Research Article

Does the Intramolecular Hydrogen Bond Affect the Spectroscopic Properties of Bicyclic Diazole Heterocycles?

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The formation of an intramolecular hydrogen bond in pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one bicyclic diazoles was analyzed, and the influence of *N*-substitution on HB formation is discussed in this study. B3LYP/aug-cc-pVDZ calculations were performed for the diazole, and the quantum theory of atoms in molecules (QTAIM) approach as well as the natural bond orbital (NBO) method was applied to analyze the strength of this interaction. It was found that the intramolecular hydrogen bond that closes an extra ring between the C=O proton acceptor group and the CH proton donor, that is, C=O $\cdots$ H–C, influences the spectroscopic properties of pyrrolopyrazine bicyclic diazoles, particularly the carbonyl frequencies. The influence of *N*-substitution on the aromaticity of heterocyclic rings is also discussed in this report.

1. Introduction

Pyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones are an important class of natural organic compounds synthesized by many grass-associated endophytic fungi [1, 2]. Symbiotic plants activate a defense reaction which allows the host plant to be protected against infection [3]. The ecological significance of pyrrolopyrazinones is related to their feeding deterrent activity. These alkaloids produced by endophytes provide protection of the host plant from herbivores as found in a large number of grass/endophyte associations [4]. A recent study has shown that peramine is transported from the endophyte into plant intercellular space where it is metabolized or removed via guttation fluid [2]. In the field of applied ecology, it is important to recognize natural chemical agents that control herbivorous insects [5]. Due to these properties, pyrrolopyrazinones can be used as structural models for studying the release mechanism, metabolism, structure of chemical compounds removed from plant tissues, and the mechanism of anti-insect activity [6].

An attempt has been made previously to identify spectroscopic properties of some pyrrolopyrazinones [7, 8]. The vibrational and electronic spectra of peramine and some of its derivatives were recorded, and assignments were made

on the basis of B3LYP/aug-cc-pVDZ level calculations; FT-IR and ¹H NMR spectra indicated the conjugation of the pyrrolo and pyrazinone rings. These previous results also show that the ring modes are insensitive to the type of substituent introduced into the side chain of peramine.

We consider here a series of pyrrolopyrazinones (Scheme 1, Table 1) that is an extension of our previous work on *N*-substituted 2-acylpyrroles [9]. For some of the heterocyclic systems analyzed recently, short C=O $\cdots$ H–C intramolecular contacts are observed [10]. This observation inspired us to undertake a theoretical study on C=O $\cdots$ H–C intramolecular hydrogen bonds in pyrrolopyrazinone species.

In the first part of this study, we carried out a detailed analysis of the geometrical parameters of the pyrrolopyrazinone derivatives (Scheme 1). These species are divided into two groups according to QTAIM results; one group includes systems with short C=O $\cdots$ H–C contacts in which O $\cdots$ H bond paths with corresponding BCPs exist (all pyrrolopyrazinones where R₂=CHCl₂ are included here); the other group consists of systems in which there is no attractive C=O $\cdots$ H–C interaction and the H $\cdots$ O bond paths are not detected; all systems where R₂=CH₂Cl are included in this group. There are also systems in which R₂=CH₃ are dispersed into both these groups.

SCHEME 1: Schematic representation of the structure and atom numbering of pyrrolopyrazinone derivatives (2–22) where $R_2 = \text{CH}_3$, CH_2Cl , or CHCl_2 ; $R_3 = \text{H}$, Cl , CH_3 , $(\text{CH}_2)_n\text{CH}_3$, $(\text{CH}_2)_n\text{CH}_2\text{Cl}$, $(\text{CH}_2)_n\text{NH}_2$, NH_2 , and $(\text{CH}_2)_3\text{NHC}(\text{NH})\text{NH}_2$.

In the second part of this study, analysis of the aromaticity of the pyrrolopyrazinone derivatives was carried out to find the possible interplay between the existence of the hydrogen bonds and aromaticity of the heterocyclic rings. Aromaticity is a topic of scientific interest in the various areas of pyrrole derivative investigation. Numerous aromaticity concepts have been proposed to describe and evaluate this phenomenon. Criteria for establishing aromaticity of various species analyzed have been divided [10, 11] into energetic, [12] geometrical, [13] magnetic [14], and reactivity categories; the latter ones are mainly based on the chemical behavior of a system. There is also the harmonic oscillator model of aromaticity (HOMA) [15–18] that is classified as a geometrical index.

In general, the purpose of this study is to extend knowledge of physicochemical properties of pyrrolopyrazinones including spectroscopic properties of both heterocyclic rings. Theoretical analysis is performed using B3LYP/aug-cc-pVDZ calculations, the quantum theory of atoms in molecules (QTAIM) approach, and the natural bond orbital (NBO) method. The intramolecular $\text{C}=\text{O}\cdots\text{H}-\text{C}$ hydrogen bonds in the pyrrolopyrazinone molecules (1–22) are analyzed in terms of the NBO method, and orbital-orbital overlapping energy, $\Delta E_{n\rightarrow\sigma^*}$, is discussed [19]. To the best of our knowledge, NBO, QTAIM, or HOMA approaches have not been applied so far to analyze the intramolecular $\text{C}=\text{O}\cdots\text{H}-\text{C}$ interactions in pyrrolopyrazinones (2–22).

2. Experimental FT-IR Spectra

The infrared spectrum of peramine 20 was investigated at room temperature in KBr pellets containing dispersed compounds. The FT-IR absorption spectrum was recorded in the range between 400 and 4000 cm^{-1} with a Nicolet Magna-IR 550 Series II instrument.

3. Computational Details

The calculations were performed with the Gaussian 09 sets of codes [20]. The geometries of the investigated species (1–22) were fully optimized using the aug-cc-pVDZ Dunning's correlation consistent basis set [21, 22] and B3LYP functional [23, 24]. Calculations of normal modes were performed with

the use of the same level as that for the optimizations. The results of optimization correspond to energy minima since no imaginary frequencies were detected. The initial geometry of the pyrrolopyrazinone system was taken from X-ray data, and it was further applied in the geometry optimization [9]. The computed frequencies were multiplied by the uniform factor of 0.97 to obtain a good estimate of the experimental results and to eliminate known systematic errors related to anharmonicity [25].

Gaussian output wfn files were used as inputs for the AIM2000 [26] program to calculate topological properties of the systems investigated. The bond and ring critical points were located (BCPs and RCPs), and their properties, such as electron densities at critical points (ρ_{BCP} and ρ_{RCP}) and their Laplacians ($\nabla^2\rho_{\text{BCP}}$ and $\nabla^2\rho_{\text{RCP}}$), were calculated. The additional characteristics of BCPs were analyzed, such as total electron energy density at BCP (H_{BCP}) and its components, potential electron energy density (V_{BCP}), and kinetic electron energy density (G_{BCP}).

Particularly, for the $\text{C}-\text{H}\cdots\text{O}$ hydrogen bond, these are the characteristics of the $\text{H}\cdots\text{O}$ bond critical point and the properties of the ring critical point that exist within the ring closed by the $\text{C}=\text{O}\cdots\text{H}-\text{C}$ intramolecular hydrogen bond. Relationships between topological parameters at the critical point are given by [27]

$$0.25\nabla^2\rho_{\text{BCP}} = 2G_{\text{BCP}} + V_{\text{BCP}}; H_{\text{BCP}} = G_{\text{BCP}} + V_{\text{BCP}}. \quad (1)$$

Kinetic electron energy density G_{BCP} has a positive value, whereas potential electron energy density V_{BCP} has a negative value. If the absolute value of V_{BCP} is two times greater than the G_{BCP} value, the Laplacian $\nabla^2\rho_{\text{BCP}}$ is negative. The classification of hydrogen bonds based on these parameters has been proposed by Rozas and coworkers [28]. $\nabla^2\rho_{\text{BCP}}$ and H_{BCP} values are positive for weak and medium-strength HB interactions; $\nabla^2\rho_{\text{BCP}}$ is positive and H_{BCP} is negative for strong hydrogen bonds; both these values are negative for very strong HBs. The electron density at $\text{H}\cdots\text{B}$ BCP, ρ_{BCP} , is often considered as a measure of $\text{A}-\text{H}\cdots\text{B}$ hydrogen bond strength since correlations between ρ_{BCP} and interaction energy or other HB strength descriptors have been found, especially for homogenous samples of interactions [29]. Similarly, in this study, ρ_{BCP} that corresponds to the $\text{H}\cdots\text{O}$ BCP of the $\text{C}-\text{H}\cdots\text{O}$ intramolecular hydrogen bond may be considered a descriptor of HB strength.

