Quantifying aromaticity with electron delocalisation measures

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Abstract

Aromaticity cannot be measured directly by any physical or chemical experiment because it is not a well-defined magnitude. Its quantification is done indirectly from the measure of different properties that are usually found in aromatic compounds such as bond length equalisation, energetic stabilisation, and particular magnetic behaviour associated with induced ring currents. These properties have been used to set up the myriad of structural-, energetic- and magnetic-based indices of aromaticity known to date. Cyclic delocalisation of mobile electrons in two or three dimensions is probably one of the key aspects that characterise aromatic compounds. However, it has not been until the last decade that electron delocalisation measures have been widely employed to quantify aromaticity. Some of these new indicators of aromaticity such as the *PDI*, *FLU*, I_{NG}, and I_{NB} were defined in our group. In this paper, we review the different existent descriptors of aromaticity that are based on electron delocalisation properties, we compare their performance with indices based on other properties, and we summarise a number of applications of electronic-based indices for the analysis of aromaticity in interesting chemical problems.

1. Introduction

The study of aromatic species goes back to 1825 when Michael Faraday obtained benzene by distillation and named it “dicarburet of hydrogen”. In this work, Faraday found that the empirical formula of benzene was CH. He already noted that “dicarburet of hydrogen” was much less reactive than “monocarburet of hydrogen” (trans-2-butene).[1] Such decreased reactivity was considered an experimental characteristic of aromatic compounds ever since. In 1834, Mitscherlich determined that the compound synthesised by Faraday had the molecular formula C_6H_6.[2] Since it was obtained from distillation of benzoic acid (from *gum benzoin*) and lime, he named the compound as *benzin*, which became benzene when translated into English. In 1865, a century and a half ago,[3] August Kekulé[4] proposed the molecular structure of benzene consisting in a six-membered ring (6-MR) of carbon atoms with alternating single and double bonds. Pyridine, the first heteroaromatic compound, was synthesised by Thomas Anderson[5] in 1868 through studies on the distillation of bone-oil and other animal matter. In 1911, Willstätter and Waser[6] synthesised cyclooctatetraene, an eight-membered carbon ring with alternating single and double bonds that had a reactivity very different from benzene and was classified as antiaromatic. The first synthesised inorganic heteroaromatic compound was borazine, $B_3H_6N_3$,[7] obtained in 1926 by a reaction of diborane with ammonia. In 1954, Doering and Knox[8] prepared the tropylium cation, $C_7H_7^+$, which was considered the first verification of the Hückel rule.[9] Four years later, Winstein introduced the homoaromaticity concept while studying the 3-bicyclo[3.1.0]hexyl cation.[10] Three years later, the synthesis of the first organic derivatives of closo-dodecaborate and closo-decaborate by the group of Muetterties[11] was the beginning of closo-borane chemistry and three-dimensional aromaticity, the type of aromaticity that characterises fullerenes.[12] The identification[13, 14] of the planar triplet ground states of $C_5H_5^+$ and $C_5Cl_5^+$ in the late 60's provided experimental support for the existence of triplet aromaticity as predicted by Baird.[15] In 1982 Roper et al.[16] synthesised the first metallabenzene, an osmabenzene, thus initiating a new group of aromatic species, the so-called metalloaromatic compounds.[17] Interestingly, metallabenzene species were proposed first by Thorn and Hoffmann three years before from theoretical calculations.[18] More recently, in 2001 Boldyrev, Wang, and coworkers[19] detected a series of bimetallic clusters containing Al_4^{2-}, the first all-metal aromatic cluster known, face-capped by an M^+ cation (M = Li, Na, Cu). The same group detected $Ta_3O_3^-$, the first discovered metallic cluster showing δ-aromaticity.[20] In 2003, Herges et al. synthesised the first Möbius aromatic hydrocarbon.[21] This kind of aromatic species were already predicted by Heilbronner forty years before on purely theoretical grounds.[22]

Despite the nearly two centuries of intense study and continuous progress described in the previous paragraph, the interest on aromaticity has not decreased and still stimulates the creativity of a number of contemporary chemists. Considered like a chemical unicorn by Frenking and Krapp,[23] aromaticity is not a property directly observable and it lacks a well-founded physical basis. Therefore, its definition and quantification remains elusive. Chen and Schleyer[24] defined aromaticity as "*a manifestation of electron delocalisation in closed circuits, either in two or three dimensions.*" Electron delocalisation is without doubt one of the key aspects of aromatic compounds. Since 1932 when Pauling[25, 26] introduced the concept of resonance, it is well established that delocalisation of electrons in a molecule can stabilise it. Another relevant feature of aromatic compounds is their symmetry. Despite not all aromatic compounds are symmetric and not all symmetric cyclic compounds are aromatic, it is generally the case that the most archetypal aromatic compounds are highly symmetric and possess degenerate highest-occupied molecular orbitals that are fully occupied resulting in a closed-shell structure or have a same-spin half-filled electronic structure. This is the case of benzene, but also of triplet $C_5H_5^+$, C_{60}^{10+}, Al_4^{2-} or closo borane clusters like $B_6H_6^{2-}$. The closed-shell or same-spin half-filled electronic structure is the origin of several rules of aromaticity such as the $4n+2$ Hückel,[9] $4n$ Baird,[15] $2n+2$ Wade-Mingos,[27, 28] $2(n+1)^2$ Hirsch[29] or the $2n^2+2n+1$[30] rules. This particular electronic structure of aromatic species explains their substantial energetic stabilisation and, consequently, their low reactivity. Moreover, it results in a variety of unusual chemical and physical properties, including tendency toward bond equalisation, unusual reactivity, and characteristic spectroscopic and magnetic features.

It is worth noting that the bond length equalisation observed in benzene and derivatives is enforced by the σ-electrons and not by the π-electron system. The latter is distortive and favours the D_{3h} structure of benzene over the D_{6h} one. This somewhat paradoxical observation was suggested first by Longuet-Higgins and Salem in 1959.[31] Berry[32] used this suggestion to account for the observed increased frequency of the b_{2u} Kekulé vibrational mode when going from the ground $^1A_{1g}$ to the first $^1B_{2u}$ excited state. The same idea was reinforced later on by the work of Haas and Zilberg,[33, 34] and especially by that of Hiberty, Shaik, and co-workers[35, 36] and others[37, 38] Finally, more recently Pierrefixe and Bickelhaupt[39-41] showed that the regular geometry of benzene is a consequence of how σ and π overlaps depend on bond distances. In aromatic annulenes the authors confirmed that bond equalisation is due to the σ electrons whereas the π-electron system favours double-bond localisation.

The quantification of physicochemical properties that reflect some manifestation of the aromatic character of molecules is used to evaluate their global or local (e.g., individual rings in a polycyclic arene) aromatic character.[42-44] This leads to the countless existing measures of aromaticity based on the structural,[45, 46] magnetic,[24, 47] energetic,[48] and electronic[49] properties of molecules. These indicators provide indirect measures of aromaticity that, to some extent, are somewhat arbitrary. Moreover, for a series of compounds different descriptors of aromaticity do not provide the same aromaticity ordering and some descriptors fail to correctly quantify certain changes of aromaticity in particular examples.[50] For this reason, it is widely accepted that the concept of aromaticity should be analysed by employing a set of aromaticity descriptors.[24, 51, 52]

The importance of electron delocalisation in aromatic species is universally recognised. It is thus reasonable to employ electron delocalisation as a tool to construct new aromaticity indicators. The problem is that electron delocalisation like aromaticity is not an observable and, therefore, there is not a unique way to measure it. Moreover, when devising new aromaticity descriptors three steps should be followed: development, assessment, and application. In the next sections, we describe firstly the most usual ways to quantify electron delocalisation; second, we discuss how these measures can be used to define indicators of aromaticity; third, we examine how electronic-based indices compare with other existing descriptors; and finally, we show some applications of these electronic descriptors of aromaticity carried out in our research group.

2. How can electronic delocalisation be measured?

Electron localisation/delocalisation is central in several fundamental chemical phenomena such as conjugation, hyperconjugation, and aromaticity that are important to explain the structure, stability, magnetic properties, and reactivity of many molecules. Several tools have been developed to quantify delocalisation in a molecule and to provide new insights into chemical bonding. These descriptors of delocalisation have been reviewed in several works.[49, 53-55] We just briefly mention here some of the most important and describe in more detail those utilised for the definition of aromaticity indicators.

Descriptors of electron localisation/delocalisation can be broadly grouped into three classes, namely, those computed from the wavefunction, those constructed directly from the electron density and its derivatives, and those that are derived from first- and higher-order density matrices. Among the first group of electron delocalisation indicators, we can mention the use of weights of resonance structures and energies in valence bond theory.[56, 57] Also belonging to this group are the measures of delocalisation obtained with the block-localised wavefunction (BLW) method of Mo and coworkers.[58, 59] In addition, in the framework of the molecular orbital (MO) theory, different techniques are available for the localisation of MOs to find the regions where electron pairs are located. To date the natural bond orbital (NBO) analysis of Weinhold et al.[60, 61] is one of the most used method for localising bonds and lone pairs. The importance of electron delocalisation is assessed in NBO analyses by approximated second-order perturbative expressions. Another similar tool used for obtaining patterns of chemical bonding is the adaptive natural density partitioning (AdNDP) method developed by Zubarev and Boldyrev.[62, 63] AdNDP represents the electronic structure in terms of n centre – 2 electrons (nc-2e) bonds. Starting from n = 1, AdNDP recovers Lewis bonding elements (1c-2e and 2c-2e objects) and delocalised bonding elements (for n > 2), which can be associated with the concepts of delocalisation and aromaticity. An even more recent method is the orbital localisation procedure based on the electron localisation function (ELF-LOC) of Alcoba, Tiznado, and coworkers.[64-66] This procedure localises the molecular orbitals in regions that have the highest probability for finding a pair of electrons, providing also a chemical bonding description in terms of nc-2e bonds.

In the second group of electron delocalisation descriptors, we can refer to the Laplacian of the electron density ($\nabla^2\rho(\mathbf{r})$),[67, 68] the ellipticity along the bond path ($\varepsilon=\lambda_1/\lambda_2-1$),[69] the noncovalent interactions index (*NCI*),[70] the inhomogeneity measures of the electron density,[71] the source function,[72, 73] the single exponential decay detector,[74] and a recent electron delocalisation index obtained from electron population analysis.[75] The electron delocalisation indicators collected in the third group are probably the most abundant. The reason is that the location of electron pairs involves two spatial coordinates and, therefore, methods based on functions of two (or more) positions such as the first-order density matrix and the two-electron density or pair density are more suitable to analyse electron localisation and delocalisation. This group includes the localised orbital locator,[76] the electron delocalisation range function,[77] the parity function,[78] the analytical method by Proynov to calculate the population of effectively unpaired electrons,[79] the Fermi hole density maps,[80, 81] the domain-averaged Fermi holes,[82, 83] the Laplacian of the exchange-correlation density,[84] the electron localisation function (ELF),[85-88] and the electron localisability indicator.[89, 90] Also belonging to this group are the methods for computing the probability of finding a certain number of electrons in a given volume.[91-93] And finally, although not derived directly from density matrices, the analysis of the linear response kernel (LRK),[94-96] a function of two position variables, could also be included in this third group of electron localisation/delocalisation descriptors.

