The Role of Cocrystals in Solid-State Synthesis of Imides
and the Development of Novel Crystalline Forms
of Active Pharmaceutical Ingredients

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
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Dedication

For my family
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The Role of Cocrystals in Solid-State Synthesis of Imides and the Development of Novel Crystalline Forms of Active Pharmaceutical Ingredients

Miranda L. Cheney

ABSTRACT

With a greater understanding of the fundamentals of crystal engineering lays the potential for the development of a vast array of novel materials for a plethora of applications. Addressed herein is the latent potential of the current knowledge base with an emphasis upon cocrystallization and the desire for scientific exploration that will lead to the development of a future generation of novel cocrystals. The focus of this dissertation is to expand the cocrystallization knowledge base in two directions with the utilization of cocrystals in the novel synthetic technique of cocrystal controlled solid-state synthesis and in the development of active pharmaceutical ingredients.

Cocrystal controlled solid-state synthesis uses a cocrystal to align the reactive moieties in such a way that the reaction occurs more quickly and in higher yield than the typical solution methodology. The focus herein is upon cocrystal controlled solid-state synthesis of imides where an anhydride and primary amine were the reactive moieties. Forty-nine reactions were attempted and thirty-two resulted in successful imide formation. In addition, the cocrystal was isolated as part of the reaction pathway in three cases and is described in detail.
The impact of cocrystals upon active pharmaceutical ingredients is also addressed with a focus upon generating novel crystal forms of lamotrigine and meloxicam. Cocrystallization attempts of lamotrigine resulted in ten novel crystal forms including three cocrystals, one cocrystal solvate, three salts, one solvated salt, a methanol solvate, and an ethanol hydrate. Additionally, cocrystallization attempts of meloxicam afforded seven novel cocrystals. Solubility and pharmacokinetic studies were conducted for a selected set of lamotrigine and meloxicam crystal forms to determine the crystal form with the most desirable properties. Properties between crystal form and cocrystal former were also examined.
Chapter 1 - Introduction

1.1. Introduction

1.2. Supramolecular chemistry

Supramolecular chemistry,\textsuperscript{1, 2} or the chemistry of the intermolecular bond,\textsuperscript{3} has been defined by Jean Marie Lehn as “chemistry beyond the molecule”.\textsuperscript{4} Supramolecular chemistry is therefore inherently reliant upon the understanding of molecules at the molecular level, i.e. the chemistry of covalent interactions that hold atoms together, to facilitate the study of the intermolecular interactions \textit{between} neighboring molecules. Initial studies of complexes once called “Übermoleküls”\textsuperscript{5} or “supermolecules” were examined to gain insight into the intermolecular interactions that afforded such conglomerations. The basic concepts that developed were premised upon the reliability of molecular recognition events between two different but complementary molecules initially described as the receptor and the substrate. Investigations into substrate-receptor binding was first examined in the context of biological processes which led to the development of the “lock and key” model described by Emil Fischer.\textsuperscript{6} The realization of Nature’s success with molecular recognition led to the deliberate design of complexes founded upon molecular recognition events such as crown ethers,\textsuperscript{7} cavitands,\textsuperscript{8} and cryptands\textsuperscript{9} designed for ion selection.\textsuperscript{10-12} Further exploration into molecular recognition
devices produced functional supramolecular receptors for applications such as catalysis\textsuperscript{13, 14} and carrier-mediated membrane transport\textsuperscript{15, 16}.

1.3. Self Assembly and Intermolecular Interactions

Supramolecular chemistry is reliant upon molecular recognition and self assembly of target molecules via weak non covalent intermolecular interactions such as hydrogen bonds, metal coordination bonds, CH-π, π-π, van der Waals forces, and electrostatic interactions\textsuperscript{2}. A summary of the bond energies of a select set of intermolecular interactions with a relevant example is provided in Table 1.1\textsuperscript{17}.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|l|}
\hline
Interaction & Strength (kJ/mol) & Example \\
\hline
Covalent & 150-450 & O-O to C-C bond \\
Non Covalent & 2-300 & Dispersion to ion-ion \\
Hydrogen Bond & 4-120 & CH⋯π to HF \\
Dipole-Dipole & 5-50 & Acetone \\
π-π Stacking & <50 & Benzene \\
van der Waals & <5 & Inert gas \\
\hline
\end{tabular}
\caption{Summary of intermolecular interactions commonly exhibited in supramolecular chemistry with the covalent bond included for comparison}
\end{table}

The hydrogen bond is of particular importance in supramolecular chemistry because of its relative strength and directionality\textsuperscript{18}. A definition of a hydrogen bond has been suggested by many authors with the earliest examples being the most restrictive (electronegative atom interacting with another electronegative atom with a hydrogen in
However, more recent definitions include weaker interactions such as CH\textsubscript{3}O as hydrogen bonds. For the purpose of this dissertation a hydrogen bond will include interactions between two electronegative atoms, typically separated by a distance less than the sum of the van der Waals radii, where one atom can be defined as the hydrogen bond donor and the other atom acts as the acceptor, where hydrogen is located between the two atoms and is directional in nature. Table 1.2 summarizes strong, moderate, and weak hydrogen bonds and their characteristic bond strengths, lengths, angles, interaction type, and the position of the hydrogen (closer to the donor (D) or acceptor (A)) relative to the strength of the bond.

\textbf{Table 1.2.} Summary of hydrogen bonds and their characteristics (D = donor, A = acceptor)

<table>
<thead>
<tr>
<th></th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
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<td>Hydrogen bond energy (kcal/mol)</td>
<td>15-40</td>
<td>4-15</td>
<td>Less than 4</td>
</tr>
<tr>
<td>D\textsubscript{•••}A distance (Å)</td>
<td>2.2-2.5</td>
<td>2.5-3.2</td>
<td>Less than 3.2</td>
</tr>
<tr>
<td>D-H vs. H\textsubscript{•••}A</td>
<td>X-H = H\textsubscript{•••}A</td>
<td>X-H &gt; H\textsubscript{•••}A</td>
<td>X-H &gt;&gt; H\textsubscript{•••}A</td>
</tr>
<tr>
<td>Bond angles (º)</td>
<td>170-180</td>
<td>&gt;130</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Hydrogen bond interaction type</td>
<td>covalent</td>
<td>electrostatic</td>
<td>electrostatic or dispersion</td>
</tr>
</tbody>
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Hydrogen bonding is also of great importance in biological systems. DNA, for example, is a molecular complex comprised of two strands of long chains of base pairs held together by hydrogen bonds. The replication of DNA relies upon the reversibility of hydrogen bonding as the process breaks then makes new hydrogen bonds facilitating data transcription and eventually cell replication. Without the occurrence of hydrogen bonds base pairs would not interact, DNA could not replicate, and life could not exist.
Hydrogen bonding is a key element throughout this dissertation and it will be the main intermolecular interaction focused upon for crystal structure analysis. π system overlap resulting in charge-transfer complexes will also be highlighted.

1.4. The Design of Supramolecular Solids – Crystal Engineering

Supramolecular chemistry was initially focused upon the study of supermolecules in solution. However, the field has since split into two directions: the study of supermolecules in solution and the study of supermolecules in the solid-state. The explorations into solid-state supramolecular chemistry led to the development of crystal engineering. The term crystal engineering was introduced by Pepinsky26, 27 in 1955 and was first practiced by Schmidt who utilized trans-cinnamic acids to design organic solid-state photochemical reactions.26, 28 The term “molecular engineering” was also introduced and used by Hippel to describe the building of materials and devices to order.29 Crystal engineering was later defined in 1989 by Desiraju as “the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties”.30 Thus, Desiraju’s definition portrays the potential of crystal engineering to result in the development of novel materials. Further exploration of organic supramolecular assemblies via crystal engineering by Etter,31-33 Desiraju, 30, 34-37 Wuest,38-41 Aoyama,42, 43 Whitesides,44-48 Stoddart,49-51 and many others has since realized this potential, affording a plethora of materials that are sustained by various molecular recognition events, including supramolecular synthons.34, 37
1.4.1. Supramolecular Synthons

Supramolecular synthons have been defined as non-covalent bonding between at least two complementary functional groups. The study of supramolecular synthons began with the carboxylic acid dimer formation with acetic acid in solution and has since progressed into two distinct types: the supramolecular homosynthon and the supramolecular heterosynthon. The supramolecular homosynthon is generated by a non-covalent interaction between two of the same moieties. A supramolecular heterosynthon also incorporates a non-covalent interaction however the interaction is between two different but complementary moieties.

Supramolecular synthons are typically sustained via hydrogen bonds formed between two electronegative atoms where one atom is also covalently bound to a hydrogen atom. Additionally, other weaker interactions such as $\pi-\pi$ stacking can also be considered a supramolecular synthon. Commonly employed supramolecular heterosynthons sustained via hydrogen bonding include carboxylic acid-amide, carboxylic acid-aromatic nitrogen, carboxylate-aromatic nitrogen, alcohol-aromatic nitrogen, and alcohol-amine. Typical distance ranges for these common supramolecular heterosynthons are ca. 2.5-2.8 Å, 2.4-2.8 Å, 2.5-3.0 Å, and 2.5-3.1 Å, respectively. Supramolecular homosynthons can also exist with any self complementary moiety such as a carboxylic acid or a primary amide. An example of an amide-amide supramolecular homosynthon and a carboxylic acid-amide supramolecular heterosynthon are shown in Figure 1.1. (a) and (b), respectively.
A commonly employed supramolecular heterosynthon is the carboxylic acid-aromatic nitrogen supramolecular heterosynthon, most likely due to its strength and reliability. Additionally, the aromatic nitrogen-alcohol supramolecular heterosynthon has also been researched to examine its dependability. A pictorial representation of the two supramolecular heterosynthons is provided in Figure 1.2.

The ability to manipulate supramolecular synthon formation to generate a desired supramolecular synthon has been explored by many. The work of Margret Etter is particularly noteworthy as, based upon her experimental data, she developed a set of rules to determine the potential for supramolecular synthon formation given various donor-acceptor systems. Her studies concluded with the development of three general
rules: (1) all good proton donors and acceptors are used (2) six membered ring
intramolecular hydrogen bonds will form in preference to intermolecular hydrogen bonds
and (3) the best proton donors and acceptors remaining after intramolecular hydrogen
bonding will form intermolecular hydrogen bonds with each other.\textsuperscript{33} She also developed
a plethora of more specific rules that applied only to certain functionalities. For further
knowledge one is directed to her \textit{Accounts of Chemical Research} article entitled
“Encoding and Decoding Hydrogen-Bond Patterns of Organic Compounds”. Etter was
also influential in the development of graph set analysis of supramolecular synthons.\textsuperscript{32}
Although the use of graph set notation to describe a supramolecular synthon can be
beneficial, the complexity that arises from larger supramolecular synthons has limited the
use of the terminology.

1.5. Cocrystals – A History

The history of cocrystals began in 1844 with Friedrich Wöhler’s synthesis of
quinhydrone from hydroquinone and quinone.\textsuperscript{108} The material, however, was not called a
cocrystal. In fact, many early cocrystals were hidden under the guise of other names such
as addition compounds,\textsuperscript{109} molecular complexes,\textsuperscript{110} organic molecular compounds,\textsuperscript{111} and
solid-state complexes.\textsuperscript{112} The term “co-crystal” was not used until 1967 to describe the
hydrogen bonded complex formed between 9-methyladenine and 1-methylthymine.\textsuperscript{113}
The term was then later popularized by Margret Etter in the 1990’s.

The debate over the term cocrystal began in 2003 with a controversial letter from
Desiraju where he asks: “what is co- to what?”\textsuperscript{114} Desiraju continues to explain that he
would prefer to call a multiple component system that is held together by non-covalent
interactions a “molecular complex”. Dunitz replies to Desiraju’s letter in agreement that the term is inaccurate and inelegant; however, he argues that the term molecular complex is too vague and could be interpreted to include solvates, inclusion compounds or amorphous solids. Dunitz also insists that the hyphen remain as it is used to signify a “togetherness” of two components.\textsuperscript{115} Aakeröy later defined cocrystals with a strict definition where three criteria must be satisfied: the components must be neutral, the solid must be made from components that are solids under ambient conditions, and it must consist of homogenous crystalline material where the components are present in stoichiometric ratios.\textsuperscript{116} However, Andrew Bond did not agree with the restrictions placed by Aakeröy (specifically that all components must be solids) as he calls the distinction “contrived and inappropriate”. He suggests that the term “multiple-component molecular crystals” be employed to describe a crystalline material containing components that are either liquid or solid under ambient conditions.\textsuperscript{117} Currently a ubiquitous definition for the term cocrystal does not exist. For the purpose of this dissertation, however, a cocrystal is defined as a stoichiometric multiple component crystal that is formed between two crystalline materials that are solids under ambient conditions. At least one of the components is molecular and forms a supramolecular synthon with the remaining component.\textsuperscript{118, 119}

Cocrystals are typically comprised of two or more molecules that contain multiple functional groups and are sustained by various supramolecular synthons. In general supramolecular heterosynthons are used in the formation of cocrystals; however, there are a few select examples where cocrystals are sustained via supramolecular mixed homosynthons, i.e. the carboxylic acid dimer formed by two chemically distinct
carboxylic acids. Due to the frequent use of supramolecular synthons to sustain cocrystals, cocrystals have played an integral part in furthering the understanding of supramolecular synthons and their hierarchy. The seminal works of Aakeroy, Shattock, and Bis are particularly noteworthy as they employ cocrystallization to delineate supramolecular synthon formation in the presence of carboxylic acids, amides, aromatic nitrogens, alcohols, and cyanos.

Aakeröy and co-workers tested Etter’s rules to determine if the strongest acid/base from their dataset would form a supramolecular synthon with the next strongest acid/base. Specifically, Aakeröy targeted ternary cocrystal formation by using three molecules that contained carboxylic acid, amide, and aromatic nitrogen moieties to determine which of the many possible supramolecular synthons would persist, however, this resulted in ternary cocrystals that were sustained by carboxylic acid-aromatic nitrogen and carboxylic acid-amide supramolecular synthons. An additional study for the generation of ternary cocrystals involved two carboxylic acid containing molecules (one stronger acid, one weaker acid) and one molecule with two aromatic nitrogen moieties of different basicities. The results confirmed one of Etter’s rules as the ternary cocrystals were sustained by the stronger acid forming a supramolecular synthon with the stronger base while the weaker acid formed a supramolecular synthon with the weaker base. The ternary cocrystal is shown in Figure 1.3. with the stronger acid (3,5-dinitrobenzoic acid (left)) paired with the imidazole nitrogen (1-((3-pyridyl)methyl)benzimidazole) and the weaker acid (3-(dimethylamino)benzoic acid (right)) paired with the aromatic nitrogen.
Shattock\textsuperscript{121, 127} and Bis\textsuperscript{85, 128} have taken a different approach to delineating the hierarchy of supramolecular synthons with the utilization of cocrystallization. Their studies involved three functional groups and three combinations of molecules. Each experiment was comprised of two molecules, one with two moieties present on the same molecule and another molecule that only contained one moiety. All permutations of molecular combinations were attempted. The experiments were designed in such a way that if a supramolecular synthon hierarchy existed then two out of the three experimental arms would succeed in cocrystal formation while the third would not form cocrystals.

The experimental work was divided into two separate competitive studies. Bis’ work tested the supramolecular synthon formation between alcohols, aromatic nitrogens, and cyanos\textsuperscript{128} while Shattock’s studies employed carboxylic acids, aromatic nitrogens, and alcohols.\textsuperscript{127} From the first set of moieties it was determined that the alcohol preferred to form a supramolecular synthon with the aromatic nitrogen, not the cyano moiety. The second set of moieties was more complex as the number of donor molecules increased to two with still only one acceptor. An additional unforeseen problem occurred due to the selection of molecules with more than one carboxylic acid or aromatic nitrogen moiety.
Thus in some cocrystals both the carboxylic acid-aromatic nitrogen and aromatic nitrogen-alcohol supramolecular heterosynthons were visualized. However, the study concluded that the carboxylic acid-aromatic nitrogen supramolecular heterosynthon was stronger than the alcohol-aromatic nitrogen due to the absence of cocrystal formation when a molecule containing both a carboxylic acid and aromatic nitrogen moiety was paired with an alcohol. Schematic representations of the potential supramolecular heterosynthons from both studies are shown in Figure 1.4. The reliable supramolecular heterosynthons (a, c, d) are shown with a green check mark while supramolecular heterosynthons with low percentage of occurrences (b, e) are indicated by a red X.

![Diagram](image)

**Figure 1.4.** Possible supramolecular synthons from supramolecular heterosynthon competitive studies. Green check marks indicate common supramolecular synthons. Red X’s indicate supramolecular synthons with a low percentage of occurrences.

The previously described crystal engineering studies employ cocrystal formation to determine the reliability of supramolecular synthon formation in a competitive situation. The success of these studies has provided valuable insight into the
supramolecular synthon hierarchy that can be applied to future cocrystallization attempts with molecules containing more than one moiety.

That cocrystals are an expanding field that continues to gain interest from both academia and the pharmaceutical industry is made evident from a search of SciFinder Scholar for references in the chemical abstracts that contain the term “cocrystal”.\textsuperscript{129} The search provided a list of 1,523 references. Analyzing those references by year elucidates their growing popularity. A pictorial representation is highlighted in Figure 1.5. The rapid increase can be attributed to their variety of applications such as non-linear optics for polar molecules,\textsuperscript{130-132} Polaroid film development,\textsuperscript{133} decrease tendency for hydration,\textsuperscript{134-138} improve thermal stability,\textsuperscript{139-141} chiral separation,\textsuperscript{142} improve compressibility and tabletting,\textsuperscript{143} increase % yield for solid-state synthesis,\textsuperscript{144} and alter solubility\textsuperscript{139,145-154} which can lead to improved bioavailability for active pharmaceutical ingredients.

\begin{figure}[h]
\begin{center}
\includegraphics[width=\textwidth]{figure1.png}
\end{center}
\caption{Analysis of SciFinder Scholar references by year for the term “cocrystal”}
\end{figure}
1.5.1. Cocrystal Synthesis

Cocrystals can be synthesized by various techniques including dry grinding or neat grinding,\textsuperscript{155, 156} solvent-drop grinding (also called liquid-assisted grinding),\textsuperscript{119, 155, 157-167} mixing, milling,\textsuperscript{168} reaction crystallization,\textsuperscript{169} slurring,\textsuperscript{158, 170-172} sonic slurring,\textsuperscript{161} and solution crystallization techniques designed to grow single crystals\textsuperscript{119} including slow evaporation from solution, vapor diffusion, and layering for liquid diffusion. The oldest cocrystallization technique is perhaps dry grinding as it was performed as early as the 1800’s.\textsuperscript{108} It was only since 2002 that solvent-drop grinding has been implemented for the synthesis of cocrystals.\textsuperscript{164} Grinding and milling are beneficial over traditional solution techniques as they are a “greener” approach requiring much less solvent and cocrystal formation tends to occur at a faster rate with higher yields.\textsuperscript{155} Solvent-drop grinding with multiple solvents has also proven to be a reliable method to generate polymorphs of a particular cocrystal.\textsuperscript{173} Recently the ability to interconvert between cocrystals of different stoichiometries via solvent-drop grinding has also been highlighted by Jones et.al.\textsuperscript{163} Additionally, the slurry methodology, widely used as a screening technique in the pharmaceutical industry, can be advantageous when gram-level amounts of cocrystal are required.

Attempts to illuminate cocrystal formation conditions were initiated by studies of the two components interacting in solution. Rodríguez-Hornedo pioneered the area with her studies of the carbamazepine nicotinamide cocrystal in solution by measuring the amount of cocrystal formed with variable concentrations of either carbamazepine or nicotinamide present in solution.\textsuperscript{174} Her studies showed that the greater the concentration of nicotinamide in solution, the greater the reduction in solubility of the cocrystal.\textsuperscript{175}
This is most likely due to the solid phase that is present in equilibrium with the liquid phase shifting from cocrystal to nicotinamide. Additional studies to investigate the equilibrium between solid and liquid phases of two molecules in solution have been conducted by the determination of ternary phase diagrams. The ternary phase diagram plotted by Chiarella et al. for trans-cinnamic acid and nicotinamide was generated to assist in the understanding of why solvent-drop grinding can be such a successful cocrystallization technique in lieu of traditional solution crystallization methods. Chiarella concluded that in a solvent system where the two components are of similar solubility then a 1:1 stoichiometric ratio solvent-drop grind will produce the cocrystal due to the correct balance of cocrystal formers and solvent. However, if cocrystal formation is attempted in a solvent in which the two components are of varying solubility then the region where the cocrystal formation occurs will be skewed to one side of the ternary diagram. Thus if a slow evaporation experiment was attempted, which inherently progresses down the center of the phase diagram as it looses solvent, the likelihood of cocrystal formation is decreased.

1.6. The Cambridge Structural Database and the Supramolecular Synthon Approach

With the vast improvements in X-ray crystallographic equipment within the past decade the amount of crystallographic data has grown exponentially as structural data can be collected and crystallographic details resolved more quickly than ever before. The increase in crystal data is reflected in the Cambridge Structural Database (CSD) which currently contains ca. 481,000 crystal structures. The CSD is a structural visualization
and analysis software developed by the Cambridge Crystallographic Data Centre. The contents of the CSD can be readily searched by multiple methods including chemical structures, names, authors, etc. The ability to search the CSD for a desired functionality can be useful in the design of cocrystals, moreover, the ability to search for specified supramolecular homosynthons and heterosynthons make the CSD an invaluable tool for crystal engineering of supramolecular solids including cocrystals.182-186

The first step in a cocrystallization experiment is to conduct a search of the CSD for the moiety present on the target molecule. The resulting entries are then cross referenced with the presence of a plethora of additional complementary moieties. The next step is to determine if the supramolecular homosynthon or heterosynthon is the dominant interaction between the moieties in question. If the supramolecular heterosynthon has a greater percentage of occurrences then a cocrystal can most likely be made, however, if the supramolecular homosynthon is dominant then the likelihood of cocrystal formation is reduced. This type of statistical analysis of the CSD has been coined the “supramolecular synthon approach”.85,119,121 The statistics that can be procured from the CSD is beneficial for cocrystal synthesis and has proven to be fairly reliable for simple systems were there are only one or two functional groups such as carboxylic acid-aromatic nitrogen, alcohol-aromatic nitrogen, or carboxylic acid-amide. The major weakness of the CSD is that even with its ca. 481,000 entries there is still not enough data to address some competitive supramolecular synthon situations. This lack of data spawned the works of Shattock127 and Bis128 which has since provided partial guidance in the design of cocrystals in the presence of multiple functional groups.
1.7. Solid-State Synthesis is Green Chemistry

The emergence of green chemistry in the early 1990’s has lead to an increased interest in the development of many solid-state synthetic methodologies. Photodimerization, for example, is a widely accepted solid-state reaction technique first practiced in the early 1900’s, and incorporates the principles of topochemistry into solid-state organic synthesis. Schmidt’s exploration of topochemical reactions via photodimerizations led him to further develop the field of topochemistry towards the development of the topochemical postulate, first proposed by Kohlschutter in 1919. The postulate states that a “reaction in the solid state occurs with a minimum amount of atomic or molecular movement”. The postulate therefore implies that the reactivity of a complex is controlled by the distances and orientations established by the molecular packing within the crystal structure. Schmidt’s studies involving the [2+2] photodimerizations of α- and β-cinnamic acids to their corresponding truxillic acids led him to the conclusion that typically, if the reacting moieties are at a distance less than 4.2Å apart in the solid-state, the photodimerization will occur. From these findings Schmidt was able to develop a variety of principles which served to guide others in the field including the requirement for π electron system overlap for photodimerization to occur. With these imposing restrictions, solid-state reactions tend to be more selective than those in solution, however, if the reaction does occur it is typically with higher yields and greater stereospecificity.
More recently, the field of solid-state synthesis has been explored by many scientists including Fumio Toda, Reiko Kuroda, and Gerd Kaupp. Interestingly, through the use of a multiple of reaction types, Kaupp has shown that solid-state reactions can and do often result in 100% yield. Kaupp employs multiple solid-state synthetic techniques such as grinding, heating, and photoirradiation and monitors the reactions with atomic force microscopy and scanning electron microscopy. With these powerful tools, he has found that molecular movement can occur across distances of greater than 4.2Å therefore questioning the guidelines imposed by Schmidt. In particular, anthracene can undergo photodimerization when the distance between anthracene molecules is 6.038Å, as was proven by atomic force microscopy. After analysis of a group of solid-state reactions that occur where the reactants are at a distance...
greater than 4.2Å apart he concludes that “we found no fundamental differences between
topochemically allowed and forbidden reactions”.

1.7.1. Cocrystals and Solid-State Synthesis

The influence of the principles of crystal engineering upon cocrystallization in solid-state synthesis has afforded an effective synthetic reaction design strategy. As was previously discussed, a cocrystal can be designed by utilizing the supramolecular synthon approach and the crystallographic information in the Cambridge Structural Database. The target molecule and cocrystal former are chosen such that complementary moieties are present, allowing for robust and reliable supramolecular heterosynthon formation. The cocrystal is then subjected to conditions under which the reaction can occur. [2+2] photodimerization\textsuperscript{212-217} and nucleophilic substitution reactions\textsuperscript{218} have thus far been successful in the utilization of cocrystals for solid-state chemistry. It is believed that the presence of the cocrystal prior to the reaction allows for the proper orientation of the molecules in the solid-state (less than 4.2Å for the reacting synthons) such that the reaction will occur faster and with a higher yield than if the cocrystal was not formed. Primary interactions commonly employed to sustain cocrystals are strong hydrogen bonds; however, cocrystals are also supported by other weaker interactions such as CH⋯π and π-π stacking.

Leonard MacGillivray has pioneered the area of template directed solid-state synthesis via cocrystallization.\textsuperscript{212-215} A prototypal cocrystal for MacGillivray is comprised of an aromatic dialcohol such as resorcinol and an olefin containing two aromatic nitrogens. The cocrystal is sustained via alcohol-aromatic nitrogen interactions, which
forces a geometrical alignment of the alkene segments such that the cocrystal facilitates the [2+2] photodimerization reaction. A prototypal example is shown in Figure 1.7.

where the cocrystal is formed between resorcinol and trans-1,2-bis(4-pyridyl)ethylene. The cocrystal allows for the appropriate alignment of the molecules such that when the solid is photoirradiated the [2+2] photodimerizations occurs resulting in rctt-tetrakis(4-pyridyl)cyclobutane. The cocrystal is considered by MacGillivray to be a reaction template because without the formation of the cocrystal, the olefins would not be in the proper orientation in the solid for the reaction to occur. MacGillivrays recent work has implemented his cocrystal template photodimerization reactions for the development of novel ligands for the synthesis of metal-organic frameworks.

An additional example of a cocrystal incorporated in organic synthesis was conducted by Etter who performed a nucleophilic substitution reaction employing a cocrystal as a reagent. The cocrystal, generated from solvent-drop grinding of 4-
chloro-3,5-dinitrobenzoic acid and 4-aminobenzoic acid, was sustained by a carboxylic acid dimer and, in the solid state, the chlorine and the primary amine were in close proximity (less than 4.2 Å) allowing for the SN$_2$ nucleophilic substitution reaction to occur upon heating of the cocrystal at 180°C.

Cocrystallization is also particularly amenable to condensation reactions in the solid-state. The condensation of a primary amine and a carboxylic acid anhydride to generate an imide provides an exemplary case as the supramolecular synthon formation can be envisioned between the amine and anhydride moieties and the loss of water molecules can be accomplished by simple heating of solids. The focus of the second chapter of this dissertation addresses the use of cocrystals as reactive intermediates with an emphasis upon the cocrystals ability to align the reactive moieties and bring them into close proximity to encourage the minimal amount of molecular movement required to conduct the synthetic reaction in the solid-state.

1.8. The Impact of Crystal Form

A crystal has been suggested by Dunitz to be a “supermolecule par excellence” as it involves a complicated array of molecular recognition and periodic arrangement to result in long range order. The molecular recognition events and desire for energy minimizations drive the arrangement of the molecules in the crystal lattice. Additionally the particular arrangement determines the physical properties of the crystal, including polarizability, magnetic susceptibility, piezoelectricity, melting point, and solubility. The development of a crystal form is also of great importance in the pharmaceutical industry as crystalline forms tend to be more stable than amorphous
Some drugs, however, are still marketed as amorphous forms due to the improved solubility in comparison to the crystalline competitor.\textsuperscript{225} The propensity for an alternate crystal form of an active pharmaceutical ingredient (API) to possess different physical and pharmacokinetic properties from the original API is of great value to the pharmaceutical industry especially as many (ca. 60\%) of the new APIs being developed are of low solubility.\textsuperscript{226} The increased occurrence of low solubility drugs can be attributed in part to the modeling methods used in the design of some new drugs. For example, the API zanamivir\textsuperscript{227} was synthesized after molecular modeling provided insight into the binding sites of the influenza virus. The drug was then designed to bind to the virus with the intent of virus inhibition.\textsuperscript{228} This drug design plan does not consider the physicochemical properties of the resulting API.

