The role of aromaticity in the molecular structure and reactivity of (endohedral metallo)fullerenes

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REVIEW

The role of aromaticity in the molecular structure and reactivity of (endohedral metallo)fullerenes

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The encapsulation of metal clusters in endohedral metallofullerenes (EMFs) takes place in cages that in most cases are far from being the most stable isomer in the corresponding hollow fullerenes. There exist several possible explanations for the choice of the hosting cages in EMFs, although the final reasons are actually not totally well understood. Moreover, the reactivity and regioselectivity of (endohedral metallo)fullerenes has in the past decade been shown to be generally dependent on a number of factors, such as the size of the fullerene cage, the type of cluster that is being encapsulated, and the number of electrons that are transferred formally from the cluster to the fullerene cage. Different rationalizations of the observed trends had been proposed, based on bond lengths, pyramidalization angles, shape and energies of (un)occupied orbitals, deformation energies of the cages, or separation distances between the pentagon rings. Recently, in our group we proposed that the quest for the maximum aromaticity (maximum aromaticity criterion) determines the most suitable hosting carbon cage for a given metallic cluster (i.e. EMF stabilization), including those cases where the IPR rule is not fulfilled. Moreover, we suggested that local aromaticity plays a determining role in the reactivity of EMFs, which can be used as a criterion for understanding and predicting the regioselectivity of different reactions such as Diels-Alder cycloadditions or Bingel-Hirsch reactions. This review highlights different aspects of the aromaticity of fullerenes and EMFs, starting from how this can be measured and ending by how it can be used to rationalize and predict their molecular structure and reactivity.

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REVIEW

1. Historical Background

The possibility of having spherical carbon-based molecules was already hypothesized twenty years before the buckminsterfullerene (C_{60}) discovery in 1985.[1-5] The C_{60} discovery was made by Kroto, Curl, and Smalley when they tried to simulate the conditions of cool red giant stars in the laboratory and a 720 mass peak (i.e. C_{60}) appeared to be extremely strong (see Fig. 1).[2] Based on preliminary experimental evidence a soccer-ball-like structure was proposed, which was named buckminsterfullerene as homage to the geodesic dome architect, Buckminster Fuller. The structure was later confirmed using single-crystal X-ray diffraction (XRD).[6] In 1996, Kroto, Curl, and Smalley were awarded the Nobel Prize in Chemistry for the striking discovery of C_{60}. Since then, many fullerene structures have been synthesized and a variety of studies regarding the fullerene stability, characterization, properties such as aromaticity, and reactivity have been reported.[7-16] Many fullerene-based materials have been synthesized and characterized with applications in biology, medicine, electronics, and photovoltaics.[17]

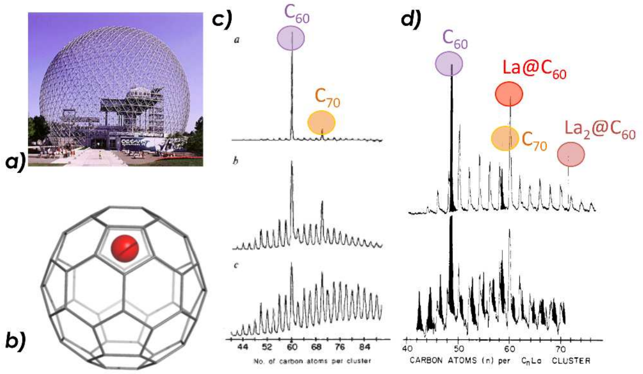


Figure 1. **Representation of: a) geodesic dome by the architect Buckminster Fuller, b) $La@C_{60}$ structure, c) first mass spectra of carbon clusters prepared by laser vaporization of graphite detecting for the first time C_{60} and C_{70},[2] d) mass spectrum of the first endohedral metallofullerenes synthesized ($La@C_{60}$).[18] Adapted from refs. 2 and 18.**

The bond structure of fullerenes corresponds to a polyhedron where atoms are situated in vertices, bonds in edges, and rings in faces. In general, all fullerene structures present 12 pentagonal rings and $2n/2 - 10$ hexagonal rings (where $2n$ is the number of atoms). In fact, the presence of pentagonal rings on their structure is the reason why fullerenes can present a closed polyhedral shape. For a given number of carbon atoms (C_{2n}), a large amount of different isomers can be obtained. In 1987, Kroto proposed the so-called Isolated Pentagon Rule (IPR), which states that the most stable fullerene structures are those that present the 12 pentagons isolated from each other.[19] When two pentagonal rings are fused, an eight-cycle around the periphery of these two rings is formed (i.e. pentalene), which has a severe steric tension associated in addition to the destabilizing effect over the π electronic structure (4N Hückel rule for antiaromatic species). The IPR rule substantially reduces the number of possible isomers for a given fullerene structure. For the C_{60} case, I_h-C_{60}:1 corresponds to the only isomer that obeys the IPR rule out of a total of 1812 possibilities, but as the cage size increases the number of isomers does also increase. For example, there are 31,924 different possible isomers for C_{80}, and only 7 of them fulfil the IPR rule.

The possibility of incarcerating atoms or small molecules inside the inner cavity of these new carbon-based molecules was considered right after their discovery. Indeed, the same year of the discovery the first stable metallofullerene, $La@C_{60}$, was detected (see Fig. 1).[18] In 1991, the formation in macroscopic quantities of lanthanum-based metallofullerenes ($La@C_{2n}$, 2n = 70, 74, 82) was achieved.[20] These new compounds were denoted as endohedral fullerenes (EFs) and in the most common case of having metal atoms or clusters in the inner cavity they were called endohedral metallofullerenes (EMFs).[21-25] The first EMF characterized by X-ray diffraction was obtained in 1995 by Shinohara and co-workers.[26] Since then, many other EMFs have been synthesized, which can be classified in five different classes: the so-called classical (such as $La@C_{2n}$, 2n= 70, 74, 82),[20] metallic carbides (for instance, $M_2C_2@C_{82}$, M= Sc, Y, and $Sc_2C_2@C_{84}$),[27, 28] metallic tri-nitride template (TNT, being $Sc_3N@I_h$-C_{80} the archetypal compound),[23, 29] metallic oxides (examples include $Sc_4(\mu_3\text{-}O)_2@I_h$-$C_{80}$, $Sc_4(\mu_3\text{-}O)_3@I_h$-$C_{80}$),[30, 31] and metallic sulfides ($M_2S@C_{3v}(8)$-C_{82}, M= Sc, Y, Dy, and Lu) (see Fig. 2).[32] For a complete and detailed explanation of the EMFs types, see references 33-35. However, most of EMFs formed macroscopically contain rare-earth metals and nearby elements.[36] In 1999, Balch, Dorn and co-workers synthesized and characterized the first member of the TNT family, $Sc_3N@I_h$-C_{80}.[23, 29] In fact, $Sc_3N@I_h$-C_{80} corresponds to the third most abundant fullerene structure after C_{60} and C_{70}.[29] Indeed, the most widely used and studied EMFs are the TNT as they can be produced in macroscopic quantities using the Krätschmer-Huffman arc method.[29] The latter procedure corresponds to the most effective method for EMF production, but as the yield is generally low, the compounds need to be extracted and purified with chromatography techniques.[37]

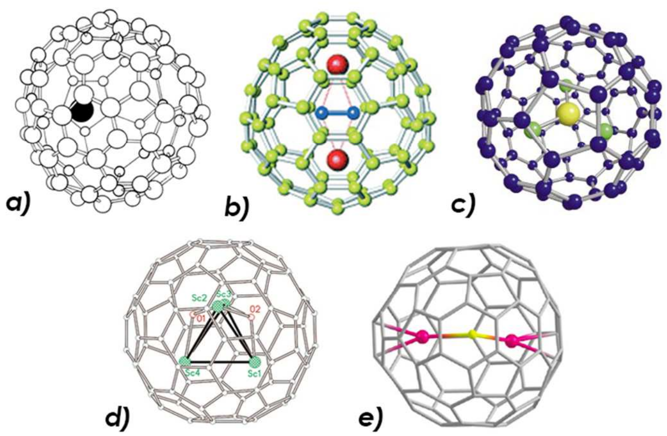


Figure 2. Classification of the EMFs: a) classical (La@C_{82}), [20] b) metallic carbide ($Sc_2C_2@C_{84}$),[28] c) TNT ($Sc_3N@C_{80}$),[29] d) metallic oxide ($Sc_4(\mu_3\text{-}O)_2@I_h\text{-}C_{80}$),[30] e) metallic sulfide ($Sc_2S@C_{3v}(8)\text{-}C_{82}$).[32] Reprinted with permission from refs. 20, 28, 29, 30, 32.

The C□C bond alternation observed in neutral fullerenes is a proof of the non-homogeneous π delocalization. The possibility of fullerenes being superaromatic molecules was considered since their discovery.[2, 38] However, the already mentioned C-C bond alternation, the impossibility of fullerenes to undergo substitution reactions,[39] and the high pyramidalization of their carbon atoms due to strain, indicated that pristine fullerenes show only a modest degree of aromaticity. While the role of aromaticity in pristine fullerenes is minor, our group has demonstrated that in EMFs it is fundamental.[40-42] The main objective of this review is to provide a comprehensive description of the role played by aromaticity in the EMFs stabilization and in their functionalization. Several studies regarding the aromatic character of neutral and charged fullerene structures have been published and are reviewed in sections 2 and 3.2, respectively. Afterwards, we highlight some recent studies performed in our group where it is shown that the local aromaticity of the EMF structures is key to rationalize (a) the preference of a given cage for the EMFs stabilization (section 3.3), and (b) the most favourable addition sites found experimentally, making the *in silico* prediction of the most reactive sites possible (section 3.4). We expect to provide with this review an important impulse for further studies in the EMF aromaticity and reactivity fields.