Because of its importance in the definition of aromaticity descriptors, we will refer with more detail to the electron sharing indices (ESI). These ESIs are electron localisation/delocalisation descriptors that can also be classified in the third group. They are defined from the spinless two-electron density or pair density, $\gamma(\overrightarrow{r_1},\overrightarrow{r_2})$. This function can be interpreted as the probability density of having simultaneously two electrons at positions $\vec{r}_1$ and $\vec{r}_2$, regardless the position of the other N-2 electrons. It can be separated into an uncorrelated part and a part that collects all exchange and correlation effects,

$$\gamma(\overrightarrow{r_1},\overrightarrow{r_2}) = \rho(\overrightarrow{r_1})\rho(\overrightarrow{r_2}) + \gamma_{XC}(\overrightarrow{r_1},\overrightarrow{r_2}) \qquad (1)$$

The uncorrelated part of the pair density is given by the product $\rho(\overrightarrow{r_1})\rho(\overrightarrow{r_2})$ and provides the probability of finding simultaneously two independent electrons at positions $\vec{r}_1$ and $\vec{r}_2$, irrespective of the position of the other N-2 electrons. The exchange-correlation density, $\gamma_{XC}(\vec{r}_1,\vec{r}_2)$, which is the difference between $\gamma(\overrightarrow{r_1},\overrightarrow{r_2})$ and $\rho(\overrightarrow{r_1})\rho(\overrightarrow{r_2})$, gives a measure of the degree to which density is excluded at $\vec{r}_2$ because of the presence of an electron at $\vec{r}_1$. The localisation and delocalisation indices (LIs and DIs) were defined by Bader and coworkers[97, 98] from the double integration of the exchange-correlation density over two atomic domains:

$$\lambda(A) = -\iint\limits_{A\,A} \gamma_{XC}(\vec{r_1},\vec{r_2})d\vec{r_1}d\vec{r_2} \tag{2}$$

$$\delta(A,B) = -2\iint\limits_{B\,A} \gamma_{XC}(\vec{r_1},\vec{r_2})d\vec{r_1}d\vec{r_2} \tag{3}$$

The DI or 2c-ESI, *δ(A,B),* gives a quantitative measure of the number of electron pairs delocalised or shared between atomic basins A and B, whereas the LI, *λ(A),* is a measure of the average number of electrons localised on atom A. The double integration of the exchange-correlation density gives $-N$ electrons, and, therefore, the following sum rule is followed:

$$N(A) = \lambda(A) + \frac{1}{2}\sum_{B\neq A}\delta(A,B) \tag{4}$$

Eqs. (2) and (3) can be applied at any level of theory, provided that the first and second-order density functions are known. At the Hartree-Fock (HF) level or with the density functional theory (DFT) approach (in this case we use the non-interacting wavefunction derived from Kohn-Sham orbitals)[99] the expressions for the LI and DI are,

$$\lambda(A) = \sum_{ij} S_{ij}^2(A) \tag{5}$$

$$\delta(A,B) = 2\sum_{ij} S_{ij}(A)S_{ij}(B) \tag{6}$$

where the summations run over all the pairs of occupied spin molecular orbitals (MO) of the molecule. The $S_{ij}(A)$ terms in Eqs. (5) and (6), needed to compute LIs and DIs, are the overlaps between MOs integrated within the basin of atom A and require integration over atomic domains. In the Quantum Theory of Atoms-in-Molecules (QTAIM) these domains are the *atomic basins* defined as the regions in real space bound by zero-flux surfaces in $\rho(\vec{r})$ or by infinity.[67, 68, 100, 101] However, other atomic partitions like the Mulliken-like partitioning in the Hilbert space spanned by the basis functions, the fuzzy-atom approach,[102] or the topological fuzzy Voronoi cell (TFVC)[103] can be used for the integration. The 2c-ESIs of organic covalent bonds give qualitatively the same results regardless the atomic partition used.[104, 105]

The definition of the ESI can be generalised to analyse multicentre delocalisation or sharing of electrons. It is possible to define a multicentre DI or *Mc*-ESI[106] between the *M* centres A_1 to A_M:

$$I_{A_1,\cdots,A_M} = \sum_{i_1\cdots i_M} n_{i_1} \cdots n_{i_M} S_{i_1 i_2}(A_1) S_{i_2 i_3}(A_2) \cdots S_{i_M i_1}(A_M) \tag{7}$$

where n_i are the occupancies of the natural orbitals. This formulation assumes that the electron sharing occurs only between neighbouring atoms. Bultinck and coworkers[107] suggested another definition that takes into account all possible permutations of the *M* atoms, the multicentre index,

$$MCI(A_1,\cdots,A_M) = \frac{1}{2M} \sum_{P(A_1,\cdots,A_M)} I_{A_1,\cdots,A_M} \tag{8}$$

where *P* represents all possible permutations between centres A_1 to A_M. Indeed, in a HF calculation, the *MCI* represents the *M*-centre moment of the *M*-variate probability distribution restricting one electron in each atomic region; i.e., for a given molecule the *MCI* reflects the simultaneous electron sharing between all centres, regardless the position of the atoms in the molecule. This definition is only valid in general if the *M*-order reduced density matrix (*M*-RDM) —which carries a large computational cost— is used for the calculation of the MCI. In practice, the calculation of MCI is performed using Eqs. (7) and (8), which is only exact for single-determinant wavefunctions, or using other approximations to the M-RDM.[108] The main drawback of MCI is that the computational cost grows very fast with the number of atoms. Although this downside does not represent a problem for most systems, it prevents the calculation of expanded porphyrins and other Möbius systems.

One should also mention another important pitfall of multicentre indices: the atomic partition. Both $I_{A1,\cdots,AM}$ and MCI are very sensible to the atomic partition, being QTAIM and TFVC partitions the most reliable ones.[109] In addition, the accuracy of the numerical integration over the atomic basins becomes an issue for large strings of atoms, as those occurring in molecules with large rings. In this sense, rings of more than ten members need very accurate calculations or the use of the Hilbert-space partition that provides analytical atomic overlaps, thus avoiding the integration hassle.

3. Electron delocalisation measures as indicators of aromaticity

In this section we will describe the electron delocalisation aromaticity indices and give the expression of the most important ones. In order to illustrate the performance of these indicators we will include the values for a small set of representative molecules: benzene, cyclohexane, borazine, pyridine, Al_4^{2-}, and the transition state of the Diels-Alder cycloaddition reaction between butadiene and ethylene that we have calculated at the CCSD/cc-pVDZ level of theory. We will consider a ring structure of M atoms represented by the string $\mathcal{A} = [A_1, A_2, \ldots, A_M]$, where the elements are ordered according to the connectivity of the atoms in the ring.

The aromaticity indices calculated from the wavefunction include an energetic criterion using the adiabatic resonance energies calculated from the BLW method.[110] From the group of indices based on the first- and higher-order density matrices, we can mention the ELF_{π} descriptor of Santos and coworkers,[111] which has been used, among others, to account for excited states aromaticity, and the *para* linear response (PLR) indicator. The PLR was defined by Sablon and coworkers[96] as the LRK integrated over the atoms in the *para* position of a 6-MR. Several aromaticity indices defined in the last years depend also on the topology of the electron density. Krygowski used the electron density calculated at the ring critical point (RCP), i.e. the lowest density point in a molecular ring plane[112] and other relevant quantities borrowed from the QTAIM.[113, 114] On his side, Noorizadeh and Shakerzadeh used the Shannon entropy of the electron density calculated at the bond critical point to define an aromaticity index.[115]

Electron delocalisation has been tightly connected to aromaticity from the very beginning. The old concept of bond order —that later evolved to electron sharing index, Eq. (3)— was brought up by Coulson in 1939 and it was first applied within the Hückel molecular orbital method to study the electronic structure of aromatic molecules.[116] Julg was among the first to suggest an index based on the uniformity of the interatomic distances, an indicator that a few years later he modified to take into account the charge gradient between bonded atom pairs in a ring.[117, 118] In 1983, Jug suggested that aromaticity could be measured by the minimal bond order in a given ring structure[119] and, two years afterwards, Bird defined a new measure of aromaticity based on the statistical deviation of the bond orders in the ring.[120] More recently, Matta et al.[121] and Bultinck and coworkers[107] suggested the θ and BOIA aromaticity indices. The former is based on the electron delocalisation of the atoms and the latter uses the 2c-ESI in a ring. These indices compared the corresponding magnitudes to some reference values, usually taken from benzene. In this line, we suggested[122] the aromatic fluctuation index (*FLU*) that employs both quantities, the 2c-ESI and the atomic delocalisation of each ring member. *FLU* measures the uniformity of the electron delocalisation along the molecular ring and its bonding difference with respect to some aromatic reference, and it is given by:[122]

$$FLU(\mathcal{A}) = \frac{1}{M}\sum_{i=1}^{M}\left[\left(\frac{\delta(A_i)}{\delta(A_{i-1})}\right)^{\alpha}\left(\frac{\delta(A_i,A_{i-1}) - \delta_{ref}(A_i,A_{i-1})}{\delta_{ref}(A_i,A_{i-1})}\right)\right]^2 \quad , \tag{9}$$

where $A_0 \equiv A_M$, the atomic delocalisation is defined as:

$$\delta(A_i) = \sum\nolimits_{A_j \neq A_i} \delta(A_i, A_j) \quad , \tag{10}$$

and α is a simple function to make sure that the first term in Eq. (9) is always greater or equal to 1,

$$\alpha = \begin{cases} 1 & \delta(A_i) > \delta(A_{i-1}) \\ -1 & \delta(A_i) \leq \delta(A_{i-1}) \end{cases} \tag{11}$$

The CC and CN bonds reference values are taken from benzene and pyridine in its ground state. *FLU* is close to 0 in aromatic species and increases as the molecule departs from the aromatic reference. Like any aromaticity index based on reference values it depends critically on the model aromatic molecules chosen and it cannot be used to study reactivity.[123] Moreover, it is difficult to compare molecules with different ring patterns. However, *FLU* gives a good account of the aromaticity for ground-state organic molecules.[124] These facts are illustrated by the numbers in Table 1, where we can see *FLU* wrongfully assigns a very low aromatic character to the transition state of the Diels-Alder reaction, it does a good job in other organic molecules but it cannot assign a value to Al_4^{2-} or borazine due to the lack of reference systems.

