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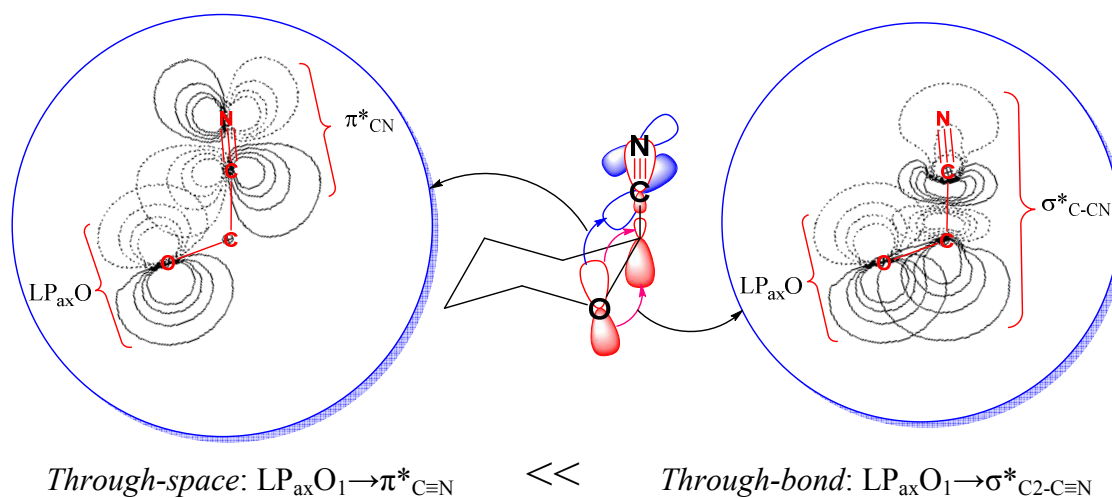
Graphical Abstract

Exploring the origin of the anomeric relationships in 2-cyanooxane, 2-cyanothiane, 2-cyanoselenane and their corresponding iso-cyano isomers. Correlations between hyperconjugative anomeric effect, hardness and electrostatic interactions

Peyvand Ghanbarpour and Davood Nori-Shargh*

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Colour graphic:



Highlight: The impacts of the *HCAE*, hardness, *PETR* and electrostatic interactions on the anomeric relationships in 2-cyanooxane, -thiane, -selenane and their iso-cyano isomers have been explored.

Exploring the origin of the anomeric relationships in 2-cyanooxane, 2-cyanothiane, 2-cyanoselenane and their corresponding iso-cyano isomers. Correlations between hyper-conjugative anomeric effect, hardness and electrostatic interactions

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Abstract

LC-wPBE, LC-BLYP, B3LYP, M06-2X and MP2 methods with the 6-311+G** basis set and natural bond orbital (NBO) interpretation were performed to explore the origin of the anomeric relationships in 2-cyanooxane (**1**), 2-cyanothiane (**2**), 2-cyanoselenane (**3**) and their iso-cyano isomers [i.e. 2-*iso*-cyanooxane (**4**), 2-*iso*-cyanothiane (**5**), 2-isocyanoselenane (**6**)]. All levels of theory used in this work showed that the axial conformations of compounds **1-6** are more stable than their corresponding equatorial forms. By deletion of the electron delocalization between the non-bonded lone pairs of the six-membered rings and the $\sigma^*_{\text{C-C}\equiv\text{N}}$ and $\sigma^*_{\text{C-N=C}}$ anti-bonding orbitals from the Fock matrixes of the axial and equatorial conformations and with re-diagonalization and comparison of the current Fock matrixes with their original forms, we found that these electron delocalizations are responsible for the axial conformation preferences in compounds **1-3** and **4-6**. Importantly, the approach mentioned above revealed that the through-space electronic interactions between the non-bonded lone pairs of the heteroatoms of the six-membered rings and the π^* anti-bonding orbitals of the cyano and isocyano groups ($\pi^*_{\text{C}\equiv\text{N}}$ and $\pi^*_{\text{N=C}}$) do not play a significant role here. Also, the variations of the differences in the total energies among the axial and equatorial conformations of compounds **1-3** correlate with the variations of differences in their corresponding dipole moments. Although the hyper-conjugative anomeric effect (*HCAE*) and Pauli exchange-type repulsions (*PETR*) are in favors of the axial conformations of compounds **1-3**; seemingly, the electrostatic model associated with the dipole-dipole interactions plays a determinant here. Interestingly, the attractive electrostatic interactions between two adjacent atoms (*AEI*) explain reasonably the variations of the structural parameters of compounds **1-3** and **4-6** which are in line with the resultant justification from the *HCAE*. The axial conformations of compounds **1-3** and **4-6** are harder than their corresponding equatorial conformations but their conformational behaviors could not be interpreted with the *Maximum Hardness Principle*.

Keywords: hyperconjugative *anomeric effect*, hardness, 2-cyanooxane

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Introduction

Due to steric hindrance in the axial conformations of the six-membered rings, substituent groups prefer to be equatorial and that chair conformer predominates in the equilibrium but the *anomeric effect* is in favor of the axial conformation of a six-membered saturated ring in

opposition to the steric effect.¹⁻¹⁶ The *anomeric effect* is known as the most dominant conformation-controlling factor in the structures of the chemical compounds including carbohydrates which is defined as the preference of the axial conformation compared to its equatorial conformation.

There are published data in the literature which implies that the *anomeric effect* has the electrostatic origin.¹⁷ On the other hand, in 2013, Bauerfeldt pointed out that the energy differences between the most stable rotamers of each anomer correlate very well with their corresponding the exchange component differences, implying that the anomeric effect has no electrostatic origin.¹⁸

Obviously, there is no general consensus about the actual origin of the *anomeric effect*,^{14,19} however, it is understood to be the result of multiple steric (i.e. Pauli exchange) and stereoelectronic interactions (associated with the dipole-dipole interactions and donor-acceptor electron delocalization).

Recently, we reported that the stabilization energies associated with the electron delocalization (*SE*), electrostatic model associated with the dipole-dipole interactions (*EM*) and Pauli exchange-type repulsions (*PETR*) are not solely responsible for the calculated *anomeric effect* in 2,3- and 2,5-dihalo-1,4-oxathianes but it results from their cooperative or uncooperative (confrontational) impacts.¹⁴ In addition, we pointed out that the *SE* has a determinant impact on the structural properties of 2,3- and 2,5-dihalo-1,4-oxathianes but fails to account solely for their *anomeric* relationships. Accordingly, the origin of the *anomeric effect* has remained an open question.^{14,19}

In 2010, Benn, Rauk and co-workers performed the natural bond orbital analysis to investigate the conformational behaviors of 2-cyanooxane (**1**), 2-cyanothiane (**2**) and 2-cyanoselenane (**3**).²⁰ They pointed out that a new mechanism [i.e. the through-space electronic interactions between the nonbonded lone pairs of the heteroatoms of the six-membered rings and π^* anti-bonding orbitals of the cyano groups, $LP_{ax}M \rightarrow \pi^*_{C\equiv N}$, M=O (**1**), S (**2**), Se (**3**)] selects for the axial conformation and the hyperconjugative anomeric effect (*HCAE*) associated with $LP_{ax}M \rightarrow \sigma^*_{C-C\equiv N}$ is not responsible for this observation.

To gain further insight on the origin of the *anomeric* relationships in compounds **1-3**, we have investigated the correlations between the differences in the total energies, steric exchanges [total steric exchange energies, *TSEE*, which is considered to represent Pauli exchange-type

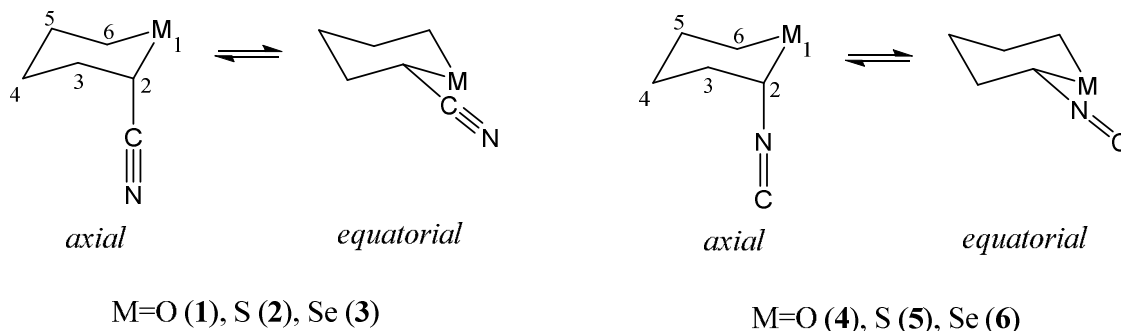
repulsions between filled orbitals (or the quasi-classical "Lennard-Jones repulsion") between hard-shell sphere atoms],²¹⁻²⁵ electrostatic model associated with the dipole-dipole interactions, hyperconjugative anomeric effect (*HCAE*) and structural parameters among the axial and equatorial conformations of compounds **1-3** and also their iso-cyano isomers [i.e. 2-iso-cyanooxane (**4**), 2-iso-cyanothiane (**5**), 2-isocyanoselenane (**6**)] (Scheme 1).

It is known that the preferred conformation or configuration of a molecule may possess the maximum interaction between the best donor and the best acceptor bond,^{26,27} therefore, the stereoelectronic interactions associated with the antiperiplanar donor-acceptor interactions are expected to play an important role in the conformational properties of heterocyclic compounds.

Since there are *HCAE* in the axial and equatorial conformations of compounds **1-6**, the $HCAE_{total}$ can be estimated from the differences between the *HCAE* for the axial (ax) and equatorial (eq) forms¹² of compounds **1-6** by the following equation (1):

$$HCAE_{total} = \Delta(HCAE_{eq} - HCAE_{ax}) = \Sigma(HC-exo-AE_{eq} + HC-endo-AE_{eq}) - \Sigma(HC-exo-AE_{ax} + HC-endo-AE_{ax}) \quad \text{Eq. (1)}$$

Although there are published experimental^{20,28-30} and theoretical²⁰ data concerning the structural properties of compounds **1-3**, there are no published data about the cooperative or uncooperative (confrontational) impacts of the $HCAE_{total}$, electrostatic model associated with the dipole-dipole interactions (*EM*) and steric repulsions [i.e. Pauli exchange-type repulsions (*PETR*)] on the conformational preferences in compounds **1-6**. In the present work, we investigate the impacts of the above-mentioned factors on the structural and conformational behaviors of compounds **1-6** by means of the long-range corrected density functional (LC-BLYP,³¹ LC- ω PBE³²), hybrid meta exchange-correlation functional (M06-2X)³³, hybrid density functional (B3LYP)³⁴⁻³⁶ theory based methods, second-order Møller-Plesset perturbation theory (MP2) calculations^{37,38} with 6-311+G**³⁹⁻⁴² basis set on all atoms and natural bond orbital (NBO) interpretation.⁴³ It is worth noting that the validity of the conclusion presented in Reference 20 was examined by deletion of the $LP_{ax}M \rightarrow \pi^*_{C=N}$ [$M=O$ (**1**), S (**2**), Se (**3**)] electron delocalization from the Fock matrixes of their axial and equatorial conformations and by re-diagonalizing and comparing the current Fock matrixes with their original forms. Our results do not correlate with the conclusion mentioned in the Reference 20.



