

Isostructural Materials Achieved by Using Structurally Equivalent Donors and Acceptors in Halogen-Bonded Cocrystals

Dominik Cinčić,^[b] Tomislav Friščić,^[a] and William Jones*^[a]

Abstract: We demonstrate the supra-molecular and structural equivalence of two halogen-bond donors (I and Br) and three acceptors (O, NH and S) through the synthesis of seven isostructural halogen-bonded cocrystals, involving six different molecules: 1,4-dibromo- and 1,4-diiodotetrafluorobenzene (donors) and thiomorpholine, thioxane, morpholine, and piperazine (acceptors). The formation of isostructural cocrystals indicates how cocrystallization may be used to overcome shape

and functional group dissimilarities that control molecular arrangement in the solid state. The differences in composition between the seven isostructural cocrystals directly affect the strength and nature of halogen bonds between their constituents, allowing the system-

Keywords: mechanochemistry • cocrystals • functional materials • halogen bonds • supramolecular chemistry

atic variation of cocrystal physical properties, in particular the melting point, without affecting their crystal structure. Replacement of each O or S halogen-bond acceptor with an NH group provided an approximate 70 °C increase in melting point, whereas the replacement of I with Br as the halogen-bond donor lowered the melting point of the resulting solid by a similar amount.

Introduction

The steadily growing number of reports on the application of multicomponent crystals (cocrystals^[1]) as pharmaceutical,^[2] optical,^[3] or synthetic materials^[4] has attracted the interest of materials scientists. Their goal is to further understand the principles and methods associated with cocrystal synthesis. The result is the emergence of reliable strategies to construct two- and three-component cocrystals,^[5] using certain principles of supramolecular chemistry, such as hydrogen-bonding hierarchy^[6] and supramolecular synthons.^[7] In addition, novel methods, such as neat^[8] and liquid-assisted grinding,^[9] have been developed by our group, and

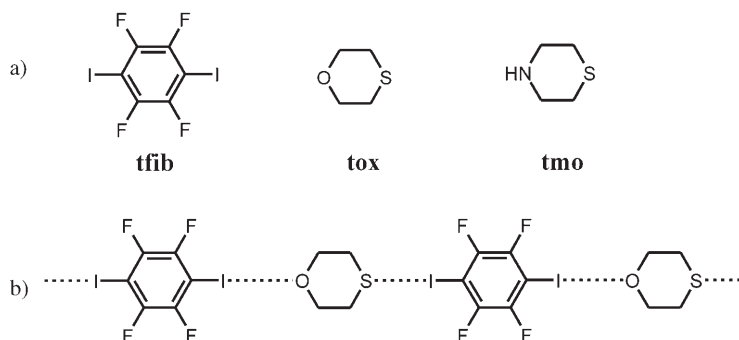
others,^[10] as a means of constructing and for screening cocrystals more efficiently and in a more environmentally friendly fashion than traditional approaches that involve cocrystallization from solution. An overview of the currently available literature on cocrystals reveals that an overwhelming majority of reported cocrystals have been constructed through the use of hydrogen bonds as design elements. The observed bias of crystal engineers towards the hydrogen bond^[11] is most likely caused by its exceptional strength and directionality. However, Resnati and co-workers have recently demonstrated that noncovalent interactions of strength and directionality comparable to hydrogen bonds can be achieved via halogen bonding^[12] involving an electron-deficient halogen atom and an electron-donating group.^[13] For this reason, halogen bonding provides an additional opportunity for the crystal engineer to design functional solid-state architectures.^[14] Indeed, the potential of using halogen bonds to construct functional cocrystals has already been demonstrated in the context of solid-state diacetylene polymerization by Lauher and co-workers and in the context of [2+2] photodimerization by Metrangolo, Resnati, and co-workers.^[15] In comparison to hydrogen bonds, which usually involve a modest number of acceptor atoms (typically O or N), the set of halogen-bond acceptors is larger, encompassing, among others, O, N, S, and Se.^[16] With our interest in exploring halogen bonds involving

[a] Dr. T. Friščić, Dr. W. Jones
Department of Chemistry
and Pfizer Institute for Pharmaceutical Materials Science
University of Cambridge
Lensfield Road, Cambridge CB2 1EW (UK)
E-mail: wj10@cam.ac.uk

[b] D. Cinčić
Laboratory of General and Inorganic Chemistry
Department of Chemistry, Faculty of Science
University of Zagreb, Horvatovac 102a, Zagreb 10000 (Croatia)

Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author.

atoms heavier than oxygen, we decided to construct cocrystals using tetrafluoro-1,4-diiodobenzene (tfib) as a halogen-bond donor^[17] and readily available sulfur-containing molecules 1,4-thioxane (tox) and 1,4-thiomorpholine (tmo) as the acceptors (Scheme 1a).^[18] We anticipated that cocrystallization of tfib with either tox or tmo would result in the formation of one-dimensional polymer chains of alternating donor and acceptor molecules, held together by halogen bonds (Scheme 1b).



Scheme 1. Chemical diagrams of: a) reactants employed and b) expected halogen-bonded chain product.

