On the Performance of Some Aromaticity Indices: A Critical Assessment Using a Test Set

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Abstract: Aromaticity is a central chemical concept widely used in modern chemistry for the interpretation of molecular structure, stability, reactivity, and magnetic properties of many compounds. As such, its reliable prediction is an important task of computational chemistry. In recent years, many methods to quantify aromaticity based on different physicochemical properties of molecules have been proposed. However, the nonobservable nature of aromaticity makes difficult to assess the performance of the numerous existing indices. In the present work, we introduce a series of fifteen aromaticity tests that can be used to analyze the advantages and drawbacks of a group of aromaticity descriptors. On the basis of the results obtained for a set of ten indicators of aromaticity, we conclude that indices based on the study of electron delocalization in aromatic species are the most accurate among those examined in this work.

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Introduction

One of the most controversial and debated issues in chemistry, especially in theoretical and computational chemistry, is aromaticity. Since aromaticity is not a directly measurable property, it can not be defined unambiguously. Consequently, it constitutes a chemical *unicorn* in the signification given by Frenking and Krapp.[1] However, in this respect, aromaticity is not different from many important nonobservable concepts in chemistry.[2] In spite of the lack of a proper definition and the fuzzy nature of aromaticity,[3] its usefulness as a central chemical concept for the interpretation of molecular structure, stability, reactivity, and magnetic properties of many compounds remains still unquestionable.[4–10] In addition, the recent discovery of all-metal aromatic clusters has shown that its scope of application is far wider than what has been appreciated formerly.[11,12]

The evaluation of aromaticity in the whole molecule or parts thereof is usually done indirectly by measuring some physicochemical property that reflects a manifestation of its aromatic character.[10,13,14] This leads to the myriad of classical structural,[15] magnetic,[16,17] energetic,[18] electronic,[19] and reactivity-based measures of aromaticity. All current available indices represent approximations (sometimes arbitrary) to the problem of measuring aromaticity and no single property exists that could be taken as a direct measure of aromaticity. Although some authors suggest abandoning the search for new quantitative measures of aromaticity,[3] others believe that more precise quantitative descriptors can be helpful to reach a better understanding of aromaticity. Interestingly, some researchers have recently proposed to use neural networks to classify compounds according to their aromaticity.[20]

All existent indices are, in general, easily calculated but unfortunately they do not always give consistent results among themselves.[8,21] Thus, for instance, predictions based on magnetic criteria of aromaticity often deviates from those based on energetic grounds.[22] Many times the apparent contradictions found among differently based indices are overcome by addressing to

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the so-called multidimensional character of aromaticity.[14,15,23–26] In this way, one can argue that it is understandable that different indices afford divergent orderings since one compound may be more aromatic than other in one dimension and less aromatic in another.[10] This explains why many authors advise to use a set of indices based on different physical properties to characterize aromatic compounds.[12,16,21,27–29] In this case, one can feel safe about the derived conclusions only when all criteria provide the same results for the set of compounds analyzed. If different criteria produce contradictory results, the final conclusions, if any, are necessarily much weaker.

When a new index of aromaticity is defined, usually the results obtained by this new index in a set of chosen aromatic compounds are correlated with some previously defined descriptors of aromaticity. If correlations are acceptable it is reported that the new index is a good indicator of aromaticity. If not, many times it is simply said that the result obtained is a manifestation of the multidimensional character of aromaticity. The problem with this approach is obvious: how can one differentiate methods that provide essentially spurious results from those that simply do not correlate because of the multidimensional character of aromaticity? In this work, we neither doubt about nor assume the multidimensional character of aromaticity, but as pointed out by Bultinck et al.,[30,31] the use of the multidimensional character of aromaticity as a generic excuse to allow considering any local aromaticity index defined a good descriptor irrespective of the results obtained should be avoided. Fortunately, the accumulated chemical experience provides several examples for which most chemists would agree about the expected aromaticity trends in a given series of compounds. In this paper, we build a set of aromaticity tests using a number of such examples. The chosen tests must fulfill two requirements: first, the size of the systems involved must be relatively small to facilitate a fast application and, second, controversial cases must be avoided. We consider here that, as far as aromaticity is concerned, a series of aromatic rings is controversial when using a large enough set of aromaticity descriptors the aromaticity ordering of the rings cannot be decided unambiguously.

As an example of a controversial case, we can mention the case of the inner and outer rings of anthracene and, in general, of the aromaticity order for the different six-membered rings (6-MRs) of any linear polyacene. This series is excluded because of the existence of contradicting predictions of various aromaticity indices, which prevents to achieve the consensus about the order of aromaticity of individual benzene rings with at least similar reliability as in other cases.[31,32] Thus, the NICS and the HOMA descriptors of aromaticity indicate that the local aromaticity increases from the external to the central ring.[33–35] The FLU index[36] points out the same trend in aromaticity, as well as a scaled SCI index,[37] the analysis of ring currents,[38–41] the calculation of resonance energies[42,43] and bond orders,[44] some graph theory-based descriptors,[2,45] and several aromaticity indicators based on charge density properties derived from the Quantum Theory of Atoms in Molecules (QTAIM).[46] On the other hand, other different graph theory-based descriptors,[2,45] together with molecular quantum similarity calculations,[47] the Fermi Hole Density Delocalization index of Matta,[32,48,49] ring currents at a semiempirical level,[50] MCI and I_{ring} indices,[32,37,47,51,52] as well as bond resonance energies[53–55] yield the opposite trend of outer rings more aromatic than the inner ones. Finally, the PDI basically attributes the same aromaticity to the inner and outer rings of anthracene,[32,35,56,57] which is what is expected from a simple model such as the Clar's aromatic π-sextet rule.[58,59] In our opinion, it is clear that the relative aromaticity of the two different rings in anthracene is a controversial issue and it should not be included in a list of aromaticity tests.

With this in mind, the tests proposed in this work are depicted in Scheme 1. It contains five tests that analyze different benzene distortions, two tests that study the effect of substitution and complexation in the benzene ring, a couple more that check the ring and atom size dependence, another two including heteroaromatic systems of different sizes, two containing a series of the so-called Clar's and fulvenes systems, and, finally, two tests that analyze aromaticity in chemical reactions. All these tests share widely accepted and well-understood aromatic trends. The results obtained will show, however, that many of the most common indices of aromaticity fail predicting some of the expected behaviors. We hope that the fifteen proposed tests (together with others that can be added in future work) can be a useful tool to check whether a new index of aromaticity is better than previous existing ones to quantify aromaticity in organic compounds and to establish the performance of existing indices in order to decide which set of indices has to be used for a given study.

Measures of Aromaticity

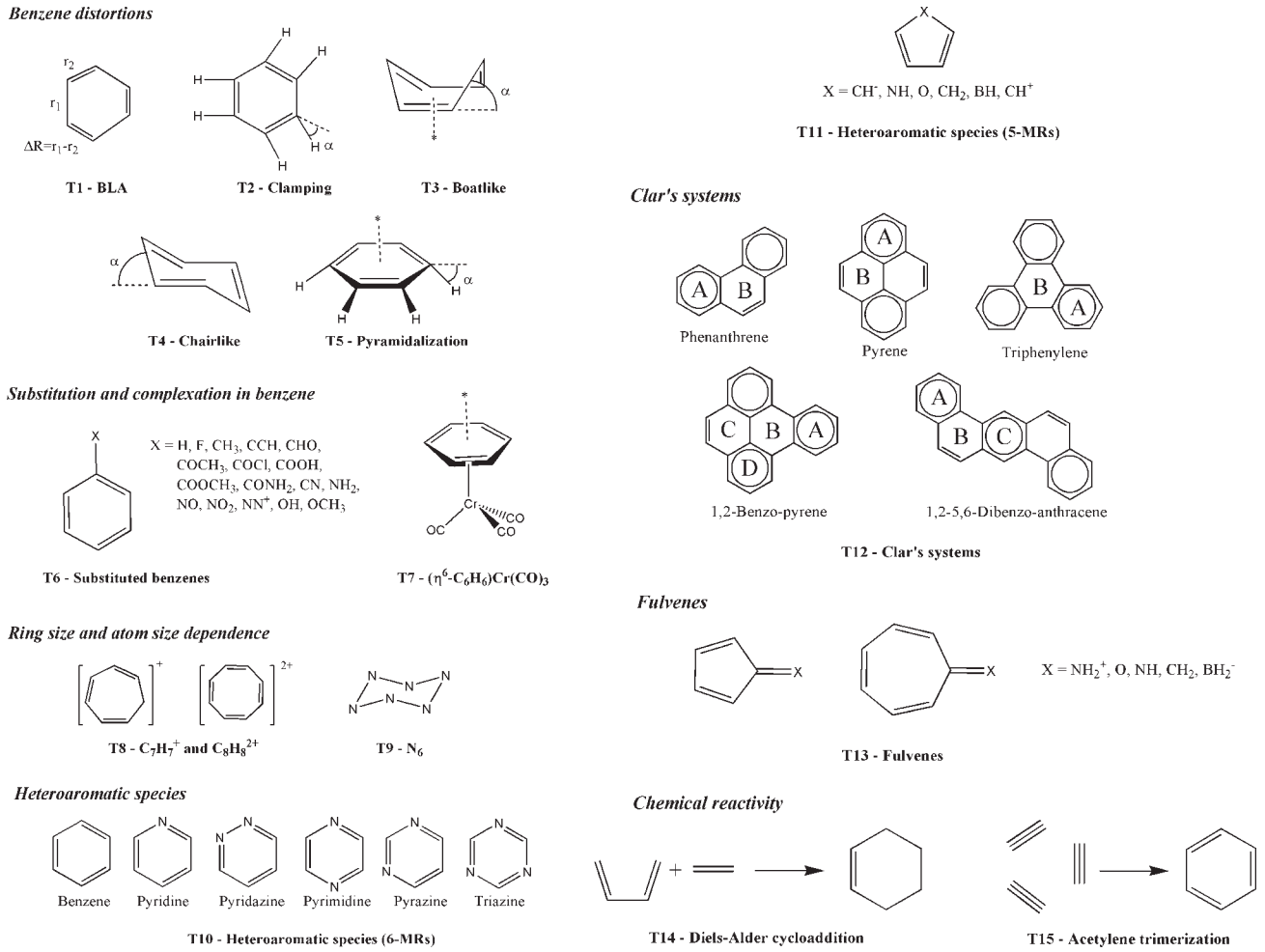
It is not viable to apply all the indices of local aromaticity published to date to the fifteen tests of Scheme 1 and, consequently, we have made a selection of ten descriptors of local aromaticity based on structural, magnetic, and electronic manifestations of aromaticity. For some particular cases, we have included in the discussion aromatic stabilization energies (ASEs) (tests 6 and 11) and resonance energies (REs) (test 10) reported in the literature.[18] We want to emphasize here that we are not advocating that the indices analyzed here are the best among those that can be found in the literature, but what is true is that they are among the most widely-used descriptors of aromaticity.

