Self-association during heterogeneous nucleation onto well-defined templates

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Abstract

We investigated the interplay between self-associates in solution and surface templating by studying the crystallization behavior of isonicotinamide (INA) and 2,6-dihydroxy benzoic acid (DHB) in the presence of self-assembled monolayers (SAM). The end group of the SAM as well as the hydrogen bonding capabilities of the solvent and self-association of INA and DHB were found to be important in polymorph crystallization on SAMs. In the case of INA in ethanol, both chain and dimer self-associates are present in the solution. In the absence of SAMs the polymorph form II (dimer structure) is the crystallization outcome. In ethanol the 4-mercaptopyridine and 4-mercaptobenzoic acid SAMs organize INA chain associates at the template surface and enable the crystallization of form I while the 16-mercaptohexadecanoic acid SAM results in the crystallization of form II . Raman spectroscopy suggests that molecular interactions between INA and the SAM are responsible for the formation of specific polymorphs. XRPD results in the identification of the orientation of the crystal on the surface that further verified the results obtained by Raman spectroscopy. In nitrobenzene and nitromethane INA associates in solution only as chains and crystallization results in the formation of form IV and form I, respectively (both chain forms). The crystals formed in the bulk solution and on SAMs were the same, which seems to indicate that the self-association in nitrobenzene and nitromethane are not influenced by the presence of templates. In the case of DHB in toluene and chloroform, all three SAMs nucleated only one type of polymorph (stable form 2). In the case of toluene the polymorphic outcome was stable form 2 instead of metastable form 1, which is favored in toluene in the absence of the SAMs. Again, Raman spectroscopy and XRPD suggest that DHB-SAM molecular interactions may be responsible for the formation of form 2.

Introduction

An industrial crystallization has to be carefully controlled in order to meet crystal product quality demands like crystal form, particle size distribution, crystal shape and purity.[1] A fundamental understanding of crystal nucleation is of major importance for the control and prediction of product quality from industrial crystallization processes.[2, 3] Polymorphism is the ability of a compound to self-assemble into different crystal structures.[4-6] Although many factors are known to influence the nature of the crystallized polymorph, for example supersaturation and temperature, a fundamental understanding of the mechanism is still lacking.[4, 7] Understanding the principles which influence the nature of the polymorph that crystallizes will improve the prediction and control of crystallization of desired polymorphs.[8-10]

To some extent polymorph control can be achieved by choosing a solvent that results in solute association related to the preferred polymorphic form.[8, 11] In solution different intermolecular interactions between like (solute-solute) and unlike (solute-solvent) molecules occur leading to the formation of different associates or building units.[8] The solute self-associates or building units will be a function of, among other factors, the solvent used.[8] The dominant building unit can be either a single molecule or differently associated molecules like dimers, tetramers and catemers. For example 2,6-dihydroxy benzoic acid (DHB) forms dimers in toluene and catemers in chloroform.[12] Crystallization from toluene leads to form 1 which is constructed of dimers while crystallization from chloroform leads to form 2 constructed of the catemer.[12] Isonicotinamide (INA) forms amide-pyridine heterosynthons (head-to-tail chains) in solvents like nitromethane and forms both amide-amide homosynthons (head-to-head dimers) and amide-pyridine heterosynthons (head-to-tail chains) in solvents like methanol.[13] This self-association in solution controls the polymorph crystallization by controlling the crystal building unit.[13]

It is also known that templates or organized substrates can be used to facilitate the formation of specific types of polymorphs.[14-16] Heterogeneous nucleation is the type of primary nucleation for which the nuclei are formed at surfaces such as dust particles, glass walls and stirrers.[17, 18] On an industrial scales these dust particles or small impurities are very difficult to remove. A more practical approach is to add effective particles or well-defined surfaces to control polymorph crystallization. Self-assembled monolayers (SAMs) have been used to control crystallization.[14, 17, 19-22] One type of SAM involves the use of thiol molecules assembled with a head group (thiol) bound to a substrate (gold), a chain or backbone and the free end group pointing outwards. The SAM surface can act as template for nucleation and crystal growth through functional group interactions and by providing a surface for the nucleation and growth of crystals.[14]

The interplay between template interaction and solution association is still not well understood. We chose SAMs with strong hydrogen bond acceptor and donor surface groups to favor specific molecular interactions between the solute and surface to enable the crystallization of polymorphs structurally related or unrelated to the associates in solution. The solution crystallization and template induced nucleation may provide an understanding of polymorph nucleation from solution and also the underlying surface chemistry that controls nucleation and growth.

Experimental

Materials. INA (isonicotinamide) and DHB (2,6-dihydroxy benzoic acid) with a purity of ≥99% and ≥99.5% respectively, were obtained from Sigma Aldrich. The solvents ethanol, nitromethane, nitrobenzene, chloroform and toluene were used as received and were of ACS reagent grade with a purity of ≥99.5%, 99+% and 99+% respectively. 4MP (4-mercaptopyridine), 4MBA (4-mercaptobenzoic acid) and MHDA (16-mercaptohexadecanoic acid) were purchased from Sigma Aldrich. Gold coated (100 nm thick coating of gold) glass substrates with a size of 25×120 mm were purchased from Evaporated Metal Films Corporation, New York and used as SAM substrate.

