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Peering at a Buried Polymer-Crystal Interface: Probing Heterogeneous Nucleation by Sum Frequency Generation Vibrational Spectroscopy

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Abstract

Sum frequency generation vibrational spectroscopy (SFG-VS) has been applied to investigate the selective crystallization of two forms of acetaminophen (ACM) on polymer surfaces. To our knowledge this is the first account of SFG-VS being applied to study a polymer-crystal interface. SFG elucidates the molecular level interactions governing phase selection at this buried interface, providing insight to the process of polymer-induced heteronucleation (PIHn) in solution as well as from the vapor phase. ACM heteronucleates from supersaturated aqueous solution in the metastable orthorhombic crystal form, on poly(methyl methacrylate) (PMMA) surfaces, whereas the thermodynamically stable monoclinic crystal form is observed to form on poly(*n*-butyl methacrylate) (PBMA) surfaces. When the ACM crystals were grown by sublimation, only the monoclinic form was observed on both PMMA and PBMA. SFG-VS results indicate that hydrogen bonds are formed between PMMA C=O groups and the orthorhombic ACM crystals at the PMMA-ACM interface. At PBMA-monoclinic ACM interfaces, no hydrogen bond formation was observed. This research demonstrates that SFG-VS can be used to probe molecular interactions at the polymer-crystal interfaces. Understanding the interfacial molecular interactions will ultimately provide a rational basis to improve methods for polymorph discovery and selection based on heteronucleation on polymer surfaces.

Introduction

The formation of a crystal from a supersaturated solution requires the assembly of molecules to form a structured motif which, at a critical size, leads to nucleation; this early stage of self-assembly typically dictates the ultimate solid-state form.¹ Nucleation is generally a heterogeneous process, during which nuclei develop on a surface so that the entropic penalty associated with ordering can be offset by favorable enthalpic interactions at the interface. These assembly processes on a foreign surface can occur with different degrees of specificity ranging from non-specific adsorption to the oriented growth of crystals on the nucleating surface.² Appropriate choice of heterogeneous nucleation promoters can exercise control over crystal polymorphism by manipulating the nature of molecular recognition events occurring at the crystal-heteronucleant interface.

Recently, SFG-VS has emerged as a valuable analytical technique to examine molecular structures, and orientation distributions at interfaces with submonolayer sensitivity.^{3–17} By exploiting a second order nonlinear optical process which provides sensitivity to vibrational

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Supporting Information Available: Experimental preparation, Raman spectra, and SFG spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

modes taking place in non-centrosymmetric environments,^{3–17} SFG-VS offers the unique opportunity to unravel the interactions governing phase selection at the polymer-crystal interface during the process of polymer-induced heteronucleation (PIHn). PIHn has recently been established as a powerful screening technique for novel solid-form discovery of single and multicomponent composition^{18–20} in addition to demonstrating promise in metal-organic systems.²¹

ACM (Figure 1), a common analgesic and antipyretic drug which crystallizes in two stable forms,^{22,23} was utilized as the model compound in this study. The less thermodynamically stable orthorhombic form was shown to have better physical properties when compared to the pharmaceutically distributed monoclinic form.¹⁸ Therefore, the selective production of different ACM forms has been the subject of numerous investigations aimed at elucidating the properties of different ACM polymorphs and exploring their commercial viability. ACM heteronucleates from aqueous solution in the less thermodynamically stable crystal form, the orthorhombic form, on PMMA (Figure 1), whereas the monoclinic crystal form is observed on PBMA (Figure 1).¹⁸ Because the polymers employed are completely insoluble under these crystallization conditions, the differences in the polymorphs observed are a product of the unique and directional interfacial interactions between ACM and each heteronucleant surface. Revealing the differences in the SFG vibrational spectra collected from the interfaces between these two polymers and ACM crystals of different polymorphs should provide a better understanding of the molecular interactions occurring at each interface, as well as suggest a pathway for the selective formation of the metastable polymorph.

