1.1 Introduction

Supramolecular chemistry is a new and rapidly progressing field on the crossroads between chemistry, biology, physics and materials science. It is the chemistry of molecular assemblies (beyond molecules) and of intermolecular interactions (non-covalent bonds). This not only provides the basis for revolutionizing numerous branches of industry but also improves our understanding of the functioning of living organisms and of the origin of life. Designing a new supramolecular system with desired properties will provide us a better understanding about non-covalent interactions between molecules within the molecular aggregates and it will transform the pharmaceutical industry and medicine by developing new ways of drug administration and new composite biocompatible materials which will serve as implants of new generation. The existence of intermolecular forces was first postulated by Johannes Diderik van der Waals in 1873. In the early twentieth century noncovalent bonds were understood in greater detail, with the hydrogen bond being first described by Latimer and Rodebush in 1920 and later by Linus Pauling in an extended treatment. The importance of supramolecular chemistry was established by the 1987 Nobel Prize for Chemistry being awarded to Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen in recognition of their work in the development and synthesis of shape and ion selective receptors or "host-guest" complexes. Afterwards it took a rapid pace with the concepts of mechanically-interlocked molecular architectures, crystal engineering and supramolecular materials coming within its fold. In the 1990s, supramolecular chemistry became even more sophisticated. The science of nanotechnology also had a strong influence on the subject, with building blocks such as fullerenes, nanoparticles, and dendrimers becoming part of synthetic systems.
Within the realm of supramolecular chemistry another well-defined area is crystal engineering, devoted to the design and studies of crystals built of two or more components with desirable properties. Pepinsky first introduced the term “Crystal Engineering” in 1955 and the subject was elaborated by Schmidt during 1950 to 1970 to address the issue of crystal packing in the context of organic solid state photochemical reactions of cinnamic acids and amides. A general meaning of the term was proposed by Desiraju of Crystal Engineering as "the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties". Crystal engineering is a mainline interdisciplinary subject today that was started with organic solids and now deals with the self-assembly of molecular crystals, metal–organic architectures, nanostructures, and coordination polymers using hydrogen bonding, electrostatic, van der Waals interactions, and metal coordination bonding. It is an interdisciplinary field that seeks to develop protocols for predicting and controlling the structure and functional properties of solids. Catalysis, optical materials, conducting and magnetic materials, nanotechnology, electronic materials and sensors, nano and microporous materials, supramolecular devices, protein-receptor binding, molecular modeling, drug design and improving properties of existing APIs are some of the key research areas within the realm of crystal engineering.

1.2 Intermolecular Interactions and Supramolecular Synthons

Crystal, the supramolecule par excellence, is an assembly of millions of molecules held together in a periodic arrangement at an amazing level of precision by intermolecular interactions, guided by molecular recognition and organized self assembly. Intermolecular interactions include ion-ion, ion-dipole, dipole-dipole interactions, hydrogen bonding, London forces, etc. The close packing principle of Kitaigorodski postulates that molecules in a crystal pack such that the projections of one molecule dovetail into the hollows of its neighbour, i.e. bumps fit into hollows just like lock and key, so that the maximum numbers of intermolecular contacts are achieved. The crystal structure of a molecule is the free energy minimum resulting from the optimization of several attractive and repulsive intermolecular interactions with varying
strengths, directional preferences and distance-dependence properties. Therefore understanding the nature and strength of intermolecular interactions is of fundamental importance in supramolecular chemistry. Intermolecular forces are mainly of two types, (i) isotropic or non-directional (C···C, C···H, H···H interactions) that defines the shape, size and close packing and (ii) anisotropic or directional\textsuperscript{3a} as hydrogen bonds, charge transfer interactions, halogen interaction, and heteroatom interactions (e.g. O–H···O, N–H···O, C–H···O, C–H···N, O–H···π, halogen···halogen, nitrogen···halogen, sulfur···halogen etc). Long range dispersion forces and short range repulsive forces are isotropic. These interactions vary with $r^{-n}$, where $r$ is the distance between relevant non-bonded atoms and $n$ is a positive integer. The attractive forces vary from $r^{-1}$ to $r^{-6}$ depending upon the interaction type and short range exchange repulsion varies with $r^{-12}$. Among all intermolecular interactions hydrogen bonding is the most reliable directional interaction and it has a fundamental role in crystal engineering.\textsuperscript{3a} Hydrogen bonds are classified into three categories based on their strength as very strong, strong and weak hydrogen bonds (Table 1).\textsuperscript{7} The properties of a crystalline material are the result of molecular arrangement in the crystal lattice, which is controlled by intermolecular interactions.

Table 1 Some properties of very strong, strong and weak H-bonds.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Very strong</th>
<th>Strong</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bond energy (–kcal mol\textsuperscript{–1})</td>
<td>15–40</td>
<td>4–15</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Examples</td>
<td>[F···H···F]</td>
<td>O–H···O=C</td>
<td>C–H···O</td>
</tr>
<tr>
<td></td>
<td>[N···H···N]\textsuperscript{+}</td>
<td>O–H···O=C</td>
<td>O–H···π</td>
</tr>
<tr>
<td></td>
<td>P–OH···O=P</td>
<td>O–H···O–H</td>
<td>Os–H···O</td>
</tr>
<tr>
<td>Red shift in IR</td>
<td>&gt;25%</td>
<td>5–25%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>$D$(X···A) (Å)</td>
<td>2.2–2.5</td>
<td>2.5–3.2</td>
<td>3.0–4.0</td>
</tr>
<tr>
<td>$D$(H···A) (Å)</td>
<td>1.2–1.5</td>
<td>1.5–2.2</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>$θ$(X–H···A) (°)</td>
<td>175–180</td>
<td>130–180</td>
<td>90–180</td>
</tr>
<tr>
<td>Covalency</td>
<td>Pronounced</td>
<td>Weak</td>
<td>Vanishing</td>
</tr>
<tr>
<td>Electrostatic</td>
<td>Significant</td>
<td>Dominant</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

