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On the Mechanism of Crystalline Polymorph Selection by Polymer Heteronuclei

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Abstract

The phase-selective crystallization of acetaminophen (ACM) using insoluble polymers as heteronuclei was investigated in a combined experimental and computational effort to elucidate the mechanism of polymer-induced heteronucleation (PIHn). ACM heteronucleates from supersaturated aqueous solution in its most thermodynamically stable monoclinic form on poly(*n*-butyl methacrylate), whereas the metastable orthorhombic form is observed on poly(methyl methacrylate). When ACM crystals were grown through vapor deposition, only the monoclinic polymorph was observed on each polymer. Each crystallization condition leads to a unique powder X-ray diffraction pattern with the major preferred orientation corresponding to the crystallographic faces in which these crystal phases nucleate from surfaces of the polymers. The molecular recognition events leading to these outcomes are elucidated with the aid of computed polymer-crystal binding energies using docking simulations. This investigation illuminates the mechanism by which phase-selection occurs during the crystallization of ACM using polymers as heteronuclei paving the way for the improvement of methods for polymorph selection and discovery based on heterogeneous nucleation promoters.

Keywords

crystal polymorphism; X-ray diffractometry; preferred orientation; molecular dynamics; binding energy

In the pursuit of new crystalline phases of molecular compounds, altering crystallization variables such as temperature, solvent and degree of supersaturation is common. However, such methods do not explicitly target nucleation which is often the critical step in determining the ultimate solid-state form produced. Polymer-induced heteronucleation (PIHn) has been established as a general approach for controlling solid form selection and discovery in which an array of polymer heteronucleants provides kinetic access to polymorphs.¹ Demonstrations of PIHn for small molecules,^{2–5} supramolecular

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Supporting Information. Experimental procedure, optical microscopy, powder X-ray diffraction, docking simulations, and binding energy calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

complexes,^{6, 7} and proteins^{8,9} are established; however, in spite of its success in controlling crystal polymorphism, little is understood about its mechanism.

PIHn utilizes insoluble polymers to affect solid form selection. Unlike soluble additives, heterogeneous additives can only interact with molecules at the solid-solution interface which leads to crystal growth where interactions are confined to one crystal face; this stands in stark contrast to the use of soluble additives where inhibition can occur to varying degrees through blocking the addition of subsequent molecules to all of the growing crystal faces.^{10–12} As a result the phase-selection mechanism occurring during PIHn cannot be explained using the same rationale as with soluble additives. An alternative mechanism could be that the polymer inhibits crystal growth by preferential retention of specific nuclei types inside the swollen polymer, which in turn would delay the onset of crystallization and inhibit formation of a given polymorph. Experimentally, acceleration of crystal formation is instead observed ruling out inhibition through competitive retention of nuclei inside a polymer matrix as a mechanism for PIHn and pointing to a promotion of growth at a heterogeneous interface.

Heterogeneous nucleation can occur with different levels of specificity ranging from nonspecific adsorption to the oriented growth of crystals on a surface. During nonspecific adsorption, solute molecules cluster on the surface without specific orientation and the mere presence of an interface promotes nucleation by lowering surface energy of the aggregate. Other modes of promoting nucleation include employing structural matching between the nucleating crystal and the surface, as in the case of epitaxial crystal growth;^{13–15} however the oriented arrangement of molecules by means of selective interfacial interactions should also be possible at an amorphous surface. Epitaxy does not present a viable explanation for the success of PIHn because the polymers utilized do not present significant order. As a result two possible mechanisms remain plausible to explain phase-selection using polymers as heteronuclei, one involves nonspecific adsorption of molecules to form crystal nuclei and the other involves the oriented arrangement of nucleating molecules on the polymer surface. These outcomes are differentiated between here by elucidating the preferred modes of crystal growth in PIHn under several conditions and the results are interpreted with the aid of computation.

