

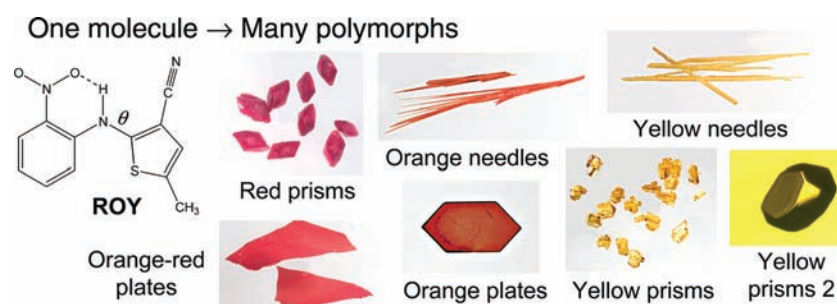
Polymorphism in Molecular Solids: An Extraordinary System of Red, Orange, and Yellow Crystals

LIAN YU*

School of Pharmacy and Department of Chemistry, University of Wisconsin—Madison, 777 Highland Avenue, Madison, Wisconsin 53705

RECEIVED ON MARCH 4, 2010

CON SPECTUS



Diamond and graphite are polymorphs of each other: they have the same composition but different structures and properties. Many other substances exhibit polymorphism: inorganic and organic, natural and manmade. Polymorphs are encountered in studies of crystallization, phase transition, materials synthesis, and biomineralization and in the manufacture of specialty chemicals. Polymorphs can provide valuable insights into crystal packing and structure–property relationships. 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophencarbonitrile, known as ROY for its red, orange, and yellow crystals, has seven polymorphs with solved structures, the largest number in the Cambridge Structural Database.

First synthesized by medicinal chemists, ROY has attracted attention from solid-state chemists because it demonstrates the remarkable diversity possible in organic solids. Many structures of ROY polymorphs and their thermodynamic properties are known, making ROY an important model system for testing computational models. Though not the most polymorphic substance on record, ROY is extraordinary in that many of its polymorphs can crystallize simultaneously from the same liquid and are kinetically stable under the same conditions. Studies of ROY polymorphs have revealed a new crystallization mechanism that invalidates the common view that nucleation defines the polymorph of crystallization. A slow-nucleating polymorph can still dominate the product if it grows rapidly and nucleates on another polymorph. Studies of ROY have also helped understand a new, surprisingly fast mode of crystal growth in organic liquids cooled to the glass transition temperature. This growth mode exists only for those polymorphs that have more isotropic, and perhaps more liquid-like, packing.

The rich polymorphism of ROY results from a combination of favorable thermodynamics and kinetics. Not only must there be many polymorphs of comparable energies or free energies, many polymorphs must be kinetically stable and crystallize at comparable rates to be observed. This system demonstrates the unique insights that polymorphism provides into solid-state structures and properties, as well as the inadequacy of our current understanding of the phenomenon. Despite many studies of ROY, it is still impossible to predict the next molecule that is equally or more polymorphic. ROY is a lucky gift from medicinal chemists.

Introduction

Diamond and graphite have the same composition but different structures and properties. This phenomenon, polymorphism, is known for many

substances, inorganic and organic, natural and manmade. It is encountered in studies of crystallization, phase transition, materials synthesis, and biomineralization; it is important in the manufac-

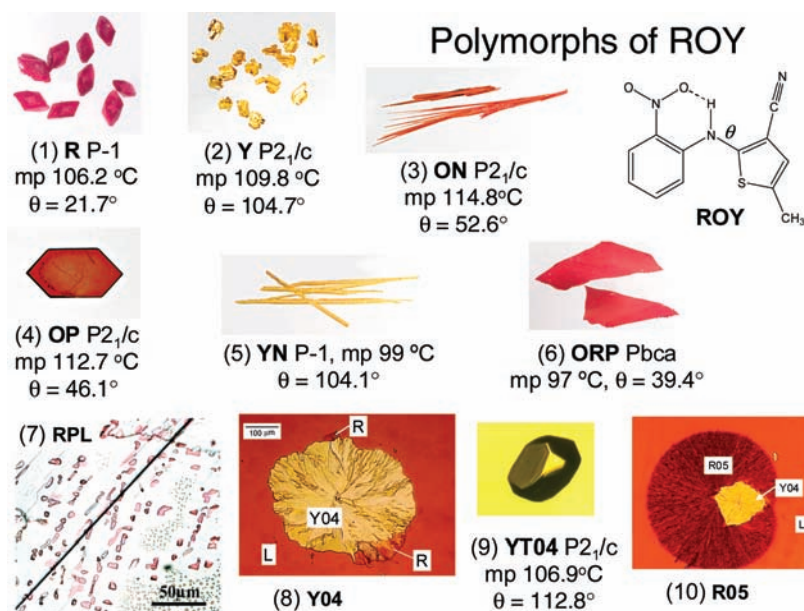


FIGURE 1. Polymorphs of ROY. The number 1–10 indicates the order of discovery. The polymorphs have different colors, melting points, and molecular conformations (most pronounced in the torsional angle θ).

TABLE 1. Crystal Structures and Selected Properties of ROY Polymorphs^a

form	Y	YT04	R	OP	ON	YN	ORP
crystal system	monoclinic	monoclinic	triclinic	monoclinic	monoclinic	triclinic	orthorhombic
space group [No.]	<i>P2₁/n</i> [14]	<i>P2₁/n</i> [14]	<i>P1</i> [2]	<i>P2₁/n</i> [14]	<i>P2₁/c</i> [14]	<i>P1</i> [2]	<i>Pbca</i> [61]
description	yellow prism	yellow prism	red prism	orange plate	orange needle	yellow needle	orange-red plate
<i>a</i> , Å	8.5001	8.2324	7.4918	7.9760	3.9453	4.5918	13.177
<i>b</i> , Å	16.413	11.8173	7.7902	13.319	18.685	11.249	8.0209
<i>c</i> , Å	8.5371	12.3121	11.9110	11.676	16.3948	12.315	22.801
α , deg	90	90	75.494	90	90	71.194	90
β , deg	91.767	102.505	77.806	104.683	93.830	89.852	90
γ , deg	90	90	63.617	90	90	88.174	90
<i>Z</i>	4	4	2	4	4	2	8
<i>D</i> _{calc} , g cm ⁻³	1.447	1.473	1.438	1.435	1.428	1.431	1.429
θ (deg)	104.7	112.8	21.7	46.1	52.6	104.1	39.4
ν _{CN} , cm ⁻¹	2231	2224	2212	2226	2224	2222	2217
mp, °C	109.8	106.9	106.2	112.7	114.8	99	97
ΔH_m , kJ/mol	27.2	26.6	26.0	25.5	25.1	24.2	24.2
<i>H</i> – <i>H</i> _r , kJ/mol ^b	0	0.9	1.4	1.9	2.6	3.0	4.1

