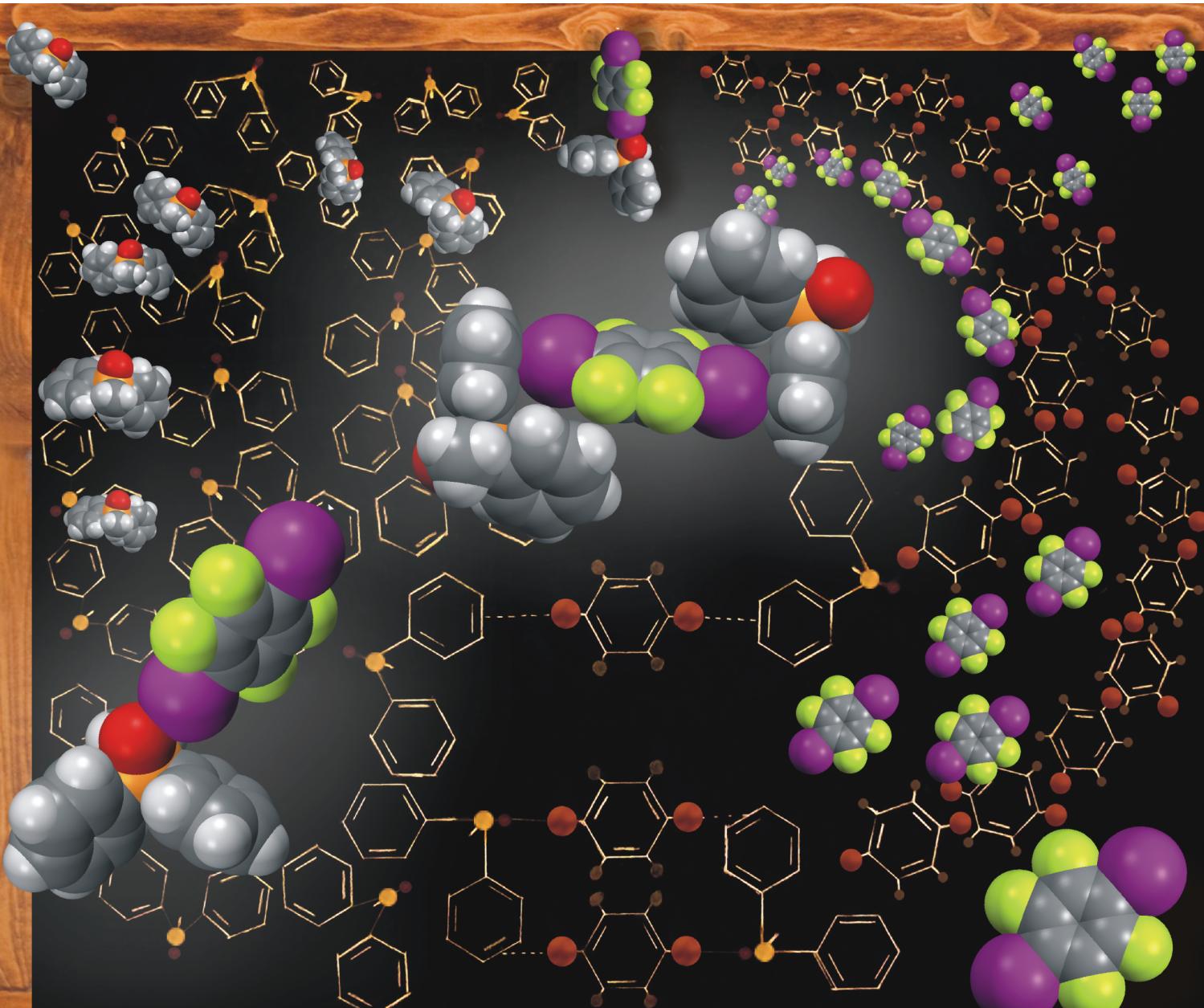


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## COMMUNICATION

# Switching between halogen- and hydrogen-bonding in stoichiometric variations of a cocrystal of a phosphine oxide†

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We describe a two-component cocrystal composition which appears in two stoichiometric variations exhibiting different supramolecular architectures: whereas one stoichiometric variation displays C-H···O hydrogen bonds, the second form exhibits short I···O halogen bonds alongside I···π halogen-bonded contacts; the two forms are readily prepared mechanochimically by varying the relative amounts of starting materials in a liquid-assisted grinding process.

