

Electronic Supplementary Information

Mechanochemistry vs. solution growth: striking differences in bench stability of a cimetidine salt based on synthetic method

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Experimental details

General details

Reagents cimetidine (**cim**), cimetidine hydrochloride salt (**cim**·HCl), and fumaric acid (**H₂fum**) were purchased from Sigma Aldrich (St. Louis, MO, USA) and used without modification. Acetonitrile (ACS certified) was purchased from Fisher Scientific (Waltham, MA USA).

Instrumentation

Single crystal X-ray diffraction

The crystal structure of (**cimH⁺**)(**Hfum⁻**)·0.50 MeCN (**1**) was collected on a Bruker D8 Advance diffractometer (Bruker-AXS, Madison, WI, USA) with a Photon 100 CMOS area detector and an I μ S microfocus X-ray source (Bruker AXS) using Cu-K α ($\lambda=1.54060$ Å) radiation. Crystals were coated with Paratone oil (Hampton Research, Aliso Viejo, CA, USA) and cooled to 100 K under a cold stream of nitrogen using an Oxford cryostat (Oxford Cryosystems, Oxford, UK). The structures were determined by least squares refinement against F^2 using SHELX-2014¹ software running under the WinGX user interface. Non-hydrogen atoms were located from the difference map and refined anisotropically. All hydrogen atom coordinates and thermal parameters were constrained to ride on the carrier atoms. The acetonitrile was located on centre of inversion and it was successfully modeled with partial occupancy.

Powder X-ray diffraction (PXRD)

Powder X-ray diffraction patterns were collected using a Bruker D2 powder diffractometer equipped with a CuK α ($\lambda=1.54060$ Å) source and Lynxeye detector (Bruker AXS, Madison, WI) with a lower and upper discriminant of 0.110 V and 0.250 V respectively. The patterns were collected in the range of 5° to 40°. Analysis of PXRD patterns was conducted using Panalytical X'Pert Highscore Plus software. Experimental patterns were compared to simulated patterns calculated from single crystal structures using Mercury software package.

Fourier-transform infrared attenuated total reflection (FTIR-ATR)

All FTIR-ATR spectra were collected in the solid state using a Bruker Vertex 70 FTIR-ATR spectrometer (Milton, ON, CA) in the range of 4000 cm⁻¹ to 400 cm⁻¹. FTIR spectra were analysed using Bruker OPUS software.

Thermogravimetric analysis (TGA)

Thermograms were collected using a TA Instruments TGA Q500 thermogravimetric analyser at a heating rate of 10°C/min from 25°C to 700°C under dynamic atmosphere of nitrogen and air. The flow rates of the

purge gas and sample gas were set at 50 mL/min and 50 mL/min respectively. TGA curves were analyzed with TA Universal Analysis software.

Solid-state ^{15}N CP-MAS NMR (ssNMR)

Natural abundance ^{15}N ssNMR spectra were collected on a Varian VNMRS NMR spectrometer (Palo Alto, CA, USA) operating at a ^1H frequency of 399.77 MHz and an ^{15}N frequency of 40.53 MHz using a 7.5 mm double-resonance Varian T3 probe. All spectra were collected at a spin rate of 5 kHz using cross-polarization with a contact time of 1.5 ms and a recycle delay ranging between 2 s and 20 s. Spectra were referenced using glycine at -347.1 ppm with respect to CH_3NO_2 . NMR spectra were analysed using MestreNova software.

Solution NMR Spectroscopy

All ^1H NMR solution spectra (Bruker Optics Ltd, Milton, ON, Canada) were collected using $\text{DMSO-}d_6$ as the solvent, on a Bruker 400 MHz spectrometer and interpreted using MestreNova software. The samples were dissolved in one ampule of $\text{DMSO-}d_6$.

Synthesis of the salts

(Hcim $^+$)(Hfum $^-$)\cdot 0.50 MeCN (compound 1)

Cimetidine (0.54 mmol, 137 mg) and fumaric acid (0.54 mmol, 63 mg) were milled in a stainless-steel jar in the presence of acetonitrile (60 μL) on a Retsch MM400 shaker mill for 30 minutes. The salt solvate was characterized by PXRD, TGA, and FTIR-ATR.