Scheme 1. Schematic representation of the axial and equatorial conformations of compounds **1-3** and **4-6**.

Computational details

LC-BLYP,³¹ LC- ω PBE³², M06-2X³³, B3LYP³⁴⁻³⁶, MP2 calculations^{37,38} with 6-311+G**³⁹⁻⁴² basis set on all atoms were performed to optimize the structural parameters and also to calculate the electronic energies and the thermodynamic functions of compounds **1-6** with the GAMESS US package of programs.^{44,45}

The NBO- LC- ω PBE/6-311+G** interpretation was performed to estimate quantitatively the magnitude of the plausible donor-acceptor hyperconjugative attractive interactions, the bonding and antibonding orbital occupancies and energies and also the total steric exchange energies for the axial and equatorial conformations of compounds **1-6** by means of the NBO 5.G program.⁴³

The stabilization energies associated with the donor (i) \rightarrow acceptor (j) interactions are proportional inversely to the energy differences between the donor and acceptor orbitals and directly to the magnitudes of the orbital overlap integrals:^{13-15,26,27}

$$\text{Stabilization or resonance energy} \propto \left(\frac{S_{ij}^2}{\Delta\epsilon_{ij}} \right)$$

Accordingly, the stabilization energy (E_2) associated with $i\rightarrow j$ electron delocalization, is explicitly estimated by the following equation (2):

$$E_2 = \frac{F_{(i,j)}^2}{\epsilon_j - \epsilon_i} \quad \text{Eq. (2)}$$

where q_i is the i^{th} donor orbital occupancy, ϵ_i , ϵ_j are diagonal elements (orbital energies) and $F(i,j)$ off-diagonal elements, respectively, associated with the NBO Fock matrix. Substantial adjustments of off-diagonal elements are required to reach the desirable orbital overlapping going from one compound to the next.^{46,47}

The hyper-conjugative *anomeric effects* (*HCAEs*) associated with the *HC-endo-AE* ($LP_{eq}M_1 \rightarrow \sigma^*_{C2-C\equiv N}$, $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C\equiv N}$, $LP_{ax}M_1 \rightarrow \pi^*_{C\equiv N}$, $\sigma_{M1-C2} \rightarrow \pi^*_{C\equiv N}$, $\sigma_{M1-C2} \rightarrow \sigma^*_{C\equiv N}$, $\sigma_{C3-Hax} \rightarrow \sigma^*_{C2-C\equiv N}$, $\sigma_{C3-Hax} \rightarrow \sigma^*_{C2-Hax}$, $LP_{eq}M_1 \rightarrow \sigma^*_{C2-N=C}$, $LP_{ax}M_1 \rightarrow \sigma^*_{C2-N=C}$, $LP_{ax}M_1 \rightarrow \pi^*_{N=C}$, $\sigma_{M1-C2} \rightarrow \pi^*_{N=C}$, $\sigma_{M1-C2} \rightarrow \sigma^*_{N=C}$, $\sigma_{C3-Hax} \rightarrow \sigma^*_{C2-N=C}$) and *HC-exo-AE* ($\pi_{C\equiv N} \rightarrow \sigma^*_{M1-C2}$, $\sigma_{C\equiv N} \rightarrow \sigma^*_{M1-C2}$, $\sigma_{C2-C\equiv N} \rightarrow \sigma^*_{C3-Hax}$, $\sigma_{C2-Hax} \rightarrow \sigma^*_{C3-Hax}$, $\pi_{N=C} \rightarrow \sigma^*_{M1-C2}$, $\sigma_{C2-N=C} \rightarrow \sigma^*_{C3-Hax}$) (Figure 1), the attractive electrostatic interactions between two adjacent atoms (*AEI*), dipole-dipole interactions and steric repulsions (i.e. *TSEE*) and their influences on the structural and conformational properties of compounds **1-6** were quantitatively investigated by means of the natural bond orbital (NBO) interpretations.⁴³ In order to assess the impacts of the electron delocalization between the non-bonded lone pairs of the six-membered rings and the $\sigma^*_{C-C\equiv N}$ and $\sigma^*_{C-N=C}$ anti-bonding orbitals and also the $\pi^*_{C\equiv N}$ and $\pi^*_{N=C}$ anti-bonding orbitals, we deleted these hyper-conjugative interactions (i.e. $LP_{ax}M_1 \rightarrow \sigma^*_{C2-CN}$, $LP_{ax}M_1 \rightarrow \sigma^*_{C2-NC}$, $LP_{ax}M_1 \rightarrow \pi^*_{C\equiv N}$, $LP_{ax}M_1 \rightarrow \pi^*_{N=C}$ electron delocalizations) from the Fock matrixes of the axial and equatorial conformations of compounds **1-3** and **4-6**. Then, by re-diagonalizing and comparing the current Fock matrixes with their original forms, we estimated the contributions and impacts of the above mentioned electron delocalizations on the total energy differences between the equatorial and axial conformations of compounds **1-3** and **4-6**. It is worth noting that the NBO interpretation is a sufficient approach to investigate quantitatively the impacts of the stereo-electronic interactions and exchange component (*PETR*) on the reactivity and conformational or configurational behaviors of chemical compounds.⁴⁸

Results and Discussion

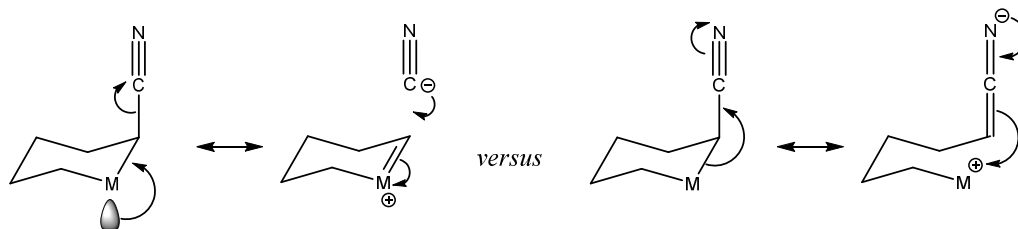
1-Structural parameters

Representative structural parameters [bond lengths (r), bond angles (θ), torsion angles (ϕ) and their differences: Δr , $\Delta \theta$ and $\Delta \phi$ parameters] for the axial and equatorial conformations of compounds **1-3** and **4-6**, as calculated at the LC-wPBE/6-311+G** level of theory, are summarized in Table 1. Also, the above mentioned structural parameters for the axial and equatorial conformations of compounds **1-3** and **4-6** were obtained at the B3LYP/6-311+G**, LC-BLYP/6-311+G**, M06-2X/6-311+G** and MP2/6-311+G** levels of theory (Table SI-1). Effectively, the calculated structural parameters of the axial conformations of compounds **2** and **3** at the LC-wPBE/6-311+G** level are in excellent agreement with the reported crystallographic

data compared to the other levels. Note that the long-rang corrected PBE (LC-wPBE) functional is known to smallest “many-electron self-interaction errors (*MESIE*)” among widely used exchange-correlation functional and correctly predicts the degree of electron localization and delocalization.⁴⁹ By performing these methods, we do not expect to obtain exactly the experimental values; however, it is possible to carry out theoretical calculations to obtain many properties and structures with an accuracy that is competitive with experiments.

The $\sigma_{\text{M1-C2}}$ bond lengths in the axial conformations of compounds of **1-3** are smaller than those in their corresponding equatorial conformations. The hyper-conjugative interactions between the non-bonded lone pairs of the six-membered rings [LPM, M=O(1), S(2), Se(3)] and the $\sigma^*_{\text{C-C}\equiv\text{N}}$ and $\sigma^*_{\text{C-N=C}}$ anti-bonding orbitals ($\text{LP}_{\text{ax}}\text{M}_1 \rightarrow \sigma^*_{\text{C2-C}\equiv\text{N}}$) tend to decrease the $\sigma_{\text{M1-C2}}$ bond lengths by increasing their double bond characters but the $\sigma_{\text{M1-C2}} \rightarrow \pi^*_{\text{C}\equiv\text{N}}$ and $\sigma_{\text{M1-C2}} \rightarrow \sigma^*_{\text{C}\equiv\text{N}}$ electron delocalizations have opposite impacts. The confrontations between the impacts of the $\text{LP}_{\text{ax}}\text{M}_1 \rightarrow \sigma^*_{\text{C2-C}\equiv\text{N}}$ and $\sigma_{\text{M1-C2}} \rightarrow \pi^*_{\text{C}\equiv\text{N}}$ electron delocalizations on the bond orders of the $\sigma_{\text{M1-C2}}$ bonds (Scheme 2) lead to decrease of the differences between the $\sigma_{\text{M1-C2}}$ bond lengths in the axial and equatorial conformations of compounds **1-3**. This fact is reflected in the variations of the $\sigma_{\text{M1-C2}}$ bond length differences between the axial and equatorial conformations (i.e. $\Delta[r_{1-2}(\text{eq})-r_{1-2}(\text{ax})]$ parameters) ongoing from compound **1** to compound **3**. $\Delta[r_{1-2}(\text{eq})-r_{1-2}(\text{ax})]$ parameter is increased slightly from compound **1** to compound **2** but does not change ongoing from compound **2** to compound **3**.

The $\sigma_{\text{C2-C}\equiv\text{N}}$ bond lengths in the axial conformations of compounds **1-3** are longer than those in their corresponding equatorial conformations. It is worth noting that the $\sigma_{\text{C2-C}\equiv\text{N}}$ bond length differences in the axial and equatorial conformations ($\Delta[r_{\text{C2-C}\equiv\text{N}}(\text{ax})-r_{\text{C2-C}\equiv\text{N}}(\text{eq})]$) have positive values and decrease from compound **1** to compound **3**. This trend is similar to that obtained for the variations of the $\text{LP}_{\text{ax}}\text{M}_1 \rightarrow \sigma^*_{\text{C2-C}\equiv\text{N}}$ electron delocalizations from the axial conformations of compound **1** to compound **3**. Therefore, the $\text{LP}_{\text{ax}}\text{M}_1 \rightarrow \sigma^*_{\text{C2-C}\equiv\text{N}}$ hyperconjugative interactions have determinant impacts on the variations of the $\sigma_{\text{C2-C}\equiv\text{N}}$ bond lengths ongoing from the axial conformations of compound **1** to compound **3** compared to the $\sigma_{\text{M1-C2}} \rightarrow \pi^*_{\text{C}\equiv\text{N}}$, $\sigma_{\text{M1-C2}} \rightarrow \sigma^*_{\text{C}\equiv\text{N}}$ and $\pi_{\text{C}\equiv\text{N}} \rightarrow \sigma^*_{\text{M1-C2}}$ electron delocalizations which tend to decrease of the $\sigma_{\text{C2-C}\equiv\text{N}}$ bond lengths. Note that the impacts of the $\sigma_{\text{M1-C2}} \rightarrow \pi^*_{\text{C}\equiv\text{N}}$, $\sigma_{\text{M1-C2}} \rightarrow \sigma^*_{\text{C}\equiv\text{N}}$ and $\pi_{\text{C}\equiv\text{N}} \rightarrow \sigma^*_{\text{M1-C2}}$ electron delocalizations on the decrease of the $\sigma_{\text{C2-C}\equiv\text{N}}$ bond lengths and also on the increase of the $\sigma_{\text{M1-C2}}$ bond lengths in the axial and equatorial conformations of compounds **1-3** are relatively the same.



