# **Electronic Supplementary Information**

for

# Sustainable solid form screening: mechanochemical control over nucleobase hydrogen-bonded organic framework polymorphism

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### **Chemicals**

DAP was purchased from Carbosynth, Thermo Scientific, and Sigma Aldrich. Methanol (MeOH), ethanol abs. (EtOH), acetonitrile (ACN), iso-propanol (*i*-PrOH), ethyl acetate (EtOAc) solvents for LAG reactions and solution crystallization were purchased from Gram-mol and used without further purification. EtOH and EtOAc for soaking HOF samples were purchased from Fisher Scientific and used without further purification.

## Mechanochemical reactions

All ball milling experiments were conducted for 60 min in poly (methyl methacrylate) (PMMA) jars using two 7 mm stainless steel (SS) balls as a grinding media. LAG experiments were conducted with the same abovementioned reaction conditions using 200 mg of DAP and 40  $\mu$ L of a specific liquid additive for a liquid-to-solid  $\eta$  ratio of 0.2  $\mu$ L/mg. If not stated otherwise, all LAG experiments were performed using the same reaction conditions. We used IST 500 vibratory ball mill.

# **Crystallization**

For growing single crystals, 5 mg of solid was mixed with 3 mL of specific solvent and refluxed. After that the content was filtrated through Chromafil Xtra CA-20/13 filters ( $0.20 \mu m$  pore sizes) and clear solution was left for solvent to evaporate at room temperature.

### Single-crystal diffraction

Single-crystal diffraction experiments were performed on Rigaku Oxford Diffraction XtaLAB Synergy-S diffractometer (Cu K $\alpha$ ,  $\lambda$ =1,54184 Å). Program package CrysAlisPro<sup>1</sup> was used for data collection, cell refinement, and data reduction. Structures were solved by direct methods and refined using the SHELXT<sup>2</sup> and SHELXL<sup>3</sup> programs, respectively. The refinement procedure by the full-matrix least squares methods based on *F*<sup>2</sup> values against all reflections included anisotropic displacement parameters for all non-H atoms. The SHELX programs operated within the Olex2 crystallographic suite. The CIF files of DAP-HOF-1 (with and without solvent) and DAP-HOF-2 have been deposited with the Cambridge Crystallographic Data Centre (CCDC) under the deposition numbers 2168450, 2168451, and 2168452. These data can be obtained from the CCDC upon request.

# Powder diffraction

PXRD data for structure solution of DAP-anhydrate was collected in a spinning capillary on Malvern Panalytical Empyrean multipurpose diffractometer using Mo K $\alpha$  radiation ( $\lambda$ =0.71073 Å) and Galypix detector at room temperature. After indexing, we identified several unit cells as good candidates for Pawley fitting. Subsequently, Pawley fitting highlighted the following

cells as equally good candidates for simulated annealing: orthorhombic *Pbca*, orthorhombic  $P2_12_12_1$ , monoclinic  $P2_1/c$ , and monoclinic  $P2_1$ . The structure was solved in all four cells by simulated annealing of DAP molecule(s) as a rigid body in direct space (*Pbca*–one DAP molecule in the asymmetric unit,  $P2_12_12_1$ –two DAP molecules in the asymmetric unit,  $P2_1/c$ –two DAP molecules in the asymmetric unit,  $P2_12_12_1$ –four DAP molecules in the asymmetric unit,  $P2_1/c$ –two DAP molecules in the asymmetric unit, and  $P2_1$ –four DAP molecules in the asymmetric unit). Rietveld refinements were performed on all four structural models. Notably, after inspecting CIF files of all four structural models, we concluded that they had the same hydrogen-bonding motifs. Unit cell parameters from each structural model were as following:

