A STUDY OF DESIGN AND NON-COVALENT SYNTHESIS OF SUPRAMOLECULAR ASSEMBLIES

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by

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Dedicated to my

BELOVED PARENTS

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CERTIFICATE

This is to certify that the work presented in the thesis entitled **"A STUDY OF DESIGN AND NON-COVALENT SYNTHESIS OF SUPRAMOLECULAR ASSEMBLIES"** submitted by **Kapildev K. Arora**, was carried out by the candidate at National Chemical Laboratory, Pune, under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

December 2006 **Dr. V. R. Pedireddi, FRSC**

Pune *(Research Guide)*

NATIONAL CHEMICAL LABORATORY

DECLARATION

I here by declare that the thesis entitled **"A STUDY OF DESIGN AND NON-COVALENT SYNTHESIS OF SUPRAMOLECULAR ASSEMBLIES"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

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ABSTRACT

This abstract of the thesis entitled, **"A STUDY OF DESIGN AND NON-COVALENT SYNTHESIS OF SUPRAMOLECULAR ASSEMBLIES",** consists of four chapters. Chapter 1 with illustrative examples gives an introduction of the contemporary research areas in the solid-state chemistry such as supramolecular chemistry, crystal engineering, host-guest complexes, pharmaceutical co-crystallizations, etc. A rational study of the host-guest complexes formed by tetra and tri-substituted carboxylic acids employing various aza-donor molecules are described in Chapter 2, while host-guest complexes of 3,5-dinitrobenzonitrile with various hydrocarbons as well as aza-donor molecules utilizing the weak hydrogen bonds such as C-H···N, C-H···O, etc., are described in Chapter 3. Finally, in Chapter 4, co-crystallization of bioactive compounds with nucleobases is illustrated through salicylic acid and adenine to demonstrate the application of supramolecular synthesis in pharmaceutics.

CHAPTER ONE

Noncovalent synthesis or supramolecular synthesis[1] is a novel synthetic approach that deals with the creation of supermolecules and subsequently network structures using hydrogen bonding[2] and other noncovalent interactions. Supramolecular chemistry has grown around Lehn's analogy that "*supermolecules are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond*".

One of the important aims of noncovalent synthesis is to establish the relationship between the molecular and supramolecular chemistry using intermolecular interactions. Thus, prediction, rationalization, and analysis are the key components in the supramolecular chemistry. Design and prediction are often being initiated with the analysis of structural data archived in the Cambridge Structural Database[3] (CSD) and also through computational methods, leading towards the synthesis of functional solids with specific tailor-made properties such as catalysis, optical, conducting and magnetic materials, nanotechnology, electronic materials and sensors, protein-receptor binding, nano and microporous materials, supramolecular devices, molecular modeling and drug design. In this regard, host-guest complexes[4-5] gained popularity in recent times especially employing organic substrates that possess cavities and channels. Host-guest complexes are a class of molecular complexes in which a macromolecule or a group of molecules encompass other molecules.

Also, in the recent years the concepts of supramolecular synthesis are well extended to pharmaceutics by creating co-crystals of bioactive entities.[6] This concept has attracted enormous interest in academia and pharmaceutical industry as the strategy directs innovations of challenging novel routes for the synthesis of co-crystals and also affords new intellectual rights and the enhanced properties for the active pharmaceutical ingredients (API's).

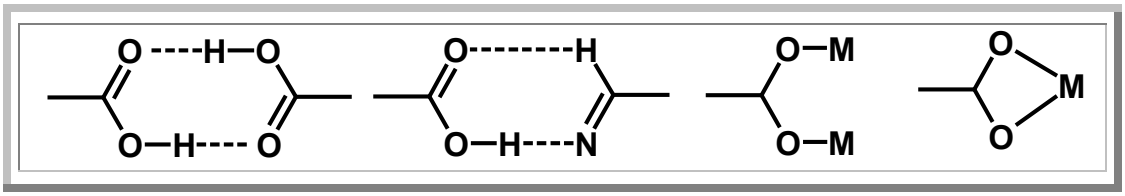
A detailed account of these salient areas of supramolecular chemistry is presented in chapter 1.

CHAPTER TWO

In chapter 2, the rational study of supramolecular assemblies of some polycarboxylic acids are compiled into two sections describing the host-guest arrangements obtained in the complexes with aza-donor moieties.

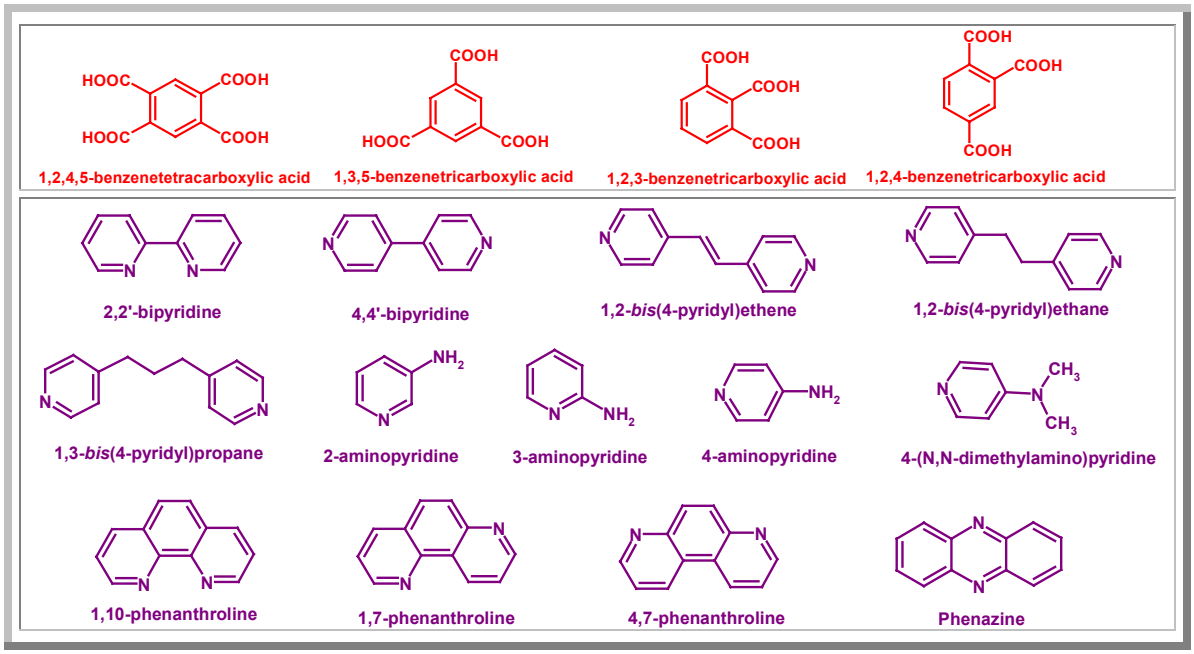
The design of nanoporous solids with controlled sizes and shapes and chemical environments using the concepts of supramolecular chemistry through noncovalent synthesis has generated enormous interest in recent years. Supramolecular synthesis of organic ensembles employing two or more components is a two-step process, formation of a supermolecule between the constituents followed by self-assembly or packing of the supermolecules in the three-dimensional space. However, in all these cases, invariably, evolution of an assembly depends on the properties of the functional group under consideration. In this respect, carboxylic acid group (-COOH) is the best among the several hydrogen-bonded functionalities investigated in the contemporary supramolecular chemistry.

Carboxylic acids are well-known to form robust cyclic dimer and open catemer motifs and also with several aza-donor compounds forming either O-H$^{\cdots}$N or O-H$^{\cdots}$N/C-H$^{\cdots}$O pairwise hydrogen bonds, as well as dative bonds through the carboxylate group.[7] A schematic representation of some of these networks is shown in Scheme 1.



Scheme 1

In the present study, the synthesis of molecular complexes of tetracarboxylic acid (1,2,4,5-benzenetetracarboxylic acid) and tricarboxylic acid (1,3,5-, 1,2,3- and 1,2,4-benzenetricarboxylic acid) with various aza derivatives are reported (see Scheme 2). All the complexes gave novel supramolecular assemblies utilizing the directional features of the hydrogen bonds formed by –COOH group present at different positions on the aromatic moieties.



Scheme 2

Part A: Host-guest complexes of a benzenetetracarboxylic acid

Co-crystallization of 1,2,4,5-benzenetetracarboxylic acid with various aza-donor compounds such as 1,10-phenanthroline, 1,7-phenanthroline, 4,7-phenanthroline, phenazine, 4-(N,N-dimethylamino)pyridine, 1,2-bis(4-pyridyl)ethene, 1,2-bis(4-pyridyl)ethane, yielded good quality single crystals of molecular complexes, from either methanol or dimethyl sulfoxide (DMSO), as the case may be.

The assemblies formed are divided into two classes, host-guest systems (with aza-donor molecules being in the channels created by the acid molecules) and assemblies with infinite molecular tapes (see Figure 1).

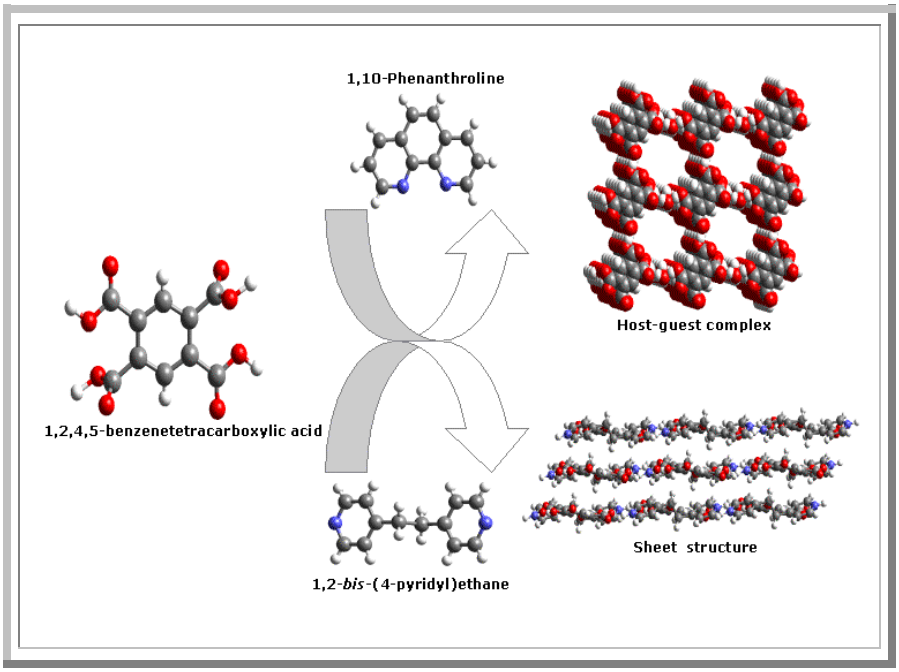


Figure 1

However, with 1,7-phenanthroline, forms two types of complexes, a hydrated and nonhydrated complex. In fact, this bridges the two classes of the complexes

(channels and tapes) with each one falling into different categories. In all the host-guest assemblies, water plays a crucial role by facilitating the formation of cavities in accordance with the dimension of the guest molecule.

Part B: Host-guest complexes of isomers of tricarboxylic acids

1,3,5-benzenetricarboxylic acid is well known for its exotic three-dimensional structure in the form of chicken-wire network[8a] and also known to form varied supramolecular architectures with appropriate receptors.[8b-e] Extending these observations to further develop novel supramolecular assemblies in the form of host-guest type complexes, co-crystallization of the acid with aza-donor compounds such as 4,4'-bipyridine, 4-aminopyridine and 1,7-phenanthroline have been proposed. The host-guest complex is shown in the Figure 2 as one of the representative examples.

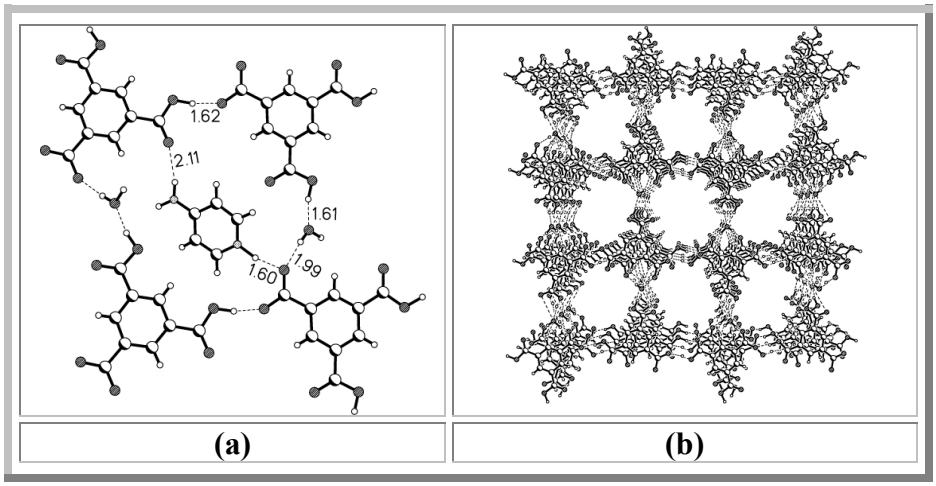


Figure 2: (a) Two-dimensional arrangement of complex formed between 1,3,5-benzenetricarboxylic acid and 4-aminopyridine, showing the cavity formed by acid molecules utilizing the water molecules and also occupied by 4-aminopyridine molecules. **(b)** Three-dimensional arrangement showing one-dimensional channels in the complex.

Similarly, co-crystallization studies of 1,2,3- and 1,2,4-tricarboxylic acids with various aza-donor molecules, as listed in scheme 2, gave molecular complexes with various supramolecular networks. All these assemblies form invariably two-dimensional sheet structures, but differ in the mode of stacking, resulting in the formation of either channels or sheet networks in three-dimensional arrangement. The host-guest complex formed between 1,2,3-benzenetricarboxylic acid and 2,2'-bipyridine is shown in Figure 3. A detailed discussion of the salient features of all other complexes is discussed in this chapter.

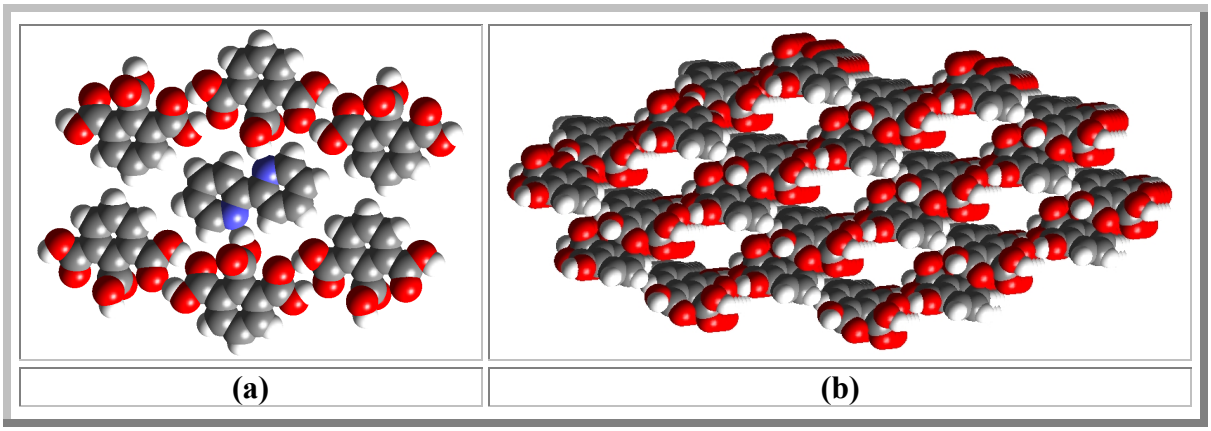
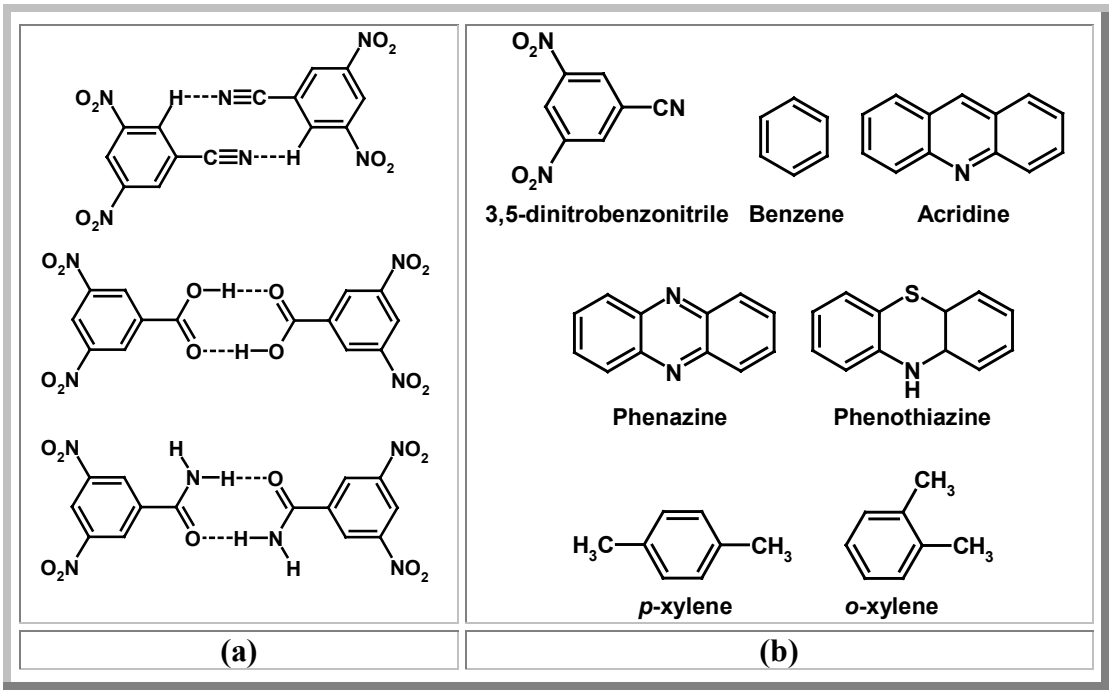


Figure 3: (a) Two-dimensional arrangement of 1,2,3-benzenetricarboxylic acid and 2,2'-bipyridine complex showing 2,2'-bipyridine molecule occupying the cavity formed by acid molecules. **(b)** Host-network formed by acid molecules to form one-dimensional channels in three-dimensions.

CHAPTER THREE

While, 1,2,4,5-benzenetetracarboxylic acid, 1,3,5-benzenetricarboxylic acid, 1,2,3-benzenetricarboxylic acid, etc. served as representative examples for a class of organic host structures accommodating aza-donor molecules as the guest species utilizing strong hydrogen bonds, 3,5-dinitrobenzonitrile,[9a] the crystal structure of which

was determined in our laboratory shows several intriguing features to utilize it in the supramolecular synthesis through weak hydrogen bonds as the topology of the hydrogen bond arrangement is identical with that of 3,5-dinitrobenzoic acid[9b] and 3,5-dinitrobenzamide[9a] as shown in Scheme 3(a). Hence, to evaluate the nitrile as a potential host to accommodate different types of guest species, it was co-crystallized with various substrates as shown in Scheme 3(b).



Scheme 3: (a) Hydrogen bonding arrangement between the adjacent molecules of (top) 3,5-dinitrobenzonitrile (middle) 3,5-dinitrobenzoic acid and (bottom) 3,5-dinitrobenzamide. **(b)** Molecular structure of 3,5-dinitrobenzonitrile and substrates.

In all these assemblies a hexagonal host network is formed by the benzonitrile through the formation of hydrogen bonds such as C-H···O and C-H···N except in the molecular complex with *p*-xylene (see Figure 4). In the molecular complex with *p*-xylene, however, a sheet structure is formed, such that in three-dimensional

arrangement *p*-xylene molecules are embedded between the layers of the nitrile. The structural features of all these host-guest complexes are discussed in detail in this section of the thesis.

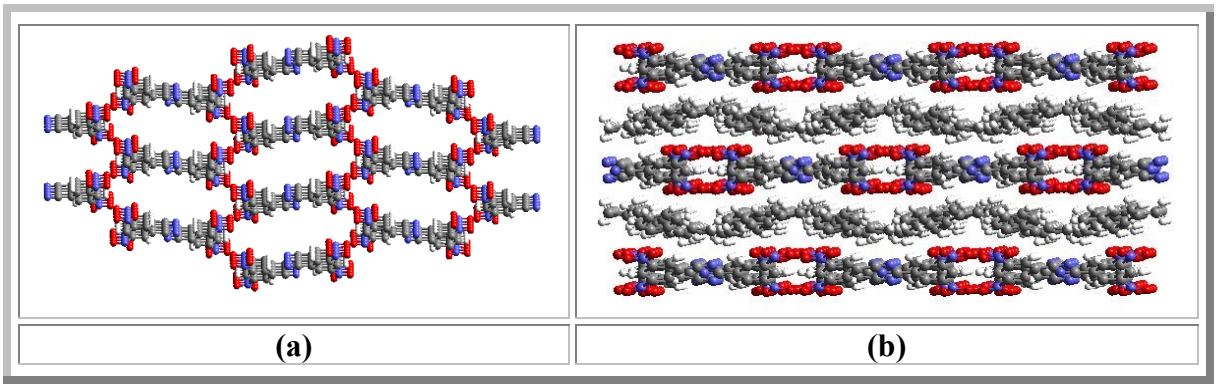


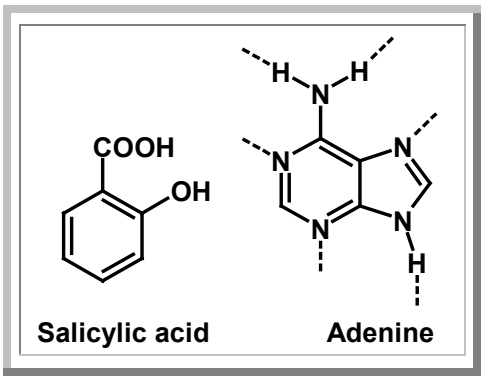
Figure 4: (a) Hexagonal host-network formed by 3,5-dinitrobenzonitrile. **(b)** Host-guest complex of 3,5-dinitrobenzonitrile with *p*-xylene.

CHAPTER FOUR

In the drug development process, devising methods for the delivery of the active pharmaceutical ingredients is one of the challenging tasks. Most API's are crystalline solids at room temperature and are commonly delivered as tablets.

Recent developments in the supramolecular synthesis through co-crystallization methods, employing different API's, found to be a novel and potential methodology to improve the formulations of pharmaceutics as explored by Zaworotko and others.[6]

Considering developments and the knowledge obtained through various co-crystallization experiments described in the previous chapters, co-crystallization of salicylic acid (**SA**), a potential pharmaceutical reagent, for its effective utilization as a drug have been carried out.



Scheme 4

For this purpose, as co-crystallizing agents, nucleobases have been considered, taking into account the recent findings of their selective molecular recognition with carboxylic acid moiety.[10] Thus, co-crystallization of **SA** and adenine in 3:1, 2:1 and 1:1 ratios from either methanol or water were carried out and the structural characteristics of these complexes are discussed in chapter 4.

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CHAPTER ONE

AN INTRODUCTION TO SUPRAMOLECULAR CHEMISTRY

"Supramolecular chemistry embodies the creative power of chemistry. By it's very essence, by its ability to create and through the beauty of its objects, chemistry is an art as well as a science. Indeed, it fashions entire new worlds that do not exist before they are shaped by the hand of the chemist, just as matter, shaped by the hand of the sculpture, becomes a work of art."

Jean-Marie Lehn 1995

1.1 INTRODUCTION

Molecules are collection of atoms that are connected by a continuous network of covalent bonds.[1] However, kinetically labile, noncovalent bonds such as hydrogen bonds, electrostatic and van der Waals forces, π – π stacking interactions, etc., play a significant role to establish interactions between/among the molecules. In biology, such interactions are responsible for the transduction of signals, the selective transport of ions and small molecules across membranes, expression and transfer of genetic information, enzymatic reactions, protein folding or the formation of larger aggregates, recognition between DNA base pairs, α-helix or β-sheets (see Figure 1.1).[2]

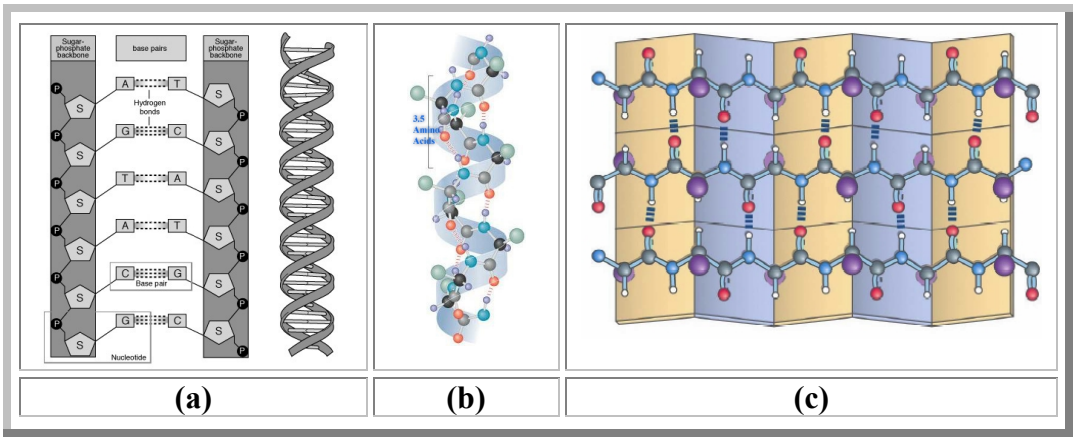


Figure 1.1: (a) Recognition between DNA base pairs. **(b)** A diagram of the α-helix structure of amino acids. **(c)** β-sheet.

However, in chemistry, such noncovalent interactions determine the physical properties of molecules, for example, the properties of liquids, the solubility of solids, or the organization of amphiphillic molecules in larger aggregates such as membranes, micelles and vesicles. In the late 1960s, Lehn,[3] Cram,[4] Pederson,[5] and others worked on the synthesis of macrocylic molecules, such as crown ethers, cryptands, spherands and

so on, that are able to selectively bind ions or small organic molecules *via* noncovalent interactions. Although the synthesis of these molecular receptors involves the formation of covalent bonds, the purpose of the synthesis was achieved as the molecular receptors were displaying the properties of specific recognition functions such as selective binding.

1.2 SUPRAMOLECULAR CHEMISTRY

Molecular associations have been recognized and studied for a long time and the term "Übermoleküle", i.e., supermolecules, was introduced in the mid 1930's to describe entities of higher organization resulting from the association of coordinatively saturated species.[6] However, in 1988, J. M. Lehn coined the term "*supramolecular chemistry*" or "*chemistry beyond the molecule*" for the field of molecular recognition.[3] It is the chemistry of the intermolecular bond, covering the structures and functions of the entities formed by association of two or more chemical species. Its development requires the use of all resources of molecular chemistry combined with the designed manipulation of noncovalent interactions so as to form supramolecular entities. Supramolecular chemistry concerns the investigation of nature's principles to produce fascinating complex and functional molecular assemblies, as well as the utilization of these principles to generate novel devices and materials, potentially useful for sensing, catalysis, transport and other applications in medicinal or engineering science. Thus, the essence of chemical science finds its full expression in the words of Leonardo da Vinci: *"Where Nature finishes producing its own species, man begins, using natural things and with the help of this nature, to create an infinity of species."* [7]

The early focus of supramolecular chemistry was on the concept of the design and synthesis of molecules (hosts) with ability to interact specifically with other molecules (guests) or to form larger aggregates, based on the "*lock and key*" concept enunciated by Emil Fishcer in 1894 (see Figure 1.2).[8]

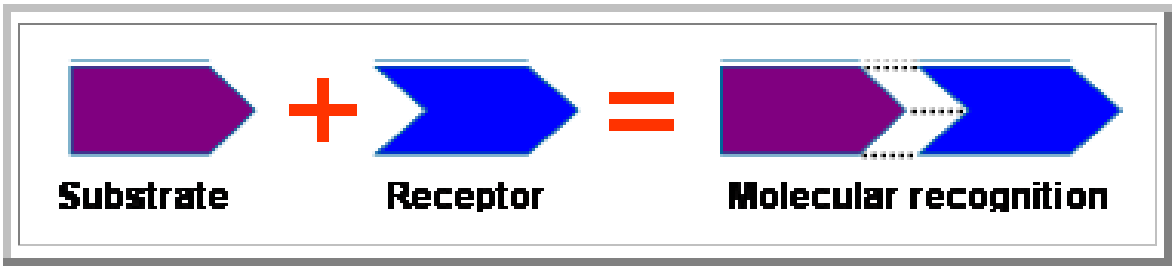


Figure 1.2: "*Lock and Key"* concept to show the molecular recognition.

At a fundamental level, supramolecular entities possess a primary structure, corresponding to the molecular skeletons of their building blocks (tectons or motifs), which may then associate with one another via noncovalent bonds to generate higher order supramolecular composites. The intermolecular association of a small number of component tectons leads to the formation of finite oligomolecular aggregates termed supermolecules, and in turn these supermolecules forms infinite polymolecular systems *via* the noncovalent polymerization, may be called supramolecular arrays. Ultimately supermolecules and supramolecular arrays may associate with one another, particularly in the solid state, to yield gigantic macroscopic conglomerates, i.e., higher order supramolecular arrays.[9]

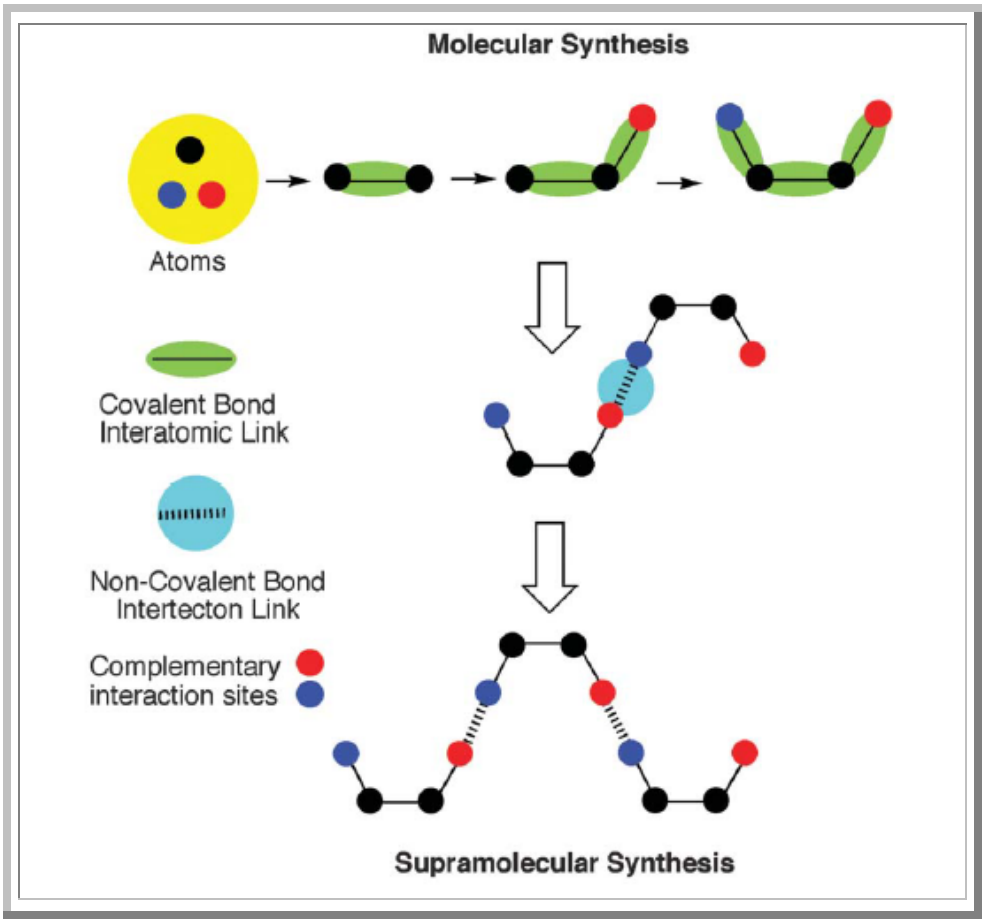
However, the aim of supramolecular chemistry is not only the creation of a particular structure, but also the introduction of specific chemical functions in these supermolecules. In the words of Nobel laureate, J. M. Lehn that, *"Molecular chemistry*

rules the covalent bond. Supramolecular chemistry is 'chemistry beyond the molecule', whose goal is to gain control over the intermolecular noncovalent bond. It is concerned with the entities of higher complexity than molecules themselves--supramolecular species and assemblies held together and organized by means of intermolecular, binding interactions. It is a highly interdisciplinary field of science and technology, bridging chemistry with biology and physics." [7a]

Thus, the ultimate goal of supramolecular chemistry is to become the "science of informed matter", i.e. it seeks to create functioning, organized nanoscale devices which will be able to stock-pile and process information. There are two facets of modern-day chemical synthesis that are influenced by supramolecular chemistry. These are 1) noncovalent or supramolecular synthesis and 2) supramolecular assistance to molecular synthesis.[10]

1.3 NONCOVALENT SYNTHESIS

The concepts developed in supramolecular chemistry are increasingly used in fields like material science, surface science, sensor technology, and nanotechnology.[11] With increasing understanding of the individual interactions that govern the molecular recognition process, the focus is now shifting towards noncovalent synthesis which utilizes noncovalent interactions as a tool for the creation of unprecedented assemblies. Thus, this emerging field of noncovalent synthesis could be defined as "a collection of atoms held together by covalent and noncovalent bonds (see Scheme 1.1)." [12]



Scheme 1.1: Schematic representation of molecular (top) and supramolecular synthesis (bottom)

Supramolecular synthesis, by combining molecules through noncovalent interactions, makes it possible to build up exotic supramolecular assemblies in the solid-state and offers superb architectural possibilities. The advantage of noncovalent synthesis is that noncovalent bonds are formed spontaneously and reversibly under the conditions of thermodynamic equilibrium, without undesired side products. In supramolecular or noncovalent synthesis the use of noncovalent interactions becomes important for two reasons: 1) the noncovalent interactions holding the molecules together incorporate a large degree of flexibility into molecules which allows conformational changes that are often necessary for function, and 2) the larger number

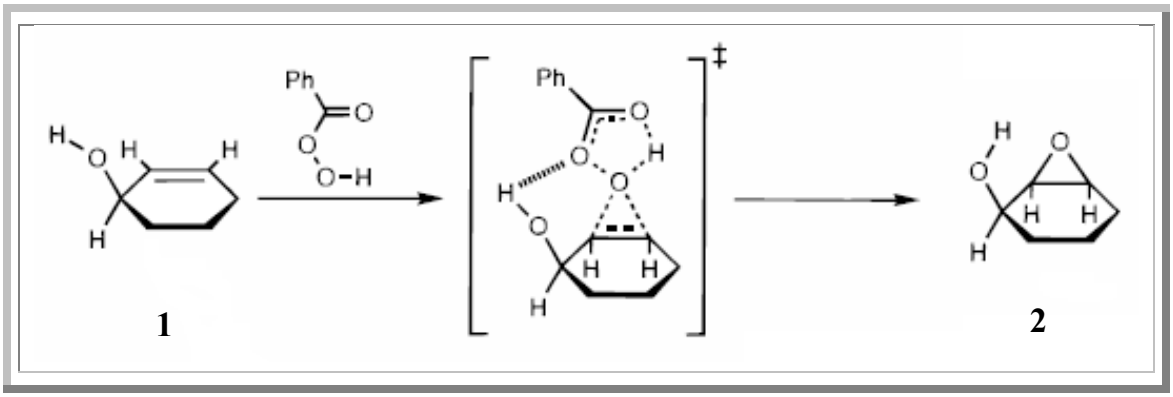
of noncovalent interactions allow for greater specificity through annealing processes which ultimately form the most thermodynamically favourable structure. The salient features of noncovalent synthesis in comparison with covalent synthesis are summarized in Table 1.1.[13]

Table 1.1: Characteristics of covalent and noncovalent synthesis

	Covalent Synthesis	Noncovalent Synthesis
Building block	Atoms	Molecules, ions
Target	Molecules	Supermolecule, Crystal
Molecular weight	1–1000 Da	1–100 kDa
Bond type	Covalent	Ionic, hydrophobic, metal coordination, hydrogen bond
Bond energy	50–135 kcal/mol	2–20 kcal/mol
Reaction path	Reactant → Transition state → Product	Molecule → Crystal nucleus → Crystal
Kinetic Stability	High	Low
Components	$\Delta H >> T\Delta S$	$\Delta H \approx T\Delta S$
Solvent effects	Secondary	Primary
Characteristics	–	Cooperativity

The (noncovalent) intermolecular bond has not only manifested itself in the creation of supramolecular assemblies, but it has also found application in the preparation of discrete molecular targets by conventional synthetic strategies. One of the best-known examples of the noncovalent bond assisting the covalent synthesis is the *syn* epoxidation of cycloalkenes possessing allylic hydroxyl groups with peroxy acids, in reactions that afford epoxides, as described below.[14]

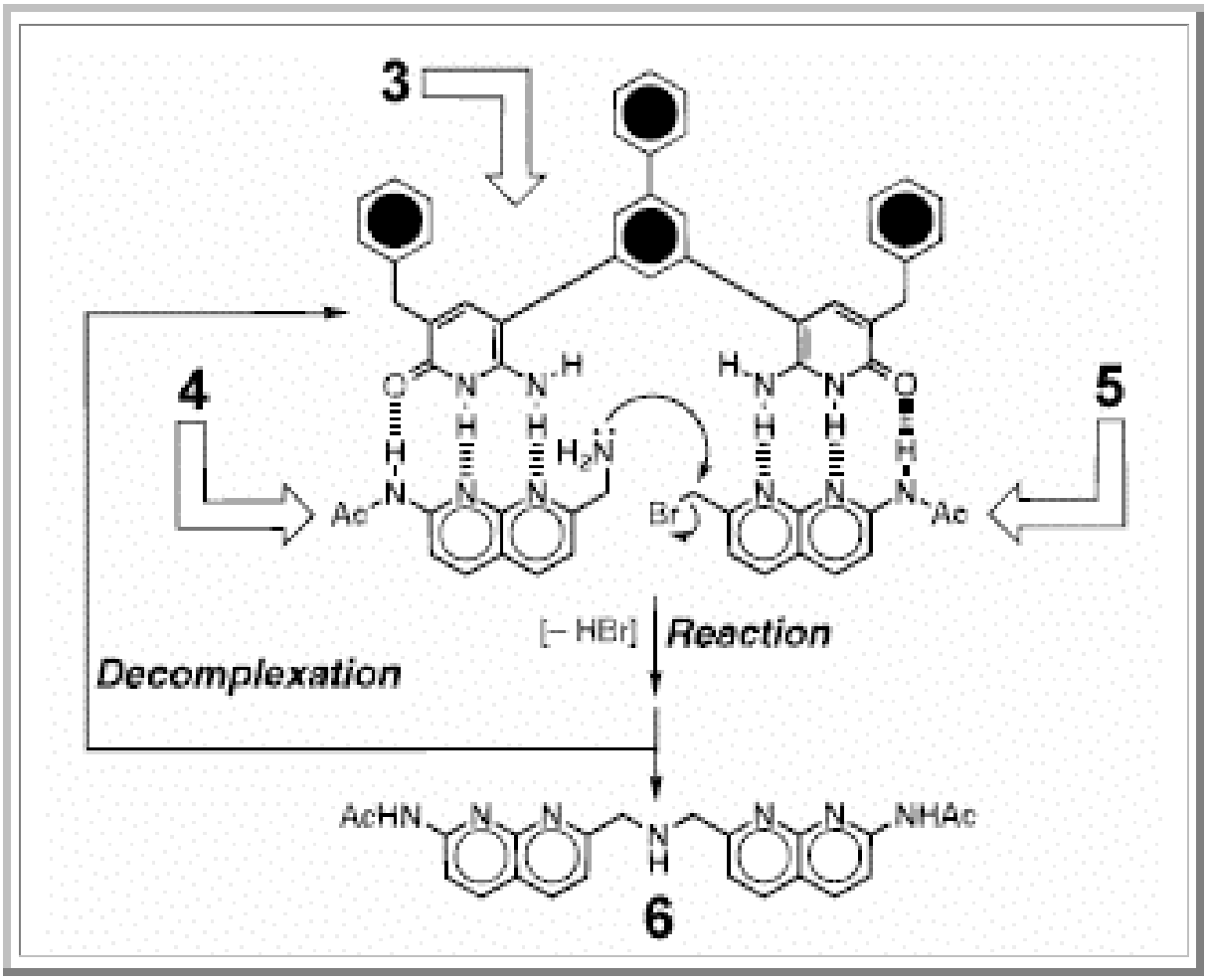
2-cyclohexen-1-ol, **1,** is converted by perbenzoic acid into *cis* epoxide, **2,** preferentially. The stereochemical outcome of this reaction is believed to be influenced by the intermolecular bond. Here, the incoming oxygen atom is delivered to the alkene in a *syn* orientation on account of hydrogen bonding interactions between the allylic alcohol moiety (H-bond donor) and the peroxy acid (H-bond acceptor) in the transition state (see Scheme 1.2).[15]



Scheme 1.2: *cis*-epoxidation of 2-Cyclohexen-1-ol, **1,** using the supramolecular assistance to synthesis provided by hydrogen-bonding interactions.

Also, template – directed synthesis assisted by noncovalent interactions is a way to achieve stereospecific covalent synthesis.[16] Here, a "template" induces the creation of a specific product by juxtaposing reactive sites in a favorable orientation for the formation of covalent bonds. The template holds these sites in the preferred bond-forming orientation with noncovalent intermolecular bonds. For example, as illustrated in Scheme 1.3, the ditopic template molecule, 5,5'-(biphenyl-3,5-diyl)*bis*(6-amino-3-benzylpyridin-2(1*H*)-one), **3,** binds two substrate molecules specifically, the amine, *N*-(7-(aminomethyl)-1,8-naphthyridin-2-yl)acetamide, **4,** and the bromide, *N*-(7-(bromomethyl)-1,8-naphthyridin-2-yl)acetamide, **5,** simultaneously in an orientation

which encourages the formation of the product, *N*-(7-(((7-acetamido-1,8-naphthyridin-2-yl)methylamino)methyl)-1,8-naphthyridin-2-yl)acetamide, **6,** via a ternary hydrogen-bonded [**3.4.5**] complex.[17]



Scheme 1.3: Synthesis of **6** assisted by the template **3.**

1.4 CRYSTAL ENGINEERING

Supramolecular chemistry has contributed many examples of finite multicomponent supermolecules to the recent literature in chemical sciences: these include supramolecular cages, macrocycles, grids, racks, ladders, clusters and

helices.[18-21] Also, target oriented solid-state supramolecular synthesis, i.e. crystal engineering – has provided much of the driving force for the maturation of this area. The phrase crystal engineering was coined by G. M. J. Schmidt in 1971 through his studies of topochemical reactions of *trans*-cinnamic acids and amides in the solid-state.[22] A major advance in the practice of crystal engineering came about in the early 1990s with the awareness that a crystal is one of the finest examples of a supramolecular entity with intermolecular interactions between functional groups as the major structural elements.[23]

1.5 INTERMOLECULAR INTERACTIONS

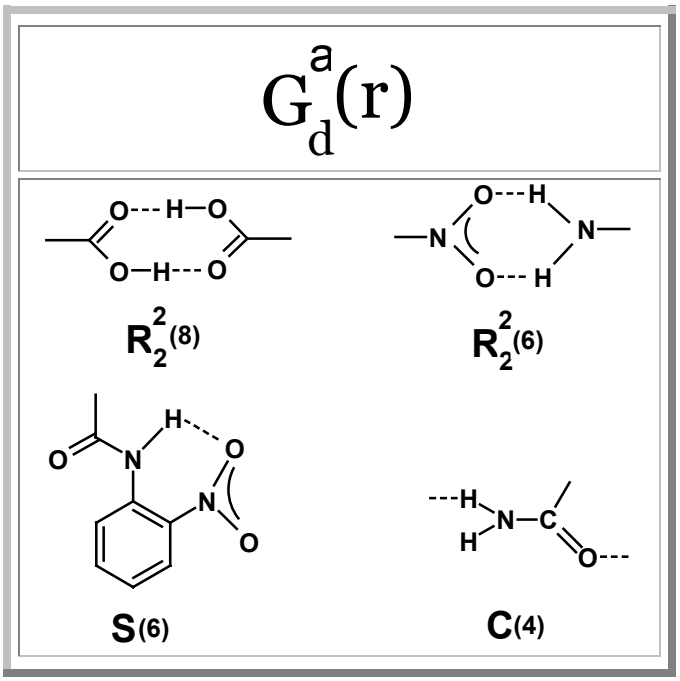
The crystal structure of a molecule is the free energy minimum resulting from the optimization of attractive and repulsive intermolecular interactions with varying strengths, directional preferences and distance-dependence properties. Hence, understanding the nature and strength of intermolecular interactions is of fundamental importance in supramolecular chemistry. Intermolecular interactions in organic compounds can be classified as isotropic, medium-range forces, which define molecular shape, size and close packing; and anisotropic, long-range forces which are electrostatic and involve heteroatom interactions.[24] Thus, the observed three-dimensional architecture in the crystal is the result of the interplay between the isotropic van der Waals forces whose magnitude is proportional to the size of the molecule, and the anisotropic hydrogen bond interactions whose strength are related to the acid-base properties of donor and acceptor groups. However, hydrogen bonds play an important role in determining the three-dimensional structure of chemical and biological systems

as a consequence of their stability and directionality.[9b-c, 10a-c, e, f, 12b, 25] The formation of one or multiple hydrogen bonds, especially in combination with other noncovalent forces, such as ionic or hydrophobic interactions, can lead to a dramatic change in the micro- and macroscopic properties of the resulting supramolecular assemblies. In contrast to covalent bonds which are once formed are stable under normal conditions and can only be broken by providing sufficient energy, the formation of hydrogen bonds is reversible and their strength depends on the chemical environment, such as the solvent or temperature. Also, through the variation of the external parameters, the reversibility of hydrogen bonds allows the direct control of the physical properties of supramolecular assemblies that are determined by the hydrogen bonds. Thus, hydrogen bonding acts as "supramolecular adhesive" in the supramolecular synthesis.[26]

1.6 HYDROGEN BOND

The hydrogen bond [27] (see Box 1.1), perhaps, has been at the forefront of the drive toward the targeted synthesis of well-defined distinct supramolecular entities, so several studies of systematic analysis of hydrogen bonding patterns have been carried out. Thus, elaborating on earlier studies by Robertson and Donohue, a graph set analysis with empirical rules in order to define the formation of hydrogen bonded arrays was developed by Etter.[28] The purpose of graph-set assignments is to define the morphology of hydrogen-bonded arrays. The process of assigning a graph set begins with identification of a number of different types of hydrogen bonds, as defined by the nature of the donors and acceptors in a hydrogen bond, that are present in the structure. A graph set is specified using the pattern designator (G), its degree (r), and the number of

donors (d) and acceptors (a). The designators are C (chain), R (ring), D (finite set), and S denotes self or an intramolecular hydrogen bond (see Scheme 1.4).

