CRYSTAL GROWTH & DESIGN

Subscriber access provided by Vanderbilt Libraries

Article

Co-crystals: solution, mechanochemistry and sublimation

Thalia Carstens, Delia A. Haynes, and Vincent J. Smith

Cryst. Growth Des., **Just Accepted Manuscript** • DOI: 10.1021/acs.cgd.9b01450 • Publication Date (Web): 27 Dec 2019

Downloaded from pubs.acs.org on December 28, 2019

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Co-crystals: solution, mechanochemistry and sublimation.

Thalia Carstens[a], Delia A. Haynes[a] and Vincent J. Smith[b*]

a. Department of Chemistry and Polymer Science, Stellenbosch University, P. Bag X1, Matieland, Stellenbosch, 7602, South Africa.
b. Department of Chemistry, Rhodes University, PO Box 94, Grahamstown, 6140, South Africa.

Abstract

A systematic study of the effect of crystallization method on the resulting solid-state form of a series of organic co-crystals has been carried out. Co-crystals of *p*-benzoquinone (BQ) and one of four monosubstituted *p*-halophenols were made by crystallization from chloroform, co-sublimation *in vacuo,* and neat grinding. Co-crystals with both 1:1 and 2:1 donor-acceptor ratios can be prepared from all four BQ-halophenol combinations. Here we report the preparation of four new co-crystals of BQ with either 4-fluorophenol or 4-iodophenol. In the case of the 1:1 4-fluorophenol-BQ co-crystal, different polymorphs were isolated by recrystallization from solution and co-sublimation. Sublimation is shown to be an important technique in accessing the phase space of co-crystals.

Introduction

The physicochemical properties of solid (crystalline) materials are strongly dependent on how the atoms, ions or molecules that make up these materials arrange in the solid state. Since X-ray diffraction (powder and single-crystal), thermal analysis and spectroscopy are still our most important methods for characterizing the solid state, it is important to produce crystalline materials of high quality suitable for these methods.[1,2] Of higher importance still is the discovery and characterization of new solid phases such as polymorphs, co-crystals, solid solutions and various other crystalline forms.

Polymorphism is of particular interest to pharmaceutical chemists,[3–6] in non-linear optics,[7,8] for molecular electronics[9–12] and in many other areas. The different packing arrangements of polymorphs are usually associated with differences in intermolecular interactions, which often result in different bulk properties. In general, the importance of intermolecular interactions in the occurrence of new phases cannot be understated, especially for systems such as co-crystals. Co-crystals are an alternative to polymorphism for phase modification, and for the generation of physical and chemical properties which differ from those of the starting materials.[13] Co-crystals are essentially crystalline single-phase materials made up of two or more different molecules in a stoichiometric ratio.[14] Co-crystallization has become a preferred method for altering the bulk properties of compounds since the effects of co-crystallization can be quite pronounced.[15] Co-crystallization is facilitated by taking advantage of the inherent directionality and selectivity of many noncovalent interactions.[16] However, even a deep understanding of these structure-directing interactions does not always result in successful co-crystallization; in other words, whether or not a particular co-crystal will form under certain experimental conditions is not predictable.[17,18] Many factors, both physical and chemical, contribute to successful co-crystal formation and it is rather unsurprising that the method of preparation has some impact on the outcome of a co-crystallization experiment.[19–21] It is for this reason that crystal growth techniques are constantly being discovered, modified and refined in order to access new phase space.

Crystal growth by recrystallization from solution remains the most common approach, but a number of other methods have come to the fore.[22] These methods include melt recrystallization,[23] vacuum[24] and in-air sublimation,[25] crystallization in micro-emulsion droplets,[26] crystallization in small molecule organogels[27] and so forth. Mechanochemical methods (both neat and liquid assisted grinding) are also used to access new phases, even though the products of these methods are usually polycrystalline and require further processing in order to obtain single crystals for X-ray diffraction.[28]

Growing single crystals by sublimation is still comparatively unexplored, even though almost two thirds of all pure organic compounds sublime.[29] However, this method has several advantages: it greatly simplifies separating out impurities, is easily tuneable, fast and can produce diffraction-quality crystals. Moreover, sublimation eliminates the need for solvent considerations and allows for the molecules of interest to interact directly with each other.[30] As with any crystallization process, new solid-state forms may be isolated during sublimation, such as apohost phases, polymorphs, gas-solid inclusion complexes and even co-crystals.[2,30–37]

Preparing co-crystals by the co-sublimation of two or more different molecules was initially considered a difficult task owing to the possibility that the individual components may exert very different vapour pressures and would therefore have very different sublimation temperatures. However, with a suitably well-designed apparatus this hindrance can easily be overcome.[32] Furthermore, the literature with respect to co-sublimation is rather sparse with only limited accounts on this topic.[2,13,18,24]

In this work, we have investigated the formation of co-crystals between *p*-benzoquinone (BQ) and four different halophenol co-formers by co-sublimation, along with other more common crystallization methods. We aimed to establish whether these co-crystals could be produced by sublimation, and if the forms obtained would be the same as that obtained using solution crystallization or mechanochemistry. We therefore carried out a systematic investigation of the effect of crystallization method on stochiomorphic and polymorphic variation in the BQ-halophenol system. The choice of BQ as the primary molecule in this investigation is because BQ is known to readily co-crystallize with a variety of small organic molecules such as *bis-β*-naphthols,[38–41] and it easily sublimes. Owing to its high vapor pressure, co-crystals with BQ are known to readily form simply by being in contact with a co-former, and without grinding. Kuroda *et al.*[42] have termed this phenomenon co-crystallization through '*molecular diffusion*'. Co-crystal formation by molecular diffusion is known to be a slow process, and mechanochemical grinding speeds up this process. However, since these co-crystals form by diffusion through the vapour phase, we hypothesized that co-crystallization by co-sublimation of the components would be an effective and potentially faster method of forming multicomponent materials with BQ.

In 1967, Shipley *et al.* reported the synthesis of four co-crystals formed between BQ, the common component, and 4-chlorophenol (ClP) or 4-bromophenol (BrP) as the accompanying co-former.[43,44] Each combination has both a 1:1 and a 2:1 stoichiometric form (stoichiomorphs). The 1:1 {BrP}{BQ} and {ClP}{BQ}[i] co-crystals are isostructural to one another, as are the 2:1 forms. We decided

---

[i] Curly brackets indicate co-crystals.

to investigate co-crystallization by sublimation using the Shipley *et al*. series, while also completing the set by using all four halophenols.

Results and Discussion

In this study, three methods for preparing co-crystals of BQ and four *p*-halophenols were investigated: i) mechanochemical neat grinding using a mortar and pestle, ii) recrystallization from solution (ex chloroform) and, iii) co-sublimation. In order to create a sublimation environment that is tuned to the properties of each co-former, a co-sublimation apparatus was designed to allow for co-crystallization using this method. The two co-formers (BQ and a halophenol) are heated and sublimed at different temperatures. Both components are driven into the gas phase simultaneously, crystallizing in the upper (cooler) parts of the apparatus, affording a degree of control over the co-sublimation environment (conditions). Details of this apparatus, and of all crystallization methods, are given in the experimental section (see also Figure S1, ESI). Nine co-crystal forms were characterized in this system and are summarized in Figure 1.

To allow for appropriate comparison, co-crystals prepared by Shipley *et al.*[50,51] were also prepared using the same methods as previously reported, and X-ray diffraction data were re-collected. We observed interesting spectroscopic behavior upon formation of the co-crystals in the form of a distinct color change. According to Shipley *et al.*[50,51] these co-crystals are charge transfer complexes and the observed color changes are evidence thereof. The 4-halophenols (HP) are the charge donor molecules (CD) and BQ is the charge acceptor molecule (CA). Two different co-crystal stoichiometries were observed (1:1 and 2:1 CD:CA ratios) as bright orange- and deep red-colored crystals, respectively. In this text, co-crystals with 1:1 ratios are denoted by the co-crystal code followed by the letter **a**, while the 2:1 co-crystals are indicated by the letter **b** (Fig. 1).

