

**SUPRAMOLECULAR COCRYSTALS:
SYNTHESIS, STRUCTURAL
CHARACTERIZATIONS AND THEORETICAL
STUDIES**

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SYNTHESIS, STRUCTURAL
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STUDIES**

by

NURIDAYANTI BINTI CHE KHALIB

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LIST OF ABBREVIATIONS

2ABA	2-aminobenzoic acid
2A3BP	2-amino-3-bromopyridine
2A5BP	2-amino-5-bromopyridine
2A4CP	2-amino-4-chloropyridine
2A5CP	2-amino-5-chloropyridine
2A5NP	2-amino-5-nitropyridine
2CMEP	2-amino-4-chloro-6-methylpyrimidine
2CMOP	2-amino-4-chloro-6-methoxypyrimidine
2DMPT	2, 4-diamino-6-(4-methylphenyl) – 1, 3, 5 – triazine
2MBA	2-methylbenzoic acid
2MOBA	2-methoxybenzoic acid
3CBA	3-chlorobenzoic acid
3MBA	3-methylbenzoic acid
4MBA	4-methylbenzoic acid
BA	Benzoic acid
CSD	Cambridge Structural Database
CCD	Charge-Coupled Device
DADA	Donor-Acceptor-Donor-Acceptor
DCPY	2, 6-diamino-4-chloropyrimidine
DFT	Density Functional Theory
FT-IR	Fourier Transform Infra-Red
IR	Infra-Red

NMR	Nuclear Magnetic Resonance
ppm	parts per million
PXRD	Powder X-Ray Diffraction
SXRD	Single X-Ray Diffraction
SADABS	Siemens Area Detector Absorption Correction
SAINT	SAX Area-detector Integration (SAX-Siemens Analytical X-ray)
SMART	Siemens Molecular Analysis Research Tools
TMS	Tetramethylsilane
wR	Weighted Reliability Index

HABLUR GABUNGAN SUPRAMOLEKUL: SINTESIS, PENCIRIAN STRUKTUR DAN KAJIAN TEORI

ABSTRAK

Dalam kajian ini, sembilan belas hablur gabungan yang baharu dari pelbagai jenis asid karboksilik dan bes telah dikaji menggunakan kaedah spektroskopi seperti Kristalografi sinar-X serbuk dan hablur tunggal, Inframerah (FT-IR) dan Resonan Magnetik Nukleor (NMR). Pengiraan secara teori hablur gabungan telah dilakukan menggunakan kaedah Teori Fungsi Ketumpatan (DFT) dan analisis Permukaan Hirshfeld. Secara umumnya, keputusan DFT dan eksperimen adalah bersesuaian antara satu sama lain kecuali perubahan konformasi di sekeliling kumpulan karbonil. Ciri spektroskopi hablur gabungan telah dikaji menggunakan FT-IR dan NMR. Selain daripada ramalan nilai pKa, pembelauan sinar-X hablur tunggal dan serbuk menunjukkan kesemua sampel adalah hablur gabungan. Struktur molekul dan kehadiran interaksi intermolekul telah disahkan oleh pembelauan sinar-X hablur tunggal dan sumbangan interaksi telah ditunjukkan dengan analisis kuantitatif Permukaan Hirshfeld. Pembentukan motif $R_2^2(8)$ heterosinton supramolekul di antara asid karboksilik dan bahagian aminopiridin, aminopirimidin dan aminotriazin boleh dijumpai dalam semua struktur hablur gabungan yang membentuk asas kepada struktur supramolekul. Susunan heterosynthon ini dalam struktur hablur sebahagian dari hablur gabungan telah menghasilkan susunan DADA sinton heterotetramerik kitaran dan sinton heterotetramerik linear. Sinton ini saling bersambungan di dalam struktur hablur semua hablur gabungan melalui pelbagai interaksi intermolekul yang membentuk struktur hablur rangkaian, satah 2-dimensi dan rangkaian 3-dimensi.

SUPRAMOLECULAR COCRYSTALS: SYNTHESIS, STRUCTURAL CHARACTERIZATIONS AND THEORETICAL STUDIES

ABSTRACT

In this research work, nineteen novel cocrystals of various carboxylic acids and bases have been investigated using spectroscopic methods such as powder and single crystal X-ray Crystallography, Infrared (FT-IR) and Nuclear Magnetic Resonance (NMR). The theoretical calculations of the cocrystals were performed using Density Functional Theory (DFT) method and Hirshfeld Surfaces analysis. Generally, the DFT and experimental results are comparable to each other except for the conformational difference around the carboxyl groups. Spectroscopic properties of the cocrystals were examined by FT-IR and NMR. Apart from the pKa values prediction, single crystal and powder X-ray diffractions show that all the samples are cocrystals. The molecular structures and the existence of intermolecular interactions have been confirmed by single crystal X-ray diffraction and the contribution of the interactions is shown by quantitative analysis of the Hirshfeld Surfaces. The formation of $R_2^2(8)$ supramolecular heterosynthons motifs between the carboxylic acid and the aminopyridine, aminopyrimidine and aminotriazine moieties can be found in all the cocrystal structures forming the basis of the supramolecular structures. The arrangement of the heterosynthons in the crystal structure of some of the cocrystals generates a DADA array of cyclic heterotetrameric synthon and linear heterotetrameric synthon. These synthons are interconnected within the crystal structure of the cocrystals through various intermolecular interactions forming chains, 2-dimensional planes and 3-dimensional network of crystal structures.

CHAPTER 1

INTRODUCTION

Supramolecular chemistry is generally a study of intermolecular interactions between molecules forming one, two or three – dimensional network. Co-crystallization is a process that unites different molecular species within a single crystalline lattice without involving the formation or breaking of covalent bonds (Gale & Steed, 2012). Cocrystal is a crystalline material that is structurally homogenous with at least two building blocks with definite stoichiometric amounts (Hemamalini *et al.*, 2014).

1.1 Supramolecular Chemistry

Supramolecular chemistry is a highly interdisciplinary field of sciences covering chemical, physical and biological studies of molecular assemblies. Supramolecular chemistry is defined as “*the chemistry of the intermolecular bond, covering the structures and functions of the entities formed by the association of two or more chemical species*” (Lehn, 1995). The most important feature of supramolecular chemistry is the building blocks are reversibly held by intermolecular force that results in non-covalent assembly. The term ‘*non-covalent*’ is related to a vast range of intermolecular interactions that include hydrophobic, electrostatic, hydrogen bond, π - π aromatic and Van der Waals (Lehn, 1995). The non-covalent joining two or more species, termed self-assembly is strictly an equilibrium between two or more molecular components to produce an aggregate with a structure dependent only on the nature of the chemical building blocks (Steed *et al.*, 2007).

1.2 Crystal Engineering

Crystal engineering has been described by a pioneer in the field, as “*the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of a new solids with desirable physical and chemical properties*” (Desiraju, 1995). Crystal engineering has been approached by mean of understanding of how the molecules interact with other molecules throughout the intermolecular network and then designing a supramolecular strategy to synthesize novel materials with preferred properties and architecture (Moulton & Zaworotko, 2001). The objective of crystal engineering is to design crystal structures by using the molecule as a building block (Desiraju, 2013).

A lot of research in polymorphism (Bernstein, 2002), coordination polymers (Zaworotko, 2001; Mueller *et al.*, 2006), supramolecular synthons (Aakeröy *et al.*, 2001; Aakeröy *et al.*, 2002; Bis *et al.*, 2007; Bis & Zaworotko, 2005; Shattock *et al.*, 2008; Kavuru *et al.*, 2010; Vishweshar *et al.*, 2003), and even pharmaceutical industry (Almarsson & Zaworotko, 2004; Shan & Zaworotko, 2008; Trask *et al.*, 2005; Good & Rodríguez-Hornedo, 2009; Vishweshar *et al.*, 2005) capitalize the crystal engineering concepts.

In crystal engineering features, the identification of proper synthon is very important. Crystal structure of organic compounds is represented as networks of molecules linked by intermolecular interactions. The expectable self-arrangement of molecules into one-, two- or three-dimensional network is of extreme importance in crystal engineering and the structural units forming the network is called supramolecular synthons (Desiraju, 1995).

