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Regioselective [2 + 2] cycloaddition reaction within a pair of polymorphic co-crystals based upon halogen bonding interactions†

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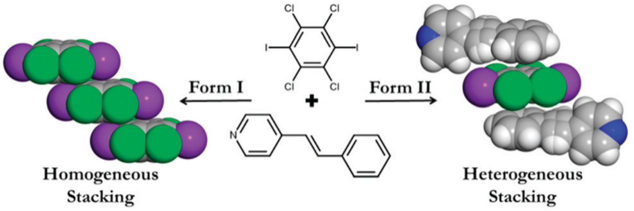
The realization of a pair of photoreactive polymorphic co-crystals that are held together by the combination of I⋯N halogen bonding interactions and C–H⋯Cl contacts is reported. The reactant molecule within these co-crystals is based upon an unsymmetrical olefin, namely 4-stilbazole, that results in a regioselective solid-state [2 + 2] cycloaddition reaction in both polymorphic forms. Each solid undergoes a quantitative photoreaction which yields exclusively the head-to-tail photoproduct.

Introduction

Halogen bonding continues to be a reliable and highly investigated non-covalent interaction employed in the formation of numerous molecular solids.[1] In particular, halogen bonding continues to be an important interaction in the area of co-crystallization where it has been used to control various physical and chemical properties of these multi-component materials.[2] The solid-state photoreactivity, in terms of the [2 + 2] cycloaddition reaction, of halogen-bonded co-crystals is still surprisingly limited in the chemical literature. To the best of our knowledge, all of the reported examples are based on the alignment of a symmetric olefin-containing reactant molecule. For example, Metrangolo and Resnati used a tetratopic halogen-bond donor to align a pair of *trans*-1,2-bis(4-pyridyl)ethylene[3] (**4,4-BPE**) molecules to undergo a cycloaddition reaction. Similarly, MacGillivray then reported the use of a ditopic halogen-bond acceptor to align a pair of *trans*-1,2-bis(2,3,5,6-tetrafluoro-4-iodophenyl)ethylene molecules to achieve a photoreaction.[4] Lastly, the resulting photoproduct subsequently aligned a pair of **4,4-BPE** molecules in a photoreactive configuration.[5]

Recently, we reported the ability to achieve a [2 + 2] cycloaddition reaction within a co-crystal based upon a new halogen-bond donor 1,4-diiodoperchlorobenzene (**$C_6I_2Cl_4$**).[6] Thus the co-crystal with **4,4-BPE**, namely (**$C_6I_2Cl_4$**)·(**4,4-BPE**), underwent a solid-state photoreaction since molecules of **$C_6I_2Cl_4$** π–π stacked in a homogeneous manner along with a face-to-face configuration. As a consequence of this type of stacking and crystal symmetry, a pair of carbon–carbon double bonds (C═C) on neighbouring **4,4-BPE** molecules are found at a distance of 4.08 Å which meets the distance criteria for a photoreaction developed by Schmidt.[7] The preferred homogeneous π–π stacking pattern for **$C_6I_2Cl_4$** was confirmed by utilizing density functional theory calculations that determined a lower energy for this configuration when compared to a hypothetical heterogeneous stacking pattern of the aromatic rings.

Using this as inspiration, we report here the ability to form a pair of polymorphic co-crystals based upon **$C_6I_2Cl_4$** with an unsymmetrical reactant molecule, namely 4-stilbazole (**4-SB**) (Scheme 1). Each polymorph is held together by the combination of I⋯N halogen bonds along with C–H⋯Cl contacts to yield an infinite one-dimensional chain. The different polymorphic forms come about due to the stacking pattern of the **$C_6I_2Cl_4$** molecules in the various solids. In particular, form I has a homogeneous offset π–π stacking



Scheme 1 The π–π stacking arrangement within the two polymorphs of (**$C_6I_2Cl_4$**)·2(**4-SB**).

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† Electronic supplementary information (ESI) available: Experimental details, single crystal X-ray data, ^{1}H NMR spectra, and powder X-ray diffractograms. CCDC 1947988, 1947989, 1947991–1947993. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ce01379b

arrangement of **$C_6I_2Cl_4$** while form II has a heterogeneous pattern (Scheme 1).