The NBO method [19] was applied to calculate $n_B \rightarrow \sigma_{\text{AH}}^*$ interaction energies. n_B designates the lone pair of the B proton acceptor, and σ_{AH}^* is an antibonding orbital of the A-H bond. Interaction energy was calculated from second-order perturbation theory energy according to

$$E_{\text{AB}}^{(2)} = -n_Y \frac{F_{\sigma_{\text{AH}}^*}^2}{\varepsilon_{\sigma_{\text{AH}}^*} - \varepsilon_{n_B}}, \quad (2)$$

where $F_{\sigma_{\text{AH}}^*}^2$ is the Fock matrix element, $\varepsilon_{\sigma_{\text{AH}}^*} - \varepsilon_{n_B}$ is the orbital energy difference, and n_B is the population of the donor B orbital. The $E_{\text{AB}}^{(2)}$ energy term can be considered a part of charge transfer energy or stabilization energy associated with delocalization.

TABLE 1: Selected bond lengths of pyrrolo[1,2-a]pyrazin-1(2H)-ones (1–22), optimized at the B3LYP/aug-cc-pVDZ level of theory, HOMA indices, and calculated C=C and C=O stretching frequencies.

Compound			Bond length [Å]					Pyrrole ring			Calculated B3LYP/aug-cc-pVDZ	Calculated B3LYP/aug-cc-pVDZ
	3,4-Dihydropyrrolopyrazinones	Pyrrolopyrazinones	N5C9	C9C8	C8C7	C7C6	C6N5	HOMA	EN	GEO		$\nu_{C=O}$ (cm ⁻¹)
1			1.376	1.383	1.428	1.382	1.376	0.833	0.071	0.096		1568
1a	$R_2 = CH_3, R_3 = H$		1.383	1.390	1.418	1.390	1.383	0.876	0.082	0.043		1578
1b	$R_2 = CH_2Cl, R_3 = H$		1.384	1.392	1.416	1.391	1.384	0.882	0.082	0.036		1575
1c	$R_2 = CHCl_2, R_3 = H$		1.385	1.393	1.414	1.392	1.384	0.885	0.082	0.032		1573
2		$R_2 = CH_3, R_3 = H$	1.396	1.390	1.416	1.390	1.396	0.848	0.097	0.055		1564
3		$R_2 = CH_2Cl, R_3 = H$	1.396	1.391	1.415	1.390	1.396	0.852	0.095	0.053		1567
4		$R_2 = CHCl_2, R_3 = H$	1.389	1.393	1.413	1.393	1.388	0.875	0.091	0.034		1565
5		$R_2 = CH_3, R_3 = Cl$	1.394	1.391	1.415	1.391	1.393	0.859	0.095	0.046		1562
6		$R_2 = CH_2Cl, R_3 = Cl$	1.393	1.392	1.414	1.391	1.393	0.862	0.093	0.045		1565
7		$R_2 = CHCl_2, R_3 = Cl$	1.391	1.392	1.413	1.392	1.391	0.869	0.091	0.039		1564
8		$R_2 = CH_3, R_3 = NH_2$	1.391	1.395	1.412	1.395	1.390	0.873	0.098	0.029		1555
9		$R_2 = CH_2Cl, R_3 = NH_2$	1.390	1.394	1.412	1.394	1.390	0.875	0.095	0.030		1560
10		$R_2 = CHCl_2, R_3 = NH_2$	1.389	1.397	1.409	1.397	1.388	0.883	0.096	0.021		1555
11		$R_2 = CH_3, R_3 = CH_3$	1.392	1.392	1.415	1.391	1.391	0.863	0.095	0.042		1564
12		$R_2 = CH_2Cl, R_3 = CH_3$	1.391	1.392	1.392	1.392	1.391	0.905	0.053	0.042		1567
13		$R_2 = CHCl_2, R_3 = CH_3$	1.389	1.393	1.413	1.393	1.388	0.875	0.091	0.034		1565
14		$R_2 = CH_3, R_3 = CH_2CH_2CH_2Cl$	1.390	1.392	1.415	1.391	1.390	0.865	0.093	0.042		1565
15		$R_2 = CH_2Cl, R_3 = CH_2CH_2CH_2Cl$	1.390	1.392	1.414	1.391	1.389	0.868	0.091	0.041		1568
16		$R_2 = CHCl_2, R_3 = CH_2CH_2CH_2Cl$	1.387	1.393	1.413	1.392	1.387	0.876	0.089	0.035		1567
17		$R_2 = CH_3, R_3 = CH_2CH_2CH_2NH_2$	1.390	1.392	1.415	1.392	1.390	0.864	0.095	0.040		1561
18		$R_2 = CH_2Cl, R_3 = CH_2CH_2CH_2NH_2$	1.390	1.392	1.414	1.392	1.389	0.869	0.092	0.039		1567
19		$R_2 = CHCl_2, R_3 = CH_2CH_2CH_2NH_2$	1.388	1.393	1.413	1.393	1.387	0.877	0.090	0.033		1565
20		$R_2 = CH_3, R_3 = CH_2CH_2CH_2NHC(NH)NH_2$	1.390	1.392	1.415	1.391	1.390	0.865	0.094	0.042		1564
21		$R_2 = CH_2Cl, R_3 = CH_2CH_2CH_2NHC(NH)NH_2$	1.390	1.392	1.414	1.392	1.390	0.869	0.092	0.040		1568
22		$R_2 = CHCl_2, R_3 = CH_2CH_2CH_2NHC(NH)NH_2$	1.387	1.393	1.413	1.393	1.387	0.877	0.089	0.034		1566

TABLE 1: Continued.