2. Aromaticity in hollow fullerenes

The use of the word *aromatic* to refer to a group of molecules with certain particular properties appears for the first time in an article by August Wilhelm Hofmann in 1855.[43] For many years, this concept was used to classify derivatives of benzene. Since then the boundaries of aromaticity have been extended to new areas of chemistry and to a large list of highly diverse species.[44-46] In spite of the many studies devoted to this subject, the concept of aromaticity has remained elusive. The reason for that is the non-observable nature of aromaticity that precludes a unambiguous quantitative definition[47] (for this reason it is sometimes called the chemical equivalence of *beauty*). As a consequence, numerous indirect measures have been proposed based on the different manifestations and ramifications of aromaticity.[48, 49] This leads to a countless number of classical structural,[50] magnetic,[51, 52] energetic,[53] electronic,[54-57] and reactivity[58-60]-based measures of aromaticity. Because all current available descriptors of aromaticity represent approximations to the problem of measuring this phenomenon, it is widely accepted that the concept of aromaticity should be analysed by employing several of these indicators.[61-63]

Fullerenes, like nanotubes and graphene, are molecules composed entirely of carbon atoms (with the exception of some heterofullerenes and endohedral (metallo)fullerenes). Therefore, most of the current available methods to quantify aromaticity designed to measure the aromaticity of classical aromatic organic molecules can be applied to fullerenes, nanotubes, and graphene nanoribbons without further refinements.[7] From an experimental point of view, the aromaticity of fullerenes has been assessed using magnetic measures by determining the chemical shifts of encapsulated atoms and molecules such as ^3He,[64-68] ^{129}Xe,[69, 70] and $^1H_2$,[71, 72] by obtaining ^1H NMR resonances of addends attached to the fullerene cage,[73] or by measuring magnetic susceptibilities.[74-76] The number of indicators employed to quantify aromaticity in fullerenes using theoretical methods is much wider. Magnetic-based descriptors of aromaticity such as the nucleus-independent chemical shifts (NICS) and its variants like NICS(1) or $NICS_{zz}$,[77, 78] ^3He and ^{129}Xe chemical shifts,[79-82] ring currents,[83-86] and magnetic susceptibilities[74, 76, 87-90] have been employed to assess the local and global aromaticity of fullerenes. For this purpose, the harmonic model oscillator of aromaticity (HOMA), which is a structural-based descriptor, has been also calculated.[40, 41, 81, 91-93] Indices such as the aromatic stabilization energies (ASE),[81] homodesmotic stabilization energies (HSE),[94] and topological resonance energies (TRE)[95, 96] based on energetic grounds have been also used for evaluating the global aromaticity of fullerenes. Finally, indicators based on electronic delocalization properties like multicentre index (MCI),[42, 97] the para-delocalization index (PDI)[92, 93, 98, 99] and the aromatic fluctuation index (FLU)[99] have been also computed to quantify the local aromaticity in fullerenes. A description of these indices can be found in issue 10 of volume 105 of the Chemical Reviews journal. For the indices discussed in the present review, the aromaticity of the ring or species is larger when: the higher the value of the HOMA, ASE, HSE, TRE, PDI, and MCI indexes is, and the lower (or more negative) the NICS, chemical shifts, and FLU values are.

2.1. Aromaticity in pristine fullerene cages

In the original paper that reported the discovery of C_{60} by Kroto, Curl, Smalley, and co-workers,[2] the authors already hypothesize about the possible aromatic character of this molecule.[2] One year later, Klein and co-workers[38] proposed a superaromatic character of buckminsterfullerene based on the large number (K = 12500) of Kekulé resonance structures that can be depicted for this species. Two years later, Aihara and Hosoya concluded based on TRE values that the aromatic stabilization of C_{60} was not enough to guarantee isolation in macroscopic quantities.[95] Fortunately, in 1991 Krätschmer and co-workers[100] experimentally proved that this prediction was wrong. From the very beginning the aromatic character of C_{60} was controversial. It is now accepted that fullerenes have ambiguous aromatic character,[7, 101, 102] with some properties that are typical of aromatic compounds and others that are not. For instance, magnetic and NMR properties indicate that cyclic delocalization of π-electrons takes place in fullerenes as expected for aromatic molecules.[83, 103, 104] This fact, together with their rather considerable stability, seems to stress their aromatic character.[102] However, evidence from chemical reactivity is against the aromaticity of these systems since fullerenes are very reactive molecules that easily undergo a large variety of chemical transformations.[39, 105-110] The endothermic enthalpy of formation of fullerenes does not support the aromatic character, either.[111]

2.1.1 Global Aromaticity

The global aromatic character of C_{60} has been computationally assessed through the calculation of ASE, HSE, and TRE energy-based descriptors, the use of the structural-based index HOMA, and by determining the magnetic susceptibility and the NICS and ^{3}He and ^{129}Xe chemical shifts values in the centre of the fullerene cage. Cyrański and co-workers[81] obtained an ASE per π electron of about 0.6 kJ·mol^{-1} for C_{60}, which can be compared with the ASE per π electron of 20.1 kJ·mol^{-1} for benzene.[112] From these values it is clear that the aromaticity of C_{60} is much less than that of classical organic aromatic compounds. Similarly, the HSE values of □11 for C_{60} and □8 kJ·mol^{-1} for C_{70} suggest that these molecules are not aromatic and are better classified as antiaromatic.[94] On the other hand, a TRE of 1.79 indicates a slight aromatic character for C_{60}.[95, 96] This aromaticity increases for larger fullerenes according to TRE values.[113, 114] The HOMA of C_{60} is 0.263 consistent with the consideration of a compound with low aromaticity.[81] Interestingly, the geometric HOMA index increases somewhat with the size of the fullerene (for C_{96} it is 0.371).[81] As to the magnetic susceptibility (χ), although results obtained by different authors were somewhat inconsistent,[74, 115-117] there was consensus about the fact that the magnetic susceptibility of C_{60} is much less than that of benzene or graphite due to partial cancellation of diamagnetic and paramagnetic contributions to χ.[75] Another index of global aromaticity is the NICS value of a hollow fullerene calculated in the centre of the cage.[118, 119] It is usually agreed upon that NICS computed in the cage centre of C_{60} (-11.2 ppm) is small enough to consider this molecule as a weak aromatic molecule.[120,118] However, the $NICS_\pi$[121] value of +21.2 ppm calculated at the centre of C_{60} by taking into account only the radial set of MOs with π character led Chen and co-workers[120] to classify C_{60} as a spherically π-antiaromatic molecule. In Ng@C_{2n} fullerenes, the chemical shift of the Ng (δ(Ng), usually Ng = ^{3}He or ^{129}Xe) nucleus measured relative to free Ng acts as a probe for the ring currents and magnetic properties of the fullerene cage.[79] According to δ(^{3}He) values, C_{60} (□6.3 ppm) is one of the less aromatic fullerenes and C_{70} (□28.8 ppm) one of the fullerenes with the higher aromaticity.[64, 66, 81, 82, 122] On the other hand, the δ(^{3}He) values of C_{76}, C_{78}, and C_{84} fell in the region between those of C_{60} and C_{70}, and, therefore, δ(^{3}He) is not a function of the ratio of the 6- and 5-membered rings (MRs).[66] Finally, a study of the electron delocalization in C_{60} showed that the global electronic charge delocalized per carbon atom is similar to that of benzene or naphthalene.[98]

2.1.2 Spherical Aromaticity: The $2(N+1)^2$ and $2N^2+2N+1$ ($S=N+1/2$) rules in fullerenes

Hückel's rule[123-126] of aromaticity indicates that a cyclic conjugated planar molecule of D_{nh} symmetry with n = 4N + 2 π-electrons is aromatic and antiaromatic when it possesses 4N π-electrons. In these 4N + 2 species, aromaticity is achieved when a closed-shell electronic structure is fulfilled. This situation provides extra energetic stability, similar to the situation found in noble gas elements. The Baird rule represents an extension of the Hückel rule for open-shell systems. Thus, according to Baird's rule[46, 127, 128] the lowest-lying triplet state in the 4N π-annulenes with D_{nh} symmetry (with n = 4N) is aromatic and that of a system with 4N + 2 π-electrons is antiaromatic. The extra stability of the 4N π-electron Baird species is given by the half-filled degenerate highest-occupied with same spin electrons MOs.

In 2000, Hirsch and co-workers found a rule for predicting the aromaticity of spherical systems, known as the $2(N+1)^2$ rule.[129] Hirsch considered that the π-electron system of a roughly spherical fullerene can be approximated by a spherical electron gas surrounding the surface of a sphere. The wave functions of this electron gas are characterized by the angular momentum quantum number l (l = 0, 1, 2, 3…) similar to the situation found for the atomic orbitals, each energy level being 2l+1 times degenerated. Consequently, all π-shells are totally filled when we have $2(N+1)^2$ electrons. Therefore, spherical species with $2(N+1)^2$ π-electrons are aromatic in an analogous way to 4N+2 π-annulenes. According to Hirsch's rule, icosahedral C_{20}^{+2}, C_{60}^{10+} or C_{80}^{8+} are aromatic fullerenes. This prediction has been confirmed by using NICS and MCI indicators of aromaticity.[97, 119, 122, 129] TRE values also give the same trend as NICS in this case, but in general TRE results do not support the validity of the Hirsch rule.[96] Recently, Schleyer, Hirsch, and co-workers[120] concluded that the $2(N+1)^2$ rule breaks down when the energies of subshells with different angular quantum numbers intercalated. This happens for relatively large values of N, and, for instance, they found that contrary to the prediction of the $2(N+1)^2$ rule, C_{60}^{-12} is not magnetically aromatic.

With the same philosophy that Baird used to extend the Hückel rule to open-shell systems, some of us have proposed extending the Hirsch rule to spherical open-shell systems.[97] Thus, spherical compounds with a half-filled last energy level, i.e. those with $2N^2 + 2N + 1$ electrons and spin N + ½, should be aromatic.[97] Computational studies based on the analysis of MCI indices, the bond length alternation, and NICS calculations support this hypothesis and show that, for example, systems such as the C_{60}^{19+} (S = 9/2) and C_{60}^{1-} (S = 11/2) are aromatic. It is worth noting that neither the S = 9/2 electronic state for C_{60}^{19+} nor the S = 11/2 for C_{60}^{1-} are the ground state for these species. Moreover, these systems have not been experimentally detected. In addition, as for the $2(N+1)^2$ rule, it is expected that the $2N^2 + 2N + 1$ (S = N + ½) rule will be disobeyed for large values of N. Still, it is possible that this new rule of aromaticity may be a useful tool for researchers working on the development of molecular magnets (stable molecules with high spin).