^a Empirical formula C₁₂H₉N₃O₂S. MW = 259.29. The structures were determined at 20–23 °C. ^b From fitting melting and eutectic melting data.^{4,6,7}

ture of drugs, explosives, dyes and pigments, and chocolates. Polymorphs are valuable for understanding crystal packing and structure–property relations;¹ for example, they have been used to test the third law of thermodynamics² and the relation between molecular arrangement and chemical reactivity.³

This Account is concerned with the rich polymorphism of an organic substance, 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, also known as ROY for its red, orange, and yellow crystals (Figure 1 and Table 1).^{4–7} ROY is currently the top system for the number of polymorphs of known structures in the Cambridge Structural Database (CSD),⁸ which archives structures of organic and organometallic crystals.⁹ First prepared by medicinal chemists,¹⁰ ROY has been stud-

ied by solid-state chemists. Besides the seven known structures, ROY has three other polymorphs whose structures have not been determined. The latest CSD search that names ROY the most polymorphic⁸ was performed with carefully defined criteria for data quality.¹¹ That search also found 58 substances with three polymorphs, 11 with four, 2 with five, and zero with six.

ROY is not the most polymorphic substance on record. Water, for example, has 10 or more solid phases. The polymorphism of ROY is remarkable, however, in two respects. First, all known polymorphs have been prepared near ambient conditions; many can even crystallize simultaneously from the same liquid. In contrast, the polymorphs of some substances are formed under extremely different conditions. High

pressure is needed to produce all but the ordinary ice; silica (SiO_2) polymorphs are obtained by hydrothermal growth (α -quartz), high-pressure synthesis (coesite and stishovite), phase transformation, and other means. In this property, ROY is similar to other organic substances whose polymorphs can crystallize "concomitantly".¹² Second, the known polymorphs of ROY are sufficiently stable kinetically to be studied under the same conditions; all seven crystal structures of ROY have been determined under ambient conditions. In contrast, the polymorphs of some substances (e.g, water, ammonium nitrate, and *n*-alkanes) exist only in separate regions of temperature and pressure.

The possibility to crystallize many polymorphs from the same liquid makes ROY especially useful for studying the process of crystallization. To this end, ROY has found use in two lines of research. The first pertains to the manner in which crystallization occurs in a liquid that can form many polymorphs, a question important for the industrial control of polymorphism. A common answer to this question is that the first step of crystallization, nucleation, defines the polymorph(s) of the final product.^{12,13} This view does not describe the crystallization of ROY⁷ and other substances because an early nucleating polymorph can nucleate another, faster-growing polymorph and it is the latter that goes on to dominate the crystallization product.

A second line of study to which ROY polymorphs have contributed pertains to an anomalously fast mode of crystal growth in organic glasses.^{14–16} The phenomenon is of interest for understanding the stability of amorphous materials, especially amorphous drugs, against crystallization. The crystal growth in some organic liquids shows a remarkable transition from being diffusion-controlled to "diffusionless" as the liquid is cooled to the glass transition temperature.^{17,18} With ROY, it is possible to study which polymorphs develop this growth mode and which do not, thereby learning the dependence of the phenomenon on crystal structure. The philosophy of using polymorphs to study crystallization follows the tradition of using polymorphs to establish structure–property relations.³ In a similar manner, polymorphs have been used to determine whether the activation barrier of crystal growth is controlled by liquid dynamics or properties of the crystal–liquid interface.¹⁹ Below I will review the structures, properties, and structure–property relations of ROY polymorphs and their role in understanding the process of crystallization. I will also speculate on the possibility of discovering even more polymorphs of ROY.

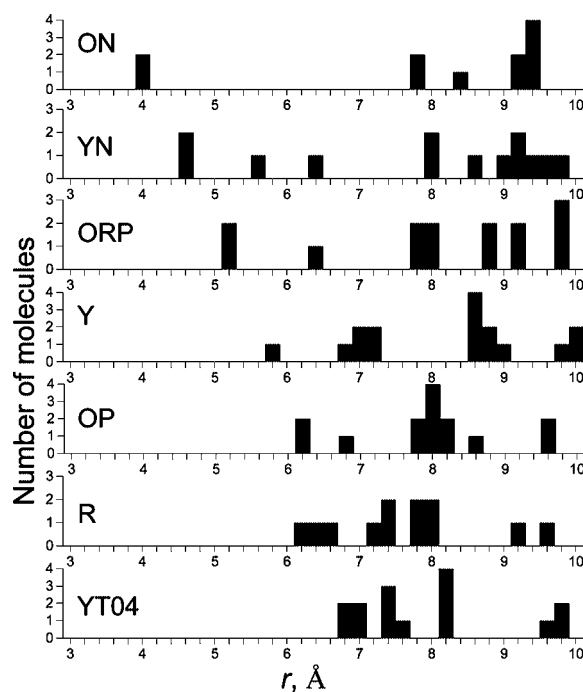


FIGURE 2. Radial distribution functions of molecular centers of mass in ROY polymorphs. By this measure, the molecular environment becomes more anisotropic from bottom to top.

Structures of ROY Polymorphs

ROY is conformationally flexible and a chiral object unless in a planar conformation. Each polymorph of known structure has one crystallographically independent molecule ($Z' = 1$) in centrosymmetric packing and therefore two mirror-related conformations. It is noteworthy that ROY can adopt different conformations in different polymorphs. The largest conformational difference is seen in the torsional angle θ (Figure 1), which ranges from 21 to 104°. Spectroscopic data indicate that ROY exists as many conformers in a liquid, with the "perpendicular" conformer ($\theta \approx 90^\circ$) being slightly favored over the "co-planar" conformer ($\theta \approx 0^\circ$).^{4,20} The process of crystallization therefore converts a wide range of conformers in the liquid to only two mirror-related conformers in each known polymorph.