1.3 Hydrogen Bonding

Hydrogen bonds are highly important in all directional intermolecular interactions in the formation of supramolecular structure. Etter *et al.* (1990) and Bernstein *et al.* (1995) have studied the preferred hydrogen bond arrangement in organic crystals and have suggested the following rules:

- All good proton donors and acceptors are involved in hydrogen bonding.
- Six-membered ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds.
- The best proton donor and acceptor remaining after intramolecular hydrogen bond formation will form intermolecular hydrogen bonds.

1.3.1 Graph-sets of Hydrogen Bonded Motifs

The graph-theory for describing and analyzing hydrogen bond networks in three-dimensional solids was discussed by Etter *et al.* (1990) and Bernstein *et al.* (1995). A generic graph-set descriptor is

$$G_d^a(n) \tag{1.0}$$

Where, G = Graph set designator C, R, D and S

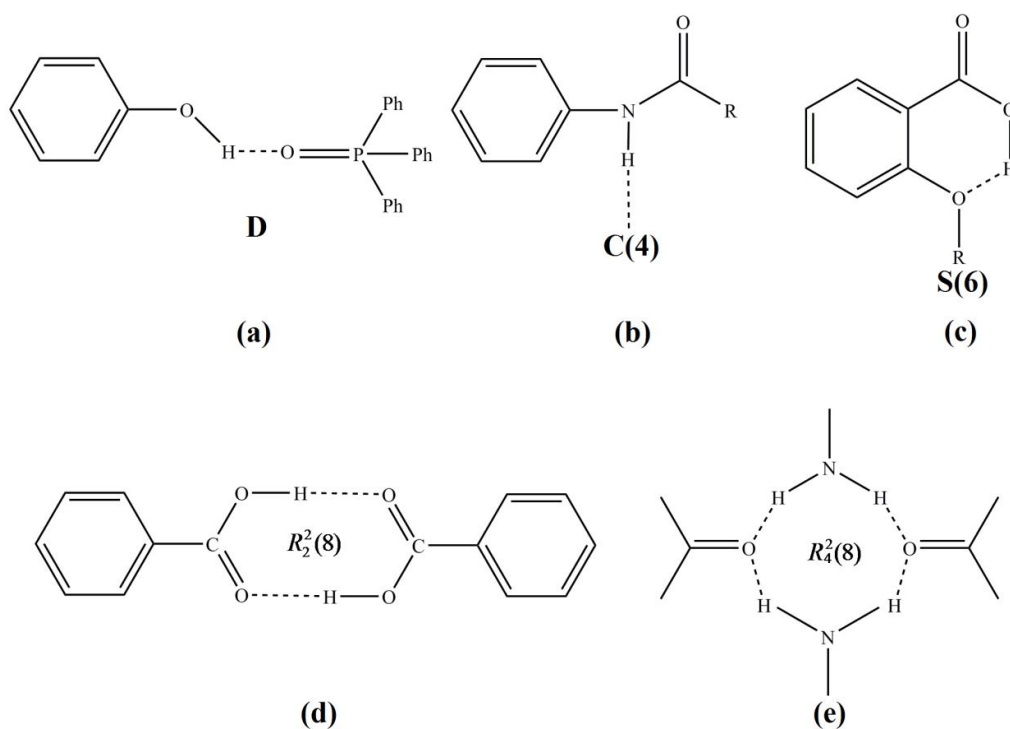
d = Number of donor atoms

a = Number of acceptor atoms

n = Total number of atoms present in the hydrogen bonded motif

The pattern designator has four different assignments which are C, R, D and S based on whether the hydrogen bonds are inter- or intramolecular. C refers to hydrogen-bonded infinite chains, R refers to rings, D refers to non-cyclic dimers. These

designators are used when the graph set is formed by intermolecular hydrogen bonds. *S* (self) denotes a ring made of intramolecular hydrogen bonds. The number of donors (*d*) and acceptor (*a*) used in each motif are assigned as a subscript and superscript respectively and the number of atoms (*n*) involved in the pattern is indicated in the parenthesis. For example, $R_2^2(8)$ graph set notation denotes an eight-membered ring with two hydrogen acceptors and two hydrogen donors, and is exemplified by the carboxylic acid dimer in Scheme 1.1(d).



Scheme 1.1 Examples of graph-set notations in hydrogen-bonded motifs (Etter, 1990).

Scheme 1.1 illustrates the examples of graph-set notations in hydrogen-bonded motifs. The use of graph-sets provide an approach in describing the pattern of hydrogen bonded molecules.

1.3.2 Supramolecular Synthons

Supramolecular synthons are intermolecular interactions and hydrogen bond motifs that are formed repetitively in molecular crystal structures (Desiraju, 1995). Supramolecular synthons are divided into two categories which are supramolecular homosynthons and supramolecular heterosynthons.

A supramolecular homosynthon is formed between identical functional groups, for example between two carboxylic acid moieties to form a dimer while a supramolecular heterosynthon is formed between complementary but different functional groups, such as between carboxylic acid and amide moieties (Rodríguez-Spong *et al.*, 2004). Figure 1.1 illustrates the most common supramolecular synthons in crystal engineering.

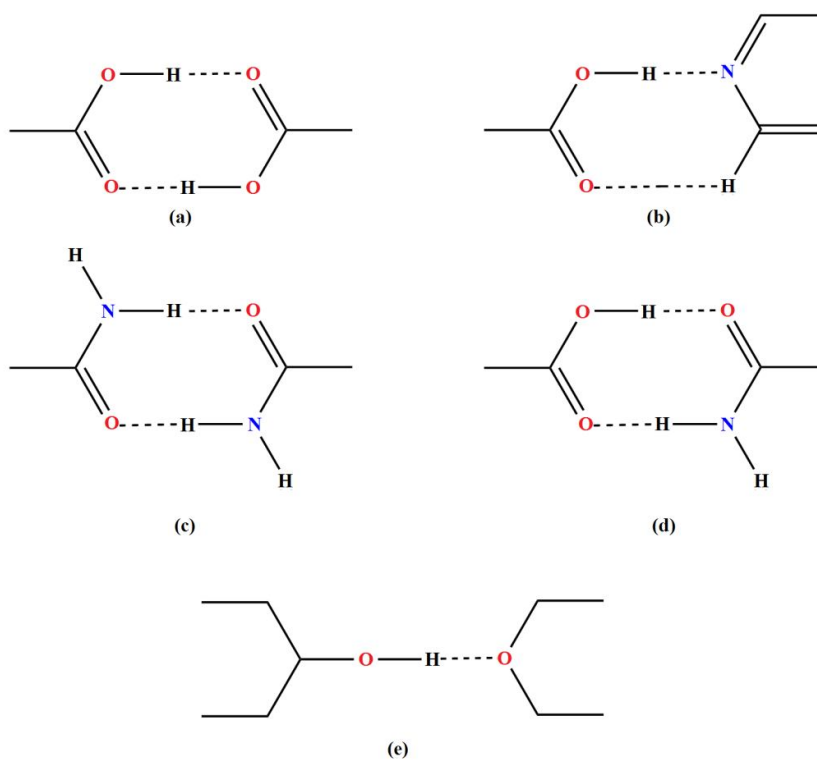


Figure 1.1 The most common supramolecular synthons (Qiao *et al.*, 2011).

The most commonly used supramolecular synthons in crystal engineering are homosynthon formed between carboxylic acid dimer (Figure 1.1a), heterosynthon formed between carboxylic acid and pyridine groups (Figure 1.1b), homosynthon formed between amide dimer (Figure 1.1c), heterosynthon formed between carboxylic acid and amide groups (Figure 1.1d) and heterosynthon formed between alcohol and ether groups (Figure 1.1e) (Qiao *et al.*, 2011).