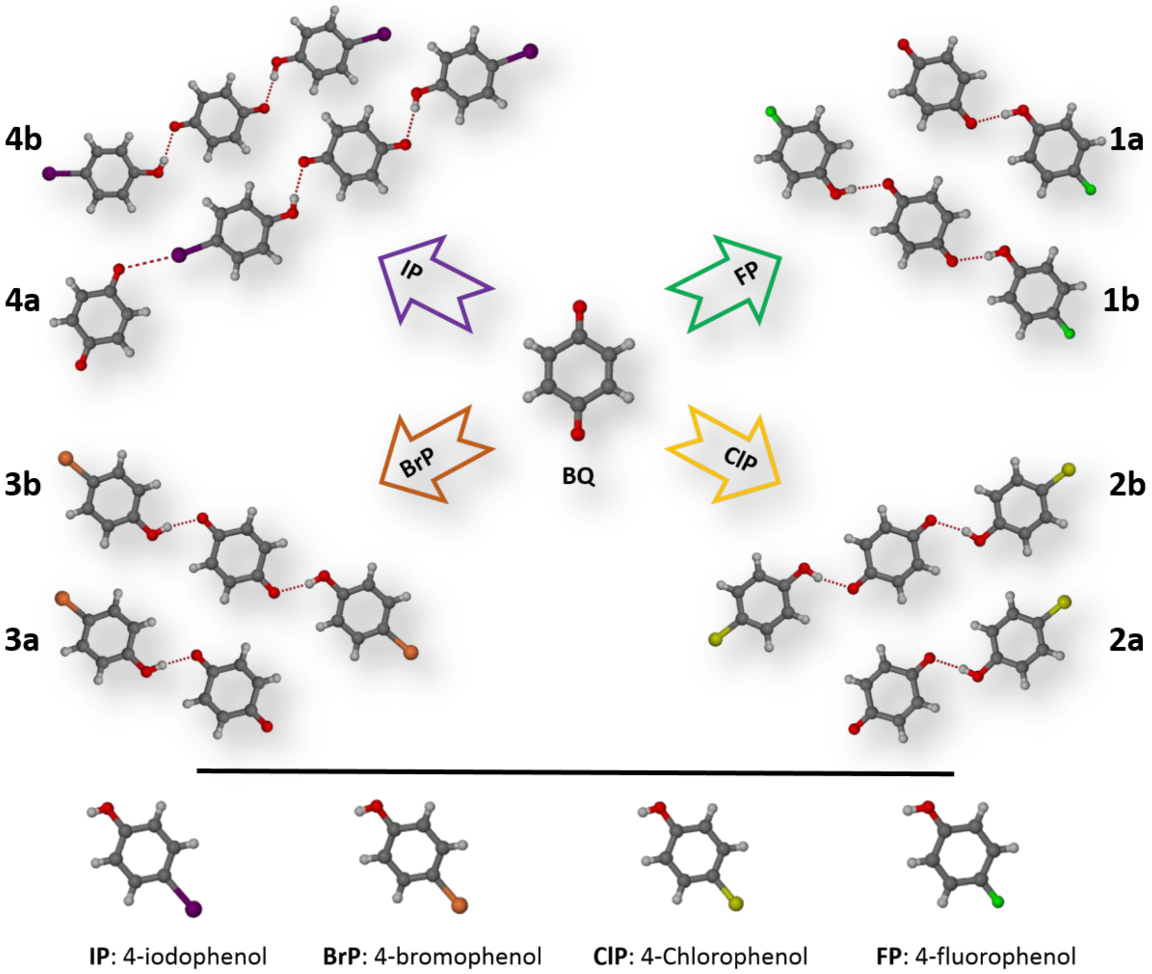


Figure 1. A summary of the products obtained when the 4-halophenols are reacted with *p*-benzoquinone to yield co-crystals. Co-crystals with a 1:1 stoichiometry (halophenol:benzoquinone) are denoted by the letter "**a**", whereas co-crystals with 2:1 stoichiometries are represented with the letter "**b**". Co-crystals **2a/b** and **3a/b** have been previously reported. **1a** has two polymorphs.

As mentioned above, the co-crystals investigated in this work are charge transfer materials, as indicated by the colour of the co-crystals (red, orange, yellow). In reported studies on similar materials,[45–47] the charge donor molecule is often kept constant while the charge acceptor molecule is halogenated to observe what effect the electron-withdrawing halogen substituents would have on the structure and electronic properties of the resulting material. In this study, we vary the halogen substituent on the charge donor while keeping the charge acceptor molecule constant. The degree of charge transfer is expected to be rather low in these materials, due to the halogen substituents on the donor atoms decreasing the donor ability of the 4-halophenols. Since these co-crystals were not prepared to investigate their potential as charge-transfer complexes, but rather to investigate the efficacy of co-sublimation in a new apparatus and structural differences resulting from the halogen substituent or crystallization conditions, the degree of charge transfer in these materials has not been quantified, but see Table S3 in the ESI for calculated HOMO/LUMO energies.

The effect of crystallization method on the stoichiomorphic and polymorphic form of the co-crystal is discussed below, followed by a description of the crystal structures of the nine co-crystal forms obtained.

Effect of crystallization method

Reaction of a particular halophenol with benzoquinone yielded both 1:1 (**a**) and 2:1 (**b**) co-crystals for all four halophenols (stoichiometries are given as halophenol:benzoquinone) (Fig. 1).

Solution crystallization

Recrystallization of a pre-ground powder[ii] from solution yielded either the 1:1 or the 2:1 form exclusively, depending on the stoichiometry of the starting materials used. This is true for all cases except the {IP}{BQ} co-crystal, which exclusively yielded crystals of the 2:1 form from solution recrystallization.

Crystallization by sublimation

Sublimation, using our in-house designed apparatus (Fig. S1), yielded 1:1 and 2:1 forms simultaneously, independent of the ratio of starting materials. The two stoichiomorphs crystallize separately in different parts of the sublimation apparatus, presumably due to the difference in sublimation temperatures of the co-crystals themselves, which leads to the different forms crystallizing at different temperatures: the 1:1 form always crystallized in the cooler parts of the apparatus. The exception to this is the IP-BQ combination, which only gave a 1:1 form from sublimation. In other words, an exact molar ratio of co-formers is not a requirement to form these co-crystals by sublimation; co-crystals with both stoichiometries will form even when there is an excess of one co-former. This is not an uncommon observation for the formation of co-crystals,[48,49] however it makes

---

[ii] Attempts to produce co-crystals by dissolving the starting materials together without pre-grinding only yielded crystals of the respective starting materials.

an interesting contrast to solution crystallization, where the stochiomorphic form obtained depends on the ratio of starting materials.

Co-crystal **1a** is polymorphic, with solution crystallization and sublimation yielding different forms. The polymorph obtained from solution is designated the α-phase (α-**1a**), while the form obtained from sublimation is the β-phase (β-**1a**).

Mechanochemistry

Both 1:1 and 2:1 forms could also be prepared mechanochemically in most cases (see ESI for details). In the case of ClP and BrP, the co-crystal obtained mechanochemically is the same form as that obtained from both solution crystallisation and co-sublimation, and is dependent on the ratio of the starting materials. For FP, β-**1a**, the polymorph obtained from sublimation, is also obtained from a 1:1 grind while a 2:1 grind yields **1b**. A 1:1 grind of IP and BQ yields **4a**, which can also be obtained from sublimation.

Mechanochemical experiments indicated the existence of a potentially extremely short-lived additional phase of co-crystal **4** (Fig. 2). On commencing the grinding experiment, an orange powder forms almost immediately. However, within seconds and without sufficient time to characterise the material that forms, the powder converts to a deep coral red colour, shown to be the 1:1 co-crystal **4a** (Fig. S8).

The stoichiometry of the co-crystal forms can be interchanged repeatedly using mechanochemistry, which simply requires adding a molar equivalent of the relevant co-former and grinding (Figures S2-S8). For example, **2a** can be converted to **2b** by adding a molar equivalent of ClP followed by grinding the sample; **2b** can then be converted to **2a** by adding a molar equivalent of BQ, and this can be done repeatedly. This is not the first report of such a phenomenon; however, it is still quite rare in the field of mechanochemistry and solid state reactions.[50–52]

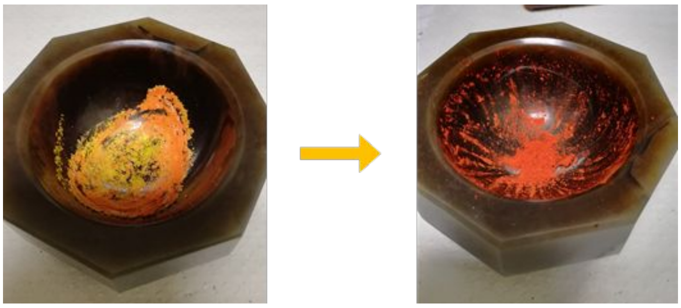


Figure 2. Neat grinding of 4-iodophenol and benzoquinone together to form **4a**. Left: Short-lived form of co-crystal **4** (orange), Right: the 1:1 form, co-crystal **4a**.

In order to further investigate the polymorphs of **1a**, we used liquid-assisted grinding (LAG). Co-crystal **1a** has two polymorphic forms; β-**1a** is the major product from neat grinding using a mortar and pestle. We investigated the effects of LAG with chloroform using both a mortar and pestle and a ball mill to determine whether either the addition of solvent or the change in grinding conditions would yield α-**1a**. In both instances, identical PXRD patterns were obtained; demonstrating no change from the product obtained using neat grinding (Fig. S14). However, we were unable to identify unambiguously the form obtained after conversion to **1b** and its subsequent reaction to reform the 1:1 form. Furthermore, this form persists for all subsequent interconversions (Fig. S2). Differential Scanning Calorimetry also showed no evidence for conversion between the two polymorphs (Fig. S14-15).

Crystal structures

The unit cell and space group information for the nine co-crystal forms discussed in this work are given in Table 1 (for complete crystallographic data see Table S1). Hydrogen bond parameters are reported in the Supplementary Information (Table S2).

Table 1. Unit cell parameters for the co-crystals discussed in this work.

Unit cell	α-1a	β-1a	1b	2a	2b	3a	3b	4a	4b
T (K)	293(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)
Space group	$P1$	Pc	$P2_1/c$	$P1$	$P2_1/c$	$P1$	$P2_1/c$	$P2_1/c$	$P2_1/n$
a (Å)	3.606(4)	3.8460(2)	11.0335(7)	6.8353(4)	11.6009(7)	6.8467(5)	11.8101(4)	11.6713(4)	10.807(2)
b (Å)	6.446(8)	6.390(2)	5.9058(4)	7.0972(4)	6.0460(3)	7.117(5)	6.0966(2)	10.3145(4)	6.1013(12)
c (Å)	11.35(1)	22.184(1)	11.4954(7)	12.2879(7)	11.7339(7)	12.5065(9)	11.8626(4)	9.4247(2)	27.325(5)
α/°	91.77(2)			93.639(2)		94.746(2)			
β/°	98.42(2)	90.478(2)	98.597(2)	106.001(2)	96.987(2)	104.692(2)	96.849(1)	92.901(1)	92.846(2)
γ/°	102.19(2)			112.347(2)		112.515(2)			
V (Å^3)	254.5(5)	481.10(4)	740.64(8)	520.40(5)	816.89(8)	533.41(7)	848.03(5)	1133.13(7)	1799.5(6)

Co-crystals with 1:1 stoichiometry

1a

Two different methods of crystallization, solution crystallization and sublimation, yielded two different polymorphs of **1a**, α-**1a** and β-**1a**. The α-phase, obtained by crystallization from chloroform, crystallizes in the triclinic space group *P*1. The asymmetric unit of α-**1a** consists of a single molecule each of both BQ and FP. The molecules form a 1:1 hydrogen-bonded dimer through O-H···O hydrogen bonds that are 2.761(7) Å in length (donor-acceptor) with a bond angle of 171(1)°. The dimers stack in an offset manner to form columns down the *a* axis. The intra-stack distance, measured as the distance between the planes of the FP rings, is 3.606(6) Å. Columns of dimers are connected by two different types of $R_2^2(8)$ hydrogen-bonded rings – one between two BQ molecules, involving only C=**O** as hydrogen-bond acceptor, and another between two fluorophenol molecules, with fluorine and C-**OH** as H-bond acceptors (Fig. 3a).[48] The resulting three-dimensional packing arrangement is polar (Fig. 3b).

