10-29-2003

Crystal Engineering of Binary Compounds Containing Pharmaceutical Molecules

Leslie Ann Morales
University of South Florida

Crystal Engineering of Binary Compounds Containing Pharmaceutical Molecules

By

Leslie Ann Morales

A thesis submitted in partial fulfillment
Of the requirements for the degree of
Master of Science
Department of Chemistry
College of Arts and Sciences
University of South Florida

Major Professor: Michael J. Zaworotko, Ph.D.
Gregory Baker, Ph.D.
Edward Turos, Ph.D.

Date of Approval:
October 29, 2003

Keywords: crystal engineering, supramolecular chemistry, supramolecular synthons, Pharmaceuticals, hydrogen bonding

Acknowledgements

The author would like to express her sincere appreciation to Dr. Michael Zaworotko for his guidance and support. Also to Dr. Rosa Walsh, Dr. Brian Moulton, Dr. Victor Kravtsov and Dr. Srinivassan Kuduva for their contributions with the crystallographic data in this work. The author is also grateful to Dr. Rosa Walsh and Dr. John Osegovic for their advice and input during her graduate career as well as in the writing of this thesis.

Most importantly, the author would like to thank her parents, Hector and Belkys Morales, her brother Hector, sister-in-law Edna and niece Alyssa for being my inspiration, my constant support and my motivation. A special thank you goes to her grandmother Ana Luisa Navarro for always being there, her loving friends Diana Acosta, Lena Lago, Dahianna Ramirez and Christopher Brazel. Chris, even though you came at the tail end of this journey, your support and advice proved to be immeasurable. You came at the perfect time, thank you very much.

Lastly, the author extends her sincere appreciation to her laboratory friends, Jennifer McMahon, Heba Abourahma, Joanna Bis, Tanise Shattock, Kadine Mohomed, LaNetra Clayton, Vicky Likourinou, Jarrod Eubank, John Perry and Gregory McManus for their help and for making the last couple of years more enjoyable and interesting. Thank you once again and God bless you all.

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List of Abbreviations

CSD= Cambridge Structural Database

DB18C6= Dibenzo-18-crown-6

18C6= 18-crown-6

TMA= Trimesic acid or 1,3,5-benzenetricarboxylic acid

FTIR=Fourier Transform Infra-red

Bipy= 4,4'-dipyridyl

THF= tetrahydorfuran

AcOH= Acetic acid

TGA= Thermal Gravimetric Analysis

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ABSTRACT

The synthesis or the interaction between two or more molecules is known as supramolecular chemistry. The concept of supramolecular chemistry can be applied to the design of new pharmaceutical materials affording new compositions of matter with desirable composition, structure and properties.

The design of a two-molecule, or binary, compound using complementary molecules represents an example of an application of crystal engineering. Crystal engineering is the understanding of intermolecular interactions, in the context of crystal packing, in the design of new solid materials. By identifying reliable connectors through molecular recognition or self-assembly, one can build predictable architectures.

The study of supramolecular synthesis was accomplished using known pharmaceutical molecules such as Nifedipine (calcium channel blocker used for cardiovascular diseases) and Phenytoin (used as an anticonvulsant drug) and model compounds containing synthons common in pharmaceutical drugs (Crown ethers and

Trimesic acid with ether linkages and carboxylic acid dimers, respectively) with complementary molecular additives.

The co-crystals formed were characterized by various techniques (IR, m.p., XPD, single X-ray diffraction) and preliminary results were found to exhibit characteristics different from the parent compounds as a direct result of hydrogen bonding and self-assembly interactions. These crystalline assemblies could afford improved solubility, dissolution rate, stability and bioavailability.

Chapter 1

Introduction

1.1 Supramolecular Chemistry and Crystal Engineering

The concept of crystal engineering was introduced by Pepinsky in 1955[1] and was first applied by Schmidt in the context of covalent bond formation in the solid state, i.e. topochemical reactions.[2] More recent developments have expanded this concept into areas as diverse as supramolecular synthesis, crystal structure analysis and prediction.[3,4] Crystal engineering is a field that offers varying paths for the rational design of functional solids.

Supramolecular synthesis offers a paradigm for the facile design and isolation of supramolecular complexes using self-assembly of different, but complementary supramolecular synthons. The subsequent ability to generate a diverse range of multiple component crystalline solids affords new compositions of matter and an ability to engage in systematic analysis of the factors that control structure/function relationships in the solid state.

Self-assembly of pre-selected molecular components,[5] or supramolecular synthesis,[4,6] represents a paradigm for the generation of chemical structures with nanoscale features. Supramolecular synthetic approaches offer a number of attractive features: the ability to exploit readily available molecules or ions in novel ways, their inherent modularity

affords compositional and structural diversity, and the use of non-covalent interactions (such as ion-ion, ion-dipole, dipole-dipole, π-π stacking, Van der Waals forces and hydrogen bonding) makes for facile synthesis. Supramolecular synthesis offers a combinatorial type of approach to synthesis of new structures and can afford a wide range of structural diversity without the need to break and form covalent bonds. The paradigm is exemplified by the use of geometric considerations to guide the preparation of nanoscale hydrogen bonded polyhedra[7] and by development of rational approaches to the design of ternary structures.The fact that hydrogen bonds are formed in a hierarchical fashion (strongest H-bond acceptor to strongest H-bond donor, and so on) and that crystal stability depends on specific intermolecular interactions[8] is the basis for this arrangement.

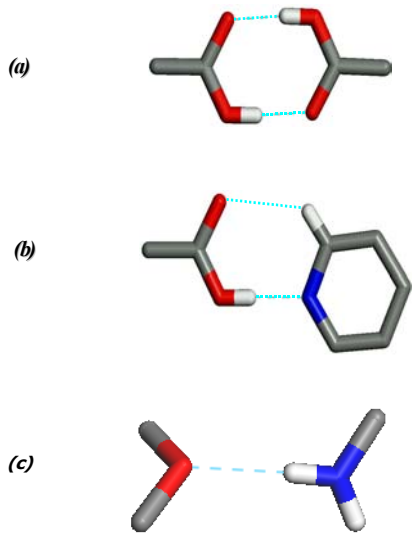


Figure 1. Schematic representation of (a) supramolecular homosynthon (i.e. carboxylic acid dimer), (b) supramolecular heterosynthon (i.e. a carboxylic acid- pyridyl dimer), (c) supramolecular heterosynthon (i.e. ether linkage-amine).

1.2 Supramolecular Synthons

Supramolecular synthons[6] depict the possible ways in which complementary functionalities of molecules interact by non-covalent interactions. One of such

interactions is the hydrogen bond. A hydrogen bond is a strong, directional, selective and stabilizing interaction between a hydrogen atom and an electronegative atom. As revealed by Figure 1, supramolecular synthons can either be self-complementary (a supramolecular homosynthon such as a carboxylic acid dimer[9]) or the result of complementary interactions between different moieties (a supramolecular heterosynthon such as a DNA base pair or the well-known carboxylic acid-pyridyl interaction[10]). The latter brings with it the opportunity to build multiple component superstructures and is the main focus of this study.

1.3 Polymorphism

The occurrence of polymorphism in crystal engineering cannot be ignored. Polymorphism is defined as the phenomenon where the same chemical substance exists in different crystalline forms or different crystalline patterns.[11] This trend is more common among molecules with flexible conformations capable of hydrogen bonding.[6] The internal arrangement of molecules in the solid state has a pronounced influence on chemical and physical properties. In this context, the existence of more than one crystalline form of a given compound, typically in the form of polymorphs or solvates, represents both a problem and an opportunity[12] in organic synthesis and early stage development of pharmaceuticals.

Supramolecular synthons are the structural units within molecules, which can be formed and/or assembled by synthetic operations[6]. The supramolecular synthons present in polymorphic forms may be intact from form to form, therefore it can be stated that the supramolecular equivalents of structural isomers are crystalline polymorphs[6]. The criteria

for assessing the existence of polymorphs are different unit cell parameters, crystal packing arrangements and physical properties.[11]

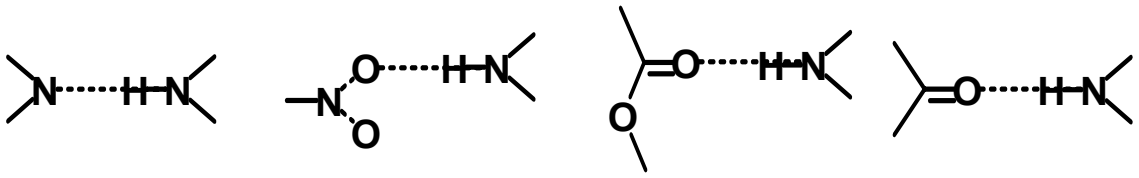
The study of the phenomenon of polymorphism has many implications. It has increased due to the "great importance of legal and regulatory issues" that faces the pharmaceutical industry to date.[13] The US Patent Office permits a new phase (*i.e.* polymorph, solvate or binary compound) of a drug to be patented if there is any processing or bioavailability benefit to the new solid phase. This may be problematic since many drug molecules are prone to polymorphism and crystal size and morphology can vary for any given phase. This can have significant commercial relevance because patents can be extended or effectively voided, translating into monetary gain or loss.

1.4 Cambridge Structural Database

As previously stated, crystal engineering and supramolecular chemistry are intricately intertwined and the common theme between the two is the connection between structure and architecture control via intermolecular interactions, namely hydrogen bonding between supramolecular synthons. Self-assembly of the targeted synthons through hydrogen bonding of complementary functional groups contributes to the control and possible prediction of the supramolecular structure, thus changing the physical properties of the material. Rationalization and design of these supramolecular solids is the basis of crystal engineering. A survey of existing supramolecular synthons and structures can be carried out through the Cambridge Structural Database (CSD).[14] By analyzing the existing structures and/or synthons in the CSD, new compositions of matter can be obtained, achieving new phases with new properties. An extensive analysis of the

supramolecular synthons involved in the compounds described in this thesis was carried out and a library with average hydrogen bond distances was formulated. The CSD has a total of 296,427 hits as of July 2003. Out of the 296,427 hits, 127,003 hits are considered organic, and out of that subset, 118,322 are organics with no metals, which accounts for ~40% of the total hits in the CSD.[14] All searches had as search parameters R factor <0.075, no ions and organics only. All searches were done with specific hydrogen bond distances, which were narrowed down through statistics and histograms. The distances ranged from the two non-hydrogen atoms "sharing" the hydrogen atom since the hydrogen atom cannot be given a specific position due to its movement.

1.4.1 **Nifedipine Synthons**



1 **2** **3** **4**

Figure 2. Supramolecular synthons in nifedipine

Table 1 Nifedipine Hydrogen bonded synthons and distances.

	# hits	distance	min	Max	ave	std	Single*	Multi*
1	147	2.8-3.25	2.801	3.247	3.074	0.1186	122	25
2	55	2.8-3.4	2.847	3.391	3.148	0.1313	48	7
3	244	2.8-3.3	2.806	3.298	3.006	0.1172	224	20
4	118	2.8-3.1	2.801	3.097	2.917	0.0752	106	15

*Single and multi-component corresponds to the homo/heterosynthons being formed by the synthons on the same molecules (single) or the formation between two molecules (multi) with complementary synthons.

Nifedipine has three possible hydrogen-bonding sites, the secondary amine (H-bond donor), the ester carbonyl (H-bond acceptor) and the nitro group (H-bond acceptor). Out of these three possible sites, the secondary amine is involved in hydrogen bonding most often and there are many more structures or hits of this interaction in the CSD as can be seen above. A secondary amide is involved in all of the CSD searches that were carried out in the nifedipine analysis. The ester carbonyl and the nitro group form secondary hydrogen bonds. nifedipine will always be involved in a heterosupramolecular synthon. The use of the secondary amine as a designing tool seems promising since interactions with this functional group is very prevalent in the CSD.

1.4.2 **Phenytoin Synthons**

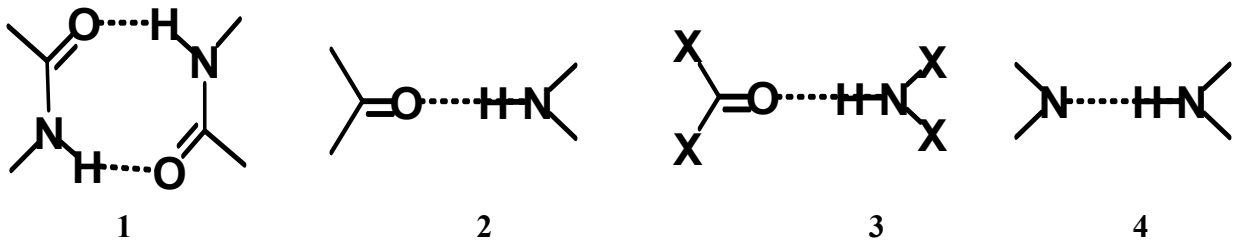


Figure 3. Supramolecular synthons in phenytoin

Table 2. Phenytoin Hydrogen bonded synthons and distances.

	# hits	Distance	min	max	mean	σ	Single*	Multi*
1	970	2.4-3.3	2.707	3.297	2.908	0.1015	804	166
2	340	2.7-3.2	2.701	3.2	2.939	0.1195	283	57
3	1441	2.7-3.2	2.7	3.198	2.924	0.1014	1224	217
4	147	2.8-3.25	2.801	3.247	3.074	0.1186	122	25

*Single and multi-component corresponds to the homo/heterosynthons being formed by the synthons on the same molecules (single) or the formation between two molecules (multi) with complementary synthons.

Phenytoin has two hydrogen bond donors (secondary amine) and acceptors (carbonyls) and they are complementary with one another as seen from the CSD searches. Search number **2** is a subset of search **3** and makes the results more relevant toward phenytoin. Phenytoin can hydrogen bond as amide dimers or as heterosynthons between complementary functional groups or synthons present on different molecules. As seen in the table above, the amide dimer is prevalent in structures containing the same molecule and the average distance is very similar when considering other ways of forming synthons.

1.4.3 **Crown Ethers Synthons**

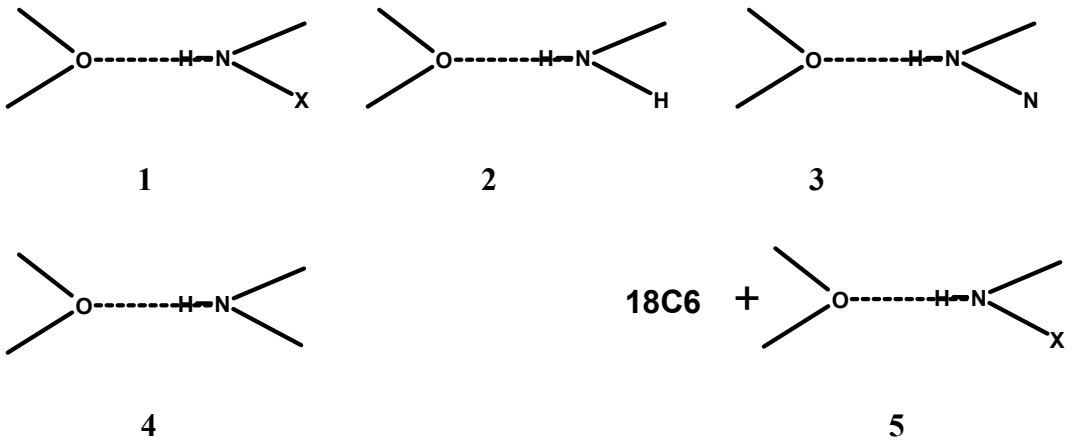


Figure 4. Supramolecular synthons in crown ethers

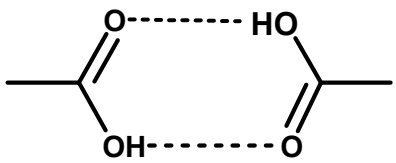
Table 3. Possible ether hydrogen bonded synthons and distances.

	# hits	distance	min	max	ave	std	Single*	Multi*
1	473	2.8-3.35	2.801	3.349	3.112	0.1319	328	141
2	225	2.8-3.35	2.801	3.348	3.103	0.1256	133	92
3	36	2.8-3.35	2.801	3.345	3.084	0.1226	26	10
4	446	2.8-3.35	2.801	3.349	3.114	0.1323	319	127
5	21	2.8-3.35	2.801	3.314	3.062	0.1246	21	0

*Single and multi-component corresponds to the homo/heterosynthons being formed by the synthons on the same molecules (single) or the formation between two molecules (multi) with complementary synthons.

