

## Metastable Crystalline Phase Formation in Deep Eutectic Systems Revealed by Simultaneous Synchrotron XRD and DSC

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### Supplementary Information

#### Experimental

##### Sample preparation

Samples were prepared by weighing out specific molar ratios of constituents up to a total mass of 1 g. To facilitate the melting of the eutectic liquids, the samples were thoroughly mixed and left in an oven at 50 °C for 12 hours.

##### Synchrotron Differential Scanning Calorimetry

A Q20 DSC (TA Instruments, Waters, USA) had been previously modified by drilling two holes (entry hole 3mm, exit hole 5mm) in the furnace head to permit the monochromated X-ray beam (ca. 53 keV) on beamline I12 (JEEP) to pass through the sample pan (thin-walled aluminium) and sample. The sample was mounted in the DSC as standard, and the drilling of holes did not affect the thermal performance of the calorimeter. The diameter of the X-ray beam was 0.5 mm and a Pilatus 2M CdTe detector was placed 1.887 m behind the sample. Calibration of the detector was performed using cerium dioxide. Patterns were recorded by collecting data for 4s, with a 2s pause.

DSC measurements were performed at a heating rate of 10 °C/min (and so 1 powder pattern was recorded per degree centigrade). A TA Instruments controlled cooling unit (RSC 90) was used with the DSC, allowing us to precisely control both heating and cooling rates on the instrument. Samples were liquid at room temperature and were pipetted directly into the DSC Tzero pans (sample mass range ca. 5-10 mg). Tzero hermetic lids were used to seal the pans before being placed in the DSC. The DSC was calibrated before for cell contact and enthalpy using an indium standard (melting onset temperature =  $156.6 \pm 0.5$  °C, enthalpy =  $28.72 \text{ J.g}^{-1} \pm 3\%$ ), according to the manufacturer's instruction. Two aluminium hermetic lids were used to raise the pans inside the DSC furnace to centre the sample in the beam, which was also included in the calibration. Data were collected with TA Instruments Advantage software and initially analysed with TA Universal Analysis software.

DAWN<sup>1</sup> Science Workbench was first used to mask regions of unrepresentative spots of high intensity in the 2D Pilatus data, which are usually caused by large grain/crystal size of the samples.

##### Additional Differential Scanning Calorimetry

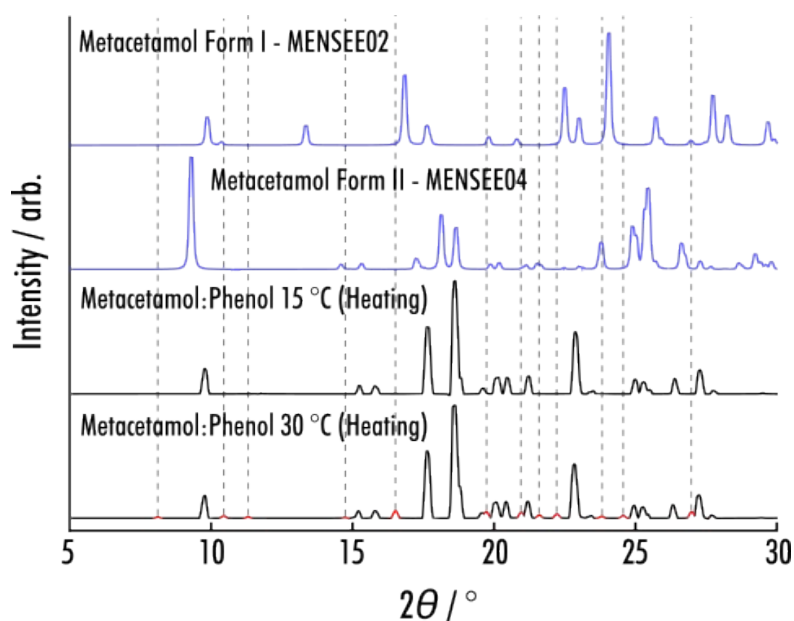
Supplementary DSC, carried out after the synchrotron-DSC analysis, was taken using a TA Instruments Discovery DSC 25. 10-20 mg of samples were weighed out on a 4-point scale and placed into hermetically sealed Tzero aluminium pans. The cell was purged with nitrogen gas at a flow rate of 50 mL.min<sup>-1</sup>. Data were analysed using the TRIOS software (version: 4.5.0.42498). Calibrations were carried out using an indium standard (temperature =  $156.6 \pm 0.5$  °C, enthalpy =  $28.72 \text{ J.g}^{-1} \pm 4\%$ ).