Compound			Bond length [Å]	Pyrrole ring					Calculated B3LYP/aug- cc-pVDZ	Calculated B3LYP/aug- cc-pVDZ			
				C1N2	N2C3	C3- C4	C4N5	N5C9			C9C1	HOMA	EN
3,4-Dihydropyrrolopyrazinones			Pyrrolopyrazinones										
Pyrazinone ring			Pyrzine ν _{C=C} stretching vibrations(cm ⁻¹)										
1a	R ₂ = CH ₃ , R ₃ = H		1.390	1.462	1.525	1.453	1.383	1.470				1705	
1b	R ₂ = CH ₂ Cl, R ₃ = H		1.404	1.467	1.525	1.455	1.384	1.463				1721	
1c	R ₂ = CHCl ₂ , R ₃ = H		1.414	1.468	1.524	1.456	1.385	1.459				1726	
1d			1.338	1.338	1.400	1.338	1.338	1.400	0.985	0.010	0.005	—	1617
1e			1.400	1.367	1.364	1.374	1.303	1.469	0.591	0.087	0.322	1743	1645
2	R ₂ = CH ₃ , R ₃ = H		1.406	1.388	1.349	1.391	1.396	1.456	0.466	0.199	0.335	1721	1695
3	R ₂ = CH ₂ Cl, R ₃ = H		1.421	1.396	1.346	1.392	1.396	1.452	0.414	0.209	0.376	1738	1705
4	R ₂ = CHCl ₂ , R ₃ = H		1.440	1.419	1.351	1.391	1.389	1.442	0.408	0.251	0.341	1741	1703
5	R ₂ = CH ₃ , R ₃ = Cl		1.420	1.390	1.351	1.390	1.394	1.450	0.470	0.210	0.320	1726	1686
6	R ₂ = CH ₂ Cl, R ₃ = Cl		1.435	1.400	1.348	1.391	1.393	1.447	0.416	0.224	0.360	1745	1694
7	R ₂ = CHCl ₂ , R ₃ = Cl		1.446	1.406	1.349	1.389	1.391	1.443	0.402	0.234	0.364	1744	1690
8	R ₂ = CH ₃ , R ₃ = NH ₂		1.415	1.396	1.358	1.396	1.391	1.448	0.512	0.234	0.254	1734	1695
9	R ₂ = CH ₂ Cl, R ₃ = NH ₂		1.431	1.407	1.354	1.396	1.390	1.445	0.444	0.250	0.306	1748	1711
10	R ₂ = CHCl ₂ , R ₃ = NH ₂		1.445	1.414	1.356	1.395	1.389	1.438	0.440	0.268	0.292	1750	1703
11	R ₂ = CH ₃ , R ₃ = CH ₃		1.411	1.401	1.354	1.392	1.392	1.451	0.487	0.225	0.288	1726	1693
12	R ₂ = CH ₂ Cl, R ₃ = CH ₃		1.427	1.411	1.351	1.393	1.391	1.447	0.429	0.239	0.332	1742	1708
13	R ₂ = CHCl ₂ , R ₃ = CH ₃		1.440	1.419	1.351	1.391	1.389	1.442	0.408	0.251	0.341	1741	1703
14	R ₂ = CH ₃ , R ₃ = CH ₂ CH ₂ CH ₂ Cl		1.413	1.404	1.355	1.392	1.390	1.450	0.488	0.229	0.282	1723	1692
15	R ₂ = CH ₂ Cl, R ₃ = CH ₂ CH ₂ CH ₂ Cl		1.428	1.414	1.352	1.392	1.390	1.446	0.432	0.243	0.325	1740	1705
16	R ₂ = CHCl ₂ , R ₃ = CH ₂ CH ₂ CH ₂ Cl		1.441	1.422	1.352	1.391	1.387	1.442	0.407	0.255	0.339	1740	1700
17	R ₂ = CH ₃ , R ₃ = CH ₂ CH ₂ CH ₂ NH ₂		1.411	1.403	1.356	1.390	1.390	1.451	0.495	0.229	0.276	1715	1683
18	R ₂ = CH ₂ Cl, R ₃ = CH ₂ CH ₂ CH ₂ NH ₂		1.428	1.415	1.350	1.393	1.390	1.446	0.423	0.240	0.337	1740	1705
19	R ₂ = CHCl ₂ , R ₃ = CH ₂ CH ₂ CH ₂ NH ₂		1.441	1.423	1.351	1.391	1.388	1.441	0.400	0.253	0.347	1739	1699
20	R ₂ = CH ₃ , R ₃ = CH ₂ CH ₂ CH ₂ NHC(NH)NH ₂		1.412	1.405	1.355	1.392	1.390	1.450	0.487	0.229	0.284	1723	1691
21	R ₂ = CH ₂ Cl, R ₃ = CH ₂ CH ₂ CH ₂ NHC(NH)NH ₂		1.428	1.414	1.351	1.393	1.390	1.446	0.427	0.243	0.330	1741	1706
22	R ₂ = CHCl ₂ , R ₃ = CH ₂ CH ₂ CH ₂ NHC(NH)NH ₂		1.441	1.423	1.352	1.391	1.387	1.441	0.404	0.256	0.340	1740	1700

The HOMA index is expressed by

$$\text{HOMA} = 1 - \frac{\alpha}{n} \sum (R_{\text{opt}} - R_i)^2, \quad (3)$$

where n is the number of bonds taken into account, α is an empirical constant chosen to give $\text{HOMA} = 0$ for a nonaromatic system and $\text{HOMA} = 1$ for a system with all bonds equal to the optimal value R_{opt} , and R_i is the individual bond length [30]. The HOMA index has a value between 1 for entirely aromatic molecules and 0 for nonaromatic systems. When the value of the HOMA index is less than zero, the structure is antiaromatic.

The Pauling bond number and virtual CC and CN bond lengths have been applied to the HOMA aromaticity index. This allows separation of HOMA into energetic and geometric contributions for heterocyclic π -electron systems [29]. The expression for the HOMA term is as follows:

$$\text{HOMA} = 1 - \left[257.7(1.388 - R_{\text{av}})^2 + \frac{257.7}{N} \sum (R_{\text{av}} - R_i)^2 \right], \quad (4)$$

where N is the number of bonds taken into calculation, R_{av} is the averaged bond length, $R_{\text{av}} = 1/n \sum_{i=1}^n R_i$, and R_i is the virtual bond length calculated from the Pauling bond number [29] $n_i = \exp(R(1) - R(n)/c)$.

According to the general formula,

$$R_n = 1.467 - 0.1702 \ln(n). \quad (5)$$

4. Results and Discussion

4.1. Geometry of the C-H $\cdots$ O=C Intramolecular Contact. Scheme 1 presents pyrrolopyrazinone systems analyzed here, 2–22. Pyrrole, 1, and pyrazine, 1d, 1a–c, and 1e, which may be treated as fragments of these systems, are also analyzed for comparison. Selected geometrical parameters for all these species (1–22) are listed in Table 1. Three sets of samples of pyrrolopyrazinone systems which differ in the R_2 substituent may be selected here; the sample where $R_2 = \text{CH}_3$ (2, 5, 8, 11, 14, 17, and 20), $R_2 = \text{CH}_2\text{Cl}$ (3, 6, 9, 12, 15, 18, and 21), and the sample where $R_2 = \text{CHCl}_2$ (4, 7, 10, 13, 16, 19, and 22).

For some of the systems analyzed, the existence of C-H $\cdots$ O intramolecular hydrogen bonds is observed which close additional five-membered rings. We can expect here weak hydrogen bonds which are formed when the hydrogen atom is covalently bonded to a slightly more electronegative atom relative to hydrogen; the electronegativity of carbon of 2.55 is only slightly higher than that of hydrogen, that is, 2.20, according to the Pauling electronegativity scale. The identification of the A-H $\cdots$ B hydrogen bond is often based on the A $\cdots$ B distance which should be lower than the sum of their van der Waals radii; this criterion can be applied for strong and medium strength interactions. It is inadequate for weaker hydrogen bonds that are mainly electrostatic in nature. This is why the criterion of the sum of van der Waals radii is more often applied for the H $\cdots$ B distances; however, it is also sometimes not fulfilled for weaker interactions. The most probable interpretation is that for weak hydrogen

bonds the long-range electrostatic forces act far beyond the van der Waals radii cutoff [31, 32] while for strong and very strong interactions the additional forces related to electron density shifts are more important; these forces lead to the enormous shortening of the H $\cdots$ B hydrogen bond contact [31]. The role of electrostatic forces in hydrogen bonds and in other interactions, such as for example, halogen bonds, is in line with the σ -hole concept [33].

Table 2 presents the geometrical parameters corresponding to the C-H $\cdots$ O=C hydrogen bonds, H $\cdots$ O distances, d_{HO} 's and $\angle\text{C-H}\cdots\text{O}$ angles. We can observe that among the C-H $\cdots$ O=C contacts there are systems with short H $\cdots$ O distances below the sum of vdW radii—2.72 Å (O, 1.52 Å and H, 1.20 Å), according to Bondi [34, 35]. One of the most important geometrical characteristics of hydrogen bonds is that the distance between the proton and the proton-accepting atom is shorter than the sum of their van der Waals radii. Additional generally accepted criterion is that the donor-proton-acceptor angle in hydrogen bond must be at least 90° [36]. For 3, 6, 9, 12, 15, 18, and 21, in which $R_2 = \text{CH}_2\text{Cl}$, the H $\cdots$ O distance varies from 2.19 to 2.27 Å. Systems 2, 5, 8, 11, 14, 17, and 20, where R_2 is a methyl group (CH_3), are characterized by the H $\cdots$ O distance range of 2.17–2.24 Å and the $\angle\text{C-H}\cdots\text{O}$ angle range of 106–118° (Table 2). The systems with the $R_2 = \text{CHCl}_2$ group (4, 7, 10, 13, 16, 19, and 22) are characterized by the shortest H $\cdots$ O distances of 2.03–2.06 Å, much shorter than the sum of vdW radii of H and O atoms (2.68 Å); the $\angle\text{C-H}\cdots\text{O}$ angle range of 111–113° is observed here (Table 2). It is noted that the above values are within the range acceptable for intramolecular H-bonds since the accepted H $\cdots$ O distance range for the C-H $\cdots$ O hydrogen bonds is 2.0–2.7 Å [36]. Recent studies have also suggested the C-H $\cdots$ X angles up to 90° for acceptable hydrogen bonds [37].

