Can 2-acylpyrroles form an intramolecular hydrogen bond?

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The formation of intramolecular hydrogen bonding by certain N-substituted 2-acylpyrroles has been demonstrated by B3LYP/aug-cc-pVDZ calculations, the quantum theory of atoms in molecules, and the natural bond orbital method.

Total electron densities $\rho_{\text{EBP}}$ at the bond critical point of the H⋯O bond were applied to analyze the strength of these interactions. The relations between quantum theory of atoms in molecules, carbonyl stretching vibrational modes $\nu_{\text{C}=\text{O}}$, and natural bond orbital parameters associated with the formation of the C–H⋯O interaction have been established. The short contacts were found experimentally in the crystal structure of a new 2-acylpyrrole derivative 5-chloro-2-oxopentyl-1-(5-chloro-2-oxopentyl)pyrrolo-2-carboxylate. The influence of 2- and N-substitution of 2-acylpyrroles on C–H⋯O interaction energy is discussed. It was found that the methylene group may act as a proton donor leading to a red-shift or blue-shift phenomenon of the $\nu_{\text{C}=\text{H}}$ stretching mode. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: DFT calculations; intramolecular hydrogen bonds; IR spectroscopy; NBO; QTAIM; 2-acylpyrroles

INTRODUCTION

Certain 2-acylpyrroles have been investigated in the last decades to acquire an insight into the nature of intermolecular hydrogen bonds (HBs). For these systems presented in Scheme 1, R1 = H and R2 = OH, OCH\textsubscript{3}, NH\textsubscript{2}, NHCH\textsubscript{3}, N(CH\textsubscript{3})\textsubscript{2}, CCl\textsubscript{3}, CHCl\textsubscript{2}, CH\textsubscript{2}Cl were taken into account. Formation of dimeric species connected by two N–H⋯O=C intermolecular HBs was observed.\textsuperscript{1}

The intermolecular HB interaction between two molecules of pyrrole-2-carbaldehyde derivatives has been studied by means of spectroscopic, diffraction, and theoretical methods including the Bader theory of atoms in molecules.\textsuperscript{2-5} The calculated HB energy for these dimers is comparable with the HB energy found for many typical acid dimers.\textsuperscript{6} Its value is $–6.90$, $–6.23$, $–6.45$, $–6.63$, $–5.26$, and $–5.90$ kcal/mol for a single N–H⋯O interaction within the pyrrol-2-carbaldehyde dimer,\textsuperscript{7} pyrrol-2-yl methyl ketone dimer, pyrrol-2-yl dichloromethyl ketone dimer, pyrrol-2-yl trichloromethyl ketone,\textsuperscript{8} and pyrrole-2-carboxylic acid dimers,\textsuperscript{9} respectively. The introduction of a –CH\textsubscript{3} group (R1 = CH\textsubscript{3}) into position N1 results in a loss of the proton-donating N–H group.

In the earlier study, the possibility of formation of an intramolecular HB C = O ⋯ H–N within pyrrole-2-carbaldehyde was suggested.\textsuperscript{8} This belief was based on infrared (IR) spectroscopic data analysis of the carbonyl absorption band. It was suggested\textsuperscript{8} that an intramolecular HB forms in pyrrole-2-carbaldehyde, while such interaction does not exist for N-methylpyrrole-2-carbaldehyde.\textsuperscript{9} These results inspired us to undertake a theoretical study of intramolecular HBs, such as N–H⋯O=C or C–H⋯O=C, within 2-acylpyrrole systems.

In most cases, X–H⋯Y HB interactions involve proton donor (X–H) and proton-acceptor groups (Y). Early works report that for such X–H⋯Y interactions, X and Y should be electronegative atoms. Currently, the scientific community has accepted the existence of so-called unconventional (or weak) HBs with X being carbon atoms.\textsuperscript{10} These interactions involve a C–H and C=O group of one molecule and form a short C–H⋯Y contact.\textsuperscript{11} A major part of this class of non-conventional HBs is C–H⋯O bonds.\textsuperscript{12}

In the 1990s, weak HBs were recognized as an important factor determining the stability of many biological systems.\textsuperscript{13,14} In molecular crystals, C–H⋯O non-conventional H-bonds are the most common intermolecular interactions.\textsuperscript{15} Recently, the existence of unconventional HB C–H⋯O in the crystal structure of 1-methylpyrrol-2-yl trichloromethyl ketone has also been reported.\textsuperscript{16} For this compound, there is only one typical proton accepting C=O group, and there are no typical proton donors. In this case, the C–H group of the pyrrole ring acts as the proton donor. For some C–H⋯Y systems, there is no typical elongation of the proton-donating bond, but a decrease of the C–H bond length occurs.\textsuperscript{17} This phenomenon is called blue-shifting HBs because the proton-stretching vibrational mode $\nu_{\text{C}=\text{H}}$ is upshifted to higher wavenumbers compared with that in the non-bonded moiety.\textsuperscript{18,19}

