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Acta Cryst. (2018). **B74**, 618–627



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Crystal packing and theoretical analysis of halogen- and hydrogen-bonded hydrazones from pharmaceuticals. Evidence of type I and II halogen bonds in extended chains of dichloromethane

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Received 27 July 2018

Accepted 8 October 2018

Edited by J. Lipkowski, Polish Academy of Sciences, Poland

Keywords: halogen bonding; pharmaceuticals; dichloromethane; hydrazones.

CCDC references: 1820529; 1820530; 1820531; 1820532; 1820533

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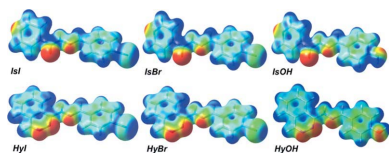
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The supramolecular assembly of halogenated and hydroxyl hydrazones derived from two well known pharmaceuticals, isoniazid (IsX, where X = I, Br, OH) and hydralazine (HyX, where X = I, Br, OH), was studied by X-ray crystallography and theoretical methods. Crystal packing of IsI and HyI shows weak I...N and I... π halogen bonds, whereas the hydrogen bonds are dominant in the brominated scaffolds IsBr and HyBr. Although the calculated I...N interaction strength appears almost three times weaker than the O—H...N contacts in the isoniazid-based hydrazones, the higher directionality of the halogen bonds induces a linear and planar architecture of self-complementary tectons, observed only with the help of a bridging water molecule in the case of IsOH. Finally, the X-ray structure of HyOH is characterized by an unexpected linear arrangement of clathrated dichloromethane molecules bound through type I and II halogen bonds. This rare phenomenon, observed in less than ten structures, was studied by coupled cluster-based energy decomposition.

1. Introduction

Since the early 2000s, halogen bonding (XB) has become a new paradigm in the field of non-covalent interactions (Cavallo *et al.*, 2016; Gilday *et al.*, 2015). From fundamental studies focused on crystal engineering, investigations slowly shifted toward applied sciences (Rissanen, 2008; Metrangolo *et al.*, 2008). The combination of high directionality and tuneable interaction strength makes the halogen bond a reliable and versatile approach for the design of novel functional materials and polymers (Meyer & Dubois, 2013; Berger *et al.*, 2015). In parallel, synthetic chemistry developed with a wide range of XB-controlled reactions, thus competing with the well established hydrogen bonding based organocatalysis (Bulfield & Huber, 2016). Finally, a survey of the literature supported by recent works highlighted the key role of XB in medicinal chemistry and chemical biology (Auffinger *et al.*, 2004; Wilcken *et al.*, 2013), whereas XB-based metal–organic supramolecular frameworks were endowed with particular behaviours (Li *et al.*, 2016).

Engineering of halogen-bonded architectures needs an adequate and precise choice of partners, *i.e.* electron donors and acceptors. Thus, a large variety of functional groups can play the role of electron donors such as heteroatoms, halogens, π systems, anions or radicals (Metrangolo *et al.*, 2008, 2009; Cavallotti *et al.*, 2008). Concerning XB donors, both the



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halogen atom itself and its close environment are determinant to the success of the recognition process, for which the strength of interaction usually follows the order: $I > Br > Cl$. In addition, halogens bound to electron-withdrawing groups such as in haloperfluorocarbons (Metrangolo *et al.*, 2005), iodoalkynes (Aakeröy *et al.*, 2013), halo-imidazoliums and iodo-triazoliums account for a lower electronic density (positive region or σ -hole), strengthening their ability to accept electrons (Brown & Beer, 2016; Riley *et al.*, 2011). The tunability of the size and depth of the σ -hole represents a reliable strategy to ensure self-assembly by halogen bonding. In contrast, the design of supramolecular systems using poorly activated halogenated structures appears more challenging and difficult to anticipate. Yet weak halogen bond donors, such as iodo- and bromophenyl derivatives, were able to promote the fibril formation of a pentapeptide and the phosphorescence of organic materials, respectively (Bertolani *et al.*, 2015; Bolton *et al.*, 2011). In contrast, diiodobenzene was unable to create a complex with two alkoxystilbazoles, whereas its fluorinated counterpart diiodotetrafluorobenzene gave rise to halogen-bonded liquid crystals (Bruce *et al.*, 2008). However, weak halogen-bond donor groups or those considered as such can be used to stabilize an architecture (Berger, Fusaro *et al.*, 2014) or to become good electron acceptors through electron transfer in conjugated structures (Langton *et al.*, 2014).

As a preliminary study, we decided to investigate the self-assembly properties of halogenated hydrazones and their hydroxyl-substituted analogues derived from two well known pharmaceuticals, isoniazid and hydralazine. Hydrazones are an important class of molecules endowed with a wide range of applications that are used for their photo/chemical switching properties (Aprahamian, 2017), their pH-responsive behaviour in drug delivery systems (Sonawane *et al.*, 2017) or as inhibitors of myeloperoxidase (Soubhye *et al.*, 2017) and metal ligands (Mandal *et al.*, 2017). Here, the supramolecular organizations of 4-iodo-, 4-bromo- and 4-hydroxyhydrazones (Fig. 1) were studied by X-ray crystallography, density functional theory (DFT) and coupled cluster-based energy decomposition.

2. Experimental

2.1. Synthetic procedures

^1H and ^{13}C NMR spectra were recorded on a Jeol 400 MHz spectrometer at 293 K. Chemical shifts (δ) are given in parts per million (p.p.m.) relative to the solvent residual peaks, and

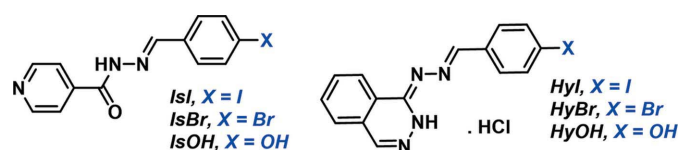


Figure 1
Structures of isoniazid- and hydralazine-based hydrazones.

the coupling constants are expressed in Hz. Hydralazine, isoniazid, 4-iodobenzaldehyde, 4-bromobenzaldehyde and 4-hydroxybenzaldehyde were purchased from TCI (Japan), Sigma-Aldrich (Belgium) or Apollo Scientific (UK). Ethanol ($\geq 99.8\%$) and dichloromethane were used as received from Chemlab. Melting points were measured on a Büchi B-545 apparatus.

2.1.1. General procedure for the synthesis of hydrazones IsX (X = I, Br) and HyX (X = I, Br, OH). Isoniazid (300 mg, 2.19 mmol) and 4-iodobenzaldehyde (508 mg, 2.19 mmol) were stirred in refluxing ethanol (10 ml). After 3 h, the reaction was cooled to room temperature, the resulting white solid filtered off and washed with ethanol to give pure hydrazine IsI in 88% yield. Hydralazine-based compounds further underwent alkaline treatment before NMR analysis.