- 1) Pbca (a=14.97434 Å, b=12.37809 Å, c=6.76487 Å,  $\alpha = \beta = \gamma = 90^{\circ}$ , V=1253.894 Å<sup>3</sup>)
- 2) P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (*a*=14.97562 Å, *b*=12.37909 Å, *c*=6.76511 Å, α=β=γ=90°, V=1254.147 Å<sup>3</sup>)
- 3) P2<sub>1</sub>/c (a=16.3804181 Å, b=12.3759547 Å, c=6.77093838 Å, α=γ=90°, β= 113.938216°, V=1254.559 Å<sup>3</sup>)
- 4) P2<sub>1</sub>(a=12.37974 Å, b=14.97675 Å, c=6.76536 Å, α=γ=90°, β= 89.87754°, V=1254.331 Å<sup>3</sup>)

Finally, we identified *Pbca* structural model as the one with the best Rietveld fit. Importantly, we also compared relative lattice energies of all four structural models by using the same DFT method and functional as in the main manuscript part (VASP.6.3., r2SCAN+D4 exchange-correlation functional, energy cut-off for plane waves was set to 440 eV, and the smallest allowed spacing between k-points was set to 0.2 Å<sup>-1</sup>). The following energies were obtained which confirmed *Pbca* structural model as the most optimal one:

DAP\_anhydrate-Pbca 0.0 kJ/mol
DAP\_anhydrate\_P21 1.3 kJ/mol
DAP\_anhydrate\_P21c 0.1 kJ/mol
DAP-anhydrate-P212121 29.2 kJ/mol

Final Rietveld refinement for *Pbca* structural model was performed using rigid bodies with the additional rotational degrees of freedom for the protons from the amino groups. All calculations were performed using the program Topas.<sup>4</sup> The CIF file of DAP-anhydrate has been deposited with the CCDC under the deposition number 2164594 and can be obtained from the CCDC upon request.

#### In situ Raman monitoring

We used portable Raman system with OceanOptics Maya2000Pro spectrometer coupled with BlueBox laser source ( $\lambda$  = 785 nm) with B&W-Tek fiber optic Raman BAC102 probe. Raman

probe was positioned ~1 cm from the bottom of the jar. Total monitoring time was 60 min. Raman spectra were collected every 2 seconds with a new dark spectrum collected before each data spectrum. Laser power was 485 mW. Jar was subtracted according to the published procedure.<sup>5</sup> Any spikes arising from the misappropriate jar subtraction or the detector were removed by dividing the sum of the two nearest points. Data analysis and visualization was performed in Origin. Reaction profiles were estimated by plotting normalized values of the maximum intensity band against time. Each in situ Raman monitoring experiment was repeated three times.

#### **Instrumentation**

FTIR spectra were recorded on a PerkinElmer SpectrumTwo spectrometer equipped with a diamond cell in a 4000-400 cm<sup>-1</sup> range. PXRD patterns were collected on a PanAlytical Aeris diffractometer (Cu Kα radiation and Ni filter) in Bragg-Brentano geometry using zero background sample holder. Thermogravimetric analysis (TGA) was performed using Simultaneous Thermal Analyzer (STA) 6000 (PerkinElmer, Inc.) in open platinum crucibles at 10°C/min heating rate under 20 mL/min nitrogen gas flow.

#### Supercritical CO<sub>2</sub> activation

Supercritical CO<sub>2</sub> activation was performed on a Tousimis Samdri PVT-30 critical point dryer. Initially, the samples were soaked either in EtOH or EtOAc for 10 min. The solvent was exchanged with fresh liquid CO<sub>2</sub> every two hour for five times. The sample was then taken beyond the critical point of CO<sub>2</sub> where T ~ 38 °C and P ~ 1300 psi and slowly vented over the course of 24h at a bleeding rate of 0.5 cc/min. N<sub>2</sub> isotherms were collected at 77 K on a Micromeritics Tristar II 3020. Prior to measurement, samples were activated at 25-100 °C under vacuum for 24h for the supercritical CO<sub>2</sub> dried samples. Powder X-ray diffraction data were obtained at room temperature on a STOE-STADI P powder diffractometer equipped with an asymmetric curved Germanium monochromator (CuKα1 radiation,  $\lambda = 1.54056$  Å) and a one-dimensional silicon strip detector (MYTHEN2 1K from DECTRIS). The line focused Cu X-ray tube was operated at 40 kV and 40 mA.