As a structure-based measure, we have employed the harmonic oscillator model of aromaticity (HOMA) index, defined by Kruszewski and Krygowski as[60,61]:

$$\mathrm{HOMA} = 1 - \frac{\alpha}{n}\sum_{i=1}^{n}\left(R_{\mathrm{opt}} - R_i\right)^2 \qquad (1)$$

where n is the number of bonds considered, and α is an empirical constant (for C—C, C—N, C—O, and N—N bonds α = 257.7, 93.5, 157.4, and 130.3, respectively) fixed to give HOMA = 0 for a model nonaromatic system, and HOMA = 1 for a system with all bonds equal to an optimal value R_{opt} (1.388, 1.334, 1.265, and 1.309 Å for C—C, C—N, C—O, and N—N bonds, respectively), assumed to be achieved for fully aromatic systems. R_i stands for a running bond length. This index has been found to be one of the most effective structural indicators of aromaticity.[4,15]

As magnetic indices of aromaticity, we have used three derivations of the nucleus-independent chemical shift (NICS) index,



Scheme 1. Schematic representation of the fifteen proposed tests. The sign "*" indicates the position where NICS(1) has been calculated.

proposed by Schleyer and co-workers.[62,63] NICS is defined as the negative value of the absolute shielding computed at a ring center or at some other interesting point of the system. Rings with large negative NICS values are considered aromatic.

Finally, six aromaticity criteria based on electron delocalization measures have been employed.[19,64] These indices measure the cyclic electron delocalization of mobile electrons in aromatic rings. First, the para-delocalization index (PDI),[56,65] which is obtained using the delocalization index (DI)[66,67] as defined in the framework of the QTAIM of Bader.[68–70] The PDI is an average of all DI of para-related carbon atoms in a given 6-MR. The DI value between atoms A and B, $\delta(A,B)$, is obtained by double integration of the exchange-correlation density ($\Gamma_{XC}(\vec{\mathbf{r}}_1, \vec{\mathbf{r}}_2)$) over the basins of atoms A and B, which are defined from the condition of zero-flux gradient in the one-electron density, $\rho(\boldsymbol{r})$[68–70]:

$$\delta(A,B) = -2 \int_A \int_B \Gamma_{XC}(\vec{\mathbf{r}}_1, \vec{\mathbf{r}}_2) d\vec{\mathbf{r}}_1 d\vec{\mathbf{r}}_2 \qquad (2)$$

For monodeterminantal closed-shell wavefunctions one obtains:

$$\delta(A,B) = 4 \sum_{i,j}^{\text{occ.MO}} S_{ij}(A) S_{ij}(B) \qquad (3)$$

The summations in Eq. (3) run over all occupied molecular orbitals. $S_{ij}(A)$ is the overlap between molecular orbitals i and j within the basin of atom A. $\delta(A,B)$ provides a quantitative idea of the number of electrons delocalized or shared between atoms A and B.

Second, the aromatic fluctuation index (FLU)[36] that is constructed considering the amount of electron sharing between contiguous atoms, which should be substantial in aromatic molecules, and also taking into account the similarity of electron sharing between adjacent atoms. Let us consider a ring structure of N atoms represented by the following string $\mathcal{A} = \{A_1, A_2, \ldots, A_N\}$, whose elements are ordered according to the connectivity of the atoms in the ring. For such ring, the FLU index is defined as:

$$\mathrm{FLU}(\mathcal{A}) = \frac{1}{N}\sum_{i=1}^{N}\left[\left(\frac{V(A_i)}{V(A_{i-1})}\right)^{\alpha}\left(\frac{\delta(A_i,A_{i-1}) - \delta_{\mathrm{ref}}(A_i,A_{i-1})}{\delta_{\mathrm{ref}}(A_i,A_{i-1})}\right)\right]^2 \tag{4}$$

where $A_0 \equiv A_N$ and $V(A)$ is the atomic valence that for a closed-shell system reads:

$$V(A_i) = \sum_{A_j \neq A_i} \delta(A_i, A_j) \tag{5}$$

and α is a simple function to make sure that the first term in Eq. (4) is always greater or equal to 1, so it takes the values:

$$\alpha = \begin{cases} 1 & V(A_i) > V(A_{i-1}) \\ -1 & V(A_i) \leq V(A_{i-1}) \end{cases} \tag{6}$$

Finally, the $\delta_{\mathrm{ref}}(A_i, A_{i-1})$ values are δ_{ref}(C,C) = 1.389e, δ_{ref}(C,N) = 1.318e, δ_{ref}(N,N) = 1.518e, and δ_{ref}(C,O) = 0.970e, the δ(C,C), δ(C,N), δ(N,N), and δ(C,O) values in benzene, pyridine, pyridazine, and furan, respectively, at the B3LYP/6-311++G(d,p) level. FLU is close to 0 in aromatic species, and differs from it in nonaromatic ones. Obviously, being FLU a positive quantity, the tendencies obtained from the FLU or $\mathrm{FLU}^{1/2}$ values are exactly the same. However, we have preferred using $\mathrm{FLU}^{1/2}$ instead of FLU because $\mathrm{FLU}^{1/2}$ values are scattered over a wider range and, therefore, the trends derived are clearer. In addition, we have recently shown that $\mathrm{FLU}^{1/2}$ presents better correlations with classical aromaticity indices.[71]

Third, we have employed a set of four multicenter indices, namely, the I_{ring}, I_{NG}, MCI, and I_{NB}. The multicenter index (I_{ring}) of Giambiagi et al. reads[51]:

$$I_{\mathrm{ring}}(\mathcal{A}) = \sum_{i_1,i_2,\cdots,i_N} n_{i_1}\cdots n_{i_N} S_{i_1 i_2}(A_1) S_{i_2 i_3}(A_2)\cdots S_{i_N i_1}(A_N) \tag{7}$$

where $S_{ij}(A)$ is the overlap of natural orbitals i and j in the atom A, and n_i are their occupancies. For a closed-shell monodeterminantal wavefunction we have:

$$I_{\mathrm{ring}}(\mathcal{A}) = 2^N \sum_{i_1,i_2,\cdots,i_N}^{\text{occ. MO}} S_{i_1 i_2}(A_1) S_{i_2 i_3}(A_2)\cdots S_{i_N i_1}(A_N) \tag{8}$$

Some of us have recently proposed a normalized version of the I_{ring} index,[72] the so-called I_{NG}, which is expected to be less dependent on the ring size than its unnormalized homologues, and it is written for aromatic species as:

$$I_{\mathrm{NG}}(\mathcal{A}) = \frac{\pi^2}{4NN_\pi} I_{\mathrm{ring}}^{1/N} \tag{9}$$

where N is the total number of atoms in the ring and N_π the total number of π electrons. I_{NG} has the peculiarity of reproducing the so-called TREPE[73] values at the Hückel Molecular Orbital (HMO) level of theory.

