Chapter 1

Introduction

Solids that have orderliness in their arrangement are defined as crystals. One of the phenomenal differences between crystals and other forms of solids lie in their ability to diffract X-rays since interatomic distances in the crystals are at the same range of X-ray wavelengths.

The X-ray diffraction technique involved in determining the arrangement of atoms within the crystal is known as X-ray crystallography. This is one of the most powerful methods of unambiguously determining the complete 3D structures besides confirming the connectivity and stereochemistry of molecules. It is moreover capable of providing precise information concerning bond lengths, bond angles, torsion angles and molecular dimensions in a way no other methods could deliver.

Understanding the physical principles those govern the crystal packing and building novel functional solids is the motivation behind the interest in this field of research.

1.1 Supramolecular chemistry

Supramolecular chemistry is a highly interdisciplinary field of science covering chemical, physical and biological studies of molecular assemblies rather than the individual molecules themselves. Supramolecular chemistry is defined by J.M. Lehn as “the chemistry of the intermolecular bond, covering the structure and function of the entities formed by the association of two or more chemical species”.

The concepts of supramolecular chemistry rely solely on the phenomena of molecular recognition and self-assembly. Molecules recognize complementary sites on other molecules and associate into larger entities to form supermolecules via weaker, non-covalent interactions such as hydrogen bonding and π-π stacking interactions. The phenomenon of molecular association has long been recognized and the term supermolecule
was introduced as early as 1930s to describe highly organized assemblies that result from the association of units.\(^3\)

In contrast to molecular chemistry, which is predominantly based upon the covalent bonding of atoms, supramolecular chemistry is based upon intermolecular interactions. In recent years, supramolecular chemistry\(^1,4-6\) has established itself as one of the most active fields of science. Charles Pederson,\(^7\) Donald Cram \(^8\) and Jean-Marie Lehn \(^9-12\) are the pioneers in the field of supramolecular chemistry and their work on the host-guest chemistry of cryptands and crown ether has won them Nobel prize in chemistry in the year 1987.

The recent trend has been to apply the concepts of supramolecular chemistry in synthesis of novel functional solids.\(^13,14\) Such an approach to synthesis presents an attractive alternative to traditional, multi-step synthesis. Unlike traditional organic synthesis, supramolecular interactions are specific and kinetically labile and defect-free products are obtained in a single step, often in high yield.

Hydrogen bonds,\(^15,16\) coordinate covalent bonds, electrostatic, charge transfer interactions and aromatic \(\pi-\pi\) stacking interactions are the various supramolecular interactions that are exploited in building well-defined supramolecular architecture through self-assembly.

Consequently, there has been a wide shift towards the use of this synthetic approach to building nanoscale architectures over the last decade as it offers the possibility of preparing compounds with complexity nearing those of biological systems.\(^17\)

### 1.2 Crystal Engineering

It goes way back to 1971 when J. Schmidt first coined the term ‘crystal engineering’ when he attempted some topochemical reactions of cinnamic acids and amides in the solid state.\(^18\) The field was further developed by many pioneers such as M.D.Cohen, M. Lahav, L.Leiserowitz, D.Y.Curtin, I.C.Paul, G.Wegner, V.Enkelmann, J.M.Thomas, W.Jones, G.R.Desiraju and J.M.Lehn who took forward it to new heights.

As crystal engineering of new crystalline materials is critically dependent on the understanding of intermolecular interactions, a more accurate definition was later given by Desiraju \(^19\) after more than a decade and a half:
“the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desirable physical and chemical properties.”

It was in the year 1989 when the first monograph was written by G.R. Desiraju on this subject. “Crystal engineering : The design of organic solids, Elsevier, Amsterdam”.

Crystal engineering in other terms can be also called as the application of molecular recognition and supramolecular chemistry to the solid state. In general the term Crystal engineering covers the processes of purposeful design of functional three dimensional crystal structures which are of fundamental importance in the development of functional materials. It so happened that in the last two decades, this new phenomenon has spread into such diverse fields as material chemistry, pharmacy, nanotechnology and other fields.

