grade reagents. Urea (USP grade) and urea phosphate (98%) were purchased from Sigma Aldrich.

FTIR-ATR spectroscopy: Fourier-transform infrared attenuated total reflectance (FTIR-ATR) were recorded on Bruker Vertex 70 spectrometer with a RockSolid interferometer in the range of 3500-400 cm^{-1}.

X-ray powder diffraction (XRPD): Patterns used for *ex situ* qualitative analysis of the samples were collected as flat plate samples on a Bruker D2 diffractometer, using Ni-filtered Cu-*Kα* radiation on a zero background sample holder in Bragg-Brentano geometry, tension 30kV, and current 10 mA.

***In situ* Raman Spectroscopy:** Reactions were conducted in an approximately 10 mL sapphire milling jar, using a 2 g zirconia ball and a Retsch® MM400 mixer mill running at 30 Hz. These were monitored using a RamanRxn1™ analyzer by Kaiser Optical Systems Inc. every 10 seconds using a 785 nm laser. Spectra were dark and intensity corrected using the Holograms® software package before being processed. All data was processed using MATLAB in accordance with previously published procedures.[1]

***In situ* X-ray powder diffraction (XRPD):** Reactions were conducted in a 15 mL polymethylmethacrylate (PMMA) milling jar, using two 1.3 g stainless steel ball in a modified Retsch® MM400 mixer mill running at 30 Hz. Reaction monitoring was performed at the high-resolution powder diffraction beamline PETRA III (P02.1) beamline at DESY using an unfocused and collimated X-ray beam with the size of ca. 1 x 1 mm^2 and a time resolution of 10 seconds.

The beamline is equipped with a PerkinElmer 2D area detector. The wavelength was determined with the NIST NSR 660a (LaB_6) standard using two different detector positions, λ = 0.207 Å (59.9 keV). All 2D XRPD patterns were integrated using Dioptas.[2] Sequential Rietveld analysis was performed in TOPAS-Academic V5.[3] A silicon standard was measured under identical experimental conditions as the *in situ* monitoring experiments and was used to describe the instrumental profile function (IPF). The IPF was modelled with a modified Thompson-Cox-Hasting pseudo-Voight function using $|Z/cos^2(\theta)|^{0.5}$ for the Gaussian and $X\ tan(\theta)+Ycos(\theta)$ for the Lorentzian profile as implemented in TOPAS (for further information see [3]).

The background of each powder pattern was modelled with a Pawley pseudo-phase (*Pmmm*, a = 40 Å, $b = c$ = 0.1 Å, crystallite size with a Lorentzian crystallite size of 1.5). All XRPD pattern were analyzed from 0.5 to 5 ° 2θ. The known crystal structures calcite (Open Crystal Structure Database number 1010928), urea (CSD code UREAXX01), urea phosphate (CSD code CRBAMP01), and compound 1 (CSD code URECAP) were taken from the corresponding databases. The lattice parameters and crystallite size of each phase were refined from the powder pattern, where the phase was most prominent and fixed afterwards. During the sequential Rietveld refinement only the scale factor of each phase was freely refined.[4]

TGA and DSC experiments: Thermogravimetric analyses were performed on a Mettler-Toledo TGA DSC 1 Star$_e$ system thermobalance using alumina crucibles under air stream with the heating rate of 10 °C min^{-1}. The results were processed with the Mettler STARe 9.01 software.

Dynamic Vapor Sorption Experiments: The DVS Intrinsic dynamic vapor sorption (DVS) apparatus (Surface Measurement Systems, USA), equipped with an SMS ultrabalance with a mass resolution of ±0.1 µg, was used to obtain ramping and equilibrium water vapor sorption isotherms. Approximately 5 mg of powder samples was placed in the apparatus using aluminum pans and initially dried over 600 min with a stream of dry nitrogen to establish a dry mass at 25 °C. The dry mass was calculated after the end of the first drying stage (0% RH). The sorption cycle experiments were performed from 0% relative humidity (RH) to 95% RH in a step of 5% RH in a pre-programmed sequence before decreasing to 0% RH in a reverse order. The instrument maintained a constant target RH until the moisture content change per minute (*dm/dt*) was <0.002% per minute over a 10 min period.

The relative humidity (RH) here is defined as where P_o is the saturated vapor pressure of water at 298 K and 1 atm and P is the actual water pressure at the same temperature and pressure, e.g.

$$RH = \frac{P}{P_o} * \ 100\ (\%)$$

b. Synthesis

Calcium Carbonate Reactions: For all reactions containing only calcium carbonate as the calcium source, 40 mg of urea (0.67 mmol), 106 mg of urea phosphate (0.67 mmol), and 34 mg calcium carbonate (0.34 mmol) were combined in the milling vessel along with the milling ball(s). For liquid additions, 2.5 or 5 microliters of distilled water were added using a micropipette. For the reactions in with premade **1**, either 3 mg or 6 mg of **1** was added to the reaction mixture before milling.

Calcium Hydroxide Reactions: For all reactions containing only calcium hydroxide as the calcium source, 42 mg of urea (0.7 mmol), 111 mg of urea phosphate (0.7 mmol), and 26 mg calcium hydroxide (0.35 mmol) were added into the milling vessel along with the milling ball(s).

Mixed Reactions: Reactions containing both calcium hydroxide and calcium carbonate were run with 40 mg of urea (0.67 mmol), and 106 mg of urea phosphate (0.67 mmol) with the following amounts of calcium carbonate and hydroxide:

mol% $Ca(OH)_2$ to $CaCO_3$	**5**	**10**	**13**	**17**
mg of $CaCO_3$	31.6	30	28.3	26.6
mg $Ca(OH)_2$	1.17	2.2	3.14	3.94

2. Reaction rheology

Figure SI-1. Visual difference in reaction rheology between the synthesis of calcium urea phosphate from calcium hydroxide (left) and calcium carbonate (right). The calcium hydroxide reaction proceeds more as a wet paste, in contrast to the solid powder present in the reaction of calcium carbonate. The rheology of the product after full conversion is similar between calcium carbonate and calcium hydroxide.

3. Comparison of Raman signal in PMMA vs. sapphire milling jars

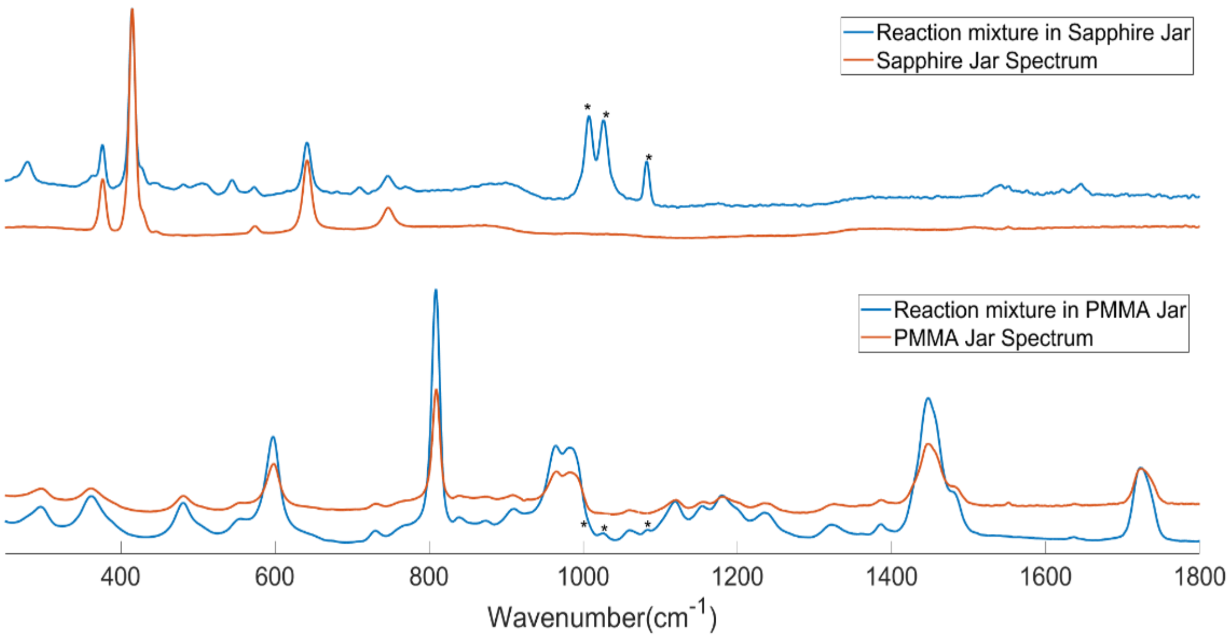

Figure SI-2. Normalized *in situ* Raman spectra for the reaction of calcium carbonate with urea and urea phosphate in sapphire (top) and PMMA (bottom) jars. * denote the most prominent peaks of the starting materials of the reaction.