##### pXRD data analysis

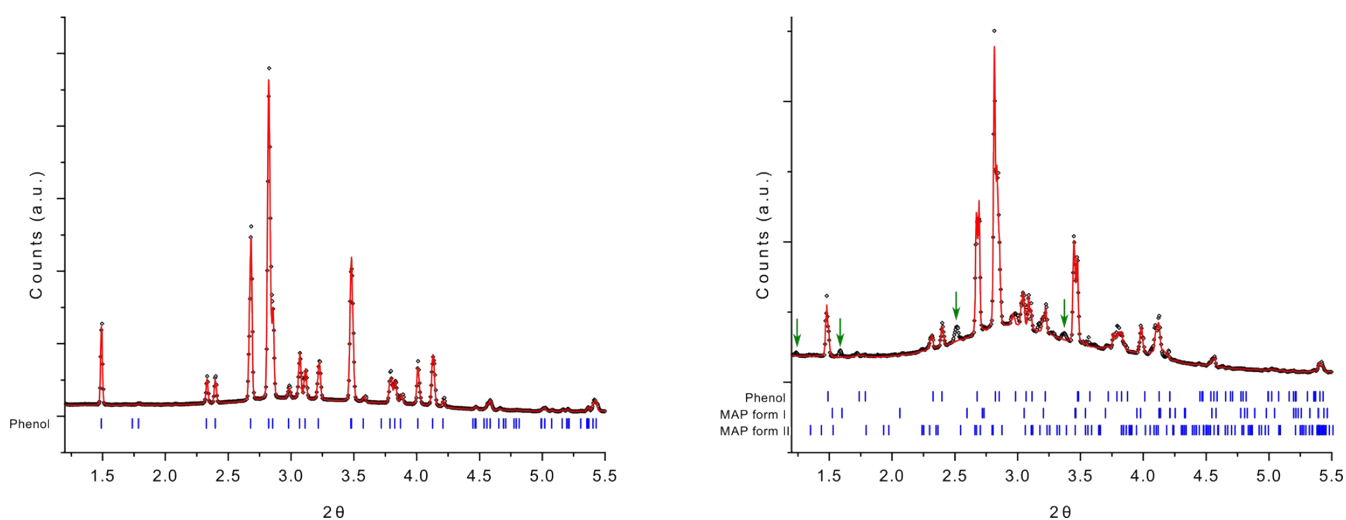
All powder patterns were refined using Maud<sup>2</sup> (version: 2.93, build: 10728). After matching the ring patterns to their specific temperatures using DAWN Science<sup>1</sup> (version: 2.16.1) 2D transmission images were contrast-balanced using ImageJ<sup>3</sup> (version: 1.51r26) then split into 72, 5° segments and ring intensities averaged to build 1D powder patterns. Each of the powder patterns were refined against

the orthorhombic form of phenol (CCDC: PHENOL01, space group:  $P2_122_1$ ) using an isotropic strain-size model with crystallite size of  $0.6 \mu\text{m}$  and arbitrary texture. All patterns containing exclusively phenol were refined to  $\chi < 1.5$ . Patterns containing reflections that were not indexable to the orthorhombic form of phenol were refined using all known possible structures (native forms and phenolates) as additional phases. No known phases were able to adequately fit to the unknown reflections, keeping  $\chi$  arbitrarily high, implying that no known structures are present concomitantly with the phenol.

