Crystal engineering of organic compounds including pharmaceuticals

Joanna A. Bis
University of South Florida

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Crystal Engineering of Organic Compounds Including Pharmaceuticals

by

Joanna A. Bis

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
Department of Chemistry
College of Arts and Sciences
University of South Florida

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Dedication

To my parents and grandparents
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Crystal Engineering of Organic Compounds Including Pharmaceuticals

Joanna Bis

ABSTRACT

Neutral or charge-assisted hydrogen bonds occurring between organic molecules represent strong and directional forces that mediate the molecular self-assembly into well defined supramolecular architectures. A proper understanding of hydrogen bonding interactions, their types, geometries, and occurrence in supramolecular motifs, is a prerequisite to crystal engineering, i.e. to the rational design of functional solid materials.

Multiple-component organic crystals represent ideal systems to study the intermolecular interactions between the constituent molecules that can be pre-selected for their hydrogen bonding sites and geometrical capabilities. In particular, the systematic structural analysis of supramolecular systems that are comprised of simple molecules facilitates the development of strategies for the rational design of new multiple-component compounds involving more complex components such as drug molecules.

The work presented herein shows a combination of systematic database and experimental studies in the context of reliability and hierarchy of several hydrogen bonded supramolecular synthons that exist in a series of model co-crystals and organic salts. The acquired paradigms are ultimately utilized in crystal engineering of
pharmaceuticals. In addition, the viability of a mechanichemical approach toward supramolecular synthesis in the context of its efficacy and the effect on polymorphism in multiple-component compounds is also addressed.
Chapter 1 — Introduction

1.1. Supramolecular Chemistry

“Beyond molecular chemistry based on the covalent bond there lies the field of supramolecular chemistry, whose goal it is to gain control over the intermolecular bond”
Jean-Marie Lehn

1.1.1. Fundamentals

Supramolecular chemistry,\textsuperscript{1-3} known also as chemistry beyond the molecule,\textsuperscript{4} is based on the underlying phenomena of mutual affinity and selective recognition of molecules interacting via a variety of non-covalent forces to form well organized assemblies. The origin of supramolecular chemistry can perhaps be traced back to the 19\textsuperscript{th} century, when the concepts of lock-and-key,\textsuperscript{5} “Corpora non agunt nisi fixata” (agents cannot act unless they are bound),\textsuperscript{6} and Übermoleküle (supermolecule)\textsuperscript{7} emerged. Much of this discipline has been delineated by 1960’s and 1970’s research involving host-guest systems\textsuperscript{8} for selective binding of small alkali metal cations by macrocyclic receptors, which encompassed mostly crown ethers\textsuperscript{9} and cryptands.\textsuperscript{10} The continued fascination of molecular recognition phenomena illustrated by Nature (the self-assembly of DNA, antigen-antibody recognition, protein folding, etc.), inspired chemists to further explore supramolecular systems in the context of weaker intermolecular interactions such as hydrogen bonds and π-π stacking.\textsuperscript{11-17} In particular, the manipulation of intermolecular
interactions, that leads to spontaneous, but controllable self-assembly of complementary moieties, has become one of the major interests in supramolecular design.

The growing interest in the novel *supramolecular* approach can be considered as the manifestation of a conceptual change toward chemical synthesis.\(^\text{18}\) The emphasis on *interaction*, rather than *reaction* between molecules,\(^\text{19}\) has opened a great opportunity to generate a novel class of supramolecular structures, or *supermolecules*,\(^\text{20}\) with a wide range of complexity. Although supramolecular synthesis has not yet reached the level of sophistication represented by advanced organic syntheses (e.g. those of vitamin B\(_{12}\)\(^\text{21}\) and taxol\(^\text{22}\)), the influx of progress in this field has indicated its potential to generate recognition-directed assemblies in simple procedures and without the need of making or breaking covalent bonds.

1.1.2.  Supramolecular Interactions and the Role of Hydrogen Bonds

Generally, chemical bonds are considered to fall into two categories: short-range and long-range.\(^\text{23}\) While the short-range forces (e.g. covalent) are responsible for the formation of molecular systems, the long-range interactions, including dipole-dipole interactions, \(\pi-\pi\) stacking, and hydrogen bonds, are those that contribute to the association of molecules into supramolecular structures with defined stoichiometries. Thus, a thorough knowledge of the non-covalent bonds, their various types and their relative strengths is of crucial importance in the context of controlling supramolecular assemblies. A general comparison of selected chemical bond types is presented in Table 1.1.
Table 1.1. Comparison of selected chemical bond types and their features

<table>
<thead>
<tr>
<th>Chemical Bonds</th>
<th>Bond Energies (kJ/mol)</th>
<th>Building blocks</th>
<th>Products</th>
<th>Features</th>
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<tr>
<td>Covalent</td>
<td>200 - 400</td>
<td>Atoms</td>
<td>Molecules</td>
<td>$\Delta H &gt; T \Delta S$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MW: 1 - 1000 Da</td>
</tr>
<tr>
<td>Hydrogen Bond</td>
<td>4 - 120</td>
<td></td>
<td>Molecules</td>
<td>$\Delta H \approx T \Delta S$</td>
</tr>
<tr>
<td>Dipole-Dipole</td>
<td>5 - 50</td>
<td></td>
<td>Supermolecules</td>
<td>MW: 1 - 100 kDa</td>
</tr>
<tr>
<td>$\pi-\pi$ stacking</td>
<td>&lt; 50</td>
<td></td>
<td></td>
<td>Solvent effect: Primary</td>
</tr>
<tr>
<td>Van der Waals</td>
<td>&lt; 5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“…I believe that as the methods of structural chemistry are further applied to physiological problems it will be found that the significance of the hydrogen bond for physiology is greater than that of any other single structural feature.”

Linus Pauling

In particular, hydrogen bonds\textsuperscript{24-26} are very important in the context of molecular recognition and, as anticipated at early stages by L. Pauling,\textsuperscript{27} they are responsible for numerous phenomena occurring in biological systems. Due to their strength and directionality, the role of hydrogen bonds in the formation of supramolecular assemblies has been studied with respect to molecular association in both solution and solid state.\textsuperscript{14,25,28-39} Specifically, the pre-determined formation of supramolecular species mediated via hydrogen bonds in the solid state, has become a foundation for generating novel materials with well defined structures and useful properties.

1.2. Crystal Engineering

“Crystal engineering is the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties”

Gautam Desiraju
1.2.1. Fundamentals

In an ultimate case of molecular recognition, molecules associate into a perfectly organized, single chemical entity held by periodic, three dimensional arrays of non-covalent forces, thereby generating a crystal. As the formation of crystalline architectures involves a series of complex molecular recognition events that occur at a high level of precision, crystals have been described as the “supermolecules par excellence”.40 The idea of applying the principles delineated by supramolecular chemistry to solid state for the rational design of novel crystalline materials, has led to the development of the new field of crystal engineering.41-43 The term “crystal engineering” was originally introduced in 1955 by Pepinsky,44 who demonstrated that crystallization of organic ions with metal-containing complexes results in structures with controllable cell dimensions and symmetries. Subsequently, from an important work of Schmidt45 related to the solid-state photodimerization, it became clear that a crystal can be thought as a self-assembly resulting from a series of molecular recognition events and that the physicochemical properties of a crystal depend upon the internal arrangement of the molecules in the crystal lattice. Now, as illustrated by Desiraju’s definition,41 crystal engineering has become synonymous with a broader discipline of “making crystals by design”42 toward the utilization of their specific properties. In particular, the area of organic compounds has witnessed a remarkable expansion in result of crystal engineered materials for specific applications, e.g.: non-linear optics (NLO),46 porous materials,47 photographic materials,48 and pharmaceuticals.49
Although the field of crystal engineering is indirectly related to the prediction of the ultimate crystal structure of the designed compound, it should be noted that there are fundamental differences between the two research areas.\textsuperscript{43} Crystal structure prediction (CSP) requires specification of molecular geometry and orientation, unit cell dimensions and the space group. In contrast, crystal engineering is much less restrictive in the perspective that it involves the design of crystals with well defined non-covalent connectivities and networks based upon pre-selected molecular components that possess specific moieties.

“One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition”

John Maddox

A comprehensive prediction of the lowest energy crystal structure through computational methods\textsuperscript{50} still remains elusive,\textsuperscript{51-58} although the field is advancing rapidly.\textsuperscript{59-61} As highlighted by Maddox,\textsuperscript{62} the prediction of an unknown crystal structure in a complete fashion remains a formidable challenge, and supramolecular synthesis of crystals has alternatively been directed toward empirical approaches, based upon analysis of crystal packing modes present in selected sets of existing crystal structures. With the aid of extended databases, the broader anticipation of structural patterns resulting from molecular recognition has become an inherent practice in crystal engineering. In this respect, the suitability of hydrogen bonds to generate pre-determined motifs has already been mentioned. In particular, a solid knowledge of the hydrogen bonding capabilities and geometrical complementarities exhibited by specific moieties as well as a rational
selection of molecular building blocks can afford novel compounds with pre-defined composition and supramolecular architectures.

1.2.2. Hydrogen Bonded Supramolecular Synthons

“Supramolecular synthons are structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions”

Gautam Desiraju

Given that the ultimate organization of molecules in a crystal, or crystal packing, results de facto from a series of molecular recognition phenomena, crystal engineering has naturally emerged around the idea of establishing, and later utilizing, intermolecular connectivities that are strong and directional enough to govern crystal packing with a reasonable degree of predictability. In this respect and based upon the analogy to covalent synthesis,63 the term supramolecular synthon64 has been introduced. Supramolecular synthons, also called motifs65 or patterns,66 can be regarded as regions within a crystal structure where the recognition between the constituent functional groups occurs, and this retrosynthetic approach67 helps to simplify the intrinsically difficult task of analyzing supramolecular architectures in the solid state.51,54 Considering that neutral and charge-assisted68-74 hydrogen bonds have been recognized as the most important non-covalent interactions in solid state supramolecular chemistry,25,39 it is not surprising that the utilization of hydrogen bonded supramolecular synthons in crystal engineering of organic solids has become ubiquitous.41,75-79 Supramolecular synthons can be separated into two distinct categories: supramolecular homosynthons,80 that result from the interaction
between alike, self-complementary functional groups and *supramolecular heterosynthons*,\(^8^0\) composed of different but complementary functional groups. Examples of supramolecular homosynthons include the carboxylic acid\(^8^1,8^2\) and amide dimers,\(^8^3\) whereas supramolecular heterosynthons include carboxylic acid···amide,\(^8^4-8^7\) hydroxyl···pyridine,\(^8^8-9^0\) and carboxylic acid···pyridine.\(^8^0,9^1-9^5\) Examples of a supramolecular homosynthon and heterosynthon is presented in Figure 1.1.

![Figure 1.1. Examples of supramolecular synthons: carboxylic acid homosynthon (left) and carboxylic acid···pyridine heterosynthon (right)](image)

Supramolecular homosynthons tend to exist in structures of single-component compounds, although their existence has also been observed in several crystals comprised by, for example, two different carboxylic acids.\(^9^6-9^8\) On the other hand, if multiple functional groups are present, it is more likely that they would engage in supramolecular heterosynthons. Furthermore, if a preferential supramolecular heterosynthon can be formed between functional groups that are located on different molecules, a multi-component compound would be generated. In this respect, a better understanding of the interplay between supramolecular synthons facilitated by the interpretation of existing crystal structures would help in the design of new multiple-component crystals. Specifically, the general trends observed in a series of relevant crystal structures, in terms of the prevalence of specific supramolecular synthons over others, would provide a
valuable insight for crystal engineering strategies toward the generation of new multiple-component materials comprised of polyfunctional (therefore more complex) molecules.

1.2.3. The Cambridge Structural Database

“…studies of individual structures are of limited value: if an unexpected structural feature is observed, it may not be statistically significant and may well be ascribed to experimental errors or packing effects. (…) Thus, the systematic analysis of large numbers of related structures is a powerful research technique, capable of yielding results that could not be obtained by any other method.”

Frank Allen, et al.

The identification and analysis of specific supramolecular synthons existing in a large set of correlated crystal structures in order to assess their general organizational tendencies is now a prerequisite for crystal engineering. In this regard, investigating hundreds of thousands of crystal structures reported to date is currently facilitated by the Cambridge Structural Database, CSD.99 As a collection of X-ray and neutron diffraction data for over 350,000 organic and organometallic compounds (ConQuest V1.7, August 2005), the CSD provides a great amount of statistically valuable information regarding the molecular and supramolecular structure of these compounds.100-103 In the context of the later, the quantitative (frequency of occurrence) and qualitative (geometrical attributes: distances, angles, etc.) analyses of intermolecular interactions allow for a comprehensive evaluation of the robustness of supramolecular synthons. In particular, earlier reports from Etter66,75,76 and Desiraju64,104 have concentrated on the investigation of hydrogen bonding patterns with the aid of the CSD and they have contributed to the proliferation of hydrogen bonded supramolecular synthons as design tools in crystal
1.3. Hydrogen Bonded Organic Co-crystals

“There is still plenty of room at the bottom”

Richard Feynman

The physicochemical properties of a crystalline material are inherently dependant upon the chemical nature of its constituents and the crystal packing. The properties of a compound can therefore be changed if the internal arrangement of molecules is altered.\textsuperscript{105} An alternative to influence the crystal packing of a compound can be based on the manipulation of the non-covalent forces that hold the constituents together, by introduction of another, rationally pre-selected for its hydrogen bonding sites, component. In effect, a multi-component compound, or a co-crystal, results. The meaning of the term co-crystal is currently a subject of debate.\textsuperscript{106,107} A broad definition of a co-crystal given by Dunitz: “a crystal containing two or more components together”\textsuperscript{107} would include molecular adducts, salts, solvates/hydrates, inclusion compounds, etc. In a more specific perspective taken by others\textsuperscript{49,108} a co-crystal is perceived as a \textit{multiple component crystal formed between compounds that are solid under ambient conditions: at least one component is molecular and forms a supramolecular synthon with the remaining components}. That all components of a co-crystal (co-crystal formers) are solids under ambient conditions has important implications with respect to the stability of a co-crystal and its susceptibility for preparation in the solid-state.

In light of the above description, co-crystals have been encountered in the
literature for a long time under various terms, e.g. molecular compounds, addition compounds, molecular complexes, solid-state complexes, or heteromolecular crystals. The first co-crystals appeared during the 19th century. A prototypal example of co-crystallization is perhaps the synthesis of p-benzoquinone and hydroquinone (quinhydrone), reported in 1844 by Wöhler, which was then followed by studies of halogen derivatives of quinhydrone. Structural information about quinhydrone (Figure 1.2), however, was not available until the 1960's. Inspired by the elucidation of DNA structure through X-ray analysis, numerous nucleobase complexes were reported in the 1950’s and 60’s. The molecular recognition between methyl derivatives of adenine and thymine is presented in Figure 1.3.

Figure 1.2. Crystal structure of the triclinic form of quinhydrone

Figure 1.3. The Hoogsteen base-pairing in the structure of 9-methyladenine 1-methylthymine co-crystal
Although long known, co-crystals are not as widely studied as single-component crystals or solvates. There are ca. 1,487 hydrogen bonded molecular co-crystals which constitute only ca. 0.42% of all structures archived in the CSD, as compared to 35,882 hydrates (ca. 10%). However, based upon the increasing number of relevant literature, it is clear that the interest in co-crystals is growing, Figure 1.4. The salient feature of co-crystals is that they can be designed from first principles. An appropriate knowledge of the supramolecular chemistry of the functional groups present in a given molecule can facilitate selection of an appropriate co-crystal fromer which will form supramolecular heterosynthon(s) with the target molecule.

In summary, co-crystals constitute a particularly attractive class of compounds that can be studied toward fundamental aspects such as: modification of physicochemical properties, understanding non-covalent interactions, viability toward green chemistry preparation, polymorphism, etc.
1.3.1. Co-Crystals in the Context of Investigation of Supramolecular Heterosynthons

The challenge of qualitative classification of hydrogen bonded motifs was addressed by Etter et al., based upon a graph-set system.\textsuperscript{75} In this approach, hydrogen bonded patterns can be described as chains (C), dimers (D), rings (R), or intramolecular hydrogen bonds (S). Each specific descriptor is then followed by the number of proton acceptors (superscript), number of proton donors (subscripts) and the number of atoms involved in a particular motif. For instance, R\textsuperscript{2}_{2}(8) notation is used to describe an eight-membered ring with two hydrogen bond acceptors and two hydrogen bond donors, and can be exemplified by carboxylic acid and amide homosynthons, or carboxylic acid···amide and carboxylic acid···pyridine heterosynthons. Graph-sets are useful to evaluate the frequency of a given hydrogen bonding pattern, however, they do not provide information related to the types of proton donors and proton acceptors engaged in the pattern. Therefore the frequency of supramolecular heterosynthons composed of specific hydrogen bond donors/acceptors could not be addressed via the graph-set systematization.

As already mentioned, a thorough understanding of supramolecular heterosynthons is a prerequisite for developing crystal engineering of co-crystals. On the other hand, co-crystals represent ideal systems for systematic studies of non-covalent heterointeractions, as the majority of co-crystals is sustained by supramolecular heterosynthons rather than supramolecular homosynthons.\textsuperscript{124-127} Based on earlier studies of Robertson and Donohue,\textsuperscript{128} and from the work in the context of utilizing co-crystals to delineate hydrogen bonding preferences, Etter proposed several hydrogen bonding rules,
one of which states: “the best hydrogen-bond donor and the best hydrogen-bond acceptor will preferentially form hydrogen bonds to one another”. For instance, the studies based upon co-crystallizations of 2-aminopyrimidine (hydrogen bond acceptor) with two carboxylic acids of different strengths (hydrogen bond donors) revealed selective binding of the 2-aminopyrimidines to the stronger acid. These and related results were rationalized based upon the differences in pKₐ values of the interacting molecules. It should be noted, however, that there have been inconsistencies with the above rule, as exemplified by co-crystals, in which carboxylic acid moieties interact with the weaker, rather than the stronger sites of a basic co-crystal former. Such observations suggest that the differences in pKₐ may not reliably predict the interactions between the components in co-crystals. Considering that the pKₐ is a property of solution that is not defined in crystals, such relationships may not be simply transferred to the solid state.

In the context of systematization of different hydrogen bonded synthons, Aakeröy et al. presented systematic studies of the competition between three distinct hydrogen bonding moieties: primary amide, pyridine, and carboxylic acid. The study involved co-crystals of iso-nicotinamide (4-pyridinecarboxamide) and a range of aromatic and aliphatic acids. The generated co-crystals revealed consistent hydrogen bonding patterns comprised of two robust supramolecular synthons: acid···pyridine heterosynthon and self-complementary amide homosynthon. The reproducibility of the hydrogen bonded motifs suggests a dominant tendency of the acid···pyridine heterosynthon over the acid···amide heterosynthon, that is formed in acid/amide-containing compounds in the absence of pyridines. Further examples based on these results include rational
design of ternary co-crystals of iso-nicotinamide with two different carboxylic acids.\textsuperscript{138}

Notwithstanding the valuable contribution of the presented work, delineation of the hierarchies of supramolecular heterosynths that can occur within a variety of functional groups in a competitive environment represents a crystal engineering challenge. Furthermore, the utilization of the CSD to assess the prevalence of one supramolecular heterosynthon over another can be addressed only in a few instances, i.e. the most ubiquitous functional groups.\textsuperscript{139} Thus, the relative ranking involving numerous supramolecular heterosynthons, such as hydroxyl···pyridine vs. hydroxyl···amine, hydroxyl···pyridine vs. hydroxyl···cyano, hydroxyl···amine vs. hydroxyl-cyano, etc. still remains an issue that needs to be addressed experimentally.\textsuperscript{140}

1.3.2. Co-Crystals in the Context of Green Chemistry

The advantage of obtaining well defined single crystals of a synthesized product is inherently related to the possibility of direct determination of its crystal structure. Additional benefits linked to the speed and accuracy of single crystal X-ray diffraction instrumentation have directed supramolecular synthesis of crystalline materials toward solution-based methods, e.g. slow evaporation, heating/cooling, addition of anti-solvent (solvent in which the components are not or sparingly soluble), etc. However, other aspects associated with solution co-crystallization, namely, mismatched solubility of the reactants, the possibility of unexpected solvate formation, or uncontrollable effects of solvents on polymorphic behaviors, could represent significant challenges for a crystal engineer. With this viewpoint, using less conventional methods of co-crystallization\textsuperscript{141}
such as growth from the melt or grinding the co-crystal formers not only overcomes 
aforementioned problems, but also can be of interest from the perspectives of green 
chemistry,\textsuperscript{142} which seeks to reduce and prevent pollution via implementation of 
environment-friendly chemical processes. In particular, the mechanochemical\textsuperscript{143} 
approach to supramolecular reactions, represented by grinding of two or more solids 
entirely eliminates some of the aspects accompanied with solution crystallizations, e.g. 
the recovery, storage and disposal of organic solvents.

Whereas grinding has been a commonplace in the context of classic covalent 
synthesis,\textsuperscript{144,145} its utilization with respect to co-crystallization has not been as common. 
Even though grinding by mortar and pestle to induce co-crystal formation has been 
known since late 19th century,\textsuperscript{109} it was implemented nearly one century later by Etter, in 
the research originally directed toward the understanding of preference of hydrogen 
bonds, and their role in the structures of a variety of organic co-crystals that involved 
nucleobases and acentric organic molecules.\textsuperscript{95,146-150} Recent advances in the area have 
introduced a novel grinding technique, termed “solvent-drop grinding”.\textsuperscript{151} The addition 
of small amounts of solvent to a grinding procedure in order to accelerate the reaction has 
been found to be a method especially effective for the preparation of multiple-component 
compounds, such as inclusion compounds, salts and co-crystals.\textsuperscript{152-154}

Although, the recent reports illustrate that the grinding approach is a viable means 
of preparing hydrogen bonded co-crystals, mehcanochemical techniques have not been 
routinely used on the academic level of research, and their further exploration in the 
context of co-crystal reproducibility, stability, and polymorphism still remains to be
addressed.

1.3.3. Co-Crystals in the Context of Polymorphism

“A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state”

Walter C. McCrone

Polymorphism, a phenomenon recognized in 1822, can be described as the existence of a substance in more than one crystalline form. The inability to reliably predict the existence of polymorphs or, for that matter, crystal structures in general, has important intellectual property and scientific implications. For example, the appearance of an undesired polymorph can invoke problems during the formulation process of a commercial compound and lead to patent litigations. On the other hand, a novel polymorph can offer an opportunity in terms of better physicochemical performance and new product development. Furthermore, since physicochemical properties of a compound can differ critically from one form to another, inducing and controlling a specific polymorph is of utmost importance in the chemistry of pharmaceuticals, explosives, pigments, etc.

