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Polymorph Selectivity under Nanoscopic Confinement

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The regulation of crystal nucleation and growth is essential for many processes, from the production of pharmaceuticals to the formation of biominerals. Any crystallization process involves the assembly of molecular growth units into nuclei. According to classical theory, these nuclei become stable and grow into mature crystals upon achieving a critical size.[1] Generally thought to have structures mimicking the crystal packing of their corresponding mature forms, these nuclei determine crystallization outcomes such as crystal size, crystal habit, and polymorphism,[2,3] the latter pertaining to the ability of a material to adopt different crystal structures. This has prompted many investigations aimed at exploring fundamental aspects of nucleation and developing strategies for manipulating the nucleation process.[4−8]

Despite these efforts, however, reliable protocols for controlling crystallization and crystal properties, particularly polymorphism, remain a central challenge. The unique characteristics of nucleation suggest that crystallization in well-defined pores having dimensions near the critical nucleus size (typically nanometer-scale) can be regulated systematically by adjustment of the pore size. For example, it may be possible to prescribe pore sizes that discriminate between polymorphs, which can be expected to have different critical nuclei sizes. Moreover, the large internal surface area of materials containing nanometer-scale pores can provide an additional tool for regulating crystallization through heterogeneous nucleation on the pore walls. We describe herein the crystallization of organic polymorphs in nanoporous polymer and glass matrices using illustrative combinations, chosen for their thermal compatibility and pore-wetting characteristics, which reveal the influence of pore confinement on polymorph discrimination.

The crystallization of metals,[9] ice,[10] and organic solids[11] has been examined in porous media, including commercially available controlled pore glass (CPG)[12] with pore dimensions <100 nm. These studies have largely focused on the melting (or freezing) point depression resulting from the nanometer-scale dimensions of the crystals within the pores. Recently, we described polycyclohexylethylene−polylactide (**PCHE**−**PLA**) block copolymer monoliths, which after shearing and chemical etching of the **PLA** produced *macroscopic* nanoporous **PCHE** monoliths with hexagonal arrays of cylindrical pores.[13,14] (Figure 1). These pores can be filled with liquids, either solvents or molten solids, thereby providing a route to examining crystallization within the pores. The pore size can be adjusted to values near those of the commercially available CPG, allowing comparison of crystallization in different pore environments.

Anthranilic acid (AA) is known to crystallize in three polymorphs.[15] According to a previous report,[16] form II crystallizes by cooling supersaturated solutions or by rapid evaporation of those solutions at room temperature (RT). In contrast, III can be crystallized from its melt, and mixtures of II and III can be obtained by sublimation. Furthermore, upon standing at RT for several weeks

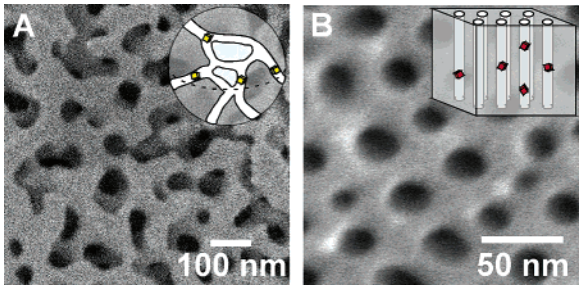

Figure 1. Scanning electron micrographs of (A) commercially available controlled porous glass (CPG) with a pore diameter ($d \cong 55$ nm) and (B) a platinum-coated (ca.. 2 nm thick) porous **PCHE** monolith with a hexagonal array of cylindrical pores ($d \cong 30$ nm). (Insets) Schematic representations of nanocrystals grown in the pores.

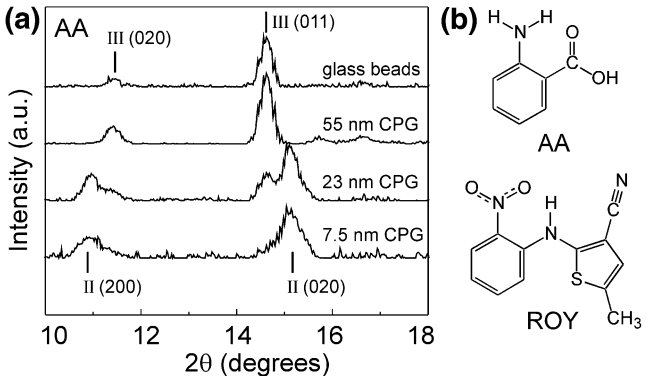

Figure 2. (a) PXRD data for anthranilic acid crystallized by cooling of its melt on nonporous glass beads and within CPGs of various pore sizes. (b) Structures AA and ROY.

II will transform, in the solid state, to I. We determined that II will transform to I upon standing in methanol. These studies suggest that form II is not a thermodynamically stable form under the conditions examined. We also demonstrated that polymorph selectivity during sublimation of AA was influenced by the surface properties of glass substrates.[17]

AA, obtained commercially as form I, was mixed with nonporous glass beads (particle size ≤108 μm, Aldrich) or CPG and heated to 155 °C, (T_m(AA) = 148 °C). The mixtures were then cooled to RT at 5 °C/min. Whereas powder X-ray diffraction (PXRD) of these mixtures at RT revealed only form III on nonporous glass beads and in the pores of 55-nm CPG, form II became evident in 23-nm CPG and was clearly predominant in 7.5-nm CPG (Figure 2). The embedded crystals of II afforded broad X-ray diffraction peaks and depressed melting points characteristic of nanometer-scale crystals.[18] The distribution of the polymorphs in these mixtures remained unchanged upon standing at RT for at least one month. The preference for metastable II in smaller pores can be attributed to a smaller critical nucleus size compared with the other forms. Contributions from preferred heterogeneous nucleation of form II, which would become more significant as the pore size decreases,

