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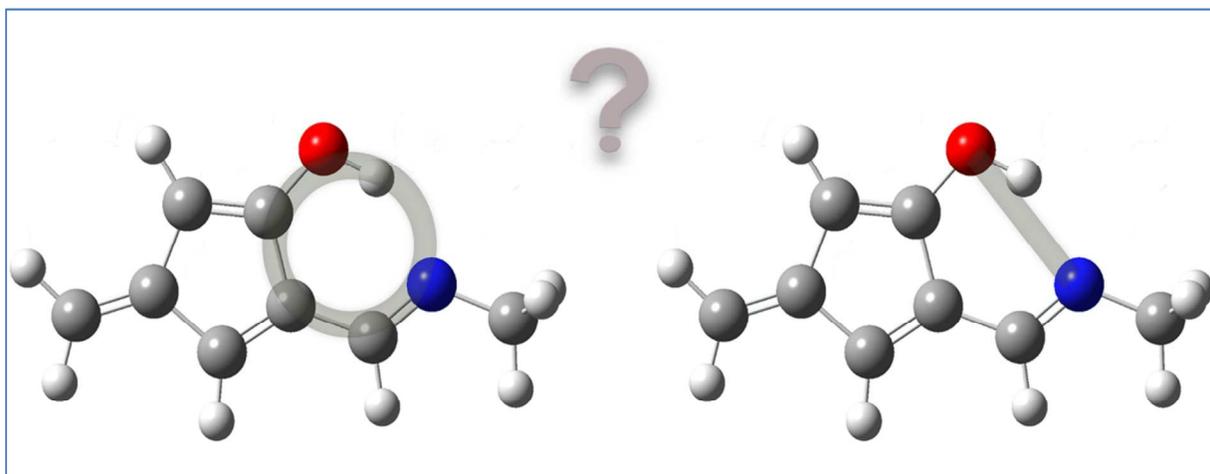
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Intramolecular hydrogen bond study in some schiff bases of fulvene; A challenge between RAHB concept and σ -skeleton influence

DFT, NBO and AIM analyses have been employed to investigate which one of resonance assisting or σ -skeleton of the system has more influence on making intramolecular hydrogen bond stronger.



ARTICLE

Intramolecular hydrogen bond study in some schiff bases of fulvene; A challenge between RAHB concept and σ -skeleton influence

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The characteristics of intramolecular hydrogen bonds (IHB) of some substituted derivatives of hydroxyl schiff base of fulvene have been investigated. For this purpose, the quantum mechanical calculations using density functional theory at the B3LYP/6-311++G(d,p) level of theory, also natural bond orbital and atoms in molecules analyses have been employed. Investigations on some aromaticity indicators (HOMA and pEDA) confirm that aromaticity and electron delocalization in the IHB quasi-ring of 3-hydroxy-2-((methylimino)methyl)fulvene derivatives increase by increasing the electron-donating character of substituents. Unexpectedly, the IHB strength decreases with increasing of π -electron delocalization in quasi-ring of these fulvene derivatives. According to this study, at least for this series of compounds, the resonance-assisted hydrogen bond (RAHB) concept could not explain the trend of the IHB strength. Alternatively, we present a good correlation between the IHB strength and the σ -skeleton of the studied molecules, which keeps the HB donor and the HB acceptor coplanar and closer to each other to form stronger IHB.

1. Introduction

Hydrogen bonds (HBs) play major roles in chemical and biochemical reactions¹⁻⁴. The hydrogen bond interaction may also play an important role in the crystal structures and in the geometry of many molecules engaged in this kind of interaction^{1, 5, 6}. The hydrogen bonds has general form of RA–H...BR', where A and B are the electronegative atoms, and, AH and B are proton-donor and proton-acceptor groups, respectively. In the case that R and R' are bonded covalently to each other, forming one molecule, the hydrogen bond is an intramolecular hydrogen bond (IHB)⁷.

