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Supporting information for article:

Mechanochemical synthesis insights and solid-state characterization of quininium aspirinate, a glass-forming drug–drug salt

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The crystal structure of quininium aspirinate (at 100 K) discussed in the manuscript has been submitted to the CCDC with the deposition number 2003354. The crystal structure of quininium salicylate has been released as a communication with the CCDC deposition number 2003355.

S1. X-ray powder diffraction

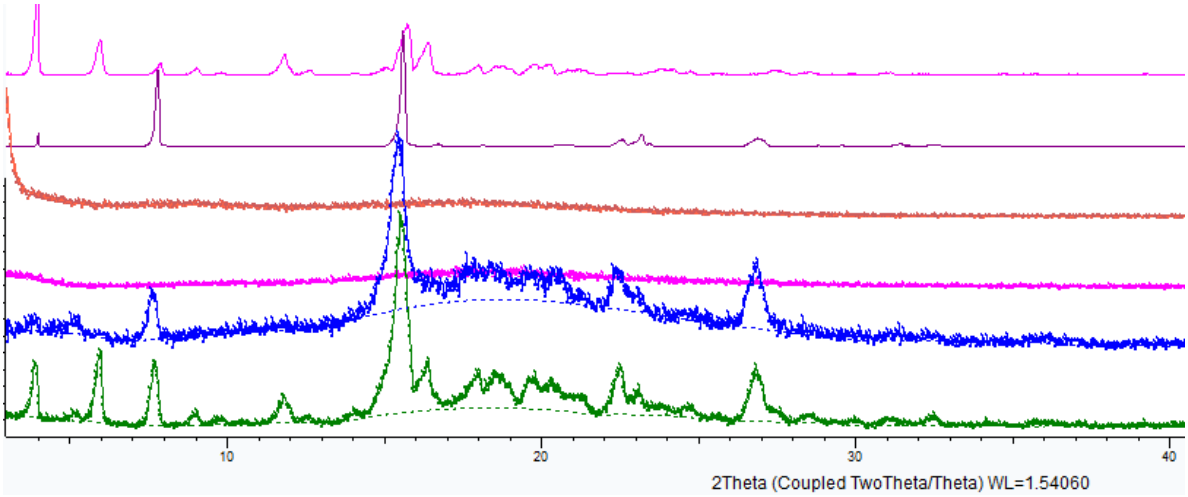

Figure S1 PXRD data of the reactants in 1:1 molar ratio neat milled at 10 Hz (green) showing diffraction peaks of quinine and aspirin; neat ball milled at 15 Hz (blue) showing aspirin peaks; and amorphous phases obtained by milling at 20 Hz (magenta), and at 30 Hz (red). The calculated patterns of aspirin and quinine are shown as violet and magenta solid lines, respectively.