The phenomenon which influences the geometry of C-H $\cdots$ O=C interactions is the acidity of the proton donating C-H group [38]. The main factor that controls both lengths and energies is the acidity of the C-H group. The acidity of the C-H group can sweep over a wide range of pKa values prompted by changes of the hybridization state of the carbon and for effect of electron-withdrawing substituents. The acidity of the C-H bond is increasing in the following order: $\text{sp}^3\text{C-H}$, $\text{sp}^2\text{C-H}$, and spC-H . For instance, pKa in water of CH_4 , C_2H_4 , and C_2H_2 decreases in the order 48, 44, and 26. The effects of the C-H acidity on the geometry of the C-H $\cdots$ O bonds have been studied by Desiraju [38]. It was found that C $\cdots$ O contact distances correlate with pKa values. Shorter bonds are associated with the more acidic C-H group [39, 40].

Replacement of the H atom from the group $R_2 = \text{CH}_3$ by Cl results in a reduction in the H $\cdots$ O distance [9]. This is also observed for the systems analyzed here; for example, the H $\cdots$ O distance is equal to 2.17, 2.03 Å for 20 ($R_2 = \text{CH}_3$) and 22 ($R_2 = \text{CHCl}_2$), respectively (Table 2); it means that shorter H $\cdots$ O distances occur for more acidic C-H donors. The C-H $\cdots$ O angle varies from 102.8° in 12 ($R_2 = \text{CH}_2\text{Cl}$) to 104.91° in 21 ($R_2 = \text{CH}_2\text{Cl}$). For systems with $R_2 = \text{CH}_3$, the C-H $\cdots$ O angle varies from 106.1° in 2 to 112.42° in 22. For systems with $R_2 = \text{CHCl}_2$, the C-H $\cdots$ O angle varies from 107.67° in 4 to

Compound		d _{H...O} (Å)	∠ _{C-H...O} (°)	d _{C-H} (Å)	ρ _{RCP}	∇ ² ρ _{RCP}	ρ _{BCP}	∇ ² ρ _{BCP}	H _{BCP}	V (a.u.)	G	ρ _{BCP} (C-H) (C-H...O-C)
2	R ₂ = CH ₃ , R ₃ = H	2.26	106.10	1.09								0.2844
3	R ₂ = CH ₂ Cl, R ₃ = H	2.27	103.44	1.09								0.2899
4	R ₂ = CHCl ₂ , R ₃ = H	2.17	107.67	1.09	0.0213	0.1078	0.0217	0.0840	0.0010	-0.0173	0.0191	0.2925
5	R ₂ = CH ₃ , R ₃ = Cl	2.20	108.38	1.09	0.0202	0.0925	0.0203	0.0839	0.0006	-0.0197	0.0203	0.2853
6	R ₂ = CH ₂ Cl, R ₃ = Cl	2.23	103.71	1.09								0.2898
7	R ₂ = CHCl ₂ , R ₃ = Cl	2.06	112.13	1.09	0.0241	0.1231	0.0253	0.1065	0.0005	-0.0255	0.0260	0.2933
8	R ₂ = CH ₃ , R ₃ = NH ₂	2.21	106.89	1.09	0.0203	0.0882	0.0203	0.0862	0.0008	-0.0199	0.0207	0.2851
9	R ₂ = CH ₂ Cl, R ₃ = NH ₂	2.24	102.82	1.09								0.2896
10	R ₂ = CHCl ₂ , R ₃ = NH ₂	2.06	111.48	1.09	0.0244	0.1241	0.0255	0.1078	0.0006	-0.0257	0.0263	0.2931
11	R ₂ = CH ₃ , R ₃ = CH ₃	2.19	108.16	1.09	0.0207	0.0939	0.0208	0.0860	0.0007	-0.0202	0.0209	0.2856
12	R ₂ = CH ₂ Cl, R ₃ = CH ₃	2.23	102.80	1.09								0.2902
13	R ₂ = CHCl ₂ , R ₃ = CH ₃	2.04	111.90	1.09	0.0248	0.1277	0.0261	0.1108	0.0006	-0.0265	0.0271	0.2938
14	R ₂ = CH ₃ , R ₃ = CH ₂ CH ₂ Cl	2.17	108.23	1.09	0.0211	0.0971	0.0213	0.0876	0.0007	-0.0206	0.0213	0.2861
15	R ₂ = CH ₂ Cl, R ₃ = CH ₂ CH ₂ CH ₂ Cl	2.20	104.08	1.09								0.2905
16	R ₂ = CHCl ₂ , R ₃ = CH ₂ CH ₂ CH ₂ Cl	2.03	112.42	1.09	0.0257	0.1311	0.0269	0.1140	0.0006	-0.0273	0.0279	0.2943
17	R ₂ = CH ₃ , R ₃ = CH ₂ CH ₂ CH ₂ NH ₂	2.20	106.73	1.09	0.0207	0.0922	0.0207	0.0868	0.0008	-0.0201	0.0209	0.2857
18	R ₂ = CH ₂ Cl, R ₃ = CH ₂ CH ₂ CH ₂ NH ₂	2.19	104.19	1.09								0.2906
19	R ₂ = CHCl ₂ , R ₃ = CH ₂ CH ₂ CH ₂ NH ₂	2.03	112.18	1.09	0.0252	0.1307	0.0267	0.1138	0.0006	-0.0272	0.0278	0.2942
20	R ₂ = CH ₃ , R ₃ = CH ₂ CH ₂ CH ₂ NHC(NH)NH ₂	2.17	108.54	1.09	0.0211	0.0969	0.0212	0.0873	0.0006	-0.0206	0.0212	0.2860
21	R ₂ = CH ₂ Cl, R ₃ = CH ₂ CH ₂ CH ₂ NHC(NH)NH ₂	2.20	104.91	1.09								0.2906
22	R ₂ = CHCl ₂ , R ₃ = CH ₂ CH ₂ CH ₂ NHC(NH)NH ₂	2.03	112.36	1.09	0.0253	0.1311	0.0268	0.1140	0.0006	-0.0273	0.0279	0.2942

SCHEME 2: Schematic representation of the endophyte-infected plant.

108.54 in 20. It means that electron-withdrawing substituents affect $\text{CH}\cdots\text{O}$ bond geometry. It is observed that the introduction of two chlorine atoms where $\text{R}_2 = \text{CHCl}_2$ (4, 7, 10, 13, 16, 19, and 22) led to an increase of the $\text{C-H}\cdots\text{O}$ angle in comparison with molecules where $\text{R}_2 = \text{CH}_3$ as well as $\text{R}_2 = \text{CH}_2\text{Cl}$. It is interesting to compare the $\text{C-H}\cdots\text{O}$ angle of systems where $\text{R}_2 = \text{CH}_3$ and the $\text{C-H}\cdots\text{O}$ angle of systems where $\text{R}_2 = \text{CH}_2\text{Cl}$. Bond angle $\angle\text{C-H}\cdots\text{O}$ values for a system where $\text{R}_2 = \text{CH}_3$ are larger than $\angle\text{C-H}\cdots\text{O}$ for a system where $\text{R}_2 = \text{CH}_2\text{Cl}$.

For all molecules, under consideration (2–22), the $\text{H}\cdots\text{O}$ distances are within the range acceptable for intramolecular H-bonds. To find whether these $\text{H}\cdots\text{O}$ contacts may be classified as attractive hydrogen bonds, additional QTAIM and NBO analyses were performed here.

4.2. QTAIM Analysis. The quantum theory of atoms in molecules, QTAIM [27], is often applied to analyze different inter- and intramolecular interactions, such as $\text{A-H}\cdots\text{B}$ hydrogen bonds [41]. The existence of the $\text{H}\cdots\text{B}$ bond path as well as the characteristics of the corresponding bond critical point such as electron density, ρ_{BCP} , and its Laplacian, $\nabla^2\rho_{\text{BCP}}$, is often used as criteria for the existence of the hydrogen bond [42]. That is why QTAIM analysis was also performed here for pyrrolopyrazinones (2–22). Figure 1 presents molecular graphs of peramine derivatives 21 ($\text{X}=\text{H}$, $\text{Y}=\text{Cl}$) and 22 ($\text{X}=\text{Cl}$, $\text{Y}=\text{Cl}$) which are analyzed in this study; these are two examples of systems where the QTAIM approach confirms the existence of HB (22), or it does not confirm such interaction since the $\text{H}\cdots\text{O}$ intramolecular

bond path was not detected (21). Based on QTAIM, there are no bond paths connecting the oxygen atom and the methylene hydrogen atom for 2, 3, 6, 9, 12, 15, 18, and 21, that is, for all systems where $\text{R}_2 = \text{CH}_2\text{Cl}$ and for certain systems where $\text{R}_2 = \text{CH}_3$ (Scheme 1). The H atom $=\text{CH}_3$ is located at 2.6 Å distance from the hydrogen atom of the R_3 group and has no steric repulsion between the R_2 and R_3 electron clouds. This effect leads to the lack of attractive interaction of HB between the carbonyl group and the neighboring CH_3 group [9].