Crowns ethers are deficient in hydrogen bond donors; therefore they are very susceptible to forming hydrogen bonds when molecules with amines or any other complementary hydrogen bonding functional group are present. Searches 2, 3 and 4 are all subsets of search 1. Search 1 encompasses all possibilities, from primary amines, secondary amides, pyridines, etc. Most of the structures or hydrogen-bonded synthons found in the CSD regarding ethers involved the same molecule. On the contrary, when 18-crown-6 (18C6) was specified as the ether to be analyzed, none of the 21 hits involved single molecules since 18C6 only has hydrogen bond donors. In this case, molecules with complementary functional groups for hydrogen bonding were needed. This is an example of how new phases and compositions of matter can be manipulated or designed in order to achieve different physical properties.

1.4.4 **Trimesic acid Synthons**



1

Figure 5. Supramolecular synthons in trimesic acid

Table 4. Trimesic acid carboxylic acid dimer hydrogen bond distances

	# hits	**distance**	**min**	**max**	**ave**	**std**	**Single***	**Multi***
1	1193	2.4-3.2	2.554	3.196	2.657	0.0644	1059	134

*Single and multi-component corresponds to the homo/heterosynthons being formed by the synthons on the same molecules (single) or the formation between two molecules (multi) with complementary synthons.

Trimesic acid forms honeycomb networks by means of carboxylic acid dimers. The carboxylic acid dimer is the basis for all of the TMA structures that will be discussed in

Chapter 5. There are many forms of TMA and all involve the carboxylic acid dimer. The new structures incorporate a neutral guest in the cavities formed by six trimesic acid molecules bonding in a honeycomb fashion (~14Å pore diameter). The distances of the hydrogen bonds between the carboxylic acid functional groups on separate molecules are very consistent when it comes to the network.

1.4.5 **Secondary Hydrogen Bonds**

1 **2**

Figure 6. Secondary hydrogen bonds involving methyl hydrogens and hydrogen bond acceptors nitrogen and oxygen.

There are two secondary hydrogen bonds which need to be specified since they are used to further stabilize the crystal packing of the supramolecular structures discussed in this work. Synthon 1 is seen in the nifedipine/4,4'-dipyridyl structure while synthon 2 is seen in the phenytoin/trans-1,2-(4-pyridyl) ethylene structure. Further discussion on all of these structures will be available in the following chapters.

Table 5. Possible secondary hydrogen bond synthons and distances

	# hits	**distance**	**min**	**max**	**ave**	**std**	**Single***	**Multi***
1	10317	3.3-4.2	3.4	3.199	3.8872	0.1038	8606	1711
2	13921	3.35-4.2	3.349	4.199	3.8976	0.1995	11766	2155

*Single and multi-component corresponds to the homo/heterosynthons being formed by the synthons on the same molecules (single) or the formation between two molecules (multi) with complementary synthons.

This thesis is based on the principles of crystal engineering in order to generate new compositions of matter through supramolecular synthesis and self-assembly of complementary synthons. This presents an increase in the potential need to control solid-state structures, changing their physical properties and leading to improved solubility and bioavailability. The study chose pharmaceutical molecules as the target system since they contain a wide range of synthons and understanding of the crystal structure – physical property relationship is essential for the continued application of these essential chemicals toward improving the overall health of society.

Chapter 2

Nifedipine

2.1 Description

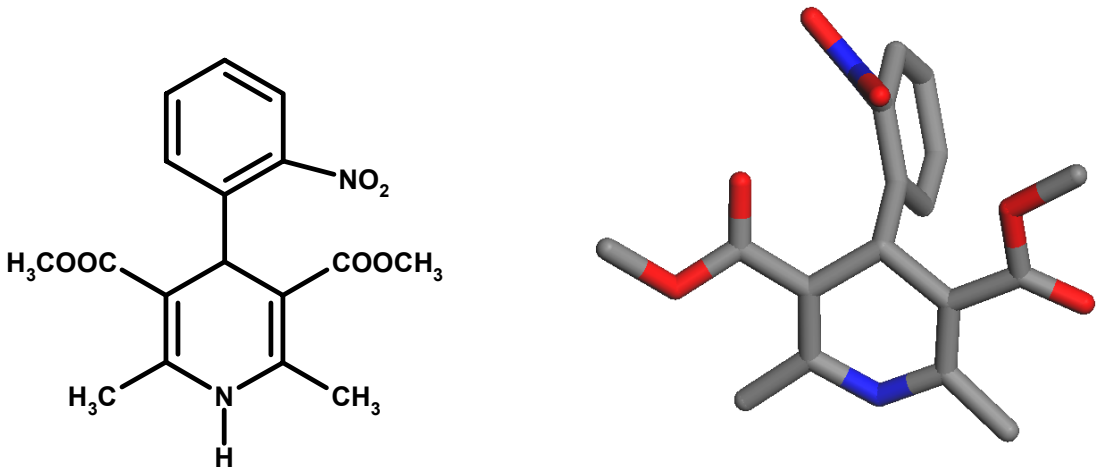


Figure 7. Pure nifedipine stick models. Oxygen atoms are in red (hydrogen bond acceptor); nitrogen atoms are in blue (hydrogen bond donor). All hydrogen atoms on the figure to the right have been omitted for clarity.

Nifedipine,[15] with MW of 246.34g/mol and m.p. of 172-174°C, is a calcium antagonist used in the treatment of cardiovascular disorders such as hypertension and angina pectoris. Nifedipine exhibits low water solubility (less than 10μg/mL) and erratic bioavailability. There is a direct correlation between structure and function of new pharmaceutical phases of nifedipine. Modifying the structure of the compound, thus creating new and different phases, may affect different properties. Differing the phases or crystalline self-assemblies of nifedipine may improve the drug's solubility, dissolution rate, stability and bioavailability.

Dihydropyridine chemistry[16] began in 1882 when Hantzsch first reported dihydropyridines as stable intermediates in the pyridine synthesis that bears his name. The recent interest in dihydropyridines can be traced to the coenzyme reduced nicotinamide adenine dinucleotide (NADH) and the unique ability of this compound in biological systems to reduce unsaturated functional groups.[15] In 1949 A.P. Phillips reported on the weak analgesic and curare-like activities of a few dihydropyridine derivatives. In the search for orally active drugs for the treatment of coronary insufficiency, F. Bosset synthesized in 1966 a compound designated Bay a 1040, which following its introduction as nifedipine in 1975 has since become one of the major cardiovascular drugs.

Nifedipine[16] is sensitive to light in solid form and extremely sensitive to light in dissolved state in solution. In the crystal lattice, the almost flat dihydropyridine ring lies at a practically perpendicular angle to the nitrophenyl group, the ortho-nitro group facing away from the dihydropyridine ring. Under the influence of visible and ultra-violet light nifedipine in solutions is converted into a nitroso compound.

2.2 Strategy

In view of the fact that nifedipine contains hydrogen bond acceptors and donors, complementary molecules can be compounds with both acceptor and donor synthons. The main hydrogen-bonding site is the secondary amine, which can bond to carbonyl as well as nitrogen (*e.g.* pyridines).

Crystals of **A**, **B** and **C** were obtained via slow evaporation of stoichiometric amounts of nifedipine and cocrystal formers in the appropriate solvents. All crystallization

experiments were conducted in an unmodified atmosphere and the solvents were dried by standard methods prior to use. All chemicals used are commercially available and were purchased from Aldrich®.

Table 6. Nifedipine Supramolecular Complexes

Nifedipine/formamide	**A**
Nifedipine/isonicotinamide	**B**
Nifedipine/4,4'-dipyridyl	**C**

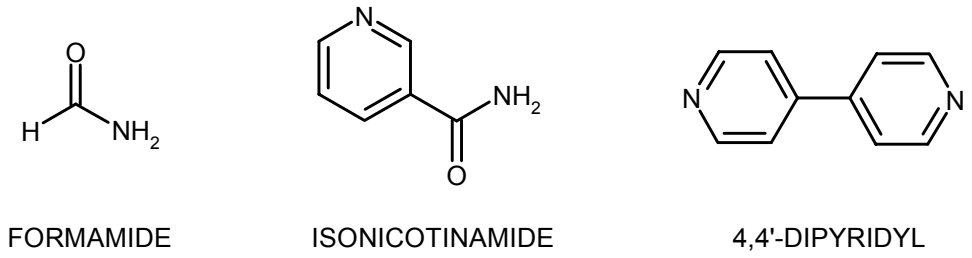


Figure 8. Structures of the co-crystal formers used in the supramolecular complexes involving nifedipine.

2.3 **Structures**

2.3.1 **Nifedipine/formamide (A)**

Crystallization of nifedipine from formamide results in a 1:1 supramolecular complex that is sustained by amine-carbonyl H-bonds. In **A**, as revealed by Figure 3 (synthons 3), one of the hydrogen atoms in the amino moiety of the formamide hydrogen bonds to the carbonyl oxygen of the ester on one nifedipine molecule with bond distance of 3.024Å, which falls well within the distance range found in the CSD and stated in chapter 1 (nifedipine search 3) of 2.8-3.3 Å. The other amine hydrogen atom found in formamide is engaged in a hydrogen bond with the nitro oxygen on another nifedipine

molecule. The distance for this bond is 3.155 Å and falls within the range obtained from the CSD search (nifedipine search 2) for this synthon (2.8-3.4 Å). Formamide has two hydrogen bond donors (the amine hydrogens) but also has a hydrogen bond acceptor (the aldehyde carbonyl). The carbonyl is also involved in a hydrogen bond with a third nifedipine molecule. The carbonyl is bonded to the secondary amine of the nifedipine molecule and has a distance of 2.906 Å and falls within the range set from the CSD search (nifedipine search 4) of 2.8-3.1 Å.

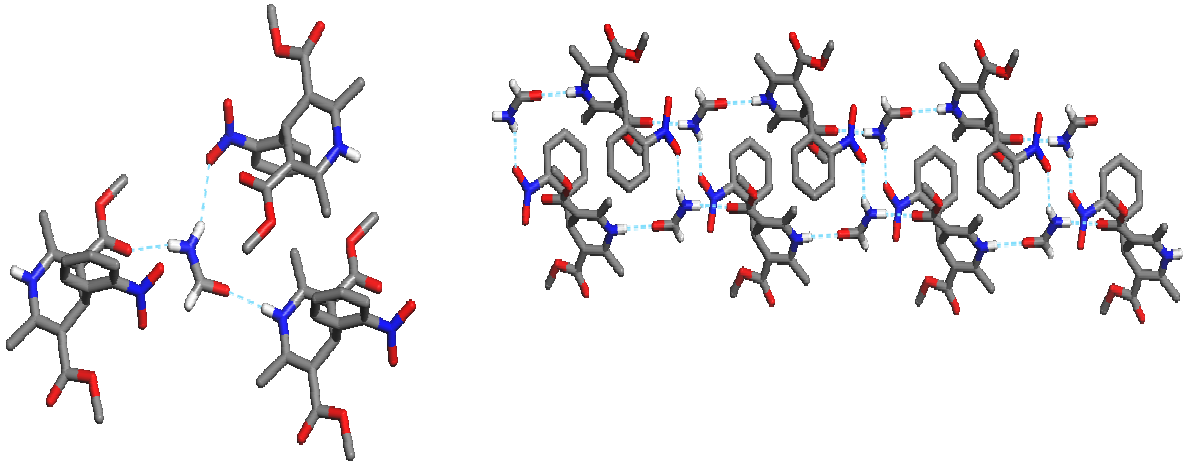


Figure 9. The 1:1 adduct formed between nifedipine and formamide. The hydrogen-bonded motif is also shown.

2.3.2 **Nifedipine/isonicotinamide (B)**

Crystallization of nifedipine and isonicotinamide from methanol results in a 1:1 supramolecular complex that is sustained by amine-carbonyl and amine-pyridine H-bonds. In **B**, as revealed by Figure 4, one of the hydrogen atoms in the amino moiety of the Isonicotinamide hydrogen bonds to the carbonyl oxygen of the ester on one nifedipine molecule with bond distance of 3.097Å which falls well within the distance range found in the CSD and stated in chapter 1 (nifedipine search 3) of 2.8-3.3 Å. The other amine

hydrogen atom found in isonicotinamide is engaged in a hydrogen bond with another isonicotinamide molecule. The distance for the amine hydrogen and the pyridine nitrogen bond on separate isonicotinamide molecules is 2.911 Å and falls within the range obtained from the CSD search (nifedipine search 1) for this synthon (2.8-3.25 Å). Isonicotinamide has two hydrogen bond donors (the amine hydrogens) but also has a hydrogen bond acceptor (the amide carbonyl). This carbonyl oxygen is involved in a hydrogen bond to a second nifedipine molecule. The carbonyl is bonded to the secondary amine of the nifedipine molecule and has a distance of 2.878 Å and falls within the range set from the CSD search (nifedipine search 4) of 2.8-3.1 Å. **B** differs from **A** in that a new synthon is involved, the amine-pyridine hydrogen bond is seen in **B** which facilitates many more arrangements and new phases for nifedipine.

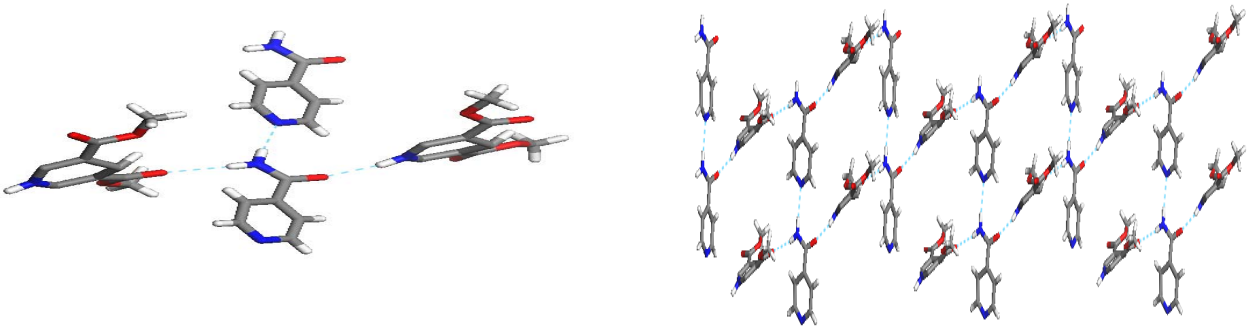


Figure 10. The 1:1 adduct formed between nifedipine and isonicotinamide.

2.3.3 Nifedipine/4,4'-dipyridyl (C)

Crystallization of nifedipine and 4,4'-dipyridyl from methanol results in a 1:1 supramolecular complex which is sustained by amine-pyridine H-bonds. 4,4'-dipyridyl is only a hydrogen bond acceptor; therefore the secondary amine in the nifedipine is the

most likely hydrogen bonding site. In **C**, as revealed by Figure 5, the amine-pyridine hydrogen bond is evident with a bond distance of 3.134Å. This distance does fall within the nifedipine CSD search from chapter 1 (search 1, 2.8-3.25 Å). A secondary hydrogen bond is formed between one methyl hydrogen (from the ester group) and the other pyridine nitrogen available. This bond's purpose is for stability in the crystal packing and the distance is 3.295 Å. The range distance for this secondary hydrogen bond is 3.3-4.2 Å; therefore, it is on the lower limit of this type of bond (Search 1, section 1.25).

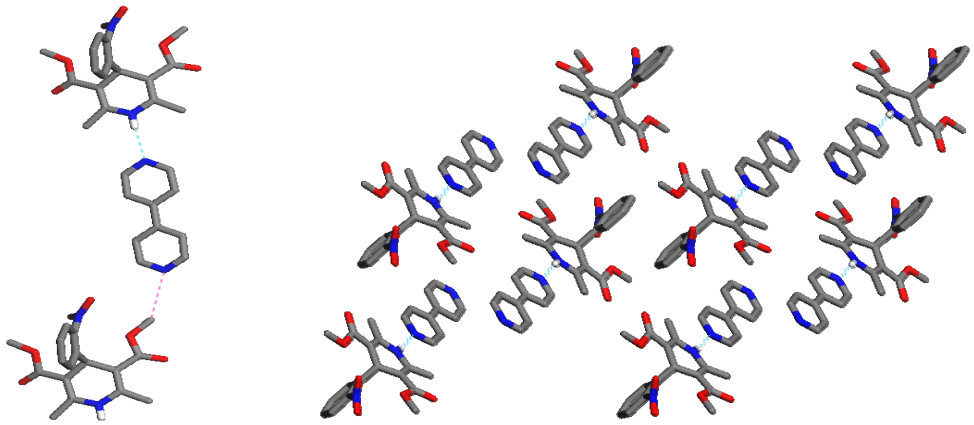


Figure 11. The 1:1 adduct formed between nifedipine and 4,4'-dipyridyl.

