

Directing Polymorph Selectivity During Nucleation of Anthranilic Acid on Molecular Substrates

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Polymorphism plays an important role in the physical properties of organic crystals, including solid-state reactivity,¹ optical and electronic properties,^{2,3} morphology, and solubility properties. For example, solid-state structure and morphology strongly affect the sensitization provided by photographic dyes and the crystal dissolution and bioavailability of pharmaceutical chemicals.⁴ The differing properties exhibited by polymorphs of a given compound can be attributed to variations in intra- and intermolecular bonding and the corresponding packing motifs.^{5,6} The difference in packing energies among a given polymorphic family are typically small, and crystallization of a metastable polymorph is a consequence of kinetic selectivity during the nucleation and growth process. The tendency for nucleation to occur heterogeneously^{7,8} and recent reports that nucleation can be directed by specific interfacial interactions at molecular interfaces^{9,10} suggest that substrate composition and structure can play an important role in directing selectivity toward different polymorphs. Indeed, growth of inorganic crystals that normally crystallize in the CsCl structure will crystallize into NaCl lattices when grown on NaCl-type substrates.¹¹ These considerations prompted us to examine nucleation of polymorphic organic crystals on solid substrates modified with self-assembled films.¹² We have discovered that the composition of these monolayers significantly influences the selectivity toward different polymorphs of anthranilic acid (2-aminobenzoic acid). The selectivity suggests that the availability of hydrogen-bonding functionality at the nucleation interface plays an important role.

Anthranilic acid exhibits a rich but poorly understood trimorphic phase behavior.^{13,14} Polymorph I is brown and exhibits zwitterionic character.¹⁵ Polymorphs II and III, however, are colorless and have uncharged molecules in their unit cells. The crystal structures of polymorphs II¹⁶ and III¹⁷ consist of hydrogen-bonded carboxylic acid dimers stacked into layers ($d_{\text{O}\cdots\text{H}\cdots\text{O}} = 2.654$ and 2.651 Å for polymorphs II and III, respectively). These

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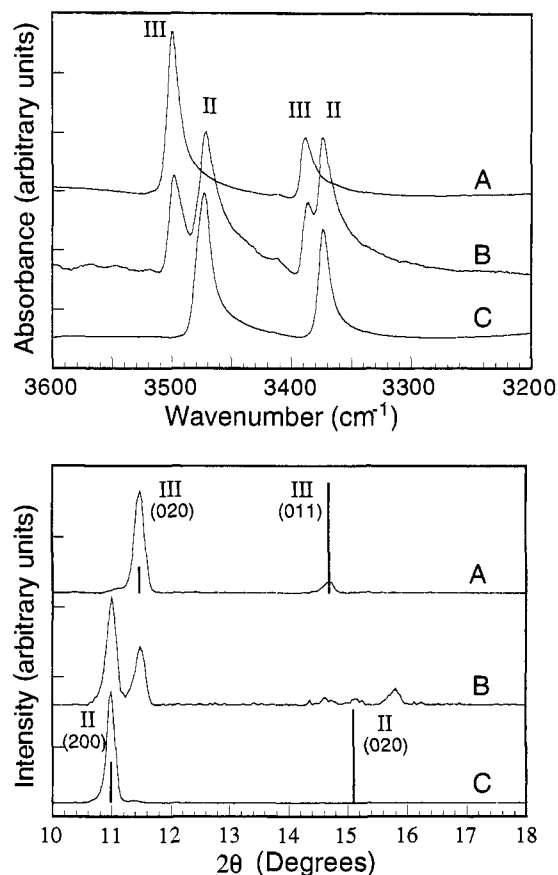


Figure 1. Top: FTIR spectra and X-ray diffraction data for anthranilic acid nucleated on (A) glass/trimethoxysilane, (B) bare glass, and (C) glass/chlorotriisobutylsilane. The N–H stretching region in A shows only polymorph III, B shows both II and III, and C shows only polymorph II. Bottom: The X-ray diffraction data differ significantly from randomly oriented powder intensities (vertical lines). The data in A correspond to preferential orientation of III-(020) planes parallel to the substrate surface, whereas the data in C correspond to preferential orientation of II-(200) planes. The (hkl) assignments for the important peaks are shown.

