Investigation of the co-crystallisation of N-heterocycles

By

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at

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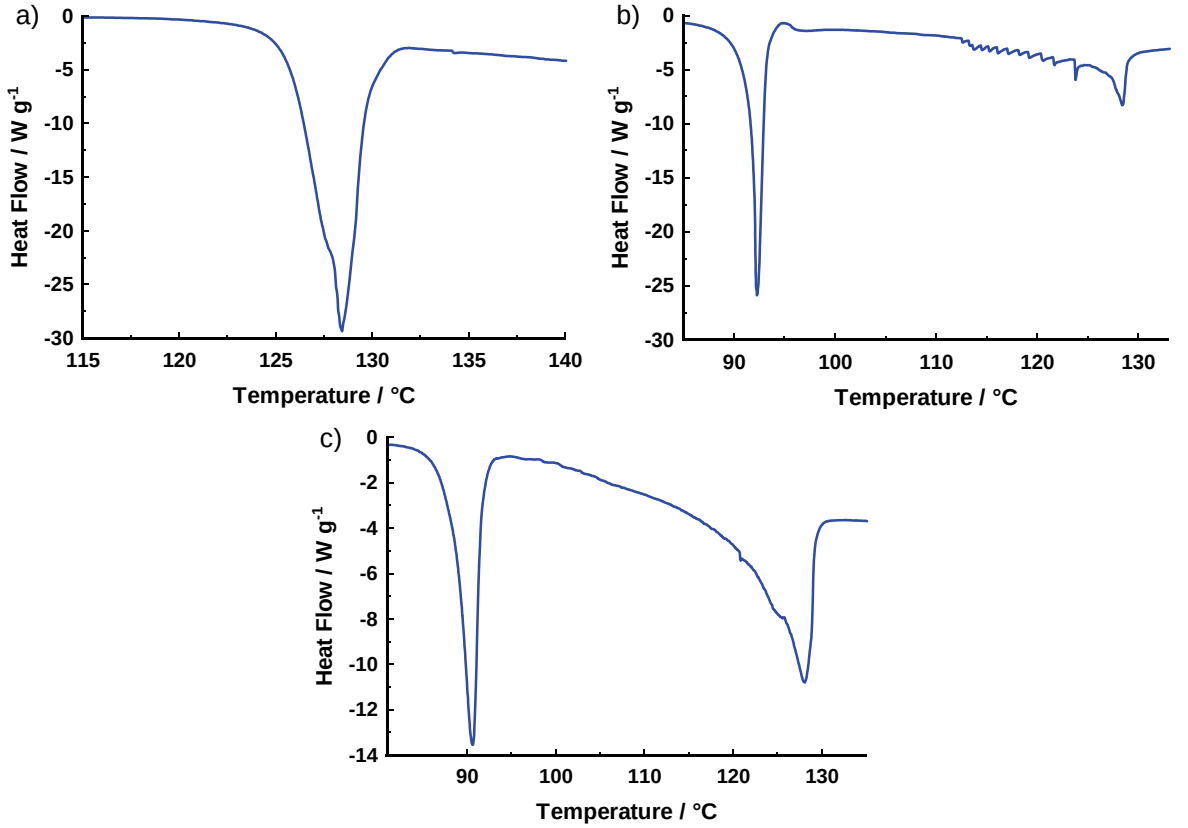
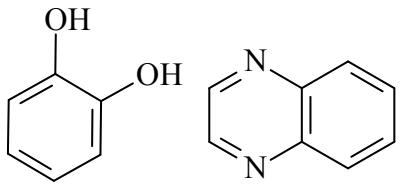


Figure 4.36 DSC trace of a) 2:1, b) 1:2 (top right) and c) 1:1 (bottom) SDG products of O4BN3.

