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Supporting information for the manuscript

Determining short-lived solid forms during phase transformations using molecular dynamics

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Experimental procedures

Sample preparation The metastable form was prepared by dissolving 6 g of the stable anhydrate, as obtained from Sigma-Aldrich, in 6 mL of water, followed by grinding with mortar and pestle until a paste-like consistency. The paste was placed in a desiccator above potassium sulphate, at 35-40 °C for 24 hours, followed by grinding with mortar and pestle. Then it was dried at room temperature under vacuum for 3-4 days. The final solid was also ground before use. The metastable form appears to be stable as long as it is kept under vacuum. We prolonged the existence of this form by sealing in a glass capillary and performed measurements as soon as possible thereafter.

Crystallography The PXRD measurements were performed on a Bruker D8 Discover instrument at room temperature and relative humidity of 23-33 %. The sampled was placed in a 0.8 mm capillary and sealed immediately. The sample was rotated during the measurements in transmission mode using Cu-Kalpha radiation. A variable counting time strategy was used to collect data in the 2θ range of 5-70 degrees with a step size of 0.02 degrees. The counting time was increased in a stepwise manner from 3 seconds per step at the lowest angles to 87 seconds per step at the highest angles. The total measurement time was 26 hours. The structure retrieved from the MD simulation and optimized using periodic DFT-D calculations was used as input for a rigid-body Rietveld refinement in the programme DASH[25]. The diffraction data and the refined structure has been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 1842250.

NMR measurements The NMR spectra were recorded on a Bruker Avance 400 spectrometer (Bruker Biospin, GmbH, Karlsruhe, Germany) operating at Larmor frequencies of 40.54, 100.62 and 400.13 MHz for ^{13}C and ^{1}H, respectively, using a double-tuned CP/MAS (Cross polarization/Magic Angle Spinning) probe equipped for 4 mm (o.d.) rotors. The ^{13}C CP/MAS spectra were recorded at 294 K using a contact time of 9.0 ms, a spin-rate of 9500 Hz, a recycle delay of 512 s, an acquisition time of 37.2 ms during which ^{1}H TPPM decoupling (80 kHz rf-field strength)[26] was employed, and 16 scans. The cross polarization was carried out using variable amplitude CP[27] with a maximum rf-field strength of 80 kHz for both ^{1}H and ^{13}C. ^{13}C chemical shifts were referenced to an external sample of α-glycine (carbonyl group) at 176.5 ppm. The ^{15}N CP/MAS spectra were recorded at 294 K using a contact time of 9.5 ms, a spin-rate of 8000 Hz, a recycle delay of 256 s, an acquisition time of 47.9 ms during which ^{1}H TPPM decoupling (67 kHz rf-field strength)[26] was employed, and 680 scans. The cross polarization was carried out using variable amplitude CP[27] with a maximum rf-field strength of 43 kHz for both ^{1}H and ^{15}N. ^{15}N chemical shifts were referenced to an external sample of ^{15}N enriched (98 %) L-Leucine at 43.4 ppm. Data were processed using TopSpin 3.5 (Bruker Biospin GmbH, Karlsruhe, Germany) and then transferred to Matlab 9.3.0 (MathWorks Inc., Natick, MA) to set up figures.

Molecular dynamics and DFT The theophylline molecule was modelled using the GAFF2[28,29] force field with RESP atomic charges found using the R.E.D. server[30] and the SPC[31] water model. All MD simulations were performed using he GROMACS 5.1.1 software package[32] the electrostatics and van der Waals were calculated with the particle mesh Ewald approach.[33] The leap-frog algorithm was used as integrator together with the velocity rescaling thermostat[34] and the Berendsen barostat.[35] The simulation cell was made from 20 by 4 by 4 unit cells of the experimental monohydrate crystal with 200 Å of vacuum added along the A-axis. The structure was initially energy minimised using the force field and then heated in a temperature series until the dehydration target temperature of

375K. The dehydrating simulation was run for 260 ns and every 200 ps the water molecules in the vacuum region were removed in order to simulate dehydration at 0% RH. Proposed unit cells of the intermediate and metastable structures were cut from the simulation cell at 20 ns and 260 ns respectively

The unit cells were energy minimised using DFT-D with the CASTEP software package[36]. This was done using the Perdew-Burke-Ernzerhof(PBE)[37] functional with the D2[38] dispersion correction and a plane wave basis set cut-off of 520 eV.