There is a bond path connecting $\text{C}=\text{O}$ and C-H groups for systems 4, 7, 10, 13, 16, 19, 22, that is, for structures where $\text{R}_2 = \text{CHCl}_2$ ($\text{X}=\text{Cl}$, $\text{Y}=\text{Cl}$ according to Table 2) and where the $\text{H}\cdots\text{O}$ distance is much shorter than the corresponding sum of the vdW radii (see the discussion in the previous section). There is also a subset of the group in which $\text{R}_2 = \text{CH}_3$ (5, 8, 11, 14, 17, and 20) where a bond path exists connecting the oxygen atom of the carbonyl group and the hydrogen atom of the CH_3 group (Table 2).

Table 2 presents selected QTAIM parameters for the systems analyzed here, that is, characteristics of the $\text{H}\cdots\text{O}$ BCP corresponding to the intramolecular hydrogen bond: electron density at the bond critical point, ρ_{BCP} , its Laplacian, $\nabla^2\rho_{\text{BCP}}$, and the energetic BCP characteristics (H_{BCP} , V_{BCP} , and G_{BCP}), as well as the properties of the ring critical point corresponding to the ring closed by this hydrogen bond: electron density at the ring critical point, ρ_{RCP} , and its Laplacian, $\nabla^2\rho_{\text{RCP}}$. The typical topological parameters at the bond critical point for the hydrogen bond are 0.002–0.34 a.u. for

FIGURE 1: Molecular graphs (representation of bonding interactions according to QTAIM results) of the system analyzed in this study: 23 (a), 22 (b), and 21 (c). The dotted line corresponds to a bond path.

electron density and 0.02–0.139 a.u. for its Laplacian [27]. The QTAIM analysis of electron densities at the $H\cdots O$ bond critical points of the systems under consideration (2–22) showed that ρ_{BCP} is in a range of 0.0269 to 0.0203 a.u., and Laplacian varies from 0.0839 to 0.114 a.u. It has been shown earlier that electron density and its Laplacian correlate with H-bond energy, especially for homogeneous samples of interactions [31, 40, 43]. The increase of HB strength is related to the increase of electron density at the BCP.

The largest electron density at the proton-acceptor ($H\cdots O$) bond critical point is observed for 16 ($R_2 = CHCl_2$, $R_3 = (CH_2)_3Cl$), peramine derivative 19 ($R_2 = CHCl_2$, $R_3 = (CH_2)_3NH_2$), and 22 ($R_2 = CHCl_2$, $R_3 = (CH_2)_3NHC(NH)NH_2$), 0.0269, 0.0267, and 0.0268 a.u., respectively.

Figure 1(c) presents a molecular graph of system 22 where $R_2 = CHCl_2$. In this structure, shown in Figure 1(c), there is a bond path connecting oxygen atom and H8 atom of the R_2 group. There is also a bond path connecting atom Cl34 and atom H18 of methylene group as well as atom Cl35 and atom H33. The Cl34...H18 distance is 2.57 Å; the Cl34...H33 distance is 2.71 Å. We believe that carbon atom of the proton donor group ($R_2 = CHCl_2$) carries a more positive charge than the carbon atom of the CH_2Cl group. Furthermore, for these systems, the $\angle C-H\cdots O$ bond angle is closest to 120° compared with that of the other species ($R_2 = CH_2Cl$) in Table 2 and Figures 1(a) and 1(c). In such a case, the proton of R_2 group is located in the chelate ring plane. In spite of this results obtained, it seems that the path linking both $C=O\cdots H-C$ is an attractive interaction.

For the sample 21 where $R_2 = CH_2Cl$, the $Cl\cdots H$ distance is 2.81 Å, and the $\angle C-H\cdots O$ bond angle is 104.91° . In such a case, there is not a bond path connecting carbonyl oxygen

with hydrogen of the R_2 group (Figure 1(b)). This may be explained because of minimal $n_B \rightarrow \sigma^*_{AH}$ overlap [44]. Hence, if hydrogen bonding is stronger, thus the $C-H\cdots O$ angle is closer to 120° .

It is seen that systems with $R_2 = CHCl_2$ correspond to the strongest interactions since it is also supported by other results collected in Table 2 that the shortest $H\cdots O$ distances are observed for the systems mentioned above. It is in agreement with the properties of the Cl atom as an electron-withdrawing substituent that enhances the proton-donating ability of the adjacent CH group. The latter was suggested in a previous study [45] that the strength of the $C-H\cdots B$ hydrogen bond strongly depends on the nature of the proton donor and increases when hydrogen atoms are replaced by electron-withdrawing substituents [9, 46].

The correlation between the length of the hydrogen bond and electron density at the corresponding bond critical point, ρ_{BCP} , which is often analyzed for samples of related species, is also observed here (Figure 2). Pyrrolopyrazinones analyzed here, where the $H\cdots O$ bond path corresponding to the intramolecular hydrogen bond was detected, can be divided into two groups (Figure 2); the group where $R_2 = CHCl_2$ and the group where $R_2 = CH_3$. For the first group, stronger interactions characterized by shorter $H\cdots O$ distances and greater ρ_{BCP} values are observed than those for the second group (Figure 2).

The properties of the ring critical point which is observed for the intramolecular hydrogen bonds often correlate with other measures of HB strength. It is noted that for the HBs analyzed here there is a linear correlation between the ρ_{BCP} and ρ_{RCP} values ($R^2 = 0.998$). The H_{BCP} value is also useful to describe properties of hydrogen bonds. It is

FIGURE 2: Correlation between electron density at the H-bond critical points ρ_{BCP} (in a.u.) and the $\text{H}\cdots\text{O}$ distance (in Å) was calculated at the B3LYP/aug-cc-pVDZ level. (4, 7, 10, 13, 16, 19, and 22; $\text{R}_2 = \text{CHCl}_2$) (5, 8, 11, 14, 17, and 20; $\text{R}_2 = \text{CH}_3$).

negative for interactions which are at least partly covalent in nature; for the systems analyzed here, it is positive and equal to ~ 0.001 a.u.

According to the latest studies on HB description, HB strength is related to the kinetic energy of electron density at the BCP and the decrease of potential energy and decrease of total electron energy density at the BCP [29]. G , V , and H_{BCP} are the kinetic, potential, and total electron energy densities at critical point, respectively. G is a positive value, whereas V is a negative one. Rozas et al. have classified HB based on Laplacian of electron density at BCP and HBCP values [28]. Medium and weak in strength HBs show positive value of Laplacian of electron density at BCP as well as H value. It is seen that for systems analyzed here, $\nabla^2\rho_{\text{BCP}}$ is positive, which means that HBs could be classified as weak. For the highest $\nabla^2\rho_{\text{BCP}}$ value of 0.1140, H_{BCP} is 0.0006, while V is -0.0273 . For the lowest $\nabla^2\rho_{\text{BCP}}$ value of 0.0839, H_{BCP} is 0.0006, while V is -0.0197 .

4.3. NBO Analysis. The NBO method is a useful tool to analyze intra- and intermolecular interactions. There are two effects that are often attributed to $\text{A-H}\cdots\text{B}$ hydrogen bond formation: a hyper conjugative effect of A-H bond weakening and rehybridization-promoted A-H bond strengthening [47]. The hyper conjugative effect is related to electron charge transfer from the lone pair at the donor (B) into the antibonding σ^* orbital of the A-H bond. The interaction between these orbitals corresponds to the deviation of the molecule from the Lewis structure [48]. The $E_{\text{AB}}^{(2)}$ energy term mentioned earlier can be considered a part of charge transfer energy or the stabilization energy associated with the delocalization [49].