Recently Bultinck and coworkers have worked on a particular extension of the I_{ring} index. According to these authors summing up all the I_{ring} values resulting from the permutations of indices $A_1, A_2, \ldots, A_N$ defines a new index of aromaticity, the so-called multicenter index (MCI),[32] whose formula reads:

$$\mathrm{MCI}(\mathcal{A}) = \frac{1}{2N}\sum_{P(\mathcal{A})} I_{\mathrm{ring}}(\mathcal{A}) \tag{10}$$

where $P(\mathcal{A})$ stands for a permutation operator which interchanges the atomic labels $A_1, A_2, \ldots, A_N$ to generate up to the $N!$ permutations of the elements in the string $\mathcal{A}$. Generally the values of MCI and I_{ring} are in tight correlation because the dominant contribution to MCI is the Kekulé structure, nonetheless some exceptions may arise.[72] Finally, there is a normalized version of the MCI index for aromatic rings,[72] the so-called I_{NB}, given by:

$$I_{\mathrm{NB}}(\mathcal{A}) = \frac{C}{NN_\pi}[2N \cdot \mathrm{MCI}(\mathcal{A})]^{1/N} \tag{11}$$

where $C \approx 1.5155$. An obvious advantage of multicenter indices is that they can be applied quite generally even in the situation where PDI, FLU or HOMA can not be used.

For the series of indices used, we have that the more negative the NICS, the lower the $\mathrm{FLU}^{1/2}$ index, and the higher the HOMA, PDI, I_{ring}, I_{NG}, MCI, and I_{NB} values, the more aromatic the rings are.

Computational Details

All calculations have been performed with the Gaussian 03[74] and AIMPAC[75] packages of programs, at the B3LYP level of theory[76–78] with the 6-311++G(d,p) basis set.[79,80] The intrinsic reaction paths (IRP)[81,82] for the Diels–Alder (DA) and acetylene trimerization reactions have been computed going downhill from the transition state (TS) in mass-weighted coordinates using the algorithm by Gonzalez and Schlegel.[83]

The GIAO method[84] has been used to perform calculations of NICS at ring centers (NICS(0)) determined by the non-weighted mean of the heavy atoms coordinates and at 1 Å above or below the center of the ring taken into analysis (NICS(1)). It has been postulated that NICS(1) better reflects aromaticity patterns because at 1 Å the effects of the π-electron ring current are dominant and local σ-bonding contributions are diminished.[85,86] We have also analyzed the out-of-plane component of the NICS(1), the $\mathrm{NICS}(1)_{zz}$, which was found to be (together with the so-called $\mathrm{NICS}(0)_{\pi zz}$) the best NICS-based indicator of aromaticity.[86,87]

Calculation of atomic overlap matrices (AOM) and computation of DI, I_{ring}, I_{NG}, MCI, and I_{NB} have been performed with the AIMPAC[75] and ESI-3D[88] collection of programs. Calculation of these DIs with the density functional theory (DFT) can not be performed exactly because the electron-pair density is not available at this level of theory.[89] As an approximation, we have used the Kohn–Sham orbitals obtained from a DFT calculation to compute Hartree–Fock-like DIs through Eq. (3) that do not

Table 1. Summary of the Fifteen Tests Applied at the B3LYP/6-311++G(d,p) Level for the Ten Descriptors of Aromaticity Analyzed.

	PDI	$FLU^{1/2}$	MCI	I_{NB}	I_{ring}	I_{NG}	HOMA	NICS(0)	NICS(1)	$NICS(1)_{zz}$
T1	Yes	Yes	Yes	Yes	Yes	Yes	Unclear[a]	Yes	Yes	Yes
T2	Unclear[b]	Yes	Yes	Yes	Yes	Yes	Unclear[a]	Unclear[c]	Yes	Yes
T3	Unclear[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
T4	Unclear[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
T5	Unclear[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
T6	Yes	Yes	Yes	Yes	Yes	Yes	Unclear[d]	No	No	Yes
T7	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
T8	N/A	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
T9	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
T10	No	Unclear[e]	Unclear[f]	Unclear[f]	Unclear[f]	Unclear[f]	No	No	No	No
T11	N/A	Unclear[e]	Yes	Yes	Yes	Unclear[e]	Unclear[e]	Unclear[e]	Unclear[e]	Yes
T12	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
T13	N/A	No	Yes	Yes	Unclear[e]	Unclear[e]	Unclear[e]	Yes	Yes	Yes
T14	Yes	No	Yes	Yes	Yes	Yes	No	Unclear[g]	Unclear[g]	Yes
T15	Yes	No	Yes	Yes	Yes	Yes	No	Unclear[g]	Unclear[g]	Unclear[g]

[a]Loss of aromaticity is overemphasized (see text).
[b]The aromaticity remains almost unchanged with the distortion (see text).
[c]The trend in aromaticity remains almost unchanged with some oscillations (see text).
[d]The aromaticity is higher than that of benzene only for a small number of molecules (see text).
[e]Fails only in ordering one molecule (see text).
[f]Fails only in ordering one molecule (see text). At the CCSD level, this index passes the test.
[g]The aromaticity of the TS is higher than that of benzene (see text).

account for electron correlation effects. In practice the values of the DIs obtained using this approximation are generally closer to the Hartree–Fock values than correlated DIs obtained with a configuration interaction method.[57,89]

In some particular cases, we have computed I_{ring}, I_{NG}, MCI, and I_{NB} indices at a correlated level with the MP2 and CCSD methods using Eqs. (7), (9), (10), and (11). To obtain the correlated versions of the PDI and FLU indices the following substitution has been performed in Eq. (3):

$$S_{ij}(A) \rightarrow \frac{\sqrt{n_i n_j}\, S_{ij}^{NO}(A)}{2} \tag{12}$$

where $S_{ij}^{NO}(\boldsymbol{A})$ is now the AOM of atom A in terms of natural orbitals and the summations in Eq. (3) run over the whole set of natural orbitals, instead of only the occupied molecular orbitals.

The numerical accuracy of the QTAIM calculations has been assessed using two criteria: (i) The integration of the Laplacian of the electron density ($\nabla^2\rho(r)$) within an atomic basin must be close to zero; (ii) The number of electrons in a molecule must be equal to the sum of all the electron populations of the molecule, and also equal to the sum of all the localization indices and half of the delocalization indices in the molecule. For all atomic calculations, integrated absolute values of $\nabla^2\rho(r)$ were always lower than 0.001 a.u. For all molecules, errors in the calculated number of electrons were always lower than 0.01 a.u.

Results

Scheme 1 depicts the fifteen tests considered in the present work. We have applied these tests to ten indicators of aromaticity, namely, PDI, $FLU^{1/2}$, MCI, I_{NB}, I_{ring}, I_{NG}, HOMA, NICS(0), NICS(1), and $NICS(1)_{zz}$. In cases where ASEs or REs were available in the literature (tests 6, 10, and 11), they have been included in the discussion. The optimized geometries of all species analyzed are given in Table S1 of the supporting information. The numerical results obtained for each test with the ten descriptors used have been gathered in Tables S2 to S16 of the supporting information. The summary of the results obtained in all tests can be found in Table 1. In this table, we write "yes" when a certain index follows the expected trend in aromaticity for a given test, "no" otherwise, and "unclear" when the failure of the index is minor (for instance, when the index produces an almost constant trend in aromaticity or when the index falls short only for the ordering of one species in a given series).

The format of our presentation is divided into seven major topical subsections, each corresponding to a different group of tests as shown in Scheme 1.

Benzene Deformations

In this group of tests (T1 to T5), we have gathered five distortions of the benzene ring: two in-plane (bond length alternation (BLA) and clamping) and three out-of-plane deformations (boatlike, chairlike, and pyramidalization) corresponding to tests number T1 to T5. For the BLA distortion, we have introduced the deformation with consecutive steps of 0.05 Å without further reoptimization of the distorted benzene ring geometry. For the rest of distortions, we have modified the relevant angle (α in Scheme 1) in the range 0° to 25° with steps of 5°, and we have reoptimized the remaining geometrical parameters at every point. The change in aromaticity along these distortions together

with the bond length elongation (BLE) have been studied in a previous work with the PDI, $FLU^{1/2}$, MCI, I_{ring}, HOMA, NICS(0), NICS(1), $NICS(1)_{zz}$, and hardness as indicators of aromaticity.[29] In the present paper, we add the results obtained with the I_{NB} and I_{NG} indices. We have not included the BLE distortion as a possible test of aromaticity since, unlike the other distortions, the BLE preserves the D_{6h} symmetry, and, therefore, our hypothesis that a maximum of aromaticity is found for the optimal geometry of benzene is at least arguable. Neither have we considered the hardness in our study since we are interested in the performance of local indices of aromaticity. In the future, however, the possibility to obtain local values of hardness[90,91] may result in good indicators of aromaticity based on local hardnesses. The results collected in Tables S2 to S6 of the supporting information show that the $FLU^{1/2}$, MCI, I_{NB}, I_{ring}, I_{NG}, HOMA, NICS(1), $NICS(1)_{zz}$ are able to point out the expected loss of aromaticity in the five benzene distortions analyzed. However, the HOMA index overestimates the loss of aromaticity for the BLA and clamping deformation for angles larger than 20°. On the other hand, NICS(0) fails for the clamping deformation (test T2), indicating an almost constant aromaticity with a slight increase of aromaticity up to $\alpha = 15°$ and a minor reduction from 15° to 25°. Finally, the PDI gives incorrect trends for all distortions excepting the BLA, although it is observed that the PDI remains almost unaffected by the different ring deformations analyzed. Finally, let us briefly mention here that despite the failure of PDI to show the expected reduction of aromaticity in boatlike distortions, the PDI correctly indicated the loss of aromaticity of the 6-MRs when going from planar to pyramidalized pyracylene at variance with NICS(0).[92] A more detailed analysis of the results can be found in ref. 29.

