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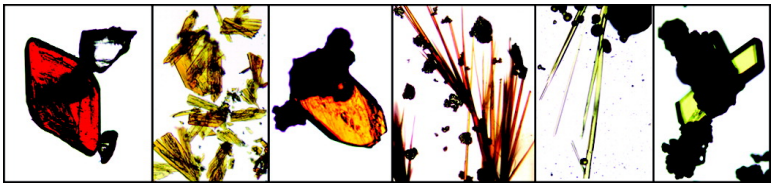

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Crystalline Polymorph Selection and Discovery with Polymer Heteronuclei

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Abstract: The discovery and selective production of crystalline polymorphs, an outstanding problem in solid-state chemistry, is of great importance industrially in, for example, the manufacture of pharmaceuticals and pigments. Despite considerable efforts, no reliable method exists to produce all of the stable polymorphs of a given compound. Herein, we report methodology to control the phenomenon of crystal polymorphism through the use of diverse libraries of polymer heteronuclei including both commercially available polymers and combinatorially synthesized cross-linked polymers. This new approach for exploring polymorph space offers the advantage of high throughput crystallization to discover multiple polymorphs combined with the ability to selectively produce a given form from a single solvent and temperature condition by simply varying the nature of the polymer substrate. This technique is successfully demonstrated on the pharmaceuticals acetaminophen, sulfamethoxazole, and carbamazepine and on the pharmaceutical intermediate 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY). High throughput screening, accomplished by optical microscopy and Raman spectroscopy, identified the selective production of the two stable polymorphs of acetaminophen and all six stable forms of ROY. Furthermore, one new form of carbamazepine and two new forms of sulfamethoxazole were discovered; in these cases, single crystals were obtained enabling the structural characterization of two new tetramorphic systems.

Introduction

Despite the profound importance of controlling the crystalline form of compounds for applications from materials science to drug delivery, there exists no general method for producing all of the energetically reasonable polymorphs of a given compound. In fact, there is no guarantee that the modification with the lowest free energy has ever been obtained. This creates a troubling situation particularly for pharmaceutical researchers trying to employ a given solid form for studies such as bioavailability and dosage formulation[1] and a point of legal exposure for companies whose intellectual property can be threatened by the unexpected discovery of new polymorphs of a drug substance.[2] Therefore, much effort has been expended on creating tools for controlling crystallization with varying degrees of success.

Current approaches for discovery and selection of polymorphic forms of a compound include crystallization with tailor-made soluble additives,[3,4] epitaxial growth,[5,6] laser induced nucleation,[7] crystallization in capillaries,[8,9] confinement within porous materials,[10] and more traditional methods, such as varying solvent, temperature, and extent of supersaturation. Most high throughput polymorph generation is limited to combinatorially changing solvent, temperature, and supersaturation conditions.[11] Such approaches do not explicitly address the vital role of nucleation despite the fact that this is the decisive step in controlling the phenomenon of polymorphism. Moreover, heterogeneous nucleation, the process by which nucleation occurs due to foreign particles or surfaces that are not chemically identical to the nucleated material, is generally believed to be responsible for the majority of crystallizations conducted on the laboratory scale.[12]

We recently introduced the method of using polymers as heteronuclei for the discovery and selection of organic polymorphs as demonstrated for carbamazepine and acetaminophen (ACM) (Figure 1).[13] A fourth polymorph of the anticonvulsant carbamazepine, a pharmaceutical whose polymorphism has been

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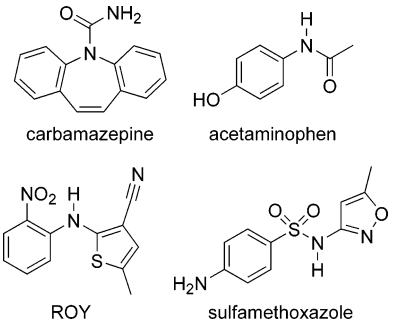

Figure 1. Chemical structures of the polymorphic compounds studied.

studied for over 30 years, was discovered.[14,15] Polymer heteronucleation was also successful in achieving selective production between two polymorphs of ACM from aqueous solution by varying exclusively the identity of the polymer employed.[13] Here, we discuss the application of the technique to 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY), the organic compound with the largest number of structurally characterized polymorphs,[16,17] and the widely prescribed antibiotic sulfamethoxazole (SMA) in addition to conducting expanded investigations on ACM (Figure 1).