Reaction	V (solvent) / mL	
LAG i-PrOH	0,04	
LAG H <sub>2</sub> O #1	0,04	
LAG H <sub>2</sub> O	0,02	
LAG H <sub>2</sub> O	0,0175	
LAG H <sub>2</sub> O	0,015	
LAG H <sub>2</sub> O	0,0125	
LAG H <sub>2</sub> O	0,01	
LAG H <sub>2</sub> O	0,005	
LAG H <sub>2</sub> O	0,002	
LAG H <sub>2</sub> O #2	0,04	
LAG EtOH	0,04	
LAG ACN	0,04	
LAG MeOH	0,04	
LAG EtOAc	0,04	
LAG EtOH Raman monitoring #1	0,04	
LAG EtOH Raman monitoring #2	0,04	
LAG EtOH Raman monitoring #3	0,04	
LAG EtOAc Raman monitoring #1	0,04	
LAG EtOAc Raman monitoring #2	0,04	
LAG EtOAc Raman monitoring #3	0,04	
Total solvent consumption = 0.602 mL		

**Table S1**. List of all experiments with solvents that were conducted for DAP solid form screening.



**Figure S1.** DSC trace of starting DAP (Carbosynth) heated by 10 °C/min heating rate in an open platinum pan under 20 mL/min nitrogen gas flow.

molecular formula	$C_5H_6N_6$
formula weight (g mol <sup>-1</sup> )	150.16
space group	Pbca
<i>a</i> (Å)	14.97434 (81)
b (Å)	12.37809 (44)
<i>c</i> (Å)	6.76487 (19)
α (deg)	90
β (deg)	90
γ(deg)	90
V (Å <sup>3</sup> )	1253.894 (88)
Z	8
temperature (K)	295
radiation type	Μο Κα
wavelength (Å)	0.71073
R <sub>p</sub>	0.054
R <sub>wp</sub>	0.071
GOF	1.97
<i>R</i> (F <sup>2</sup> )	0.023

**Table S2.** Crystallographic data for DAP-anhydrate.



**Figure S2.** Crystal packing in DAP-anhydrate. Densely packed HB layers are vertically connected by Van der Waals interactions. View along crystallographic *b*-axis.



**Figure S3.** PXRD patterns demonstrating the presence of an impurity Bragg reflection around 15.7° 2Theta in DAP-anhydrate as well as in different kind of samples. Besides being present in DAP-anhydrate, this peak could be present in all commercial DAP samples ("a" part of the figure), as well as in DAP-alpha and DAP-hemihydrate ("b" part of the figure).



**Figure S4.** a) Simultaneous TGA (blue curve) and DSC (red curve) of DAP- $\alpha$  heated by 10 °C/min heating rate in an open platinum pan under 20 mL/min nitrogen gas flow. Around 6% solvent loss upon heating to 180 °C can be seen. b) PXRD patterns showing that DAP- $\alpha$  transformed to DAP-anhydrate after heating to 240 °C (in a repeated experiment, we have stopped heating at 240 °C after an exotherm that is visible in a DSC curve and measured PXRD pattern of that sample).



**Figure S5.** Best Topas Pawley fit for DAP- $\alpha$  (sample obtained by NG DAP for 60 min) using P<sup>1</sup> space group (*a*=4.570 Å, *b*=9.553 Å, *c*=16.448 Å, *α*=84.453°, *β*=82.151°, *γ*=110.992°, *V*=655.85 Å<sup>3</sup>).  $\lambda$ = Cu K $\alpha$ . Simulated annealing failed to provide any reasonable structural model, which is not surprising due to the lower crystallinity of DAP-  $\alpha$  sample. There is a peak around 5.5 2Theta degrees that is not included in the fit.