Substitution and Complexation in Benzene

In test T6, we analyze the aromaticity of a series of sixteen monosubstituted benzene derivatives, the same set of compounds considered in previous studies on the relation of the substituent effect and aromaticity.[93,94] The nature of the substituent changes from the strongly electron-donating NH_2 group to the strongly electron accepting NN^+ substituent. As shown by Krygowski et al.,[93–95] substituents perturb the π-electron delocalization inducing a partial π localization and, therefore, a loss of symmetry and aromaticity irrespective of their electron donating or accepting character. So, for a certain index we consider that the test has been passed if the unsubstituted benzene is found to be the most aromatic 6-MR in the series. All indices, except HOMA, NICS(0), and NICS(1) indicate a loss of aromaticity for all monosubstituted benzene derivatives studied as compared with the unsubstituted benzene molecule. For the HOMA index, there are two minor exceptions (X = F and NO_2) that show an HOMA value slightly larger than that found for benzene; however, the difference is lower than 0.005. Moreover, it is worth noting that these results are quite dependent on the R_{opt} value for C—C bonds taken as the reference for HOMA calculations. For NICS(0) and NICS(1), nine and five, respectively, out of sixteen substituted benzenes have more negative values than those of benzene itself. Interestingly, $NICS(1)_{zz}$ gives the expected more negative value for benzene than for monosubstituted species. In addition, all indices point out a small variation of aromaticity upon substitution and, therefore, they indicate a minor change in the cyclic π-electron delocalization.[93–95] The X = NN^+ substituent is found by most of the indices (the only exceptions are NICS(0) and NICS(1)) as the substituent that leads to the largest loss of aromaticity among the sixteen studied. Finally, it is interesting to note that all ASEs values[93] listed in Table S7 fail to indicate benzene as the most aromatic species among systems studied in test T6. What is maybe more critical is that different ASE values derived from different homodesmotic or isodesmic reactions lead to different aromaticity orderings.

The aromaticity of the benzene ring in the $(\eta^6\text{-}C_6H_6)Cr(CO)_3$ complex is analyzed in test T7. It is widely accepted that the structure, reactivity, and aromaticity of the benzene ring are altered significantly upon complexation with the chromium tricarbonyl complex. Thus, after coordination the ring expands, loses its planarity (the hydrogen atoms of the benzene ring slightly bent towards the $Cr(CO)_3$ fragment[96]), and shows an increased difference between alternated short and long C—C bonds.[97] The nature of the bond between the arene and the metal in (η^6-arene)tricarbonylchromium complexes was discussed by Albright, Hoffmann, and coworkers some years ago.[98] These authors found that the interaction of the degenerate *2e* LUMO and $2a_1$ LUMO+1 orbitals of the $Cr(CO)_3$ moiety with the highest occupied π-orbitals of the arene with the appropriated symmetry is the dominant bonding mechanism.[99] Charge transfer from the highest occupied π-orbitals of the arene to the lowest unoccupied *2e* and $2a_1$ orbitals of $Cr(CO)_3$ partially breaks the C—C bonds, thus explaining the observed expansion of the aromatic ring and the increase in BLA in $(\eta^6\text{-}C_6H_6)Cr(CO)_3$. Because of the loss of π electron density in the ring, one should expect a partial disruption of aromaticity in the 6-MR of $(\eta^6\text{-}C_6H_6)Cr(CO)_3$ in comparison to free benzene, as discussed by Hubig et al.[97] Indeed, all indices used in the present work, except NICS(0) and NICS(1), show that there is a clear reduction of the aromaticity of benzene upon coordination to the $Cr(CO)_3$ complex. We analyzed the particular behavior of the NICS index in this case in a previous work[100] and we concluded that the reduction of the NICS value in the benzene ring of the $(\eta^6\text{-}C_6H_6)Cr(CO)_3$ complex is not a manifestation of an increased aromaticity of the 6-MR but is due to the ring currents generated by the electron pairs that take part in the benzene-$Cr(CO)_3$ bonding. This effect also explains why the claims of Mitchell and co-workers[17,101–103] about the fact that the benzene ring in tricarbonylchromium-complexed benzene is ca. 30–40% more aromatic than benzene itself are unjustified.[100]

Ring Size and Atom Size Dependence

Test T8 analyzes the dependence of the index on the size of the ring, which has been shown to be critical for certain aromaticity descriptors.[104–107] PDI has not been analyzed in this test because it can be only applied for 6-MRs (N/A in Table 1). To analyze ring size dependence, we compare the aromaticity of three 6π-electron systems with different ring sizes, namely, benzene, cycloheptatrienyl cation ($C_7H_7^+$), and cyclooctatetraenyl dication ($C_8H_8^{2+}$). Because of the increase of the ring size, one

expects the following order of aromaticity for the series of systems: $C_6H_6 > C_7H_7^+ > C_8H_8^{2+}$. The expected order is followed by all indices but the NICS(0) descriptor that places incorrectly the $C_7H_7^+$ species. Several authors have pointed out the ring size dependence of NICS[104,105] here supported by the failure of NICS(0) to reproduce this test.

Test T9 analyzes the ability of a given index to account for the change in the size of the atoms forming the aromatic ring. To this end, the aromaticity of C_6H_6 is compared with that of the isoelectronic 6-MR N_6. Sakai[108] found that planar N_6 species (D_{6h} symmetry) is less aromatic than the benzene ring. So, we expect a reduction of aromaticity even larger for the chairlike nonplanar optimized N_6 structure. In general, most indices indicate a slight loss of aromaticity when going from benzene to fully optimized N_6 species. Only the PDI, NICS(1), and NICS(1)$_{zz}$ indices fail to account for this aromaticity order. It is usually said that NICS(1) and, particularly, NICS(1)$_{zz}$ are better indicators of aromaticity than NICS(0) itself,[86,87] and this is probably one of the few examples in which NICS(0) provides better results than NICS(1) and NICS(1)$_{zz}$. As to the PDI, its error in this test can be attributed to both the chairlike structure of N_6 (PDI did not already pass test T4) and the atom size dependence of this index. The latter is due to the fact that the increase in the number of electrons when going from C to N leads to large delocalization indices between para-related atoms that do not go with an increase of aromaticity.

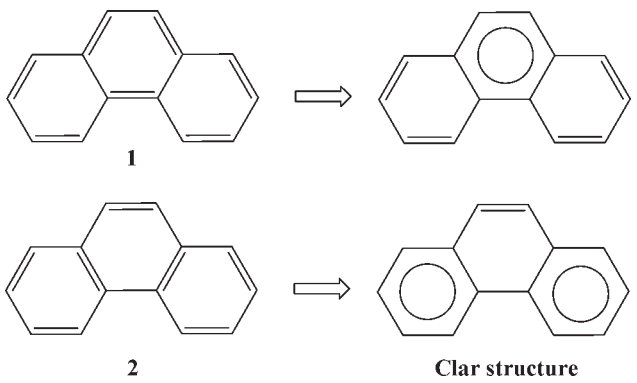
Heteroaromatic Species

For the heteroaromatic species shown in Scheme 1 as test T10, the expected order of aromaticity is benzene > pyridine > pyridazine > pyrimidine > pyrazine > triazine. Except for triazine, this is the order found from the calculation of REs.[18] Thus, the aromaticity decreases when the number of CH by N replacements increases.[109] For the same number of N atoms in the 6-MR, the most aromatic are those having the largest number of N—N bonds.[107] The expected order of aromaticity is not exactly followed by any of the indices analyzed. MCI, I_{ring}, together with their normalized versions and FLU$^{1/2}$ fail only in the ordering of pyradizine that is considered more aromatic than pyridine. Let us add here in favor of the MCI, I_{ring}, I_{NB}, and I_{NG} that the CCSD/6-311++G(d,p) indices for the set of heteroaromatic rings considered in test T10 give exactly the expected order of aromaticity (see Table S16 in the supporting information).[72] However, it is also true that these multicenter indices when computed at the MP2/6-311++G(d,p) level (Table S17) give a completely erroneous ordering of the N-substituted 6-MRs. In general, it is found that the results of the MCI, I_{ring} and their normalized versions are quite dependent on the level of calculation and, consequently, it is important to use accurate methods to distinguish rings with similar degrees of aromaticity.[72] PDI is unsuccessful by considering pyrazine and pyradizine more aromatic than benzene itself. HOMA fails completely in the ordering of the 6-MRs.