2.4 Synthesis and Results

2.4.1 Nifedipine/formamide (A)

Synthesis: In a typical reaction, 32 mg ($1.29x10^{-4}$ mol) of nifedipine was dissolved in 2 mL of formamide. The reaction vial was kept tightly capped to avoid any solvent evaporation. The vial was covered in aluminum foil to protect from light. In approximately two days yellow crystals appeared.

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

Crystal packing: Crystallization of nifedipine from formamide results in a 1:1 supramolecular complex that is sustained by amine-carbonyl H-bonds. Distances range between 3.024-3.155Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3443, 3303 cm^{-1} (N-H stretch, 1° amine, formamide); 1684 cm^{-1} (C=O stretch, formamide) 1310, 1248, 1217 cm^{-1} (C-O stretching).

Melt-temp: 136-138°C

X-ray powder diffraction: in 2θ, simulated derived from the single crystal data; experimental (simulated): 8.461(8.850), 9.955(9.923), 12.682(12.893), 13.080(13.420), 14.954(15.307), 16.966(17.022), 17.082 (17.034), 21.036(20.827), 23.539(23.437), 24.658(24.682), 26.725(26.715), 27.039(27.028).

2.4.2 Nifedipine/isonicotinamide (B)

Synthesis: In a typical reaction, 31 mg ($1.26x10^{-4}$ mol) of nifedipine and 28 mg ($2.29x10^{-4}$ mol) of isonicotinamide were dissolved in approximately 1 mL of methanol. Slow evaporation of the solvent for approximately a week yielded 1:1 crystals. The reaction vial was covered in aluminum foil to prevent light degradation.

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

Crystal packing: Crystallization of nifedipine and isonicotinamide from methanol results in a 1:1 supramolecular complex that is sustained by amine-carbonyl and amine-pyridine H-bonds. Distances range between 2.878-3.097Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3408 cm^{-1} (N-H stretch, 2° amine); 3286 cm^{-1} (-OH stretch); 1669 cm^{-1} (C=O stretch); 1209, 1118 cm^{-1} (C-O stretching).

Melt-temp: 148-153°C

X-ray powder diffraction: in 2θ, simulated derived from the single crystal data; experimental (simulated): 10.418(10.636), 11.561(11.823), 11.880(11.849), 13.003(13.212), 19.404(19.739), 19.660(19.771), 21.142(21.167), 22.739(22.779), 23.739(23.774), 26.399(26.407), 31.820(31.806).

2.4.3 Nifedipine/4,4'-dipyridyl (C)

Synthesis: In a typical reaction, 30 mg ($1.22x10^{-4}$ mol) of nifedipine and 43 mg ($2.75x10^{-4}$ mol) of 4,4'-dipyridyl were dissolved in approximately 1 mL of methanol. Slow evaporation of the solvent for approximately two week yielded 1:1 nifedipine/4,4'-dipyridyl crystals.

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

Crystal packing: Crystallization of nifedipine and 4,4'-dipyridyl from methanol results in a 1:1 supramolecular complex that is sustained by amine-pyridine H-bonds. 4,4'-Dipyridyl is only a hydrogen bond acceptor; therefore the secondary amine in the

nifedipine is the most likely hydrogen bonding site. Distances range between 3.134-3.295Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3275 cm^{-1} (N-H stretch, 2° amine); 3213 (-OH stretch); 1687 cm^{-1} (C=O stretch); 1263, 1208 cm^{-1} (C-O stretching).

Melt-temp: 137-139°C

X-ray powder diffraction: experimental done, calculated could not be done. 4.039, 11.459, 12.281, 19.362, 20.200, 21.601, 24.802, 24.958, 25.340, 25.419.

2.5 Discussion

Presented above were three examples of the use of supramolecular synthesis to generate new compositions of matter containing molecules of interest to materials scientists. These supramolecular complexes show how secondary amines, nitro groups and carbonyls present in pharmaceutical drugs can be exploited via crystal engineering. This has increased the potential to control solid-state structures, changing their physical properties and leading to improved solubility and bioavailability. Pure nifedipine H-bonds forming a chain, secondary amine to ether carbonyl, but as seen in the previous co-crystals, other synthons are exploited and the crystal structure therefore has to adjust. Careful analysis of the existing supramolecular synthons on nifedipine provides an educated guess that allows scientists to choose other molecules with complementary components, designing supramolecules. The exact connection sites for the synthons cannot always be predicted since other factors such as solvent, sterics and number of possible hydrogen bonding sites has a powerful effect on the outcome.

Chapter 3

Phenytoin

3.1. Description

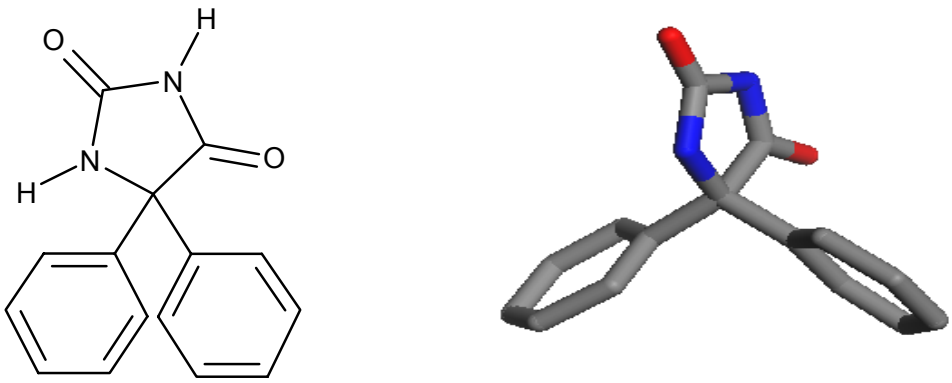


Figure 12. Pure phenytoin stick models. Oxygen atoms (in red) are the hydrogen bond acceptors and the nitrogen atoms (in blue) are the hydrogen bond donors. Hydrogen atoms have been deleted for clarity.

Phenytoin,[17] or 5,5-diphenylhydantoin, is a pharmaceutical drug used for the treatment of seizures. It is sparingly soluble in water (20-25mcg/mL). Compounds with aliphatic side groups at position C5 are commonly used as sedatives, and phenyl rings at this position lead to anticonvulsant properties without the need to impair consciousness. It is also sparingly soluble in ethanol and acetone and has a M.W. of 252.272g/mol and m.p. of 295°C. According to Chakrabati,[18] phenytoin exists in two forms. Form 1: rodlike plates or regular crystalline shape, and form 2: needle shaped. The existence of these two forms is due to differences in the crystalline state.

In 1938 Merrit and Putnam[19] found that 5,5-diphenylhydantoin (phenytoin) showed anticonvulsant properties. Twelve years later it was stated that apart from antiepileptic activity, phenytoin possessed antiarrhythmic activity. It belongs to class 1b according to Vaughan Williams classification of antiarrhythmic agents modulating voltage-gated sodium channels conductance. Limited clinical effectiveness and undesired side effects are the driving force to using supramolecular chemistry in order to change the structure, therefore changing the physical properties since there is a direct correlation between the two.

Diphenylhydantoin and phenobarbital are the most widely used drugs in the treatment of grand mal, psychomotor, and focal epilepsies. The similarity of barbiturates to uracil has prompted investigations into their hydrogen-bonding capabilities with adenine molecules. Some of the biological effects of these drugs may derive from an ability to specifically bind and inactivate adenine-containing nucleic acids or coenzymes.[20] Comparisons of the complexes formed by these drugs with adenine containing molecules may prove helpful in understanding the modes of action of these drugs.[20]

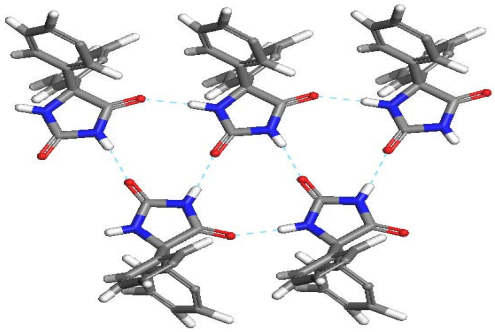


Figure 13. Hydrogen bonded motif of pure phenytoin.

The crystals are orthorhombic and systematic absences indicate space groups Pnma or $Pn2_1a$. $Pn2_1a$ (centrosymmetric space group), indicated by structure analysis, was yielded by the hydantoin group atomic positions even though the true space group for phenytoin

is non-centrosymmetric, but the proximity of the hydantoin group plane was very close to 0 or π (approximating a centrosymmetric arrangement in the unit cell). The hydrogen-bonded motif, figure 2, shows the hydrogen bonds between amine hydrogens and carbonyl oxygens between phenytoin molecules with distances ranging from 2.784-2.844 Å. These distances fall within the range obtained from the CSD search in Chapter 1 (phenytoin search 2) which is 2.7-3.2 Å.

3.2 **Strategy**

In view of the fact that phenytoin has both hydrogen bond acceptors (carbonyl oxygens) as well as hydrogen bond donors (secondary amines), a complementary molecule can be one that has at least one hydrogen bond acceptor moiety (example amines, alcohols, carboxylic acids, *etc.*) or at least one hydrogen bond donor moiety (amines, amides, alcohols, etc). Phenytoin has the added characteristic that it can form amide dimers between two phenytoin molecules since the synthon is complementary with itself.

Crystals of **A**, **B**, and **C** were obtained via slow evaporation of stoichiometric amounts of phenytoin and cocrystal formers in the appropriate solvents. All crystallization experiments were conducted in an unmodified atmosphere and the solvents were dried by standard methods prior to use. All chemicals used are commercially available and were purchased from Aldrich®.

Table 7. Phenytoin Supramolecular Complexes

Phenytoin/4(1H) pyridone	**A**
Phenytoin/4,4'-dipyridyl	**B**
Phenytoin/trans-1,2-bis(4-pyridyl) ethylene	**C**

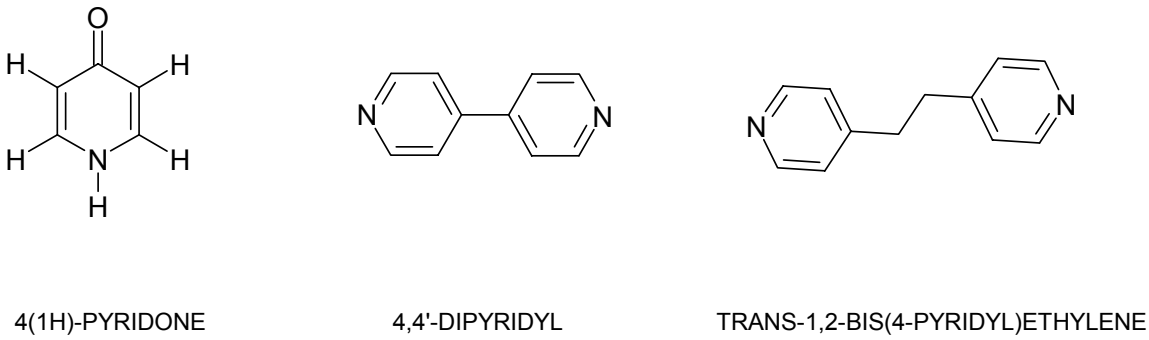


Figure 14. Structures of the co-crystal formers used in the supramolecular complexes involving phenytoin.

3.3 Structures

3.3.1 Phenytoin/4(1H)-pyridone (A)

Crystallization of phenytoin and 4-hydroxypyridine (which later tautomerized to 4(1H)-pyridone) from ethanol results in a 1:1 supramolecular complex that is sustained by amine-carbonyl H-bonds between phenytoin molecules and pyridone molecules. In **A**, as revealed by Figure 4, there is a chain formed of phenytoin molecules. The pyridones also arrange consecutively with one another forming another chain by means of N-H···O=C bonds. These hydrogen bonds average 2.665 Å, well within the range obtained from the CSD (2.7-3.2 Å). These two independent chains, phenytoin and pyridone, are connected to each other by means of another N-H···O=C bond. The carbonyl present in the pyridone molecule is bifurcated, H-bonding to both the secondary amine in phenytoin as well as the secondary amine in the pyridone molecule. In the crystal packing of **A** one

can observe that two pyridone chains are sandwiched between two phenytoin chains. If one examines figure 2 one can see how that motif was simply expanded enough to fit the two H-bonded pyridone chains.

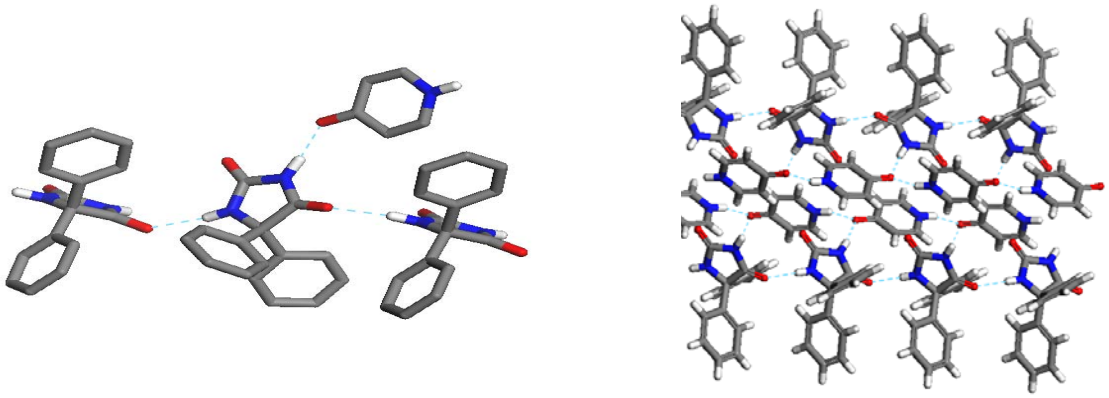


Figure 15. The 1:1 adduct formed between phenytoin and 4(1H) pyridone. The hydrogen bonded crystal packing is shown to the left.

3.3.2 Phenytoin/4,4'-dipyridyl (B)

Crystallization of phenytoin and 4,4'-dipyridyl from 2,4-pentanedione results in a 1:1 supramolecular complex that is sustained by amine-pyridine H-bonds between the phenytoin and 4,4'-dipyridyl (Bipy) molecules as well as phenytoin amide dimers. In **B**, (Figure 5) there is a chain of phenytoin and bipy molecules formed. The N-H···N distance is 2.861Å and falls within the distance range obtained from the CSD search in Chapter 1 (phenytoin search 4), which is 2.8-3.25 Å. The phenytoin molecules also H-bond and form amide dimers. The hydrogen bond distance between the N-H···O=C dimers on separate phenytoin molecules is 2.791 Å and according to the information obtained from the CSD searches on Chapter 1 (phenytoin search 1) fall within the distance range of 2.4-3.3Å. The phenytoin molecules arrange in dimers and the secondary amine not involved in the dimer is available to H-bond to the pyridine nitrogen

of the 4,4'-dipyridyl, forming a zigzag chain. The other carbonyl is not involved in any other hydrogen bonds. The crystal packing of this supramolecular structure orients the hydrophobic phenyl rings on the inside of the chains, keeping the hydrophilic parts of the structure on the outside and susceptible to forming bonds with complementary synthons (figure 5).

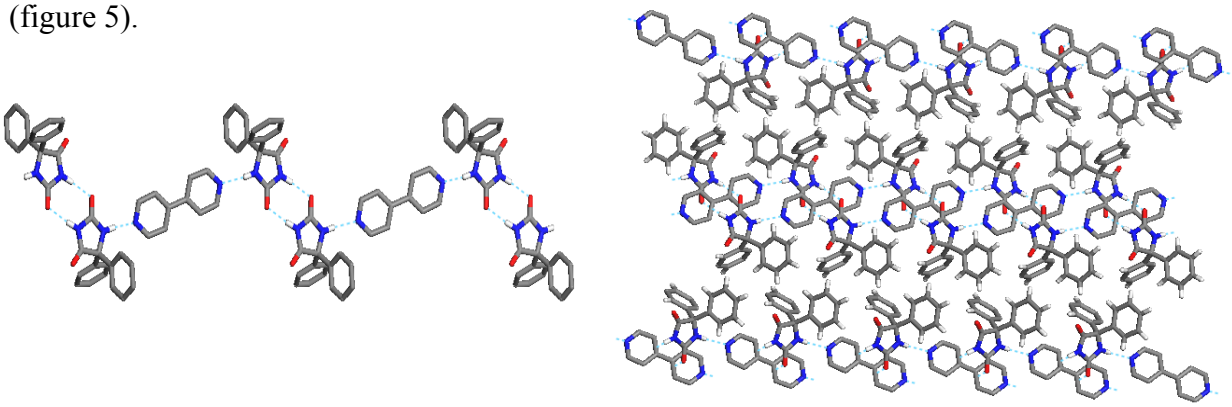


Figure 16. The 1:1 adduct formed between phenytoin and 4,4'-dipyridyl. The hydrogen bonded crystal packing is shown.

