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Electronic Supplementary Information

Monitoring polymer-assisted mechanochemical cocrystallisation through *in situ* X-ray powder diffraction

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1. METHODS

1.1. Synthetic procedure

All reactions were performed with a total reactant mass of 300 mg with 2 x 7 mm (1.38 g each) steel balls using the *CBL* mill, developed (by *C*asati, *B*an, *L*ange) at the X04SA Material Science (MS) beamline at the Swiss Light Source (SLS) in Villigen, Switzerland.[1] The mill was operated at a milling frequency of 30 Hz.

Neat grinding experiments

121.4 mg (0.92 mmol) glutaric acid and 178.7 mg (0.92 mmol) caffeine were milled without the addition of a grinding additive.

LAG experiments using acetonitrile (ACN)

121.5 mg (0.92 mmol) glutaric acid and 178.7 mg (0.92 mmol) caffeine were milled with 15 µL (η = 0.05 μL/mg) ACN.

121.4 mg (0.92 mmol) glutaric acid and 178.8 mg (0.92 mmol) caffeine were milled with 35 µL (η = 0.12 µL/mg) ACN.

121.5 mg (0.92 mmol) glutaric acid and 178.5 mg (0.92 mmol) caffeine were milled with 50 µL (η = 0.17 µL/mg) ACN.

LAG experiments using 1-dodecanol

121.7 mg (0.92 mmol) glutaric acid and 179.2 mg (0.92 mmol) caffeine were milled with 15 µL (η = 0.05 µL/mg) 1-dodecanol.

121.8 mg (0.92 mmol) glutaric acid and 178.6 mg (0.92 mmol) caffeine were milled with 35 µL (η = 0.12 µL/mg) 1-dodecanol.

121.7 mg (0.92 mmol) glutaric acid and 178.5 mg (0.92 mmol) caffeine were milled with 50 µL (η = 0.17 µL/mg) 1-dodecanol.

POLAG experiments using PEG-3000

121.4 mg (0.92 mmol) glutaric acid and 178.8 mg (0.92 mmol) caffeine were milled with 15.4 mg polyethylene glycol 3000 (PEG-3000), δ = 0.05.

121.5 mg (0.92 mmol) glutaric acid and 178.6 mg (0.92 mmol) caffeine were milled with 35 mg PEG-3000, δ = 0.12.

121.4 mg (0.92 mmol) glutaric acid and 178.6 mg (0.92 mmol) caffeine were milled with 149.6 mg PEG-3000, δ = 0.50.

LAG experiments using PEG-10’000

121.1 mg (0.92 mmol) glutaric acid and 178.5 mg (0.92 mmol) caffeine were milled with 15 mg polyethylene glycol 10’000 (PEG-10’000), δ = 0.05.

121.5 mg (0.92 mmol) glutaric acid and 178.5 mg (0.92 mmol) caffeine were milled with 35.1 mg PEG-10’000, δ = 0.12.

121.5 mg (0.92 mmol) glutaric acid and 178.3 mg (0.92 mmol) caffeine were milled with 149.4 mg PEG-10’000, δ = 0.50.

1.2 *In situ* synchrotron XRPD

The *in situ* XRPD experiments were performed at the X04SA Materials Science (MS) beamline at the Swiss Light Source (SLS), Paul Scherrer Institute.[2] For all measurements a monochromatic beam was used with an energy of 17.48 keV (λ = 0.709452 Å), a collimated Xray beam with the size of ca. 400 x 400 µm, and a Pilatus 6M detector. The exact wavelength was refined using a calibrated LaB_6 standard (SRM 660a, NIST USA). The measured 2D XRPD patterns were calibrated using Dioptas[3] and integrated using the Bubble software.[4]

All *in situ* milling experiments were performed with a total reactant mass of 300 mg in using the *CBL* mill[1] with steel jars and 2 x 7 mm (1.38 g each) steel balls operated at 30 Hz. Each XRPD pattern was measured with a time-resolution of 10s. Background subtracted 2D XRPD plots (milling time *versus* scattering angle) were created using MATLAB.

A LaB_6 standard was measured under identical experimental conditions as the other experiments and was used to describe the instrumental profile function (IPF). The IPF was modelled by convoluting a hat, a Lorentzian, and a Gaussian function. 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 2.7 to 22.4 ° 2θ, excluding the steel signal from the jar around 20 ° 2θ. The known crystal structures of caffeine (CSD code NIWFEE03), glutaric acid (CSD code GLURAC04), (caf)·(glu) – Form I (CSD code EXUQUJ04), and (caf)·(glu) – Form II (CSD code EXUQUJ) were obtained from the Cambridge Structural Database (CSD). The lattice parameters and microstructure of each phase were refined from the powder pattern, where the phase was most prominent and fixed afterwards. During the sequential Rietveld refinements only the scale factor of each phase was freely refined.[5]

Qualitative assessment of reaction progress and rate was conducted by measuring the time delay until the reaction started (induction time), as well as the time when 50 % conversion of Form I or Form II was reached ($\tau_{1/2}$).