Test T11 analyzes a series of six heteroaromatic 5-MRs. Electron counting indicates that for X = CH^-, NH, and O we have aromatic rings. In this case it is expected that, owing to its lower electronegativity, the NH group does not decrease the electronic delocalization as much as oxygen,[110] and, therefore, pyrrole is more aromatic than furan. The system with X = CH_2 is anticipated to give a nonaromatic ring while for X = BH and CH^+ antiaromatic rings should be found. Hence, the expected order of aromaticity for this set of molecules is $CH^- > NH > O > CH_2 > BH > CH^+$. This is indeed the order provided by the ASE values of Cyrański et al.[25] MCI, I_{NB}, I_{ring}, and NICS(1)$_{zz}$ succeed in giving the expected trend. On the other hand, NICS(0), NICS(1), FLU$^{1/2}$, HOMA, and I_{NG} fail in the ordering of one system. Finally, the ring size dependency of the NICS indices shows up and both NICS(0) and NICS(1)$_{zz}$ point out that pyrrole is more aromatic than any of the six aromatic rings considered in test T10.

Clar's Systems

According to the Clar's rule, the Kekulé resonance structure with the largest number of disjoint aromatic π-sextets, i.e., benzene-like moieties, is the most important for the characterization of properties of polycyclic aromatic hydrocarbons (PAHs). 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. For instance, application of this rule to phenanthrene indicates that the resonance structure **2** is more important than resonance structure **1**. Therefore, outer rings in phenanthrene are expected to have a larger local aromaticity than the central ring. This result has been confirmed by several measures of local aromaticity.[33,35,59,111] It is also generally recognized,[112] with some exceptions,[113,114] that phenanthrene with two π-sextets is more aromatic than anthracene that has a single π-sextet. Moreover, recent experimental results on the distribution of π-electrons in large PAHs[115] together with Valence Bond calculations,[116] NICS,[117] and other aromaticity analyses[59] on pericondensed benzenoid PAHs have provided extensive support to the Clar's rule.



There are PAHs that present a unique Clar structure (i.e., phenanthrene), whereas several Clar structures are possible for other PAHs.[2] For these latter, Clar's rule cannot differentiate which of the corresponding resonance structures is the main responsible for the aromaticity of the system. So, in test T12, we have included five of the smallest benzenoid species that present a unique Clar structure. The position of the aromatic π-sextets in

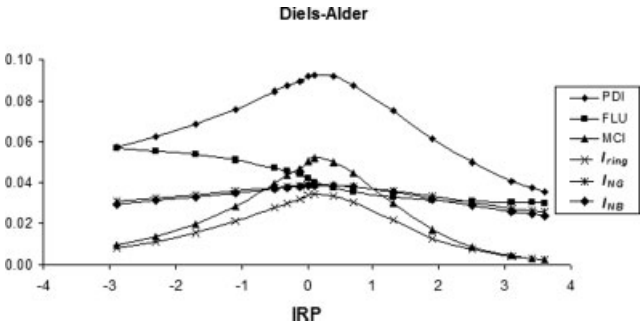


Figure 1. Plot of PDI (electrons), $FLU^{1/2}$ (values divided by 10), MCI (electrons), I_{ring} (electrons), I_{NG}, and I_{NB} versus the reaction coordinate (IRP in $amu^{1/2}$·Bohr). Negative values of the IRP correspond to the reactants side of the reaction path and positive values to the product side of the DA cycloaddition.

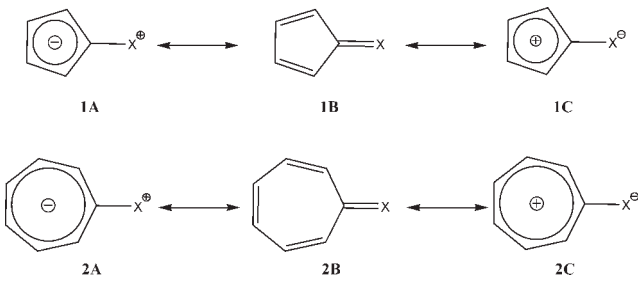
the Clar structure depicted in Scheme 1 shows the rings which are the most aromatic according to this rule. Interestingly, all indices analyzed in this work indicate that rings with the aromatic π-sextets are the most aromatic in the set of molecules studied. So, this is probably the easiest test to pass for indices of aromaticity. It is worth mentioning here that despite the NICS index behaves notably well for the Clar's systems analyzed here, it has well-known problems in many condensed benzenoid species,[35,92,118–121] while electronic indices perform reasonably well for several condensed benzenoid species.[71]

Fulvenes

The physical and chemical behavior of substituted penta- and hepta-fulvenes are usually rationalized in terms of the weights of the different resonance structures **1A–C** for penta-fulvenes and **2A–C** for hepta-fulvenes.[122] The relative weights of these structures depend on the electronegativity of the X substituent. Thus, electron donating substituents favor structures **1A** and **2A** while electron withdrawing groups lead to the dominance of structures **1C** and **2C**. Therefore, as indicated by several authors using magnetic and structural descriptors of aromaticity,[122–125] electron donating substituents enhance the aromaticity of the penta-fulvenes by increasing the weight of the 6π-electron structure **1A** and decrease the aromatic character of the 7-MR in hepta-fulvenes by increasing the weight of the 8π-electron structure **2A**. The behavior of electron withdrawing substituents is just the opposite favoring 4π-electron structure **1C** and 6π-electron structure **2C**. Thus, a good aromaticity indicator should give the following order of aromaticity for the 5-MR in penta-fulvenes $BH_2^- > CH_2 > NH > O > NH_2^+$ and just the opposite order for the 7-MR of hepta-fulvenes (Test 13). This is exactly the order found for all NICS magnetic indices and MCI and I_{NB} electronic descriptors. HOMA, I_{ring}, and I_{NG} fail only in the order of cyclopentadienone. Finally, $FLU^{1/2}$, like HOMA, I_{ring}, and I_{NG} is unsuccessful for cyclopentadienone but also fails to give the correct order for several hepta-fulvenes.

Chemical Reactivity

In this last subsection, we have included two chemical reactions as tests of aromaticity: the simplest DA cycloaddition (test T14) and the acetylene trimerization (test T15). For these two reactions, we have applied the aromaticity criteria along the IRP.



The well-known DA[126–130] reaction between ethene and 1,3-butadiene to render cyclohexene is the prototype of a thermally allowed [4 + 2] cycloaddition. This reaction has been extensively investigated using different theoretical methods. It is now widely-accepted that this reaction takes place via a synchronous and concerted mechanism through an aromatic boatlike TS.[127,131–136] By 1938[137] it was already recognized the analogy between the π-electrons of benzene and the six delocalized electrons in the cyclic TS of the DA reaction. The aromatic nature of this TS has been later confirmed theoretically using magnetic-based indices such as NICS and the magnetic susceptibility exaltations,[130,138–141] as well as by means of PDI,[141] SCI[54] and energetic measures.[142] For this reaction, we have considered that a given method succeeds when along the reaction path it finds a peak of aromaticity around the TS. The behavior of the different indices along the reaction coordinate has been depicted in Figures 1 and 2. Results in Table S15 and Figure 1 and 2 show that only $FLU^{1/2}$ and HOMA break down in this test. These two indices consider the cyclohexene molecule (product), as the most aromatic species in the reaction. As discussed in our previous work,[141] HOMA and $FLU^{1/2}$ values measure variances of

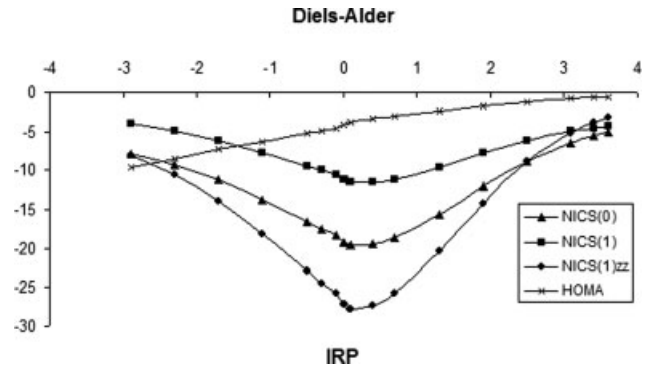


Figure 2. Plot of NICS(0) (ppm), NICS(1) (ppm), $NICS(1)_{zz}$ (ppm) and HOMA (values divided by 15) versus the reaction coordinate (IRP in $amu^{1/2}$·Bohr). Negative values of the IRP correspond to the reactants side of the reaction path and positive values to the product side of the DA cycloaddition. NICS(0) and NICS(1) values have been computed at the RCP and at 1 Å above the RCP, respectively.