Results and Discussion

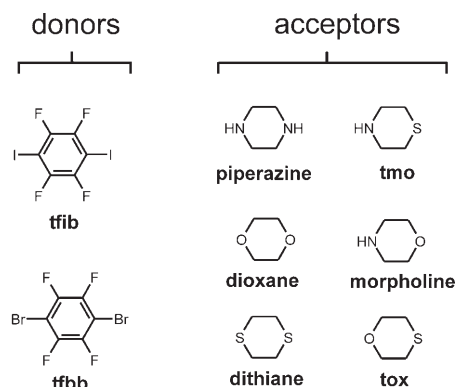
Unexpectedly, cocrystallization of tfib with tox and tmo provided solids that were isostructural. Single-crystal X-ray diffraction revealed that both solids were 1:1 cocrystals of tmo or tox with tfib, composed of anticipated chains that are held together via S...I, N...I, and O...I halogen bonds (Figure 1). In both cocrystals, molecules of tmo or tox were situated on a crystallographic center of symmetry, resulting in a 50:50 disorder of the imino or oxo groups with the thio group. Isostructurality of the cocrystals indicates that the ether oxygen atom in (tox)·(tfib) adopts a structural role equivalent to that of the imino group in (tmo)·(tfib). Furthermore, the disorder of thio with imino or oxo groups suggests that all three groups may exhibit structural equivalence.^[19] This is a surprising observation, considering the significant differences in size and shape between an oxygen atom, a sulfur atom, and the two-atom NH group.

The anticipated structural equivalence of these three halogen-bond acceptor groups may permit, in a crystal engineer-

ing sense, the construction of almost identical supramolecular architectures by using different molecular building blocks. In that way, solids with different physicochemical properties could be systematically constructed following the same blueprint. The difference in properties of the synthesized materials would then largely be the result of different strengths of donor...acceptor halogen bonds. The variety of isostructural solids that could be constructed by this approach could be further extended by using bromine-based halogen-bond donors. This is supported by the similarity of structural motifs found in cocrystals involving either tfib or 1,4-dibromotetrafluorobenzene (tfbb).^[17,20]

As a means of exploring the anticipated isostructurality, we attempted the synthesis of tfib cocrystals with all HN-, O-, and S-congeners of tox and tmo: morpholine, piperazine, dioxane and dithiane. We also proceeded to construct corresponding cocrystals using tfbb

(Scheme 2). To maximize the efficiency of our cocrystal synthesis, we have used grinding as a method of screening for cocrystal formation. Notably,



Scheme 2. The list of halogen bond donors and acceptor molecules utilized to test for structural equivalence of NH, O, and S acceptors and Br and I donors.

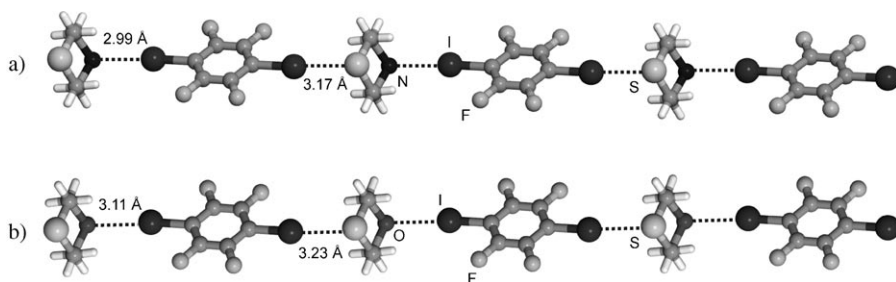


Figure 1. Ball-and-stick representations of a single halogen-bonded chain in the cocrystals of: a) (tfib)-(tmo) and b) (tfib)-(tox).

grinding and liquid-assisted grinding have recently been demonstrated to be superior to solution methods in the synthesis and screening for two- and three-component cocrystals.^[21,22] The ability to synthesize both (tfib)-(tmo) and (tfib)-(tox) cocrystals by grinding together the appropriate components has been con-

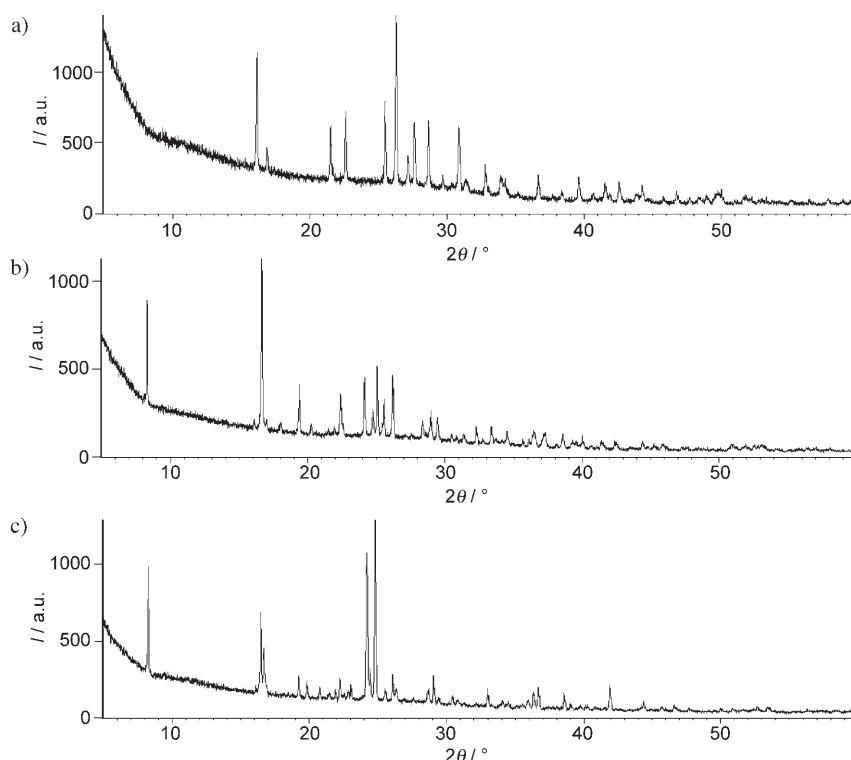


Figure 2. PXRD patterns of: a) tfib; b) grinding product of tfib and tmo and c) grinding product of tfib and tox.