Supramolecular heterosynthons generally employed the carboxylic acid-aromatic N-heterocyclic due to its strength and reliability (Desiraju, 1995). Cambridge Structural Database (CSD) analysis by Shattock *et al.* (2008), they revealed that the $\text{COOH}\cdots\text{N}_{\text{arom}}$ supramolecular heterosynthon involving carboxylic acids (-COOH) are strongly favoured over supramolecular homosynthons. This thesis are focusing on the ability of carboxylic acid to form reliable supramolecular heterosynthons with N-heterocyclics such as pyridines, pyrimidines and triazines derivatives which are useful in preparing desired multi-component system in material science research.

Several reports have discussed the importance of understanding supramolecular heterosynthons in the synthesis of cocrystals (Trask *et al.*, 2005; Vishweswar *et al.*, 2005; Fleischman *et al.*, 2003; Bettinetti, *et al.*, 2000; Mohamed *et al.*, 2009). Figure 1.2 shows the example of supramolecular heterosynthons reported previously.

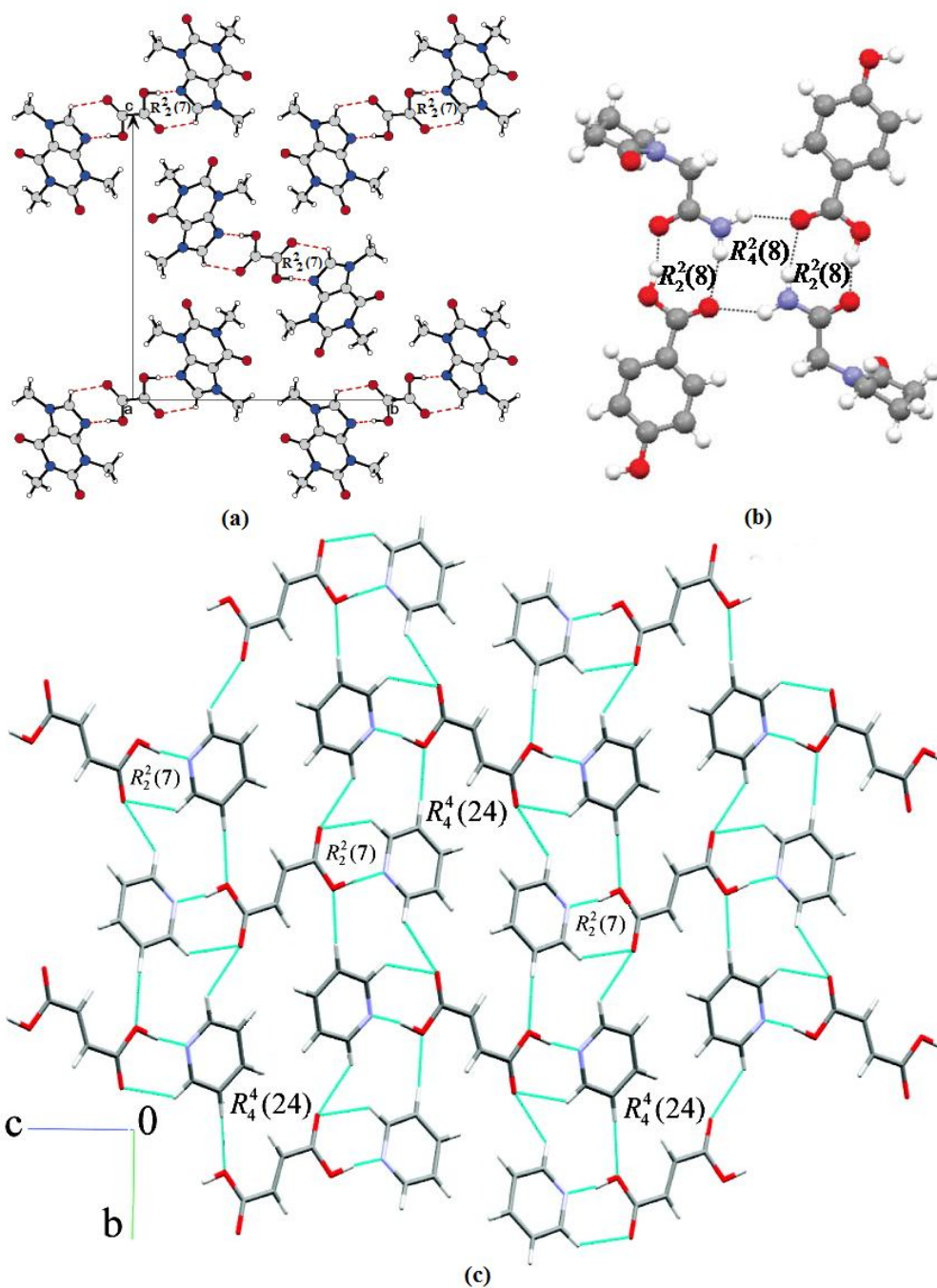


Figure 1.2 Supramolecular heterosynths (a) $R_2^2(7)$ acid-base heterodimer synthon (Trask *et al.*, 2005), (b) The carboxylic acid–amide supramolecular heterosynthon in the tetrameric motif (Vishweswar *et al.*, 2005) and (c) The heterodimer, $R_2^2(7)$ and expanded ring $R_4^4(24)$ (Mohamed *et al.*, 2009).

1.4 Cocrystals

Cocrystal can be defined as a crystalline solid containing multiple components with at least two or more molecules associated through intermolecular interactions (Childs *et al.*, 2007). In a supramolecular perspective, the molecules of the crystal are held together by supramolecular synthons. One of these molecules is known as the cocrystal former which forms supramolecular synthons with the other molecules (Shattock *et al.*, 2008).

Cocrystal is one of the important themes in supramolecular studies and is gaining interest across a variety of research disciplines. Crystal engineering and supramolecular chemistry have motivated researches on the design of materials by directing molecular assembly of different components in the crystalline state to form cocrystals (Trask *et al.*, 2005). Intermolecular interactions have a significant contribution in the synthesis of cocrystal due to their strength and directional nature. Traditional O—H \cdots O and O—H \cdots N strong hydrogen bonds, weaker C—H \cdots π or C—H \cdots Cl and other molecules association such as halogen-halogen, nitro-nitro and $\pi \cdots \pi$ interactions are normally employed in cocrystal synthesis (Trask & Jones, 2005).

A neutral compound has potential to interact with a cocrystal former in cocrystallization processes as shown in Figure 1.3. Cocrystal former can include organic acids or bases that remain in their neutral form within the multi-component crystal and exists as a solid at ambient conditions (Almarsson & Zaworotko, 2004; Aakeröy *et al.*, 2007).

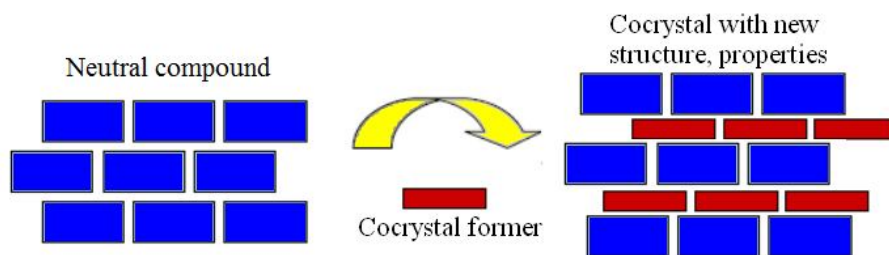


Figure 1.3 Schematic of cocrystals.

Cocrystal is one of a variety of distinct solid forms that display the unique of physicochemical properties which can greatly influence the bioavailability, manufacturability, purification, stability and other performance characteristics of drug (Yadav *et al.*, 2009). Most of cocrystals have been reacted through strong hydrogen bonds, $O-H\cdots N$ which is notable between a carboxylic acid and an N-heterocyclic hydrogen-bond acceptor (Aakeröy *et al.*, 2007; Aakeröy *et al.*, 2006; Aakeröy *et al.*, 2005). However, the reaction between these components can also result in a salt formation when the acid is protonated to the base/ ligand (Banerjee *et al.*, 2005). The interaction of $O-H\cdots N$ will be replaced with a charge transferred $O^-\cdots H-N^+$ hydrogen bond (Aakeröy *et al.*, 2007). The design of complexes of cocrystals and salts, with neutral and charged components, respectively, are the current avenue of research in solid-state organic chemistry (Lemmerer *et al.*, 2015). The design of molecular network based on hydrogen bond has appeared as an impressive mechanism in the discovery of cocrystals (Hornedo, 2007).

