Crystal engineering of novel pharmaceutical forms

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Crystal Engineering of Novel Pharmaceutical Forms

by

Jennifer Anne McMahon

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science
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Crystal Engineering of Novel Pharmaceutical Forms

Jennifer Anne McMahon

ABSTRACT

In the context of pharmaceutical development, it is abundantly clear that there is a need for greater understanding and control of crystalline phases. The field of crystal engineering is poised to address such issues and has matured into a paradigm for the supramolecular synthesis of new compounds with desired properties.

Crystal structures are unpredictable by nature, however, the interactions that lead to crystal formation are becoming much more predictable. By means of model compound studies, the delineation of the hierarchy of hydrogen bonding between complementary functional groups or supramolecular heterosynthons can be accomplished. Competitive co-crystallization studies along with data extracted from the Cambridge Structural Database (CSD) can be utilized in understanding the reliability of supramolecular heterosynthons without the need for endless co-crystallization experiments. In effect, this ability to understand supramolecular heterosynthons can allow crystal engineers to rationally design co-crystals with a high rate of success.

It has been suggested that pharmaceutical co-crystals could play a significant part in the future of API formulation since in principle they will outnumber pharmaceutical salts, polymorphs and solvates combined.
The focus of this thesis is the understanding of the primary amide functional group and its hydrogen bonding capabilities; as well as the synthesis of model compounds in order to develop a blueprint for the design of pharmaceutical co-crystals using API’s that contain a primary amide functional group.
Chapter 1

Introduction

1.1 Crystal Engineering

The term “crystal engineering” was introduced by R. Pepinsky in 1955 [1] and was implemented in the context of organic solid-state photochemical reactions by G.M.J. Schmidt in the 1960’s [2]. Today solid-state synthesis continues to represent an active area of research in the context of crystal engineering [3].

Crystal engineering can be defined as “the application of the concepts of supramolecular chemistry to the solid state with particular emphasis upon the idea that crystalline solids are de facto manifestations of self-assembly” [4]. Consequently, crystal structures can be regarded as the result of a series of weak but directional molecular recognition events.

Crystal engineering has since grown into a form of supramolecular synthesis using these directional molecular recognition events as the critical design element for the generation of new compositions of matter with markedly different physical and chemical properties [5].

The idea that molecular recognition lies in the complementarity of interacting surfaces was first clearly formulated by Dutch chemist Emil Fisher, who proposed in 1894 that the enzyme and substrate fit together "like lock and key" [6]. A modern
A definition of molecular recognition is the assembly of two molecules through molecular functionalities that can be anticipated to interact with each other in an expected fashion. These molecular recognition events have been termed supramolecular synthons [7]. The ability to make use of these supramolecular synthons as building blocks in larger assemblies lies in the understanding of the strength and reliability of these interactions as well as how to reliably direct the self-assembly process.

Crystal engineered structures are designed from first principles and therefore can consist of a wide range of chemical components as demonstrated by coordination polymers [8], polymers sustained by organometallic linkages [9], and hydrogen bonded organic networks [10].

The work of this thesis has focused upon a more recent application of crystal engineering, which is to generate novel pharmaceutical compositions [11]. Pharmaceuticals were chosen because they are highly amenable to crystal engineering studies due to the fact that the majority of API’s are crystalline solids. The benefits of this include the physico-chemical stability of the crystalline solid state and the ease of isolating a pure product [4].

What are the advantages of applying crystal engineering to pharmaceutical development? Crystal engineering allows for the design of new compositions of matter using existing pharmaceuticals, which allows for a much wider range of possible pharmaceutical compositions than present methods such as ion-pairing (salt formation). It has been suggested that pharmaceutical co-crystals could play a significant part in the future of API formulation given that they, in principle, will outnumber pharmaceutical salts, polymorphs and solvates combined.
The physical properties of interest for specific active pharmaceutical ingredients (API’s) could be scientifically optimized by rational design rather than serendipitous experimentation. In addition, preliminary indications show that a compound with polymorphic tendencies could display a decreased propensity toward polymorphism as a co-crystal, rather than a pure phase, although significant research is needed to support or repudiate this argument [4].

1.2 Supramolecular Synthons

A supramolecular synthon is a reliable and well-defined linear connection between molecular building blocks. Synthons are formed by the assembly of two molecules through molecular functionalities that interact with each other in a predictable fashion. Self-complementary functional groups, such as carboxylic acids, amides, and alcohols contain both a hydrogen bond donor and acceptor and are therefore capable of forming supramolecular homosynthons (fig. 1). Other functionalities, which contain only hydrogen bond donors or acceptors, do not have this capability. However, all functionalities are capable of forming supramolecular heterosynthons with other complementary functional groups (fig. 2).
Figure 1. Supramolecular Homosynthon Examples; (a) Carboxylic acid dimer (b) Primary amide dimer (c) Alcohol homosynthon.

Groups that are capable of forming supramolecular synthons include, but are not limited to; acids (carboxylic, sulfonic, phosphonic, and boronic), primary and secondary amide, alcohol, amino-pyridine, ketone, aldehyde, ether, ester, primary and secondary amine, aromatic nitrogen, cyano, imine, nitro, sulfonyl, sulfoxide, sulfonamide, water, and ions such as Cl$^-$ and Br$^-$. Also, competition between intermolecular interactions can occur within a structure that contains a multiple number of functional groups capable of hydrogen bonding.

Figure 2. Supramolecular Heterosynthon Examples; (a) Carboxylic acid/ Primary amide (b) Carboxylic acid/ Pyridine (c) Cyano/ Alcohol.
Even though hydrogen bonding is considered a weak interaction (table 1), it is the most important of all directional intermolecular interactions [12]. It is of tremendous importance to the structure, function, and dynamics of a vast number of chemical systems [13]. Hydrogen bonds result from the interaction of an electropositive hydrogen atom on one molecule with a lone pair of an electronegative atom on a second molecule. The result is highly selective and directional interactions that are also responsible for the formation of highly ordered crystalline solids [5c]. This makes them highly amenable to crystal engineering.

Table 1. Bond Energy Comparison

<table>
<thead>
<tr>
<th>Interaction type</th>
<th>Energy (kJ/mol)</th>
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<tr>
<td>Covalent bond</td>
<td>100 - 900</td>
</tr>
<tr>
<td>Hydrogen bond</td>
<td>10 - 40</td>
</tr>
<tr>
<td>Dipole-dipole forces</td>
<td>19</td>
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<tr>
<td>van der Waals forces</td>
<td>0.5 – 5</td>
</tr>
</tbody>
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Understanding supramolecular homosynthons and heterosynthons; i.e. their probability of formation, reliability, and hierarchy in competitive situations represents an opportunity for the synthesis of co-crystals, and therefore, the design of unlimited new compositions of matter with modified solid-state physical properties.

1.3 Co-crystals

What are co-crystals? Co-crystals are multiple component structures whose components interact by hydrogen bonding or other weak intermolecular interactions rather than by ion pairing. A valuable approach to understanding and designing co-crystals is to employ supramolecular synthesis, in particular exploitation of
supramolecular heterosynthons [11,14]. In the context of co-crystals, supramolecular synthesis is a relatively low-risk strategy, because the approach employs principles of molecular recognition and self-assembly rather than creating covalent bonds. A detailed understanding of the supramolecular chemistry of the functional groups present in a given molecule is the first step in designing a co-crystal since it facilitates selection of molecules that contain the appropriate complementary functional groups. Herein, these complementary molecules will be referred to as co-crystal formers.

While co-crystals can be easily obtained under the proper conditions, this does not mean that their synthesis and isolation is nonetheless routine. Solvent selection can be critical in obtaining a particular co-crystal; however the role of solvent in the nucleation of crystals and co-crystals remains poorly understood [15]. In addition, undesired products such as solvates, hydrates, polymorphs, or pure compounds can often result from co-crystallization experiments.

Synthesis of a co-crystal from solution might be thought of as counterintuitive since crystallization is such an efficient and effective method of purification and it is used extensively in the fine chemicals and pharmaceutical industries for such a purpose. However, if different molecules with complementary functional groups result in hydrogen bonds that are energetically more favorable than those between like molecules of either component, then co-crystals are likely to be favored.

Techniques used for the characterization of co-crystals include single crystal x-ray diffraction, infrared spectroscopy, differential scanning calorimetry, thermogravimetric analysis, melting point apparatus, and powder x-ray diffraction.
The prospective impact of co-crystals is broad-ranging as suggested by recent studies which indicate that co-crystals can play a role in solvent-free organic synthesis (photodimerization of olefins using linear templates) [16], for design of host–guest systems [17], in modification of photographic films [18], for reformulation of active pharmaceutical ingredients (APIs) [4, 11, 19] and for generation new classes of NLO materials [20].

1.4 Pharmaceutical Co-crystals

Co-crystals are currently of interest to several research groups [21] and have been known for decades [22], however, their systematic design and application to active pharmaceutical ingredients (API’s) has not.

The complex nature of APIs means that they inherently contain peripheral functional groups that engage in molecular recognition events. Indeed, it is the very presence of these functional groups that affords biological activity but also provides an ability to engage in more than one supramolecular event with itself, a solvent molecule or co-crystal former, thereby forming polymorphs, solvates or co-crystals, respectively.

The preferred form of most APIs is a crystalline solid since they are of high purity, high stability and are easy to handle and characterize during the numerous stages of drug development. The use of crystalline solids in pharmaceutical formulations is preferred over the metastable amorphous form in order to limit physical and chemical instability of the marketed drug [23]. Crystalline API’s are also easier to isolate and purify.
Herein pharmaceutical co-crystals will be defined as being a subset of a broader group of multi-component crystals that also includes salts, solvates, hydrates, clathrates, and inclusion crystals. In a supramolecular context, solvates/hydrates and pharmaceutical co-crystals are related to one another in that at least two components of the crystal interact by hydrogen bonding and, perhaps, other noncovalent interactions rather than by ion-pairing. Both neutral compounds and salt forms have the potential to be solvated (i.e. interact with solvent molecules) or co-crystallized (i.e. interact with a co-crystal former). Solvate molecules and co-crystal formers can include organic acids or bases that remain in their neutral form within the multi-component crystal. The primary difference lies in the physical state of the isolated parent components: if one component is a liquid at room temperature, the crystals are referred to as solvates; if both components are solids at room temperature, the products are referred to as co-crystals. Upon first glance these differences may seem insignificant; however, they can profoundly impact the stability, preparation, and development of products.

Another advantage of pharmaceutical co-crystals is that they can be rationally designed unlike solvates, which often occur unanticipated from solution. In addition, while there are a limited number of solvents and counter-ions, potential co-crystal formers such as compounds from the FDA’s GRAS list, sugars, natural products, vitamins, and flavorings are much more numerous. This allows for the design of new compositions of matter using existing pharmaceuticals, which opens up a wide range of possible pharmaceutical compositions.
1.5 Polymorphism

The ability of a molecule to form both homosynthons and heterosynthons can also lead to a phenomenon known as polymorphism. Polymorphism is the ability of a substance to exist in more than one crystalline form [24]. Although polymorphs contain the same chemical composition, their solid-state properties generally differ as a consequence.

Polymorphism is a major concern for the pharmaceutical industry for many reasons. Properties such as solubility, bioavailability, hygroscopicity, stability, and toxicity of an API are dependent on the polymorphic state. It is essential that the desired form be reproducible and that it can remain stable during production and marketing.

