Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl19

The Crystallization of 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile in the Presence of Structurally Similar Compounds

Thomas B. Borchardt [a], Joseph G. Stowell [a] & Stephen R. Byrn [a]

[a] Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN, 47907-1333

Version of record first published: 04 Oct 2006

To cite this article: Thomas B. Borchardt, Joseph G. Stowell & Stephen R. Byrn (1998): The Crystallization of 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile in the Presence of Structurally Similar Compounds, Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals, 313:1, 271-276

To link to this article: http://dx.doi.org/10.1080/10587259808044287

Mol. Cryst. Liq. Cryst., 1998, Vol. 313, pp. 271–276
Reprints available directly from the publisher
Photocopying permitted by license only

The Crystallization of 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile in the Presence of Structurally Similar Compounds

THOMAS B. BORCHARDT, JOSEPH G. STOWELL, STEPHEN R. BYRN
Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN 47907-1333.

The lab-scale crystallization of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY) has been investigated either alone or in the presence of structurally similar derivatives. Derivatives have been prepared that either change the crystal form or morphology of the product crystals as compared to 100% ROY crystallization experiments.

Keywords: polymorphism; crystallization; additives; morphology; color

INTRODUCTION

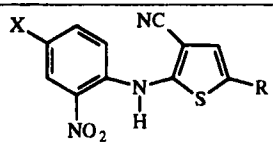
Crystallization is a key step in the production of any material in the solid state. Suprisingly, little research has involved the investigation of the factors in the crystallization environment that may influence the crystallization of polymorphs. Recent interest has involved the study of structurally similar additive molecules, otherwise known as "tailor-made" additives, to control crystal form and shape.[1,2] We are investigating the use of additives on a polymorphic, conformationally flexible molecule, that adopts primarily intramolecular hydrogen bonds in the crystal lattice. In this arena, the role of conformational and steric effects between additive and solute molecule on crystal growth can be investigated. We previously had been presented a molecule that crystallizes into red (R), orange (O), and yellow (Y) polymorphs, referred to affectionately as ROY.[3] The compound is ideal for the study of the crystallization of polymorphs since the polymorphs can be identified visually.

Crystallization experiments were performed in absolute ethanol at 25 °C and at a saturation level of 2.25 times the equilibrium saturation at 25 °C (based on solubility of the Y form). Additives were present in the crystallization solution at a concentration of 10% (w/w) relative to the ROY concentration. A hot solution of the mixture was filtered through a 0.45-μm filter and transferred to the crystallizer (a 1000-mL jacketed reaction vessel fitted with a three-neck head). The resulting solution was heated to 70 °C and then cooled to 25 °C while stirring at 300 rpm. Crystallization was initiated at 25 °C by addition of approximately 8.5 mg of seed crystals of the ROY R form. The solution was then stirred an additional three hours at 25 °C and 300 rpm. At the end of this time, the resulting crystals were harvested and analyzed. All crystallization experiments were performed in triplicate.

RESULTS AND DISCUSSION

Table 1 lists the derivatives prepared for use as additives and their polymorphs. The derivatives are structurally similar to the title compound in either the thiophene or nitrophenyl portion of the molecule. Table 2 summarizes the results of the crystallization experiments. Crystallization with 100% ROY and no additive was used as a control. In the presence of any of the three additives, crystals that are structurally identical to the corresponding ROY crystal forms (R or Y) were obtained as determined by X-ray powder

TABLE 1 ROY Derivatives Used in Crystallization Experiments.



