Spectroscopic and theoretical studies on the aromaticity of pyrrol-2-yl-carbonyl conformers

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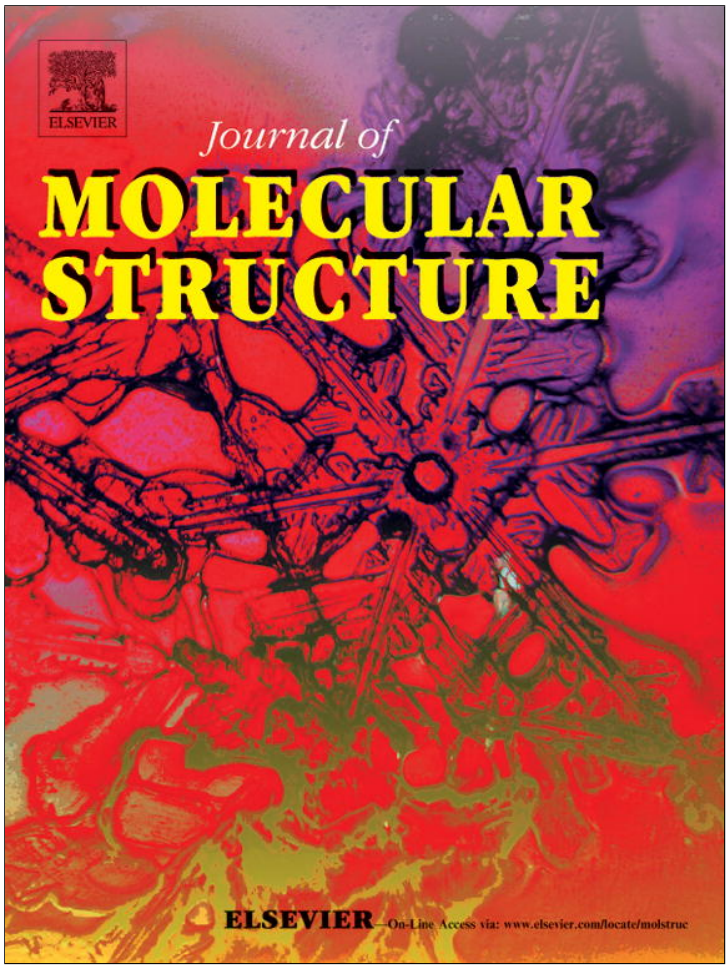

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Spectroscopic and theoretical studies on the aromaticity of pyrrol-2-yl-carbonyl conformers

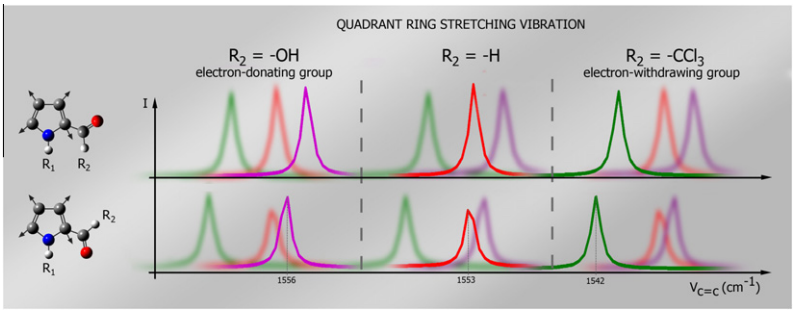
Alina T. Dubis *, Sławomir Wojtulewski, Karol Filipkowski

Institute of Chemistry, University of Białystok, Hurtowa 1, 15-399 Białystok, Poland

HIGHLIGHTS

- Pyrrol-2-yl carbonyl conformers; IR, NMR.
- Density functional theory (DFT).
- Harmonic Oscillator Model of Aromaticity (HOMA).
- Nucleus Independent Chemical Shift (NICS).
- Experimental measures of π-electron delocalization.

GRAPHICAL ABSTRACT



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ABSTRACT

The aromaticity of *s*-cis and *s*-trans pyrrol-2-yl carbonyl conformers was studied by FT-IR, ^{1}H NMR spectroscopy and DFT calculations at the B3LYP/6-311++G(d,p) level of theory. The Harmonic Oscillator Model of Aromaticity (HOMA) and Nucleus Independent Chemical Shift (NICS) indices were calculated to estimate π-electron delocalization in the pyrrole ring. The usefulness of infrared spectroscopy in the evaluation of the aromaticity of the homogeneous set of pyrroles is discussed. The influence of 2-substitution on different aspects of aromaticity and stability of the pyrrol-2-yl carbonyl conformers is also discussed. It is concluded that the substitution effect of the title pyrrole derivatives can be explained on the basis of theoretical and experimental measurements of π-electron delocalization, including IR data.

1. Introduction

Five-membered heterocycles are the most widespread and important building blocks of Nature's molecular structures and in synthetic chemistry. The pyrrole ring very often appears as a building element of many natural products such as heme [1], chlorophylls [2], and bioactive alkaloids [3–6]. These molecules take part in many biological processes in the human body, plants, animals and microorganisms. Among heterocyclic compounds, pyrrole alkaloids are a prominent class of bioactive substances [7]. They represent an example of the large variety of secondary metabolites which protect plants against herbivores [8,9]. Among them peramine [4] which is known to deter herbivorous insects by attacking their taste sensors [3] may have the most interesting properties. There are also some other fascinating examples of pyrrole alkaloids. Oroidin [10] and hymenidin [11] are marine alkaloids produced by see sponges which defend themselves from fish predation [12]. Pyrrole alkaloids are important for their ecological and chemotaxonomic considerations, and also for the number of interesting pharmacological activities [13]. Much research till now has been devoted to studying substituted pyrroles, because chemists use them as lead compounds for the synthesis of known plant antifeedants and development of a wide variety of new ones. There are almost 500 instances of organic structures

* Corresponding author. Tel.: +48 600 447 773.
E-mail addresses: alina@uwb.edu.pl (A.T. Dubis), slawoj@uwb.edu.pl (S. Wojtulewski), karolu77@gmail.com (K. Filipkowski).

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with a 2-substituted pyrrole core and almost 100 instances with the pyrrol-2-yl carbonyl core in the Cambridge Structural Database [14]. In spite of the vast range of biological activities provided by pyrrole compounds, we have undertaken research to extend theoretical and spectroscopic studies to cover some of the pyrrol-2-yl carbonyl compounds. Although many papers have been devoted to the properties of heterocyclic compounds such as pyrroles [15,16], there is still a lack of certain knowledge about the aromaticity of pyrrol-2-yl-carbonyl compounds.

