

Investigation of the co-crystallisation of N-heterocycles

By

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CHAPTER 3

Co-crystals of Benzenediol and Diazine Isomers

Introduction

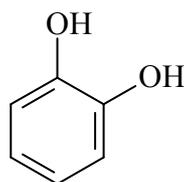
A systematic 3×3 grid was constructed from the related benzenediols catechol (*ortho*), resorcinol (*meta*) and hydroquinone (*para*), co-crystallised with the three diazine isomers pyridazine (*ortho*), pyrimidine (*meta*) and pyrazine (*para*). Thirteen co-crystals resulted from the study, of which twelve are novel. These molecules were selected for their rigidity, which promotes the formation of strong, directional hydrogen bonds that can be easily distinguished from more subtle interactions such as $\pi\cdots\pi$ contacts. The molecules are also complementary to one another, having either two donors or two acceptors in the *ortho*, *meta* and *para* positions.

The solid-state structures of the six starting materials used in the co-crystallisation experiments are discussed briefly too. An understanding of the solid-state structure of the starting materials allows patterns in hydrogen bonding as well as weaker interactions to be recognised in subsequent structures. Each of the thirteen co-crystal structures is discussed in terms of intermolecular interactions and packing in 3-D and interesting features of particular structures are also highlighted.

Hydrogen-bonding patterns or structural similarities are highlighted in related co-crystal structures, as well as between co-crystals and their starting materials. Conformational preferences of benzenediol isomers are established within the small array of co-crystals prepared in this 3×3 grid.

3.1 Starting Materials:

3.1.1 O2 – Catechol (Refcode¹: CATCOL13²)



Scheme 3.1 Catechol

Catechol, also known as pyrocatechol, crystallises in the monoclinic space group $P2_1/n$ with only one form known to date. One entire molecule makes up the ASU (Figure 3.1), with both hydroxyl hydrogen atoms facing in the same direction (*syn-anti*, Scheme 3.2).

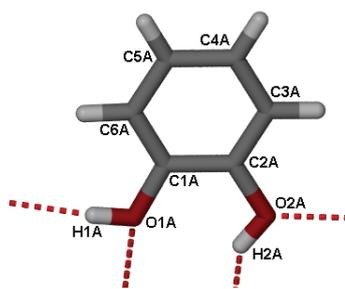


Figure 3.1 Capped stick representation of the ASU of catechol.

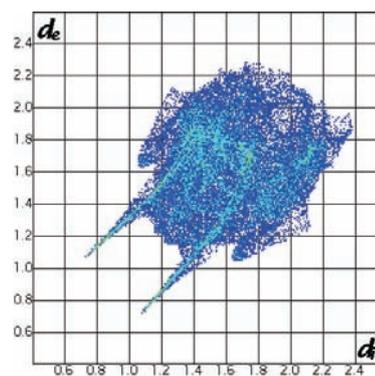
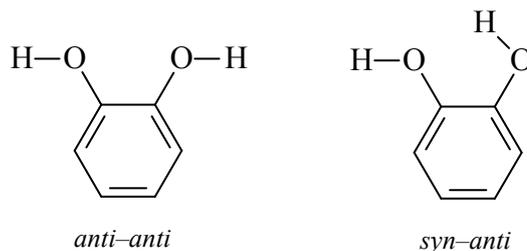


Figure 3.2 Fingerprint plot of catechol

The hydroxyl hydrogen atoms of catechol can adopt two different conformations. One in which both hydrogen atoms face in opposite directions, the *anti-anti* conformation, and the *syn-anti* conformation where the hydrogen atoms face in the same direction (Scheme 3.2). A *syn-syn* conformation is unlikely due to the unfavourable proximity of the two hydrogen atoms. As expected, the oxygen atoms act as both H-bond donors and acceptors. No polymorphs of catechol have been reported to date.



Scheme 3.2 The two possible conformations of catechol.

For the purposes of discussion, the structure of the pure form of catechol is deconstructed into smaller hydrogen bonding motifs that are easier to visualise. These can then be expanded into a hydrogen bonded network using graph-set analysis. In this structure the *syn-anti* conformation is adopted by the catechol molecule and the *syn*-orientated hydroxyl groups act as hydrogen bond donors to form a ring, $R_2^2(10)$ (green molecules, Figure 3.), with the *anti*-hydroxyl O-atom acting as acceptors. Hydrogen bonded chains, $C_2^2(10)$, are then formed by the *anti*-hydroxyl groups acting as donors to a *syn*-hydroxyl O-atom acceptors. The overall H-bonded network is constructed from the hydrogen-bonded rings orientated approximately perpendicular to one another, linked *via* hydrogen bond chains propagated diagonally across the *ac* plane (Figure 3.3).

The characteristic C–H $\cdots\pi$ “wings” in the fingerprint plot (Figure 3.2) of the molecule are not prominent features, indicating that these interactions are present in the structure, but play

only a minor role. Although the lone-pair $\cdots\pi$ interaction has been accepted³ as an intermolecular interaction, the impact of this interaction is still under investigation and therefore the close proximity of the O-atom and the aromatic ring is presumed to be the result of the stronger interactions present in the structure.