Although the awareness among chemists of polymorphism increases, the frequency of occurrence of polymorphic compounds is not entirely obvious. The generality of McCrone’s statement that the “number of forms known for a given compound is proportional to the time and money spent in research on that compound” remains unclear, despite the indications that the frequency of polymorphism represented
by the CSD may be underestimated.\textsuperscript{56,166} As suggested by Desiraju,\textsuperscript{167} polymorphism may not be equally apparent in different categories of compounds, and it tends to be prominent in molecules that contain multiple hydrogen bonding moieties (thereby forming multiple supramolecular synthons), and/or possess conformational flexibility.\textsuperscript{18,168} Considering that these two features are inherently exhibited by drug molecules, polymorphism, as well as solvate formation (pseudopolymorphism),\textsuperscript{169,170} in pharmaceuticals is well documented.\textsuperscript{61,161,171-173} Specific examples of the existence of polymorphism in popular compounds include, for instance, ROY,\textsuperscript{174,175} aspirin,\textsuperscript{61} piracetam,\textsuperscript{176,177} and virazole.\textsuperscript{178}

Conformational flexibility of molecules can also lead to conformational isomorphism,\textsuperscript{156,168,179,180} where more than one molecular conformer exists in the same crystal structure. In addition, simultaneous crystallization of polymorphs, known as concomitant polymorphism, can occur under certain conditions.\textsuperscript{181}

Despite the fact that most of the polymorphs have been observed in single-component compounds, co-crystals also exhibit polymorphism.\textsuperscript{182,183} A CSD survey reveals ca. 94,900 single-component organic compounds, of which ca. 1,600 are polymorphic.\textsuperscript{184} On the other hand, there are only ca. 1,487 hydrogen bonded molecular co-crystals (comprised of components that are solid at room temperature), of which 21 are polymorphic; yet only 11 have 3D coordinates determined for two or more forms.\textsuperscript{185} The percentage occurrences of polymorphism in single-component compounds and co-crystals suggest that its extent is comparable (1.7 % vs. 1.5%).
Table 1.2. The occurrence of polymorphism in organic compounds. Data adapted from Zaworotko M. et al. J. Pharm. Sci., 2006

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Polymorphic compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-component compounds</td>
<td>94,900</td>
<td>1600 (1.7 %)</td>
</tr>
<tr>
<td>Co-crystals</td>
<td>1,487</td>
<td>21 (1.4 %)</td>
</tr>
</tbody>
</table>

Interestingly, a comparative structural study of co-crystal polymorphs (albeit based upon limited data), revealed that the supramolecular synthons exhibited in all cases are persistent and polymorphism is related to rather subtle conformational or crystal packing variations.\textsuperscript{182,183}

In general, the existence of polymorphism is not yet entirely understood, however, there have been advances in controlling this phenomenon. Specifically, recent literature revealed that the utilization of solvent-drop grinding approach can be an efficient way to achieve selective transformations between specific polymorphs in both single-component compounds and co-crystals.\textsuperscript{186-188}

1.3.4. Co-Crystals in the Context of Pharmaceuticals

The idea of utilizing co-crystals to modify physicochemical properties of compounds has attracted considerable attention with respect to pharmaceuticals. The majority of active pharmaceutical ingredients (APIs) occur as solids and their crystalline forms are highly preferred over the amorphous forms, due to the physicochemical stability considerations.\textsuperscript{171} Although amorphous APIs often exhibit enhanced solubility in aqueous systems, they are thermodynamically unstable and tend to revert into more stable crystalline products. The rejection of impurities and the ease of the isolation of single
crystals are additional benefits associated with dealing with crystalline materials. The problems with the utilization of crystalline APIs are related to their poor solubility which in turn negatively affects the bioavailability of an API. Therefore the development of crystalline forms of API that exhibit optimized physicochemical performance is of utmost importance in the field of pharmaceuticals.

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Top 100 Prescription Drugs %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>39</td>
</tr>
<tr>
<td>3° amine</td>
<td>37</td>
</tr>
<tr>
<td>Carbonyl</td>
<td>35</td>
</tr>
<tr>
<td>Ether</td>
<td>33</td>
</tr>
<tr>
<td>2° amine</td>
<td>31</td>
</tr>
<tr>
<td>Carboxylic acid</td>
<td>30</td>
</tr>
<tr>
<td>Ester</td>
<td>22</td>
</tr>
<tr>
<td>Aromatic N</td>
<td>12</td>
</tr>
<tr>
<td>2° amide</td>
<td>11</td>
</tr>
<tr>
<td>Sulfonamide</td>
<td>3</td>
</tr>
</tbody>
</table>

The inherent nature exhibited by APIs, namely their hydrogen bonding sites amenable to engage in supramolecular heterosynthons, constitutes a particularly suitable system for crystal engineering studies. Indeed, the 100-top selling prescription drugs contain hydrogen bond donors and acceptors, e.g. hydroxyl (39%) and carboxylic acid (30%) moieties, Table 1.3. In this respect, the interest in developing new forms of APIs resulted in the emergence of a new class of APIs, pharmaceutical co-crystals. A pharmaceutical co-crystal can be described as “a multiple component crystal in which at
at least one component is molecular and a solid at room temperature (the co-crystal former) and forms a supramolecular synthon with a molecular or ionic API’.49,190

Crystalline APIs have traditionally been limited to solvates/hydrates, polymorphs, and salts.171 Solvates/hydrates are usually discovered as a result of adventitious uptake of solvent/water upon crystallization and, like polymorphs, they are difficult to be rationally designed. Additional complications of the usage of API solvates/hydrates may be related to the possibility of desolvation/dehydration, followed by formation of amorphous material, which may occur as a function of time and storage conditions. In this respect, co-crystals are less likely to exhibit such behavior as their components are solids. Salt forms of APIs are commonplace and their role in the optimization of API properties, including solubility, has been established.191-194 Nevertheless, it is important to note, that salt formation is targeted in the case of drugs possessing ionizable (basic or acidic) moieties. In contrast, co-crystallization of APIs can be expanded over molecules that possess a broader range of hydrogen bonding moieties. Thus, API co-crystals exhibit advantages over API solvates/hydrates, polymorphs, and salts in the way that based upon rational design it is possible to generate diverse range of API forms with optimized physicochemical properties, e.g. solubility, thermal stability, and hygroscopicity, without the need of covalent modification and without altering their original biological activity.

Co-crystals of several important APIs have been reported in the scientific and patent literature, and they include: carbamazepine (CBZ), aspirin, profens, piracetam, caffeine, loracarbef, cephalexin, cefaclor, conazoles, topiramate, modafinil, phenytoin, olanzapine, nabumetone, fluoxetine, theophylline, sulfadimidine, trimethoprim, and
Detailed investigations of physicochemical performance of some of the reported APIs showed that their co-crystallization is inherently related to the modification of the physical properties, such as solubility, dissolution rate, thermal stability, etc. For instance, the dissolution studies in aqueous medium of co-crystals of itraconazole (Sporanox) and dicarboxylic acids, e.g. itraconazole•succinic acid (Figure 1.5), indicate that the co-crystals achieve and sustain from 4 to 20-fold higher concentrations as compared to the highly insoluble pure itraconazole.132

![Figure 1.5. Itraconazole•succinic acid co-crystal](image)

Another example, carbamazepine (Tegretol®) co-crystal with saccharin, Figure 1.6, in addition to its enhanced solubility, was found to be resistant to undesired hydrate formation and has not exhibited polymorphism based upon 1200 high-throughput (HT)209,210 screening experiments.211
In summary, the application of the concepts of supramolecular chemistry and crystal engineering to the development of pharmaceuticals offers an opportunity towards the generation of novel API forms. Specifically, the alteration of the physical properties of the solid dosage form with simultaneous retention of the therapeutic attributes of an API represents an attractive approach to balance the bioavailability, stability and other performance characteristics.

1.4.  Summary

The presented work will focus on applying the concepts of crystal engineering to the design and generation of novel multi-component compounds with pre-determined composition and intermolecular interactions. Particular emphasis will be placed upon co-crystals and their further exploration toward the following aspects:

- Delineation of the reliability of hydrogen bonded supramolecular heterosynthons and their hierarchies in a competitive environment. Advances in
understanding the mechanisms that govern molecular recognition in the crystalline state will lead to insights toward rational design of co-crystals of more complex molecules. In addition, the investigation of neutral and charge-assisted supramolecular heterosynthons (co-crystal vs. salt) will be addressed.

- Viability of mechanochemical methods toward preparation of multiple-component compounds (organic salts and co-crystals). Reduction or entire elimination of organic solvents from the experimental co-crystallization procedures can be advantageous from the perspectives of green chemistry principles, as well as from the viewpoint of reproducibility of the products obtained from solution crystallizations.

- Polymorphism in co-crystals. The susceptibility of co-crystals toward polymorphism or solvate formation will be addressed based upon traditional solution techniques and innovative solvent-drop grinding screening methods.

- Pharmaceutical co-crystals. Rational co-crystallization of API molecules, which represent more complex systems due to their multiple hydrogen bonding sites, with judiciously selected co-crystals formers will be demonstrated as a result of the acquired knowledge from the preceding model compound investigations.
Chapter 2 — Recurrence of hydroxyl···aromatic nitrogen supramolecular heterosynthon in the presence of a competing cyano acceptor

2.1. Focus

As already mentioned, the CSD contains enough information to evaluate competitiveness of some supramolecular homosynthons vs. supramolecular heterosynthons.\textsuperscript{65,137,212} However, the prevalence of one supramolecular heterosynthon over another can be addressed only in a few instances, i.e. the most ubiquitous functional groups.\textsuperscript{139,140} Therefore, assessing the hierarchies that exist within a given set of supramolecular heterosynthons still represents a challenge and complicates crystal engineering of compounds that possess multiple functionalities.

In an effort to explore pharmaceutical co-crystals, studies on model co-crystals that contain hydroxyl (OH), aromatic nitrogen ($N_{\text{arom}}$), and cyano (CN) moieties have been conducted. A combination of such functionalities is present in a range of vitamins and API’s, e.g. vitamin B$_1$, cimetidine, bicalutamide, etc. An analysis of the crystal structures of the model co-crystals is expected to facilitate the delineation of hierarchies between hydroxyl···aromatic nitrogen (O–H···$N_{\text{arom}}$) and hydroxyl···cyano (O–H···N≡C) supramolecular heterosynthons.
2.2. Results and Discussion

The co-crystallization experiments involved co-crystal formers that possess the OH, N_{arom}, and/or CN moieties, and these functional groups: (a) are sterically accessible, (b) are not involved in intramolecular interactions, and c) are not accompanied by other competing hydrogen bond donors and acceptors. In an individual experiment two co-crystal formers were combined. Within a pair, one co-crystal former possessed two of the three moieties (e.g. N_{arom}/CN) and the second co-crystal former possessed the remaining moiety (e.g. OH). According to this strategy, the individual pairs of co-crystal formers are combined as follows: N_{arom}/CN with OH, OH/CN with N_{arom}, and OH/N_{arom} with CN. Such an approach to delineate the hierarchies of two supramolecular heterosynthons relies on the idea that a co-crystal can result only if the favored supramolecular heterosynthon is formed between the co-crystal formers. Conversely, a co-crystal is not expected to be formed if a dominant supramolecular heterosynthon already exists in one of the pure components. The formation of a co-crystal is determined by multiple techniques: melting point measurements, DSC, IR spectroscopy, powder X-ray diffraction (PXRD), and single crystal X-ray diffraction. The crystal structures of all obtained co-crystals were analyzed in the context of the existence of specific supramolecular heterosynthons.

Small organic molecules that contain OH, N_{arom}, and CN moieties used in this study are shown on Scheme 2.1. Co-crystallizations of these chemicals afforded the following co-crystals: 3-cyanophenol•4-phenylpyridine, 1; (3-cyanophenol)_{2}•1,2-bis(4-pyridyl)ethane, 2; (3-cyanophenol)_{2}•trans-1,2-bis(4-pyridyl)ethylene, 3; 3-
cyanophenol•trans-1,2-\textit{bis}(4-pyridyl)ethylene, 4; 4-cyanophenol•4-phenylpyridine, 5; (4-cyanophenol)\textsubscript{2}•4,4’-bipyridine, 6; (4-cyanophenol)\textsubscript{2}•1,2-\textit{bis}(4-pyridyl)ethane, 7; (4-cyanophenol)\textsubscript{2}•trans-1,2-\textit{bis}(4-pyridyl)ethylene, 8; (3-cyanopyridine)\textsubscript{2}•4,4’-biphenol, 9; (4-cyanopyridine)\textsubscript{2}•resorcinol, 10; (4-cyanopyridine)\textsubscript{2}•4,4’-biphenol, 11; and (4-cyanopyridine)\textsubscript{3}•phloroglucinol, 12.

Scheme 2.1. Co-crystal formers used in the investigation of the hierarchy of O–H···N<sub>arom</sub> and O–H···N≡C supramolecular heterosynthons

2.2.1. CSD Analysis

There are three possible supramolecular synthons that can be formed when OH, N<sub>arom</sub>, and CN moieties are present in the same crystal structure: a hydroxyl···pyridine supramolecular heterosynthon I, a hydroxyl···cyano supramolecular heterosynthon II, and
a hydroxyl supramolecular homosynthon III (Scheme 2.2).

\[
\begin{align*}
\text{I} & : R \overset{\text{O-H}}{\cdots} \overset{\text{N}}{\text{N}} \\
\text{II} & : R \overset{\text{O-H}}{\cdots} \overset{\text{N}}{\text{N}} \overset{\text{R}}{\text{R}} \\
\text{III} & : R \overset{\text{O-H}}{\cdots} \overset{\text{O}}{\text{O}} \\
\end{align*}
\]

Scheme 2.2. Supramolecular synthons that can form when OH, N and CN are present in the same structure

A CSD survey of compounds that contain OH, N$_{\text{arom}}$, and CN moieties was conducted to evaluate the frequency of occurrence of supramolecular synthons I, II and III.\(^{213}\) In order to determine appropriate distance ranges, within which I, II and III exist, distance distribution plots were generated, Figure 2.1.\(^{214}\) Based on visual inspection of the resulting histograms, the lower and higher cut offs for hydrogen bonds were determined. The histograms reveal that the supramolecular heterosynthon I and II occur within the ranges of 2.50 - 3.00 Å and 2.70 - 3.20 Å, respectively, whereas supramolecular homosynthon III exhibits range of 2.50 – 3.00 Å.\(^{215}\) Based upon these limits the number of entries that exhibit the targeted supramolecular synthons was determined, Table 2.1. It should be noted that the frequencies of occurrence of supramolecular synthons can be influenced by the presence of other hydrogen bond donors and acceptors, therefore the competing moieties, such as carboxylic acids, amines, amides, sulfonamides, carbonyls, water, chloride and bromide ions, etc. were removed from the analyzed sets of structures.
Table 2.1. CSD statistics related to supramolecular synthons that occur in structures containing only OH, Narom, and CN

<table>
<thead>
<tr>
<th>Moieties present in a structure</th>
<th>No. of structures</th>
<th>Supramolecular synthon</th>
<th>Structures with synthon</th>
<th>D···A [Å]</th>
<th>Mean (σ) [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH and Narom</td>
<td>136</td>
<td>O–H···Narom</td>
<td>135 (99%)</td>
<td>2.50-3.00</td>
<td>2.77(8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O–H···O</td>
<td>37 (27%)</td>
<td>2.50-3.00</td>
<td>2.78(8)</td>
</tr>
<tr>
<td>OH and CN</td>
<td>61</td>
<td>O–H···N≡C</td>
<td>56 (92%)</td>
<td>2.70-3.20</td>
<td>2.9(1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O–H···O</td>
<td>18 (29%)</td>
<td>2.50-3.00</td>
<td>2.78(8)</td>
</tr>
<tr>
<td>OH, Narom, and CN</td>
<td>3</td>
<td>O–H···Narom</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O–H···N≡C</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O–H···O</td>
<td>0</td>
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</table>

Supramolecular heterosynthon I is well established in crystal engineering.\(^{88,89,216}\) The CSD analysis reveals that in the structures containing only OH and Narom I exists in 135 of 136 crystal structures. Therefore I is favored over III as its occurrence reaches ca. 99% vs. 27% of the occurrence of III.\(^{217}\) On the other hand, of 61 crystal structures that contain only OH and CN, 56 (92%) entries exhibited supramolecular heterosynthon II, whereas 18 (29%) structures exhibited III, which indicates the dominance of heterosynthon II over homosynthon III, as shown in Table 2.1. It should be noted, that 13 structures contained both II and III, due to the presence of multiple OH moieties. However, the number of crystal structures archived in the CSD that possess all three OH and Narom and CN moieties (competing moieties are absent) resulted in only 3 entries, thereby precluding a meaningful statistical evaluation.\(^{218}\) Thus, the competition between I and II could only be assessed based upon experimental results. Herein, a series of co-crystals that can help to evaluate the relative hierarchy of I and II is presented.
2.2.2. Structural Features of Neutral and Ionic Hydroxyl···Aromatic Nitrogen Interaction

Phenols and pyridines can form neutral co-crystals or organic salts. The neutral nature of heterosynthton I was confirmed by spectroscopy, proton location in the difference Fourier map, and structural parameters of ancillary groups, namely the C–N–C angle in the pyridine moieties and C–O bond lengths in the phenolic moieties. The C–N–C angle in pyridines is known to be sensitive to protonation and its cationic form exhibits higher values (ca. 121°) than that of the corresponding neutral molecules (ca. 116°). The histograms representing carbon-oxygen bond lengths distribution in neutral and ionic phenolic moieties were generated using the CSD and are shown in Figure 2.2 (only good quality crystal structures: ordered, error free, nonpolymeric with...
3D coordinates determined and R<5%, were chosen for the analysis). The CSD analysis of 2588 crystal structures that contain neutral phenolic moieties reveals that the average C–OH bond length is 1.36(2) Å. There are 260 crystal structures that contain deprotonated phenolic moieties. The calculated average for ionic C–O` bond length in such structures is 1.28(3) Å.\(^{224}\)

![Figure 2.2. Histograms representing the distribution of carbon-oxygen bond lengths in a) neutral phenolic moieties and b) deprotonated phenolic moieties](image)

2.2.3. Crystal Structure Descriptions

The crystal structure of 3-cyanophenol•4-phenylpyridine, \(I\), reveals discrete 1:1 supramolecular adducts sustained by O–H···N\(_{\text{arom}}\) supramolecular heterosynthon \(I\), also coded as D graph-set.\(^{75}\) In addition to IR spectroscopic evidence, the neutral nature of \(I\) is supported by structural data: the C–O distance is 1.363(6) Å and the C–N–C angle within the pyridine ring is 115.6(2)°. The O–H···N\(_{\text{arom}}\) hydrogen bond distance (D: 2.708(3) Å) is within the expected range for hydroxyl···pyridine interactions (Table 2.1). In this structure the phenpy is twisted, with a torsion angle of 24.6° between the aromatic rings. The dihedral angle formed by the 3cyphe and phenpy rings is 79.7°. The glide related supramolecular adducts are stabilized via π- π stacking occurring between the adjacent
phenpy molecules with an interplanar separation of ca. 3.79 Å. Such organization of molecules results in a columnar arrangement of the supramolecular adducts along the $c$ axis. The adjacent columns are related by translation along the $b$ axis and are connected via weak C–H···N≡C interactions, which results in 2D molecular sheets (Figure 2.3).

Figure 2.3. Crystal structure of 3-cyanophenol•4-phenylpyridine, $I$

The crystal structure of (3-cyanophenol)$_2$•1,2-bis-(4-pyridyl)ethane, $2$, reveals centrosymmetric 2:1 adducts sustained by two supramolecular heterosynthons I (D: 2.691(2) Å). The C–O distance is 1.352(2) Å and the C–N–C angle within the pyridine ring is 116.6(2)$^\circ$, indicating a neutral O–H···N$_{\text{arom}}$ hydrogen bond. The dihedral angle formed by 3cyph and the bipyeta rings is 132.5$^\circ$. The adjacent adducts interact via weak C–H···N≡C forces forming 1D zigzag chains. Translation related chains are connected via weak C–H···N≡C interaction along the $b$ axis, thereby forming 2D
molecular sheets (Figure 2.4).

![Figure 2.4. Crystal structure of (3-cyanophenol)$_2$$\cdot$1,2-\textit{bis}-(4-pyridyl)ethane, 2](image)

The asymmetric unit of (3-cyanophenol)$_2$$\cdot$\textit{trans}-1,2-\textit{bis}-(4-pyridyl)ethylene, 3, consists of two 3cyphe molecules and one bipyete molecule. The components form non-centrosymmetric supramolecular adducts sustained by two supramolecular heterosynthons I ($D_1$: 2.727(2) Å, $D_2$: 2.730(2) Å). The C–O distances are 1.351(2) Å and 1.357(2) Å and the C–N–C angles within the two bipyete rings are 116.2(2)$^\circ$ and 116.1(2)$^\circ$, respectively. The dihedral angles between the 3cyphe and the bipyete rings are 145.4$^\circ$ and 66.9$^\circ$. The adjacent supramolecular adducts are stabilized by face-to-face stacking occurring between the aromatic moieties of 3cyphe and bipyete molecules. Such molecular assembly affords a columnar alignment of the adducts along the $b$ axis. The molecular columns are further interconnected by weak C–H···N≡C interactions, thereby forming 2D sheets (Figure 2.5).
Figure 2.5. Crystal structure of (3-cyanophenol)₂•t-1,2-bis-(4-pyridyl)ethylene, 3

3-cyanophenol•trans-1,2-bis-(4-pyridyl)ethylene co-crystal 4 consists of 1:1 discrete supramolecular adducts sustained by I (D: 2.663(3) Å). The C–O distance is 1.361(3) Å and the C–N–C angle of the hydrogen bonded bipyete pyridyl ring is 116.2(3)°. The dihedral angle between the 3cyphe and the bipyete ring is 98.8°. The inversion related dimers are stabilized by π–π stacking along b axis. The stacking occurs between parallel oriented bipyete molecules with the interplanar separation of ca. 3.44 Å. The presence of the weak C−H···N≡C interaction between the adjacent 3cyphe molecules leads to the formation of centrosymmetric pairs of the supramolecular adducts, which in turn directs the molecular assembly into 2D layers (Figure 2.6). It should be noted that the alignment of the two bipyete in 4, satisfies the topochemical principle for [2+2] photodimerization in the solid state, which states that the olefins should be parallel and separated by less than 4.2 Å. In this context, successful covalent synthesis of new cyclic molecules in high yields and in a solvent-free manner based upon bipyete and
resorcinol co-crystals has been recently demonstrated.\textsuperscript{89,226} Furthermore, it should be pointed out that the 1:1 stoichiometry of the components in 4 is somewhat unexpected, considering that the ratio of hydrogen bond acceptor : donor (in this case $N_{\text{arom}}$ : OH) between the two components is 2:1. While the O–H moieties of 3cyphe are utilized in a strong O–H···$N_{\text{arom}}$ hydrogen bond, only one of the two $N_{\text{arom}}$ sites of bipyete acts as an O–H···$N_{\text{arom}}$ acceptor. The remaining $N_{\text{arom}}$ moiety participates in a weak C–H···$N_{\text{arom}}$ interaction\textsuperscript{227-230} with the neighboring 3cyphe molecules. In effect, the adjacent bipyete molecules are aligned on top of each other and stabilized via continuous $\pi$-$\pi$ stacking.

A literature search reveals that similar molecular arrangements are exhibited in several co-crystals of phenazines.\textsuperscript{231,232} For instance, the crystal structure of phenazine•hydroquinone, (CSD refcode FOQHEY),\textsuperscript{231} Figure 2.7, is reminiscent of the crystal structure of 4 with respect to the unexpected 2:1 stoichiometry of the components interacting via a similar set of intermolecular interactions. These observations suggest a significant contribution of C–H···$N_{\text{arom}}$ and aromatic stacking to the overall crystal packing of the presented co-crystals. In particular, the existence of non-bonded $N_{\text{arom}}$ is not uncommon, as revealed by the CSD survey. In the set of 135 crystal structures comprised only by OH and $N_{\text{arom}}$ moieties (Table 2.1) there are 19 entries (14\%) that exhibit non-bonded weak C–H···$N_{\text{arom}}$ interactions, in addition to the primary supramolecular heterosynthon I.
Similarly to 1, co-crystal of 4-cyanophenol•4-phenylpyridine, 5, is comprised of 1:1 discrete supramolecular entities sustained via I (D: 2.695(4) Å). The C–O distance is 1.345(3) Å and the C–N–C angle within the phenpy rings is 116.9(3)° and the dihedral angle between the 4cyphe and the phenpy rings is 108.8°. In this crystal structure the phenpy is twisted, and the torsion angle is 33.6°, which is similar to phenpy in 1 (24.6°). The glide related supramolecular adducts are stabilized via π–π stacking (ca. 3.74 Å)
occurring between the \textit{phenpy} molecules along the \textit{b} axis. The adjacent columns of the 1:1 adducts are connected by centrosymmetric C–H···N≡C dimers thereby generating 2D sheets (Figure 2.8).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.8.png}
\caption{Crystal structure of 4-cyanophenol\textbullet4-phenylpyridine, 5}
\end{figure}

The crystal structure of \textit{(4-cyanophenol)}\textbullet4,4'-\textit{bipyridine}, 6, reveals 2:1 centrosymmetric supramolecular adduct sustained by 1 (D: 2.718(3) Å). The C–O distance is 1.346(3) Å and the C–N–C angle is 116.3(3)°. The dihedral angle between the \textit{4cyphe} and the pyridine ring is 30.1°. The \textit{bipy} molecules are flat and stack on top of each other along the \textit{a} axis with an interplanar separation of ca. 3.59 Å. The packing of supramolecular adducts is further extended into 2D through centrosymmetric C–H···N≡C dimer formed between the neighboring \textit{4cyphe} molecules (Figure 2.9).
Figure 2.9. Crystal structure of (4-cyanophenol)$_2$\(\cdot\)4,4'-bipyridine, 6

In the crystal structure of (4-cyanophenol)$_2$\(\cdot\)1,2-\textit{bis}-(4-pyridyl)ethane, 7, the 2:1 supramolecular aggregates are sustained by supramolecular heterosynthons I (D: 2.698(4) Å), Figure 2.10. The C–O distance is 1.359(4) Å and the C–N–C angle is 117.2(3)°. The dihedral angle between the 4cyphe and the bipyeta ring is ca. 66.8°. The adducts interact via C–H···O dimer along the \(c\) axis, thereby forming 1D chains. These chains are then interconnected via weak C–H···N=O thus generating 2D molecular sheets.