The *ab initio* MD simulation using DFT were performed using the CP2K software package[39] with the PBE[37] functional and D3 dispersion correction.[40] The CSVR thermo and barostat[34] was used in the NPT ensemble with a 1 fs timestep. The 4 by 2 by 2 simulation cell of the monohydrate was heated in a temperature series to 375K and equilibrated for 2 ps. All water molecules were deleted from the last frame of the temperature series and the desolvated system was simulated for 6 ps. A 3 by 3 by 2 simulation cell of the intermediate **T1** structure was heated to 375K and simulate in a NPT ensemble for 10 ps.

For the calculation of the chemical shifts, the unit cells were energy minimised using DFT-D with the CASTEP software package, using the PBE functional with the Grimme 2006 dispersion correction (PBE-D2). The optimization was started with an energy cut-off of 520 eV, where the atomic positions were allowed to vary with the unit-cell parameters fixed and the core-valence electron interactions are described by ultrasoft pseudopotentials, afterwards both the atomic positions and the unit cell were allowed to vary, with the same energy cut-off and pseudopotentials. Finally norm-conserving pseudopotentials were used with an energy cut-off of 1200 eV. Integrals taken over the Brillouin zone were performed using Monkhorst–Pack grid with a maximum sample spacing of 0.07 $Å^{-1}$ for both step I and II geometry optimization and 0.05 $Å^{-1}$ for step III, with at least two k-points along each direction.

The NMR chemical shielding tensors were also calculated using CASTEP with the GIPAW method using ultrasoft pseudopotentials generated on-the-fly, a maximum plane wave cut-off energy of 1200 eV, and the integrals performed over the Brillouin zone using a Monkhorst–Pack grid with a sample spacing of 0.05 $Å^{-1}$. The convergence with respect to plane waves was controlled by varying the maximal plane wave cut-off energy from 800 top 1600 eV. The same convergence behavior was observed for both compounds, the variation being less than 1 ppm. Also the convergence with the sampling of the Brillouin zone was checked by changing the spacing from 0.05 to 0.1 $Å^{-1}$, which also let to changes smaller than 1 ppm. The output of this NMR calculation is the absolute nuclear shielding tensor. In order to compare the results directly to experiment, it was converted to the chemical shift on the appropriate scale. For ^{13}C a value of 188 ppm for tetramethylsilane (TMS) was employed (Table S2) and for 15N a unified scale[41] (Table S3).

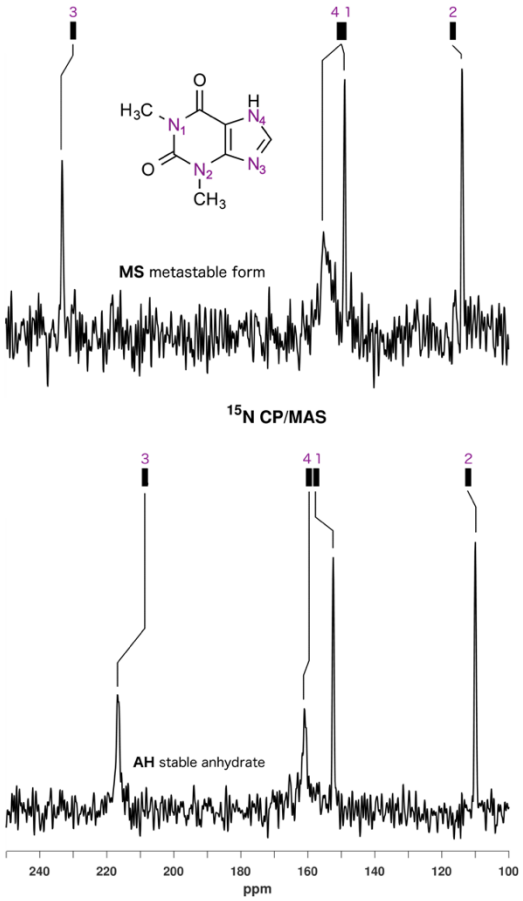

Figure S5: Solid-state ^{15}N NMR spectre of the metastable form and stable anhydrate. The absolute values refer to a unified scale[41]. The DFT computed shielding constants σ_{calc} were converted into calculated chemical shifts δ_{calc} using the relation $\delta_{calc} = \sigma_{ref} - \sigma_{calc}$ with the value of σ_{ref} determined for each molecule by a linear regression between calculated and experimental shifts, imposing a slope of unity[44]