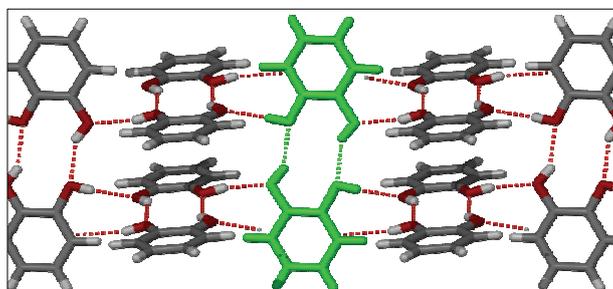
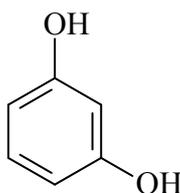


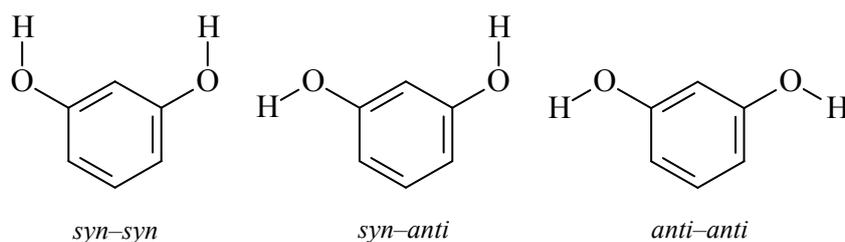
Figure 3.3 Hydrogen bonding between catechol molecules showing linkage of catechol “dimers”.

3.1.2 O3 – Resorcinol (RESORA03⁴)



Scheme 3.3 Resorcinol

Resorcinol is known to crystallise in the orthorhombic space group $Pna2_1$ in both the α - and β -forms. The α -form is more stable at ambient temperatures and can be transformed into the β -form if subjected to specific physical conditions.⁵ The more stable α -form is also unexpectedly the less dense form ($\rho_\alpha = 1.31 \text{ g cm}^{-3}$; $\rho_\beta = 1.40 \text{ g cm}^{-3}$); the *syn-anti* conformation of the β -form may account for the higher density compared to that of the α -form in which the molecules are in the *anti-anti* conformation. Three conformations of the hydroxyl hydrogen atoms are possible – (*syn-syn*); (*syn-anti*) or (*anti-anti*)⁶ as shown in Scheme 3.4. Examples of all three conformations are present in the co-crystals described in this study.



Scheme 3.4 Three possible conformations of resorcinol.⁶

Only the structural parameters of the α -form will be discussed further. One entire resorcinol molecule makes up the ASU (Figure 3.4). In this instance both hydroxyl hydrogen atoms face outwards – *i.e.* *anti-anti* conformation. A deconstruction of the structure of α -resorcinol enables a simplified description of

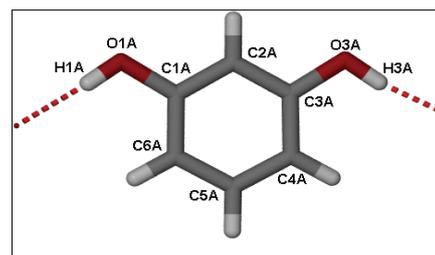


Figure 3.4 The ASU of resorcinol.

the intermolecular interactions. Molecules form H-bonded chains that resemble squashed helices, but are simply contracted chains. These chains are organised such that unused donor atoms hydrogen bond to adjacent chains running *anti-parallel* to one another (Figure 3.5). This arrangement forms helices that extend the network into three dimensions. The 3-D structure is difficult to classify in terms of graph-set notation. However, it is clear from examining the packing that the molecules organise themselves into a structure that is as dense as possible for the adopted *anti-anti* conformation.

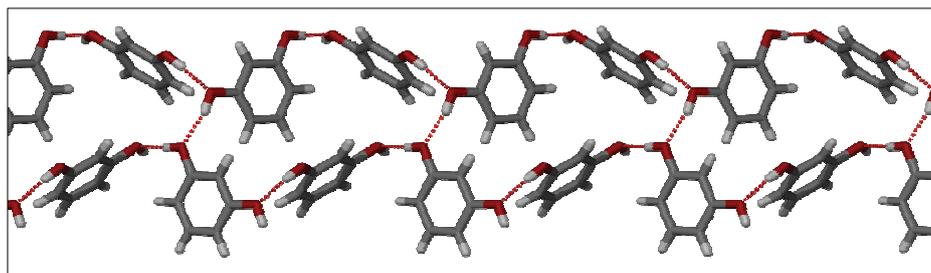


Figure 3.5 Two anti-parallel rows of resorcinol; hydrogen bonding extending into the 3rd dimension has been omitted for clarity.

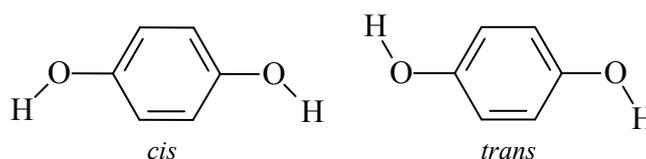
3.1.3 O4 – Hydroquinone



Scheme 3.5 Hydroquinone

Numerous structural studies have been carried out on the *para*-substituted phenol, including those involving enclathration (α -hydroquinone) and investigation of substituent effects (β -hydroquinone)⁷ (Scheme 3.5). Hydroquinone (*p*-benzenediol), also referred to as quinol, is known to crystallise in three polymorphic forms – alpha (α), beta (β), and gamma (γ). The most stable form at ambient temperature is α -hydroquinone (confirmed by PXRD of pure hydroquinone), whereas the γ -form is said to be metastable⁸.

