# Systematic Construction of Ternary Cocrystals by Orthogonal and Robust Hydrogen and Halogen Bonds

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Ⓢ *Supporting Information*

**ABSTRACT:** A carefully designed strategy is presented for the construction of ternary cocrystals, based on the orthogonality of two supramolecular interaction modes: hydrogen bonding between crown ethers and thioureas and the halogen bonding between thioureas and perfluorohalocarbons. Tested on a set comprising two crown ethers, two thioureas and five halogen bond donors, the strategy resulted in a high, 75% success rate, with 15/20 component combinations yielding at least one cocrystal. Crystal structure analysis revealed the interplay between the hydrogen and halogen bonding motifs, also shedding light on the variables affecting their formation.
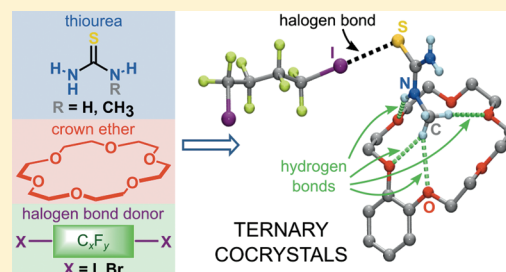
## 1. INTRODUCTION

In the past two decades, one of the intensively pursued research topics in crystal engineering has been that of cocrystals,[1,2] although they have been known for much longer.[3] However, this comes as no surprise, given their great potential as e.g. pharmaceutical,[4−6] luminescent,[7] photomechanical,[8] ferroelectric,[9] or energetic[10,11] (explosive!) materials. From the beginning, one of the challenges has been the rational design of strategies enabling deliberate and systematic construction of cocrystals. While this has largely been overcome in the case of binary cocrystals (i.e., comprising two components), fewer strategies have been developed for successful construction of ternary and more complex cocrystals. The seminal paper, not only posing this challenge, but also offering the first examples of design-based hydrogen-bonded ternary molecular solids (cocrystal), was that of Aakeröy et al.,[12] wherein two different carboxylic acid molecules were cocrystallized with isonicotinamide. More specifically, the stronger of the two acids was postulated to bind to the pyridine moiety of isonicotinamide while the weaker acid binds to the amide moiety, yielding a discrete 1:1:1 ternary supermolecule, by exploiting the hierarchy[13] of supramolecular synthons.[14] The strategy was later shown to be a general one, using different components selected based on the same principles.[15−17]

A great body of work on the preparation of ternary[18−22] and even quaternary[23,24] cocrystals has been recently reported by Desiraju and co-workers. First, a shape-based approach was devised, where one component in a binary cocrystal can be partially replaced by a third component,[25] in such a way that the molecules participating in (stronger) hydrogen bonding are left in place, while the weakly interacting molecules of the same kind are substituted by similarly shaped ones. This was demonstrated through successful substitution of loosely bound 4,4′-bipyridine molecules in its cocrystals with 2- or 5-methylresorcinol by similarly shaped molecules.[18] In what

could be considered as an extension of this approach, robust synthons were identified in a series of crystal forms based on binary cocrystals comprising heterocyclic bases and polyhydroxyphenols. Upon the introduction of a third component, the more robust synthons persisted while the presumably less reliable ones incorporated the newly introduced third component instead, yielding ternary cocrystals.[19,20] Remarkably, the same reasoning could be applied sequentially to afford quaternary[23,24] and even quinternary[23] cocrystals. Finally, Desiraju and colleagues also reported the, to date, only strategy utilizing a combination of halogen (C−X···O₂N; X = I, Br) and hydrogen bonding (carboxylic acid−amide heterosynthon) to construct binary or ternary cocrystals,[21] depending on the exact nature of the components bearing these functional groups.[22]

We have recently been interested in using concerted hydrogen and halogen bonding to construct sophisticated supramolecular assemblies in both solution and the solid state. A particularly efficient approach was adopted where *N*-alkylammonium resorcinarene halide (NARX),[26,27] supramolecular species consisting of different cationic resorcinarene derivatives and hydrogen bonded halide anions, were used as halogen bond acceptors with a number of donors. All three components (*N*-alkylammonium resorcinarene cations, halide anions, and halogen bond donors) could be varied in an orthogonal manner to yield deep cavity cavitands[28,29] and capsules,[30] as well as various dumbbell-like and polymeric pseudocapsular architectures.[31] Inspired by this, we set out to devise a strategy for assembling ternary cocrystals with a distinct supramolecular role for each component which would, by virtue of the orthogonality of hydrogen and halogen bonds, also allow for tuning of the structure by changing one, two, or

all of the components while still successfully producing the ternary cocrystal.