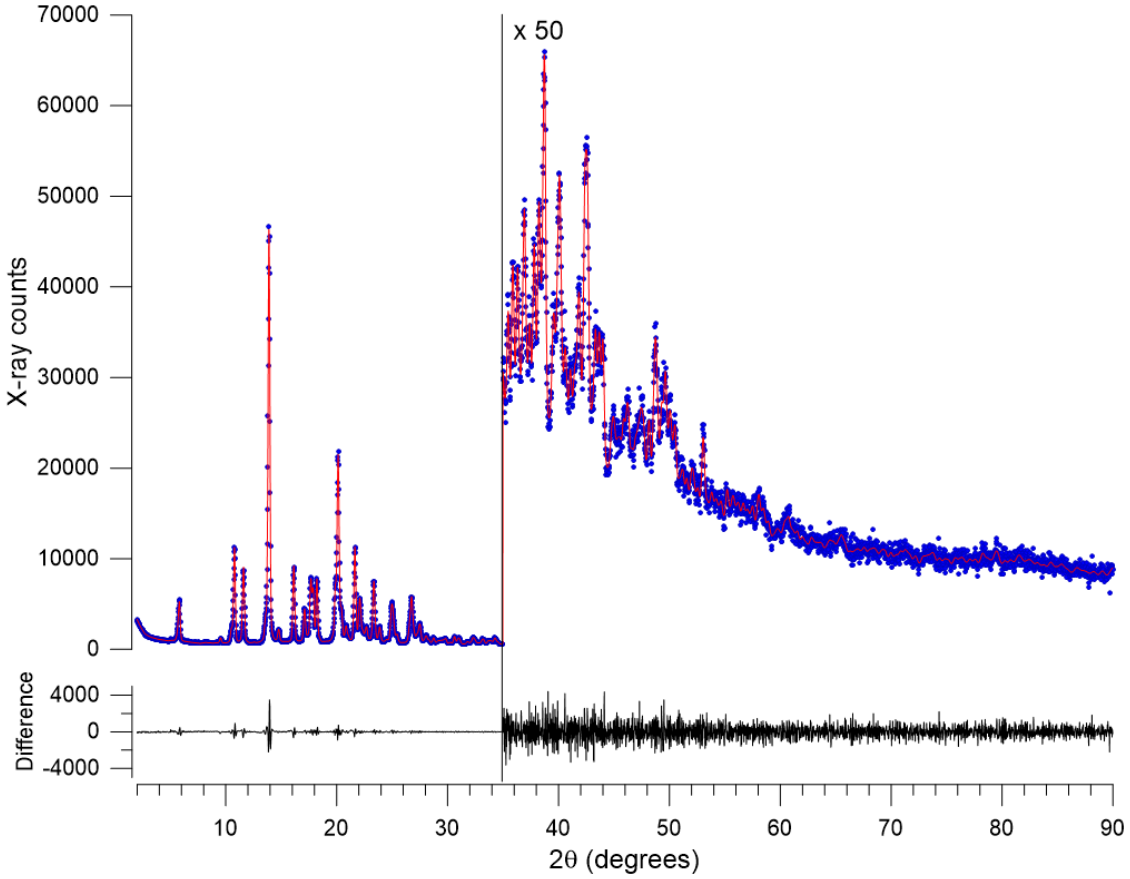

Figure S2 Le Bail fit of quininium aspirinate (**I**) at 295 K. The experimental data is shown with blue circles, the calculated profile with a red, solid line, and the difference is shown at the bottom (black line).

