

Selective growth of a less stable polymorph of 2-iodo-4-nitroaniline on a self-assembled monolayer template

Rupa Hiremath, Stephen W. Varney and Jennifer A. Swift*

Georgetown University, Department of Chemistry, 37th and O Streets NW, Washington DC 20057-1227, USA. E-mail: jas2@georgetown.edu; Fax: +1 (202) 687-6209; Tel: +1 (202) 687-5567

Received (in Columbia, MO, USA) 28th July 2004, Accepted 8th September 2004

First published as an Advance Article on the web 15th October 2004

Orthorhombic and triclinic crystals of 2-iodo-4-nitroaniline (INA) grow concomitantly from supersaturated ethanol solutions, but the less stable orthorhombic phase can be selectively grown on 3'-X-4-mercaptobiphenyl (X = NO₂, I) self-assembled monolayer templates.

A number of molecules are known to crystallize in at least two different solid state arrangements, and the resultant crystalline forms are known as polymorphs. When more than one polymorphic form is simultaneously obtained from the same growth solution, these entities are referred to as concomitant polymorphs.¹ Polymorphs are different materials, and can often exhibit very different physical properties. In a commercial setting where process control is important, conditions under which concomitant polymorphs form are intentionally avoided. Usually this is achieved by empirically altering the crystallization conditions (*e.g.* temperature, cooling rate, solvent, concentration, *etc.*) until only a single desired phase results. An alternative strategy for avoiding concomitant polymorphs explored in this work, is to introduce a template into the crystallization solution which can selectively promote the heterogeneous nucleation of a single phase.

Previous studies have demonstrated that functionalized self-assembled monolayers (SAMs) can be used as substrates for the growth of inorganic² and molecular crystals containing carboxylic acids such as leucine,^{3a} L-alanine,^{3b} DL-valine,^{3c} α -glycine,^{3d} and malonic acid.^{3e} Recently we demonstrated that SAMs of 4'-nitro-4-mercaptobiphenyl (**1**) and 4'-iodo-4-mercaptobiphenyl (**2**) could also be used to control the nucleation and the absolute growth direction of 4-iodo-4-nitroaniline polar crystals through interfacial NO₂...I interactions and geometric lattice matching.⁴ In the present study, the selectivity of these SAMs, as well as SAMs of their 3'-analogues, 3'-nitro-4-mercaptobiphenyl (**3**) and 3'-iodo-4-mercaptobiphenyl (**4**), are examined as possible template-directing agents for 2-iodo-4-nitroaniline (INA).

Crystallization of INA from saturated room temperature ethanolic solutions results in the formation of triclinic (*P* $\bar{1}$) and orthorhombic (*Pbca*) phases simultaneously (Fig. 1).⁵ The two modifications are easily distinguished on the basis of habit and melting point. Triclinic crystals grow as needles elongated about the crystallographic *b* axis, and are bounded by {100}, {001} and {010} faces (Fig. 2). Orthorhombic crystals adopt a plate-like habit

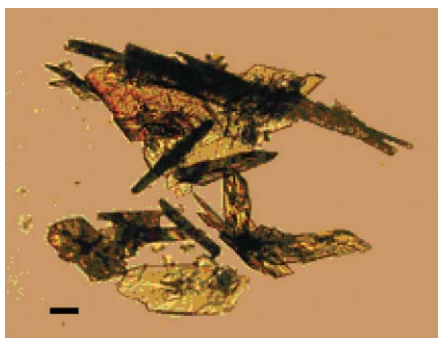


Fig. 1 Optical micrograph of INA orthorhombic plates and monoclinic needles grown simultaneously from ethanol solutions. Scale bar = 0.2 mm.

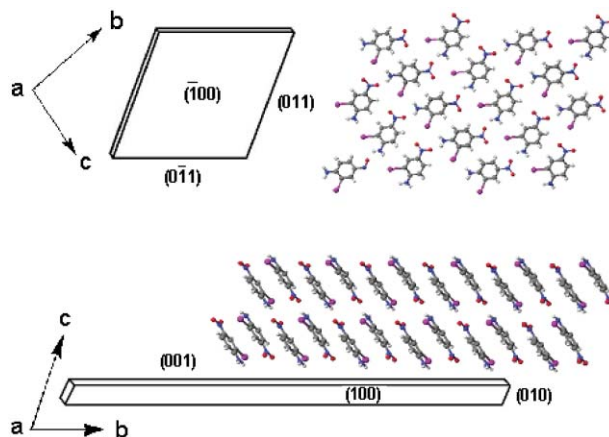


Fig. 2 Miller indices of orthorhombic plates and triclinic needles were determined by X-ray goniometry. Crystal packing diagrams were constructed from the fractional coordinates in ref. 5.

bounded by large {100} faces and smaller {011} and {01 $\bar{1}$ } side faces. While the lattice energies of the two polymorphs must be similar enough so as to enable their simultaneous formation, the triclinic phase is more thermodynamically stable than the orthorhombic phase on the basis of both melting temperature and density (P $\bar{1}$ needles: mp = 115–116 °C, density = 2.278 g cm⁻³; *Pbca* plates: mp = 105–106 °C, density = 2.265 g cm⁻³).

