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Local aromaticity study of heterocycles using *n*-center delocalization indices: the role of aromaticity on the relative stability of position isomers

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Abstract—A quantitative study on local aromaticity based on *n*-center electron delocalization indices, *n* being the number of atoms in the ring, is performed on a series of heterocycles containing N, O or S. The results indicate that the order of stability within a series of position isomers is not controlled by aromaticity but by other structural factors. Thus, for a certain series of monocycles position isomers (diazoles, triazoles, tetrazoles, diazines, triazines, and tetrazines) the most stable compound is the least aromatic one and vice versa. However, aromaticity controls the stability for series of isomers where these structural factors are similar. For the case of isocompounds, like isobenzopyrrole, isobenzofuran or isobenzothiophene, the large decrease in the aromaticity of the benzene ring with regard to their isomers makes them less stable.

1. Introduction

The concept of aromaticity was first introduced by Kekulé in 1865,[1] who related the 'extra stabilization' displayed by certain cyclic unsaturated compounds to a cyclic π electron delocalization. The most significant example of aromatic compound is benzene, the cyclic π electron delocalization of this compound, as it is well known, was represented by Kekulé as the coexistence of two equivalent valence structures, called since then Kekulé valence structures or Kekulé resonance structures.

Clar's rule, also known as π-sextets rule,[2,3] and Chemical Graph Theory (CGT) indices[4–18] are qualitative measures of the local aromaticity based on the Kekulé valence structures for polycyclic aromatic hydrocarbons (PAH's). Clar's rule states that the Kekulé valence structure with the largest number of disjoint aromatic π-sextets is the most important for the characterization of the properties of PAH's. Aromatic π-sextets are defined as six π-electrons localized in a single benzene-like ring separated from adjacent rings by formal C–C single bonds. The Clar's structure for a given PAH is the valence structure having the maximum number of isolated and localized aromatic π-sextets, with a minimum number of localized double bonds. It also indicates that the most aromatic rings are those displaying π-sextets at the Clar's structure. According to CGT, the local aromaticity is given by the quotient of the number of times a ring appears in all Kekulé valence structures as a benzene Kekulé ring and the number of Kekulé valence structures. Aromaticity indices so obtained were demonstrated to be a more quantitative description of Clar's rule.[18] For instance, Scheme 1 shows the Kekulé structures for phenanthrene, the Clar's structure (the π-sextets are indicated with a circle) and the values of the CGT indices, reflecting larger aromaticity for the outer rings.

The partitioning of the π electrons into individual rings using the 'numerical Kekulé valence structures', NKVS, has also been employed as an aromaticity index.[18,19] For a certain Kekulé structure the corresponding NKVS represents the number of π electrons within each individual ring (6, 3, and 5 according to the first Kekulé valence structure in Scheme 1). The number of π electrons of a certain ring is calculated by adding all the NKVS and dividing by the total number of Kekulé structures (26/5 and 18/5 for, respectively, outer and inner rings of phenanthrene). The larger the number of π electrons in the ring the larger is the local aromaticity.

Other indices of local aromaticity are based on quantitative measures. Most of them belong to two groups: structure based indices and magnetic-based indices. All of them were completely reviewed in two recent special issues of Chemical Reviews.[20] The most widely used magnetic-based index is the NICS (nucleus-independent chemical shift) index,[21] which is defined as the negative value of the shielding, computed at a ring center (NICS(0)) or at some other

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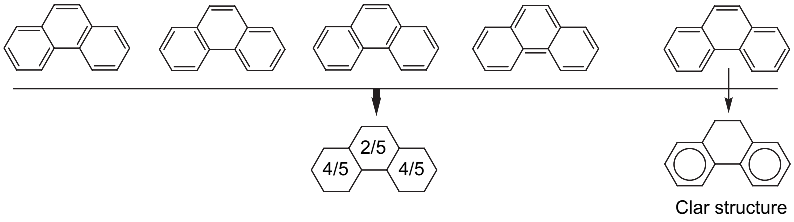


Scheme 1. Kekulé structure, the Clar's structure and the values of the CGT indices for phenanthrene.

