Electronic Supplementary Information

On the Kinetics of Solvate Formation through Mechanochemistry

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1. METHODS

1.1. Differential Scanning Calorimetry (DSC)

DSC analyses were performed using a Mettler Toledo DSC822 instrument. The selected heating rate was 10°C/min and scanning range from 25°C to 300°C under nitrogen purge flow. Solid samples were prepared by placing the material in a 40 μ l standard aluminium pan (2-4 mg), and subsequently sealed using an aluminium lid.

1.2 Thermogravimetric analysis (TGA)

TGA analyses were performed in air conditions using a Mettler Toledo TGA/SDTA851e/SF/1100 instrument, while for data acquisition and analysis STARe software was used. Approximately 5 to 20 mg of sample was analysed in a 100 μ l aluminium pan at a heating rate of 10 °C/min.

2. RESULTS

2.1 PXRD patterns



Fig S1. PXRD patterns of the products THEO-PYR in 1:0.1 molar ratio obtained after 60 min of grinding.



Fig S2. PXRD patterns of the products THEO-PYR in 1:0.2 molar ratio obtained after 60 min of grinding.



Fig S3. PXRD patterns of the products THEO-PYR in 1:0.3 molar ratio obtained after 60 min of grinding.



Fig S4. PXRD patterns of the products THEO-PYR in 1:0.4 molar ratio obtained after 60 min of grinding.



Fig S5. PXRD patterns of the products THEO-PYR in 1:0.5 molar ratio obtained after 60 min of grinding.



Fig S6. PXRD patterns of the products THEO-PYR in 1:0.6 molar ratio obtained after 60 min of grinding.



Fig S7. PXRD patterns of the products THEO-PYR in 1:0.7 molar ratio obtained after 60 min of grinding.



Fig S8. PXRD patterns of the products THEO-PYR in 1:0.8 molar ratio obtained after 60 min of grinding.



Fig S9. PXRD patterns of the products THEO-PYR in 1:0.9 molar ratio obtained after 60 min of grinding.



Fig S10. PXRD patterns of the products THEO-PYR in 1:1 molar ratio obtained after 60 min of grinding.



Fig S11. PXRD patterns of the products THEO-PYR in 1:1.1 molar ratio obtained after 60 min of grinding.



Fig S12. PXRD patterns of the products THEO-PYR in 1:1.2 molar ratio obtained after 60 min of grinding.



Fig S13. PXRD patterns of the products THEO-PYR in 1:1.3 molar ratio obtained after 60 min of grinding.



Fig S14. PXRD patterns of the products THEO-PYR in 1:1.4 molar ratio obtained after 60 min of grinding.



Fig S15. PXRD patterns of the products THEO-PYR in 1:1.5 molar ratio obtained after 60 min of grinding.



Fig S16. PXRD patterns of the products THEO-PYR in 1:1.6 molar ratio obtained after 60 min of grinding.



Fig S17. PXRD patterns of the products THEO-PYR in 1:1.7 molar ratio obtained after 60 min of grinding.



Fig S18. PXRD patterns of the products THEO-PYR in 1:1.8 molar ratio obtained after 60 min of grinding.



Fig S19. PXRD patterns of the products THEO-PYR in 1:1.9 molar ratio obtained after 60 min of grinding.



Fig S20. PXRD patterns of the products THEO-PYR in 1:2 molar ratio obtained after 60 min of grinding.



Fig S21. PXRD patterns of the products THEO-PYR in 1:3 and 1:4 molar ratios obtained after 60 min of grinding.



Fig S22. PXRD patterns of the products containing THEO:PYR in 1:1 molar ratio ground for different periods of time.



Fig S23. PXRD patterns of the products containing THEO:PYR in 1:1.5 molar ratio ground for different periods of time.



Fig S24. PXRD patterns of the products containing THEO:PYR in 1:1.7 molar ratio ground for different periods of time.



Fig S24. PXRD patterns of the products containing THEO:PYR in 1:2 molar ratio ground for different periods of time.



Fig S25. PXRD patterns of a) THEO-PYR monosolvate (calculated), b) THEO-PYR monosolvate neat ground for 180 min, c) THEO-PYR sesquisolvate (calculated) and d) THEO-PYR sesquisolvate neat for 180 min.



Fig S26. PXRD patterns of a) pure THEO (calculated), b) THEO-PYR monosolvate (calculated) c) THEO-PYR sesquisolvate (calculated), d) 1:1 weight mixture of pure THEO and THEO monosolvate neat ground for 60 min, e) 1:1 weight mixture of THEO monosolvate and sesquisolvate neat ground for 60 min, f) 1:1 weight mixture of pure THEO and THEO sesquisolvate neat ground for 60 min and g) 1:1:1 weight mixture of pure THEO, monosolvate and sesquisolvate neat ground for 60 min.

2.2 Rietveld refinement



Fig. S27. Rietveld refinement of a mixture of THEO with 0.1 eq. PYR after 1 hour grinding. The product mixture contains 83.5% THEO and 16.5% THEO:PYR monoslovate by weight. The experimental diffraction profile is shown in blue, while the calculated profile is shown in red. The difference curve is shown in grey.



