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Preference of halogen bonds over hydrogen bonds within a discrete three-component co-crystal that undergo a [2+2] cycloaddition reaction†

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The formation of a series of isostructural three-component co-crystals between 1,2,4,5-tetrachloro-3-iodobenzene (C_6HICl_4) and each of three isosteric bipyridines is reported. Even though C_6HICl_4 is capable of forming both halogen and hydrogen bonds the donor is found to form co-crystals with only I···N halogen bonds when the initial ratio of the molecular components is 2 : 1. Molecules of C_6HICl_4 stack in a homogeneous and face-to-face configuration which aligns the bipyridine-based acceptor molecule in a similar π-stacked orientation. As a result, the co-crystal containing *trans*-1,2-bis(4-pyridyl)ethylene undergoes a nearly quantitative [2+2] cycloaddition reaction in the solid state.

The design of molecular co-crystals with controllable chemical and physical properties remains a central goal in crystal engineering.[1] A co-crystal is defined as a crystalline solid that contains at least two molecular components at a fixed whole number ratio.[2] In general, the driving force in the formation of these co-crystals is complimentary non-covalent donor and acceptor sites between the constituent molecules. In particular, halogen and hydrogen bonding interactions have been extensively utilized in the formation of these multicomponent solids due to the strength and directionality of these supramolecular forces. A related, but less investigated, class of these molecular solids are stoichiometric co-crystals which are crystalline solids that contain the same components, but at different molar ratios.[3] Due to the change in molar amounts, these stoichiometric co-crystals will have different structures that will ultimately influence and alter the properties of these related solids.

A continued focus between our research groups has been in the formation of halogen-bonded co-crystals that will undergo the [2+2] cycloaddition reaction.[4] In particular, we have exploited the tendency of polychlorohalobenzenes to form uniform π-stacks within single-component solids and multicomponent co-crystals as a means to orient alkenes in face-to-face π-stacks.[4] Recently, we reported the ability of 1,2,4,5-tetrachloro-3-iodobenzene (C_6HICl_4) to act as a molecular template to achieve a [2+2] cycloaddition reaction when combined with *trans*-1,2-bis(4-pyridyl)ethylene (**BPE**).[5] The ability of C_6HICl_4 to form both I···N halogen bonds along with C-H···N hydrogen bonds produced a pair of concomitant polymorphs each comprised of a one-dimensional chain with a formula of (C_6HICl_4)·(**BPE**) with alternating halogen and hydrogen bonds. Molecules of C_6HICl_4 formed homogenous and face-to-face π-stacks thereby positioning the carbon–carbon double bond (C=C) within **BPE** in a similar photoreactive position. We reasoned that doubling the stoichiometric amount of C_6HICl_4 would lead to a 2 : 1 stoichiometric co-crystal in which we expected C_6HICl_4 to again π-stack in a similar manner and generate a photoreactive co-crystal with **BPE**.

Using this as inspiration, we report here the formation of a series of isostructural co-crystals with C_6HICl_4 along with one of three isosteric bipyridines, namely **BPE**, 1,2-bis(4-pyridyl)acetylene (**BPA**), or azobipyridine (**AP**) (Scheme 1a). These solids are based upon three-component assemblies held together by I···N halogen bonds rather than C–H···N hydrogen bonds. In each co-crystal, molecules of C_6HICl_4 are found to stack in a homogenous pattern that in the case of **BPE** places it in a suitable position to photoreact. As a result, the co-crystal 2(C_6HICl_4)·(**BPE**) undergoes a solid-state [2+2] cycloaddition reaction upon exposure to ultraviolet radiation (Scheme 1b). These solids are all discrete 2 : 1 stoichiometric co-crystals rather than the 1 : 1 co-crystal (C_6HICl_4)·(**BPE**) featuring the one-dimensional chain with both halogen and hydrogen bonds.[5] Doubling the initial stoichiometric amount of C_6HICl_4 lead to the change in structure that reflects the preference of the I···N halogen bond over the C–H···N hydrogen bond in these solids.