The synthesis† of **1–4** was accomplished by the palladium-assisted coupling of a 4-bromothioanisole Grignard reagent to the appropriate 3-X- or 4-X-substituted-iodobenzene, followed by reduction with sodium ethanethiolate and DMF according to the procedure of Kang *et al.*⁶ SAMs were prepared by sputtering 30 Å chromium and 3000 Å gold on 5 mm² mica squares followed by immersion in a 2 mM ethanolic thiol solution of **1–4** for 24 h. SAMs were rinsed with ethanol, dried under nitrogen, and characterized by ellipsometry and contact angle measurements (Table 1).

Previous studies of 4'-substituted-mercaptobiphenyl SAMs reveal that a number of these monolayers are stable, and that small tilt angles and herringbone packing arrangements are favored.⁷ The thickness of an unsubstituted 4-mercaptobiphenyl monolayer is 14 (\pm 1) Å, and the addition of a substituent to the 4'-position generally increases the monolayer height. We note that the thicknesses of 3'-X-mercaptobiphenyl monolayers **3** and **4** are actually smaller than that of 4-mercaptobiphenyl. While we do not yet have a clear picture of the 2D ordering of these SAMs, these

Table 1 Experimentally determined thickness and contact angle measurements of SAMs **1–4**. Literature values cited refer to ref. 7b

SAM	1 (4'-NO ₂)	2 (4'-I-)	3 (3'-NO ₂ -)	4 (3'-I-)
Ellipsometry	14	15	12	11
\pm 1 Å (lit)	(14)	(15)		
Contact angle	61°	78°	82	83
\pm 0.8° (lit)	(64°)	(79°)		

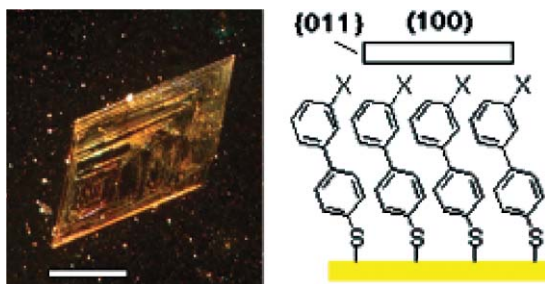


Fig. 3 Orthorhombic plate crystals of INA grown on a SAM of 3. The contacting crystal face is {100}. Scale bar = 0.2 mm.

values presumably reflect a significant increase in the tilt angle made between the long axis of the molecule and the surface normal. Such a change also alters the 2D lattice dimensions of the monolayer as well as the orientation of the functional groups presented on the SAM surface. The qualitative difference between 3'- and 4'-substituted SAMs is especially striking in SAMs 1 and 3 whose contact angles differ by $>20^\circ$.

SAM templates 1–4 were introduced into vials containing ethanolic solutions of INA, and positioned vertically so that they leaned against the side of the vial. The vials were covered with parafilm containing small holes and left undisturbed for 72 h or more so that growth by slow evaporation could occur. Repeated attempts to grow INA crystals of either phase on SAMs 1 and 2 proved unsuccessful. However, on SAMs 3 and 4 the growth of exclusively orthorhombic plates was observed (Fig. 3). Optical microscopy revealed that the contacting crystal/SAM interface was always formed between the {100} plane of INA and the monolayer surface.

