CHAPTER THREE
COCRYSTALS OF PYROGALLOL AND CATECHOL WITH N-HETEROCYCLE BASES

3.1 INTRODUCTION

Hydrogen bond and supramolecular synthons are the first step towards crystal engineering. If the molecules are considered as the bricks for making a supramolecule then hydrogen bond and supramolecular synthons are the cementing materials. Therefore before going into the details of supramolecular assembly it is necessary to be familiarized with hydrogen bond and supramolecular synthon. Pauling defined hydrogen bond as “under certain conditions an atom of hydrogen is attracted by rather strong forces to two atoms, instead of only one, so that it may be considered to be acting as a bond between them”. Typically for strong interactions like N–H···O, O–H···O, O–H···X−, F–H···F− there is no problem because they are very strong, linear, energetically favorable and spectroscopically identifiable. But this definition did not fit for the weaker interactions like C–H···O, C–H···N, O–H···π, N–H···π and C–H···π interactions which are difficult for analysis crystallographically, spectroscopically or computationally. From then several definitions have been proposed. Prominent among them were by Pimentel and McClellan, later by Jeffrey and Saenger and then in 1993 by Steiner and Saenger. Recently in 2005 the IUPAC core group have stated that “a typical hydrogen bond may be depicted as X–H···Y–Z, where the three dots denote the bond. X–H represents the hydrogen-bond donor. The acceptor may be an atom or an anion Y, or a fragment or a molecule Y–Z, where Y is bonded to Z. In specific cases X and Y can be the same with both X–H and Y–H bonds being equal. In any event, the acceptor is an electron-rich region such as, but not limited to, a lone pair in Y or a π-bonded pair in Y–Z”. When hydrogen bond forms between the molecular functionalities the supramolecular synthon comes into play. Desiraju defined supramolecular synthon as “structural units within supermolecules which can be formed and/or assembled by known or conceivable
synthetic operations involving intermolecular interactions”.

The situation is very simple for a homomeric crystal or heteromeric cocrystal with only one or two functionalities, but it becomes complicated when more number of functional groups are present and a synthon competition exists. In such cases Etter’s hydrogen bond rules (1990) apply where (1) all acidic hydrogens available in a molecule will be used in hydrogen bonding in the crystal structure of that compound. (2) All good proton acceptors will be used in hydrogen bonding when there are available hydrogen-bond donors. (3) The best hydrogen-bond donor and the best hydrogen acceptor will preferentially form hydrogen bonds to one another. Some common hydrogen bond synthons present in the crystal structures and also encountered in the cocrystals prepared are shown in the Scheme 1.

Scheme 1 Some examples of supramolecular synthons.
Cocrystal, also known as a multicomponent crystal under the subset of solid-state chemistry is a familiar word and has 166 year old history. In 1844, Friedrich Wöhler prepared the Quinhydrone from a 1:1 molar combination of quinone and hydroquinone and this can be regarded as the starting point of the cocrystal field. Later after the discovery of X-rays by Röntgen in 1895, in the early 20th century the X-ray crystallography flourished and a large number of cocrystals were determined along with single component crystals. Though they have a long history, cocrystals represent only 0.5% of the crystal structures archived in the Cambridge Structural Database (CSD) as of 2009. Regarding the nomenclature of cocrystals, they are also referred to as co-crystal, molecular complex, multicomponent molecular crystal, molecular compound, heteromolecular crystal, neutral molecular complex, etc. Again a universal or agreeable definition of cocrystal in the literature is unavailable till date. Various parameters have been applied by Stahly, Nangia, Childs, Jones, Zaworotko etc. to define the cocrystal. According to Aakeröy cocrystal can be defined as “compounds constructed from discrete neutral molecular species, made from reactants that are solids at ambient conditions and structurally homogeneous crystalline material and contains two or more neutral building blocks that are present in definite stoichiometric amounts”. There is a scope for confusion in case of certain multi-component crystals like the picric acid with benzene, naphthalene and anthracene. Though stable at room temperature, benzene is a solvent and it is debatable whether it can be categorized as solvate or cocrystal. Therefore in a broader sense all these hydrates, clathrates, solvates and cocrystals can be considered as multi-component systems. Again salts and cocrystals are also closely related to each other and generally the acid ionization constant, \( pK_a \) is a common parameter to differentiate between them. The \( \Delta pK_a \) rule states that when the \( pK_a \) difference between the two components is sufficiently large (\( \Delta pK_a > 3 \)) salt formation is very likely, otherwise it is referred to as cocrystal. But there are enormous examples where partial proton transfer occurs. Aakeröy, Childs, Price and coworkers in their recent reports mentioned about the intermediacy of salt and cocrystal structures. Nangia et. al. also discussed recently about synthon competition in molecular salts.
Cocrystals consists of components that interact through non-covalent interactions such as hydrogen bonding, π stacking, van der Waals forces etc. They exhibit physical and chemical properties that can differ from the individual components like the melting point, solubility, chemical stability, and mechanical stability etc. They are widely used in many industries like pharmaceutical, textile, paper, chemical processing, photographic, propellant, and electronics. From the last decade the concept of cocrystallization is widely used in the pharmaceutical industry and a field of Pharmaceutical cocrystals has developed. Zaworotko define pharmaceutical cocrystal as “a multi-component system formed between a molecular or ionic API and a co-crystal former that is a solid under ambient conditions”. According to a recent analysis by SSCI, the solid state chemistry business of Aptuit have screened about 64 compounds out of which 60 % formed cocrystals other than hydrates or solvates. Zaworotko and coworkers studied supramolecular heterosynthon as a starting point for cocrystal design. Nangia et. al. have studied temperature effects, reactivity of hydrogen-bonding groups in aromatic carboxylic acid and carboxamide cocrystals, also on the amide-N-oxide heterosynthon of model APIs. Jones group explored the methods of preparing cocrystals by liquid-assisted and neat grinding. Based on the grinding technique they explained the mechanism of cocrystal formation and also improvement in chemical and mechanical stability. Rodríguez’s group studied the thermodynamics of cocrystal formation and their stability-solubility relationship. Childs group and some of the research and development wings of Merck, Purdue, Pfizer etc have improved the solubility and dissolution of various APIs through their cocrystals.