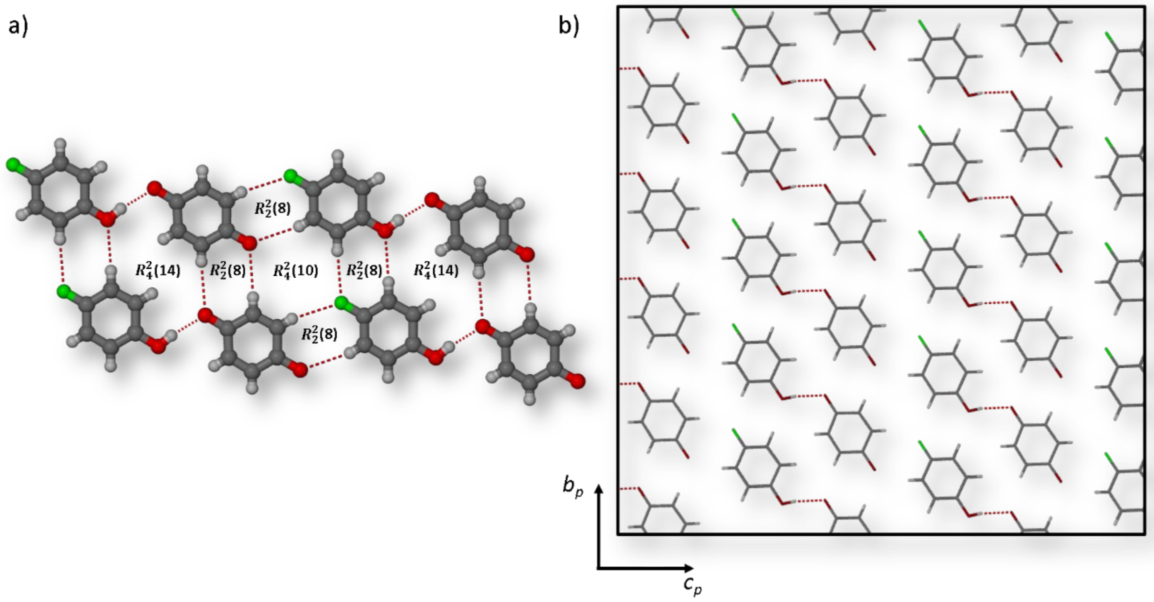


Figure 3. Packing in **α-1a**. (a) Hydrogen bonding between two BQ molecules as well as two FP units in **α-1a**. (b) Polar packing arrangement of **α-1a** viewed down the *a* axis.

Co-sublimation of FP and BQ results in a second polymorph, **β-1a**, which crystallizes in the monoclinic space group *Pc.* The asymmetric unit of this polymorph contains one molecule of BQ and one molecule of FP, which are hydrogen bonded to each other forming a hydrogen bonded dimer similar to **α-1a**. The O-H···O hydrogen bond (D···A) distance is 2.741(5) Å and the bond angle is 177(6)°. However, the dimeric units, which stack in offset columns along *c* are also inclined by 62.5° relative to each other (Fig. 4). The intra-stack distance (centroid-to-centroid) is 3.846(3) Å while consecutive stacks are linked by C-F···H interactions.

IR spectroscopy gives some insight into the intermolecular interactions in **β-1a** compared to those in **α-1a** and BQ (Figures S20-22). Both the hydrogen bond stretches as well as the C-F bond stretch show a clear shift to lower frequencies from **α-1a** to **β-1a**. This indicates a strengthening of the hydrogen bonding and C-F···X (X = H, O) interactions in the structure of **β-1a** when compared to those in **α-1a**.

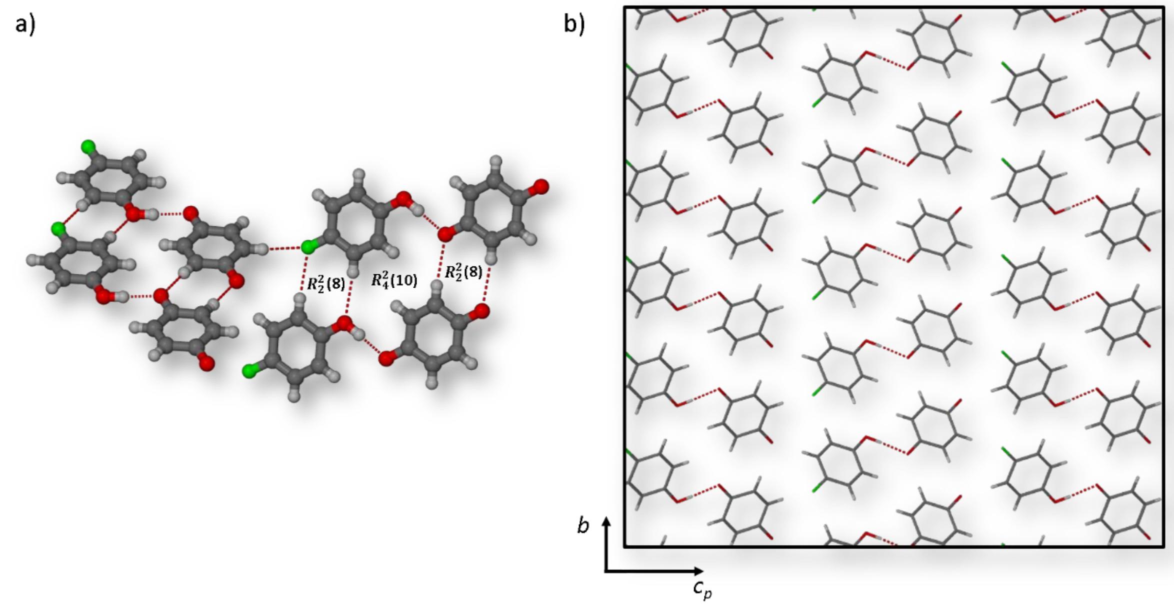


Figure 4. (a) The hydrogen bonding scheme of **β-1a**. (b) The packing arrangement of **β-1a** viewed down the *a* axis.

2a and 3a

The crystal structures of the 1:1 co-crystals formed between ClP/BrP and BQ have been described by Shipley and Wallwork.[43] The main features of these structures are highlighted here, to facilitate comparison with the new structures reported in the current study.

The co-crystals **2a** (ClP·BQ, CSD refcode BNQCLP) and **3a** (BrP·BQ, CSD refcode BNQBRP) crystallize in the triclinic space group $P1$, and are isostructural to one another. The BQ and ClP/BrP molecules form hydrogen-bonded dimers, which stack along the *b* axis such that BQ and HP molecules alternate in the stack (Fig. 5). Stacks pack alongside one another along *a* such that BQ and HP are adjacent along the 100 direction. Along the *c* axis, stacks are packed alongside one another in a slipped fashion. Short contacts (Br···O, 3.170(1) Å; C-Br-O, 160.61(4)°) propagate through the structure of **3a**, alongside hydrogen bonding, to form infinite chains of alternating hydrogen and halogen bonds that are parallel to the *ac* plane (Fig. 5). Similar halogen-bonding contacts are observed for the isostructural co-crystal **2a**, however the contacts are longer (3.2854(9) Å) and marginally less linear (C-Cl-O

157.46(4)°), indicating a weaker halogen bond. This is not uncommon for halogen bonds involving chlorine[iii][53].