1.5 Problem Statement

Cocrystals have attracted a lot of attentions in recent years especially in pharmaceutical industries. These cocrystals are used to improve the physicochemical properties of drugs. Before the physicochemical test can be done, the candidate cocrystals must be identified, synthesized and analyzed for their structural properties. These would consumed extra time before they can be tested for physicochemical improvement. This research would identify cocrystals to be synthesized and analyzed. These cocrystals would provide a pool of candidates for the physicochemical test to analyze the improvement of the physicochemical properties of the drug substance. This would help in rapid testing of the physicochemical properties with the help of readily available candidates to be chosen from.

1.6 Scope of the Research Work

The most widely used synthons for directed assembly of cocrystals involve a carboxylic acid in combination with a suitable N-heterocyclic compound (Shattock *et al.*, 2008). Most of organic molecular cocrystals have been assembled through a strong hydrogen bond, O—H···N that is expected from a carboxylic acid···N (heterocyclic) interaction. This research will be focusing on the synthesis of the supramolecular cocrystals from N-heterocyclic compounds such as pyridine, pyrimidine and triazine with carboxylic acid to form reliable supramolecular heterosynthons that persist in the presence of competing functionalities. The structural behaviour of the compounds will also be analyzed using experimental and theoretical methods. The formation of non-covalent interactions will be studied to determine their effect on the supramolecular structure of the compounds.

1.7 Objectives

The objectives of this study are:

1. To synthesize new cocrystals compounds of aminopyridine, aminopyrimidine and aminotriazine derivatives with a variety of carboxylic acids.
2. To characterize and analyze the formation of supramolecular assembly of the cocrystals.
3. To investigate the effect of hydrogen bond interaction by theoretical analysis.
4. To study the effect of the synthons on the supramolecular network of the compounds.

CHAPTER 2

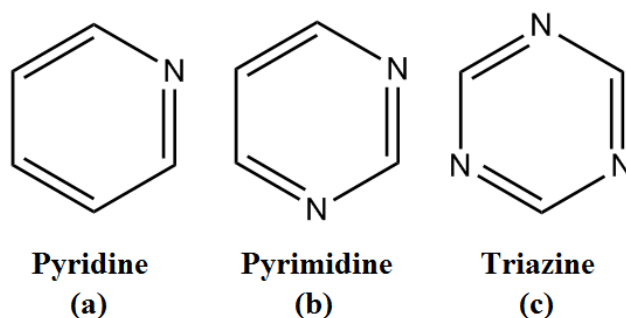
LITERATURE REVIEW

In the crystal engineering, the design and synthesis of cocrystals have become a popular area of cocrystal research due to their versatility to exhibit the supramolecular synthons network. The synthons that formed between carboxylic acids and nitrogen heterocyclic rings is the most exploited synthons for designing cocrystal especially ring system forming a graph-set motif of $R_2^2(8)$ (Lynch & Jones, 2004). Carboxylic acid groups are very useful in molecular recognition (Arbuse *et al.*, 2007). They also possess tremendous ability in forming self assemblies and can easily bind with heterocyclic compounds (Lackinge *et al.*, 2009; Kathalikkattil *et al.*, 2011; Somphon *et al.*, 2013). Generally, in a cocrystal architecture, homosynthons and heterosynthons are formed depending on the molecular architecture and the positions and properties of functional groups. However, supramolecular heterosynthons (the substituted nitrogen heterocyclic system with carboxylic acids group) are statistically higher compared to the individual homosynthons (Allen *et al.*, 1998; Allen *et al.*, 1999).

The introduction of spectroscopic method has helped researchers to characterize, determine and understand the molecular and crystal structure of a cocrystal. Fourier Transform Infra-Red (FT-IR) spectroscopy, Nuclear Magnetic Resonance (NMR), Powder X-ray Diffraction (PXRD) and Single Crystal X-ray Crystallography are the most common methods being used for characterization and structural determination of cocrystals.

2.1 Nitrogen Heterocyclic Compound

Nitrogen heterocyclic compounds play an important role in the study of pharmaceuticals and agrochemicals. Many derivatives of nitrogen heterocyclic rings such as pyridine, pyrimidine and triazine derivatives have been synthesized in recent years. The schematic of the nitrogen heterocyclics are shown in Scheme 2.1.



Scheme 2.1 The schematic of nitrogen heterocyclic such as pyridine, pyrimidine and triazine (Joule & Mills, 2010).

This study focuses specifically on the ability of carboxylic acids to form reliable and stable supramolecular heterosynthons with the aminopyridine, aminopyrimidine and aminotriazine derivatives to form cocrystals. The addition of an amino group to the former N-heterocyclic gives a stronger balancing as a competitive binding site for carboxylic acids (Aakeröy *et al.*, 2006). The probabilities of formation of intermolecular hydrogen bonds between chemical groups containing at least one strong hydrogen bond donor group formed the most exploited supramolecular synthon in designing cocrystals (Shattock *et al.*, 2008).

Pyridine and its derivative, 2-aminopyridine is primarily used as an intermediate in the manufacturing of pharmaceuticals, particularly in anti-histamines and piroxicam. Lornoxicam and Tenoxicam are considered as new non-steroidal,

anti-inflammatory drugs of the oxicam class inhibiting cyclooxygenase, the key enzyme of prostaglandin biosynthesis at the site of inflammation (Baltork *et al.*, 2008).

Pyrimidines and aminopyrimidine derivatives are biologically important compounds that manifest themselves in nature as components of nucleic acids. The functions of nucleic acids are explicitly determined by hydrogen-bonding patterns including base pairing, which is responsible for genetic information transfer. Their interactions with carboxylic acids are involved in protein–nucleic acid recognition and drug–protein recognition processes. Cocrystals of aminopyrimidine with carboxylic acids represent model systems where the hydrogen-bonded supramolecular motifs can be studied (Ebenezer & Muthiah, 2012).

Triazine derivatives have shown antitumor activity as well as broad range of biological activities like anti-angiogenesis and antimicrobial effects (Bork *et al.*, 2003). The organic and inorganic complexes of triazine form well defined non-covalent supramolecular architectures *via* multiple hydrogen bonds constituting arrays of hydrogen-bonding sites (MacDonald & Whitesides, 1994).

2.2 Supramolecular Structure and Characterization of Cocrystal

From the best of our knowledge, there is no theoretical calculations have been reported so far for acid-base cocrystals consisted of 2-aminopyridine, 2-aminopyrimidine or 2-aminotriazine with various of carboxylic acid moieties. Therefore, the literature review in this thesis will discuss the supramolecular structure of cocrystals in the solid state condition.

Lemmerer *et al.* (2015) have studied cocrystals and salts to analyze the pKa values for the formation of the crystals. They have studied 2-chloro-4-nitrobenzoic acid donor with different substituents of pyridine acceptor which formed cocrystals and salts. Figure 2.1 shows the molecular structure of the cocrystals and salts with their ΔpK_a values. The supramolecular heterosynthon $\text{COO}\cdots\text{H}\cdots\text{N}_{\text{pyridine}}$ formed between a carboxylic acid donor and a pyridine acceptor is observed in all the cocrystals. In the molecular salt structures, proton transfer has occurred to the pyridinium base to form a $\text{COO}^-\cdots\text{H}\text{---}\text{N}_{\text{pyridine}}^+$ hydrogen bond. They found out that the ΔpK_a values above 3 formed molecular salts and values below zero formed cocrystals. However, in intermediate range, there is a possibility of salts or cocrystals formation.