firmed by X-ray powder diffraction (XRPD). In each case the product of grinding exhibited an XRPD pattern that was characteristic of the expected cocrystal (Figure 2). Consequently, XRPD was used as the principal tool to screen for cocrystal formation via grinding. The formation of a solid product with an XRPD pattern different than any of the known polymorphs of the reactant tfib was taken as a proof of cocrystal formation. The similarity of the XRPD pattern of the grinding product with the pattern of solid (tfib)·(tmo) was taken as evidence of isostructurality of the two solids. Detailed results of all grinding-induced cocrystallization experiments are summarized in Table 1. Entries 1–4 reveal the formation of isostructural cocrystals of tfib with tox, tmo, morpholine, and piperazine, confirming the structural equivalence of NH, O, and S groups in halogen bonding. Furthermore, entries 9–11 reveal that cocrystals isomorphous to (tfib)·(tmo) are also obtained using tfbb as the halogen-bond donor and tmo, morpholine, or piperazine as acceptors. For all cocrystals, isostructurality observed by XRPD was also confirmed by single-crystal X-ray structure determination (Table 2). Thus, identical cocrystal architectures have been achieved in at least seven binary cocrystals, involving six different molecular components.^[23] Albeit the structural differences between utilized acceptors are not exceptionally large, we find them significant enough to speculate that the formation of cocrystals can sometimes help overcome the differences in shape and functionality that control the crystal packing properties^[24] of cocrystal compo-

nents on their own.^[25] Indeed, halogen bonding could play an important role in achieving the observed isostructurality, since a previous report on hydrogen-bonded cocrystals of dioxane, morpholine, and piperazine with paracetamol did not reveal any structural similarity between the three.^[26] We find the observed isostructurality particularly interesting in cases of morpholine as the halogen-bond acceptor (Table 1, entries 3 and 10). Namely, morpholine can participate in hydrogen-, as well as halogen-bonding interactions, through its hydrogen-bond acceptor (O) and donor (NH) sites. Indeed, an intermolecular N–H···O hydrogen bond was previously observed in a halogen-bonded cocrystal of morpholine.^[27] Presumably, the ability to form hydrogen bonds might provide another structure-directing interaction in cocrystals of morpholine and so challenge

their isostructurality to (tfib)·(tox). Nevertheless, N–H···O hydrogen bonding is not realized in (tfib)·(morpholine) or (tfbb)·(morpholine), and the two cocrystals retain a structure identical to (tfib)·(tox), based on N···X and O···X (where X=Br, I) halogen bonds.

To explore whether the properties of isostructural cocrystals can be systematically varied through exchanging their components, we have turned to the thermal stability of the cocrystals. Owing to their isostructurality, the difference in thermal stability of the cocrystals would result from permutations of different halogen bonds (i.e. N···I, O···I, S···I, N···Br, O···Br, and S···Br bonds). This expectation is encouraged by the general observation, made by Metrangolo and co-workers, that differences in melting points of halogen-bonded cocrystals reflect the relative strengths of halogen bonds between cocrystal constituents.^[28] In particular, cocrystals with brominated fluorocarbons and iodinated hydrocarbons were found to have a lower melting point than the ones involving iodinated fluorocarbons. Differential scanning calorimetry (DSC) analysis of the synthesized cocrystals revealed that each cocrystal exhibited a different thermal stability. In particular, the melting points of all tfbb cocrystals are lower than for the corresponding tfib analogues. Since halogen bonds with bromine are typically weaker than those involving iodine,^[28] this observation illustrates how halogen-bond strength can be applied to manipulate the thermal behavior of isostructural cocrystals. On the other hand, the comparison of the melting points of isomorphous

Table 1. Results of mechanochemical cocrystallization experiments and melting points of obtained products.

Entry	Donor	Acceptor	Cocrystal ^[c]	Melting point [°C]
1	tfib		yes ^[a]	54 ^[d]
2	tfib		yes ^[a]	133
3	tfib		yes ^[a]	134
4	tfib		yes ^[a]	190 ^[d]
5	tfib		yes ^[b,c]	–
6	tfib		yes ^[c]	112
7	tfib		yes ^[c]	198 ^[d]
8	tfbb		no	–
9	tfbb		yes ^[a]	54
10	tfbb		yes ^[a]	59 ^[d]
11	tfbb		yes ^[a]	116
12	tfbb		no	–
13	tfbb		no	–
14	tfbb		yes ^[c]	107

[a] Cocrystal is isomorphous to (tfib)·(tox). [b] Cocrystal rapidly decomposes in air. [c] Cocrystal is not isomorphous to (tfib)·(tox). [d] Melting is accompanied with decomposition.

cocrystals also allows conclusions to be made about the relative strengths of N···X, O···X, and S···X (with X=Br, I) bonds. Namely, replacement of either one oxygen or one sulfur atom in the structure of (tfib)·(tox) with an NH group results in an increase in the melting point of approximately 80°C (Table 1, entries 1–3). Further replacement of the remaining O or S atom with an imino group provides an additional 60°C increase in the melting point (Table 1, entry 4). A similar relationship is observed for cocrystals of tfbb (Table 1, entries 9–11). The observed differences suggest that the O···I and S···I interactions are of similar strengths, whereas the N···I bond is considerably stronger, consistent with previous observations.^[28] To ascertain that the observed differences in cocrystal melting point are due to the strength

of the N···I bond, rather than an overlooked effect related to the presence of the imino hydrogen atom, we have constructed the cocrystals of both tfib and tfbb with 1,4-diazabicyclo[2.2.2]octane (dabco) (Table 1, entries 7 and 14).^[29] Although (tfib)·(dabco) and (tfbb)·(dabco) cocrystals are not isomorphous with (tfib)·(tox) (Table 2),^[30] they consist of similar halogen-bonded chains, but lack the imino hydrogen atom (Figure 3).