From crystal engineering point of view the strong, directional forces are more helpful to design target crystal structures. The interaction motifs for designing crystals
are termed as *supramolecular synthons*\(^{8a,b}\) and Desiraju defined it as “*supramolecular synthons are structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions.*” The concept is widely used in the design of solids which are important from scientific and commercial viewpoints. The synthesis of supramolecular structures in the solid state dealing with the self-assembly of molecular crystals using hydrogen bonding, electrostatics, \(\pi\)-stacking, halogen bonding, van der Waals interactions, and metal-coordination bonding. Crystal engineering is effectively like supramolecular synthesis in the solid state, and there is a direct analogy between the *supramolecular synthon* and the *molecular synthon*\(^{8c,d}\) that was originally proposed for organic synthesis by E. J. Corey\(^{8c}\) in 1967. The advantage of using the synthon approach is that it offers a simplification in the understanding of crystal structures. Zaworotko sub-classified synthons as homosynthons and heterosynthons based on the interacting functional groups. If supramolecular synthon is formed between the same functional group it is a homosynthon, if it forms between two different functional groups it is called as heterosynthon.\(^{9}\) Some of the well known homosynthons are COOH···COOH, CONH\(_2\)···CONH\(_2\), OH···OH, NH\(_2\)···NH\(_2\), halogen···halogen, etc. which are between similar functional groups and COOH···pyridine, CONH\(_2\)···pyridine, COOH···CONH\(_2\), OH···NH\(_2\), CONH\(_2\)···N-oxide, halogen bonds, etc. are heterosynthons (Figure 1).

![Homosynthons and Heterosynthons](image)

**Figure 1** Examples of homosynthons and heterosynthons.

Similar to hydrogen bonds, halogen bonds\(^{10}\) are the noncovalent interaction between halogen atoms (Lewis acids) and neutral or anionic Lewis bases, emerging as prototype to hydrogen bonding. The interaction energy for halogen bond spans over a
wide range from 1 to 35 kcal mol$^{-1}$. The weak Cl···Cl interaction between chlorocarbons and the very strong I···I$_2$ interaction in I$_3^-$ being the extremes. Weak interactions$^{11}$ that include C−H···O and C−H···N hydrogen bonds,$^{11a}$ C−H···π,$^{11i}$ halogen···halogen interactions$^{10}$ etc. are important in crystal design. C−H···O and C−H···N hydrogen bonds are electrostatic in nature and have long-range distance character that have importance in wide variety of chemical and biological systems. C−H···O hydrogen bonds are capable of exhibiting all the properties$^{11e}$ that are similar to strong hydrogen bonds such as dependence on the acidity and basicity of donor and acceptor strengths and near linearity of the interaction and lone-pair directionality of the acceptor.

Identification of molecular functionalities that will generate predictable or robust intermolecular interactions/ synthons is the key step of crystal engineering. The situation will become more complicated in multi-functional molecules because of competition between similar strength donor/acceptor groups. To understand hydrogen bonding and its competition in organic compounds, Etter proposed$^{12}$ three hydrogen bond rules as, (a) “all acidic hydrogens available in a molecule will be used in hydrogen bonding in the crystal structure of that compound,” (b) “all good proton acceptors will be used in hydrogen bonding when there are available hydrogen-bond donors,” and the third rule is that (c) “the best hydrogen-bond donor and the best hydrogen acceptor will preferentially form hydrogen bonds to one another.” These rules provide useful information about the preferred connectivity patterns, hydrogen bond competition and stereoelectronic properties of hydrogen bonds for a particular functional group or for sets of functional groups. The methods of ranking solid-state hydrogen bond preferences are based on functional group competitions in homomeric crystals or heteromeric cocrystals. These rules involved in analyzing which donors are selected by a limited number of acceptors or vice versa during crystallization. The analysis of hydrogen bonds and other weak interactions and its cooperation and competition will guide the construction of target architectures and functions. A huge storehouse of crystal structures in the Cambridge Structural Database (CSD)$^{13}$ of nearly 4,83,000 crystal structures up to May 2009 (compared to very small sized 2000 entries in 1965) provides an excellent tool for accessing the efficiency and reproducibility of a particular supramolecular synthon in molecular crystals. A study on the probabilities of occurrence of supramolecular
synthons in a supramolecular system in presence or absence of second competing functionality is discussed in Chapter 6 with a detailed chronological literature survey. Our synthon analysis study\textsuperscript{14} of carboxylic acid, pyridine, amine, and hydroxyl functional groups while present in same supramolecular system is discussed in Chapter 6.

Bernstein\textsuperscript{15} developed geometrical notations to recognize the hydrogen bond patterns that are known as Graph Set Notation. Graph set approach is nothing but to analyze the hydrogen-bond patterns from a complicated networks structure to a reduced simple pattern. There are combinations of four, each specified by a designator: chains (C), rings (R), intramolecular hydrogen-bonded patterns (S), and other finite patterns (D). Specification of a pattern is augmented by a subscript designating the number of hydrogen-bond donors $d$ and a superscript giving the number of hydrogen-bond acceptors $a$. In addition, the number of atoms $n$ in the pattern is called the degree of the pattern and is specified in parentheses. The graph set descriptor is then given as $[G_d^a(n)]$, where $G$ represents one of the four possible designators. Some examples are given in Figure 2.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures}
\caption{Examples of various graph set descriptors.}
\end{figure}

\subsection*{1.3 Organic Solid-State Forms}

A crystal is "a three dimensional atomic, ionic, or molecular structure consisting of periodically repeated, identically constituted, congruent unit cells"\textsuperscript{16a} and the process of the formation of solid crystals from the homogeneous solution, melt or by direct vapor
deposition is known as crystallization.\textsuperscript{16b} Crystal is a well-defined pattern, or structure, dictated by forces acting at the molecular level and during its formation process the solute concentration should reach a certain critical value, before changing status otherwise solid formation is impossible below the solubility threshold at the given temperature and pressure conditions. Crystallization process consists of two main events, (i) nucleation and (ii) crystal growth. Nucleation is the step where the solute molecules dispersed in the solvent start to assemble into clusters, on the nanometer scale (elevating solute concentration in a small region), that becomes stable under that conditions. The stable clusters constitute the nuclei otherwise they re-dissolve and form the stable once again. Supersaturation is the driving force for initial nucleation step. The nuclei are stable only when they reach a critical size and such critical size is dictated by the operating conditions (temperature, supersaturation, etc.). Single crystal X-ray diffraction and powder X-ray diffraction are two very powerful techniques to determine crystal structures. Crystal structures offer an understanding of various forces responsible for holding the organic crystalline solids that can be engineered to have desired properties. The nature of crystallization process is governed by thermodynamic and kinetic factors (Figure 3). Several research groups studied crystal growth aspect.\textsuperscript{17} Davey \textit{et al.}\textsuperscript{17a,b} and Desiraju \textit{et al.}\textsuperscript{17c} studied nucleation and crystal growth on the crystal formation pathway of tetrolic acid and Na(saccharinate).nH\textsubscript{2}O systems respectively. These are some of the typical studies to understand primary stage of crystallization. Ostwald\textsuperscript{18} stated that a system moves to equilibrium from an initial high-energy state through minimal changes in free energy. Therefore the structure that crystallizes first is one which has the lowest energy barrier (highest energy, kinetically metastable). This form would then transform to the next lower energy polymorph until a thermodynamically stable state is reached, the so-called Ostwald’s Law of Stages (Figure 4).
Figure 3 Hypothetical transitions from solution to thermodynamic and kinetic crystals. Small difference between $\Delta G_{\text{thermodynamic}}$ and $\Delta G_{\text{kinetic}}$ determines formation of kinetic crystals.