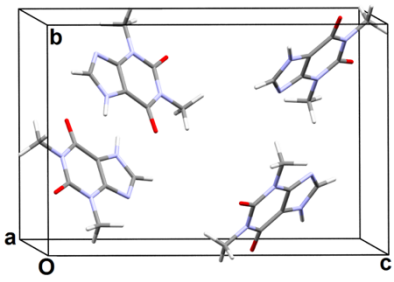

Figure S1: *Unit cell of the metastable (MS) form.*

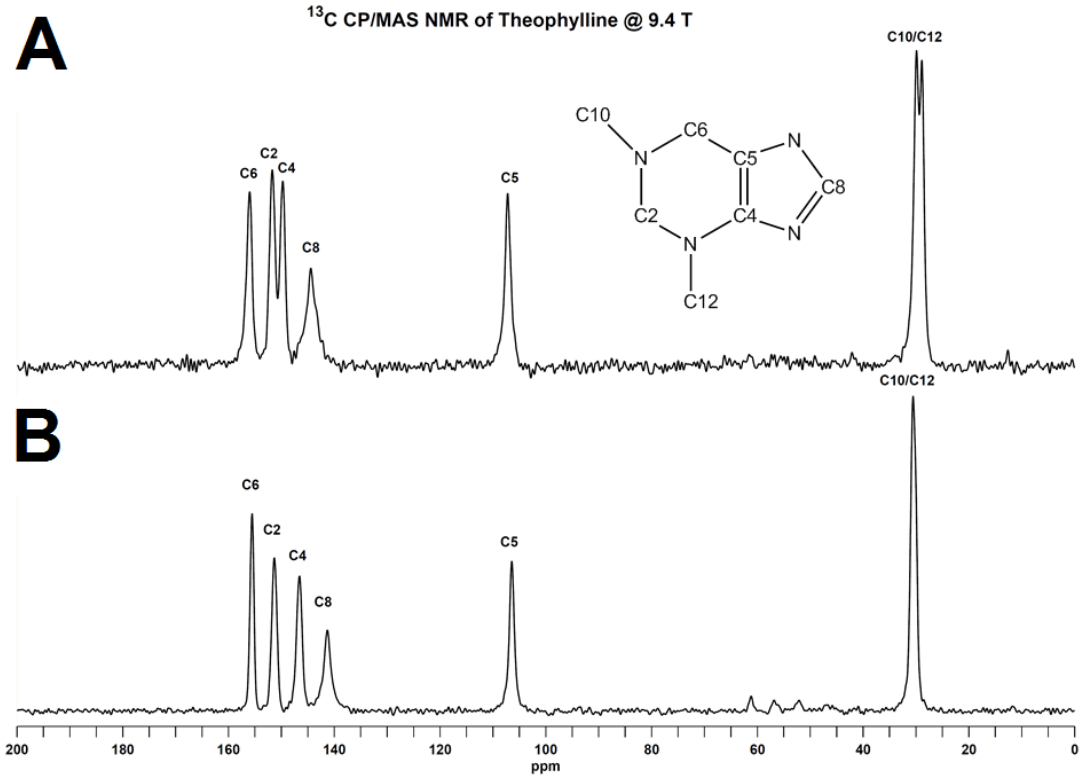

Figure *s7*: Solid-state ^{13}C CP/MAS NMR spectra of the (A) metastable form and (B) stable anhydrate of theophylline.

Structure	a (Å)	b (Å)	c (Å)	α (deg)	β (deg)	γ (deg)	Space group	Energy (kJ mol^{-1} molecule^{-1})
Stable anhydrate **AH**	24.24	3.63	8.53	90	90	90	$Pna2_1$	0
Metastable anhydrate **MS**	4.50	11.16	15.39	90	91.94	90	$P2_1/c$	5.57
Metastable anhydr. exp	4.5310(7)	11.5783(1)	15.7188(2)	90	93.69(1)	90	$P2_1/c$	-
Intermediate Phase **T1**	3.72	13.16	15.47	90	98.73	90	-	7.86
Monohydrate **MH**	4.30	14.99	13.51	90	101.71	90	$P2_1/n$	-

Table S1: DFT optimised and experimental unit cell parameters and energies relative to the stable anhydrate.