In NBO theory, a donor-acceptor picture of H-bonding is based on overlap-type ionic resonance. The resonance hybrid $\text{O}\cdots\text{H-C} \leftrightarrow \text{OH}^+\cdots\text{C}^-$ corresponds to a two-electron intermolecular donor-acceptor interaction of the form $n_{\text{O}} \rightarrow \sigma_{\text{C-H}}^*$ in which electron density from the lone pair n_{O} of Lewis base (oxygen atom) delocalizes into the unfilled $\sigma_{\text{C-H}}^*$

hydride antibonding orbital of the Lewis acid (C-H) [44]. Such intermolecular delocalization corresponds to partial charge transfer from the Lewis base to the Lewis acid. The larger the $E^{(2)}$ value, the more intensive is the interaction between the donor and electron acceptor and the greater the extent of conjugation of the systems.

Table 3 presents NBO parameters for the molecules considered in this study. The charge transfer energy contribution denoted by $E_{\text{AB}}^{(2)}$ that derives from the $n_{\text{O}} \rightarrow \sigma_{\text{C-H}}^*$ orbital-orbital interaction is included. This energy ranges from 1.19 kcal/mol in system 12 to 2.87 kcal/mol in system 4. Table 3 indicates that the interaction energy $E^{(2)}$ between the lone pair of oxygen atom $\text{LP}(2)\text{O} \rightarrow \sigma_{\text{C-H}}^*$ for 4 ($\text{R}_2 = \text{CHCl}_2$) and 2 ($\text{R}_2 = \text{CH}_3$) is 2.87 and 1.32 kcal/mol, respectively. Similarly, the interaction energy $E^{(2)}$ between the lone pair of oxygen atom $\text{LP}(2)\text{O} \rightarrow \sigma_{\text{C-H}}^*$ for 22 ($\text{R}_2 = \text{CHCl}_2$) and 20 ($\text{R}_2 = \text{CH}_3$) is 1.95 and 1.83 kcal/mol, respectively.

The s-character for the Lewis acid C-H increases in the order $\text{R}_2 = \text{CH}_3$, $\text{R}_2 = \text{CH}_2\text{Cl}$, $\text{R}_2 = \text{CHCl}_2$. For example, for 2, 3, and 4, C-H acceptor occupancy is equal to 0.0094, 0.0178, and 0.0317, respectively. This effect was observed previously for the hydrogen bonding complexes [50]. The increase of s-character is accompanied by the increase of polarization of the C-H bond. The electron density at the C-H BCP in $\text{R}_2 = \text{CH}_3$ is lower than the electron density at C-H BCP in $\text{R}_2 = \text{CHCl}_2$ (Table 2).

NBO results enable us to suggest the presence of an attractive $\text{C}=\text{O}\cdots\text{H-C}$ intramolecular interactions for all compound under study. Contrary to expectations, there is no QTAIM evidence of the existence of the hydrogen bond, 3, 6, 9, 12, and 15 (where $\text{R}_2 = \text{CH}_2\text{Cl}$), since the $\text{H}\cdots\text{O}$ bond path is not observed.

There was a similar earlier finding for the intramolecular dihydrogen bonds where for some systems the NBO method showed an orbital-orbital overlap typical for the intramolecular interaction while QTAIM did not show the corresponding bond path [51].

It is noted that the results presented here are partly consistent with AIM analysis. The greatest values of electron density at the $\text{H}\cdots\text{O}$ bond critical point are observed for moieties where $\text{R}_2 = \text{CHCl}_2$ (Table 2). The latter approximately corresponds to the greatest orbital-orbital $n_{\text{O}} \rightarrow \sigma_{\text{C-H}}^*$ energies.

Interestingly, the lone pair electrons localized on the oxygen atom in the systems where $\text{R}_2 = \text{CHCl}_2$ point toward the C-H hydride atom as seen in Figure 3. For the systems where $\text{R}_2 = \text{CH}_3$, $n_{\text{O}} \rightarrow \sigma_{\text{C-H}}^*$ orbitals are held much farther apart than in the former species where Cl substituents enhance the strength of the hydrogen bond. Figure 3 shows an overlap surface-rendered diagram for the interacting n_{O} and $\sigma_{\text{C-H}}^*$ orbitals in pyrrolepyrazinones 22 and 20. It reveals a propensity for the $\text{C-H}\cdots\text{O}=\text{C}$ bonding for pyrrolepyrazinone 22, whereas 20 ($\text{R}_2 = \text{CH}_3$) exhibits a weak $n_{\text{O}} \rightarrow \sigma_{\text{C-H}}^*$ interaction with the backside of the CH antibond.

It seems most likely that the changes observed in the H-bonding can be due to the steric repulsion between oxygen and chlorine atoms. The presence of H-bond depends on geometrical arrangement of the oxygen and hydrogen atoms determined by its repulsion. In $\text{R}_2 = \text{CHCl}_2$, two chlorine atoms are forced to be in the anticlinal configuration with

TABLE 3: Occupancy of natural orbitals (NBO), corresponding to the C-H $\cdots$ O intramolecular contacts, obtained at B3LYP/aug-cc-pVDZ; $E^{(2)}$ means energy of hyperconjugative interactions; $E_i - E_j$ is energy difference between donor and acceptor NBO orbitals. Designation of species according to Scheme 1.

Compound	Acceptor (A) C-H			Donor (B) C=O			$E^{(2)}$ $E_i - E_j$ (kcal/mol) (a.u.)
	Type	Occupancy	Type	Occupancy	Hybrid (O)		
2	BD*	0.00944	LP(2)	1.85498	s (0.00%), p 1.00 (99.67%), and d 0.00 (0.33%)	1.32	0.67
3	BD*	0.01785	LP(2)	1.85014	s (0.00%), p 1.00 (99.66%), and d 0.00 (0.34%)	1.37	0.65
4	BD*	0.03173	LP(2)	1.84338	s (0.01%), p 1.00 (99.65%), and d 0.00 (0.34%)	2.87	0.67
5	BD*	0.01231	LP(2)	1.84837	s (0.01%), p 1.00 (99.66%), and d 0.00 (0.33%)	1.63	0.68
6	BD*	0.01943	LP(2)	1.84368	s (0.01%), p 1.00 (99.64%), and d 0.00 (0.34%)	1.71	0.66
7	BD*	0.03248	LP(2)	1.84651	s (0.00%), p 1.00 (99.66%), and d 0.00 (0.34%)	2.65	0.67
8	BD*	0.01129	LP(2)	1.85463	s (0.00%), p 1.00 (99.67%), and d 0.00 (0.33%)	1.48	0.68
9	BD*	0.01876	LP(2)	1.85009	s (0.00%), p 1.00 (99.66%), and d 0.00 (0.34%)	1.56	0.66
10	BD*	0.03187	LP(2)	1.84175	s (0.01%), p 1.00 (99.65%), and d 0.00 (0.34%)	1.57	0.64
11	BD*	0.01110	LP(2)	1.85514	s (0.00%), p 1.00 (99.67%), and d 0.00 (0.33%)	1.74	0.68
12	BD*	0.01830	LP(2)	1.85056	s (0.00%), p 1.00 (99.66%), and d 0.00 (0.34%)	1.19	0.66
13	BD*	0.03176	LP(2)	1.84328	s (0.01%), p 1.00 (99.65%), and d 0.00 (0.34%)	1.41	0.64
14	BD*	0.01154	LP(2)	1.85466	s (0.00%), p 1.00 (99.67%), and d 0.00 (0.32%)	1.77	0.68
15	BD*	0.01891	LP(2)	1.85004	s (0.00%), p 1.00 (99.66%), and d 0.00 (0.34%)	1.86	0.66
16	BD*	0.03221	LP(2)	1.85237	s (0.01%), p 1.00 (99.66%), and d 0.00 (0.33%)	1.89	0.65
17	BD*	0.01102	LP(2)	1.85699	s (0.00%), p 1.00 (99.67%), and d 0.00 (0.32%)	1.53	0.68
18	BD*	0.01866	LP(2)	1.85040	s (0.00%), p 1.00 (99.66%), and d 0.00 (0.34%)	1.62	0.66
19	BD*	0.03193	LP(2)	1.84319	s (0.01%), p 1.00 (99.65%), and d 0.00 (0.34%)	1.47	0.65
20	BD*	0.01143	LP(2)	1.85483	s (0.00%), p 1.00 (99.67%), and d 0.00 (0.32%)	1.83	0.68
21	BD*	0.01838	LP(2)	1.85023	s (0.00%), p 1.00 (99.66%), and d 0.00 (0.34%)	1.92	0.66
22	BD*	0.03209	LP(2)	1.84293	s (0.01%), p 1.00 (99.65%), and d 0.00 (0.34%)	1.95	0.65

FIGURE 3: NBO overlap interaction surface plot for the bay region of pyrrolopyrazinones 22 ($R_2 = \text{CHCl}_2$) and 20 ($R_2 = \text{CH}_3$) showing stabilizing donor-acceptor $n_{\text{O}} \rightarrow \sigma^*_{\text{C-H}}$ interaction.

respect to oxygen. Such behavior minimizes repulsion, and therefore the H atom of the CHCl_2 group is in a synperiplanar configuration that is favorable for H-bonding.