4.2.7 O2BN4 – Catechol and Quinoxaline (1:1)



Scheme 4.8 Co-crystal formers catechol and quinoxaline

O2BN4 crystallises in the monoclinic space group, $P2_1/c$ with its ASU comprising one molecule each of catechol and quinoxaline (Figure 4.37). Catechol and quinoxaline molecules hydrogen bond, *via* the O–H⋯N synthon, to form chains, $C_2^2(10)$, that propagate along the *a* axis. Hydrogen bonded chains stack along [010] forming 2-D sheets parallel to the *ab* plane. Two adjacent sheets are 'sandwiched' together by π⋯π stacking between catechol and the diazine moiety of the quinoxaline molecule. These 'sandwiches' are stabilised by C–H⋯π interactions between the benzene moiety of quinoxaline and catechol molecule of an adjacent sandwich. Individual sheets fit together to maximise close-packing, forming a pattern that repeats every fourth layer *i.e.* ABCDABCD (Figure 4.39, right). The

existence of C–H⋯π interactions is evidenced by the characteristic wings in the fingerprint plot (Figure 4.38).

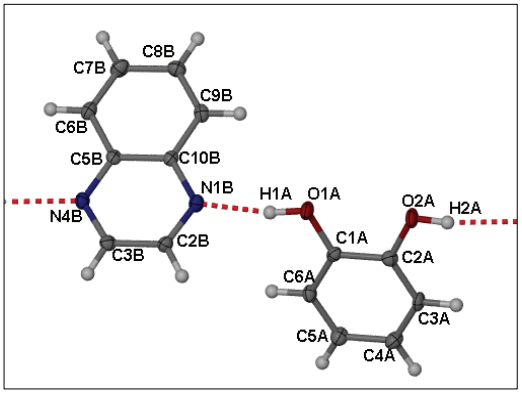


Figure 4.37 Thermal ellipsoid plot of the ASU of O2BN4.

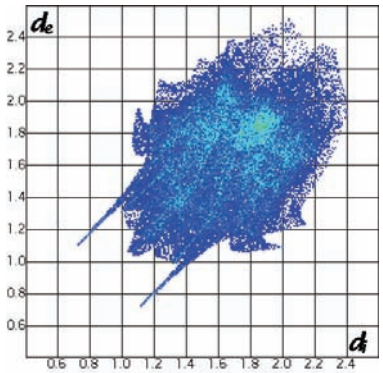


Figure 4.38 Fingerprint plot of O2BN4.

Within each zigzagged sheet, catechol molecules are aligned in the same direction as shown in Figure 4.39 (left). This differs from the arrangement of catechol observed in O2BN2 (Figure 4.12) where the molecules were aligned in alternating columns. It is difficult to compare the structures of O2BN4 and O2N4 (Chapter 3) since the molar ratios are different, consequently having differing packing arrangements. However, both form hydrogen bonded chains. The conformation of the catechol molecules in each structure is different. In O2N4, catechol adopts the *syn–anti* conformation such that it bonds to both a symmetry-independent instance of itself as well as a pyrazine (N4) molecule. The *anti–anti* conformation is preferred in the structure of O2BN4, resulting in a 1:1 hydrogen bonded chain.