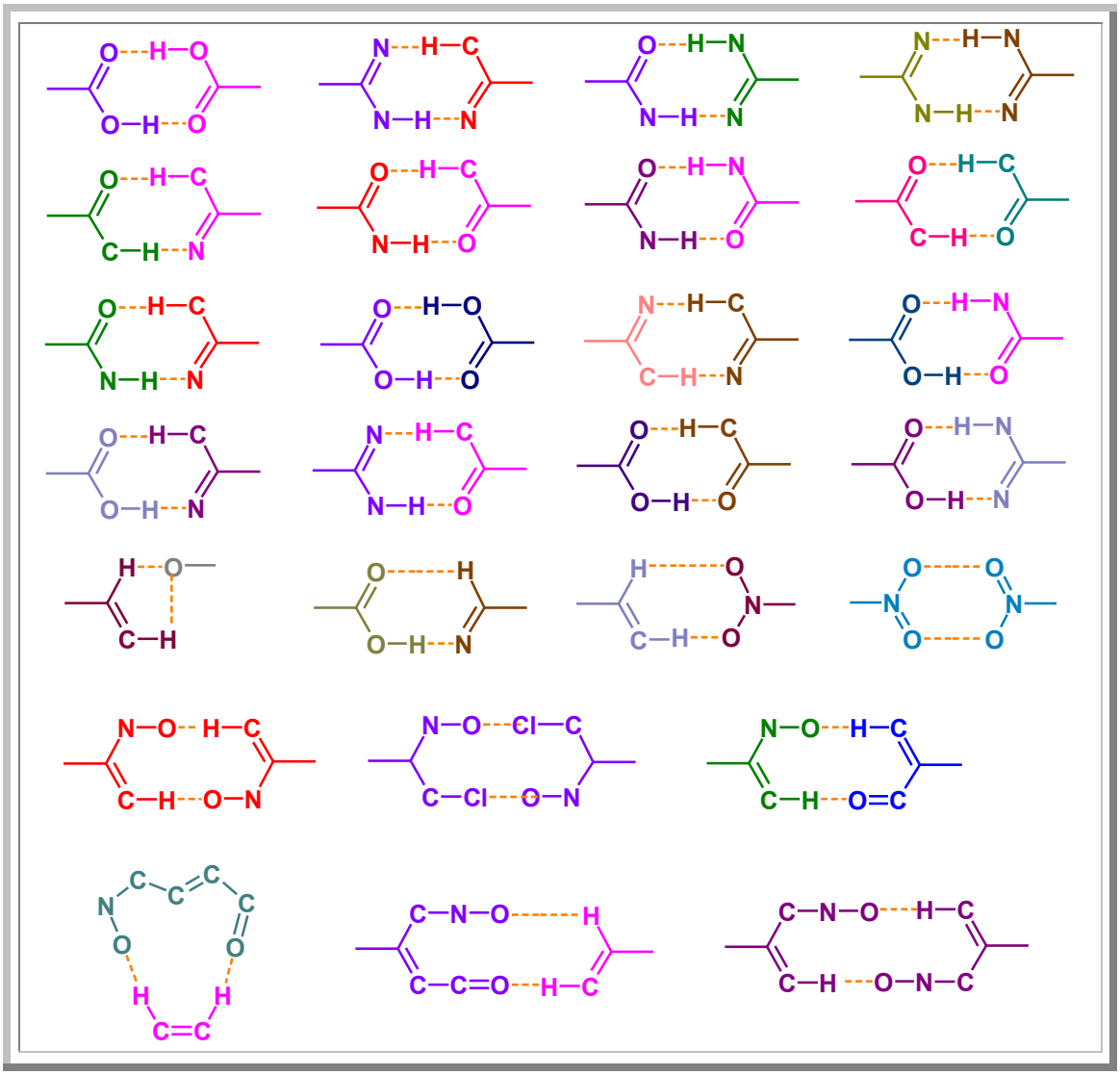


Scheme 1.4: Graph set notations for some hydrogen bonding networks.

With the help of graph set notations, at least in strongly hydrogen-bonded systems, it is possible to make some predictions about the resulting crystal structures. Also, the major outcome of this analysis is evolution of some principles that have more impact than the actual numerical codings developed. A fundamental rule is that *"all good proton donors and acceptors are used in hydrogen bonding."* [29] Second rule states that *"six-membered-ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds."* The third rule is that *"the best proton donors and acceptors remaining after intramolecular hydrogen bond formation form intermolecular hydrogen bonds to one another."* [30] The hydrogen bond rules provide useful information about the preferred connectivity patterns,[31] hydrogen bond

selectivity, and stereoelectronic properties of hydrogen bonds for a particular functional group or sets of functional group which further can be made useful in the preparation of functional solids such as host networks that can selectively bind the guest molecules. Some of the intermolecular interactions which are involved in the construction and stabilization of large noncovalently linked supramolecular architectures are listed in Chart 1.1

Chart 1.1

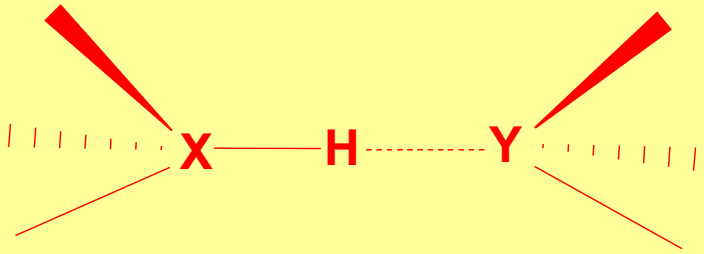


Box 1.1

The Hydrogen Bond †

Pauling's early definition of the hydrogen bond: [1a]

"A hydrogen bond is an interaction that directs the association of a covalently bound hydrogen atom with one or more other atoms, groups of atoms, or molecules into an aggregate structures that is sufficiently stable to make it convenient for the chemist to consider it as an independent chemical species."



X = F, Cl, O, S, N, C **Y** = F, Cl, O, S, N, π-system

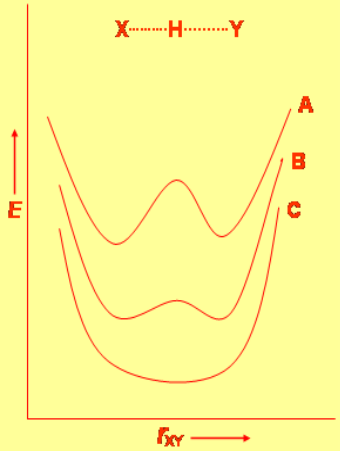
Weak interactions between molecules containing hydroxyl groups were already noted in 1892 by Nernst. Although nameless at that time, Werner included them ten years later in his concept of "Nebenvalenz" (minor valence), which was in fact a proper description of the phenomenon of hydrogen bonding. Suggestions that the hydrogen atom was the center of this weak interaction were first made in 1920 by Huggins as well as Latimer and Rodebush. It was not until 1935 ± 6 that Bernal and Huggins proposed the actual term "hydrogen bond" (abbreviated as H-bond), which has become generally adopted to describe this phenomenon. Soon after, it became apparent that associations between molecules containing polar X-H bonds and nonbonding electron pairs on atom Y are generally characterized by relatively high interaction energies. Since then, H-bonding interactions have continued to fascinate chemists – from theoreticians to biochemists and material scientists. H-bonds connect atoms X and Y that have electronegativities larger than that of hydrogen, namely, C, N, O, F, P, S, Cl, Se, Br, and I. The XH group is generally referred to as the "proton donor" (D) and the Y atom is called the "proton acceptor" (A) group. The strength of a H-bond increases with an increase in the dipole moment of the X-H bond and the electron lone pair on atom Y. Hence, the strongest H-bonds are formed between atoms N, O, and F acting as X and Y, although C-H can also act as a donor. "π" H-bonds involve an interaction between a partially positive hydrogen atom and the electrons of unsaturated double and/or triple bonds.

The first theoretical models suggested that H-bonding exclusively involves an electrostatic interaction between the partially positive hydrogen atom of the donor and the lone pair of the acceptor. Nowadays, it is generally accepted that H-bonding can be described neither by electrostatic theory nor by weak covalent bonding alone, but involves a complicated superposition of five individual contributions which are of similar magnitude:

1) electrostatic or coulomb energy (DECOU)
2) exchange repulsion (DEEX)
3) polarization energy (DEPOL)
4) charge-transfer energy or covalent bonding (DECHT)
5) dispersion forces (DEDIS).

The energy of a H-bond in the gas phase is typically in the range of 2 ± 20 $kcalmol^{-1}$, which is much weaker than covalent bonds, but significantly larger than dipolar or London dispersion force energies (<2 $kcalmol^{-1}$). If either the donor or acceptor is charged the electronic attraction will be amplified, and consequently the H-bonds become much stronger (10 ± 45 $kcalmol^{-1}$). The thermodynamic stabilities of H-bonded complexes in solution are very dependent on the solvent. The stabilities are usually highest in apolar solvents without H-bonding properties, such as alkanes. The stabilities are lower for solvents that can act either as a H-bond donor or acceptor by themselves, because of competitive H-bonding with the solvent.

H-bonds have been classified into three different types: A) weak or double-well H-bonds, B) lowbarrier H-bonds (LBHBs), and C) very strong or single-well H-bonds (see Graph 1.1). For singlewell potentials the hydrogen atom is symmetrically fixed between the two donor atoms, while for doublewell potentials there are two minima in which the hydrogen atom is closer to one of the donors. The single-well potential is generally observed for short, “strong” H-bonds.



Graph 1.1: Potential energy wells for three different types of hydrogen bonds:A) the double-well potential, B) the low-barrier potential, and C) the singlewell potential.

† Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem. Int. Ed*. **1990**, *40*, 2382-2426 and references therein.

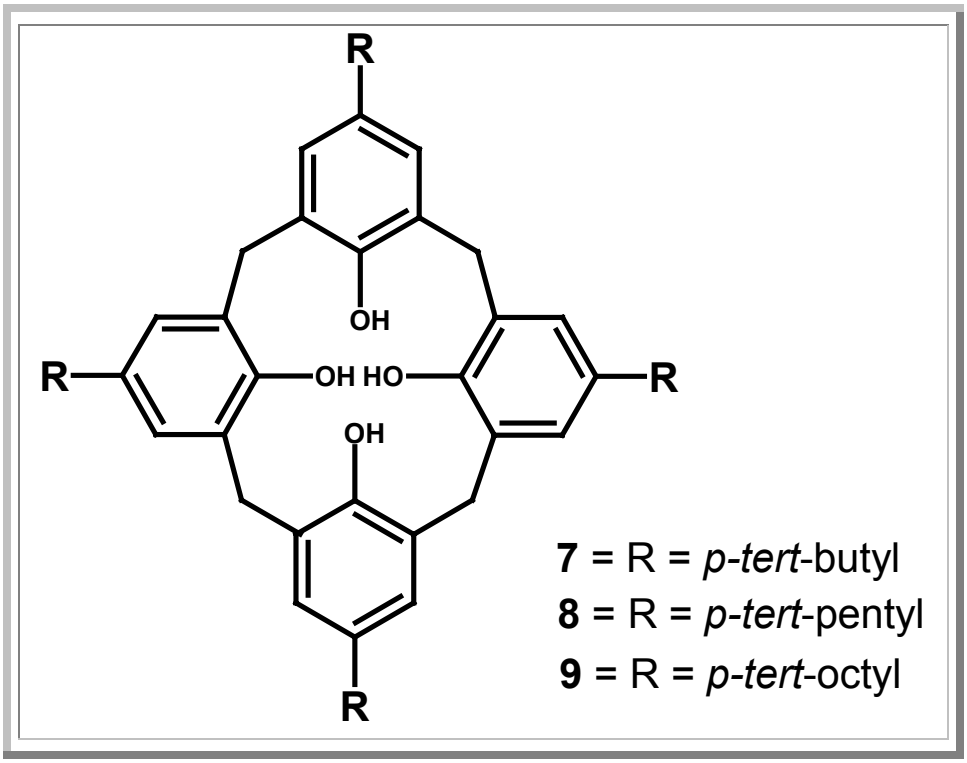
1.7 INTRODUCTION TO HOST-GUEST COMPLEXES

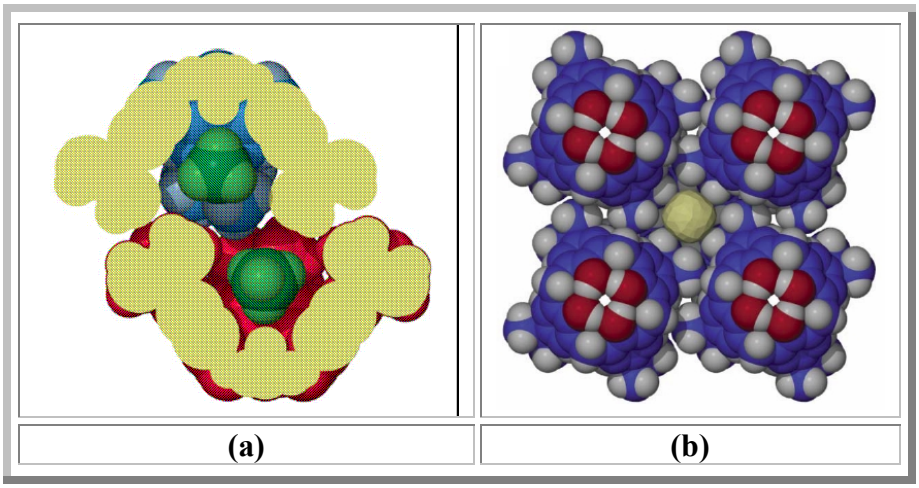
Logical supramolecular synthesis analyzing the noncovalent bonding motifs and the coordinate covalent bonding between ligands and metals has played a pivotal role in the supramolecular chemistry. [32] The design and synthesis of organic and inorganic porous solids with controlled sizes and shapes and chemical environments has generated enormous interest in recent years because such designer solids may be exploited for various applications.[33] In this regard, host-guest complexes,[34] especially employing organic substrates that possess cavities and channels, gained popularity in recent times. Host-guest complexes are a class of molecular complexes in which a macromolecule or a group of molecules encompass other molecules either by covalent or noncovalent bonds between them. Molecules that are able to encapsulate other entities are referred to as the hosts while the captured entities are termed as the guests. The hosts, in general, form structures with voids of dimensions sufficient enough to accommodate the guests. Complexes made by hosts that completely surround their guests provide a means to stabilize reaction and transient chemical intermediates to transfer the active molecules to target cells and to construct molecular scale devices. The organic and inorganic building blocks could be used to synthesize diverse families of shells as demonstrated by the emergence of container molecules, ions, and assemblies.[35]

Crystalline host-guest compounds, however, are important because of their extensive applications, especially in chemical separation.[36] In recent times, organic host-guest complexes have been applied for the chemical sensor development and gas-

storage processes.[37] Thus, host-guest frameworks possess cavities capable of entrapping atomic and/or molecular sized guests and have application in chemistry (for example catalysis),[38] biology (drug delivery)[39] and materials sciences (molecular devices).[40]

In recent times, there are numerous reports of the absorption of gases such as H_2, CH_4, CO_2, etc., by crystalline organic hosts, for example, *p-tert*-butylcalix[4]arene, **7**, *p-tert*-pentylcalix[4]arene, **8** and *p-tert*-octylcalix[4]arene, **9**.[41] The results demonstrates that the low density organic systems do indeed merit consideration as potential sorbants for volatile gases, and that such sorption processes can occur under desirable conditions close to standard temperature and pressure. This is a new concept in the field of gas storage materials. It shows the possibility of usage of organic materials for gas sorption as shown in Figure 1.3.

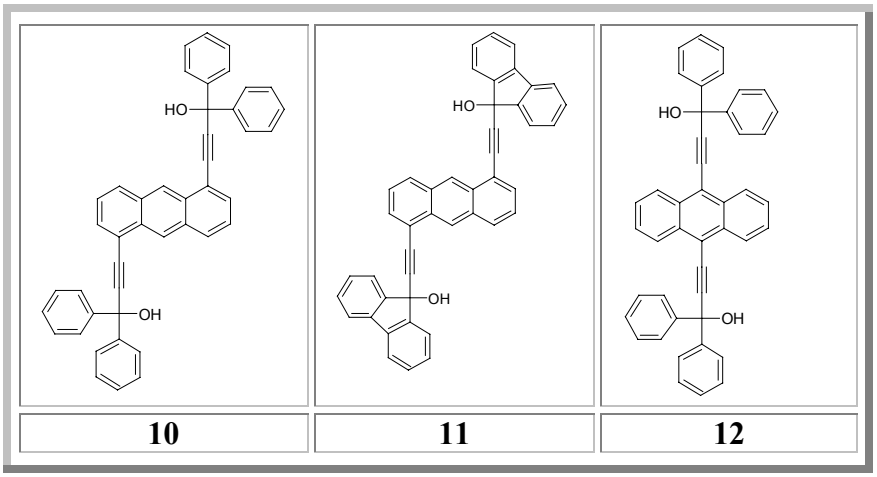




(a) **(b)**

Figure 1.3: (a) The section of a dimeric capsule formed by calixarene, **7**, showing the cavity occupied by the methane molecules. **(b)** Calixarene, **9,** columns showing void space (yellow color) for methane sorption.

Further, Weber and co-workers reported substituted derivatives of anthracene such as 1,5-*bis*[(diphenylhydroxymethyl)ethynyl]anthracene, **10**, 1,5-*bis*[(9-hydroxyfluoren-9-yl)ethynyl]anthracene, **11**, 1,8-*bis*[(diphenylhydroxymethyl)ethynyl]anthracene, **12**, etc., as being very efficient in clathrate formation. These compounds give a number of host-guest complexes with various solvents such as *n*-proplyamine, *n*-butylamine, triethylamine, DMSO, DMF and THF.[42]



10 **11** **12**

However, one of the main drawbacks for the creation of channel structures is that the open frameworks often are tends to interpenetrate. Thus, two (2D) and three-dimensional (3D) frameworks typically fail to yield the potential porosity because of interpenetration or self-inclusion of identical frameworks (apohost). In this context, 1,3,5-benzenetricarboxylic acid (**135btc**), is prototypal since it predictably self-assembles through the well-known carboxylic acid dimer motif into an interpenetrating honeycomb grid with 14 Å cavities (see Figure 1.4).[43]

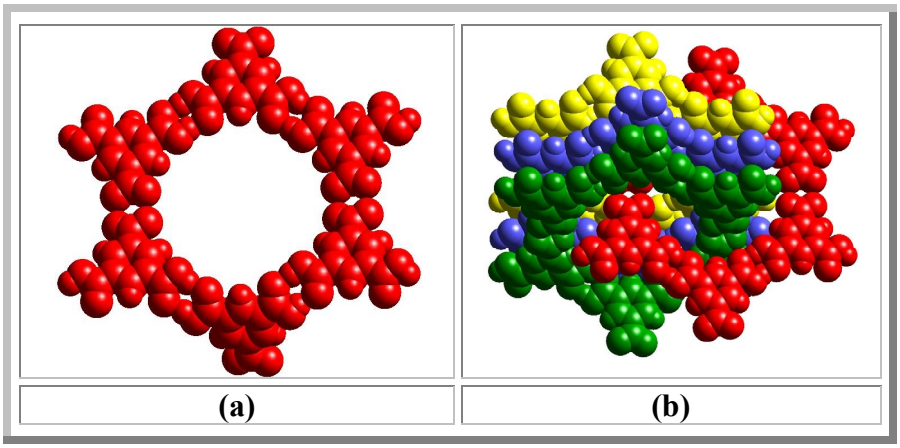


Figure 1.4: (a) 135btc forms chicken wire network in two-dimension showing the 14 Å cavity. **(b)** The triple catenation leads to the utilization of the cavity.

Zimmerman et al. reported an exotic hexagonal network of **135btc**. In this case **135btc** and pyrene were co-crystallized from ethanol and the resulting assembly forms the host-guest complex. The hexagonal host network is formed by the **135btc** and ethanol molecules forming the two dimensional cavity which is occupied by pyrene and ethanol molecules respectively as shown in Figure 1.5.[44]

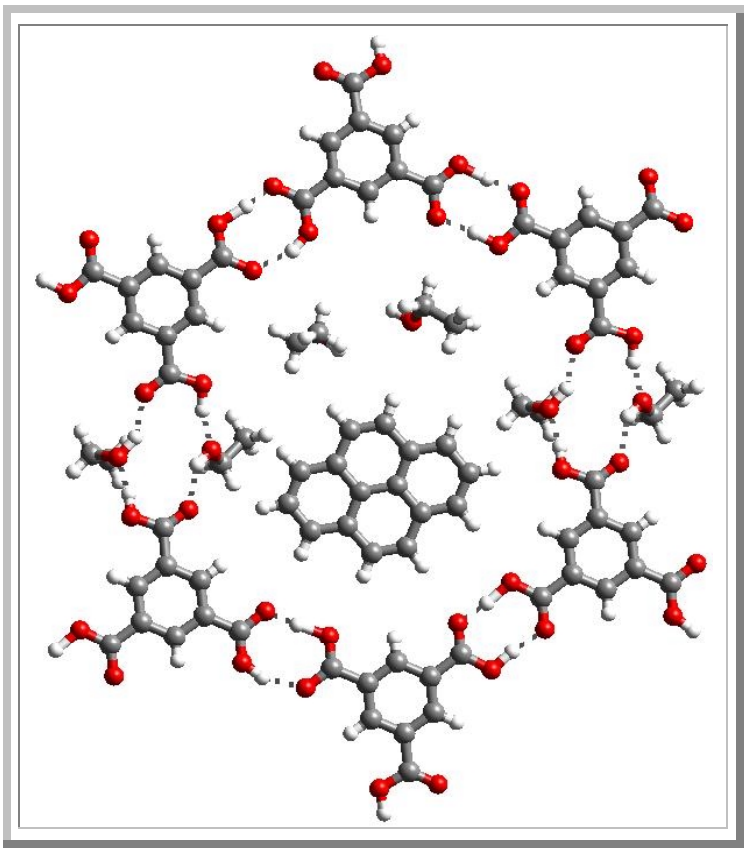
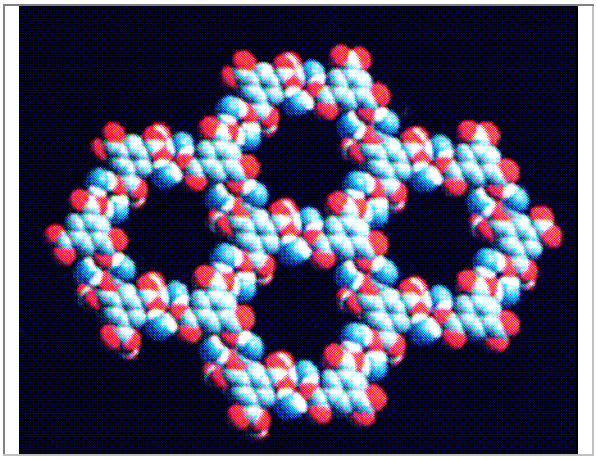


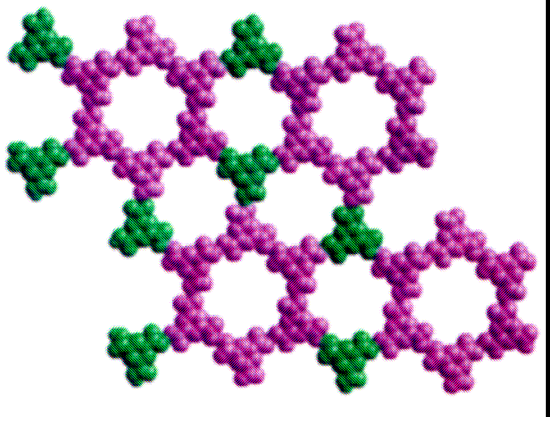
Figure 1.5: 135btc forming a hexagonal network utilizing the ethanol molecules to accommodate the guest molecules.

Zaworotko et al. reported two ammonium salts of **135btc**, *tris*(N,N-dicyclohexylammonium)benzene-1,3,5-tricarboylate, **13** and *dodecakis*(N,N-dimethylammonium)benzene-1,3,5-tricarboxylic acid *tris*(benzene-1,3-dicarboxylate-5-carboxylic acid) *tris*(benzene-1-carboxylate-3,5-dicarboyxlic acid) benzene-1,3,5-tricarboxylate, **14**. While a neutral honeycomb grid was observed in **13**, an anionic honeycomb grid, based upon the hydrogen *bis* carboxylate hydrogen bonds was found in **14** (see Figure 1.6).[45] There are two common motifs occur between secondary ammonium cations and carboxylate anions (see Scheme 1.5). Also these two motifs would readily propagate **135btc**$^{3-}$ into a honeycomb grid (see Scheme 1.6).

$[NH_2(c\text{-}C_6H_{11})_2]_3[135btc]$	$[NH_2(CH_2)_{12}\{H_3135btc\}\{H_2135btc\}\{H135btc\}\{135btc\}]$
13	**14**

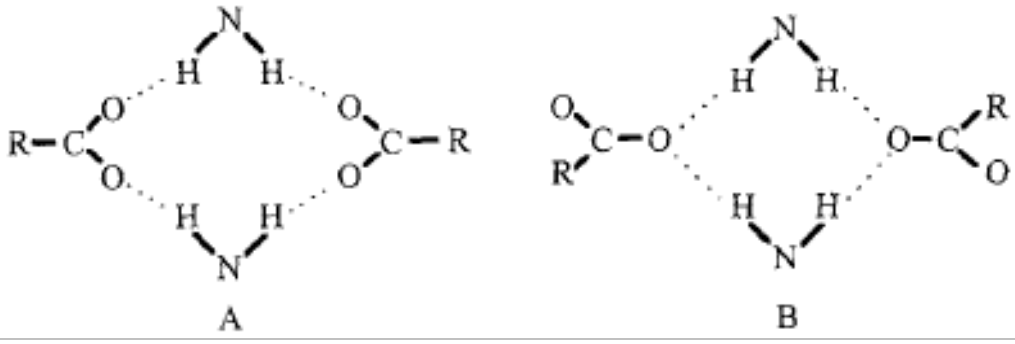


(a)

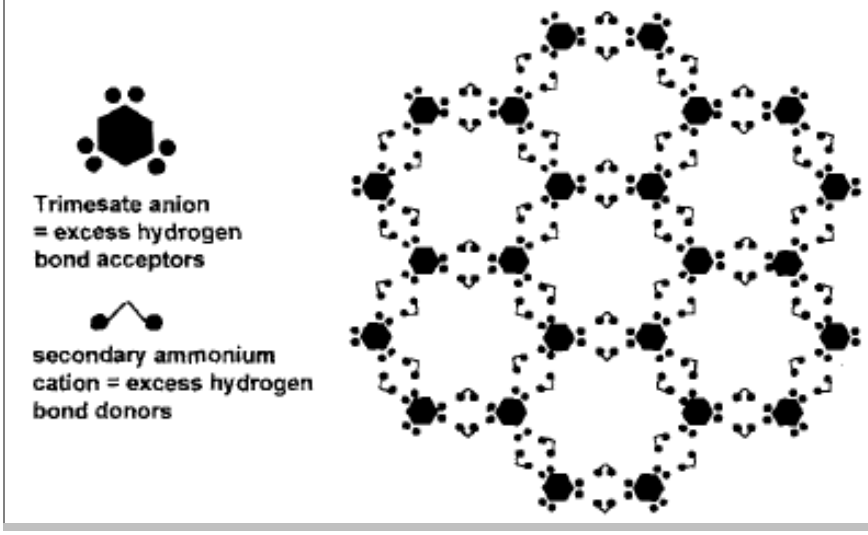


(b)

Figure 1.6: (a) A space filling model of the honeycomb grid in **15. 135btc** anions are bridged by cations through motif B (Scheme 1.5). **(b)** The honeycomb grid in **16.** Grid consists of H_3**135btc** and H**135btc**$^{2-}$ ions in the ratio 1:3.



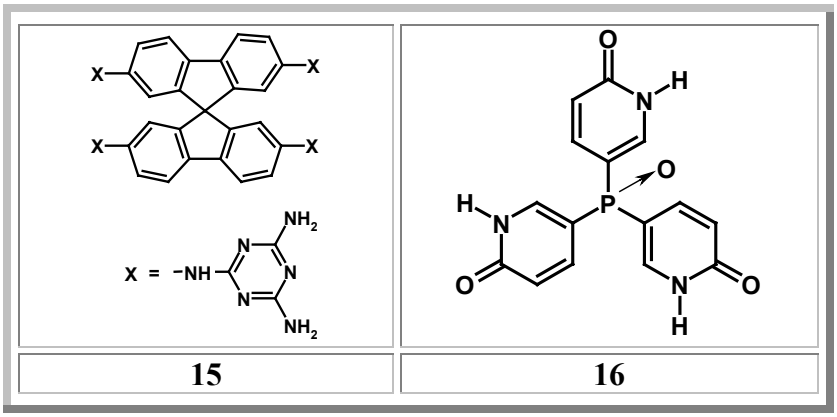
Scheme 1.5



Scheme 1.6

Wuest and co-workers showed molecular tectons approach for the synthesis of cavity structures. Strong directional interactions in the tectons usually dominate, leading to the formation of open networks with a significant capacity for inclusion. Porous networks derived from tectons are molecular analogues of zeolites, but they are held together by hydrogen bonds and other weak interactions. Guests located in these channels can often be exchanged without loss of crystallinity, simply by exposing single crystals to new guests. In crystals of spirobifluorene, **15**, which incorporates four sticky aminotriazine groups, 75% of the volume is accessible to guests and the hydrogen-bonded network formed by tecton **15** is the most porous ever built from small molecules (see Figure 1.7(a)). Also, the crystallization of trigonal tecton **16** was directed reliably by hydrogen bonding of pyridinone groups to form porous corrugated sheets, which then stack in a translational symmetry to yield pores as shown in Figure 1.7(b). Thus, the study represents the potential of molecular tectonics as a strategy for the purposeful construction of ordered materials. The principles of the strategy are simple and their

roots are old. Hence, molecular tectonics offers a very powerful tool and will continue to be a prolific source of new crystalline materials with predictable structural features and properties.[46]



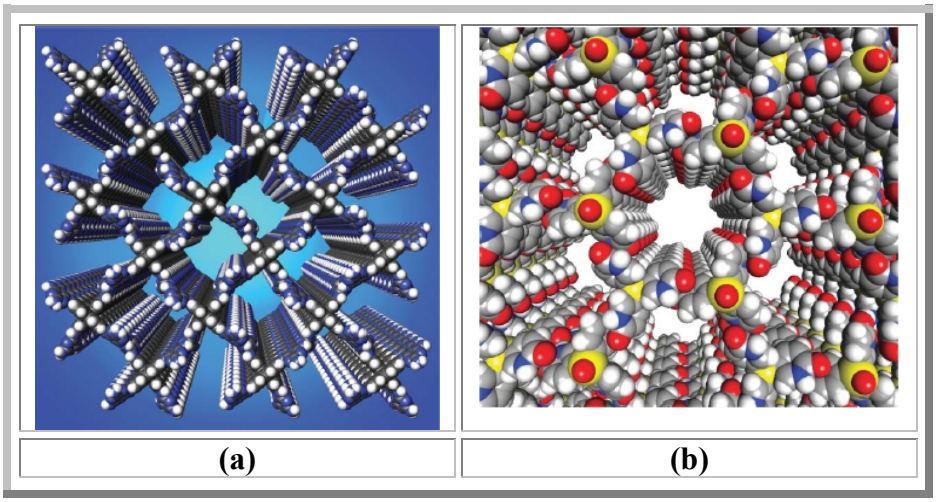


Figure 1.7: (a) The porous network constructed by crystallizing **15. (b)** The porous network constructed by crystallizing trigonal tecton **16**. In both the networks guests are omitted for clarity purpose.

Further, Ghosh et al. illustrated the solid-state structural evidence of $CHCl_3$-C_6H_6-$CHCl_3$ adduct trapped in the channels formed by hexaanthryl octaaminocryptand, **17**, utilizing the weak C-H···π interaction between the chloroform and benzene

molecules.[47] Six molecules of **17** self-assembled together to form a symmetrical organic channels in the solid state, which acts as a host for the $CHCl_3$-C_6H_6-$CHCl_3$ adducts as shown in Figure 1.8.

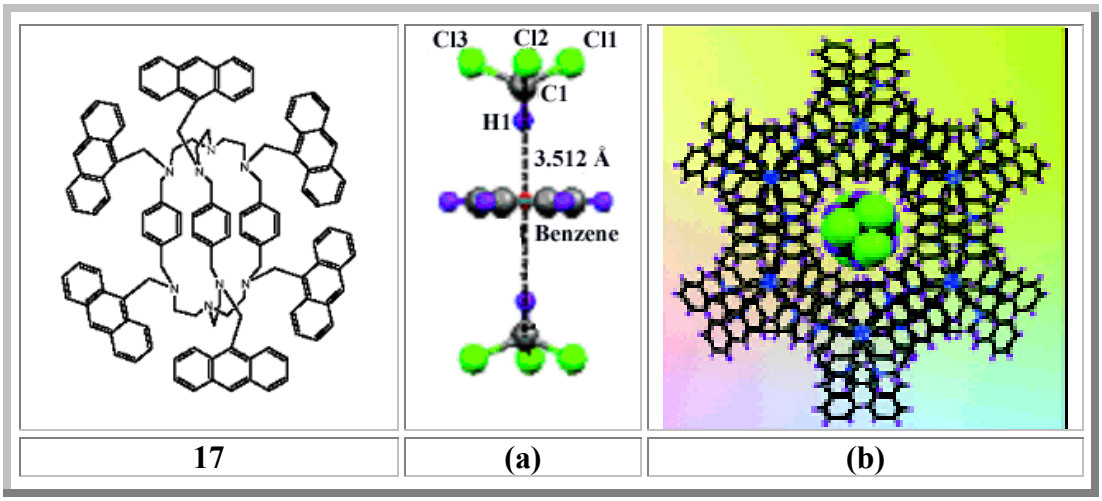


Figure 1.8: (a) Ball and stick model of the $CHCl_3$-C_6H_6-$CHCl_3$ adduct. **(b)** Self-assembly of six molecules of **17** forming channel where adduct **(a)** is stabilized.

In this connection, looking at the different types of host-guest complexes formed by a variety of chemical species, it is evident that the molecules containing –COOH groups are potential precursors for the synthesis of cyclic networks as it is exemplified by the **135btc** molecule. Thus, a rational study of the host-guest complexes formed by the tetra and tri-substituted carboxylic acids employing various aza-donor molecules are described in chapter two.

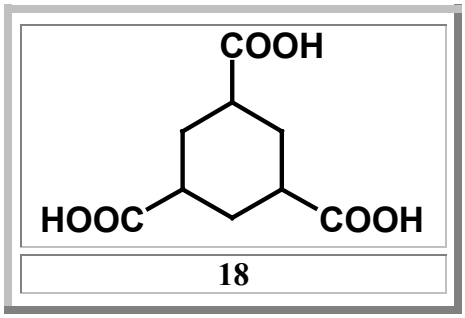
1.8 MOLECULAR COMPLEXES

The current interests in the structural aspects of hydrogen bonds stems from their specificity and directionality. This leads to interactions between different molecular species with well-defined stoichiometry and structure. The complementary of

hydrogen bonding functional groups may be utilized for the design of materials with desired physical, chemical or biological properties. Co-crystal is a crystal that contains two or more different molecular species also referred to as molecular complexes.[48] Co-crystals have free energy that is lower than that of the individual pure components. Once this condition is fulfilled, there is a driving force for the spontaneous formation of co-crystals. The presence of two compounds with different functional groups can provide the opportunity for the formation of hydrogen bonds between components, which are energetically more favorable than those between same molecules of either of the components.[49] However, the analysis of single component crystal structure is useful for studying the structures of ensemble of molecules after association has taken place, while molecular complexation studies are useful for monitoring competitive interactions that determine the selectivity of recognition processes. A substantial amount of work has been done in this area with well established protocols for the design and synthesis of one-, two- and three-dimensional hydrogen bonded networks.

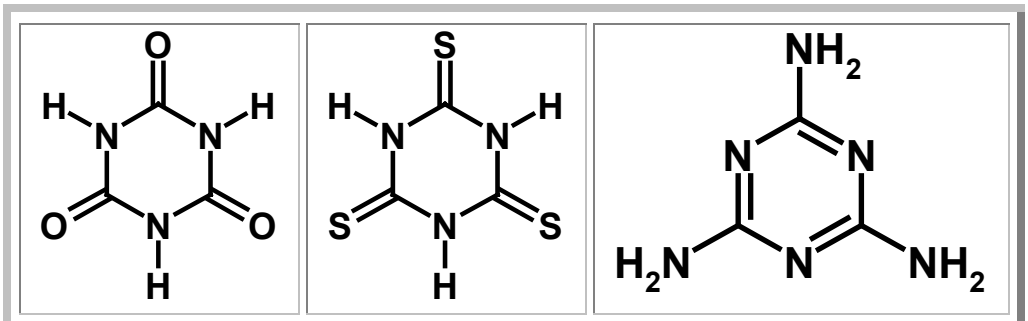
Co-crystals are generally formed by evaporation of solution containing stoichiometric moles of the components, although sublimation and growth from the melt are also used. They can also be prepared by grinding the two solid reagents together.[50] Depending on the rate and vigour of grinding, particle size, and vapor pressures of the reagents; a complete conversion to the new hydrogen-bonded co-crystal phase can be accomplished in the solid state. More often than not, the phase that is obtained is identical with that obtained from the solution crystal growth, implying that solvent is not necessary to direct molecules with strong directional intermolecular interactions into their preferred crystal form. In recent times Jones and coworkers[51]

prepared the molecular complexes of cyclohexane-1,3-*cis*-5-*cis*-tricarboxylic acid, **18** with various aza-donor moieties such as hexamethyltetramine, 4,4'-bipyridine and 4,7-phenanthroline respectively simply by grinding the components in the ball mill. The complexation of hexamethyltetramine does not require the addition of solvent to the grinding mixture whereas the complexes with 4,4'-bipyridine and 4,7-phenanthroline require addition of a small amount of solvent to the grinding mixture. It was observed that with the addition of a small amount of solvent (methanol), co-crystallization is found to be significantly accelerated such that complete conversion is achieved within a few minutes. The enhancement in kinetics might be rationalized by the additional degrees of orientational and conformational freedom at the various interfaces as well as the enhancement of opportunities for molecular collisions.



18

Molecular complexes can also be prepared using the hydrothermal techniques. For example, Pedireddi et al.[52] reported the synthesis of a novel rosette molecular complex of cyanuric acid, **19** and trithiocyanuric acid, **20** with melamine, **21** utilizing the hydrothermal synthetic route (see Figure 1.9). The difficulty in growing crystals of these molecular complexes is partly because the components are highly hydrogen bonded solids melting at high temperatures, with limited solubility in most organic solvents.



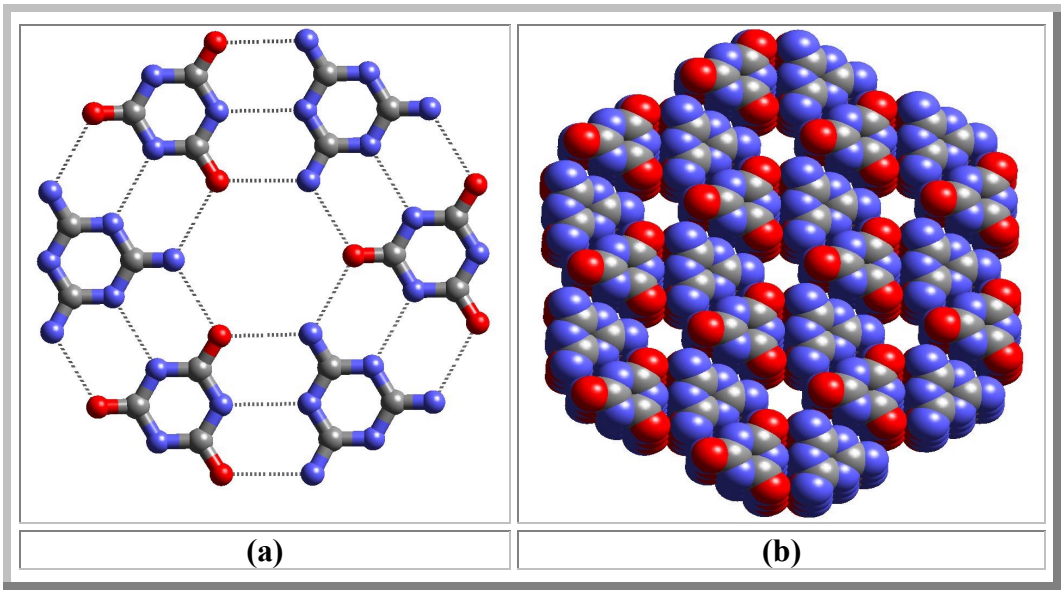
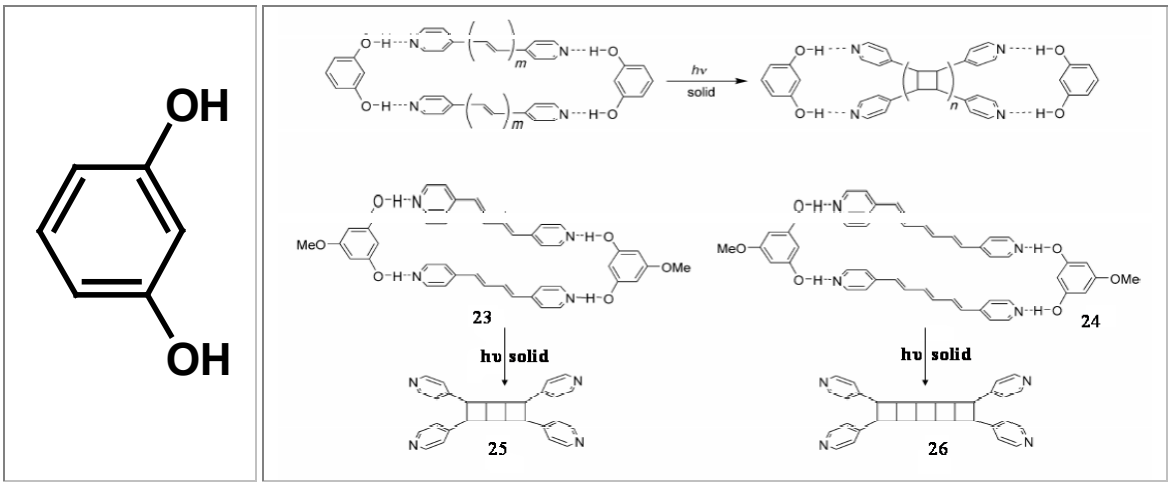


Figure 1.9: (a) A rosette network formed between **19** and **21** with a cavity diameter of ≈ 4Å. **(b)** Three-dimensional arrangement of the, **19.21**, adduct forming channels.

Further, in the contemporary supramolecular synthesis aza-donor moieties and their analogues have employed as spacer group in many of the molecular complexes due to its preferential formation of rigid and strong O-H···N hydrogen bonds with many co-crystallizing agents.[53] MacGillivray and co-workers[54] have shown that the co-crystallization technique can be exploited for the photodimerization of olefins. Co-crystallization of resorcinol, **22**, with an all-*trans*-*bis*(4-pyridyl)poly-m-ene (m = 2, 3,

4….) gave a four component discrete molecular solid-state assembly, **23** and **24**, in which each **22** preorganizes, through two O-H···N hydrogen-bonding interactions, with two poly-m-enes for [2+2] photoaddition. In this design, the two polyenes would be positioned by the templates such that the C=C bonds of the olefins lie parallel and separated by < 4.2Å, a position suitable for the photoreaction. UV irradiation of the solid would produce the targeted [n]ladderanes, **25** and **26**, with the C=C bonds reacting to form the fused cyclobutane framework (see Scheme 1.7).



22 | **Scheme 1.7**

Very recently Boese et al.[55] have shown that cooling of gases in the presence of solvents under elevated pressure, co-crystals may form, in which the gas molecules act as guests in the lattice of the host of solvent molecules. Acetylene gas has been co-crystallized with N-heteroaromatic compounds such as pyridine, 2,5-dimethylpyrazine, 2,5-dimethylpyridine hydrate, 2,5-dimethylpyridine and 2,6-di-*tert*-butylpyridine, as shown in the Figure 1.10.

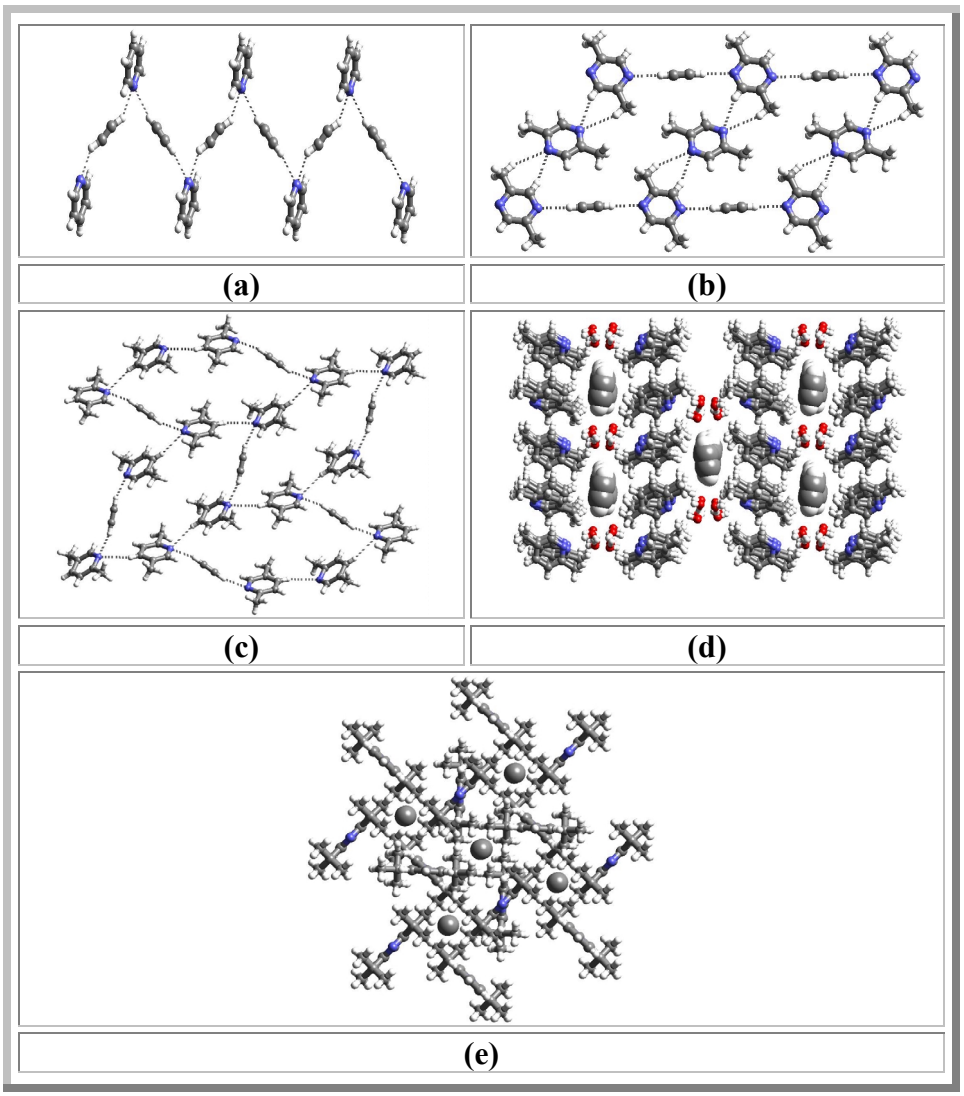


Figure 1.10: (a) Co-crystal of acetylene with pyridine. **(b)** Co-crystal of acetylene with 2,5-dimethylpyrazine. **(c)** Co-crystal of acetylene with 2,5-dimethylpyridine hydrate. **(d)** Co-crystal of acetylene with 2,5-dimethylpyridine. **(e)** Co-crystal of acetylene with 2,6-di-*tert*-butylpyridine.

