Electronic Supplementary Material (ESI) for ChemComm.

Supplementary Information

Controlled production of the elusive metastable form II of paracetamol: a fully scalable multicomponent templating approach in a cooling environment

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Experimental

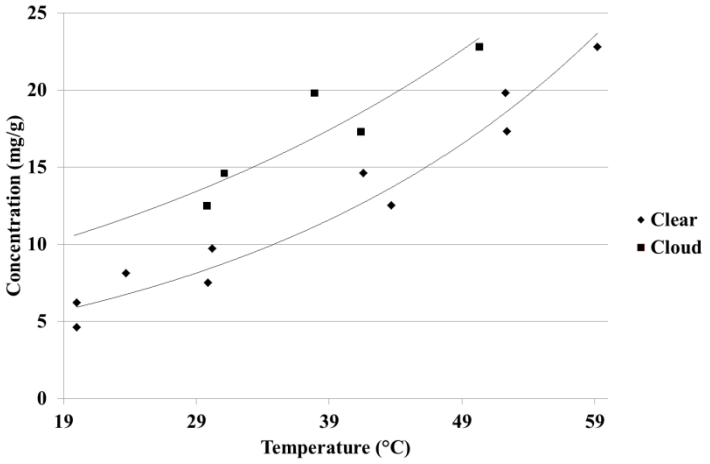
PC, 4-BrBA, 4-ClBA and 4-FBA were all purchased from Sigma Aldrich Chemie Gmbh (Steinheim, Germany). Metacetamol (3'-hydroxyacetanilide) was purchased from TCI Ltd. All were used without further purification. Laboratory grade solvents purchased from Sigma Aldrich were used for all crystallisations.

Powder X-ray diffraction (PXRD). PXRD patterns were collected in flat plate mode on a Bruker D8 Advance equipped with monochromated Cu-K_α radiation (λ = 1.54056 Å) in reflection geometry at 298 K.

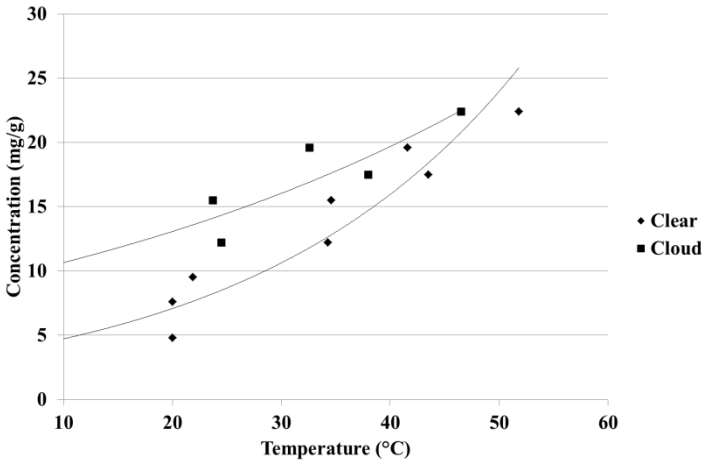
Differential Scanning Calorimetry (DSC). Differential scanning calorimetry studies were carried out using a Thermal Advantage Q20 DSC from TA Instruments, equipped with Thermal Advantage Cooling System 90 and operated with a dry nitrogen purge gas at a flow rate of 18 cm^3 min^{-1}. The samples were placed in sealed Tzero aluminium pans and a heating rate of 5 K min^{-1} was used. Data were collected using the software Advantage for Qseries (Ver. 5.40 software © 2001-2011 TA Instruments-Waters LLC).

Solubility Measurements. Solubility measurements were carried out in a 60:40 Water:IPA solvent system using a Crystal16 parallel crystalliser from Technobis using turbidity probes on 1mL samples. Vials were subjected to a heat/ cool cycle from 20 °C to 75 °C and back again using a heating rate of 0.5 °C min^{-1} and bottom stirring at 800 rpm using standard magnetic stirrer bars. Data were analysed using CrystalClear software version 1.0.1.614 supplied by Technobis.