Although this has been the subject of various challenges, Gilli et al. introduced a concept of resonance-assisted hydrogen bond (RAHB) in which the intramolecular hydrogen bond strength is attributed to the π -electron delocalization in the spacer between the proton-donating AH group and the proton-accepting B group⁸⁻¹². Based on many studies, it is assumed that there is a cooperative effect between the HB strength and the π -electron delocalization of the system in the region of IHB¹³⁻²¹. On the other hand, some studies suggested that the strength of the HB is due to the σ -skeleton of the molecule that keeps the HB donor and the HB acceptor coplanar and closer to each other²²⁻

²⁴. For instance, the results of NMR studies (chemical shifts and coupling constants) were examined, where some of these results showed that there is a significant correlation between the resonance effect and the strength of the IHB^{4, 25}, and according to some other results, the strength of IHB was explained as an effect of the σ -skeleton of the system^{26, 27}.

Schiff bases are very important compounds in organic and medicinal chemistry²⁸, while they could act as anticancer²⁹, antibacterial³⁰, antifungal³¹, antiviral³², and anti-parasitic³³ agents, in addition to their other performances³⁴. The aim of this study is exploration of the IHB nature of some derivatives of 3-hydroxy-2-((methylimino)methyl) fulvene (also named as 3-[(methylimino)methyl]-2-fulvenol and also as (E)-3-methylene-5-((methylimino)methyl) cyclopenta-1,4-dien-1-ol) (see Fig. 1).

Modern density functional theory, (DFT)^{35, 36}, natural bond orbital, NBO³⁷, and atoms in molecules, AIM³⁸, analyses have been employed in order to realize the correlation of the IHB strength with the π -electron resonance and the σ -skeleton of the molecule. The influences of various substitutions (in the methylene segment) with different electronic properties on the π -electron delocalization have been investigated. Also the

influences of the π -electron delocalization on the molecular structure and the strength of IHB have been studied.

2. Computational Methods

All calculations have been performed with the Gaussian 03W program package³⁹ and with the aid of GaussView 5.0 molecular visualization program⁴⁰. The modern DFT method at B3LYP level (a combination of the Becke's three-parameter (B3) hybrid exchange functional⁴¹ and Lee-Yang-Parr (LYP) nonlocal correlation functional⁴²) has been employed for all computations, using standard Pople-style 6-311++G(d,p) basis set. Vibrational frequency calculations were also performed at B3LYP/6-311++G(d,p) level of approximation in order to characterize the nature of stationary points.

As a geometry based indicator for local aromaticity, the HOMA (harmonic oscillator model of aromaticity) index was applied, which according to definition^{43, 44}, can be expressed by the following equation:

$$\text{HOMA} = 1 - \frac{1}{n} \sum_{i=1}^n \alpha_i (R_{\text{opt},i} - R_i)^2,$$

where n represents the total number of bonds in the molecule, and, α_i is a normalization constant fixed to give HOMA=0, for nonaromatic, and HOMA=1, for fully aromatic system. $R_{\text{opt},i}$ is the optimal aromatic bond length in a fully aromatic systems, while R_i is the computed bond length of the optimized structure. Geometrical parameters of the fulvene rings and quasi-rings (C–C, C–O and C–N bond lengths) were used to calculate the HOMA index (for C–C, C–O and C–N bonds: $\alpha_{\text{CC}}=257.7$, $\alpha_{\text{CO}}=157.38$, $\alpha_{\text{CN}}=93.52$, $R_{\text{opt,CC}}=1.388$ Å, $R_{\text{opt,CO}}=1.265$ Å and $R_{\text{opt,CN}}=1.334$ Å). The higher value of the HOMA index is related to the more π -electron delocalization of the system¹⁹.

As an electronic index of aromaticity, the pEDA (pi electron donor-acceptor) index^{20, 45}, calculated by employing the natural population analysis (NPA)⁴⁶, was used. In the case of the fulvene ring, pEDA is defined as a sum of occupations for perpendicular $2p$ natural atomic orbitals (NAO) on all five carbon atoms of the ring, subtracted by symbolic number of π -electrons on this ring (five), as shown in the following equation:

$$pEDA = \sum_{i=1}^5 \pi_i - 5$$

where π_i is occupation of the perpendicular $2p$ NAO of the i -th carbon atom of the ring. The NBO analysis was used in order to

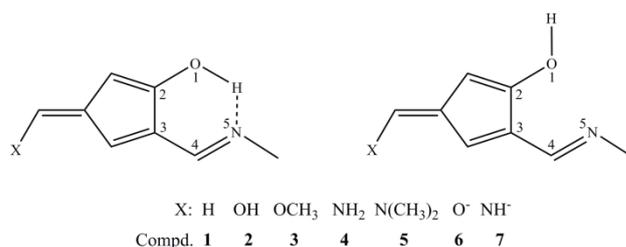


Fig. 1 Structure and atom labeling for closed (left) and open (right) conformations of the studied compounds with different X substitutions.