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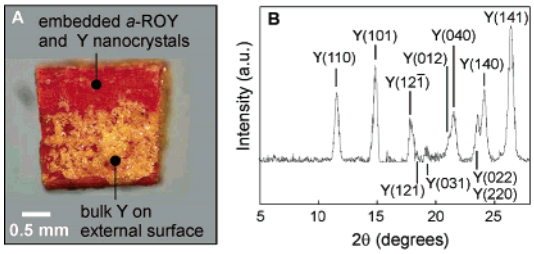

Figure 3. (A) Optical micrograph of a *p*-**PCHE** monolith with nanocrystals of Y and *a*-ROY embedded within the pores and bulk crystals of Y on the external surface. The pores are oriented horizontally in the plane of the page. (B) XRμD pattern for a monolith after washing with methanol to remove the bulk crystals (the amorphous background from *p*-**PCHE** and *a*-ROY is subtracted).

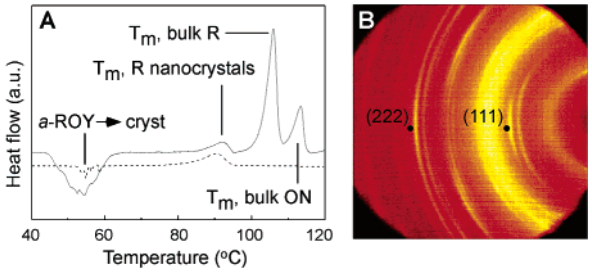

Figure 4. (A) DSC of an unwashed (solid line) and washed (dashed line) *p*-**PCHE** monolith impregnated with ROY (from pyridine) that has been subjected to heating at 120 °C and cooled to −25 °C (5 °C/min in both directions). (B) 2-D diffraction pattern of an aligned monolith containing only R nanocrystals (i.e., after washing with methanol to remove bulk R and ON from the external surface). Preferred orientation of R nanocrystals is evident. For clarity, only the (111) and (222) reflections are denoted here.

cannot be discounted (the internal surface area−volume ratio for 7.5-nm pores is 7 times that of 55-nm pores).

The pharmaceutical intermediate 5-methyl-2-[(2-nitrophenyl)-amino]-3-thiophenecarbonitrile has been dubbed ROY for the different colors of its six fully characterized polymorphs: red prisms (R), orange-red plates (ORP), orange plates (OP), orange needles (ON), yellow needles (YN), and yellow prisms (Y).[19] Evaporation of a pyridine solution of ROY in contact with either a nanoporous **PCHE** monolith with 30-nm diameter pores (*p*-**PCHE**) or nonporous **PCHE** produced only form Y, as determined by X-ray microdiffraction (XRμD) of a single monolith (Figure 3). In the case of *p*-**PCHE**, the diffraction peaks remained after washing the external surfaces of the monolith with methanol, confirming the existence of nanocrystals of Y embedded in the *p*-**PCHE** pores.[20] Like AA, these nanocrystals afforded broad diffraction peaks and depressed melting points characteristic of their small size.[21] Interestingly, the monoliths exhibited a red color before and after washing. In the absence of diffraction peaks assignable to polymorphs other than Y, this persistent red color can be attributed to amorphous ROY (*a*-ROY) embedded in the pores of *p*-**PCHE**. Molten ROY and *a*-ROY are red, and the *a*-ROY glass transition at $T_g \cong -13$ °C was observed in these monoliths by DSC (not shown).

If an unwashed *p*-**PCHE** monolith impregnated with Y nanocrystals and *a*-ROY (from pyridine) was heated to 120 °C (above the bulk melting temperature of ROY but below the glass transition temperature, T_g, of **PCHE**[22]) and then cooled, upon heating again the DSC revealed an exotherm due to crystallization of *a*-ROY (Figure 4), an endotherm for melting of R nanocrystals, and endotherms for bulk R and ON on the external surface (Figure 4A). Forms R and ON crystallize on the surfaces of nonporous **PCHE** as well, but the YN form predominates in the absence of **PCHE**, not unlike polymorph selectivity recently reported for other crystal/polymer substrate combinations.[23] Measurements performed after the external surfaces of the monoliths were washed with methanol revealed that the pores contained a smaller amount of *a*-ROY (by DSC) and *only* R nanocrystals (i.e. no ON, by XRμD, DSC). The 2-D diffraction pattern generated from a monolith aligned with its pores perpendicular to the equatorial plane of the microdiffractometer revealed that the (111) planes of the embedded R nanocrystals were aligned with the pore axis (Figure 4B). Interestingly, crystallization of ROY in 20-nm pores is substantially suppressed compared with crystallization in 30-nm pores, whether from evaporation of imbibed solutions or from *a*-ROY during melting/cooling cycles, suggesting critical size effects.

These observations demonstrate that crystal nucleation and polymorph selectivity are influenced by confinement in nanometer-scale pores, most likely due to critical size constraints. The nanoporous polymer monoliths used in this study are particularly interesting because the polymer matrix can be fractured or dissolved to release polymorph seeds that otherwise may be difficult to generate. The ability to achieve polymorph selectivity in both glass and polymer matrices suggests wide-ranging compatibility with various organic crystalline solids, promising a new approach to controlling polymorphism and searching for unknown polymorphs.

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