UNIVERSITY OF LATVIA

Summary of Doctoral Thesis

Aina Semjonova

STUDY OF POLYMORPHISM CONTROL OF ORGANIC SUBSTANCES USING CRYSTALLIZATION ADDITIVES

Riga 2024

UNIVERSITY OF LATVIA

FACULTY OF CHEMISTRY

Aina Semjonova

STUDY OF POLYMORPHISM CONTROL OF ORGANIC SUBSTANCES USING CRYSTALLIZATION ADDITIVES

SUMMARY OF THE DOCTORAL THESIS

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ABSTRACT

Crystallization of several model compounds, namely 2,6-dimethoxybenzoic acid, 2,6-dimethoxyphenylboronic acid and isonicotinamide, were studied in the thesis. The model compounds were chosen based on their ability to form polymorphs with different hydrogen bonding synthons, i.e., structures containing hydrogen bonded dimers and chains, in the crystallization. The formation of different crystalline phases of these model compounds in crystallisation from different solvents with different crystallization methods has been studied. The obtained crystalline phases were characterised by X-ray diffraction and thermal analysis. For the most stable polymorphs the solubility and relative thermodynamic stability were also determined. Crystallization was performed by testing the effect of different types of crystallization additives – polymers, surfactants, and structurally similar compounds, on the polymorphic outcome. The effect of crystallization additives on the solubility and relative stability of the most stable polymorphs was also investigated. Crystal structures of four new phases of the studied compounds were determined from powder and single crystal X-ray diffraction. Crystallographic and computational analysis of all the relevant crystal structures of the model compounds were performed to provide a possible mechanism for the observed control of the crystallization polymorphic outcome by the most efficient crystallization additives.

Keywords: polymorphism, crystallization, crystallization additives, crystal structure analysis, powder X-ray diffraction, thermal analysis.

TABLE OF CONTENTS

ABBREVIATIONS

AA	acetic acid
API	active pharmaceutical ingredient
BA	butyric acid
BFDH	Bravais–Friedel–Donnay–Harker
Btriol	benzene-1,2,3-triol
CSD	Cambridge Structural Database
CSP	crystal structure prediction
DSC	differential scanning calorimetry
FA	formic acid
FAM	formamide
FIM	full interaction map
INA	isonicotinamide
IPA	isopropanol
HPC	hydroxypropyl cellulose
MPBA	2,6-dimethoxyphenylboronic acid
MD	molecular dynamic
NA	nicotinic acid
ND	naphthalene-1,5-diol
OGP	octyl β-D-glucopyranoside
PA	propionic acid
PEG	polyethylene glycol
PhGlu	phloroglucinol
Poly80	polysorbate 80
PXRD	powder X-ray diffraction
SAM	self-assembled monolayers
SCXRD	single crystal X-ray diffraction
SMPT	solvent-mediated phase transition
Span 20	sorbitan laurate
$S_{solvent}$	solvate
TFE	2,2,2-trifluoroethanol
TG	thermogravimetry
THF	tetrahydrofuran
Tween 20	polysorbate 20
2PA	2-picolinic acid
4CPBA	4-carboxyphenylboronic acid
5OH2NBA	5-hydroxy-2-nitrobenzoic acid
2,6MeOBA	2,6-dimethoxybenzoic acid

INTRODUCTION

The vast majority of active pharmaceutical ingredients (APIs) can crystallize in different crystalline forms.[1] In the pharmaceutical manufacturing the crystalline form obtained must meet the reference requirements, so the control of the obtained crystalline form is a mandatory requirement.[2] Often a mixture of different forms is obtained in a crystallization from solution,[3] which can further affect solubility,[4] bioavailability[5] or other physical properties of the API. Such undesired formation of polymorph mixtures has been observed in crystallization of multiple APIs.[3] Moreover, more than one polymorph can often be obtained under very similar conditions,[6] which does not guarantee selectivity in the crystallization and does not ensure repeatability, thus does not meet the requirements of the industry.

In the pharmaceutical production, it is safer to choose the most stable polymorphs for the finished dosage form, as it has the lowest energy, and thus is stable at all stages of the production. However, if the solubility of the compound is low, the fact that the most stable form has the lowest solubility can cause problems. For this reason, sometimes metastable polymorphs are preferred because of their better solubility.[7] Alternatively, they can be selected because the more stable polymorphs are patent protected.[8] In the process of obtaining a metastable polymorph, the thermodynamically stable polymorph is often formed as an impurity.[3] In such cases it is practically impossible to separate them or convert the mixture into the required polymorph, moreover, during storage a phase transition to the most stable polymorph is promoted by the presence of this phase in the mixture.[6] For the reasons mentioned above, it is necessary to optimize and control the processes of crystallization, production and storage of the finished product.[9] One of the options for ensuring that a pure polymorph is obtained in the crystallization is the use of additives.[10]

The control of the crystallization process using additives is currently still empirical.[10] Employing the available computational description of the possible interactions between API molecules as well as the conformation energy penalty, it is already possible to predict what are the most stable crystal structures of an API using crystal structure prediction (CSP) technique. However, currently there are no tools that would allow determining the likelihood of crystallization of a crystal form with a given crystal structure, particularly if the crystal form outcome depends on the crystallization conditions. Moreover, there is neither a general method that would allow predicting the polymorphic outcome of the crystallization from pure solvents, nor approach for evaluating how any particular additive would alter it. Therefore, for each API, a selective method of obtaining a particular crystalline form is being developed in long-term experimental studies.[11] To achieve ability to design additive controlled crystallization of particular crystalline form, a molecular level understanding

of the crystallization process and the role of the additive in it is required.[10] The associates present in solution sometimes can be lined to the resulting polymorph,[12] but it has also been shown that in other cases they do not affect the crystallization outcome.[13] In the scientific literature, information on the use of additives (such as Langmuir monolayers[14] and self-assembled monolayers (SAM)[15]) to control the crystallization process can be found for several APIs and model substances,[16] but often the additives are expensive or impossible to separate from the API crystals. Moreover, they often do not ensure selective crystallization of one desired form, but only promote its formation. Due to the complexity of the factors determining the polymorphic outcome, even nowadays computational calculations does not provide a clear approach for finding a crystallization procedure to obtain a selected crystal form. There is also no clearly confirmed approach for performing MD simulations which would be able to determine the crystal structure obtained in the crystallization from solution.

The **aim** of the doctoral thesis is to gain an understanding of the possible mechanism of crystallization in the presence of additives, which could be applied to control the crystallization polymorphic outcome of APIs. The following **tasks** were set to achieve the goal:

1. To explore the crystallization polymorphic outcome of the model substances 2,6-dimethoxybenzoic acid, 2,6-dimethoxyphenylboronic acid and isonicotinamide using different crystallization approaches, conditions and solvents;
2. To characterize the newly obtained crystalline forms with X-ray diffraction and thermal analysis and determine their crystal structure using single crystal or powder X-ray diffraction data;
3. To explore the effect of various types of crystallization additives on the crystallization polymorphic outcome of the model substances;
4. To identify the additives potentially providing ability to selectively affect the crystallization polymorphic outcome and perform experiments to evaluate the effect of conditions and other factors on the polymorphic outcome of the crystallization in presence of these additives;
5. To determine the effect of the selected additives on the solubility and thermodynamic stability of the most stable polymorphs of model compounds;
6. To perform crystallographic and computational analysis of the crystal structures of the obtained solid phases to provide a possible mechanism of the crystallization in the presence of the additives.

Scientific Novelty and Practical Significance

- This research contributes to the development of an additive assisted crystallization method allowing use of cost-effective crystallization additives (SAM costs can exceed several hundred euros per laboratory-scale crystallisation experiment, whereas the substances used in this study cost less than a ten

euros per gram) that are either easily separable or can be included in the dosage forms, such as surfactants and polymers.

- Part of the results of the research are knowledge about the factors that ensure selective crystallization, including additives providing control of the crystallization outcome. These can be further used in the development of a general guidelines or model of crystallization process control.
- The use of crystallographic analysis and theoretical calculations provided information on the differences between the crystal forms which allowed to propose a mechanism explaining the additive assisted change of the polymorphic outcome of crystallization. Additionally, combination of theoretical calculations and experimental results contributed to the understanding of the interactions at the molecular level that overall determine the crystallization outcome.
- The crystallization control method developed employing this knowledge has potential to be used in the pharmaceutical industry to control the crystallization of various structurally similar APIs, for example, APIs corresponding to low molecular weight benzoic acids, which form polymorphs containing hydrogen bond dimers and chains – similar hydrogen bonded motifs to those formed by the studied compounds.

RESULTS PUBLISHED

Publications

1. **Semjonova, A.,** Bērziņš, A. Controlling the Polymorphic Outcome of 2,6-Dimethoxybenzoic Acid Crystallization Using Additives. *Crystals,* **2022**, *12*, 1161. (IF_{2022} = 2.67)
   A. Semjonova carried out 100 % of the experimental work, contributed to writing the article (80%), prepared the experimental results according to the journal guidelines, as well as prepared the answers to the questions and remarks given by reviewers.
2. **Semjonova, A.,** Bērziņš, A. Surfactant Provided Control of Crystallization Polymorphic Outcome and Stabilization of Metastable Polymorphs of 2,6-Dimethoxyphenylboronic Acid. *Crystals*, **2022**, *12*, 1738. (IF_{2022} = 2.67)
   A. Semjonova carried out 100 % of the experimental work, contributed to writing the article (80%), prepared the experimental results according to the journal guidelines, as well as prepared the answers to the questions and remarks given by reviewers.
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   A. Semjonova carried out 100 % of the experimental work, contributed to writing the article (80%), prepared the experimental results according to the journal guidelines, as well as prepared the answers to the questions and remarks given by reviewers.
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- **Semjonova, A.**; Bērziņš, A. Influence of Crystallization Additives on Morphology of Selected Benzoic Acids – a Molecular Dynamics (MD) Simulation Study. *Key Engineering Materials*, **2021**, 903, 22–27.