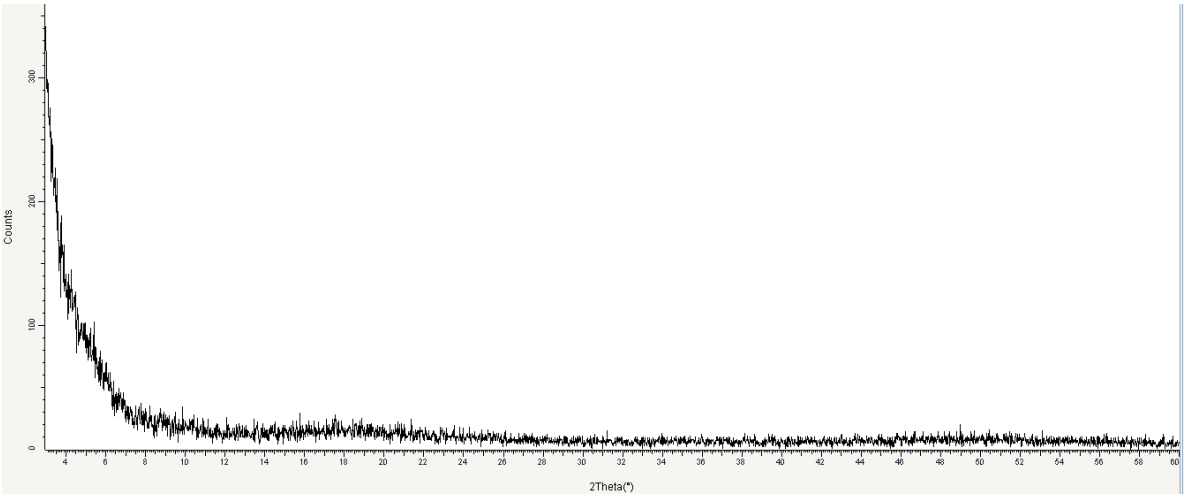

Figure S3 PXRD of an initially crystalline quininium aspirinate sample (prepared by LAG water) after it was heated at 125 °C for 1.5 hours, indicating that an amorphous phase has been obtained. This supports the observation indicating that the endothermal event in the DSC data shown in Figure 7 (a) corresponds to the transition to a glass.

