

Supporting Information for

Catalytic Effect of Solvent Vapors on the Spontaneous Formation of Caffeine-Malonic Acid Co-Crystal

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SAMPLE PREPARATION, GRINDING, SIEVING, AND MIXING

Natural abundance caffeine (CA) and malonic acid (MA) were purchased from Sigma-Aldrich and used without further purification. The caffeine and malonic acid were ground separately using a Retsch MM 400 ball mill. The caffeine was ground in a 25 mL stainless steel jar with one stainless steel ball for 15 to 30 minutes, depending on the quantity of sample, which was between 3 to 5 grams, at a shaking frequency of 20 Hz. The malonic acid was ground in a 25 mL stainless steel jar with one stainless steel ball for 12 to 25 minutes, depending on the quantity of sample, which was between 2 to 4 grams, at a shaking frequency of 30 Hz. For the purpose of selecting particle size fractions, the powders were separately sifted using a stack of 200 (75 μ m opening) and 325 (45 μ m opening) mesh, 8-inch sieves in a Retsch AS 200 sieve shaker. The 200-mesh sieve was placed on top to catch particles larger than 75 μ m, while the 325-mesh sieve below it captured particles larger than 45 μ m. For both caffeine and malonic acid, the 45-75 μ m fractions were collected from the 325-mesh sieve. Unless indicated otherwise, the 45-75 μ m particle size fractions were used in all the experiments.

The caffeine and malonic acid were weighed out in a 2:1 stoichiometric mixture (approximately 2 grams total) and vortexed in a 20 mL glass vial for roughly 3 minutes at maximum speed using a bench top vortexer. Immediately following the vortexing, the powders were triple-sifted by hand using a stack of the 40 (425 μ m), 60 (250 μ m) and 80 (180 μ m) mesh sieves. The reacting powders were deposited on the 40-mesh sieve at the top of the stack and

allowed to fall through all three meshes onto a weighing paper at the bottom. This sifting process was performed three times to ensure complete mixing of the reacting powders.

SOLVENT EXPOSURE

An aliquot of the 2:1 mixture of caffeine and malonic acid powders, mixed as described above, was packed into aluminum sample holders for the powder X-ray diffractometer (PXRD). The powder was flattened in the sample trough using a glass microscope slide to give a uniform sample thickness. The vapor exposures took place in clear 500 mL wide mouth screw top glass jars (Thermo Scientific). For each solvent, approximately 50 mL of solvent was put at the bottom of a jar. Before any exposure, the lid was closed and the vapor pressure in the jar allowed to equilibrate for a few minutes. The caffeine and malonic acid powders were freshly ground at the start of each day.

For each exposure to solvent vapor, the PXRD sample holder containing reacting powders was placed on a perforated, raised metal platform in the jar and the lid closed. To further ensure that neither the sample nor sample holder came into contact with the liquid solvent, the sample holder was placed on an aluminum foil ring, which was placed on top of the perforated metal platform. Once the exposure was finished, the sample holder was removed from the jar and placed in a vacuum jar attached to a VirTis lyophilizer. The sample was placed under vacuum of approximately 50 mTorr for 3 minutes. If, during the exposure, the layer of powder had bubbled or bowed, it was repacked to maintain a flat surface for PXRD analysis. All exposures were performed at ambient laboratory conditions (20-22 °C). For each set of exposure experiments, we set aside an aliquot of the mixed powders at ambient conditions to serve as a control. In all instances the amount of spontaneous conversion to co-crystal seen over the course of the exposure experiments was negligible, in line with previously reported spontaneous conversion rates.

We found it necessary to subject exposed samples to vacuum to remove all vapor catalyst. We observed that failing to do so allowed adsorbed vapors to continue to effect conversion to co-crystal for several minutes after the sample was removed from the exposure chamber. We have also observed a slight variation in the results due to seasonal variation in atmospheric humidity.

POWDER X-RAY DIFFRACTION (PXRD) DETAILS

All PXRD patterns were obtained using a Rigaku Ultima IV powder diffractometer (Cu K α , 1.5418 Å) with aluminum sample holders. Patterns were collected at room temperature from 5° to 40° 2 θ with a scan rate of 4° min⁻¹ and 0.02° sampling window. The samples were prepared as described above. Experimental and calculated PXRD patterns of CA, MA and the co-crystal are shown in Figure S1.