One of the first questions one faces when designing such a strategy is evaluating its outcomes. When can a strategy be deemed successful? We propose the following criteria: First, as an obvious *conditio sine qua non*, it has to yield ternary cocrystals. Second, it should do so with a high supramolecular yield,[32] and finally, the precise control of the stoichiometry and structure should be achieved.

In order to achieve all these goals, we adopted an entirely new approach. Arman et al. reported that the N−H···S type hydrogen bonding between thiourea-type molecules is preserved in the structures of their C−I···S halogen bonded cocrystals.[33] Moreover, the set of cocrystals described consisted of three different thioureas and three different halogen bond donors, suggesting that the orthogonality of hydrogen and halogen bonding could be a general property of such systems. Later, Robertson et al. showed the halogen bonds between diiodine as the donor and tetramethylthiourea as the acceptor to be particularly robust in solution, which was ascribed to their pronounced charge-transfer character.[34] Inspired by the former and encouraged by the latter, we decided to combine these approaches by introducing a third component which would engage in hydrogen bonding with thiourea without competing for the halogen bond donor, yielding ternary cocrystals by two parallel but orthogonal self-assembly processes. Here, crown ethers emerged as an unorthodox but promising choice (Scheme 1).

**Scheme 1. Motif Combination**
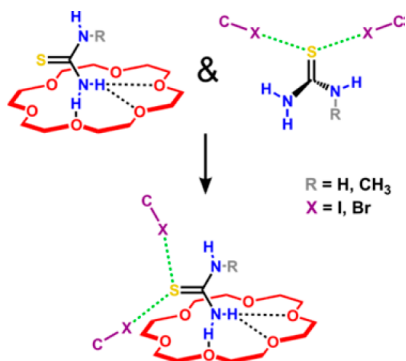


Possessing only ether oxygen atoms as possible acceptors, they were expected to reliably interact with thiourea NHR (R = H, alkyl) groups through multiple hydrogen bonds, thanks to the macrocyclic effect.[35−37] At the same time, due to the high directionality of halogen bonds with respect to the donor,[38] hypothetical formation of halogen bonds with crown ether would not benefit from such enhancement, thus being restricted to C−X···O(ether) interactions, which we expected to be easily outcompeted by C−X···S(thiourea) interactions with their more pronounced covalent character.[34,39] Finally, as our design proved successful, these components will allow for easy expansion of the component set; a large number of thioureas, crown ethers of various sizes, and perfluorinated halogen bond donors are commercially available, not to mention the easy synthetic accessibility of many more.

## 2. RESULTS AND DISCUSSION

Our starting component set (Scheme 2) thus comprised two crown ethers (**A** and **B**), two different thioureas (**C** and **D**), and

**Scheme 2. Components Used**
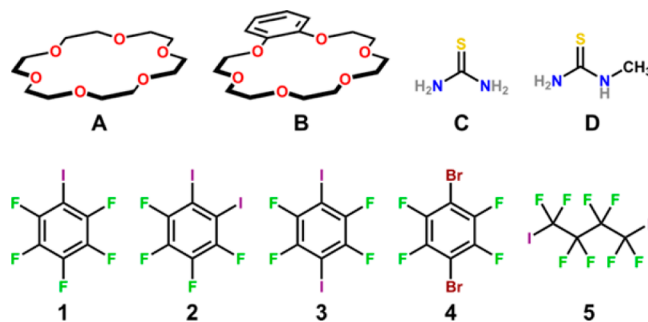


five different perfluorinated halogen bond donors, encompassing mono- and ditopic, aromatic and nonaromatic, linear and nonlinear, and iodine- and bromine-based ones (**1−5**). The cocrystallization screening was initially conducted by simple solution crystallization, which was subsequently modulated where necessary to yield better diffraction quality crystals or a pure bulk phase (see Supporting Information).

The results are summarized in Table 1. Out of 20 possible (2 × 2 × 5) combinations, 15 yielded at least one ternary

**Table 1. Obtained Ternary Cocrystals**

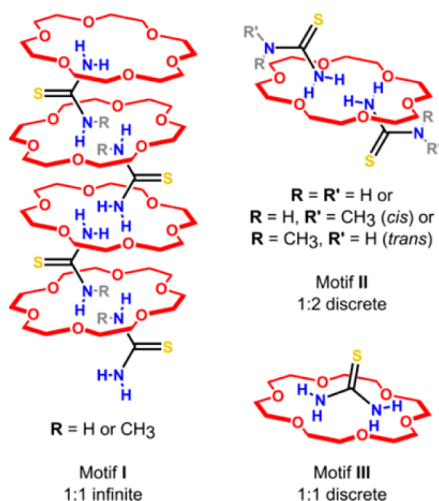|   |   | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| **A** | **C** | A·C·1$_2$ | A·C$_2$·2$_2$ | A·C$_2$·3$_2$ | A·C$_2$·4$_2$ | A·C·5 |
|   | **D** | A·D·1$_{2.2}$ | A·D·2$_2$ | A·D$_2$·3$_2$ | A·D·4$_2$ | A·D·5 |
|   |   |   | A·D$_2$·2$_2$ |   |   |   |
| **B** | **C** | α-B·C·1$_2$ | −[a] | B·C·3 | −[a] | B·C·5 |
|   |   | β-B·C·1$_2$ |   |   |   |   |
|   | **D** | −[a] | −[a] | B·D$_2$·3$_2$ | −[a] | B·D·5 |