SAM preparation. Self-assembled monolayer (SAM) surfaces were prepared by immersing gold coated glass substrates in 10 mM solutions of 4MP, 4MBA, and MHDA in ethanol for 18 hours, following the SAM preparation procedure described by Yang et al.[14] After removing the substrates from solution, they

were rinsed with copious amounts of toluene and then carefully blow-dried with ultrahigh purity nitrogen.

Cooling Crystallization on immerged SAMs. During INA crystallization experiments using ethanol, four concentrations (70, 87, 93 and 96 mg/mL) were used. The solids were suspended in 10 mL of ethanol and complete dissolution was obtained after heating the solution up to 60 °C. The samples were then cooled to 40 °C with a cooling rate of 0.1 °C/min and the SAM was carefully placed into the solution in an almost vertical position to prevent any crystals forming in the bulk solution attaching to the SAM surface. The solution was further cooled to 10 °C with a cooling rate of 0.1 °C/min and crystallization occurred either on the SAM, in the bulk solution or both. The SAM was removed from the solution in order to investigate the connected crystals. The SAM was carefully washed with ethanol to avoid nucleation of other crystals due to evaporation of the adhering solution. In all cases force was needed to remove the crystals from the SAM surface. The crystals were further analyzed with Raman spectroscopy and XRPD. The crystals formed in the bulk solution were also collected and analyzed. The same procedure was followed for INA in nitromethane (2 to 10 mg/mL) and nitrobenzene (10 to 20 mg/mL) and DHB in chloroform (60 to 90 mg/mL) and toluene (30 to 45 mg/mL). The experiments were repeated three times for each solvent and concentration to check the reproducibility of polymorph formation. Every crystal that nucleated and grew on the SAM surface was analyzed by XRPD to determine their orientation with respect to the SAM.

The transformation of metastable to stable polymorphic forms of INA and DHBA were studied. A suspension of metastable form I of INA only very slowly transform to stable form II (>24 hours only trace of form II be seen) whereas form IV transforms to stable form II after 21 hours. In the case of DHBA the transformation from metastable to stable form takes more than 72 hours. The crystals produced from the cooling procedure above were quickly removed following their nucleation and growth, minimizing the possibility of any transformation.

Crystal-SAM interface

The Raman microscope (Kaiser Optical Systems, Inc.), equipped with a 785 nm exciting line using a 600 grooves/mm grating and a 100× microscope objective, was used to obtain a Raman spectrum of the crystal-SAM interface. This objective gives a working distance of 0.27 mm and spot size of ~5 μm. The spectra were collected from 100 to 4000 cm^{-1}. The SAM surface with the attached crystals was placed on a microscope slide and placed under the microscope. Manual focusing of Raman spectroscope was used to locate the interface position within the crystalline sample. The same sample was measured number of times to locate the surface. Once found, a Raman spectrum was then obtained using the Raman instrument. Longer exposure times (20 sec) were used to obtain Raman spectra of a decent quality. The spectrum of the interface either shows an additional peaks or peak shifts when compared to the pure solid forms. Raman spectra were obtained for samples of each of the pure polymorphs away from the interface for comparison. It is clear that the relevant Raman spectra of the interface regions are spectroscopically distinct from the bulk indicating that the shifts observed are likely due to surface interactions.

Crystal orientation on the SAM surface

Each crystal on the SAM surface was picked up very carefully, collected and analyzed using XRPD. Keeping track of the orientation of the crystals on the SAM, they were carefully removed from the SAM surfaces and each crystal was separately analyzed by XRPD to determine the crystal surface connecting with the SAM. The XRPD pattern of the crystals bound to the SAM showed preferred orientation of the crystal face of the compound with respect to the SAM surface. X-ray powder diffraction data were collected using a PANalytical X'Pert PRO Theta/Theta powder X-ray diffraction system with a Cu tube and X'Celerator high-speed detector. All the XRPD patterns were added as electronic supplementary information (ESI).

Results

First, we describe the experimentally determined self-association of INA and DHB in different solvents. Then we focus on the crystallization outcome of INA and DHB from different solvents and on a number of templates. Finally, we discuss the competition between self-association and templates during crystallization. Figure 1 shows the molecular structures of INA and DHB.