Single crystals suitable for single crystal X-ray diffraction were obtained by slow evaporation of a solution in MeCN.

(Hcim $^+$)(Hfum $^-$) made by milling (compound 2)

Cimetidine (0.54 mmol, 137 mg) and fumaric acid (0.54 mmol, 63mg) were milled in a stainless-steel jar in the presence of water (60 μL) as a liquid additive on a Retsch MM400 mill for 30 minutes. The product was characterized by PXRD, TGA, and FTIR-ATR. The crystal structure of the salt was solved and refined from PXRD using Rietveld refinement technique.

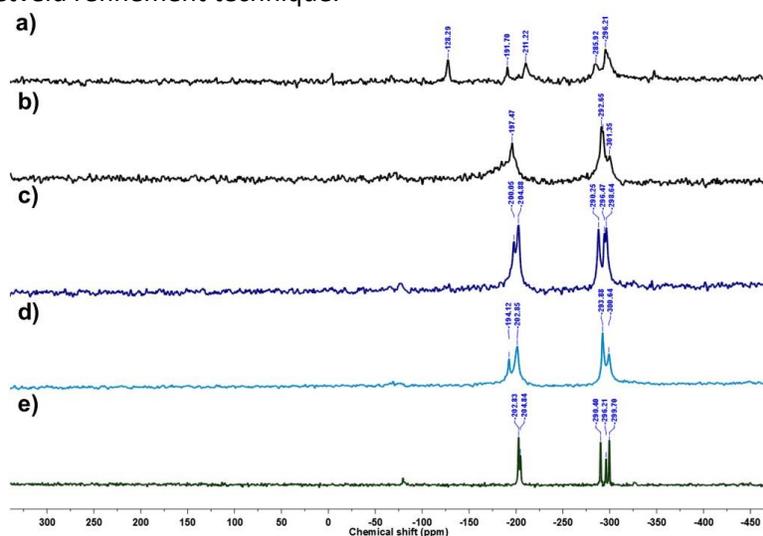


Figure S1. Solid-state ^{15}N CP-MAS NMR spectra of commercially available (a) **cim**, (b) **cimH $^+$ Cl $^-$** salt, (c) **(cimH $^+$)(Hfum $^-$)\cdot 0.50 MeCN (compound 1)**, (d) **(cimH $^+$)(Hfum $^-$)** made mechanochemically (compound 2) and (e) **(cimH $^+$)(Hfum $^-$)** made by desolvation of 1 (compound 1'). The similarity in the spectra between (b), (c), (d) and (e) confirms that compounds 1, 2 and 1' are salts.