Polymorphism opens up an avenue for studies of structure-property relations [25] since the only variable between polymorphs is that of the crystal packing and/or conformation. The chemical composition does not change. The physical properties of organic materials are inherently dependent upon not only the nature of the molecules but also the nature in which they interact with each other in the solid state. The variation of physical properties in a polymorphic system can give insight into the role of intermolecular interactions. However, the fact remains that polymorphs cannot be designed and often are found serendipitously.

1.6 Cambridge Structural Database

Started in 1965, the Cambridge Structural Database (CSD) [26] is an important tool for the solid-state chemist. As of the February 2005 update, the CSD (v. 5.26) contains 338,445 structures. The database records bibliographic, 2D chemical and 3D
structural information for organocarbon compounds studied by X-ray and neutron diffraction. Given the large amount of data available, there are many research applications including conformational analysis, structural correlation, and statistical analysis, studies of crystal packing and intermolecular interactions, crystal engineering, polymorphism and crystal structure prediction [27]. The CSD allows statistical analysis not only of molecular structure but also of packing motifs. Functional groups that are common or of special interest can therefore be studied in terms of how they associate with themselves or other functional groups.

In order to properly design a supramolecular structure, one must understand what intermolecular operations are possible, and be able to predict which will occur. Etter formulated a set of hierarchy rules for hydrogen bonding in systems with multiple functionalities that are capable of hydrogen bonding that is based upon best (strongest) donor to best acceptor, second best donor to second best acceptor [28].

Competitive studies on the hydrogen bonding preferences of numerous functional groups using co-crystals are underway in several research groups [10c, 29]. These competitive studies are the start to delineation of the hierarchy involved in the supramolecular interactions between these functional groups. This will allow for the ability to predict with a higher degree of accuracy which molecular recognition events will occur between specific functional groups and increase the number of designed co-crystals.
Chapter 2
Polymorphism in Single Component Systems

2.1 Introduction
Pharmaceutical manufacturers have taken notice since the first case of polymorphism with dramatically different biological activity between two forms of the same drug, chloramphenicol palmitate (CAPP), was discovered [30]. Form A of the broad-spectrum antibiotic is the most stable and the marketed form. Form B has been shown to have an eightfold higher bioactivity than Form A. The possibility of fatal dosing exists if the unwanted polymorph were to be administered [31].

Commercial drug formulations have been taken off the market due to an unexpected appearance of an undesired polymorph. In 1998, Abbott Laboratories had to pull the HIV protease inhibitor Ritonavir (Norvir) off the market because a new polymorphic form of the drug, Form II, had popped up in the manufacturing process. This new form was less than 50% as soluble as the marketed form and compromised the oral bioavailability of the capsules. The drug had to be reintroduced in a liquid form due to the inability to regenerate the original form [32].

Polymorphs are also established in law as discrete materials, which, when considering the intellectual property implications, can be extremely important. The best example of this is the case of Ranitidine hydrochloride (Zantac), an ulcer drug.
Glaxo Wellcome, now GlaxoSmithKline (GSK), introduced Zantac in 1981 and for a decade it was the world’s best selling prescription drug. GSK’s patent for Zantac designated Form II of the drug as the form that would be marketed. Novopharm, a Canadian pharmaceutical company, wished to market a generic form of the drug using Form I. GSK brought an action suit against Novopharm claiming that any process to manufacture Form I would result in some Form II being present, therefore infringing on GSK’s patent. The court ruled in favor of Novopharm and GSK lost its monopoly on Zantac [5c].

2.2 BHA (antioxidant)

2.2.1 Description

Butylated hydroxy anisole (BHA; 3-tert-butyl-4-hydroxy anisole) (fig. 3) represents a small molecule that contains flexible groups and hydrogen bond donor and acceptor sites that has not been structurally characterized even though its use as an antioxidant in solid dosage forms is ubiquitous throughout the pharmaceutical industry. The ability of BHA to effectively retard degradation varies depending on concentration, choice of excipients and processing methods, and storage conditions [33]. The behaviour of BHA is complex. In some cases, it appears to cause oxidation of the drug in certain formulations while protecting it in others, even at the same BHA loading [34]. The primary mode of action of BHA is well known [35]; it becomes a free radical by donating a hydrogen atom to a free radical. The BHA radical is stabilized by resonance and interferes with the propagation step of the radical reaction, thereby retarding the degradation.
We have reported the single crystal x-ray characterizations of both the commercially available form of 3-BHA and a new polymorph designated herein as form I and form II, respectively [36].

2.2.2 Synthesis and Characterization

Form I of BHA (A) forms rod-like triclinic crystals (fig. 4). Molecules of BHA self-assemble via OH–ether hydrogen bonds. This head-to-tail interaction results in a 4-fold helix, which intertwines with a second helix to form a double helical structure similar to that of DNA. The O–O distances of 2.707, 2.710 and 2.740 Å are within expected ranges for such interactions. The t-butyl groups orient outward meaning that the exterior surface of the helix is hydrophobic. Form I melts at 61°C and the calculated density is 1.158 g/cm³.
**Form II** (B) (fig. 5) exists as block-like trigonal crystals. It also consists of supramolecular structures that are the result of head-to-tail OH–ether hydrogen bonds (O–O = 2.778 Å). However, form II is a discrete species that results from the self-assembly of 6 molecules and, unlike form I, all t-butyl groups face inward. Form II melts at 64.8°C and the calculated density, 1.136 g/cm³, is slightly lower than that of form I.

![Figure 5. BHA Form II; The hexameric supramolecular structure exhibited by Form II.](image)

### 2.2.3 Discussion

The OH–ether supramolecular synthon that occurs in these BHA polymorphs represents an example of a one-point interaction and therefore it should be unsurprising that the angle of interaction between adjacent molecules can vary enough to generate such different supramolecular structures as in Forms I and II of BHA. However, it is perhaps surprising that it occurs instead of the OH–OH supramolecular synthon. Indeed, a CSD [37] survey revealed the presence of 693 crystal structures that have both a hydroxy and methoxy group. Of these, only 57 (8%) were found to contain the OH–ether interaction.

The crystal packing of a number of BHA-related molecules (fig. 6) was therefore analyzed to compare hydrogen bonding motifs. In simple alcohols such as methanol,
ethanol and t-butanol, OH…OH interactions afford zigzag chains or helices. Phenol and 2-methylphenol form OH…OH 3-fold helices, whereas 4-methoxyphenol forms an OH…OH zigzag chain. A similar situation was observed in 4-bromo-phenol, which forms a 4-fold helix via OH…OH hydrogen bonds. It is interesting to note that the methoxy group in 4-methoxyphenol does not interfere with the alcohol-alcohol interactions and is excluded from any involvement in hydrogen bonding. However, for 2,6-di-t-butyl-4-methoxyphenol, an OH…ether hydrogen bond occurs rather than an OH…OH interaction and in 4-bromo-2,6-di-t-butylphenol there are no hydrogen bond interactions. Therefore, there is precedence for adjacent t-butyl groups to sterically hinder OH…OH interactions and thereby facilitate OH…ether hydrogen bonds, as is the case for both forms of BHA.

\[
\begin{align*}
&\text{OH} & \text{OH} & \text{OH} & \text{OH} \\
&\text{CH}_3 & \text{OMe} & \text{OMe} & \text{Br}
\end{align*}
\]

Figure 6. Molecular structure of BHA-related molecules; Top: phenol, 2-methylphenol, 4-methoxyphenol, 4-bromophenol; Bottom: 2,6-di-tert-butyl-4-methoxyphenol, 4-bromo-2,6-di-tert-butylphenol.

2.3 Aspirin (API)

2.3.1 Description

Aspirin (acetylsalicylic acid) is one of the most widely used drugs in the world and has been shown to be effective as an anti-inflammatory, anti-pyretic, and anti-
rheumatic agent as well as in reducing the risks of heart attack and stroke. Aspirin (fig. 7) is a molecule that needs little introduction. It has a long and varied history that begins with the use of sodium salicylate as a painkiller in the 1800’s. The main drawback of this drug was irritation to the stomach lining. In 1853, a French chemist named Charles Frederic Gerhardt tried to improve on sodium salicylate by combining it with acetyl chloride [38]. Although he actually succeeded in producing a new compound that was less irritating to the stomach, he saw little promise for the compound and abandoned his discovery.

![Aspirin Molecular Structure](image)

**Figure 7.** Molecular structure of Aspirin.

In 1897, Felix Hoffman, a German chemist who worked for Bayer, began searching for a less-irritating substitute for salicylic acid and synthesized a stable derivative known as acetylsalicylic acid. By the turn of the century, it became the number one drug worldwide [39].

Despite the fact that aspirin has been widely studied and repeatedly crystallized under a variety of conditions, only one crystalline form has been structurally characterized. **Form I** of aspirin (C) was first determined by Wheatley [40] in 1964, and later refined by Kim et al. [41] in 1985. In 2002, Wilson [42] determined the structure by neutron single crystal diffraction (CSD refcode: ACSALA02). The crystal packing of the known form of aspirin consists of hydrogen bonded centrosymmetric carboxylic acid

The first report of a potential aspirin polymorph was published in Science in 1968 by Tawashi [43]. Observations were based on x-ray diffraction patterns and the dissolution rates of different formulations of aspirin; form I from ethanol and form II from n-hexane, however, unequivocal evidence for polymorphism could not be obtained.

In the 1970’s and 80’s, several experimental studies were carried out to determine if aspirin did indeed exhibit polymorphism [44]. Although many of these studies reported considerable variations in the physical properties of aspirin (i.e., morphology, dissolution rate, heats of fusion, melting point, etc.), no conclusive evidence for the existence of a polymorph was revealed.

The considerable debate about whether or not experimental observations have confirmed the existence of a second polymorph of aspirin has driven chemists to find other ways to answer this question. In 1988, Etter, et al. first touched on the possibility of molecular modeling by identifying unknown low energy conformers, predicting their crystal structures, and consequently devising experimental conditions which are most likely to produce the desired form [45]. Although molecular modeling for crystal structure prediction is still in the early stages of development, computational studies have proved useful in aiding in the characterization of polymorphs from powder X-ray data, as well as in providing insight into the types of packing that may be adopted by a given molecule [46].

According to Dunitz [47], advances in technology should lead to improved methods of obtaining data such as the range of thermodynamic stability for hypothetical
structures, vibrational frequency measurements for individual molecules, and better methods of converting potential energies to free energies. From only a molecular formula, a list of 10-20 crystal structures within an energy window of a few kJ mol\(^{-1}\) can be obtained, which, in theory, will most likely contain all observable polymorphs.

The discovery of this once elusive new form of aspirin, herein referred to as **Form II**, was isolated during co-crystallization experiments with aspirin and other compounds containing primary amides [48]. The expected outcome of the experiment was a co-crystal containing the acid-amide supramolecular heterosynthon. Indeed, co-crystallization of aspirin with carbamazepine did result in the expected 1:1 co-crystal, the structure of which is described in Section 6.6.1 (fig. 27) of this thesis.