As a consequence of both I⋯N halogen bonds and C–H⋯Cl contacts, each polymorph forms an infinite assembly where nearest neighbouring **4-SB** molecules are aligned parallel and in an *anti*-orientation. The two polymorphs have different separation distance between the pair of C=C within the solid, but after exposure to light both polymorphs undergo a solid-state [2 + 2] cycloaddition reaction. The *anti*-orientation of the pair of **4-SB** reactant molecules as well as the resulting ^1H NMR of the photoproduct are in agreement that the head-to-tail photoproduct, namely 1,3-bis(4-pyridyl)-2,4-bis(phenyl)cyclobutane (***ht*-PP**), was realized (Scheme 2). This is the first reported regioselective [2 + 2] cycloaddition reaction of an unsymmetrical alkene based upon halogen bonding interactions.

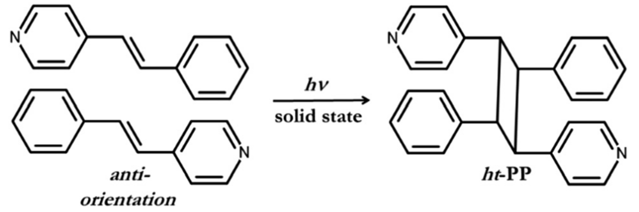
Experimental

Materials

4-Stilbazole (**4-SB**) as well as the solvent toluene were purchased from Sigma-Aldrich Chemical (St. Louis, MO, USA) and used as received. The halogen bond donor 1,4-diiodoperchlorobenzene (**$C_6I_2Cl_4$**) was synthesized by a previous reported method.[8]

General methods

Photoreactions were conducted using UV-radiation from a 450 W medium-pressure mercury lamp in an ACE Glass photochemistry cabinet. Each polymorph of (**$C_6I_2Cl_4$**)·2(**4-SB**) were placed between a pair of Pyrex glass plates for irradiation. The photoreactivity and the overall yield for the photoreaction were determined by using ^1H NMR Spectroscopy. ^1H NMR spectra were collected using a Bruker Avance 400 MHz spectrometer using DMSO-d_6 as the solvent. X-ray powder diffraction data was collected at room temperature on a Rigaku Ultima IV X-ray diffractometer using Cu $K_{\alpha}1$ radiation (λ = 1.54056 Å) between 5° to 40° two-theta.



Scheme 2 The *anti*-orientation of **4-SB** before photoreaction and the resulting regiochemistry of the head-to-tail photoproduct, namely ***ht*-PP**.

Table 1 Unit cell data for the two polymorphs of (**$C_6I_2Cl_4$**)·2(**4-SB**) at 290 K and the partial photoproduct co-crystal at 100 K

Polymorphic form	I	Partial photoproduct	II
Crystal system	Triclinic	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
a/Å	5.7320(3)	5.6832(2)	10.9356(2)
b/Å	11.2839(6)	11.0865(4)	16.4835(3)
c/Å	12.3090(7)	12.2076(5)	8.6541(2)
α/°	83.794(2)	82.9822(14)	90
β/°	82.313(2)	82.3948(12)	96.0154(8)
γ/°	77.034(2)	77.3857(12)	90
V/Å^3	766.35(7)	740.53(5)	1551.37(5)

Synthesis of form I and form II

Co-crystals of (**$C_6I_2Cl_4$**)·2(**4-SB**) in both forms were synthesized by dissolving 25.0 mg of **$C_6I_2Cl_4$** in 2.0 mL of toluene, which was then combined with a separate 2.0 mL toluene solution containing 19.4 mg of **4-SB** (1 : 2 molar equivalent). Form I was achieved by removing the cap of the 20 mL scintillation vial while form II was formed by covering the vial with either a folded Kimwipe or placing cotton in the opening. The rate of solvent evaporation is attributed to the formation of the particular polymorph. In both cases, after most of the solvent was evaporated plate-like single crystals suitable for X-ray diffraction were realized ranging from two days for form I and up to three days for form II.

Single crystal X-ray diffraction data collection

Crystals were mounted on a MiTeGen cryoloop in random orientations for data collection. Data collections were performed using a Bruker Venture Duo Photon-II single crystal X-ray diffractometer equipped with an Oxford Cryostream device. Apex II and SAINT software packages were used for data collection and integration. All of the data were corrected for systematic errors using SADABS based on the Laue symmetry using equivalent reflections. Structure solution and refinement were carried out using the SHELXTL-PLUS software package. All structures were solved by direct methods with a full matrix least-squares refinement. Non-hydrogen atoms were refined anisotropically to convergence. All hydrogen atoms were treated using an appropriate riding model (AFIX m3). Unit cell parameters for both polymorphs and the partial photoproduct co-crystal are found within Table 1. X-ray diffraction and refinement data are also found in Tables S1 and S2.†