Acetaminophen (ACM, Figure 1) is a common analgesic and antipyretic drug which crystallizes in two stable forms,¹⁶ the less thermodynamically favorable orthorhombic form¹⁷ and the monoclinic form.¹⁸ Selective crystallization of orthorhombic and monoclinic ACM using various insoluble polymers as heteronuclei has previously been reported.¹ ACM heteronucleates from aqueous supersaturated solution in the monoclinic form on poly(*n*-butyl methacrylate) (PBMA, Figure 1), whereas the orthorhombic form is observed on structurally similar poly(methyl methacrylate) (PMMA, Figure 1).¹ Therefore, ACM serves as a good model compound for understanding how these polymer heteronucleants exercise control over crystallization of these polymorphs.

Experimental Section

Materials

ACM was obtained from ICN Biomedicals Inc. (Irvine, CA) and was stored at room temperature. PBMA, PMMA, Nylon 6/9, Nylon 6/12 and Nylon 11 were purchased from Scientific Polymer Products Inc. (Ontario, NY).

Preparation of Polymer Thin Films

All polymer samples were prepared by spin coating 3 w/w % polymer solutions (benzene) onto microscope slides ($75 \times 25 \times 1$ mm) at 2500 rpm on a Specialty Coatings Systems G3P-8 spin coater. Coated slides were annealed at 85 °C under vacuum for 4 hours.

Crystallizations from Aqueous Solution

ACM crystals were grown from aqueous supersaturated solutions (17 mg/mL, at 25 °C) on submerged microscope slides coated with polymer. The slides were aligned vertically in the vial to minimize the possibility that crystals that nucleated in solution would deposit on the microscope slide. Samples were air dried prior to analysis.

Crystallizations from Vapor Phase Deposition

Powdered ACM (~200 mg) was added to a sublimation chamber. Polymer-coated microscope slides were held in contact with a flat aluminum plate cooled by an ice/water bath, and sublimation proceeded while the chamber was evacuated ($\sim 15 \times 10^{-3}$ Torr) and submerged in an oil bath at 150 °C. After ~15 min, all ACM had sublimed from the bottom of the chamber.

Powder X-ray Diffraction (PXRD)

PXRD analysis was performed using a Bruker D8 Advance diffractometer equipped with a LynxEye detector and graphite monochromated Cu-K α radiation (1.5406 Å, 40 kV, 40 mA). Diffractograms were collected at room temperature from 5° to 50° with a 0.05° step size while the sample was rotated at 60 rpm. All powder patterns were processed in Jade Plus (v. 8.2).

Molecular Modeling

Vapor phase crystallization of ACM utilizing PBMA and PMMA as heteronucleants was mimicked by docking polymer models onto seven different faces of the monoclinic ACM crystal lattice ((001), (002), (020), (021), (120), (21-1), and (110) faces) and onto seven different faces of the orthorhombic ACM crystal lattice ((002) (121), (201), (212), (222), (221), and (220) faces). PBMA (MW = 431 g/mol) and PMMA (MW = 293 g/mol) were represented as trimers with syndiotactic configuration¹⁹ and capped with hydrogen atoms at the terminal sites. Docking was achieved via simulated annealing. For each of three simulated annealing cooling schedules (Supporting Information), one hundred independent trials were performed for each combination of polymer model and ACM face. The overall surface binding energies ($\Phi_{\text{BE}(h,k,l)}$) were estimated from the energy difference between the lowest energy of the complex in vacuum (Φ_{IE}) and the minimized energy of the free components (Φ_{PM} , polymer model and $\Phi_{\text{CF}(h,k,l)}$, crystal face) in vacuum (Equation 1).²⁰

$$\Phi_{\text{BE}(h,k,l)} = \Phi_{\text{IE}} - (\Phi_{\text{PM}} + \Phi_{\text{CF}(h,k,l)}) \quad (1)$$

All simulations and surface binding energy (Φ_{BE}) calculations were performed using the CHARMM macromolecular modeling package version c36a4^{21, 22} on dual 2.66 GHz Intel Quad Core Xeon CPUs. Parameters and partial charges for ACM molecules were taken from the CHARMM Generalized Force Field (CGenFF);²³ PBMA and PMMA trimer parameters and partial charges for each polymer model were assigned from the parameterization tool.²⁴