Figure 2 shows the radial distribution functions of molecular centers of mass in ROY polymorphs. This function is one measure of the molecular environment in each crystal structure. For a molecule in YT04 (bottom histogram), the nearest 12 molecules are approximately equally distant (6.9–8.2 Å) and these distances are comparable to the "diameter" of ROY. In contrast, for a molecule in ON (top histogram), the neighbors are distributed more anisotropically: the two closest are 3.9 Å away and the next is 8.4 Å away (the two molecules at 7.8 Å are actually two molecular layers away). Significant differences in molecular packing exist not only for the poly-

morphs composed of different conformers but also for those composed of similar conformers. Thus, the molecular conformations are similar in ON and OP and in YN, Y, and YT04 (see their θ values in Table 1), but the corresponding radial distribution functions differ significantly.

Besides the distribution of molecular centers of mass, other aspects of molecular packing in ROY polymorphs have been analyzed. With respect to hydrogen bonding, an *intramolecular* hydrogen bond exists between the amino group and the nitro group (Figure 1) in all known polymorphs, thus consuming the best hydrogen-bond donor and making strong *intermolecular* hydrogen bonds improbable. It follows that ROY solids are well described as being bound mainly by van der Waals forces. The energies of intermolecular interactions have been calculated one molecular pair at a time to rank their relative contributions to the cohesive energy of each polymorph.²¹ The molecular environments in different ROY polymorphs have also been analyzed in detail with the aid of Hirshfeld surfaces²² and “crystallization forces”.²³

Properties of ROY Polymorphs and Structure–Property Relations

We now consider a few properties of ROY polymorphs and their relation to crystal structures. The properties considered include crystal colors and spectra, thermodynamic properties, kinetic stability, and crystallization properties.

Crystal Colors. A striking feature of ROY polymorphs is their red, orange, and yellow colors. The different colors result from the polymorphs' different visible absorption spectra and are reasonably well explained by the conformational differences between the polymorphs.²⁰ As the torsional angle θ (Figure 1) approaches zero, a greater degree of π -conjugation exists between the thiophene and phenyl aromatic rings, which should lead to a red shift of the visible absorption spectrum. This trend is observed experimentally and approximately reproduced by computation.²⁰ The isolation of different conformers in crystal polymorphs permits an evaluation of computational models of electronic structures and transitions against experimental data. The newly matured time-dependent density functional theory reproduced the best the observed wavelengths, oscillator strengths, and directions of electronic transition dipole moments, outperforming configuration interaction singles, and even ZINDO, a semiempirical model specially calibrated on electronic spectra.²⁰

Although the conformational differences approximately explain the different colors of ROY polymorphs, a few discrepancies are too large to be discounted. They suggest inadequacies of the present theories, errors from ignoring

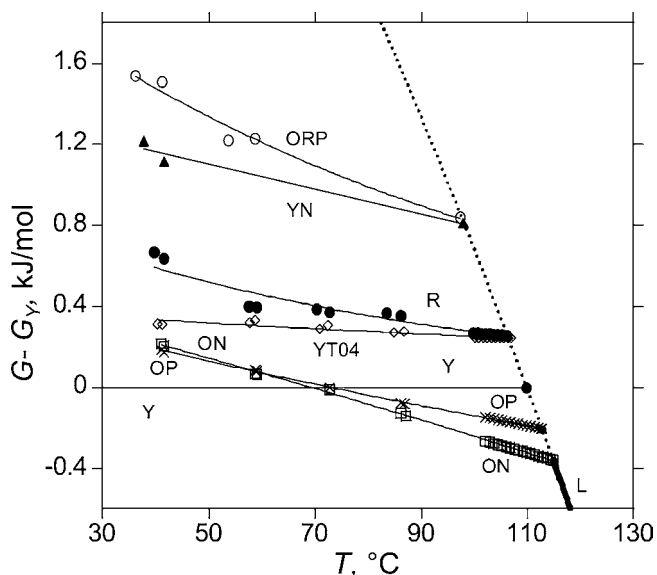


FIGURE 3. Free energies of ROY polymorphs relative to Y. L indicates liquid.

intermolecular interactions, or both. The same holds for other spectral data. For the solid-state NMR spectra,²⁴ theoretical calculation can reproduce many observed features, but significant disagreements exist. For the CN stretch frequency (Table 1), a decrease is expected as θ approaches zero, again because of greater π -conjugation. This prediction broadly agrees with the experimental data, but significant discrepancies exist; for example, polymorphs Y and YN have similar molecular conformations, but their CN stretch frequencies are significantly different.

Thermodynamic Properties. The relative free energies of seven ROY polymorphs have been obtained (Figure 3) using a differential scanning calorimetry method.^{25,26} This method relies on the melting and eutectic melting data of polymorphs to calculate their free-energy differences. In Figure 3, the reference polymorph is Y, the most stable under ambient conditions, and each polymorph line ends at its melting point (intersection with the liquid line, L). A pair of polymorphs can be related monotonically (same order of stability at any temperature) or enantiotropically (stability order changing with temperature). For example, Y is more stable than ON below 70 °C but less stable above 70 °C. These free-energy relations have been confirmed using polymorphic conversions.

The polymorphs for which data exist span a relatively small range of free energy: ca. 1.5 kJ/mol at 40 °C. Their relative enthalpies cover a range of 4 kJ/mol. In reference to the polymorphs, the liquid is much higher in energy: +18 kJ/mol above Y under ambient conditions. The enthalpies of the polymorphs follow the order Y (lowest) < YT04 < R < OP < ON < YN < ORP (highest), which is presumably their stability order

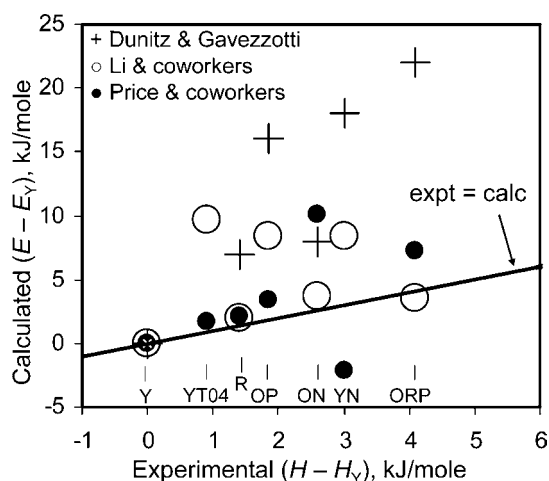


FIGURE 4. Relative energies between ROY polymorphs measured experimentally and calculated with different methods.^{21,23,27}

at 0 K. The thermodynamic properties of ROY polymorphs are typical for organic polymorphs observed under ambient conditions.^{25,28} Thus, what distinguishes ROY is not the unusual properties of its polymorphs but the abundance of them observed within “expected” ranges.