4. Kinetic Analysis of reaction of $CaCO_3$ with urea and urea phosphate

a. Data Trendline

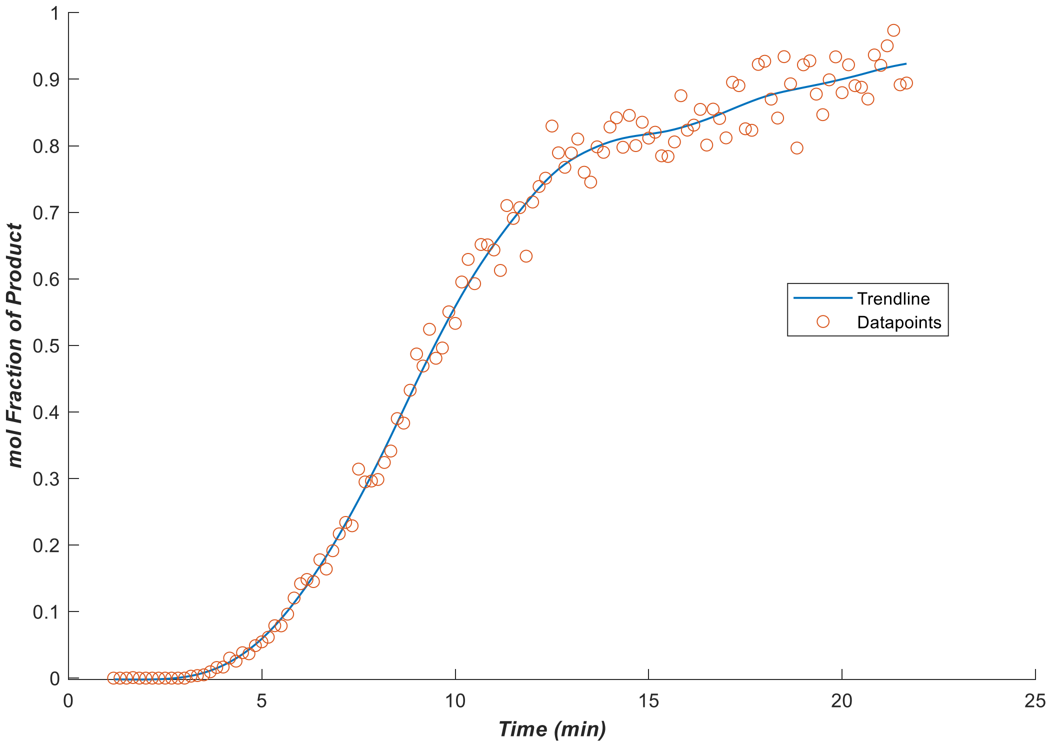

Figure SI-3. mol fraction of calcium-urea-phosphate in the reaction of calcium carbonate, urea, and urea phosphate from *in situ* Raman spectroscopy. Trendline generated via smoothing spline fitting in the curve fitting toolbox of MATLAB.

Fitting results and Parameters for Smoothing Spline fit:

Smoothing spline:

f(x) = piecewise polynomial computed from p

Smoothing parameter, p:	0.39472418
Sum of Squares Due to Error:	0.08659
R-square:	0.9943
Adjusted R-square:	0.9938
RMSE:	0.02771

b. Reaction Rate: Derivative of mol fraction trendline

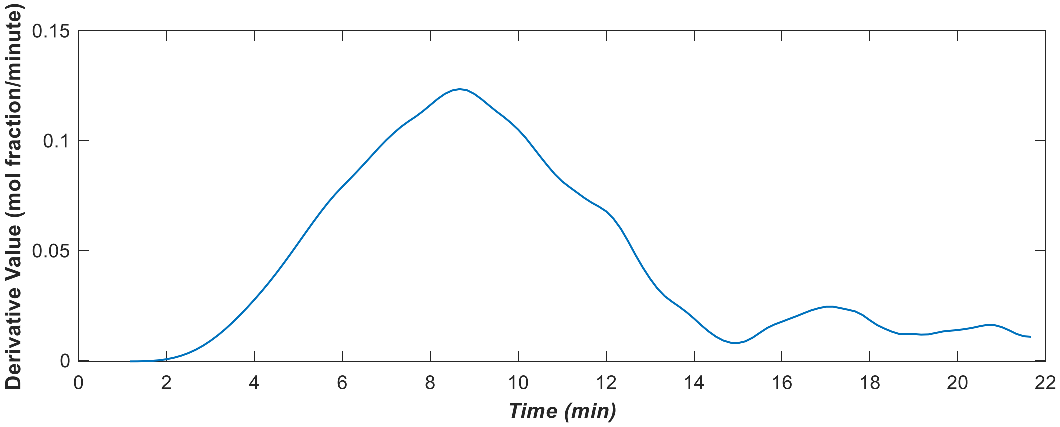

Figure SI-4. Computed derivative (using MATLAB *differentiate* function) of the trendline of the mol fraction of product, with parabolic shape characteristic of autocatalytic reactions.

Fitting results and Parameters for Figure 7:

Linear model Poly1:

f(x) = p1*x + p2

Coefficients (with 95% confidence bounds):

p1 = -0.7183 (-0.7385, -0.698)

p2 = 0.6006 (0.589, 0.6121)

Goodness of fit:

Sum of Squares Due to Error:	0.006319
R-square:	0.9923
Adjusted R-square:	0.9921
RMSE:	0.01257

5. XRPD Data

a. Starting Materials

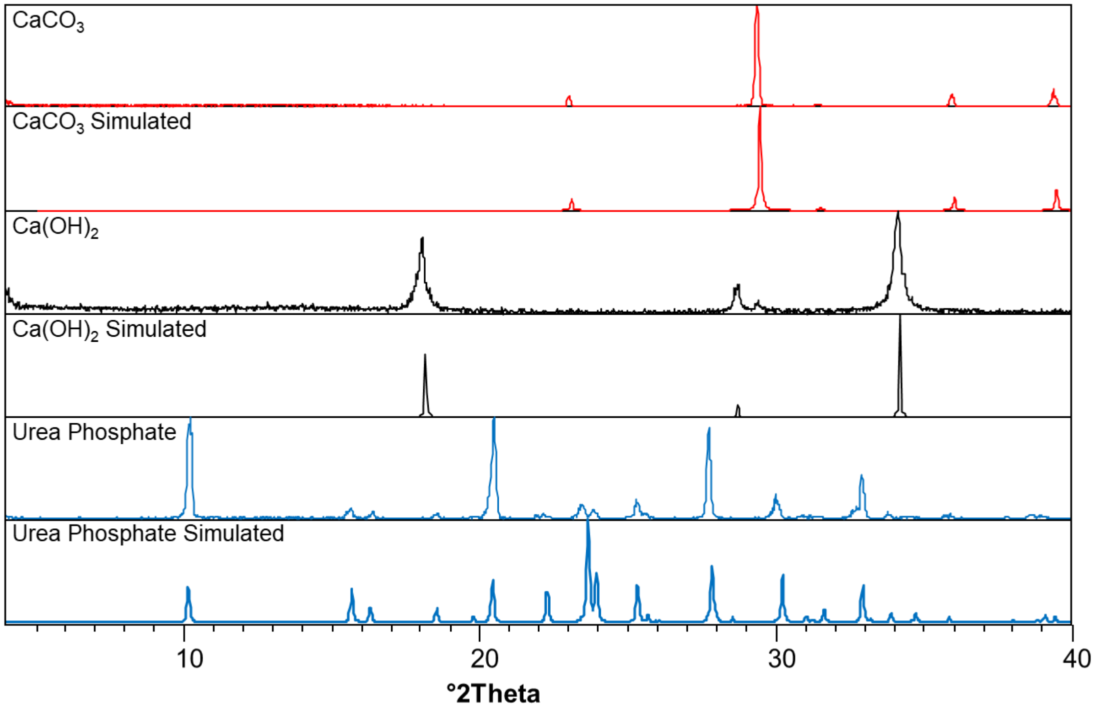

Figure SI-5. Measured and calculated XRPD patterns of the reactants used. A small amount of calcium carbonate can be observed in calcium hydroxide pattern.