\subsection*{1.8.1. Crystal Form Types}

There are a plethora of crystal form types that can be isolated for an API. The synthesis and investigation of physical properties of various crystal forms is the subject of many review articles.\textsuperscript{229-243} The diversity of moieties and torsional flexibility of many APIs predisposes the formation of multiple crystal forms including, pharmaceutical salts, cocrystals, solvates, hydrates, cocrystals of salts, and polymorphs of all of the above. Some API’s, however, may not possess an ionizable group thus limiting its ability to form salts. In such a situation the API can then be targeted for cocrystal formation. Additional crystal forms such as solvates and hydrates that may not be intentionally created are not uncommon in the pharmaceutical industry. Polymorphs may also be formed for all crystal forms and are prevalent in ca. 50\% of all drug substances.\textsuperscript{244}
All of the crystal forms highlighted above can alter the physicochemical properties of the API. The earliest crystal forms intentionally studied for their unique properties were pharmaceutical salts. Due to the well established history of pharmaceutical salts and their ability to alter physicochemical and pharmacokinetic properties, only one example will be provided herein. Pharmaceutical cocrystals, first developed in 2003, will be addressed in much greater detail as there are only a few published reports providing solubility or pharmacokinetic data of pharmaceutical cocrystals.

Pharmaceutical salts are materials formed by an ionic API and a suitable, pharmaceutically acceptable counterion. They have been a part of crystal form selection for decades as they offer diversity of composition and can therefore exhibit a wide range of physicochemical properties. The most commonly used anion and cation in the generation of pharmaceutical salts is chloride and sodium, respectively. Pharmaceutical salts have been used to enhance the solubility of poorly soluble APIs which represent approximately 40% of the drugs on the market and as many as 60% of APIs in development. Improving the solubility or dissolution rate of a Biopharmaceutics Classification System (BCS) Class II API is possible via pharmaceutical salt formation. For example, in the late 1950’s Juncher and Raaschou developed three novel salt forms of penicillin V that exhibited superior dissolution profiles in comparison to the original API. When conducting a pharmacokinetic study, it was observed that the salt form enabling the highest in vivo exposure of penicillin V was the same form that possessed the most rapid dissolution rate.
The BCS scheme was developed as a method of classifying drugs based upon their solubility and permeability. A BCS type I drug is high solubility and high permeability, type II shows low solubility but high permeability, type III is high solubility and low permeability, and type IV exhibits low solubility and low permeability. The definition of high solubility for the BCS system is determined by the ability of the largest dose size of the drug to dissolve in less than 250 mL of water over the pH range of 1-7.5. If the API does not fit these criteria then it is classified as low solubility. BCS defines high permeability as the ability for greater than 90% of the dose of the API to be absorbed. If the absorption is less than 90% then it is classified as low permeability. The initial intention of the BCS was to correlate the solubility and permeability of a drug such that an estimation of absorption could be made. Currently the federal drug administration implements the BCS as guidance for qualification for a biowaiver, i.e. a waiver for the \textit{in vivo} bioavailability and bioequivalence studies. To obtain a biowaiver from the federal drug administration there are many restrictions including that the drug must be BCS class I (high solubility, high permeability) and must be an immediate release drug that is administered as a solid dosage form.\textsuperscript{252}

The importance of hydrates and solvates in pharmaceutical development has also been recognized.\textsuperscript{253,254} Various examples have demonstrated that the formation of hydrates and solvates can significantly alter the physicochemical properties of APIs, such as chemical stability, solubility, and dissolution rate.\textsuperscript{255-258}

A more recently applied technique for crystal form development is pharmaceutical cocrystallization.\textsuperscript{118} Pharmaceutical cocrystals can be defined as multiple component crystals in which at least one component is molecular and a solid at room
temperature (the cocrystal former) and forms a supramolecular synthon with a molecular or ionic API.\textsuperscript{118} The cocrystal former must also be a pharmaceutically acceptable compound.\textsuperscript{119,121} Pharmaceutical cocrystals have demonstrated that they can profoundly modify the physicochemical properties of the parent API molecule\textsuperscript{136, 139-141, 145-147, 149-154, 259-268} and at least 90 APIs have been studied in the context of cocrystallization. Often APIs that are targeted for pharmaceutical cocrystallization experience undesirable solubility and/or stability and possess multiple hydrogen bonding sites.\textsuperscript{269} The following sections summarize a set of existing pharmaceutical cocrystals were their solubility and animal pharmacokinetic behavior is known.

1.8.2. Pharmaceutical Cocrystals with Solubility Data

Solubility can be defined as the concentration at which the solution phase is in equilibrium with the solid phase at a given temperature and pressure.\textsuperscript{270} The solubility of a pharmaceutical cocrystal is of great importance as it can be the limiting factor in the absorption of a drug.\textsuperscript{271} Solubilities of pharmaceutical cocrystals have been measured in water, pH 1 HCl solutions, fasted and fed simulated gastric fluid, and fasted and fed simulated intestinal fluid. Variability amongst the conditions is attributed to the desire to mimic specific regions along the gastrointestinal tract to gain a better understanding of the drugs behavior after it is administered orally. Furthermore a solubility study can indicate whether the cocrystal disassociates back to its original components in solution by testing the solid post solubility study.

The first dissolution profile for a pharmaceutical cocrystal was published by Almarsson et.al.\textsuperscript{154} The target API was itraconazole, an antifungal drug with poor
aqueous solubility. The resulting pharmaceutical cocrystals include a fumaric acid, succinic acid, L-malic acid, L-tartaric acid, D-tartaric acid, and DL-tartaric acid cocrystal. The crystal structure of the itraconazole succinic acid cocrystal is shown in Figure 1.8. The solubility of the succinic acid, L-malic acid, and L-tartaric acid cocrystals was measured in 0.1 N HCl and compared to an amorphous formulation of itraconazole coated on Sporanox® beads and a crystalline form of itraconazole. The study showed that the L-malic acid cocrystal was as soluble as the on the market Sporonox® bead form of itraconazole thus proving that a cocrystal can be just as soluble as an amorphous form.

**Figure 1.8.** Hydrogen bonding of itraconazole succinic acid cocrystal with succinic acid molecule in green

During an attempt to generate pharmaceutical cocrystals of fluoxetine HCl a unique supramolecular synthon was discovered in 2004 by Childs et.al.\textsuperscript{153} The supramolecular synthon involved a secondary amine and a carboxylic acid hydrogen bonded together with a chloride anion positioned in between. Childs’ JACS article published in 2004 highlighted three pharmaceutical cocrystals with the commonly prescribed antidepressant that were all sustained via the novel supramolecular synthon. Fluoxetine HCl fumaric acid, fluoxetine HCl succinic acid, fluoxetine HCl benzoic acid
cocrystals were synthesized from crystallization of the HCl salt of fluoxetine with the respective cocrystal formers. The supramolecular synthon is exemplified in the fluoxetine HCl succinic acid cocrystal shown in Figure 1.9. The dissolution profiles were conducted both on free flowing powdered cocrystal and on compressed tablets of cocrystal. Both methods were conducted to elucidate the solubility of the cocrystals before forty minutes. The dissolution profiles from the free flowing powder study showed that the benzoic acid cocrystal was the least soluble cocrystal. The fumaric acid cocrystal achieved a 30% improvement in solubility in comparison to fluoxetine HCl and the succinic acid cocrystal doubled the concentration of fluoxetine HCl. Interestingly, the succinic acid cocrystal concentration begins to decline after twenty minutes into a profile that is now commonly referred to as a spring and parachute profile.\textsuperscript{272} This behavior is attributed to the cocrystal initially enhancing the solubility of the API but then disassociating into the original components in solution.

\textbf{Figure 1.9.} Fluoxetine HCl succinic acid cocrystal supramolecular synths were the Cl is shown in dark green
The next solubility study published chronologically incorporated both salts and cocrystals of saccharin with various APIs.\textsuperscript{152} When saccharin was complexed with quinine, hapoperidol, mirtazapine, pseudoephedrine, lamivudine, risperidone, sertraline, venlafaxine, zolepidem, and amlodipine the result was a pharmaceutical salt. Attempts to complex saccharin to piroxicam led to the only cocrystal reported in the study. The solubilities of the various saccharin salts previously mentioned will not be covered in detail, however, it is noteworthy to mention that eight out of the ten saccharin salts showed appreciably higher solubility than the pure API. The piroxicam saccharin cocrystal, shown in Figure 1.10., obtained a solubility level similar to that of pure piroxicam. Thus the conclusions of this study imply that salts can be more soluble than cocrystals.

\textbf{Figure 1.10.} Intermolecular and intramolecular interactions found in the piroxicam saccharin cocrystal

Norfloxacin, a potent antibacterial agent, was targeted for salt and cocrystal formation due to its low aqueous solubility.\textsuperscript{151} When complexed with acidic molecules such as succinic acid, malonic acid, and maleic acid norfloxacin has formed salts. When
complexed with isonicotinamide norfloxacin remained neutral thus generating a cocrystal. The cocrystal was determined via single crystal X-ray diffraction to be a chloroform solvate. Figure 1.11. highlights the key supramolecular synthons including the persistent isonicotinamide dimer. Equilibrium solubility measurements were conducted for anhydrous norfloxacin, the cocrystal solvate, and three hydrated salts. The solubility of the cocrystal improved by ca. 3-fold and the solubility of the salts improved ca. 20-45 fold.

![Figure 1.11. Supramolecular synthons present in the norfloxacin isonicotinamide cocrystal solvate highlighting the persistence of the amide dimer, solvent molecules have been deleted for clarity](image)

Another interesting complex from a supramolecular synthon perspective is the pharmaceutical cocrystal of a monophosphate salt, illustrated in Figure 1.12. The phosphoric acid cocrystal of a monophosphate salt is the first example of a salt cocrystallized with an inorganic acid. Early attempts to develop a suitable crystal form of the target API resulted in an unstable hydrochloride salt. Furthermore, attempts to develop a stable crystalline form of the free base were unsuccessful. An extensive
screening process provided the phosphoric acid cocrystal of the phosphate salt that achieved a solubility greater than 250 mg/ml in water.

Figure 1.12. Phosphoric acid cocrystal of a monophosphate salt

Sildenafil, the active ingredient in Viagra®, was also a target for cocrystallization. The currently marketed crystal form of Viagra® is the citric acid salt of sildenafil that was synthesized to improve the poor aqueous solubility of sildenafil. However, the citrate salt proved to be only moderately soluble in water. Zegarac and coworkers have since developed an aspirin cocrystal of sildenafil with improved solubility under acidic conditions. Specifically, the intrinsic dissolution rate for the aspirin cocrystal was approximately twice that of the citrate salt. Due to the increased solubility of the aspirin cocrystal under acidic conditions, the crystal form is particularly amenable as an oral dosage form. Desiraju has also targeted sildenafil for the development of novel crystal forms. Eleven different solvates of the saccharinate salt of sildenafil were identified and characterized via single crystal X-ray diffraction. The solubility of the solvated crystal forms was not determined.
A study reported by Remenar et.al., highlighted the importance of excipients when measuring the solubility of a cocrystal.\textsuperscript{150} The celecoxib nicotinamide cocrystal, shown in Figure 1.13., was presented as an example. Celecoxib is a COX-2 inhibitor and anti-inflammatory agent with an aqueous solubility of less than 1 μgram/ml and is known to exist in four polymorphic forms. An examination of the literature of pure celecoxib revealed that the bioavailability could be altered based upon the formulation technique employed. The article attributed the differences in dissolution profiles, which varied with the formulation technique, to the variability in bioavailability. The focus of Remenar’s study was similar, except the dissolution study was of the celecoxib nicotinamide cocrystal. The solubility of the cocrystal was measured in aqueous solutions containing small percentages of sodium dodecyl sulfate on polyvinylpyrolle. It was found that the cocrystal was more soluble in solutions containing higher levels of the excipients.

\textbf{Figure 1.13.} Hydrogen bonding of the celecoxib nicotinamide cocrystal
The solubility and stability of twenty-seven carbamazepine cocrystals has also been recently investigated. Carboxamazepine has been extensively studied for cocrystal formation (carbamazepine aspirin cocrystal shown in Figure 1.14.) and solution behavior in the presence of cocrystal formers. The most recent contribution of carbamazepine cocrystals incorporated both diacids and monoacids as cocrystal formers and in many cases led to polymorphic cocrystals. While no numerical solubility values were given, it was stated that the solubility of the cocrystal was dependent upon the cocrystal former concentrations. The stability of the cocrystal was measured by testing the solid phase post slurry. The cocrystals were stirred in water and allowed to reach equilibrium. The remaining solid was tested post slurry and for thirteen cocrystals, was found to convert to carbamazepine dihydrate. Seven of the cocrystals remained intact during the study.

![Figure 1.14. Carbamazepine aspirin cocrystal](image)

AMG 517, an API in development stages at Amgen for indications of chronic pain was recently the target for cocrystallization. Ten cocrystals were developed
employing cocrystal formers containing carboxylic acid moieties. The solubility of AMG 517 is very low in 0.01N HCl but slightly higher in fasted simulated gastric fluid (FSGF) (5 µg/mL) thus the dissolution profiles for AMG 517 and its cocrystals were measured in FSGF. All cocrystals except for the tartaric acid cocrystal were examined. Six of the nine cocrystals obtained their maximum solubility within 1-2 hours. Their concentrations then decreased throughout the remainder of the study producing a spring and parachute profile reminiscent of the fluoxetine HCl succinic acid cocrystal previously mentioned. The solubility of the three remaining cocrystals was less than that of AMG 517. Interestingly, powder X-ray diffraction studies confirmed that the solids remaining after the dissolution study were AMG 517 hydrate in all cases except for with the benzoic acid cocrystal. While the spring and parachute type profile indicated that the benzoic acid cocrystal had converted to the dihydrate, powder X-ray diffraction showed that the remaining solid was in fact cocrystal. The DSC, however, suggested that the benzoic acid was not present in the crystal lattice, but was instead in solution. This argument was supported by HPLC analysis that indicated an increase in benzoic acid concentration in solution.
Figure 1.15. 2-point recognition supramolecular synthon of AMG 517 succinic acid cocrystal

The next study describes the cocrystallization of two steroid-type molecules, exemestane and megestrol acetate, that could not be formulated as pharmaceutical salts due to their lack of strongly acidic or basic functionalities. Exemestane is used to treat breast cancer while megestrol acetate is used to reduce the suffering caused by some cancers and treats the loss of appetite in some AIDS patients. The unique cocrystal screening technique employed in this study involving dimethylsulfoxide slurries followed by lyophilization produced two novel cocrystals, exemestane maleic acid and megestrol saccharin. The solubility was obtained via intrinsic dissolution and loose powder dissolution measurements. Intrinsic dissolution studies showed that the exemestane maleic acid cocrystal solubility was of similar solubility to that of the pure drug while the megestrol saccharin cocrystal was twice that of the pure drug. The free flowing powder dissolution profiles indicate a similar solubility trend, with the megestrol cocrystal achieving a six-fold increase in solubility. The influence of particle size of the cocrystal was also measured but it did not have a strong impact upon the cocrystal solubility.
The most recent cocrystallization study that measures the solubility of the cocrystals was reported by Bak et.al.\textsuperscript{145} AMG 517 was again employed but complexed with alternative cocrystal formers containing either amide or carboxylic acid moieties. In addition to AMG 517, six more transient receptor potential vanilloid 1 antagonist APIs were targeted producing 15 cocrystals in total. AMG 517 produced 12 cocrystals while 3 (AMG 678809, AMG 831664, AMG 670129) of the additional 6 APIs each formed a cocrystal with sorbic acid. The solubility and dissolution profiles were measured for all 15 cocrystals in fasted simulated intestinal fluid. Many of the cocrystals resulted in a spring and parachute dissolution profile with the remaining solid converting to either the free base or hydrated free base. However, two of the AMG 517 cocrystals remained intact throughout the study. The most soluble cocrystal of AMG 517 was the L-malic acid cocrystal, highlighting an increase from 5 μg/mL to 24 μg/mL. A comparison of the two AMG 517 cocrystallization studies shows that both cocrystal formers containing carboxylic acids or amides can improve the solubility of the API. The sorbic acid cocrystals of AMG 678809, AMG 831664, and AMG 670129 also displayed marked improvements in solubility with the most notable increase of 0.9 μg/mL to 14.8 μg/mL for the AMG 670129 sorbic acid cocrystal.

1.8.3. Pharmaceutical Cocrystals with Animal Data

Many of the APIs targeted for cocrystallization are selected because of their low solubility and/or poor bioavailability. Enhancing the solubility of a crystal form via cocrystallization can translate to an increase in drug present in solution and available at the absorption site \textit{in vivo}. Depending on the mechanism of absorption, a more
concentrated solution of API can ultimately lead to a higher bioavailability (i.e. increased concentration of unchanged drug in the plasma). In each of the following case studies the solubility of a low solubility drug was increased via cocrystallization. The effect of solubility improvement upon drug absorption and bioavailability is summarized herein.

The first publically available study where an animal was administered a cocrystal was performed at Transform Pharmaceuticals Inc. Itraconazole, an antifungal drug, was the target API. The cocrystal with L-malic acid was dosed to dogs and found to reduce the time required to reach the maximum concentration (Tmax) by 10-80% over the pure drug. The maximum concentration (Cmax) and area under the curve (AUC) were also increased by 10-80%. The bioavailability (reported as 40%) for the cocrystal was equivalent to the currently administered amorphous form of itraconazole coated on Sporanox beads.

Transform Pharmaceuticals Inc. also filed a patent in 2004 containing the results of an in vivo testing of the modafinil malonic acid cocrystal. Modafinil, used for indications of narcolepsy, is practically insoluble in water, however, the malonic acid cocrystal dissolved at a faster rate than the pure API. The pharmacokinetic study utilizing a capsule formulation of the cocrystal administered in a single dose study to dogs highlighted an increase in Cmax and bioavailability. The Tmax was practically unchanged despite the increase in solubility at early time points.

In 2006 Childs et al. reported a set of five novel solid phases of 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide, or CFPPC. CFPPC is a sodium channel blocker used for alleviating pain with an aqueous solubility of < 0.1 μg/ml. Interestingly, the cocrystal comprised of CFPPC and glutaric acid showed an intrinsic
dissolution rate ca. 18 times greater than pure CFPPC. The dog pharmacokinetic study resulted in an AUC increase from 374 to 1,234 ng h/ml for the 5 mg/kg dose and an increase from 889 to 2,230 ng h/ml for the 50 mg/kg dose. Thus after a single oral dose of the cocrystal the dogs exhibited an approximately 4-fold increase in plasma concentration over the pure API.

Chronologically, the next cocrystal pharmacokinetic study details to appear in the literature pertained to the carbamazepine saccharin cocrystal.\textsuperscript{141} The study was a single dose administration of the cocrystal and the marketed Tegretol\textsuperscript{®} tablet to beagle dogs. The results showed higher $C_{\text{max}}$ and AUC values for the cocrystal and a $T_{\text{max}}$ value that was one hour for the cocrystal and 1.75 hours for the Tegretol\textsuperscript{®} tablet. Furthermore the cocrystal reached slightly higher plasma levels than the marketed drug, but remained within the standard error and therefore was not statistically significant.

The pharmaceutical cocrystal of a monophosphate salt with phosphoric acid, previously mentioned for its improved solubility in comparison to the free base, is noteworthy as it briefly mentions the results of a pharmacokinetic study. Unfortunately there are no details concerning this portion of the study in the article. The article simply claims that the cocrystal “exhibited excellent \textit{in vivo} performance”.\textsuperscript{139}

In 2008 Bak and co-workers highlighted the ability of a series of pharmaceutical cocrystals to improve the solubility of AMG 517.\textsuperscript{146,259} A particular focus was upon the AMG 517 sorbic acid cocrystal and it was studied with respect to its stability \textit{in vitro} as well as its ability to modify the plasma concentration of AMG 517 in Sprague-Dawley rats. It was found that after oral administration of a 500 mg dose of the cocrystal, the
C<sub>max</sub> and AUC<sub>0-inf</sub> was 8 and 9 times greater, respectively, compared to oral administration of the same dose of pure API.

The two most recent studies are from the patent literature. The first describes tenofovir which is a nucleotide reverse transcriptase inhibitor for the treatment of HIV. The commercially available form of tenofovir is a fumarate salt however, the product contains various mixture of solid forms in unpredictable ratios. In an attempt to solve the commercial product problem, tenofovir was cocrystallized with fumaric acid resulting in a 2:1 molecular complex that could be isolated cleanly. A pharmacokinetic study (a single dose Male Wister rat study) comparing the cocrystal to the existing salt form proved that the cocrystal was bioequivalent to the on the market product.

The most recent pharmacokinetic study of a pharmaceutical cocrystal describes the cocrystal formed between a C-glycoside derivative and proline. Previously the pure drug was found to crystallize as a clathrate hydrate that interconverts from an anhydrous compound to a non-stoichiometric hydrate. The instability of the API led to the develop the additional crystal forms. The resulting 1:1 C-glycoside derivative L-proline cocrystal was administered as a suspension to non-fasted mice. Levels of the cocrystal and original API were measured in the blood concluding that the cocrystal was present at a sufficient level to treat diabetes. The patent further claims that the patient would experience the same or higher efficacy after administration of the cocrystal.

As was made evident in the previously mentioned studies, the crystal form of a pharmaceutical can have a significant impact upon the solubility and pharmacokinetic properties of an API. Table 1.3 provides a summary of the pharmacokinetic data presented in this chapter.
Table 1.3. Summary of the pharmacokinetic metrics for the presented pharmaceutical cocrystals

<table>
<thead>
<tr>
<th>API</th>
<th>Cocrystal former</th>
<th>Pharmacokinetic metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>L-Malic acid</td>
<td>Bioavailability = 40%, Equivalent to amorphous drug</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Malonic acid</td>
<td>Increase C&lt;sub&gt;max&lt;/sub&gt; and bioavailability</td>
</tr>
<tr>
<td>CFPPC</td>
<td>Glutaric acid</td>
<td>Decrease T&lt;sub&gt;max&lt;/sub&gt;, increase C&lt;sub&gt;max&lt;/sub&gt; and AUC by 4-fold</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Saccharin</td>
<td>Increase AUC and C&lt;sub&gt;max&lt;/sub&gt;, however, not statistically significant plasma level</td>
</tr>
<tr>
<td>Monophosphate salt</td>
<td>Phosphoric acid</td>
<td>No data, stated “excellent in vivo performance”</td>
</tr>
<tr>
<td>AMG 517</td>
<td>Sorbic acid</td>
<td>Increased C&lt;sub&gt;max&lt;/sub&gt; and AUC by 8 and 9 fold</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Fumaric acid</td>
<td>Bioequivalent to commercially available drug</td>
</tr>
<tr>
<td>C-Glycoside</td>
<td>L-proline</td>
<td>Cocrystal showed strong antihypoglycemic action</td>
</tr>
</tbody>
</table>

1.8.4. Polymorphism and the Pharmaceutical Industry

A polymorph has been defined by McCrone as “a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state”.<sup>273</sup> The number of compounds that exhibit polymorphism is uncertain as McCrone argues that the number of polymorphic compounds is proportional to the time and money spent in research on that compound.<sup>274</sup> In an attempt to quantify the number of known polymorphs a search of the CSD was conducted. The term “polymorph” retrieved 15,633 entries out of 481,521 or 3% of the entire database.

An important aspect of polymorphism is the inherent differences in physical properties between crystal forms.<sup>258, 275</sup> Variations in properties such as solubility can have a dramatic impact upon the pharmacokinetic behavior of an API. Thus crystal form
screening is of utmost importance in the pharmaceutical industry. However, traditional
crystal form screening does not always reveal all possible polymorphs. The negative
impact that crystal form screening can have upon the pharmaceutical industry is
exemplified in the historic cases of ritonavir, ranitidine HCl, and paroxetine HCl.

Ritonavir, marketed as Norvir®, was formulated as an oral liquid and a semi-solid
capsule. Since both formulations were solutions of ritonavir there was little concern with
crystal form. During early manufacturing of the capsules only the one crystal form of
ritonavir was found. However, years later, a new form was discovered that was much
less soluble than the original form. This new form was referred to as form II. Form II
was soon found at all manufacturing facilities, dramatically reducing the supply of the
original form. Form II was so much less soluble that it could not be used to make the oral
liquid or semi-solid capsule formulations via the current methods. Ultimately ritonavir
had to be reformulated due to the omnipotent less soluble form II.

Ranitidine HCl (Zantac®), a histamine H2 antagonist originally developed by
GlaxoSmithKline, was also found to be polymorphic. The polymorphic transformation
of what is now called form I to form II occurred during the scale up manufacturing
process. Form I was covered under an original synthesis patent and form II was
subsequently covered under an additional patent. Due to the success of the drug, many
generic companies were waiting for form I to go off patent to introduce their own generic
version on the market. Novopharm in particular attempted to reproduce form I from the
claimed method in the patent, however, Novopharm produced form II. Novopharm then
tried to invalidate Glaxo’s patent for form II citing that they had reported a method for
form I that actually produced form II; therefore form II would be anticipated from the
earlier patent. Novopharm eventually lost the case as Glaxo was able to prove that their method did lead to generation of form I in the original researchers’ notebook. However, Novopharm was granted the ability to market a pure product of form I.

GlaxoSmithKline also entered into a legal battle over paroxetine HCl (Paxil®). The original form developed was a hemihydrate of paroxetine marketed since 1993. While waiting for Glaxo’s patent to expire, Apotex developed an anhydrate crystalline form of paroxetine HCl. Glaxo was aware of the anhydrate and its conversion to the hemihydrate under specific conditions that were claimed in their original patent. Glaxo claimed that Apotex was operating under conditions that would partially convert the anhydrate to the hemihydrate that was covered under their patent. The legal battle ensued with the court ultimately ruling against Glaxo as they could not prove that Apotex would make the hemihydrate in sufficient quantities.

1.9. Summary

Supramolecular chemistry has grown exponentially since the description of the lock and key model in 1890. The subset of crystal engineering has also grown and attracted interest from many different facets including academia and industry. Contributing factors that have fueled the rapid development have been the advancements in X-ray technology as well as augmented interest from large corporations and university collaborations. In particular the pharmaceutical industry is currently infatuated with the ability to fine tune a crystal form to possess desired physical and pharmacokinetic properties. The potentials and pitfalls of polymorphism are also a topic of current interest.
Cocrystals in solid-state synthesis and cocrystals in pharmaceutical development both show great promise in their respective areas. Cocrystals as reaction intermediates or photodimerization templates have afforded novel materials typically coupled with increased reaction yields. Pharmaceutical cocrystals have also proven their utility with their ability to change an API’s solubility and bioavailability. The ability to manipulate the properties of a cocrystal to customize a product is still a future goal but as the field of crystal engineering continues to grow and its applications extend, new materials will emerge with inherent properties that will most likely be the result of a designed experiment rather than serendipity.

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Chapter 2 – Cocrystal Controlled Solid-State Synthesis of Imides

2.1. Preamble

The chemical industry has played a major role in the production and accumulation of hazardous waste and toxins in the environment.\(^1\) Unfortunately, it was not until the 1960’s that the public became aware of the toxicity and harm to human health some chemicals, such as DDT (dichlorodiphenyltrichloroethane),\(^2-4\) in the environment could cause. The increased public awareness began the conscious effort to reduce chemical waste and its presence in the environment. A giant leap forward was made in 1990 with the Pollution Prevention Act\(^5\) which stated that one should strive to prevent or reduce pollution whenever possible.\(^6\) This act facilitated the development of more environmentally friendly chemical practices that lead to the creation of the chemical genre of green chemistry.\(^7-12\) Green chemistry has been defined as “the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products”.\(^13\) Implementation of the twelve principles of green chemistry can provide greater reaction yields and less hazardous waste production, resulting in cheaper overall chemical synthetic methodologies.\(^14\) With the consideration of these benefits in mind, many chemists have strived to develop the field of solid-state synthesis, however, in some areas their focus has been relatively narrow in scope.\(^15-17\) For example, the particular application of
cocrystal controlled solid-state synthesis ($C^3S^3$) has thus far been limited to photodimerizations or photopolymerizations$^{18-27}$ and nucleophilic substitution.$^{28}$ In the case of the former, one cocrystal former typically serves to align or “template” the reactant, which is the other cocrystal former. In the case of the latter both cocrystal formers are reactants although there are examples in which the reactive moieties are in the same molecule and therefore generate polymeric structures.$^{29}$ In this chapter, the details of an exploration into furthering the development of $C^3S^3$ are delineated for the design and synthesis of novel materials.