investigate the nature of the intramolecular interactions in the studied compounds. The B3LYP/6-311++G(d,p) level of theory using the NBO 3 program⁴⁷ which is implemented in Gaussian 03W package³⁹ has been employed for performing the NBO analyses. The topological properties of the electron density at the bond critical points (BCPs) have been characterized using the atoms in molecules (AIM) methodology³⁸ by means of the AIM2000 software⁴⁸ at the B3LYP/6-311++G(d,p) level of calculation.

3. Results and Discussion

3.1. Aromaticity

To investigate the influence of the π -system delocalization on the IHB strength, it is first useful to study the substitution influences on the aromaticity of the target compounds. The structures of closed and open conformers of 3-hydroxy-2-((methylimino)methyl) fulvene derivatives with X=H, OH, OCH₃, NH₂, N(CH₃)₂, O⁻, and NH⁻ substituents are presented in Fig. 1. As an electron-donating strength criterion, the substituent constants σ_p^+ are -0.92, -0.78, -1.30, -1.50, -2.30, -2.43 for X=OH, OCH₃, NH₂, N(CH₃)₂, O⁻, and NH⁻, respectively⁴⁹.

The values of the calculated HOMA and pEDA indices at B3LYP/6-311++G(d,p) level for the optimized geometries of the closed and open conformations of the target compounds are summarized in Table 1. Since HOMA may be also estimated for a part of a ring or for a sequence of bonds for which delocalization can be considered, we also estimated this index for the sequence of O1–C2–C3–C4=N5 bonds of the 6-membered quasi-ring in the closed and open conformations. Comparison of the HOMA and pEDA values for the molecules with different X substituent, indicates that the aromaticity of the fulvene ring and the quasi-ring increases with increasing the

Table 1 HOMA and pEDA aromaticity indices for the closed and open conformers of the target compounds

Compound	HOMA		HOMA (quasi-ring)		pEDA	
	Closed	Open	Closed	Open	Closed	Open
1	-0.279	-0.218	-0.187	-0.306	0.117	0.127
2	-0.014	0.031	-0.074	-0.201	0.263	0.267
3	0.015	0.060	-0.057	-0.195	0.361	0.269
4	0.187	0.229	0.039	-0.107	0.364	0.372
5	0.207	0.252	0.114	-0.048	0.387	0.393
6	0.514	0.593	0.223	0.035	0.561	0.594
7	0.527	0.613	0.261	0.068	0.587	0.627

electron-donating character of the substitution in the exocyclic position of the fulvene ring. As can be seen from Table 1, the aromaticity of the fulvene rings in the open conformation is more than that in the closed conformation in all compounds considered (for instance, the HOMA values for X=NH⁻ are 0.527 and 0.613 in the closed and open conformations, respectively). On the other hand, contrary to observed for the fulvene ring, HOMA values show that the aromaticity of the quasi-rings in the closed conformation are more than that in the open conformation (for instance, the HOMA values for X=NH⁻ are 0.261 and 0.068 in the closed and open conformations, respectively). These results may be attributed to the formation of resonance-assisted hydrogen bonds (RAHB), associated with increasing in the π -system delocalization in the quasi-rings of the closed forms.

The plots of the HOMA index versus the substituent constants σ_p^+ for the closed and open conformers of the target compounds are shown in Fig. 2. As could be seen in this figure, very good linear correlations are observed between HOMA and σ_p^+ in the fulvene and quasi-rings for both closed and open forms in all studied molecules (the correlation coefficients are also shown in Fig. 2). The negative slope in all cases shows that the aromaticity decreases with increasing the substituent constants σ_p^+ , which means decreasing in the electron-donating character of the substitutions.

The absolute values of slope for the mentioned plots, in the case of the fulvene ring, are 0.337 and 0.350, for the closed and open conformations, respectively. This indicates that the influences of the electron-donating strength of the substitutions on the aromaticity of the fulvene ring in the open conformation are more than that in the closed conformation. Also, in the case of quasi-ring plots, the higher absolute value of the slope for the closed conformer shows that the influences of the electron-donating strength of the substitutions on the aromaticity of the quasi-ring in the closed conformation is more than that in the open conformation.