There have been attempts to calculate the energy difference between ROY polymorphs.^{21,23,27} Figure 4 compares their results with experimentally determined energy differences (taken to be the enthalpy differences, a valid approximation at 1 bar). There is no satisfactory agreement between experiment and theory and between the various computational methods. By one study,²¹ polymorph ORP is more energetic than the ROY liquid under ambient conditions. This comparison demonstrates the difficulty of calculating the small energy differences between polymorphs and the importance of experimental data for testing computational models.

Densities and Their Relation to Energies. The ROY polymorphs of known structures (Table 1) span a range of 3% in density at room temperature. There seems no simple explanation for the density differences observed, although high density is apparently correlated with more isotropic packing as measured by the radial distribution function of molecular centers of mass (Figure 2). The denser polymorphs generally have lower enthalpies (Figure 5), with the notable exception of YT04, which is the densest but the second lowest in enthalpy. The density range observed is again typical of organic polymorphs under ambient conditions in the CSD.²⁸

Kinetic Stability. For each set of polymorphs at a given temperature and pressure, only one is stable in the thermodynamic sense. Polymorphic conversions can be so slow, however, that polymorphs can coexist under the same condition. Diamond, less stable than graphite under ambient conditions, persists “forever”. For many organic polymorphs, such kinetic

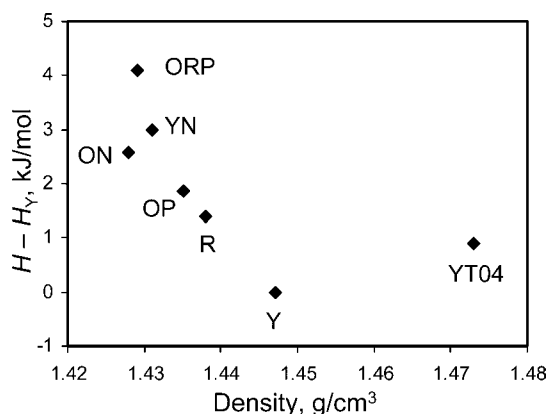


FIGURE 5. Relative enthalpies and densities of ROY polymorphs.

stability exists even near their melting points, allowing the observation of congruent melting (melting without prior phase transition).²⁶ Kinetic stability also allows the observation of several organic polymorphs to crystallize from the same liquid,¹² which requires that polymorphic conversion be slow on the time scale of crystallization.

ROY has many kinetically stable polymorphs. Under ambient conditions, polymorph Y is the most stable thermodynamically, but ON, OP, R, and YT04 can persist for at least many years. The others polymorphs are shorter-lived (YN and ORP for weeks to months; RPL, Y04, and R05 for hours to days), though they are long-lived enough for many studies. For this system of polymorphs, kinetic stability approximately follows thermodynamic stability: higher free-energy polymorphs tend to be shorter-lived. The kinetic stability of ROY polymorphs has enabled the determination of seven crystal structures under ambient conditions (Table 1), the measurement of their congruent melting, and the study of their crystallization from the same liquid (see below).

Crystallization. A supercooled liquid of ROY is thermodynamically allowed to crystallize many polymorphs. Below 100 °C, at least seven polymorphs have lower free energies than the liquid (Figure 3). Which polymorph(s) actually crystallize is a question of practical and fundamental interest. According to Ostwald, the liquid will crystallize first as the least thermodynamically stable polymorph, which then converts to the next least stable, and so on to the most stable.²⁹ Others envision no such thermodynamic control and allow independent crystallization of different polymorphs.¹² Although crystallization consists of nucleation and growth, a common view is that the initial nucleation defines the product polymorph(s).^{12,13}

These views do not describe the crystallization of ROY. Near room temperature, the pure melt of ROY crystallizes several polymorphs spontaneously (YN, Y04, ON, and R05), yielding crystals of different colors.⁷ This observation contradicts

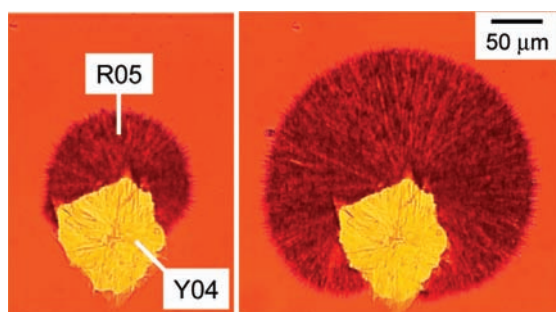


FIGURE 6. Cross-nucleation between two polymorphs of ROY. From liquid ROY at room temperature, Y04 (yellow) nucleates first but grows slowly; R05 (red) nucleates on Y04 and grows rapidly to dominate the product.

Ostwald's prediction. Moreover, the initial nucleation may not define the product polymorph(s). In the process shown in Figure 6, a yellow polymorph (Y04) nucleates first but cannot consume the remaining liquid because a faster-growing polymorph (red, R05) nucleates on it.⁷ Through seeding, more cases of cross-nucleation between polymorphs can be observed, in which the seed polymorph shows slow or no apparent growth and induces the crystallization of another polymorph. This phenomenon has been observed in other systems^{30–34} and in Lennard-Jones liquids by molecular simulation.³⁵ The new polymorph is found to be more or less thermodynamically stable than the initial one but always grow faster or as fast as the initial one. This phenomenon indicates that the initial nucleation may not define the product polymorph, and other important factors are the relative growth rates of polymorphs and cross-nucleation between polymorphs.

