Investigation of the co-crystallisation of N-heterocycles

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motifs established in the first component of the study, it was intended to compare the structures of the first grid with their analogues in the second. Direct comparison of these analogues is not possible in all situations owing, to different molar ratios.

The three co-crystals obtained utilising catechol as the hydrogen bond donor showed remarkable likeness to three of the analogous structures obtained in the first grid. In the structure of O2BN23, catechol adopts the *anti–anti* conformation, hydrogen bonding to two phthalazine molecules to form ternary adducts. These adducts appear to be similar to those formed in *β*–O2N2 (Grid 1). However, owing to increased π⋯π interactions between the larger aromatic rings of phthalazine compared to pyridazine, the adducts form approximately linear strings. It is observed that the structure of O2BN23 is more similar to that of O4BN23 than it is to that of the analogous structure of *β*–O2N2. Different hydrogen bonding motifs in the structures of O2BN3 (chains) and O2N3 (rings) do not prevent these structures from packing in a similar fashion. When viewed along a particular axis, the structure of O2BN3 resembles a quaternary adduct formed in O2BN3. Catechol, once again, adopts the *anti–anti* conformation in the structure of O2BN4 and forms polymeric chains in a 1:1 molar ratio with quinoxaline. The chains pack into a herringbone motif, much as in the structure of O2N4 of the first grid.

Only one co-crystal structure, O3BN4, was successfully obtained utilising resorcinol and a benzodiazine. Resorcinol, in a *syn–syn* conformation, hydrogen bonds to two quinoxaline molecules that are held at a distance ideal for π⋯π interactions between the two benzodiazine rings. This structure resembles the structure of *α*–O3N4 obtained in the first grid.

Hydroquinone adopts the *trans*-conformation in the structure of O4BN23 and hydrogen bonds to two molecules of phthalazine to form ternary adducts. Adducts are similar to those formed in *β*–O4N2. However, owing to enhanced π⋯π interactions between phthalazine molecules, the adducts resemble the packing arrangement in O2BN23 more closely. The fingerprint plots of the four similar co-crystals provide a visual aid that clearly highlights the similarities between the structures (Figure 6.2).

