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

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Synopsis Supramolecular assemblies of halogenated and hydroxyl hydrazones derived from pharmaceuticals are governed by $I \cdots N$ and $I \cdots \pi$ halogen bonds or O-H $\cdots N$ hydrogen bonds. An unexpected linear arrangement of clathrated dichloromethane molecules bound through type I and II halogen bonds is observed. Theoretical calculations support the crystallographic study.

Abstract The supramolecular assembly of halogenated and hydroxyl hydrazones derived from two well-known pharmaceuticals, *i.e.* isoniazid (IsX with X = I, Br, OH) and hydralazine (HyX with X = I, Br, OH), were 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. While 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, that is 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, only observed in less than ten structures, was studied by coupled cluster-based energy decomposition.

Keywords: Halogen bond, pharmaceuticals, dichloromethane, hydrazones

1. Introduction

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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). Starting from fundamental studies focusing on crystal engineering, investigations slowly shifted toward applied science (Rissanen, 2008; Metrangolo *et al.*, 2008). Hence, 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). On a parallel scene, synthetic chemistry developed with a wide range of XB-controlled reactions, competing thus 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; Metrangolo et al., 2009; Cavallotti et al., 2008). As concerns the XB donors, both the 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 selfassembly 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 bromo-phenyl 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 considered as such can find an interest to stabilize an architecture (Berger et al., 2014a) 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, *i.e.* isoniazid and hydralazine. Hydrazones are an important class of molecules endowed with a wide range of applications that are used for their switch properties (Aprahamian, 2017), pH-responsive behaviour in drug delivery systems (Sonawane *et al.*, 2017), 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-hydroxy-hydrazones were studied by X-ray crystallography, density functional theory (DFT) and coupled cluster-based energy decomposition (**Figure 1**).



Figure 1 Structures of isoniazid and hydralazine-based hydrazones.

2. Experimental

2.1. Synthetic procedures

¹H- and ¹³C-NMR spectra were recorded on a JEOL 400 MHz spectrometer at 293 K. Chemical shifts (δ) are given in parts per million (ppm) relative to the solvent residual peaks, and the coupling constants are expressed in hertz. 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.

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 10 mL refluxing ethanol. After 3 h, the reaction was cooled down 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; mp. = 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). ¹³C-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; mp. = 232 °C. δ 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; mp. = 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). ¹³C-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 crystal structures were measured on a MAR345 image plate using MoK α radiation (Rigaku UltraX 18S rotating anode, Fox3D mirrors). Indexing, integration and data reduction was performed by CrysAlisPRO and the implemented absorption correction was applied. All structures were measured at room temperature. The structures were solved by SHELXT and then refined on $|F^2|$ using SHELXL-2014/7 (Sheldrick, 2015a; Sheldrick, 2015b). Non-hydrogen atoms were anisotropically refined. The hydrogen atoms were located in the Fourier maps and refined in riding mode with isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms. CrysAlisPRO: Rigaku Oxford Diffraction, *CrysAlisPro Software System*, Version 1.171.37.35; Rigaku Corporation: Oxford, UK, 2015. Visualization and analysis of the crystal structures were performed with Mercury (Macrae *et al.*, 2006). The database analysis was performed using the Cambridge Structural Database CSD version 5.38 +3 updates (Groom & Allen, 2014). The structures have been deposited at the Cambridge Crystallographic Data Centre. CCDC 1820529-1820533 contain the supplementary crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

2.3. General quantum mechanical methods.

All quantum mechanical calculations have been achieved using Gaussian09 rev. D.01 and Orca 4.0.1 (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 (BSSE) (Boys & Bernardy, 1970). Cube densities were generated at the 80 points/Bohr³ mesh resolution.

DLPNO-CCSD(T) calculations of isolated and interacting CH_2Cl_2 molecules were carried out with TightPNO settings as described by Liakos (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 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 in Schneider *et al.* (Schneider *et al.*, 2016).