interesting point of the system. For instance, the NICS(1) is computed at the distance of 1 Å above the ring center, where the π orbitals have their maximum density. For planar or nearly planar molecules, the influences of other magnetic shielding contributions different from the π system are reduced using NICS(1).[21]

The use of multicenter bond indices or *n*-center delocalization indices, *n*-DI's, as a measure of aromaticity in 5 and 6-center rings was initially proposed by Giambiagi et al.[22–25] They interpreted all the possible valence structures of benzene, including those of Kekulé, in terms of 6-center electron delocalization.[24,25] Since the *n*-DI measures the extension of the electron delocalization to *n* atoms, aromatic molecules are expected to display larger *n*-DI's than those of non-aromatic when they are computed for all atoms of the ring. *n*-DI's have been recently applied to study the total and local aromaticity of a large number of aromatic and antiaromatic systems.[26–32] In our previous work[32] we have compared indices derived from the *n*-DI's with the CGT indices, and the total and ring resonance energies, RE, calculated by the Conjugated Ring Circuits Model,[18,33–36] obtaining a very good agreement between qualitative and quantitative indices for polybenzenoid hydrocarbons. Overall, *n*-DI's are a quantitative representation of electron delocalization not influenced by other factors, contrary to what happens to magnetic indices (like NICS) and measure local aromaticity due to a certain ring current.[30,32] Moreover, they can be applied on any system, contrary to structural based indices, like HOMA's, or aromatic stabilization energies, which require a reference system that, for instance, make them not useful for transition states.

In this work, we study heterocyclic aromatic compounds, containing four-, five-, or six-membered rings with N, O, and S atoms. Our aim is to discuss the contribution of aromaticity to the relative stability for some series of positional isomers, showing that the small differences of aromaticity are less important than other structural factors, but in the absence of these factors aromaticity controls stability. These results are also in line with NICS(0) and NICS(1) values. However, one should be careful when using NICS, especially when studying systems that contain a different number of rings because they are not always straightforwardly related to local aromaticity.[30,37–39] We also show that *n*-DI's provide a quantitative interpretation of the qualitative predictions on local aromaticity based on CGT. To reach this conclusion, the values of the *n*-DI's are compared to the CGT indices and the ring π electron populations obtained from the NKVS.

Successful comparison of *n*-DI's with resonance energies of some of the molecules studied here has already been presented in our previous work.[31] We are not comparing *n*-DI's with isodesmic and homodesmotic aromatic stabilization energies as most of the molecules studied here contain heteroatoms. Recent studies[40,41] have evidenced some shortcomings in the calculation of strain energies employing these processes that are also expected to hold for the calculation of aromatic stabilization energies.

1.1. Calculation of *n*-DI's and computational details

Since the mathematical derivation of the *n*-center delocalization index via Generalized Population Analysis, GPA, in the context of Mulliken analysis[42] and QTAIM,[31] has been presented in previous papers, we are only showing the relevant expressions employed for its calculation. Thus, expanding the number of electrons of a molecule, *N*, in terms of the *n*-order spin free density matrix, the expressions 1 and 2 for the *n*-center electron delocalization are obtained within the framework of the QTAIM. $\Delta_n(A,B,\ldots,M)$ represents the electron population correlated along the *n*-centers, in other words, the delocalized-electron population among those *n* atoms. Thus, it is defined as the summation running over those permutations (denoted by *P*) of the *n* atoms *A*, *B*, …, *M* that provide different values of $\delta_n(A,B,\ldots,M)$, as defined by Eq. 2. The summation in $\delta_n(A,B,\ldots,M)$ is the '*n*-center electron delocalization term' assigned to every specific permutation. Permutations of the atoms in Eq. 2 provide different values when $n>3$ unless symmetry makes some of them equivalent.