Figure 4 Ostwald’s Rule of Stages. Initial high-energy state (metastable A) through minimal changes in free energy crystallizes first is one which has the lowest energy barrier. Metastable A form will then transform to the next lower energy polymorph (metastable B) and so on (metastable C) until thermodynamically stable crystal D.
Crystal engineering deals with various solid forms. It includes polymorphs, host-guest complexes, network solids, salts, hydrates, cocrystals, more preferably pharmaceutical cocrystals, and this chapter will cover a brief introduction to various organic solid-state forms and the concept and its importance. When a compound crystallized in two or more different crystalline modifications, they are known as polymorphs and the phenomenon is polymorphism.\textsuperscript{19} Cocrystals\textsuperscript{20} can be defined as multiple-component crystal structure in which two or more compounds coexist through hydrogen bonds or non-covalent interactions. If the reactants are solids at ambient conditions, the multi-component crystalline materials are cocrystals and those composed of one or more solids and a liquid are known solvates or pseudopolymorphs\textsuperscript{21} and hydrates\textsuperscript{22} when solvent is water. However the multi-component system is known as molecular salt/salt\textsuperscript{14,23} if proton is transferred from acid to base and retains as ionic state. Thus salts and cocrystals are multicomponent crystals that can be distinguished by the location of the proton between an acid and a base. Cartoon depictions of all these solid phases are illustrated in Figure 5.

\textbf{Figure 5} Cartoon depictions of various organic solid forms and discussed in the corresponding Chapters.
1.4 Polymorphism

The word ‘Polymorphism’ originally comes from the Greek literature (poly = many, morph = form). Polymorphism was first realized in 1798, when the German chemist Martin Heinrich Klaproth discovered calcite minerals and aragonite had the same chemical composition (CaCO₃). Mitscherlich first documented polymorphism in 1822 in the context of crystallography²⁴a of arsenate and phosphate salts that can exist as different crystal forms. Ostwald’s work¹⁸ on the relative stability of different crystal structures of the same compound was a major development in polymorphism. Polymorphism acquired potential importance after Buerger and McCrone’s work²⁴c on change in properties like melting point and solubility of different crystal forms of the same chemical compound. The existence of different crystal structures for the same element or atom is known as allotrope first described by Berzelius.²⁴d Allotropes are at the elemental (e.g. C, S, P, Sn etc.) level whereas polymorphism is used to refer structural diversity of molecular compounds.²⁴c For example carbon has three allotropes, diamond, graphite and fullerene. Depending on the atomic arrangement in their lattice they show quite different properties. A widely accepted definition of polymorphism was given by McCrone²⁴f which states that “a solid crystalline phase of a given compound resulting from the possibility of at least two crystalline arrangements of the molecules of that compound in the solid state”. Buerger²⁴g tried to simplify the definition limiting only for solids composed of one component, but the concept was confusing and misleading as polymorphism can exists in multi-component system as well.

Polymorphism may occur due to various reasons, packing of molecules, conformational or molecular flexibilities, supramolecular synthon competitions are the main reasons and subsequently they are called as packing, conformational and synthon polymorphs¹⁹,²⁵ (Scheme 1). Packing polymorphism exists when the molecule is mostly rigid. Conformationally flexible molecules have greater scope for their polymorphic occurrence because of large number of degrees of freedom as the energy differences between conformational polymorphs lies in a small window of 0.5-3 kcal mol⁻¹. A metastable conformation may be stabilized by stronger hydrogen bonds in the crystal structure while a stable conformer may not be able to form strong hydrogen bonds, although they lead to a balance of energy state and the overall stability of a polymorph is accounted by measuring conformation energy and lattice energy. The energy
compensation towards overall energy of a polymorphic system and the phenomenon known as systematic effect was recently reviewed by Nangia\textsuperscript{25c} with several examples of conformational polymorphs. Our result on conformational and synthon polymorphism is discussed in Chapter 2 and 4.

Scheme 1 Schematic illustrations of different arrangement of molecules in the crystalline lattice that leads to different kinds of polymorphism. This scheme is culled from A. Nangia \textit{Acc. Chem. Res. 2008, 41, 595}. 

\textbf{Polymorph i} \\
\textbf{Packing Polymorphs} \\
\textbf{Conformational Polymorphs} \\
\textbf{cisoid} \\
\textbf{transoid} \\
\textbf{Packing Polymorphs} \\
\textbf{Conformational Polymorphs} \\
\textbf{Polymorph ii} \\
\textbf{Polymorph iii} \\
\textbf{Conformational Isomorphs, v} \\
\textbf{Packing Polymorphs} \\
\textbf{Polymorph iv} \\
\textbf{Polymorph vi} \\
\textbf{Synthon Polymorphs} \\
\textbf{Polymorph vii}
Different polymorphs have different physical and chemical properties (Table 2). Thus characterization of all polymorphs through polymorph screening using various methods like solvent less methods of melt and sublimation via green methodology, solution crystallization etc. and then identification of stable form and control over the preparation of that particular form has become a major goal for academic (crystal engineering and solid-state chemistry) and industry research. Polymorphism of drugs is of central interest after the Norvir and Zantac incidents in the last decade. Dissolution profile of Ritonavir polymorphs shows a significant difference with unique crystal structures. Polymorph I is almost five times more soluble compared with Polymorph II which is almost insoluble. Thus a thorough screening and complete characterization of all possible polymorphs is considered an essential step in pharmaceutical industry to choose the best drug formulation with desirable properties. The extensive study on polymorphism gives fundamental understanding on molecular recognition, crystal nucleation, and structure–property relationships. Among the various methods of polymorph generation, solution crystallization and/or high-throughput crystallization are default. Recent approaches for polymorph generation include crystallization with structurally related additives, epitaxial growth, laser induced nucleation, crystallization in capillaries, confinement within porous materials, using polymers as heteronuclei, mechanical grinding, using supercritical liquids, using self assembled monolayer with different functional moieties, potentiometric cycling etc. Recently melting and sublimation, the two solvent less high temperature techniques to afford guest free host structures were explored by our group and those techniques were employed to generate new polymorphs of compound that are prone to give guest included crystal on solution crystallization with very good probabilities.
Table 2 Properties that can be different for polymorphs. This table is culled from, S. Dutta, D. J. W. Grant, *Nat. Rev. Drug Discovery*, 2004, 3, 42.