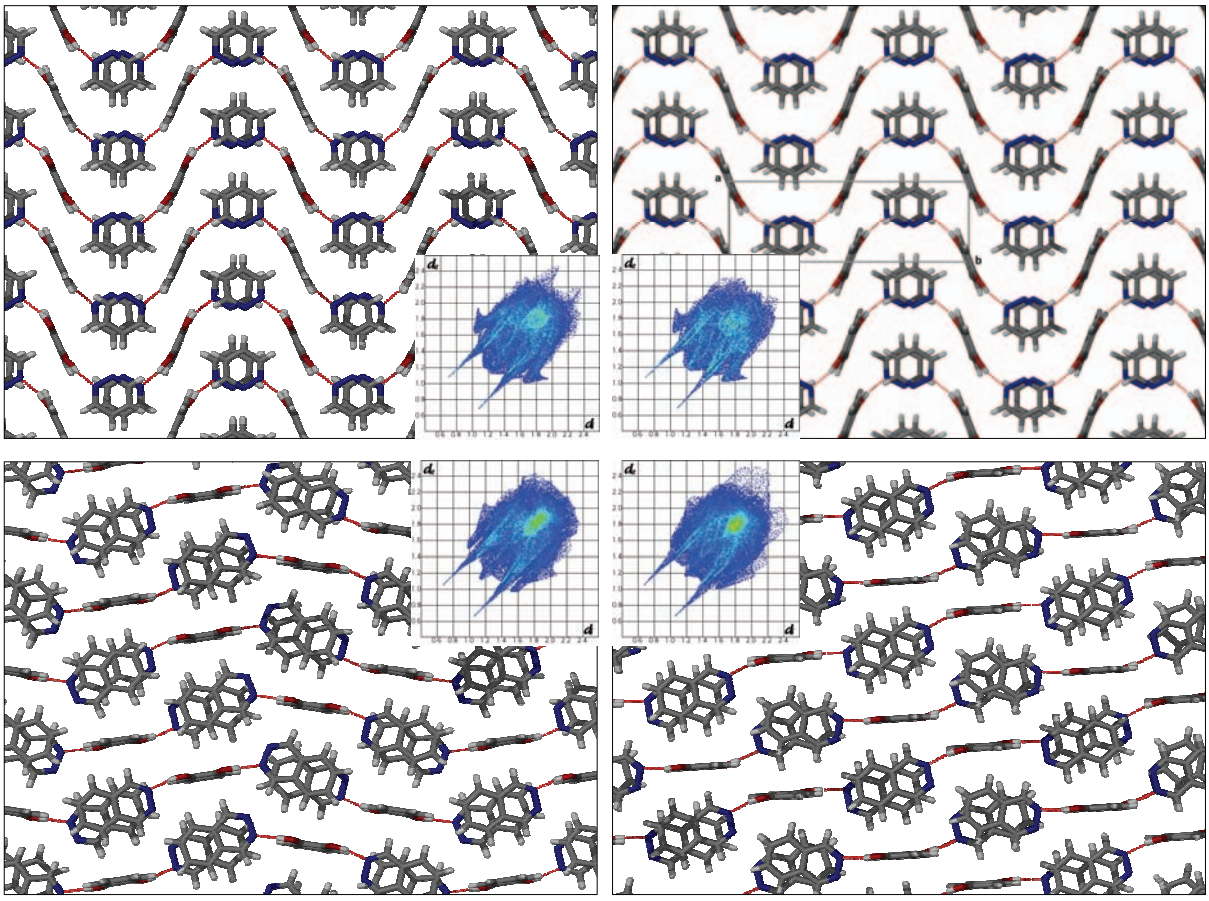

Figure 6.2 Comparison of the co-crystal structures of *β*–O2N2 (top left), *β*–O4N2 (top right), O2BN23 (bottom left) and O4BN23 (bottom right). The fingerprint plots are inset and show the close similarities of the two N2 structures and the two BN23 structures.

Once again the combination of hydroquinone with the 1,3-diazine molecule provides the most intriguing results. In this instance, two structures were obtained from this combination. The *α*–form of O4BN3 yields a co-crystal with a benzodiazine molecule that participates exclusively in weaker intermolecular interactions, forming part of offset, π⋯π stacks with the other BN3 that is hydrogen bonded to hydroquinone. The second structure resulting from this combination contains excess hydroquinone. The hydroquinone molecules in this structure adopt both the *cis*- and *trans*-conformations, leading to the formation of both hydrogen bonded ring (*cis*) and chain (*trans*) motifs. This co-crystal can be compared to O4N3 obtained in the previous grid to a certain extent. While the structures are not obviously similar, they display similar features and the structure of O4BN3 suggests the possibility of both rings and chains existing in the O4N3 co-crystal. The final structure of this 3×3 grid is that of the 1:2 molar ratio O4BN4 that forms hydrogen bonded ternary adducts. These adducts can be correlated to those found in O4BN23 and both pack in a similar manner, maximising π⋯π interactions between benzodiazine molecules, although their orientation in

relation to hydroquinone is different. The BN4 molecules are rotated 90° to the hydroquinone, while BN23 are aligned with hydroquinone molecules.

Although single-crystal structures were not obtained for O3BN23, solvent-drop grinding experiments, analysed by PXRD, showed the formation of new phases for this combination. Comparisons of single-crystal data with PXRD patterns obtained from solvent-drop grinding were made for all crystal structures in this 3×3 grid and a number of new co-crystal phases were obtained in this manner. A mixture of the 1:2 and 2:1 molar ratios was observed in the 1:1 solvent-drop grinding experiments with phthalazine, whereas a 1:2 molar ratio was obtained for all the SDG experiments of O4BN4. This result is somewhat surprising since the BN4 molecules have remotely located hydrogen bond acceptor sites and there appear to be no steric effects preventing a 1:1 molar ratio. A 1:1 molar ratio would be expected to form 1:1 hydrogen bonded chains similar to those observed in the O2BN4 co-crystal. The results of the SDG experiment, however, do not exclude the possibility of the 1:1 co-crystal forming.