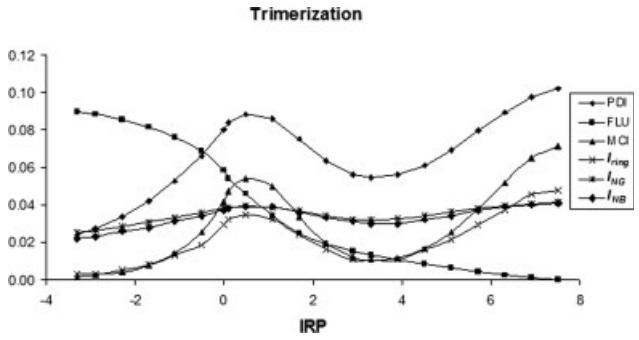


Figure 3. Plot of PDI (electrons), $FLU^{1/2}$ (values divided by 10), MCI (electrons), I_{ring} (electrons), I_{NG}, and I_{NB} versus the reaction coordinate (IRP in $amu^{1/2}$·Bohr). Negative values of the IRP correspond to the reactants side of the reaction path and positive values to the product side of the trimerization of acetylene.

the structural and electronic patterns, respectively, around the ring. Therefore, HOMA and $FLU^{1/2}$ might fail if they are not applied to stable species because, while reactions are occurring, structural and electronic parameters suffer major changes. Finally, it is also worth noting that NICS(0) and NICS(1) incorrectly assign a larger aromaticity to the TS of this DA than to the benzene molecule. The calculation of NICS(0) in nonplanar species has been carried out in two different ways. First, in the ring critical point (RCPs)[68,69] that appears within the ring defined by the six C atoms as proposed by Morao and Cossío.[143] Second, in the geometrical center of this ring which is obtained after finding the best fitted plane to a given set of nuclei.[141] The two methods lead basically to the same results.

The last test proposed corresponds to the Woodward-Hoffmann thermally allowed [2 + 2 + 2] trimerization of acetylene to yield benzene. In the course of this reaction, three acetylenic π-bonds are converted into C—C σ-bonds to form benzene, the archetypal aromatic molecule. This is a highly exothermic reaction (exp. $\Delta H_r^o = -142.76$ kcal mol^{-1})[143] with an unexpectedly large enthalpy barrier for a thermally allowed reaction (best theoretical estimate of 53.1 kcal mol^{-1} obtained at the CCSD(T)/6-311G(d,p)//QCISD/6-311G(d,p) level of theory).[144] Our B3LYP/6-311++G(d,p) calculation yields a reaction energy of −137.8 kcal mol^{-1} and an energy barrier of 51.9 kcal mol^{-1}, not far from the experimental reaction enthalpy and best theoretical estimate of the enthalpy barrier. At the B3LYP/6-311++G(d,p) level, the TS has D_{3h} symmetry, although the potential energy surface is extremely flat along different distortion paths and, actually, the symmetry of the TS depends critically on the level of calculation employed.[144] There have been several studies on the change of aromaticity along the reaction coordinate that transforms three acetylene molecules into benzene.[130,143,145–148] Although there is a lack of consensus of how aromaticity changes during the transformation from reactants to products, most authors found that the system evolves from localized σ and π electrons in the reactants to the well-know π-delocalization in benzene through a TS which has mainly in-plane σ electron delocalization with only minor π electron delocalization. Many thermally allowed reactions have aromatic TSs. So, it seems reasonable to think that, in this reaction, the aromatic character of the 6-MR being formed increases more or less uniformly from the initial reactants to the TS. At this point it reduces somewhat along the reaction coordinate until the final increase before reaching the benzene molecule that should be the most aromatic species in the whole reaction coordinate.[146–148] This is indeed what electronic-based PDI, MCI, I_{NB}, I_{ring}, and I_{NG} show (see Fig. 3), and therefore, we consider that these indices pass the test. The magnetic-based NICS indices also indicate a maximum of aromaticity along the reaction coordinate around the TS but NICS results find that the transition structure of this reaction is more aromatic than benzene,[130,143] and for this reason we consider that the performance of NICS is "unclear" in this test (see Fig. 4). Finally, $FLU^{1/2}$ fails to detect the maximum of aromaticity in the TS region and indicates a continuous increase of aromaticity from reactants to products. The same situation occurs for HOMA (see Fig. 4). Let us emphasize here that neither $FLU^{1/2}$ nor HOMA (and, in general, any index that uses reference parameters from well-established aromatic compounds) should be used to study aromaticity changes along a reaction path, especially in regions far from equilibrium structures.

Discussion and Concluding Remarks

Exploring the successes and breakdowns of the different descriptors of aromaticity is relevant not only for its own sake but as a way to get ideas of how to improve present indicators of aromaticity and define new indices that correlate better with chemical intuition for most of the well-established cases. For this reason, it is very important, in our opinion, to devise methodologies that allow quantifying the performance of the existing and new defined indices of local aromaticity. To this end, we consider that the use of a set of simple tests, as those proposed in the present paper, that include systems having widely-accepted aromaticity behaviors can be extremely helpful to discuss aromaticity in organic species.

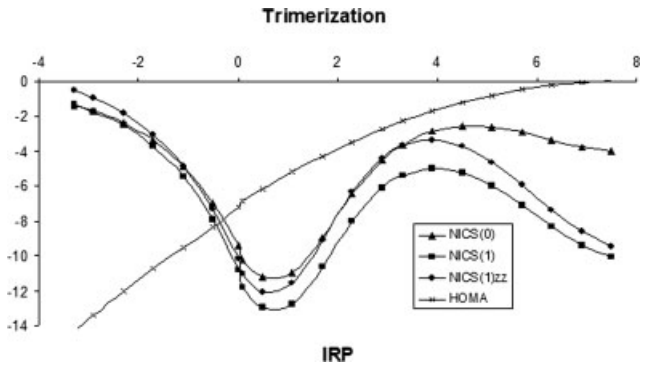


Figure 4. Plot of NICS(0) (ppm) (values divided by 2), NICS(1) (ppm), $NICS(1)_{zz}$ (ppm) (values divided by 3), and HOMA (values divided by 15) versus the reaction coordinate (IRP in $amu^{1/2}$·Bohr). Negative values of the IRP correspond to the reactants side of the reaction path and positive values to the product side of the trimerization of acetylene. NICS(0) and NICS(1) values have been computed at the RCP and at 1 Å above the RCP, respectively.

Our results (see Table 1) indicate that the best indices are the multicenter indices, especially the MCI that fails only in the ordering of one molecule in test T10 on heteroaromatic rings. The problem with these multicenter electronic indices is, on the one hand, the high computational cost and, on the other hand, their large dependence on the level of calculation. The high computational cost of multicenter indices can be highly reduced by using the pseudo-π method of Bultinck and coworkers.[149] Another cheaper alternative that provides also quite good results is the $FLU^{1/2}$ indicator of aromaticity. This index only clearly fails to detect the aromaticity of the TSs of the DA and acetylene trimerization reactions, for the aromaticity order of pyrimidine in test T10 on heteroaromatic 6-MRs, and for tests T11 on heteroaromatic 5-MRs and T12 on fulvenes. PDI has a similar cost to $FLU^{1/2}$ but performs not as well as $FLU^{1/2}$ in tests T2-5, T9, and T10 although it is superior to $FLU^{1/2}$ in tests T14 on the DA reaction and T15 on the acetylene trimerization reaction. Like $FLU^{1/2}$, HOMA fails to detect aromaticity in the TSs of the DA and acetylene trimerization reactions. It also falls short in the ordering of several heteroaromatic rings. In addition, the HOMA index overestimates the loss of aromaticity for the BLA and clamping deformations. But, in general, HOMA performs notably well if one considers its low computational cost. Finally, as to NICS, NICS(0) clearly fails for tests T6-8 and T10, while in tests T14 and T15 it erroneously points out that the TSs are more aromatic than benzene. For test T2, NICS(0) yields an almost unchanged value with clamping. NICS(1) improves the results in tests T2 and T8 but, unexpectedly, it goes wrong for test T9 corresponding to N_6. In test T11, both NICS(0) and NICS(1) overestimate the aromaticity of pyrrole. Our results clearly reinforce the superior behavior of $NICS(1)_{zz}$ as compared to NICS(0) and NICS(1).[86,87] Indeed, $NICS(1)_{zz}$ only collapses for tests T9 and T10 and gives not totally satisfactory results for test T15. The results collected in Table 1 indicate that the electronic-based indices of aromaticity have a superior behavior than both geometrically- and magnetically-based indicators of aromaticity. It is perhaps worthwhile noting that although the calculation of multicenter indices using QTAIM partitioning of space is relatively expensive, the use of Mulliken-like or fuzzy atom partitioning[150,151] or the pseudo-π method[149] can reduce drastically the computational costs with only a minor loss of accuracy in most cases.

As a final list of recommendations derived from the application of the fifteen tests to the ten indices explored, we can say that, first, indices including reference values in their expressions such as HOMA and $FLU^{1/2}$ should not be used for the analysis of aromaticity changes in chemical reactions; second, NICS indices should be avoided when comparing rings with different sizes and different kinds of atoms; third, one should be careful when using electronic indices because although electronic turn out to be the most reliable indices, PDI does not treat correctly the aromaticity in out-of-plane deformations of aromatic rings and rings with different kinds of atoms, and finally multicenter indices are found to be quite dependent on the level of calculation and good accuracy is only guaranteed at a high correlated level. As a final point, let us mention that the extrapolation of the results derived using these tests to the analysis of aromaticity in inorganic compounds should be done with care.