2.4. Local Energy Decomposition (LED)

The DLPNO-CCSD(T) method provides accurate correlation energies that allows to predict many chemical phenomena and investigate weak interactions. To facilitate the interpretation of coupled cluster results, we used the 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:

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

The LED is a physical meaningful decomposition of ΔE_{int} within the DLPNO-CCSD(T) scheme that is provided in ORCA 4 and which first decomposes the electronic interaction between its Hartree-Fock (HF) and electronic correlation contributions:

$$\Delta E_{int} = \Delta E_{int}^{HF} + \Delta E_{int}^{Corr}$$
 (eq. 2)

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

$$\Delta E_{int}^{Corr} = \Delta E_{Disp(X,Y)}^{Corr} + \Delta E_{CT(X \to Y)}^{Corr} + \Delta E_{CT(Y \to X)}^{Corr}$$
(eq. 2)

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 CH_2Cl_2 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. Isoniazid was stirred in refluxing ethanol with an equimolar amount of 4-iodo- or 4-bromo-benzaldehyde, 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 (**Figure 2**).



Figure 2 Synthesis of isoniazid- and hydralazine-based hydrazones (panel A: IsI, IsBr and IsOH, panel B: HyI, HyBr and HyOH).

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 that purpose, suitable crystalline material of compounds IsI and IsBr was obtained by slow cooling of an ethanolic solution. The presence of multiple electron-rich moieties (π systems, carbonyl groups and nitrogen atoms) offers a large panel of partners to the halogen atoms. The solid-state structure analysis of IsI reveals a linear arrangement between the two crystallographic independent molecules governed by two types of $N \cdots I$ halogen bonds (Figure 3, up). The interatomic distances between the corresponding nitrogen and iodine atoms are measured at 3.079 and 3.098 Å, *i.e.* about 16% shorter than the sum of the van der Waals radii of nitrogen and iodine (3.70 Å), considering Batsanov's values (Batsanov, 2001). The N···I-C angles are nearly linear (174.7° and 175.5°), attesting to a fairly strong interaction due to the nature of the halogenated group. Interestingly, the units form parallel infinite head-to-tail chains, which give rise to 2D sheets and alternating parallel planes are comprised of molecules that are rotated 180° around the molecules main axis (Figure 3, up). Other hydrogen bonds govern the supramolecular organization. Indeed, the carbonyl groups point toward a bottom adjacent layer, binding aromatic hydrazone hydrogens. Two types of O···H-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, Figure 3, down).



Figure 3 Halogen and hydrogen bonded molecules of **IsI** developing infinite chains (up). Three parallel planes (highlighted in transparent red, with interplanar distances in black labels) and the $O \cdots H$ -N hydrogen bonds linking neighbouring layers (cyan) (down). Colours are as follows: H, light grey; C, grey; N, blue; O, red; I, purple.

The substitution of iodine for bromine dramatically modifies the overall organization, as seen from the crystal structure of **IsBr** (**Figure 4**). This structure is identical to a previously solved and deposited one, yet not discussed (Li & Jian, 2008). Halogen bonds between the pyridyl ring and the bromine atom no longer governs the crystal architecture. In opposite with the iodine case, molecules are paired in a head-to-head fashion and develop a staggered columnar arrangement in the direction of the c-axes, still maintaining the same O···H-N hydrogen bonds (2.137 Å) as seen in **IsI** (**Figure 4**, up).





Figure 4 O····H-N hydrogen bonds linking neighbouring molecules (up). Short distances involving Br atoms contributing to the supramolecular arrangement of **IsBr** (down). Colours are as follows: H, light grey; C, grey; N, blue; O, red; Br, brown.

The shortest measured Br…Br distance at 3.886 Å is associated to Br…Br-C angles of 130.4° (**Figure** 4, down). Considering the sum of van der Waals radii for bromine (3.8 Å), the Br…Br separation is within the limit of precision for a XB interaction. As both angles are roughly equivalent, these very weak contacts should be considered as type I halogen bonds, namely when $\Theta 1 \approx \Theta 2$ (where $\Theta 1$ and $\Theta 2$ are the R–X1…X2 and X1…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 Br…Ce (centroid) distance is 3.757 Å and the C-Br…Ce angle is close to 146°, which is consistent with an electron donation from the aromatic π -system toward the halogen atom (**Figure 4**, down).