	FLU	*PDI*	I_{ring}	*MCI*	I_{NG}	I_{NB}
benzene	0	58.9	32.3	47.3	38.7	38.3
pyridine	11.9	59.1	30.4	44.2	38.3	37.9
borazine	—	10.4	0.9	1.0	21.1	20.2
cyclohexane	339	6.3	0.2	0.2	16.7	15.9
TS-DA	315	51.0	21.5	31.0	36.1	35.7
Al_4^{2-}	—	—	74.9	258.3	53.8	75.7

Table 1 The CCSD/cc-pVDZ electronic-based aromaticity indices for a set of representative molecules and the transition state of the Diels-Alder cycloaddition (TS-DA). With the exception of *FLU*, for all indicators the larger the index, the more aromatic the species are. Values multiplied by 1000.

The *para*-delocalisation index (*PDI*) measures the electron delocalisation across the ring by averaging the three *para*-related positions in a 6-MR.[125] *PDI* is, obviously, limited to rings of six members and it suffers to describe molecular rings containing atoms with lone-pairs (it finds pyridine more aromatic than benzene) or to explain the small distortions around the equilibrium geometry (see section 4).[50, 126] On the other hand, it does a good job in polycyclic aromatic hydrocarbons.[127] Ángyán[128, 129] showed the connection between the 2c-ESI and the LRK for the QTAIM partition, which suggests that the *PLR* and the *PDI* could be measuring the same effect in a molecular ring.

The I_{ring} was defined by Giambiagi and coworkers[130] as their own multicentre index, Eq. (7), applied to ring structures, assuming the obvious link between cyclic electron delocalisation and aromaticity. The *MCI* of Bultinck can also be used to quantify aromaticity. Unlike I_{ring}, which only takes into account the *Kekulé arrangement* of the atoms in a ring, *MCI* considers all possible arrangements. The Kekulé structure contribution is usually the most important one and, therefore, I_{ring} and *MCI* rarely give disparate results. In such eventuality, the ring cross-contributions play a prominent role, as it happens in Al_4^{2-}, where the delocalisation between non-bonded atoms is half as large as the delocalisation of neighbouring pairs. Unlike *PDI* and *FLU*, these multicentre indices do not have severe restrictions that limit its range of application, except for the numerical accuracy problems already mentioned. However, both I_{ring} and *MCI* multiply a number of overlaps that depend on the ring size, leading to a size-extensivity problem. Since overlap values are lower than one in absolute value, the MCI becomes artificially large for small rings, as we can see in the case of Al_4^{2-}, which has an *MCI* value an order of magnitude larger than benzene. The latter issue was recently solved in our group by taking the *M*th root of these two indices.[131] In addition, we also proved that taking into account the appropriate normalization factor these indices showed a good linear correlation with the topological resonance energy per π electron (TREPE). The normalised I_{ring} and *MCI* values were named I_{NG} and I_{NB},[131] their expression reading:

$$I_{NB}(\mathcal{A}) = \frac{\pi^2}{4}\frac{G(N_\pi)}{MN_\pi} I_{ring}(\mathcal{A})^{1/M} \tag{12}$$

$$I_{NB}(\mathcal{A}) = C\frac{G(N_\pi)}{MN_\pi} MCI(\mathcal{A})^{1/M} \tag{13}$$

where N_π is the number of π electrons of the atoms in the ring, $G(N_\pi)$ equals 1 and -3 for aromatic and antiaromatic systems, respectively, and C=1.5155 is a proportionality constant. These indices have the serious disadvantage of relying upon $G(N_\pi)$, which might not be known *a priori*. However, one can give up the correlation with TREPE in favour of practicality and use the unnormalised *MCI* and I_{ring}, or their *M*th root when comparing rings of different size. Finally, it is worth noting that —unlike I_{ring} and I_{NG}— both *MCI* and I_{NB} admit local and global counterparts depending on whether the index is calculated just for the atoms in the ring or all the atoms in the molecule. This feature opens the possibility of interesting analyses on the effect of individual rings in the global aromaticity of a molecule, which to the best of our knowledge has not been explored thus far.

All electronic indices used in this section as well as the Harmonic Oscillator Model of Aromaticity (HOMA) and TREPE indices can be calculated using the software generated in our group, ESI-3D,[132] in conjunction with AIMPAC,[133] AIMall[134] or APOST-3D[135] packages to generate the atomic overlaps in the pertinent partition. These programmes read wavefunction or formatted checkpoint files from Gaussian, Gamess, Turbomole and NWChem, among other software. ESI-3D also reads the output of Gaussian, permitting the calculation of the electronic indices within a Hilbert-space partition.

A longstanding goal within the field of aromaticity has been the classification of molecules into different groups (aromatic, non-aromatic, antiaromatic) to rationalise structure, reactivity, and molecular properties. This classification was usually done on the grounds of chemical intuition or by examination of the occupied MOs. The discovery of new and more exotic molecules makes this classification more and more complicated, and for the past twenty years several aromaticity indices have been constructed to simplify this task. However, there has been such a proliferation of indices (often giving opposite answers) that is barely impossible to unambiguously characterise new molecules. To gain insight into the nature of aromatic molecules or to design and discover new molecules, aromaticity indices need to be validated.

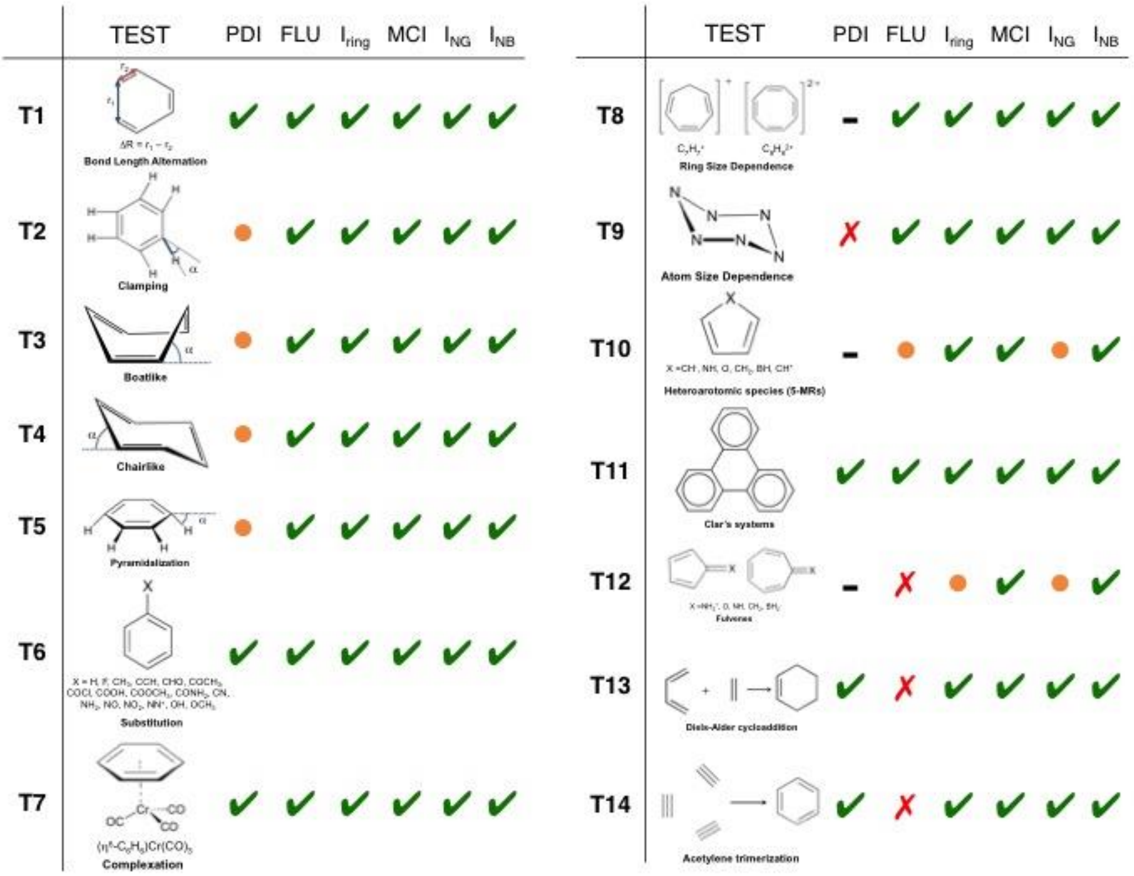
4. Assessing the performance of aromaticity indices using a test set

A central tenet in the study of aromaticity is that it cannot be unambiguously defined and no single property exists that can be taken as a direct measure of aromaticity. Thus, directly comparing indicators of aromaticity for a given set of related compounds, e.g. polyaromatic hydrocarbons (PAH), is a daunting task as some of them measure distinct properties. In the literature several examples showing poor correlations between descriptors of different nature (i.e. magnetic-, energy-, structural-, or electronic-based indicators) have been reported, which prevents the use of this strategy to assess its performance. As illustrated by Bultinck, favourable correlations are observed, in general, among a set of electronic-based indices (*MCI*, *PDI*, BOIA, or θ), while comparing these descriptors with NICS gives poor correlations.[136] Similarly, work by Bickelhaupt et al. provided evidence that magnetic aromaticity is orthogonal to structural and energetic aromaticity for [5]paracyclophane.[137] In addition, aromaticity indices do not often give consistent results for long-established cases and these failures sometimes do not stand out in correlations of large data sets. The apparent contradictions obtained are occasionally justified by invoking the multidimensional character of aromaticity.[138] Therefore, it is not possible to discern between spurious results given by a descriptor and deviations due to the multidimensional character of aromaticity. These studies advocate for the use of more than one descriptor of aromaticity. While we agree on such approach, one should first know the range of applicability of these indices, in order to choose the most appropriate ones.

In the last section we have seen how electronic aromaticity can be measured in a variety of flavours. The question now is how accurately electronic-based descriptors perform in a more diverse and complete set of systems and how they compare to other well-known descriptors of aromaticity. To gain insight into the accuracy and range of applicability of a particular descriptor it is crucial to assess the advantages and drawbacks of each measure in a variety of simple well-established situations before extending its application to more complex systems. If descriptors are not properly validated incorrect conclusions may arise when they are applied to characterise potential aromatic molecules. The aim of this section is to propose a simple protocol for assessing the performance of existing and prospective aromaticity descriptors and to provide a list of recommendations that may serve as a guide for future studies involving more complex systems.

In a series of papers we analysed whether a descriptor is able to properly account for the trends of aromaticity in a variety of well-established cases. For example, it is clear that benzene is more aromatic than toluene and a good descriptor of aromaticity should capture this fact. Since the development of the first descriptors, authors focused on identifying failures of descriptors in particular cases. However, there is a need for a more robust methodology to assess the performance of an index. The use of test or training sets comprising a number of representative molecules is of common practice in other theoretical chemistry fields, such as density functional theory development, to judge the validity and range of applicability of a new method. In 2008, we proposed to extend this idea to the field of aromaticity suggesting the use of a test set as a tool to assess the performance of aromaticity descriptors.[50, 139] To this end, we proposed a series of tests with well-known trends that can be used to appraise the performance of existing and new indices of aromaticity (see Fig. 1). In this sense we are not strictly comparing indices between them but we are analysing their behaviour in a variety of cases that account for situations found along the spectra of aromatic molecules.