The expressions 1 and 2 are strictly valid for mono-determinant wave functions, the MO's employed can be HF or Kohn–Sham (KS). Nevertheless, it has to be noticed that, for KS formalism, the mono-determinant wave function is an approximation to the real one. So that Eq. 2 is an approximation to the correct DFT delocalization index, which does not include electron correlation explicitly and corresponds to some effective independent particle model.[43]

$$\Delta_n(A,B,\ldots,M) = \sum_P \delta_n(A,B,\ldots,M) \tag{1}$$

$$\delta_n(A,B,\ldots,M) = 4n \sum_{i,j,k,\ldots,m}^{N/2} \langle i|j\rangle_A \langle j|k\rangle_B \cdots \langle m|i\rangle_M \tag{2}$$

We have studied a series of polycyclic aromatic molecules containing 1–3 rings (Fig. 1). In particular, 29 monocyclic, 23 bicyclic and 4 tricyclic compounds. All the bicycles and tricycles considered are formed by benzenoid rings fused to one of the monocycles studied. The nomenclature employed is an acronym where the first letter indicates whether the

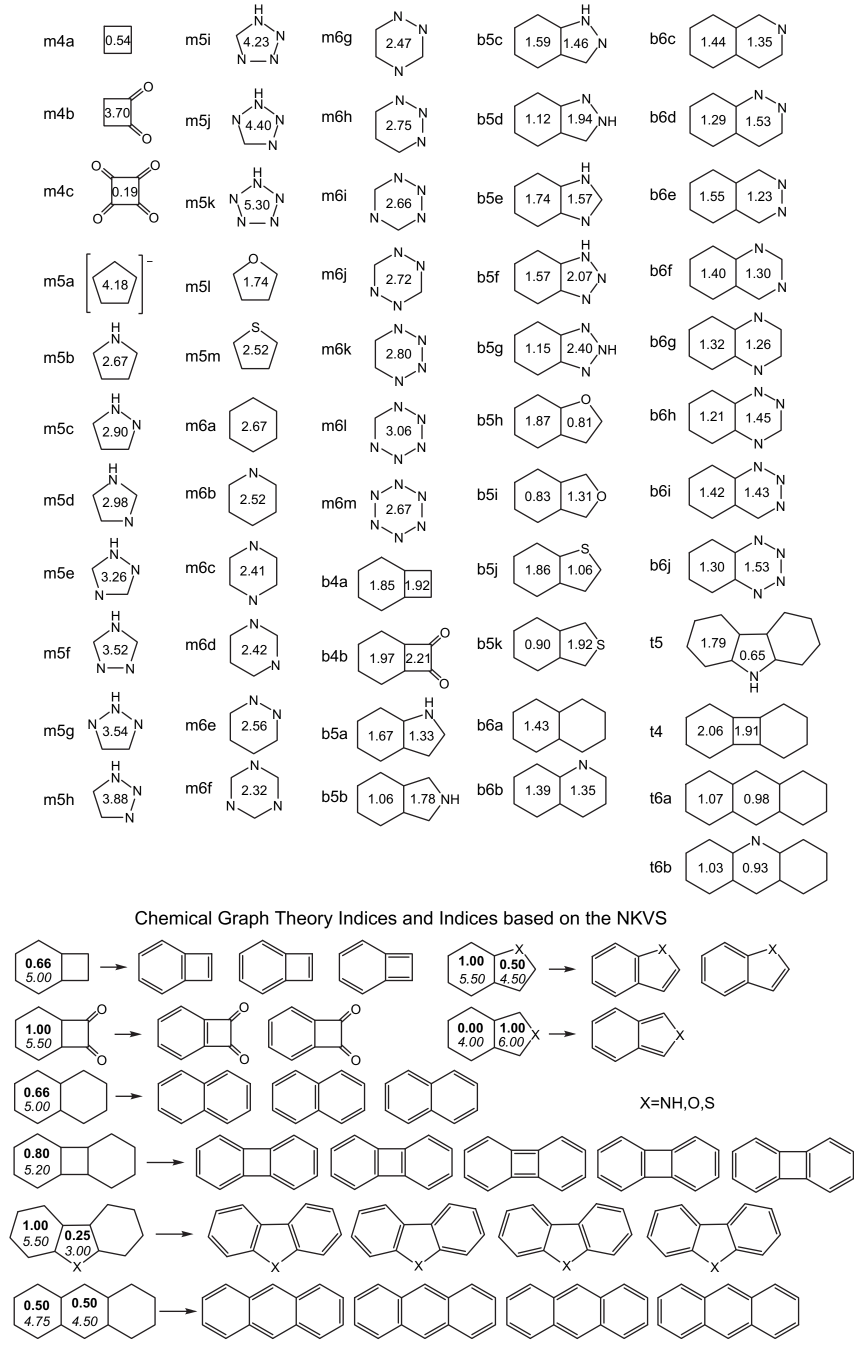


Figure 1. Molecular nomenclature and values of *n*-DI's (in au), CGT indices (in boldface) and ring π electron populations obtained from NKVS's (in italics).

molecule is monocyclic (m), bicyclic (b) or tricyclic (t); it is followed by a number indicating the number of centers in the non-benzenoid ring (except for benzene, naphthalene, and anthracene where all the rings are benzenoids), finally another letter is added to differentiate compounds.

The calculations were carried out on Kohn–Shan MO's computed at the B3LYP/6-311++G(d,p) level of calculation. The Gaussian 03 program[44] was employed to obtain the molecular geometries, energies and the MO's. The AIMPAC package of programs developed by Bader and co-workers[45] was used to integrate the Atomic Overlap Matrix (AOM) within the atomic domains. Our own program, NDELOC,[46] was used to compute the *n*-DI's according to Eqs. 1 and 2. *n*-DI's can be rigorously split into σ and π contributions for planar molecules bearing always in mind that the zero-flux surfaces must be determined using the total electron density. We have found in previous studies on polycyclic aromatic hydrocarbons that the π contribution, π *n*-DI's, correspond to 95% of the total *n*-DI's for highly delocalized systems with $n \geq 5$.[31] Because of computational reasons, we have only calculated the π *n*-DI's but not the total *n*-DI's. The non-planar **m6m** molecule is an exception where the 6-DI value was calculated using all the occupied MO's. The accuracy of the QTAIM numerical integration was checked by comparing the summation of the AOM terms for a pair of MO's *i*,*j*, $\sum_A \langle i|j\rangle_A$, with the value of the overlap integral over the whole space, $\langle i|j\rangle$, which is expected to be 0. We found that the differences between $\langle i|j\rangle$ and $\sum_A \langle i|j\rangle_A$ is less than 2×10^{-5} for all cases.