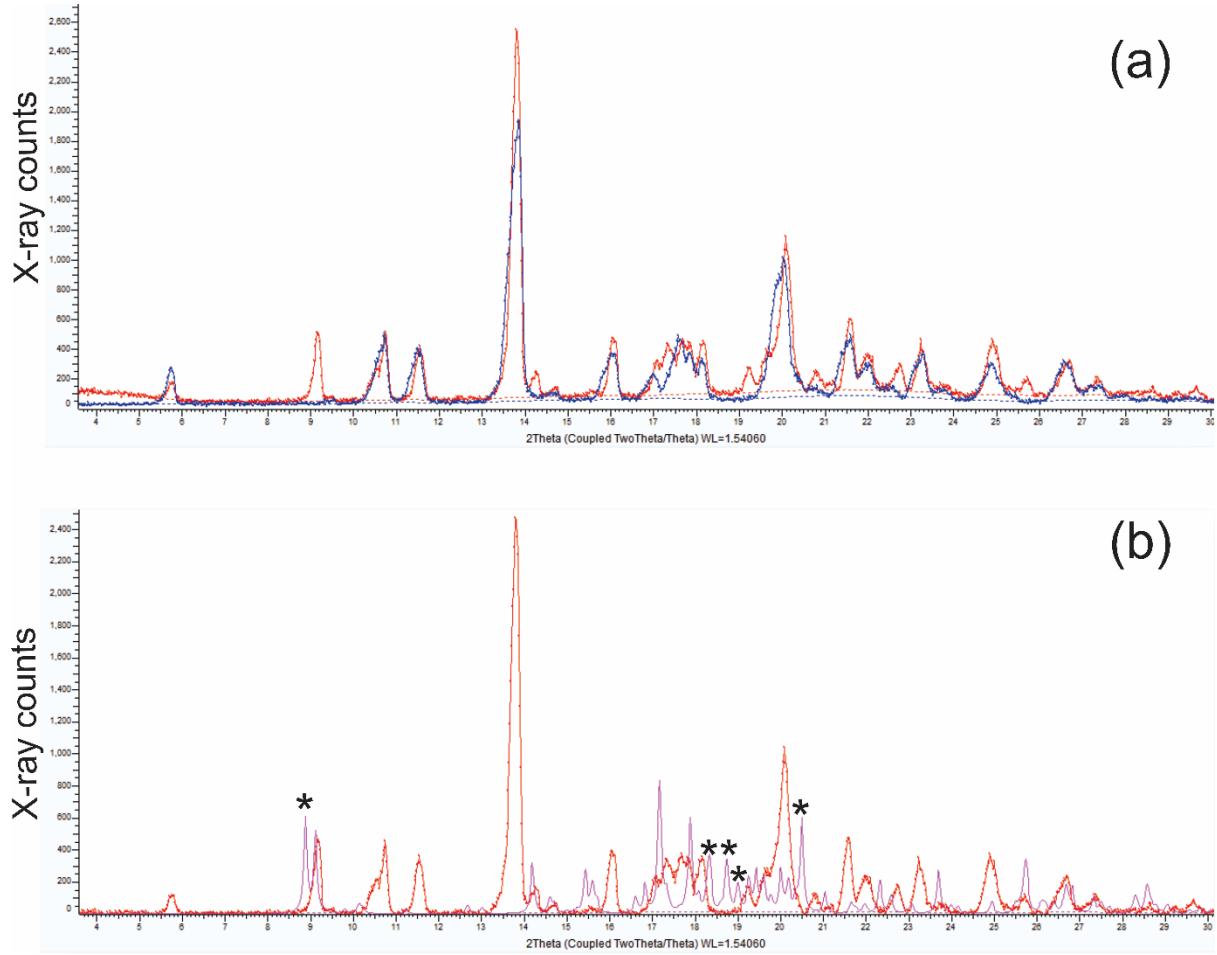

Figure S4 (a) PXRD collected on 02/26/2021 (red) of the products neat ground in an agate mortar in 2019 (amorphous by PXRD collected on 07/25/2019), overlaid with the PXRD of **I** prepared by LAG with water (blue). The 3° – 30° 2θ interval is shown for clarity. (b) Overlay of the PXRD data of the above product crystallized upon storage (also in red) with the calculated data of quininium salicylate (pink solid line). Selected diffraction peaks of the latter are marked with * symbols. They are not present in the pattern of the sample crystallized upon storage (in red), indicating the absence of the quininium salicylate phase.

S2. Thermogravimetry and Differential Scanning Calorimetry

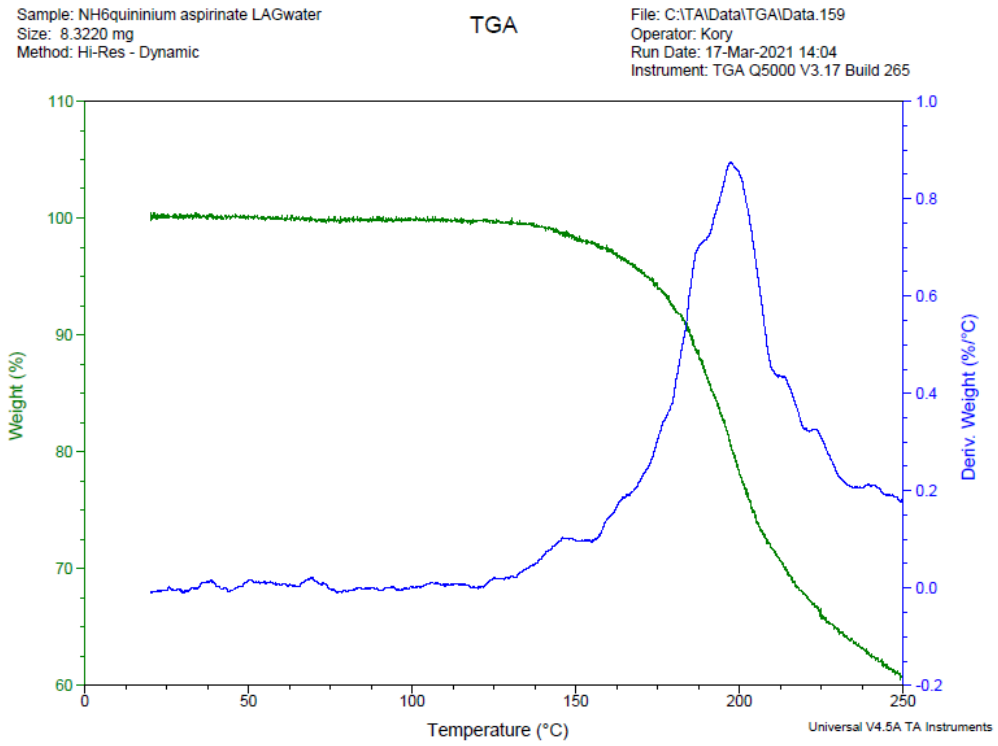

Figure S5 Thermogravimetric curve (green), and its derivative (blue) for **I** prepared by LAG with water.