Table S2: DFT calculated ^{13}C chemical shifts (in ppm) of the metastable form (**MS**) and the stable anhydrate (**AH**, CSD code BAPLOT01).

	C_6	C_2	C_4	C_8	C_5	C_{10}	C_{12}
Stable Anhydrate	172.9	168.8	165.9	161.0	127.5	48.7	46.4
Metastable Anhydrate	172.1	170.2	168.1	165.7	128.4	45.1	44.0

Table S3: DFT calculated ^{15}N chemical shifts (in ppm) of the metastable form (**MS**) and the stable anhydrate (**AH**, CSD code BAPLOT01).

	N_1	N_2	N_3	N_4
Stable Anhydrate	186.2	140.6	237.3	187.8
Metastable Anhydrate	180.4	146.3	259.8	181.1

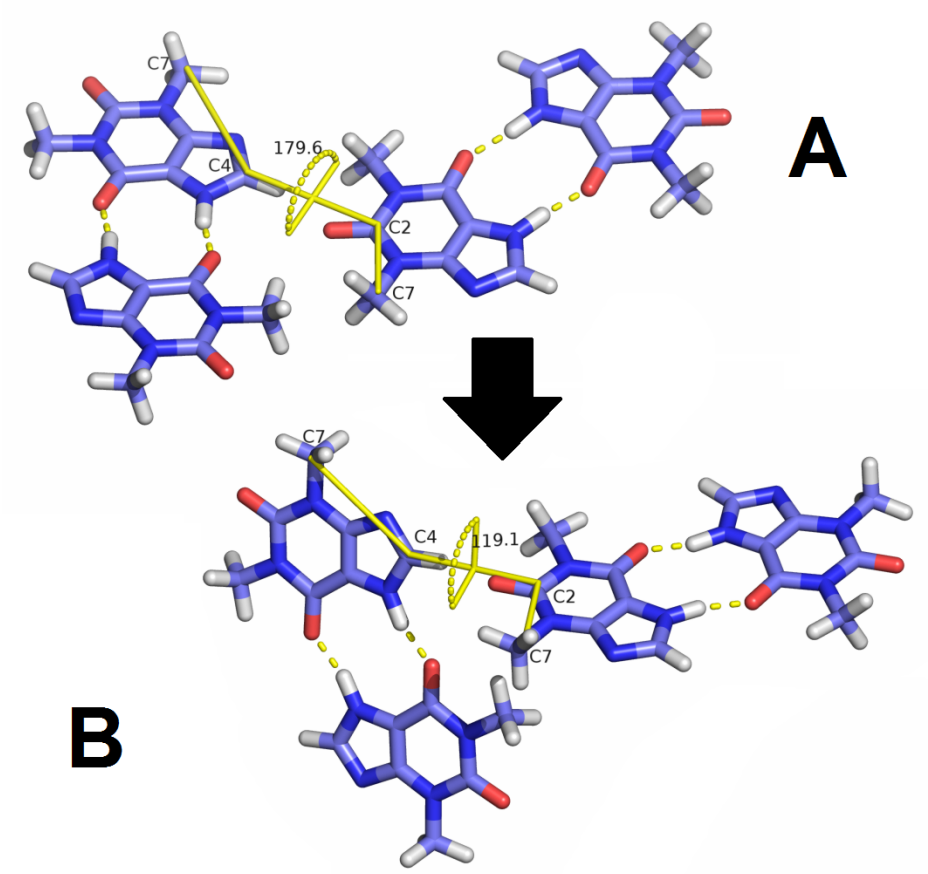

Figure S8: (A) two hydrogen bonded dimers from adjacent layers in the transition phase, with the dihedral angle C7-C4-C2-C7 of 179.6° highlighted. (B) The same hydrogen bond dimers in the metastable form with the C7-C4-C2-C7 angle of 119.1°.