To set up a test of aromaticity we considered some guidelines. First, all tests must be based on well-established cases. Accumulated chemical experience provides several series of compounds with predictable trends of aromaticity. Second, controversial examples reported in the literature should be avoided e.g. whether the inner or the outer ring in anthracene is more aromatic. Third, the size of the systems should be relatively small so that the test can be readily performed. Initially, we proposed a total of fifteen tests including: five benzene distortions, one test that evaluates the substitution effects in the benzene ring, another that analyses the consequences of complexation, a couple that study ring and atom size dependence, two that check the trends of aromaticity in a series of heteroaromatic species of different sizes, one for reproducing the expected trends in a series of Clar's systems, another that studies the changes on aromaticity in a series of fulvenes, and two tests that assess the changes on aromaticity along the reaction path of two chemical reactions. Later on we added a test for performance appraisal in all-metal clusters. We propose now to exclude the test corresponding to the aromaticity trends in a series of heteroaromatic 6-MRs (Test 10 in ref. 50) due to its slightly controversial results. Therefore the final set comprises a total of fifteen tests (see Figs. 1 and 2).



	TEST	PDI	FLU	I_{ring}	MCI	I_{NG}	I_{NB}
T1	$\Delta R = r_1 - r_2$ Bond Length Alternation	✓	✓	✓	✓	✓	✓
T2	Clamping	●	✓	✓	✓	✓	✓
T3	Boatlike	●	✓	✓	✓	✓	✓
T4	Chairlike	●	✓	✓	✓	✓	✓
T5	Pyramidalization	●	✓	✓	✓	✓	✓
T6	X = H, F, CH_3, CCH, CHO, $COCH_3$, COCl, COOH, $COOCH_3$, $CONH_2$, CN, NH_2, NO, NO_2, NN^+, OH, OCH_3 Substitution	✓	✓	✓	✓	✓	✓
T7	$(\eta^6\text{-}C_6H_6)Cr(CO)_3$ Complexation	✓	✓	✓	✓	✓	✓
T8	$C_7H_7^+$ $C_8H_8^{2+}$ Ring Size Dependence	-	✓	✓	✓	✓	✓
T9	Atom Size Dependence	✗	✓	✓	✓	✓	✓
T10	X = CH, NH, O, CH_2, BH, CH^- Heteroaromatic species (5-MRs)	-	●	✓	✓	●	✓
T11	Clar's systems	✓	✓	✓	✓	✓	✓
T12	X = NH_2^+, O, NH, CH_2, BH^- Fulvenes	-	✗	●	✓	●	✓
T13	Diels-Alder cycloaddition	✓	✗	✓	✓	✓	✓
T14	Acetylene trimerization	✓	✗	✓	✓	✓	✓

Fig. 1 Summary of the first fourteen tests used to assess the performance of six electronic descriptors of aromaticity. Green tick implies that the index follows the expected trend of aromaticity, red wrong mark indicates a major failure, while orange round represents a minor failure. See ref. 50 for a more detailed discussion.

We have used these tests to assess the performance of some of the electronic-based indices described in the previous section. If a descriptor is to be used in complex systems, first it should properly reproduce simple cases as the ones gathered in this test set. We anticipate that most of the indices evaluated fail in some of these well-established cases. Once the pitfalls and range of applicability of a particular descriptor of aromaticity are validated, it can be applied to drive the discovery of new aromatic compounds. Otherwise, the inadequate use of an indicator can lead to the incorrect classification of a compound as aromatic (or antiaromatic) and the wrong assignment of its molecular properties. Evidently, these tests are not limited to electronic indices and we encourage and challenge researchers in the field to assess the performance of their indices using a test set instead of doing direct comparisons. This will provide valuable information about the limitations of the indices and help to avoid misinterpretations. For the sake of comparison, we also choose the simplest aromaticity index, HOMA, and the most popular one, NICS, to assess their performance in our test set.

Benzene distortions. Benzene is the archetypical organic aromatic molecule; it is planar and shows perfect bond length equalisation. However, when benzene is fused to another aromatic ring (e.g. to form naphthalene) the characteristic bond length equalisation is broken as is observed, for example, in C_{60}. In addition, pyramidalisation of CC bonds commonly shows in large, strained systems, illustrating the certain ring flexibility of benzene. It is well known that in-plane or out-of-plane distortions alter the natural electron delocalisation patterns of benzene leading to a situation where the electrons are more localised. Thus, by altering planarity or bond lengths with respect to benzene's reference geometry a slight decrease on the aromatic character is expected. Common in-plane deformations found in benzene-containing molecules are bond-length alternation and clamping, while boat-like, chair-like, and pyramidalisation are found among the most frequent out-of-plane deformations.[126] A satisfactory descriptor should reproduce the decrease of aromaticity when the five above-mentioned distortions are applied. We proposed to determine the quality of existing electronic aromaticity indices by means of such deformations. As Fig. 1 shows, all multicentre indices evaluated in this study perfectly reproduce the decrease of aromaticity when a distortion is applied. The correct performance of reference-based indices like *FLU* and HOMA is certainly good in these particular tests because they actually measure aromaticity as the deviation from benzene's electronic distribution and geometry, respectively. Interestingly, delocalisation between carbons in *para* position (*PDI*) is quite sensitive to the BLA distortion but not to the other four distortions (clamping, pyramidalisation, boat-like, and chair-like). We compared the trends obtained by electronic-based indices with structural (HOMA) and magnetic (a number of NICS descriptors comprising NICS(0), NICS(1), NICS(1)$_{zz}$ and NICS(0)$_{\pi zz}$), which are, in general, in line with the expected trends. Only NICS(0) seems to be non-sensitive to clamping while HOMA tends to overestimate the loss of aromaticity for in-plane-distortions. We recommend the use of multicentre indices and *FLU* for a quantitative analysis of distorted benzene-related compounds while *PDI* is only recommended for systems presenting bond length alternation. The concept of aromaticity can have a major impact in the design of benzene-based molecules like graphene, nanotubes and fullerenes. For example, Martín-Martínez et al. employed multicentre indices to characterise the properties of several graphene nanoribbons and carbon nanotubes.[140]

Substitution and complexation. Substitution and complexation to an aromatic ring are also common features found in a vast number of molecules spanning the whole chemical space. The nature of the substituent is key to explain the reactivity of an aromatic ring while complexation of an ion to aromatic rings plays major role, for example, in molecular recognition. Therefore, these situations need to be considered to assess the proper performance of aromaticity descriptors. As shown by Krygowski et al., the effects of substituents in benzene, either electron-donating or electron-accepting groups, alter the π-delocalisation inducing partial localisation of π-electrons.[141, 142] Therefore, a decrease on aromatic character with respect to benzene is expected for substituted benzenes and this trend should be reproduced by aromaticity descriptors. We selected a representative set of sixteen substituted benzenes as a test set. As shown in Fig. 1, all electronic indices are in conformity with this statement indicating a loss of aromaticity with respect to benzene. On the contrary, NICS(0) and NICS(1) assign a higher aromatic character to several substituted benzenes, although this trend is corrected by the more robust $\mathrm{NICS(1)_{zz}}$ and $\mathrm{NICS(0)_{\pi zz}}$ descriptors. Structural indices as HOMA also suffer minor deviations from the expected tendency. A similar behaviour is observed when a metal atom is complexed to benzene, as in the case of $(\eta^6\text{-}C_6H_6)Cr(CO)_3$. Surprisingly, it was found that the aromatic character of a benzene ring complexed to $CrCO_3$ was 40% higher than benzene itself according to magnetic-based descriptors. Analysing the characteristics of the complexed ring in detail, we observe several deformations including pyramidalisation, loss of planarity, ring expansion, and bond length alternation. Charge transfer between highest occupied π-orbitals of benzene and LUMO orbitals of the $CrCO_3$ moiety is the main responsible of such ring distortion. We studied this particular case in detail by means of electronic-based descriptors and NICS-scan techniques concluding that a significant loss of aromaticity is observed in contrast to the original predictions.[143] NICS(0) and NICS(1) values are strongly affected by ring currents involved in the Cr-C_6H_6 bonding, unlike the out-of-plane zz counterparts (NICS(0)$_{\pi zz}$ and NICS(1)$_{zz}$) that provide the correct trend. In general, to study the effects of substitution and metal complexation all electronic indices perform remarkably well and their use is recommended. These observations pave the ways towards the study of more complex systems involving substitution and complexation as the ones described in section 5.

Ring-size dependence. Most aromatic molecules contain 6-MRs. However, there are a number of molecules with as few as three ring members and, on the contrary, large rings such as porphyrins. Here, we explore the applicability of electronic-based indices to describe the aromatic character of rings with different size. To study ring-size dependence of aromaticity descriptors, we proposed the series C_6H_6, $C_7H_7^+$, $C_8H_8^{2+}$ where a reduction of aromatic character is expected as the size of the ring increases while the number of π-electrons remains constant. Interestingly, *FLU*, *MCI*, I_{ring}, I_{NG}, and I_{NB} are all in agreement with the expected trend. *PDI* cannot be computed for rings other than 6-MRs. In comparison to electronic indices, magnetic-based NICS(0) places incorrectly the $C_7H_7^+$ species. HOMA results are in line with the expected trend. A second relevant question is whether the values obtained for a set of rings with different size are comparable between them. I_{ring} and *MCI* are not normalised and thus may suffer ring-size dependence as some of us demonstrated before.[131] Their normalised versions, I_{NG} and I_{NB}, are specifically designed to account for systems of different sizes and expected to show the correct behaviour when increasing ring size. The substantial computational cost and the numerical accuracy problems associated with the calculation of multicentre indices for large rings, leaves *FLU* as one of the few electronic-based measures that can be applied beyond rings of ten members.

Atom size dependence. Since the very beginning, aromaticity rapidly broadened its realm to atoms other than carbon. Atoms of different type are commonly found to form rings that display typically aromatic properties. Substituting carbon for other atoms perturbs the π-delocalisation patterns of such molecules with respect to benzene. Therefore, by substituting carbon-hydrogen fragments by nitrogen atoms to form a chair-like N_6 ring one expects a reduction of the aromatic character. All multicentre indices and *FLU* account for the decrease of aromaticity when going from C_6H_6 to N_6. On the contrary, *PDI* value increases significantly from 0.103e in benzene to 0.131e in N_6, showing *PDI* is quite dependent on the atom nature. The same trend is observed for NICS(1) and NICS(1)$_{zz}$, which assign a higher aromatic character to N_6, revealing the atom-size dependence of these descriptors. Structure-based HOMA index gives the proper results. However, *FLU* and HOMA are limited by available reference values, which significantly restrict their applicability to rings containing elements other than carbon. In general, we recommend the use of multicentre indices to study rings with a variety of elements including metalloaromatic systems such as metallacycles and all-metal clusters. These indices shall aid the design and characterization of all-metal clusters with specific properties (see section 5.2).