Acknowledgments

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Notes Added in Proof

In the discussion about the multidimensional character of aromaticity it is worth noting that according to Schleyer and coworkers the "classical" and "magnetic" measures of aromaticity are not necessarily "orthogonal" (see Schleyer, P. V. R.; Jiao, H.; Goldfuß, B.; Freeman, P. K. Angew. Chem. Int. Ed. Engl. 1995, 34, 337–340).

References

1. Frenking, G.; Krapp, A. J Comput Chem 2007, 28, 15.
2. Randić, M. Chem Rev 2003, 103, 3449.
3. Baldridge, K. K.; Siegel, J. S. J Phys Org Chem 2004, 17, 740.
4. Schleyer, P. V. R. Chem Rev 2001, 101, 1115.
5. Schleyer, P. V. R. Chem Rev 2005, 105, 3433.
6. Minkin, V. I.; Glukhovtsev, M. N.; Simkin, B. Y. Aromaticity and Antiaromaticity: Electronic and Structural Aspects; Wiley: New York, 1994.
7. Garrat, P. J. Aromaticity; Wiley: New York, 1986.
8. Balaban, A. T. Pure Appl Chem 1980, 52, 1409.
9. Lloyd, D. J Chem Inf Comp Sci 1996, 36, 442.
10. Krygowski, T. M.; Cyrański, M. K.; Czarnocki, Z.; Häfelinger, G.; Katritzky, A. R. Tetrahedron 2000, 56, 1783.
11. Boldyrev, A. I.; Wang, L.-S. Chem Rev 2005, 105, 3716.
12. Tsipis, C. A. Coord Chem Rev 2005, 249, 2740.
13. Wiberg, K. B. In Theoretical and Computational Chemistry; Maksic, Z. B.; Orville-Thomas, W. J., Eds.; Elsevier: Amsterdam, 1999; pp. 519–536.
14. Katritzky, A. R.; Jug, K.; Oniciu, D. C. Chem Rev 2001, 101, 1421.
15. Krygowski, T. M.; Cyrański, M. K. Chem Rev 2001, 101, 1385.
16. Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. V. R. Chem Rev 2005, 105, 3842.
17. Mitchell, R. H. Chem Rev 2001, 101, 1301.
18. Cyrański, M. K. Chem Rev 2005, 105, 3773.
19. Poater, J.; Duran, M.; Solà, M.; Silvi, B. Chem Rev 2005, 105, 3911.
20. Alonso, M.; Herradón, B. Chem Eur J 2007, 13, 3913.
21. Poater, J.; García-Cruz, I.; Illas, F.; Solà, M. Phys Chem Chem Phys 2004, 6, 314.
22. Aihara, J. J Am Chem Soc 2006, 128, 2873.
23. Katritzky, A. R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. J Am Chem Soc 1989, 111, 7.
24. Katritzky, A. R.; Karelson, M.; Sild, S.; Krygowski, T. M.; Jug, K. J Org Chem 1998, 63, 5228.
25. Cyrański, M. K.; Krygowski, T. M.; Katritzky, A. R.; Schleyer, P. V. R. J Org Chem 2002, 67, 1333.
26. Jug, K.; Köster, A. M. J Phys Org Chem 1991, 4, 163.
27. Hoffmann, R.; Minkin, V. I.; Carpenter, B. K. HYLE – Int J Philos Chem 1997, 3, 3.
28. Van Droogenbroek, J.; Van Alsenoy, C.; Blockhuys, F. J Phys Chem A 2005, 209, 4847.
29. Feixas, F.; Matito, E.; Poater, J.; Solà, M. J Phys Chem A 2007, 111, 4513.

30. Bultinck, P.; Fias, S.; Ponec, R. Chem Eur J 2006, 12, 8813.
31. Bultinck, P. Faraday Discuss 2007, 135, 347.
32. Bultinck, P.; Rafat, M.; Ponec, R.; van Gheluwe, B.; Carbó-Dorca, R.; Popelier, P. J Phys Chem A 2006, 110, 7642.
33. Cyrański, M. K.; Stepién, B. T.; Krygowski, T. M. Tetrahedron 2000, 56, 9663.
34. Schleyer, P. V. R.; Manoharan, M.; Jiao, H. J.; Stahl, F. Org Lett 2001, 3, 3643.
35. Portella, G.; Poater, J.; Bofill, J. M.; Alemany, P.; Solà, M. J Org Chem 2005, 70, 2509. Erratum, íbid, 2005, 70, 4560.
36. Matito, E.; Duran, M.; Solà, M. J Chem Phys 2005, 122, 014109. Erratum, íbid, 125:059901, 2006.
37. Mandado, M.; González-Moa, M. J.; Mosquera, R. A. J Comput Chem 2007, 28, 127.
38. Steiner, E.; Fowler, P. W. Int J Quantum Chem 1996, 60, 609.
39. Steiner, E.; Fowler, P. W. J Phys Chem A 2001, 105, 9553.
40. Steiner, E.; Fowler, P. W.; Havenith, R. W. A. J Phys Chem A 2002, 106, 7048.
41. Ligabue, A.; Pincelli, U.; Lazzeretti, P.; Zanasi, P. J Am Chem Soc 1999, 121, 5513.
42. Moyano, A.; Paniagua, J. C. J Org Chem 1991, 56, 1858.
43. Moyano, A.; Paniagua, J. C. Trends Org Chem 1993, 4, 697.
44. Glidewell, C.; Lloyd, D. Tetrahedron 1984, 40, 4455.
45. Balaban, A. T.; Randić, M. J Math Chem 2005, 37, 443.
46. Howard, S. T.; Krygowski, T. M. Can J Chem 1997, 75, 1174.
47. Bultinck, P.; Ponec, R.; Carbó-Dorca, R. J Comput Chem 2007, 28, 152.
48. Matta, C. F.; Hernández-Trujillo, J. J Phys Chem A 2003, 107, 7496.
49. Matta, C. F.; Hernández-Trujillo, J. J Phys Chem A 2005, 109, 10798.
50. Anusooya, Y.; Chakrabarti, A.; Pati, S. K.; Ramasesha, S. Int J Quantum Chem 1998, 70, 503.
51. Giambiagi, M.; de Giambiagi, M. S.; dos Santos, C. D.; de Figueiredo, A. P. Phys Chem Chem Phys 2000, 2, 3381.
52. Bultinck, P.; Ponec, R.; Van Damme, S. J Phys Org Chem 2005, 18, 706.
53. Aihara, J.; Kanno, H. J Phys Chem A 2005, 109, 3717.
54. Faraday Discuss. 2007, 135, 367.
55. Wu, J.; Jiang, Y. J Comput Chem 2000, 21, 856.
56. Poater, J.; Fradera, X.; Duran, M.; Solà, M. Chem Eur J 2003, 9, 400.
57. Matito, E.; Solà, M.; Salvador, P.; Duran, M. Faraday Discuss 2007, 135, 325.
58. Clar, E. The Aromatic Sextet; Wiley: New York, 1972.
59. Portella, G.; Poater, J.; Solà, M. J Phys Org Chem 2005, 18, 785.
60. Kruszewski, J.; Krygowski, T. M. Tetrahedron Lett 1972, 13, 3839.
61. Krygowski, T. M. J Chem Inf Comp Sci 1993, 33, 70.
62. Schleyer, P. V. R.; Jiao, H. Pure Appl Chem 1996, 68, 209.
63. Schleyer, P. V. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; van Eikema Hommes, N. J. R. J Am Chem Soc 1996, 118, 6317.
64. Merino, G.; Vela, A.; Heine, T. Chem Rev 2005, 105, 3812.
65. Poater, J.; Fradera, X.; Duran, M.; Solà, M. Chem Eur J 2003, 9, 1113.
66. Fradera, X.; Austen, M. A.; Bader, R. F. W. J Phys Chem A 1999, 103, 304.
67. Fradera, X.; Poater, J.; Simon, S.; Duran, M.; Solà, M. Theor Chem Acc 2002, 108, 214.
68. Bader, R. F. W. Atoms in Molecules: A Quantum Theory; Clarendon: Oxford, 1990.
69. Bader, R. F. W. Acc Chem Res 1985, 18, 9.
70. Bader, R. F. W. Chem Rev 1991, 91, 893.
71. Matito, E.; Feixas, F.; Solà, M. J Mol Struct (Theochem) 2007, 811, 3.
72. Cioslowski, J.; Matito, E.; Solà, M. J Phys Chem A 2007, 111, 6521.
73. Gutman, I.; Milun, M.; Trinajstic, N. J Am Chem Soc 1977, 99, 1692.
74. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: Pittsburgh, PA, 2003.
75. Biegler-König, F. W.; Bader, R. F. W.; Tang, T.-H. J Comput Chem 1982, 3, 317.
76. Becke, A. D. J Chem Phys 1993, 98, 5648.
77. Lee, C.; Yang, W.; Parr, R. G. Phys Rev B 1988, 37, 785.
78. Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. J Phys Chem 1994, 98, 11623.
79. Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. J Chem Phys 1980, 72, 650.
80. Frisch, M. J.; Pople, J. A.; Binkley, J. S. J Chem Phys 1984, 80, 3265.
81. Fukui, K. J Chem Phys 1970, 74, 4161.
82. Fukui, K. Acc Chem Res 1981, 14, 363.
83. Gonzalez, C.; Schlegel, H. B. J Chem Phys 1988, 90, 2154.
84. Wolinski, K.; Hilton, J. F.; Pulay, P. J Am Chem Soc 1990, 112, 8251.
85. Schleyer, P. V. R.; Manoharan, M.; Wang, Z. X.; Kiran, B.; Jiao, H. J.; Puchta, R.; van Eikema Hommes, N. J. R. Org Lett 2001, 3, 2465.
86. Corminboeuf, C.; Heine, T.; Seifert, G.; Schleyer, P. V. R.; Weber, J. Phys Chem Chem Phys 2004, 6, 273.
87. Fallah-Bagher-Shaidaei, H.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. V. R. Org Lett 2006, 8, 863.
88. Matito, E. ESI-3D: Electron Sharing Indexes Program for 3D Molecular Space Partitioning http://iqc.udg.es/∼eduard/ESI; Institute of Computational Chemistry: Girona, 2006.
89. Poater, J.; Solà, M.; Duran, M.; Fradera, X. Theor Chem Acc 2002, 107, 362.
90. Chattaraj, P. K.; Roy, D. R.; Geerlings, P.; Torrent-Sucarrat, M. Theor Chem Acc 2007, 118, 923.
91. Torrent-Sucarrat, M.; Salvador, P.; Solà, M.; Geerlings, P. J Comput Chem 2007, DOI 10.1002/jcc.20866.
92. Poater, J.; Solà, M.; Viglione, R. G.; Zanasi, R. J Org Chem 2004, 69, 7537.
93. Krygowski, T. M.; Ejsmont, K.; Stepień, B. T.; Cyrański, M. K.; Poater, J.; Solà, M. J Org Chem 2004, 69, 6634.
94. Krygowski, T. M.; Stepień, B. T. Polish J Chem 2004, 78, 2213.
95. Krygowski, T. M.; Stepień, B. T. Chem Rev 2005, 105, 3482.
96. Low, A. A.; Hall, M. B. Int J Quantum Chem 2000, 77, 152.
97. Hubig, S. M.; Lindeman, S. V.; Kochi, J. K. Coord Chem Rev 2006, 200–202, 831.
98. Albright, T. A.; Hofmann, P.; Hoffmann, R.; Lillya, C. P.; Dobosh, P. A. J Am Chem Soc 1983, 105, 3396.