3.2 RESULTS AND DISCUSSION

It is reported in the literature that aromatic alcohols such as phenols, naphthols etc. readily form cocrystals with aromatic amines, N-heterocyclic aromatics, ureas and acetamide. Cocrystals of antipyrine, an analgesic, with various alcohols like 2-methylphenol, 3-methylphenol, 2-methoxyphenol, resorcinol, pyrogallol etc were reported at the turn of the last century. Apart from that few cocrystals of pyrogallol and
catechol with 4,4'-trimethylene-dipyridine, triazine, pyrimidine, HMTA etc were reported by various groups. Pyrogallol or benzene-1,2,3-triol is a white crystalline powder and a powerful reducing agent. It was prepared by Scheele in 1786 by heating gallic acid. It is a common laboratory reagent used to calculate amount of oxygen in air, in making dry nitrogen line, in absorption of moisture, in the early days as dying material and in photography as developing agent. In the recent past, there is a renewed interest on the pharmaceutical utility of pyrogallol as it is a good superoxide generator which induces cell apoptosis. As a result, it has been explored as a potential candidate for anti-lung cancer drug particularly for the non-small cell lung cancer (NSCLC) and Cystic Fibrosis (CF) chronic lung inflammatory disease. In the Cambridge Structural Database (CSD) the crystal structure of pyrogallol is not reported till date, however Becker et. al. have determined the cell parameters of the guest-free form and a 0.25-hydrate. Cocrystals of pyrogallol (Pyro) and catechol (Cate) with N-heterocycle bases (Scheme 2) were prepared along with the guest-free form and 0.25-hydrate of pyrogallol and their structural, spectroscopic, solubility and dissolution behavior were studied. All the crystals 16–27 were prepared by solution crystallization method using ethyl acetate-toluene mixture solvent, except cocrystal 25 (from acetonitrile solvent).

Scheme 2 Molecular structure of molecules used in the study and the list of cocrystals obtained.
Z' (Z prime) is a common symbol to designate the number of molecules in the asymmetric unit for a single component system. Z' may be defined in relation to the number of molecules in the unit cell: \( Z = Z' \times \text{number of lattice points} \times \text{number of symmetry operations} \). Eijck and Kroon introduced the symbol \( Z'' \) to denote the number of crystallographically non equivalent molecules for multicomponent systems like cocrystals, salts, hydrates and solvates. There is renewed interest on why molecules crystallize with \( Z' > 1 \) from a structural viewpoint, because the factors leading to its occurrence are still not properly understood. Steed, Padmaja, Gavezzotti and many more research groups studied on the occurrence of more than one molecule in the asymmetric unit. It was mentioned in the literature about awkwardly shaped molecules like monoalcohols, phenols, primary amine etc. which often cannot crystallize out in simple packing modes, give rise to multiple molecules in the asymmetric unit. Apart from that molecular pseudosymmetry, chirality, strong hydrogen bond, polymorphs and modulated structures are some of the reasons for the occurrence of high \( Z' \). As pyrogallol is a noncentrosymmetric molecule with three hydroxyl groups on adjacent side hence most of the cocrystals with N-heterocycle bases having nonstoichiometric donor and acceptor groups resulted in high \( Z'' \) structure. But it is difficult to comment about the exact reason for the occurrence of high \( Z'' \) in some of the cocrystals of pyrogallol.

Vibrational spectroscopy is a very useful tool to characterize the formation of cocrystal/salt with respect to the co-formers. Hydrogen bonding between the functional groups alters bond strength thus affecting the stretching and bending vibrations involving them. The common proton donor groups in organic molecules are carboxyl, hydroxyl, amine or amide groups. Common proton acceptor groups are oxygen, nitrogen, the halogens, and even C=C linkage also acts as proton acceptor. When a hydrogen bond forms between \( X-H \cdots Y-Z \), the strength of \( X-H \) bond decreases, the \( X-H \) stretching band move to lower frequencies (longer wavelength) usually with increased intensity and band widening. The stretching frequency of the acceptor group also reduces but to a lower extent. The \( H-X \) bending vibration shifts to a shorter wavelength but the shift is less pronounced than that of the stretching frequency. The pyrogallol/ catechol cocrystals with
N-heterocycle base were characterized by IR, NIR and Raman spectroscopy. The strong hydrogen bond between the various functional groups present in the cocrystals results in the characteristic changes in stretching and bending vibrations. Apart from X-ray crystallography and vibrational spectroscopy, X-ray photoelectron spectroscopy (XPES) is also a very good technique to differentiate salt/cocrystal. The FT-IR, NIR and Raman spectra of some of the cocrystals are shown in the Figure 1, 2, 3 and 4 respectively.

**Figure 1** FT-IR spectra of Pyrogallol 0.25-hydrate 17 and their cocrystals 18, 19, 21, 24 and 25. Spectral region (a) from 3700–2800 cm⁻¹ and (b) from 1800–500 cm⁻¹.
Figure 2 FT-IR spectra of Catechol and their cocrystals 26 and 27. Spectral region (a) from 3600–2200 cm\(^{-1}\) and (b) from 2000–500 cm\(^{-1}\).
Figure 3 (a) FT-NIR spectra of Pyrogallol 0.25-hydrate 17 and their cocrystals 18, 19, 21, 24 and 25. (b) FT-NIR spectra of Catechol and their cocrystals 26 and 27. Spectral region from 7500–4000 cm$^{-1}$.
Figure 4 (a) FT-Raman spectra of Pyrogallol 0.25-hydrate 17 and their cocrystals 18, 19, 21, 24 and 25. (b) FT-Raman spectra of Catechol and their cocrystals 26 and 27. Spectral region from 3200–400 cm⁻¹.