3.2. Intramolecular Hydrogen Bonding

This section presents the influences of electron-donating strength of substituent and the aromaticity of the fulvene ring and quasi-ring on the IHB strength of the closed conformers. It is well known that parameters such as O–H bond length, H \cdots N IHB length, O \cdots N distance, and electron density at the BCP of H \cdots N could be applied to estimate such OH \cdots N IHB strength^{11, 50, 51}.

The selected structural parameters for the fully optimized geometries of the studied compounds at B3LYP/6-311++G(d,p) level, correlated with the IHB strength, are summarized in Table 2. From this table, it can be seen that O1–H, C2–C3 and C4=N5 bond lengths in the closed conformation (which are engaged in IHB system) are longer than those in the open conformation, while O1–C2 and C3–C4 bond lengths show a reverse trend. These changes in the bond lengths are attributed to the delocalization of the π -system in the quasi-ring region associated with RAHB in the closed conformations.

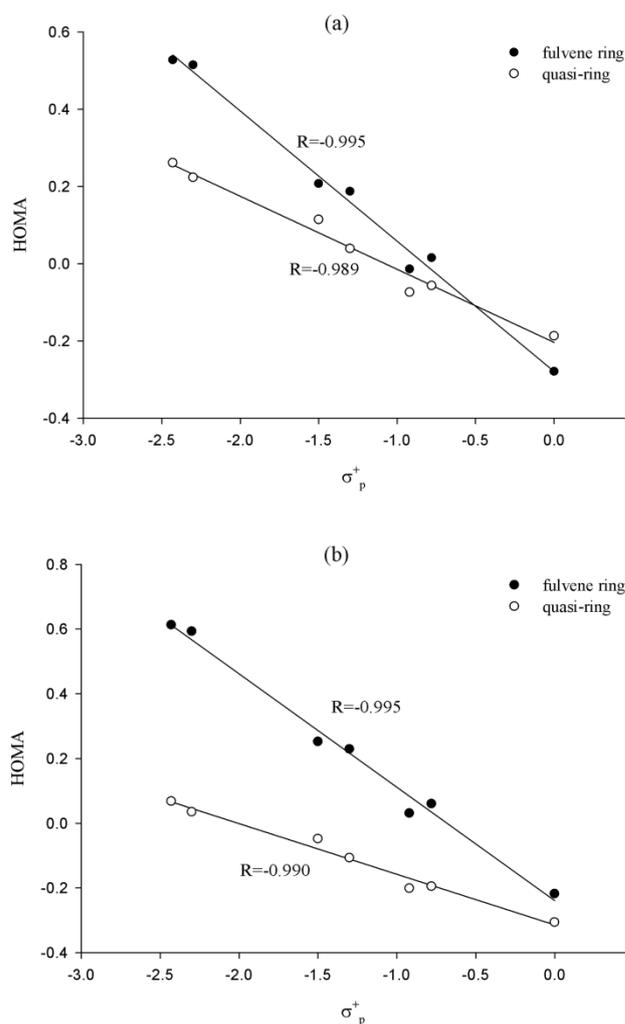


Fig. 2 The plots of HOMA versus the substituent constants σ_p^+ : (a) closed conformers (b) open conformers.

According to the data of Table 2, the IHB length (H \cdots N5) and O1 \cdots N5 distance increase with increasing of the electron-donating character of the substituents. The increase in the mentioned distance is more for the open conformers, compared to that for the closed forms. These results, besides decrease of the OH bond length by increasing the electron-donating nature of the substitute, indicate that the IHB strength decreases with increasing of the electron-donating power of the substituents and the aromaticity of the target compounds.