$C^3S^3$, defined as the generation of a cocrystal in the solid-state which can then be utilized to conduct a chemical reaction, typically condensation, in order to generate novel materials, can be described as a two part process. The initial stage applies crystal engineering$^{30,31}$ design principles to a recently developed low waste, high yield cocrystal synthesis method which is followed by a traditional condensation reaction that has been modified to be conducted in the solid-state. There are two strict sets of criteria for conducting a reaction by $C^3S^3$: 1) the materials must posses the appropriate moieties to sustain a reliable supramolecular synthon$^{32,33}$ and 2) the moieties required for the supramolecular heterosynthon must be chemically reactive such that when heated they lose a volatile component, typically water. Based upon the requirements imposed for $C^3S^3$, there are six reactions that fit this criteria, aldehyde + primary amine to generate a Schiff base,$^{34}$ carboxylic acid + primary amine to make a secondary amide,$^{35}$ carboxylic acid + carboxylic acid to form an anhydride,$^{36}$ carboxylic acid + alcohol to generate an ester,$^{37}$ alcohol + alcohol to make an ether,$^{35}$ and anhydride + primary amine to form an
Imides represent a class of compound that is primarily synthesized in solution; however, there are prior examples that highlight the ability to synthesize imides in the solid-state via microwave chemistry or upon a solid-phase support. Both methods prepare imides via condensation of carboxylic acid anhydrides and primary amines (mechanism shown in Figure 2.2.) i.e. two functional groups that are complementary and could form a supramolecular synthon; however, prior to 2007, there were only two entries (REFCODES: AMYGLA, BEFWEO) in the Cambridge Structural Database (CSD) that exhibit both the amine and anhydride moieties in the same entry, both of which were comprised of a single component therefore neither were cocrystals. The lack of data in the CSD precludes a definitive statement concerning the reliability of the supramolecular heterosynthon formation. C3S3 provides the opportunity to address the occurrence of this supramolecular heterosynthon and its potential to generate novel imides.
Figure 2.2. Proposed reaction mechanism for carboxylic acid anhydride and primary amine producing an imide

Cocrystals can be synthesized by various methodologies\textsuperscript{47-49} including the established solvent-drop grinding technique, i.e. two or more solid cocrystal formers are ground in the presence of a microliter amount of solvent.\textsuperscript{50-54} In the study presented herein, the cocrystals will be synthesized via solvent-drop grinding as it is the most environmentally friendly cocrystallization technique. The groups of acid anhydrides and primary amines depicted in Figures 2.3. and 2.4. respectively that were selected for this study include: AA1 = 1,4,5,8-naphthalenetetracarboxylic acid dianhydride (NTCDA), AA2 = pyromellitic dianhydride, AA3 = maleic anhydride, AA4 = phthalic anhydride, AA5 = 3,3',4,4'-biphenyltetracarboxylic dianhydride, AA6 = 1,8-naphthalic anhydride, AA7 = 3,4,9,10-perylenetetracarboxylic dianhydride, PA1 = 2-methyl-4-nitroaniline, PA2 = 3-aminobenzoic acid, PA3 = melamine, PA4 = 1,4-phenylenediamine, PA5 = 1,5-diaminonaphthalene, PA6 = 1-adamantylamine, and PA7 = triphenylmethylamine. All combinations of the 7 anhydrides with 7 primary amines was investigated (49 total reactions) to determine the following: if they form cocrystals via solvent-drop grinding under ambient conditions; furthermore if the ground mixtures so obtained can be
converted to imides simply by applying heat. A summary of the results after grinding then heating are presented in Table 2.1. The majority of reactions studied were observed to form imides after heating but it was not always possible to isolate a cocrystal. However, three combinations of anhydride + amine were isolated as cocrystals that resulted in high yield, low waste formation of imides and will be discussed herein. An additional reaction where the imide condensation reaction intermediate was isolated in high yield will also be discussed. The analysis for reactions 1-4 includes reaction conditions and discussion of the differential scanning calorimetry (DSC) traces, UV-vis spectra, and color schemes for reactants, cocrystals, and imides where appropriate. In addition the use of DSC to discover cocrystal formation in situ will be addressed. Finally, the use of characterization techniques such as powder X-ray diffraction (PXRD) and Fourier transform infrared (FT-IR) spectroscopy will be discussed for the detection of cocrystal and imide formation with a broad set of amines and anhydrides.
Figure 2.3. Carboxylic acid anhydrides

Figure 2.4. Primary amines
Table 2.1. Table of 49 reactions color coded to differentiate outcomes after solvent-drop grinding and heating

<table>
<thead>
<tr>
<th></th>
<th>AA1</th>
<th>AA2</th>
<th>AA3</th>
<th>AA4</th>
<th>AA5</th>
<th>AA6</th>
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<td>PA7</td>
<td>1:1</td>
<td>3:1</td>
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</tbody>
</table>

Yellow=Grinds=mixtures, heating=imid. Red=DMF/DMF grinds=start reaction, heating=imid. Green=DMF grinds=co-crystal, heating=imid. Black=No reaction observed. Orange=Grinds=intermediate formation, heating=imid.

PA=Primary Amine; AA=Acid Anhydride. E.g., 1:2 (1 mole of amine and 2 moles of anhydride).

2.2. Results and Discussion

2.2.1. Reaction 1 2-methyl-4-nitroaniline and NTCDA

2.2.1.1. Synthetic Techniques and Characterization

As revealed in Figure 2.8, 1,4,5,8-naphthalenetetracarboxylic dianhydride (NTCDA) and 2-methyl-4-nitroaniline form a 1:2 cocrystal, 1a, which converts cleanly to diimide, 1b, when heated at 180 °C for 3 hours in 75% yield. Conversion to 1b is expected as the distance between the amino moiety and carbonyl carbon of the anhydride is ca. 3.42 Å, which is less than the 4.2 Å restriction of the topochemical postulate. 1b crystallized from DMF and DMSO, affording solvated single crystals of 1b. Figure 2.11.
represents the DMSO solvate of 1b and is presented in detail herein. The DMF solvate of 1b is not covered in detail as the solvate is isostructural to the DMSO solvate.

The cocrystal of NTCDA and 2-methyl-4-nitroaniline (1a) is purple in color. The purple color of 1a contrasts the starting materials (pale yellow) and reaction product (orange) and is indicative of charge transfer complex. The solid-state UV-Vis spectrum of 1a exhibits a broad band at ca. 600nm and is shown in Figure 2.5. The UV-Vis spectrum of 2-methyl-4-nitroaniline, NTCDA, and an ethanol grind are also shown for comparison purposes.

![Figure 2.5. UV-Vis spectrum of DMF solvent drop grind versus Methanol grind, NTCDA, and 2-methyl-4-nitroaniline](image)

1a can be prepared from solution, solvent-drop grinding with DMF or solvent-drop grinding followed by heating and is sustained by charge transfer interactions between the aromatic rings of NTCDA and 2-methyl-4-nitroaniline. Toda et al. has also shown the ability to generate charge transfer complexes from solid-state grinding. Interestingly, solvent-drop grinding with other solvents (chloroform, cyclohexane,
DMSO, ethyl acetate, methanol, toluene, and water) affords mixtures of NTCDA and 2-methyl-4-nitroaniline. However, heating of a mixture above the melting point of 2-methyl-4-nitroaniline results in formation of 1a and additional heating at 150 ºC for three hours affords 1b. These observations suggest that formation of 1a is a key step for facilitating or even controlling the condensation process.

The progression of the reaction can be monitored in the DSC (Figure 2.6.). The DSC trace for 1a (shown on the right in Figure 2.6.) exhibits only one phase transition as the cocrystal melts and converts to the diimide 1b. However, the DSC trace of a mixture (shown on the left in Figure 2.6.) shows two phase transitions. Once the mixture reaches the melting point of the 2-methyl-4-nitroaniline (130 ºC) the first phase transition occurs. Here the amine melts and recrystallizes to form the cocrystal. The second phase transition corresponds to the melt of the cocrystal at ca. 155 ºC. After the melt of the cocrystal the dehydration occurs and the resulting solid is the diimide. The color changes due to the phase transitions from both 1a and the physical mixture (Figure 2.7) can be monitored in a Mel-temp® device. 1a (purple) becomes orange after heating past 160 ºC and the yellow mixture turns purple as it converts to 1a. 1a then becomes orange as it converts to the diimide.
Figure 2.6. DSCs highlighting the phase transitions that occur for mixtures (left) and cocrystal (right). All temperatures are in degrees Celsius.

Figure 2.7. Color changes for reaction 1

2.2.1.2. Analysis of Crystal Structures

The 2-methyl-4-nitroaniline NTCDA cocrystal, 2:1 (1a) crystallizes in the space group $P_{m{1}}$. The basic supramolecular unit contains two 2-methyl-4-nitroaniline molecules and one NTCDA molecule. The self complementary hydrogen bonding capability of 2-methyl-4-nitroaniline between the primary amine donor and nitro acceptor moieties is the primary driving force sustaining 1a. The amino moieties that hydrogen bond to neighboring nitro moieties allow for an NH···O hydrogen bond distance of
2.946(6) Å [N22-H22B⋯O21: N⋯O 2.946(6) Å, H⋯O 2.178 Å, N-H⋯O 145.47°] resulting in infinite chains of 2-methyl-4-nitroaniline molecules along the $b$-axis. The chains are related by an inversion center located in the center of an NTCDA molecule positioned between two 2-methyl-4-nitroaniline chains. The centroid-plane distance between the 2-methyl-4-nitroaniline and NTCDA is ca. 3.32 Å, which is within the typical π-π interaction range and further supports the charge transfer interaction. The carbonyl carbon atom of the NTCDA and the amine nitrogen atom of the 2-methyl-4-nitroaniline are separated by only 3.42 Å, i.e. well within the 4.2 Å limit of the topochemical postulate.$^{57,58}$ The intermolecular interactions sustaining 1a are shown in Figure 2.8. The hydrogen bonding and charge transfer interactions exhibited by 1a collectively generate a lattice that can be envisioned as two chains of 2-methyl-4-nitroaniline molecules with NTCDA molecules inserted in between the chains stacking in an AABAAB fashion as is shown in Figure 2.9. Furthermore, this 2:1 cocrystal supports the required stoichiometry and conformation for the topochemical reaction.

Figure 2.8. Intermolecular interactions sustaining 1a. 1a obeys the topochemical postulate as the shortest distance between the nitrogen atoms of the amine moieties and the carbon atoms of the carbonyl moieties is 3.42Å.
Heating the cocrystal and recrystallizing the resulting imide from DMSO produces the solvated diimide of 1b shown in Figure 2.10. and 2.11. There are three independent diimides and one DMSO molecule in the asymmetric unit. Diimide A (Figure 2.12. red) interacts via CH···π from the center of the molecule to the central π region of neighboring diimide C (Figure 2.12. green) with a CH to ring centroid distance of 3.52 Å. Diimide B (Figure 2.12. blue) is held in position via a CH···π interaction of 3.21 Å sustained between the central CH region and the aromatic benzene ring of neighboring diimide A (Figure 2.12. red). Diimides A and C continue in infinite chains parallel to the b-axis, packing in an alternating ABAB motif. Diimide B also forms infinite chains along the b-axis; however, the cavity between chains is filled by two equivalent DMSO molecules. Diimide B and DMSO also pack in an alternating ABAB motif. The dihedral angles of diimides A, B, and C are 82.41 °, 85.12 °, and 79.18 °, respectively.
Figure 2.10. Molecular structure of diimide 1b as generated via recrystallization of 1b from DMSO

Figure 2.11. Crystal packing of 1b DMSO solvate (3:2) obtained via recrystallization from DMSO
2.2.2. Reaction 2 3-aminobenzoic acid and NTCDA

2.2.2.1. Synthetic Techniques and Characterization

NTCDA and 3-aminobenzoic acid also form a purple cocrystal (2a) via solvent-drop grinding with DMF. Solvent-drop grinding with other solvents leads to mixtures of starting materials. Attempts at crystallization resulted in the formation of the less reactive 1,4-dioxane solvate of the cocrystal, 2a·1,4-dioxane, shown in Figure 2.16. The solid-state UV-Vis spectrum of 2a, shown in Figure 2.13., exhibits a broad band at 550 nm which is consistent with a charge-transfer complex. Furthermore, the distance between the reactive moieties (amine nitrogen and the carbonyl) was 3.14 Å. Therefore 2a also obeys the topochemical postulate as it converts to diimide 2b after heating for 24 hours at 200 °C in 99% yield. Interestingly, the cocrystal also undergoes dehydration to the corresponding diimide after a few days under ambient conditions. Crystallization
attempts of \(2b\) were arduous due to the low solubility of the diimide in many common organic solvents. However, \(2b\) can be recrystallized from pyridine as the pyridine solvate of the 1:2 complex of \(4\) with pyridine.

![Figure 2.13. UV-Vis spectrum of DMF solvent-drop grind versus 3-aminobenzoic acid, methanol solvent-drop grind, and NDTCA](image)

The dehydration of \(2a\) to \(2b\) was also monitored in the DSC; however, it was not as straightforward as the previously described dehydration of \(1a\) to \(1b\). The DSC (shown in Figure 2.14., left) indicates that the cocrystal melt occurs at ca. 127 °C; however, the first phase transition of the mixture (shown in Figure 2.14., right) does not occur until ca. 155 °C. The melting points do not correlate due to the melting point of the cocrystal occurring before the melt of the lowest melting starting material (3-aminobenzoic acid). Thus, the DSC of the mixture is a unique case highlighting the ability of the material to melt, rearrange to the cocrystal which instantaneously melts and dehydrates to complete the condensation reaction generating \(2b\). The array of colors that are seen for this reaction (Figure 2.15.) are similar to that of reaction 1 where the same anhydride is
employed and the cocrystal is a purple charge transfer complex, however, the resulting imide (2b) is gold whereas 1b is orange.

**Figure 2.14.** DSCs highlighting the phase transitions that occur for cocrystal (left) and mixture (right). All temperatures are in degrees Celsius

**Figure 2.15.** Colors of 3-aminobenzoic acid, NTCDA, dry grinding product, DMF grinding product, and final imide 2b

2.2.2.2. **Analysis of Crystal Structures**

The 3-aminobenzoic acid NTCDA cocrystal 1,4-dioxane solvate (2a·1,4-dioxane) crystallizes in a 2:1:1 stoichiometry in the space group $P\overline{1}$ with two molecules of 3-aminobenzoic acid, one molecule of NTCDA, and one molecule of 1,4-dioxane in
the asymmetric unit. Similarly to 1a, the primary amine molecule assists in the formation of infinite chains, however, in 2a·1,4-dioxane the primary amine molecules require the insertion of a 1,4-dioxane molecule to sustain the chain. The 3-aminobenzoic acid molecules do not favor the head to tail chain most likely because of the meta-positioning of the amino moiety. The preferred orientation is a centrosymmetric dimer centered above and below the NTCDA molecule. The 3-aminobenzoic acid centrosymmetric dimer is sustained via NH···O=C [N11-H11A···O11: N···O 3.066(4) Å, H···O 2.245 Å, N-H···O 155.15°] hydrogen bonds which link to additional dimers through 1,4-dioxane molecules [O12-H12···O31: O···O 2.643(3) Å, H···O 1.807 Å, N-H···O 172.36°] to generate chains that stack along the α-axis. As shown in Figure 2.16., NTCDA molecules stack in between the 3-aminobenzoic acid dimers with an amine-carbonyl distance of ca. 3.14 Å. The distance between these reactive groups is much less than the requirement for the topochemical postulate therefore the condensation reaction should occur. In addition, the distance measured between a centroid in the center of the 3-aminobenzoic acid dimer and the plane of a neighboring NCDTA molecule was found to be 3.17 Å. This distance is well within the typical π-π interaction and further supports the potential for charge transfer interactions. The 1,4-dioxane molecules can be removed with heat to obtain anhydrous 2a. However, a single crystal structure of the anhydrous cocystal could not be obtained as the sample did not retain crystallinity after heating.
Attempts at crystallization of the 3-aminobenzoic acid NTCDA diimide (2b) resulted in a pyridine solvate of the 1:2 complex of 2b with pyridine. The solvate of 2b crystallizes in the space group $P\overline{1}$. The basic supramolecular unit is comprised of one diimide, two pyridine molecules hydrogen bonded to the carboxylic acid moieties of the diimide, and one disordered pyridine molecule centered in the cavity between two diimide molecules. The crystal packing is sustained by various weak interactions including multiple $\text{CH} \cdots \text{O}$ interactions such as pyridyl $\text{CH}$ to carbonyl of the imide (ca. 3.25 Å) and C=O of the carboxylic acid to the central CH region of the imide (ca. 3.49 Å). As shown in Figure 2.17. and 2.18., additional weak interactions ($\pi$ system overlap of 6-membered aromatic rings) sustain the diimide molecules as they progress along the $c$-axis. The dihedral angle between the naphthyl and benzene rings of the diimide is 79.04°.
Figure 2.17. Simplified crystal packing of the 1:2 complex of 2b with pyridine

Figure 2.18. Crystal packing of the pyridine solvate of the 1:2 complex of 2b with pyridine
2.2.3. Reaction 3  2-methyl-4-nitroaniline and pyromellitic anhydride

2.2.3.1. Synthetic Techniques and Characterization

Interestingly, solvent-drop grinding with DMF of 2-methyl-4-nitroaniline and pyromellitic anhydride does not give a purple cocrystal. The cocrystal (3a) is orange most likely due to the reduction of the conjugated ring system from naphthyl (NTCDA) to benzyl (pyromellitic anhydride). 3a can be synthesized from various techniques including solvent-drop grinding with DMF or methanol, solution crystallization, and grinding with heating. The UV-Vis absorbance maximum for 3a is ca. 400 wavenumbers which is expected for an orange complex, but is similar to the absorbance of the π systems used for the reactants and therefore is not included. The single crystal structure of 3a illuminates the bond distances from the amino group to the carbon of the carbonyl group on a neighboring anhydride. Based upon the topochemical postulate, the distance between the reactive groups in 3a (ca. 3.78 Å) is within range for the condensation reaction to occur. Furthermore, 3a can be converted cleanly to 3b in approximately 80 % yield after heating for ca. 2 days at 150 ºC. The different solid-state reaction rates of 1a, 2a·1.4-dioxane solvate, the unsolvated form of 2a, and 3a is presumably an artifact of crystal packing.

DSC traces for 3a and a mixture of the reactants are shown in Figure 2.19. with 3a on the left and the mixture on the right. The DSC trace of the cocrystal shows two phase transitions at 138 ºC and 247 ºC. The literature melting point of 2-methyl-4-nitroaniline (130 ºC) is similar to the first phase transition suggesting that either the cocrystal may begin to disassociate at a similar temperature or some excess amine may be present. Additional characterization techniques (FT-IR, PXRD calculated vs.
experimental) confirm that the solid is at least 90% cocrystal. Thus it is likely that the melting point of the cocrystal is merely a few degrees higher than the melting point of 2-methyl-4-nitroaniline. 3a continues to rearrange on the molecular level in the DSC as it converts to the diimide (3b), indicated by the undulating baseline. The second phase transition at ca. 248 °C is attributed to the melt of 3b. The mixture shown on the right in Figure 2.19. shows the melt of the amine at ca. 131 °C followed by a sharp recrystallization as the cocrystal (3a) is formed. 3a then melts around 200 °C and rearranges to generate 3b which melts at ca. 243 °C. The color changes as the starting materials are heated to produce 3a then subsequently to 3b can be followed in the Mel-temp® device. Representative vials are shown in Figure 2.20.

![Figure 2.19. DSCs highlighting the phase transitions that occur for cocrystal (left) and mixture (right). All temperatures are in degrees Celsius.](image)

**Figure 2.19.** DSCs highlighting the phase transitions that occur for cocrystal (left) and mixture (right). All temperatures are in degrees Celsius.
2.2.3.2. Analysis of Crystal Structures

The 2-methyl-4-nitroaniline pyromellitic anhydride cocrystal (3a) crystallizes in the space group $P2_1/n$. The basic supramolecular unit is comprised of two 2-methyl-4-nitroaniline molecules and one pyromellitic anhydride molecule. As was seen in 1a, the 2-methyl-4-nitroaniline molecules in 3a form head-to-tail chains sustained by hydrogen bonds. The 2-methyl-4-nitroaniline molecules hydrogen bond via amine-nitro NH···O interactions [N12-H12A···O12: N···O 2.943(5) Å, H···O 2.159 Å, N-H···O 148.06 °] that translate along the 2-fold axis. Pyromellitic anhydride molecules are inserted between the 2-methyl-4-nitroaniline chains interacting via NH···O hydrogen bonds [N12-H12B···O22: N···O 3.089(5) Å, H···O 2.307 Å, N-H···O 147.98 °] and N-O···O-C interactions (ca. 2.90 Å). A centroid to plane distance measured between the center of the 2-methyl-4-nitroaniline molecule and pyromellitic anhydride plane was found to be 3.26 Å, which is within the range for π-π interaction. The distance from the reactive
amino group to the carbon of the anhydride carbonyl is ca. 3.78 Å which is within the distance requirements set by the topochemical postulate.

![Crystal structure of cocrystal 3a formed between 2-methyl-4-nitroaniline and pyromellitic anhydride](image)

**Figure 2.21.** Crystal structure of cocrystal 3a formed between 2-methyl-4-nitroaniline and pyromellitic anhydride

The diimide 3b, synthesized from the dehydration of cocrystal 3a, crystallizes in the space group $P2_1/c$. The asymmetric unit contains half of the molecule with the inversion center located at its center. 3b translates along the $b$-axis at an angle such that the translation about the 2$_1$ screw axis results in a herringbone motif. The interplanar spacing between the central region of the diimide molecules is ca. 3.28 Å and is sustained mainly via CH···O interactions, specifically from CH···O=C (ca. 3.34 Å) and CH···O-N (ca.3.10 Å). The dihedral angle between the central and exterior rings of the diimide is 75.82°.
2.2.4. Reaction 4 \textit{1-adamantylamine and phthalic anhydride}

2.2.4.1. \textit{Synthetic Techniques and Characterization}

When performing synthetic reactions the experimental outcome is not always what is expected. Reaction 4 was an exemplary case where a synthetic pathway led to the unexpected isolation of the condensation reaction intermediate instead of the imide.
The amic-acid condensation intermediate of 1-adamantylamine and phthalic anhydride (4a) has been isolated from traditional solution methods for this particular reaction in 48% yield;\(^5^9\) however, in the solid-state under the conditions described herein, the intermediate can be isolated cleanly in ca. 90 % yield. 4a is synthesized via solvent-drop grinding of 1-adamantylamine and phthalic anhydride together in a stoichiometric ratio followed by heating of the solid at 110 °C for 1.5 hours. Suitable quality single crystals for of 4a single crystal X-ray analysis were obtained from recrystallization of the heated material. The intermediate can then be heated further at 120 °C for ca. 1 week to afford the imide 4b. 4b was previously reported in the literature and appears in the CSD under refcode: QUSKUK.

The DSC of 4a shows two phase transitions (Figure 2.24.). The initial phase transition corresponds to the literature melting point of 185 °C.\(^5^9\) The breadth of the second phase transition is indicative of an impure material but it could also be caused by degradation after the melt of 4a. An additional factor that must be considered is that the imide condensation reaction is reversible. 4a can hydrolyze due to excess moisture in the air producing phthalic acid and 1-adamantylamine which melt at 210 °C and 205 °C, respectively. Therefore the second phase transition may be caused in part by the presence of either material. Heating 4a in an oven in the solid-state can result in the formation of 4b following the conditions previously mentioned. A DSC of the solid after heating confirms the synthesis of 4b as the DSC trace (Figure 2.25.) has one phase transition at ca. 142 °C which corresponds to the literature melting point of 140 °C.\(^6^0\)
Figure 2.24. DSC of 4a

Figure 2.25. DSC of 4b
2.2.4.2. Analysis of Crystal Structures

The intermediate 4a formed from the reaction of 1-adamantylamine and phthalic anhydride crystallizes with one molecule in the asymmetric unit. 4a crystallizes in the space group \( P2_1/c \) and is primarily sustained by an atypical 2-point recognition dimer. The dimer is centrosymmetric and incorporates two carboxylic acid moieties and the carbonyl of the adjacent secondary amide. The carboxylic acid-carbonyl \( \text{OH}^{-}\cdots\text{O} \) hydrogen bond distance is 2.682(3) Å [O12-H12\cdotsO11: O\cdotsO 2.682(3) Å, H\cdotsO 1.868 Å, N-H\cdotsO 171.61 °] and the carbonyl-carbonyl intramolecular bond distance is ca. 3.01 Å. Additional molecules of 4a are generated by a \( 2_1 \) rotation around the \( b \)-axis and a reflection about the \( c \)-axis followed by a translation. A depiction of the crystal packing is shown in Figure 2.26.

To determine the probability of this particular synthon formation, a CSD search was conducted. The CSD revealed 803 entries that contained a carboxylic acid and a secondary amide. However when the search was restricted by two criteria: the moieties must both be on the same molecule and the amide must also be ortho to the acid the number of entries reduced to 43. Of those 43 entries only 1 was sustained by the same synthon that is shown. If the amide is not restricted to a secondary amide then an additional 6 entries are revealed. Based upon the relatively low number of entries in the CSD, the supramolecular heterosynthon highlighted in Figure 2.26. can be considered rare in the presence of carboxylic acid and amide moieties.
Figure 2.26. Crystal packing of 4a
Table 2.2. Crystal structure parameters for cocrystals 1a-4a

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2.2.5. C$_3$S$_3$ for the General Formation of Imides

Whereas C$_3$S$_3$ can only be confirmed in the three reactions for which isolation of an anhydride-amine cocrystal occurred, conversion of solvent-ground anhydride-amine mixtures to imides was a more general occurrence. 32 out of the total 49 reactions resulted in imide formation. 17 reactions did not produce an imide. A summary of the results is presented in Table 2.1. Solvent-drop grinding followed by heating therefore appears to represent a feasible and general methodology for the preparation of imides. In the following segments the reaction purity and percent yield will be addressed via DSC and $^1$HNMR. Additionally, the ability to monitor the reactions by FT-IR and PXRD will be discussed as well as the possibility of cocrystal formation in situ in the DSC.

2.2.5.1. Imide Purity

Initial monitoring for reaction completion included FT-IR and PXRD measurements. Additional characterization was conducted on the 32 successful imide formation reactions via DSC and $^1$HNMR. A typical DSC scan was 10 °C/min from ca. 30 °C-350 °C. Analysis of the 32 samples indicated that 20/32 melted below 350 °C; however, 6/32 showed no clear melt in the DSC which is most likely indicative of imide formation due to the lack of melt from either starting material. Unfortunately 13/32 samples gave either multiple or broad phase transitions, reducing the number of high purity reactions to 19. However, literature melting points were compared to experimental DSC melts when possible resulting in 7/7 correlating melting points. A potential cause for some of the low purity reactions could be the ratio at which the reactions were
conducted. 5 of the reactions were performed in the presence of excess amine (PA4 or PA5) in an attempt to terminate the potentially polymeric reaction with free amines.

$^1$HNMR characterization was attempted on the 32 samples; however, due to the limited solubility of some of the imides, six (PA1+AA2, PA2+AA2, PA2+AA5, PA2+AA6, PA4+AA1, PA4+AA4) of the $^1$HNMR’s could not be obtained. In general the purity of the imides was relatively high based on the low incidence of occurrence of excess signals in the $^1$HNMR. In reactions PA5+AA6, PA4+AA5, and PA4+AA2 the purity level appears lower but the additional peaks can be associated with the excess amine that was input into the reaction. The purity could perhaps be improved by following the heating with a washing step with an organic solvent such as methanol.