Further, Zaworotko et al. have reported the crystal structure of **135btc** – 1,2-*bis*(4-pyridyl)ethane, ***bpyea***, (2:3) complex, which exhibits an unprecedented degree of interpenetration.[56] The x-ray structure analysis reveals that the complex exhibits the (6,3) network with linear spacer molecules expanding the 14 x 14 $Å^2$ **135btc** cavity to ca. 39 x 27 $Å^2$ (see Figure 1.11(a)). Three (6,3) networks engage in parallel

interpenetration and the void left over after the catenation is filled by interdigitation of **135btc** and ***bpyea*** molecules from adjacent layers. This was the first observation of a hydrogen bonded (10, 3) network in the co-crystal as shown in Figure 1.11(b)

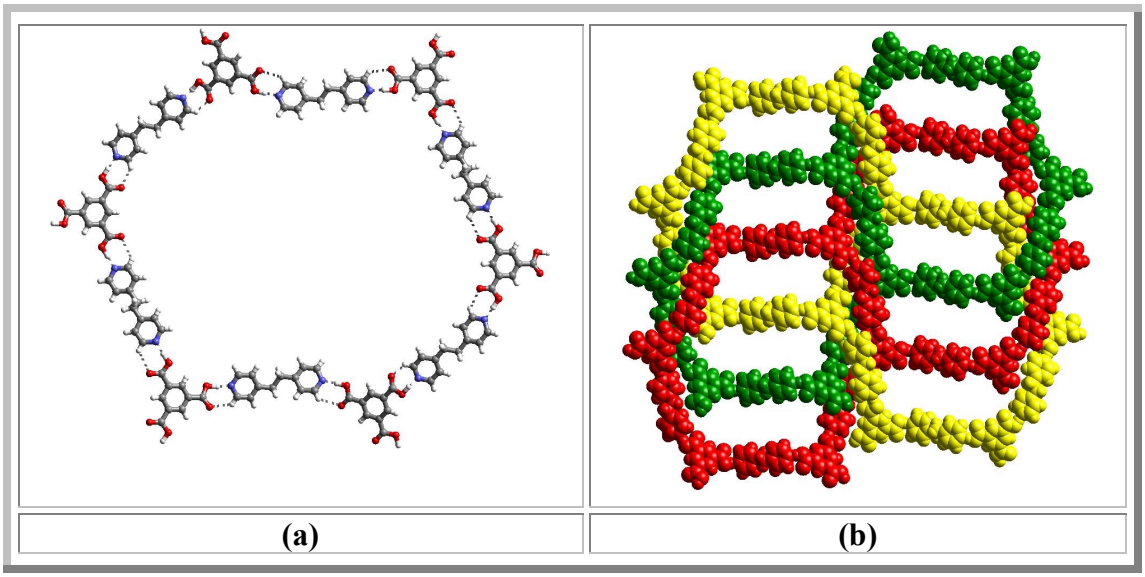


Figure 1.11: (a) Super honeycomb (6,3) network in the molecular complex of **135btc** and ***bpyea***. **(b)** Space filling view of triply parallel interpenetrated nets.

In recent times, Wuest and co-workers reported the preparation of amorphous molecular materials from small symmetric molecules that form multiple hydrogen bonds.[57] The crystallization of methyl 4,6-*bis*(mexylamino)-1,3,5-triazine-2-carboxylate, **27**, from $CHCl_3$ gave an inclusion compound of composition **27**.$CHCl_3$.xH_2O. Approximately 39% of the volume of the crystals is accessible to guests, and it was suggested that the failure of compound **27** to yield a normal close-packed structure without included guests helps provide the free volume typically associated with molecular glasses (see Figure 1.12).

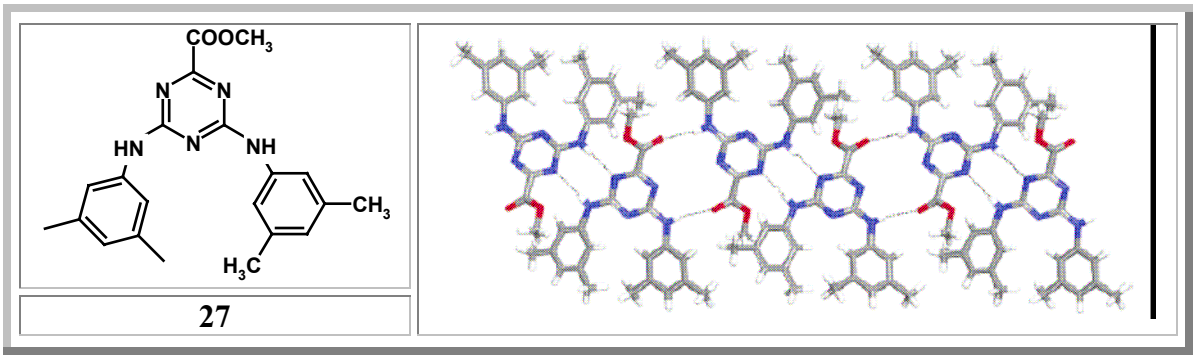
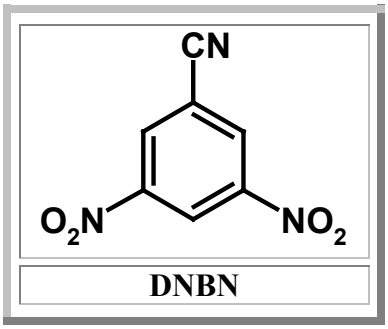


Figure 1.12: View of the structure of crystals of **27** grown from $CHCl_3$.

Thus, to study the phenomenon of molecular complexation, employing different noncovalent bonds, especially weak hydrogen bonds such as C-H···N, C-H···O, etc., molecular complexes of 3,5-dinitrobenzonitrile, **DNBN**, with various hydrocarbons as well as aza-donor molecules were prepared and are described in chapter three.

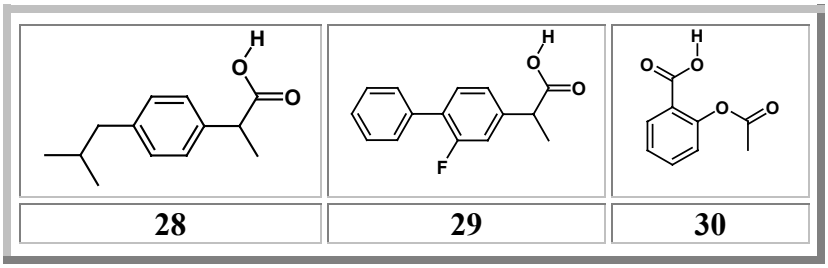


1.9 PHARMACEUTICAL CO-CRYSTALLIZATION

The concept of supramolecular synthesis of pharmaceutical solids represents a fertile, emerging area of research and affords a paradigm for rapid development of a fourth class of API's (after polymorphs, solvates and salts of API's), that of pharmaceutical co-crystals. Co-crystallization offers an option that has enormous potential to provide new, stable structures that may improve the properties of an API's. According to Almarsson and Zaworotko pharmaceutical co-crystal is *''a crystalline*

material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point and heats of fusion''. Pharmaceutical co-crystals have the potential to be much more useful in pharmaceutical products than solvates or hydrates. In contrast to solvates, most co-crystal formers are unlikely to evaporate from solid dosage forms, making phase separation less likely. The strategies for the preparation of pharmaceutical co-crystals include melt-crystallization, grinding, high-throughput crystallization screening and recrystallization from solvents.[58,59]

In this process, the principles of crystal engineering were used to the realm of pharmaceutical molecules by forming novel compositions of ibuprofen, **28**, flurbiprofen, **29**, and aspirin, **30**, with 4,4'-bipyridine, ***bpy***, and the molecular recognition is shown in the Figure 1.13. It was suggested that the nature of the non-pharmaceutical component (in the above mentioned case – ***bpy***) can dramatically affect crystal packing and hence the physical properties, such as melting point, etc. Also, the concept of pharmaceutical co-crystals could have broader implications for the formulation of API's since control of composition can, in appropriate circumstances, be regarded as being addressable via a supramolecular retrosynthetic approach.



28 **29** **30**

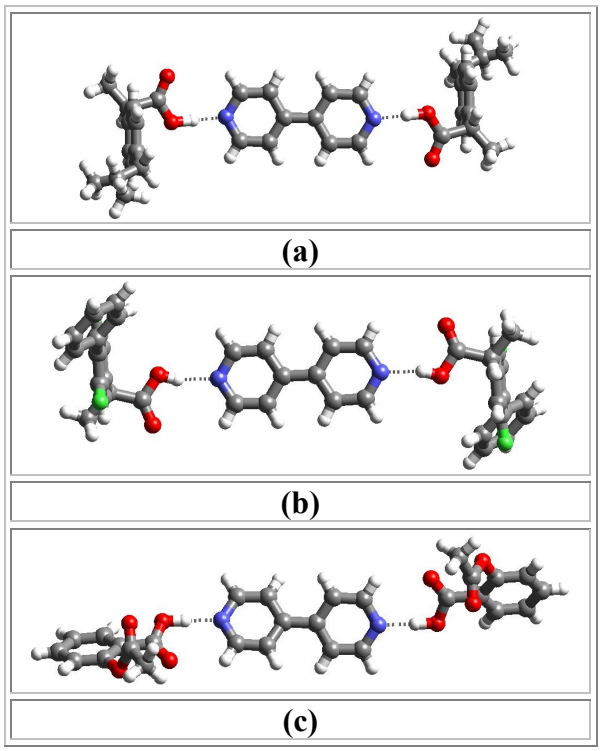
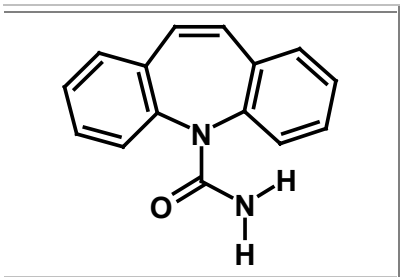


Figure 1.13: Molecular recognition pattern of (a) **28** : ***bpy***, (b) **29** : ***bpy*** and (c) **30** : ***bpy***.

Further, an outstanding example in this direction is the co-crystallization studies on carbamazepine, **31**, an analgesic and anticonvulsant with known problems related to solubility and polymorphism, in which 13 new crystalline phases of **31** were identified.[60]



31

The experiments include the selection of complementary hydrogen-bond functionalities and the utilization of supramolecular motifs. The first strategy exploits the

exofunctional nature of the carboxamide dimer of **31** as either a hydrogen bond donor or a hydrogen bond acceptor, whereas, the second strategy perturbs the carboxamide homomeric interactions by forming a heteromeric interaction between the carboxamide moiety of the **31** and the carboxylic acid moieties of other substrates used in the co-crystallization studies. The second concept profoundly modifies the crystal packing and thus could affect the physical and pharmaceutical properties of **31**. Thus, the supramolecular synthesis concept has the ability to generate a diverse range of multiple-component crystalline solids that offers new compositions of a matter and the systematic analysis of the factors that control structure-function relationships in the solid state. This approach represents a complementary strategy to the use of techniques such as high throughput crystallization[61] and polymer nucleation[62] and utilizaion of self-assembled monolayers for the control of polymorphs.[63] It offers a much wider range of possible pharmaceutical compositions without the need for covalent modifications of API's.

The recent advancements towards the synthesis of multiple component pharmaceutical phases, so called pharmaceutical co-crystals that afford new intellectual property and enhanced properties for pharmaceutical ingredients, are the focus of the research themes in the contemporary supramolecular chemistry. Thus, the challenges of pharmaceutical research and development provide a unique opportunity to demonstrate the power and utility of supramolecular chemistry and noncovalent synthesis to solve real-world problems. Thus, preparation of molecular complexes of salicylic acid is discussed in chapter four.

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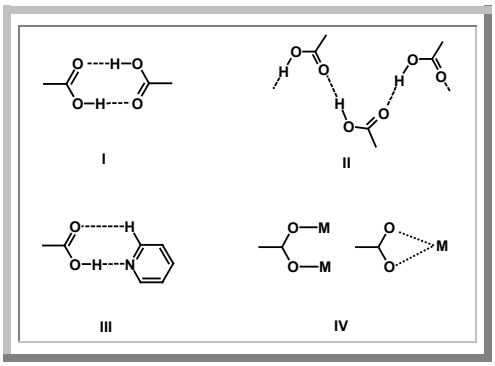
CHAPTER TWO

NONCOVALENT SYNTHESIS AND RATIONAL ANALYSIS OF SUPRAMOLECULAR ASSEMBLIES OF AROMATIC POLYCARBOXYLIC ACIDS

2.1 INTRODUCTION

Open network structures, in particular, formed by organic compounds, are of challenging for a variety of fundamental and practical issues.[1] Among many properties the abilities to accommodate guest molecules, to separate small molecules based on size exclusion or chemical affinity, or to provide tailored environments to be used in chemical sensor development is of special interest in the developments of contemporary structural chemistry.[2-3] The building blocks, which are assembled in these networks, give rise to porous host lattice and shows control at the molecular level. The host network may be formed by large molecules like crown ethers, calixarenes or cyclodextrins, or assemblies of small molecules forming a host lattice with the formation of ionic bonds, hydrogen bonds, etc.,[4-7] as illustrated in chapter one. Within the broad range of organic porous lattices, channel-type inclusion host architectures are attractive because they provide a one-dimensional environment to probe a specific phenomenon or to manifest a particular property. The strategies adopted for the synthesis of host frameworks are based on a placement of appropriate functional groups on a molecular skeleton that optimizes their chemical and topological complementarity. Thus, in a broader sense, it can be suggested that, supramolecular synthesis of organic ensembles employing two or more components is a two step process, formation of a supermolecule between the constituents through the recognition of the complementary functional groups followed by self-assembly or packing of the supermolecules in the three-dimensional space.[8]

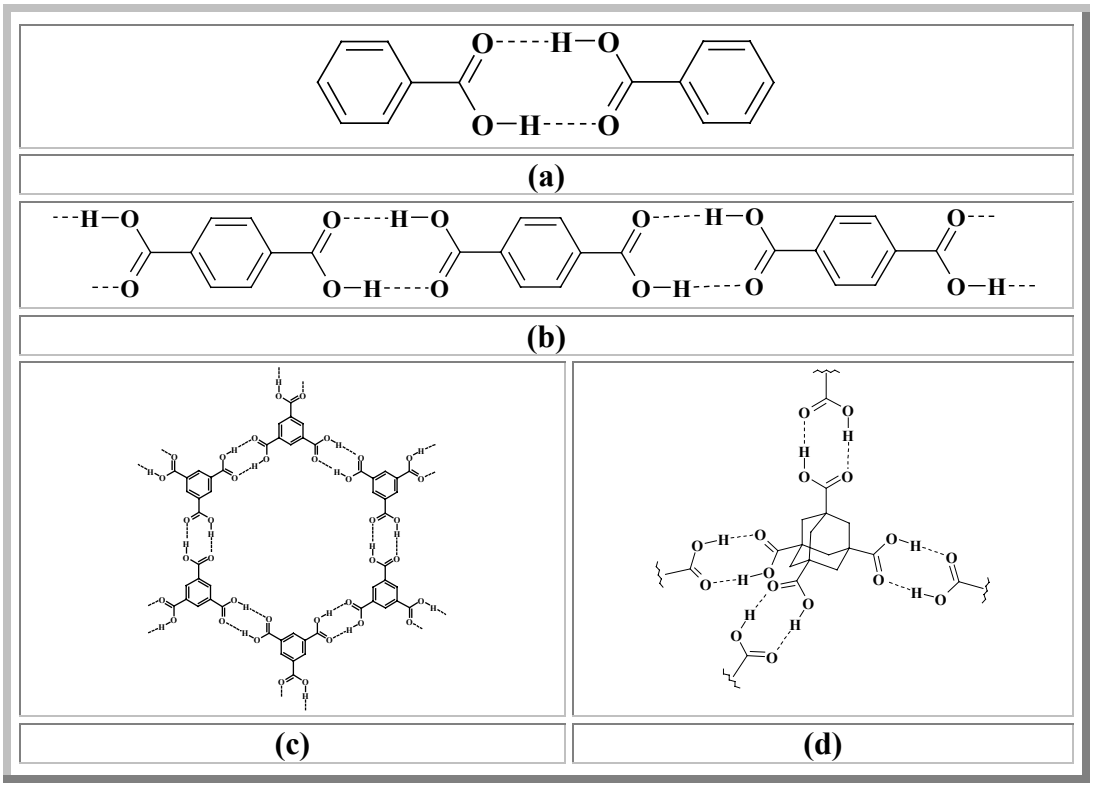
In this respect, carboxylic acid moieties represent perhaps the most widely studied functional group in terms of understanding the hydrogen bonding in both solution and the solid state. In the context of crystal structures, carboxylic acids exhibit a remarkable range of diversity, as there are two primary modes for carboxylic acids to self-organize, the dimer and the catemer. Further it can also interact with several aza compounds forming either O-H···N or O-H···N/C-H···O pairwise hydrogen bonds, as well as dative bonds, through the carboxylate group, with different metal ions.[9-12] A schematic representation of some of these networks is shown in Scheme 2.1. The Cambridge Structural Database[13] analysis reveals that, around 5000 entries of crystal structures in which at least one carboxylic acid moiety is present, 1483 exhibit the dimer motif (29.86%) and only 226 exhibit the catemer motif (4.55%). An analysis of the remaining carboxylic acid containing crystal structures reveals that they form supramolecular structures that involve a carboxylic acid and a different functional group.



Scheme 2.1

The ability of –COOH moiety to yield different type of architectures by appropriately placing it in different position of benzene moiety is illustrated in Scheme

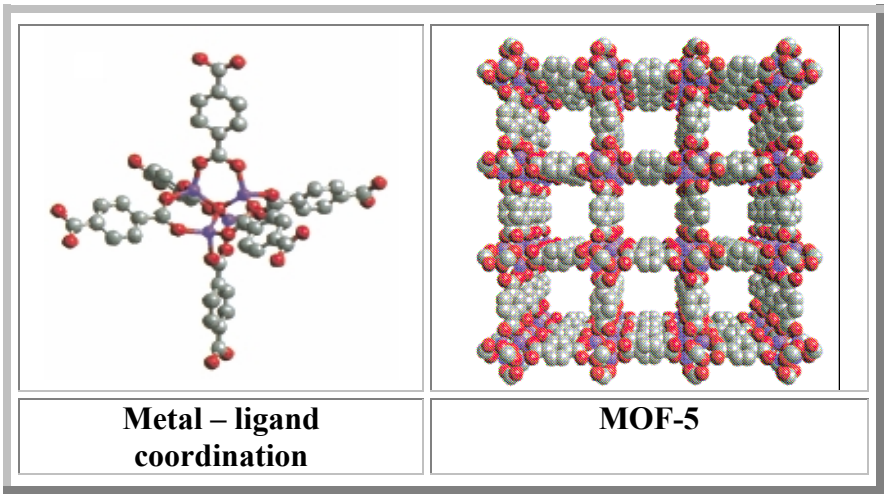
2.2. Thus, benzoic acid forms zero-dimensional units, terephthalic acid forms one-dimensional tapes, trimesic acid with its three fold symmetry forms a two-dimensional chicken wire network and adamantane tetracarboxylic acid with its tetrahedrally disposed carboxylic acid group forms a diamondoid network in three-dimension, utilizing the strength and directionality of –COOH group.[14]



Scheme 2.2: (a) Benzoic acid forms zero-dimensional carboxylic acid dimer. **(b)** Terephthalic acid forms one-dimensional tape. **(c)** Trimesic acid forms a two-dimensional honeycomb network structure with carboxylic acid dimer supramolecular motif. **(d)** Adamantane tetracarboxylic acid forms diamondoid network structure with robust carboxylic acid dimer motif.

In addition, demonstration of the robustness of carboxylate and metal bond for the creation of a myriad of channel structures employing –COOH moiety was also well documented in the literature.[11-12] For example, Yaghi et al. reported the synthesis of a

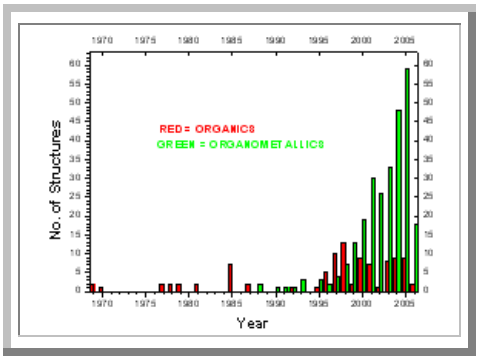
highly porous networks, the reaction of 1,4-dicarboxylic acid and zinc (II) nitrate gave a metal organic framework representated as **MOF-5** (see Scheme 2.3).[15]



Metal – ligand coordination	MOF-5

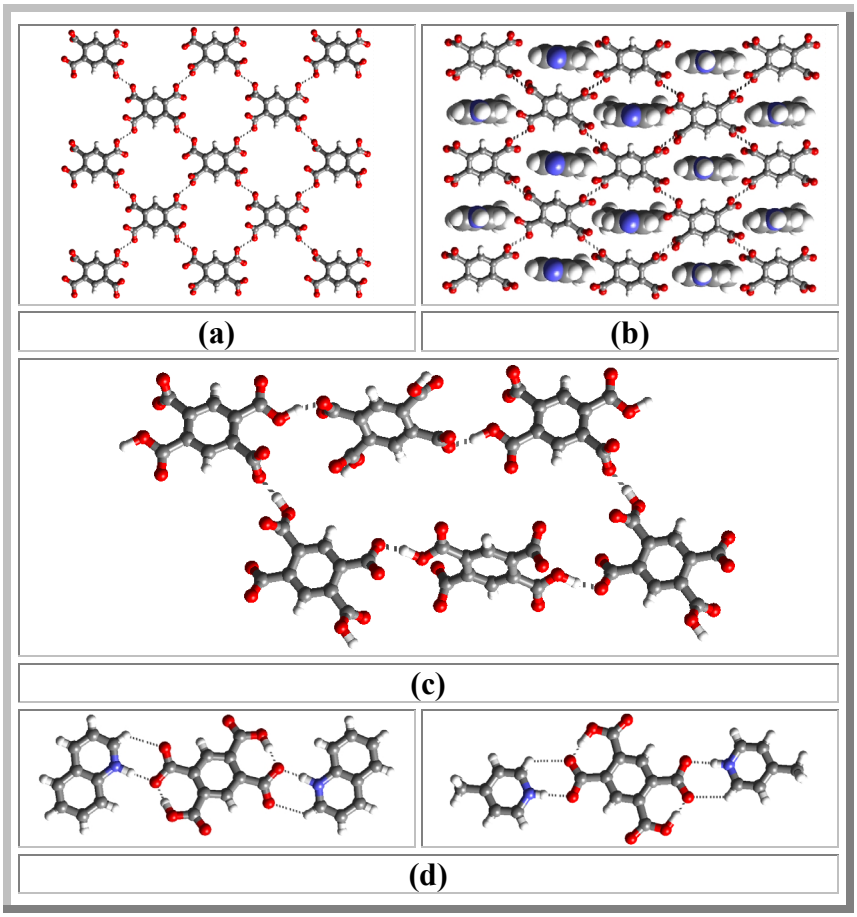
Scheme 2.3

However, it is observed from the literature that the studies utilizing carboxylic acid moiety of pure organic assemblies are very much limited as compared to the studies done with the metal salts. For instance, extensive study has been done so far with trimesic acid and metal salts as compared to the preparation of organic molecular complexes as it is shown in the Graph 2.1.



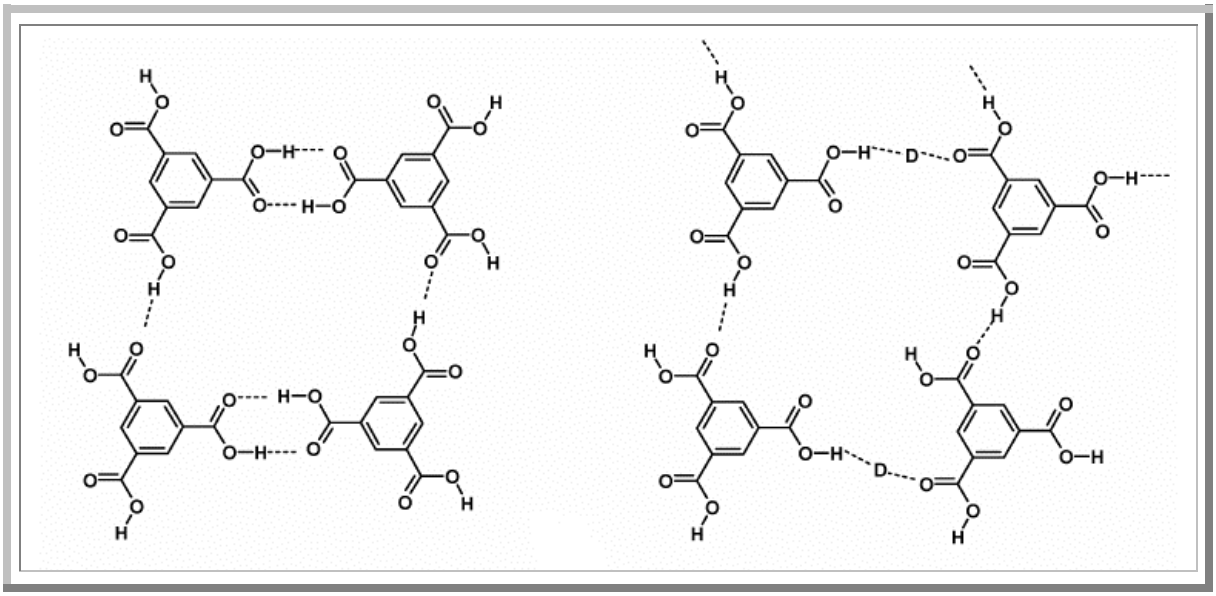
Graph 2.1

Similar is the case with other derivatives of benzene tricarboxylic acids such as 1,2,3-benzenetricarboxylic acid and 1,2,4-benzenetricarboxylic acid and benzene tetracarboxylic acid such as 1,2,4,5-benzenetetracarboxylic acid. Regarding benzene tetracarboxylic acid among the known structures, cyclic network mediated supramolecular assemblies of the tetracarboxylic acid, with pyridine and some of its derivatives are quite significant. (Scheme 2.4)[16]



Scheme 2.4: (a) The 2D square grid of acid molecules sustained by O-H···O⁻ hydrogen bonds in the molecular complex of tetracarboxylic acid and 3-methylpyridine. **(b)** Inclusion complex formed with 3-methylpyridine. **(c)** A cavity formed in the molecular complex with 2,3,5-trimethylpyridine. **(d)** Molecular recognition with (left) quinolinium ion (right) 4-aminopyridinium ion.

Also, looking at the geometries obtained by trimesic acid involving simple molecules such as methanol to a long-chain molecule like tetramethylethylenediamine, as square networks reported by Pedireddi et al. it is evident that the –COOH groups situated at *meta* position to each other are potential precursors for the synthesis of cyclic networks (see Scheme 2.5).[17] When this feature is taken into account and also the geometries noted in the supramolecular assemblies of the tetracarboxylic acid (though limited in number), it is apparent that the –COOH moiety can form robust cyclic networks. Hence, the synthesis of molecular complexes of benzene tetracarboxylic acid and benzene tricarboxylic acids with various aza-donor derivatives, utilizing the directional features of the hydrogen bonds formed by –COOH group present at different positions on the aromatic ring were carried out.



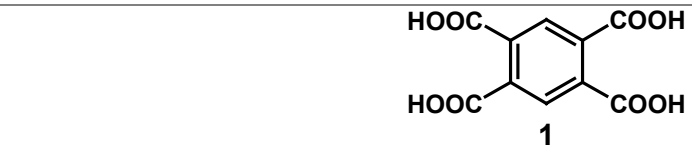
Scheme 2.5

In the present study the synthesis of molecular complexes of benzene tetracarboxylic acid (1,2,4,5-benzenetetracarboxylic acid) and isomers of benzene

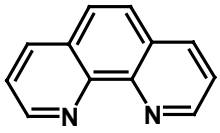
tricarboxylic acids (1,3,5-, 1,2,3- and 1,2,4-benzenetricarboxylic acid) with various aza derivatives are reported. The molecular complexes are divided into two sections (A) the complexes obtained by benzene tetracarboxylic acid and (B) the complexes of benzene tricarboxylic acid isomers. Structure determination of all the complexes in both the sections reveals several common features as well as distinctly unique features.

PART A: MOLECULAR COMPLEXES OF 1,2,4,5-BENZENETETRACARBOXYLIC ACID, 1

Co-crystallization of 1,2,4,5-benzenetetracarboxylic acid, **1**, with aza-donor compounds such as 1,10-phenanthroline, ***110phe***, 1,7-phenanthroline, ***17phe***, 4,7-phenanthroline, ***47phe***, phenazine, ***phnz***, 4-(*N*,*N*-dimethylamino)pyridine, ***dmap***, 1,2-*bis*(4-pyridyl)ethene, ***bpyee*** and 1,2-*bis*(4-pyridyl)ethane, ***bpyea***, yielded good quality single crystals of molecular complexes **1a - 1g**, respectively, from either methanol or dimethyl sulfoxide (DMSO) as the case may be. In addition, compound ***17phe*** forms a hydrate structure also, **1b.H_2O,** upon crystallization from water. The resulting complexes are labeled as given in Chart 2.1. The complexes are divided into two categories with respect to the arrangement of the molecules in three dimensions, host-guest complexes and planar sheet structures.

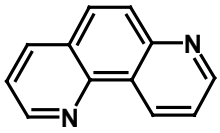


1



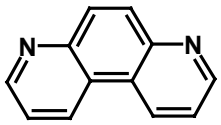
1,10-phenanthroline

110phe



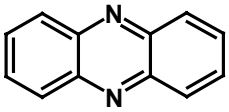
1,7-phenanthroline

17phe



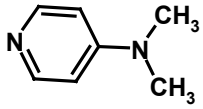
4,7-phenanthroline

47phe



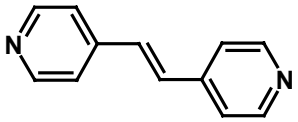
phenazine

phnz



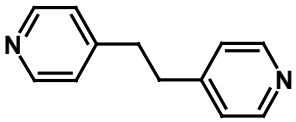
4-(N,N-dimethylamino) pyridine

dmap



1,2-*bis*(4-pyridyl)ethene

bpyee



1,2-*bis*(4-pyridyl)ethane

bpyea

Reactants	Solvent of Crystallization	Molecular complexes	Composition (including solvent molecules)
1 + ***110phe***	Methanol or water	**1a**	1:1:1
1 + ***17phe***	Methanol	**1b**	1:2
1 + ***17phe***	Water	**1b.H_2O**	1:1:2
1 + ***47phe***	Methanol or water	**1c**	1:2
1 + ***phnz***	Methanol or water	**1d**	1:2:4
1 + ***dmap***	Methanol or water	**1e**	2:2
1 + ***bpyee***	Dimethylsulfoxide or water	**1f**	1:1
1 + ***bpyea***	Dimethylsulfoxide or water	**1g**	1:1

Chart 2.1: Molecular structures and designations of compounds and complexes.

2.2 MOLECULAR COMPLEXES OF 1 FORMING HOST-GUEST NETWORKS AND STAIRCASE ARRANGEMENTS

2.2.1 MOLECULAR COMPLEX OF ACID 1 AND 1,10-PHENANTHROLINE, 1a

Crystallization of acid **1** with 1,10-phenanthroline, ***110phe***, from a methanol solution gave block-like colorless crystals, suitable for x-ray diffraction studies. The structure determination reveals that the acid **1** forms a hydrated molecular complex, **1a** with ***110phe***, with the constituents in the asymmetric unit being in a 1:1:1 ratio of the reactants. The ORTEP diagram is shown in Figure 2.1. The complete crystallographic details are given in Table 2.1.

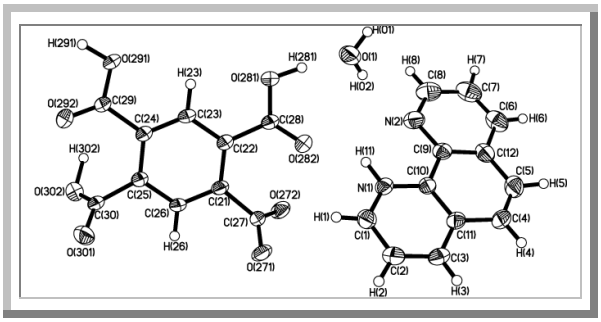


Figure 2.1: ORTEP (50% probability level) drawing of the molecular complex **1a.**

The structure analysis reveals that one of the four carbonyl groups is converted to a carboxylate. These molecules are then arranged in such a manner that adjacent acid molecules constitute chains through O-H···O$^-$ hydrogen bonds (H···O, 1.68 Å). The other characteristics of the hydrogen bonds are given in Table 2.2. In the two-dimensional arrangement, water molecules hold these chains together by forming O-H···O hydrogen bonds (H···O, 1.55 and 1.87 Å; Table 2.2) leading to the formation of a closed network, with cavities of 9 x 12 Å^2 in dimension, as shown in Figure 2.2.

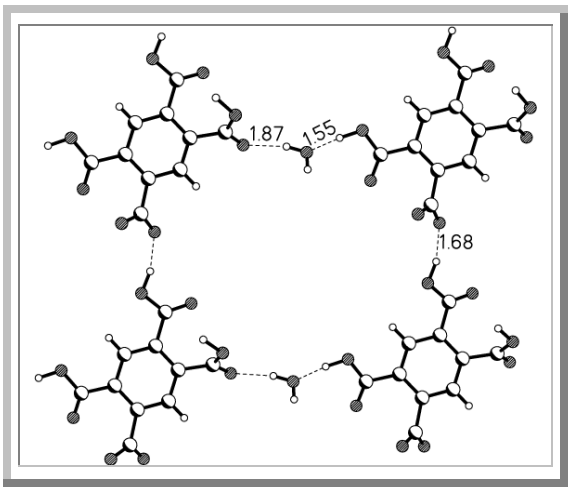


Figure 2.2: Cavity (9 x 12 $Å^2$) formed by the acid, **1,** molecules in two-dimensional arrangement in complex **1a**.

The molecules of ***110phe*** fill these cavities (see Figure 2.3). In fact, the phenanthroline molecules are not in the plane of the acid layers, but protrude through the cavity as shown in the inset of Figure 2.3.

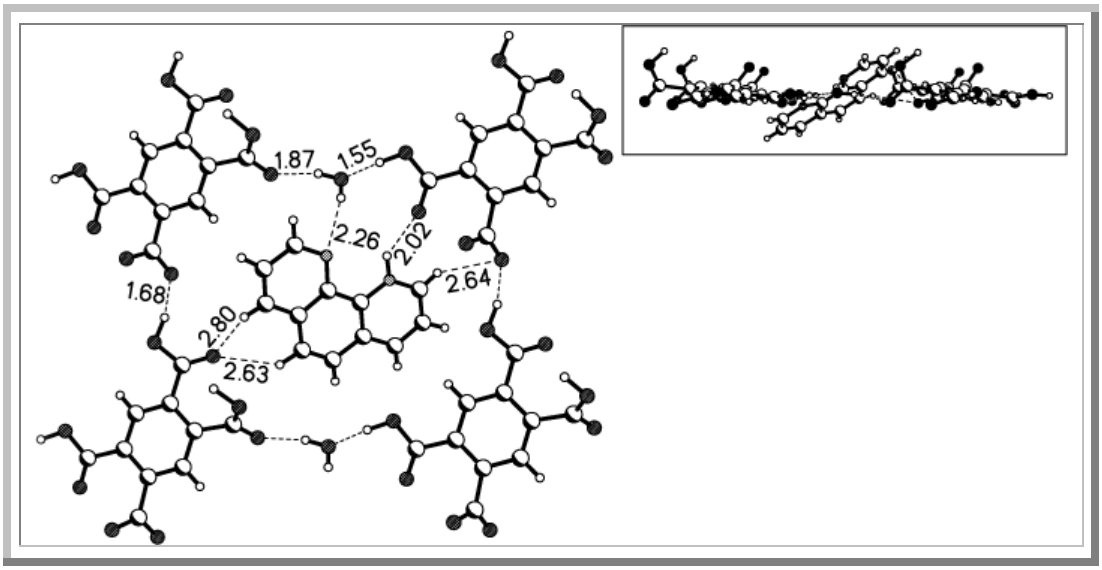


Figure 2.3: ***110phe*** molecule occupying the cavity formed by acid **1**. (actual orientation of ***110phe*** molecule is shown in the inset).

In the three-dimensional arrangement, the layers are stacked such that the cavities align to yield channels as shown in Figure 2.4(a). Phenanthroline molecules, which lie in the channels, are removed for the purpose of clarity. Further, the stacking of the sheets is quite interesting as each of the two adjacent layers, with an interlayer distance of 3.88 Å, connected by catemeric O-H···O hydrogen bonds (H···O, 1.22 Å; Table 2.2), constitute bilayers. These bilayers stack with a separation distance of 4.13 Å as shown in Figure 2.4(b).

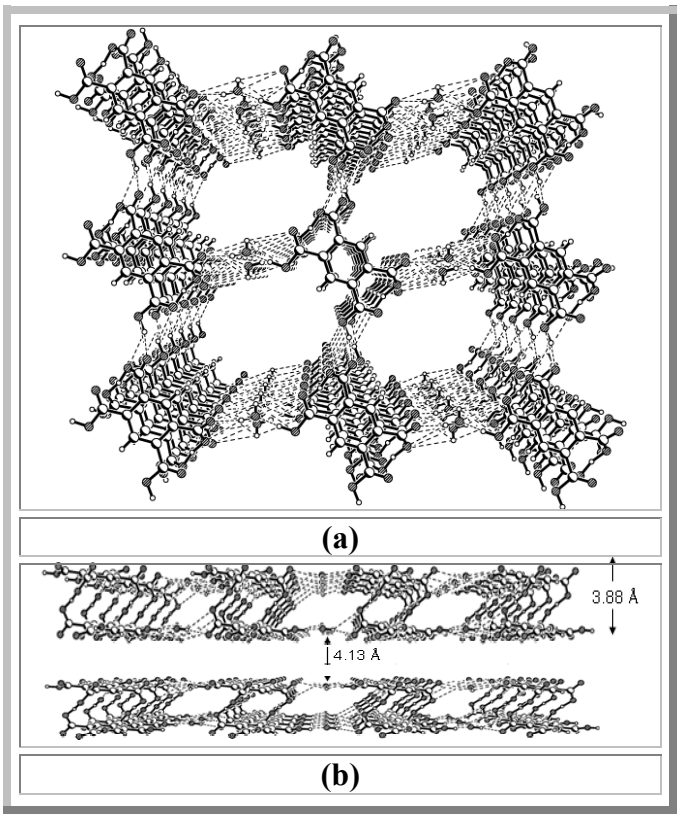


Figure 2.4: (a) Channels in three-dimensional arrangement in complex **1a**. **(b)** Representation of bilayers and their stacking in complex **1a**.

To rationalize, further, the guest inclusion in the host-network of **1,** other aza-donor molecules having similar dimension of ***110phe***, were chosen to co-crystallize

with acid **1**. Thus, complexes **1b-1d** were obtained with 1,7-phenanthroline, ***17phe***, 4,7-phenanthroline, ***47phe***, and phenazine, ***phnz***, respectively.

2.2.2 MOLECULAR COMPLEXES OF ACID 1 AND 1,7-PHENANTHROLINE, 1b AND 1b.H_2O

Co-crystallization of 1,7-phenanthroline, ***17phe***, and acid **1** from a methanol solution gave a complex, **1b**, in a 1:1 ratio as shown in Figure 2.5.

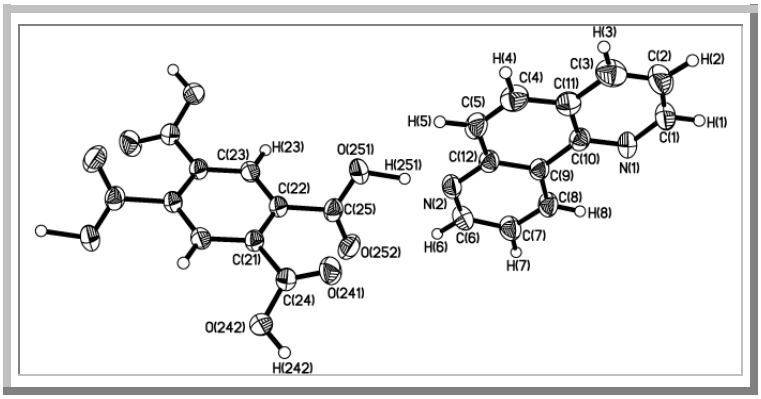


Figure 2.5: ORTEP (50% probability level) drawing of the molecular complex **1b** of acid **1** and ***17phe***.

The two reactants primarily recognize each other through the formation of O-H···N and C-H···O pairwise hydrogen bonds and bifurcated C-H···O hydrogen bonds (Table 2.2) as shown in the Figure 2.6, forming a cyclic assembly. The H···O and H···N distances, respectively, in this assembly are 2.66 and 1.30 Å in the pairwise hydrogen bond pattern and 2.69 and 2.74 Å in the bifurcated pattern. This kind of assembly, indeed, is known to exist in the complexes of various carboxylic acids especially with spacer ligands, like 4,4'-bipyridyl, as shown in Figure 2.7(a).[18] For example, the

molecular complex of acid **1** and 4,4'-bipyridyl (see Figure 2.7(b)) shows a close relation to the pattern observed in the complex **1b**.[19]

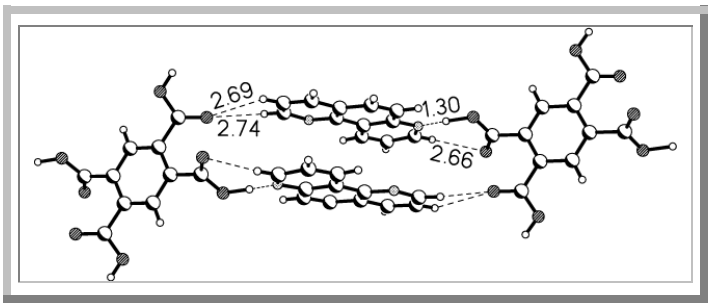


Figure 2.6: Molecular recognition pattern between acid **1** and 1,7-phenanthroline molecules.

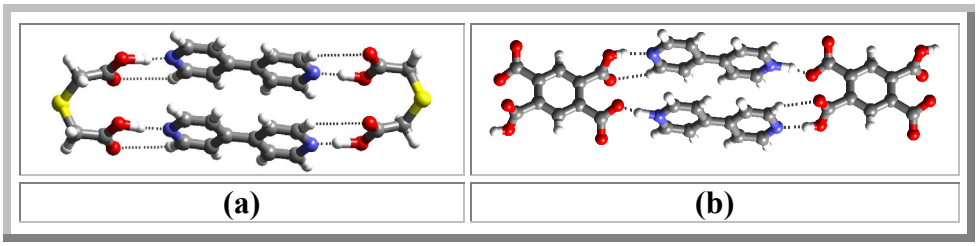


Figure 2.7: Molecular recognition pattern between **(a)** Thiodiglycolic acid with 4,4'-bipyridyl and **(b) 1** with 4,4'-bipyridyl.

Complex **1b**, however, is unique in the three-dimensional arrangement, forming a novel staircase type structure as shown in Figure 2.8(a). Within this ensemble, the acid molecules are connected with the adjacent molecules by O-H···O hydrogen bonds (H···O, 1.66 Å; Table 2.2) formed between the -COOH groups positioned *ortho* to each other as shown in the Figure 2.8(b). Such linear acid chains are further linked together by phenanthroline molecules in a stepwise manner such that adjacent molecules of ***17phe*** are separated by two types of distances 3.77 and 2.56 Å, alternately.

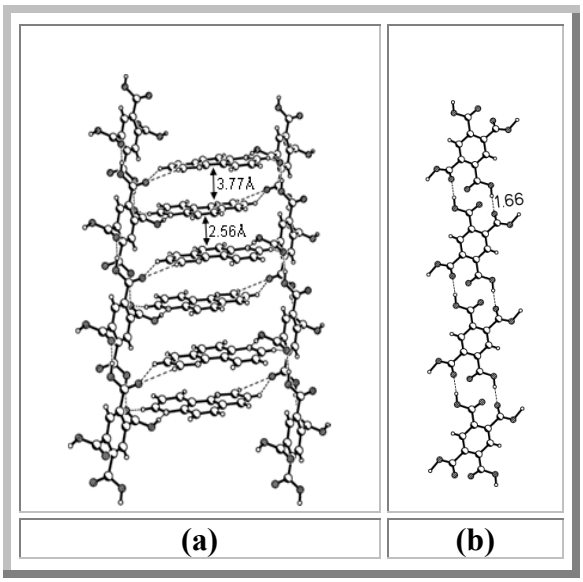


Figure 2.8: (a) Staircase structure observed in the molecular complex **1b**. **(b)** Interaction among the acid molecules, forming the pillars of the staircase.

It is interesting, however, to note that, although complexes **1a** and **1b** were crystallized from CH_3OH, the later one did not absorb water from atmosphere. Indeed, the water molecules played a crucial role in the formation of channel structure in the complex **1a**. In the case of **1b**, though a novel staircase structure was obtained, it is still interesting to explore whether a channel structure could be synthesized between the acid **1** and ***17phe***. For this purpose, a deliberate co-crystallization of acid **1** and ***17phe*** from water was carried out to obtain a complex, **1b.H_2O**. The single crystals of **1b.H_2O** obtained from water gave an entirely different unit cell, suggesting, at least, a different packing arrangement between acid **1** and ***17phe***. However, the structure determination revealed that, in fact, two molecules of water (solvent of crystallization) are present in the asymmetric unit, with other constituents in a 1:1 ratio. The ORTEP diagram of complex **1b.H_2O** is shown in Figure 2.9 and it is evident that one of the -COOH groups is deprotonated unlike in the complex **1b** and akin to complex **1a**.

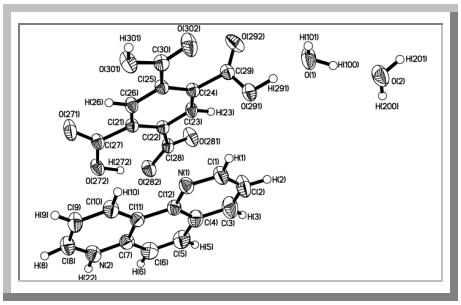


Figure 2.9: ORTEP (50% probability level) drawing of the molecular complex, **1b.H_2O,** of acid **1** and ***17phe*** with water.