**Form I** is kinetically stable at 100° K, however, **Form II** is relatively unstable and converts back to Form I at ambient conditions. Both forms contain a centrosymmetric carboxylic acid dimer (fig. 8), however, there is a slight difference in the torsion angle defined by the acetyl and carboxylic acid groups [O…O\(_{\text{Form I}}\): 164.0°; O…O\(_{\text{Form II}}\): 173.1°]. There are clear differences in the crystal packing of adjacent dimers. Form I assembles into 1D chains sustained by alternating carboxylic acid and acetyl group dimers, whereas Form II assembles into chains of carboxylic acid dimers that are connected via weak catemeric C–H…O hydrogen bonds [C…O: 3.85(2) Å, 164.0°] between the methyl groups and the carbonyl oxygen of the acetyl group.
2.3.2 Synthesis and Characterization

We report herein single crystal X-ray characterization of a new polymorph of aspirin (C₉H₈O₄; mw = 180.16). The crystal packing in Form II (D) is remarkably similar to that of Form I (C) (fig. 9) with the cell parameters differing only by a 15.6° change in the β angle. The centrosymmetric carboxylic acid dimer is intact; however, the change in β interrupts the formation of the centrosymmetric ester dimer. The ester carbonyl in Form II is bound by a weak C–H–O hydrogen bond to the methyl group of a neighboring ester group [C–O 3.343 Å].

Figure 8. Centrosymmetric Aspirin Dimer.
Figure 9. Aspirin Polymorph Comparison; *Left:* Form I consists of 1D chains of alternating acid and acetyl dimers; *Right:* Form II assembles into chains of carboxylic acid dimers that are connected via catemeric C-H–O hydrogen bonds.

**Form II** of aspirin exists as thin monoclinic plates that were synthesized from binary co-crystallization experiments with the following molecules; acetamide and levetiracetam; both of which contain a primary amide functional group. The co-crystallization experiments were carried out using a 1:1 stoichiometry of aspirin and co-crystal former dissolved over heat in acetonitrile. The colorless plates formed in approximately 3 days via slow evaporation and were preserved in a small amount (<0.10 mL) of the mother liquor until put on the diffractometer. Form II was characterized by melting point, IR, DSC, simulated X-ray powder diffraction and single crystal x-ray diffraction. (for crystallographic data, see Appendix I)
2.4 Discussion

Aspirin is an excellent candidate for studies on polymorphism. It has been studied and crystallized extensively for many years; however, a new polymorph was found only after co-crystallization experiments using primary amides as potential co-crystal formers. Its ability to exhibit polymorphism has been speculated on since 1968 [43,49].

Depending on one’s point of view, polymorphism can either be viewed as a nuisance or an opportunity. The potential effects of an unintended polymorph on the pharmaceutical industry can be daunting. First and foremost, the bioavailability of a marketed drug depends entirely on the polymorphic form present in the drug’s formulation. Crystallization of an inadvertent polymorph can mean months of production downtime, loss of revenue, and even life-threatening consequences for the consumer. Also, the ability to patent new polymorphs as discrete materials can have give competitors legal loopholes that can have a large effect on the profitability of a new drug.

On the other hand, a thorough understanding of polymorphism gives companies a distinct advantage in bringing new drugs to market. Polymorphic forms can be used to maximize a drug’s chemical and physical stability, hygroscopicity, solubility, bioavailability and/or manufacturability. Also, the ability to identify new crystal forms of a drug can provide a higher level of intellectual property protection.
Chapter 3
Primary Amides

3.1 Primary Amide Homosynthons

In the context of primary amides, early research on hydrogen bonding is exemplified by Schmidt’s seminal work in the 1960’s [50]. Primary amides illustrate remarkable diversity in their ability to form hydrogen bonds due to the fact that they contain two hydrogen bond donors (NH₂) and an acceptor (CO) [51]. They exhibit two basic modes of self-organization to form supramolecular homosynthons: the dimer and the catemer (fig. 10).

![Figure 10. Primary Amide Homosynthon motifs: a) primary amide dimer; b) primary amide catemer.](image)

A Cambridge Structural Database (CSD) survey of compounds in which a primary amide is the only functional group capable of forming strong hydrogen bonds was conducted in order to understand the statistics of supramolecular homosynthon
formation of primary amides [52]. This survey revealed the percentage of occurrence and the structural parameters of supramolecular homosynthons involving a primary amide.

Contact limits for each interaction were determined from histograms obtained by applying contact distances well beyond the sum of the van der Waals radii of the acceptor and the donor atoms. The survey revealed that there are 1151 crystal structures in which at least one primary amide functional group is present. Three hundred ninety of these structures (34%) exhibit the dimer motif whereas 261 structures (23%) were found to exhibit the catemer. The average N···O distance of N−H···O hydrogen bond for the dimer and catemer are 2.95(5) and 2.96(8) Å respectively. Many of these structures contain other functional groups that can compete for the hydrogen bonding capabilities of the primary amide; consequently the remaining 500 of the 1151 structures (43%) are those that contain supramolecular heterosynthons, which will be discussed in 3.2.

There are only 101 primary amide structures in which competing hydrogen bond donor and/or acceptor groups are absent. The percentage of occurrence of the dimer and catemer increases to 82% (83) and 16% (16) respectively in these structures, while two structures (2%) contained both a dimer and catemer.

The primary amide dimer has the potential to form larger assemblies because it has both donors and acceptors at its periphery. Three distinct patterns are possible: discrete, catenated and shallow glide motif (fig. 11). In the discrete dimer, the anti-oriented NH does not engage in further hydrogen bonding, most frequently because of steric hindrance. The catenated dimer, sometimes referred to as an amide tape or ribbon, is a chain of translational related dimers linked along a 5.1 Å short axis by N−H···O bonds. The third pattern is the shallow glide motif in which the amide dimers are
hydrogen bonded to four other dimers through exterior hydrogen bonding. The dihedral angle between the central dimer and the adjacent dimers in these structures is highly variable. Of the 83 structures found containing a primary amide dimer in the absence of other competing donors and/or acceptors, the percentage of occurrence for each type of pattern is; discrete (22%), catenated (23%) and shallow glide (55%).

![Diagrams of primary amide dimer motifs](https://via.placeholder.com/150)

**Figure 11.** Primary amide dimer motifs: a) discrete; b) catenated; c) shallow glide motif.

### 3.2 Primary Amide Heterosynthons

Given that 500 of the 1151 total primary amide structures did not contain a primary amide homosynthon, subsequent searches focused on supramolecular heterosynthons involving the primary amide moiety. Primary amides can form a diverse
range of supramolecular heterosynthons with a number of other complementary functional groups such as chloride, cyano, carboxylic acid and alcohol.

The primary amide-chloride ion heterosynthon \((N-H\cdots Cl^-)\) represents an example of a charge-assisted one-point hydrogen bond and was found to occur in the highest percentage for primary amide heterosynthon formation. The 38 structures containing both groups reveal 29 crystal structures (76%) that exhibit the primary amide-chloride ion supramolecular heterosynthon and 3 structures (8%) that form an exterior heterosynthon through the anti-oriented NH of the amide dimer. Six structures (16%) contain a primary amide heterosynthon with a functional group other than the chloride ion.

There were no structures found that exclusively exhibited an amide homosynthon. The amide-chloride ion heterosynthon was found to occur within the range 3.10-3.60 Å \((N\cdots Cl^-)\) with an average hydrogen bond distance of 3.34(8) Å.

The primary amide-cyano supramolecular heterosynthon \((N-H\cdots NC)\) is another example of 1-point recognition. There are 51 crystal structures in which both primary amide and cyano groups are present. Twenty-six of these structures (51%) contained the amide-cyano supramolecular heterosynthon. Five of these structures (10%) exhibit the primary amide-cyano supramolecular heterosynthon exclusively with no primary amide homosynthon present. In approximately 41% of the 51 structures containing this supramolecular heterosynthon, the cyano group hydrogen bonds to the anti-oriented NH of the amide dimer or catemer. In the remaining 25 structures, 18 contain an amide homosynthon, and 7 contain an amide involved in a heterosynthon with another functional group. The amide-cyano supramolecular heterosynthon was found to occur
within the range of 3.00-3.30 Å (N···N), with a mean hydrogen bond distance of 3.15(9) Å.

The primary amide-carboxylic acid heterosynthon has been previously utilized [50] in forming co-crystals and appears to be a robust and reliable supramolecular heterosynthon. There are 125 crystal structures in which both a carboxylic acid and a primary amide moiety are present; 53 of these (42%) exhibit the two-point primary amide-carboxylic acid supramolecular heterosynthon whereas only 5 structures (4%) exhibit an acid homosynthon and 49 structures (39%) form an amide homosynthon.

Seventy percent of the 53 structures containing an acid-amide supramolecular heterosynthon are exclusive of any acid or amide homosynthon (dimer or catemer). Since this supramolecular heterosynthon is a two-point recognition event, there are two ranges corresponding to O−H···O and N−H···O interactions. The O···O range for O−H···O hydrogen bond is 2.40-2.80 Å and the mean hydrogen bond distance is 2.56(6) Å. This distance is shorter than that of the carboxylic acid homosynthon (dimer or catemer), for which the O−H···O range is 2.40-3.00 Å with a mean of 2.65(3) Å. The N···O range for (amide)N−H···O(acid) hydrogen bond was found to be 2.80-3.25 Å with a mean of 2.96(8) Å, which is longer than that observed for the amide dimer 2.75-3.15 Å [mean 2.95(5) Å] or catemer 2.75-3.20 Å [mean 2.96(8) Å]. These data suggest that the amide carbonyl could be a stronger H-bond acceptor than the acid carbonyl.

The ability of alcohols to operate as either hydrogen bond donors and/or acceptors [53], leads to two very different heterosynthons with primary amides (fig. 12). The (amide)O···O(alcohol) supramolecular heterosynthon occurs in 110 (43%) of the 255 crystal structures in which both a primary amide and an alcohol moiety is present,
whereas 78 crystal structures (31%) exhibit the primary amide homosynthon and 60 structures (24%) form the alcohol homosynthon. Thirty seven percent of the 110 structures containing the heterosynthon are exclusive of either primary amide or alcohol homosynthons. The O–H···O heterosynthon exhibits a range 2.60-3.00 Å with a mean of 2.75(8) Å.

A similar trend is observed in the case of the (amide)N–H···O(alcohol) synthon (fig. 12). One hundred twelve out of the 255 total structures (44%) were found to contain an amide NH-alcohol supramolecular heterosynthon, thirty eight percent of which occur exclusive of amide or alcohol supramolecular homosynthons. The (amide)N–H···O(alcohol) distance was found to occur within the range 2.73-3.20 Å (N···O), with a mean of 3.00(9) Å.

![Figure 12](image-url) Primary Amide-Alcohol Heterosynthon Motifs: a) amide carbonyl/alcohol; b) amide amine/alcohol.