Additionally, six samples (PA1+AA3, PA1+AA5, PA2+AA3, PA4+AA3, PA5+AA4, PA7+AA4) had a signal at ca.10 ppm which is indicative of the amic-acid reaction intermediate. Due to the reversibility of the reaction, the presence of some of the intermediate is not unlikely, especially after long term sample storage. The six samples that contained some intermediate could most likely be converted to the imide cleanly upon further heating. A summary of the DSC and $^1$HNMR data is presented in Table 2.3.
Table 2.3. Summary of DSC and $^1$HNMR data (S.M. = starting materials, int. = intermediate, Lit. = literature value of melting point)

<table>
<thead>
<tr>
<th>Reactants</th>
<th>DSC Mixture</th>
<th>DSC Imide Melt</th>
<th>Lit. Imide</th>
<th>$^1$HNMR</th>
<th>Input</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA1+AA1</td>
<td>S.M. to Cocrystal to Imide</td>
<td>&gt;350</td>
<td>N/A</td>
<td>imide</td>
<td>2:1</td>
</tr>
<tr>
<td>PA1+AA2</td>
<td>S.M. to Cocrystal to Imide</td>
<td>247</td>
<td>N/A</td>
<td>insoluble</td>
<td>2:1</td>
</tr>
<tr>
<td>PA1+AA3</td>
<td>S.M.</td>
<td>137-broad</td>
<td>N/A</td>
<td>int. present</td>
<td>1:1</td>
</tr>
<tr>
<td>PA1+AA4</td>
<td>S.M.</td>
<td>202</td>
<td>202$^{64}$</td>
<td>imide</td>
<td>1:1</td>
</tr>
<tr>
<td>PA1+AA5</td>
<td>S.M. to Imide</td>
<td>263</td>
<td>N/A</td>
<td>int. present</td>
<td>2:1</td>
</tr>
<tr>
<td>PA2+AA1</td>
<td>S.M. to Cocrystal to Imide</td>
<td>&gt;350</td>
<td>N/A</td>
<td>imide</td>
<td>2:1</td>
</tr>
<tr>
<td>PA2+AA2</td>
<td>S.M. to Imide</td>
<td>237-broad</td>
<td>N/A</td>
<td>insoluble</td>
<td>2:1</td>
</tr>
<tr>
<td>PA2+AA3</td>
<td>S.M. to Imide</td>
<td>230</td>
<td>230$^{64}$</td>
<td>int. present</td>
<td>1:1</td>
</tr>
<tr>
<td>PA2+AA4</td>
<td>S.M. to Cocrystal to Imide</td>
<td>289</td>
<td>290$^{65}$</td>
<td>imide</td>
<td>1:1</td>
</tr>
<tr>
<td>PA2+AA5</td>
<td>S.M.</td>
<td>&gt;350</td>
<td>N/A</td>
<td>insoluble</td>
<td>2:1</td>
</tr>
<tr>
<td>PA2+AA6</td>
<td>S.M.</td>
<td>350</td>
<td>N/A</td>
<td>insoluble</td>
<td>1:1</td>
</tr>
<tr>
<td>PA3+AA2</td>
<td>S.M. to Imide</td>
<td>230</td>
<td>230$^{64}$</td>
<td>int. present</td>
<td>1:1</td>
</tr>
<tr>
<td>PA3+AA3</td>
<td>S.M.</td>
<td>&gt;350</td>
<td>N/A</td>
<td>impurities</td>
<td>2:3</td>
</tr>
<tr>
<td>PA3+AA4</td>
<td>S.M. to Imide</td>
<td>276-broad</td>
<td>N/A</td>
<td>imide</td>
<td>1:3</td>
</tr>
<tr>
<td>PA4+AA1</td>
<td>S.M. to Cocrystal to Imide</td>
<td>&gt;350</td>
<td>N/A</td>
<td>insoluble</td>
<td>1:1</td>
</tr>
<tr>
<td>PA4+AA2</td>
<td>S.M.</td>
<td>&gt;350</td>
<td>N/A</td>
<td>excess amine</td>
<td>5:1</td>
</tr>
<tr>
<td>PA4+AA3</td>
<td>S.M.</td>
<td>268</td>
<td>N/A</td>
<td>int. present</td>
<td>1:2</td>
</tr>
<tr>
<td>PA4+AA4</td>
<td>S.M.</td>
<td>246-broad</td>
<td>247$^{66}$</td>
<td>insoluble</td>
<td>1:2</td>
</tr>
<tr>
<td>PA4+AA5</td>
<td>S.M.</td>
<td>350-broad</td>
<td>N/A</td>
<td>excess amine</td>
<td>5:1</td>
</tr>
<tr>
<td>PA4+AA6</td>
<td>S.M. to Cocrystal to Imide</td>
<td>285</td>
<td>N/A</td>
<td>imide</td>
<td>1:1</td>
</tr>
<tr>
<td>PA5+AA1</td>
<td>S.M.</td>
<td>320-broad</td>
<td>N/A</td>
<td>excess amine</td>
<td>5:1</td>
</tr>
<tr>
<td>PA5+AA2</td>
<td>S.M.</td>
<td>233-broad</td>
<td>N/A</td>
<td>imide, low conc.</td>
<td>1:1</td>
</tr>
<tr>
<td>PA5+AA3</td>
<td>S.M. to Cocrystal to Imide</td>
<td>210-broad</td>
<td>N/A</td>
<td>minor impurities</td>
<td>1:2</td>
</tr>
<tr>
<td>PA5+AA4</td>
<td>S.M. to Imide</td>
<td>240</td>
<td>250$^{67}$</td>
<td>int. present</td>
<td>1:2</td>
</tr>
<tr>
<td>PA5+AA5</td>
<td>S.M.</td>
<td>298-broad</td>
<td>N/A</td>
<td>excess amine</td>
<td>5:1</td>
</tr>
<tr>
<td>PA5+AA6</td>
<td>S.M.</td>
<td>&gt;350</td>
<td>N/A</td>
<td>excess amine</td>
<td>5:1</td>
</tr>
<tr>
<td>PA6+AA3</td>
<td>S.M. to Imide</td>
<td>242-broad</td>
<td>N/A</td>
<td>minor impurities</td>
<td>1:1</td>
</tr>
<tr>
<td>PA6+AA4</td>
<td>S.M.</td>
<td>142</td>
<td>140$^{69}$</td>
<td>imide</td>
<td>1:1</td>
</tr>
<tr>
<td>PA7+AA2</td>
<td>S.M.</td>
<td>&gt;350</td>
<td>N/A</td>
<td>minor impurities</td>
<td>1:1</td>
</tr>
<tr>
<td>PA7+AA3</td>
<td>S.M.</td>
<td>206-broad</td>
<td>N/A</td>
<td>minor impurities</td>
<td>1:1</td>
</tr>
<tr>
<td>PA7+AA4</td>
<td>S.M.</td>
<td>154</td>
<td>172$^{68}$</td>
<td>int. present</td>
<td>1:1</td>
</tr>
<tr>
<td>PA7+AA5</td>
<td>S.M.</td>
<td>&gt;350</td>
<td>N/A</td>
<td>imide, low conc.</td>
<td>1:1</td>
</tr>
</tbody>
</table>
2.2.5.2. Monitoring the Condensation Reaction via DSC

The DSC has been an invaluable tool for the discovery and development of $C_3S_3$. The DSC can illuminate the phase transformation of a mixture of an amine and an anhydride to an imide by first capturing the melt of the lower melting component as it converts to the cocrystal then showing the cocrystal melt as it converts to the imide. Examples illustrating the process were presented in Figures 2.6, 2.14, and 2.19. With these details in mind, two questions are posed: can a cocrystal that could not be made by solvent-drop grinding be made in situ after melting the lower melting starting material in the DSC? Also, can the DSC run produce an imide that had otherwise failed from the synthetic method of applying heat in an oven?

To address the initial question, stoichiometric mixtures of starting materials were weighed out and ground together by hand without solvent. The physical mixtures of 46 reactions were analyzed via DSC at a scan rate of 10 °C/min from ca. 30 °C to 350 °C. The results from this screen are shown in Table 2.3. Many of the DSC traces showed phase transitions corresponding to the melts of the individual starting materials and some were followed by a melt of the imide. Interestingly, seven of the physical mixtures showed a phase transition that occurred after the melt of the lower melting component and did not correspond to either starting material or to the imide. Based upon the prototypal DSC traces from reactions 1-3, this phase transition is most likely the melt of a cocrystal, thus revealing 4 additional condensation reactions controlled by a cocrystal intermediate.

In situ cocrystal formation was possibly observed for reactions of 3-aminobenzoic acid with phthalic anhydride (PA2-AA4), 1,4-phenylenediamine with NTCDA (PA4-N17),
AA1), 1,4-phenylenediamine with 1,8-naphthalic anhydride (PA4-AA6), and 1,5-
naphthalenediamine with maleic anhydride (PA5-AA3). Figure 2.27. illustrates the
mixture of 3-aminobenzoic acid and phthalic anhydride. The melting point of phthalic
anhydride is 130 °C, which correlates to the first phase transition of the DSC. The
recrystallization immediately following that transition is believed to be the cocrystal
formation which is quickly followed by the melt of the cocrystal. The last sharp phase
transition occurs at 289 °C and is associated with the melt of the imide.

Figure 2.27. DSC trace of mixture of 3-aminobenzoic acid and phthalic anhydride

Figure 2.28. highlights the DSC trace of the mixture of 1,4-phenylenediamine and
NTCDA. Of the seven anhydrides employed in this study, NTCDA appears to be the
strongest supporter of the supramolecular synthon as it is utilized in the formation of two
out of the three cocrystals, thus considering the formation of additional cocrystals with
NTCDA is quite likely. The melting point of the amine is 145 °C which can be attributed

95
to the first endothermic melt. The initial exothermic phase transitions that occurs at ca. 100 °C is unique to this sample and may be an artifact of the amine. However, after the melt of 1,4-phenylenediamine a recrystallization occurs wherein the cocrystal is most likely formed. The cocrystal is then heated until melting at ca. 257 °C. The DSC does not show a melt for the imide as the melting point is greater than 350 °C.

Figure 2.28. DSC trace of a mixture of 1,4-phenylenediamine and NTCDA

The DSC trace of a mixture of 1,4-phenylenediamine and 1,8-naphthalic anhydride is shown in Figure 2.29. The initial sharp phase transition can be attributed to the melt of 1,4-phenylenediamine which melts at 145 °C. The recrystallization that occurs thereafter is associated with cocrystal formation. The melt at 178 °C does not correspond to either starting material or the imide and is therefore most likely the melt of the cocrystal. Once the cocrystal melts the condensation reaction occurs generating the imide. The melting point of the synthesized imide was 284 °C which is within a few degrees of the final phase transition from the mixture.
Figure 2.29. DSC trace of a mixture of 1,4-phenylenediamine and 1,8-naphthalic anhydride

Figure 2.30. depicts the DSC trace of a mixture of 1,5-naphthalenediamine and maleic anhydride. Maleic anhydride was the lowest melting anhydride but also proved to be the most reactive as solvent-drop grinding with DMF or DMSO lead to imide formation in many reactions. Due to solvent-drop grinding generating the imide instead of the cocrystal, the potential for isolation of a cocrystal was low. However, using a mixture of anhydride and amine may have generated a cocrystal in situ in the DSC. The first phase transition corresponds to the melt of maleic anhydride (51 °C). Unlike the previous examples, only a subtle recrystallization is present after the melt. But a phase transition that does not correlate to either starting materials occurs at 140 °C and is therefore attributed to the melt of the cocrystal. The final phase change at 209 °C is consistent with the melt of the imide.
Figure 2.30. DSC trace of a mixture of 1,5-naphthalenediamine and maleic anhydride

The possibility of synthesizing an imide that could not be generated in the oven during the temperature ramp run in the DSC was also addressed. Unfortunately, analysis of the 17 DSC traces of the mixtures (PA1+AA6, PA1+AA7, PA2+AA7, PA3+AA1, PA3+AA5, PA3+AA6, PA3+AA7, PA4+AA7, PA5+AA7, PA6+AA1, PA6+AA2, PA6+AA5, PA6+AA6, PA6+AA7, PA7+AA1, PA7+AA6, PA7+AA7) concluded that no new imides were generated as there were no unidentifiable phase transitions.

2.2.5.3. Analysis of Cocrystals and Imides via PXRD

PXRD diffractograms were collected at two points during the reaction: once after solvent-drop grinding and again after heating. For the three reactions described in detail in sections 2.2.1-2.2.3 the PXRD diffractogram from the bulk ground cocrystal sample could be compared to the calculated PXRD diffractogram from the single crystal structure. An example of this is featured in Figure 2.31. The limitation of PXRD of the
ground material is that without the calculated diffractogram, it is unclear what the new diffractogram corresponds to. The calculated diffractogram for the imide can be compared to the resulting imide to confirm bulk sample reaction completion, such as in Figure 2.32. However, to employ PXRD to confirm imide formation, a calculated pattern is also required. Therefore, coupled with single crystal analysis of the imide, PXRD can be a powerful tool for analysis of a $C^3S^3$ type reaction.

**Figure 2.31.** PXRD diffractograms of eight solvent drop grinds, starting materials, and calculated cocrystal
2.2.5.4. Monitoring the Condensation Reaction via FT-IR

Monitoring the C$_3$S$_3$ reaction by FT-IR was an excellent method for determining cocrystal formation after solvent-drop grinding due to the predictable shift in strong carbonyl peaks to higher wavenumbers coupled with variable shifts in the NH$_2$ region. An exemplary case is shown in Figure 2.33. After heating the ground solid in the oven the FT-IR spectrum was again collected and examined. Imide formation was easily monitored by further examination of two specified regions. Disappearance of the NH$_2$ peaks and a shift to lower wavenumbers for the carbonyl peak (typically ca. 40 wavenumbers lower), shown in Figure 2.34., was indicative of imide formation.
Figure 2.33. Infrared spectra (FT-IR) of NTCDA and 2-methyl-4-nitroaniline DMF solvent drop grind (red) compared to anhydride (purple) and amine (blue)

Figure 2.34. FT-IR of imide (red) with starting materials
For reactions where there was no cocrystal formation from the solvent-drop grinding the FT-IR spectra appeared as compilations of the respective amine and anhydride starting material. For reaction 4 where the solvent-drop grinding produced the amic-acid reaction intermediate, i.e. the anhydride ring opens affording a carboxylic acid and the amine covalently binds to the carbonyl producing a secondary amide, the carbonyl peak in the FT-IR spectrum is shifted to a lower wavenumber (Figure 2.35.) which could be confused with the imide formation, however, additional heating shifts the carbonyl region even lower by ca. 30 wavenumbers as shown in Figure 2.36.

**Figure 2.35.** FT-IR of intermediate (red) formed from phthalic anhydride (purple) and 1-adamantylamine (green)
2.3. Conclusions

Cocrystal controlled solid-state synthesis is an invaluable synthetic methodology for the generation of new molecules with very little solvent waste and with high yield. Additionally, the incorporation of cocrystallization into organic synthesis is exemplary evidence for the vast utility of cocrystals. Of the 49 reactions attempted in this study 32 resulted in imide formation while 17 showed no reactivity. 3 of the 32 also proved to be controlled by a reactive cocrystal intermediate that, once heated, dehydrated to form the imide. The formation of the cocrystals was facilitated via the well established technique of solvent-drop grinding. Once the cocrystals were generated they were heated until the condensation reaction was completed. The temperatures and reaction times varied depending upon the starting materials, however, the sample was always heated above the melting point of the lowest melting component. Interestingly, a total of 4 additional
cocrystals may have been isolated from heating a mixture of the reactants in the DSC, illustrating that the cocrystal can also be generated in situ as a reactive intermediate that can ultimately lead to imide formation.

The development of novel materials via C\textsuperscript{3}S\textsuperscript{3} with the isolation of a cocrystal as a reactive intermediate provides additional insight into the method by which the reaction occurs. The greater understanding of the solid-state synthesis reaction of imides gained in this study serves as a model to be applied to other solid-state or solution based reactions. The expansion of the field of solid-state organic synthesis will lead to the reduction of hazardous waste production, increase reaction yields, and make the overall synthetic process cheaper and more environmentally friendly.

2.4. Materials and Methods

2.4.1. Materials

All materials were used as received without further purification from Sigma-Aldrich or Alfa Aesar.

2.4.2. Synthetic Methods

A typical reaction involved solvent-drop grinding with chloroform, cyclohexane, DMSO, DMF, ethyl acetate, methanol, toluene, and water for ca. 4 minutes by hand with an agate mortar and pestle. The solid was then transferred to a glass vial and heated in an oven at a temperature above the melting point of the lowest melting component to facilitate imide formation. Reaction conditions for each of the 32 successful imide formations are provided below:
2-methyl-4-nitroaniline and NTCDA (PA1+AA1):

100 mg (0.66 mmol) of 2-methyl-4-nitroaniline and 88 mg (0.33 mmol) of NTCDA were ground with ca. 20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting purple cocrystal was then heated for 3 hours at 180 °C to produce the imide. The imide was synthesized in ca. 75% yield.

2-methyl-4-nitroaniline and pyromellitic anhydride (PA1+AA2):

100 mg (0.66 mmol) of 2-methyl-4-nitroaniline and 72 mg (0.33 mmol) of pyromellitic anhydride were ground with ca. 20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting orange cocrystal was then heated for 50 hours at 150 °C to produce the imide. The imide was synthesized in ca. 80% yield.

2-methyl-4-nitroaniline and maleic anhydride (PA1+AA3):

100 mg (0.66 mmol) of 2-methyl-4-nitroaniline and 64 mg (0.65 mmol) of maleic anhydride were ground with ca. 20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 40 hours at 60 °C to produce the imide. The imide was synthesized in ca. 92% yield.

2-methyl-4-nitroaniline and phthalic anhydride (PA1+AA4):

100 mg (0.66 mmol) of 2-methyl-4-nitroaniline and 98 mg (0.65 mmol) of phthalic anhydride were ground with ca. 20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 16 hours at 150 °C to produce the imide. The imide was synthesized in ca. 73% yield.
2-methyl-4-nitroaniline and 3,3',4,4'-biphenyltetracarboxylic acid dianhydride (PA1+AA5):

100 mg (0.66 mmol) of 2-methyl-4-nitroaniline and 97 mg (0.33 mmol) of 3,3',4,4'-biphenyltetracarboxylic acid dianhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 21 hours at 120 °C to produce the imide. The imide was synthesized in ca. 87% yield.

3-aminobenzoic acid and NTCDA (PA2+AA1):

100 mg (0.73mmol) of 3-aminobenzoic acid and 98 mg (0.36 mmol) of NTCDA were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting purple cocrystal was then heated for 14 hours at 150 °C to produce the imide. The imide was synthesized in ca. 99% yield.

3-aminobenzoic acid and pyromellitic anhydride (PA2+AA2):

100 mg (0.73mmol) of 3-aminobenzoic acid and 79 mg (0.36 mmol) of pyromellitic anhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 16 hours at 180 °C to produce the imide. The imide was synthesized in ca. 90% yield.

3-aminobenzoic acid and maleic anhydride (PA2+AA3):

100 mg (0.73mmol) of 3-aminobenzoic acid and 72 mg (0.35 mmol) of maleic anhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 19 hours at 150 °C to produce the imide. The imide was synthesized in ca. 92% yield.
3-aminobenzoic acid and phthalic anhydride (PA2+AA4):

100 mg (0.73mmol) of 3-aminobenzoic acid and 108 mg (0.73 mmol) of phthalic anhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 26 hours at 150 °C to produce the imide. The imide was synthesized in ca. 88% yield.

3-aminobenzoic acid and 3,3’,4,4’-biphenyltetracarboxylic dianhydride (PA2+AA5):

100 mg (0.73mmol) of 3-aminobenzoic acid and 107 mg (0.36 mmol) of 3,3’,4,4’-biphenyltetracarboxylic dianhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 14 hours at 150 °C to produce the imide. The imide was synthesized in ca. 85% yield.

3-aminobenzoic acid and 1,8-naphthalic anhydride (PA2+AA6):

100 mg (0.73mmol) of 3-aminobenzoic acid and 145 mg (0.73 mmol) of 1,8-naphthalic anhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 23 hours at 150 °C to produce the imide. The imide was synthesized in ca. 79% yield.

Melamine and pyromellitic anhydride (PA3+AA2):

200 mg (1.6 mmol) of melamine and 519 mg (2.4 mmol) of pyromellitic anhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 75 hours at 180 °C and 26 hours at 150 °C to produce the imide. The imide was synthesized in ca. 88% yield.
melamine and maleic anhydride (PA3+AA3):

100 mg (0.79 mmol) of melamine and 26 mg (0.26 mmol) of maleic anhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 23 hours at 115 ºC to produce the imide. The imide was synthesized in ca. 79% yield.

melamine and 1,8-naphthalic anhydride (PA3+AA4):

100 mg (0.79 mmol) of melamine and 471 mg (2.4 mmol) of 1,8-naphthalic anhydride were ground with ca. 40μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 23 hours at 115 ºC to produce the imide. The imide was synthesized in ca. 70% yield.

1,4-phenylenediamine and NTCDA (PA4+AA1):

100 mg (0.92 mmol) of 1,4-phenylenediamine and 247 mg (0.92 mmol) of NTCDA were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 5 hours at 115 ºC to produce the imide. The imide was synthesized in ca. 98% yield.

1,4-phenylenediamine and pyromellitic anhydride (PA4+AA2):

200 mg (1.8 mmol) of 1,4-phenylenediamine and 81 mg (0.36 mmol) of pyromellitic anhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 68 hours at 180 ºC to produce the imide. The imide was synthesized in ca. 78% yield.

1,4-phenylenediamine and maleic anhydride (PA4+AA3):

100 mg (0.92 mmol) of 1,4-phenylenediamine and 45 mg (0.46 mmol) of maleic anhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 23 hours at 180 ºC to produce the imide. The imide was synthesized in ca. 79% yield.
minutes. The resulting solid was then heated for 23 hours at 115 ºC to produce the imide. The imide was synthesized in ca. 71% yield.

1,4-phenylenediamine and phthalic anhydride (PA4+AA4):

100 mg (0.92 mmol) of 1,4-phenylenediamine and 98 mg (0.46 mmol) of phthalic anhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 5 hours at 115 ºC to produce the imide. The imide was synthesized in ca. 85% yield.

1,4-phenylenediamine and 3,3’,4,4’-biphenyltetracarboxylic dianhydride (PA4+AA5):

100 mg (0.92 mmol) of 1,4-phenylenediamine and 54 mg (0.18 mmol) of 3,3’,4,4’-biphenyltetracarboxylic dianhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 68 hours at 180 ºC to produce the imide. The imide was synthesized in ca. 82% yield.

1,4-phenylenediamine and 1,8-naphthalic anhydride (PA4+AA6):

100 mg (0.92 mmol) of 1,4-phenylenediamine and 183 mg (0.93 mmol) of 1,8-naphthalic anhydride were ground with ca. 20μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 64 hours at 150 ºC to produce the imide. The imide was synthesized in ca. 78% yield.

1,5-diaminonaphthalene and NTCDA (PA5+AA1):

100 mg (0.63 mmol) of 1,5-diaminonaphthalene and 34 mg (0.12 mmol) of NTCDA were ground with ca.10 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 68 hours at 180 ºC to produce the imide. The imide was synthesized in ca. 86% yield.
1,5-diaminonaphthalene and pyromellitic anhydride (PA5+AA2):

100 mg (0.63 mmol) of 1,5-diaminonaphthalene and 137 mg (0.63 mmol) of pyromellitic anhydride were ground with ca.20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 107 hours at 120 °C to produce the imide. The imide was synthesized in ca. 84% yield.

1,5-diaminonaphthalene and maleic anhydride (PA5+AA3):

100 mg (0.63 mmol) of 1,5-diaminonaphthalene and 31 mg (0.31 mmol) of maleic anhydride were ground with ca.20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 23 hours at 115 °C to produce the imide. The imide was synthesized in ca. 79% yield.

1,5-diaminonaphthalene and phthalic anhydride (PA5+AA4):

100 mg (0.63 mmol) of 1,5-diaminonaphthalene and 47 mg (0.31 mmol) of phthalic anhydride were ground with ca.20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 19 hours at 115 °C to produce the imide. The imide was synthesized in ca. 82% yield.

1,5-diaminonaphthalene and 3,3’,4,4’-biphenyltetracarboxylic dianhydride (PA5+AA5):

100 mg (0.63 mmol) of 1,5-diaminonaphthalene and 37 mg (0.13 mmol) of 3,3’,4,4’-biphenyltetracarboxylic dianhydride were ground with ca.20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 68 hours at 180 °C to produce the imide. The imide was synthesized in ca. 77% yield.
1,5-diaminonaphthalene and 1,8-naphthalic anhydride (PA5+AA6):

100 mg (0.63 mmol) of 1,5-diaminonaphthalene and 25 mg (0.12 mmol) of 1,8-naphthalic anhydride were ground with ca. 20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 68 hours at 180 °C to produce the imide. The imide was synthesized in ca. 73% yield.

1-adamantylamine and maleic anhydride (PA6+AA3):

100 mg (0.66 mmol) of 1-adamantylamine and 64 mg (0.66 mmol) of maleic anhydride were ground with ca. 20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 20 hours at 120 °C to produce the imide. The imide was synthesized in ca. 92% yield.

1-adamantylamine and phthalic anhydride (PA6+AA4):

100 mg (0.66 mmol) of 1-adamantylamine and 97 mg (0.66 mmol) of phthalic anhydride were ground with ca. 20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 144 hours at 120 °C to produce the imide. The imide was synthesized in ca. 96% yield.

triphenylmethylamine and pyromellitic anhydride (PA7+AA2):

100 mg (0.39 mmol) of triphenylmethylamine and 84 mg (0.66 mmol) of pyromellitic anhydride were ground with ca. 20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 48 hours at 140 °C to produce the imide. The imide was synthesized in ca. 77% yield.
triphenylmethylamine and maleic anhydride (PA7+AA3):

100 mg (0.39 mmol) of triphenylmethylamine and 38 mg (0.39 mmol) of maleic anhydride were ground with ca.20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 23 hours at 115 ºC to produce the imide. The imide was synthesized in ca. 86% yield.

triphenylmethylamine and phthalic anhydride (PA7+AA4):

100 mg (0.39 mmol) of triphenylmethylamine and 57 mg (0.39 mmol) of phthalic anhydride were ground with ca.20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 26 hours at 115 ºC to produce the imide. The imide was synthesized in ca. 90% yield.

triphenylmethylamine and 3,3’,4,4’-biphenyltetracarboxylic dianhydride (PA7+AA5):

100 mg (0.39 mmol) of triphenylmethylamine and 113 mg (0.39 mmol) of 3,3’,4,4’-biphenyltetracarboxylic dianhydride were ground with ca.20 μL of DMF by hand in an agate mortar and pestle for 4 minutes. The resulting solid was then heated for 48 hours at 140 ºC and 29 hours at 180 ºC to produce the imide. The imide was synthesized in ca. 86% yield.

Single crystal growth of 2-methyl-4-nitroaniline NTCDA cocrystal (1a):

Purple single crystals were obtained from dissolving approximately 20 mg of the cocrystal in 2 ml of 1,4-dioxane. The solution was partially covered with parafilm left to slowly evaporate under ambient conditions. Single crystals of 1a were afforded within 14 days in ca. 20 % yield.
Single crystal growth of 2-methyl-4-nitroaniline NTCDA diimide (1b):
Orange single crystals were obtained by dissolving approximately 35 mg of 1b in 1 ml of DMSO. The solution was partially covered with parafilm left to slowly evaporate under ambient conditions. Single crystals of 1b•DMSO were afforded within 7 days in ca. 60 % yield.

Single crystal growth of 3-aminobenzoic acid NTCDA cocrystal (2a):
Purple single crystals were obtained from dissolving approximately 20 mg of the cocrystal in 2 ml of 1,4-dioxane. The solution was partially covered with parafilm left to slowly evaporate under ambient conditions. Single crystals of 2a were afforded within 3 days in ca. 43 % yield.

Single crystal growth of 3-aminobenzoic acid NTCDA diimide (2b):
Yellow single crystals were obtained from dissolving approximately 15 mg of 2b in 2 ml of pyridine. The solution was partially covered with parafilm left to slowly evaporate under ambient conditions. Single crystals of 2b•pyridine were afforded within 20 days in ca. 55 % yield.

Single crystal growth of 2-methyl-4-nitroaniline pyromellitic anhydride cocrystal (3a): Orange single crystals were obtained from dissolving approximately 20 mg of the cocrystal 3a in 2 ml of a 1:1 solvent mixture of chloroform and ethyl acetate. The solution was partially covered with parafilm left to slowly evaporate under ambient conditions. Single crystals of 3a were afforded within 22 days in ca. 15 % yield.

Single crystal growth of 2-methyl-4-nitroaniline pyromellitic anhydride diimide (3b): Yellow single crystals were obtained from dissolving approximately 30 mg of 3b in 1 ml of DMF. The solution was partially covered with parafilm left to slowly evaporate
under ambient conditions. Single crystals of 3b were afforded within 14 days in ca. 36 % yield.

**Single crystal growth of 1-adamantylamine phthalic anhydride intermediate (4a):**

Single crystals of the intermediate were obtained from dissolving approximately 50 mg (0.33 mmol) of 1-adamantylamine and 49 mg (0.33 mmol) of phthalic anhydride in 4 ml of methanol. The solution was partially covered with parafilm left to slowly evaporate under ambient conditions. Single crystals of 4a were afforded within 6 days in ca. 68 % yield.

**Single crystal growth of 1-adamantylamine phthalic anhydride imide (4b):**

Single crystals of the imide product were obtained by dissolving the heated material in ca. 2ml of distilled methanol and slow evaporation over several days. The unit cell parameters match the crystal structure of Refcode QUSKUK as deposited in the Cambridge Structural Database.

**2.4.3. Characterization Methods**

**Single-Crystal X-ray Diffraction:** Single crystals were obtained for nine compounds. Attempts to crystallize 3 did not afford crystals suitable for single crystal X-ray crystallographic analysis. Single crystal analysis for 1, 2, and 5-10 was performed on a Bruker-AXS SMART APEX CCD diffractometer with monochromatized Mo Kα radiation (λ = 0.71073 Å) connected to a KRYO-FLEX low-temperature device. Data for 1, 2, and 5-10 were collected at 100 K or 298 K. Lattice parameters were determined from least-squares analysis, and reflection data were integrated using SAINT.69
Structures were solved by direct methods and refined by full matrix least squares based on F^2 using the SHELXTL package. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms bonded to carbon, nitrogen, and oxygen atoms were placed geometrically and refined with an isotropic displacement parameter fixed at 1.2 times U_q of the atoms to which they were attached. Hydrogen atoms bonded to methyl groups were placed geometrically and refined with an isotropic displacement parameter fixed at 1.5 times U_q of the carbon atoms.

**Powder X-Ray Diffraction (PXRD):** 2-8 were characterized by a D-8 Bruker X-ray Powder Diffractometer using a Cu Kα radiation (λ = 1.54178 Å), 50kV, 40mA. Data was collected over an angular range of 3° to 40° 2θ value in continuous scan mode using a step size of 0.05° 2θ value and a scan speed of 1.0 °/min.

**Calculated PXRD:** Calculated PXRD diffractograms were generated from the single crystal structures using Mercury 1.5 (Cambridge Crystallographic Data Centre, UK).

**Differential Scanning Calorimetry (DSC):** Differential Scanning Calorimetry was performed on a TA Instruments 2920 DSC with a typical scan range of 35 °C – 350 °C, scan rate of 10 °C/min, and nitrogen purge of ca. 70 psi.

**Fourier Transform Infrared Spectroscopy (FT-IR):** FT-IR analysis was performed on a Nicolet Avatar 320 FT-IR spectrometer equipped with a solid-state ATR accessory.