Aromaticity has been widely used to predict stability and reactivity and to design new compounds. For this reason, we focused our attention on structural and spectroscopic properties in connection with the aromaticity of the pyrrol-2-yl carbonyl compounds. Aromaticity is one of the fundamental concepts of chemistry. This term was initially used to describe the unique stability of benzene and was very soon extended to five-membered heterocycles [17,18]. To determine whether a molecule is aromatic or not, we can apply the so-called Hückel rule [19,20]. Following this rule, a planar and cyclic molecule with a delocalized cloud of $4n + 2$ π-electrons (where n is a positive integer or zero) is aromatic. This rule is still an important criterion for aromaticity, but the remarkable development of theoretical methods in the last decades resulted in the application of the aromaticity concept even to non-planar systems [21]. It was recognized that molecules can also be stabilized by the cyclic delocalization of σ-electrons [22] as well as delocalization of d-electrons in transition metals [23].

Criteria for establishing the aromaticity of a compound have been divided [24,25] into four main categories: energetic [26], geometrical [27], magnetic [28] and reactivity, based on the chemical behavior of a system. Scientists have proposed several quantitative measures of aromaticity. On the basis of geometrical parameter considerations, Krygowski et al. [29–32] introduced the Harmonic Oscillator Model of Aromaticity (HOMA). There are several other indices of structural aromaticity: A_j index by Julg [33], SAI, I_A [34] and I_6 indices by Bird [35]. The magnetic criterion is probably the most widely used measure of electron delocalization. Among others, the Nucleus Independent Chemical Shift (NICS) index, introduced by Schleyer [36,25], has become the most popular magnetic factor of aromaticity. NICS is a theoretical parameter defined as a negative value of absolute magnetic shielding estimated in the arbitrarily chosen point of space, usually the geometric center of a given ring (NICS(0)) or 1 Å above the center of the ring (NICS(1)). It is worth noting that NICS indices are a measure of the diamagnetic ring current and are not a measure of ring stability. The more negative the NICS value, the more aromatic the ring according to the magnetic criterion. Spectroscopy also provides tools for predicting the aromatic nature of a compound. Some authors suggest applying ^{1}H NMR spectroscopy as a useful tool for determining aromaticity [37]. The NMR method can yield information on the relative aromaticity of compounds by measuring and comparing chemical shifts as experimental representation of a theoretical property of the molecule as a ring current. Chemical shifts might be correlated to the aromaticity of a system if the molecules to be compared have similar geometries [38,39]. In other words, the protons must be located in similar regions of the magnetic field. That means the molecules must have similar planarity and not be subjected to strong anisotropic or charge effects.

The aromaticity of several pyrroles has been studied by Cyrański [40] and Alkorta [42] using both the geometry-based aromaticity index (HOMA) and the magnetic-based (NICS) descriptor of aromaticity. The effect of substitution of N by S, O, and Se atoms has also been studied. Schleyer et al. [41] demonstrated the existence of linear relationships among the energetic, geometrical and magnetic criteria of aromaticity for a set of five-membered $(CH)_4X$ ring systems. In 1996, Bird [42] also showed good linear relationships

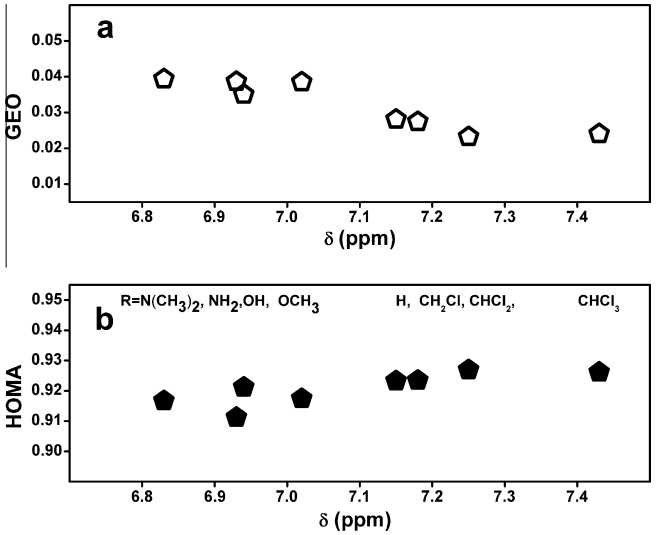


Fig. 1. Plot of (a) GEO *versus* experimental δ5-H chemical shift (R^2 = 0.83) and (b) HOMA *versus* δ5-H chemical shift for the *s*-cis conformer of 2-substituted pyrroles (**2**–**19**).

which exist between experimental diamagnetic susceptibility and resonance energy.

Although some studies have been devoted to 2-substituted pyrroles [43], the aromaticity of these pyrrole conformers has not received any attention yet. Early experimental work on the conformational preferences for a variety of 2-substituted heterocycles showed that the preferred conformation of these compounds in solution and solid state is the *s*-cis form [44–49].

The purpose of this study was to use the geometry-based HOMA index and magnetic-based NICS indices to discuss the aromaticity of *s*-cis and *s*-trans conformers of pyrrol-2-yl-carbonyl compounds (Fig. 1) in connection with the type of R_1 and R_2 substituent groups. The main goal of this work was to discuss the usefulness of the frequency of quadrant ring stretching vibration as a sensitive measure of π-electron delocalization of the pyrrole ring within the set of pyrrol-2-yl-carbonyl compounds. The following experimental and theoretical methods were applied: FT-IR spectroscopy, ^{1}H NMR and DFT calculations [50].

To the best of our knowledge, neither structural nor magnetic indices of aromaticity of pyrrol-2-yl-carbonyl conformers (**2**–**19** and **21**–**38**) were calculated earlier.

2. Experimental section

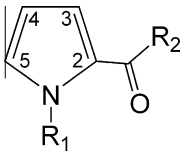
2.1. Spectroscopic methods

The FT-IR spectra were recorded using a Nicolet 6700 FTIR Advanced Gold Spectrometer equipped with KBr beam splitter and DLaTGS detector. Samples were measured in CCl_4, $CHCl_3$ solutions and as KBr pellets. A spectral resolution of 2 cm^{-1} was used. ^{1}H and ^{13}C NMR spectra were recorded using NMR Spectrometer Bruker Avance II 400 MHz using $CDCl_3$ or DMSO solution with $(CH_3)_4Si$ as an internal standard.