The observed melting points of (tfib)·(dabco) and (tfbb)·(dabco) are very similar to the melting points of the corresponding piperazine cocrystals, indicating that the observed increases in melting point are the result of different relative strengths of the N···I, O···I, and S···I bonds, and that the role of the imino hydrogen atom is, at best, minor.

Although the imino hydrogen atom is probably not a determining factor in controlling thermal properties of the cocrystals synthesized, it may nevertheless play a significant role in steering the formation of identical structures. This is suggested by the differences between the structures of (tfib)·(tmo) (representative of seven isostructural cocrystals) and the cocrystal of tfib with dioxane (Table 2). In (tfib)·(tmo) the hydrogen atom of the imino group occupies the equatorial position on the six-membered ring of the halogen-bond acceptor tmo. In that conformation, the halogen-bond donor (i.e. the I or Br atom of tfib or tfbb, respectively) must approach the trisubstituted imino nitrogen atom of tmo through the axial position (Figure 4a). In case of (tfib)·(dioxane), the halogen-bond acceptor atom is a disubstituted ether oxygen, and tfib molecules can approach the dioxane ring from sterically less hindered equatorial positions. These differences in halogen-bonding geometry suggest that the covalently bonded imino hydrogen atom is a sterically more demanding substituent than the halogen-bonded iodine atom. As a result, an imino group directs halogen-bond formation through the axial position, facilitating the formation of a cocrystal isostructural to (tfib)·(tmo). However, although the presence of an imino group is likely to be important for the formation of a structure similar to (tfib)·(tmo), it is not essential, as illustrated by the cocrystal of tfib with tox.

Conclusion

In summary, we have established that three distinct halogen-bonding acceptors: O, S, and NH groups, can exhibit identical structural behavior. In combination with two structurally equivalent halogen-bond donors iodine and bromine, these acceptors provide a means to construct a variety of isostructural solids.^[23] In particular, we have obtained seven isostructural cocrystals through different pairing of six different halogen-bonding components: tfib, tfbb, tmo, tox, piperazine, and morpholine. To the best of our knowledge, isostructurality encompassing such a large number of compounds and solids has not yet been observed in molecular solids,^[31–33] with the obvious exception of lattice host inclusion compounds.^[19,22,24] However, in lattice host inclusion

Table 2. Principal crystallographic parameters of all cocrystals characterized by single-crystal X-ray diffraction.

Cocrystal	Crystal system, space group	Unit cell parameters (\AA , $^\circ$)
(tfib)-(tox)	triclinic, $P\bar{1}$	$a = 5.3461(2)$; $b = 6.1306(3)$; $c = 10.7131(5)$; $\alpha = 90.110(2)$; $\beta = 93.987(2)$; $\gamma = 100.688(2)$
(tfib)-(tmo)	triclinic, $P\bar{1}$	$a = 5.3592(1)$; $b = 6.1210(2)$; $c = 10.6330(3)$; $\alpha = 90.470(2)$; $\beta = 95.167(2)$; $\gamma = 100.205(2)$
(tfib)-(morpholine)	triclinic, $P\bar{1}$	$a = 5.3012(1)$; $b = 6.0926(2)$; $c = 10.3171(3)$; $\alpha = 90.587(2)$; $\beta = 97.132(2)$; $\gamma = 99.809(2)$
(tfib)-(piperazine)	triclinic, $P\bar{1}$	$a = 5.2777(2)$; $b = 6.0948(2)$; $c = 10.3019(3)$; $\alpha = 90.851(2)$; $\beta = 96.934(2)$; $\gamma = 99.1130(10)$
(tfbb)-(tmo)	triclinic, $P\bar{1}$	$a = 5.2826(3)$; $b = 5.9859(4)$; $c = 10.5152(6)$; $\alpha = 93.304(3)$; $\beta = 95.141(3)$; $\gamma = 100.653(3)$
(tfbb)-(morpholine)	triclinic, $P\bar{1}$	$a = 5.1405(2)$; $b = 5.8904(2)$; $c = 10.2902(4)$; $\alpha = 93.408(2)$; $\beta = 95.712(2)$; $\gamma = 99.554(2)$
(tfbb)-(piperazine)	triclinic, $P\bar{1}$	$a = 5.1235(1)$; $b = 5.9063(2)$; $c = 10.2851(4)$; $\alpha = 93.385(2)$; $\beta = 95.970(2)$; $\gamma = 98.947(2)$
(tfib)-(dioxane)	triclinic, $P\bar{1}$	$a = 4.3981(1)$; $b = 6.4612(2)$; $c = 12.1120(4)$; $\alpha = 81.976(1)$; $\beta = 88.002(1)$; $\gamma = 81.159(1)$
(tfib)-(dabco)	triclinic, $P\bar{1}$	$a = 6.8112(1)$; $b = 10.8944(2)$; $c = 11.4157(2)$; $\alpha = 107.263(1)$; $\beta = 92.854(1)$; $\gamma = 105.076(1)$
(tfbb)-(dabco)	triclinic, $P\bar{1}$	$a = 6.0248(1)$; $b = 10.3547(2)$; $c = 12.2080(3)$; $\alpha = 102.983(1)$; $\beta = 102.568(1)$; $\gamma = 105.033(1)$