Starting material	Solvent	Result of solvent evaporation
DAP-α	MeOH	DAP-monohydrate
DAP-α	EtOH	DAP-HOF-1
DAP-α	i-PrOH	DAP-HOF-2



Figure S6. PXRD patterns of the products from LAG DAP with different liquid additives.



**Figure S7.** PXRD patterns showing that LAG DAP with H<sub>2</sub>O resulted in the mixture of known DAP-monohydrate- $\alpha$  and unidentified phase (peaks around 5.5 20 °, 12.5 20 °, 18 20 ° and 23.5 20 °).



**Figure S8.** Simultaneous DSC and TGA traces of the product from LAG DAP with  $H_2O$ . Heated by 10 °C/min heating rate in an open platinum pan under 20 mL/min nitrogen gas flow.



**Figure S9.** PXRD patterns of the product from LAG DAP with  $H_2O$  after heating to 268 °C in DSC experiments using different heating rates in an open platinum pan under 20 mL/min nitrogen gas flow.



**Figure S10.** PXRD patterns of the products from mechanochemical experiments. After 60 min of LAG DAP with H<sub>2</sub>O (blue pattern) along with DAP-monohydrate- $\alpha$  (red pattern), resulting product contains DAP-hemihydrate as well (black pattern). DAP-hemihydrate was obtained by heating the product of LAG DAP with H<sub>2</sub>O to 121 °C. Overnight milling (for 16h) of LAG DAP with H<sub>2</sub>O resulted in obtaining pure DAP-monohydrate- $\alpha$  (green pattern).



**Figure S11.** PXRD patterns of products of LAG DAP with different volumes of  $H_2O$  and their comparison to DAP-monohydrate- $\alpha$ , DAP-hemihydrate, and DAP- $\alpha$ .

**Table S4.** Attempts to grow single crystals of DAP-hemihydrate resulted in different DAP solid forms.

Starting material	Solvent	Result of solvent evaporation
DAP-hemihydrate	H <sub>2</sub> O	DAP-monohydrate
DAP-hemihydrate	MeOH	DAP-monohydrate
DAP-hemihydrate	EtOH	DAP-HOF-1
DAP-hemihydrate	i-PrOH	DAP-HOF-2

 Table S5. Crystallographic data for DAP-HOF-1.

Identification code	exp_3525_auto
Empirical formula	C <sub>5</sub> H <sub>6</sub> N <sub>6</sub>
Formula weight	150.16
Temperature/K	169.99(10)
Crystal system	trigonal
Space group	R-3
a/Å	18.8845(7)
b/Å	18.8845(7)
c/Å	10.7786(4)
α/°	90
β/°	90
$\gamma^{/\circ}$	120
Volume/Å <sup>3</sup>	3328.9(3)
Z	18
$\rho_{calc}g/cm^3$	1.348
µ/mm <sup>-1</sup>	0.806
F(000)	1404.0
Crystal size/mm <sup>3</sup>	0.24  imes 0.11  imes 0.1
Radiation	Cu K $\alpha$ ( $\lambda$ = 1.54184)
2@ range for data collection/° 9.828 to 131.994	
Index ranges	-19 $\leq h \leq$ 22, -22 $\leq k \leq$ 19, -12 $\leq l \leq$ 10
Reflections collected	3452
Independent reflections	1293 [ $R_{int} = 0.0461, R_{sigma} = 0.0376$ ]
Data/restraints/parameters	1293/0/109
Goodness-of-fit on $F^2$	1.054
Final R indexes [I>= $2\sigma$ (I)]	$R_1 = 0.0547, wR_2 = 0.1546$
Final R indexes [all data]	$R_1 = 0.0592, wR_2 = 0.1564$
Largest diff. peak/hole / e Å <sup>-3</sup> 0.27/-0.29	



**Figure S12.** ORTEP representation of the asymmetric unit of DAP-HOF-1. Displacement ellipsoids are drawn for the probability of 50% and hydrogen atoms are shown as spheres of arbitrary radii.