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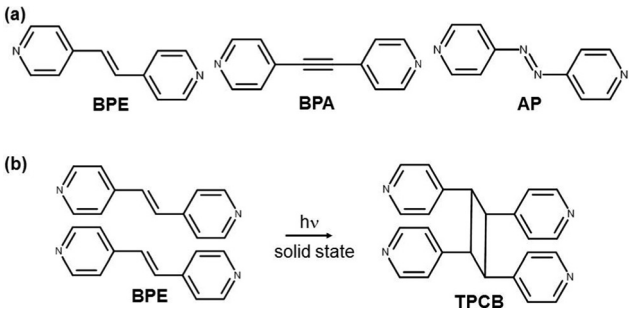

Scheme 1 Renderings of (a) the halogen-bond acceptor molecules and (b) the photoproduct from the solid-state [2+2] cycloaddition reaction.

The donor $\mathbf{C_6HICl_4}$ was synthesized from 2,3,5,6-tetrachloroaniline using the one-pot diazotization-iodination reaction using conditions reported in the single step synthesis of 1,3,5-trichloro-2-iodobenzene from 2,4,6-trichloroaniline.[6] The three isostructural co-crystals were all formed in a similar manner. Thus, 50.0 mg of $\mathbf{C_6HICl_4}$ was dissolved in 2 mL of toluene and then combined with either 13.3 mg of **BPE**, 13.2 mg of **BPA**, or 13.4 mg of **AP** in 2 mL of toluene (2 : 1 molar equivalents). In all cases, crystals suitable for X-ray diffraction formed within 3 days after slow evaporation of the solvent.

Single crystal analysis revealed that the components within these co-crystals had identical formulas, namely 2($\mathbf{C_6HICl_4}$)·(**BPE**), 2($\mathbf{C_6HICl_4}$)·(**BPA**), and 2($\mathbf{C_6HICl_4}$)·(**AP**). In addition, all three solids crystallize in the centrosymmetric monoclinic space group $P2_1/c$ with similar crystallographic parameters (Table 1) and are isostructural or isomorphous in nature. The asymmetric unit for each co-crystal contains a single molecule of $\mathbf{C_6HICl_4}$ along with half of an isosteric bipyridine.

The X-ray structure of 2($\mathbf{C_6HICl_4}$)·(**BPE**) features a three-component unit held together by I···N halogen bonds [I···N 2.917(4) Å; normalised contact[7] .83; C–I···N 174.34(18)°] as a discrete assembly (Fig. 1). The aromatic rings of the halogen-bond donor and acceptor are found to be twisted at an angle of 49.4(2)°. The ethylene core on **BPE** molecule is found to be disordered over two positions at 299 K. These were refined with the aid of a free-variable where the relative populations refined to a final ratio of 0.81 : 0.19. This type of crystallographic disorder is observed in crystalline **BPE**,[8] stilbene,[9] and other related bipyridines.[10] As expected in our hypothesis, $\mathbf{C_6HICl_4}$ is found to engage in homogeneous and face-to-face π–π stacking interactions running along the crystallographic *a*-axis. Due to this stacking pattern along with I···N halogen bonding interactions molecules of **BPE** are also π-stacked in a similar manner

Table 1 Unit cell parameters for the three isostructural co-crystals

Co-crystal	2($\mathbf{C_6HICl_4}$)·(**BPE**)	2($\mathbf{C_6HICl_4}$)·(**BPA**)	2($\mathbf{C_6HICl_4}$)·(**AP**)
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a Å^{-1}	4.0650(1)	4.0163(1)	4.0199(1)
b Å^{-1}	11.0283(2)	11.2938(1)	10.8882(3)
c Å^{-1}	32.1854(6)	31.5449(4)	32.3284(10)
β/°	91.484(2)	91.831(1)	91.490(3)