Halogen bonds<sup>1</sup> are a viable alternative to hydrogen bonding<sup>2</sup> in crystal engineering, with potential significance in biological systems.<sup>3</sup> In particular, the strength and directionality of halogen bonds allows the formation of multi-component crystals (cocrystals) using a diverse set of acceptor (*e.g.* N, O, S, C)<sup>4,5</sup> and donor atoms (Br, I)<sup>6</sup> which are not common in the context of hydrogen bonding. Halogen bond-driven cocrystallisation has been used in constructing liquid crystals,<sup>7</sup> photoactive materials, catenanes and porous organic solids,<sup>8</sup> metal-organic and organometallic solids,<sup>5</sup> anion recognition and materials for the separation of long-chain fluorocarbon derivatives.<sup>9</sup> More recently, halogen bonds have been explored in the formation of self-assembled single- and two-component molecular monolayers.<sup>10</sup>

The design of cocrystals is based on robust supramolecular synthons based on directional interactions.<sup>11</sup> However, the availability of different binding sites on the acceptor or donor molecules can sometimes lead to the formation of alternative supramolecular structures, *e.g.* cocrystals with different stoichiometric compositions.<sup>12</sup> While the formation of such cocrystal stoichiometric variations has been well documented in the context of hydrogen-bonded cocrystals, we have also demonstrated how the competition of nitrogen and sulfur halogen bond acceptor sites can lead to halogen-bonded cocrystals with different stoichiometric

ratios of acceptor and donor.<sup>13a</sup> A similar effect was observed in the competition of sp<sup>2</sup> nitrogen and oxygen atom acceptors.<sup>13b</sup> Moreover, understanding of cocrystal stoichiometry and stoichiometric variations has attracted considerable interest in the context of hydrogen-bonded pharmaceutical cocrystals.<sup>14</sup>

In principle, the competition between supramolecular interactions can also lead to a different type of frustration in solid state structures, in which the structure can be assembled through different kinds of supramolecular interactions. To the best of our knowledge there have been no reports of cocrystal stoichiometric variations in which different compositions are associated with a competition between halogen and hydrogen bonds. We now describe the first case of a two-component cocrystal which can exist in two stoichiometric variations, one defined by hydrogen-bonded and the other through halogen-bonded contacts.

The potential of phosphine oxides as acceptors of I···O halogen bond was recently explored.<sup>15</sup> Our experiments<sup>15a</sup> with triphenylphosphine oxide as the halogen bond acceptor also suggested that cocrystals based on such building blocks are sensitive to the effects of crystal packing. As an extension of this work, we have explored cocrystallisation of methyl diphenylphosphine oxide (**mdppo**) as the acceptor with the conventional halogen bond donor 1,4-diiodotetrafluorobenzene (**tfib**) (Fig. 1a).