The studied compound were synthesized by authors of this paper. The synthetic procedures were described elsewhere [46,47,49,51].

3. Computational details

The calculations have been performed with the Gaussian 03 sets of codes [52]. The B3LYP hybrid density functional was applied



Scheme 1. Schematic representation of the structure of the pyrrol-2-yl carbonyl conformers where R_1 = —H or —CH_3; and R_2 = —H, —OH, —OCH_3, —NH_2, —$NHCH_3$, —$N(CH_3)_2$, —CH_2Cl, —$CHCl_2$, and —CCl_3.

which combines Becke's three-parameter nonlocal exchange potential with the nonlocal correlation functional of Lee, Yang and Parr [53]. The 6-311++G(d,p) Pople style basis set was used [54–57]. These calculations were performed on two, more stable, conformers. For *s*-cis conformer the C═O carbonyl group is at the same side as the N—H bond or N—CH_3 group of the pyrrole ring (Scheme 1), for *s*-trans conformer the C═O group is located on opposed side as the N—H group. The geometries of both conformers were fully optimized. The results of optimizations correspond to energy minima since no imaginary frequencies were found. The computed frequencies were multiplied by the uniform factor 0.98 to obtain a good estimate of the experimental results and to eliminate known systematic errors related to the anharmonicity. Aromaticity of the structures **1**–**38** was evaluated using two quantitative criteria: the geometry-based index HOMA [32], and nucleus-independent chemical shifts NICS [36,25]. The NICS indices were calculated at ring centers and 1 Å above the ring centers [58] at GIAO–B3LYP/6-311++G(d,p) level of theory using optimized geometries (see Supplementary data: Tables S1–S10).

3.1. Calculation of the HOMA, NICS(0), NICS(1), $NICS(0)_{zz}$ and $NICS(1)_{zz}$

The HOMA index represents aromaticity in relation to the optimal bond length concept. This index is expressed by the following equation:

$$\mathrm{HOMA} = 1 - \frac{\alpha}{n}\sum(R_{opt} - R_i)^2$$

where n is the number of bonds taken into account, α is an empirical constant chosen to give HOMA = 0 for a non-aromatic system and HOMA = 1 for one with all bonds equal to the optimal value R_{opt}, R_i is individual bond length [30,32,59].

The HOMA index can also be depicted as a linear combination of EN and GEO terms. These terms describe the decreasing aromaticity degree due to a decrease of resonance energy and an increase of bond length alternation, respectively. This leads to formula:

$$\mathrm{HOMA} = 1 - \mathrm{EN} - \mathrm{GEO}$$

where $\mathrm{EN} = \alpha(R_{opt} - R_{av})^2$ and $\mathrm{GEO} = \frac{\alpha}{n}\sum(R_{av} - R_i)^2$.

The HOMA index has a value between 1, for entirely aromatic molecules, and 0 for non-aromatic systems. When the value of the HOMA index is less than zero the structure is anti-aromatic. Recently, the Pauling bond number and virtual CC and CN bond lengths have been applied to the aromaticity index HOMA. It allows separation of HOMA into the energetic and geometric contributions for the heterocyclic π-electron systems [32]. The expression for the HOMA term is a follows:

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

where N is the number of bonds taken into calculation, R_{av} is an averaged bond length $R_{av} = \frac{1}{n}\sum_{i=1}^{n} R_i$, and R_i is the virtual bond length calculated from the Pauling bond number [32] $n_1 = exp^{\frac{R(1)-R(n)}{c}}$ according to general formula:

$$R_n = 1.467 - 0.1702\ln(n)$$

The NICS(0) and NICS(1) values were calculated at ring centers and 1 Å above the ring centers [60] at GIAO–B3LYP/6-311++G(d,p) level of theory using computed geometries (Fig. 1). The NICS calculations were performed by placing the probe (Bq) at the center of the pyrrole ring and 1 Å above the ring centers [58]. The $NICS(0)_{zz}$ and $NICS(1)_{zz}$ were calculated using the component of the magnetic shift tensor in the z direction, perpendicular to the plane of the ring, for a dummy atom in the plane and 1 Å above the plane of the ring. The NICS index is a negative absolute magnetic shielding computed in the center of the ring, and it is a theoretical measure of diamagnetic ring current. According to the Schleyer magnetic model [36] the more negative the NICS value at ring center and the more downfield shifted the proton signals in experimental measurements, the more aromatic the ring.

4. Results and discussion

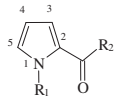
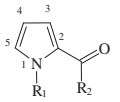
The molecular geometries of the most stable *s*-cis and *s*-trans pyrrol-2-carbonyl conformers (**2**–**19**, **21**–**38**), which differ in the spatial arrangement of the carbonyl group about the inverting single bond (C—C), are depicted with atom numbering as in Scheme 1. According to current knowledge [49,60], the *s*-cis conformer, in which the N—H and C═O groups are located at the same side of the moiety, is more stable than the *s*-trans conformer. Theoretical calculations and crystal structure data show that the carbonyl group adopts, in general, the same plane as the pyrrole ring [47,49]. It is worth noting that the flat arrangement of the carbonyl group in respect to the pyrrole ring favors the formation of centrosymmetric dimers with two equivalent N—H ⋯ O═C hydrogen bonds. Using spectroscopic techniques, supported by theoretical calculations and X-ray methods, the formation of hydrogen bonded dimers has been shown [60]. For some conformers (**27**–**32**) under investigation, the carbonyl group is twisted in respect to the pyrrole ring plane (see Supplementary data). The twist of the dihedral angle connecting the carbonyl C═O group and the N—C bond of the pyrrole ring ($\varphi_{N=C-C=O}$), is most likely related to the effect of the bulky substituent group (R_2).

As an extension of previous studies, we have considered in this paper a series of 2-substituted pyrrole conformers (**2**–**19**, **21**–**38**) to investigate the influence of substituent groups R_1 and R_2 on pyrrole π-electron delocalization.