**Figure S13.** PXRD patterns showing that a mixture of new crystalline phase (DAP-HOF-1) and contamination (peaks marked with an asterisk) likely coming from DAP hemihydrate (black pattern) formed after LAG DAP with EtOH for 60 min (red pattern). Continuation of milling for 16h resulted in disappearance of those extra peaks (blue pattern).



**Figure S14.** Topas Rietveld refinement of blue PXRD pattern from Fig. S14 showing that pure DAP-HOF-1 was synthesized by mechanochemistry ( $\lambda$ =Cu K $\alpha$ ). Blue – experimental PXRD pattern, red – calculated PXRD pattern, grey – difference curve. CIF of DAP-HOF-1 without solvent was used for the refinement (Table S5).



Figure S15. Unit cell of DAP-HOF-1. View along crystallographic *c*-axis.



**Figure S16.** TGA curve for DAP-HOF-1 heated by 10 °C/min heating rate in an open platinum pan under 20 mL/min nitrogen gas flow.



**Figure S17.** DSC trace for DAP-HOF-1 heated by 10 °C/min heating rate in an open platinum pan under 20 mL/min nitrogen gas flow.



**Figure S18.** PXRD patterns showing that DAP-HOF-1 undergoes a phase transition to DAPanhydrate after heating to 240 °C (in a repeated experiment from Figure S17).

 Table S6. Crystallographic data for DAP-HOF-2.

Empirical formula	C <sub>5</sub> H <sub>6</sub> N <sub>6</sub>
Formula weight	225.24
Temperature/K	169.99(10)
Crystal system	triclinic
Space group	P-1
a/Å	10.7265(5)
b/Å	11.3448(2)
c/Å	11.6327(4)
a/°	109.619(3)
β/°	108.625(3)
$\gamma^{/\circ}$	107.919(3)
Volume/Å <sup>3</sup>	1118.77(8)
Z	6
$\rho_{calc}g/cm^3$	1.337
$\mu/\text{mm}^{-1}$	0.800
F(000)	468.0
Crystal size/mm <sup>3</sup>	$0.24\times0.17\times0.11$
Radiation	$Cu K\alpha (\lambda = 1.54184)$
2@ range for data collection/° 9.348 to 131.99	
Index ranges	$\text{-}12 \leq h \leq 12,  \text{-}13 \leq k \leq 13,  \text{-}13 \leq l \leq 13$
Reflections collected	7318
Independent reflections	7318 [ $R_{int} = 0.0791$ , $R_{sigma} = 0.0109$ ]
Data/restraints/parameters	7318/0/309
Goodness-of-fit on $F^2$	1.095
Final R indexes [I>= $2\sigma$ (I)]	$R_1 = 0.0804, wR_2 = 0.2400$
Final R indexes [all data]	$R_1 = 0.0839, wR_2 = 0.2464$
Largest diff. peak/hole / e Å <sup>-3</sup> 0.64/-0.46	



**Figure S19.** ORTEP representation of the asymmetric unit of DAP-HOF-2. Displacement ellipsoids are drawn for the probability of 50% and hydrogen atoms are shown as spheres of arbitrary radii.



**Figure S20.** PXRD patterns showing that a mixture of new crystalline phase (DAP-HOF-2) and contamination (peaks marked with an asterisk) partly coming from DAP hemihydrate (black pattern) formed after LAG DAP with EtOAc for 60 min (red pattern). Continuation of milling for 16h resulted in disappearance of those extra peaks (blue pattern).