The hydrogen bond metrics for the crystal structures 16–27 are given in Table 1.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>O1–H1···O2</td>
<td>1.96</td>
<td>2.830(2)</td>
<td>145.8</td>
<td>1/2–x,1/2+y,3/2–z</td>
</tr>
<tr>
<td></td>
<td>O2–H2···O3</td>
<td>1.86</td>
<td>2.733(2)</td>
<td>146.5</td>
<td>–x,2–y,1–z</td>
</tr>
<tr>
<td></td>
<td>O1–H1···O2</td>
<td>2.21</td>
<td>2.729(2)</td>
<td>111.5</td>
<td>***b</td>
</tr>
<tr>
<td></td>
<td>O2–H2···O3</td>
<td>2.31</td>
<td>2.724(2)</td>
<td>104.0</td>
<td>***b</td>
</tr>
<tr>
<td></td>
<td>O3–H3···O1</td>
<td>1.74</td>
<td>2.686(2)</td>
<td>160.2</td>
<td>–1/2+x,3/2–y,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−1/2+z</td>
</tr>
<tr>
<td>17</td>
<td>O1–H1A···O5</td>
<td>1.83</td>
<td>2.749(3)</td>
<td>155.0</td>
<td>1–y,−1/2+x,−1/2+z</td>
</tr>
<tr>
<td></td>
<td>O2–H2A···O4</td>
<td>1.85</td>
<td>2.807(3)</td>
<td>164.2</td>
<td>y,3/2–x,3/2–z</td>
</tr>
<tr>
<td></td>
<td>O1–H1A···O2</td>
<td>2.22</td>
<td>2.715(3)</td>
<td>109.4</td>
<td>***b</td>
</tr>
<tr>
<td></td>
<td>O3–H3A···O6</td>
<td>1.76</td>
<td>2.723(3)</td>
<td>166.6</td>
<td>3/2–x,3/2–y,−1+z</td>
</tr>
<tr>
<td></td>
<td>O4–H4A···O3</td>
<td>1.81</td>
<td>2.760(4)</td>
<td>162.5</td>
<td>3/2–y,x,1/2–z</td>
</tr>
<tr>
<td></td>
<td>O5–H5A···O7</td>
<td>1.91</td>
<td>2.818(5)</td>
<td>152.0</td>
<td>1/2+y,1–x,1/2+z</td>
</tr>
<tr>
<td></td>
<td>O5–H5A···*O7</td>
<td>1.94</td>
<td>2.586(5)</td>
<td>120.7</td>
<td>3/2–y,x,1/2–z</td>
</tr>
<tr>
<td></td>
<td>O6–H6A···O1</td>
<td>1.88</td>
<td>2.767(3)</td>
<td>149.0</td>
<td>1/2+y,1–x,3/2+z</td>
</tr>
<tr>
<td></td>
<td>O6–H6A···O5</td>
<td>2.38</td>
<td>2.746(4)</td>
<td>101.0</td>
<td>***b</td>
</tr>
<tr>
<td></td>
<td>O7–H7A···O2</td>
<td>1.95</td>
<td>2.835(6)</td>
<td>148.5</td>
<td>−1+x,−y,−z</td>
</tr>
<tr>
<td>18</td>
<td>O1–H1···N1</td>
<td>2.25</td>
<td>2.988(5)</td>
<td>131.1</td>
<td>1–x,2–y,1–z</td>
</tr>
<tr>
<td></td>
<td>O2–H2···O4</td>
<td>1.74</td>
<td>2.697(5)</td>
<td>162.3</td>
<td>−1+x,1+y,z</td>
</tr>
<tr>
<td></td>
<td>O1–H1···O2</td>
<td>2.15</td>
<td>2.710(5)</td>
<td>114.6</td>
<td>***b</td>
</tr>
<tr>
<td></td>
<td>O3–H3···N2</td>
<td>1.85</td>
<td>2.819(5)</td>
<td>170.1</td>
<td>1–x,2–y,2–z</td>
</tr>
<tr>
<td></td>
<td>N3–H3A···O2</td>
<td>2.17</td>
<td>3.018(6)</td>
<td>141.1</td>
<td>1–x,2–y,1–z</td>
</tr>
<tr>
<td></td>
<td>N3–H3A···N1</td>
<td>2.33</td>
<td>2.728(6)</td>
<td>102.1</td>
<td>***b</td>
</tr>
<tr>
<td></td>
<td>N3–H3B···O1</td>
<td>2.10</td>
<td>3.093(6)</td>
<td>167.8</td>
<td>1–x,1–y,1–z</td>
</tr>
<tr>
<td>19</td>
<td>O1–H1···O4</td>
<td>1.76</td>
<td>2.722(2)</td>
<td>164.9</td>
<td>1–x,1–y,1–z</td>
</tr>
<tr>
<td></td>
<td>N1–H1A···O2</td>
<td>1.89</td>
<td>2.896(2)</td>
<td>175.4</td>
<td>***a</td>
</tr>
<tr>
<td></td>
<td>N1–H1B···O1</td>
<td>2.06</td>
<td>3.040(2)</td>
<td>162.5</td>
<td>1–x,2–y,1–z</td>
</tr>
<tr>
<td></td>
<td>O2–H2···O6</td>
<td>1.92</td>
<td>2.766(2)</td>
<td>142.7</td>
<td>x,1+y,z</td>
</tr>
<tr>
<td></td>
<td>O2–H2···O3</td>
<td>2.16</td>
<td>2.678(2)</td>
<td>111.0</td>
<td>***b</td>
</tr>
<tr>
<td></td>
<td>O3–H3···N2</td>
<td>1.67</td>
<td>2.654(2)</td>
<td>173.4</td>
<td>−1+x,y,1+z</td>
</tr>
<tr>
<td></td>
<td>O4–H4A···O7</td>
<td>1.78</td>
<td>2.732(2)</td>
<td>162.2</td>
<td>***a</td>
</tr>
<tr>
<td></td>
<td>O5–H5A···O3</td>
<td>2.02</td>
<td>2.851(2)</td>
<td>140.5</td>
<td>−x,1–y,1–z</td>
</tr>
<tr>
<td></td>
<td>O5–H5A···O6</td>
<td>2.23</td>
<td>2.730(2)</td>
<td>110.0</td>
<td>***b</td>
</tr>
<tr>
<td></td>
<td>O6–H6A···O7</td>
<td>1.84</td>
<td>2.818(2)</td>
<td>175.6</td>
<td>−x,1–y,1–z</td>
</tr>
<tr>
<td></td>
<td>C14–H14···O2</td>
<td>2.26</td>
<td>3.241(2)</td>
<td>149.3</td>
<td>1–x,2–y,1–z</td>
</tr>
<tr>
<td>20</td>
<td>O1–H1A···N3</td>
<td>1.74</td>
<td>2.699(4)</td>
<td>165.2</td>
<td>x,1+y,z</td>
</tr>
<tr>
<td></td>
<td>O2–H2A···O9</td>
<td>1.89</td>
<td>2.763(4)</td>
<td>145.9</td>
<td>1–x,1/2+y,1–z</td>
</tr>
</tbody>
</table>
O2–H2A···O3 2.22 2.721(4) 110.34 ---
N2–H2B···O9 2.04 3.042(5) 169.2 1–x,1/2+y,1–z
N2–H2C···O1 1.90 2.895(5) 168.7 x,–1+y,z
O3–H3A···N7 1.79 2.729(4) 158.6 1–x,–1/2+y,1–z
O4–H4A···N1 1.74 2.703(5) 165.0 x,1+y,–1+z
N4–H4B···O4 2.07 2.921(5) 140.4 x,y,1+z
N4–H4B···O5 2.38 3.251(5) 143.7 x,y,1+z
N4–H4C···O10 2.15 3.107(5) 157.5 1–x,1/2+y,2–z
O5–H5A···O10 1.77 2.717(4) 161.4 1–x,–1/2+y,1–z
O5–H5A···O6 2.23 2.702(4) 103.38 ---
O6–H6A···N5 1.74 2.708(4) 165.4 1–x,–1/2+y,1–z
N6–H6B···O7 1.94 2.892(4) 156.8 –1+x,–1+y,z
N6–H6C···O9 1.86 2.846(4) 163.9 –x,–1/2+y,1–z
N8–H8A···O8 1.86 2.865(5) 171.6 x,–1+y,z
N8–H8B···O10 1.89 2.862(4) 160.2 1–x,–1/2+y,2–z
C23–H23···O5 2.28 3.356(4) 172.4 x,y,1+z
C35–H35···O8 2.44 3.488(5) 162.8 x,–1+y,z