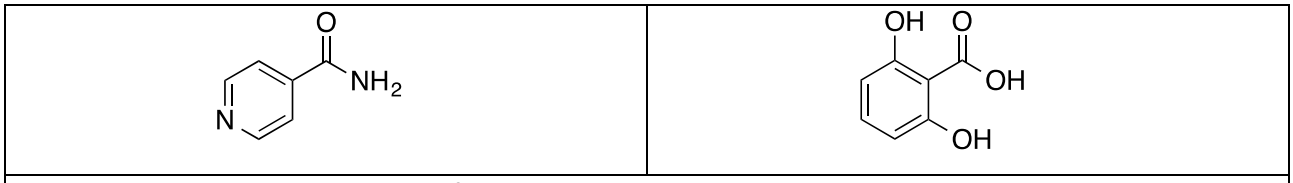


Figure 1: The molecular structures of INA and DHB.

1. Solvent dependent self-association of INA and DHB

The crystal structures of five polymorphs of INA have previously been reported in the literature (ESI).[23, 24] Form II is reported to be the most stable at room temperature. In this polymorph the amide group forms a homosynthon with the amide group of another INA, while the pyridine groups are not involved in hydrogen bonding. Forms I, III, IV and V consist of differently packed head-to-tail chains connected through heterosynthons of the amide and the pyridine group with subtle differences in the crystal structure between each polymorph.[23, 24]

Figure 2 shows Raman solution spectra of dissolved INA in different solvents. Similar to the solid phase Raman spectra, the pyridine region in the solution spectra is related to the pyridine group of INA being present in either a chain form (1002 cm^{-1}) or a non-chain form (994 cm^{-1}); the latter is then either a dimer or a single INA molecule, possibly associated with the solvent. A similar IR spectral analysis leads to information on the hydrogen bonding of the amide group of INA in solutions.[13] In ethanol, for instance, INA self-associates in both head-to-head amide group dimers and head-to-tail amide-pyridine chains while in nitrobenzene and nitromethane only chains are present.

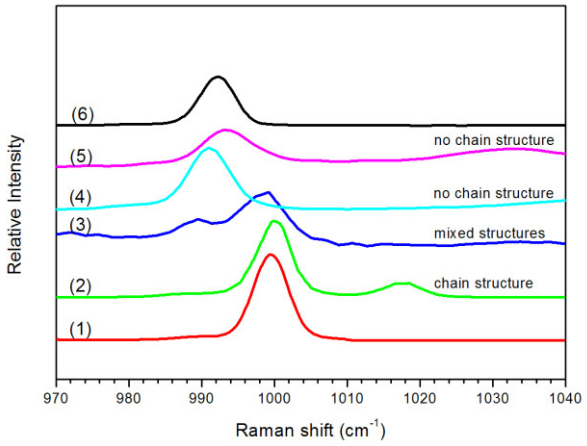


Figure 2: Raman spectra of isonicotinamide in different solvents and of solid samples. (1) Form I crystals; (2) In nitromethane; (3) In ethanol; (4) In acetone; (5) In chloroform (6) Form II crystals.[13]

Self-association of INA plays a key role in the crystallization outcome of INA.[13] For example, INA in ethanol self-associates into both dimers and chains. In this case, since different building units are present, the polymorphic outcome is determined by the competing processes of cluster formation of the different associates. In ethanol the dimer associates dominate and form the dimer structure form II.[13] Solvents like nitromethane and nitrobenzene enable the association of INA into chains leading to the formation of metastable forms I and form IV respectively. The form I and IV crystal structures both contain chains of INA.[13]

DHB also shows solvent dependent self-association.[25] DHB forms hydrogen bonded catemers in chloroform and dimers in toluene.[12] Crystallization of DHB from chloroform solutions at low supersaturations results in the most stable form 2 consisting of catemers. Crystallization of DHB from toluene always yields the metastable form 1 consisting of dimers (ESI).[12]

2. Crystallization of INA and DHB in the presence of SAM templates

The SAM components 4MP, 4MBA and MHDA (ESI) consist of a thiol group which connects to the gold surface, a backbone and either a pyridine or a carboxylic acid group that defines the character of the SAM surface onto which crystals would form. The pyridine group on the SAM serves as an hydrogen bonds acceptor while the carboxyl group on SAM can donate and accept hydrogen bonds via the acidic OH group and the C=O group.[14]

2.1 Isonicotinamide (INA)

Upon cooling crystallization of INA from ethanol in the presence of the 4MBA SAM, two different types of crystals were observed in the vials (Figure 3). The first type crystallized on the SAM while the other crystallized in the bulk solution. Analysis of crystals with Raman spectroscopy and XRPD showed that the

bulk solution crystals were form II, as expected. However, the crystals formed on the SAM were identified as form I crystals (Table 1).

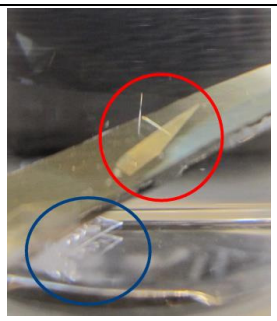


Figure 3: Cooling crystallization of INA from ethanol in the presence of the 4MBA SAM. The tilted surface contains the SAM onto the gold-coated surface. The INA form I crystals on the 4MBA SAM are marked with a red circle while INA form II crystals in the bulk solution are marked with a blue circle.