There are two possible conformations for the hydroxyl hydrogen atoms to assume: (1) the *trans*-conformation, where hydrogen atoms face in opposite directions, or (2) the *cis*-conformation, where they are orientated in the same direction (Scheme 3.6). In all its pure forms, as well as in most multi-component crystals, hydroquinone adopts the *trans*-conformation. Of the 142 structures analysed in a Cambridge Structural Database (CSD) survey carried out as part of this work, 18 contain hydroquinone in the *cis*-conformation, and of those 18, only four display both conformations in the same structure.



Scheme 3.6 The two possible conformations of hydroquinone.

3.1.3.a α -Form (HYQUIN06⁹)

The α -form of hydroquinone crystallises in the trigonal space group $R\bar{3}$ with three symmetry-independent molecules in the ASU (Figure 3.6).

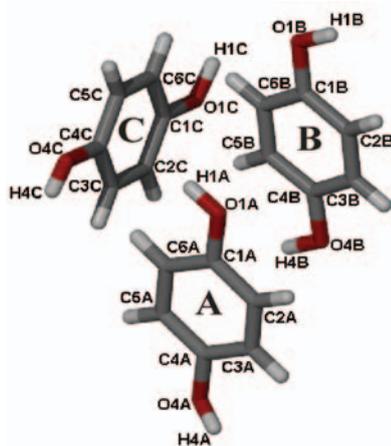


Figure 3.6 The ASU of the α -form of hydroquinone

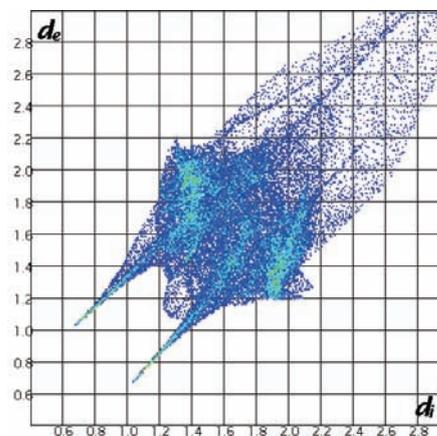


Figure 3.7 Fingerprint plot of the α -form of hydroquinone

A hydroquinone molecule (**A**) (green, Figure 3.8) hydrogen bonds to symmetry-related instances of itself to form a six-membered ring $R_6^6(12)$ (red). These rings are surrounded by six crystallographically independent molecules (**B**) (blue) to form a cage-like network. This network is similar to that seen in the β -form of hydroquinone, which is capable of enclathrating (Figure 3.9) small molecules. Interspersed between the cages is another crystallographically-independent molecule (**C**) (orange), which arranges themselves into a double helical chain.¹⁰ Two molecules of the outer ring of the cage link two independent

helices to complete the network ($R_6^6(22)$, yellow). Weaker intermolecular interactions in the form of C–H \cdots O and C–H \cdots π interactions play a minor role in stabilising the structure.

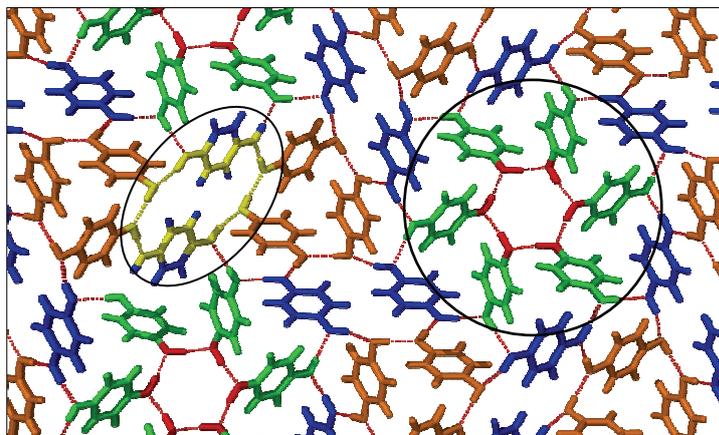


Figure 3.8 Crystallographically-independent molecules are indicated by orange, green or blue atoms. Double helices are portrayed in orange; the red H-bonded ring to the right of the figure resembles the rings created in the β -phase, and the yellow atoms indicate the $R_6^6(22)$ ring formed between helices.

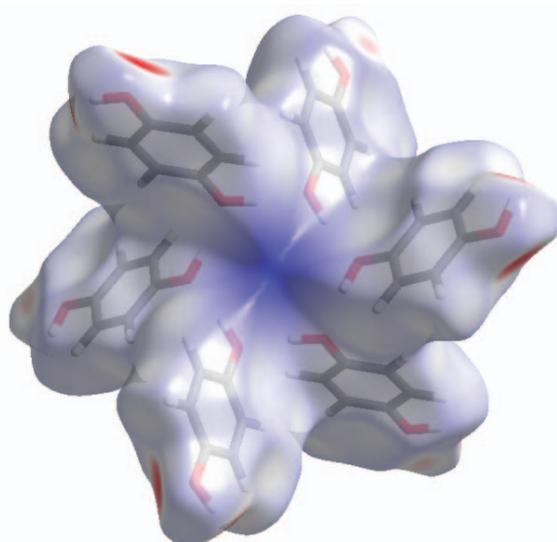


Figure 3.9 Hirshfeld surface of the hexameric hydrogen bonded adduct showing the void space (dark blue area indicates a lack of electron density) created by molecule C.