Results and discussion

Structure and photoreactivity of form I

Single crystal analysis revealed that form I crystallizes in the centrosymmetric triclinic space group $P\bar{1}$. The asymmetric unit contains a half of **$C_6I_2Cl_4$** and a single molecule of **4-SB.** The co-crystal is sustained by I⋯N halogen bonds [I⋯N 2.9047(1) Å] with a C–I⋯N bond angle of 175.0519(2)° at 290 K (Fig. 1). The aromatic rings within **4-SB** are nearly coplanar with an angle of 5.96°. In contrast, the angle between **$C_6I_2Cl_4$** and the pyridine ring within **4-SB** is found to be 75.29°. The ethylene bridge in **4-SB** is found to be disordered over two position which is common in other similar shaped molecules.[9] After a free variable refinement of the diffraction data the ratios of the two components were determined to be 0.89/0.11 at 290 K.‡ In order

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‡ Modelling the observed disorder over the entire molecule of **4-SB** was attempted but did not result in a better overall model of the structure.

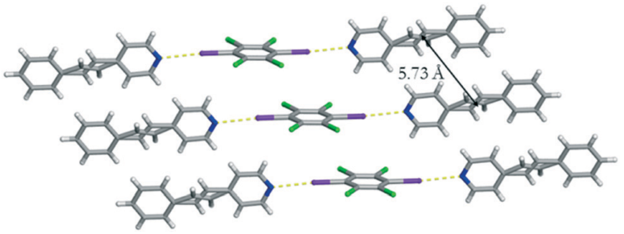

Fig. 1 X-ray structure of form I illustrating the I⋯N halogen bonds as well as the offset homogeneous π–π stacking arrangement of **$C_6I_2Cl_4$**. The I⋯N halogen bonds are shown with yellow dashed lines.

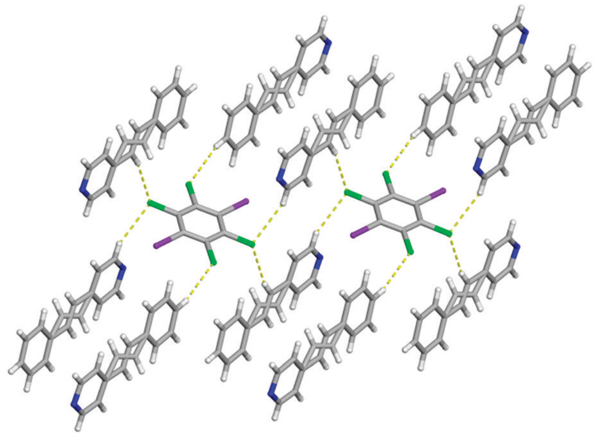

Fig. 3 X-ray structure of form I illustrating all of the different types of C–H⋯Cl contacts. The C–H⋯Cl contacts are shown with yellow dashed lines.

to determine the type of disorder, a multivariable crystallographic study was undertaken. The same crystal was then cooled to 250 K and a second complete data set was collected. Again, only the disorder in the ethylene bridge within **4-SB** was able to be modelled. After a free variable refinement the ratios of the ethylene group changed to 0.92/0.08 which is indicative of dynamic motion (*i.e.* pedal motion)[9] within form I. To determine the overall purity of the bulk material a powder X-ray diffraction study was performed on the resulting solid after complete evaporation of the solvent when the vial is completely open. The resulting diffractogram is in good agreement with the calculated powder pattern of form I (Fig. S4†).

Unlike our previous photoreactive solid **($C_6I_2Cl_4$)·(4,4-BPE)**,[6] molecules of **$C_6I_2Cl_4$** within form I are found to be offset with a centroid-to-centroid distance of 5.73 Å. Due to crystal symmetry, a pair of C=C are also found to be at a distance of 5.73 Å which is beyond the accepted limit for a photoreaction (Fig. 1). In addition, a pair of **4-SB** molecules between nearest neighbouring halogen bonded assemblies is found to be in a *syn*-orientation.