During the course of studies employing a diverse library of commercial polymers (hereafter library A, see Supporting Information), solvent compatibility was revealed to be an important issue because several of the polymers are at least partially soluble in common solvents. This raises the possibility that polymer in solution is modifying the morphology,[18] and perhaps polymorph,[19,20] of a growing crystal. Because crystal morphology is the most rapid and convenient initial screen for new polymorph generation, soluble polymers could complicate identifying polymorphs during screening by optical microscopy.[21] In the present study, this limitation is addressed by combinatorial synthesis of highly cross-linked polymers. This approach offers an additional element of diversity during crystallization without sacrificing the ability to perform high throughput measurements by Raman spectroscopy or powder X-ray diffraction, two of the most widely employed high throughput screening techniques.

Results and Discussion

To produce polymer libraries that were broadly solvent compatible and with systematically varied composition for use as heteronuclei for polymorph selection and discovery, we chose combinatorial synthesis of cross-linked terpolymers in which one component is the cross-linker. This approach offers a means to create libraries of insoluble polymers with a defined set of functionality that, although clearly possessing a decreased diversity of functionality as compared to polymer library A employed earlier, affords a higher potential for correlating polymer-polymorph selectivity due to the greater control over polymer composition. Furthermore, highly cross-linked polymers lack crystallinity,[22,23] and therefore the role of nucleation by an epitaxial mechanism is minimized.[24,25] These libraries combined with library A allow for an even more diverse set of polymers to screen the crystallization of a given compound against. Binary mixtures, derived combinatorially from a stock of 16 monomers (Figure 2), were polymerized with the cross-linker divinylbenzene (DVB) in the 96 wells of a polypropylene micro titer plate. This provided three cross-linked polymer libraries (libraries B, C, and D) composed of 280 unique polymers that were employed as heteronuclei in crystallizations with the following compositions: library B contained methyl methacrylate (MMA), *tert*-butyl methacrylate (*t*-BuMA), *n*-butyl methacrylate (*n*-BuMA), benzyl methacrylate (BzMA), 2-ethoxyethyl methacrylate (EEMA), and styrene (STY) with DVB; library C contained methacrylonitrile (MAN), *N*,*N*-dimethylmethacrylamide (DMMAA), *N*-methacryloylmorpholine (MAM), 2-dimethylaminoethyl methacrylate (DMAEMA), 2-vinylpyridine (2VP), and 4-vinylpyridine (4VP) with DVB; library D contained methacrylic acid (MAA), methyl methacrylate (MMA), 2-hydroxyethyl methacrylate (HEMA), ethylene glycol methacrylate phosphate (EGMAP), styrene (STY), and 4-acetoxystyrene (AOS) with DVB. In contrast to library A, where the polymers are typically powders or beads, the surfaces of the polymers in libraries B−D are relatively smooth facilitating high throughput optical, Raman, and X-ray diffraction screening in situ because the amorphous polymers are easily distinguished from the crystalline products. In this study, we utilize morphology as a primary screen and Raman microscopy as a secondary screen.