Fig. S28. Rietveld refinement of a mixture of THEO with 0.4 eq. PYR after 1 hour grinding. The product mixture contains 47.9% THEO and 52.1% THEO:PYR monoslovate by weight. The experimental diffraction profile is shown in blue, while the calculated profile is shown in red. The difference curve is shown in grey.



Fig. S29. Rietveld refinement of a mixture of THEO with 0.6 eq. PYR after 1 hour grinding. The product mixture contains 35.4% THEO and 64.6% THEO:PYR monoslovate by weight. The experimental diffraction profile is shown in blue, while the calculated profile is shown in red. The difference curve is shown in grey.



Fig. S30. Rietveld refinement of a mixture of THEO with 1.4 eq. PYR after 1 hour grinding. The product mixture contains 34.04% THEO:PYR monosolvate, 66.6% THEO:PYR sesquislovate by weight and no anhydrous THEO. The experimental diffraction profile is shown in blue, while the calculated profile is shown in red. The difference curve is shown in grey.

2.3 Calorimetric analysis



Fig S31. TGA of THEO-PYR monosolvate (theoretical weight loss is 31%) prepared by grinding THEO and PYR for 60 min in 1:1.1 molar ratio.



Fig S32. TGA of THEO-PYR sesquisolvate (theoretical weight loss is 43%) prepared by grinding THEO and PYR for 60 min in 1:1.7 molar ratio.



Fig S33. DSC of THEO-PYR monosolvate prepared by grinding THEO and PYR for 60 min in 1:1.1 molar ratio.



Fig S34. DSC of THEO-PYR monosolvate prepared by grinding THEO and PYR for 60 min in 1:1.7 molar ratio.

2.4 Microscope photographs



Fig S35. Microscope photograph of a single crystal of THEO-PYR monosolvate.



Fig S36. Microscope photograph of a single crystal of THEO-PYR sesquisolvate.

2.5 Structure analysis of Form II and the Solvates



Fig S37. Illustration of key planes in (a) THEO Form II , (b) THEO-PYR monosolvate and (c) THEO-PYR sesquisolvate. PYR molecules are not shown, however location is illustrated with a blue hypersurface.

The structures of THEO Form II and the solvates can be viewed as layer structures (Figure S37). To aid the visualisation, PYR molecules have been removed from the solvates and a blue hypersurface has been shown instead. In going from pure THEO to the monosolvate, the THEO-THEO hydrogen bonds are broken and new THEO-PYR hydrogen bonds are formed. In going from the monosolvate to the sesquisolvate, the THEO-PYR hydrogen bonds are partially broken in order to form PYR-PYR H-bond dimers. We notice that the THEO stacks is the main interaction that remains across the anhydrous form II and the solvates. The symmetry of the stacks changes, however, between forms. A view of these structures across the stack directions clearly shows well-defined THEO layers. We can postulate that in going from THEO Form II to the monosolvate, the solvent might find its easiest

way into the crystal through the (200) crystallographic plane of THEO Form II. This is the weakest crystallographic cleave plane as revealed from the Crystal Energy Framework Calculations. This results in a monosolvate that can be viewed as layers of THEO-PYR_THEO (Figure S37b). On further insertion of solvent molecules in the PYR layer of the monosolvate (which corresponds with the (001) crystallographic plane), the sesquisolvate is formed which is also has a THEO-PYR-THEO layered structure.



Fig S38. Softest planes in the Theo Form II (left) and Theo Form IV (right) structures.

2.6 Energy Gain Calculations

As described in the main article, we calculate the reaction energy or energy gain (E_{gain}) as the difference between the energy of the products minus the energy of the reactants weighted by their stoichiometries.

$$E_{gain} = \sum x_{product} E_{product} - \sum x_{reactant} E_{reactant}$$



Figure S39. Plot of overall energy gain as a function of PYR:THEO stoichiometric ratio for different products when a) the lattice energy of PYR was used or b) the experimental heat of vaporisation of PYR was used).

This energy gain can be calculated for all possible outcomes of this supramolecular reaction, those being: i) only the 1:1.5 solvate forming, ii) only the 1:1 solvate forming, iii) the 1:1 solvate forming up to 1:1 stoichiometries followed by formation of 1:1.5 solvate and iv) no solvate formation at all. The energy gain can then be calculated for a whole range of stoichiometries (Fig S39). For the energetics of products and reactants, we used the computed lattice energies. For PYR, however, this is a crude approximation given that PYR is a liquid (and not a crystal) at room temperature. The E_{gain} as calculated using the lattice energy of PYR (model 1) is presented in Fig 39a, whereas the E_{gain} as calculated using the experimental heat of vaporisation of PYR liquid (model 2) is presented in Fig 39b.