Similarly, upon cooling crystallization from ethanol the crystals obtained on the 4MP SAM were form I, whereas form II was crystallized in the bulk of the solution. The crystals obtained on the MHDA SAM surface were form II, the same as obtained from the bulk solution. Thus, although the 4MBA SAM and MHDA SAM have the same functionalized surface of carboxylic acids, two different polymorphs were obtained (Table 1).

Upon cooling crystallization of INA from nitrobenzene, crystals formed on the 4MP SAM. These crystals were form IV, the same form as crystallized in the bulk solution. In this solvent no crystals were obtained on the 4MBA and MHDA SAM while form IV crystals were formed in the bulk.

Upon cooling crystallization of INA from nitromethane, form I was crystallized on 4MP and 4MBA SAMs as well as in bulk solution. There were no crystals formed on the MHDA SAM as the form I crystals were only formed in the bulk solution. See Table 1 for a summary of the results.

Table 1: Polymorphic outcomes for cooling crystallization of INA and DHB from different solvents in the presence of 4MP, 4MBA and MHDA SAMs. The dashes indicate experiments without any crystal formation on the SAM. The table also shows experimentally derived solution associates of INA and DHB found in previous studies.[13, 25]

Compound	Solvent	Self-Association	Form in Bulk	SAM component	Form on SAM	Crystal-SAM interface	Connecting crystal faces on SAM
INA	Ethanol	Dimer + Chain	Dimer (Form II)	4MP (Pyridine)	Form I (Chain)	NH_2 of INA-Pyridine of 4MP	(0 2 0)
			Dimer (Form II)	4MBA (Ar-COOH)	Form I (Chain)	i) NH_2 of INA-CO of 4MBA and ii) INA CO-OH of 4MBA	(4 0 -2)
			Dimer (Form II)	MHDA ($C_{16}H_{32}COOH$)	Form II (Dimer)	pyridine of INA-COOH of MHDA	(1 0 0) and (4 1 0)

INA	Nitrobenzene	Chain	Chain (Form IV)	4MP (Pyridine)	Form IV (Chain)	NH_2 of INA-Pyridine of 4MP	(1 0 0) and (0 0 2)
			Chain (Form IV)	4MBA (Ar-COOH)	-	-	-
			Chain (Form IV)	MHDA ($C_{16}H_{32}COOH$)	-	-	-
INA	Nitromethane	Chain	Chain (Form I)	4MP Pyridine	Form I (Chain)	NH_2 of INA-Pyridine of 4MP	-
			Chain (Form I)	4MBA (Ar-COOH)	Form I (Chain)	NH_2 of INA-CO of 4MBA	-
			Chain (Form I)	MHDA ($C_{16}H_{32}COOH$)	-	None	-
DHB	Chloroform	Catemers	Catemer (Form 2)	4MP Pyridine	Form 2 (Catemer)	OH of DHB-Pyridine of 4MP	(2 1 0)
			Catemer (Form 2)	4MBA (Ar-COOH)	Form 2 (Catemer)	i) OH of DHB-CO of 4MBA and ii) CO of DHB-OH of 4MBA	(2 1 0)
			Catemer (Form 2)	MHDA ($C_{16}H_{32}COOH$)	Form 2 (Catemer)	i) OH of DHB-CO of MHDA and ii) CO of DHB-OH of MHDA	(2 1 0)
DHB	Toluene	Dimer	-	4MP Pyridine	Form 2 (Catemer)	i) OH of DHB-pyridine of 4MP	(2 1 0)
			Dimer (Form 1)	4MBA (Ar-COOH)	Form 2 (Catemer)	i) OH of DHB-CO of 4MBA and ii) CO of DHB-OH of 4MBA	(2 1 0)
			-	MHDA ($C_{16}H_{32}COOH$)	Form 2 (Catemer)	i) OH of DHB-CO of MHDA and ii) CO of DHB-OH of MHDA	(2 1 0)

With aid of Raman spectroscopy coupled to a microscope, Raman spectra of the SAM-crystal interfaces could be obtained. For INA, the region of the NH_2 and CO stretching vibrations of (respectively 3030 -3090 cm^{-1} and 1580 -1680 cm^{-1}) as well as the ring breathing region of INA pyridine (950 -1050 cm^{-1}) reflect how the crystals are molecularly connected to the SAM surface.[13] The Raman spectra of the SAM-crystal interfaces are compared with that of INA form I and form II in Figure 4 and Figure 6 for INA crystals on the 4MP, 4MBA and MHDA SAMs. Analysis of XRPD data of the crystals bound to the SAM showed preferred orientation of the crystal face of the compound with respect to the SAM surface, which further verified the results obtained by Raman spectroscopy.