3.3.3 **Phenytoin/trans-1,2-bis(4-pyridyl) ethylene (C)**

Crystallization of phenytoin and trans-1,2-bis(4-pyridyl) ethylene from 2,4-pentanedione results in a 1:5 supramolecular complex that is sustained by amine-pyridine H-bonds between the phenytoin and trans-1,2-bis(4-pyridyl) ethylene molecules as well as dimers between the phenytoin amides. In **C** (Figure 6), there is a chain formed of phenytoin and trans-1,2-bis(4-pyridyl) ethylene molecules. The N-H···N distance is 2.844 Å and falls within the distance range obtained from the CSD search on Chapter 1 (phenytoin search 4) which is 2.8-3.25 Å. The phenytoin molecules also H-bond and form amide dimers. The hydrogen bond distance between the N-H···O=C on separate phenytoin molecules is 2.891 Å and according to the information obtained from the CSD searches on Chapter 1 (phenytoin search 1) falls within the distance range of 2.4-3.3Å. Structure **C** is very similar to structure **B** in its hydrogen bonding, the only difference is

that in addition to forming dimers between the phenytoin molecules and N-H···N bond to the additive, there are also additives interacting in a secondary hydrogen bond with the available phenytoin carbonyl. The bond distance is 3.386 Å and falls within the range for the CH···O carbonyl synthon (range 3.1-3.9 Å). This hydrogen bond permits the trans-1,2-bis(4-pyridyl) ethylene to stay in the cavity.

The phenytoin molecules arrange in dimers and the secondary amine not involved in the dimer is available to H-bond to the pyridine nitrogen of the trans-1,2-bis(4-pyridyl) ethylene, forming a zigzag chain. The crystal packing of this supramolecular structure arranges in such a way that allows for the accommodation of an additive molecule in the hydrophobic cavity.

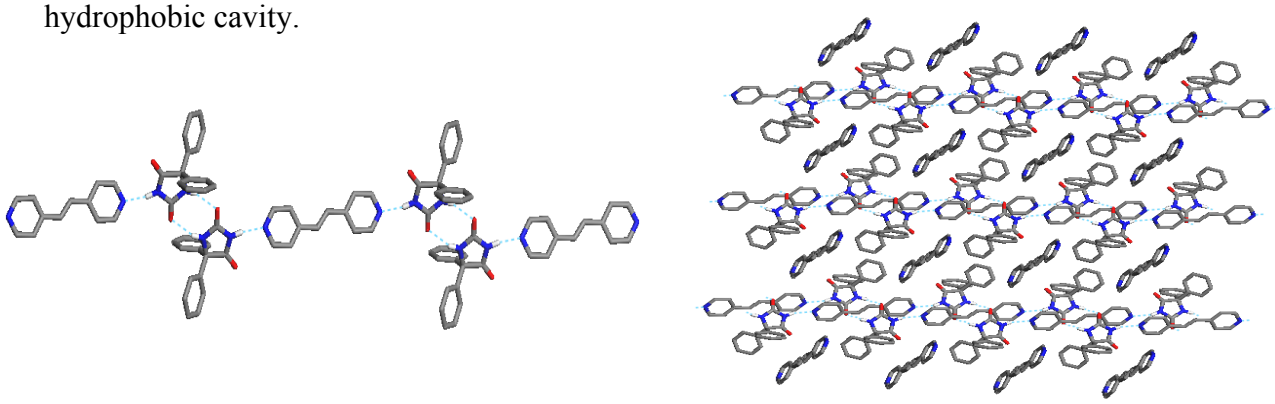


Figure 17. The 1:5 adduct formed between phenytoin and trans-1,2-bis(4-pyridyl) ethylene. The hydrogen bonded crystal packing is shown.

3.4 **Synthesis and Results**

3.4.1 **Phenytoin/4(1H)-pyridone (A)**

Synthesis: In a typical reaction, 28 mg (1.11×10^{-4} mol) of phenytoin and 11 mg (1.16×10^{-4} mol) of 4-hydorxypyridine (which later tautomerizes to 4(1H)pyridone) were dissolved in approximately 2 mL ethanol and 1 mL acetone. The reaction vial was kept tightly capped to avoid solvent evaporation. After a few weeks clear 1:1 crystals formed.

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

Crystal packing: Crystallization of phenytoin and 4-hydroxypyridine (which later tautomerized to 4(1H)-pyridone) from ethanol results in a 1:1 supramolecular complex

that is sustained by amine-carbonyl H-bonds between phenytoin molecules and pyridone molecules. Distances averaged 2.665Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3311 cm^{-1} (N-H stretch, 2° amine, phenytoin); 1758, 1711, 1497cm^{-1} (C-O stretching).

Melt-temp: 234-239°C

X-ray powder diffraction: in 2θ, simulated derived from the single crystal data; experimental (simulated): 5.336(5.212), 11.332(11.137), 15.250(15.097), 16.419(16.228), 17.000(17.763), 17.977(18.019), 19.364(19.362), 19.679(19.821), 20.055(20.341), 21.417(21.160), 23.724(23.341), 26.348(26.054), 26.628(26.418), 27.643(27.260), 29.868(29.479).

3.4.2 **Phenytoin/4,4'-dipyridyl (B)**

Synthesis: In a typical reaction, 28 mg ($1.11x10^{-4}$ mol) of phenytoin and 19 mg ($1.22x10^{-4}$ mol) of 4,4'-dipyridyl were dissolved in approximately 1 mL of 2,4-pentanedione. Slow evaporation of the solvent for a few weeks yielded 1:1 crystals.

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

Crystal packing: Crystallization of phenytoin and 4,4'-dipyridyl from 2,4-pentanedione results in a 1:1 supramolecular complex that is sustained by amine-pyridine H-bonds between the phenytoin and 4,4'-dipyridyl (bipy) molecules as well as phenytoin amide dimers. Distances range between 2.791-2.861Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). N/A

Melt-temp: 225-227°C

X-ray powder diffraction: experimental done, calculated could not be done. 12.974, 17.461, 18.798, 20.613, 22.180, 24.902, 26.717, 28.599, 31.931.

3.4.3 **Phenytoin/trans-1,2-bis(4-pyridyl) ethylene (C)**

Synthesis: In a typical reaction, 29 mg ($1.15x10^{-4}$ mol) of phenytoin and 108.35 mg ($5.93x10^{-4}$ mol) of trans-1,2-bis(4-pyridyl) ethane were dissolved in approximately 1 mL 2,4-pentanedione. Slow evaporation of the solvent for approximately a week yielded yellow 1:5 crystals.

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

Crystal packing: Crystallization of phenytoin and trans-1,2-bis(4-pyridyl) ethane from 2,4-pentanedione results in a 1:5 supramolecular complex that is sustained by amine-pyridine H-bonds between the phenytoin and trans-1,2-bis(4-pyridyl) ethane molecules as well as dimers between the phenytoin. Distances range between 2.844-3.273Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3264, 3194 cm^{-1} (N-H stretch, 1° amine); 3066, 3029 cm^{-1} alkenes; 1713 cm^{-1} (C=O stretch); 1310, 1248, 1209 cm^{-1} (C-O stretching), 985 cm^{-1} (aromatic hydrogens).

Melt-temp: 254-257°C

X-ray powder diffraction: experimental done, calculated could not be done. 15.919, 19.370, 19.866, 2.159, 22.089, 22.215, 23.815, 34.826, 36.701.

3.5 **Discussion**

Presented above were three examples of the use of supramolecular synthesis to generate new compositions of matter that contains molecules of interest to materials scientists. These supramolecular complexes show how carbonyl and secondary amines if viewed separately, or known as amides if both synthons (functional groups) are viewed together, in pharmaceutical drugs can be exploited via crystal engineering. This has increased the potential to control solid-state structures, changing their physical properties and leading to improved solubility and bioavailability. Pure phenytoin makes full use of all available synthons when hydrogen bonding, forming a tape. In the co-crystals, modifications to this hydrogen bonded motif are necessary when accommodating other complementary compounds. Not all available synthons will be exploited, as see in structure **A,** where one of the two carbonyls available in each phenytoin molecule is not involved in a hydrogen bond with another phenytoin molecule, additive molecule or solvent molecule. In structure **B**, the supramolecular tape found in pure phenytoin has been expanded to accommodate the bipy molecules. Phenytoin molecules still hydrogen

bond to each other forming dimers. One secondary amine is involved in the hydrogen bond with the bipy molecule, but the other carbonyl is not involved in a synthon (as seen with structure **A**). Structure **C** is very similar to structure **B,** having the same hydrogen bonding with the additive and also an available carbonyl not involved in a hydrogen bond, but differs in that it fits another additive molecule in the cavities formed from the arrangements of the Phenytoin/trans-1,2-(4-pyridyl) ethylene chains. This elucidates the fact that just because the same synthons are being used, does not mean that the same arrangements will be seen from structure to structure.

Chapter 4

Crown Ethers

4.1 Description

Crown ethers are toxic compounds and serve as model compounds for pharmaceutical molecules that contain ether linkages. Ether moieties are deficient in H-bond donors and contain excess H-bond acceptors. They are therefore predisposed to become involved in supramolecular heterosynthons and it should not be surprising that well known ethers such as 18-Crown-6[21] (18C6) and Dibenzo-18-Crown-6[22] (DB18C6) form co-crystals and solvates with complementary molecules. Since the crown ether has only hydrogen bond acceptors (oxygen atoms), a complementary molecule should be one that has at least one hydrogen bond donor moiety (amines, alcohols, carboxylic acids, *etc.*). The pure phase for 18C6[21] has been isolated, and the pure phase for DB18C6 has been solved, but is pending publication.

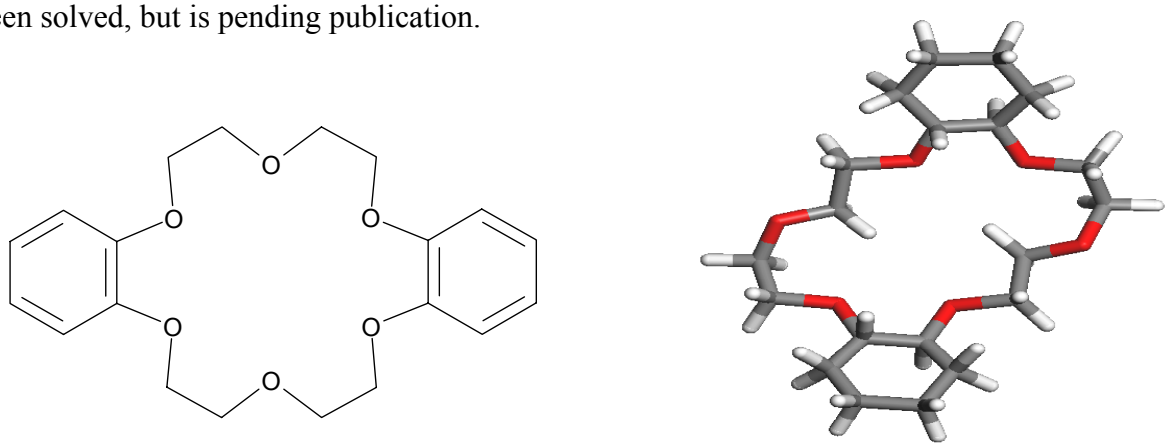


Figure 18. Pure Dibenzo-18-crown-6 stick models. Oxygens (in red) are the hydrogen bond acceptors.

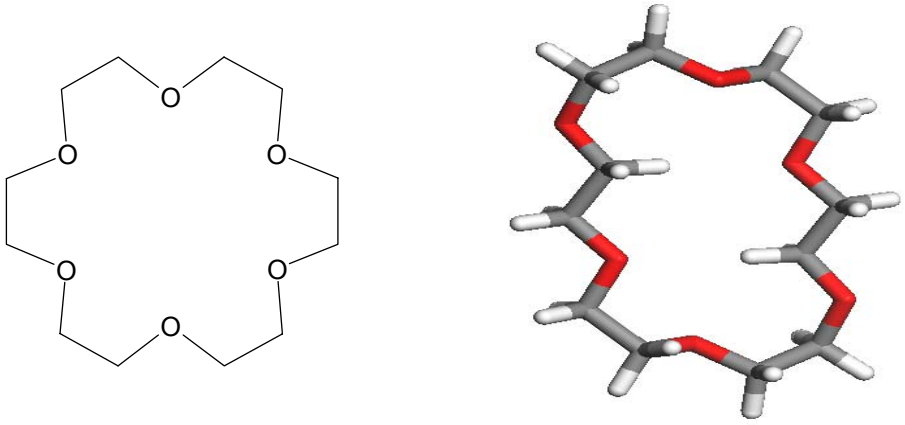


Figure 19. Pure 18-crown-6 stick models. Oxygens (in red) are the hydrogen bond acceptors.

4.2 Polymorphism

The phenomenon of polymorphism in crystal engineering cannot be ignored. Polymorphism is defined as the phenomenon where the same chemical substance exists in different crystalline forms or different crystalline patterns.[11] This phenomenon is more common among molecules with flexible conformations capable of hydrogen bonding.[6] Supramolecular synthons are the structural units within molecules, which can be formed and/or assembled by synthetic operations.[6] The supramolecular synthons present in polymorphic forms may be intact from form to form, therefore it can be stated that the supramolecular equivalents of structural isomers are crystalline polymorphs.[6] The criteria for assessing the existence of polymorphs are different unit cell parameters, crystal packing arrangements and physical properties.[6]

4.3 Strategy

In view of the fact that the crown ethers only have hydrogen bond acceptors (oxygen atoms), a complementary molecule should be one that has at least one hydrogen bond acceptor moiety (example amines, alcohols, carboxylic acids, *etc*.). A survey of the

Cambridge Structural Database (CSD) [14] shows that out of 362 hits (146 single-component, 208 multi-component) for 18C6 foundation, 177 included metals, 39 had hydrogen bonding to amine groups, and the remaining 88 hits were of crown derivatives. The same trend was observed for DB18C6. Out of the 26 hits (15 single-component, 11 multi-component), 16 included metals, and only one hit had a hydrogen bond to an amine group. The remaining three hits were DB18C6 derivatives. No hits showed hydrogen bonding with amine groups and the remaining 13 hits were of crown derivatives.

Crystals of **A**, **B**, **C**, **D**, **E**, **F, G, and H** were obtained via slow evaporation of stoichiometric amounts of crown ether and cocrystal formers in the appropriate solvents. All crystallization experiments were conducted in an unmodified atmosphere and the solvents were dried by standard methods prior to use. All chemicals used are commercially available and were purchased from Aldrich®.