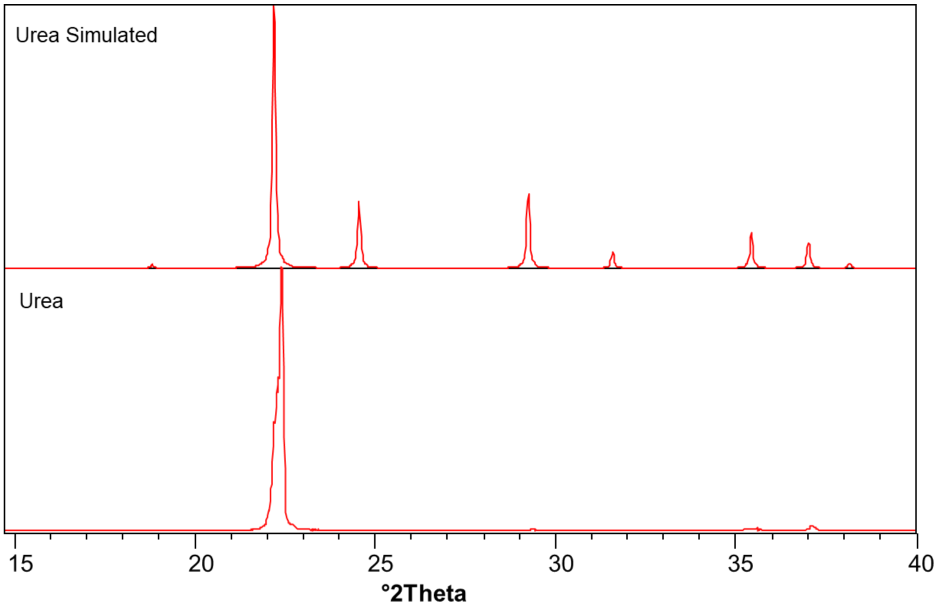

Figure SI-6. Simulated (top) and measured (bottom) XRPD patterns of urea. A very strong preferred orientation effect is observed in the sample.

b. Products

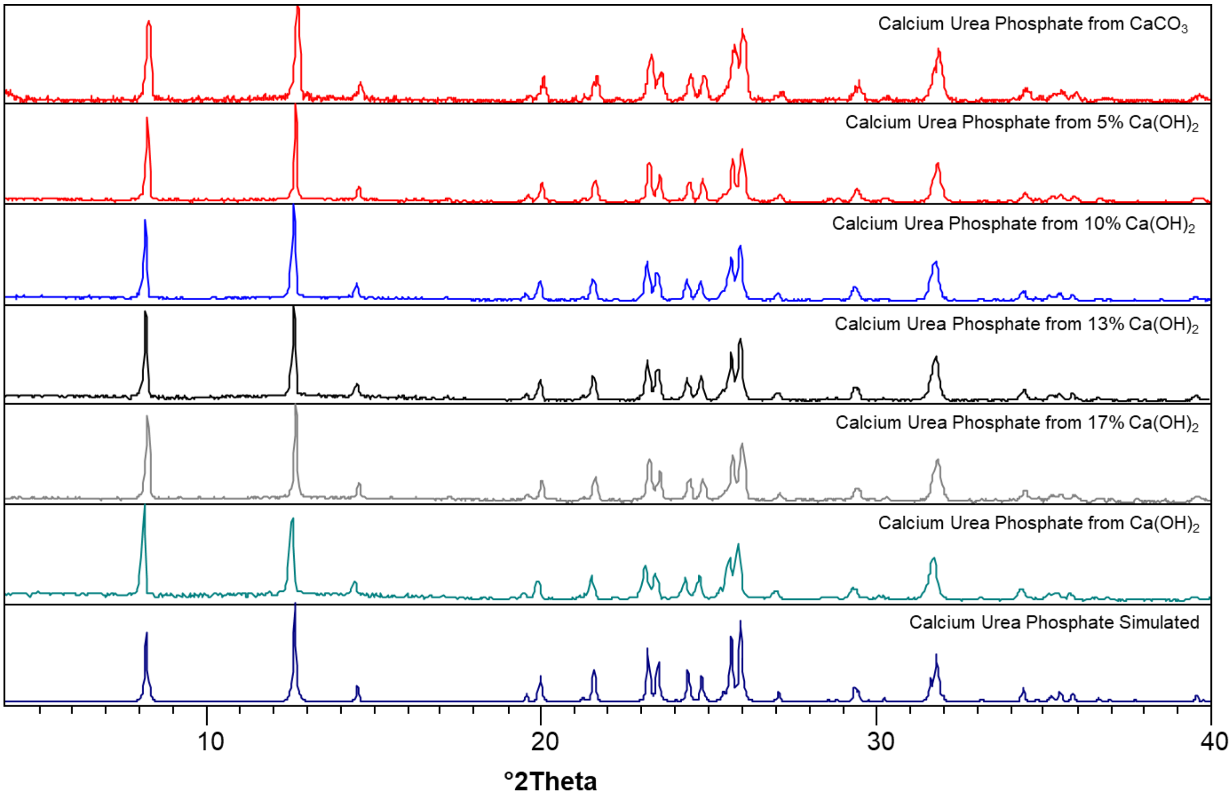

Figure SI-7. XRPD patterns of the reaction products. All products match the simulated XRPD pattern of **1** (calcium urea phosphate, CSD code URECAP) at the bottom.

6. Infrared Spectroscopy Data

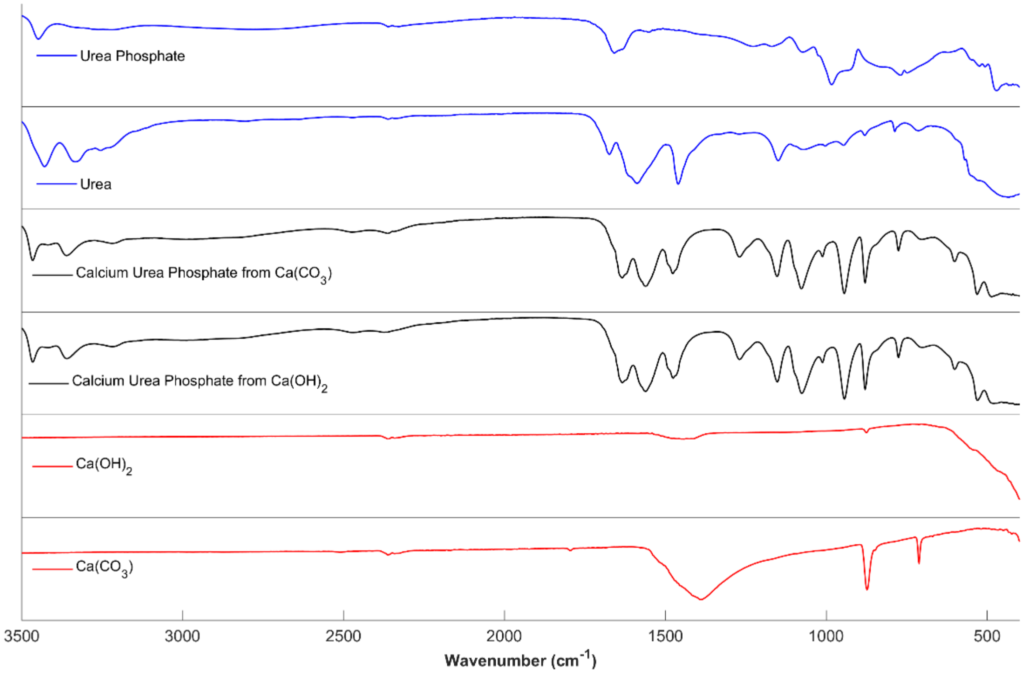

Figure SI-8. Comparison FTIR spectra of both calcium sources (red), urea and urea phosphate (red), and **1** (calcium urea phosphate) synthesized from both calcium hydroxide and calcium carbonate (black).