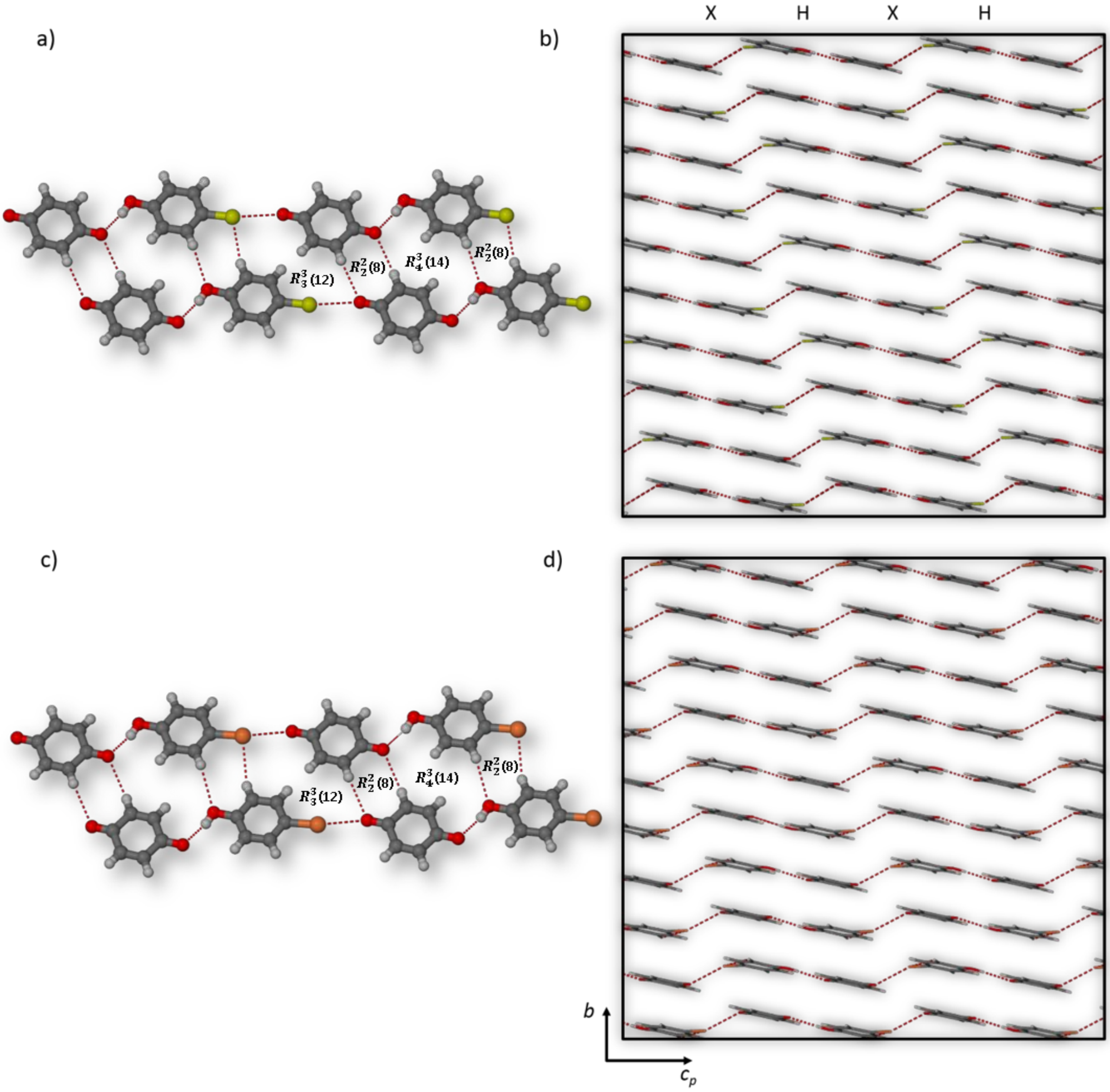


Figure 5. Hydrogen and halogen bonding motifs for **2a** (a) and **3a** (c). Infinite chains of alternating hydrogen (H) and halogen (X) bonds, propagating along the *c* axis in co-crystals **2a** (b) and **3a** (d). Both the hydrogen and halogen bonds are displayed as red dotted lines.

4a

Co-crystal **4a** crystallizes in the monoclinic space group $P2_1/c$. The asymmetric unit consists of two half molecules of BQ and one molecule of 4-iodophenol, which form a hydrogen-bonded trimer. The

---

[iii] Atomic radii used here for the determination of the potential presence of halogen bonding interactions are as published by A. Bondi[64], in particular the atomic radii of halogens as substituents to phenyl rings. The atomic radius of a halogen atom appears to increase slightly when bonded to a phenyl ring.

molecules are arranged in alternating stacks or columns parallel to the *ac* diagonal. The structure has a single layer of BQ molecules that separate consecutive hydrogen-bonded units from one another (Fig. 6). The BQ layers are held in place by I···O halogen bonds at both carbonyl moieties on the BQ molecule. Thus, an infinite hydrogen- and halogen-bonded chain propagates through the structure. The OH···O contact distances in the trimer are 2.749(3) Å, which are in the same range as that of both **1a** co-crystals, albeit slightly longer than the H-bonding distances in co-crystals **2a** and **3a**.

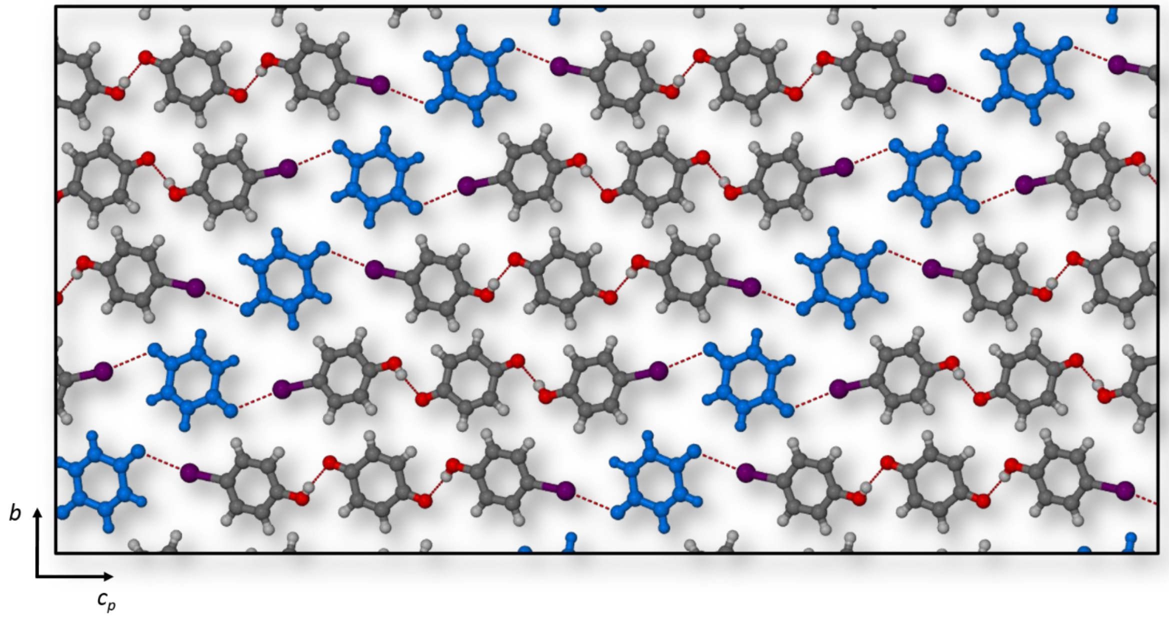


Figure 6. View of **4a** down the *a* axis showing the columns of 2:1 H-bonded trimers separated by a single column of *p*-benzoquinone (highlighted in blue). OH···O hydrogen-bonded contacts and CO···I halogen bonding contacts are shown as red dotted lines.

Co-crystals with 2:1 stoichiometry

1b, **2b and 3b**

Co-crystals **1b**, **2b and 3b,** the latter pair previously reported by Shipley and Wallwork,[50] are isostructural to one another, crystallizing in the monoclinic space group $P2_1/c$. In each case the asymmetric unit contains half a molecule of BQ and a molecule of 4-halophenol (halo = F, Cl and Br), which are hydrogen bonded together to form a trimer. Within each hydrogen-bonded unit of **1b**, OH···O contacts are 2.741(1) Å in length, which is slightly longer than those observed in the structures of **2b** and **3b** (2.7258(17) and 2.7194(15) Å respectively). In each case the trimers are arranged in slipped stacks, such that the hydroxyl moiety (C–O(H)) of the 4-halophenol molecules in one trimer are positioned over the center of a BQ ring in the trimer below (C-O(H)···π 3.028 Å for **1b**, C-O(H)···π 3.070

Å for **2b** and C-O(H)···π 3.083 Å for **3b**), typical of a lone pair···π interaction. Similarly, the carbonyl moiety of BQ is located over the center of a 4-halophenol ring in the trimer below (C=O···π 3.164 Å for **1b**, C=O···π 3.319 Å for **2b**, and C=O···π 3.417 Å for **3b**). Consecutive layers down the *c* axis have a crisscrossed appearance when viewed down *c* (Fig. 7). The crisscrossed stacks/layers pack alongside one another along the *a* direction and are interleaved by the halogen atoms.

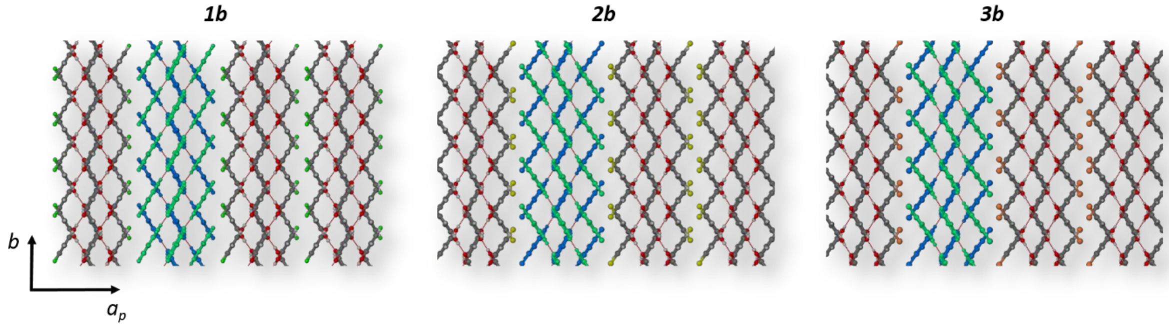


Figure 7. View of **1b, 2b and 3b** down the *c* axis. This view is edge-on to the hydrogen-bonded trimers. Blue and green colors are used to highlight crisscrossed stacks.

An overlay of the crystal structures of **1b**, **2b** and **3b** confirms that they are isostructural (Fig. 8 and Table 1).