Table 8. Crown ether Supramolecular Complexes

Dibenzo-18-crown-6/4-nitroaniline	A
Dibenzo-18-crown-6/2-methyl-4-nitroaniline	B
Dibenzo-18-C-6/nicotinamide *Polymorph A*	C
Dibenzo-18-C-6/nicotinamide *Polymorph B*	D
18-crown-6/2,6-diaminopurine	E
18-crown-6/dicyandiamide	F
18-crown-6/5-aminoisophthalic acid	G
18-crown-6/tetrafluoroisophthalic acid/H2O	H

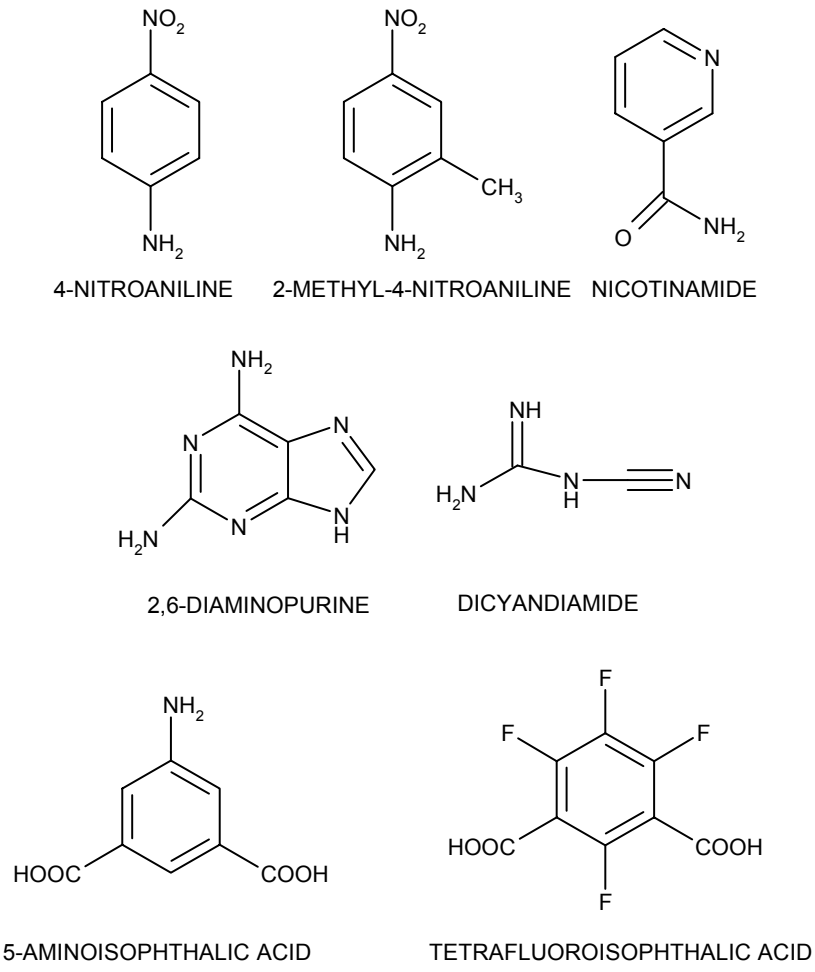


Figure 20. Structures of the co-crystal formers used in the supramolecular complexes.

4.4 Structures

4.4.1 Dibenzo-18-crown-6/4-nitroaniline (A)

Crystallization of DB18C6 and 4-nitroaniline from benzene affords a 1:1 co-crystal, **A**. Grinding a 1:1 mole ratio of DB18C6 and 4-nitroaniline also forms the co-crystal. As revealed by Figure 4, the amine moiety forms H-bonds with four of the six ether oxygens and generates a supramolecular complex. The hydrogen bond distances between the oxygen atoms in the ether linkages closest to the aromatic rings and the bifurcated

hydrogens in the amino group range from 3.050-3.145Å, with the 4-nitroaniline bonded to the outside of the crown ether bowl.

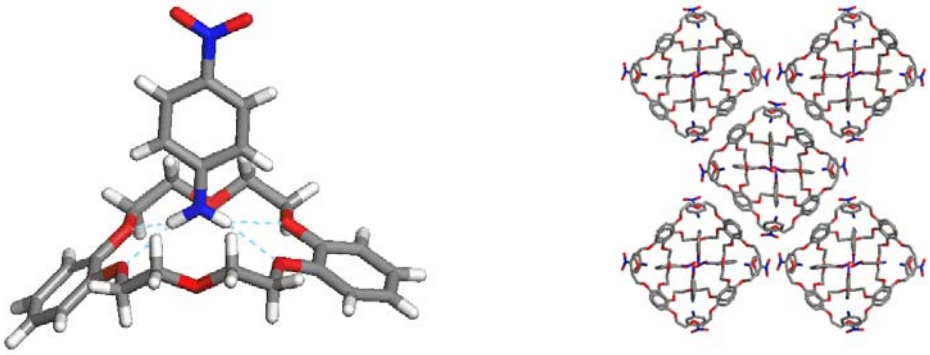


Figure 21. The 1:1 adduct formed between DB-18-C-6 and 4-nitroaniline.

These supramolecular complexes pack into tubular arrangements with solvent channels on the interior of the nanotubes (Figure 5). The tubular structure is not sustained by π-π stacking or C-H···O- C hydrogen bonding. The tubular arrangements are held together through steric effects.

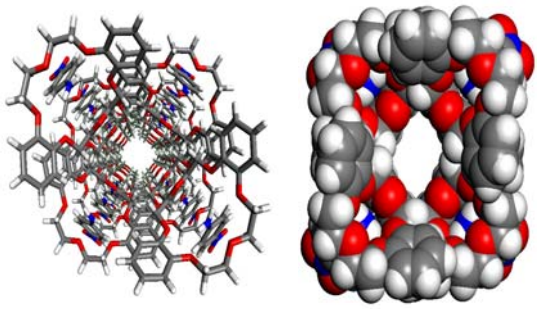


Figure 22. Stick and space-filling models of one of the nanotubes formed by self-assembly of DB18C6/4-nitroaniline. The nanotubes have an exterior diameter of ca. 2.3nm and the solvent channels have an effective cross-section of 0.35nm.

The nature of the crystal packing is of particular note since the nanotubes are inherently polar and they crystallize parallel to one another. Furthermore, as revealed by Figure 6, the 4-nitroaniline molecules are oriented at ca. 60° to the polar axis. This

represents a close to ideal alignment of dipoles that in most systems is usually frustrated because of the tendency of molecules with high polarizability to pack in anti-parallel arrangements.[23]

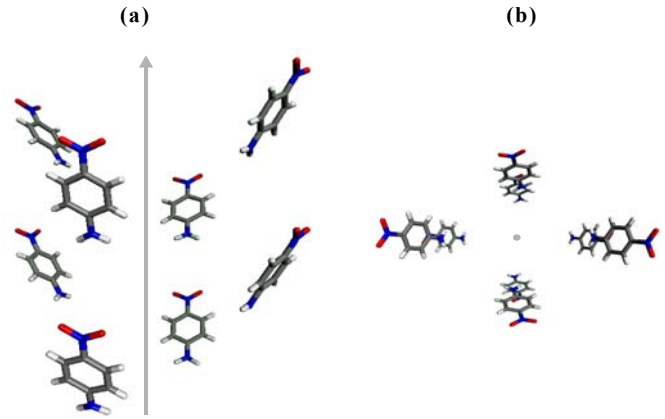


Figure 23. Views of the orientation of the p-nitroaniline molecules in 1: (a) parallel to the polar axis; (b) looking down the polar axis.

4.4.2 **Dibenzo-18-crown-6/2-methyl-4-nitroaniline (B)**

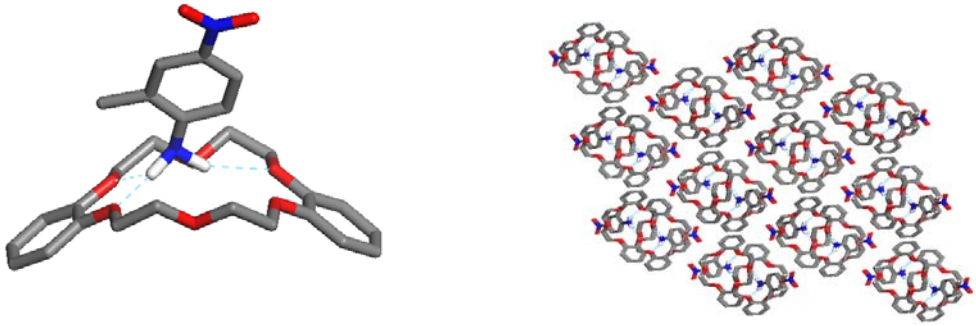


Figure 24. The 1:1 adduct formed between DB-18-C-6 and 2-methyl-4-nitroaniline.

Crystallization of DB18C6 and 2-methyl-4-nitroaniline also results in a 1:1 supramolecular complex that is sustained by amine-ether H-bonds. In **B**, as revealed by Figure 7, the amino moiety hydrogen bonds through the outside of the bowl to three oxygen atoms of the crown. One amino hydrogen is bifurcated, the other is not. The distances between the hydrogen atoms of the 2-methyl-4-nitroaniline and the oxygen atoms of the ether linkages range from 2.695-3.465Å. However, in this case, non-

centrosymmetric crystals are obtained. The molecule contains a donor amine and an acceptor nitro group at the para position. This positioning allows for maximum acentricity of the molecule. A methyl group is substituted at the ortho position, which affects the non-centrosymmetric structure. The methyl group may also act as weak H-bond donor, but it is not evident in this case.[24]

4.4.3 **Dibenzo-18-crown-6/nicotinamide *Polymorph A* (C)**

Nicotinamide,[25] vitamin B_3 and a well known hydrotropic agent, was chosen as a complementary additive to DB18C6 due to the presence of the amino group. Crystallization of DB18C6 and nicotinamide from THF results in a 1:1 supramolecular complex that is sustained by amine-ether H-bonds. Nevertheless, this supramolecular organic solid is distinguished by the fact that it can form two crystalline phases that differ in how the amine moieties H-bond to the DB18C6 molecules. In **C**, the amine group of the nicotinamide molecule is hydrogen bonded to the ether oxygens through the outside part of the crown bowl. The hydrogen bond distances between the hydrogen to the oxygen range from 3.134 to 3.362Å

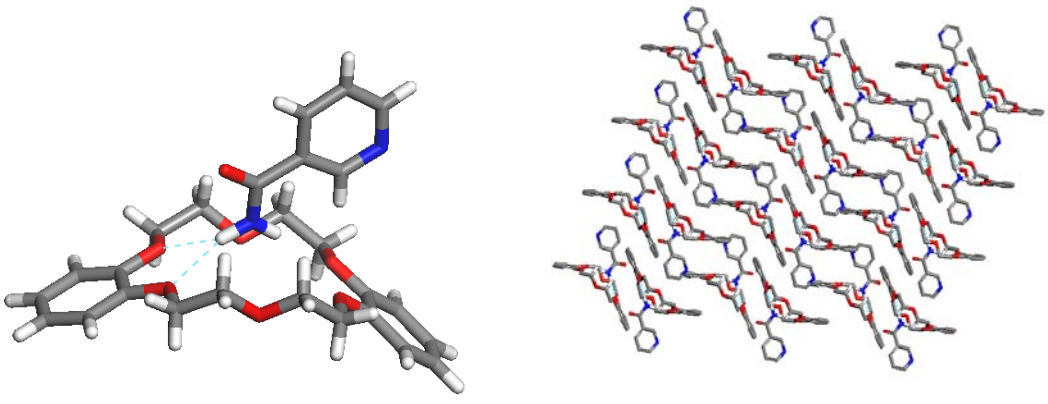


Figure 25. Outside bowl polymorphic form of the 1:1 adduct formed between DB18C6 and nicotinamide. Crystal Packing of the 1:1 polymorphic co-crystals of DB18C6 and nicotinamide.

4.4.4 Dibenzo-18-crown-6/nicotinamide *Polymorph B* (D)

In **D** the nicotinamide molecule is hydrogen bonded to the inside of the crown bowl with hydrogen bond distances ranging from 2.995 to 3.043Å. A notable difference between the hydrogen bonding of the two polymorphic forms is the fact that in **C,** one hydrogen from the amino group bifurcates and bonds to two oxygen atoms closets to one benzene ring.

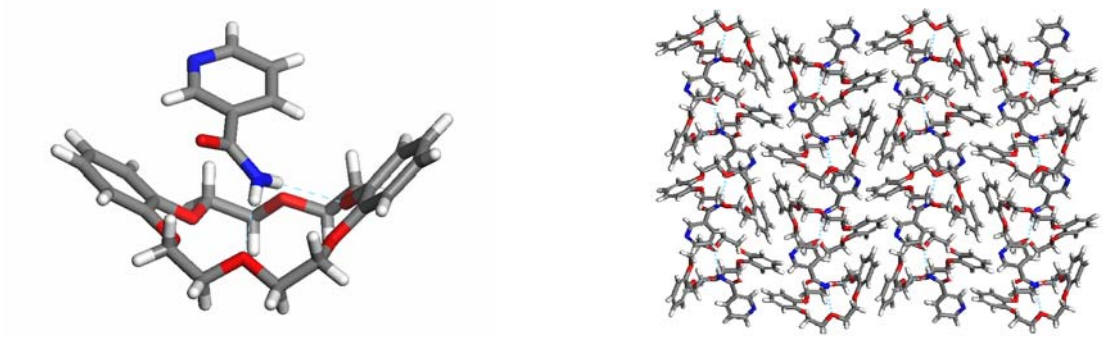


Figure 26. Inside bowl polymorphic form of the 1:1 adduct formed between DB18C6 and nicotinamide Crystal Packing of the 1:1 polymorphic co-crystals of DB18C6 and nicotinamide.

In **D**, each hydrogen atom from the amine is involved in a hydrogen bond with one of the oxygen atoms, not being the same two oxygen atoms as in **C**. In the CSD,[5] seven structures have been reported of co-crystals involving crown ethers [DB18C6 (1 structure) and 18C6 (6 structures)] hydrogen bonded to amino groups.

4.4.5 **18-crown-6/2,6-diaminopurine (E)**

Crystallization of 18C6 and 2,6-diaminopurine from ethanol affords a 1:1 co-crystal, **E**. As revealed by Figure 11, co-crystal **E** is sustained by hydrogen bonds between the secondary amine hydrogen from the 2,6-diaminopurine molecule and an ether linkages

from the crown. Two 2,6-diaminopurine molecules are involved in a dimer ($NH_2\cdots N$). The secondary amine is then H-bonded to a crown oxygen. Distances range between 2.836-3.072Å.

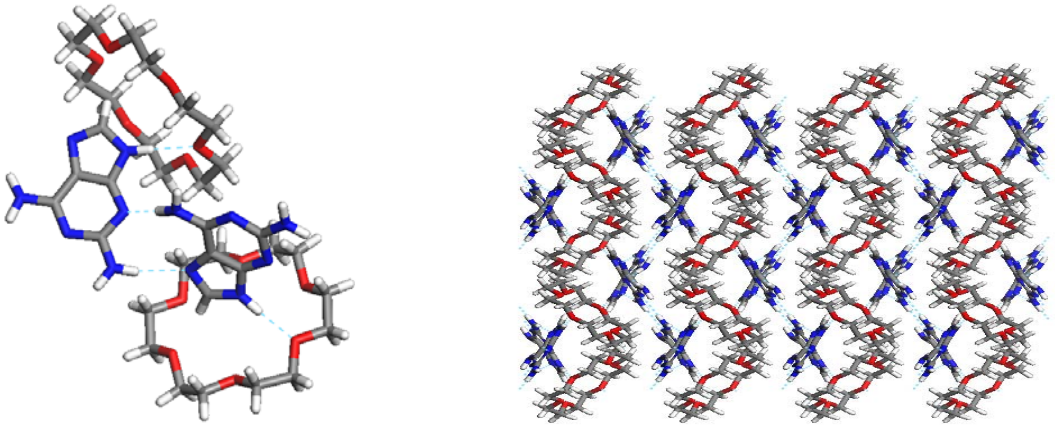


Figure 27. The 1:1 adduct of 18C6 and 2,6-diaminopurine

4.4.6 **18-crown-6/dicyandiamide (F)**

Crystallization of 18C6 and dicyandiamide affords a 1:1 supramolecular complex. The co-crystal, **F**, as shown in Figure 12, is sustained by hydrogen bonds from the two amino group hydrogens from the dicyandiamide and two ether linkages from the crown. Distances range between 2.901-2.998Å. Only one hydrogen atom from each amine group is involved in a hydrogen bond with the ether linkages. The other hydrogen atoms are hydrogen bonded to other dicyandiamides, as in the 2,6-diaminopurine dimers of co-crystal **E.** Crown ether sheets are interlinked to each other by means of the dicyandiamide.