It is noted that not all short contacts have HB properties. Based on Pauling’s definition of the bond,\textsuperscript{20} scientists have proposed that a short contact must be energetically attractive to be regarded as a bond. For this reason, the criteria used for establishing an X–H⋯Y attractive interaction include the following: force involved in the formation of an HB, geometrical, spectroscopic, and energetic parameters associated with the formation of the HB. According to latest definition of H-bonds, based on International Union of Pure and Applied...
The QTAIM is a useful tool to identify HBs. Based on topological points (BCPs) between H and Y atoms. Many studies show that a bond path connecting H and Y and a bond critical point; BCP, bond critical point because analysis of the electron density topology of HB system (QTAIM) has been widely used to analyze HB interactions, dimers, where $R_1 = H$ and $R_2 = H$, OH, OCH$_3$, CHCl$_3$, CCl$_3$, NH$_2$, NHCH$_3$, N(CH$_3$)$_2$.

Chemistry recommendations, the evidence for HB formation may be determined by theoretical and experimental methods. Recently, the quantum theory of atoms in molecules (QTAIM) has been widely used to analyze HB interactions, because analysis of the electron density topology of HB system shows a bond path connecting H and Y atoms. Many studies show that the QTAIM is a useful tool to identify HBs. Based on topological features of the electron density of an X·H·⋯Y contact, the (3, –1) BCP occurs. Electron density ($\rho_{BCP}$) and the Laplacian of electron density at the BCP is of the order of 0.01 a.u. or less, and $\nabla^2 \rho_{BCP}$ is positive. Electron density at the H·⋯Y BCP is also an indicator of HB strength because correlations between this value and the other descriptors of an HB interaction have been found.

To acquire better insight into a nature of the intramolecular interactions within 2-acylpyrrole molecules (1–20), their electronic structure were also characterized by natural bond orbital (NBO)-based charge transfer descriptors such as perturbative electron energy lowering $\Delta E_{\text{P}} \rightarrow \sigma^*$. The main goal of this work was to discuss whether QTAIM topological parameters in connection with NBO analysis could be an effective tool for the recognition of an intramolecular interaction within a set of 2-acylpyrroles (Scheme 2). The usefulness of IR data as descriptors of the intramolecular HB in a six-membered chelate ring within 2-acylpyrroles was discussed. The following theoretical methods were applied: DFT B3LYP/aug-cc-pVDZ calculations, QTAIM theory, and NBO analysis.

To the best of our knowledge, neither NBO nor topological data of intramolecular interactions within 2-acylpyrroles (1–20) have been calculated or discussed earlier.

### Computational Details

The calculations were performed with the Gaussian 09 (Gaussian, Inc.; Wallingford, CT, USA.) sets of codes. The geometries of the investigated samples (1–20) were fully optimized using aug-cc-pVDZ Dunning’s correlated consistent basis set and B3LYP functional. The results of optimization correspond to energy minima because no imaginary frequencies were detected.

In this study, intramolecular HB energy calculations were performed with the Gaussian 09 set of codes on system 1. In the case of the intramolecular HB, where the acceptor and the donor are parts of the same molecule, binding energy for the analyzed complexes has been computed as a difference between the total energy of the sample 1 where short C-H·⋯O contact exists ($\angle_{\text{C-H-O}} = 108.8^\circ$, $d_{\text{H-O}} = 2.39\,\text{Å}$) and the energy of system 2 where ($\angle_{\text{C-H-O}} = 83.9^\circ$, $d_{\text{H-O}} = 2.82\,\text{Å}$).

Gaussian output wfn files were used as inputs for the AIM2000 program (based on Bader theory) to calculate topological properties of the systems under investigation. Hence, critical points were localized, and their properties, such as electron densities at BCPs ($\rho_{BCP}$), RCPs ($\rho_{RCP}$), and their Laplacians ($\nabla^2 \rho_{BCP}$), total electron energy density at BCP ($E_{BCP}$), potential electron energy density ($V_{BCP}$), and kinetic electron energy density ($G_{BCP}$), were analyzed. Particularly, for the C-H·⋯O HB, these are the characteristics of the H·⋯O BCP. It was reported previously that there are relationships between topological parameters at the critical point.
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 as high as the $G_{BCP}$ value, the Laplacian $\nabla^2 V_{BCP}$ is negative. A classification of HBs based on these criteria has been proposed by the Rozas group.[36] $\nabla^2 V_{BCP}$ and $H_{BCP}$ values are positive for weak and medium HB interactions, whereas $\nabla^2 V_{BCP}$ is positive and $H_{BCP}$ is negative for strong HB interactions. For a very strong HB interaction, both values are negative. Electron density at the C–H···O BCP may be considered a measure of HB strength, because some correlation between $\nabla^2 V_{BCP}$ and other HB descriptors has been found.