Acetaminophen. Acetaminophen (ACM) possesses two well-characterized polymorphs, and properties of these monoclinic and orthorhombic forms have been studied extensively.[11,26−34] The less thermodynamically stable orthorhombic polymorph,[32] the exclusive production of which from solution has remained elusive[31] since its initial discovery,[26] was shown to have better physical properties in terms of solubility[28] and compressibility[29] when compared to the pharmaceutically distributed monoclinic form. Therefore, the selective production of orthorhombic ACM has been the subject of numerous investigations aimed at elucidating the properties of this form and exploring its commercial viability.[11,26,28−33] It was found that when crystal-

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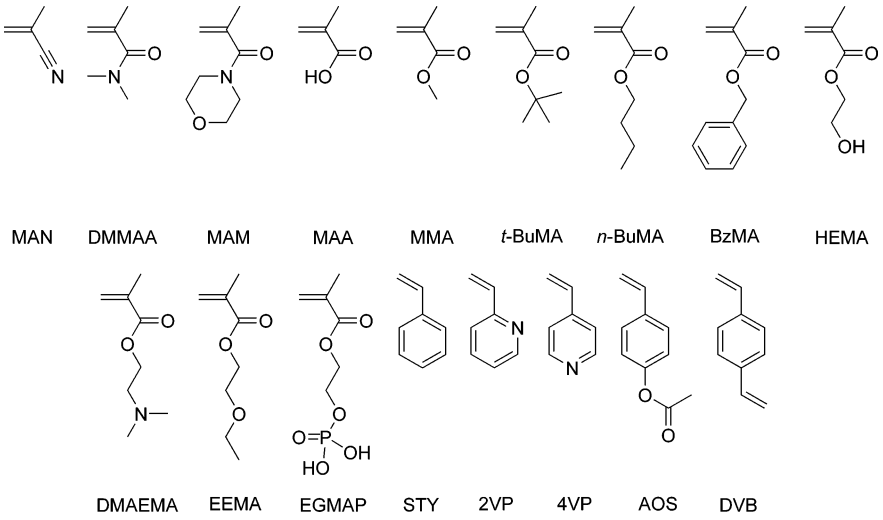

Figure 2. Monomers used in combinatorial cross-linked polymer libraries.

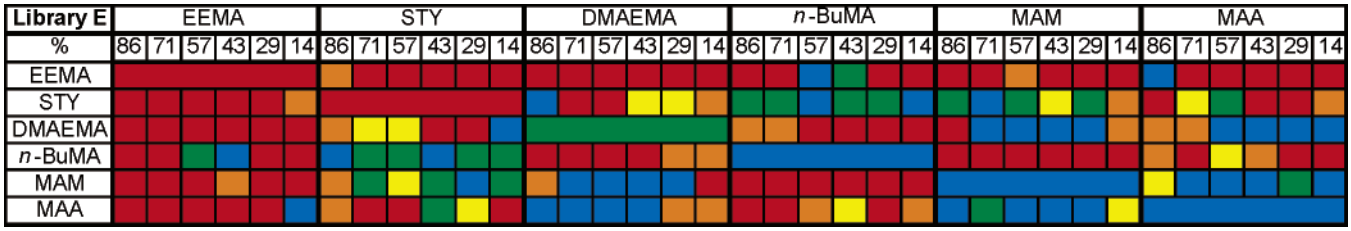

Figure 3. The occurrence rate of acetaminophen polymorphs grown from polymer library E based on a composite of three trails. Red = 100% orthorhombic, orange = 66−75% orthorhombic, yellow = 40−60% orthorhombic (or monoclinic), green = 66−75% monoclinic, blue = 100% monoclinic. Percentages do not reflect the amount of DVB used in each polymer (see Experimental Section), and the large rectangles indicate when a monomer is copolymerized with DVB alone.

lized by cooling and subsequent room temperature-evaporation of aqueous ACM solutions in the presence of library A that kinetic access to the orthorhombic form of ACM was gained; this method is unique in providing this polymorph from aqueous solution. Moreover, either the monoclinic or the orthorhombic polymorphs of ACM can be selectively crystallized depending on which polymer is employed as the heteronucleus.[13]