[a]No ternary phases were observed.

cocrystal, thus giving a high supramolecular yield of 15/20 = 75%. Taking into account the stoichiometric variations (**A·D·2$_2$**/**A·D$_2$·2$_2$**), polymorphism (**α-B·C·1$_2$**/**β-B·C·1$_2$**), and the fact that some structures were determined at different temperatures, this resulted in a total of 21 different crystal structures (Tables S1a−S1e).

Given the expected orthogonality of hydrogen and halogen bonds in the ternary cocrystal structures, it should be possible to analyze the hydrogen and halogen bonding motifs independently. Focusing on the hydrogen bonding between **A/B** and **C/D**, two binding stoichiometries can be observed, respectively 1:1 and 1:2, originating in three different binding motifs between them (Scheme 3). Whereas the motif **III** only appears in two polymorphs of **B·C·1$_2$** and can thus be considered somewhat exotic, the rest of the structures exhibit either motif **I** or **II**, which makes it worthwhile to explore the possible factors that steer the formation of one or the other. Fortunately, our component set was tailored to enable the comparative analysis of the behavior of each crown ether/thiourea combination in ternary cocrystals with up to five different halogen bond donors.

Thus, for the cocrystal subset with **A** and **C**, motif **II** occurs in 3/5 cocrystals (**A·C$_2$·2$_2$**, **A·C$_2$·3$_2$**, **A·C$_2$·4$_2$**), with the remaining two exhibiting motif **I** (Table 1; also *vide infra*). This might be correlated with the structure of previously described binary cocrystal **A·C$_2$**,[35] which also shows motif **II**, indicating a slight preference for this binding motif, i.e. stoichiometry, with the combination of **A** and **C**. Moreover,

**Scheme 3. Hydrogen Bond-Mediated Binding Motifs between Crown Ethers and Thioureas**[a]



R = R' = H or
R = H, R' = CH₃ (cis) or
R = CH₃, R' = H (trans)

**Motif II**
1:2 discrete

R = H or CH₃

**Motif I**
1:1 infinite

**Motif III**
1:1 discrete

[a]Individual hydrogen bonds are not marked, as they vary between different occurrences of the same motif.

in the systems where **II** is present, with only one NH₂ group fully engaged in hydrogen bonding with **A**, the other NH₂ group is able to facilitate aggregation of **A·C₂** moieties by forming further hydrogen bonds. This is indeed the case for **A·C₂·3₂** and **A·C₂·4₂**, where 2D sheets are formed through N−H⋯S hydrogen bonds between **A·C₂** moieties (Figure 1a). It thus comes as no surprise that the two cocrystals are in fact isomorphous, with the sheets interlinked through halogen bonding with **3** or **4**, respectively, which also form stacks between the sheets (Figure 1b, 1c). Contrasting that is **A·C₂·2₂**, where the **A·C₂** moieties are instead linked into chains by C−I⋯S halogen bonding with **2** (Figure 2). This reveals a clear hydrogen bonding hierarchy in these systems, where the recognition of **C** by **A** through multiple N−H⋯O hydrogen bonds is much more reliable than the N−H⋯S hydrogen bonding, which can be overruled even by C−I⋯S halogen bonding.