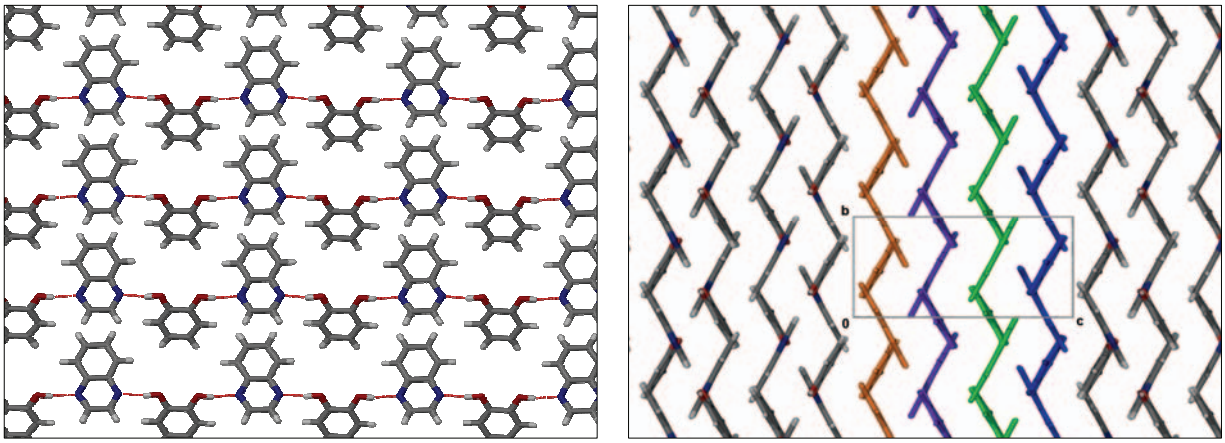


Figure 4.39 The packing diagram of a single layer of O2BN4 viewed perpendicular to the *ab* plane (left). This view shows the polar alignment of the catechol molecules. The zigzag layers stack in an ABCDA pattern (right).

Remarkably, the only two structures in this series that hydrogen bond in a 1:1 molar ratio have similar unit cell parameters (differing only in β angle, Table 4.2) and pack in a similar manner (Figure 4.40). Although, the tapes in O2BN3 are not identical in form to the chains in O2BN4, they arrange themselves in a similar manner. The packing of O2BN4 involves both face-to-face and edge-to-face $\pi\cdots\pi$ interactions between adjacent sheets. However, O2BN3 utilises face-to-face interactions within the same hydrogen bonded tape, and edge-to-face interactions are involved between adjacent tapes.

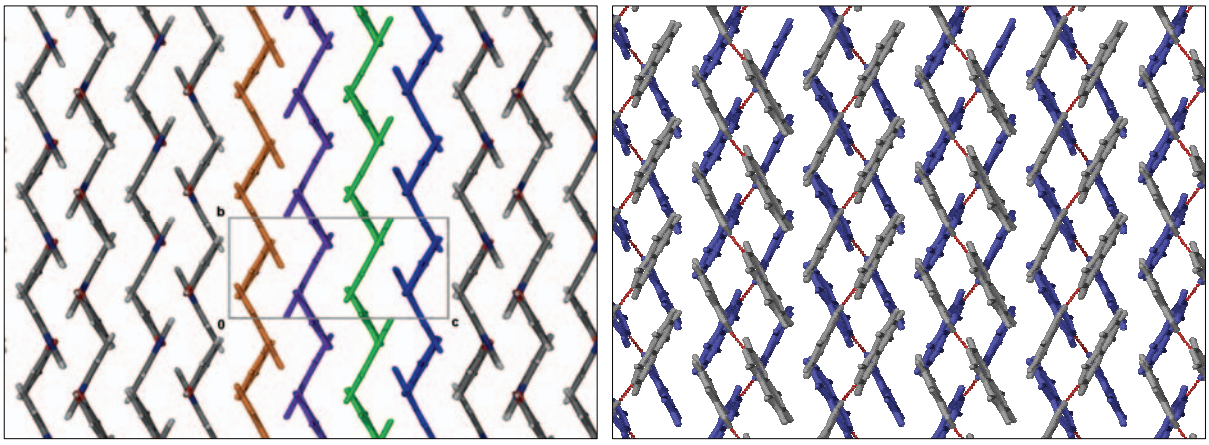


Figure 4.40 Comparison of a single layer of O2BN4 (left) with a layer of tapes assembled in O2BN3 (right). Both structures show a similar packing arrangement of chains and tapes.

The diffractogram simulated from the single-crystal data of O2BN4 is comparable to a 1:1 SDG product (Figure 4.41), which is somewhat expected based on the molar ratio in the crystal structure. However, the crystal was prepared from a solution of a 1:2 SDG product whose PXRD diffractogram is not comparable to the simulated diffractogram. A third product was prepared from a 2:1 molar ratio of O2 and BN4.