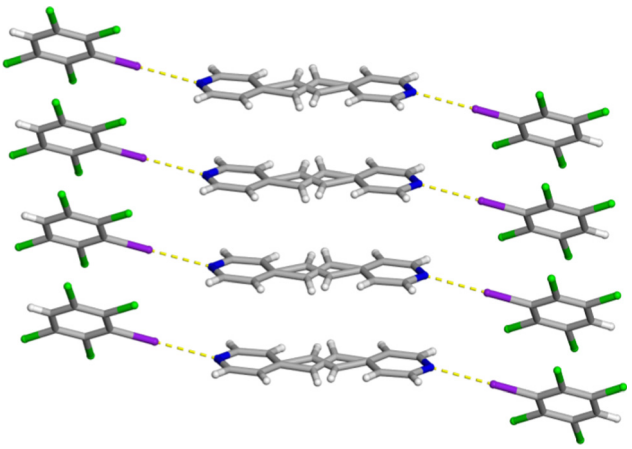

Fig. 1 X-ray crystal structure of 2($\mathbf{C_6HICl_4}$)·(**BPE**) illustrating the infinite homogeneous and face-to-face π–π stacking arrangement of the aromatic rings. The I···N halogen bonds are shown with yellow dashed lines.

forming an infinite array. Consequently, nearest neighboring C═C are parallel and at a distance of 4.0650(1) equal to the crystallographic *a*-axis. These parameters meet the requirements for a [2+2] cycloaddition reaction as defined by Schmidt.[11]

These three-component assemblies interact with nearest neighbours *via* a combination of Cl···π and Type II Cl···Cl interactions. In particular, the Cl···π contact is found between an *ortho*-chlorine atom, with respect to the iodine, that is interacting with the π-surface of the ethylene group on **BPE** [Cl···π 3.297(6) Å] (Fig. 2).[12] In addition, the two *meta*-chlorine atoms on $\mathbf{C_6HICl_4}$ are found to engage in Type II Cl···Cl interactions where the Cl···Cl separation is slightly less than the sum of the van der Waals radii at 3.577(2) Å with C–Cl···Cl angles of 163.73(19) and 104. 98(17)° between a pair of halogen-bond donors (Fig. 3).[13] A second Type II Cl···Cl interaction was found between an *ortho*-chlorine atom which interacts with a *meta*-chlorine on a neighboring donor that has a Cl···Cl separation distance slightly above the sum of the van der Waals radii at 3.695(2) Å. The combination of I···N halogen bonds along with these other non-covalent interactions gives rise to a two-dimensional corrugated sheet-like structure.

To determine the photoreactivity of 2($\mathbf{C_6HICl_4}$)·(**BPE**), in terms of the [2+2] cycloaddition reaction, a powdered sample was exposed to broadband ultraviolet radiation from a 450 W medium-pressure mercury lamp in a photoreactor cabinet.

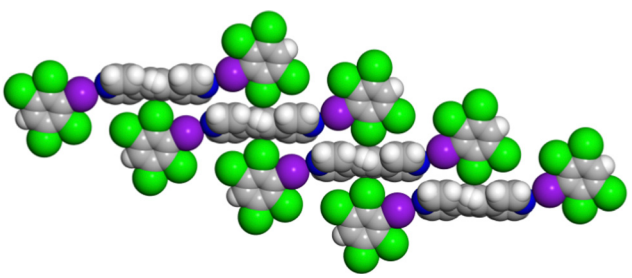

Fig. 2 X-ray crystal structure of 2($\mathbf{C_6HICl_4}$)·(**BPE**) illustrating the Cl···π contact between neighbouring three-component assemblies.

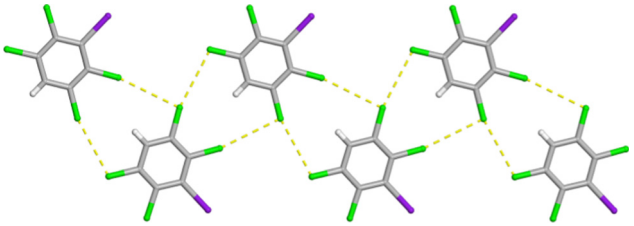

Fig. 3 X-ray crystal structures of 2(**C_6HICl_4**)·(**BPE**) illustrating the different Type II Cl···Cl contacts between neighbouring **C_6HICl_4** molecules. The Cl···Cl interactions are shown with yellow dashed lines.