Numerous studies compared halogen and hydrogen bonds in competitive settings using 4halotetrafluorophenols or diazobenzene species bearing 4-hydroxy- and 4-halotetrafluoro-phenyl rings (Takemura et al., 2014; Priimagi et al., 2012). Here, the structural features of the hydroxyl analogue of *N*'-(4-IsI IsBr were investigated. So far. two X-ray structures of and 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 (Figure 5). We already observed such counterintuitive system between an oxygen donor and a pyridyl group (Berger et al., 2014b). 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. As concerns the pyridyl ring, it makes a weak interaction with NH, the N-H…N length being 2.398 Å.



Figure 5 X-ray structure of **IsOH** highlighting the short O···Ce (pyridyl ring centre) and N···Ce (phenyl ring centre) distances and the multiple hydrogen bonds.

The hydrogen bond propensity tool (in the Mercury software) indicates that the hydrated structure is the most stable form. Interestingly, the supramolecular arrangement of **IsOH.H**₂**O** is very different from **IsOH** and is comparable to that of **IsI**. Indeed, the pyridyl ring binds the hydroxyphenyl group through N…H interaction (distance is 1.920 Å), developing infinite undulating chains (**Figure 6** up).



Figure 6 Hydrogen bonded molecules of IsOH.H2O developing infinite chains with a water molecule bridging the units (up). Undulating parallel planes highlighting the water molecules bound by two O…H and one O…H hydrogen bonds (down).

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 $O \cdots H$ and $N \cdots H$ 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 (**Figure 6** down). Examination of crystal packings of **IsI**, **IsOH** and **IsOH.H₂O** provides an interesting information regarding the specificities of halogen and hydrogen bonding. The highly planar and linear molecular architecture observed in **IsI** seems to be dependent of the high directionality of 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. 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 $\cdots \pi$ 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. As concerns **HyI**, the structural analysis reveals the presence of weak I $\cdots \pi$ interactions. The shortest I \cdots Ar (Ar = 4-Iodophenyl group) distance is 3.448 Å, associated to a C-I \cdots C(7) angle of 163.8° which is consistent with those of a halogen bond. The supramolecular architecture is also supported by close contacts between the aromatic groups.



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

 $\pi \cdots \pi$ stacking between phthalazine rings is indeed present (centroid \cdot 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 being slightly twisted (**Figure 7**). It seems that in this structure the halogen

bond dominates the crystal packing as the classical double hydrogen 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···HN, 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 **Figure 10** up), and similarly to the couple **IsI/IsBr**, halogen bonds are no longer observed in **HyBr**. The X-ray structure rather reveals a combination of π ··· π stacking and N···H hydrogen bonds that govern the supramolecular system. Intra-molecular N···H contacts lock the conformation in the middle of each unit for both **HyI** (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 (NH···N distance is 2.325 Å) around an inversion centre (**Figure 8** up).



Figure 8 X-ray structure of **HyBr** (up) and **HyOH** (down) showing the $\pi \cdots \pi$ stacking and N \cdots H hydrogen bonds.

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



Figure 9 X-ray structure of **HyOH** highlighting the multiple hydrogen bonds involved in hydrazone...hydrazone and hydrazone...dichloromethane interactions (up). Linear organization of dichloromethane molecules due to Cl...Cl and Cl... π halogen bonds between dichloromethane and **HyOH** (down). Colours are as follows: H, light grey; C, grey; N, blue; O, red; Cl, green.

Compared to **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 hydrazone function (N···H-O distances of 1.931 and 1.948 Å). Due to either the angular constraints or the OH···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 CH₂Cl₂ molecules in this solvent channel, for which additional O···H contacts of 2.405 and 2.540 Å are present and link the clathrate solvent to the hydrazones (**Figure 9** up).