Although correlations between the types of polymers that selectively produced a given polymorph were readily apparent in the initial studies, drawing conclusions about the properties of those polymers that led to the outcome was complicated by the possibility that both polymer functionality and crystallinity were playing a role in, for example, the selective crystallization of orthorhombic acetaminophen. To resolve this ambiguity, crystallization of ACM was performed in the presence of cross-linked polymer libraries B−D, which, although less structurally and chemically diverse, provide an excellent opportunity to probe the effect of systematically varied substrate compositions on ACM crystallization. It was found that polymers in library B, which are derived from monomers with relatively nonpolar side chains, led to the production of the orthorhombic polymorph in approximately 75% of the crystallizations based on results from three separate trials (see Supporting Information). However, libraries C and D, both of which were produced from monomers with significantly more polar side chains, led to nearly equal quantities of both ACM polymorphs. The effect of monomer functionality on the selective polymorph production of ACM was further explored by creating a focused combinatorial library from six monomers that when copolymerized with DVB alone yielded a single ACM polymorph. Library E was constructed from binary mixtures of the monoclinic-selecting monomers *n*-BuMA, MMA, DMAEMA, and MAM and the orthorhombic-selecting monomers EEMA and STY combined with DVB.

Crystallization of ACM in the presence of library E was accomplished in the same manner as in libraries B−D (three trials). From this study, it was found that polymers containing EEMA have the highest selectivity for the orthorhombic polymorph (Figure 3). On the other hand, orthorhombic-selective STY was found to have lower selectivity than EEMA for the orthorhombic form because STY terpolymers containing either *n*-BuMA or MAM yield more of the monoclinic polymorph. It was further determined that MAM- and MAA-containing terpolymers have the highest selectivity for monoclinic ACM, although significant amounts of the orthorhombic form were observed, for example, when EEMA was a component. Significantly, *n*-BuMA-MAM and *n*-BuMA-MAA cross-linked terpolymers tend to yield the orthorhombic form, but each of these three monomers exclusively produce the monoclinic form when copolymerized with DVB alone. This suggests a very delicate balance of functionality, in this case polar and nonpolar side chains, and concentration thereof that is governing the production of a given form. Furthermore, these results indicate that polymer functionality is a primary driving force in stabilizing a given crystal nucleus, leading to the controlled production of a particular polymorph.

ROY. The polymer libraries B−E were successful in selecting between two polymorphs of ACM. However, to test the full capability of polymer heteronucleation, we chose to explore the crystallization of ROY in the presence of these libraries with a

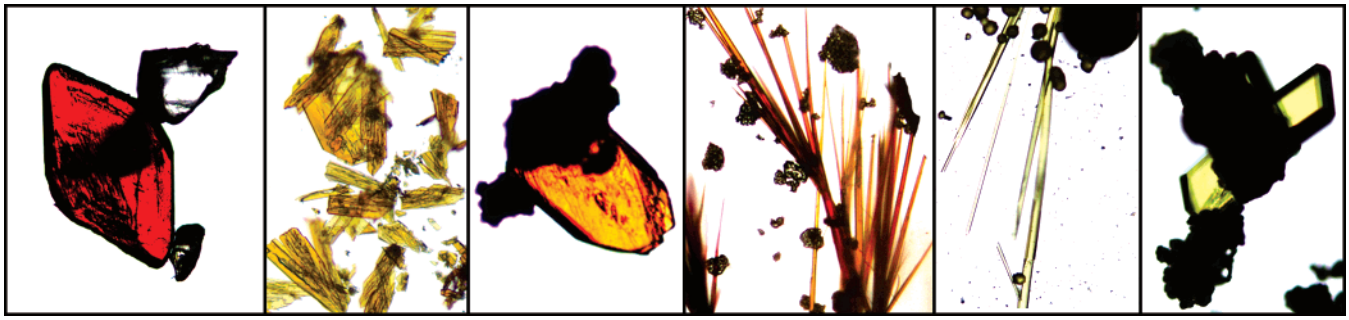

Figure 4. Photomicrographs of ROY polymorphs produced in the presence of polymers. From left to right: red prism (hydrolyzed poly(vinyl alcohol)), orange-red plates (acetoxystyrene/hydroxyethyl methacrylate/divinylbenzene terpolymer, not shown), orange plate (vinyl chloride/vinyl acetate/hydroxypropyl acrylate terpolymer), orange needles (ethylene/propylene copolymer), yellow needles (styrene/butyl methacrylate copolymer), and yellow prism (vinyl chloride/vinyl acetate copolymer).