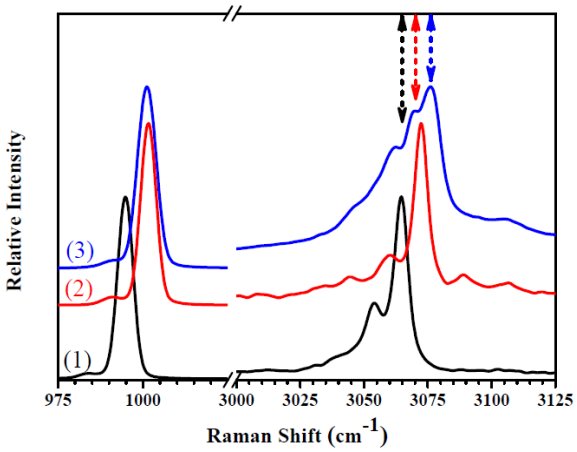


Figure 4: Raman spectra of INA crystals showing the NH_2 stretching vibrations (3000-3125 cm^{-1}) and pyridine ring breathing mode (975 -1100 cm^{-1}) vibrations. (1) Pure form II, (2) Pure form I, (3) interface region of form I on the 4MP surface in ethanol. The arrow indicates the position of an additional peak in (3). This additional peak is positioned at higher wavenumbers compared to pure form I reflecting interactions between the pyridine of the 4MP SAM and the amide group of INA.

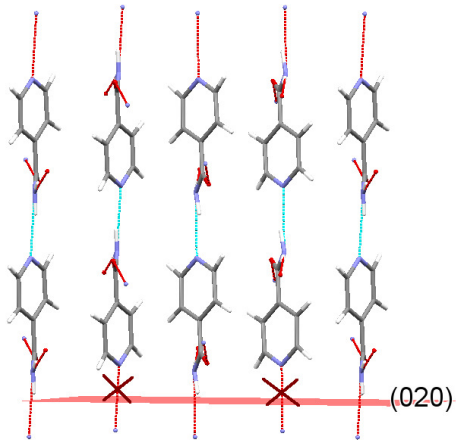


Figure 5: The 4MP SAM and the INA crystal grown from ethanol are connected through the (0 2 0) face of INA form I. The NH_2 group of INA is pointing towards the pyridine group of the 4MP SAM. The red crosses indicate molecules in an orientation without hydrogen bonding with the template surface.

The Raman spectrum of the template-crystal interface for the INA form I crystal formed on the 4MP SAM in ethanol shows that the pyridine ring breathing mode (990-1010 cm^{-1}) has the same peak position as that of INA form I (figure 4). Compared to INA form I and form II the NH_2 stretching vibration region (3000-3125 cm^{-1}) shows an additional peak at slightly higher wavenumber for the interface spectrum. An explanation for this extra peak is the occurrence of additional interactions compared to the internal crystal. One such interaction that would create an additional peak is hydrogen bonding between the pyridine group of the 4MP SAM and the NH_2 group of INA. The shift to the higher wavenumber could be because the pyridine N^+ stretching vibrations of 4MP are between 3300 to 1900 cm^{-1}. The NH_2 group of INA is a strong hydrogen bond donor which can interact with pyridine of 4MP which is strong hydrogen bond acceptor. We further analyzed the same crystals using XRPD in order to find out the crystal orientation on the surface. In the case of INA on the 4MP surface it was found that the interface is the (0 2 0) face.

Figure 5 shows the (0 2 0) face with the NH_2 group of INA points towards the surface. This is consistent with our hypothesis from the Raman spectroscopy results that hydrogen bonding interactions between the pyridine group on the SAM surface and INA amide groups play a key role in the formation of INA form I on the 4MP SAM.

In the case of the interface between form I grown from ethanol and the 4MBA SAM, the NH_2 stretching vibrations of INA between 3040-3100 cm^{-1} show an additional peak as compared to pure form I (Figure 6). An explanation for this extra peak at 3069 cm^{-1} is the occurrence of additional interactions at the interface compared to the internal crystal. This interaction could include hydrogen bonding between the CO group (1700 cm^{-1}) of the 4MBA SAM and the NH_2 group of INA. The peak at 1635 cm^{-1} in the carbonyl region also shows a shift to lower wavenumbers. This shift can be explained by the formation of hydrogen bonding interactions between the carbonyl group of INA (hydrogen bond acceptor) with the hydroxyl group (hydrogen bond acceptor/donor) of the carboxylic acid of the 4MBA SAM.