The NBO method[37] implemented within the GAUSSIAN 09 package was also applied to calculate $n_B \rightarrow \sigma^*_AH$ interaction energies. $n_B$ designates the lone pair of the B proton acceptor, and $\sigma^*_AH$ is an antibonding orbital of the A–H. The interaction energy was calculated as second-order perturbation theory energy according to the equation

$$E^{(2)}_{AB} = -\frac{F^2_{\sigma^*_AH}}{\varepsilon_{\sigma^*_AH} - \varepsilon_n}$$

where $F_{\sigma^*_AH}$ is the Fock matrix element, and $\varepsilon_{\sigma^*_AH} - \varepsilon_n$ is the orbital energy difference, and $n_B$ is the population of the donor $Y$ orbital. The $\Delta E = \varepsilon_{\sigma^*_AH} - \varepsilon_n$ measures the strength of the donor–acceptor interaction between NBOs orbitals. The $E^{(2)}_{AB}$ terms corresponding to HB interactions can be considered to be the charge transfer energy or stabilization energy associates with the delocalization.

Calculations of normal modes were performed with GAUSSIAN 09 using the aug-cc-pVQZ density basis set at the hybrid Hartree–Fock functional (B3LYP).[30] The initial geometry of the compound (1) was taken from X-ray data (Supplementary Information) and applied in the geometry optimization job. The result of optimization corresponds to the energy minimum because no imaginary frequencies were found. 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.[36]

**RESULTS AND DISCUSSION**

**Geometry of the C–H···O = C intramolecular contact**

The analyses are related to the C–H···O = C intramolecular contact within systems 1–20 shown in Scheme 2. Among these systems, there are C–H···O = C short contacts. They are usually classified as weak HBs. It is currently believed that weak H-bond donors should include hydrides of the main group elements such as C–H, P–H, or S–H.[39] The heteronuclear contact C–H···O = C was observed experimentally in the early 1960s. Since then, a number of short C–H···O contacts, with lengths below the sum of vDW radii, were observed experimentally.[40] The X-ray structure of molecule 1 provided another example of the existence of a short C–H···O contact in crystals (Supplementary Information). The acidity of the C–H bonds is an important factor that affects the formation of energetically attractive C–H···O bonding. Therefore, pyrrole molecules 3–20, which may be treated as a fragment of molecule 1, have been analyzed here for comparison purposes. We performed combined B3LYP, QTAIM, and NBO computations on a series of representative systems including pyrrole-2-carbaldehyde (5) and N-methylpyrrole-2-carbaldehyde, where $R_3 = H$ (6), and some systems, where $R_2 = H$ (7, 8, 9, 10, 15, 16, 20). For some systems, $R_3$ is an electron accepting group (7–11, 13, 15–20) or an electron donating group (12, 14).

In order to identify the most attractive contacts, we compared geometrical parameters of the intramolecular C–H···O contact with parameters of the other 2-acylpyrroles (3–20). A characteristic feature of these molecules is that they are composed of a proton-donating group – CH$_2$– or – CH$_3$ located at the same side of the pyrrole ring as the carbonyl group. Such a spatial structure allows the formation of short C–H···O contacts. Our previous studies show that related systems such as pyrrole-2-carbaldehyde (5) and its N-methyl derivative (6) are characterized by the lack of an intramolecular C–H···O interaction.[41] Therefore, these systems (5 and 6) were chosen as the reference species.

Table 1 presents some of the geometrical parameters calculated for the C–H···O contacts considered in this study. These are H···O and C–H distances $\delta_{H\cdots O}$, $\delta_{C\cdots H}$, and angles $\angle_{C\cdots H\cdots O}$. The H···O distance varies from 2.19 Å in 18 to 2.82 Å in 2. The normally accepted ranges of contact distances ($\delta_{C\cdots O}$) are 2.0–2.7 Å.[42] It is seen in Table 1 that H···O contact length for 4 and 5 is 2.67 and 2.63 Å and the N–H···O angle is 89.7° and 91.8°, respectively. For 6, the H···O distance is 2.72 Å, and $\angle_{C\cdots H\cdots O}$ is 90.4°. For systems 4 and 5, H···O distances are approximately close to the corresponding sum of van der Waals radii (2.68 Å)[43], whereas for 6, the H···O distance is slightly larger than the sum of van der Waals radii. Bond angle $\angle_{C\cdots H\cdots O}$ values for 4, 5, and 6 are barely within the range acceptable for intramolecular H-bonds.

The phenomenon that allows C–H···O to be considered as an attractive interaction is the acidity of the C–H group.[44] An effect of electron withdrawing substituents on C–H···O bond geometry was observed. It is observed that the introduction of a chlorine atom in the adjacent position to the hydride atom for 7 ($R_2 = H$; $R_3 = Cl$) led to a meaningful decrease of the H···O distance in comparison with pyrrole-2-carbaldehyde (6). It is 0.48 Å, which represents about 17.6% of the intramolecular H···O contact. – CH$_2$Cl introduced in 8 ($R_2 = H$, $R_3 = CH_2Cl$) in the adjacent position to the hydride atom, which was engaged in the intramolecular H-bond interaction, led to a decrease of the H···O distance in comparison with compound 6 as well. In this case, the H···O distance was reduced by 10% (0.27 Å). It means that for this system, with a chlorine atom located far from the proton-donating group, the H···O distance is the largest. It is observed that generally shorter H···O distances occur for more acidic C–H donors.