21
O1–H1···O4 1.85 2.787(2) 158.8 1–x,–y,1–z
N1–H1A···O1 2.40 3.029(2) 119.4 –1+x,1/2–y,1/2+z
N1–H1A···O2 1.92 2.912(2) 166.0 –1+x,1/2–y,1/2+z
N1–H1B···O6 2.07 3.066(2) 167.6 –x,1–y,1–z
O2–H2···O3 1.95 2.781(2) 140.1 1+y,x,y,z
O2–H2···O3 2.21 2.696(2) 108.8 ---
O3–H3···N2 1.66 2.632(2) 167.5 1–x,1–y,1–z
O4–H4···O7 1.68 2.663(2) 176.1 x,1/2–y,–1/2+z
O5–H5···O7 1.77 2.745(2) 169.5 x,1/2–y,–1/2+z
O6–H6···O3 1.94 2.763(2) 139.3 –1+x,1/2–y,–1/2+z
O6–H6···O5 2.23 2.728(2) 110.0 ---
C5–H5A···O4 2.41 3.478(2) 169.2 ---
C14–H14···O6 2.42 3.431(2) 155.5 –x,1–y,1–z

22
O1–H1A···N5 1.69 2.670(6) 171.1 –x,1–y,1–z
O2–H2A···O6 1.80 2.769(5) 167.8 1–x,1–y,1–z
O3–H3A···N1 1.65 2.604(6) 161.7 1–x,–y,1–z
O4–H4A···O5 2.25 2.732(6) 109.1 ---
O4–H4A···O1 2.01 2.905(6) 151.0 –x,1–y,1–z
O5–H5A···O6 2.28 2.752(5) 108.1 ---
O5–H5A···O3 1.82 2.750(5) 156.6 1–x,–y,1–z
O6–H6A···N2 1.68 2.658(6) 171.5 1–x,1–y,1–z
O7–H7A···O8 2.28 2.770(7) 109.8 ---
O7–H7A···N4 1.89 2.741(7) 143.2 1–x,1–y,–z
| Bond                  | Distance (Å) | Angle (°) | Symmetry
|----------------------|--------------|-----------|-----------
| O8–H8A···O9          | 2.25         | 107.8     | ---b      |
| O8–H8A···O9          | 1.96         | 148.5     | -x,1-y,-z |
| O9–H9A···N3          | 1.67         | 165.7     | -1+x,y,z  |
| C23–H23···O2         | 2.49         | 131.7     | ---a      |
| C50–H50···O2         | 2.40         | 156.9     | 1-x,1-y,1-z |
| O1–H1A···N2          | 1.76         | 167.6     | 1+x,y,z   |
| O2–H2A···O3          | 2.07         | 118.7     | ---b      |
| O3–H3A···N3          | 1.72         | 178.5     | 1-x,1-y,1-z |
| O4–H4A···N1          | 1.65         | 172.0     | 2-x,1-y,-z |
| O5–H5A···O4          | 1.76         | 155.7     | 1-x,2-y,-z |
| O5–H5A···O4          | 2.38         | 101.9     | ---b      |
| O6–H6A···O5          | 1.97         | 143.4     | -x,2-y,-z |
| O6–H6A···O5          | 2.26         | 109.9     | ---b      |
| C38–H38···O2         | 2.43         | 145.5     | x,-1+y,z  |
| O1–H1···O4           | 1.69         | 164.3     | -x,1-y,1-z |
| N1–H1A···O5          | 1.81         | 170.4     | -1+x,-1+y,z |
| O2–H2···O5           | 1.74         | 155.4     | -1+x,y,z  |
| N2–H2A···O4          | 1.85         | 178.9     | 1-x,1+y,z  |
| O3–H3···O4           | 1.93         | 158.0     | 1-x,1-y,1-z |
| O3–H3···O2           | 2.25         | 108.62    | ---a      |
| C9–H9···O2           | 2.35         | 173.6     | ---a      |
| C13–H13···O2         | 2.33         | 173.0     | x,-1+y,z  |

---

| Bond                  | Distance (Å) | Angle (°) | Symmetry
|----------------------|--------------|-----------|-----------
| O1–H1A···N1          | 1.77         | 167.1     | 1+x,y,z   |
| O2–H2A···O8          | 1.61         | 165.6     | ---a      |
| O3–H3A···N2          | 1.82         | 152.8     | -1+x,-1+y,z |
| O4–H4A···N3          | 1.82         | 150.3     | 1+x,1+y,z  |
| O5–H5A···O7          | 1.59         | 164.9     | ---a      |
| O6–H6A···N4          | 1.80         | 166.4     | -1+x,y,z  |
| O7–H7A···O2          | 2.14         | 129.7     | 1+x,1+y,z  |
| O7–H7A···O3          | 2.09         | 154.6     | 1+x,1+y,z  |
| O7–H7B···N6          | 1.78         | 176.8     | -1+x,y,z  |
| O8–H8A···O4          | 2.08         | 158.1     | -1+x,-1+y,z |
| O8–H8A···O5          | 2.19         | 127.0     | -1+x,-1+y,z |
| O8–H8B···N5          | 1.79         | 175.1     | ---a      |

---

| Bond                  | Distance (Å) | Angle (°) | Symmetry
|----------------------|--------------|-----------|-----------
| O1–H1···N1           | 1.71         | 163.3     | 1-x,1-y,2-z |
| O2–H2···O3           | 1.68         | 170.2     | x,3/2-y,1/2+z |
| O3–H3A···O1          | 1.87         | 158.9     | x,y,-1+z   |
| O3–H3B···N2          | 1.85         | 167.1     | ---a      |

---

79 | Chapter 3
3.3 STRUCTURAL ANALYSIS

PYROGALLOL GUEST-FREE 16

On crystallization of pyrogallol from a mixture of ethyl acetate and toluene plate shaped crystals of guest-free form 16 was obtained in $P2_1/n$ space group. It has all the three hydroxyl groups on the same side, (conformer A) and forms a O–H···O helical trimer synthon along the [010] axis (Figure 5a) and the pyrogallol molecules are stacked through $\pi$ interaction. In 3D the helical trimer motif of pyrogallol molecules formed an infinite tape parallel to (–101) plane (Figure 5b) and connected to the neighbouring tape through close packing.