The possibility for liquid ROY to crystallize many polymorphs has proven useful for studying a fast mode of crystal growth that is activated as organic liquids are cooled to the glass transition temperature, T_g , and continues deep into the glassy state.^{17,18} Greet and Turnbull were apparently the first to notice the phenomenon in 1967.¹⁷ By comparing the observed crystal growth rates with those calculated on the assumption that crystals cannot grow faster than molecules can diffuse, they found that crystal growth in liquid *o*-terphenyl is accurately described as diffusion-controlled over a wide range of temperature above T_g but is orders of magnitude too fast near and below T_g . This growth mode, named GC for glass-to-crystal, is not anticipated by current theories of crystal growth,³⁶ which generally assume that diffusion defines the kinetic barrier to crystal growth. The activation of the GC mode marks a transition from diffusion-controlled to diffusion-less crystal growth. To our knowledge, this transition has been observed only in organic glass formers, although fast crystal

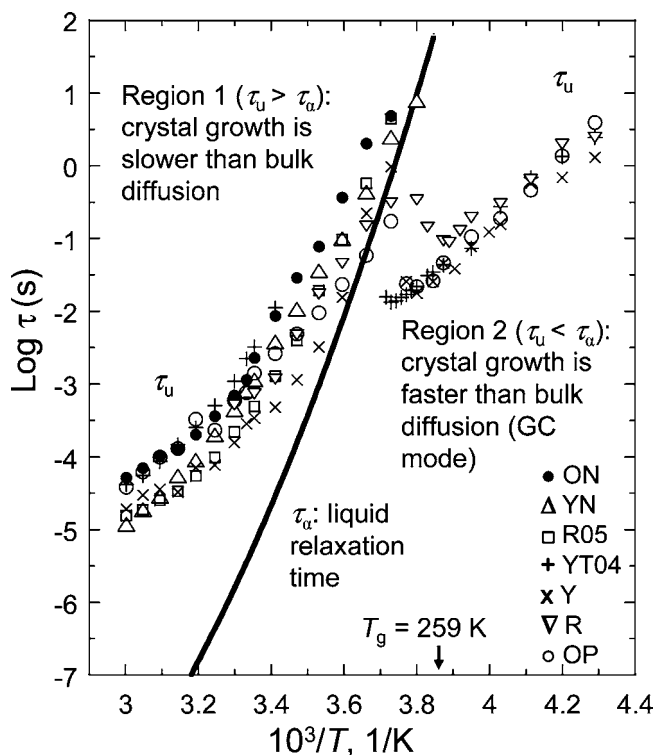


FIGURE 7. Comparison of the time scales of crystal growth and liquid relaxation. τ_u is the time required for the crystal to grow one molecular layer: $\tau_u = a/u$, where a is the molecular diameter and u is the crystal growth rate. τ_α is the liquid's structural relaxation time. For some polymorphs (ON, YN, and R05), τ_u is substantially longer than τ_α and their growth can be described as under the control of bulk diffusion. For the other polymorphs, a new mode of crystal growth (GC mode) is activated near the glass transition temperature and characterized by τ_u being substantially shorter than τ_α . The GC mode is too fast to be controlled by bulk diffusion.

growth is known in inorganic glasses (e.g., amorphous silicon and metallic glasses). The GC mode is important for understanding the stability of amorphous materials against crystallization and especially the stability of amorphous drugs, which are often stored and used near T_g .

ROY polymorphs have been used to study the effect of crystal structure on the existence of GC growth.^{14–16} Of the seven polymorphs whose growth can be studied near T_g , three (ON, YN, and R05) do not show GC growth, while four others (YT04, Y, R, and OP) do. As a result, the growth rates of the two groups of polymorphs differ by 10^3 – 10^4 times (Figure 7). The structures of the polymorphs showing GC growth are more isotropic, as measured by the radial distribution function of molecular centers-of-mass (Figure 2), and perhaps more “liquid-like” than those not showing GC growth. We hypothesize that given sufficient similarity between crystal and liquid structures, GC growth can occur via molecular motions native

to the glassy state, without involving substantial diffusion in the bulk material.

Discovery of ROY Polymorphs

Medicinal chemists at Eli Lilly first synthesized ROY as a reagent to prepare the schizophrenia drug olanzapine.¹⁰ ROY's polymorphism was studied not so much for its pharmaceutical relevance as for the many polymorphs of different colors. In the industrial process, ROY is crystallized from solutions (e.g., DMSO and ethyl acetate). Early batches of ROY contained red prismatic crystals (polymorph R). The first signs of polymorphism were crystals of different colors formed in the supercooled melt and occasional yellow crystals in crystallization products and in materials aged at elevated temperatures. For ROY, recognizing polymorphism was made easier by the different colors and the concomitant crystallization of polymorphs.

Solution crystallization yielded the first six polymorphs:⁴ R, Y, ON, OP, YN, and ORP. A seventh, RPL, was obtained by vapor deposition on single-crystal substrates.⁵ The next three were found during the study of pure-melt crystallization:^{6,7} Y04, YT04, and R05. Among these, YT04 is noteworthy because it is the densest under ambient conditions and the second lowest in energy. Such a polymorph might be expected to be among the first discovered by solution crystallization. But it was not. It was discovered by the transformation of a metastable polymorph (Y04) crystallized from the melt. The seeds thus obtained were then used to grow single crystals from solution.

ROY has also been crystallized from liquids in contact with polymer surfaces³⁷ or gold islands³⁸ and from liquids held in capillary tubes³⁹ or in porous solids.⁴⁰ These studies showed that the polymorphic outcome can be altered by changing crystallization conditions but reported no new polymorphs.

To date all but one polymorph of ROY have been discovered by crystallization from melt or solutions near ambient conditions. This method of discovering polymorphs is common for organic substances (e.g., pharmaceuticals). By this test, ROY is remarkably polymorphic. There are, however, other methods for discovering polymorphs that have not been applied to ROY, a few of which will be discussed below.

Can Other Polymorphs of ROY Be Found?

One argument for the possibility to find more polymorphs of ROY is that the known polymorphs cover a relatively small range of energy: 4 kJ/mol for the seven for which data exist (Table 1). On average, these polymorphs are 16 kJ/mol below the liquid in energy under ambient conditions. If the density

of crystalline states remains the same (seven polymorphs per 4 kJ/mol) as the crystal energy rises, there should be dozens more polymorphs before the crystal energy reaches the liquid energy. One could make the same argument in terms of free energy: the known ROY polymorphs are within ca. 1.5 kJ/mol in free energy at 40 °C, whereas the liquid lies ca. 5 kJ/mol higher.

There seems no compelling argument for a sharp decrease of the density of crystalline states with increasing energy. No such decrease has been observed in computational studies of crystal energy landscapes of organic molecules.⁴¹ In making this analysis, we have treated the liquid (or glassy) state as a natural upper limit for crystal energies (a crystal more energetic would melt with release of heat). This need not be the case, however, if we allow superheated polymorphs. Stishovite, a silica polymorph synthesized at high pressure and quenched to the ambient pressure, has higher energy and free energy than the silica glass under ambient conditions.^{42,43}

The relatively low energies of the known ROY polymorphs could be a result of their method of preparation. The polymorphs for which enthalpic data exist can crystallize from low-viscosity solvents and persist under ambient conditions. Their structures were solved using solution-grown, high-quality single crystals, implying that they are stable against polymorphic conversion even in contact with solutions. There could be other polymorphs that are unobservable under such conditions. The chemical potential of a pure liquid generally decreases upon dilution with a solvent. The solution, as a result, may be under-saturated relative to some polymorphs. A low-viscosity solvent, meanwhile, may accelerate polymorphic conversions, making some polymorphs too short-lived to be isolated. It is also possible that undiscovered polymorphs are too slow to crystallize, though this effect need not handicap only high-energy polymorphs.