Beside the I⋯N halogen bonds, there are C–H⋯Cl contacts[10] [C⋯Cl 3.8357(15) Å] within form I where the chlorine atoms interact with the *para* hydrogen atom on the benzene ring producing a one-dimensional chain (Fig. 2). This combination of non-covalent interactions positions a pair of **4-SB** molecules in an *anti*-orientation with the shortest C=C separation distance of 4.16 Å, which is within the limit for a photoreaction (Fig. 2). All four chlorine atoms accept C–H⋯Cl contacts, in particular the other crystallographically unique chlorine is interacting with both a α-hydrogen atom on the pyridine ring [C⋯Cl 3.8525(2) Å] as well as the disordered ethylene hydrogen atom [C⋯Cl 3.8574(2) Å] ultimately yielding a three dimensional solid (Fig. 3). Lastly, form I also contains some weak Cl⋯π interactions between the chlorine and the pyridine ring with an atom-to-centroid distance of 3.37 Å.

To determine if a solid-state photoreaction would occur, a powdered sample of form I was placed between glass plates and put in a photoreactor cabinet to be exposed to broadband UV radiation from a 450 W medium-pressure mercury lamp. A photoreaction was detected as evidenced by the loss of the olefinic peak on **4-SB** at 7.57 ppm (Fig. S1†) along with the appearance of the cyclobutane peak at 4.59 ppm (Fig. S2†) in the ^{1}H NMR spectrum. The position and the particular shape of the ^{1}H NMR signal for the cyclobutane ring confirms the photoproduct to be the ***ht*-PP** regioisomer.[11] The yield for the [2 + 2] cycloaddition reaction was determined to be quantitative after 30 hours of irradiation.

During X-ray data collection, an additional crystal of form I was investigated *via* single crystal X-ray diffraction. Again, the solid crystallizes in the centrosymmetric triclinic space group $P\bar{1}$; however, new atoms appeared in the difference map. After refinement, it was determined that the crystal was partially photoreacted forming the ***ht*-PP** *via* a single-crystal-to-single-crystal reaction[12] with an overall yield of 8.3% (Fig. 4). The unit cell parameters are similar to the unreacted form I (Table 1) making these two structures isomorphic in nature. The solid is again held together by the combination of both I⋯N halogen bonds [I⋯N 2.9910(1) Å; C–I⋯N

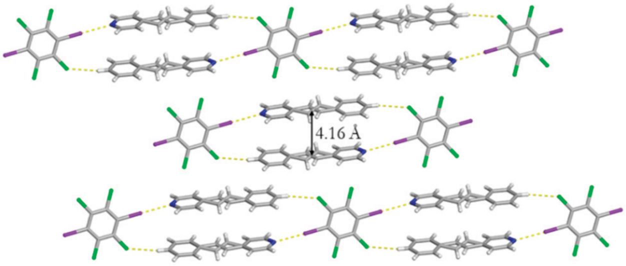

Fig. 2 X-ray structure of form I illustrating the *anti*-orientation within the one-dimensional chain. The I⋯N halogen bonds and C–H⋯Cl contacts are shown with yellow dashed lines.

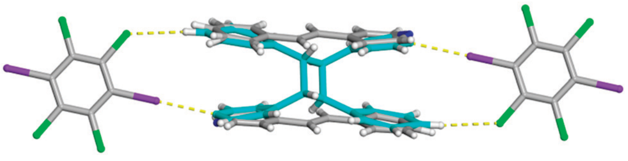

Fig. 4 X-ray structure of the partially photoreacted co-crystal of form I forming the ***ht*-PP** shown in turquoise. The I⋯N halogen bonds and C–H⋯Cl contacts are shown with yellow dashed lines.

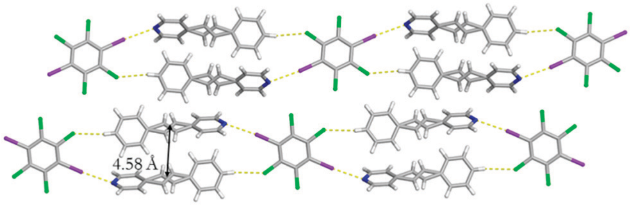

Fig. 5 X-ray structure of form II illustrating the *anti*-orientation within the one-dimensional chain. The I⋯N halogen bonds and C–H⋯Cl contacts are shown with yellow dashed lines. The disorder observed in $C_6I_2Cl_4$ was removed for clarity.

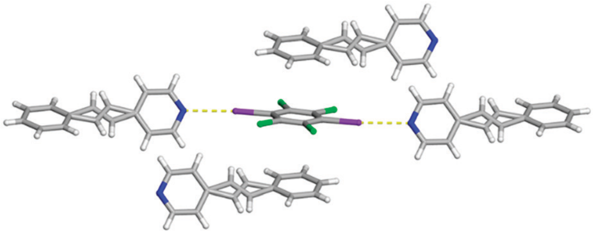

Fig. 6 X-ray structure of form II illustrating the I⋯N halogen bonds as well as the heterogeneous π–π stacking arrangement of $C_6I_2Cl_4$. The I⋯N halogen bonds are shown with yellow dashed lines. The disorder observed in $C_6I_2Cl_4$ was removed for clarity.