Still, judging from the relevant ternary cocrystal structures described here as well as the structure of their binary cocrystal, motif **II** is clearly preferred with **A** and **C**. The combination of **A** and **D** shows significantly different trends, with the preference for motif **I** starting from the previously described binary cocrystal **A·D**[36] and also observed in 4/6 ternary cocrystals reported here. With the potential of halogen bond (XB) donors **1** and **5** for facilitating the formation of motif **I** already established, its reappearance in **A·D·1₂·₂** and **A·D·5** is of little surprise (Table 1; also *vide infra*). However, it might be much more interesting to contrast the behavior of XB donors **2−4** with **A** and **D** to that with **A** and **C**. Especially with **2**, the isolation of two stoichiometric variations, **A·D·2₂** and **A·D₂·2₂**, witnesses the delicate interplay of interactions dictating the exact supramolecular outcome. Initially, **A·D·2₂** is formed as the kinetic product, with **A** and **D** assembling into motif **I** and **2** only serving as a monotopic halogen bond donor, not utilizing its full potential (Figure 3a).[33] The system evolves, however, resulting in the formation of **A·D₂·2₂** with the re-emerging motif **II**, and the formation of chains through N−H⋯S hydrogen bonds supported by C−I⋯S and C−I⋯O halogen bonding with **2** again acting as a ditopic donor (Figure 3b).
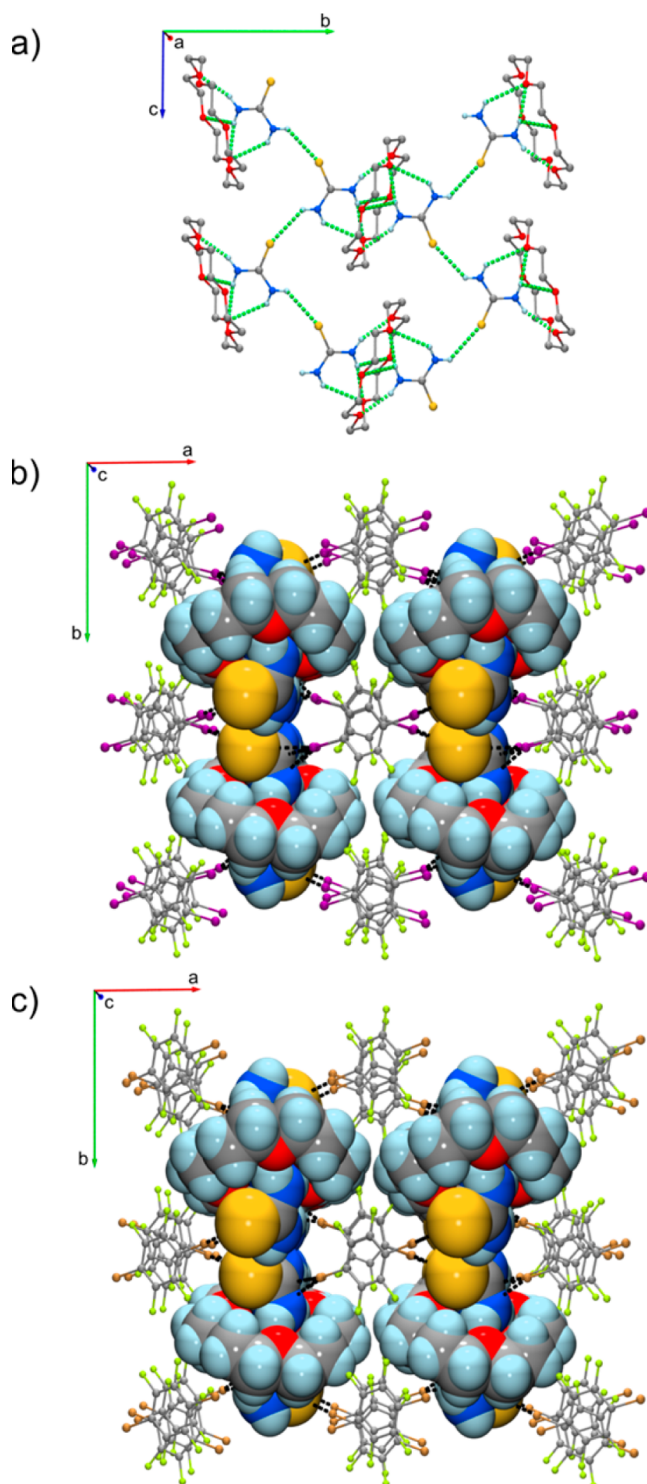


**Figure 1.** (a) Hydrogen bonded **A·C₂** 2D sheets in **A·C₂·3₂** (and **A·C₂·4₂**) with hydrogen atoms of **A** omitted for clarity; (b) packing of **A·C₂·3₂**, with columns of **3** between the **A·C₂** sheets; (c) packing of **A·C₂·4₂**, with columns of **4** between the **A·C₂** sheets.