(*E*)-*N'*-(4-Iodobenzylidene)isonicotinohydrazide (IsI): white solid, yield: 88%. ^1H NMR (400 MHz, DMSO- d_6) δ 12.12 (s, 1H), 8.81–8.77 (m, 2H), 8.41 (s, 1H), 7.85 (d, J = 8 Hz, 2H), 7.86–7.79 (m, 2H), 7.55 (d, J = 8 Hz, 2H).

(*E*)-*N'*-(4-Bromobenzylidene)isonicotinohydrazide (IsBr): white solid, yield: 77%. ^1H NMR (400 MHz, DMSO- d_6) δ 12.15 (s, 1H), 8.85–8.74 (m, 2H), 8.43 (s, 1H), 7.86–7.78 (m, 2H), 7.75–7.62 (m, 4H).

(*E*)-1-[2-(4-Iodobenzylidene)hydrazinyl]phthalazine (HyI): white solid, yield: quantitative; m.p. = 227°C. ^1H NMR (400 MHz, chloroform- d) δ 10.62 (s, 1H), 8.45 (s, 1H), 8.45–8.36 (m, 1H), 7.89 (s, 1H), 7.76 (d, J = 8 Hz, 2H), 7.74–7.61 (m, 2H), 7.59–7.48 (m, 3H). ^{13}C NMR (101 MHz, chloroform- d) δ 153.7, 149.7, 138.7, 138.1, 135.0, 132.5, 132.0, 129.4, 127.6, 126.7, 126.4, 124.5, 100.1.

(*E*)-1-[2-(4-Bromobenzylidene)hydrazinyl]phthalazine (HyBr): white solid; yield: quantitative; m.p. = 232°C. ^1H NMR (400 MHz, chloroform- d) δ 10.61 (s, 1H), 8.47 (s, 1H), 8.43–8.35 (m, 1H), 7.89 (s, 1H), 7.84–7.62 (m, 4H), 7.58–7.47 (m, 3H).

(*E*)-4-[[2-(Phthalazin-1-yl)hydrazono]methyl]phenol (HyOH): white solid, yield: quantitative; m.p. = 222°C. ^1H NMR (400 MHz, DMSO- d_6) δ 11.89 (s, 1H), 8.34 (s, 1H), 8.25 (d, J = 7 Hz, 1H), 8.01 (s, 1H), 7.83 (d, J = 9 Hz, 2H), 7.77–7.63 (m, 3H), 6.81 (d, J = 9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 159.5, 153.7, 148.0, 137.6, 132.4, 131.9, 130.1, 127.2, 126.8, 126.6, 126.4, 123.7, 115.7.

2.2. X-ray crystallography

All diffraction data were measured at ambient temperature on a MAR345 image plate using Mo $K\alpha$ radiation (Rigaku UltraX 18S rotating anode, Fox3D mirrors). Indexing, integration and data reduction were performed using *CrysAlisPRO* (Rigaku Oxford Diffraction, 2015) and a semi-empirical absorption correction was applied. The structures were solved by *SHELXT* (Sheldrick, 2015a) and then refined on $|F^2|$ using *SHELXL2014/7* (Sheldrick, 2015b). Non-hydrogen atoms were anisotropically refined. The hydrogen atoms were located in Fourier maps and refined in riding mode with isotropic temperature factors fixed at $1.2 \times U_{eq}$ of the parent atoms. Visualization and analysis of the crystal struc-

tures were performed with *Mercury* (Macrae *et al.*, 2008). The database analysis was performed using the Cambridge Structural Database (version 5.38 +3 updates; Groom, 2016).

2.3. General quantum mechanical methods

All quantum mechanical calculations were performed using *Gaussian09* (rev. D.01; Frisch *et al.*, 2009) and *ORCA4.0.1* (Neese, 2012). Geometries of the different IsX and HyX systems were fully optimized at the spin-restricted density functional theory level using the dispersion-corrected ω B97x-D exchange-correlation functional (Chai & Head-Gordon, 2008). The balanced polarized triple-zeta basis set def2-TZVP from Ahlrichs and co-workers (Weigend & Ahlrichs, 2005; Weigend, 2006) has been used for all atoms. Potential energy surface minima found upon optimization were confirmed by frequency calculations (*i.e.* zero imaginary frequencies) and free energies were corrected to account for the zero-point energy. All binding energies were counterpoise-corrected using the Boys and Bernardy procedure to account for the basis set superposition error (Boys & Bernardi, 1970). Cube densities were generated at the 80 points per Bohr³ mesh resolution.

Domain-based local pair natural orbital coupled-cluster singles doubles perturbative triples [DLPNO-CCSD(T)] calculations of isolated and interacting CH₂Cl₂ molecules were carried out with TightPNO settings as described by Neese *et al.* (2009), using the cc-pVTZ basis set and the corresponding auxiliary basis set. Vibrational frequencies were numerically computed. For the localization of the MOs, the Foster–Boys localization scheme has been applied. The pair natural orbitals (PNOs) were localized by using the Pipek–Mezey-localization scheme. Local energy decomposition was carried out for the interacting molecules and the energy terms were subsumed as described by Schneider *et al.* (2016).

2.4. Local energy decomposition

The DLPNO-CCSD(T) method provides accurate correlation energies that allows us to predict many chemical phenomena and investigate weak interactions. To facilitate the interpretation of coupled cluster results, we used the local energy decomposition (LED) analysis (Schneider *et al.*, 2016), which divides the interaction energies between fragments into physically meaningful contributions and a short theoretical background is provided here.

The counterpoise-corrected dissociation energy can be expressed within the Boys and Bernardy scheme as the sum of a geometric preparation term (the geometric relaxation of the interacting molecules) and a genuine electronic interaction term:

$$\Delta E = \Delta E_{\text{geo-prep}} + \Delta E_{\text{int}}. \quad (1)$$

The LED is a physical meaningful decomposition of ΔE_{int} within the DLPNO-CCSD(T) scheme that is provided in *ORCA4.0.1* and which first decomposes the electronic inter-

action between its Hartree–Fock (HF) and electronic correlation contributions:

$$\Delta E_{\text{int}} = \Delta E_{\text{int}}^{\text{HF}} + \Delta E_{\text{int}}^{\text{corr}}. \quad (2)$$

The HF part accounts for the polarization effects, static and donor–acceptor interactions, while the correlation part corrects these components and adds the dispersive attraction resulting from instantaneous dipole–dipole interactions, which is central for weak interactions. We therefore focused on the decomposition of the correlative component of the interaction energy, which from LED is split into dispersive and dynamic polarization (*i.e.* charge-transfer components at the correlated level) parts:

$$\Delta E_{\text{int}}^{\text{corr}} = E_{\text{disp}(X,Y)}^{\text{corr}} + \Delta E_{\text{CT}(X \rightarrow Y)}^{\text{corr}} + \Delta E_{\text{CT}(Y \rightarrow X)}^{\text{corr}}. \quad (3)$$

Both the HF electrostatic and exchange terms, as well as the correlation energies from equation (2) are all negative (*i.e.* attractive), whereas geometric and electronic preparation terms are positive and the overall sum accounts for the interaction energy (Schneider *et al.*, 2016).