The calculated electron density properties at the IHB critical point (ρ_{HBCP} and $\nabla^2\rho_{\text{HBCP}}$) and at the quasi-ring critical point (ρ_{RCP} and $\nabla^2\rho_{\text{RCP}}$) are collected in Table 3. The results show that all the values of the electronic density Laplacian at the BCP are positive, indicating interatomic interactions for which the depletion of the electron density from BCP in the direction of the nuclei dominates. Such a closed-shell interaction in the studied compounds confirms the intramolecular hydrogen bond formation. The magnitude of the electron density of the IHB critical point, which could be related to the IHB strength, decreases with increasing of the electron-donating power of the

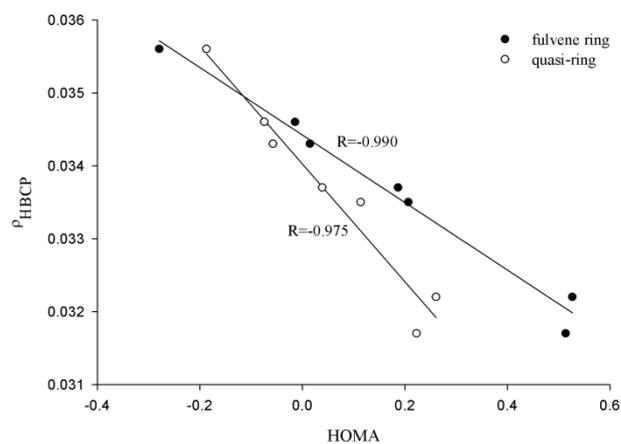
Table 2 Selected geometrical parameters for the closed and open conformations of the studied compounds, calculated at the B3LYP/6-311++G(d,p) level of theory (distances in angstroms, angles in degrees)

Compound	H...N5	O1...N5	O1-H	O1-C2	C2-C3	C3-C4	C4=N5	O1C2C3	C2C3C4
Closed con.									
1	1.886	2.754	0.984	1.340	1.490	1.447	1.279	122.4	123.8
2	1.897	2.762	0.983	1.346	1.479	1.446	1.281	122.9	123.9
3	1.901	2.765	0.983	1.347	1.478	1.445	1.281	122.9	123.9
4	1.908	2.770	0.982	1.351	1.468	1.443	1.282	123.2	124.0
5	1.911	2.773	0.982	1.351	1.462	1.441	1.283	123.4	124.1
6	1.928	2.798	0.981	1.372	1.448	1.420	1.299	123.2	124.4
7	1.921	2.793	0.981	1.373	1.444	1.417	1.302	123.2	124.2
Open con.									
1	–	2.992	0.964	1.348	1.488	1.456	1.271	120.9	129.1
2	–	3.006	0.964	1.354	1.477	1.455	1.272	121.4	129.2
3	–	3.007	0.964	1.355	1.476	1.455	1.272	121.4	129.2
4	–	3.021	0.963	1.359	1.466	1.454	1.273	121.8	129.5
5	–	3.029	0.963	1.360	1.460	1.453	1.273	122.1	129.6
6	–	3.136	0.962	1.385	1.442	1.437	1.285	123.4	130.9
7	–	3.147	0.962	1.387	1.438	1.434	1.288	123.7	131.0

substitutions in the exocyclic position of the fulvene ring. The plots of the electron density at the IHB critical point, ρ_{HBCP} , versus the HOMA indices in the fulvene and quasi-ring, which are shown in Fig. 3, show that contrary to expected from RAHB idea, ρ_{HBCP} decreases with increasing of the aromaticity in the target compounds.

Another useful criterion for the IHB strength is the interaction energy between the lone pair (LP) orbital of the HB acceptor, as electron donor orbital, and the anti-bonding sigma orbital (σ^*) of the HB donor, as electron acceptor orbital. The second-order perturbation theory has been employed to evaluate the stabilization energy for the donor-acceptor orbital interactions in the NBO analyses of the target compounds. The results of the charge transfer energy between the LP orbital of N5 atom (LP_N) and the σ^* orbital of the O–H bond (σ^*_{OH}) are also presented in Table 3. It can be seen that the energy of $\text{LP}_\text{N} \rightarrow \sigma^*_{\text{OH}}$ interaction decreases with increasing of the electron-donating power of the substituents. Good linear relationships with correlation coefficients of -0.987 and -0.997 between the stabilization energy of $\text{LP}_\text{N} \rightarrow \sigma^*_{\text{OH}}$ interaction respectively with O1...N5 and H...N5 IHB distances could be plotted. Such correlations have been also established in the literature^{52,53}. It is worth noting that this result of the NBO analysis is in perfect agreement with the results obtained by the AIM method.

In summary of this section, according to the obtained results, the studied molecules with less electron delocalization have stronger IHB, in contrast with RAHB concept.