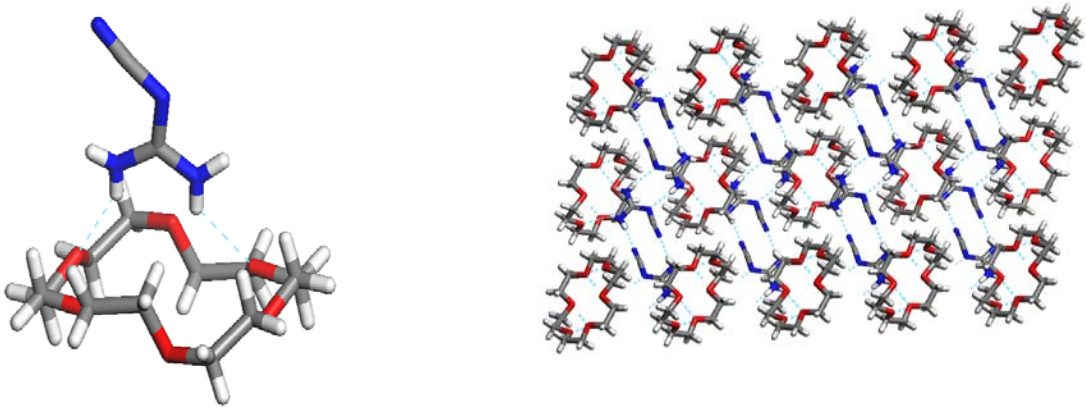


Figure 28. The 1:1 adduct of 18C6 and dicyandiamide.

4.4.7 **18-crown-6/5-aminoisophthalic acid (G)**

Crystallization of 18C6 and 5-aminoisophthalic acid affords a 1:1 supramolecular complex. The co-crystal, **G**, as shown in Figure 13, is sustained in a honeycomb network by carboxylic acid dimers between the 5-aminoisophthalic acids and between amino hydrogens from the 5-aminoisophthalic acid and the crown ether linkages. Distances range between 2.545-2.748Å for the carboxylic acid dimer and 3.008-3.179 Å for the two amino hydrogens and two ether linkages. Two zigzag 5-aminoisophthalic acid chains are H-bonded to each other through the amino-ether H-bonds, forming the honeycomb network. Each crown ether is bonded to two amine groups of the 5-aminoisophthalic acid molecule, one above and one below.

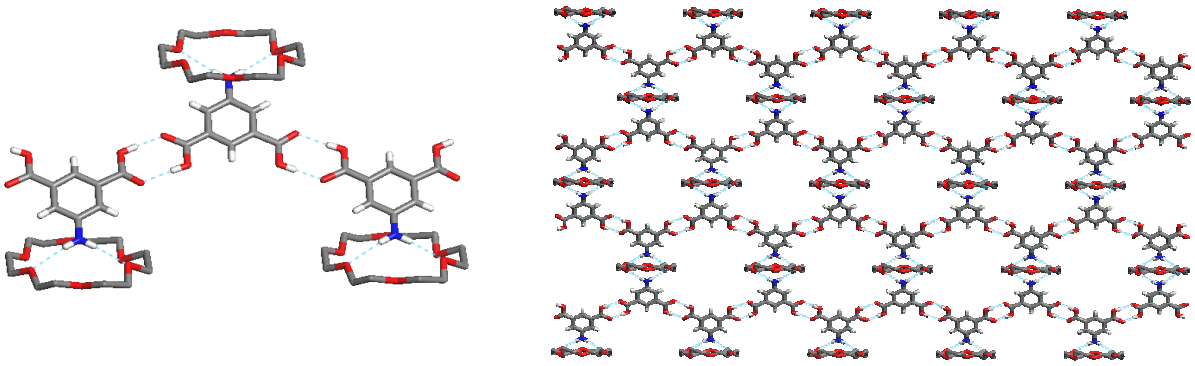


Figure 29. The 1:1 adduct of 18C6 and 5-aminoisophthalic acid.

4.4.8 **18-crown-6/tetrafluoroisophthalic acid/H_2O (H)**

Crystallization of 18C6 and tetrafluoroisophthalic acid/H_2O affords a 1:1 supramolecular complex. The co-crystal, **H**, as shown in Figure 14, is sustained by hydrogen bonds through a bridging water molecule. The hydroxy group of the carboxylic acid is H-bonded to the oxygen in the water molecule and the distances range from 2.856-2.891Å. The water hydrogens are then H-bonded to two ether linkages at a distance of 2.553 Å. The tetrafluoroisophthalic acid bonded to the water molecule, which is then H-bonded to the crown ether forming a screw.

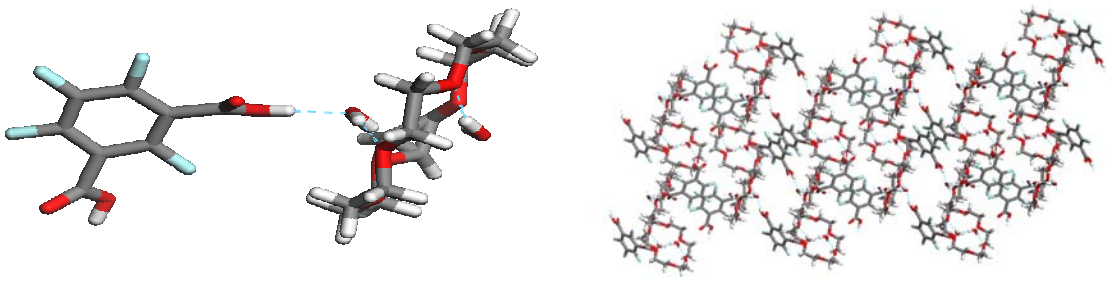


Figure 30. The 1:1 adduct of 18C6 and tetrafluoroisphthalic acid and water.

4.5 **Synthesis and Results**

4.5.1 Dibenzo-18-crown-6/4-nitroaniline 1:1 (A)

Synthesis: In a typical reaction, 30 mg ($8.32x10^{-5}$ mol) Dibenzo-18-crown-6 and 17 mg ($1.23x10^{-4}$ mol) 4-nitroaniline were dissolved in approximately 5 mL benzene. Slow evaporation of the solvent for approximately a week yielded yellow 1:1 dibenzo-18-crown-6/4-nitroaniline crystals.

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

Crystal packing: The co-crystals are sustained by hydrogen bonds between the amine hydrogens and four ether linkages from the crown. The two amino hydrogens involved in the H-bond are bifurcated. Distances range between 3.050-3.115Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3459 cm^{-1} (N-H stretch, 1° amine, 4-nitroaniline); 1310, 1248, 1217 cm^{-1} (C-O stretching, crown).

Melt-temp: 120-122°C

X-ray powder diffraction: experimental done, calculated could not be done. 16.451, 19.422, 20.340, 21.284, 21.422, 21.601, 21.749, 24.416.

4.5.2 **Dibenzo-18-crown-6/2-methyl-4-nitroaniline 1:1 (B)**

Synthesis: In a typical reaction, 30 mg ($8.32x10^{-5}$ mol) dibenzo-18-crown-6 and 14 mg ($9.20x10^{-5}$ mol) of 2-methyl-4-nitroaniline were dissolved in approximately 5 mL benzene. Slow evaporation of the solvent for approximately a week yielded yellow 1:1 dibenzo-18-crown-6/2-methyl-4-nitroaniline crystals.

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

Crystal packing: The co-crystals are sustained by hydrogen bonds between the amine hydrogens and three oxygens from the crown. One of the amino hydrogens involved in the H-bond are bifurcated, the other is involved in a H-bond with just one oxygen. The H-bond distances range between 2.484-3.465Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3369 cm^{-1}(N-H stretch, 1° amine, 2-methyl-4-nitroaniline); 1306, 1248cm^{-1} (C-O stretching, crown).

Melt-temp: 137-139°C

X-ray powder diffraction: **N/A**

4.5.3 **Dibenzo-18-crown-6/Nicotinamide 1:1 Polymorph A (C)**

Synthesis: In a typical reaction, 29 mg ($8.05x10^{-5}$ mol) Dibenzo-18-crown-6 and 28 mg ($1.53x10^{-4}$ mol) of nicotinamide were dissolved in approximately 4 mL THF. Slow evaporation of the solvent for approximately a week yielded white 1:1 dibenzo-18-crown-6/nicotinamide crystals.

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

Crystal packing: The co-crystals are sustained by hydrogen bonds between one of the amino hydrogens and two ether linkages from the crown. The amino hydrogen involved in the H-bond is bifurcated. Distances range between 3.134-3.161Å. The other hydrogen is at a distance of 3.330-3.362 Å away from two ether linkages as well. This co-crystal has the nicotinamide molecule bonded through the outside of the crown ether bowl and will be referred to as Polymorph A.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3334 cm^{-1}(N-H stretch, 1° amine, nicotinamide); 1326, 1252, 1227 cm^{-1} (C-O stretching, crown).

Melt-temp: N/A

X-ray powder diffraction: in 2θ, simulated derived from the single the single crystal data; experimental (simulated): 13.239(13.092), 17.761(17.853), 19.679(19.482), 22.006(22.134), 22.358(22.383), 24.142(24.170), 26.479(26.360), 30.239(30.256).

4.5.4 **Dibenzo-18-crown-6/nicotinamide 1:1 Polymorph B (D)**

Synthesis: In a typical reaction, 290 mg ($8.05x10^{-4}$ mol) Dibenzo-18-crown-6 and 123 mg ($1.01x10^{-3}$ mol) of nicotinamide were dissolved in approximately 24 mL THF. Slow evaporation of the solvent for approximately a week yielded white 1:1 dibenzo-18-crown-6/nicotinamide crystals.

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

Crystal packing: The co-crystals are sustained by hydrogen bonds between the two amino hydrogens and two ether linkages from the crown. Distances range between 2.995-3.043Å. This co-crystal has the nicotinamide molecule bonded through the inside of the crown ether bowl and will be referred to as Polymorph B.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3349 cm^{-1}(N-H stretch, 1° amine, Nicotinamide); 1256, 1217 cm^{-1} (C-O stretching, crown).

Melt-temp: 158-160°C

X-ray powder diffraction: in 2θ, simulated derived from the single the single crystal data; experimental (simulated): 13.038(13.081), 17.736(17.842), 20.100(20.133), 20.985(21.125), 22.225(22.201), 22.432(22.418), 23.716(23.751), 26.219(26.337), 27.753(27.929), 30.052(30.191).

4.5.5 **18-crown-6/2,6-diaminopurine 1:1 (E)**

Synthesis: In a typical reaction, 31 mg ($1.17x10^{-4}$ mol) 18-crown-6 and 30 mg ($2x10^{-4}$ mol) 2,6-diaminopurine were dissolved in approximately 4 mL ethanol. Slow evaporation of the solvent for approximately a week yielded white 1:1 18-crown-6/2,6-diaminopurine crystals.

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

Crystal packing: The co-crystals are sustained by hydrogen bonds between the secondary amine hydrogen and ether linkages from the crown. Two 2,6-diaminopurine molecules are involved in a dimer ($NH_2\cdots N$). The secondary amine is then H-bonded to a crown oxygen. Distances range between 2.836-3.072Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3319 cm^{-1} (N-H stretch, 1° amine, 2,6-diaminopurine); 3443 and 3478 cm^{-1} (secondary amine); 1391 cm^{-1} (C-O stretching, crown).

Melt-temp: 223-227°C

X-ray powder diffraction: in 2θ, simulated derived from the single the single crystal data; experimental (simulated): 9.382(9.459), 12.641(12.767), 18.441(18.347), 18.899(18.982), 21.077(21.468), 22.960(22.640), 24.669(24.695), 24.801(24.877), 28.204(28.221).

4.5.6 **18-crown-6/dicyandiamide 1:1 (F)**

Synthesis: In a typical reaction, 30 mg ($1.13x10^{-4}$ mol) 18-crown-6 and 9 mg ($1.07x10^{-4}$ mol) of dicyandiamide were dissolved in a solvent system of 2mL of ethyl ether and 2mL of methanol. Heated the solution, then slow evaporation of the solvent system for approximately a week. Yielded colorless 1:1 dibenzo-18-crown-6/nicotinamide crystals.

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

Crystal packing: The co-crystals are sustained by hydrogen bonds between the two amino hydrogens from the dicyandiamide and two ether linkages from the crown. Distances range between 2.901-2.998Å

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3341, 3147 cm^{-1} (N-H stretch, 2° amine); 2878 cm^{-1} (2° amide); 1640 cm^{-1} (C=O),1096 cm^{-1} (C-O stretching).

Melt-temp: 198-201

X-ray Powder Diffraction: in 2θ, simulated derived from the single the single crystal data; experimental (simulated): 9.680(9.837), 14.897(15.124), 17.239(17.181),

19.521(19.748), 20.403(20.389), 23.359(23.325), 23.519(23.802), 23.779(23.849), 26.281(26.441), 27.567(27.519), 27.856(27.844), 29.143(29.483), 29.998(29.810).

4.5.7 **18-crown-6/5-aminoisophthalic acid 1:1 (G)**

Synthesis: In a typical reaction, 30 mg ($1.134x10^{-4}$ mol) of 18-crown-6 and 21 mg ($1.23x10^{-4}$ mol) of 5-aminoisophthalic acid were dissolved separately in 2mL toluene and 2mL THF respectively. The two solvent mixtures were layered on top of one another according to their densities, with a 1mL layer of blank THF separating the two layers to make diffusion slower. The reaction vial remained tightly capped in order to avoid solvent evaporation. A few days later 1:1 crystals emerged.

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

Crystal packing: Crystallization of 18-C-6 and 5-aminoisophthalic acid affords a 1:1 supramolecular complex sustained in a honeycomb network by carboxylic acid dimers and between amino hydrogens and the crown ether linkages. Distances range between 2.545-2.748Å for the carboxylic acid dimer and 3.008-3.179 Å for the two amino hydrogens and two ether linkages.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3437, 3356 cm^{-1} (N-H stretch, 2° amine); 2878 cm^{-1} (2° amide); 1342, 1261, 1110 cm^{-1} (C-O stretching).

Melt-temp: 276-280°C

X-ray powder diffraction: in 2θ, simulated derived from the single the single crystal data; experimental (simulated): 14.528(14.761), 18.144(18.407), 19.100(19.521), 20.502(20.953), 22.558(22.317), 24.021(24.425), 24.898(25.098), 25.880(25.954).

4.5.8 18-crown-6/tetrafluoroisophthalic acid 1:1 (H)

Synthesis: In a typical reaction, 30 mg ($1.134x10^{-4}$ mol) of 18-crown-6 and 25 mg ($1.05x10^{-4}$ mol) tetrafluoroisphthalic acid were dissolved in approximately 1 mL of methanol. Slow evaporation of the solvent for approximately a month yielded yellow 1:1 crystals.

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

Crystal packing: Crystallization of 18-C-6 and tetrafluoroisophthalic acid/H_2O affords a 1:1 supramolecular complex sustained by hydrogen bonds of OH groups and ether linkages through a bridging water molecule. The HO···O distance is 2.553Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). N/A, not enough crystal sample and could not reproduce results.

Melt-temp: N/A

X-ray powder diffraction: **N/A**

4.6 **Discussion**

Presented above were eight examples of the use of supramolecular synthesis to generate new compositions of matter that contains molecules of interest to materials scientists. These results also indicate that hitherto inaccessible alignments of dipoles can be generated and that polymorphism in multiple component phases further adds to the structural diversity of such compounds. Although all structures presented involved hydrogen bond donors (amines, carboxylic acids, etc), the crystal structure was not uniform from co-crystal to co-crystal. Geometry, sterics, solvent systems, and synthons in the additives accounted for many differences when compared to the pure crystal structures of the pure crown ethers. It is important to point out that not all available hydrogen atoms were involved, in the hydrogen bonding. There are distance ranges (obtained from statistical data) that must be taken into account. These supramolecular complexes show how ether linkages in pharmaceutical drugs can be exploited via crystal engineering. This has increased the potential to control solid-state structures, changing their physical properties and leading to improved solubility and bioavailability.

Chapter 5

Trimesic Acid

5.1 Porous Materials

Trimesic acid (benzene-1,3,5-tricarboxylic acid, TMA) predictably generates honeycomb networks with interesting supramolecular properties because of its molecular symmetry and complementary hydrogen-bonding capabilities.[26]

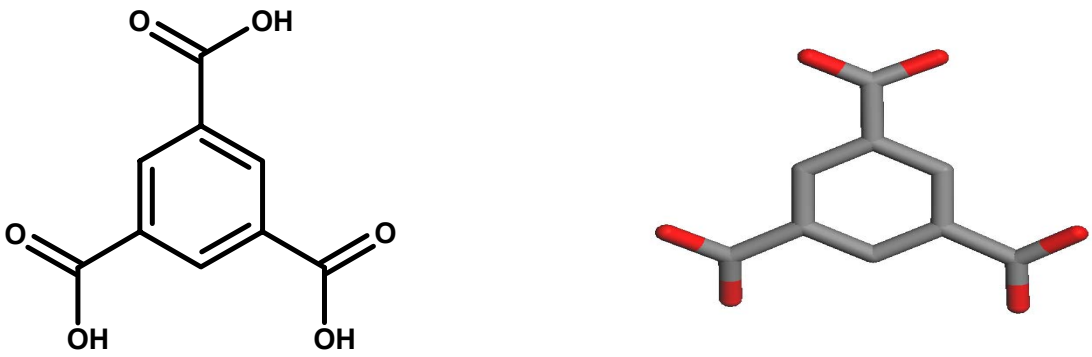


Figure 31. Trimesic acid stick models. The hydrogens have been omitted for clarity.