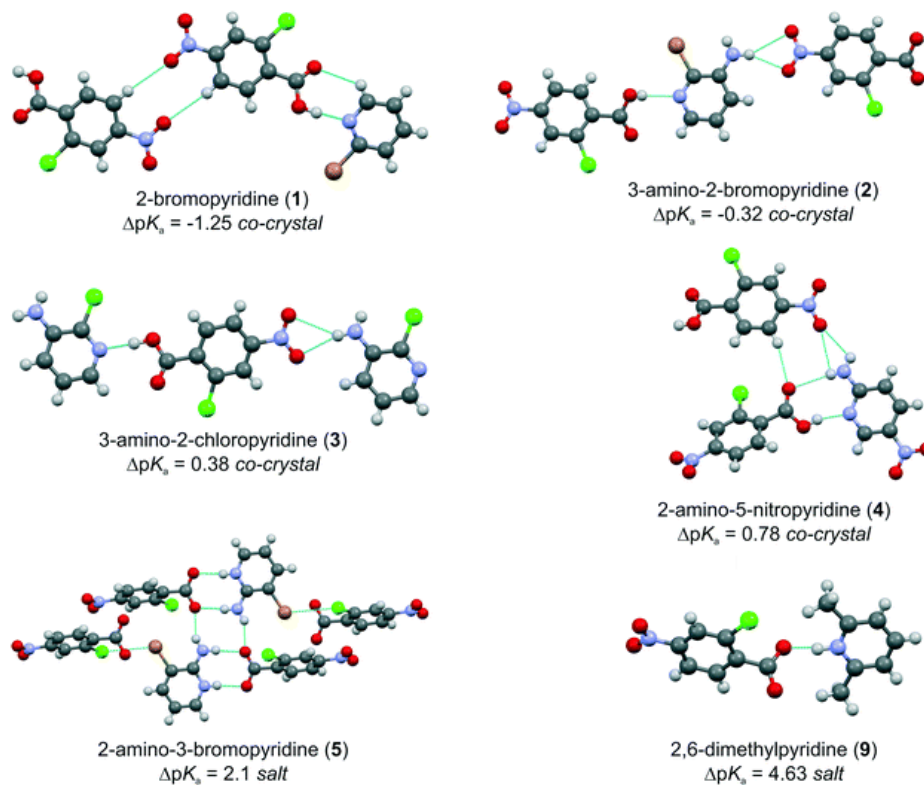


Figure 2.1 Examples of cocrystals and salts (Lemmerer *et al.*, 2015).

The cocrystal structure of 2-amino-5-chloropyridine benzoic acid studied by Hemamalini and Fun (2010a) (Figure 2.2b) shows that 2-amino-5-chloropyridine molecules interact with the carboxyl group of benzoic acid molecules through N—H···O and O—H···N hydrogen bonds to form a cyclic hydrogen-bonded motif $R_2^2(8)$ (Bernstein *et al.*, 1995). The C—O bond lengths for the carboxylic acid of the benzoic acid are 1.3190 (15) Å for O—C and 1.2250 (15) Å for O=C, thus, no proton transfer from the carboxyl group of benzoic acid. The molecules are linked into chains parallel to the [001] direction (Figure 2.2b). The neighbouring 2-amino-5-chloropyridine molecules are centrosymmetrically paired through C—H···Cl hydrogen bonds, forming another $R_2^2(8)$ motif and are further stabilized by weak C—H···O hydrogen bonds.

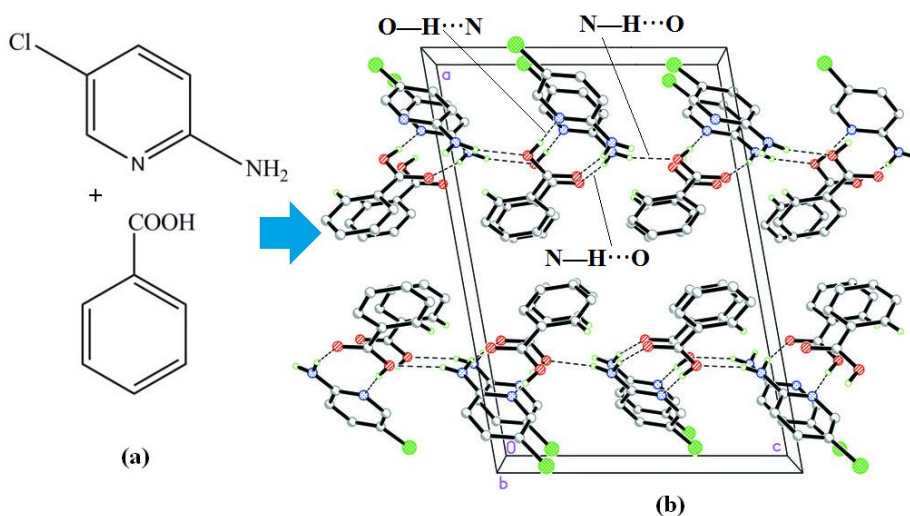


Figure 2.2 (a) Scheme and (b) the crystal packing of the molecular structure of 2-amino-5-chloropyridine benzoic acid (Hemamalini & Fun, 2010a).

The formation of $R_2^2(8)$ ring motif is also reported by Hemamalini and Fun (2010b) in the cocrystal structure of 2-amino-5-bromopyridine benzoic acid where the N_{pyridine} molecule interact with the carboxylic group of the respective benzoic acid molecules through N—H···O and O—H···N hydrogen bonds as shown in

Figure 2.3. This cocrystal structure also shows that no proton transfers from the carboxyl group of benzoic acid since the C–O bond lengths for the carboxylic acid of the benzoic acid are 1.317 (2) Å for O—C and 1.225 (2) Å for O=C.

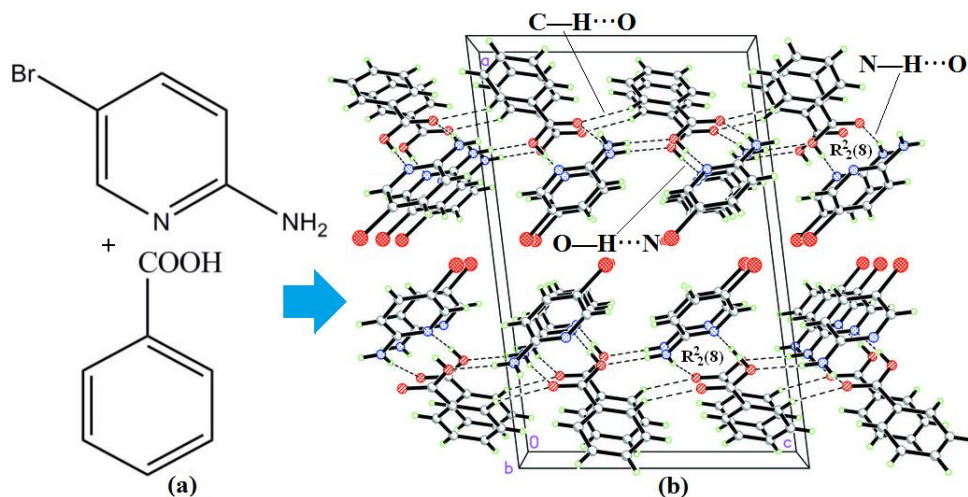


Figure 2.3 (a) Scheme and (b) the crystal packing of the molecular structure of 2-amino-5-bromopyridine benzoic acid (Hemamalini & Fun, 2010b).

In the crystal packing (Figure 2.3b), the $R_2^2(8)$ ring motifs are linked into 2-dimensional networks parallel to the (100) plane by strong N—H...O and weak C—H...O interactions.

Thanigaimani *et al.* (2006) reported an array of six hydrogen bonds forming ring motifs of $R_2^3(6)$, $R_2^2(8)$, $R_2^4(8)$, $R_2^2(8)$ and $R_2^3(6)$ (Figure 2.4a) within the 2-amino-4, 6-dimethoxypyrimidine 4-aminobenzoic acid crystal structure.