Heteroaromatic series, Clar's systems, and fulvene series. To complete the proposed test set with other relevant situations displayed by aromatic molecules, we included a total of three more tests. First, we introduced a test to predict the proper trend of aromaticity along the following well-established heteroaromatic series C_4H_4X (X= CH^-, NH, O, CH_2, BH, CH^+). Second, we proposed a test that analyses the effect of fusing aromatic rings represented by five Clar systems. Third, we included a test to assess the expected trend of aromaticity in 5-MR and 7-MR fulvenes with different substituents. In general, all electronic-based indices passed the three tests (see Fig. 1). The only exception to properly account for the predicted order of aromaticity in a series of fulvenes is *FLU*. Magnetic (NICS(0), NICS(1), NICS(1)_{zz}, $\text{NICS(0)}_{\pi zz}$) and structural indices (HOMA) are also in line with the expected trends for all three tests. Only NICS(0) and NICS(1) incorrectly predict C_4H_4NH to be more aromatic than $C_5H_5^-$. Therefore, electronic based indices are a good choice for this kind of systems. In particular, fulvenes, termed aromatic chameleons by Ottosson and coworkers,[144] display a wide range of interesting properties. The application of electronic descriptors to describe the tuneable aromatic character of these species at their excited states will be highlighted in section 5.3.

Chemical Reactions. Reactivity is strongly linked to the concept of aromaticity. A considerable number of reactions present reactants, products or transition states (TS) with a clear aromatic or antiaromatic character. For example, aromaticity determines the regioselectivity of Diels-Alder reactions in fullerenes as discussed in section 5.1.6. In a recent review, Schleyer, Wu, Cossío, and Fernández have extensively discussed the concept of transition state-aromaticity and its role in pericyclic, pseudopericyclic, and non-pericyclic reactions.[145] In this work the authors point out the importance of properly determining the aromaticity of transition states to understand the reaction mechanism. Are electronic indices capable of recovering the aromaticity changes along the reaction path? To answer this question, we suggested the study of a

Diels-Alder cycloaddition and the acetylene trimerisation. In the case of the Diels-Alder reaction it is well-known that the reaction takes place through a boat-like aromatic transition state. Along the reaction path, we expect to observe a peak of cyclic electron delocalisation in the ring at vicinity of the TS. *PDI*, multicentre, and magnetic indices clearly reproduce this trend. On the contrary, *FLU* and HOMA break down in this test, showing a steady increase of aromaticity from reactants to products.[123] The case of the [2+2+2] trimerisation of acetylene is slightly different. An increase of aromaticity is expected when going from reactants to TS, after this point it reduces somewhat the aromatic character until a final increase is observed to form benzene as a final product. Again, this trend is perfectly reproduced by all electronic indices besides *FLU*. HOMA shows exactly the same erroneous behaviour. These findings support the idea that reference-based aromaticity indices such as HOMA and *FLU* should never be used to study changes of aromaticity along a reaction path. On the other hand, NICS indices correctly reproduce the shape of the curve but assign a more aromatic value to the TS than to benzene itself. Recently, Mandado and Ponec assessed the performance of *MCI* for a number of pericyclic reactions further proving the validity of this electronic measure for chemical reactivity.[146] In general, electronic-based multicentre indices perform better for this test set than other indices analysed either structural or magnetic.

All-metal clusters. The recent discovery of metallabenzenes,[147] heterometallabenzenes,[148, 149] metallabenzynes,[150] metallacyclopentadienes,[151] all-metal[152, 153] and semimetal clusters, etc. has prompted a revolution in the study of aromaticity.[17] At variance with the classical aromatic organic molecules that only possess π-electron delocalisation, these compounds have σ-, π-, δ- and

ϕ-electron delocalisation, which can be even combined to give double or triple aromaticity, the so-called multifold aromaticity. This latter issue makes most of the classic indicators of aromaticity not valid to discuss these complex systems,[49, 50] and for such reason more general and reliable indices of aromaticity are needed. These indices must fulfil two requirements: first, to be free from reference values (since it is difficult to choose a most aromatic reference molecule); and second, indices should be separable into σ-, π-, δ-, and ϕ-components of aromaticity. Multicentre electronic delocalisation indices and NICS are among the few indicators that fulfil these two requirements for rings of arbitrary size.[139, 154]

The new aromaticity test consists of the 4-MR series of valence isoelectronic species $[X_nY_{4-n}]^{q\pm}$ (X, Y = Al, Ga, Si, and Ge; n = 0-4), which should exhibit particular aromaticity trends.[154] Let us focus on the series from Al_4^{2-} to Ge_4^{2+}; similar trends are expected for the other series. We anticipate a steep decrease in aromaticity when going from Al_4^{2-} to Al_3Ge^- due to the reduction of symmetry and to the substitution of one Al atom by a more electronegative Ge atom. Although more arguable, we anticipate a smooth aromaticity reduction going from Al_3Ge^- to Al_2Ge_2. The same decrease should occur from Ge_4^{2+} to Al_2Ge_2; giving the following trend of aromaticity: $Al_4^{2-} > Al_3Ge^- \geq Al_2Ge_2 \leq AlGe_3^+ < Ge_4^{2+}$. From Fig. 2, it is observed how both total MCI and its π-component (MCI_π) successfully provide the expected order of aromaticity, showing a concave U shape. NICS indices were submitted to the same test but only $\mathrm{NICS}(0)_\pi^{\mathrm{RCP}}$ provided the expected trend. In these rings, with different atomic sizes, the calculation of NICS should be performed at the ring critical point (RCP), as suggested by Morao and coworkers.[155] The different analogous series analysed yield similar conclusions. Therefore, we concluded that electronic indices are also suitable to analyse aromaticity in all-metal and semimetal clusters.

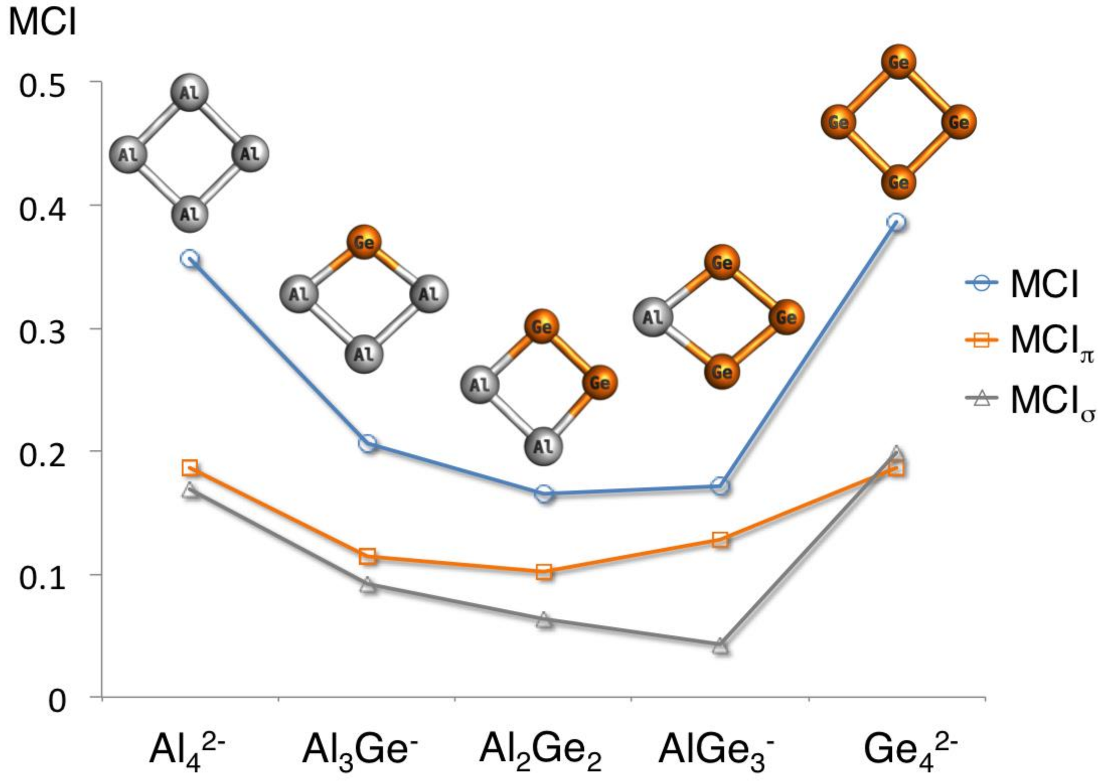


Fig. 2 Variation of multicentre indices MCI, MCI_π, and MCI_σ (in electrons) along the series Al_4^{2-}, Al_3Ge^-, Al_2Ge_2, $AlGe_3^+$, and Ge_4^{2+} (adapted from ref. 154).

As we have seen, none of the indices analysed is infallible and some of them fail in a number of simple cases, putting forward important limitations of these indicators. These results are summarised in Figs. 1 and 2. We hope that the results of this test set will provide a set of guidelines that will drive the choice of aromaticity indicators in future studies and will lead to the construction of more robust and applicable descriptors.

5. Some applications

In this section, we present some of the most relevant applications carried out by our research group using the above defined electronic-based measures of aromaticity.

5.1 Electronic measures of aromaticity in classical aromatic compounds

5.1.1 Polycyclic aromatic hydrocarbons and derivatives

In our first application, a set of planar and bowl-shaped PAHs, together with C_{60} and C_{70} fullerenes, were evaluated by means of *PDI* and *FLU* indices, showing that these indices could identify regions of local aromaticity and antiaromaticity in PAHs and fullerenes. *PDI* and *FLU* values for C_{60} and C_{70} indicated the relatively weak local aromaticity of the 6-MRs and the non-aromatic or antiaromatic character of the 5-MRs in fullerenes.[125, 127, 156]

Acenes, phenacenes, and non-planar helicenes are three different series of benzenoid compounds. Using *FLU* and *PDI*[157] we found that the most reactive inner rings are somewhat more aromatic than the outer ones in [n]acenes, whereas for [n]phenacenes the external rings are clearly the most aromatic. And for [n]helicenes, despite the departure from planarity, we observed almost the same aromaticity trends as in [n]phenacenes.[158]

5.1.2 Substituent effects on aromaticity. The analysis of the substituent effects on benzene proved the high resistance of aromatic systems to disrupt the π-electron structure in electrophilic aromatic substitution reactions. In particular, changes of *PDI* when going from benzene to substituted benzene derivatives are small and correlated with Hammett substituent constants.[142] The same behaviour was observed for the complexation of a lithium cation to a series of PAHs.[159] Substituent effects were also studied in 4-substituted-1,2-

benzoquinones. Results show that only the keto group in *meta* position is affected by the electron-donating/attracting power of the substituent, whereas the *para*-related C=O is not. Although *MCI* and *FLU* display small changes, these indices agree on assigning a more aromatic character to rings with electron-donating substituents.[160] On the other hand, the substituents do have a large effect on the aromaticity of pyrazoles and imidazoles with N-substituents.[161] We found that the imidazole ring is more stable than the pyrazole one. The reason for the relative energy difference was attributed to the weakness of the NN bond in the latter, and not to a higher aromaticity of the former, as both rings present similar *MCI* and *FLU* values.[162] By comparison to the corresponding substituted series of benzene, this latter appears not only to be more aromatic, but also more robust towards substitution effects as denoted by the slope of the $FLU^{1/2}$ vs. σ_R correlation (see Fig. 3). A recent work showed that 1-indenones and their aza derivatives are more stable than 2-indenones because their 6-MR is more aromatic.[163] Interestingly, tetrafluorination of the 6-MR in such compounds hardly causes any change in the local aromaticity of this ring, thus confirming that the aromaticity of benzene rings is quite robust.