These quantities are reported in Section 3.5.2 for the CH₂Cl₂ molecules interacting through type I and II XB.

3. Results and discussion

3.1. Synthesis of hydrazones

The synthesis of the substituted hydrazones was performed under conventional conditions (Soubhye *et al.*, 2017). Isoniazid was stirred in refluxing ethanol with an equimolar amount of 4-iodo- or 4-bromobenzaldehyde, resulting in the acyl hydrazones IsI and IsBr in 88 and 77% yields, respectively (Hearn *et al.*, 2009). Hydrazones HyI, HyBr and HyOH were isolated quantitatively by condensation with 4-iodo-, 4-bromo- or 4-hydroxybenzaldehyde, respectively (Fig. 2).

3.2. Structural features of isoniazid-based hydrazones

3.2.1. X-ray crystallography. The supramolecular organizations of these hydrazones were investigated by single-crystal X-ray diffraction analysis. For this purpose, suitable crystals of compounds IsI and IsBr were obtained by slow cooling of the ethanolic solution. The presence of multiple electron-rich moieties (π systems, carbonyl groups and nitrogen atoms)

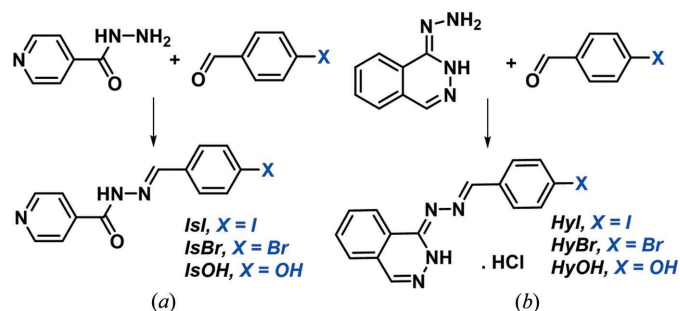


Figure 2
Synthesis of isoniazid- and hydrazalazine-based hydrazones: (a) IsI, IsBr and IsOH; (b) HyI, HyBr and HyOH.

offers a large panel of partners to the halogen atoms. The solid-state structure analysis of IsI reveals a linear arrangement between the two crystallographically independent molecules governed by two types of $\text{N} \cdots \text{I}$ halogen bonds (Fig. 3*a*). The interatomic distances between the corresponding nitrogen and iodine atoms are measured at 3.079 (2) and 3.098 (2) Å, *i.e.* about 16% shorter than the sum of the van der Waals radii of nitrogen and iodine (3.70 Å), using the values given by Batsanov (2001). The $\text{N} \cdots \text{I} \cdots \text{C}$ angles are nearly linear [174.66 (9) and 175.46 (9)°], attesting to a fairly strong interaction owing to the nature of the halogenated group. Interestingly, the units form parallel extended head-to-tail chains, which give rise to two-dimensional sheets and alternating parallel planes comprise molecules that are rotated 180° around the molecules main axis (Fig. 3*a*). Other hydrogen bonds govern the supramolecular organization. Indeed, the carbonyl groups point toward a bottom adjacent layer, binding aromatic hydrazone hydrogen atoms. Two types of $\text{O} \cdots \text{H} \cdots \text{N}$ hydrogen bonds are present, characterized by a distance of 2.087 and 2.195 Å, with an almost equidistant separation between the crystallographic planes [3.198 and 3.279 Å; Fig. 3(*b*)].

The substitution of iodine for bromine dramatically modifies the overall organization, as seen from the crystal structure of IsBr (Fig. 4). This structure is identical to a previously solved and deposited one, but not discussed (Li & Jian, 2008). Halogen bonds between the pyridyl ring and the bromine atom no longer govern the crystal architecture. Unlike the

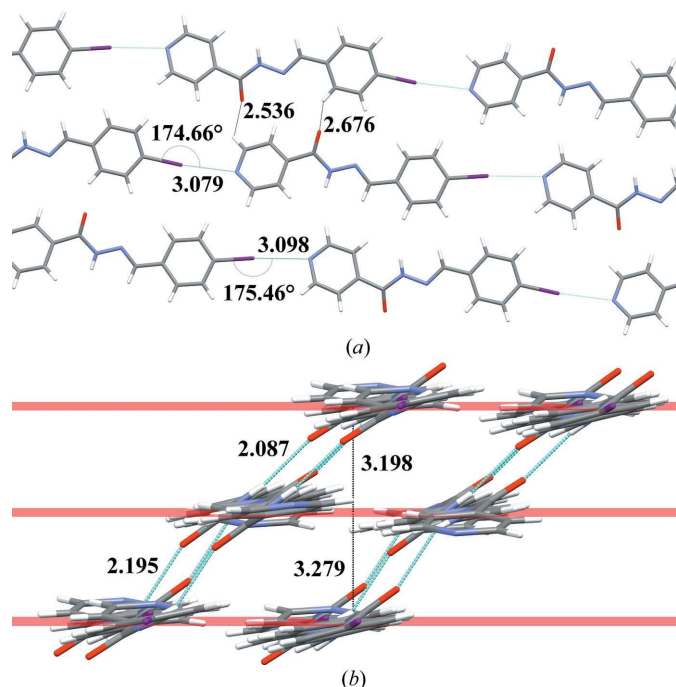


Figure 3
(*a*) Halogen- and hydrogen-bonded molecules of IsI developing extended chains. (*b*) Three parallel planes (highlighted in transparent red, with interplanar distances (Å) in given black) and the $\text{O} \cdots \text{H} \cdots \text{N}$ hydrogen bonds linking neighbouring layers (cyan). The colour scheme is as follows: H, light grey; C, grey; N, blue; O, red; I, purple.

iodine structure, molecules are paired in a head-to-head fashion and develop a staggered columnar arrangement in the direction of the *c* axis, still maintaining the same $\text{O} \cdots \text{H} \cdots \text{N}$ hydrogen bonds (2.137 Å) as seen in IsI (Fig. 4*a*).