3.3 Discussion

The first step in generating co-crystals is a detailed understanding of the supramolecular chemistry of the functional group present in given molecule. A CSD survey was conducted in order to understand the statistics of supramolecular homosynthon and heterosynthon formation of primary amides. Primary amides, which
contain two hydrogen bond donors (NH₂) and an acceptor (C=O), demonstrate a remarkable ability to form hydrogen bonds [51]. This survey has shown that the occurrence of the primary amide dimer drops from 82% in structures where only a primary amide moiety is present to 34% when one or more complementary functional groups are involved. Identification of reliable supramolecular heterosynthons from an analysis of the functional groups that inhibit primary amide dimer formation can then facilitate the selection of appropriate co-crystal formers for the generation of co-crystals. Such a strategy was employed using both model compounds and pharmaceutical molecules containing a primary amide moiety as a result of this analysis, the details of which are revealed in the following chapters of this thesis.
Chapter 4

Model Compounds

4.1 Description

CSD surveys reveal that primary amides seem to favor heterosynthon formation over that of the homosynthon motifs when certain complementary groups are also present. This understanding of self-assembly involving primary amides facilitates a rational approach to the design of co-crystals that are sustained by hydrogen bonding. In particular, co-crystal formers can be selected based upon our knowledge of the statistical probability of the occurrence of a particular supramolecular heterosynthon. Co-crystals are likely to be formed if the groups that sustain a robust supramolecular heterosynthon are in different molecules. However, the situation in real molecules, especially pharmaceuticals, is often more complicated since there might be several potential supramolecular heterosynthons. Through model compounds, the hydrogen bonding preferences of common functional groups can be studied and applied to design and synthesize co-crystals for a number of uses. Compounds A-E represent model compounds in this context since they represent co-crystals in which there is a competition between multiple supramolecular homosynthons and supramolecular heterosynthons.
4.2 Strategy

A model compound study was done to in order to delineate the hierarchy of the hydrogen bonding in co-crystals in which there is a competition between multiple supramolecular homosynthons and supramolecular heterosynthons. The functional groups of interest in the study are primary amide, carboxylic acid, aromatic nitrogen, and alcohol.

4.3 Structures

4.3.1 nicotinamide / 3-hydroxybenzoic acid 1:1 (A)

A contains an alcohol moiety which is capable of competing with the acid moiety for the pyridine group because it is unable to form an intramolecular hydrogen bond. The CSD reveals that supramolecular heterosynthon occurrence for an acid-pyridine is 63% whereas alcohol-pyridine occurs in 50% of the structures in which both groups are present. The presence of an alcohol-nitrogen hydrogen bond would presumably free the carboxylic acid moiety to form an acid-amide heterosynthon.

The crystal structure of A reveals that the alcohol does indeed hydrogen bond to the pyridine moiety and the amide-acid supramolecular heterosynthon is formed. Each amide-acid supramolecular heterosynthon is hydrogen bonded to four other amide-acid dimers through (alc)O−H⋯N(amine) [O⋯N 2.693(2) Å] and amide N−H⋯O [N⋯O 2.943(2) Å] hydrogen bonds (fig. 13). The four exterior-bonding pairs are situated at approximately a 90° angle, thereby generating a 2D network. The O−H⋯O [O⋯O 2.593(2) Å] and (amide)N−H⋯O(acid) [N⋯O 2.934(2) Å] hydrogen bond lengths for the
amide-acid supramolecular heterosynthon are in the expected range and compare closely to mean values of 2.56(6) Å and 2.96(8) Å respectively.

![Figure 13. Nicotinamide / 3-hydroxybenzoic acid 1:1 co-crystal.](image)

4.3.2 Nicotinamide / 4-hydroxybenzoic acid 1:1 (B)

Similarly to A, complex B (fig. 14) also contains an alcohol moiety capable of competing with the acid group for the pyridine. The crystal structure of B also contains an alcohol-pyridine interaction, as well as an amide-acid supramolecular heterosynthon. In A, single amide-acid dimers are formed, however in B, the amide-acid dimers form a tetrameric motif, presumably due to the position of the hydroxyl group on the acid. The alcohol-pyridine hydrogen bond length is 2.725(2) Å [O···N]. The O–H···O [O···O 2.613(2) Å] and (amide)N–H···O(acid) [N···O 2.902(2) Å] hydrogen bond lengths for the amide-acid supramolecular heterosynthon are in the expected range, and the amide anti-oriented N–H···O(acid) bond that connects the two dimers exhibits an N···O distance of 2.942(2) Å.
4.3.3 Nicotinamide / gentisic acid 1:1 (C)

Structure C (fig. 15) contains the same functional groups as A and B, with the addition of an ortho-substituted (intramolecularly bonded) hydroxyl group. In this case, the supramolecular synthons are entirely different. The acid-pyridine OH···N supramolecular heterosynthon is formed [O···N 2.575(5) Å], and the primary amide is hydrogen bonded to three alcohol groups [O···O 2.688(5) Å; N_{syn}···O 2.942(5) Å; N_{anti}···O 2.916(5) Å]. The lone interaction to the acid carbonyl is with the ortho-substitued alcohol group which exhibits a hydrogen bond length of 2.600(5) Å.
4.3.4 Pyrazinamide / gentisic acid 1:1 (D)

D is another example of a co-crystal that exhibits the amide-acid and alcohol-pyridine supramolecular heterosynthons. The molecules in D (fig. 16) form a tetrameric unit that consists of two molecules of each component that form two acid-amide heterosynthons connected by alcohol O–H···N interactions at the periphery of the supermolecule. Each tetramer is bridged to four others via hydrogen bonds between alcohol moieties and anti-oriented amide NH’s that are not involved in the amide-acid supramolecular heterosynthon (fig. 16). The O–H···O [O···O 2.597(2) Å] and N–H···O [N···O 2.935(2) Å] hydrogen bond lengths for the amide-acid heterosynthon are within the expected ranges.

![Figure 16. Pyrazinamide / gentisic acid 1:1 co-crystal.](image)

4.3.5 Acetamide / gentisic acid 1:1 (E)

E is a 1:1 complex (fig. 17), which is dominated by the amide-acid supramolecular heterosynthon, as there is no pyridine moiety available to compete for the acid. The O–H···O [O···O 2.607(1) Å] and N–H···O [N···O 2.949(2) Å] hydrogen bond lengths for the amide-acid supramolecular heterosynthon are within the expected ranges.
The alcohol moieties link each dimer through interactions with both the amide carbonyl [O···O 2.732(1) Å] and the *anti-oriented* NH [N···O 2.950(2) Å].

**Figure 17.** Acetamide / gentisic acid 1:1 co-crystal.

### 4.4 Synthesis and Characterization

Melting points for each structure are presented in Table 2 along with melting points for starting materials.

**Table 2.** Melting points of starting materials and model co-crystals, A-E.

<table>
<thead>
<tr>
<th>Co-crystals</th>
<th>Starting Materials °C</th>
<th>Co-crystal °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Nicotinamide / 3-hydroxybenzoic acid (1:1)</td>
<td>130-133</td>
<td>203</td>
</tr>
<tr>
<td>B. Nicotinamide / 4-hydroxybenzoic acid (1:1)</td>
<td>130-133</td>
<td>217</td>
</tr>
<tr>
<td>C. Nicotinamide / gentisic acid (1:1)</td>
<td>130-133</td>
<td>205</td>
</tr>
<tr>
<td>D. Pyrazinamide / gentisic acid (1:1)</td>
<td>189-191</td>
<td>205</td>
</tr>
<tr>
<td>E. Acetamide / gentisic acid (1:1)</td>
<td>81</td>
<td>205</td>
</tr>
</tbody>
</table>

### 4.4.1 Nicotinamide / 3-hydroxybenzoic acid 1:1 (A)

*Synthesis:* Colorless crystals were obtained within three days via slow evaporation of a solution containing nicotinamide (0.015 g, 0.123 mmol) and 3-hydroxybenzoic acid (0.017 g, 0.123 mmol) dissolved in 1 ml of acetonitrile.

*Crystal data:* (Bruker SMART-APEX CCD Diffractometer) Appendix B.
Melting Point: (Mel-temp®) 123-125 °C.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR) 3404 cm\(^{-1}\) (Amide NH stretch); 3205 cm\(^{-1}\) (C-H stretch, alkene); 1662 cm\(^{-1}\) (C=O); 1595 cm\(^{-1}\) (C=C).

X-ray Powder Diffraction: (Rigaku Miniflex Diffractometer using CuK\(\alpha\) (\(\lambda=1.540562\)), 30kV, 15mA). All powder data were collected over an angular range of 3 to 40 theta in continuous scan mode using a stepsize of 0.02 theta and a scan speed of 2.0 /min unless otherwise noted. XPD analysis (experimental): 7.480, 16.539, 19.263, 23.538, 26.400.

4.4.2 Nicotinamide / 4-hydroxybenzoic acid 1:1 (B)

Synthesis: Colorless crystals were obtained within 3 days via slow evaporation of a solution containing nicotinamide (0.015 g, 0.123 mmol) and 4-hydroxybenzoic acid (0.017 g, 0.123 mmol) dissolved in 1 ml of 50:50 ethanol/acetonitrile.

Crystal data: (Bruker SMART-APEX CCD Diffractometer) Appendix B.

Melting Point: (Mel-temp®) 185-186 °C.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR) 3433 cm\(^{-1}\) (Amide NH stretch); 3198 cm\(^{-1}\) (C-H stretch, alkene); 1669 cm\(^{-1}\) (C=O); 1592 cm\(^{-1}\) (C=C).


4.4.3 Nicotinamide / gentisic acid 1:1 (C)

Synthesis: Colorless crystals were obtained within four days via slow evaporation of a solution containing nicotinamide (0.015 g, 0.123 mmol) and gentisic acid (0.019 g, 0.123 mmol) dissolved in 1 ml ethanol.

Crystal data: (Bruker SMART-APEX CCD Diffractometer) Appendix B.

Melting Point: (Mel-temp®) 171-172 °C.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR) 3404 cm\(^{-1}\) (Amide NH stretch); 3231 cm\(^{-1}\) (C-H stretch, alkene); 1691 cm\(^{-1}\) (C=O); 1603 cm\(^{-1}\) (C=C).

4.4.4 Pyrazinamide / gentisic acid 1:1 (D)

Synthesis: Colorless crystals were obtained within two days via slow evaporation of a solution containing pyrazinamide (0.020 g, 0.162 mmol) and gentisic acid (0.025 g, 0.162 mmol) dissolved in 1 ml of acetonitrile.

Crystal data: (Bruker SMART-APEX CCD Diffractometer) Appendix B.

Melting Point: (Mel-temp®) 164-166°C.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR) 3400 cm\(^{-1}\) (Amide NH stretch); 3231 cm\(^{-1}\) (C-H stretch, alkene); 1669 cm\(^{-1}\) (C=O); 1603 cm\(^{-1}\) (C=C).


4.4.5 Acetamide / gentisic acid 1:1 (E)

Synthesis: Colorless crystals were obtained within two days via slow evaporation of a solution containing acetamide (0.059 g, 0.100 mmol) and gentisic acid (0.015 g, 0.100 mmol) dissolved in 1 ml of acetonitrile.

Crystal data: (Bruker SMART-APEX CCD Diffractometer) Appendix B.

Melting Point: (Mel-temp®) 141°C.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR) 3371 cm\(^{-1}\) (Amide NH stretch); 3198 cm\(^{-1}\) (C-H stretch, alkene); 1658 cm\(^{-1}\) (C=O); 1544 cm\(^{-1}\) (C=C).

4.5 Discussion

The hydrogen bonding capabilities of functional groups are varied and are not yet predictable. The application of crystal engineering to competitive studies between functional groups capable of hydrogen bonding will lead to a greater understanding of the hierarchy of these interactions and to the ability to design a series of structures with molecules of interest.