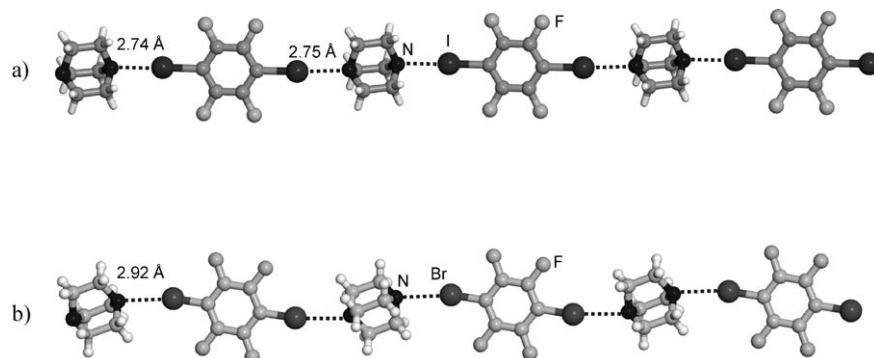


Figure 3. Ball-and-stick representations of a single halogen-bonded chain: a) (tfib)-(dabco) and b) (tfbb)-(dabco) cocrystal.

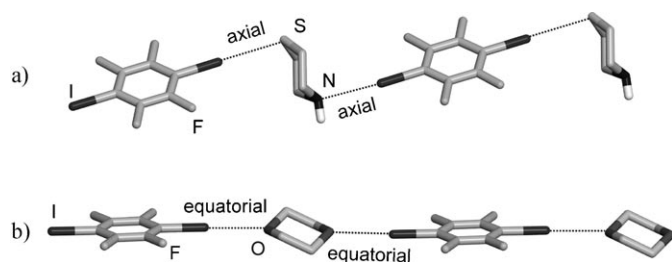


Figure 4. Wireframe representations of halogen-bonded chains in: a) (tfib)-(tmo) and b) (tfib)-(dioxane), displaying the differences in halogen-bonding geometry.

compounds isostructurality is achieved by introducing changes to a loosely bound guest molecule, leaving the overall host structure largely intact.^[22] In the cases reported here, changes to cocrystal components modify the halogen bonds that support the supramolecular architecture of the cocrystal. As a result, we were able to systematically modify the strength of the halogen bond, and alter the thermal

properties of the cocrystal without changes to its supra-molecular architecture. This is exemplified by the cocrystal melting point that varied from 55 °C for (tfbb)-(tmo) to 195 °C for (tfib)-(piperazine). In the context of materials design, we notice that the isostructurality of the seven cocrystals also enables further fine-tuning of the properties of the solids, through the formation of solid solutions.^[34] That pure cocrystal components adopt different crystal structures in the solid state^[25,26] suggests isostructurality is facilitated by cocrystallization and halogen-bond formation. To understand how halogen bonding might help overcome shape and functionality differences between individual cocrystal components, we are now exploring further halogen-bonded cocrystal systems.

Experimental Section

General considerations: All materials were commercially available from Sigma-Aldrich Chemical Co. and were used without purification. In a typical grinding experiment, either tfib or tfbb (200 mg) were placed in a stainless steel grinding jar (10 mL), along with an equimolar amount of the halogen-bond acceptor. No additional liquid was used in case of liquid acceptors, whereas for dithiane

and piperazine 50 μL of nitromethane were added to the grinding mixture before the experiment. Two stainless steel balls of 7 mm radius were used for grinding, that was performed for 30–40 min on a Retsch MM200 grinder mill. Typically, the mill operated at a frequency of 30 Hz. CCDC-649667–CCDC-649676 contain the supplementary crystallographic data for (tfib)-(tmo), (tfib)-(tox), (tfib)-(morpholine), (tfib)-(piperazine), (tfib)-(dioxane), (tfib)-(dabco), (tfbb)-(tmo), (tfbb)-(morpholine), (tfbb)-(piperazine), and (tfbb)-(dabco), respectively, this paper. These data can be obtained free of charge The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Details of single crystal growth from solution for each experiment are provided as Supporting Information, along with experimental and simulated XRPD patterns, and DSC thermograms for all relevant materials.

Mechanochemical synthesis of (tfib)-(tmo): tfib (200 mg, 0.50 mmol) was placed in a 10-mL stainless steel grinding jar along with tmo (51 μL , 52 mg, 0.51 mmol) and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 30 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated complete conversion of the starting materials to (tfib)-(tmo).

Mechanochemical synthesis of (tfib)-(tox): tfib (200 mg, 0.50 mmol) was placed in a 10-mL stainless steel grinding jar along with tox (47 μL ,

52 mg, 0.50 mmol) and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 30 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated complete conversion of the starting materials to (tfib)-(tox).

Mechanochemical synthesis of (tfib)-(morpholine): tfib (200 mg, 0.50 mmol) was placed in a 10-mL stainless steel grinding jar along with morpholine (44 μ L, 44 mg, 0.51 mmol) and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 30 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated complete conversion of the starting materials to (tfib)-(morpholine).