Further, complex **1b.H_2O** distinctly differs from the complexes **1a** and **1b** with respect to the conformation of acid molecules. The acid molecules in **1b.H_2O** form an intramolecular hydrogen bonding (Table 2.2) between one pair of –COOH groups situated at *ortho* position to each other. The structural analysis reveals that the complex **1b.H_2O** also adopts a similar arrangement that was noted in complex **1a** by forming a chain of molecules of acid **1,** connected together by O-H···O^- hydrogen bonds, with an H···O distance of 1.59 Å (see Figure 2.10(a)), which are further held together by water molecules, forming a network with larger cavities (7 x 13 $Å^2$), and these cavities are occupied by phenanthroline molecules, as shown in Figure 2.10(b). These two-dimensional sheets align to form channels in the three-dimensional arrangement as shown in Figure 2.10(c). Thus, it appears that water molecules play a crucial role in the formation of channel structures in the supramolecular assemblies of acid **1**. In the complex **1a**, while one water molecule is holding the chains, in the complex **1b.H_2O**, two water molecules, which are interconnected to each other by O-H···O hydrogen bonds (H···O, 1.74 Å; Table 2.2), join the adjacent chains of acid **1**. It is also interesting to note that ***17phe*** molecules interact with the host lattice through O-H···N hydrogen bonds formed by water molecules rather than by –COOH groups, being another distinct

difference between the complexes **1a** and **1b.H_2O**. Also, in contrast to **1a**, molecules of ***17phe*** were found to be coplanar with the layers of acid molecules as shown in Figure 2.10(d).

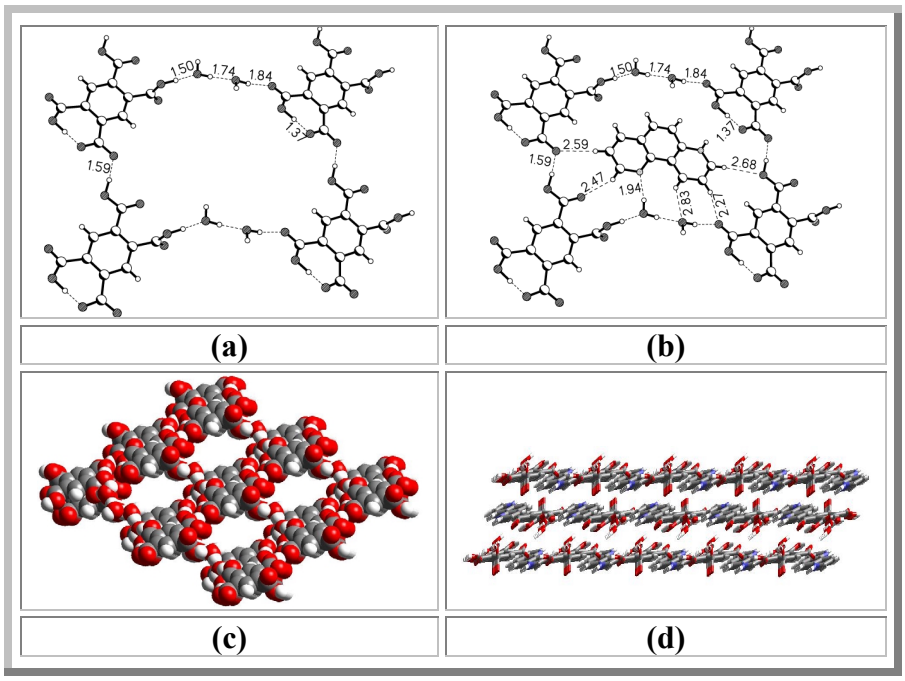


Figure 2.10: Recognition and packing of molecules in the crystal structure of molecular complex, **1b.H_2O**. **(a)** Cavity (7 x 13 $Å^2$) created by the acid molecules along with water molecules. **(b)** Occupation of the cavity by ***17phe*** molecule in the two-dimensional arrangement. **(c)** Channels noted in the three-dimensional arrangement. **(d)** Planar geometry of the sheets with both the acid and ***17phe*** molecules remains coplanar with each other.

2.2.3 MOLECULAR COMPLEX OF ACID 1 AND 4,7-PHENANTHROLINE, 1c

Acid **1** and 4,7-phenanthroline, ***47phe***, form a 1:2 complex without any solvent molecule in the asymmetric unit irrespective of the solvent employed for co-crystallization. The ORTEP diagram is as shown in the Figure 2.11. The complete crystallographic details are given in Table 2.1.

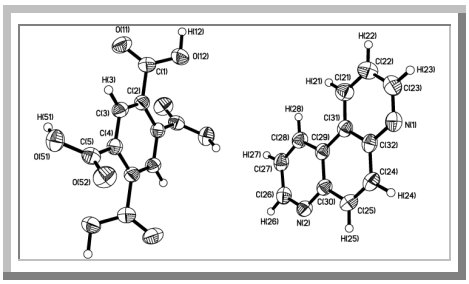


Figure 2.11: ORTEP (50% probability level) drawing of the molecular complex, **1c**, of acid **1** and ***47phe***.

The two reactants primarily recognize each other through O-H···N hydrogen bonds (H···N, 1.54 Å and 1.64 Å, Table 2.2) formed between the hydroxyl group of the acid, **1** and the pyridyl nitrogen of the ***47phe*** as shown in the Figure 2.12.

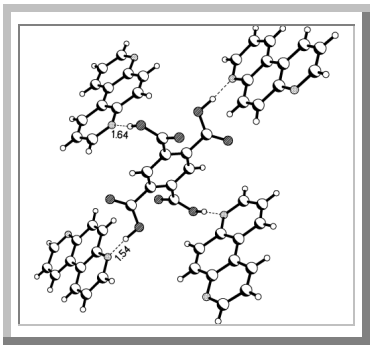


Figure 2.12: Molecular recognition between acid **1** and ***47phe*** molecules in complex **1c**.

The structural analysis reveals that none of the –COOH groups of the acid, **1**, are deprotonated and also complex **1c** has a close resemblance with complex **1b**, as both are forming staircase type structure in two-dimensions (see Figure 2.13 (a)). However in complex **1c**, the acid molecules are connected with the adjacent molecules by C-H···O hydrogen bonds (H···O, 2.73 Å, Table 2.2) forming a linear chain of acid molecules as compared to the complex **1b**, while the acid chain is formed through O-H···O hydrogen bonds (see Figure 2.8(b)). Further, alike complex **1b**, such linear acid chains are linked

together by ***47phe*** molecules in a stepwise manner forming a staircase type structure. Also, this staircase further extends in two-dimension to form a sheet structure and in three-dimension these sheets stack to form a planar sheet structure, as shown in the Figure 2.13 (b).

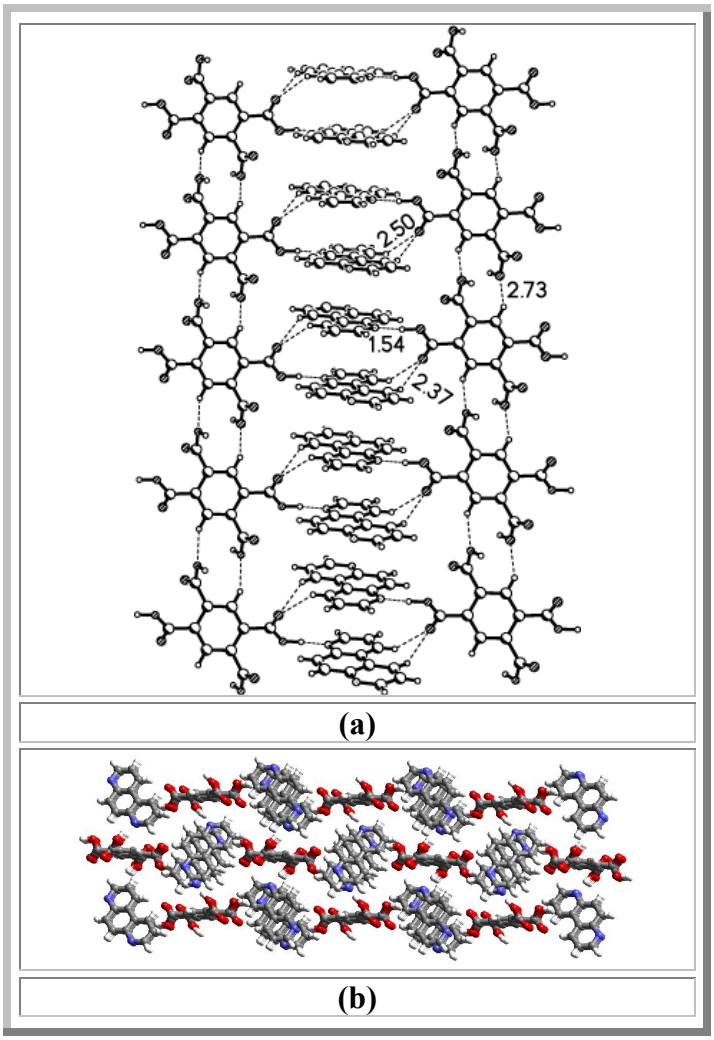


Figure 2.13: (a) Two-dimensional staircase arrangement formed in complex **1c**. **(b)** Three-dimensional sheet structure of complex **1c**.

2.2.4 MOLECULAR COMPLEX OF ACID 1 AND PHENAZINE, 1d

Acid, **1** and phenazine, ***phnz*,** form 1:2 complex, **1d**, along with four molecules of water in the asymmetric unit, irrespective of solvent employed for crystallization. The ORTEP diagram is as shown in the Figure 2.14.

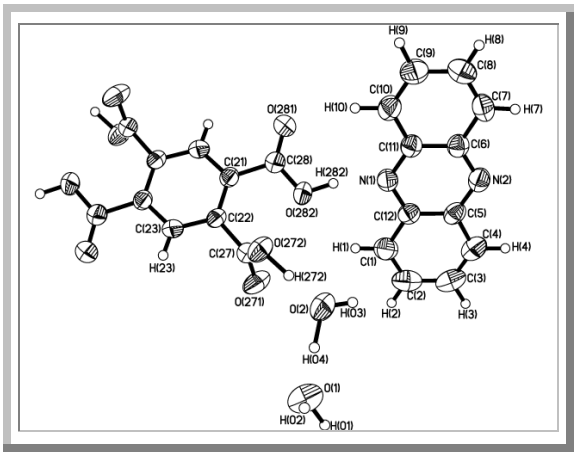


Figure 2.14: ORTEP (50% probability level) drawing of the molecular complex, **1d**, of acid **1** and ***phnz***.

In this complex, in contrast to the molecular complexes **1a** and **1b.H_2O**, none of the carboxylic acid moieties of **1** are deprotonated and it is somewhat similar to the complex **1b** and **1c**. The molecular interactions and their characteristics among the constituents are shown in Figure 2.15(a) and Table 2.2, respectively. It is interesting to note that each acid molecule interacts with two phenazine molecules through the formation of O-H···N and C-H···O pairwise hydrogen bonds (H···N, 1.68 Å and H···O, 2.54 Å, respectively). Such adjacent supermolecules further join together through two water molecules forming O-H···N and C-H···O hydrogen bonds (H···N, 1.99 and H···O, 2.61 Å, respectively) leading to the formation of infinite tapes. The two water molecules in the assembly are, in turn, coupled through O-H···O hydrogen bond with an H···O

distance of 1.48 Å and ultimately, these infinite tapes are arranged in two dimensions in such a manner that two types of void space are generated. One of these voids is occupied by two symmetry related water molecules, forming O-H···O hydrogen bonds (H···O, 1.82 and 1.93 Å; Table 2.2) with the free acid groups that are not participated in the interaction with phenazine molecules. However, the second cavity remains unoccupied in a two-dimensional arrangement, but it is being masked by the molecules from the adjacent layers in three-dimensional packing as shown in Figure 2.15(b). As a result, complex **1d** could not yield a channel structure like **1a** and **1b.H_2O**. In three-dimension the complex forms a planar sheet structure as shown in the Figure 2.15(c).

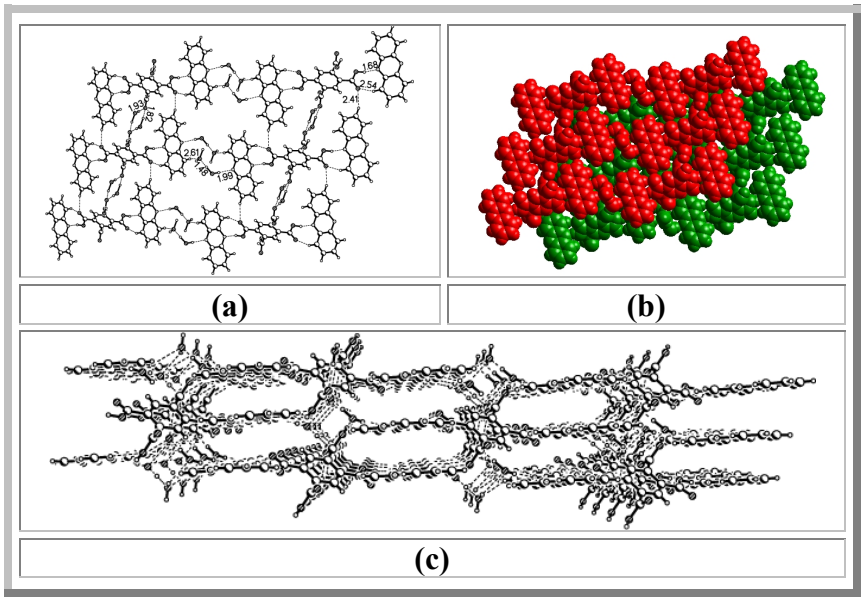


Figure 2.15: (a) Two-dimensional arrangement of molecules of acid **1** and ***phnz*** with two types of cavities, of which one is being filled by water molecules. **(b)** Stacking of two-dimensional sheets with the masking of vacant cavities by the molecules from the adjacent sheets.**(c)** Three-dimensional arrangement of complex **1d**.

To ascertain the formation of host-guest complexes by 1,2,4,5-benzenetetracarboxylic acid, the acid **1** was co-crystallized with other aza-donor

compounds of varying dimensions. For this purpose the molecules such as 4-(N,N-dimethylamino)pyridine, 2-aminopyridine, 3-aminopyridine, and 4-aminopyridine were selected to co-crystallize with acid **1**. All these reactions yielded precipitates, however, single crystals of a complex between acid **1** and 4-(*N*,*N*-dimethylamino)pyridine were isolated and characterized by single crystal x-ray diffraction technique and the structural characteristics are discussed in the following section.

2.2.5 MOLECULAR COMPLEX OF ACID 1 AND 4-(*N*,*N*-DIMETHYLAMINO)PYRIDINE, 1e

Crystal structure determination of complex **1e**, obtained between acid **1** and 4-(*N*,*N*-dimethylamino)pyridine, ***dmap***, reveals that it forms a 1:1 complex with two molecules of each in the asymmetric unit, upon co-crystallization from a CH_3OH solution. Structural analysis reveals that the symmetry independent acid molecules adopt different conformations. In one of the acids (B), all the four carboxylic acids are intact without deprotonation, but in the second acid molecule (A), two of the -COOH moieties were deprotonated and also form intramolecular hydrogen bonding (Table 2.2) between the *ortho* substituents (see Figure 2.16).

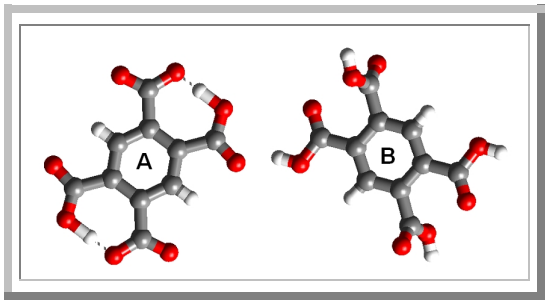


Figure 2.16: Different conformations of two acid molecules in the crystal structure of complex **1d**. (Molecules labeled A exhibit intramolecular hydrogen bonding).

It is noteworthy to mention that in the complexes **1a-1d** and **1b.H_2O,** the conformation of the acid molecules is unique by forming either intramolecular hydrogen bonding or intermolecular hydrogen bonding. Hence, complex **1e** with dual patterns could be considered as a bridge between the complexes possessing either of the types of hydrogen bonds. The recognition pattern between the acid **1** and pyridine, ***dmap***, is established through C-H···O hydrogen bonds (H···O, 2.70 and 2.79 Å; Table 2.2) formed between -$N(CH_3)_2$ and a keto group of acid moieties as shown in Figure 2.17.

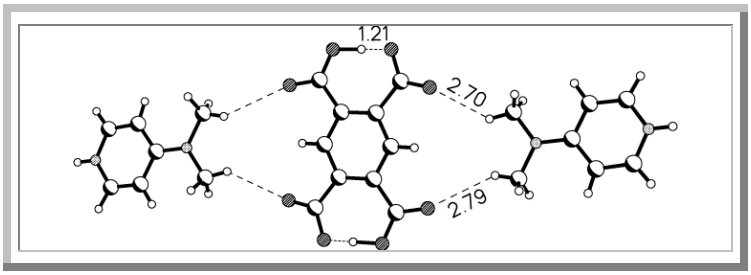


Figure 2.17: Recognition pattern between the acid, **1** and pyridine, ***dmap*,** in complex **1e**.

Further arrangement of the molecules in the molecular complex is shown in Figure 2.18. It is evident from Figure 2.18(a) that the two symmetry independent acid molecules do form a cyclic network with the aid of O-H···O and O-H···O^- hydrogen bonds (1.72 and 1.79Å, respectively) forming cavities of 7 x 11 $Å^2$ dimension which are being filled by the molecules of pyridine, ***dmap*,** as shown in Figure 2.18(b). The pyridine molecules interact with the host through a series of C-H···O hydrogen bonds (Table 2.2), and the H···O distances are in the range 2.61-2.78 Å. In the three-dimensional arrangement, the sheets are aligned to form channels as shown in Figure

2.18(c). Also, the pyridine molecules, ***dmap***, acting as a guest lie between the sheets as shown in the Figure 2.18(d).

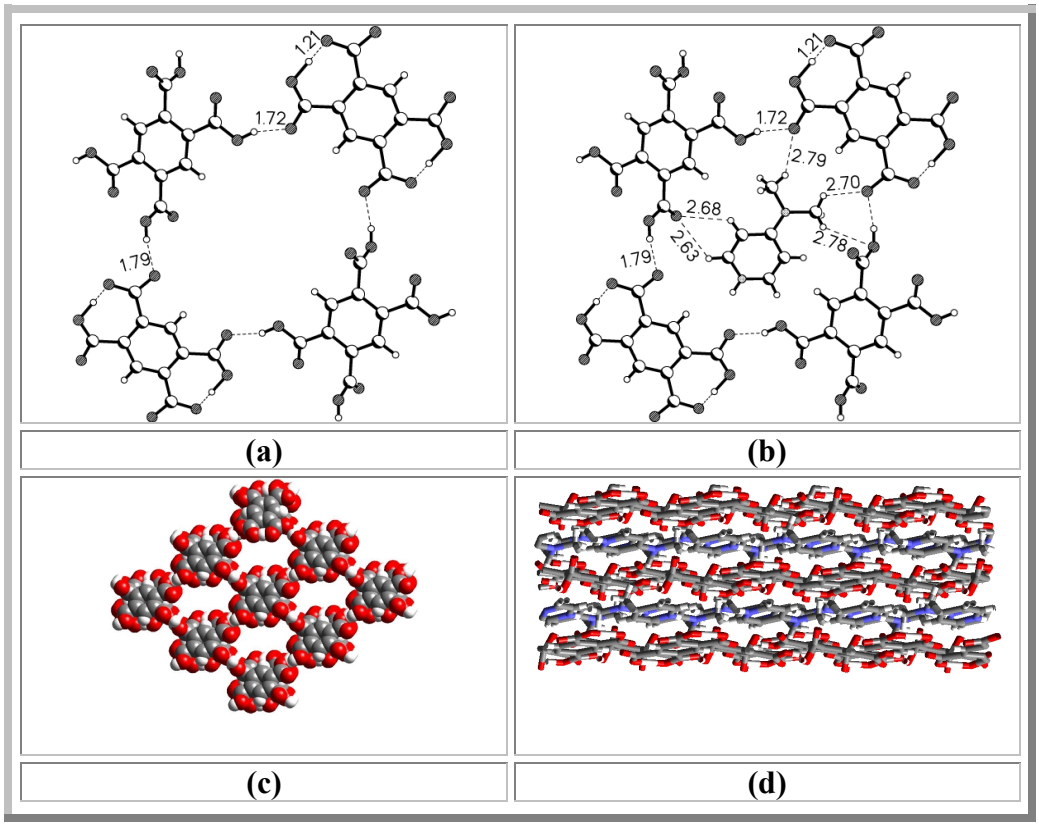


Figure 2.18: Assembly of molecules in the molecular complex **1e** **(a)** Formation of cavities (7 x 11 $Å^2$) by each of the four acid molecules connected together by O-H···O and O-H···O^- hydrogen bonds. **(b)** Arrangement of guest molecules, pyridine, ***dmap*****,** in the voids created by acid **1**. **(c)** Channels created in the three-dimensional arrangement by the stacking of layers of acid molecules (***dmap*** molecules in the channels are not shown). **(d)** Arrangement of sheets of acids separated by the molecules of ***dmap*** (the ***dmap*** molecules are not in the same plane of ensemble of acid molecules).

Further analysis of the guest inclusion phenomenon, to establish a relation between the dimension of the guest species and ability to yield host-guest complexes has been carried out using the larger aza-donor moieties such as 1,2-*bis*(4-

pyridyl)ethene and 1,2-*bis*(4-pyridyl)ethane as compared to the phenazine and phenanthrolines respectively.

2.3 MOLECULAR COMPLEXES OF ACID 1 FORMING PLANAR SHEETS

2.3.1 MOLECULAR COMPLEXES OF ACID 1 WITH 1,2-*BIS*(4-PYRIDYL)ETHENE AND 1,2-*BIS*(4-PYRIDYL)ETHANE, 1f AND 1g RESPECTIVELY

Complexes **1f** and **1g** were prepared by co-crystallization of acid **1** with 1,2-*bis*(4- pyridyl)ethene, ***bpyee***, and 1,2-*bis*(4-pyridyl)ethane, ***bpyea,*** respectively, from dimethyl sulfoxide (DMSO) solution. Both the complexes **1f** and **1g** are isomorphous, crystallizing in a 1:1 ratio, and are also in the same space group, $P\bar{1}$, with similar unit cell dimensions. The ORTEP diagrams for both the complexes are shown in the Figure 2.19.

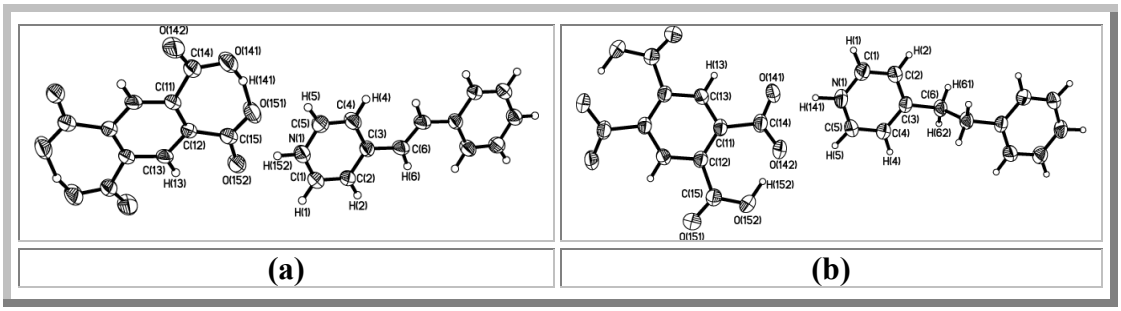


Figure 2.19: ORTEP (50% probability level) drawing of the molecular complexes **1f** and **1g** formed between **(a)** acid **1** with ***bpyee*** and **(b)** acid **1** with ***bpyea*** respectively.

Further, structural analysis reveals that complexes **1f** and **1g** are also *iso*-structural adopting identical packing arrangement both in two dimensions as well as in three dimensions. The arrangement of molecules is shown in Figures 2.20 and 2.21 for the

complexes **1f** and **1g**, respectively. Further, this arrangement is distinctly different from the molecular complex formed by acid **1** with 4,4'-bipyridyl,[19] an analogue of ***bpyee*** and ***bpyea***. Acid molecules in both the complexes exist in a deprotonated form with intramolecular hydrogen bonding (Table 2.2) between the adjacent *ortho* substituents. Further, the constituent reactants interact with each other forming N^{+}-H···O^{-} and C-H···O^{-} pairwise hydrogen bonds and constitute infinite tapes. These tapes are held together by C-H···O hydrogen bonds with H···O distances of 2.28 and 2.53 Å in the complex **1f** (Figure 2.20(a)) and by 2.46 and 2.69 Å in the complex **1g** (Figure 2.21(a)), in the two-dimensional arrangement. The planar sheets are stacked to yield a three-dimensional structure with C-H···O hydrogen bonds between the sheets as shown in Figures 2.20(b) and 2.21(b). The corresponding H···O distances are 2.51 Å (complex **1f**) and 2.42 and 2.71 Å (complex **1g**). Other characteristics of hydrogen bonds are given in Table 2.2.

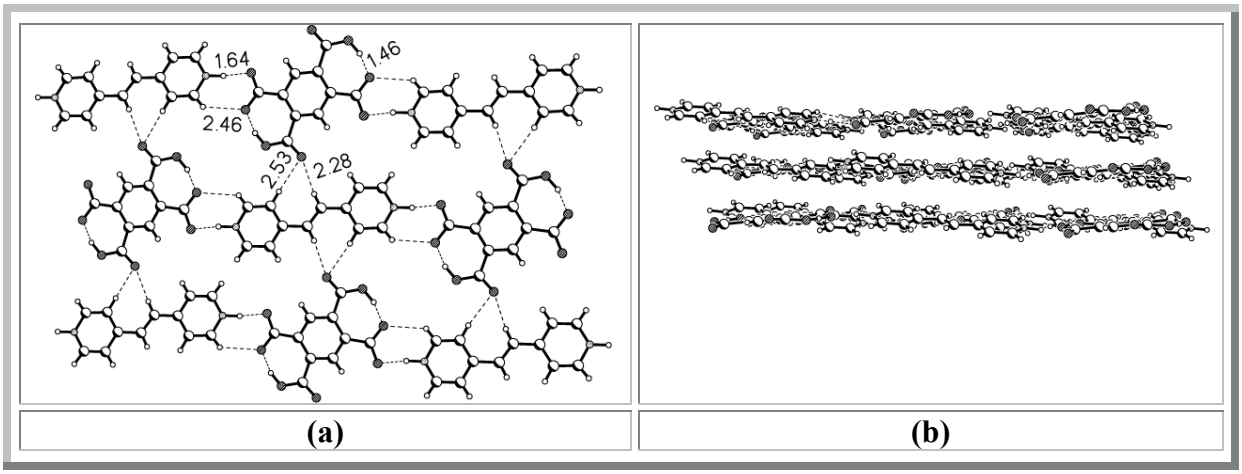


Figure 2.20: (a) Interaction between the molecules of acid **1** and ***bpyee*** in the molecular complex **1f**. Notice the formation of molecular tapes through pairwise hydrogen bonds. **(b)** Stacking of the planar sheets in three-dimensional arrangement of complex **1f**.

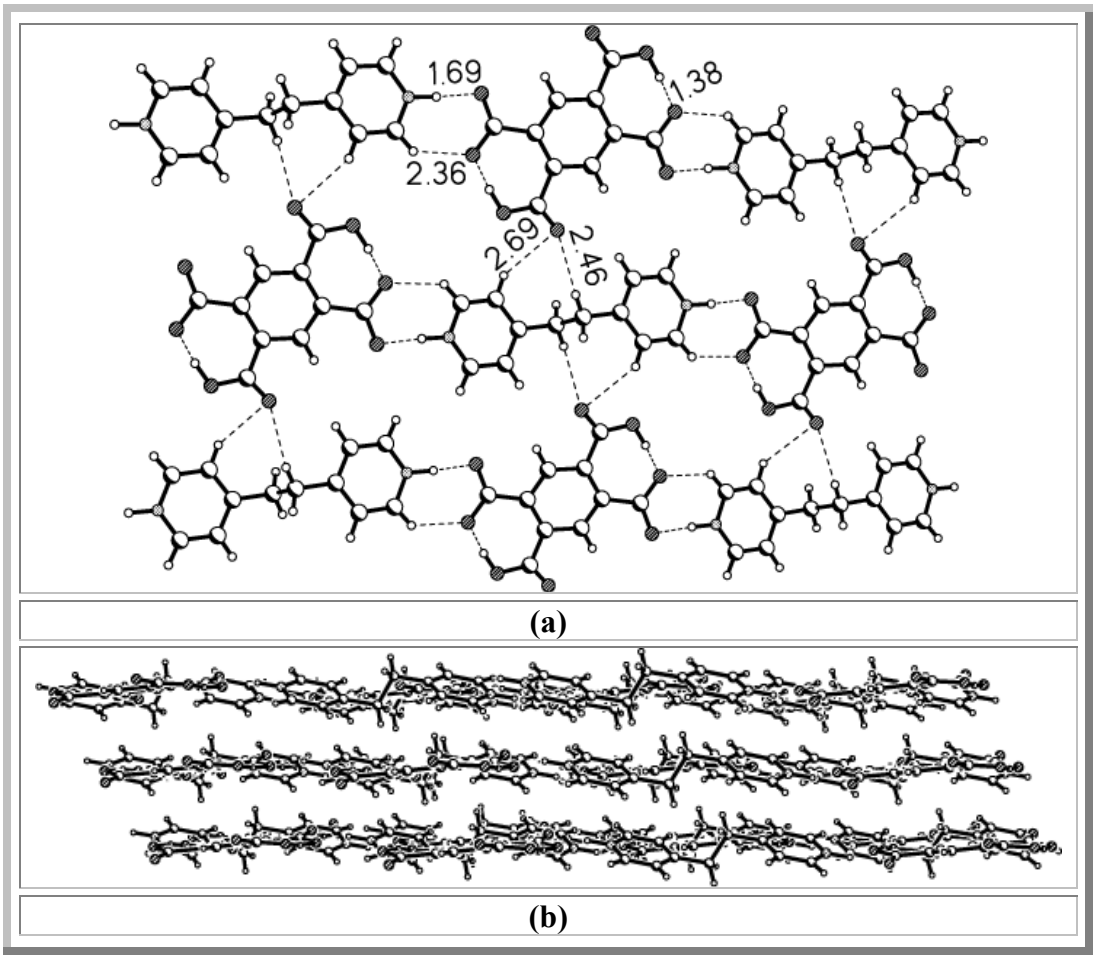


Figure 2.21: (a) Arrangement of acid 1 and *bpyea* in the molecular complex **1g** in two dimensions. Notice the formation of molecular tapes through pairwise hydrogen bonds as in **1f**. **(b)** Stacking of the planar sheets in three-dimensional arrangement of complex **1g**.

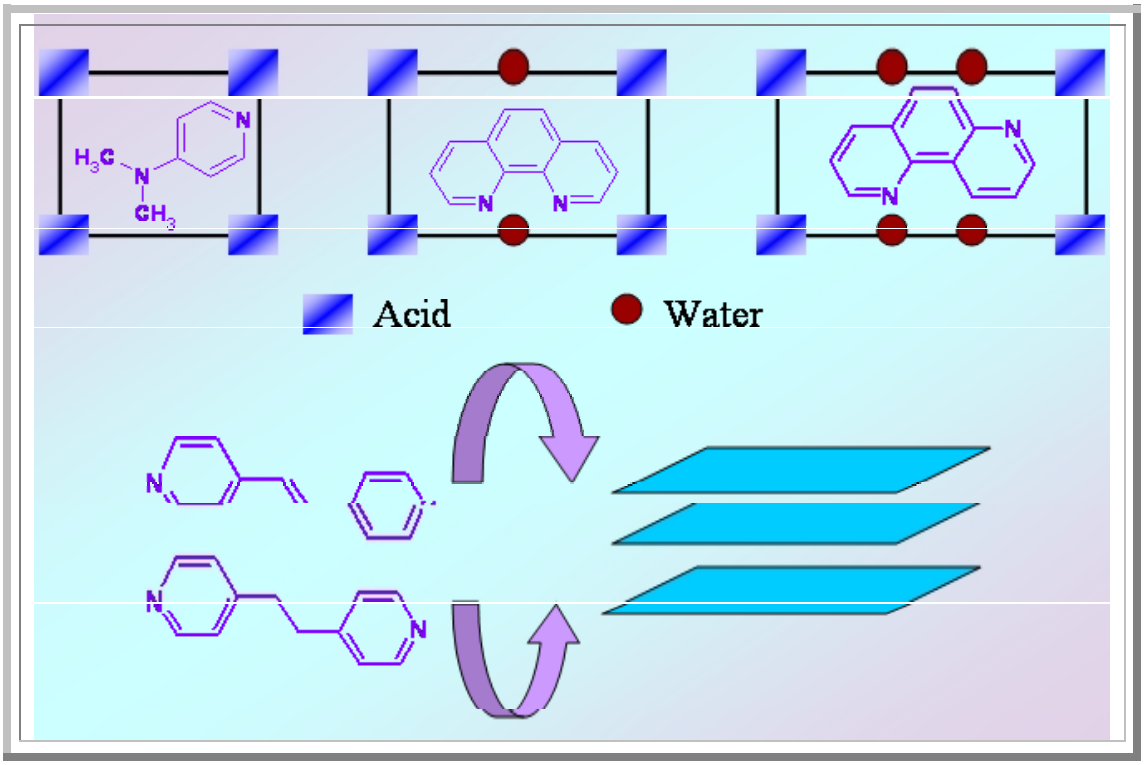
2.4 HOST-GUEST COMPLEXES VERSUS PLANAR SHEETS: INTRA- AND INTERMOLECULAR HYDROGEN BONDING IN ACID 1

The supramolecular assemblies of the molecular complexes **1a** - **1g** and **1b**.$\mathbf{H_2O}$ described in the earlier sections reveal that in none of the structures, the acid molecules form centrosymmetric cyclic hydrogen bonding patterns usually observed in –COOH groups (see Scheme 2.1(I)). In all the structures, the acid molecules do interact with the

adjacent acid molecules by single O-H···O or O-H···O$^-$ hydrogen bonds. Further, all the structures **1a** - **1g** and **1b**.$\mathbf{H_2O}$ basically form sheet structures in a two-dimensional arrangement. Within these sheets, in the complexes **1a**, **1b**.$\mathbf{H_2O}$ and **1e**, void space exists, which constitutes channels in a three-dimensional arrangement. The void space observed in the complex **1d** is stabilized by the electron density from the adjacent layers, and hence, no channels were observed in this structure. While **1f** and **1g** form perfect planar sheet structures, complex **1b** and **1c** adopts a staircase structure. Other noteworthy features of these structures are intra- and intermolecular hydrogen bonding patterns shown by acid **1** molecules and the presence of water in the complexes **1a**, **1b**.$\mathbf{H_2O}$, and **1d**.

Analysis of all these molecular complexes further reveals the role of water, which is embedded into some of the crystal lattices, irrespective of whether it is used for crystallization or not in the formation of host-guest complexes. It is apparent from all the hydrated structures that incorporation of water molecules occurred to commensurate the size of the cavities with the guest dimension. In this study, the number of water molecules crystallized into the crystal lattices are 0 - 4 for the complexes **1a**, **1b.**$\mathbf{H_2O}$, and **1d**. This is clearly evident from Scheme 2.6 that the cavity dimension increases with the increase in the incorporation of number of water molecules. However, if the molecular dimension is beyond a threshold limit, naturally a large number of water molecules may be needed to create the required cavity to insert the guest molecule. Hence, such components may adopt other structural patterns, for instance, simple sheet structures as observed in the molecular complexes of **1f** and **1g**, as the reactants ***bpyee***

and ***bpyea*** are certainly quite large in dimensions compared to the phenanthrolines and phenazine respectively.



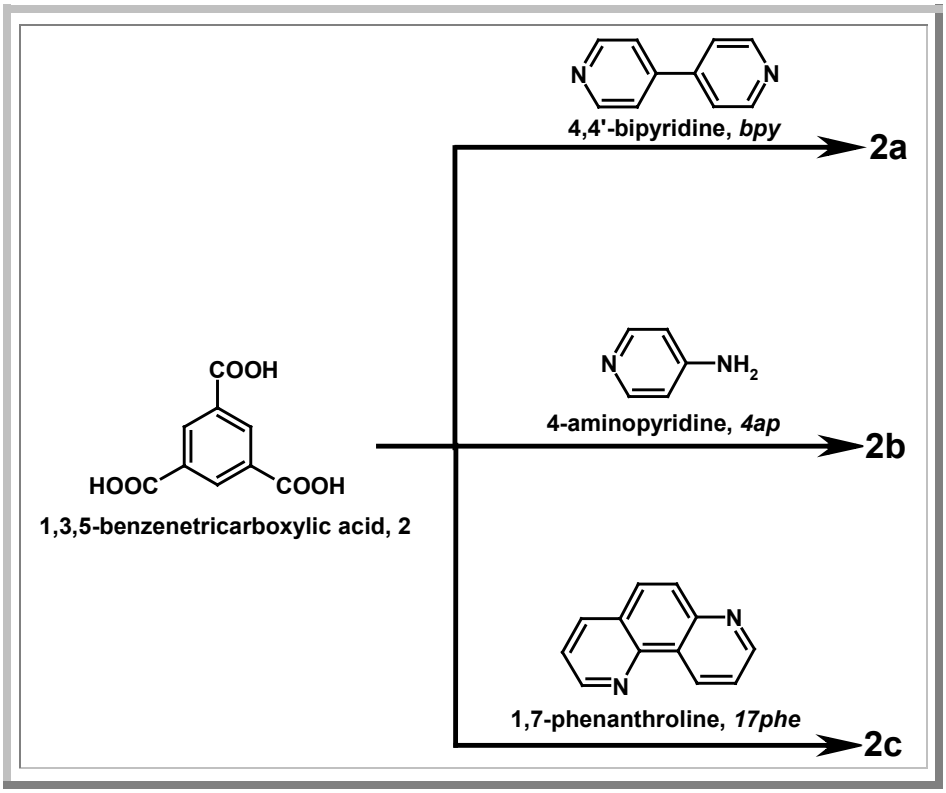
Scheme 2.6

PART B: MOLECULAR COMPLEXES OF BENZENETRICARBOXYLIC ACIDS

Encouraged by the exotic structural features of the complexes formed by **1** with various aza-donor compounds, to further explore the features of different aromatic polycarboxylic acids, co-crystallization of tricarboxylic acid isomers (1,3,5, 1,2,3, and 1,2,4-benzenetricarboxylic acids), with various aza donor compounds were carried out.

2.5 MOLECULAR COMPLEXES OF 1,3,5-BENZENETRICARBOXYLIC ACID, 2 (HOST-GUEST COMPLEXES)

In this section molecular complexes of acid **2**, with some aza donor molecules such as, 4,4'-bipyridine, ***bpy,*** 4-aminopyridine, ***4ap*** and 1,7-phenanthroline, ***17phe***, are discussed. All the complexes (**2a - 2c**) formed the host-guest networks, with acid, **2,** molecules forming the host network. Although, many other aza-donor molecules were used, but unfortunately, single crystals of the complexes could not be obtained for characterization by X-ray diffraction studies. The resulting complexes are labeled as given in Scheme 2.7. Structural characteristics and the preparation methods of all these complexes would be discussed in detail in the sections given below.



Scheme 2.7

2.5.1 MOLECULAR COMPLEX OF ACID 2 AND 4,4'-BIPYRIDINE, 2a

In an attempt to prepare a coordination polymer of acid, **2** and Hg(II) in the presence of aza-donor ligand 4,4'-bipyridine, ***bpy,*** under hydrothermal condition, pale yellow, block-like, single crystals were obtained upon slow cooling. The structural analysis, however, revealed that it is a 3:1 molecular complex, **2a,** of acid **2** and ***bpy*** with three water molecules. The complete crystallographic details are given in Table 2.3. However, this complex is reported in the literature by Li and co-workers.[20] It is interesting to note that attempts to obtain the complex **2a**, without $HgCl_2$, were not successful. In fact, literature evidences also confirms the role of metal salts, perhaps as an additive, because Li et al also reported as obtained in the presence of $La_2(SO_4)_3{\cdot}9H_2O$. Since the structural description in terms of hydrogen bonding patterns is not discussed in detail in the reported literature, re-analysis of the structural features of **2a** has been carried out as described below.

In the complex **2a**, the acid molecules are held together by hydrogen bonded dimers as well as catemers with the corresponding H···O distances as 1.71 and 1.65 Å, respectively. Other characteristics of hydrogen bonds are given in Table 2.4. Also, one of the –COOH groups is deprotonated and the structure analysis reveals that the complex **2a** forms a cavity, in two-dimension, with the aid of water molecules as shown in the Figure 2.22.

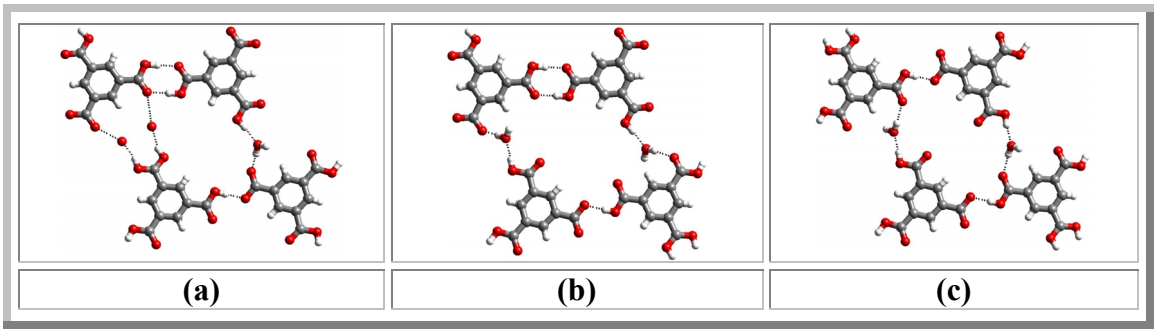


Figure 2.22: Cavity formed by acid **2** molecules with the aid of water molecules.

The cavities so formed align to constitute channels in three-dimensional packing. The channels are occupied by the ***bpy*** molecules, lying perpendicular to the host network and interact with the water molecules through N^{+}-H···O^{-} hydrogen bonding. The arrangement of the molecules is shown in the Figure 2.23(a) and (b). In complex **2a,** the acid molecules form a cavity structure involving four molecules rather than the usually observed six molecules.

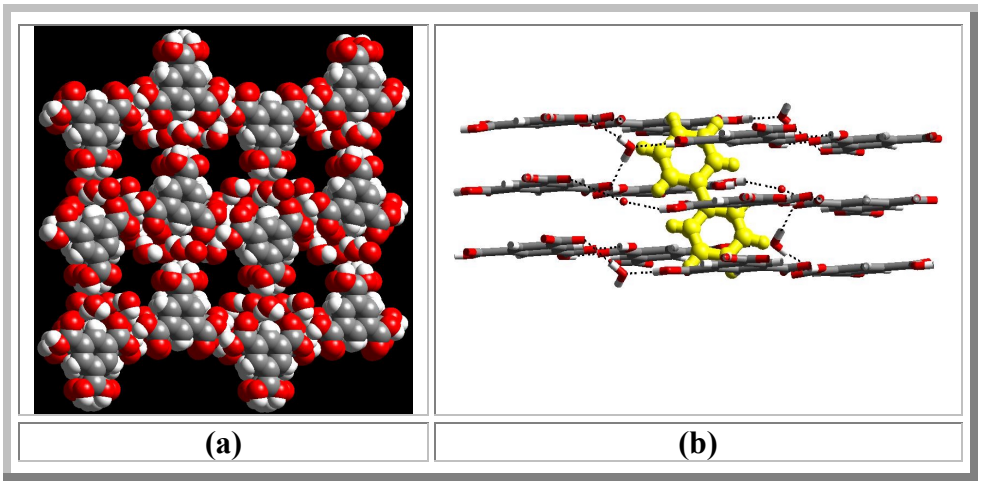


Figure 2.23: (a) Three-dimensional arrangement of complex **2a** showing the formation of one-dimensional channels (***bpy*** molecules are removed for clarity). **(b)** The arrangement of ***bpy*** molecule in the channels.

Further to evaluate the feasibility of replacing guests in the channels formed by **2**, by other aza-donor molecules, co-crystallization of **2** only with 4-aminopyridine, ***4ap*** and 1,7-phenanthroline, ***17phe*** gave good quality single crystals, **2b** and **2c**, respectively, to analyze by single crystal x-ray diffraction methods.

2.5.2 MOLECULAR COMPLEX OF ACID 2 AND 4-AMINOPYRIDINE, 2b

Complex **2b** formed between acid **2** and ***4ap*** is a 1:1 ratio complex with a water molecule in the crystal lattice. Also, one of the –COOH groups of the acid molecules is deprotonated. The ORTEP diagram is shown in the Figure 2.24.

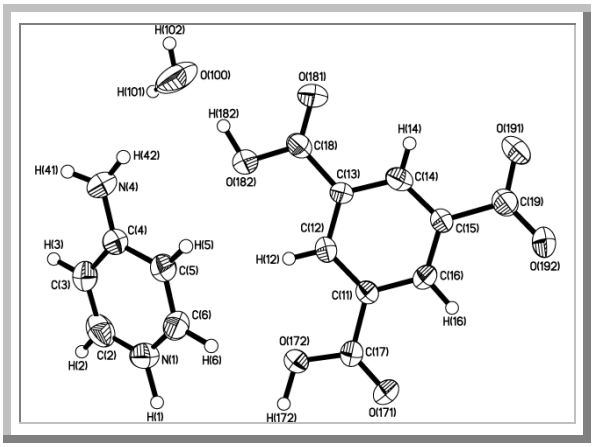


Figure 2.24: ORTEP (50% probability level) drawing of the molecular complex, **2b** of acid **2** and 4-aminopyridine, ***4ap*.**

The arrangement of the molecules in the complex **2b** is shown in the Figure 2.25. In two-dimension, the complex **2b** forms a layer structure. The acid molecules recognize each other through catameric O-H···O hydrogen bonds (H···O, 1.62 Å, Table 2.4) and form a cavity with the aid of water molecules. The pyridine molecule, acting as guest, interacts with host network through pyridinium ion forming N^{+}-H···O^{-} hydrogen

bond (H···O, 1.60 Å) with the oxygen atom of –COOH group. In addition, N-H···O hydrogen bonding is observed between $–NH_2$ group and oxygen atom of –COOH group with an H···O distance of 2.11Å, as shown in Figure 2.25(a). In three-dimension, the layers align to yield channels occupied by ***4ap*** molecules.