![Figure 5](image_url)

**Figure 5** (a) O–H···O helical trimer synthon along the [010] axis. (b) 3D packing showing the infinite tape parallel to (–101) plane in 16.
**PYROGALLOL 0.25-HYDRATE 17**

On attempted co-crystallization of pyrogallol with pyrazinamide in 1:1 ratio and isonicotinamide in 2:1 ratio respectively in ethyl acetate-toluene mixture solvent two different morphology crystals, needle shaped pyrogallol 0.25-hydrate 17 in tetragonal space group $P4_2/n$ and block shaped crystals of corresponding cocrystals were obtained. The water molecule is present in the crystallographic inversion center with a site occupancy factor of 0.5 along with two pyrogallol molecules (conformer A) in the asymmetric unit. Hence the resulted crystal structure is a 0.25-hydrate. In the crystal structure four pyrogallol molecules forms a helical tetrameric synthon through O–H···O hydrogen bond and a water channel resides in the centre of the tetramer along [001] axis (Figure 6).

![Figure 6](image)

(a) Hydrogen bonded O–H···O tetrameric synthon with the shape of a crystal (inset). (b) 3D packing arrangement for pyrogallol 0.25-hydrate 17. (c) Water channel in 17 along [001] axis.

Presence of the channel water is confirmed by thermal methods like DSC, TGA and hot stage microscopy. In the DSC thermogram an endotherm at 78.8 °C is attributed
to the release of water molecule and the stoichiometry of the released water was further confirmed by TGA analysis which showed a weight loss of 3.18%, matching the theoretical value of 3.12% for 0.25-hydrate (Figure 7). The endotherm at 134.2 °C corresponds to the melting point of pyrogallol. The events are also observed in hot stage microscopic images (Figure 8).

![Graph](image)

**Figure 7** DSC (black) and TGA (red) of pyrogallol 0.25-hydrate crystal 17.

![Images](image)

**Figure 8** HSM snapshots of pyrogallol 0.25-hydrate 17. The crystal is stable at 25 °C, on heating started getting opaque at 75 °C, 80 °C and melted around 131 °C corresponding to the melting point of pyrogallol guest-free form.
Cocrystal 18: Pyro•Pza (1:1)

On attempted cocrystallization of pyrogallol with pyrazinamide in 1:1 ratio along with the needle shaped crystals of pyrogallol 0.25-hydrate 17, blocked shaped cocrystal 18 of pyrogallol and pyrazinamide was obtained. It solved in triclinic space group $P\bar{1}$ containing one molecule each of pyrogallol (conformer A) and pyrazinamide in the asymmetric unit. Pyrogallol is connected to pyrazinamide through $O\cdots H\cdots O$, $N\cdots H\cdots O$ and $O\cdots H\cdots N$ hydrogen bonding with the graph set notations $R_2^2(10), R_4^4(12)$ and $R_4^4(22)$ to give a tape like structure, where the second layer is connected through $\pi\cdots\pi$ interaction. Pyrogallol and pyrazinamide forms a tetrameric synthon in a non-planar situation as shown in Figure 9.

![Figure 9](image)

**Figure 9** (a) $R_2^2(10), R_4^4(12)$ and $R_4^4(22)$ synthon present in cocrystal 18. (b) Non-planar tetrameric synthon formed by pyrogallol and pyrazinamide and the stacking of layers. (c) 3D packing arrangements of the layers in offset manner in cocrystal 18.
**Cocrystal 19: Pyro•Isonico (2:1)**

This cocrystal 19 which crystallized in \( P\bar{1} \) space group from ethyl acetate-toluene mixture solvent contained pyrogallol (conformer C) and isonicotinamide in 2:1 ratio. It was obtained as a block shaped crystal in addition to needle shaped crystals of pyrogallol 0.25-hydrate 17. Because of the strong acceptor groups like pyridine N and amide O and strong donor group O–H in the components, the cocrystal uses all the donor and acceptor groups to form O–H···O, O–H···N and N–H···O hydrogen bonds to give a complicated 3D structure (Figure 10).

![Figure 10 Different hydrogen bonded synthons present in the cocrystal 19.](image)

**Cocrystal 20: Pyro•Isonico (2:4)**

On cocrystallizing pyrogallol and isonicotinamide in the reverse ratio i.e. 1:2 from ethyl acetate-toluene mixture a 2:4 cocystal of pyrogallol and isonicotinamide 20 was obtained. The cocrystal 20 is solved in Sohncke (chiral) space group \( P2_1 \). Structurally the
two cocrystals 19 and 20 are completely different from each other. While the former is a centrosymmetric structure with a complicated 3D packing without any dimer or catemer synthon between the isonicotinamide molecules, the latter is a chiral structure having two unidirectional catemer networks between two symmetry independent isonicotinamide molecules along the [010] axis. Supramolecular chirality due to hydrogen bonding is the result of occurrence of chiral \( P2_1 \) space group for cocrystal 20 from two achiral coformers. Isonicotinamide and pyrogallol molecules are connected to each catemer unit through O–H···O and N–H···O hydrogen bond between the amide group of isonicotinamide and hydroxyl group of pyrogallol. These two independent units are further connected by O–H···N hydrogen bond through the hydroxyl group of pyrogallol and the pyridine N of isonicotinamide (Figure 11).

![Image](a)

![Image](b)

**Figure 11** (a) The catemer synthon formed by the isonicotinamide molecule along [010] axis. (b) 3D molecular packing with the symmetry independent molecules coated with different colors in cocrystal 20.