The preceding model compounds were used to study the hydrogen bonding preferences of primary amides when in competitive situations with the following functional groups: aromatic nitrogens, alcohols, and carboxylic acids. The crystal structure of the 1:1 acetamide/ gentisic acid co-crystal (E), which contains a primary amide, a carboxylic acid, and both meta and ortho-substituted alcohol moieties, exhibits the expected amide-acid supramolecular heterosynthon. This projected amide-acid supramolecular heterosynthon, as well as the alcohol-pyridine supramolecular heterosynthon, are found in three of the remaining four structures that contain a primary amide, a carboxylic acid, an aromatic nitrogen, and an alcohol moiety (A, B, D). The fifth structure, that of nicotinamide and gentisic acid (C), contains an acid-pyridine supramolecular heterosynthon, while the primary amide moiety is hydrogen bonded to three alcohol moieties from three separate gentisic acid molecules. With four of the five structures (80%) exhibiting the intended primary amide-carboxylic acid supramolecular heterosynthon, there seems to be some degree of predictability regarding the hydrogen bonding preferences of these two groups in the presence of aromatic nitrogen and alcohol moieties.
These results are based upon co-crystallizations with combinations of molecules that contain a primary amide (with or without aromatic nitrogen moieties) and those that contained a carboxylic acid (with one or more hydroxyl groups). Co-crystallization was also attempted with molecules containing a reverse combination of functional groups, however; attempts were unsuccessful due to a lack of suitable compounds containing both primary amide and alcohol moieties. Further research is needed in order to support any observations regarding the hydrogen bonding preferences in this group of selected functionalities.
5.1 Description

Piracetam, (2-oxo-1-pyrrolidinyl)acetamide (fig. 18), is a nootropic drug that works to boost intelligence by stimulating the central nervous system [54]. Three polymorphic forms of Piracetam, refcode BISMEV, have been deposited in the CSD. Two forms, a triclinic and a monoclinic modification, crystallize via an amide-amide supramolecular homosynthon (fig. 19a), while the third, a monoclinic form, crystallizes in a catemeric fashion (fig. 19b). In all three forms, the ring carbonyl is involved in hydrogen bonding to the anti-oriented NH of the primary amide. No co-crystals, solvates or hydrates have been reported although one study suggests that Piracetam may exhibit 6 polymorphs [55].

![Molecular Structure of Piracetam](image.png)

**Figure 18.** Molecular Structure of Piracetam.
5.2 Strategy

Piracetam contains two functional groups: a primary amide and a ring carbonyl. The design strategy for this drug was to use a co-crystal former containing a carboxylic acid moiety in order to exploit the robust primary amide-acid supramolecular heterosynthon, while also containing a hydrogen bond donor that could interact with the ring carbonyl. Two such structures were synthesized with Piracetam.

![Figure 19. Piracetam Polymorph Homosynthon Motifs (a) Piracetam dimer (b) Piracetam catemer.](image)

5.3 Structures

5.3.1 Piracetam / gentisic acid 1:1 (A)

Single crystals of the 1:1 co-crystal of Piracetam and gentisic acid, A, were obtained via slow evaporation and Figure 20 reveals that A is sustained by the primary amide-carboxylic acid supramolecular heterosynthon. The 5-hydroxy group of gentisic acid serves as a hydrogen bond donor to the ring carbonyl of Piracetam, resulting in a 4,4-topology network that is 2-fold interpenetrated.
5.3.2 Piracetam / 4-hydroxybenzoic acid 1:1 (B)

B is a 1:1 co-crystal of Piracetam and 4-hydroxybenzoic acid (fig. 21). The crystal structure of B also reveals the presence of the amide-acid supramolecular heterosynthon, which in turn dimerizes to form a tetrameric motif sustained by anti N-H···O hydrogen bonding. The ring carbonyl of Piracetam and the hydroxyl group of 4-hydroxybenzoic acid also form hydrogen bonds which link each tetramer to four others at the corners, thereby affording a 3-fold interpenetrated network.
A and B were screened for the existence of polymorphs using solvent-drop grinding, a technique that has been shown to be able to generate and control polymorphism [56]. Mechanical grinding experiments were conducted in reaction vessels by adding gentisic acid or p-hydroxybenzoic acid to solid Piracetam form A. Twenty three solvents (water, acetone, methanol, ethanol, ethyl acetate, n-hexane, toluene, acetonitrile, tetrahydrofuran, isopropyl acetate, benzyl alcohol, nitromethane, dimethyl amine, 2-butanol, ethyl formate, acetic acid, methyl ethyl ketone, methyl tertiary butyl ether, chlorobenzene, N-methyl pyrrolidone, 1,2-dichloroethane, dimethylsulfoxide, dimethoxy ethane) was evaluated by adding a different solvent to each well. The samples were ground for 20 minutes and characterized using powder X-ray diffraction. Co-crystals A or B were obtained from all conditions as a mixture with one or both of the
starting materials, *i.e.* A and B do not exhibit polymorphism based on a series of solvent mediated grinding experiments.

### 5.4 Synthesis and Characterization

Melting points for structures are presented in Table 3 along with melting points for starting materials.

**Table 3.** Melting points of starting materials and structures, A-B.

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<tr>
<td>A. Piracetam / gentisic acid (1:1)</td>
<td>138 205</td>
<td>123-125</td>
</tr>
<tr>
<td>B. Piracetam / 4-hydroxybenzoic acid (1:1)</td>
<td>138 217</td>
<td>141-142</td>
</tr>
</tbody>
</table>

#### 5.4.1 Piracetam / gentisic acid 1:1 (A)

*Synthesis:* Colorless crystals were obtained within 7 days via slow evaporation of a solution containing Piracetam (0.016 g, 0.11 mmol) and gentisic acid (0.017g, 0.11 mmol) dissolved in 1 ml of acetonitrile.

*Crystal data:* (Bruker SMART-APEX CCD Diffractometer) Appendix C.

*Melting Point:* (Mel-temp®) 123-125°C.

*Infrared Spectroscopy:* (Nicolet Avatar 320 FTIR) 3360 cm\(^{-1}\) (Amide NH stretch); 3180 cm\(^{-1}\) (C-H stretch, alkene); 1651 cm\(^{-1}\) (C=O); 1595 cm\(^{-1}\) (C=C).


#### 5.4.2 Piracetam / 4-hydroxybenzoic acid 1:1 (B)

*Synthesis:* Colorless crystals were obtained within 2 days via slow evaporation of a solution containing Piracetam (0.010 g, 0.07 mmol) and 4-hydroxybenzoic acid (0.010 g, 0.07 mmol) dissolved in 1 ml of acetonitrile.

*Crystal data:* (Bruker SMART-APEX CCD Diffractometer) Appendix C.

*Melting Point:* (Mel-temp®) 141-142°C.
**Infrared Spectroscopy:** (Nicolet Avatar 320 FTIR) 3408 cm\(^{-1}\) (Amide NH stretch); 3187 cm\(^{-1}\) (C-H stretch, alkene); 1658 cm\(^{-1}\) (C=O); 1595 cm\(^{-1}\) (C=C).


### 5.5 Discussion

Piracetam contains both a primary amide and a ring ketone, two functional groups with hydrogen bonding capabilities. According to the CSD, Piracetam has 3 known polymorphs, all which exhibit ring carbonyl hydrogen bonding to the \textit{anti} oriented NH of the primary amide functional group.

Attempts at co-crystallization afforded two new structures; the first co-crystals formed with this API. Both structures contain a primary amide-carboxylic acid supramolecular heterosynthon as well as a ketone-alcohol heterosynthon. This suggests that the amide-acid heterosynthon is more robust than amide-amide homosynthon interactions. The ring ketone is then free to hydrogen bond with the alcohol group present.

With both structures (100%) containing the intended primary amide-carboxylic acid supramolecular heterosynthon, it would seem there is some degree of predictability regarding the hydrogen bonding preferences of these two groups in the presence of ring ketone and alcohol moieties, however; further research is needed in order to support any observations regarding the hydrogen bonding preferences in this group of selected functionalities.

Both co-crystals were screened for the existence of polymorphs using solvent mediated grinding experiments with 23 different solvents. After grinding for 20 minutes
the samples were characterized using powder X-ray diffraction. Co-crystals were obtained from all conditions as a mixture with one or both of the starting materials, therefore, based upon these grinding experiments, A and B do not exhibit polymorphism.
Chapter 6
Carbamazepine

6.1 Study of an API- CBZ

The pharmaceutically active molecule Carbamazepine (CBZ) [5H-Dibenz(b,f)azepine-5-carboxamide] (fig. 22) was of interest to us because of its limited bioavailability [57] and four reported polymorphs [58,59]. A review of the literature and a CSD search also reveal a dihydrate [60], an acetone solvate [58c] and two ammonium salts [61]. It is an important drug for the treatment of epilepsy and trigeminal neuralgia and pure CBZ crystallizes as one of four polymorphs: triclinic (form I); trigonal (form II); monoclinic (forms III and IV). Its relevance, limited solubility and the fact that it exists in multiple crystalline forms therefore makes CBZ an ideal candidate for a crystal-engineering case study.

Figure 22. Molecular structure of Carbamazepine (CBZ).

Only five of the eight forms of CBZ isolated thus far have been reported with full structural data (polymorphs II [58c] and III [58d], a dihydrate [60] with R factor of ~10%
and two multiple component phases [61]) although the cell parameters of the acetone solvate have also been reported [58c]. Analysis of crystal packing in these structures reveals that the supramolecular primary amide homosynthon (fig. 1b) generates CBZ dimers in all compounds and that the azepine ring adopts a boat conformation. Form II is trigonal (fig. 23) and form III is a monoclinic phase (fig. 23) that contains cavities. The syn- oriented N–H of the primary amide group forms the expected primary amide dimer while the anti- oriented N–H does not engage in intermolecular interactions. A search of the CSD revealed 440 structures containing a primary amide dimer. (organics only, N–H…O contact 0-3.3Å). Of those 440 structures, 30% have an anti- oriented N–H that is not involved in hydrogen bonding, most commonly due to steric hindrance.

![Figure 23. Forms II and III of Carbamazepine (CBZ): Left; Trigonal Form II, Right; Monoclinic Form III.](image)

The presence of unused hydrogen bond donor and acceptor sites is an important issue in the context of crystal engineering. Furthermore, the different crystal packing motifs in the polymorphs of CBZ might be attributed to molecular shape of the CBZ
dimer and its inability to efficiently pack or utilize the inactivated anti-oriented N–H group. Interestingly, isostructural crystal packing with the trigonal form II was identified from the CSD. N-acetyl dibenz (b,f) azepine [62] is an analogue of CBZ in which the amide NH$_2$ group in CBZ is replaced with a CH$_3$ group and therefore the supramolecular synthon is the result of a C–H···O=C mediated homosynthon instead of a N–H···O=C homosynthon. Form III has been reported to be the most thermodynamically stable phase at room temperature and the one selected for use herein [63]. Interestingly, the dihydrate structure of CBZ forms N–H···O hydrogen bonds via the anti-oriented N–H of the amide group in addition to the two-point primary amide homosynthon and is even less soluble in water than the pure forms [60]. It is this low solubility of CBZ in water that makes it difficult to further extend its utility as a pharmaceutical and justifies CBZ as a candidate for a search for more crystalline phases.

In this contribution, we present two basic strategies for such a search, both of which might be generally applicable to APIs that contain primary amide moieties.

6.2 Strategy 1

Strategy 1 exploits the exofunctional nature of the primary amide dimer as either a hydrogen bond donor or a hydrogen bond acceptor and thereby retains the primary amide dimer that is present in all previously isolated forms of CBZ.

While all co-crystals and solvates generated from strategy 1 retain the primary amide dimer motif, there are two distinct modes by which they exploit their remaining H-bonding sites: H-bond donor of CBZ to the H-bond acceptor of co-crystal former (CBZ/benzoquinone, A (fig. 24); CBZ/4,4’-bipyridine, B (fig. 25); and both H-bond
donor and H-bond acceptors of the CBZ to H-bond donor and H-bond acceptor sites of the co-crystal former or solvent molecule (CBZ/cinnamic acid, C (fig. 26); CBZ/formamide solvate, D (fig. 27).