**UV-Vis Spectrophotometer (UV-vis):** Purple co-crystals from reactions 1 and 2 were additionally characterized by UV-vis from 350-800nm on a PerkinElmer Lambda 900 UV/Vis/NIR spectrometer.
Table 2.4. Hydrogen bond distances and parameters

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hydrogen Bond</th>
<th>d(H...A)/ Å</th>
<th>d(D...A)/ Å</th>
<th>θ/ º</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>N-H⋯O</td>
<td>2.18</td>
<td>2.946(6)</td>
<td>145.5</td>
</tr>
<tr>
<td></td>
<td>N-H⋯O</td>
<td>2.55</td>
<td>3.194(7)</td>
<td>130.3</td>
</tr>
<tr>
<td></td>
<td>N-H⋯O</td>
<td>2.39</td>
<td>3.255(8)</td>
<td>166.9</td>
</tr>
<tr>
<td>2a</td>
<td>N-H⋯O</td>
<td>2.24</td>
<td>3.066(4)</td>
<td>155.2</td>
</tr>
<tr>
<td></td>
<td>N-H⋯O</td>
<td>2.46</td>
<td>3.217(4)</td>
<td>144.4</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>1.81</td>
<td>2.643(3)</td>
<td>172.3</td>
</tr>
<tr>
<td>3a</td>
<td>N-H⋯O</td>
<td>2.16</td>
<td>2.943(5)</td>
<td>148.1</td>
</tr>
<tr>
<td></td>
<td>N-H⋯O</td>
<td>2.31</td>
<td>3.089(5)</td>
<td>148.0</td>
</tr>
<tr>
<td>4a</td>
<td>O-H⋯O</td>
<td>1.87</td>
<td>2.682(3)</td>
<td>171.6</td>
</tr>
<tr>
<td></td>
<td>N-H⋯O</td>
<td>2.34</td>
<td>3.318(3)</td>
<td>157.5</td>
</tr>
</tbody>
</table>
2.5. References Cited


(22) Santra, R.; Biradha, K., *Crystengcomm* **2008**, *10*, 1524.


(61) CSD version 5.30, November 2007 release including May 2009 update. Search parameters: organics only, no ions, 3D coordinates determined, R<7.5%. 2009


(70) Sheldrick, G. M. *SHELXTL*, University of Gottingen: Germany, 1997.
Chapter 3: Lamotrigine Crystal Forms: Synthesis, Characterization, and Evaluation

3.1 Preamble

Crystal form development for an active pharmaceutical ingredient (API) typically results in a plethora of crystal forms including salts, cocrystals, solvates, hydrates, etc. which can be beneficial to the pharmaceutical industry.

Pharmaceutical salts are materials formed by an ionic API and a suitable, pharmaceutically acceptable counterion. They have been a part of crystal form selection for decades as they offer diversity of composition and can therefore exhibit a wide range of physicochemical properties. Pharmaceutical cocrystals are a relatively new technology with the first pharmaceutical cocrystal developed within the decade. The current focus of pharmaceutical cocrystallization is, much like a pharmaceutical salt, their inherent ability to change the properties of an API. A review of the literature reveals that there have been eight pharmaceutical cocrystal case studies with pharmacokinetic details reported to date, all of which support that pharmaceutical cocrystals are a viable option to enhance the clinical performance of a poorly soluble API. Pharmaceutical cocrystals are a particularly attractive crystal form option because they maintain the criteria for patentability. That is, they are novel, non-obvious, and of utility to the pharmaceutical industry.
The importance of hydrates and solvates in pharmaceutical development has also been recognized. Various examples have demonstrated that the formation of hydrates and solvates can significantly alter the physicochemical properties of APIs, such as chemical stability, solubility and dissolution rate.

With this in mind, we report a study of lamotrigine (6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine), a triazine drug amenable to crystal engineering design strategies that exhibits poor solubility and dissolution rate in its pure crystalline form. Lamotrigine is marketed as Lamictal® by GlaxoSmithKline for oral administration as a compressed or chewable tablet. It is primarily used as an anti-convulsant drug for the treatment of epilepsy as well as in the treatment of psychiatric disorders such as bipolar disorder. In particular, lamotrigine is used for the treatment of generalized seizures associated with Lennox-Gastaud syndrome and it can be used in conjunction with other anti-epileptic drugs such as carbamazepine, phenytoin, phenobarbital, primidone or valproate. An additional and perhaps less common use for lamotrigine is for the treatment of neuropathic pain, cluster headaches, and migraines. Lamotrigine, a white to pale cream-colored powder with a pKa of 5.7, is very slightly soluble in water (0.17 mg/mL at 25 °C) and only slightly soluble in 0.1 M HCl (4.1 mg/mL at 25 °C). Various attempts have been made to solve the use limitations of lamotrigine due to its poor solubility. Briefly, these approaches have involved the exploration of a plethora of crystal forms, including salt forms, and reduction of the particle size. Recently eight novel crystal forms of lamotrigine were reported by Galcera et al., with only two salt forms (saccharinate and DL-hemitartrate dimethylsulfoxide solvate) reaching a greater maximum aqueous solubility than pure lamotrigine. A benzoate dimethylformamide
solvate, hydrogen phthalate dimethylformamide solvate, methanol solvate, isoethoinate, dimethylformamide solvate, methanesulfonate, and a monohydrate have also been reported; however only limited solubility data is available concerning these crystal forms. Some of the aforementioned crystal forms, particularly those involving certain salt forms, are undesirable for certain routes of administration, such as parenteral, due to their acidity. Other formulations contain ingredients that are not safe for human consumption such as dimethylformamide. Clearly, there is a strong scientific and clinical need to develop novel forms of lamotrigine that have significantly improved physicochemical properties, including aqueous solubility, which can be formulated for use in various delivery routes, such as oral administration.

To generate novel crystal forms of lamotrigine an analysis based upon crystal engineering molecular recognition, and supramolecular synthons, was conducted to determine complementarities between a number of pharmaceutically acceptable and approved materials containing carboxylic acid, alcohol, and primary amide moieties and lamotrigine. It showed that lamotrigine can form complexes with two dominant supramolecular synthon motifs, with or without the aminopyridine dimer. Among all pharmaceutically acceptable and/or approved compounds with hydrogen-bonding functionality, a variety of guest molecules that were likely to form either of these two motifs with lamotrigine were selected for this study and are shown in Figure 3.1. All selected guest molecules except butylated hydroxyanisole successfully formed complexes with lamotrigine, resulting in ten novel lamotrigine crystal forms. Details of the supramolecular synthon approach and the development of ten crystal forms of lamotrigine from established cocrystallization techniques are presented herein.
Additionally, solubility and pharmacokinetic studies were conducted upon a subset of these crystal forms and are described herein.

3.2 Results and Discussion

3.2.1 Salt vs Cocrystal

Lamotrigine has the ability to form both salts and cocrystals due to its relatively basic nature (pKa = 5.7). By selecting cocrystal formers with a range of varying acidities, the formation of lamotrigine pharmaceutical salts or cocrystals would be expected. The pKa difference between lamotrigine and the adduct, ΔpKa (i.e. ΔpKa = pKa base - pKa acid), is widely accepted as the key to predicting whether a salt or a cocrystal will form. It is generally considered that if ΔpKa > 3 the resulting compound will be a salt (exemplified in this study by saccharin); whereas the result is typically a cocrystal if ΔpKa < 0. For ΔpKa between 0 < ΔpKa < 3 the outcome can be either a salt or cocrystal or a complex with partial proton transfer. The pKa and ΔpKa values involved in this study are summarized in Table 3.1. It is noted that the ΔpKa values of three cocrystal formers (i.e. adipic acid, L-malic acid and nicotinic acid) fall in the variable region. Interestingly, all of these cocrystal formers produce lamotrigine salts, as evidenced by the proton location and bond length analysis from the single crystal X-ray diffraction data. Analysis of the carbonyl region of the solid-state FTIR spectrum also supports the formation of lamotrigine salts.
Table 3.1. pKa values and the resulting ΔpKa values for the lamotrigine salts

<table>
<thead>
<tr>
<th>Acid</th>
<th>pKa</th>
<th>ΔpKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipic acid</td>
<td>4.43</td>
<td>1.27</td>
</tr>
<tr>
<td>L-Malic acid</td>
<td>3.44</td>
<td>2.26</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>4.92</td>
<td>0.78</td>
</tr>
<tr>
<td>Saccharin</td>
<td>1.60</td>
<td>4.10</td>
</tr>
</tbody>
</table>

**Figure 3.1** Molecular structures of cocrystal and salt formers

3.2.2 CSD Analysis

In order to prepare novel crystal forms of lamotrigine, a crystal engineering study incorporating supramolecular design and the molecular functionality of lamotrigine, i.e. the supramolecular synthon approach, was conducted. The crystal structure of pure lamotrigine exhibits two dominant supramolecular synthon motifs, the aminopyridine dimer (motif 1) and the amine-aromatic nitrogen synthon (motif 2). Motif 1 and motif 2 are depicted in Figure 3.2.
The introduction of an additional complementary component to the crystal lattice of lamotrigine could lead to an interruption of motifs 1 or 2 by either: breaking the aminopyridine dimer (breaking motif 1) or breaking the exterior bifurcated interactions between the aromatic nitrogen moieties of one lamotrigine to the primary amine moieties of two additional lamotrigine molecules (breaking motif 2). An analysis of the Cambridge Structural Database (CSD)\textsuperscript{56, 57} indicates that breaking either motif is feasible given a complementary secondary component. Disruption of motif 1 occurs in 26 out of 81 aminopyridine entries (32\%) and disruption of motif 2 occurs in 39 out of those 81 entries, or 48\% of the time. In order to understand the hydrogen bonding of the primary amine moiety of the diaminopyridine moiety, the 39 entries that break motif 2 were analyzed. Among those entries 95\% (37/39) show the exterior amine moiety hydrogen
bonding to the second molecule while only 2 entries (5%) show the exterior amine moiety hydrogen bonding to a molecule of the same kind, i.e. another diaminopyridine (Refcodes: AMCQUN, GICWOF). Based on these CSD statistics, breaking the supramolecular synthons of motif 1 and motif 2 is feasible, however, there remains a tendency towards persistence of the aminopyridine dimer.

Identification of complementary cocrystal formers for lamotrigine by statistical examination of the percentage of occurrence of supramolecular homosynthons versus supramolecular heterosynthons was also addressed via a CSD analysis. Interactions between an aminopyridine moieties and carboxylic acid, primary amide, and alcohol moieties were examined in order to determine if the supramolecular heterosynthon or the supramolecular homosynthon would be more prominent (Table 3.2., aminopyridine was chosen instead of diaminopyridine to provide a larger dataset for the statistical analysis).
Table 3.2 Comparison of supramolecular homosynthon versus supramolecular heterosynthon with aminopyridines and complementary moieties

<table>
<thead>
<tr>
<th>Complementary Moiety</th>
<th>No. of entries w/ both groups</th>
<th>% Homosynthon occurrence: Aminopyridine Refined dataset (distance range Å)</th>
<th>% Homosynthon occurrence: Cocrystal former Refined dataset (distance range Å)</th>
<th>% Heterosynthon occurrence refined dataset</th>
<th>Heterosynthon Distance Range (Å) Refined dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxylic acid</td>
<td>91</td>
<td>40/91 (44%) (N N 2.92-3.17)</td>
<td>0</td>
<td>42/91-acid (46%) 28/91-carboxylate (31%)</td>
<td>N(py) O 2.50-2.80 N(am) O 2.71-3.10 (acid and carboxylate)</td>
</tr>
<tr>
<td>Primary amide</td>
<td>15</td>
<td>2/15 (13%) (N N 3.04-3.077)</td>
<td>1/15 (6%) (N O 2.98)</td>
<td>1/15 (6%)</td>
<td>N(py) N 2.97 N(am) O 3.06</td>
</tr>
<tr>
<td>Alcohol</td>
<td>307</td>
<td>66/307 (21%) (N N 2.92-3.17)</td>
<td>78/307 (25%) (O O 2.61-2.92)</td>
<td>100/307 (33%)</td>
<td>N(py) O 2.67-2.90 N(am) O 2.78-3.19</td>
</tr>
</tbody>
</table>

To conduct the supramolecular homosynthon and heterosynthon analysis, a broad distance range was initially selected and then reduced by visual inspection to determine the appropriate ranges for defining hydrogen bond contact limits. The values given in Table 3.2. are a refined dataset which includes only aminopyridine and one additional
moiety sustained by a specified supramolecular hetero- or homosynthon interaction within a defined distance range. Our analysis concluded that, in general, the supramolecular heterosynthons were more dominant than the homosynthons. The alcohol moiety was the most statistically favored to interact with the aminopyridine moiety as there was 33% (100/307) versus 21% (66/307) occurrence for the supramolecular heterosynthon and homosynthon, respectively. However, the addition of a carboxylic acid to a molecule sustained via an aminopyridine supramolecular homosynthon has previously been explored and successfully resulted in the formation of cocrystals and salts. Thus it is not surprising that there was also a preference for the aminopyridine-acid supramolecular heterosynthon, with a higher percentage of occurrence attributed to the carboxylic acid group (43/91, 46%) than the carboxylate group (28/91, 31%). Interestingly, the carboxylic acid homosynthon does not occur in the presence of the aminopyridine functional group. There are 15 structures that contain aminopyridine and primary amide moieties, 2 of which form the aminopyridine supramolecular homosynthon, 1 forms the amide dimer, and 1 forms the aminopyridine-amide supramolecular heterosynthon. Unfortunately, this paucity of data precludes determination of the reliability of the aminopyridine-amide supramolecular heterosynthon. However, the CSD analysis indicates that aminopyridines are likely to form supramolecular heterosynthons with molecules containing alcohols and carboxylic acids. A general observation when searching for entries with an aminopyridine was the numerous examples of aminopyridines with barbituric acid derivatives. Specifically, the CSD contains a set of 35 aminopyridine-barbituric acid derivative cocrystals synthesized by Whitesides et al. This dataset indicates that the aminopyridine-amide
supramolecular heterosynthon is a reliable synthon. However, due to the nature of the study, cocrystal formers that are utilized must at least be on the generally regarded as safe (GRAS) list, precluding the selection of cocrystal formers containing amide moieties. Thus a range of carboxylic acids, alcohols, and amides were chosen for crystal form development however, only six resulted in novel crystal forms. Figure 3.1. illustrates the formers that resulted in novel crystal forms.

3.2.3 Motif 1 versus Motif 2

The crystal forms presented herein break either motif 1 or motif 2 present in pure lamotrigine by incorporating a complementary cocrystal former. Motif 1 is broken in 4 out of 9 structures while the remaining crystal forms contain motif 1 but break motif 2. Specifically, crystal forms 2, 4, 7, 9, and 10 break motif 2 while forms 1, 5, 6, and 8 break motif 1. The individual motifs and how they impact the physicochemical properties of the crystal form are discussed in the following segments.

3.2.4 Crystal Structure Descriptions

Cocrystals of lamotrigine methylparaben form I (1) crystallize in the space group $P2_1/n$. 1 crystallizes concomitantly in the presence of pure methylparaben and lamotrigine tetrahydrofuran solvate. The asymmetric unit contains one lamotrigine and one methylparaben molecule. The lamotrigine aminopyridine dimer is not observed in 1 (Figure 3.3.). Instead the structure is a corrugated tape comprised of individual chains of alternating lamotrigine methylparaben molecules sustained primarily by two hydrogen bonds (Figure 3.4.). Specifically, the aromatic nitrogen N2 of the triazine ring is
hydrogen bonded to the hydroxyl moiety of the methylparaben [O1-H1O···N2: O···N 2.651(4) Å, H···N 1.831 Å, O-H···N 164.8 °] and the amine in the 5-position of lamotrigine is hydrogen bonded to the carbonyl group of the ester moiety of methylparaben [N5-H3N···O2: N···O 2.823(4) Å, H···O 1.971 Å, N-H···O 162.7 °]. The chains of extend parallel to the 2-fold axis. Neighboring chains are related by a center of inversion and are held together by various weak interactions including C-H···N and Cl···Cl interactions to form a corrugated tape. The phenyl rings of the lamotrigine molecule are twisted to a dihedral angle of 88.03 °.

*Figure 3.3* Supramolecular synthons exhibited by 1
Lamotrigine methylparaben form II (2) can be obtained via grinding, slurry, or melt. Crystals of 2 exist in space group $P\bar{i}$ with one lamotrigine and one methylparaben in the asymmetric unit (Figure 3). The chlorinated phenyl ring backbone of lamotrigine is disordered over two distinct positions with 40% and 60% occupancies, respectively. The attached chlorine atoms are refined over three positions with occupancies of 40%, 40% and 20%, respectively. A comparison of the crystal structures of 1 and 2 reveals that they exhibit different molecular packing arrangements. Unlike 1, 2 exhibits lamotrigine centrosymmetric aminopyridine dimers [$N3-H3B\cdots N4: N\cdots N 3.121(4) \, \text{Å}, H\cdots N 2.246 \, \text{Å}, N-H\cdots N 172.3 ^\circ$]. The lamotrigine dimers connect to neighboring dimers via methylparaben molecules, thereby forming supramolecular ribbons that extend parallel to the $a$-axis [$N5-H5A\cdots O1: N\cdots O 3.036(4) \, \text{Å}, H\cdots O 2.205 \, \text{Å}, N-H\cdots O 157.3 ^\circ; O1-$}
H1C···N2: O···N 2.711(4) Å, H···N 1.876 Å, O-H···N 173.3 °. The methylparaben molecule also serves as a bridge to join these supramolecular ribbons via N-H···O interactions [N5-H5B···O2: N···O 2.931(4) Å, H···O 2.129 Å, N-H···O 151.2 °].

**Figure 3.5** Breaking motif 2 shown in the hydrogen bonding of 2
Figure 3.6 Crystal packing of 2

The **cocrystal of lamotrigine and nicotinamide** (3) was prepared from a melt of a 1:1 ratio of lamotrigine and nicotinamide, as evidenced by PXRD characterization. Efforts to prepare quality single crystals of 3 for single crystal XRD analysis are unsuccessful to date.

**4 (lamotrigine nicotinamide monohydrate)** crystallizes in the space group $P\overline{1}$, with the asymmetric unit consisting of one molecule of lamotrigine, one molecule of nicotinamide and one water molecule. Motif 2 is broken by the double insertion of water molecules while the lamotrigine aminopyridine dimer persists [N3-H2N⋯N4: N⋯N 3.039(2) Å, H⋯N 2.243 Å, N-H⋯N 154.2 °]. The water molecules facilitate the formation of a supramolecular ribbon motif. The ribbon is formed along the $b$-axis as the lamotrigine dimers are linked by water molecules via N-H⋯O and O-H⋯N interactions.
[N5-H3N⋯O1-H5O⋯N2: N⋯O 2.930(2) Å, H⋯O 2.089 Å, N-H⋯O 165.3 °, O⋯N 2.822(2) Å, H⋯N 1.967 Å, O⋯N 171.7 °]. In addition, nicotinamide molecules form centrosymmetric amide dimers that pack perpendicularly in between the lamotrigine water ribbons forcing a separation between the supramolecular ribbons approximately the length of two nicotinamide molecules (Figure 3.7.) [N7-H8N⋯O2: N⋯O 2.915(3) Å, H⋯O 2.056 Å, N-H⋯O 176.7 °]. The water molecules within the supramolecular ribbons also hydrogen bond to the nicotinamide dimers via additional O-H⋯N interactions that are highlighted in Figure 3.8. [O1-H⋯N6: O⋯N 3.039(3) Å, H⋯N 2.162 Å, O-H⋯N 166.5 °]. The voids generated by the nicotinamide dimers separating the supramolecular ribbons are filled by additional supramolecular ribbon-nicotinamide dimer units. These supramolecular units are stabilized by π-π interactions between the chlorinated lamotrigine ring and the nicotinamide aromatic ring.

Figure 3.7. Supramolecular synthons present in 4
The salt of lamotrigine and saccharin (5) crystallizes in space group $P2_1/c$. The asymmetric unit contains one lamotrigine cation and one saccharin anion. The structure of 5 does not contain the aminopyridine dimer; however, formation of the dimer is possible with protonation of the most basic nitrogen (N2) as it is not incorporated in the lamotrigine dimer. The basic supramolecular unit in 5 is a tetramer formed between two lamotrigine and two saccharin ions where the N2 is protonated. Lamotrigine and saccharin are associated via two 2-point recognition aminopyridine-sulfonamide supramolecular heterosynthons [$N^+\cdot-H\cdot\cdot\cdot N$: $N\cdot\cdot\cdot N$ 2.819(2) Å, $H\cdot\cdot\cdot N$ 1.940 Å, $N^+\cdot-H\cdot\cdot\cdot N$ 177.5°; $N3-H2N\cdot\cdot\cdot O1$: $N\cdot\cdot\cdot O$ 2.830(2) Å, $H\cdot\cdot\cdot O$ 1.954 Å, $N-H\cdot\cdot\cdot O$ 173.5°]. The C3-N2-N1 angle of the triazine ring in the crystal structure of 5 is 123.4° which correlates to the previously reported values for protonated lamotrigine\textsuperscript{63} and the expected
trend for protonated aminopyridines, i.e. higher angles than those of a neutral aminopyridine.\textsuperscript{63, 64} The tetramer is formed from two adjacent supramolecular heterosynthton dimers, shown in Figure 3.9., that are further connected by primary amine-carbonyl interactions \([\text{N3-H3N} \cdots \text{O1}: \text{N} \cdots \text{O} 2.818(2) \text{ Å}, \text{H} \cdots \text{O} 2.054 \text{ Å}, \text{N-H} \cdots \text{O} 144.7^\circ] \). Each tetramer is hydrogen bonded to four additional tetramers \textit{via} either sulfonyl-amine or sulfonyl-chlorine interactions \([\text{N5-H4N} \cdots \text{O2}: \text{N} \cdots \text{O} 2.889(2) \text{ Å}, \text{H} \cdots \text{O} 2.194 \text{ Å}, \text{N-H} \cdots \text{O} 135.5^\circ; \text{Cl1} \cdots \text{O3} 3.068(3) \text{ Å}] \). A view of the overall crystal packing can be seen in Figure 3.10.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure39.png}
\caption{Tetrameric motif present in 5}
\end{figure}
Figure 3.10. Crystal packing of 5

6 (lamotrigine adipate salt) crystallizes in space group of $P_{2_1}/c$ with two lamotrigine cations and one adipate anion in the asymmetric unit (Figure 3.11.). The molecular packing of 6 is based upon 2-point supramolecular heterosynthons between the aminopyridinium and carboxylate moieties, involving an N-H···O hydrogen bond [N3-H3N···O1: N···O 2.942(2) Å, H···O 2.110 Å, N-H···O 157.5 °] and a N$^+$-H···O$^-$ charge-assisted hydrogen bond [N2$^+$-H1N···O2$: N···O 2.627(2) Å, H···O 1.790 Å, N-H···O 158.1 °]. Proton transfer is evidenced by the C-O bond distances of the carboxylate group (1.248(2) Å and 1.272(2) Å) and the geometry of the lamotrigine triazine ring. The C3-N2-N1 angle of the triazine ring in the crystal structure of 6 is 122.4(2) °. Each discrete unit, comprised of two lamotrigine cations and one adipate anion, is hydrogen bonded to
eight nearby lamotrigine-adipate units through the lamotrigine NH$_2$ moieties and neighboring carboxylate [N3-H2N···O1: N···O 2.861(2) Å, H···O 2.057 Å, N-H···O 151.5 °; N5-H4N···O2: N···O 2.760(2) Å, H···O 1.931 Å, N-H···O 156.5 °]. Each adipate anion is hydrogen bonded to four additional discrete units via C-O···H-N interactions. The overall packing can be viewed in Figure 3.12. as staggered supramolecular units of lamotrigine-adipate running parallel to either (010) or (001) with Cl···π interactions.

Figure 3.11. Supramolecular synthons of 6 do not form motif 1
The lamotrigine and L-malic acid salt (7) crystallizes in $P2_1/c$. The asymmetric unit is comprised of two lamotrigine cations and one L-malate anion (Figure 3.13.). Lamotrigine dimers are formed via a noncentrosymmetric dimer sustained by N-H···N hydrogen bonds [$N5\cdot\cdot\cdotH5\cdot\cdot\cdotN14$: N···N 2.956(6) Å, H···N 2.078 Å, N-H···N 174.6 °; $N15\cdot\cdot\cdotH15\cdot\cdot\cdotN4$: N···N 3.082(6) Å, H···N 2.215 Å, N-H···N 168.6 °]. The L-malate anion hydrogen bonds to the lamotrigine dimer such that a supramolecular chain is formed. Proton transfer occurs between both carboxylate groups (C20-O1: 1.275(5); C20-O2: 1.235(6); C23-O4: 1.257(6); C23-O5: 1.275(6)) of L-malate and aromatic nitrogen atoms of lamotrigine [$N12\cdot\cdot\cdotH12\cdot\cdot\cdotO1$: N···O 2.632(5) Å, H···O 1.766 Å, N-H···O 167.8 °; C19-N12-N11 angle 123.16 °]. The lengths of the C-O bonds are typical of a carboxylate moiety and the C19-N12-N11 angle of 123.2 ° is consistent with that of a protonated
aromatic nitrogen. The supramolecular chains, generated from two lamotrigine cations alternating with one l-malate anion, hydrogen bond to an additional l-malate anion forming a sheet perpendicular to the $bc$-plane. The sheets interact via NH⋯O hydrogen bonds [N3-H3NA⋯O1: N⋯O 2.790(5) Å, H⋯O 2.086 Å, N-H⋯O 136.3 °; N13-H13A⋯O5: N⋯O 2.928(5) Å, H⋯O 2.135 Å, N-H⋯O 149.6 °] to chains that run through the $ac$-plane, thereby generating a 3D structure. Figure 3.14. highlights the supramolecular sheet with only one row of perpendicular chains present for clarity.

**Figure 3.13.** Supramolecular synthons of 7 generating motif 1, breaking motif 2
The dimethanol solvate of the salt formed by lamotrigine and nicotinic acid (8) crystallizes in space group $P2_1/c$ with proton transfer observed from the carboxylic acid group to N2 on the triazine ring [N2$^+$-H1N···O2$: N···O 2.729(3) Å, H···O 1.880 Å, N-H···O 161.7 °; C3-N2-N1 angle 122.8 °]. The basic supramolecular unit is comprised of one lamotrigine cation, one nicotinate anion, and two methanol molecules. The structure of 8 reveals that the nicotinate anion breaks the lamotrigine dimer. Similarly to 5, two pairs of lamotrigine nicotinate adducts interact to form tetrameric motifs sustained by charge assisted N$^+$-H···O$^{-}$ and N-H···O hydrogen bonds (Figure 3.15.) [N3-H2N···O3: N···O 2.764(3) Å, H···O 1.9223 Å, N-H···O 159.4 °, N3-H3N···O3: N···O 2.872(3) Å H···O 2.061 Å N-H···O 152.8 °]. In addition, four methanol molecules attach to the exterior of each tetramer by hydrogen bonding to lamotrigine cations and nicotinate.
anions. Two methanol molecules interact with carboxylate groups via O-H\cdots O hydrogen bonds [O1S-H6S\cdots O2: O\cdots O 2.777(2) Å, H\cdots O 1.974 Å, O-H\cdots O 159.7 °], while the other two methanol molecules are inserted between N5 and the aromatic nitrogen of the nicotinate [N5-H4N\cdots O4S: N\cdots O 2.755(3) Å, H\cdots O 1.881 Å, N-H\cdots O 171.8 °, O4S-H7S\cdots N6: O\cdots N 2.699(3) Å, H\cdots N 1.863 Å, O\cdots N 172.7 °]. The methanol molecules that interact with the carboxylate moiety act as hydrogen bond donors to the carboxylate while also accepting a hydrogen bond from a lamotrigine of an adjacent tetramer disposed perpendicularly [N5-H5N\cdots O1S: N\cdots O 2.816(3) Å, H\cdots O 2.012 Å, N-H\cdots O 151.3 °]. The crystal packing of the tetrameric units is shown in Figure 3.16.

Figure 3.15. Breaking motif 1 shown in the hydrogen bonded assembly of 8
A small set of lamotrigine solvates, including a monomethanol solvate, have previously been reported in the literature. Details of the monomethanol solvate crystal packing that supports the overall structure were also provided. Herein the crystal structures of the monomethanol solvate and a novel dimethanol solvate are explored. The lamotrigine dimethanol solvate (9) was obtained from an attempted cocrystallization of lamotrigine and butylated hydroxyanisole from methanol. 9 crystallizes in $C2/c$ with the asymmetric unit comprised of one lamotrigine and two methanol molecules. 9 retains the lamotrigine dimer motif and the supramolecular unit consists of one lamotrigine dimer and two separately hydrogen bonded methanol molecules. The lamotrigine supramolecular homosynthethon dimer in 9 is centrosymmetric $[\text{N3-H1N} \cdots \text{N4: N} \cdots \text{N}$ $3.084(3) \text{ Å, H} \cdots \text{N 2.213 Å, N-H} \cdots \text{N 170.6 °}].$ In addition, N3 and N5 amines form
hydrogen bonds with methanol molecules (Figure 3.17.) \[N3-H2N\cdots O2: N\cdots O 2.824(2) \ Å, H\cdots O 2.210 \ Å, N-H\cdots O 126.6 ^\circ; N5-H3N\cdots O2: N\cdots O 2.862(2) \ Å, H\cdots O 2.109 \ Å, N-H\cdots O 143.1 ^\circ]\). Hydrogen bonds are also observed between methanol molecules and aromatic nitrogen atoms N1 and N2 \[O1-H6O\cdots N1: N\cdots O 2.987(2) \ Å, H\cdots N 2.159 \ Å, N-H\cdots O 168.6 ^\circ; O2-H5O\cdots N2: N\cdots O 2.654(2) \ Å, H\cdots N 1.824 \ Å, N-H\cdots O 169.9 ^\circ]\].

The lamotrigine dimers and methanol molecules hydrogen bond to form a ribbon that extends along the c-axis. A ribbon is highlighted in yellow in Figure 3.18. Two inversion center related ribbons interact via CH-N and Cl-\pi interactions thus forming a ribbon bilayer. The bilayers stack along the b-axis in an abab motif, as shown in Figure 3.18.

