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The Use of Polymer Heteronuclei for Crystalline Polymorph Selection

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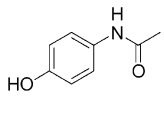
The close packing of a given molecule into a crystalline lattice can be accomplished in a number of nearly isoenergetic, but structurally distinct, motifs. Different arrangements of the same compound in the solid state are termed crystal polymorphs, and these have different thermodynamic stabilities. In addition key properties that affect performance, such as bioavailability for pharmaceuticals and color for pigments, can vary between polymorphs. The prevalence of this phenomenon in pharmaceutical solids is approximately 30%,[1] although the overall occurrence in the Cambridge Structural Database (CSD) is approximately $^1/_{10}$ this value.[2] One reason for this disparity is the amount of effort expended in searching for polymorphs of pharmaceuticals driven, in part, by regulatory considerations.[3] Our goal is the development of new and efficient methods for the selective production of crystalline polymorphs to study and control this fundamental issue of solid-state isomerism.

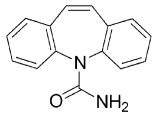
Stunning examples of polymorphic control are offered by organisms, such as mollusks, that can selectively deposit a specific polymorph of $CaCO_3$ (calcite or aragonite) under the control of biological macromolecules.[4,5] The same degree of control has not been universally achievable by chemists although elegant examples of selective polymorph production using monolayers[6] or designed additives[7,8] have been demonstrated for specialized cases where knowledge of the crystal structure can guide selection of conditions. Traditional strategies for discovery and selection of polymorphs often involve changing solvents, temperature, and other growth conditions in an attempt to control crystal formation.[9] We disclose here a general strategy for nucleating the growth of polymorphs that is applicable to a variety of systems using polymer heteronuclei. Furthermore, this technique is well-suited for the direct production of single crystals, thus facilitating the determination of polymorph structures.

It is widely recognized that the phenomenon of crystallization is primarily kinetic and that the majority of crystallizations occurring on laboratory scale are the result of heterogeneous nucleation.[10,11] The efficiency of a surface in heteronucleating growth of a given polymorph is expected to depend on the complementarity between the surface and the crystal nucleus. Since we required a general method that did not rely on prior knowledge of the lattice or surface chemistry of a polymorph to be produced, we employed a library of surfaces with diverse functional groups and spacing of these groups. This first library of heteronuclei was drawn from polymers that were insoluble in the medium employed such that interactions with only a small number of faces of a given crystal would be observed. The success of this approach in controlling polymorphism of the important pharmaceuticals acetaminophen and carbamazepine is described below.

The polymorphism of acetaminophen has been studied extensively, yielding structural characterization of two forms.[12−15]



Acetaminophen



Carbamazepine

Monoclinic acetaminophen (form I)[13] is thermodynamically more stable at room temperature with respect to the orthorhombic modification (form II).[16] This latter form was obtained in 1974 by evaporation from ethanol[12] and was later shown to be more soluble[17] and directly compressible into tablets.[18] Despite considerable effort by subsequent researchers, including the authors of this communication, its production in pure form from solution has remained elusive.[14] Compounding this problem is the propensity of acetaminophen solutions seeded with the orthorhombic polymorph to give the more stable monoclinic form.[14]

To determine if heteroseeding could provide kinetic access to orthorhombic acetaminophen, we investigated the effect of polymers on the crystallization of acetaminophen (Table 1).[19] We found that the presence of certain polymers including Nylons, isotactic polypropylene, chlorinated polyethylene, poly(tetrafluoroethylene), poly(2,3,5-tribromostyrene), and poly(vinyl chloride) caused the growth of the orthorhombic polymorph from evaporation of aqueous solution, usually as single crystals (Figure 1).[20]

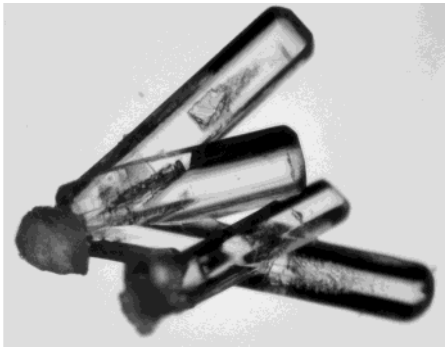


Figure 1. Orthorhombic acetaminophen growing from isotactic polypropylene beads. This morphology does not vary substantially with the polymer heteronucleus employed.

Other members of the polymer library studied favored the monoclinic form, while others led to mixtures of both polymorphs (Table 1). The variety of polymer structures that produced orthorhombic acetaminophen suggests that epitaxy[8] is not critical for the production of this metastable form. However, the orientation of crystal growth from the polymer surface varied between polymer types, indicating an important role for stabilization of the crystal faces by the polymers through specific interactions (see Supporting Information).