The shortest measured $\text{Br} \cdots \text{Br}$ distance at 3.886 (9) Å is associated with $\text{Br} \cdots \text{Br} \cdots \text{C}$ angles $\sim 130.4^\circ$ (Fig. 4*b*). Considering the sum of van der Waals radii for bromine (3.8 Å), the $\text{Br} \cdots \text{Br}$ separation is within the limit of precision for an XB interaction. As both angles are roughly equivalent, these very weak contacts should be considered as type I halogen bonds, namely when $\theta_1 \simeq \theta_2$ (where θ_1 and θ_2 are the $R-X1 \cdots X2$ and $X1 \cdots X2-R$ angles, respectively) (Awwadi *et al.*, 2006; Duarte *et al.*, 2015). A more detailed look reveals that a Br atom points toward an electron-rich region, the bromophenyl group. Considering the centre of the C—Br bond, the $\text{Br} \cdots \text{Ce}$ (centroid) distance is 3.757 Å and the C— $\text{Br} \cdots \text{Ce}$ angle is close to 146° , which is consistent with an electron donation from the aromatic π -system toward the halogen atom (Fig. 4*b*).

Numerous studies compare halogen and hydrogen bonds in competitive settings using 4-halotetrafluorophenols or diazobenzene species bearing 4-hydroxy- and 4-halotetrafluorophenyl rings (Takemura *et al.*, 2014; Priimagi *et al.*,

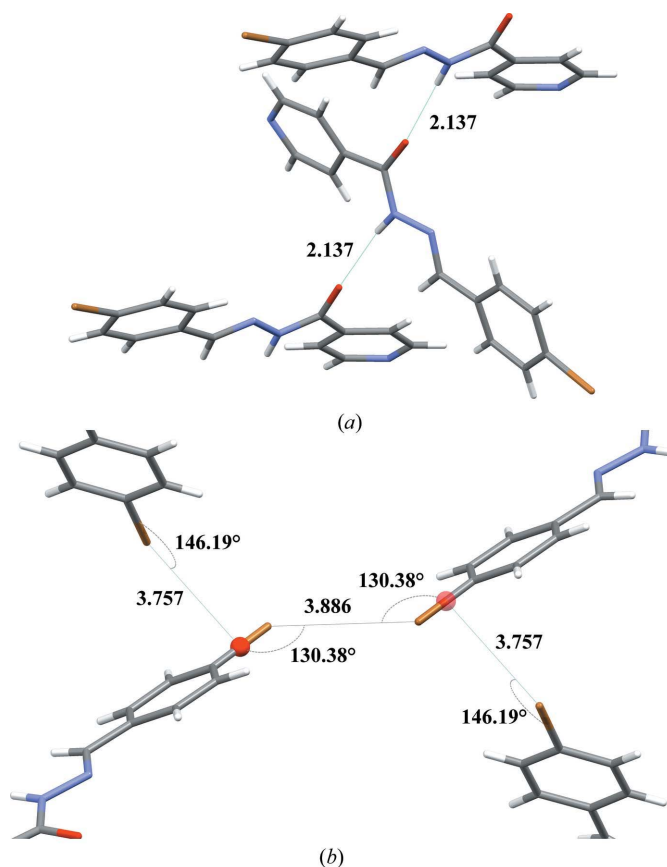


Figure 4
(*a*) $\text{O} \cdots \text{H} \cdots \text{N}$ hydrogen bonds linking neighbouring molecules. (*b*) Short distances (Å) involving Br atoms contribute to the supramolecular arrangement of IsBr. The colour scheme is as follows: H, light grey; C, grey; N, blue; O, red; Br, brown.

2012). Here, the structural features of the hydroxyl analogue of IsI and IsBr are investigated. So far, two X-ray structures of *N'*-(4-hydroxybenzylidene)isonicotinohydrazide have been reported, namely in pure form (IsOH) and as the monohydrate (IsOH·H₂O) (Deng *et al.*, 2005; Tai *et al.*, 2007). In IsOH, molecules are superposed in a parallel displaced stacking and head-to-tail mode, with rather short O···Ce (pyridyl ring centre) and N···Ce (phenyl ring centre) distances of 3.298 and 3.449 Å, respectively (Fig. 5). We have already observed such a counterintuitive system between an oxygen donor and a pyridyl group (Berger, Soubhye *et al.*, 2014). In addition, both OH and NH groups are hydrogen bonded. The hydroxyl is involved in a bifurcated hydrogen-bond interaction with O—H···O and O—H···N contacts of 1.994 and 2.464 Å, respectively. The pyridyl ring forms a weak interaction with NH, the N—H···N length being 2.398 Å.

The hydrogen bond propensity tool (in the *Mercury* software) predicts that the hydrated structure is the most stable form. Interestingly, the supramolecular arrangement of IsOH·H₂O is very different from IsOH and is comparable with that of IsI. Indeed, the pyridyl ring binds the hydroxyphenyl group through N···H interactions (distance = 1.920 Å), developing extended undulating chains (Fig. 6a).

More strikingly and similarly to the IsI structure, chains belonging to the same undulating sheet point toward the same direction, whereas molecules of neighbouring medium planes are oriented in opposite directions. The water molecule here plays a decisive role in the crystal organization since all atoms are involved in close contacts and parallel chains of hydrazones accommodate a water molecule in between. As a result, adjacent units are bridged through two O···H and N···H hydrogen bonds of 2.014 and 2.216 Å, respectively. The second hydrogen further interacts with the carbonyl group of a neighbouring plane, the separation being 1.969 Å (Fig. 6b). Examination of crystal packings of IsI, IsOH and IsOH·H₂O provides interesting information regarding the specificities of halogen and hydrogen bonding. The highly planar and linear molecular architecture observed in IsI seems to be dependent on the high directionality of the N···I interactions, which is one of the main characteristics of halogen bonding. In

contrast, IsOH units form undulating chains and sheets in IsOH·H₂O only with the help of bridging water molecules filling the empty space between the hydrazones.

3.3. Structural features of hydralazine-based hydrazones

The structural features of hydrazine-based hydrazones HyI and HyBr were expected to mainly imply $\pi\cdots\pi$ and halogen··· π contacts, owing to the prevalence of aromatic systems. Hydrochloride salts of HyI, HyBr and HyOH first underwent alkaline treatment followed by extraction with CH₂Cl₂ and suitable crystals for single-crystal X-ray diffraction were obtained by slow evaporation of the CH₂Cl₂ solution. For HyI, the structural analysis reveals the presence of weak I··· π interactions. The shortest I···Ar (Ar = 4-iodophenyl group) distance is 3.448 Å, associated with a C—I···C7 angle of 163.8 (2)°, which is consistent with those of a halogen bond. The supramolecular architecture is also supported by close contacts between the aromatic groups.

