# Electronic Supplementary Information

## Cocrystal Dissociation and Molecular Demixing in the Solid State

Mark D. Eddleston,[a*] Gareth O. Lloyd[a] and William Jones[a]

[a] Department of Chemistry, University of Cambridge, Cambridge, CB2 1EW, UK. Tel: +44 (0)1223 336465, Email: mde32@cam.ac.uk

### Experimental Section

The 1:1 caffeine:theophylline cocrystal was generated by preparing a 3:2 DMF:dioxane solution saturated in both caffeine and theophylline at ambient temperature, and then cooling this solution to 4°C to induce precipitation. Single crystals of this phase were obtained by preparing a slightly supersaturated solution of caffeine and theophylline in the same solvent mixture from which crystals grew over a period of several months.

Transmission electron microscopy characterization was performed at room temperature on a Philips CM30 instrument operating at 300 kV, and data were collected on photographic films which were scanned in order to generate electronic images. Crystals were prepared on copper grids coated with a lacey (amorphous) carbon film. Electron diffraction patterns were indexed by comparison with known crystal structures. Simulated electron diffraction patterns were generated using Crystal Maker Single Crystal Software (version 2.2.3) and are based on a kinematic model. Hot-stage microscopy was performed on a Leica DM1000 instrument with a polarising filter. Sample heating was achieved with a Mettler Toledo FP84HT TA microscopy cell. X-ray powder diffraction analysis was performed on a Philips X'Pert Diffractometer with Cu Kα radiation at a wavelength of 1.5406 Å and data collected between 3 and 50 °2θ at ambient temperature. A suitable single crystal was mounted using perflouropolyether on a thin glass fibre. Crystallographic measurements were carried out using an Agilent Gemini Ultra Diffractometer. The instrument was equipped with a mirror monochromatic CuKα radiation (γ = 1.5418). The standard data collection temperature was 120 K, maintained using an open flow $N_2$ Oxford Cryostream device. Integration was carried out using CrysAlisPro software. Data sets were corrected for Lorentz and polarization effects and for the effects of absorption using SCALE3 ABSPACK. Structures were solved using direct methods in SHELXS-97[1] and developed using conventional alternating cycles of least-squares refinement with SHELXL-97[1] and difference Fourier synthesis with the aid of the graphical interface program X-Seed.[2] Non-hydrogen atoms were treated as anisotropic. Hydrogen atoms were fixed in idealised positions and allowed to ride on the parent atom to which they were attached. Hydrogen atom thermal parameters were tied to those of the parent atom. Differential scanning calorimetry thermograms were recorded in a nitrogen atmosphere using a Mettler Toledo STARe DSC822e/700 calorimeter. The heating rate was 10 °C.min$^{-1}$ and endotherms are plotted as downward peaks. Thermogravimetric analysis was performed in air in a Mettler Toledo TGA/SDTA851e/SF/1100 instrument with a heating rate of 10 °C.min$^{-1}$.

Crystal data for Caffeine:Theophylline Cocrystal (CCDC 881269): $C_{15}H_{18}N_8O_4$, $M$ = 374.37, Colourless lath, 0.697 x 0.123 x 0.033 mm$^3$, triclinic, space group $P$-1 (No. 2), $a$ = 7.0081(7),

*b* = 8.7904(7), *c* = 13.0856(15) Å, *α* = 95.648(8), *β* = 97.090(9), *γ* = 91.667(8)°, *V* = 795.38(14) Å$^3$, *Z* = 2, $D_c$ = 1.563 g/cm$^3$, $F_{000}$ = 392, Xcalibur, Eos, Gemini ultra, CuK*α* radiation, λ = 1.54184 Å, *T* = 120(2)K, $2\theta_{max}$ = 143.1º, 4706 reflections collected, 2974 unique ($R_{int}$ = 0.0259). Final *GooF* = 1.029, *R1* = 0.0696, *wR2* = 0.1938, *R* indices based on 2390 reflections with I >2sigma(I) (refinement on $F^2$), 212 parameters, 0 restraints. Lp and absorption corrections applied, $\mu$ = 0.996 mm$^{-1}$.

1. G. M. Sheldrick, *Acta Crystallogr., Sect. A Found. Crystallogr.*, 2008, **A64**, 112-122.
2. L. J. Barbour, *J. Supramol. Chem.*, 2003, **1**, 189-191.

**XRPD Analysis**

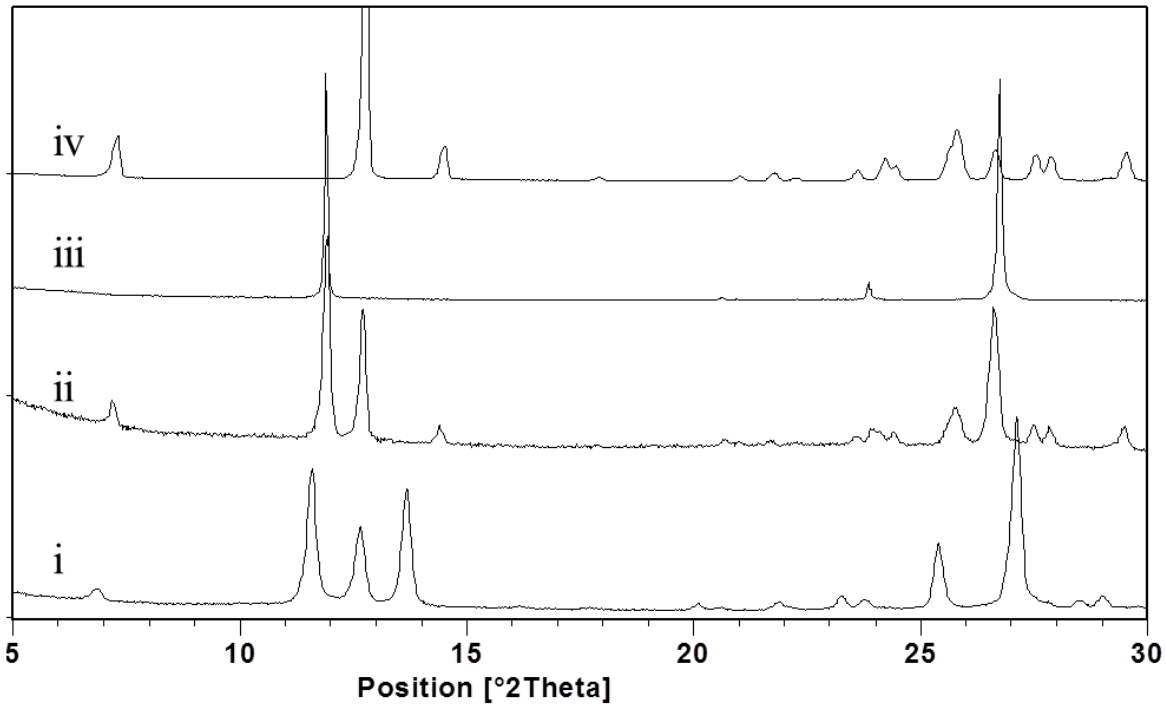


**Fig. S1** Overlay of XRPD traces of (i) a sample of the 1:1 caffeine: theophylline cocrystal, (ii) the same sample after heating to 170 °C, (iii) a reference trace of Form I of caffeine and (iv) a reference trace of Form II of theophylline.