172.2938(2)°] and C–H⋯Cl contacts [C⋯Cl 3.7864(1) Å] at 100 K. It must be noted that the crystal underwent the [2 + 2] cycloaddition reaction from ambient light and not from UV light in the photoreactor. The partial photoproduct crystal structure is in agreement with the regiochemistry determined by ^{1}H NMR for form I to be the ***ht*-PP**.

Structure and photoreactivity of form II

Changing the evaporation rate of toluene led to the formation of a second polymorph of ($C_6I_2Cl_4$)·2(**4-SB**), namely form II. Unlike before, form II crystallizes in the centrosymmetric monoclinic space group $P2_1/c$. Again, the asymmetric unit contains a half of $C_6I_2Cl_4$ and a whole molecule of **4-SB**. A similar one-dimensional chain held together by a combination of I⋯N halogen bonds [I⋯N 2.9292(1) Å; C–I⋯N 174.9740(1)°] along with C–H⋯Cl contacts [C⋯Cl 3.7445(1) Å] at 290 K was observed for form II (Fig. 5). The aromatic rings within **4-SB** are twisted at a much larger angle than observed in form I with a value of 54.91°. The ethylene bridge in **4-SB** is again found to be disordered over two positions and after a free variable refinement the ratios were determined to be 0.55/0.45 at 290 K.‡ A second data set at 250 K, on the same crystal, resulted in a final free variable refinement of 0.56/0.44 which is inconclusive on the presence of pedal motion within form II.[9] A second type of disorder was observed in the form of rotational disorder of the $C_6I_2Cl_4$ template where after refinement the ratios were determined to be 0.98/0.02. As before, the **4-SB** molecules within the one-dimensional chain are found to be in an *anti*-orientation with a slightly greater C=C separation distance of 4.58 Å (Fig. 5). Again, the bulk material was studied *via* powder X-ray diffraction to determine the purity after complete evaporation of the solvent when the opening of the vial is covered with cotton. The diffractogram partially agrees with the calculated powder pattern for form II, but a mixture of products is likely (Fig. S5†).

The difference in the π–π stacking arrangement of $C_6I_2Cl_4$ gave rise to the different polymorphs. In form I, $C_6I_2Cl_4$ are found to stack in a homogeneous offset pattern which is drastically different than form II where $C_6I_2Cl_4$ π–π stacks with benzene rings in a heterogeneous configuration (Fig. 6). This stacking arrangement does not place any other pair of C=C at a closer distance than was observed within the one-dimensional chain.

To determine if form II would undergo a solid-state [2 + 2] cycloaddition reaction a powdered sample was again placed between glass plates and put in a photoreactor. As before, a photoreaction was observed by the loss of the olefinic peak on **4-SB** at 7.57 ppm in the ^{1}H NMR spectrum along with the presence of a peak at 4.59 ppm which belongs to the cyclobutane ring on ***ht*-PP** (Fig. S1 and S3†). The closest C=C separation distance is found when the **4-SB** molecules are in an *anti*-orientation which is in agreement with the observed ^{1}H NMR spectrum that only the ***ht*-PP** was formed within form II. Again, a quantitative yield for the photoreaction was reached after 30 hours of irradiation. The disordered olefin within form II must undergo molecular pedal motion in order to reach the observed quantitative yield for the photoreaction.[13] Even though the olefin–olefin distance within form II is beyond the accepted value for a photoreaction, there are numerous examples in the literature that have reported photoreactions at even greater distances. In particular, a solid-state photoreaction was observed for *p*-formylcinnamic acid which has a separation distance of 4.825 Å between neighbouring olefins.[14]

Conclusions

In this contribution, we report a pair of regioselective [2 + 2] cycloaddition reactions based upon halogen bonding interactions. The combination of both I⋯N halogen bonds and C–H⋯Cl contacts position a pair of unsymmetrical **4-SB** reactant molecules in the correct orientation to undergo a solid-state photoreaction in both polymorphs resulting in the head-to-tail photoproduct. Currently, we are investigating functionalized olefin-based pyridines to determine if $C_6I_2Cl_4$ can act as a template to achieve additional solid-state photoreactions.

Conflicts of interest

There are no conflicts to declare.

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