Experimental Section

Materials

Acetaminophen (ACM) was obtained from ICN Biomedicals Inc. (Irvine, CA) and was stored at room temperature. Deuterated polymer poly(methyl methacrylate) (PMMA) was purchased from Polymer Source Inc., (Montreal, Canada) and was stored at room temperature. Deuterated polymer poly(*n*-methyl methacrylate) (PBMA) was synthesized following a previously reported method.²⁴

Preparation of polymer thin films

All polymer samples were prepared by spin coating 2 w/w% polymer solutions onto optically clear right angle CaF₂ prisms (Altos Photonics, Bozeman, MT) at 2500 rpm on a Speedline Technologies Spin Coater. Thicknesses of both PMMA (Aldrich, MW 15,000) and PBMA (Scientific Polymer Products Inc.) thin films were approximately 100 nm.

Crystallizations from aqueous solution

The ACM crystals examined were grown from aqueous supersaturated solutions (17 mg/mL at 25 °C) by submerging the entire prism with the polymer film in the supersaturated solution overnight. Samples were left to dry in air prior to any measurement. Raman spectroscopy confirmed that the ACM formed orthorhombic crystals on the PMMA surface and monoclinic crystals on the PBMA surfaces when grown from solution (Supporting Information).

Crystallizations from vapor phase deposition

Powdered ACM (~200 mg) was added to a sublimation chamber. Polymer coated prisms 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 120 °C. After ~15 min, all ACM had sublimed from the bottom of the chamber. Raman spectroscopy confirmed that only monoclinic crystals formed on both

PMMA and PBMA surfaces when the ACM crystals were sublimed onto the polymer coated prisms.

Sum Frequency Generation Measurements

The SFG setup is a commercial system from Ekspla (Vilnius, Lithuania). The system is driven by a 20 ps 20 Hz Nd:YAG laser. A portion of the laser beam is frequency doubled to 532 nm and used for the visible beam in the SFG experiments. Another portion of the beam is tripled and passed to an Optical Parametric Generation/Optical Parametric Amplification stage. The tunable visible beam that is generated there is then sent to a Difference Frequency Generation stage with a portion of the fundamental 1064 nm beam to produce the tunable infrared beam that is used in the SFG experiment. The 532 nm beam and the tunable IR beam are mixed on the sample to produce SFG, which is then collected and sent through a computer controlled monochromator and detected by a PMT. The resolution of the system $\sim 5 \text{ cm}^{-1}$. We did not calibrate the absolute intensity of the SFG spectra collected from different days, because the focus of this research is to understanding the interfacial hydrogen bonding formation (or lack of) by observing the peak center shift.

Results and Discussions

Crystal formation in PIHn typically occurs on a polymer surface in contact with a supersaturated solution. Bulk polymer structure provides only limited insight into functionality displayed on the surface of a polymer and therefore to elucidate the interactions occurring at an interface with a polymer in contact with solution, structure at the solid-liquid interface must be determined. Previous reports^{25,26} on the surface chemical structure of PMMA and PBMA, indicate that the PMMA surface is dominated by ester methyl groups, orienting towards the surface normal in air. When PMMA is contacted with water, these ester methyl groups do not reorient. The PBMA surface in air is dominated by the side chain terminal methyl groups, tilting towards the surface normal with a broad distribution. In water, these methyl groups still dominate the PBMA surface, but reorient towards the surface with a much narrower orientation distribution. SFG-VS studies of PMMA and PBMA in the C=O stretching frequency region imply the presence of C=O groups on both PMMA and PBMA surfaces. By comparing the ratios of peak intensities in different polarization combinations the orientation of C=O functional groups can be determined.²⁷ The C=O orientation is similar on both surfaces in both air and water (Supporting Information).

SFG spectra of the crystal/polymer interfaces with crystals grown from solution and dried in air are presented in Figure 2. In the SFG spectra of the interface between orthorhombic ACM crystals grown on PMMA, two peaks are observed (Figure 2, A and B). The peak at $\sim 1730 \text{ cm}^{-1}$ originates from the unbound C=O of the PMMA, as established by the FTIR spectra of bulk PMMA and PBMA, which presents a single peak around 1730 cm^{-1} corresponding to the C=O stretch (Supporting Information). Raman vibrational spectroscopy confirms that ACM does not have a C=O stretch around 1730 cm^{-1} (Supporting Information). The peak at 1705 cm^{-1} is produced by the hydrogen bonded C=O of PMMA with ACM. This clearly shows hydrogen bonding occurs between the ACM crystals and the C=O group in the case of PMMA.