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1. THEORETICAL BACKGROUND

1.1. Polymorphism of active pharmaceutical ingredients

Polymorphism is the ability of a substances to crystallize in different crystal structures (see Figure 1.1).[9] Polymorphs have identical chemical composition but differ by the molecule arrangement or conformation in the crystal structure. Solvate structure additionally contain stoichiometric or variable amounts of a solvent. Solvates containing water are named hydrates. Co-crystals are composed of two or more different non-ionized molecules in the same crystal structure in stoichiometric ratio, while the molecules in salts are ionized.[17] Solids with different crystal structures often have different physical properties, such as solubility,[4] dissolution rate,[18] stability[19] and bioavailability.[20] Therefore, crystal engineering opens new opportunities to obtain APIs with improved physicochemical properties.[21] Solvates and co-crystals often have better solubility and dissolution rate than phases formed by pure API and, therefore, increase bioavailability and drug efficacy,[22] synergistic effect and lower the necessary drug dose,[21] or just have more optimal properties for the manufacturing

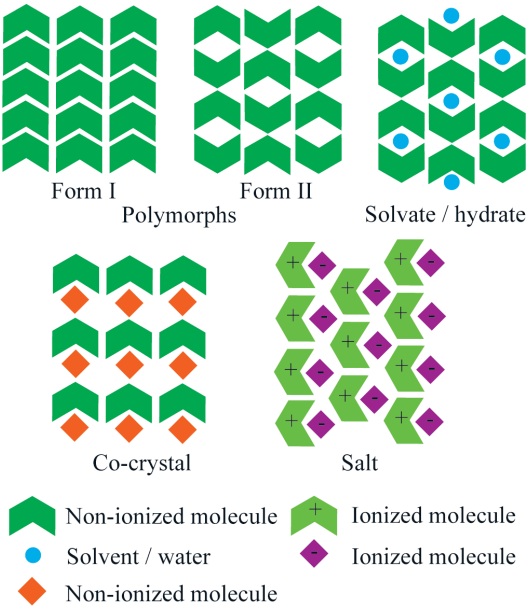

Figure 1.1. **Schematic representation of different types of phases formed by active pharmaceutical ingredients**

processes.[23] Change of the crystal form can also enhance the chemical stability of API.[24]

Polymorphic forms can be classified,[25] depending on differences in polymorphic structures:

- conformational polymorphism – polymorphs contain molecules with different molecular conformations; [26,27]
- synthon or hydrogen bond polymorphism – polymorphs have different hydrogen bond synthons in their structures; [25,28]
- configurational polymorphism – observed in substances whose different configurations or tautomers can form different crystal structures.[25]
- packing polymorphism – molecules in polymorphs have the same conformation, but different molecule packing.[29]

Control of the crystal phase is one of the most challenging steps in the drug production process in the pharmaceutical industry.[30] Before developing the finished dosage form, it is important to identify all possible crystalline forms and characterize their properties, because the choice of the dosage form, the required excipients and the dose of API itself depends on for the physical properties of the crystalline form.[31]

Concomitant crystallization occurs when at least two different polymorphs crystallize simultaneously.[32] This phenomenon is observed due to competing nucleation and growth rates of different polymorphs.[33] The concomitant crystallization are related to various kinetic and thermodynamic factors.[34] Most often, a mixture of different polymorphs is subjected for solvent-mediated phase transition (SMPT), and only the most stable polymorph can be observed in the final product.[3] In addition, it is required to check the stability of the selected crystalline phase in long-term storage. There have been several cases[35] where a new and more stable polymorph appeared many years after drug development. Such late appearance of a more stable polymorph often have caused problems for patients, from low drug efficacy to eventually disrupting the supply of medicines.[36]

Conventional crystal phase preparation methods are crystallization by cooling a solution, evaporation of a solution, precipitation, vapor diffusion etc. The obtained phase can depend on solvent used, cooling or evaporation rate, start and end temperature used for the cooling crystallization or evaporation temperature, concentration of solution (supersaturation) used and other variables.[9] Classical crystallization approaches, however, often do not provide crystallization of a pure polymorph. In such cases seeding is the most common approach to control the polymorph obtained, but also this does not always provide the desired crystalline form. Alternatively, other crystallization methods or approaches are introduced, for example, ultrasound-assisted crystallization,[37] laser-induced nucleation,[38] crystallization in gels[39] and in presence of additives[16] and templates.[40]

1.2. Crystallization additives for polymorphism control

Crystallization in presence of additives or templates is one of the empirical methods for controlling polymorphic outcomes. There are several approaches to crystallization with the presence of additives:[41]

- crystallization with insoluble additives or templates:
  - Langmuir monolayers;[14]
  - self-assembled monolayers (SAM);[15]
  - polymers;[42]
  - surfaces of other insoluble additives acting as templates;[43]
- crystallization with soluble additives.[44]

Langmuir monolayers and SAMs are efficient templates for control of the crystallization outcome but has to be designed for each specific crystal structure, and it is necessary to regenerate the monolayers after each crystallization, and often it is difficult to collect the obtained crystals without the impurities from the layer material.[45] Soluble additives can be divided in structurally similar (also known as tailor made additives) and structurally different from the compound which is being crystallized. Although it is easier to separate these additives from the crystals, sometimes they can integrate into the crystal structure.[46] Structurally related additives have been used to obtain metastable forms of paracetamol,[11] *para*-aminobenzoic acid,[47] benzamide,[48] etc. However, there are also risks in using structurally similar additives, as they can have pharmacological or even toxic effects, and because of the similar structure can incorporate in the obtained crystals, for example, by forming a solid solution.[49] Therefore, not all structurally related compounds can be used as additives to stabilize polymorphs of pharmaceutical products. Excipients used in the drug dosage forms can be employed as additives in the crystallization of the API,[44] as it would not be necessary to separate these additives after the crystallization because these additives (such as polymers, surfactants[50]) can be used in pharmaceutical products.

The use of crystallization additives may prevent concomitant crystallization and stabilize metastable forms,[51] promote their nucleation,[46] change the relative stability of polymorphs[52] or prevent nucleation of the stable form. Crystallization in presence of additives is widely used in natural crystallization and manufacturing processes, such as biomineralization, material synthesis.[53]

There are many possible mechanisms by which additives can control the outcomes of crystallization. For example:

- additives can work as nucleation sites;[10]
- additives can selectively adsorb to some of the crystal surface faces by inhibiting their growth and, therefore, the growth of this polymorph;[54]
- additives can also help to organize the crystallizable substance molecules to obtain the desired polymorph;[55]

- additives can lower the activation energy of nucleation.[34]

However, the exact mechanism for the control mechanism by the additives in most cases is still not explored.

1.3. Crystallographic analysis and theoretical calculations

Nowadays, various crystallographic analysis tools and theoretical calculations are available and used to compare crystal structures and justify polymorphic outcome of crystallization.

The stability of conformers affects the stability of polymorphs and also determines the conformation in which molecules exist in solution, so it is necessary to determine which are the most stable conformers and what is the stability of conformers in crystalline structures. Determination of the stability of the conformers requires the geometry optimisation of individual molecules and energy calculations in vacuum or in a solvent continuum. This is nowadays normally done using a quantum mechanics approach by one of the density functional theory methods or *ab initio* electron correlation methods. [56]

An equally important factor affecting the stability of polymorphs is the intermolecular interactions present in the crystal structure.[57–59] This calculation requires the optimisation of the geometry of the periodic crystal structure, which is nowadays possible by density functional theory methods. Further calculation of the interaction energy between the molecules in the structure allows the determination of the total energy of the intermolecular interactions, for which either empirical,[60] semi-empirical [61,62] or *ab initio* [63] methods are used. The crystal lattice energy characterising the stability of polymorphs can be calculated either by summing the total intermolecular interaction energy and the relative conformer energy or simply as the difference between the crystal structure energy and the energy of isolated molecules in the gas phase adopting the global energy minimum geometry. Note, however, that the crystal lattice energy does not include the thermal effects and thus provides information on the relative stability of polymorphs at 0 K.[64]

Crystallographic analysis tools such as energy frameworks, Hirshfeld surfaces and their 2D fingerprint plots and full-interaction maps are used to compare crystalline structures (see Figure 1.2).

Energy frameworks visualize the intermolecular interaction energy in crystal structures of polymorphs, further demonstrating the distribution of crystal lattice energy into different energy contributions (electrostatic and dispersion energy).[65] Hirshfeld surfaces provide information on intermolecular interactions and electron density in the structure, allowing a better understanding of differences in hydrogen bonding and other interactions in the structure, as well as in crystal packing.[66,67] Hirshfeld surface 2D fingerprint plots provide deeper insights into the interactions in the crystal structure and the contribution of specific interaction types.

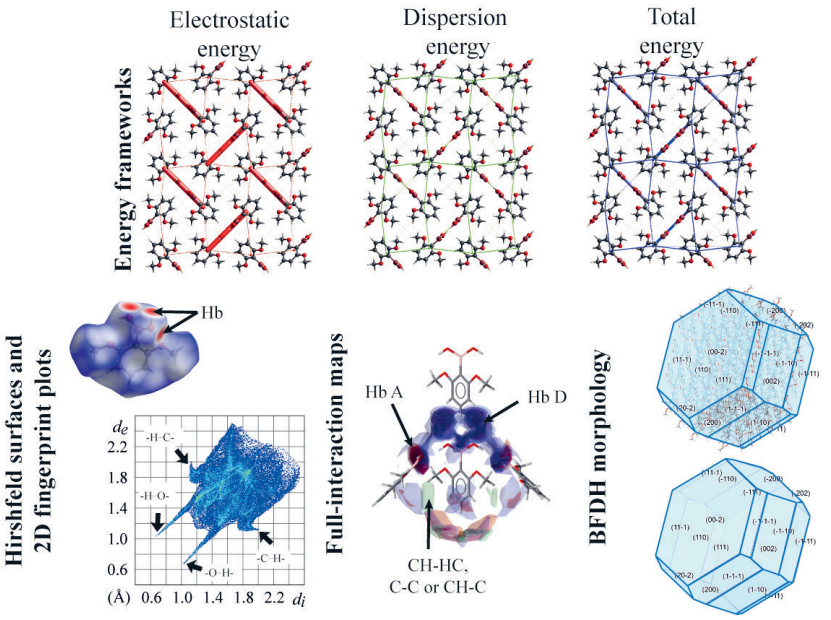

Figure 1.2. **Graphical representation of crystallographic analysis methods. Hb – hydrogen bond; Hb A – hydrogen bond acceptor; Hb D – hydrogen bond donor**

Full-interaction maps (FIMs) visualize the regions around a molecule where, based on pre-extracted *IsoStar* interaction data from the Cambridge Structural Database (CSD),[68] intermolecular interactions are expected to occur, allowing to assess whether interaction preferences are satisfied in a structure. FIM analysis has been shown to allow the assessment of polymorph stability.[69,70]

Many physical properties of crystals depend on their morphology. Several models exist for predicting crystal morphology, but the most commonly used is the **B**ravais-**F**riedel-**D**onnay-**H**arker (BFDH) model, because of the easier approach used to predict the morphology compared to other models. This model uses an inversely proportional relationship between interplanar spacing and growth rate, but does not take into account kinetic factors and the role of solvent or additives on the crystal growth.[71] Since it can be assumed that if there are regions in the structure where intermolecular interactions are not satisfied based on the FIM, then additional interactions provided by the additives may stabilize the polymorph. However, such an effect can only occur on the crystal surface, hence it is beneficial to use FIMs projected onto the BFDH morphology. Despite the overall inaccuracy of the BFDH model, FIM analysis combined with BFDH morphology can predict potential adsorption sites for additive molecules.[68]

1.4. The studied compounds

In this study three model substances were investigated: 2,6-dimethoxybenzoic acid (2,6MeOBA), 2,6-dimethoxyphenylboronic acid (MPBA) and isonicotinamide (INA) (see Figure 1.3).

For all three model substances, crystal structures of at least two polymorphs in which different supramolecular synthons are found (dimers and chains, see Figure 1.4. for schematic differences between these synthons) have been published in CSD. The existence of polymorphs containing different supramolecular synthons was used as a criteria for the choice of the model substances because the polymorphs containing different molecular synthons were expected to be more easily controllable by the additives assuming the importance of intermolecular interactions in the control mechanism.