3.1.3.b β -Form (HYQUIN05¹¹)

The β -form of hydroquinone also crystallises in $R\bar{3}$, but with a smaller unit cell. The ASU (Figure 3.10) consists of half a molecule of hydroquinone located on an inversion centre $(\frac{1}{3}, \frac{1}{6}, \frac{2}{3})$.

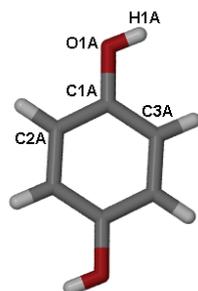


Figure 3.10 The ASU of the β -form of hydroquinone. Only the ASU atoms are labelled.

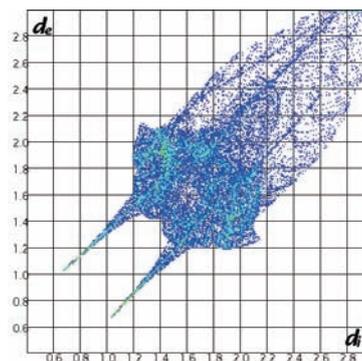


Figure 3.11 The fingerprint plot of β -hydroquinone.

β -Hydroquinone is a recognised host molecule (inclusion compound) capable of forming clathrates with small guest molecules. Molecules H-bond by means of O–H \cdots O interactions to form 6-membered H-bonded rings (Figure 3.13). C–H \cdots π interactions (3.868 Å, 146.52°) are responsible for the stabilization of the molecules around the hexameric rings created by the stronger O–H \cdots O interactions. The voids created by hydrogen bonding provide the β -form with the ability to form clathrates. Nine structures were retrieved from the CSD to confirm the β -form's propensity for enclathration; examples include small molecules such as NO, SO₂, CH₃CN, HCl, Xe and H₂S.

The Hirshfeld surface (Figure 3.12) clearly depicts the space created by the hydrogen bonded rings of hydroquinone that are accessible to small molecules. There exists a clear difference in the voids produced by the β -form and those in the α -form of hydroquinone. This is evident in the Hirshfeld surfaces generated for both structures (Figures 3.9 and 3.12). The β -form “hexamer” assumes a different shape to that of the α -form and it is evident that the honeycomb hydrogen bonded network of the β -form is more easily accessible to small molecules. Fingerprint plots (Figures 3.7 and 3.11) of the two polymorphs are also comparable, with very slight differences due to a higher number of C–H \cdots π interactions in the α -form.

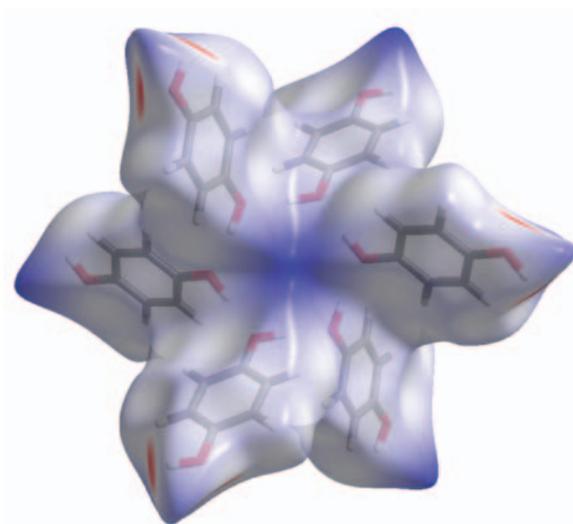


Figure 3.12 Hirshfeld surface depicting the void space created by the hydrogen bonded ring, which is accessible to small molecules for enclathration.

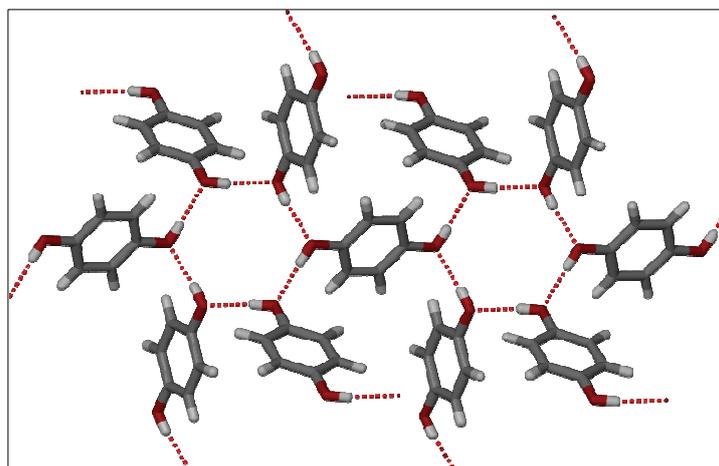


Figure 3.13 Hydrogen bonding motif of β -hydroquinone showing the hexagonal hydrogen bonded voids available for enclathration of small molecules.

3.1.3.c γ -Form (HYQUIN¹²)

The third polymorph of hydroquinone (γ -form) is more distinct from its counterparts. It crystallises in the monoclinic space group $P2_1/c$ with an ASU (Figure 3.14) comprised of two half molecules. Molecule **A** is located on an inversion centre at the origin (0,0,0), and molecule **B** is situated on the inversion centre at $\frac{1}{2}, \frac{1}{2}, 0$.