In $R_2 = \text{CH}_2\text{Cl}$, the minimal repulsion is present in the antiperiplanar configuration of the oxygen and chlorine atom. This phenomenon forces the synclinal conformation of two hydrogen atoms of R_2 with respect to O atom. It is much less favorable for H-bond formation between $\text{C}=\text{O}$ and $R_2 = \text{CH}_2\text{Cl}$.

4.4. Intramolecular Hydrogen Bond and HOMA Aromaticity Interrelation. Palusiak et al. [52] revealed the interplay between local aromaticity of a polycyclic aromatic hydrocarbon and the strength of the intramolecular HB. It is also interesting to recognize the role of substituents and the hydrogen bond to stabilize pyrrolopyrazinone molecules analyzed here, particularly the effect of these factors on local aromaticities. It is worth to mention that the local aromaticity analyzed for the numerous systems considered in this study characterizes the aromaticity of a particular ring of the system [53].

The HOMA indices calculated for pyrrole (1), 3,4-dihydropyrrolopyrazinones (1a–c), pyrazine (1d), 2-oxypyrazine (1e), and pyrrolopyrazinones (2–22) are shown in Table 1. There are substituents in 2 and 3 positions (R_2 and R_3) for the species analyzed here: 3,4-dihydropyrrolopyrazinones (1a–c) and pyrrolopyrazinones (2–22). Table 1 is divided into two sections; the first section shows the local aromaticity of the pyrrole ring whereas the second section lists the local aromaticity of the pyrazinone ring. C–C and C–N bond lengths and HOMA values as well as calculated $\nu_{\text{C}=\text{C}}$ and $\nu_{\text{C}=\text{O}}$ frequencies are also included.

The HOMA index of pyrrole (1) is 0.833, whereas local HOMAs of 3,4-dihydropyrrolopyrazinones (1a–c) range from 0.876 to 0.885. The aromaticity of the pyrrole ring in 2–22 moieties varies between 0.848 and 0.905 HOMA units. It is seen that the HOMAs of the pyrrole ring for structures 1c, 4, 7, 10, 13, 16, 19, and 22 where $R_2 = \text{CHCl}_2$ are higher than those for structures 1a, 2, 5, 8, 11, 14, 17, and 20, and 1b, 3, 6, 9, 12, 15, 18, and 21 where $R_2 = \text{CH}_3$ or CH_2Cl , respectively. For instance, the HOMA value for the pyrrole ring of peramine (20) where $R_2 = \text{CH}_3$ is 0.865, for the chloromethylene derivative (21) where $R_2 = \text{CH}_2\text{Cl}$ is 0.869, and

for the dichloromethylene derivative (22) where $R_2 = \text{CHCl}_2$ is 0.877 a.u.

The local HOMA indices of the pyrrole ring for 3,4-dihydropyrrolopyrazinones 1a, 1b, and 1c are higher than those of pyrrolopyrazinone 2, 3, and 4 (Table 1). For instance, the HOMA for pyrrolopyrazinones 2 and 3 is 0.848 and 0.852, respectively, while for 3,4-dihydropyrrolopyrazinone 1a and 1b, it is 0.876 and 0.882, respectively. An analogous situation is observed for residual pairs of pyrrolopyrazinone moieties ($R_2 = \text{CH}_2\text{Cl}$ and $R_2 = \text{CH}_3$), such as 5 and 6, 8 and 9, 11 and 12, 14 and 15, 17 and 18, and 20 and 21, as compared with HOMA indices of the pyrrole ring for 3,4-dihydropyrrolopyrazinones 1a and 1b (Table 1). This means that the addition of a pyrazinone ring reduces the aromaticity of the pyrrole ring in a pyrrolopyrazinone system as compared with an isolated pyrrole molecule. Aside from the above-mentioned pairs of systems, the HOMA index for the pyrrole ring is typically higher for species with the CH_2Cl substituent than for those where $R_2 = \text{CH}_3$.

It is worth mentioning that the so-called Clar's rules represent a qualitative description of the aromatic character of a particular ring in a molecule of polycyclic species. These rules classify rings according to their π -electron structure into aromatic sextets, empty rings, migrating rings, and those with localized double bonds [54]. The HOMA approach enables distinguishing Clar's sextets (very high HOMA close to 1.00) and empty rings and those with a localized double bond (low HOMA values). This may be performed by HOMA partitioning in energetic (EN) and geometric (GEO) terms [18]. The EN and GEO contributions express the aromaticity contributions related to a decrease in resonance energy and to an increase in bond length alternation, respectively [29]. These contributions for the species analyzed here are shown in Table 1. It is seen that the GEO term varies significantly with the R_2 substituent, for example for the 2, 3, 4 and 5, 6, 7 triads where $R_2 = \text{CH}_3$, $R_2 = \text{CH}_2\text{Cl}$, and $R_2 = \text{CHCl}_2$, respectively. The formation of the $\text{C-H}\cdots\text{O}=\text{C}$ intramolecular hydrogen bond for systems where $R_2 = \text{CHCl}_2$ leads to a decreased GEO contribution and consequently an increase in the HOMA value ($\text{HOMA} = 1 - \text{GEO} - \text{EN}$).

It is concluded based on the results from Table 1 that the HOMA aromaticity of heterocyclic rings is directly related to the structural properties of the R_2 substituent

and to the geometry of the $\text{H}\cdots\text{O}$ contact in the chelate ring. It should be noted that HOMA differences for the pair of compounds where $\text{R}_2 = \text{CH}_2\text{Cl}$ or $\text{R}_2 = \text{CHCl}_2$ are small, $\Delta\text{HOMA} = 0.002\text{--}0.008$. However, a trend is observed that HOMA is greater for species where $\text{R}_2 = \text{CHCl}_2$ than for the ones where $\text{R}_2 = \text{CH}_2\text{Cl}$. It may suggest that the relatively larger stability of the aromatic pyrrole ring in pyrrolepyrazinone moieties where $\text{R}_2 = \text{CHCl}_2$ compared to its $\text{R}_2 = \text{CH}_2\text{Cl}$ counterpart results from the slightly larger aromatic character due to the formation of the HB chelate ring.

The HOMA index of pyrazine (1d) [55] is 0.985, whereas HOMA of 2-oxo-pyrazine (1e) is 0.591. Both heterocycles may be treated as reference moieties. Local aromaticity expressed by HOMA of the pyrazinone ring in moieties 2–22 varies in a range of 0.400–0.512. The HOMAs of the pyrazinone ring for structures 4, 7, 10, 13, 16, 19, and 22 where $\text{R}_2 = \text{CHCl}_2$ are lower than the HOMAs for structures 2, 5, 8, 11, 14, 17, and 20, and 3, 6, 9, 12, 15, 18, and 21 where $\text{R}_2 = \text{CH}_3$ or CH_2Cl , respectively. For example, the HOMA value for the pyrazinone ring of peramine (20) where $\text{R}_2 = \text{CH}_3$ is 0.487, while that for the chloromethylene derivative (21) where $\text{R}_2 = \text{CH}_2\text{Cl}$ is 0.427. For the dichloromethylene derivative (22) where $\text{R}_2 = \text{CHCl}_2$, it is 0.404.

It is worth noting that the opposite relationship is observed for the local HOMA aromaticity index of the pyrrole ring; it is greater for $\text{R}_2 = \text{CHCl}_2$ than for $\text{R}_2 = \text{CH}_3$ or $\text{R}_2 = \text{CH}_2\text{Cl}$.