Several position isomers are included within the series of molecules studied, we have computed the relative energies of these isomers with regard to the most stable one, ΔE, and compared the results with their relative aromaticities. The structures were confirmed as energy minima, but the zero point vibrational energy correction (ZPVE) was not included in the calculation of ΔE since only electronic effects are going to be compared.

2. Results and discussion

2.1. Monoheterocycles

Figure 1 shows the molecules studied and the values of 4, 5, and 6-DI's computed for them. It has to be noticed that the direct comparison of *n*-DI's computed for rings with a different number of centers does not provide a picture of relative aromatic stabilization. In fact, aromatic stabilization does not only depend on the extension of the electron delocalization over the *n* centers, but also on the number of centers (see Ref. 31 for a detailed discussion). The fact that **m5a–m5k** molecules display much larger 5-DI's than the 6-DI of benzene cannot be interpreted as an indication as these five-membered rings are more aromatic than benzene. This is not a shortcoming affecting to this work as our goal is to compare the aromaticity and stability of isomers.

The monocyclic compounds **m4a**, **m4b**, and **m4c** display 4-DI values that can be justified by the well-known Hückel rule. Hence, the 4*n*-electron systems (**m4a** and **m4c**) are antiaromatic and therefore show very small 4-DI values, on the contrary the 4*n*+2-system (**m4b**) is aromatic and therefore shows a large 4-DI.

All the five centers and six electrons ([5c–6e]) monocycles studied here are aromatic and display large 5-DI's. The order of aromaticity indicated by 5-DI's follows some trends: (i) inclusion of heteroatoms decreases the aromaticity with regard to the cyclopentadienyl anion (**m5a**) in the order $O>S\approx N$; (ii) in contrast, the inclusion of more and more N's in the pyrrole ring (**m5b**) increases the aromaticity up to reach values larger than that of **m5a** for systems with four (**m5i** and **m5j**) and five N's (**m5k**); (iii) for 5-center rings with the same number of N's the most aromatic ring is that having the largest number of N–N bonds, in the case of two compounds with the same number of N–N bonds the most aromatic is that having the smallest number of –N–N–H units.