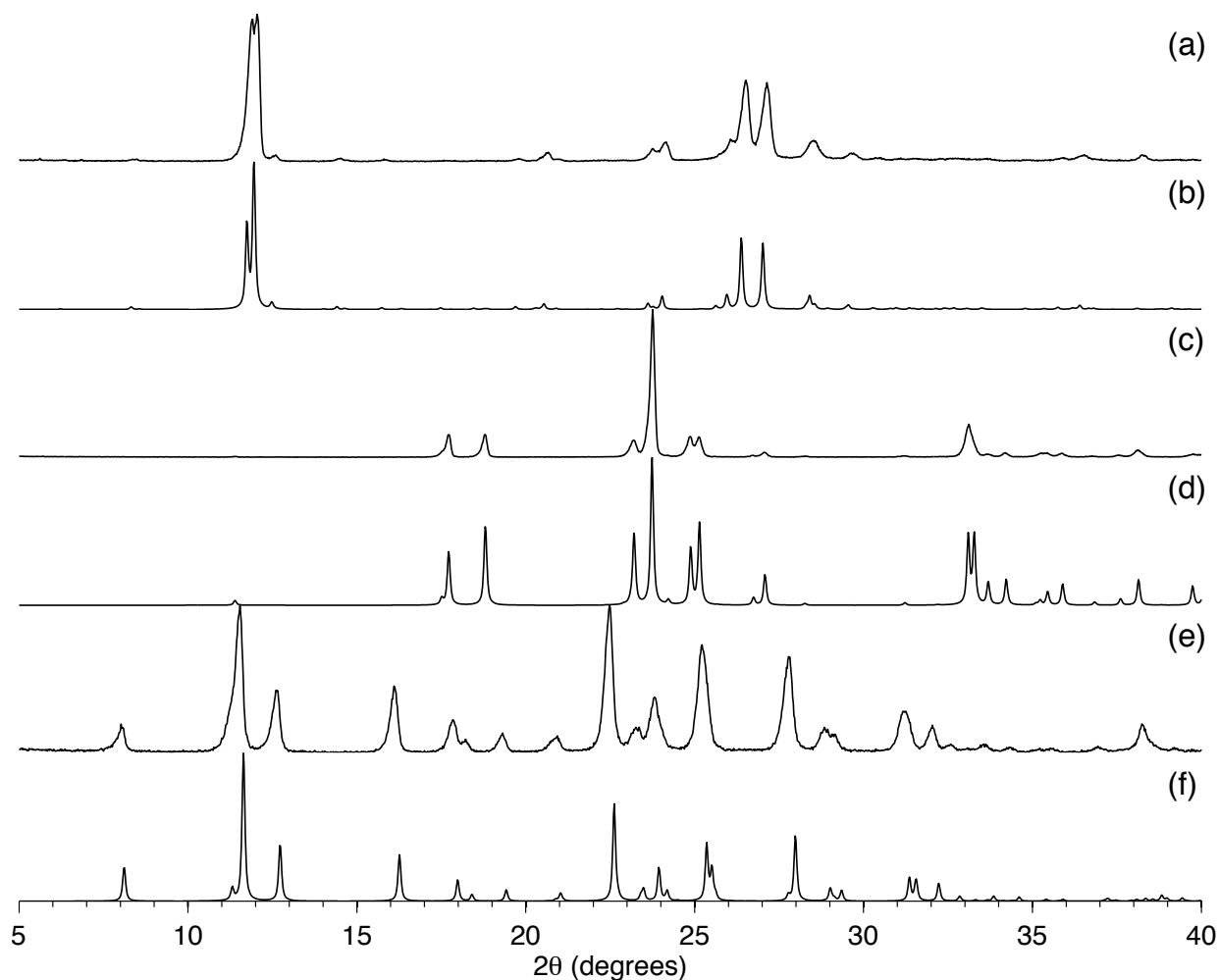


Figure S1. Experimental PXRD trace of Caffeine (a) and the trace calculated from the crystal structure (b). In (c) is given the experimental trace of malonic acid, and in (d) the trace calculated from the crystal structure. Shown in (e) is the experimental trace of the 2:1 CA-MA co-crystal, and in (f) the trace calculated from the crystal structure.

START AND STOP EXPERIMENTS

Experiments (data shown in Figure 5) were carried out using two different organic solvent vapors. The prepared mixture of reacting powders was exposed in the first solvent, as described above, for a fixed amount of time. The exposed sample was then transferred to vacuum for 3 minutes to remove solvent vapors. A PXRD pattern was collected to record the degree of conversion to co-crystal. The sample was then placed in the chamber of a second solvent for a specified time, transferred to vacuum, and a PXRD pattern collected to assess further conversion.