6.3 Structures

6.3.1 CBZ / benzoquinone 2:1 (A)

The asymmetric unit of A (fig. 24) consists of one molecule of CBZ and a half molecule of benzoquinone. The primary amide dimer [NH···O 2.900 Å] is observed between inversion related CBZ molecules, and the benzoquinone molecules lie around crystallographic inversion centers. The benzoquinone molecules are held by the anti N–H···O hydrogen bond of the CBZ dimers [NH···O 3.126Å] and not only generate a void space between the CBZ dimers but also sustain a one-dimensional ribbon due to the presence of two acceptor sites.

Figure 24. CBZ / benzoquinone 2:1 pharmaceutical co-crystal.
6.3.2 CBZ / 4,4'-bipyridine 2:1 (B)

The crystal structure of B reveals that the CBZ amide dimer remains intact and the pyridine moieties act as acceptors to the anti- oriented NHs of CBZ (fig. 25). There are 10 CSD structures that exhibit the same type of motif with a pyridine moiety [64] and the mean bond length for the (amide)N–Hₐ···N (pyridine) interaction is 3.06(7) Å. B exhibits two unique N–Hₐ···N bond lengths, 2.967 and 2.992 Å, as well as two distinct primary amide dimer bond lengths of 2.908 and 2.880 Å.

![Figure 25. CBZ / 4,4'-bipyridine 2:1 pharmaceutical co-crystal.](image)

6.3.3 CBZ / cinnamic acid 1:1 (C)

In structure C, the CBZ primary amide dimer is intact and is linked with each consecutive dimer by exterior hydrogen bonding with cinnamic acid (fig. 26). The primary amide dimer bond length of 2.956(17) Å is very close to the mean of 2.95(5) Å for this interaction. The mean bond length for the (amide)N–H···O(acid) interaction is 2.96(8) Å and was found to be 3.039(18) Å for C, while the mean for the (acid)O–H···O(amide) is 2.56(6) Å and was 2.621(15) Å in this structure.
6.3.4 CBZ / formamide solvate 1:1 (D)

The CBZ / formamide solvate, D (fig. 27), is a rare example of a crystal structure that contains two chemically different amide groups that each form primary amide homosynthons that interact only by peripheral hydrogen bonding, thereby forming an amide-amide’ alternating tape. The pure forms of CBZ do not exhibit this tape motif, most likely due to the sterically bulky azepine rings. In the structure D, the formamide and CBZ dimers alternate through exterior hydrogen bonding. There are two inversion related CBZ dimers, denoted 1 and 2, that generate a two-dimensional hydrogen bonded pattern.
6.4 Synthesis and Characterization

Melting points for structures are presented in Table 4 along with melting points for starting materials.

Table 4. Melting points of starting materials and structures, A-D.

<table>
<thead>
<tr>
<th>Co-crystal/Solvate</th>
<th>Starting Materials [ºC]</th>
<th>Structure [ºC]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. CBZ / benzoquinone (1:1)</td>
<td>191-192</td>
<td>116</td>
</tr>
<tr>
<td>B. CBZ / 4,4’-bipyridine (1:1)</td>
<td>191-192</td>
<td>111-114</td>
</tr>
<tr>
<td>C. CBZ / cinnamic acid (1:1)</td>
<td>191-192</td>
<td>133</td>
</tr>
<tr>
<td>D. CBZ / formamide solvate (1:1)</td>
<td>191-192</td>
<td>2.5</td>
</tr>
</tbody>
</table>

6.4.1 CBZ / benzoquinone 2:1 (A)

*Synthesis:* Colorless crystals were obtained within five days via slow evaporation of a solution containing Carbamazepine (0.037 g, 0.157 mmol) and benzoquinone (0.008 g, 0.078 mmol) dissolved in 1 ml of methanol.

*Crystal data:* (Bruker SMART-APEX CCD Diffractometer) Appendix D.

*Melting Point:* (Mel-temp®) 170°C.

*Infrared Spectroscopy:* (Nicolet Avatar 320 FTIR) 3420 cm⁻¹ (Amide NH stretch); 3190 cm⁻¹ (C-H stretch, alkene); 1672 cm⁻¹ (C=O); 1587 cm⁻¹ (C=C).


6.4.2 CBZ / 4,4’-bipyridine 2:1 (B)

*Synthesis:* Colorless crystals were obtained within three days via slow evaporation of a solution containing Carbamazepine (0.030 g, 0.127 mmol) and 4,4’- bipyridine (0.027 g, 0.127 mmol) dissolved in 2 ml of 50:50 mixture of THF/CS₂.

*Crystal data:* (Bruker SMART-APEX CCD Diffractometer) Appendix D.

*Melting Point:* (Mel-temp®) 152-160°C.

*Infrared Spectroscopy:* (Nicolet Avatar 320 FTIR) 3426 cm⁻¹ (Amide NH stretch); 3183 cm⁻¹ (C-H stretch, alkene); 1676 cm⁻¹ (C=O); 1566 cm⁻¹ (C=C).
**X-ray Powder Diffraction:** (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). XPD analysis (simulated): 9.03, 12.13, 13.49, 15.18, 26.95.

### 6.4.3 CBZ / cinnamic acid 1:1 (C)

**Synthesis:** Colorless crystals were obtained within five days via slow evaporation of a solution containing Carbamazepine (0.024 g, 0.100 mmol) and cinnamic acid (0.015 g, 0.100 mmol) dissolved in 1 ml of ethyl acetate.

**Crystal data:** (Bruker SMART-APEX CCD Diffractometer) Appendix D.

**Melting Point:** (Mel-temp®) 142-143°C.

**Infrared Spectroscopy:** (Nicolet Avatar 320 FTIR) 3433 cm\(^{-1}\) (Amide NH stretch); 3319 cm\(^{-1}\) (C-H stretch, alkene); 1702 cm\(^{-1}\) (C=O); 1573 cm\(^{-1}\) (C=C).

**X-ray Powder Diffraction:** (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). XPD analysis (experimental): 5.78, 9.91, 16.70, 21.82, 27.24.

### 6.4.4 CBZ / formamide solvate 1:1 (D)

**Synthesis:** Colorless crystals were obtained within six days via slow evaporation of a solution containing Carbamazepine (0.030 g, 0.127 mmol) dissolved in 1 ml of formamide.

**Crystal data:** (Bruker SMART-APEX CCD Diffractometer) Appendix D.

**Melting Point:** (Mel-temp®) 142-144°C.

**Infrared Spectroscopy:** (Nicolet Avatar 320 FTIR) 3392 cm\(^{-1}\) (Amide NH stretch); 3178 cm\(^{-1}\) (C-H stretch, alkene); 1684 cm\(^{-1}\) (C=O); 1590 cm\(^{-1}\) (C=C).

**X-ray Powder Diffraction:** (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). XPD analysis (simulated): 8.74, 13.15, 18.74, 26.12, 26.72.
6.5 Strategy 2

Strategy 2 breaks the CBZ primary amide dimer using co-crystal formers that are capable of two-point interactions, thereby forming a heterosynthon between the primary amide moiety of CBZ and a complementary functional group. In nine of following structures, six of which are pharmaceutical co-crystals and three of which are solvates of CBZ, the supramolecular primary amide heterosynthon is formed with a carboxylic acid moiety. The tenth structure is an ionic compound in which the deprotonated primary amide functional group forms a supramolecular heterosynthon with a sulfonic acid.

6.6 Structures

6.6.1 CBZ / acetylsalicylic acid 1:1 (E)

Co-crystallization of CBZ with acetylsalicylic acid (aspirin) resulted in a 1:1 co-crystal (fig. 28). The crystal structure reveals the expected amide-acid supramolecular heterosynthon formed through O–H···O [O···O 2.564(2) Å, 167.5°] and N–H···O [N···O 2.914(3) Å, 168.4°] hydrogen bonds. Interestingly, the closest contact with the anti-oriented N–H of the CBZ amide moiety is the carbonyl of the acetylsalicylic acid acetyl group with a distance of 3.187(2) Å.
6.6.2 CBZ / 4-Aminobenzoic acid 2:1 (F)

Co-crystal F also exhibits 2:1 stoichiometry and contains both the expected amide-acid supramolecular heterosynthon and a primary amide dimer. Two amide-acid supramolecular heterosynthons form a tetrameric motif, which is bonded to the primary amide dimers on each side through the amino N–H···O hydrogen bonds (fig. 29). This tetrameric motif is found in 9 of the 69 (13%) structures in the CSD that contain amide-acid supramolecular heterosynthons including CBZ solvates with acetic acid, formic acid and butyric acid [65]. The O–H···O and N–H···O hydrogen bond lengths for the amide-acid supramolecular heterosynthon are 2.540(1) Å and 2.982(2) Å, which compare to the mean values of 2.56(6) and 2.96(8) Å, respectively.
6.6.3 CBZ / 4-Aminobenzoic acid / H₂O 2:1:1 (G)

Co-crystallizing the same components as F in ethanol produced a 2:1:1 co-crystal hydrate of CBZ with 4-aminobenzoic acid and adventitious H₂O. The crystal packing of G is markedly different from that of F. It forms an eight molecule discrete unit through O–H⋯O and N–H⋯O hydrogen bonds that contains four CBZ molecules, two 4-aminobenzoic acid molecules and two water molecules (fig. 30). The insertion of the water molecule into the amide-acid supramolecular heterosynthon to form a different supramolecular heterosynthon is unusual but not unprecedented. Hydration or solvation of carboxylic acids by water or alcohol molecules as open or cyclic hydrogen bond motifs is a common phenomenon during crystallization [66] and water molecules have been thought to facilitate interactions in organic crystals [67].

The water molecules insert between the primary amide carbonyl and the acid OH, thereby sustaining 1-point N–H⋯O acid-amide supramolecular heterosynthons. The (amide) N–H⋯O (acid) bond length is 2.878(2) Å vs. a mean of 2.96(8) Å. Notably, the amide anti-oriented NH’s are not involved in hydrogen bonding.
6.6.4 CBZ / trimesic acid 1:1 (H)

A 1:1 supramolecular complex, H, of CBZ and trimesic acid (1,3,5-benzenetricarboxylic acid) was obtained (fig. 31). The structure consists of both carboxylic acid dimers and amide-acid supramolecular heterosynthons and forms a one-dimensional pattern. One carboxylic acid group of trimesic acid forms the amide-acid supramolecular heterosynthon with the primary amide moiety of CBZ, while carboxylic acid groups two and three of trimesic form carboxylic acid dimers.
6.6.5 CBZ / 5-nitroisophthalic acid 1:1 (I)

By replacing one carboxylic acid group in the trimesic acid with a size matching nitro group, the hydrogen-bonding pattern is converted into a discrete one. Co-crystallization of CBZ with 5-nitroisophthalic acid yielded a supramolecular complex (fig. 32) with disordered solvent molecules (not shown). Supramolecular complex I is isostructural with H and the crystal structure of I consists of a carboxylic acid dimer and an amide-acid supramolecular heterosynthon. The anti N–H group is activated by N–H···O hydrogen bonding with solvent molecules. Thus all hydrogen-bonding considerations are satisfied.