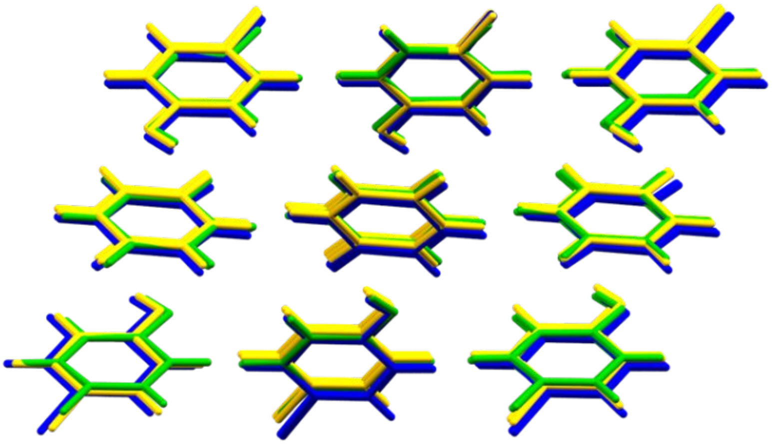


Figure 8. Structural overlay (Mercury 3.10.3)[54,55] of **1b** (green), **2b** (yellow) and **3b** (blue) viewed down the *b* axis, highlighting the similarity of the packing arrangements.

4b

The asymmetric unit of **4b** consists of a molecule of BQ and two molecules of IP, which form a hydrogen bonded trimer analogous to those seen in the other 2:1 co-crystals. However, the IP molecules are not symmetry related, as in the other 2:1 forms, having OH···O contact distances of 2.719(2) and 2.770(3) Å. The shorter OH···O distance results from an out-of-plane rotation (mean plane through the central BQ molecule) of an IP molecule and the longer OH···O distance is owing to an in-plane rotation (mean plane through the central BQ molecule) of the second IP molecule (Fig. 9a). The rotations of the IP molecules occur to accommodate the size of the iodine atoms and the strength of the iodine-iodine interactions. The absence of crystallographic symmetry between the two IP molecules (either side of BQ) results in a doubling of the unit cell along the *c* axis (Fig. 10 bottom right), when compared to the other 2:1 forms. As with **1b**, **2b** and **3b**, the hydrogen bonded trimers in **4b** form slipped stacks, which pack alongside one another in a crisscrossed fashion. The larger size of the iodine atoms (compared to the other halogens) result in the hydrogen-bonded trimers in **4b** being rotated such that they are no longer edge-on (Fig. 9b).

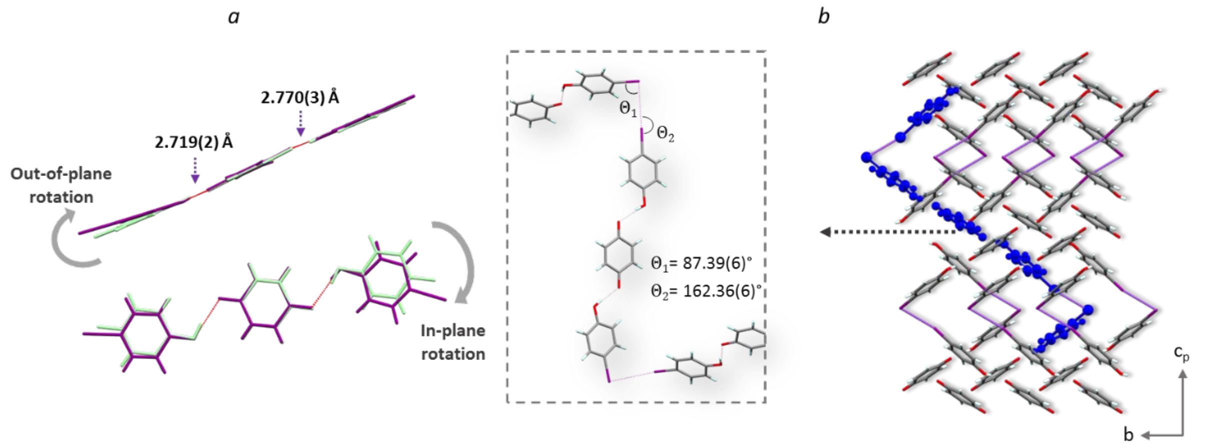


Figure 9. a) An overlay of the hydrogen bonded units of **1b** (green) and **4b** (purple) viewed in different orientations (top and bottom). The distortion in the trimer in **4b** is clear. b) Type II halogen bonding between iodine molecules (purple) in **4b**. The distortion of the trimers away from the plane is highlighted in the packing diagram on the right, where I···I contacts are shown in purple.

Unlike the other 2:1 forms, the structure of **4b** contains short I···I interactions (Fig. 9b). One of the 4-iodophenol molecules is involved in Type II halogen bonding[56] with an iodine atom belonging to an iodophenol molecule in an adjacent layer. The extensive Type II I···I halogen-bonding interactions present in this structure appear to be responsible for the distortion of the hydrogen-bonded units (as mentioned previously). The size of the iodine atoms as well as the different iodine environments result in **4b** not being isostructural to the other 2:1 co-crystals, despite the packing arrangements being very closely related (Fig. 10).

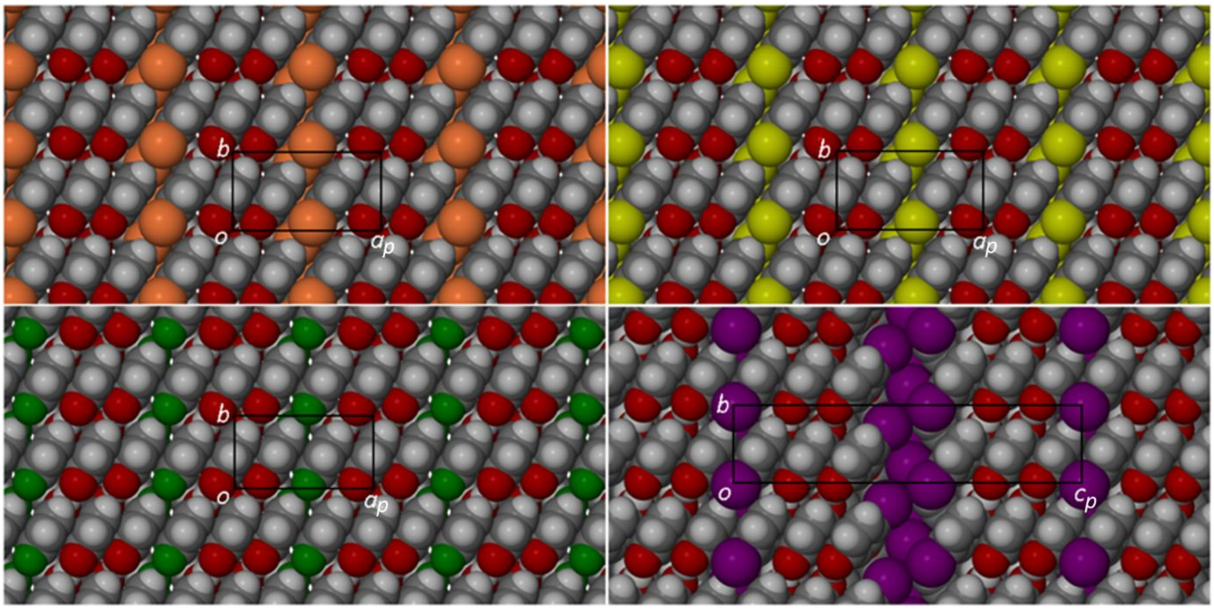
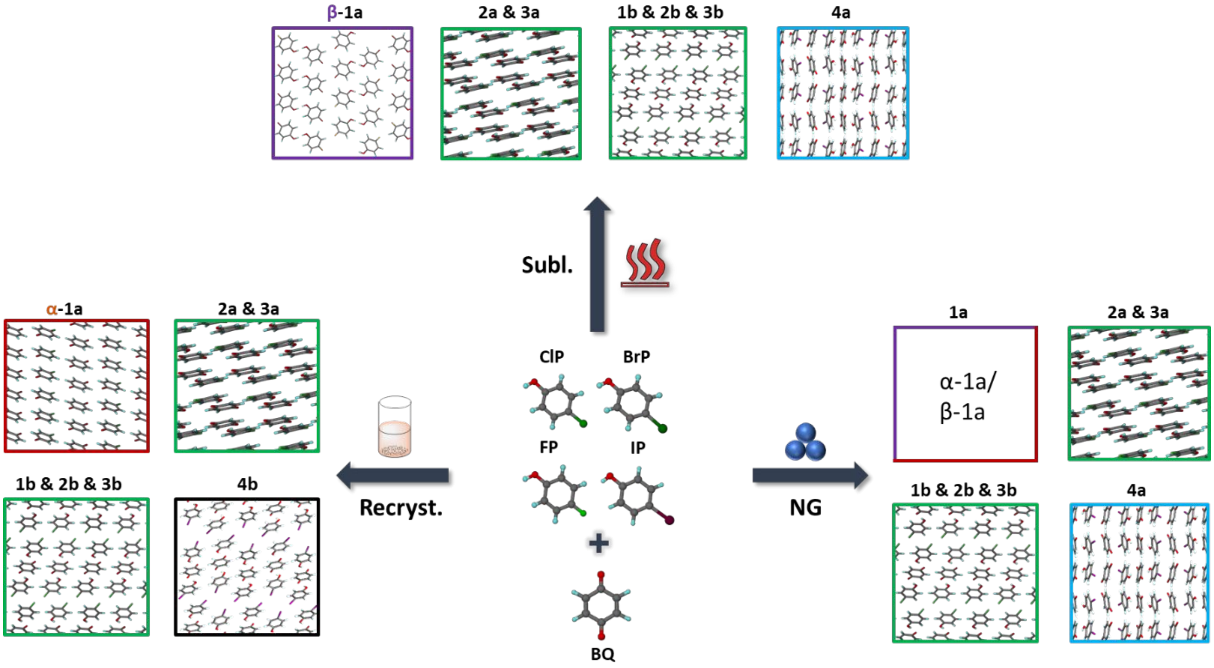


Figure 10. The space fill packing arrangement of the 2:1 co-crystal forms: **3b** (top left), **2b** (top right), **1b** (bottom left) and **4b** (bottom right). The packing arrangement in **4b** shows two environments for iodine resulting in a doubled *c* axis.