99. Arrais, A.; Diana, E.; Gervasio, G.; Gobetto, R.; Marabello, D.; Stanghellini, P. L. Eur J Inorg Chem 2004, 1505.
100. Feixas, F.; Jiménez-Halla, J. O. C.; Matito, E.; Poater, J.; Solà, M. Polish J Chem 2007, 81, 783.
101. Mitchell, R. H.; Brkic, Z.; Berg, D. J.; Barclay, T. M. J Am Chem Soc 2002, 124, 11983.
102. Mitchell, R. H.; Chen, Y.; Khalifa, N.; Zhou, P. J Am Chem Soc 1998, 120, 1785.
103. Mitchell, R. H.; Zhou, P.; Venugopalan, S.; Dingle, T. W. J Am Chem Soc 1990, 112, 7812.
104. Stanger, A. J Org Chem 2006, 71, 883.
105. Jiménez-Halla, J. O. C.; Matito, E.; Robles, J.; Solà, M. J Organomet Chem 2006, 691, 4359.
106. Schleyer, P. V. R.; Jiao, H. J.; van Eikema Hommes, N. J. R.; Malkin, V. G.; Malkina, O. L. J Am Chem Soc 1997, 119, 12669.
107. Mandado, M.; Otero, N.; Mosquera, R. A. Tetrahedron 2006, 62, 12204.
108. Sakai, S. J Phys Chem A 2002, 106, 10370.
109. Hoffmann, R. J Chem Phys 1964, 40, 2745.
110. Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. Chem Rev 2004, 104, 2777.
111. Schulman, J. M.; Disch, R. L. J Phys Chem A 1999, 103, 6669.
112. Poater, J.; Visser, R.; Solà, M.; Bickelhaupt, F. M. J Org Chem 2007, 72, 1134.
113. Santos, J. C.; Tiznado, W.; Contreras, R.; Fuentealba, P. J Chem Phys 2004, 120, 1670.
114. Santos, J. C.; Andres, J.; Aizman, A.; Fuentealba, P. J. Chem Theor Comput 2005, 1, 83.
115. Gutman, I.; Tomovic, Z.; Müllen, K.; Rabe, J. P. Chem Phys Lett 2004, 397, 412.
116. Havenith, R. W. A.; van Lenthe, J. H.; Dijkstra, F.; Jenneskens, L. W. J Phys Chem A 2001, 105, 3838.
117. Ruiz-Morales, Y. J Phys Chem A 2004, 108, 10873.
118. Lazzeretti, P. In Progress in Nuclear Magnetic Resonance Spectroscopy; Emsley, J. W.; Feeney, J.; Sutcliffe, L. H., Eds.; Elsevier: Amsterdam, 2000; pp 1–88.
119. Lazzeretti, P. Phys Chem Chem Phys 2004, 6, 217.
120. Poater, J.; Bofill, J. M.; Alemany, P.; Solà, M. J Org Chem 2006, 71, 1700.
121. Osuna, S.; Poater, J.; Bofill, J. M.; Alemany, P.; Solà, M. Chem Phys Lett 2006, 428, 191.
122. Havenith, R. W. A.; Fowler, P. W.; Steiner, E. J Chem Soc Perkin Trans 2 2002, 502.
123. Collier, W.; Saebø, S.; Pittman, C. U., Jr. J Mol Struct (Theochem) 2001, 549, 1.
124. Saebø, S.; Stroble, S.; Collier, W.; Ethridge, R.; Wilson, Z.; Tahai, M.; Pittman, C. U., Jr. J Org Chem 1999, 64, 1311.
125. Scott, A. P.; Agranat, I.; Biedermann, P. U.; Riggs, N. V.; Radom, L. J Org Chem 1997, 62, 2026.
126. Houk, K. N. J Chem Soc Faraday Trans 1994, 90, 1599.
127. Houk, K. N.; Gonzalez, J.; Li, Y. Acc Chem Res 1995, 28, 81.
128. Bernardi, F.; Celani, P.; Olivucci, M.; Robb, M. A.; Suzzi-Valli, G. J Am Chem Soc 1995, 117, 10531.
129. Herges, R.; Jiao, H.; Schleyer, P. V. R. Angew Chem Int Ed Engl 1994, 33, 1376.
130. Jiao, H.; Schleyer, P. V. R. J Phys Org Chem 1998, 11, 655.
131. Woodward, R. B.; Hoffmann, R. The Conservation of Orbital Symmetry; Verlag Chemie: Weinheim, 1970.
132. Zimmermann, H. Acc Chem Res 1971, 33, 272.
133. Dewar, M. J. S. Angew Chem Int Ed Engl 1971, 10, 761.
134. Sakai, S. J Phys Chem A 2000, 104, 922.
135. Wiest, O.; Houk, K. N. Top Curr Chem 1996, 183, 1.
136. Lischka, H.; Ventura, E.; Dallos, M. Chem Phys Chem 2004, 5, 1365.
137. Evans, M. G.; Warhust, E. Trans Faraday Soc 1938, 34, 614.
138. Manoharan, M.; De Proft, F.; Geerlings, P. J Org Chem 2000, 65, 7971.
139. Manoharan, M.; De Proft, F.; Geerlings, P. J Chem Soc Perkin Trans 2 2000, 1767.
140. Manoharan, M.; De Proft, F.; Geerlings, P. J Org Chem 2000, 65, 6132.
141. Matito, E.; Poater, J.; Duran, M.; Solà, M. J Mol Struct (Theochem) 2005, 727, 165.
142. Bachrach, S. M.; White, P. B. J Mol Struct (Theochem) 2007, 819, 72.
143. Morao, I.; Cossio, F. P. J Org Chem 1999, 64, 1868.
144. Cioslowski, J.; Liu, G.; Moncrieff, D. Chem Phys Lett 2000, 316, 536.
145. Havenith, R. W. A.; Fowler, P. W.; Jenneskens, L. W.; Steiner, E. J Phys Chem A 2003, 107, 1867.
146. Santos, J. C.; Polo, V.; Andrés, J. Chem Phys Lett 2005, 406, 393.
147. Mandado, M.; González-Moa, M. J.; Mosquera, R. A. Chem Phys Chem 2007, 8, 696.
148. Fuentealba, P.; Chamorro, E.; Santos, J. C. In Theoretical Aspects of Chemical Reactivity; Toro-Labbé, A., Eds.; Elsevier: Amsterdam, 2007; pp. 57–85.
149. Bultinck, P.; Mandado, M.; Mosquera, R. A. J Math Chem 2007, 43, 111.
150. Matito, E.; Poater, J.; Solà, M.; Duran, M.; Salvador, P. J Phys Chem A 2005, 109, 9904.
151. Matito, E.; Salvador, P.; Duran, M.; Solà, M. J Phys Chem A 2006, 110, 5108.