[6c–6e] monocyclic polyazoles (**m6b–m6m**) are all planar but **m6m**, which presents a twisted-boat geometry due to the important electron–electron repulsion between N-lone pairs. 6-DI's calculated for this series indicate that insertion of N atoms decreases the aromaticity unless they form N–N bonds. Thus, we observe Δ_6(**m6a**)$>\Delta_6$(**m6b**)$>\Delta_6$(**m6c**)$\approx$ Δ_6(**m6d**)$>\Delta_6$(**m6f**) for compounds with increasing number of nitrogens with no N–N bond. The same trend holds for series where N atoms are inserted in rings with one N–N bond: Δ_6(**m6e**)$>\Delta_6$(**m6g**), and two N–N bonds: Δ_6(**m6h**)$>$ Δ_6(**m6i**) (Fig. 1). On the contrary, progressive formation of N–N bonds increases Δ_6 values, thus: Δ_6(**m6b**)$<\Delta_6$(**m6e**)$<$ Δ_6(**m6h**)$<\Delta_6$(**m6k**)$<\Delta_6$(**m6l**). This series breaks for **m6m**, whose Δ_6 is equivalent to that of benzene. Nevertheless, this can be expected from its non-planar geometry, which decreases the effective π overlapping.

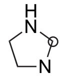
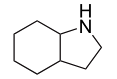
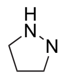
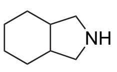
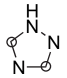
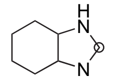
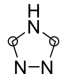
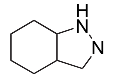
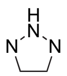
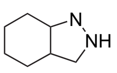
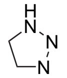
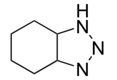
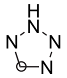
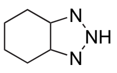
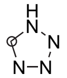
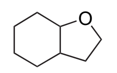
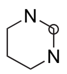
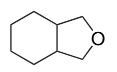
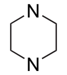
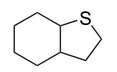
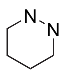
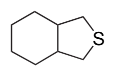
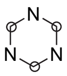
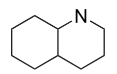
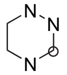
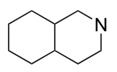
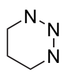
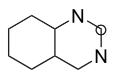
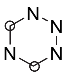
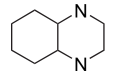
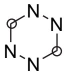
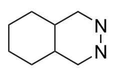
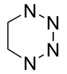
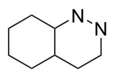
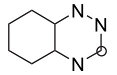
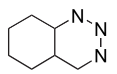
Table 1 also collects the values of the B3LYP/6-311++G(d,p) relative energies of position isomers in the series. It shows that the order of stability is reversed with regard to the order of aromaticity. Thus, in the series of diazoles (**m5c** and **m5d**), triazoles (**m5e–m5h**), tetrazoles (**m5i** and **m5j**), diazines (**m6c–m6e**), triazines (**m6f–m6h**), and tetrazines (**m6i–m6k**) the most stable compound is the least aromatic one and vice versa. The fact that the most stable isomer is not necessarily the most aromatic was already discussed by Havenith et al.[47] This trend is supported by values of NICS(0) and NICS(1) calculated by Schleyer et al.[21] for the same compounds, if we exclude diazoles and diazines. Thus, NICS(0) and NICS(1) indicate that the most aromatic isomer is the most stable for diazoles, whereas for diazines the most stable isomer is the most aromatic using NICS(0) but the contrary is found using NICS(1).[21] Also, particular cases are observed for NICS(0) values in the series of triazines and tetrazines; i.e., according to NICS(0) the least stable is the most aromatic but the most stable does not correspond to the least aromatic isomer. Summarizing, the order of stability seems not to be controlled by the aromaticity but other structural factors. Thus, aromaticity is just a small stabilizing factor compared to other destabilizing factors.