**Figure 3.17.** Crystal form 9 breaking motif 2
Figure 3.18. Bilayers formed in crystal packing of 9

Comparison of literature monomethanol solvate (Refcode KADPAG)

The methanol solvate preexisting in the literature from 1989\textsuperscript{35} contains one lamotrigine and one methanol molecule in the basic supramolecular unit and crystallizes in the $P2_1/n$ space group. The lamotrigine dimethanolate presented herein (Figure 3.17 and 3.18) sustains a 1:2 ratio (lamotrigine:methanol) and crystallizes in the $C2/c$ space group. Interestingly, the monomethanol and dimethanol solvate both crystallize by breaking motif 2. The centrosymmetric lamotrigine aminopyridine dimer is exhibited by both solvates; the distinction can clearly be seen when looking at the ribbons of lamotrigine aminopyridine dimers. In the dimethanol solvate, the ribbon is flat extending along the $b$-axis (Figure 3.18., yellow ribbon), however, in the monomethanol solvate the ribbon is corrugated with a dihedral angle of 65.14° (Figure 3.19., yellow ribbon).
Variations can also be found in the hydrogen bonding scheme of the amine moieties in the 3 and 5-positions. Notably the amine in the 3-position is hydrogen bonded to a methanol in the dimethanol solvate, whereas in the monomethanol solvate the methanol exhibits a short contact to a neighboring chlorine atom.

![Figure 3.19. Crystal packing of KADPAG in CSD highlighting a corrugated chain of lamotrigine methanol units](image)

Crystals of 10 (lamotrigine ethanolate monohydrate) form in space group $P2_1/c$ with an asymmetric unit that is comprised of one lamotrigine, one ethanol and one water molecule. 10 exhibits the lamotrigine dimer as shown in Figure 3.20. In the crystal structure of 10, the basic supramolecular unit is the lamotrigine aminopyridine dimer sustained by two symmetrically related hydrogen bonds [N3-H2N···N4: N···N 3.006(2) Å, H···N 2.191 Å, N-H···N 153.7 º]. The lamotrigine dimers are further hydrogen bonded via water molecules [N3-H1N···O1: N···O 2.928(2) Å, H···O 2.295 Å, N-H···O
128.8 ° ; N5-H3N···O1: N···O 2.848(2) Å, H···O 1.973 Å, N-H···O 173.2 °] and ethanol molecules [N5-H4N···O2: N···O 3.042(2) Å, H···O 2.346 Å, N-H···O 136.2 °] to form a supramolecular ribbon that translates along the 2-fold axis. The ribbons, shown in Figure 3.21., illustrate the water hydrogen bonding in the central region of the ribbon while the ethanol molecules hydrogen bond to the exterior. Individual supramolecular ribbons interact via Cl-π interactions to form a corrugated layer. The layers are connected through hydrogen bonds that occur between water and ethanol molecules [O1-H9O···O2: O···O 2.829(2) Å, H···O 1.942 Å, O-H···O 178.8 °], thereby generating a brickwall motif. The supramolecular synthons involved in the structure of 10 are reminiscent of pure lamotrigine; however, the insertion of the water and ethanol molecules force neighboring lamotrigine dimers further apart than in the pure crystalline material.

**Figure 3.20.** Crystal form 10 interrupting motif 2
Figure 3.21. Ethanol water lamotrigine ribbons
Table 3.3 Crystallographic data and structure refinement parameters for compounds 1-2, 4-10

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3.3. Solubility and Dissolution Study

As shown in Figures 3.22 and 3.23, solubility and dissolution studies were conducted for 2, 3, 4, 5 and pure lamotrigine. The solubility of 5 has been reported...
elsewhere\textsuperscript{32} and is re-examined in this study. The maximum concentration of pure lamotrigine in water and pH 1 HCl solution differ by approximately 10% with the higher solubility of lamotrigine exhibited under more acidic conditions. The dissolution study in water revealed that 5 reached a maximum concentration of ca. 0.45 mg/ml. This observation is in agreement with the reported literature aqueous solubility.\textsuperscript{65} However, given that the solubility of lamotrigine increases under more acidic conditions, the improved solubility of 5 in water might be rationalized by the inadvertent decrease in pH due to the dissolution of saccharin. The maximum concentrations of the other crystal forms in water were ca. 0.21 mg/ml, 0.30 mg/ml, 0.23 mg/ml, and 0.28 mg/ml for 2, 3, 4, and pure lamotrigine, respectively. It was also found that 4 exhibited the lowest concentration in water after 4 hours, which is not surprising as hydrates are typically considered to be less soluble than the corresponding anhydride.\textsuperscript{4, 66}

An examination of the dissolution profiles generated at pH 1 indicates that 2 sustains the highest concentration throughout the four-hour study achieving a maximum concentration of ca. 3.8 mg/ml. 4, however, also reaches a maximum concentration of ca. 3.8 mg/ml after only 5 minutes, but it then proceeds to decline over the remainder of the study. This particular type of profile is a product of the “spring and parachute effect” and has been exhibited by a number of pharmaceutical cocrystals reported recently.\textsuperscript{13, 67, 68} This profile is significant because it shows that a greater concentration of API can be achieved at a much faster rate depending upon the crystal form. A similar trend is also exhibited by 4 under aqueous conditions; however, the maximum concentration of 4 was less than that of pure lamotrigine. A slurry of 3, stirred for 5 minutes in acidic media, achieved a concentration ca. 36% greater than pure lamotrigine. Interestingly, 5 which
exhibits the highest concentration in aqueous solution, achieves the lowest concentration in acidic media (1.3 mg/ml). Overall, the dissolution profiles revealed that, in pure water, 5 is the most soluble crystal form but under acidic conditions (pH = 1), 2 is the more soluble crystal form.

A recently published article suggests that the solubility of the cocrystal is directly proportional to the solubility of its components, more specifically, the solubility ratio plotted against the solubility of the cocrystal former divided by the solubility of the API should result in a linear relationship. A similar analysis of crystal forms 2-5 reported herein, however, does not generate a linear plot. In fact, within this set of case studies, no clear correlation exists with respect to the solubility of the salt/cocrystal former and the solubility of the resulting crystal form. The aqueous solubility of nicotinamide is ca. 1 g/ml, the highest of all cocrystal formers studied (methylparaben = 1 g/400ml and saccharin = 1 g/290ml), and it is also a hydrotrope that is frequently used for solubility improvement, however, the crystal forms containing nicotinamide (3 and 4) are not the most soluble in aqueous solutions. Instead 5 is the most soluble crystal form most likely due to the acidic saccharin molecule altering the pH of the solution to favor the dissolution of lamotrigine. The low correlations may be due to the small dataset or the inclusion of both protonated and unprotonated species in the dataset.

Correlations between solubility and crystal packing were also investigated. 5, which breaks motif 1, achieved a greater concentration in water than under acidic conditions (pH = 1). 2 and 4 which break motif 2, show markedly improved concentrations in the acidic solution (pH = 1) but exhibited much lower concentrations in water. Based on this dataset it can be concluded that, for this particular case study,
lamotrigine cocrystals that break motif 2 are more soluble than pure lamotrigine under acidic conditions (pH = 1) while lamotrigine salts that break motif 1 are more soluble than pure lamotrigine in aqueous solutions. However, the enhanced aqueous solubility of 5 may be attributed to the inherent acidity of saccharin.

3.4. Animal Pharmacokinetic (PK) Study

A single dose rat pharmacokinetic study was conducted by Vasyl Sava and Shijie Song at the James A. Haley VA hospital in Tampa. The serum concentration of lamotrigine that resulted from single-dose oral gavage of 3, 4, 5, and pure lamotrigine was measured in Sprague-Dawley rats over a 24-hour time period (Figure 3.24). 2 was not studied due to its instability after three months of aging at 40 °C in variable humidity. An examination of the serum concentrations after dosing with 3, 4, and 5 shows that the PK profile can be substantially altered via cocrystal or salt formation. Two hours after dosing the average serum concentration of 5 was 3.5 μg/ml which is ca. 1.5 times the level shown for pure lamotrigine (2.3 μg/ml). 3 and 4 showed a decrease in the serum concentration by ca. 40% and 68%, respectively, compared to the pure lamotrigine. The area under the curve (AUC<sub>0-24hr</sub>) for 3, 4, 5 and pure lamotrigine was calculated to be 37, 26, 66, and 60 μg/ml, respectively. A comparison of the average serum concentrations reveals that 5 is clearly the desired crystal form for further pharmaceutical development as 5 exhibits the highest initial serum concentration and achieves the greatest AUC<sub>0-24hr</sub>.
An analysis of the serum concentrations for 3, 4, and 5 in the rat in terms of crystal packing concluded that 5, which broke motif 1, experienced an initial boost in serum concentration of lamotrigine. Meanwhile, serum levels for cocrystals 3 and 4, which retained the aminopyridine dimer and broke motif 2, were an average of ca. 54% less than that of pure lamotrigine, thus suggesting that crystal forms that break motif 1 could exhibit higher serum concentrations than forms that break motif 2. Interestingly, the greatest improvements in the PK study and the dissolution study occur when the aminopyridine dimer is broken. This case study also illustrates that pharmaceutical cocrystals and salts can have a significant impact upon drug development as they can greatly alter the PK profile of the parent drugs.
3.5 Conclusions

In summary, the work presented herein exemplifies how salt or cocrystal formers can generate novel crystalline forms of preexisting APIs with different physicochemical properties. Lamotrigine was targeted for crystal form development with the goal of improving its solubility and clinical performance. Ten crystal forms of lamotrigine were developed via the supramolecular synthon approach. The new crystal forms differed from pure lamotrigine in that either supramolecular synthon motif 1 (the aminopyridine dimer) or motif 2 (the amine-aromatic nitrogen hydrogen bond) were broken. Motif 2 was broken in 5 out of 10 structures (50%) while only 4 out of 10 structures (40%) broke motif 1. Interestingly, the majority of the crystal forms that did not contain motif 1, with the exception of 1, were all lamotrigine salts.

Several crystal forms were tested to determine solubility, dissolution rate and rat PK profiles. Out of ten crystal forms, four (2, 3, 4 and 5) were selected for dissolution studies and three (3, 4 and 5) were selected for PK studies. The solubility/dissolution study was conducted under aqueous conditions and under acidified (pH = 1) aqueous conditions. The dissolution profiles for 2 and 4 achieved concentration levels similar to lamotrigine in aqueous media while 3 maintained a concentration equivalent to the maximum solubility of lamotrigine. The average concentrations achieved from 2, 3, 4 and 5 during dissolution measurements from the acidic media surpassed the levels of pure lamotrigine by ca. 48%, 19%, 18%, and 58% respectively. In the rat PK study, the serum concentrations for 3 and 4 were less than pure lamotrigine by 37% and 26%, respectively. 5, however, exhibited an initial increase in the serum concentration of ca. 66%. After
approximately 3 hours the serum concentration of 5 reduced to a level similar to that of pure lamotrigine.

The influence of a particular cocrystal former upon solubility and rat PK was examined. The analysis compared the solubility of the cocrystal former and the solubility and serum concentration of the subsequent crystal form. For this dataset, the most soluble cocrystal former did not lead to the most soluble crystal form. In addition, a comparison of the rat PK data to the solubility of the crystal form revealed that the crystal forms that achieved the greatest aqueous solubility also reached the highest concentrations in the rat PK data. The solubility of the crystal form in the acidic solution did not correspond to the PK data.

The influence of supramolecular synthon motif upon solubility and PK was also examined. Of the crystal forms where the solubility and rat PK was measured (3, 4, 5) the only crystal form that broke the aminopyridine dimer (5) also achieved the highest concentration in aqueous solution and rat serum, suggesting that breaking the lamotrigine aminopyridine dimer can lead to crystal forms with desirable physicochemical properties. Therefore when considering both aqueous dissolution and animal PK data of the crystal forms presented herein collectively, 5 exhibited the targeted physicochemical properties with substantial improvements, and would be an appropriate candidate for further development.
3.6 Materials and Methods

3.6.1 Materials

Lamotrigine was supplied by Jai Radhe Sales, India with a purity of 99.79% and was used without further purification. All other chemicals were supplied by Sigma-Aldrich and used without further purification.

3.6.2 Synthesis of Compounds 1-10

Lamotrigine was reacted with six compounds shown in Figure 3.1, namely methylparaben, nicotinamide, saccharin, adipic acid, L-malic acid, and nicotinic acid, resulting in the formation of ten crystalline cocrystals, salts, or solvates of lamotrigine.

**Synthesis of lamotrigine methylparaben cocrystal form I (1:1), 1.** 0.0117 g (0.046 mmol) lamotrigine and 0.0750 g (0.490 mmol) methylparaben were dissolved in ca. 2 ml tetrahydrofuran (THF) and left to evaporate at room temperature. Colorless crystals were afforded within seven days. 1 crystallized concomitantly with methylparaben and lamotrigine THF solvate. Single crystals of 1 were isolated from this mixture.

**Synthesis of lamotrigine methylparaben cocrystal form II (1:1), 2.** This cocrystal was made via multiple methods: (i) solvent-drop grinding – 0.0722 g (0.282 mmol) lamotrigine was ground with 0.0458 g (0.301 mmol) methylparaben with 40 μl of THF for 30 minutes in a mechanical ball-mill with ca. 100% conversion; (ii) slurry – 0.0486 g (0.190 mmol) lamotrigine and 0.0294 g (0.193 mmol) methylparaben were slurried with ca. 3 ml water at room temperature for 24 hours. 2 was isolated via filtration in 70% yield; (iii) melt – 0.0751 g (0.293 mmol) lamotrigine and 0.0485 g 160
(0.319 mmol) methylparaben were placed in an oven at 115 ºC for 2 hours. 2 was obtained via slow cooling to room temperature in 97% yield. Single crystals of X-ray diffraction quality were obtained from slow cooling of the melt.

**Synthesis of lamotrigine nicotinamide cocrystal (1:1), 3.** This cocrystal was prepared via multiple methods: (i) solvent-drop grinding – 0.2081 g (0.813 mmol) lamotrigine and 0.2056 g (1.68 mmol) nicotinamide were ground with 40 µl of methanol for 30 minutes in a mechanical ball-mill with ca. 100% conversion; (ii) melt – 0.7105 g (2.77 mmol) lamotrigine and 0.3496 g (2.86 mmol) nicotinamide were heated at 125 ºC for 2.5 hours resulting in 98% yield; (iii) lamotrigine nicotinamide cocrystal hydrate, 4 can be dehydrated to isolate 3 after heating at 160 ºC for 6 hours.

**Synthesis of lamotrigine nicotinamide cocrystal monohydrate (1:1:1), 4.** This cocrystal was made from two methods: (i) slurry – 0.0641 g (0.250 mmol) lamotrigine and 0.0614 g (0.503 mmol) nicotinamide (1:2 molar ratio) were slurried with ca. 1 ml ethyl acetate for 24 hours. The resulting solid was isolated and filtered for further use with 92% yield; (ii) solution – 0.1021 g (0.399 mmol) lamotrigine and 0.0515 g (0.422 mmol) nicotinamide dissolved in 600 µl of n-butanol and left to slowly evaporate at room temperature. Colorless crystals of 4 were formed within two weeks in 95% yield. The crystals were dehydrated in an oven at 160 ºC for 6 hours to form anhydrous cocrystal 3.

**Synthesis of lamotrigine saccharinate salt (1:1), 5.** This salt was made via multiple methods: (i) slurry – 50.20 g (196 mmol) lamotrigine and 35.50 g (194 mmol) saccharin were slurried in 500 mL water overnight under ambient conditions. The solid was isolated via filtration in 83% yield. (ii) solution – 0.0102 g (0.040 mmol) lamotrigine and 0.0103 g (0.056 mmol) saccharin were dissolved in ca. 2 ml methanol
and slowly evaporated at room temperature. Colorless crystals of 5 were afforded within seven days in 94% yield.

**Synthesis of lamotrigine adipate salt (2:1), 6.** 0.0158 g (0.062 mmol) lamotrigine and 0.0108 g (0.074 mmol) of adipic acid were dissolved in ca. 2 ml methanol and left to slowly evaporate at room temperature. Colorless crystals of 6 appeared within seven days in 91% yield.

**Synthesis of lamotrigine malate salt (1:1), 7.** 0.0199 g (0.078 mmol) lamotrigine and 0.0120 g (0.089 mmol) L-malic acid were dissolved in ca. 2 ml methanol and left to slowly evaporate at room temperature. Colorless crystals of 7 appeared within seven days in 92% yield.

**Synthesis of lamotrigine nicotinate dimethanol solvate (1:1:2), 8.** A solution of ca. 2 ml methanol, 0.0148 g (0.058 mmol) lamotrigine and 0.0075 g (0.061 mmol) nicotinic acid was left at room temperature to slowly evaporate. Colorless crystals of 8 formed after two days in 78% yield.

**Synthesis of lamotrigine dimethanol solvate (1:2), 9.** 0.0213 g (0.083 mmol) lamotrigine and 0.0148 g (0.082 mmol) butylated hydroxyanisole were dissolved in ca. 2 ml methanol and left to slowly evaporate at room temperature. Colorless crystals of 9 were afforded within five days in 93% yield.

**Synthesis of lamotrigine ethanol monohydrate (1:1:1), 10.** 0.0819 g (0.320 mmol) lamotrigine and 0.0415 g (0.340 mmol) nicotinamide were dissolved in ca. 3 ml of a 1:1 ethanol:water solution mixture while heating followed by rapid cooling. The sample was left at room temperature and allowed to slowly evaporate. Colorless crystals of 10 were afforded within two weeks in 74% yield.
3.6.3 Crystal Form Characterization

Single-Crystal X-ray Diffraction: Single crystals were obtained for nine compounds. Attempts to crystallize 3 did not afford crystals suitable for single crystal X-ray crystallographic analysis. Single crystal analysis for 1, 2, and 5-10 was performed on a Bruker-AXS SMART APEX CCD diffractometer with monochromatized Mo Kα radiation (λ = 0.71073 Å) connected to a KRYO-FLEX low-temperature device while 4 was collected using Cu Kα radiation (λ = 1.54178 Å). Data for 1, 2, and 5-10 were collected at 100 K. Data for 4 was collected at 296 K. Lattice parameters were determined from least-squares analysis, and reflection data were integrated using SAINT. Structures were solved by direct methods and refined by full matrix least squares based on F² using the SHELXTL package. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms bonded to carbon, nitrogen, and oxygen atoms were placed geometrically and refined with an isotropic displacement parameter fixed at 1.2 times Uq of the atoms to which they were attached. Hydrogen atoms bonded to methyl groups were placed geometrically and refined with an isotropic displacement parameter fixed at 1.5 times Uq of the carbon atoms.

Powder X-Ray Diffraction (PXRD): 2-8 were characterized by a D-8 Bruker X-ray Powder Diffractometer using a Cu Kα radiation (λ = 1.54178 Å), 40kV, 40mA. Data was collected over an angular range of 3° to 40° 2θ value in continuous scan mode using a step size of 0.05° 2θ value and a scan speed of 1.0 °/min. Crystal form 1 could not be made in sufficient quantities to collect an experimental PXRD.
**Calculated PXRD:** Calculated PXRD diffractograms were generated from the single crystal structures using Mercury 1.5 (Cambridge Crystallographic Data Centre, UK) for the following complexes: 1-2, 4-10.

**Differential Scanning Calorimetry (DSC):** Differential Scanning Calorimetry was performed on a Perkin Elmer Diamond DSC with a typical scan range of 25 °C – 280 °C, scan rate of 10 °C/min, and nitrogen purge of ca. 30 psi.

**Fourier Transform Infrared Spectroscopy (FT-IR):** FT-IR analysis was performed on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a solid-state ATR accessory.

**Ultraviolet-Visible Spectroscopy (UV/Vis):** UV/Vis analysis was performed on a Perkin Elmer Lambda 25 UV/Vis spectrophotometer.

**High Performance Liquid Chromatography (HPLC):** Analysis was performed on an HPLC system (Perkin Elmer Instruments LLC) comprising the following units: a series 200 Gradient Pump; a 785A UV/VIS Detector; a series 200 Autosampler; an NCI 900 Network Chromatography Interface and a 600 Series Link. The system was operated by a Total Chrome Workstation. The sample holder temperature was kept at 4 °C with a flow rate of 1 mL/min. The column was a Microsorb-MV 300-5 C-18 (250 x 4.6 mm x 1/4’’). The mobile phase consisted of a mixture of phosphate buffer (pH 3.0) with methanol (1/1, v/v). The phosphate buffer was prepared from 50 mmol/L Na₂HPO₃ water solution with pH-controlled HCl titration.

**Thermal Gravimetric Analysis (TGA):** TGA analysis was performed on a Perkin Elmer STA 6000 with a typical scan range of 30 °C – 300 °C, scan rate of 10
165 °C/min, and nitrogen purge of ca. 20 psi. The resulting thermograms were processed using Pyris version 9.

3.6.4 Solubility and Dissolution Study

Dissolution studies were performed on 2, 3, 4, and 5 allowing for representative crystal forms from different crystal form categories (i.e. salt, cocrystal and solvate) to be compared against the original API. Both deionized water (25 °C) and pH 1 aqueous solution (0.1 M HCl, 37 °C) were used. The crystal forms were sieved to achieve a particle size between 53 and 75 μm. The dissolution study was conducted using an excess of free flowing solid in ca. 100 ml solvent that was stirred with a magnetic stir bar at a rate of ca. 200-300 rpm. Aliquots were filtered with 0.45 μm filters after 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, and 240 minutes. The resulting solution was processed and the concentration of lamotrigine was measured using a UV-Vis spectrophotometer. The experiment was repeated twice to allow for statistical analysis.

3.6.5 Animal Pharmacokinetic (PK) Study

Twenty-four hour animal PK studies were conducted using a single-dose oral administration of lamotrigine as well as 3, 4, and 5. 5 male Sprague-Dawley rats (225-250 g) with pre-implanted indwelling jugular vein catheters were used for each crystal form. The animals were allowed water ad libitum and fasted overnight before drug administration. The crystal forms were administered via oral gavage with a dosage of 10 mg/kg lamotrigine or its equivalent, in the suspension vehicle of a 5% PEG and 95% methyl cellulose aqueous solution. After dosing, 0.2 ml of blood was withdrawn at 0, 30, 165
The blood samples were processed and analyzed by HPLC according to the literature.

Table 3.4. Hydrogen bond distances and parameters

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Chapter 4 - Meloxicam crystal forms: Synthesis, Characterization, and Evaluation

4.1. Preamble

The ability to alter the physicochemical properties of an active pharmaceutical ingredient (API) by changing the crystal form has had a major impact upon the pharmaceutical industry and has lead to the development of a crystal form screening process that is now a routine technology implemented to discover crystal forms including, but not limited to, salts, hydrates, solvates, and cocrystals with desired properties. In this chapter a crystal engineering based crystal form screening process will be exploited to generate novel crystal forms of meloxicam with a particular focus upon generating pharmaceutical cocrystals with desired physicochemical properties.

Meloxicam or (4-hydroxy-2-methyl-N(5-methyl-1,3-thiazol-2-yl)-2H-1,2-benzothiazin-3-carboxamide,1,1-dioxide) is a non-steroidal anti-inflammatory (NSAID) and antipyretic drug used for indications of rheumatoid and osteoarthritis, postoperative pain and fever. Originally developed by Boehringer Ingleheim, meloxicam is marketed in Europe under the brand names Melox or Recoxa. Meloxicam is available as a tablet (7.5 or 15 mg dose) and as an oral suspension (7.5mg/5ml dose). The pure active pharmaceutical ingredient (API) is a yellow solid that is practically insoluble in water, but a greater solubility can be achieved under more basic conditions. Meloxicam
is also very slightly soluble in various organic solvents. The variability in solubility related to change in pH is due to the different crystal forms of meloxicam. Under acidic conditions meloxicam is present in solution in its cationic form and in basic solutions meloxicam is present in its anionic form. Under more neutral pH conditions meloxicam will either be in its zwitterionic or enolic form, depending on the polarity of the solvent. The different crystal forms are shown in Figure 4.1.

Meloxicam Anion

Meloxicam Cation

Meloxicam Zwitterion

**Figure 4.1** Anionic, Cationic, and Zwitterionic forms of Meloxicam

Meloxicam is effective at relieving various types of pain and patients experience fewer side effects with meloxicam than with other NSAIDS, however, the drug can take more than two hours to reach a therapeutic concentration in humans. This may be caused by the inherently low solubility of meloxicam under acidic conditions such as
inside the stomach. Meloxicam dissolves and is absorbed once in the more basic conditions of the small intestines, achieving a bioavailability of 89% with substantial protein binding. For meloxicam, the poor solubility of the API has been determined to be the rate limiting step in the absorption, distribution, metabolism, and excretion (ADME) process. Enhancement of meloxicam’s low aqueous solubility has been the subject of many publications resulting in various solvates, ethanolamine salts, cyclodextrin inclusion complexes, or metal complexes with potassium and calcium. Other crystal forms include ammonium salts and sulfate salts. Preparation of different polymorphic crystal forms of meloxicam and improvements to the dissolution profile are also discussed in recent patent literature. Due to the low solubility of meloxicam impairing the absorption, the goal is to improve the solubility of meloxicam via pharmaceutical cocrystallization to potentially reduce the time needed for absorption. With a faster absorption rate the patient will reach therapeutic levels in the bloodstream and achieve efficacy in less than two hours.

4.2. Results and Discussion

4.2.1. Reliability of Cocrystal or Salt Formation

A literature search for crystal forms of meloxicam provided numerous examples including pharmaceutical salts such as those generated via complexation with mono-, di-, and triethanolamine. Due to the plethora of preexisting salt forms in the scientific literature that do not show earlier efficacy, the purpose of this study was to generate pharmaceutical cocrystals of meloxicam as studies have shown that they can increase the plasma concentration at early time points. The pKa values for meloxicam are 1.09
The 1.09 is associated with the enolic OH group while the 4.18 is linked to the nitrogen on the sulfathiazole ring. The enolic OH is much less accessible from a crystal engineering perspective as it is involved in intramolecular hydrogen bonding to the neighboring ketone or NH moieties. Therefore a set of molecules containing carboxylic acid moieties were chosen as cocrystal formers for their ability to potentially interact with the sulfathiazole ring.

It is generally accepted as a rule that the difference in the $pK_a$ of the base minus the $pK_a$ of the acid must be less than zero if the desired outcome is a neutral complex (i.e. cocrystal). To generate a salt one would select two molecules with a difference in $pK_a$ of three or more units. For the region in between ($\Delta pK_a$ 0-3) the ability to predetermine whether the resulting complex will be neutral or charged is difficult. Due to the relatively acidic nature of the sulfathiazole moiety, there remains a fairly large library of molecules that possess a carboxylic acid moiety that are also generally regarded as safe (GRAS) that can be employed to form pharmaceutical cocrystals of meloxicam. The carboxylic acids that were chosen for this study include: 1-hydroxy-2-naphthoic acid (HNA), glutaric acid, L-malic acid, aspirin, and salicylic acid. The acids are represented by line drawings in Figure 4.2. The $pK_a$’s of the carboxylic acids that were chosen and the difference in $pK_a$ between meloxicam and the former are shown in Table 4.1. Based upon the rules described above all of the crystal forms reside in the ambiguous region thus a detailed analysis of the resulting crystal form will be required to determine salt or cocrystal formation.
Table 4.1. pKa values and \(\Delta\)pKa values for meloxicam and a set of carboxylic acids

<table>
<thead>
<tr>
<th>Acid</th>
<th>pKa</th>
<th>(\Delta)pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam</td>
<td>4.18</td>
<td>0</td>
</tr>
<tr>
<td>HNA</td>
<td>3.02</td>
<td>1.16</td>
</tr>
<tr>
<td>Glutaric acid</td>
<td>4.13</td>
<td>0.05</td>
</tr>
<tr>
<td>L-Malic acid</td>
<td>3.46</td>
<td>0.72</td>
</tr>
<tr>
<td>Asprin</td>
<td>3.50</td>
<td>0.68</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>2.90</td>
<td>1.28</td>
</tr>
</tbody>
</table>

Figure 4.2. Line drawings of the carboxylic acids used to form pharmaceutical cocrystals with meloxicam
4.2.2. Cambridge Structural Database (CSD) Analysis

A key step in developing pharmaceutical cocrystals is to analyze the target active pharmaceutical ingredient (API) from a crystal engineering\textsuperscript{10} perspective, i.e. to analyze the molecule from a supramolecular synthon approach. This methodology partitions the target molecule into its simplest functionalities and statistically examines the percentage of occurrence of supramolecular homo- and heterosynthons. The targeted supramolecular synthons are typically sustained via hydrogen bonds as they are strong and directional in nature.

The supramolecular synthon approach can be applied for the synthesis of novel pharmaceutical cocrystals of meloxicam. The strategy involves an understanding of the supramolecular chemistry of meloxicam including the feasibility of supramolecular synthon formation therefore requiring an analysis of the supramolecular synthons present in pure meloxicam. Form I of meloxicam, found in the Cambridge Structural Database (CSD)\textsuperscript{51} (Refcode: SEDZ0Q) indicates that meloxicam forms chains that are sustained by sulfonyl-amide dimers and sulfathiazole-alcohol supramolecular synthons, shown in Figure 4.3. The chains are held together by various weak interactions, stacking along the $a$-axis in a slipped fashion.
Thus for cocrystallization, one or all of these supramolecular synthon motifs must be interrupted. A target moiety for meloxicam is the aromatic nitrogen of the sulfathiazole and the NH of the neighboring amide. When in the proper conformation, these moieties have the ability to provide an ideal two-point recognition site for an additional molecule that contains a donor and an adjacent acceptor such as a carboxylic acid or amide moiety.