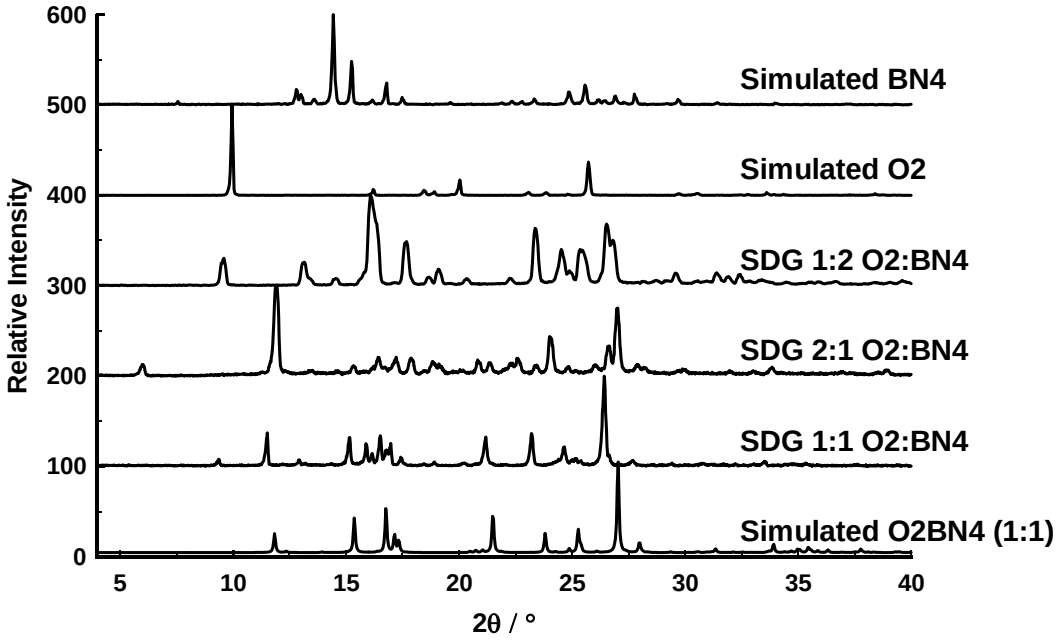


Figure 4.41 PXRD comparison of varying molar ratios of SDG experiments with the simulated pattern of O2BN4.

Thermal analysis (Figure 4.42) of the material corresponding to O2BN4 shows two closely related thermal events, with a near identical trace observed for the product prepared with excess catechol. Onset of the first event is at 82 °C with the second commencing during the upward curve of the first, at approximately 86 °C. The third product (1:2) has a single thermal event with an onset temperature of 84 °C. From these results, the three products appear to be closely related. It is speculated that the two thermal events observed in the same sample are due to one of three possibilities: (1) the product converts from a kinetic product to the thermodynamic product; (2) the product converts from one molar ratio form to one with a different molar ratio – or a polymorph of either of these forms – or (3) the sample is a mixture of two forms and the two events are the result of overlapping melting points. Further investigation is required to provide an empirical explanation for this observed phenomenon.