GRAVIMETRIC TRACKING

A custom written automated data logging program system was used to record mass readings from a Mettler Toledo AB135-S analytical balance (precision $\pm 10 \mu\text{g}$) every 10 seconds. The main balance chamber was turned into a vapor exposure chamber by placing two 50 mL beakers and two glass petri dishes with organic solvent in the corners of the chamber of the balance. An empty sample holder was exposed to solvent vapors to record background mass gain, which was found to be negligible. Before any exposure, the empty sample holder mass and sample mass were recorded. Then the sample holder with sample was placed on the balance pan, and the beakers and dishes were placed around it. The automated mass recording was started. Once the sample stopped gaining mass, the beakers and dishes were removed, allowing the sample to outgas. The automated mass logging was continued until mass loss ceased. The improvised balance chamber was not well sealed (even with the sliding doors fully closed), compared with the glass jars used in the main exposure experiments. As such, the balance chamber was likely not saturated with solvent vapors, which accounts for the timescale of the mass uptake being longer than in the sealed chamber exposure experiments.

NMR SPECTROSCOPY

All NMR measurements were made on a custom assembled spectrometer with a Discovery console (Tecmag; Houston, TX), 14.1 T magnet (600.381 MHz for ^1H , 150.987 MHz for ^{13}C ; Magnex Scientific; Oxford, England), a 39-channel matrix shim system (Resonance Research, Inc.; Billerica, MA), and a 1.6 mm magic angle spinning (MAS) probe (Agilent Technologies; Santa Clara, CA). Magic angle spinning was regulated to ± 2 Hz using a custom-built controller. An exceptionally low drift rate of the magnetic field (less than 0.1 Hz/hour for

^{13}C) obviated the need for a field frequency lock or a counter ramp on the Z_0 shims to achieve field stability. Cross-polarization magic angle spinning (CP-MAS) NMR spectra were collected at 30 kHz MAS with a CP contact time between 2-to-4 milliseconds, along with a 20% linear ramp on the ^{13}C power levels. Composite broadband decoupling (SPINAL-64) was applied on the proton channel during acquisition (38.4 milliseconds). Recycle delay of 20 seconds was used between scans. Spectra shown in Figure 2 were collected using 1024 transients. All spectra were collected at room temperature, with a sweep width of 80 kHz. A large sweep width was used to make sure that there were no spinning side bands. The spectra were processed with no apodization and two zero fills for a spectral resolution of 0.065 ppm/point. The ^{13}C spectra were externally referenced to neat TMS by setting the downfield resonance of adamantane to 38.48 ppm [1].

VACUUM STOP EXPERIMENTS

We performed further experiments to make sure that exposure to vacuum for 3 minutes arrested the vapor catalysis of co-crystal formation and did not compromise later results. Figure S2(a) shows the PXRD trace of the caffeine-malonic acid system after exposure to acetone vapor for 2 minutes, with no vacuum exposure. The trace shows nearly complete conversion to co-crystal. Combined with the gravimetric data, which shows that the vapors take some minutes to outgas from the sample, this data indicates that the conversion to co-crystal likely continued after the sample was removed from the vapor chamber with no vacuum exposure. For the trace in Figure S2(b), the reacting powder was exposed to acetone vapor for 2 minutes, then immediately placed in vacuum for 3 minutes. The trace shows less conversion and indicates that the exposure to vacuum arrested the vapor catalysis. For the trace in Figure S2(c), the same procedure was followed as in Figure S2(b), but the sample was left at ambient conditions for several hours after exposure to vacuum. This trace, which is nearly identical to that in Figure S2(b), shows that not only did exposure to vacuum arrest the vapor catalysis, but also that leaving the arrested sample out at ambient conditions had no further effect on the conversion to co-crystal.

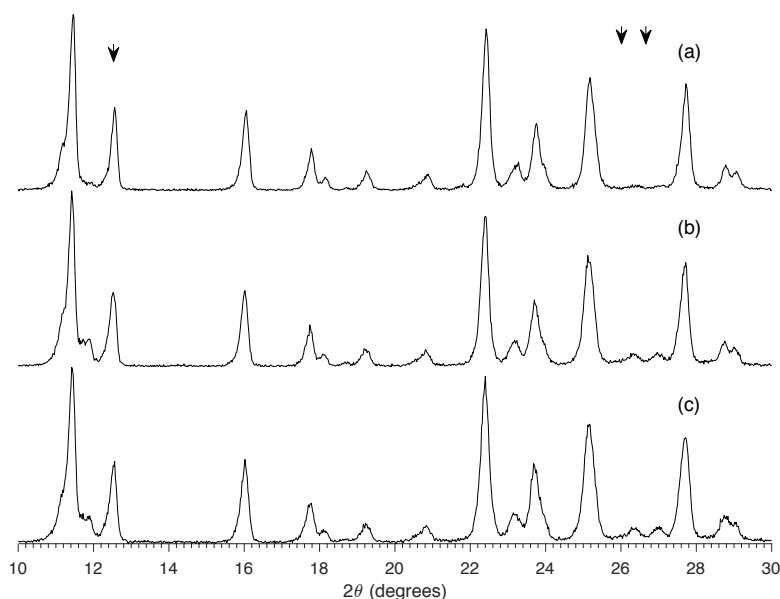


Figure S2. Vacuum exposure PXRD traces of the caffeine-malonic acid system. (a) Trace after 2 minutes of exposure to acetone, with no exposure to vacuum following. The reaction appears to be nearly complete, as indicated by the three resonances highlighted by the arrows. (b) Trace collected following 2 minutes of exposure to acetone, followed by 3 minutes in vacuum. The residual reactant signal shows that vacuum exposure arrests the vapor catalysis. (c) Same as (b), with the sample left at ambient conditions for several hours before collection of the trace.