It is interesting to compare the H···O distance of these systems with $\delta_{C\cdots O}$ of other systems analyzed here (Table 1) such as 1, 3, 11, and 13, where $R_3 = COR$. That is, these compounds are ketones. For the latter species, the longest H···O distance is 2.49 Å (13), whereas $\angle_{C\cdots H\cdots O}$ is 97.5°. X-ray structure of molecule 1 provided evidence of the existence of a short C–H···O contact in crystals. The experimental H···O distance is 2.48 Å (Supplementary Information). It is very close to the calculated H···O distance of 2.39 Å for 1.

For sample 1, C–H···O intramolecular interaction energy was also calculated. It was elucidated as the difference between the energy of systems 2 and 1. For system 2, the intramolecular H···O distance increased to 2.82 Å in molecule 1, and such geometry was frozen to obtain an open form, which did not fulfill the geometrical criteria of the existence of HBs. It is worth mentioning that the stable configuration was achieved for system 1 corresponding to 5-chloro-2-oxopentyl-1-(5-chloro-2-oxopentyl)
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<td>108.3</td>
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Table 1 presents selected QTAIM parameters, such as electron density at the BCPs $\rho_{BCP}$ (Scheme 3), the Laplacian of electron density at the BCP and $\nabla^2 \rho_{BCP}$, and electron density at the ring critical points $\rho_{RC}$, and their Laplacian $\nabla^2 \rho_{RC}$. The typical topological parameters at the $H\cdots Y$ BCPs are $0.002–0.34$ a.u. for electron density and $0.02–0.139$ a.u. for its Laplacian.\(^{11}\) It was pointed out that the electron density and its Laplacian correlate with H-bond energy.\(^{48}\) The increase of HB strength is connected with the increase of electron density at the BCP, with the increase of kinetic energy electron density at the BCP and the decrease of potential energy at the BCP.\(^{49}\) Recently, a relationship between QTAIM topological parameters of the HB and HB strength has been questioned for some intramolecular HBs.\(^{50}\)

The QTAIM analysis of electron densities at the $H\cdots O$ BCPs of the systems under consideration (1–20) showed that $\rho_{BCP}$ is in a range of 0.0109–0.0189 a.u. and the Laplacians vary from 0.0425 to 0.0586 a.u.

Electron density at the proton-acceptor BCPs ($\rho_{H\cdots O}$) is the highest for 18 ($R_2 = $OCH$_3$, $R_3 = $Cl), 17 ($R_2 = $OCH$_3$, $R_3 = $F), 7 ($R_2 = H$, $R_3 = $Cl), and 15 ($R_2 = H$, $R_3 = $F). 0.0189, 0.0179, 0.0173, and 0.0175 a.u., respectively. The Laplacians vary from 0.0476 to 0.0586 a.u., with the highest for 18 ($R_2 = $OCH$_3$, $R_3 = $Cl), 17 ($R_2 = $OCH$_3$, $R_3 = $F), 7 ($R_2 = H$, $R_3 = $Cl), and 15 ($R_2 = H$, $R_3 = $F).
and 0.0163 a.u., respectively). Fluorine and chlorine atoms, being R3 (Scheme 3), are electron-withdrawing substituents, which enhance the proton-donating ability of the adjacent CH group. It is in line with earlier findings of Schleyer\textsuperscript{[51]} who suggested that the strength of C–H⋯Y HBs strongly depends on the nature of the proton donor and increases when hydrogen atoms are replaced by electron-withdrawing groups.\textsuperscript{[52]} The most probable interpretation is that the carbon atom of the proton donor group – CH\textsubscript{2}Cl carries a more positive charge than the carbon atom of the methylene group (–CH\textsubscript{2}). As a result, a significant attraction between the carbon atom and the oxygen atom arises, in addition to the H⋯O interaction. This is also supported by the results of Table 1 with the H⋯O distances being the shortest for systems 7, 15, 17, and 18. Furthermore, for these systems, the $\angle$C–H⋯O bond angle is closest to 120° compared with that of the other species in Table 1.

It has been observed previously that the length of the HB is related to electron density at the BCP ($\rho_{\text{BCP}}$).\textsuperscript{[48]} For the samples 1, 7–11, 13, and 15–20, there is an exponential relationship between electron density at the H⋯O BCPs ($\rho_{\text{BCP}}$) and the O⋯H bond distance ($d_{O\cdots H}$). The correlation coefficient $R^2$ is 0.94. The change of topological properties of $\nabla^2 \rho_{\text{BCP}}$ along the change of the H-bond distance shows exponential dependence. It means that for the system under investigation, interaction strength should be a combination of attractive and repulsive forces, because Pauli repulsion increases exponentially with bond shortening (Fig. 1).