Results and Discussion

Phase determination and preferred orientation (PO) analysis was conducted by PXRD on polymer coated glass slides with the as-grown ACM crystals. Comparison of the diffraction patterns with the 2θ values of known crystal structures was used for phase identification.^{17, 18} In accord with what was previously reported,¹ ACM heteronucleates from aqueous supersaturated solution in the monoclinic form on PBMA (Figure 2a), whereas the orthorhombic form is observed on PMMA (Figure 2b). In both polymer-polymorph combinations the crystals were found to be strongly oriented along specific crystallographic planes. Because both polymers are insoluble under this crystallization condition and possess no long range order it can be concluded that the difference in PO observed by PXRD results from unique interactions that occur at the polymer-crystal interface when molecules selectively nucleate on the surface. Analysis of the relevant polymer-crystal interfaces provides insights into some of the kinetic aspects of polymer-induced phase selection.

ACM crystals heteronucleated on PBMA present a prismatic morphology (Supporting Information). PXRD analysis revealed two prominent reflections occurring at 13.8° (001) and 27.8° (002), (Figure 2a), these correspond to those of monoclinic ACM with orientation of the crystals along {001}. This could arise through crystal nucleation from the (001) face or the (002) face, which cannot be distinguished by PXRD. Hydroxyl groups appear perpendicular to the (001) face whereas in the case of the (002) face, the amide portion of the ACM molecule is perpendicular to the surface (Figure 3). This indicates that PBMA is interacting either with the amide or with the hydroxyl portion of ACM in the case of the (002) face and the (001) face, respectively (Figure 3a). Hydrogen-bonding is typically assumed to be among the most directional types of intermolecular interactions, but interfacial hydrogen-bonding to either the amide or the hydroxyl groups on monoclinic ACM is not likely given that the PBMA surface is dominated by terminal methyl groups of the ester side chain when in contact with both air and water.²⁵ Examination of the crystal structure of monoclinic ACM reveals the presence of grooves when observed along the *ac* plane (Figure 3b). Therefore, crystal nucleation mediated by hydrophobic interactions between the ester side chain in PBMA and the grooves at this interface, the (001) face, provides a possible pathway for the nucleation of monoclinic ACM on PBMA in the presence of water as solvent.

ACM crystals heteronucleated on PMMA present a plate-like habit (Supporting Information). PXRD of ACM crystals grown on PMMA yields a diffractogram with a single major reflection at 24.1° (002) in 2θ (Figure 2b). The presence of PO along the (002) face indicates that crystal nucleation occurs from the family of planes along *ac*, {001}, in orthorhombic ACM. A view of the *ac*-plane of orthorhombic ACM with the (002) face indicated is shown in Figure 4. Hydrogen-bonded molecular sheets lay planar along {001}. Morphology predictions suggest that fast growth for orthorhombic ACM occurs along {100}, {010}, and {001}.²⁶ These predictions and the PXRD results suggest that when PMMA is utilized as the heteronucleant in aqueous media, it has the ability to secure the hydrogen-bonded molecular sheets of ACM that form along the fast growing {001}, making it possible to harvest this polymorph versus the thermodynamically more stable monoclinic form.

In a previous study, the polymer-crystal interface of ACM grown from supersaturated aqueous solution on PBMA and PMMA was investigated through Sum Frequency Generation Vibrational Spectroscopy (SFG-VS)²⁷ in order to determine the molecular-level interactions responsible for phase-selection. The presence of the amide I stretch in the SFG-VS spectra was only observed for monoclinic ACM crystals grown on PBMA. The absence

of the amide I stretch signal at the PMMA–orthorhombic ACM interface suggested that the amide was oriented parallel to the interface which is consistent with the molecular structure of {001} in orthorhombic ACM (Figure 4), and supports the current experimental data indicating that orthorhombic ACM preferentially nucleates along {001} on PMMA when it crystallizes from water. Additionally, the SFG-VS study of the polymer–crystal interface revealed that hydrogen-bonding to the polymer carbonyl oxygen only occurred in the case of PMMA–orthorhombic ACM, which confirms that phase-selection is dictated by hydrogen-bonding for this particular polymer–crystal combination.