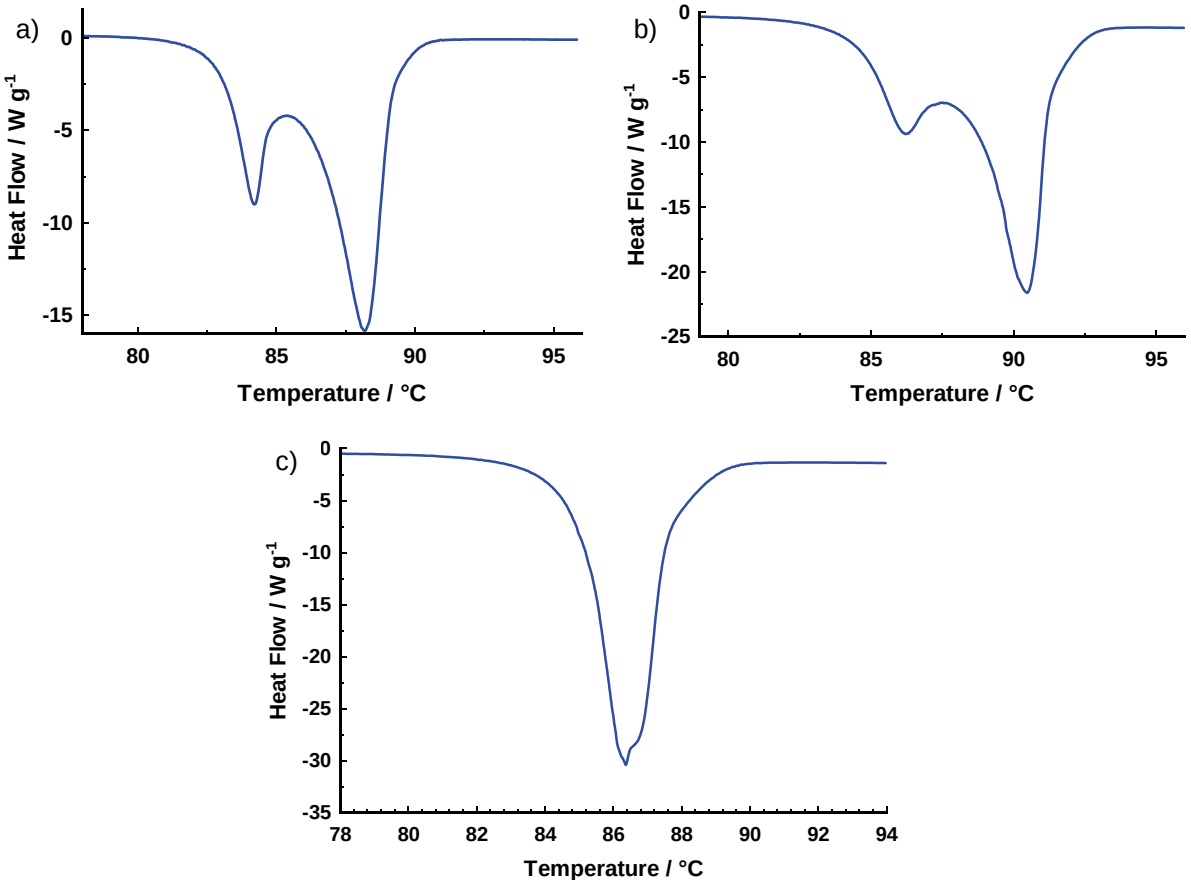
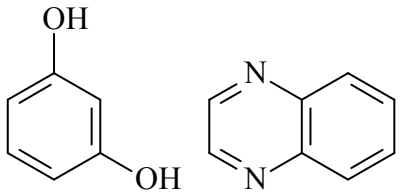


Figure 4.42 DSC trace of a) 1:1, b) 2:1 and c) 1:2 SDG products of O2BN4

4.2.8 O3BN4 – Resorcinol and Quinoxaline (1:2)



Scheme 4.9 Co-crystal formers resorcinol and quinoxaline

The co-crystal of O3BN4 crystallises in the monoclinic space group, *C*2/*c*. The resorcinol molecule is located on a two-fold rotation axis ($\frac{1}{2}$,y,$\frac{1}{4}$) such that only half the molecule is present in the ASU, along with an entire molecule of quinoxaline. A second, symmetry-generated, quinoxaline molecule hydrogen bonds to resorcinol to form a ternary adduct (Figure 4.43). In this instance, only one of the two nitrogen atoms on the quinoxaline molecules is utilised in the O–H⋯N hydrogen bonds. The 'unused' acceptor atoms are involved in C–H⋯N interactions with a resorcinol molecule of an adduct translated along the *b* axis (Figure 4.45, right).