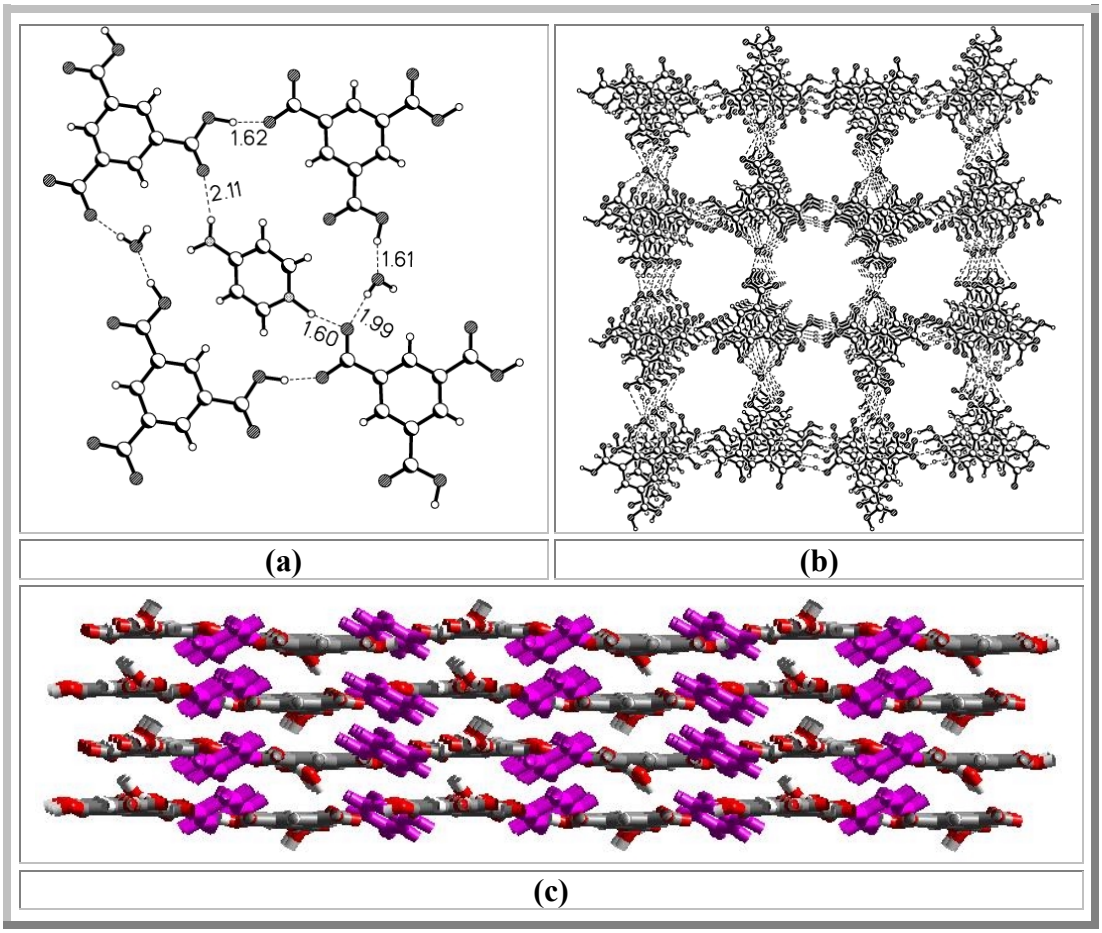


Figure 2.25: (a) Two-dimensional arrangement of complex **2b**, showing the cavity formed by acid molecules utilizing the water molecules and also occupied by ***4ap*** molecules. **(b)** Three-dimensional arrangement showing one-dimensional channels in complex **2b**. **(c)** Three-dimensional arrangement of sheets in complex **2b.**

2.5.3 MOLECULAR COMPLEX OF ACID 2 AND 1,7-PHENANTHROLINE, 2c

The structure analysis reveals that complex **2c** forms a 1:3 ratio molecular complex of acid **2** and 1,7-phenanthroline, ***17phe***, along with eight water molecules in the asymmetric unit. The arrangement of molecules in the complex **2c** is shown in the Figure 2.26. The structure analysis reveals that the complex forms a sandwich like structure in three-dimension as shown in Figure 2.26(a). The acid molecules form a layer structure and typical analysis of one such layer is shown in Figure 2.26(b). It is interesting to note that neither dimeric nor catameric hydrogen bonding is observed between the acid molecules, unlike in the complexes noted above, rather connected by water molecules through O-H···O hydrogen bonding with O···O distances in the range 2.74-2.90 Å.

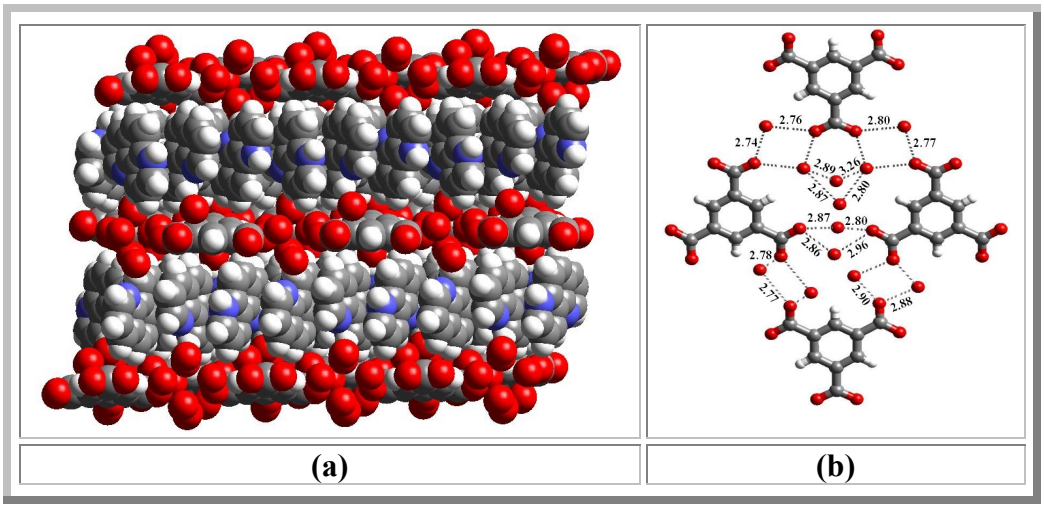
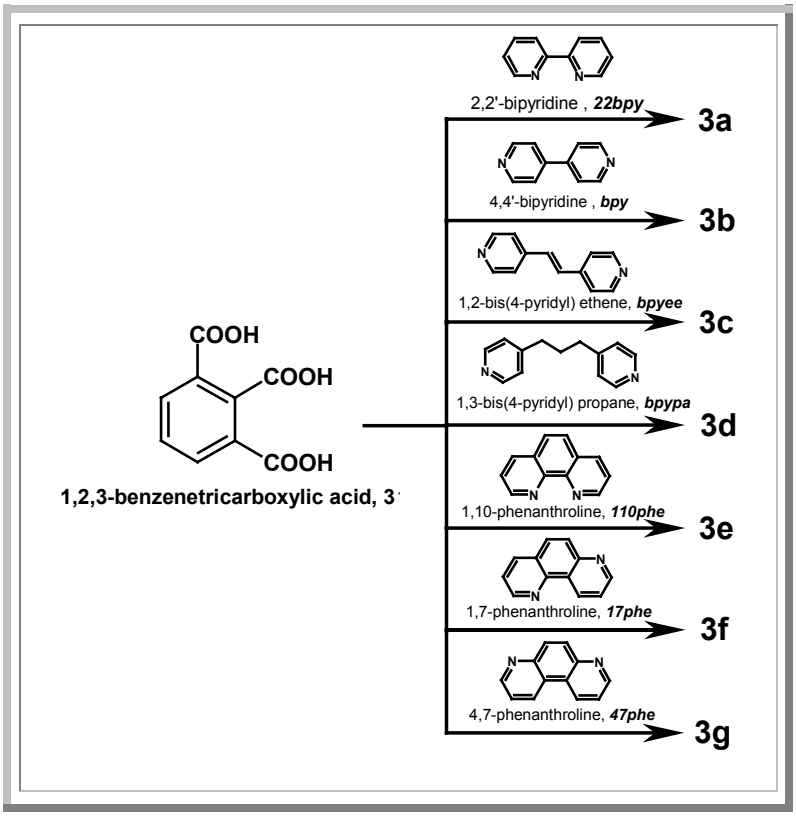


Figure 2.26: (a) Sandwich type arrangement in complex **2b (b)** Interaction of acid **2** with water molecules forming a layer in two-dimension.

2.6 MOLECULAR COMPLEXES OF 1,2,3-BENZENETRICARBOXYLIC ACID, 3

In continuation of systematic analysis of utilization of –COOH group in the supramolecular synthesis, utilizing other isomers of tricarboxylic acids, co-crystallization studies of acid **3** with 2,2'-bipyridine, ***22bpy***, 4,4'-bipyridine, ***bpy*****,** 1,2-bis-(4-pyridyl)ethene, ***bpyee*****,** 1,3-*bis*-(4-pyridyl)propane, ***bpypa*****,** 10-phenanthroline, ***110phe***, 1,7-phenanthroline, ***17phe*** and 4,7-phenanthroline, ***47phe*****,** were carried out (see Scheme 2.8). All the complexes formed between acid **3** and aza-donor molecules comprise of the layers, in two-dimensions, but in three-dimensions the complexes form either host-guest networks or planar sheets.



Scheme 2.8

2.6.1 MOLECULAR COMPLEX OF ACID 3 AND 2,2'-BIPYRIDINE, 3a

Co-crystallization of acid, **3**, and 2,2'-bipyridine, ***22bpy,*** from methanol gave single crystals suitable for x-ray diffraction studies. The structure analysis revealed that a molecular complex, **3a**, in a 2:1 ratio of acid **3** and ***22bpy***, is formed. The complete crystallographic details are given in Table 2.5.

In two-dimensional arrangement complex **3a** forms a layer structure. Arrangement of molecules in a typical layer is shown in the Figure 2.27. In each layer, the acid molecules form a zigzag tape with the formation of two centrosymmetric O-H···O (H···O 1.76, 1.84 Å) hydrogen bonded dimers. Other characteristics of hydrogen bonds are given in Table 2.6.

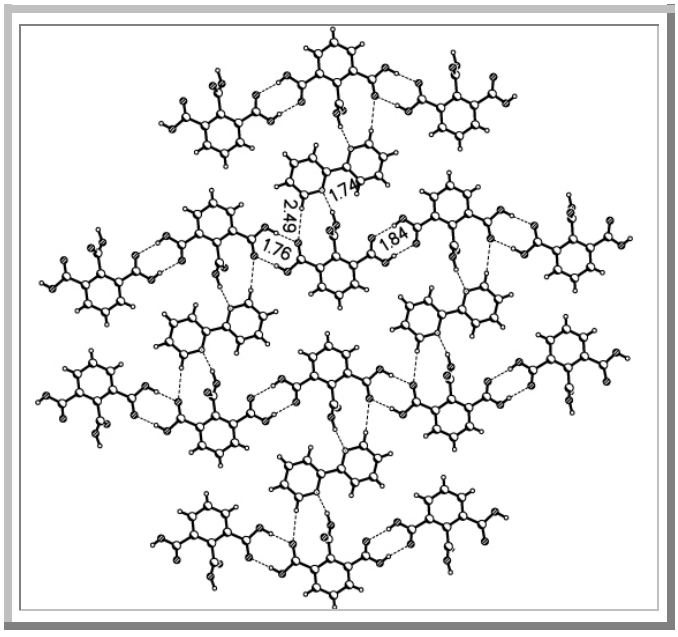


Figure 2.27: A two-dimension layer formed in the complex **3a**.

Two such consecutive zigzag tapes, related by an inversion symmetry, arrange to form cavities with 6 x 16 $Å^2$ void space, with ***22bpy*** molecules filling these voids.

Also the ***22bpy*** molecules interact with the zigzag tapes of the acid molecules by O-H···N (H···N, 1.74 Å) hydrogen bonds formed between the –COOH moiety of acid and pyridyl N atom of the ***22bpy*** molecule. Further, in three-dimensions, these layers stacked and stabilized by the formation of C-H···O (H···O, 2.58 Å) hydrogen bonds. (see Figure 2.28(a)). Also the stacking of layers occur with the translational symmetry resulting in one-dimensional channel, that are occupied by ***22bpy*** molecules, leading to the host-guest network as shown in the Figure 2.28(b).

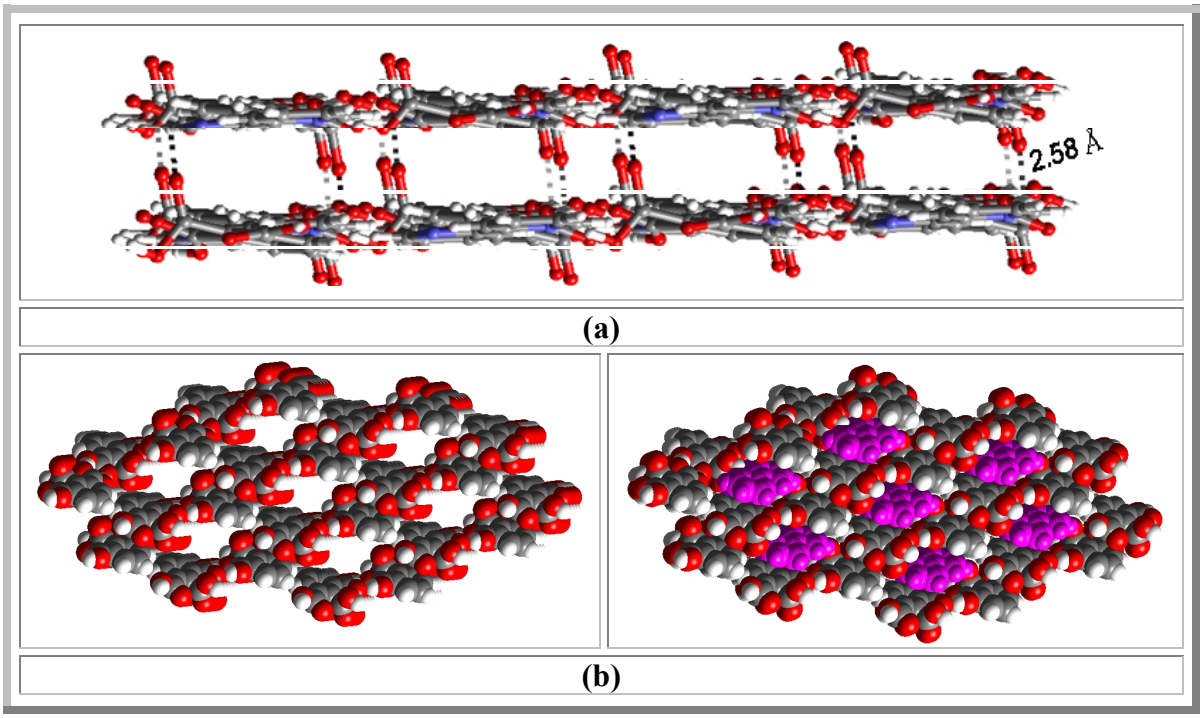


Figure 2.28: (a) Stacking of layers of complex **3a** in three-dimension. **(b)** left: A space filling diagram showing the one-dimensional channel (without guest) in complex **3a**. right: A space filling diagram showing inclusion of ***22bpy*** molecules (magenta color) into the one-dimensional channel formed by acid **3** in complex **3a.**

2.6.2 MOLECULAR COMPLEX OF ACID 3 AND 4,4'-BIPYRIDINE, 3b

Co-crystallization reaction between acid, **3**, and 4,4'-bipyridine, ***bpy*****,** in methanol solution, gave good quality single crystals suitable for the x-ray diffraction studies. The x-ray structure determination revealed that the complex has constituents in a 1:1 ratio. However, a CSD search revealed that the crystal structure of **3b** with a 1:1 ratio is known.[21] Furthermore, the unit-cell dimensions of **3b** synthesized, herein, (a=26.095, b=7.805 c=19.868 Å, β = 127.00°) were similar to those of the reported structure (a=26.118(9), b=7.813(2), c=19.881 (2) Å, β = 127.00 (1)°); so the determination of the crystal structure of **3b** was not carried out. However, since the focus of the study is to compare the ability of the –COOH group to yield O-H···N hydrogen bonds with N-donor compounds in a series of carboxylic acids, analysis of structural features of complex **3b** has been carried out using the data retrieved from the CSD.

The molecular recognition between acid **3** and ***bpy*** has been established by the formation of O-H···N / C-H···O (H···N, 1.58; H···O 2.80 Å, Table 2.6) and N^{+}-H···O / C-H···O (H···O, 1.82, 2.51 Å) pairwise hydrogen bonds (see Figure 2.29).

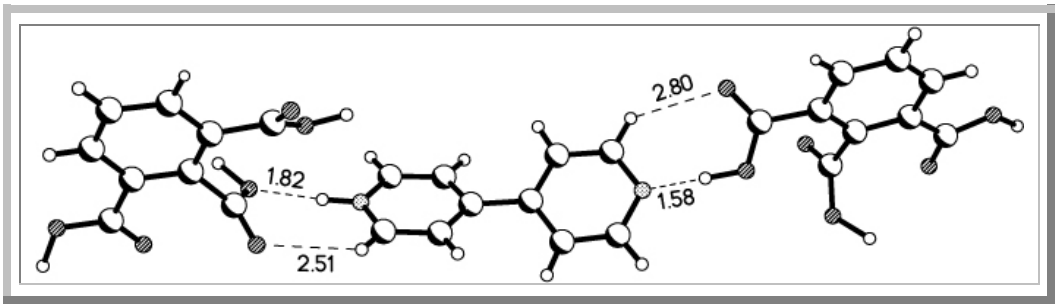


Figure 2.29: Molecular recognition pattern of acid **3** and ***bpy*** in complex **3b.**

Further, the complex **3b** forms a layer structure that comprises of the ladders as shown in the Figure 2.30. The typical ladder is formed with acid molecules as pillars and the ***bpy*** molecules as the rungs. The acid **3** molecules in pillars are connected with each other through two C-H···O (2.29, 2.70 Å) hydrogen bonds, formed between the carbonyl group and the phenyl hydrogen atom of acid molecules. Also the alternate ladders are connected through the hydrogen atom shared between the two carboxylic acids.

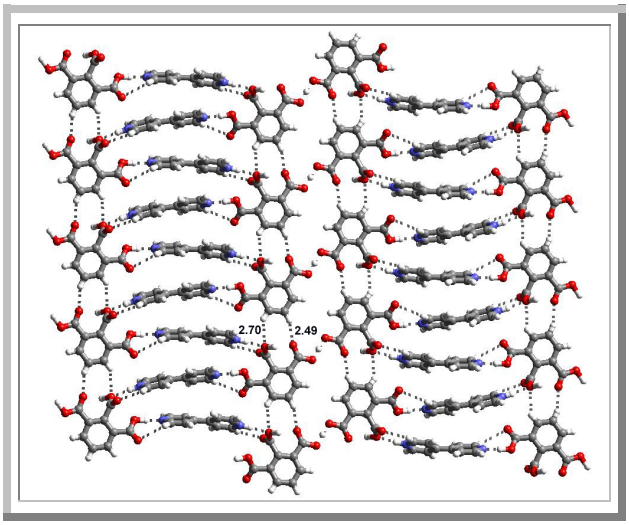


Figure 2.30: Two-dimensional layer formed by the ladders in complex **3b**.

2.6.3 MOLECULAR COMPLEX OF ACID 3 AND 1,2-*BIS*(4-PYRIDYL)ETHENE, 3c

Co-crystallization between acid, **3** and 1,2-*bis*(4-pyridyl)ethene, ***bpyee,*** in methanol gave single crystals suitable for x-ray diffraction studies in 5-7 days at room temperature. The x-ray structure determination revealed the formation of a molecular

complex, **3c**, in a 1:2 ratio of acid **3** and ***bpyee***. The asymmetric unit is as shown in the Figure 2.31.

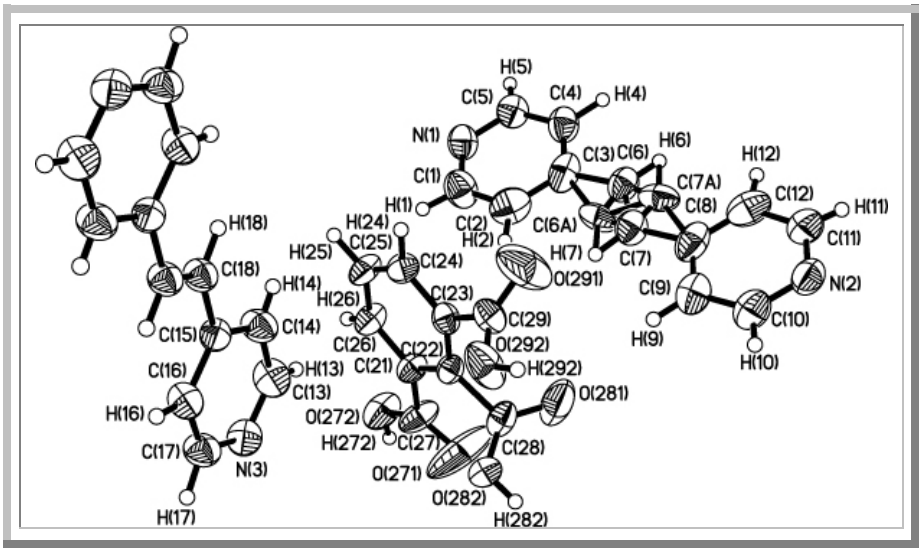


Figure 2.31: ORTEP (50% probability level) diagram showing 1:2 molecular complex **3c,** of acid **3** and ***bpyee***.

In the complex **3c,** one of the ***bpyee*** molecules is disordered at the C_6 and C_7 positions. The arrangement of molecules in complex **3c** is shown in the Figure 2.32. In the two-dimensional arrangement, the complex **3c** forms a zigzag sheet-like structure comprising of ladders of two different types with common pillars (see Figure 2.32(a)). In both the ladders, molecules of **3** are held together by C-H···O hydrogen bond (H···O, 2.31 Å, Table 2.6), constituting pillars of the ladder, while ***bpyee*** molecules act as rungs. Further, in the ladder comprising of disordered ***bpyee*** molecule, the ***bpyee*** rungs interact with pillars of acid molecules by a pairwise O-H···N / C-H···O hydrogen bonds (H···N, 1.79,1.62 / H···O, 2.48, 2.82 Å, Table 2.6), as shown in the Figure 2.32(b). However, in the ladders with the ordered ***bpyee*** molecules, the interaction is established only by O-H···N hydrogen bond (H···N, 1.70 Å).

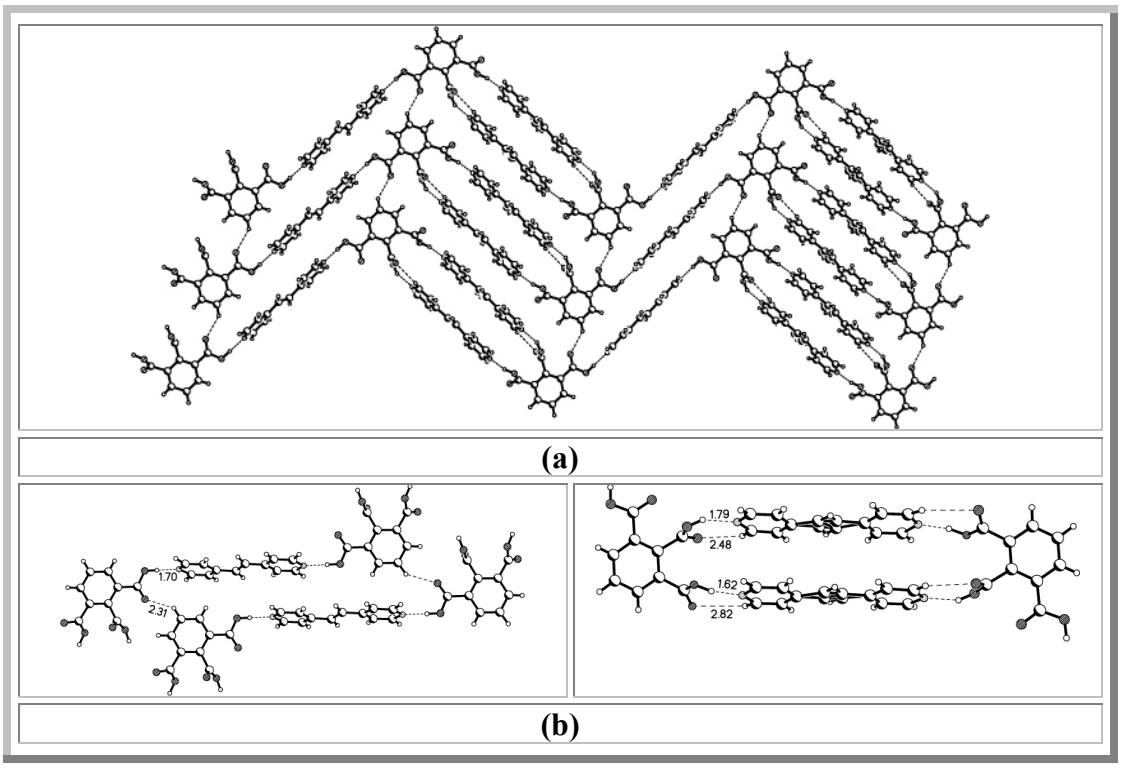


Figure 2.32: (a) 2D structure showing the merging of ladders to form planar sheets in the complex **3c. (b)** Molecular recognition between acid **3** and ***bpyee*** in two different ladders.

2.6.4 MOLECULAR COMPLEX OF ACID 3 AND 1,3-*BIS*(4-PYRIDYL)PROPANE, 3d

Reaction of acid, **3** with 1,3-*bis*(4-pyridyl)propane*,* ***bpypa,*** forms a molecular complex, **3d**, from a methanol solution. The structure determination reveals that the complex **3d** exists in 1:1 ratio, of acid **3** and ***bpypa***, with an asymmetric unit comprising of two symmetry independent molecules of each reactant (see Figure 2.33).

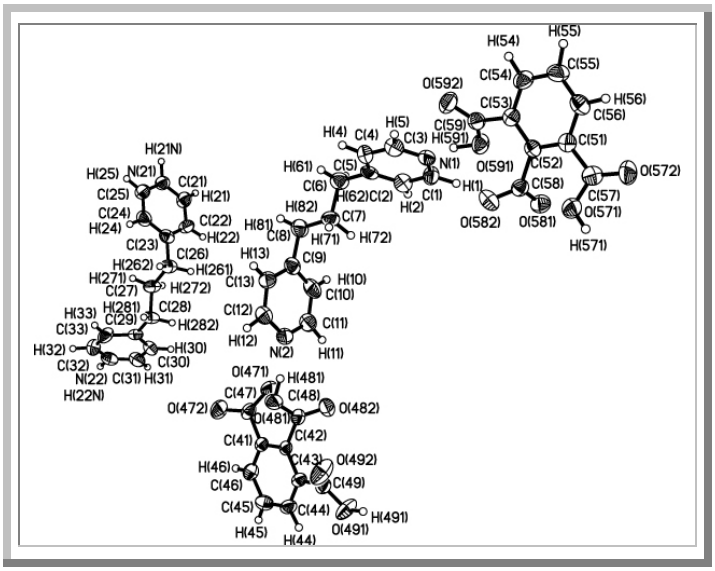


Figure 2.33: ORTEP diagram showing two molecules each of acid, **3** and ***bpypa,*** in the complex **3d**.

The two-dimensional arrangement shows the formation of a sheet structure (see Figure 2.34(a)). The basic recognition pattern shows the formation of different types of hydrogen bonding patterns by two symmetry independent acid molecules. Also, one of the –COOH moieties in both the acid molecules is deprotonated. Further the interaction with the aza-donor molecules have been established by the formation of O-H···N (H···N, 1.66, 1.42 Å, Table 2.6) and O^--H···N^+ (H···N^+, 1.53; 1.57 Å, Table 2.6) hydrogen bonds to form sheets in two-dimensions. Thus, a cyclic network comprises of two aza donor molecules, ***bpypa***, and three acid molecules (2A's and 1B) is established as shown in the Figure 2.34(b). Further these zigzag (crinkled) sheets stack to form a three-dimensional network, (see Figure 2.34(c), stabilized by C-H···O hydrogen bonds. In principle, both the acid molecules form strong O-H···O hydrogen bonds, while the molecules of A interact with each other through catemeric hydrogen bonds, the

molecules of B exist as dimers through the interaction established between the adjacent –COOH groups.

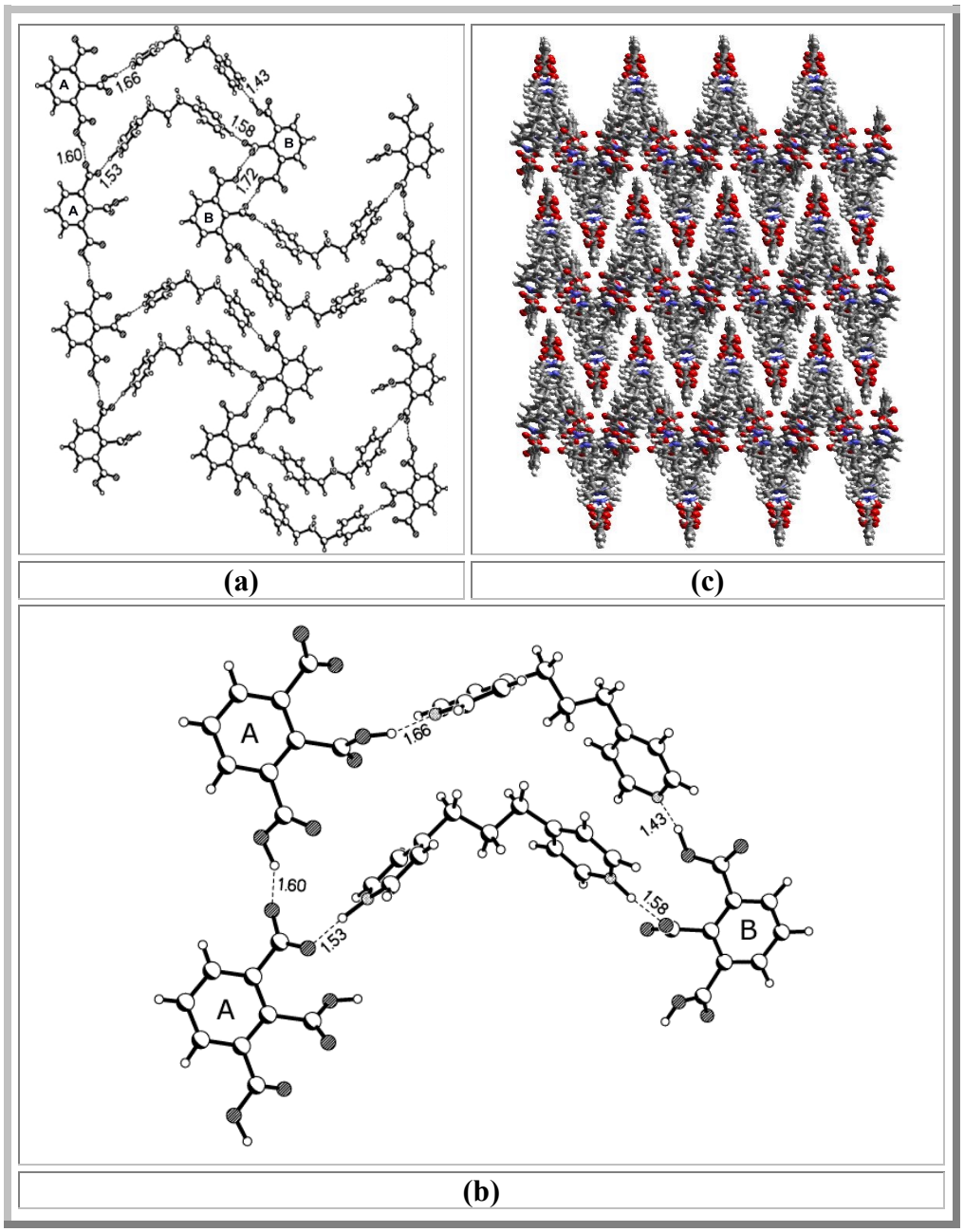


Figure 2.34: (a) Two-dimensional sheet arrangement in complex **3d**. **(b)** Molecular recognition between the acid, **3** and the ***bpypa*** molecules in complex **3d**. **(c)** The three-dimensional arrangement of the crinkled sheets in complex **3d**.

2.6.5 MOLECULAR COMPLEX OF ACID 3 AND 1,10-PHENANTHROLINE, 3e

Co-crystallization of acid, **3**, and 1,10-phenanthroline, ***110phe,*** from a mixture of methanol and acetonitrile gave single crystals, complex **3e**, suitable for x-ray analysis. The X-ray structure determination revealed that in the complex **3e**, one acetonitrile molecule is also present in the crystal lattice and one of the –COOH moieties of **3** is deprotonated.

In two-dimensional arrangement, complex **3e** forms zigzag layer structure, comprising of acid **3** molecules and the acetonitrile molecules. A typical layer is as shown in the Figure 2.35. In each layer, molecules of acid **3**, are held together through O-H···O$^-$ (H···O$^-$, 1.61; 1.50 Å, Table 2.6) as well as C-H···O (H···O 2.78 Å) hydrogen bonds. Such an arrangement, thus, constituted double tapes of acid molecules, which are in turn held together by chains of acetonitrile molecules through C-H···O (H···O, 2.31 Å) hydrogen bonds, as shown in the Figure 2.35. The adjacent acetonitrile molecules in each chain are held together by C-H···N (H···N, 2.79Å) hydrogen bonds.

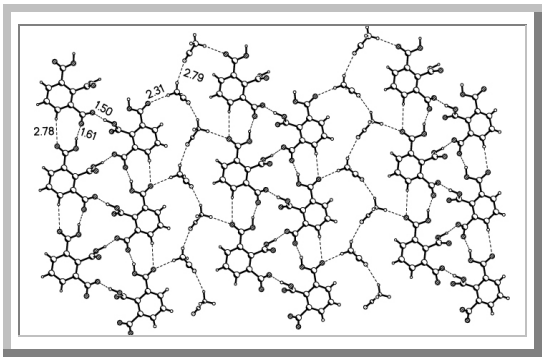


Figure 2.35: The arrangement of acid, **3** and acetonitrile molecules in the layer of complex **3e**.

In the three-dimensional arrangement, the zigzag layers are stacked such that the cavities align to yield channels (13 x10Å^2) as shown in Figure 2.36(a), while the molecules of ***110phe***, occupy the channels forming a host-guest network as shown in the Figure 2.36(b).

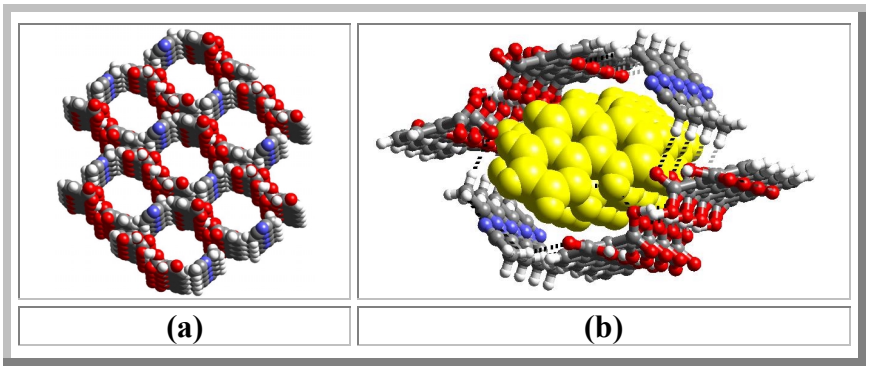


Figure 2.36: (a) The one-dimensional channel formed by acid **3** and acetonitrile molecules to accommodate the guest molecules, ***110phe***. **(b)** The channel formed by acid **3** and acetonitrile molecule, occupied by the phenanthroline molecules (yellow color) in complex **3e**.

2.6.6 MOLECULAR COMPLEX OF ACID 3 AND 1,7-PHENANTHROLINE, 3f

The co-crystallization experiment between acid **3** and 1,7-phenanthroline, ***17phe***, from methanol gave a 1:1 hydrated complex of the reactants. The complete crystallographic details are given in Table 2.5. The structure determination by single crystal x-ray diffraction revealed that the acid **3** and ***17phe*** molecules interact with each other through the formation of O-H···N / C-H···O (1.75, 2.48; 1.35, 3.03 Å, Table 2.6) pairwise hydrogen bonding pattern involving both the nitrogen atoms of the phenanthroline molecule forming a one-dimensional zigzag tape arrangement. The adjacent tapes are connected each other through two types of C-H···O hydrogen bonds, constituting a sheet structure (see Figure 2.37(a)). Further, the adjacent sheets are

connected by O-H···O (1.40 Å) hydrogen bonds with the aid of water molecules (see Figure 2.37(b)).

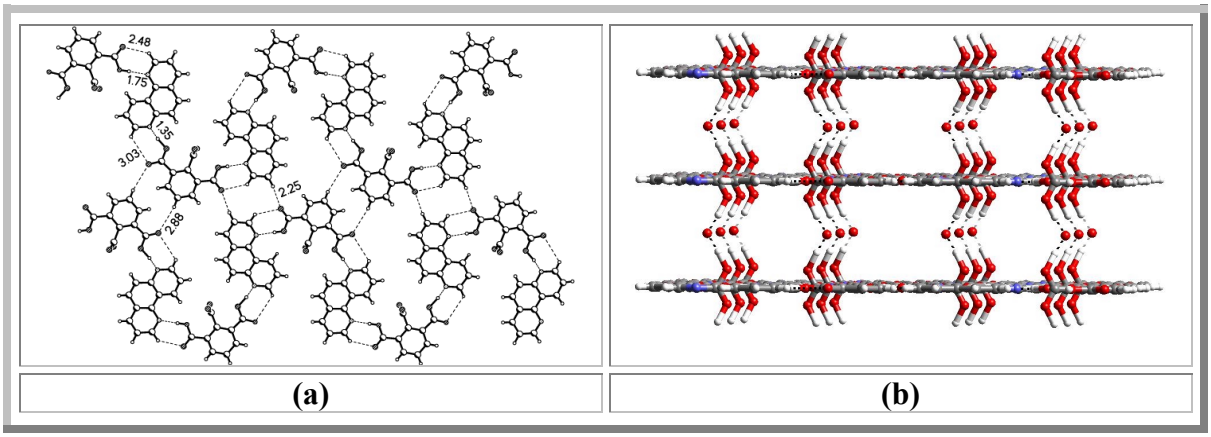


Figure 2.37: (a) 2D structure showing the formation of layer by the merging of the tapes in complex **3f (b)** 3D structure showing the stacking of the layers connected through H_2O molecules.

2.6.7 MOLECULAR COMPLEX OF ACID 3 AND 4,7-PHENANTHROLINE, 3g

Co-crystallization of acid **3** and 4,7-phenanthroline, ***47phe*** in a 1:1 ratio from methanol gave a complex **3g**, as a dihydrate of ***47phe*** and **3** in 1:1 ratio. The structure is characterized by single crystal X-ray diffraction methods. The complete crystallographic details are given in Table 2.5.

The structure analysis reveals that the complex **3g** forms a four member discrete unit consisting of two acid and two phenanthroline molecules as shown in the Figure 2.38(a) with a cavity of 4 x 7 $Å^2$. In each tetramer, acid, **3** and ***47phe*** molecules were held together by O-H···N/C-H···O (H···N, 1.26, 2.67; H···O, 1.70, 2.75 Å, Table 2.6) pairwise hydrogen bonds. Two symmetry dependent water molecules holding the two acid molecules, occupied the cavities formed by the tetramers. Further these discrete

units aggregate to form a planar layer structure in two-dimensions (see Figure 2.38(b)), that are stacked in three-dimension as shown in the Figure 2.38(c).

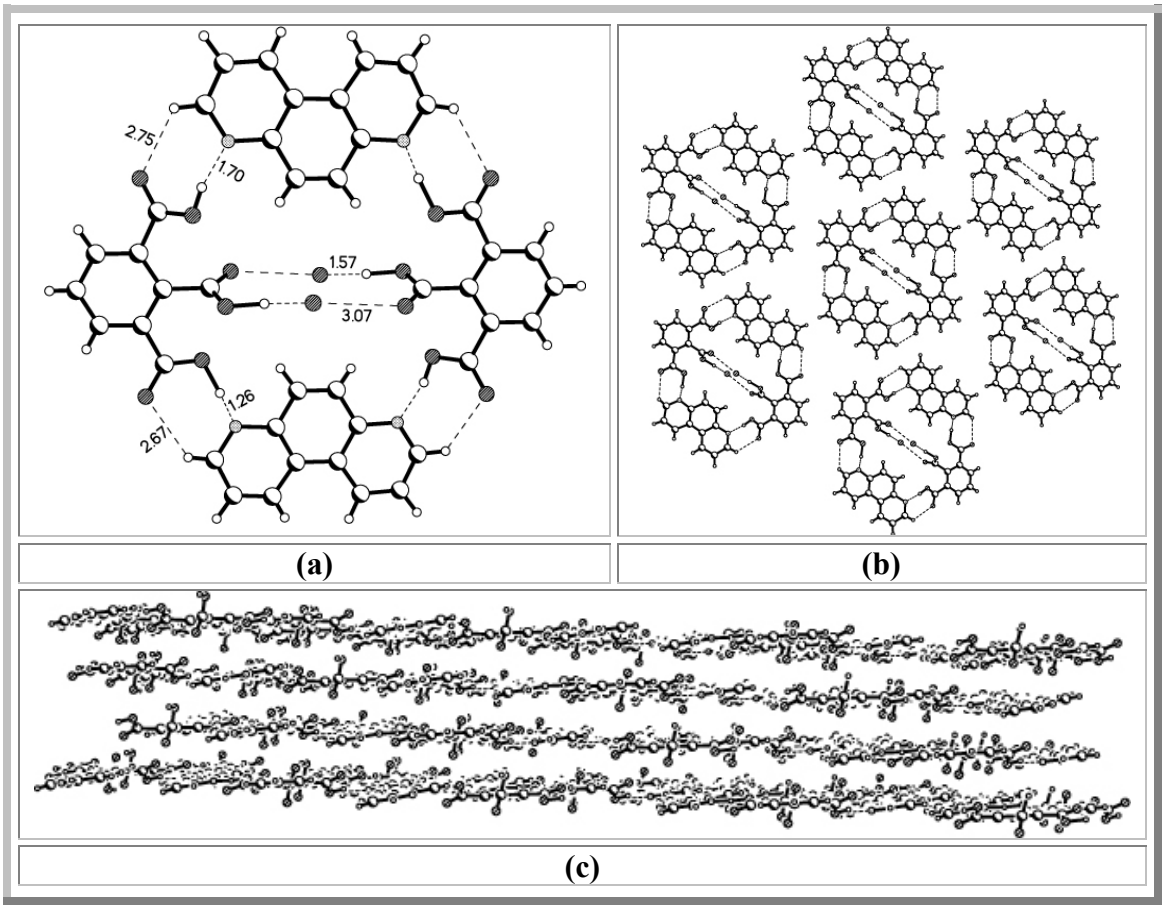


Figure 2.38: (a) A discrete tetramer unit formed by acid, **3** and ***47phe***, in complex **3g**. **(b)** The formation of layer by the systematic arrangement of the tetramers. **(c)** The three-dimensional sheet structure formed by the stacking of the layers.

2.7 MOLECULAR COMPLEXES OF 1,2,4-BENZENETRICARBOXYLIC ACID, 4

In continuation of supramolecular synthesis with other tricarboxylic acids, experiments with 1,2,4-benzenetricarboxylic acid, **4**, have been carried out by co-crystallizing it with 1,2-*bis*(4-pyridyl)ethene, ***bpyee***, 1,2-*bis*(4-pyridyl)ethane, ***bpyea***,

1,3-*tris*(4-pyridyl)propane, ***bpypa***, which gave molecular complexes **4a**, **4b** and **4c** respectively. All the complexes form planar sheet structures. The structural details of all these complexes are discussed in the following sections.

2.7.1 MOLECULAR COMPLEX OF ACID 4 AND 1,2-*BIS*(4-PYRIDYL)ETHENE, 4a

The co-crystallization reaction of acid, **4** and 1,2-*bis*(4-pyridyl)ethene, ***bpyee,*** in a 1:1 ratio from methanol yielded complex **4a**. Structure determination revealed that acid, **4** and ***bpyee*** molecules are present in a 1:1 ratio, with two symmetry independent molecules of acid **4** and ***bpyee***, in the asymmetric unit, as shown in the Figure 2.39. The complete crystallographic details are given in Table 2.7.

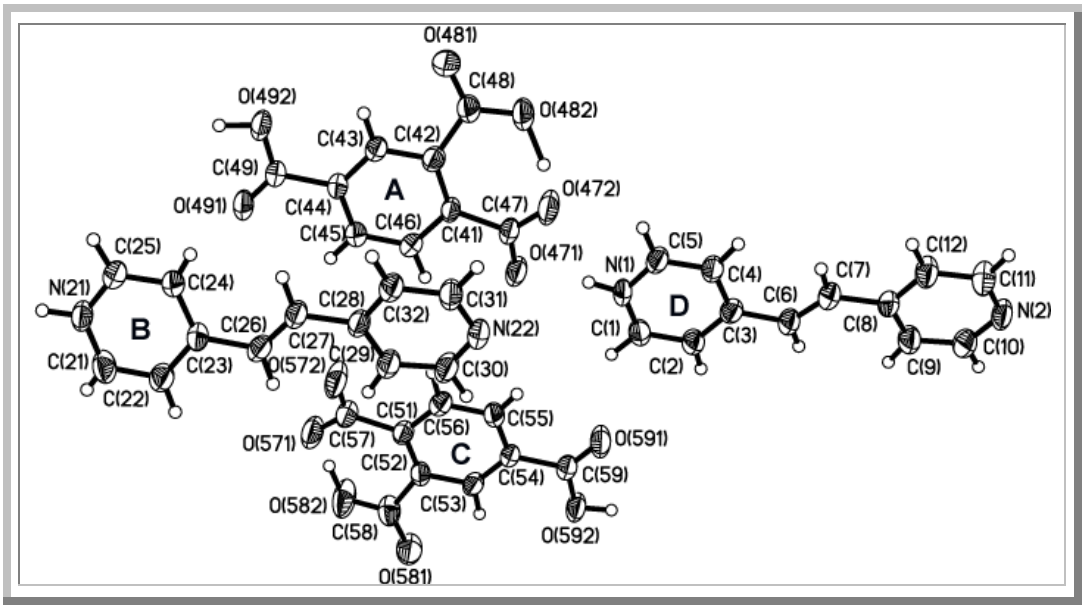


Figure 2.39: ORTEP (50 % probability level) diagram of asymmetric unit of the complex **4a**.

The molecular recognition between the acid **4** and ***bpyee*** molecules have been established by the formation of O-H···N/C-H···O (1.71/2.43 Å; 1.82/2.34 Å) and N^{+}-H···O^{-}/C-H···O^{-} (1.73/2.37 Å; 1.69/2.54 Å) pairwise hydrogen bonds and form one dimensional tapes of two different types, by utilizing two symmetry independent molecules as shown in the Figure 2.40(a). Other characteristics of hydrogen bonds are given in Table 2.8. Also it has been noted that one of the –COOH moieties is deprotonated in both the acid molecules. Further, the tapes formed, by each symmetry independent molecules, are arranged in an alternate manner and are held together by C-H···O hydrogen bonds, constituting a layer in the two-dimension arrangement. These layers stack to form a three-dimensional structure, as shown in the Figure 2.40(b) that is stabilized by π-π interactions.