A CSD analysis was conducted that examined the percentage of supramolecular synthon formation of the amino-azole functionality (5-membered ring containing a nitrogen and primary amine) with carboxylic acid, primary amide, and alcohol moieties. Specifically the analysis examined the likelihood of supramolecular homosynthon versus supramolecular heterosynthon formation. A search of the CSD for entries containing the amino-azole moiety revealed 505 hits. Interestingly 214/505 or 42% exhibited the 2-pt recognition amino-azole supramolecular homosynthon dimer. Examining the CSD for
entries containing both amino-azole and carboxylic acid moieties afforded 7 entries. The amino-azole supramolecular homosynthon was seen in only 1 out of the 7 entries (14%). The carboxylic acid dimer or catemer supramolecular homosynthon was not present in any of the 7 entries. The supramolecular heterosynthon, however, was exhibited in 4/7 or 57% of the time. Thus the amino-azole – carboxylic acid supramolecular heterosynthon is more likely to occur than the supramolecular homosynthon. Due to the potential for meloxicam to generate salts or neutral complexes the potential for the amino-azole to generate a supramolecular heterosynthon with a carboxylate was also examined. A search for crystal structures that contain both moieties resulted in 24 hits. The amino-azole supramolecular homosynthon appeared in only 1 entry (4%) where a carboxylate was also present. The carboxylate – amino-azole 2-pt recognition supramolecular heterosynthon dimer was much more prominent, appearing in 13/24 or 54% of the entries. Thus the supramolecular heterosynthon is more likely to occur than the supramolecular homosynthon for an amino-azole in the presence of a carboxylate. The occurrence of supramolecular homosynthon versus heterosynthon was also questioned in the presence of a primary amide moiety. However, only 1 entry was revealed in the CSD that contained both functionalities and neither supramolecular synthon was present precluding a conclusion of the reliability of supramolecular synthon formation. A search of the CSD for entries containing an amino-azole and alcohol was also conducted. The two moieties were present in 38 entries with the amino-azole supramolecular homosynthon being the dominant interaction. The alcohol supramolecular synthon occurs in 5 out of 38 entries or 13% of the time. The supramolecular heterosynthon occurs in 6/38 entries (16%) while the amino-azole supramolecular homosynthon occurs
in 13/38 entries (43%). Clearly with the supramolecular homosynthon occurrence greater than the supramolecular heterosynthon, the potential for cocrystal formation is low by employing a cocrystal former that contains an alcohol functional group. A summary of the results from the amino-azole moiety supramolecular homosynthon and heterosynthon formation is presented in Table 4.2.

A closer look at the data gathered from the CSD reveals that many of the searches for the amino-azole moiety coupled with an additional functional group consisted of a relatively small number of entries. Furthermore, the conclusions from the data could be considered not statistically significant due to the lack of information. Therefore further CSD analysis was conducted employing a simple azole (5-membered ring containing a nitrogen). The reliability of supramolecular heterosynthon versus homosynthon formation between an azole and a carboxylic acid, primary amide, and alcohol were examined in the CSD. Due to the inability of the azole to form a supramolecular synthon with itself; only the homosynthon formation of the carboxylic acid, primary amide, and alcohol moieties in the presence of an azole was examined. A search of the CSD for entries that contained an azole and a carboxylic acid moiety resulted in 269 hits. A closer look at the 269 entries revealed that the carboxylic acid dimer or catemer occurred in 41 entries, or 15% of the time. However, when the 269 entries were investigated for the presence of the azole-carboxylic acid supramolecular heterosynthon 120 entries were identified, suggesting that the heterosynthon will occur 45% of the time. Thus when an azole and carboxylic acid are present in the same crystal structure the supramolecular heterosynthon is statistically more likely to occur. When complexing a carboxylic acid to a basic moiety were the ΔpKa is large, the acid will protonate the basic moiety, resulting
in a carboxylate. Due to the possibility of protonation with meloxicam, carboxylate-azole interactions were also searched in the CSD. 56 entries contained both moieties. 20 (36%) contained the carboxylate-azole supramolecular heterosynthon in the crystal structure, suggesting that it is a viable target supramolecular heterosynthon. A search of the CSD for the azole and primary amide moiety in the same crystal structure revealed 115 entries. 66 (58%) of those entries were found to contain the amide dimer or catemer while only 37 (32%) were sustained via the amide-azole supramolecular heterosynthon. These statistics elucidate the strength of the amide supramolecular homosynthon in the presence of the azole functional group and further indicate that a cocrystal of meloxicam with a molecule containing a primary amide moiety is unlikely to occur. The complexing of alcohols and azoles was also studied in the CSD. There were 977 entries that contained both moieties. 21% (202) possess the alcohol homosynthon but 40% (386) were sustained by the supramolecular heterosynthon formation. Statistically this suggests that the supramolecular heterosynthon is almost twice as likely to form as the homosynthon. Collectively comparing the occurrence of the supramolecular homosynthon to the heterosynthon, the heterosynthon formation dominates in all cases except when in the presence of a primary amide. Carboxylic acid and alcohol functionalities proved to be quite reliable for generating supramolecular heterosynthons and can be complexed with an azole moiety ca. 40% of the time. The results of these searches are depicted in Table 4.3.
Table 4.2. Percent occurrence for supramolecular homosynthons and heterosynthons with amino-azoles in the presence of carboxylic acids, carboxylates, primary amides, and alcohols

<table>
<thead>
<tr>
<th>Complementary Moiety</th>
<th>No. of entries w/ both groups</th>
<th>% Homosynthon occurrence: amino-azole</th>
<th>% Homosynthon occurrence: Cocrystal former</th>
<th>% Heterosynthon occurrence</th>
<th>Heterosynthon Distance Range (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxylic acid</td>
<td>7</td>
<td>1/7 (14%)</td>
<td>0</td>
<td>4/7 (57%)</td>
<td>2.60-2.80</td>
</tr>
<tr>
<td>Carboxylate</td>
<td>24</td>
<td>1/24 (4%)</td>
<td>N/A</td>
<td>13/24 (54%)</td>
<td>2.60-2.80</td>
</tr>
<tr>
<td>Primary amide</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Alcohol</td>
<td>38</td>
<td>13/38 (43%)</td>
<td>5/38 (13%)</td>
<td>6/38 (16%)</td>
<td>2.60-3.00</td>
</tr>
</tbody>
</table>

Table 4.3. Percent occurrence for supramolecular homosynthons and heterosynthons with azoles in the presence of carboxylic acids, carboxylates, primary amides, and alcohols

<table>
<thead>
<tr>
<th>Complementary Moiety</th>
<th>No. of entries w/ both groups</th>
<th>% Homosynthon occurrence: Cocrystal former</th>
<th>% Heterosynthon occurrence</th>
<th>Heterosynthon Distance Range (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxylic acid</td>
<td>269</td>
<td>41/269 (15%)</td>
<td>120/269 (45%)</td>
<td>2.50-2.90</td>
</tr>
<tr>
<td>Carboxylate</td>
<td>56</td>
<td>N/A</td>
<td>20/56 (36%)</td>
<td>2.60-2.90</td>
</tr>
<tr>
<td>Primary amide</td>
<td>115</td>
<td>66/115 (58%)</td>
<td>37/115 (32%)</td>
<td>2.60-3.30</td>
</tr>
<tr>
<td>Alcohol</td>
<td>977</td>
<td>202/977(21%)</td>
<td>386/977 (40%)</td>
<td>2.60-3.00</td>
</tr>
</tbody>
</table>

Based on the success rate of supramolecular heterosynthon formation with azoles and carboxylic acids, a meloxicam cocrystal screen with cocrystal formers containing carboxylic acid moieties was conducted. Meloxicam was reacted with 1-hydroxy-2-naphthoic acid, glutaric acid, L-malic acid, aspirin, and salicylic acid. The cocrystallization attempts resulted in seven crystal forms, namely meloxicam 1-hydroxy-2-naphthoic acid cocrystal, meloxicam glutaric acid cocrystal, meloxicam L-malic acid cocrystal of a salt, meloxicam aspirin cocrystal, meloxicam salicylic acid cocrystal form
I, II, and III. All crystal forms were analyzed in terms of supramolecular synthons as well as physical and pharmacokinetic properties and are presented herein.

4.2.3. Crystal Structure Descriptions

The meloxicam 1-hydroxy-2-naphthoic acid cocrystal, 1 crystallizes in the space group \( P\bar{1} \). The asymmetric unit contains one meloxicam and one 1-hydroxy-2-naphthoic acid molecule. The basic supramolecular unit is comprised of two meloxicam molecules and two 1-hydroxy-2-naphthoic acid molecules with the inversion center located in the center of the meloxicam dimer (shown in Figure 4.4.). The meloxicam dimer is a common motif found in many meloxicam cocrystals and is sustained by two planar meloxicam molecules interacting via electrostatic interactions between the alcohol, ketone and sulfathiazole moieties. In 1 meloxicam sustains intramolecular alcohol-ketone interactions and binds to the neighboring meloxicam via an S\( \cdot \cdot \cdot \)OH interaction at a distance of 3.148(6) Å to form the meloxicam dimer. The exterior of the meloxicam dimer hydrogen bonds to two 1-hydroxy-2-naphthoic acid molecules via two 2-point recognition carboxylic acid-thiazole/NH interactions \([\text{O2-H2}\cdots\text{N1}: \text{O}\cdots\text{N} 2.596(6) \text{Å}, \text{H}\cdots\text{N} 1.763 \text{Å}, \text{O-H}\cdots\text{N} 170.90^\circ, \text{N2-H2}\cdots\text{O2}: \text{N}\cdots\text{O} 2.935(6) \text{Å}, \text{H}\cdots\text{O} 2.086 \text{Å}, \text{N-H}\cdots\text{O} 161.66^\circ]\). This two point recognition supramolecular synthon motif is quite robust as it is found in all cocrystal forms reported herein. The hydroxyl group of the 1-hydroxy-2-naphthoic acid ortho to the carboxylic acid moiety is involved in intramolecular hydrogen bonding which is expected based upon Etter’s rules.\(^{53}\) The overall packing, illustrated in Figure 4.5 is sustained by supramolecular units of
meloxicam and 1-hydroxy-2-naphthoic acid molecules that stack upon each other along the \( a \)-axis in a slipped fashion with an interplanar spacing of 3.735 Å.

**Figure 4.4.** Supramolecular unit of 1

Crystal form 2 is the **meloxicam glutaric acid cocrystal**. The asymmetric unit of 2 is comprised of one meloxicam and one glutaric acid molecule and crystallizes in the space group \( P\overline{1} \). The meloxicam centrosymmetric dimer is also present in 2 and is sustained by an S\(\cdots\)OH interaction between two planar meloxicam molecules with a
distance of 3.224(2) Å. Meloxicam also participates in OH⋯O (ca. 2.62 Å) intramolecular hydrogen bonding. Interestingly, glutaric acid utilizes one of its carboxylic acid moieties to form a centrosymmetric carboxylic acid dimer [O4-H4⋯O3: O⋯O 2.646(2) Å, H⋯O 1.808 Å, O-H⋯O 175.96°] with a neighboring glutaric acid. The second free carboxylic acid moiety hydrogen bonds to the meloxicam molecule resulting in the unexpected 1:1 stoichiometry. The carboxylic acid-azole supramolecular heterosynthon dimer is sustained by hydrogen bond interactions that afford the common 2-point recognition motif. The OH⋯N and NH⋯O interaction are shown in Figure 4.6. [O2-H2⋯N1: O⋯N 2.675(2) Å, H⋯N 1.837 Å, O-H⋯N 174.24°; N2-H2⋯O1: N⋯O 2.849(2) Å, H⋯O 1.990 Å, 165.07°]. The culmination of supramolecular homosynthon and heterosynthon dimers ultimately results in the formation of a zig-zag chain that cuts through the ac-plane. The chains stack along the a-axis and are separated by a meloxicam plane to plane distance of 3.502 Å. Figure 4.7. highlights the crystal packing of multiple chains with the meloxicam dimers and glutaric acid dimers disposed in a columnar arrangement. The angle sustained between the C1-C2-C3 of the glutaric acid molecule in 2 is atypical. The C1-C2-C3-C4 torsion angle in both polymorphs of pure glutaric acid is ca.170°, however, in 2; the same angle is 52.89°. A search of the CSD for additional glutaric acid cocrystals afforded multiple hits however; examining the glutaric acid molecules for the similar smaller torsion angle resulted in only two hits: caffèine glutaric acid cocrystal (REFCODE: EXUQUJ) and theophylline glutaric acid cocrystal (REFCODE: XEJXIU). The conformations of the glutaric acid molecules present torsion angles of 79.34° and 65.18°, respectively.
Figure 4.6. Meloxicam glutaric acid cocrystal (2) supramolecular synthons highlighting the meloxicam and glutaric acid dimers

Figure 4.7. Crystal packing of multiple chains of 2
The asymmetric unit of the **meloxicam L-malic acid cocrystal of a salt** (3) contains one meloxicam cation, one neutral meloxicam, and one L-malate anion. 3 is therefore considered a cocrystal of a salt and crystallizes in the space group *P*1. Based upon the ΔpKa it was not predicted that the L-malic acid would protonate meloxicam, however, crystal forms do not always follow the ΔpKa general guidelines. In 3 the meloxicam dimer persists but is unique as it is comprised of one cation and one neutral meloxicam and is sustained by two S⋯OH interactions (3.20(2) Å, 3.28(2) Å). Figure 4.8. illustrates the interactions between the anion, cation, and neutral molecule. 3 is primarily sustained by the L-malate anion acting as a bridge to connect the meloxicam dimers ultimately forming a chain. The L-malate bridge protonates the sulfathiazole ring via the O⋯+HN interactions [O1⋯+H1-N1: O⋯+N 2.70(3) Å, H⋯O 1.849 Å, O⋯+H-N 168.90°; O2⋯+H2-N2: O⋯+N 2.89(3) Å, H⋯O 2.045 Å, O⋯+H-N 168.31°] and hydrogen bonds to the sulfathiazole of the neutral meloxicam via OH⋯N and NH⋯O interactions [O4-H4⋯N4: O⋯N 2.73(3) Å, H⋯N 1.919 Å, O-H⋯N 172.42 °; O5⋯H5-N5: O⋯N 2.90(3) Å, H⋯O 2.078 Å, O-H⋯N 160.08 °]. Thus the L-malate and meloxicams generate a 2D structure comprised of chains that stack parallel along the *a*-axis with an interplanar spacing of 3.176 Å, shown in Figure 4.9. The supramolecular chains exhibited by 3 are reminiscent of those seen in 2 which is unsurprising due to the employment of a diacid as a cocrystal former in both cocrystallization experiments. The supramolecular synthon analysis of 3 proves that the sulfathiazole ring and the NH of the amide is an excellent synthon recognition point for both carboxylic acids and carboxylates.
Figure 4.8. Supramolecular synthons in 3 showing a neutral and cationic meloxicam and an anionic L-malate

Figure 4.9. Stacked layers of the meloxicam L-malic acid cocrystal of a salt (3), L-malate anions are shown in green.

The **meloxicam aspirin cocrystal (4)** crystallizes in the space group $P2_1/c$. The asymmetric unit contains one meloxicam molecule and one aspirin molecule, shown in Figure 4.10. The meloxicam dimer is again present in 4; however, the planar meloxicam molecules are held into the dimer conformation at a distance of 3.632(2) Å apart by weak
interactions. This distance is the furthest distance of all the cocrystals in this study that contain the dimer. The primary interactions sustaining the cocrystal are the hydrogen bonds present between the carboxylic acid moiety of the aspirin molecule and the sulfathiazole/NH moiety of the meloxicam. The resulting supramolecular heterosynthon is the 2-point recognition hydrogen bonded dimer which affords the basic meloxicam:aspirin supramolecular unit shown in Figure 4.10. The OH⋯N hydrogen bond distance is 2.665(3) Å [O2-H2⋯N1: O⋯N 2.665(3) Å, H⋯N 1.850 Å, O-H⋯N 173.36°] and the NH⋯O distance is 2.856(3) Å [N2-H2⋯O1: N⋯O 2.856(3) Å, H⋯O 2.015 Å, N-H⋯O 165.60°]. Additional meloxicam:aspirin supramolecular units are generated by translation along the 21 screw axis running parallel to the a-axis (Figure 4.11.). As the meloxicam:aspirin units extend along the a-axis they simulate a corrugated sheet that propagates with a dihedral angle of 73.69°. The corrugated sheets then stack upon each other separated by a distance of ca. 3.87 Å producing a herringbone motif.

Figure 4.10. Meloxicam aspirin cocrystal (4) basic supramolecular unit
Figure 4.11. Units of the meloxicam aspirin cocrystal (4) translating along a $2_1$ screw axis

The supramolecular unit of the meloxicam salicylic acid cocrystal form III (5) is comprised of one molecular meloxicam and one molecular salicylic acid, shown in Figure 4.12. and crystallizes in the space group $P2_1/c$. The cocrystal is primarily sustained by the salicylic acid hydrogen bonding to the meloxicam via the carboxylic acid to sulfathiazole/NH supramolecular heterosynthon. The carboxylic acid-sulfathiazole OH···N hydrogen bond distance is 2.627(5) Å [O2-H2···N1: O···N 2.627(5) Å, H···N 1.836 Å, O-H···N 161.74 °] and the NH-carboxylic acid NH···O distance is 2.975(5) Å [N2-H2···O1: N···O 2.975(5) Å, H···O 2.139 Å, N-H···O 164.02°]. This hydrogen bonding motif generates a discrete unit containing one meloxicam and one salicylic acid molecule. The salicylic acid OH moiety is involved in intramolecular hydrogen bonding with its carboxylic acid. The meloxicam dimer does not exist in 5 as the meloxicam molecules in the neighboring supramolecular units are perpendicular rather than parallel. The supramolecular units in 5 translate along the $2_1$ screw axis at a dihedral angle of 88.80° and are sustained by various weak interactions (Figure 4.13.).
is the only cocrystal reported herein that does not exhibit the meloxicam dimer. The absence of the dimer may contribute to its unique solubility and pharmacokinetic properties. Single crystals of suitable quality for single crystal X-ray diffraction of the meloxicam salicylic acid form I (7) or form II (6) could not be obtained.

**Figure 4.12.** Meloxicam salicylic acid cocrystal form III (5) 2-point recognition supramolecular synthon

**Figure 4.13.** Meloxicam salicylic acid units translating along a $2_1$ screw axis
4.2.4. Melting Point Analysis

It has been shown that the melting point of the cocrystal can typically be found in between the melt of the cocrystal former and the target active pharmaceutical ingredient.\textsuperscript{54, 55} Recent literature has also attempted to predict melting points\textsuperscript{56} and correlate melting points of materials to chemical structure of small simple molecules with some success.\textsuperscript{57} However, predicting melting points of larger molecules such as pharmaceuticals proves to be a nontrivial task.
The melting points of the meloxicam crystal forms 1-7 were measured via differential scanning calorimetry (DSC) and compared to the melting points of both meloxicam and the respective cocrystal former. The melting points of the cocrystal formers were obtained from materials safety datasheets. A summary of the results are presented in Table 4.5. The melting points for all the cocrystals were found to follow the trends found in the literature. The cocrystals melted above the melt of the cocrystal former and below the melting point of meloxicam. The polymorphic salicylic acid cocrystals resulted in similar melting points with little variation between crystal forms. A graphical representation of the data is shown in Figure 4.12, where the melting point of the cocrystal is plotted vs. the melting point of the cocrystal former. The $R^2$ value was calculated to be 0.7335 thus showing an overall good correlation between the melting points of the two materials.

Table 4.5. Melting points for meloxicam, cocrystal formers, and their corresponding cocrystals

<table>
<thead>
<tr>
<th>Crystal form</th>
<th>Melting point of former °C</th>
<th>Melting point of cocrystal °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam</td>
<td>254</td>
<td>254</td>
</tr>
<tr>
<td>1-Hydroxy-2-naphthoic acid</td>
<td>183</td>
<td>225</td>
</tr>
<tr>
<td>Glutaric acid</td>
<td>95</td>
<td>149</td>
</tr>
<tr>
<td>L-Malic acid</td>
<td>101</td>
<td>200</td>
</tr>
<tr>
<td>Aspirin</td>
<td>136</td>
<td>164</td>
</tr>
<tr>
<td>Salicylic acid form III</td>
<td>159</td>
<td>210</td>
</tr>
<tr>
<td>Salicylic acid form I</td>
<td>159</td>
<td>205</td>
</tr>
<tr>
<td>Salicylic acid form II</td>
<td>159</td>
<td>206</td>
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</tbody>
</table>
4.2.5. Solubility and Dissolution Study

Solubility and dissolution measurements of five cocrystal forms (1-5) and pure meloxicam were conducted at 37 °C in pH 8 phosphate buffer. A pH 8 buffer was chosen because it is believed that meloxicam is absorbed in the more basic conditions of the intestine where the most basic regions can reach a pH of 8.26,63 A phosphate buffer was employed so that the pH of the solution could not vary with the addition of acidic cocrystal formers. 6 was not tested because the cocrystal could not be made in gram level quantities. 7 was also not tested because it did not pass 1 month of the accelerated stability test (40 °C, uncontrolled humidity). The dissolution profiles are shown in Figure 4.15.

The maximum solubility achieved for pure meloxicam after four hours was ca. 0.8 mg/mL which is similar to the reported literature solubility of (ca. 1 mg/mL in a pH 8 solution).27 The cocrystal that achieved the highest and lowest solubility after four hours
was 1 and 2, respectively. Since the project goal was to reduce the time it takes for the meloxicam to reach therapeutic levels, the cocrystals that obtained the highest concentrations at the earliest time points were the most desirable. 3 reached a concentration of 1.06 mg/ml at the 5 minute time point, the highest of all the cocrystals tested. 5 was second with a concentration of 0.967 mg/ml after 5 minutes. Cocrystals 1, 2, and 4 obtained similar low concentrations (ca. 0.4 mg/ml) and pure meloxicam reached a 0.100 mg/ml concentration after 5 minutes.

The dissolution profile for 3 was an exemplary “spring and parachute” model that unfortunately experienced a receding concentration that decreased by half after 1 hour. The inflated early concentration was most likely due to the high solubility of the cocrystal former, L-malic acid, which was the most soluble cocrystal former in the pH 8 buffer solution (961 mg/ml).

The spring and parachute type dissolution profile is becoming more of a common occurrence amongst cocrystals. First shown by Childs in the dissolution of fluoxetine HCl succinic acid cocrystal, the spring and parachute model portrays the ability of the cocrystal former to improve the solubility of the API at early time points. This can be advantageous for decreasing the time required for the API to reach maximum concentration. Over time, at a rate that is cocrystal dependant, the cocrystal falls apart and the concentration in solution reduces back down to a level similar to that of the pure API. It has been postulated by Rodríguez-Hornedo that the change in solubility of the API is related to the solubility of the cocrystal former. Specifically, the solubility of the cocrystal former is directly proportional to the solubility of the related cocrystal. Her theory is predicated upon the analysis of a selected set of carbamazepine, theophylline,
and caffeine cocrystals. To determine if her findings were more of a general occurrence or an anomaly, the solubility of the cocrystal formers employed herein were compared to the solubility of the resulting cocrystals.

The solubility of glutaric acid, aspirin, 1-hydroxy-2-naphthoic acid, and salicylic acid were measured at 741, 14, 11, and 10 mg/ml, respectively. Based upon the observations with L-malic acid one would expect that 2 (meloxicam glutaric acid cocrystal) would achieve the second highest initial solubility, but it did not. 5, with a cocrystal former solubility of 10 mg/ml was second, with a dissolution profile that was also a spring and parachute. Therefore the solubility of the cocrystal former did not correlate to the solubility of the cocrystals presented here. These findings are contradictory to recently published results.67

The maximum concentration achieved by 5 was 1.29 mg/ml after 20 minutes of slurring, which was greater than a 3-fold improvement over meloxicam. This improvement in solubility could provide the improved absorption required for patients to reach an earlier efficacy. Interestingly, the dissolution profile for 5 and 4 merge after approximately 1 hour and both cocrystals maintain a similar concentration for the remainder of the study. This may be due to the hydrolysis of aspirin to salicylic acid in aqueous solutions.

The dissolution profile for 1 was unique as the thermodynamic solubility was not obtained after 4 hours of slurring. The maximum concentration measured for 1 in this study was 1.35 mg/ml. 1 was also intriguing because the solid material remaining after the dissolution study was intact cocrystal based on powder X-ray diffraction. The remaining solids post dissolution study for 2-5 and pure meloxicam were found to be
meloxicam form I also based upon powder X-ray diffraction. The stability of 1 in solution is most likely a reflection of its high melting point which is indicative of high lattice energy \(^{68}\) (225 °C, the highest of all reported cocrystals).

![Dissolution Profiles Meloxicam Crystal forms pH 8, 37°C](image)

**Figure 4.15.** Dissolution profiles for meloxicam and five crystal forms in pH 8 buffer, 37 °C

### 4.2.6. Animal Pharmacokinetic (PK) Study

The single dose rat pharmacokinetic study was conducted by Vasyl Sava and Shijie Song at the James A. Haley VA hospital in Tampa. Samples 1-6 and pure meloxicam were tested. The plasma concentrations as a function of time are shown in Figure 4.16. 7 was not studied because the cocrystal lattice collapsed after 1 month of exposure to 40 °C in uncontrolled humidity. The maximum plasma concentration achieved at the end of the 4 hour study was 60.9 μg/ml by form 4. The concentrations for 3 and 6 were similar to the maximum obtained for meloxicam; however, all three crystal forms showed similarly low plasma levels averaging ca. 38 μg/ml. The plasma concentration for 2, however, led to a
very intriguing profile. During the first hour of the study 2 had a profile similar to the meloxicam profile. But, during the last 3 hours the concentration increased at a faster rate than pure meloxicam resulting in a 4 hour plasma concentration that was 15 μg/ml greater than pure meloxicam. An examination of the areas under the curve (AUC) for the cocrystals presented in this study shows that 4 has the highest AUC, followed by 1. The AUC’s for 3 and 6 are similar and greater than pure meloxicam, however, they exhibit the lowest for all cocrystals in this study. 5 exhibits a similar profile to 1, but 5 experiences a much higher plasma concentration after 15 minutes. Since the goal of the study was to generate cocrystals with an earlier onset of efficacy, the desired crystal form must show a plasma concentration at the earliest time point that is equivalent to the maximum obtained by pure meloxicam. This criterion eliminates 1 and 4 even though they show the greatest AUCs because they take over an hour to reach their maximum concentrations. 5 is therefore the cocrystal to take further into additional studies.

Interestingly, 5 obtains the highest plasma concentration after 15 minutes and is also the most soluble cocrystal after a 10 minute slurry in pH 8 solution at 37°C. The solubility of cocrystals 1-4 after 10 minutes and their plasma concentrations after 15 minutes were examined further to determine if a general correlation existed between the solubility and plasma concentration. Figure 4.17. highlights the linear trend (R² = 0.8651) that can be drawn illustrating that the more soluble the cocrystal at 10 minutes the greater the improvement in plasma concentration at early time points. These results show that to quicken the onset of a drug that is well absorbed but has low solubility; a more soluble cocrystal will increase the early plasma concentrations such that the drug could reach therapeutic concentrations at a faster rate.
**Figure 4.16.** Rat plasma concentrations after single dose administration of meloxicam and six cocrystals

**Figure 4.17.** Cocrystal and meloxicam solubility versus rat plasma concentration
4.3. Conclusions

The ability to modify the physical properties of an API but still maintain its therapeutic attributes by altering the crystal form is an important area of research and discovery. In this contribution seven novel crystal forms of meloxicam are presented and analyzed based upon their supramolecular synthons, melting points, solubility, and PK profiles. A prominent aspect of cocrystals 1-4 is the presence of the meloxicam dimer. The meloxicam molecules in 5, however, are juxtaposed such that the dimer cannot form. A salient feature in 1-5 is the 2-point recognition carboxylic acid-azole/NH supramolecular heterosynthon. An analysis of the melting points of 1-7 and the respective cocrystal formers illustrated that the melting points of the cocrystals were typically in between the melting points of meloxicam and the cocrystal former. The highest melting cocrystal, 1, was also the only cocrystal to remain intact throughout the solubility/dissolution study.

The solubility and dissolution profiles for 1-5 showed that after 4 hours 1 was the most soluble and 2 was the least soluble cocrystal. The solubility of the cocrystal was not related to the solubility of the cocrystal former. Due to the purpose of the study, i.e. decrease the time taken for meloxicam to reach therapeutic concentrations, the greater solubility of the cocrystal at the early time points was of greater importance than the solubility at 4 hours thus narrowing the desirable cocrystal list down to 3 and 5. To select one both solubility/dissolution and PK data was considered.

The AUCs from the rat PK data were the lowest for 2, 3, and 6. 1 and 4 showed a plasma concentration that gradually increased over the 4 hour period resulting in therapeutic concentrations after approximately 30 minutes to 1 hour. 5, however, reached
the therapeutic concentration after 15 minutes thus 5 would be the desired crystal form for future product development as it experienced the solubility and pharmacokinetic profile that is most likely to reduce the time needed to obtain the therapeutic concentration and patient efficacy. Unfortunately, there are known complications when aspirin, which hydrolyzes to salicylic acid, is administered concomitantly with meloxicam. The acid causes an increase in the AUC by 10% and the maximum concentration increases by 24%. There is no explanation in the literature for this conundrum but results presented in this study indicate that the effect is most likely due to cocrystal formation.