The field of crystal engineering further extended itself from organic molecules to organometallics and coordination compounds.

1.3 Intermolecular Forces

Since crystal engineering and supramolecular chemistry are closely intertwined, the common theme between the two lies only in the structure and architecture control via intermolecular interactions. Therefore study of intermolecular forces is essential for understanding the structural stability and function of biological systems. The intermolecular interactions are classified according to the strength and directionality.

(i) Hydrogen bond interactions
(ii) Dipole-dipole interactions
(iii) Ion-dipole interactions
(iv) van der Waals interactions
(v) π-π stacking interactions
(vi) Cation-π interactions
(vii) Anion-π interactions
(viii) Halogen bonds
1.3.1 Hydrogen bonds

1.3.1a Historical background

It is probably in early years of 1930s that the term hydrogen bond started appearing. It was first used by Pauling. Although the definition of the term hydrogen bond has evolved over the years, there is still some dispute over the less typical varieties and the boundaries of what should be included within the class of interaction.

Even though hydrogen bonds are much weaker than the conventional chemical bonds such as metallic, ionic and covalent; they are extremely important and significant in a wide range of materials affecting many physical and chemical properties of solids. Their importance can be seen in an enormous number of situations such as in melting and boiling points, solubility, the layout of crystal structures, viscosity, molar volume, reactivity, and colour.

Hydrogen bonds are known for their directionality and reliability. They are extremely important and play a major role in biological systems. For example, it is present in DNA and proteins and accounts for many of their important properties. In fact the hydrogen bonds are operative in determining molecular conformation, molecular aggregation, and function of vast number of chemical systems ranging from inorganic to biological. Therefore it is not surprising that they are also important to all fields of chemistry where they determine structure and reactivity. Their applications range from biological and chemical fields to physics, where charge transfer and other physical properties can be important.

Many techniques are used to study the effects of hydrogen bonds. In fact it was IR spectroscopy that first proved the existence of hydrogen bonds by showing shifts in peaks of OH groups. Since then, many techniques have been and are still used to look at hydrogen bonds, but importantly, it was with the advent of X-ray crystallography that a direct visual representation of hydrogen bonds was produced.

1.3.1b Types of Hydrogen bonds

Hydrogen bond is an interaction between a proton donor group D-H and a proton acceptor atom A, (D-H...A) as illustrated in Figure 1.1.
Generally hydrogen bonds are classified into three types such as strong, moderate and weak hydrogen bonds.\textsuperscript{43,49,50}

\[
\delta^- \delta^+ \delta^-
\]

\[
\text{D—H} \quad \text{A}
\]

**Figure 1.1** Partial positive and negative charges associated with the hydrogen atom (H), the donor atom (D) and the acceptor atom (A) in a hydrogen bond.

**Strong Hydrogen bonds**

Strong hydrogen bonds are mostly covalent in nature and normally arise because of increased attraction resulting from either a deficiency of electron density on the donor group or a surplus of electron density on the acceptor group. With deficiency of electrons on the donor group there is decreased shielding in the hydrogen atom leading to a more positive charge on the atom which ultimately strengthens bond. The same will happen if there is a surplus of electron density on the acceptor. The strong hydrogen bond tends to be linear (D-H···A angle close to 180°) with a short distance between the acceptor and donor atom of around 2.2 to 2.5 Å. Their energies are in the range \(\sim 15-40\) kcal/mol.

**Moderate Hydrogen bonds**

Moderate bonds are mostly electrostatic in nature and the donor and acceptor atoms are normally neutral. The bonds are rather longer than strong bonds and are with typical distances around 2.5-3.2 Å. The directionality of the bond is generally less constrained with D-H···A bond angles typically in the range of 130° and above. They are far more commonly observed than strong hydrogen bonds. Their energies are in the range \(\sim 4-15\) kcal/mol.

