

Article



Cooperation/Competition between Halogen Bonds and Hydrogen Bonds in Complexes of 2,6-Diaminopyridines and X-CY₃ (X = Cl, Br; Y = H, F)

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Abstract: The DFT calculations have been performed on a series of two-element complexes formed by substituted 2,6-diaminopyridine (R–PDA) and pyridine (R–Pyr) with X–CY₃ molecules (where X = CI, Br and Y = H, F). The primary aim of this study was to examine the intermolecular hydrogen and halogen bonds in the condition of their mutual coexistence. Symmetry/antisymmetry of the interrelation between three individual interactions is addressed. It appears that halogen bonds play the main role in the stabilization of the structures of the selected systems. However, the occurrence of one or two hydrogen bonds was associated with the favourable geometry of the complexes. Moreover, the impact of different substituent groups attached in the *para* position to the aromatic ring of the 2,6-diaminopyridine and pyridine on the character of the intermolecular hydrogen and halogen bonds. In turn, the presence of electron-withdrawing substituents reduces the strength of halogen bonds. Additionally, when hydrogen and halogen bonds lose their leading role in the complex formation, the nonspecific electrostatic interactions between dipole moments take their place. Analysis was based on geometric, energetic, and topological parameters of the studied systems.

Keywords: halogen bond; hydrogen bond; competition; cooperation; DFT; QTAIM

1. Introduction

Intermolecular interactions have received much attention from researchers in the last few decades due to their wide application in fields like chemistry, biology, and physics. Among various types of noncovalent interactions, those where halogen atoms are involved are of a particular interest. High susceptibility to polarizing effects means that electron charge distribution around nuclei of a halogen atom is not homogeneous. Negative and positive electrostatic potential regions are simultaneously observed on the outer surface of covalently bonded halogen atoms [1–4]. As a result, the halogen atoms gain a dual nature (Figure 1). They adopt the role of a Lewis acid due to the region of positive electrostatic potential usually referred to as the σ hole, and interact with an electron-rich region of a neighbouring atom or molecule. They could also adopt the role of the Lewis base and interact with electrophiles through the partial negative charge on the surface of their valence sphere. Those two mechanisms describe the formation of halogen and hydrogen bonds by halogen atoms, respectively. In some cases, the halogen atom can be involved in creating various interactions simultaneously. Often, halogen and hydrogen bonds occur in parallel.

The halogen and hydrogen bonds exhibit numerous similarities, which has already been described in many theoretical studies [5–14]. For example, both of these interactions



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Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). are characterized by a similar strength and similar topological electron density properties. Among other interactions, they are distinguished by their highly directional nature. The exploration of self-assembly processes and molecular recognition in chemistry revealed the prominence of weak directional interactions in naturally occurring systems and synthetic assemblies. Hydrogen and halogen bonds have been exploited in the fields of supramolecular chemistry [15,16], crystal engineering [17–19], biochemistry [20–24], and drug design [25–27]. Intermolecular interactions have a large impact on the chemical and physical properties of crystal structures and macrobiological systems. Consequently, much of scientific research focuses on cooperativity [28,29] and competition [8,30–34] between hydrogen and halogen bonding. There are also numerous examples of experimental and theoretical studies in the literature that report on the coexistence of both of these interactions [8,35–38]. Moreover, they also explain synergistic effects causing stabilization of molecular structures [39,40]. Despite a growing number of studies on co-crystal structures, including X-ray [41–43], NMR, and IR spectroscopy [35], knowledge about the cooperative and competitive behaviour of halogen and hydrogen bonds is insufficient and requires expansion.



Figure 1. Dual nature of a halogen atom acting as a Lewis acid and Lewis base, depending on its chemical environment.

In this research, computational investigation of a range of halogen and hydrogen bonds was performed under the condition of their mutual coexistence. The study was limited to two-element complexes of derivatives of 2,6-diaminopyridine and pyridine (Figure 2) with small molecules like chloromethane, chlorotrifluoromethane, bromomethane, and bromotrifluoromethane. Moreover, the selected structures allowed us to examine the impact of different substituent groups present on the aromatic ring on the properties of the intermolecular hydrogen and halogen bonds.



Figure 2. The 2,6-diaminopyridine and pyridine derivatives included in the analysis.

The characteristics of the intermolecular interactions in our target complexes were developed based on theoretical density functional theory (DFT) calculations. The study focused on the analysis of the energetic, geometric, and topological parameters. We also address the aspect of symmetry/antisymmetry of the interrelation between three individual interactions. To gain additional insight into the bonding properties expressed by the electron density distribution, the Quantum Theory of Atom in Molecules (QTAIM) was utilized. Therefore, quantum chemical calculations were performed to study the structural, energy, and electron density parameters of the intermolecular halogen and hydrogen bonds within the [R–PDA][X–CY₃] and [R–Pyr][X–CY₃] model complexes. A substituent group R was attached in the *para* position of the aromatic ring of 2,6-diaminopyridine or pyridine. General structures of the investigated complexes are illustrated in Figure 3. In total, forty different systems were analysed.