layers are held together by van der Waals forces. The intramolecular N–H \cdots O contacts for each anthranilic acid molecule are 2.682 and 2.688 Å for II and III, respectively. However, weak intermolecular N–H \cdots O interactions are evident in polymorph II ($d_{\text{N}\cdots\text{H}\cdots\text{O}} = 3.122$ Å) but not in polymorph III ($d_{\text{N}\cdots\text{H}\cdots\text{O}} = 3.385$ Å). As a consequence of their different hydrogen-bonding, polymorphs I, II, and III of anthranilic acid are readily identified by their $\nu_{\text{N-H}}$ infrared stretching frequencies.¹⁸

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- (18) Polymorph I: $\nu_{\text{N-H}} = 3324, 3240$ cm⁻¹. Polymorph II: $\nu_{\text{N-H}} = 3474, 3374$ cm⁻¹. Polymorph III: $\nu_{\text{N-H}} = 3495, 3382$ cm⁻¹. Ojala, W. H.; Etter, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 10288.

Sublimation of recrystallized anthranilic acid (a mixture of polymorphs **II** and **III**) onto glass, mica, and self-assembled monolayer substrates resulted in the formation of thin anthranilic acid films whose coverage and polymorph composition was substrate dependent.¹⁹ The anthranilic acid films consisted of colorless needle crystals 20–1000 μm in length. FTIR spectroscopy revealed that *only* polymorphs **II** and/or **III** were present on all substrates. The absence of polymorph **I** probably reflects the difficulty of forming the zwitterionic phase in the low dielectric medium present in vapor-phase sublimation and is in agreement with a previous study in which sublimation afforded only a mixture of **II** and **III**.¹⁸ Notably, the mole fractions of polymorphs **II** and **III**, estimated from the integrated intensities of the $\nu_{\text{N-H}}$ bands at 3495 and 3474 cm^{-1} , respectively, differed substantially on various substrates (Figure 1, top). The fraction of **III** (f_{III}) decreases in the order glass/trimethoxysilane (1.0) \approx glass/trichlorosilane (0.9) > bare glass \approx mica (0.5) > glass/chlorotriisobutylsilane (0.0).

The observed trend in selectivity strongly suggests specific interactions between the substrates and anthranilic acid molecules during the self-assembly process leading up to nucleation. Cleaved mica surfaces possess oxyanion sites,²⁰ whereas bare glass, glass/trimethoxysilane, and glass/trichlorosilane surfaces possess surface hydroxyls in concentrations that depend upon substrate preparation and history.¹¹ The presence of hydroxyl groups on glass/trimethoxysilane and glass/trichlorosilane surfaces was confirmed by FTIR spectroscopy by a $\nu_{\text{Si-H}}$ band at 2147 cm^{-1} , previously assigned to (HO)Si-H surface species.^{21,22} In contrast, surfaces treated with chlorotriisobutylsilane do not possess surface hydroxyls. These characteristics implicate interfacial hydrogen-bonding events during the nucleation of anthranilic acid polymorphs. Significantly, grazing angle X-ray diffraction reveals that polymorph **II** and polymorph **III** are preferentially oriented with their (100) and (010) planes parallel to the substrate surface, respectively, as evidenced by the strong (200) and (020) reflections (Figure 1, bottom).²³ The (100) plane of polymorph **II** is best described as a dispersive plane with low surface energy, as the hydrogen-bonding is contained *within* this plane. In contrast, non-hydrogen-bonded NH_2 groups of **III** are exposed on the (010) plane and therefore are accessible to the substrate during nucleation. This suggests that the observed polymorph selectivity is due to competition for anthranilic acid NH_2 groups in incipient nuclei by the substrates. Competitive binding of the substrate hydroxyls with NH_2 groups in the early stages of nucleation would interfere with the intermolecular N—H...O hydrogen-bonding in nuclei of **II**, suppressing its formation. Nucleation of **III** would be enhanced by hydrogen-bonding interaction of the substrate with free NH_2 groups on the (010) plane, as this would lower the