Figure 2.10. Crystal structures of (4-cyanophenol)$_2$\(\cdot\)1,2-\textit{bis}-(4-pyridyl)ethane, 7

The crystal structure of (4-cyanophenol)$_2$\(\cdot\)trans-1,2-\textit{bis}-(4-pyridyl)ethylene, 8, is reminiscent of that in co-crystal 6. It is comprised by 2:1 centrosymmetric supramolecular adducts sustained by I (D: 2.714(4) Å vs. 2.718(3) Å in 6). The C–O distance is 1.349(3) Å and the C–N–C angle of the bipyete ring is 114.8(3)°. The
dihedral angle between the 4cyphe and the bipyete rings is 142.6° (vs. 30.1° in 6). The supramolecular adducts are stabilized by π-π interactions occurring between the bipyete molecules (ca. 3.66 Å) along b axis and they further extended into 2D through a centrosymmetric C–H···N=С dimer formed between the neighboring 4cyphe molecules (Figure 2.11). Although the primary (stacked 2:1 adducts) and secondary (2D network resulting from the presence of the C–H···N=С dimers) architectures of 6 and 8 are similar, the two crystal structures differ in the relative orientations of the 2:1 adducts down the a and b axes for 6 and 8 respectively. In 6, the 2:1 adducts are packed side by side, and generate planar layers, Figure 2.12a. In 8 the adjacent adducts, rather than adopting co-planar orientation, are aligned at ca. 40° with respect to each other, Figure 2.12b.

Figure 2.11. Crystal structure of (4-cyanophenol)₂·t-1,2-bis-(4-pyridyl)ethylene, 8

Figure 2.12. Representation of the relative orientation of the adjacent 2:1 adducts: a) down the a axis in 6, and b) down the b axis in 8

38
In the crystal structure of \((3\text{-cyanopyridine})_2\cdot4,4'\text{-biphenol}, \text{9}\), a 2:1 centrosymmetric supramolecular aggregate exists that is sustained by two supramolecular heterosynthons \(\text{I} \) (D: 2.765(3) Å). The C–O distance is 1.381(3) Å and the C–N–C angle of the hydrogen bonded 3cypy ring is 117.79(2)° suggesting the neutral nature of the O–H···N_{arom} hydrogen bond. The dihedral angle between the flat bphe and the 3cypy rings is 54.1°. The adducts assemble further through C–H···N≡C dimer into 2D molecular sheets (Figure 2.13).

![Crystal structure of (3-cyanopyridine)_2\cdot4,4'-biphenol, 9](image)

Figure 2.13. Crystal structure of (3-cyanopyridine)_2\cdot4,4'-biphenol, 9

The components of \((4\text{-cyanopyridine})_2\cdot\text{resorcinol} \) co-crystal, \textit{10}, assemble to form 2:1 discrete adducts sustained by \(\text{I} \) (D_1: 2.856(2) Å, D_2: 2.763(2) Å). The C–O distances in a res molecule are 1.361(2) Å and 1.360(2) Å and the C–N–C angles of the hydrogen bonded 4cypy rings are 117.1(1)° and 117.2(1)°, respectively. The dihedral angle between the res and the 4cypy rings are 68.6° and 75.1°. The hydroxyl moieties of res molecules adopt a convergent orientation and interact with two 4cypy molecules (ca.
3.88 Å) which are stacked in face-to-face manner. These discrete 2:1 entities are extended into 1D chain via weak C–H⋯O\textsuperscript{233,234} and C–H⋯N≡C forces along c axis. The translation related 1D chains are then packed side by side through weak C–H⋯N≡C interactions to form 2D layers (Figure 2.14).

![Figure 2.14. Crystal structure of (4-cyanopyridine)\textsubscript{2}•resorcinol, 10](image)

The asymmetric unit of \((4\text{-cyanopyridine})\textsubscript{2}•4,4'\text{-biphenol}, 11\), consists of half a \textit{bphe} molecule and one \textit{4cypy} molecule and the resulting 2:1 centrosymmetric supramolecular adducts are sustained by I (D: 2.733(4) Å; C–O distance: 1.353(3) Å; C–N–C angle: 116.3(3)°). The \textit{bphe} molecules are flat (similarly to \textit{bphe} in 9) and the dihedral angle between the \textit{bphe} and the \textit{4cypy} rings is 49.2°. The 2:1 adducts are connected through C–H⋯N≡C dimers forming 1D chains. The packing is further stabilized by C–H⋯O and C–H⋯N≡C interactions existing between chains which are aligned side by side along the b axis (Figure 2.15). Based upon further investigations
involving solid state co-crystallization, co-crystal 11 (thereafter form I, 11a) was found to exhibit additional polymorphic modification. The comparative structural analysis of both forms I and II will be discussed in more details in chapter 3.

Figure 2.15. Crystal structure of (4-cyanopyridine)$_2$•4,4’-biphenol, 11a

Co-crystal of (4-cyanopyridine)$_3$•phloroglucinol, 12, consists of discrete 3:1 entities sustained by 1 (D$_1$: 2.721(4) Å, D$_2$: 2.784(3) Å, D$_3$: 2.795(3) Å), Figure 2.16. The C–O distances are 1.353(3) Å, 1.359(3) Å, 1.367(3) Å, and the C–N–C angle of the hydrogen bonded 4cyp rings are 116.3(3)$^\circ$, 116.8(3)$^\circ$, and 116.3(3)$^\circ$, respectively. The dihedral angles between the phlgl and the 4cyp rings are 94.9$^\circ$, 98.4$^\circ$, and 99.3$^\circ$.

Despite that phlgl can adopt a 3-fold geometry, in this structure, the phlgl molecules exhibit convergent orientation. In effect, two of the three 4cyp molecules interact via face-to-face stacking (ca. 3.84 Å). Such aggregates self-assemble via C–H···N≡C dimers into centrosymmetric pairs of adducts. These pairs are further extended through a C–H···N≡C interactions to form 1D tapes. Such tapes are then packed side by side along the $b$ axis forming 2D molecular layers.
The CSD analysis contain several co-crystals of phlgl with pyridines, of which one is particularly relevant from the crystal structure perspective, namely (4,4’-bipyridine)$_3$•(phloroglucinol)$_2$ (CSD refcode: TEKKOY),$^{236}$ Figure 2.17. Its crystal structures are also sustained by heterosynthon I, and the O–H···N$_\text{arom}$ hydrogen bond lengths are similar to those observed in 12 (D$_1$: 2.71(1) Å, D$_2$: 2.75(1) Å, D$_3$: 2.794(9), D$_4$: 2.71(1) Å, D$_5$: 2.73(1) Å, D$_6$: 2.76(1) Å). In the crystal structure of TEKKOJ, phlgl molecules also adopt convergent conformation. In effect, the adjacent bipy molecules stack in face-to-face manner (ca. 4.02 Å). Similar arrangement of molecules is observed in 12 (4cypy molecules indicated by the capped stick style). Such aggregates are then linked together by the remaining bipy molecule into 1D chains. The adjacent chains are related by 2$_1$ screw axis and stabilized via weak C–H···O interactions occurring between the phlgl molecules, thereby generating 2D molecular sheets.

![Figure 2.16. Crystal structure of (4-cyanopyridine)$_3$•phloroglucinol, 12](image)
While the presented co-crystal structures resulted from successful experiments, attempts that involved co-crystallization of 1-hexadecanol (**hexdec**) with 3-cyanopyridine (**3cyp**y) and 4-cyanopyridine (**4cyp**y) were ineffective. The unsuccessful attempts were also confirmed by grinding, solvent-drop grinding and melting procedures (more details in chapter 3). Since both (**3cyp**y) and (**4cyp**y) are capable of forming co-crystals with other molecules, e.g. **res, bphe, phlgl**, the lack of success with **hexdec** perhaps can be contributed to the molecular features of **hexdec**. The existence of long hydrophobic chains that are stabilized by a series of cooperative van der Waal forces\(^\text{237}\) can possibly inhibit the dissociation of **hexdec** structure and the formation of hydrogen bonded adducts with other molecules. An analysis of the CSD showed that of the 135 structures that are sustained by **I** (Table 2.1), none contain long chain aliphatic monoalcohols.

In summary, the crystal structures of the 12 co-crystals demonstrate the recurrence of supramolecular heterosynthon **I** in the presence of the CN moiety in all
reported cases. Such a high reliability of \textbf{I} is further confirmed by the unsuccessful co-crystallizations of \textbf{3hypy} and \textbf{5hyquin} with CN-containing compounds: \textit{cynaphth}, \textit{o-cyben}, and \textit{p-cyben}. These “negative” results can be rationalized by the existence of OH/N_{arom} moieties in the molecular structures of \textbf{3hypy} and \textbf{5hyquin}. For instance, the crystal structure of \textbf{3hypy}\textsuperscript{238} exhibits the O–H···N_{arom} supramolecular heterosynthon (Figure 2.18), which, as shown by \textbf{1-12}, can not be easily altered by the introduction of a CN moiety.

![Figure 2.18. Supramolecular heterosynthon I present in the crystal structure of 3-hydroxypyridine](image)

The hydrogen bond lengths of \textbf{I} in all co-crystals correspond to the expected values of a typical O–H···N_{arom} interaction (Table 2.1) and the structural parameters (C–O lengths and C–N–C angles) of the ancillary groups suggest a neutral character of \textbf{I}. The supramolecular chemistry of \textbf{I} can also be predicted to a certain extent. Depending on the geometrical distribution and the ratio of the OH and N_{arom} moieties, the formation of \textbf{I} leads to 1:1 or 1:2 discrete supramolecular entities, which due to the presence of CN moieties, can be further extended to 1D chains or 2D sheets sustained by weak C–H···N≡C interactions.

The existence of co-crystal \textbf{4} and the CSD statistical data that reveals the presence
of the C–H···N_{arom} interaction in ca. 14% of the crystal structures sustained primarily by I, indicates the importance of these weak interactions in the molecular association.\textsuperscript{104,233,239-242} Although inherently soft, these interactions combined with other weak forces, e.g. π-π stacking, prove to be directional enough to lead to the formation of co-crystals that would otherwise be unexpected if only strong hydrogen bonds would be taken into consideration.\textsuperscript{243} Furthermore, this result suggests that, while it is possible to anticipate the existence of some primary interactions, due to the contribution of weaker forces, it is difficult to predict the ultimate crystal packing of a substance based upon the knowledge of molecular structure of the constituent(s).

Co-crystals 1-12 were examined in the context of their thermal stability. Recent reports of Aakeröy \textit{et al.} and Nangia \textit{et al.}, related to systematic studies of co-crystals that contain dicarboxylic acid as one of the components, suggest that their melting point alteration can be rationalized based upon the thermal properties of the acid component; i.e. the alternating trend exhibited in the aliphatic carboxylic acid series (in a homologous series, a carboxylic acid with odd number of carbon atoms has a relatively lower melting point than those with an even number of carbon atoms)\textsuperscript{244} is maintained in co-crystals.\textsuperscript{133,245} However, whether a co-crystal will melt at a temperature higher, lower, or in between the melting temperatures of the co-crystal constituents, could not be predicted. The analysis of the thermal behavior of co-crystals 1-12 (Table 2.3) shows no correlation with respect to the melting points of the corresponding co-crystal formers. Co-crystals 1 and 5 melt at temperatures lower than their constituents, while co-crystals 6 and 7 melt at temperatures higher than their components. The remaining co-crystals 2, 3,
4, 8, 9, 10, and 12 melt at temperatures within the ranges indicated by the melting points of the respective co-crystal formers. Therefore, although the rationalization of the melting trends in a specific class of co-crystals can be possible,94,246 the anticipation of the melting point for a given co-crystal still remains elusive.91,98,247

2.3. Conclusions

In summary, the study presented herein involves a series of model co-crystals adds to the limited amount of the CSD information related to the frequency of occurrence of supramolecular heterosynthon I in the presence of the competing acceptor, CN moiety. That I occurs reliably in the presence of a CN moiety, suggests that O–H⋯N_{arom} hydrogen bond is favored over the possible O–H⋯N≡C hydrogen bond II. Considering that I and II are favored over III, the relative ranking of these supramolecular synthons can be presented as: I>II>III. Therefore, I can be particularly suitable for crystal engineering of co-crystals comprised by the OH, N_{arom}, and CN moieties. Furthermore, if the robustness of I remains intact in the presence of broader range of hydrogen bonding donors and acceptors, I could perhaps, be considered as a remarkably predictable interaction, which can be reliably utilized in co-crystallization of more complex compounds that possess multiple hydrogen bonding sites. This conclusion is particularly relevant to co-crystals of APIs, since they are relatively complex molecules that often contain either OH or N_{arom} moieties, or can interact with OH- or N_{arom}-containing co-crystal formers. Modification of the physicochemical properties that is associated with the co-crystal formation may lead to interesting opportunities toward new formulations
for the improved performance of an API.

2.4. Experimental

2.4.1. Syntheses

All reagents were purchased from Aldrich and used without further purification. Single crystals of compounds 1-12 were obtained via slow evaporation of stoichiometric amounts of starting materials in appropriate solvents and were isolated from solution before complete evaporation of the solvents.

**Co-crystal 1: 3-Cyanophenol • 4-phenylpyridine.** To 3-cyanophenol (0.015 g, 0.13 mmol) was added 4-phenylpyridine (0.020 g, 0.13 mmol) and 2 mL of 1:1 of acetone and ethyl acetate solvent mixture. Slow evaporation of the solution afforded colorless crystals of 1 (0.027 g, 0.10 mmol, 77%), mp = 54-57 °C after 3 days.

**Co-crystal 2: (3-Cyanophenol)₂ • 1,2-bis(4-pyridyl)ethane.** To 3-cyanophenol (0.026 g, 0.22 mmol) was added 1,2-bis-(4-pyridyl)ethane (0.020 g, 0.11 mmol) and the mixture was dissolved in 2 mL of acetone. After 3 days colorless crystals of 2 (0.035 g, 0.083 mmol, 75%), mp = 106-108 °C, were observed.

**Co-crystal 3: (3-Cyanophenol)₂ • trans-1,2-bis(4-pyridyl)ethylene.** Co-crystal 3 was obtained using the reagents in 4:1 molar ratio. To 3-cyanophenol (0.052 g, 0.44 mmol) was added trans-1,2-bis(4-pyridyl)ethylene (0.020 g, 0.11 mmol) and 2 mL of 1:1 acetone and ethyl acetate mixture. After 2 days colorless crystals of 3 (0.031 g, 0.074 mmol, 67%), mp = 112-114 °C, were obtained.
**Co-crystal 4: 3-Cyanophenol•trans-1,2-bis(4-pyridyl)ethylene.** Co-crystal 4 was obtained using the starting materials in 2:1 ratio. To 3-cyanophenol (0.026 g, 0.22 mmol) was added trans-1,2-bis(4-pyridyl)ethylene (0.020 g, 0.11 mmol) and the mixture was dissolved in 2 mL of ethyl acetate. Colorless crystals of 4 (0.026 g, 0.086 mmol, 79%), mp = 124-125 °C, appeared after 2 days. Co-crystal 4 can also be obtained by using the reagents in 1:1 molar ratio.

**Co-crystal 5: 4-Cyanophenol•4-phenylpyridine.** To 4-cyanophenol (0.015 g, 0.13 mmol) was added 4-phenylpyridine (0.020 g, 0.13 mmol). The mixture was dissolved in 2 mL of chloroform and left to evaporate slowly at 4 °C. After 4 days colorless crystals of 5 (0.030 g, 0.11 mmol, 85%), mp = 65-66 °C, were observed.

**Co-crystal 6: (4-Cyanophenol)₂•4,4’-bipyridine.** To 4-cyanophenol (0.031 g, 0.26 mmol) was added 4,4’-bipyridine (0.020 g, 0.13 mmol). The solid mixture was dissolved in 2 mL of methanol and the solution was left undisturbed to evaporate under ambient conditions. After 12 days yellow needles of 6, (0.042 g, 0.097 mmol, 0.75%), mp = 143-146 °C, were formed.

**Co-crystal 7: (4-Cyanophenol)₂•1,2-bis(4-pyridyl)ethane.** To 4-cyanophenol (0.026 g, 0.22 mmol) was added 1,2-bis(4-pyridyl)ethane (0.020 g, 0.11 mmol) and the mixture was dissolved in 2 mL of methanol. After 8 days colorless crystals of 7 (0.031 g, 0.073 mmol, 67%), mp = 138-139 °C, were obtained.

**Co-crystal 8: (4-Cyanophenol)₂•trans-1,2-bis(4-pyridyl)ethylene.** To 4-cyanophenol (0.026 mg, 0.22 mmol) was added 1,2-bis(4-pyridyl)ethylene (0.020 mg, 0.11 mmol). The solid mixture was dissolved in 2 mL of acetonitrile. After 2 days
colorless crystals of \(8\), mp = 141-142 °C were observed.

**Co-crystal 9: (3-Cyanopyridine)\(_2\)•4,4'-biphenol.** To 3-cyanopyridine (0.040 g, 0.38 mmol) was added 4,4'-biphenol (0.036 g, 0.19 mmol) and the mixture was dissolved in 2 mL of methanol. After 6 days colorless crystals of 9 (0.052 g, 0.13 mmol, 68%), mp = 250 °C (followed by decomposition), were observed.

**Co-crystal 10: (4-Cyanopyridine)\(_2\)•resorcinol.** To 4-cyanopyridine (0.040 g, 0.38 mmol) was added resorcinol (0.021 g, 0.19 mmol) and 2 mL of acetonitrile. The solution was left to evaporate at ambient temperature and after 8 days colorless crystals of 10 (0.055 g, 0.16 mmol, 84%), mp = 93-94 °C, were formed.

**Co-crystal 11a: (4-Cyanopyridine)\(_2\)•4,4'-biphenol.** To 4-cyanopyridine (0.040 g, 0.38 mmol) was added 4,4'-biphenol (0.036 g, 0.19 mmol). To the solid mixture was added 2 mL of methanol and the solution was left to evaporate at ambient conditions. After 4 days, yellow crystals of 11a (0.044 g, 0.13 mmol, 67%) were formed. Melting point of 11a was not determined due to its decomposition followed by melting of 4,4'-biphenol (more details related to this co-crystal and its polymorphs are included in chapter 3).

**Co-crystal 12: (4-Cyanopyridine)\(_3\)•phloroglucinol.** To 4-cyanopyridine (0.041 g, 0.39 mmol) was added phloroglucinol (0.016 g, 0.13 mmol) and the mixture was dissolved in 2 mL of acetone. After 3 days yellow needles of 13 (0.045 g, 0.10 mmol, 77%), mp = 116-117 °C were observed.

**Additional data:**
Solution co-crystallization attempts to obtain 3-cyanopyridine•1-hexadecanol and 4-cyanopyridine•1-hexadecanol were unsuccessful; the IR spectroscopy and PXRD spectra of the solid obtained from solution evaporation of the corresponding components in equimolar ratio revealed a mixture of starting materials.

Solution co-crystallizations that involved stoichiometric amounts of the following pairs: 3-cyanopyridine and 1-naphthol, 3-cyanopyridine and resorcinol, 3-cyanopyridine and phloroglucinol, and 4-cyanopyridine and 1-naphthol, resulted in liquid products, unsuitable for solid state characterizations.

Solution co-crystallization attempts to obtain: 3-hydroxypyridine•1-cyanonaphthalene, (3-hydroxypyridine)\textsubscript{2}•1,3-dicyanobenzene, (3-hydroxypyridine)\textsubscript{2}•1,4-dicyanobenzene, 5-hydroxyisoquinoline•1-cyanonaphthalene, (5-hydroxyisoquinoline)\textsubscript{2}•1,3-dicyanobenzene, and (5-hydroxyisoquinoline)\textsubscript{2}•1,4-dicyanobenzene resulted in mixtures of the starting materials.

All co-crystals were analyzed by infrared spectroscopy using a Nicolet Avatar 320 FTIR instrument. The purity of bulk samples was confirmed by X-ray powder diffraction. Co-crystals 1, 5, 6, 8, 9, and 11\textsubscript{a} were analyzed on a Rigaku Miniflex Diffractometer using Cu Kα (\(\lambda = 1.54056\) Å), 30 kV, 15 mA. The data was collected over an angular range of 3° to 40° 2\(\theta\) in continuous scan mode using a step size of 0.02° 2\(\theta\) and a scan speed of 2.0°/min. Compounds 2-4, 7, 10, and 12 were analyzed on Bruker AXS D8 discover X-ray diffractometer equipped with GADDS\textsuperscript{TM} (General Area Diffraction Detection System), a Bruker AXS HI-STAR area detector at a distance of
15.05 cm as per system calibration, a copper source, automated x-y-z stage, and 0.5 mm collimator. Data were collected over 2.1-37.0 \( \theta \) range at a step size of 0.02 \( \theta \). Melting points of compounds 1-10 and 12 were determined on a MEL-TEMP\(^\circledR\) apparatus, and the comparison of the melting points of 1-12 with the corresponding constituents is summarized in Table 2.2.