The $\pi\cdots\pi$ stacking between phthalazine rings is indeed present [centroid···plane distance of 3.576 Å], whereas the centroid of the iodo-arene is separated by a distance of 3.758 Å from the neighbouring iodo-arene plane, those rings are slightly twisted (Fig. 7). It seems that in this structure the halogen bond dominates the crystal packing as the classical double hydrogen-bond interaction patterns that are found in both HyBr and HyOH (see below) are not observed and reduced to a weaker out-of-plane interaction (NH···N, 2.273 Å). The replacement of I by Br provokes a dramatic change of organization. As mentioned in the *Introduction*, the σ -hole size decreases from I to Br (see Fig. 10a), and similarly to the couple IsI/IsBr, halogen bonds are no longer observed in HyBr. The X-ray structure reveals a combination of $\pi\cdots\pi$

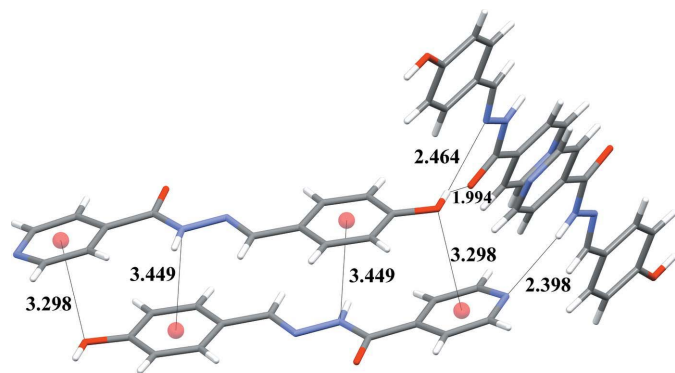


Figure 5

X-ray structure of IsOH, highlighting the short O···Ce (pyridyl ring centre) and N···Ce (phenyl ring centre) distances (Å) and the multiple hydrogen bonds (Å).

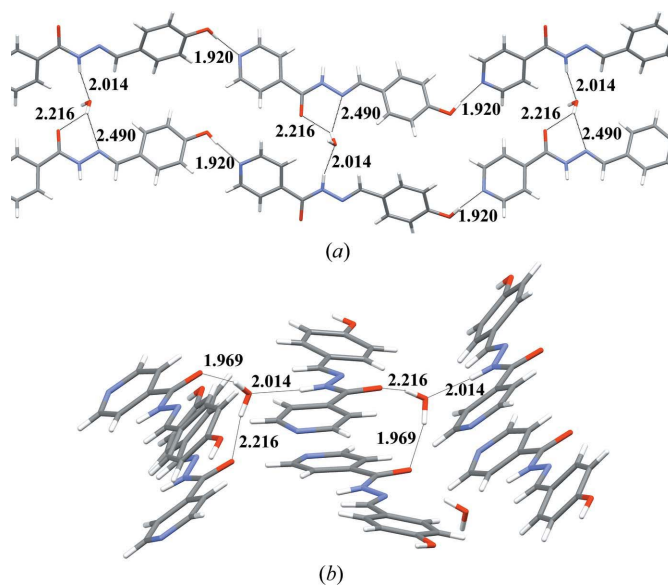


Figure 6

(a) Hydrogen-bonded molecules of IsOH···H₂O developing extended chains with a water molecule bridging the units. (b) Undulating parallel planes highlight the water molecules bound by two O···H and one O···H hydrogen bonds (Å).

stacking and $\text{N} \cdots \text{H}$ hydrogen bonds that govern the supramolecular system. Intra-molecular $\text{N} \cdots \text{H}$ contacts lock the conformation in the middle of each unit for both HyI

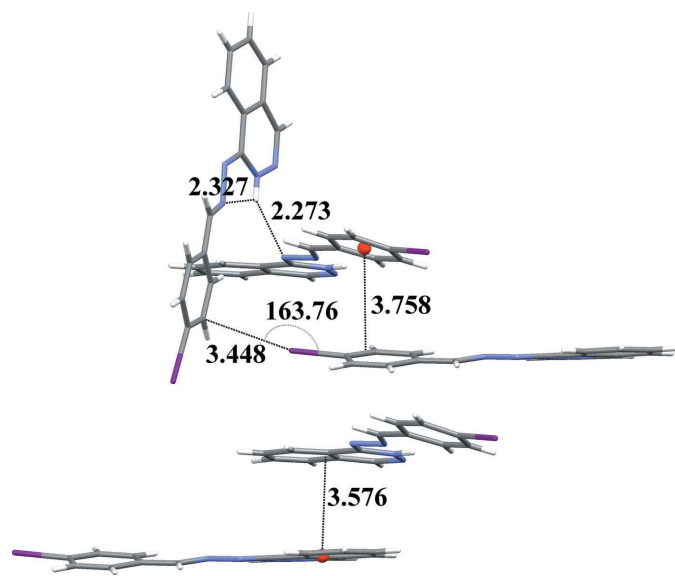


Figure 7
X-ray structure of HyI showing the $\text{I} \cdots \pi$ halogen bonding and the $\pi \cdots \pi$ stacking between aromatic rings.

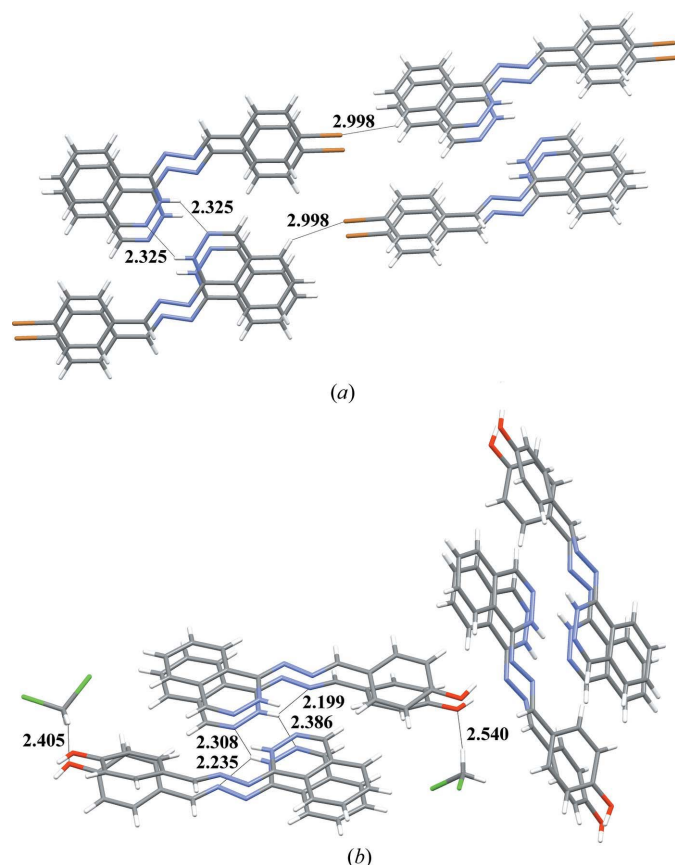


Figure 8
X-ray structure of (a) HyBr and (b) HyOH, showing the $\pi \cdots \pi$ stacking and $\text{N} \cdots \text{H}$ hydrogen bonds (Å).

