Effect of alkyl chain parity on the face-selective crystal growth of a drug polymorph†

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Carboxy terminated alkanethiol self-assembled monolayers promote the face-selective nucleation of the *P*-monoclinic polymorph of carbamazepine; the type of face nucleated depends on the parity of the alkyl chain.

The emergence of thiol self-assembled monolayers (SAMs) formed on metal substrates as templates for heterogeneous crystal growth can be related to, among other things, their structural modularity. Fig. 1(a) shows the schematic structure of a SAM:[1] we and others have explored the variations in the nature of the terminal groups (*e.g.* NH_2, SO_3H), spacers (*e.g.* alkyl, aryl), and the metal substrates (*e.g.* Au, Ag) towards applications such as control of nucleation, formation of patterned arrays of crystals, interfacial enantioselectivity, and growth of polymorphs and semiconducting materials.[2] In this work we report the effect of another variable, the parity of alkyl chain, on the face-selective crystal growth of a drug polymorph.[3] In Au-SAMs based on alkyl spacers, the terminal groups adopt two different orientations with respect to the SAM surface depending on whether the alkyl chain contains an even or odd number of methylene groups (Fig. 1(b) and (c)).[3,4] While exploring the effect of synthetic surfaces on the polymorphism of pharmaceutical drugs, we discovered that SAMs made of mercaptoundecanoic acid (**1**) and mercaptohexadecanoic acid (**2**) nucleate different faces of the *P*-monoclinic polymorph (*PMP*) of carbamazepine.[5] These two SAMs have the same terminal groups; they differ in the parity of the alkyl chain.

Carbamazepine, a drug used in the treatment of epilepsy, trigeminal neuralgia, and other diseases, has been used as a model pharmaceutical to study cocrystal formation,[6] crystal structure prediction,[7] and polymorphism.[8] Of the four known polymorphs of this drug, the *PMP* and trigonal polymorphs can be readily crystallized from ethanol solutions, the former being more stable than the latter.[5] These two polymorphs have distinct morphologies: *PMP* crystallizes as blocks (Fig. 2) and the trigonal polymorph as needles.

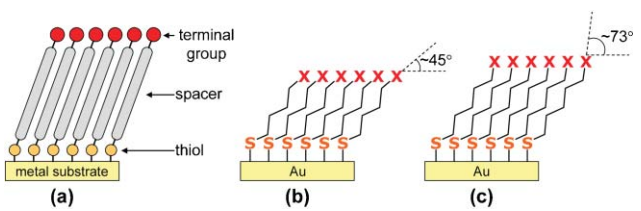

Fig. 1 (a) Schematic representation of a thiol SAM showing its structural modularity: different parts of the SAM (terminal group, spacer and the metal substrate) can be varied independent of each other. Idealized structures of alkanethiol SAMs containing (b) even and (c) odd number of methylene groups. Notice the difference in the angles between C–X bonds and the SAM surface.

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We fabricated thiol SAMs on gold coated glass slides by immersing the slides in ethanolic solutions of thiols **1** and **2**, and 1-undecanethiol (**3**) and 1-hexadecanethiol (**4**). We used untreated gold slides (**5**) as controls. We kept the SAM substrates **1–4** and **5** slides at the bottom of 50 mL beakers; to each of these beakers we added 15 mL of freshly prepared benzene solution (25 mM) of carbamazepine. We allowed the solvent to evaporate in a dry environment at 25 °C. Crystals of *PMP* appeared on SAMs **1–2** in three to four days; we removed the substrates from solutions, rinsed them with small volumes (~2 mL) of benzene, and analyzed them using optical microscopy and powder X-ray diffraction (PXRD). Crystal growth did not occur on substrates **3–5**; few crystals that appeared on these surfaces got washed away when the substrates were rinsed with benzene. We repeated these experiments at least five times; all the results (given below) from these repeats are qualitatively similar.

Examination of the SAM substrates under an optical microscope (Fig. 2(b)) revealed that crystals grow on different faces on SAMs **1** and **2**. In order to test the facial selectivity across the whole surface, we analyzed the crystals with PXRD while they were still intact on the substrate. We modified the sample holder for the PXRD such that the SAM substrate can be subjected to X-ray diffraction directly (Fig. 3(a)). We collected the X-ray data

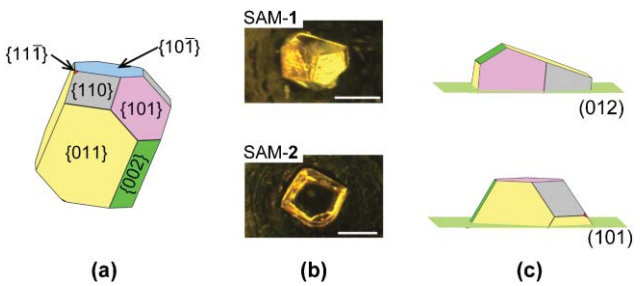

Fig. 2 (a) Morphology of the *PMP* calculated using the Bravais–Friedel–Donnay–Harker theory. Symmetry independent faces are shaded with different colors. (b) Microscopic images of the crystals grown on SAMs **1** and **2**. Scale bars = 1 mm. (c) View down (101) and (012) showing the relative orientation of crystal faces with respect to the growth planes. Color scheme is the same as in (a).