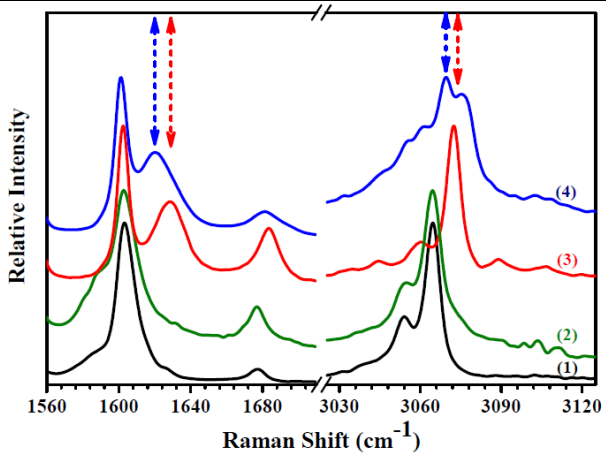


Figure 6: Raman spectra of INA crystals showing the NH_2 stretching vibrations (3000-3125 cm^{-1}) and the CO stretching (1550 -1650 cm^{-1}) vibrations. (1) Pure form II, (2) interface region of form II grown from ethanol on the MHDA SAM, (3) pure form I, and (4) interface region of form I grown from ethanol on the 4MBA SAM. The arrows indicates the position of an extra peak at lower wavenumber other than pure form I and a peak shift.

XRPD shows that peculiarly the crystal-SAM interface is the relatively high index face (4 0 -2) of INA form I. Figure 7a shows the (4 0 -2) face with the NH_2 and CO groups of two different molecules of INA pointing towards the surface. This suggests a surface interaction involving a CO group (hydrogen bond acceptor) of 4MBA with an NH_2 group of INA (hydrogen bond donor) and an OH group of 4MBA (hydrogen bond acceptor/donor) with a CO group of INA (hydrogen bond acceptor), respectively, which is in accordance with the interpretation of the Raman spectrum.

In case of INA form II crystallized from ethanol on the MHDA SAM, the plate-like crystals grew laterally and flat on the SAM. Figure 6 shows the Raman spectrum of the template-crystal interface, which is similar to that of INA form II. The Raman spectrum of the template-crystal interface for the INA form II crystal formed on the MHDA SAM in ethanol shows that the carbonyl region (1560-1700 cm^{-1}) and NH_2 stretching region (3030-3090 cm^{-1}) has the same peak position as that of INA form II (Figure 6). As established with XRPD analysis the (1 0 0) and (4 1 0) faces of INA is the interface between the MHDA SAM and the INA form II crystal (Figure 6b).

Figure 7 (b) indicates that the amide group and pyridine groups of INA are pointing towards the carboxylic acid group of MHDA. While the results obtained by Raman spectroscopy do not indicate a significant interaction between the amide group of INA with the carboxylic group of MHDA SAM, XRPD suggests a surface interaction involving a pyridine group (hydrogen bond acceptor) of INA with an OH group of 4MBA (hydrogen bond acceptor/donor) may be present. The lack of a change in Raman spectral features indicates that this may be a relatively weak interaction compared to the results discussed above for INA with the 4MP and 4MBA SAMs.

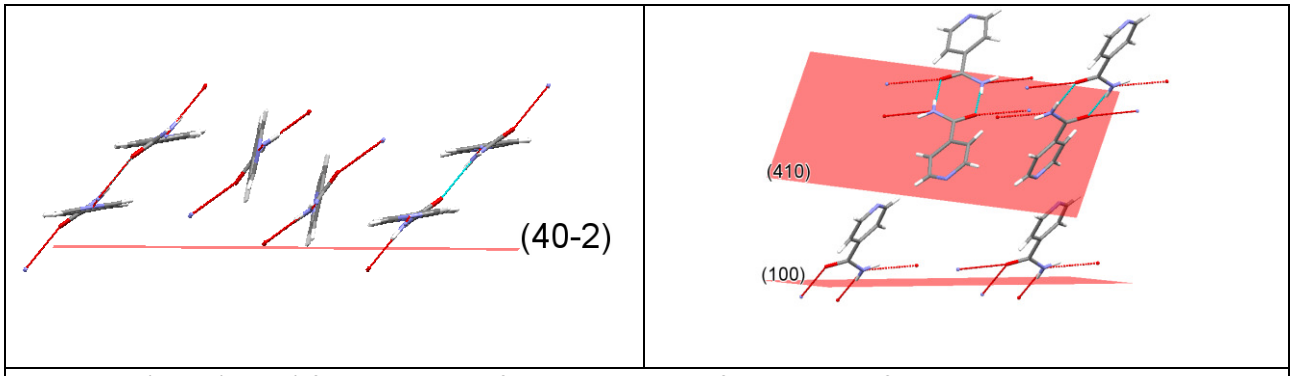


Figure 7: a) The (4 0 -2) face is the interface between INA form I grown from ethanol on the 4MBA SAM. The NH_2 and CO groups of some molecules are pointing towards the SAM surface. b) The (1 0 0) and (4 1 0) faces are the interface between INA form II grown from ethanol on the MHDA SAM. The amide group of INA ($-CONH_2$) is pointing towards the template surface.

2.2. 2,6-dihydroxy benzoic acid (DHB)

When DHB is crystallized from chloroform in the presence of 4MP, 4MBA and MHDA SAMs, only form 2 crystals were observed in the vials. Analysis with Raman spectroscopy and XRPD showed that the bulk solution crystals were form 2 (table 1).

