Effect of Alkyl Chain Parity on the Face-Selective Crystal Growth of a Drug Polymorph

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SUPPORTING INFORMATION

Preparation and Characterization of SAMs: Gold coated glass slides purchased from Evaporated Metal Films had two layers of metal coating: a 50 Å thick chromium adhesive layer and a 1000 Å thick gold layer. The slides had a thickness of 1 mm; they were cut into 15 mm × 25 mm pieces and treated with an oxygen plasma for 30 sec in a plasma etcher to remove any organic contaminants adsorbed on the surface. The SAMs **1-4** were fabricated by immersing these cleaned gold slides in 1-3 mM ethanolic solutions of the corresponding thiols. After 8-16 h the substrates were taken from the solution and rinsed with copious amounts of ethanol and blown dry with a stream of nitrogen. Freshly prepared SAM substrates were used in the characterization and crystal growth experiments. The SAMs were characterized using contact angle goniometry and ellipsometry; the values are within the range reported in the literature. The measured contact angles had a maximum error of 2.5°: SAM-**1** (28.2°); SAM-**2** (26.4°); SAM-**3** (94.3°); SAM-**4** (98.6°); and bare gold (76.2°). The heights of SAMs measured with ellipsometry had a maximum error of 1.2 Å: SAM-**1** (13.1 Å); SAM-**2** (22.2 Å); SAM-**3** (18.5 Å); and SAM-**4** (21.7 Å).

Crystal Growth: Carbamazepine was dissolved in benzene and heated at 60 °C for 20 min until the volume of the solution was reduced to reach a concentration of 25 mM. The solution was cooled to room temperature and filtered into 50 mL beakers containing SAM substrates. The beakers were covered with perforated aluminum foils and kept in a desiccator. The relative humidity inside the desiccator was maintained at ~ 0% by using freshly baked drierite (97% $CaSO_4$ and 3% $CoCl_2$). The solvent evaporated slowly under equilibrium conditions inside the desiccator and crystals appeared on SAMs **1** and **2** in three to four days. The solvent was allowed to evaporate for three to four more days and the substrates were carefully taken out from the solution. A small fraction of crystals (~5% on SAMs **1** and **2**) fell off the surface during this withdrawal; these crystals did not bond strongly to the substrate and we assumed that they were grown in solution. A small number of crystals were seen on hydrophobic SAMs; they fell off during the withdrawal of the substrate. At the time of the withdrawal, the remaining solution in the beakers was fairly concentrated (supersaturated); removal of substrates from solution led to the precipitation of a thin layer of carbamazepine on the slides and also on the crystals.

The substrates were washed with small volumes of benzene to partially remove this precipitate and also to detach any weakly bound crystals. In the case of hydrophobic SAMs **3-4** and bare gold substrate, this washing removed one or two crystals that still remained on the substrates. On SAMs **1** and **2**, however, this washing dissolved small portions (~ 2-5%) of the crystals and left trace amounts of precipitate around the crystals (see Figure S3). This precipitate was predominantly the trigonal polymorph (needle shaped crystals). The trigonal polymorph is a less stable, kinetic polymorph. Crystals of this polymorph grow when a supersaturated solution evaporates at a rapid rate (few seconds). A small peak (at $2\theta \approx 9°$) corresponding to the trigonal polymorph can be seen in the diffraction patterns of crystals grown on SAMs (Figures S1 and S2).

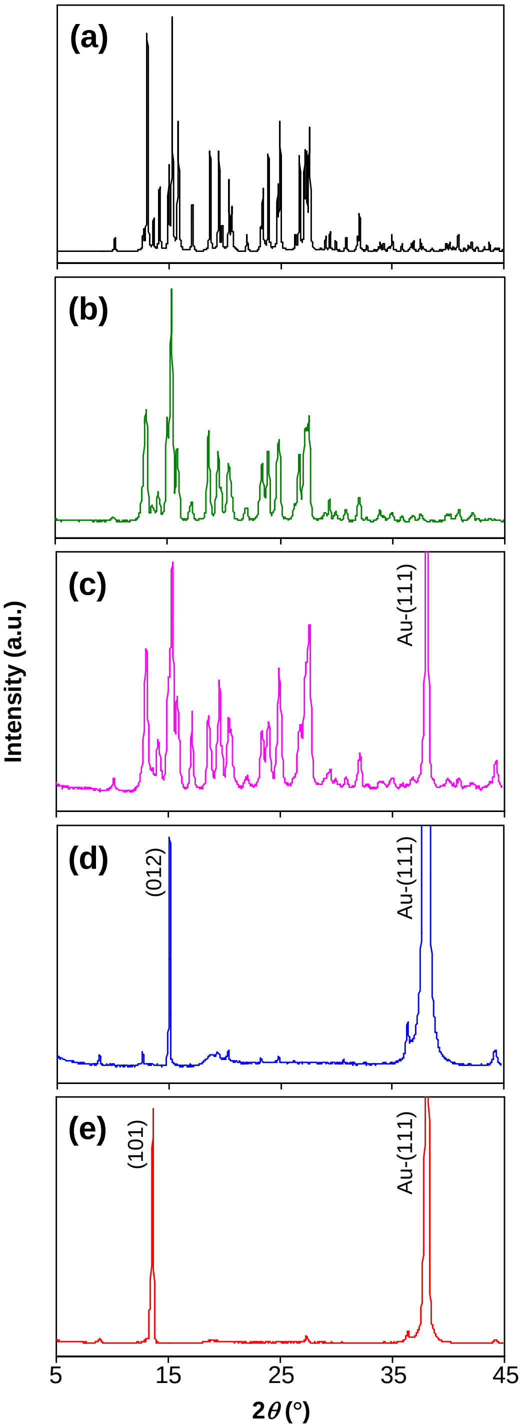

Figure S1. (**a**) Calculated and (**b**-**e**) experimental PXRD patterns. The pattern in (**b**) is taken by placing the powdered *PMP* samples on regular sample holder and the one in (**c**) by placing the sample on a gold slide in the modified holder. The patterns in (**d**) and (**e**) belong to crystals grown on SAMs **1** and **2**. The peaks belonging to the Au substrates can be seen at $2\theta \approx 36.5$, 38 and 44°.