(2.327 Å) and HyBr (2.265 Å), while pairs of molecules construct parallel displaced stacking, these units having the same orientation. The stacked couples are hydrogen bonded *via* two equal hydrogen bonds ($\text{NH} \cdots \text{N}$ distance is 2.325 Å) around an inversion centre (Fig. 8a).

For the purpose of comparison, HyOH was synthesized and its structure studied by X-ray diffraction. As for HyBr, the hydrogen bonds play a predominant role in the supramolecular organization. As previously observed, the hydrazazine-based building blocks are characterized by an intramolecular $\text{N} \cdots \text{H}$ hydrogen bond (2.199 or 2.235 Å) which acts as a conformational lock. Adjacent crystallographically independent molecules are held together by two intermolecular $\text{N} \cdots \text{H}$ hydrogen bonds of 2.308 and 2.386 Å.

Compared with HyBr, these modules adopt very similar packing features, namely a dimer formation due to the complementarity of the bicycles, and a parallel displaced stacking into columns. The main difference is induced by the presence of the hydroxyphenyl group and the additional classical hydrogen donor OH, which forms a hydrogen bond with the only remaining acceptor site, being the nitrogen of the

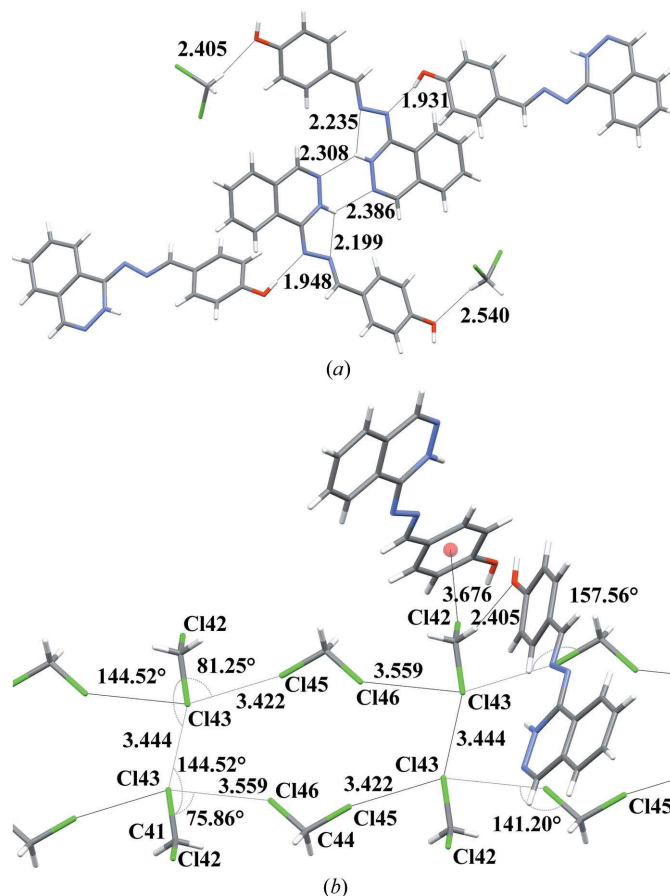


Figure 9
(a) X-ray structure of HyOH, highlighting the multiple hydrogen bonds involved in hydrazone $\cdots$ hydrazone and hydrazone $\cdots$ dichloromethane interactions (Å). (b) Linear organization of dichloromethane molecules due to $\text{Cl} \cdots \text{Cl}$ and $\text{Cl} \cdots \pi$ halogen bonds (Å) between dichloromethane and HyOH. The colour scheme is as follows: H, light grey; C, grey; N, blue; O, red; Cl, green.

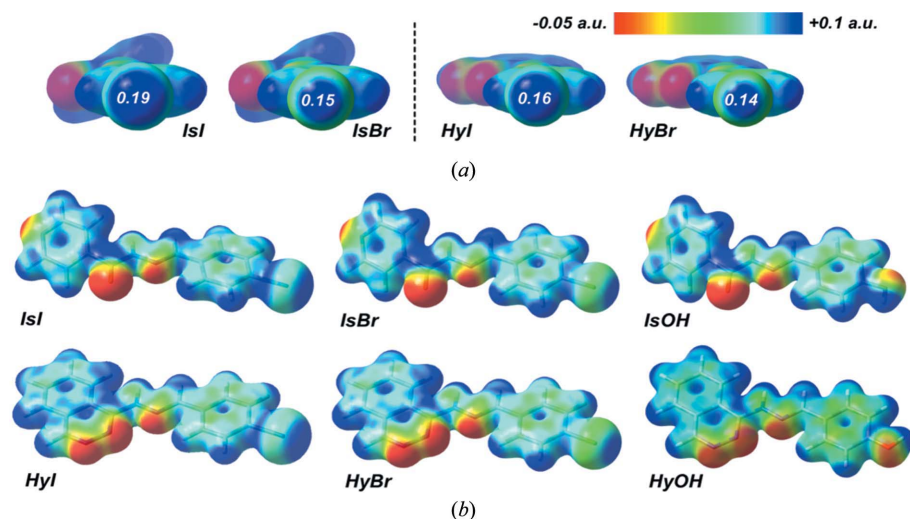


Figure 10
ESP maps for hydrazones IsX and HyX ($X = \text{I}, \text{Br}, \text{OH}$). The σ -hole depth for IsX and HyX ($X = \text{I}, \text{Br}$) is highlighted in (a).

hydrazone function ($\text{N} \cdots \text{HO}$ distances of 1.931 and 1.948 Å). As a result of either the angular constraints or the $\text{OH} \cdots \text{N}$ hydrogen bond, stacks of dimer columns show an offset rotation to one another, with four columns enclosing a solvent channel. The crystallization process surprisingly provoked the clathration of CH_2Cl_2 molecules in this solvent channel, for which additional $\text{O} \cdots \text{H}$ contacts of 2.405 and 2.540 Å are present and link the clathrate solvent to the hydrazones (Fig. 9a).