According to the latest studies on HB description, HB strength is related to electron density at the BCP ($\rho_{\text{BCP}}$)\textsuperscript{[49,53]} and the Laplacian of charge density at BCP ($\nabla^2 \rho_{\text{BCP}}$)\textsuperscript{[54]} It is noted that the Laplacian ($\nabla^2 \rho_{\text{BCP}}$) of electron density is a sensitive probe for identifying spatial changes of electron concentrations. Some sophisticated classifications of bond types are based on the Laplacian and total energy density at BCPs.\textsuperscript{[54]} It is seen that for systems analyzed here, $\nabla^2 \rho_{\text{BCP}}$ is positive, which means that HBs could be classified as weak. Furthermore, all $\nabla^2 \rho_{\text{BCP}}$ values are positive, which also indicates that such interactions are rather weak. For the highest $\nabla^2 \rho_{\text{BCP}}$ value of 0.00586 a.u., $\nabla^2 \rho_{\text{BCP}}$ is 0.00042 a.u., while for the lowest $\nabla^2 \rho_{\text{BCP}}$ value of 0.0425 a.u., $\nabla^2 \rho_{\text{BCP}}$ is 0.00127 a.u.

Table 1 also presents the IR frequencies of the carbonyl group, $\nu_{\text{C=O}}$ which may be also treated as an indicator of the formation of HBs. According to current knowledge, conventional H-bonds X–H⋯Y include the bonds formed by main-group elements such as N, O, F, Cl, and Br, with electronegativity higher than 3.00. On the other hand, weak H-bonds or unconventional H-bonds indicate a group of bonds formed by a non-conventional proton-donating group. Such a bond is characterized by low electronegativity of the donor or acceptor or both. Weak H-bond donors should include hydrides of the main-group elements, such as C–H, P–H, and Si–H. A non-conventional proton donor C–H may yield C–H⋯O bonds.

Spectroscopically, H-bond formation heavily affects the stretching band of the X–H bond by red shifting its frequency, $\nu_{\text{X–H}}$, as well as by small red shifting of the stretching vibrational mode of the proton-accepting center (for instance the C=O group). Searching for a suitable method for HB detection, a frequency shift of the carbonyl stretching band was proposed for consideration. Carbonyl compounds are capable of forming internal HBs, and for such a feature, carbonyl frequency is shifted much more significantly than for intermolecular interactions. Current computational studies revealed that the strength of C–H⋯Y interactions and $\nu_{\text{C–H}}$ stretching modes depends on the nature of the proton donor and increases when the carbon atom is connected with electron withdrawing groups.\textsuperscript{[55]} For some categories of molecular systems, the C–H⋯O bond length decreases in length by 0.006 Å, and for 8, 15, and 16, C–H bond length decreases in length by 0.002, 0.004, and 0.001 Å compared with C–H bond length of N-methylpyrrole-2-carbaldehyde (6).

Interestingly, the frequency of the C=O stretching mode of the systems under investigation for which R2 = H ranges from 1666 cm$^{-1}$ in N-methylpyrrole-2-carbaldehyde (6) without intramolecular C–H⋯O interactions to 1650 cm$^{-1}$ for system 10. Thus, the red shift of C=O frequency is observed for systems 8, 9, 10, and 16. There are some exceptions such as 7, 15, and 20 for which R2 = Cl, R3 = F, and R3 = COCl, respectively. For these systems, the C=O stretching mode was upshifted to

![Scheme 3. Molecular graphs (representation of bonding interactions) of systems analyzed in this study.](image-url)

**Figure 1.** Exponential correlation between electron density at the H-bond critical points $\rho_{\text{BCP}}$ (in atomic unit) and the H⋯O distance (in Ångstrom) calculated at the B3LYP/ aug-cc-pVDZ level.
The frequency of the C=O stretching mode of systems 1, 2, 11, 12, 13, 14, 17, 18, and 19, for which R2=OR, ranges from 1673 cm\(^{-1}\) in system 2 to 1687 and 1684 cm\(^{-1}\) for systems 17 and 18. It means that carbonyl frequency of systems 17 and 18 is significantly blue-shifted compared with system 2.

Bearing in mind that the HB interaction affects the vibrational mode of the proton-donating group, such as C=H, and the proton accepting group, such as C=O, and the fact that the HB interaction is connected with electron density at the BCP, a correlation between total electron energy density \(\rho_{BCP}\) at the H⋯O BCP and the stretching frequency of the carbonyl group, \(\nu_{C=O}\), is proposed. Figure 2 reveals the relationship between the \(\rho_{BCP}\) value at the C-H⋯O BCP and the frequency of stretching vibration of the accepting center (C=O). This is linear correlation, and the correlation coefficient, \(R^2\), is 0.918 (Fig. 2). Series represents compounds 1, 11, 13, 17, 18, and 19, where R2=O(CH3)(CO)R; R3=(CO)R. Systems 7 and 15 were excluded because of shortening of the C9-H8 bonds, which occurs for these systems. This effect is related to the attractive interaction that involves rearrangement of electronic density distribution within the systems. Upon formation of an HB, charge transfer occurs between the proton donor and the proton acceptor. Electron density flows from lone electron pairs of proton acceptor B to the \(\sigma^*\) antibonding molecular orbital of proton donor A–H. This causes weakening of the A–H bond, its elongation, and concomitant red shifting of the v(A–H) stretching vibrational mode. Systems 7 and 15 belong to a rather strong C–H⋯X class of unconventional HBs. The class includes, for instance, F=C–H⋯O(CH3)2 and also FH2C–H⋯OH2. For such systems, C–H bond length undergoes compression, and its stretching vibrational mode \(\nu_{C=H}\) undergoes a blue shift with respect to the non-bonded system.