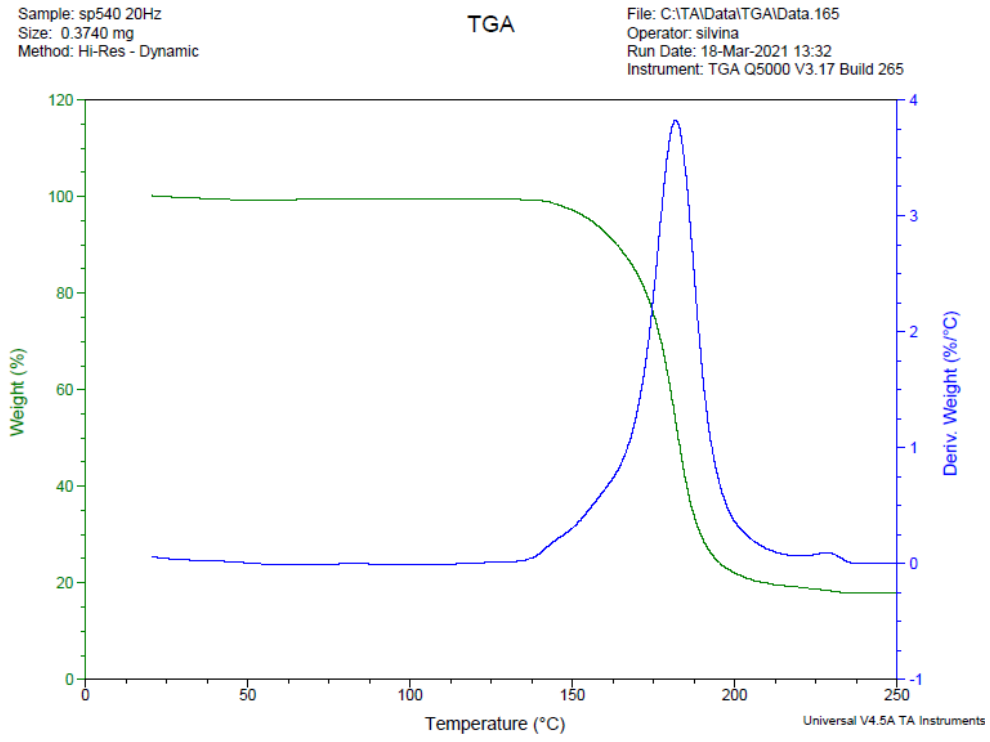

Figure S6 Thermogravimetric curve (green) and its derivative (blue) for the amorphous product obtained by milling at 20 Hz for 35 min.