Next, the structure of **A·D₂·3₂**, featuring thiourea **D** in the more stable *cis* conformation,[40] still exhibits motif **II**, with **A·D₂** moieties connected into chains through C−I⋯S halogen bonds with XB donor **3** (Figure 4a). Based on previous observations with **A** and **C**, formation of an isomorphous structure might be expected with **4**. Yet, with the C−I⋯S halogen bonds playing a pivotal role in the structure of **A·D₂·3₂**, it seems that the
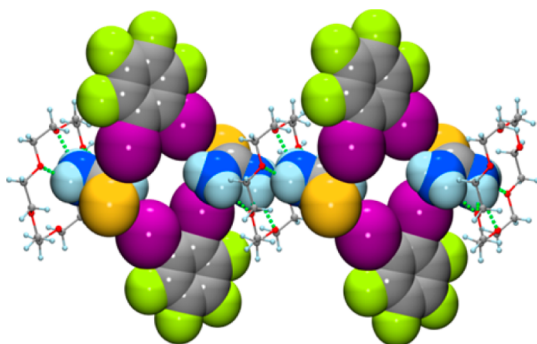
**Figure 2.** Chains of $A \cdot C_2$ motif **II** moieties, formed through C−I···S halogen bonding with **2** as a ditopic donor.
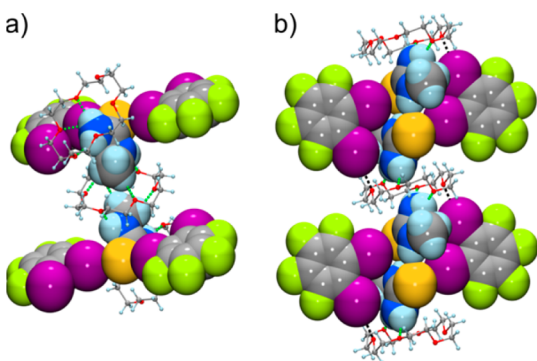


**Figure 3.** (a) Hydrogen bonded motif **I** formed in $A \cdot D \cdot 2_2$, decorated by **2** acting as a monotopic halogen bond donor; (b) motif **II** in $A \cdot D_2 \cdot 2_2$, with $A \cdot D_2$ moieties connected by N−H···S hydrogen bonds and C−I···S halogen bonds with **2**, now as a ditopic donor. Disorder of **2** is omitted in (a).
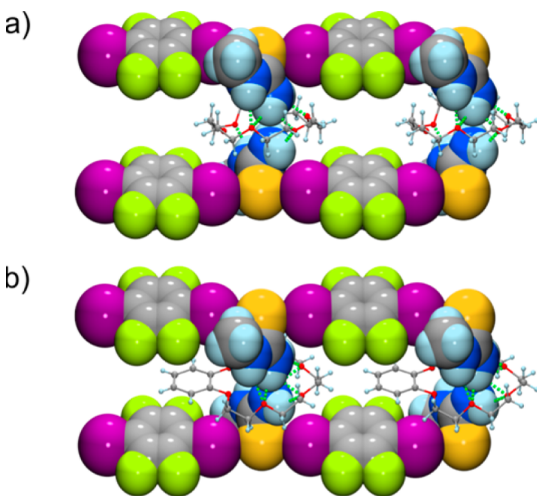


**Figure 4.** Halogen bonded ribbons in the isomorphous structures of (a) $A \cdot D_2 \cdot 3_2$ and (b) $B \cdot D_2 \cdot 3_2$, comprising motif **II** type $A \cdot D_2 / B \cdot D_2$ moieties linked by C−I···S halogen bonds with **3**. Disorder of **A** is not shown in (a).

presumably weaker XB donor **4** cannot support the formation of an isomorphous structure through C−Br···S halogen bonds. Instead, the balance of interactions is once again tipped in favor of motif **I**, resulting in $A \cdot D \cdot 4_2$. While the stoichiometry might be surprising at first, given that **4** is a ditopic XB donor, it is a result of each molecule of **4** forming one C−Br···S and one C−Br···O halogen bond respectively with **D** and **A** (Figure 5).



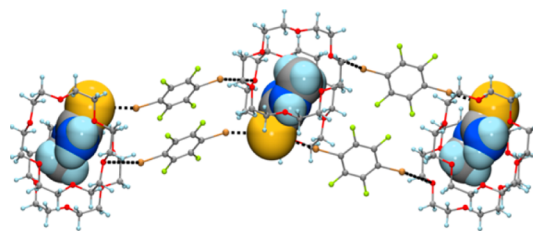**Figure 5.** Hydrogen bonded columns (motif **I**) connected by C−Br···S and C−Br···O halogen bonds with **4** in $A \cdot D \cdot 4_2$.

Remarkably, cocrystallization experiments on the component subset comprising crown ether **A**, thioureas **C** and **D**, and XB donors **1**−**5** resulted in a 100% success rate, with each of the combinations yielding at least one ternary cocrystal. Repeating all these experiments with benzo-crown ether **B** instead of **A**, however, halved the success rate, showing **B** to be a much more selective coformer than **A**. Still, the structures of the ternary cocrystals obtained with such a selective coformer might reveal particularly robust supramolecular motifs, suggesting possible improvements to our synthetic strategy.