A photoreaction was confirmed by using ^{1}H NMR spectroscopy that revealed the near loss of the olefinic peak at 7.55 ppm on **BPE** with the concomitant appearance of a peak at 4.67 ppm corresponding to the expected proton on the cyclobutane ring (Fig. S1 and S2, ESI†). Here, the cyclobutane peak position confirms the formation of the photoproduct *rctt*-tetrakis(4-pyridyl)cyclobutane (**TPCB**).[14] After 40 hours of irradiation the overall yield for the [2+2] cycloaddition reaction was determined to be 91%. A similar yield for the photoreaction was observed for the stoichiometric co-crystals (**C_6HICl_4**)·(**BPE**).[5]

A pair of additional isostructural co-crystals were realized when **C_6HICl_4** was combined with two other isosteric halogen-bond acceptor molecules, namely **BPA** and **AP**. In particular, 2(**C_6HICl_4**)·(**BPA**) and 2(**C_6HICl_4**)·(**AP**) were also discrete solids held together by I···N halogen bonds [I···N (Å): **BPA** 2.937(3) and **AP** 2.959(8); normalised contact .83 for **BPA** and .84 for **AP**; C-I···N (°): **BPA** 174.41(12) and **AP** 175.8(3)] to yield a similar three-component structure (Fig. 4). Again, the aromatic rings were found twisted with similar angles as before with values of 44.67(15) and 46.7(5)° for 2(**C_6HICl_4**)·(**BPA**) and 2(**C_6HICl_4**)·(**AP**), respectively. Within 2(**C_6ICl_5**)·(**AP**), the azo-group was found to be disordered over two locations similar to the disordered found within 2(**C_6HICl_4**)·(**BPE**). A free-variable refinement determined the relative occupancies for this disorder to be 0.51 : 0.49 at 298 K. As seen in 2(**C_6HICl_4**)·(**BPE**), all of the aromatic components are π–π stacking in a homogeneous and a face-to-face pattern running along the crystallographic *a*-axis with distances of 4.0163(1) and 4.0199(1) Å for **BPA** and **AP**, respectively (Table 1).

As seen in 2(**C_6HICl_4**)·(**BPE**), neighbouring three-component assemblies are interacting with each other *via* Cl···π and Type II Cl···Cl interactions. Again, the Cl···π contact is interacting with the π-surface on both the acetylene group on **BPA** [Cl···π 3.405(4) Å] and the azo-group on **AP** [Cl···π 3.11(3) Å]. As before, both of the *meta*-chlorine atoms are found to engage in Type II Cl···Cl interactions within 2(**C_6HICl_4**)·(**BPA**) [Cl···Cl 3.612(14) Å; C-Cl···Cl 159.48(15) and 107.40(13)°] and 2(**C_6HICl_4**)·(**AP**) [Cl···Cl 3.56(4) Å; C-Cl···Cl 165.0(4) and 104.4(4)°] with a pair of nearest neighbouring donors. These two co-crystals also engage in a second Type II Cl···Cl interactions between a *ortho*- and *meta*-chlorine with a Cl···Cl separation distance of 3.741(2) and 3.667(4) Å for 2(**C_6HICl_4**)·(**BPA**) and 2(**C_6HICl_4**)·(**AP**), respectively. Again, a two-dimensional corrugated sheet-like structure for both co-crystals was realized as a result of all of these non-covalent interactions.