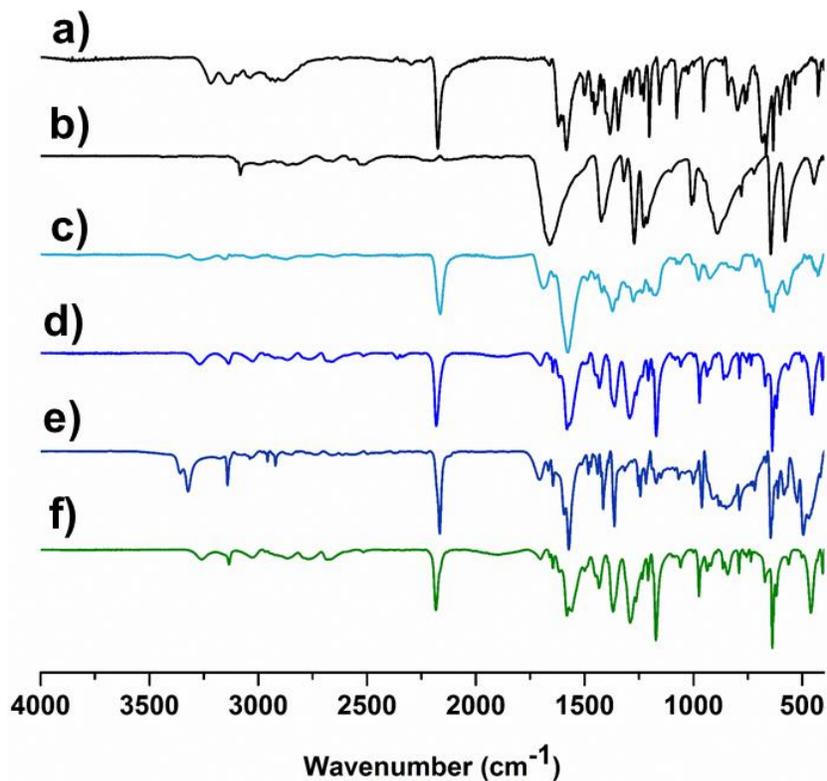


Figure S2. FTIR-ATR spectra for: (a) **cim**, (b) **H₂fum**, (c) neat milling of **cim** and **H₂fum**, (d) compound **1** formed by milling **cim** and **H₂fum** in the presence of MeCN as a liquid additive, (e) compound **2** formed by milling **cim** and **H₂fum** in the presence of water as a liquid additive, (f) compound **1'** obtained by desolvation of mechanochemically prepared compound **1**.

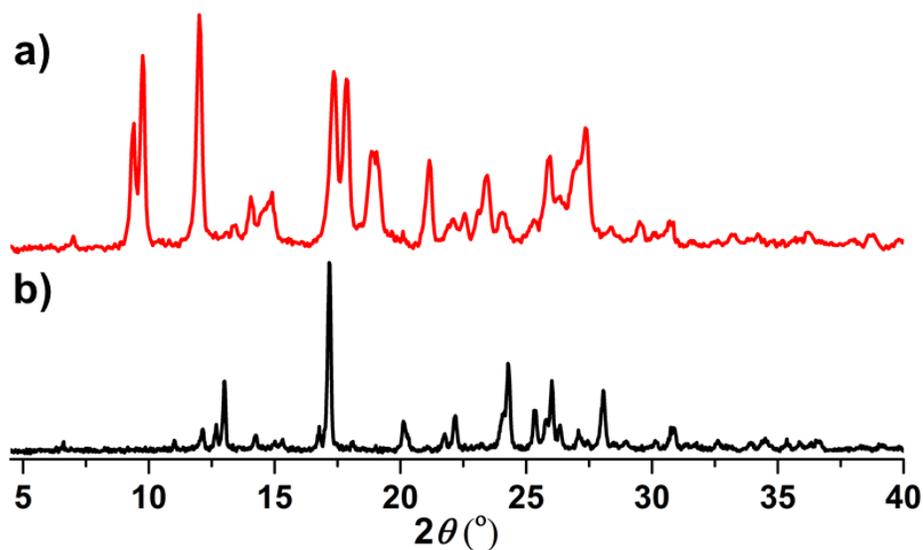


Figure S3. Polymorphs of $(\text{Hcim}^+)(\text{Hfum}^-)$ salt generated by: (a) heating form **1** for two days at 45°C to yield **1'** and (b) milling **cim** and **H₂fum** in the presence of water as a LAG to yield **2**.

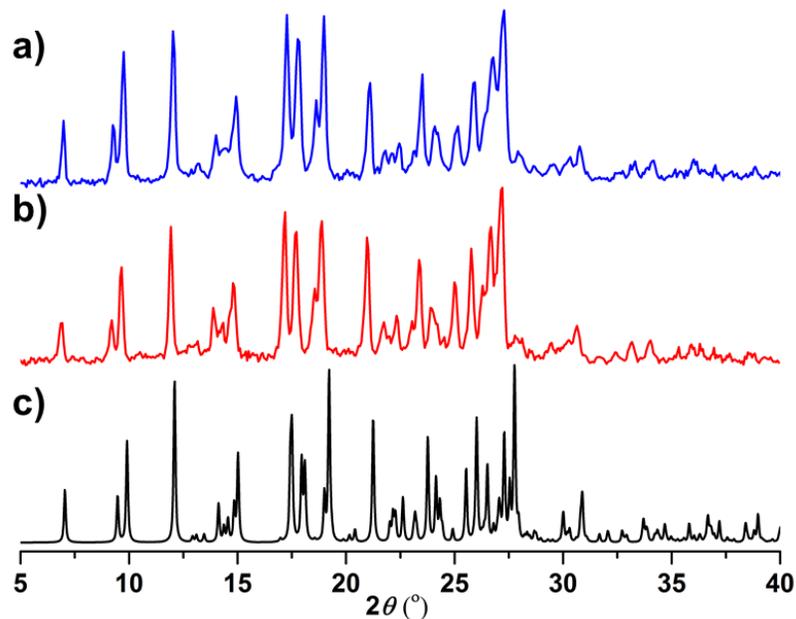


Figure S4. Comparison of PXRD patterns of **1** prepared by: (a) solution synthesis, (b) mechano-synthesis, c) simulated for the crystal structure of **1**.