### Table 2.2. Comparison of the melting points of co-crystals 1-12 and the corresponding components

<table>
<thead>
<tr>
<th>Co-crystal</th>
<th>Mp of co-crystal [(^\circ)C]</th>
<th>Mp of component 1 [(^\circ)C]</th>
<th>Mp of component 2 [(^\circ)C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54 – 57</td>
<td>81 - 82 (3cyph)</td>
<td>68 - 71 (phenpy)</td>
</tr>
<tr>
<td>2</td>
<td>106 – 108</td>
<td>81 - 82 (3cyph)</td>
<td>110 - 112 (bipyeta)</td>
</tr>
<tr>
<td>3</td>
<td>112 – 114</td>
<td>81 - 82 (3cyph)</td>
<td>150 - 153 (bipyte)</td>
</tr>
<tr>
<td>4</td>
<td>124 - 125</td>
<td>81 - 82 (3cyph)</td>
<td>150 - 153 (bipyte)</td>
</tr>
<tr>
<td>5</td>
<td>65 - 66</td>
<td>110 - 113 (4cyph)</td>
<td>68 - 71 (phenpy)</td>
</tr>
<tr>
<td>6</td>
<td>143 - 146</td>
<td>110 - 113 (4cyph)</td>
<td>110 - 114 (bipy)</td>
</tr>
<tr>
<td>7</td>
<td>138 - 139</td>
<td>110 - 113 (4cyph)</td>
<td>110 - 112 (bipyeta)</td>
</tr>
<tr>
<td>8</td>
<td>141 - 142</td>
<td>110 - 113 (4cyph)</td>
<td>150 - 153 (bipyte)</td>
</tr>
<tr>
<td>9</td>
<td>250 (dec)</td>
<td>49 - 50 (3cypy)</td>
<td>283 (bphe)</td>
</tr>
<tr>
<td>10</td>
<td>93 - 94</td>
<td>76 - 79 (4cypy)</td>
<td>109 - 111 (res)</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>76 - 79 (4cypy)</td>
<td>283 (bphe)</td>
</tr>
<tr>
<td>12</td>
<td>116 - 117</td>
<td>76 - 79 (4cypy)</td>
<td>216 (phlgl)</td>
</tr>
</tbody>
</table>

### 2.4.2. Single Crystal X-ray Crystallography

Co-crystals 1-12 were examined under a microscope and suitable single crystals were selected for X-ray diffraction. Data were collected on a Bruker–AXS SMART APEX CCD diffractometer with monochromatized Mo K\( \alpha \) radiation \((\lambda = 0.71073 \text{ Å})\) connected to KRYO-FLEX low temperature device. Data for 2, 3, 6, 7, and 9, were collected at 100 K. Data for 1, 4, 5, 8, and 10-12 were collected at 298 K. Lattice parameters were determined from least square analysis, and reflection data were
integrated using the program SAINT. Lorentz and polarization corrections were applied for diffracted reflections. In addition, the data of all compounds, except one (I2) was corrected for absorption using SADABS.\(^{248}\) Structures were solved by direct methods and refined by full matrix least squares based on \(F^2\) using SHELXTL.\(^{249}\) All non-hydrogen atoms were refined with anisotropic displacement parameters. All H-atoms bonded to carbon atoms, were placed geometrically and refined with an isotropic displacement parameter fixed at 1.2 times \(U_q\) of the atoms to which they were attached. The O bonded protons were located from Fourier difference map and refined isotropically based upon the corresponding O atom (\(U(H) = 1.2U_q(O)\)). Crystallographic data for I-12 are presented in Table 2.3 and selected hydrogen bond distances are listed in Table 2.4.
# Table 2.3. Crystallographic data and structure refinement parameters for co-crystals 1-12

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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</thead>
<tbody>
<tr>
<td><strong>Chemical formula</strong></td>
<td>C$_7$H$<em>5$NO • C$</em>{11}$H$_9$N</td>
<td>(C$_7$H$<em>5$NO)$<em>2$ • C$</em>{12}$H$</em>{12}$N$_2$</td>
<td>(C$_7$H$<em>5$NO)$<em>2$ • C$</em>{12}$H$</em>{10}$N$_2$</td>
<td>C$_7$H$<em>5$NO • C$</em>{10}$H$_8$N$_2$</td>
<td>(C$_7$H$<em>5$NO)$<em>2$ • C$</em>{12}$H$</em>{12}$N$_2$</td>
<td>(C$_7$H$<em>5$NO)$<em>2$ • C$</em>{12}$H$</em>{10}$N$_2$</td>
<td>C$_7$H$<em>5$NO • C$</em>{11}$H$_9$N</td>
<td>(C$_7$H$<em>5$NO)$<em>2$ • C$</em>{12}$H$</em>{10}$N$_2$</td>
<td>(C$_6$H$_4$N$<em>2$)$<em>2$ • C$</em>{12}$H$</em>{10}$O$_2$</td>
</tr>
<tr>
<td><strong>Formula .wt.</strong></td>
<td>274.31</td>
<td>422.48</td>
<td>420.46</td>
<td>301.34</td>
<td>274.31</td>
<td>394.42</td>
<td>422.48</td>
<td>420.46</td>
<td>394.42</td>
</tr>
<tr>
<td><strong>Crystal system</strong></td>
<td>Monoclinic</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
<td>Triclinic</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
</tr>
<tr>
<td><strong>Space group</strong></td>
<td>P$_2_1$/c</td>
<td>P$_2_1$/c</td>
<td>P$_2_1$/n</td>
<td>C$_2$/c</td>
<td>C$_2$/c</td>
<td>P$\bar{1}$</td>
<td>P$_2_1$/c</td>
<td>P$_2_1$/c</td>
<td>P$_2_1$/c</td>
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<td><strong>a (Å)</strong></td>
<td>9.90(1)</td>
<td>13.223(3)</td>
<td>16.542(2)</td>
<td>18.715(8)</td>
<td>26.22(1)</td>
<td>3.848(2)</td>
<td>11.195(3)</td>
<td>14.660(3)</td>
<td>20.866(6)</td>
</tr>
<tr>
<td><strong>b (Å)</strong></td>
<td>21.65(3)</td>
<td>6.197(1)</td>
<td>7.506(1)</td>
<td>7.228(3)</td>
<td>7.481(5)</td>
<td>8.755(4)</td>
<td>7.335(2)</td>
<td>4.110(1)</td>
<td>7.437(2)</td>
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<tr>
<td><strong>c (Å)</strong></td>
<td>7.590(9)</td>
<td>14.630(3)</td>
<td>18.709(2)</td>
<td>23.208(9)</td>
<td>19.41(1)</td>
<td>14.364(6)</td>
<td>13.530(4)</td>
<td>18.290(4)</td>
<td>6.766(2)</td>
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<tr>
<td><strong>α (°)</strong></td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90.647(7)</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td><strong>β (°)</strong></td>
<td>112.14(2)</td>
<td>113.661(3)</td>
<td>106.763(2)</td>
<td>90.48(1)</td>
<td>128.31(1)</td>
<td>94.498(8)</td>
<td>99.456(7)</td>
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<td>98.142(5)</td>
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<td><strong>γ (°)</strong></td>
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<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90.547(7)</td>
<td>90</td>
<td>90</td>
<td>90</td>
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<td><strong>Volume (Å$^3$)</strong></td>
<td>1508(3)</td>
<td>1098.1(4)</td>
<td>2224.2(4)</td>
<td>3139(2)</td>
<td>2987(3)</td>
<td>476.6(4)</td>
<td>1095.9(6)</td>
<td>1101.9(4)</td>
<td>1039.4(5)</td>
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<tr>
<td><strong>D$_{calc}$ (g cm$^{-3}$)</strong></td>
<td>1.208</td>
<td>1.278</td>
<td>1.256</td>
<td>1.275</td>
<td>1.220</td>
<td>1.374</td>
<td>1.280</td>
<td>1.267</td>
<td>1.260</td>
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<td>2</td>
<td>4</td>
<td>8</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>θ range</strong></td>
<td>1.88-24.99</td>
<td>1.68-26.73</td>
<td>1.95-25.00</td>
<td>1.75-24.99</td>
<td>1.98-25.00</td>
<td>1.43-26.37</td>
<td>1.84-25.00</td>
<td>2.61-23.35</td>
<td>0.99-26.73</td>
</tr>
<tr>
<td><strong>Nref./Npara.</strong></td>
<td>2607/191</td>
<td>2314/145</td>
<td>3798/290</td>
<td>2748/208</td>
<td>2585/190</td>
<td>1888/136</td>
<td>1818/145</td>
<td>1565/145</td>
<td>2181/136</td>
</tr>
<tr>
<td><strong>T (K)</strong></td>
<td>298</td>
<td>100</td>
<td>298</td>
<td>100</td>
<td>298</td>
<td>100</td>
<td>298</td>
<td>100</td>
<td>298</td>
</tr>
<tr>
<td><strong>R$_1$</strong></td>
<td>0.0558</td>
<td>0.0597</td>
<td>0.0504</td>
<td>0.0688</td>
<td>0.0630</td>
<td>0.0659</td>
<td>0.0672</td>
<td>0.0502</td>
<td>0.0685</td>
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<tr>
<td><strong>wR$_2$</strong></td>
<td>0.1461</td>
<td>0.1550</td>
<td>0.1501</td>
<td>0.1492</td>
<td>0.1759</td>
<td>0.1926</td>
<td>0.1752</td>
<td>0.1307</td>
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<tr>
<td><strong>GOF</strong></td>
<td>0.924</td>
<td>1.103</td>
<td>1.069</td>
<td>1.002</td>
<td>0.805</td>
<td>1.042</td>
<td>1.044</td>
<td>0.814</td>
<td>1.082</td>
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<tr>
<td><strong>Abs coef.</strong></td>
<td>0.076</td>
<td>0.083</td>
<td>0.082</td>
<td>0.081</td>
<td>0.077</td>
<td>0.090</td>
<td>0.083</td>
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Table 2.3. Crystallographic data and structure refinement parameters for co-crystals 1-12 (continued)

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<th>10</th>
<th>11a</th>
<th>12</th>
</tr>
</thead>
<tbody>
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<td>Chemical formula</td>
<td>(C₆H₄N₂)₂ • C₆H₆O₂</td>
<td>(C₆H₄N₂)₂ • C₁₂H₁₀O₂</td>
<td>(C₆H₄N₂)₃ • C₆H₆O₃</td>
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<tr>
<td>Formula .wt.</td>
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<td>394.42</td>
<td>438.44</td>
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<td>Crystal system</td>
<td>Triclinic</td>
<td>Monoclinic</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P T</td>
<td>C2/c</td>
<td>P T</td>
</tr>
<tr>
<td>a (Å)</td>
<td>9.171(4)</td>
<td>39.87(2)</td>
<td>7.889(3)</td>
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<tr>
<td>b (Å)</td>
<td>9.941(5)</td>
<td>7.586(5)</td>
<td>8.156(3)</td>
</tr>
<tr>
<td>c (Å)</td>
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<td>α (°)</td>
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<td>90</td>
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<td>β (°)</td>
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<td>γ (°)</td>
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<td>90</td>
<td>63.512(5)</td>
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<td>Dcalc ( g cm⁻³)</td>
<td>1.263</td>
<td>1.253</td>
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<td>Z</td>
<td>2</td>
<td>4</td>
<td>2</td>
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<tr>
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<td>1.02-25.09</td>
<td>1.04-25.00</td>
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<td>Nref./Npara.</td>
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<td>1830/136</td>
<td>3915/298</td>
</tr>
<tr>
<td>T (K)</td>
<td>298</td>
<td>298</td>
<td>298</td>
</tr>
<tr>
<td>R₁</td>
<td>0.0506</td>
<td>0.0682</td>
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</tr>
<tr>
<td>wR₂</td>
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</tr>
<tr>
<td>GOF</td>
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<tr>
<td>Abs coef.</td>
<td>0.086</td>
<td>0.082</td>
<td>0.089</td>
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Table 2.4. Geometrical parameters of supramolecular heterosynthon I present in co-crystals

<table>
<thead>
<tr>
<th>Hydrogen bond</th>
<th>( d ) (Å)</th>
<th>( D ) (Å)</th>
<th>( \theta ) (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O–H···N\text{arom}</td>
<td>1.63</td>
<td>2.708(3)</td>
</tr>
<tr>
<td>2</td>
<td>O–H···N\text{arom}</td>
<td>1.77</td>
<td>2.691(2)</td>
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<tr>
<td>3</td>
<td>O–H···N\text{arom}</td>
<td>1.69</td>
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<tr>
<td></td>
<td>O–H···N\text{arom}</td>
<td>1.75</td>
<td>2.729(2)</td>
</tr>
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<td>5</td>
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<td>6</td>
<td>O–H···N\text{arom}</td>
<td>1.84</td>
<td>2.718(3)</td>
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</tr>
<tr>
<td>8</td>
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<td>2.765(3)</td>
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<td>O–H···N\text{arom}</td>
<td>1.77</td>
<td>2.795(3)</td>
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Chapter 3 — Methods of Preparation of Co-crystals and Polymorphism in Co-crystals

3.1. Focus

As demonstrated in chapter 2, the single crystal analysis of model co-crystals revealed the existence of the O–H···N_{arom} supramolecular heterosynthon (I) in all described structures. The reliability of supramolecular synthons can be related to their recurrence in co-crystals prepared via different methods and under variable conditions. Considering the recent reports related to the successful utilization of mechanochemical approach toward co-crystallization,^{141,151} model co-crystals 1-12 have been investigated in the context of their reproducibility via dry grinding and solvent-drop grinding. Grinding co-crystallization procedures involve grinding stoichiometric amounts of two (or more) co-crystal formers using mortal and pestle or in a mechanical grinder.^{143} Solvent-drop grinding relies on the addition of a small amount of solvent to the grinding procedure.\textsuperscript{151} In addition, growth of co-crystals from melt was utilized and was based upon melting stoichiometric amounts of co-crystal formers to a temperature slightly higher than the melting point of the higher melting co-crystal former and allowing the melted mixture to cool down to room temperature.

Due to the increasing awareness of polymorphism in organic compounds and its
important implications in terms of both fundamental and commercial interest, it was appropriate to address the existence of this phenomenon in the set of model co-crystals presented herein, with special emphasis on the origin of polymorphism. Solvent-drop grinding method has been utilized herein, due to its efficiency in the polymorphism screen and control, as reported in recent literature.\textsuperscript{186,188,208}

3.2. Results and Discussion

3.2.1. Methods of Preparations of Co-crystals

The reproducibility of co-crystals obtained from solvent evaporation approach was evaluated via co-crystallization methods that involved dry grinding, solvent-drop grinding, and growth from melt. To search for other possible polymorphs of co-crystals 1-12, solvent-drop grinding involving seven solvents of different polarities: cyclohexane, toluene, chloroform, ethyl acetate, methanol, dimethyl sulfoxide (DMSO), and water were utilized. It was observed that whereas 4-minute grinding with solvent-drop was efficient enough to obtain pure co-crystals, the dry grinding approach has not always led to complete conversions. To achieve complete co-crystallizations, the time of dry grinding needed to be extended to 20 minutes.

As confirmed by PXRD and FTIR analysis, co-crystals 1, 2, 5, 6, 7, 9, 10, and 12 were reproduced using the above procedures and no additional forms were observed. However, the mechanical co-crystallization was found to have additional effects on the remaining co-crystals 3, 4, 8, and 11.
Co-crystallization of 3-cyanophenol and trans-1,2-bis(4-pyridyl)ethylene. 3cyphe and bipyete can form co-crystals with 2:1 stoichiometry (3) and with 1:1 stoichiometry (4). It was observed that dry grinding or melting the components in 2:1 ratio result in mixtures of 3 and 4, whereas solvent-drop grinding with all the applied solvents affords pure 3. When the two components are combined in 1:1 ratio, the dry grinding and melting, also afford mixtures of 3 and 4. The solvent-drop grinding with cyclohexane, toluene, chloroform, ethyl acetate, methanol, and water solvents afforded mixtures of 3 and 4, however, DMSO-drop grinding revealed the formation of pure 4.

Co-crystallization of 4-cyanophenol and trans-1,2-bis(4-pyridyl)ethylene. The PXRD patterns obtained based upon melting, dry grinding, solvent-drop grinding (cyclohexane, toluene, chloroform, ethyl acetate, methanol, and water) of 4cyphe and bipyete in 2:1 ratio revealed additional peaks and shifts as compared to the PXRD pattern of 8. Of the seven solvents only DMSO-drop grinding resulted in a product of which the PXRD pattern matched the pattern of 8. Interestingly, when the components in 1:1 ratio were subjected to melting, grinding and solvent-drop grinding, similar peaks and shifts were observed. Search for additional forms of this co-crystal based upon a series of solution crystallizations of the components in various ratios (1:1, 2:1, and 4:1), followed by single crystal X-ray analysis, revealed the existence of a 1:1 co-crystal of 4cyphe and bipyete, which exhibit two concomitant polymorphic modifications, form I (13a) and from II (13b). Detailed discussion and structural comparison of 13a and 13b will be presented in section 3.2.2.

Co-crystallization of 4-cyanopyridine and 4,4′-biphenol. Dry grinding and
solvent-drop grinding of 4cypy and bphe in 2:1 ratio revealed consistent, however drastically different PXRD patterns, as compared to the XPD pattern of 11a (the crystal structure of 11a was introduced in chapter 2). In search for the unknown forms, a series of solution crystallization experiments, followed by single crystal X-ray analysis, revealed the existence of an additional polymorph form II, 11b. The two polymorphs appeared concomitantly when a mixture of MeOH and EtOAc in 1:1 ratio was used. It was established that form II was exclusively afforded from the solvent-drop grinding experiments involving cyclohexane, toluene, chloroform, ethyl acetate, methanol, and water, whereas the utilization of DMSO lead to the formation of a reported DMSO solvate of bphe (CSD refcode ECELON01, see appendix 24). Detailed discussion and structural comparison of 11a and 11b will be presented in section 3.2.3.

The attempts to obtain 3-hydroxypyridine•1-cyanonaphthalene, (3-hydroxypyridine)2•1,3-dicyanobenzene, (3-hydroxypyridine)2•1,4-dicyanobenzene, 5-hydroxyisoquinoline•1-cyanonaphthalene, (5-hydroxyisoquinoline)2•1,3-dicyanobenzene, and (5-hydroxyisoquinoline)2•1,4-dicyanobenzene via mechanochemical and melting co-crystallizations resulted in mixtures of the corresponding starting materials, which confirmed, mentioned in chapter 2, unsuccessful solution co-crystallizations of the listed pairs of co-crystal formers. These results were expected based upon the observation that CN-containing compounds would not interact with the OH/Narom-containing compounds.

A series of co-crystallization experiments that involved stoichiometric amounts of the following pairs: 3-cyanopyridine and 1-naphthol, 3-cyanopyridine and resorcinol, 3-
cyanopyridine and phloroglucinol, and 4-cyanopyridine and 1-naphthol, resulted in liquid products. Additional co-crystallization experiments carried out at -4 °C also resulted in liquid products. An illustration of the solid-to-liquid conversion when 3-cyanopyridine and 1-naphthol are combined is presented in Figure 3.1. Based upon the high reliability of heterosynthon I (chapter 2) and the fact that co-crystals 9-12 (comprised of 3cyp, 4cyp and phenols) exist, it could be speculated that the listed co-crystal formers reacted, and that the melting points of the co-crystalline products are much lower than room temperature. However, to prove or disprove this hypothesis additional experimentations are needed.

![Figure 3.1. Solid-to-liquid conversion occurring in a mixture of 3-cyanopyridine and 1-naphthol](image)

3.2.2. Polymorphism in 4-cyanophenol\textbullet trans-1,2-bis-(4-pyridyl)ethylene co-crystal

**4-cyanophenol\textbullet trans-1,2-bis-(4-pyridyl)ethylene** co-crystal, \textit{13}, exhibits two concomitant polymorphs: monoclinic form I (\textit{13a}) and triclinic form II (\textit{13b}). The asymmetric unit of \textit{13a} consists of two 4cyphe molecules and two bipyete molecules. Interestingly, the assembly of the two components results in two distinct supramolecular
entities (Figure 3.2). The first entity is a non-centrosymmetric 2:1 adduct sustained by I (D1: 2.721(3) Å, D2: 2.669(4) Å; C–O distances: 1.336(3) Å, 1.355(4) Å; C–N–C angles: 116.6(3)° and 116.1(3)°) with the dihedral angle between the 4cyphe and the bipyete rings being ca. 76.9° and 79.4°. The second entity is a non-hydrogen bonded bipyete residing in between the 2:1 adducts. The free and hydrogen bonded bipyete molecules alternate through π-π stacking along the b axis. The stacking involves face-to-face aromatic interactions of relatively short interplanar distance of ca. 3.61 Å, which can make the unsaturated moieties of bipyete suitable for [2+2] photodimerization in the solid state. The crystal packing is further extended into 2D planar sheets in result of the formation of C–H···N≡C dimer between the stacked columns.

Figure 3.2. Crystal structure of 4-cyanophenol•t-1,2-bis(4-pyridyl)bipyethylene form I, 13a
The asymmetric unit of 13b also consists of two 4cyphe molecules and two bipyete molecules. However, unlike in 13a, the components form two crystallographically independent 1:1 supramolecular adducts sustained by I (D1: 2.689(4) Å, D2: 2.717(4) Å; C–O distances: 1.327(5) Å, 1.347(4) Å; C–N–C angles: 117.2(3)°, 116.6(4)°). The dihedral angles between the 4cyphe and the bipyete rings in the respective adducts are ca. 74.5° and 79.7°. The 1:1 adducts stack on top of each other in face-to-face fashion along the a axis, and the distance between the adjacent bipyete molecules is ca. 3.48 Å. Such columns of the stacked adducts expand into 2D planar sheets through centrosymmetric C–H···N=C dimer formed between adjacent 4cyphe molecules (Figure 3.3). The similarity of crystal packings of 13a and 13b is manifested on the calculated powder diffraction patterns (Figure 3.4.). The major peaks of the two forms overlap, while the difference between the patterns lay in the small intensity peaks.
at ca. 16°-17° 2θ and ca. 26° 2θ.

![X-ray powder diffraction patterns](image)

**Figure 3.4.** X-ray powder diffraction patterns of 4-cyanophenol•t-1,2-bis(4-pyridyl)bipethylene polymorphs: bulk sample (green) and simulated patterns of form I (black) and form II (red)

3.2.3. Polymorphism in (4-cyanopyridine)$_2$•4,4’-biphenol co-crystal

An examination by IR spectroscopy, powder X-ray diffraction and single crystal X-ray diffraction of the irregular hexagons and parallelepiped plates (Figure 3.5) obtained from solution crystallization confirmed the presence of two concomitant polymorphs of (4cyp)$_2$•bphe, form I ($11a$) and form II ($11b$), respectively (numbering is based on order of discovery).
Figure 3.5. Concomitant polymorphs of (4-cyanopyridine)$_2$•4,4’-biphenol co-crystal: a) form I – irregular hexagons, b) form II – parallelepiped plates

The single crystal X-ray structures of form I and form II confirm the expected 2:1 stoichiometry and reveal the presence of supramolecular heterosynthons I between the 4cyp and bphe molecules. However, the crystal packing patterns of the two forms are distinct due to conformational differences in the bphe molecules (Figures 3.6 and 3.7). Form I crystallizes in $C_2/c$ and the asymmetric unit consists of half a bphe molecule (residing on crystallographic inversion center) and one 4cyp molecule. The bphe molecules are flat (torsion angle between two phenol rings is 180.0°), sustain centrosymmetric (4cyp)$_2$•bphe supramolecular adducts (Figure 3.6a). The dihedral angle between 4cyp and bphe molecules (planes of the aromatic rings represented by atoms C11–N11–C15 and C2–C1–C6) is 128.5°. The O–H⋯N$_\text{arom}$ hydrogen bond distance (D: 2.733(4) Å) is within the expected range for alcohol-aromatic nitrogen interactions (Table 2.1). The crystal structure of 11a was already described in chapter 2 (co-crystal 11a).

Form II (11b) crystallizes in $P2_1/n$. The asymmetric unit consists of four bphe
molecules and two \textbf{bphe} molecules, which differ in their torsion angles: ca. 145.7(3)° (torsion represented by C3–C4–C7–C12) in \textbf{bphe}', and ca. 160.2(3)° (torsion represented by C23–C24–C27–C32) in \textbf{bphe}'', Figure 3.5b. The dihedral angles between the planes of the aromatic rings of \textbf{4cypy} and \textbf{bphe}' are 153.1° (planes represented by C61–N61–C65 and C9–C10–C11) and 112.0° (planes represented by C41–N41–C45 and C2–C1–C6). The dihedral angles between the planes of the aromatic rings of \textbf{4cypy} and \textbf{bphe}'' are 141.1° (planes represented by C51–N51–C55 and C22–C21–C26) and 104.1° (planes represented by C71–N71–C75 and C29–C30–C31). This range of dihedral angles in the \textbf{(4cypy)$_2$bphe} adducts in form II (Figure 3.6b) is unsurprising given that supramolecular heterosynthons \textbf{I} is a one-point recognition interaction with rotational freedom. The O–H···N$_\text{arom}$ hydrogen bond distances within the supramolecular adducts are 2.693(3) Å and 2.789(4) Å in \textbf{(4cypy)$_2$bphe}'', and 2.838(3) Å and 2.766(3) Å in \textbf{(4cypy)$_2$bphe}''.
Figure 3.6. ORTEP plot of supramolecular adducts in (4-cyanopyridine)$_2$$\cdot$4,4'-biphenol drawn at 50% probability level for non-hydrogen atoms: (a) form I, (b) form II. Note that bphe molecules are flat in form I, whereas twisted in form II.

The crystal structure of 11b is shown in Figure 3.7. The adjacent 2:1 adducts are connected via non-centrosymmetric C–H···N=C dimers forming 1D chains. The chains are packed side by side along the $a$ axis, thereby generating a 2D network.

Figure 3.7. Crystal packing in (4-cyanopyridine)$_2$$\cdot$4,4'-biphenol form II, 11b
The CSD contains only 22 structures involving \textit{bphe}.\textsuperscript{251} The number of crystallographically independent \textit{bphe} molecules in these structures is 33. Figure 3.8 reveals that one molecule is flat (torsion angle is 0°), 16 molecules are slightly twisted (0-5°), and torsion angles of the remaining 16 molecules are spread over a wide range (5-70°). Furthermore, 3 of the 22 structures exhibit conformational isomorphism\textsuperscript{252} and one compound exhibits conformational polymorphism.\textsuperscript{253} To our knowledge, (4\textit{cypy})\textsubscript{2}\textit{bphe} form II is the first \textit{bphe}-containing compound that exhibits both phenomena.

A similar analysis involving biphenyl derivatives and their complexes reveals 623 structures with 1,026 crystallographically independent molecules. The histogram of torsion angles (Figure 3.9a) shows a maximum corresponding to a 1-5° torsion angle range (189 molecules), however there is a second maximum occurring within the torsion angle range of 25-45° (651 molecules). These statistics are in agreement with previous reports and suggest that such molecules are especially influential upon crystal packing effects because of a small rotational barrier around the central C–C bond.\textsuperscript{254,255} The torsion angles encountered in \textit{bphe} (form I), \textit{bphe′} and \textit{bphe″} (form II), ca. 0.0°, 34.3° and 19.8°, respectively, are consistent with the statistical data. Interestingly, 92 of the 623 structures were found to exhibit conformational isomorphism. Furthermore, 19 of the 623 exhibit conformational polymorphism, of which 11 also exhibit conformational isomorphism. This subset of 92 structures was analyzed to determine the torsion angle differences between conformers that co-exist in the same crystal structure. To simplify the analysis, only structures that contain two conformational isomorphs were taken into consideration. This resulted in a subset of 67 entries. In 57 of these structures the torsion
angle differences are rather subtle (ca. 1-10°), whereas the remaining 10 pairs of conformational isomorphs exhibit higher torsion angle deviations (10-40°), Figure 3.9b.