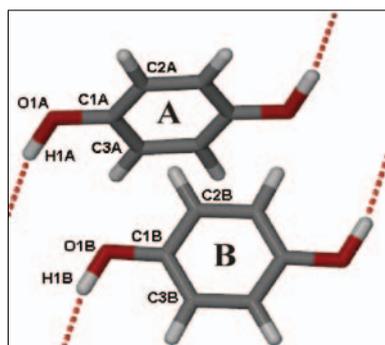


Figure 3.14 ASU of the γ -form of hydroquinone. Only ASU atoms are labelled.

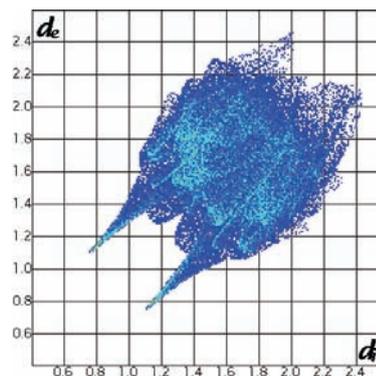


Figure 3.15 Fingerprint plot of γ -hydroquinone

Molecules **A** and **B** each hydrogen bond to symmetry-related instances of themselves to form 2-D layers. Symmetry-independent 2-D layers interact *via* $C-H \cdots \pi$ (Figure 3.17) and $C-H \cdots O$ interactions. The hydrogen bonded array can be described in terms of graph set notation; the primary motif consists of chains, $C_2^2(14)$, with a ring motif, $R_4^4(18)$, making up the network (Figure 3.16). The motif observed in the γ -form of hydroquinone is the most significant one for the subsequent study of hydroquinone co-crystals and is referred to as applicable.

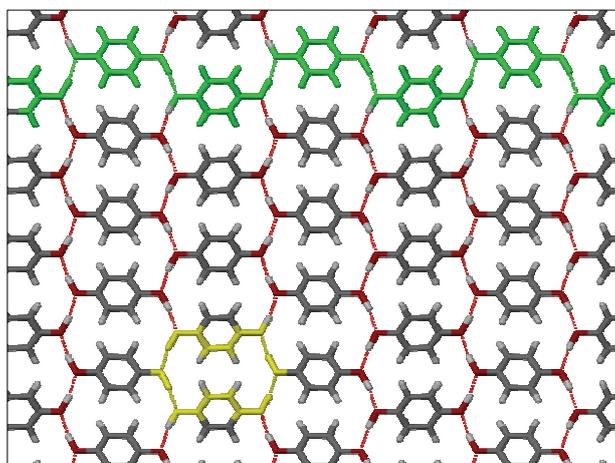


Figure 3.16 One hydrogen bonded layer viewed perpendicular to the bc plane (100); green molecules represent the hydrogen bonded chain $C_2^2(14)$ and yellow molecules represent rings $R_4^4(18)$.

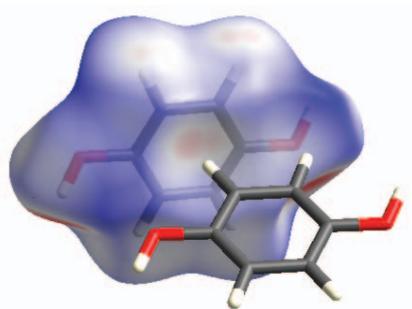


Figure 3.17 Hirshfeld surface of ring **A** in the presence of ring **B**, showing C–H \cdots π interaction.

3.1.4 N2 – Pyridazine (VOBJEB¹³)

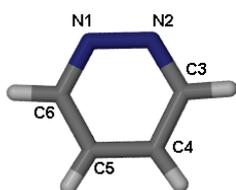


Figure 3.18 The ASU of pyridazine.

The structure of pyridazine has been deposited in the CSD (VOBJEB¹³) and the an entire molecule constitutes the ASU in the monoclinic space group $P2_1/n$ (Figure 3.18). Owing to a lack of strong hydrogen bond donors, weaker interactions of the C–H \cdots N and $\pi\cdots\pi$ types, are expected to stabilise the crystal structure. Stabilisation by only weak interactions leads to a low melting point ($-8\text{ }^\circ\text{C}$) for this diazine molecule such that it is a liquid at ambient temperatures. Pyridazine molecules $\pi\cdots\pi$ stack (offset) into inclined pillars such that molecules in adjacent pillars interact *via* C–H \cdots N interactions. The Hirshfeld surface (Figure 3.19) reveals the atoms involved in intermolecular interactions, and indicates the relative strengths of these interactions. The fingerprint plot (Figure 3.20) clearly depicts the $\pi\cdots\pi$ interactions (the green area on the diagonal at approximately 1.8 \AA), with two short tails indicating C–H \cdots N interactions; H \cdots H interactions dominate the plot.