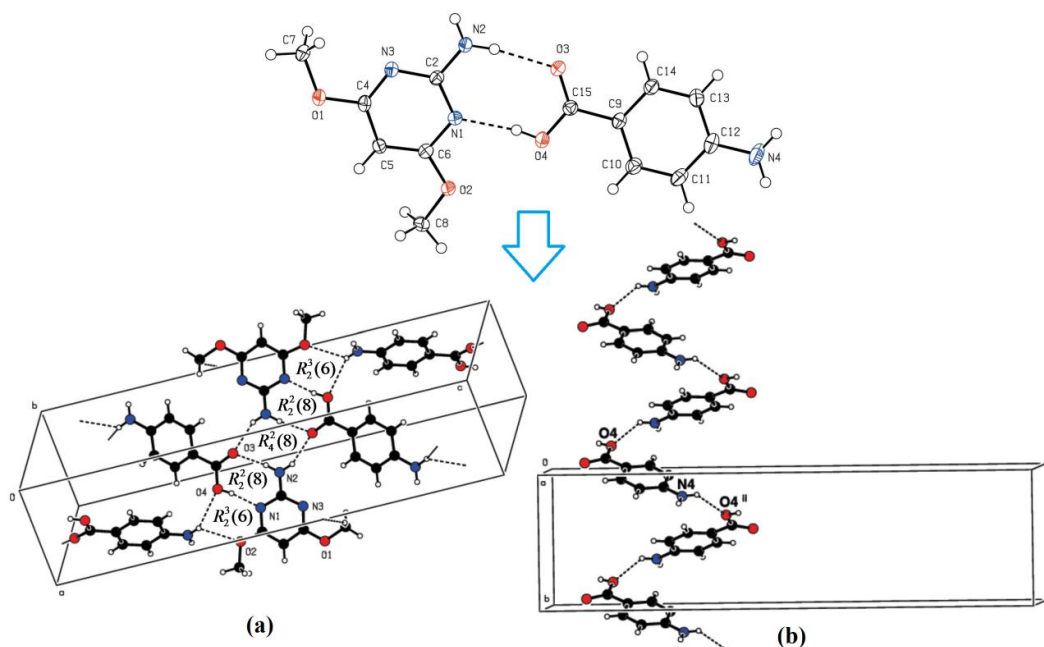


Figure 2.4 Molecular structure of 2-amino-4,6-dimethoxybenzoic acid: (a) Hydrogen bond pattern and (b) hydrogen bond pattern in supramolecular chain along the *c*-axis (Thanigaimani *et al.*, 2006).

The generation of homosynthon and heterosynthon through hydrogen interactions was reported by Hemamalini *et al.* (2014). In their report, 2-amino-6-chloropyridine in neutral form can be self-assembled through N—H...N hydrogen bonds to form $R_2^2(8)$ ring motif homosynthon (Figure 2.5). These dimers are further interconnected by another N—H...N and C—H...Cl hydrogen bonds, forming sheets parallel to the *bc* plane as shown in Figure 2.5.

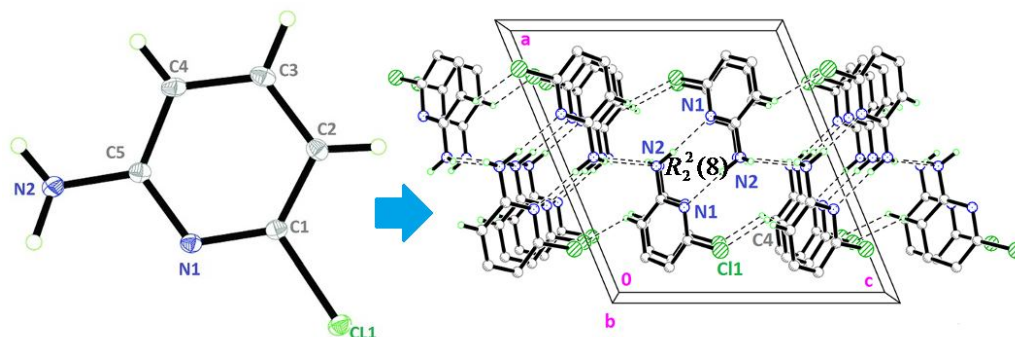


Figure 2.5 Hydrogen pattern in 2-amino-6-chloropyridine represent homosynthon (Hemamalini *et al.*, 2014).

This ligand can also form $R_2^2(8)$ ring motif heterosynthon by interacting with carboxylic acid molecules through N—H···O and O—H···N hydrogen bonds (Figure 2.6a). Intermolecular N—H···O ($1/2+x, 3/2-y, 2-z$) hydrogen bonds link the heterosynthons into zig-zag chains as illustrated in Figure 2.6(b).

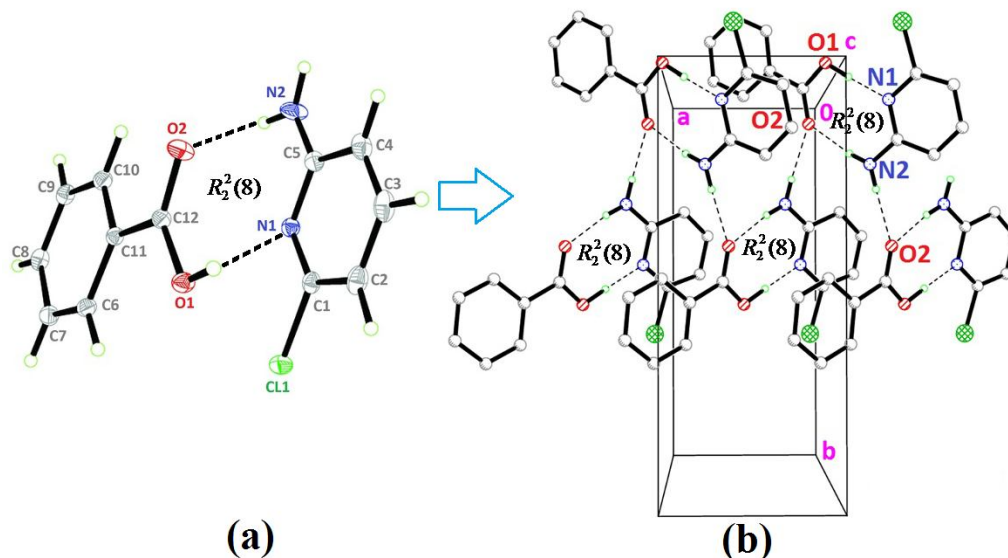


Figure 2.6 Hydrogen pattern in 2-amino-6-chloropyridine benzoic acid represent (a) $R_2^2(8)$ ring motif heterosynthon; (b) supramolecular zig-zag chains (Hemamalini *et al.*, 2014).

Hemamalini *et al.* (2014) also reported the existence of non-covalent interactions has forming arrays of donor (D) and acceptor (A) atoms within the crystal structure. In 2-amino-6-chloropyridine 3-chlorobenzoic acid, the heterosynthons are centrosymmetrically paired via N—H···O hydrogen bonds, forming a complementary DADA [D = donor and A = acceptor] array of quadruple hydrogen bonds. The DADA array of hydrogen bonding motif is represented by graph-set notations of $R_2^2(8)$, $R_4^2(8)$ and $R_2^2(8)$ in sequence as shown in Figures 2.7.

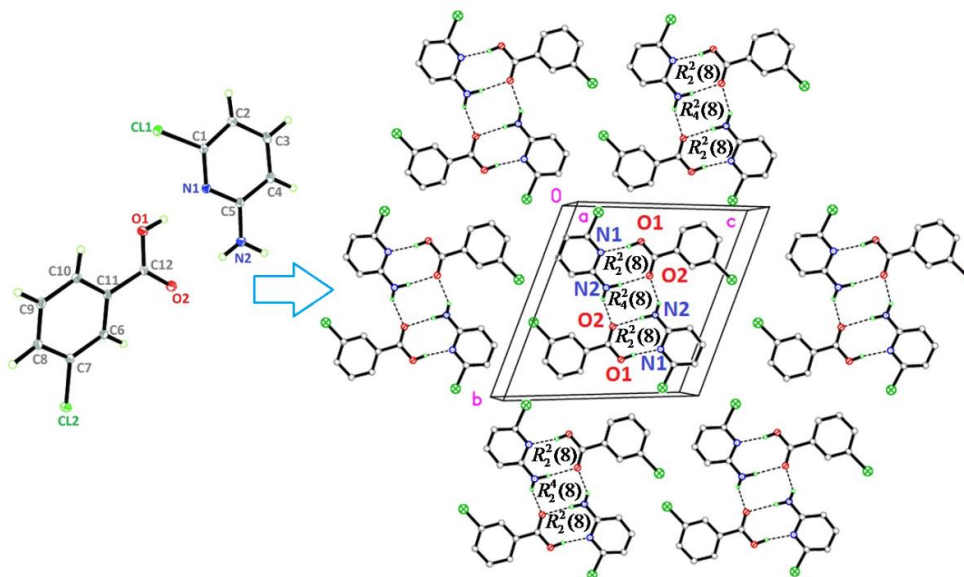


Figure 2.7 View of the complementary DADA arrays of quadruple hydrogen pattern in 2-amino-6-chloropyridine 3-chloropyridine (Hemamalini *et al.*, 2014).