2.1.3 Local Aromaticity

The local aromatic character of fullerenes is quantified by looking at the aromaticity of their 6- and 5-MRs. The HOMA values for the gas-phase electron diffraction structure of C_{60} and C_{70} agreed with weak aromatic 6-MRs and nonaromatic or antiaromatic 5-MRs.[91] This result is in line with strong paramagnetic currents associated with the 5-MRs and the relatively weak diamagnetic currents of the 6-MRs found in neutral, empty, and nonfunctionalized fullerenes.[83-85, 103] Partial cancellation of these diamagnetic and paramagnetic currents results in vanishingly small magnetic susceptibilities.[75, 76] 6-MRs have negative NICS values usually (but not always) smaller than that of benzene, while 5-MRs have positive or close to zero NICS measures, indicating a non-aromatic character.[7, 93, 118, 122, 130] The electronic delocalization index PDI values for C_{60} and C_{70} again indicate the relatively weak local aromatic character of the 6-MRs.[93] The FLU index values for C_{60} concurred with previous results.[99] Finally, multicentre MCI index also agreed with the 6-MRs of C_{60} being more aromatic than the 5-MRs.[97] Interestingly, Van Lier and co-workers noted that the local aromatic character of a given 6-MR in fullerenes and nanotubes increases the farther away the 5-MRs are from this 6-MR.[130]

2.2 Aromaticity in heterofullerenes and functionalized fullerenes

Possible changes of carbon made hollow fullerenes can be introduced by substitution of C atoms of the cage by other atoms such are N, B, P, Si among others (i.e. heterofullerenes, see Fig. 3) or by exohedral functionalization.

The $C_{59}NH$ compound is a good example of a stable heterofullerene.[131, 132] Its aromaticity was evaluated by computing the NICS value at the centre of the cage. It was found that $C_{59}NH$ presents a lower aromaticity than C_{60}.[7] Nevertheless, BN doped fullerenes such $C_{58}(BN)$ or $C_{54}(BN)_3$ are slightly more aromatic than C_{60} as indicated by the computed NICS at the cage centre (see Fig. 3).[133] Interestingly, NICS values indicated that for $C_{60-n}N_n$ (n = 0 to 12) aromaticity increases for larger values of n until n = 7 and then it decreases.[134] In some cases, the relative stability of heterofullerene isomers was discussed in terms of aromaticity. Thus, Chen and co-workers showed that for the two S_6 symmetrical heterofullerene $C_{48}X_{12}$ (X = N, P, B, Si) isomers, the one having aromatic triphenylene units is the most stable due to its larger local and global aromaticity.[135] The extended aromaticity of this isomer for X = N was already predicted by Manaa and coworkers in 2002.[136]

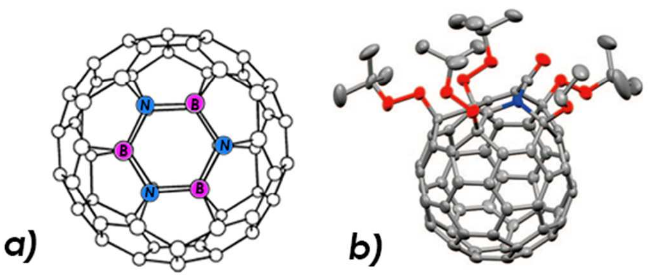


Figure 3. Examples of heterofullerene structures: a) $C_{54}(BN)_3$,[133] b) $C_{59}N$ azafullerene derivative.[137] Reprinted with permission from refs. 133, 137.

Regarding functionalization, the most usual reactions involving fullerenes are organic additions.[138] ^{3}He chemical shifts for a number of C_{60} adducts are known[7] and, in general, as compared to He@C_{60}, $\delta(^3He)$ indicates an increase in the global aromaticity. Similarly, considering a H_2 addition on C_{60}, i.e. when going from C_{60} to $C_{60}H_2$, NICS values computed in the centre of the cage also predict a slight increase of the global aromaticity.[118] This result is attributed to the removal of paramagnetic currents in the 5-MRs that share the C atoms where the [6,6] addition took place.[139] NICS for $C_{60}H_2$, $C_{70}H_2$, and $C_{76}H_2$ showed, first, that the four rings of the pyracylene unit containing the C atoms involved in the C–H bonding became non-aromatic, second, the NICS changes occurred mostly in the neighbourhood of the addition site and third, in most cases the addition occurred on the [6,6] bond joining the 6-MRs with the lowest aromaticity.[89, 90] The results obtained for the analogous $C_{60}HR$ (R = OH, OCH_3, NH_2, $NHCH_3$, $N(CH_3)_2$, CH_3, CH=CH_2, Ph, and C≡CH) substituted hydrofullerene species were in the same line.[88] For the $C_{60}(CHR)$ carbene counterparts, it was found that, for the same R substituent, the carbene is somewhat more aromatic than the hydrofullerene.[88] In $C_{60}F_{18}$,[140] half of the fullerene cage is flattened and one of the 6-MRs is completely aromatic as revealed by its NICS(0), PDI, HOMA and average pyramidalization values.[93] This result already pointed out the significance of aromaticity in the functionalization of fullerenes. The importance of local aromaticity to explain the site-specific polyaddition in exoderivatized IPR and non-IPR fullerenes was confirmed by several studies.[141-144]

In some cases, addition to a certain C–C bond of a fullerene led to the breaking of the attacked C–C bond and the formation of adducts called fulleroids with an open bond on the surface of the cage, that are more stable than their closed bond counterparts (see Fig. 4a).[145] They are considered π-homoaromatic species[146] and in these adducts the 60 π-electron systems remain more or less intact, because all carbon atoms keep their sp^2 hybridization (see Fig. 4b). Confirmation of this homo-conjugation comes from the similarity of the endohedral chemical shifts and UV spectra to that of the parent fullerenes,[147-149] significant π-overlap values in Hückel MO theory[145] and from NICS(0) and PDI values.[93]

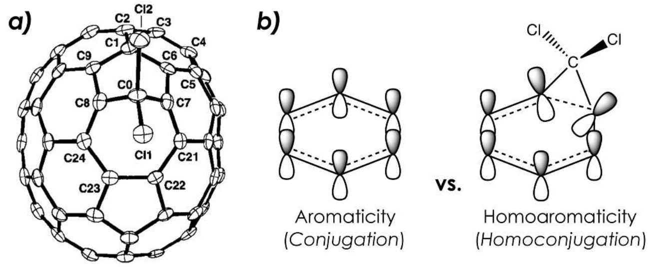


Figure 4. a) X-ray of the $C_{71}Cl_2$ fulleroid structure,[145] (reprinted with permission from ref. 145) b) schematic representation of aromaticity vs homoaromaticity.

3. Aromaticity in endohedral metallofullerenes

The presence of a metal atom or metal cluster inside a fullerene cage has large consequences and effects on their electronic structure, stability, and reactivity. In this section, we will introduce all these effects, and focusing on the aromaticity and its role on EMF stabilization and reactivity.

3.1. Molecular and electronic structure of EMFs

For a given C_{2n} fullerene, there may exist several hundreds of different possible isomers, although usually just one or a few ones are experimentally formed.[150] In these cases, the most stable neutral empty fullerenes strictly obey the IPR rule, since the strain produced by two fused pentagons strongly destabilize the isomers with adjacent pentagon pairs (APPs).[151] Surprisingly, the encapsulation of metal cluster in fullerene cages takes place in isomers that are far from being the ones most stable in the corresponding hollow fullerenes. During the last decades, a growing interest towards the understanding of the structure and reactivity of EMFs from both experiment and computation has raised because of their potential use in biology, medicine, and material science.

It is widely accepted that the electronic charge distribution in $X_3N@C_{2n}$ EMFs may be formally described as $(X_3N)^{6+}@C_{2n}^{6-}$ using an ionic model (see Fig. 5a).[152] It should be noted that depending on the nature of the encapsulated cluster, the formal charge transferred to the fullerene cage may be lower, for example, $(M_2C_2)^{4+}@C_{2n}^{4-}$.[153] The number of electrons formally transferred from the metallic cluster to the cage ranges from 2e (for instance, when having only one Sm atom) to 6e (the case of Sc_3N). However, the real charge transferred from the TNT unit to the fullerene is always lower as covalent interactions between the cluster and the cage are rather strong.[154, 155] Within this simple ionic model, Poblet and co-workers proposed that those empty fullerene cage isomers presenting a large (LUMO+3)-(LUMO+4) gap could be good candidates to form TNT-based EMFs, because they can better stabilize these newly transferred 6 electrons in the first 3 LUMO orbitals.[34, 152, 156] This molecular orbital rule provides a useful guideline to identify the best hosting cages, however it does not provide a physical explanation for the experimental preference of a fullerene cage for a given metal cluster. Popov and Dunsch[157] observed that the relative stabilities of different $M_3N^{6+}@C_{2n}^{6-}$ (2n= 68–98) isomers always correlate well with those of the corresponding empty charged cages (C_{2n}^{6-}), showing that C_{2n}^{6-} systems can be used as a good models to describe the corresponding EMF stabilities (see Fig. 5b). It is worth noting here that in these charged species, the negative charge is not evenly distributed.[158-160] Pentagonal rings tend to better stabilize the negative charge, as *anionic* cyclopentadiene and pentalene units are aromatic unlike their neutral forms.