**Weak Hydrogen bonds**

Weak hydrogen bonds are weakly electrostatic and are closer to van der Waals force of attraction. These bonds have even longer D···A lengths typically greater than 3.2 Å and wider range of bond angles, around 90° and above. Even these types of bond are thought to be important in crystal engineering as it can be used to tailor intermolecular interactions in
arranging molecules to produce crystals with the desired architecture and hence the properties. Their energies are in the range of < 4 kcal/mol.

1.3.2 Dipole-dipole interaction

Dipole-dipole interactions are forces that exist between polar molecules where the positive end of one molecule attracts the negative end of another molecule (Figure 1.2). Only polar molecules can exhibit this type of forces and are considered to be quite strong. The energies are in the range 5-50 kJ/mol.

![Figure 1.2 Dipole-dipole interactions](image)

**Figure 1.2** Dipole-dipole interactions where blue dash lines indicate the repulsion force and the red lines indicate the attractive forces.

1.3.3 Ion-dipole interactions

Ion-dipole interactions are forces that exist between a *charged ion* and a *polar molecule* (i.e. a molecule with a *dipole*) as shown in Figure 1.3. The cations are attracted towards the negative end of a dipole and the anions are attracted towards the positive end of a dipole Ion-dipole forces are important in solutions of ionic substances in polar solvents (e.g. a salt in aqueous solvent). The energies are in the range 50-200 kJ/mol.

![Figure 1.3 Atractive Ion-dipole interactions](image)

**Figure 1.3** Atractive Ion-dipole interactions.
1.3.4 van der Waals interactions
van der Waals interactions arise from the polarization of an electron cloud by the proximity of an adjacent nucleus resulting in a weak electrostatic attraction (Figure 1.4). They are non-directional.

Figure 1.4 Induced dipole moment on neighbouring Helium atoms.

1.3.5 π-π stacking interactions
π-π stacking interactions are weak electrostatic interaction between two aromatic rings. There are of two general types namely face-to-face and offset interaction

1.3.5a Face-to-face interaction
The stacking that occurs one over the other in a perfectly aligned fashion is called face-to-face interaction (Figure 1.5). The centroid-centroid distance is almost equal with the interplanar distance.

Figure 1.5 View of Face-to-face stacking between two aromatic molecules.
1.3.5b Offset interaction

The stacking that occurs one over the other in a slightly parallel displaced fashion is called Offset interaction (Figure 1.6). The other names used to denote this type of interaction is slipped or parallel displaced interaction.

![Figure 1.6 View of Offset stacking between two aromatic molecules.](image)

1.3.5c C-H...π interactions

The interaction between the positively charged H of an aromatic molecule with the π-cloud of another aromatic ring is called C-H...π interaction (Figure 1.7). This is otherwise called as Point-to-face, Edge-to-face, Edge-on, T-shaped or Herringbone interaction. This type is generally included in the π-type of interactions.

![Figure 1.7 View of Edge-on interaction between two aromatic molecules.](image)
1.3.6 Cation-π interactions

The cation-π interaction is a non-covalent molecular interaction between the electron-rich π orbitals of an aromatic ring and the adjacent cation (Figure 1.8). Such type of interactions is relatively strong and is roughly equivalent in energy to that of a hydrogen bond. Cation-π interactions are important forces for molecular recognition in biological receptors.

![Figure 1.8 Interaction of Sodium ion with the π cloud of benzene ring, an example for cation-π interaction.](image)

1.3.7 Anion-π interactions

An attractive interaction between an aromatic system and an anion is known as anion-π interaction (Figure 1.9). Such type of interaction occurs only when the aromatic ring becomes electron-poor by any means.

![Figure 1.9 Interaction of fluoride ion hexafluorobenzene ring, an example of anion-π interaction.](image)
1.3.8 Halogen bonding

The term halogen bonding encompasses any non-covalent interaction involving halogens as electrophilic species. It is indicated by D...X-Y in which X is the electrophilic halogen (lewis acid, XB donor) and D is a donor of electron density (Lewis base, XB acceptor), and Y is carbon, nitrogen, halogen, etc (Figure 1.10). The remarkable features of this type of bonds are justified by the high strength and directionality.53

\[ \text{D} + \text{X-Y} \rightarrow \text{D} \cdots \text{X-Y} \]

Where D=N, O, S, Se... X= I, Br, Cl... Y= C, Halogen, N...