Some attention was paid previously to the intermolecular interactions affecting aromaticity of certain phenol derivatives [56, 57]. It was concluded that an increase in the H-bond strength of phenol derivatives resulted in a decrease in aromaticity. It was also stated that the main structural factor contributing to the decreased aromaticity of the ring resulted mostly from bond length alternations. The increase in GEO leads to a decrease in aromaticity (HOMA diminishes). For the species analyzed here, the local HOMA aromaticity of the pyrazinone ring decreases (Table 1), which is connected with the increase in the GEO and EN terms.

The electron-withdrawing substituents, such as $-\text{CHCl}_2$, lead to a local EN increase for pyrazinone that consequently results in the decrease in the corresponding local HOMA index. The lower local aromaticity of the pyrazinone ring may result from the methyl group electron-withdrawing properties that increase if hydrogen atoms are substituted by chlorine atoms. It is also noted, however, that the increase of stability of the other ring, pyrrole, is expressed in the increase of the corresponding local HOMA index. In other words, an increase in the aromaticity of one ring leads to lower aromaticity of the other ring. This result is consistent with the earlier findings for pyrrole and *N*-methylpyrrole reported by Dubis et al. [9].

Moreover, it is worth noting that the HOMA aromaticity index for the pyrazine ring, 1d, of 0.985 is greater than that calculated for 2-oxo-pyrazine, 1e, of 0.591. This may be compared with the pyrazinone ring HOMA values for 2, 3, and 4, equal to 0.466, 0.414, and 0.408, respectively. An analogous situation is observed for residual pairs of pyrrolopyrazine moieties.

These observations can be concluded in the following way. The $\text{C-H}\cdots\text{O}$ contact is shorter with higher local HOMA aromaticity of the pyrrole ring and lower HOMA aromaticity of the pyrazinone ring. These interrelated changes may be explained by a decrease in bond length alternation in the pyrrole ring confirmed by a decrease in GEO increments and a decrease in resonance energy of the pyrazinone ring confirmed by an increase in the EN increment to HOMA.

4.5. Vibrational Properties. Table 1 also shows the IR frequencies of the carbonyl group, ν_{CO} , which may be considered as an indicator of HB interaction. Conventional $\text{A-H}\cdots\text{B}$ hydrogen bonds include the bonds formed by main group elements such as N, O, F, Cl, and Br, whereas for weak H-bonds, C-H, P-H, and Si-H are often nonconventional proton-donating bonds. Such a situation occurs for the $\text{C-H}\cdots\text{O}$ hydrogen bonds analyzed here.

H-bond formation affects the stretching band of the A-H bond as well as the stretching vibrational mode of the proton-accepting center, that is, the C=O group in this study. Current computational studies reveal that the frequency of the C=O stretching mode of systems 2, 3, and 4 for which $\text{R}_2 = \text{CH}_3$, $\text{R}_2 = \text{CH}_2\text{Cl}$, and $\text{R}_2 = \text{CHCl}_2$ ranges from 1669 cm^{-1} in 2 ($\text{R}_2 = \text{CH}_3$) without intramolecular $\text{C-H}\cdots\text{O}$ interactions to 1689 cm^{-1} for system 4 ($\text{R}_2 = \text{CHCl}_2$). The frequency of the C=O stretching mode of systems 2, 5, 8, 11, 14, 17, and 20 for which $\text{R}_2 = \text{CH}_3$ ranges from 1674 cm^{-1} in system 5 to 1664 cm^{-1} in system 17.

The frequency of the C=O stretching mode of systems 3, 6, 9, 12, 15, 18, and 21 for which $\text{R}_2 = \text{CH}_2\text{Cl}$ ranges from 1696 cm^{-1} in system 9 to 1686 cm^{-1} in system 3.

The formation of the hydrogen bond leads to an electron density shift from the Lewis base to the Lewis acid unit; for the $\text{C-H}\cdots\text{O}$ interactions analyzed here; from the lone pairs of oxygen (C=O group) to the C-H proton donor. It is expressed as the $\text{n}(\text{O}) \rightarrow \sigma^*(\text{CH})$ orbital-orbital overlap in terms of the NBO approach. The latter causes weakening of the C=O bond, its elongation, and red shifting of the $\nu(\text{C=O})$ stretching vibrational mode. The frequency of the C=O stretching mode of systems 4, 7, 10, 13, 16, 19, and 22 for which $\text{R}_2 = \text{CHCl}_2$ ranges from 1798 cm^{-1} in system 13 to 1687 cm^{-1} in system 19. $\nu(\text{C=O})$ is lower for a system in which $\text{R}_2 = \text{CH}_2\text{Cl}$ than for a system where $\text{R}_2 = \text{CHCl}_2$.

Figure 4 presents an experimental and theoretical spectrum of peramine (20) where $\text{R}_2 = \text{CH}_3$ (Figures 4(a) and 4(b)) and theoretical spectra of 21 and 22 (Figures 4(c) and 4(d)) where $\text{R}_2 = \text{CH}_2\text{Cl}$ and CHCl_2 , respectively.

It has been found on the basis of the previous study [8] that bands within the spectral ranges $1671\text{--}1688\text{ cm}^{-1}$ and $1640\text{--}1655\text{ cm}^{-1}$ are not simple C=O or C=C stretching modes, but they are the result of the mixing of C=O and C=C stretching vibrations. The mode ν_α has C=O and C=C double bonds with stretching “out of phase” vibration, whereas ν_β is the “in phase” mode (Figure 4(b)).

When $\text{R}_2 = \text{CHCl}_2$, an intramolecular $\text{CH}\cdots\text{O}=\text{C}$ hydrogen bond is formed. This effect causes the shift of ν_α to higher frequencies ($\Delta\nu \sim 18\text{ cm}^{-1}$) in comparison with peramine (20).

FIGURE 4: Experimental (a, b) and calculated (c, d) IR spectra (B3LYP/aug-cc-pVDZ level of theory) of peramine 20 ($R_2 = \text{CH}_3$), 21 ($R_2 = \text{CH}_2\text{Cl}$), and 22 ($R_2 = \text{CHCl}_2$) according to Scheme 1.

It seems that $\nu_{\text{C=O}}$ increases with the $\text{C-H}\cdots\text{O}=\text{C}$ distance decrease (Table 2). It could be explained as follows: the greater the chelate ring tension, the higher $\nu_{\text{C=O}}$. The carbonyl group is sp^2 hybridized (120°). Bending the $\text{C-H}\cdots\text{O}$ toward each other from 116.63° in 20 to 112.91° in 22 results in changes in carbonyl carbon hybridization that leads to a strengthening of the C=O bond and weakening of the adjacent C-C bond.

5. Conclusions

Pyrrolo[1,2-a]pyrazin-1(2H)-ones as an important class of natural organic compounds were analyzed here. The emphasis was put on structures of these species and on factors which determine their unique properties and play a crucial role in numerous reactions, also those which are important in ecology.

For the pyrrolopyrazinone derivatives analyzed here, formation of the intramolecular $\text{C-H}\cdots\text{O}$ hydrogen bond is observed. In general, geometrical and NBO criteria confirm the existence of such interactions for all systems since the $\text{H}\cdots\text{O}$ distances for all of them are shorter than the corresponding sum of hydrogen and oxygen van der Waals radii

as well as for all species in which $n_{\text{O}} \rightarrow \sigma_{\text{C-H}}^*$ orbital-orbital overlap is observed with the corresponding interaction energy of 1.19–2.87 kcal/mol. However, for certain species (those with the $R_2 = \text{CH}_2\text{Cl}$ substituent and some of the systems where $R_2 = \text{CH}_3$), the QTAIM approach does not detect the existence of the hydrogen bond; $\text{H}\cdots\text{O}$ bond paths are not observed for these systems. It is seen that the substitution of the hydrogen atoms by chlorine atoms enhances the strength of the hydrogen bond; the approximate strength order of the hydrogen bond is observed here according to the following types of R_2 groups: $\text{CHCl}_2 > \text{CH}_2\text{Cl} > \text{CH}_3$.

The changes observed in the H-bonding can be due to the steric repulsion between oxygen and chlorine atoms. The presence of H-bond depends on the geometrical arrangement of the oxygen and hydrogen atoms determined by its repulsion.

The aromaticity changes are discussed here in terms of the HOMA index and its EN and GEO components. The shortest $\text{C-H}\cdots\text{O}=\text{C}$ contact is related to a higher $\nu_{\text{C=O}}$ value.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Calculations were carried out in the Warsaw Supercomputer Center (ICM) (G53-7).

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