Summary

The results of this systematic study, summarised in Scheme 1, confirm that by simply applying a different crystallization technique, different solid forms may be obtained from the same molecular components. This emphasises the importance of varying crystallization methods and techniques when screening for potential solid forms of a material.



Scheme 1. Summary of the results obtained when using different methods to crystallize co-crystals of benzoquinone and the *p*-halophenols. In the case of **2a**, **3a**, **1b**, **2b** and **3b** (highlighted by green boxes), recrystallization from solution, sublimation

and neat grinding yields the same crystal form, with the result dependent only on the stoichiometry of the starting materials. Co-crystal **1a** is polymorphic, and recrystallization yields the **α**-phase (red) whereas sublimation yields the β-phase (purple). For combination **4**, the 1:1 form **4a** was obtained from sublimation and neat grinding (blue boxes), whereas recrystallization from solution yields only the 2:1 form **4b** (black).

Unique to this study is the systematic investigation of the use of sublimation to grow crystals. We successfully, and with some measure of control, produced co-crystals using an in-house built co-sublimation apparatus of simple design. We were able to grow crystals of different stoichiometries at the same time in the same apparatus, but, significantly, in such a way that the different forms are easily separable after crystal growth.

It is particularly noteworthy that when different forms are obtained from solution recrystallization and mechanochemistry (the polymorphs of **1a** and stoichiomorphs **4a**/**4b**), the form obtained from sublimation is the same as that obtained mechanochemically.

Conclusions

It is well established that different crystallization methods may yield different solid forms of a material, which is an important consideration in many fields. This systematic study of co-crystals formed between benzoquinone and the *p*-halophenols strengthens this observation. Recrystallization from solution and mechanochemical synthesis gave different solid-state forms for both the fluorophenol/benzoquinone and the iodophenol/benzoquinone systems. Additionally, we found that sublimation yields the same form as the mechanochemical method. This may prove to be a useful technique to obtain single crystals of solid forms previously only accessible by mechanochemistry. Sublimation, in our opinion, is an underutilized crystal growth method and these results reveal that there is room for further investigation.

Finally, the sublimation apparatus developed for this study proved to be a fast and effective route to make multicomponent crystals, with control over the sublimation environment for each component. Stoichiomorphs were obtained simultaneously and in such a way that they could be easily separated. It is clear from the work presented here that sublimation should be more widely employed as a means to access new parts of solid-state phase space.

Experimental

Co-formers *p*-benzoquinone (BQ), 4-fluorophenol (FP), 4-chlorophenol (ClP), 4-bromophenol (BrP) and 4-iodophenol (IP) were purchased from Sigma Aldrich and used without further purification. Three different crystallization techniques were used to produce co-crystals.

Solution crystallization. All co-crystals were prepared from solution using the same general methodology. Details of the preparation of **1a** (1:1 form) and **1b** (2:1 form) are given as representative procedures.

p-Benzoquinone (10 mg, 1 eq.) and 4-fluorophenol (11 mg, 1 eq.) were ground together until a color change was visible. The resulting powder was dissolved in chloroform (3-5 ml) and allowed to crystallize in the refrigerator at 4 °C, yielding orange rods and plates of the alpha form of **1a** (α-**1a**). The same procedure was followed for the synthesis of **1b**: 4-fluorophenol (22 mg 2 eq.) was ground together with BQ (10 mg, 1 eq.), the powder dissolved in chloroform and the resulting solution allowed to crystallize in the refrigerator. Orange rods and plates (α-**1a**) or deep red needles (**1b**) of diffraction quality were obtained after 2-3 weeks. Crystals were repeatedly harvested as the solvent evaporated.

Co-crystals of BQ with 4-chlorophenol (**2a** and **2b**), 4-bromophenol (**3a** and **3b**) and 4-iodophenol (**4b**) were obtained from solution in the same manner. Three halophenols yielded both a 1:1 (**a**) and 2:1 (**b**) form from the appropriate solution. However the 4-iodophenol/BQ combination yielded only a 2:1 form, even from crystallization experiments containing a 1:1 molar ratio of co-formers. All 1:1 co-crystals were observed to have the same color and morphology, orange rods and plates, where all the 2:1 co-crystals were deep red needles. The methodology described here gave the same forms for **2a/b** and **3a/b** as reported previously by Shipley and Wallwork,[43,44] and yielded the 2:1 form, **4b**.

All attempts to prepare co-crystals by dissolving the components in chloroform without prior grinding were unsuccessful, resulting in isolation of crystals of the coformers.

Table 2. Details of conditions used to form co-crystals by sublimation as well as mechanochemical methods, using benzoquinone and a halophenol. Numbers in brackets indicate the relative equivalents of halophenol. Temperature is that used in sublimation experiments.

Co-former	Mass (mg)	Temperature (°C)
p-benzoquinone	10	50
4-fluorophenol	11(1), 22(2)	50
4-chlorophenol	11.7(1), 23.4(2)	45
4-bromophenol	16.5(1), 33(2)	65
4-iodophenol	20(1), 40(2)	95

Sublimation. Co-crystals were also grown by co-sublimation under vacuum using an in-house designed apparatus containing two bulbs that can be heated to different temperatures under reduced pressure (see ESI for a detailed description of the apparatus).

The beta phase of co-crystal **1a** (β-**1a**) and co-crystal **1b** were synthesized concomitantly by adding BQ (10 mg, 1 eq.) and either 1 or 2 equivalents of FP (see Table 2) separately to the two sample chambers of the sublimation apparatus. Each component was heated to the temperature specified in Table 2, whist the apparatus was kept under a dynamic vacuum of 14 mbar. Crystals of β-**1a** and **1b** were isolated from the glass wall inside the chamber. Unreacted starting material remained in the sample bulbs and did not crystallize on the walls of the sublimation apparatus.

The same procedure was followed for the synthesis of co-crystals **2a**/**b, 3a**/**b** and **4a**. Quantities and sublimation temperatures are given in Table 2. Diffraction-quality crystals formed on the walls of the glass tube after a few minutes in the case of combinations **1**-**3**, and overnight in the case of co-crystal **4a**. For co-crystal combinations **1**-**3**, the 1:1 and 2:1 co-crystals grew concomitantly, independent of the starting ratio of co-formers. In all cases where the 1:1 and 2:1 forms grew at the same time, we observed that the 1:1 form crystallized closer to the U-bend of the apparatus where the glass wall is cooler, whereas the 2:1 form always crystallized on the warmer areas of the glass wall. The polymorphs α-**1a** and β-**1a** appear to be morphologically identical, both crystallizing as orange rods and plates.

Mechanochemistry. Neat grinding (NG) of the co-formers in their respective 1:1 and 2:1 molar ratios in a mortar and pestle yielded co-crystals, as confirmed by powder X-ray diffraction (see ESI Figs S2-9).

The only exception was IP-BQ, which only produced the 1:1 form on grinding. Grinding experiments were performed using 10 mg of benzoquinone with the appropriate equivalent amount of halophenol (see Table 2 for masses). The two components were added to a mortar and ground for 2-5 minutes with a pestle. The color of the resulting co-crystal powders for all 1:1 forms, apart from the IP-BQ cocrystal, was orange-light brown, whereas all 2:1 powders were dark brown-red in color (Figures S16-S19).

In order to establish whether conversion to the α-phase of co-crystal **β-1a** could be carried out by extended grinding, selected liquid-assisted grinding experiments were performed. A 100 mg sample of the **β-1a** co-crystal powder was added to a 15 ml stainless steel milling jar with two stainless steel balls, using an FTS1000 ball mill from Form-Tech Scientific. The samples of co-crystal were combined with 25 μL chloroform and ground for 20 minutes at 1800 rpm. No conversion to **α-1a** was observed: the resulting powder pattern matches that of the neat grinding experiments (Fig. S14).

Instrumentation. Ambient temperature powder X-ray diffraction profiles were collected using a PANalytical X'Pert Pro Instrument, with CuKα radiation (λ = 1.5418 Å, 40 kV, 30 mA) and Bragg-Brentano geometry. 2θ scans were performed in the range 4-50° with a 0.016° step size.

Infrared spectroscopy (IR) was performed on a Bruker ALPHA ATR-FTIR.

Single crystal X-ray data were collected on a Bruker D8 Venture diffractometer using the Apex3[57] software. The diffractometer is equipped with a microfocus MoKα sealed-tube X-ray source as well as a Photon II detector. It is fitted with an Oxford Cryostream 800 Series cryostat. Data reduction and absorption corrections were done using SAINT[57]and SADABS,[57,58] respectively. For the purposes of this work, the data for the known co-crystals were recollected at 100 K. Structures were solved and refined using the SHELXS[59]and SHELXT[60,61]using XSEED[62,63]as the interface.

Acknowledgements

We acknowledge the National Research Foundation[‡] of South Africa, Rhodes University and Stellenbosch University for funding. We thank D de Villiers for assistance in the development of the sublimation apparatus.

‡ This material is based upon work supported financially by the National Research Foundation. Any opinion, findings and conclusions or recommendations expressed in this material are those of the author(s) and therefore the NRF does not accept any liability in regard thereto.

The Supporting Information is available free of charge at https://pubs.acs.org. The ESI contains details on the glassware used for the sublimation experiments, powder X-ray diffraction data, thermal analysis data, tabulated crystal structure data, HOMO and LUMO orbital energies for the *p*-halophenol and *p*-benzoquinone co-formers calculated using DFT, mechanochemistry and FTIR spectra.

AUTHOR INFORMATION

Corresponding Author

*v.smith@ru.ac.za

Author Contributions

All authors contributed to the writing of the manuscript and approved the final version of the manuscript.

CCDC deposit codes: 1959377-1959385

References

(1) Griesser, U. J.; Szelagiewicz, M.; Hofmeier, U. C.; Pitt, C.; Cianferani, S. Vapor Pressure and Heat of Sublimation of Crystal Polymorphs. *J. Therm. Anal. Chem.* **1999**, *57*, 45–60.