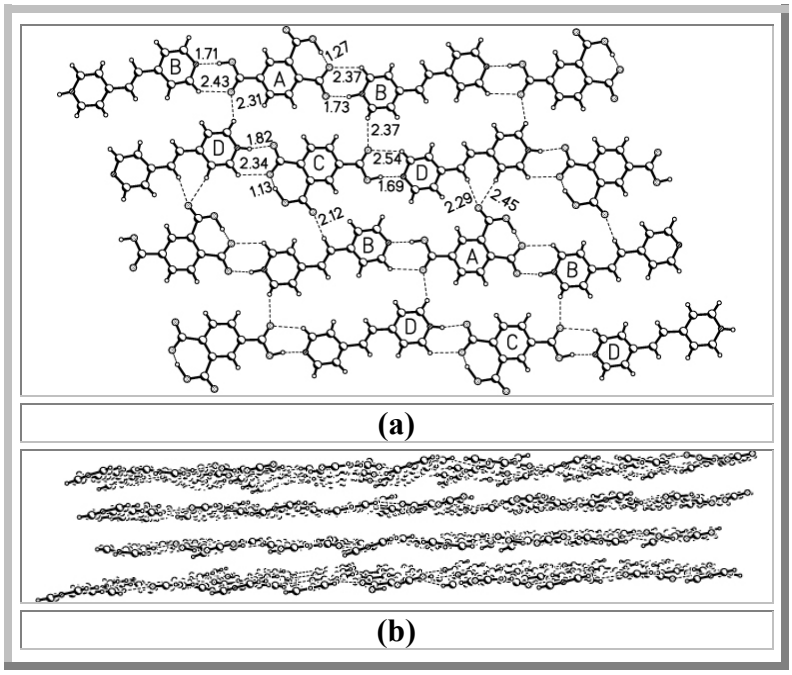


Figure 2.40: (a) Alternate arrangement of the tapes formed by acid, **4** and ***bpyee*** forming the layer in two-dimension. **(b)** Three-dimensional arrangement forming sheet structure in complex **4a**.

2.7.2 MOLECULAR COMPLEX OF ACID 4 AND 1,2-*BIS*(4-PYRIDYL)ETHANE, 4b

The reaction between acid **4** and 1,2-*bis*(4-pyridyl)ethane, ***bpyea,*** in methanol gave good quality crystals suitable for x-ray diffraction studies. The structure analysis revealed that the crystals consist of acid **4** and ***bpyea*** in a 1:1 ratio. The contents of the asymmetric unit are shown in the Figure 2.41.

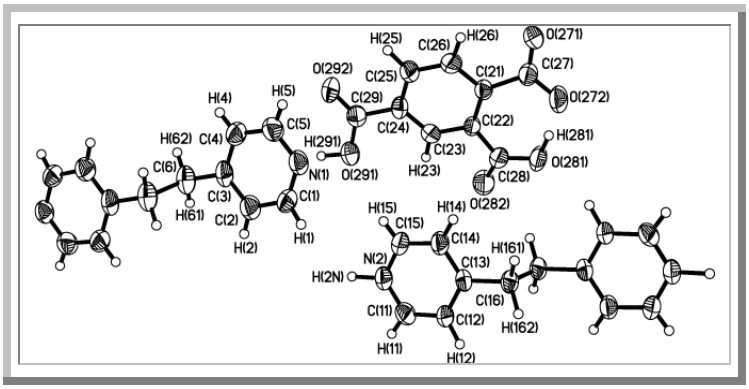


Figure 2.41: ORTEP (50 % probability level) diagram showing the 1:1 molecular complex **4b**, of acid **4** and ***bpyea***.

The arrangement of molecules in the complex **4b** is shown in the Figure 2.42. In a typical layer, molecules of **4** and ***bpyea*** form tapes by O-H···N/C-H···O (1.52, 2.76 Å, Table 2.8) and N^{+}-H···O^{-}/C-H···O^{-} (1.57, 2.32 Å, Table 2.8) pairwise hydrogen bonds. Such adjacent tapes are held together by bifurcated C-H···O (H···O, 2.52, 2.38 Å) hydrogen bonds formed between –COOH moiety of acid, **4** and hydrogen atom of the phenyl ring and the hydrogen atom of the $–CH_2$ group of ***bpyea*** molecules.

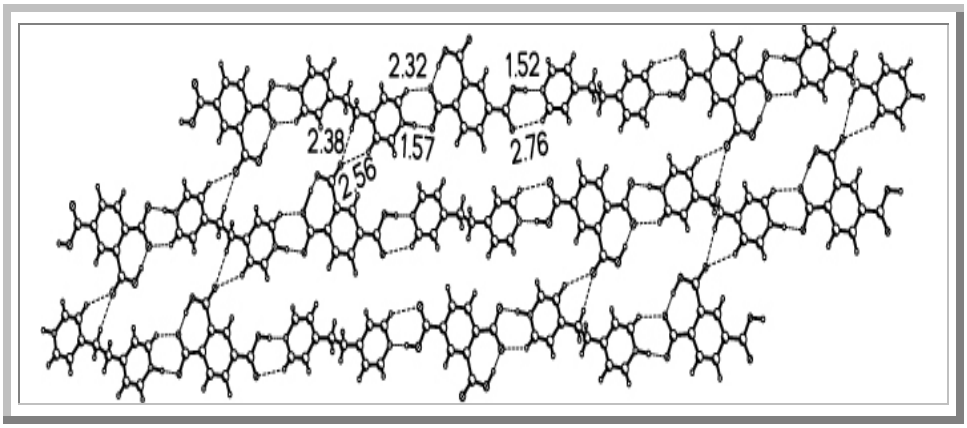


Figure 2.42: A typical layer formed in two-dimension in complex **4b**.

2.7.3 MOLECULAR COMPLEX OF ACID 4 AND 1,3-*BIS*(4-PYRIDYL)PROPANE, 4c

The reaction between **4** and 1,3-*bis*(4-pyridyl)propane, ***bpypa***, in methanol yielded good quality crystals. X-ray structure determination revealed the formation of 1:1 complex, **4c**, of acid **4** and ***bpypa***. The complete crystallographic details are given in Table 2.7. Structure analysis revealed that one of the –COOH moiety of acid **4** is deprotonated. The arrangement of molecules in the complex **4c** is shown in the Figure 2.43. The two-dimensional arrangement shows that the complex **4c** forms a ladder like structure (see Figure 2.43(a)). In these ladders, molecules of **4** formed the pillars through catemeric O-H$^{\cdots}$O^{-} hydrogen bond (H$^{\cdots}$O^{-}, 2.65 Å) while the rungs are formed by the protonated ***bpypa*** molecules. The interaction between acid and aza-donor molecules is established through O-H$^{\cdots}$N (H$^{\cdots}$N, 1.30 Å) and N^{+}-H$^{\cdots}$O^{-} (H$^{\cdots}$O^{-}, 1.66 Å) hydrogen bonds. Other characteristics of hydrogen bonds are given in Table 2.8. The adjacent ladders are held together through C-H$^{\cdots}$O (H$^{\cdots}$O, 2.53 Å) hydrogen bonds, as shown in the Figure 2.43(a) forming a two-dimensional layer. In three-dimensional

arrangement, the layers are stabilized by the formation of C-H···O (H···O, 2.08; 2.54 Å) hydrogen bonds, as shown in Figure 2.43(b).

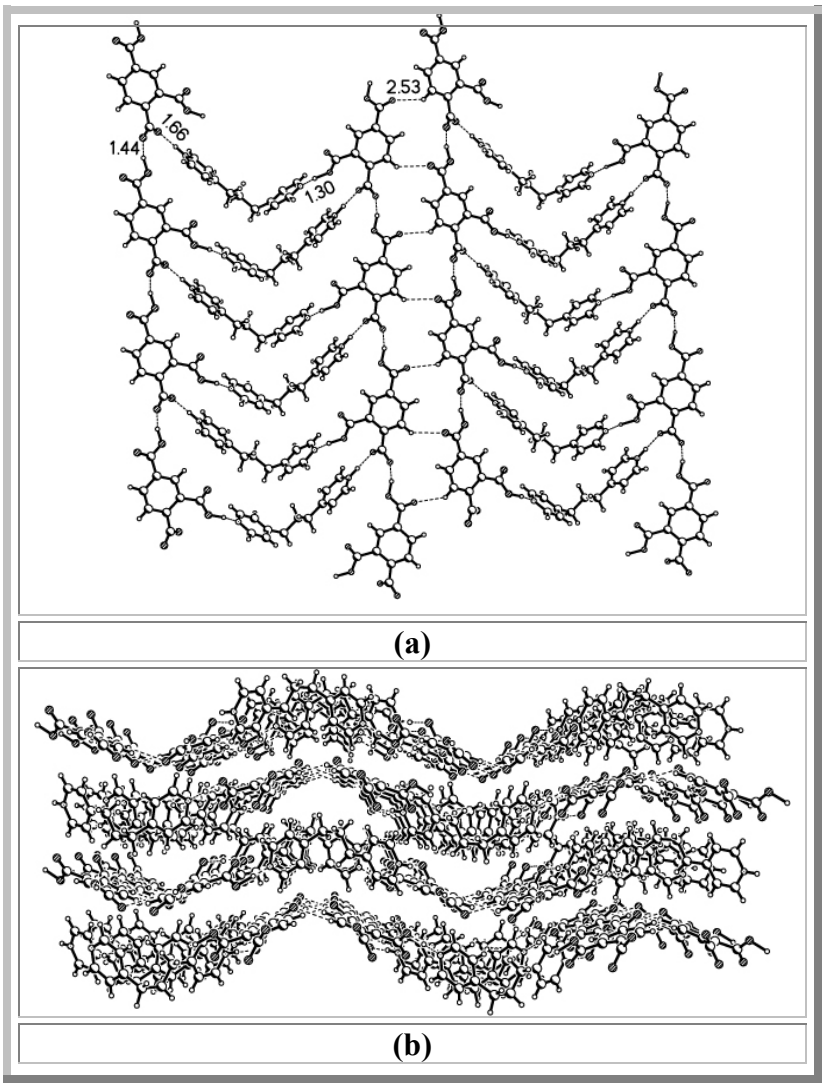


Figure 2.43: (a) The two-dimensional layer formed by acid **4** and ***bpypa*** in complex **4c**. **(b)** Three-dimensional stacking of layers in complex **4c**.

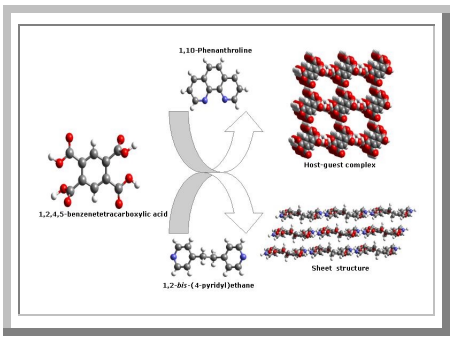
2.8 CONCLUSIONS

The synthesis and rational analysis of supramolecular assemblies formed by 1,2,4,5-benzenetetracarboxylic acid, **1** and isomers of tricarboxylic acids, **2**, **3** and **4**,

with various aromatic aza compounds such as 1,10-phenanthroline, 1,7-phenanthroline, 4,7-phenanthroline, phenazine, 4-(*N*,*N*-dimethylamino)pyridine, 2-aminopyridine, 3-aminopyridine, 4-aminopyridine, 2,2'-bipyridine, 4,4'-bipyridine, 1,2-*bis*(4-pyridyl)ethene, 1,2-*bis*(4-pyridyl)ethane, 1,3-*bis*(4-pyridyl)propane, have been reported.

The molecular complexes of aromatic polycarboxylic acids have demonstrated the ability of –COOH moiety to form various supramolecular networks such as host-guest complexes, ladders, planar sheets, etc. It is evident that the polycarboxylic acids have robust hydrogen-bonding donors/acceptors to fulfill the diversiform motives. All these assemblies form invariably two-dimensional sheet structures but differ in the mode of stacking. Additionally, the relative orientation of acid and base subunits, within a co-crystals, also makes a significant effect on forming the final diverse networks from two-dimensional arrangement to three-dimensional architectures. Also, hydrogen bonding interactions between the pyridyl and carboxylic acid moieties supply the dominating steering force for the synthesis of these supramolecular assemblies.

In the molecular complexes of acid **1**, while the complexes **1a**, **1b**.$\mathbf{H_2O}$, and **1e** form channel structures in three-dimensional lattices, complexes **1d**, **1f**, and **1g** yielded simple planar sheet structures. However, complex **1b** and **1c** gave a unique staircase structure. These differences in the three-dimensional lattice arrangement are accounted for the ability of the water molecules to be part of the lattices of the assemblies as it played an important role for the creation of host networks of the required dimensions, to accommodate the incoming guest molecules. The schematic representation for the molecular complexes of acid **1** is as shown in Scheme 2.9.



Scheme 2.9

In the molecular complexes of acid **2**, the complexes **2a**, **2b** and **2c** form the host-guest networks, with the formation of host network by acid molecules, in the form of either tetrameric cavities (complexes **2a** and **2b**) or intercalated planar sheets (complex **2c**), accommodating guest molecules. The host network in all the molecular complexes was formed with the aid of water molecules.

In the molecular complexes of acids **3** and **4,** the complexes **3a, 3e**, and **3g** form the channels accommodating the guest molecules, whereas the molecular complexes **3b-3d, 3f** and **4a-4c** form stacked sheet structures. In the molecular complexes **3b-3d, 3f** and **4a - 4c**, the heteromeric O-H···N/C-H···O pairwise motif was consistently observed in the supramolecular tapes formed by polycarboxylic acids and aza-donor compounds.

Thus, the study has shed more light on the further tuning of the intermolecular interactions of –COOH group, to obtain exotic architectures of supramolecular assemblies. Also, it reveals the vital role of the intermolecular interactions in the formation of host-guest systems based on the strength and rigidity of the host framework.

2.9 EXPERIMENTAL SECTION

2.9.1 CO-CRYSTALLIZATION

All the chemicals used in this study were obtained commercially, and used as such without any further purification. HPLC grade solvents were used for carrying out experiments. The syntheses of molecular complexes of acid **1**, **2**, **3** and **4** were carried out at room temperature by dissolving the constituent reactants in the appropriate spectroscopic grade solvents, as the case may be. For a typical crystallization, in a 25 mL conical flask, 127 mg (0.5 mmol) of acid **1** and 90 mg (0.5 mmol) of 1,10-phenanthroline, ***110phe*****,** were dissolved in CH_3OH by heating CH_3OH to the boiling temperature and then subsequently cooling to room temperature at ambient conditions. Colorless rectangular block type single crystals of good quality were obtained within 2 days, which were used for single-crystal structure determination studies by X-ray diffraction methods. However, in the case of **1f, 1g** and **2c**, the reactants ***bpyee***, ***bpyea*** and ***17phe***, formed an insoluble precipitate from CH_3OH upon mixing with either of the acids. However, the resultant precipitate upon dissolving in dimethyl sulfoxide (DMSO) gave single crystals over a period of 7 days.

The molecular complex **2a** was prepared by dissolving 105 mg (0.5 mmol) of acid **2**, 135.5 mg (0.5 mmol) of $HgCl_2$, 78.09 mg (0.5 mmol) of ***bpy*** in 15 ml of water in a Teflon flask and kept in an autoclave at 170°C for 24 hours. Colorless, block-like single crystals were obtained upon slow cooling.

2.9.2 X-RAY CRYSTALLOGRAPHY

Good quality single crystals of molecular complexes of acid **1, 2, 3** and **4** were carefully chosen after viewing through a Leica microscope supported by a rotatable polarizing stage and a CCD camera. The crystals were glued to a thin glass fiber using an adhesive (cyano acrylate) and mounted on a diffractometer equipped with an APEX CCD area detector. The X-ray intensity data were collected into 2424 frames with varying exposure time depending upon the quality of the crystal(s). The data collection was smooth in all the cases, and no extraordinary methods have been employed, as the crystals were quite stable. The intensity data were processed using Bruker's suite of data processing programs (SAINT),[22] and absorption corrections were applied using SADABS.[23] The structure solution of all the complexes have been carried out by direct methods, and refinements were performed by fullmatrix least squares on F^2 using the SHELXTL-PLUS[24] suite of programs. All the structures converged to good *R* factors. All the non-hydrogen atoms were refined anisotropically, and the hydrogen atoms obtained from Fourier maps were refined isotropically. All the refinements were smooth in all the structures. All the intermolecular interactions were computed using PLATON.[25]

Table 2.1: Crystallograhic data of the molecular complexes of acid **1**.

	1a	**1b**	**1b.H_2O**	**1c**
formula	$(C_{10}H_6O_8)$: $(C_{12}H_8N_2)$: (H_2O)	$(C_{10}H_6O_8)$: $2(C_{12}H_8N_2)$	$(C_{10}H_6O_8)$: $(C_{12}H_8N_2)$: $2(H_2O)$	$(C_{10}H_6O_8)$: $2(C_{12}H_8N_2)$
fw	451.36	614.56	470.38	307.28
crystal habit	blocks	blocks	blocks	blocks
crystal color	colorless	colorless	light yellow	light yellow
crystal system	triclinic	triclinic	triclinic	monoclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
a(Å)	8.001(1)	7.084(1)	9.752(2)	7.686(2)
b(Å)	9.822(2)	7.253(1)	9.822(2)	15.310(3)
c(Å)	12.257(2)	13.933(2)	12.034(3)	12.137(3)
α(deg)	94.85(1)	90.68(1)	80.10(1)	90
β(deg)	92.10(1)	102.41(1)	69.38(1)	101.29(1)
γ(deg)	94.63(1)	106.30(1)	67.38(1)	90
V(Å^3)	955.7(3)	669.1(2)	994.9(4)	1400.6(6)
Z	2	1	2	4
D_{calc}(g cm^{-3})	1.572	1.525	1.570	1.457
T(K)	298(2)	298(2)	298(2)	298(2)
Mo kα	0.71073	0.71073	0.71073	0.71073
μ (mm^{-1})	0.124	0.111	0.126	0.106
2θ range (deg)	46	46	46	52.62
limiting indices	$-8 \le h \le 6$ $-10 \le k \le 10$ $-13 \le l \le 13$	$-7 \le h \le 7$ $-8 \le k \le 8$ $-15 \le l \le 15$	$-10 \le h \le 10$ $-10 \le k \le 10$ $-13 \le l \le 13$	$-9 \le h \le 5$ $-19 \le k \le 18$ $-15 \le l \le 14$
F(000)	468	318	488	636
no. reflns measured	4124	7055	8265	7536
no. unique reflns [R(int)]	2723 [0.0481]	1928 [0.0528]	2865 [0.0291]	2835 [0.0205]
no. reflns used	2460	1654	2510	2578
no. parameters	363	252	379	252
reflection\parameter	7.50	7.65	7.56	10.23
GOF on F^2	1.012	1.045	1.049	1.124
R1[I>2σ(I)]	0.0658	0.0426	0.0379	0.0473
wR2	0.1762	0.0984	0.1018	0.1188
Final diff. four map (e^- . Å^{-3}) max, min	0.37, -0.44	0.20, -0.21	0.18, -0.30	0.19, -0.29

Table 2.1: ***contd…***

	1d	**1e**	**1f**	**1g**
formula	$(C_{10}H_6O_8)$: $2(C_{12}H_8N_2)$: $4(H_2O)$	$(C_{10}H_6O_8)$: $(C_7H_{10}N_2)$	$(C_{10}H_6O_8)$: $(C_{12}H_{10}N_2)$	$(C_{10}H_6O_8)$: $(C_{12}H_{12}N_2)$
fw	343.31	376.61	436.37	438.38
crystal habit	plates	blocks	blocks	blocks
crystal color	yellow	colorless	colorless	colorless
crystal system	triclinic	triclinic	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a(Å)	7.084(2)	9.230(2)	3.850(1)	4.321(1)
b(Å)	10.221(3)	9.844(2)	11.162(3)	10.239(2)
c(Å)	11.829(3)	10.127(2)	12.126(4)	12.121(2)
α(deg)	85.52(1)	108.46(1)	113.46(1)	113.91(1)
β(deg)	76.42(1)	103.28(1)	95.26(1)	97.71(1)
γ(deg)	74.67(1)	99.61(1)	92.35(1)	92.57(1)
V(Å^3)	802.8(4)	820.3(3)	474.3(2)	482.9(2)
Z	2	2	1	1
D_{calc}(g cm^{-3})	1.420	1.524	1.528	1.507
T(K)	298(2)	298(2)	298(2)	298(2)
Mo kα	0.71073	0.71073	0.71073	0.71073
μ (mm^{-1})	0.109	0.123	0.119	0.117
2θ range (deg)	46	46	46	46
limiting indices	$-7 \le h \le 7$ $-11 \le k \le 11$ $-13 \le l \le 13$	$-10 \le h \le 10$ $-10 \le k \le 10$ $-11 \le l \le 11$	$-4 \le h \le 4$ $-12 \le k \le 12$ $-13 \le l \le 13$	$-4 \le h \le 4$ $-11 \le k \le 11$ $-13 \le l \le 13$
F(000)	358	392	226	228
no. reflns measured	5502	6808	3977	4061
no. unique reflns [R(int)]	2306 [0.0585]	2355 [0.0401]	1377 [0.0827]	1386 [0.0661]
no. reflns used	1436	2106	1050	1136
no. parameters	286	308	177	181
reflection\parameter	8.06	7.65	7.78	7.66
GOF on F^2	0.904	1.048	1.072	0.968
R1[I>2σ(I)]	0.0423	0.0469	0.0705	0.0371
wR2	0.0803	0.1241	0.1839	0.0858
Final diff. four map (e^- . Å^{-3}) max, min	0.17, -0.16	0.20, -0.30	0.26, -0.29	0.19, -0.28

Table 2.2: Characteristics of hydrogen bonds in the molecular complexes of acid **1** (distances/Å and angles/deg)[#].

Hydrogen bonds	1a			1b			1b.H_2O			1c		
O-H···O	1.55	2.55	170.2	1.66	2.61	172.1	1.74	2.67	175.3			
	1.87	2.73	165.2				1.84	2.79	172.1			
							1.50	2.51	177.6			
O-H···O^-	1.68	2.66	164.0				2.09	2.95	172.8			
							1.59	2.61	174.5			
							1.37	2.40	170.6			
O-H···N	2.26	3.00	163.2	1.30	2.56	176.9	1.94	2.81	170.0	1.54	2.59	175.4
										1.64	2.62	173.6
N^+-H···O	2.02	2.74	129.3				1.91	2.78	172.3			
C-H···O	2.37	3.25	175.6	2.50	3.29	140.7	2.62	3.21	120.0	2.37	3.21	142.3
	2.45	3.10	127.5	2.65	3.47	138.9	2.47	3.10	123.5	2.46	3.32	150.4
	2.47	3.32	145.8	2.66	3.28	123.4	2.92	3.80	155.6	2.49	3.31	144.3
	2.56	3.35	141.9	2.69	3.34	126.1	2.67	3.35	131.1	2.73	3.42	129.9
	2.63	3.41	136.8	2.69	3.45	133.0	2.68	3.51	148.8	2.73	3.42	127.7
	2.79	3.61	145.5	2.74	3.36	121.1	2.27	3.20	161.9	2.79	3.43	125.6
	2.80	3.42	127.6	2.85	3.74	153.9	2.83	3.64	144.0	2.83	3.63	140.5
	2.86	3.66	139.1	2.86	3.50	126.8				2.84	3.52	128.0
	2.97	3.79	143.8							2.86	3.74	153.0
C-H···O^-	2.31	3.26	162.5				2.59	3.49	166.5			
	2.64	3.37	137.3									
	2.65	3.49	156.4									

[#] The three numbers in each column indicate H···O(N); (N^+,C)O···O(O^-,N) and angles, respectively.

Table 2.2: ***contd…***

Hydrogen bonds	1d			1e			1f			1g		
O-H···O	1.48	2.68	178.3	1.72	2.56	158.3						
	1.93	2.85	176.1									
	1.82	2.86	136.7									
	1.38	2.53	173.3									
O-H···O$^-$				1.79	2.65	170.0	1.46	2.41	161.3	1.38	2.40	170.6
O-H···N	1.99	2.89	173.6									
	1.68	2.65	164.6									
N$^+$-H···O				2.41	3.12	142.1	1.64	2.67	173.1	1.69	2.72	176.2
				2.32	2.89	124.9						
C-H···O	2.59	3.33	132.5	2.63	3.25	123.1	2.99	3.73	138.9	2.67	3.46	143.6
	2.41	3.35	153.6	2.68	3.31	126.7	2.78	3.50	130.7	2.69	3.42	133.5
	2.61	3.47	152.3	2.34	2.98	122.1	2.53	3.43	153.3	2.88	3.61	134.3
	2.86	3.51	128.2	2.36	3.17	140.4	2.28	3.15	157.9	2.73	3.37	125.0
	2.84	3.53	127.3	2.78	3.55	142.5				2.46	3.28	142.5
	2.54	3.48	151.5	2.65	3.48	142.2				2.90	3.83	155.7
				2.78	3.47	123.6				2.71	3.65	158.6
C-H···O$^-$				2.98	3.78	143.4	2.51	3.32	143.6	2.42	3.32	156.8
				2.66	3.53	153.0	2.46	3.11	130.1	2.36	3.06	130.8
				2.70	3.33	126.2						

[#] The three numbers in each column indicate H···O(N); (N^+,C)O···O(O^-,N) and angles, respectively.

Table 2.3: Crystallograhic data of the molecular complexes of acid **2**.

	2a	**2b**	**2c**
formula	$3(C_9H_6O_6)$: $C_{10}H_8N_2$: $6(H_2O)$	$C_9H_6O_6$: $C_5H_6N_2$: H_2O	$C_9H_6O_6$): $3(C_{12}H_8N_2)$: $8(H_2O)$
fw	890.66	322.27	878.75
Crystal shape	blocks	plates	plates
Crystal color	colorless	colorless	light yellow
Crystal system	monoclinic	monoclinic	monoclinic
Space group	*C*2/*c*	$P2_1/c$	$P2_1/n$
a(Å)	10.736(2)	10.512(3)	11.231(2)
b(Å)	21.528(5)	18.906(5)	18.308(3)
c(Å)	16.244(4)	7.318(2)	21.933(4)
α(deg)	90	90	90
β(deg)	90.35(1)	106.04(1)	100.90(1)
γ(deg)	90	90	90
V(Å^3)	3754.3(15)	1397.8(7)	4428.7(2)
Z	4	4	4
D_{calc}(g cm^{-3})	1.576	1.531	1.318
T(K)	298(2)	298	298
Mo kα	0.71073	0.71073	0.71073
μ (mm^{-1})	0.135	0.125	0.100
2θ range (deg)	46.62	46.72	56.14
Limiting indices	$-11 \le h \le 11$ $-23 \le k \le 23$ $-18 \le l \le 17$	$-11 \le h \le 11$ $-20 \le k \le 20$ $-8 \le l \le 8$	$-14 \le h \le 9$ $-24 \le k \le 23$ $-25 \le l \le 28$
F(000)	1848	672	1816
No. reflns measured	11578	8616	25299
No. unique reflns [*R*(int)]	2710 [0.0260]	2023 [0.0688]	9806 [0.0376]
No. reflns used	2437	1089	5050
No. parameters	350	264	586
Reflection\ Parameter ratio	7.74	7.55	16.73
GOF on F^2	1.075	0.783	1.161
*R*1[$I>2\sigma(I)$]	0.0396	0.0408	0.0759
*w*R2	0.0953	0.0539	0.2026
Final diff. Fourier map (e$^-$. Å^{-3}) max, min	0.33, -0.21	0.15, -0.15	0.44, -0.43

Table 2.4: Characteristics of hydrogen bonds in the molecular complexes of acid **2.** (distances/Å and angles/deg)[#]

Hydrogen bonds	2a			2b			2c		
O-H···O	1.65	2.47	178.4	1.56	2.73	164.5			
	1.71	2.69	176.5	1.61	2.58	166.6			
	1.75	2.61	174.0	1.62	2.64	166.9			
	1.83	2.71	176.2	1.99	2.81	169.8			
	1.89	2.74	168.4						
	1.90	2.68	157.6						
	1.99	2.83	172.3						
	2.29	3.02	154.5						
N-H···O				1.60	2.72	166.4			
				2.11	2.98	163.7			
C-H···O	2.23	3.10	147.2	2.37	3.18	143.8	2.04	2.96	168.7
	2.37	3.24	148.7	2.53	3.43	162.0	2.06	2.98	169.4
	2.54	3.29	138.1	2.66	3.60	157.0	2.34	3.27	174.8
	2.77	3.39	126.7	2.90	3.73	146.2	2.47	3.36	161.3
	2.82	3.60	139.3	3.00	3.90	150.6	2.49	3.37	157.5
	2.86	3.72	155.4				2.62	3.54	172.3
							2.67	3.51	150.3
							2.67	3.54	155.6
							2.69	3.60	164.5
							2.76	3.62	153.5
							2.79	3.44	127.9
							2.80	3.52	134.7
							2.80	3.69	160.8
							2.85	3.75	165.5
							2.88	3.56	130.9
							2.93	3.60	130.0
							2.96	3.64	130.3
							2.97	3.88	163.5
							2.98	3.78	144.7
							3.05	3.88	149.6

[#] The three numbers in each column indicate H···O(N,S); (N,C)O···O(N,S) and angles, respectively.

Table 2.5: Crystallograhic data of the molecular complexes of acid **3**.

	3a	**3c**	**3d**	**3e**	**3f**	**3g**
formula	$2(C_9H_6O_6)$: $(C_{10}H_8N_2)$	$2(C_9H_6O_6)$: $3(C_{12}H_{10}N_2)$	$2(C_9H_6O_6)$: $2(C_{13}H_{14}N_2)$	$(C_9H_6O_6)$: $(C_{12}H_8N_2)$: (CH_3CN)	$(C_9H_6O_6)$: $(C_{12}H_8N_2)$: (H_2O)	$(C_9H_6O_6)$: $(C_{12}H_8N_2)$: $2(H_2O)$
fw	288.23	483.47	816.80	431.40	408.36	424.36
crystal habit	blocks	blocks	blocks	blocks	plates	blocks
crystal color	colorless	colorless	colorless	colorless	light yellow	colorless
crystal system	triclinic	triclinic	monoclinic	monoclinic	orthorhombic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P2_1/n$	*Ibam*	$P\bar{1}$
a(Å)	7.659(1)	7.879(2)	23.283(3)	13.546(3)	30.004(10)	10.348(2)
b(Å)	8.479(1)	9.967(2)	9.953(2)	8.603(2)	18.099(6)	10.614(2)
c(Å)	11.367(2)	15.325(4)	18.681(3)	17.572(4)	6.788(2)	10.838(2)
α(deg)	108.91(1)	81.56(1)	90	90	90	74.17(2)
β(deg)	95.30(1)	87.55(1)	113.49(3)	95.07(4)	90	62.13(2)
γ(deg)	113.12(1)	75.43(1)	90	90	90	67.04(2)
V(Å^3)	621.45(15)	1152.1(5)	3970.2(9)	2039.9(7)	3686(2)	963(2)
Z	2	2	4	4	8	2
D_{calc}(g cm^{-3})	1.540	1.394	1.367	1.405	1.472	1.464
T(K)	298(2)	298(2)	298(2)	298(2)	298(2)	298(2)
Mo kα	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
μ (mm^{-1})	0.123	0.100	0.101	0.104	0.112	0.114
2θ range (deg)	56.48	50.06	50	56.58	56.66	50.84
limiting indices	$-9 \le h \le 9$ $-8 \le k \le 11$ $-15 \le l \le 11$	$-9 \le h \le 9$ $-11 \le k \le 11$ $-18 \le l \le 18$	$-27 \le h \le 27$ $-11 \le k \le 11$ $-19 \le l \le 22$	$-17 \le h \le 16$ $-9 \le k \le 11$ $-18 \le l \le 23$	$-33 \le h \le 38$ $-23 \le k \le 24$ $-5 \le l \le 8$	$-12 \le h \le 12$ $-12 \le k \le 12$ $-13 \le l \le 13$
F(000)	298	504	1712	896	1696	440
no. reflns measured	3695	8253	19301	11931	10825	7153
no. unique reflns [R(int)]	2718 [0.0157]	4045 [0.1189]	6963 [0.0921]	4747 [0.0516]	2387 [0.0465]	3493 [0.0382]
no. reflns used	2312	3083	3530	2564	1547	2236
no. parameters	230	429	701	302	215	344
reflection\parameter	10.05	9.43	9.93	15.72	11.10	10.15
GOF on F^2	1.095	1.027	1.022	0.999	1.043	1.047
R1[I>2σ(I)]	0.0469	0.0840	0.0754	0.0613	0.0699	0.0706
wR2	0.1384	0.2310	0.1427	0.1161	0.1620	0.1704
Final diff. four map (e^- . Å^{-3}) max, min	0.33, –0.24	0.87, -0.56	0.21, -0.20	0.21, –0.21	0.24, -0.28	0.41, -0.27

Table 2.6: Characteristics of hydrogen bonds in the molecular complexes of acid **3.** (distances/Å and angles/deg)[#]

Hydrogen bonds	3a			3c			3d		
O-H···O	1.76	2.66	175.8				1.60	2.55	149.3
	1.83	2.62	169.1				1.72	2.56	159.1
O-H···N	1.74	2.71	167.3	1.62	2.56	165.9	1.43	2.55	165.0
				1.70	2.64	178.3	1.66	2.61	162.8
				1.79	2.61	152.0			
N-H···O							1.53	2.59	174.8
							1.58	2.61	166.9
C-H···N				2.93	3.74	140.7			
C-H···O	2.49	3.45	174.3	2.31	3.15	141.2	2.20	3.18	150.1
	2.57	3.31	131.9	2.46	3.40	154.7	2.34	3.12	133.2
	2.64	3.31	130.5	2.48	3.16	134.6	2.36	3.30	157.9
	2.69	3.60	158.7	2.72	3.33	121.5	2.53	3.36	141.3
	2.78	3.55	139.7	2.74	3.67	169.7	2.56	3.22	126.3
	2.82	3.65	148.7	2.75	3.38	128.6	2.71	3.28	123.7
	2.90	3.51	122.5	2.81	3.45	122.9	2.72	3.45	128.4
				2.82	3.53	131.2	2.75	3.62	162.2
				2.82	3.72	153.8	2.76	3.36	122.6
				2.85	3.70	162.1	2.77	3.71	149.5
				2.89	3.54	134.7	2.78	3.48	136.8
				3.01	3.68	128.8	2.80	3.40	126.4
							2.83	3.66	136.0
							2.85	3.51	125.0
							2.86	3.46	122.3
							2.86	3.52	122.5
							2.86	3.76	150.1
							2.87	3.44	123.8
							2.88	3.68	159.1
							2.90	3.50	120.1
							2.93	3.68	144.3
							2.93	3.76	146.6

[#] The three numbers in each column indicate H···O(N); (N,C)O···O(N) and angles, respectively.

Table 2.6: ***contd…***

Hydrogen bonds	3e			3f			3g		
O-H···O	1.50	2.51	170.9	1.40	2.70	176.4	1.57	2.78	169.6
	1.61	2.56	159.1	2.05	2.78	168.8	1.58	2.72	146.0
							1.78	2.80	157.6
O-H···N				1.37	2.55	172.0	1.30	2.56	173.2
				1.61	2.62	175.0	1.70	2.58	161.1
N-H···O	2.10	2.88	142.8						
C-H···N	2.78	3.58	145.2						
	2.79	3.65	149.0						
	2.86	3.59	135.9						
C-H···O	2.31	3.26	170.5	2.26	3.18	160.7	2.62	3.53	150.1
	2.47	3.15	129.5	2.31	3.25	171.8	2.66	3.39	133.7
	2.58	3.44	152.5	2.49	3.27	137.2	2.67	3.30	128.9
	2.68	3.33	126.9	2.55	3.55	179.4	2.70	3.40	131.5
	2.68	3.42	137.5	2.66	3.33	129.1	2.75	3.36	122.1
	2.71	3.64	161.9	2.70	3.57	170.3	2.76	3.69	166.4
	2.77	3.44	129.1	2.88	3.80	169.4	2.77	3.42	132.0
	2.78	3.67	160.3	2.94	3.64	130.6	2.81	3.50	136.2
				3.02	3.73	134.4	2.86	3.49	120.5
							2.90	3.73	162.2
							2.97	3.86	171.7

[#] The three numbers in each column indicate H···O(N); (N,C)O···O(N) and angles, respectively.

Table 2.7: Crystallograhic data of the molecular complexes of acid **4**.

	4a	**4b**	**4c**
formula	$2(C_9H_6O_6)$: $2(C_{12}H_{10}N_2)$	$(C_9H_6O_6)$: $(C_{12}H_{12}N_2)$	$(C_9H_6O_6)$: $(C_{13}H_{14}N_2)$:
fw	784.72	394.37	408.40
crystal habit	blocks	blocks	blocks
crystal color	colorless	colorless	colorless
crystal system	triclinic	triclinic	monoclinic
space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
a(Å)	7.330(2)	4.421(3)	10.142(2)
b(Å)	13.881(3)	10.234(7)	21.916(2)
c(Å)	17.857(4)	20.490(2)	9.757 (2)
α(deg)	82.96(4)	89.92(2)	90
β(deg)	89.64(4)	86.64(2)	114.95(2)
γ(deg)	82.55(4)	86.25(2)	90
V(Å^3)	1788.0(7)	923.5(2)	1966.3(3)
Z	2	2	4
D_{calc}(g cm^{-3})	1.458	1.418	1.380
T(K)	298(2)	298(2)	298(2)
Mo kα	0.71073	0.71073	0.71073
μ (mm^{-1})	0.109	0.105	0.102
2θ range (deg)	56.72	45	50
limiting indices	$-9 \le h \le 9$ $-18 \le k \le 18$ $-23 \le l \le 13$	$-4 \le h \le 4$ $-10 \le k \le 10$ $-20 \le l \le 22$	$-12 \le h \le 12$ $-24 \le k \le 26$ $-11 \le l \le 9$
F(000)	816	412	856
no. reflns measured	10676	3726	9676
no. unique reflns [R(int)]	7811 [0.0186]	2391 [0.0346]	3451 [0.0586]
no. reflns used	5075	1319	2617
no. parameters	650	334	351
reflection\parameter	12.01	7.16	9.83
GOF on F^2	1.070	0.925	1.199
R1[I>2σ(I)]	0.0819	0.0692	0.0783
wR2	0.2180	0.1714	0.1524
Final diff. four map (e$^-$. Å^{-3}) max, min	0.28, -0.27	0.26, -0.26	0.26, -0.28

Table 2.8: Characteristics of hydrogen bonds in the molecular complexes of acid **4** (distances/Å and angles/deg)[#].

Hydrogen bonds	4a			4b			4c		
O-H···O							1.44	2.55	164.4
O-H···N	1.69	2.66	165.5	1.52	2.60	175.0	1.30	2.59	173.7
	1.71	2.64	173.8						
N-H···O	1.73	2.72	166.0	1.57	2.71	168.5	1.66	2.61	175.7
	1.81	2.69	164.5						
	2.40	3.08	133.7						
C-H···N									
C-H···O	2.12	3.13	170.8	2.32	3.04	135.4	2.08	3.10	165.7
	2.29	3.19	149.8	2.38	3.22	144.8	2.16	3.16	173.7
	2.31	3.09	136.5	2.53	3.41	166.4	2.53	3.29	138.2
	2.34	3.02	124.4	2.56	3.34	150.3	2.54	3.42	146.7
	2.37	3.07	127.2	2.56	3.48	149.0	2.56	3.46	156.0
	2.37	3.09	154.2	2.65	3.67	157.1	2.63	3.24	123.6
	2.43	3.16	130.0	2.74	3.65	150.2	2.66	3.43	140.5
	2.45	3.41	161.6	2.76	3.40	132.0	2.79	3.61	139.5
	2.54	3.21	128.7	2.81	3.82	156.0	2.81	3.52	128.1
	2.55	3.29	133.2	2.86	3.66	149.0	2.86	3.71	156.3
	2.65	3.41	151.3				3.01	3.90	158.4
	2.78	3.57	140.5				3.02	3.89	146.0
	2.81	3.57	130.7						
	2.83	3.63	138.3						
	2.89	3.60	139.1						
	2.90	3.62	145.7						
	2.93	3.68	132.3						
	2.97	3.75	140.0						
	2.99	3.77	135.9						

[#] The three numbers in each column indicate H···O(N); (N,C)O···O(N) and angles, respectively.

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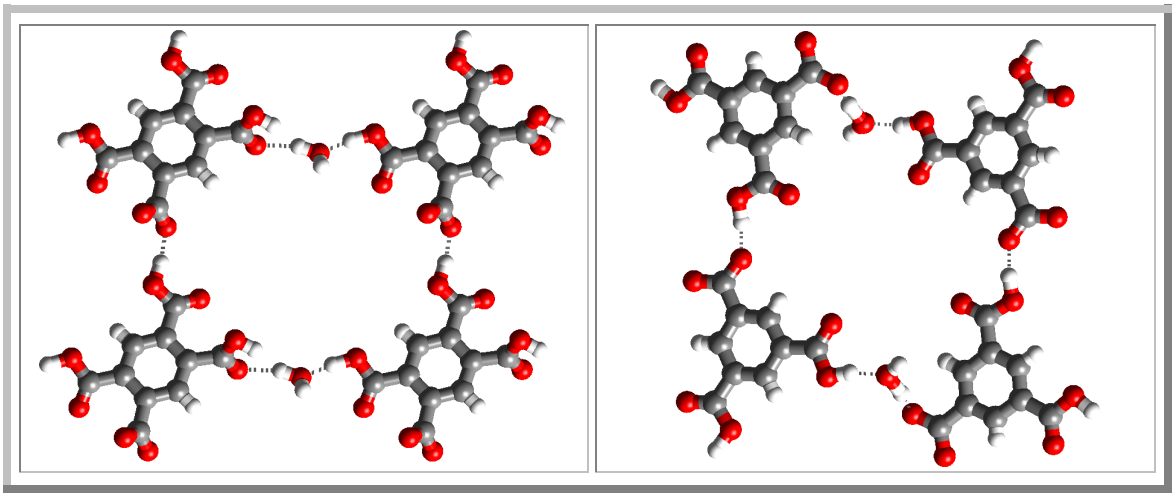
CHAPTER THREE

HOST-GUEST COMPLEXES OF 3,5-DINITROBENZONITRILE: THE ROLE OF C-H···N HYDROGEN BONDS

3.1 INTRODUCTION

Inclusion phenomenon is widespread in the current frontier areas of research in chemistry and have gained special attention for possible applications in the areas of catalysis, separation technology, biomimetics, etc. as vividly described in chapter one.[1-3] While the hydrogen bond play an important role in the creation of the host-guest complexes, as it is well known from the literature that hosts formed by functional groups like –COOH, $–CONH_2$ etc., which are essentially yield strong hydrogen bonds, are well studied.[4-5]

Indeed, the examples discussed in chapter two are illustrative to exemplify the influence of such hydrogen bonds in the design and synthesis of host-guest assemblies as schematically shown in Scheme 3.1.



Scheme 3.1

Also creation of host-guest type systems by utilizing both strong and weak hydrogen bonds, as exemplified by the adducts of 3,5-dinitrobenzoic acid, and its

4-methyl and 4-chloro derivatives, with anthracene are also well known in the literature.[6] In these complexes, the acid molecules form an hexagonal ensemble with cavities, which are being occupied by anthracene molecules (see Figure 3.1).

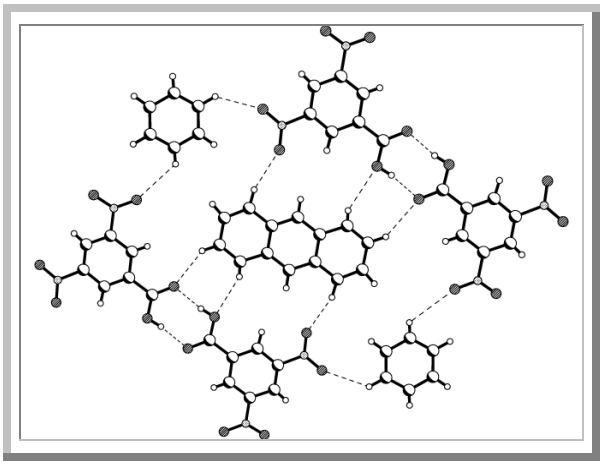


Figure 3.1: Host-guest complex of 3,5-dinitrobenzoic acid with anthracene in the presence of benzene.

In these studies, cavity structures were exclusively obtained only in the presence of hydrocarbon moieties and while replacing the anthracene with aza-donor molecules like acridine, phenazine, 4,4'-bipyridine, etc., gave different assemblies possessing molecular tapes (see Figure 3.2).[7]

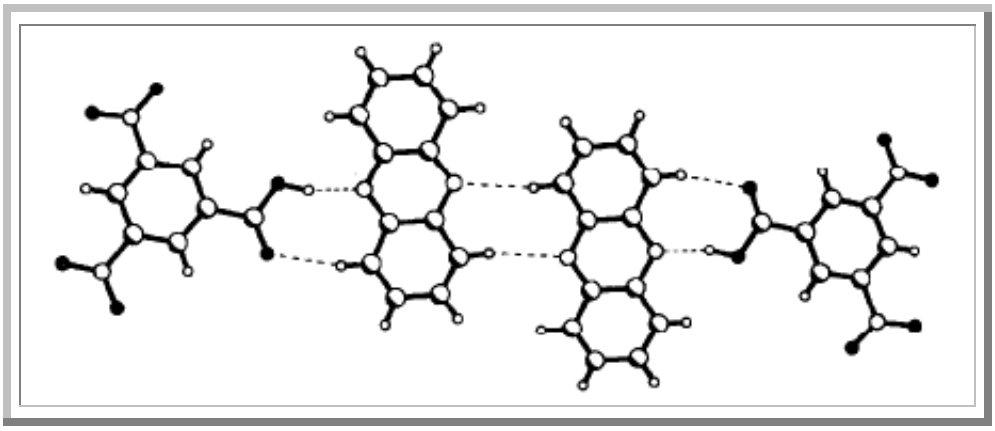


Figure 3.2: Molecular tapes of 3,5-dinitrobenzoic acid and phenazine.

Nevertheless, aza-donor molecules could be incorporated as guests upon replacement of the acid group on 3,5-dinitrobenzoic acid with an amide group as shown in Figure 3.3. But surprisingly, hydrocarbons failed to form host-guest systems with such amides.[5g, 8]

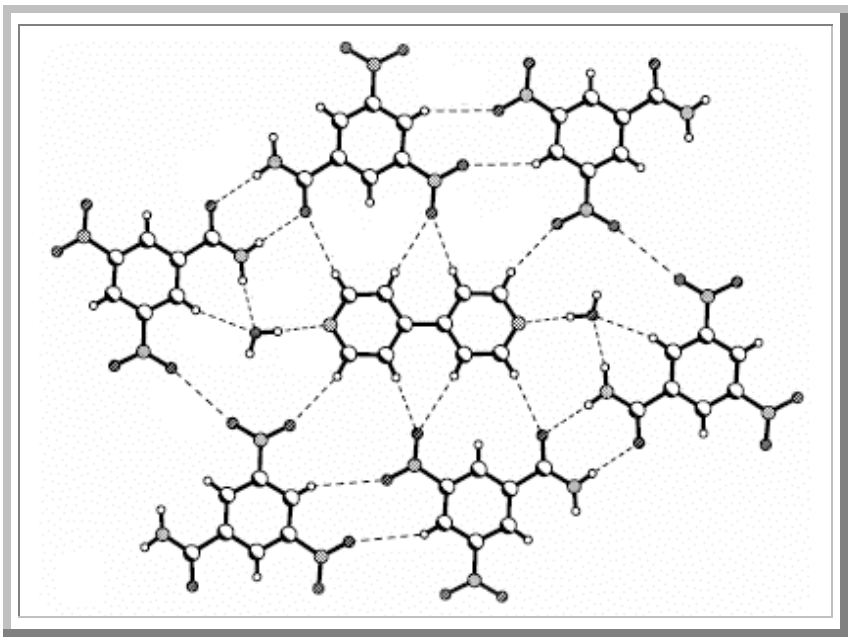


Figure 3.3: Molecular complex of 3,5-dinitrobenzamide and 4,4'-bipyridine.