**COCRYSTAL 21: PYRO•NICO (2:1)**

On cocrystallizing pyrogallol and nicotinamide in 2:1 ratio from ethyl acetate-toluene mixture, cocrystal 21 was obtained with two molecules of pyrogallol (conformers C and D) and one molecule of nicotinamide in the asymmetric unit solved in \( P2_1/c \) space group. The commonly observed amide dimer or the catemer synthon is absent. Two pyrogallol molecules are hydrogen bonded to the nicotinamide molecule through strong O–H···O,
O–H···N and N–H···O hydrogen bonds (Figure 12). In the 3D structure, one of the pyrogallol (conformer C) and nicotinamide molecules form a layer and a symmetry independent pyrogallol molecule which is offset (conformer D) connects the next layer through O–H···O hydrogen bond. There is π···π stacking between the layers and are separated by a distance of 3.26 Å. A plausible reason for the occurrence of high energy conformer D of pyrogallol is to satisfy all H bonding sites present.

Figure 12 (a) Hydrogen bonded synthon in the cocrystal 21 (different colors are shown for the symmetry independent molecules) (b) Layers formed by pyrogallol and nicotinamide molecules with a second pyrogallol molecule (blue) connecting the layers through O–H···O hydrogen bond. (c) 3D molecular packing of cocrystal 21 along [001] axis.
**Cocrystal 22: Pyro•Quin (3:5)**

Cocrystallization of pyrogallol with quinoline was done by adding a solution of quinoline (1 mL of quinoline diluted in 50 mL of ethyl acetate-toluene) to 50 mg of pyrogallol and kept for slow evaporation. It resulted in two different stoichiometric cocrystals 22 and 23 from different batches.

The cocrystal 22 is solved in $P\bar{1}$ space group containing three molecules of pyrogallol and five molecules of quinoline in the asymmetric unit. The crystal structure contained two domains. Domain 1 contains two molecules of pyrogallol (conformer A and C) and three molecules of quinoline and domain 2 with one pyrogallol (conformer A) and two quinoline molecules. In domain 1 pyrogallol molecules are connected to each other through a zigzag tape of O–H···O hydrogen bond and the flanking hydroxyl groups of pyrogallol are connected to the three symmetry independent quinoline molecules through O–H···N hydrogen bond (Figure 13a, b). In domain 2 the pyrogallol molecule forms a centrosymmetric O–H···O dimer synthon and the terminal hydroxyl groups are connected to two symmetry independent quinoline molecules through O–H···N hydrogen bonds. Domain 1 and 2 forms a layer along [100] axis with both the domains stacked together through weak π···π interactions as shown in Figure 13d.
Figure 13 (a) Infinite O–H···O zigzag tape of pyrogallol connecting three symmetry independent quinoline molecules through O–H···N hydrogen bond (domain 1). (b) Single unit of domain 1 to show the hydrogen bond. (c) Domain 2 with the pyrogallol O–H···O dimer synthon connecting the quinoline molecules. (d) 3D molecular packing showing domain 1 and domain 2 with different colors.

Cocrystal 23: Pyro•Quin (2:3)

Along with the cocrystal 22, pyrogallol and quinoline formed cocrystal 23, solved in $P\bar{1}$ space group. The asymmetric unit of the cocrystal 23 contains two molecules of pyrogallol and three molecules of quinoline. Like the cocrystal 22, cocrystal 23 also has the same type of structural domains and conformers of pyrogallol (A and C). The domain 1 has one molecule of pyrogallol (conformer A) and quinoline. The pyrogallol molecule forms an infinite O–H···O hydrogen bond chain along [100] axis and one of the terminal hydroxyl group is hydrogen bonded to quinoline molecule through O–H···N interaction. In domain 2, one pyrogallol (conformer C) and two quinoline molecules are present. The two symmetry independent quinoline molecules are connected to the terminal hydroxyl groups of the pyrogallol molecule through O–H···N hydrogen bond. Domain 1 and 2 are stacked together through $\pi$···$\pi$ interaction and fulfill the 3D packing (Figure 14).
Figure 14 (a) Domain 1 containing infinite O–H···O hydrogen bonded chain along [100] axis. (b) Domain 2 with discrete O–H···N synthon between pyrogallol and quinoline. (c) 3D molecular packing showing the two domains with different colors.

Cocrystal 24: Pyro•2HQUI (1:2)

Pyrogallol and 2-Hydroxyquinoline on crystallizing in 1:2 ratio from ethyl acetate-toluene mixture resulted in cocrystal 24 of the same stoichiometry which solved in $P\bar{1}$ space group. 2-Hydroxyquinoline, in its amide tautomeric form results in a
noncentrosymmetric amide dimer synthon with a graph set notation $R_2^2(8)$. The pyrogallol molecules (conformer A) are connected to the 2-hydroxyquinoline dimer motif through O–H···O hydrogen bond forming a tape along [100] axis. The 2-hydroxyquinoline dimer motifs are stacked through π···π interactions (Figure 15). These 1D tapes are arranged parallel to each other through short contacts.

![Diagram](image)

**Figure 15** (a) 2-Hydroxyquinoline amide dimer connected to the pyrogallol molecule through O–H···O hydrogen bond. (b) O–H···O hydrogen bond between pyrogallol and 2-Hydroxyquinoline of three different layers. (c) Infinite tape of pyrogallol connecting the π stacked 2-Hydroxyquinoline layers along [100] axis.

**Cocrystal 25: Pyro•Bipy•H₂O (2:3:2)**

Cocrystallization of pyrogallol with bipyridine in 2:3 ratio from acetonitrile resulted in block shaped cocrystals of 25 solved in $P\overline{1}$ space group containing two pyrogallol, three bipyridine along with two water molecules in the asymmetric unit. Structurally the cocrystal 25 consists of an O–H···O tetrameric synthon with graph set notation $R_2^2(8)$.
formed by two water molecules and two symmetry independent pyrogallol units (Figure 16a). These pyrogallol-water tetramers are connected to each other by the three symmetry independent bipyridine molecules through O–H···N hydrogen bond which forms a layer parallel to the (–12–2) plane. Within the layer, bipyridine molecules are orthogonal to the pyrogallol molecules and the next layer consists of alternate stacks of pyrogallol and bipyridine units through weak C–H···π interactions (Figure 16).

**Figure 16** (a) O–H···O tetrameric synthon between pyrogallol and water which is connected to the bipyridine through O–H···N hydrogen bond. (b) Two pyrogallol-bipyridine layers connected through weak C–H···π interaction.