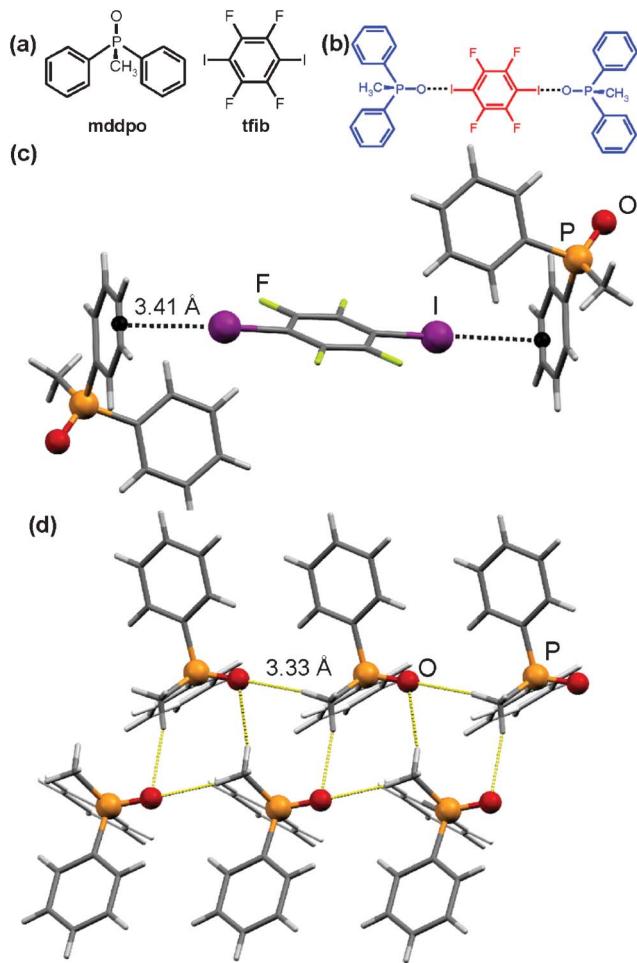
Our first attempt to obtain cocrystals of **mdppo** and **tfib** by crystallisation from nitromethane solution provided needle-like single crystals. Crystal structure determination‡ revealed the composition of the cocrystal was (**mdppo**)<sub>2</sub>·(**tfib**). Instead of forming the anticipated I···O halogen bonds, **mdppo** and **tfib** in (**mdppo**)<sub>2</sub>·(**tfib**) were found to connect through I···C interactions involving the phenyl rings of **mdppo** (Fig. 1c). The iodine atom forms two almost identical interactions with carbon atoms of the phenyl ring (I···C distances 3.478(3) Å and 3.481(3) Å), with the separation between the iodine atom and a centroid between the two carbon atoms of 3.41 Å. Each of the two I···C distances is *ca.* 6% shorter than the expected sum of van der Waals radii (3.7 Å).<sup>16</sup> The molecules of **mdppo** in (**mdppo**)<sub>2</sub>·(**tfib**) assemble into ladders with C<sub>1</sub><sup>1</sup>(4) R<sub>3</sub><sup>2</sup>(8) topology<sup>17</sup> based on C-H···O hydrogen bonds (Fig. 1d, C···O separations 3.328(3) Å and 3.390(3) Å with associated C-H···O angles 172.7° and 162.8°). The molecules of **tfib** form columns separating the ladders of **mdppo** (Fig. 2a). The nearest-neighbor **mdppo** molecules that form opposite sides of each supramolecular ladder are related through glide mirror symmetry, resulting in a *cis*-orientation of equivalent phenyl rings. Such

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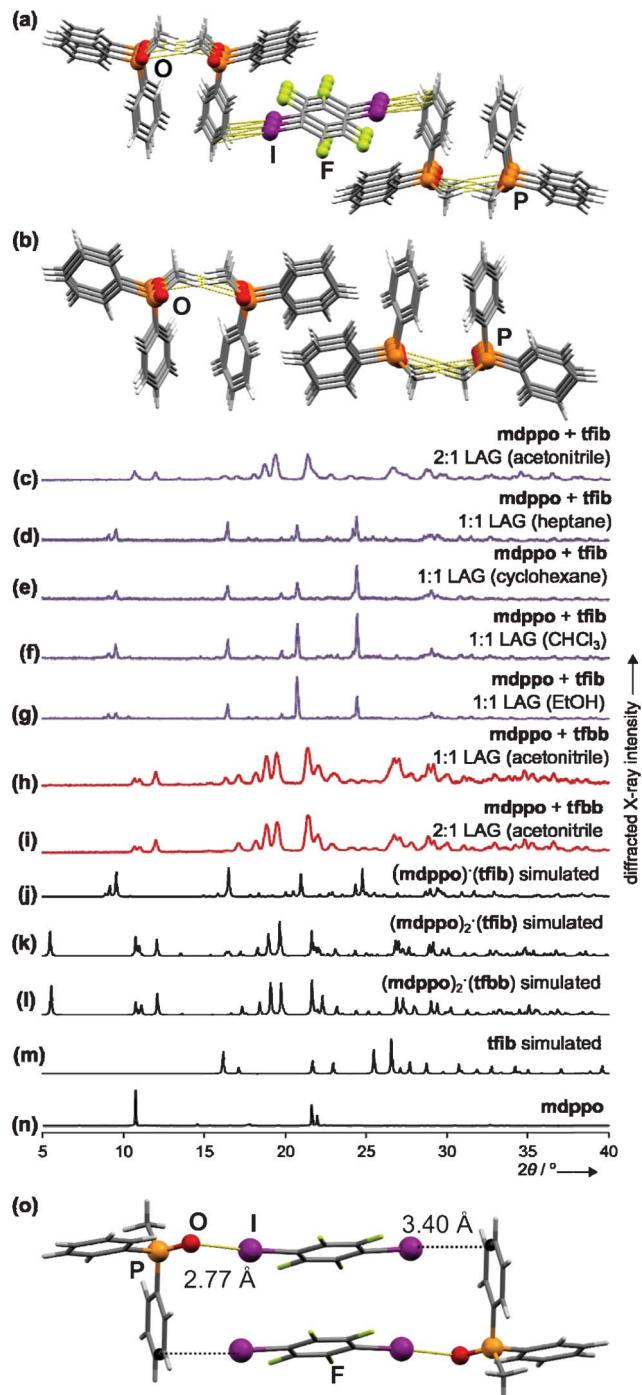
† Electronic supplementary information (ESI) available: Experimental details, additional selected PXRD patterns, DSC thermograms and FTIR-ATR spectra. CCDC reference numbers 819334–819337 and 878592. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ce25653c