Figure 3. Scheme representing analysed dimers stabilized by hydrogen bonds (blue dotted line) and halogen bonds (green dotted line).

2. Methods

All quantum mechanical calculations were performed under gas phase conditions using the density functional theory method (DFT) [44–47] with the aid of the Gaussian 09 (Revision D) software package [48]. The long-range corrected hybrid density functional wB97XD [49,50], which includes empirical dispersion corrections, was applied for optimization calculations (see the recent benchmark studies for the report on the importance of dispersion effects in halogen bond DFT computational modeling [51]). It has been proven that the counterpoise-corrected ω B97X-D calculations of the hydrogen bonds binding energies are close to reliable CCSD(T) results [52]. Functional was used in conjunction with the Pople type basis set 6-311++G(d,p) [53,54]. Stationary points were found and verified as local minima with no imaginary frequencies for the ground state for all but three complexes. In the case of complexes [Pyr][Cl-CF₃], [ON-Pyr][Cl-CF₃] and [O₂N-Pyr][Cl-CF₃], imaginary frequencies of -2.39 cm⁻¹, -8.5 cm⁻¹ and -3.31 cm⁻¹, respectively, were observed. The occurrence of imaginary frequencies is related to the accuracy of the numerical integration model in a given calculation method. Systems with very low imaginary frequencies (close-to-zero frequencies) are close to equilibrium state and are located in proximity to the minimum on the potential energy surface [55]. For this reason, analysing systems with imaginary frequencies of up to -20 cm^{-1} is sometimes allowed, considering them as representative and equal to the ground state. On the basis of the above assumption, the mentioned three systems with singular imaginary frequencies of close to zero were also taken into consideration to assure the consistent set of investigated models.

The interaction energy in the complexes (E_{int}) was calculated using the supermolecular approach, that is, as a difference between the total energy of the complex and a sum of the energies of the isolated monomers in their geometries found in the parent complexes.

Additionally, the deformation energy (E_{def}) was estimated as a difference between energy of fragments in their geometry from the complex and after geometry relaxation. The sum of interaction energy and deformation energy, as defined above, is the total interaction energy, E_{tot} .

In order to verify the quality of our potential results, we selected two representative models from crystal structures. After searching through Crystal Structure Database (CSD, release 2018 with all current updates) [56], we selected two halogen bonded complexes of pyridine with 4-chloro-2,3,5,6-tetrafluoropyridine (CSD refcode: FOFZUY) and 4-bromo-2,3,5,6-tetrafluoropyridine (CSD refcode: FOFZOS). In both, the R–X…N intermolecular halogen bond was stabilizing the system. The estimated values of interaction energies were -3.39 kcal/mol and -6.63 kcal/mol, respectively. This result was in good agreement with general knowledge on halogen bond strength [51,57,58] (see Supporting Information associated with this article for geometries and energies of these two models taken from experimental conditions (Table S1)).

Additionally, the Quantum Theory of Atoms in Molecules (QTAIM) [59,60] was applied to explore the electronic structure of the studied model complexes. Calculations were performed using the AIMAII software package [61]. Analysis of electron density topology concerns only the halogen and hydrogen bonds within complexes. The examination is based on selected topological parameters; electron density function (ρ_{BCP}), the Laplacian of electron density function ($\nabla^2 \rho_{BCP}$), the electron kinetic (G_{BCP}), potential (V_{BCP}) and total (H_{BCP}) energy densities, all calculated at the bond critical points (BCPs).

3. Results and Discussion

3.1. Interaction Energy

Table 1 shows the energy parameters of $[R-PDA][X-CY_3]$ and $[R-Pyr][X-CY_3]$ model complexes. Higher values of interaction energy (note that here and through the whole paper a larger interaction energy means a more negative value or in other words a larger absolute value) are observed for complexes where bromine atoms are involved in halogen and hydrogen bonds comparing to those where chlorine atoms are present. This tendency is maintained regardless of whether the halogen atoms are bonded to the trifluoromethyl or methyl group.

Table 1. Energy parameters of the analysed model complexes. The values of the interaction energy (E_{int}) , deformation energy (E_{def}) and the total interaction energy (E_{tot}) are expressed in [kcal/mol].