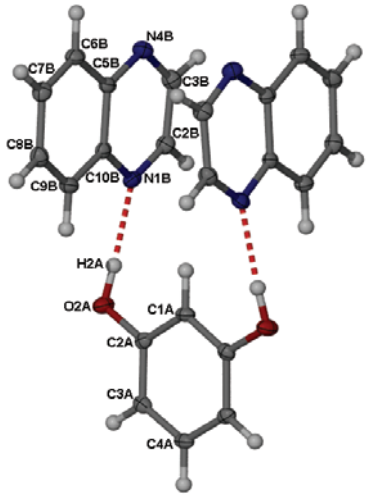


Figure 4.43 A thermal ellipsoid plot showing the ASU of co-crystal O3BN4. Only the ASU atoms are labelled

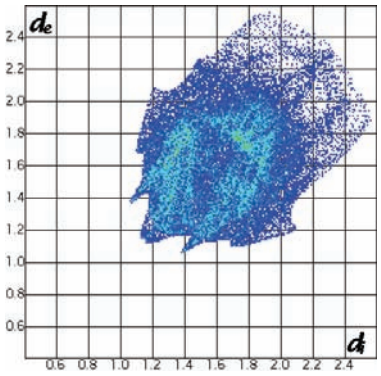
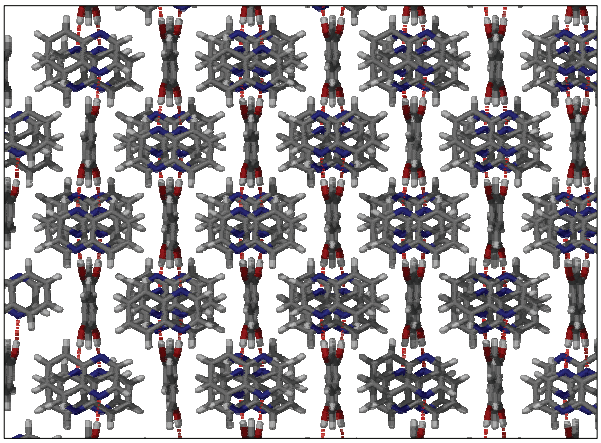
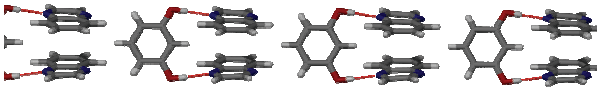


Figure 4.44 Fingerprint plot of O3BN4.

Resorcinol molecules steer quinoxaline into an *anti*-parallel orientation, facilitating favourable π⋯π stacking association between quinoxaline molecules. Direct comparison between the structures of *α*–O3N4 (Chapter 3) and O3BN4 cannot be made owing to differences in molar ratios. However, resorcinol molecules are in the *syn–syn* conformation in both structures. The increased size of the quinoxaline molecule compared to that of pyrazine (N4) has obvious structural effects in their respective co-crystals. In *α*–O3N4 (Chapter 3), molecules are assembled into discrete quaternary adducts with the pyrazine molecules being slightly offset for stable π⋯π stacking. A similar scenario is observed in O3BN4 with the quinoxaline molecules orientated anti-parallel and slightly offset for π⋯π stacking. The quaternary adducts of α–O3N4 are less efficiently packed (density = 1.35 g cm^{-3}) than the unsaturated hydrogen bonding structure of O3BN4 (density = 1.40 g cm^{-3}). Therefore it appears that the O3BN4 co-crystal opts for a more efficiently packed structure over saturating hydrogen bond options. The 1:1 quaternary adduct may be possible with quinoxaline molecules – however, packing would arguably be less efficient owing to the benzene moiety of quinoxaline protruding out of the adduct.





A column viewed along [10-1]

Figure 4.45 Packing of O3BN4 viewed along [101].