Figure 3.8. Histogram representing the torsion angle distribution in 22 crystal structures of 4,4’-biphenols

Figure 3.9. a) Distribution of torsion angles in the 623 crystal structures that contain biphenyl moieties; b) Distribution of torsion angle deviations within pairs of conformers present in 67 crystal structures

The calculated density of form I is slightly lower than the calculated density of form II (1.253 Mg/m³ vs. 1.266 Mg/m³). The melting points of both co-crystal forms was not recorded because (4cypy)$_2$•bphe decomposes upon heating. The DSC thermograms
(see appendix 11) of the two polymorphs show two endothermic peaks; one corresponding to the co-crystal decomposition (ca. 94.3°C in form I and ca. 96.1°C in form II) and another corresponding to melting of bphe (ca. 284.1°C), respectively.

Polymorphic transformations between the two forms of \((4\text{cyp})_2\cdot\text{bphe}\) were also investigated, as illustrated in Figure 3.10. When form I is dry or solvent-drop ground with methanol, acetone, or ethyl acetate, conversion to form II is observed. Conversely, slow evaporation of methanol, ethyl acetate, or acetone solutions of form II yield form I. Slurry experiments involving 1:1 mixtures of form I and form II in methanol, ethyl acetate or acetone afford form II. Experimental and simulated PXRD patterns of both polymorphs are presented in Figure 3.11.

![Figure 3.10. Polymorphic conversions between form I and form II of the \((4\text{-cyanopyridine})_2\cdot4,4'\text{-biphenol co-crystal}\)](image-url)
In summary, the combination of various methods of co-crystallization, namely grinding, solvent-drop grinding, growth from melt, and solution co-crystallization, have led to new discoveries. The first finding is related to the existence of a dimorphic co-crystal of \textbf{4cyphe\textbullet bipyete} (13\textit{a} and 13\textit{b}), which was observed in result of grinding, solvent-drop grinding and melting co-crystallization methods. The two forms of \textbf{4cyphe\textbullet bipyete} exhibit 1:1 stoichiometry and they occur concomitantly. The formation of this co-crystal is somewhat surprising from the perspective that a co-crystal of \textbf{4cyphe} and \textbf{bipyete} with the expected 2:1 stoichiometry exists (8). Interestingly, 2:1 and 1:1 stoichiometries, although polymorphic forms were not detected, also exist in the co-crystals of \textbf{3cyphe} and \textbf{bipyete} (3 and 4). Similar molecular arrangement of \textbf{bipyete} in co-crystals 4, 13\textit{a}, and 13\textit{b}, may suggest that the crystal packings are strongly stabilized by aromatic stacking and C–H···N_{arom} interactions, in addition to the primary supramolecular heterosynthon 1.

The second finding is related to the existence of an additional polymorph of
(4cypyl)$_2$•bphe, form II, which was discovered based on grinding and solvent-drop grinding co-crystallizations. Form II of (4cypyl)$_2$•bphe (11a) exhibits concomitant and conformational polymorphism and conformational isomorphism. To our knowledge, concomitant or conformational polymorphism, or both phenomena, have been observed in several co-crystals,\textsuperscript{186,256,257} whereas all three phenomena have only been reported for the triphenylsilanol•4,4’-dipyridyl co-crystal.\textsuperscript{256}

It is interesting to note that the supramolecular heterosynthon, I, which sustains both (4cypyl)$_2$•bphe and 4cyphe•bipyete co-crystals remains unchanged in their polymorphic modifications. The origin of polymorphism in 11a and 11b can be related to the conformational flexibility of the bphe molecules, while polymorphism in 13a and 13b results from the variations in the crystal packing. A detailed structural analysis of the 11 polymorphic co-crystals reported in the CSD reveals, that within the set of polymorphs of a given co-crystal, supramolecular heterosynthons also persist.\textsuperscript{182,183,185} For instance, the crystal structures of two quinhydrone polymorphs, form $\alpha$ and form $\beta$, Figure 3.12, are sustained by alternating $p$-benzoquinone and hydroquinone molecules that interact via O–H…O hydrogen bonds. Such a molecular arrangement leads to the generation of infinite linear chains.\textsuperscript{116,258} The two crystal packings differ in the relative orientation of these chains. In form $\alpha$ (Figure 3.12a) the chains are oriented nearly orthogonally with respect to each other, whereas in form $\beta$, (Figure 3.12b) the chains are packed side by side. Although concomitant polymorphism was not reported, a review of the relevant literature, revealed that both forms of quinhydrone can be crystallized from acetone.
The persistency of supramolecular heterosynthons is also seen in the dimorphic co-crystal of caffeine•glutaric acid. In form I and form II of this co-crystal the components interact via carboxylic acid···imidazole supramolecular heterosynthon, Figure 3.13. The difference between the two polymorphs is related to rather subtle conformational variations of the methylene groups of glutaric acid (conformational polymorphism). Form I and form II occur concomitantly when the co-crystallization is carried out in chloroform. Interestingly, the polymorphic outcome of co-crystallization can be controlled by applying solvent-drop grinding methodology. Form I could be obtained when non-polar solvents (e.g. hexane) were added to the grinding procedure, whereas form II could be obtained upon the addition of polar solvents (e.g. acetonitrile).

Further structural analysis of the 9 remaining co-crystals shows that the supramolecular heterosynthons also persist within a given set of polymorphs. This indicates that the differences in crystal packings that result from the engagement of molecules in different hydrogen bonding modes, observed in single-component compounds, do not occur in co-crystals.
The existence of concomitant polymorphism in co-crystals 11 and 13 implies that the free energy difference between the crystalline forms is small.\textsuperscript{56,181} Despite the fact that the phenomenon of concomitancy of polymorphs has been long known,\textsuperscript{259} there has been little information related to the frequency of its occurrence in organic compounds.\textsuperscript{260} This perhaps can be explained by the general difficulty to quantitatively assess polymorphism. An overview of the literature related to the 11 existing polymorphic co-crystals revealed that in four cases, concomitant polymorphism was apparent.\textsuperscript{261} By including (4cypy)$_2$•bphe and 4cyphe•bipyete to the total number of structurally characterized polymorphic co-crystals, it becomes clear that in nearly 50\% of cases concomitancy is present. This is a relatively high frequency of occurrence, which perhaps could be higher considering that not all polymorphs may have been reported or discovered yet. With the emergence of X-ray diffraction and the development of more sophisticated methods of analysis, as well as the increasing awareness of the
phenomenon, more discoveries of concomitant polymorphism could perhaps be expected.

3.3. Conclusions

The presented series of co-crystallization experiments have demonstrated that the utilization of grinding, solvent-drop grinding and melting techniques in the co-crystallization procedures offers a viable means for supramolecular synthesis. Such synthetic approaches can be advantageous from the perspective of green chemistry principles. Additionally, the solvent-drop grinding approach showed to be useful in addressing the issue of stoichiometry and polymorph control in co-crystals. Although the role of a solvent in the nucleation process is still not entirely understood, the results obtained based upon solvent-drop grinding suggest that it is generally possible to find experimental conditions, under which a specific co-crystal form exists.\textsuperscript{187}

In the total number of co-crystals, (13 presented herein and 1487 archived the CSD), 23 have been found to exhibit polymorphic behavior (2 presented herein and 21 archived in the CSD).\textsuperscript{185} Thus, the percentage occurrence of polymorphic co-crystals is 1.5\%, as compared to the 1.7\% of occurrence of polymorphic single component compounds (Table 1.2).\textsuperscript{183} It can be therefore concluded that the extent of polymorphism in both classes of compounds is comparable. It should be noted, however, that the information related to polymorphism in co-crystals is limited (23 polymorphic co-crystals vs. 1600 polymorphic single component compounds) and that further investigations conducted on a broader range of co-crystals would enhance the significance of the presented results. Furthermore, drawing a meaningful conclusion from such studies is
complicated by the fact that the absence of a polymorphic behavior in a given co-crystal at given experimental conditions does not mean that polymorphism can not be observed at other conditions. From this perspective, assessing the frequency of concomitant polymorphism is also complicated, although based on the available data (albeit limited) it could be determined that at least ca. 50% of known co-crystal polymorphs can exist concomitantly. This result may be relevant from a commercial perspective, as concomitant crystallizations need to be avoided because they can lead to materials that do not meet prescribed norms.\textsuperscript{181} In this context, utilization of high-throughput screening within a wider range of experimental conditions (e.g. range of solvent systems, temperature variations) offers a suitable means in the identification of polymorphs.

If the persistency of supramolecular heterosynthons within a set of polymorphs holds true over a broader range of co-crystals it may become of importance in the context of polymorphism control. In particular, the variety of factors that influence polymorphic behaviors of organic compounds (supramolecular synthon, conformational, and crystal packing variations) could be reduced by eliminating the possibility for molecular self-assembly through different supramolecular synthons. Advancements in the context of understanding and controlling polymorphism is of high relevance from the perspective of crystal engineering, where the control over the design and preparation of desired crystal structures is fundamental. Polymorphism is also of utmost importance in the context of preparation of solid forms of APIs and the opportunity to reduce its extent co-crystal formulations would represent a particularly attractive approach.
3.4. Experimental

3.4.1. Syntheses

Co-crystallization via grinding: Stoichiometric amounts of the starting materials were ground with a mortar and pestle for ca. 20 minutes.

Co-crystallization via solvent-drop grinding: Stoichiometric amounts of the starting materials were ground with a mortar and pestle for ca. 4 minutes with the addition of seven solvents (10 μL per 50 mg of co-crystal): cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.

Co-crystallization via melting: Stoichiometric amounts of the starting materials were heated until melt and the mixture was left to crystallize at ambient conditions. Co-crystals 11 and 12 could not be obtained by this procedure due to decomposition of 4,4’-biphenol and sublimation of phloroglucinol upon heating.

Co-crystallization via solution evaporation.

Co-crystal 11a and 11b: (4-cyanopyridine)$_2$$\cdot$4,4’-biphenol, form I and form II.

A solution of 4-cyanopyridine (0.040 g, 0.38 mmol) and 4,4’-biphenol (0.036 g, 0.19 mmol) in 2 mL of 1:1 methanol and ethyl acetate was allowed to evaporate slowly at ambient conditions. Yellow crystals of two distinct morphologies, irregular hexagonal plates and parallelepiped plates (total: 0.056 g, 0.14 mmol, 74%), appeared within four days.

Co-crystal 13a and 13b: 4-cyanophenol•trans-1,2-bis(4-pyridyl)ethylene, form I
**and form II.** To 4-cyanophenol (0.026 g, 0.22 mmol) was added trans-1,2-bis(4-pyridyl)ethylene (0.040 g, 0.22 mmol) and the mixture was dissolved in 2 mL of methanol. After 14 days colorless crystalline product (total: 0.029 g, 0.096 mmol, 88%), mp = 153-156 °C was observed. Single crystal X-ray diffraction analysis performed on several selected crystals revealed the presence of two concomitant polymorphs.

3.4.2. Single Crystal X-ray Crystallography

Suitable crystals of the polymorphs studied herein were examined under a microscope and suitable single crystals were selected for X-ray analysis. Data were collected on a Bruker–AXS SMART APEX CCD diffractometer with monochromatized Mo Kα radiation (λ = 0.71073 Å). Data were collected at 298 K. Lattice parameters were determined from least square analysis, and reflection data were integrated using the program SAINT. Lorentz and polarization corrections were applied for diffracted reflections. In addition, the data was corrected for absorption using SADABS.248 Structures were solved by direct methods and refined by full matrix least squares based on $F^2$ using SHELXTL.249 All non-hydrogen atoms were refined with anisotropic displacement parameters. All H-atoms bonded to carbon atoms were placed geometrically and refined with an isotropic displacement parameter fixed at 1.2 times $U_q$ of C atoms. OH protons were located from Fourier difference map inspection and refined isotropically with thermal parameters based upon the corresponding O atom (U(H)=1.2U_q(O)). Crystallographic data for 11b, 13a and 13b are presented in Table 3.1 and selected hydrogen bond distances are listed in Table 3.2. Crystallographic data and
selected hydrogen bond distances of 11a were included in the experimental section of chapter 2).

Table 3.1. Crystallographic data and structure refinement parameters for co-crystals 11b, 13a, and 13b

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Table 3.2. Geometrical parameters of supramolecular heterosynthon I present in co-crystals

11b, 13a, and 13b

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<td>O–H⋯N&lt;sub&gt;arom&lt;/sub&gt;</td>
<td>1.72</td>
<td>2.838(3)</td>
<td>173.7</td>
</tr>
<tr>
<td>O–H⋯N&lt;sub&gt;arom&lt;/sub&gt;</td>
<td>1.69</td>
<td>2.766(3)</td>
<td>164.2</td>
</tr>
<tr>
<td>O–H⋯N&lt;sub&gt;arom&lt;/sub&gt;</td>
<td>1.56</td>
<td>2.693(3)</td>
<td>163.2</td>
</tr>
<tr>
<td>O–H⋯N&lt;sub&gt;arom&lt;/sub&gt;</td>
<td>1.79</td>
<td>2.789(4)</td>
<td>172.3</td>
</tr>
<tr>
<td>13a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O–H⋯N&lt;sub&gt;arom&lt;/sub&gt;</td>
<td>1.73</td>
<td>2.721(3)</td>
<td>160.9</td>
</tr>
<tr>
<td>O–H⋯N&lt;sub&gt;arom&lt;/sub&gt;</td>
<td>1.72</td>
<td>2.669(4)</td>
<td>161.3</td>
</tr>
<tr>
<td>13b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O–H⋯N&lt;sub&gt;arom&lt;/sub&gt;</td>
<td>1.52</td>
<td>2.689(4)</td>
<td>164.9</td>
</tr>
<tr>
<td>O–H⋯N&lt;sub&gt;arom&lt;/sub&gt;</td>
<td>1.52</td>
<td>2.717(4)</td>
<td>172.0</td>
</tr>
</tbody>
</table>
Chapter 4 — Robustness of Supramolecular Heterosynthons: 2-Aminopyridinium Carboxylate

4.1. Focus

In the previous sections, it was illustrated that the understanding of the interplay of intermolecular interactions in the solid state can be facilitated by studies of model co-crystals comprised of components preselected for their chemical and geometrical attributes. Thus far the presented investigations have been related to 1-point recognition supramolecular synthons, such as hydroxyl···pyridine, hydroxyl···cyano, and hydroxyl···hydroxyl.

It is generally accepted that the probability of formation of a supramolecular motif increases proportionally to the number of involved hydrogen bonds. In this context, carboxylic acids and 2-aminopyrdines represent a suitable pair of moieties that engage in a 2-point recognition supramolecular synthon with high probability of formation, as determined by the pioneering work of Allen et al. based upon extensive CSD studies.

Carboxylic acids play a significant role in crystal engineering because they are self-complementary and they can form supramolecular heterosynthons with a wide range of other functional groups. In fact, a CSD search reveals that there are over 7,500 crystal structures of carboxylic acids. However, only ca. 25% of total structures exhibit homosynthon IV (Figure 4.1), whereas the remaining 75% of compounds exhibit
a variety of supramolecular heterosynthons. 2-aminopyridines and their derivatives such as 2-aminopyrimidines and melamines, which are often encountered in biological systems, are likewise capable of forming either supramolecular homosynthon V (Figure 4.1)\textsuperscript{263} or supramolecular heterosynthons.\textsuperscript{264,265}

![Supramolecular Heterosynthon IV and V](image)

*Figure 4.1. Examples of supramolecular homosynthons: a carboxylic acid homosynthon IV and a 2-aminopyridine homosynthon V*

In this section, the presented research is focused on the ability of 2-aminopyridines and carboxylic acids to form a reliable supramolecular heterosynthon, with an ultimate view to employing this supramolecular heterosynthon in a rational design of new multiple-component compounds that also contain structurally more complex APIs.

4.2. Results and Discussion

2-aminopyridine and 2-amino-5-methylpyridine were used in this study. They were reacted with a series of mono- and di-carboxylic acids (Scheme 4.1) to form the following compounds: 2-aminopyridinium 4-aminobenzoate, \textbf{14}; 2-aminopyridinium

\begin{center}
\begin{tabular}{ll}
2-aminopyridine & 2-amino-5-methylpyridine \\
COOH & COOH \\
benzoic acid & 4-aminobenzoic acid \\
terephthalic acid & 2,6-napthalenedicarboxylic acid \\
2,5-thiophenedicarboxylic acid & isophthalic acid \\
t-Bu & adpic acid \\
isophthalic acid & 5-t-butyliisophthalic acid \\
\end{tabular}
\end{center}

\textbf{Scheme 4.1. Molecular structures of components present in complexes 14-22}

\subsection*{4.2.1. CSD Analysis}

There are several possible two-point recognition supramolecular synthons that can be formed between 2-aminopyridines and carboxylic acids: supramolecular homosynthon \textit{IV}; a 2-aminopyridine supramolecular homosynthon \textit{V}; a 2-aminopyridine-carboxylic acid supramolecular heterosynthon \textit{VI}; the ionic form of \textit{VI}, i.e. supramolecular
heterosynthons VII (Scheme 4.2). As will become clear, both statistical and experimental
data indicate that the supramolecular heterosynthons VI or VII are favored over the
related supramolecular homosynthons IV and V.

\[
\begin{align*}
\text{VI} & \quad \text{VII} \\
& \quad \text{Scheme 4.2. Supramolecular heterosynthons that can be formed between carboxylic acids and 2-aminopyridines: 2-aminopyridine-carboxylic acid supramolecular heterosynthon VI and 2-aminopyridinium-carboxylate supramolecular heterosynthon VII}
\end{align*}
\]

A CSD study of compounds that contain at least one 2-aminopyridine and one
carboxylic acid moiety was conducted in order to determine the occurrence of 2-point
molecular recognition supramolecular heterosynthon, also coded as \(R^2_4(8)\) graph-set.\(^{66,75}\)

It should be noted that ambiguity can arise with regards to the position of carboxylic acid
proton in such complexes. However, the character of the interaction does not influence
whether or not a supramolecular heterosynthon occurs. The proton position was therefore
omitted from the search parameters, and the resulting data covers both neutral and
charge-assisted hydrogen bonds. The percentage occurrence and hydrogen bond distances
of supramolecular synthons IV-VII are presented in Table 4.1.
Table 4.1. Percentage occurrence, distance ranges, and average distance for supramolecular synthons IV-VII

<table>
<thead>
<tr>
<th></th>
<th>Number of entries</th>
<th>Distance range [Å]</th>
<th>Mean (σ) [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both groups</td>
<td>123</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Synthon IV</td>
<td>0</td>
<td>O···O</td>
<td>2.50-3.00</td>
</tr>
<tr>
<td>Synthon V</td>
<td>40 (33%)</td>
<td>N···N</td>
<td>2.90-3.25</td>
</tr>
<tr>
<td>Synthon VI or VII</td>
<td>95 (77%)</td>
<td>N(py)···O</td>
<td>2.50-2.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N(am)···O</td>
<td>2.70-3.10</td>
</tr>
</tbody>
</table>

The CSD contains 123 crystal structures with both 2-aminopyridine and carboxylic acid groups. In order to determine appropriate ranges for defining contact limits, distance distribution plots were generated. Based on visual inspection of the resulting histograms, the lower and higher cut offs for hydrogen bonds were determined. The histograms (Figure 4.2) reveal that VI or VII exhibit ranges of 2.50 - 2.85 Å (average 2.66(6) Å) for N(py)···O and 2.70 - 3.10 Å (average of 2.87(8) Å) for N(am)···O, respectively. Based upon these limits, IV is not found in any of the 123 compounds, while 40/123 structures (33%) exhibit the 2-aminopyridine supramolecular homosynthons V. 95/123 structures (77%) exhibit supramolecular heterosynthons VI or VII. It should be noted that 12 structures that exhibit VI or VII, also contain V due to the presence of multiple 2-aminopyridine moieties. In the remaining 27/123 structures that do not exhibit VI or VII, the carboxylic acid functionality forms hydrogen bonds with other competitive proton donors or acceptors such as amines, amides, imidazoles, water molecules and chloride ions. The same search was performed in the absence of other strong donors.
and/or acceptors that can compete with either aminopyridine or carboxylic acid moieties, e.g. alcohols, $1^\circ$ and $2^\circ$ amides, $1^\circ$ and $2^\circ$ sulfonamides, imidazoles, carbonyls, nitriles, nitro-compounds, phosphine oxides, chloride ions, bromide ions and water molecules. The number of structures containing both 2-aminopyridine and carboxylic acid moieties is thereby reduced from 123 to 34. In this subset, the percentage occurrence of VI or VII increased to 97% (33/34), although 7/33 compounds also contained the 2-aminopyridine supramolecular homosysonth V. These statistics suggest that supramolecular heterosynthons VI or VII are robust even in the presence of competing hydrogen bonding moieties. This observation is tested based upon study of the new compounds presented herein.

Figure 4.2. Histograms of contacts for crystal structures containing both 2-aminopyridine and carboxylic acid moieties: a) N(py)···O contacts in supramolecular heterosysonth VI or VII, b) N(am)···O contacts in supramolecular heterosysonth VI or VII, c) N(am)···N(py) contacts in supramolecular homosysonth V.
4.2.2. Structural Features of Neutral and Ionic 2-Aminopyridine···Carboxylic Acid Interaction

The ionic nature of the supramolecular heterosynthon present in compounds 14-22 was confirmed by spectroscopy, proton location, and structural parameters of ancillary groups. It is well known that the geometrical features of neutral carboxylic group are different from those of a carboxylate anion.267 The scatter plot for C–O vs. C=O bond distances in carboxylic acids and carboxylate anions is presented in Figure 4.3 (only good quality neutral carboxylic acid structures containing ordered, error free and non-polymeric organic compounds with 3D coordinates determined and R < 5% were chosen for the analysis). 1827 carboxylic acid crystal structures reveal that C–O distances average is 1.31(2) Å, whereas C=O distances average is 1.21(2) Å. On the other hand, the scatter plot of the 1696 compounds containing at least one carboxylate moiety indicates that the C–O distances average is 1.25(2) Å.

**Figure 4.3. Scatter plot of carbon-oxygen bond lengths in: a) neutral carboxylic acids, b) carboxylate anions**
The C–N–C angle in pyridines is known to be sensitive to protonation, and the cationic form exhibits higher values than that of the corresponding neutral molecules. A graphical representation of the C–N–C angle distribution in both protonated and unprotonated 2-aminopyridines is presented in Figure 4.4. Histograms were generated from good quality crystal structures (only ordered, error free and non-polymeric organic compounds with 3D coordinates determined and R < 5%). In order to distinguish protonated 2-aminopyridines from neutral 2-aminopyridines specific restrictions were applied during the CSD searches. For neutral 2-aminopyridines, the aromatic nitrogen was defined to be uncharged and the number of bonded atoms was set to 2. In the case of protonated 2-aminopyridines, hydrogen atoms were placed on the aromatic nitrogen, the charge was set to +1 and the coordination number was set to 3. The average C–N–C angle encountered in 213 neutral 2-aminopyridines is 116(2)°. In comparison, the set of 127 cationic 2-aminopyridines exhibits a higher C–N–C angle with an average value of 121(2)°.

![Histograms](image)

**Figure 4.4.** Histograms that present distribution of the C–N–C angle in a) neutral 2-aminopyridines, and b) protonated 2-aminopyridines
4.2.3. Crystal Structure Descriptions

The crystal structure of 2-aminopyridinium 4-aminobenzoate, \textit{I4} reveals the expected 1:1 cation:anion supramolecular complex, sustained by supramolecular heterosynthon \textit{VII} (Figure 4.5). The hydrogen atom of the primary amine moiety involved in the formation of the R\textsuperscript{2}(8) supramolecular heterosynthon is assigned as \textit{syn}-oriented, and the exterior hydrogen atom as \textit{anti}-oriented. This terminology is used herein.