**Fig. 1** (a) Reactant molecules; (b) schematic diagram of a proposed supramolecular assembly of **mddpo** and **tfib** based on I···O halogen bonds; (c) fragment of the cocrystal structure of  $(\text{mddpo})_2 \cdot (\text{tfib})$ , displaying the short I···C contacts and centroids representing the midpoint of the C–C aromatic bond. (d) fragment of the C–H···O hydrogen-bonded framework in solid  $(\text{mddpo})_2 \cdot (\text{tfib})$ .

hydrogen-bonded ladders in  $(\text{mddpo})_2 \cdot (\text{tfib})$  strongly resemble the supramolecular motif previously observed in pure **mddpo** (CCDC code NAXBIO, Fig. 2b).<sup>18</sup>

The unexpected absence of strong I···O halogen bonding in  $(\text{mddpo})_2 \cdot (\text{tfib})$  led us to extend our cocrystal search with liquid-assisted grinding (LAG).<sup>19</sup> The LAG experiments were conducted using three different stoichiometric ratios of **mddpo** and **tfib**: 2 : 1, 1 : 1 and 1 : 2. Grinding of equimolar amounts of **mddpo** and **tfib** in the presence of small amounts of different liquids provided a new crystalline product whose composition was anticipated as  $(\text{mddpo}) \cdot (\text{tfib})$ , based on the composition of the reaction mixture and the absence of reflections belonging to reactants in the PXRD pattern of the reaction mixture after LAG. The PXRD pattern of  $(\text{mddpo}) \cdot (\text{tfib})$  was different from that of  $(\text{mddpo})_2 \cdot (\text{tfib})$  and any known polymorphs<sup>8</sup> of solid reactants (Fig. 2c–n). Cocrystallisation of **mddpo** and **tfib** from a nitromethane solution seeded with  $(\text{mddpo}) \cdot (\text{tfib})$  provided prismatic crystals. Powder X-ray diffraction (PXRD) confirmed the crystals are identical to the material obtained by the 1 : 1 LAG procedure. Single crystal X-ray diffraction structure determination confirmed the composition



**Fig. 2** Crystal structures of: (a)  $(\text{mddpo})_2 \cdot (\text{tfib})$  and (b) pure **mddpo** (CCDC code NAXBIO)<sup>18</sup> viewed along the hydrogen-bonded **mddpo** chains. PXRD patterns for: (c) LAG reaction of **mddpo** and **tfib** in ratio 2 : 1, using acetonitrile as the grinding liquid; (d) LAG of **mddpo** and **tfib** in ratio 1 : 1, using heptane as the grinding liquid; (e) LAG of **mddpo** and **tfib** in ratio 1 : 1, using cyclohexane; (f) LAG of **mddpo** and **tfib** in ratio 1 : 1, using  $\text{CHCl}_3$  as the grinding liquid; (g) LAG of **mddpo** and **tfib** in ratio 1 : 1, using ethanol as the grinding liquid; (h) LAG of **mddpo** and **tfbb** in ratio 1 : 1; (i) LAG of **mddpo** and **tfbb** in ratio 2 : 1; (j) simulated for  $(\text{mddpo}) \cdot (\text{tfib})$ ; (k) simulated for  $(\text{mddpo})_2 \cdot (\text{tfib})$ ; (l) simulated for  $(\text{mddpo})_2 \cdot (\text{tfbb})$ ; (m) simulated for the room-temperature polymorph of **tfib**; (n) solid **mddpo**; (o) fragment of the crystal structure of  $(\text{mddpo}) \cdot (\text{tfib})$ , displaying I···O (yellow) and I···C (black) interactions; centroids represent the midpoint of the C–C aromatic bond.