Considering the results from Table 1, it seems that \(\rho_{BCP}\) decreases with increased electron density at the H⋯O BCP. It means that the greater \(\rho_{BCP}\), the lower \(\nu_{C=O}\). The data from Table 1 also reveal that the lower value of \(\rho_{BCP}\) at the H⋯O BCP, the higher value of \(\nu_{C=O}\) frequency. This phenomenon is understandable as it is believed that a larger red shift corresponds to a stronger H-bond interaction. In consequence, it seems that \(\rho_{BCP}\) is reversely proportional to \(\nu_{C=O}\).

Furthermore, \(\Delta\nu_{C=H}\) is negligible for systems 1, 11, 13, and 19 for which R2=OR; R3=(CO)R. \(\Delta\nu_{C=H}\) denotes the difference between the frequency of stretching vibration of the C–H group involved in the HB interaction and \(\nu_{C=H}\) of system 2, which does not fulfill the geometrical criteria for the existence of HBs. Similarly, \(\Delta\nu_{C=O}\) is 5, 1, and 3 cm\(^{-1}\), for systems 1, 11, and 13, respectively. \(\Delta\nu_{C=O}\) denotes the modulus of difference between the frequency of stretching vibration of the C=O group involved in the HB interaction and \(\nu_{C=O}\) of system 2.

For systems 8 and 9, \(\Delta\nu_{C=O}\) is 2 and 6 cm\(^{-1}\), respectively. \(\Delta\nu_{C=O}\) denotes the difference between the frequency of stretching vibration of the C=O group involved in the HB interaction and \(\nu_{C=O}\) of model system 6. For system 8, \(\rho_{BCP}\) is 0.00127 a.u., whereas for system 9, it is 0.00106 a.u. Similarly, the Laplacian of electron density at the ring critical point \(\nabla^2\rho_{BCP}\) is 0.0491 and 0.0555 for 8 and 9, respectively. It means that topological parameters are in line with spectroscopic parameters \(\Delta\nu_{C=O}\) (Table 1). Geometrical parameters, such as the H⋯O intramolecular bond distance, are also in line with the \(\rho_{BCP}\) and \(\nabla^2\rho_{BCP}\) values. It seems that QTAIM and geometrical and spectroscopic parameters of the C–H⋯O contact are useful tools for the analysis of intramolecular interaction within 2-acylpyrrole systems.

Quantum theory of atoms in molecule results show that there are C–H⋯O bond path and BCPs for samples 1, 7–11, 13, 15–20. To investigate intramolecular interactions in more detail, various descriptors originating from the NBO methodology were applied.

**Natural bond orbital analysis**

The NBO method is an effective tool that enhances the analysis of intramolecular and intermolecular interactions. There are two effects that are often attributed to A–H⋯B HB formation: a hyperconjugative effect of X–H bond weakening and rehybridization-promoted A–H bond strengthening. The hyperconjugative effect is related to electron charge transfer from the lone pair at the donor (Y) into the antibonding \(\sigma^*\) orbital of the A–H bond. The interaction between lone pair electrons and antibonding orbitals corresponds to the deviation of the molecule from the Lewis structure. The \(\sigma^*_{XY}\) terms corresponding to HB interactions can be considered charge transfer energy or stabilization energy associated with the delocalization.