R	Eint	E _{def}	Etot	R	Eint	E _{def}	Etot
	R-PDA-ClCH	3 complexes	:		R-Pyr-ClCF	3 complexes	
NH_2	-2.974	0.203	-2.771	NH_2	-3.088	0.097	-2.991
OH	-2.788	0.042	-2.746	OH	-2.813	0.074	-2.739
Η	-2.690	0.050	-2.640	Η	-2.723	0.067	-2.655
NO	-2.390	0.032	-2.358	NO	-2.234	0.039	-2.195
NO_2	-2.334	0.021	-2.313	NO_2	-2.105	0.032	-2.074
	R-PDA-ClCH	I ₃ complexes	3		R-Pyr-ClCH	3 complexes	
NH_2	-1.393	0.014	-1.378	NH_2	-0.237	0.008	-0.229
OH	-1.540	0.019	-1.521	OH	-0.375	0.007	-0.368
Η	-1.545	0.019	-1.526	Η	-0.372	0.007	-0.365
NO	-1.896	0.022	-1.874	NO	-0.754	0.005	-0.748
NO_2	-2.106	0.026	-2.081	NO_2	-0.866	0.005	-0.860
	R-PDA-BrCl	₃ complexes	;		R-Pyr-BrCF	3 complexes	
NH_2	-5.057	0.338	-4.719	NH_2	-5.448	0.190	-5.258
OH	-4.750	0.154	-4.596	OH	-4.961	0.146	-4.815
Η	-4.660	0.156	-4.504	Η	-4.804	0.131	-4.674
NO	-4.101	0.110	-3.991	NO	-3.973	0.080	-3.894
NO ₂	-3.948	0.091	-3.856	NO ₂	-3.740	0.068	-3.672

R	Eint	E _{def}	E _{tot}	R	Eint	E _{def}	E _{tot}
	R-PDA-BrCH	H_3 complexes			R-Pyr-BrCH	3 complexes	
NH_2	-2.870	0.173	-2.697	NH_2	-1.627	0.024	-1.603
OH	-2.930	0.022	-2.908	OH	-1.640	0.024	-1.616
Η	-2.905	0.020	-2.885	Н	-1.607	0.026	-1.581
NO	-3.103	0.014	-3.089	NO	-1.690	0.014	-1.676
NO_2	-3.178	0.018	-3.160	NO_2	-1.714	0.016	-1.697

Table 1. Cont.

Analysis of complexes containing the chlorotrifluoromethane and bromotrifluoromethane molecules shows an interesting regularity. Depending on the substituent group attached to the aromatic ring of the 2,6-diaminopyridine and pyridine it can be seen that the interaction energy increases in the series $NO_2 < NO < H < OH < NH_2$ for all complexes. Higher values of energy in the case of complexes containing the hydroxyl and amine groups compared to complexes containing nitroso and nitro groups can be explained by the character of substituent group (substituent effect). The symmetry of distribution of electron charge in the aromatic ring could be disturbed as a consequence of inductive and/or resonance effects due to the presence of different types of substituents. Electron-donating groups, like hydroxyl and amino groups, increase the electron density in the aromatic ring in which the partial negative charge accumulates in *ortho* and *para* positions relative to the substituent (see Figure 4). However, electron-withdrawing groups, like nitroso and nitro groups, decrease the electron density in the aromatic ring and a negative partial charge appears only in the *meta* position relative to the substituent. The substituent effect caused by the presence of the nitrogen atom in the pyridine and 2,6-diaminopyridine aromatic ring is also important. It is an electron-withdrawing centre and makes the partial positive charge to appear in the ortho and para position, thus, the most relatively electron-rich carbon atoms are those in the *meta* position. The changes in the distribution of electron charge in the pyridine ring under the influence of the substituent effect are illustrated in Figure 4.



Figure 4. Distribution of partial charges in the pyridine ring caused by substituent effect (**a**) and the consequences in distribution of electrostatic potential (**b**) on the example (from left) of 4-aminopiridine, pyridine, and 4-nitrosopyridine molecules. All MEPs are generated in the same scale, being between -0.1 and 0.1 a.u. and mapped at 0.008 a.u. electron density isosurface.

Therefore, the hydroxyl or amino group attached to the pyridine ring promotes the accumulation of electron charge near the nitrogen atom of the pyridine ring. The effect is even more noticeable for the 2,6-diaminopyridine molecule. An additional two amino groups enhance the negative charge concentration on the nitrogen atom within the ring.

An increase of electron density supports the formation of stronger halogen bonds between the nitrogen atom of the pyridine ring and halogen atom, which could be revealed by relatively a higher value of interaction energy.

When analysing the interaction energy of $[R-PDA][X-CF_3]$ and $[R-Pyr][X-CF_3]$ complexes, it is crucial to remember the anisotropic properties of the halogen atoms. The ability to form halogen bonds increases with increasing halogen atom size. Heavier halogen atoms with higher polarizability, characterized by greater anisotropy of charge distribution around their nuclei, have the greatest ability to form halogen bonds [62,63]. Among the analysed complexes, the highest interaction energy is observed for the $[H_2N-PDA][Br-CF_3]$ and $[H_2N-Pyr][Br-CF_3]$. The values of total interaction energy are equal to -4.719 and -5.258 kcal/mol, respectively.

Moving further to complexes containing the chloromethane and bromomethane molecules, lower interaction energy values can be expected. The methyl group has a weaker electron-withdrawing capability compared to the trifluoromethyl group. The area of the positive electrostatic potential on the surface of the valence sphere of a halogen atom, the so-called σ *hole*, shrinks in the case of chloromethane and bromomethane molecules compared to their fluorinated counterparts. As a result, the ability of halogen atoms to form halogen bonds is reduced.