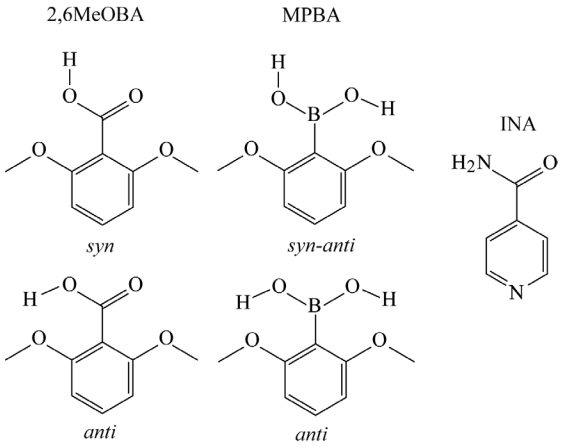

Figure 1.3. **Structural formulas and conformations of the model substances used in the study**

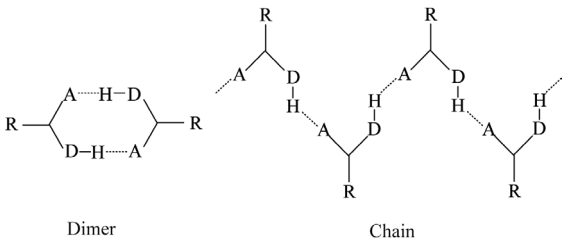

Figure 1.4. **Schematic representation of dimer and chain synthons observed in the crystal structures of all model substances. A – hydrogen bond acceptor; D – hydrogen bond donor**

2,6MeOBA is reported to crystallize in three polymorphs.[26,72–74] Form I is the thermodynamically stable polymorph.[26,74] It contains 2,6MeOBA molecules in the *anti*-planar conformation linked by hydrogen-bonded chains forming catemer.[72,75] Form II and Form III contain 2,6MeOBA molecules in a *syn*-planar conformation that forms carboxylic acid homodimers.[26,73,74] Besides, phenylboronic acid was successfully used as an additive to crystallize the form II in one of the previous studies.[73]

MPBA has two known polymorphs.[76] Form I is the thermodynamically stable polymorph. Form I contains typical hydrogen bonded homodimers of boronic acid that adopts *syn-anti*-conformation, whereas Form II contains an unusual hydrogen-bonded boronic acid synthon formed by three molecules.

INA is reported to crystallize in six polymorphs,[77–80] two monohydrates[81] and few solvates: acetic,[28] formic,[82] and propionic[83] acid as well as formamide[84] solvates. Form I contains amide homodimers arranged in isolated corrugated sheets.[78] In contrast, all the other INA polymorphs contain hydrogen bonded chains formed by amide functionals and by amide and pyridine moieties.[77–80] Form I has been shown to be the stable polymorph in ambient conditions.[77,79] Although crystallization of INA in presence of additives and templates has been studied previously,[43,79,80] selective and repeatable crystallization was not achieved for any of the polymorphs

2. EXPERIMENTAL SECTION

Solid phase characterization and structure determination

Routine solid phase identification was performed on a *Bruker D8 Advance* powder X-ray diffractometer (PXRD) using copper radiation (Cu K_α), equipped with a *LynxEye* position sensitive detector. The patterns were recorded from 3° to 35° on the 2θ scale using the scan speed of 0.2 s / 0.02°. To prevent the desolvation of INA solvates, during the analysis the samples were covered with a 10 μm polyethylene film. Quantification of polymorphic forms was performed with Rietveld refinement using Profex 4.3.6.

The PXRD patterns for crystal structure determination were measured on a *Bruker D8 Discover* diffractometer using copper radiation (Cu K_α), equipped with a *LynxEye* position sensitive detector in transmission mode. Samples were sealed in rotating (60 rpm) borosilicate glass capillaries of 0.5 mm outer diameter (Hilgenberg glass No. 10), and a capillary sample stage with upper and lower knife edges were used. The diffraction patterns were collected using 36 s / 0.01° scanning speed from 3° to 70° on the 2θ scale. Indexing, space group determination, and structure solution from PXRD data were performed using *EXPO2014*. The best structure solution was then used for Rietveld refinement using *TOPAS5*.

Single crystals for structure determination were investigated on a *Rigaku XtaLAB Synergy-S dualflex* diffractometer (SCXRD) equipped with *HyPix6000* detector and a microfocus sealed X-ray tube with copper radiation (Cu K_α). Single crystals were fixed with oil in a nylon loop of a magnetic *Cry°Cap* and set on a goniometer head. The structures were solved with the *ShelXT* program using Intrinsic Phasing and refined with the full-matrix least-squares method using *SHELXL*. (Latvian Institute of Organic Synthesis, Riga, Latvia)

The differential scanning calorimetry / thermogravimetry (DSC/TG) analysis to characterize the solid phases and to determine the stoichiometry of the solvent present in the solvates were performed with a *Mettler Toledo TGA/DSC2* instrument. The heating of the samples from 25 to 200 °C was carried out at a heating rate of 10 °C min^{-1} in nitrogen atmosphere. DSC analysis was performed using a *TA Instruments DSC 25* calorimeter. The heating of the samples from 25 to 200 °C was carried out at a heating rate of 10 °C·min^{-1} or 2 °C·min^{-1} in nitrogen atmosphere.

Selection of solvent and crystallization additives

Common organic solvents chosen from different solvent classes were selected for the cooling and evaporation crystallization of model substances. Additionally, alkyl carboxylic acids and few other uncommon solvents were

selected for solid phase screening of INA because INA is reported to form acetic acid solvate (S_{AA}) and propionic acid disolvate (S_{dPA}). After evaluation of the crystallization result few solvents were selected for further investigation of the effect of supersaturation and cooling rate on the crystallization outcome. They selection was based on the following criteria:

- model substance solubility is between 5 and 50 mg mL^{-1};
- for 2,6MeOBA: it is possible to obtain the desired metastable polymorph in a mixture with the stable polymorph;
- for MPBA: only the stable polymorph could be obtained;
- for INA: a mixture of several polymorphs could be obtained.

Then, in limited number of solvents, the effect of different crystallization additives on the polymorphic outcome was determined. Surfactants, polymers, and different molecular compounds with diverse possibilities to form intermolecular interactions were selected as additives. From all the tested additive, few additives showing the highest ability to promote the crystallization of the metastable polymorph (for 2,6MeOBA and MPBA) or preventing the concomitant crystallization and promoting the crystallization of metastable polymorph (for INA) were selected for extensive studies.

Crystallization experiments

Crystallization and solvent mediated phase transformation (SMPT) experiments under controlled conditions as well as solubility determination was carried out using the automatic crystallization equipment *Technobis Crystal16*. The temperature range from 5 to 100°C, heating and cooling rate from 0.1 to 20 °C min^{-1}, and stirring speed from 0 to 1250 rpm was used.

Theoretical calculations

ConQuest 2022.2.0 was used to perform crystal structure searches in the CSD (CSD version 5.43). Quantum Espresso 6.4.1 was used for the optimization of the crystal structure geometries, while the molecular geometry optimization was performed with Gaussian09 Revision D.01. The ISOCIF tool (version 3.1.0) was used to search for the highest symmetry of the geometry optimized crystal structures. Lattice energy calculation and construction of Hirshfeld surfaces and their 3D fingerprint plots were done using CrystalExplorer21. Mercury2020.3.0 was used for hydrogen bond identification and simulation of full interaction maps (FIM) and crystal morphologies by Bravais–Friedel–Donnay–Harker (BFDH) method. Molecular packaging of polymorphs was compared with CrystalCMP using crystal structures from the CSD database. The obtained solubility temperature dependence was described with the van't Hoff equation using the linear regression implemented in the Microsoft Excel Linest function.

3. RESULTS AND DISCUSSION

3.1. Crystallization from pure solvents

Initially for all the model substances it is necessary to determine which polymorphs can be obtained using different crystallization techniques and different solvents selected for the study. Therefore, each model substance underwent an extensive polymorph screening from a large range of solvents using cooling and evaporation crystallization methods under different temperatures. The list of used solvents for each model substance varies depending on the previously obtained phases, solubility, and availability in the laboratory.

In most of the performed 2,6MeOBA cooling crystallization experiments Form I was obtained, although impurity of Form III was sometimes present (see Table 3.1). In the evaporation crystallization experiments the polymorph obtained correlated with the temperature: at lower temperature (5 °C) in most of the experiments Form I was obtained, frequently with some impurities of Form III. However, at higher temperature (50 °C) Form III with impurity of Form I was obtained.

In contrast, in almost all MPBA crystallization experiments, particularly from aprotic solvents, pure Form I was obtained (see Table 3.1). However, from polar protic solvent (isopropanol (IPA), methanol, and isobutanol) it was possible to obtain the metastable MPBA Form II. Besides the already known polymorphs, a new MPBA polymorph, designated as Form III, was obtained. Form III crystallized together with Form II in evaporation crystallization from isopropanol and heptanol. Unfortunately, the attempts to determine the crystal structure of Form III were unsuccessful, as crystals suitable for SCXRD analysis were not obtained and the bulk sample contained an impurity of Form II (see Figure 3.1).

Crystallization results of INA were completely different from the other two model substances (see Table 3.1). In most of the conditions several INA polymorphs were present in the obtained crystallization products which agrees with the results from other studies.[80,85] Usually, Forms II and VI or Forms II and IV crystallized together, but from some solvents a mixture of all these three forms was obtained. Moreover, despite Form I is determined to be the stable polymorph,[77,79,85] it was rarely obtained in the crystallization, whereas Form II, the high temperature polymorph, was the most frequently obtained crystallization product. In crystallization from acetic acid (AA) and formamide (FAM) the already known INA solvates[28,84] were obtained. Additionally, crystallization products with distinct and from the known INA polymorphs or solvates differing PXRD patterns (see Figure 3.1) were obtained in cooling crystallization from formic acid (FA), propionic acid (PA), butyric acid (BA), and 2,2,2-trifluoroethanol (TFE). The new crystalline forms obtained were analyzed by DSC/TG and their structures were determined. The obtained results show

Table 3.1. **Summary of the crystallization polymorphic outcome of the model substances from pure solvents**