Ebenezer and Muthiah (2012) were investigating aminopyrimidine derivatives with carboxylic acid through recurrently occurring synthons. In their report on 2-amino-4, 6-dimethoxypyrimidine 2-chlorobenzoic acid cocrystal, the main motif $R_2^2(8)$ is assembled through a complimentary hydrogen bond interactions between the carboxylic acid and the amino-pyrimidine moiety to form a dimeric unit. In the crystal structure of the cocrystal, these dimeric units are connected by N—H \cdots O ($2-x, -y, 1-z$) hydrogen bonds forming linear heterotetrameric synthons (Figure 2.8). These tetramers are planar and are interconnected into infinite 1-D tape *via* two symmetry related hydrogen bonds involving O atoms of symmetry related methoxy group of neighbouring pyrimidine rings forming a homosynthon with graph set notation $R_2^2(6)$.

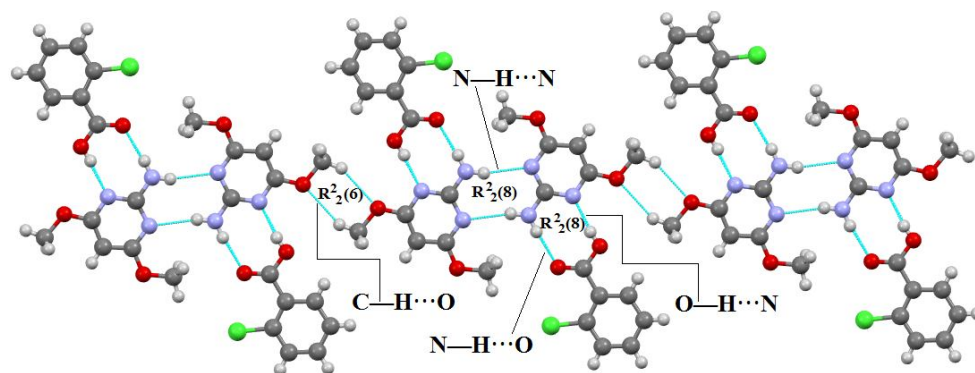


Figure 2.8 View of heterotetramer infinite tape connected by $R_2^2(6)$ synthon (Ebenezer & Muthiah, 2012).

The neighbouring tapes are interconnected through weak C—H...O intermolecular hydrogen bonds involving the acid rings and one of the methoxy groups attached to the pyrimidine rings to form a supramolecular sheet (Figure 2.9).

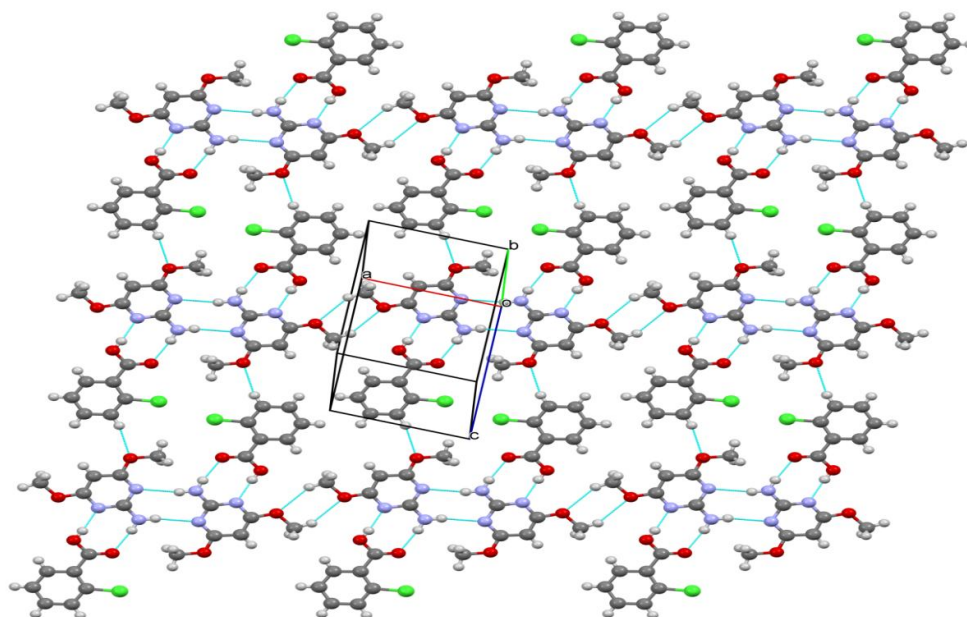


Figure 2.9 Supramolecular sheet formed by interconnection of tape along (122) plane (Ebenezer & Muthiah, 2012).

Ebenezer and Muthiah (2012) also reported the primary $R_2^2(8)$ synthon found in 2-amino-4, 6-dimethoxypyrimidine 3-methylbenzoic acid where the hydrogen bonds (O—H...N, N—H...O and N—H...N) involving the amino and hydroxyl

protons of carboxylic acid as donors and the two pyrimidine nitrogens including the oxygen of the carbonyl group as acceptors formed a linear heterotetrameric synthon. These tetramers are connected *via* $R_2^2(6)$ synthon generated from symmetry related C—H···O intermolecular hydrogen bonds and assembled into infinite 1-D tapes (Figure 2.10).

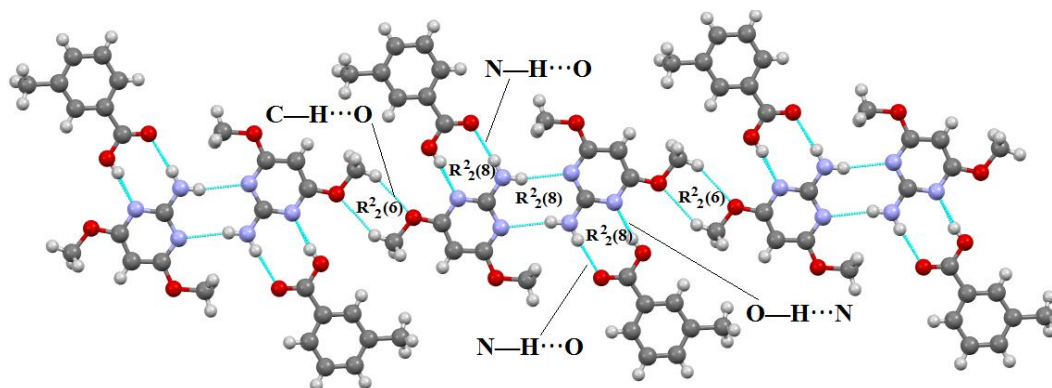


Figure 2.10 View of extension infinite tape connected by $R_2^2(6)$ synthon (Ebenezer & Muthiah, 2012).

Interactions between aminotriazine and the carboxyl group of sorbic acid molecules *via* N—H···O and O—H···N hydrogen bonds form a supramolecular heterosynthon with graph set notation $R_2^2(8)$ (Thanigaimani *et al.*, 2007). In the crystal packing, the triazine molecules are base-paired with a graph set of $R_2^2(8)$ on either side *via* N—H···N hydrogen bonds, forming a supramolecular ribbon along the *c*-axis (Figure 2.11). These supramolecular ribbons are interlinked by N—H···O hydrogen bonds involving the 2-amino group of the triazine molecules and the carboxyl O atom of the sorbic acid molecules.