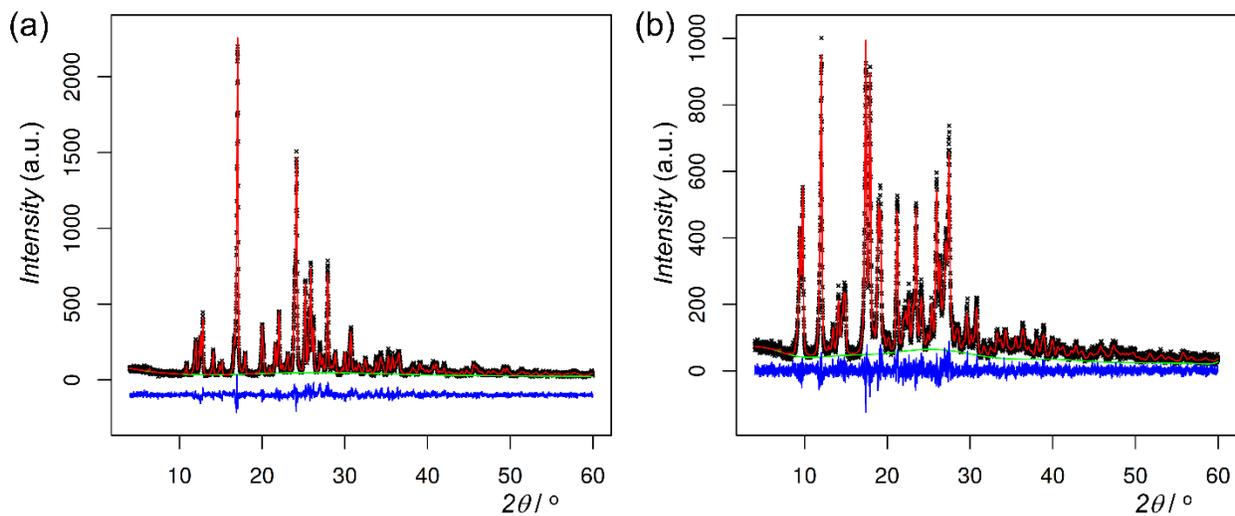


Figure S5. Final Rietveld fit for the structures of (a) compound **2** and (b) compound **1'**, determined from PXRD data.