Mechanochemical synthesis of (tfib)-(dioxane): tfib (200 mg, 0.50 mmol) was placed in a 10-mL stainless steel grinding jar along with dioxane (45 μ L, 47 mg, 0.53 mmol) and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 30 min in a Retsch MM200 Shaker Mill. Analysis of the solid product via XRPD indicated incomplete conversion of the starting materials to (tfib)-(dioxane). According to relative intensities of XRPD peaks of reactant and product, using larger amount of dioxane led to a higher yield of the cocrystal. Upon standing at room temperature the obtained cocrystal decomposed to tfib within 15 min.^[23]

Mechanochemical synthesis of (tfib)-(piperazine): An equimolar mixture of tfib (164 mg, 0.41 mmol) and piperazine (36 mg, 0.41 mmol) was placed in a 10-mL stainless steel grinding jar, along with nitromethane (50 μ L) and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 60 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated complete conversion of the starting materials to (tfib)-(piperazine).

Mechanochemical reaction of tfib and dithiane: tfib (150 mg, 0.37 mmol) was placed in a 10-mL stainless steel grinding jar along with dithiane (23 mg, 0.19 mmol), nitromethane (50 μ L), and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 45 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated complete conversion of the starting materials to a yet unidentified product. Repeating the reaction with different stoichiometric amounts of the two components suggests the product is a cocrystal of composition (tfib)₂:(dithiane).

Mechanochemical synthesis of (tfib)-(dabco): An equimolar mixture of tfib (156 mg, 0.39 mmol) and dabco (44 mg, 0.39 mmol) was placed in a 10-mL stainless steel grinding jar, along with nitromethane (50 μ L) and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 60 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated complete conversion of the starting materials to (tfib)-(dabco).

Mechanochemical synthesis of (tfbb)-(tmo): tfbb (200 mg, 0.65 mmol) was placed in a 10-mL stainless steel grinding jar along with tmo (66 μ L, 68 mg, 0.66 mmol) and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 30 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated complete conversion of the starting materials to (tfbb)-(tmo).

Attempt of mechanochemical synthesis of (tfbb)-(tox): tfbb (200 mg, 0.65 mmol) was placed in a 10-mL stainless steel grinding jar along with tox (63 μ L, 70 mg, 0.67 mmol) and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 30 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD revealed only the presence of solid tfbb.

Mechanochemical synthesis of (tfbb)-(morpholine): tfbb (200 mg, 0.65 mmol) was placed in a 10-mL stainless steel grinding jar along with morpholine (60 μ L, 60 mg, 0.69 mmol), acetonitrile (20 μ L), and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 40 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated complete conversion of the starting materials to (tfbb)-(morpholine).

Attempt of mechanochemical synthesis of (tfbb)-(dioxane): tfbb (200 mg, 0.65 mmol) was placed in a 10-mL stainless steel grinding jar along with dioxane (60 μ L, 62 mg, 0.70 mmol) and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 30 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated only the presence of solid tfbb.

Mechanochemical synthesis of (tfbb)-(piperazine): tfbb (120 mg, 0.39 mmol) was placed in a 10-mL stainless steel grinding jar along with piperazine (34 mg, 0.39 mmol), nitromethane (50 μ L), and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 30 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated complete conversion of the starting materials to (tfbb)-(piperazine).

Attempt of mechanochemical reaction of tfbb and dithiane: tfbb (130 mg, 0.42 mmol) was placed in a 10-mL stainless steel grinding jar along with dithiane (51 mg, 0.43 mmol), nitromethane (50 μ L), and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 40 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated only the presence of solids tfbb and dithiane.

Mechanochemical synthesis of (tfbb)-(dabco): tfbb (130 mg, 0.42 mmol) was placed in a 10-mL stainless steel grinding jar along with dabco (48 mg, 0.43 mmol), nitromethane (50 μ L), and two 7 mm-diameter stainless steel grinding balls. The mixture was then milled for 40 min in a Retsch MM200 Shaker Mill. Analysis of the solid product by XRPD indicated complete conversion of the starting materials to (tfbb)-(dabco).

Acknowledgements

Drs Pete Marshall and Neil Feeder of Pfizer Global R&D are acknowledged for fruitful discussions. We also thank Prof. Branko Kaitner at the Laboratory of General and Inorganic Chemistry, Department of Chemistry, University of Zagreb, for helpful advice and support, and Dr John E. Davies for collecting the single-crystal X-ray diffraction data.