Thus, in all these illustrative examples, the host-network is created by either strong hydrogen bonds or both strong (O-H···O, N-H···O) and weak (C-H···O) hydrogen bonds. However, the construction of host lattices entirely through weak hydrogen bonds (C-H···O, C-H···N, C-H···π, etc.) are not well explored, as only a very limited examples are known in the literature as described below.

For example, 1,2,4,5-tetracyanobenzene has been used for the preparation of various molecular complexes utilizing weak hydrogen bonds with various hydrocarbons as well as aza-donor compounds (see Figure 3.4)[9]

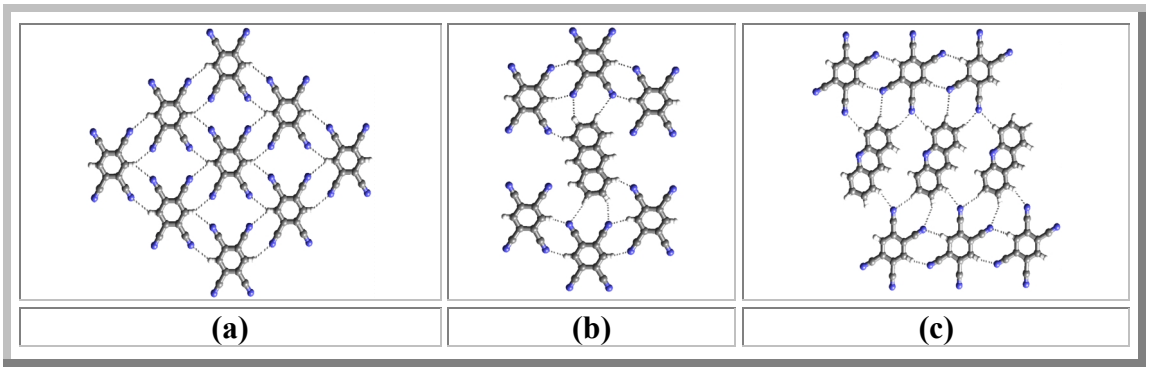


Figure 3.4: (a) Formation of sheets within the crystal structure of 1,2,4,5-tetracyanobenzene stabilized by C-H···N hydrogen bonds. **(b)** and **(c)** Molecular complex of the cyanobenzene with anthracene and acridine respectively, stabilized by C-H···N and C-H···O hydrogen bonds.

Also, the observation of C-H···N hydrogen bonds between the –C≡N groups and the aromatic H-atoms in crystalline cyanocinnamic acids directed the utilization of 1,3,5-tricyanobenzene to create an hexagonal network structure in the presence of hexamethylbenzene (see Figure 3.5), exclusively obtained then C-H···N hydrogen bonds.[10]

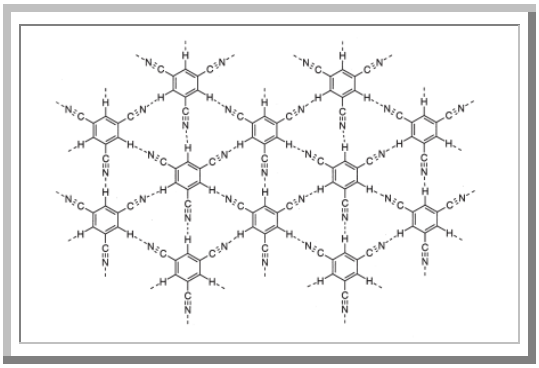


Figure 3.5: Formation of sheets in the crystal structure of 1,3,5-tricyanobenzene stabilized by C-H···N hydrogen bonds.

Hence, it was aimed to explore further feasibility of construction of host lattices utilizing the flexible nature of the weak hydrogen bonds like C-H···O, C-H···N, C-H···π,

etc. for the creation of a wide variety of host-guest complexes. For this purpose, 3,5-dinitrobenzonitrile, **1**, was considered to serve the purpose, as the topology of the hydrogen bond arrangement in **1** is identical to that of 3,5-dinitrobenzoic acid and 3,5-dinitrobenzamide, except for the strength of the hydrogen bond, with a hope that **1** would also yield host networks with appropriate guest molecules. The topological arrangement of two neighbouring molecules of **1** is shown in Figure 3.6(a) along with the similar arrangements for acid and amide analogues in Figure 3.6 (b) and (c), respectively.

In fact, **1** was found to form a host network utilizing C-H···N hydrogen bonds (see Figure 3.7) with anthracene[11] as revealed from an analysis on Cambridge Structural Database (CSD).[12] Hence, co-crystallization of **1** with different hydrocarbons and aza-donor compounds like benzene, naphthalene, acridine, phenazine, phenothiazine, -*o*, -*m* and –*p* xylenes, mesitylene etc., were carried out. Structural aspects of some of these molecular complexes will be discussed in a detailed manner.

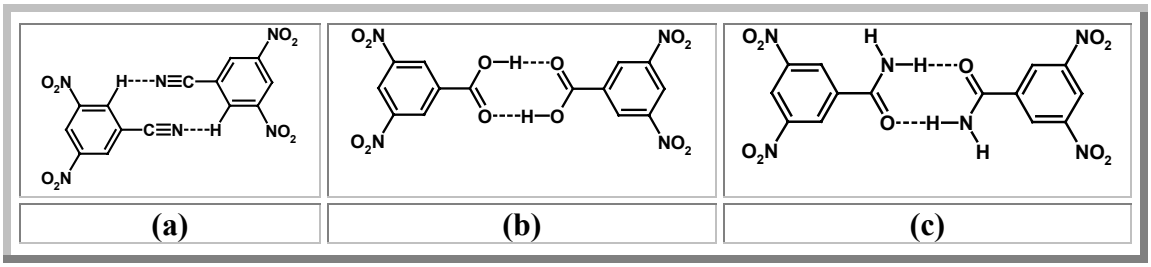


Figure 3.6: Hydrogen bonding arrangement between the adjacent molecules of **(a)** 3,5-dinitrobenzinitrile, **1 (b)** 3,5-dinitrobenzoic acid and **(c)** 3,5-dinitrobenzamide.

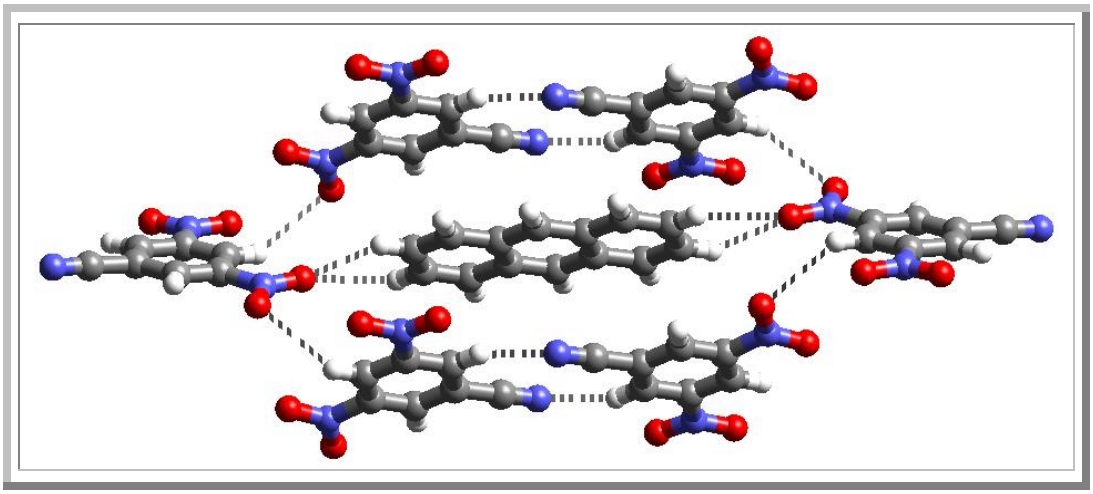


Figure 3.7: Molecular complex of **1** and anthracene.

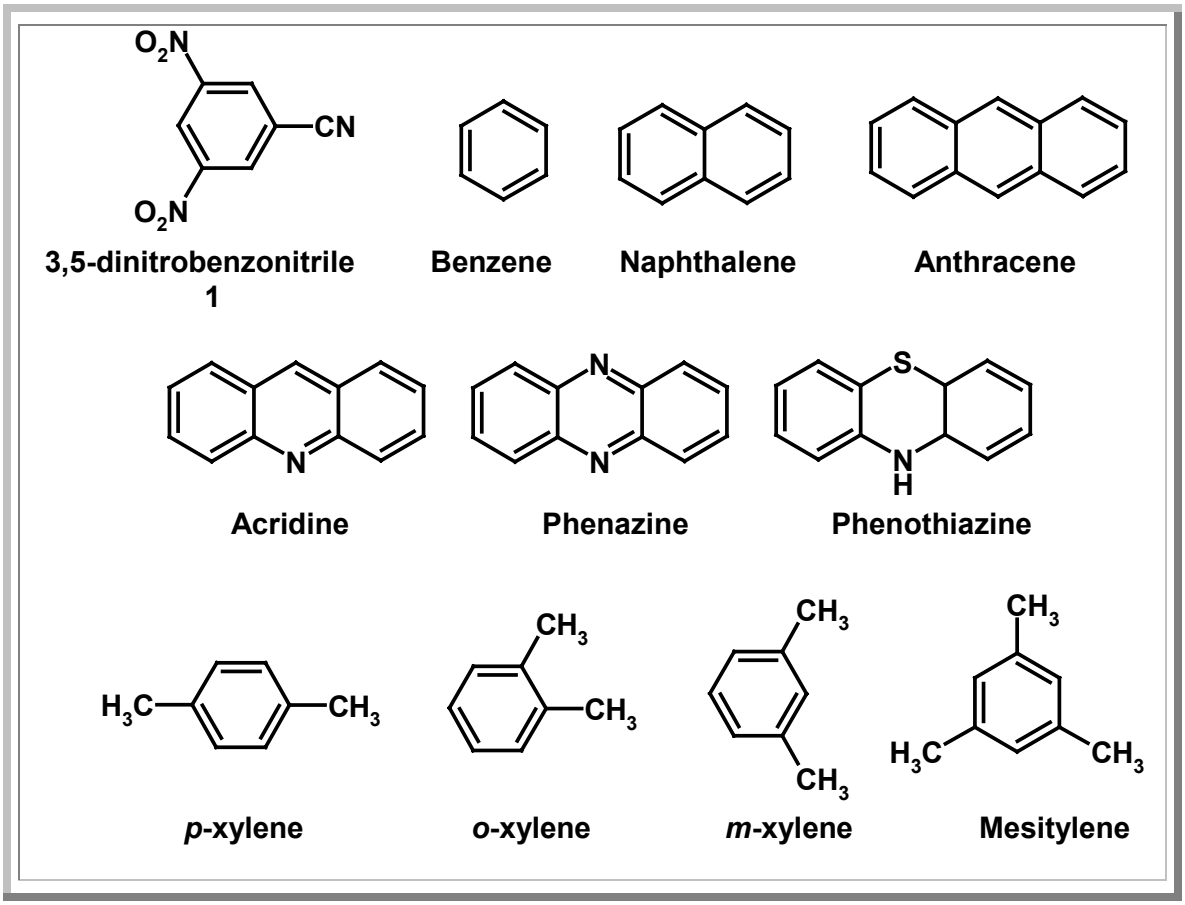


Chart 1

3.2 MOLECULAR COMPLEX OF 3,5-DINITROBENZONITRILE AND BENZENE, 1a

Crystallization of 3,5-dinitrobenzonitrile**, 1,** from benzene gave single crystals, which are quite unstable at ambient conditions, suggesting that a solvated complex is resulted. However, characterization of the single crystals by x-ray diffraction studies by protecting crystals from ambient conditions, reveals the formation of benzene adduct of **1** and the adduct is labeled as **1a**. The complete crystallographic details are given in Table 3.1. The ORTEP diagram is as shown in the Figure 3.8.

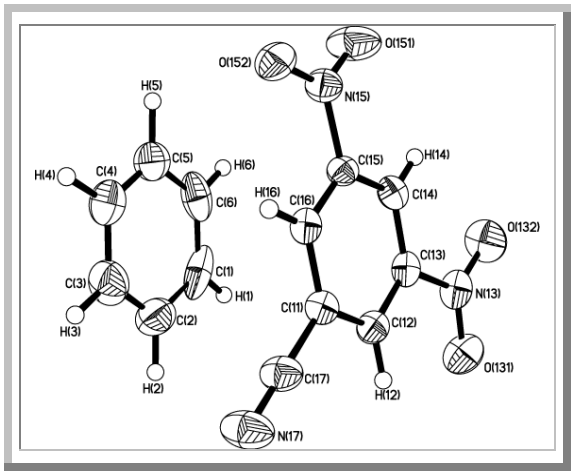


Figure 3.8: ORTEP (50% probability level) drawing of the molecular adduct of **1** and benzene, **1a**.

Packing analysis reveals that this complex forms channels in its three-dimensional structure along a crystallographic axis. The three-dimensional structure along with channels is shown in Figure 3.9(a).

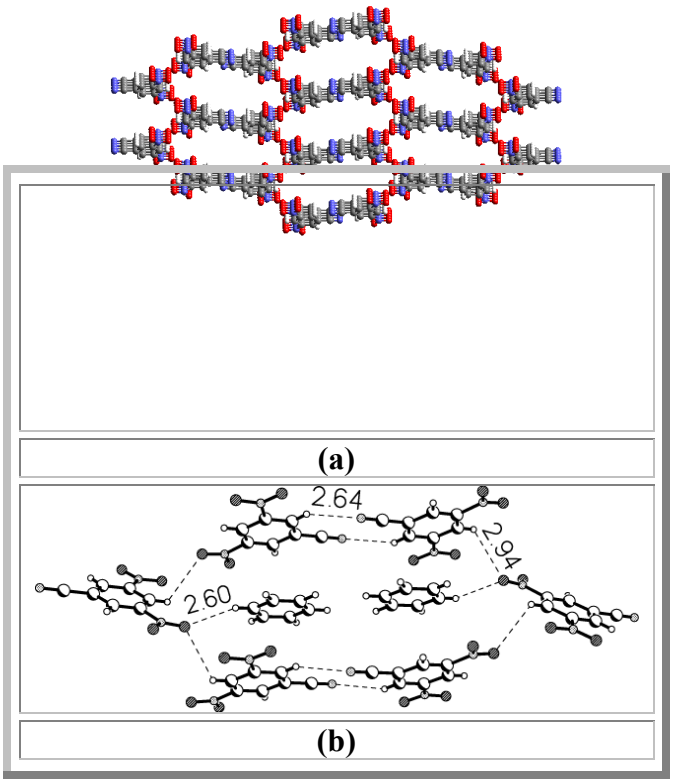


Figure 3.9: (a) Representation of channels observed in the three-dimensional arrangement of the adduct **1a**, formed between **1** with benzene. **(b)** Hexagonal arrangement of molecules of **1** forming a cavity of dimension, (7 x 15 $Å^2$).

In further analysis of molecular arrangement around channels, each of six molecules of **1** form a hexagonal network. In each hexagon, dimers of **1** (held together by centrosymmetric cyclic C-H···N hydrogen bonds) are held together by acyclic

C-H···O hydrogen bonds (Figure 3.9(b)). The H···N distance in the cyclic pattern is 2.64 Å with the C-H···N angle of 146°, and the H···O distance in the acyclic C-H···O hydrogen bond is 2.94 Å. Other characteristics of the hydrogen bonds are given in Table 3.2. Thus, a cavity of 7 x 15 $Å^2$ in dimension is created and benzene molecules fit in these cavities interacting with the host network through the formation of C-H···O hydrogen bonds (H···O, 2.60 Å, Table 3.2). Thus, adduct **1a**, (as anticipated) entirely made up of weak hydrogen bonds, C-H···N and C-H···O, gave a host-guest channel structure.

Further, a close look at Figure 3.9(b) shows that molecules having dimensions equivalent to that of two or three fused benzene moieties can also form similar complexes. As a complex with anthracene is already known in the literature, attempts were done to co-crystallize **1** with naphthalene. However, the crystals obtained were highly unstable as well as of poor quality to carry out any further analysis. But, stable and good quality single crystals were obtained with anthracene analogues, acridine and phenazine in a 2:1 ratio. The two-complexes have been labeled as **1b** and **1c**, respectively.

3.3 MOLECULAR COMPLEXES OF 3,5-DINITROBENZONITRILE WITH ACRIDINE AND PHENAZINE 1b AND 1c RESPECTIVELY

Analysis of X-ray diffraction data of **1b** and **1c** reveals that these two complexes are isomorphous to adduct **1a**, with similar unit cell dimensions and crystallizing in the same space group, $P2_1/c$. The complete crystallographic details are given in Table 3.1. The ORTEP diagram of the complexes **1b** and **1c** are given in the Figure 3.10.

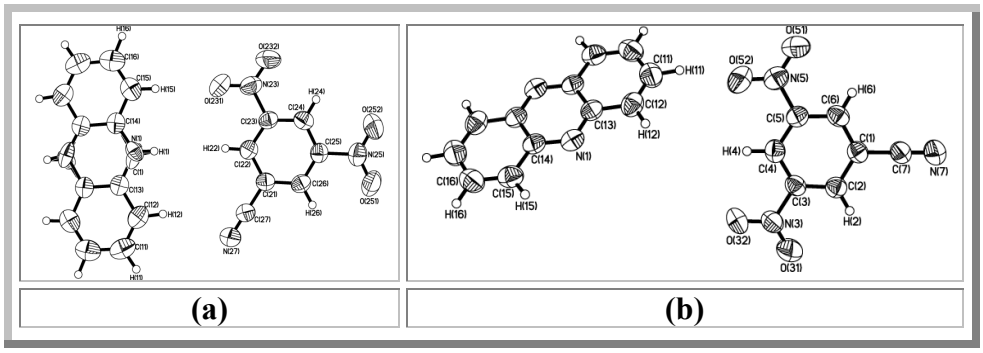


Figure 3.10: ORTEP (50% probability level) drawing of the molecular adduct of **(a) 1** and acridine, complex **1b** and **(b) 1** and phenazine, complex **1c**.

Further, adduct **1a** and complexes **1b** and **1c** are also iso-structural by forming channel structures in the three-dimensional arrangement, similar to the one shown in Figure 3.9(a) for **1a**; the only difference being that the channels are occupied by single molecules of either acridine or phenazine molecules in **1b** and **1c** respectively, as shown in Figure 3.11(a) and (b).

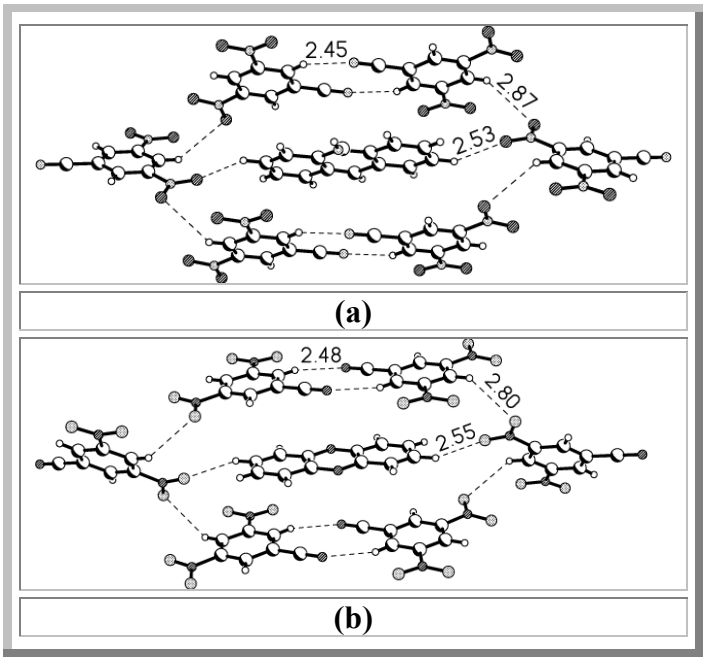


Figure 3.11: Arrangement of molecules in the molecular complexes **(a) 1b** and **(b) 1c**, in an hexagonal manner creating voids, which are occupied by guest molecules.

In each hexagon, the molecules of **1** exist as dimers by forming a centrosymmetric 10-membered ring pattern through C-H···N hydrogen bonds (H···N, 2.45 and 2.48 Å for complexes **1b** and **1c** respectively, Table 3.2). Such adjacent dimers are further held together by C-H···O hydrogen bonds (**1b**, H···O, 2.87 and **1c**, 2.80 Å) leading to the formation of cavities and these cavities in three dimension form channels as shown in Figure 3.12.

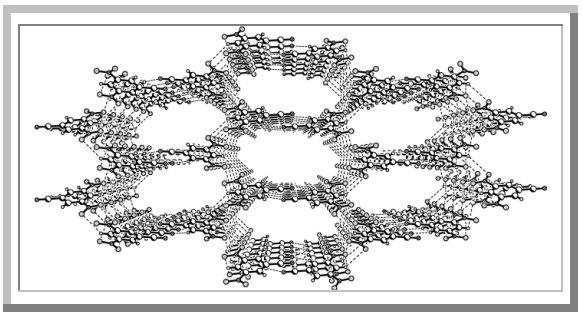


Figure 3.12: Representation of channels observed in the three-dimensional arrangement of adducts **1b** and **1c**, formed between **1** with acridine and phenazine respectively. The guest molecules are omitted for clarity purpose.

A noteworthy and unique nature of the adducts and complexes **1a**, **1b** and **1c** is the retention of the host lattice by **1**, irrespective of the nature of the guest molecules, (hydrocarbon in **1a** and aza-donor moieties in **1b** and **1c**) unlike in the corresponding acid and amide analogues. This is further reflected in the formation of an iso-structural complex between **1** and phenothiazine, as confirmed by single crystal as well as powder x-ray diffraction techniques.

3.4 MOLECULAR COMPLEX OF 3,5-DINITROBENZONITRILE AND PHENOTHIAZINE, 1d

Crystallization of 3,5-dinitrobenzonitrile**, 1,** with phenothiazine, from a methanol solution gave single crystals, suitable for x-ray analysis. The structural analysis reveals that the phenothiazine molecule is disordered at sulphur and nitrogen postions and hence the structure solution upto an acceptable accuracy could not be established. However from the preliminary x-ray data, it was clear that the complex **1d** forms a 2:1 complex with a space group $P2_1/c$ similar to that of complexes **1a**, **1b** and **1c**. The asymmetric unit of the complex **1d** is as shown in the Figure 3.13.

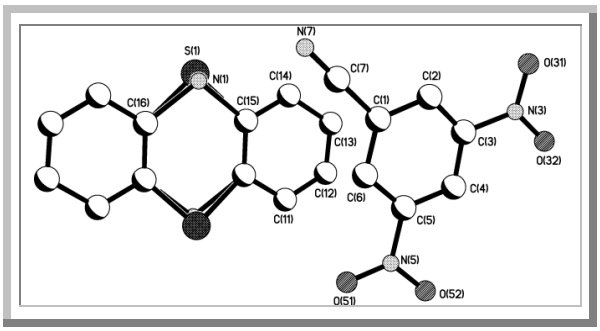


Figure 3.13: Molecular complex of **1** and phenothiazine, **(**complex **1d).** A disorder at sulphur and nitrogen positions of phenothiazine molecule is shown.

Further the iso-structurality of **1d** with that of **la – 1c** is established by comparing powder patterns. The powder patterns recorded for **1b, 1c** and **1d** are shown in Figure 3.14. It is evident that the intense peak at 25.5^{o}, as well as other minor peaks in Figure 3.14(c) match with similar peaks shown in Figures 3.14(a) and (b). Hence, it could be concluded that in **1d** also, a hexagonal network of **1** prevails, while phenothiazine molecules sit in the void space, thus, created.

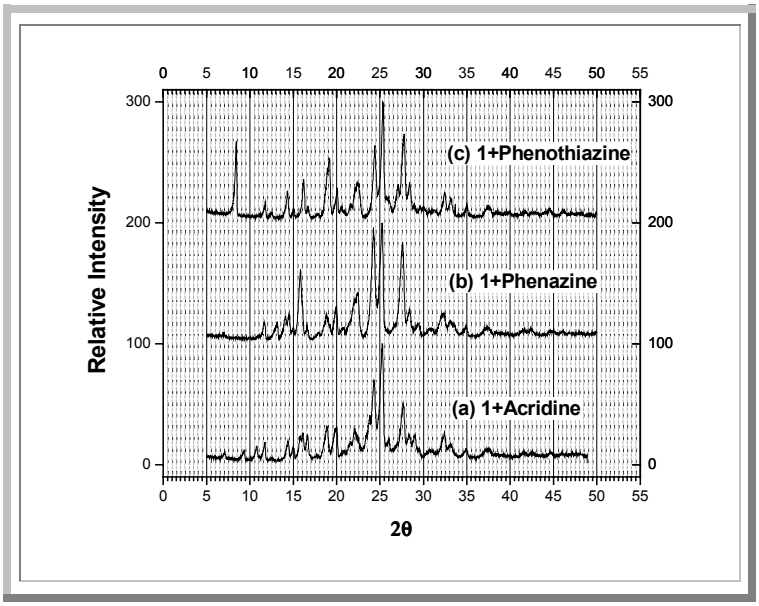


Figure 3.14: Powder X-ray diffraction patterns of ground mixture of complexes of **1** with **(a)** acridine **(b)** phenazine and **(c)** phenothiazine.

3.5 MOLECULAR COMPLEXES OF 3,5-DINITROBENZONITRILE WITH *o*-, *m*-, and *p*-XYLENES

Crystallization of 3,5-dinitrobenzonitrile**, 1,** from *o*-, *m*-, and *p*-xylenes as well as mesitylene gave colorless, block-like single crystals from only *o*-xylene and *p*-xylene, which were also unstable like **1a**, while stable crystals obtained from *m*-xylene and mesitylene, are found to be parent crystals of **1**. The crystals obtained from *p*-xylene, however, could be used for structure determination by protecting from ambient conditions but it was not successful with the crystals obtained from *o*-xylene. Thus, the crystals **1e** from *p*-xylene were found to be an adduct of 1:1 of **1** and *p*-xylene with two molecules of each in the asymmetric unit. The complete crystallographic details are given in Table 3.1. The two symmetry independent molecules of **1** are labeled as A and B, while the *p*-xylene molecules are labeled as C and D, as shown in Figure 3.15.

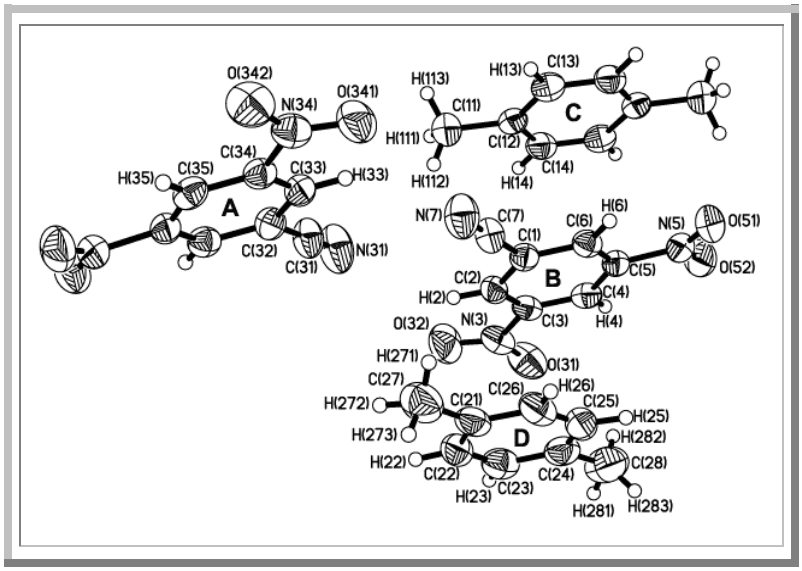


Figure 3.15: ORTEP (50% probability level) drawing of the molecular adduct, **1e** of **1** and *p*-xylene.

In adduct **1e**, molecules of *p*-xylene and **1** form a stacked sheet structure, in the three-dimensional arrangement as shown in Figure 3.16(a), such that *p*-xylene molecules are embedded between the layers of **1**, with a close resemblance to inorganic clay structures (see Figure 3.16(b)).[13]

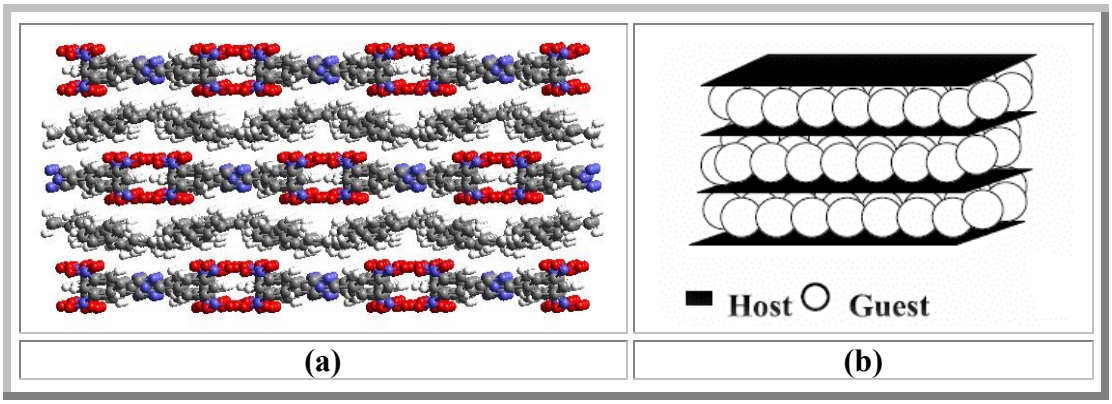


Figure 3.16: (a) Three-dimensional arrangements of **1** and *p*-xylene molecules in the alternate layers in the crystal structure of adduct **1e**. **(b)** Schematic representation of intercalated host–guest complexes.

Within the layers of **1**, the molecules are arranged in such a way that interaction between the symmetry independent molecules (A-B) and symmetry dependent molecules (B-B) constitute zig-zag molecular tapes. There is no interaction of the type A-A. This arrangement is shown in Figure 3.17(a). In each tape, molecules A and B are held together by C-H···N hydrogen bond dimers with H···N distances of 2.65 and 2.88 Å (Table 3.2). However, symmetry dependent molecules (B) form centrosymmetric cyclic C-H···O hydrogen-bonded coupling, with an H···O distance of 2.60 Å. Such adjacent tapes are further connected to each other forming a centrosymmetric cyclic coupling consisting of C-H···N hydrogen bonds, (H···N, 2.85 Å, Table 3.2). However, in the *p*-xylene layers, the two symmetry independent molecules arrange such that each of

six molecules of a particular symmetry (say D) form a hexagonal network around the other molecules (say C), as shown in Figure 3.17(b). This network is stabilized by typical H···H van der Waals interactions, generally known for hydrocarbons.[14]

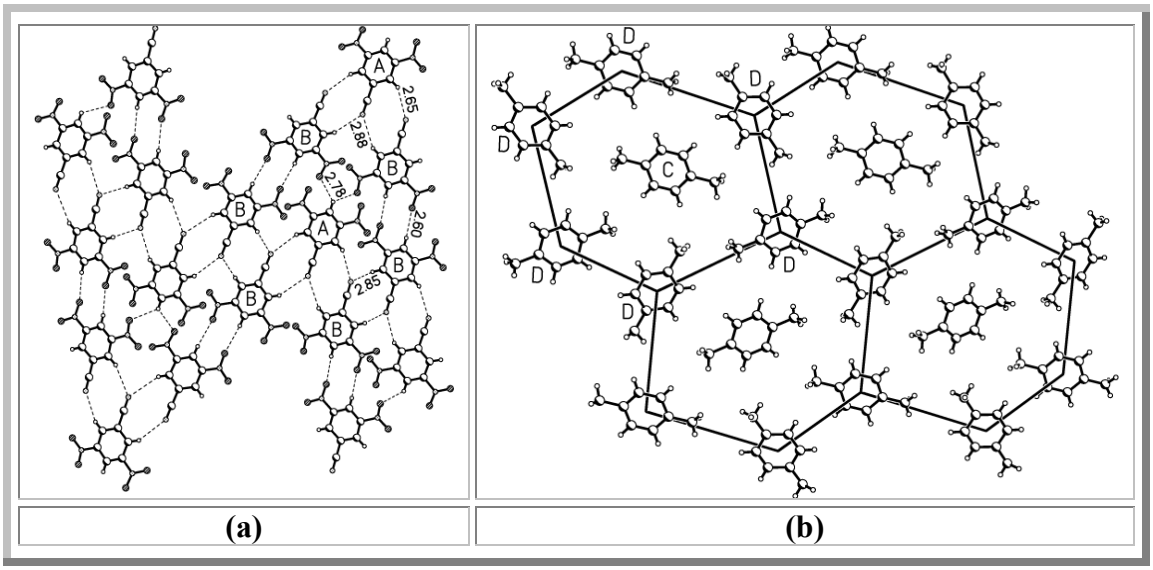


Figure 3.17: (a) Interaction among the molecules of **1** within a two-dimensional sheet in the complex, **1e**. **(b)** Two-dimensional sheet arrangement of *p*-xylene molecules constituting a hexagonal arrangement in complex **1e.**

3.6 COMPARISON OF ALL THE HOST-GUEST COMPLEXES

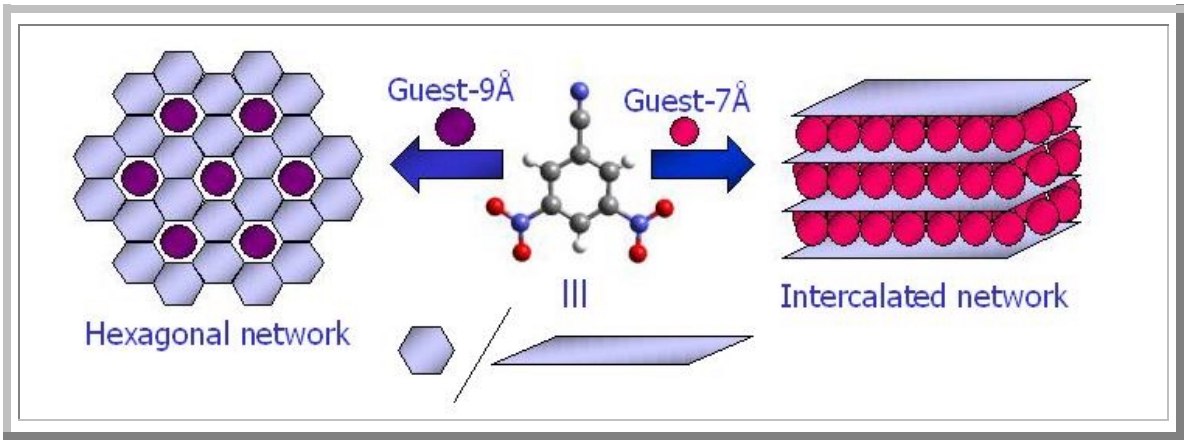
A comparison of structures of **1a – 1e** reveals that the dimension of the guest molecules (benzene, phenazine, acridine and phenothiazine) in adducts, **1a**, **1b, 1c** and **1d** is approximately 9 Å. Thus, those molecules could fit into the channels with average dimensions 14 x 7 $Å^2$ formed by the hexagonal arrangement of host molecules. However, *p*-xylene with the dimension of ~7 Å appears to be too small to remain in the channels of 14 Å as a single molecule like acridine, phenazine and phenothiazine in **1b, 1c** and **1d**, respectively, and at the same time it would be large to occupy as two molecules like benzene in **1a**. Hence, *p*-xylene apparently failed to yield an

iso-structural complex. In general, if the dimension of the guest molecules is inappropriate to the void space that is being created by the hexagonal arrangement of host molecules, the result is often the formation of a different type of assembly, as it was described in the earlier chapter. Nevertheless, still, **1** is able to form a host-guest type complex with *p*-xylene, perhaps, due to the flexibility of the weak C-H···N hydrogen bonds for the reorganization, commensurating with the dimensions of guest molecules. Thus, it may be concluded that **1**, would yield host-guest type complexes, possessing hexagonal channels with the guests of dimension ~9 Å, otherwise, it may form intercalated channel structures. However, if the incoming substrate possesses strong donor/acceptor groups, naturally, **1** would yield different types of molecular adducts as it formed in adduct of **1** and 3,5-dinitrobenzamide.[15]

3.7 CONCLUSIONS

In conclusion, host-guest complexes of 3,5-dinitrobenzonitrile, **1**, with various hydrocarbons, as well as aza-donor molecules in which **1** acts as a host lattice accommodating different types of guest molecules are discussed (see Scheme 3.2). It is also observed that depending upon the dimensions of the guest molecules, different types of host networks are created to yield either hexagonal channels or intercalated lamellar type structures. These variations appear to be the result of involvement of only weak hydrogen bonds in the formation of either host-network or host-guest interactions. Thus, these examples have demonstrated the utility of the weak hydrogen bonds such as C-H···N, C-H···O, etc. for the creation of flexible supramolecular

assemblies, which may have potential applications in the areas of catalysis, separation technology etc., due to the formation of structures with void space.



Scheme 3.2

3.8 EXPERIMENTAL SECTION

3.8.1 SYNTHESIS OF 1a - 1e

All the chemicals were obtained from commercial suppliers and used without further purification. HPLC grade solvents were used for the crystallization experiments. Synthesis of co-crystals was carried out by dissolving the reactants in the appropriate solvents, either at room temperature or by warming on a water bath, and subsequently cooling by a slow-evaporation method. In a typical experiment, 96.5 mg (0.5 mmol) of 3,5-dinitrobenzonitrile, **1**, and 45.1 mg of phenazine, (0.25 mmol) were dissolved in a boiling methanol solution and then subsequently cooled to room temperature. Yellow colored stable and plate-like single crystals of good quality were obtained over a period of 3 days and were used for X-ray diffraction studies. However, in the case of adducts of hydrocarbons like benzene, *p*-xylene, the obtained complexes

were found to be unstable upon removing from the mother liquor. Crystallographic studies on these crystals were carried out following special procedures as described in the following section.

3.8.2 X-RAY CRYSTALLOGRAPHY

Good-quality single crystals carefully chosen using a Leica microscope equipped with CCD camera were used to collect X-ray intensity data on a Bruker diffractometer (APEX CCD area detector). The data collections were carried out at 133 K for **1a** and **1e**, whereas for **1b, 1c** and **1d** were carried out at room temperature (298 K). The unstable crystals **1a** and **1e** were smeared in paraffin oil as soon as removed from the mother liquor, to protect from decomposition during the data collection period. The data were processed using Bruker suite of programmes (SAINT).[16] Structure determination and refinements were carried out using SHELXTL package.[17] All the intermolecular interactions were computed using PLATON prorgramme.[18]

Table 3.1: Crystallographic information of molecular complexes of **1 (1a, 1b, 1c** and **1e)**

	1a	**1b**	**1c**	**1e**
formula	$(C_7H_3N_3O_4):(C_6H_6)$	$2(C_7H_3N_3O_4):(C_{13}H_9N_1)$	$2(C_7H_3N_3O_4):(C_{12}H_8N_2)$	$(C_7H_3N_3O_4):(C_8H_{10})$
fw	271.23	283.23	283.23	897.85
crystal morphology	blocks	blocks	plates	blocks
crystal color	colorless	light yellow	yellow	colorless
crystal system	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	C_2/c
a (Å)	6.836(2)	6.979(1)	6.873(1)	16.628(5)
b (Å)	7.229(2)	7.277(1)	7.308(1)	13.530(4)
c (Å)	25.840(1)	24.807(4)	24.871(5)	21.080(6)
α(deg)	90	90	90	90
β(deg)	92.44 (1)	90.48 (1)	90.68(1)	112.95(1)
γ(deg)	90	90	90	90
V (Å^3)	1275.8(5)	1259.8(3)	1249.1(4)	4367(2)
Z	4	4	4	4
D_{calc} (g cm^{-3})	1.412	1.493	1.506	1.366
T (K)	133(2)	298(2)	298(2)	133(2)
Mo-kα	0.71073	0.71073	0.71073	0.71073
μ (mm^{-1})	0.108	0.114	0.116	0.102
2*θ* range (deg)	46.56	46.54	46.54	46.64
limiting indices	$-7 \le h \le 7$ $-7 \le k \le 8$ $-19 \le l \le 28$	$-7 \le h \le 7$ $-8 \le k \le 8$ $-23 \le l \le 27$	$-7 \le h \le 7$ $-8 \le k \le 8$ $-19 \le l \le 27$	$-15 \le h \le 18$ $-14 \le k \le 14$ $-23 \le l \le 23$
F(000)	560	582	580	1872
no. reflns measured	5167	5201	5094	9077
no. unique reflns [R(int)]	1806 [0.0362]	1803 [0.0212]	1787 [0.0176]	3131 [0.0264]
no. reflns used	1633	1482	1546	2560
no. parameters	217	232	219	378
reflection\parameter	8.32	7.77	8.16	8.28
GOF on F^2	1.210	1.038	1.046	1.128
R_1 [$I > 2\sigma(I)$]	0.0592	0.0368	0.0390	0.0491
wR_2	0.1391	0.0983	0.0988	0.1068
Final diff. Four map (e^- . Å^{-3}) max, min	0.17, –0.16	0.10, –0.14	0.16, –0.15	0.19, –0.14

Table 3.2: Characteristics of hydrogen bonds (distances/Å and angles/deg)[#]

Hydrogen Bonds	1a			1b			1c			1e		
C−H···O	2.47	3.24	130.0	2.52	3.47	166.2	2.48	3.41	162.7	2.60	3.45	162.9
	2.60	3.46	157.1	2.53	3.35	138.5	2.55	3.37	137.0	2.74	3.44	137.9
	2.61	3.33	125.2	2.59	3.42	139.9	2.57	3.43	142.4	2.78	3.31	120.9
	2.64	3.43	149.5	2.85	3.75	160.6	2.80	3.57	139.6	2.81	3.63	145.0
	2.87	3.42	120.0	2.87	3.63	139.9	2.82	3.72	159.2	2.82	3.57	140.1
	2.94	3.42	113.6							2.85	3.43	125.3
										2.89	3.72	146.6
										2.90	3.75	168.4
										2.90	3.53	124.8
C−H···N	2.64	3.42	145.8	2.45	3.33	158.6	2.48	3.34	161.5	2.65	3.44	143.4
	2.81	3.44	123.9	2.93	3.76	144.1	2.86	3.68	144.1	2.88	3.66	143.5
	2.87	3.60	131.9							2.91	3.58	129.9

[#] The three numbers in each column indicate H···O(N), C···O(N) and angles, respectively.

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CHAPTER FOUR

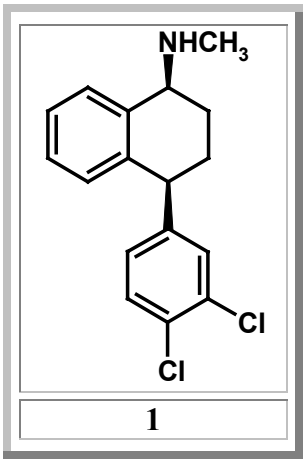
NONCOVALENT SYNTHESIS: A TOOL FOR THE PREPARATION OF PHARMACEUTICAL CO-CRYSTALS

4.1 INTRODUCTION

In the process of drug developments, exploration of novel methodologies for the delivery of the active pharmaceutical ingredients (API's) is a continuous challenging task.[1] Most API's are crystalline solids at room temperature and are commonly delivered as tablets. However, recent advancements in the areas of supramolecular chemistry,[2] under the umbrella of polymorphism,[3] as described in chapter one, reveals that different solid forms of the same compound show different chemical and physical properties. Thus, the solid-state chemistry of API's has become a subject of fundamental, practical and legal interest. As a result, polymorphs, solvates, salts, and co-crystals of API's represent extensions of chemical space wherein enhanced or new chemical and physical properties may lead to extended patent coverage and consequent legal protection of products that may be of great concern to innovator and generic pharmaceutical companies.[4] Hence, complete understanding of the physico-chemical properties of the drug substances or API's is critical in the development of profiling strategies and in the setting of criteria for physiological evaluation. The strategies to deal with inadequate solubility, dissolution rate, and absorption of neutral crystal forms include salt formation, physical stabilization of amorphous solids, complexation, or encapsulation of organic solutions are of current interest.[5]

Salt selection is one of the most acceptable procedures for the improvements in the properties of the API's.[6] It attributes towards the improved aqueous solubility, chemical stability and high bioavailability as compared to those of the free base or acid of the active pharmaceutical ingredients. Recently salt selection is becoming

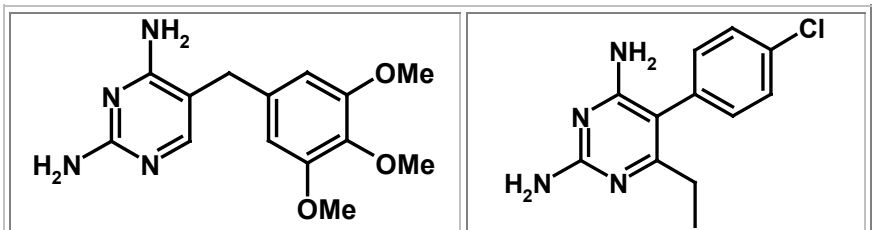
increasingly automated to meet the need for rapid identification of crystalline salt forms in early drug development. Salt selection at earlier stages has also been demonstrated, using high-throughput crystallization techniques. Sertraline HCl (Zoloft), **1**, is an example of a salt form that is highly polymorphic and prone to form solvates. High-throughput (HT) crystallization experiments were conducted with sertraline free base in the presence of mono-, di- and triacidic salt formers. Over 3600 crysallization trials were conducted, leading to the identification and characterization of 18 crystalline salt forms.[7]



1

Further, the recent studies by Jones and co-workers show that the screening of the salts can also be done by mechanochemical approach as the strategy affords the effective and selective approach to pharmaceutical salt screening in today's urgent pace of drug development process. The strategy includes neat grinding and also recently developed technique, solvent-drop grinding that provides rate enhancement and added selectivity in certain cases *via* the addition of sub-stoichiometric amounts of solvent to the grinding mixture. The significance of this approach was well demonstrated by

performing salt screening process on two structurally similar API's, the antibacterial drug trimethoprim, **2**, and the antimalarial drug pyrimethamine, **3**.[8]



2 **3**

In summary, neat grinding provided approximately 40% overall screening efficiency as compared to the remarkable 100% efficiency obtained by solvent-drop grinding as shown in the Figure 4.1.

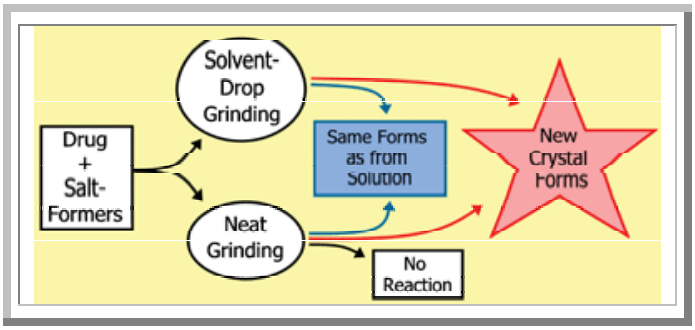
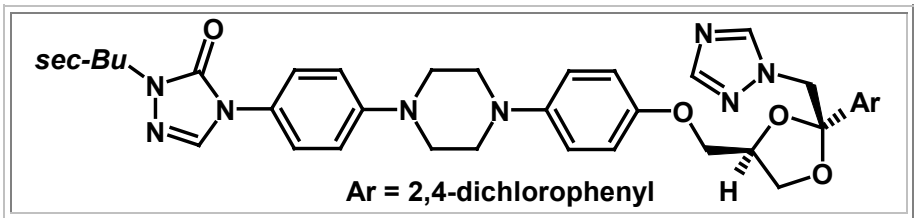


Figure 4.1: Diagram showing results from salt screening *via* grinding.