**(mdppo)·(tfib)** and revealed it is a stoichiometric variation of **(mdppo)<sub>2</sub>·(tfib)** with C–H···O interactions replaced by the initially expected I···O halogen bonds (Fig. 2o).‡ The I···O separation is remarkably short (2.768(2) Å, with the C–I···O angle 171.88(9)°), consistent with using a phosphine oxide acceptor.<sup>20</sup> The I···phenyl interaction was retained in **(mdppo)·(tfib)**, again with two almost identical I···C separations of 3.473(4) Å and 3.465(4) Å. The corresponding separation between the iodine atom and the centroid of the C–C bond in the aromatic ring was established as 3.40 Å. The cocrystal **(mdppo)·(tfib)** was readily obtained by LAG experiments involving equimolar amounts of starting materials, regardless of the choice of the grinding liquid (Fig. 2d–g). To the best of our knowledge, **(mdppo)<sub>2</sub>·(tfib)** and **(mdppo)·(tfib)** represent the first example of a cocrystal system in which variation in component stoichiometry results in switching between hydrogen- and halogen-bonding motifs.

As a means to explore the generality of stoichiometry-dependent switching between hydrogen and halogen bonding, we attempted the cocrystallisation of **mdppo** with the bromo-analogue of **tfib**, 1,4-dibromotetrafluorobenzene (**tfbb**).

As evidenced by PXRD, cocrystallisation of **tfbb** and **mdppo** either by LAG or from solution produced a material of composition **(mdppo)<sub>2</sub>·(tfbb)** which is isostructural to **(mdppo)<sub>2</sub>·(tfib)** (Fig. 2c–n). Isostructurality is serendipitous, but not surprising due to often observed supramolecular equivalence of halogen-bonded Br and I.<sup>6</sup> To confirm the isostructurality of **(mdppo)<sub>2</sub>·(tfib)** and **(mdppo)<sub>2</sub>·(tfbb)** we have grown single crystals of **(mdppo)<sub>2</sub>·(tfbb)** by slow evaporation of a nitromethane solution. Crystal structure analysis (Fig. 3) revealed a structure analogous to **(mdppo)<sub>2</sub>·(tfib)**, with **mdppo** assembled into chains held by C–H···O hydrogen bonds, and **tfbb** in close interaction with **mdppo** phenyl rings.‡ Surprisingly, attempts to cocrystallise **tfbb** and **mdppo** in a 1 : 1 stoichiometric ratio, either mechanochemically or in solution, did not lead to the formation of a bromo-analogue of the crystal **(mdppo)·(tfib)**. As **tfbb** is a poorer halogen bond donor than **tfib**, this suggests that the strength of the potential Br···O interactions that would form in the bromo-analogue of **(mdppo)·(tfib)** cannot outweigh the strength of the C–H···O interactions existing in **(mdppo)<sub>2</sub>·(tfib)** and **(mdppo)<sub>2</sub>·(tfbb)**.<sup>21</sup>

Whereas our analyses of cocrystal screening are based on PXRD, we also explored Fourier-transform infrared attenuated

total reflectance (FTIR-ATR) as an alternative analytical tool. The resulting spectra, however, displayed significantly less contrast between cocrystals as compared to X-ray powder diffractograms.† Thermal behavior of the **mdppo** cocrystals was found to be complex. DSC measurements on **(mdppo)<sub>2</sub>·(tfib)** and **(mdppo)<sub>2</sub>·(tfbb)** revealed complex behaviour, with endothermic processes taking place at or below 100 °C and potentially leading to partial decomposition into **mdppo**, as suggested by a sharp melting process at 115 °C. Similarly, **(mdppo)·(tfib)** exhibited a broad endothermic process at 100 °C, which could be resolved into at least two endothermic signals by varying the amount of the sample (see ESI†). As another approach to access a cocrystal system that might demonstrate switching between hydrogen- and halogen-bonded architectures upon variation of stoichiometric composition, we explored the cocrystallisation of **mdppo** and octafluoro-1,4-diiodobutane (**ofib**, Fig. 4a).