3.4. Interaction energies and electrostatic potential maps

The molecular electrostatic potential (ESP) has been mapped to the total DFT density (at the isodensity value of 0.02 a.u.) and compared 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 C-X axis, namely the σ hole. The magnitude of the induced hole on the halogen follows the expected I > Br order, as does the maximum value of the ESP on the C-X axis (*i.e.* the σ hole depth, 0.19 a.u. for IsI and 0.15 a.u. for IsBr, Figure 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 into the structure and therefore not expected to participate in intermolecular 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 with, however, lower ESP values are calculated (from 0.16 to 0.14 a.u. for HyI and HyBr, respectively).

Interactions 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, and the Kohn-Sham energies of complexation are given in (**Figure 10**).



Figure 10 ESP maps for hydrazones IsX and HyX (X = I, Br, OH). The σ -hole depth for IsX and HyX (X = I, Br) is highlighted in A.



Figure 11 DFT-optimized structures of interacting dimers and their electronic complexation energies.

The halogen bond enthalpies between **IsI** molecules is calculated around -3 kcal.mol⁻¹, which is consistent with mildly-activated iodine XB-donors (**Figure 11A**) (Tsuzuki *et al.*, 2013). The same two compounds interacting through the carbonyl reveal a hydrogen-bonded dimer with a much stronger interaction found around -13 kcal.mol⁻¹, showing that antiparallel sheets are strongly tighten in the crystal, whereas chains are propagating through rather mild halogen bonds (**Figure 11B**). A third structure resulting from a water-bridged dimer of **IsOH** was examined and delivered an expected increase in interaction enthalpy (-18 kcal.mol⁻¹) due to the two hydrogen bonds made via the bridging water molecule (**Figure 11C**). Finally, a calculated system composed of **IsI** and **IsOH** molecules interacting through N···HO contacts, gave a complexation enthalpy around -9 kcal.mol⁻¹ (**Figure 11D**). Hence, the N····H hydrogen bonds appear almost three times stronger than the N····I halogen bonds.

Combining the crystallographic and calculation data, the high directionality of the halogen bonding tends to compensate its weaker strength of interaction and allows developing 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 an unexpected behaviour: infinite parallel chains of CH_2Cl_2 molecules are formed due to multiple intra- and inter-chain $Cl\cdots Cl$ interactions. Each chain is composed of nearly perpendicular alternating units; the angle formed by the Cl-C-Cl planes being of 78.3° (**Figure 9** down). In detail, interchain non-covalent bonds are in agreement with a type I halogen…halogen interaction since both C41-Cl43…Cl43 angles are identical (144.5°) and the Cl43…Cl43 distance is 3.444 Å. Considering the linear organization, one molecule bridges neighbouring partners, the Cl45…Cl43 and Cl46…Cl43 separations being 3.422 and 3.559 Å, respectively. As aforementioned for Br…Br contacts in **IsBr**, distances are within the limit of precision for Cl…Cl XB interactions (sum of van der Waals radii is 3.5 Å) and should reveal type II halogen…halogen links. The electron donation from Cl43 to Cl45 and Cl46 is thereby demonstrated by the C44-Cl45…Cl43 and C44-Cl46…Cl43 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 Å and the C41-Cl42…Ce angle is 155.5° (**Figure 9** down). The electron transfer from the aromatic system to the chlorine atom may have a role in the behaviour of Cl43 to XI45 and Cl45.

It is worthy to note that assemblies of CH_2Cl_2 molecules have been scarcely observed in the literature, keeping in mind that it is commonly used as crystallization medium. Except for its X-ray structures obtained in pure form under high pressure (Podsiadło *et al.*, 2005) and very low temperature (Kawaguchi *et al.*, 1973), the Cambridge Structural Database contains less than ten complexes comprising type II Cl···Cl XBs between CH_2Cl_2 molecules. Reference codes of structures containing type II contacts between CH_2Cl_2 molecules, considering the following crystallographic parameters C-Cl(1)···Cl(2) and Cl(1)···Cl(2)-C angles in the range 150-180° and 70-110°, respectively, and Cl(1)···Cl(2) distances in the 2.5-3.6 Å range : FAHGON, HIQDUI, REGTED, YIHKAD, OZIJUE, PAQTAD, TIYQOJ. In these structures, the halogen bonds are present as part of a more elaborate network between CH_2Cl_2 molecules, forming 2D sheets or 1D propagating ribbons.