<table>
<thead>
<tr>
<th>Packing properties</th>
<th>Thermodynamic properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Molar volume and density</td>
<td>• Melting and sublimation temperatures</td>
</tr>
<tr>
<td>• Refractive index, optical properties</td>
<td>• Internal energy</td>
</tr>
<tr>
<td>• Conductivity, electrical and thermal</td>
<td>• Enthalpy</td>
</tr>
<tr>
<td>• Hygroscopicity</td>
<td>• Heat capacity</td>
</tr>
<tr>
<td><strong>Kinetic properties</strong></td>
<td>• Entropy</td>
</tr>
<tr>
<td>• Dissolution rate</td>
<td>• Free energy and chemical potential</td>
</tr>
<tr>
<td>• Rates of solid state reactions</td>
<td>• Thermodynamic activity</td>
</tr>
<tr>
<td>• Stability</td>
<td>• Vapour pressure</td>
</tr>
<tr>
<td><strong>Surface properties</strong></td>
<td>• Solubility</td>
</tr>
<tr>
<td>• Surface free energy</td>
<td><strong>Spectroscopic properties</strong></td>
</tr>
<tr>
<td>• Interfacial tensions</td>
<td>• Electronic transitions, ultraviolet-visible</td>
</tr>
<tr>
<td>• Habit</td>
<td>spectra</td>
</tr>
<tr>
<td><strong>Mechanical properties</strong></td>
<td>• Vibrational transitions, infrared and</td>
</tr>
<tr>
<td>• Hardness</td>
<td>Raman spectra</td>
</tr>
<tr>
<td>• Tensile strength</td>
<td>• Rotational transitions</td>
</tr>
<tr>
<td>• Compactibility, tabletability</td>
<td>• Nuclear magnetic resonance chemical shifts</td>
</tr>
<tr>
<td>• Handling, flow and blending</td>
<td></td>
</tr>
</tbody>
</table>

### 1.5 Enantiotropic and Monotropic Related Polymorphs

The thermodynamics of polymorphs of molecular crystals can be represented by pressure-temperature or commonly used energy-temperature phase diagram that are helpful for characterizing and understanding polymorphic behavior of a compound. Polymorphism exists in the solid state and natural physical process phase transition between polymorphs is a common phenomenon. The stability relationship of polymorphs of a molecule can be established by measuring their enantiotropic or monotropic relationship.9a The two polymorphic modifications are said to be enantiotropic when the transition point between the two phases is found at a temperature below the melting point of either of them (Figure 6a). When there is no transition point below the melting point
of the two polymorphs then the two forms are monotropically related (Figure 6b). This is known as heat-of-transition rule.\textsuperscript{9a} The heat-of-fusion rule states that in an enantiotropic system higher melting polymorph will have the lower heat of fusion. If the higher melting polymorph has a higher heat of fusion the two polymorphs are monotropically related. Solid and liquid will be in equilibrium at melting point and Gibbs free energy will be zero for two phases. The entropy of fusion can be expressed as,

$$\Delta S_f = \Delta H_f / T_f$$

Entropy of fusion rule states that two modifications are enantiotropically related if polymorph with higher melting point has the lower entropy of fusion and monotropically related if lower melting polymorph has lower entropy of fusion. eg. for a dimorphic system (Figure 6a) it is seen that the thermodynamic transition point $T_{p,I/II}$ defined by the point at which $G_I$ and $G_{II}$ cross, falls at a temperature below the melting point of lower melting form, $m_{p,II}$ and hence enantiotropically related. However the free energy curves do not cross at a temperature below the two melting points (Figure 6b) and so they are monotropically related.

Several analytical techniques are being used to establish the thermodynamic behaviour of polymorphs, eg. Optical and/ or Hot Stage Microscopy (HSM), Differential Scanning Calorimetry (DSC) etc. HSM can be used to obtain qualitative information on polymorphic behaviour however thermal analysis (DSC or DTA) provides quantitative

\textbf{Figure 6} (a) Fundamental E/T diagram for dimorphic enantiotropic system. Form I is stable below transition point. Above transition point Form II is stable. (b) Fundamental E/T diagram for dimorphic monotropic system. Form I is more stable at all temperature below melting point than form II.
information about the relative stability of polymorphic modifications, the energies involved in phase changes between them and the monotropic and enantiotropic nature of those transitions. Tolbutamide [1-butyl-3-(4-methylphenylsulfonyl)urea], an oral hypoglycaemic agent exists in four polymorphic modifications. Polymorph I is stable and phase transition from polymorph III, II and IV can clearly be described by DSC thermograms (Figure 7). Transitions III→I, II→I, IV→I show those pairs are enantiotropically related. Monotropic and enantiotropic relation between polymorphs in several instances are observed and discussed in Chapter 2 and 4 with the help of HSM, DSC and X-ray diffractions. For characterization of polymorphs spectroscopic methods that include infrared (FT-IR), near infrared (NIR) and Raman spectroscopy etc., thermal analysis (DSC, TGA, HSM etc) and finally X-ray diffraction (single crystal and powder X-ray diffraction) are used.

Figure 7 DSC thermogram of Tolbutamide polymorphs: (a) Form I, (b) Form II, (c) Form III and (d) Form IV. The polymorph conversions from other forms to Form I are shown. These transitions are enantiotropically related.