**Fig. 3** The plots of the electron density at the IHB bond critical point versus HOMA index for the closed conformers of the studied compounds.

3.3. Molecular Structure

The fully optimized molecular structures of the target compounds have been studied in order to investigate the influences of the σ -skeleton of the molecule on the IHB strength. Investigation of the C2–C3 bond lengths in the closed and open conformations show that increasing the electron-donating character of the substituents makes this bond shorter the C2–C3 bond length is attributed to the aromaticity enhancement in the fulvene ring and in the quasi-ring.

Table 3 Some AIM and NBO results for the target compounds, calculated at the B3LYP/6-311++G(d,p) level of theory^a

Compound	ρ_{HBCP} (au)	$\nabla^2\rho_{\text{HBCP}}$ (au)	ρ_{RCP} (au)	$\nabla^2\rho_{\text{RCP}}$ (au)	$\text{LP}_\text{N} \rightarrow \sigma^*_{\text{OH}}$ (kcal/mol)	$\text{pop}(\sigma^*_{\text{OH}})$ (au)
1	0.0356	0.0952	0.0156	0.0916	14.51	0.0443
2	0.0346	0.0943	0.0154	0.0905	13.75	0.0423
3	0.0343	0.0938	0.0154	0.0901	13.56	0.0418
4	0.0337	0.0933	0.0153	0.0895	13.03	0.0403
5	0.0335	0.0927	0.0153	0.0894	12.92	0.0403
6	0.0317	0.0901	0.0149	0.0869	11.57	0.0385
7	0.0322	0.0908	0.0150	0.0878	11.96	0.0397

^a HBCP, IHB critical point; RCP, ring CP; LP, lone pair non-bonding orbital; pop, orbital population

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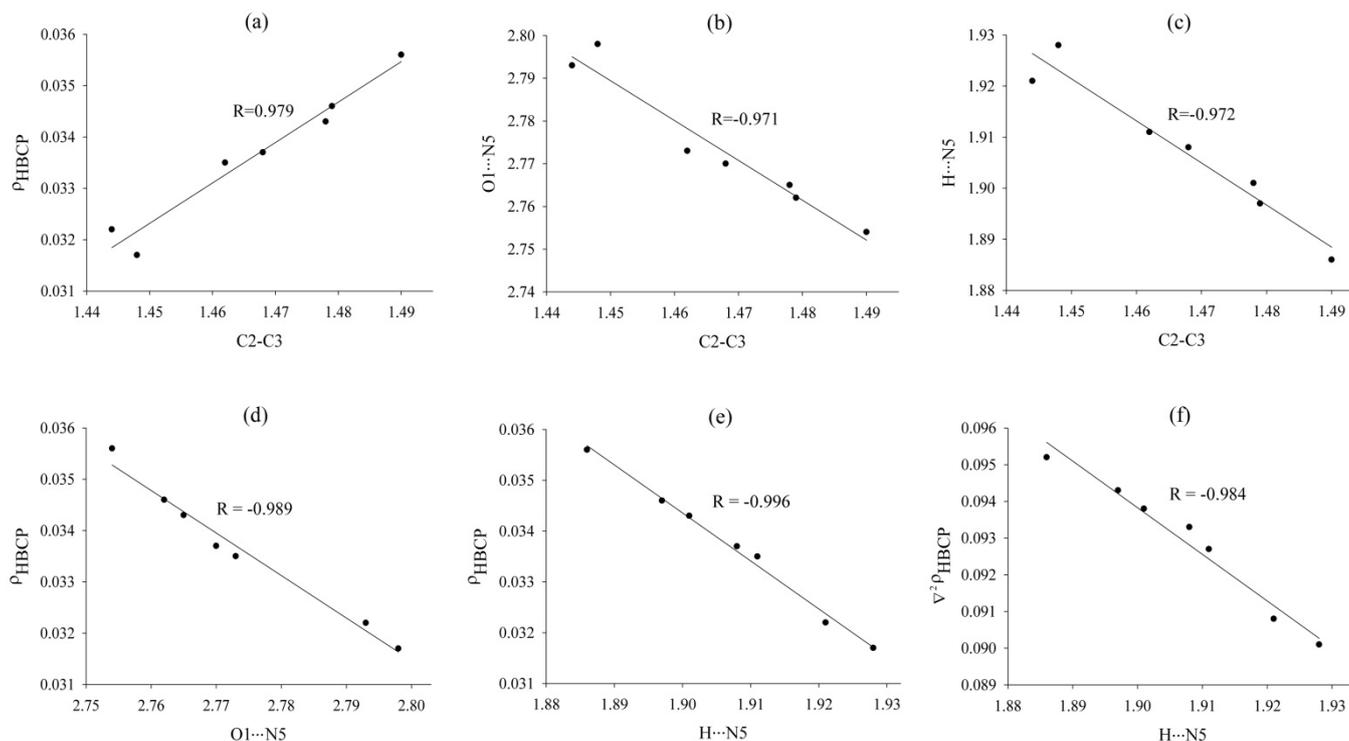