4.1. HOMA as a measure of π-electron delocalization in pyrrole derivatives

The HOMA indices calculated for pyrrol-2-yl carbonyl compounds (**2**–**19**, **21**–**38**) and for unsubstituted parent moieties (**1**, **20**) are shown in Table 1. For pyrrole (**1**) and N-methylpyrrole (**20**) systems there is no substituent in the 2-position of the ring. The analysis of data from Table 1 leads to some new findings about pyrrole ring aromaticity expressed by HOMA. The aromaticity of 2-substituted pyrroles varies in a range of 0.863–0.927 HOMA units. The HOMA indexes of the N—H moieties (**2**–**18**) range from 0.886 to 0.927, whereas those of the N—CH_3 moieties (**21**–**38**) range from 0.863 to 0.914. It is noted that the HOMA of N—H pyrrole derivatives (**2**–**19**) are larger than those of the N-methylpyrrole moieties (**21**–**38**). For instance the HOMA values for *s*-cis aldehyde (**2**) and *s*-cis acid (**4**) are HOMA(**2**) = 0.923 and HOMA(**4**) = 0.921, respectively. This may be compared with the HOMA values for N-methyl *s*-cis aldehyde (**21**) and N-methyl *s*-cis acid (**23**) equal to HOMA(**21**) = 0.914 and HOMA(**23**) = 0.913. An analogous situation is observed for residual pairs of the *s*-cis pyrrole/N-methylpyrrole moieties (**6**/**25**; **8**/**27**; **10**/**29**; 12/31; 14/33; 16/35; and 18/37) or *s*-trans pyrrole/N-methylpyrrole moieties (**7**/**26**; **9**/**28**; **11**/**30**; 13/

Table 1
Selected structural parameters, of the pyrrole conformers (**1**–**38**), optimized at the B3LYP/6-311++(d,p) level of theory. HOMA indices and experimental and calculated ring stretching frequencies $\nu_{C=C}$.

Compounds			Bond length (Å)								Experimental $\nu_{C=C}$ (cm^{-1})	Calculated B3LYP/6-311(d,p) $\nu_{C=C}$ (cm^{-1})
			C2N1	C2C3	C3C4	C4C5	C5N1	HOMA	EN	GEO		
1	Pyrole		1.374	1.377	1.425	1.377	1.375	0.854	0.043	0.103	1532[b]	1540
2	R_1 = H, R_2 = H		1.378	1.392	1.411	1.388	1.359	0.923	0.049	0.027	1552[b]	1553
3		R_1 = H, R_2 = H	1.386	1.390	1.409	1.387	1.360	0.911	0.052	0.037		1554
4	R_1 = H, R_2 = OH		1.377	1.388	1.412	1.387	1.360	0.921	0.044	0.035	1555[c]	1556
5		R_1 = H, R_2 = OH	1.381	1.387	1.412	1.386	1.361	0.916	0.044	0.040		1561
6	R_1 = H, R_2 = OCH3		1.377	1.388	1.413	1.386	1.361	0.917	0.044	0.039	1554[b], 1557[c]	1555
7		R_1 = H, R_2 = OCH_3	1.380	1.386	1.413	1.385	1.362	0.913	0.044	0.043		1559
8	R_1 = H, R_2 = NH2		1.373	1.389	1.416	1.385	1.361	0.917	0.044	0.039	1552[c]	1550
9		R_1 = H, R_2 = NH_2	1.386	1.383	1.416	1.381	1.369	0.882	0.048	0.069		1560
10	R_1 = H, R_2 = $NHCH_3$		1.373	1.389	1.416	1.384	1.362	0.914	0.044	0.042		1558
11		R_1 = H, R_2 = $NHCH_3$	1.385	1.382	1.417	1.380	1.371	0.875	0.049	0.077		1548
12	R_1 = H, R_2 = $N(CH_3)_2$		1.377	1.393	1.416	1.383	1.359	0.911	0.050	0.039	1548[a], 1547[b]	1544
13		R_1 = H, R_2 = $N(CH_3)_2$	1.368	1.387	1.413	1.380	1.389	0.886	0.050	0.064		1560
14	R_1 = H, R_2 = CH_2Cl		1.378	1.393	1.411	1.387	1.358	0.923	0.049	0.027	1546[a], 1545[c]	1546
15		R_1 = H, R_2 = CH_2Cl	1.389	1.389	1.410	1.384	1.364	0.899	0.052	0.049		1552
16	R_1 = H, R_2 = CHCl2		1.382	1.395	1.407	1.390	1.355	0.927	0.050	0.023	1543[a], 1542[c]	1546
17		R_1 = H, R_2 = $CHCl_2$	1.386	1.394	1.406	1.388	1.358	0.921	0.050	0.029		1548
18	R_1 = H, R_2 = CCl_3		1.382	1.396	1.407	1.389	1.354	0.926	0.050	0.024	1538[a], 1539[b], 1538[c]	1542
19		R_1 = H, R_2 = CCl_3	1.385	1.395	1.405	1.388	1.358	0.922	0.049	0.029		1545
20	Methylpyrole		1.375	1.378	1.422	1.378	1.375	0.865	0.044	0.091		1517
21	R_1 = CH_3, R_2 = H		1.388	1.396	1.405	1.389	1.360	0.914	0.057	0.029	1528[b]	1531
22		R_1 = CH_3, R_2 = H	1.392	1.394	1.405	1.388	1.361	0.906	0.057	0.037		1533
23	R_1 = CH_3, R_2 = OH		1.388	1.392	1.406	1.387	1.361	0.913	0.051	0.036	1530[d], 1536[b]	1531
24		R_1 = CH_3, R_2 = OH	1.392	1.391	1.405	1.386	1.363	0.904	0.052	0.044		1536
25	R_1 = CH_3, R_2 = OCH_3		1.388	1.391	1.407	1.386	1.362	0.910	0.050	0.039	1532[b]	1531
26		R_1 = CH_3, R_2 = OCH_3	1.391	1.390	1.407	1.384	1.365	0.902	0.051	0.048		1537
27	R_1 = CH_3, R_2 = NH_2		1.386	1.393	1.408	1.383	1.364	0.908	0.051	0.041	1529[c]	1528
28		R_1 = CH_3, R_2 = NH_2	1.393	1.387	1.410	1.381	1.370	0.882	0.052	0.066		1537
29	R_1 = CH_3, R_2 = $NHCH_3$		1.384	1.391	1.410	1.382	1.365	0.908	0.048	0.044		1537
30		R_1 = CH_3, R_2 = $NHCH_3$	1.392	1.385	1.412	1.379	1.371	0.877	0.047	0.075		1542
31	R_1 = CH_3, R_2 = $N(CH_3)_2$		1.385	1.391	1.411	1.381	1.366	0.902	0.051	0.047	1537[a], 1536[b]	1529
32		R_1 = CH_3, R_2 = $N(CH_3)_2$	1.387	1.382	1.417	1.377	1.371	0.870	0.046	0.085		1542
33	R_1 = CH_3, R_2 = CH_2Cl		1.391	1.397	1.405	1.387	1.359	0.909	0.057	0.035	1527[a], 1522[c]	1526
34		R_1 = CH_3, R_2 = CH_2Cl	1.389	1.400	1.401	1.385	1.363	0.886	0.058	0.056		1527
35	R_1 = CH_3, R_2 = $CHCl_2$		1.395	1.400	1.400	1.389	1.356	0.905	0.059	0.036	1526[a], 1524[c]	1526
36		R_1 = CH_3, R_2 = $CHCl_2$	1.400	1.396	1.401	1.385	1.363	0.889	0.058	0.052		1527
37	R_1 = CH_3, R_2 = CCl_3		1.398	1.400	1.399	1.388	1.355	0.899	0.058	0.042	1524[a], 1522[c]	1526
38		R_1 = CH_3, R_2 = CCl_3	1.408	1.415	1.423	1.411	1.376	0.878	0.061	0.061		1522