single solvent and temperature condition. ROY, an intermediate in the production of the pharmaceutical olanzapine, is named for the color of its red, orange, and yellow polymorphs (Figure 4). Its color polymorphism is attributed to a variation in torsion angle (C−N−C−S) among forms.[16,17] With six structurally characterized polymorphs, it has the most forms of any organic molecule to date in the Cambridge Structural Database. Originally, five forms of ROY were identified and crystal structures of three of these were reported.[16] Five years later, an additional form was discovered and the structural characterization of all six forms was completed.[17] ROY and its derivatives have served as model compounds for groups exploring polymorph selection and discovery, including the demonstration of new techniques.[6,9,10,16,17,35] Numerous methodologies have been applied to ROY with varying degrees of success in producing its polymorphs. For example, sublimation onto single-crystal surfaces yielded three forms, including one whose structure is unknown.[6] Crystallizations of ROY within capillaries led to the production of primarily two forms (precipitation of all polymorphs of ROY was observed),[9] and crystallization in the presence of nanoporous polymers produced three polymorphs.[10] Because of its high degree of polymorphism and extensive investigation in the literature, ROY offers a critical challenge for any new methodology and it is extremely suitable for high throughput screening both optically and spectroscopically. Because the polymorphs have varying color and morphology, they are readily identifiable by optical microscopy if the morphology is not altered by the discovery method; this condition is rigorously met in polymer heteronucleation with cross-linked polymers. Furthermore, the forms are all unambiguously distinguishable by their vibrational spectra enabling conclusive polymorph identification by infrared or Raman spectroscopy.[17]

ROY was crystallized from ethanol solutions in the presence of polymer libraries B−D. Although these libraries possess a significantly smaller level of functional group diversity as compared to library A, five of the six structurally characterized polymorphs were produced: yellow prism (Y), yellow needle (YN), orange needle (ON), orange-red plate (ORP), and red prism (R) all formed as single crystals suitable for structure determination. Particularly significant is that ORP was found to crystallize in pure form in the presence of cross-linked terpolymers containing AOS and HEMA, and this allowed the first determination of its melting point (97.4−97.8 °C); this value is the lowest among the six ROY polymorphs.[17] The identity of this material was confirmed both by Raman spectroscopy and by unit cell determination with single-crystal X-ray diffraction.

A polymorph that was not produced using libraries B−D as heteronuclei, orange plate (OP), was readily obtained when a more diverse library of polymers was employed. ROY crystallized in the presence of polymer library A led to nucleation of five polymorphs of ROY: Y, YN, ON, OP, and R. Thus, all six structurally characterized polymorphs of ROY were obtained from crystallizations in the presence of polymer heteronuclei, whereas, in the absence of added polymers under the same conditions, only the YN and R polymorphs were observed. In contrast, using previous crystallization methods, it took investigators several years to discover and discern the structure of these six polymorphs.[16,17] However, excellent single crystals of all six forms were produced via polymer heteronucleation in just a few days (Figure 4). Therefore, this technique is capable of producing pure polymorphs as single crystals routinely, such that full characterization of all forms of a compound can be achieved rapidly.