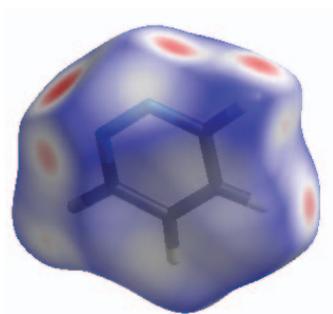


Figure 3.19 Hirshfeld surface of a pyridazine molecule

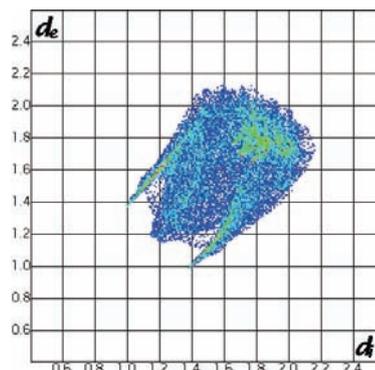


Figure 3.20 Fingerprint plot of pyridazine.

3.1.5 N3 – Pyrimidine (PRMDIN01¹⁴)

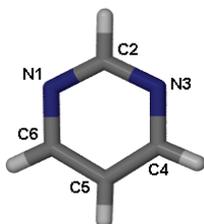


Figure 3.21 The ASU of pyrimidine.

Pyrimidine crystallises in the orthorhombic space group $Pna2_1$ with a complete molecule in the ASU (Figure 3.21). The structure of pyrimidine is somewhat similar to that of pyridazine, exhibiting similar offset $\pi \cdots \pi$ stacks that are inclined such that molecules are oriented for participation in C–H \cdots N interactions. The concentrated red region on the diagonal (1.9 Å) in the fingerprint plot (Figure 3.23) of pyrimidine highlights the importance of $\pi \cdots \pi$ interactions in the structure. Short tails in this plot are characteristic of the C–H \cdots N interactions. The higher melting point of pyrimidine (19–22 °C) compared to pyridazine can be rationalized by the higher level of organisation of the molecules in pyrimidine. This is attributed to the separation of the two nitrogen atoms inducing more favourable charge distribution about the ring, which allows stronger interaction between nearby neighbours.

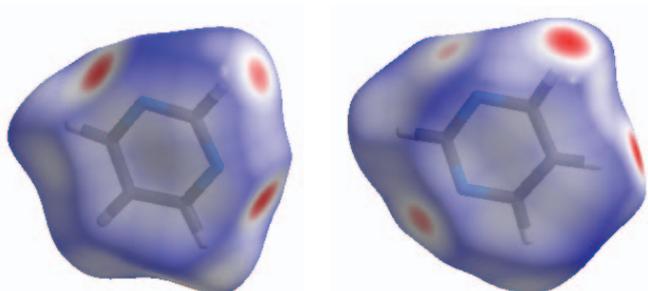


Figure 3.22 Hirshfeld surfaces of the pyrimidine molecule illustrating areas of interaction with neighbouring molecules.

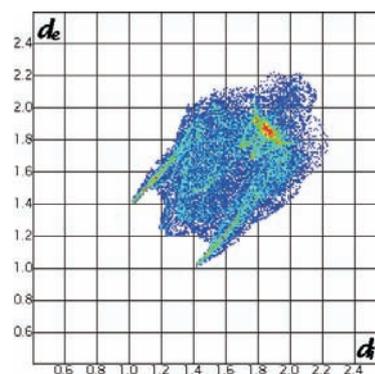


Figure 3.23 Fingerprint plot of pyrimidine

3.1.6 N4 – Pyrazine (PYRAZI01¹⁵)



Figure 3.24 The ASU of pyrazine. Only the ASU is labelled.

The structure of pyrazine was retrieved from the CSD, and shows the molecule to crystallise in the orthorhombic space group $Pmnn$. The molecule is situated on the origin ($2/m$ site symmetry) such that only a quarter of the molecule represents the ASU (Figure 3.24). Analogous to the structures of N2 and N3, pyrazine also makes use of weaker intermolecular interactions such that molecules align themselves for offset $\pi \cdots \pi$ stacking. It is clear from the packing arrangement (Figure 3.27) that this is the least dense (1.306 g cm^{-3}) of the diazine isomers.

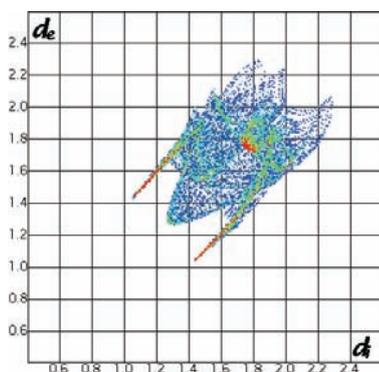


Figure 3.25 Fingerprint plot of pyrazine

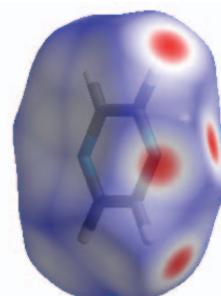


Figure 3.26 The Hirshfeld surface of pyrazine

The C–H \cdots N interactions are more prominent (tails in the fingerprint plot, Figure 3.25) in this structure compared to N2 and N3 and molecules are highly ordered in the solid-state owing to this interaction. The Hirshfeld surface (Figure 3.26) for this structure shows the

complementary red spots indicative of the close C–H \cdots N interactions in which all atoms of the molecule are involved. It is also evident that the C–H groups donate electron density from both above and below the plane of the nitrogen acceptor atoms.