1.6 Isostructurality

Geometrical properties like shape, size and chemical like electronegativity, polarizability of functional group influence crystal packing. Kitaigorodskii has given
importance to the volume and shape of functional groups in crystal packing, however the electronic properties of functional groups cannot be over looked. As the size of the molecule increases the significance of geometric effects becomes important. A given packing motif may be able to tolerate small changes in the molecular structure without a considerable change in the close-packed crystal structure. These changes are minor alterations in substitution and/or epimerization. The tolerance may be ascribed to the presence of ~30% free space in close-packed structures because the packing coefficients of organic crystals are generally about 70%. The phenomenon by which different molecules pack in a similar fashion to produce similar crystal structures is called isostructurality and the structures are called isostructural and is inversely related to the phenomenon of polymorphism. Isostructurality and Isomorphism are two commonly used terms in literature. Two crystals are said to be isomorphous if (a) they have the same space group and unit-cell dimensions and (b) the types and the positions of atoms in both are same except for a replacement of one or more atoms in one structure with different types of atoms in the other (isomorphous replacement), such as heavy atoms, or the presence of one or more additional atoms in one of them (isomorphous addition). The substances are so closely similar that they can form a continuous series of solid solutions. On the other hand, two crystals are said to be isostructural if they have the same structure, but not necessarily the same cell dimensions nor the same chemical composition, and with a comparable variability in the atomic coordinates to that of the cell dimensions and chemical composition. e.g. calcite (CaCO₃), sodium nitrate (NaNO₃) and iron borate (FeBO₃) are isostructural. The phenomenon of isomorphism is known for more than two centuries with the growth of potassium alum crystals from a saturated solution of ammonium alum. Kitaigorodskii was the first to review isostructurality in organic molecular crystals. Kálmán et al. have divided isostructurality into two categories—isostructural crystals or main-part isostructuralism of related molecules and homeostructural crystals and proposed two descriptors to quantify isostructurality. They are unit-cell similarity index Π and isostructurality index I(n) and can be defined as the following equations. When the related molecules differing by substitutions on more than one atomic site have similar packing, it is called homeostructural crystals.
\[
\Pi = \left| \frac{a + b + c}{a' + b' + c'} \right| - 1 \cong 0
\]

where \(a, b, c\) and \(a', b', c'\) are orthogonalized lattice parameters of the related structures. For a pair of completely isostructural crystals \(\Pi\) should be close to zero.

\[
I_i(n) = \left[ 1 - \left( \frac{\sum \Delta R_i}{n} \right)^{1/2} \right] \times 100
\]

The isostructurality index, \([I_i(n)]\) is a measure of the degree of internal isostructurality where \(n\) is the number of distance differences (\(\Delta R_i\)) between the absolute coordinates of identical non-hydrogen atoms within the same section of asymmetric units of related structures. \(I_i(n)\) should be close to 100% for isomorphous crystals.

Isostructurality in three dimensions means the complete crystal packing. However one- and two dimensional isostructurality\(^{32}\) is documented. When two structures show similar infinite two-dimensional molecular arrangements they are called as two-dimensionally isostructural. Accordingly similar arrangement of molecules in 1D is one-dimensionally isostructural. It is important to have some knowledge about which groups are interchangeable and under which circumstances to see the isostructural behavior between two structures. Kitaigorodskii\(^{33}\) has ranked them as, (i) the halogens Cl, Br, I; (ii) O and S; (iii) C, quadrivalent Si, Ge, Sn and Pb. There are some examples where strong hydrogen bonding functional groups, such as –OH, –NH\(_2\), =O, can also replace hydrogen to produce isostructural crystals (Figure 8). Isostructurality phenomenon was investigated for steroids by Kálmán with an exchange of functional groups (gamabufotalin/arenobufagin) or by epimerization (5\(\alpha\)- and 5\(\beta\)-androstane-3 \(\alpha,17\beta\)-diol).\(^{34}\) 2-oxa-4-androstene-3,17-dione is isostructural with 6\(\alpha\)-hydroxy analogue, replaced C–H···O interaction by C–O–H···O hydrogen bond is an example of 1D isostructurality from our group (Figure 8b).\(^{32b,c}\) The fact that these two compounds form solid solution validates the isomorphous replacement of C–H atom by C–OH group (Figure 8d, 8e).
Figure 8 (a) H/NH₂ exchange forms isostructural crystals. (b) In 6α-Hydroxy-2-oxa-4-androstene-3,17-dione, H/OH exchange produces isostructural crystals. (c) H₂/O exchange generates isostructurality. (c) via C–O–H···O synthon in (d) without disturbing the overall arrangement of molecules; (d) Hydrogen bonding of 2-oxa-4-androstene-3-17-dione when R = H and (e) R = OH. Identical a-axis and the similarity in hydrogen bonding and arrangement of molecule in both structures lead to isostructural, due to replacement of C–H···O synthon by C–O–H···O.

Triiodoresorcinol and triiodophloroglucinol are rare case of examples which are both polymorphic and isostructural recently reported from our group. They crystallized as orthorhombic (P2₁2₁2₁) and monoclinic (P2₁/n) polymorphs and the orthorhombic polymorphs of both compounds are isostructural and correspondingly monoclinic polymorphs are also identical. These examples illustrate isostructurality via C–H ⇔ C–OH replacements. Another example that shows both polymorphism and isostructurality is 2-amino-4-chloro-6-morpholinepyrimidine and 2-amino-4-chloro-6-piperidino pyrimidine. Exceptions are also reported. For example room temperature form of 2,6-dichloro-N-phenylformamide and 2-chloro-6-methyl N-phenylformamide (both orthorhombic) are isomorphous but their high temperature forms (both in monoclinic) are not isomorphous. 2-Amino-4-chloro-6-morpholinopyrimidine is dimorphic with Z' = 2 and 1 in space group P2₁/c. The Z' = 2 polymorph is isostructural with 2-Amino-4-chloro-6-piperidinopyrimidine that has only one crystal structure with Z' = 2 showing O
CH₂ replacement. Chloro–methyl exchange is well known and this rule states that when the geometry of the groups governs the crystal packing they produce isostructural crystals due to their similar size and shape (Cl 20 Å³ and Me 24 Å³), discussed thoroughly and calculated isostructurality index and unit cell similarity index of newly synthesized series of similar phenylbenzenesulfonamides and its polymorph structures that is covered in Chapter 4. Isostructurality in organic solids is well documented in literature. There is a report on bromide and nitrate exchange in isostructural crystals in spite of their different shapes where both of the anions make strong H-bonds with the cation counterpart. Above all these groups, the halogen exchange, specially Cl, Br and I to produce isostructurality, are more frequent. Propargylammonium halides (Cl⁻, Br⁻, I⁻) are isostructural where halide ions accept three H-bonds from ammonium group and one from terminal alkyne group. Another interesting isostructurality has been reported by Bar et al. in para substituted X-C₆H₄-CH=N-C₆H₄-X' molecules. When X = X' = Cl or Br, the molecules are not isostructural, but molecule with X = Cl and X' = Br is isostructural to the dichloro compound. On the other hand X = Br and X' = Cl substituted molecule is isostructural to dibromo derivative. It indicates the importance of halogens as well as the position of substitution in the molecules. In principle, two isostructural compounds are expected to yield the similar polymorphs and the idea is similarly applicable for multi-component systems like solvate, salt and cocrystals etc. Isostructural crystals often lead to similar kind of properties.