Derivative	Polymorphs Observed
ROY; (X=H, R=CH_3)	red, orange, lt. red, two yellow
5-Nor-methyl; (X=H, R=H)	red, orange, yellow
4'-Methyl; (X=CH_3, R=CH_3)	dk. red, red, lt. red, orange,
4'-Fluoro; (X=F, R=CH_3)	red

TABLE 2 Summary of Crystallization Results

Additive	Initial Crystals Observed Visually	Product Crystals [ABBREVIATION] (Crystal Shape)
--	red (convert to Yellow over 60-90 minutes.)	yellow [YP] (elongated hexagonal prism)
5-Nor-methyl	red	yellow [YNME] (distorted bypyramid)
4'-Methyl	yellow	yellow [Y4'ME] (plates)
4'-Fluoro	red (convert to Yellow within first 30 minutes)	yellow [Y4'F] (elongated hexagonal prism)

diffraction (XRPD). It is important to note that with the 5-nor-methyl compound primarily the R form was obtained, whereas, all other crystallizations yielded the Y form.

The current research has investigated the changes in morphology of the yellow product crystals from the various crystallization conditions. The crystal morphology was determined by measuring the angle between crystal faces by optical goniometry. The measured angles were compared to theoretical values obtained from the Morphology Predictor available as a part of *Cerius2*.[4] Figure 1 shows the SEM and morphology of the yellow crystals (YP) obtained from crystallization of pure ROY. The YP crystals are bound by the (110) and (120) faces perpendicular to the short crystal axis and by the (111) and (101) crystal faces perpendicular to the long crystal axis.

Crystallization of ROY the 5-nor-methyl derivative (10% w/w) results in preferential growth of the ROY R form within the time frame of the experiment. The crystallization is not completely selective for the R form because of the presence of a few yellow (YNME) crystals. The YNME crystals yield a powder pattern virtually identical to the YP crystals, verifying that a change in crystal packing in the presence of the additive did not occur. The morphology of the YNME crystals is drastically different from that of the

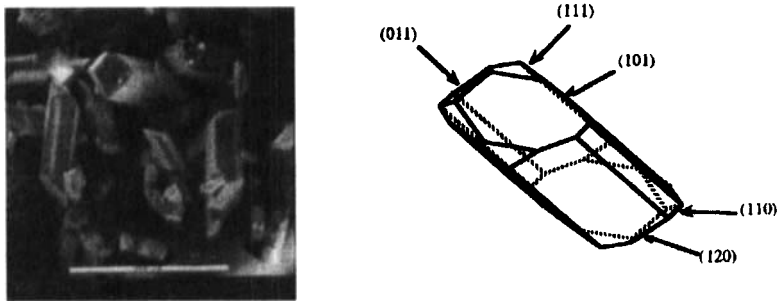


FIGURE 1 SEM and morphology of the YP crystals. The white box in the SEM represents 250 μm.

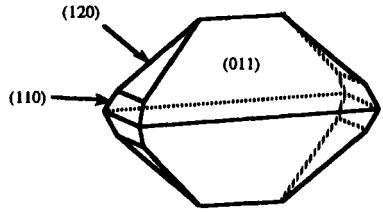


FIGURE 2 Crystal morphology of the YNME crystals.

YP crystals. In particular, the YNME crystals are dominated by the (011) crystal faces in contrast to the YP crystals in which this face has a minor morphological importance. The morphology of the YNME crystals is shown in Figure 2. Changes in morphology are likewise seen between the R (ROY) seed crystals used to initiate crystallization and the red product crystals (RNME). The indexation of the faces of both the R (seeds) and RNME crystals is currently under investigation.

The crystallization of ROY and the 4'-methyl derivative (10% w/w) leads to initial growth of a yellow crystal form (Y4'ME) even though crystallization was initiated by addition of R ROY seeds. No change in internal crystal packing of the Y4'ME crystals as compared to the YP crystals was observed by XRPD. The morphology of the Y4'ME crystals is dominated by the (101) faces, leading to a more plate-like crystal as compared to the YP crystals

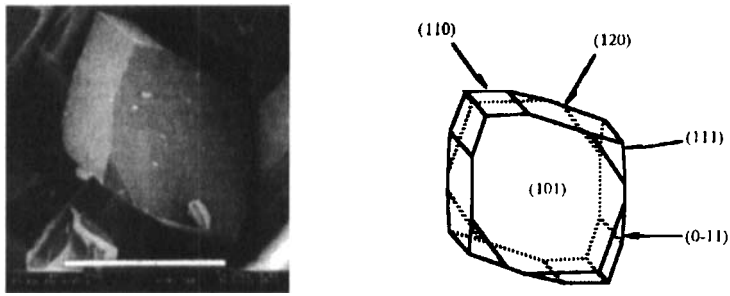


FIGURE 3 SEM and crystal morphology of the Y4'ME crystals. The white box in the SEM represents 250 μm.