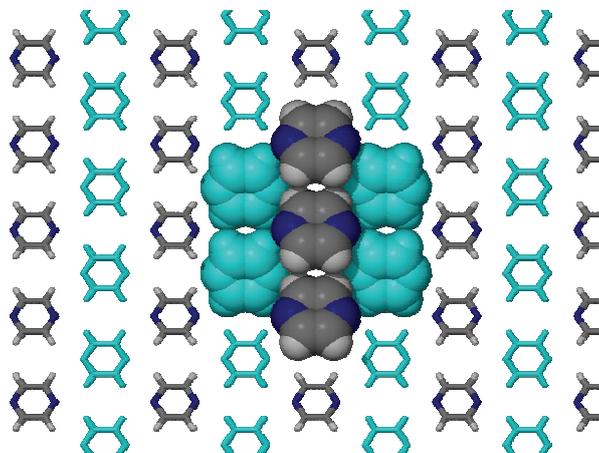


Figure 3.27 Alternating layers of pyrazine viewed down [001]. One layer is shown in light blue, while the other is shown using CPK colours. Molecules represented in space-fill in the centre of the figure illustrate the voids created by the molecules thereby decreasing the density of the structure.

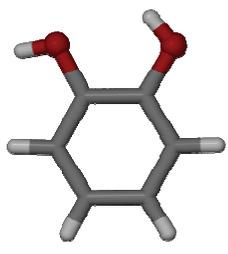
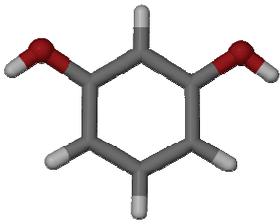
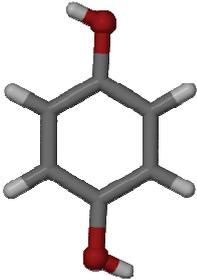
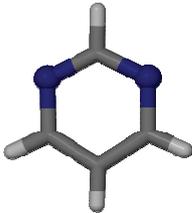
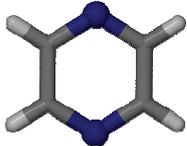
3.2 Co-crystals

Thirteen co-crystal structures, each comprised of two complementary hydrogen bonded molecules, are presented in this chapter. Benzenediol isomers are combined with diazine molecules (Table 3.1), in order to investigate the intermolecular interactions that influence the packing arrangement of the molecules in the solid-state.

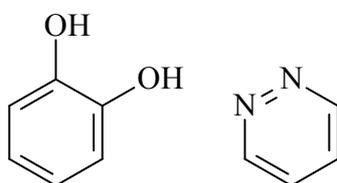
Throughout the study of these co-crystals, comparisons are made with regard to structural motifs and other similarities that arise between the structures. Similarities between pure components and the co-crystal forms are also highlighted. Supporting data are provided by PXRD and DSC analysis of most of the compounds obtained.

Hydrogen bond distances and θ angles can be found in tables in the Appendices. Crystallographic data for each of the co-crystals described here are made available in Table 3.2 at the end of the chapter. The Crystallographic Information Files, included for each structure, provide information regarding the atomic coordinates, bond lengths and angles, torsion angles, thermal parameters and hydrogen bonding parameters, and can also be found in the Appendices.

Table 3.1: Benzenediols and diazines used in co-crystallisation experiments

			
	O2N2 α 2:1 β 1:2	O3N2 1:1	O4N2 α 1:1 β 1:2
	O2N3 1:1	O3N3 α 1:1 β 2:1	O4N3 1:1
	O2N4 2:1	O3N4 α 1:1 β 3:1	O4N4 1:1

3.2.1 O2N2 – Catechol and Pyridazine (2:1 and 1:2 ratios)

**Scheme 3.7** Co-crystal formers catechol and pyridazine

α -O2N2 (2:1)

The ASU of α -O2N2 consists of two molecules of catechol and one molecule of pyridazine (Figure 3.28) in the monoclinic space group $P2_1/c$. The structure was checked for missed

symmetry – however, it was established that the different orientations of the two catechol molecules with regard to the pyridazine molecule are the reason for the large ASU. It is difficult to assign graph set notation to the hydrogen-bonding network since there are two different bonding motifs that appear to overlap. A six-membered adduct is formed by O–H⋯N interactions between two catechol molecules and a single pyridazine molecule, as

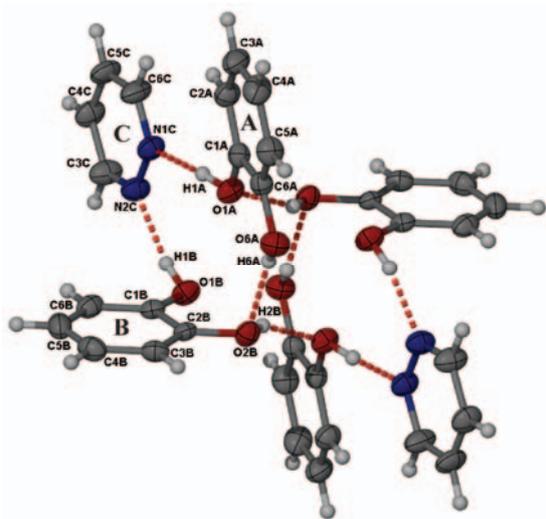


Figure 3.28 Thermal ellipsoid plot of a six-membered adduct comprising of α -O2N2. Only the ASU is labelled.

well as O–H⋯O interactions between two symmetry-independent catechol molecules, thereby yielding a 2:1 ratio of benzenediol to diazine. Because of the departure from a 1:1 ratio, catechol molecules are forced to act as both hydrogen bond donors and acceptors. In this case, only one of the symmetry independent molecules has this duality, while the other acts only as a donor.