As a unique example among all the ternary cocrystals presented here, the combination of benzo-crown ether **B**, thiourea **C**, and XB donor **1** yielded a polymorphic pair of cocrystals $\alpha$-$B \cdot C \cdot 1_2$ (Figure 6a) and $\beta$-$B \cdot C \cdot 1_2$ (Figure 6b), both of which feature the motif **III**, not observed in any of the other structures.
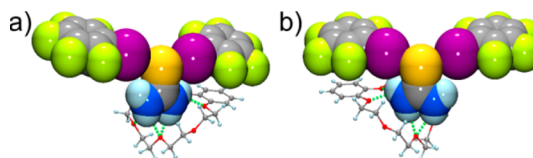


**Figure 6.** Discrete $B \cdot C \cdot 1_2$ assemblies in the two polymorphs (a) $\alpha$-$B \cdot C \cdot 1_2$ and (b) $\beta$-$B \cdot C \cdot 1_2$.

The two polymorphs arise from different packing of the discrete $B \cdot C \cdot 1_2$ moieties: in both structures, they can be seen as forming layers through stacking of the aromatic rings of **B** and **1**. These layers then pack in a parallel [$\beta$-$B \cdot C \cdot 1_2$] or antiparallel fashion [$\alpha$-$B \cdot C \cdot 1_2$], giving rise to two polymorphs (Figures S21−S24). To the best of our knowledge, this is the first example of polymorphism in ternary cocrystals. Both of the other two structures with the combination of **B** and **C**, namely $B \cdot C \cdot 3$ and $B \cdot C \cdot 5$, show the **B** and **C** forming motif **I**, with the hydrogen bonded columns $B \cdot C$ interlinked by C−I···S halogen bonds, respectively through **3** (Figures S25, S26b) or **5** (Figure 8c). Surprisingly, the stacking of the phenyl rings of **B** and **3** does not seem to interfere with the formation of motif **I** between **B** and **C** (Figure S26a) or the infinite halogen-bonded chains between **C** and **3**, with all three seemingly acting in concert (Figure S26b).

Finally, only two ternary cocrystals were observed when the combination of **B** and **D** was employed. One of the two is $B \cdot D_2 \cdot 3_2$, reminiscent of $A \cdot D_2 \cdot 3_2$ not only in its stoichiometry but also in its formation of an isomorphous structure consisting of $B \cdot D_2$ motif **II**-type moieties forming ribbons through C−I···S halogen bonds with **3** (Figure 4b). This might be a unique example of quite a drastic perturbation (replacement of the plain 18-crown-6 **A** with benzo-substituted **B**) which does not radically influence the overall structure. No less remarkably, like

all the cocrystals involving XB donor **5** so far, the **B·D·5** once again sports the motif **I** columns of **B** and **D** interlinked by halogen bonding with **5** (*vide infra*).

Clearly, two intriguing aspects of the mentioned structures deserve particular highlighting. First, the curious stoichiometry of **A·D·1**$_{2.2}$ compared to similar **A·C·1**$_2$ merits further explanation. This seems to be a consequence of the elongation of motif **I**-type columns upon changing from **C** to **D**, which is best quantified through the distance between the centroids of neighboring molecules of **A** in the same column (Figure 7).
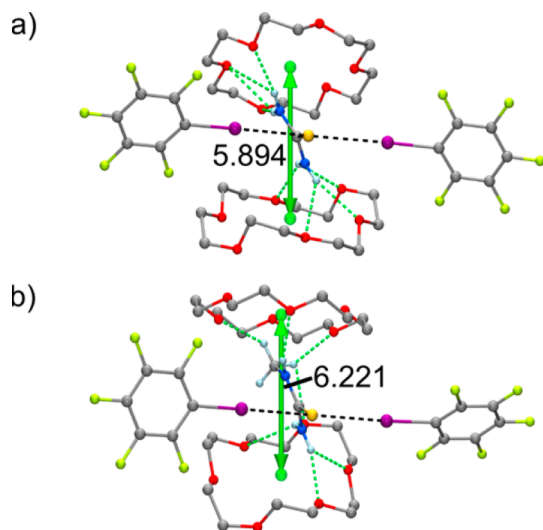


**Figure 7.** Different metrics of the motif **I** columns in (a) **A·C·1**$_2$ and (b) **A·D·1**$_{2.2}$. Hydrogen and halogen bonds are shown as dashed green and black lines, respectively, while the hydrogen atoms of **A** are omitted for clarity.

This expansion of the structure is also reflected in the increased distance between molecules of XB donor **1** in **A·D·1**$_{2.2}$ (Figure 7b), allowing for inclusion of an excess of **1** (Figure S10).