Scheme 2. Schematic representation of the impacts of the $LP_{ax}M_1 \rightarrow \sigma^*_{C_2-CN}$ and $\sigma_{M_1-C_2} \rightarrow \pi^*_{C\equiv N}$ electron delocalizations on the M_1-C_2 and C_2-CN bond lengths in the axial conformations of compounds **1-3** [$M=O$ (**1**), S (**2**), Se (**3**)].

Interestingly, in the axial and equatorial conformations of compound **1**, the $\sigma_{C_6-M_1}$ bonds are longer than the $\sigma_{M_1-C_2}$ bonds but this trend is reversed ongoing from compound **1** to compound **3**. There are two explanations for these observations. First explanation is based on the impacts of the $\sigma_{M_1-C_2} \rightarrow \pi^*_{C\equiv N}$, $\sigma_{M_1-C_2} \rightarrow \sigma^*_{C\equiv N}$ and $\pi_{C\equiv N} \rightarrow \sigma^*_{M_1-C_2}$ electron delocalizations and the second one is attributed to the attractive or repulsive electrostatic interactions (*AREI*) between two adjacent C_6 and M_1 atoms. The NBO-LC-wPBE/6-311+G** analysis revealed that two adjacent C_6 and M_1 atoms in the axial and equatorial conformations of compound **1** possess negative natural atomic charges (*NAC*), leading to the repulsive electrostatic interactions (*REI*) between them, causing the increase of the $\sigma_{C_6-M_1}$ bond lengths compared to the $\sigma_{M_1-C_2}$ bonds. It should be noted that there are attractive electrostatic interactions (*AEI*) between two adjacent M_1 and C_2 atoms in the axial and equatorial conformations of compound **1**, leading to the decrease of the $\sigma_{M_1-C_2}$ bond lengths compared to the $\sigma_{C_6-M_1}$ bonds. Contrary to compound **1**, there are *AEI* between two adjacent C_6 and M_1 atoms in the axial and equatorial conformations of compounds **2** and **3**. The calculated natural atomic charge differences between two adjacent M_1 and C_6 atoms in the axial and equatorial conformations ($\Delta[NAC(M_1)_{ax}-NAC(C_6)_{ax}]$, $\Delta[NAC(M_1)_{eq}-NAC(C_6)_{eq}]$) increase from compound **1** to compound **3** (Table 2). This fact reasonably explain the variations of the $r_{M_1-C_2}$ and $r_{M_1-C_6}$ bond length differences in the axial and equatorial conformations ($\Delta[r_{M_1-C_2(ax)}-r_{M_1-C_6(ax)}]$ and $\Delta[r_{M_1-C_2(eq)}-r_{M_1-C_6(eq)}]$) ongoing from compound **1** to compound **3**. Therefore, the *AREI* succeeds in accounting for the variations of the $\sigma_{M_1-C_2}$ and $\sigma_{M_1-C_2}$ bond lengths in the axial and equatorial conformations ongoing from compound **1** to compound **3**. The above mentioned justifications can be used to interpret the structural properties of compounds **4-6**.

The evidence which illustrates the importance of the hyper-conjugative interaction impacts on the structural parameters is the decrease of the $\Delta[\phi_{(6-1-2-3)eq}-\phi_{(6-1-2-3)ax}]$ parameter ongoing from the axial conformations of compound **1** to compound **3** and from compound **4** to compound **6**. Note that the strong $LP_{ax}M_1\rightarrow\sigma^*_{C_2-C\equiv N}$ and $LP_{ax}M_1\rightarrow\sigma^*_{C_2-N=C}$ electron delocalizations in the axial conformations of compounds **1-3** and **4-6**, respectively, increase the double bond characters of the M_1-C_2 bonds, decreasing the $\phi_{(6-1-2-3)}$ torsion angle values in the axial conformation compared to those in their corresponding equatorial forms. Interestingly, the variations of $\Delta[\phi_{(6-1-2-3)eq}-\phi_{(6-1-2-3)ax}]$ parameters ongoing from compound **1** to compound **3** and also from compound **4** to compound **6** correlate well with the variations of the C_2-M_1 bond order (Wiberg bond index, *WBI*) differences between their corresponding axial and equatorial conformations (*i.e.* $\Delta[WBI(C_2-M_1)_{ax}-WBI(C_2-M_1)_{eq}]$ parameters).

2-Conformational preference

The calculated Gibbs free energy, enthalpy, entropy, corrected electronic energy differences (*i.e.* ΔG , ΔH , ΔS and ΔE_0) for the axial and equatorial conformations of compounds **1-3** and **4-6**, as calculated at the LC-wPBE/6-311+G** are given in Table 3. Further, Table SI-2 shows the calculated ΔG , ΔH , ΔS and ΔE_0 parameters for the axial and equatorial conformations of compounds **1-6** at the LC-BLYP/6-311+G** and B3LYP/6-311+G** levels. Furthermore, B3LYP/6-311+G** and M06-2X/6-311+G** results are summarized in Table SI-3.

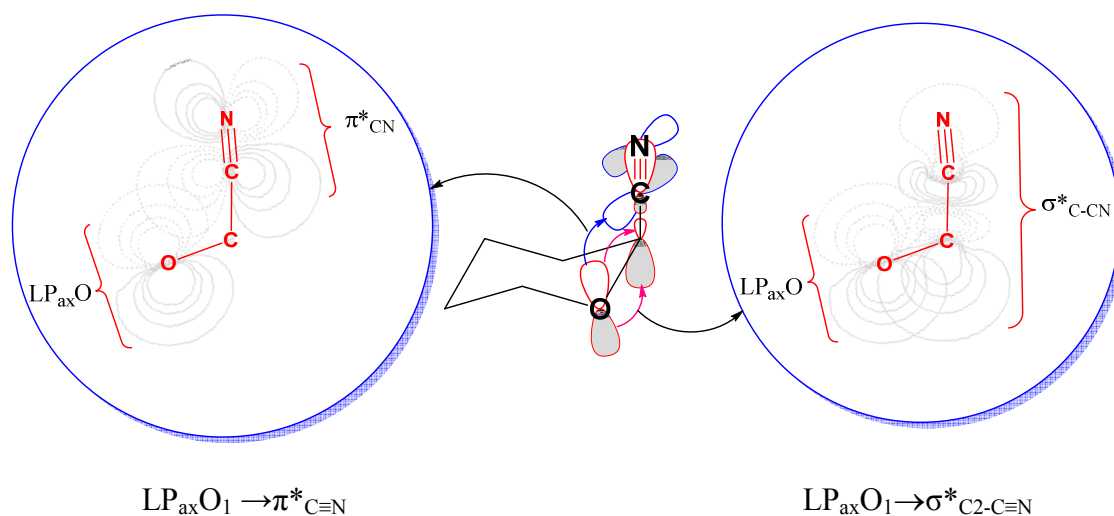
LC-wPBE/6-311+G** results showed that the axial conformations of compounds **1-3** and **4-6** are more stable than their corresponding equatorial conformations. The energy difference between the equatorial and axial conformations increases from compound **1** to compound **2** but decreases from compound **2** to compound **3**. This trend is also observed for compounds **4-6** but there are no significant differences between the axial conformation preferences in compounds **4** and **5**. All levels of theory used in this work showed that the axial preferences in compounds **4-6** are greater than those obtained for compounds **1-3**. This fact may be of justified by the greater corresponding *HCAEs* values of compounds **4-6** compared to those in compounds **1-3**. The stronger $LP_{ax}M_1\rightarrow\sigma^*_{C_2-N=C}$ electron delocalizations in the axial conformations of compounds **4-6** compared to the $LP_{ax}M_1\rightarrow\sigma^*_{C_2-C\equiv N}$ electron delocalizations in the axial conformations of compounds **1-3** cause the greater *HCAEs* values in compounds **4-6** compared to those in compounds **1-3** (Table 2).

2-Assesing the impacts of the hyperconjugative interactions on the conformational preferences

Since the hyperconjugative *anomeric effects* (HCAEs) play an important role on the structural properties and the energy differences between the axial and equatorial conformations of compounds **1-3** and **4-6**, we conducted NBO analyses to estimate quantitatively the magnitude of the plausible donor-acceptor hyperconjugative interactions. The NBO-LC-wPBE/6-311+G** analysis showed that the $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C \equiv N}$ [M=O (**1**), S (**2**), Se (**3**)] and $LP_{ax}M_1 \rightarrow \sigma^*_{C2-N=C}$ [M=O (**4**), S (**5**), Se (**6**)] electron delocalizations have the most impacts on the magnitudes of the total hyperconjugative anomeric effect ($HCAE_{total}$) of compounds **1-3** and **4-6**. In fact, the calculated *HC-endo-AE* values in the axial conformations of compounds **1-3** and **4-6** are controlled by the $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C \equiv N}$ and $LP_{ax}M_1 \rightarrow \sigma^*_{C2-N=C}$ electron delocalizations, respectively. The results obtained showed that the stabilization (resonance) energies associated with $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C \equiv N}$ delocalizations decrease from the axial conformations of compound **1** to compound **3** (Table 2). This trend is also observed for the variations of the $LP_{ax}M_1 \rightarrow \sigma^*_{C2-N=C}$ delocalizations in the axial conformations of compounds **4-6**.

Benn, Rauk and co-workers²⁰ pointed out that the through-space electron delocalizations between the non-bonded lone pairs of the heteroatoms of the six-membered rings and the $\pi^*_{C \equiv N}$ anti-bonding orbitals [i.e. $LP_{ax}M_1 \rightarrow \pi^*_{C \equiv N}$, M=O (**1**), S (**2**), Se (**3**)] have determinant impacts on the axial conformation preferences in compounds **1-3** (Scheme 3). Contrary to their conclusion, our results showed that the $LP_{ax}M_1 \rightarrow \pi^*_{C \equiv N}$ electron delocalizations have much weaker impacts on the axial conformation preferences in compounds **1-3** than the $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C \equiv N}$ hyperconjugative interactions. In order to estimate quantitatively the impacts of the $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C \equiv N}$ and $LP_{ax}M_1 \rightarrow \pi^*_{C \equiv N}$ electron delocalizations on the axial conformation preferences in compounds **1-3**, we deleted these electron delocalizations from the Fock matrixes of the axial and equatorial conformations. Then, by re-diagonalizing the current Fock matrixes, we found the total self-consistent field energies are higher than the values which obtained from the original Fock matrixes (Table 4). Effectively, the energy changes [energy changes (EC)=energies of deletions-total SCF energies] in the axial conformations of compounds **1-3** associated with the deletions of the $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C \equiv N}$ electron delocalizations from their corresponding Fock matrixes are significantly greater than those obtained from the deletions of the $LP_{ax}M_1 \rightarrow \pi^*_{C \equiv N}$ hyperconjugative interactions. Accordingly, contrary to the published

conclusion in the literature²⁰ concerning the origin of the axial preferences in compounds **1-3**, our findings revealed that the $LP_{ax}M_1 \rightarrow \sigma^*_{C_2-C \equiv N}$ hyperconjugative interactions have determinant impacts on the axial preferences in compounds **1-3**. It is worth noting that by deletions of the $LP_{ax}M_1 \rightarrow \sigma^*_{C_2-C \equiv N}$ electron delocalizations from the axial and equatorial conformations of compounds **1-3**, their axial conformations become less stable than their corresponding equatorial conformations. Therefore, contrary to the published conclusions in the literature,^{17,18} the *HCAE* has a determinant impact on the conformational preferences in compounds **1-3**.