To determine the role of solvent during the PIHn process, ACM crystals were deposited by sublimation onto PBMA and PMMA. Under the vapor phase deposition condition, only the monoclinic form of ACM was observed (Figure 5). Although the same form is selectively produced in the absence of solvent, PXRD revealed POs that are unique to each of the polymers utilized for heteronucleation. The experimental PXRD pattern of ACM crystals deposited on PMMA (Figure 5b) indicate that the extent of PO along {001} is significantly greater than that of ACM crystals deposited on PBMA (Figure 5a) where multiple orientations are observed. These observations are discussed below in the context of the computed interaction energies.

Surface binding energies (Φ_{BE}) between various ACM crystal faces interacting with PBMA and PMMA trimers were estimated using docking simulations to reveal molecular-level factors influencing phase-selection during PIHn in vacuum. These data are summarized in Table 1. These relative binding energies are in good agreement with bulk experimental observations; however, there may be some limitations in extending the findings from the truncated trimer models to represent the full polymer-ACM interactions. Among the crystal faces interacting with PBMA trimers, six of them have significantly favorable Φ_{BE} . These six faces with lower Φ_{BE} values belong to those of the monoclinic crystal phase and the calculated Φ_{BE} values are within 4 kcal/mol of the lowest energy complex which suggests a thermodynamically driven competition among these faces. Indeed, in Figure 5a the reflections associated with each of these faces are observed in the diffractograms of ACM crystals grown on PBMA through vapor deposition, suggesting that a significant population of each of these crystal faces are aligned along the polymer substrate.

The Φ_{BE} value for the polymer–crystal interface involving PBMA and the (002) face in monoclinic ACM is significantly less favorable than those from the (001) face. This difference arises from the more favorable electrostatic energy contributions for the (001) face compared to the (002) face in the monoclinic crystal phase. In both the (001) and the (002) faces, the trimer is able to maintain extensive nonspecific interactions within the surface grooves which results in dispersion (van der Waals) interactions of comparable magnitude. PXRD is unable to distinguish if crystals are nucleated from the (001) face or the (002) face, therefore the docking simulations provide the best evidence that a larger numbers of crystals nucleate from the (001) face.

Unlike the case of PBMA-induced heteronucleation, the results for PMMA presented in Table 1 show a clear preference for the (001) face, where Φ_{BE} for this face is over 6 kcal/mol more favorable than any other face examined. These results are consistent with the PO observed in the diffractogram of ACM crystals grown on PMMA by vapor deposition where mainly two reflections occurring at 13.8°(001) and 27.8°(002) are observed (Figure 5b). The large difference in Φ_{BE} between the (001) face and the (002) face modeled in the presence of PMMA seems to arise from a different mechanism from that of PBMA-induced nucleation. In this case, the docked PMMA trimer exhibits more favorable dispersion (van der Waals) interactions with the (001) face than the (002) face of the monoclinic crystal while the electrostatic energy contributions are comparable.

For both polymer models, the most favorable orthorhombic face is more than 4 kcal/mol higher in energy than the most favorable monoclinic face, reaffirming that under vapor phase crystallization conditions the emergence of orthorhombic ACM is unlikely. The calculated Φ_{BE} for the orthorhombic (002) face in contact with both PBMA and PMMA was the least favorable among all the faces studied and more than 10 kcal/mol less favorable than the most favorable monoclinic face. Not surprisingly, it is the weaker electrostatic interactions that result in the relative disfavoring of the orthorhombic (002) face over the other faces. The presence of only the monoclinic form in ACM crystals deposited from sublimation suggests a possible role of solvent in aiding the nucleation process of orthorhombic ACM on the PMMA surface.

In order to establish the role of solvent in facilitating nucleation under the polymer-induced heteronucleation condition, an additional class of polymers was tested. Nylon 6/9, Nylon 6/12 and Nylon 11 (Figure 6) were utilized as polymer heteronucleants for ACM crystals in ethanol, acetonitrile, and acetone where, unlike PBMA and PMMA, no dissolution of the polymer will occur. These Nylons were also utilized as heteronucleants under vapor phase deposition. Table 2 summarizes these results.

Results are consistent across the three Nylons and indicate that aprotic solvents facilitate nucleation along {001} in monoclinic ACM (Supporting Information). In the absence of solvent, nucleation along {001} in monoclinic ACM is also favored whereas in the presence of a protic solvent Nylons promote the nucleation along {001} in orthorhombic ACM (Supporting Information). The results obtained for Nylons support the hypothesis that the presence of a protic solvent, in this case water, working in concert with the polymer is responsible for directing the phase selectivity of orthorhombic ACM grown on PMMA.