Analysis of complexes with the X-CH₃ fragment shows some regularity. This time the situation is reversed. The interaction energy of the [R–PDA][Cl–CH₃], [R–PDA][Br–CH₃], and [R–Pyr][Cl–CH₃] complexes increases in series NH₂ < H ~ OH < NO < NO₂. A slightly different trend occurs in the case of the [R–Pyr][Br–CH₃] complexes for which the total interaction energy increases in series H < NH₂ < OH < NO₂ < NO.

All $[R-PDA][X-CH_3]$ and $[R-Pyr][X-CH_3]$ systems substituted with electronwithdrawing groups show higher interaction energy values than systems substituted with electron-donating groups. These are unexpected results, considering the influence of substituent groups on the electron charge distribution in the complexes. The presence of amino or hydroxyl group in the pyridine ring promotes the accumulation of electron charge on the nitrogen atom within the ring. This creates favourable conditions to form halogen bonds and as a consequence, should lead to a stronger interaction between the fragments of the studied complexes. However, it seems that the strongest intermolecular interactions appear for complexes containing an aromatic ring substituted with nitroso and nitro groups. The differences of total interaction energy values of the strongest and the weakest systems are close to 0.70 and 0.63 kcal/mol for $[R-PDA][Cl-CH_3]$ and $[R-Pyr][Cl-CH_3]$ complexes, 0.46 kcal/mol for $[R-PDA][Br-CH_3]$ complexes and only 0.12 kcal/mol for $[R-Pyr][Br-CH_3]$. The lowest interaction energy value can be observed for the $[H_2N-Pyr][Cl-CH_3]$ complex and it is equal to -0.229 kcal/mol.

Depending on the substituent group attached to the aromatic ring of the 2,6-diaminopyridine or pyridine, the interaction energy follows the pattern $NO_2 < NO < H < OH < NH_2$ or $NH_2 < H ~ OH < NO < NO_2$ for complexes with the X-CF₃ and X-CH₃ fragment, respectively. It appears that differences in these trends reflect the attractive or repulsive interaction between dipole moments of the fragments of analysed complexes. The dipole moment is a significant feature of the molecules. For example, it determines the physical and chemical properties of solutions and affects the distribution of molecules in molecular crystals.

When directional non-covalent interactions, such as hydrogen or halogen bonds, lose their leading role in the complex formation, electrostatic interactions of dipole moments begin to play a key role. Among $[R-PDA][X-CF_3]$ and $[R-Pyr][X-CF_3]$ complexes, the higher interaction energy observed for systems substituted with OH and NH₂ groups reflects the attraction of dipolar monomers of complexes. However, systems with NO and NO₂ groups, having the lowest energy in the series, are those where monomers endowed with a dipole moment repel each other. In the case of $[R-PDA][X-CH_3]$ and $[R-Pyr][X-CH_3]$ complexes, the convergence between the values of interaction energy and the attracting or repulsive interaction of dipole moments of the fragments of complexes is also noticeable. This time, systems substituted with OH and NH₂ groups are those in which the dipole moments of the monomers repel each other. However, in systems substituted with NO and NO₂ groups, attractive forces appear between fragments of the complexes. These complexes have the highest energy in the series. The orientation of the dipole moment of the fragments of 2,6-diamino-4-hydroxypyridine and 2,6-diamino-4-nitropyridine dimers with chloromethane and bromotrifluoromethane molecules, as representatives of the analysed complexes, are presented in Figure S1 in the Supporting Information. The direction of dipole moments of the fragments of $[R-PDA][X-CY_3]$ and $[R-Pyr][X-CY_3]$ complexes are shown in Table 2. The values of dipole moments are gathered in Table S2 in the Supporting Information.

Table 2. Direction of a dipole moment vectors ($\delta - \rightarrow \delta +$) and interaction between dipole moments of fragments of analysed complexes.

Fragment I	Direction of Dipole Moment Vector		Fragment II	INTERACTION	Fragment I	Direction of Dipole Moment Vector		Fragment II
R-PDA-XCF ₃ complexes						R-Pyr-XCF	3 complexes	
H ₂ N-PDA	\leftarrow	\leftarrow	Cl/Br-CF ₃	Attraction	H ₂ N-Pyr	\leftarrow	\leftarrow	Cl/Br-CF ₃
HO-PDA	\leftarrow	\leftarrow	Cl/Br-CF ₃	Attraction	HO-Pyr	\leftarrow	\leftarrow	Cl/Br-CF ₃
H-PDA	\leftarrow	\leftarrow	Cl/Br-CF ₃	Attraction	H-Pyr	\leftarrow	\leftarrow	Cl/Br-CF ₃
ON-PDA	\rightarrow	\leftarrow	Cl/Br-CF ₃	Repulsion	ON-Pyr	\rightarrow	\leftarrow	Cl/Br-CF ₃
O ₂ N-PDA	\rightarrow	\leftarrow	Cl/Br-CF ₃	Repulsion	O ₂ N-Pyr	\rightarrow	\leftarrow	Cl/Br-CF ₃
R-PDA-XCH ₃ complexes						R-Pyr-XCH	3 complexes	
H ₂ N-PDA	\leftarrow	\rightarrow	Cl/Br-CH ₃	Repulsion	H ₂ N-Pyr	~	\rightarrow	Cl/Br-CH ₃
HO-PDA	\leftarrow	\rightarrow	Cl/Br-CH ₃	Repulsion	HO-Pyr	\leftarrow	\rightarrow	Cl/Br-CH ₃
H-PDA	\leftarrow	\rightarrow	Cl/Br-CH ₃	Repulsion	H-Pyr	\leftarrow	\rightarrow	Cl/Br-CH ₃
ON-PDA	\rightarrow	\rightarrow	Cl/Br-CH ₃	Attraction	ON-Pyr	\rightarrow	\rightarrow	Cl/Br-CH ₃
O ₂ N-PDA	\rightarrow	\rightarrow	Cl/Br-CH ₃	Attraction	O ₂ N-Pyr	\rightarrow	\rightarrow	Cl/Br-CH ₃