Scheme 3. Schematic representation of the orbital amplitudes (electron densities) associated with the through-space $LP_{ax}O_1 \rightarrow \pi^*_{C \equiv N}$ and through-bond $LP_{ax}O_1 \rightarrow \sigma^*_{C_2-C \equiv N}$ electron delocalizations in the axial conformation of compound **1**.

The above mentioned procedure (deletions of the $LP_{ax}M_1 \rightarrow \sigma^*_{C_2-N=C}$ and $LP_{ax}M_1 \rightarrow \pi^*_{N=C}$ electron delocalizations from the Fock matrixes) were performed for the axial and equatorial conformations of compounds **4-6** (Table 5). The results obtained showed that the impacts of the $LP_{ax}M_1 \rightarrow \pi^*_{N=C}$ hyperconjugative interactions on the axial conformation preferences in compounds **4-6** are also negligible compared to those obtained from the $LP_{ax}M_1 \rightarrow \sigma^*_{C_2-N=C}$ hyperconjugative interactions. Effectively, the stabilization energies associated with the $LP_{ax}M_1 \rightarrow \pi^*_{C \equiv N}$ electron delocalizations in the axial conformations of compounds **1-3** are greater than those obtained for the $LP_{ax}M_1 \rightarrow \pi^*_{N=C}$ electron delocalizations in compounds **4-6**. This fact can also be explained by the profiles of the orbital amplitudes (or electron densities) for the mixing of the doubly occupied orbitals of $LP_{ax}M_1$ [$M=O$ (**1**), S (**2**), Se (**3**)] with the adjacent

unoccupied orbitals of $\pi_{C\equiv N}$ and $\pi_{N=C}$ bonds (i.e. $LP_{ax}M_1+\pi^*_{C\equiv N}$ and $LP_{ax}M_1+\pi^*_{N=C}$ in the axial conformations of compounds **1-3** and **4-6**, respectively). Since the nitrogen atom of the *iso*-cyano ($N=C$) group is more electronegative than its carbon atom, the contribution of the nitrogen atom in the π^* anti-bonding orbital of the *iso*-cyano group is smaller than that of the carbon atom. As can be seen from Figure 1, the overlap of the main lobe of the M_1 non-bonding orbital ($LP_{ax}M_1$, [$M=O$ (**1**), S (**2**), Se (**3**)])) with the anti-bonding orbital of $C\equiv N$ bond ($\pi^*_{C\equiv N}$) is greater than the corresponding value for the overlap of $LP_{ax}M_1$ with $\pi^*_{N=C}$. This fact justifies the greater $LP_{ax}M_1\rightarrow\pi^*_{C\equiv N}$ electron delocalizations in the axial conformations of compounds **1-3** compared to the $LP_{ax}M_1\rightarrow\pi^*_{N=C}$ electron delocalizations in the axial conformations of compounds **4-6**.

In order to better illustration of the impacts of the $LP_{ax}M_1\rightarrow\sigma^*_{C_2-C\equiv N}$ and $LP_{ax}M_1\rightarrow\sigma^*_{C_2-N=C}$ electron delocalizations, respectively, on the axial preferences in compounds **1-3** and **4-6**, we also investigated the profiles of the orbital amplitudes (or electron densities) for the mixing of $LP_{ax}M_1$ non-bonding orbitals with the $\sigma^*_{C_2-C\equiv N}$ and $\sigma^*_{C_2-N=C}$ anti-bonding orbitals. Figure 2 shows that the mixing of $LP_{ax}M_1$ non-bonding orbitals with the $\sigma^*_{C_2-N=C}$ anti-bonding orbitals in the axial conformations of compounds **4-6** are greater than their mixings with the $\sigma^*_{C_2-C\equiv N}$ anti-bonding orbitals in the axial conformations of compounds **1-3**. This fact justifies reasonably the greater stabilization energies associated with the $LP_{ax}M_1\rightarrow\sigma^*_{C_2-N=C}$ electron delocalizations in the axial conformations of compounds **4-6** compared to those obtained from the $LP_{ax}M_1\rightarrow\sigma^*_{C_2-C\equiv N}$ electron delocalizations in the axial conformations of compounds **1-3**.

As Benn, Rauk and co-workers²⁰ pointed out previously, the $\sigma_{M_1-C_2}\rightarrow\pi^*_{C\equiv N}$ electron delocalization increases drastically from the axial and equatorial conformations of compound **1** to compound **3**. Our findings revealed that this trend is also observed for the $\sigma_{M_1-C_2}\rightarrow\pi^*_{N=C}$ electron delocalizations in the axial and equatorial conformations of compounds **4-6**. The $\sigma_{M_1-C_2}\rightarrow\pi^*_{C\equiv N}$ and $\sigma_{M_1-C_2}\rightarrow\pi^*_{N=C}$ hyperconjugative interactions decrease the electron occupancies of the $\sigma_{M_1-C_2}$ bonding orbitals, causing the increase of the $\sigma_{M_1-C_2}$ bond lengths and the decrease of the $\sigma_{C_2-C\equiv N}$ and $\sigma_{C_2-N=C}$ bond lengths in the axial and equatorial conformations of compounds **1-3** and **4-6**. Not that the $LP_{ax}M_1\rightarrow\sigma^*_{C_2-C\equiv N}$ and $LP_{ax}M_1\rightarrow\sigma^*_{C_2-N=C}$ electron delocalizations tend to increase the $\sigma_{C_2-C\equiv N}$ and $\sigma_{C_2-N=C}$ bond lengths in the axial conformations of compounds **1-3** and **4-6** but the $\sigma_{M_1-C_2}\rightarrow\pi^*_{C\equiv N}$ and $\sigma_{M_1-C_2}\rightarrow\pi^*_{N=C}$ electron delocalizations have opposite impacts. Accordingly, the variations of the $\sigma_{C_2-C\equiv N}$ and $\sigma_{C_2-N=C}$ bond lengths in the axial and equatorial conformations of compounds **1-3** and **4-6**, respectively, results from the confrontations between the impacts of the

$LP_{ax}M_1 \rightarrow \sigma^*_{C_2-C \equiv N}$ and $\sigma_{M_1-C_2} \rightarrow \pi^*_{C \equiv N}$ electron delocalizations in compounds **1-3** and also the $LP_{ax}M_1 \rightarrow \sigma^*_{C_2-N=C}$ and $\sigma_{M_1-C_2} \rightarrow \pi^*_{N=C}$ electron delocalizations in compounds **4-6**.

Based on equation 1, the $HCAE_{total}$ associated with the *HC-endo-AEs* and *HC-exo-AEs* in the equatorial and axial conformations decrease ongoing from compound **1** to compound **3** and also from compound **4** to compound **6**. The decrease of $HCAE_{total}$ values from compound **1** to **3** and also from compound **4** to compound **6** do not justify solely their anomeric relationships. Obviously, there are other factors that may have cooperative or uncooperative impacts with the $HCAE$ on the conformational properties of compounds **1-3** and **4-6**.

3-Assesing the impacts of the electrostatic model associated with the dipole-dipole interactions

In the gas phase or in the nonpolar media, the conformations with the larger dipole moments may have the greater overall energy compared to those with the smaller dipole moments.⁶ In order to examine the impacts of the electrostatic model associated with the dipole-dipole interactions, we compared the calculated total dipole moment values of the axial and equatorial conformations of compounds **1-3** and **4-6**. LC-wPBE/6-311+G** results showed that the dipole moments (μ) of the axial conformations of compounds **1-3** and **4-6** are smaller than those of their equatorial forms. Due to the contributions of the electrostatic energies associated with the dipole-dipole interactions on the total energies of the molecules, we calculated the differences between the dipole moments of the equatorial and axial conformations of compounds **1-3** and **4-6**. Interestingly, a similar trend observed for the variations of $\Delta(\mu_{eq}-\mu_{ax})$ parameters and the energy differences between the equatorial and axial conformations of compounds **1-3**. Accordingly, the variations of $\Delta(\mu_{eq}-\mu_{ax})$ parameters correlate very well with the differences between the equatorial and axial conformations of compounds **1-3**. Since $\Delta(\mu_{eq}-\mu_{ax})$ parameter increases significantly from compound **4** to compound **5** but decreases from compound **5** to compound **6**, its variations do not justify the variations of the axial conformation preferences in compounds **4-6**. This fact obviously demonstrates that the energy differences between the equatorial and axial conformations of compounds **4-6** results from the conflict between their corresponding $HCAEs$ and $\Delta(\mu_{eq}-\mu_{ax})$ parameters. Apart of $HCAEs$ and $\Delta(\mu_{eq}-\mu_{ax})$ parameters, we investigated the contributions of steric repulsions on the conformational behaviors of compounds **1-3** and **4-6**.

4-Total steric exchange energies (*TSEE*)

Steric exchange repulsion as the energy difference due to orbital orthogonalization can be expressed by natural steric analysis in accordance with a well-established physical picture of steric repulsions.²¹⁻²⁵ The Pauli exchange-type repulsion (*PETR*) (or steric exchange energy) includes effects from all occupied orbitals, therefore, the *PETR* typically contains contributions from covalent (intrabond) groups.

The NBO-LC-wPBE/6-311+G** analysis revealed that axial conformations of compounds **1-3** possess smaller *PETR* values compared to their equatorial conformations. This trend is also observed for compounds **4** and **5** but it is reversed in compound **6** (Table 2). Based on the results obtained, the calculated total steric exchange energy differences between the equatorial and axial forms [*i.e.* $\Delta(TSEE_{\text{eq}} - TSEE_{\text{ax}})$] decrease from compound **1** to compound **3** and also from compound **4** to compound **6**. These findings show that the *HCAE* and *PETR* tend to decrease the energy differences between the equatorial and axial conformations ongoing from compound **1** to compound **3** and also from compound **4** to compound **6** but the electrostatic model (*EM*) associated with the dipole-dipole interactions has different impacts. Obviously, the anomeric relationships in compounds **1-3** and **4-6** result from the cooperative and uncooperative impacts of *HCAE*, *PETR* and *EM*.

5-Orbital occupancies

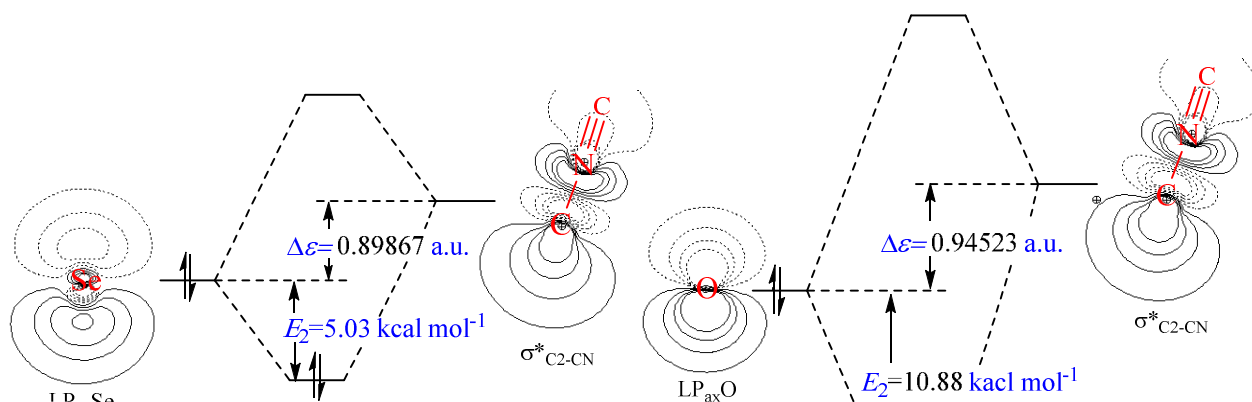
The occupancies of the non-bonded lone pairs of the six-membered rings [LPM, M=O(**1,4**), S(**2,5**), Se(**3,6**)] increase from compound **1** to compound **3** and from compound **4** to compound **6** while the $\sigma^*_{\text{C-C}\equiv\text{N}}$ and $\sigma^*_{\text{C-N}=\text{C}}$ anti-bonding orbital occupancies decrease inversely. These trends result from the decrease of the *HCAE* associated with the $\text{LP}_{\text{ax}}\text{M}_1 \rightarrow \sigma^*_{\text{C2-C}\equiv\text{N}}$ and $\text{LP}_{\text{ax}}\text{M}_1 \rightarrow \sigma^*_{\text{C2-N}=\text{C}}$ electron delocalizations ongoing from compound **1** to compound **3** and also from compound **4** to compound **6**, respectively (Table 2).