Fig. 4 Some obtained correlations between the electron density properties and interatomic distances of the studied closed systems.

Increasing the electron-donating character of the substitution leads to the more overlap of the perpendicular 2p orbitals at C2 and C3 carbon atoms with each other and with the perpendicular 2p orbitals of the neighboring carbon atoms in fulvene ring and perpendicular 2p orbitals of C4 and N5 atoms in quasi-ring, which in turn leads to the more π -electron delocalization in the mentioned rings. The same description could be employed for the observed decrease in the C4–N5 bond length. This is also confirmed by the pEDA values, which show the occupancy of π -electron orbitals.

The plots of the ρ_{HBCP} versus the C2–C3 bond length and also versus the O1...N5 distance, and the plots of the O1...N5 and H...N5 distances versus C2–C3 bond length are shown in Fig. 4. As can be seen in Fig. 4a, there is a good linear correlation ($R=0.979$) between the calculated ρ_{HBCP} (which is directly related to the IHB strength) and the C2–C3 bond length. This result clearly shows that the strength of the IHB increases with the increase of the C2–C3 bond length. Fig. 4 (b and c) also shows that shorter C2–C3 bond length, caused by more electron delocalization and aromaticity of the quasi-ring, leads to longer IHB lengths with very good correlations. Furthermore, Fig. 4d

presents a strong linear relationship between the ρ_{HBCP} and the O1...N5 distances in all compounds ($R=-0.989$). The correlation between the hydrogen bond distance and the electron density has been also established in the literature⁵²⁻⁵⁴. Figs. 4e and 4f show such correlations between H...N5 distance with ρ_{HBCP} and $\nabla^2\rho_{\text{HBCP}}$, respectively. Accordingly, the strength of the IHB increases with the increasing of the C2–C3 bond length (that leads to a decrease in the O1...N5 distance in all studied compounds). For better understanding, remember this well-known fact that the IHB in a 7-member quasi-ring is stronger than that in a 6-member quasi-ring, which is, in turn, stronger than that in a 5-member quasi-ring. In fact, longer C2–C3 bond length make the HB donor and HB acceptor of the quasi-ring to be in better positions to form a shorter and more linear IHB, which should be stronger, consequently.

Therefore, the strength of the IHB of the target compounds depends on the structure of the σ -skeleton of the molecule, in which shorter O1...N5 distance lead to more interaction between the HB donor and acceptor.

4. Conclusions

According to the calculations for the geometry based and the electronic based indicators of the ring aromaticity in 3-hydroxy-2-((methylimino)methyl) fulvene derivatives, the aromaticity of the fulvene ring and the quasi-ring (formed due to intramolecular hydrogen bond formation) increases by increasing the electron-donating character of the substitutions in the exocyclic position of the fulvene ring. The plots of the electron density at the intramolecular hydrogen bond critical point versus the HOMA (harmonic oscillator model of aromaticity) index of the aromaticity shows a negative slope, indicating that contrary to expected from resonance-assisted hydrogen bond, RAHB, concept, the intramolecular hydrogen bond strength decreases with increasing the π -electron delocalization in the quasi-ring of the target compounds. Analyses of the molecular structure show that for all the systems studied in the present work the intramolecular hydrogen bond strength is correlated to the structure of the σ -skeleton of the system. Longer C2–C3 bond leads to more proper positions for the hydrogen bond donor and acceptor in the quasi-ring (better direction and shorter distance between them), which in turn, result in an enhancement in the intended intramolecular hydrogen bonding interaction.

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