![Figure 1.10](image.png)

Figure 1.10 An example of halogen bonding in a complex between monochloride and trimethylamine is shown.

1.4 Describing Hydrogen bonded motifs using Graph-sets

In order to describe and analyse hydrogen bonded networks in three-dimensional solids, a language based upon graph-theory was introduced by Etter, Bernstein and co-workers.54-56 A generic graph set descriptor is shown in Figure 1.11

\[ G_d^a(n) \]

Where \( G = \) Graph set designator C/R/D/S
\( d = \) Number of donor atoms
\( a = \) Number of acceptor atoms
\( n = \) Total number of atoms present in the hydrogen-bonded motif

![Figure 1.11](image.png)

Figure 1.11 A generic graph-set descriptor
The first step is to identify the number of different types of hydrogen bonds present in the structure following which one must define the bonds present by the nature of its donors and acceptors inorder to systematically assign a graph set. The hydrogen-bonded motif is characterized by any one of the four designators, R (ring), D (dimer), C (chain) and S (self, for intramolecular hydrogen bond). The numbers of donors and acceptors used in each motif are designated as subscripts and superscripts respectively and the total number of atoms present in the repeat unit is denoted in brackets. The graph-set notations for some hydrogen-bonded motifs are shown in Scheme 1.1.

A benefit of using graph sets is that it brings the focus on to the hydrogen-bonded pattern and not simply on the geometrical constraints of non-covalent interactions. The retrieval and analysis of crystal data from the Cambridge Structural Database (CSD) on the basis of hydrogen bonding patterns are also some of the important uses of graph-set assignments.

\[ G_d^q(n) \]

Scheme 1.1 Examples of graph set notation in hydrogen-bond patterns.

1.5 Scope of the research work

Salts, co-crystals and polymorphs are variety of distinct solid forms that display unique physicochemical properties that can greatly influence the bioavailability, manufacturability, purification, stability and other performance characteristics of the drug. It is therefore critical to understand
the relationship between these forms of solid structures and their functional properties. Since the structure-activity relationship is responsible for the different biological functions of a drug, knowing the precise molecular structure of these solids using crystallographic studies would help in understanding molecular basis for drug design.

1.6 Methodology

The following rules are used as guidelines in the systematic study of the supramolecular synthons.

From analysis of Cambridge Structural Database for the preferred hydrogen bond motifs for certain functional groups, came about the formulation of four general hydrogen bond rules:

1. All acidic hydrogens available in a molecule will be used in hydrogen bonding in the crystal structure of that compound.
2. All good proton donors and acceptors are used in hydrogen bonding.
4. The best proton donor and acceptor remaining after intramolecular hydrogen bond formation will form intermolecular hydrogens to one another (all acceptors may not necessarily interact with the donors)

The first rule was developed by Donohue upon observation of only a handful of organic crystal structure whereas the other rules were formulated by Etter based on her work on organic co-crystals. These rules are based on energetically favorable types of hydrogen bonds which determine the packing patterns of organic crystal structures.

Apart from this, the literature has been used to identify the most stable hydrogen bonded motifs with the idea that they lie intact among a family of related structures.

1.6.1 Preparation of salts/co-crystals

The compounds are prepared by mixing the relevant molar ratios of the reactants in a suitable solvent and heated in a water bath or refluxed in mantle for an hour. The resultant solution is covered with a parafilm and
allowed to evaporate in room temperature for a few days when crystals separate out of the mother liquor.

This thesis deals with the crystal structures of some heterocyclic salts and co-crystals in addition to the new polymorphs that were obtained by serendipity. The objective of this work is to systematically study the different hydrogen bonding patterns evolved from the same supramolecular synthon and to compare their structural patterns with related systems in the in-house database as well as the literature in order to understand their biological, crystal engineering and supramolecular implications.