![Figure 32. CBZ / 5-nitroisophthalic acid 1:1 pharmaceutical co-crystal.](image)

6.6.6 CBZ / 2,6-pyridinedicarboxylic acid 1:1 (J)

CBZ was co-crystallized with 2,6-pyridinedicarboxylic acid from ethanol. The expected amide-acid supramolecular heterosynthon is not seen in this structure. Rather, the co-crystal exhibits an unusual hydrogen-bonding motif. Only one-point interactions are present, with each CBZ molecule bonding to three distinct acid molecules. It is
interesting to note that two carboxylic acid OH donors are hydrogen bonding with one amide carbonyl. The two (acid)O–H···O(amide) hydrogen bonds are in the normal distance and angle range [2.949(2) Å, 172°; 2.983(2) Å, 148.6°]. There is no disorder in the crystal structure and the protons are located in the difference Fourier map. The two acid OH donors are also involved in an intramolecular O–H···N [O···N 2.654, 2.681 Å] hydrogen bond with the pyridine moiety. This unusual hydrogen bonded motif (fig. 33) is stabilized through both intra- and intermolecular interactions thus forming an intricate hydrogen bonded network. While it is fairly common to have (acid)OH hydrogen bonding to a carbonyl, bifurcation [68] of a carbonyl (amide or simple ketone) to two (acid)OH groups without a 2-point supramolecular heterosynthon present is only seen in one structure from the CSD [69].

Figure 33. CBZ / 2,6-pyridinedicarboxylic acid 1:1 pharmaceutical co-crystal.
6.6.7 CBZ /acetic acid solvate 1:1 (K)

X-ray quality single crystals of K (fig. 34) were grown from acetic acid. The structure exhibits the expected amide-acid supramolecular heterosynthon, however, the \textit{anti}-oriented N–H of the amide moiety forms an inversion related N–H\textsubscript{a}⋯O hydrogen bond [2.919(2) Å] with the acetic acid carbonyl group, which generates a discrete 4-component supramolecular complex rather than a tape. The length of the amide-acid O–H⋯O hydrogen bond was found to be 2.553(2) Å. The orientation of CBZ azepine rings above and below the glide related hydrogen bonded complexes form a hydrophobic region.

![Figure 34. 4-component supramolecular complex of the 1:1 acetic acid solvate of CBZ.](image)

6.6.8 CBZ / formic acid solvate 1:1 (L)

Structure L (fig. 35) is isostructural with K. The tetrameric motif is replicated in this solvate of CBZ with formic acid. The N–H\textsubscript{a}⋯O hydrogen bond length is 2.894(2) Å, while the amide-acid O–H⋯O hydrogen bond length is 2.548(2) Å. The hydrophobic region is again present between the CBZ azepine rings of each tetramer.
6.6.9 CBZ / butyric acid solvate 1:1 (M)

Structure M (fig. 36) also exhibits the tetrameric motif, however, is not isostructural with K and L. The butyric alkyl groups fold, causing a bending of the N-H<sub>a</sub>···O bond [2.929(2) Å], presumably in order to facilitate the formation of the tetrameric motif. The (acid)O-H···O(amide) hydrogen bonds are in the normal distance range [2.589(2) Å].
6.6.10 CBZ / benzenesulfonate 1:1 (N)

Complex N (fig. 36) consists of a previously unknown heterosynthon. It exhibits a similar tetrameric motif as seen in previous CBZ / carboxylic acid structures. The CBZ primary amide carbonyl is protonated by the sulfonic acid making this a charge-assisted interaction. Protonated amides can be found in the CSD with nitric [70] and phosphoric acids [71], however; they have not been seen with sulfonic acids. Two supramolecular heterosynthons are joined by both remaining S=O groups bonding to the anti-oriented amide NH’s.

![Figure 37. 4-component supramolecular complex of the 1:1 CBZ benzenesulfonate.](image)

6.7 Synthesis and Characterization

Melting points for structures are presented in Tables 5-6 along with melting points for starting materials.

Table 5. Melting points of starting materials and structures, E-I.

<table>
<thead>
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<th>Co-crystal</th>
<th>Starting Materials [ºC]</th>
<th>Co-crystal [ºC]</th>
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<tr>
<td>A. CBZ / acetylsalicylic acid (1:1)</td>
<td>191-192</td>
<td>135</td>
</tr>
<tr>
<td>B. CBZ / 4-aminobenzoic acid (1:1)</td>
<td>191-192</td>
<td>189</td>
</tr>
<tr>
<td>C. CBZ / 4-aminobenzoic acid hydrate (2:1:1)</td>
<td>191-192</td>
<td>189</td>
</tr>
<tr>
<td>D. CBZ / trimesic acid (1:1)</td>
<td>191-192</td>
<td>380</td>
</tr>
<tr>
<td>E. CBZ / 5-nitroisophthalic acid (1:1)</td>
<td>191-192</td>
<td>260-261</td>
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[62]
Table 6. Melting points of starting materials and structures, J-N.

<table>
<thead>
<tr>
<th>Co-crystal/Salt</th>
<th>Starting Materials [ºC]</th>
<th>Structure [ºC]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. CBZ / 2,6-pyridinedicarboxylic acid (1:1)</td>
<td>191-192</td>
<td>245-250</td>
</tr>
<tr>
<td>B. CBZ / acetic acid solvate (1:1)</td>
<td>191-192</td>
<td>16.6</td>
</tr>
<tr>
<td>C. CBZ / formic acid solvate (1:1)</td>
<td>191-192</td>
<td>8.4</td>
</tr>
<tr>
<td>D. CBZ / butyric acid solvate (1:1)</td>
<td>191-192</td>
<td>-7.9</td>
</tr>
<tr>
<td>E. CBZ benzenesulfonate (1:1)</td>
<td>191-192</td>
<td>43-44</td>
</tr>
</tbody>
</table>

6.7.1 CBZ / acetylsalicylic acid 1:1 (E)

*Synthesis:* Colorless crystals were obtained within one day via slow evaporation of a solution containing Carbamazepine (0.024 g, 0.100 mmol) and acetylsalicylic acid (0.018 g, 0.100 mmol) dissolved in 1 ml of ethyl acetate.

*Crystal data:* (Bruker SMART-APEX CCD Diffractometer) Appendix E.

*Melting Point:* (Mel-temp®) 125-126 ºC.

*Infrared Spectroscopy:* (Nicolet Avatar 320 FTIR) 3422 cm⁻¹ (Amide NH stretch); 3216 cm⁻¹ (C-H stretch, alkene); 1691 cm⁻¹ (C=O); 1606 cm⁻¹ (C=C).


6.7.2 CBZ / 4-aminobenzoic acid 2:1 (F)

*Synthesis:* Yellow crystals were obtained within three days via slow evaporation of a solution containing Carbamazepine (0.014 g, 0.059 mmol) and 4-aminobenzoic acid (0.016 g, 0.118 mmol) dissolved in 1 ml of methanol.

*Crystal data:* (Bruker SMART-APEX CCD Diffractometer) Appendix E.

*Melting Point:* (Mel-temp®) 185-187 ºC.

*Infrared Spectroscopy:* (Nicolet Avatar 320 FTIR) 3460 cm⁻¹ (Amide NH stretch); 3162 cm⁻¹ (C-H stretch, alkene); 1673 cm⁻¹ (C=O); 1603 cm⁻¹ (C=C).

6.7.3 CBZ / 4-aminobenzoic acid / H₂O 2:1:1 (G)

Synthesis: Yellow crystals were obtained within three days via slow evaporation of a solution containing CBZ (0.015 g, 0.063 mmol) and 4-aminobenzoic acid (0.0087 g, 0.063 mmol) dissolved in 1 ml of ethanol.

Crystal data: (Bruker SMART-APEX CCD Diffractometer) Appendix E.

Melting Point: (Mel-temp®) 143°C.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR) 3480 cm⁻¹ (Amide NH stretch); 3217 cm⁻¹ (C-H stretch, alkene); 1658 cm⁻¹ (C=O); 1547 cm⁻¹ (C=C).


6.7.4 CBZ / trimesic acid 1:1 (H)

Synthesis: Colorless crystals were obtained within seven days via slow evaporation of a solution containing Carbamazepine (0.036 g, 0.152 mmol) and trimesic acid (0.032 g, 0.152 mmol) dissolved in 4 ml of a 50:50 mixture of methanol and dichloromethane.

Crystal data: (Bruker SMART-APEX CCD Diffractometer) Appendix E.

Melting Point: (Mel-temp®) 278°C (dec).

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR) 3486 cm⁻¹ (Amide NH stretch); 3206 cm⁻¹ (C-H stretch, alkene); 1688 cm⁻¹ (C=O); 1602 cm⁻¹ (C=C).


6.7.5 CBZ / 5-nitroisophthalic acid 1:1 (I)

Synthesis: Yellow crystals were obtained within four days via slow evaporation of a solution containing Carbamazepine (0.015 g, 0.123 mmol) and 5-nitroisophthalic acid (0.017 g, 0.123 mmol) dissolved in 1 ml of methanol.

Crystal data: (Bruker SMART-APEX CCD Diffractometer) Appendix E.

Melting Point: (Mel-temp®) 190°C (dec).
**Infrared Spectroscopy:** (Nicolet Avatar 320 FTIR) 3470 cm\(^{-1}\) (Amide NH stretch); 3178 cm\(^{-1}\) (C-H stretch, alkene); 1688 cm\(^{-1}\) (C=O); 1602 cm\(^{-1}\) (C=C).


### 6.7.6 CBZ / 2,6-pyridinedicarboxylic acid 1:1 (J)

**Synthesis:** Colorless crystals were obtained within one half hour via slow evaporation of a solution containing Carbamazepine (0.034 g, 0.144 mmol) and (0.024 g, 0.144 mmol) dissolved in 1 ml of ethanol.

**Crystal data:** (Bruker SMART-APEX CCD Diffractometer) Appendix F.

**Melting Point:** (Mel-temp\®) 214-216°C.

**Infrared Spectroscopy:** (Nicolet Avatar 320 FTIR) 3439 cm\(^{-1}\) (Amide NH stretch); 3186 cm\(^{-1}\) (C-H stretch, alkene); 1734 cm\(^{-1}\) (C=O); 1649 cm\(^{-1}\) (C=C).

**X-ray Powder Diffraction:** (Rigaku Miniflex Diffractometer using CuK\(_\alpha\) \((\lambda=1.540562)\), 30kV, 15mA). XPD analysis (simulated): 7.85, 13.09, 14.58, 17.98, 25.94, 27.41, 29.06.

### 6.7.7 CBZ / acetic acid solvate 1:1 (K)

**Synthesis:** Colorless crystals were obtained within five days via slow evaporation of a solution containing Carbamazepine (0.024 g, 0.100 mmol) dissolved in 1 ml of acetic acid.

**Crystal data:** (Bruker SMART-APEX CCD Diffractometer) Appendix F.

**Melting Point:** (Mel-temp\®) 187°C.

**Infrared Spectroscopy:** (Nicolet Avatar 320 FTIR) 3462 cm\(^{-1}\) (Amide NH stretch); 3315 cm\(^{-1}\) (C-H stretch, alkene); 1699 cm\(^{-1}\) (C=O); 1629 cm\(^{-1}\) (C=C).

6.7.8 CBZ / formic acid solvate 1:1 (L)

Synthesis: Colorless crystals were obtained within five days via slow evaporation of a solution containing Carbamazepine (0.024 g, 0.100 mmol) dissolved in 1 ml of formic acid.