[a] $CHCl_3$.
[b] CCl_4.
[c] KBr.

32, 15/34; 17/36; and 19/38) (Table 1). Moreover, it is worth noting that the HOMA aromaticity index for N-methylpyrrole (**20**) is larger than that calculated for unsubstituted pyrrole (**1**). This result is consistent with the earlier findings for pyrrole and N-methylpyrrole reported by Elguero [61]. Table 1 shows that the HOMA values for *s*-cis pyrrole moieties are higher than those of *s*-trans conformers. The HOMA for *s*-cis aldehyde (**2**) and *s*-cis acid (**4**) are HOMA(**2**) = 0.923 and HOMA(**4**) = 0.921, respectively, which may be compared with the HOMA values for *s*-trans aldehyde (**3**) and *s*-trans acid (**5**) equal to HOMA(**3**) = 0.911 and HOMA(**5**) = 0.916, respectively. Similarly, HOMA indices for N—CH_3 *s*-cis conformers are higher than those of N—CH_3 *s*-trans conformers (Table 1). For instance, the HOMA for N-methyl *s*-cis aldehyde (**21**) and *s*-cis acid (**23**) is HOMA(**21**) = 0.914 and HOMA(**23**) = 0.913, respectively, while that for N-methyl-s-trans aldehyde (**22**) and *s*-trans acid (**24**) is HOMA(**22**) = 0.906 and HOMA(**24**) = 0.904, respectively.

It is worth noting that the difference in HOMA between the highest and lowest HOMA values is: $\Delta HOMA_{NH}^{s\text{-}cis} = 0.016$, $\Delta HOMA_{NCH_3}^{s\text{-}cis} = 0.015$ units for *s*-cis forms, and $\Delta HOMA_{NH}^{s\text{-}trans} = 0.039$ units and $\Delta HOMA_{NCH_3}^{s\text{-}cis} = 0.039$ units for *s*-trans conformers. $\Delta HOMA_{NH}^{s\text{-}cis}$ was calculated from the equation: $\Delta HOMA_{NH}^{s\text{-}cis} = HOMA_{highest}^{s\text{-}cis} - HOMA_{lowest}^{s\text{-}cis}$. It is seen (Table 1) that the HOMA indices are twice as high scattered for *s*-trans as compared with *s*-cis conformers. It should be noted that the HOMA differences for the pair of conformers are very small, but there is a trend that HOMAs for *s*-cis conformers are higher than those for s-trans conformers. These observations may suggest that the relatively larger stability of the *s*-cis conformer in respect to its *s*-trans counterpart results from the more effective π-electron delocalization (slightly larger aromatic character).

Comparing the HOMA aromaticity of 2-substituted pyrroles with the aromaticity of an unsubstituted pyrrole ring, we note that electron-accepting substituents, such as R_2 = —$COCCl_3$, —$COCHCl_2$, —$COCH_2Cl$, or —CHO, play a role in the stabilization of the systems. The HOMA indices for 2-substituted moieties increase significantly in comparison with the aromaticity index of the unsubstituted pyrrole ring (**1**). For instance the HOMA of pyrrole (**1**) is 0.854, whereas that for a pyrrole ring substituted with formyl (**2**) or —$COCHCl_2$ groups (**16**) is 0.923 and 0.927, respectively. Moreover, the HOMA value for **16** could be compared with that calculated for the other conformers with electronegative chlorine atoms, such as **14** and **18**. These pyrrole derivatives have by HOMA values of

HOMA(**14**) = 0.923 and HOMA(**18**) = 0.926. This suggests that compounds **16** and **18** are more aromatic than pyrrole-2-carboxaldehyde (**2**). It is also worth noting that HOMA for amide moieties of HOMA(**8**) = 0.917, HOMA(**10**) = 0.914 and HOMA(**12**) = 0.911 was lower than that calculated for the aldehyde moiety, HOMA(**2**) = 0.927. Having considered these observations, it is concluded that the introduction of the formyl group (R_2 = H) into the pyrrole ring results in higher aromaticity in comparison with that of unsubstituted pyrrole (**1**). Replacing a hydrogen atom of the formyl group with the R_2 group, listed in the table, affects aromaticity expressed by HOMA. We observe that π-electron delocalization is greater for **8**, **10**, **12**, where R_2 is the electron-withdrawing substituent, compared with π-electron delocalization for **14**, **16**, **18** where R_2 is the electron-donating group. The result of calculation demonstrate that the presence of a substituent (R_2) does not lead to any considerable changes in degree of aromaticity of pyrrole ring.

Data from Table 1 shows that HOMAs for N—H pyrroles (**8**, **10** and **12**) differ slightly from those calculated for their N-methyl analogs (**14**, **16** and **18**). By contrast, HOMA values for *s*-cis conformers are higher as compared with those calculated for the *s*-trans conformer. For instance, HOMA for the *s*-cis amide moiety is HOMA(**8**) = 0.917, whereas it is 0.882 for the *s*-trans conformer (**9**). A similar trend is observed for N-methylpyrrole moieties (**20**–**38**). HOMA values are greater for *s*-cis than for *s*-trans conformers. For example, HOMA for the *s*-cis N-methylamide moiety is HOMA(**27**) = 0.908, whereas HOMA(**28**) = 0.882 for the *s*-trans isomer. It is concluded that the HOMA indices calculated for *s*-cis species are larger than those for s-trans conformers. However, it should be noted that these differences in HOMA for the pair of conformers are very small. Considering these results, we note that the spatial arrangement of the carbonyl group plays a role in π-electron delocalization over the pyrrole ring. It leads to higher pyrrole π-electron delocalization and stabilizes the planar *s*-cis conformation rather than the s-trans form.