3.2. Geometries and QTAIM Analysis

Analysis of the electronic structure, based on the Quantum Theory of Atoms in Molecules (QTAIM), confirmed the presence of intermolecular noncovalent bonds in the analysed complexes. For all studied model systems, bond critical points (BCPs) of halogen bonds were observed. The contact length between interacting halogen atoms, chlorine or bromine, and nitrogen atoms within the ring is smaller than the sum of van der Waals radii of these atoms for almost all of the analysed systems. The exception is $[R-Pyr][Cl-CH_3]$ complexes, where the distance between chlorine and nitrogen atoms is greater than 3.3 Å, which corresponds to the sum of their van der Waals radii [64]. Moreover, in the case of the $[R-Pyr][Cl-CH_3]$ complexes, the halogen bonds are the longest. Most likely, this could be the reason why, among all of the studied complexes, these systems are characterized by the lowest values of interaction energy. The lengths of N…Cl and N…Br contacts are shown in Table 3.

In the case of $[R-PDA][X-CY_3]$ complexes, the presence of hydrogen bond CPs was also expected. The symmetrical 2,6-diaminopyridine molecule is built of the pyridine ring and two amino groups. This creates perfect conditions for the formation of noncovalent interactions (i.e., hydrogen and halogen bonds) and, as a result, the formation of molecular complexes. However, the hydrogen bonds between the halogen atom and hydrogen atoms belonging to the amino groups attached to the pyridine ring do not appear in all $[R-PDA][X-CY_3]$ complexes. The one halogen bond and two additional hydrogen bonds occur only in dimers in which a bromine atom was present. The situation is slightly different in the case of complexes containing a chlorine atom. Among complexes of 2,6diaminopyridine derivatives with chloromethane, only in two, namely [PDA][Cl-CH₃] and $[O_2N-PDA][Cl-CH_3]$, were two hydrogen bonds observed. In other complexes, namely [ON-PDA][Cl-CH₃], [HO-PDA][Cl-CH₃], and [H₂N-PDA][Cl-CH₃], only one hydrogen bridge appears. In the case of complexes of 2,6-diaminopyridine derivatives with chlorotrifluoromethane, one hydrogen bond appears only in the [ON-PDA][Cl-CF₃]. No intermolecular hydrogen bridges were observed in other $[R-PDA][Cl-CF_3]$ complexes. The molecular graphs of the 2,6-diamino-4-hydroxypyridine dimers with chloromethane, chlorotrifluoromethane, bromomethane, and bromotrifluoromethane molecules, as representatives of the $[R-PDA][X-CY_3]$ complexes, are presented in Figure 5.

Table 3.	Halogen	and hyd	rogen bon	d lengths ir	n the analys	ed model	complexes.

	NH ₂	ОН	Н	NO	NO ₂	NH ₂	ОН	Н	NO	NO ₂
R-PDA-ClCF ₃ complexes							R-Py	r-ClCF ₃ com	plexes	
$N \cdots Cl$	3.009	3.028	3.057	3.078	3.073	2.951	2.974	2.985	3.029	3.043
$H \cdots Cl$	3.098 *	3.083 *	2.967 *	2.971 *	3.046 *	-	-	-	-	-
$H \cdots Cl$	3.101 *	3.086 *	2.964 *	2.987 *	3.046 *	-	-	-	-	-
<i>R-PDA-ClCH</i> ₃ complexes							R-Py	r-ClCH ₃ com	plexes	
$N \cdots Cl$	3.219	3.214	3.218	3.22	3.211	3.445 *	3.425 *	3.402 *	3.518 *	3.461 *
$H \cdots Cl$	3.176 *	3.057 *	3.065 *	2.978 *	3.066 *	3.038 *	3.031 *	3.034 *	2.962 *	3.018 *
$H \cdots Cl$	2.951	3.081 *	3.065 *	3.134 *	3.066 *	-	-	-	-	-
		R-PD	A-BrCF ₃ con	ıplexes		<i>R-Pyr-BrCF</i> ₃ complexes				
$N \cdots Br$	2.958	2.979	2.989	3.026	3.03	2.881	2.905	2.915	2.962	2.974
$H \cdots Br$	2.931	2.94	2.936	2.949	2.992	-	-	-	-	-
$H \cdots Br$	2.929	2.932	2.937	2.969	2.99	-	-	-	-	-
<i>R-PDA-BrCH</i> ₃ complexes							R-Py	r-BrCH ₃ com	plexes	
$N \cdots Br$	3.162	3.166	3.171	3.18	3.179	3.134	3.148	3.148	3.176	3.178
$H \cdots Br$	3.047	3.042	3.038	3.025	3.051	-	-	-	-	-
$H \cdots Br$	3.047	3.05	3.038	3.052	3.052	-	-	-	-	-