In particular, **ofib** was chosen as a halogen bond donor because it exhibits a similar length of the fluorocarbon chain as **tfib**. Mechanochemical screening for different cocrystal compositions revealed only the formation of one cocrystal phase, corresponding to the composition **(mdppo)<sub>2</sub>·(ofib)**. The same solid was also obtained if milling was conducted with stoichiometric ratios of **mdppo** and **ofib** of 1 : 1 and 1 : 2 (Fig. 4c,d). Cocrystallisation of **mdppo** and **ofib** from nitromethane solution produced single crystals that were, according to PXRD analysis, identical to the **(mdppo)<sub>2</sub>·(ofib)** cocrystal phase obtained by milling. Single crystal X-ray diffraction confirmed that the cocrystal was composed of **mdppo** and **ofib** in the respective stoichiometric ratio 2 : 1.‡ In the structure, each **ofib** molecule bridges two **mdppo** molecules by way of a pair of short I···O halogen bonds (I···O separation: 2.809(1) Å, C–I···O angle: 173.13(5)°). Unlike in cocrystals involving **tfib**, the **mdppo** components in **(mdppo)<sub>2</sub>·(ofib)** are also assembled by way of two distinct types of C–H···O hydrogen bonds (C···O separations: 3.370(2) Å and 3.318(2) Å with associated C–H···O angles of 147.1° and 145.5°, respectively) into ladder motifs whose hydrogen-bonded connectivity resembles that previously observed in **(mdppo)<sub>2</sub>·(tfib)** and **(mdppo)<sub>2</sub>·(tfbb)** (Fig. 4b). However, the neighboring molecules forming the sides of each hydrogen-bonded ladder are now related through two-fold screw rotation axes, resulting in a *trans*-orientation of equivalent phenyl rings in neighboring **mdppo** molecules across the ladder. This leads to an additional C–H···O contact (C···O separation 3.510(2) Å, C–H···O angle 154.6°) involving phenyl rings within each supramolecular ladder (Fig. 4g).

Consequently, the absence of stoichiometric variations in the system of **mdppo** and **ofib** can be rationalized by the fact that both C–H···O hydrogen- and I···O halogen-bonding are simultaneously accomplished in **(mdppo)<sub>2</sub>·(ofib)**. This can be explained by the smaller steric hindrance of the halogen bond donor in **ofib**, as opposed to **tfib**. That the phosphine oxide moiety is now involved in hydrogen as well as halogen bonding can tentatively explain a slightly longer I···O interaction in **(mdppo)<sub>2</sub>·(ofib)** as compared to **(mdppo)·(tfib)**.

In summary, the cocrystal of 1,4-tetrafluorodiiodobenzene and methyl diphenylphosphine oxide represents an interesting example in which the competition between hydrogen- and halogen-bonded interactions leads to the formation of stoichiometric variations. With few exceptions,<sup>21</sup> cocrystal design usually relies on either halogen or hydrogen bonds as dominant structure-directing

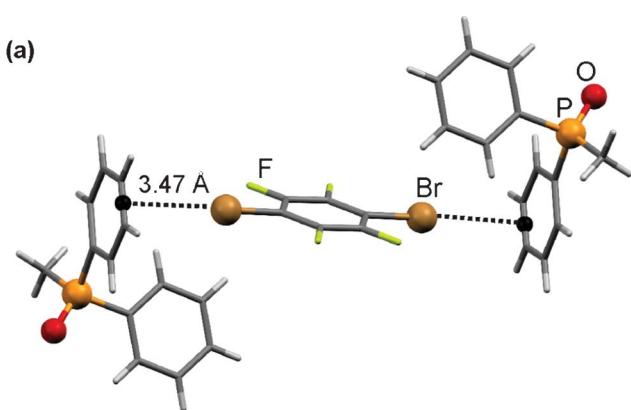
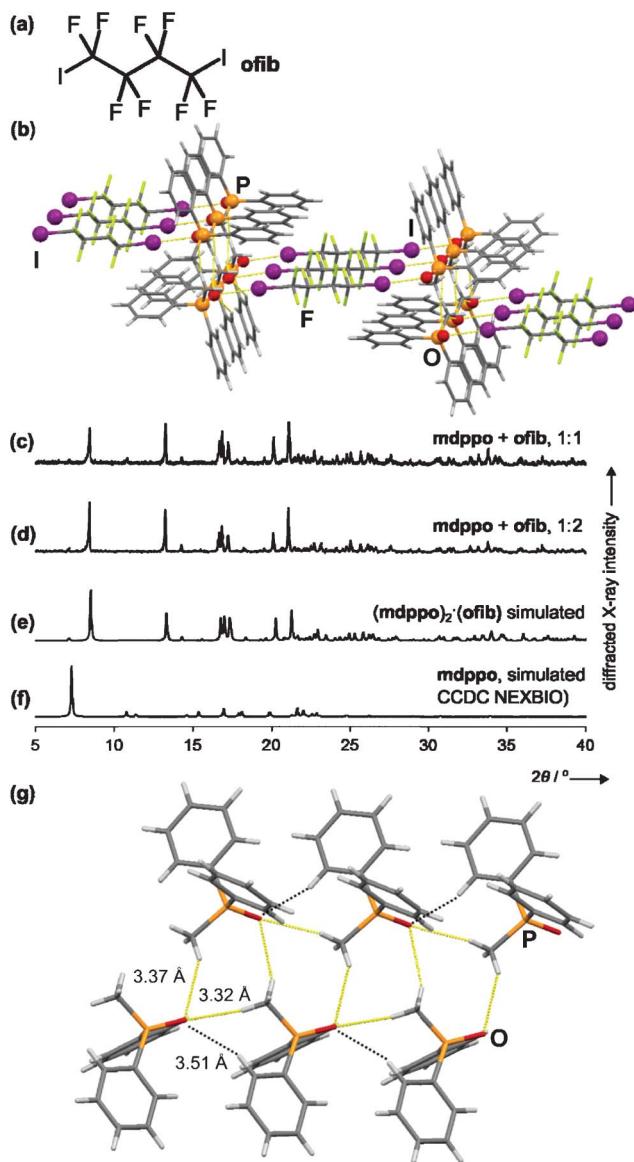