The DSC traces of all co-crystals of Grid 1 show that the melting points of all co-crystals occur between the melting points of the two starting materials. The co-crystals of the second 3×3 grid follow the same trend, with the exception of O2BN23 and the 1:2 form of O4BN3, which melt below the melting points of both starting components.

An increase in π⋯π interactions is observed for the larger aromatic rings of the bicyclic benzodiazine isomers compared to the monocyclic diazines. It is not clear whether this is the result of the larger aromatic rings, or whether there are other implications of the hydrogen bond that result in fewer π⋯π interactions of the monocyclic diazines. Most structures showed a preference towards the use of excess benzodiazine in the formation of co-crystals such that the N–atom acceptor sites are unsaturated in terms of strong hydrogen bonds. It can only be speculated that the molecules disregard saturating all possible synthons in favour of a more efficiently packed structure. Further investigation is required in order to provide a more informed explanation.

Somewhat related dinitrogen acceptor compounds have been synthesised with a view to co-crystallise them with the benzenediol isomers utilised in the two 3×3 grids already discussed. Three crystal structures of the ligands were analysed by SCD to elucidate packing motifs of these molecules, all of which exhibit the γ–herringbone motif, with weak C–H⋯N interactions driving the arrangement. A number of similar ligands are being considered for further synthesis.

Future investigations into the co-crystals reported here would involve theoretical modelling to determine the nature of the interactions (stabilising or destabilising) established in this study. From these calculations, it may be possible to determine which interactions steer the packing of the structure. Further examination of the thermal behaviour of these co-crystals is required, coupled with variable temperature PXRD experiments to determine whether structures undergo phase changes. The supramolecular synthon, O–H$\cdots$N$_{arom}$, will be explored further in competition studies with other known synthons in order to establish a hierarchy. Attempts will be made to construct higher order co-crystals i.e. multi-component crystals (ternary, quaternary and higher).

General Observations:

From investigation of the 21 co-crystal structures reported here, there are a number of general observations, which will be discussed briefly. Some of these observations agree with previously reported findings, while others have raised questions that can only be addressed by speculation or by further investigation.

Because both the donor and acceptor molecules in this study have two hydrogen bonding sites, it was anticipated that molecules would interact in a 1:1 molar ratio to saturate all possible binding sites. However, heteromolecules do not always interact in a 1:1 molar ratio. When the diazine molecule is in excess in the motif, only one of the two possible nitrogen acceptor sites is utilised in hydrogen bonding. However, when the donor molecule is in excess, the acceptor sites of the diazine are saturated and donor molecules act as additional H–bond acceptors.

Solvent-drop grinding proved to be highly beneficial in the investigation of these co-crystals. Single-crystals of a number of structures were successfully grown from solutions of the solvent-drop grinding preparations. New or different phases of co-crystals are easily identified during the screening process using PXRD. SDG can also be used as a rapid method for replicating co-crystals that have already been analysed by SCD, resulting, in general, in pure phase co-crystal. Once the single-crystal structure had been elucidated, preparation of pure phase co-crystal could be carried out by solvent-drop grinding that can rapidly be screened with PXRD analysis. There are a number of parameters that should be taken into account in the preparation of co-crystals by solvent-drop grinding: *viz*. grinding time, solvent used (if any), component molar ratio, *etc*. Solvent choice may have an effect on the resulting packing arrangement with the use of polar or non-polar solvents. It may even be possible to force a particular packing arrangement by the use of polar or non-polar solvents.