The above analysis suggests that crystallization from pure melt could more effectively trap less stable polymorphs. For ROY, melt crystallization has indeed yielded polymorphs (Y04 and R05) not observed by solution crystallization. These polymorphs are shorter-lived and probably more energetic than those crystallized from solutions. In similar observations, melt crystallization of indomethacin yields a less stable polymorph (δ) than solution crystallization (α and γ);¹⁹ melt crystallization of triglycerides can yield the least stable polymorph known (α), whereas the most stable polymorph β is obtained by solution crystallization or "tempering" less stable polymorphs.⁴⁴

Vapor deposition can produce solids not readily obtained by other routes.⁴⁵ This method has yielded one known poly-

morph of ROY (RPL),⁵ but otherwise not been extensively explored. While liquid crystallization places the liquid energy as the upper bound for crystal energy, vapor deposition need not impose such a limit. There has been a long tradition of using pressure to discover polymorphs.^{46,47} Many high-pressure polymorphs do not survive decompression, but some do (e.g., diamond). It would be interesting to determine whether pressure yields new polymorphs of ROY.

Another route to solid structures inaccessible by liquid crystallization is removing the volatiles in another solid. Porous silica prepared by removing water and organic components from solution-precipitated “water glass” have different structures and energies from the high-density polymorphs.⁴³ Gentle dehydration of trehalose dihydrate yields an anhydrous polymorph that has substantially higher energy than the melt-crystallized polymorph.⁴⁸ For some solvated organic crystals, desolvation does not substantially alter the crystal lattice, yielding a porous, high-energy, and hygroscopic solid.⁴⁹ This method has so far been irrelevant for ROY because no solvated crystals have been observed.

What could undiscovered polymorphs of ROY be like? This question is probably best answered with a computational search of ROY's polymorphic space, perhaps with models calibrated on the known structures. The known crystal structures of ROY are free of disorder and centrosymmetric. It would be of interest to learn whether ROY could be crystallized in disordered structures (e.g., rotator phases) and chiral structures.

Is ROY Extraordinary? If so, Why?

ROY has no more polymorphs on record than water or silica; ROY polymorphs have structures and properties within the norm for molecular solids; the color and conformational polymorphism of ROY, though noteworthy, is known for other substances. What makes ROY extraordinary, however, is the abundance of polymorphs that are kinetically stable and can crystallize simultaneously from the same liquid. In these properties, ROY differs from many richly polymorphic substances, whose polymorphs exist only in separate regions of temperature and pressure and are prepared under very different conditions. Another way to appreciate ROY is to note that if the molecule is altered, fewer polymorphs are observed under comparable conditions.^{50,51}

It remains poorly understood what makes ROY so polymorphic. One indicator of this insufficient understanding is the fact that despite many studies, it is still impossible to predict the next molecule that is equally or more polymorphic. To explore the origin of its polymorphism, it is natural to think about whether ROY has an unusually high number of crystal struc-

tures per unit energy or free energy, a question perhaps answerable computationally. Attention has been paid to whether lower lattice energy is achieved at the cost of conformational strains and whether the increase of crystal energy is balanced by the decrease of crystal entropy so that the net change of free energy is small.^{4,6} It seems reasonable to believe that ROY's conformational flexibility contributes to its rich polymorphism. The intermolecular interactions have been scrutinized in the known ROY polymorphs.^{21–23} While revealing rich details of local interactions, these analyses have provided limited insight on what makes ROY so polymorphic. Chemical approaches have also been used to explore the origin of ROY's polymorphism: the ROY molecule was modified to see whether the resulting substance is more or less polymorphic.^{50,51}

While it is still unclear whether there is a structural basis for ROY's polymorphism, it is clear that kinetic factors must enter the inquiry. It is necessary to understand how different structures can be comparably stable kinetically and can crystallize at comparable rates to be observed. This is a problem of a different nature, requiring an understanding of the nucleation, growth, and kinetic stability of different polymorphs.

Bridgeman believes polymorphism is more prevalent in organic substances than in inorganic substances.⁴⁶ He bases this conclusion on the greater number of polymorphic transitions observed if organic substances are subjected to comparable changes of temperature and pressure. He attributes this difference to the lower melting points of organic substances: a search for polymorphs over the same temperature–pressure range would cover a greater portion of the stability field of organic solids than inorganic solids. Consistent with his observation is the general experience that new polymorphs are often found upon recrystallizing organic substances (e.g., pharmaceuticals) near ambient conditions and that it is not uncommon for several organic polymorphs to crystallize concomitantly from the same liquid.¹² In this context, ROY is perhaps an extreme example of organic polymorphism.

Conclusions

ROY is currently the top system in the Cambridge Structural Database for the number of polymorphs of known structures. The kinetic stability of ROY polymorphs allows many to be studied under the same conditions. Because thermodynamic properties are known for many polymorphs, ROY is an ideal system for testing computational models. The possibility to crystallize many polymorphs from the same liquid makes ROY especially valuable for studying the process of crystallization. This way of using polymorphs to study structure–property

relations follows a well-established tradition in solid-state chemistry. Studies of ROY have revealed a new mechanism of crystallization in polymorphic systems, cross-nucleation between polymorphs, which invalidates the view that the initial nucleation defines the final polymorph of crystallization. Studies of ROY have shown that the activation of a fast mode of crystal growth in organic glasses favors crystal structures that are more isotropic and perhaps more liquid like.

It seems possible to discover even more polymorphs of ROY. This speculation is based on the fact that the known polymorphs have relatively low energies and are obtained by methods (melt and solution crystallization) that favor kinetically stable polymorphs. There could be more polymorphs that are more energetic and shorter-lived but nonetheless obtainable under other conditions.

The origin of ROY's polymorphism remains to be understood and is probably a combined result of favorable thermodynamics and kinetics. Not only must there be many polymorphs of similar energies or free energies, the polymorphs must be kinetically stable and able to crystallize at comparable rates to be observed. The complexity of this problem is well captured by the fact that despite many studies, it is still impossible to predict the next molecule that is equally or more polymorphic. ROY is a lucky gift from medicinal chemists.