Solvent	Cooling			Evaporation						
				5 °C	25 °C			50 °C		
	2,6MeOBA	MPBA	INA	2,6MeOBA	2,6MeOBA	MPBA	INA	2,6MeOBA	MPBA	INA
1,4-Dioxane	I + III↓	I	III	III	I + III	I	II + VI	III	I	II
Methanol	I + III↓	II	II + IV	III	I↓ + II + III	II	II + IV + VI	I	I	II + IV
Acetone	I	I	I	I + III	I	I	II + IV + VI	III	I	II + IV + VI
Tetrahydrofuran (THF)	I	I	II + VI	I + III	I + III	I	II + III	I↓ + III	I	II + IV + VI
Isopropanol (IPA)	I	I	II + IV + III + VI	I	I + III↓	II + III	III	III	I + II	II + III
Acetonitrile	I	I	II + IV + VI	I + III↓	I + III	I	I + II + IV	I / III	I	II + IV
4-Methyl-2-pentanone	I	I	II + VI	I	I + III↓	I	II + IV	I + III	I	II + IV
Methyl acetate	I	N/A	N/A	I + III↓	I + III	N/A	N/A	I↓ + III	N/A	N/A
terc-Butyl methyl ether	I	I	II + VI	I	I	I	IV + VI	I + III	I	IV + VI
Water	I	I	N/A	I	I	I	N/A	I	I + II	N/A
Toluene	I	I	N/A	N/A	I + III	I	N/A	N/A	I	N/A
Chloroform	I	I	II + IV	N/A	I + III↓	I	II + IV + VI	N/A	I	IV + VI
Dichloromethane	I + III↓	I	N/A	N/A	I + III↓	I	N/A	N/A	I	N/A
Ethyl acetate	I	I	N/A	N/A	I	I	N/A	N/A	I	N/A
Formic acid (FA)	I	N/A	S_{FA}	N/A	I	N/A	N/A	N/A	N/A	N/A
Nitromethane	I	I	II + IV	N/A	I	I	II + IV	N/A	I	II + IV
o-Xylene	N/A	I	N/A	N/A	N/A	I	N/A	N/A	I	N/A
Diethyl carbonate	N/A	I	II + IV + VI	N/A	N/A	I	II + IV + VI	N/A	I	II + IV + VI
Cyclohexanol	N/A	I	N/A	N/A	N/A	I	N/A	N/A	I	N/A
2,2,2-Trifluoroethanol	N/A	I	S_{TFE}*	N/A	N/A	I	N/A	N/A	I + II	N/A
Heptanol	N/A	I	N/A	N/A	N/A	II + III	N/A	N/A	I	N/A
Isopentanol	N/A	I	N/A	N/A	N/A	I + II	N/A	N/A	I	N/A
n-Buthyl acetate	N/A	N/A	II + IV	N/A	N/A	N/A	IV + VI	N/A	N/A	II + IV + VI
Acetic acid (AA)	N/A	N/A	S_{AA}	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Formamide (FAM)	N/A	N/A	S_{FAM}	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Propionic acid (PA)	N/A	N/A	S_{mPA}* (5 °C); S_{dPA} (−10 °C)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Buthyric acid (BA)	N/A	N/A	S_{dBA}*	N/A	N/A	N/A	N/A	N/A	N/A	N/A

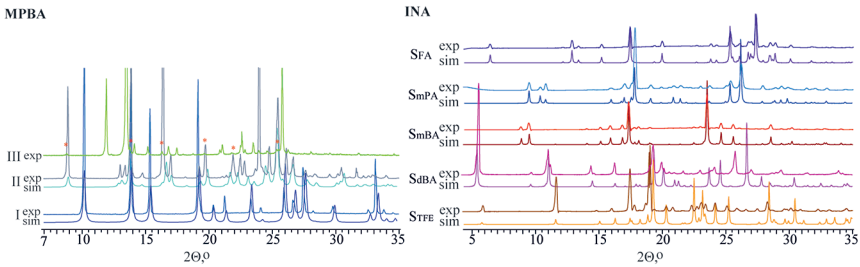

Figure 3.1. **Experimental and from crystal structures simulated PXRD patterns of MPBA polymorphs and INA solvates. For MPBA the Form II impurity in the Form III sample is marked with red asterisks**

that these forms are INA solvates (see section 3.2). In Table 3.1 for all the model substances the newly obtained crystalline forms are market with an asterisk.

For more detailed investigation of the effect of cooling rate on the crystallization polymorphic outcome the below mentioned solvents were selected:

- water (for 2,6MeOBA);
- toluene (for MPBA);
- IPA, 1,4-dioxane, nitromethane, and acetone (for INA).

Repeated crystallizations of 2,6MeOBA from pure water with immediate filtration and analysis of the obtained crystals showed that a mixture of Forms I and III is obtained in the crystallization, followed by a SMPT to Form I if the crystallization product is kept in a suspension. Therefore, only Form I was observed in the above-described crystallization experiments. Mixture of all three polymorphs was obtained in crystallization from a highly concentrated pure water solution with the fastest cooling rate (see Figure 3.2), while in all four experiments using the lowest cooling rate Form III was obtained, even though at a slower cooling rate the formation of the thermodynamically stable Form I was expected. The phase transition to Form I was prevented as the crystals formed near the water surface and formed large agglomerates. In contrast, in crystallization of MPBA from toluene the cooling rate did not affect the polymorphic outcome, and Form I was always obtained in the crystallization.

Different polymorphic outcomes were observed in crystallization of INA using different cooling rates. Pure Form III was obtained from 1,4-dioxane using the fastest cooling rate, but the decrease of the cooling rate facilitated formation of the more stable Forms II and VI.[85] Mixtures of different polymorphs containing Form III were obtained from IPA using the fastest cooling rates, but using lower cooling rates more stable forms were obtained. In contrast, Form III did not crystallize from nitromethane or acetone.

Overall, except for the MPBA, the obtained results agree with the Ostwald's rule of stages,[86] as instead of the nucleation of the most stable form the polymorph corresponding to the closest energy nucleates.

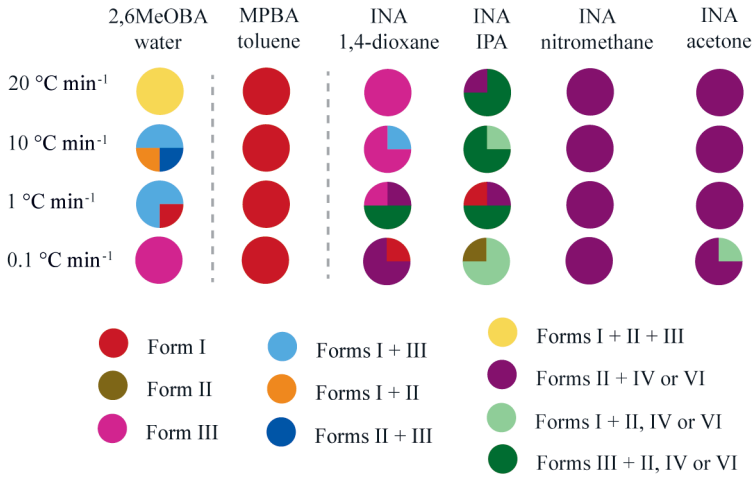

Figure 3.2. **Summary of polymorphs obtained using different cooling rates and a stirring rate of 900 RPM. Each ¼ of the pie chart represents one of the parallel experiments**

3.2. Diversity and similarity in isonicotinamide solvates

Four new INA solvates were obtained as part of this study: PA monosolvate (S_{mPA}), BA monosolvate (S_{mBA}) and disolvate (S_{dBA}), and TFE solvate (S_{TFE}). In addition, the already known FA solvate (S_{FA}),[82] FAM solvate (S_{FAM}), AA solvate (S_{AA}) and PA disolvate (S_{dPA}) were obtained and analysed. The crystal structure of S_{FA} was also determined, as it is not deposited in the CSD.Click or tap here to enter text. Upon storage at ambient temperature all the solvates desolvate by forming a mixture of INA Forms II, IV and VI. All the INA solvates crystallize either in monoclinic or triclinic crystal system (see Table 3.2)

In INA solvates two distinct types of hydrogen bonding motifs are observed, which can further be divided into five subtypes based on additional hydrogen bonding and relative arrangement of the hydrogen bonded units. The first hydrogen bonding motif contains typical INA $R_2^2(8)$ homodimers (see Figure 3.4), therefore, resulting in hydrogen bonded tetramers acid···INA dimer···acid. Isolated hydrogen bonded tetramers, as observed in S_{mPA}, is classified here as hydrogen bonding type A1. In other structures, however, the hydrogen bonded tetramers solvent···INA dimer···solvent are additionally linked to other tetramers by hydrogen bonds. The resulting hydrogen bonding is classified as type A2 if the linked tetramers lay in the same plane, as observed in S_{FA} and S_{AA}, or as type A3 if the linked tetramers are lying perpendicularly to each other by creating a packaging with adjacent molecule planes arranged perpendicular

Table 3.2. **Crystallographic data of INA solvates determined in this study**

	S_{FA}	S_{mPA}	S_{mBA}	S_{dBA}	S_{TFE}
CSD identifier	2236716	2236717	2236718	2302845	2237737
Formula	$C_6H_6N_2O \cdot CH_2O_2$	$C_6H_6N_2O \cdot C_3H_6O_2$	$C_6H_6N_2O \cdot C_4H_8O_2$	$C_6H_6N_2O \cdot 2C_4H_8O_2$	$C_6H_6N_2O \cdot C_2H_3F_3O$
Method of structure solution	Powder	Powder	Powder	Single crystal	Single crystal
Space group	$P2_1/c$	$P\bar{1}$	$C2/c$	$P\bar{1}$	$P2_1/c$
a, Å	3.8177(16)	5.88988	21.806(15)	5.24839(10)	15.2031(9)
b, Å	27.480(11)	9.685489	10.505(7)	9.28144(13)	5.3244(12)
c, Å	7.565(3)	10.19433	11.190(8)	16.3015(3)	11.7225(7)
α, deg	90	112.4861	90	89.7515(12)	90
β, deg	95.1158(12)	93.0070	114.2902(17)	89.8978(14)	91.303(6)
γ, deg	90	105.726	90	80.7138(14)	90

to each other, as observed in S_{mBA} and also S_{TFE}. In type A2 (S_{FA} and S_{AA}) the tetramers are essentially parallel to each other and form tetramer layers. Moreover, because of the different relative arrangement of INA molecules and acid molecules in the tetramers FA···INA dimer···FA fragments are linked by $C_2^2(11)$ chains and forms $R_6^6(26)$ rings, whereas AA···INA dimer···AA fragments by $C_3^3(13)$ chains and forms $R_4^4(22)$ rings. In S_{TFE} and S_{mBA} (belonging to type A3) each tetramer is bonded to almost perpendicularly arranged adjacent tetramers.

The second motif type B is substantially different as INA homodimers $R_2^2(8)$ are not employed (see Figure 3.4). In both subtypes of B INA forms $R_2^2(8)$ heterodimers with the carboxylic acid (see Figure 3.4), and this dimer is linked to another carboxylic acid by a hydrogen bond resulting in a trimer acid···INA:acid. In hydrogen bonding type B1 (S_{dBA}) the solvent···INA:solvent trimer is linked with hydrogen bonds to an adjacent trimer related by the symmetry centre and forms $R_4^4(22)$ rings. In type B2, however, trimers are hydrogen bonded to two other perpendicularly aligned trimers as observed in S_{dPA}, thereby, resulting in similar packing to that observed in the structures containing type A3 motif.