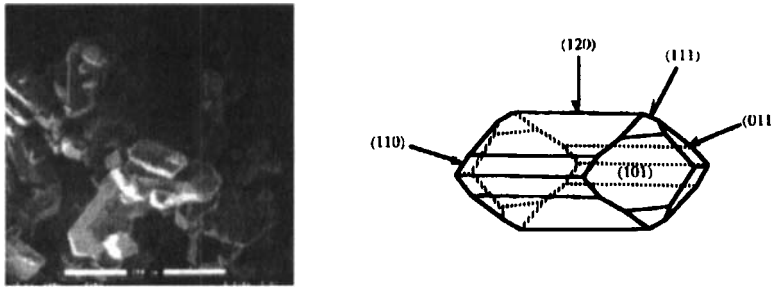


FIGURE 4 SEM and crystal morphology of the Y4'F crystals. The white box in the SEM represents 250 μm.

(Figure 3). The change in morphology indicates a selective interaction between solute and additive molecules that slows the growth of the (101) crystal faces.

Finally, crystallization of ROY and the 4'-fluoro derivative (10% w/w, used to investigate electronic instead of steric effects) gave yellow (Y4'F) crystals which were confirmed by XRPD to have the same crystal packing as the YP crystals. The morphology of the Y4'F crystals is virtually identical to that of the YP crystals and is shown in Figure 4.

Portions of the crystals obtained from the different crystallizations were washed successively on a sintered-glass funnel ten times with 2-mL portions of anhydrous ethanol. The individual wash fractions were evaporated to

dryness and analyzed by HPLC. The 5-nor-methyl and 4'-methyl derivatives were incorporated throughout the crystal lattice at a level of 1-2%. The presence of 4'-fluoro derivative in the crystals was detected by solution ^{1}H-NMR (300 MHz), and determined to be incorporated in the crystal lattice at a level of approximately 9-10%. The lack of selectivity for incorporation of the 4'-fluoro derivative into the ROY crystal lattice indicates that in this series of crystallizations, steric factors play a greater role than electronic factors.

Additives have been observed to significantly affect the crystallization of ROY. Presumably, non-bonding type interactions give rise to the observed changes in morphology since intermolecular bonding in the ROY crystal forms is weak. Current research is investigating potential mechanisms of crystal growth inhibition at each of the affected crystal faces, as well as the "effective" concentration of additive required to yield changes in crystal properties.

Acknowledgments

Eli Lilly and Company for graciously providing the ROY compound.

NIH Chemical Pharmacology training grant and the Joint Purdue/Wisconsin Program for the Study of the Effects of Water on the Molecular Mobility of Crystalline and Amorphous Pharmaceutical Solids for financial support.

References

[1]. I. Weissbuch, R. Popovitz-Buro, M. Lahav, and L. Leiserowitz, *Acta Cryst.*, **B51**, 115, (1995), and references therein.

[2]. R. J. Davey, N. Blagden, G. D. Potts, and R. Docherty, *J. Am. Chem. Soc.*, **119**, 1767, (1997).

[3]. G. A. Stephenson, T. B. Borchardt, S. R. Byrn, J. Bowyer, C. A. Bunnel, S. V. Snorek, and L. Yu, *J. Pharm. Sci*, **84**(11), 1385, (1995).

[4]. *Cerius2 2.0*, BIOSYMM/Molecular Simulations, (1995).