I thank the colleagues who have contributed to the work described here: Stephen R. Byrn, Gregory A. Stephenson, Michael D. Ward, Christine Schertz, Shuang Chen, Ye Sun, Hanmi Xi, Mark D. Ediger, and Ranko Richert. While writing this manuscript, I enjoyed the discussions with Joel Bernstein, Roger J. Davey, Sarah L. Price, and Tonglei Li. This work is supported in part by NSF (Grants DMR-0804786 and DMR-0907031) and the American Chemical Society Petroleum Research Funds (Grant 43809-AC10).

BIOGRAPHICAL INFORMATION

Lian Yu is a Professor of Pharmaceutical Sciences and Chemistry at the University of Wisconsin—Madison. He received a B.S. degree in chemistry from Peking University, China, and a Ph.D. degree in physical chemistry from The Ohio State University under the direction of Terry A. Miller. Before his current position, he worked for Eli Lilly and Company. His laboratory studies the crystallization, polymorphism, and the amorphous state of molecular solids.

FOOTNOTES

*Tel.: (608)263-2263. E-mail: lyu@pharmacy.wisc.edu.

REFERENCES

- Bernstein, J. *Polymorphism in Molecular Crystals*; Oxford University Press: New York, 2002.
- Westrum, E. F.; McCullough, J. P. Thermodynamics of Crystals. In *Physical Chemistry of the Organic Solid State*; Fox, D., Labes, M. M., Weissberger, A., Eds.; Interscience Publishers: New York, 1963.
- Schmidt, G. M. J. Photodimerization in the Solid State. *Pure Appl. Chem.* **1971**, *27*, 647–678.
- Yu, L.; Stephenson, G. A.; Mitchell, C. A.; Bunnell, C. A.; Snorek, S. V.; Bowyer, J. J.; Borchardt, T. B.; Stowell, J. G.; Byrn, S. R. Thermochemistry and Conformational Polymorphism of a Hexamorphic Crystal System. *J. Am. Chem. Soc.* **2000**, *122*, 585–591.
- Mitchell, C. A.; Yu, L.; Ward, M. D. Selective Nucleation and Discovery of Organic Polymorphs through Epitaxy with Single Crystal Substrates. *J. Am. Chem. Soc.* **2001**, *123*, 10830–10839.
- Chen, S.; Guzei, I. A.; Yu, L. New Polymorphs of ROY and New Record for Coexisting Polymorphs of Solved Structures. *J. Am. Chem. Soc.* **2005**, *127*, 9881–9885.
- Chen, S.; Xi, H.; Yu, L. Cross Nucleation between ROY Polymorphs. *J. Am. Chem. Soc.* **2005**, *127*, 17439–17444.
- Galek, P. T. A.; Fabian, L.; Allen, F. H. Persistent Hydrogen Bonding in Polymorphic Crystal Structures. *Acta Crystallogr., Sect. B: Struct. Sci.* **2009**, *B65*, 68–85.
- Allen, F. H. The Cambridge Structural Database: A Quarter of a Million Crystal Structures and Rising. *Acta Crystallogr.* **2002**, *B58*, 380–388.
- Lilly Industries Limited, Kingsclere Road, Basingstoke Hants RG21 2XA (GB), European Patent 0 454 436 A1, Date of publication October 30, 1991, Bulletin 91/44.
- Van de Streek, J. Searching the Cambridge Structural Database for the 'Best' Representative of Each Unique Polymorph. *Acta Crystallogr.* **2006**, *B62*, 567–579.
- Bernstein, J.; Davey, R. J.; Henck, J.-O. Concomitant Polymorphs. *Angew. Chem., Int. Ed.* **1999**, *38*, 3441–3461.
- Erdemir, D.; Lee, A. Y.; Myerson, A. S. Nucleation of Crystals from Solution: Classical and Two-Step Models. *Acc. Chem. Res.* **2009**, *42*, 621–629.
- Sun, Y.; Xi, H.; Chen, S.; Ediger, M. D.; Yu, L. Crystallization near Glass Transition: Transition from Diffusion-Controlled to Diffusionless Crystal Growth Studied with Seven Polymorphs. *J. Phys. Chem. B* **2008**, *112*, 5594–5601.
- Sun, Y.; Xi, H.; Ediger, M. D.; Yu, L. Diffusionless Crystal Growth from Glass Has Precursor in Equilibrium Liquid. *J. Phys. Chem. B* **2008**, *112*, 661–664.
- Sun, Y.; Xi, H.; Ediger, M. D.; Richert, R.; Yu, L. Diffusion-Controlled and "Diffusionless" Crystal Growth near the Glass Transition Temperature: Relation between Liquid Dynamics and Growth Kinetics of Seven ROY Polymorphs. *J. Chem. Phys.* **2009**, *131*, 074506.
- Greet, R. J.; Turnbull, D. J. Glass Transition in *o*-Terphenyl. *J. Chem. Phys.* **1967**, *46*, 1243–1251.
- Hikima, T.; Adachi, Y.; Hanaya, M.; Oguni, M. Determination of Potentially Homogeneous Nucleation Based Crystallization in *o*-Terphenyl and an Interpretation of the Nucleation-Enhancement Mechanism. *Phys. Rev. B* **1995**, *52*, 3900–3908.
- Wu, T.; Yu, L. Origin of Enhanced Crystal Growth Kinetics near T_g Probed with Indomethacin Polymorphs. *J. Phys. Chem. B* **2006**, *110*, 15694–15699.
- Yu, L. Red, Orange, and Yellow Polymorphs of a Conformationally Flexible Molecule: Single-Crystal Spectroscopy, Optical Crystallography, and Computational Chemistry. *J. Phys. Chem. A* **2002**, *106*, 544–550.
- Dunitz, J. D.; Gavezzotti, A. Toward a Quantitative Description of Crystal Packing in Terms of Molecular Pairs: Application to the Hexamorphic Crystal System, 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile. *Cryst. Growth Des.* **2005**, *5*, 2180–2189.
- McKinnon, J. J.; Fabbiani, F. P. A.; Spackman, M. A. Comparison of Polymorphic Molecular Crystal Structures through Hirshfeld Surface Analysis. *Cryst. Growth Des.* **2007**, *7*, 755–769.
- Li, T.; Ayers, P. W.; Liu, S.; Swadley, M. J.; Aubrey-Medendorp, C. Crystallization Force—A Density Functional Theory Concept for Revealing Intermolecular Interactions and Molecular Packing in Organic Crystals. *Chem.—Eur. J.* **2009**, *15*, 361–371.
- Smith, J. R.; Xu, W.; Raftery, D. Analysis of Conformational Polymorphism in Pharmaceutical Solids Using Solid-State NMR and Electronic Structure Calculations. *J. Phys. Chem. B* **2006**, *110*, 7766–7776.
- Yu, L. Inferring Thermodynamic Stability Relationship of Polymorphs from Melting Data. *J. Pharm. Sci.* **1995**, *84*, 966.
- Yu, L.; Huang, J.; Jones, K. J. Measuring Free-Energy Difference between Crystal Polymorphs through Eutectic Melting. *J. Phys. Chem. B* **2005**, *109*, 19915–19922.
- Kazantsev, A. V.; Karamertzanis, P. G.; Price, S. L. Private communication. This method calculates intramolecular energies quantum-mechanically and intermolecular energies with a distributed multipole model.
- Gavezzotti, A.; Fillippini, G. Polymorphic Forms of Organic Crystals at Room Conditions: Thermodynamic and Structural Implications. *J. Am. Chem. Soc.* **1995**, *117*, 12299–12305.