7. *In situ* Raman Datasets

a. Reactions with $Ca(OH)_2$ reactant

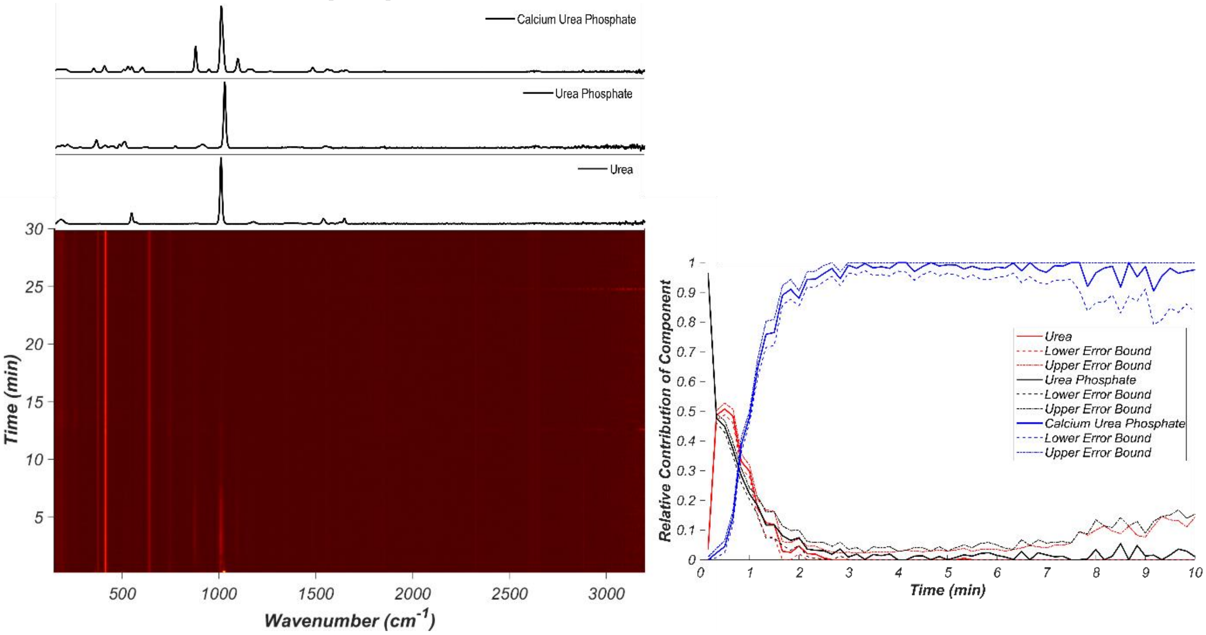

Figure SI-9. (Bottom Left) *In situ* Raman spectra for the synthesis of **1** (calcium urea phosphate) from calcium hydroxide. Calcium hydroxide is not visible due to poor intensity of the signal, so the data was fit with the Raman spectra urea and urea phosphate reactants, and calcium urea phosphate product (top left). (Bottom Right) Non-negative least squares fitting profiles, error bounds correspond to two times the standard deviation of the residual.

b. Datasets for reactions with $CaCO_3$ and $Ca(OH)_2$ reactants

Reaction of 5 mol% $Ca(OH)_2$ and 95 mol% $CaCO_3$

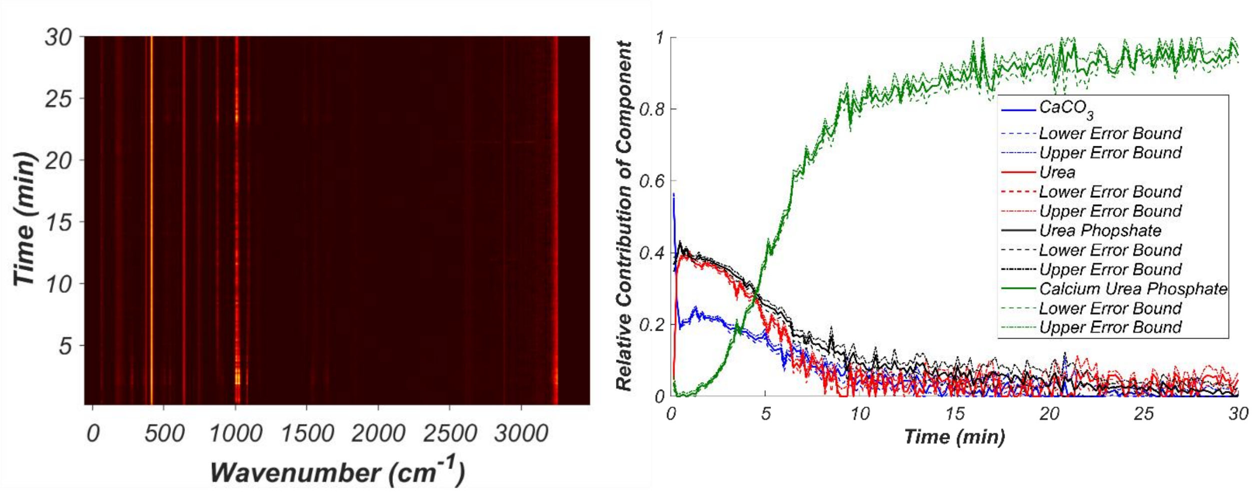

Figure SI-10. (Left) *In situ* Raman spectra for the synthesis of **1** (calcium urea phosphate) from calcium carbonate with the addition of 5 mol% $Ca(OH)_2$. (Right) Non-negative least squares fitting profiles, with errors corresponding to two times the standard deviation of the residual.

Reaction of 10 mol% $Ca(OH)_2$ and 90 mol% $CaCO_3$

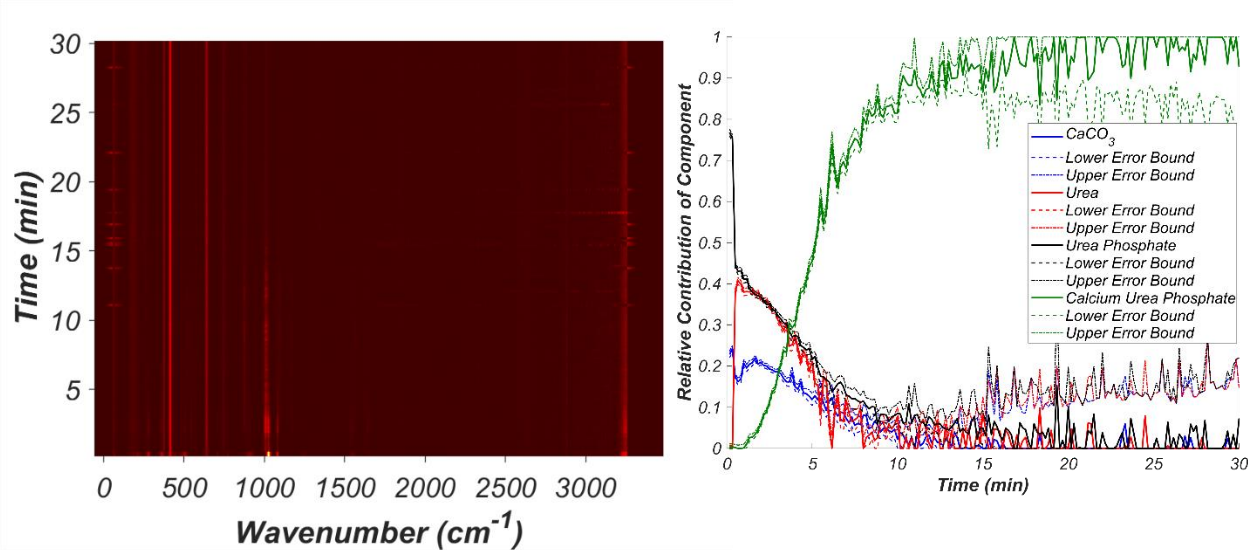

Figure SI-11. (Left) *In situ* Raman spectra for the synthesis of **1** (calcium urea phosphate) from calcium carbonate with the addition of 10 mol% $Ca(OH)_2$. (Right) Non-negative least squares fitting profiles, with errors corresponding to two times the standard deviation of the residual.