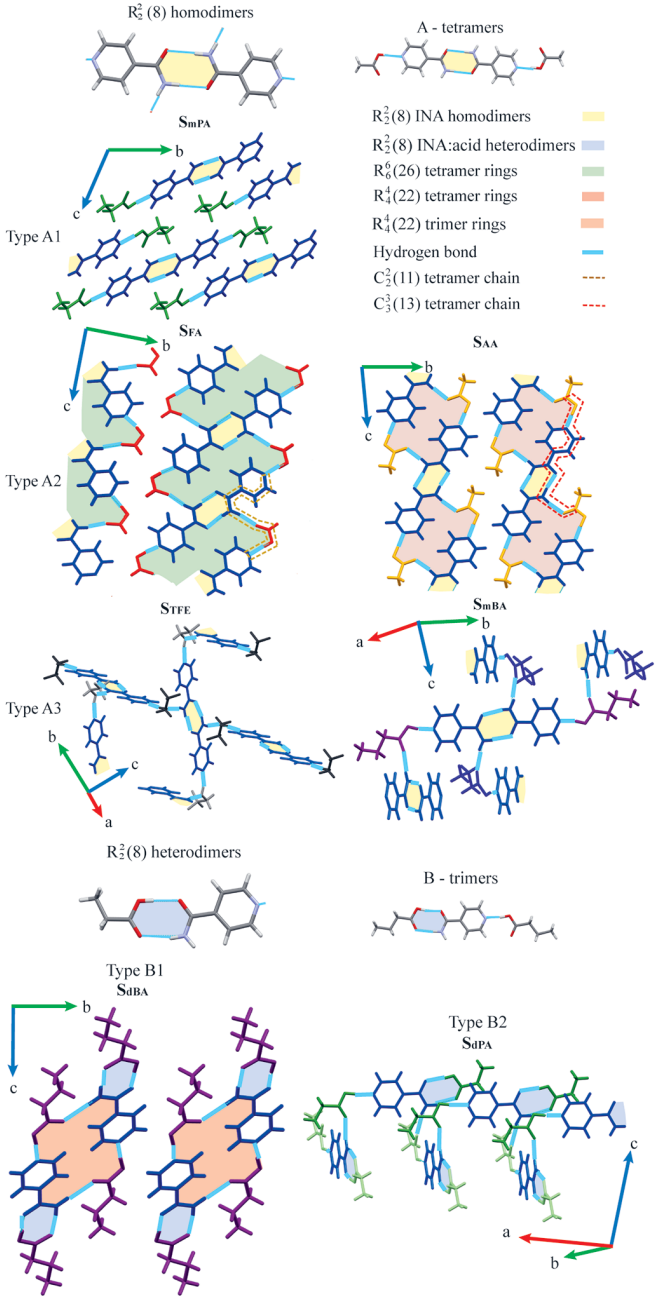

Figure 3.4. **Hydrogen bonding type A and type B as observed in INA solvates**

The hydrogen bonding in S_{FAM} is different from that in other INA solvates and, therefore, does not correspond to the described hydrogen bonding types (see Figure 3.5). In this structure two different $R_2^2(8)$ homodimers are formed by INA and FAM, and these homodimers are linked to each other by hydrogen bonds. This results in a packing where FAM homodimers connect the layer of the INA molecules.

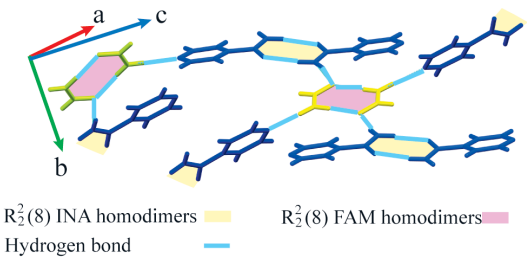

Figure 3.5. **Hydrogen bonding in S_{FAM}**

In summary, all of these solvates have similar hydrogen bond patterns. Extension of the set of the analysed structures by including also INA co-crystals (see the results and detailed discussion in publication IV) allowed to conclude that almost all INA alkyl carboxylic acid solvates and co-crystals crystallize in structures with highly similar hydrogen bond patterns, which in general could allow prediction of intermolecular interactions and molecular packaging for new solvates/co-crystals with structurally similar solvents/co-formers.

3.3. Polymorphic outcome in presence of crystallization additives

The polymorphic outcome of crystallization in the presence of additives is affected by complex and not fully understood interactions between the compound being crystallized, the solvent, and the additives, as well as by the crystallization conditions (e.g., supersaturation, cooling and stirring rate). The polymorphic outcome can be altered by changes in any of these aspects. In this study, crystallization in the presence of additives was investigated by changing the crystallization conditions to better understand the role of the additives on the crystallization polymorphic outcome.

This part of the research was a continuation of the previously described experiments aimed at identifying which additives would allow crystallization of the metastable forms. Therefore, for each model substance at least two solvents selected based on the preliminary crystallization experiments and more than 10 additives with different intermolecular interaction possibilities were tested (see Table 3.3).

Table 3.3. **Summary of the crystallization additives and solvents used for each of the model substances**

Additive	2,6MeOBA			MPBA		INA	
	THF	aceto-nitrile	water	tolu-ene	water	1,4-di-oxane	IPA
Polyethylene glycol (PEG) 6000	✓	✓	✓	✓	✓	✓	✓
Hydroxypropyl cellulose (HPC)			✓	✓	✓	✓	
MPBA			✓				
Octyl β-D-glucopyranoside (OGP)	✓	✓	✓	✓	✓	✓	✓
Polysorbate 80 (Poly80)	✓	✓	✓	✓		✓	✓
Sorbitan laurate (Span 20); Polysorbate 20 (Tween 20)	✓	✓		✓		✓	✓
4-Carboxyphenylboronic acid (4CPBA)			✓		✓	✓	✓
2-Picolinic acid (2PA)				✓		✓	✓
Naphthalene-1,5-diol (ND)						✓	✓
Benzene-1,2,3-triol (Btriol)					✓	✓	✓
Pholoroglucinol (PhGlu); Nicotinic acid (NA); 5-Hydroxy-2-nitrobenzoic acid (5OH2NBA).						✓	✓
Polycaprolactone	✓	✓				✓	✓
Polyvinyl chloride	✓	✓				✓	
Bis(2-hydroxyethyl)amino-tris(hydroxymethyl)methane			✓		✓	✓	✓
trans-Stilbene				✓		✓	✓
Poly(tetrahydrofuran), Polypropylene glycol				✓		✓	✓
4-Iodinephenylboronic acid; Glycine; NH_4Cl; Poly(acrylic acid); Poly(acrylic amide); Sodium carboxymethyl cellulose			✓		✓		
Cellulose acetate			✓			✓	
Poly(methyl methacrylate)				✓		✓	

►

Table 3.3 continued

Additive	2,6MeOBA			MPBA		INA	
	THF	aceto-nitrile	water	tolu-ene	water	1,4-di-oxane	IPA
2,6MeOBA, Phenylboronic acid				✓	✓		
PEG 200; Polyurethane; 1,3-Diphenylurea						✓	✓
Hydroxypropylmethyl cellulose; Microcrystalline cellulose			✓				
PEG 600; Salicylic acid; Polyethene; Polystyrene 2-Hydroxyphenylboronic acid;				✓			
Lactose					✓		
2-Amino-2-(hydroxymethyl) propane-1,3-diol							✓

The additives and solvents chosen for more extensive research along with the resulting effect on the polymorphic outcomes are summarized in Table 3.4, and the molecular structures of the selected additives for each model substance are shown in Figure 3.6.

Table 3.4. **The additives, solvents and crystallization methods chosen for more extensive research along with the resulting effect on the polymorphic outcome**

	2,6MeOBA	MPBA	INA			
Solvent	water	toluene	IPA	1,4-diox-ane	nitro-methane	acetone
Method	cooling	evaporation	cooling			
Additives	PEG 6000, HPC, MPBA	OGP, Poly80, Span 20, Tween 20	4CPBA, 2PA, ND, Btriol, PhGlu, NA, 5OH2NBA	4CPBA, 2PA, ND		
Poly-morphic outcome	↑Form III	Form II	↑Form III	↑Form III; ↓polymorph mixtures	–	

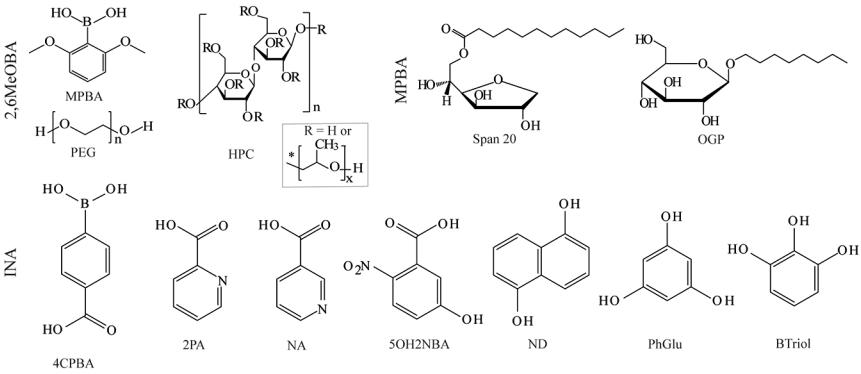

Figure 3.6. **Molecular structures of the selected additives for crystallization of the model substances**

Detailed crystallization experiments performed in the presence of additives were selected based on the results obtained and therefore were different for each of the model substances:

- crystallization using various cooling speed (2,6MeOBA, INA);
- crystallization using various additive quantity (2,6MeOBA);
- use of various crystallization techniques and solvents (MPBA);
- crystallization using various stirring (agitation) rates (INA).

3.3.1. Polymorphic outcome of crystallization of 2,6-dimethoxybenzoic acid

In most of the crystallizations by using PEG and MPBA (see Figure 3.7) as additives, a mixture of Forms I and III was obtained. In contrast, pure Form III was the most frequent crystallization product by using HPC as an additive at both additive concentrations. The formation of Form III was facilitated by the fastest cooling rates. Interestingly, at the slowest cooling rate, additives promoted crystallization of Form I. Use of 0.5% HPC suspension and 2,6MeOBA solution with lower concentration (supersaturation is designed as c/c^*, where c is the initial concentration and c^* is the solubility at 25 °C) promoted crystallization of Form III more clearly if compared to the crystallization experiments using 0.1% HPC solution and a higher concentration of 2,6MeOBA. It is possible that under the former conditions more HPC molecules could interact with 2,6MeOBA in heterogeneous crystallization and stabilize the *syn* conformation during nucleation, which in general is similar to the findings of Lin et al.[87] Also PEG has the potential to control the crystallization outcome, if a highly concentrated solution is crystallized using a moderately slow cooling rate. In general, however, the tested additives do not provide fully selective crystallization.