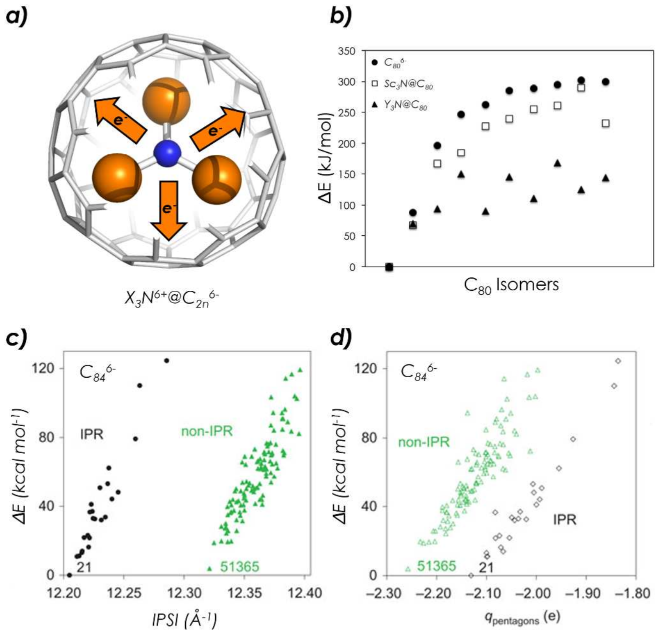
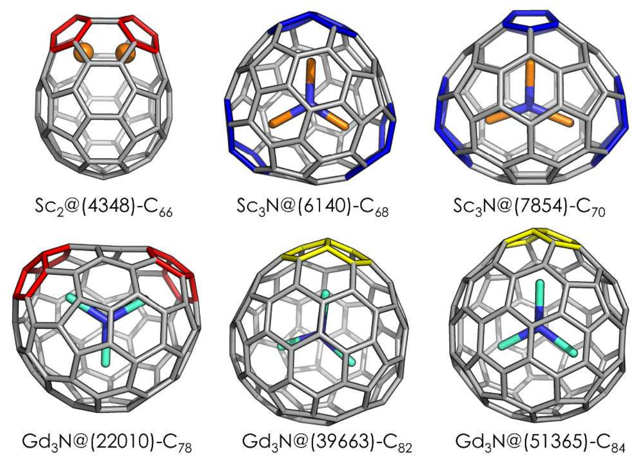


Figure 5. Representation of: a) Ionic model structure in EMF, b) relative stability of C_{80}^{6-} charged isomers and their corresponding Scandium and Yttrium-based EMF (drawn from data in ref. 157), c) relative stability of C_{84}^{6-} IPR (black) and non-IPR with 1-APP (green) with respect to the IPSI index,[158] (adapted from ref. 158) d) relative stability of C_{84}^{6-} IPR (black) and non-IPR with 1-APP (green) with respect to the charge localized on the pentagonal rings (adapted from ref. 158).

The IPR rule can satisfactorily predict the most favourable empty and neutral fullerene cages. However, many EMFs present non-IPR isomeric cages (i.e. they have adjacent pentagon pairs (APPs)). Several IPR violations in EMFs have been reported in the literature. For example, the fist non-IPR EMFs reported practically at the same time were the Sc_2@(4348)-C_{66}[161] and Sc_3N@(6140)-C_{68},[162] both presenting APP units on their structures (see Fig. 6). Since then, many other non-IPR EMFs have been synthetized, for example Sc_3N@(7854)-C_{70},[163] Gd_3N@C_2(22010)-C_{78},[164] Gd_3N@(39663)-C_{82},[165] or Gd_3N@(51365)-C_{84}[166, 167] EMFs. In 2008 Alcamí and co-workers demonstrated that those non-IPR isomers presenting a uniform and well-separated negatively charged APPs and positively charged pyrene motifs were more stable than the IPR ones.[159] Few years later, Poblet and co-workers defined the *Maximum Pentagon Separation* rule, showing that the relative stability of one EMF isomer could be related to the separation among its 12 pentagons. In that sense, they proposed the so-called *Inverse Pentagon Separation Index* (IPSI) to measure the pentagon-pentagon separation for a given carbon cage (see Fig. 5c).[158] They demonstrated that for charged IPR and non-IPR isomers presenting the same number of APPs, the most stable ones are those with the largest separation between the 12 pentagonal rings present in the structure. In addition, they also showed that the most stable negatively charged IPR and non-IPR isomers presenting the same number of APPs are those where the negative charge localized on the pentagon rings is maximized (see Fig. 5d). Nevertheless, the reason why in some EMFs a non-IPR isomer is overwhelmingly preferred over an IPR one was not clear, as comparisons could only be made for those isomers presenting the same number of APPs. Although a general explanation for the IPR rule violation was lacking, in the literature some examples have been rationalized, for example, in terms of metal-pentalene unit interactions.[163]


Sc_2@(4348)-C_{66} Sc_3N@(6140)-C_{68} Sc_3N@(7854)-C_{70}

Gd_3N@(22010)-C_{78} Gd_3N@(39663)-C_{82} Gd_3N@(51365)-C_{84}

Figure 6. Representation of synthesized non-IPR EMFs. Adjacent Pentagon Pairs (APPs) have been highlighted: 1-APP in yellow, 2-APP red, and 3-APP blue.

A complete section in this review is devoted to demonstrate the role played by aromaticity in the stabilization of a given isomeric cage for EMF formation (see section 3.3).[41]

3.2. First aromaticity studies on EMF and related systems

As shown in section 2, there are many studies related to the aromaticity of hollow fullerenes. Aromaticity studies involving EMFs are however scarcer. One key difference between the empty fullerenes and the EMFs is that in the latter there is a formal charge transfer from the metal cluster to the fullerene structure. As a result, fullerene cages experience important changes in their aromaticity,[7, 42, 120] which radically modify their relative stability.[41] Because of this charge transfer, negatively charged fullerenes can be used as a simplified model to study the structure and reactivity of EMFs.[157] As explained in previous section 3.1, the negative charge in EMFs or in negatively charged fullerenes is mainly located in the 5-MRs, increasing their aromatic character because they adopt a more cyclopentadienyl-like electronic structure. Thus, when going from C_{60} to C_{60}^{2-} the ring currents of all 6-MRs turned into paramagnetic and those of the 5-MRs became diamagnetic as confirmed by the calculated B3LYP/6-31G* NICS(0) values of the 5- and 6-MRs.[72] Although the charge transfer may decrease the aromaticity of 6-MRs, the total aromatic character of the negatively charged fullerene cages tends to increase. Indeed, C_{60} is considered spherically π-antiaromatic or at least non-aromatic, whereas its hexaanion form, C_{60}^{6-}, is π-aromatic.[120] $\delta(^3He)$ in $^3He@C_{60}^{6-}$ (and also that of $^3He@C_{70}^{6-}$) is strongly shifted to higher field[68, 168] and NICS/NICS$_\pi$ in the centre of the cage is decreased from □2.8/21.2 to □50.0/□24.4 ppm when C_{60} is reduced to C_{60}^{6-}.[120] Interestingly, while BN-doped C_{60} ($C_{60-2x}(BN)_x$; x = 1, 3, and 6) fullerenes are slightly more aromatic than C_{60}, the corresponding hexaanions are significantly less aromatic than C_{60}^{6-} according to NICS values calculated at the centre of the cage.[133] For C_{70}^{6-}, results are somewhat controversial. $\delta(^3He)$ chemical shifts in $^3He@C_{70}$ and $^3He@C_{70}^{6-}$ indicate an increase of the aromaticity after reduction, although less than in C_{60}.[68] Moreover, ^1H NMR resonances of the neutral and reduced open [5,6]methanofullerene $C_{71}H_2$ also indicated an increase in the aromaticity of C_{70} after reduction,[73] as confirmed by ^1H NMR calculations.[169] However, NICS in the centre of the 5- and 6-MRs of C_{70}^{6-} showed that the diamagnetism of the 5-MRs at the poles of the cage are larger than that of the 5-MRs at the equator, and also than that of the 6-MRs,[160] and as a whole there is a slight overall decrease of the C_{70} diamagnetism after reduction.[160] The same conclusion is reached from the calculation of NICS at the center of the C_{70} and C_{70}^{6-} cages.[118] Finally, it is important to note that, in 2006, Slanina and coworkers attributed the higher stability of the (10611)-C_{72}^{6-} non-IPR isomer as compared to its IPR isomers to the net charge that is mainly located in the polar region and formally changes the 8π antiaromatic pentalenes in 10π aromatic pentalene dianions.[170]

To our knowledge, the first evidence of the increase in aromaticity due to the explicit encapsulation of metal clusters in fullerenes was given by Hagelberg and co-workers in 2005.[171] These authors calculated the NICS(0) value of the six inequivalent rings of C_{68} and $Sc_3N@C_{68}$ and of the seven different rings in C_{78} and $Sc_3N@C_{78}$. Results show that free cages have unclear low (anti)aromaticity with small NICS(0) values for C_{68} and a mixture of positive and negative NICS(0) for C_{78}. On the contrary, $Sc_3N@C_{68}$ and $ScN_3@C_{78}$ present negative and large (in absolute value) NICS(0) values for all rings pointing out an unambiguous aromatic character.

From these results, it becomes clear that the low aromatic character of empty fullerenes significantly increases when a metal cluster is encapsulated inside. As we will see in the next sections this aromaticity change has important implications in the structure and reactivity of EMFs.

3.3 Role of Aromaticity in EMF stability

It is well established that the relative higher stability of the IPR isomers of the hollow neutral fullerenes with respect to the non-IPR isomers is due to the strain produced by two fused pentagons. But the main questions that arises is: (i) why are often the non-IPR isomers of the EMFs more stable than the IPR ones?, (ii) what is the main driving force that determines the most suitable hosting carbon cage for a given metallic cluster? The first attempts to answer these two questions centred the focus on the distribution of the charges in the fullerene cage.[157-159]

Taking into consideration that: (1) the most stable negatively charged IPR and non-IPR isomers with the same number of APPs are those which have the largest negative charge on the pentagonal rings;[158] and (2) charged fullerenes are in general more aromatic than their neutral counterparts;[42] the role played by aromaticity in the stability of charged fullerenes was investigated.[41] To that end, the Additive Local Aromaticity (ALA) index was defined as the sum of the local aromaticities of all rings in the fullerene isomer:

$$ALA = \sum_{i=1}^{n} A_i \qquad (9)$$

where A_i is the local aromaticity of ring i and n is the total number of rings in the fullerene including 5- and 6-MRs. Due to the extremely large amount of isomeric structures to compute (ca. 10.300 isomers), the authors used the computationally cheap HOMA index[172] to calculate the aromaticity of each ring, and the semi-empirical Austin model 1 (AM1)[173] method to optimize the geometries of the carbon cages.