Reaction of 13 mol% $Ca(OH)_2$ and 87 mol% $CaCO_3$

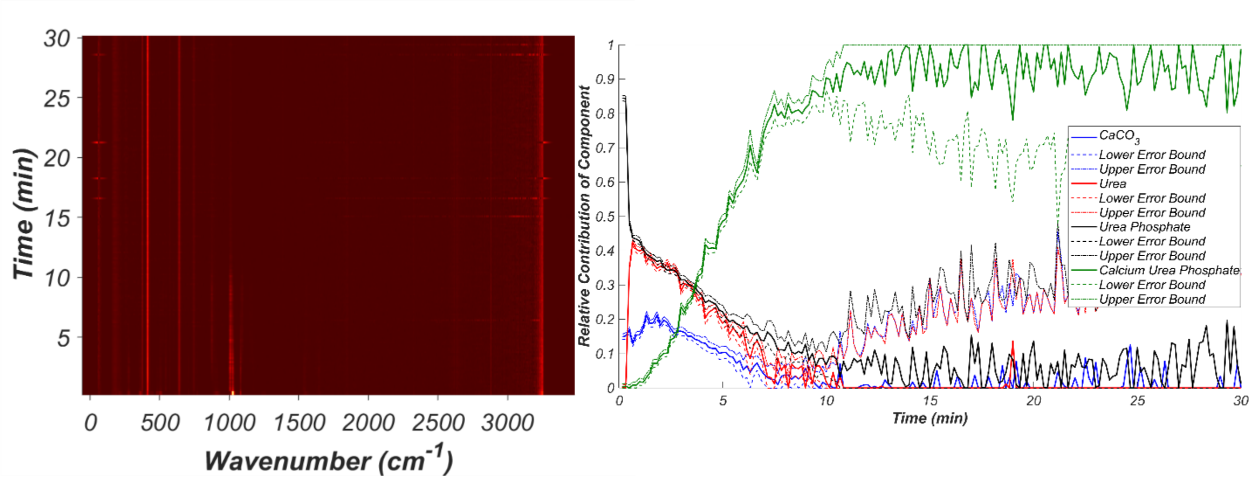

Figure SI-12. (Left) *In situ* Raman spectra for the synthesis of **1** (calcium urea phosphate) from calcium carbonate with the addition of 13 mol% $Ca(OH)_2$. (Right) Non-negative least squares fitting profiles, with errors corresponding to two times the standard deviation of the residual.

Reaction of 17 mol% $Ca(OH)_2$ and 83 mol% $CaCO_3$

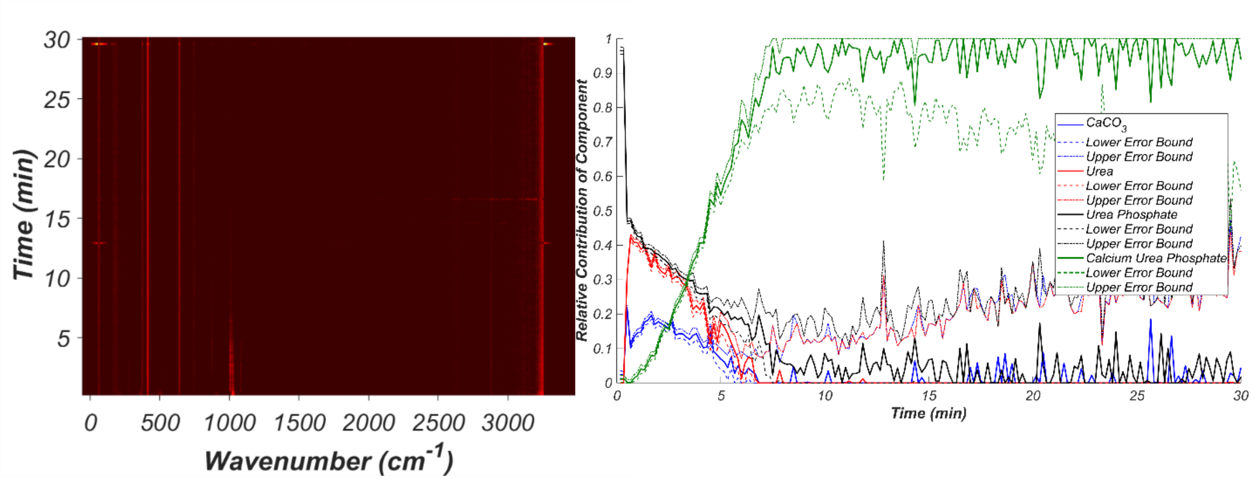

Figure SI-13. (Left) *In situ* Raman spectra for the synthesis of **1** (calcium urea phosphate) from calcium carbonate with the addition of 17 mol% $Ca(OH)_2$. (Right) Non-negative least squares fitting profiles, with errors corresponding to two times the standard deviation of the residual.

c. Datasets for reactions with deliberate addition of water

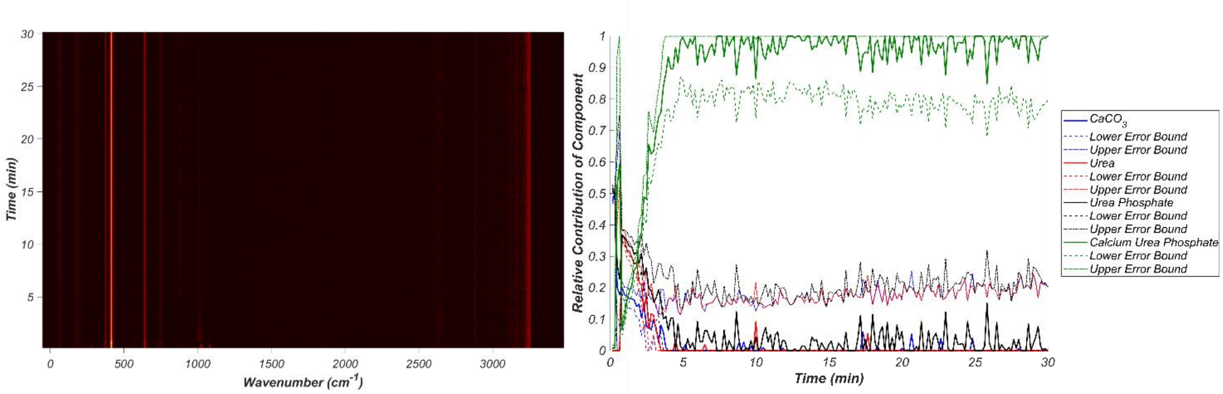

Figure SI-14. (Left) *In situ* Raman spectra for the synthesis of **1** (calcium urea phosphate) from calcium carbonate with the addition of 2.5 µL of water. (Right) Non-negative least squares fitting profiles, with errors corresponding to two times the standard deviation of the residual.

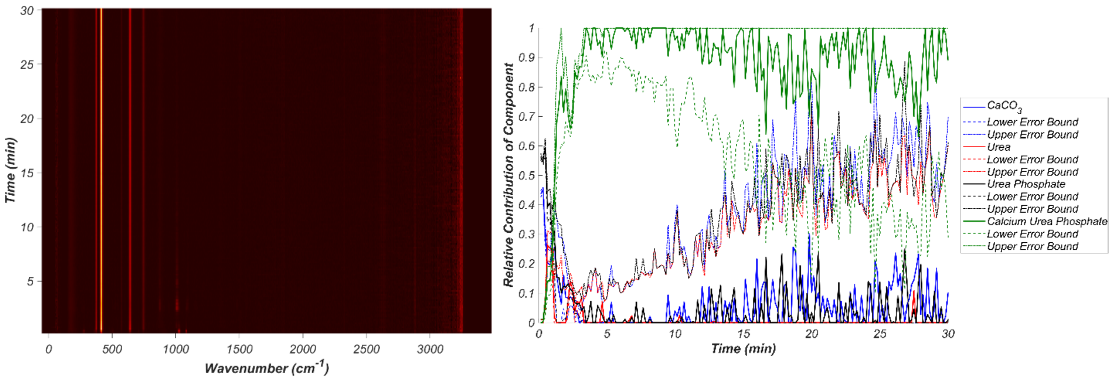

Figure SI-15. (Left) *In situ* Raman spectra for the synthesis of **1** (calcium urea phosphate) from calcium carbonate with the addition of 5 µL of water. (Right) Non-negative least squares fitting profiles, with errors corresponding to two times the standard deviation of the residual.

d. Datasets for Reactions in the Presence of Pre-made Compound 1

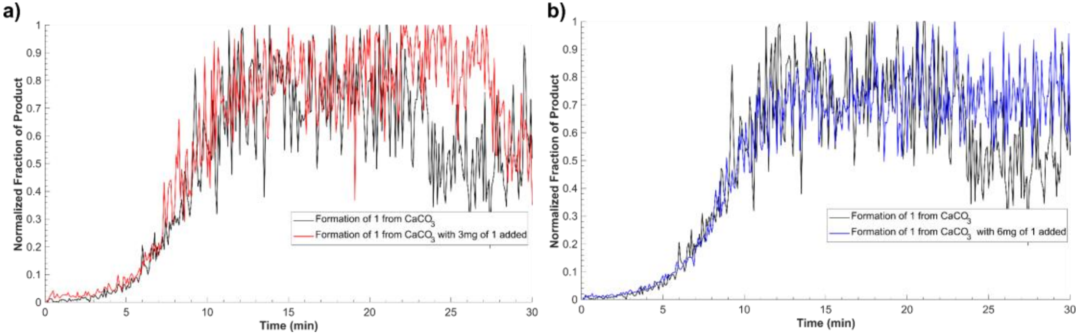

Figure SI-16. Comparison of the kinetics of formation of compound **1** from $CaCO_3$ via *in situ* Raman spectroscopy (black, trace), with the kinetics for the same reaction conducted with the addition of either 3 mg (a, red trace) or 6 mg (b, blue trace) of pre-synthesized **1**. The lack of any significant change in reaction profile suggests that the observed autocatalytic effects are not due to nucleation of **1**. Datasets for these reactions are found in the subsequent figures.