Sulfamethoxazole. To further explore the generality of the polymer heteronucleation methodology, crystallization of the antibiotic sulfamethoxazole (SMA) was undertaken in the presence of polymers. This was an attractive target not only because of its pharmaceutical importance and known polymorphism,[36−40] but also because of its structural similarity to other sulfonamides, which are some of the most widely studied polymorphic compounds.[36,41,42] SMA has two polymorphs, forms I and II, and has already been subjected to considerable scrutiny.[37−40] To achieve maximal heteronucleus diversity, SMA was crystallized in the presence of polymer library A by evaporation from different solvents selected for compound solubility and compatibility with the polymers. The two known polymorphs of SMA have distinct Raman spectra, making them suitable to study polymorph selectivity using this high throughput method.[40]

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Table 1. Crystallographic Information for the Four Polymorphs of Sulfamethoxazole

	form I[37]	form II[37]	form III	form IV
crystal system	monoclinic	monoclinic	monoclinic	monoclinic
temperature (K)	283−303	283−303	153(2)	153(2)
space group	*C*2/*c*	*C*2/*c*	$P2_1/c$	$P2_1/n$
a (Å)	16.062(2)	25.095(4)	11.640(3)	5.4895(9)
b (Å)	5.479(1)	7.226(1)	6.8189(19)	16.761(3)
c (Å)	25.757(3)	14.848(2)	15.419(4)	12.422(2)
β (deg)	96.12(2)	117.99(1)	107.106(5)	97.080(2)
cell volume (Å^3)	2253.8	2377.5	1169.7(6)	1134.2(3)
calc density (g/cm^3)	1.493	1.416	1.438	1.483
Z	8	8	4	4
data/restraints/ parameters			2690/1/167	2566/0/167
R	0.032	0.03	0.0914	0.0376
wR_2			0.2391	0.0936

Remarkably, during the course of these studies, two new polymorphs of this pharmaceutical, forms III and IV, were discovered by evaporation from ethyl acetate solutions in the presence of library A, and structures of both new forms were determined by single-crystal X-ray diffraction using crystals grown directly from the polymers (Table 1, Figure 5). SMA form III was produced in the presence of poly(4,4′-dipropoxy-2,2′-diphenyl propane fumarate). Form III has several characteristic peaks in its Raman spectrum including 1095, 1136, 1155, 1189, 1599, and 1644 cm^{-1} and has a distinct powder X-ray diffraction pattern with characteristic peaks at $2\theta = 15.27°$, 20.15°, 23.90°, and 32.05° (see Supporting Information). These peaks are in good agreement with the powder X-ray diffraction simulation from the single-crystal structure. Hot stage microscopy revealed that this polymorph transforms to form II upon heating between 145 and 150 °C, which was verified by Raman spectroscopy. Form II then transforms to form I around 166 °C, which subsequently melts at 170 °C.

SMA form IV was produced in the presence of Nylon 6/T, carboxyl modified polyacrylamide, poly(2-hydroxyethyl methacrylate), poly(4-methylpentene), 98% hydrolyzed poly(vinyl alcohol), and poly(vinyl butyral). Form IV also has a Raman spectrum and powder X-ray diffraction pattern that are substantially different from those of the other polymorphs. Form IV has characteristic Raman shifts at 1091, 1145, 1160, 1191, 1596, 1603, and 1643 cm^{-1} and powder X-ray diffraction peaks at $2\theta = 8.90°$, 10.58°, 17.07°, and 21.35°. When form IV was subjected to hot stage microscopy, it melted at 170 °C with no observed polymorphic transitions. With the determination of these two latest SMA crystal structures, it now joins an extremely small group of organic compounds that have four or more structurally characterized polymorphs in the Cambridge Structural Database (CSD). Of the more than 300 000 entries in the CSD, there are approximately 50 trimorphic,[43,44] only four tetramorphic,[15,41,45,46] and one example each of penta-[42] and hexamorphic[17] organic molecular compounds. With the addition of SMA, there will be five tetramorphic systems, and, significantly, two of these (SMA and carbamazepine) were made accessible by polymer heteronucleation. Because in the case of SMA and carbamazepine these compounds have been studied for decades by numerous other researchers, this accomplishment highlights the power of the polymer heteronucleation methodology.

