Supporting Information

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69451 Weinheim, Germany

Use of In Situ Atomic Force Microscopy to Follow Phase Changes at Crystal Surfaces in Real Time**

Ranjit Thakuria, Mark D. Eddleston, Ernest H. H. Chow, Gareth O. Lloyd, Barry J. Aldous, Joseph F. Krzyzaniak, Andrew D. Bond, and William Jones*

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Supporting Information

Experimental section for AFM imaging:

Image acquisition and processing:

A Nanoscope Multimode AFM (Veeco Instruments, Cambridge, UK) was used for this study. Samples were imaged in air under ambient conditions using intermittent contact mode with a J scanner (180 μm² maximum scan size), together with MikroMasch NSC15 SPM probes which had a typical force constant of 40 N/m and tip radius of 10 nm (MikroMasch, 2008). The tapping force which was applied to the probe while imaging was kept to a minimum to prevent the tip from damaging the sample surface. The typical scan area was 5 μm² (resolution of 256 lines), recorded at a scan rate of 1 Hz/line.

Images were processed using NanoScope Analysis v1.40 and a first order flattening was applied.

Step height measurements:

The AFM was calibrated to ensure optimum resolution and accuracy. A TGZ1 calibration grating with step height of 21.5 nm was used to calibrate the height axis.

The height of individual molecular layers on the surface of caffeine-glutaric acid crystals was measured using the step analysis function in NanoScope Analysis. An average height profile was taken from a selected rectangular region of sample surface containing the edge of a layer of molecules allowing the layer height to be measured (Figures S1 and S2). Fifty such step height measurements were recorded for each polymorphic form of the cocrystal. The average step height measured for Form I crystals was found to be 13.0 Å, with a standard deviation of 0.14 Å, while the average measured for Form II crystals was 10.5 Å with a standard deviation of 0.19 Å.
Figure S1 IC-AFM image showing the average height profile for a selected region of the surface of a crystal of Form I of the caffeine-glutaric acid cocrystal.

Figure S2 IC-AFM image showing the average height profile for a selected region of the surface of a crystal of Form II of the caffeine-glutaric acid cocrystal.
Face indexing of caffeine-glutaric acid cocrystals:

Figure S3. Morphology of Form I of the caffeine-glutaric acid cocrystal from a BFDH prediction (left). Single crystal of Form I (mounted on a diffractometer) with the crystal faces indexed (right).

Figure S4. Morphology of Form II of the caffeine-glutaric acid cocrystal from a BFDH prediction (left). Single crystal of Form II with the crystal faces indexed (right).
Optical microscopy and AFM analysis of Form II as crystallised:

Figure S5. (a) Optical image of a crystal of caffeine-glutaric acid Form II. (b) IC-AFM height image of the surface of a Form II crystal showing relatively large, rounded features protruding from the crystal surface.

Rietveld refinement of PXRD data:

The relative amounts of Forms I and II present in samples of the caffeine:glutaric acid cocrystal were quantified by Rietveld refinement using TOPAS-Academic V4.1 software.

Figure S6 Rietveld refinement of caffeine-glutaric acid Form I crystals exposed to 70 % relative humidity for 1 day. The blue outline shows the experimentally observed diffraction pattern, the red curve shows the Rietveld fit and the grey outline marks the difference between the calculated fit and the experimental pattern. The quantities of Form I of the cocrystal, Form II of the cocrystal, β-caffeine and glutaric acid present in the sample were measured to be 53.9 %, 37.6 %, 1.6 % and 6.9 % respectively (the β-caffeine and glutaric acid were present after the initial crystallisation of Form I, probably as a result of differences in the solubilities of these two compounds).[4b]