### Supplementary Figures

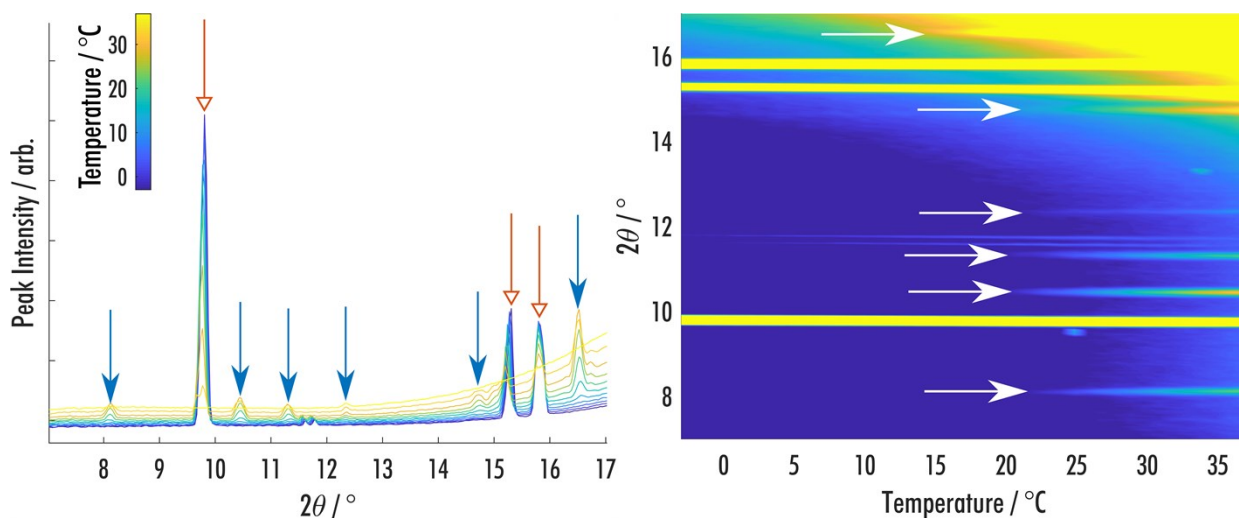


**Figure S1** pXRD patterns of an 8:1 phenol:MAP VODES. The 30 °C pattern shows both the phenol phase and the new unknown phase. The peaks from the new phase are highlighted in red and vertical dashed lines are shown to allow comparison to reference patterns. 15 °C shows only the phenol phase. The patterns shown in blue are the only known forms of MAP.

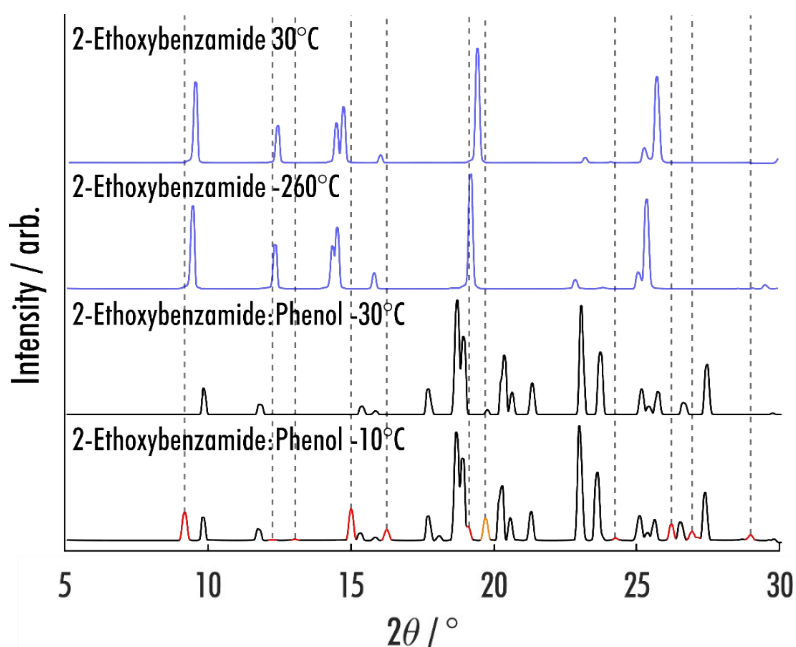


**Figure S2** Rietveld analysis for pXRD patterns from an 8:1 phenol:MAP VODES. (Left) pXRD pattern after the first crystallisation event, matched to the RTP crystal structure of phenol. (Right) pXRD pattern after the second crystallisation event. Phenol peaks are matched and tick marks for the crystal

structures of MAP forms I and II are shown. Green arrows show the positions of unmatched reflections.