1.7 Polymorphism and High Z' Structures in Solvent Less Methods

Awkward molecular shape, OH, NH₂, SO₃H like sticky functional groups, ionic nature etc. are some of the factors for hydration and/or solvent inclusion complexes of organic molecules, especially APIs. In drug industry, solvent inclusion complexes are not advisable because of the toxic vapor nature of most solvents. Thus the synthesis and characterization of guest-free crystalline forms has gained importance but difficult to crystallize because, in general a solvent or water molecule acts as a crystallization aid or filler in the voids of the host. Methods that have been used to obtain guest free structure of lattice inclusion host compounds and discussed in Chapter 2. Temperature lowering, isothermal evaporation and isothermal diffusion crystallization techniques are common.
methods to grow single crystals. Some popular methods to produce guest free host crystal structure are (a) misfit size and/or shape of the guest molecule to the void formed by the host, (b) using an appropriate dual-nature solvent or unfavourable electrostatic interactions, (c) layer-by-layer conversion of particles from the outside in as guest is leached out, (d) recrystallization with a solvent-nonsolvent system, (e) sonication, (f) gradual pH change etc. High temperature crystallization methods melting and sublimation were explored recently from our group. The two high temperature solvent less methods of green methodology generate guest free structures of well known host 1,1-bis-(4-hydroxyphenyl)cyclohexane and further illustrated with isomeric dihydroxybenzoic acid molecules and successfully isolated guest free forms and new polymorphic modification of other cases are covered.

\[ Z' \] (Z prime) is the number of symmetry independent or crystallographic unique molecules in a crystal lattice. Structure with \( Z' = 1 \) means that each molecule is surrounded by like molecules, however, \( Z' > 1 \) structure means each molecule is surrounded by molecules that are crystallographically different. The occurrence and reasons behind high \( Z' \) structures have attracted attention of crystallographers and now being intensely studied to understand the factors leading to high \( Z' \) crystal structures even as occurrence of high \( Z' \) structures is still not properly understood. Steed showed presence of pseudosymmetry, awkward shape, formation of molecular helices via hydrogen bond or other interactions, strong hydrogen bonds, chirality, kinetic or temperature effect are different reasons for high \( Z' \) structures are elaborately discussed in Chapter 3. Our observation is the frequent occurrence of high \( Z' \) structures in high temperature solvent less methods of melt and sublimation and compared with Cambridge Structural Database (CSD). It is found that solvent-free crystallization methods show a much higher probability of multiple \( Z' \) structures (~18%) compared to overall CSD trends on \( Z' \) frequencies (<12%). Generation of high \( Z' \) structures by melting and sublimation crystallization can be understood as rapid cooling of the hot liquid or vapor in the open flask or on the cold finger is a kinetic phase and the conditions under which hydrogen-bonded clusters are likely to condense in a pseudo-symmetric crystalline arrangement. Popular host 1,1-bis-(4-hydroxyphenyl)cyclohexane is found to be a remarkable example to illustrate the occurrence of high \( Z' \) structure in metastable polymorph by melting. Solvent less methods when used to generate guest free host
structures of isomeric dihydroxybenzoic acids, \( Z' > 1 \) structure is observed commonly discussed in Chapter 2 and 3. Carbamazepine\(^{37c}\) is another exciting example for which \( Z' = 1 \) from solution crystallization (3 polymorphs) whereas \( Z' = 4 \) when it is crystallized from melting.

### 1.8 Salt Cocrystal Continuum

It is a must to label and classify crystalline solid forms in order to characterize them and then make comparisons. There has been a long standing and lively debate on the nomenclature issues in crystal engineering, starting from what is a cocrystal, or cocrystal/salts, to the definition of pseudopolymorph, solvate, host–guest compounds etc. In general, molecular crystals can be classified broadly into single-component and multiple-component crystals. Salts and cocrystals are multi-component crystals there exists a continuum linking cocrystals and salts based on the extent of proton transfer between the components. Cocrystals can be defined as multiple-component crystal structure in which two or more compounds coexist through hydrogen bonds or non-covalent interactions. If the reactants are solids at ambient conditions, the multi-component crystalline materials are cocrystals and those composed of one or more solids and a liquid are known solvates or pseudopolymorphs.\(^{21}\) However the multi-component system is known as molecular salt/ salt if proton is transferred from acid to base in the ionic state. If a solution containing an organic acid and an organic base deposits a crystalline solid containing both components, the result can be a molecular salt or a cocrystal. If the proton resides on the base, then proton transfer has occurred and the crystalline acid-base complex is a molecular salt. If proton transfer has not occurred and the proton remains on the acid, then it is a cocrystal.\(^{21,38a}\) The propensity of an acid to give up a proton is represented by its p\(K_a\), the negative logarithm of the dissociation constant. p\(K_a\) relates to the equilibrium behavior in aqueous solution and measured p\(K_a\) values will vary depending on measurement technique, solvent, temperature, and other factors. The extent of proton transfer depends on the magnitude of the difference of p\(K_a\) values of the reacting acid and base. It is generally accepted that reaction of an acid with a base will be expected to form a salt if the \( \Delta pK_a \) \([\Delta pK_a = pK_a(\text{base}) – pK_a(\text{acid})]\) is greater than 3.75, which is an essential criteria while selecting the appropriate counter ions to the preparation of salts of API in order to improve its properties like solubility.

\(^{21}\) | Chapter 1
For acid-base complexes with similar pKₐ values the ΔpKₐ value and the crystalline environment determine the extent of proton transfer. Johnson and Rumon studied the type of hydrogen bonding interaction as a function of ΔpKₐ, where ΔpKₐ refers to the difference in pKₐ of pyridinium ion (BH⁺) and the benzoic acid (AH) in water via infrared spectra of solid state complexes of benzoic acid and substituted benzoic acids with pyridine and substituted pyridines. Extensive study by Nangia et al. based on the analysis of several cocrystals and salts, concluded that the carboxylic acid–pyridine O–H···N interaction will be neutral when ΔpKₐ < 0 and it will have an intermediate H bond character, O–H···N and/or N⁺–H···O, when the transition range 0 < ΔpKₐ < 3.75. The interaction will be ionic N⁺–H···O⁻ when ΔpKₐ > 3.75 (Scheme 2). Similar observation was noted by Childs and Stahly in their analysis of 20 complexes of theophylline with COOH partners, which resulted in 16 salts, 2 cocrystals and 2 mixed ionizations states with transition range 0 < ΔpKₐ < 2.5.