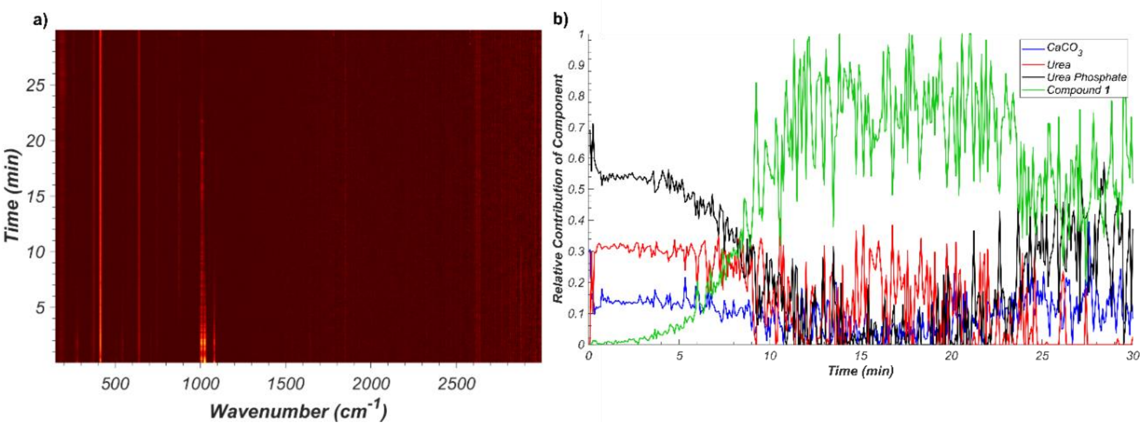

Figure SI-17. a) *In situ* Raman spectra for the synthesis of **1** (calcium urea phosphate) from calcium carbonate. b) Non-negative least squares fitting profiles estimated for the dataset.

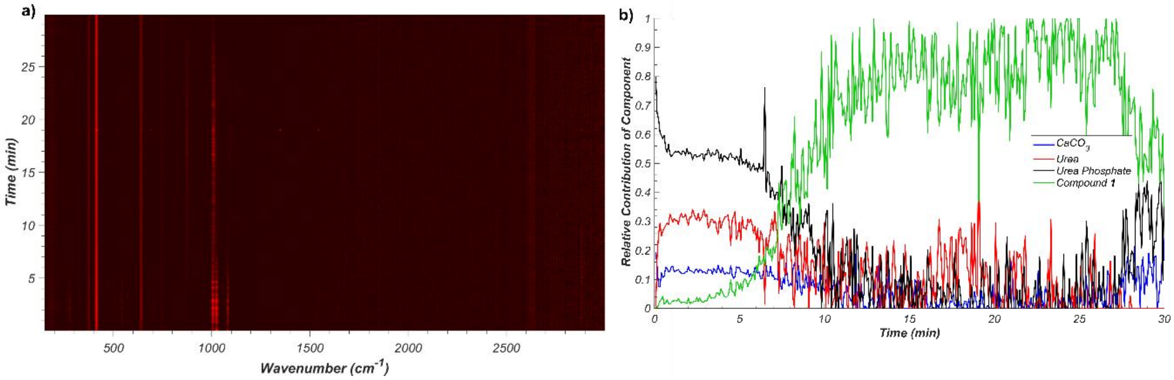

Figure SI-18. a) *In situ* Raman spectra for the synthesis of **1** (calcium urea phosphate) from calcium carbonate with the addition of 3 mg of pre-synthesized compound **1**. b) Non-negative least squares fitting profiles estimated for the dataset.

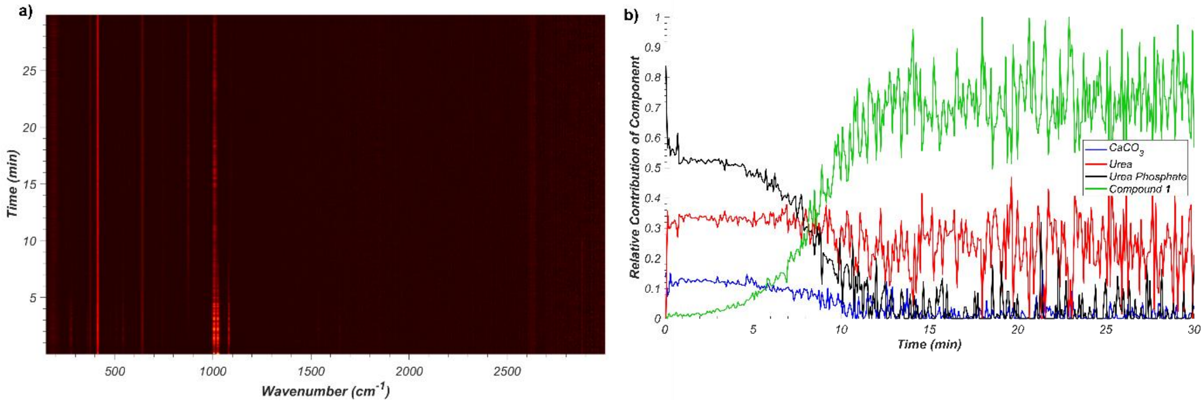

Figure SI-19. a) *In situ* Raman spectra for the synthesis of **1** (calcium urea phosphate) from calcium carbonate with the addition of 6mg of pre-synthesized compound **1**. b) Non-negative least squares fitting profiles estimated for the dataset.

8. XRPD Patterns of starting materials

a. XRPD patterns of reactants

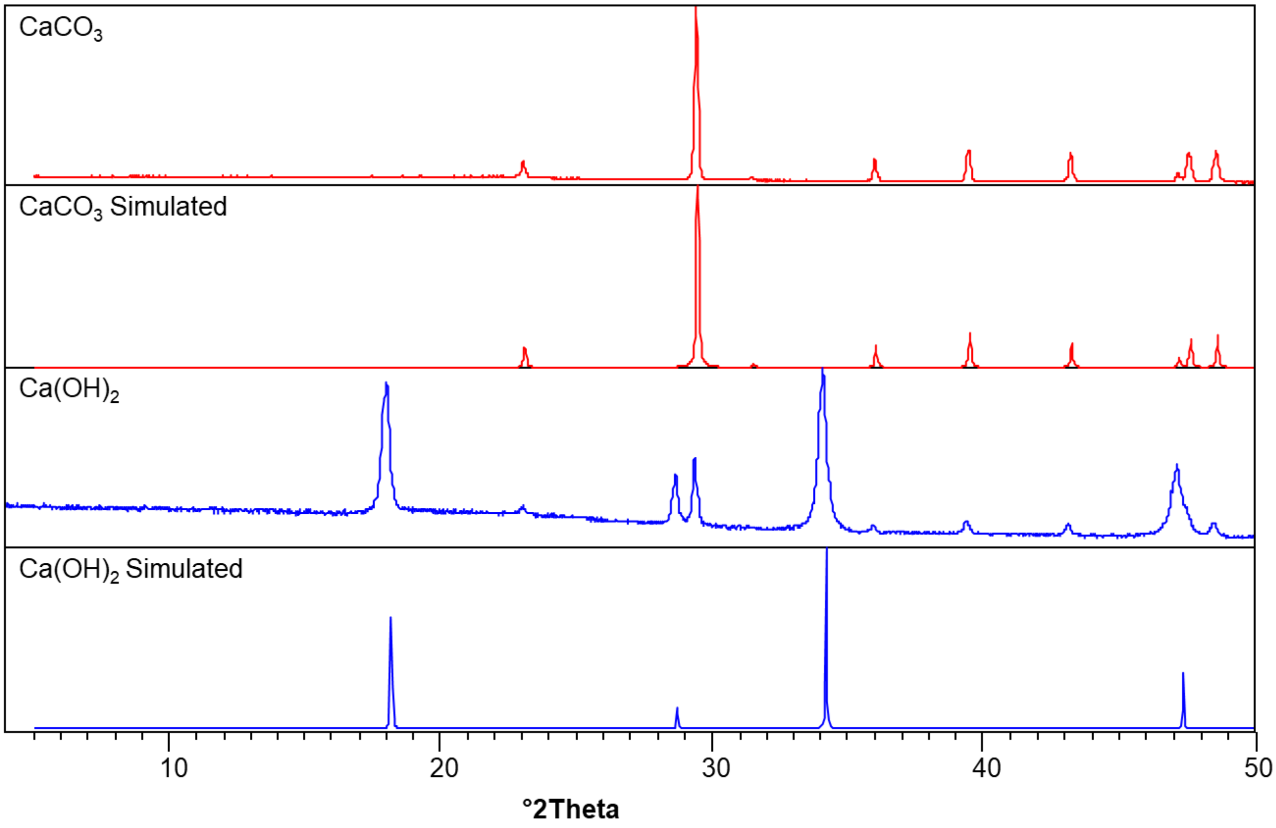

Figure SI-20. Comparison of measured and calculated XRPD patterns of the reaction starting materials used for the *in situ* XRPD measurements. The calcium carbonate phase appears to be pure while the calcium hydroxide phase contains calcium carbonate.