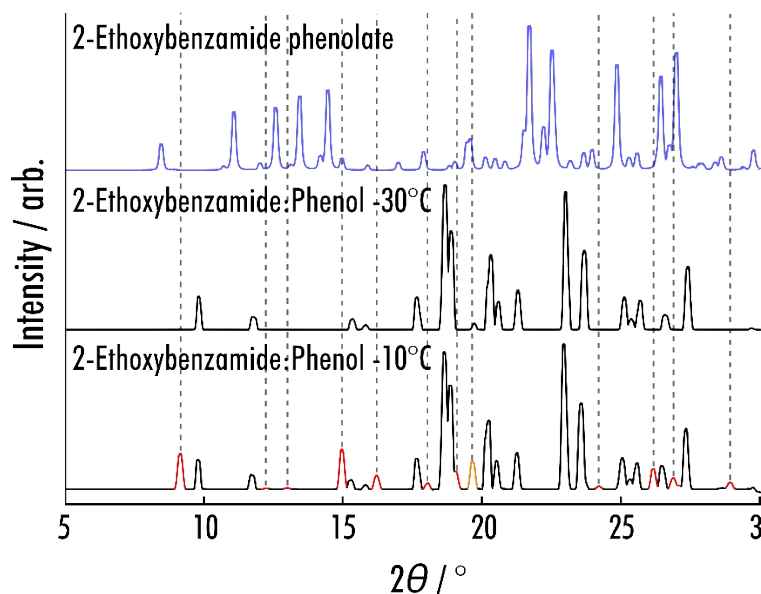


**Figure S3** A detailed view of the pXRD data for MAP over the  $2\theta$  range  $7^\circ$ - $17^\circ$  and temperature range  $0^\circ\text{C}$  to  $36^\circ\text{C}$  to show the crystallisation of the unknown phase from an 8:1 phenol:MAP VODES. The data shown are from the heating ramp starting at  $-70^\circ\text{C}$ . (left) Stacked pXRD patterns with a colour scale showing the change in temperature. Peaks due to the ambient phase of phenol are highlighted with orange arrows and peaks due to the unknown phase with blue arrows. The amorphous background has not been removed and can be seen to increase as the unknown phase forms and both phases begin to melt. (Right) Surface plot of the pXRD data with temperature to highlight to appearance of the peaks from the new phase. White arrows are used to indicate the appearance of each peak.

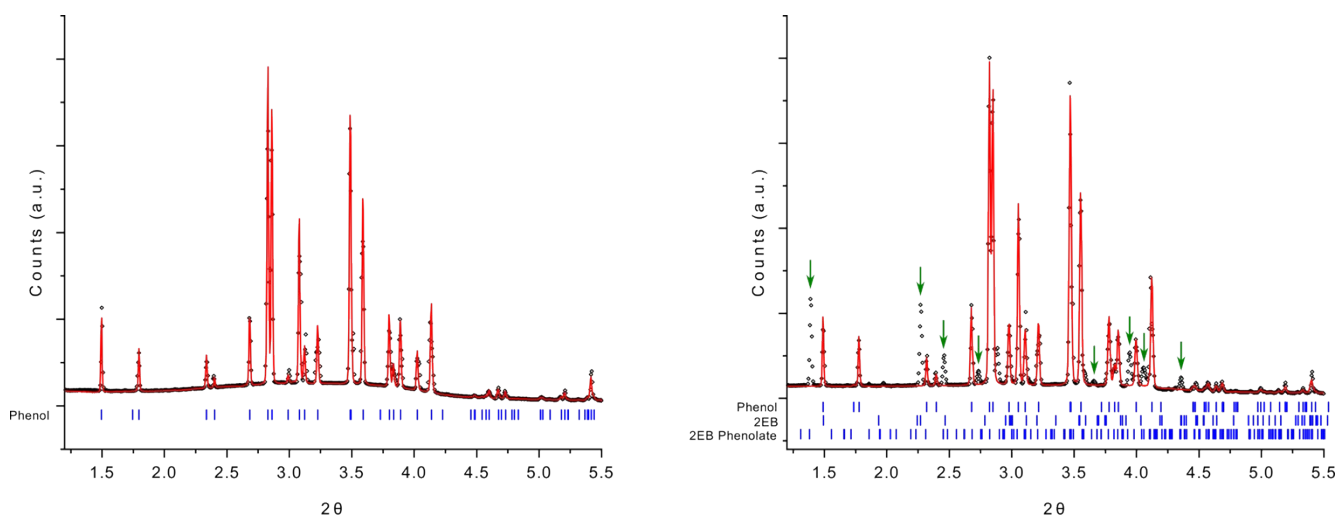


**Figure S4** pXRD patterns of an 8:1 phenol:2EB VODES. The  $-10^\circ\text{C}$  pattern shows both the ambient phenol phase and the new unknown phase. The peak from the unknown phase are shown in red and vertical dashed lines are shown for comparison with reference patterns. A peak that overlaps with one from the phenol structure is shown in orange. The  $-30^\circ\text{C}$  pattern shows the ambient phenol phase