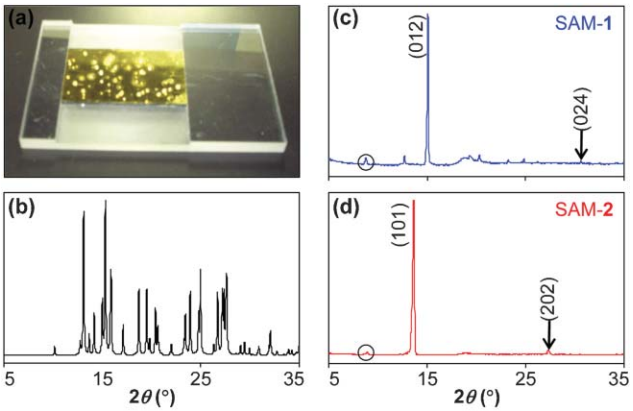

Fig. 3 (a) Sample holder for the onboard diffraction analysis of crystals grown on SAMs. Calculated (b) and experimental (c: SAM-**1**; d: SAM-**2**) powder X-ray diffraction patterns of *PMP* crystals. In (c) and (d), the hump at $2\theta \approx 17^\circ$ is due to the diffraction from background; the circled peaks at $2\theta \approx 9^\circ$ arise from the diffraction of trigonal polymorph precipitated during the handling of substrates (see ESI†).

in θ–2θ mode; in this mode the diffraction is observed only from those planes that are parallel to the SAM substrate.

The PXRD patterns of crystals grown on SAMs **1** and **2** show one strong diffraction peak in each case (Fig. 3(c) and (d)). In the case of SAM-**2** this peak corresponds to (101) indicating that crystals grow on their {101} faces on this SAM. The only other peak at $2\theta = 27.4^\circ$ corresponds to the related higher index plane (202). In the case of SAM-**1** the most intense peak corresponds to (012) suggesting that crystals grow on {012} faces on this SAM. Closer inspection of Fig. 3(c) shows peaks corresponding to the related higher index plane and planes that are nearly parallel to (012) (ESI†).

The major difference between SAMs **1** and **2** is the parity of alkyl chains. As shown in Fig. 1(b) and (c) the terminal groups in these two SAMs adopt different orientations with respect to the growth surface.[3,4] The carboxy groups on SAM-**2** are nearly perpendicular to the surface; in SAM-**1** they are at a shallower inclination with respect to the surface. Why do *PMP* crystals nucleate from different faces on SAMs **1** and **2**? The relative orientation of the amide dimers of *PMP* with respect to the (012) and (101) planes suggests a possible answer to this question.

In the crystal structure of *PMP*, molecules assemble into dimers through hydrogen bonding between the amide groups.[5] It is reasonable to assume that molecules form hydrogen bonded dimers in solution and that these dimers assemble further into nuclei and crystals. The amide H-atom not involved in dimer formation and the second lone pair of amide O-atom are capable of forming hydrogen bonds with the carboxy groups at the SAM interface. The angle between the amide dimers and (012) plane is 43°; the corresponding angle for (101) plane is 73° (Fig. 4).[9] It is instructive to compare these angles (43 and 73°) with the angles at which the carboxy groups are projected at the surface of SAMs **1** and **2** (~45 and ~73°; Fig. 1(b) and (c)). The carboxy groups on SAM-**1** are coplanar with the amide dimers at (012) planes, whereas the carboxy groups on SAM-**2** are coplanar with the amide dimers at (101) planes. Given that hydrogen bonding between carboxy groups and amide dimers is greatly facilitated when the two moieties are coplanar, it is likely that *PMP* nuclei

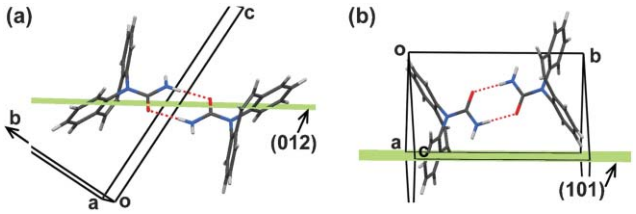

Fig. 4 Relative orientation of carbamazepine dimers with respect to (012) and (101) planes. Notice the shallow inclination of amide dimer in (a) and near perpendicular arrangement in (b).

interact with SAM-**1** through their {012} faces and with SAM-**2** through their {010} faces.[10]

The parity of alkyl chains is rarely explored as a tool to control interfacial phenomena.[11] In this work, we showed that the parity of alkyl chains does play a determining role in the face-selective nucleation of *organic* compounds. We are currently exploring the crystal growth of carbamazepine and other polymorphic drugs on SAMs with (a) different numbers of methylene groups and (b) carboxy and other terminal groups to test the generality of the parity effect on heterogeneous nucleation.

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9 The crystal structure of *PMP* has been determined by multiple authors. In this work we used the $P2_1/n$ structure reported in: V. L. Himes, A. D. Mighell and W. H. De Camp, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1981, **37**, 2242. It should be noted that the amide dimers adopt two distinct inclinations (43 and 79°) with respect to (101) planes. Whereas the dimer with shallower (43°) inclination is

located within the plane, the dimer with steeper (79°) inclination is projected away from the plane.
10 Both (012) and (101) planes show coincident geometric epitaxy with the SAM substrates. The 2D cell parameters are as follows: (012): 7.54 Å, 26.29 Å, 91.51°; (101): 11.16 Å, 16.15 Å, 90°; and SAMs **1–4**: 4.97 Å, 4.97 Å, 120°. See: A. C. Hillier and M. D. Ward, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1996, **54**, 14037, for details on geometric epitaxy.
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