9. TGA/DSC Data

a. Calcium Carbonate

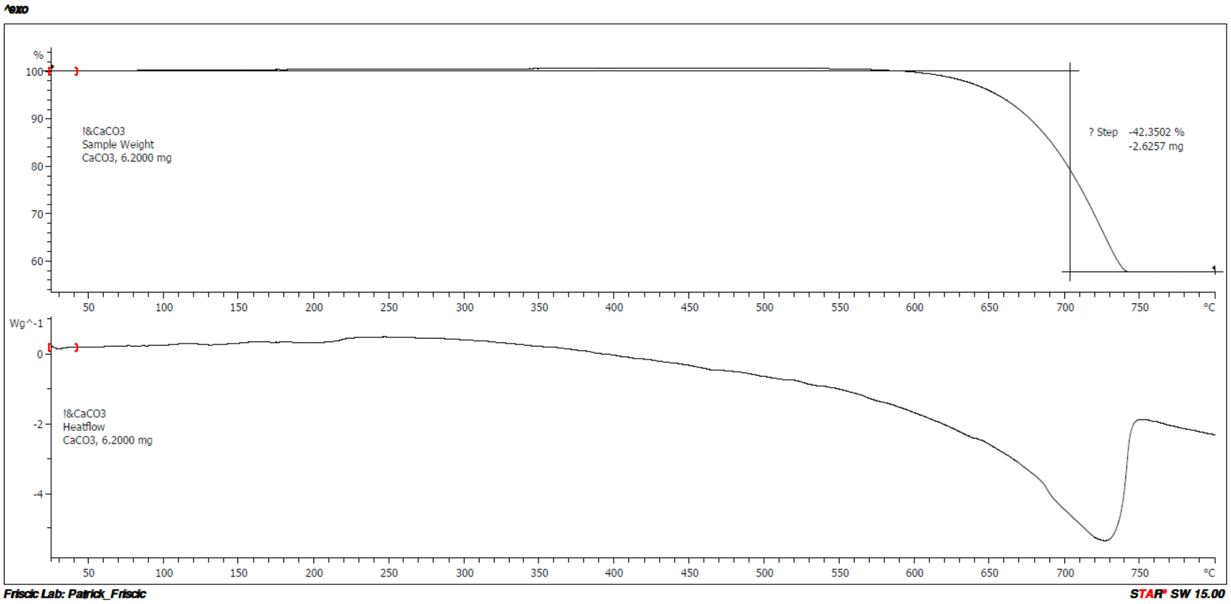

Figure SI-21. TGA (top) / DSC (bottom) curves for calcium carbonate.

b. Calcium Hydroxide

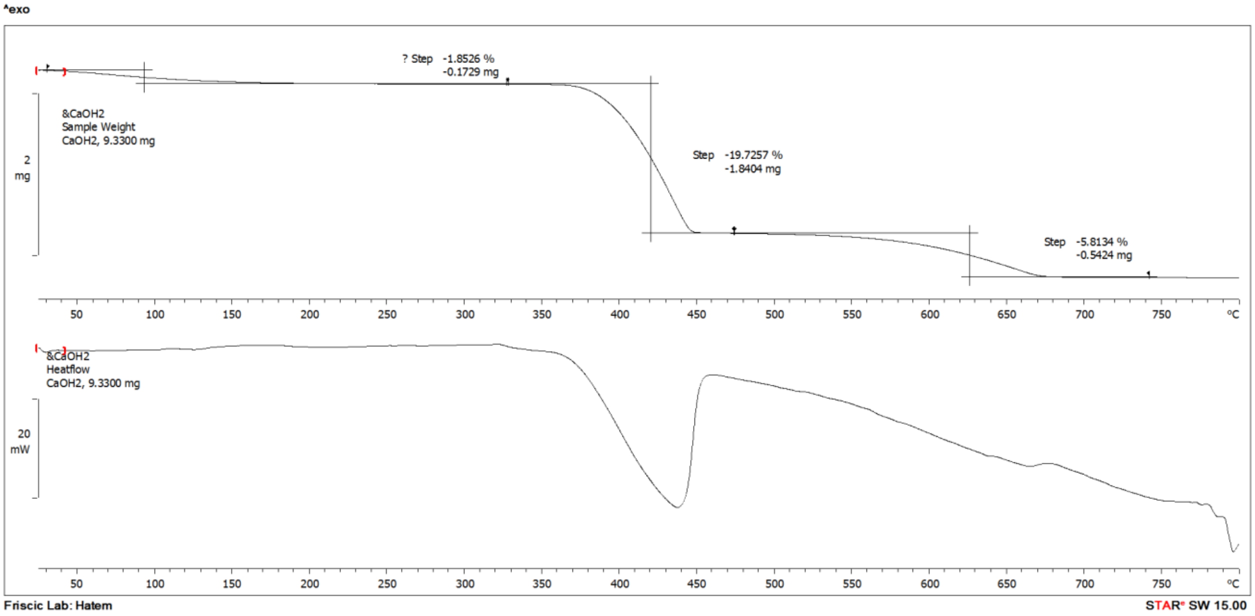

Figure SI-22. TGA (top) / DSC (bottom) curves for calcium hydroxide, showing small water loss less than 2%.

c. Urea

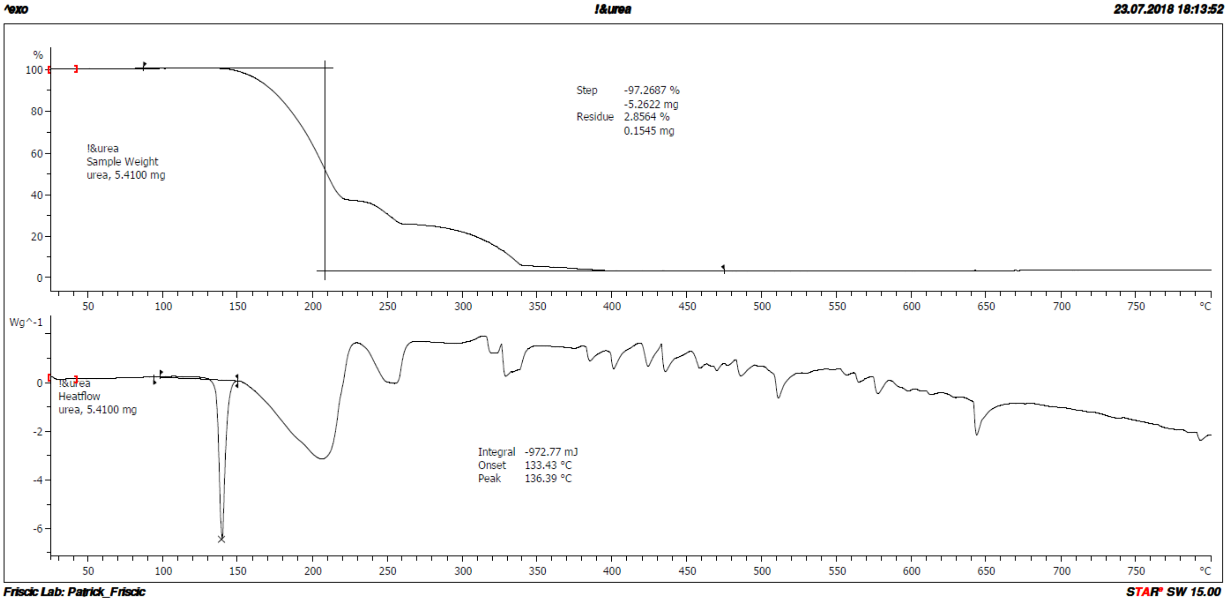

Figure SI-23. TGA (top) / DSC (bottom) curves for urea. Melting near 136 °C precedes decomposition beginning near 150 °C.