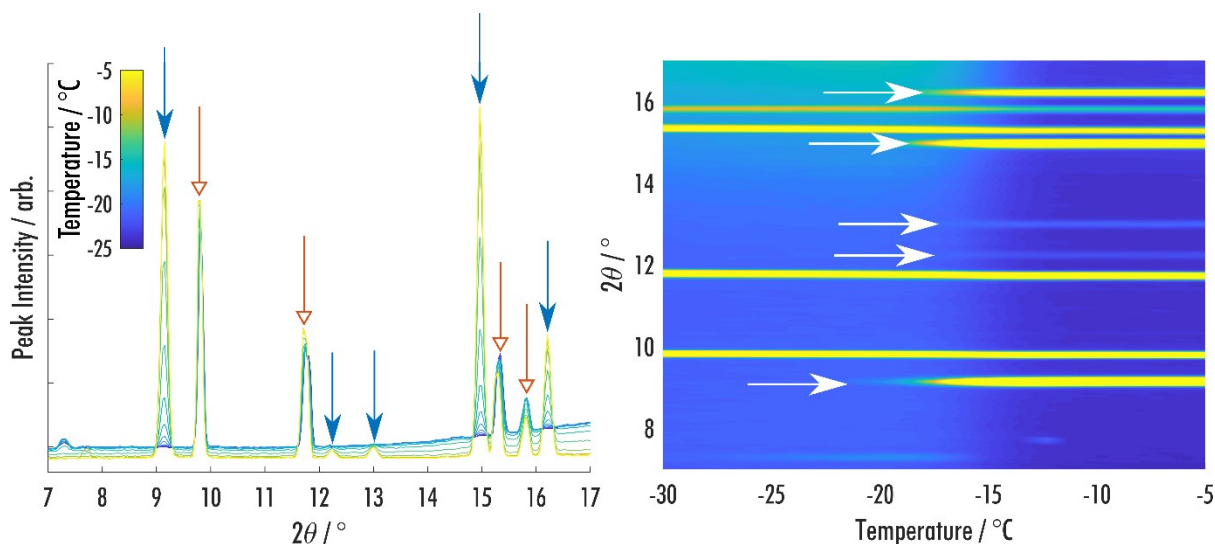
that formed on cooling. Reference patterns for the known polymorph of 2EB are shown in blue. Patterns for this polymorph are shown at both 30 °C and -260 °C to illustrate how the peaks may shift with temperature. This data is shown, as many of the peaks of the new phase are close to that of native 2EB, however it is not possible to match peaks at any temperature via Rietveld refinement.



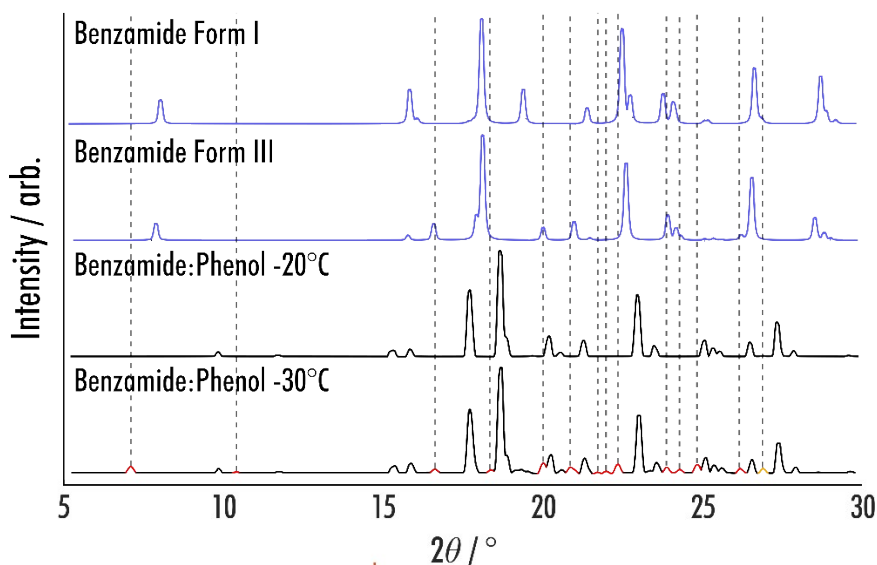
**Figure S5** pXRD patterns of an 8:1 phenol:2EB VODES. The -10 °C pattern shows both the ambient phenol phase and the new unknown phase. The peaks from the unknown phase are shown in red and vertical dashed lines are shown to allow comparison with a reference pattern for the 2EB:phenol cocrystal. A peak that overlaps with one from the phenol structure is shown in orange. The -30 °C pattern shows the ambient phenol phase formed on cooling. A reference pattern for the known 2:1 2EB:phenol co-crystal is shown in blue.