In addition to IR spectroscopic evidence, the presence of heterosynthon \textit{VII} is supported by structural data: the C–O bond distances of the carboxylate group are 1.273(2) Å and 1.256(2) Å; the C–N–C angle within the 2-aminopyridinium cation is 122.3°. The hydrogen bond distances of supramolecular heterosynthon \textit{VII}, 2.611(2) Å and 2.814(2) Å for N\textsuperscript{+}(py)···O− and N(am)···O−, respectively, are within the excepted ranges. The carboxylate group of the 4-aminobenzoate is oriented at 19.2° with respect to the benzene ring plane and the dihedral angle between the 2-aminopyridinium cation and the carboxylate group is 15.1°. However, the 1:1 supramolecular adduct is almost planar (6.8°). The \textit{anti}- oriented N–H of the amine of the 2-aminopyridinium cation is involved in an additional N(am)···O− hydrogen bond with an oxygen atom of the adjacent carboxylate (D: 2.800(2) Å), thereby generating a 1D chain of supramolecular heterosynthons along the \textit{c} axis (Figure 4.6).
Within the chain of supramolecular heterosynthons the supramolecular adducts align in a zigzag fashion. The angle between core planes parallel to the interactions $O_A\cdots N_A\cdots C_A\cdots N_A\cdots O_A$ in heterosynthon VIIA and $O_B\cdots N_B\cdots C_B\cdots N_B\cdots O_B$ in adjacent heterosynthon VIIB is 101.6° (Figure 4.7). This pattern has been called the “shallow glide motif”, and is also observed in crystal packing of primary amides. The aminopyridinium-carboxylate heterosynthons VII are related by a glide plane and are also inclined with
respect to each other. A similar networking pattern occurs in several of the compounds reported herein.

\[ \text{Figure 4.7. The angle between core planes parallel to the interactions } \text{O}_A\cdots\text{N}_A\cdots\text{C}_A\cdots\text{N}_A\cdots\text{O}_A \text{ and } \text{O}_B\cdots\text{N}_B\cdots\text{C}_B\cdots\text{N}_B\cdots\text{O}_B \]

It is interesting to note that supramolecular heterosynthon \textbf{VII} occurs even in the presence of a functional group with hydrogen bonding capability, a primary amine. The –\text{NH}_2 of the 4-aminobenzoate anion acts as a hydrogen bond donor to one of the lone pairs of the carboxylate from an adjacent chain (N\cdots\text{O}: 3.087(2) Å), thereby connecting the chains in the direction of the \(a\) axis. The overall crystal packing of \textbf{14} can therefore be described as a corrugated 2D network resulting from interconnected 1D hydrogen-bonded chains of supramolecular heterosynthons (Figure 4.6).

Isophthalic acid possesses two carboxylic groups that are amenable to the formation of \textbf{VI} or \textbf{VII}, but a 1:1 complex is formed in 2-aminopyridinium isophthalate, \textbf{15}, since the acid molecule only undergoes single deprotonation. The carboxylate and aminopyridinium moieties form the expected \(\text{R}^2_{2}(8)\) supramolecular heterosynthon \textbf{VII}. 
The C–O bond distances in the carboxylate moiety are 1.266(1) Å and 1.262(1) Å and the C–N–C angle of the 2-aminopyridinium is 122.5°. The C–O bond lengths in the acid moiety are 1.210(1) Å and 1.330(2) Å. The hydrogen bond distances of supramolecular heterosynthon VII are 2.703(1) Å and 2.836 (1) Å for N\textsubscript{py}\textsuperscript{+}···O\textsuperscript{-} and N\textsubscript{am}···O\textsuperscript{-}, respectively. The anti- oriented N–H of the amine group interacts with another carboxylate (N···O\textsuperscript{-}: 2.942(1) Å), thereby bridging the adjacent supramolecular heterosynthons. The carboxylic acid group is involved in a charge-assisted O-H···O\textsuperscript{-} (O···O\textsuperscript{-}: 2.623(2) Å) interaction with a neighboring carboxylate group (Figure 4.8).

![Figure 4.8. Hydrogen bonding interactions in 2-aminopyridinium isophthalate, 15](image)

The components of 15 form almost planar (dihedral angle is 5.8°) adducts and the angle between core planes parallel to the interactions O\textsubscript{A}···N\textsubscript{A}–C\textsubscript{A}–N\textsubscript{A}···O\textsubscript{A} in heterosynthon VIIA and O\textsubscript{B}···N\textsubscript{B}–C\textsubscript{B}–N\textsubscript{B}···O\textsubscript{B} in heterosynthon VIB is 69.6°. The existence of both carboxylic and carboxylate groups in 15 was confirmed by IR spectroscopy which revealed absorption bands at 1556 cm\textsuperscript{-1} and 1378 cm\textsuperscript{-1} (corresponding to carboxylate
ions) and 1682 cm\(^{-1}\) and 1261 cm\(^{-1}\) (corresponding to C=O and C–O stretches, respectively).

Compound **16**, *bis*(2-aminopyridinium terephthalate), is sustained by three-component aggregates consisting of two aminopyridinium cations and one terephthalate anion (Figure 4.9).

![Figure 4.9. Supramolecular interactions in *bis*(2-aminopyridinium) terephthalate, 16](image)

The hydrogen bonds within supramolecular heterosynthon VII are 2.624(2) Å and 2.797(2) Å for N\(^+\)\_(py)···O\(^-\) and N\(_\text{am}\)···O\(^-\), respectively. The C–O bond distances in the
carboxylate group (1.271(2) Å and 1.244(2) Å) and C–N–C angle in the 2-aminopyridinium (122.8°) support the proposed ionic character of 16. The anti-oriented N–H of the amine group hydrogen bonds to the carboxylate of an adjacent supramolecular adduct (D: 2.809(2) Å) and the dihedral angle between core planes of neighbouring heterosynthons is 97.9°. A chain of supramolecular heterosynthons is thereby formed and it is connected to another chain through the terephthalate anion. The overall hydrogen-bonding pattern in 16 can therefore be described as a corrugated 2D network consisting of interconnected trimeric supramolecular adducts aligning nearly perpendicularly with respect to each other (Figure 4.10).

2-amino-5-methylpyridinium benzoate, 17, consists of 1:1 supramolecular adducts sustained by supramolecular heterosynthon VII (Figure 4.11). Protonation occurs on the aromatic nitrogen of 2-amino5-methylpyridine as evidenced by the C–N–C angle of 122.8° and C–O distances of 1.271(2) Å and 1.242(2) Å. Both benzoate and 2-amino-5-methylpyridinium ions are flat (the maximum deviations from the plane are 0.95° and 0.71° for benzoate and aminopyridinium, respectively) but their planes are twisted at 9.9°. Supramolecular heterosynthons VII are connected in one direction as the result of an additional hydrogen bond involving the anti-oriented N–H of the amine (D: 2.846(2) Å). The dihedral angle between the planes parallel to the interactions, O_A⋯N_A–C_A–N_A⋯O_A in heterosynthon VIIA and O_B⋯N_B–C_B–N_B⋯O_B in adjacent heterosynthon VIIIB, is 102.5°.
Figure 4.11. Supramolecular adducts in 2-amino-5-methylpyridinium benzoate, 17, are sustained via charge-assisted heterosynthons VII that form 1D chains.

Figure 4.12. Crystal structure of 2-amino-5-methylpyridinium benzoate, 17, viewed along the c axis (down the intercalating 1D chains which are colored green, red, blue and gray).

Several 2-aminopyridinium monocarboxylate supramolecular compounds have been already reported in the literature, e.g. 2-aminopyridinium benzoate\textsuperscript{272} and 2-aminopyridinium salicylate,\textsuperscript{273} 2-aminopyridinium butynoate\textsuperscript{274} Their crystal structures are also sustained by 1D H-bonded chains. The $N^+(\text{py}) \cdots O^-$ and $N(\text{am}) \cdots O^-$ hydrogen bonds in 17 and the three related compounds are similar: 2.688 Å and 2.801 Å in 17; 2.699 Å and 2.868 Å in 2-aminopyridinium benzoate; 2.699 Å and 2.845 Å in 2-aminopyridinium salicylate; 2.670 Å and 2.889 Å in 2-aminopyridinium butynoate. These four compounds exhibit similar crystal packing in which the 1D chains intercalate with each other along the b axis (Figure 4.12). One dimensional chains of supramolecular heterosynthons also occur in 2-aminopyridinium-sulfonates\textsuperscript{275} Similarly, the aminopyridinium-sulfonate...
supramolecular heterosynthon exhibits charge-assisted character with proton transfer occurring to the aromatic nitrogen of the 2-aminopyridine moiety.

In bis(2-amino-5-methylpyridinium) 5-tertbutylisopthalate, 18, 2-amino-5-methylpyridinium ions interact with both carboxylate groups of the 5-t-butylisopthalate anions via supramolecular heterosynthon VII. The 2:1 adducts extend along the c axis via two centrosymmetric hydrogen bonds formed between the anti-oriented N–H moiety of the amine groups and adjacent carboxylates (D: 2.914(2) Å), Figure 4.13. The inversion center between two adjacent heterosynthons leads to the formation of a four component supramolecular unit consisting of three cyclic supramolecular heterosynthons (graph-set notation: R2(8), R2(8), R2(8)). This type of motif has also been observed in related aminopyrimidinium-carboxylate salts276,277 and several carboxylic acid-amide co-crystals.86,87

The C–O bond distances are 1.258(2) Å, 1.261(2) Å and 1.261(2) Å, 1.262(2) Å within the carboxylate groups and the C–N–C angles in the 2-aminopyridinium cations are 122.7° and 122.5°. The carboxylate groups are twisted from the plane of the aromatic moiety at 20.0° and 6.2°, respectively. The intermolecular hydrogen bonds of the heterosynthons VII are within anticipated ranges: 2.623(2) Å, and 2.619(2) Å, for N(py)···O–, and 2.788(2) Å and for 2.799(2) Å for N(am)···O–.
The crystal structure of bis(2-amino-5-methylpyridinium) terephthalate, 19 compares closely to that of 16. 2-amino-5-methylpyridinium cations interact with both carboxylate moieties via charge-assisted supramolecular heterosynthons VII, thereby affording 2:1 supramolecular adducts. The adducts are further interconnected into a chain of supramolecular heterosynthons via N(am)···O− hydrogen bonds formed between the anti-oriented N–H of amine groups and adjacent carboxylates (Figure 4.14).

The C–O bond lengths are 1.242(4) Å and 1.272(4) Å and the C–N–C angle in the 2-amino-5-methylpyridinium residue is 123.3°. The torsion angle of the carboxylate group with respect to the aromatic moiety of terephthalate anion is 18.6° (vs. 17.4° in 16) and the angle between core planes parallel to the supramolecular heterosynthons, O_A···N_A–C_A–N_A···O_A in VIIA and O_B···N_B–C_B–N_B···O_B in adjacent supramolecular heterosynthon VIIIB is 100.8° (vs. 97.9° in 16). The hydrogen bond distances in supramolecular heterosynthson VII are 2.679(4) Å and 2.812(4) Å for N^+_{(py)}···O− and
N(\text{am})\ldots\text{O}, respectively. The \textit{anti}- oriented N–H of the amine group hydrogen bonds with the carboxylate of the adjacent heterosynthon (D: 2.800(2) Å). All three H-bond distances are within expected ranges and they correspond closely to the distances exhibited by 16.

![Figure 4.14. Crystal structure of bis(2-amino-5-methylpyridinium) terephthalate, 19. 1D hydrogen bonded chains are cross-linked via N–H···O- interaction to form 2D sheets](image)

Therefore, compounds 16 and 19 are related in terms of their composition, hydrogen bond motifs and packing modes. The difference in the molecular structure of the components in 16 and 19 (a methyl substituent in the aminopyridinium residue) is not big enough to disrupt the 2D corrugated packing mode. Indeed, 16 and 19 are isostructural, crystallizing in space group P2_1/n with similar unit cell dimensions: 

- for 16:
  - a = 5.1991(8) Å,
  - b = 14.606(2) Å,
  - c = 11.190(2) Å,
  - β = 95.094(3)°
  - a = 5.627(2) Å,
  - b = 14.480(6) Å,
- for 19:
  - c = 11.351(4) Å
  - β = 99.622(7)°

and a unit cell similarity index (\(\prod\))^{278} of 0.013.

\textit{Bis}(2-amino-5-methylpyridinium) 2,6-napthalenedicarboxylate, 20 consists of three-component adducts sustained by supramolecular heterosynthon VII. The C–O bond
distances are 1.241(3) Å and 1.277(3) Å and C–N–C angle is 122.5°. The carboxylate functionalities are twisted at 36.7° with respect to the aromatic core of the anion and the angle between planes parallel to the interactions O_A···N_A–C_A–N_A···O_A in A and O_B···N_B–C_B–N_B···O_B in adjacent supramolecular heterosynthon B is 60.9°. The hydrogen bonds within VII are 2.631(3) Å and 2.897(3) Å for N^(+)(py)···O^- and N^(am)···O^- respectively. The anti-oriented N–H of the amine group hydrogen bonds with the carboxylate of the adjacent supramolecular heterosynthon (D: 2.837(3) Å). The crystal packing of 20 is remarkably similar to 16 and 19 (Figure 4.15).

Figure 4.15. Crystal packing of bis(2-amino-5-methylpyridinium) 2,6-napthalenedicarboxylate, 20. 1D hydrogen bonded chains are cross-linked via N–H···O hydrogen bonds to form 2D sheets

The asymmetric unit of bis(2-amino-5-methylpyridinium) adipate adipic acid, 21, consists of one 2-amino-5-methylpyridinium cation, half an adipate anion and half a free adipic acid. The crystal structure reveals formation of supramolecular heterosynthon VII
between the 2-aminopyridinium cation and both sides of the adipate anion. The ions further self-assemble via centrosymmetric hydrogen bonds between the anti-oriented N–H’s of the amine groups and adjacent carboxylates (D: 2815(2) Å), Figure 4.16. The four-component core is extended into two dimensions via charge-assisted O-H⋯O’ hydrogen bonds between neutral adipic acid molecules and adjacent carboxylate anions (O⋯O’: 2.557(1) Å). The hydrogen bonds of VII are 2.719(2) Å and 2.816(2) Å for N+(py)⋯O’ and N(am)⋯O’ respectively. The four-component supramolecular adducts are nearly flat, with the maximum deviation from planarity being 3.8°. The crystal packing of 21 can be described as 2D infinite sheets parallel to the plane with an inter-planar distance of ca. 3.3 Å. The presence of both COOH and COO’ groups is supported by structural data and IR spectroscopy. The C–O bond distances in the carboxylate groups are 1.243(2) Å and 1.280(2) Å whereas those in the acid are 1.316(2) Å and 1.217(2) Å. The C–N–C angle in the aminopyridinium residue is 122.9(1)°. IR spectroscopy reveals a strong band at 1681 cm⁻¹ and moderate band at 1265 cm⁻¹ corresponding to C=O and C–O stretches, respectively. The bands assigned to COO’ stretches are observed near 1550 cm⁻¹ and 1395 cm⁻¹.

The CSD contains several compounds that exhibit a 2-aminopyridinium cation, dicarboxylate anions, and dicarboxylic acids. One of these compounds, 2-aminopyridinium adipate adipic acid dihydrate,²⁷⁹ exhibits similar crystal packing to that of 21 (Figure 4.17).
Figure 4.16. Crystal structures of a) 2-amino-5-methylpyridinium adipate adipic acid, 2I

Figure 4.17. Crystal structure of 2-aminopyridinium adipate adipic acid dihydrate. Herein, the voids between adipic acid molecules are occupied by water molecules

In the dihydrate, water molecules occupy the voids between two adjacent adipic acids. The acid molecules can therefore form bridges between adjacent four-component cores. Unexpectedly, the presence of methyl group in 2I does not lead to changes in crystal packing. The similarity in packing between the dihydrate and 2I might result from the fact that the methyl groups of 2-amino-5-methylpyridine occupy the space of the
two water molecules. Both compounds crystallize in P-1 and their unit cell dimensions are: $a=5.070(7)$ Å, $b=7.208(1)$ Å, $c=18.388(3)$ Å, $\alpha=88.468(2)^\circ$, $\beta=85.015(2)^\circ$, $\gamma=72.373(2)^\circ$ for 21 and $a=5.019(7)$ Å, $b=7.369(1)$ Å, $c=18.025(3)$ Å, $\alpha=86.481(2)^\circ$, $\beta=88.999(2)^\circ$, $\gamma=72.231(2)^\circ$ for the dihydrate. The isostructurality descriptor, $\Pi$, is 0.078. The structures of 2-aminopyridinium succinate succinic acid (2:1:1)$^{280}$ and 2-aminopyridinium fumarate fumaric acid$^{281}$ exhibit different supramolecular networks since the components are non-planar.

The asymmetric unit of bis(2-amino-5-picolinium) 2,5-thiophenedicarboxylate 2,5-thiophenedicarboxylic acid, 22, consists of one 2-amino-5-methylpyridinium cation, half a 2,5-thiophenedicarboxylate anion and half a 2,5-thiophenedicarboxylic acid. Although the acid molecule possesses two functional groups capable of two-point recognition supramolecular heterosynthon VII is absent (Figure 4.18). Instead, the carboxylate group is involved in three 1-point supramolecular heterosynthons: one with the protonated nitrogen atom of 2-amino-5-methylpyridinium (D: 2.686(2) Å), a second with the adjacent carboxylic acid molecule (D: 2.545(1) Å), and a third with the anti-oriented N–H of the amine moiety of another 2-amino-5-methylpyridinium residue (D: 2.806(2) Å). The C–O bond distances are 1.251(2) Å, 1.267(2) Å and 1.219(2) Å, 1.318(2) Å for the carboxylate and carboxylic acid moiety, respectively. The C–N–C angle of the aminopyridinium is 123.3(2)$^\circ$. The IR spectrum supports the existence of both ionic and neutral functional groups in 9 as it exhibits absorption bands at 1673 cm$^{-1}$ and 1237 cm$^{-1}$ for C=O and C–O, respectively and a COO$^-$ asymmetric stretch is present at 1627 cm$^{-1}$. Compound 9 is the only example presented herein that does not exhibit
In summary, the CSD survey and model compound studies reported herein indicate that supramolecular heterosynthons \textbf{VI} and/or \textbf{VII} will occur reliably when 2-aminopyridine and carboxylic acid moieties are present in the same compound. The CSD analysis suggests 77\% probability of the supramolecular heterosynthon, which means that from an empirical perspective it is strongly favored over the related carboxylic acid, \textbf{IV}, or 2-aminopyridine \textbf{V}, supramolecular homosynthons. In the absence of other competing functionalities the probability of the occurrence of \textbf{VI} or \textbf{VII} is ca. 97\%. The statistical reliability of these supramolecular heterosynthons was confirmed by compounds 14-22 in which 8/9 were found to exhibit supramolecular heterosynthon \textbf{VII}. The supramolecular chemistry of supramolecular heterosynthon \textbf{VII} is also predictable to a certain extent. It is...
capable of further self-assembly into chains and sheets and it is noteworthy that very similar crystal packing was observed in several compounds despite the presence of methyl groups. That supramolecular heterosynthon VI was not observed in 14-22 does not mean it is not relevant. Indeed, several co-crystal structures have been reported that are based upon 2-aminopyrimidine. Whether or not a salt or co-crystal forms seems to be related to the ancillary groups that are bonded to the 2-aminopyridine moiety. For example, all 2-aminopyridines that interact with carboxylic acids appear to be in the form of salts whereas 2-aminopyrimidines form either neutral or ionic supramolecular heterosynthons and melamines tend to exist as monoprotonated salts. Taking into consideration the strength of the three bases (2-aminopyrimidine < melamine < 2-aminopyridine), one can speculate that the pKₐ value of the 2-aminopyridine moiety influences whether a supramolecular heterosynthon is neutral or ionic. Prediction of what will happen for a given carboxylic acid is further complicated by factors such as the pKₐ value of the acid, the nature of substituents and the fact that pKₐ values are determined in solution.

4.3. Conclusions

In conclusion, the charge assisted 2-aminopyridinium-carboxylate or neutral 2-aminopyridine-carboxylic acid supramolecular heterosynthons occur in 77% of the compounds in which these two functional groups are present. This is a high level of probability when one considers that such well-known 2-point supramolecular synthons as carboxylic acid dimers only occur in ca. 25% of the compounds in which carboxylic
acids are present because of competing supramolecular heterosynthons. This level of predictability makes the 2-aminopyridine-carboxylic acid supramolecular synthon particularly suitable for crystal engineering of networks, salts and/or co-crystals. The modification of the physicochemical properties that occurs with salt or co-crystal formation is relevant to the pharmaceutical industry, where formulation of API’s for optimal solubility, bioavailability or stability of drugs are of great importance.

4.4. Experimental

4.4.1. Syntheses

All reagents used to synthesize 14-22 were purchased from Aldrich. Compounds 14-22 were prepared by dissolving stoichiometric amounts of starting materials in an appropriate solvent. Crystals suitable for single crystal X-ray diffractometry were obtained by slow evaporation of the solvent under ambient conditions.

**Compound 14: 2-aminopyridinium 4-aminobenzoate.** A solution of 2-aminopyridine (0.010 g, 0.11 mmol) and 4-aminobenzoic acid (0.015 g, 0.11 mmol) in 2 mL of ethanol was allowed to evaporate slowly at room temperature. Colorless crystals of 14 (0.025 g, 0.065 mmol, 59%), mp=152-153 °C, were obtained after 7 days.

**Compound 15: 2-aminopyridinium isophthalate.** The crystallization of 2-aminopyridine (0.029 g, 0.31 mmol) with isophthalic acid (0.051 g, 0.31 mmol) in 2 mL of ethanol afforded colorless crystals of 15 (0.042 g, 0.16 mmol, 52%), mp=198-201 °C, within 7 days.
**Compound 16: bis(2-aminopyridinium) terephthalate.** A solution of 2-aminopyridine (0.060 g, 0.64 mmol) and terephthalic acid (0.053 g, 0.32 mmol) in 2 mL of methanol evaporated slowly at room temperature. Colorless crystals of 16 (0.056 g, 0.16 mmol, 50%), mp=294 °C dec., suitable for X-ray crystallography appeared within 6 days.

**Compound 17: 2-amino-5-methylpyridinium benzoate.** A solution of 2-amino-5-methylpyridine (0.019 g, 0.18 mmol) and benzoic acid (0.22 g, 0.18 mmol) in 2 mL of ethanol was left undisturbed to evaporate slowly under ambient conditions. Colorless crystals of 17 (0.033 g, 0.014 mmol, 77%), mp=140-141 °C, were obtained within 7 days.

**Compound 18: bis(2-amino-5-methylpyridinium) 5-tertbutylisophthalate.** Colorless crystals of 18, mp=174-175 °C, were obtained from the reaction of 2-amino-5-methylpyridine (0.020 g, 0.18 mmol) with 5-tertbutylisophthalic acid (0.021 g, 0.090 mmol) in 2 mL of ethanol. The solution was left to evaporate slowly at room temperature and yielded 0.025 g (0.057 mmol, 63%) of the product within 8 days.

**Compound 19: bis(2-amino-5-methylpyridinium) terephthalate.** Compound 19 was formed via reaction of 2-amino-5-methylpyridine (0.030 g, 0.28 mmol) with terephthalic acid (0.023 g, 0.14 mmol) in 2 mL of methanol. Colorless crystals (0.038 g, 0.099 mmol, 72%), mp=250 °C dec., appeared within 6 days.

**Compound 20: bis(2-amino-5-methylpyridinium) 2,6-napthalenedicarboxylate.** A solution of 2-amino-5-methylpyridine (0.030 g, 0.28 mmol) and 2,6-napthalenedicarboxylic acid (0.030 g, 0.14 mmol) in 2 mL of dimethyl formamide, was left undisturbed to evaporate slowly at ambient conditions. Colorless crystals of 20 (0.036
g, 0.083 mmol, 60%), mp=390 °C dec., were obtained within 9 days.

**Compound 21: bis(2-amino-5-methylpyridinium) adipate adipic acid.** 2-amino-5-methylpyridine (0.030 g, 0.28 mmol) and adipic acid (0.041 g, 0.28 mmol) dissolved in 2 mL of ethanol afforded colorless crystals of 21 (0.036 g, 0.14 mmol, 50%), mp=151-152 °C, within 7 days.