S3. FT-IR spectroscopy

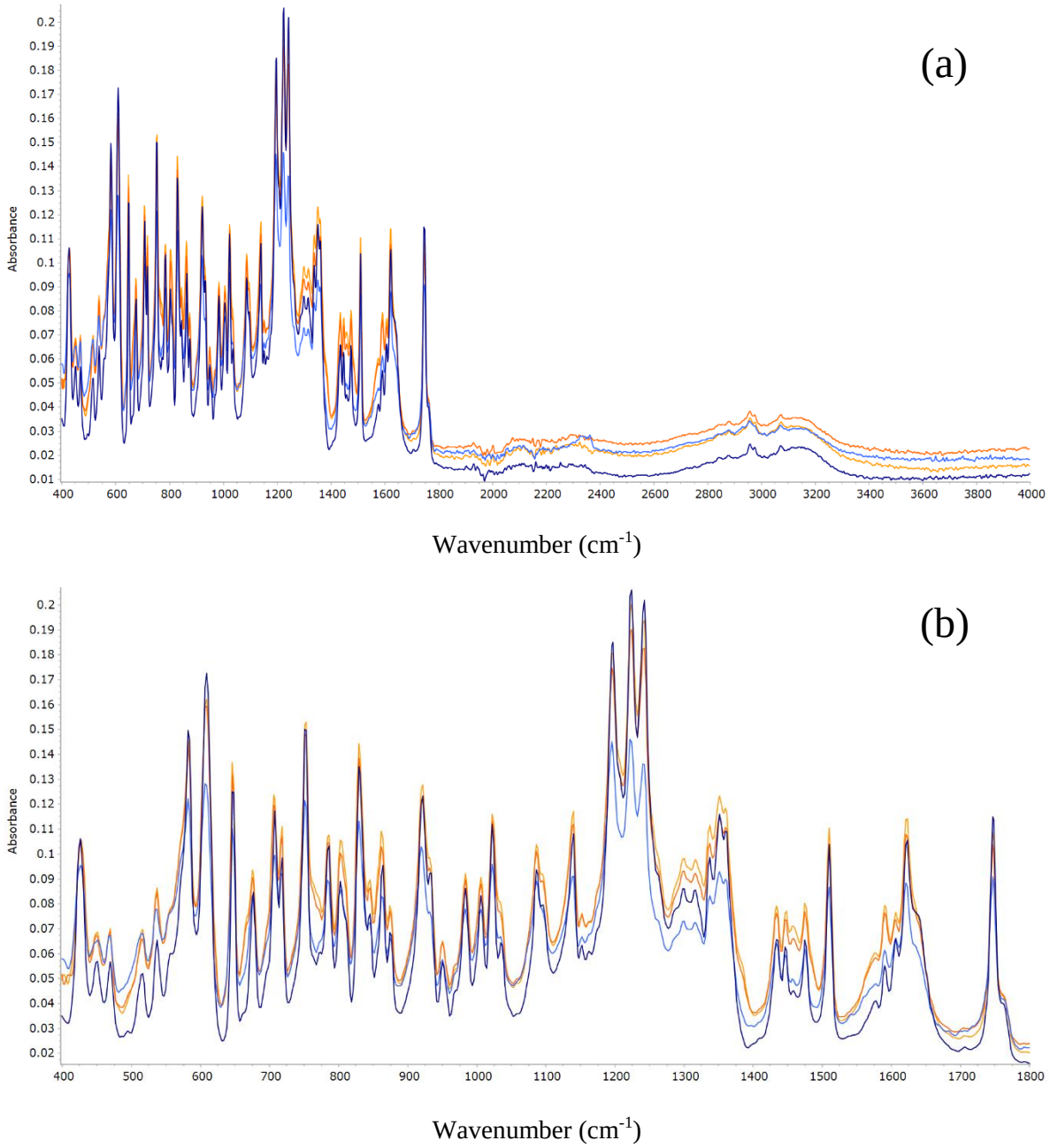

Figure S7 (a) Overlay of the FT-IR spectra in the 400 – 4,000 cm^{-1} wavenumber interval for the mechanochemical products (**I**) obtained by LAG in an agate mortar and pestle, using as LAG additives: heptane (yellowish-orange), toluene (orange), EtOH (light blue), and water (dark blue), respectively. (b) Zoom of the above overlay in the 400 – 1,800 cm^{-1} region.