This combined experimental and computational effort provides insights into the mechanism of phase-selection by PIHn through unraveling distinct intermolecular interactions occurring at each preferred nucleation face under different crystallization conditions. Results indicate that the phase-selection mechanism of PIHn depends on the difference in the accessibility of the functional groups on the surface of the polymer heteronucleants, which may affect interfacial interactions and ultimately direct nucleation along a given crystal face, the PO plane. Moreover, results emphasize the dependence of the polymorph selection process on both the polymer surface and the solvent media because it was possible to change solid form in the absence of solvent as well as in the presence of different solvents based on their ability to donate a hydrogen-bond. The rationalization of the intermolecular interactions directing phase-selection during the process of PIHn will allow for the further development of better methodology for the control and selection of solid forms based on polymer heteronucleants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Chemical structures of acetaminophen (ACM), poly(*n*-butyl methacrylate) (PBMA), and poly(methyl methacrylate) (PMMA).

Figure 2. PXRD of monoclinic ACM nucleated on PBMA (a) and orthorhombic ACM nucleated on PMMA (b) from a supersaturated aqueous solution (bottom), along with the simulated PXRD pattern of monoclinic and orthorhombic ACM with no PO (top).

Figure 3.
View of the *bc* plane (a) and the *ac* plane (b) of monoclinic ACM with the (001) and (002) faces indicated.

Figure 4.
View of the *ac*-plane of orthorhombic ACM with the (002) face indicated.

Figure 5. X-ray diffractogram of ACM deposited by sublimation on PBMA (a) and PMMA (b) (bottom) along with their simulated PXRD patterns of monoclinic ACM with no PO (top).

Nylon 6/9

Nylon 6/12

Nylon 11

Figure 6.
Chemical structures of Nylon 6/9, Nylon 6/12, and Nylon 11.

Table 1

Relative surface binding energies ($\Phi_{\text{BE(hkl)}}$, kcal/mol) of PO faces of ACM crystals interacting with PBMA and PMMA trimers estimated from docking simulations.

$\Delta(\Phi_{\text{BE}})$ (kcal/mol)	PBMA	PMMA
$\Phi_{\text{BE}(001)\text{monoclinic}}$	0.0	0.0
$\Phi_{\text{BE}(21-1)\text{monoclinic}}$	-0.9	6.4
$\Phi_{\text{BE}(020)\text{monoclinic}}$	-1.4	9.2
$\Phi_{\text{BE}(021)\text{monoclinic}}$	2.3	7.0
$\Phi_{\text{BE}(120)\text{monoclinic}}$	2.6	9.1
$\Phi_{\text{BE}(110)\text{monoclinic}}$	2.6	9.5
$\Phi_{\text{BE}(002)\text{monoclinic}}$	7.3	9.3
$\Phi_{\text{BE}(002)\text{orthorhombic}}$	9.4	14.7
$\Phi_{\text{BE}(121)\text{orthorhombic}}$	4.4	8.8
$\Phi_{\text{BE}(201)\text{orthorhombic}}$	4.0	8.0
$\Phi_{\text{BE}(212)\text{orthorhombic}}$	3.5	7.1
$\Phi_{\text{BE}(222)\text{orthorhombic}}$	3.2	7.7
$\Phi_{\text{BE}(221)\text{orthorhombic}}$	2.7	6.8
$\Phi_{\text{BE}(220)\text{orthorhombic}}$	6.6	12.5

Table 2

Summary of the major orientations observed by PXRD in ACM grown using Nylons as heteronucleants under different crystallization conditions.

Nylon	ethanol	acetonitrile	acetone	vacuum
6/9	{001} _{orthorhombic}	{001} _{monoclinic}	{001} _{monoclinic}	{001} _{monoclinic}
6/12	{001} _{orthorhombic}	{001} _{monoclinic}	{001} _{monoclinic}	{001} _{monoclinic}
11	{001} _{orthorhombic}	{001} _{monoclinic}	{001} _{monoclinic}	{001} _{monoclinic}