In the SFG spectra obtained for the monoclinic ACM grown on PBMA (Figure 2, C and D), two peaks are observed. Similar to the case of ACM crystals growth on PMMA, the weak peak at $\sim 1730 \text{ cm}^{-1}$ belongs to the free C=O in PBMA. A very distinct peak at 1650 cm^{-1} is observed which originates from the amide I stretch of the ACM crystals. The absence of a peak at $\sim 1705 \text{ cm}^{-1}$ provides evidence that no hydrogen bonding exists between the PBMA C=O groups in the case of the monoclinic crystals. The absence of amide I signal from the

orthorhombic ACM crystals grown on PMMA could be due to the orientation of the amide I transition moment in the orthorhombic crystals at the interface generating very little SFG signal, e.g., they may lie down at the interface. The differences in SFG spectra shown in Figure 2 imply that the ability of the ACM molecules in solution to hydrogen bond to the polymer C=O groups plays an important role in the polymorph selection process; this strong directional intermolecular interaction promotes the formation of the metastable form only in the case of PMMA.

In contrast to the above polymorph selection method, when the ACM crystals were grown by sublimation, only the monoclinic form was observed on both PMMA and PBMA (Supporting Information), indicating that molecular interactions at the polymer-ACM solution interface and the polymer-ACM vapor interface are different. The ACM crystals grown by sublimation display distinctive SFG vibrational spectra (Figure 3) when compared to those formed from solution (Figure 2). No discernable peak is observed at $\sim 1705\text{ cm}^{-1}$ which confirms the absence of hydrogen bonding between the polymer C=O groups and the ACM crystals for the sublimed samples. The ACM amide I signal around 1650 cm^{-1} is prominent for ACM crystals sublimed on both the PMMA and PBMA. This is a clear indication that the absence of solvent, in this case water, plays an important role in the phase selection process.

The contrasting phase selection behavior for PIHn of ACM in the presence or absence of solvent presents two possibilities for the mechanism leading to the phase selective nucleation of one polymorph versus the other: a reorientation of the polymer surface functionality or a role for solvent during crystallization. Determination of the C=O orientation on the PMMA and PBMA surfaces in air and in water by SFG-VS suggest that these surfaces are not remarkably different, which should not lead to substantial differences in the initial interactions between such surface C=O groups and ACM molecules in solution. In contrast, SFG-VS studies on the C-H stretching frequency region indicate reorientation of terminal methyl groups only in the case of PBMA. Possibly the terminal methyl groups dominating the PBMA surface interact favorably with the hydrophobic groups on ACM, leading to the steric effects which changes the surface C=O orientation to hinder the hydrogen bond formation between PBMA and ACM. For PMMA, the surface ester methyl groups would not have this steric effect, therefore the surface C=O groups can form hydrogen bonds with ACM, directing the formation of orthorhombic crystals in the case of PMMA.

Conclusions

In summary, this study highlights the ability of SFG to probe the distinct molecular interactions occurring at a solid-solid interface and demonstrates how the phase selection mechanism of PIHn is most likely determined by the different structures of surface dominating ester methyl groups on PMMA and ester butyl groups on PBMA which may affect interfacial interactions. Additionally, this study emphasizes the dependence of the polymorph selection process on both the polymer and the solvent media as it is possible to change solid-form in the presence of different solvents. Understanding the process of PIHn in the context of the observed interfacial molecular interactions will ultimately allow construction of an interface model with molecular level detail and therefore provide a rational basis to improve methods for polymorph discovery and selection based on heteronucleation on polymers.

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.

SFG spectra of polymer-ACM crystal interface with crystals grown from a supersaturated solution on: A) PMMA with PPP polarization combination, B) PMMA with SSP polarization combination C) PBMA with PPP polarization combination, D) PBMA with SSP polarization combination. (The polarization combinations are ordered sum frequency, visible, infrared.) The normalized IR absorbance of the PMMA and PBMA films are overlaid in blue and red respectively.

Figure 3.

SFG spectra of polymer-ACM crystal interface with crystal grown from sublimation A) PMMA with PPP polarization combination, B) PMMA with SSP polarization combination C) PBMA with PPP polarization combination, D) PBMA with SSP polarization combination. The normalized IR absorbance of the PMMA and PBMA films are overlaid in red and blue respectively.