Powder X-Ray Diffraction Analysis: As shown in Figure 3a we developed a modified sample holder that can hold the SAM substrate such that the diffraction is observed only from those planes that are parallel to the SAM surface. We calibrated the diffraction from the new sample holder by comparing the X-ray diffraction patterns *PMP* powders spread on regular sample holder as well as on the gold slide of the new sample holder (Figure S1).

When X-ray data were collected on *PMP* powders spread on gold slides (with the modified sample holder) strong diffraction peaks from Au(111) were seen at $2\theta \approx 38°$. We used this Au(111) peak to calibrate the diffraction patterns obtained from the crystals grown on SAMs **1** and **2**. This internal calibration allowed us to identify the peak positions with certainty. The sole peak from the trigonal polymorph (at $2\theta \approx 9°$) also acted as a second, independent peak with which we could calibrate the diffraction patterns of crystals grown on SAMs **1** and **2**. Figure S1 shows all these diffraction patterns. Figure S2 shows the diffraction patterns of crystals grown on SAMs **1** and **2** with the *y*-scale (intensity scale) expanded.

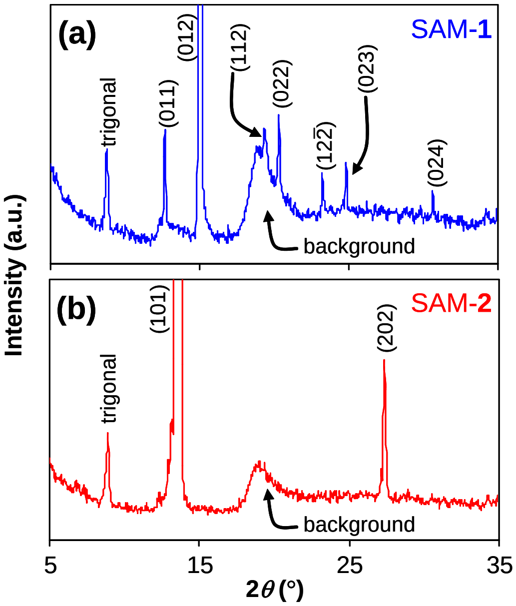

Figure S2. Experimental PXRD patterns of the crystals grown on (**a**) SAM-1 and (**b**) SAM-2 with the *y*-scale expanded. The peaks labeled 'trigonal' correspond to the trigonal polymorph. See text and Figure S3a for details.

Crystals grown on SAM-**2** show diffraction peaks from (101) and the corresponding higher index plane (202). No other peaks are seen even at this level of expansion indicating a very high degree of face-selective crystal growth on this SAM. Crystals grown on SAM-**1** show diffraction peaks from (012) and the corresponding higher index plane (024); it also shows peaks related to several other planes that are nearly parallel to (012). This may indicate partial misalignment of the crystals during the growth, or during the benzene wash, imperfections in the substrate, or growth of crystals on these other planes. In any event, the intensity of the (012) peaks is much higher (100%) than the other peaks (4-8%) and SAM-**1** indeed shows a high degree of selectivity for the growth of crystals on their {012} faces. It should be noted that occasionally (in two out of nine experiments) a small fraction of *PMP* crystals grew on their {101} faces on SAM-**1** substrates.

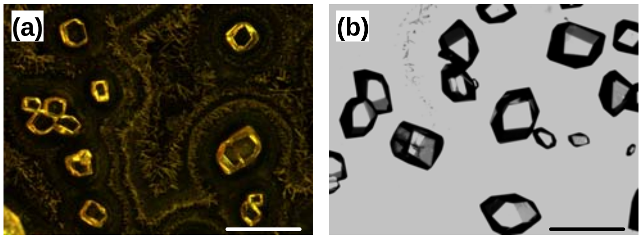

Figure S3. Optical microscopic images of crystals grown on (**a**) SAM-**2** and (**b**) glass slide. Notice in (**a**) smaller, needle like crystals that belong to the trigonal polymorph. This image was taken from the experiment where the number of trigonal polymorph crystals precipitated was high. Notice in (**b**) various growth orientations of *PMP* crystals. Scale bars = 2 mm.

Microscopic Images: Figure S3a shows a microscopic image of the crystals grown on SAM **2**. As mentioned above, washing of the substrates with benzene led to the partial dissolution of the crystals; this is the reason some of the crystal faces are not as well defined as expected. This image is selected to show the precipitation of trigonal polymorph around the *PMP* crystals grown on the SAMs. We also carried out crystallizations of carbamazepine on glass slides and plasma treated glass slides placed in 50 mL beakers. These slides are highly hydrophilic (contact angles: 19.3 and 13.9°), and they are expected to mimic the hydrogen bonding nature of the SAMs **1** and **2**, but without the structural and orientational specificity. As can be seen from Figure S3b face-selective crystal growth is not observed on glass slides, at least to the exclusive extent seen on SAMs **1** and **2**. Powder X-ray diffraction also revealed that the crystals grown on glass slides gave multiple diffraction peaks with no consistency between different trials.