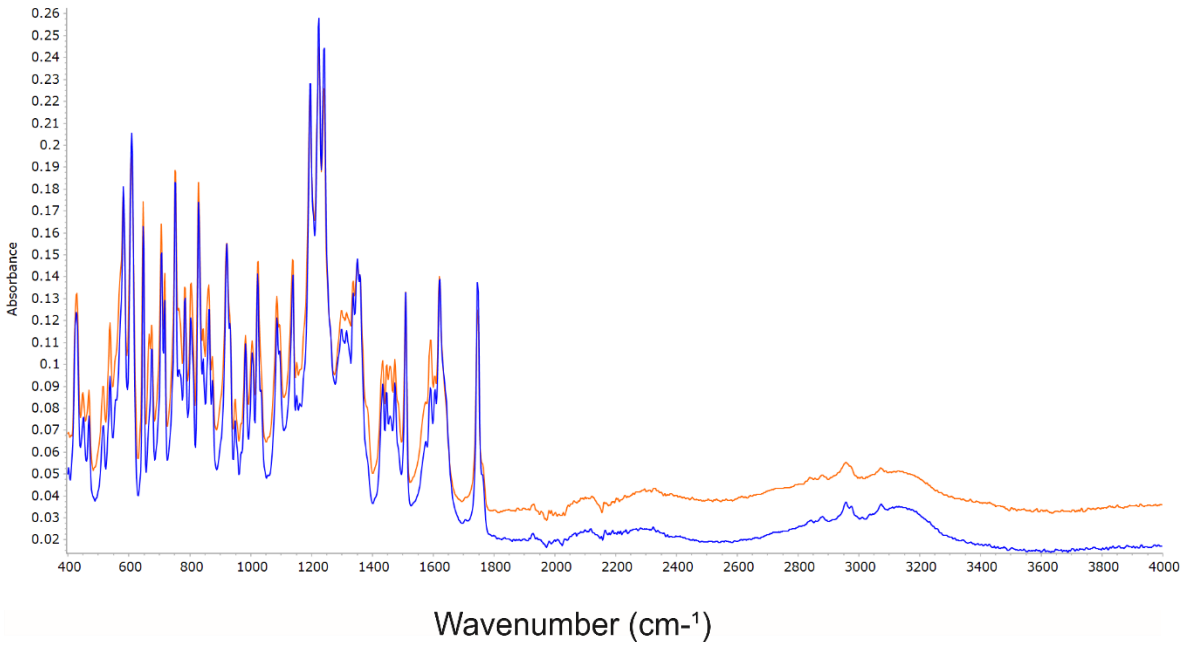

Figure S8 Overlay of the FT-IR spectra collected in 2021 (orange line) of the sample prepared by NG in an agate mortar in 2019, which crystallized upon storage as determined by PXRD (see Figure S4), with the FT-IR spectrum of **I** prepared by LAG water (blue line).

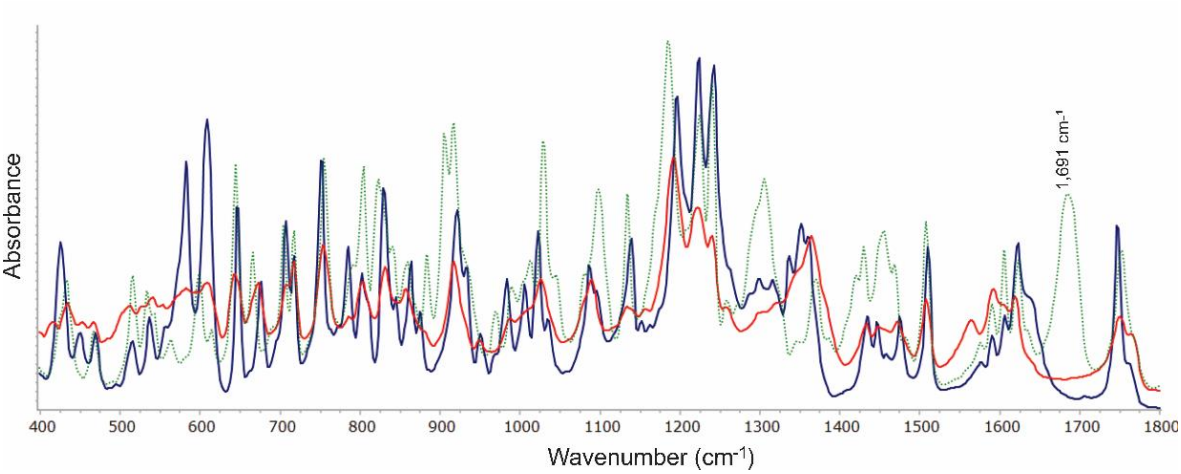

Figure S9 Overlay of the FT-IR spectra of the powders neat milled at 30 Hz milling frequency (red, solid line) with FT-IR data of the crystalline mechanochemical product **I** (LAG water) shown with a solid blue line, and the unreacted reactants in 1:1 molar ratio (green, dotted line). Note the aspirin band at 1,691 cm^{-1} is absent in the spectra of **I** and the amorphous product obtained by milling at 30 Hz.