In neutral hollow fullerenes, aromaticity was found to play no role in the final stability of the fullerene isomers. This is not unexpected because neutral fullerenes have an ambiguous (non)aromatic character. This result is nicely illustrated by Fig. 7a, which shows the relative stabilities of neutral C_{72} isomers in relation to the ALA index. Whereas the figure shows no correlation between the relative stability of the isomers and the ALA index, the decrease of the stability of the different isomer types when the number of APP increases is clear. In other words, for the neutral fullerenes the IPR rule is thus perfectly fulfilled.[19, 151]

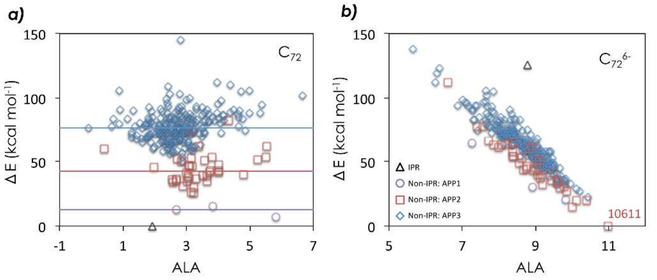


Figure 7. Relative stability (ΔE, in kcal·mol^{-1}) of IPR (represented in black triangles) and non-IPR with one pair of adjacent pentagons (APP1 in purple circles), two pairs (APP2 in red squares), and three pairs (APP3 in blue diamonds) isomers of a) C_{72} and b) C_{72}^{6-} with respect to Additive Local Aromaticity index. Isomers experimentally observed in endohedral metallofullerenes are indicated with a number. The lines represented in a) indicate the relative average energies with respect to the IPR case for each isomeric type.[41] Adapted from ref. 41 .

A representative example for EMFs is given by Fig. 7b, which shows the correlation between the relative energies and the ALA index obtained for the IPR, and non-IPR APP1, APP2, and APP3 isomers of C_{72}^{6-}. The (10611)-C_{72}^{6-} isomer with 2 APPs was found to be the most aromatic among all IPR and non-IPR isomers with one, two or three APPs (out of 269 isomers in total), and moreover, it is clearly the most stable hexaanion. Shinohara and co-workers determined that this particular isomer is also the selected cage to host the La_2 moiety in $La_2@C_{72}$ (i.e. $La_2^{6+}@C_{72}^{6-}$, see Fig. 8b).[174] Therefore, there exists a perfect agreement between the prediction based on theoretical aromaticity calculations and the experimental observations. The main driving force that determines the most stable isomeric cage is the aromaticity. Thus, it was defined the Maximum ARomaticity Criterion (MARC): the most stable anionic fullerene isomer is the one whose total aromaticity is maximized. The ALA index is the unique known criterion that allows the direct comparison of all isomers for a given fullerene C_{2n}, independently of the isomer type (IPR, non-IPR) or the number of APPs.[41]

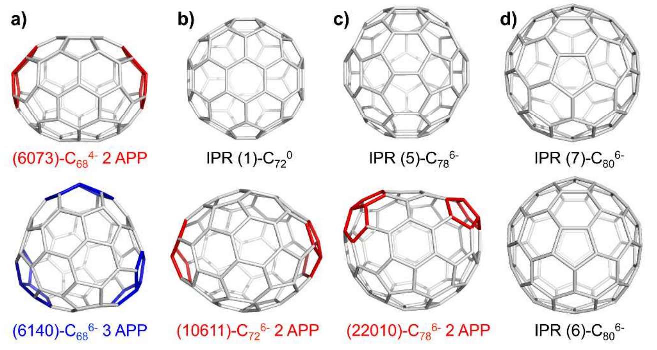


Figure 8. **Representation of the most stable isomeric cages for: a) C_{68}^{4-} and C_{68}^{6-}, b) C_{72} and C_{72}^{6-}, c) C_{78}^{6-} and d) C_{80}^{6-}. Adjacent Pentagon Pairs (APPs) have been highlighted: 2-APP red and 3-APP blue. Adapted from ref. 41.**

MARC is the key concept to understand why the IPR rule can be violated in the EMFs and to rationalize where the extra stability of these non-IPR structures comes from. The criterion holds not only when the most favoured isomers were non-IPR like for the $La_2@C_{72}$ case, but also for EMFs where the most suitable fullerene cage to host a metallic cluster was an IPR isomer, like for instance the $Sc_3N@I_h$-C_{80} EMF.[29] There are two different $Sc_3N@C_{80}$ synthesized up to date presenting either the (7)-I_h (the one most stable for TNT C_{80}-based EMF) or the (6)-D_{5h} IPR isomers (see Fig. 8d), which were the two most aromatic isomers and also the most stable hexaanions.[41] Moreover, for the C_{78} TNT-based EMFs case (i.e. transfer of 6 electrons), ALA index points that one IPR and one non-IPR with 2 APPs C_{78}^{6-} isomers present similar aromaticities (see Fig. 8c and Fig. 9). In fact, these are the two experimentally detected C_{78}-TNT isomers. The final preference for one of them also depends on the fullerene strain energy caused by the encapsulated metallic cluster: the 2210 non-IPR isomer is preferred for the larger metallic clusters (Gd_3N), while smaller clusters (Sc_3N) prefers the IPR isomer.[175]

It was found that the ALA aromaticity indicator can also describe the different hosting cages chosen by EMFs with metallic clusters that formally transfer a different number of electrons. For instance, whereas $Sc_2C_2^{4+}@C_{68}^{4-}$ corresponds to the non-IPR 6073 isomer with 2 APPs,[153] the 6140 non-IPR isomer with 3 APPs is the most suitable cage for $Sc_3N^{6+}@C_{68}^{6-}$ (see Fig. 8a).[162] Again these two isomers could be predicted using the maximum aromaticity criterion since the ALA index pointed out that isomers 6073 and 6140 were respectively the most aromatic tetra- and hexaanionic isomers among all possible C_{68} isomers.

Finally, a systematic study including all of the most common C_{2n} (2n = 66 – 104) EMFs reported to date was carried out (see Fig. 9) to fully validate the ALA criterion. The local aromaticity was not only an excellent indicator to predict the relative stability of isomers in small EMFs, such as C_{2n} (2n = 66 – 78), but also for the heavier ones (C_{100} or C_{104}). It is worth emphasizing that ALA predictions were very good even in those cases where different EMF isomers were experimentally synthetized for one metallic cluster.

The worst correlations between the stabilities and ALA index were those cases where the formal charge transfer to the fullerene was low, like for example, the C_{94}^{2-} case. When the formal charge transfer to the fullerene decreased, the geometrical strain gained more importance in determining the total energy of the systems, and then the correlations between relative stabilities and ALA worsened. Basically, there is an interplay between the strain energy and aromaticity. In neutral empty fullerenes, reducing strain energy is the main factor in determining the stability of the isomeric carbon cages. On the contrary, in highly charged fullerenes or EMFs, maximizing the total aromaticity is the main stabilizing force.

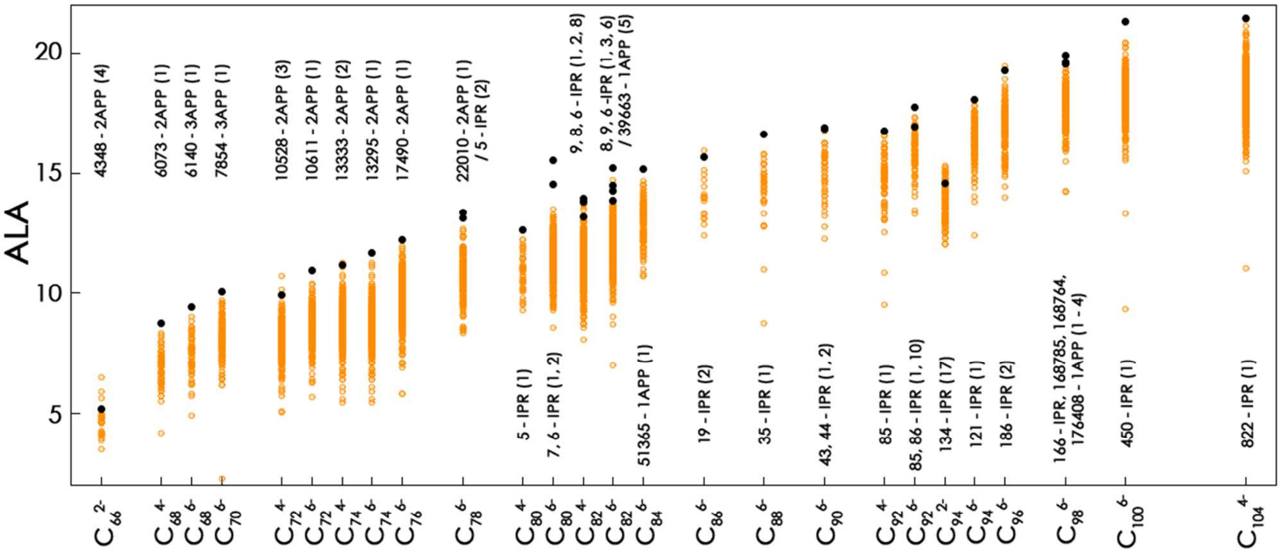


Figure 9. **Classification in terms of ALA index of the anionic IPR and non-IPR fullerene isomers for the most common C_{2n} (2n = 66 – 104) EMFs reported to date. Isomers experimentally observed are marked using black dots, and their corresponding isomer numbers are indicated. In parentheses are reported the ALA prediction ordering for the experimentally observed isomers.[41] Reprinted with permission from ref. 41.**

The high success of the ALA predictions points out that the cage aromaticity is the most important stabilizing factor in the process of EMFs formation. The MARC criterion offers a rational explanation for the breakdown of the IPR rule in EMFs: the most aromatic anionic isomer leads to the most stable EMF.

3.4 Role of Aromaticity in EMF reactivity

In the previous sections, the effect of the formal charge transfer that occurs in EMFs[152] on their aromaticity[32,111] and relative stability[157] has been discussed. However, the latter charge transfer has also direct consequences on the EMF reactivity.[42,138,176] In this section, the exohedral functionalization of TNT-based EMF will be briefly presented, and the key role played by aromaticity for guiding EMF reactivity will be highlighted.

Depending on how hexagonal and pentagonal rings are arranged in the fullerene structure, three different bond types can be present: [6,6] bonds situated between two hexagonal rings, [5,6] bonds between one hexagonal and one pentagonal ring, and [5,5] bonds (see Fig. 10a); the latter is only observed in non-IPR fullerene structures. If the type of rings that surround the C-C bond is considered, different possibilities are obtained for both [6,6] and [5,6] bonds (Fig. 10b).