- [1] a) M. J. Zaworotko, *Cryst. Growth Des.* **2007**, *7*, 4–9; b) A. N. Sokolov, T. Frišćić, L. R. MacGillivray, *J. Am. Chem. Soc.* **2006**, *128*, 2806–2807; c) G. R. Desiraju, *CrystEngComm* **2003**, *5*, 466–467.
- [2] a) P. Vishweshwar, J. A. McMahon, J. A. Bis, M. J. Zaworotko, *J. Pharm. Sci.* **2006**, *95*, 499–516; b) W. Jones, W. D. S. Motherwell, A. V. Trask, *MRS Bull.* **2006**, *31*, 875–879; c) A. V. Trask, W. D. S. Motherwell, W. Jones, *Cryst. Growth Des.* **2005**, *5*, 1013–1021; d) Ö. Almarsson, M. J. Zaworotko, *Chem. Commun.* **2004**, 1889–1896.
- [3] a) T. Frišćić, L. R. MacGillivray, *Z. Kristallogr.* **2005**, *220*, 351–363; b) G. S. Papaefstathiou, Z. Zhong, L. Geng, L. R. MacGillivray, *J. Am. Chem. Soc.* **2004**, *126*, 9158–9159.
- [4] a) T. Frišćić, L. R. MacGillivray, *Chem. Commun.* **2005**, 5748–5750; b) X. Gao, T. Frišćić, L. R. MacGillivray, *Angew. Chem.* **2003**, *115*, 234–238; *Angew. Chem. Int. Ed.* **2004**, *43*, 232–236; c) N. Shan, W. Jones, *Green Chem.* **2003**, *5*, 728–730; d) J. H. Kim, S. V. Lindeman, J. K. Kochi, *J. Am. Chem. Soc.* **2001**, *123*, 4951–4959.
- [5] a) C. B. Aakeröy, N. Schulltheiss, J. Desper, C. Moore, *New J. Chem.* **2006**, *30*, 1452–1460; b) C. B. Aakeröy, J. Desper, M. E. Fasulo, *CrystEngComm* **2006**, *8*, 586–588; c) C. B. Aakeröy, A. M. Beatty, B. A. Helfrich, *J. Am. Chem. Soc.* **2002**, *124*, 14425–14432; d) C. B. Aakeröy, A. M. Beatty, B. A. Helfrich, *Angew. Chem.* **2001**, *113*, 3340–3342; *Angew. Chem. Int. Ed.* **2001**, *40*, 3240–3242.
- [6] a) C. B. Aakeröy, K. R. Seddon, *Chem. Soc. Rev.* **1993**, *22*, 397–407; b) M. C. Etter, *J. Phys. Chem.* **1991**, *95*, 4601–4610.
- [7] G. R. Desiraju, *Angew. Chem.* **1995**, *107*, 2541–2558; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2311–2327.
- [8] a) S. Karki, T. Frišćić, W. Jones, W. D. S. Motherwell, *Mol. Pharm.* **2007**, *4*, 347–354; b) A. V. Trask, W. Jones, *Topics Curr. Chem.* **2005**, *254*, 41–70.
- [9] a) T. Frišćić, L. Fábíán, J. C. Burley, W. Jones, W. D. S. Motherwell, *Chem. Commun.* **2006**, 5009–5011; b) A. V. Trask, W. D. S. Motherwell, W. Jones, *Chem. Commun.* **2004**, 890–891; c) N. Shan, F. Toda, W. Jones, *Chem. Commun.* **2002**, 2372–2373.
- [10] a) Y. Imai, N. Tajima, T. Sato, R. Kuroda, *Org. Lett.* **2006**, *8*, 2941–2944; b) D. Braga, F. Grepioni, *Angew. Chem.* **2004**, *116*, 4092–4102; *Angew. Chem. Int. Ed.* **2004**, *43*, 4002–4011; c) M. D. Hollingsworth, B. D. Santarserio, H. Oumar-Mahamat, C. J. Nichols, *Chem.*