The distribution of SMA polymorphs grown in three organic solvents was also influenced by library A (see Supporting Information). Crystallizations in the presence of this library decreased the occurrence of form I relative to control experiments with a corresponding increase in access to the other forms of SMA, primarily form II. This trend was observed in every case regardless of which polymorph is preferentially formed from a given solvent in the absence of the library. The most striking changes in polymorph selectivity were seen from evaporations of SMA/2-propanol solutions. In this system, crystallization in the presence of the polymer library yielded equal occurrences of forms I and II. However, in the absence of this library, form I was observed in 91% of crystallizations. From these studies, it is concluded that selection between forms depends on solvent as well as polymer heteronucleus, suggesting a delicate interplay between solvation influencing nucleation and surface stabilization. Of course, the nature of the polymer surface will change in different solvents, and therefore solvent will always be another diversity element required to achieve optimal polymorph discovery.

Conclusion

The powerful method of using polymer heteronuclei to selectively produce and discover crystal forms provides a new paradigm for the exploration of polymorph space. This method is compatible with several high throughput polymorph screening techniques, allowing its implementation alongside more traditional methods for producing new solid forms. For each system investigated, all stable polymorphs could be obtained, in most cases with a high degree of selectivity, from a single solvent and temperature condition in a matter of days by simply varying the polymer heteronucleus. Furthermore, this technique lends itself to the production of single crystals, allowing definitive

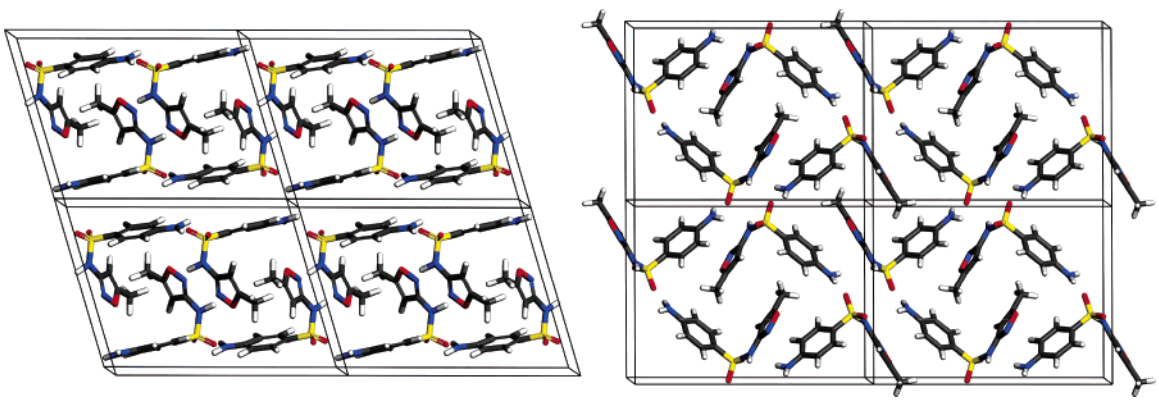

Figure 5. Packing diagrams of form III (left) and form IV (right) of sulfamethoxazole.

polymorph identification by morphology. This was especially true in the case of cross-linked polymers because the insoluble substrate does not affect the morphology of a crystal as it grows. These libraries are also extremely valuable for identifying chemical functionalities that are highly selective for a particular polymorph to guarantee the production of that form.