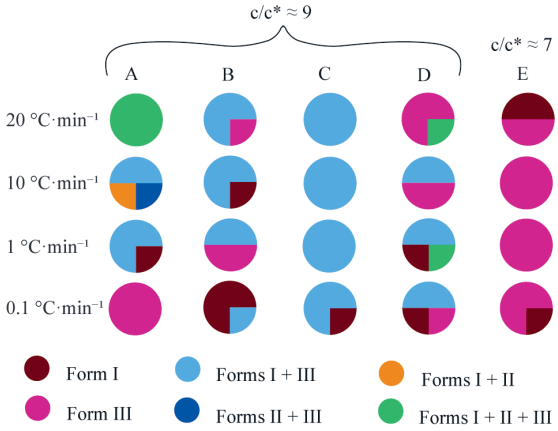

Figure 3.7. **Polymorphic outcome of the 2,6MeOBA crystallization experiments from water using different additives and cooling rates. Each ¼ of the pie chart represents one of the parallel experiments**

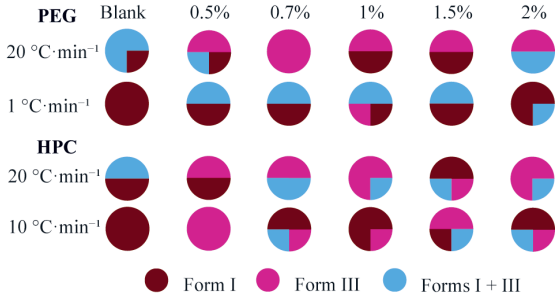

Figure 3.8. **Polymorphic outcome of the 2,6MeOBA crystallization experiments from water in the presence of different quantities of additives. Each ¼ of the pie chart represents one of the parallel experiments**

Crystallizations in the presence of PEG with a cooling rate of 20 and 1 °C·min^{-1} and in the presence of HPC with 20 and 10 °C·min^{-1} were selected for further studies to test the effect of the amount of additive on the crystallization outcome.

In most of the crystallizations using both additives and the fastest cooling rate Form III was obtained (see Figure 3.8). Again, the presence of additives did not provide selective crystallization of one of the polymorphs. Nevertheless, concomitant crystallization of both polymorphs was less frequent in the presence of HPC than in the presence of PEG. No clear correlation between the amount of additive selected and the crystallization outcome was observed.

3.3.2. Polymorphic outcome of crystallization of 2,6-dimethoxyphenylboronic acid

In the cooling crystallization with the selected additives almost exclusively Form I was obtained (see Figure 3.9). In contrast, Form II, Form III, or their mixture was obtained in evaporation crystallization in the presence of Span 20, Tween 20, and OGP. Moreover, the presence of Span 20 and OGP stabilized Form II, as in the presence of these two surfactants it was stable for up to one month. However, evaporation with stirring prevented crystallization of the metastable forms. Among the tested, the best conditions for obtaining the metastable forms were solvent evaporation at 50 °C without stirring. Under these conditions, the presence of Span 20 and OGP in the initial solution resulted in crystallization actually occurring from a MPBA solution in the surfactant after the evaporation of the initial solvent when the obtained mixture was cooled to room temperature. The crystals obtained in this procedure were very small, and pure polymorph III crystallized in the presence of Span 20 and OGP.

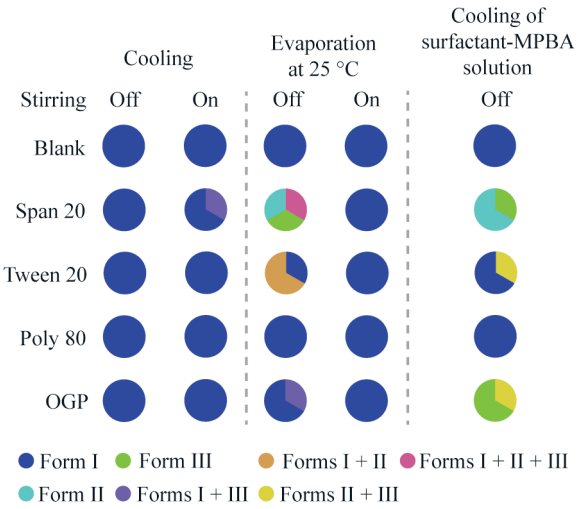

Figure 3.9. **Polymorphic outcome in MPBA crystallization from toluene in the presence of surfactants using different crystallization methods. Each ⅓ of the circle represents one of the parallel experiments**

MPBA–Span 20 solution was also obtained using other solvents to determine whether the initial solvent has a role on the polymorph obtained if the crystallization is performed in this way. Pure Form II was obtained in all 15 experiments performed using acetone, IPA, THF, acetonitrile and toluene.

Therefore, the formation of Form II under these conditions is purely determined by the Span 20.

3.3.3. Polymorphic outcome of crystallization of isonicotinamide

Almost all the selected additives facilitated the crystallization of Form III from IPA and 1,4-dioxane when the faster cooling rates were used (see Figure 3.10). 2PA showed the highest ability to provide crystallization of Form III from IPA, as Form III was obtained even using the cooling rate of 1 °C min^{-1}, at which in presence of other additives mostly mixtures of Forms II, IV and VI were obtained. ND showed the best ability to maintain Form III even in slow cooling rates from 1,4-dioxane. 4CPBA facilitated the nucleation of Form I from this solvent. Note that in the crystallization from pure 1,4-dioxane only other polymorphs were obtained in this and previous studies.[78,85] The most selective additives were also tested in acetone and nitromethane, from which crystallization of Form III was not observed in the previous experiments. 2PA and 4CPBA provided crystallization control also in these solvents: 4CPBA facilitated the crystallization of Form III, but 2PA – Form I. In presence of 2PA at the fastest cooling rate crystallization of Form III was facilitated, but at slower cooling rates pure Form I was mostly obtained. Overall, the results indicate that obtaining pure stable polymorph, Form I, in a direct crystallization is relatively challenging. In presence of all three tested additives formation of pure Form III was facilitated from nitromethane using the fastest cooling rates, whereas ND provided formation of pure Form III using all four cooling rates.

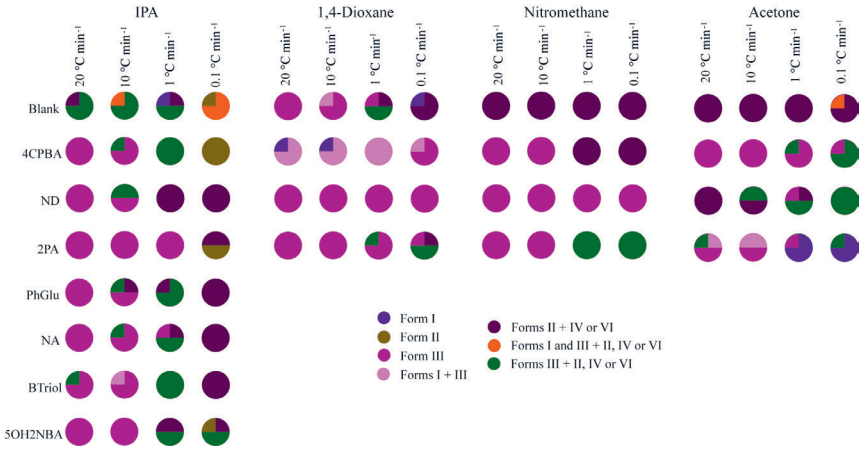

Figure 3.10. **Summary of INA polymorphs obtained in crystallization in presence of selected additives using different cooling rates. Each ¼ of the pie chart represents one of the parallel experiments**

The effect of the stirring rate on the crystallization polymorphic outcome was also tested. It was observed that the use of fast cooling rate and slow stirring rate or even crystallization without stirring facilitated formation of Form I from IPA (see Figure 3.11). The crystallization of Form III, however, was facilitated by the presence of the tested additives and use of faster cooling rate. The crystallization polymorphic outcome control by the tested additives was more feasible in 1,4-dioxane, particularly using stirring. The presence of

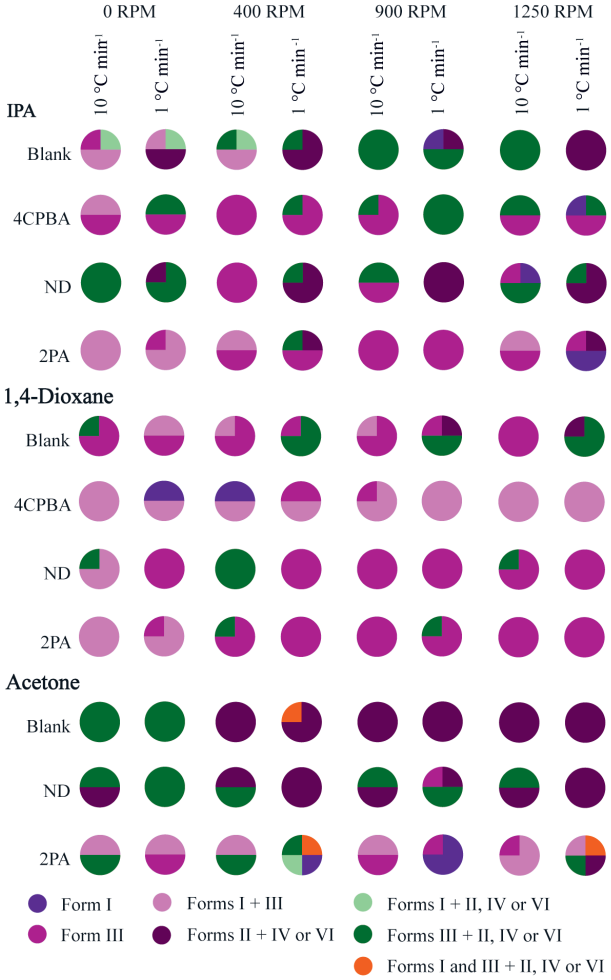

Figure 3.11. **Summary of INA polymorphs obtained in crystallization in presence of selected additives using two selected cooling rates and different stirring rates. Each ¼ of the pie chart represents one of the parallel experiments**

any of the additives provided formation of the mixture of Forms I and III when fast cooling rate and no stirring was used. The most selective crystallization of Form III was achieved in presence of ND using the slow cooling rate, and stirring rate did not affect this. The experiments using slowest cooling rates, in which the suspension obtained after the crystallization was stirred for longer time until the set end temperature of 10 °C was reached, resulted in formation of more stable polymorphs (Forms II, IV or VI[85]) compared to Form III. Therefore, using the cooling rate of 1 °C min^{-1} almost none of the additives were able to provide crystallization of Form III or Form I.

3.4. Possible effects of crystallization additives on nucleation and crystal growth

The results presented in Section 3.3. clearly show that additives can facilitate crystallization of the metastable forms, but the exact mechanisms of how the additives provide the control of crystallization polymorphic outcome are unknown. In this study different approaches were used to gain an insight into the factors determining the polymorphic outcome of all three model substances. These approaches included use of experimental data and theoretical calculations, such as:

- examination of the change of solubility (for 2,6MeOBA);
- examination of effect on the SMPT (for 2,6MeOBA, INA);
- comparison of crystal structure characteristics, such as lattice energy, Hirshfeld surfaces and their 2D fingerprint plots, FIMs and BFDH morphologies (for MPBA, INA).