It is also worth noting that the decomposition of the HOMA index gives two factors: energetic (EN) and geometric (GEO) contributions. The EN and GEO terms may be interpreted by dearomatization terms which describe the degrees of aromaticity due to a decrease in resonance energy and an increase in bond length alternation, respectively [32]. We might say that the EN factor is related to the elongation of bond length, whereas the GEO factor is related to bond length alternation. The EN and GEO terms obtained for the series of compounds are presented in Table 1. For the species under study the GEO term varies more than the EN term with the R_2 substituent. This was observed for aldehyde moieties (**2**, **3** or **21**, **22**) where R_2 = H. The EN term was more than twice as high as the GEO term. The introduction of the electron donating group with lone pairs on the atoms adjacent to the π-systems such as R_2 = —OH or —OCH_3 leads to an increase in the GEO contribution to HOMA. Thus, the calculated contribution of the EN factor to HOMA was approximately equal to the GEO part. That means that the bond length alternation of the pyrrole ring increased with the introduction of the —OH or —OCH_3 groups (**4**, **5**, **6**, and **7**). The HOMA aromaticity of amide derivatives (**8**–**13**): R_2 = —NH_2, —$NHCH_3$ or —$N(CH_3)_2$), unlike that of chlorine derivatives (**14**–**19**), decreased as a result of the increased GEO term. On the basis of these observations, we assume that the electron-donating substituents slightly destabilize the ring system, affecting the aromaticity of the pyrrole ring. The observed effect may be interpreted as follows: the substitution of the pyrrole ring in position 2 by a group such as —NH_2 leads to substantial double bond localization in the pyrrole ring and in consequence to a decrease in its aromaticity. In the case of chloroderivatives (**14**–**19** and **33**–**38**), an increase in aromaticity is mainly due to the EN contribution to HOMA. These findings are consistent as the elongation of bond length demands more energy than alternation [20].

4.2. NICS as a measure of π-electron delocalization in pyrrole derivatives

The ring current criterion is a useful diagnostic tool to investigate the aromaticity of heterocyclic rings. Absolute magnetic shielding at ring centers was calculated and nuclear independence chemical shift indices NICS(0), NICS(1), NICS $(0)_{zz}$ and NICS $(1)_{zz}$ are presented in Table 2. According to Schleyer's criterion the more negative the NICS value at the ring center the more aromatic the ring.

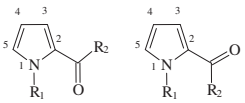
All the compounds under study are aromatic according to the NICS criterion. The NICS(0), NICS(1) for N—H pyrrole moieties (**2**–**18**) were in the range: −11.53 to −12.62 ppm for *s*-cis conformers, and −11.76 to −12.81 ppm for *s*-trans forms, whereas the NICS(0), NICS(1) values for N—CH_3 pyrroles (**20**–**38**) varied from −11.89 to −12.59 ppm for *s*-cis, and from −11.53 to −12.15 ppm for *s*-trans conformers. The values of NICS indices indicate that the aromatic ring current in substituted pyrrole conformers is very similar to that in unsubstituted pyrrole (**1**). Interestingly, the substitution of the pyrrole ring with a substituent such as —CHO (**2**, **3**, **21**, and **22**) resulted in less negative NICS(0) and NICS(1) values, as compared with the NICS(0) and NICS(1) values for the pyrrole ring (**1** and **20**).

It was also observed that the NICS index decreases while the HOMA index is reduced. In other words, the geometry-based HOMA index reveals the aromaticity of the pyrrole derivatives to be increased in respect to their parent pyrrole system (**1** and **20**), but the NICS indices to be decreased, with respect to the pyrrole systems (**1** and **20**) [62]. While the HOMA values, in line with chemical expectations, show that pyrrole (**1**) is less aromatic than its substituted conformers, NICS values give an indication of higher aromaticity of unsubstituted pyrrole (**1**). We state on the basis of these results that NICS provides an insight into azole aromaticity, but this picture is not fully consistent with the HOMA aromaticity model [63,64].

4.3. Spectroscopic ^{1}H NMR criteria of azole aromaticity

It is worth mentioning that experimental ^{1}H NMR spectroscopy is a useful tool for studying the ring current of heterocycles [39]. It has been shown that for a homogenic set of compounds, proton shielding reflects π-electron delocalization. Mitchell [38] suggests that using chemical shifts as a measure of ring currents to study aromaticity, the molecules to be compared need to be of similar geometry. One such system is the *s*-cis or the *s*-trans conformers of 2-sustituted pyrroles. There are some phenomena responsible for ^{1}H chemical shifts. Among them, the diamagnetic ring current shift [63] is considered of major importance for chemical shifts [65]. The protons of the aromatic ring experience a deshielding effect due to the aromatic ring current, which brings the chemical shift of the pyrrole protons to 6.35 and 6.87 ppm. It is noted that the proton signals of aromatic rings undergo a large downfield shift. According to the experimental ^{1}H NMR spectra of the azoles under study, there was downfield shifting of the 3-H and 5-H proton signals with respect to the proton shifts of unsubstituted pyrrole (**1**). It is seen in the data in Table 2 that electron-withdrawing substituents (R_2 = —CH_2Cl, —$CHCl_2$, —CCl_3) deshield and electron-releasing groups such as R_2 = —NH_2 shield the ring protons. It is also worth noticing that the 3-H and 5-H protons are more sensitive to ring current and electron density variation than the 4-H proton located farther from the carbonyl substituent with respect to 3-H and 5-H. Therefore the 3-H and 5-H signals are more downfield shifted than the 4-H signal. For the *s*-cis form of 2-substituted pyrroles (**2**, **4**, **6**, ..., **18**), a correlation between the ^{1}H chemical shift of the H5 pyrrole proton (δH5) and the GEO part of the HOMA index is observed. This relationship has been depicted in Fig. 1a

Table 2
NICS(0), NICS(1), NICS(0)$_{zz}$, NICS(1)$_{zz}$ indices and selected ^{1}H NMR proton chemical shifts δ_H (400 MHz; $CDCl_3$; Me_4Si) for **1**–**38**.