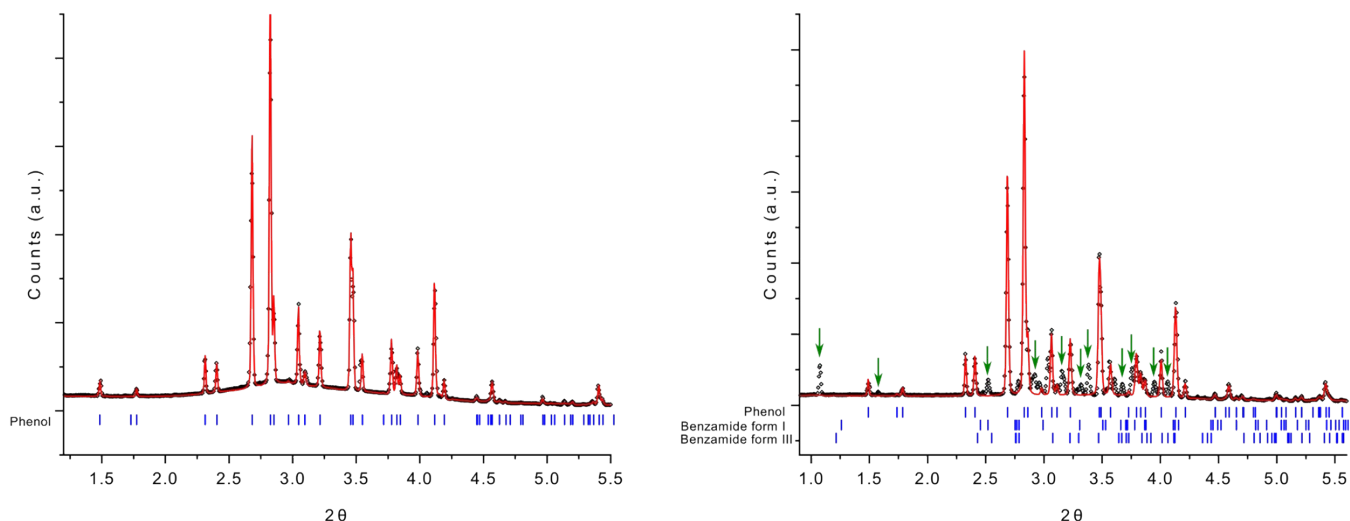
**Figure S6** Rietveld analysis for pXRD patterns from an 8:1 phenol:2EB VODES. (Left) pXRD pattern after the first crystallisation event, matched to the RTP crystal structure of phenol. (Right) pXRD pattern after the second crystallisation event. Phenol peaks are matched and tick marks for the crystal structures of 2EB and 2EB phenolate are shown. Green arrows show the positions of unmatched reflections.