Because the effect of solvents in solvent-drop grinding techniques is not yet fully understood, this observation is limited to speculation. The amount of time that a sample is subjected to pulverisation may have an impact on the products formed. During the course of the investigation, both manual and mechanical grinding were employed. Because the manual grinding is labour-intensive and the force with which the samples are pulverised cannot be measured (and is difficult to replicate), the results of these experiments vary. An approximate 5 min manual grind often led to incomplete conversion to the co-crystal product. A 10 min grind in the mill, in most instances, resulted in complete conversion. Although, it is observed that a number of the 1:1 ratios result in a mixture of two co-crystal forms. The mixture of two co-crystal forms obtained concomitantly from an initial 1:1 molar ratio is an indication of this. However, it is plausible that one form can be converted to another form by increasing the grinding time. The most important advantage of this technique is by far the speed with which experiments can be performed. This allows a large number of parameters to be tested and the resulting products to be screened rapidly with techniques such as PXRD and DSC *i.e.* high-throughput synthesis. It should, however, be noted that as with all compounds, the protocol determined for a series of co-crystals is not necessarily a universal one. It should also be noted that the product obtained from a particular method of preparation might only be obtained by that method.

Recrystallisation is a daily occurrence in the organic chemistry lab and is usually used to purify compounds as single component crystals. Why then would two components choose to crystallise together in a single lattice? For inclusion compounds, this phenomenon is more easily rationalised since the inclusion of a guest, in most instances, results in a more efficiently packed structure. However, for co-crystals involving only small organic molecules a reasonable explanation is more difficult to formulate. In order for the co-crystal to form in the first place, the formation of the heterosynthon must be more favourable than the homosynthon. So then why does the O–H⋯N hydrogen bond form over the O–H⋯O hydrogen bond? What exactly is more favourable? Thermal analysis of the co-crystals in this study showed, in general, that the co-crystals are, thermally less stable than their respective homomeric benzenediol components. Therefore, another form of stabilisation must account for co-crystal formation being favourable. Perhaps there is a gain in structural order, *i.e.*, the gain in entropy of crystallisation outweighs the concomitant loss in enthalpy. The majority of the DSC results showed that the co-crystal melts at a temperature intermediate between those of the starting materials. However, this may be a compromise for the two components, finding the most stable relationship for both to co-exist in the crystal form.

The exclusion of solvents from the structures of the co-crystals reported here is somewhat surprising. This is difficult to predict and many factors may contribute to solvent inclusion in the crystal structure. Solvents used in this study are all capable of H–bond coordination, acting as either hydrogen bond donors and/or acceptors (methanol, ethanol, water, acetone, acetonitrile). The inclusion of solvents sometimes serves to fill spaces created by a host compound (host:guest compound) that is unable to pack efficiently in its pure form. The nature of the solvent (polar or non-polar) may play a role in the formation of a particular arrangement of a compound. The solvent used may be crucial to the outcome of the crystallisation as the solvent polarity may also have an impact on the arrangement of the molecules prior to crystallisation. In this study, the absence of solvent may be due to the small heteromolecules being complementary such that no solvent accessible spaces are available. The rigidity of the aromatic molecules may also pre-empt the inclusion of solvent, resulting in a more organised structure than if solvent were included. Indeed, the shapes of the molecules may have an influence on the inclusion or exclusion of solvent molecules. It is possible that the disc-shaped aromatic molecules prefer to pack with one another rather than with the tetrahedron of MeOH, for example. The inclusion of solvent may also lead to less stable structures since solvents are prone to evaporate from the structures owing to a lower boiling point than the diazine molecules. The aliphatic alcohols used as solvents are also known to be less acidic than phenolic alcohol moieties. Therefore, in the presence of phenolic molecules, the aliphatic alcohols will not be the strongest donor molecules. Although solvent is absent in the structures reported here, it does not mean that they cannot be included.

Theoretical modelling of the structures obtained in this study may provide a better understanding of the formation of these compounds. Any trends determined in this manner may then be implemented in future studies. Energy contributions and the stabilising nature of each intermolecular interaction can be particularly useful in the design of new components for co-crystals.