As it was discussed in chapter one, co-crystallization offers another option that has enormous potential to provide new, stable structures that may improve the properties of an API's. However, the current strategies focused on the design and optimization of the multi-component crystalline phases of the API's to improve the pharmaceutical performance and contain components that are generally regarded as safe (GRAS) by the FDA.

In this direction, Remenar et al conducted the high-throughput (HT) crystallization screen to search for salts and co-crystals of Itraconazole, **4**, an extremely water-insoluble antifungal drug that is marketed in the amorphous form (Sporanox capsule) to achieve the required oral bioavailability.[9]



4

The stable co-crystals consisting of hydrogen-bonded trimers of two molecules of **4** and one molecule of a 1,4-dicarboxylic acid (succinic acid), as shown in the Figure 4.2 exemplifies the implication of co-crystallization for the identification of multiple crystal forms of the same drug (here itraconazole) with acceptable solubility.

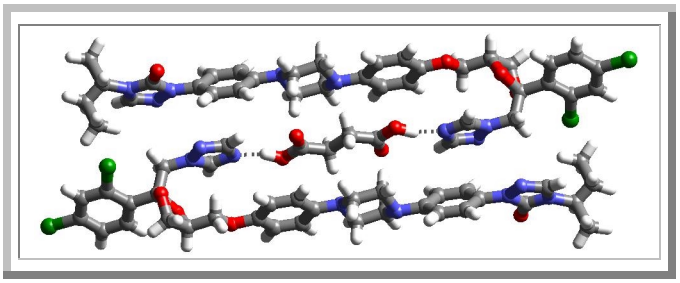
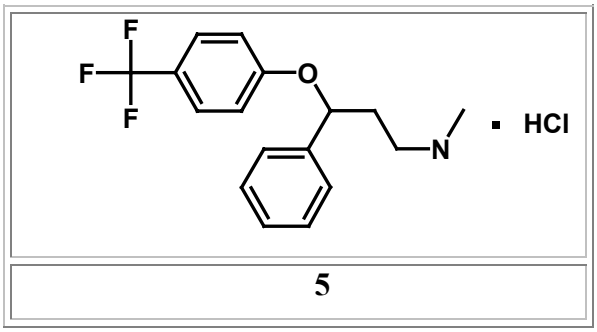


Figure 4.2: The 2:1 supramolecular adduct formed by **4** and succinic acid.

Further, Childs et al demonstrated the preparation of multicomponent co-crystals of Fluoxetine hydrochloride, **5**, using pharmaceutically acceptable compounds, as shown in Figure 4.3. The approach was based on the fact that the chloride ion is one of the most preferred anions for salts of cationic API's and also the estimation suggests that approximately half of the salts of cationic drugs are marketed as

hydrochloride salts. Thus, co-crystallizing the hydrochloride salt of an API presents an opportunity to alter the physical properties of the solid dosage form while simultaneously retaining the hydrochloride salt of the API in the crystal structure.[10]



5

Based on these exciting novel research findings promoted by the principles of supramolecular synthesis, a focus on the development of methodologies for obtaining multicomponent pharmaceutical co-crystals, using bioactive compounds such as nucleobases have been carried out as described in the following sections.

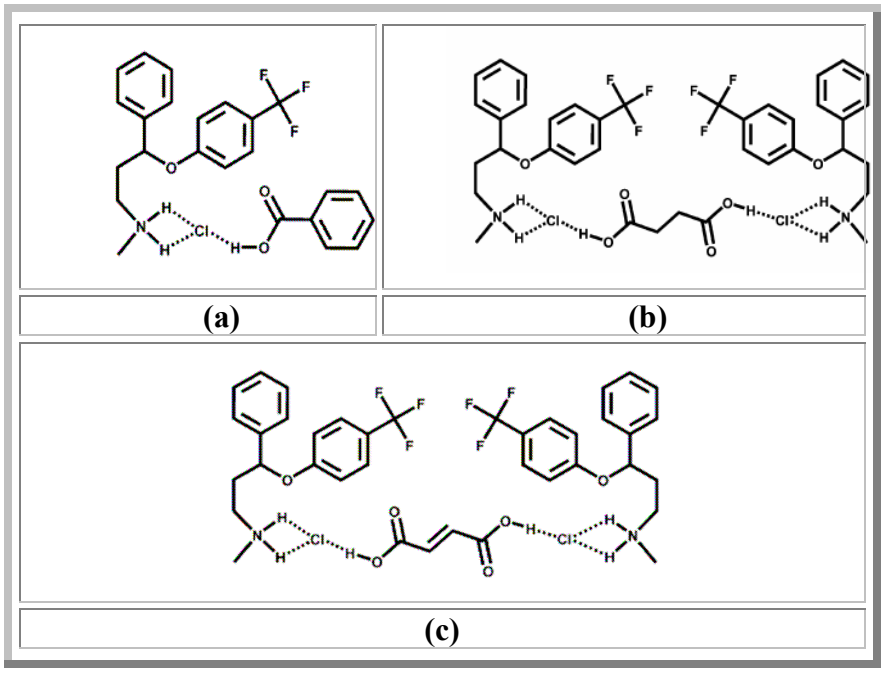


Figure 4.3: Molecular diagram of the asymmetric unit **(a) 5**:Benzoic acid **(b) 5**:Succinic acid **(c) 5**:Fumaric acid.

4.2 HISTORY OF ASPIRIN

Aspirin, acetylsalicylic acid, is well known as a wonder drug of the current century with its bioactivity to treat simple diseases like headache, body pains, fever etc., to reduce the risks of highly complicated physiological problems related to coronary artery diseases, colon cancer etc (see Box 1). However, it is known from the literature that *in vivo*, the half-life period of aspirin is 20 minutes before it converts into salicylic acid (**SA**), which is also bioactive, same as aspirin. Thus, attribution of the physiological action of aspirin to itself, or to the in-situ generated **SA** or a combination of both aspirin and **SA** is not yet been fully established authentically, as no concrete theory is able to demonstrate it. If **SA** has a major role to play in the subsequent drug-action, free **SA** oriented drugs, perhaps, would be of interesting and challenging both in scientific and economic fronts, as aspirin is often made from **SA**. However, **SA** apparently found to be an irritant than aspirin, which precludes its utilization.[11]

4.3 SYNTHESIS AND STRUCTURAL ANALYSIS OF MOLECULAR COMPLEXES OF SALICYLIC ACID AND ADENINE

Taking into account the current developments in pharmaceutical co-crystallization studies,[12] in which, it was found that the properties (in particular, physical properties like solubility, morphology etc.) of the reactants in the co-crystals form are different than in the isolated form, co-crystals of **SA** also could be evaluated for the effective utilization of it as a drug with a hope that the obtained co-crystals would alter the irritant nature of **SA**. For this purpose, a search on Cambridge Structural Database (CSD),[13] was carried out to find out if any such co-crystallization experiments

were done, as it is a highly lucrative substrate to undergo molecular recognition with the complementary receptors. Indeed, a few reports of co-crystals of salicylic acid are known in the literature that were studied as part of understanding of the molecular recognition abilities of different functional groups.[14] However, many of the substrates involved in the formation of these assemblies are either corrosive or toxic in nature; hence, such assemblies may limit the further physiological studies of the co-crystals formed by **SA**.

Recently, in our lab, it was established that carboxylic acids bind to nucleobases, which are the key organic entities of DNA, in a selective manner by interacting with only adenine and cytosine,[15] as shown in the Figure 4.4.

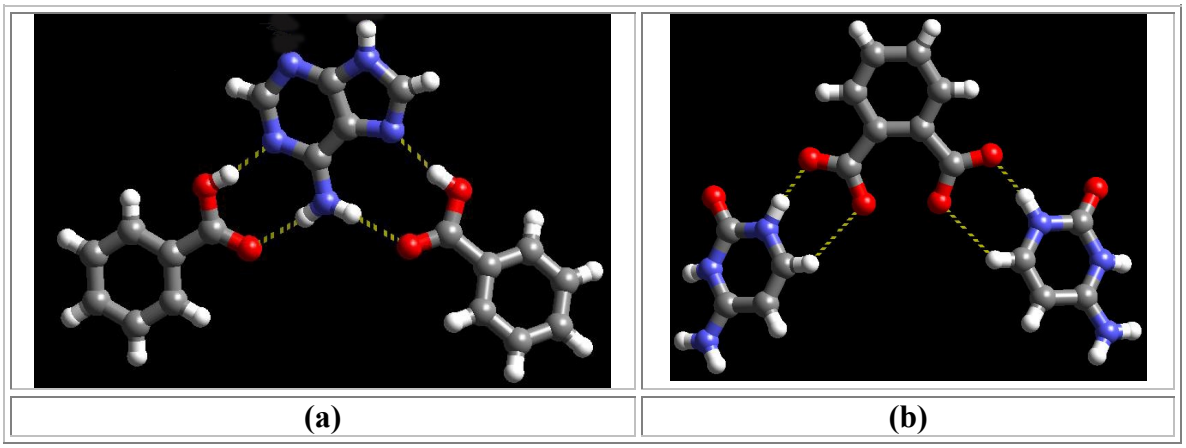
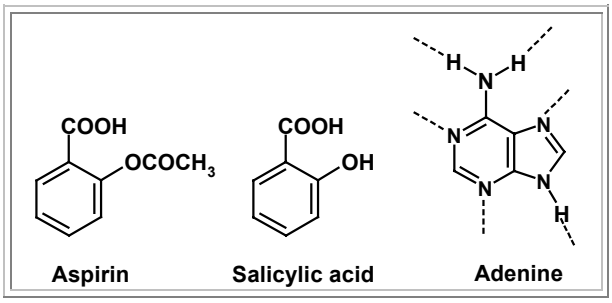


Figure 4.4: Molecular recognition between **(a)** Benzoic acid:Adenine and **(b)** Phthalic acid:Cytosine.

Looking at the present developments in the areas of nucleic acid/protein interactions, and in particular, the interaction of nucleobases with bioactive molecules, the evaluation of a large cluster of API's with nucleobases is essential as it could provide ideal basis sets for accurate predictions in biomolecular modeling

experiments.[16] Hence, co-crystallization of salicylic acid with nucleobases have been carried out and in particular with adenine and cytosine.

Considering the hydrogen bonding capabilities of adenine as shown in Scheme 4.1, formation of different co-crystals by varying molar ratios of **SA** could be anticipated. Thus, co-crystallization of **SA** and adenine was carried out in 3:1, 2:1 and 1:1 ratios from either methanol or water. The single crystals, thus obtained, upon characterization by x-ray diffraction methods, confirm the retention of the ratios of the reactants except that 1:1 complex is obtained as a hydrate. The three complexes have been labeled **SAAD31, SAAD21** and **SAAD11** for 3:1, 2:1 and the hydrate of 1:1, respectively. The contents of the asymmetric units are shown in Figure 4.5.



Scheme 4.1

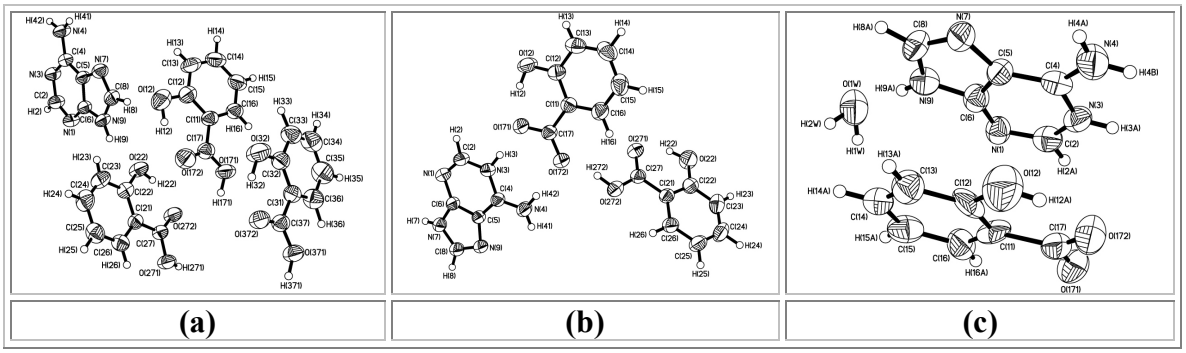


Figure 4.5: ORTEP drawings of co-crystals of **SA** and adenine in **(a)** 3:1 **(b)** 2:1 and **(c)** 1:1 in hydrate form.

Box 1

Aspirin is a member of a family of chemicals called salicylates. These chemicals have been known to people interested in medicine for centuries. One of the first and most influential physicians, Hippocrates, wrote about a bitter powder extracted from willow bark that could ease aches and pains and reduce fevers as long ago as the fifth century B.C. In the 1700s, the scientist Reverend Edmund Stone wrote about the success of the bark and the willow in the cure of the "agues," or fevers with aches. With a bit of chemical detective work, scientists found out that the part of willow bark that was bitter and good for fever and pain is a chemical known as salicin. This chemical can be converted by the body after it is eaten to another chemical, salicylic acid.

The problem with these chemicals was that they upset the user's stomach fairly badly. In fact, some people had bleeding in their digestive tracts from the high doses of these chemicals needed to control pain and swelling. One of these people was a German man named Hoffmann. His arthritis was pretty bad, but he just couldn't "stomach" his salicylic acid. Enter this man's son, German chemist Felix Hoffmann, who worked for a chemical company known as Friedrich Bayer & Co. Felix wanted to find a chemical that wouldn't be so hard on his dad's stomach lining; reasoning that salicylic acid may be irritating because it is an acid.

On August 10th 1897, Felix Hoffmann managed to acetylate the phenol group of a compound called salicylic acid. Not, on the face of it, the stuff for which front pages are held. But acetylsalicylic acid has two claims to fame. First, as the world's first truly synthetic drug (i.e., not merely an artificial copy of a naturally occurring compound), it paved the way for the modern pharmaceuticals industry. Second, it is probably the most successful medicine in history. For acetylsalicylic acid is better known as aspirin.

In the crystal structure of **SAAD31**, each adenine molecule is bound to three acid molecules, yielding a quartet supramolecular entity, utilizing all the available recognition sites, forming three pairwise O-H···N and N-H···O hydrogen bonds. The recognition pattern and one-dimensional arrangement is shown in Figure 4.6. While O-H···N hydrogen bonds are formed by –COOH group and different types of -N atoms present on pyrimidine and imidazole moieties of adenine, the N-H···O were the resultant of the interaction between -NH on pyrimidine and imidazole moieties with the carbonyl oxygen of the -COOH. The H···N distance in the three patterns is 1.67, 1.71 and 1.78 Å while the corresponding H···O distances are 2.03, 2.65 and 2.01 Å. Further, a comparison of the H···O distances in the three N-H···O hydrogen bonds indicates that -NH on imidazole ring form weak hydrogen bonds, so it may be easily tunable for altering the recognition between adenine and salicylic acid and it is reflected well in the **SAAD21** and **SAAD11** complexes which would be discussed in the later sections.

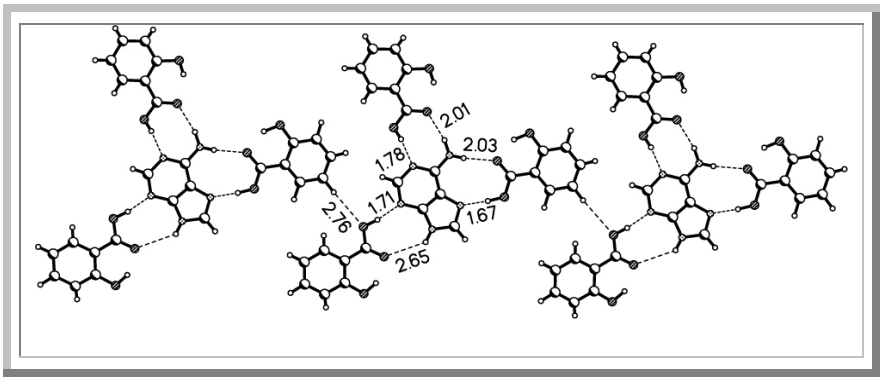


Figure 4.6: Molecular recognition between **SA** and adenine in the co-crystals, **SAAD31** and interaction between the adjacent supramolecular entities.

The quartet entities are further held together in one-dimensional arrangement through a C-H···O hydrogen bond (H···O, 2.76 Å) as shown in Figure 4.6, which are

in turn packed into crossed ribbon network in three-dimensions (see Figure 4.7). Details of the crystallographic information and hydrogen bond distances are given in Table 4.1 and 4.2 respectively.

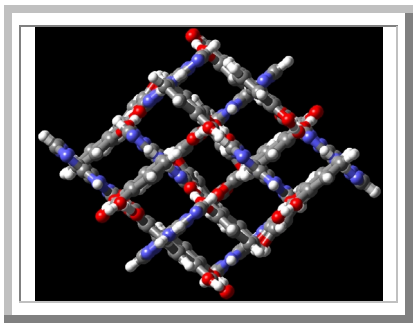


Figure 4.7: Packing of one-dimensional chains into crossed-ribbons mode in the crystal lattice of **SAAD31**.

4.3.2 STRUCTURAL PROPERTIES OF SAAD21 COMPLEX

In the 2:1 adduct, **SAAD21**, (Figure 4.5(b)), obtained between **SA** and adenine, the packing is quite intriguing with the formation of a ladder-like structure as shown in Figure 4.8.

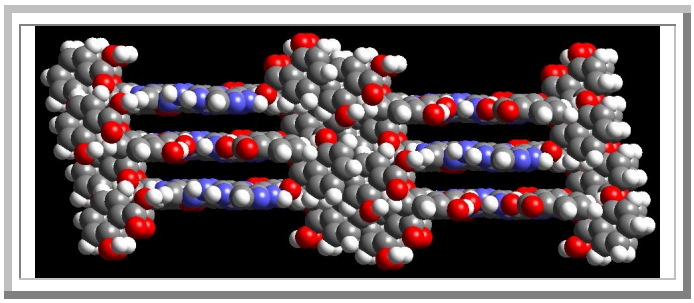


Figure 4.8: Arrangement of adenine and **SA** in the 2:1 ratio in the crystal structure of **SAAD21** forming ladder-like structure.

In such an arrangement, rungs are being formed by adenine and one of the two **SA** molecules together, while the rods are formed exclusively by the other **SA**

molecules. The molecular recognition and two-dimensional arrangement of the reactants in the crystal structure of **SAAD21** are shown in Figure 4.9.

It is evident from Figure 4.9 that in the adduct **SAAD21**, both homomeric and heteromeric recognition between adenine and **SA** prevail. The homomeric moieties between adenine molecules exist as dimers that were formed through cyclic N-H···N hydrogen bonding pattern with a H···N distance of 2.18 Å, whereas dimers of **SA** molecules are established by $\pi - \pi$ interaction (3.64 Å). In the heteromeric pattern, adenine and salicylic acid molecules are held together through the formation of pairwise N-H···O (H···O, 1.98 Å) and N^{+}-H···O^{-} (H···O^{-}, 1.74 Å) hydrogen bonds. It is interesting to note that the distances of hydrogen bonds in the cyclic pattern are very much similar in both **SAAD31** and **SAAD21** (see Table 4.2). Crystallographic details are given in Table 4.1.

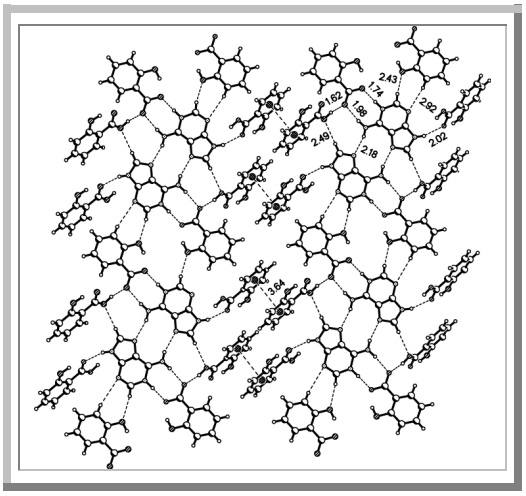


Figure 4.9: Intermolecular interactions between the molecules in the ladder-like structure formed by adenine and **SA** in the adduct, **SAAD21**.

4.3.3 STRUCTURAL PROPERTIES OF SAAD11 COMPLEX

In the crystal structure of **SAAD11**, formed between adenine and **SA** in a 1:1 ratio (Figure 4.5(c)) along with a water molecule, the recognition pattern between the reactants is exactly like in the adduct **SAAD21** by forming N-H···O and $N\text{-}H^{+}\cdots O^{-}$ pairwise hydrogen bonds (Figure 4.10). The H···O and $H^{+}\cdots O^{-}$ distances are 1.92 and 1.79 Å respectively (see Table 4.2).

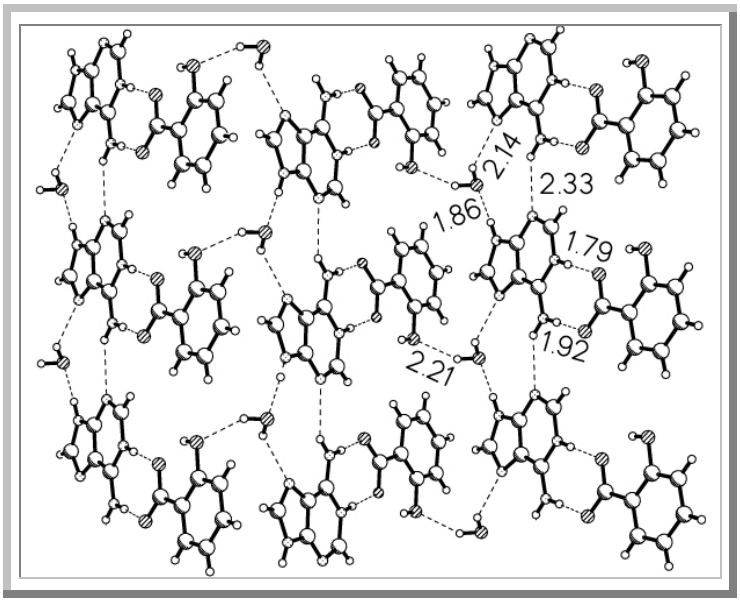


Figure 4.10: Molecular recognition pattern between adenine and **SA** along with water molecules in adduct, **SAAD11**.

But in the adduct **SAAD11**, only heteromeric moieties are observed, unlike in **SAAD21** and moreover the adjacent moieties are held together by water molecules by three different types of hydrogen bonds depending upon the nature of the donor groups. Thus, O-H···O, O-H···N and N-H···O hydrogen bonds are formed with distances 2.21, 2.14 and 1.86 Å respectively. In three-dimensional arrangement, the molecules are packed in herringbone pattern as shown in Figure 4.11.

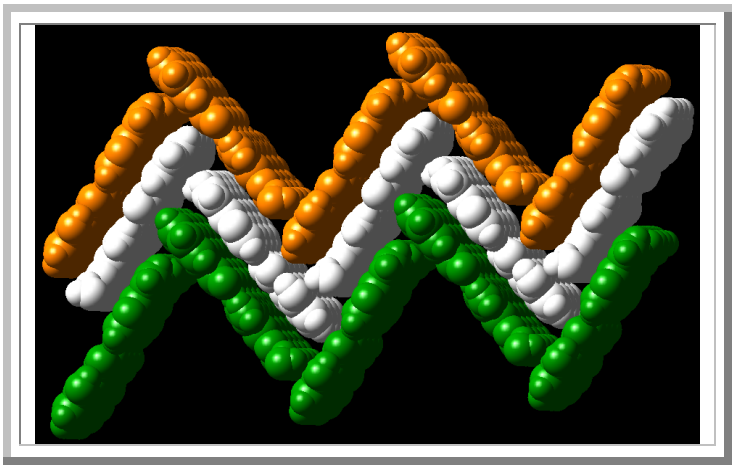


Figure 4.11: Herringbone pattern in three-dimensional arrangement of molecules in adduct, **SAAD11**.

Furthermore, knowing such high affinity of **SA** for adenine, we were curious to see what aspirin does in the presence of adenine, as aspirin was found to be yielding co-crystals through pyridyl –N atoms and –COOH moiety like in the observed **SA** adducts of adenine.[12f] Interestingly, we noted that aspirin did not form any molecular adducts with adenine but it gave structures **SAAD31**, **SAAD21** and **SAAD11** suggesting conversion of aspirin into **SA** in solution in the presence of adenine.

4.4 pH ANALYSIS OF SAAD31, SAAD21 AND SAAD11 MOLECULAR COMPLEXES

Further to the structural information, the solution properties of these molecular complexes were also studied. It was noted that pH of **SA** (2.7) and aspirin (2.9) does not show much difference between them, except that the later is towards slightly basic, perhaps, which may be responsible to make aspirin less irritant. However, the solutions of the adducts **SAAD31**, **SAAD21** and **SAAD11** show pH as 3.1, 3.3 and 3.8 respectively which can be extrapolated that these adducts are less acidic than **SA** and in

fact more basic than aspirin; so one could anticipate variations in some of the physical properties, especially irritant nature, that precluded **SA** into the pharmacological listings.

4.5 DISSOLUTION STUDIES OF SAAD31, SAAD21 AND SAAD11 MOLECULAR COMPLEXES

Powder dissolution profile experiments were carried out on compounds **SAAD31**, **SAAD21** and **SAAD11** at 25 °C. All compounds dissolve at a rapid rate such that differences in the powder dissolution rates could not be discerned at the early time points. These results are presented in graphical form in Figure 4.12. The data for the pharmaceutical co-crystals (adducts) are normalized. The comparison of solubility of pure salicylic acid and aspirin with the solubility values for the co-crystals expressed in mg/mL are provided in Table 4.3

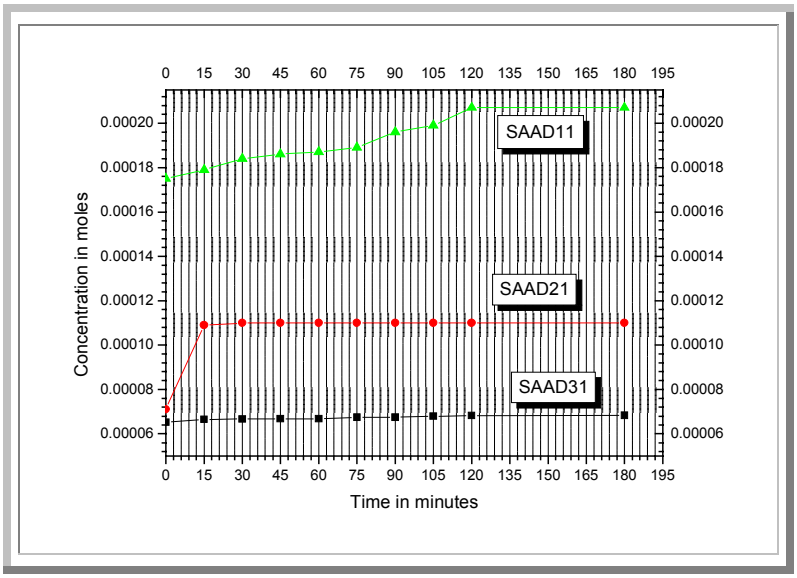
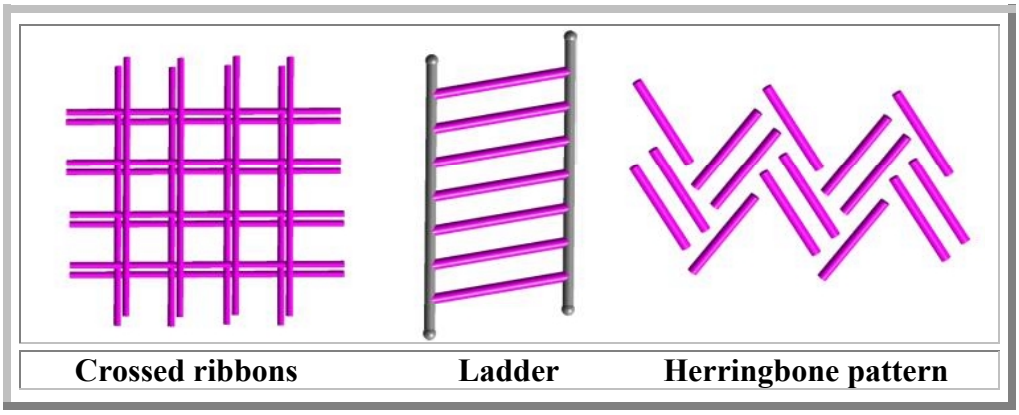


Figure 4.12: Powder dissolution profiles for **SAAD31**, **SAAD21** and **SAAD11** in water at 25 °C.

4.6 CONCLUSIONS

Solid state structures of **SAAD31**, **SAAD21** and **SAAD11** exemplifies the flexibility of structural reorganization of the supermolecules formed between **SA** and adenine into different arrangements, crossed ribbons, ladders and herringbone (see Scheme 4.2), depending upon the quantity of the **SA**, and also it demonstrates the high affinity of **SA** towards adenine. This may be inferred that adenine can extricate excessive **SA**, independent of the initial concentration. Also, adenine may be useful as a co-agent even for aspirin, as the resultant extravagant **SA** during the metabolism of aspirin can be extricated, thus, may lead to the suppression of other reactions contributing for the irritation of **SA**.



Scheme 4.2

Further the dissolution studies permit a direct comparison of the effect of the nucleobase molecule in the co-crystal on the solubility of the API. Since solubility and bioavailability are often related, these results demonstrate that, in principle, co-crystals can be used to tune the bioavailability of an API. Thus, the experiments described herein, would provide more light into new drug discovery programs that are imminent

in the contemporary research following computational as well as experimental protocols.

4.7 EXPERIMENTAL SECTION

4.7.1 CO-CRYSTALLIZATION

All the chemicals were obtained commercially and the crystallization experiments were carried out at room temperature by dissolving the constituent reactants in the stoichiometric ratios in the spectroscopic grade methanol solvent or water as the case may be. For a typical crystallization, in a 25 mL conical flask 207 mg (1.5 mmol) of **SA** and 67.5 mg (0.5 mmol) of adenine were dissolved in methanol by heating methanol to the boiling temperature and then subsequently cooling to room temperature at ambient conditions. Colorless rectangular block type single crystals of good quality were obtained within 3-4 days, which were used for single-crystal structure determination studies by X-ray diffraction methods.

4.7.2 STRUCTURE DETERMINATION BY SINGLE CRYSTAL X-RAY DIFFRACTION METHOD

Good quality single crystals of **SAAD31**, **SAAD21**, and **SAAD11** were carefully chosen after viewing through a Leica microscope supported by a rotatable polarizing stage and a CCD camera. The crystals were glued to a thin glass fiber using an adhesive (cyano acrylate) and mounted on a diffractometer equipped with an SMART APEX CCD area detector. The data collection was smooth in all the cases, and no extraordinary methods have been employed, as the crystals were quite stable. The

intensity data were processed using Bruker's suite of data processing programs (SAINT),[17] and absorption corrections were applied using SADABS.[18] The structure solution of all the complexes have been carried out by direct methods, and refinements were performed by fullmatrix least squares on F^2 using the SHELXTL-PLUS[19] suite of programs. All the structures converged to good R factors. All the non-hydrogen atoms were refined anisotropically, and the hydrogen atoms obtained from Fourier maps were refined isotropically. The details of the data collection and crystallographic information for all the structures are given in Table 4.1. All the intermolecular interactions were computed using PLATON[20] and are given in Table 4.2.

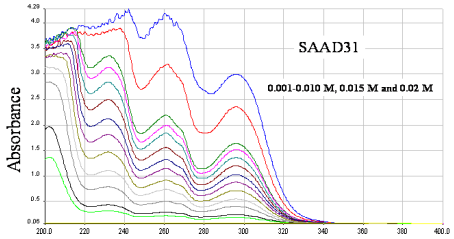
4.7.3 DISSOLUTION STUDIES

Concentrations of **SAAD31**, **SAAD21** and **SAAD11** in water were determined by UV spectrophotometry. For experiments involving compounds **SAAD31**, **SAAD21** and **SAAD11**, absorbance values were related to solution concentrations using a calibration curve for Salicylic acid (296nm). This was possible since adenine does not absorb at 296 nm and, therefore, did not interfere with determination of the concentration of **SAAD31**, **SAAD21** and **SAAD11.**

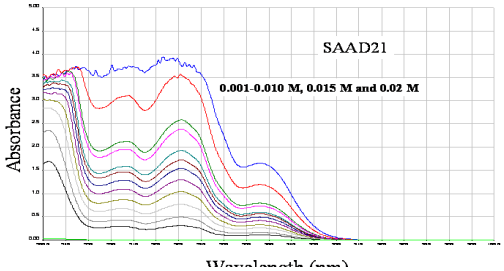
For powder dissolution studies of **SAAD31**, **SAAD21** and **SAAD11,** the starting solids were ground using pestle and mortar to provide samples with approximately similar particle size. In each experiment, a flask containing 100 mL of water was equilibrated at 25 °C in a constant temperature bath. Approximately 1000 mg of sample was added to the flask, and the resulting slurry was stirred. At each time interval, an aliquot of the slurry was withdrawn from the flask and filtered. A 0.02 mL portion of

the filtered aliquot was diluted to 2.0 mL with water. The results obtained from UV measurements for the three complexes **SAAD31**, **SAAD21** and **SAAD11** are plotted in Graphs 4.1 - 4.3 respectively and tabulated in Table 4.4 and Table 4.5. Also, the calculations of the epsilon values of the complexes **SAAD31**, **SAAD21** and **SAAD11** are determined from the slope of the straight line obtained from the graphs of absorbance *vs* wavelength, which are shown in Graphs 4.4 - 4.6. The Table 4.5 shows the concentration of the complexes **SAAD31**, **SAAD21** and **SAAD11** dissolved at that particular time interval followed by the absorbance value at that particular concentration. As the supersaturation level reached quiet early, the average absorbance was calculated, using Graphs 4.7 - 4.9, to determine the solubility of the complexes **SAAD31**, **SAAD21** and **SAAD11** using Beer – Lambert's law as follows.

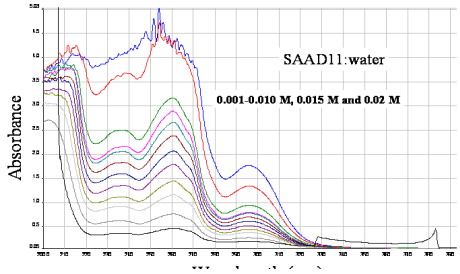
$A = \varepsilon \times c \times l$, where, A = Absorbance, ε = epsilon in L $mol^{-1}cm^{-1}$, c = concentration in mol L^{-1}, l = length of the cuvette (pathlength).



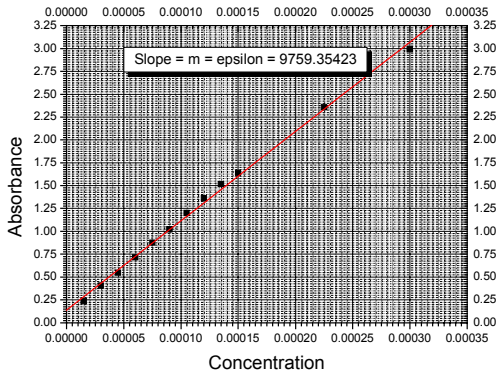
Graph 4.1: The values of absorbance for different known concentration solutions of **SAAD31** in water at 25° C.



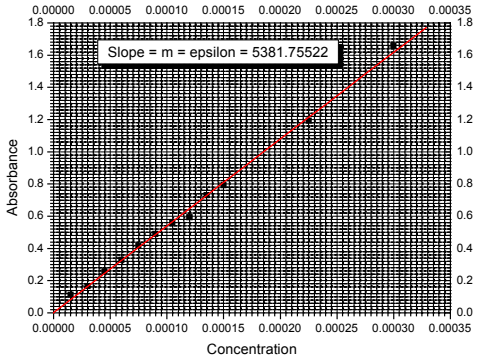
Graph 4.2: The values of absorbance for different known concentration solutions of **SAAD21** in water at 25° C.



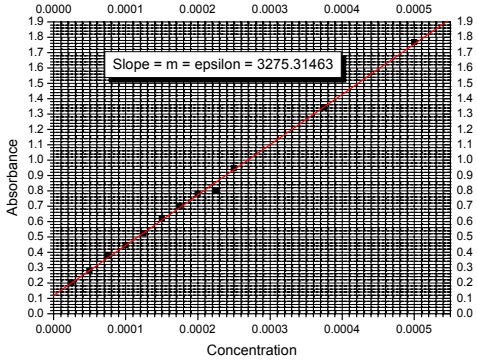
Graph 4.3: The values of absorbance for different known concentration solutions of **SAAD11** in water at 25° C.



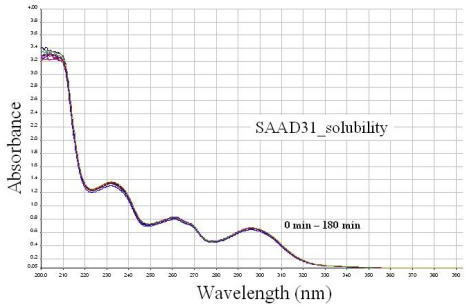
Graph 4.4: The slope of the straight line gives the epsilon *(ε)* value of the molecular complex **SAAD31.**



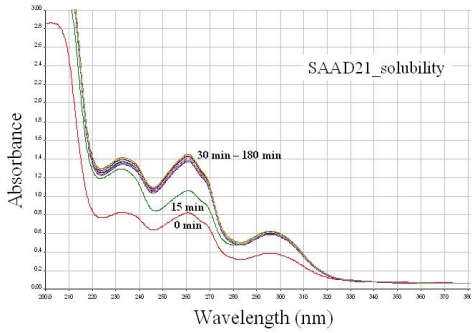
Graph 4.5: The slope of the straight line gives the epsilon *(ε)* value of the molecular complex **SAAD21**



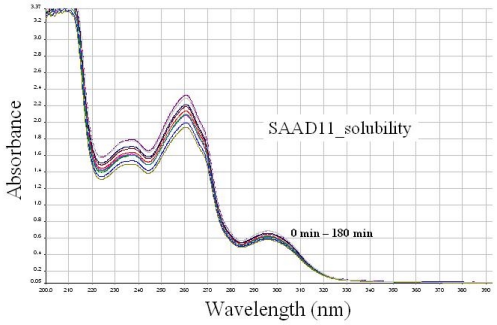
Graph 4.6: The slope of the straight line gives the epsilon *(ε)* value of the molecular complex **SAAD11**



Graph 4.7: The values of absorbance for different unknown concentration solutions of **SAAD31** in water at different time intervals at 25° C.



Graph 4.8: The values of absorbance for different unknown concentration solutions of **SAAD21** in water at different time intervals at 25° C.



Graph 4.9: The values of absorbance for different unknown concentration solutions of **SAAD11** in water at different time intervals at 25° C.

Table 4.1: Crystallographic data of molecular complexes: **SAAD31, SAAD21** and **SAAD11.**

	SAAD31	**SAAD21**	**SAAD11**
formula	$3(C_7H_6O_3):(C_5H_5N_5)$	$2(C_7H_6O_3):(C_5H_5N_5)$	$(C_7H_6O_3):(C_5H_5N_5):(H_2O)$
fw	549.49	411.38	291.27
crystal morphology	blocks	rectangular plate	blocks
crystal color	colorless	colorless	colorless
crystal system	monoclinic	triclinic	monoclinic
space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$
a (Å)	11.035(2)	7.096(1)	7.008(2)
b (Å)	10.126(2)	7.458(1)	16.805(1)
c (Å)	23.612(4)	18.091(3)	11.726(4)
α(deg)	90	99.92(1)	90
β(deg)	105.93(11)	98.16(1)	102.10(1)
γ(deg)	90	90.35(1)	90
V (Å^3)	2537.1(8)	933.1(2)	1350.3(1)
Z	4	2	4
D_{calc} (g cm^{-3})	1.439	1.464	1.433
T (K)	298(2)	298(2)	298(2)
Mo-kα	0.71073	0.71073	0.71073
μ (mm^{-1})	0.111	0.112	0.111
2θ range (deg)	50.06	50.02	50.24
limiting indices	$-13 \le h \le 12$ $-11 \le k \le 12$ $-20 \le l \le 27$	$-8 \le h \le 7$ $-8 \le k \le 8$ $-21 \le l \le 17$	$-6 \le h \le 8$ $-20 \le k \le 19$ $-13 \le l \le 12$
F(000)	1144	428	608
no. reflns measured	12365	4665	6555
no. unique reflns [R(int)]	4460 [0.0331]	3230 [0.0142]	2385 [0.0719]
no. reflns used	3255	2706	649
no. parameters	375	339	198
reflection\parameter	11.89	9.53	12.04
GOF on F^2	0.974	1.041	0.685
R_1 [$I > 2\sigma(I)$]	0.0427	0.0402	0.0558
wR_2	0.1135	0.1093	0.1050
Final diff. Four map (e^- . Å^{-3}) max, min	0.24, –0.17	0.23, –0.27	0.46, –0.28

Table 4.2: Hydrogen bond table for the molecular complexes: **SAAD31, SAAD21** and **SAAD11.**

Hydrogen Bonds	SAAD31			SAAD21			SAAD11		
N−H···O	2.01	2.96	166.7	1.98	2.87	171.4	1.86	2.72	177.2
	2.03	2.88	173.0	2.02	2.83	160.3			
	2.15	2.89	142.9						
	2.65	3.33	136.1						
N^{+}−H···O^{-}				1.74	2.69	177.7	1.79	2.65	174.8
							1.92	2.78	177.0
N−H···N				2.18	3.00	160.1	2.33	3.02	137.9
O−H···O				1.62	2.54	166.7	2.21	2.91	135.2
O−H···O	1,67	2.69	175.3				2.14	2.81	131.3
	1.71	2.64	167.4						
	1.78	2.60	167.6						
C−H···O	2.36	3.35	166.9	2.43	3.30	158.1	2.65	3.31	128.4
	2.51	3.31	136.9	2.49	3.45	175.3	2.66	3.55	161.5
	2.73	3.57	145.3	2.65	3.33	127.4	2.76	3.41	127.4
	2.76	3.81	169.7	2.77	3.58	142.6			
	2.93	3.70	156.5	2.92	3.75	155.7			
				2.99	3.83	142.5			

Table 4.3: Comparison of the solubility of pure Salicylic acid and Aspirin with **SAAD31**, **SAAD21** and **SAAD11** molecular complexes.

Compound	Solubility (mg/mL)
SA	2.173
ASPIRIN	3.334
SAAD31	3.6930
SAAD21	4.5985
SAAD11	5.6794

Table 4.4: UV measurements for the three complexes **SAAD31**, **SAAD21** and **SAAD11** at different known concentrations to obtain the values of epsilon (ε).

SAAD31		**SAAD21**		**SAAD11**	
Concentration	Absorbance	Concentration	Absorbance	Concentration	Absorbance
0.000015	0.2383	0.000015	0.11197	0.000025	0.20056
0.00003	0.40456	0.00003	0.16546	0.00005	0.27687
0.000045	0.5472	0.000045	0.25802	0.000075	0.38171
0.00006	0.7144	0.00006	0.32838	0.0001	0.44603
0.000075	0.87534	0.000075	0.41664	0.000125	0.52117
0.00009	1.02153	0.00009	0.48926	0.00015	0.61804
0.000105	1.1997	0.000105	0.55997	0.000175	0.6977
0.000120	1.36062	0.000120	0.59418	0.0002	0.78019
0.000135	1.51683	0.000135	0.72914	0.000225	0.7991
0.000150	1.63833	0.000150	0.79148	0.00025	0.9479
0.000225	2.35516	0.000225	1.19399	0.000375	1.34236
0.0003	2.99064	0.0003	1.65781	0.0005	1.76709

Table 4.5: UV measurements of the three complexes **SAAD31**, **SAAD21** and **SAAD11** at different time intervals.

	SAAD31		**SAAD21**		**SAAD11**	
Time	Concentration	Absorbance	Concentration	Absorbance	Concentration	Absorbance
0 min	0.63782	0.0000653	0.38457	0.0000714	0.57404	0.0001752
15 min	0.64984	0.0000665	0.58739	0.0001091	0.58800	0.0001795
30 min	0.65097	0.0000667	0.59830	0.0001111	0.60563	0.0001849
45 min	0.65225	0.0000668	0.59831	0.0001111	0.61206	0.0001868
60 min	0.65244	0.0000668	0.59474	0.0001105	0.61264	0.0001870
75 min	0.65929	0.0000675	0.60586	0.0001125	0.62127	0.0001896
90 min	0.65968	0.0000675	0.62157	0.0001154	0.64353	0.0001964
105 min	0.66412	0.0000680	0.59828	0.0001111	0.65301	0.0001993
120 min	0.66579	0.0000682	0.59997	0.0001114	0.68033	0.0002077
180 min	0.66707	0.0000683	0.610349	0.0001134	0.68097	0.0002079
Average Absorbance	0.655927		0.601641		0.63872	

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List of Research Publications

1. "A rational study of Crystal Engineering of Supramolecular Assemblies of 1,2,4,5-benzenetetracarboxylic acid". Arora, K. K.; Pedireddi, V. R. *J. Org. Chem.* **2003**, *68*, 9177 – 9185.
2. "A novel additive organic supramolecular assembly:Molecular complex of 3,5-dinitrobenzamide and 3,5-dinitrobenzonitrile". Pedireddi, V. R.; PrakashaReddy, J.; Arora, K. K. *Tetrahedron Lett.* **2003**, *44*, 4857 – 4860.
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5. "Pyridine mediated supramolecular assemblies of 3,5-dinitro substituted benzoic acid, benzamide and benzonitrile". Arora, K. K.; Pedireddi, V. R. *Tetrahedron* **2005**, *61*, 10793 – 10800.
6. "New synthetic approach to a [1.1.6]Metapara Cyclophane derivative via Suzuki – Miyaura Cross Coupling and Ring – Closing metathesis". Kotha, S.; Mandal, K. Arora, K. K.; Pedireddi, V. R. *Adv. Synth. Catal.* **2005**, *347*, 1215 – 1218.

Symposia / Invited Talks

- AsCA'03/Crystal-23 and Sagamore XIV Meeting, 10-18th August 2003, Broome, AUSTRALIA.
- Post – Nost Symposium, 2nd November 2003, NCL, Pune, INDIA.
- XXXIII National Seminar on Crystallography, 8-10th January 2004, NCL, Pune, INDIA.
- National Conference on Nanoscience and Technology, 7- 8th March, 2005, NCL, Pune, INDIA.
- RSC-student Symposium, West India section, 26-27th November 2005, NCL, Pune, INDIA.
- Eighth CRSI National Symposium, 3-5th February 2006, IIT Bombay, Mumbai, INDIA.

Awards

- Director's Commendation Award for the work highlighted in the cover page of *"The Journal of Organic Chemistry"*, Year **2003**, Volume *68*, Issue 24, Page no. 9177 – 9185.