**Compound 22: bis(2-amino-5-methylpyridinium) 2,5-thiophenedicarboxylate**

2,5-thiophenedicarboxylic acid. Compound 22 was obtained via reaction of 2-amino-5-methylpyridine (0.030 g, 0.28 mmol) and 2,5-thiophenedicarboxylic acid (0.048 g, 0.28 mmol) in 2 mL of ethanol. Colorless crystals (0.062 g, 0.22 mmol, 80%), mp=221-222 °C, appeared within 7 days.

All compounds were analyzed by infrared spectroscopy using a Nicolet Avatar 320 FTIR instrument. The purity of bulk samples was confirmed by X-ray powder diffraction analysis conducted on a Rigaku Miniflex Diffractometer using Cu Kα (λ=1.540562 Å), 30 kV, 15 mA. The data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/min.

The syntheses of compounds 14-22 were also accomplished via solvent-drop grinding using the same solvents as those in the solution crystallizations. Stoichiometric amounts of starting materials were processed for 4 minutes in a ball mill. The IR and XPD spectra of the products obtained from solvent-drop grindings, matched those of the products obtained from slow evaporation.
4.4.2. Single Crystal X-ray Crystallography

Compounds 14-22 were examined under a microscope and suitable single crystals were selected for X-ray analysis. Data were collected on a Bruker–AXS SMART APEX CCD diffractometer with monochromatized Mo Kα radiation (λ = 0.71073 Å) connected to KRYO-FLEX low temperature device. Data for 14-22 were collected at 100 K. Lattice parameters were determined from least square analysis, and reflection data were integrated using the program SAINT. Lorentz and polarization corrections were applied for diffracted reflections. In addition, the data was corrected for absorption using SADABS.248 Structures were solved by direct methods and refined by full matrix least squares based on \( F^2 \) using SHELXTL.249 All non-hydrogen atoms were refined with anisotropic displacement parameters. All H-atoms bonded to carbon atoms, except methyl groups, were placed geometrically and refined with an isotropic displacement parameter fixed at 1.2 times \( U_{eq} \) of the atoms to which they were attached. N or O bonded protons, as well as H-atoms of methyl groups, were located from Fourier difference map and refined isotropically based upon the corresponding N, O or C atom (U(H)=1.2U_{eq}(N, O)). Crystallographic data for 14-22 are presented in Table 4.2, whereas selected hydrogen bond distances are listed in Table 4.3.
## Table 4.2. Crystallographic data and structure refinement parameters for compounds 14-22

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Table 4.3. Geometrical parameters of selected intermolecular interactions present in compounds 14-22

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<td>1.93</td>
<td>2.806(2)</td>
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</table>

$^a$ The syn- and anti- N–H groups of the 2-aminopyridiniums are referred with subscript ‘s’ and ‘a’, respectively.
5.1. Focus

Thus far it has been demonstrated that the hydroxyl···aromatic nitrogen (I) and 2-aminopyridinium-carboxylate (VII) supramolecular heterosynthons are reliable interactions and that they persist regardless of the method of preparation of the model co-crystals and salts. However, it should be noted that the model compounds have been prepared using relatively simple and rigid molecules. The conclusions drawn from the presented studies would gain more significance if the acquired observations held true over more complex multiple-component systems. In this respect, the chemical nature of drug molecules related to their biological activity is determined by their multiple hydrogen bonding sites, which also makes them suitable for crystal engineering studies.

The research presented in this section is a strategic extension of the model compound studies and will demonstrate how the supramolecular heterosynthons I and VII can be exploited via crystal engineering of two drug molecules, bicalutamide and indomethacin, both of which contain multiple hydrogen bonding sites. Furthermore, the viability of solid-state co-crystallization and susceptibility toward polymorphism or solvate formation of the obtained API co-crystals will be addressed.
5.2. Results and Discussion

5.2.1. CSD Analysis and Literature Overview

The examination of the 1487 co-crystals archived in the CSD, has revealed that only ca. 5% of the whole dataset contain API molecules, and these include: barbital (32 entries),282 sulfonamide drugs (14),283 phenothiazines (8),284 carbamazapine (5),285 theophyllines (5),286 caffeine (6),287 flurbiprofen (2),288 ibuprofen (1),289 itraconazole (1),290 diphenylhydantoin (1),291 and trimethoprim (1).292 Whereas some of the examples tend to be the result of serendipity, perhaps the first crystal engineered API co-crystals appeared from the extensive research of Whitesides et al. concerning supramolecular assemblies sustained by 3-point recognition hydrogen bonds262 formed in co-crystals of melamine derivatives and barbital, a central nervous system depressant, Figure 5.1.293-296 Although the studies were not originally oriented toward pharmaceutical applications, the resulting series of co-crystals delineated the enormous potential represented by the APIs with respect to diversity of the co-crystal compositions and the inherent modification of their physicochemical properties.

Figure 5.1. Co-crystal of barbital and \( N,N'\)-bis(4-bromophenyl)melamine, JICTUK10, sustained by 3-point recognition supramolecular heterosynthon
Due to the growing interest in the subject, several examples of designed binary co-crystals of APIs have appeared in the recent literature. Crystal engineering approach to APIs based upon rational utilization of reliable supramolecular heterosynths have been exemplified by a series of co-crystals that involve carbamazepine, CBZ, an anti-epileptic drug. The primary amide supramolecular homosynthon present in pure CBZ crystal structures, is replaced by carboxylic acid···amide heterosynthon, through an introduction of a carboxylic acid component. As an example, CBZ•aspirin co-crystal is presented in Figure 5.3a. The successful strategic approach founded on utlilization of the same supramolecular heterosynthon has been employed in co-crystallization of several carboxylic acids with another amide-containing drug, piracetam, a nervous system stimulant The crystal structure of piracetam•gentisic acid, sustained by carboxylic acid···amide heterosynthon is shown in Figure 5.3b.

Figure 5.2. Amide supramolecular homosynthon present the crystal structure of pure CBZ
Further examples concerning crystal engineering of APIs based upon utilization of reliable intermolecular interactions include co-crystals sustained by carboxylic acid···aromatic nitrogen supramolecular heterosynthon, as exemplified by co-crystals of itraconazole,\textsuperscript{132} ibuprofen and flurbiprofen,\textsuperscript{80} and caffeine.\textsuperscript{154} Crystal structures of ibuprofen$\bullet$4,4'$\text{-}$bipyridine is presented in Figure 5.4.

Rational design of API co-crystals has been also based upon the utilization of charge-assisted O–H···Cl$^-$ and N–H···Cl$^-$ hydrogen bonds,\textsuperscript{137,302,303} as demonstrated
recently by Childs et al. The study involved successful co-crystallizations of an antidepressant, fluoxetine hydrochloride (Prozac) with several pharmaceutically acceptable carboxylic acids, of which one, Prozac•succinic acid co-crystal, is presented in Figure 5.5. An important trait resulting from this study is that depending on the aqueous solubility of the utilized co-crystal former, it is possible to fine-tune the dissolution rate of the API. In addition, it was observed that the solubility of the Prozac•succinic acid co-crystal is doubled as compared to the fluoxetine hydrochloride salt.

![Figure 5.5](image)

It should be noted, that due to the lack of a generally accepted definition of a co-crystal, there may be ambiguity concerning whether or not a compound is a co-crystal, a salt or a solvate. The distinction between a co-crystal and a salt can be especially problematic if X-ray crystallography is the only method of characterization and the difference between the two extremes is ca. 1Å in a hydrogen atom position. For instance, 3-[2-(N,N’-dimethylhydrazino)-4-thiazolylimethylthio]-N²-
sulfamoylpropionamidine•maleic acid (CSD refcode JATMEW), was reported as a neutral complex. However, the structural parameters (C–O bond lengths and C–N–C bond angles) suggest the formation of a maleate anion and a propionamidinium cation, therefore denoting a salt, Figure 5.6a. When searching for co-crystals, the physical state of the components must also be taken into consideration. For instance, a molecular complex of mebendazole and propionic acid (SAGQEW), shown in Figure 5.6b should be classified as a solvate rather than a co-crystal, as the propionic acid exists as a liquid under ambient conditions (mp \(-21^\circ\)C).

Additionally, the CSD mining for co-crystals may be complicated by the database errors; the CSD searches retrieve ionic compounds despite limiting the searches to neutral compounds. For example, salts EBIBEW, PIKLEA, QAWNAD, VAPBAP, VENLUV, etc. are all retrieved as neutral compounds. These findings suggest that the identification of co-crystals archived in the CSD should be supported by inspection of the
structural parameters of co-crystal components, and/or revision of the corresponding publications.

In summary, design strategies that target reliable supramolecular heterosynthons (determined by preceding CSD searches or model compound studies), which can be formed between an API and a co-crystal former, represents an attractive approach to discovering new crystalline forms of APIs. Considering the profound implications of developing new forms of APIs in the context of both intellectual property and physicochemical properties, it is somewhat surprising that a rational design and generation of API co-crystals has only been endeavored in recent years. The applicability of a crystal engineering approach toward generating new forms of APIs has been demonstrated by the diverse set of the reported API co-crystals, although some of them are sustained by co-crystal formers that are not pharmaceutically acceptable. However, the limited number of examples indicates the need for further exploration in order to achieve a better understanding of the intermolecular forces that influence the formation of API co-crystals, as well as the factors that determine their physicochemical properties.

5.2.2. Bicalutamide

Bicalutamide (propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-(±)), is a non-steroidal antiandrogen used in the treatment of prostate cancer. From a supramolecular perspective, bicalutamide is a relatively complex molecule due to the conformational flexibility and the presence of
multiple hydrogen bonding moieties: hydroxyl (O–H), 2° amine (N–H), carbonyl (C=O), cyano (C≡N), and sulfonyl (O=S=O), Scheme 5.1. The anticipation of the supramolecular chemistry of this API is therefore complicated by both conformational variations and the possibility of existence of various hydrogen bonded synthons. Indeed, the multiple-complementary nature of bicalutamide is manifested by the existence of two polymorphic modifications, Figure 5.7. Form I of bicalutamide is sustained by O–H···O (D: 3.145(3) Å) hydrogen bonds occurring between the hydroxyl and carbonyl moieties. Bicalutamide form II exhibits two primary supramolecular heterosynthons. The first heterosynthon, O–H···N≡C (D: 2.905(3) Å), occurs between the hydroxyl and cyano moiety and the second heterosynthon, N–H···O (D: 3.104(2) Å), exists between the N–H of the 2° amide and the sulfonyl moieties.

![Scheme 5.1. Molecular structure of bicalutamide](image)

To date, no examples of bicalutamide co-crystals, solvates, or hydrates have been deposited in the CSD. Therefore, bicalutamide represents a suitable candidate for a crystal engineering case study that addresses its feasibility toward rational design of co-crystals, considering the presence of multiple hydrogen bonding functionalities in its
118
molecular structure.

Figure 5.7. Representation of the crystal packing of bicalutamide in a) form I and b) form II

The first step of the crystal engineering experiment was based upon careful examination of molecular structure of bicalutamide to identify the hydrogen bonding sites capable of forming reliable supramolecular synthons. The next step, however, which involves a CSD analysis of the existing structures that are chemically related to the targeted compound to find how they engage in molecular association, was not successful. There are no compounds in the database that exhibit exactly the same set of hydrogen bond donors and acceptors as the set present in bicalutamide (O–H, N–H, C≡N, C=O,
and O=S=O). With this viewpoint it become apparent that the design strategy needed to rely upon a simplified approach, in which one or two moieties would be targeted at a time for their interactions with other functional groups. The formation of supramolecular heterosynthons was considered to occur with co-crystal formers that possess moieties different than those already present in bicalutamide. With the perspective of the model co-crystal studies presented in chapter 2, that delineated the remarkably high reliability of hydroxyl···aromatic nitrogen (O–H···N_{arom}) supramolecular heterosynthon I in the presence of cyano moiety, and considering that these two moieties (OH and CN) are present in bicalutamide, the OH moiety was selected as the primary target for heterosynthon formation with N_{arom}-based co-crystal formers. Taking into account the complexity of the API, the initial selection of co-crystal formers was aimed toward simple N_{arom}-containing heterocycles. Two co-crystal formers were chosen: 4,4’-bipyridyl (bipy) and trans-1,2-bis(4-pyridyl)ethylene (bipyete), and although these molecules are not pharmaceutically acceptable, they represent good model candidates from the viewpoint of a crystal engineering strategy.

From the co-crystallization experiments, two co-crystals were obtained: bicalutamide•4,4’bipyridyl (23) and bicalutamide•trans-1,2-bis(4-pyridyl)ethylene (24). In addition, it was observed that co-crystal 24 tends to be solvated in the presence of acetone. The crystal structure of (bicalutamide)_{2}•trans-1,2-bis(4-pyridyl)ethane•(acetone)_{2} (25) is also presented.

Crystal structure of bicalutamide•bipy, 23, reveals discrete 2:2 centrosymmetric supramolecular adducts sustained by the targeted heterosynthon I (O–H···N_{arom}) and a N–
The hydrogen bond distance of O–H⋯Narom is 2.759(5) Å, which corresponds to the average length of I, observed in the model co-crystals (chapter 2) and other compounds reported in the CSD (Table 2.1). The distance of the second hydrogen bond, N–H⋯Narom, is 3.499(7) Å, which is relatively long, as compared to a typical N–H⋯Narom interaction. The contacts distribution for the N–H⋯Narom heterosynthon retrieved from the CSD, (Figure 5.9) reveals that the N–H⋯Narom interaction occurs in the range of 2.75 - 3.30 Å (average of 3.0(1) Å).

Figure 5.8. 2:2 supramolecular adducts formed between bicalutamide and 4,4′-bipyridyl in 23

In this structure the bipy molecule is twisted at 26.14°. Although the bipy molecule in co-crystal 6 is flat, the torsion angle observed in 23 corresponds closely to the twist angles of the phenpy molecules in co-crystals 1 and 5 (24.6° and 30.1° respectively). The supramolecular adducts are stabilized by continuous aromatic stacking occurring between the adjacent bipy molecules, along the a axis. The stacked adducts are further connected via weak C–H⋯N=C interactions and form 2D sheets Figure 5.10. Similar crystal packing, characterized by the columnar arrangement of the
supramolecular adducts, was also observed in co-crystals 1, 4, 5, 6 and 8.

![Histogram representing the N–H···Narom contact distribution in the crystal structures containing both N–H and Narom moieties](image)

**Figure 5.9.** Histogram representing the N–H···Narom contact distribution in the crystal structures containing both N–H and Narom moieties

Co-crystal 23 can also be prepared by solvent-drop grinding. The screen for polymorphs of 23 based upon solvent-drop grinding with cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water has not revealed additional forms.

![Crystal structure of bicalutamide•4,4'bipyridyl, 23](image)

**Figure 5.10.** Crystal structure of bicalutamide•4,4'bipyridyl, 23

Crystal structure of bicalutamide•bipyete, 24, is reminiscent to that of 23. The bicalutamide and bipyete interact via heterosynthon I (D: 2.811(3) Å). The adjacent
aggregates are related by a center of inversion and engage in formation of 2:2 supramolecular adducts via N–H···N_arom (D: 3.119(3) Å) interaction, and are additionally stabilized by π-π stacking occurring between the bipyete molecules (ca. 3.76 Å), Figure 5.11. Such supramolecular dimers are further translated along the a axis forming 1D columns of continuously π-π stacked 2:2 adducts. The columns are related by translation and interconnected by weak C–H···N≡C interaction, thereby generating 2D layers, Figure 5.12. Similar crystal packing was observed in model co-crystals 6 and 8.

![Figure 5.11. 2:2 supramolecular adducts formed between bicalutamide and t-1,2-bis(4-pyridyl)ethylene in 24](image)

Co-crystal 24 can also be prepared by solvent-drop grinding. The screen for polymorphs of 24 based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water has not revealed any additional polymorphs. However, it was observed that when co-crystallization of bicalutamide and bipyete is carried out in acetone, a solvate of the co-crystal (25) results. As revealed by XPD and FTIR analysis, 25 can be reproducibly obtained from acetone-drop grinding.
The crystal structure of 25 reveals that the crystallization of bicalutamide and bipyete from acetone (acet) affords new composition of the co-crystal, (bicalutamide)$_2$•bipyete•(acet)$_2$, and the components assemble into five-member supramolecular aggregates. Two bicalutamide molecules interact with one bipyete molecule via the heterosynthon I (D: 2.739(6) Å) and with two acet molecules via a N–H···O(acet) heterosynthon (D: 3.235(7) Å), Figure 5.13. In this structure, one bipyete molecule is replaced by two acet molecules. In effect, the continuous π-π stacking observed in 24 is disrupted by the insertion of the acet molecules in between the 2:1 adducts formed by bicalutamide and bipyete molecules, Figure 5.14.
The melting points of 23-25 (Table 5.1.) are in between the melting points of the corresponding constituents. Interestingly, the melting points of 24 and 25 are very close (161-163 °C vs. 163-164 °C) despite the difference in the compositions. The solvent loss in 25 is observed at 98 °C (crystals become opaque and the phase change is confirmed by DSC) and the remaining co-crystal exhibits 2:1 stoichiometry of bicalutamide and bipyete, which differ from the 1:1 stoichiometry of bicalutamide and bipyete in 24. No correlation was observed when the melting points of 23-25 were compared to the melting
points of the related model co-crystals. The melting points distribution in co-crystals 1-13 and 23-25 highlight the difficulty in correlating the effect of the composition and structural variations with the resulting change of thermal behavior.

Table 5.1. Comparison of the melting points of co-crystals 23-25 and the corresponding components

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<tr>
<td>23</td>
<td>157-159</td>
<td>191-192</td>
<td>110 - 114 (bipy)</td>
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<tr>
<td>24</td>
<td>161-163</td>
<td>191-192</td>
<td>150 - 153 (bipyete)</td>
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<tr>
<td>25</td>
<td>164-165</td>
<td>191-192</td>
<td>150 - 153 (bipyete) - 94 (acet)</td>
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</table>

5.2.3. Indomethacin

Indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid) is known for its analgesic and anti-inflammatory activity. It possesses three functional groups that are capable of forming hydrogen bonds: carboxylic acid (COOH), methoxy (C–O–CH₃), and carbonyl (C=O), Scheme 5.2. Indomethacin exists in three polymorphic modifications: a monoclinic and two triclinic. The triclinic structures are sustained by supramolecular homosynthon VII whereas the monoclinic form, exhibits a carbonyl-carboxylic acid supramolecular heterosynthon, in addition to VII, Figure 5.15.
Scheme 5.2. Molecular structure of indomethacin

Figure 5.15. Representation of the crystal packing of bicalutamide in a) two triclinic forms and b) monoclinic form

In addition to the three polymorphs, only two solvates of indomethacin have been so far structurally characterized.\textsuperscript{318,319} The crystal structures of the reported methanol (CSD refcode: BANMUZ) and tert-butanol (CSD refcode: BANMOT) solvates are sustained by a cyclic hydrogen bonding motif formed due to an insertion of two hydroxyl moieties of the alcohol molecule in between the carboxylic acid dimer, Figure 5.16. Up to date, no co-crystals or salts of indomethacin have been deposited in the CSD.
Indomethacin was chosen for this study because it represents a suitable candidate for the extension of the model compound series (chapter 4) toward crystal engineering of APIs based upon supramolecular heterosynths I and VII. Indomethacin possesses several hydrogen bonding sites, of which one is carboxylic acid, the target moiety. Considering the high probability of formation of heterosynth VII, demonstrated based upon simple model molecules, it is anticipated that the COOH moiety of indomethacin will also be utilized in the 2-point recognition supramolecular heterosynth with 2-aminopyridines. 2-amino-5-methylpyridine was selected as a simple counterpart for cocrystallization with the relatively complex indomethacin. Although not pharmaceutically acceptable, 2-amino-5-methylpyridine is a good candidate from the perspective of its chemical and geometrical features that match with the features of the COOH functional group, as proved in the preceding studies involving model compounds (chapter 4).

Crystallization of indomethacin with 2-amino-5-methylpyridine afforded compound 26, which is sustained by supramolecular heterosynth VII (Figure 5.17).
The crystal structure of compound 26 exhibits the expected 1:1 stoichiometry. The hydrogen bond distances in the charge-assisted supramolecular heterosynthon VII are within expected ranges: 2.728(4) Å and 2.790(5) Å for N$_{\text{py}}^+$···O$^-$ and and N$_{\text{am}}$···O$^-$, respectively. The C–O bond lengths are 1.228(5) Å, 1.258(5) Å and the C–N–C angle in the 2-aminopyridinium cation is 123.1°. The angle between core planes parallel to the interactions O$_A$···N$_A$–C$_A$–N$_A$···O$_A$ in synthon VIIA and O$_B$···N$_B$–C$_B$–N$_B$···O$_B$ in synthon VIIB is 92.4° (Figure 4.7). The anti- oriented N–H of the amine moiety forms H-bond with carboxylate (D: 2.843(4) Å) of the neighboring anion thereby bridging adjacent supramolecular heterosynthons. Similar hydrogen bonding motif has also been seen in compounds 14, 16, 17, 19, and 20.

The reproducibility of 26 was confirmed by solvent-drop grinding involving seven solvents: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water no additional forms. The susceptibility of 26 toward solvent-drop grinding suggests that solid-state methods can be efficiently utilized in screening for crystalline salts of APIs.\textsuperscript{152}
In summary, the application of heterosynthon \textbf{VII} has been demonstrated in a successful crystal engineering experiment of indomethacin, a carboxylic acid API, with 2-amino-5-methylpyridine salt former. Conversely, \textbf{VII} can be targeted in crystal engineering of 2-aminopyridine-containing APIs and carboxylic acid co-crystal formers. For instance, trimethoprim, an antibacterial agent, forms organic salts with a range of carboxylic acids: formic acid\textsuperscript{320} acetic acid,\textsuperscript{321} trifluoroacetic acid,\textsuperscript{322} malonic acid,\textsuperscript{323} glutaric acid,\textsuperscript{277} benzoic acid,\textsuperscript{324} 3-chlorobenzoic acid,\textsuperscript{325} 2-nitrobenzoic acid,\textsuperscript{326} terephthalic acid,\textsuperscript{327} through the 2-point recognition interaction \textbf{VII}, Figure 5.18.

![Figure 5.18. Crystal structure of trimethoprim benzoate is sustained by the 2-aminopyridine-carboxylate supramolecular heterosynthon VII](image)

5.3. Conclusions

In summary, the use of two robust supramolecular heterosynthons \textbf{I} and \textbf{VII} has been demonstrated in crystal engineering of two APIs: bicalutamide and
indomethacin. From a supramolecular perspective, the molecular structures of both drugs are relatively complex due to their multiple hydrogen bonding sites. The successful co-crystallization of bicalutamide with pyridines confirms the robustness of I not only in the presence of the C≡N moiety, but also suggests that I can persist in the presence of other hydrogen bonding groups: carbonyl (C=O), 2° amine (N–H), and sulfonyl (O=S=O).

Similarly, the application of heterosynthon VII toward modification of crystal structure of indomethacin also proved that VII is a reliable interaction even in the presence of carbonyl (C=O) and ether (C–O–C) moieties. The reliability of I and VII was also determined based upon reproducibility of 23, 24, and 26 in solvent-drop grinding experiments. In addition, that polymorphism was not observed in 23, 24, and 26 can be an important observation considering that both bicalutamide and indomethacin are polymorphic in their pure states. It should be noted that in several cases, API co-crystals comprised by polymorphic components have not yet exhibited polymorphism,208,211 which may have an important implications from the viewpoint of polymorphism control.

With the perspective of the necessity of better understanding and control of crystalline forms of APIs, pharmaceutical co-crystals appear to represent a significant class of compounds. It is important to note that the crystal engineering approach leaves the molecular structure of an API intact, while diverse range of new compositions with modified physicochemical properties is readily accessible. Furthermore, they may offer more opportunities than, for example, salts, which are formed only when the API possesses moieties that are sufficiently basic/acidic for protonation/deprotonation. In co-crystallization, molecules possessing wider range of hydrogen bonding moieties can be
targeted. In particular, utilization of GRAS (generally regarded as safe) compounds, food additives or even sub-therapeutics, such as aspirin or acetaminophen, as the co-crystal formers is feasible.