3.5.2. LED for the CH₂Cl₂ 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 failed to reproduce the experimental geometry, the DLPNO-CCSD(T) geometry rather well preserved the crystal structure (**Figure 12A**).



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.

However, in the absence of crystal packing and other interacting neighbour, Cl…Cl distances are calculated longer than that of the crystal.

We then carried out a LED analysis on CH₂Cl₂ dimers showing type I and II XB contacts, starting from the crystal geometries and optimizing these at DLPNO-CCSD(T) level. LED analysis for the type I contacts (**Figure 12B**, left panel) gave a total interfragment correlation energy of -1.26 kcal.mol⁻¹, that decomposes into a -0.61 kcal.mol⁻¹ part of a dispersive nature, while -0.49 and -0.16 kcal.mol⁻¹ comes from charge transfer mechanisms (from $1 \rightarrow 2$ and $2 \rightarrow 1$). HF interaction energy accounts for -3.49 kcal.mol⁻¹, from which the electrostatic term vastly predominate (-2.79 kcal.mol⁻¹) over the exchange energy between the two molecules (-0.70 kcal.mol⁻¹). Type II Cl··· Cl contacts (**Figure 12B**, right panel) imply a higher interaction energy from correlation effects (-3.00 kcal.mol⁻¹), from which dispersion accounts for -1.29 kcal.mol⁻¹, and charge transfers for -0.68 and -1.03 kcal.mol⁻¹. Electrostatic interaction from the HF energy rises to -4.40 kcal.mol⁻¹ and the exchange term is calculated at -1.16 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

To summarize, we herein investigated the supramolecular arrangement of halogenated hydrazones derived from well-known pharmaceuticals, *i.e.* isoniazid and hydralazine, in comparison to their hydroxyl analogues. X-ray structures of **IsI** and **HyI** show the presence of weak I····N and I··· π 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 **IsOH**.**H**₂**O** due to a water molecule which disrupts the intermolecular C=O···H-O contacts observed in **IsOH**. Further information on the strength of interactions were obtained by theoretical calculations. It appears that N···H non-covalent bonds are much stronger than N···I interaction 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 CH₂Cl₂ molecules through type I and type II Cl···Cl contacts. The CCDC survey of halogen bonded CH₂Cl₂ from (in)organic crystals confirmed the scarce occurrence of such linear- or ribbon-like architectures since less than ten structures were found. A Local Energy Decomposition study highlights the mixed dispersive nature of the interactions, for which dynamic polarization through charge transfer mechanism accounts for more than half of the electronic correlation effects.

A step further, the use of such weak XB donor compounds is under study 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 is performed on the **HyOH**/CH₂Cl₂ system in order to define its catch and release properties.