Compounds		NICS[a](0) (ppm)	NICS(1) (ppm)	NICS(0)$_{zz}$ (ppm)	NICS(1)$_{zz}$ (ppm)	δ(H3) (ppm)	δ(H4) (ppm)	δ(H5) (ppm)
1	Pyrole	−13.64	−10.12	−12.41	−31.00	6.87	6.35	
2	R_1 = H	−11.74	−9.66	−5.83	−27.24	7.01	6.37	7.18
3	R_1 = H	−12.29	−9.80	−7.48	−28.18			
4	R_1 = OH	−12.40	−9.85	−6.94	−27.71	6.72	6.12	6.94
5	R_1 = OH	−12.53	−9.78	−7.65	−27.92			
6	R_1 = OCH_3	−12.46	−9.67	−7.04	−27.62	6.95	6.31	7.02
7	R_1 = OCH_3	−12.46	−9.68	−7.29	−27.74			
8	R_1 = NH_2	−12.63	−9.74	−7.11	−28.01	6.56	6.06	6.80
9	R_1 = NH_2	−12.54	−10.47	−8.17	−27.66			
12	R_1 = $N(CH_3)_2$	−12.74	−10.45	−7.63	−27.83	6.59	6.26	6.93
13	R_1 = $N(CH_3)_2$	−12.72	−9.97	−8.50	−28.08			
14	R_1 = CH_2Cl	−12.06	−9.55	−5.63	−26.98	7.01	6.32	7.15
15	R_1 = CH_2Cl	−12.24	−9.68	−6.82	−27.18			
16	R_1 = $CHCl_2$	−11.59	−9.31	−4.47	−25.64	6.54	6.39	7.25
17	R_1 = $CHCl_2$	−11.76	−9.39	−5.58	−26.04			
18	R_1 = CCl_3	−11.53	−9.27	−4.01	−25.31	7.22	6.41	7.43
19	R_1 = CCl_3	−11.83	−9.26	−5.08	−25.62			
20	N-methylpyrrole	−12.87	−9.66	−9.42	−28.51	6.12	6.57	
21	R_1 = H	−12.40	−10.00	−7.34	−27.05	6.88	6.21	6.91
22	R_1 = H	−11.53	−9.22	−4.66	−25.56			
23	R_1 = OH	−12.43	−9.71	−6.53	−26.84	6.84	6.16	7.11
24	R_1 = OH	−11.99	−9.55	−5.79	−26.36			
25	R_1 = OCH_3	−12.49	−9.73	−6.41	−26.81	6.83	6.12	6.92
26	R_1 = OCH_3	−11.96	−9.46	−5.62	−26.26			
27	R_1 = NH_2	−12.74	−9.97	−7.06	−27.34	6.59	6.26	6.93
28	R_1 = NH_2	−12.10	−9.58	−5.88	−26.51			
31	R_1 = $N(CH_3)_2$	−12.59	−9.86	−7.10	−27.40	6.38	6.08	6.68
32	R_1 = $N(CH_3)_2$	−11.31	−12.27	−4.36	−24.86			
33	R_1 = CH_2Cl	−12.32	−9.80	−6.10	−26.59	6.91	6.18	7.01
34	R_1 = CH_2Cl	−13.54	−10.09	−6.82	−27.18			
35	R_1 = $CHCl_2$	−11.33	−9.18	−4.95	−25.32	6.59	6.23	7.14
36	R_1 = $CHCl_2$	−11.98	−9.51	−5.12	−25.10			
37	R_1 = CCl_3	−11.89	−9.46	−4.35	−27.46	6.98	6.21	7.52
38	R_1 = CCl_3	−10.77	−8.37	−5.51	−27.78			

[a] NICS(0) corresponds to NICS calculated at centers of corresponding rings, whereas NICS(1) is calculated at 1 Å above the ring.

(upper panel). The strength of this relation was expressed by the square of correlation coefficient R_2 of 0.83. There is another relationship between the 5-H chemical shift and the HOMA index which is represented by a plot in Fig. 1b (lower panel). This result suggests that there is an inter-correlation between ring geometry and pyrrole ring π-electron delocalization. Taking this observation into consideration we can assume that the π-electron delocalization of the homogenic set of 2-substituted pyrrole conformers may be evaluated on the basis of the 5-H chemical shifts [66,67].

4.4. IR spectroscopic criteria of azole aromaticity

Generally, the delocalization of π-electrons influences the properties of molecular species, among them reactivity, H-bonds, and spectroscopic properties [24,68]. The influence of π-electron delocalization on IR frequency has not been investigated to such an extent as for pyrrole ring vibrational frequencies of pyrrol-2-yl carbonyl conformers. To explain the influence of π-electron delocalization within pyrrole rings on the ring stretching mode, DFT calculations and experimental FT-IR measurements have been performed. Table 1 presents the theoretical and experimental data of vibrational modes of the pyrroles under study. It is clear that the medium intensity band in the range 1522–1555 cm^{-1} can be assigned to the ring stretching mode (C2–C3 and C4–C5). Earlier studies of spectroscopic properties of pyrrole moieties using PED analysis [46–49,69,70] show that the band is mainly due to so-called ring quadrant stretching vibration [71]. It is also noted that the frequency of this vibrational band is much influenced by the withdrawing capabilities of the substituent (R_2) connected to the carbonyl group (Table 1). For instance, a $\nu_{C=C}$ band of **2** was observed at 1552 cm^{-1} while a $\nu_{C=C}$ band of **14**, **16**, and **18** was observed at 1546, 1543, and 1538 cm^{-1}, respectively. In contrast, the absorption bands for **4**, **6**, **8**, and **12** compounds were observed at 1555, 1557, 1552, 1548 cm^{-1}, respectively. This means that the $\nu_{C=C}$ bands of **14**, **16**, and **18** were red shifted in comparison with the $\nu_{C=C}$ band of the aldehyde (**2**) moiety. The red shift (towards lower frequencies) of the $\nu_{C=C}$ band is most likely due to an increasing electron withdrawal capability of substituent groups R_2 (compounds **14**, **16**, and **18**), which results in the higher conjugation of the pyrrole π-electrons. These phenomena lead to an increase in ring aromaticity in comparison with the aromaticity of the parent ring moiety (**2**). The ring $\nu_{C=C}$ blue shift (towards higher frequency) is most likely due to the electron-donating capabilities of substituent groups R_2 such as R = —NH_2, —$NHCH_3$, and —$N(CH_3)_2$. This phenomenon leads to an increase in bond length alternation (Table 1) and to a decrease in the ring aromatic character in comparison with the aromaticity of unsubstituted pyrrole (**2**) [62,72].