The *hexa*-adduct resembles a deformed paddlewheel, with two pyridazine molecules representing a staggered axle, while four catechol molecules constitute the wheel. The paddlewheel lies on a special position $(\frac{1}{2}, 0, \frac{1}{2})$ and “rotates” about the diagonal of the *ac* plane. In order to assign graph set notation, the “paddlewheel” and “axle” (Figure 3.29) are addressed separately. The wheel is constructed from four catechol molecules connected through a hydrogen bonded ring, $R_4^4(14)$, using O–H⋯O interactions. Usually, when assigning bonding patterns, the half axle would be assigned two motifs corresponding to the two types of hydrogen bonds involved. In this instance, it is more practical to treat the half “axle” as one entity. The half “axle”, then, is formed from two O–H⋯N interactions and one O–H⋯O hydrogen bond to form another ring, $R_3^3(13)$. Paddlewheels interdigitate to enable close-packing between adducts, this packing is stabilized by π ⋯ π stacking between pyridazine and catechol molecules of adjacent paddlewheels (Figure 3.30).

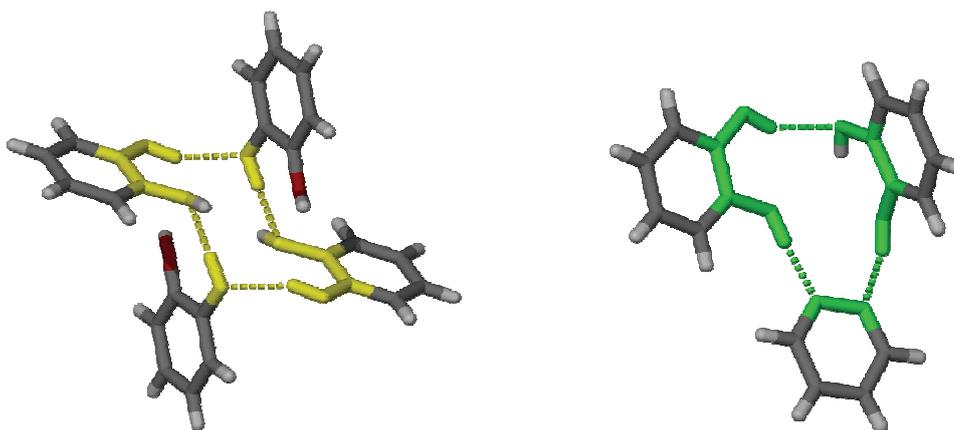


Figure 3.29 Stick representation of O2N2 showing the “paddlewheel” (left), with graph-set notation $R_4^4(14)$ indicated by the yellow atoms. The half “axle” formed by two catechols and a single pyridazine hydrogen bonding in a ring motif, $R_3^3(13)$ (right). Molecules not directly involved in each of these motifs have been omitted for clarity.

The fingerprint plot (Figure 3.31) is generated from a Hirshfeld surface surrounding the entire *hexa*-adduct and can be misleading since it depicts only the intermolecular interactions between adducts. Because all strong hydrogen bonds are saturated in the adduct, only weaker interactions are indicated in the plot *i.e.* the short O–H \cdots O interactions (tails) and possible $\pi\cdots\pi$ interactions between adducts. This highlights the care that should be taken when generating these plots especially when there are multiple components present. However, this also allows the plots to be manipulated somewhat to investigate particular interactions.

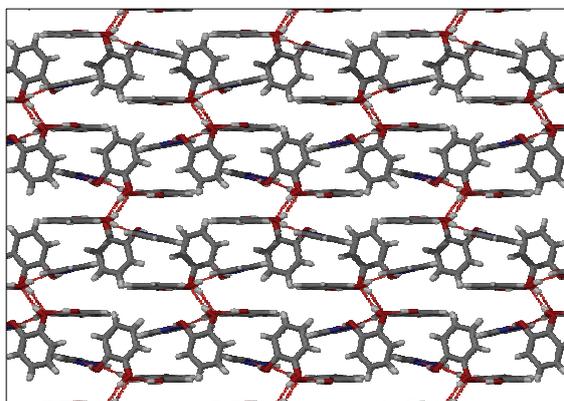


Figure 3.30 Molecular packing of α -O2N2 viewed along the *b* axis.

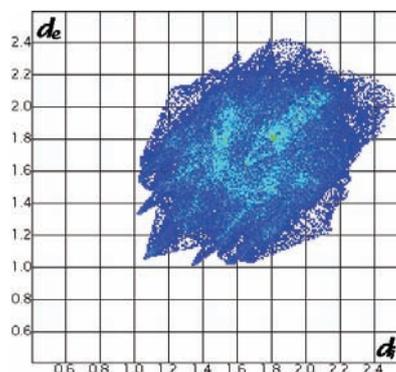


Figure 3.31 Fingerprint plot of the hexa-adduct in α -O2N2.

This structure is somewhat comparable to that of catechol (O2) (Figure 3.3). Although the hydrogen-bonding pattern is dissimilar, the positioning of the catechol molecules that make up the axle is similar to that in catechol. However, the catechol molecules in the co-crystal are forced into a perpendicular position to accommodate formation of the aggregate. Much as in the formation of octahedral coordination geometry, the molecules in this aggregate are positioned such that electron repulsion between them is at a minimum. In addition, it can be