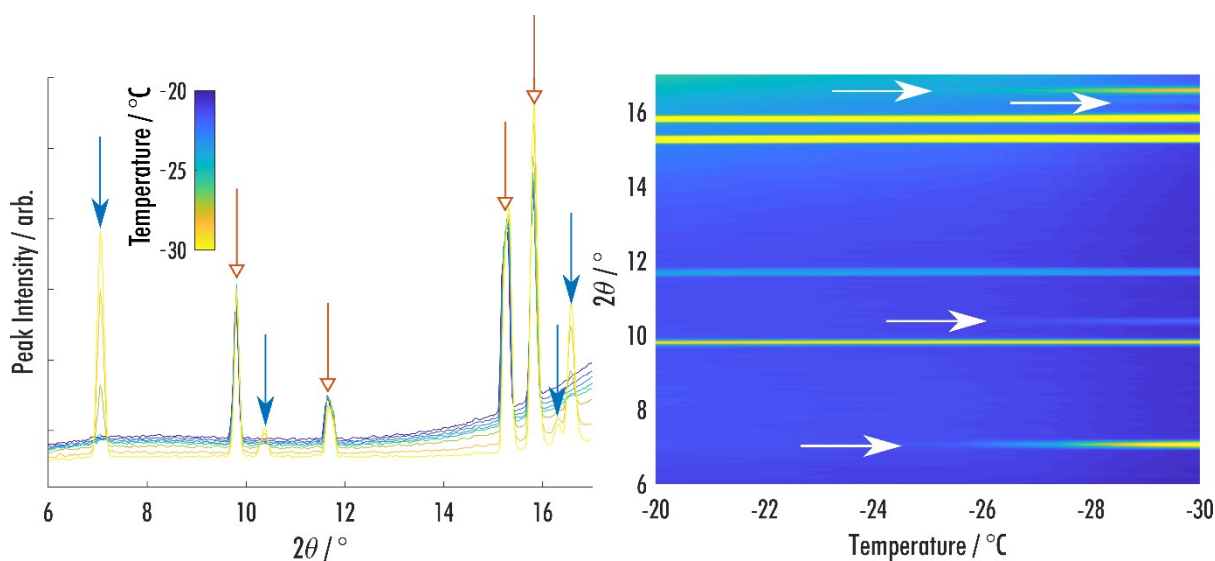
**Figure S7** A detailed view of the pXRD data for 2EB over the  $2\theta$  range  $7^\circ$ - $17^\circ$  and temperature range  $-30^\circ\text{C}$  to  $-5^\circ\text{C}$  to show the crystallisation of the unknown phase from an 8;1 phenol:2EB VODES. The data shown are from the heating ramp starting at  $-70^\circ\text{C}$ . (left) Stacked pXRD patterns with a colour scale showing the change in temperature. Peaks due to the ambient phase of phenol are highlighted with orange arrows and peaks due to the unknown phase, with blue arrows. The amorphous background has not been removed and can be seen to reduce as the unknown phase forms. (Right) Surface plot of the pXRD data with temperature to highlight to appearance of the peaks from the unknown phase. White arrows are used to indicate the appearance of each peak.



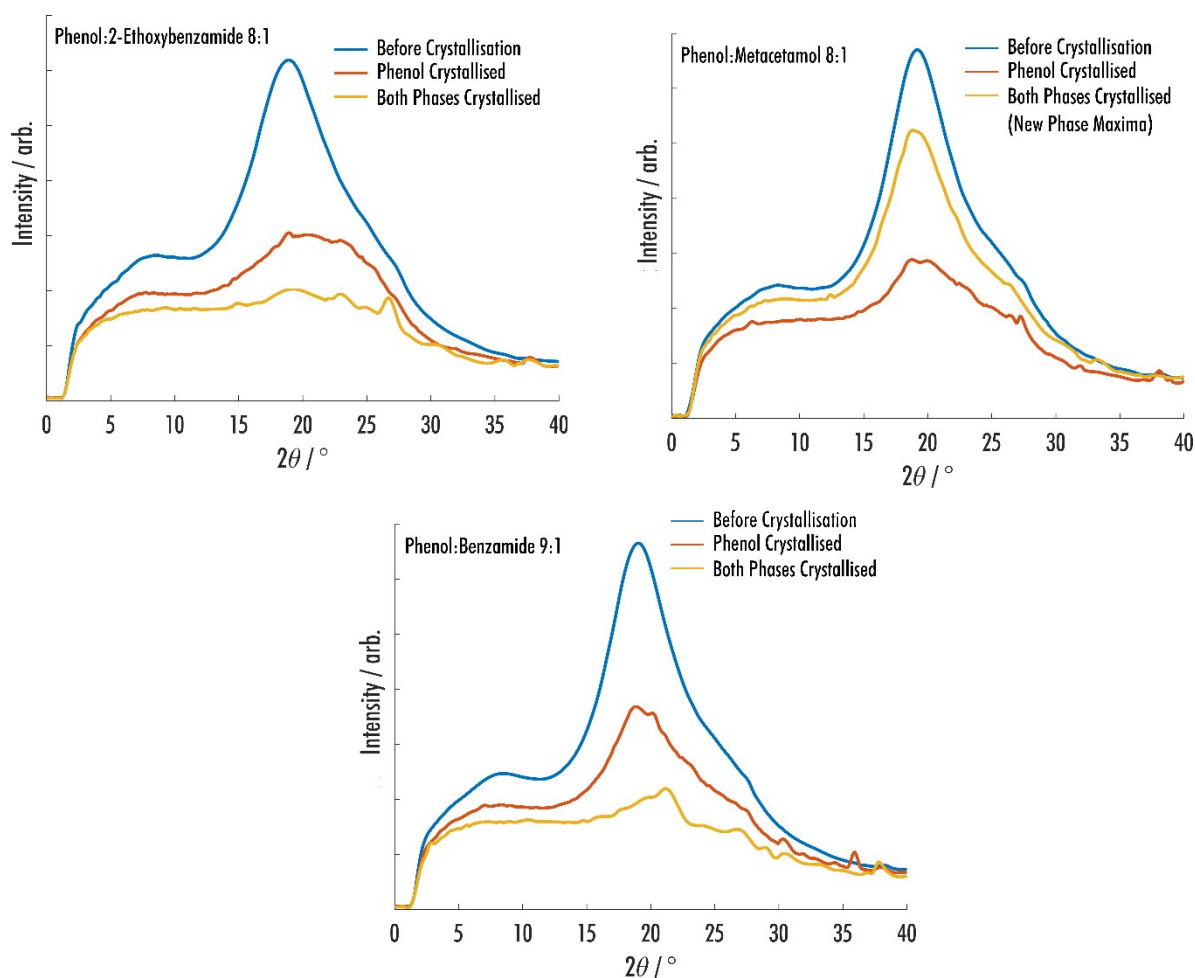
**Figure S8** pXRD patterns of a 9:1 phenol:BZM VODES. The  $-30^\circ\text{C}$  pattern shows both the ambient phenol phase and the new unknown phase. The peaks from the unknown phase are shown in red and vertical dashed lines are shown to allow comparison with reference pattern. A peak that overlaps with one from the phenol structure is shown in orange. The  $-20^\circ\text{C}$  pattern shows the ambient phenol phase formed on cooling. Reference patterns of the common benzamide form I and III are shown in blue. The unknown phase was additionally checked against the metastable benzamide phase, which also didn't match.