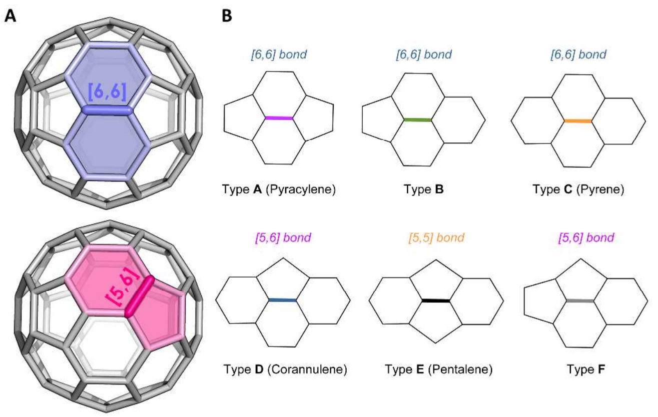


Figure 10. Classification of different bond types that might be present in a fullerene structure.

The huge interest brought forward by EMFs is mainly attributed to the potential application of these compounds in the fields of medicine and material science.[37,177] The exohedral functionalization of EMFs is of importance for the bio-application of these compounds as they usually exhibit low solubility in water, and because of the possibility to tune their properties. The chemical functionalization of EMFs and fullerenes is generally achieved *via* cycloaddition reactions. In particular, Diels-Alder (DA), 1,3-dipolar, and nucleophilic [2+1] Bingel-Hirsch (BH) additions correspond to the most widely employed strategies (see Fig. 11). Many studies have been reported regarding the exohedral reactivity of several EMFs, but only some representative examples are presented here (for a complete review see refs. 138, 178). The first exohedral functionalization of an EMF corresponded to the DA cycloaddition of 6,7-dimethoxyisochroman-3-one on the archetypal $Sc_3N@I_h-C_{80}$.[179] DFT calculations indicated that the addition to the corannulenic [5,6] bond was at least 11 kcal·mol^{-1} more favourable than the [6,6] addition.[180-182] The 1,3-dipolar cycloaddition, i.e. the Prato reaction of $M_3N@I_h-C_{80}$ was also achieved.[183] Depending on the encapsulated metal cluster, the reaction took place regioselectively at the [5,6] bond ($Sc_3N@I_h-C_{80}$, $Lu_3N@I_h-C_{80}$) or a mixture of [6,6] and [5,6] regiosiomers was obtained ($Y_3N@I_h-C_{80}$, $Gd_3N@I_h-C_{80}$).[183,184] Both [5,6] and [6,6] adducts were also observed in the synthesis of *N*-tritylpyrrolidino derivative of $Sc_3N@I_h-C_{80}$ *via* 1,3-dipolar reaction.[185] Dorn *et al.* reported DA and 1,3-dipolar cycloaddition reactions on $M_3N@D_{5h}-C_{80}$ (M = Sc, Lu).[186] The higher reactivity observed experimentally for the D_{5h} cage of C_{80} for all metal clusters considered, was later on investigated computationally via DFT calculations.[181,182] The calculations indicated that the preferred addition site for $Sc_3N@D_{5h}-C_{80}$ corresponds to a type B bond instead of the pyracylenic addition suggested experimentally from NMR experiments.[187] Cai and coworkers functionalized $Sc_3N@D_{3h}-C_{78}$ via 1,3-dipolar cycloaddition.[188] Similarly to the case of $D_{5h}-C_{80}$ EMF, the pyracylene type [6,6] bond was less reactive than type B [6,6] bonds. DFT calculations investigating the thermodynamics and kinetics of the DA reaction on $Sc_3N@D_{3h}-C_{78}$, $Y_3N@D_{3h}-C_{78}$, and $Y_3N@C_2-C_{78}$ supported the experimental findings and highlighted the importance of release of strain energy on the chemical reactivity of the cages.[175,189] The computational exploration of the same DA on the parent $Ti_2C_2@D_{3h}-C_{78}$ demonstrated that the orientation of the cluster also plays a fundamental role on the EMF reactivity.[176]

The first BH cycloaddition on EMFs was reported by Alford and co-workers in 2003,[190] while searching for a strategy to improve the water solubility of $Gd@C_{60}$. Echegoyen and co-workers reported the first monomethanofullerene derivative of I_h-C_{80} EMFs in 2005. They showed that cyclopropanation of $Y_3N@C_{80}$[191] and $Er_3N@C_{80}$[183] with diethyl bromomalonate takes place regioselectively on a [6,6] bond under mild conditions. They also showed that in EMFs the retro-cycloaddition induced by multiple electrochemically reductions did not occur, in contrast to the previously reported C_{60} case.[183,192] In 2007, the open fulleroid structure of $Y_3N@C_{80}C(CO_2CH_2Ph)_2$ was characterized by X-ray.[193] DFT calculations indicated that $Y_3N@C_{80}$ [6,6] open structures were more stable than closed ones, confirming that, in general, I_h-C_{80} EMFs fulleroid structures were better stabilized. The same year, Dorn, Gibson, and co-workers synthetized the first two examples of $Sc_3N@C_{80}$ open [6,6] methano-bridged derivatives using a manganese(III)-catalyzed free radical reaction. It is interesting to mention here that the measured $^{1}J_{(C,H)}$ = 147 Hz of the C□H bridge atoms in a [6,6]-open monoadduct containing only one ester group and a hydrogen atom on the central bridge carbon atom was completely in agreement with the one corresponding to a π-homoaromatic system.[194,195] Recently the BH reactions on non-IPR EMFs ($Gd_3N@C_{82}$, $Gd_3N@C_{84}$) have been reported by Echegoyen and co-workers,[196,197] and studied theoretically by Rodríguez-Fortea, Poblet and co-workers.[197-199] They showed that the thermodynamically more stable products presented open fulleroid structures, in the same line as the previously reported IPR EMFs.

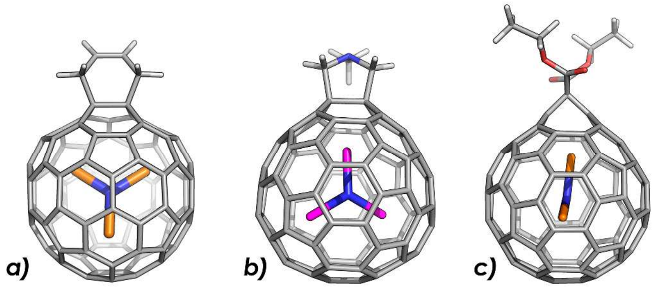


Figure 11. Examples of functionalized EMFs: a) Diels-Alder adduct on $Sc_3N@I_h$-C_{80},[182] b) Prato reaction on $Y_3N@I_h$-C_{80},[184] c) Bingel-Hirsch adduct on $Sc_3N@I_h$-C_{80}.[199] Drawn from data in refs. 182, 184, 199.

These representative examples demonstrate that the encapsulated clusters inside the fullerene cages played an important role in directing the addition sites. The computational investigation of the observed experimental selectivities has been key to rationalize, predict, give support, and even correct some experimental assignments.[138, 175, 176, 187, 189] Bond-type together with pyramidalization angles, appropriate shape of the LUMO orbitals to react, and more recently fullerene distortion energy and aromaticity are the usually employed parameters to justify and rationalise the exohedral reactivity of the fullerene cages.[138] The most reactive bonds are usually those presenting short C-C bond distances, relatively large pyramidalization angles, and appropriate LUMO orbitals to interact with the reactive species. The HOMO orbitals of fullerene structures present bonding π interactions in the [6,6] C-C bonds, and antibonding π interactions in the [5,6]. LUMO and LUMO+1 usually represent an inverse situation. The population of the LUMO orbitals when metallic clusters are encapsulated inside the cage leads to an increase of the [6,6] bond distance and a decrease of [5,6] bonds. This fact explains the higher reactivity of [5,6] bonds in EMFs structures and the importance of aromaticity in these charged species.[41, 42] Indeed, the reactivity and regioselectivity of DA or 1,3-dipolar reactions involving empty fullerenes is generally favoured for [6,6] bonds, whereas in EMFs and negatively charged C_{60}, [5,6] bonds are commonly more reactive.[42, 182]

In the final section of this review, we describe why aromaticity is suggested to play an essential role in determining the reactivity and regioselectivity when EMFs are considered, paying special attention to the particular case of the DA and the BH reactions.

a. Electrochemical control of the regioselectivity in the Diels-Alder addition to C_{60}: the role of aromaticity

As mentioned in the previous sections, the encapsulation of metal clusters inside the fullerenes has two main effects: (i) a formal charge transfer of e.g. six electrons in the case of M_3N-units, and (ii) induction of strain in the fullerene cage because of the steric contacts between the cluster and the cage. In addition to that, the stability of different $M_3N^{6+}@C_{2n}^{6-}$ (2n= 68–98) isomers correlates well with those of the charged empty cages (C_{2n}^{6-}).[157] This already indicated that the first effect of a formal charge transfer seemed to be more important than the induced strain. However, this additional charge on its own can have two effects: (a) a reduction of electron affinity and hence lower reactivity towards nucleophilic additions, and (b) an increase of aromaticity of the 5-MRs (where the additional electrons mainly end up in[158, 160]). Since the reactivity and regioselectivity are dependent on *local* aromaticity changes, the change in aromaticity could lead locally to either higher or lower reactivity. To analyse this point, the HOMA, MCI, and NICS indicators of aromaticity for the 5-MRs and 6-MRs of different C_{60}^{n-} (n = 0 – 6) species has been recently[42] calculated. BP86-D_2/DZP HOMA indices showed a decrease in the aromaticity of the 6-MRs when the number of added electrons increased, while the aromaticity of the 5-MRs remained basically constant. On the other hand, MCI results calculated at the BP86/cc-pVDZ//BP86-D_2/DZP level showed that the aromaticity of the 5- and 6-MRs increased and decreased, respectively, with the successive addition of electrons to the C_{60} molecule (see Fig. 12).[42]

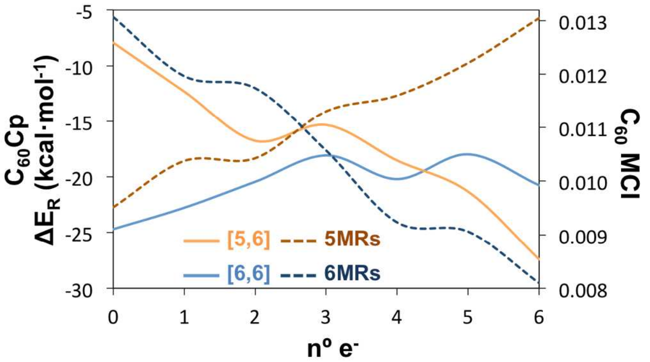


Figure 12. Change in the DA reaction energy between Cp and C_{60}^{n-}, and aromaticity (dashed lines) of five- (5-MR) and six-membered (6-MR) rings of C_{60}^{n-} as function of number of electrons added (n). Reproduced from Ref. 42 with permission from The Royal Society of Chemistry.