Hydrogen-bonded supramolecular synthons represent a primary tool for crystal engineering.[27] The rational design of host lattices using the principles of crystal engineering[9,28,29] and self-assembly through supramolecular synthons has increased in the last few years. Of particular interest are the efforts to create new clathrates or nanoporous materials, in which the target network is porous, contrary to Kitaigorodski's principle of close crystal packing.[30] Open framework structures of Trimesic acid can be designed via crystal engineering to build porous hydrogen bonded honeycomb networks.

The directional motif formed by the acid···acid dimer (Figure 1), along with the symmetric placement of acid groups around the benzene ring, derives the desired honeycomb framework with 14Å pores or cavities.[31] These pores encapsulate aromatic guests.

Figure 32. Acid…Acid Dimer motif representing a hydrogen-bonded supramolecular homosynthon.

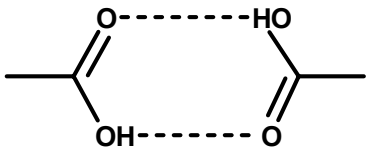


Table 9. Table shows the results of a CSD analysis of 1116 entries with the COOH···COOH synthons.

Average	Range	σ
2.657Å	2.554-3.196Å	0.06443

Porous materials are crystalline or amorphous solids that permit the inclusion of small molecules through holes in their structures. Structural chemists and materials scientists have been interested in building these frameworks not only to understand their design principles, but also because of their diverse commercial applications such as chemical separation, asymmetric synthesis, catalysis, storage, etc. Interpenetration of the host lattice is undesirable for porous networks because it fills space and usually produces global structural changes.[29]

Very few organic hydrogen bonded networks have been analyzed to date. A survey of the Cambridge Structural Database[14] (CSD) showed the crystal structure of tetrakis(4-ethynylphenyl)methane as the first example of a diamondoid packing motif generated by weak hydrogen bonding. A three-dimensional network is formed by hydrogen bonds

between the alkynyl groups of four separate molecules, which meet to form the nodes of the network. This network is absent of any guest molecules.[32]

Another example of an aromatic hydrogen bonded network is the orthogonal anthracene-bis(resorcinol) tetraol, a host structure that builds an extensive hydrogen-bonded network resulting in a molecular sheet. This sheet contains large supramolecular cavities, which incorporate two molecules of solvent guest.[33] The crystal packing of this structure is comparable to the 3-connected honeycomb network coordination polymer, topologically equivalent to the 2-D brick wall.[34] This organic network is held together by H-bonds between the OH groups of the host molecules creating cavities. Each supramolecular cavity can bind a guest molecule (i.e. benzophenone) via hydrogen bonded OH groups of the host and the carbonyl group of the guest.[32]

5.2 TMA Polymorphic Forms

Trimesic acid has been identified in four polymorphic forms, α[35],β[36],γ[36] and δ[37] (Figure 2). All of these polymorphs contain the carboxylic acid homosynthon, which generates the expected honeycomb network with an approximate 14Å diameter void. The α-form was developed by a solvent free host with non-planar two-dimensional interpenetrated networks with large rings created by six molecules of Trimesic acid.[11] The β-form is enantiotropically transformed from heating the α-form at high temperature (~543K).[12] Since the β-form is a polycrystalline phase, no known crystal structure exists for the β polymorph.[12] The γ-form is the flat triple catenated honeycomb network with inclusion of small guest molecules and it is less closely packed than the α-form.[12] The δ-

form possesses large channels which do not interpenetrate, but rather include guest molecules of bigger size.[13]

1) 2) 3)

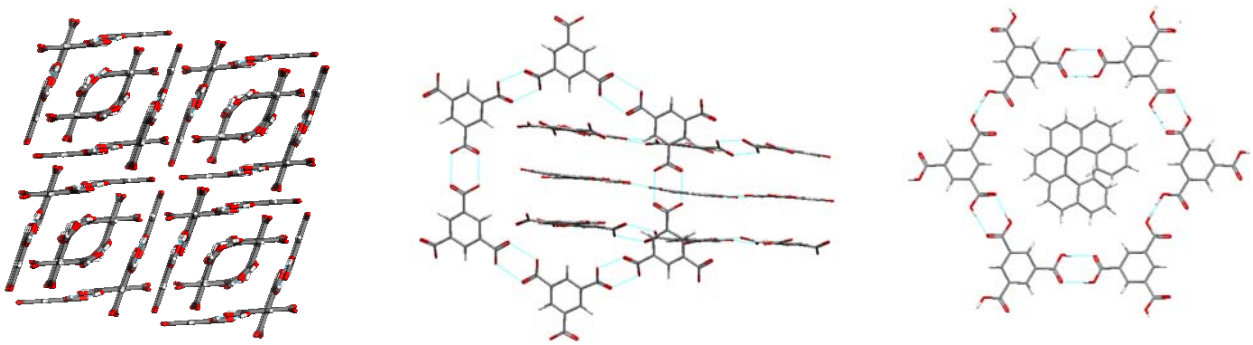


Figure 33. Schematic representations of TMA forms: 1) α-form; non-planar interpenetrated honeycombs, 2)γ-form; planar triply interpenetrated honeycombs, and 3) δ-form; non-interpenetrated honeycombs. There is no known form of the β-form at room temperature.

5.3 Strategy

Attempts to prepare the pure trimesic acid honeycomb network (with COOH dimer distances ranging from 2.609-2.657 Å) phase by breaking the interpenetration was carried out with different guest molecules, such as toluene, naphthalene, anthracene, acetic acid and biphenyl. During this study, a new TMA honeycomb network truncated by acetic acid molecules was observed. Additionally, this new form of TMA, ε-form, was observed when toluene and naphthalene are the aromatic guests held in the TMA honeycomb network cavities. Having studied each of these phases structurally, we then studied the thermal stability of these crystals by Thermal Gravimetric Analysis (TGA) experiments since the honeycomb network remained in single crystal form even after guest removal.

Table 10. Trimesic Acid Supramolecular Complexes

Trimesic Acid/Biphenyl	**A**
Trimesic acid/Anthracene	**B**
Trimesic acid/Acetic acid	**C**
Trimesic acid/Naphthalene	**D**
Trimesic acid/Toluene	**E**

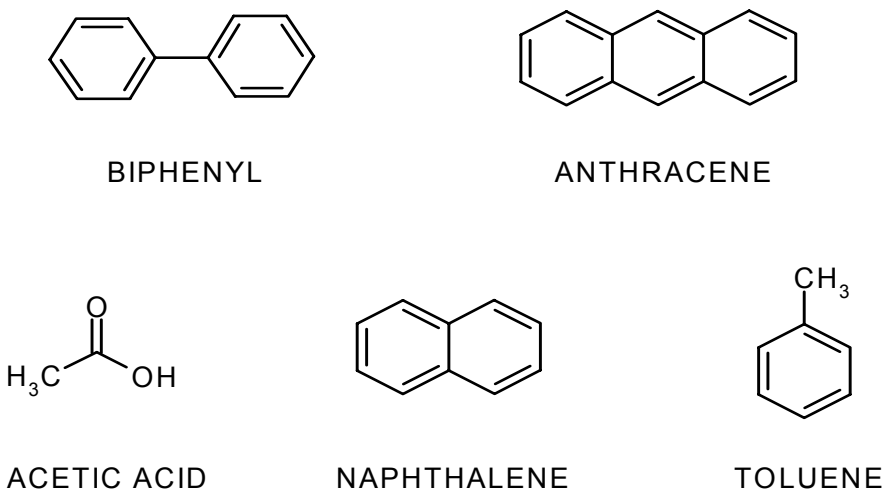


Figure 34. Structures of the co-crystal formers used in the supramolecular complexes with TMA.

5.4 Structures

5.4.1 Trimesic acid/biphenyl (A)

Laboratory results similar to the TMA δ-form include the TMA honeycomb networks with biphenyl and anthracene as the aromatic guests occupying the cavities. Crystals of TMA/biphenyl **A** were grown from CS_2/AcOH/Ethanol (EtOH); crystallized in the monoclinic $P2_1$ noncentric space group and the asymmetric unit cell consists of four trimesic acid molecules and three biphenyl molecules. The TMA/biphenyl structure differs from other TMA honeycomb networks because it does not include any solvent

molecules. The honeycomb is held together by carboxylic acid dimers ranging in distance from 2.605 to 2.627 Å, falling within the acceptable range reported in Figure 1.

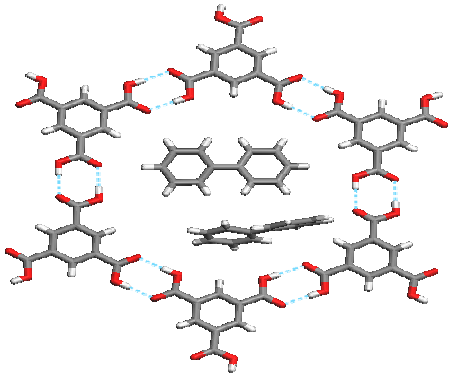


Figure 35. TMA honeycomb network with biphenyl guests in the cavity.

5.4.2 Trimesic acid/anthracene (B)

Upon crystallization of TMA/anthracene **B** from CS_2/AcOH/EtOH solvent system, crystals were obtained in the 2:1:1 ratio of TMA/anthracene/AcOH in the monoclinic $P2_1/c$ space group. The structure is not interpenetrated and each honeycomb framework (TMA dimer distance of 2.590-2.614 Å) encloses one anthracene molecule by creating C-H···O (anthracene···TMA) interactions and an acetic acid dimer orthogonal to it (acetic acid dimer distance of 2.643 Å). Again, the C-H···O hydrogen bond is due to guest inclusion rather than the stabilization of the guest by the C-H···O hydrogen bonds.

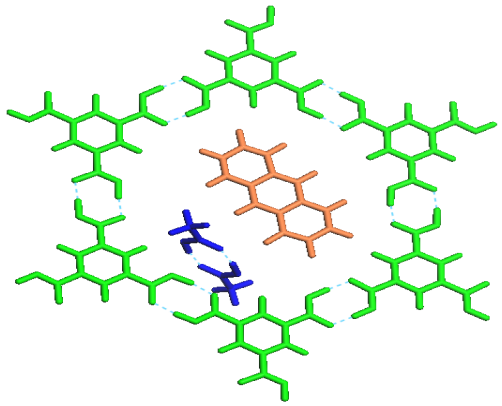


Figure 36. TMA honeycomb with anthracene and acetic acid dimer guests in the cavity.

5.4.3 Trimesic acid/acetic acid (C)

Crystals of TMA/acetic acid (AcOH) **C** were obtained when trimesic acid was crystallized from CS_2/AcOH/EtOH. It crystallizes in the Pī space group with six molecules of trimesic acid and three molecules of acetic acid in the asymmetric unit. Of the three acetic acid molecules, two produce the acetic acid dimer (Dimer distance of 2.647Å) and the third one is used in constructing the truncated TMA honeycomb network (dimer distance of 2.717 Å). Analysis of the packing of TMA/AcOH reveals that they are closely related to the γ-form, but differ by the incorporation of the acetic acid in the network. The acetic acid forms the truncated honeycomb by terminating the normal two-dimensional honeycomb framework. It is unclear why the dimer between the acetic acid (strong acid) – trimesic acid (weak acid) COOH···COOH synthon is formed. It may be rationalized that in order to include the guest, the void space must be created by terminating the two-dimensional honeycomb framework with acetic acids.

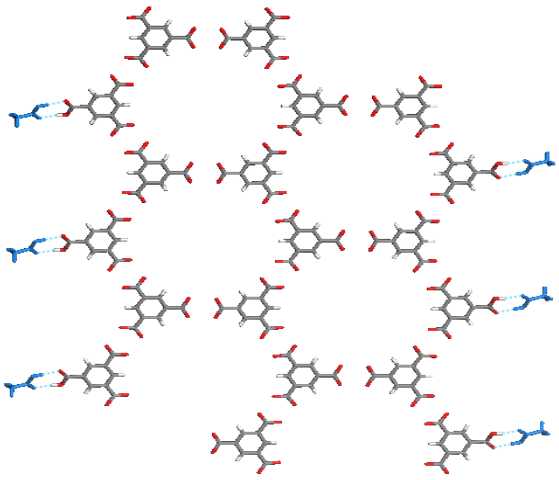


Figure 37. Truncated acetic acid TMA honeycomb network.

Results showing the new TMA polymorph with acetic acid truncated honeycomb networks, ε-form, were obtained with naphthalene and toluene as the guest molecules (Figure 6 and 7).

5.4.4 Trimesic acid/Naphthalene (D)

Crystallization from CS_2/AcOH/EtOH resulted in a 6:1:1 ratio of TMA/naphthalene/acetic acid. Due to the smaller size of the guest, the framework is triply interpenetrated (as in TMA polymorphic forms α and γ) but differs from these forms because the acetic acid instead of creating dimers with itself, generates the acid···acid (distance of 2.624-2.704 Å) dimer with trimesic acid, truncating the TMA honeycomb network. Trimesic acid forms an infinite two-dimensional honeycomb network (TMA dimer distance of 2.582-2.623 Å), which interpenetrates with three truncated honeycomb networks. The naphthalene guest molecules are disordered, occupying the void created between the interpenetration rather than fitting into the honeycomb framework.

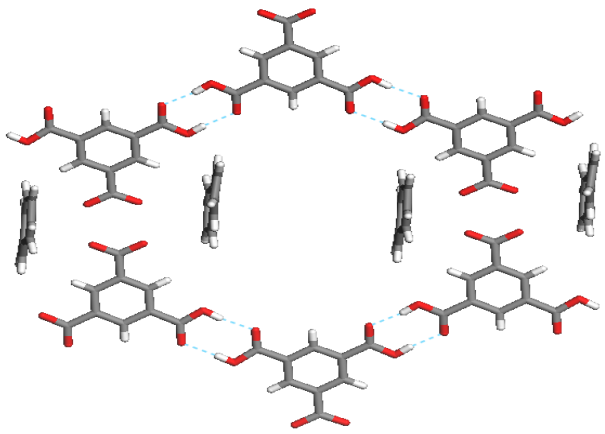


Figure 38. TMA honeycomb networks with acetic acid truncated networks with naphthalene.

5.4.5 **Trimesic acid/Toluene (E)**

Crystallization from CS2/AcOH/EtOH resulted in a 6:1:1 ratio of TMA/toluene/acetic acid. Due to the smaller size of toluene, the framework is triply interpenetrated (as in TMA polymorphic forms α and γ) but differs from these forms because the acetic acid instead of creating dimers with itself, generates the acid···acid (as in **D**) (TMA dimer distance of 2.605-2.632 Å, TMA-Acetic acid dimer distance of 2.6209-2.710 Å).

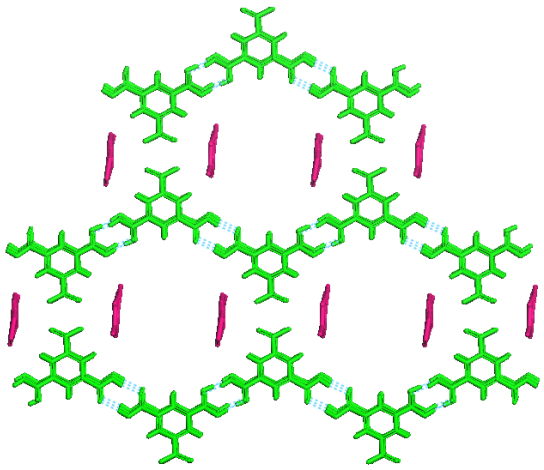


Figure 39. TMA honeycomb networks with acetic acid truncated networks with toluene guests.

5.5 **Synthesis and Results**

5.5.1 Trimesic Acid/biphenyl (A)

Synthesis: In a typical reaction, 58 mg ($2.76x10^{-4}$ mol) of TMA and 47 mg ($3.05x10^{-4}$ mol) of biphenyl were layered in 6 mL ethanol and 6 mL CS_2, respectively. A 4 mL layer of acetic acid separated the two layers. Slow evaporation and in approximately two weeks crystals appeared.