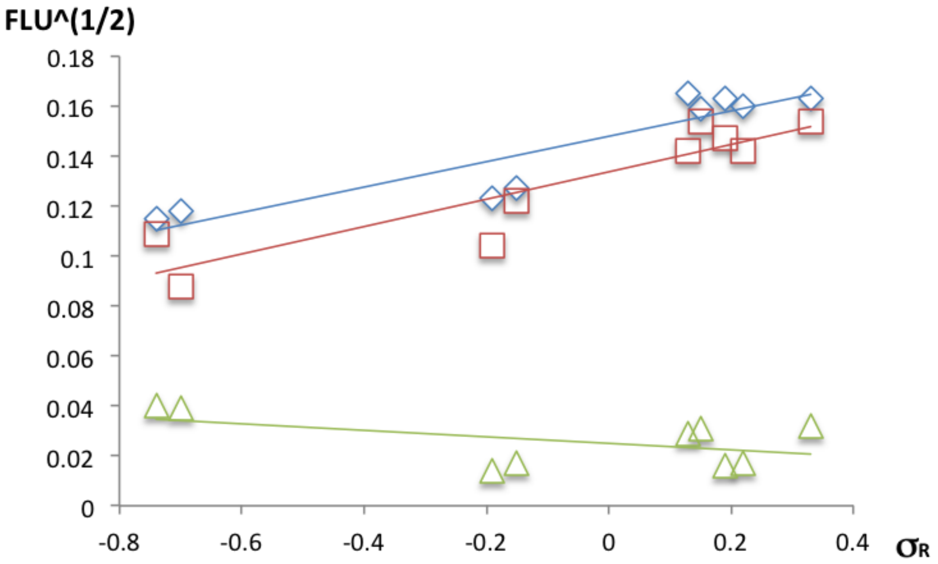
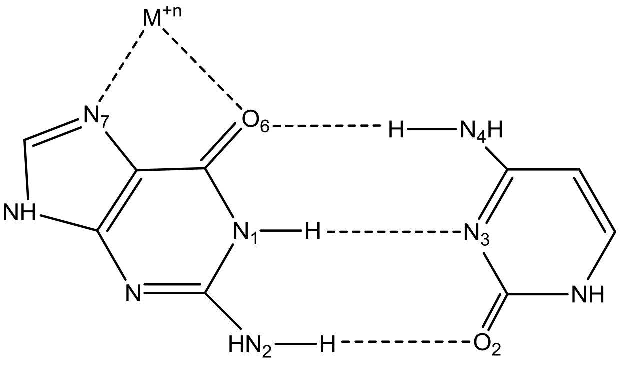


Fig. 3 Correlation between *FLU*$^{1/2}$ and Hammett substituent constant σ_R. Blue diamonds, imidazole (Im); red squares, pyrazole (Pz); and green triangles, benzene (Bz) (adapted with permission from ref. 161).

5.1.3 Discrepancy with magnetic measure of aromaticity. Pyracylene was the first case in which we showed that the calculation of NICS at the ring centre should be analysed with caution, as NICS(0) wrongly assigned an increase of the local aromaticity of 6-MRs upon distortion from planar to pyramidalised pyracylene.[164] In contrast, NICS(1) calculated 1 Å above pyracylene reported the expected decrease of aromaticity upon bending. Both *PDI* and ring currents contradicted NICS, giving the expected reduction of aromaticity with bending. Another conflicting case of NICS' performance is [2,2]paracyclophane, in which the NICS predicted decrease of local aromaticity of the stacked rings was not real, but caused by the coupling of the magnetic fields generated by these two rings.[165] The same problem was experienced when the local aromaticity of a series of polyfluorene compounds with increasing number of π-stacked layers was analysed.[166] NICS shows a spurious increase of aromaticity that is due to the coupling between the magnetic fields generated by the π-stacked rings, whereas

PDI, *FLU*, and HOMA showed that aromaticity does not change due to π-stacking. Finally, NICS also fails when attributing an aromatic character to the $(HF)_3$ ring.[167]

5.1.4 Aromaticity in DNA bases. First, we analysed how the aromaticity of the rings of the guanine-cytosine base pair was affected when a metal cation is coordinated to the N_7 position of guanine (see Scheme 1, M = Ca^{2+}, Cu^+, and Cu^{2+}). Such interaction causes a change in the strength of the hydrogen bonds (N_1-$H\cdots N_3$ and N_2-$H\cdots O_2$ become stronger, whereas $O_6\cdots H$-N_4 weakens).[168] In turn, these alterations affect the aromaticity of the 5- and 6-MRs of the nucleobases. The observed increase of the aromaticity of the guanine and cytosine 6-MRs due to the interaction with Cu^+ and Ca^{2+} was attributed to the strengthening of hydrogen bonding in the guanine-cytosine pair that stabilises the resonance structure with a π-sextet in the 6-MRs. On the other hand, the reduction of aromaticity in the 5- and 6-MRs rings of guanine due to interaction with Cu^{2+} is caused by the oxidation process, which removes a π electron disrupting the π-electron distribution. In a subsequent work, we studied the change of aromaticity in a series of size-expanded benzobases (xDNA). The insertion/addition of a benzene ring in the natural DNA bases reduces the local aromaticity of both 5- and 6-MRs of DNA bases according to *PDI* and *FLU* values. The degree of aromaticity of the added 6-MR of xDNA bases varies in the order xA > xG ~ xC > xT. Interestingly, an inverse correlation between the HOMO-LUMO gap of the size-expanded benzobases and the aromaticity of the inserted/added benzene ring was observed.[169]



Scheme 1 The guanine-cytosine base pair interacting with the metal cation (M = Ca^{2+}, Cu^{+}, and Cu^{2+}). Labels of the atoms involved in the H-bond interactions are shown.

5.1.5 Hückel's rule and beyond. Hückel's rule is essential for the comprehension of aromaticity in organic molecules. The fact that it is only valid for conjugated monocyclic systems prompted the appearance of new rules that could describe local aromaticity in PAHs. Clar's rule[170] is probably the most successful extension of the Hückel rule to PAHs.[171] According to Clar's rule, the Kekulé resonance structure with the largest number of disjoint aromatic π-sextets is most important to characterise PAHs. π-sextets are defined as six π-electrons localised in a single benzene-like ring separated from adjacent rings by formal CC single bonds. Clar's rule was validated by *PDI* values calculated in the rings of a set of PAHs.[172] For instance, phenanthrene has two π-sextets located in the outer rings, which are the most aromatic rings in the molecule according to *PDI*. The referred Hückel rule was also checked from π-electronic delocalisation measures. In particular, we studied a series of systems in which two electrons were either added or removed. In an *N*-electron aromatic system, addition of two electrons leads to an antiaromatic *N*+2 species in which we expect these extra two electrons to be essentially localised. Similarly, the extraction of two electrons to give an antiaromatic *N*-2 species should also reduce the delocalisation in the system. Our results show that there is an important increase of electronic delocalisation (of about 1 e) when going from antiaromatic $4n\pi$ systems to aromatic $(4n+2)\pi$ systems. The change in π-electronic delocalisation when we move from a $(4n+2)\pi$-aromatic to a $4(n+1)\pi$-antiaromatic species by adding a pair of electrons is much smaller (see Fig. 4). *FLU*, *PDI*, and *MCI* criteria, as well as the cross terms of the total π-electron delocalisation, correctly assign an aromatic or antiaromatic character to each system, regardless the number of electrons. Therefore, these indices provide aromaticity values in agreement with Hückel's rule.[173, 174]

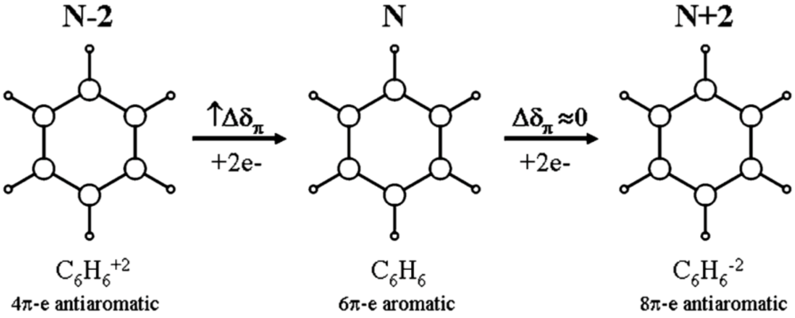


Fig. 4 Change in π-electronic delocalisation from aromatic to antiaromatic systems with the successive addition of 2 electrons (adapted from ref. 174).

$4n$ Baird's rule represented the extension of the renowned $4n+2$ Hückel rule to open-shell species,[15] while Hirsch's $2(n+1)^2$ rule[29] of aromaticity has been considered the analogue of the $4n+2$ rule for spherical systems. Our group recently extended this latter rule to open-shell spherical molecules, providing evidence that spherical species having a same-spin half-filled last energy level and the rest of the levels being fully filled ($2n^2+2n+1$ electrons and $S = n+½$) are aromatic.[30] For instance, neutral C_{60} appears to be non-aromatic according to *MCI* and $\mathrm{NICS}(1)_{zz}$; whereas singlet C_{60}^{10+} that obeys the $2(n+1)^2$ rule, is found to be aromatic. On the other hand, C_{60}^{19+} with S=9/2 and C_{60}^{1-} with S=11/2 following the $2n^2+2n+1$ rule, appear to be even more aromatic than C_{60}^{10+}. This new rule may become a powerful tool to study the stability of high-spin spherical molecules. In section 5.3 we comment on the aromaticity of excited states in connection with the Baird rule.

5.1.6 Aromaticity determines the regioselectivity of Diels-Alder reactions in fullerenes. The reactivity and regioselectivity of Diels-Alder (DA) reaction involving empty fullerenes is generally favoured for [6,6] bonds, whereas in endohedral metallofullerenes [5,6] bonds are commonly more reactive.[175, 176] When a metal cluster is encapsulated inside a fullerene there is a charge transfer from the metal cluster to the fullerene. In the case of M_3N units (M = Sc, Y, Gd…) formally six electrons are transferred to the carbon cage. We decided to analyse the effect of adding electrons to the fullerene cage by calculating the reaction profile for the DA reaction of cyclopentadiene (Cp) to the [6,6] and [5,6] bonds of C_{60}^{n-} ($n = 0 - 6$) species.[176] The C_{60}^{n-} ($n > 0$) was taken as a model for the cage of endohedral metallofullerenes. It was found that the reaction becomes more exothermic (and the barrier is reduced) for the [5,6] attack when n increases from 0 to 6 electrons (see Fig. 5). On the other hand, for the [6,6] addition the exothermicity is somewhat reduced (and the barrier increases) when n increases. For $n = 4–5$, there is a change in the regioselectivity of the process and the [5,6] becomes the preferred attack.