The occurrence of polymorphism of one or both components has been suggested to improve the likelihood of co-crystals forming, owing to the apparent flexibility of the molecule. This restricts the number of molecules that can be screened as potential co-crystallising agents. Polymorphism in these compounds should be carefully considered since a number of structures are designated as polymorphs based on different space groups and unit cell parameters, although their packing arrangements are the same. Polymorphs of this type are often not good candidates for co-crystal formation. Structural flexibility in

polymorphs is considered a more important aspect when selecting suitable co-crystal components. In this study, molecules with different conformations were shown to form co-crystals. Therefore, polymorphism is not necessarily a prerequisite for co-crystal formation. Rather, structural flexibility should be used to screen for co-crystal components.

The conformations of the three benzenediol isomers lead to contrasting hydrogen bonding patterns. The *syn–anti* conformation of catechol can be involved in formation of discrete adducts or chains owing to donors located at 1,2-positions about the aromatic ring. The *anti–anti* conformation is involved in discrete ternary adducts or hydrogen bonded chains. The differing patterns are most evident in the structures containing resorcinol. The *syn–syn* conformation enforces narrow motifs *i.e.* discrete hydrogen bonded rings or adducts that are held in position for maximising π⋯π interactions. The *syn–anti* orientation results in hydrogen bonded chains, while the *anti–anti* conformation results in more open frameworks. The *trans*–conformation of hydroquinone results in hydrogen bonded chains or unsaturated adducts, while the *cis*–conformation leads to a hydrogen-bonded ring formation.

Solvent-drop grinding experiments could be carried out to investigate competition between diazine molecules. In these studies, a co-crystal such as α–O2N2 could be ground in the presence of pyrazine to determine whether the pyrazine molecule is able to displace the pyridazine molecule. A positive result would reaffirm the robustness of the hydroquinone arrangement in the solid-state.

Although one of the four graph set descriptors can be used to describe the structures reported in this text, they have not been overly useful in the comparison of similar structures in this study. They may be instructive in determining similar hydrogen bonding motifs in co-crystals that exhibit analogous molecules; however, these structures are not always found to be similar in their packing arrangements. The degree (n) of the descriptor takes into account the number of atoms making up a particular pattern. This then results in contrasting degrees (n) for the different isomers. However, the isomers of this study have been observed to produce similar packing arrangements *e.g.* the structures *β*–O4N2 and O4BN23 have the same graph set notation, as do the structures *β*–O2N2 and O2BN23. However, it was established that the structures *β*–O4N2 and *β*–O2N2, and O2BN23 and O4BN23 are more similar in terms of their packing arrangements. Therefore, in this study graph set notation is somewhat misleading for structure comparisons and fingerprint plots are far more appropriate. It was found that the structures that seemed most similar visually do not have similar graph set notations differing mainly in the degree of the descriptor.

To date, the current literature has not produced a systematic study of co-crystals such as the one described here. A study of this nature has allowed observations that might otherwise have gone unnoticed, and correlations have been drawn between structures that appear somewhat unrelated. This investigation, therefore, contributes to the understanding of intermolecular interactions in the field of crystal engineering. With many questions still unanswered, co-crystals will remain an area of wide interest. It is believed that research on co-crystals is gaining momentum and such research is predicted to have a significant impact on the development of crystal engineering and the pharmaceuticals industry by extension. A substantial increase in the number of patent applications is anticipated in the near future with the employment of co-crystals in pharmaceutical formulations.

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APPENDICES

Supplementary data are provided on the Appended CD.

.res can be used to visualise the structures and packing features using an appropriate program such as X-Seed.

.CIF contains crystallographic data regarding atomic coordinates, thermal parameters, and bond lengths and angles.

Appendix A – Strong hydrogen bonds of the co-crystals obtained in Chapters 3 and 4

Appendix B – Selected intermolecular interactions of co-crystals O2N2 – O4N4

Appendix C – Selected intermolecular interactions of co-crystals O2BN23 – O4BN4

Appendix D - Selected intermolecular interactions of synthesised Ligands 1 and 2

Publications and Poster presentations are also included on the CD.