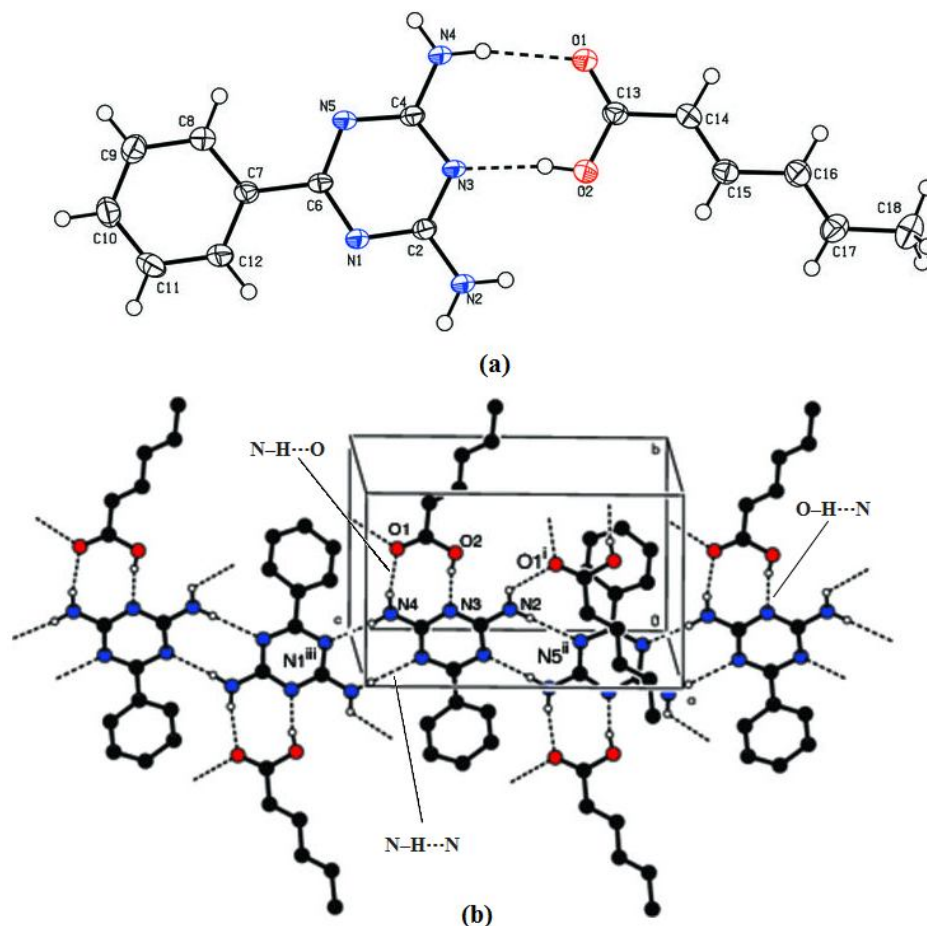


Figure 2.11 (a) The asymmetric unit and (b) the crystal packing of 2,4-diamino-6-phenyl-1,3,5-triazine-sorbic acid (1/1) showing 50% probability displacement ellipsoids. Dashed lines indicate hydrogen bonds [symmetry code: (i) $x, -y+1, z-1/2$; (ii) $x, -y, z-1/2$; (iii) $x, -y, z+1/2$] (Thanigaimani *et al.*, 2007).

Amit *et al.* (2013) studied the influence of shape of conformers on supramolecular assemblies of molecular adducts of 2, 4-diamino-6-phenyl- 1, 3, 5-triazine with conformers of different shape. They concluded that the linear ligands formed 8-membered cyclic network while bend ligands preferred to form 6-membered tapes (Figure 2.12).

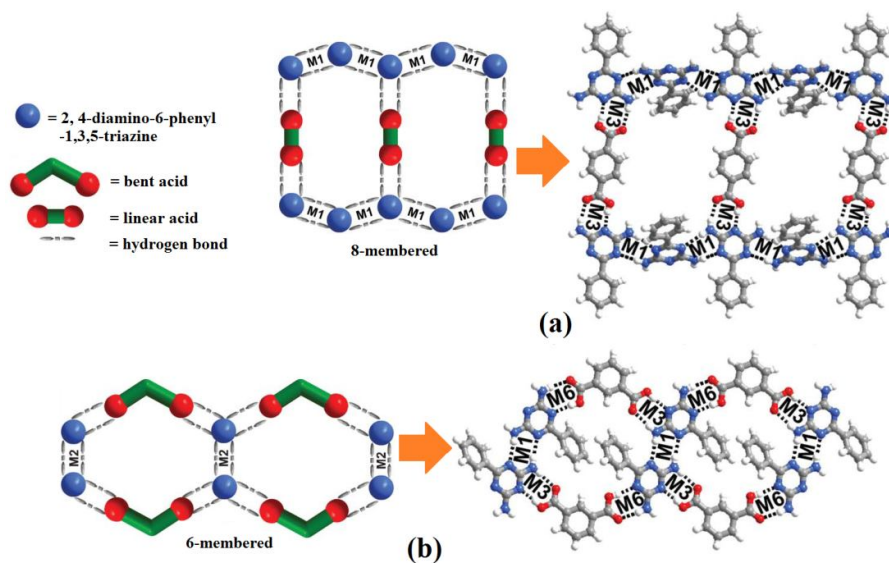


Figure 2.12 (a) Linear acid formed 8-membered cyclic tape network; (b) Bent acid formed 6-membered cyclic tape network (Amit *et al.*, 2013).

The ability of carboxylic acids to form self assemblies was discussed by Jali and Baruah (2013). They reported on the cisoid and transoid geometry of the carboxylic acids in cocrystals of 2, 4-diamino-6-phenyl- 1, 3, 5-triazine and how these geometries influence the supramolecular of the cocrystals (Figure 2.13).

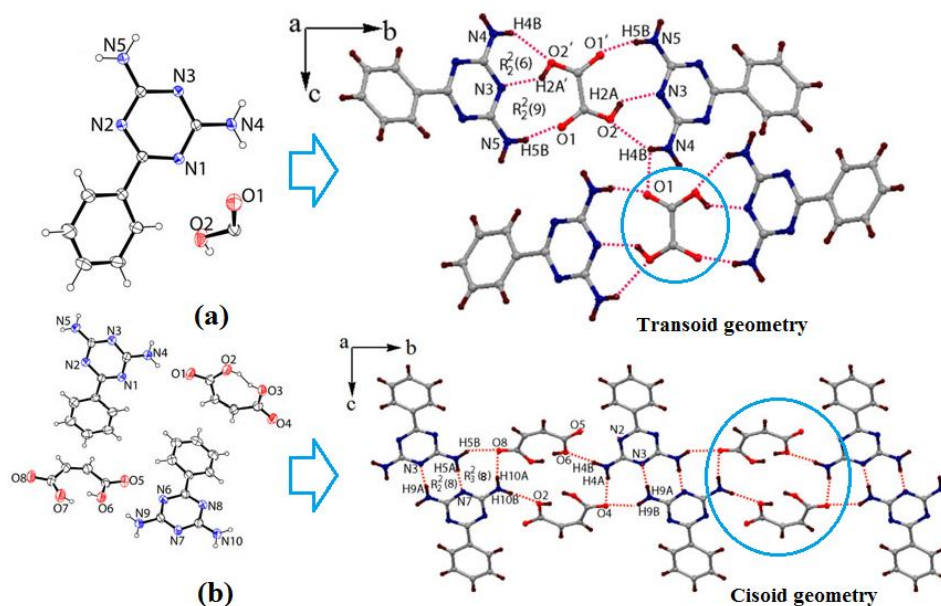


Figure 2.13 (a) The transoid geometry and (b) the cisoid geometry of the carboxylic acids in cocrystals of 2, 4-diamino-6-phenyl- 1, 3, 5-triazine (Jali & Baruah, 2013).