Fig. 3 Fragment of the crystal structure of the cocrystal **(mdppo)<sub>2</sub>·(tfbb)**. The centroids represent the midpoint of the C–C aromatic bond.



**Fig. 4** (a) molecular diagram of **ofib**; (b) view of the crystal structure of **(mdppo)<sub>2</sub>·(ofib)**, displaying two-dimensional layers held by O···I halogen and C–H···O hydrogen bonds (both types of supramolecular interactions shown as yellow dotted lines); PXRD patterns: (c) ground mixture of **mdppo** and **ofib**, ratio 1 : 1; (d) ground mixture of **mdppo** and **ofib**, ratio 1 : 2; (e) simulated for **(mdppo)<sub>2</sub>·(ofib)** cocrystal; (f) simulated for pure **mdppo** (CCDC code NEXBIO<sup>18</sup>) and (g) fragment of the C–H···O hydrogen-bonded (yellow dotted lines) framework in solid **(mdppo)<sub>2</sub>·(ofib)** with indicated Cphenyl···O contacts (black dotted lines).

interactions. We believe that the ability of the cocrystal composition presented herein to switch between hydrogen- and halogen-bonded forms demonstrates structural frustration which arises when the two interactions become comparable in strength. That switching between **(mdppo)<sub>2</sub>·(tfib)** and **(mdppo)·(tfib)** is related to such competition is supported by the observation that the hydrogen-bonded motif in **(mdppo)<sub>2</sub>·(tfib)** and **(mdppo)<sub>2</sub>·(tfbb)** is identical to that observed in pure **mdppo**.<sup>18</sup> Thus, **(mdppo)<sub>2</sub>·(tfib)** and **(mdppo)<sub>2</sub>·(tfbb)** can be considered as inclusion compounds of the hydrogen-bonded apohost **mdppo**. We believe that the cocrystals presented in this

study will help elucidate the relationship and methods of combining halogen bonding with other types of molecular self-assembly (e.g. hydrogen bonds, coordination bonds, anion···π interactions).<sup>22,23</sup>