**Figure S21.** Topas Rietveld refinement of blue PXRD pattern from Fig. S20 showing that pure DAP-HOF-2 was synthesized by mechanochemistry ( $\lambda$ =Cu K $\alpha$ ). Blue – experimental PXRD pattern, red – calculated PXRD pattern, grey – difference curve. CIF of DAP-HOF-2 without solvent was used for the refinement (Table S6).



Figure S22. The unit cell of DAP-HOF-2. View along crystallographic *a*-axis.



Figure S23. TGA curve for DAP-HOF-2 heated by 10 °C/min heating rate in an open platinum

pan under 20 mL/min nitrogen gas flow.



**Figure S24.** DSC trace for DAP-HOF-2 heated by 10 °C/min heating rate in an open platinum pan under 20 mL/min nitrogen gas flow.



**Figure S25.** PXRD patterns showing that DAP-HOF-2 undergoes a phase transition to DAPanhydrate after heating to 240 °C.



**Figure S26.** Nitrogen adsorption isotherms and pore volumes for DAP-HOF-1 and DAP-HOF-2.



**Figure S27.** PXRD patterns showing that the crystallinity of the samples was preserved after activation by supercritical  $CO_2$  and heating for 24h at 50°C.



**Figure S28.** Nitrogen adsorption isotherms for DAP- $\alpha$  confirmed that it is not a porous phase. Crystallinity of the sample was preserved after activation by supercritical CO<sub>2</sub> and heating for 24h at 50°C.



**Figure S29.** In situ Raman monitoring of mechanochemical DAP-HOF-1 synthesis using EtOH as liquid additive (reaction #2).



**Figure S30.** In situ Raman monitoring of mechanochemical DAP-HOF-1 synthesis using EtOH as liquid additive (reaction #2). Spectra during first 10 min of the reaction are shown.



**Figure S31.** In situ Raman monitoring of mechanochemical DAP-HOF-1 synthesis using EtOH as liquid additive (reaction #3).



**Figure S32.** In situ Raman monitoring of mechanochemical DAP-HOF-2 synthesis using EtOAc as liquid additive (reaction #2).



**Figure S33.** In situ Raman monitoring of mechanochemical DAP-HOF-2 synthesis using EtOAc as liquid additive (reaction #2). Spectra during 10-25 min of the reaction are shown.



**Figure S34.** In situ Raman monitoring of mechanochemical DAP-HOF-2 synthesis using EtOAc as liquid additive (reaction #3).



**Figure S35**. Ex situ Raman spectra of DAP-HOF-1 (obtained by LAG DAP with EtOH) and DAP-HOF-2 (obtained by LAG DAP with EtOAc).



**Figure S36.** PXRD patterns showing that DAP- $\alpha$  perseveres after NG for 16 h. Reduced crystallinity of the sample is observed.



Figure S37. PXRD patterns of DAP-anhydrate and DAP-anhydrate that was NG for 16 h.



Figure S38. PXRD patterns of DAP-hemihydrate and DAP-hemihydrate that was NG for 16h.



**Figure S39.** FTIR showing identical spectra of DAP-anhydrate and DAP-hemihydrate after NG for 16 h.



**Figure S40.** PXRD patterns of DAP-anhydrate (magenta in Fig. S37) and DAP-hemihydrate (grey in Fig. S38) that were milled for 16h and were left to sit on the bench for four days, compared to DAP-hemihydrate and DAP-alpha. Red pattern contains DAP-hemihydrate together with DAP-alpha, and blue pattern possibly contains some other phase besides DAP-alpha.



**Figure S41.** PXRD patterns showing that DAP purchased from Thermo Scientific/Alfa Aesar is a mixture of DAP-hemihydrate and DAP- $\alpha$ .



**Figure S42.** PXRD patterns showing that DAP purchased from Sigma Aldrich is a mixture of DAP-anhydrate, DAP- $\alpha$ , and DAP-HOF-1.

# References

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