(2) Szell, P. M. J.; Gabriel, S. A.; Caron-Poulin, E.; Jeannin, O.; Fourmigue, M.; Bryce, D. L. Cosublimation: A Rapid Route Toward Otherwise Inaccessible Halogen-Bonded Architectures. *Cryst. Growth Des.* **2018**, *18*, 6227–6238.

(3) Surov, A. O.; Manin, A. N.; Voronin, A. P.; Churakov, A. V.; Perlovich, G. L.; Vener, M. V. Weak Interactions Cause Packing Polymorphism in Pharmaceutical Two-Component Crystals. the Case Study of the Salicylamide Cocrystal. *Cryst. Growth Des* **2017**, *17*, 1425–1437.

(4) *Polymorphism in Pharmaceutical Solids*; Brittain, H. G., Ed.; Informa Healthcare USA, Inc.: New York, 2009; Vol. 192.

(5) Tan, D.; Loots, L.; Friščić, T. Towards Medicinal Mechanochemistry: Evolution of Milling from Pharmaceutical Solid Form Screening to the Synthesis of Active Pharmaceutical Ingredients (APIs). *Chem. Commun.* **2016**, *52*, 7760–7781.

(6) Trask, A. V.; Van De Streek, J.; Motherwell, W. D. S.; Jones, W. Achieving Polymorphic and Stoichiometric Diversity in Cocrystal Formation: Importance of Solid-State Grinding, Powder X-Ray Structure Determination, and Seeding. *Cryst. Growth Des.* **2005**, *5*, 2233–2241.

(7) Hasegawa, T.; Mochida, T.; Kondo, R.; Kagoshima, S.; Iwasa, Y.; Akutagawa, T.; Nakamura, T.; Saito, G. Mixed-Stack Organic Charge-Transfer Complexes with Intercolumnar Networks. *Phys. Rev. B.* **2000**, *62*, 59–66.

(8) Gujrati, M. D.; Kumar, N. S. S.; Brown, A. S.; Captain, B.; Wilson, J. N. Luminescent Charge-Transfer Complexes: Tuning Emission in Binary Fluorophore Mixtures. *Langmuir* **2011**, *27*, 6554–6558.

(9) Zhang, J.; Xu, W.; Sheng, P.; Zhao, G.; Zhu, D. Organic Donor-Acceptor Complexes as Novel Organic Semiconductors. *Acc. Chem. Res.* **2017**, *50*, 1654–1662.

(10) Nakamura, M.; Horiuchi, S.; Kagawa, F.; Ogawa, N.; Kurumaji, T.; Tokura, Y.; Kawasaki, M. Shift Current Photovoltaic Effect in a Ferroelectric Charge-Transfer Complex. *Nat. Commun.* **2017**, *8*, 1–5.

(11) D'Avino, G.; Verstraete, M. J. Are Hydrogen-Bonded Charge Transfer Crystals Room Temperature Ferroelectrics? *Phys. Rev. Lett.* **2014**, *113*, 1–5.

(12) Singleton, J. Why Do Physicists Love Charge-Transfer Salts? *J. Solid State Chem.* **2002**, *168*, 675–689.

(13) Qian, H.-F.; Wang, Y.-G.; Geng, J.; Huang, W. A Rare Case of a Dye Co-Crystal Showing Better Dyeing Performance. *CrystEngComm* **2015**, *17*, 2083–2086.

(14) Aitipamula, S.; Banerjee, R.; Bansal, A. K.; Biradha, K.; Cheney, M. L.; Choudhury, A. R.; Desiraju, G. R.; Dikundwar, A. G.; Dubey, R.; Duggirala, N.; Ghogale P. P.; Ghosh S.; Goswami P. K.; Goud N. R.; Jetti R. R. K. R.; Karpinski P.; Kaushik P.; Kumar D.; Kumar V.; Moulton B.; Mukherjee A.; Mukherjee G.; Myerson A. S.; Puri V.; Ramanan A.; Rajamannar T.; Reddy C. M.; Rodriguez-Hornedo N.; Rogers R. D.; Guru Row T. N.; Sanphui P.; Shan N.; Shete G.; Singh A.; Sun C. C.; Swift J. A.; Thaimattam R.; Thakur T. S.; Thaper R. K.; Thomas S. P.; Tothadi S.; Vangala V. R.; Variankaval N.; Vishweshwar P.; Weyna D. R.; Zaworotko M. J. Polymorphs, Salts, and Cocrystals: What's in a Name? *Cryst. Growth Des.* **2012**, *12*, 2147–2152.

(15) Aitipamula, S.; Chow, P. S.; Tan, R. B. H. Polymorphism in Cocrystals: A Review and Assessment of Its Significance. *CrystEngComm* **2014**, *16*, 3451.

(16) Aakeröy, C. B.; Sinha, A. S. Chapter 1 Co-Crystals: Introduction and Scope. In *Co-crystals: Preparation, Characterization and Applications*; The Royal Society of Chemistry **2018**; pp 1–32.

(17) Wahl, H.; Haynes, D. A.; le Roex, T. Lack of Co-Crystal Formation with Cyclotriphosphazenes: A Cautionary Tale. *S. Afr. J. Chem.* **2016**, *69*, 35–43.

(18) Robinson, S. W.; Haynes, D. A.; Rawson, J. M. Co-Crystal Formation with 1,2,3,5-Dithiadiazolyl Radicals. *CrystEngComm* **2013**, *15*, 10205–10211.

(19) Shan, N.; Zaworotko, M. J. The Role of Cocrystals in Pharmaceutical Science. *Drug Discov. Today* **2008**, *13*, 440–446.

(20) Karimi-Jafari, M.; Padrela, L.; Walker, G. M.; Croker, D. M. Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications. *Cryst. Growth Des.* **2018**, *18*, 6370–6387.

(21) Trask, A. V.; Motherwell, W. D. S.; Jones, W. Solvent-Drop Grinding : Green Polymorph Control of Cocrystallisation. *Chem. Commun.* **2004**, 890–891.

(22) Friscic, T.; Jones, W. Application of Mechanochemistry in the Synthesis and Discovery of New Pharmaceutical Forms : Co-Crystals, Salts and Coordination Compounds. In *Pharamaceutical Salts and Co-crystals*; 2012; pp 154–187.

(23) Kalra, A.; Zhang, M.; Parkin, S.; Li, T. Crystal Packing and Crystallization Tendency from the Melt of 2-((2-Ethylphenyl)Amino)Nicotinic Acid. *Z. Krist.* **2018**, *233*, 9–16.

(24) Zhang, T.; Yu, Q.; Li, X.; Ma, X. Preparation of 2:1 Urea-Succinic Acid Cocrystals by Sublimation. *J. Cryst. Growth* **2017**, *469*, 114–118.

(25) Ye, X.; Liu, Y.; Han, Q.; Ge, C.; Cui, S.; Zhang, L.; Zheng, X.; Liu, G.; Liu, J.; Liu, D.; et al. Microspacing In-Air Sublimation Growth of Organic Crystals. *Chem. Mater.* **2018**, *30*, 412–420.

(26) Liu, Z.; Gao, Q.; Chen, J.; Deng, J.; Kun, L.; Xing, X. Negative Thermal Expansion in Molecular Materials. *Chem. Commun.* **2018**, *54*, 5164–5176.

(27) Steed, J. W. 21st Century Developments in the Understanding and Control of Molecular Solids. *Chem. Commun.* **2018**, *54*, 13175–13182.

(28) Hasani, M.; Rezaei, A. Spectrophotometric Study of the Charge-Transfer Complexes of Iodine with Antipyrine in Organic Solvents. *Spectrochim. Acta A.* **2006**, *65*, 1093–1097.

(29) Friščić, T.; Jones, W. Recent Advances in Understanding the Mechanism of Cocrystal Formation via Grinding. *Cryst. Growth Des.* **2009**, *9*, 1621–1637.

(30) Solomos, M. A.; Capacci-Daniel, C.; Rubinson, J. F.; Swift, J. A. Polymorph Selection via Sublimation onto Siloxane Templates. *Cryst. Growth Des.* **2018**, *18*, 6965–6972.

(31) Yu, Q.; Dang, L.; Black, S.; Wei, H. Crystallization of the Polymorphs of Succinic Acid via Sublimation at Different Temperatures in the Presence or Absence of Water and Isopropanol Vapor. *J. Cryst. Growth* **2012**, *340*, 209–215.

(32) Wright, J. D. *Molecular Crystals*, 2nd ed.; Cambridge University Press, 1995.

(33) Atwood, J. L.; Barbour, L. J.; Jerga, A.; Schottel, B. L. Guest Transport in a Nonporous Organic Solid via Dynamic van Der Waals Cooperativity. *Science* **2002**, *298*, 1000–1002.

(34) Sarma, B.; Roy, S.; Nangia, A. Polymorphs of 1,1-Bis(4-Hydroxyphenyl)Cyclohexane and Multiple Z′ Crystal Structures by Melt and Sublimation Crystallization. *Chem. Commun.* **2006**,

4918–4920.

(35) Smith, V. J.; Marais, C. G.; Suwińska, K.; Lipkowski, J.; Szumna, A.; Esterhuysen, C.; Barbour, L. J. Concomitant Polymorphs of *p*-iso-Propylcalix[4]Arene. *CrystEngComm* **2015**, *17*, 5129–5133.

(36) Nath, N. K.; Aggarwal, H.; Nangia, A. Crystal Structure of Methyl Paraben Polymorph II. *Cryst. Growth Des.* **2011**, *11*, 967–971.

(37) Jacobs, T.; Smith, V. J.; Thomas, L. H.; Barbour, L. J. Carbon Dioxide Entrapment in an Organic Molecular Host. *Chem. Commun.* **2014**, *50*, 85–87.