Natural bond orbital analysis was performed on molecules 1–20 for the quantitative analysis of the intramolecular delocalization of electron densities within the molecules. Table 2 presents NBO parameters for molecules considered in this study. Stabilization energy \(E_{\sigma}^{(2)}\) is expressed by Equation 1. The charge transfer contribution derives from the \(n_{O} \rightarrow \sigma^*_{C=H}\) orbital interaction. It follows from Scheme 4 and Table 2 that electron density is transferred from one lone pair LPI(2)07 to the antibonding BD\(^*\) (C9-H8) orbital, which results in intramolecular charge transfer causing stabilization of the systems. \(n_{O} \rightarrow \sigma^*_{C=H}\) stabilization energies \(E_{\sigma}^{(2)}\) range from 0.51 kcal/mol in system 14 to 2.27 kcal/mol in systems 7 and 18. The most intense transitions are observed for 7 and 18 as well as for 15 and 17. Data from Table 2 indicate that the hyperconjugative interaction of lone pair electrons with antibonding C–H orbitals is rather weak but those with polar substituent R3 exhibit stronger effects. For example, the \(n_{O} \rightarrow \sigma^*_{C=H}\) stabilization energy for 7 (R3=Cl) is 2.27 kcal/mol. It is noted that \(\sigma^*_{C=H}\) antibonding orbital occupancy increases when R3 becomes a more polar group. As a consequence, the occupation (number) of \(\sigma^*_{C=H}\) antibonds increases...
| Table 2. Occupancy of natural bond orbitals and relationship with the C–H⋯O intramolecular contacts obtained at B3LYP/aug-cc-pVDZ |
|---|---|---|---|---|---|---|---|
| | Acceptor (A) C–H | Donor (B) C = O | $E^{(ii)}_q$ kcal/mol | $E_F-E_i$ [a.u.] | $F_{no}$ [a.u.] |
| | Type | Occupancy | Type | Occupancy | Hybrid (O) | $n_O \rightarrow \sigma^*_{CH}$ |
| 1 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01469 | LP(2) | 1.84202 | s(0.18%)p1.0(99.53%)d0.00(0.28%) | 0.73 | 0.65 | 0.020 |
| 2 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01499 | LP(2) | 1.84410 | s(0.09%)p1.0(99.61%)d0.00(0.31%) | 0.54 | 0.65 | 0.017 |
| 3 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01592 | LP(2) | 1.84451 | s(0.01%)p1.0(99.66%)d0.00(0.32%) | 0.53 | 0.66 | 0.017 |
| 4 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01023 | LP(2) | 1.84320 | s(0.01%)p1.0(99.66%)d0.00(0.33%) | 0.65 | 0.68 | 0.020 |
| 5 | R2 = H | LP(2) | 1.88787 | s(0.08%)p1.0(99.67%)d0.00(0.25%) | |
| 6 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01499 | LP(2) | 1.88598 | s(0.06%)p1.0(99.68%)d0.00(0.26%) | 0.64 | 0.67 | 0.019 |
| 7 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01912 | LP(2) | 1.88335 | s(0.14%)p1.0(99.59%)d0.00(0.27%) | 2.27 | 0.68 | 0.036 |
| 8 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01559 | LP(2) | 1.88757 | s(0.09%)p1.0(99.65%)d0.00(0.26%) | 0.53 | 0.65 | 0.017 |
| 9 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01455 | LP(2) | 1.88643 | s(0.10%)p1.0(99.64%)d0.00(0.26%) | 0.69 | 0.65 | 0.019 |
| 10 | R2 = H | BD$^*(1)$ | 0.01473 | LP(2) | 1.88411 | s(0.21%)p1.0(99.54%)d0.00(0.26%) | 0.73 | 0.64 | 0.020 |
| 11 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01272 | LP(2) | 1.83931 | s(0.08%)p1.0(99.60%)d0.00(0.32%) | 0.7 | 0.68 | 0.020 |
| 12 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01604 | LP(2) | 1.84378 | s(0.01%)p1.0(99.66%)d0.00(0.33%) | 0.55 | 0.69 | 0.018 |
| 13 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01200 | LP(2) | 1.84447 | s(0.05%)p1.0(99.64%)d0.00(0.31%) | 0.75 | 0.65 | 0.020 |
| 14 | R2 = OCH$_2$(CO)(CH$_2$)$_2$CH$_2$Cl | BD$^*(1)$ | 0.01599 | LP(2) | 1.84449 | s(0.02%)p1.0(99.66%)d0.00(0.32%) | 0.51 | 0.68 | 0.017 |
| 15 | R2 = H | BD$^*(1)$ | 0.02345 | LP(2) | 1.88393 | s(0.11%)p1.0(99.62%)d0.00(0.26%) | 1.95 | 0.68 | 0.033 |
| 16 | R2 = H | BD$^*(1)$ | 0.01408 | LP(2) | 1.88629 | s(0.10%)p1.0(99.64%)d0.00(0.27%) | 0.81 | 0.66 | 0.021 |
considerably upon complexation, for instance, from 0.0099 (6) to 0.0191 e (7), and the occupancy number of LP(2)O7 decreases compared with that of 6.