**Cocrystal 26: CATE•BIPY•H2O (1:1:1)**

Similarly like the cocrystal 25 of pyrogallol, on crystallizing catechol (having one hydroxyl group less than pyrogallol) with bipyridine from ethyl acetate-toluene mixture solvent, afforded cocrystal 26 having one catechol, one bipyridine and a water of crystallization in the asymmetric unit. The cocrystal 26 solved in $P2_1/c$ space group and is different from 25 due to the lack of one hydroxyl group and consequently the tetrameric synthon. Catechol along with the water molecule forms an infinite O–H···O chain along [001] axis and the bipyridine molecule acts as a spacer which connect the hydrogen bonded chains (Figure 17).
Cocrystal 27: Cate*Nico (2:1)

Cocrystallizing catechol and nicotinamide in 2:1 ratio from ethyl acetate-toluene mixture resulted in cocrystal 27 which solved in Pca2₁ space group with two catechol and one nicotinamide molecules in the asymmetric unit. In the crystal structure 27 nicotinamide molecule is disordered over two positions with the site occupancy factor 0.63 and 0.37 (Figure 18). The two symmetry independent catechol molecules form an O–H···O hydrogen bonded zigzag chain along [001] axis and the flanking hydroxyl groups are connected to the disordered nicotinamide molecule through O–H···N hydrogen bond (Figure 19).

Figure 18 Positional disorder of two nicotinamide molecules.
Figure 19 (a) Infinite O–H···O hydrogen bonded chain along [001] axis. (b) Catechol molecules of the chain that connect the disordered nicotinamide molecules through O–H···N hydrogen bond in cocrystal 27.

3.4 Conformational Analysis

Dihydroxy and trihydroxy benzene molecules generally show positional isomerism. Among them pyrogallol, 1,2,4 trihydroxybenzene and catechol have intramolecular hydrogen bond (Scheme 3). M. Gerhards et al.\textsuperscript{32} have calculated conformational energy possible for the different conformers of pyrogallol of which it was found that conformer A is the most stable one having 1664 cm\(^{-1}\) (4.76 kcal mol\(^{-1}\)) less energy than the metastable conformer C. Conformer D and E have higher energy due to inter-atomic repulsion term, similar to the case of catechol conformers B and C.
Scheme 3 Positional isomers of dihydroxy and trihydroxy benzene and various conformers of pyrogallol and catechol molecules.

The hydroxyl group conformations of pyrogallol and catechol obtained in the crystal structures 16–27 are listed in Table 2. The stable conformer A is found for most of the cocrystals of pyrogallol along with its guest-free form and 0.25-hydrate followed by the conformer C, and conformer D for structure 21 (Table 2). The occurrence of high energy conformers for structures 21 and 26 is to satisfy all possible hydrogen bond donor/acceptor sites available.

Table 2 Conformers present in the crystal structures 16–27.

<table>
<thead>
<tr>
<th>Structure</th>
<th>OH group Conformer</th>
<th>Structure</th>
<th>OH group Conformer</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Conformer A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22</td>
<td>Conformer A and C&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>17</td>
<td>Conformer A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23</td>
<td>Conformer A and C&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>18</td>
<td>Conformer A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24</td>
<td>Conformer A&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>19</td>
<td>Conformer C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25</td>
<td>Conformer C&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>20</td>
<td>Conformer C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26</td>
<td>Conformer B&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>21</td>
<td>Conformer C and D&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27</td>
<td>Conformer A&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> pyrogallol, <sup>b</sup> catechol.
3.5 **Liquid Assisted Grinding and XRPD Analysis**

Cocrystals of pyrogallol and catechol with N-heterocycle bases obtained from solution crystallization were prepared in bulk quantity using liquid assisted grinding method. For the liquid assisted grinding both the components were taken in stoichiometric amount in a mortar pestle and a few drops of ethyl acetate solvent was used and ground thoroughly for 15-20 min and XRPD of the materials were recorded. The powder patterns of the materials match the calculated XRD patterns (Figure 20).

![XRPD Overlay](image)

**Figure 20** Overlay of the calculated X-ray crystal structure (red) and experimental XRPD pattern (black) of the bulk material of 17, Catechol, 19, 20, 21 and 27.

3.6 **Solubility and Dissolution**

As reported in the literature, pyrogallol is responsible for cell apoptosis and is also an active compound responsible for the anti-inflammatory effect of *Emblica officinalis*, a medicinal plant, due to which it may be a potential candidate as an anti-lung cancer
Therefore it is important to study the solubility and dissolution behavior of pyrogallol and their cocrystals in order to have a better knowledge about the bioavailability of the molecule. Solubility and dissolution of pyrogallol and catechol and their cocrystals with nicotinamide and isonicotinamide were studied. Pyrogallol is highly soluble in water with a solubility value of 611.99 mg/mL but the solubility of the isonicotinamide cocrystals 19, 20 (187.36, 156.13 mg/mL respectively) and nicotinamide 21 (187.22 mg/mL) are less than that of the parent molecule. Similar observation is obtained in case of catechol (337.72 mg/mL) and its nicotinamide 27 (162.08 mg/mL) cocrystal. In addition the dissolution profile (Figure 21) shows that pyrogallol and catechol have higher IDR values than their respective cocrystals. The 2:1 and 2:4 isonicotinamide cocrystals of pyrogallol have almost same dissolution rate.

![Figure 21](image)

**Figure 21** Dissolution patterns of pyrogallol, catechol, and their cocrystals 19, 20, 21 and 27 in distilled water recorded upto 30 min.

### 3.7 Conclusion

Cocrystals of pyrogallol and catechol with various N-heterocycle bases were prepared. It is observed that in most of the cocrystals there are more than two molecules in the asymmetric unit. The awkward shape of the pyrogallol/ catechol molecules and the strong hydrogen bonding requirements of the OH group can dominate the crystal packing. Thus
the frustration between the conflicting needs to achieve close packing and maximal hydrogen bonding of the lone OH groups resulted in high $Z''$ structures of the cocrystals. The cocrystal 20, that solved in chiral noncentrosymmetric space group $P2_1$ is the reason for 6 molecules in the asymmetric unit ($Z''$) compared to 3 molecules for the centrosymmetric case. But it is difficult to conclude in one line for the occurrence of high $Z'$ in crystal structures. In the course of time with more number of high $Z'$ structures deposited in the CSD can help in understanding the structural reasons for high $Z'$.