Another striking observation is that of the identical 1:1:1 stoichiometry in all ternary cocrystals involving **5**, with motif **I** also appearing in all four crystal structures, despite their differences (Figure 8). Specifically, it is interesting to note how the difference in halogen bonding connectivity e.g. between **A·C·5** (Figure 8a) and **A·D·5** (Figure 8b) does not affect the above-mentioned stoichiometry and the appearance of motif **I** columns. Moreover, the effect of the motif **I** column elongation upon change from **C** to **D** again becomes evident when comparing **B·C·5** (Figure 8c) and **B·D·5** (Figure 8d), with increased distance allowing for the pairing of **B·D** columns through phenyl ring stacking in **B·D·5**.

Looking at the cocrystal series with XB donors **1** and **5** raises the question: What are the different (possibly shared) characteristics of **1** and **5** driving the formation of motif **I** (or motif **III**, still with the same stoichiometry), unlike the motif **II** formed with **2**, **3**, and **4** as halogen bond donors? In fact, it seems that XB donors **1** and **5** having little in common with **2**–**4** might just be at the root of their different behavior: While **2**–**4** are all aromatic and ditopic donors, **1** is aromatic but monotopic, and **5** is ditopic but aliphatic. Both the monotopic **1** and the conformationally flexible **5** are expected to eliminate or reduce the communication between the halogen bond acceptors, with any significant packing preferences also being absent in the case of **5**. This in turn seems to allow for the
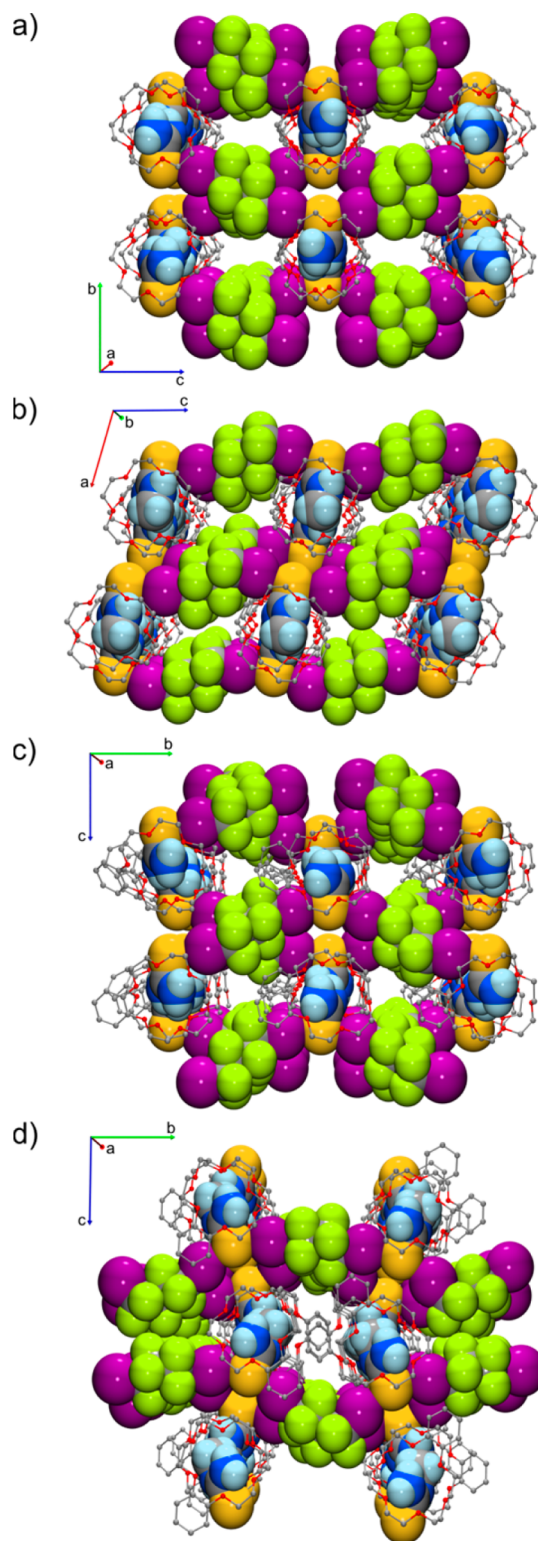


**Figure 8.** Linking of the hydrogen bonded motif **I** columns by halogen bonds with **5** in the structures of (a) **A·C·5**, (b) **A·D·5**, (c) **B·C·5**, and (d) **B·D·5**. Hydrogen atoms of **A** and **B** and minor disorder components are omitted for clarity.

almost perfect orthogonality of hydrogen and halogen bonding in these systems, reliably yielding ternary cocrystals with expected stoichiometries and supramolecular motifs.