6-Orbital energies and overlapping

The overlap between the electron donor and acceptor orbitals in their antiperiplanar positions are greater than their *syn* or *gauche* arrangements, therefore, the hyperconjugative

interactions are anticipated to be more effective in the *anti*-arrangements rather than their corresponding *syn* or *gauche* positions.

The energies of the axial nonbonding orbitals ($LP_{ax}M_1$) increase by the decrease of their electronegativity values ongoing from the oxygen to selenium atoms. Interestingly, contrary to the normal expectation, the energies of the σ^*_{C2-CN} antibonding orbitals increase from the axial conformation of compound **1** to compound **3** but the changes in their energies are smaller than those observed for $LP_{ax}M_1$. A similar trend is observed for the energies of the $\sigma^*_{C2-N=C}$ antibonding orbitals of the axial conformations of compounds **4-6**. The results of this work showed that energy difference between donor [$\epsilon(LP_{ax}M_1)$] and acceptor [$\epsilon(\sigma^*_{C2-CN})$] orbitals (i.e. $\Delta[\epsilon(\sigma^*_{C2-CN})-\epsilon(LP_{ax}M_1)]$) decreases drastically from the axial conformation of compound **1** to compound **3**. Also, $\Delta[\epsilon(\sigma^*_{C2-CN})-\epsilon(LP_{ax}M_1)]$ parameters decrease from the axial conformations of compound **4** to compound **6** (Table 2). We may expect that the *HCAE* associated with the $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C\equiv N}$ electron delocalizations may increase with the decrease of $\Delta[\epsilon(\sigma^*_{C2-CN}) - \epsilon(LP_{ax}M_1)]$ parameters ongoing from the axial conformation of compound **1** to compound **3** but the results did not confirmed this expectation. Obviously, the *orbital overlap* (*S*) [off-diagonal elements (F_{ij})] plays a determinant role here. The *orbital overlap* (*S*) [off-diagonal elements (F_{ij})] values for the $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C\equiv N}$ electron delocalizations (*HC-endo-AE*) decrease from the axial conformation of compound **1** to compound **3**, causing the decrease of their corresponding donor-acceptor orbital overlapping. This fact is reflected on the profiles of the orbital amplitudes (or electron densities) for mixing of the $LP_{ax}M_1$ non-bonding orbitals with the $\sigma^*_{C2-C\equiv N}$ anti-bonding orbitals (Scheme 4).



Scheme 4. Representation of the unusual relationships between the *HCAE* associated with the $LP_{ax}M_1 \rightarrow \sigma^*_{C_2-C \equiv N}$ [$M=O$ (**1**), S (**2**), Se (**3**)] electron delocalizations and the energy gaps between the donor ($LP_{ax}O_1$ and $LP_{ax}Se_1$) nonbonding orbitals and the acceptor ($\sigma^*_{C_2-C \equiv N}$) antibonding orbitals in the axial conformations of compounds **1** and **3**.

7-Bond orders

The *HCAE* affects the structural parameters of the different configurations of a molecule *via* affecting their corresponding bond orders. Based on the results obtained, the calculated bond orders [i.e. Wiberg Bond Index (*WBI*)] for M_1-C_2 bonds of the axial conformations of compound **1-3** and compounds **4-6** are greater than those in their corresponding equatorial forms (Table 2). Differences between the *WBI* of the M_1-C_2 bonds in the axial and equatorial conformations, $\Delta[WBI(M_1-C_2)_{ax}-WBI(M_1-C_2)_{eq}]$, decrease from compound **1** to compound **3** and also from compound **4** to compound **6**, demonstrating the dominant impacts of their *HCAE* associated with the $LP_{ax}M_1 \rightarrow \sigma^*_{C_2-N=C}$ electron delocalizations compared to the *AEI* between two adjacent M_1 and C_2 atoms.

It should also be noted that $\Delta[WBI(C_2-C \equiv N)_{eq}-WBI(C_2-C \equiv N)_{ax}]$ parameters decrease from compound **1** to compound **3**. Similar trend is also observed for the variations of $\Delta[WBI(C_2-N=C)_{eq}-WBI(C_2-N=C)_{ax}]$ parameters ongoing from compound **4** to compound **6**. These facts can be explained by the decrease of the $LP_{ax}M_1 \rightarrow \sigma^*_{C_2-C \equiv N}$ and $LP_{ax}M_1 \rightarrow \sigma^*_{C_2-N=C}$ electron

delocalizations ongoing from compound **1** to compound **3** and also from compound **4** to compound **6**, respectively

8-Application of the maximum hardness principle for the conformational properties of compounds 1-3 and 4-6

The conformational behaviors of compounds **1-3** and **4-6** may be interpreted by means of the *Principle of Maximum hardness*.⁵⁰ Global *hardness* (η) in chemical species are related to the energy gaps between their frontier molecular orbitals (i.e. the HOMO-LUMO gap)⁵⁰⁻⁵⁵:

$$\eta = 0.5 (\varepsilon_{\text{LUMO}} - \varepsilon_{\text{HOMO}}) \quad (\text{eq. 3})$$

where η donates the global *hardness*.

By considering the validity of Koopmans' theorem, the hardness (η) can be written as (eq. 4):

$$\eta = 0.5 (I - A) \quad (\text{eq. 4})$$

where I and A are ionization potential and electron affinity of the molecules, respectively.

Based on the *Maximum hardness principle*, the hardest conformation of a molecule could be its most stable form. LC-wPBE/6-311+G** results showed that the axial conformations of compounds **1-3** and **4-6** are harder than their corresponding equatorial forms (Table 6). Based on the results obtained, the calculated global hardness (η) differences between the axial and equatorial conformations ($\Delta(\eta_{ax} - \eta_{eq})$) decrease from compounds **1** to compound **3** which does not correlate well with the trend observed for the variations of the energy differences between their axial and equatorial forms. Also, $\Delta(\eta_{ax} - \eta_{eq})$ parameter decreases from compound **4** to compound **5** but increases from compound **5** to compound **6**. Accordingly, the axial conformation preferences in compounds **1-3** and **4-6** could be justified by the *Maximum hardness principle* but this principle fails to account for the variations of the energy difference between the axial and equatorial conformations.

Conclusions

The long range corrected functional (LC- wPBE) calculations reported above and NBO interpretation provided a reasonable picture from energetic, structural, bonding and stereoelectronic points of view for compounds **1-6**. By deletion of the through bond $LPM_1 \rightarrow \sigma^*_{C2-C \equiv N}$, $LPM_1 \rightarrow \sigma^*_{C2-N=C}$, $LPM_1 \rightarrow \pi^*_{C \equiv N}$ and $LPM_1 \rightarrow \pi^*_{C \equiv N}$ electron delocalization [LPM , $M=O$ (**1,4**), S (**2,5**), Se (**3,6**)] from the Fock matrixes of the axial and equatorial conformations and with re-diagonalization and comparison of the current Fock matrixes with their original forms, it has been proved that $LPM_1 \rightarrow \sigma^*_{C2-C \equiv N}$ and $LPM_1 \rightarrow \sigma^*_{C2-N=C}$ hyper-conjugative interactions are responsible for the axial conformation preferences in compounds **1-3** and **4-6**. Importantly, contrary to the published conclusion in the literature, the through-space hyper-conjugative interactions (*i.e.* $LPM_1 \rightarrow \pi^*_{C \equiv N}$ and $LPM_1 \rightarrow \pi^*_{C \equiv N}$ electron delocalization) do not play a significant role on the conformational preferences of compounds **1-3** and **4-6**. The Pauli exchange-type repulsion (*PETR*) and hyper-conjugative anomeric effect (*HCAE*) differences between the equatorial and axial conformations [*i.e.* $\Delta(PETR_{eq}-PETR_{ax})$ and $\Delta(HCAE_{eq}-PETR_{ax})$] decrease from compound **1** to compound **3** and also from compound **4** to compound **6**, tending to the decrease of their corresponding energy differences [$\Delta(G_{eq}-G_{ax})$]. In contrast, the calculated $\Delta(G_{eq}-G_{ax})$ value increases from compound **1** to compound **2** but decreases from compound **2** to compound **3**. This trend is also observed for compounds **4-6**. Accordingly, the anomeric relationships in compounds **1-3** and **4-6** result from the cooperative and uncooperative impacts of *HCAE*, *PETR* and *EM*. Interestingly, the structural parameters of the six-membered rings of the axial and equatorial conformations of compounds **1-3** and **4-6** can be reasonably explained by the attractive electrostatic interactions between two adjacent atoms (*AEI*) which are in line with the resultant justification from the *HCAE*. The axial conformations of compounds **1-3** and **4-6** are harder than their corresponding equatorial conformations but the calculated global hardness (η) differences between the axial and equatorial conformations [$\Delta(\eta_{ax}-\eta_{eq})$] fails to account the conformational behaviors of compounds **1-3** and **4-6**.