Solvent-drop grinding experiments were set-up in three different molar ratios. The simulated diffractogram of O3BN4 is compared to the experimental PXRD patterns of the three SDG experiments. The diffractogram of 2:1 molar ratio product is comparable to the simulated pattern, as can be expected from the molar ratio of the crystal structure (Figure 4.). The diffractograms also indicate a second co-crystal formed when resorcinol and quinoxaline are co-ground. This product forms irrespective of the amount of resorcinol used, as long as quinoxaline is not used in excess. It is, of course, impossible to predict a hydrogen-bonding pattern for the crystal structure corresponding to this diffractogram. However, it is plausible that the molecules might hydrogen bond in a 1:1 ratio to form discrete rings as seen in the structure of α–O3N4 (Chapter 3) although there is a possibility of hydrogen bonding chains forming.

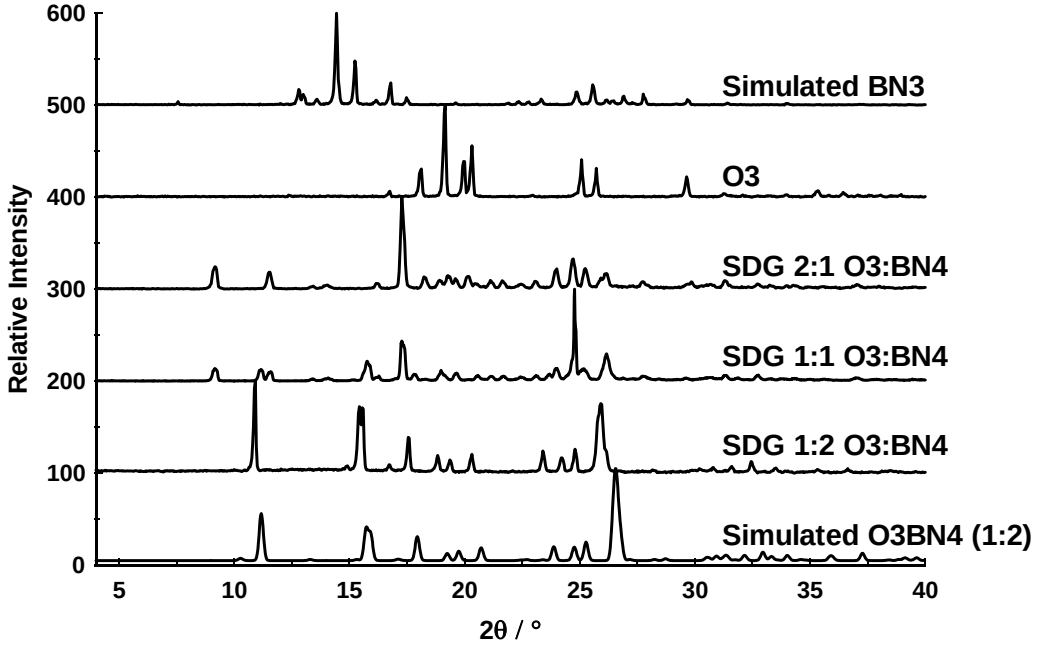


Figure 4.46 PXRD analysis of SDG experiments performed with three different molar ratios of resorcinol and quinoxaline compared to the simulated pattern of co-crystal O3BN4.

The results of the DSC analysis (Figure 4.47) of O3BN4 yielded multiple thermal events. Conclusions could not be drawn from these results and insufficient quantities of sample made the results irreproducible. Contamination of the sample or reference pan is a possible cause for this result. The second co-crystal, whose structure is yet to be determined, shows two distinct events in the DSC analysis; the first has an onset temperature of 66 °C and the second has a large range starting at 80 °C. Neither of these phase changes coincides with either of the starting materials (resorcinol at 110 °C and quinoxaline at 29-32 °C), supporting the formation of a new co-crystal. Without further investigation, comment on the nature of the phase changes is limited to speculation. The two phase changes may be the result of a kinetic product converting to a more stable thermodynamic product, and subsequently melting at the higher temperature. Variable temperature PXRD analysis would possibly verify the conversion of the one product into the other, although the molar ratios and subsequent hydrogen bonding patterns can only be established from a single-crystal structure.