2. RESULTS

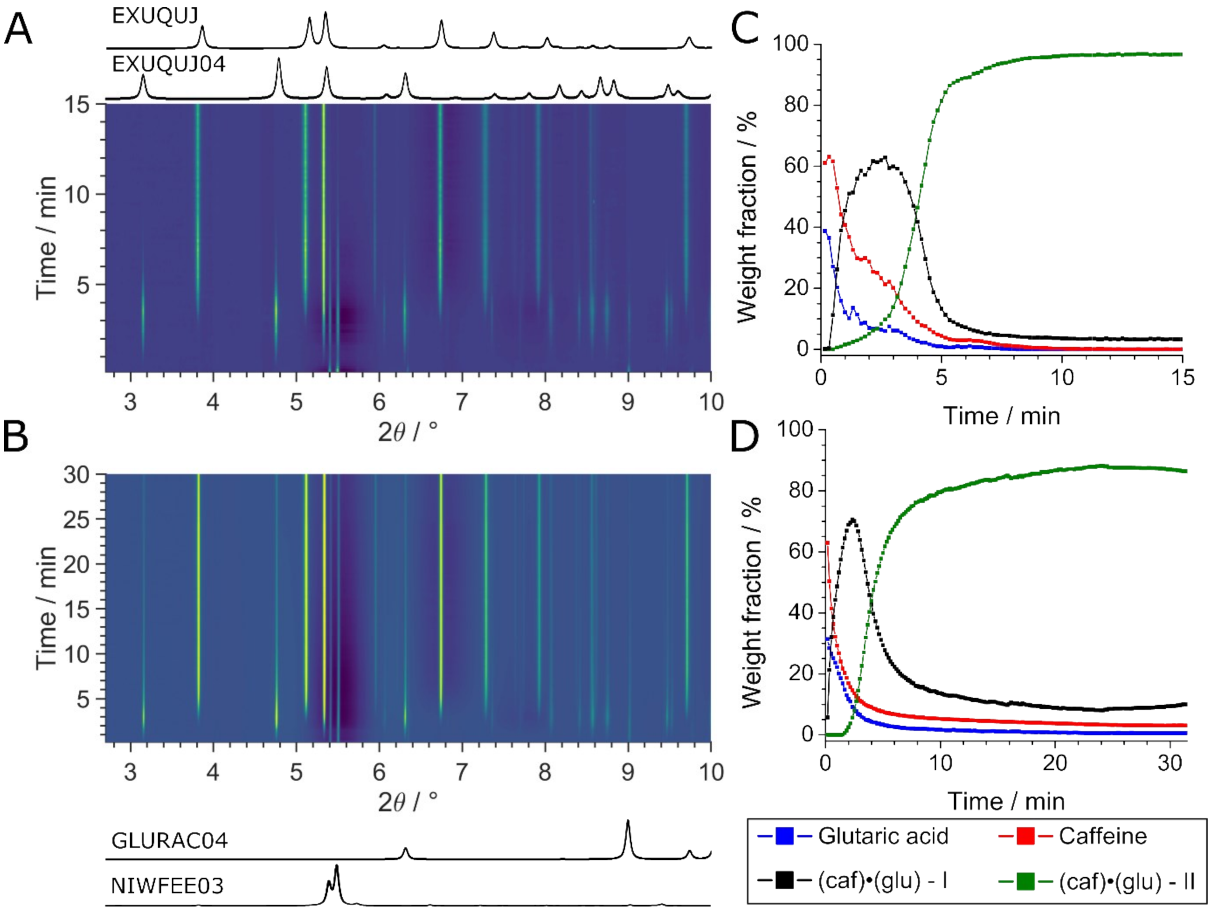

Fig. S1. 2D XRPD plots for the *in situ* monitoring of mechanochemical (caf)·(glu) formation using ACN as liquid additive with (**A**) 35 µL (η = 0.12 µL/mg), and (**B**) 50 µL (η = 0.17 µL/mg). Calculated XRPD patterns of glu (CSD code GLURAC04), caf (CSD code NIWFEE03), (caf)·(glu) – I (CSD code EXUQUJ04), and (caf)·(glu) – II (CSD code EXUQUJ) are shown below and above the 2D plots, respectively. Quantitative analysis of reaction progress via weight fraction as a function of milling time, derived from sequential Rietveld analysis (**C**) 35 µL (η = 0.12 µL/mg), and (**D**) 50 µL (η = 0.17 µL/mg) ACN.