The cocrystals of meloxicam presented herein provide further evidence that cocrystals can change the physical and pharmacokinetic properties of an API. The greatest improvements in solubility and PK profile were shown with meloxicam salicylic acid form III (5), however, due to the clinical warnings the meloxicam 1-hydroxy-2-naphthoic acid cocrystal (1) would be taken further into clinical trials as the pharmacokinetic profile suggests that 1 will achieve similar efficacy after 30 minutes.

4.4. Materials and Methods

4.4.1. Materials

Meloxicam was purchased from Jai Radhe Sales, India with a purity of 99.64% and was used without further purification. All other chemicals were supplied by Sigma-Aldrich and used without further purification.
4.4.2. Synthesis of Compounds 1-7

Meloxicam was reacted with five cocrystal formers shown in Scheme 4.2. They were 1-hydroxy-2-naphthoic acid, glutaric acid, L-malic acid, aspirin, and salicylic acid. The cocrystallization attempts resulted in seven crystal forms. All of the crystal forms can be made from solvent-drop grinding and slurrying, however, only five crystal forms can be made from solution crystallization.

**Synthesis of meloxicam 1-hydroxy-2-naphthoic acid cocrystal (1)** – (a) solvent-drop grinding – 0.176 g (0.501 mmol) meloxicam was ground together with 0.0957 g (0.508 mmol) of 1-hydroxy-2-naphthoic acid and 40 μl of tetrahydrofuran (THF) for 30 minutes in a ball-mill. 1 was generated in ca. 100% yield. (b) slurry – 0.700 g (1.99 mmol) meloxicam and 0.391 g (2.07 mmol) of 1-hydroxy-2-naphthoic acid were slurried in 3 ml of THF overnight sealed under ambient conditions at ca. 250 rpm. The resulting solid was filtered and washed with THF. 1 was obtained in ca. 90% yield. (c) solution crystallization – 0.0176 g (0.0501 mmol) meloxicam and 0.0095 g (0.505 mmol) of 1-hydroxy-2-naphthoic acid dissolved in 10 ml of ethyl acetate and left to slowly evaporate. 1 was obtained in ca. 93% yield.

**Synthesis of meloxicam glutaric acid cocrystal (2)** – (a) solvent-drop grinding – 0.179 g (0.511 mmol) meloxicam was ballmilled together with 0.0699 g (0.529 mmol) of glutaric acid and 40 μl of chloroform for 30 minutes, producing 2 in ca. 100% yield. (b) slurry – 0.892 g (2.54 mmol) meloxicam and 0.351 g (2.66 mmol) of glutaric acid were slurried in 3 ml of ethyl acetate overnight sealed under ambient conditions at ca. 250 rpm. The resulting solid was filtered and washed with ethyl acetate. 2 was made in ca. 96% yield. (c) solution crystallization – 0.0194 g (0.0552 mmol) meloxicam and 0.159 g (1.20
mmol) of glutaric acid dissolved in 2 ml of ethyl acetate and left to slowly evaporate. 2 was isolated in ca. 89% yield.

**Synthesis of meloxicam L-malic acid cocrystal of a salt (3)** – (a) solvent-drop grinding – 0.176 g (0.501 mmol) meloxicam was ground together with 0.0361 g (0.269 mmol) of L-malic acid and 40 μl of THF for 30 minutes in a mechanical ball-mill. 3 was generated in ca. 100% yield. (b) slurry – 0.897 g (2.55 mmol) meloxicam and 0.182 g (1.36 mmol) of L-malic acid were slurried in 3ml of THF overnight sealed under ambient conditions at ca. 250 rpm. The solid was filtered and washed with THF resulting in ca. 92% yield of 3. (c) solution crystallization – 0.0214 g (0.0609 mmol) meloxicam and 0.0416 g (0.301 mmol) of L-malic acid dissolved in 2 ml of a 1:1 mix of dioxane and ethyl acetate and left to slowly evaporate. The resulting single crystals of 3 were isolated in ca. 82% yield.

**Synthesis of meloxicam aspirin cocrystal (4)** – (a) solvent-drop grinding – 0.182 g (0.517 mmol) meloxicam was ball-milled together with 0.0966 g (0.536 mmol) of aspirin and 40 μl of chloroform for 30 minutes to obtain 4 in ca. 100% yield. (b) slurry – 0.905 g (2.56 mmol) meloxicam and 0.452 g (2.51 mmol) of aspirin were slurried in 3ml of THF overnight sealed under ambient conditions at ca. 250 rpm. The resulting solid was filtered and washed with THF. 4 was isolated in 96% yield. (c) solution crystallization – 0.0232 g (0.0660 mmol) meloxicam and 0.110 g (0.611 mmol) of aspirin dissolved in 8 ml of ethyl acetate and left to slowly evaporate, generating single crystals of 4 (ca. 35% yield) concomitantly with meloxicam form I and aspirin.

**Synthesis of meloxicam salicylic acid form III (5)** – (a) solvent-drop grinding – 0.174 g (0.495 mmol) meloxicam was ball-milled together with 0.0724 g (0.524 mmol)
of salicylic acid and 40 μl of ethyl acetate for 30 minutes. 5 was synthesized in ca. 100% yield. (b) slurry – 0.876 g (2.49 mmol) meloxicam and 0.350 g (2.53 mmol) of salicylic acid were slurried in 2 ml of THF overnight sealed under ambient conditions at ca. 250 rpm. The resulting solid was filtered and washed with THF. 5 was isolated in ca. 84% yield. (c) solution crystallization – 0.0226 g (0.0643 mmol) meloxicam and 0.0787 g (0.570 mmol) of salicylic acid was dissolved in 8 ml of a 6:2 mixture of ethyl acetate and dioxane, respectively, and left to slowly evaporate. Single crystals of 5 (ca. 33% yield) grew concomitantly with meloxicam form I and salicylic acid.

Synthesis of meloxicam salicylic acid form I (6) – (a) solvent-drop grinding – 0.177 g (0.504 mmol) meloxicam was ball-milled together with 0.0675 g (0.489 mmol) of salicylic acid and 40 μl of THF for 30 minutes. 6 was made in ca. 100% yield. (b) slurry – 0.871 g (2.47 mmol) meloxicam and 0.352 g (2.55 mmol) of salicylic acid were slurried in 2 ml of methanol overnight sealed under ambient conditions at ca. 250 rpm. The resulting solid was filtered and washed with methanol. 6 was obtained in ca. 91% yield.

Synthesis of meloxicam salicylic acid form II (7) – (a) solvent-drop grinding – 0.175 g (0.498 mmol) meloxicam was ball-milled together with 0.0705 g (0.510 mmol) of salicylic acid and 40 μl of chloroform for 30 minutes, generating 7 in ca. 100% yield. (b) slurry – 0.869 g (2.47 mmol) meloxicam and 0.356 g (2.58 mmol) of salicylic acid were slurried in 2 ml of chloroform overnight sealed under ambient conditions at ca. 250 rpm. The resulting solid was filtered and washed with chloroform. 7 was isolated in ca. 89% yield.
4.4.3. Crystal Form Characterization

**Single-Crystal X-ray Diffraction:** Single crystals were obtained for five compounds. Attempts to crystallize 6 and 7 did not afford crystals suitable for single crystal X-ray crystallographic analysis. Single crystal analysis for 1-3 was performed on a Bruker-AXS SMART APEX CCD diffractometer with monochromatized Mo Kα radiation (\(\lambda = 0.71073 \text{ Å}\)) connected to a KRYO-FLEX low-temperature device while 4 and 5 was collected using a Cu Kα radiation (\(\lambda = 1.54178 \text{ Å}\)). Data for 1, 2 was collected at 100 K. Data for 3-5 was collected at 293 K. Lattice parameters were determined from least-squares analysis, and reflection data were integrated using SAINT. Structures were solved by direct methods and refined by full matrix least squares based on F^2 using the SHELXTL package. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms bonded to carbon, nitrogen, and oxygen atoms were placed geometrically and refined with an isotropic displacement parameter fixed at 1.2 times U_q of the atoms to which they were attached. Hydrogen atoms bonded to methyl groups were placed geometrically and refined with an isotropic displacement parameter fixed at 1.5 times U_q of the carbon atoms.

**Powder X-Ray Diffraction (PXRD):** 1-7 were characterized by a D-8 Bruker X-ray Powder Diffractometer using a Cu Kα radiation (\(\lambda = 1.54178 \text{ Å}\)), 40kV, 40mA. Data was collected over an angular range of 3° to 40° 2θ value in continuous scan mode using a step size of 0.05° 2θ value and a scan speed of 1.0 °/min.

**Calculated PXRD:** Calculated PXRD diffractograms were generated from the single crystal structures using Mercury 1.5 (Cambridge Crystallographic Data Centre, UK) for the following complexes: 1-5 for comparison to the bulk sample.
**Differential Scanning Calorimetry (DSC):** Differential Scanning Calorimetry was performed on a Perkin Elmer Diamond DSC with a typical scan range of 25 °C – 280 °C, scan rate of 10 °C/min, and nitrogen purge of ca. 30 psi.

**Fourier Transform Infrared Spectroscopy (FT-IR):** FT-IR analysis was performed on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a solid-state ATR accessory.

**Ultraviolet-Visible Spectroscopy (UV/Vis):** UV/Vis analysis was performed on a Perkin Elmer Lambda 25 UV/Vis spectrophotometer.

**High Performance Liquid Chromatography (HPLC):** Analysis was performed on an HPLC system (Perkin Elmer Instruments LLC) comprising the following units: a series 200 Gradient Pump; a 785A UV/VIS Detector; a series 200 Autosampler; an NCI 900 Network Chromatography Interface and a 600 Series Link. The system was operated by a Total Chrome Workstation. The sample holder temperature was kept at 4 °C with a flow rate of 1 mL/min. The column was a Microsorb-MV 300-5 C-18 (250 x 4.6 mm x 1/4”). The mobile phase consisted of a mixture of phosphate buffer (pH 3.0) with methanol (1/1, v/v). The phosphate buffer was prepared from 50 mmol/L Na₂HPO₃ water solution with pH-controlled HCl titration.

### 4.4.4. Solubility and Dissolution Study

Dissolution profiles and thermodynamic solubility were obtained for five crystal forms (1-5) in pH 8 phosphate buffer at 37 °C. The study was conducted using excess free flowing solid, stirring with a magnetic stir bar at a rate of ca. 250-300 rpm. The solids were sieved to achieve a particle size between 53-75μm. Aliquots were taken out
after 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, and 240 minutes and filtered with 0.45 \( \mu \text{m} \) filters. The resulting solution was processed and the concentration of meloxicam was measured using a UV/Vis spectrophotometer. The experiment was repeated twice to allow for statistical analysis.

### 4.4.5. Animal Pharmacokinetic (PK) Study

Six crystal forms (1-6) were submitted for pharmacokinetic analysis via a single dose oral gavage administration to Sprague-Dawley rats (225-250 g). The rats were pre-implanted with jugular vein catheters for withdrawing of blood samples. The animals were allowed water *ad libitum* and fasted overnight before drug administration. The crystal forms were administered a dosage of 10 mg/kg of meloxicam or meloxicam cocrystal, in the suspension vehicle of a 5% PEG and 95% methyl cellulose aqueous solution. After dosing, 2 ml of blood was withdrawn at 0, 15, 30, 45, 60, 120, and 240 minutes. The blood samples were processed and analyzed by HPLC according to the literature procedure.\(^71\)

### Table 4.6. Hydrogen bond distances and parameters

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Chapter 5 – Summary and Future Directions

5.1. Summary

The field of supramolecular chemistry has grown dramatically since the early works of Jean-Marie Lehn, Donald Cram and others both in complexity and in scope. The subtopic crystal engineering has also grown alongside it from a [2+2] photodimerization topochemical reaction to pharmaceutical cocrystals with improved physicochemical properties. The research presented in this dissertation is a contribution to the current knowledge base of the crystal engineering of cocrystals with a particular focus upon two separate applications: cocrystal controlled solid-state synthesis and pharmaceutical cocrystallization. Cocrystal controlled solid-state synthesis targets the cocrystal as the key intermediate stage that brings the two reactive components in close proximity such that the reaction can take place. Once the cocrystal is formed then the reaction can occur faster and with greater yield than traditional solution methods. The cocrystal controlled solid-state synthesis of imides was targeted due to the potential for supramolecular heterosynthon formation with the primary amine and carboxylic acid anhydride starting materials. Three cocrystals: 1, 2-methyl-4-nitroaniline 1,4,5,8-naphthalenetetracarboxylic dianhydride, (2:1), 2, 3-aminobenzoic acid 1,4,5,8-naphthalenetetracarboxylic dianhydride, (2:1)), 3 (2-methyl-4-nitroaniline pyromellitic anhydride, (2:1))) were isolated and characterized by single crystal analysis, DSC, FTIR,
\[^1\text{HNMR, and PXRD}\]. Their transformations in the solid-state to their corresponding imides were closely monitored and the imides were also characterized. Interestingly, the envisioned supramolecular synthon (amine-anhydride hydrogen bonding) did not occur, the cocrystals were instead sustained by $\pi$ system interactions of the aromatic rings that, in some cases, was determined to be charge-transfer interaction. The project concluded in an approximate 50% success rate of imide formation.

Cocrystals were also studied in relevance to pharmaceuticals. Lamotrigine and meloxicam were the targeted pharmaceuticals due to their inherently low solubility but high bioavailability. The goal for both drugs was to improve the solubility by cocrystallizing with a pharmaceutically acceptable cocrystal former. Additionally since meloxicam is a drug used for indications of acute pain, the goal was to reduce the time taken to reach the maximum concentration by at least half.

Ten crystal forms were isolated for lamotrigine: lamotrigine methylparaben cocrystal form I (1:1) (1), lamotrigine methylparaben cocrystal form II (1:1) (2), lamotrigine nicotinamide cocrystal (1:1) (3), lamotrigine nicotinamide cocrystal monohydrate (1:1:1) (4), lamotrigine saccharin salt (1:1) (5), lamotrigine adipate salt (2:1) (6), lamotrigine malate salt (2:1) (7), lamotrigine nicotinate dimethanol solvate (1:1:2) (8), lamotrigine dimethanol solvate (1:2) (9), and lamotrigine ethanol monohydrate (1:1:1) (10). An underlying theme for the lamotrigine cocrystals, salts, and solvates was the supramolecular synthon motifs. All of the crystal forms either hydrogen bonded to the exterior of the lamotrigine dimer or they broke the lamotrigine dimer. Crystal forms 1, 5, 6, and 8 break the lamotrigine dimer while 2, 4, 7, 9, and 10 hydrogen bond to the exterior of the dimer.
Solubility and dissolution measurements were conducted on crystal forms 1-5 and pure lamotrigine in water and pH 1 HCl solution. 5 was the most soluble crystal form in water, however, it was the least soluble in the pH 1 HCl solution. Instead, 2 exhibited the highest concentration in the acidified solution. The average concentration for 2 and 4 in aqueous solution were similar to that of lamotrigine while 3 was similar to the maximum of lamotrigine. In the acidic media the concentrations for 2, 3, 4, and 5 all surpassed that of pure lamotrigine. The solubility of the cocrystal former did not correlate to the solubility of the corresponding cocrystal.

The animal pharmacokinetic data was gathered via a single dose rat study. The area under the curve for the serum concentrations after administration of 5 was increased by 66% compared to lamotrigine. The other crystal forms, 3 and 4, however, resulted in a decrease in serum concentration by 37% and 26%, respectively.

Analyzing the solubility and pharmacokinetic data in light of the original goal shows that the crystal forms of lamotrigine show great potential for an improved drug in clinical studies. 5 exhibits the greatest improvements in solubility and serum concentration thus 5 is the best candidate for further clinical studies.

Pharmaceutical cocrystallizations of meloxicam afforded seven novel cocrystals: meloxicam 1-hydroxy-2-naphthoic acid cocrystal (1:1) (1), meloxicam glutaric acid cocrystal (1:1) (2), meloxicam L-malic acid cocrystal of a salt (1:1:1) (3), meloxicam aspirin cocrystal (1:1) (4), meloxicam salicylic acid cocrystal form III (1:1) (5), meloxicam salicylic acid cocrystal form II (1:1) (6), and meloxicam salicylic acid cocrystal form I (1:1) (7). Five of the seven resulting crystal forms were analyzed in terms of their crystal packing, solubility, dissolution rate, and pharmacokinetic properties.
Crystal structures of cocrystals 1-5 were obtained from single crystal X-ray diffraction analysis of high quality single crystals grown from slow evaporation of a solution. Examination of the crystal packing revealed the common motif of the meloxicam dimer and the two-point recognition carboxylic acid-azole/NH supramolecular synthon. The meloxicam dimer was only prevalent in crystal forms 1-4 while the carboxylic acid-azole/NH supramolecular synthon sustained forms 1-5. The lack of the meloxicam dimer in 5 is unique and possibly contributes to the unique solubility and pharmacokinetic properties of 5.

The dissolution profiles, conducted in pH 8 buffer, predicated the improved solubility of many of the cocrystals. 1 was the most soluble cocrystal while 2 was the least soluble cocrystal at the end of the 4 hour trial. However, due to the desire to improve the concentration in solution at the fastest rate to decrease the onset of efficacy, the concentration after the first 15 minutes was the most crucial point. Examining of the concentrations at the early time points illustrated that 3 and 5 were the most soluble after 5 minutes but 3 quickly decreased in concentration while 5 maintained an elevated level. The solubility of the cocrystal former did not correlate to the of the corresponding cocrystal.

The single dose rat pharmacokinetic study administered forms 1-5, 7, and meloxicam. The area under the curves for the plasma concentrations of 2, 3, and 6 were lower than pure meloxicam. Two hours into the 4-hour study 1 and 4 had achieved concentrations similar to meloxicam, 5 however, reaches therapeutic concentrations 15 minutes after administration.
A consideration of the solubility and pharmacokinetic data for the meloxicam cocrystals led to the selection of 5 as the product that should be taken further into clinical trials. Unfortunately, there remains a problem with marketing 5 as it is well known that meloxicam should not be taken with other NSAID pain killers. With this in mind the next best crystal form, 1, would be selected for clinical trial testing.

5.2. Future Directions

The future for the field of crystal engineering is glowing bright. The interest in developing solids as functional materials is progressing rapidly as scientists are learning how to utilize the principles of crystal engineering and expand upon the existing synthetic methods for the design of novel materials. The advent of novel synthetic techniques such as cocrystal controlled solid-state synthesis, have been instrumental in the development of new molecules. Furthermore, with the facile generation of new molecules one can synthesize functional materials such as metal-organic frameworks that are currently being explored for applications such as hydrogen storage.

Crystal engineering has within the last decade also had a major impact upon the pharmaceutical industry with a particular emphasis upon crystal form and pharmaceutical cocrystals. Currently the physical properties of pharmaceutical cocrystals that result from the screening process are unpredictable. Perhaps with the knowledge gained from the studies presented herein coupled with future studies will allow for the generation of a library that will facilitate the estimation or possibly predict the solubility or maybe even the bioavailability of pharmaceutical cocrystals.
The scientific literature surrounding pharmaceutical cocrystals has also grown exponentially over the past decade containing many articles from major pharmaceutical companies as well as academic scientists. Furthermore, there are now more collaborations than ever between industry and academia resulting in fascinating science and influential papers. The conglomeration of industry and academia appears to be the wave of the future and cocrystals will continue to play a major role in crystal form development. The ability to control the properties of a crystal form still remains for futuristic development but as the future draws near Feynman’s dreams of possessing the ability to arrange the molecules exactly as we want them are growing one step closer to becoming the reality.
Appendices
Appendix 1. Experimental data for PA1+AA1 (2-methyl-4-nitroaniline+NTCDA)
IR and Powder X-ray diffractogram of heated and ground material and $^1$HNMR of imide
Appendix 2. Experimental data for PA1+AA2 (2-methyl-4-nitroaniline+pyromellitic anhydride) IR and Powder X-ray diffractogram of heated and ground material and $^1$HNMR of imide
Appendix 3. Experimental data for PA1+AA3 (2-methyl-4-nitroaniline+maleic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 4. Experimental data for PA1+AA4 (2-methyl-4-nitroaniline+phthalic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 5. Experimental data for PA1+AA5 (2-methyl-4-nitroaniline + 3, 3', 4, 4'-biphenyltetracarboxylic dianhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide.
Appendix 6. Experimental data for PA2+AA1 (3-aminobenzoic acid+NTCDA) IR and Powder X-ray diffractogram of heated and ground material and $^1$HNMR of imide
Appendix 7. Experimental data for PA2+AA2 (3-aminobenzoic acid+pyromellitic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
$^1$HNMR could not be obtained due to low solubility
Appendix 8. Experimental data for PA2+AA3 (3-aminobenzoic acid+maleic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 9. Experimental data for PA2+AA4 (3-aminobenzoic acid + phthalic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide.
Appendix 10. Experimental data for PA2+AA5 (3-aminobenzoic acid+3', 4, 4'--biphenyltetracarboxylic dianhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
$^1$HNMR could not be obtained due to low solubility
Appendix 11. Experimental data for PA2+AA6 (3-aminobenzoic acid+1,8-naphthalic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
$^1$HNMR could not be obtained due to low solubility
Appendix 12. Experimental data for PA3+AA2 (melamine+pyromellitic anhydride) 
IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
XPDS of heated material are not provided because the material was amorphous.
Appendix 13. Experimental data for PA3+AA3 (melamine+maleic anhydride)
IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 14. Experimental data for PA3+AA4 (melamine+phthalic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 15. Experimental data for PA4+AA1 (1,4-phenylenediamine+NTCDA) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
$^1$HNMR could not be obtained due to low solubility
Appendix 16. Experimental data for PA4+AA2 (1,4-phenylenediamine+pyromellitic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 17. Experimental data for PA4+AA3 (1,4-phenylenediamine+maleic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 18. Experimental data for PA4+AA4 (1,4-phenylenediamine+phthalic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
$^1$HNMR could not be obtained due to low solubility
Appendix 19. Experimental data for PA4+AA5 (1,4-phenylenediamine+3, 3’, 4, 4’-biphenyltetracarboxylic dianhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide.
Appendix 20. Experimental data for PA4+AA6 (1,4-phenylenediamine+1,8-naphthalic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 21. Experimental data for PA5+AA1 (1,5-naphthalenediamine+NTCDA) 
IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
XPD of heated material not included because the compound is amorphous.
Appendix 22. Experimental data for PA5+AA2 (1,5-naphthalenediamine+ pyromellitic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide.
XPD of heated material not included because the compound is amorphous.
Appendix 23. Experimental data for PA5+AA3 (1,5-naphthalenediamine+maleic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 24. Experimental data for PA5+AA4 (1,5-naphthalenediamine+phthalic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 25. Experimental data for PA5+AA5 (1,5-naphthalenediamine+3, 3’, 4, 4’-biphenyltetra carboxylic dianhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
XPD of heated material not included because the compound is amorphous.
Appendix 26. Experimental data for PA5+AA6 (1,5-naphthalenediamine+1,8-naphthalic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
XPD of heated material not included because the compound is amorphous.
Appendix 27. Experimental data for PA6+AA3 (1-adamantylamine+maleic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 28. Experimental data for PA6+AA4 (1-adamantylamine+phthalic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 29. Experimental data for PA7+AA2 (triphenylmethylamine+pyromellitic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 30. Experimental data for PA7+AA3 (triphenylmethylamine+maleic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 31. Experimental data for PA7+AA4 (triphenylmethylamine+phthalic anhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^1$HNMR of imide
Appendix 32. Experimental data for PA7+AA5 (triphenylmethyamine+3, 3’, 4, 4’-biphenyltetracarboxylic dianhydride) IR, Powder X-ray diffractogram, and DSC of heated and ground material and $^{1}$HNMR of imide
Appendix 33. Histograms for specified contacts between aminopyridine to carboxylic acid and aminopyridine to alcohol moieties (comprised of entries in the CSD)

Distance distribution plots for select sets of crystal structures in the CSD. (a), (b), and (c) show the contact distances for the aminopyridine (with acid), aminopyridine (with alcohol), and the alcohol homocymians respectively.
Distance distribution plots for select sets of crystal structures in the CSD. (a) and (b) highlight the contacts for entries containing an aminopyridine and carboxylic acid or carboxylate. (c) and (d) show the contacts for entries containing an aminopyridine and an alcohol.
Appendix 34. Experimental data for lamotrigine methylparaben form I
Powder X-ray diffractogram comparison of cocrystal to starting material

An experimental PXRD is not shown because the crystallization results in multiple products in the same vial.
Appendix 35. Experimental data for lamotrigine methylparaben form II
Powder X-ray diffractogram, DSC, and IR for lamotrigine methylparaben form II
Appendix 36. Experimental data for lamotrigine nicotinamide cocrystal

Powder X-ray diffractogram, DSC, and IR for lamotrigine nicotinamide cocrystal

![Graph showing powder X-ray diffractogram, DSC, and IR for lamotrigine nicotinamide cocrystal]
Appendix 37. Experimental data for lamotrigine nicotinamide monohydrate
Powder X-ray diffractogram, DSC, IR, and TGA for lamotrigine nicotinamide monohydrate
Appendix 38. Experimental data for lamotrigine saccharinate salt

Powder X-ray diffractogram, DSC, and IR for lamotrigine saccharinate salt

[Graphs showing experimental and calculated data for lamotrigine saccharinate salt]
Appendix 39. Experimental data for lamotrigine adipate salt

Powder X-ray diffractogram, DSC, and IR for lamotrigine adipate salt

Calculated Lamotrigine adipate salt

Experimental Lamotrigine adipate salt

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Peak: 175.45 °C
Appendix 40. Experimental data for lamotrigine malate salt

Powder X-ray diffractogram, DSC, and IR for lamotrigine malate salt

Experimental Lamotrigine L-malate salt

Calculated Lamotrigine L-malate salt

Heat Flow/Energy (mW)

Temperature (°C)

%T

λ (cm⁻¹)

2Theta (deg)
Appendix 41. Experimental data for lamotrigine nicotinate dimethanol solvate
Powder X-ray diffractogram, DSC, IR, and TGA for lamotrigine nicotinate dimethanol solvate
Appendix 42. Experimental data for lamotrigine dimethanol solvate
Powder X-ray diffractogram, DSC, IR, and TGA for lamotrigine dimethanol solvate
Appendix 43. Experimental data for lamotrigine ethanol hydrate
Powder X-ray diffractogram, DSC, IR, and TGA for lamotrigine ethanol hydrate
Appendix 44. Histograms for specified contacts between carboxylic acid-azole, alcohol-azole, and primary amide-azole compiled from entries in the CSD

(a) Acid homosynthon in the presence of azole

(b) Acid-azole supramolecular heterosynthon

(c) Alcohol homosynthon in the presence of azole

(d) Alcohol-azole supramolecular heterosynthon

(e) Amide homosynthon in the presence of azole

(f) Amide-azole supramolecular heterosynthon
Appendix 45. Experimental data for meloxicam 1-hydroxy-2-naphthoic acid cocrystal. Powder X-ray diffractogram, DSC, IR, and for meloxicam 1-hydroxy-2-naphthoic acid cocrystal.

*Graphs showing experimental and calculated diffractograms, DSC thermograms, and IR spectra.*
Appendix 46. Experimental data for meloxicam glutaric acid cocrystal
Powder X-ray diffractogram, DSC, IR, and for meloxicam glutaric acid cocrystal

![Graph showing experimental and calculated diffraction patterns for meloxicam glutaric acid cocrystal](image)

![Graph showing DSC data for meloxicam glutaric acid cocrystal](image)

![Graph showing IR spectra for meloxicam glutaric acid cocrystal](image)
Appendix 47. Experimental data for meloxicam L-malic acid cocrystal of a salt
Powder X-ray diffractogram, DSC, IR, and for meloxicam L-malic acid cocrystal of a salt
Appendix 48. Experimental data for meloxicam aspirin cocrystal
Powder X-ray diffractogram, DSC, IR, and for meloxicam aspirin cocrystal
Appendix 49. Experimental data for meloxicam salicylic acid co-crystal form III
Powder X-ray diffractogram, DSC, IR, and for meloxicam salicylic acid co-crystal form III

Experimental Meloxicam Salicylic acid form III co-crystal

Calculated Meloxicam Salicylic acid form III co-crystal

Area = 111.017 mJ
ΔHf = 54.0922 J/g

Peak = 210.30 °C

Thermal analysis graph showing DSC trace with peak at 210.30 °C.
Appendix 50. Experimental data for meloxicam salicylic acid cocrystal form I
Powder X-ray diffractogram, DSC, IR, and for meloxicam salicylic acid cocrystal form I

[Graphs and data plots showing X-ray diffractogram, DSC, and IR spectra for meloxicam salicylic acid cocrystal form I]
Appendix 51. Experimental data for meloxicam salicylic acid cocrystal form II
Powder X-ray diffractogram, DSC, IR, and for meloxicam salicylic acid cocrystal form II
About the Author

Miranda Cheney received her Bachelor’s degree in Chemistry from the University of West Florida in 2004. In the fall of 2004 she entered the Ph.D. program at the University of South Florida and became a member of Dr. Zaworotko’s research group. Under the guidance of Dr. Zaworotko, she developed the synthetic technique of cocrystal controlled solid-state synthesis. In 2007 she joined Thar Pharmaceuticals where her primary objective became the development of pharmaceutical cocrystals. She has since presented her research at regional, national, and international conferences sponsored by the American Chemical Society and the Canadian Society for Chemistry. Her work has also been published in *Crystal Growth & Design* and *The Journal of Chemical Education*. Additionally, she is a co-inventor on eleven patent applications filed for cocrystal controlled solid-state synthesis and pharmaceutical cocrystallization.