* the length of interatomic contacts larger than the sum of van der Waals radii of interacting atoms.



Figure 5. Molecular graphs of the [HO–PDA][X–CY₃] complexes. Spheres coloured as follows: C—grey, H—white, N—blue, O—red, F—light blue, Cl—green, Br—brown, BCPs—small red spheres, RCPs—yellow small spheres.

In general, the proton-acceptor properties of halogen atoms decrease with increasing atom size [65]. Chlorine atoms usually form stronger hydrogen bonds than bromine atoms, therefore the chloromethane molecule should be a relatively more effective Lewis base, but a less effective Lewis acid than the bromomethane molecule. The lack of hydrogen bridges in complexes with chloromethane and their presence in complexes with bromomethane is quite surprising. For this reason, the observations described above cannot be explained by comparing only the ability of halogen atoms to form different kinds of interactions.

The important factor determining the presence of hydrogen bonds in the $[R-PDA][X-CY_3]$ complexes seems to be their geometry. The contact length between hydrogen and chlorine atoms in all complexes is greater than the sum of van der Waals radii of these atoms, which is equal to 2.95 Å [64]. The distance between hydrogen and bromine atoms, for all studied complexes, is smaller or very close to 3.05 Å, which corresponds to the sum of their van der Waals radii. The lengths of H…Cl and H…Br contacts are shown in Table 3.

It is also important to remember the anisotropic distribution of electron charge around the nucleus of a halogen atom [4]. The geometry of studied [R–PDA][X–CY₃] complexes shows that the negative charge accumulates on chlorine or bromine atom valence spheres in a perpendicular direction to the halogen bond formed between the nitrogen atom of the pyridine ring and those halogen atoms. This promotes formation of hydrogen bonds between amino groups of 2,6-diaminopyridine and both halogen atoms. However, the longer radius of the bromine atom compared to the chlorine atom (1.85 Å and 1.75 Å respectively) is additionally lengthened due to anisotropy and allows for a more effective overlap of the valence spheres of hydrogen and bromine atoms, and consequently the formation of a bond.

In the case of pyridine complexes, $[R-Pyr][X-CY_3]$, it can be expected that the halogen bond would be the only intermolecular interaction observed in model systems. However, next to the halogen bond, one additional hydrogen bond appears in all complexes of pyridine derivatives with chloromethane. The reason for the formation of a hydrogen bridge between the chlorine atom and the hydrogen atom of an aromatic ring can be a favourable distribution of electron density in given systems. The relatively stronger proton-acceptor properties of the chlorine atom, as compared to the bromine atom, are also significant [62]. However, the presence of three fluorine atoms in the chlorotrifluoromethane molecule changes the electron charge distribution of the chlorine atom and reduces its proton-acceptor ability [62]. As a result, there are no N-H···Cl type hydrogen bridges in the [R-Pyr][Cl-CF₃] complexes. The molecular graphs of 4-hydroxypyridine dimers with chloromethane, chlorotrifluoromethane, bromomethane, and bromotrifluoromethane molecules, as representatives of the [R-Pyr][X-CY₃] complexes, are presented in Figure 6.

Selected topological parameters of the critical points of halogen and hydrogen bonds occurring in the $[R-PDA][X-CY_3]$ and $[R-Pyr][X-CY_3]$ complexes are gathered in Tables S3–S7 in the Supporting Information. Low values of electron density, positive values of the Laplacian of electron density, and positive values of the total energy of electron density indicate the closed-shell nature of the analysed interactions [59,66,67]. In general, the electron density at the critical points of halogen and hydrogen bonds varies by an order of magnitude. Its values are also on average twice as high at the critical point of a halogen bond as compared to the values at the critical points of hydrogen bonds occurring within a given dimer. The exceptions are complexes of pyridine derivatives and chloromethane molecules, in which the values of electron density at the critical points are similar for both non-covalent interactions.