3.4. Interaction energies and electrostatic potential maps

The molecular electrostatic potential (ESP) has been mapped to the total DFT density (at an isodensity value of 0.02 a.u.) and comparisons are made between the different compounds within the isoniazid and hydralazine series. The expected electron-density anisotropy around the halogen atom is observed, with an equatorial electronegative corolla and an electropositive region along the $\text{C}-\text{X}$ axis, namely the σ -hole. The magnitude of the induced hole on the halogen follows the expected $\text{I} > \text{Br}$ order, as does the maximum value of the ESP on the $\text{C}-\text{X}$ axis (*i.e.* the σ -hole depth, 0.19 a.u. for IsI and 0.15 a.u. for IsBr , see Fig. 10). A second look shows that strongly negative regions are found in the vicinity of the basic pyridine nitrogen and the carbonyl oxygen for which maximum ESP values are both calculated at -0.08 a.u. The negative region surrounding the hydrazone nitrogen is buried in the structure and, therefore, not expected to participate in intermolecular interactions and that has been confirmed from the X-ray structures. The partners for molecular recognition are thus well identified from ESP maps, the electron acceptors being the halogen atom and the aromatic proton. Electron donors are the pyridine nitrogen and the carbonyl oxygen, confirming the observations in the crystal structures. The same structural features are seen for the hydralazine series,

however, lower ESP values are calculated (from 0.16 to 0.14 a.u. for HyI and HyBr , respectively).

Interaction energies of dimers were further calculated at the DFT level with counterpoise correction. Geometries of interacting molecules either through the halogen atom or the carbonyl group were optimized from their crystal geometries to evaluate the contributions of these two major interactions as found from X-ray crystallography. The Kohn–Sham energies of complexation are given in Fig. 10.

The halogen bond enthalpy between IsI molecules was calculated to be around -3 kcal mol^{-1} , which is consistent with mildly activated iodine XB donors (Fig. 11a) (Tsuzuki *et al.*, 2013). The same two compounds interacting through the carbonyl reveal a hydrogen-bonded dimer with a much stronger interaction found at around $-13 \text{ kcal mol}^{-1}$, showing that antiparallel sheets are strongly bound in the crystal, whereas chains propagate through rather weak halogen bonds (Fig. 11b). A third structure resulting from a water-bridged dimer of IsOH was examined and delivered an expected increase in interaction enthalpy ($-18 \text{ kcal mol}^{-1}$) due to the two hydrogen bonds formed *via* the bridging water molecule (Fig. 11c). Finally, a calculated system composed of IsI and IsOH molecules interacting through $\text{N} \cdots \text{HO}$ contacts gave a complexation enthalpy of around -9 kcal mol^{-1} (Fig. 11d). Hence, the $\text{N} \cdots \text{H}$ hydrogen bonds appear almost three times stronger than the $\text{N} \cdots \text{I}$ halogen bonds. Combining the crystallographic and calculated data, the high directionality of the halogen bonding tends to compensate for its weaker strength of interaction and allows development of the linear organization as seen in the crystal structure of IsI .

3.5. Type I and II halogen-bonded dichloromethane

3.5.1. X-ray crystallography. A closer look at the guest solvent in the HyOH crystals reveals unexpected behaviour; extended parallel chains of CH_2Cl_2 molecules are formed due to multiple intra- and inter-chain $\text{Cl} \cdots \text{Cl}$ interactions. Each chain is composed of nearly perpendicular alternating units, the angle formed by the $\text{Cl}-\text{C}-\text{Cl}$ planes is 78.3° (Fig. 9b). In detail, interchain non-covalent bonds are in agreement with a type I halogen $\cdots$ halogen interaction because both $\text{C41}-\text{Cl43} \cdots \text{Cl43}$ angles are identical (144.5°) and the $\text{Cl43} \cdots \text{Cl43}$ distance is 3.444 Å. Considering the linear organization, one molecule bridges neighbouring partners, the $\text{Cl45} \cdots \text{Cl43}$ and $\text{Cl46} \cdots \text{Cl43}$ separations are 3.422 and 3.559 Å, respectively. As mentioned for $\text{Br} \cdots \text{Br}$ contacts in IsBr , distances are within the limit of precision for $\text{Cl} \cdots \text{Cl}$ XB interactions (the sum of the van der Waals radii is 3.5 Å) and should reveal type II halogen $\cdots$ halogen links. The electron donation from Cl43

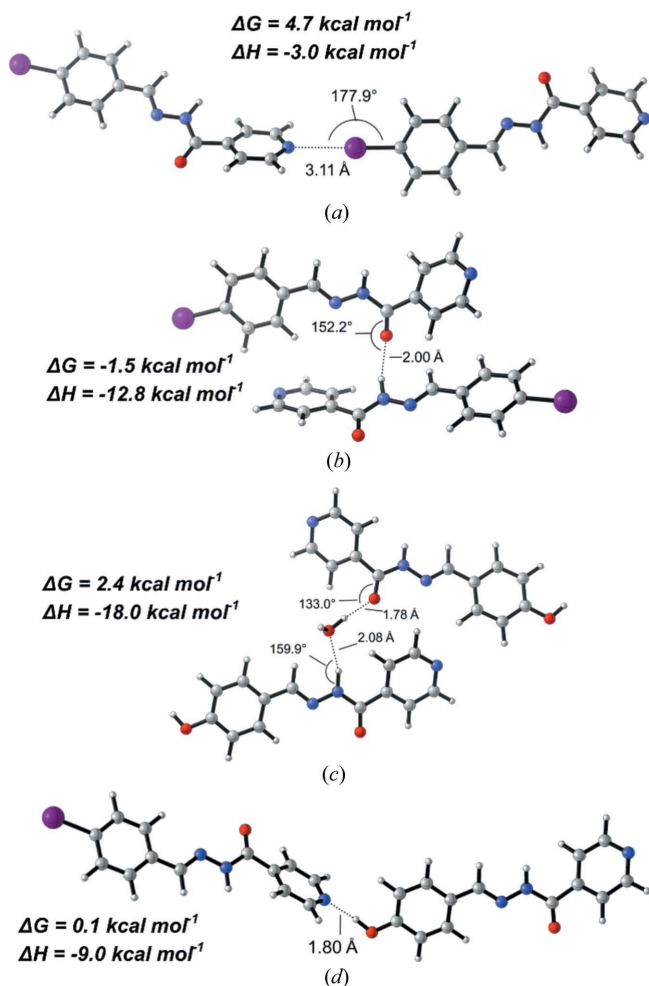


Figure 11

DFT-optimized structures of interacting dimers and their electronic complexation energies ($1 \text{ kcal mol}^{-1} = 4.184 \text{ kJ mol}^{-1}$).

to Cl45 and Cl46 is thereby demonstrated by the C44—Cl45...Cl43 and C44—Cl46...Cl43 angles of 157.5° and 141.2° , whereas the associated C41—Cl43...Cl45 and C41—Cl43...Cl46 angles are 81.2 and 75.9° , respectively. In addition, the remaining chlorine atom (Cl42) is close to the hydroxyphenyl ring; the Cl42...Ce (centroid) length is $3.676 \text{ \AA}$ and the C41—Cl42...Ce angle is 155.5° (Fig. 9b). The electron transfer from the aromatic system to the chlorine atom may have a role in the behaviour of Cl43 toward Cl45 and Cl46.