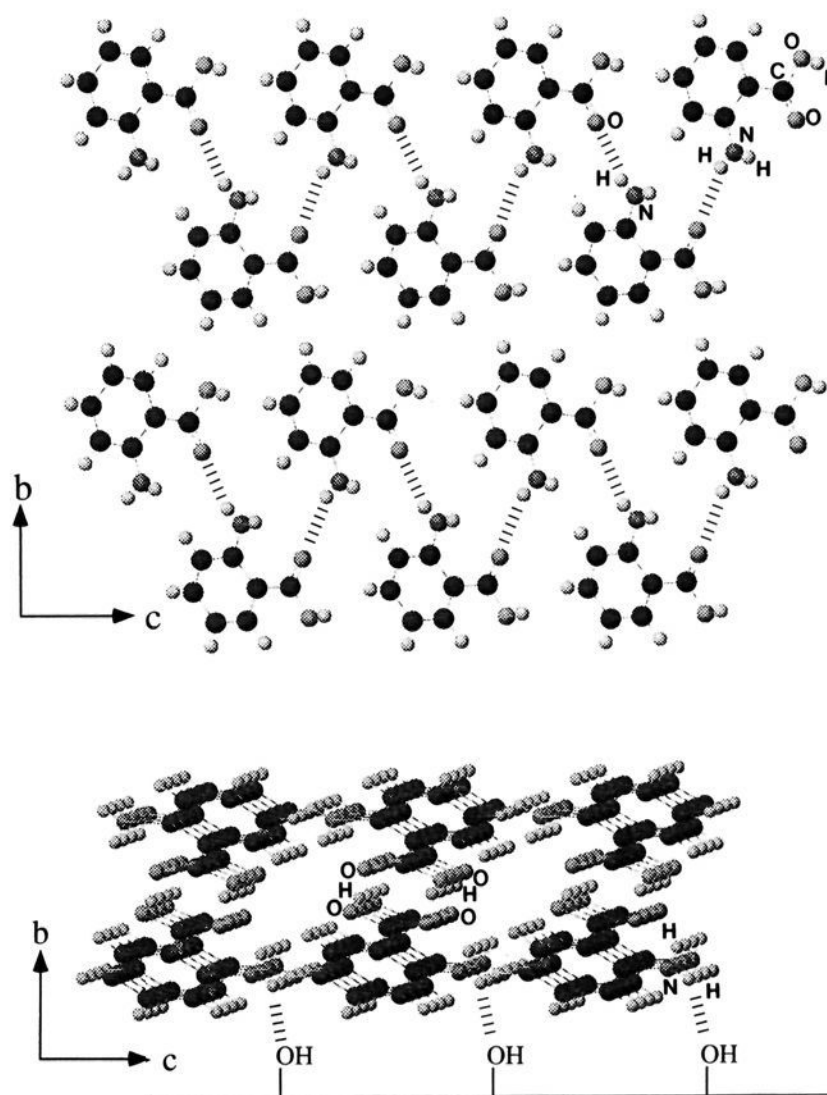


Figure 2. Top: Molecular packing of the (100) plane of anthranilic acid polymorph **II** depicting N—H...O contacts of 3.12 Å (dotted lines) within the plane. Only one-half of the anthranilic acid dimer pair is shown here for clarity. The other half of the dimer projects into the bulk. Bottom: Proposed orientation of polymorph **III** on hydrogen-bonding substrate surfaces, with the (010) plane parallel to the surface and with N—H...O hydrogen-bonds between anthranilic acid and surface hydroxyl groups. The crystal structures were retrieved from the Cambridge Crystal Structural Database, Cambridge Crystallographic Data Centre, University Chemical Library, Cambridge, England, Version 5.05, update April 1993.

surface energy of the nucleus. Conversely, the intermolecular N—H...O hydrogen-bonding in **II** is not disrupted when the substrate lacks hydrogen-bonding functionality, allowing stabilization of **II** nuclei by dispersive interactions of its (100) plane with the substrate (Figure 2).

The results described above demonstrate the importance of surface functionality on polymorph selectivity and growth orientation. These results strongly suggest that hydrogen-bonding plays an important role in stabilizing incipient nuclei of anthranilic acid and provide further evidence that the phase behavior of polymorphic systems can be influenced by complex, kinetically controlled, heterogeneous nucleation events. We anticipate that molecular level design of solid substrates for heterogeneous nucleation processes can have significant fundamental and commercial impact, including the crystallization of commercially important materials such as photographic dyes and pharmaceutical reagents.

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(19) Sublimations were performed so that the differently modified substrates were examined simultaneously. Glass substrates were treated with nitric acid, rinsed in 18 M Ω deionized water, and dried with filtered air prior to modification with the silane reagents or use as bare substrates. Trimethoxysilane and trichlorosilane films were prepared by exposure of the glass substrate to the vapor, whereas chlorotriisobutylsilane films were prepared by immersion of the glass substrate in the neat liquid. Mica substrates were freshly cleaved prior to use. The substrates were placed 4 cm above the anthranilic acid, which was sublimed at 1 atm from a hot plate (surface temperature = 170 °C) for 4 min. After sublimation, weakly bound crystals were removed by a gentle stream of filtered air. These conditions were found to be optimal for observing substrate effects on polymorph selectivity. It is important to note that the observed selectivity trends are very sensitive to experimental conditions.

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