\[ \Delta pK_a = pK_a (pyrNH^+) - pK_a (COOH) \]

\[ \Delta pK_a < 0, \text{ neutral synthon (I), O–H···N} \]

\[ 0 < \Delta pK_a < 3.75, \text{ mixed ionization state, O···H···N (II) or I/III, O–H···N/} \]

\[ \Delta pK_a > 3.75, \text{ ionic N⁺–H···O⁻} \]

**Scheme 2** The pKₐ rule thumb to predict the H-bonding motifs in multi-component crystals.

Although the contribution from Aakeroy, Black, Price, Tocher etc. is worthy, it is really difficult to predict any general conclusions about proton transfer in acid-base systems. A detailed discussion is recently reported from our group and presented in Chapter 6. The pKₐ scale, proposed by Laurence, measures the free energy of hydrogen bonded complex (1.364 pKₐ = −ΔG in kcal mol⁻¹) could be a better guide in predicting H-bond pairing compared to pKₐ values as it deals with sharing of H atom.
between two electronegative atoms, while the $pK_a$ scale considers only the ability of the proton to be transferred from acid to base. The $pK_{\text{HB}}$ values are quite sensitive to factors that modify H-bonding ability, e.g. inductive/resonance effects, steric hindrance, lone-pair repulsion, and intramolecular H-bonding.

1.9 Pharmaceutical Cocrystals

Cocrystals and salts are very useful in designing extended supramolecular architectures; prepare NLO materials, solid-state photodimerisation reactions, enantioseparation of racemic compounds, pharmaceuticals developments etc. Cocrystallization is a very important technique to develop new pharmaceutical phases of active pharmaceutical ingredients (APIs). Pharmaceutical cocrystals are crystalline molecular complexes of an Active Pharmaceutical Ingredient (API) with another pharmaceutically acceptable molecule or Generally Regarded As Safe (GRAS) chemicals. Food additives, preservatives, excipients, vitamins, minerals, amino acids, bio-molecules, and other APIs can be selected as cocrystal formers (CCF). Zaworotko et al. stated that polymorphs, pseudopolymorphs, salts, molecular complexes and cocrystals of APIs can modify chemical and physical properties that may lead to extended patent coverage and consequent legal protection of products. Several pharmaceutical crystals are known to undergo a variety of phase transformations. Phase transformations during processing and formulation can affect the stability and bioavailability of drugs. Crystalline APIs are strongly preferred due to their relative ease of isolation, the rejection of impurities inherent to the crystallization process and the physico-chemical stability that the crystalline solid state affords. Crystal engineering affords a paradigm for rapid development of APIs, that of pharmaceutical cocrystals and salts which can be rationally designed. Recent articles emphasize the development and importance of pharmaceutical cocrystals. For example, cocrystallization of aspirin, rac-ibuprofen, and rac-flurbiprofen with 4,4′-bipyridine by Zaworotko; Fluoxetine hydrochloride with pharmaceutically acceptable carboxylic acids (Figure 9b) by Childs; several drug molecules with Saccharine as API saccharinate salts by Desiraju; Itraconazole with 1,4-dicarboxylic acids by Remenar; Carbamazepine with Saccharin as saccharinate salts etc. were the well known strategies to deal with inadequate solubility, dissolution
rate, absorption, physical stability, complexation etc. of APIs. Extremely water insoluble nature of Itraconazole, an antifungal agent, is solved by making itraconazole–succinic acid cocrystals (Figure 9a) as oral formulation. Cocrystal of carbamazepine and saccharin (CBZ–SAC) appears to be superior to existing crystal forms of CBZ with respect to stability, favourable dissolution, suspension stability, and favourable oral absorption profile. Hydration behaviour of caffeine and theophylline was controlled by their 1:1 cocrystals with oxalic and other diacids. These cocrystals or salts exhibit physical properties different from those of the parent compounds as a direct result of hydrogen-bonding interactions between the binary components of the crystals. However, the utility of cocrystal formers in pharmaceutical products is limited by their pharmacological and toxicological properties.

Cocrystallization of polymorphic APIs may provide a route to obtain a single pharmaceutical phase by controlled formation of specific supramolecular synthons between functional groups. For example, Cocrystals of a polymorphic drug Piracetam and Gentisic acid, \( p \)-hydroxybenzoic acids as cocrystal formers which are also polymorphic and APIs were synthesized via acid-amide heterosynthon (Figure 9c).\(^{42i}\) The cocrystals do not exhibit polymorphism. However polymorphism in cocrystals or multi-component systems is not so uncommon.\(^{43}\) A recent study from our group\(^{35b}\) showed there are 33 cocrystal polymorph sets up to the January 2008 release of the CSD when compared to more than 1600 polymorphic systems of single component crystals with our own results on cocrystal polymorphs of Temozolamide and bipyridine-N-oxide. The cocrystal former strategy is being applied for the optimization of the drug design, processing, and delivery procedures.
Figure 9  (a) Structure of cis-itraconazole and succinic acid cocrystal. Succinic acid molecule is closely fitting between the two itraconazole molecules via O–H···N hydrogen bonding. (b) Hydrogen bonds between fluoxetine cations, benzoic acids and chloride ions in the cocrystals of fluoxetine hydrochloride with benzoic acid to improve physical properties of fluoxetine. (b) Cocrystals of piracetam with gentisic acid via acid-amide heterosynthon to control polymorphism. (d) Caffeine-glutaric acid cocrystals to solve hydration.

Salts and cocrystals have the potential to be much more useful in pharmaceutical products than solvates or hydrates. But it is also true that making cocrystal or salt may have adverse effects on physiological systems. For example nearly 4000 deaths of pets occurred due to the renal failure is due to the additive in food. Melamine–cyanuric acid cocrystal was given as protein additive. Investigations concluded the presence of cyanuric acid as another co-contaminant along with melamine causes intratubular precipitation of cocrystal leading to the kidney failure and the death of animals. Crystal engineering of melamine and cyanuric acid (1:1 molar ratio) cocrystals show two-dimensional networks in the solid-state that is highly insoluble in water and causes immediate precipitation, which was the reason for deaths of animals.