Upon cooling crystallization of DHB from toluene in the presence of the 4MBA SAM, two different types of crystals were observed in the vials. The first type crystallized on the SAM while the other crystallized in the bulk solution. Analysis with Raman spectroscopy and XRPD showed that the bulk solution crystals were metastable form 1, as expected. However, the crystals formed on the SAM were identified as stable form 2 crystals (Table 1). Similarly, crystals obtained on the 4MP and MHDA SAM upon cooling crystallization from toluene were form 2, although there were no crystals in the bulk of the same solution.

Figure 8 shows the CO stretching region (1650 -1700 cm^{-1}) of the Raman spectra of the crystal-SAM interfaces. In the case of DHB form 2 grown from toluene on the 4MP SAM the Raman spectrum shows shifts in this region (Figure 8). This shift can be explained by the occurrence of hydrogen bonding between the hydrogen bond accepting pyridine group of the template surface and the hydrogen bond donating OH-group of DHB. The Raman spectra of the crystal-SAM interfaces in the case of DHB form 2 grown from toluene on the 4MBA and MHDA SAMs show no substantial peak shifts. This might indicate

that the carboxylic acid groups of DHB and of the template surface interact in a similar way as the carboxylic acid groups in the crystal structure of DHB.

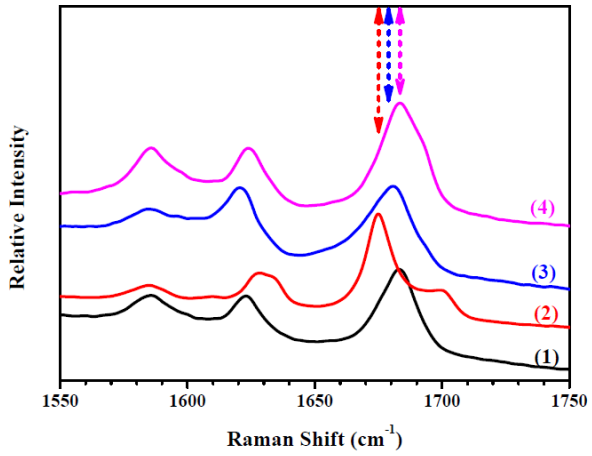


Figure 8: Raman spectra of the CO stretching vibration region of DHB. (1) Pure form 2, (2) the interface region of a DHB form 2 crystal grown from toluene on the 4MP SAM, (3) the interface region of a DHB form 2 crystal grown from toluene on the 4MBA surface, and (4) the interface region of a DHB form 2 crystal grown from toluene on the MHDA surface. Arrows are drawn in order to compare the shift of DHB due to surface interactions.

XRPD show that peculiarly the crystal-SAM interface in toluene and chloroform are the relatively high index face (2 1 0) of DHB form 2. From the Raman and XRPD results we can conclude that at the interface the OH and CO groups of the DHB molecules point towards the surface and interact with 4MP, 4MBA and MHDA. For instance, the OH of DHB interacts with the pyridine of 4MP while both the CO and OH of DHB interacts with COOH group of 4MBA and MHDA SAM (Figure 9).

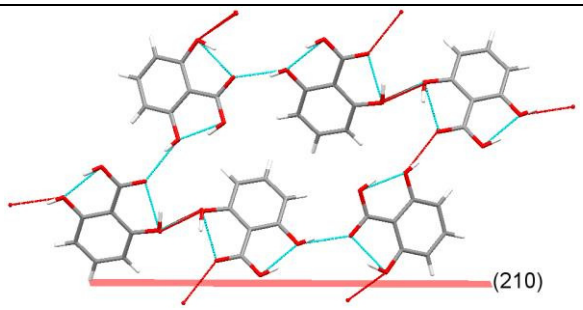
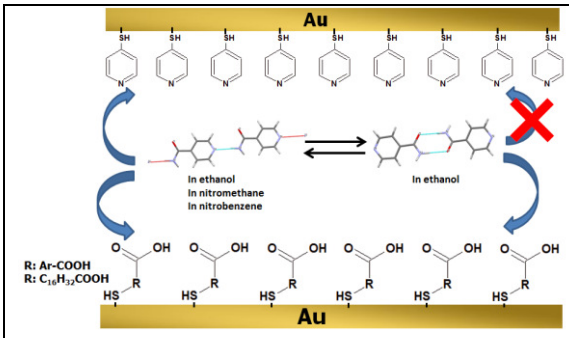


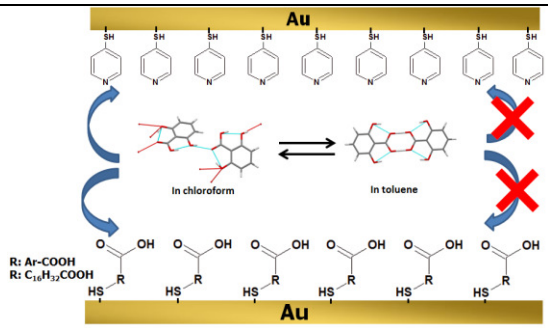
Figure 9: The (2 1 0) face of DHB as the interface on the SAM. The OH group of DHB interacts with the 4MP SAM surface while in the case of 4MBA and MHDA SAMs both CO and OH groups are responsible for the formation of catemers of DHB.