Using the data in Table 1, a relationship between calculated quadrant ring stretching vibration $\nu_{C=C}$ and the HOMA index of aromaticity was found. Fig. 2a and b shows changes of the HOMA index of the *s*-trans and *s*-cis conformers (**2**–**19**) and the calculated ring frequencies (ν_{ring}) due to substitution. It was observed that electron-withdrawing substituents, such as —CH_2Cl, —$CHCl_2$, and —CCl_3, lead to an increase in HOMA indices [73]. The —CCl_3 group induces the largest HOMA increase, but R = —CH_2Cl, —$CHCl_2$ also

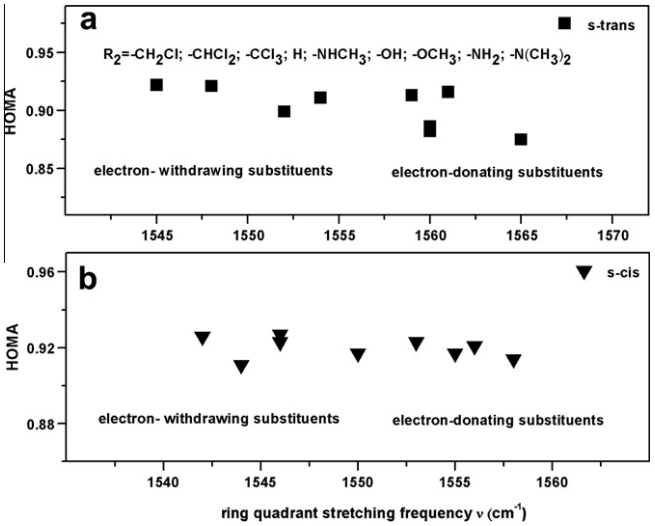


Fig. 2. Plot of (a) changes of the HOMA index and calculated ring frequencies ν_{ring} of the *s*-trans conformers (**3**, **5**, **7**, . . . , **19**) and (b) *s*-cis conformers (**2**, **4**, **6**, . . . , **18**) due to substitution.

Table 3
HOMA and NICS(1) indices for thiophene, pyrrole and furan and their ring stretching vibrations $\nu_{C=C}$ calculated at the B3LYP/6-311++(d,p) level of theory.

Compounds	HOMA[a]	NICS(1) [a]	Experimental[b] $\nu_{C=C}$ (cm^{-1})	Calculated[c] B3LYP/6-311(d,p) $\nu_{C=C}$ (cm^{-1})
Thiophene	0.891	−10.79	1506	1520
Furan	0.298	−9.36	1556	1552
Pyrrole	0.876	−10.60	1531	1540

[a] Values of HOMA and NICS(1) taken from Ref. [51].
[b] Vibrational frequencies taken from Ref. [55].
[c] The scaling factor of 0.98 was used.

make some contribution to HOMA aromaticity. An opposite effect was observed for substituent groups, such as R_2 = —$NHCH_3$, —$N(CH_3)_2$, —NH_2, —OH, and —OCH_3. HOMA aromaticity of the pyrrole rings decreased. The electron-donating capabilities of these substituents cause an increase in bond length alternation in the pyrrole ring (Table 1). The degree of ring bond alternation is generally considered a measure of the HOMA aromaticity of a compound. We believe that the variation in the quadrant stretching vibration ν_{ring} of the pyrrole ring is closely related to π-electron delocalization in the systems under consideration.

There is evidence in support of the hypothesis. According to results by Katricky [69], the quadrant ring stretching vibration ν_{ring} of five-membered heterocyclic rings, such as thiophene, pyrrole, and furan, occurs at 1506, 1531 and 1556 cm^{-1}, respectively. Furthermore, it has also been reported [68] that aromaticity measured by I_A [34] for thiophene, pyrrole and furan decreases in the series in the order given [72]. The calculated ring frequencies ν_{ring} for these heterocyclic rings are shown in Table 3. Ring stretching vibration is 1520, 1540, and 1552 cm^{-1} for thiophene, pyrrole, and furan, respectively. From these observations, the following hypothesis is proposed: the frequency of ring quadrant stretching ν_{ring} is related with the aromaticity of the five-membered rings as measured by HOMA. For more aromatic moieties lower frequencies ν_{ring} of ring stretching vibration are observed. This statement is also in line with our findings that there is a correlation with HOMA aromaticity and the frequency of the stretching vibration $\nu_{C=C}$ of the pyrrole ring of *s*-cis and *s*-trans pyrrol-2-yl carbonyl conformers. Taking this result into consideration, we state that π-electron delocalization in the pyrrol-2-yl-carbonyl conformers can be expressed in terms of the frequency of quadrant ring stretching vibration.

5. Conclusions

The effect of carbonyl substituents at 2-position on the aromaticity of the series of the *s*-cis and *s*-trans pyrrol-2-yl carbonyl conformers (**2**–**19** and **21**–**38**) was studied. The analysis was based on the following criteria: HOMA, NICS, ^{1}H NMR chemical shifts, and vibrational frequencies of the pyrrole ring. The following conclusions can be drawn from the experimental and theoretical studies: (i) the calculated HOMA indices proved the role of *s*-cis and *s*-trans conformations on π-electron delocalization; (ii) the HOMA index classified 2-substituted pyrroles according to the electron withdrawal capability of the R_2 substituent attached to the carbonyl group. The electron-donating substituent groups, such as R_2 = —$NHCH_3$, —$N(CH_3)_2$, —NH_2, —OH, and —OCH_3, cause a decrease in π-electron delocalization as pumping of π-electrons to pyrrole leads to increased bond length alternation. The electron-withdrawing groups, such as —CH_2Cl, —$CHCl_2$, and —CCl_3, cause an increase in π-electron delocalization in comparison with the parent pyrrole 2-carbaldehyde moiety (**2**); (iii) the vibrational frequency of the pyrrole ring may be used as a measure of π-electron delocalization over the pyrrole ring. The higher ν_{ring}, the lower the aromaticity expressed by HOMA of the pyrrole ring in all pyrrol-2-yl carbonyl conformers.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2013.02.030.

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