The increase in the 5-MR aromaticity is likely the result of the extra charge located in these rings. The NICS(1) values for C_{60} and C_{60}^{6-} molecules showed a similar trend for the 5-MR. However a slight increase of the aromaticity of 6-MR was observed, although this increase could be an artefact due to the magnetic field created by the neighbouring diatropic 5-MR currents. As a whole, six-electron addition to C_{60} resulted in a clear increase of the aromaticity of the cage.[160]

Interestingly enough, the change in aromaticity of C_{60}^{n-} rings correlated well with the change in the energy profile for the DA reaction with cyclopentadiene. I.e. for neutral C_{60}, there was a clear preference for reacting with [6,6]-bonds from both the kinetic and thermodynamic point of view (see Figure 13). Instead, for hexaanionic C_{60}^{6-}, the preference reversed and it was now the [5,6]-bonds that were more reactive. This change in regioselectivity was gradual as can be seen in Fig. 12.

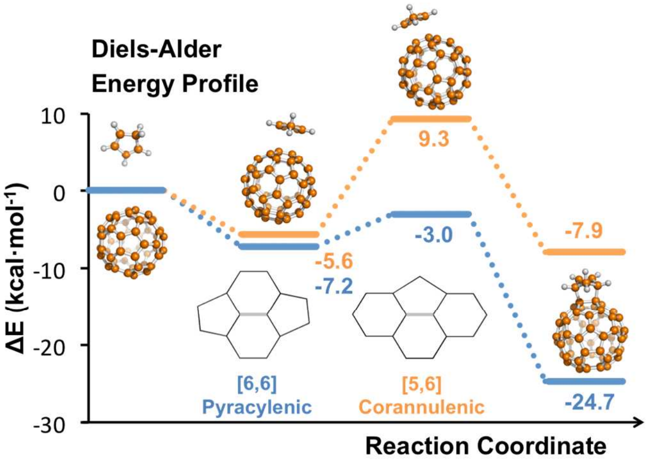


Figure 13. Schematic representation of the energy profiles of the Diels–Alder addition of cyclopentadiene to the [6,6] and [5,6] bonds of neutral C_{60}. Reproduced from Ref. 42 with permission from The Royal Society of Chemistry

The aromaticity changes of the 5-MR and 6-MR as function of the number of electrons added (n) on their own do not give an explanation for the gradually changing preference towards [5,6]-bonds. For that, it was proposed to take into account all of the four rings surrounding a particular bond, and investigate how the aromaticity changes along the reaction path. Because the Diels-Alder addition leads to a change from planar sp^2 to tetrahedral sp^3 for the attacked carbon bond, when the addition took place on a pyracylenic [6,6]-bond type, the π-conjugation of two 5-MRs and two 6-MRs was lost. On the other hand, when the addition was on a corannulenic [5,6]-bond, the conjugation vanished in three 6-MRs and one 5-MR. Therefore, it was the *difference* for the changes in aromaticity between a 6-MR and a 5-MR along the reaction that determined the regioselectivity.[42] It was therefore not sufficient to simply look at the reactant, but one must take into account how the aromaticity changed from reactant to product, for both the 5-MR and 6-MRs. If the neutral C_{60} is considered, the four rings surrounding a [6,6]-bond lost aromaticity *less* than the four rings around a [5,6]-bond ($\Delta MCI_{[6,6]}-\Delta MCI_{[5,6]}>0$).[42] On the other hand, for C_{60}^{6-} the situation was reversed, and now $\Delta MCI_{[6,6]}-\Delta MCI_{[5,6]}<0$. Based on these results, it was easy to understand why in EMFs with an elevated number of electrons transferred formally (n>4), there was a general tendency for attack on [5,6] bonds, in contrast to the situation of empty and neutral fullerenes. It has to be mentioned here that similar trends were found for the 1,3-dipolar cycloaddition on C_{60}^{n-}.[42]

These observations revealed that when the reactivity of charged fullerenes (i.e. EMFs) is considered, the stabilizing role played by the aromaticity is a determining factor. We expect that in next few years, different reactions on EMFs and specially the regioselectivities of the processes could be rationalized and understood using this kind of aromaticity-based analysis. In this direction, our group has started to explore and analyse different reactions involving EMFs in terms of the fullerene local aromaticities.[40, 184] In the next subsection, we will describe the particular case of the widely used BH reaction on EMFs.

b. The Bingel-Hirsch Reaction on EMFs: aromaticity as a descriptive tool

The BH reaction, a [2+1] cycloaddition reaction,[200] between bromomalonate and EMFs was shown to be a very powerful and versatile tool for functionalizing EMFs in a rapid and efficient manner.[39] Through the BH reaction, one could tune and modify physical (solubility, for example) and (electro)chemical properties (such as band-gaps) of EMFs. The BH reaction takes place in the presence of a strong base to deprotonate the bromomalonate and form an enolate, and proceeds following a two-step mechanism as represented in Fig. 14a. In the first step, the bromomalonate carbanion attacks the fullerene cage *via* nucleophilic addition in a barrierless process. During the second step, a cyclopropane ring closure takes place when the newly generated carbanion on the fullerene cage displaces the bromine anion in an intramolecular nucleophilic substitution.[39]

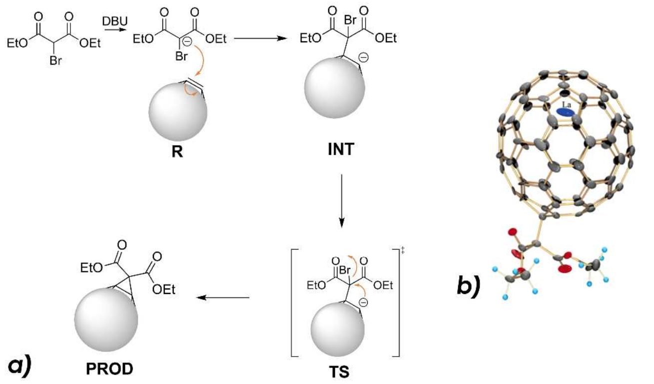


Figure 14. a) General mechanism of the Bingel-Hirsch [2+1] nucleophilic addition of diethylbromomalonate over fullerenes in the presence of 1,8-diazabicycloundec-7-ene (DBU), b) X-ray structure of the singly bonded Bingel-Hirsch intermediate La@C_{82}CBr($CO_2C_2H_5$)$_2$.[201] Reprinted with permission from ref. 201.

In 2005, Akasaka, Nagase, and co-workers synthetized and reported the first singly bonded BH intermediate confirming the described BH reaction mechanism.[201] The isolation of the EPR-inactive La@C_{82}CBr($CO_2C_2H_5$)$_2$ monoadduct (see Fig. 14b) demonstrated that the BH reaction took place through a two-step process, as described previously. The authors could capture the [La@C_{82}CBr($CO_2C_2H_5$)$_2$]$^-$ intermediate formed during the nucleophilic attack at the first step of the reaction by treating it with oxidants in order to get the La@C_{82}CBr($CO_2C_2H_5$)$_2$ species.[201]

In 2013, Garcia-Borràs *et al.* rationalized the larger stabilization of the open-cage fulleroids monoadduct stabilities in terms of aromaticity.[40] The authors reported that there exists a direct relationship between the stabilities of the BH monoadducts and their degree of aromaticity measured in terms of the ALA index. Although large bond distances and higher pyramidalization angles usually favour thermodynamically the BH additions, very frequently it is not possible to rationalize the computed relative stabilities of the different monoadducts in terms of bond distances and pyramidalization angles. They showed that the Maximum ARomaticity Criterion[41] also applies for the BH monoadducts thermodynamic stabilities (i.e. "the most aromatic adduct = the most stable").[40] In general, open-cage fulleroids are more stable than closed ones, as described previously in section 2.2. In the open-cage structures, all carbon cage atoms kept their sp^2 hybridization forming homoaromatic rings, to give rise to the so-called homofullerenes observed experimentally (*vide supra*).[145, 194, 195] The ALA index pointed out that the aromaticity enhanced by the presence of these homoaromatic rings was responsible for the better stabilization of the open-cage fulleroids in contrast to the closed-cage adducts, where the hybridization of the attacked carbon atoms changed towards sp^3 without allowing π delocalization.[40, 41] Moreover, the presence of a metallic atom facing the open-cage monoadduct attacked bond (experimentally observed in the $Y_3N@C_{80}$ X-Ray monoadduct structures) improved the *p-p* overlap between the carbon atom orbitals enhancing the ring π-homoaromaticity (see Fig. 4 and Fig. 15).

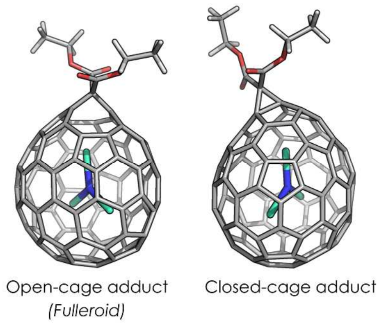


Figure 15. DFT optimized open/closed Bingel-Hirsch monoadducts of $Gd_3N@C_s(51365)$-C_{84}.[40] The most favourable open-cage Bingel-Hirsch monoadduct isomer is found to be >20 kcal mol^{-1} more stable than the most stable closed-cage monoadduct.[40] Drawn from data in ref. 40.