In all cases, the observed H···Br and H···Cl contacts do not exactly fulfill the hydrogen bond criteria previously proposed by Koch and Popelier [67]. The presence of bond path and the bond critical point between hydrogen and halogen atoms fulfills the necessary and sufficient topological conditions that confirm the existence of a chemical bond between the two atoms. The values of electron density in the range from 0.004 to 0.006 a.u. are in agreement with the range of 0.002 to 0.034 a.u., a typical range for hydrogen bonds. The Laplacian of the electron density values however range from 0.013 to 0.021 a.u. and those are outside of the typical range of 0.024 to 0.139 a.u. for hydrogen bridges. Therefore, it can be assumed that the hydrogen bonds found in the analysed complexes do not play a main role in the complexation.



Figure 6. Molecular graphs of the [HO–Pyr][X–CY₃] complexes. Spheres coloured as follows: C—grey, H—white, N—blue, O—red, F—light blue, Cl—green, Br—brown, BCPs—small red spheres, RCPs—yellow small spheres.

Comparing topological parameters of halogen and hydrogen bonds in complexes containing bromine atoms and their counterparts with chlorine atoms, some systematic differences can be observed. The values of the electron density, its Laplacian, potential energy density, kinetic energy density, and total energy density, considering its absolute values, are higher for BCPs of intermolecular bonds in which bromine atoms are involved. Furthermore, higher values of topological parameters of electron density reflect higher values of the total energy of interaction of the [R-PDA][Br-CY₃] and [R-Pyr][Br-CY₃] complexes containing stronger N···Br and H···Br bonds in relation to N···Cl and H···Cl bonds present in the [R-PDA][Cl-CY₃] and [R-Pyr][Cl-CY₃]. Usually, increasing values of the electron density are associated with an increase of interaction energy, and electron density is often used as a measure of the strength of a given interaction [68]. The higher the electron density value, the stronger the interactions in the intermolecular complexes are. In general, the lowest values of electron density at critical points of halogen bonds are observed for complexes of pyridine and 2,6-diaminopyridine derivatives with chloromethane molecule. These dimers are also characterized by the lowest total energy of interaction among all of the analysed systems.

The electron density at the bond critical point is a parameter closely related to the type of atoms forming the interaction. Thus, it can be used to approximately determine in which of the analysed complexes stronger intermolecular bonds occur. Subtracting the values of electron density of halogen bonds measured for $[R-PDA][X-CY_3]$ complexes and the values measured for corresponding $[R-Pyr][X-CY_3]$ complexes, we can obtain information on which bonds are stronger. The results are gathered in Table 4. Differences in the electron density values indicate that the halogen bonds present in the $[R-PDA][X-CY_3]$ complexes are relatively weaker than those in the $[R-Pyr][X-CY_3]$ systems. The exceptions are complexes with chloromethane where stronger halogen bonds are formed in the $[R-PDA][Cl-CH_3]$ systems.

Table 4. Differences in the value of electron density measured at critical points of halogen bonds of the $[R-PDA][X-CY_3]$ and $[R-Pyr][X-CY_3]$ complexes. The percentage increase or decrease (in brackets) electron density was calculated relative to the values of electron density at halogen bond critical point of the $[R-PDA][X-CY_3]$ systems.

R	$\Delta \varrho_{\mathbf{N}\cdots\mathbf{X}}$									
	ClCF ₃		ClCH ₃		BrCF ₃		BrCH ₃			
NH ₂	-0.0016	(-12.5%)	0.0037	(+42.8%)	-0.0022	(-13.2%)	-0.0002	(-1.7%)		
OH	-0.0013	(-10.9%)	0.0036	(+40.7%)	-0.0019	(-11.8%)	0.00004	(+0.4%)		
Η	-0.0013	(-10.8%)	0.0032	(+37.4%)	-0.0019	(-11.7%)	-0.0001	(-0.7%)		
NO	-0.0006	(-5.4%)	0.0044	(+50.9%)	-0.0013	(-9.2%)	0.0004	(+3.9%)		
NO ₂	-0.0004	(-3.6%)	0.0040	(+45.5%)	-0.0012	(-8.3%)	-0.0071	(-64.9%)		

The analysis of electron density fluctuations in a more homogeneous group of complexes simplifies the determination of the nature of changes of intermolecular interactions caused by the appearance of electron-donating or electron-withdrawing substituents. The variations in the electron charge distribution in the $[R-PDA][X-CY_3]$ and $[R-Pyr][X-CY_3]$ complexes were examined in relation to the unsubstituted 2,6diaminopyridine and pyridine systems. As expected, the higher values of electron density were observed at critical points of halogen bonds for $[R-PDA][X-CY_3]$ complexes where hydroxyl and amino groups were attached to the 2,6-diaminopyridine molecule (Table S8). While thinning of the electron charge can be noticed in the case of complexes containing nitroso and nitro groups. There were no noticeable changes in the electron density value of the hydrogen bridges correlated with the presence of various substituents in $[R-PDA][X-CY_3]$ complexes.

Moving along to the $[R-Pyr][X-CY_3]$ complexes, the expected increase or decrease of the electron density at critical points of the halogen bonds is visible only for dimers of pyridine derivatives with chlorotrifluoromethane and bromotrifluoromethane molecules (Table S9). The situation is slightly different in the case of $[H_2N-Pyr][Cl-CH_3]$, $[HO-Pyr][Cl-CH_3]$, and $[HO-Pyr][Br-CH_3]$ complexes where presence of electron-donating groups at the aromatic ring do not cause expected changes in the value of the electron density.