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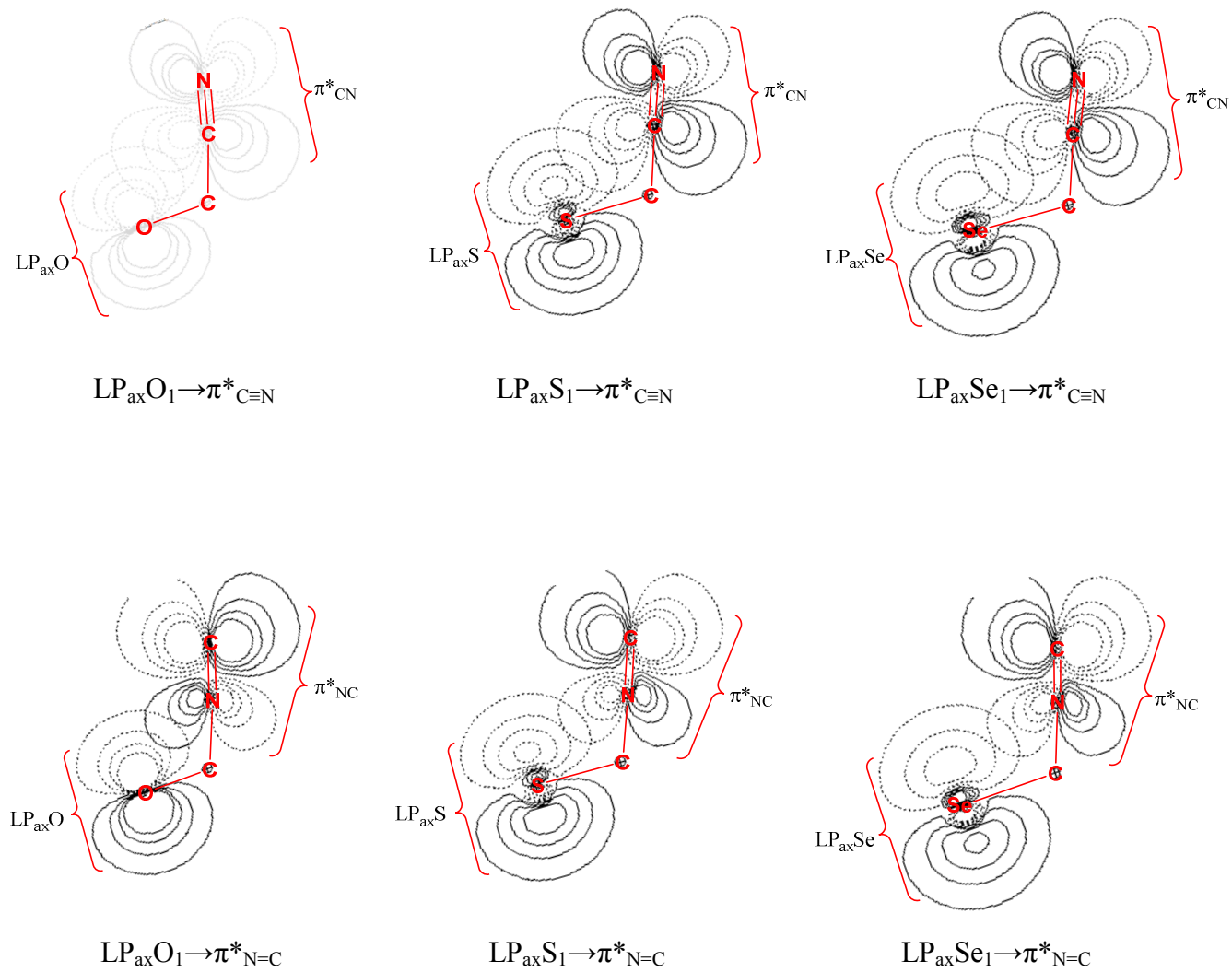


Figure 1. The calculated profiles of the orbital amplitudes (electron densities) for the through-space $LP_{ax}M_1 \rightarrow \pi^*_{C=N}$ [$M=O$ (1), S (2), Se (3)] and $LP_{ax}M_1 \rightarrow \pi^*_{N=C}$ [$M=O$ (4), S (5), Se (6)] electron delocalizations in the axial conformations of compounds 1-3 and 4-6.

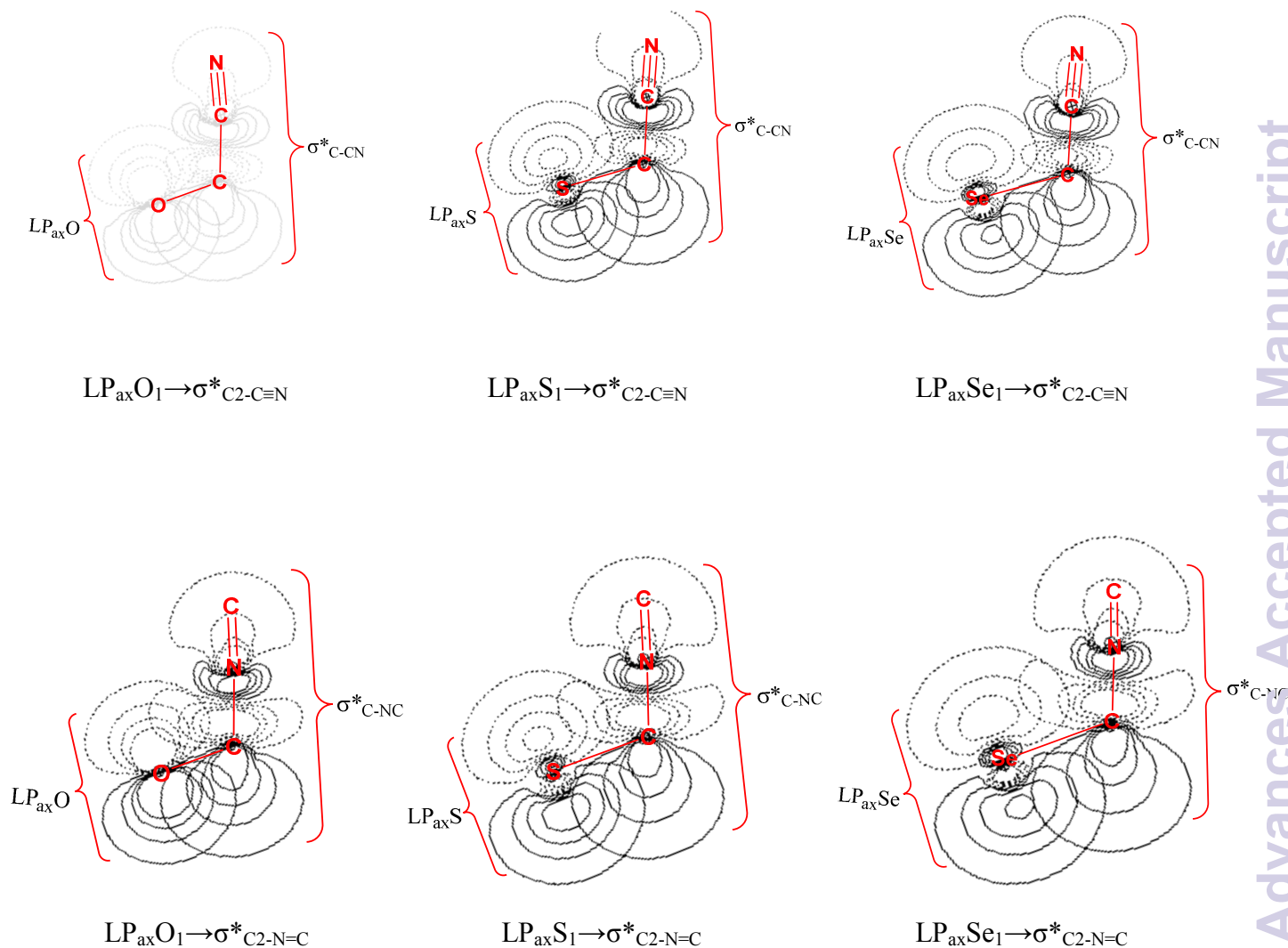


Figure 2. The calculated profiles of the orbital amplitudes (electron densities) for the through-bond LP_{ax}M₁ → σ*_{C2-C≡N} [M=O (1), S (2), Se (3)] and LP_{ax}M₁ → σ*_{C2-N=C} [M=O (4), S (5), Se (6)] electron delocalizations in the axial conformations of compounds 1-3 and 4-6.

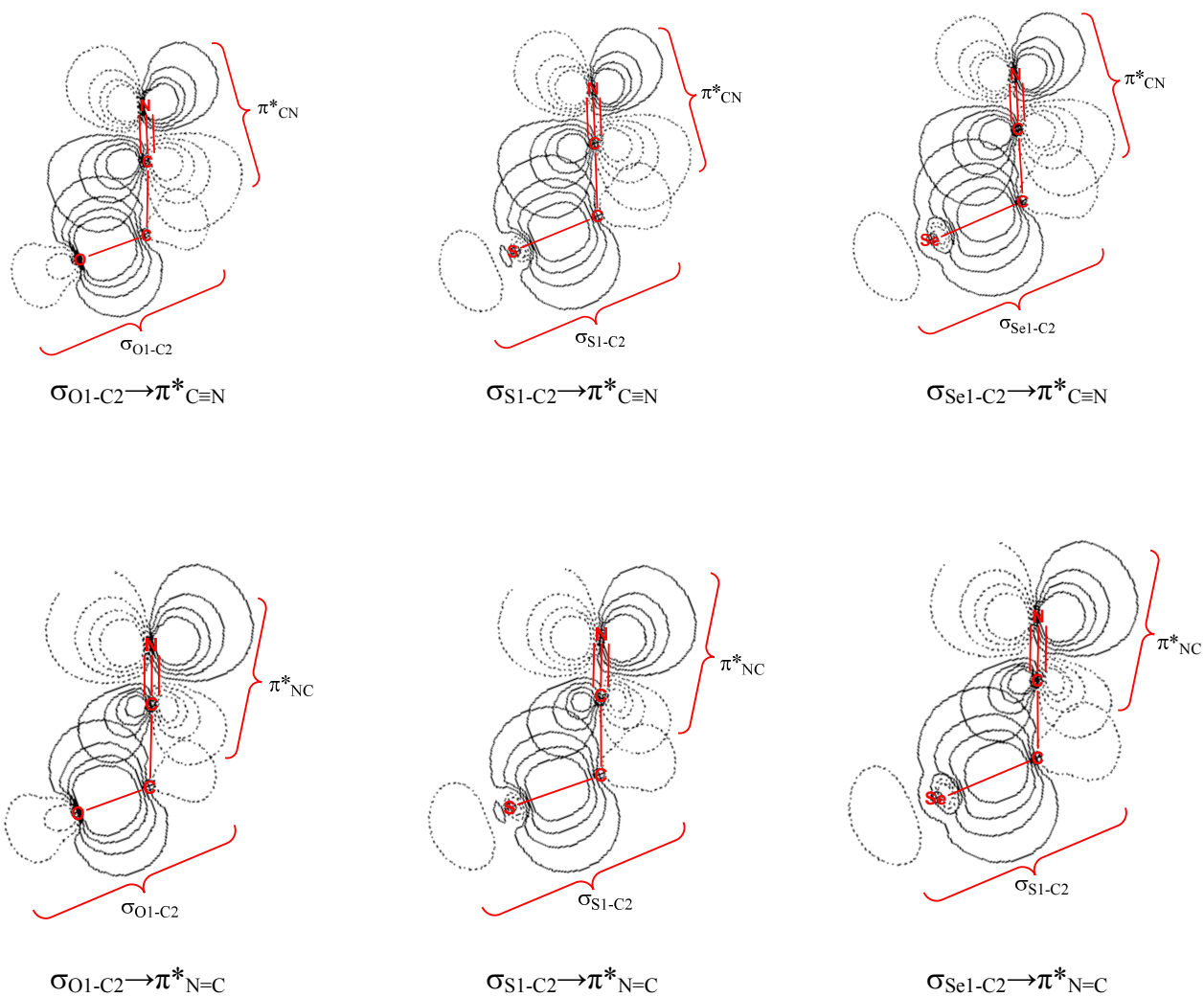


Figure 3. The calculated profiles of the orbital amplitudes (electron densities) for the through-bond $\sigma_{M1-C2} \rightarrow \pi^*_{C=N}$ [M=O (1), S (2), Se (3)] and $\sigma_{M1-C2} \rightarrow \pi^*_{N=C}$ [M=O (4), S (5), Se (6)] electron delocalizations in the axial conformations of compounds 1-3 and 4-6.

Table 1. LC- ω PBE/6-311+G** calculated structural parameters for the axial and equatorial conformations of compounds 1-6.