1.10 Hydrates and Host Guest Compounds

Hydration of molecules in the crystal structure is a common phenomenon, especially in pharmaceutical industries. Hydrated structures received considerable attention because of its different topologies in the structure, conformations and functions. Hydrates are commonly used in pharmaceutical solids because of its abundance, flexibility, small size and ability to act as both a strong hydrogen bond donor and acceptor and obviously its non toxic nature. The study of different water clusters is also important to understand the bulk properties of water and its role in different biological processes, such as protein–DNA binding, ion transport, protein folding–defolding,
structure determination of the fibrous proteins, etc. Included water molecules can form discrete and extended motifs, e.g. finite and infinite chains, ring motifs and different topologies. In biological systems water channels have been found and water topology is widely studied because of its application in water and ion transport.\textsuperscript{46} In red blood cells and the renal tubules water can rapidly and selectively cross the plasma membrane. Thus water release from the interface, in general, is favored entropically but enthalpically unfavorable. Infantes and co-workers\textsuperscript{47} showed that 6.6\% of organic compounds are hydrated and this value increases to 75\% for bioactive pharmaceutical compounds or APIs and categorized and given rank for different functional groups that promote hydration. Molecules containing charged or strong H-bonding functional groups favor entrapment of waters into its crystalline lattice. Many fundamental biological processes depend on potentially important water chains.\textsuperscript{48} Water chain motif is responsible in proton transport in Gramicidin-A.\textsuperscript{48d} Buchanan,\textsuperscript{48e} Ripmeester\textsuperscript{48f} and others have studied water chains that can serve as a model for biological proton wires or water transport. Henry showed that water can act also as templating nanoporous material.\textsuperscript{49} Due to the difficulties in studying the role of water molecules in macromolecular systems, entrapment of water in small molecular environment and then study has become an interesting topic in recent solid state supramolecular chemistry.

Davy’s discovery\textsuperscript{50} of chlorine hydrate in 1811 can be recognized as the origin of host-guest chemistry as well supramolecular chemistry. But the field took a rapid pace after the seminal contribution from Busch, Curtis, Jägar, Pederson, and then Lehn’s work towards host–guest compounds in the development and synthesizing shape and ion selective receptors with macrocyclic ligands (Figure 10). The host-guest relationships involve a complementary stereoelectronic arrangement of binding sites between host and guest. The host component is defined as an organic molecule or ion whose binding sites converge in the complex and the guest component are any molecule, ion whose binding sites diverge in the complex. Host guest chemistry has received particular interest because of their diverse applications in chemical separation, reactions and catalysis in a microcavity, and for electrooptic, nonlinear and magnetic materials.\textsuperscript{51} Hydrogen bonds or other weak interactions mediated self-assembly and directional metal–ligand coordination bonding are used to synthesize porous materials or low density frameworks.\textsuperscript{52}
Host-guest compounds are mainly divided into Cavitands and Clathrands based on the nature of the host. Cavitands are intra-molecular cavities however clathrands are hosts with extra-molecular cavities resulted from aggregation of more than one molecule. Based on the size of porosity, open frameworks are divided into three categories, such as nanoporous or microporous (<15 Å), mesoporous (15–500 Å) and macroporous (>500 Å) materials. The cavities formed by host molecules can either be of zero dimensional (cage), one dimensional (channel) or two dimensional (layered). To design porous solids various methods have been developed based on crystal engineering principles and hydrogen bonds or metal coordination bonds. Weber rules for designing host framework are discussed in Chapter 5. Bulky shape, rigid framework structure, strong and directional bonding properties are some requirements to construct host-guest crystals.

1.11 Network Solids

The rational construction of novel open-framework organic solids has received considerable attention because of their diverse applications. One of the main challenges in the approaches of constructing host-guest compounds is to prevent interpenetration to obtain open frameworks. Selection of suitable building blocks is must to construct a particular architecture. In supramolecular chemistry building architectures is important and the molecular building blocks are known as “molecular tectonics” defined by Wuest. The word “tecton” is taken from Greek for “builder.”
Scheme 3 Examples of molecule to supermolecule relationship and showed how linear, trigonal and tetrahedral tectons produce one-, two- and three dimensional networks. H-tecton can afford either ladders or (6,3) hexagonal nets.
This approach is a modular, programmed build up from molecule to crystal—rod type molecules form linear aggregates, chiral and $C_2$-symmetry molecules lead to helical networks, $C_3/D_3$ symmetry molecules produce honeycomb grid or hexagonal layer structures, and $T_d/S_4$ symmetry tectons self-assemble as adamantane or diamondoid networks.\(^5\) H-shaped 1,4-di[bis(4’-hydroxyphenyl)methyl]benzene and its CH$_3$ and CH$_3$O derivatives are synthesized and used to construct a diverge network topologies recently reported from our group.\(^5\) The ability to predict the network architecture from the shape and symmetry of the functionalized tecton is fundamental to crystal design. For instance benzoic, terephthalic, trimesic and adamantane-1,3,5,7-tetracarboxylic acids produce zero-, one-, two- and three-dimensional supramolecular structures respectively, based on molecular geometry and carboxylic acid dimer synthon (Scheme 3). Our results of ladder networks, (6,3) hexagonal network, rare pentagonal tiling by superposition of two (6,3) hexagonal net, interpenetration and catenation are discussed in Chapter 5.

### 1.12 Conclusions

Single-component crystals (polymorphs) and multi-component crystals (salts, solvates, hydrates, cocrystals and their polymorphs) are equally important to modify the physical and chemical properties of drugs. Unsolvated forms are advisable because most solvents are toxic and volatile in nature. Melt and sublimation are two high temperature solvent less methods explored by our group to find guest free structures of those compounds that are prone to give solvates upon solution crystallization. Thus a thorough screening of all possible forms of API is considered to be very important step in pharmaceutical industry. Single crystal X-ray diffraction, powder XRD diffraction, FT-IR, NIR, Raman Spectroscopy, DSC, TGA and other thermal methods, Microscopy and Solid-state NMR spectroscopy techniques are currently used to characterize these various crystalline phases. Solving the crystal structure from powder X-ray diffraction data is slowly becoming a solvable problem.\(^5\)

To summarize, crystal engineering is an emerging and interdisciplinary subject of chemistry, physics, biology, materials and pharmaceutical science. This involves synthesis, crystallography, crystal structure analysis, analysis of all kinds of interactions, property study, and computation. Study on the molecular recognition events during nucleation and growth, crystal engineering has acquired control over the internal
structure and symmetry of crystals and of producing materials with modified chemical and physical properties. Recent literature reflects the advances in crystal engineering and its success. This subject is successfully emerged in several exciting new areas of research, such as catalysis, electronic materials, magnetic sensors, non-linear optics, nanotechnology, protein-receptor binding, microporous materials, supramolecular devices, molecular modelling and drug design.

1.13 References