The effect of additives on the solubility was investigated only for 2,6MeOBA, as for the other substances pure polymorphs could not be obtained in crystallization in the absence of additives. As calculations of lattice energy and analysis of Hirshfeld surfaces and their 2D fingerprint plots for 2,6MeOBA have already been published[74] they were not repeated as part of this study. Theoretical calculations were performed only for INA polymorphs obtained in the crystallization experiments, therefore, Form V was not analysed.

3.4.1. Solubility study

The most stable form has the lowest solubility, but additives in the solution can affect the solubility, therefore, increasing the likelihood of the crystallization of metastable form. For example, additives have been demonstrated to decrease the solubility but increase the crystal nucleation and growth rates of p-methylacetanilide.[88] The solubility of Form I is almost unaffected by the use of 1% PEG solution (see Figure 3.12). At temperatures up to 30 °C, the solubility is almost identical to that in pure water, but at higher temperatures, the solubility slightly decreased. In contrast, the solubility of Form III in the presence of PEG increases

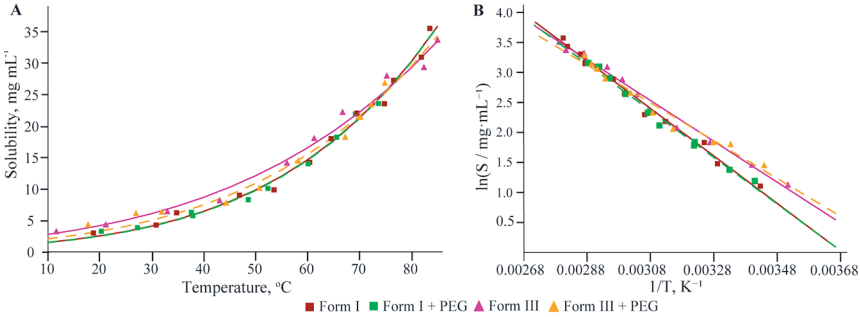

Figure 3.12. **The solubility curves of 2,6MeOBA polymorphs I and III in pure water and 1% PEG aqueous solution. A – exponential graph; B – linear graph. Brown solid line – Form I in pure water; Green dashed line – Form I in 1% PEG solution; Magenta solid line – Form III in pure water; Orange dashed line – Form III in a 1% PEG solution. Triangles and squares represent the experimental data**

slightly at temperatures up to 35 °C, but the solubility at higher temperatures is lower than in the pure solvent. The highly similar solubility of both forms can explain the nearly always observed concomitant crystallization in the presence of this additive, as observed in the crystallization experiments described in Section 3.3.1. The thermodynamic equilibrium point in 1% PEG solution was determined to be 8 °C lower than that in pure water (79 °C).

3.4.2. Solvent mediated phase transition study

Measurements of 2,6MeOBA SMPT kinetics show that the transformation rate in the slurry-bridging experiments is very fast (see Figure 3.13). From a mixture of both polymorphs pure Form I was obtained in less than 15 min in the tested solvents and 1% PEG aqueous solution, but use of 0.1% HPC aqueous solution decelerated the SMPT to Form I. A complete transformation of pure Form III to pure Form I in water was slower. The time of SMPT from pure Form III in 1% PEG solution is longer than from the mixture of both polymorphs, but the use of 0.1% HPC solution inhibited the SMPT of pure Form III to Form I. SMPT was not detected even in a sample slurred for 24 h.

Crystallization outcome of INA in the presence of crystallization additives (see Section 3.3.3) in general suggest a possibility that Form III nucleates first and then by stirring the suspension transforms into other more stable forms via SMPT. The results of SMPT experiments (see Figure 3.14) showed that the crystal form obtained in presence of all the tested additives did not change notably within 30 minutes after the nucleation, which is in agreement with SMPT seeding experiment by Kulkarni et al.[89] Therefore, the various polymorphic outcome using different stirring rate is not because of an SMPT but instead

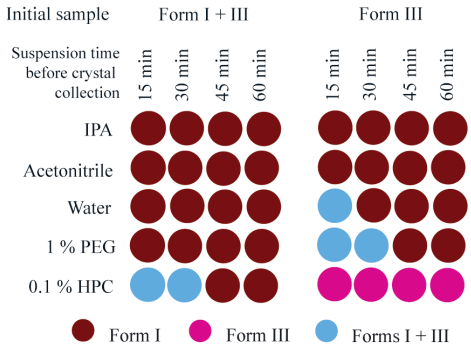

Figure 3.13. **Polymorphic composition of the solid phase after selected times during SMPT kinetic experiments at 25 °C**

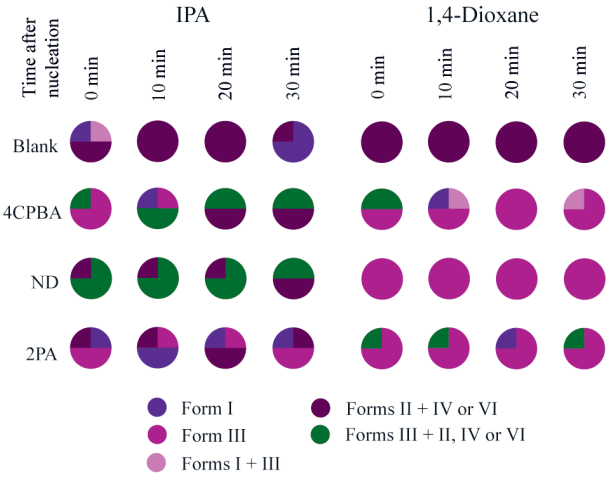

Figure 3.14. **Summary of INA polymorphs obtained in crystallization in presence of selected additives using 1 °C min^{-1} cooling rate and different time when crystals were collected after the nucleation. Each ¼ of the pie chart represents one of the parallel experiments**

because of the distinct ability of additives to affect the crystallization outcome. When higher cooling rates are used, the nucleation occurs at lower temperature and therefore at higher supersaturation, whereas, when slower cooling rates are used, the nucleation occurs at higher temperatures and therefore lower supersaturation. Additives decreased the nucleation temperature by increasing the supersaturation, and this, in fact, might be one of the potential effects of additives which could alter the obtained crystallization products.

3.4.3. Crystallographic characterization

The *anti* conformer of MPBA with two intramolecular hydrogen bonds between boronic acid hydroxyl groups and methoxy groups was found to be the global energy minimum conformation. Analysis of INA molecular conformation showed that in the most stable conformation the benzene ring and the amide group are twisted and the torsion angle between them is 21.9°.

For the calculation of intermolecular energy, the crystal structure of MPBA Form I in the monoclinic *Pc* space group without disorder in the dimers formed by the *syn-anti*-conformers was used. The lattice energy of both polymorphs is almost identical (see Table 3.5). Although the calculated relative energy contradicts Form I being determined as the thermodynamically stable polymorph, the possibility for different hydrogen atom arrangement in dimers could provide an entropy increase, resulting in lowering of the free energy of Form I. For INA, the lowest lattice energy is calculated for Form I, with the lattice energy of the Form II being the second lowest of the lattice energy values. All the other polymorphs have almost identical lattice energy. The very close lattice energy values agree with the observed concomitant crystallization of the polymorphs. Calculated energy differences of polymorphs for both substances corresponds to the typical energy difference (<5 kJ·mol^{-1}) of organic polymorphs.[64,69]

The pronounced differences in the hydrogen bonding in both MPBA polymorphs result in high differences in the lattice energy component contributions and energy frameworks of both forms. The electrostatic energy in Form I is the dominant component of the lattice energy, which can be associated with

Table 3.5. **Selected crystallographic and intramolecular, intermolecular and lattice energy data of MPBA and INA polymorphs**

Model substance	Polymorph	CSD Refcode	Z/Z'	E_{intra}, kJ mol^{-1}	E_{inter}, kJ mol^{-1}	$E_{lattice}$, kJ mol^{-1}
MPBA	Form I	UJACIT01 (original $P\bar{4}n2$ structure)	4/0.5 ($P\bar{4}n2$); 4/2 (Pc)	15.2	–144.4	–129.2
	Form II	UJACIT	12/1.5	6.0	–135.9	–129.8
INA	Form I	EHOWIH01	4 / 1	0.46	–124.7	–124.3
	Form II	EHOWIH02	8 / 2	0.05	–122.2	–122.2
	Form III	EHOWIH03	8 / 1	0.51	–120.6	–120.1
	Form IV	EHOWIH04	6 / 3	0.12	–119.8	–119.7
	Form VI	EHOWIH06	8 / 2	0.04	–121.4	–121.4

the extensive strong hydrogen bond network in this structure. In contrast, the electrostatic energy and dispersion energy in Form II have a very similar contribution in the lattice energy, because of a much smaller amount of intermolecular hydrogen bonds and higher importance of the aromatic interactions, including π-π stacking. To sum up, despite overall more efficient dispersion interactions in Form II, the notably stronger hydrogen bonds in Form I are the reason for the higher intermolecular energy of this form, which could also explain its higher stability. The ability of hydrogen bonding to provide stabilization of the crystal structure has been shown before, e.g., in studies of proteins[90,91] and ritonavir.[92] As expected, based on the highly similar intramolecular interactions and molecular packing, all INA polymorphs, except for Form I, have almost identical layout of energy frameworks. The main interactions stabilizing the crystal structure of all forms are dominated by electrostatic energy components, and the dispersion energy components are notably weaker than the electrostatic energy components. The most notable of electrostatic energy dominated interactions in Form I are interactions between molecules forming hydrogen bonded dimers. In contrast, the most notable interactions dominated by electrostatic energy in all the other INA polymorphs are among molecules forming hydrogen bonded INA molecule chains in two spatial directions and, therefore, forming hydrogen bonded INA molecule layers. The interactions having the most negative dispersion energy in Forms I and III are between the same molecules as those also have the most negative electrostatic energy. In contrast, in Form II, IV and VI these are aromatic and π-π interactions between oppositely oriented molecules from adjacent INA molecule layer and interactions with molecules hydrogen bonded to the mentioned molecules from adjacent layers.

Differences in the intermolecular interactions of both MPBA forms and similarity of INA Forms II, IV and VI can also clearly be seen on the Hirshfeld surfaces and in the analysis of their 2D fingerprint plots, but notable differences were observed in INA Forms I and III (see Figure 3.15). In MPBA Form I the hydrogen bonds forming the boronic acid dimers and chains, and different H···C interactions are the main observable interactions. Both symmetrically independent molecules of MPBA Form II have only one sharp peak corresponding to being a donor (molecule A) or acceptor (molecule B) of the strong intermolecular hydrogen bond. Also, interactions associated with π-π stacking are present for MPBA Form II molecule B. In the Hirshfeld surface fingerprint plot of INA Form I there are two sharp peaks corresponding to interactions CO···H_2N, whereas for all the other forms these peaks are wider and each corresponds to two interactions: N_{pyr}···H_2N or CO···H_2N. In the fingerprint plots of Forms II, IV and VI there is a distinct peak in the middle of the plot corresponding to CH···HC interactions. Another difference between the fingerprint plots of these three forms and Forms I and III is present in the region corresponding to π-π interactions in the middle of the plot.