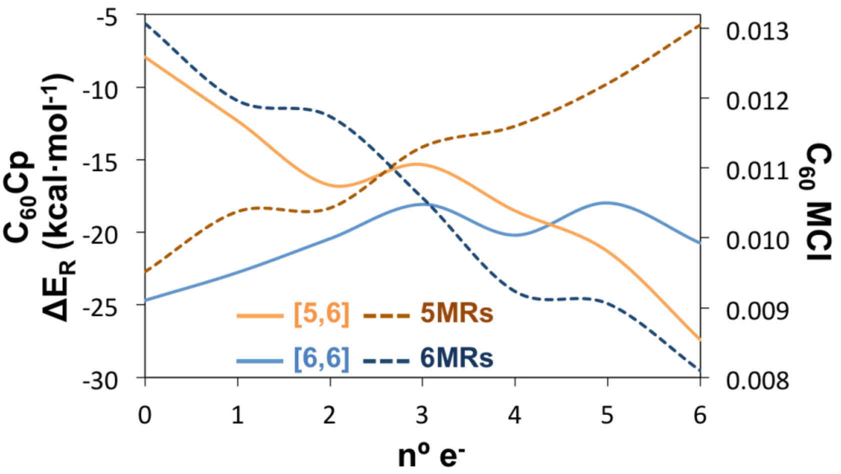


Fig. 5. Change in the reaction energy of the DA between Cp and C_{60}^{n-} and in the aromaticity (dashed lines) of five- and six-membered rings of C_{60}^{n-} as function of number of electrons added (n). Reproduced from ref. 176 with permission from the Royal Society of Chemistry.

To understand the change of regioselectivity in C_{60} upon reduction, we calculated the *MCI* for the 5- and 6-MRs of C_{60}^{n-} showing that the aromaticity of the 5- and 6-MRs increase and decrease, respectively, with the successive addition of electrons to the C_{60} molecule (see Fig. 5). Because the DA addition leads to a change from planar sp^2 to tetrahedral sp^3 for the C atoms of the attacked bond, when the addition occurs on a [6,6]-bond type, the π-conjugation of two 5-MRs and two 6-MRs is lost. On the other hand, when the addition is on a corannulenic [5,6]-bond, the conjugation vanishes in three 6-MRs and one 5-MR. For neutral C_{60}, the preferred attack is the [6,6] addition because the aromaticity of only two of the most aromatic 6-MRs is lost (the [5,6] attack affects the aromaticity of three 6-MRs). On the other hand, for C_{60}^{6-} the most favourable addition is at the [5,6] bond because the aromaticity of only one of the most aromatic 5-MRs is lost. In this case, the changes in aromaticity between a 6-MR and a 5-MR upon reduction determine the regioselectivity of the DA additions to fullerenes.[176]

5.1.7 Aromaticity in Metalloporphyrins. Assessing the aromatic character of rings beyond ten members corresponds to one of the current challenges of electronic descriptors of aromaticity. Porphyrins and its derivatives are macrocycles with highly delocalised π-electrons that play a key role in a number of biological processes and catalysis. Some of the molecular properties exhibited by porphyrins can be rationalised in terms of their aromatic character. To this end, structural and magnetic descriptors have been used to estimate the role of aromaticity in a variety of porphyrin-related systems. However, the large size and peculiarities of these molecules prevent the application of some well-known measures. Observations based on structural indices and ring currents reveal that the inner porphyrin ring is significantly more aromatic than the outer ring.

Porphyrins are often coordinated to a metal atom, which plays a major role in determining shape, reactivity, and molecular properties. The effects of metal coordination and spin state on the electronic delocalisation patterns of metalloporphyrins were unknown. For this reason, we decided to explore the chemical bonding and aromaticity patterns in a series of metalloporphyrins that include first row transition metals (Sc-Zn), alkaline earth metals (Mg, Ca), and second-row transition metals (Ru, Pd, Ag, Cd) in a variety of spin states.[177] The quantification of aromaticity in metalloporphyrins is challenging because the metal placed in the ring centre makes the calculation of some well-known descriptors such as NICS quite troublesome. Therefore, magnetic indices were discarded for this study. The use of electronic indices in porphyrins is scarce because of the computational cost and the accuracy problem associated with multicentre indices. As we mentioned above, *FLU* is one of the few electronic indices that can be applied to measure aromaticity in large rings. Considering that *FLU* performs remarkably well for heteroaromatic 5-MR (see section 4) it was our descriptor of choice to study aromaticity patterns in a number of metalloporphyrins. In comparison to the metal free porphyrin, *FLU* values indicated that the aromatic character of the inner ring (16π-electrons) is hardly affected by the metal complexation whereas the electron delocalisation of the outer ring (20π-electrons) is significantly enhanced by the presence of the metal (see Fig. 6). This was notably clear in the case of ^{5}Ru where the value of *FLU* is roughly equal for inner and outer rings. Therefore, *FLU* is an attractive alternative to structural and magnetic indices for the analysis of aromaticity in porphyrins and metalloporphyrins. Otero et al. made also use of an approximation of *MCI* employing Aihara's circuit resonance energy to study the role of aromaticity on the thermodynamic stability of hydroporphyrins.[178] Their study provides a good starting point for the application of multicentre indices towards larger systems. Recently, the synthesis and characterization of expanded porphyrins with Hückel and Möbius topologies showing aromatic and antiaromatic character has gained a lot attraction.[179] Identifying methods to properly characterise the aromaticity of these peculiar systems may help on the design of expanded porphyrins.

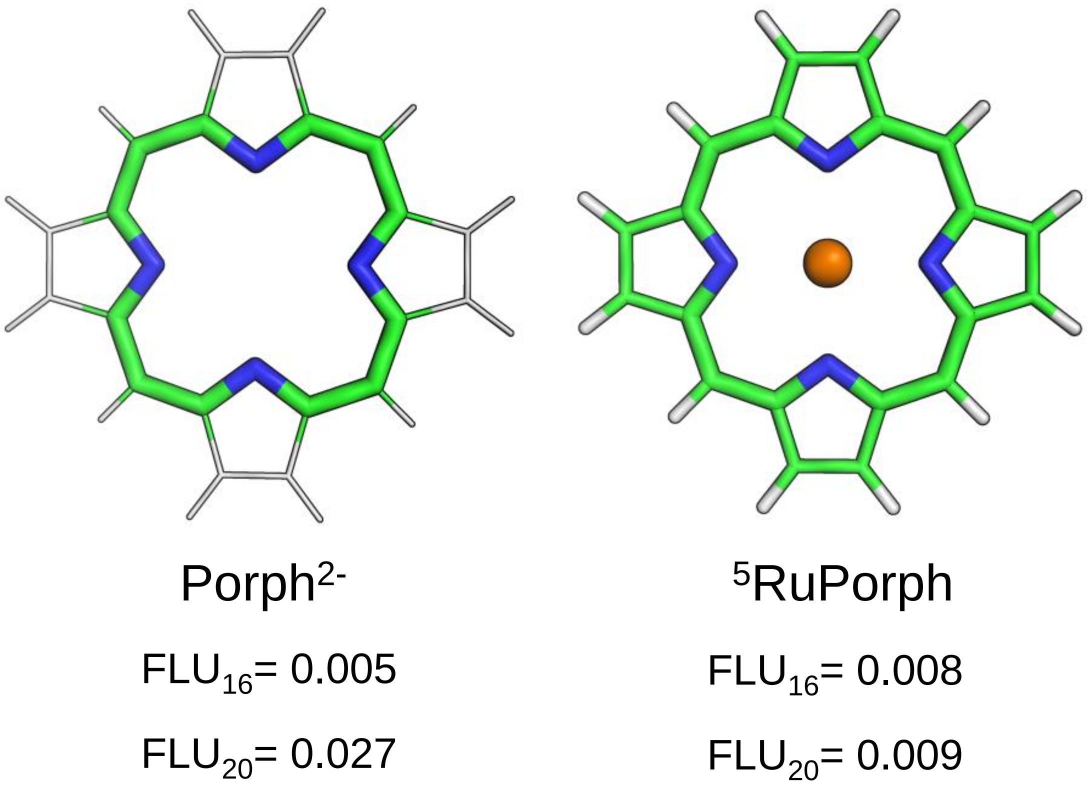


Fig. 6 *FLU* values obtained for the inner (16-MR) and outer (20-MR) rings of the free-based and ^{5}Ru porphyrins. Electron delocalisation patterns are highlighted in green for both systems.

5.2 Metalloaromaticity

One of the most important findings in metalloaromaticity was the discovery of the Al_4^{2-} cluster by Boldyrev, Wang, and coworkers.[19] This cluster was the first example of all-metal species with σ- and π-aromaticity. It is well known that π-electrons in benzene are distortive and it is the σ-skeleton the responsible for the D_{6h} symmetry of benzene. We wondered whether the σ- and π-electrons in Al_4^{2-} favoured the D_{4h} or the D_{2h} structure. To solve this question, we performed an energy decomposition analysis (EDA, see Fig. 7) showing that the π-electrons in Al_4^{2-} prefer the D_{2h} structure but the σ-electrons force the double bond to delocalise, leading to the regular D_{4h} geometry.[153] This analogue behaviour to benzene was explained through the corresponding MO diagram (see Fig. 8), where it is observed how both the π and the radial-σ (σ_R) orbitals induce distortion, whereas the tangential occupied orbitals (σ_T) are the ones responsible for the D_{4h} structure. This different character of σ_R and σ_T orbitals is also supported by *MCI* indices that show a more important contribution to the total σ-aromaticity from the radial than from the tangential orbitals.

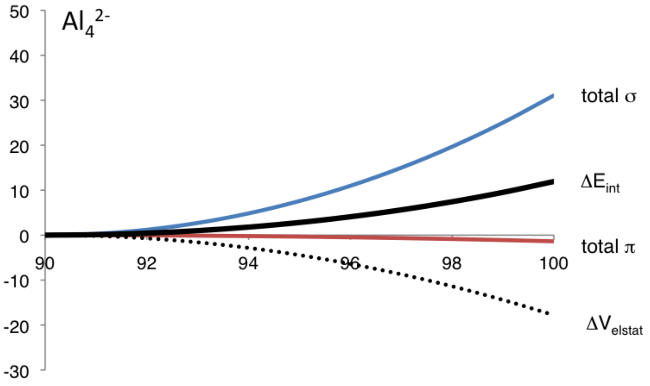


Fig. 7 Bond-energy decomposition (in kcal/mol) of Al_4^{2-} along the D_{4h} to D_{2h} distortion (in deg.) from delocalised to localised structure (adapted from ref. 153).