Why SAMs 3 and 4 only template the growth of the orthorhombic phase is still a matter of some conjecture, but the analysis of the principal crystal faces of the known INA polymorphs does provide some clues. In the orthorhombic phase, the planes of the INA aromatic rings and all nitro-, iodo- and amino- substituents lie nearly parallel to the {100} crystal surface, while on the {011} surface, the aromatic planes are oriented edge-on. In the triclinic needles, the plane of the aromatic rings are also oriented edge-on in all three of the principal {100}, {010} and {001} faces. The orientation and density of polar groups on the INA surface are significantly different when the aromatic rings lie parallel to the surface. The 2D lattice dimensions \ddagger of the orthorhombic {100} and all other INA crystal planes of orthorhombic or triclinic crystals are also quite different, and preferred geometric matching (*i.e.* epitaxy) between {100} and the underlying monolayer may be a factor. This templating effect observed on SAMs is presumably analogous to the polymorph selectivity achieved in other systems by the epitaxial growth on crystalline substrates⁸ or in the presence of polymeric additives.⁹

The crystallization process is governed by a combination of thermodynamic and kinetic factors, and the function of a template is to reduce the barrier to nucleation. This study establishes that for a molecular crystal system that yields simultaneously more than one crystalline phase under a particular set of solution conditions, the introduction of an appropriate SAM template into the growth solution may offer an alternative method for limiting the number of polymorphs formed. The introduction of a SAM template may also lead to the discovery of unknown polymorphs. Ongoing studies are focused on this and other polymorphic systems in order to discern some of the more subtle structural and chemical parameters required in template design.

J. A. S. gratefully acknowledges financial support from the Henry Luce Foundation, the National Science Foundation and the

Camille and Henry Dreyfus Foundation. S. W. V. thanks Georgetown University for GUROP support and an undergraduate summer Adams fellowship.

Notes and references

† A solution containing 4-bromothioanisole (20 mmol, Aldrich, 97%), magnesium turnings (20 mmol, Aldrich, 98%) and anhydrous THF (15 mL) was refluxed under dry nitrogen for 75 min or until no magnesium remained. The Grignard solution was cooled and added dropwise to a solution of 1,3-diiodobenzene (20 mmol, Aldrich, 98%) and tetrakis-(triphenylphosphine) palladium catalyst (0.2 mmol, Aldrich, 99.9%) in anhydrous THF. After refluxing for 30 min, the solution was cooled to room temperature, and quenched in an ice cold solution of 5% HCl. Recrystallization from 1 : 1 heptane : 2-propanol yielded a 3'-iodo-4-methylthiobiphenyl intermediate. The 3'-iodo-4-methylthiobiphenyl intermediate was isolated and characterized: mp = 125–127 °C; $^1\text{H NMR}$ (δ (ppm), CDCl_3) 2.50–2.54 (3H), 7.03–7.36 (4H), 7.48–7.58 (4H). The intermediate (10 mmol) was reduced in anhydrous *N,N*-dimethylformamide (12 mL, Aldrich, 99.8%) by adding sodium ethanethiolate (16 mmol, Aldrich, 80%) and refluxing under dry nitrogen for 6 h. The solution was cooled to room temperature and added to ice cold 5% HCl. Recrystallization from 1 : 1 heptane : 2-propanol followed by silica column purification with 1 : 1 hexane : CH_2Cl_2 ($R_f = 0.77$) yielded 3'-iodo-4-mercaptobiphenyl (4): mp = 135–137 °C; $^1\text{H NMR}$ (δ (ppm), CDCl_3) 2.51–2.53 (1H), 7.30–7.38 (4H), 7.45–7.60 (4H). † 3'-Nitro-4-methylthiobiphenyl was synthesized according to the procedure for 4, using 1-iodo-3-nitrobenzene (Aldrich, 99%) instead of 1,3-diiodobenzene. The 3'-nitro-4-methylthiobiphenyl intermediate was isolated and characterized: mp = 173–175 °C; $^1\text{H NMR}$ (δ (ppm), CDCl_3) 2.51–2.53 (3H), 7.21–7.34 (4H), 7.46–7.53 (4H). Subsequent reduction to the thiol yielded 3'-nitro-4-mercaptobiphenyl (3): mp = 183–184 °C; $^1\text{H NMR}$ (δ (ppm), CDCl_3) 2.50 (1H), 7.28–7.33 (4H), 7.46–7.50 (4H). R_f (1 : 1 CH_2Cl_2 : hexane) = 0.71. † Details on the syntheses of 1 and 2 are described in ref. 4.

‡ 2D lattice parameters for surfaces of the orthorhombic plates: {100} $16.46 \times 12.68 \text{ \AA}$, $\alpha = 90^\circ$; {011} $7.42 \times 20.78 \text{ \AA}$, $\alpha = 90^\circ$, and triclinic needles: {100} $8.05 \times 7.96 \text{ \AA}$, 67.9° ; {001} $7.96 \times 7.16 \text{ \AA}$, 65.74° ; {010} $7.16 \times 16.10 \text{ \AA}$, 86.96° .

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