Geometry	1		2		3		4		5		6	
	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>
Bond lengths (Å)												
r_{1-2}	1.403	1.406	1.812 (1.815±1) ^a	1.817	1.949 (1.953±4) ^a	1.954	1.391	1.401	1.806	1.817	1.944	1.954
r_{2-3}	1.527	1.525	1.530 (1.534±2) ^a	1.529	1.530 (1.536±6) ^a	1.528	1.523	1.520	1.526	1.522	1.525	1.521
r_{3-4}	1.522	1.523	1.523 (1.526±2) ^a	1.523	1.524 (1.522±7) ^a	1.523	1.522	1.523	1.523	1.523	1.523	1.524
r_{4-5}	1.523	1.523	1.524 (1.517±2) ^a	1.523	1.525 (1.530±7) ^a	1.524	1.523	1.523	1.524	1.523	1.524	1.524
r_{5-6}	1.516	1.516	1.520 (1.519±2) ^a	1.519	1.519 (1.515±7) ^a	1.518	1.516	1.517	1.519	1.519	1.519	1.518
r_{6-1}	1.422	1.418	1.804 (1.8080±15) ^a	1.803	1.936 (1.937±5) ^a	1.936	1.424	1.418	1.804	1.804	1.936	1.938
$r_{2-C\equiv N}$	1.481	1.467	1.463 (1.477±2) ^a	1.458	1.459 (1.465±6) ^a	1.455	-	-	-	-	-	-
$r_{C\equiv N}$	1.146	1.145	1.147 (1.138±2) ^a	1.146	1.147 (1.137±6) ^a	1.147	-	-	-	-	-	-
$r_{2-N=C}$	-	-	-	-	-	-	1.442	1.420	1.428	1.419	1.423	1.417
$r_{N=C}$	-	-	-	-	-	-	1.165	1.164	1.165	1.165	1.165	1.165
$\Delta[r_{1-2}(eq)-r_{1-2}(ax)]$	0.003		0.005		0.005		0.010		0.011		(0.010	
$\Delta[r_{2-C\equiv N}(ax)-r_{2-C\equiv N}(eq)]$	0.014		0.005		0.004		-		-		-	
$\Delta[r_{2-N=C}(ax)-r_{2-N=C}(eq)]$	-		-		-		0.022		0.009		0.006	
$\Delta[r_{1-2}(ax)-r_{1-6}(ax)]$	-0.019		0.008		0.013		-0.033		0.002		0.008	
$\Delta[r_{1-2}(eq)-r_{1-6}(eq)]$	-0.012		0.014		0.018		-0.017		0.013		0.016	
Bond angles (°)												
θ_{1-2-3}	112.1	111.9	112.1 (112.73±9) ^a	112.4	111.8 (112.4±3) ^a	112.1	112.6	111.8	112.4	112.4	112.0	112.1

Table 1 continued...

θ_{2-3-4}	110.5	109.2	112.8 (112.50±11) ^a	111.8	113.6 (113.1±4) ^a	112.6	110.8	109.3	113.1	111.9	113.9	112.6
θ_{3-4-5}	109.7	110.1	113.0 (113.27±12) ^a	113.1	114.0 (114.1±4) ^a	114.1	109.6	110.1	112.9	113.1	113.9	114.0
θ_{4-5-6}	110.1	110.0	112.5 (112.51±12) ^a	112.3	113.2 (113.6±3) ^a	113.1	110.0	109.9	112.3	112.2	113.1	113.0
θ_{5-6-1}	111.6	111.5	112.6 (112.93±10) ^a	112.8	112.4 (113.1±3) ^a	112.6	111.6	111.4	112.6	112.8	112.4	112.6
θ_{6-1-2}	113.3	111.5	97.8 (98.93±7) ^a	96.9	94.5 (95.7±2) ^a	94.0	114.1	111.5	98.0	96.7	94.7	94.1
$\theta_{1-2-C=N}$	110.9	(107.8	110.7 (109.55±10) ^a	108.3	110.3 (110.1±3) ^a	108.1	-	-	-	-	-	-
$\theta_{1-2-N=C}$	-	-	-	-	-	-	110.5	107.2	111.3	107.8	111.1	107.9
$\Delta[\theta_{6-1-2(ax)}-\theta_{6-1-2(eq)}]$	1.8		0.9		0.5		2.6		1.3		0.6	
Torsion angles (°)												
$\phi_{1-2-3-4}$	54.3	57.0	60.5	61.9	61.7	62.5	53.3	57.3	59.9	62.2	61.1	62.7
$\phi_{2-3-4-5}$	-52.2	-52.4	-59.0	-59.6	-61.8	-62.6	-52.0	-52.4	-58.8	-59.7	-61.6	-63.0
$\phi_{3-4-5-6}$	53.29	52.6	59.3	59.5	61.9	62.5	53.6	52.3	59.4	59.3	62.0	62.6
$\phi_{4-5-6-1}$	-56.1	-56.3	-61.5	-61.8	-62.5	-62.5	-55.8	-56.2	-61.6	-61.8	-62.6	-62.3
$\phi_{5-6-1-2}$	58.8	60.9	55.6	56.0	53.9	53.6	57.8	61.2	55.2	56.1	53.6	53.4
$\phi_{6-1-2-3}$	-57.7	-61.4	-54.8	-56.1	-53.2	-53.6	-56.3	-61.9	-54.0	-56.3	-52.5	-53.6
$\Delta[\phi_{6-1-2-3(eq)}-\phi_{6-1-2-3(ax)}]$	3.7		1.3		0.4		5.6		2.3		1.1	

^a From X-ray crystallography, Ref. 20.

Table 2. NBO-LC-wPBE/6-311+G** calculated stabilization energies (E_2 , in kcal mol⁻¹) associated with the *HC-endo-AE* and *HC-exo-AE*, off-diagonal elements (F_{ij} , in a.u.), orbital energy (ε , in a.u.), orbital energy differences ($\Delta\varepsilon$, in a.u.), orbital occupancies (e), bond orders (Wiberg bond indexes, *WBI*), dipole moments (μ , in debye) and total steric exchange energies (*TSEE*) for the axial and equatorial conformations of compounds **1-6**.

	1		2		3		4		5		6	
	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>
<i>HC-endo-AE</i>												
LP _{eq} M ₁ →σ* _{C2-CN}	0.69	2.80	0.61	-	-	-	-	-	-	-	-	-
LP _{ax} M ₁ →σ* _{C2-CN}	10.88	-	6.53	-	5.03	-	-	-	-	-	-	-
LP _{ax} M ₁ →π* _{C≡N}	1.83	-	2.39	-	2.36	-	-	-	-	-	-	-
σ _{M1-C2} →π* _{C≡N}	1.81	2.10	7.22	8.05	9.56	10.58	-	-	-	-	-	-
σ _{M1-C2} →σ* _{C≡N}	2.29	2.48	3.01	3.24	2.97	3.12	-	-	-	-	-	-
σ _{C3-Hax} →σ* _{C2-C≡N}	4.10	-	4.27	-	4.28	-	-	-	-	-	-	-
σ _{C3-Hax} →σ* _{C2-Hax}	-	3.38	-	3.52	-	3.56	-	3.43	-	3.57	-	3.58
LP _{eq} M ₁ →σ* _{C2-NC}	-	-	-	-	-	-	0.53	4.87	0.66	0.65	0.54	-
LP _{ax} M ₁ →σ* _{C2-NC}	-	-	-	-	-	-	17.52	-	11.11	-	8.66	-
LP _{ax} M ₁ →π* _{N=C}	-	-	-	-	-	-	0.98	-	1.01	-	0.93	-
σ _{M1-C2} →π* _{N=C}	-	-	-	-	-	-	1.23	1.49	4.70	5.27	6.12	6.68
σ _{M1-C2} →σ* _{N=C}	-	-	-	-	-	-	1.81	1.99	2.47	2.69	2.49	2.65
σ _{C3-Hax} →σ* _{C2-N=C}	-	-	-	-	-	-	5.47	0.60	5.72	-	5.75	-
<i>HC-exo-AE</i>												
π _{C≡N} →σ* _{M1-C2}	5.31	5.61	3.91	3.87	3.92	3.82	-	-	-	-	-	-
σ _{C≡N} →σ* _{M1-C2}	-	-	-	-	-	-	-	-	-	-	-	-
σ _{C2-C≡N} →σ* _{C3-Hax}	1.96	-	1.83	-	1.82	-	-	-	-	-	-	-
σ _{C2-Hax} →σ* _{C3-Hax}	0.67	3.03	-	3.09	-	3.11	-	2.87	-	3.05	-	3.10
π _{N=C} →σ* _{M1-C2}	-	-	-	-	-	-	8.39	9.30	6.51	6.34	6.64	6.31

Table 2 continued...

$\sigma_{\text{C2-N=C}} \rightarrow \sigma_{\text{C3-Hax}}^*$	-	-	-	-	-	-	1.27	-	1.21	-	1.20	-
$\Sigma(\text{HCAE})$	29.54	19.40	29.77	21.77	29.94	24.19	37.20	24.55	33.39	21.57	32.33	22.33
$\text{HCAE}_{\text{total}} = \Sigma(\text{HCAE})_{\text{eq}} - \Sigma(\text{HCAE})_{\text{ax}}$	-10.14		-8.00		-5.75		-12.65		-11.82		-10.00	
F_{ij}												
$\text{LP}_{\text{ax}}\text{M}_1 \rightarrow \sigma_{\text{C2-CN}}^*$	10.88	-	6.53	-	5.03	-	-	-	-	-	-	-
$\text{LP}_{\text{ax}}\text{M}_1 \rightarrow \sigma_{\text{C2-NC}}^*$	-	-	-	-	-	-	17.52	-	11.11	-	8.66	-
ε												
$\text{LP}_{\text{ax}}\text{M}_1$	-0.43188	-0.42925	-0.35809	-0.35769	-0.34388	-0.34349	-0.43368	-0.42837	-0.35714	-0.35581	-0.34276	-0.34121
$\sigma_{\text{C2-C}\equiv\text{N}}^*$	0.51335	0.54186	0.54339	0.55837	0.55479	0.56671	-	-	-	-	-	-
$\sigma_{\text{C2-N=C}}^*$	-	-	-	-	-	-	0.43867	0.47675	0.45481	0.47516	0.46401	0.47925
$\Delta[\varepsilon(\sigma_{\text{C2-C}\equiv\text{N}}^*) - \varepsilon(\text{LP}_{\text{ax}}\text{M}_1)]$	0.94523	0.97111	0.90148	0.91606	0.89867	0.91020	-	-	-	-	-	-
$\Delta[\varepsilon(\sigma_{\text{C2-N=C}}^*) - \varepsilon(\text{LP}_{\text{ax}}\text{M}_1)]$	-	-	-	-	-	-	0.87235	0.90512	0.81195	0.83097	0.80677	0.82032
e												
$\text{LP}_{\text{ax}}\text{M}_1$	1.92329	1.92894	1.92854	1.93667	1.94031	1.94946	1.91428	1.92878	1.92387	1.93806	1.93769	1.95072
$\sigma_{\text{C2-C}\equiv\text{N}}^*$	0.04363	0.03028	0.03729	0.02602	0.03394	0.02490	-	-	-	-	-	-
$\sigma_{\text{C2-N=C}}^*$	-	-	-	-	-	-	0.06868	0.47675	0.45481	0.04035	0.05533	0.03362
μ												
$\Delta(\mu_{\text{eq}} - \mu_{\text{ax}})$	3.8042	5.4707	3.8647	5.6068	3.9238	5.5597	3.7173	5.3409	3.6976	5.4205	3.7142	5.3367
	1.6665		1.7421		1.6359		1.6236		1.7229		1.6225	
	-		-		-		-		-		-	

Table 2 continued...