- 29 Ostwald, W. Z. *Phys. Chem.* **1879**, *22*, 289–330.
- 30 Yu, L. Nucleation of One Polymorph by Another. *J. Am. Chem. Soc.* **2003**, *125*, 6380–6381.
- 31 Tao, J.; Yu, L. Kinetics of Cross-Nucleation between Polymorphs. *J. Phys. Chem. B* **2006**, *110*, 7098–7101.
- 32 Tao, J.; Yu, L. Cross-Nucleation between D-Mannitol Polymorphs in Seeded Crystallization. *Cryst. Growth Des.* **2007**, *7*, 2410–2414.
- 33 Huang, J.; Chen, S.; Guzei, I. A.; Yu, L. Discovery of a Solid Solution of Enantiomers in a Racemate-Forming System by Seeding. *J. Am. Chem. Soc.* **2006**, *128*, 11985–11992.
- 34 Yu, L. Survival of the Fittest Polymorph: How Fast Nucleator Can Lose to Fast Grower. *CrystEngComm* **2007**, *9*, 847–851.
- 35 Desgranges, C.; Delhommelle, J. Molecular Mechanism for the Cross-Nucleation between Polymorphs. *J. Am. Chem. Soc.* **2006**, *128*, 10368–10369.
- 36 Uhlmann, D. R.; Uhlmann, E. V. In *Nucleation and Crystallization in Liquids and Glasses*; Weinberg, M. C., Ed.; The American Ceramic Society: Westerville, OH, 1993.
- 37 Price, C. P.; Grzesiak, A. L.; Matzger, A. J. Crystalline Polymorph Selection and Discovery with Polymer Heteronuclei. *J. Am. Chem. Soc.* **2005**, *127*, 5512–5517.
- 38 Singh, A.; Lee, I. S.; Myerson, A. S. Concomitant Crystallization of ROY on Patterned Substrates: Using a High Throughput Method To Improve the Chances of Crystallization of Different Polymorphs. *Cryst. Growth Des.* **2009**, *9*, 1182–1185.
- 39 Hilden, J. L.; Reyes, C. E.; Kelm, M. J.; Tan, J. S.; Stowell, J. G.; Morris, K. R. Capillary Precipitation of a Highly Polymorphic Organic Compound. *Cryst. Growth Des.* **2003**, *3*, 921–926.
- 40 Ha, J.-M.; Wolf, J. H.; Hillmyer, M. A.; Ward, M. D. Polymorph Selectivity under Nanoscopic Confinement. *J. Am. Chem. Soc.* **2004**, *126*, 3382–3383.
- 41 Price, S. L. From Crystal Structure Prediction to Polymorph Prediction: Interpreting the Crystal Energy Landscape. *Phys. Chem. Chem. Phys.* **2008**, *10*, 1996–2009.
- 42 Richet, P. Superheating, Melting and Vitrification through Decompression of High-Pressure Minerals. *Nature* **1988**, *331*, 56–58.
- 43 Navrotsky, A. Thermochemistry of Crystalline and Amorphous Silica. *Rev. Mineral.* **1994**, *29* (SILICA), 309–329.
- 44 Garti, N.; Sato, K., Eds. *Crystallization and Polymorphism of Fats and Fatty Acids*; Marcel Dekker: New York, 1988.
- 45 Swallen, S.; Kearns, K.; Mapes, M.; McMahon, R.; Kim, S.; Ediger, M.; Yu, L.; Wu, T.; Satija, S. Extraordinarily Stable Glassy Materials Prepared by Vapor Deposition. *Science* **2007**, *315*, 353–356.
- 46 Bridgman, P. W. Recent Work in the Field of High Pressures. *Rev. Mod. Phys.* **1946**, *18*, 1–93.
- 47 Fabbiani, F. P. A.; Allan, D. R.; Parsons, S.; Pulham, C. R. Exploration of the High-Pressure Behaviour of Polycyclic Aromatic Hydrocarbons: Naphthalene, Phenanthrene and Pyrene. *Acta Crystallogr., Sect. B: Struct. Sci.* **2006**, *B62*, 826–842.
- 48 Willart, J. F.; Hedoux, A.; Guinet, Y.; Danede, F.; Paccou, L.; Capet, F.; Descamps, M. Metastability Release of the Form a of Trehalose by Isothermal Solid State Vitrification. *J. Phys. Chem. B* **2006**, *110*, 11040–11043.
- 49 Stephenson, G. A.; Groleau, E. G.; Kleemann, R. L.; Xu, W.; Rigsbee, D. R. Formation of Isomorphic Desolvates: Creating a Molecular Vacuum. *J. Pharm. Sci.* **1998**, *87*, 536–542.
- 50 He, X.; Griesser, U. J.; Stowell, J. G.; Borchardt, T. B.; Byrn, S. R. Conformational Color Polymorphism and Control of Crystallization of 5-Methyl-2-[[4-methyl-2-nitrophenyl]amino]-3-thiophenecarbonitrile. *J. Pharm. Sci.* **2001**, *90*, 371–388.
- 51 Lutker, K. M.; Tolstyka, Z. P.; Matzger, A. J. Investigation of a Privileged Polymorphic Motif: A Dimeric ROY Derivative. *Cryst. Growth Des.* **2008**, *8*, 136–139.