Experimental Section

Cross-Linked Polymer Synthesis. Cross-linked polymer libraries were prepared using six 1:1 (v:v) monomer solutions in ethanol. These solutions were mixed pairwise in six ratios (86:14, 71:29, 57:43, 43:57, 29:71, 14:86) in 96-well polypropylene plates with a Gilson 215 liquid handler. Thus, 90 pairwise monomer mixtures and six pure monomer solutions were prepared each with a volume of 100 μL. To these 96 solutions was added 50 μL of a 1:1 (v:v) solution of the cross-linker divinylbenzene (DVB) in ethanol containing 2 mol % AIBN with respect to DVB. The plates were placed in a nitrogen atmosphere and purged with nitrogen gas while irradiating for 4 h with a 60 W UVA source to yield cross-linked polymers. After irradiation, the polymers were annealed at 85 °C in a vacuum oven (<1 Torr) for an additional 4 h to remove solvent and other residual small molecules. This afforded polymers with relatively smooth surfaces that conformed to the shape of the polypropylene wells. All crystallizations in the presence of libraries B−E were carried out directly in the wells with the as-produced polymer disks coating the bottom part of the well.

Acetaminophen (ACM) Crystallization. Solutions prepared by heating 480 mg of ACM in 30 mL of water at 100 °C were cooled to room temperature and dispensed into the wells of a micro titer plate containing a polymer library. The plate was covered, heated to 90 °C for 30 min, cooled to room temperature by removal from the heat source, and the solvent was allowed to evaporate. Studies were done in triplicate to gauge reproducibility.

5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY) Crystallization. Solutions of ROY were made by heating 100 mg in 8 mL of ethanol at 85 °C. The solution was cooled to room temperature by removal from the heat source, and prior to the onset of crystallization all 8 mL was equally distributed among the wells of a micro titer plate containing polymers. Studies were done in triplicate to gauge reproducibility.

Sulfamethoxazole (SMA) Crystallization. Solutions of SMA in ethyl acetate (20 mg/mL) or methanol (30 mg/mL) were added to polymer-containing micro titer plates such that ~3 mg of SMA was dispensed into each well. These were allowed to slowly evaporate at room temperature. Heating of 2-propanol solutions (17 mg/mL) to 70 °C was employed due to relatively lower solubility. After dispensing the solution in 2-propanol such that ~3 mg SMA was in each well, the micro titer plate was sealed and heated to 70 °C to ensure all SMA was dissolved. The plate was then cooled to room temperature by removal from the heat source, and the seal was removed. No significant crystallization was observed prior to the room-temperature evaporation. All trials were done in triplicate to gauge reproducibility.

Raman Spectroscopy. Raman spectra were obtained using a Renishaw inVia Raman microscope equipped with a 785 nm diode laser and a 1200 lines/mm grating. Spectra were collected and analyzed using the WiRE 2.0 software package. Calibration was performed using a silicon standard. Spectra were typically collected using an Olympus SLMPlan 20× objective (numerical aperture = 0.35) and 50 μm slit in either extended scan mode with a range of 100−3200 cm^{-1} or static scan mode centered at 1350 cm^{-1} for SMA and 2200 cm^{-1} for ROY.

Thermomicroscopy. Melting behavior was determined using a Mettler Toledo FP82HT hot stage connected to a FP90 control processor and viewed under crossed polarizers with a Leica DMLP microscope. Heating rates were typically between 1.0 and 5.0 °C/min.

Single-Crystal X-ray Diffraction. Single-crystal X-ray diffraction data were recorded on a Bruker SMART CCD-based X-ray diffractometer equipped with an Oxford 700 low-temperature device and graphite monochromated Mo Kα source (λ = 0.71073 Å). The structures were solved and refined using the Bruker SHELXTL software package (version 6.14). Hydrogen atoms were generated at idealized positions and refined as riding atoms with individual isotropic displacement parameters with the exception of those involved in hydrogen bonding, which were allowed to refine independently.

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Supporting Information Available: Composition of library A, results from acetaminophen crystallizations from libraries B−E, Raman spectra for all ROY and sulfamethoxazole polymorphs, powder X-ray diffraction data for sulfamethoxazole, and crystallographic information files (CIF) for sulfamethoxazole forms III and IV. This material is available free of charge via the Internet at http://pubs.acs.org.

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