Crystal data: (Bruker SMART-APEX CCD Diffractometer) Appendix F.

Melting Point: (Mel-temp®) 187°C.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR) 3439 cm\(^{-1}\) (Amide NH stretch); 3318 cm\(^{-1}\) (C-H stretch, alkene); 1692 cm\(^{-1}\) (C=O); 1633 cm\(^{-1}\) (C=C).


6.7.9 CBZ / butyric acid solvate 1:1 (M)

Synthesis: Colorless crystals were obtained within six days via slow evaporation of a solution containing Carbamazepine (0.024 g, 0.100 mmol) dissolved in 1 ml of butyric acid.

Crystal data: (Bruker SMART-APEX CCD Diffractometer) Appendix F.

Melting Point: (Mel-temp®) 120°C.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR) 3486 cm\(^{-1}\) (Amide NH stretch); 3307 cm\(^{-1}\) (C-H stretch, alkene); 1684 cm\(^{-1}\) (C=O); 1540 cm\(^{-1}\) (C=C).


6.7.10 CBZ / benzenesulfonate 1:1 (N)

Synthesis: Yellow crystals were obtained within four days via slow evaporation of a solution containing Carbamazepine (0.024 g, 0.100 mmol) and benzenesulfonic acid (0.016 g, 0.100 mmol) dissolved in 1 ml of ethyl acetate.

Crystal data: (Bruker SMART-APEX CCD Diffractometer) Appendix F.

Melting Point: (Mel-temp®) 118-122°C.
**Infrared Spectroscopy:** (Nicolet Avatar 320 FTIR) 3462 cm\(^{-1}\) (Amide NH stretch); 3171 cm\(^{-1}\) (C-H stretch, alkene); 1649 cm\(^{-1}\) (C=O); 1583 cm\(^{-1}\) (C=C).


**6.8 Discussion**

The focus of this study is the understanding of the primary amide functional group and its hydrogen bonding capabilities; as well as the synthesis of multiple-component crystalline phases in order to develop a method for the design of pharmaceutical co-crystals using API’s that contain a primary amide functional group.

The pharmaceutically active molecule carbamazepine (CBZ) is a well-known drug used in the treatment of epilepsy and trigeminal neuralgia and was chosen as a candidate for this crystal engineering case study due to its limited bioavailability, limited solubility in water, and the existence of multiple crystalline forms.

The key supramolecular synthon in CBZ is the primary amide moiety, which has already been shown to be a reliable supramolecular synthon in the formation of multiple-component crystalline architectures [51,72].

Two basic strategies were employed to exploit the hydrogen bonding capabilities of the primary amide moiety found in CBZ. **Strategy 1** takes advantage of the exofunctional nature of the primary amide dimer as either a hydrogen bond donor or a hydrogen bond acceptor and in so doing retains the primary amide dimer that is present in all previously isolated forms of CBZ. **Strategy 2** breaks the CBZ primary amide dimer using co-crystal formers that are capable of two-point interactions, thereby forming a supramolecular heterosynthon between the primary amide moiety of CBZ and the
complementary functional group of a co-crystal former or solvate molecule. The results of these two strategies are 9 pharmaceutical co-crystals, 4 solvates, and 1 salt of this well-studied API.

Of the 10 CBZ structures containing a carboxylic acid co-crystal former, 9 (90%) exhibit the expected primary amide-carboxylic acid supramolecular heterosynthon. It would seem there is a high degree of predictability regarding the hydrogen bonding preferences of these two groups. Further research is needed in order to support any observations regarding the hydrogen bonding preferences between these selected functionalities.

In summary, we have shown that it is possible to exploit an API containing a primary amide moiety for the formation of a diverse range of multiple-component crystalline phases by utilizing appropriate co-crystal formers. This paradigm of modular design means that even without covalent modification a wide range of new compositions of matter are readily accessible utilizing existing APIs.
Chapter 7

Conclusions

Crystal engineering can be defined as the application of supramolecular chemistry to the solid state. Although it was initially introduced in the context of stereochemical control of photochemical reactions [2], it has most recently evolved into a form of supramolecular synthesis for new solid phases using directional and reproducible molecular recognition events known as supramolecular synthons. The work of this thesis is based upon the exploitation of these supramolecular synthons in order to rationally design multiple component crystalline phases or co-crystals with predictable stoichiometry and architecture.

The potential impacts of co-crystals appear to be quite broad. They have been shown to be applicable to many types of studies including new classes of NLO materials [20], organic solid-state synthesis [21], reformulation of APIs [4,11,19], design of host-guest systems [17] and delineation of the hierarchy of hydrogen bonded supramolecular synthons in competitive situations [29].

Crystal structures are unpredictable by nature, however, the interactions that lead to crystal formation are becoming much more predictable. By means of model compound studies, the delineation of the hierarchy of hydrogen bonding between complementary
functional groups or supramolecular heterosynthons can be accomplished. Competitive co-crystallization studies along with data extracted from the Cambridge Structural Database (CSD) can be utilized in understanding the reliability of supramolecular heterosynthons without the need for endless co-crystallization experiments which involve numerous variables including, but not limited to temperature, solvent selection, concentration, and crystallinity and packing efficiency of the starting materials.

Co-crystals are typically synthesized by slow evaporation from solution that contains stoichiometric amounts of the parent compounds; however, sublimation, growth from the melt, slurry conversion and grinding are also suitable methodologies.

Techniques used for the characterization of co-crystals include single crystal x-ray diffraction, infrared spectroscopy, differential scanning calorimetry, thermogravimetric analysis, melting point apparatus, and powder x-ray diffraction.

In effect, this ability to understand supramolecular heterosynthons, along with knowledge of optimal crystallization and characterization techniques, can allow crystal engineers to reasonably design co-crystals with a high rate of success. Using a rational design plan, supramolecular synthesis of 17 new structures containing both a primary amide and a carboxylic acid functional group was achieved, wherein 15 of the 17 structures (88%) exhibit the amide-acid supramolecular heterosynthon. In this contribution, it has been demonstrated that, whereas functional groups can exhibit varied hydrogen bonding motifs, there is some degree of predictability in the formation of supramolecular heterosynthons.

Although co-crystals have been recognized for decades, they have only recently been of interest in the pharmaceutical industry due to the fact that they are amenable to
control and design (crystal engineering) in a manner not possible with other forms of API's such as salts, solvates, and polymorphs. Also, as APIs can exhibit problems ranging from poor solubility, polymorphism and inadequate dissolution properties to lack of crystallinity and instability, pharmaceutical co-crystals offer an opportunity to increase the number of forms of an API and to address some these problems.

It has been suggested that pharmaceutical co-crystals could play a significant part in the future of API formulation since in principle they will outnumber pharmaceutical salts, polymorphs and solvates combined.

The relevance of crystal engineering in API formulation includes the ability to fine-tune physical properties without changing the molecular structure of the API, identification of novel forms of polymorphic API's, and the opportunity to generate a broader range of intellectual property than with present methods.
References


37. CSD Search Parameters: February 2005 update, 3D coordinates determined, R<7.5%, organics only.


52. CSD Search Parameters: February 2005 update, 3D coordinates determined, R<7.5%, organics only, excludes urea.


64. CSD refcodes: AMILEN, AMILUD, BATHOU, BOHJIR, JUYGUF, MFCBXB, PYRZIN, WUPZUC, WUQMIE AND ZAQTUG.

65. CSD refcodes: AJALAY, FURAOX, RAHGEM, UNEZIW, UNEZOC, UNEZUI, UROXAM, UROXAM01, XEWTIC, ZODWIY.


Appendices
### Appendix A: Crystallographic Data for Polymorphic Structures A-D

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### Appendix B: Crystallographic Data for Model Compound Structures A-E

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### Appendix C: Crystallographic Data for Piracetam Structures A-B

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### Appendix D: Crystallographic Data for Carbamazepine Structures A-D

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<td>1.439</td>
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<tr>
<td><strong>Solvent</strong></td>
<td>EtoAC</td>
<td>EtOH</td>
<td>MeOH</td>
<td>MeOH/CH₂Cl₂</td>
<td>MeOH</td>
</tr>
<tr>
<td><strong>Melting Point (°C)</strong></td>
<td>125-126</td>
<td>185-187</td>
<td>143</td>
<td>278(dec)</td>
<td>190(dec)</td>
</tr>
</tbody>
</table>
### Appendix F: Crystallographic Data for Carbamazepine Structures J-N

<table>
<thead>
<tr>
<th></th>
<th>J</th>
<th>K</th>
<th>L</th>
<th>M</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td><strong>Formula</strong></td>
<td>c22h17n4o5</td>
<td>c17h16n2o2</td>
<td>c16h14n2o3</td>
<td>c19h20n2o3</td>
<td>c21h18n2o4s</td>
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<tr>
<td><strong>Molecular Weight</strong></td>
<td>403.39</td>
<td>296.32</td>
<td>282.29</td>
<td>324.37</td>
<td>394.43</td>
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<tr>
<td><strong>Crystal System</strong></td>
<td>Orthorhombic</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
<td>Triclinic</td>
<td>Monoclinic</td>
</tr>
<tr>
<td><strong>Space Group</strong></td>
<td>P2(1)2(1)2(1)</td>
<td>P2(1)/c</td>
<td>P2(1)/c</td>
<td>P-1</td>
<td>P2(1)/n</td>
</tr>
<tr>
<td><strong>Temperature (K)</strong></td>
<td>153(2)</td>
<td>100(2)</td>
<td>100(2)</td>
<td>100(2)</td>
<td>100(2)</td>
</tr>
<tr>
<td><strong>a (Å)</strong></td>
<td>7.208(1)</td>
<td>5.1206(4)</td>
<td>5.2031(9)</td>
<td>9.1567(12)</td>
<td>13.8557(16)</td>
</tr>
<tr>
<td><strong>b (Å)</strong></td>
<td>14.644(3)</td>
<td>15.7136(13)</td>
<td>14.741(2)</td>
<td>10.1745(13)</td>
<td>8.0697(10)</td>
</tr>
<tr>
<td><strong>c (Å)</strong></td>
<td>17.577(4)</td>
<td>18.4986(15)</td>
<td>17.882(3)</td>
<td>10.5116(14)</td>
<td>16.847(2)</td>
</tr>
<tr>
<td><strong>α (deg)</strong></td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>72.850(3)</td>
<td>90</td>
</tr>
<tr>
<td><strong>β (deg)</strong></td>
<td>90</td>
<td>96.5460(10)</td>
<td>98.132(3)</td>
<td>70.288(2)</td>
<td>94.815(2)</td>
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<tr>
<td><strong>γ (deg)</strong></td>
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<td>90</td>
<td>90</td>
<td>67.269(2)</td>
<td>90</td>
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<tr>
<td><strong>Volume (Å³)</strong></td>
<td>1855.4(6)</td>
<td>1478.8(2)</td>
<td>1357.7(4)</td>
<td>834.91(19)</td>
<td>1877.0(4)</td>
</tr>
<tr>
<td><strong>Calc Density (mg/cm³)</strong></td>
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<tr>
<td><strong>Solvent</strong></td>
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<td>acetic acid</td>
<td>formic acid</td>
<td>butyric acid</td>
<td>EtoAC</td>
</tr>
<tr>
<td><strong>Melting Point (ºC)</strong></td>
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<td>187</td>
<td>187</td>
<td>63-64</td>
<td>118-122</td>
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