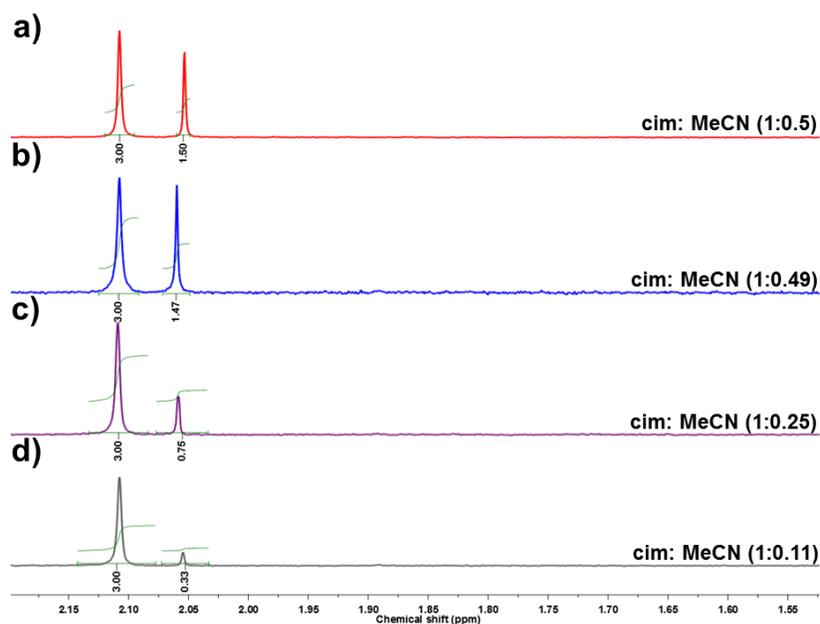


Figure S6. High field portion of ^1H -NMR spectra of single crystals of **1**: a) freshly prepared from MeCN solution, b) kept at 45°C for two days, c) gently ground and kept for 2 days at 45°C for two days and d) harshly ground and kept for 2 days at 45°C .

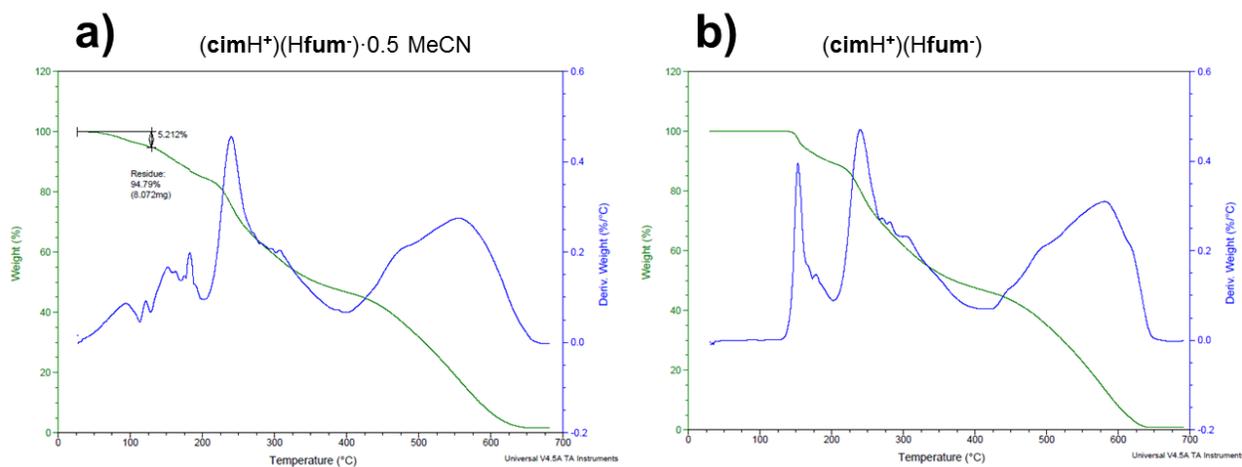


Figure S7. TGA thermograms of: a) compound **1** and b) compound **2**. The first step in a) corresponds to the weight loss of ca 5 wt%, which matches the theoretically calculated weight content of MeCN in the solvated salt **1** (5.2%). Notably, the step does not appear in the TGA thermogram of the nonsolvated compound **2** shown in b).

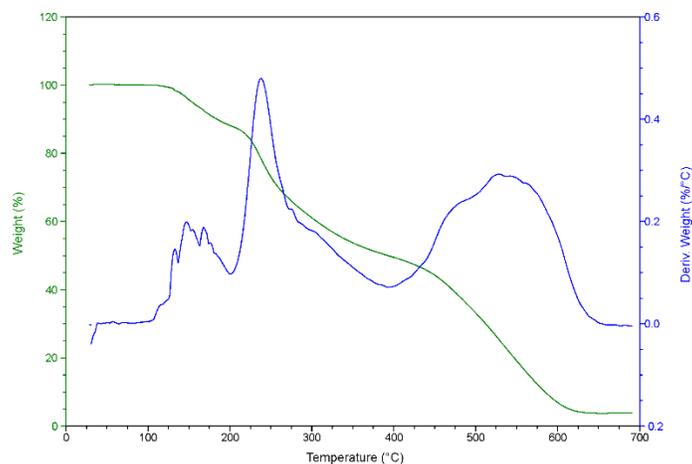


Figure S8. TGA thermogram of compound **1'**. In contrast to compound **1**, no weight loss is observed below 100 °C, and the thermogram is similar to that of the non-solvated salt **2**.