Over the last two decades based on the hydrogen bonding and supramolecular synthon approach, cocrystals were prepared. Therefore to have a better understanding of the non-covalent interactions, cocrystallization is a good approach from the crystal engineering point of view. The field of cocrystal chemistry is maturing from the supramolecular perspective towards the structure-property relationship of materials. Similar to the salt form of drugs, the utility of cocrystals for modifying the physical and chemical properties of drugs has increased its importance in pharmaceutical industry. So far there is no drug cocrystal formulation in the market but a large number of patent applications are filed for pharmaceutical cocrystals and are undergoing bioavailability and animal studies. It is only a matter of time before this imagination becomes a reality.

3.8 EXPERIMENTAL SECTION

X-RAY CRYSTALLOGRAPHY

X-ray reflections for all compounds were collected at 100 K (except 25 at 298K) on Bruker SMART APEX CCD equipped with a graphite monochromator and Mo-Kα fine-focus sealed tube ($\lambda = 0.71073 \text{ Å}$). Data integration was done using SAINT.\textsuperscript{33} Intensities for absorption were corrected using SADABS.\textsuperscript{34} Structure solution and refinement were carried out using Bruker SHELXTL.\textsuperscript{35} The hydrogen atoms were refined isotropically and the heavy atoms were refined anisotropically. N–H and O–H hydrogens were located from difference electron density maps and C–H hydrogens were fixed using HFIX command in SHELXTL. In case of cocrystal 27 the nicotinamide molecule is disordered over two positions. It was modeled using FVAR command with s.o.f. of 0.63 and 0.37
respectively refining the disordered non-hydrogen atoms isotropically. Crystallographic data were summarized in Appendix. Packing diagrams were prepared in X-Seed.36

**X-ray Powder Diffraction**

X-ray powder diffraction of all samples were recorded on Bruker D8 Advance diffractometer using Cu-Kα X-radiation (λ = 1.54056 Å) at 40 kV and 30 mA. Diffraction patterns were collected over a 2θ range of 5-50° at a scan rate of 1° min⁻¹. Powder Cell 2.4 was used for Rietveld refinement.37

**Vibrational Spectroscopy**

Nicolet 6700 FT-IR spectrometer with an NXR FT-Raman module was used to record IR, NIR and Raman spectra. IR and NIR spectra were recorded on samples dispersed in KBr pellets. Raman spectra were recorded on solid samples contained in standard NMR diameter tubes or on compressed samples contained in a gold-coated sample holder.

**Thermal Analysis**

DSC was performed on Mettler Toledo DSC 822e module. Samples were placed in crimped but vented aluminum sample pans. The typical sample size was 3-4 mg, and the temperature range was 30-200 °C at heating rate of 5 °C min⁻¹. Samples were purged by a stream of dry nitrogen flowing at 150 mL min⁻¹. For TGA, the sample size was 7-9 mg, the heating rate was 10 °C min⁻¹, and the N₂ flow was 50 mL min⁻¹. HSM was performed on a Wagner & Munz PolythermA Hot Stage and Heiztisch microscope. A Moticam 1000 (1.3 MP) camera supported by software Motic Image Plus 2.0ML was used to record images.

**Intrinsic Dissolution Testing of Disc**

IDR measurements were carried on a USP-certified Electrolab TDT-08 L Dissolution Tester. Equilibrium solubility was determined in water using the shakeflask method. Excess amount of the powdered materials were added to 5 mL of water, and the resulting
suspension was stirred at room temperature for 24 hr. The suspension was then filtered through 2.5 µm Whatman filter paper. The concentration of the solution thus obtained was determined on a Thermo Scientific Evolution 300 UV-vis spectrometer based on the absorbance maxima with appropriate dilution using a predetermined calibration curve.

For IDR experiments, 200 mg of the pure pyrogallol, catechol and the cocrystals 19, 20, 21 and 27 were taken in the intrinsic attachment and compressed to a 0.5 cm² pellet using a hydraulic press at a pressure of 2.5 ton inch⁻² for 5 min. There is no polymorphic transformation or dissociation of the sample upon compression. The intrinsic attachment was placed in a jar of 900 mL of water at 37 °C and rotated at 50 rpm. 7 mL aliquots were collected at specific time intervals and concentrations of the aliquots were determined with proper dilution from the predetermined calibration curves of the respective materials using their individual molar extinction coefficients (Pyrogallol 0.67, Catechol 2.48, cocrystal 19 4.30, 20 11.78, 21 4.45 and 27 5.97 /mmol/cm) by UV-Vis spectrophotometry. The IDR values were 34.75, 19.48, 11.39, 10.78, 26.07 and 10.99 mg/cm²/min (at 10 min interval) respectively.

Calculation: Beer Lambert’s Law:  
\[ A = \varepsilon cl \]

where A is the absorbance, \( \varepsilon \) is coefficient of absorbance, c is the concentration and l is path length of the sample.

3.9 REFERENCES


to Hydrogen Bonding, Oxford University Press, Oxford, 1997. (d) T. Steiner, 


5. (a) G. R. Desiraju, Perspectives in Supramolecular Chemistry: The Crystal as a 
Supramolecular Entity, Ed., Vol. 2, Wiley: Chichester, 1996. (b) G. R. Desiraju, 


9. (a) J. D. Dunitz, CrystEngComm, 4, 2003, 506. (b) G. R. Desiraju, 
CrystEngComm, 5, 2003, 466. (c) A. D. Bond, CrystEngComm, 9, 2007, 833. (d) 

Nangia, New J. Chem., 32, 2008, 800. (c) S. L. Childs and K. I. Hardcastle, 
Trask, MRS Bull., 341, 2006, 875. (e) P. Vishweshwar, J. A. McMahon, J. A. Bis 
and M. J. Zaworotko, J. Pharm. Sci., 95, 2006, 499. (f) C. B. Aakeröy and D. J. 
Salmon, CrystEngComm, 7, 2005, 439. (g) C. B. Aakeröy, J. Desper, M. Fasulo, 


12. (a) S. L. Johnson and K. A. Rumon, J. Phys. Chem., 69, 1965, 74. (b) B. Sarma, 


34. G. M. Sheldrick, *SADABS, Program for Empirical Absorption Correction of Area Detector Data*, University of Göttingen, Germany, **1997**.

35. *SHELXS-97 and SHELXL-97, Programs for the Solution and Refinement of Crystal Structures*, G. M. Sheldrick, University of Göttingen, Germany, **1997**.

36. *X-Seed, Graphical Interface to SHELX-97 and POVRay*, L. J. Barbour, University of Missouri-Columbia, Columbia, MO, **1999**.

37. Powder Cell 2.4, Program for structure visualization, powder pattern calculation and profile fitting, [www.ccp14.ac.uk](http://www.ccp14.ac.uk).