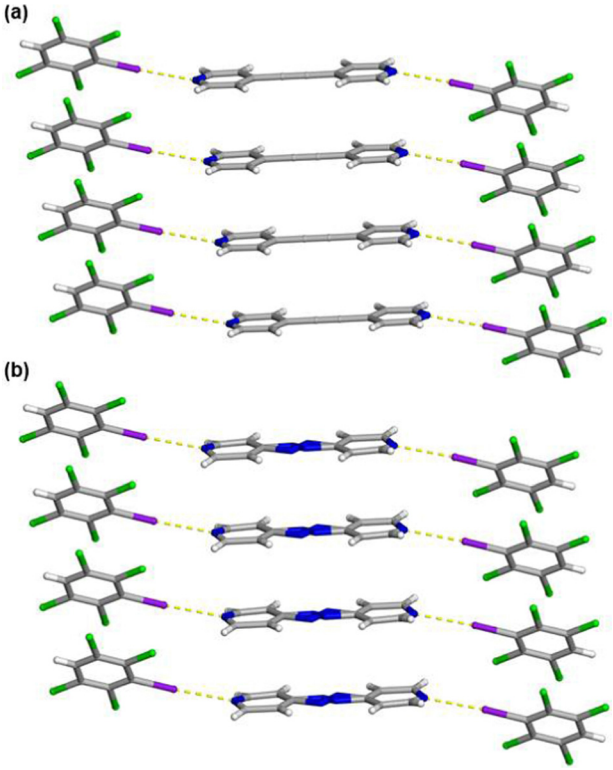

Fig. 4 X-ray crystal structure of (a) 2(**C_6HICl_4**)·(**BPA**) and (b) 2(**C_6HICl_4**)·(**AP**) illustrating the isostructural features along with the infinite homogeneous and face-to-face π–π stacking arrangement of the aromatic rings. The I···N halogen bonds are shown with yellow dashed lines. The disorder within the aromatic rings of **AP** was removed for clarity.

To determine the overall purity of the resulting crystalline phase for each co-crystal a powder X-ray diffraction experiment was performed. Noteworthy, the diffractogram of both 2(**C_6HICl_4**)·(**BPA**) and 2(**C_6HICl_4**)·(**AP**) confirms that the bulk solid matches the calculated powder pattern based upon the single-crystal structure for this co-crystal (Fig. S3 and S4, ESI†). Curious, the bulk powder pattern for 2(**C_6HICl_4**)·(**BPE**) was a partial match to the expected discrete pattern, but also present was Form I of (**C_6HICl_4**)·(**BPE**) (Fig. S5, ESI†).[5] Even though the solid containing **BPE** was prepared with a 2 : 1 stoichiometric ratio the 1 : 1 co-crystal was also observed in the bulk solid.

To understand the role that the homogeneous π–π stacking as well as the I···N halogen bonding interactions play in the formation of these isostructural co-crystals a theoretical study utilizing Density Functional Theory at the M062X/aug-cc-pVTZ level of theory was undertaken. These binding energies were calculated using atomic positions determined from the single-crystal X-ray diffraction data for a given co-crystal. In particular, the π–π stacking energy for 2(**C_6HICl_4**)·(**BPE**) was calculated to be −30.7 kJ mol^{-1}. A similar value for the related stoichiometric co-crystal (**C_6HICl_4**)·(**BPE**), namely Form I, had a value of −29.7 kJ mol^{-1} for its π–π stacking energy. The other isostructural co-crystals had similar π-stacking energies with values of −30.7 and −31.0 kJ mole^{-1} for 2(**C_6HICl_4**)·(**BPA**) and 2(**C_6HICl_4**)·(**AP**), respectively. Lastly, the I···N halogen-bonding energies were also calculated for all three

co-crystals. The strongest halogen bond was observed within 2(**C_6HICl_4**)·(**BPE**) with an energy of −22.9 kJ mol^{-1} followed by 2(**C_6HICl_4**)·(**BPA**) with a value of −22.1 kJ mol^{-1} and then 2(**C_6HICl_4**)·(**AP**) at −20.1 kJ mol^{-1}. Again, these energies are similar to the two polymorphic co-crystals of (**C_6HICl_4**)·(**BPE**) that had values of −23.5 and −22.7 kJ mol^{-1} for Form I and Form II, respectively. It is clear that the difference in structure between these stoichiometric co-crystals comes from the initial amount of the molecular components rather than the strength of these non-covalent interactions.

Conclusions

In this communication, we report a series of isostructural co-crystals held together I···N halogen bonds between **C_6HICl_4** and three isosteric bipyridines. As excepted, **C_6HICl_4** is found to engage in a homogeneous and face-to-face π–π-stacking arrangements which along with the I···N halogen bond positions a pair of carbon–carbon double bond within the co-crystal 2(**C_6HICl_4**)·(**BPE**) in a suitable position to undergo a [2+2] cycloaddition reaction. Currently, we are investigating the ability of **C_6HICl_4** to template additional photoreactions with other olefin-based reactant molecules including unsymmetrical reactants such as 4-stilbazole.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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