On the other hand, focusing the analysis on the halogen bonding reveals very few surprises and only a few general

structural features are worth commenting. Both thioureas **C** and **D** seem to act almost exclusively as bifurcated acceptors,[41] with the only exception being $\mathbf{A \cdot D_2 \cdot 2_2}$ (Figure 3b). The relative geometries manifest a notable degree of variation, judged especially by the X···S···X and X···S−C angles (Tables S3, S5, ..., S35). While the former can be explained by a relatively weak interaction energy dependence on the X···S distance and the N−C−S···X torsional angle on the relevant intervals, as established by Pennington and co-workers,[33] the latter can be explained by a partial C−X···π character due to the π(C=S) electron participation. Moreover, the quadrupolar stacking of the aromatic rings also influences the orientation of the aromatic halogen bond donor with respect to the thiourea acceptor, such as in $\alpha/\beta$-$\mathbf{B \cdot C \cdot 1_2}$ (Figure 6). Nevertheless, the halogen bonding seems to operate rather predictably especially with **1**, **3**, and **5** as donors, forming discrete **1**···**C/D**···**1** assemblies or infinite ···**C/D**···**3/5**···**C/D**···**3/5**··· chains.

In contrast, the sterical crowding of the donor iodine atoms in *ortho*-positions of **2** seems to induce some peculiarity in its behavior, causing it to act as a monotopic donor in $\mathbf{A \cdot D \cdot 2_2}$ (Figure 3a), to form one C−I···S and one C−I···O halogen bond in $\mathbf{A \cdot D_2 \cdot 2_2}$, reinforcing the hydrogen bonded chains (Figure 3b), only to emerge as the seemingly key interaction in linking individual $\mathbf{A \cdot C_2}$ moieties into chains in $\mathbf{A \cdot C_2 \cdot 2_2}$ (Figure 2). Similarly, the expectedly weaker C−Br···S halogen bonding seems to fall victim to aromatic ring stacking of **4** in $\mathbf{A \cdot C_2 \cdot 4_2}$, with one of the two symmetrically independent C−Br···S halogen bonds assuming exclusively C−Br···π character (Figure S6), or to the realization of the robust hydrogen bonding motif **I** and stacking of **4** in $\mathbf{A \cdot D \cdot 4_2}$, forming one C−Br···S and one C−Br···O halogen bond instead (Figure 5), reminiscent of **2** in $\mathbf{A \cdot D_2 \cdot 2_2}$.

## 3. SUMMARY AND CONCLUSIONS

Our work outlines a design-based strategy for construction of ternary cocrystals based on the ability of thioureas to simultaneously engage in hydrogen and halogen bonding in an orthogonal manner, with the crown ethers and the perfluorocarbon halides as the other coformers. This ability is presumed to arise from the fundamentally different nature of the two interactions, the predominantly electrostatic hydrogen bonding, and the halogen bonding with significant charge-transfer character. The strategy was tested on a compact but diverse set of commercially available components, yielding ternary cocrystals for 15/20 different component combinations. Detailed structural analysis was undertaken in order to identify and critically examine the variables influencing its efficacy.

The hydrogen bonding in the obtained ternary cocrystal structures is classified as belonging to one of three different motifs (**I**, **II**, and **III**), whose formation can be correlated with the particular structural features of the components. Namely, the stacking of the aromatic rings (present in benzo-crown ether **B** and XB donors **1–4**), sterical crowding of halogen bond donor atoms (as in, e.g., **2**), or the Br-based donor (**4**) all seem to be important variables which can influence the cocrystal formation. On the other hand, crown ethers **A** and **B** as well as thioureas **C** and **D** are shown to be structurally equivalent to a great degree, with the structural features often preserved on changing between **A** and **B** (e.g., for $\mathbf{A \cdot D_2 \cdot 3_2}$/$\mathbf{B \cdot D_2 \cdot 3_2}$) or **C** or **D** (e.g., for $\mathbf{A \cdot C \cdot 1_2}$/$\mathbf{A \cdot D \cdot 1_{2.2}}$). Remarkably, all of these observations are validated by cocrystals with the nonaromatic, linear, flexible, and iodine-based XB donor **5**,

which all exhibit the same hydrogen bonding motif **I** and the same halogen bonded infinite chains.

Finally, the presented results show how the orthogonality of hydrogen and halogen bonding can be achieved and employed to prepare complex molecular solids—ternary cocrystals. The principles outlined here hold great potential for the effective design of highly complex, functional molecular solids from simple building blocks. This research direction, as well as a detailed study of the particular interactions and their interplay in these systems, is currently being pursued in our laboratory.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02854.

> Experimental details, powder diffraction studies, single crystal X-ray structure analysis with additional figures and tables of selected hydrogen and halogen bonds (PDF) Crystallographic data (CCDC 1469004−1469024 contain the supplementary crystallographic data for this paper; the data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures) (CIF)

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### Notes
The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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