Interestingly, only in the case of derivatives of 2,6-diaminopyridine and pyridine complexes with chlorotrifluoromethane and bromotrifluoromethane, the energy effects reflect the electron density fluctuations at critical points of halogen bonds (Table S10). Moreover, there are linear correlations between the differences of the electron density value $\Delta \varrho_{N...X}$ and the total interaction energy changes ΔE_{tot} (Figure 7). This undeniably proves the main role of halogen bonds in the stabilization of studied [R–PDA][X–CF₃] and [R–Pyr][X–CF₃] dimers. No similar correlations were observed in the case of complexes of derivatives of 2,6-diaminopyridine and pyridine with chloromethane or bromomethane.



Figure 7. Graph of the dependence of the total interaction energy changes ΔE_{tot} as a function of the electron density changes ($\Delta \varrho_{N...X}$) at critical points of halogen bonds of [R–PDA][X–CF₃] and [R–Pyr][X–CF₃] complexes where X = Cl, Br.

4. Conclusions

Concluding, our results indicate that the halogen bonds play the main role in the stabilization of the structures of the $[R-PDA][X-CY_3]$ complexes. In contrast, hydrogen bonds do not play a primary role in the formation of 2,6-diaminopyridine dimers. They appear mostly due to the favourable geometry of the complexes, so can be considered secondary interactions. Moreover, we analysed the influence of the presence of electrondonating/withdrawing substituents, on the properties of intermolecular interactions. The presence of electron-donating groups increased the electron density at critical points of halogen bonds, which is manifested by their strengthening and the higher energy of interaction of $[HO-PDA][X-CY_3]$ and $[H_2N-PDA][X-CY_3]$ complexes. In turn, substitution with electron-withdrawing groups lowers the amount of electron charge shared between interacting halogen atoms and the ring nitrogen atom, and as result reduces the strength of halogen bonds and consequently the energy of interaction of $[ON-PDA][X-CY_3]$ and $[O_2N-PDA][X-CY_3]$ complexes. The influence of the substituent effect on the strength of halogen bonds is especially visible when a chlorine or bromine atom forming the interaction is attached to a trifluoromethyl group that increases the electron-accepting properties of halogen centres. Furthermore, interactions between dipole moments of complexes fragments (monomers) are undeniably significant in the complexation process. Interaction between polarised fragments of the complexes takes the leading role when specific directional interactions (halogen and hydrogen bonds in our case) became less effective. Summarising, the mutual interrelation between the chemical structure of the complexes, the energy parameters, and the electron density distribution has been discussed and explained in detail.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/ 10.3390/sym13050766/s1, Table S1: Cartesian coordinates of calculated geometries of the halogen bonded complexes of pyridine with 4-chloro-2,3,5,6-tetrafluoropyridine (CSD refcode: FOFZUY) and 4-bromo-2,3,5,6-tetrafluoropyridine (CSD refcode: FOFZOS), Figure S1: The orientation of dipole moment vectors of the fragments of selected complexes, Table S2: Dipole moments of the fragments of $[R-PDA][X-CY_3]$ and $[R-Pyr][X-CY_3]$ complexes ($\omega B97X-D/6-311++G(d,p)$) level of theory), Table S3: Bond lengths and selected topological parameters of distribution of electron density [a.u.] in bonds critical points for [PDA][X–CY₃] and [Pyr][X–CY₃] complexes, Table S4: Bond lengths and selected topological parameters of distribution of electron density [a.u.] in bonds critical points for [ON–PDA][X–CY₃] and [ON–Pyr][X–CY₃] complexes, Table S5: Bond lengths and selected topological parameters of distribution of electron density [a.u.] in bonds critical points for $[O_2N-PDA][X-CY_3]$ and $[O_2N-Pyr][X-CY_3]$ complexes, Table S6: Bond lengths and selected topological parameters of distribution of electron density [a.u.] in bonds critical points for [HO–PDA][X–CY₃] and [HO–Pyr][X–CY₃] complexes, Table S7: Bond lengths and selected topological parameters of distribution of electron density [a.u.] in bonds critical points for [H₂N–PDA][X–CY₃] and [H₂N–Pyr][X–CY₃] complexes, Table S8: Fluctuations of the electron density values at the critical points of halogen and hydrogen bonds in complexes of the [R-PDA][X-CY₃] in relation to [PDA][X-CY₃], Table S9: Fluctuations of the electron density values at the critical points of halogen and hydrogen bonds in complexes of the $[R-Pyr][X-CY_3]$ in relation to [Pyr][X–CY₃], Table S10: Fluctuations of the total interaction energy values of the [R–PDA][X–CY₃] and [R-Pyr][X-CY₃] complexes in relation to [PDA][X-CY₃] and [Pyr][X-CY₃], Table S11: Cartesian coordinates of calculated geometries of the studied complexes.

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