<i>WBI</i>												
C ₂ -M ₁	0.9356	0.9256	0.9759	0.9743	0.9361	0.9349	0.9495	0.9256	0.9928	0.9715	0.9541	0.9369
C ₂ -C≡N	1.0097	1.0207	1.0334	1.0423	1.0447	1.0517	-	-	-	-	-	-
C ₂ -N=C	-	-	-	-	-	-	0.9223	0.9590	0.9516	0.9727	0.9610	0.9769
M ₁ -C ₆	0.9013	0.9059	1.0099	1.0094	0.9904	0.9871	0.8976	0.9057	1.0105	0.9715	0.9910	0.9871
$\Delta[WBI(C_2-M_1)_{ax}-WBI(C_2-M_1)_{eq}]$	0.0100		0.0016		0.0012		0.0239		0.0213		0.0172	
$\Delta[WBI(C_2-CN)_{eq}-WBI(C_2-CN)_{ax}]$	0.0110		0.0089		0.0070		-		-		-	
$\Delta[WBI(C_2-NC)_{eq}-WBI(C_2-NC)_{ax}]$	-		-		-		0.0367		0.0211		0.0159	
<i>NAC</i>												
M ₁	-0.57104	-0.57753	0.23728	0.23679	0.35416	0.35542	-0.57388	-0.53052	0.22489	0.22104	0.33788	0.33676
C ₂	0.01505	0.01517	-0.46998	-0.46831	-0.52262	-0.52099	0.27435	0.27315	-0.19130	-0.17709	-0.24032	-0.22807
C ₆	-0.05441	-0.04640	-0.53681	-0.53407	-0.58939	-0.58891	-0.05536	-0.04860	-0.53656	-0.53682	-0.58887	-0.59081
C ₇	0.26964	0.29782	0.28870	0.29780	0.28663	0.29198	-	-	-	-	-	-
N ₇	-	-	-	-	-	-	-0.55511	-0.53052	-0.54181	-0.53473	-0.54243	-0.53853
$\Delta[NAC(M_1)_{ax}-NAC(C_2)_{ax}]$	0.58609	-	0.70726	-	0.87678	-	0.84823	-	0.41619	-	0.57820	-
$\Delta[NAC(M_1)_{eq}-NAC(C_2)_{eq}]$	-	0.59270	-	0.70510	-	0.87641	-	0.80367	-	0.39813	-	0.56482
$\Delta[NAC(M_1)_{ax}-NAC(C_6)_{ax}]$	0.51663	-	0.77409	-	0.94355	-	0.51852	-	0.76145	-	0.92675	-
$\Delta[NAC(M_1)_{eq}-NAC(C_6)_{eq}]$	-	0.53113	-	0.77086	-	0.94433	-	0.48192	-	0.75786	-	0.92757
$\Delta[NAC(M_1)_{ax}-NAC(M_1)_{eq}]$	0.00649		0.00049		-0.00126		-0.04336		0.00385		0.00112	
$\Delta[NAC(C_7)_{eq}-NAC(C_7)_{ax}]$	0.02818		0.00910		0.00535		-		-		-	
<i>TSEE</i>												
$\Delta[TSEE_{eq}-TSEE_{ax}]$	6.91		4.73		3.44		9.88		3.74		-0.73	

Table 3. LC- ω PBE/6-311+G** calculated zero-point energies (ZPE), corrected electronic energies (E_o), thermodynamic functions (H , G in hartree, S in $\text{cal mol}^{-1}\text{K}^{-1}$) and parameters [ΔZPE , ΔE_o , ΔH , ΔG (in kcal mol^{-1}) and ΔS (in $\text{cal mol}^{-1}\text{K}^{-1}$)] at 25 °C and 1 atm pressure for the axial and equatorial conformations of compounds **1-6**.

	H	S	G	ZPE	E_o	ΔH	ΔS	ΔG	ΔZPE	ΔE_o
1-ax	-363.714233	82.483	-363.753423	0.147672	-363.722205	0.00	0.000	0.00	0.18	0.00
1-eq	-363.712609	82.754	-363.751928	0.147378	-363.720626	1.02	0.271	0.94	0.00	0.99
2-ax	-686.613462	85.571	-686.654120	0.144436	-686.621945	0.00	0.000	0.00	0.10	0.00
2-eq	-686.611058	86.005	-686.651922	0.144272	-686.619609	1.52	0.434	1.38	0.00	1.47
3-ax	-2689.714633	88.809	-2689.756831	0.143163	-2689.723471	0.00	0.000	0.00	0.10	0.00
3-eq	-2689.712719	89.255	-2689.755130	0.142983	-2689.721629	1.18	0.446	1.05	0.00	1.14
4-ax	-363.686485	82.957	-363.725904	0.147332	-363.694590	0.00	0.000	0.00	0.24	0.00
4-eq	-363.683530	83.299	-363.723113	0.146942	-363.691699	1.87	0.342	1.77	0.00	1.83
5-ax	-686.579949	86.007	-686.620814	0.143995	-686.588564	0.00	0.000	0.00	0.13	0.00
5-eq	-686.576874	86.503	-686.617975	0.143781	-686.585575	1.93	0.496	1.78	0.00	1.88
6-ax	-2689.679948	89.235	-2689.722351	0.142728	-2689.688920	0.00	0.000	0.00	0.14	0.00
6-eq	-2689.677757	89.737	-2689.720399	0.142499	-2689.686817	1.37	0.502	1.22	0.00	1.31

Table 4. LC-wPBE/6-311+G** calculated total SCF energies, energies of deletions associated with the deletion of $LP_{ax}M_1 \rightarrow \pi^*_{C=N}$ and $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C=N}$ electron delocalizations and their corresponding energy changes (EC , in: a.u.) in the axial and equatorial conformations of compounds **1-3**.

Deletion of $LP_{ax}M_1 \rightarrow \pi^*_{C=N}$ electron delocalizations						
Geometries	1		2		3	
	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>
Total SCF energies	-363.869877235	-363.868003429	-686.76638123	-686.763875372	-2689.866435031	-2689.864455657
Energies of deletions	-363.867840505	-363.868003429	-686.763756547	-686.763875372	-2689.863827828	-2689.864455657
Energy changes (EC)	0.002037(1.28) ^a	0.000000(0.00) ^a	0.002625(1.65) ^a	0.00000(0.00) ^a	0.002607(1.64) ^a	0.00000(0.00) ^a
$\Delta(EC_{ax}-EC_{eq})$	1.28 ^a		1.65 ^a		1.64 ^a	
Deletion of $LP_{ax}M_1 \rightarrow \sigma^*_{C2-C=N}$ electron delocalizations						
Geometries	1		2		3	
	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>
Total SCF energies	-363.869877235	-363.868003429	-686.766381230	-686.763875372	-2689.866435031	-2689.864455657
Energies of deletions	-363.857058514	-363.864217316	-686.758315947	-686.763875372	-2689.860081504	-2689.864455657
Energy changes (EC)	0.012819(8.04) ^a	0.003786(2.38) ^a	0.008065(5.06) ^a	0.00000(0.00) ^a	0.006354(3.99) ^a	0.00000(0.00) ^a
$\Delta(EC_{ax}-EC_{eq})$	5.66 ^a		5.06 ^a		3.99 ^a	

^a Values in kcal mol⁻¹.

Table 5. LC-wPBE/6-311+G** calculated total SCF energies, energies of deletions associated with the deletion of $LPM_1 \rightarrow \pi^*_{N=C}$ and $LPM_1 \rightarrow \sigma^*_{C_2-N=C}$ electron delocalizations and their corresponding energy changes (in a.u.) in the axial and equatorial conformations of compounds **4-6**.

Deletion of $LPM_1 \rightarrow \pi^*_{C=N}$ electron delocalizations						
Geometries	4		5		6	
	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>
Total SCF energies	-363.841757985	-363.838451146	-686.732558783	-686.729356039	-2689.831467104	-2689.829148277
Energies of deletions	-363.840621750	-363.838451146	-686.731407801	-686.729356039	-2689.830397069	-2689.829148277
Energy changes (<i>EC</i>)	0.001136 (0.71) ^a	0.000000(0.00) ^a	0.001151 (0.72) ^a	0.000000(0.00) ^a	0.001070 (0.67) ^a	0.000000(0.00) ^a
$\Delta(EC_{ax}-EC_{eq})$	0.71 ^a		0.75 ^a		1.64 ^a	
Deletion of $LPM_1 \rightarrow \sigma^*_{C_2-N=C}$ electron delocalizations						
Geometries	4		5		6	
	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>	<i>ax</i>	<i>eq</i>
Total SCF energies	-363.841757985	-363.838451146	-686.732558783	-686.729356039	-2689.831467104	-2689.829148277
Energies of deletions	-363.822130797	-363.832057026	-686.719659598	-686.728381467	-2689.821194057	-2689.829148277
Energy changes (<i>EC</i>)	0.019627 (12.32) ^a	0.006394 (4.01) ^a	0.012899 (8.09) ^a	0.000975 (0.61) ^a	0.010273 (6.45) ^a	0.000000(0.00) ^a
$\Delta(EC_{ax}-EC_{eq})$	8.31 ^a		7.48 ^a		6.45 ^a	

^a Values in kcal mol⁻¹.

Table 6. LC- ω PBE/6-311+G** calculated energies (in hartree) of HOMO (ϵ_{HOMO}), LUMO (ϵ_{LUMO}), $\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}}$ and global hardness (η) for the axial and equatorial conformations of compounds **1-6**.

	ϵ_{HOMO}	ϵ_{LUMO}	$\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}}$	I	A	η	$\Delta(\eta_{ax} - \eta_{eq})$
1-ax	-0.39652	0.05380	0.45032	0.39652	-0.05380	0.22516	0.00256(1.60) ^a
1-eq	-0.39330	0.05191	0.44521	0.39330	-0.05191	0.22261	0.00000
2-ax	-0.35476	0.05257	0.40733	0.35476	-0.05257	0.20367	0.00225(1.41) ^a
2-eq	-0.35409	0.04874	0.40283	0.35409	-0.04874	0.20142	0.00000
3-ax	-0.34019	0.04657	0.38676	0.34019	-0.04657	0.19338	0.00179(1.12) ^a
3-eq	-0.34020	0.04298	0.38318	0.34020	-0.04298	0.19159	0.00000
4-ax	-0.39844	0.05340	0.45184	0.39844	-0.05340	0.22592	0.00349(2.19) ^a
4-eq	-0.39154	0.05332	0.44486	0.39154	-0.05332	0.22243	0.00000
5-ax	-0.35521	0.05203	0.40724	0.35521	-0.05203	0.20362	0.00252(1.58) ^a
5-eq	-0.35216	0.05005	0.40221	0.35216	-0.05005	0.20111	0.00000
6-ax	-0.33979	0.04733	0.38712	0.33979	-0.04733	0.19356	0.00272(1.701) ^a
6-eq	-0.33802	0.04366	0.38168	0.33802	-0.04366	0.19084	0.00000

^a Values in kcal mol