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- † Crystal data for **(mdppo)<sub>2</sub>·(tfib)**: (C<sub>13</sub>H<sub>13</sub>OP)<sub>2</sub>·(C<sub>6</sub>F<sub>4</sub>I<sub>2</sub>), CCDC deposition number 819334,  $M_r = 834.27$ , orthorhombic,  $a = 5.7447(1)$  Å,  $b = 16.4119(2)$  Å,  $c = 32.2290(5)$  Å,  $V = 3038.60(8)$  Å<sup>3</sup>,  $T = 180(2)$  K, space group *Pbca*,  $Z = 4$ , 17114 reflections measured, 3408 independent reflections ( $R_{\text{int}} = 0.0413$ ). The final  $R_1$  values were 0.0294 ( $I > 2\sigma(I)$ ) and 0.0418 (all data). The final  $wR(F^2)$  values were 0.0630 ( $I > 2\sigma(I)$ ) and 0.0657 (all data). The goodness of fit on  $F^2$  was 1.078. Crystal data for **(mdppo)·(tfib)**: (C<sub>13</sub>H<sub>13</sub>OP)·(C<sub>6</sub>F<sub>4</sub>I<sub>2</sub>), CCDC deposition number 819335,  $M_r = 618.06$ , triclinic,  $a = 9.4440(3)$  Å,  $b = 10.8391(4)$  Å,  $c = 11.7728(4)$  Å,  $\alpha = 111.084(2)$ °,  $\beta = 110.207(2)$ °,  $\gamma = 97.956(2)$ °,  $V = 1006.63(6)$  Å<sup>3</sup>,  $T = 180(2)$  K, space group *P*̄,  $Z = 2$ , 16805 reflections measured, 6858 independent reflections ( $R_{\text{int}} = 0.0391$ ). The final  $R_1$  values were 0.0338 ( $I > 2\sigma(I)$ ) and 0.0447 (all data). The final  $wR(F^2)$  values were 0.0819 ( $I > 2\sigma(I)$ ) and 0.0892 (all data). The goodness of fit on  $F^2$  was 1.039. Crystal data for **(mdppo)<sub>2</sub>·(tfbb)**: (C<sub>13</sub>H<sub>13</sub>OP)<sub>2</sub>·C<sub>6</sub>Br<sub>2</sub>F<sub>4</sub>, CCDC deposition number 819336,  $M_r = 740.29$ , orthorhombic,  $a = 5.7074(1)$  Å,  $b = 16.4007(2)$  Å,  $c = 31.8690(5)$  Å,  $V = 2983.11(8)$  Å<sup>3</sup>,  $T = 180(2)$  K, space group *Pbca*,  $Z = 4$ , 14509 reflections measured, 3381 independent reflections ( $R_{\text{int}} = 0.0427$ ). The final  $R_1$  values were 0.0327 ( $I > 2\sigma(I)$ ) and 0.0419 (all data). The final  $wR(F^2)$  values were 0.0718 ( $I > 2\sigma(I)$ ) and 0.0754 (all data). The goodness of fit on  $F^2$  was 1.063. Crystal data for **tfib**: C<sub>6</sub>F<sub>4</sub>I<sub>2</sub>, CCDC deposition number 819337,  $M_r = 401.86$ , monoclinic,  $a = 6.2187(3)$  Å,  $b = 11.6168(7)$  Å,  $c = 5.7876(5)$  Å,  $\beta = 93.61(3)$ °,  $V = 417.28(5)$  Å<sup>3</sup>,  $T = 180(2)$  K, space group *P*2<sub>1</sub>/c,  $Z = 2$ , 4851 reflections measured, 1212 independent reflections ( $R_{\text{int}} = 0.0468$ ). The final  $R_1$  values were 0.0313 ( $I > 2\sigma(I)$ ) and 0.0393 (all data). The final  $wR(F^2)$  values were 0.0773 ( $I > 2\sigma(I)$ ) and 0.0830 (all data). The goodness of fit on  $F^2$  was 1.048. Crystal data for **(mdppo)<sub>2</sub>·(ofib)**: (C<sub>13</sub>H<sub>13</sub>OP)<sub>2</sub>·C<sub>6</sub>F<sub>8</sub>I<sub>2</sub>, CCDC deposition number 878592,  $M_r = 886.25$ , monoclinic,  $a = 11.5465(2)$  Å,  $b = 5.8340(1)$  Å,  $c = 24.7421(5)$  Å,  $\beta = 91.269(1)$ °,  $V = 1666.28(5)$  Å<sup>3</sup>,  $T = 180(2)$  K, space group *P*2<sub>1</sub>/n,  $Z = 2$ , 16708 reflections measured, 5692 independent reflections ( $R_{\text{int}} = 0.0468$ ). The final  $R_1$  values were 0.0255 ( $I > 2\sigma(I)$ ) and 0.0514 (all data). The final  $wR(F^2)$  values were 0.0463 ( $I > 2\sigma(I)$ ) and 0.0474 (all data). The goodness of fit on  $F^2$  was 0.849.
- ‡ We also report the structure of the room-temperature polymorph of **tfib** from single crystal X-ray diffraction.

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