These results are consistent with AIM analysis. The highest values of electron density at the C–H⋯O BCPs ρBCP are noted for 7, 18, 15, and 17, respectively (Table 1). This is presumably due to the electron-acceptor effect of the substituent being a halogen atom. This can be explained through general electronegativity and bond polarity aspects. NBO strength of the C9–H8 acceptor decreases in the order

\[ σ^*\text{CICH} > σ^*\text{OCICICH} > σ^*\text{CHOCH} > σ^*\text{CH₂CICH} > σ^*\text{CH₂CH} > σ^*\text{CH₃(CH₂)₅CH} \]

which leads to greater stabilization of systems 7, 8, 9, 10, 15, 16, and 20, where R2 = H, compared with system 6. This is related to C–H bond weakening and rehybridization-promoted C–H bond strengthening. The rehybridization effect is in line with Bent’s rule. An atom maximizes its p-character and minimizes its s-character in such an orbital aimed toward the electronegative substituent.\(^{[59]}\)

Interestingly, the lone pair electrons localized on the oxygen atom (O7) in systems 3, 6, 12, and 14 point toward the C–H hydride atom as seen in Schemes 3c and 1b. Compared with 7 or 15, the \( n_O → σ^*_\text{C–H} \) orbitals are held much farther apart than those in samples 7 or 15 (\( \angle C–H–O = 124.8°, R3 = Cl, \) and \( \angle C–H–O = 123°, R3 = F \)). This reduces the overlap p-type lone pair on the carbonyl oxygen with an oppositely directed C–H antibond as shown in Scheme 4b.

Scheme 4 shows an overlap surface-rendered diagram for the interacting \( n_O → σ^*_\text{C–H} \) NBOs of 2-acylpyrroles 6, 15, and 20. It reveals propensity for C–H⋯O = C bonding for 15 and 20, whereas 6 exhibits weak \( n_O → σ^*_\text{C–H} \) interaction with the back side of the CH antibond.

In sample 7 (R3 = Cl), charge density transfer to the antibonding orbitals is greater compared with that in 9 (R3 = CHO), which leads to the reduction of C–H bonds followed by a blue shift of stretching vibrational frequencies (Table 2).

Using the data in Table 2, a relationship between stabilization energies due to \( n_O → σ^*_\text{C–H} \) orbital interactions \( E_{1σ}^{(2)} \), energy of electron density at the H⋯O BCPs was found. It has previously been found that that NBO energy \( E_{1σ}^{(2)} \), related to \( n_O → σ^*_\text{C–H} \) interaction strongly correlates with a topological parameter of electron density at the H⋯O BCP.\(^{[62,63]}\) Figure 3 shows the relationship between NBO energy \( E_{1σ}^{(2)} \) and electron density at the H⋯O BCP. The series represents systems 1, 11, 13, 17, 18, and 19, where R2 = OCH₂(CH₂)₅CH. The strength of this relation is expressed by the square of correlation coefficient \( R^2 \) of 0.99. It is noted that the R3 group is part of the proton-donating group. It was observed that electron-withdrawing groups R3, such as (CO)(CH₃)₂Cl, (CO)(CH₃)₂Cl, (CO)(CH₃)₂F, CHO, F, and Cl, increase stabilization energy. The R3 = Cl group induces the largest stabilization energy. The R3 = Cl group induces the largest stabilization energy. The R3 = Cl group induces the largest stabilization energy. The R3 = Cl group induces the largest stabilization energy. The R3 = Cl group induces the largest stabilization energy. The R3 = Cl group induces the largest stabilization energy. The R3 = Cl group induces the largest stabilization energy. The R3 = Cl group induces the largest stabilization energy.

The different behaviors of the C–H bond in a series of 2-acylpyrroles forming short intramolecular contacts were observed for samples where R3 is an alkyl group. The bonding characteristic investigated by QTAIM show that there is a bond path connecting atoms H8 and C9. Considering these results, the charge transfer effects on the C9 and H8 contact were...
intramolecular hydrogen bond within a set of 2-acylpyroles

For some 2-acylpyroles, the NBO stabilization energy of $n_O \rightarrow \sigma_{C-H}^*$ interaction and $\rho_{BCP}$ factor show that HB interactions between the overlapping p-type lone pair on the carbonyl oxygen and C–H antibond may exist. Taking into account only the geometrical and topological description of the C–H⋯O contact within 2-acylpyroles (1–20), it cannot be clearly determined whether 2-acylpyroles can form intramolecular HBs.

- Based on the topological description of the C–H⋯O BCP and the NBO stabilization energy of the $n_O \rightarrow \sigma_{C-H}^*$ interaction, it seems most likely that the C–H⋯O interaction has a HB character if the C–H⋯O angle is larger than 109°.

- A good linear correlation between QTAIM-based topological electron density at the H⋯O BCP $\rho_{BCP}$ and the NBO stabilization energy of $n_O \rightarrow \sigma_{C-H}^*$ interaction was found. The higher the $\rho_{BCP}$, the greater the $E_{XY}$.

- Based on the calculated stabilization energy of $n_O \rightarrow \sigma_{C-H}^*$ interaction, it seems that greater stabilization of the systems where $R_2 = H$ (7, 8, 9, 10, 15, 16, 20) compared with pyrrole-2-carbaldehyde results from C–H bond weakening and rehybridization-promoted C–H bond strengthening.

It was found that for samples 7 and 15, (R3 = Cl or F), the C–H bond is contracted causing a blue-shift effect.

C–H⋯O bond shortening and strengthening are reflected in the spectroscopic properties of the C=O accepting center. The higher value of $h_{BCP}$ at the H⋯O BCP, the lower value of $\nu_{C=O}$ frequency.

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