(38) Toda, F.; Senzaki, M.; Kuroda, R. A New Supramolecular System of Racemic-Bis-β-Naphthol, Benzoquinone and Aromatic Hydrocarbon, which Shows High Molecular Recognition Ability. *Chem. Commun.* **2002**, 1788–1789.

(39) Kuroda, R.; Imai, Y.; Tajima, N. Generation of a Co-Crystal Phase with Novel Coloristic Properties via Solid State Grinding Procedures. *Chem. Commun.* **2002**, *2*, 2848–2849.

(40) Cheung, E. Y.; Kitchin, S. J.; Harris, K. D. M.; Imai, Y.; Tajima, N.; Kuroda, R. Direct Structure Determination of a Multicomponent Molecular Crystal Prepared by a Solid-State Grinding Procedure. *J. Am. Chem. Soc.* **2003**, *125*, 14658–14659.

(41) Imai, Y.; Tajima, N.; Sato, T.; Kuroda, R. Visualization of Molecular Recognition : A Novel System Based on Charge-Transfer Complexes Composed. *Org. Lett.* **2006**, *8*, 2941–2944.

(42) Kuroda, R.; Higashiguchi, K.; Imai, Y. Crystal to Crystal Transformation in the Solid State. *CrystEngComm* **2004**, *6*, 463–468.

(43) Shipley, G. G.; Wallwork, S. C. Molecular Complexes Exhibiting Polarization Bonding. VIII. The Crystal Structures of the 1:1 Complexes Formed by *p*-Chlorophenol and *p*-Bromophenol with *p*-Benzoquinone. *Acta Cryst.* **1967**, *22*, 593–601.

(44) Shipley, G. G.; Wallwork, S. C. Molecular Complexes Exhibiting Polarization Bonding. VII. The Crystal Structures of 2:1 Complexes Formed by *p*-Chlorophenol and *p*-Bromophenol with *p*-Benzoquinone. *Acta Cryst.* **1967**, *22*, 585–592.

(45) Jiang, H.; Hu, P.; Ye, J.; Zhang, K.; Long, Y.; Hu, W.; Kloc, C. Tuning of the Degree of Charge Transfer and Electronic Properties in Organic Binary Compounds by Crystal Engineering: A Perspective. *J. Mater. Chem. C.* **2017**, *6*, 1884–1902.

(46) Hu, P.; Du, K.; Wei, F.; Jiang, H.; Kloc, C. Crystal Growth, HOMO − LUMO Engineering, and Charge Transfer Degree in Perylene-F_xTCNQ (x = 1, 2, 4) Organic Charge Transfer Binary Compounds. *Cryst. Growth Des.* **2016**, *16*, 3019–3027.

(47) Behera, R. K.; Goud, N. R.; Matzger, A. J.; Coropceanu, V. Electronic Properties of 1,5-Diaminonaphthalene:Tetrahalo-1,4-Benzoquinone Donor−Acceptor Cocrystals. *J. Phys. Chem. C.* **2017**, *121*, 23633–23641.

(48) Goetz, K. P.; Vermeulen, D.; Payne, M. E.; Kloc, C.; McNeil, L. E.; Jurchescu, O. D. Charge-Transfer Complexes: New Perspectives on an Old Class of Compounds. *J. Mater. Chem. C.* **2014**, *2*, 3065–3076.

(49) Alimi, L. O.; Lama, P.; Smith, V. J.; Barbour, L. J. Large Volumetric Thermal Expansion of a Novel Organic Cocrystal over a Wide Temperature Range. *CrystEngComm* **2018**, *20*, 631–635.

(50) Braga, D.; Grepioni, F.; Lampronti, G. I. Supramolecular Metathesis: Co-Former Exchange in Co-Crystals of Pyrazine with (R,R)-,(S,S)-,(R,S)-and (S,S/R,R)-Tartaric Acid. *CrystEngComm* **2011**, *13*, 3122–3124.

(51) Karki, S.; Friscic, T.; Jones, W. Control and Interconversion of Cocrystal Stoichiometry in

Grinding: Stepwise Mechanism for the Formation of a Hydrogen-Bonded Cocrystal. *CrystEngComm* **2008**, *11*, 470–481.

(52) Loots, L.; Wahl, H.; van der Westhuizen, L.; Haynes, D. A.; le Roux, T. Interconversion between Different Stoichiometric Forms of a Three-Component Crystal via Liquid-Assisted Grinding. *Chem. Commun.* **2012**, *48*, 11507–11509.

(53) Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. The Halogen Bond. *Chem. Rev.* **2016**, *116*, 2478–2601.

(54) Macrae, C. F.; Bruno, I. J.; Chisholm, P. R.; Edgington, P.; McCabe, E.; Pidock, L.; Rodriguez-Monge, R.; Taylor, J.; Van De Streek, J.; Wood, P. A. Mercury CSD 2.0 - New Features for the Visualization and Investigation of Crystal Structures. *J. Appl. Cryst.* **2008**, *41*, 466–470.

(55) Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. Mercury: Visualization and Analysis of Crystal Structures. *J. Appl. Cryst.* **2006**, *39*, 453–457.

(56) Metrangolo, P.; Resnati, G. Type II Halogen...Halogen Contacts Are Halogen Bonds. *IUCrJ* **2014**, *1*, 5–7.

(57) Bruker APEX3, SAINT and SADABS. Bruker AXS Inc., Madison, Wisconson, USA, 2016.

(58) Blessing, R. SADABS. *Acta Cryst.* **1995**, *A51*, 33–38.

(59) Sheldrick, G. M. SHELXS-97. *Acta Cryst.* **2008**, *A64*, 112–122.

(60) Sheldrick, G. M. SHELXT - Integrated Space-Group and Crystal-Structure Determination. *Acta Crystallogr. Sect. A* **2015**, *71*, 3–8.

(61) Sheldrick, G. M. Crystal Structure Refinement with SHELXL. *Acta Crystallogr. Sect. C.* **2015**, *71*, 3–8.

(62) Barbour, L. J. X-Seed1. *J. Supramol. Chem.* **2001**, *1*, 189–191.

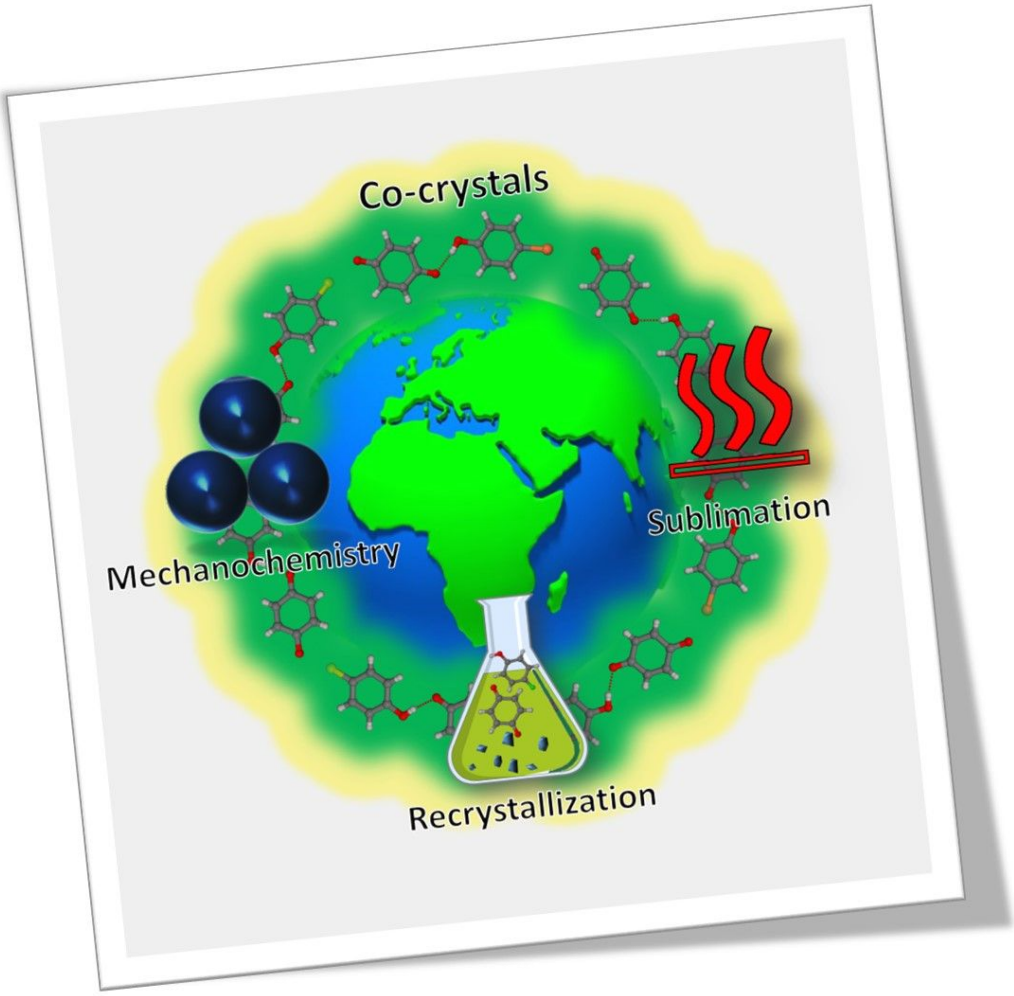
(63) Atwood, J. L.; Barbour, L. J. X-Seed2. *Cryst. Growth Des.* **2003**, *3*, 3–8.

(64) Bondi, A. Van Der Waals Volumes and Radii. *J. Chem. Phys.* **1964**, *68*, 441–451.

For Table of Contents Use Only.

Co-crystals: solution, mechanochemistry and sublimation

Thalia Carstens, Delia A. Haynes and Vincent J. Smith*



Synopsis: Co-crystallization of a series of *p*-halophenols with benzoquinone using solution recrystallization, mechanochemistry and sublimation.