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

Crystal Packing: TMA honeycomb networks with biphenyl as the aromatic guests occupying the cavities. The honeycomb is held together by carboxylic acid dimers ranging in distance from 2.605 to 2.627Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Not much changes from pure TMA since the honeycomb network remained the same. The peaks did shift slightly downfield. 3127 cm^{-1} (-OH stretch), 1691 cm^{-1} (C=O stretch), 1261 cm^{-1} (C-O stretch).

Melt-temp: 362-370ºC

X-ray powder diffraction: in 2θ, simulated derived from the single the single crystal data; experimental (simulated): 9.296(9.297), 12.240(12.112), 16.081(16.374), 17.243(17.480), 22.206(22.330), 26.721(26.769), 33.499(33.370).

5.5.2 Trimesic Acid/anthracene (B)

Synthesis: In a typical reaction, 20 mg ($9.51x10^{-4}$ mol) of TMA and 17 mg ($9.54x10^{-5}$ mol) of anthracene were layered in 1 mL ethanol and 1 mL CS_2, respectively. A 1 mL layer of acetic acid separated the two layers. Slow evaporation and in approximately two to three weeks crystals appeared.

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

Crystal packing: Crystallization of TMA with anthracene resulted in a structure that is not interpenetrated and each honeycomb framework (TMA dimer distance of 2.590-2.614 Å) encloses one anthracene molecule by creating C-H…O (anthracene…TMA) interactions and an acetic acid dimer orthogonal to it (acetic acid dimer distance of 2.643 Å).

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Not much changes from pure TMA since the honeycomb network remained the same. The peaks did shift slightly downfield. 3209 cm^{-1} (-OH stretch), 1698 cm^{-1} (C=O stretch), 1276 cm^{-1} (C-O stretch).

Melt-temp: started melting 278ºC, decomposed before melting completely.

X-ray powder diffraction: in 2θ, simulated derived from the single the single crystal data; experimental (simulated): 11.035(11.056), 12.526(12.480), 13.010(13.070), 14.198(14.121), 17.324(17.153), 22.979(22.905), 23.080(23.035), 25.119(25.111), 26.300(26.314), 27.121(27.188), 30.011(30.002).

5.5.3 **Trimesic Acid/acetic Acid (C)**

Synthesis: In a typical reaction, 24 mg ($1.14x10^{-4}$ mol) of TMA was dissolved in 1 mL of ethanol. Separately, 4 drops of benzene were dissolved in 1 mL of CS_2. The two layers were put in a reaction vial with a 1 mL layer of acetic acid between then to slow down diffusion. Slow evaporation and in approximately two weeks crystals appeared. The benzene served only as a template and did not appear in the crystal structure.

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

Crystal Packing: Crystallization of TMA and acetic acid results in a 1:1 supramolecular complex that is sustained by carboxylic acid H-bonds. The acetic acid forms the truncated honeycomb by terminating the normal two-dimensional honeycomb framework. Distances range between 2.647-2.717 Å.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Not much changes from pure TMA since the honeycomb network remained the same. The peaks did shift slightly downfield. 3117 cm^{-1} (-OH stretch), 1684 cm^{-1} (C=O stretch), 1397 and 1275 cm^{-1} (C-O stretch).

Melt-temp: 363-364ºC

X-ray powder diffraction: in 2θ, simulated derived from the single the single crystal data; experimental (simulated): 12.887(12.906), 19.962(19.669), 20.037(20.039), 22.463(22.461), 24.442(368), 26.841(26.974), 29.183(29.173), 30.319(30.333), 30.880(30.879), 33.475(33.478), 35.127(35.127), 36.158 (36.154), 37.638(37.674), 39.562(39.561).

5.5.4 **Trimesic Acid/naphthalene (D)**

Synthesis: In a typical reaction, 21 mg ($9.99x10^{-5}$ mol) of TMA and 11 mg ($8.58x10^{-5}$ mol) of naphthalene were dissolved separately in 1 mL ethanol and 1 mL CS_2, respectively. A 1 mL layer of acetic acid separated the two layers. Slow evaporation and in approximately two weeks crystals appeared.

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

Crystal Packing: Crystallization from CS2/AcOH/EtOH resulted in a 6:1:1 ratio of TMA/naphthalene/acetic acid. Due to the smaller size of the guest, the framework is triply interpenetrated (as in TMA polymorphic forms α and γ), but differs from these forms because acetic acid instead of creating dimers with itself, generates the acid···acid

dimer (distance of 2.624-2.704Å) with TMA, truncating the TMA honeycomb network.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Not much changes from pure TMA since the honeycomb network remained the same. The peaks did shift slightly downfield. 3138 cm^{-1} (-OH stretch), 1684 cm^{-1} (C=O stretch), 1268 cm^{-1} (C-O stretch).

Melt-temp: 360-363ºC

X-ray powder diffraction: in 2θ, simulated derived from the single the single crystal data; experimental (simulated): 11.858(11.473), 12.701(12.742), 16.457(16.469), 22.960(22.900), 24.459(24.550), 26.658(26.656), 27.824(27.806), 30.897(30.877), 35.265(35.260).

5.5.5 **Trimesic Acid/toluene (E)**

Synthesis: In a typical reaction, 25 mg ($1.19x10^{-4}$ mol) of TMA was dissolved separately in 1 mL ethanol and ~5 drops of toluene was dissolved in 1 mL CS_2, respectively. A 1 mL layer of acetic acid separated the two layers. Slow evaporation and in approximately two days crystals appeared.

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

Crystal Packing: Crystallization from CS_2/AcOH/EtOH resulted in a 6:1:1 ratio of TMA/toluene/acetic acid. Due to the smaller size of the guest, the framework is triply interpenetrated, but differs from these forms because acetic acid instead of creating dimers with itself, generates the acid···acid dimer (distance of 2.6209-2.710Å) with TMA, truncating the TMA honeycomb network.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Not much changes from pure TMA since the honeycomb network remained the same. The peaks did shift slightly downfield. 3127 cm^{-1} (-OH stretch), 1695 cm^{-1} (C=O stretch), 1397 and 1265 cm^{-1} (C-O stretch).

Melt-temp: 366-367ºC

X-ray powder diffraction: in 2θ, simulated derived from the single the single crystal data; experimental (simulated): 16.344(16.345), 20.080(20.205), 22.335(22.283), 24.522(24.567), 25.487(25.508), 27.001(27.017), 28.061(28.055), 29.301(29.351), 30.582(30.503), 30.841(30.822), 33.028(33.036), 36.099(36.096), 37.703(37.700), 39.079(39.062).

5.6 **Discussion**

Is it really possible to maintain the crystallinity and pores present in the TMA honeycomb networks even in the absence of guests? Thermal Gravimetric Analysis (TGA) experiments carried out with the ε-form crystal of TMA/toluene and the single crystal were performed. TGA measures the weight change in materials as a function of time and temperature. The measurement provides basic information about the thermal stability of a chemical and its composition (change in mass of a sample vs. temperature).[38,39] The samples were heated to 180°C to ensure the removal of all guest molecules (a weight % loss of ~12% was evident in both TGA spectra). Single crystal X-ray data revealed that cell parameters before TGA and after guest removal by TGA remained the same, confirming retention of crystallinity and the hydrogen-bonded network.

Table 11. TMA/toluene crystal data before and after TGA analysis.

	Before TGA	**After TGA**
a (Å)	15.4991	15.2245
b (Å)	16.2684	16.345
c (Å)	16.4957	16.54
α(°)	119.309	119.556
β(°)	90.907	90.477
γ (°)	117.171	116.276
Volume (Å^3)	N/A	3072.9
Space grp	P-1	P-1

The large open honeycomb network of TMA is built by strong, yet, flexible supramolecular synthons (acid···acid) and by accommodating aromatic guests in the cavities. These guest molecules inhibit the honeycomb networks from interpenetrating and assembling into a close packed conformation. Removal of the guest can be accomplished while retaining the hydrogen bonded aromatic framework.

Chapter 6

Conclusion

The concept of crystal engineering was first coined by Schmidt in the context of covalent synthesis in the solid state, i.e. topochemical reactions.[2] However, recent development of this subject has expanded it into areas as diverse as supramolecular synthesis,[3,4,9,40] crystal structure analysis and prediction[41-45] and functional materials.[46-48] As previously stated, the concept of crystal engineering was originally introduced in the context of stereochemical control of photochemical reactions,[2] but it has subsequently been shown to have wider implications for materials science. In the context of pharmaceuticals, there are important process and intellectual property implications related to control and reproducibility of composition and polymorphism.[12,49] This work focused upon how previously known supramolecular synthons could be exploited to rationally generate binary crystals with "engineered" compositions. The study chose pharmaceutical molecules as the target system since they contain a wide range of synthons and understanding of the crystal structure – physical property relationship is essential for the continued application of these essential chemicals toward improving the overall health of society.

Hydrogen bonded supramolecular synthons represent a prototypal tool for crystal engineering[9] and can be categorized as follows: 1) self-complementary synthons, in

which a single molecule self-assembles to form a "homosupramolecular synthon" (*e.g.* carboxylic acid dimer) or 2) two or more complementary components, thereby creating a multiple component or "heterosupramolecular synthon" (*e.g.* the hetero-dimer formed by pyridines and carboxylic acids).

Supramolecular synthetic approaches offer a number of attractive features: the ability to exploit readily available molecules or ions in novel ways; their inherent modularity affords compositional and structural diversity; the use of non-covalent interactions makes for facile synthesis. In short, supramolecular synthesis offers a combinatorial type of approach to synthesis of new structures and can afford a wide range of structural diversity without the need to break and form covalent bonds. The phenomenon of polymorphism in crystal engineering cannot be ignored. Polymorphism is defined as the phenomenon where the same chemical substance exists in different crystalline forms or different crystalline patterns.[11] This phenomenon is more common among molecules with flexible conformations capable of hydrogen bonding.[6] Supramolecular synthons are the structural units within molecules, which can be formed and/or assembled by synthetic operations[6]. The supramolecular synthons present in polymorphic forms may be intact from form to form, therefore it can be stated that the supramolecular equivalents of structural isomers are crystalline polymorphs.[6] The criteria for assessing the existence of polymorphs are different unit cell parameters, crystal packing arrangements and physical properties.[11]

Rationally generating organic binary crystals that contain pharmaceutical components by exploiting supramolecular chemistry concepts should further the development of other novel pharmaceutical phases. Indeed, the creation of model binary crystals provides

supramolecular insight that could lead to structures that have a pharmaceutical advantage[50] over the pure phase pharmaceuticals. The necessary information to create and develop binary crystals should be stored already in the known pharmaceutical molecule. It should be intuitive that modular structures, *e.g.* binary crystals based upon more than one component, are often more diverse and controllable than single component phases. It is now evident that supramolecular chemistry, defined as chemistry beyond the molecule,[4] and "supramolecular assemblies" are inherently linked to the concepts of crystal engineering.

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Appendices

Appendix A: Crystallographic Data for Nifedipine Structures

	A	B	C
Formula	$C_{18}H_{21}N_3O_7$	$C_{92}H_{96}N_{12}O_{28}$	$C_{27}H_{26}N_4O_6$
m.p. (°C)	136-138	148-153	137-139
Mol. Wt.	391.38	1817.81	502.52
Crystal System	Triclinic	Monoclinic	Triclinic
Space Group	P-1	P2(1)n	P-1
a (Å)	7.8268(11)	7.9310(14)	7.6332(7)
b (Å)	10.667(15)	12.4945(22)	9.8375(9)
c (Å)	11.8401(16)	22.2611(37)	16.6567(15)
α (°)	70.065(3)	90	101.689(2)
β (°)	76.766(3)	90.198(8)	93.132(2)
γ (°)	80.56(3)	90	95.396(2)
Volume (Å^3)	900.7(2)	2205.93(4)	1215.92(19)
calc density (mg/cm^3)	1.443	1.373	1.373
Solvent	Formamide	Methanol	Methanol

Appendix B: Crystallographic data for Phenytoin Structures

	A	B	C
Formula	$C_{80}H_{22}N_4O_2$	$C_{80}H_{64}N_{12}O_8$	$C_{27}H_{22}N_4O_2$
m.p. (℃)	234-239	225-227	254-257
Mol. Wt.	347.37	440.48	434.49
Crystal System	Monoclinic	Monoclinic	Triclinic
Space Group	P21/c	P21/c	P-1
a (Å)	16.6583(19)	8.0106(10)	8.620(14)
b (Å)	8.8478(10)	26.2398(33)	9.929(14)
c (Å)	11.9546(14)	7.981(10)	13.29(2)
α (°)	90	90	87.47(4)
β (°)	96.618(2)	91.069(2)	84.03(3)
γ (°)	90	90	86.13(3)
Volume ($Å^3$)	1750.2(3)	1677.4(4)	1128(3)
calc density (mg/cm^3)	1.318	1.308	1.28
Solvent	Ethanol/acetone	2,4-pentanedione	2,4-pentanedione

Appendix C: Crystallographic Data for Crown Ether Structures

	A	B	C	D	E	F	G	H
Formula	$C_{58}H_{66}N_6O_{18}$	$C_{27}H_{30}N_2O_7$	$C_{26}H_{30}N_2O_7$	$C_{26}H_{30}N_2O_7$	$C_{51}H_{87}N_{18}O_{18}$	$C_{16}H_{32}N_8O_6$	$C_{60}H_{60}N_2O_{20}$	$C_{78}H_{132}O_{39}F_{16}$
m.p. (°C)	120-122	137-139	N/A	158-160	284-286	194-198	276-280	1997.84
Mol. Wt.	1135.17	512.55	482.52	482.52	1240.206	432.5	1129.14	1997.84
Crystal System	Orthorhombic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space Group	Fdd2	$P2_1/n$	$P2_1/c$	$P2_12_12_1$	$P2_1/c$	I2/a	C2	$P2_1/n$
a (Å)	42.769(3)	13.5993(14)	15.956(3)	8.4015(13)	7.9634(28)	15.452(2)	7.6625(48)	8.8849(28)
b (Å)	52.193(3)	9.3950(10)	9.8132(16)	13.650(2)	13.8565(51)	8.1949(10)	16.929(99)	20.584(71)
c (Å)	11.1128(7)	20.885(2)	17.266(3)	20.705(3)	12.6933(40)	18.215(3)	11.713(73)	14.102(42)
β (°)	90	103.445(2)	111.615(3)	90	94.661(12)	99.445(2)	90	105.952(8)
Volume ($Å^3$)	24806(3)	2595.2(5)	2513.3(7)	2374.5(7)	1396.008	2275.2(6)	1579.4(16)	2479.67(4)
calc density ng/cm^3)	1.216	1.312	1.275	1.35	1.475	1.263	1.317	1.338
Solvent	Benzene	Benzene	THF	THF	Ethanol	Ether/ Methanol	Toluene/ THF	Methanol

Appendix D: Crystallographic Data for Trimesic Acid Structures.

	A	B	C	D	E
Formula	$C_{72}H_{54}O_{24}$	$C_{34}H_{24}O_{24}$	$C_{120}H96O8_4$	$C_{133}H_{98}O_{42}$	$C_{126}H_{112}O4_8$
m.p. (°C)	362-370	decomposed	363-364	360-363	366-367
Mol. Wt.	186.16	656.53	2881.97	2368.11	2418.18
Crystal System	Monoclinic	Monoclinic	Triclinic	Triclinic	Triclinic
Space Group	P21	P-1	P-1	P-1	P-1
a (Å)	9.9791(10)	10.4027(8)	15.4543(14)	15.4148(21)	15.4991(34)
b (Å)	28.424(3)	28.560(2)	16.3494(15)	16.3203(22)	16.2684(35)
c (Å)	11.0164(11)	10.4430(8)	16.5130(14)	16.3669(23)	16.4957(36)
α (°)	90	90	119.409(2)	119.516(2)	119.309(6)
β (°)	104.243(3)	105.226(2)	90.449(2)	90.349(3)	90.907(9)
γ (°)	90	90	117.481(1)	117.499(2)	119.171(5)
Volume (Å^3)	3028.7(5)	2993.7(4)	3072.21(2)	3029.29(7)	3069.21(5)
calc density (mg/cm^3)	1.429	1.312	1.558	1.298	1.308
Solvent	CS_2/AcOH/EtOH	CS_2/AcOH/EtOH	CS_2/AcOH/EtOH	CS_2/AcOH/EtOH	CS_2/AcOH/EtOH