(a)



(b)



(c)

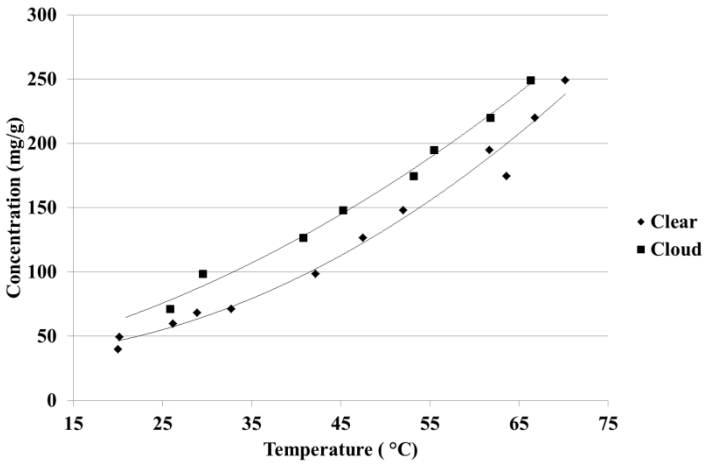


Figure S1. Solubility curves of the templating co-formers (a) 4-bromobenzoic acid, (b) 4-chlorobenzoic acid, (c) 4-fluorobenzoic acid

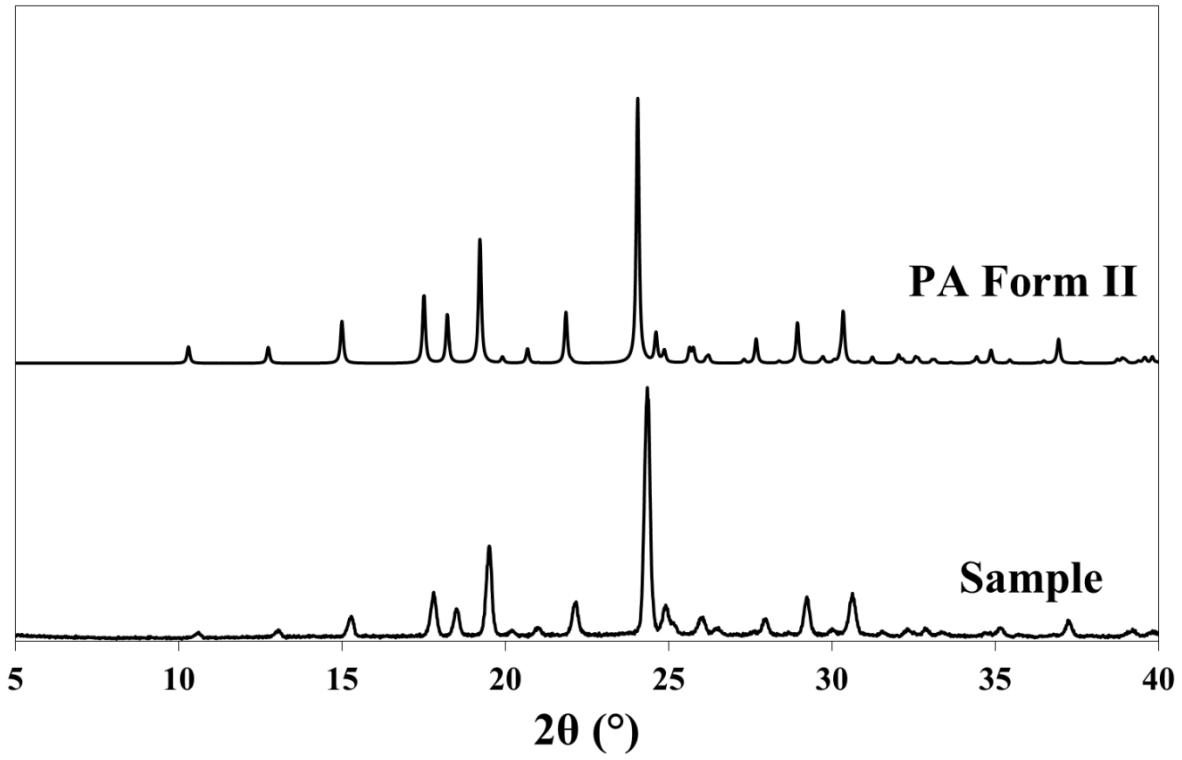


Figure S2. PXRD pattern showing the match of the bulk sample to that calculated from single crystal data