- Mater.* **1991**, 3, 23–25; d) M. C. Etter, S. M. Reutzel, C. G. Choo, *J. Am. Chem. Soc.* **1993**, 115, 4411–4412.
- [11] M. D. Ward, *Chem. Commun.* **2005**, 5838–5842.
- [12] a) P. Metrangolo, H. Neukirch, T. Pilati, G. Resnati, *Acc. Chem. Res.* **2005**, 38, 386–395; b) P. Metrangolo, G. Resnati, *Chem. Eur. J.* **2001**, 7, 2511–2519.
- [13] P. Metrangolo, T. Pilati, G. Resnati, *CrystEngComm* **2006**, 8, 946–947.
- [14] a) P. Metrangolo, G. Resnati, T. Pilati, R. Liantonio, F. Meyer, *J. Pol. Sci. A*, **2007**, 45, 1–15; b) K. Bouchmella, B. Boury, S. G. Dutremez, A. van der Lee, *Chem. Eur. J.* **2007**, 13, 6130–6138; c) E. Corradi, S. V. Meille, M. T. Messina, P. Metrangolo, G. Resnati, *Angew. Chem.* **2000**, 112, 1852–1856; *Angew. Chem. Int. Ed.* **2000**, 39, 1782–1786.
- [15] a) A. Sun, J. W. Lauher, N. S. Goroff, *Science* **2006**, 312, 1030–1034; b) T. Carona, R. Liantonio, T. A. Logothetis, P. Metrangolo, T. Pilati, G. Resnati, *J. Am. Chem. Soc.* **2004**, 126, 4500–4501.
- [16] a) M. T. Messina, P. Metrangolo, W. Panzeri, T. Pilati, G. Resnati, *Tetrahedron* **2001**, 57, 8543–8550; b) O. Holmesland, C. Romming, *Acta Chem. Scand.* **1966**, 20, 2601–2610; c) P. Gagnaux, B. P. Susz, *Helv. Chim. Acta* **1960**, 43, 948–956.
- [17] R. Bailey Walsh, C. W. Padgett, P. Metrangolo, G. Resnati, T. W. Hanks, W. T. Pennington, *Cryst. Growth Des.* **2001**, 1, 165–175.
- [18] The reported adduct of tmo and molecular iodine is most likely held together via halogen bonds, see: M. Arca, F. Cristiani, F. A. Devillanova, A. Garau, F. Isaia, V. Lippolis, G. Verani, *Heteroat. Chem.* **1997**, 8, 139–146.
- [19] A. Dey, G. R. Desiraju, *CrystEngComm* **2004**, 6, 642–646.
- [20] a) A. Forni, P. Metrangolo, T. Pilati, G. Resnati, *Cryst. Growth Des.* **2004**, 4, 291–295; b) A. De Santis, A. Forni, R. Liantonio, P. Metrangolo, T. Pilati, G. Resnati, *Chem. Eur. J.* **2003**, 9, 3974–3983.
- [21] a) D. Braga, S. L. Giuffreda, F. Grepioni, A. Pettersen, L. Maini, M. Curzi, M. Polito, *Dalton Trans.* **2006**, 10, 1249–1263; b) D. Braga, D. D'Addario, S. L. Giuffreda, L.; Maini, M. Polito, F. Grepioni, *Topics Curr. Chem.* **2005**, 254, 71–94.
- [22] a) T. Friščić, A. V. Trask, W. Jones, W. D. S. Motherwell, *Angew. Chem.* **2006**, 118, 7708–7712; *Angew. Chem. Int. Ed.* **2006**, 45, 7546–7550; b) R. K. R. Jetti, A. Nangia, F. Xue, T. C. W. Mak, *Chem. Commun.* **2001**, 919–920; c) C. M. Reddy, L. S. Reddy, S. Aitipamula, A. Nangia, C.-K. Lam, T. C. W. Mak, *CrystEngComm* **2005**, 7, 44–52; d) D. K. Saha, R. K. R. Jetti, S. Reddy, S. Aitipamula, A. Nangia, *Cryst. Growth Des.* **2005**, 5, 887–899.
- [23] In a single instance, grinding of tfib and dioxane provided a product with a PXRD pattern similar to the one of (tfib)-(tmo), suggesting altogether eight isostructural solids. However, the solid rapidly decomposed into tfib and all subsequent attempts to synthesize the solid again failed, leading only to the structurally different (tfib)-(dioxane) cocrystal described in the text.
- [24] a) A. J. Cruz-Cabeza, G. M. Day, W. D. S. Motherwell, W. Jones, *J. Am. Chem. Soc.* **2006**, 128, 14466–14467; b) A. I. Kitaigorodsky, *Chem. Soc. Rev.* **1978**, 7, 133–163; c) A. I. Kitaigorodsky, in: 'Molecular Crystals and Molecules', Academic Press, New York, **1973**.
- [25] Solid piperazine, morpholine, and dioxane have different crystal structures: a) A. Parkin, I. D. H. Oswald, S. Parsons, *Acta Crystallogr. Sect. B* **2004**, 60, 219; b) T. Koritsánsky, M. K. Strumpel, J. Buschmann, P. Luger, N. K. Hansen, V. J. Pichon-Pesme, *J. Am. Chem. Soc.* **1991**, 113, 9148–9154.
- [26] I. D. H. Oswald, D. R. Allan, P. A. McGregor, W. D. S. Motherwell, S. Parsons, C. R. Pulham, *Acta Crystallogr. Sect. B*, **2002**, 58, 1057–1058.
- [27] A. S. Batsanov, J. A. K. Howard, *Acta Crystallogr. Sect. C*, **2000**, 56, 252–253.
- [28] a) R. Liantonio, P. Metrangolo, T. Pilati, G. Resnati, A. Stevenazzi, *Cryst. Growth Des.* **2003**, 3, 799–803; b) W. Navarrini, P. Metrangolo, T. Pilati, G. Resnati, *New. J. Chem.* **2000**, 24, 777–780; c) M. T. Messina, P. Metrangolo, W. Panzeri, E. Ragg, G. Resnati, *Tetrahedron Lett.* **1998**, 39, 9069–9072.
- [29] The crystal structure of (tfib)-(dabco) has previously been reported, see: M. Bolte, private communication in the CSD, **2004**. CCDC reference code: ISIHUN.
- [30] Cocrystals of (tfib)-(dabco) and (tfbb)-(dabco) are not isostructural.
- [31] For examples of isostructurality in molecular crystals see: a) L. Fábán, G. Argay, A. Kálmán, M. Báthori, *Acta Crystallogr. Sect. B*, **2002**, 58, 710–720; b) L. Fábán, A. Kálmán, G. Argay, G. Bernáth, Z. Cs. Gyarmati, *Chem. Commun.* **2004**, 2114–2115; c) L. Fábán, A. Kálmán, *Acta Crystallogr. Sect. B*, **1999**, 55, 1099–1108.
- [32] Isostructural molecular crystals usually appear as pairs, but several examples of up to four isostructural molecular crystals are known, see: a) N. J. Babu, A. Nangia, *Cryst. Growth Des.* **2006**, 6, 1753–1756; b) J. Kansikas, K. Sipila, *Acta Crystallogr. Sect. C*, **1997**, 53, 1127–1131; c) L. Párkányi, A. Kálmán, S. Sharma, D. M. Nolen, K. H. Pannell, *Inorg. Chem.* **1994**, 33, 180–182; d) S. Stankovic, J. Petrovic, D. Miljkovic, V. Pejanovic, R. Kovacevic, A. Stefanovic, M. Bruvo, *Acta Crystallogr. Sect. C* **1993**, 49, 1248–1552; e) A. Kálmán, L. Párkányi, G. Argay, *Acta Crystallogr. Sect. B*, **1993**, 49, 1039–1049.
- [33] Two pairs of isostructural halogen-bonded cocrystals have been reported so far, see: a) R. Liantonio, P. Metrangolo, F. Meyer, T. Pilati, W. Navarrini, G. Resnati, *Chem. Commun.* **2006**, 1819–1821; b) P. Metrangolo, T. Pilati, G. Resnati, A. Stevenazzi, *Chem. Commun.* **2004**, 1492–1493.
- [34] Formation of a solid solution between two cocrystals has recently been reported, see: M. Dabros, P. R. Emery, V. R. Thalladi, *Angew. Chem.* **2007**, 119, 4210–4213; *Angew. Chem. Int. Ed.* **2007**, 46, 4132–4135; .

Received: July 19, 2007

Published online: October 23, 2007