The relative energies of isomers shown in Table 1 point out that three structural factors are of main importance for the stability: (i) N–N bonds destabilize the energy of diazines and diazoles, thus the most stable isomer is that showing the smallest number of N–N bonds; (ii) N–N bonds where none of the nitrogens is attached to a hydrogen destabilize more than –N–N–H units for azoles, as can be seen from the relative energies of the following pairs of isomers: **m5e/m5f**, **m5g/m5h**, and **m5j/m5i**; (iii) the –N–C–N–C– structure is more stabilizing than the –N–C–C–N– one and the –N–N–N– unit is less destabilizing than the presence of two N–N bonds for azines, look for instance at the pairs **m6c/m6d** and **m6i/m6j**. A simple qualitative rule that summarizes the relative stability of the isomers of azoles and azines can be derived from (i), (ii), and (iii). The larger the number of –N–C–N– units (marked in Table 1 with an open circle on the C atom) the larger is the stability of the compound. When two isomers present the same number of –N–C–N– units, the most stable is that showing the largest number of –N–N–H units for azoles and –N–N–N– units for azines.

2.2. Polyheterocycles

The *n*-DI's computed for this series agree perfectly with aromaticity indices based on CGT (Fig. 1). Thus, CGT indices and the ring π electron populations obtained from the NKVS (also included in Fig. 1) suggest that the local aromaticity of the benzene ring is larger in **b4b** than in **b4a**. Moreover, CGT indices and NKVS's suggest a large decrease on the local aromaticity of benzene rings fused to five-membered

Table 1. Relative energies (in kcal mol^{-1}) for the series of isomers drawn in Figure 1

m5d		0.0	**b5a**		0.0
m5c		10.6	**b5b**		9.1
m5e		0.0	**b5e**		0.0
m5f		6.8	**b5c**		14.6
m5g		12.7	**b5d**		19.5
m5h		17.4	**b5g**		0.0
m5j		0.0	**b5f**		0.2
m5i		2.9	**b5h**		0.0
m6d		0.0	**b5i**		14.4
m6c		4.1	**b5j**		0.0
m6e		23.0	**b5k**		11.0
m6f		0.0	**b6b**		0.0
m6g		27.3	**b6c**		1.2
m6h		44.0	**b6f**		0.0
m6i		0.0	**b6g**		3.1
m6j		7.1	**b6e**		23.0
m6k		20.9	**b6d**		24.1
			b6h		0.0
			b6i		16.3

Open circles indicate –N–C–N– units (see text for details).

rings in isocompounds, like isobenzopyrrole (**b5b**), isobenzofuran (**b5i**), and isobenzothiophene (**b5k**) (Fig. 1), with regard to the corresponding non-isocompounds. In contrast, the local aromaticity of the corresponding five-membered ring increases from non-iso to isocompounds. This qualitative expectation is confirmed by the values of the 6-DI's and 5-DI's of the series comprising from **b5a** to **b5k**. Also, the values of the NICS(0) and NICS(1) for benzopyrrole, benzofuran, benzothiophene, and the corresponding isocompounds confirm this trend.[21] However, Martínez et al.[48] reported NICS values that showed the opposite trend for the same molecules. It seems that they mistook the values of the six-membered rings for the five-membered rings.

The qualitative character of CGT indices and NKVS's does not allow distinguishing the local aromaticity of the two six-membered rings fused in the **b6a**–**b6j** series. This trend is not changed by the presence of N atoms. On the contrary, 6-DI's show small differences among the rings (Fig. 1). These differences can be explained considering the different weight of Kekulé valence structures; the one with the smallest number of N$=$N formal double bonds being the most important. Thus, when this structure does not display a π-sextet on the benzene ring, the aromaticity of the benzene ring decreases and that of the nitrogenated ring increases (**b6d**, **b6h**, and **b6j**). The contrary is found for **b6e**, where the benzene ring shows the largest local aromaticity of the series. As for the remaining molecules of the series, there is no favored Kekulé valence structure on the basis of the number of N$=$N formal double bonds. The same trend is followed by NICS(0) and NICS(1) values calculated by Schleyer et al.[21] For instance, NICS(0) for the benzene ring of **b6d** and **b6e** are, respectively, -8.76 and -9.93, and NICS(1) are -10.85 and -11.28. Moreover, the opposite trend is displayed by the nitrogenated rings, the NICS(0) values are, respectively, -6.81 and -5.61 for **b6d** and **b6e**, and the NICS(1) are -11.50 and -10.13.