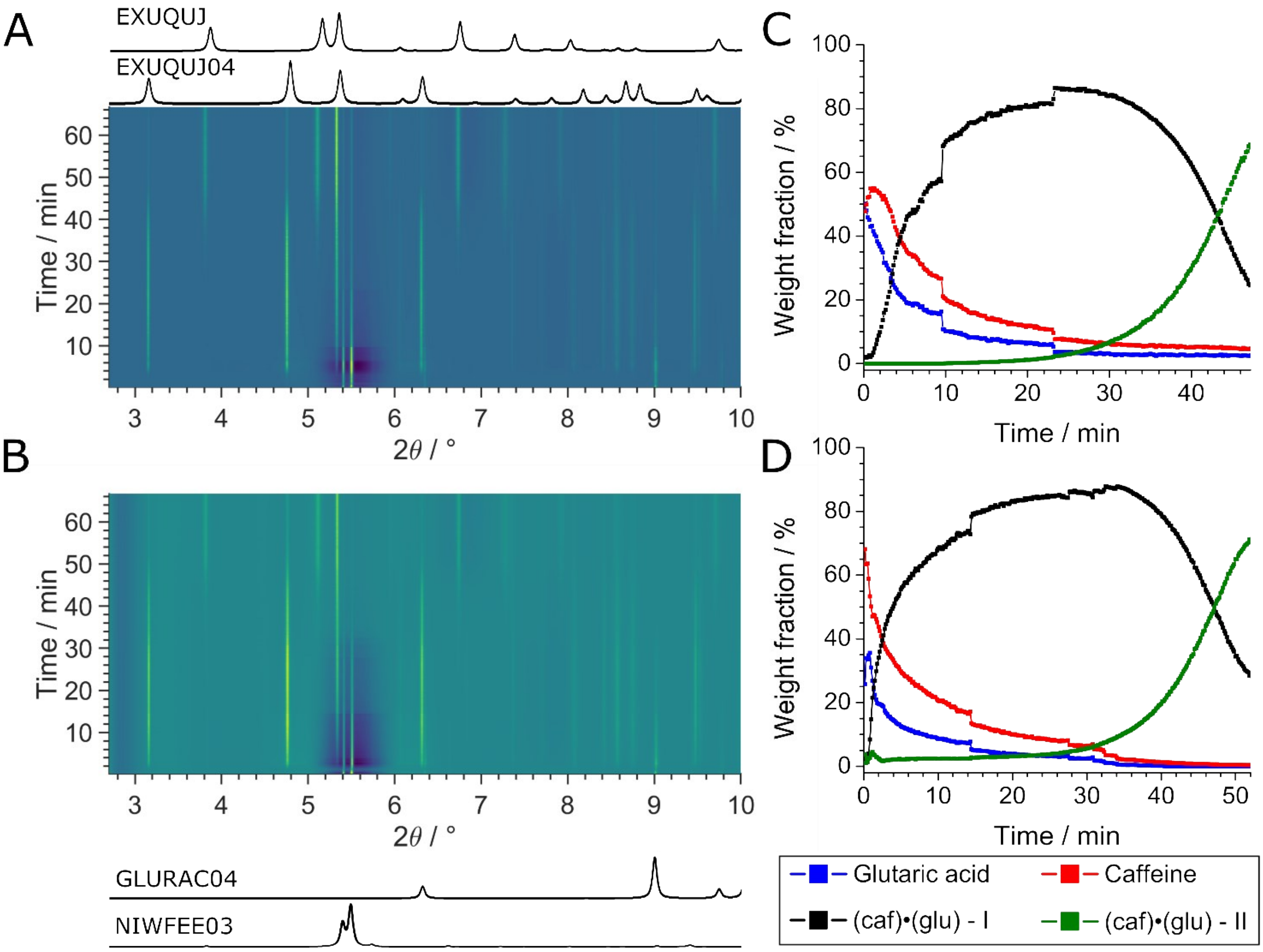

Fig. S2. 2D XRPD plots for the *in situ* monitoring of mechanochemical (caf)·(glu) formation using 1-dodecanol as liquid additive with (**A**) 35 µL (η = 0.12 µL/mg), and (**B**) 50 µL (η = 0.17 µL/mg). Calculated XRPD patterns of glu (CSD code GLURAC04), caf (CSD code NIWFEE03), (caf)·(glu) – I (CSD code EXUQUJ04), and (caf)·(glu) – II (CSD code EXUQUJ) are shown below and above the 2D plots, respectively. Quantitative analysis of reaction progress via weight fraction as a function of milling time, derived from sequential Rietveld analysis (**C**) 35 µL (η = 0.12 µL/mg), and (**D**) 50 µL (η = 0.17 µL/mg) 1-dodecanol.