With both models, there is a favourable (negative) energy gain in forming the monosolvate. Both models, therefore, predict that in the 0:1-1:1 THEO:PYR stoichiometric range, the thermodynamically stable product of the reaction is the 1:1 solvate (black or green lines). The energy gain in forming this solvate, however, is much more significant in model 2. The first model predicts the sesquisolvate to be slightly less stable (by 4kJ/mol) than no sesquisolvate formation. These energies are very small and are not quite representative of the PYR case where PYR is a liquid at room temperature. The second model, however, predicts the sesquisolvate to be thermodynamically more stable than the monosolvate formation alone at higher PYR stoichiometries. The energy gains are more significant too.

2.7 Synthesis of THEO Form IV

Theophylline Form IV was obtained by solvent-mediated phase transformation [1] from theophylline Form II (Sigma Aldrich, anhydrous) as described in [2]. A slurry of 4g of Theophylline Form II into 100mL of Methanol (Acros Organics, Extra Dry, over Molecular Sieves) was stirred continuously over 50 days at constant temperature of 23±0.2°C. 3mL of the solution with the particles in suspension were syringed every few days without stopping the stirring and consecutively dried. PXRD measurement was therefore carried out at room temperature to monitor qualitatively the transformation (Figure S40). The form IV started to appear after 30 days and no trace of form II was detectable after 40 days. The stirring was stopped day 50 to ensure the completeness of the phase transformation.



FigureS40: Evolution of PXRD patterns over time of the solvent-mediated phase transformed solute compared to calculated theophylline Form II (BAPLOT01) and Form IV (BAPLOT02).

2.8 DSC for Theophylline Forms II and IV



Figure S41. DSC thermographs for THEO Form II (black) and Form IV (red).

For THEO Form II, one large endothermic thermal event is registered at 270.5 °C. This event corresponds to the melting of form II and has an enthalpy of 27 kJ/mol.

For THEO Form IV thermograph, a small endothermic event is first registered at T 230 °C. This corresponds to the form IV to form II conversion which requires 0.5 kJ/mol. The second event, is the melting of form II at 270.5 °C.

2.9 Kinetic studies of the Form II vs. Form IV conversion to the monosolvate

200 mg of both THEO Forms II and IV were placed inside a test sieve (aperture: 90µm, Endecotts). The test sieve was screwed at the top of a copper pan filled with 10g of PYR. The copper pan was placed on a hot plate at 130°C for one hour in order for the PYR to evaporate on the powder (Fig S38). Because the system was open, PYR did not condensate in the test sieve. Possible transformation to a solvated form was assessed via PXRD. As a comparison, 100mg of both THEO Forms II and IV were gently stirred using a spatula with two drops of PYR, and consecutive PXRD measurements were carried out (Fig. S39).



Figure S42. Experimental set up by which THEO Forms II and IV were put in contact with PYR vapour.



Figure S43. PXRD patterns of Theo Forms IV (top) and Form II (bottom) after mixed with a spatula and being exposed to PYR in vapour.

2.10 Crystal data and structure refinement

Crystal data and structure refinement details		
	THEO-PYR monosolvate	THEO-PYR sesquisolvate
CCDC number	1844138	1844137
Empirical formula	(C ₇ H ₈ N ₄ O ₂)·(C ₄ H ₇ NO)	2(C ₇ H ₈ N ₄ O ₂)·3(C ₄ H ₇ NO)
Formula weight	265.28	615.66
Temperature / K	180(2)	180(2)
Crystal system	triclinic	monoclinic
Space group	<i>P</i> –1	P21/n
a / Å	6.6482(3)	7.5056(3)
b / Å	8.7311(4)	25.0862(9)
c/Å	10.9852(5)	15.2376(6)
α/°	82.631(2)	90
β/°	84.273(2)	93.195(2)
γ/°	83.701(3)	90
Volume / ų	626.18(15)	2864.58(19)
Z	2	4
$ ho_{calc}$ / g cm $^{-3}$	1.407	1.428
μ / mm ⁻¹	1.887	0.893
F(000)	280	1304
Crystal size / mm ³	0.22×0.07×0.02	0.25×0.15×0.08
Radiation	CuKα (λ = 1.5418 Å)	CuKα (λ = 1.5418 Å)
2θ range / °	8.14 to 133.20	6.80 to 133.60
Reflections collected	14518	49605
Independent reflections	2206	5085
R _{int}	0.0442	0.0465
Goodness-of-fit on <i>F</i> ²	1.05	1.06
Data/restraints/parameters	2206/0/182	5085/0/423
<i>R</i> 1 [<i>I</i> >2σ(I)]	0.0351	0.0414
wR2 [all data]	0.0896	0.1110
Largest diff. peak/hole / eÅ ⁻³	0.27/-0.22	0.31/-0.34

Table S1. Crystal data for THEO-PYR monosolvate and sesquisolvate.

3. REFERENCES

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- 2. Bobrovs, R., Seton, L. & Dempster, N. The reluctant polymorph: investigation into the effect of selfassociation on the solvent mediated phase transformation and nucleation of theophylline. *CrystEngComm* **17**, 5237–5251 (2015).