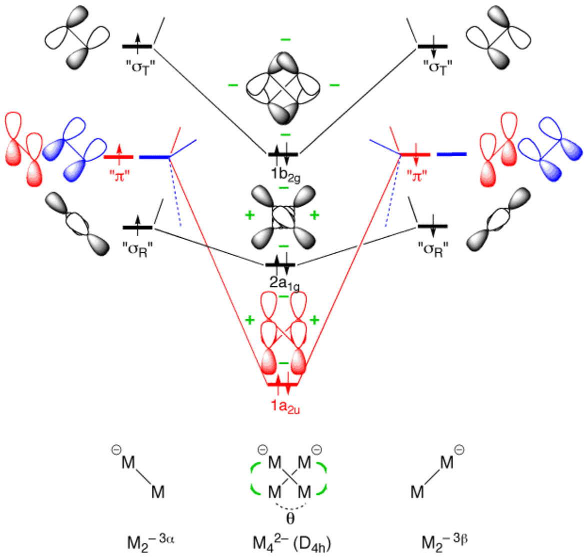


Fig. 8 Schematic molecular orbital interaction diagram of Al_4^{2-} constructed from two $[M_2^-]^{\cdots}$ fragments at BP86/TZ2P level (adapted from ref. 153). The positive and negative signs in green indicate whether there is a gain or loss of interaction when going from D_{4h} to D_{2h} structure.

The geometrical conformers of $M_2N_2^{2-}$ (M and N = B, Al, and Ga) clusters that are valence isoelectronic with Al_4^{2-} were studied with a gradient embedded genetic algorithm.[180] For $Al_2B_2^{2-}$ and $Ga_2B_2^{2-}$, the C_{2v} structures with a short B–B bond are more stable than the D_{2h} alternate structure. On the other hand, this latter symmetry is the most stable for $Ga_2Al_2^{2-}$. Clusters with B atoms prefer the C_{2v} structure (with X-X, Y-Y, and two X-Y bonds) to form strong B–B bonds. In the $Ga_2Al_2^{2-}$ species this is not possible and the two structures are almost thermoneutral with the D_{2h} (with four X-Y bonds) being somewhat more stable. Finally, for all cyclic $M_2N_2^{2-}$ isomers we found large MCI_{σ} and MCI_{π} values, similar to those obtained for Al_4^{2-}.

$NaMg_3^-$ and Na_2Mg_3 clusters containing the *cyclo*-$[Mg_3]^{2-}$ unit are two of the very few electronic species with π-bonding without the occurrence of a σ-framework.[181, 182] Interestingly, the aromaticity switches from σ to π when the Mg_3^{2-} unit coordinates Na atoms to give $NaMg_3^-$ and Na_2Mg_3 clusters. The distance between the coordinated Na atom and Mg_3 can be used to tune the aromaticity and prompt an unprecedented switch from σ- to π-aromaticity.

The aromaticity of all-metal clusters with transition metal complexes involving d and f orbitals implies more complicated analyses due to the large number of electrons involved and the inclusion of relativistic effects. The occurrence of highly delocalised valence electrons occupying the large angular momentum orbitals in transition metals, gives rise to multifold aromaticity. To study this phenomenon, we analysed the aromaticity of the series Cu_3^+, Y_3^-, La_3^-, $Ta_3O_3^-$, Hf_3, $^5Ta_3^-$, and $^3Hf_3$ with the *MCI* index.[183] Cu_3^+ was confirmed to present exclusive σ-aromatic character; whereas Y_3^- and La_3^- present σ- and π-aromaticity, supported by MCI_{σ} and MCI_{π} values. On the other hand, $Ta_3O_3^-$ is the first cluster presenting both π- and δ-aromaticity, as confirmed by the small value of MCI_{σ}, and the twice as large MCI_{π} and MCI_{δ} values. The aromaticity patterns of Hf_3 were even more complex, showing prominent σ-, but also significant π- and δ-orbital contributions (the so-called threefold aromaticity). According to *MCI*, the open-shell molecules $^5Ta_3^-$ and $^3Hf_3$ show σ+π+δ and σ+π aromatic character, respectively.

In a recent work[184] we analysed the metalloaromaticity of the 5-MR of the $M(XC_3H_3)(PH_3)_2$ species (M = OsH_3, $OsCl_3$, $OsCl_2$, $RuCl_2$, $RhCl_2$, and $IrCl_2$ and X = NH, O, S, CH^-, and CH^+). Our results showed that the heterometallacycle 5-MR has a low aromatic character (*MCI* values of about 0.01 e) except for X = CH^+ compounds in which this 5-MR is antiaromatic as denoted by negative *MCI* values. Finally, it is worth mentioning that Möbius metalloaromaticity was found in the $Cu(OC_3H_3NH)_2$ and related complexes and confirmed through I_{NB} values.[149]

From these analyses, it becomes clear that the characterization of metalloaromaticity is much more complex than in classic organic compounds and that multicentre electronic indices are well suited for analysing aromaticity in metalloaromatic species. In general, one should make a judicious choice of the indicators used to evaluate aromaticity. Aromatic indices should not be limited to classify existing molecular systems. The main purpose of aromaticity indices is actually to improve our understanding in order to design new compounds with compelling properties.[24]

5.3 Aromaticity of excited states

In a recent review, Ottosson and co-workers underlined the importance of applying the concept of aromaticity to rationalise excited state properties and reactions.[144] Aromaticity and antiaromaticity effects observed in the excited states may play a similar role in understanding reactivity and molecular properties as in the ground state. To gain insight into the nature of these effects we need to know which ground-state descriptors of aromaticity are transferable to excited states. One of the main difficulties that one encounters is that few descriptors of aromaticity can be easily employed to assess the aromatic character of excited states. Karadakov made the first calculations at the CASSCF level of magnetic aromaticity using NICS and other measures to describe the aromatic character of low-lying singlet and triplet excited states of benzene and related compounds. The results obtained were shown to be in line with Baird's rule. Among electronic-based descriptors only ELF_π has played a major role in studying the aromatic character of lowest-lying triplet states in fulvenes but no attempts have been done to quantify the electronic delocalisation in electronic states of higher energy.[144] To bridge this gap, we proposed to generalise the use of electronic indices, *PDI*, *FLU*, I_{ring}, and *MCI* to study the aromaticity of a set of simple molecules in a number of excited states.[185] To this end, by means of DFT and CASSCF calculations, we studied the aromaticity patterns of the low-lying singlet, triplet, quintet, and septet excited states of benzene, cyclobutadiene, and D_{4h} cyclooctatetraene. The results of electronic indices based on DFT calculations are in agreement with the generalization of Baird's rule proposed by Soncini and Fowler to account for high-order multiplicities such as quintet and septet states.[186] That is, compounds with $(4n+2)\pi$-electrons that are aromatic in their lowest-lying singlet state should also be aromatic in their lowest-lying quintet state and antiaromatic in their lowest-lying triplet and septet states. On the contrary, molecules with 4*n*π-electrons are antiaromatic in their lowest-lying singlet and triplet states and aromatic in their triplet and septet states. These trends are perfectly followed by the I_{ring} and *MCI* values summarised in Table 2, while *FLU* shows some discrepancies. However, CASSCF-based calculations do not assign an aromatic character to the lowest-lying quintet state of benzene and the lowest-lying septet state of cyclooctatetraene. On the other hand, our calculations clearly showed the aromatic character of the vertical S_2 and T_1 states of cyclobutadiene and cyclooctatetraene in agreement with Baird's rule. This new methodology paves the way towards the possibility of studying the role of aromaticity in reactions occurring in the excited state.

	State	*FLU*	I_{ring}	*MCI*
C_6H_6	S_0	0.000	0.0478	0.0721
D_{6h}	T_1	0.025	0.0028	-0.0015
	Q_1	0.029	0.0011	0.0451
C_4H_4	S_0	0.104	0.0054	0.0101
D_{2h}	T_1	0.012	0.0385	0.1271
C_8H_8	S_0	0.051	0.0244	-0.0005
D_{4h}	T_1	0.001	0.0071	0.0271
	Q_1	0.029	0.0001	0.0013
	Septet_1	0.033	0.0000	0.0178

Table 2 Values of *FLU*, I_{ring}, and *MCI* for low-lying singlet, triplet, quintet, and septet states of C_6H_6, C_4H_4, and C_8H_8 at the B3LYP/6-311++G(d,p) level of theory. All units are in a.u. Reproduced from ref. 185 with permission of the Royal Society of Chemistry.

6. Conclusions

Over the last decades there has been a remarkable expansion in the number of different types of aromatic systems and in our understanding of aromaticity. The field of aromaticity is in constant evolution and the variety of molecules that present properties related to aromaticity is growing exponentially. It is our opinion that the field of aromaticity has been enriched (and not cheapened as pointed out by Hoffmann[187] recently) by all these fascinating new aromatic compounds. One of the main difficulties faced by researchers interested in aromaticity characterization is the lack of a physical basis for this property, which makes its quantification difficult. Despite the great progress in the field over the last years, the range of applicability of many descriptors is still limited to simple organic compounds. In this review, we have shown that indices based on electron delocalisation measures are all-round indicators of aromaticity that outperform most of the classical structural- and magnetic-based indices. Despite the success of these indicators, there is still room for improvement. Although the definition of the I_{NB} and I_{NG} indicators represented a big step forward in the correct direction, more efforts need to be carried out in order to extent the applicability of these indices. The major difficulty is describing aromaticity in large rings or in tridimensional circuits. Developers of electronic based indices should also work to enhance the scope of applicability towards larger and more complex systems. For example, systems like expanded porphyrins are still out of the scope of multicentre descriptors. Future challenges include the generalization of some of these tools to study the aromaticity of such intricate molecules and the possibility of obtaining both local and global measures in porphyrins, borane clusters, fullerenes or nanotubes.

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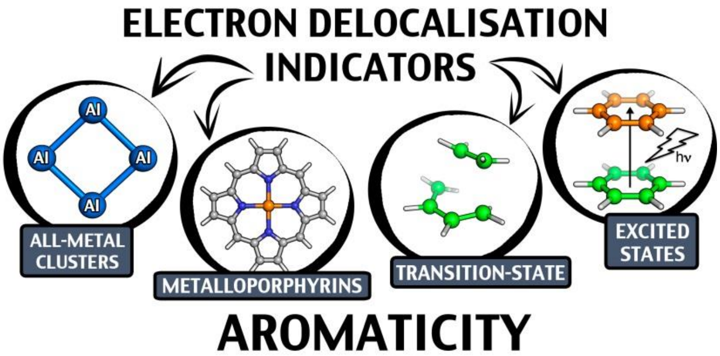
TABLE OF CONTENTS GRAPHIC



Aromaticity descriptors based on the quantification of electron delocalization are all-round indicators that outperform most of the classical structural- and magnetic-based indices.