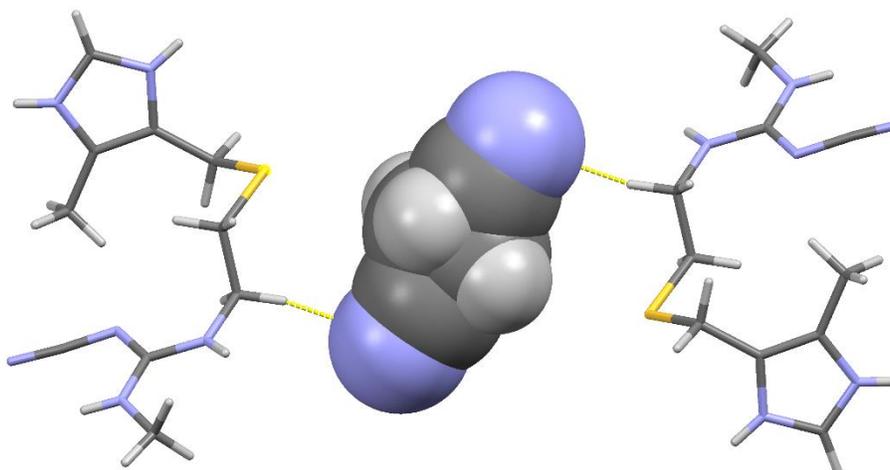


Figure S9. View of the disordered guest molecule of acetonitrile (shown in space-filling) in the crystal structure of **1**, illustrating C-H...N interactions (C...N separation 3.66 Å, C-H...N angle 165°) to neighboring **cimH⁺**.

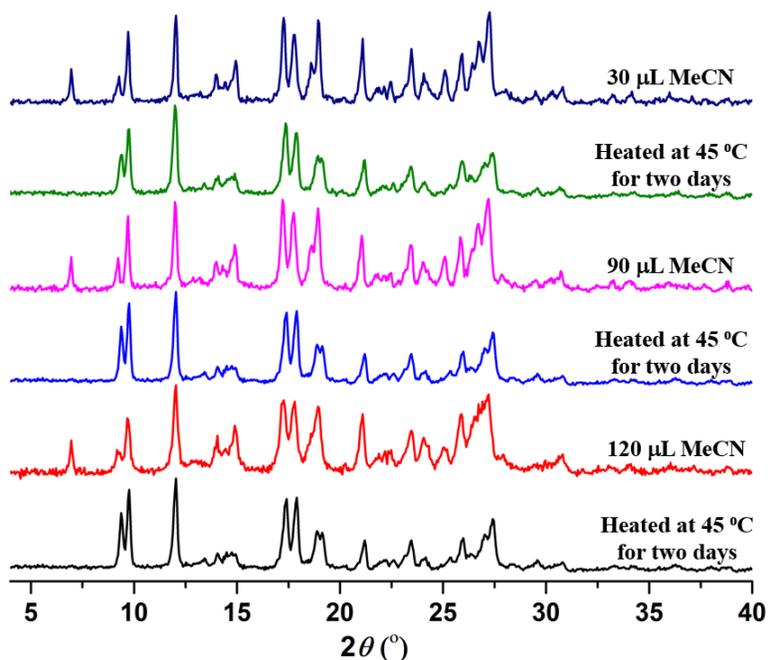


Figure S10. Comparison of PXRD patterns for samples of **1** mechanochemically prepared using different amounts of MeCN as the LAG additive, fresh and after exposure to 45 °C over 2 days.