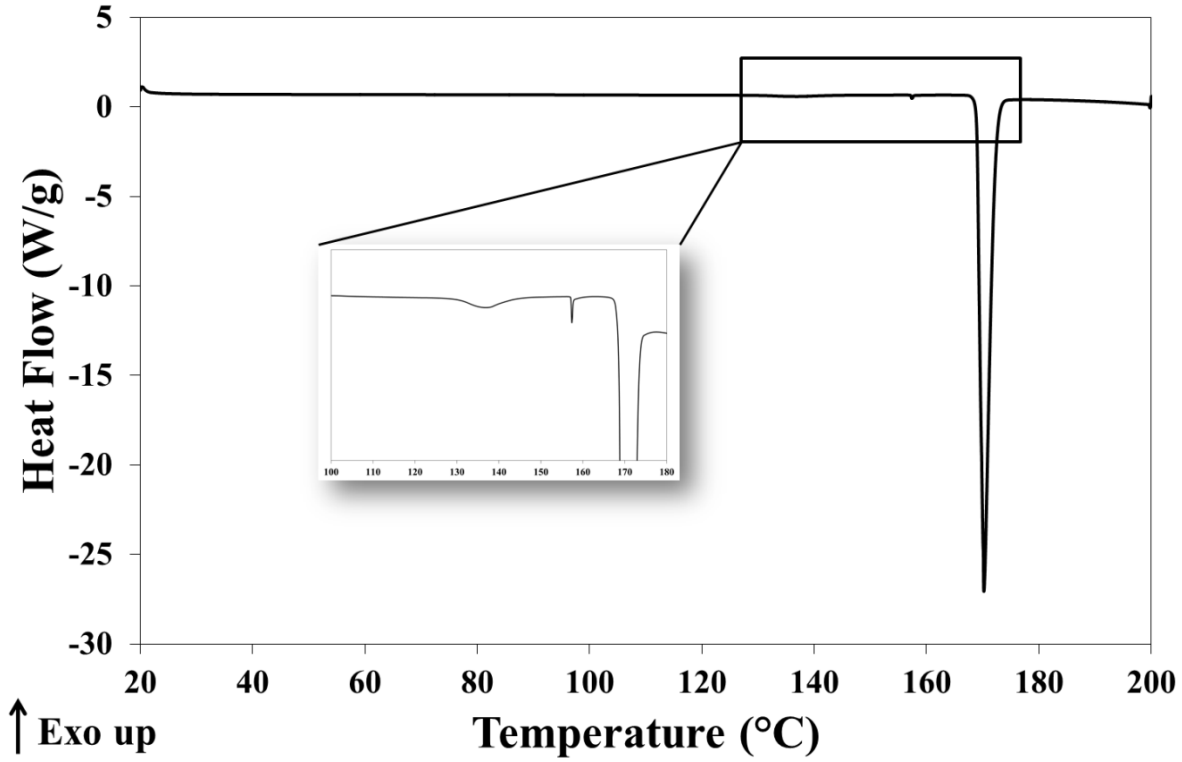


Figure S3. DSC pattern showing a phase transition between 130-140 °C

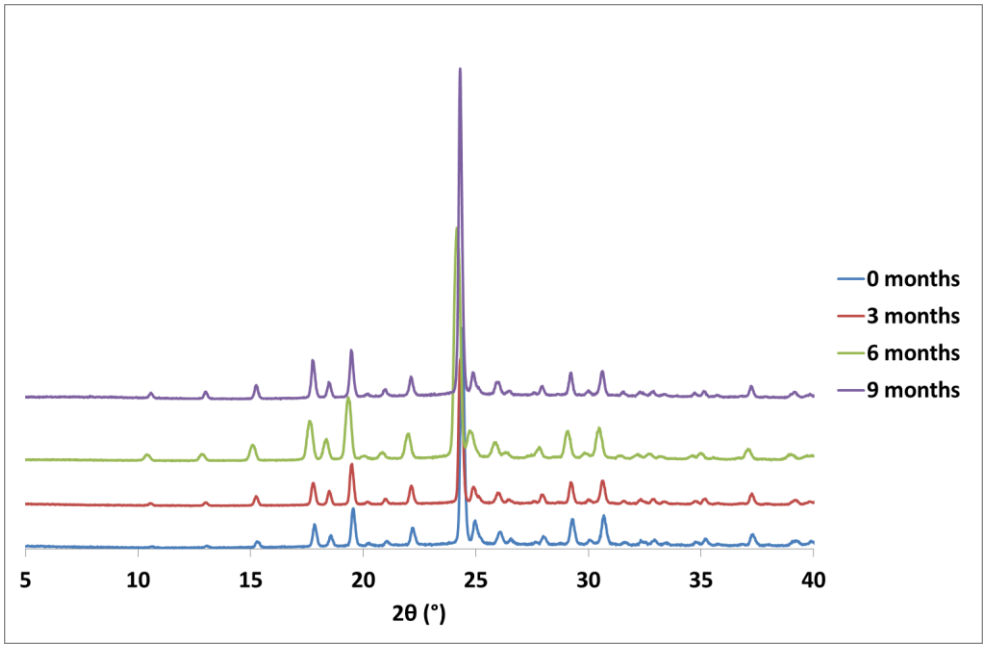


Figure S4: PXRD patterns showing the stability of the form II samples produced over a period of 9 months