d. Urea Phosphate

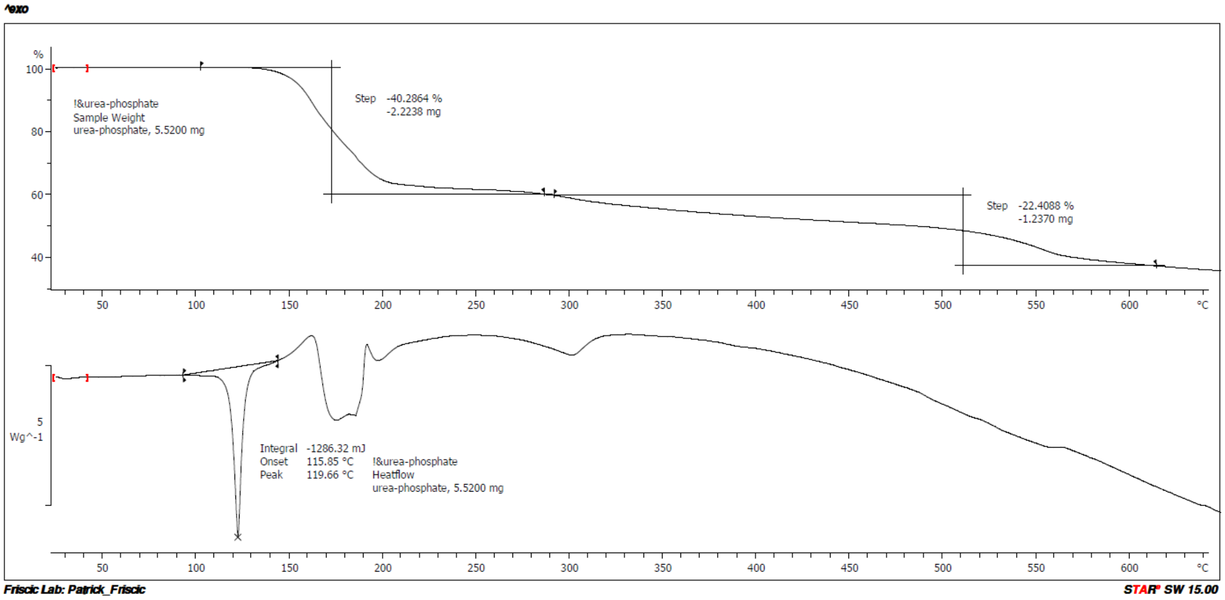

Figure SI-24. TGA (top) / DSC (bottom) curves for urea phosphate. Melting near 120 °C precedes decomposition beginning near 140 °C.

e. Compound **1** (Calcium Urea Phosphate)

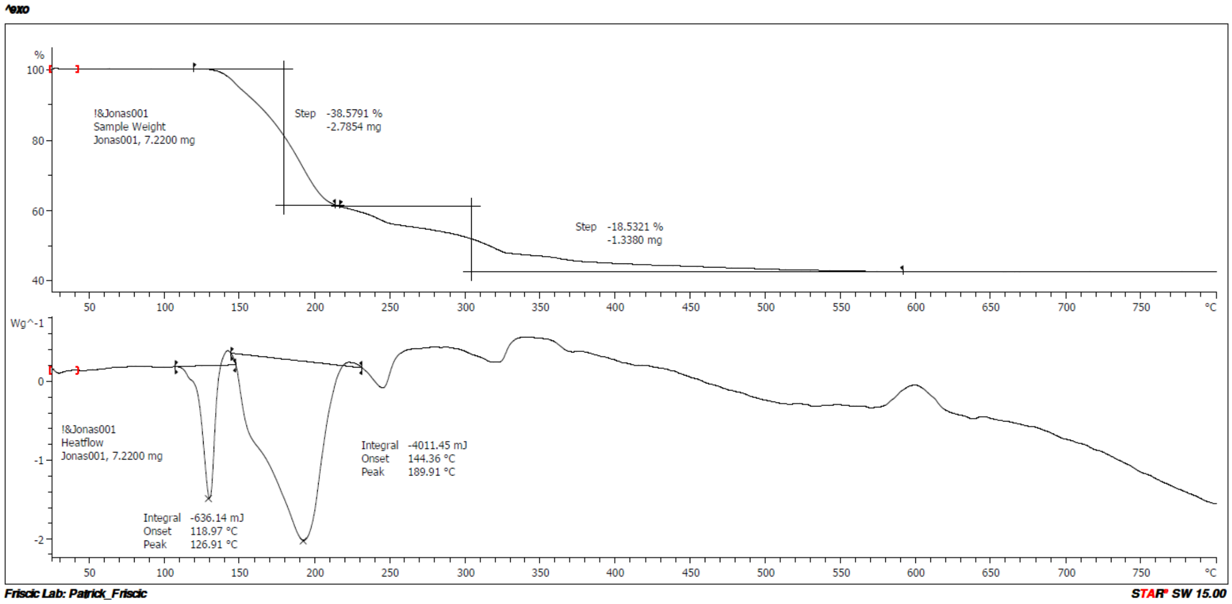

Figure SI-25. TGA (top) / DSC (bottom) curves for **1** (calcium urea phosphate), as synthesized from $Ca(CO_3)$. Melting near 125 °C precedes decomposition beginning near 150 °C.

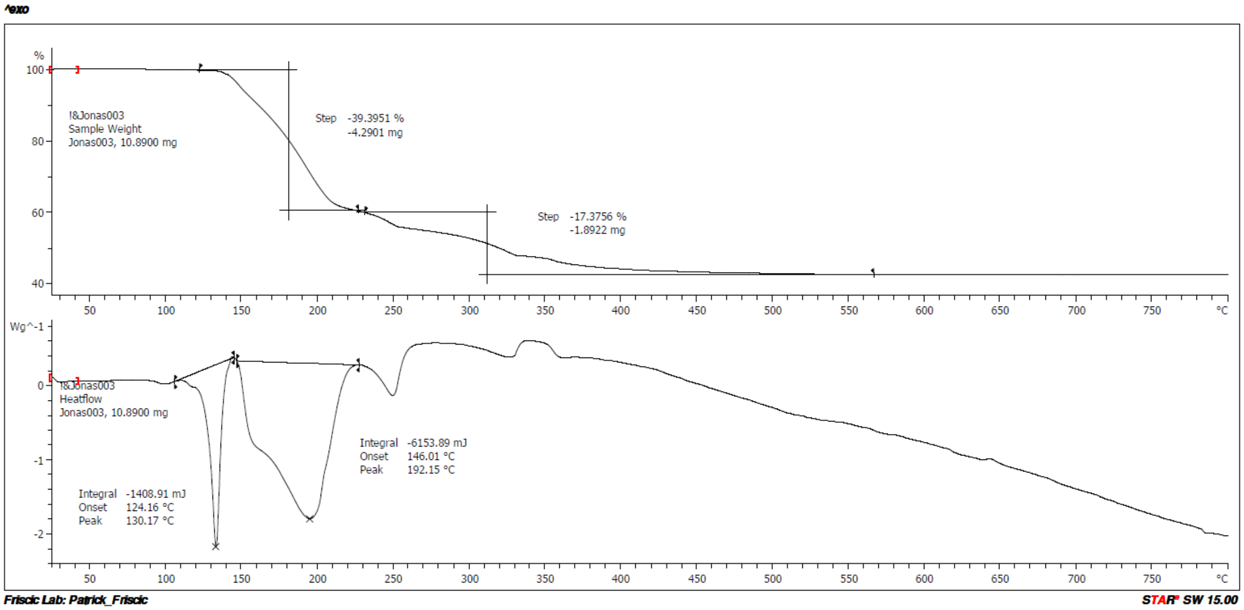

Figure SI-26. TGA (top) / DSC (bottom) curves for **1** (calcium urea phosphate), as synthesized from $Ca(OH)_2$. Melting near 128 °C precedes decomposition beginning near 150 °C.

10. References

1. P. A. Julien, I. Malvestiti and T. Friščić, *Beil. J. Org. Chem.*, 2017, **13**, 2160-2168.
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3. a) A. Coelho, Topas Academic Version 5, Coelho Software, Brisbane, 2012

   b) R. A. Young, *Introduction to the Rietveld method*, Oxford University Press, 1993.
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