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Supporting information

S1. Crystal data and structure refinement details

Identification code	НуІ	HyBr	НуОН	Isl	lsBr			
Empirical formula	C15 H11 N4	C15 H11 Br N4	C16 H14 Cl2 N4 O	C13 H10 I N3 O	C13 H10 Br N3 O			
Formula weight	374.18	327.19	349.21	351.14	304.15			
Temperature	297(2) К							
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å			
Crystal system	Tetragonal	Monoclinic	Monoclinic	Triclinic	Monoclinic			
Space group	<i>1</i> 4 ₁	P21/c	P21/c	<i>P</i> -1	P21/c			
Unit cell	a = 15.0197(4) Å	a = 14.8761(7) Å	a = 9.51859(16) Å	a = 10.0223(9) Å	a = 18.763(3) Å			
dimensions								
	b = 15.0197(4) Å	b = 4.0269(2) Å	b = 15.70955(19) Å	b = 11.1984(3) Å	b = 6.5126(7) Å			
	c = 12.8791(6) Å	c = 23.1830(12) Å	c = 21.6869(3) Å	c = 12.4505(10)	c = 10.1237(15) Å			
				Å				
	α = 90°.	α = 90°.	α = 90°.	$\alpha = 109.836(6)^{\circ}.$	α = 90°.			
	β = 90°.	$\beta = 105.810(5)^{\circ}.$	β = 98.0651(15)°.	$\beta = 101.250(7)^{\circ}.$	β = 95.458(15)°.			
	γ = 90°.	γ = 90°.	γ = 90°.	γ = 97.494(6)°.	γ = 90°.			
Volume	2905.40(19) Å ³	1336.24(12) Å ³	3210.83(8) Å ³	1259.58(17) Å ³	1231.5(3) Å ³			
Z	8	4	8	4	4			
ρ (calculated)	1.711	1.626	1.445	1.852	1.640			
g/cm³								
Absorption	2.199	3.071	0.414	2.533	3.328			
coefficient mm ⁻¹								
F(000)	1456	656	1440	680	608			
Crystal size mm ³	0.50 x 0.02 x 0.02	0.50 x 0.12 x 0.07	0.5 x 0.5 x 0.32	0.50 x 0.20 x	0.18 x 0.18 x 0.03			
				0.10				
Theta range for	3.421 to 25.258°.	3.541 to 26.177°.	3.070 to 26.190°.	3.025 to	3.272 to 25.381°.			
data collection				25.904°.				
Reflections	13780	12533	22125	18494	8113			
collected								
Independent	2616 [R _(int) =	2600 [R _(int) =	6290 [R _(int) =	4823 [R _(int) =	2245 [R _(int) =			
reflections	0.0396]	0.0489]	0.0196]	0.0379]	0.0590]			
Completeness to 🛛	99.5 %	98.3 %	98.2 %	98.3 %	99.5 %			
= 25.242°								
Absorption	Semi-empirical from equivalents							
correction								
Max. and min.	1.00000 and	1.00000 and	1.00000 and	1.00000 and	1.00000 and			
transmission	0.90524	0.37783	0.87464	0.50646	0.53317			
Refinement	Full-matrix least-squares on F ²							

method					
Data / restraints /	2616/1/181	2600/0/181	6290/0/417	4823 / 0 / 325	2245 / 0 / 163
parameters					
Goodness-of-fit on	1.058	1.079	1.016	1.046	1.043
F ²					
Final R indices	R ₁ = 0.0353,	R ₁ = 0.0384,	R ₁ = 0.0526,	$R_1 = 0.0285$,	$R_1 = 0.0475$,
[I>2sigma(I)]	$wR_2 = 0.0799$	$wR_2 = 0.1073$	$wR_2 = 0.1329$	$wR_2 = 0.0783$	$wR_2 = 0.1160$
R indices (all data)	R ₁ = 0.0408,	R ₁ = 0.0433,	$R_1 = 0.0566,$	$R_1 = 0.0300,$	$R_1 = 0.0613$,
	$wR_2 = 0.0830$	$wR_2 = 0.1112$	$wR_2 = 0.1361$	$wR_2 = 0.0795$	$wR_2 = 0.1250$
Largest diff. peak	1.169 and -0.598	0.409 and -0.491	1.237 and -1.132	0.612 and -0.487	0.431 and -0.571
and hole e.Å ⁻³					

S2. Crystal structures







Figure S2 X-ray structure of IsBr (ellipsoids drawn at the 50% probability level).



Figure S3 X-ray structure of IsOH (ellipsoids drawn at the 50% probability level).



Figure S4 X-ray structure of HyI (ellipsoids drawn at the 50% probability level).



Figure S5 X-ray structure of HyBr (ellipsoids drawn at the 50% probability level).



Figure S6 X-ray structure of HyOH (ellipsoids drawn at the 50% probability level).

S3. Gaussian full reference

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