Nevertheless, there still remains a need for further exploration of API co-crystals in order to address some fundamental issues. For instance, while the role of API salt forms in the optimization of API properties, e.g. solubility, has been established, the role of API co-crystals in this context has been addressed only in a few cases. Another question could be related to whether API co-crystals are more or less prone to polymorphism as compared to the pure API. It is not a trivial task to assess the frequency of occurrence of polymorphism in either of the mentioned categories as the absence of polymorphism is not synonymous with its non-existence. However, if one considers that co-crystallization is based upon satisfying the molecular recognition sites of a targeted API by matching it with a complementary co-crystal former, it is possible to anticipate a decreased tendency of the co-crystal to exhibit polymorphism as compared to the pure components. The fact that polymorphism seen in the 11 reported co-crystals has not been related to hydrogen bonding variations, could support these arguments, however more research needs to be conducted in this context.

In conclusion, it is appropriate to highlight that despite many questions and challenges, API co-crystals represent valuable category of compounds. They offer many opportunities in the context of their viability to rational design and large diversity of composition and physicochemical properties, which can be utilized in new API formulations.
5.4. Experimental

Bicalutamide was used as received from Transform Pharmaceuticals Inc., MA. Indomethacin was used as received from the Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan.

5.4.1. Syntheses

*Co-crystal 23: bicalutamide•4,4’bipyridyl.* To bicalutamide (0.050 g, 0.115 mmol) was added 4,4’-bipyridine (0.018 g, 0.115 mmol). To the solid mixture was added acetone (1 mL) and the solution was left to evaporate at ambient temperature. After 3 days colorless plates of 23 were formed, mp=157-159 °C.

*Co-crystal 24: bicalutamide•t-1,2-bis(4-pyridyl)ethylene.* To bicalutamide (0.100 g, 0.23 mmol) was added t-1,2-bis(4-pyridyl)ethene (0.021 g, 0.115 mmol). To the solid mixture was added DMSO (0.5 mL) and the solution was left to evaporate at ambient temperature. After 3 days colorless plates of 24 were formed, mp=161-163 °C.

*Co-crystal solvate 25: (bicalutamide)₂•trans-1,2-bis(4-pyridyl)ethane•(acetone)₂.* To bicalutamide (0.100 g, 0.23 mmol) was added t-1,2-bis(4-pyridyl)ethene (0.021 g, 0.115 mmol) in 2:1 molar ratio. To the solid mixture was added 1mL hexane / acetone (1:1) and the solution was left to evaporate at ambient temperature. After 3 days colorless plates of 25 were formed, mp=163-164 °C (at 98 °C the crystal became opaque).

*Compound 26: 2-amino-5-methylpyridinium indomethacin.* A solution of 2-
amino-5-methylpyridine (0.010 g, 0.093 mmol) and indomethacin (0.033 g, 0.093 mmol) in 2 mL of ethanol was left undisturbed to evaporate slowly at room temperature. Yellow crystals of 26, mp=146-148 °C, appeared after 7 days.

Co-crystallization via solvent-drop grinding: Stoichiometric amounts of the starting materials were ground with a mortar and pestle for ca. 4 minutes with the addition of seven solvents (10 μL per 50 mg of product): cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water. In case of 25, acetone was also used.

5.4.2. Single Crystal X-ray Crystallography

Compounds 23-26 were examined under a microscope and suitable single crystals were selected for X-ray analysis. Data were collected on a Bruker–AXS SMART APEX CCD diffractometer with monochromatized Mo Kα radiation (λ = 0.71073 Å) connected to KRYO-FLEX low temperature device. Data for 23-25 were collected at 298 K, whereas data for 26 were collected at 100 K. Lattice parameters were determined from least square analysis, and reflection data were integrated using the program SAINT. Lorentz and polarization corrections were applied for diffracted reflections. In addition, the data was corrected for absorption using SADABS.248 Structures were solved by direct methods and refined by full matrix least squares based on F² using SHELXTL.249 All non-hydrogen atoms were refined with anisotropic displacement parameters. All H-atoms bonded to carbon atoms, except methyl groups, were placed geometrically and refined with an isotropic displacement parameter fixed at 1.2 times U(eq) of the atoms to which they
were attached. N or O bonded protons, as well as H-atoms of methyl groups, were located from Fourier difference map and refined isotropically based upon the corresponding N, O or C atom (U(H)=1.2U_{eq}(N, O)). Crystallographic data for 23-25 are presented in Table 5.2, whereas selected hydrogen bond distances are listed in Table 5.3.

Table 5.2. Crystallographic data and structure refinement parameters for compounds 23-26

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<tr>
<td>space group</td>
<td>P-1</td>
<td>P-1</td>
<td>P-1</td>
<td>Pca2_1</td>
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<tr>
<td>a (Å)</td>
<td>8.298(2)</td>
<td>8.274(3)</td>
<td>11.214(2)</td>
<td>12.564(2)</td>
</tr>
<tr>
<td>b (Å)</td>
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<td>10.172(3)</td>
<td>11.724(2)</td>
<td>11.338(1)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>15.299(4)</td>
<td>18.601(7)</td>
<td>12.198(3)</td>
<td>30.501(4)</td>
</tr>
<tr>
<td>α (°)</td>
<td>74.506(4)</td>
<td>87.521(7)</td>
<td>73.721(4)</td>
<td>90</td>
</tr>
<tr>
<td>β (°)</td>
<td>75.852(5)</td>
<td>78.256(6)</td>
<td>83.866(4)</td>
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</tr>
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<td>γ (°)</td>
<td>79.963(4)</td>
<td>71.067(7)</td>
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</tr>
<tr>
<td>volume (Å³)</td>
<td>1347.0(6)</td>
<td>1449.4(9)</td>
<td>1411.4(5)</td>
<td>4344.7(1)</td>
</tr>
<tr>
<td>D_{calc} (g cm⁻³)</td>
<td>1.446</td>
<td>1.404</td>
<td>1.364</td>
<td>1.425</td>
</tr>
<tr>
<td>Z</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>θ range</td>
<td>1.41-25.00</td>
<td>1.12-26.73</td>
<td>1.74 to 25.00</td>
<td>1.34-28.29</td>
</tr>
<tr>
<td>Nref./Npara.</td>
<td>4680/370</td>
<td>5985/388</td>
<td>4786/363</td>
<td>10289/595</td>
</tr>
<tr>
<td>T (K)</td>
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<td>298</td>
<td>100</td>
</tr>
<tr>
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<td>wR₂</td>
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Table 5.3. Geometrical parameters of supramolecular heterosynths present in compounds 23-26

<table>
<thead>
<tr>
<th>Interaction</th>
<th>d(Å)</th>
<th>D (Å)</th>
<th>θ (deg)</th>
</tr>
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<tr>
<td>23</td>
<td>O–H···N_{arom}</td>
<td>1.68</td>
<td>2.759(5)</td>
</tr>
<tr>
<td></td>
<td>N–H···N_{arom}</td>
<td>2.55</td>
<td>3.499(7)</td>
</tr>
<tr>
<td>24</td>
<td>O–H···N_{arom}</td>
<td>1.93</td>
<td>2.811(3)</td>
</tr>
<tr>
<td></td>
<td>N–H···N_{arom}</td>
<td>2.25</td>
<td>3.119(3)</td>
</tr>
<tr>
<td>25</td>
<td>O–H···N_{arom}</td>
<td>1.81</td>
<td>2.739(6)</td>
</tr>
<tr>
<td></td>
<td>N–H···O_{acet}</td>
<td>2.33</td>
<td>3.235(7)</td>
</tr>
<tr>
<td>26</td>
<td>N^−–H_{sp2})···O^-</td>
<td>1.87</td>
<td>2.728(4)</td>
</tr>
<tr>
<td></td>
<td>N–H\textsubscript{a}···O^-</td>
<td>1.82</td>
<td>2.790(5)</td>
</tr>
<tr>
<td></td>
<td>N–H\textsubscript{a}···O^-</td>
<td>1.76</td>
<td>2.843(4)</td>
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</table>
Chapter 6 — Summary and Future Directions

6.1. Summary

The goal of the presented work is to illustrate the application of crystal engineering principles toward a generation of multiple-component organic crystalline materials with pre-determined composition and intermolecular interactions in a rational and controllable manner. Specifically, the systematic studies involving preparation and structural analysis of hydrogen bonded multi-component compounds have afforded a basis for a better understanding and control of the supramolecular synthons in the solid state. In particular, the knowledge acquired from the investigation of organic co-crystals and salts sustained by simple components has led to the delineation of the reliability of two supramolecular synthons, namely hydroxyl···aromatic nitrogen (I) and 2-aminopyridine···carboxylate (VII) heterosynthons. The determination of the reliable recurrence of I and VII subsequently lead to a development of strategies for the design of multiple-component compounds that involve more complex molecules possessing multiple functional groups, such as APIs. The exploitation of these strategies toward drug molecules that possess several hydrogen bonding sites has proved to be successful in the case of bicalutamide and indomethacin. Both bicalutamide and indomethacin formed co-crystals and a salt, respectively, with pre-determined composition and predictable intermolecular interactions. The presented results can be particularly
attractive, from the viewpoint that the traditional API forms, such as polymorphs and solvates/hydrates tend to appear serendipitously, rather than based upon a rationally designed experiment.

In addition, it has been illustrated that organic co-crystals and salts exhibit high susceptibility toward solid-state preparation methods, such as growth form melt, dry grinding, and solvent-drop grinding. In particular, the later has been confirmed to constitute a reliable technique for a reproducible formation of multiple-component compounds. It has been determined that the utilization of an appropriate solvent can direct co-crystallization toward specific co-crystal stoichiometries. In particular, DMSO-drop grinding of 3-cyanophenol and \( \text{trans}-1,2\text{-bis}(4\text{-pyridyl})\text{ethylene} \) in 1:1 ratio affords complete conversion of the starting materials into a 3-cyanophenol\( \textbullet\text{trans}-1,2\text{-bis}(4\text{-pyridyl})\text{ethylene} \) co-crystal, which otherwise occurs concomitantly with the (3-cyanophenol)\( \textbullet\text{t}-1,2\text{-bis}(4\text{-pyridyl})\text{ethylene} \) co-crystal when other solvents are used in the grinding or solution evaporation methods. In addition, the mechanochemical approach to supramolecular synthesis is inherently relevant in the generation of a bulk material according to green chemistry practices: directly from starting materials and based upon clean and high yielding procedures.

The investigations in the context of polymorphism provided new insights concerning the origin of this phenomenon in co-crystals. Specifically, the structural analysis of the two dimorphic co-crystals, \((4\text{-cyanopyridine})\textbullet4,4'\text{-biphenol}\) and \(4\text{-cyanophenol}\textbullet\text{t}-1,2\text{-bis}(4\text{-pyridyl})\text{ethylene}\), revealed the existence of identical hydrogen bonded heterosynthons in both forms of the corresponding co-crystals. These results
support the observations formulated based upon the analysis of the existing polymorphic co-crystals: polymorphism in co-crystals is related to conformational and crystal packing variations rather than supramolecular synths. Although these conclusions are made from the study of a limited number of examples, a generality of this observation over a broader set of co-crystals may have important implications in the context of controlling polymorphism. Furthermore, the use of solvent-drop grinding to obtain specific polymorphs of co-crystals has been successful, as illustrated based on (4-cyanopyridine)$_2$•4,4’-biphenol co-crystal.

In summary, the presented research has contributed to the overall progress of the field of crystal engineering, whose ultimate goal is the understanding of intermolecular interactions and the ability to rationally design new crystalline solids for useful applications. Specifically, it has been demonstrated that crystal engineering of pharmaceuticals is possible with an appropriate understanding of their supramolecular chemistry and the interplay of a supramolecular synths that can potentially exist when other components are introduced. Considering the dependability of physichochemical properties of APIs on the molecular arrangement in their crystals, the advantage of crystal engineered APIs is inherently related to the control of their physicochemical performance: solubility, bioavailability, stability, etc. While the role of salt forms of APIs can be considered as established, the role of co-crystal forms of APIs still remains to be explored and there are many questions and challenges that will need to be addressed. These challenges can be linked to scale up processes, evaluating properties of the bulk co-crystalline material, utilization of automatized methodologies, such as high-
throughput co-crystallization, issues related to regulatory procedures, etc. Nevertheless, the need for further exploration of APIs remains clear because the value and opportunities of a successful development of co-crystallization strategies of APIs is significant in the context of both drug development and intellectual property.

6.2. Future Directions

In conclusion, several directions for future research in the field of crystal engineering of can be highlighted.

- Considering the viability of multi-component compounds, co-crystals or organic salts, toward the investigation of robustness and hierarchies of various supramolecular synthons, the potential of further studies that focus on an even broader range of hydrogen bonding moieties has become apparent. In particular, a systematic investigation of the competition of various hydrogen bonds in the presence of three, four, or even more functional groups should be addressed.

- In the context of API co-crystals, the studies should be expanded to utilization of pharmaceutically acceptable co-crystal formers and further evaluation of their physicochemical performance, i.e. solubility, bioavailability, stability, toxicology, etc. In addition, the experimental protocols related to API co-crystallization on a large scale and determination of bulk properties may be important.

- Since the existence of polymorphism in API co-crystals has attracted attention, exhaustive screen involving an HT approach could provide more insight toward better understanding the phenomenon and evaluating its frequency. Specifically, addressing
whether or not co-crystals of APIs are more or less prone to polymorphism may lead to important scientific and intellectual property implications. Additionally, the observation related to the persistence of supramolecular synthons within a set of polymorphs perhaps requires further investigation.

- Considering the multi-disciplinary character of crystal engineering, it would be interesting to utilize other classes of co-crystal formers, for instance, molecules that mimic biologically active compounds. When coupled with APIs, such biomolecular co-crystals could be of use to study drug-DNA or drug-enzyme interactions in the solid state. The stability of co-crystals in aqueous environment could be evaluated based upon slurry experiments.
Reference List


57. Motherwell, W. D. S.; Ammon, H. L.; Dunitz, J. D.; Dzyabchenko, A.; Erk, P.;
   Gavezzotti, A.; Hofmann, D. W. M.; Leusen, F. J. J.; Lommerse, J. P. M.; Mooij,
   W. T. M.; Price, S. L.; Scheraga, H.; Schweizer, B.; Schmidt, M. U.; Van Eijck,

58. Day, G. M.; Motherwell, W. D. S.; Ammon, H. L.; Boerrigter, S. X. M.; Della
   Valle, R. G.; Venuti, E.; Dzyabchenko, A.; Dunitz, J. D.; Schweizer, B.; Van
   Eijck, B. P.; Erk, P.; Facelli, J. C.; Bazterra, V. E.; Ferraro, M. B.; Hofmann, D.
   W. M.; Leusen, F. J. J.; Liang, C.; Pantelides, C. C.; Karamertzannis, P. G.; Price,
   S. L.; Lewis, T. C.; Nowell, H.; Torrisi, A.; Scheraga, H. A.; Arnautova, Y. A.;


61. Vishweshwar, P.; McMahon, J. A.; Oliveira, M.; Peterson, M. L.; Zaworotko, M.


65. Allen, F. H.; Motherwell, W. D. S.; Raithby, P. R.; Shields, G. P.; Taylor, R. New


   118, 10134.


105. A typical example of a drastic difference in properties of two crystal forms of chemically identical compound is that of diamond (transparent and hard) and graphite (black and soft). Other examples include pharmaceuticals, e.g. ritonavir exhibits varying solubilities (and bioavailability) depending on the polymorphic form used.


139. CSD (ConQuest 1.7, August 2005) reveals 10,709 crystal structures which contain hydroxyl moieties (one of the most ubiquitous functional group with ca. 22,000 structures) in the presence of ethers (the most ubiquitous functional group with ca. 36,846 entries) and 1,434 crystal structures in the presence of pyridines. The three moieties are present simultaneously in 451 crystal structures. The analysis of the 451 entries reveals that the occurrence of the hydroxyl-pyridine heterosynthon is 9 times higher (125/14) than the hydroxyl-ether heterosynthon.

140. CSD reveals that the number of entries that contain hydroxyl, pyridine, and amine is only 36, of which the majority additionally contain other hydrogen bond donor and acceptors.


175. ROY, stands for Red, Orange, and Yellow colors of the polymorphs of 5-methyl-2-[(2-nitrophenyl)-amino]-3-thiophenecarbonitrile.


184. CSD search parameters: ConQuest Version 1.7, August 2005, organics, no ions, no alkali metals, number of chemical units = 1. In addition, text search "polymorph" was used and only one refcode was counted for a polymorphic compound.

185. CSD contains 11 polymorphic co-crystals with determined 3D coordinates: AJAJEA (AJAJEA01), EXUQUJ (EXUQUJ01), HADKUT (HADKUT01), JICTUK (JICTUK01), MACCID (MACCID01, MACCID02), MUROXA (MUROXA01), PDTOMS10 (PDTOMS11), PTZTCQ (PTZTCQ01), QUIDON (QUIDON02), TECCAF01 (TECCAF02), ZIGPAG (ZIGPAG01).


211. Hickey, M. B.; Peterson, M. L.; Almarsson Ö. private communication.


213. CSD search parameters: ConQuest Version 1.7, August 2005 release, organics only, 3D coordinates determined, and R<7.5%. All statistics presented in this section relate to OH, Narom, and CN moieties and their engagement in forming synthons I, II, and III in the absence of other functional groups.

214. CSD search parameters: ConQuest Version 1.7, August 2005 release, organic compounds with 3D coordinates determined, and R < 7.5%

215. CSD search parameters: organics, 3D coordinates determined, R < 7.5%. The histograms were generated based upon general searches for structures that contain the targeted interactions in a broad range of contacts. 592 entries were for heterosynthon I, 174 entries for II, and 6588 entries for III.


217. CSD reveals 136 crystal structures containing OH and Narom, of which 135 entries exhibited I (99%). In one entry, REPPEH, I is absent due to a steric hindrance of the Narom moiety. The 27% of OH···OH homosynthon occurrence is due to the presence of multiple OH moieties in 37 entries.

218. CSD contains 3 crystal structures that possess OH, Narom, and CN moieties in the absence of other competing functional groups: FOMWIN, YAMMIJ, YAMMOP.


221. Brzezinski, B.; Grech, E.; Malarski, Z.; Rospenk, M.; Schroeder, G.; Sobczyk, L.


224. CSD searches for neutral C-OH and ionic C-O\(^-\) bonds involved specific restrictions on the oxygen atoms. For neutral C-OH bond, the presence of the hydrogen atom bonded to oxygen atom was acquired, the oxygen atom was defined to be uncharged and the number of bonded atoms was set to 2. In the case of ionic C-O\(^-\) bond, the charge of the oxygen was set to -1 and the number of bonded atoms was set to 1.


251. CSD search parameters: organics only, no alkali metals, and 3D coordinates determined. Hydrogen atoms were placed at 2,2‘,6,6’-position to avoid steric restraints.

252. CSD contains 3 conformational isomorphs: COBLAG, CUVNAI, and NISLUW.

253. Conformational polymorphism has been reported for ECELON (ECELON01)


261. Concomitant polymorphism was reported for MACCID (MACCID01, MACCID02), JICTUK10 (JICTUK01), HADKUT01 (HADKUT), and EXUQUJ01 (EXUQUJ).


266. CSD search parameters: ConQuest Version 1.6, July 2004 release, organics, 3D coordinates determined, and R < 7.5%.


155


282. CSD refcodes of 32 co-crystals of barbital: AEPDEB, AMIWUO, BARAPY10, BARBAM, BARBUR, BARHMP, BARIMZ10, BARMPN, BIGCUP, CAFBAR20, EADBAR10, HIBJUX, HIBKEI, JICTIY, JICTOE, JICTUK, JICVAS, JICVEW, JICVIA, JICVOG, JICVUM, JUBRAZ, KEPGHP, KUFPIK, MUDSAF, MUDSEJ, MUDSIN, PIYGEJ, QQQEUV, QQQFVA, WETSOD, WETTKU.

283. CSD refcodes of 14 co-crystals of sulfonamide drugs: GEYSAE, SACCAF, SANAPY, SMZTMP, SORWEB, SORWIF, STHSAM, SULTHE, VIGVOW, VUGMIT, VUGMOZ, XEXCAE, XEXCEI, YOSMOI

284. CSD refcodes of 8 co-crystals of phenathiazine: BUNRAD, DAPXUN, LENGOA, NIWCEB, PHNSNB10, PHTNBA, PTZPMA, PTZTCQ

285. CSD refcodes of 5 co-crystals of CBZ: UNEYOB, UNEYKH, UNEZAO, UNEZES, UNIBIC

286. CSD refcodes of 5 co-crystals of theophylline: CSATEO, DUXZAX, SULTHE, THOPBA, ZEXTIF

287. CSD refcodes of 6 co-crystals of caffeine: CAFSAL, DIJVOW, DIJVUN, SACCAF, VIGVOW, EXUQUJ

288. CSD refcodes of 2 co-crystals of fluribuprofen: HUPPEN, HUPPIR

289. CSD refcode of the co-crystal of ibuprofen: HUPPAJ

290. CSD refcode of the co-crystal of itraconazole: IKEQEU

291. CSD refcode of the co-crystal of diphenylhydantoin: DPHPZL

292. CSD refcode of the co-crystal of trimethoprim: BIGCUP


314. CSD search for the distance distribution the NH…N arom interaction (organics, 3D coordinates determined, and R < 7.5%) afforded 420 entries that occur within a range of 2.75 - 3.30 A, with the average of 3.0(1) A.


328. GRAS compounds can be found at www.cfsan.fda.gov/~dms/eafus.html.
Appendices
Appendix 1. Experimental data for compound 1

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 2. Experimental data for compound 2

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 3. Experimental data for compound 3

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black)
Appendix 4. Experimental data for compound 4

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 5. Experimental data for compound 5

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 6. Experimental data for compound 6

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 7. Experimental data for compound 7

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 8. Experimental data for compound 8

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 9. Experimental data for compound 9

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 10. Experimental data for compound 10

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 11. Experimental data for compounds 11a and 11b

DSC termograms, FT-IR spectra of Form I and Form II.
Appendix 12. Experimental data for compound 12

DSC termogram, FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 13. Experimental data for compound 13a and 13b

DSC termogram, FT-IR spectra Form I (blue) and Form II (red).
Appendix 14. Polymorphism screen data for compound 1

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 15. Polymorphism screen data for compound 2

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 16. Polymorphism screen data for compound 3

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 17. Polymorphism screen data for compound 4

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 18. Polymorphism screen data for compound 5

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 19. Polymorphism screen data for compound 6

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 20. Polymorphism screen data for compound 7

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 21. Polymorphism screen data for compound 8

X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 22. Polymorphism screen data for compound 9

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 23. Polymorphism screen data for compound 10

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 24. Polymorphism screen data for compound 11a and 11b

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 24. Polymorphism screen data for compound 11a and 11b (continued)

Comparison of experimental (pink) and calculated X-ray powder diffraction patterns of 4,4’-biphenol DMSO solvate, ECElon01 (black).
Appendix 25. Polymorphism screen data for compound 12

FT-IR spectra and X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 26. Polymorphism screen data for compound 13a and 13b

X-ray powder diffraction patterns of powders obtained based upon solvent-drop grinding with: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water.
Appendix 27. Experimental data for compound 14

FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 28. Experimental data for compound 15

FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 29. Experimental data for compound 16

FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 30. Experimental data for compound 17

FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 31. Experimental data for compound 18

FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 32. Experimental data for compound 19

FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 33. Experimental data for compound 20

FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 34. Experimental data for compound 21

FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 35. Experimental data for compound 22

FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 36. Experimental data for compound 23

X-ray powder diffraction patterns of bulk sample (black) and calculated from the single crystal structure (red) of compound 14.
Appendix 37. Experimental data for compound 24

X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 38. Experimental data for compound 25

X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
Appendix 39. Experimental data for compound 26

FT-IR spectrum and X-ray powder diffraction patterns of bulk sample (red) and calculated from the single crystal structure (black).
About the Author

Joanna A. Bis received M. Sc. degree in analytical chemistry from Jagiellonian University, Cracow, Poland, in 2002, where she worked in the area of analysis of inks extracted from documents in the context of criminalistics. While studying there she was honored with the Socrates Erasmus Programme scholarship for academic achievements. This gave her the opportunity to study and conduct a research project at Strathclyde University, Glasgow, Scotland.

In 2002, Joanna joined the University of South Florida and started working toward her Ph. D. in Dr. Michael Zaworotko’s research group. While in the Ph.D. program, she obtained a Research Assistantship from TransForm Pharmaceuticals Inc. Joanna is a co-inventor on a patent application, has co-authored four scientific publications, and has presented her research at regional, national, and international scientific meetings of the American Chemical Society, Scientific Advisory Board of TransForm Pharmaceuticals Inc., and International Quality & Productivity Center.