Assemblies of CH_2Cl_2 molecules have rarely been reported in the literature, bearing in mind that it is commonly used as a crystallization medium. Except for its X-ray structures obtained in pure form under high pressure (Podsiadlo *et al.*, 2005) and very low temperature (Kawaguchi *et al.*, 1973), the Cambridge Structural Database contains fewer than ten complexes comprising type II Cl...Cl halogen bonds between CH_2Cl_2 molecules. Hereafter are provided the CSD reference codes of structures containing type II contacts between CH_2Cl_2 molecules, considering the following crystallographic parameters C—Cl1...Cl2 and Cl1...Cl2—C angles in the ranges 150 – 180° and 70 – 110° , respectively, and Cl1...Cl2

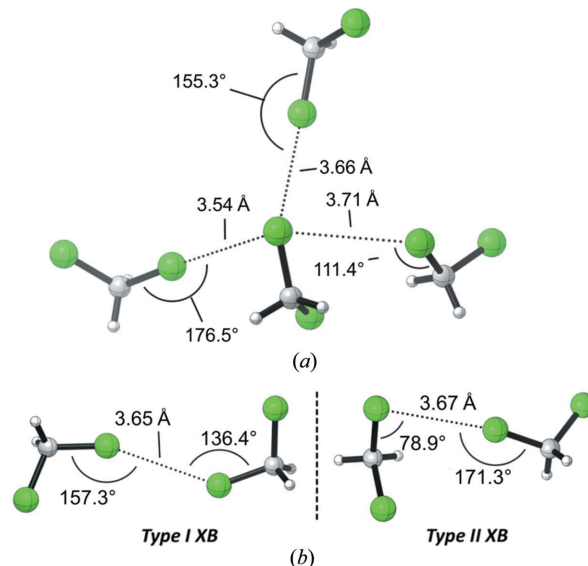


Figure 12

(a) DLPNO-CCSD(T)/cc-PVTZ-optimized geometry of four interacting CH_2Cl_2 molecules as observed from the crystal structure of HyOH. (b) DLPNO-CCSD(T)/cc-PVTZ-optimized type I and II XB contacts as used for the LED analysis.

distances in the range 2.5 – $3.6 \text{ \AA}$: FAHGON (Kubota *et al.*, 2016), HIQDUI (Kenny *et al.*, 2013), REGTED (Pasynskii *et al.*, 2005), YIHKAD (Nishimura *et al.*, 2013), OZIJUE (Raducan *et al.*, 2011), PAQTAD (Oberbeckmann-Winter *et al.*, 2005), TIYQOJ (Wang *et al.*, 2013). In these structures, the halogen bonds are present as part of a more elaborate network between CH_2Cl_2 molecules, forming two-dimensional sheets or one-dimensional propagating ribbons.

3.5.2. LED for the CH_2Cl_2 dimers and tetramer. To get further insight into the short distances observed between CH_2Cl_2 molecules in the crystal, the solid-state geometry of four interacting molecules was optimized at the DLPNO-CCSD(T) level in the gas phase. If dispersion-corrected DFT fails to reproduce the experimental geometry, the DLPNO-CCSD(T) geometry rather well preserved the crystal structure (Fig. 12a).

However, in the absence of crystal packing and other interacting neighbours, Cl...Cl distances are calculated to be longer than that of the crystal.

We then carried out a LED analysis on CH_2Cl_2 dimers showing type I and II XB contacts, starting from the crystal geometries and optimizing these at the DLPNO-CCSD(T) level. LED analysis for type I contacts (Fig. 12b, left view) gave a total interfragment correlation energy of $-1.26 \text{ kcal mol}^{-1}$ that decomposes into a $-0.61 \text{ kcal mol}^{-1}$ part of a dispersive nature, while -0.49 and $-0.16 \text{ kcal mol}^{-1}$ comes from charge-transfer mechanisms (from $1 \rightarrow 2$ and $2 \rightarrow 1$). HF interaction energy accounts for $-3.49 \text{ kcal mol}^{-1}$, from which the electrostatic term vastly predominates ($-2.79 \text{ kcal mol}^{-1}$) over the exchange energy between the two molecules ($-0.70 \text{ kcal mol}^{-1}$). Type II Cl...Cl contacts (Fig. 12b, right view) imply a higher interaction energy from correlation effects ($-3.00 \text{ kcal mol}^{-1}$), from which dispersion

accounts for $-1.29 \text{ kcal mol}^{-1}$, and charge transfers for -0.68 and $-1.03 \text{ kcal mol}^{-1}$. Electrostatic interaction from HF energy rises to $-4.40 \text{ kcal mol}^{-1}$ and the exchange term is calculated at $-1.16 \text{ kcal mol}^{-1}$. These stabilizing attractive energies are partly compensated by the geometric and electronic preparation terms, which can be seen as the required energy to adopt the geometric and electronic configuration as found in the dimers with respect to their relaxed monomeric forms.

4. Conclusions

We investigated the supramolecular arrangement of halogenated hydrazones derived from the well known pharmaceuticals isoniazid and hydralazine, and compared them with their hydroxyl analogues. X-ray structures of IsI and HyI show the presence of weak $\text{I} \cdots \text{N}$ and $\text{I} \cdots \pi$ halogen bonds, respectively, whereas the weaker XB donors, IsBr and HyBr scaffolds, are predominantly governed by hydrogen bonds. A similar linear organization is observed in IsI and $\text{IsOH} \cdot \text{H}_2\text{O}$ caused by a water molecule which disrupts the intermolecular $\text{C}=\text{O} \cdots \text{H}-\text{O}$ contacts observed in IsOH. Further information on the strength of interactions are obtained by theoretical calculations. It appears that $\text{N} \cdots \text{H}$ non-covalent bonds are much stronger than $\text{N} \cdots \text{I}$ interactions; however, the high directionality of the halogen bonds contributes to the linear molecular organization in IsI. The crystal packing of HyOH highlights an unexpected halogen-bonded system based on a linear arrangement of CH_2Cl_2 molecules through type I and type II $\text{Cl} \cdots \text{Cl}$ contacts. The CSD survey of halogen-bonded CH_2Cl_2 from (in)organic crystals confirmed the rare occurrence of such linear or ribbon-like architectures as less than ten structures were found. A LED study highlights the mixed dispersive nature of the interactions, for which dynamic polarization through a charge-transfer mechanism accounts for more than half of the electronic correlation effects.

A step further would involve the use of such weak XB donor compounds to form metal-based materials, as metal chelation by such ligands is expected to reinforce the σ -hole depth due to donation to the metal and π -conjugation over the molecule. Moreover, a comprehensive investigation will be performed on the $\text{HyOH}/\text{CH}_2\text{Cl}_2$ system in order to define its catch and release properties.

Acknowledgements

GB thanks the ULB-VUB computing centre for providing high-performance computing facilities and useful technical support.

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