To explore the generality of this approach for polymorphic control, the same library of polymers was applied to the growth of

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Table 1. Acetaminophen Polymorphs Resulting from Crystallization in the Presence of 84 Different Polymers over Three Trials

Orthorhombic form induced	Monoclinic form induced	Mixtures of orthorhombic and monoclinic induced
Alginic acid, sodium salt	Butyl methacrylate/isobutyl methacrylate copolymer	Acrylonitrile/butadiene/styrene resin
Nylon 6, 11, 6/6, 6/9, 6/10, 6/12,	Cellulose acetate butyrate	Ethylene/acrylic acid copolymer
6/T(polytrimethyl	Cellulose propionate	Ethylene/vinyl acetate (25, 28, 33, and 40% VA) copolymer
hexamethylene	Cellulose triacetate	Phenoxy resin
terephthalamide)	Ethyl cellulose	Polyacrylamide, carboxyl modified (low content)
Polyacetal	Ethylene/ethyl acrylate copolymer	Poly(diallyl isophthalate) and Poly(diallyl phthalate)
1,2-Polybutadiene	Ethylene/propylene copolymer	Poly(4,4-dipropoxy-2,2-diphenyl propane fumarate)
Polycaprolactone	Ethylene/vinyl acetate (14 and 18% VA) copolymer	Poly(ethyl methacrylate)
Poly(2,6-dimethyl-*p*-phenylene	Hydroxypropyl methyl cellulose	Polyethylene, chlorinated (25% chlorine)
oxide)	Polyamide resin	Polyethylene, oxidized
Polyethylene, high density	Poly(1-butene), isotactic	Poly(ethylene terephthalate)
Polyethylene, chlorinated (36,	Poly(*n*-butyl methacrylate)	Poly(isobutyl methacrylate)
42, and 48% chlorine)	Polycarbonate	Polyisoprene, chlorinated
Polyethylene, chlorosulfonated	Poly(2-hydroxyethyl methylate)	Poly(phenylene sulfide)
Poly(methyl methacrylate)	Poly(α-methylstyrene)	Polystyrene
Poly(4-methyl-1-pentene)	Poly(*p*-phenylene ether-sulphone)	Polysulfone
Polypropylene, isotactic and	Poly(vinyl acetate)	Poly(vinyl stearate)
isotactic, chlorinated	Poly(vinyl alcohol), 98 and 99.7% hydrolyzed	Poly(vinylidene fluoride)
Poly(tetrafluoroethylene)	Poly(vinyl butyral) and Poly(vinyl formal)	Styrene/acrylonitrile copolymer (75/25)
Poly(2,4,6-tribromostyrene)	Styrene/acrylonitrile copolymer (70/30)	Styrene/isoprene ABA block copolymer
Poly(vinyl chloride), and PVC	Styrene/allyl alcohol copolymer	Vinyl chloride/vinyl acetate (81, 88 and 90% VCl) copolymer
1.8% carboxylated	Styrene/butadiene, ABA block copolymer	and 1% carboxylated
Styrene/ethylene-butylene, ABA	Styrene/butyl methacrylate copolymer	Vinyl chloride/vinyl acetate/hydroxylpropyl acrylate
block copolymer	Styrene/maleic anhydride copolymer	terpolymer
	Vinyl alcohol/vinyl butyral copolymer (20/80)	Vinyl chloride/vinyl acetate/vinyl alcohol terpolymer

carbamazepine polymorphs from methanol. From this library four polymers were identified that yielded the previously inaccessible fourth polymorph[21] of this well-studied pharmaceutical: hydroxypropyl cellulose, poly(4-methylpentene), poly(α-methylstyrene), and poly(*p*-phenylene ether-sulfone). These provided crystals of the new form that were directly suitable for single-crystal X-ray diffraction. As in the case of acetaminophen, a chemically diverse set of polymers is able to induce the growth of the metastable polymorph, albeit a more limited group. This observation points to the fact that very large polymer libraries may be necessary to ensure production of all polymorphs of a given compound.

In summary, a powerful new method for controlling crystal polymorphism was demonstrated both in the control of a dimorphic system and in a tetramorphic system. This method provides a new paradigm for polymorph selection, where solvent and temperature conditions can be chosen on the basis of process considerations and the polymer heteronucleus can be varied for specific polymorph production. Understanding the process of nucleation of these crystals in the presence of polymers by studying growth orientation and the influence of polymer alignment will constitute a major area of future exploration. In addition, studies on inorganic systems have the potential to provide a strategy to mimic biomineralization processes.

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Supporting Information Available: Powder X-ray diffraction pattern of orthorhombic acetaminophen; images showing acetaminophen growth from various polymer surfaces (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Acetaminophen crystallization was carried out by the following procedure: A different polymer (3−10 mg, Scientific Polymer Products) was added into each well of a 96-well polypropylene plate. After adding 4.8 mg of acetaminophen and 0.3 mL of water, the plate was heated to 100 °C for 30 min with periodic addition of water to maintain volume. The plate was cooled to room temperature and loosely covered, allowing slow evaporation. Two crystal morphologies were observed. Powder X-ray diffraction showed that the prismatic crystals were monoclinic, while the elongated prisms were orthorhombic. Repeating this analysis in plates with no added polymer led exclusively to monoclinic acetaminophen. The reported results were collected from three separate plates to gauge reproducibility, and only the 84 polymers that consistently yielded orthorhombic, monoclinic, or a mixture of both polymorphs are reported.
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