**Figure S9** Rietveld analysis for pXRD patterns from a 9:1 phenol:BZM VODES. (Left) pXRD pattern after the first crystallisation event, matched to the RTP crystal structure of phenol. (Right) pXRD pattern after the second crystallisation event. Phenol peaks are matched and tick marks for the crystal structures of BZM forms I and III are shown. Green arrows show the positions of unmatched reflections.



**Figure S10** A detailed view of the pXRD data for BZM over the  $2\theta$  range  $6^\circ$ - $17^\circ$  and temperature range  $-20^\circ\text{C}$  to  $-30^\circ\text{C}$  to show the crystallisation of the unknown phase from a 9:1 phenol:BZM VODES. The data shown are from the cooling run starting at  $70^\circ\text{C}$ . (left) Stacked pXRD patterns with a colour scale showing the change in temperature. Peaks due to the ambient phase of phenol are highlighted with orange arrows and peaks due to the unknown phase, with blue arrows. The amorphous background has not been removed and can be seen to reduce as the unknown phase forms. (Right) Surface plot of the pXRD data with temperature to highlight to appearance of the peaks from the unknown phase. White arrows are used to indicate the appearance of each peak.



**Figure S11** Calculated background from the pXRD of samples during synchrotron-DSC analysis. Data is shown for the background after each of the different phases has crystallised. Due to the increased number of peaks, the background determination becomes more difficult as the crystalline material present in the sample increases. However, it appears that in all cases there is at least a small amorphous component. In the phenol:metacetamol system, the overlap of the formation of the new phase and the melting of crystalline phenol means that there is more amorphous component at the point where there is the maximum amount of the new phase, compared to the point where only crystalline phenol is present. The drop-off at low angles is due to the beam-stop.

## Notes and references

1. Basham M., Filik J., Wharmby M. T., Chang P. C. Y., Kassaby B. E., Gerring M., Aishima J., Levik K., Pulford B. C. A, Sikharulidze I., Sneddon D., Webber M., Dhesi S. S., Maccherozzi F., Svensson O., Brockhauser S., Nàray G. and Ashton A.W., *J. Synch. Rad.*, 2015, **22:3**.
2. L. Lutterotti, S. Matthies and H. R. Wenk, *Proceeding of the Twelfth International Conference on Textures of Materials (ICOTOM-12)*, 1999, **1**, 1599.
3. Schneider, C. A.; Rasband, W. S. & Eliceiri, K. W., *Nat. methods.*, 2012, **9(7)**: 671-675.