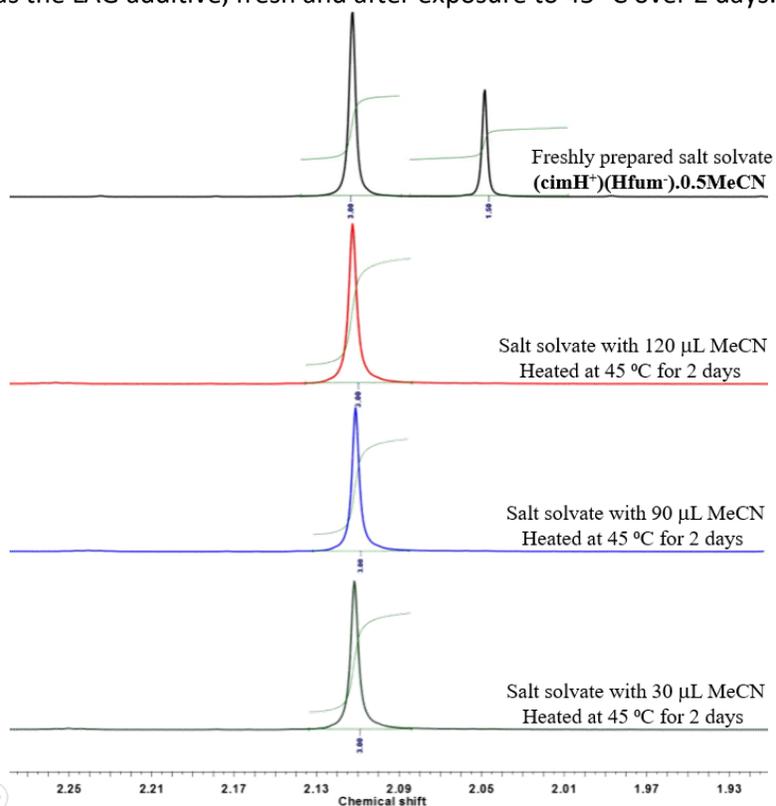


Figure S11. Comparison of ^1H NMR solution spectra for (top to bottom): a sample of freshly prepared **1** and samples of **1** prepared by using different amounts of MeCN as the milling liquid, after exposure to 45 °C over 2 days.

Table S1. Quantitative comparison of the particle size and MeCN content for differently prepared and treated samples of **1**.

Type of material	Treatment	longest particle dimension	Mole ratio
Single crystals	Before treatment	1.2 mm	0.50
	After treatment ^a	1.2 mm	0.49
	Gently ground after treatment	230 μm	0.25
	Thoroughly pulverized after treatment ^a	19 μm	0.11
Powder	Mechanochemically	228 nm	0.50
	Mechanochemically after treatment ^a	228 nm	none

^adesolvation conditions are after 45 °C, 2 days

Table S2. Crystallographic data for a crystal of **1**, (cimH⁺)(Hfum⁻)-0.5MeCN, before and after exposure to 45 °C.

Unit cell parameters	<i>a</i> (Å)	<i>b</i> (Å)	<i>c</i> (Å)	<i>β</i> (Å)	<i>V</i> (Å ³)
before heating	13.8039(12)	8.0191(7)	18.7153(16)	107.580(2)	1974.93
after heating (day=5)	13.7985(12)	8.0172(7)	18.7226(17)	107.657(3)	1973.62
after heating (day=10)	13.7920(11)	8.0148(7)	18.7259(16)	107.555(3)	1973.56

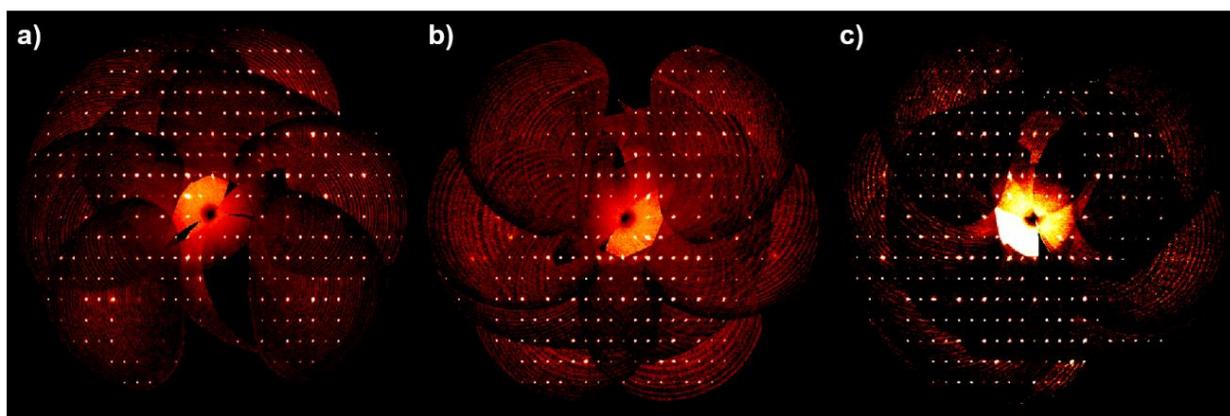


Figure S12. Diffraction images collected in the 0kl plane for the single crystals a) freshly prepared, b) heated at 45°C for five days, and c) heated at 45°C for ten days.