In a very recent study, Poblet and co-workers have theoretically studied the complete electronic reaction paths for the BH additions on $Sc_3N@I_h$-C_{80} and $Sc_3N@D_3(6140)$-C_{68},[199] and on $Gd_3N@C_s(39663)$-C_{82} and $Gd_3N@C_s(51365)$-C_{84} EMFs.[198] By using DFT calculations, they observed that the BH thermodynamic and kinetic products do not coincide. And, more importantly, they showed that the BH reaction under common reaction conditions leads to kinetically controlled products.[198, 199] The reaction barrier corresponding to the addition on a [6,6] bond in $Sc_3N@I_h$-C_{80} was 5 kcal mol^{-1} lower in energy than the one corresponding to the [5,6] addition. These results were in perfect agreement with the previously reported experimental observations on I_h-C_{80} EMF BH additions that took place regioselectively on [6,6] positions.[197, 198] For the non-IPR $Sc_3N@D_3(6140)$-C_{68} EMF, the DFT calculations indicated that the kinetic product corresponded to the addition to a type-B [6,6] bond, placed in an adjacent position to a pentalene unit, coinciding with the ^{13}C-NMR experimental assignment by Dorn and co-workers.[202] A similar situation was found for the $Gd_3N@C_s(39663)$-C_{82} and $Gd_3N@C_s(51365)$-C_{84} systems, where kinetic products were predicted to be the ones corresponding to the additions on [6,6] B-type bonds placed near the pentalene unit in both cases.[198]

Garcia-Borràs et al. have recently explored the complete BH reaction mechanism for different EMF systems.[203] Their results clearly show that the aromaticity of the first step intermediate of the reaction dictates the BH kinetic addition site. Based on these observations, we have proposed some general aromaticity-based rules that correctly predict the most suitable BH addition sites for experimentally studied EMFs. We hope that this new tool will be helpful to identify the BH adducts in future experimental syntheses.

4. Conclusions

Since the discovery of fullerenes, many studies devoted to analyze the aromaticity of this new allotropic form of carbon have been reported. These studies show that fullerenes have ambiguous low aromatic character. Since the aromatic stabilization energy associated to these species is relatively small, it is widely accepted that aromaticity does not play a fundamental role in determining the molecular structure and reactivity of neutral and hollow fullerenes. The situation is totally reversed when we consider charged fullerenes. For instance, whereas C_{60} is non- or antiaromatic, its hexaanion form, C_{60}^{6-}, is aromatic. Thus, in reduced fullerenes or fullerenes with encapsulated metal clusters (endohedral metallofullerenes, EMFs), aromaticity plays a key role that has been overlooked until now in most cases. In this review we emphasize the role that aromaticity plays in determining the molecular structure and reactivity of endohedral metallofullerenes and negatively charged fullerenes.

For the molecular structure it was reported that the increase in the additive local aromaticity (ALA) value of the negatively charged cage is the main driving force that determines the most suitable hosting carbon cage for a given metallic cluster. The ALA predictions offered a rational explanation for the breakdown of the Isolated Pentagon Rule (IPR) in EMFs: the most stable anionic fullerene isomer is the one whose total aromaticity is maximized (the so-called Maximum ARomaticity Criterion, MARC). This simple criterion allows to directly compare IPR and non-IPR anionic isomers irrespective of the number of adjacent pentagon pairs they have.

Regarding reactivity, it was revealed that the effect of successive reductions of C_{60} molecule dramatically changed the regioselectivity of the Diels-Alder cycloadditions, from the usual [6,6] addition in neutral species to addition to the [5,6] bond when the number of electrons added to C_{60} was higher than 4. Moreover, it was demonstrated that this regioselectivity change could be rationalized in terms of local aromaticity variations in the 5- and 6-MRs of the fullerene due to the reduction process. Finally, it has been shown that there exists a direct relationship between the relative stabilities of Bingel-Hirsch adducts of non-IPR EMFs and their aromaticity as measured with the ALA index. This observation is of great relevance, as there were no previous studies where a single parameter, either geometric or electronic (such as fullerene strain, bond length, pyramidalization angles, etc.), was able to unequivocally describe and rationalize the preferred addition sites in Bingel-Hirsch additions.

We hope the present review helps to make the chemical community aware of the fact that the molecular structure and chemical reactivity behaviour of EMFs and negatively charged fullerenes can be greatly predicted and rationalized by the local and global aromaticity of these species. In our opinion, future studies will reinforce the importance of aromaticity in the field of fullerene and particularly endohedral metallofullerene chemistry.

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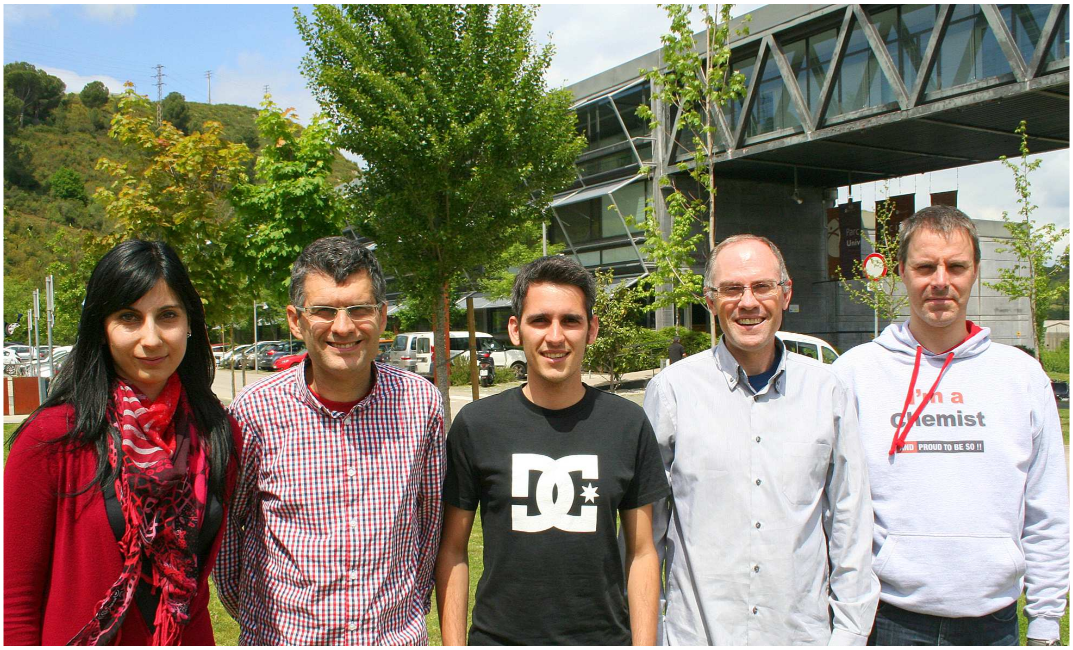


Group Photo. From left to right: Sílvia Osuna, Josep M. Luis, Marc Garcia-Borràs, Miquel Solà and Marcel Swart.

Marc Garcia-Borràs

Marc Garcia-Borràs (1988) graduated in Chemistry in 2010, was awarded the Degree Extraordinary Award by the University of Girona (UdG). In 2011 he finished the Interuniversity Master in Computational and Theoretical Chemistry, obtaining the Master Extraordinary Award from the University Rovira i Virgili (Tarragona). He then started his PhD studies under of the supervision of Prof. M. Solà and Dr. J. M. Luis at the Institute of Computational Chemistry and Catalysis, UdG. Marc works on the computational study of (metallo)fullerenes structure and reactivity, Host-Guest complexes interactions, and the evaluation of Non-Linear Optical properties (NLOP) of molecules. He is the co-author of 12 scientific publications.

Sílvia Osuna

Sílvia Osuna obtained her PhD (Girona, 2010) for a thesis on metallofullerenes, and received the special award for her thesis by the University of Girona. She was awarded a Marie Curie IOF fellowship for a 2-year postdoctoral position at the group of Prof. K. N. Houk at the University of California, Los Angeles (UCLA). She is currently a Juan de la Cierva researcher at the Institute of Computational Chemistry and Catalysis (IQCC, UdG) and has recently obtained a Career Integration Grant project. She has co-authored more than 36 publications, 2 book chapters, and has participated in more than 40 conferences.

Marcel Swart

Marcel Swart obtained his PhD (Groningen, 2002) for a thesis on copper proteins. He then moved to Amsterdam as post-doc to work on cytochrome P450s, and later DNA, for which he was given the Young Scientist Excellence award. In 2006 he moved to Girona (ICREA-Júnior), where in 2009 he obtained a permanent position as ICREA Research Professor. He is member of the Editorial Board of international scientific journals, and has co-authored more than 110 scientific papers. In 2012 he was awarded the MGMS Silver Jubilee Prize and currently he is coordinator of the ECOSTBio COST Action (started April 2014).

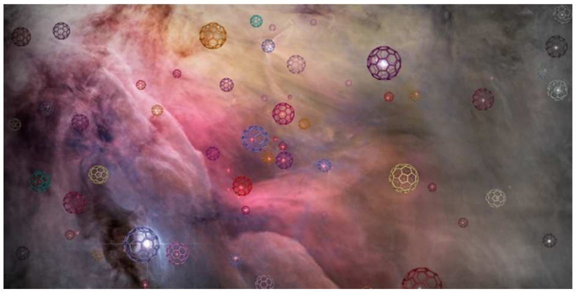
Josep M. Luis

Josep M. Luis obtained his PhD (Girona, 1999) for a thesis on the evaluation of Non-linear optical properties, and received the special award for his thesis by the University of Girona. He performed several post-doc stays at the University of California-Santa Barbara at the group of Prof. Kirtman. In 2000 obtained a position as assistant professor in the University of Girona, and in 2005 a permanent position as associate Professor. His research interest are (endohedral metallo)fullerene reactivity, the C-H Oxidation and water oxidation by bioinspired Iron Catalysts and the host-guest complexes interactions. He has co-authored more than 82 publications and 2 book chapters.

Miquel Solà

Miquel Solà (Fonteta, 1964) obtained his PhD at the Autonomous University of Barcelona in 1991. After several months in a consultant company, in 1993 he moved to the University of Girona (UdG) as assistant researcher. He was appointed assistant professor of the UdG in 1997. In 2001, he was awarded with the Catalan Distinction for the Promotion of University Research (young scientist category). Since 2003, he holds a permanent position as full professor in the UdG. In 2009, he was awarded with the ICREA Academia Prize and with the Physical Chemistry prize of the Spanish Royal Society of Chemistry in 2013. He is member of the Editorial Board of international scientific journals, and has co-authored about 300 scientific papers.

TABLE OF CONTENTS ENTRY



The molecular structure and chemical reactivity of endohedral metallofullerenes can be greatly predicted and rationalized by their local and global aromaticity