6-DI's and 5-DI's are also in good agreement with CGT indices and NKVS's for tricyclic compounds. Thus, the most aromatic benzenoid rings correspond to **t4** and **t5**, where all the Kekulé valence structures display π-sextets on these rings. The valence structure of **t4** where the benzenoid and cyclobutadiene rings display 4π electrons is the only exception. However, this valence structure is expected to have a very small weight for obvious reasons. As CGT Indices do not consider different weights for valence structures, the local aromaticity they reflect for the benzenoid rings of **t4** is smaller than those of **t5**. On the other hand, the 5-DI of pyrrole ring in **t5** shows an important decrease in aromaticity as expected from CGT indices. **t6a** and **t6b** are other examples of good agreement between qualitative and quantitative indices. Thus, 6-DI's are quite similar between outer and inner rings but slightly larger for the former. The ring π electron populations obtained from NKVS's display the same trend. However, NICS(0) and NICS(1) values show larger aromaticity for the inner rings in **t6a** and **t6b**.[49] The reasons for discrepancies displayed by different indices (like PDI, HOMA, ring critical points, ring currents, circuit resonance energies, etc.) about the local aromaticity in linear polyacenes have been extensively discussed in a series of recent articles.[30–32,50]

Finally, the relative energies of series of bicyclic isomers are also collected in Table 1. Contrary to that found for monocyclic compounds, the effect of aromaticity on the stability of different isomers can be noticed in the absence of other significant structural factors. Thus, the pairs **b5a/b5b**, **b5j/b5k**, and **b5h/b5i** display energies that are 9.1, 11.0, and 14.4 kcal mol^{-1} higher for the iso-compounds. These relative energies follow the same trend as the differences on the

6-DI's of the benzene ring, the most aromatic ring of both. Moreover, the relative energy increases as the aromaticity of the five-membered ring decreases (see values of 5-DI's for pyrrole, furan, and thiophene). The pair **b5c/b5d** is another example for the influence of aromaticity. In this case, the energy of the iso-compound is 4.9 kcal mol^{-1} higher. The relative energies of the remaining isomers can be explained by the same rules as stated above for monocyclic compounds.

3. Conclusions

n-DI's have been employed to study the local aromaticity of heterocycles containing –N, –O, and –S quantitatively, as well as the corresponding polyheterocycles formed by fusing benzene rings to one of them. The values of the *n*-DI's are in agreement with the qualitative interpretation of the local aromaticity provided by the Chemical Graph Theory. In addition, *n*-DI's provide information about the aromaticity changes arising from the substitution of C's by N's in benzene rings. According to the *n*-DI's we can get the following conclusions:

(i) The aromaticity of five-membered rings is reduced by the inclusion of a heteroatom ($O>S\approx N$). However, the inclusion of more and more N atoms in the pyrrole ring increases the aromaticity reaching values larger than that of cyclopentadienyl anion for 4- and 5-nitrogen systems.
(ii) For 5- and 6-center rings with the same number of nitrogens the most aromatic ring is that having the largest number of N–N bonds.
(iii) The order of stability within a series of position isomers is not controlled by aromaticity but by other important structural factors as the increase of intramolecular electrostatic repulsions. Thus, for certain series of monocycles position isomers (diazoles, triazoles, tetrazoles, diazines, triazines, and tetrazines) the most stable compound is the least aromatic one and vice versa. However, aromaticity controls the stability for series of isomers where these structural factors are constant. For the case of isocompounds, like isobenzopyrrole, isobenzofuran or isobenzothiophene, the large decrease of the aromaticity of the benzene ring with regard to their isomers makes them less stable. NICS(0) and NICS(1) indices are in line with these results.

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