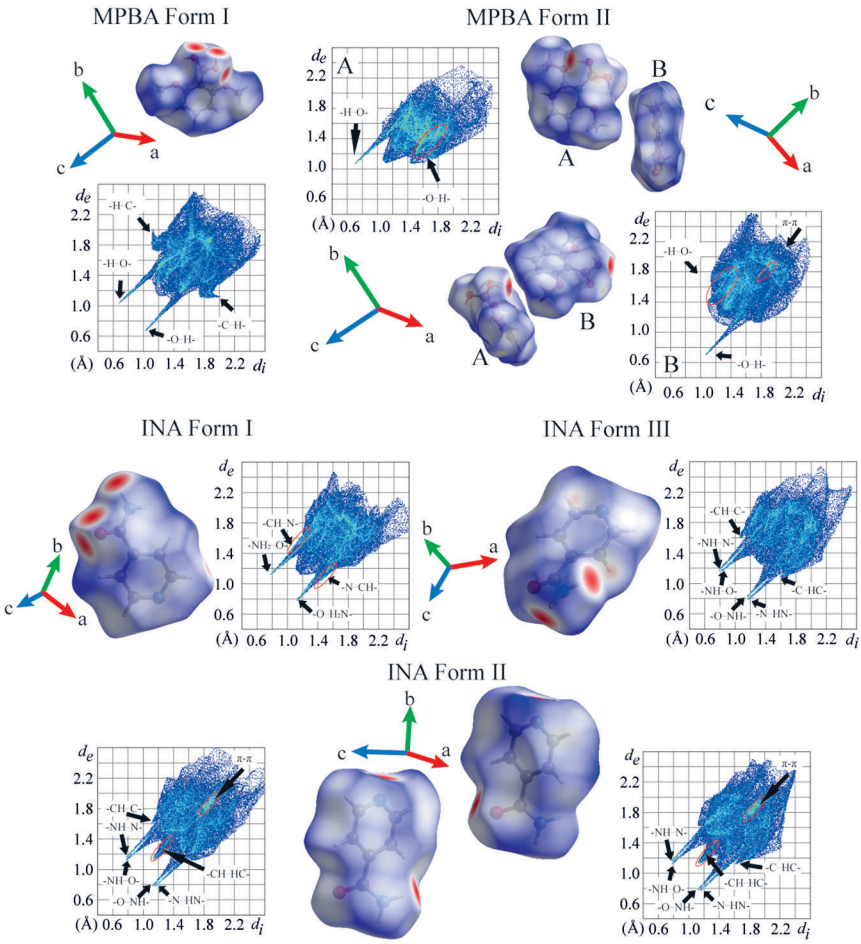

Figure 3.15. **Hirshfeld surfaces and their 2D fingerprinting plots of MPBA Forms I and II and INA Forms I – III by providing the most characteristic intermolecular interactions observed in the plots**

3.4.4. FIM and BFDH analysis

In the MPBA Form I formed by homodimers, most of the interaction preferences are satisfied. In contrast, only half of the interaction preferences for hydrogen bonding are satisfied in Form II. Therefore, the hydrogen bonding in MPBA Form II does not match the interaction preferences as in the CSD, and the three unsatisfied hydrogen bond acceptors may be the reason for the low

stability of Form II and formation of this polymorph only under specific conditions. FIM analysis for INA molecules were not performed, because in all polymorphs INA molecules adopt essentially identical conformation and all the interactions are satisfied.

There are large differences between both MPBA polymorphs when FIMs on crystal facets are compared (see Figure 3.16). Form I crystals have a larger probability of being involved in hydrophobic interactions and interact with hydrogen bond acceptors when compared to Form II. The MPBA Form II crystal has a larger probability of interacting with hydrogen bond donors on the largest facets when compared to Form I. On these facets, the oxygen atoms of the boronic acid groups in *anti*-planar conformation are forming hydrogen bonds and the facets are growing by formation of trimers, so hydrogen bond acceptors are exposed and there is a great propensity to interact with hydrogen bond donors by these facets. Therefore, surfactants can interact as hydrogen bond donors with these facets more easily if compared to Form I, for which hydrogen bond acceptor groups cover a smaller area. Span 20 and OGP both have hydrogen bond donor groups that can interact with the boronic acid group of MPBA and stabilize Form II crystals. Additionally, the hydrophobic site of the surfactants can decelerate phase transition by forming micelles or hemispheres and therefore prevent the reorganization of molecules required for the transformation of Form II to Form I.

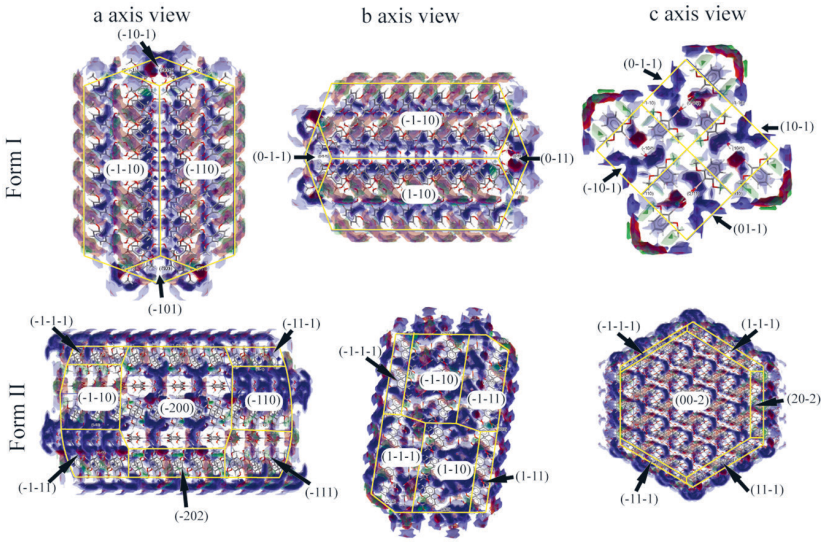

Figure 3.16. **FIMs combined on the BFDH morphology of MPBA Form I and II. Regions of hydrogen bond donor probability are shown in blue, hydrogen bond acceptors are shown in red, and hydrophobic interactions are shown in green**

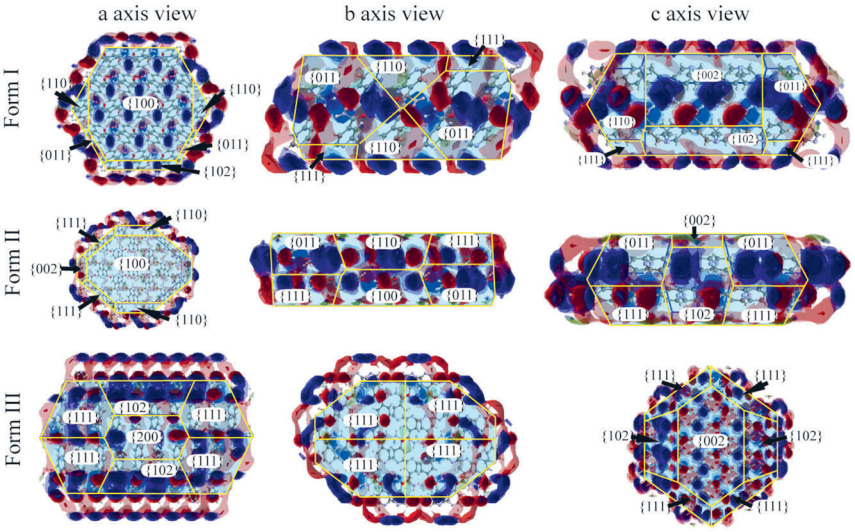

Figure 3.17. **FIMs combined on the BFDH morphology of INA Forms I-III. Regions of hydrogen bond donor probability are shown in blue, hydrogen bond acceptors are shown in red, and hydrophobic interactions are shown in green**

Because of the highly similar molecular packing also BFDH morphology and FIMs plotted on the crystal faces of INA Forms II, IV and VI are very similar (see Figure 3.17). The largest crystal faces of these polymorphs are growing by attaching molecules linked by different π-π and CH···π interactions, whereas the smallest faster growing planes by attaching molecules linked by hydrogen bonds. In contrast, for INA Forms I and III also on the largest planes hydrogen bond acceptors and donors are exposed and therefore these are among the interactions forming by growth of these faces. Face group {100} of Form I is growing by formation of amide $R_2^2(8)$ homodimers, but plane groups {111} and {002} of Form III are growing by continuation of CO···H_2N chains, therefore, hydrogen bond donors such as 2PA or 4CPBA can interact with this plane or facilitate growth of polymorph with such surface by activating the growth site and facilitating growth of these polymorphs.

CONCLUSIONS

1. In crystal structures of the four new (propionic acid, butyric acid mono- and disolvate, trifluoroethanol) and four already known (formic acid, acetic acid, formamide and propionic acid disolvate) isonicotinamide solvates similar hydrogen bond patterns are observed, and in general this allow prediction of intermolecular interactions and molecular packaging for new solvates/co-crystals with structurally similar solvents/co-formers.
2. Polyethylene glycol and hydroxypropyl cellulose facilitate the crystallization of 2,6-dimethoxybenzoic acid Form III, but the effect is not selective since it can also crystallise with impurity of Form I.
3. Hydroxypropyl cellulose inhibits the solvent mediated phase transformation of Form III of 2,6-dimethoxybenzoic acid, which enables this form to crystallize more frequently.
4. In the presence of sorbitan laurate (Span 20) and octyl β-D-glucopyranoside it is possible to crystallise 2,6-dimethoxyphenylboronic acid Form II. These crystallisation additives improve the stability of 2,6-dimethoxyphenylboronic acid Form II by stabilising it for up to 1 month. It has been observed that in the presence of sorbitan laurate the solvent has no effect on the polymorph obtained in the crystallisation of 2,6-dimethoxyphenylboronic acid.
5. Analysis of the morphology and full-interaction maps allowed to determine that the additives can adsorb on the surface of the crystal planes {002} and {110} of 2,6-dimethoxyphenylboronic acid Form II, which is likely to prevent the phase transition to Form I.
6. Crystallization of isonicotinamide in the presence of naphthalene-1,5-diol facilitated crystallization of Form III, while 2-picolinic acid facilitated crystallization of Form I. Most of the additives used reduced the content of other polymorphic forms in the crystallisation products. By employing fast cooling rates (20 °C min^{-1}) additives allowed crystallization of isonicotinamide Form III, but almost all the additives lost their ability to provide crystallization control at low cooling rates (0.1 °C min^{-1}).
7. Isonicotinamide polymorphs crystallizing concomitantly (Forms II, IV and VI) exhibit similar lattice energy and intermolecular interactions. Therefore, it is possible that the energy barrier of the nucleation and crystal growth rate of these polymorphs are very similar, while the presence of additives, by altering the crystallization conditions, may lead to crystallization of structurally different forms.
8. Analysis of the morphology and full-interaction maps allowed to identificate that the additives can adsorb to the surface of the {100} crystal planes of isonicotinamide Form I and the {111} and {002} crystal planes of Form III, which could involve activation of these growth sites to crystallize Form I or III.

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