TIME SAMPLED DATA FOR ETHANOL VAPOR EXPOSURE

Time-sampled data is shown in Figure S3 for exposure to ethanol vapor. A steady conversion to co-crystal is seen, with complete conversion at approximately 10 minutes.

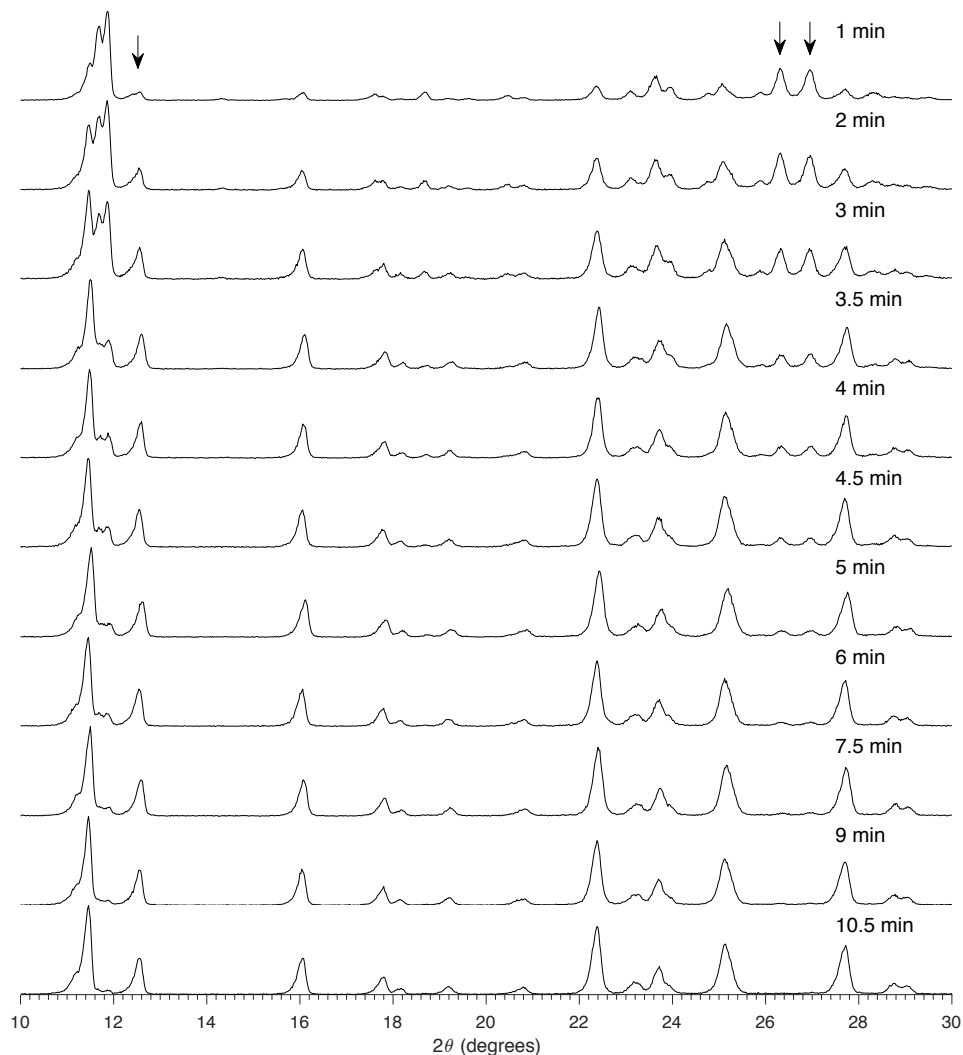


Figure S3. Time sampled PXRD traces for the caffeine-malonic acid reacting system exposed to ethanol vapor for 1 minute up to 10.5 minutes. In each instance, the 45-75 μm grain size fraction was used and prepared as described in the main text. For each trace, the powder mixture was exposed to ethanol vapor for the amount stated, then immediately exposed to vacuum for 3 minutes, then the PXRD trace collected. The reactant signal, indicated by the two arrows on the right, is seen to disappear, and the co-crystal product signal, indicated by the arrow on the left, is seen to grow in.

References.

1. Morcombe, C. R.; Zilm, K. W. *J. Magn. Reson.* **2003**, *162*, 479-486.