Discussion

In this paper we investigate the effect of both solution self-association and templates on polymorph crystallization behavior. If we assume that the polymorphic outcome is determined in the heterogeneous nucleation stage of the process we can identify a number of factors that may influence this. First, solutes associate to create building units in solution. Second, molecular interactions between associated solute and template can create additional specific pre-arrangement at the template-solution interface of these building units, templating the nucleation of a specific polymorph. This template can stimulate either the already abundantly present associates or associates present in minor amounts into a specific organization leading to polymorphs that are otherwise not able to be obtained.



a)



b)

Figure 10: Schematic of the interplay between self-association of a) INA and template b) DHB and template. The arrows indicate their relation to the final polymorphic outcome from experiments.

INA in ethanol is an interesting case since in this solvent the dimer and chain building units are both present to form the dimer (form II) and chain polymorphic forms (other forms). In the absence of deliberately added templates polymorph form II is the crystallization outcome. Providing the right template would organize INA chain associates at the template surface and enable the nucleation of an alternative form, for instance form I (Figure 10). This is exactly what happens in case of the 4MP and the 4MBA templates.

Interestingly, crystallization of INA from ethanol in the presence of the MHDA template results in form II, the dimer form. Apparently this template does not sufficiently promote the chain arrangement on its surface although it does have the same functional group, the carboxylic acid, as the 4MBA template. In nitrobenzene and nitromethane INA associates as chains and we could not find evidence of the presence of dimers in these solutions. Crystallization of INA from nitromethane in the presence of the 4MP and 4MBA templates results in form I, while in case of nitrobenzene in the presence of 4MP results in form IV (both chain forms). Crystallization of INA from nitromethane and nitrobenzene in the presence of the MHDA and 4MBA template respectively, did not result in crystals on the template. This indicates that the chain associates do not seem to organize on the MHDA and 4MBA template sufficiently to cause template nucleation of a chain form of INA. The crystals formed in the bulk solution were INA form IV and the self-association in nitrobenzene was hard to overcome.

DHB is a similar case. Dimers do not interact with all templates used. Apparently, although catemer associates are undetectable in toluene solutions, they are present in sufficient concentrations or form in the presence of suitable surface interactions enabling their organization on the templates to form the catemer form 2.

The other factor that may influence the heterogeneous nucleation of polymorphic compounds is the balance of the interfacial energies of the crystal-solution (γ_{CS}), crystal-template (γ_{CT}) and solution-template (γ_{ST}) interfaces which might promote the formation of specific crystalline forms as the crystals on the SAM have a very specific orientation. The rather high Miller indices of the faces connected to the SAMs might indicate that the nucleation process is influenced by interfacial energies while molecular interactions might be less important. For example, the (4 0 -2) face of INA form I grows on the 4MBA surface and the (2 1 0) face of DHB form 2 grows on 4MP, 4MBA and MHDA surfaces (ESI).

Another possibility is that the template contains stacking faults which provide additional positions on the surface that energetically favor heterogeneous nucleation of specific polymorphs.[26, 27] However, all of our results appear to show that polymorph nucleation is likely due to molecular interactions or interfacial energies.

Conclusions

Solvents have a large effect on the kind of associates present in solution. For instance, INA is present as chains in the solvents nitrobenzene and nitromethane. These building units have a significant influence on the polymorphic outcome of crystallization. INA, for instance, crystallizes as a form containing chains from nitrobenzene. Additionally, many of the used template surfaces are effective in promoting crystallization; some even promote the crystallization of a different polymorph.

Understanding solution self-association offers the ability to develop a more fundamental understanding of the heterogeneous nucleation process in terms of the interplay between association and templates. The interfacial energies as well as the molecular interactions between solute and SAM play an important role during polymorph nucleation of INA. The type of end group of the SAMs as well as the hydrogen bonding capabilities of solvent and self-association of INA are important for polymorph nucleation. If both chain and dimer self-associates of INA are present in the solution, it is possible to provide surfaces that induce crystallization of forms that are related to these self-associates. However, the templates are not able to crystallize polymorphs containing dimer association motifs unless these are present in solution. The crystallized polymorphs in all cases arises from matching the hydrogen bond donor or acceptor sites of INA or DHB with complementary sites on the SAM, suggesting an approach for polymorph control within a given solvent system. Further systematic analysis of the association processes in solutions and the interplay with well-defined templates would be beneficial in the development of polymorph control, discovery and preparation within crystallization processes.

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Electronic supplementary information (ESI) available:

Electronic supplementary information contains INA crystal structure motifs, XRPD patterns of polymorphs of INA and DHB. This information is available free of charge via the Internet at http://pubs.acs.org/.

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