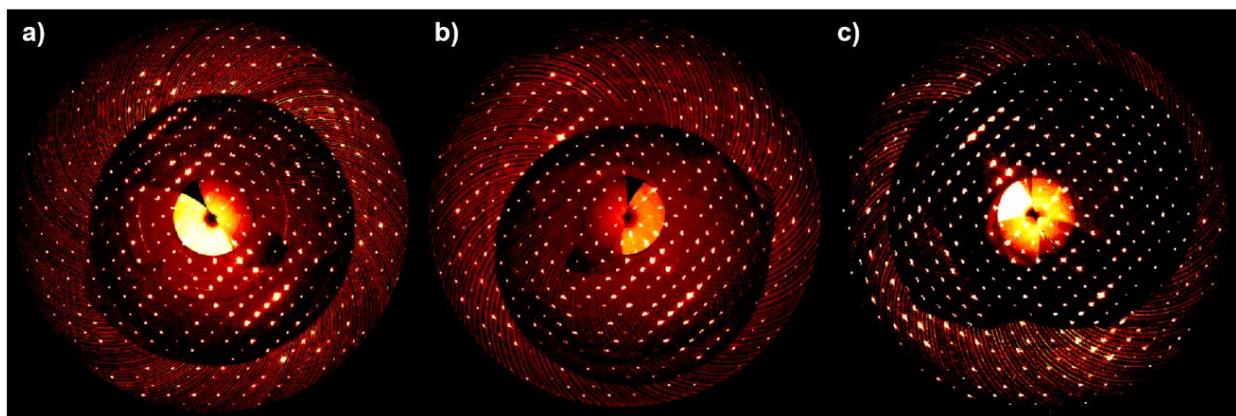


Figure S13. Diffraction images collected in the $h0l$ plane for the single crystals a) freshly prepared, b) heated at 45°C for five days, and c) heated at 45°C for ten days.

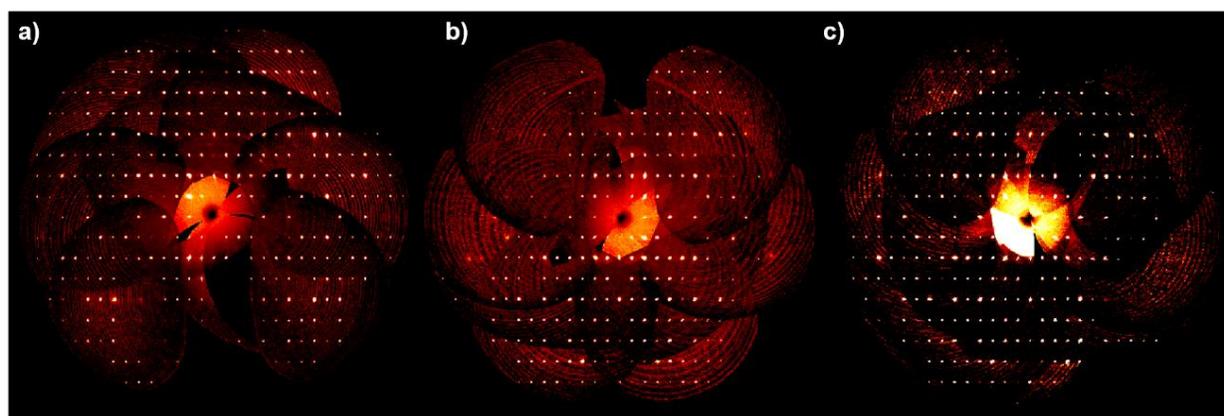


Figure S14. Diffraction images collected in the $hk0$ plane for the single crystals a) freshly prepared, b) heated at 45°C for five days, and c) heated at 45°C for ten days.

¹G.M. Sheldrick. *Acta Cryst.* 2015, **C71**, 3-8