The sudden drop of intensity (2D plot) and change in the weight fraction (S2C, S2D) are due to inhomogeneity during milling.

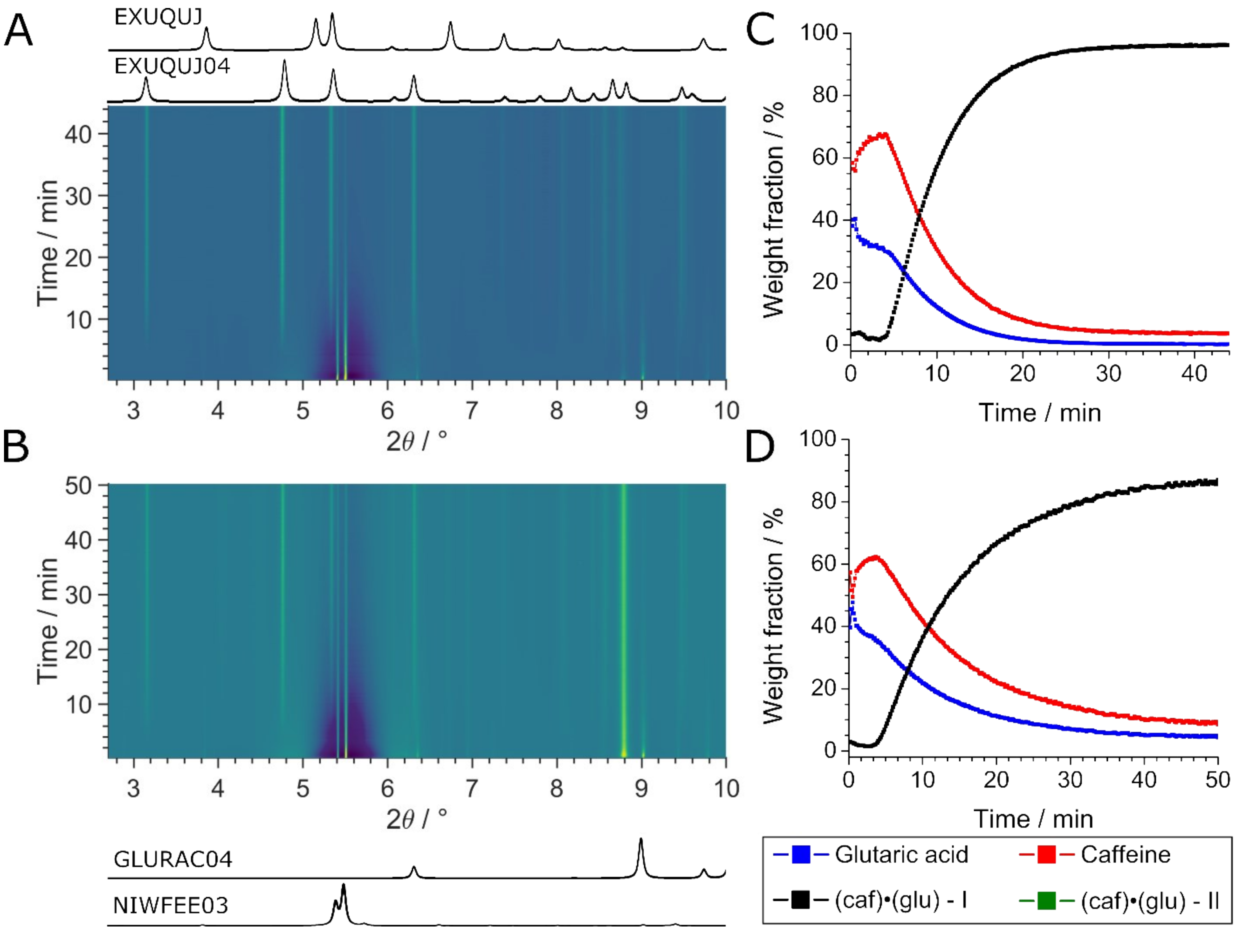

Fig. S3. 2D XRPD plots for the *in situ* monitoring of mechanochemical (caf)·(glu)formation using PEG 10,000 as polymer additive with (**A**) 35 mg (δ = 0.12), and (**B**) 150 mg (δ = 0.50). Calculated XRPD patterns of glu (CSD code GLURAC04), caf (CSD code NIWFEE03), (caf)·(glu) – I (CSD code EXUQUJ04), and (caf)·(glu) – II (CSD code EXUQUJ) are shown below and above the 2D plots, respectively. Quantitative analysis of reaction progress via weight fraction as a function of milling time, derived from sequential Rietveld analysis (**C**) 35 mg (δ = 0.12), and (**D**) 150 mg (δ = 0.50) PEG 10,000.

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